A UNIFIED STRATEGY FOR PENOSTATIN (BIO)SYNTHESIS

AND

FORAYS IN COMPUTATIONAL CHEMISTRY

A DISSERTATION
SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL
OF THE UNIVERSITY OF MINNESOTA
BY

Matthew James Jansma

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

Thomas R. Hoye, Adviser

July 2012

ACKNOWLEDGEMENTS

It has truly been an honor and a pleasure to work under the guidance of my adviser, Professor Thomas R. Hoye, and I would like to thank him for giving me the opportunity to pursue graduate studies in his laboratory. To say that Tom is an excellent adviser, though an unarguable truth, is, quite frankly, a gross understatement. Alas, it is practically impossible to capture here in words how profoundly he has impacted my growth as a scientist and an individual, but suffice it to say that Tom is a superb teacher, a chemist of the absolute highest caliber, and, above all, a wonderful human being for whom I have a tremendous amount of respect. Throughout my entire graduate career, Tom granted me the scientific freedom to pursue my ideas in an environment where I was viewed as a colleague in the research process; yet, when called upon to do so, he was *always* available when I needed his guidance the most. For Tom's dedicated service to his students, his institution, and the chemistry community at large, I will always be grateful.

I would like to acknowledge Professors Robert A. Fecik, Andrew M. Harned, and Wayland E. Noland for their service on my preliminary and final oral defense committees and Professor Christopher J. Douglas for his helpful input as I set out to establish a career after graduate school. In particular, Robert kindly gave me the opportunity to work in his laboratory as an undergraduate researcher during the summer of 2005, which was a rewarding educational experience that solidified my desire to pursue graduate studies in the field of organic synthesis.

I must express my sincere gratitude to and utmost respect for Professor Colleen M. Byron, once my undergraduate adviser at Ripon College but now a dear friend. Without her mentorship, personal sacrifice, and constant encouragement, I dare say that I would not have set foot in a graduate research laboratory, let alone have had the opportunity to write this Thesis. Colleen recognized something in me that I was incapable of seeing and invested a great deal of her own time and energy to guarantee that I would be given the opportunity to pursue my goals.

There are many Hoye group members, both past and present, whose camaraderie and guidance made my graduate school tenure immeasurably more enjoyable. First and foremost, I would like to thank Dr. Aaron Burns for enlightening and highly entertaining discussions during our daily coffee breaks and Dr. Chris Jeffrey, Dr. Junha Jeon, and Dr. Lucas Kopel for embodying, and thus demonstrating by example, the attributes and work ethic that a successful graduate student must possess. I would also like to thank Susan Brown, Enver Cagri Izgu, Dr. Dorian Nelson, Patrick Willoughby, Adam Wohl, and Brian Woods for their friendship, fruitful collaborations, and insightful conversations regarding all manner of subjects. I would like to acknowledge T. Aaron Bedell, Ashley Garr (Professor C. J. Cramer research group), Dr. Keith Wiitala, and Patrick for their invaluable contributions to the advancement of computational chemistry methodology in the Hoye group. Additionally, I am indebted to Dr. Michael Wentzel, Patrick, Adam, and Brian for their willingness to volunteer their time to review and critically assess early drafts of this Thesis.

A special thanks goes out to my good friend Dr. Aalo K. Gupta, a former member of the Tolman research group. Our discussions over coffee/a beer (or two) about chemistry, life, and the relative merits of Vince Lombardi versus Mike Ditka were, among many other unforgettable events, much-needed departures from the unrelenting minutiae of graduate school.

Finally, throughout this entire journey, my mother Mary Ann, my father James, my sister Heather, my brother(in-law) Gavin, and my girlfriend Kate have been a permanent source of love, encouragement, and unconditional support (in *every* sense of that word). This Thesis is as much a triumph for them as it is for me.

DEDICATION

To my mother, Mary Ann, and my father, James

ABSTRACT

PART 1: Comprising Chapters I–IV, the studies described in the first part of this Thesis have as their overarching goal the utilization of organic synthesis to address questions of biosynthetic import. The impetus for this work has been provided by the penostatins A–I, a family of biologically active, structurally atypical, polyketide-derived secondary metabolites isolated from the fungus *Penicillium* sp. OUPS-79. Critical mechanistic and structural analyses have compelled the hypothesis that the penostatins arise via spontaneous (i.e., *non* enzyme-catalyzed) pericyclic reaction cascades that emanate from a single biogenetic precursor. Part 1 is inaugurated with a concise summary of the isolation, structure determination, and biological activity of the penostatins (Chapter I). In addition, a discussion of others' previous synthetic efforts toward members of the family is presented. Chapter II describes a campaign that has culminated in the stereoselective synthesis and study of the putative biosynthetic precursor to penostatins A and B, which constitutes the vast majority of the work conducted during the author's tenure. A pertinent model study that involved the design, synthesis, and subsequent investigation of (the enolates derived from) a pair of model dihydropyran substrates is detailed in Chapter III. This work has tentatively supported the notion that penostatins I and F arise via spontaneous [3,3]-sigmatropic (Claisen) rearrangements. Finally, Chapter IV documents progress toward the synthesis of a model substrate relevant to the biosynthesis of penostatins G and H.

PART 2: The ability to reliably deduce the constitution and relative configuration of newly isolated organic molecules lies at the very core of all endeavors in the fields of synthetic organic and natural products chemistry. Nuclear magnetic resonance (NMR) spectroscopy is unarguably the single most powerful spectroscopic tool for this task; however, the unambiguous assignment of these structural properties via spectroscopic data alone is rarely a trivial matter. In Part 2 of this Thesis, the power and utility of DFT-based computational methods for the structure determination of small organic molecules are showcased. Chapter V includes a short discussion of the motivation for these studies and previous work from the Hoye/Cramer team. Then, in Chapter VI, computed proton (^{1}H) and carbon (^{13}C) NMR chemical shifts (δ) are employed to address structural issues that have arisen from two concurrent synthetic endeavors in the Hoye group. On the basis of the computational results described therein, reassignments of (i) the structures of the 'Jones isomers' and (ii) the relative configuration within (at least) the AB ring system of phomopsichalasin are strongly recommended. Additionally, a reexamination of the reported ^{1}H NMR chemical shift assignments for patchouli alcohol has emerged from a collaborative effort with the Cramer group.

TABLE OF CONTENTS

NUMBERING ROADMAP

CHAPTER	STRUCTURES	SCHEMES	FIGURES	TABLES
I	**1001 – 1056**	**I–1** to **I–17**	**I–1** to **I–2**	---
II	**2001 – 2308**	**II–1** to **II–85**	**II–1** to **II–5**	**II–1** to **II–8**
III	**3001 – 3059**	**III–1** to **III–24**	**III–1** to **III–2**	**III–1** to **III–4**
IV	**4001 – 4031**	**IV–1** to **IV–10**	**IV–I**	**IV–1**
V	**5001 – 5014**	---	**V–1** to **V–3**	**V–1** to **V–2**
VI	**6001 – 6016**	**VI–1** to **VI–2**	**VI–1** to **VI–10**	**VI–1** to **VI–9**

PART 2. FORAYS IN COMPUTATIONAL CHEMISTRY

LIST OF FIGURES

CHAPTER I

CHAPTER II

CHAPTER III

CHAPTER IV

CHAPTER V

CHAPTER VI

LIST OF TABLES

CHAPTER II

CHAPTER III

CHAPTER IV

CHAPTER V

CHAPTER VI

APPENDIX A

APPENDIX B

LIST OF ABBREVIATIONS

Ac	Acetyl
3Å/4Å MS	3 or 4 Angstrom molecular sieves
APCI	Atmospheric-pressure chemical ionization
aq	Aqueous
ATR	Attenuated total reflectance
AVE	Allyl vinyl ether
BHT	Butylated hydroxytoluene
Bn	Benzyl ($C_6H_5CH_2$–)
BP or **bp**	Boiling point, °C
BSA	*N*,*O*-Bis(trimethylsilyl)acetamide
***n*-Bu**	*normal*-Butyl
***sec*-Bu**	*secondary*-Butyl
***t*-Bu**	*tertiary*-Butyl
CAN	Ammonium cerium(IV) nitrate [$(NH_4)_2Ce(NO_3)_6$]
cat	Catechol
CD	Circular dichroism
CMAE	Corrected mean absolute error
COSY	Correlation spectroscopy
Cp	Cyclopentadienyl
$[Cp_2Fe]^+ PF_6^-$	Ferrocenium hexafluorophosphate
CuTC	Copper(I) thiophene-2-carboxylate

Cy	Cyclohexyl
d	doublet, in NMR spectroscopy
DA	Diels–Alder
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
°C	Degree(s) Celsius
δ	Chemical shift, in NMR spectroscopy
DEPT	Distortionless enhancement by polarization transfer
DFT	Density functional theory
$(DHQD)_2PHAL$	Hydroquinidine 1,4-phthalazinediyl diether
DIBAL-H	Diisobutylaluminum hydride
***i*-PP_2BH**	Di(*iso*-propylprenyl)borane
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMF	*N*,*N*-Dimethylformamide
DMI	1,3-Dimethyl-2-imidazolidinone
DMP	Dess–Martin Periodinane
DMSO	Dimethylsulfoxide

DPEPhos	(Oxydi-2,1-phenylene)bis(diphenylphosphine)
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
DVTMDS	1,3-Divinyl-1,1,3,3-tetramethyldisiloxane
ED_{50}	Median effective dose
EI	Electron impact ionization
equiv	Equivalent(s)
ESI	Electrospray ionization
Et	Ethyl
FVP	Flash vacuum pyrolysis
G2	Grubbs 2^{ND}-generation initiator
g	Gram(s)
GC	Gas chromatography
GIAO	Gauge-including/independent atomic orbital
GOESY	Gradient 1-D NOE spectroscopy
h	Hour(s)
HDA	Hetero-Diels–Alder
HDDA	Hydroxyl-directed Diels–Alder
HG2	Hoveyda–Grubbs 2^{ND}-generation initiator
HMBC	Heteronuclear multiple-bond quantum correlation spectroscopy
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide

HMQC	Heteronuclear multiple quantum correlation spectroscopy
HPLC	High performance/pressure liquid chromatography
HSQC	Heteronuclear single-quantum correlation spectroscopy
HTIB	[Hydroxyl(tosyloxy)iodo]benzene
HWE	Horner–Wadsworth–Emmons
Hz	Hertz
IBA	2-Iodosobenzoic acid
IBX	1-Hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide
IEFPCM	Integral equation formalism polarized continuum model
IMDA	Intramolecular Diels–Alder
IMHDA	Intramolecular hetero-Diels–Alder
imH	Imidazole
Ipc	Isopinocampheyl
IR	Infrared spectroscopy
J	Scalar coupling constant, in Hz
kcal	Kilocalorie(s)
KET	Keto-enol tautomerization
KHMDS	Potassium bis(trimethylsilyl)amide
KIE	Kinetic isotope effect
L	Liter(s)
LA	Lewis acid
LAH	Lithium aluminum hydride

LC Liquid chromatography

LDA Lithium diisopropylamide

LG Leaving group

LiDBB Lithium 4,4′-di-*tert*-butylbiphenyl

LiHMDS Lithium bis(trimethylsilyl)amide

LR Low resolution

L-SELECTRIDE® Lithium tri-*sec*-butylborohydride

MABR Methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide)

MAE Mean absolute error

MCMM Monte Carlo Multiple Minimum

Me Methyl

Meerwein's salt Trimethyloxonium tetrafluoroborate, $[Me_3O]^+ [BF_4]^-$

MEM 2-Methoxyethoxymethyl

µmol Micromole(s)

mmol Millimole(s)

mg Milligram(s)

MIDA *N*-Methyliminodiacetic acid

mL Milliliter(s)

MM Molecular mechanics

MMFF Merck Molecular Force Field

mmHg Millimeter(s) of mercury

MNBA 2-Methyl-6-nitrobenzoic anhydride

MOM	Methoxymethyl
MP or **mp**	Melting point, °C
MPLC	Medium pressure liquid chromatography
Ms	Methanesulfonyl or mesyl
MS	Mass spectrometry
MTBSA	*N*-Methyl-*N*-(*tert*-butyldimethylsilyl)acetamide
MTM	Methylthiomethyl
MTPA	α-Methoxytrifluoromethylphenylacetyl
NaHMDS	Sodium bis(trimethylsilyl)amide
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NHC	*N*-Heterocyclic carbene
NHPI	*N*-hydroxyphthalimide
NIS	*N*-Iodosuccinimide
NMO	4-Methylmorpholine *N*-oxide
NMP	*N*-Methylpyrrolidinone
NMR	Nuclear magnetic resonance spectroscopy
No-D	No-deuterium proton NMR spectroscopy
NOE	Nuclear Overhauser enhancement/effect
NOESY	Nuclear Overhauser enhancement/effect spectroscopy
[O]	Oxidation
PCC	Pyridinium chlorochromate, $[pyrH]^+[CrO_3Cl]^-$

PDC Pyridinium dichromate, $[pyrH]_2^{2+}\ [Cr_2O_7]^{2-}$

PEG Polyethylene glycol

PEPPSI™ Pyridine-enhanced precatalyst preparation, stabilization, and initiation

Ph Phenyl

PIFA [bis(trifluoroacetoxy)iodo]benzene

pin Pinacol or pinacolato

PKS Polyketide synthase

ppm Parts per million, in NMR spectroscopy

***i*-Pr** *iso*-Propyl

PTAD 4-Phenyl-1,2,4-triazole-3,5-dione

pyr Pyridine

q quartet, in NMR spectroscopy

R Rectus (absolute configuration)

RCM Ring-closing metathesis

RED-Al® Sodium bis(2-methoxyethoxy)aluminum hydride

R_f Ratio to front

RRCM Relay ring-closing metathesis

rt Room temperature

s singlet, in NMR spectroscopy

S Sinister (absolute configuration)

satd Saturated

SPhos 2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl

t	Triplet, in NMR spectroscopy
TBAF	Tetra-*n*-butylammonium fluoride
TBDPS	*tertiary*-Butyldiphenylsilyl
TBS	*tertiary*-Butyldimethylsilyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TES	Triethylsilyl
TFA	Trifluoroacetic acid or trifluoroacetyl
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMANO	Trimethylamine *N*-oxide
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl
TOF	Time of flight
TPAP	Tetra-*n*-propylammonium perruthenate, $[Pr_4N]^+ [RuO_4]^-$
$\mathbf{t_R}$	Retention time
TRIBAL	Triisobutylaluminum
Ts or ***p*-Ts**	*para*-Toluenesulfonyl
$\mathbf{\lvert \Delta\delta \rvert_T}$	Total absolute error
UA0	United-atom radii
ZMA	Zirconium-catalyzed alkyne methylalumination

PART 1

A UNIFIED STRATEGY

FOR

PENOSTATIN (BIO)SYNTHESIS

CHAPTER I

INTRODUCTION AND BACKGROUND

A. ISOLATION, STRUCTURE DETERMINATION, AND BIOLOGICAL ACTIVITY OF THE PENOSTATINS

The penostatins A–I (**1-A**–**I**, Figure I–1) represent a structurally diverse subset of polyketide-derived secondary metabolites that have been isolated from the microorganism *Penicillium* sp. OUPS-79, a fungus that was originally separated from the marine alga *Enteromorpha intestinalis*.[1] In the mid-to-late 1990s, Numata and co-workers reported the identification of **1-A**–**E** as bioactive components of the crude methanol extract of the fungal strain mycelium that was obtained from 40 L of culture broth.[1a,c] A bioassay-guided fractionation strategy, which employed gel filtration, silica gel, and high-performance liquid chromatographic methods, provided pure samples of **1-A** (45 mg), **1-B** (9 mg), **1-C** (37 mg), **1-D** (6 mg), and **1-E** (10 mg). An additional report from the Numata research group appeared in 1998[1b] wherein they disclosed the isolation and structure elucidation of four distinct, but clearly related members of the penostatin family–namely, **1-F** (9 mg), **1-G** (5 mg), **1-H** (5 mg), and **1-I** (12 mg)–that were produced by the *same* fungal strain.

---

[1] (a) Takahashi, C.; Numata, A.; Yamada, T.; Minoura, K.; Enomoto, S.; Konishi, K.; Nakai, M.; Matsuda, C.; Nomoto, K. Penostatins, Novel Cytotoxic Metabolites from a *Penicillium* Species Separated from a Green Alga. *Tetrahedron Lett.* **1996**, *37*, 655–658. (b) Iwamoto, C.; Minoura, K.; Hagishita, S.; Nomoto, K.; Numata, A. Penostatins F–I, Novel Cytotoxic Metabolites from a *Penicillium* Species Separated from an *Enteromorpha* Marine Alga. *J. Chem. Soc., Perkin Trans. 1* **1998**, 449–456. (c) Iwamoto, C.; Minoura, K.; Oka, T.; Ohta, T.; Hagishita, S.; Numata, A. Absolute Stereostructures of Novel Cytotoxic Metabolites, Penostatins A–E, from a *Penicillium* Species Separated from an *Enteromorpha* Alga. *Tetrahedron* **1999**, *55*, 14353–14368.

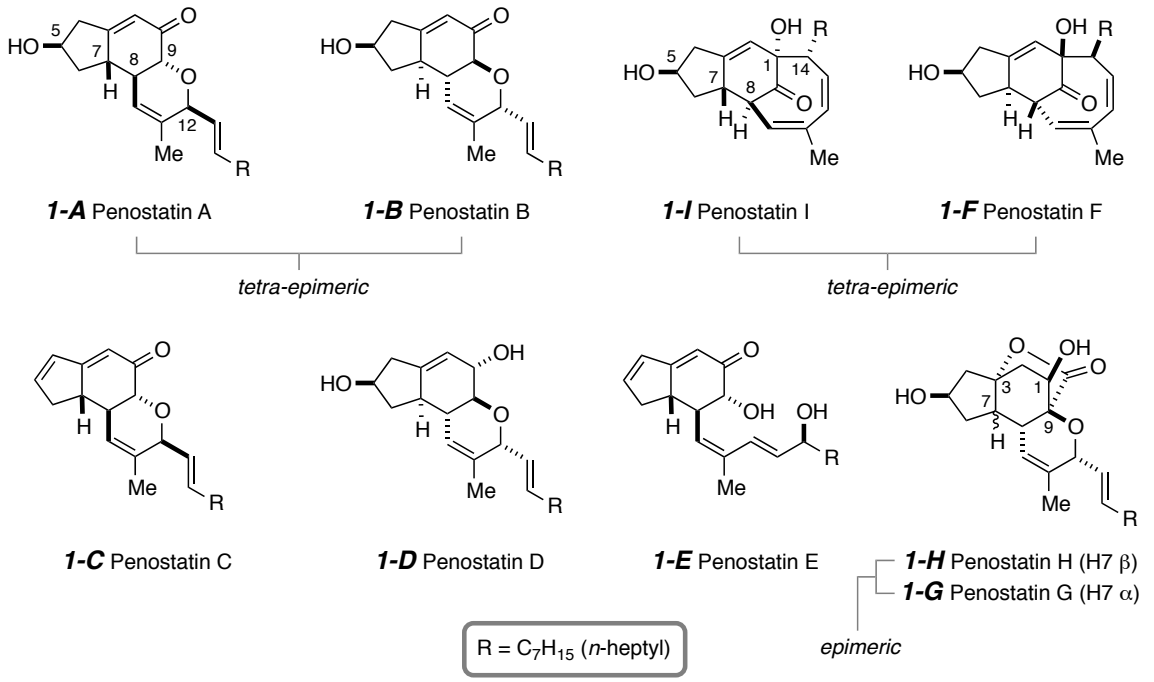


Figure I–1 | Chemical structures of the penostatins A–I (**1-A–I**), highly atypical secondary metabolites of the fungus *Penicillium* sp. OUPS-79.

The penostatins are not the only structurally intriguing secondary metabolites to be produced by *Penicillium* sp. OUPS-79. Indeed, Numata and co-workers have studied this particular fungal strain for the better part of a decade, a campaign that has culminated in the isolation and structural elucidation of the communesins A (**1001**) and B (not shown),[1c,2] (+)-epiepoxydon (**1002**),[1c] patulin (**1003**),[1c] and several cytotoxic cytochalasans that include the penochalasins[3,4] (e.g., **1004** and **1005**) and a few members of the chaetoglobosin family (e.g., **1006**)[3,4] (Figure I–2).

2 Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Ito, Y.; Hasegawa, T. Communesins, Cytotoxic Metabolites of a Fungus Isolated from a Marine Alga. *Tetrahedron Lett.* **1993**, *34*, 2355–2358.

3 Numata, A.; Takahashi, C.; Ito, Y.; Minoura, K.; Yamada, T.; Matsuda, C.; Nomoto, K. Penochalasins, a Novel Class of Cytotoxic Cytochalasans from a *Penicillium* Species Separated from a Marine Alga: Structure Determination of Solution Conformation. *J. Chem. Soc., Perkin Trans. 1* **1996**, 239–245.

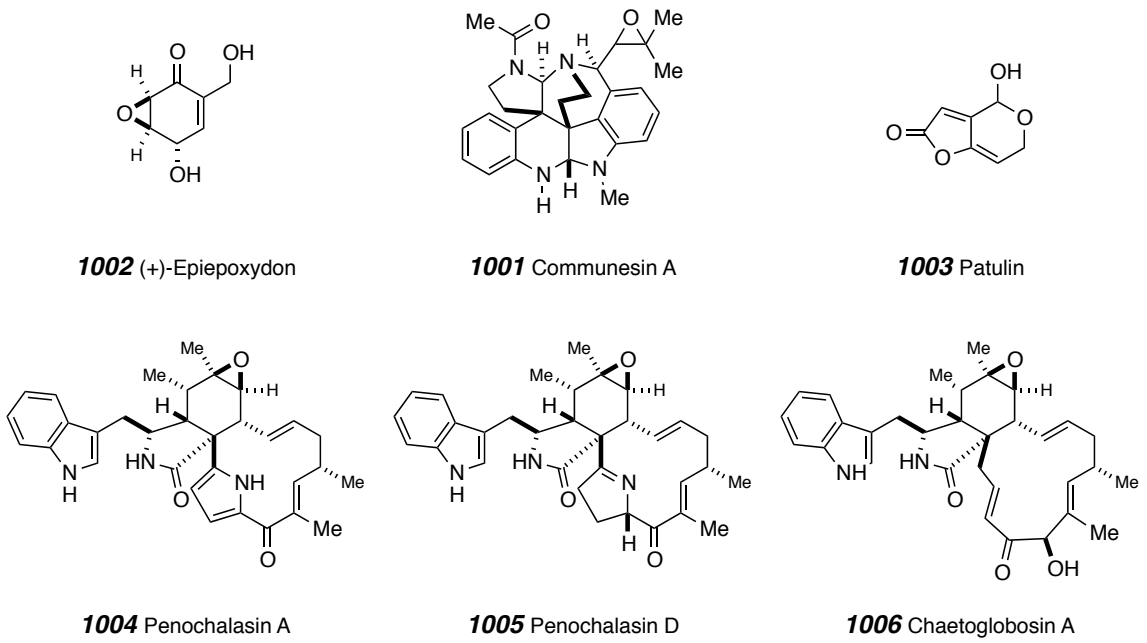


Figure I–2 | Secondary metabolites produced by the fungus *Penicillium* sp. OUPS-79.

The constitution and relative configuration of **1-A**–**I** was rigorously established by Numata and co-workers on the basis of extensive 1-D (i.e., ^{1}H, ^{13}C, and DEPT, NOE) and 2-D (i.e., ^{1}H–^{1}H and ^{1}H–^{13}C COSY, HMBC, and NOESY) NMR spectroscopic experiments that were complemented by ESI/EI mass spectrometry and IR spectroscopy.[1] Additionally, analysis of several key $^{3}J_{H,H}$ coupling values according to the generalized Karplus equation[5] played an important role in assigning the relative configuration within the C3–C7 cyclopentanol ring of **1-A**–**I**.

---

4 Iwamoto, C.; Yamada, T.; Ito, Y.; Minoura, K.; Numata, A. Cytotoxic Cytochalasans from a *Penicillium* Species Separated from a Marine Alga. *Tetrahedron* **2001**, *57*, 2997–3004.

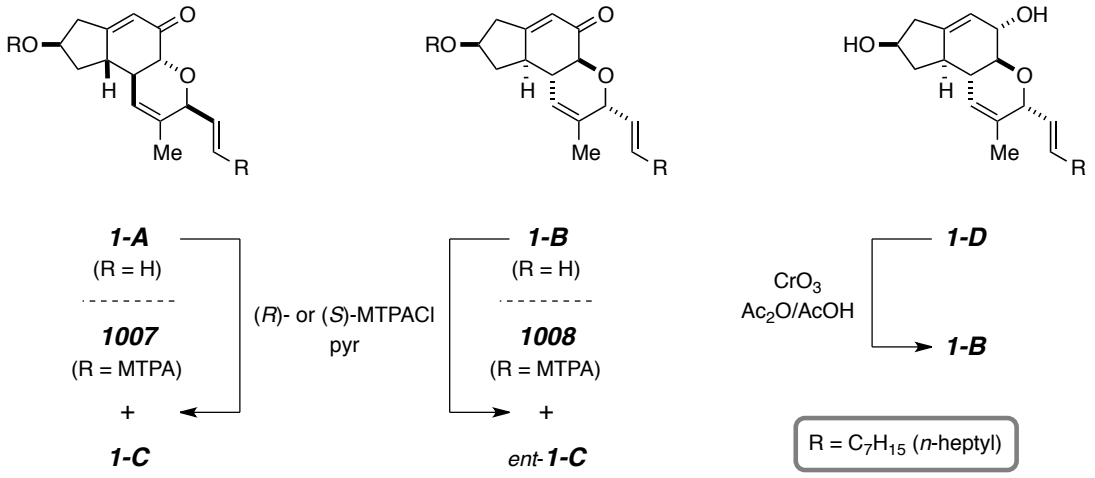
5 (a) Karplus, M. Contact Electron-Spin Coupling of Nuclear Magnetic Moments. *J. Chem. Phys.* **1959**, *30*, 11–15. (b) Abraham, R. J.; Holker, J. S. E. 150. An Investigation by Proton Magnetic Resonance of the Conformation of Ring A in Some 2-Bromo-3-oxo-steroids. *J. Chem. Soc.* **1963**, 806–811.

The absolute configurations of all nine secondary metabolites were deduced by tandem application of the modified Mosher ester method[6] and analysis of their respective circular dichroism (CD) spectra.[1b,c] Thus, acylation of the C5 carbinol oxygen atoms within **1-A**, **-B**, **-F**, **-G**, and **-H**, and with (*R*)- or (*S*)-MTPACl gave rise to the corresponding (*S*)- and (*R*)-MTPA esters, respectively (**1-E** was acylated in a similar fashion, but at the C14 carbinol oxygen atom). The assigned absolute configurations, which were obtained from the usual analysis of ^{1}H NMR chemical shift differences between the diastereomeric MTPA esters, then served as the basis for the assignment of the remaining members of the family. For example, formation of the MTPA esters derived from **1-A** and **1-B** (**1007** and **1008**, respectively) was accompanied by elimination to deliver **1-C** and *ent*-**1-C**, the former of which displayed an identical CD spectrum in comparison to the natural material (Scheme I–1). Similarly, the absolute configuration of **1-D** was deduced by its oxidative conversion (with CrO_3) to a substance that was identical to natural **1-B**.

---

6 (a) Kusumi, T.; Ohtani, I.; Inouye, Y.; Kakisawa, H. Absolute Configurations of Cytotoxic Marine Cembranolides; Consideration of Mosher's Method. *Tetrahedron Lett.* **1988**, *29*, 4731–4734. (b) Ohtani, I.; Kusumi, T.; Ishitsuka, M. O.; Kakisawa, H. Absolute Configurations of Marine Diterpenes Possessing a Xenicane Skeleton. An Application of an Advanced Mosher's Method. *Tetrahedron Lett.* **1989**, *30*, 3147–3150. (c) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. High-Field FT NMR Application of Mosher's Method. The Absolute Configurations of Marine Terpenoids. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.

Scheme I–1 | Deduction of the absolute configurations of **1-C** and **1-D** via chemical interconversion with other members of the penostatin family [adapted from ref 1c].



With the exception of **1-D**, all members of the penostatin family were shown to display potent cytotoxic activity against P388 lymphocytic leukemia tumor cell lines, with ED_{50} values ranging from 0.5–1.4 μg/mL.[1] Additionally, the cytotoxicity of **1-C** was further investigated, wherein it was discovered that it exhibited ED_{50} values ranging from 1.6–2.5 μg/mL against i) human brain tumor (BSY-1 and MCF-7), ii) human colon cancer (HCC2998), iii) human lung cancer (NCI-H522 and DMS114), iv) human ovarian cancer (OVCAR-3), and v) human gastric carcinoma (MKN1) cell lines.[1c]

B. INTERLUDE

Penostatin A–I (**1-A–I**, Figure I–1) possess structures that are unique–indeed, *atypical*–and thus are quite distinct from any known class of polyketide-derived secondary metabolites. The fused dihydropyran/bicyclo[4.3.0]nonane subunit that is common to **1-A**–**E**, the bicyclo[5.3.1]undecenone core of **1-F** and **1-I**, and the lactone-containing bicyclo[2.2.2]-octane system of **1-G** and **1-H** are all structural motifs that are without precedent. The configurational relationships that are shared by these natural products are also quite interesting. This latter point was not lost on Numata and co-workers, the research group that isolated and characterized the penostatins:

"*It is of great interest that one fungus produces a pair of stereoisomers* (*such as **4*** [**1-A**] *and **5*** [**1-B**])*, in which all the asymmetric centers except for one position have the opposite absolute configurations.*"[1c] And, moreover, that "*The absolute stereochemistry of penostatins F and I corresponds to that of penostatins B* (***5*** [**1-B**]) *and A* (***4*** [**1-A**])*, respectively.*"[1c]

This type of configurational relationship between members of the same natural product family is certainly rare, if not unprecedented. Although the biological potency of **1-A**–**I** would, in and of itself, justify their laboratory synthesis, our group's interest in this family of natural products has stemmed from a series of structural and mechanistic considerations. Namely, why is it that **1-A**–**I** are produced by the same fungus (*Penicillium* sp. OUPS-79)? Could it be that there is a common biogenetic intermediate from which all of the penostatins ultimately arise? If so, could a unified synthesis strategy to all members of this family be devised and subsequently capitalized upon in the laboratory? Prior to detailing our own hypotheses that address these questions in Chapters II, III, and IV of this Thesis, a summary of previous synthetic efforts toward some members of the penostatin family will be presented in the remaining Section of Chapter I.

C. PREVIOUS SYNTHETIC EFFORTS TOWARD PENOSTATINS A, B, AND F

C–1. SNIDER'S APPROACH TO (±)-PENOSTATIN A AND B (2000)

In 1999 Barry B. Snider and Tao Liu of Brandeis University reported the total synthesis of (±)-C5-deoxypenostatin A (C5-deoxy-**1-A**),[7a] and this preliminary report was soon followed by a full account in 2000 that included a synthesis of the 9,12-*bis*-epimer of penostatin A [(±)-9,12-bis-*epi*-**1-A**].[7b] At the outset of their studies, Snider and Liu quickly realized the enticing possibility that that dihydropyran core common to both **1-A** and **1-B** could be accessed via intramolecular hetero-Diels–Alder (IMHDA) reactions. They stated, however, that the most obvious cycloaddition substrates–namely, the α-keto aldehyde **1011** (bottom left of Scheme I–2) was "*...rejected because the tetraenonal functionality was expected to be both synthetically inaccessible and too unstable.*"[7]

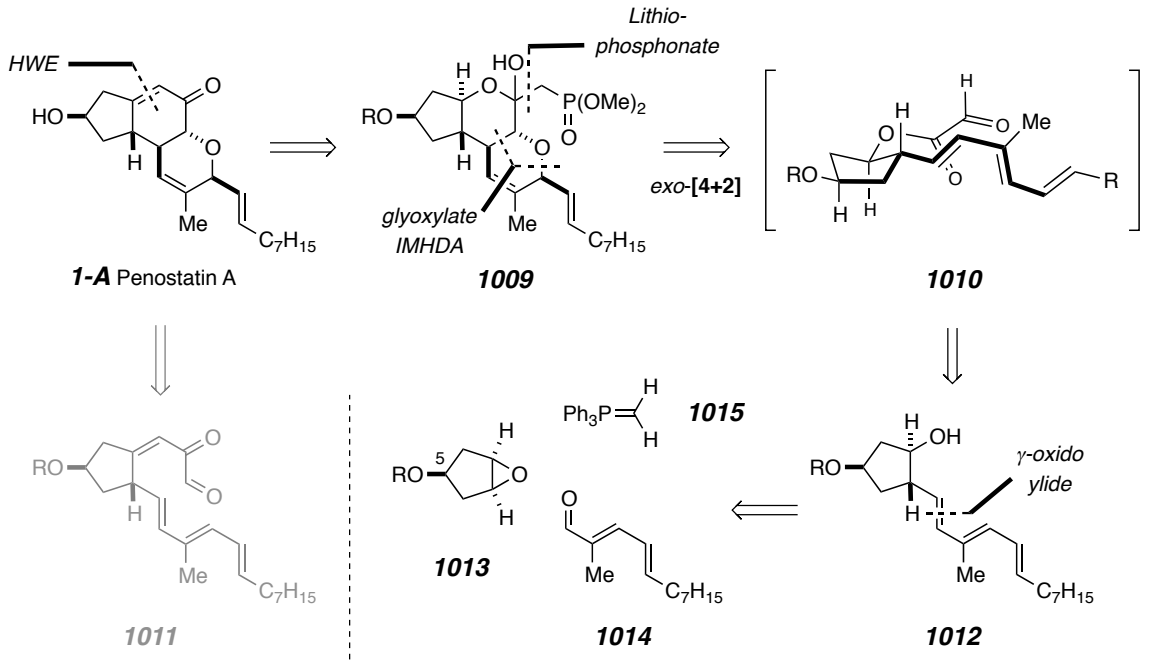
In order to circumvent this perceived obstacle, Snider and Liu's synthetic strategy toward **1-A** and **1-B** was modified as depicted in Scheme I–2. Retrosynthetically, **1-A** could arise from the protected phosphonate **1009** via oxidation of the ring-opened keto-alcohol derived therefrom followed by intramolecular Horner–Wadsworth–Emmons (HWE) olefination. The key intermediate in the sequence was glyoxylate ester **1010**, which the authors believed would participate in a diastereoselective IMHDA reaction to give, after exposure of the product lactone to lithiated dimethyl methylphosphonate, the phosphonate **1009**. The venerable Emmons–Kornblum protocol would be applied to the secondary alcohol **1012**, which was viewed as an ideal strategy for accessing the partially hydrated glyoxylate **1010**. Finally, a three-component coupling of epoxide **1013**, methylenetriphenylphosphorane (**1015**), and dienal **1014** through the intermediacy of a γ-

---

7 (a) Snider, B. B.; Liu, T. Total Synthesis of (±)-Deoxypenostatin A. *J. Org. Chem.* **1999**, *64*, 1088–1089. (b) Snider, B. B.; Liu, T. Total Synthesis of (±)-Deoxypenostatin A. Approaches to the Syntheses of Penostatins A and B. *J. Org. Chem.* **2000**, *65*, 8490–8498.

oxido ylide[8] would deliver the secondary alcohol **1012**. Although the retrosynthetic strategy for **1-B** has not been shown, an entirely parallel analysis emanating from the C5 epimer of epoxide **1013** would apply.

Scheme I–2 | Snider and Liu's retrosynthetic strategy for the total synthesis of **1-A** (R = generic protecting group) [adapted from ref 7].

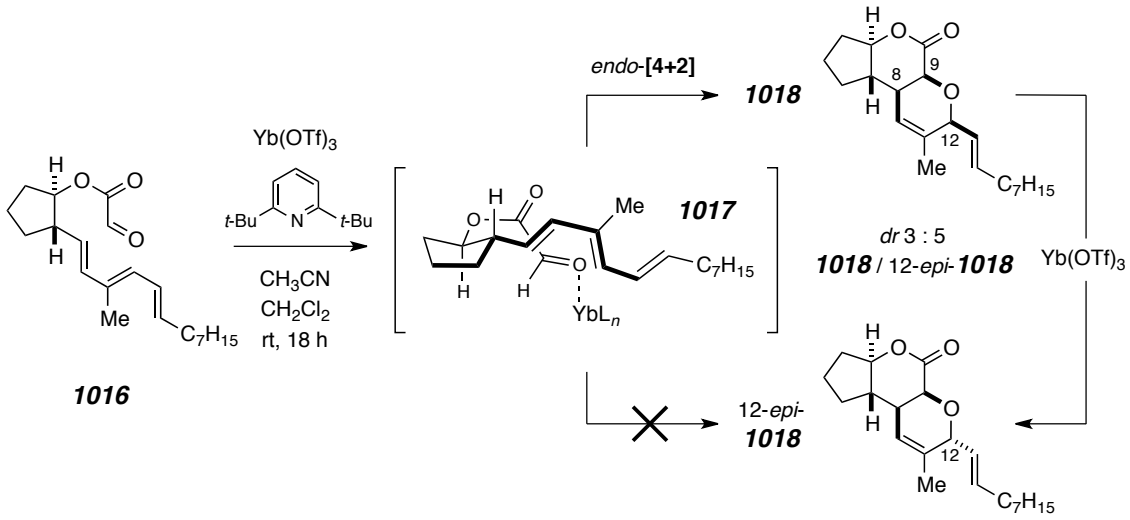


In their preliminary report regarding the total synthesis of (±)-C5-deoxy-**1-A**,[7a] Snider and Liu attempted the model IMHDA reaction of **1016** by employing the Lewis acid catalyst $Yb(OTf)_3$ (Scheme I–3). The primary impetus for employing this rather unusual reagent for the IMHDA cycloaddition was drawn from work reported by Qian

8 (a) Corey, E. J.; Kang, J. α-Lithiomethylenetriphenylphosphorane, a Highly Reactive Ylide Equivalent. *J. Am. Chem. Soc.* **1982**, *104*, 4724–4725. (b) Corey, E. J.; Kang, J.; Kyler, K. Activation of Methylenetriphenylphosphorane by Reaction with *t*-Butyl- or *sec*-Butyllithium. *Tetrahedron Lett.* **1985**, *26*, 555–558.

and Huang.[9] The authors observed that lanthanide(III) triflates could serve as reusable, water-soluble catalysts to supplant traditional reagents such as $TiCl_4$ and $SnCl_4$ in the ene reactions of glyoxylate esters with disubstituted alkenes. These reactions produced α-hydroxy esters under mild conditions; however, reaction of ethyl- and methyl glyoxylate with 2-methyl-1,3-butadiene (isoprene) in the presence of catalytic $Yb(OTf)_3$ gave high yields of the hetero-Diels–Alder adducts at the exclusion of ene-products.[9]

Scheme I–3 | Snider and Liu's model lanthanide(III) triflate-catalyzed IMHDA reaction of glyoxylate ester **1016** [adapted from ref 7].



Implementation of the modified conditions in the IMHDA reaction of **1016**, which included the addition of 2,6-di-*tert*-butylpyridine, resulted in the formation of **1018** and its C12 epimer (12-*epi*-**1018**) as a 3:5 mixture of diastereomers (Scheme I–3). The lactone **1018** was elaborated to (±)-C5-deoxy-**1-A** in 15% yield over 4 steps, the final step involving isomerization of the C9 stereocenter in basic methanolic solution. It is evident that **1018** could arise from concerted *endo* addition of the heterodienophile to the

9 Qian, C.; Huang, T. Glyoxylate-Ene Reaction Catalyzed by $Ln(OTf)_3$. *Tetrahedron Lett.* **1997**, *38*, 6721–6724.

diene within **1017**, but 12-*epi*-**1018** cannot be a primary IMHDA cycloadduct since a *cis*-relationship between H8 and H12 would be a consequence of the (*E*,*E*)-diene configuration of the reactant. Furthermore, the authors demonstrated that the presence of Lewis or Brønsted acids promoted epimerization of **1018** to 12-*epi*-**1018** (C12 is doubly allylic)–but not the reverse reaction–thereby indirectly supporting the (apparent) concerted nature of the IMHDA event.

Snider and Liu did not offer an explanation regarding the highly diastereoselective formation of **1018**, but the *endo* orientation of the glyoxylate ester carbonyl could be a consequence of an *exo* preference of the coordinated Lewis acid (cf. **1017**, Scheme I–3).[10c,d] An anti orientation between the glyoxylate ester carbonyl and the Lewis acid should be more favorable based on steric grounds.[11] This type of analysis has often been invoked to rationalize the diastereoselectivity of Lewis acid-catalyzed HDA reactions of aldehyde dienophiles,[12] particularly in the work of Danishefsky and co-workers.[10] In general, the thermal HDA cycloadditions of aldehydes are not highly stereoselective,[13] yet in Lewis acid-promoted reactions of aliphatic aldehyde dienophiles a preponderance of *endo* addition has been observed.[10d]

---

[10] (a) Larson, E. R.; Danishefsky, S. On the Mechanism of the Lewis Acid Catalyzed Cyclocondensation of Aldehydes with Siloxydienes. *Tetrahedron Lett.* **1982**, *23*, 1975–1978. (b) Danishefsky, S.; Kerwin, J. F.; Kobayashi, S. Lewis Acid Catalyzed Cyclocondensations of Functionalized Dienes with Aldehydes. *J. Am. Chem. Soc.* **1982**, *104*, 358–360. (c) Larson, E. R.; Danishefsky, S. Mechanistic Variations in the Lewis Acid Catalyzed Cyclocondensation of Siloxydienes with Aldehydes. *J. Am. Chem. Soc.* **1982**, *104*, 6458–6460. (d) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. On the Scope, Mechanism, and Stereoselectivity of the Lewis Acid Catalyzed Cyclocondensation of Activated Dienes with Aldehydes: An Application to the Erythronolide Problem. *J. Am. Chem. Soc.* **1985**, *107*, 1246–1255.

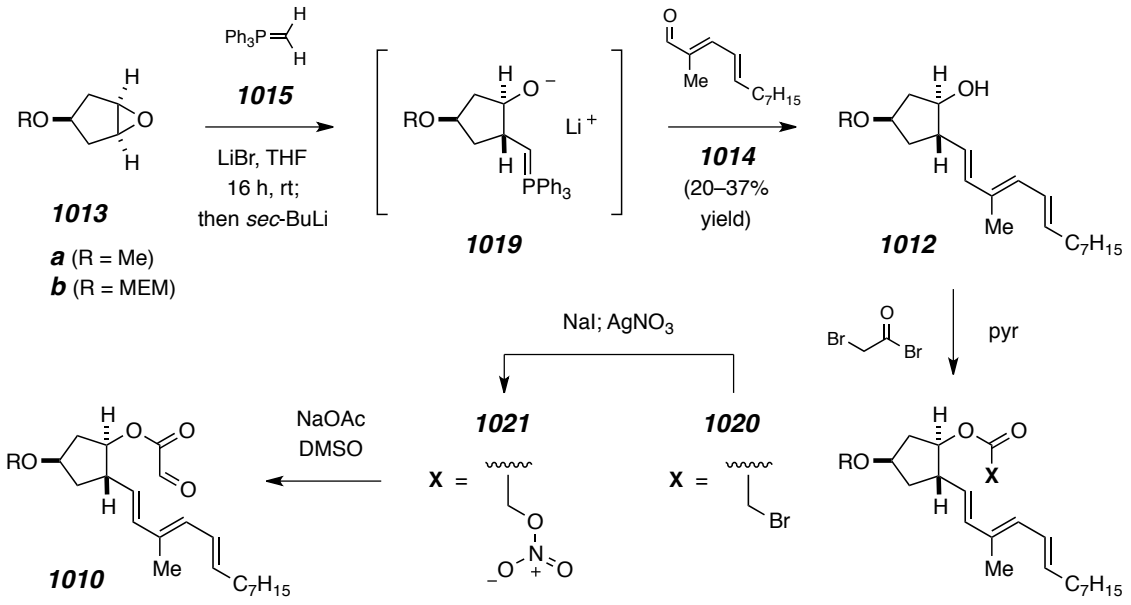
[11] Terada, M.; Mikami, K.; Nakai, T. Enantioselective Hetero-Diels–Alder Reaction with Glyoxylate Catalyzed by Chiral Titanium Complex: Asymmetric Synthesis of the Lactone Portion of Mevinolin and Compactin. *Tetrahedron Lett.* **1991**, *32*, 935–938.

[12] Jørgensen, K. A. Catalytic Asymmetric Hetero-Diels–Alder Reactions of Carbonyl Compounds and Imines. *Angew. Chem. Int. Ed.* **2000**, *39*, 3558–3588.

[13] Jurczak, J.; Gołębiowski, A.; Rahm, A. High-Pressure [4+2] Cycloaddition of 1-Methoxy-3-trialkylsilyloxybuta-1,3-dienes to Butyl Glyoxylate. Isolation of Primary Cycloadducts. *Tetrahedron*

Encouraged by the outcome of the model studies, Snider and Liu shifted their focus to the total synthesis of **1-A**. In accordance with the retrosynthetic plan, a salad of glyoxylate esters (**1010**) was prepared; only those routes emanating from the methyl (**1013a**) and MEM (**1013b**) ether-protected epoxycyclopentanols are shown (Scheme I–4). Addition of **1015** to these epoxides followed by treatment of the intermediate ylides with *sec*-butyllithium generated a phosphorane (**1019**). Subsequent *in situ* Wittig olefination of dienal **1014** with this reagent provided the homoallylic alcohols **1012** in moderate yield.

Scheme I–4 | Synthesis of the glyoxylate esters **1010a**–**b**, the key IMHDA substrates [adapted from ref 7].



The Emmons–Kornblum protocol[14] was then employed for the construction of **1010** (Scheme I–4). Thus, reaction of **1012** with bromoacetyl bromide gave a bromo ester

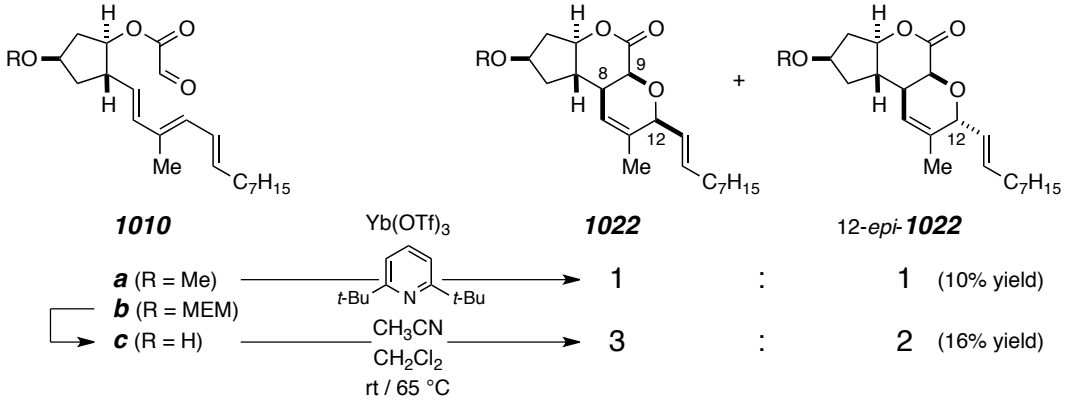
Lett. **1986**, *27*, 853–856.

14 (a) Kornblum, N.; Frazier, H. W. A New and Convenient Synthesis of Glyoxals, Glyoxalate Esters, and α-Diketones. *J. Am. Chem. Soc.* **1966**, *88*, 865–866. (b) Emmons, W. D.; Freeman, J. P. The

(**1020**) that was converted to the iodo ester by Finkelstein exchange. Treatment of the iodo ester with $AgNO_3$ yielded an intermediate nitrate ester (**1021**) that provided the crude, partially hydrated glyoxylate ester (**1010**) after NaOAc-induced α-hydrogen abstraction and concomitant elimination of nitrite ion.

The nature of the C5 hydroxyl-protecting group proved to be an important and unforeseen parameter in the attempted IMHDA reactions of glyoxylate ester **1010**. For example, in studies directed toward the synthesis of **1-B**, wherein the C5 epimer of **1010** was subjected to the $Yb(OTf)_3$-catalyzed conditions, substrates protected as their TBS, TBDPS, THP, and *tert*-butyl ethers were entirely unproductive, resulting in no reaction or decomposition of the starting material.

Scheme I–5 | Lanthanide(III) triflate-catalyzed MHDA reactions of glyoxylate esters **1010a** and **1010b** [adapted from ref 7].



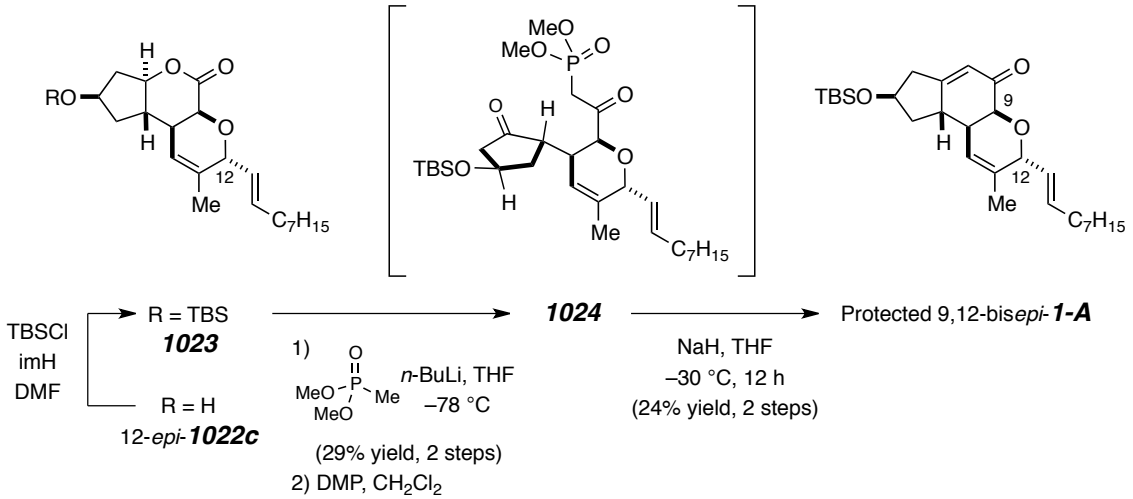
Further experimentation revealed, however, that these complications could be overcome by utilizing either the methyl (**1010a**) or MEM (**1010b**) ether derivatives (Scheme I–5). Glyoxylate **1010a** underwent IMHDA cyclization at room temperature to provide a 1:1 mixture of **1022a** and 12-*epi*-**1022a** in 10% over yield from the alcohol **1012a**. Realizing that late-stage cleavage of the methyl ether would be fraught with

Synthesis of Diketones from Nitratoketones. *J. Am. Chem. Soc.* **1955**, *77*, 4415–4416.

disaster, IMHDA cyclization of **1010b** was also attempted. In this instance, loss of the MEM ether was found to precede the cycloaddition event, and, although the overall yield was still modest, **1022c** and 12-*epi*-**1022c** could be isolated in a slightly improved diastereomeric ratio (*dr* 3:2).

The elaboration of both lactones (**1022c** and 12-*epi*-**1022c**) was attempted; only the sequence for the latter is shown (Scheme I–6). Formation of the TBS ether was accomplished under standard conditions to yield **1023**, which then gave rise to the hydroxy keto phosphonate hemiacetal **1024** upon treatment with lithiated dimethyl methylphosphonate. Oxidation of this adduct with DMP gave a diketophosphonate that was treated in crude form with sodium hydride. The phosphonate anion thus generated underwent an intramolecular HWE reaction to deliver TBS protected 9,12-bis-*epi*-**1-A**.

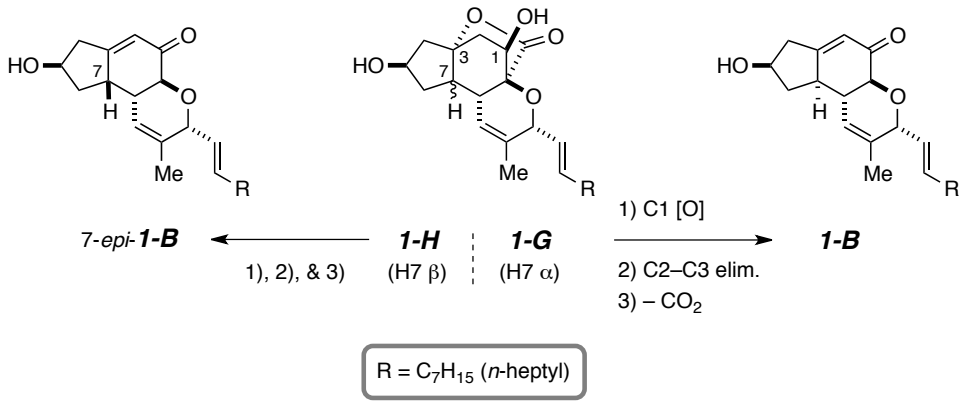
Scheme I–6 | Synthesis of protected 9,12-bis-*epi*-**1-A** from the IMHDA cycloadduct 12-*epi*-**1022c** [adapted from ref 7].



Snider and Liu proposed[7a] a possible biosynthetic origin for **1-B** that merits brief discussion. They postulated that **1-B** was derived from 1) oxidation of penostatin G (**1-G**) at C1, 2) elimination (ring-opening) to form the $\Delta^{2,3}$ enone, and 3) decarboxylation

(Scheme I–7). However, it seems unlikely, *prima facie*, that this proposal could account for the formation of other members of the family. Namely, the analogous diastereomeric pathway emanating from **1-H** does not give **1-A**, but rather 7-*epi*-**1-B**.

Scheme I–7 | Proposed biosynthetic origin of **1-B** from **1-G** [adapted from ref 7a].



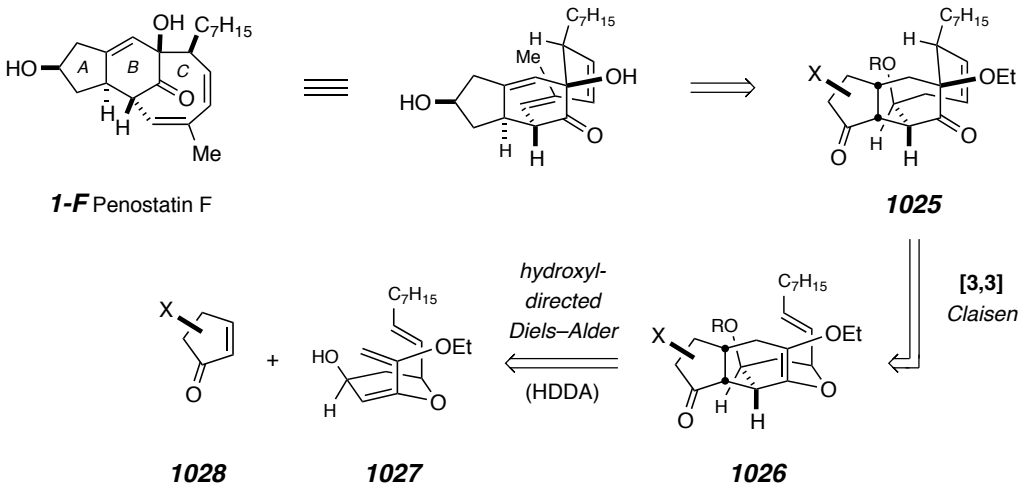
C–2. BARRIAULT'S SYNTHESIS OF THE PENOSTATIN F CORE (2004)

Barriault and co-workers[15] recently reported their successful synthesis of the unique bicyclo[5.3.1]undecenone ring system of penostatin F (**1-F**). The authors proposed that **1-F** could be derived from a precursor such as **1025** wherein the A-ring of the natural product would arise via redox manipulation of a suitably functionalized cyclopentenone ring (Scheme I–8). The **1-F** core architecture present in the γ,δ-unsaturated ketone **1025** would arise via thermal [3,3]-sigmatropic rearrangement of the allyl vinyl ether **1026**, which in turn could be prepared by a highly stereoselective

15 Barriault, L.; Ang, P. J. A.; Lavigne, R. M. A. Rapid Assembly of the Bicyclo[5.3.1]undecenone Core of Penostatin F: A Successive Diels–Alder/Claisen Reaction Strategy with an Efficient Stereochemical Relay. *Org. Lett.* **2004**, *6*, 1317–1319.

hydroxyl-directed Diels-Alder (HDDA) reaction[16] between the enol ether **1027** and an appropriately functionalized carbocyclic dienophile (**1028**).

Scheme I–8 | Barriault and co-workers' retrosynthetic analysis of **1-F** [adapted from ref 15].



The racemic diene **1027** was prepared in seven steps from readily available starting materials (Scheme I–9). The Weiler[17] dianion **1029**, generated by sequential treatment of methylacetoacetate with sodium hydride and *n*-butyllithium, was trapped with (*E*)-2-decenal to provide the racemic keto alcohol **1030** that was then converted to the 1,3-*anti* diol **1031** via diastereoselective reduction.[18] A pedestrian but high yielding two-step sequence that consisted of lactonization and silylation produced the functionalized δ-valerolactone **1032**. Exposure of this intermediate to (α-ethoxyvinyl)-lithium produced an intermediate lactol that, upon chlorination and *in situ*

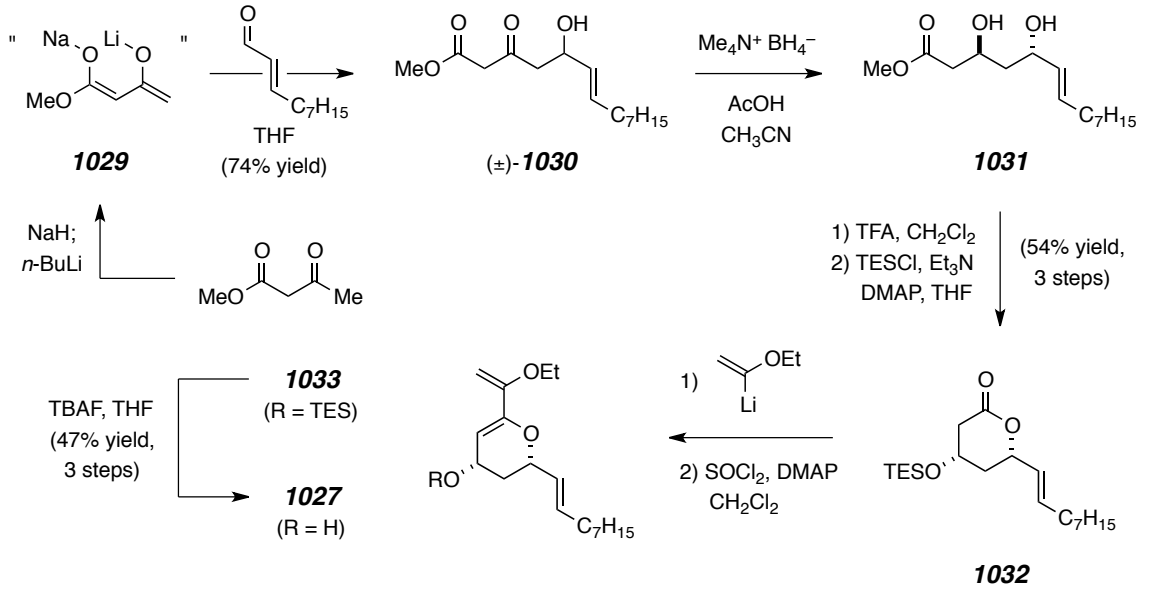
16 Barriault, L.; Thomas, J. D. O.; Clément, R. Highly Stereoselective Hydroxy-Directed Diels–Alder Reaction. *J. Org. Chem.* **2003**, *68*, 2317–2323.

17 Huckin, S. N.; Weiler, L. Alkylation of Dianions of β-Keto Esters. *J. Am. Chem. Soc.* **1974**, *96*, 1082–1087.

18 Evans, D. A.; Chapman, K. T.; Carreira, E. M. Directed Reduction of β-Hydroxy Ketones Employing Tetramethylammonium Triacetoxyborohydride. *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.

dehydrochlorination, delivered the TES protected diene **1033**. Finally, TBAF-mediated desilylation provided the free alcohol **1027**, the key substrate for the HDDA reaction.

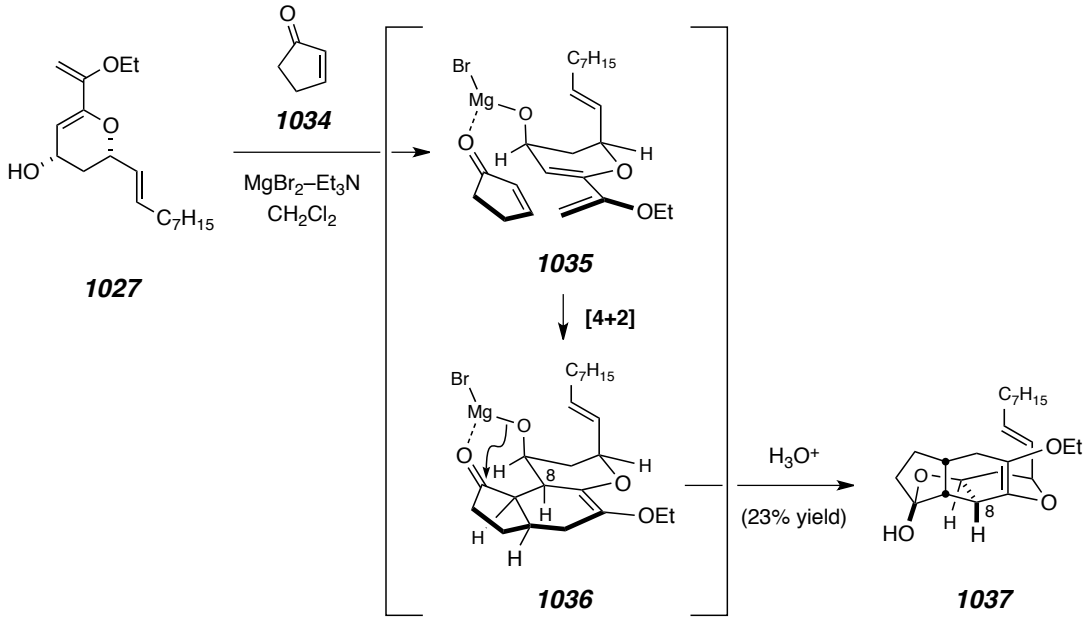
Scheme I–9 | Synthesis of the key HDDA substrate **11003** [adapted from ref 15].



The HDDA technology that was developed by the Barriault group[16] involves the *in situ* generation of semi-cyclic diene magnesium alkoxides that, upon treatment with dienophilic acrolein, acrylate, or maleimide derivatives, yield the corresponding cycloadduct with complete diastereo- and regiochemical control. Sequential treatment of diene **1027** with $MgBr_2$–Et_3N[19] and 2-cyclopentene-1-one (**1034**) in CH_2Cl_2 resulted in the isolation of the cycloadduct **1037** with exquisite diastereoselectivity (*dr* >25:1), albeit in modest yield (Scheme I–10).

19 Vedejs, E.; Daugulis, O. Dual Activation in the Esterification of Hindered Alcohols with Anhydrides using $MgBr_2$ and a Tertiary Amine. *J. Org. Chem.* **1996**, *61*, 5702–5703.

Scheme I–10 | HDDA reaction of diene **1027** and dienophile **1034** [adapted from ref 15].



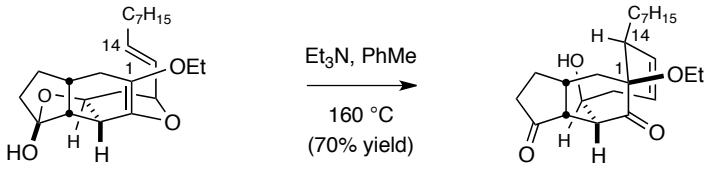
The outcome of the HDDA event was rationalized by the initial (reversible) formation of a magnesium alkoxide–dienophile complex **1035** (Scheme I–10).[20] Delivery of the dienophile to the same face of the diene as the directing magnesium alkoxide followed by cyclization through an *endo* DA transition state geometry would give rise to cycloadduct **1036**. Final hemiketalization of this intermediate alkoxide followed by reaction quench provided **1037**. It should be noted that Barriault and co-workers also reported the HDDA reactions of **1027** with *N*-phenylmaleimide and *N*-benzylmaleimide, both of which proceeded in higher yields (80% and 79% yields, respectively). However, since the functionality present in these HDDA adducts does not easily map onto the structure of **1-F**, they have been excluded to simplify the present discussion.

---

20 Ward, D. E.; Abaee, M. S. Intramolecular Diels–Alder Reaction by Self-Assembly of the Components on a Lewis Acid Template. *Org. Lett.* **2000**, *2*, 3937–3940.

The quasi-intramolecular HDDA reaction generated two new stereogenic centers at the bicyclo[3.4.0] ring junction. Crucially, ^{1}H NMR, COSY, and NOESY experiments established that the hydrogen atom located at the bicyclo[4.4.0] ring junction was *anti* to the olefinic side chain (H8, as in **1037**, Scheme I–10). This relative configuration was pivotal to the success of the thermal Claisen rearrangement. Heating of the HDDA adduct **1037** in toluene with a trace of Et_3N promoted the [3,3]-sigmatropic event and released the free keto-alcohol to afford **1038** in respectable yield (Scheme I–11). The relative configuration at C1, C8, and C14, which presumably arose via the chair-like reactive conformation implied by structure **1037**, corresponds to that found in **1-F**.

Scheme I–11 | Claisen rearrangement of **1037** to give the penostatin F (**1-F**) core structure **1038** [adapted from ref 15].



1037 ***1038***

C–3. SHISHIDO'S TOTAL SYNTHESIS OF (±)-PENOSTATIN B (2012)

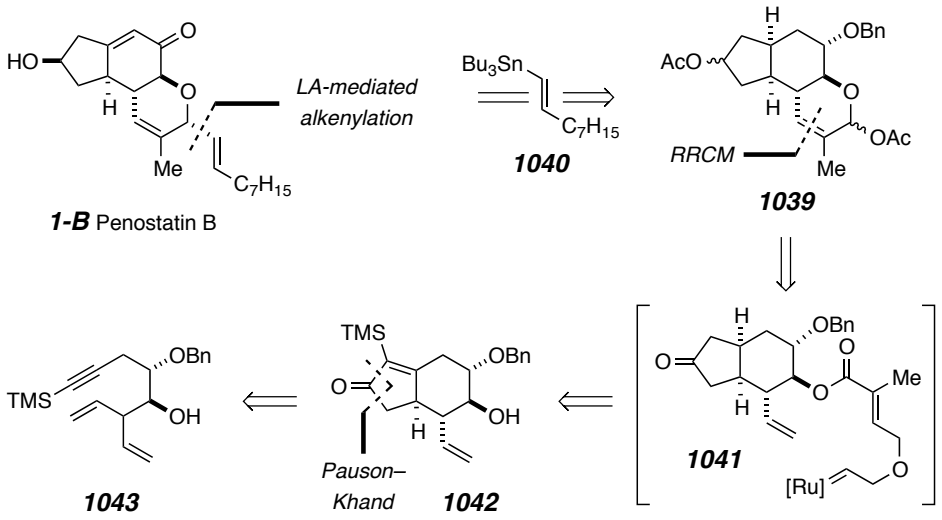
In early 2012, Shishido and co-workers[21] reported the first successful laboratory synthesis of any member of the penostatin family. The two previous synthesis efforts described in this section–namely, Snider and Liu's[7] synthesis of (±)-5-deoxypenostatin A (C5-deoxy-**1-A**) and Barriault and co-workers'[15] synthesis of the penostatin F (**1-F**) core–deployed strategies that were inspired, at least in part, by the postulated biosynthetic origin of members of the penostatin family. The synthesis plan that Shishido and co-

[21] Fujioka, K.; Yokoe, H.; Yoshida, M.; Shishido, K. Total Synthesis of Penostatin B. *Org. Lett.* **2012**, *14*, 244–247.

workers reduced to practice, however, represents a significant departure from these other biomimetic-type strategies that have appeared in the literature.

Shishido and co-workers' retrosynthetic plan of attack for **1-B** is depicted in Scheme I–12. A transform that disconnects the nonenyl side chain of **1-B** reveals acetylated lactol **1039** as a target for Lewis acid (LA)-mediated vinylation with stannane **1040**. The dihydropyran ring within *bis*-acetate **1039**, in turn, was envisioned to arise through relay ring-closing metathesis (RRCM)[22] of an *in situ* generated intermediate alkylidene such as **1041**. The cyclopentenone **1042** was identified as an appropriate progenitor to **1041** *via* esterification of the secondary alcohol followed by subjection to an appropriate metathesis initiator. Finally, a diastereoselective Pauson–Khand cyclization of the protected dienyne **1043** was viewed as the key step in the birth of the **1-B** core structure **1042**.

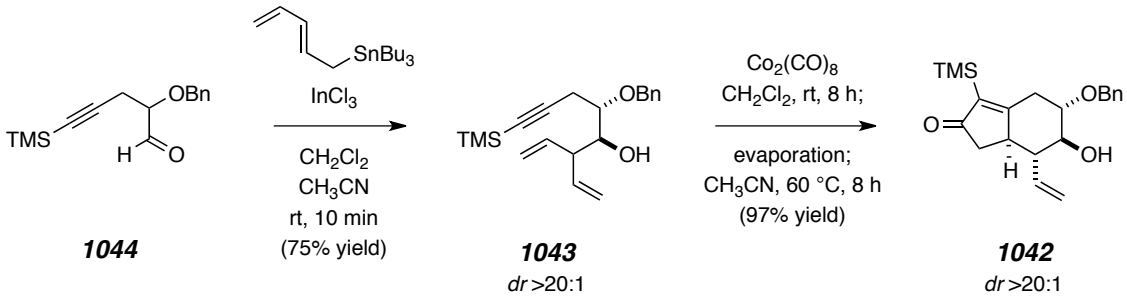
Scheme I–12 | Shishido's retrosynthetic analysis of **1-B** [adapted from ref 21].



[22] (a) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. Relay Ring-Closing Metathesis (RRCM): A Strategy for Directing Metal Movement Throughout Olefin Metathesis Sequences. *J. Am. Chem. Soc.* **2004**, *126*, 10210–10211. (b) Hoye, T. R.; Danielson, M. E.; May, A. E.; Zhao, H. Total Synthesis of (–)-Callipeltoside A. *J. Org. Chem.* **2010**, *75*, 7052–7060.

The synthesis commenced (Scheme I–13) with pentadienylation of the racemic aldehyde **1044** [prepared from (±)-glycidyl butyrate] with (*E*)-tri-*n*-butyl(penta-2,4-dienyl)stannane under the influence of $InCl_3$,[23] which gave rise to the skipped diene **1043** with excellent diastereoselectivity (>20:1). A high yielding Pauson–Khand cyclization[24] was subsequently induced by treatment of **1043** with dicobalt octacarbonyl [$Co_2(CO)_8$] followed by heating in CH_3CN, which delivered the α-silyl cyclopentenone **1042**. The authors noted that when the oxidant NMO was employed in this transformation,[25] both the yield and diastereoselectivity were noticeably reduced. Furthermore, the desilylated derivative of **1043** (i.e., the terminal alkyne) also participated in the Pauson–Khand cyclization; however, a considerably lower diastereomeric ratio (*dr* 4:1) was obtained.

Scheme I–13 | Pauson–Khand cyclization of dienyne **1043** [adapted from ref 21].



The α-silyl group present in **1042** was cleaved with TBAF/AcOH and the resulting cyclopentene was subjected to MeCu(I)-catalyzed conjugate reduction in the

---

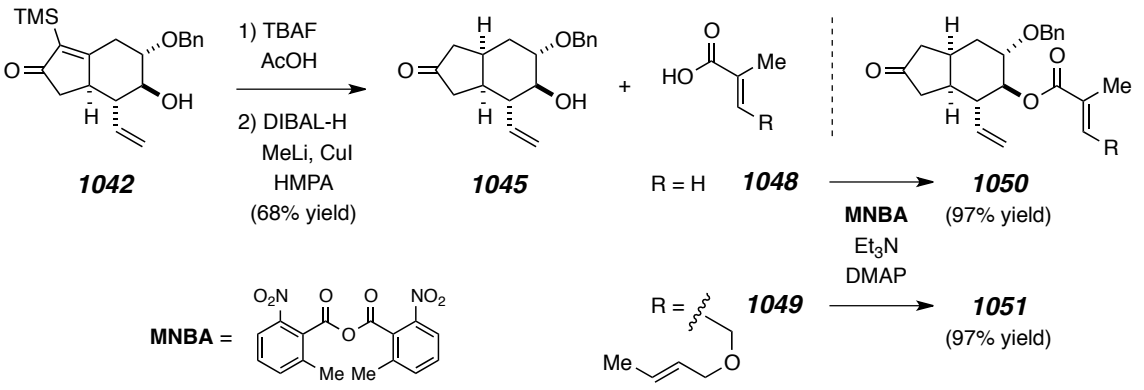
23 Nishigaichi, Y.; Hanano, Y.; Takuwa, A. Simultaneous Control of Regio- and Stereochemistries in the Reaction between α-Alkoxyaldehydes and Pentadienyltin. Selective Preparations of the Four Regio- and Diastereomers. *Chem. Lett.* **1998**, 33–34.

24 Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. Organocobalt Complexes. Part II. Reaction of Acetylenehexacarbonyldicobalt Complexes, $(R^1C_2R^2)Co_2(CO)_6$, with Norbornene and its Derivatives. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977–981.

25 Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *N*-Oxide Promoted Pauson–Khand Cyclizations at Room Temperature. *Tetrahedron Lett.* **1990**, *31*, 5289–5292.

presence of DIBAL-H[26] to provide the saturated bicycle **1045** (Scheme I–14). At this stage, the secondary alcohol of **1045** could be acylated under Shiina's[27] conditions by reaction with either of the carboxylic acids **1048** or **1049**. With these substrates in hand, the direct RCM of **1050** and the RRCM of **1051** could be explored.

Scheme I–14 | Preparation of the (R)RCM substrates **1050** / **1051** [adapted from ref 21].



Despite the fact that precedent existed[28] to suggest that RCM of **1050** would be difficult–if not impossible–to achieve, its closure in the presence of the Grubbs 2ND-generation initiator (**G2**) was attempted (Scheme I–15). When diene **1050** was exposed to **G2** (25 mol%) in refluxing CH_2Cl_2, a disappointingly low yield of the desired product (**1052**) was obtained. This situation was made considerably worse when the Hoveyda–Grubbs 2ND-generation initiator (**HG2**) was employed, in which case none of the desired

---

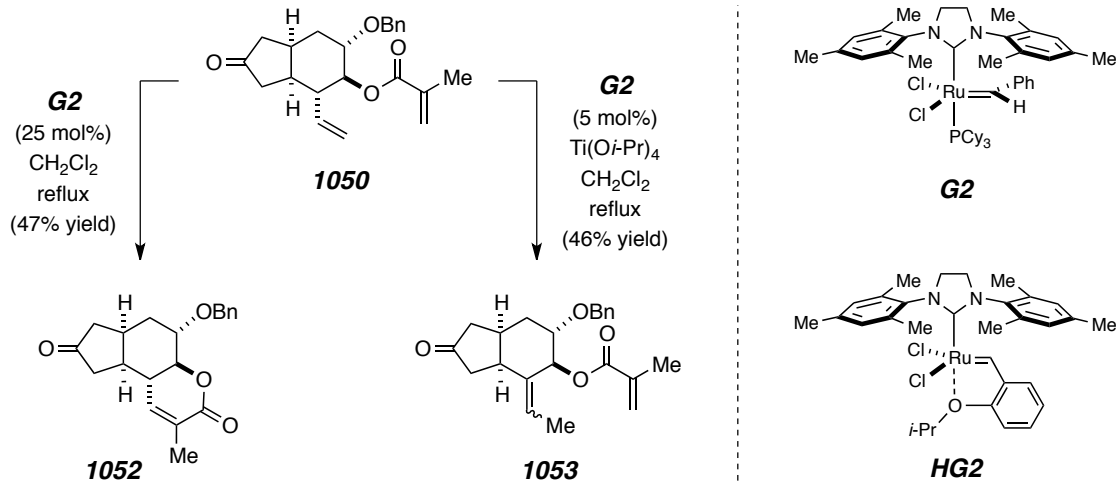
26 Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. Methylcopper(I)-Catalyzed Selective Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds by Diisobutylaluminum Hydride in the Presence of Hexamethylphosphoric Triamide. *J. Org. Chem.* **1986**, *51*, 537–540.

27 Shiina, I.; Ibuka, R.; Kubota, M. A New Condensation Reaction for the Synthesis of Carboxylic Esters from Nearly Equimolar Amounts of Carboxylic Acids and Alcohols using 2-Methyl-6-nitrobenzoic Anhydride. *Chem. Lett.* **2002**, 286–287.

28 Cossy, J.; Bauer, D.; Bellosta, V. A Short Synthesis of the C1–C7 Fragment of Methymycin by Ring-Closing Olefin Metathesis. *Tetrahedron Lett.* **1999**, *40*, 4187–4188.

product could be isolated. In an effort to discourage the presumed[29] internal coordination of the emerging ruthenium alkylidene with the polar functionality of **1050**, the RCM conditions were modified to include the Lewis acid Ti(O*i*-Pr)$_4$.[30] Unfortunately, only the isomerized product **1053** was isolated.

Scheme I–15 | Attempted RCM of diene **1050** with initiator **G2** [adapted from ref 21].



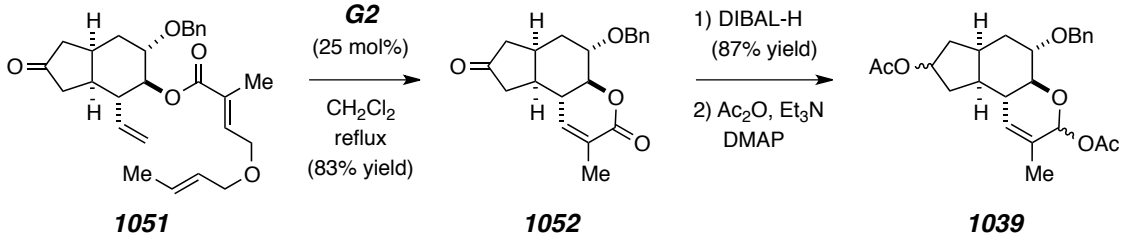
A solution to this problem was eventually realized when the relay-modified triene **1051** was employed (Scheme I–16). Exposure of this material to the **G2** initiator in refluxing CH_2Cl_2 resulted in smooth RRCM to provide the dihydropyranone **1052**. As the authors correctly state, this result clearly demonstrates the power of the RRCM strategy for the synthesis of functionalized dihydropyranones.[22] Exhaustive reduction of **1052** with DIBAL-H followed by acetylation of the incipient diol provided the *bis*-acetate **1039** as a mixture of diastereomers that was immediately carried forward.

---

[29] Fürstner, A.; Langemann, K. Total Synthesis of (+)-Ricinelaidic Acid Lactone and of (–)-Gloeosporone Based on Transition-Metal-Catalyzed C–C Bond Formations. *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136.

[30] Ghosh, A. K.; Cappiello, J.; Shin, D. Ring-Closing Metathesis Strategy to Unsaturated γ- and δ-Lactones: Synthesis of Hydroxyethylene Isostere for Protease Inhibitors. *Tetrahedron Lett.* **1998**, *39*, 4651–4654.

Scheme I–16 | Successful implementation of RRCM of **1051** and subsequent manipulation of **1052** [adapted from ref 21].



Now that the core tricyclic skeleton of **1-B** had been forged, the stage was set for the installation of the C13–C21 nonenyl appendage (Scheme I–17). Treatment of the acetylated lactol **1039** with the vinyl stannane **1040** under the influence of BF_3•OEt_2 cleanly provided the vinylated product **1054** as a 9:1 inseparable mixture of diastereomers at C5. Cleavage of the secondary acetate within **1054** with methanolic K_2CO_3 followed by silylation of the resulting secondary alcohol delivered the silyl ether **1055**. The C5-epimeric silyl ethers could be separated chromatographically at this stage, at which point **1055** was isolated as a single diastereomer (5*S**). The C1 secondary alcohol was liberated by debenzylation with LiDBB in the presence of $MgBr_2$•OEt_2[31] and then oxidized under Ley's conditions[32] to provide ketone **1056**. A straightforward two-step sequence was all that remained to complete the total synthesis of **1-B**. Thus, Ito-Saegusa oxidation[33] of **1056** to an α,β-unsaturated ketone and subsequent hydrogen fluoride-induced removal of the C5 silyl ether protecting group yielded the natural

---

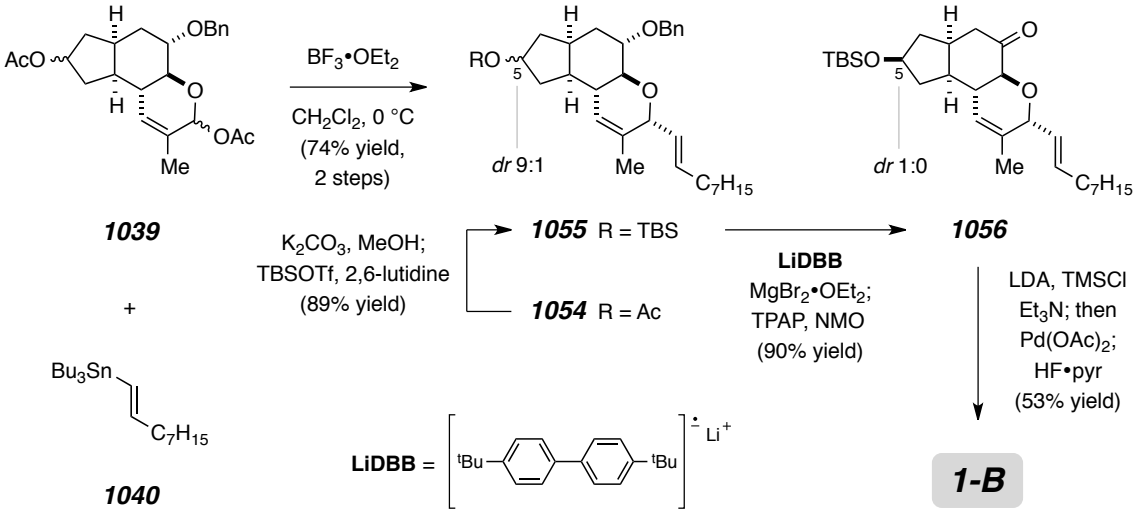
31 Fukuda, K.; Miyashita, M.; Tanino, K. Practical Synthesis of (*E*)- and (*Z*)-2-Silyl-3-penten-1-ols with High Enantiopurity. *Tetrahedron Lett.* **2010**, *51*, 4523–4525.

32 Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. Tetrapropylammonium Perruthenate, $Pr_4N^+RuO_4^-$, TPAP: A Catalytic Oxidant for Organic Synthesis. *Synthesis* **1994**, 639–666.

33 Ito, Y.; Hirao, T.; Saegusa, T. Synthesis of α,β-Unsaturated Carbonyl Compounds by Palladium(II)-Catalyzed Dehydrosilylation of Silyl Enol Ethers. *J. Org. Chem.* **1978**, *43*, 1011–1013.

product, thereby finalizing a synthetic route that proceeded in 12% overall yield from **1044** with a longest linear sequence of 16 steps.

Scheme I–17 | Lewis acid-mediated vinylation of **1039** and completion of the total synthesis of penostatin B (**1-B**) [adapted from ref 21].



CHAPTER II

PENOSTATIN A AND B SYNTHESIS STUDIES

A. HYPOTHESIS FOR THE BIOSYNTHESIS OF PENOSTATINS A AND B

HYPOTHESIS STATEMENT:

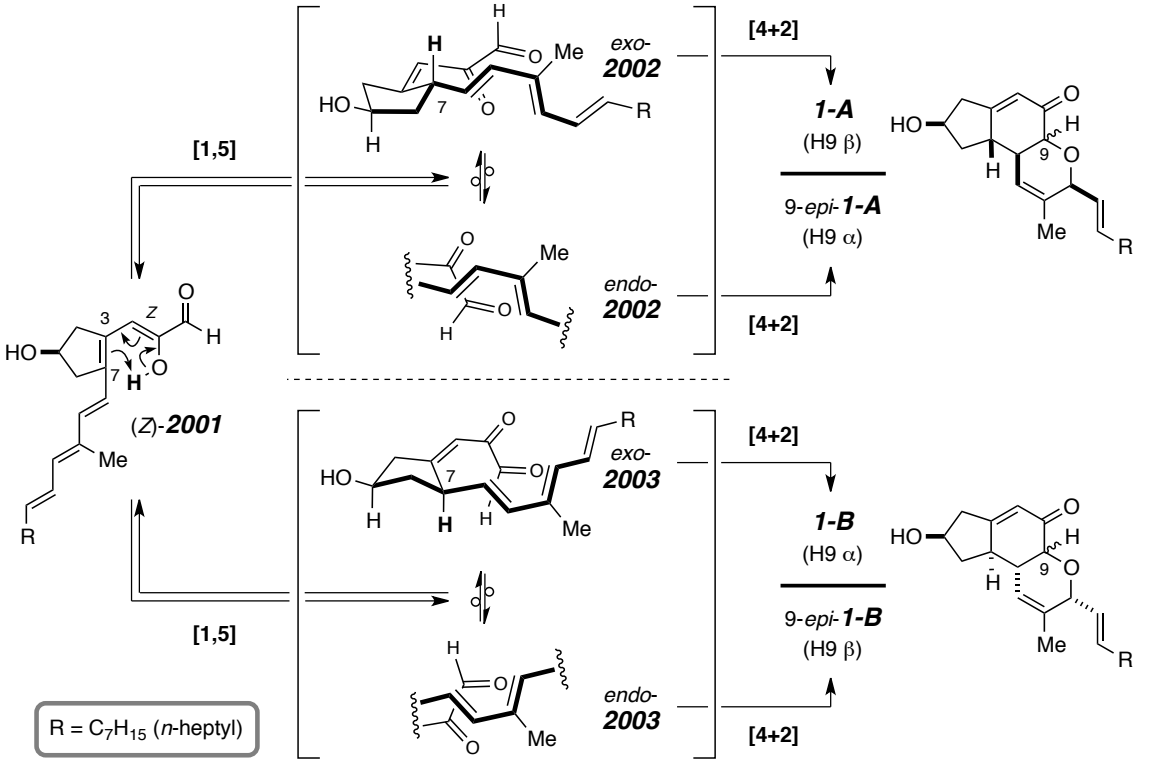
> *PENOSTATIN A (**1-A**) AND PENOSTATIN B (**1-B**) ARISE FROM A SINGLE (i.e., COMMON) BIOGENETIC INTERMEDIATE (**2001**) THAT DIVERGES INTO PARALLEL, DIASTEREOMERIC REACTION MANIFOLDS. THESE CASCADE TO THE NATURAL PRODUCTS THROUGH COMPETITIVE SPONTANEOUS INTRAMOLECULAR HETERO-DIELS–ALDER REACTIONS.*

A–1. CYCLOADDITION CASCADES EN ROUTE TO PENOSTATINS A AND B

The intriguing fact that **1-A** and **1-B** share the *same* absolute configuration at the C5 carbinol stereocenter but the *opposite* absolute configurations at the remaining four (C7, C8, C9, and C12) stereocenters immediately compels the proposal that each is formed via an intramolecular [4+2]-cycloaddition of the hetero-Diels–Alder (IMHDA) class (Scheme II–1). The substrates for these IMHDA events would ultimately be derived from a common, linear precursor *that possesses only the C5 stereogenic center*–namely, the pentaenol (*Z*)-**2001**. This enol tautomer would likely be in dynamic equilibrium with the diastereomeric α-keto aldehydes **2002** and **2003** via a pair of (presumably) energetically similar [1,5]-hydrogen atom shifts. Specifically, internal delivery of a proton from the enol oxygen to either the β- or α-diastereoface of the $\Delta^{3,7}$ π-bond within (*Z*)-**2001** would lead to divergence of the reaction manifold. Were the diastereomeric α-keto aldehyde rotamers *exo*-**2002** and *exo*-**2003** to undergo IMHDA cycloadditions, they

would directly give rise to **1-A** and **1-B**, respectively. Conversely, the IMHDA cycloadditions of *endo*-**2002** and *endo*-**2003** would result in the co-production of 9-*epi*-**1-A** and 9-*epi*-**1-B**, respectively. It should be noted that, although these latter two intermediates are *not* isolated as secondary metabolites of the fungus *Penicillium* sp. OUPS-79, their potential role in the biosynthesis of penostatin I (**1-I**) and penostatin F (**1-F**) will be addressed in Chapter III.

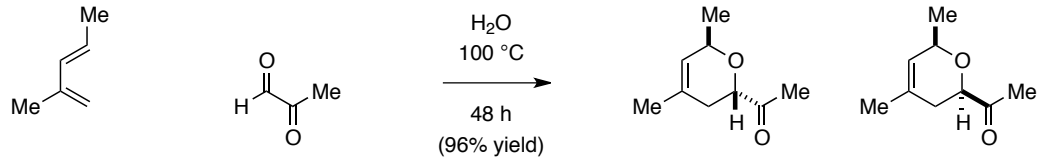
Scheme II–1 | Proposed biosynthetic origin of penostatins A (**1-A**) and B (**1-B**), and the co-production of 9-*epi*-penostatins A (9-*epi*-**1-A**) and B (9-*epi*-**1-B**), from the common pentaenol tautomer (*Z*)-**2001**.



Because of the unique nature of the α-keto aldehyde dienophiles present in **2002** and **2003**, there is no *a priori* basis for judging the sense of diastereoselectivity that will attend their IHMDA reactions. Although the hetero-Diels–Alder (HDA) reactions of

particularly reactive dicarbonyl compounds have been well known for many years,[34] such as pyruvates (i.e. α-keto carboxylates), glyoxylates (i.e., α-carboxyl aldehydes), and mesoxalates (i.e., α,α′-dicarboxyl ketones), the same cannot be said of glyoxal and its derivatives (i.e., α-keto aldehydes). Indeed, the only previous study relevant to the question at hand has been reported by Lubineau and co-workers,[35] wherein they demonstrated, among other things, that the dihydropyrans **2006a** and **2006b** were produced by a formal [4+2]-cycloaddition of 2-methylpenta-1,3-diene (**2004**) and methyl glyoxal (**2005**) (Scheme II–2). Notice also that *pure water* was the reaction solvent of choice. This final point not only underscores the rate-accelerating effect[36] that water has on the Diels–Alder reaction, but it also demonstrates that aldehyde hydration does not impede [4+2]-cycloaddition. In other words, just as methyl glyoxal (**2005**) would be heavily hydrated under aqueous conditions, so too will the diastereomeric α-keto aldehydes **2002** and **2003** (cf. Scheme II–1).

Scheme II–2 | A relevant aqueous hetero-Diels–Alder reaction [adapted from ref 35].



2004 + ***2005*** ***2006a*** + ***2006b***

47 : 53

[34] Weinreb, S. M. Heterodienophile Additions to Dienes. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: New York, **1991**; Vol. 5, pp 401–449.

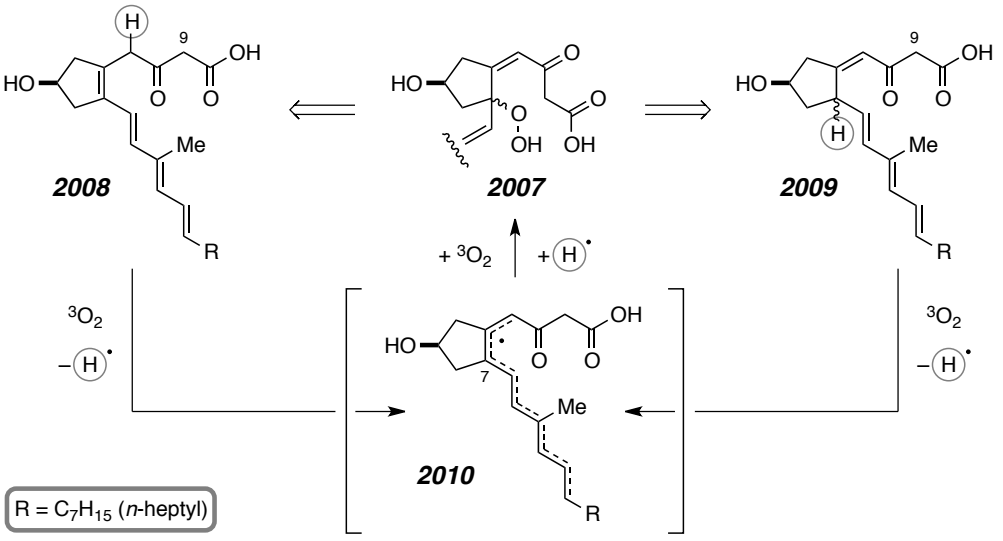
[35] Lubineau, A.; Augé, J.; Grand, E.; Lubin, N. Aqueous Hetero Diels–Alder Reactions: The Carbonyl Case. *Tetrahedron* **1994**, *50*, 10265–10276.

[36] (a) Rideout, D. C.; Breslow, R. Hydrophobic Acceleration of Diels–Alder Reactions. *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817. (b) Grieco, P. A.; Garner, P.; He, Z. "Micellar" Catalysis in the Aqueous Intermolecular Diels–Alder Reaction: Rate Acceleration and Enhanced Selectivity. *Tetrahedron Lett.* **1983**, *24*, 1897–1900. (c) Otto, S.; Engberts, J. B. F. N. Diels–Alder Reactions in Water. *Pure Appl. Chem.* **2000**, *72*, 1365–1372.

A–2. ON THE ORIGIN OF C9 OXYGENATION

Let us now briefly contemplate the biosynthetic origin of the common pentaenol **2001** (Scheme II–3). This intermediate, and ultimately the entire penostatin family of natural products, could be derived from either of the isomeric β-keto acids **2008** or **2009**. Both contain 22 carbons in their longest linear chain and thus are reasonable candidates for production by polyketide synthase (PKS) enzymatic machinery.[37] One would expect the (circled) allylic hydrogen atoms within **2008** and **2009** to be exceedingly labile; their abstraction by $^3O_2$ would initiate an autoxidation event that, through propagative capture of the common, highly delocalized allylic radical **2010** by another molecule of $^3O_2$, would culminate in the formation of the hydroperoxide **2007**.

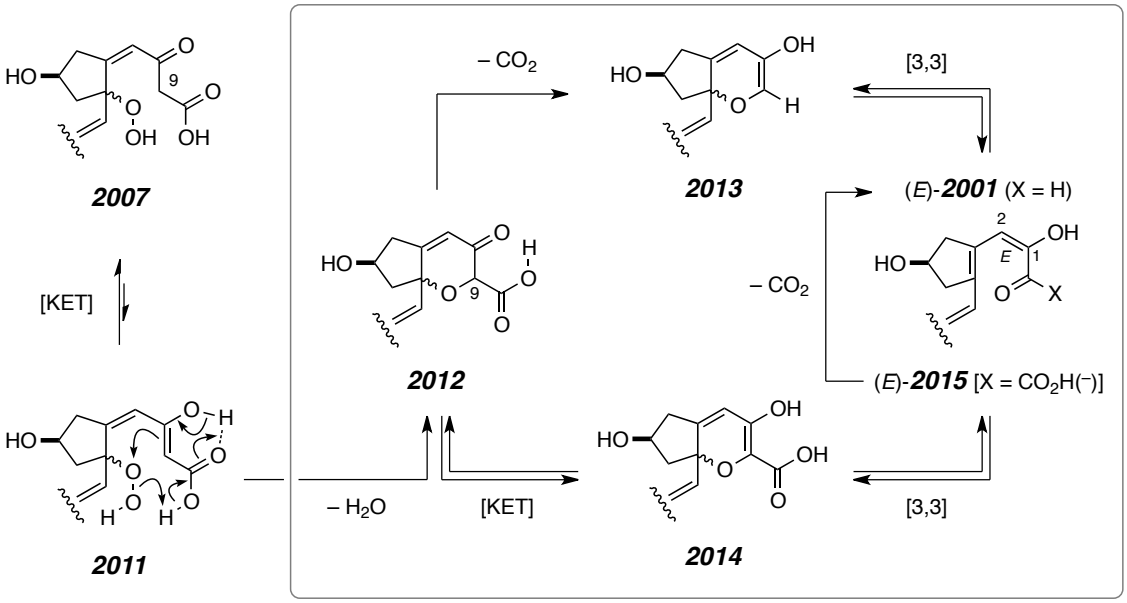
Scheme II–3 | Formation of the common hydroperoxide **2007** from **2008** or **2009**.



[37] (a) Staunton, J.; Weissman, K. J. Polyketide Biosynthesis: A Millennium Review. *Nat. Prod. Rep.* **2001**, *18*, 380–416. (b) Fischbach, M. A.; Walsh, C. T. Assembly-Line Enzymology for Polyketide and Nonribosomal Peptide Antibiotics: Logic, Machinery, and Mechanisms. *Chem. Rev.* **2006**, *106*, 3468–3496. (c) Hertweck, C. The Biosynthetic Logic of Polyketide Diversity. *Angew. Chem. Int. Ed.* **2009**, *48*, 4688–4716.

The presence of the terminal carboxyl group within **2007** activates C9 toward oxidative transfer (Scheme II–4). Most certainly, this species would be in equilibrium with its enol tautomer **2011**; were this latter intermediate to undergo dehydrative oxidative transfer to the enol α-carbon (C9), then it would give rise to the pyrone **2012**. Reversible[38] valence isomerization (oxa-6π electrocyclization[39]) of the 2*H*-pyran **2013**, itself produced upon decarboxylation of **2012**, would give rise to (*E*)-**2001**. Alternatively, KET of **2012** prior to decarboxylation would generate a different 2*H*-pyran (**2014**). Then, valence isomerization of this species would produce the enol pyruvate (*E*)-**2015**, from which (*E*)-**2001** would arise via decarboxylation.

Scheme II–4 | Production of the common pentaenol **2001** from the enol **2011**.



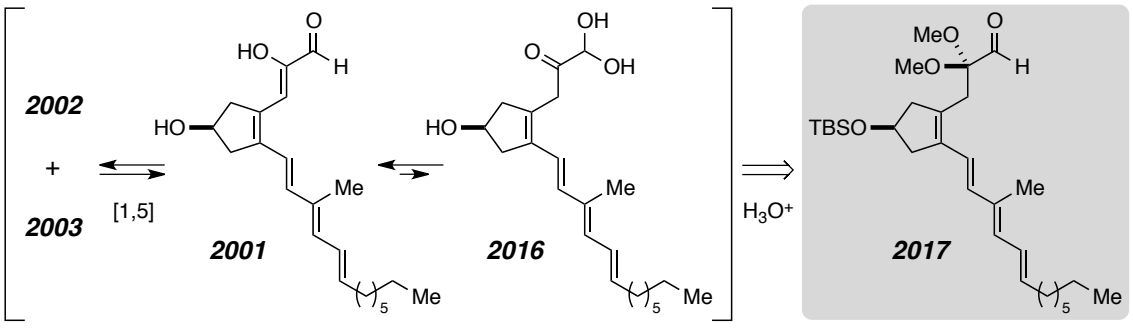
[38] The activation barrier and enthalpy of reaction for the valence isomerization of (*Z*)-penta-2,4-dienal to 2*H*-pyran have been computed to be 22–25 kcal/mol and ≈ 0 kcal/mol, respectively; see: Rodríguez–Otero, J. Study of the Electrocyclization of (*Z*)-Hexa-1,3,5-triene and Its Heterosubstituted Analogues Based on Ab Initio and DFT Calculations. *J. Org. Chem.* **1999**, *64*, 6842-6848.

[39] Beaudry, C. M.; Malerich, J. P.; Trauner, D. Biosynthetic and Biomimetic Electrocyclizations. *Chem. Rev.* **2005**, *105*, 4757–4778.

B. SYNTHESIS PLAN

If the hypothesis for the formation of **1-A** and **1-B** (and 9-*epi*-**1-A** and **1-B**) is an accurate formulation of biosynthetic reality, then one could reasonably anticipate that the α-keto aldehydes **2002** and **2003** would be chemical entities with fleeting lifetimes–i.e., they would be too reactive to be isolated. Indeed, during synthesis studies directed toward **1-A** and **1-B**, Snider and Liu fashioned a strategy that, in a sense, circumvented these intermediates (see Chapter I, Section C–1).[7] Elegant though this approach certainly was, their stated reasons for pursuing it ("*synthetically inaccessible and too unstable*"[7]) may have cloaked an otherwise viable, but less obvious, synthetic strategy. The key intermediate that has been identified as the common entry point to the (bio)synthetic studies described herein is the pentaenol tautomer **2001**. Thus, **2002** and **2003** needn't (and perhaps won't) be isolable; rather, they will be generated upon tautomerization of this common intermediate (Scheme II–5). The highly unsaturated pentaenol **2001**, in turn, would be formed by collapse of the hydrate **2016**, itself produced upon hydrolysis of a relatively more stable, *latent* progenitor–the protected aldehyde **2017**. Thus, the advantage afforded by this strategy can be seen: The cascade of spontaneous pericyclic reactions leading to **1-A** and **1-B** would occur under the same set of reaction conditions that induce the formation of the pentaenol **2001**.

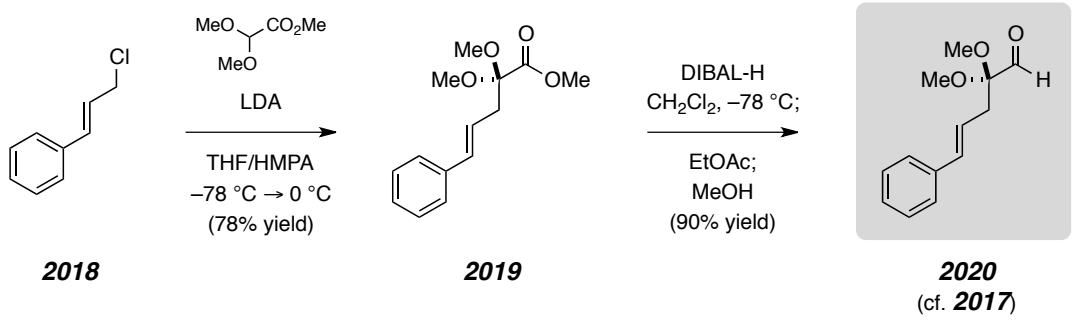
Scheme II–5 | Synthetic strategy for accessing the common pentaenol **2001**.



C. MODEL HYDROLYSIS STUDY OF THE DIMETHOXY ALDEHYDE **2020**

It seemed prudent at this early juncture to firmly establish that an aldehyde such as **2017** could indeed serve as a precursor to the α-keto aldehyde enol present in **2001**. A simplified model substrate was prepared as described in Scheme II–6. Alkylation of the lithium enolate derived from methyl dimethoxyacetate[40] with cinnamyl chloride (**2018**) in THF/HMPA delivered the allylic 2,2-dimethoxy ester **2019** in good yield. Then, partial reduction of the ester was affected with DIBAL-H at low temperature, which cleanly produced the aldehyde **2020**. Although quenching this reaction with MeOH did produce significant quantities of the methyl hemiacetal along with **2020**, these intermediates were readily converted to the free aldehyde upon SiO_2 chromatography.

Scheme II–6 | Straightforward synthesis of the 2,2-dimethoxy aldehyde **2020**, a model hydrolysis substrate.



2018 ***2019*** ***2020*** (cf. ***2017***)

When a purified sample of the aldehyde **2020** was dissolved in 4:1 CD_3CN/D_2O (25 mM), a mixture of the free aldehyde and its hydrate **2021** were observed. The ^1H NMR spectrum (500 MHz) of this sample collected at various time points (6, 24, and 48 h) indicated that the equilibrium ratio between these two species (*ca.* 2.5:1 **2020**/**2021**) was established within 24 h. This ratio did not change after 7 d nor did any observable

[40] Huet, F.; Pellet, M.; Conia, J. M. Preparation of Acetals of Substituted Glyoxylic Esters (Methyl 2,2-Dimethoxylalkanoates). *Synthesis* **1979**, 33–34.

hydrolysis occur. However, when **2020** was dissolved in 4:1 CD_3CN/0.1 M DCl (25 mM) and its fate observed by ^1H NMR spectroscopy (500 MHz), a considerably more interesting series of events occurred (Figure II–1). As expected, the equilibrium between **2020** and its hydrate **2021**[41a] was rapidly (< 5 min) established under these conditions, as evidenced by slight upfield shift of the allylic methylene (▲) resonance of the latter species (the acetal resonance is not shown). After a short reaction period (0.5 h), a new intermediate, which has been assigned the structure of the α-keto aldehyde acetal **2022**,[41b] began to dominate the ^1H NMR spectrum. The substantial downfield shifts experienced by the allylic methylene (▲), β-alkenyl (◆), and acetal (**H**) resonances are consistent with this structural assignment. Over the course of 24 h, the α-keto aldehyde acetal **2022** was slowly converted to yet another new species, the dienol **2023**.[41c] The loss of the upfield allylic methylene (▲) resonance that was present in **2022** and the appearance of new aldehydic (**H**), alkenyl (▲, ◆, and ●), and downfield-shifted *ortho*-arene (✱) resonances are all strongly suggestive of this structural assignment.

---

41 [*MJJ-III-157*] Diagnostic ^1H NMR resonances for the two principal species (**2021** and **2022**) observed during the hydrolysis of **2020**, including the final product **2023**, are provided [500 MHz, CD_3CN/0.1 M DCl (4:1)]. (a) **2021**: δ 6.43 (ddd, J = 1.5, 1.5, 16.0 Hz, 1H, PhC*H*=$CHCH_2$), 6.29 (ddd, J = 7.0, 7.0, 16.0 Hz, 1H, PhCH=C*H*CH_2), 4.89 [s, 1H, C*H*$(OD)_2$], and 2.59 (dd, J = 1.5, 7.0 Hz, 2H, PhCH=CHCH_2). (b) **2022**: δ 6.48 (ddd, J = 1.5, 1.5, 16.0 Hz, 1H, PhC*H*=$CHCH_2$), 6.31 (ddd, J = 7.0, 7.0, 16.0 Hz, 1H, PhCH=C*H*CH_2), 5.11 [s, 1H, C*H*$(OD)_2$], and 3.53 (dd, J = 1.5, 7.0 Hz, 2H, PhCH=CHCH_2). (c) **2023**: δ 9.13 (s, 1H, C*H*O), 7.55-7.52 (m, 2H, *ortho*-C_6H_5), 6.94 (dd, J = 1.0, 16.0 Hz, 1H, PhC*H*=CHCH), and 6.26 (dd, J = 1.0, 11.0 Hz, 1H, PhCH=CHC*H*).

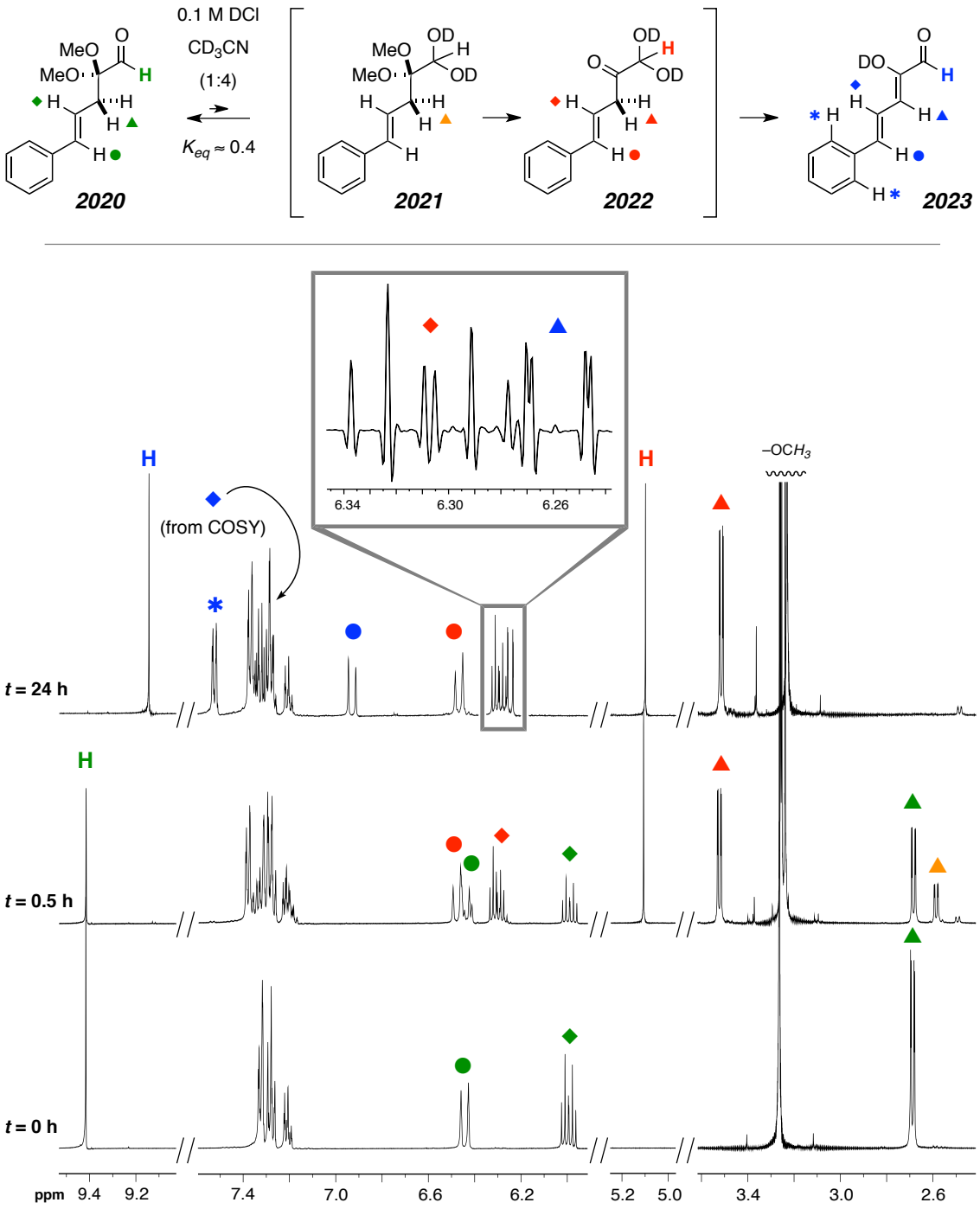
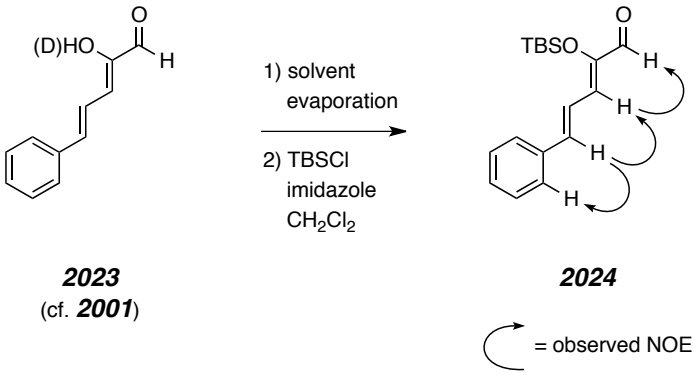


Figure II–1 | Hydrolysis of the aldehyde **2020** monitored by ^{1}H NMR spectroscopy.

The structure of the dienol **2023** was definitively established by its subsequent conversion to the silyl enol ether **2024**[42] (Scheme II–7). Analysis of $^{3}J_{H,H}$ coupling constant values in combination with 1-D NOE studies has strongly supported the configurational assignment that is represented by structure **2024**. Furthermore, it is both encouraging and important to note the structural similarities–both of constitution *and* configuration–that **2023** shares with the pentaenol **2001**.

Scheme II–7 | Derivatization of **2023** and confirmation of the relative configuration of **2024** by 1-D NOE studies.

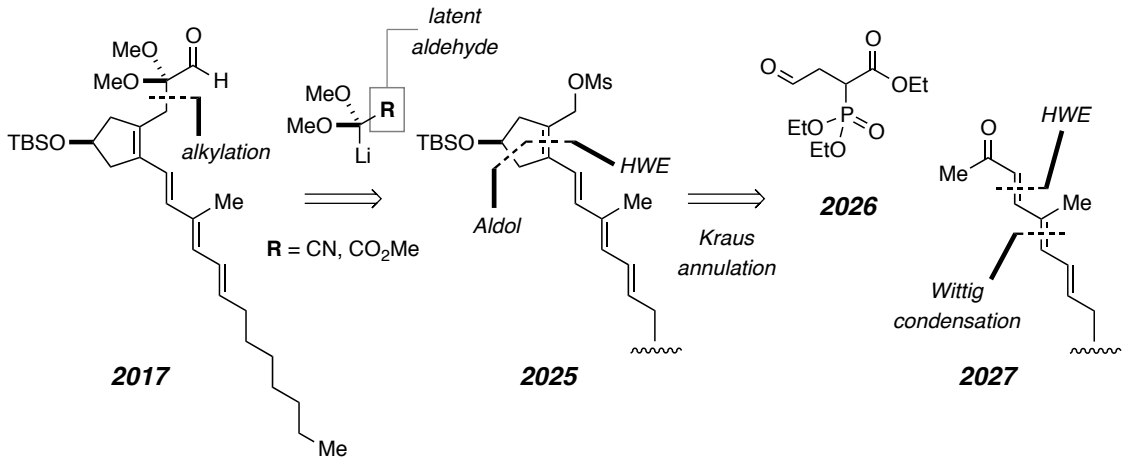


[42] [*MJJ-III-147*] **^{1}H NMR** (500 MHz, CD_3CN): δ 9.23 (s, C*H*O), 7.54-7.51 (nfom, 2H, *o*-C_6H_5), 7.41-7.31 (m, 3H, *m*- and *p*-C_6H_5), 7.35 [dd, *J* = 11.0, 16.0 Hz, 1H, CH=C*H*CH=C(OTBS)CHO], 7.00 [d, *J* = 15.5 Hz, 1H, C*H*=CHCH=C(OTBS)CHO], 6.58 [dd, *J* = 1.0, 11.5 Hz, 1H, CH=CH–C*H*=C(OTBS)CHO], 1.03 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], and 0.20 [s, 6H, $(CH_3)_3CSi(CH_3)_2$].

D. PHOSPHONATE ALDEHYDE ANNULATION-BASED APPROACH TO **2017**

The hydrolysis study that was presented in the previous section was certainly encouraging. Not only did it validate the general strategy that has been proposed to access the common pentaenol **2001**, but it also focused synthetic efforts directly upon the dimethoxy aldehyde **2017**. It was anticipated that the tetraenyl mesylate **2025**, itself produced upon reduction and activation of an ester precursor, could be used to alkylate an acyl anion equivalent (Scheme II–8). Were the carbanions derived from either 2,2-dimethoxyacetonitrile or methyl dimethoxyacetate to be employed, then a simple reduction of these latent aldehyde species should provide ready entry to **2017**. The framework of the mesylate **2025**, in turn, should be accessible by an adaptation of G. A. Kraus' elegant phosphonate aldehyde annulation strategy.[43]

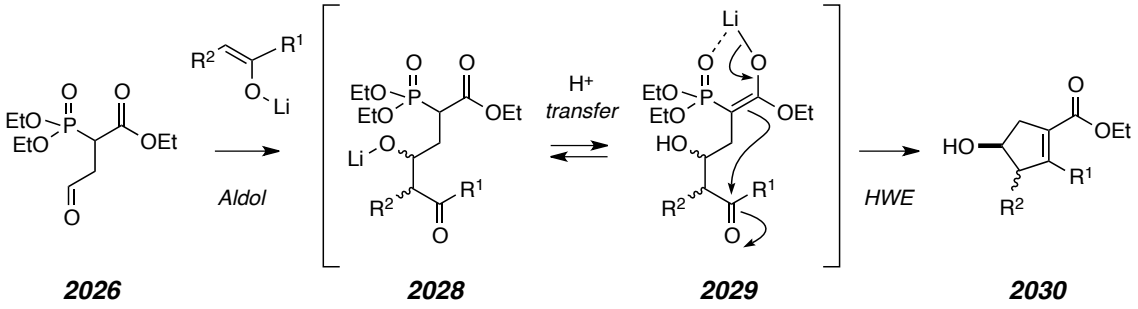
Scheme II–8 | Retrosynthetic analysis of the key 2,2-dimethoxy aldehyde **2017**.



[43] (a) Kraus, G. A.; Jones, C. The Reaction of Ketone Enolates with a δ-Oxo Phosphonate: A Carbanion-Based [4+2] Annulation. *Synlett* **2001**, 793–794. (b) Kraus, G. A.; Choudhury, P. K. Phosphonate Aldehyde Annulation. A One-Pot Synthesis of δ-Hydroxy Cyclopentenoic Esters. *Org. Lett.* **2002**, *4*, 2033–2034. (c) Kraus, G. A.; Choudhury, P. K. Phosphonate Aldehyde Annulation – A One-Pot Synthesis of Hydroxycycloalkenoic Esters – Application to Analogs of Glycinoeclepin A. *Eur. J. Org. Chem.* **2004**, 2193–2197.

The annulation reaction of **2026** and **2027** was particularly appealing because nearly the entire carbon skeleton of **2017** could be assembled in one fell swoop. Indeed, Kraus and co-workers[43] have demonstrated that alkyl, alkenyl, and aryl ketones are competent partners in this annulation reaction, giving rise to a variety of hydroxy cycloalkenoic esters (cf. **2030**, Scheme II–8). The key to the success of this methodology was the formation of an intermediate lithium alkoxide **2028** via aldol addition of a lithium enolate to the aldehyde within **2026** (rather than abstraction of the phosphonoacetate methine proton). An intramolecular proton transfer within **2028** would most likely result in **2029**, and a subsequent intramolecular HWE reaction would afford the cyclic products **2030**. A limitation of the aforementioned method was found when R^1 was branched; the enolates α-tetralone and *iso*-propyl methyl ketone gave no products resulting from this mechanistic pathway, presumably due to severe steric interactions during the penultimate ring-closing event.

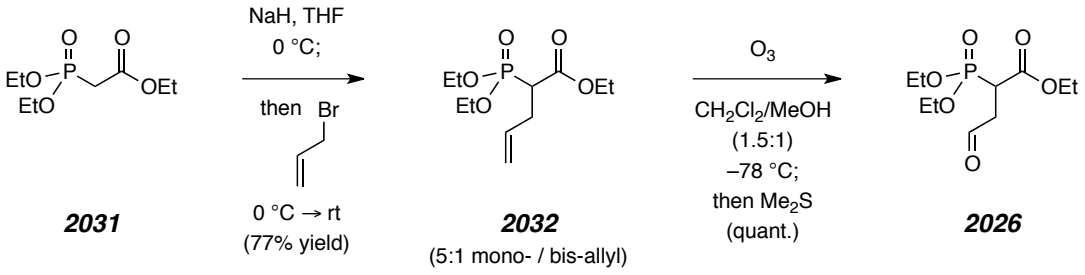
Scheme II–9 | Mechanistic proposal for the one-pot aldol/HWE cascade cyclization between a lithium enolate and the phosphonate aldehyde **2026** [adapted from refs 43b,c].



The phosphonate aldehyde was easily assembled as described in Scheme II–10. Addition of triethylphosphonoacetate (**2030**) to a suspension of NaH in THF and subsequent alkylation of allyl bromide with this anion generated the phosphonoacetate

derivative **2032**.[44] Under these conditions, a chromatographically inseparable mixture (5:1) of the mono- and bis-allylated derivatives was consistently generated, and this ratio could not be improved by alternative means (i.e., **2031**, *t*-BuOK in DMSO, then allyl bromide; neat **2031**, K_2CO_3, NaI, allyl bromide[45]). Finally, ozonolysis of **2032** and reductive work-up according to Kraus' procedure[43c] cleanly generated **2026**.

Scheme II–10 | Preparation of the phosphonate aldehyde **2026** from **2031**.



2031 ***2032*** ***2026***

The synthesis of the requisite dienal **1014** followed a route that was very similar to that reported by Snider and Liu[7] (Scheme II–11). The imine **2034** could be prepared in quantitative yield by exposure of cyclohexylamine (**2033**) to propionaldehyde under dehydrative conditions. Although **2034** could be isolated and purified by vacuum distillation, it was more conveniently generated as a stock solution in THF under the second set of conditions (3Å MS, THF). Thus, direct addition of a solution of the imine **2034** to a solution of LDA at 0 °C provided a convenient method by which the lithium enamide **2035** could be prepared. Exposure of this species to commercially available (*E*)-2-decenal (**2036**) affected the directed aldol reaction.[46] After subjection of the crude

---

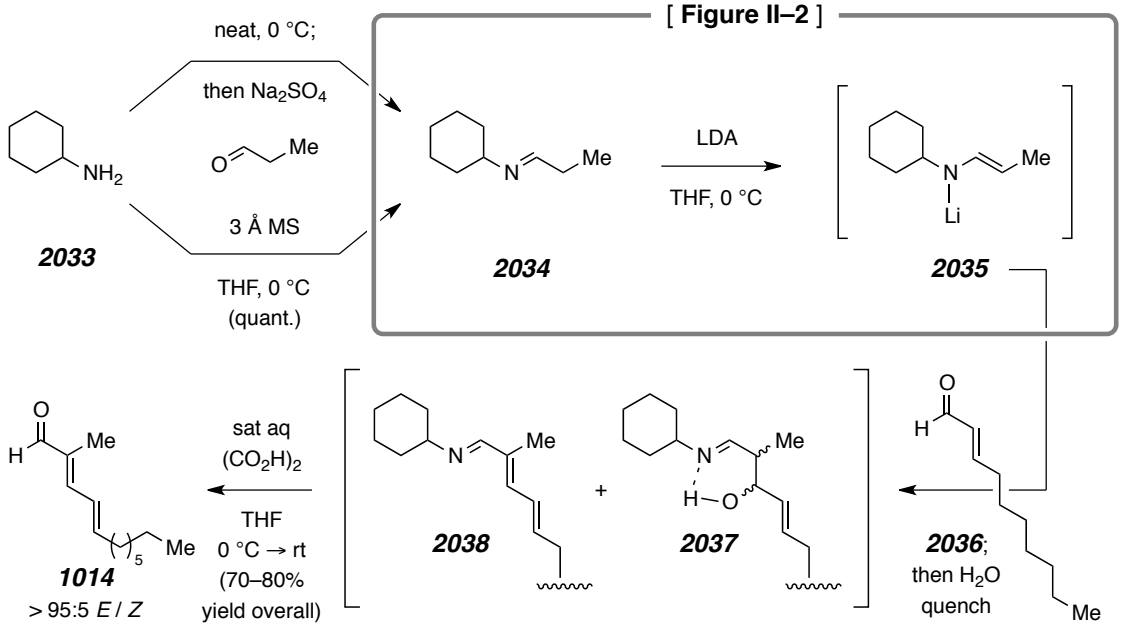
44 Minami, T.; Hirakawa, K.; Koyanagi, S.; Nakamura, S.; Yamaguchi, M. A New Synthesis of α-Methylene Lactones. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2385–2390.

45 Kirschleger, B.; Queignec, R. Heterogeneous Mediated Alkylation of Ethyl Diethylphosphonoacetate. A "One-Pot" Access to α-Alkylated Acrylic Esters. *Synthesis* **1986**, 926-928.

46 Wittig, G.; Hesse, A. Directed Aldol Condensations: β-Phenylcinnamaldehyde. *Org. Synth.* **1970**, *50*, 66.

mixture of imines **2037** and **2038** to sat aq oxalic acid in THF, the dienal **1014** could be isolated in good overall yield and with excellent stereoselectivity.[7]

Scheme II–11 | Synthesis of the dienal **1014** via Wittig condensation of the propionaldehyde imine (**2034**) of cyclohexylamine (**2033**).



In connection with a series of related studies,[47] the course of the deprotonation of the imine **2034** with LDA in THF was conveniently observed by No-D NMR spectroscopy[48] (Figure II–2). The intermediacy of the (*E*)-lithium enamide **2035** was strongly supported by the appearance of new alkenyl [● ($^3J_{H,H}$ = 13.0 Hz) and ✱ ($^3J_{H,H}$ = 6.0, 13.0 Hz)] and allylic methyl [▲ ($^3J_{H,H}$ = 6.0 Hz)] resonances. Additional evidence

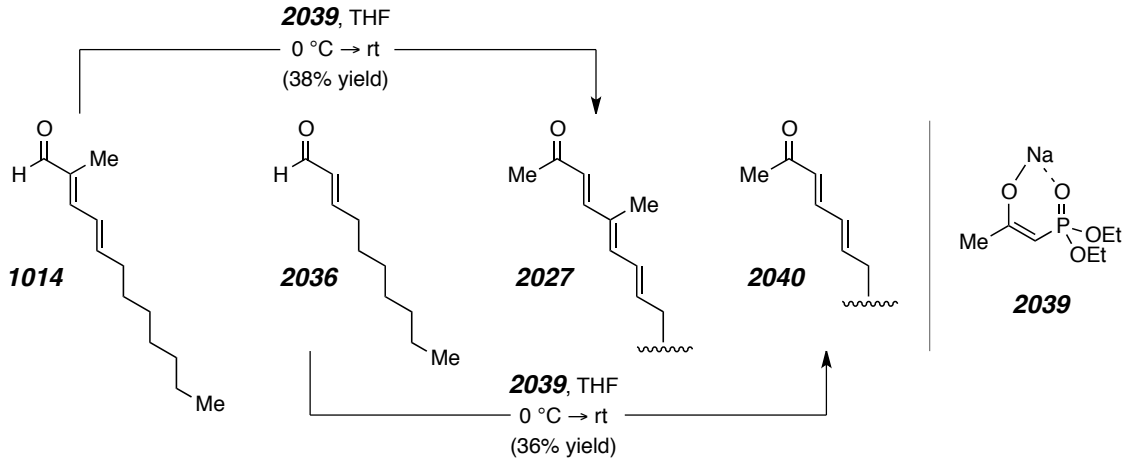
47 Bialke, A. L.; Izgu, E. C.; Jansma, M. J.; Jeon, J.; May, A. E.; Sizova, E. P.; Hoye, T. R. Gallery I of No-D ^{1}H NMR Snapshots of Carbanionic Species. *Proceedings of the 8th International Symposium on Carbanion Chemistry (ISCC-8)*, Madison, WI, June 6-10, **2007**, P-15.

48 Hoye, T. R.; Eklov, B. M.; Ryba, T. D.; Voloshin, M.; Yao, L. J. No-D NMR (No-Deuterium Proton NMR) Spectroscopy: A Simple Yet Powerful Method for Analyzing Reaction and Reagent Solutions. *Org. Lett.* **2004**, *6*, 953–956.

was provided by a $^{1}H–^{1}H$ COSY experiment,[49] wherein cross peaks were observed between the α- (●) and β- (✱) alkenyl and the β-alkenyl (✱) and allylic methyl (▲) protons.

With both the dienal **1014** and the phosphonate aldehyde **2026** in hand, the installation of the methyl ketone by HWE elongation[50] was next undertaken (Scheme II–11). Thus, preparation of the sodium anion of diethyl 2-oxopropylphosphonate[51] (**2039**) in the usual manner and subsequent reaction of it with the dienal **1014** delivered the trienone **2027** in modest yield. Similarly, the dienone **2040** was prepared under essentially identical conditions.

Scheme II–12 | Synthesis of the methyl ketones **2027** and **2040** via HWE elongation.



[49] Hoye, T. R.; Kabrhel, J. E.; Hoye, R. C. No-D NMR Study of the Pathway for *n*-BuLi "Oxidation" of 1,5-Cyclooctadiene to Dilithium Cyclooctatetraene Dianion [Li_2COT^{2-}]. *Org. Lett.* **2005**, *7*, 275-277.

[50] (a) Wadsworth, Jr., W. S.; Emmons, W. D. The Utility of Phosphonate Carbanions in Olefin Synthesis. *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738. (b) Spino, C.; Crawford, J.; Bishop, J. Sequential Diels–Alder Reactions on a 1,3,7,9-Tetraene: An Efficient and Stereoselective Route to the Perhydrophenanthrene Skeleton. *J. Org. Chem.* **1995**, *60*, 844-851.

[51] Kitamura, M.; Tokunaga, M.; Noyori, R. Asymmetric Hydrogenation of β-Keto Phosphonates: A Practical Way to Fosfomycin. *J. Am. Chem. Soc.* **1995**, *117*, 2931-2932. The phosphonate **2039** was prepared according to the procedure described in footnote 7 of this report.

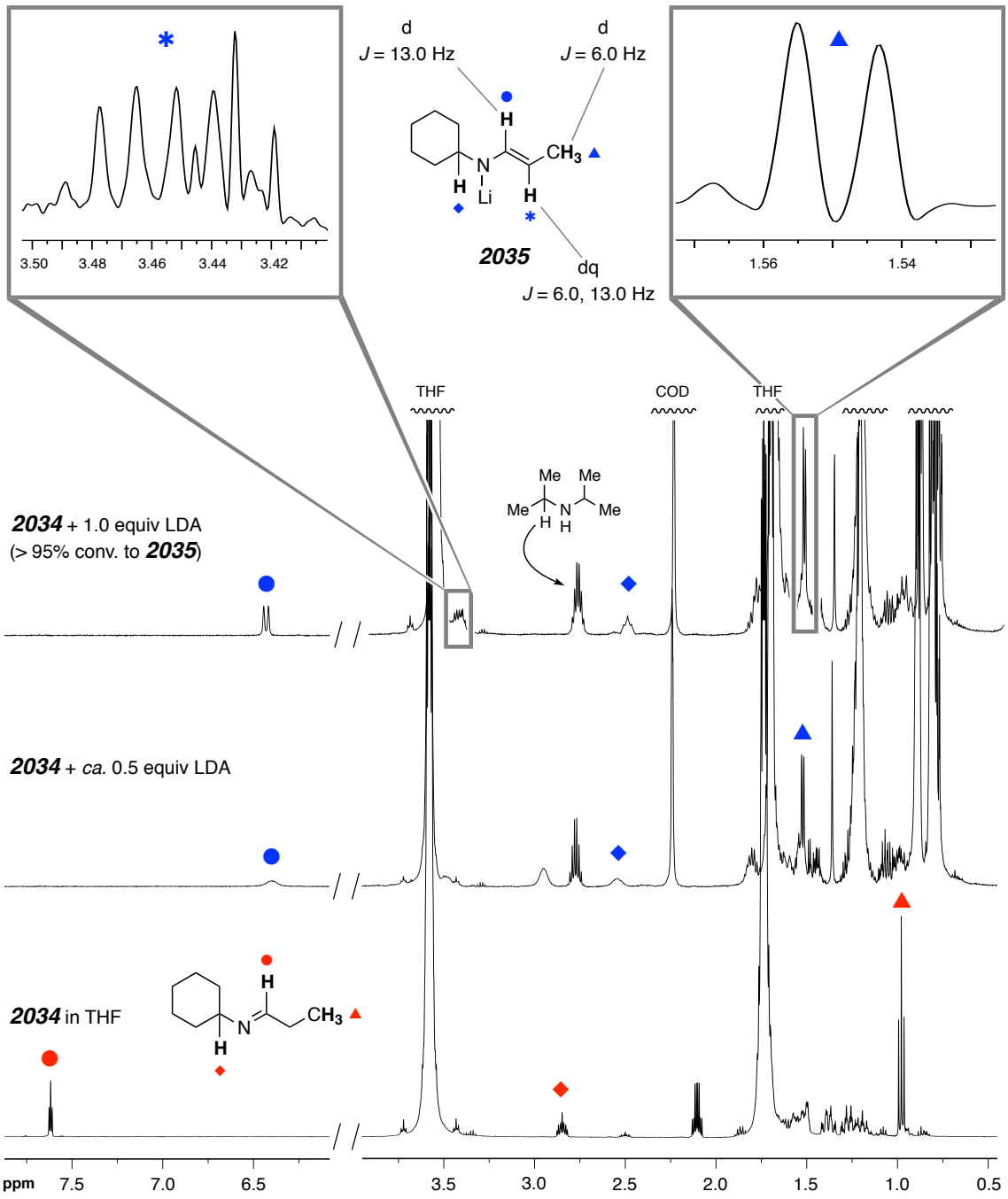
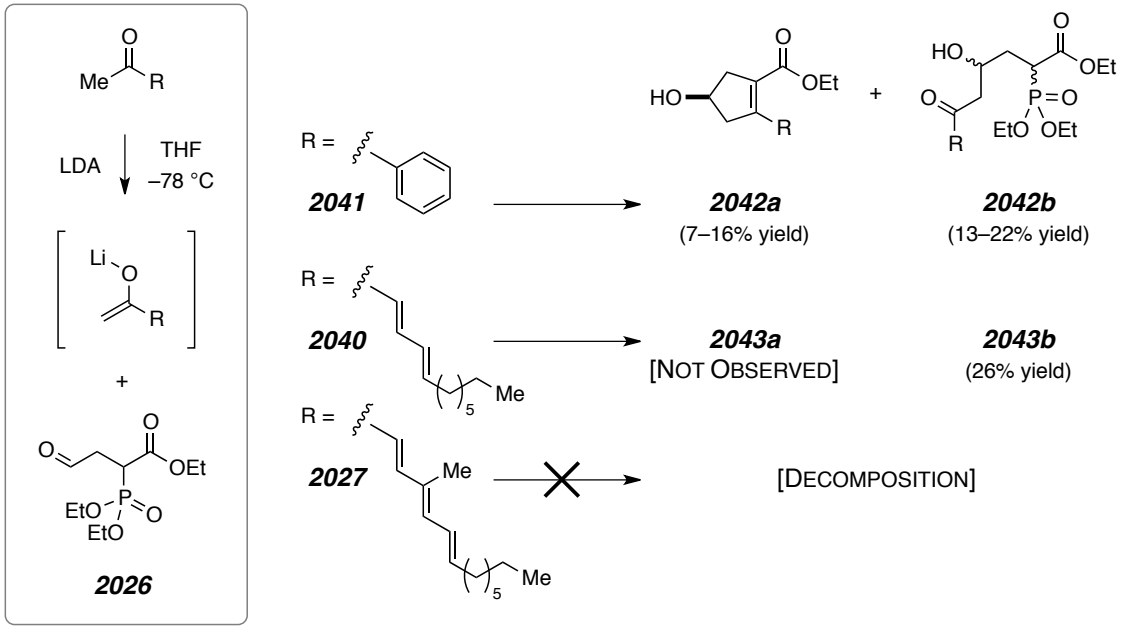


Figure II–2 | No-D NMR spectroscopy (500 MHz) enabled the direct observation of the formation of the lithium enamide **2035** by reaction of the imine **2034** with LDA.

Prior to beginning the studies of the annulation reactions of **2027** and **2040**, the reactivity of acetophenone (**2041**) was first interrogated. Indeed, Kraus and co-workers have reported that, upon reaction of the enolate derived from **2041** with the phosphonate aldehyde **2026**, the hydroxycyclopentenoic ester **2042a** was isolated in 40% yield.[43c] However, when this model reaction was carried out under the prescribed conditions (Scheme II–13), **2042a** was consistently isolated in disappointingly low yields (7–16%). The major product was the adduct **2042b**, a species that had undergone the initial aldol addition but had failed to participate in HWE ring closure. Matters became considerably worse when the annulation was attempted with the enolates derived from **2040** and **2027**. When the former species was employed, none of the cyclopentenoic ester **2043a** was observed, and only the aldol adduct **2043b** was obtained in low yield. Finally, and most discouraging of all, when **2027** was exposed to the annulation conditions only starting material decomposition was observed.

Scheme II–13 | Evaluation of the phosphonate aldehyde annulation-based strategy.



As the examples provided in Scheme II–12 make abundantly clear, the phosphonate annulation-based strategy for the synthesis of **2017** had some serious drawbacks. Even *if* the annulation product derived from the trienone **2027** could have been prepared efficiently, questions were raised regarding the stability of the highly conjugated allylic mesylate **2025** (Scheme II–8), let alone whether or not it could be used to alkylate a highly reactive carbanion. Therefore, these studies were abandoned in favor of more convergent approaches toward the assembly of the polyene **2017**.

E. CONVERGENT ASSEMBLY OF **2017** VIA CROSS-COUPLING

The palladium(0)-catalyzed cross-coupling reactions of alkenyl boronates (Suzuki–Miyaura reaction[52]) and stannanes (Stille reaction[53]) with alkenyl halides and pseudohalides are arguably among the most powerful methods for the stereoselective construction of conjugated polyenes. One needs look no further than the arena of natural products total synthesis, where these processes have proven to be of incredibly broad utility.[54] The stereospecific nature of the Suzuki–Miyaura and Stille reactions coupled with their non-acidic and mild reaction conditions have no doubt contributed to this fact. Were a more convergent synthesis route toward the tetraene **2017** to be developed, as was clearly necessary at this stage, then, it seemed, that route would be rendered more robust were it to incorporate one (or more) of these processes. As the reader will soon learn, if there is one single theme that unites nearly all of the subsequent sections in Chapter II, then it is that of palladium(0)-catalyzed cross-coupling reactions.

Two key bond disconnections were initially proposed to access the tetraene **2017** (Scheme II–14). The first of these (route **a**) would aim to forge the C7–C8 bond by a late stage Stille cross-coupling reaction between an enol triflate such as **2044** and a vinyl stannane (**2045**). The alternative route (route **b**) would rely heavily upon the 1,1-dibromoolefin Suzuki cross-coupling technology that has been introduced by Roush.[55]

---

52 Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457–2483.

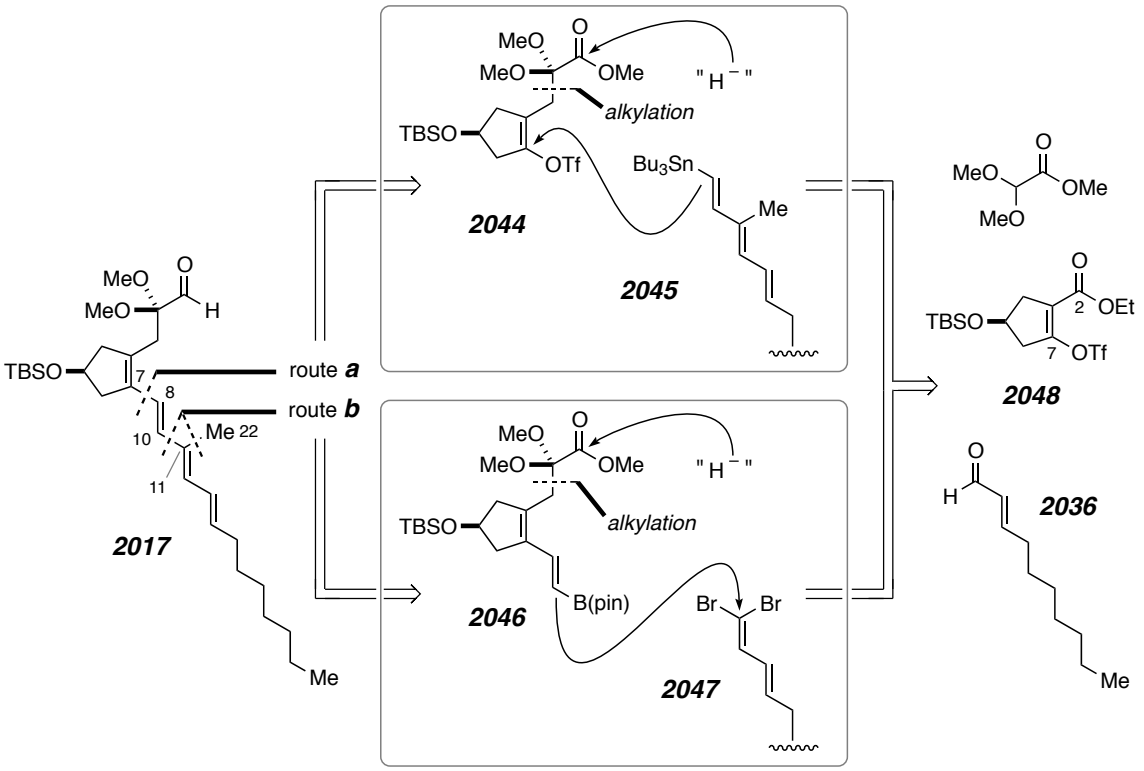
53 (a) Stille, J. K. The Palladium-Catalyzed Cross-Coupling Reactions of Organotin Reagents with Organic Electrophiles. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. The Stille Reaction. *Org. React.* **1997**, *50*, 1–652.

54 Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489.

55 (a) Roush, W. R.; Moriarty, K. J.; Brown, B. B. Stereoselective Synthesis of (*Z*,*E*)-2-Bromo-1,3-dienes via the Palladium(0) Catalyzed Cross Coupling Reactions of 1,1-Dibromoolefins and Vinylboronic Acids. *Tetrahedron Lett.* **1990**, *31*, 6509–6512. (b) Frank, S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. Use of Thallium(I) Ethoxide in Suzuki Cross Coupling Reactions. *Org. Lett.* **2000**, *2*, 2691–2694.

Thus, the C10–C11 bond and the C22 methyl group would be sequentially forged by 1) a regioselective cross-coupling event between the vinyl pinacol boronate **2046** and the dibromoolefin **2047** and 2) methylation of the resulting vinyl bromide (not shown). As before, both routes would capitalize on the selective reduction of the ester (post-cross-coupling) to provide **2017**.

Scheme II–14 | Revised retrosynthetic analysis of the key tetraene **2017** via either C7–C8 or C10–C11 bond disconnections.



All four of the intermediates involved in routes **a** and **b** would ultimately be derived from the same three precursors: i) methyl dimethoxyacetate (deprotonation of which would generate an acyl anion equivalent), ii) the C2–C7 enol triflate **2048**, and iii) (*E*)-2-deceanl (**2036**). The final of these three species has already been used to prepare the dienal **1014**, itself a potential precursor to stannane **2045**. However, the enol triflate

2048 has not been reported in the literature, nor has any closely related structure. Therefore, a straightforward synthesis route to prepare this material was desirable.

E–1. SYNTHESIS OF THE C2–C7 HYDROXYCYCLOPENTENE CORE

The racemic enone **2055** was identified as an ideal entry point to the C2–C7 enol triflate **2048**, and the preparation of this substance is shown in Scheme II–15. Epoxidation of freshly cracked cyclopentadiene (**2049**) with 35% peracid acid according to Rideout's well established procedure[56] delivered cyclopentadiene monoepoxide (**2050**) in 36% yield and 92% purity. Although the epoxide was purified by distillation, the thermal instability of **2050** did result in the formation of trace amounts of cyclopent-3-enone and (*Z*)-penta-2,4-dienal, presumably via the zwitterion **2051**. Moreover, the relatively modest yield of **2050** was more than compensated for by the ability to conduct this reaction on large (0.4–0.5 mol) scale.

Without much delay, a purified sample of **2050** was exposed to catalytic palladium(0) in the presence of acetic acid[57] to provide *cis*-3-acetoxy-5-hydroxycyclopent-1-ene (**2052**) (Scheme II–15). Silylation of **2052** with TBSCl afforded the orthogonally protected diol **2053**[58] that, after subjection to methanolic K_2CO_3, yielded the secondary alcohol **2054**.[59] This material did not require further purification, and as a result was directly oxidized in crude form with finely powdered PCC to give the racemic enone **2055**[58] in good overall yield. As someone once told me, there's nothing like a good

---

56 Korach, M.; Nielsen, D. R.; Rideout, W. H. Dihydroxycyclopentene. *Org. Synth.* **1962**, *42*, 50–54.

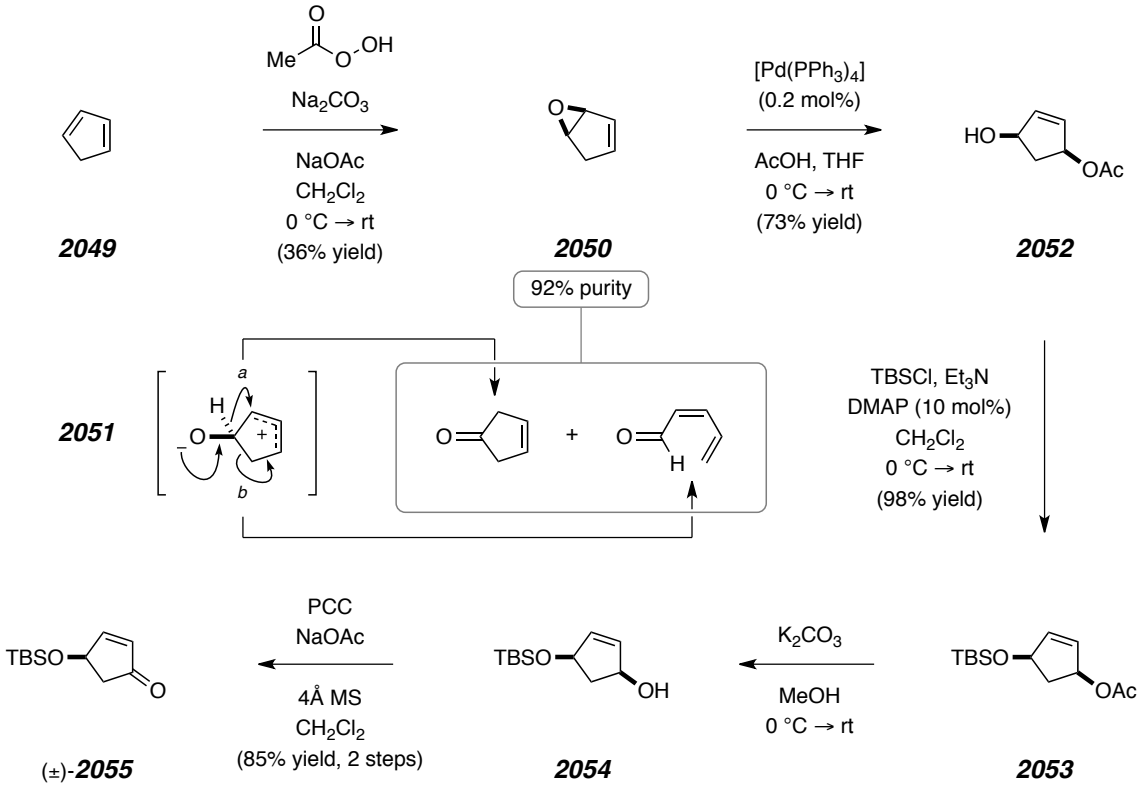
57 Deardorff, D. R.; Myles, D. C. Palladium(0)-catalyzed *syn*-1,4-Addition of Carboxylic Acids to Cyclopentadiene Monoepoxide: *cis*-3-Acetoxy-5-hydroxycyclopent-1-ene. *Org. Synth.* **1989**, *67*, 114–117.

58 An adaptation of the reported procedure: Paquette, L. A.; Earle, M. J.; Smith, G. F. (4*R*)-(+)-*tert*-Butyldimethylsiloxy-2-cyclopenten-1-one. *Org. Synth.* **1996**, *73*, 36–40.

59 Slight modification of the reported procedure: Shizuka, M.; Snapper, M. L. Selective Synthesis of *ent*-15-*epi*-F_{2t}-Isoprostane and a Deuterated Derivative. *Synthesis* **2007**, 2397–2403.

vacuum distillation. Indeed, each of the intermediates in this 5-step sequence was easily purified by this method.

Scheme II–15 | Synthesis of the racemic enone **2055** from cyclopentadiene (**2049**).

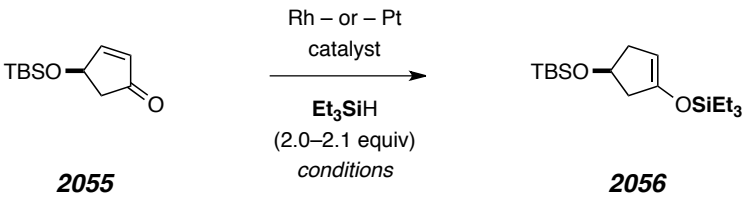


At the outset of these studies, it was anticipated that the TES enol ether derived from the enone **2055** could be employed for the regioselective generation of an enolate.[60] Thus, the catalytic hydrosilylation of **2055** in the presence of triethylsilane (Et_3SiH) was investigated (Table II–1). Although Wilkinson's catalyst [$(Ph_3P)_3RhCl$] is commonly

60 (a) Stork, G.; Hudrlik, P. F. Generation, Nuclear Magnetic Resonance Spectra, and Alkylation of Enolates from Trialkylsilyl Enol Ethers. *J. Am. Chem. Soc.* **1968**, *90*, 4464–4465. (b) Brown, M. K.; Hoveyda, A. H. Enantioselective Total Synthesis of Clavirolide C. Applications of Cu-Catalyzed Asymmetric Conjugate Additions and Ru-Catalyzed Ring-Closing Metathesis. *J. Am. Chem. Soc.* **2008**, *130*, 12904–12906.

employed to accomplish this task,[61] exposure of **2055** to this species gave rise to the TES enol ether **2056** in consistently low yields (entry 1). However, when the hydrosilylation was carried out under similar conditions with $Pt(DVTMDS)_2$ (Karstedt's catalyst) according to Johnson's method,[62] a substantial improvement in the yield was observed (entry 2). It was eventually discovered that the yield could be optimized when the reaction was conducted in solvent (*ca.* 1 M) (entries 3 and 4), wherein Et_2O was found to be superior. Noteworthy in entries 2, 3, and 4 of Table II–1 are the extremely low catalyst loadings that are required when $Pt(DVTMDS)_2$ was employed.

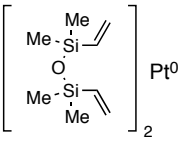
Table II–1 | Optimization of the catalytic hydrosilylation of **2055**.



2055 ***2056***

entry	catalyst	mol%	*conditions*	% yield
1	$(Ph_3P)_3RhCl$	1	neat, rt	48–52
2	$Pt(DVTMDS)_2$	~ 0.4	neat, 100 °C	71
3	$Pt(DVTMDS)_2$	~ 0.3	PhMe, rt	88
4	$Pt(DVTMDS)_2$	~ 0.2–0.3	Et_2O, 0 °C → rt	90–quant.

$Pt(DVTMDS)_2$



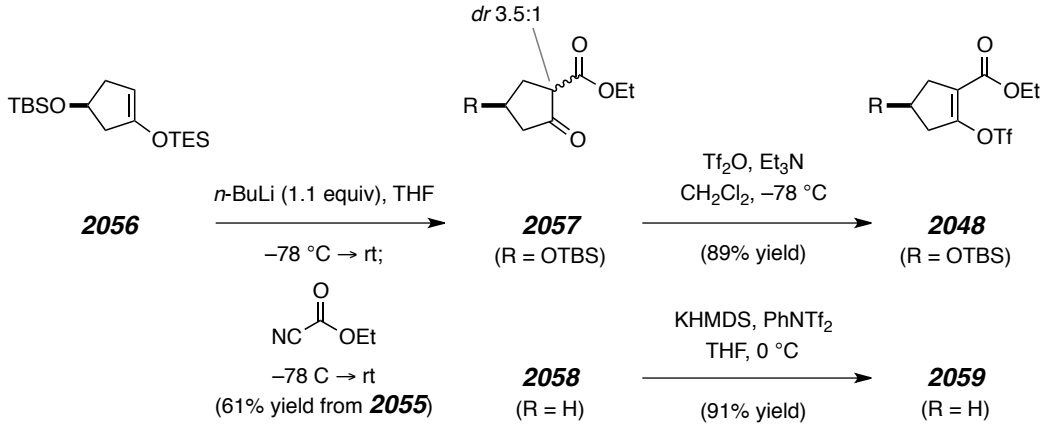
(Karstedt's catalyst)

61 (a) Ojima, I.; Nihonyanagi, M.; Kogure, T.; Kumagai, M.; Horiuchi, S.; Nakatsugawa, K. Reduction of Carbonyl Compounds via Hydrosilylation. I. Hydrosilylation of Carbonyl Compounds Catalyzed by Tris(triphenylphosphine)chlororhodium. *J. Organomet. Chem.* **1975**, *94*, 449–461. (b) Corey, E. J.; Su, W. Identification of a Crucial Substructural Unit for Thromboxane A_2 Receptor Binding. *Tetrahedron Lett.* **1990**, *31*, 2677–2680.

62 Johnson, C. R.; Raheja, R. K. Hydrosilylation of Enones: Platinum Divinyltetramethyldisiloxane Complex in the Preparation of Triisopropylsilyl and Triphenylsilyl Enol Ethers. *J. Org. Chem.* **1994**, *59*, 2287–2288.

In a reaction that is closely related to Stork's well known protocol,[60a] Brown and Hoveyda have demonstrated that the enolate derived from a cyclopentyl TES enol ether could be regioselectively generated by treatment with *n*-BuLi.[60b] This type of reactivity turned out to be applicable to **2056** as well (Scheme II–16). In the event, the lithium enolate was generated from **2056** (*n*-BuLi, 1.5 h, rt) and then exposed to ethyl cyanoformate (Mander's reagent[63]) at –78 °C. This procedure provided as the major product the *C*-acylated β-keto ester **2057** as a mixture of diastereomers that, more importantly, was formed at the exclusion of any *O*-acylated materials. It should be mentioned that **2057** could also be obtained by direct conjugate reduction of the enone **2055** (L-Selectride®, THF, –78 °C) followed by ethyl cyanoformate quench, but that these conditions delivered the desired product in lower yields and with less reproducibility (34–53% yield).

Scheme II–16 | Desilylative acylation of **2056** and formation of the target enol triflate **2048** from the β-keto ester **2057**, and preparation of the model enol triflate **2059**.



63 Mander, L. N.; Sethi, S. P. Regioselective Synthesis of β-Ketoesters from Lithium Enolates and Methyl Cyanoformate. *Tetrahedron Lett.* **1983**, *24*, 5425–5428.

Now that the β-keto ester **2057** was in hand, its subsequent conversion to the enol triflate **2048** was accomplished in high yield with the Tf_2O/Et_3N reagent combination (Scheme II–16). Additionally, it was realized that a simplified, more readily accessible analog of **2048** would be advantageous during subsequent exploratory synthesis studies. Therefore, the known enol triflate **2059**[64] was also prepared, but this time by treatment of a mixture of (commercially available) ethyl 2-oxocyclopentanecarboxylate (**2058**) and $PhNTf_2$ with KHMDS under Barbier-like conditions.

E–2. C7–C8 BOND CONSTRUCTION MODEL STUDIES (ROUTE **a**)

In order to establish whether or not C7–C8 bond construction via the Stille cross-coupling reaction would be a viable route to **2017**, a series of exploratory studies was initiated that emanated from the model C5-deshydroxyl enol triflate **2059** (Scheme II–17). This readily accessible substrate was reduced to the corresponding allylic alcohol with DIBAL-H and then subsequently converted to the mesylate **2060**. Displacement of this highly reactive electrophile with either NaI or LiBr cleanly delivered the allylic iodide **2061** or the allylic bromide **2062**, respectively, in good overall yield from the intermediate allylic alcohol.

It was anticipated that the allylic halides **2061** and **2062** could be used to alkylate lithiated dimethoxyacetonitrile[65] and that the resulting adducts would serve as precursors to the 2,2-methoxy aldehyde present in **2017** (via nitrile reduction[66] and hydrolysis). However, it was soon realized that, when either the lithium or potassium carbanions of dimethoxyacetonitrile were allowed to react with either **2061** or **2062**, rapid

---

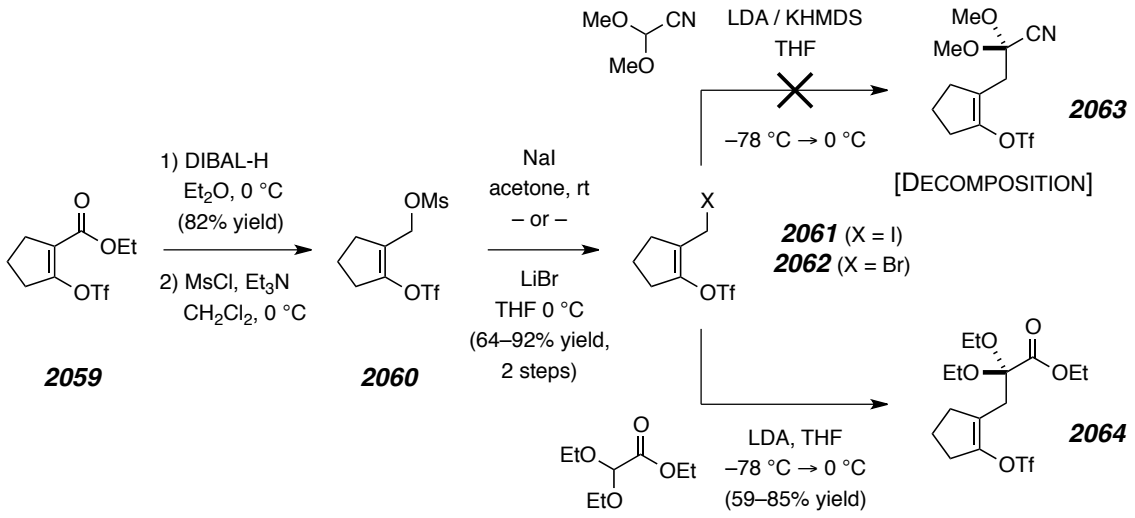
64 Ohe, T.; Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds with Organic Triflates. *J. Org. Chem.* **1993**, *58*, 2201–2208.

65 Utimoto, K.; Wakabayashi, Y.; Shishiyama, Y.; Inoue, M.; Nozaki, H. 2-Alkoxy and 2,2-Dialkoxy Nitriles from Acetals and Orthoesters–Exchange of Alkoxy into Cyano Group by Means of Cyanotrimethylsilane. *Tetrahedron Lett.* **1981**, *22*, 4279–4280.

66 Babler, J. H. An Expeditious Route to Monoprotected α-Keto Aldehydes with Control of Regiochemistry. *Synth. Commun.* **1989**, *19*, 355–358.

decomposition of the starting materials took place (Scheme II–17). Indeed, even attempts to alkylate these anions with benzyl- and cinnamyl bromide (with or without added HMPA) were thwarted by extensive starting material decomposition. Interestingly, the major by-products of the reaction of benzyl bromide with lithiated dimethoxy-acetonitrile were in fact *trans*- and *cis*-stillbene, which implicates α-deprotonation, rather than halide displacement, as the event that initiates decomposition. Fortunately, the lithium enolate of ethyl diethoxyacetate[40] was cleanly alkylated by both **2061** and **2062** to provide the 2,2-diethoxy ester **2064**.

Scheme II–17 | Preparation of the allylic halides **2061** and **2062** and their subsequent use as alkylating agents.



Since sufficient quantities of the dienal **1014** were already in hand at this stage, a synthesis route toward the trienyl stannane **2045** was designed that incorporated this intermediate (Scheme II–18). Thus, Seyferth–Gilbert homologation[67] of **1014** with the

67 (a) Seyferth, D.; Marmor, R. S.; Hilbert, P. Some Reactions of Dimethylphosphono-Substituted Diazoalkanes. $(MeO)_2P(O)CR$ Transfer to Olefins and 1,3-Dipolar Additions of $(MeO)_2P(O)C(N_2)R^1$. *J. Org. Chem.* **1971**, *36*, 1379–1386. (b) Gilbert, J. C.; Weerasooriya, U. Diazoethenes: Their

potassium anion derived from dimethyl (diazomethyl)phosphonate[68] provided the dienyne **2065**. Although the yield of this transformation was consistently low, it was nevertheless reproducible, and **2065** was produced with high isomeric purity. A palladium(0)-catalyzed hydrostannylation of this material under the conditions of Zhang and co-workers[69] {Bu_3SnH, cat. [$(Ph_3P)_2PdCl_2$]} gave rise to a 3:1 mixture of the terminal stannane **2045** and the internal (undesired) stannane **2066**.[70,71] A significant improvement in the ratio of these two species was realized when **2065** was exposed to the "mixed" higher order stannyl cyanocuprate[72] $(Bu_3Sn)(n\text{-Bu})Cu(CN)Li_2$ [derived from CuCN (1.0 equiv), *n*-BuLi (2.1 equiv), and then Bu_3SnH (2.1 equiv)] followed by a 1:1 MeOH/satd aq NH_4Cl quench at low temperature.[73]

Attempted Synthesis from Aldehydes and Aromatic Ketones by Way of the Horner–Emmons Modification of the Wittig Reaction. A Facile Synthesis of Alkynes. *J. Org. Chem.* **1982**, *47*, 1837–1845.

68 Brown, D. G.; Velthuisen, E. J.; Commerford, J. R.; Brisbois, R. G.; Hoye, T. R. A Convenient Synthesis of Dimethyl (Diazomethyl)phosphonate (Seyferth/Gilbert Reagent). *J. Org. Chem.* **1996**, *61*, 2540–2541.

69 Zhang, H. X.; Guibé, F.; Balavoine, G. Palladium- and Molybdenum-Catalyzed Hydrostannation of Alkynes. A Novel Access to Regio- and Stereodefined Vinylstannanes. *J. Org. Chem.* **1990**, *55*, 1857–1867.

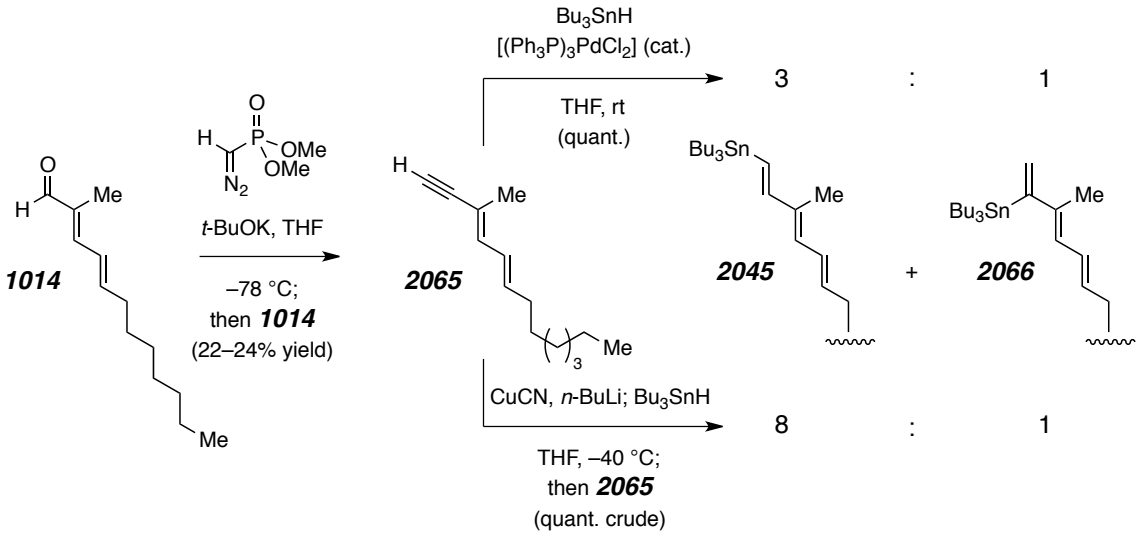
70 The following diagnostic ^{1}H NMR (500 MHz, $CDCl_3$) resonances were observed for **2066**: δ 5.89 [d, J = 2.0 Hz, 1H, $(Bu_3Sn)C{=}CH_2$] and 5.21 [d, J = 2.0 Hz, 1H, $(Bu_3Sn)C{=}CH_2$].

71 In addition to **2045** and **2066**, the reduced terminal olefin, which was presumably derived from protodestannylation of **2045**, was also observed (relative ratio *ca.* 2). Diagnostic ^{1}H NMR (500 MHz, $CDCl_3$) resonances for this species: δ 6.39 (dd, J = 10.5, 17.5 Hz, 1H, $CH{=}CH_{trans}H_{cis}$), 5.16 (d, J = 17.0 Hz, 1H, $CH{=}CH_{trans}H_{cis}$), and 5.00 (d, J = 11.0 Hz, 1H, $CH{=}CH_{trans}H_{cis}$).

72 Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. Transmetalation Reactions of Higher Order Cyanocuprates: Direct Formation of Trialkyltin Cuprates from Tin Hydrides which Bypasses Organolithium Intermediates. *Tetrahedron Lett.* **1989**, *30*, 2065–2068.

73 The regio- and stereoselectivity of $(Bu_3Sn)(n\text{-Bu})Cu(CN)Li_2$-mediated stannylcupration of enynes has been studied. See: Le Ménez, P.; Berque, I.; Fargeas, V.; Ardisson, J.; Pancrazi, A. New Synthetic Approach to the Western Part C_{10}–C_{15} of (±)-Des-Epoxy-Rosaramycin. *Synlett* **1994**, 998–1000.

Scheme II–18 | Seyferth–Gilbert homologation of the enal **1014** and hydrostannylation studies of the resulting dienyne **2065**.



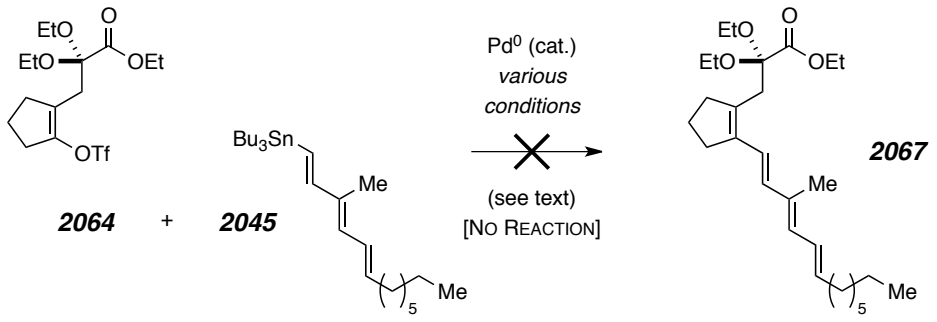
The successful preparation of **2064** and **2045** was quickly rendered a moot point when it was discovered that the former species was completely inert under a small sampling of cross-coupling conditions: a) cat. [$Pd(PPh_3)_4$], LiCl, THF or 1,4-dioxane, heat; b) cat. [$Pd_2(dba)_3$], cat. $AsPh_3$, NMP, heat; c) cat. [$Pd(PPh_3)_4$], copper(I) thiophene-2-carboxylate (CuTC[74]), NMP[75] (Scheme II–19). In each of these instances, analysis of the crude reaction profiles by ^{1}H NMR spectroscopy revealed that the vinyl triflate **2064** had been recovered unharmed. Moreover, that the trienyl stannane **2045** was being unproductively destroyed under the reaction conditions was implied by its unmistakable *absence* from these crude reaction mixtures.

---

74 Allred, G. D.; Liebeskind, L. S. Copper-Mediated Cross-Coupling of Organostannanes with Organic Iodides at or Below Room Temperature. *J. Am. Chem. Soc.* **1996**, *118*, 2748–2749.

75 Fürstner, A.; Funel, J. –A.; Tremblay, M.; Bouchez, L. C.; Nevado, C.; Waser, M.; Ackerstaff, J.; Stimson, C. C. A Versatile Protocol for Stille–Migita Cross Coupling Reactions. *Chem. Commun.* **2008**, 2873–2875.

Scheme II–19 | Unproductive Stille cross-coupling of triflate **2064** and stannane **2045**.



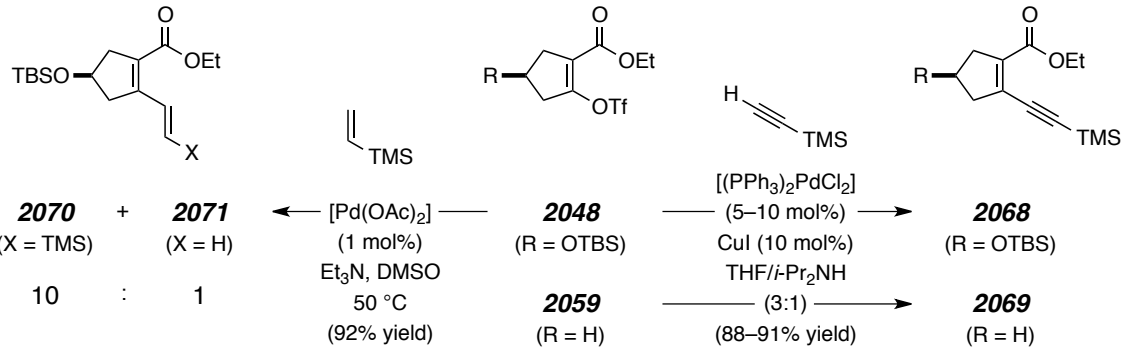
On the basis of the observations of Scheme II–19, one might reasonably surmise that the rate of oxidative insertion of palladium(0) into the C–O triflate bond of **2064** is simply too slow. Indeed, the outcome of the attempted Sonogashira cross-coupling of **2064** with (trimethylsilyl)acetylene {cat. [$(PPh_3)_2PdCl_2$], cat. CuI, THF/*i*-Pr_2NH (3:1)}, which resulted only in the isolation of unreacted starting material and 1,4-bis(trimethylsilyl)buta-1,3-diyne [i.e., the oxidative coupling product of (trimethylsilyl)acetylene], would seem to support this notion.

E–3. C10–C11 ASSEMBLY VIA SEQUENTIAL CROSS-COUPLING (ROUTE **b**)

A reassessment of the previously explored synthetic sequence lead to the identification of the enol triflate **2048** and the model substrate **2059** as far more competent partners in a palladium(0)-catalyzed cross-coupling reaction. Insofar as C–O oxidative insertion is the problematic step for a substrate such as **2064** (cf. Scheme II–19), then a substantial increase in the rate of cross-coupling would be expected when a β-carboethoxy group (relative to the triflate C–O bond) is present (as is the case for **2048** and **12059**). This expectation was indeed an accurate reflection of experimental reality

(Scheme II–20). Both **2048** and **2059** smoothly underwent Sonogashira cross-coupling[76] with (trimethylsilyl)acetylene to provide the conjugated ynoates **2068** and **2069**. Additionally, Heck cross-coupling of **2048** with trimethyl(vinyl)silane under Hallberg's conditions[77] cleanly delivered the dienoate **2070**. Although a small amount of the reduced terminal olefin **2071** was observed, it was readily removed by flash chromatography at a later stage (*vide infra*).

Scheme II–20 | Efficient Sonogashira and Heck cross-coupling reactions with the enol triflates **2048** and **2059**.



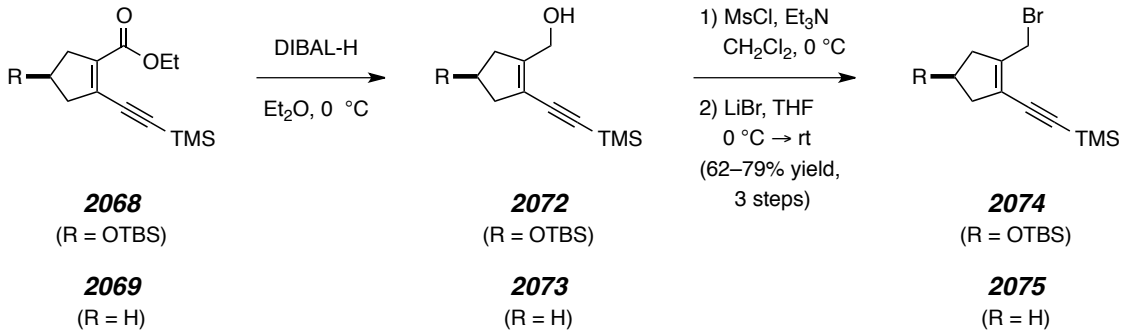
Just as the ester **2059** was converted into the allylic bromide **2062**, so too were the ynoates **2068** and **2069** transformed into **2074** and **2075** (Scheme II–21). The intermediate alcohols (**2072** and **2073**) that were produced upon DIBAL-H reduction were typically taken forward in crude form and converted into the corresponding allylic mesylates. Subsequent exposure to these species to LiBr afforded the allylic bromides **2074** and **2075**, both of which proved to be stable, storable intermediates.

---

[76] Gebauer, O.; Brückner, R. β-Alkoxycarbonyl Enol Triflates as Precursors to Stereopure 3-Ene-1,5-diyne Building Blocks for the Chromophores of Neocarzinostatin, C-1027, Kedarcidin, Maduropeptin, and N1999A2. *Synthesis* **2000**, 588–602.

[77] Karabelas, K.; Hallberg, A. Synthesis of 1-Trimethylsilyl 1,3-Dienes by the Palladium-Catalyzed Reaction of Trimethylvinylsilane with Vinyl Iodides/Silver Nitrate or Vinyl Triflates. *J. Org. Chem.* **1988**, *53*, 4909–4914.

Scheme II–21 | Synthesis of the allylic bromides **2074**/**2075** from the esters **2068**/**2069**.



2068
(R = OTBS)

2069
(R = H)

2072
(R = OTBS)

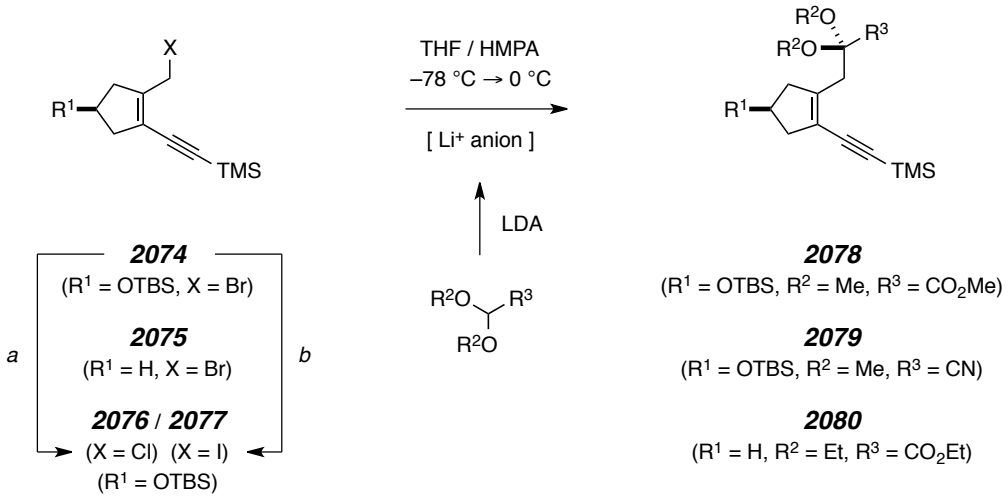
2073
(R = H)

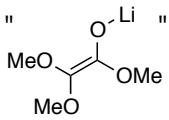
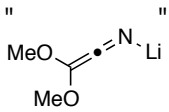
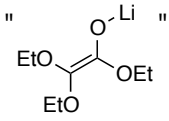
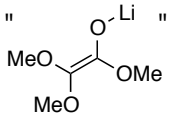
2074
(R = OTBS)

2075
(R = H)

The alkylation of an acyl anion equivalent by either **2074** or **2075** proved to be both far more irreproducible and less trivial than was experienced in the conversion of **2062** to **2064** (cf. Scheme II–17), and thus an attempt was made to explore and/or optimize some of the aspects of this chemistry (Table II–2). When the alkylation of lithiated methyl dimethoxyacetate with **2074** was attempted under similar conditions to that described previously (i.e., no HMPA, entry 1), the variation in the isolated yield of the 2,2-dimethoxy ester **2078** was over 40%. Although an incremental increase in the equivalents of HMPA (entries 2–4) did result in an improved isolated yield on certain occasions (>95% yield, entry 4), at other times this value could drop to as low as 21% (entry 3). The fact that the isolated yield of **2078** could be neither reliably predicted nor controlled is best illustrated by the following: Two experiments were run side-by-side on the same day, both of which were conducted with the allylic bromide **2074** (0.13 mmol), lithiated methyl dimethoxyacetate (10 equiv), and HMPA (100 equiv), that gave rise to **2078** with two very different isolated yields–67% and >95%.

Table II–2 | Exploration and attempted optimization of the alkylation of various acyl anion equivalents by the allylic halides **2074**–**2077** to produce the 2,2-dialkoxy esters **2078**–**2080**.



entry	SM #	[Li^+ anion] (5-10 equiv)	HMPA (equiv)	expected pdt	% yield
1	***2074***		none	***2078***	33 – 76
2	***2074***		20	***2078***	45
3	***2074***		50	***2078***	21 – 72
4	***2074***		100	***2078***	41 – >95
5	***2074***		20	***2079***	[DECOMP.]
6	***2075***		none	***2080***	48 – 49
7	***2076***		40	***2078***	[DECOMP.]
8	***2077***		50	***2078***	[DECOMP.]

[a] $BnEt_3N^+ Cl^-$, CH_3CN (91% yield). [b] NaI, acetone (97% yield).

The attempted alkylation of lithiated dimethoxyacetonitrile with **2074** resulted in complete decomposition of the starting material (Table II–2, entry 5), which again affirms the rather unforgiving nature of this particular carbanion (cf. Scheme II–17). The reaction of the model allylic bromide **2075** with lithiated ethyl diethoxyacetate (entry 6), although no less capricious and low yielding, did provide a 2,2-diethoxy ester (**2080**) that would be useful for exploratory studies. Finally, both the allylic chloride **2076** (entry 7) and iodide **2077** (entry 8) were unproductively consumed under reaction conditions that were similar to those employed in entry 3.

Although Roush's 1,1-dibromoolefin Suzuki protocol[55] relies entirely upon vinyl boronates as coupling partners, the analogous Stille variant, which employs vinyl and aryl stannanes, is known.[78] Using the 2,2-diethoxy ester **2080** as a test substrate, the preparation of a vinyl organometallic donor that could be utilized in either of these types of Suzuki or Stille reactions was explored (Scheme II–22). The free alkyne **2081** was liberated from **2080** by exposure of the latter species to TBAF in THF. Hydrostannylation of **2081**, again under the palladium(0)-catalyzed conditions of Zhang and co-workers,[69] provided the undesired internal vinyl stannane **2083**;[79a] only a trace amount of the terminal stannane **2084**[79b] was detected (left hand portion of Scheme II–22). This observation was particularly surprising since, as the reader will recall, the hydrostannylation of the dienyne **2065** under essentially identical conditions was *not* highly regioselective, and in fact favored the formation of the terminal trienyl stannane **2045** (see Scheme II–18). The hydrostannylation of 1-bromo-1-alkynes is a tactic that is often used to overcome this type of regioselectivity issue.[69,80] Accordingly, **2080** was

---

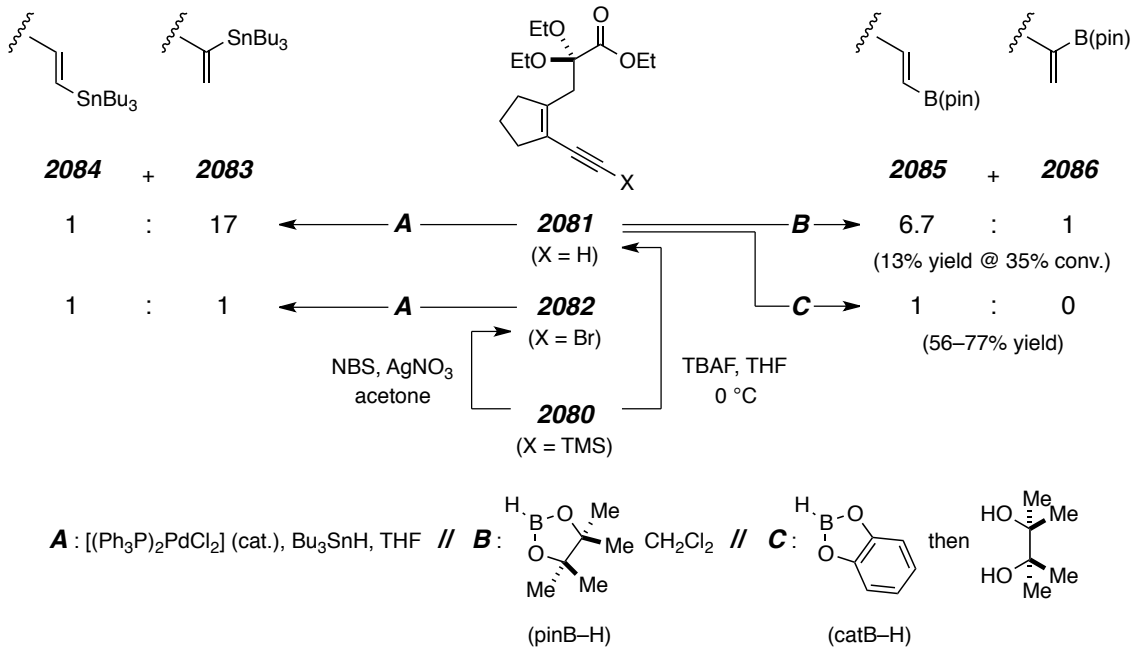
78 Shen, W.; Wang, L. The Stille Reaction of 1,1-Dibromo-1-alkenes: Preparation of Trisubstituted Alkenes and Internal Alkynes. *J. Org. Chem.* **1999**, *64*, 8873–8879.

79 The diagnostic ^{1}H NMR (500 MHz, $CDCl_3$) resonances that were observed for each of these species are provided. (a) **2083**: δ 5.63 [d, *J* = 3.0 Hz, 1H, $(Bu_3Sn)C{=}CH_2$] and 5.28 [d, *J* = 3.5 Hz, 1H, $(Bu_3Sn)C{=}CH_2$]. (b) **2084**: δ 6.83 (d, *J* = 19.0 Hz, 1H $Bu_3SnCH{=}CH$) and 6.07 (d, *J* = 19.0 Hz, 1H, $Bu_3SnCH{=}CH$).

80 Boden, C. D. J.; Pattenden, G.; Ye, T. Palladium-Catalyzed Hydrostannylations of 1-Bromoalkynes. A Practical Synthesis of (*E*)-1-Stannylalk-1-enes. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2417–2419.

converted into the corresponding bromoalkyne **2082**, but, unfortunately, hydrostannylation of this material provided a 1:1 mixture of the desired and undesired vinyl stannane regioisomers.

Scheme II–22 | Exploration of hydrostannylation and hydroboration chemistry with the free alkyne **2081** and the bromo alkyne **2082**.



Efforts immediately shifted toward an alkyne hydroboration strategy (right hand portion of Scheme II–22). Exposure of **2081** to pinacolborane (pinB–H) according to Knochel's *in situ* protocol[81] afforded, albeit at very low conversion, a mixture of the terminal (**2085**) and internal (**2086**[82]) vinyl boronates. This outcome was obviously

81 Tucker, C. E.; Davidson, J.; Knochel, P. Mild and Stereoselective Hydroborations of Functionalized Alkynes and Alkenes Using Pinacolborane. *J. Org. Chem.* **1992**, *57*, 3482–3485.

82 The following diagnostic ^{1}H NMR (500 MHz, $CDCl_3$) resonances were observed for **2086**: δ 5.85 [d, J = 3.5 Hz, 1H, (Bpin)C=CH_2] and 5.61 [d, J = 3.5 Hz, 1H, (Bpin)C=CH_2].

unsatisfactory. However, when **2081** was allowed to react with neat catecholborane[83] (catB–H), a highly regioselective hydroboration took place that, after transesterification of the labile catechol ester with pinacol, gave rise to **2085** as a single regioisomer exclusively to the limit of ^{1}H NMR spectroscopic detection.

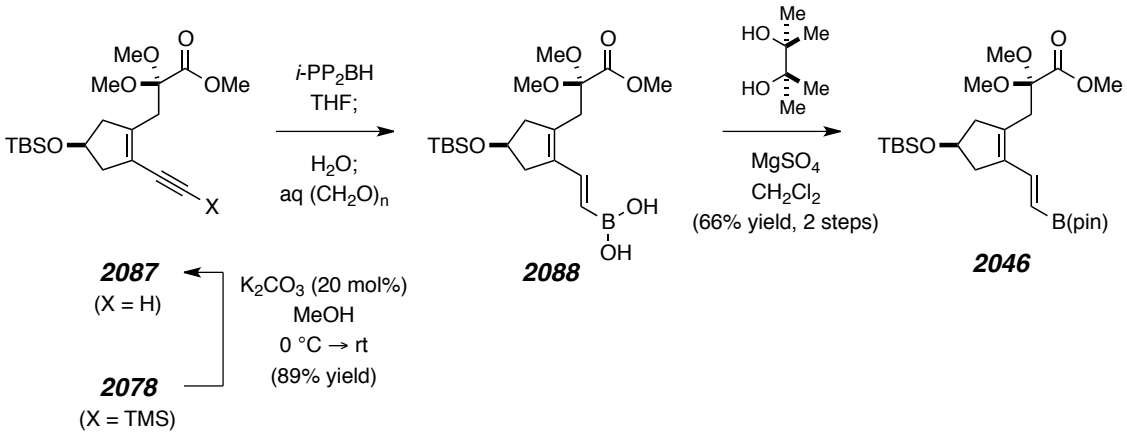
Extension of the above chemistry to the 2,2-dimethoxy ester **2078** was not without some modifications (Scheme II–23). Because TBAF-induced alkyne deprotection was obviously precluded, an alternative, but no less high yielding, method to accomplish this transformation was deployed (cat. K_2CO_3, MeOH, 89% yield). Noteworthy here was the vastly inferior isolated yield (47%) that was obtained when an alternative method [$AgNO_3$, THF/H_2O/EtOH/2,6-lutidine (1:1:1:0.1); then aq KH_2PO_4] was used to produce **2087**. Finally, it was found that the hydroboration of **2087** could be more reliably carried with the agency of di(isopropylprenyl)borane (*i*-PP_2BH, the Snieckus reagent [84]). This two-pot process, which delivered the pinacol boronate **2046** in good overall yield and with exquisite isomeric purity, entailed isolation of the intermediate boronic acid **2088** and subsequent esterification with pinacol.

---

83 Brown, H. C.; Gupta, S. K. Hydroboration. XXXIX. 1,3,2-Benzodioxaborole (Catecholborane) as a New Hydroboration Reagent for Alkenes and Alkynes. A General Synthesis of Alkane- and Alkeneboronic Acids and Esters via Hydroboration. Directive Effects in the Hydroboration of Alkenes and Alkynes with Catecholborane. *J. Am. Chem. Soc.* **1975**, *97*, 5249–5255.

84 Kalinin, A. V.; Scherer, S.; Snieckus, V. Di(isopropylprenyl)borane: A New Hydroboration Reagent for the Synthesis of Alkyl and Alkenyl Boronic Acids. *Angew. Chem. Int. Ed.* **2003**, *42*, 3399–3404.

Scheme II–23 | Synthesis of the key vinyl pinacol boronate **2046** via the alkyne **2087**.



The conditions developed by Roush and co-workers for the 1,1-dibromoolefin Suzuki reaction, which employ aq TlOH[85] or, much more preferably, neat TlOEt[55b] as the base, have been shown to be quite tolerant of both acetates and carboxylic esters.[55a] One could be reasonably confident, then, that these reaction conditions would be tolerant of the 2,2-dialkoxy esters present in the vinyl boronates **2046** and **2085**. In addition to TlOEt, an alternative thallium(I) base, namely, Tl_2CO_3, has also been shown to have a beneficial influence on both the rate of the Suzuki reaction[86] and the regioselectivity of the 1,1-dibromoolefin variant.[87] Thus, the use of both of these bases was explored in the preparation of the vinyl bromides **2091** and **2092** (Scheme II–24). The requisite 1,1-dibromoolefin **2047** was trivially prepared from (*E*)-2-deceanl (**2036**) by the Corey-Fuchs

---

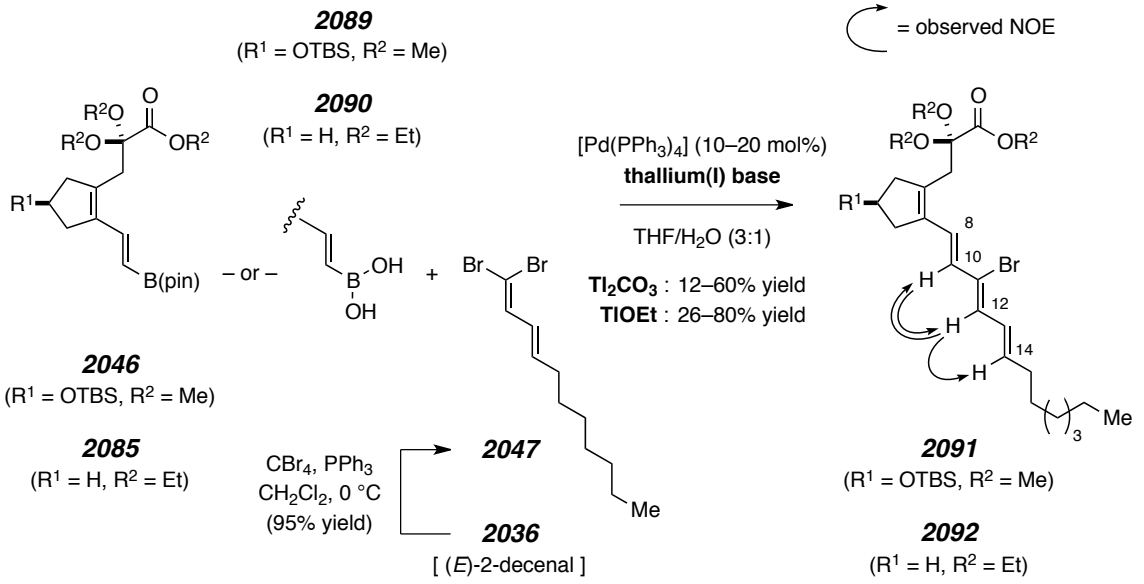
85 Uenishi, J.; Beau, J. –M.; Armstrong, R. W.; Kishi, Y. Dramatic Rate Enhancement of Suzuki Diene Synthesis: Its Application to Palytoxin Synthesis. *J. Am. Chem. Soc.* **1987**, *109*, 4756–4758.

86 Markó, I. E.; Murphy, F.; Dolan, S. Efficient Synthesis of the Left-Hand Subunit of Milbemycin β3 Using a Suzuki Coupling Reaction. *Tetrahedron Lett.* **1996**, *37*, 2507–2510.

87 Evans, D. A.; Starr, J. T. A Cycloaddition Cascade Approach to the Total Synthesis of (–)-FR182877. *J. Am. Chem. Soc.* **2003**, *125*, 13531–13540.

homologation.[88] Generally speaking, the isolated yields of the vinyl bromides **2091**/**2092** were slightly better when the pinacol boronic esters **2046**/**2085** were employed (29–80%) rather than the corresponding boronic acids **2088**/**2089** (12–40%). But above all, neither of theses substrates nor any one base in particular (cf. isolated yields with TlOEt vs. Tl_2CO_3) provided satisfactory yields in a reproducible fashion. It should be mentioned that the carboxylic acids derived from either **2046**/**2085** or **2091**/**2092** have never been observed (by analysis of the crude reaction profiles by ^{1}H NMR spectroscopy) or isolated from these reactions. However, the empirical yield data and the author's experience have both suggested that base-induced decomposition of these substrates does occur, but through a pathway that likely *does not* involve ester hydrolysis.

Scheme II–24 | The Suzuki reactions of the pinacol boronates **2046**/**2085** and boronic acids **2089**/**2090** with the 1,1-dibromoolefin **2047**.



88 Corey, E. J.; Fuchs, P. L. A Synthetic Method for Formyl → Ethynyl Conversion (RCHO → RC≡CH or RC≡CR′). *Tetrahedron Lett.* **1972**, *13*, 3769–3772.

Nevertheless, the vinyl bromides **2091** and **2092** were isolated as essentially single geometric isomers; the former of these compounds was subjected to the full battery of 1-D and 2-D NMR spectroscopic analyses (i.e., ^{1}H, ^{13}C, HMQC, and HMBC) that resulted in the complete structural assignment shown in Table II–4. The latter species–namely, **2092**–displayed spectral properties that were in very close agreement with those observed for **2091**, and thus its constitution rests upon firm ground as well. Of particular interest at this stage was the configuration of the newly forged C10–C11 bond; specifically, was the relative configuration of the polyene (*E*,*Z*,*E*) or (*E*,*E*,*E*)? The magnitudes of the $^{3}J_{H8,H10}$ and $^{3}J_{H13,H14}$ coupling values (both *ca.* 14.5 Hz) made it clear that the $\Delta^{8,10}$ and $\Delta^{13,14}$ olefins, as expected, possessed the (*E*)-configuration. The (*Z*)-configuration of the $\Delta^{11,12}$ olefin, on the other hand, was definitely established by a 1-D gradient NOE (GOESY) study. It was empirically determined that C_6D_6, rather than $CDCl_3$, provided the greatest dispersion of the individual olefinic resonances; thus, irradiation of H12 in this solvent clearly showed an enhancement of the resonances corresponding to H10 and H14 (Scheme II–24).

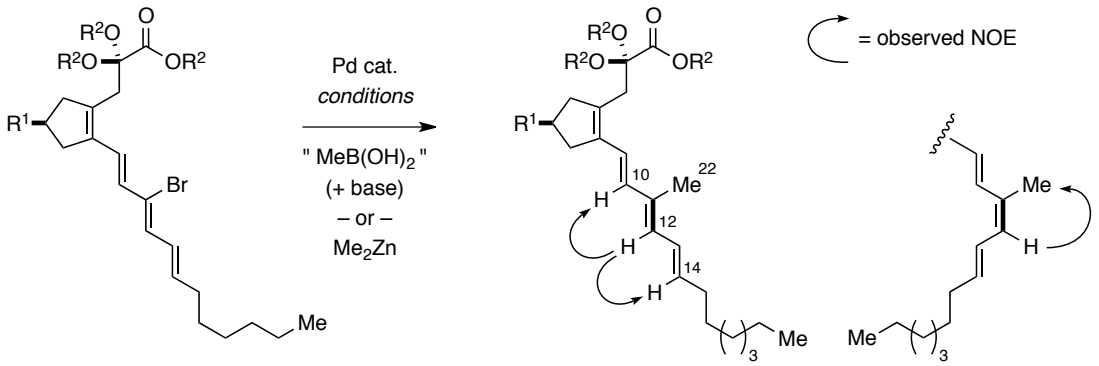
The opportunity to evaluate the palladium(0)-catalyzed methylation of the vinyl bromide **2091**, perhaps being the most crucial transformation in the synthetic sequence leading to the 2,2-dimethoxy aldehyde **2017**, was now at hand (Table II–3). Encouraged by a recent report from Gray and co-workers[89] regarding the methylation of aryl halides and the successful use of this methodology by Evans and Starr,[87] the trisubstituted olefin within **2017** was envisioned to arise via Suzuki cross-coupling of **2091** with Cs_2CO_3/trimethylboroxine [$Me_3B_3O_3$, a latent form of $MeB(OH)_2$]. In the event (entry 1), the reaction did indeed proceed to give rise to the desired product **2093**, but, annoyingly, this material was isolated as an inseparable mixture (7:1) of (11*E*)- and (11*Z*)-isomers. Similarly, when the model compound **2092** was permitted to react under similar

---

89 Gray, M.; Andrews, I. P.; Hook, D. F.; Kitteringham, J.; Voyle, M. Practical Methylation of Aryl Halides by Suzuki–Miyaura Coupling. *Tetrahedron Lett.* **2000**, *41*, 6237–6240.

conditions (entry 2), again an isomeric mixture (*ca.* 4:1) of **2094**, this time slightly enriched in the (11*Z*) isomer, was obtained.

Table II–3 | Installation of the C22 vinyl methyl group by Suzuki and Negishi cross-coupling reactions of **2091** and **2092** produced (11*E*)- and (11*Z*)-**2093**/**2094**.



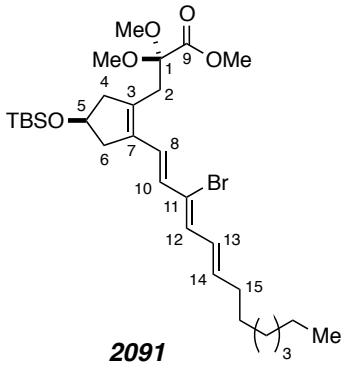
2091 (R¹ = OTBS, R² = Me) — (11*E*)-***2093*** + (11*Z*)-***2093***

2092 (R¹ = H, R² = Et) — (11*E*)-***2094*** + (11*Z*)-***2094***

entry	SM #	Pd cat.	donor	*conditions*	(*E*) : (*Z*)	pdt (% yield)
1	***2091***	$[Pd(dppf)Cl_2]$	$Me_3B_3O_3$ + Cs_2CO_3	DMF/H_2O 80 °C	7 : 1	***2093*** (46[a])
2	***2092***	$[Pd(dppf)Cl_2]$	$Me_3B_3O_3$ + Cs_2CO_3	DMF/H_2O 80 °C	3.2–4 : 1	***2094*** (41–53)
3	***2091***	PEPPSI™-IPr	Me_2Zn	THF 0 °C → rt	*ca.* 13 : 1[b]	***2093*** (67)
4	***2091***	$Pd[P(t\text{-}Bu)_3]_2$	Me_2Zn	THF 0 °C → rt	10–15 : 1	***2093*** (57–86)

[a] 67% yield based on recovered starting material. [b] At least 2 other isomeric components were present.

Table II–4 | Carbon (^{13}C) and proton (^{1}H) NMR spectroscopic data for **2091** in $CDCl_3$ at 125 and 500 MHz, respectively.[a]



2091

ATOM	CARBON	PROTON			HMBC
#	δ_C	δ_H	mult.	*J* [Hz]	(from ^{1}H → ^{13}C-#)
1	102.6	---	---	---	---
2	33.7	2.90	ABq	14.0	1, 3, 4, 9
3	134.8	---	---	---	---
4	47.4	2.42	dd	4.0, 18.0	3, 5
		2.86	dd	6.5, 18.0	3, 6
5	71.0	4.45	dddd	4.5, 4.5, 7.0, 7.0	
6	43.1	2.38	dd	4.0, 16.0	5, 7
		2.70	dd	7.5, 15.5	3, 4
7	135.4	---	---	---	---
8	126.7	6.83	d	14.5	3, 6, 10, 11
9	168.8	---	---	---	---
10	129.0	6.10	d	14.5	7, 11, 12
11	123.2	---	---	---	---
12	132.1	6.47	d	10.0	11, 13, 14
13	128.7	6.51	dddd	1.5, 1.5, 10.5, 14.0	11, 15
14	140.2	5.95	ddd	6.5, 6.5, 14.5	12, 15
15	33.5	2.16	dddd	1.5, 7.5, 7.5, 7.5	13, 14

[a] The ^{13}C and ^{1}H NMR chemical shifts for the methyl ester (CO_2CH_3), dimethyl ketal [$(CH_3O)_2C$], saturated alkyl side chain (16–21), and silyl ether [$(CH_3)_3CSi(CH_3)_2$] atoms have been excluded. For a complete listing of all chemical shifts, see the EXPERIMENTAL SECTION.

This type of isomerization is not without precedent; in fact, Negishi and co-workers[90] have reported that the cross-coupling reactions of 2-bromo-1,3-dienes occur with essentially complete *inversion* of configuration at the Br-bearing center. They have further shown that these cross-coupling reactions can be directed to proceed with *retention* of configuration when either bulky phosphines (e.g., *t*-Bu_3P[91]) or NHC-based ligands are employed.[92] When the cross-coupling of **2091** with Me_2Zn was carried out in the presence of PEPPSI™-IPr–an NHC-based palladium(II) precatalyst[93]–a noticeable improvement in the (11*E*)- (11*Z*)-**2093** ratio was observed (entry 3). However, due to the presence of *at least* two other isomeric components, this ratio could not be accurately measured, nor could the relative abundance or configuration of the minor components be established. Finally, the utilization of $Pd[P(t\text{-}Bu)_3]_2$ in place of PEPPSI™-IPr (entry 4) induced a cleaner and higher yielding transformation, but nonetheless gave rise to varying amounts of the undesired isomer (11*Z*)-**2093**.

The constitution of the model tetraene (11*E*)-**2094** and, by close spectral comparison, (11*E*)-**2093**, was ascertained through analysis of 1-D and 2-D NMR data (i.e., ^1H, ^{13}C, HMQC, HMBC, and COSY), and the results of these experiments are complied in Table II–5. In a similar manner to that described for the characterization of **2091** (cf. Table II–4), the $^3J_{H8,H10}$ and $^3J_{H13,H14}$ coupling values strongly supported the *trans* relationship between H8/H10 and H13/H14. That the major isomer (11*E*)-**2094**

---

90 Zeng, X.; Hu, Q.; Qian, M.; Negishi, E. Clean Inversion of Configuration in the Pd-Catalyzed Cross-Coupling of 2-Bromo-1,3-dienes. *J. Am. Chem. Soc.* **2003**, *125*, 13636–13637.

91 Dai, C.; Fu, G. C. The First General Method for Palladium-Catalyzed Negishi Cross-Coupling of Aryl and Vinyl Chlorides: Use of Commercially Available $Pd(P(t\text{-}Bu)_3)_2$ as a Catalyst. *J. Am. Chem. Soc.* **2001**, *123*, 2719–2724.

92 Zeng, X.; Qian, M.; Hu, Q.; Negishi, E. Highly Stereoselective Synthesis of (1*E*)-2-Methyl-1,3-dienes by Palladium-Catalyzed *trans*-Selective Cross-Coupling of 1,1-Dibromo-1-alkenes with Alkenylzinc Reagents. *Angew. Chem. Int. Ed.* **2004**, *43*, 2259–2263.

93 O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. Easily Prepared Air- and Moisture-Stable Pd–NHC (NHC = *N*-Heterocyclic Carbene) Complexes: A Reliable, User-Friendly, Highly Active Palladium Precatalyst for the Suzuki–Miyaura Reaction. *Chem. Eur. J.* **2006**, *12*, 4743–4748.

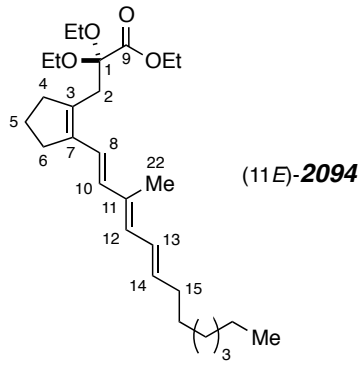
possessed the indicated $\Delta^{11,12}$ configuration was determined by a GOESY experiment, wherein irradiation of the resonance corresponding to H12 elicited an enhancement of the resonances corresponding to H10 and H14. Although the minor isomer (11*Z*)-**2094**[94a,c] was not separable, all of its olefinic resonances could be readily discerned from the major component [as were all but one of those belonging to (11*Z*)-**2093**[94b,c]]. In particular, irradiation of H12 during a GOESY experiment resulted in an enhancement of the resonance corresponding to H22, which unambiguously established their *cis* relationship.

At present, a plausible mechanism by which 2-bromo-1,3-dienes of the type **2091** and **2092** might give rise to isomeric products mixtures [i.e., (11*Z*)-**2093** and **2094**, respectively] under palladium(0)-catalyzed cross-coupling conditions has not appeared in the literature. One of the unusual features of the chemistry described in Table II–3 is that inversion of configuration occurs primarily at the Br-bearing carbon atom (which, in this instance, is C11). This observation is entirely consistent with the report of Negishi and co-workers,[90,92] wherein they further established that a conjugated C=C bond that was allylic to the Br-bearing carbon atom was required for (partial) inversion. Moreover, they also showed that this inversion process was suppressed in substrates that contained a conjugated C=C bond that was *homo*allylic to the Br-bearing carbon atom.[90] Both of these structural requirements are satisfied by the $\Delta^{8,10}$ and $\Delta^{13,14}$ olefins, respectively, within **2091** and **2092**.

---

94 Diagnostic ^{1}H NMR (500 MHz, $CDCl_3$) resonances for (11*Z*)-**2094** and (11*Z*)-**2093** are provided. (a) (11*Z*)-**2094**: δ 6.67 (d, *J* = 15.5 Hz, 1H, H8), 6.50 (d, *J* = 15.5 Hz, 1H, H10), 6.50 (dddd, *J* = 1.5, 1.5, 11.0, 15.0 Hz, 1H, H13), 5.93 (d, *J* = 11.5 Hz, 1H, H12), 5.67 (ddd, *J* = 7.5, 7.5, 15.0 Hz, 1H, H14), and 1.92 (s, 3H, H22). (b) (11*Z*)-**2093**: δ 6.65 (d, *J* = 16.5 Hz, 1H, H8), 6.50 (dddd, *J* = 1.5, 1.5, 11.0, 15.0 Hz, 1H, H13), 5.95 (d, *J* = 11.0 Hz, 1H, H12), 5.68 (ddd, *J* = 7.0, 7.0, 14.5 Hz, 1H, H14), and 1.91 (s, 3H, H22). (c) In both instances, the remaining ^{1}H NMR resonances were obscured by the major components, (11*E*)-**2094** and (11*E*)-**2093**, respectively.

Table II–5 | ^{13}C and ^{1}H NMR spectroscopic data for (11*E*)-**2094** in $CDCl_3$ at 125 and 500 MHz, respectively.[a]



(11*E*)-***2094***

ATOM	CARBON	PROTON			HMBC	COSY
#	δ_C	δ_H	mult.	*J* [Hz]	(from $^{1}H \rightarrow {}^{13}C$-#)	(from $^{1}H \rightarrow {}^{1}H$-#)
1	102.0	---	---	---	---	---
2	34.5	2.88	dd	1.5, 1.5	1, 3, 4, 7, 9	4, 6
3	135.2	---	---	---	---	---
4	37.2	2.51	dd	7.0, 7.0	3, 5, 7	2, 5
5	22.0	1.79	dddd	7.5, 7.5, 7.5, 7.5	3, 4, 6, 7	4, 6
6	32.9	2.45	dd	7.5, 7.5	3, 5, 7	2, 5
7	138.2	---	---	---	---	---
8	121.4	6.48	d	15.5	3, 6, 7, 11	10
9	169.1	---	---	---	---	---
10	134.3	6.17	d	15.5	7, 11, 12, 22	8
11	133.7	---	---	---	---	---
12	131.4	6.07	d	11.0	10, 13, 14, 22	13, 22
13	127.1	6.39	dddd	1.5, 1.5, 11.0, 15.0	n/o[b]	12, 14, 15
14	136.0	5.74	ddd	7.0, 7.0, 15.0	12, 15	13, 15
15	33.4	2.14	br ddd	7.5, 7.5, 7.5	13, 14	14, 16
22	12.9	1.91	d	1.0	11, 12	12

[a] The ^{13}C and ^{1}H NMR chemical shifts for the ethyl ester ($CO_2CH_2CH_3$), diethyl ketal [$(CH_3CH_2O)_2C$], and saturated alkyl side chain (16–21) atoms have been excluded. For a complete listing of all chemical shifts, see the EXPERIMENTAL SECTION.

[b] No HMBC correlations were observed.

A reasonable, albeit speculative, mechanistic proposal has been put forth in Scheme II–25. What this mechanism must account for is the interconversion (perhaps equilibration?) of the isomeric *cis*- and *trans*-palladium(II) complexes **2095** and **2096**, respectively, that ultimately give rise, via transmetalation and reductive elimination, to the observed products [e.g., (11*E*)- and (11*Z*)-**2093**, respectively]. Furthermore, one would expect[95] these species to be in equilibrium with their corresponding (alkylidene-π-allyl)palladium(II) complexes **2097** and **2100**, respectively. Negishi was quick to point out,[90] however, that further isomerization of these intermediates through the universally accepted π-σ-π mechanism[96] would not account for the observed outcome. Namely, bond rotation within the σ-(allenylmethyl)palladium(II) complex **2098**, itself formed from **2097**, would give **2099** wherein H8 and H10 share a *cis* relationship (rather than the *trans* relationship that is present in **2093** and **2094**).

Might it be the case that **2097** and **2100** are being directly interconverted under the reaction conditions? Granberg and Bäckvall have demonstrated that palladium(0) can catalyze the isomerization of (η^3-allyl)palladium(II) complexes derived from cyclic allylic electrophiles.[97] They proposed a mechanism involving nucleophilic "S_N2-type" displacement by palladium(0) in order to account for the loss of stereospecificity that has been observed in these and related systems.[98] By analogy, were free palladium(0) (and its

---

95 (a) Ogasawara, M.; Okada, A.; Watanabe, S.; Fan, L.; Uetake, K.; Nakajima, K.; Takahashi, T. Synthesis, Structure, and Reactivity of (1,2,3-η^3-Butadien-3-yl)palladium Complexes. *Organometallics* **2007**, *26*, 5025–5029. (b) Ogasawara, M.; Fan, L.; Ge, Y.; Takahashi, T. Palladium-Catalyzed Preparation of Vinylallenes from 2-Bromo-1,3,5-trienes via an Alkylidene-π-allylpalladium-Mediated Formal S_N2'' Pathway. *Org. Lett.* **2006**, *8*, 5409–5412.

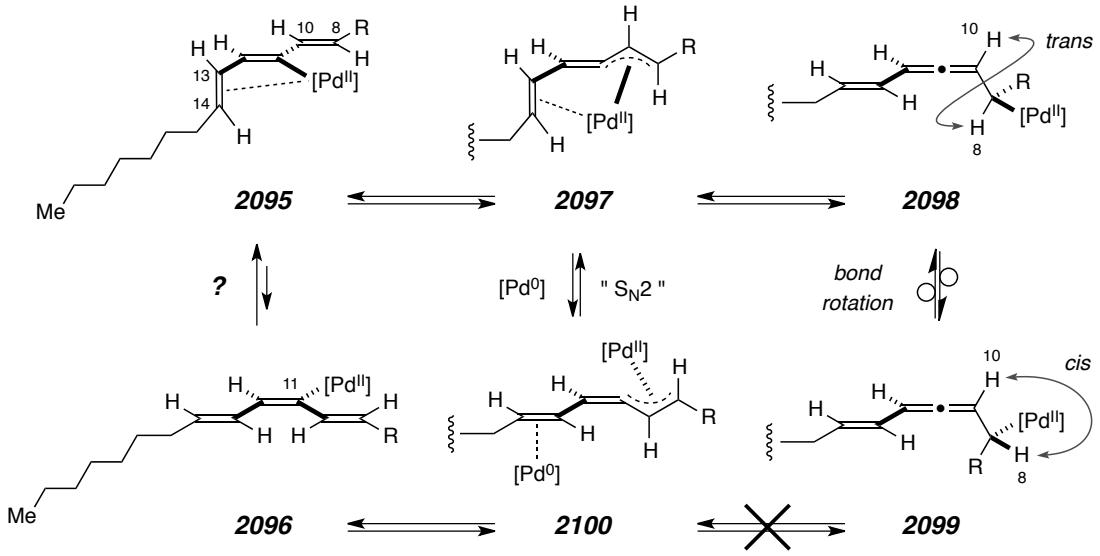
96 E.g.: Tsuji, J. Pd(0)-Catalyzed Reactions of Allylic Compounds via π-Allylpalladium Complexes. In *Palladium Reagents and Catalysts: New Perspectives for the 21ST Century*. 2ND ed; John Wiley & Sons: Hoboken, NJ, **2004**; pp 431–517.

97 Granberg, K. L.; Bäckvall, J. –E. Isomerization of (π-Allyl)palladium Complexes via Nucleophilic Displacement by Palladium(0). A Common Mechanism in Palladium(0)-Catalyzed Allylic Substitution. *J. Am. Chem. Soc.* **1992**, *114*, 6858–6863.

98 (a) Takahashi, T.; Jinbo, Y.; Kitamura, K.; Tsuji, J. Chirality Transfer from C–O to C–C in the Palladium Catalyzed ScN′ Reaction of (*E*)- and (*Z*)-Allylic Carbonates with Carbonucleophile.

associated ligand set) to attack the initially generated (alkylidene-π-allyl)palladium(II) complex **2097**, a pathway would then be available by which inversion at C11 could occur (via **2100**) without concomitant inversion of the $\Delta^{8,10}$ olefin.

Scheme II–25 | A possible mechanistic scenario that accounts for the formation of (11*E*)- and (11*Z*)-**2093** and -**2094** via palladium(0)-catalyzed methylation of **2091** and **2092**, respectively.



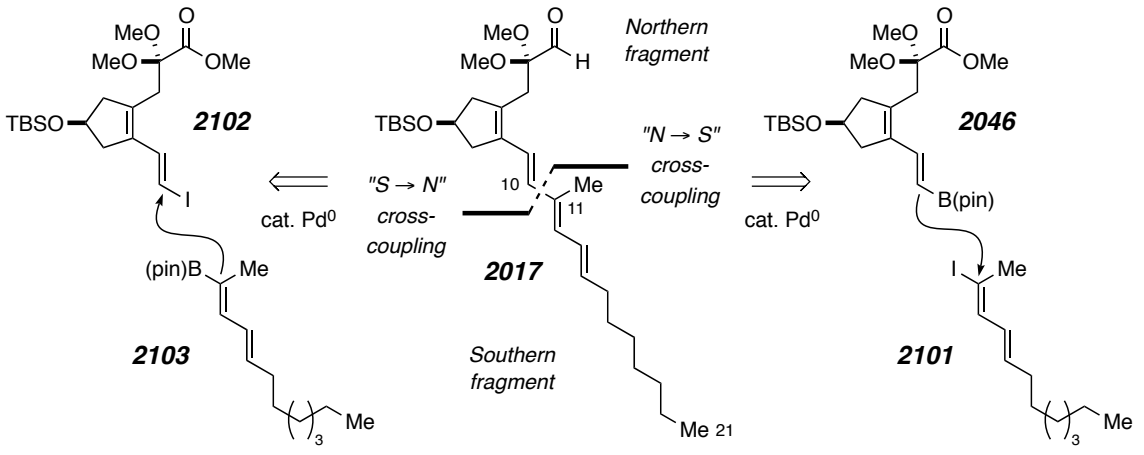
The fact that the configuration of the desired product (11*E*)-**2093** could not be reproducibly controlled, even when the same catalyst system was employed (entries 2 and 4, Table II–3), was perhaps the most frustrating aspect of this chemistry. Nonetheless, the convergent nature of the route that was developed in this section was certainly appealing. In order to more effectively capitalize on this convergency, however, a cross-coupling protocol that installed the polyene in a highly stereoselective fashion would be desirable.

Tetrahedron Lett. **1984**, *25*, 5921–5924. (b) Mackenzie, P. B.; Whelan, J.; Bosnich, B. Asymmetric Synthesis. Mechanism of Asymmetric Catalytic Allylation. *J. Am. Chem. Soc.* **1985**, *107*, 2046–2054.

F. SYNTHESIS OF THE C11–C22 DIENE FRAGMENT

Now that the inherent limitations associated with two-step introduction of the trisubstituted olefin within **2017** have made themselves abundantly clear, an alteration of the synthesis strategy was required. Assuming for the moment that the vinyl iodide **2101** and vinyl boronate **2103** are both synthetically accessible, then there are two obvious means by which the polyene may be assembled (Scheme II–26). What distinguishes these two approaches is the directionality of the cross-coupling event, i.e., retrosynthetic disconnection of the "northern" (*N*) and "southern" (*S*) fragments of **2017** via C10–C11 bond rupture reveals two pairs of potential reactants. The "*N* → *S*" cross-coupling places the organometallic donor atom on the more complex northern fragment (**2046**) and the acceptor atom on the southern fragment **2101**, whereas the obverse situation is true of the "*S* → *N*" cross-coupling pathway (i.e., **2102** + **2103** → **2017**).

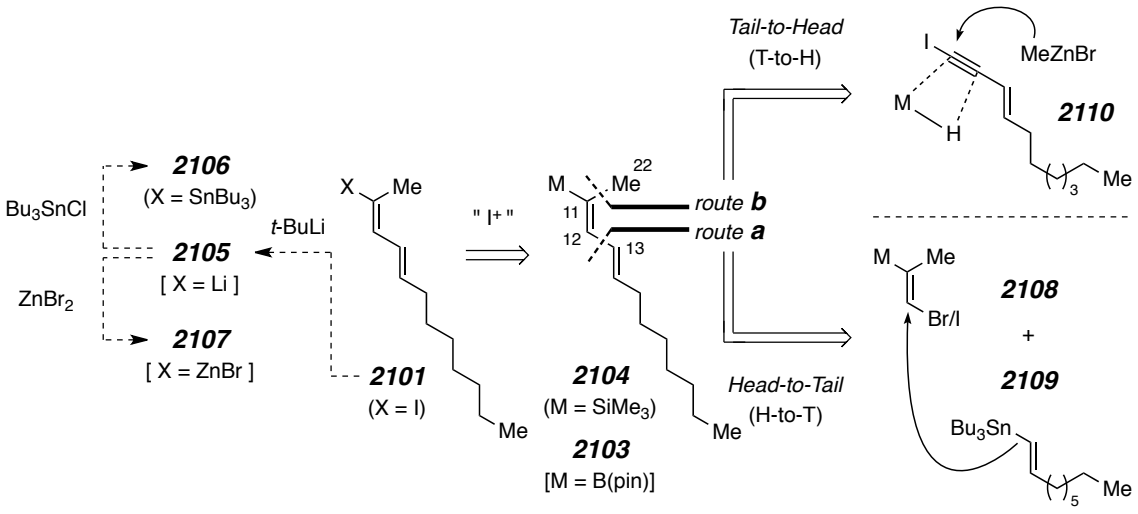
Scheme II–26 | Revised retrosynthetic analysis via convergent, one-step polyene assembly.



The strategy described above would remove the single step that was most problematic, i.e., the conversion of vinyl bromide **2091** to the isomeric polyenes **2093** (recall Table II–4). The removal of one linear step would of course be paid for by the

preparation of either of the dienes **2101** or **2103**, which, presumably, would require more than one synthetic operation. However, it was reasoned that if either of these materials could be produced in isomerically pure form, and if their subsequent palladium(0)-catalyzed cross-coupling reactions with either of **2046** or **2102** proceeded–as they should–stereospecifically, then certainly these benefits would far outweigh the price paid during their synthesis.

Scheme II–27 | Retrosynthetic analysis of vinyl boronate **2103** and silane **2104**.



The vinyl silane **2104** and the vinyl pinacol boronic ester **2103** were targeted for synthesis, the rationale being that practically all other useful vinyl organometallic species could be generated therefrom (Scheme II–27). For example, generation of the vinyl iodide **2101** from either **2104**[99] or **2103**[100] are both well documented processes. The vinyl iodide **2101**, in turn, could seed the formation of the vinyl stannane (**2106**) and vinyl zinc

99 Stamos, D. P.; Taylor, A. G.; Kishi, Y. A Mild Preparation of Vinyliodides from Vinylsilanes. *Tetrahedron Lett.* **1996**, *37*, 8647–8650.

100 Brown, H. C.; Hamaoka, T.; Ravindran, N. Reaction of Alkenylboronic Acids with Iodine Under the Influence of Base. Simple Procedure for the Stereospecific Conversion of Terminal Alkynes into *trans*-1-Alkenyl Iodides via Hydroboration. *J. Am. Chem. Soc.* **1973**, *95*, 5786–5788.

(**2107**) species via the intermediacy of the trivially available vinyllithium (**2105**) reagent. A route that incorporates this type of flexibility, where the Stille, Suzuki–Miyaura, and Negishi variants of palladium(0)-catalyzed cross-coupling reactions could be employed at will, could certainly serve as a robust synthetic platform.

Two separate routes were explored for the preparation of these vinyl organometallic species (Scheme II–27). The "H-to-T"[101] union of an orthogonally functionalized synthon such as **2108** with the vinyl stannane **2109** represented an appealing and convergent entry point (route **a**). Alternatively, the sequential hydrometalation/Negishi cross-coupling of a 1-iodo-1-alkyne (**2110**) could provide a stereoselective, albeit less convergent (i.e., "T-to-H"), route to either **2103** or **2104** (route **b**). Based upon the notoriously capricious regioselectivity in the hydroboration of disubstituted alkynes,[102] the possibility of employing the 1-propynyl derivative of **2110** at any point in this route was immediately rejected. The regioselective hydroboration of a 1-halo-1-alkyne, though it has received far less attention in the literature, was viewed as a superior tactic.

F–1. HEAD-TO-TAIL C12–C13 CROSS-COUPLING STUDIES (ROUTE **a**)

It has been reported that the hydrozirconation of (trimethylsilyl)acetylene with the Schwartz reagent proceeded regioselectively to give a β-trimethylsilyl nonagostic

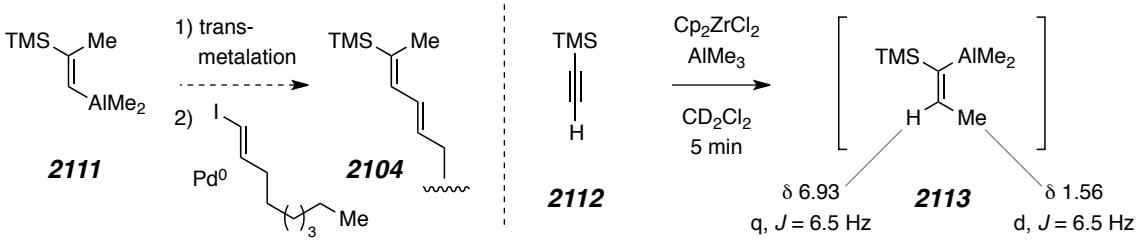
---

101 For a description of the "H-to-T" and "T-to-H" nomenclature as it applies to trisubstituted olefin synthesis, see: (a) Negishi, E.; Liou, S.; Xu, C.; Huo, S. A Novel, Highly Selective, and General Methodology for the Synthesis of 1,5-Diene-Containing Oligoisoprenoids of All Possible Geometrical Combinations Exemplified by an Iterative and Convergent Synthesis of Coenzyme Q_{10}. *Org. Lett.* **2002**, *4*, 261–264. (b) Negishi, E.; Wang, G.; Rao, H.; Xu, Z. Alkyne Elementometalation–Pd-Catalyzed Cross-Coupling. Toward Synthesis of All Conceivable Types of Acyclic Alkenes in High Yields, Efficiently, Selectively, Economically, and Safely: "Green" Way. *J. Org. Chem.* **2010**, *75*, 3151–3182.

102 Trost, B. M.; Ball, Z. T. Addition of Metalloid Hydrides to Alkynes: Hydrometallation with Boron, Silicon, and Tin. *Synthesis* **2005**, 853–887.

alkenylzirconocene complex.[103] Given this precedent, it seemed reasonable to expect that Negishi's Zr-catalyzed alkyne methylalumination (ZMA)[104] would proceed similarly to give rise to vinyl alane **2111** (left portion of Scheme II–28), from which *in situ* transmetalation and subsequent cross-coupling could be a convenient means to prepare the vinyl silane **2104**. Unfortunately, the ZMA reaction of (trimethylsilyl)acetylene (**2112**), when monitored by ^{1}H NMR spectroscopy, clearly gave rise to the α-trimethylsilyl vinyl alane **2113**. The diagnostic resonances along with their *J*-coupling values are consistent with this structure, and therefore this route was not pursued further.

Scheme II–28 | Attempted ZMA reaction of (trimethylsilyl)acetylene (**2112**).



At the time that these studies were initiated, there was scarcely a general method for the synthesis of (*Z*,*E*)-dienyl boronic esters of the type **2103**.[101b] Although the attempted ZMA of acetylene **2112** was unsuccessful, Burke and co-workers have recently reported the synthesis of the *N*-methyliminodiacetic acid (MIDA) boronate **2117**[105] (Scheme II–29, analogous to **2108** in Scheme II–27) that is ideally suited to engage in a Pd(0)-catalyzed cross-coupling reaction.

---

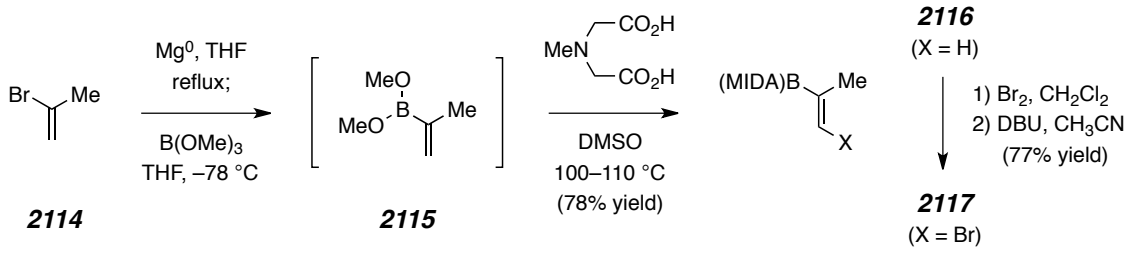
103 Hyla-Kryspin, I.; Gleiter, R.; Kureger, C.; Zwettler, R.; Erker, G. Formation of β-CH Agostic Alkenyl-zirconocene Complexes. *Organomettalics* **1990**, *9*, 517–523.

104 Van Horn, D. E.; Negishi, E. Controlled Carbometalation. Reaction of Acetylenes with Organoalane–Zirconocene Dichloride Complexes as a Route to Stereo- and Regio-Defined Trisubstituted Olefins. *J. Am. Chem. Soc.* **1978**, *100*, 2252–2254.

105 Woerly, E. M.; Cherney, A. H.; Davis, E. K.; Burke, M. D. Stereoretentive Suzuki-Miyaura Coupling of Haloallenes Enables Fully Stereocontrolled Access to (–)-Peridinin. *J. Am. Chem. Soc.* **2010**, *132*, 6941–6943.

According to the reported procedure, a four-step sequence was employed to prepare (MIDA) boronate **2117** (Scheme II–29). The Grignard reagent derived from isopropenyl bromide (**2114**) was quenched with trimethyl borate to give rise to the vinyl boronate **2115**. Without further manipulation, a solution of this material was cannula transferred into a hot solution of MIDA in DMSO and, after a simple work-up and precipitation of the crude product from THF/Et_2O,[105] a crystalline sample of the isoprenyl MIDA boronate **2116** was obtained. Finally, bromination of **2116** followed by DBU-induced dehydrobromination cleanly provided the bromo MIDA boronate **2117**.[105]

Scheme II–29 | Preparation of the difunctional MIDA boronate **2117**.

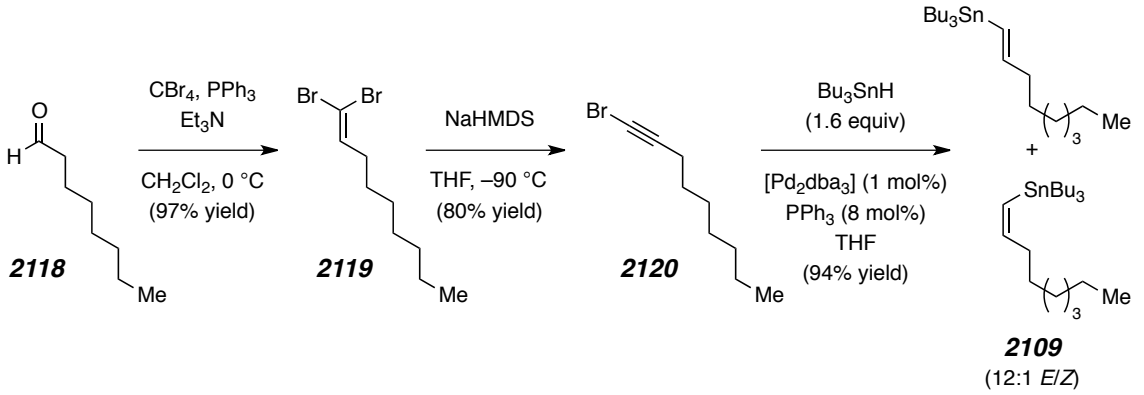


With the intent of employing **2117** in a Stille cross-coupling (similar to that reported by Burke[105]), the vinyl stannane **2109** was required (Scheme II–30). I elected to employ the 1-bromoalkyne hydrostannylation technology that was introduced by Zhang and co-workers[106] to overcome the regio- and stereochemical issues associated with conducting this reaction on a terminal alkyne. Through the intermediacy to the 1,1-

[106] Zhang, H. X.; Guibé, F.; Balavoine, G. Palladium- and Molybdenum-Catalyzed Hydrostannation of Alkynes. A Novel Access to Regio- and Stereodefined Vinylstannanes. *J. Org. Chem.* **1990**, *55*, 1857–1867.

dibromolefin **2119**,[107] the 1-bromoalkyne **2120**[108] was uneventfully generated from octanal (**2118**) according to Grandjean's modification[109] of the Corey-Fuchs protocol.

Scheme II–30 | Synthesis of the bromoalkyne **2120** and its subsequent hydrostannylation.



Hydrostannylation of the bromoalkyne **2120** under the conditions reported by Pattenden[80] did indeed provide the vinyl stannane **2109**,[110] but, surprisingly, the product

---

107 [*MJJ-V-284/294*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.39 [dd, *J* = 7.0, 7.0 Hz, 1H, $(Br)_2C{=}CH$], 2.09 [ddd, *J* = 7.0, 7.0, 7.0 Hz, 2H, $(Br)_2C{=}CHCH_2$], 1.46-1.39 [m, 2H, $CH_2CH_2(CH_2)_4CH_3$], 1.34-1.23 [m, 8H, $CH_2CH_2(CH_2)_4CH_3$], and 0.89 [t, *J* = 7.0 Hz, 3H, $CH_2CH_2(CH_2)_4CH_3$].
GC / LR EI-MS [5025015]: t_R 6.49 min; *m/z* (rel. int.) 286 [12, $M^{+\bullet}(^{81}Br/^{81}Br)$], 284 [23, $M^{+\bullet}(^{79}Br/^{81}Br)$], 282 [17, $M^{+\bullet}(^{79}Br/^{79}Br)$], 201 [31, $M^{+\bullet}(^{81}Br/^{81}Br)–C_6H_{13}^{\bullet}$], 199 [64, $M^{+\bullet}(^{79}Br/^{81}Br)–C_6H_{13}^{\bullet}$], 197 [31, $M^{+\bullet}(^{79}Br/^{79}Br)–C_6H_{13}^{\bullet}$], 123 (85), and 81 (100).

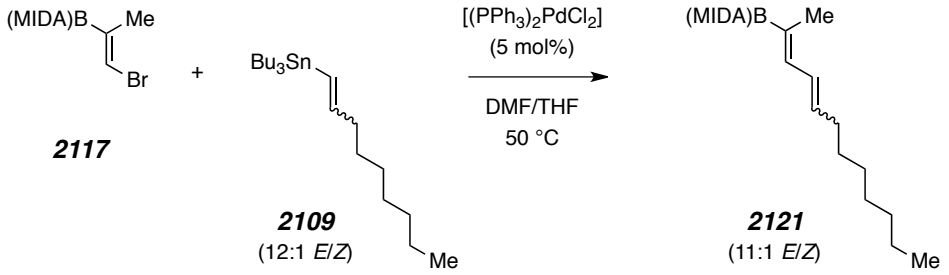
108 [*MJJ-V-286/296*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.20 (dd, *J* = 7.0, 7.0 Hz, 2H, $BrC{\equiv}CCH_2CH_2$), 1.51 (dddd, *J* = 1.0, 7.0, 7.0, 16.0 Hz, 2H, $BrC{\equiv}CCH_2CH_2$), 1.39-1.34 [m, 2H, $BrC{\equiv}CCH_2CH_2CH_2(CH_2)_3CH_3$], 1.32-1.24 [m, 6H, $BrC{\equiv}CCH_2CH_2CH_2(CH_2)_3CH_3$], and 0.89 [t, *J* = 7.0 Hz, 3H, $BrC{\equiv}CCH_2CH_2CH_2(CH_2)_3CH_3$].
GC / LR EI-MS [5025015]: t_R 4.97 min; *m/z* (rel. int.) 161 [7, $M^{+\bullet}(^{81}Br)–C_3H_7^{\bullet}$], 159 [7, $M^{+\bullet}(^{79}Br)–C_3H_7^{\bullet}$], 147 [7, $M^{+\bullet}(^{81}Br)–C_4H_9^{\bullet}$], 145 [7, $M^{+\bullet}(^{79}Br)–C_4H_9^{\bullet}$], 134 (13), 132 (14), 119 [24, $M^{+\bullet}(^{81}Br)–C_6H_{13}^{\bullet}$], 117 [22, $M^{+\bullet}(^{79}Br)–C_6H_{13}^{\bullet}$], 81 (100), and 79 (71).

109 Grandjean, D.; Pale, P.; Chuche, J. An Improved Procedure for Aldehyde-to-Alkyne Homologation via 1,1-Dibromoalkenes; Synthesis of 1-Bromoalkynes. *Tetrahedron Lett.* **1994**, *35*, 3529–3530.

110 [*MJJ-VI-21*] The *E* (†) and *Z* (‡) isomers have been indicated. **^{1}H NMR** (500 MHz, $CDCl_3$): δ $6.51^{‡}$ (ddd, *J* = 7.0, 7.0, 12.0 Hz, 1H, $Bu_3SnCH{=}CH$), $5.94^{†}$ (ddd, *J* = 6.0, 6.0, 19.0 Hz, 1H, $Bu_3SnCH{=}CH$), $5.85^{†}$ (ddd, *J* = 1.0, 1.0, 19.0 Hz, 1H, $Bu_3SnCH{=}CH$), $5.77^{‡}$ (ddd, *J* = 1.0, 1.0, 12.0 Hz, 1H,

was formed as an inseparable 12:1 mixture of (*E*)- and (*Z*)-isomers.[111] This outcome certainly did not bode well for the production of isomerically pure **2121**. When the Stille coupling of MIDA boronate **2117** and vinyl stannane **2109** was carried out under the conditions utilized by Burke,[105] an inseparable 11:1 mixture of (*E*)- and (*Z*)-**2121** was obtained (Scheme II–31). The isomeric purity of **2121** vis-à-vis **2109** suggests that (*E*)- and (*Z*)-isomers of this latter species are consumed at essentially identical rates.

Scheme II–31 | Stille cross-coupling of **2117** with (*E*)- and (*Z*)-**2109** to provide an isomeric mixture of the dienyl MIDA boronate **2121**.



F–2. TAIL-TO-HEAD C11–C22 CROSS-COUPLING STUDIES (ROUTE **b**)

In the next stage of development, attention was turned to the sequential 1-haloenyne hydroboration/Negishi cross-coupling (route **b**, Scheme II–27) as a

Bu_3SnCH=CH), 2.12† (dddd, J = 1.0, 6.5, 7.0, 7.0 Hz, 2H, Bu_3SnCH=CHCH_2), 2.01‡ (dddd, J = 1.0, 7.0, 7.0, 7.0 Hz, 2H, Bu_3SnCH=CHCH_2), 1.54-1.43†‡ [m, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$], 1.42-1.36†‡ [m, 2H, $CH_2CH_2(CH_2)_4CH_3$], 1.34-1.25†‡ [m, 14H, overlapping $CH_2CH_2(CH_2)_4CH_3$ and $Sn(CH_2CH_2$-$CH_2CH_3)_3$], 0.89†‡ [t, J = 7.5 Hz, 12H, overlapping $CH_2CH_2(CH_2)_4CH_3$ and $Sn(CH_2CH_2CH_2CH_3)_3$], and 0.88-0.84†‡ [m, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$].

GC / LR EI-MS [5025015]: t_R 10.09 min (*E* isomer) and 10.05 min (*Z* isomer); *m*/*z* (rel. int.) 359 [100, $M^{+\bullet}$(^{120}Sn)–$C_4H_9^\bullet$], 357 [75, $M^{+\bullet}$(^{118}Sn)–$C_4H_9^\bullet$], 355 [41, $M^{+\bullet}$(^{116}Sn)–$C_4H_9^\bullet$], 303 (58), 301 (44), 299 (25), 247 (59), 245 (47), and 243 (28). The LR EI-MS fragmentation patterns for the (*E*)- and (*Z*)-isomers were indistinguishable.

111 In contrast to the isomeric purity of **2109**, the *E*/*Z* ratios for the product vinyl stannanes in Pattendens's report always exceeded 95:5; see ref 80.

stereospecific means by which the trisubstituted vinyl boronic ester **2103** could be constructed. At the outset of these studies, the hydroboration of simple 1-bromo- and 1-iodo-1-alkynes to produce (*Z*)-(1-halo-1-alkenyl)boranes (and boronic esters) was a well known reaction.[112] Several perturbations of Zweifel's method[112a] were reported by Negishi,[112b] Molander,[112c] and Brown[112d] demonstrating that these intermediates were particularly fertile ground for the highly stereoselective synthesis of (*Z*)-1-alkenylboranes. However, until the recent report by Negishi and co-workers,[113] the subsequent use of (*Z*)-(1-halo-1-alkenyl)boronic esters in palladium(0)-catalyzed cross-coupling reactions hath lain fallow for nearly 20 years.[114] Moreover, and in contrast to the hydroboration of simple 1-haloalkynes, the regio- and stereoselective hydroboration of 1-haloalk-1-yn-3-enes (i.e., 1-haloenynes) was *not* a well-established reaction at the outset of these studies.[115]

---

[112] For key examples, see: (a) Zweifel, G.; Arzoumanian, H. α-Halovinylboranes. Their Preparation and Conversion into *cis*-Vinylhalides, *trans*-Olefins, Ketones, and *trans*-Vinylboranes. *J. Am. Chem. Soc.* **1967**, *89*, 5086–5088. (b) Negishi, E.; Williams, R. M.; Lew, G.; Yoshida, T. A Stereoselective Synthesis of *cis*-Alkenylboranes. *J. Organomet. Chem.* **1975**, *92*, C4–C6. (c) Campbell, J. B.; Molander, G. A. An Improved Synthesis of *cis*-Alkenylboranes. *J. Organomet. Chem.* **1978**, *156*, 71–79. (d) Brown, H. C.; Imai, T. Organoboranes. 37. Synthesis and Properties of (*Z*)-1-Alkenylboronic Esters. *Organometallics* **1984**, *3*, 1392–1395 and references therein. (e) Kamabuchi, A.; Moriya, T.; Miyaura, N.; Suzuki, A. Synthesis of Functionalized 1-Alkenylboronates via Hydroboration-Dealkylation of Alkynes with Diisopinocampheylborane. *Synth. Commun.* **1993**, *23*, 2851–2859.

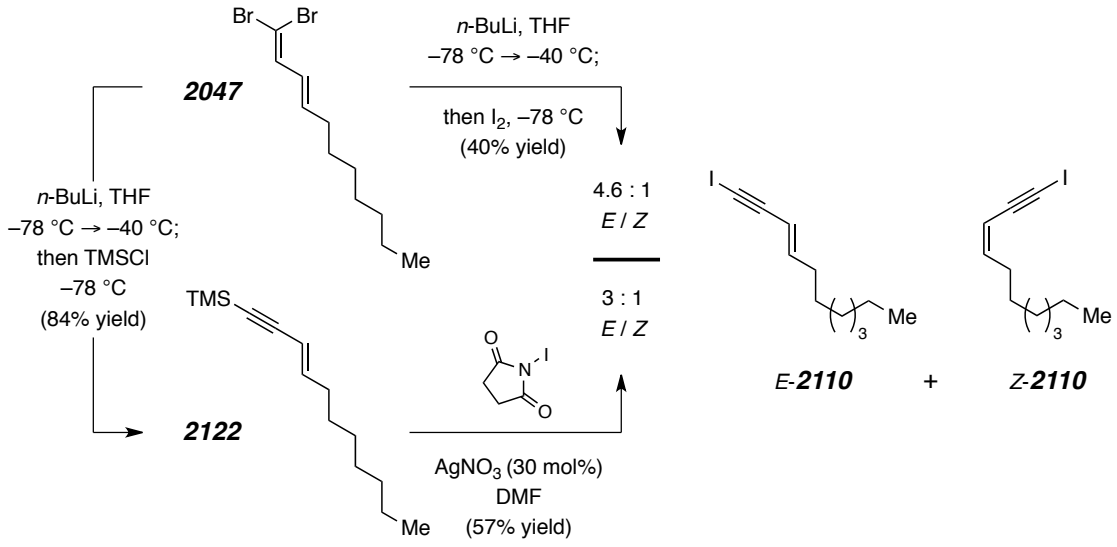
[113] Xu, S.; Lee, C. –T.; Rao, H.; Negishi, E. Highly (≥98%) Stereo- and Regioselective Trisubstituted Alkene Synthesis of Wide Applicability *via* 1-Halo-1-alkyne Hydroboration-Tandem Negishi-Suzuki Coupling or Organoborate Migratory Insertion. *Adv. Synth. Catal.* **2011**, *353*, 2981–2987. It should be noted that the studies described in this section were well underway at the time of this publication's appearance.

[114] Suzuki and co-workers were the first to demonstrate the feasibility of this approach: Moriya, T.; Miyaura, N.; Suzuki, A. Stereoselective Synthesis of (*Z*)-(1-Organo-1-alkenyl)boronic Esters by the Palladium-Catalyzed Cross-Coupling Reaction of (*Z*)-(1-Iodo-1-alkenyl)boronic esters with Organozinc Reagents. *Chem. Lett.* **1993**, 1429–1432.

[115] Only two examples of the hydroboration of 1-haloenynes can be located: (a) Jeon, S. –J.; Fisher, E. L.; Carroll, P. J.; Walsh, P. J. Direct Stereospecific Generation of (*Z*)-Disubstituted Allylic Alcohols. *J. Am. Chem. Soc.* **2006**, *128*, 9618–9619. (b) Hoshi, M.; Kawamura, N.; Shirakawa, K. Construction of Terminal Conjugated Enynes: Cu-Mediated Cross-Coupling Reaction of Alkenyldialkylborane with

It was believed that the requisite 1-haloenynes could, in more than one way, be generated from the dibromoolefin **2047**, which in turn has already been prepared via the Corey-Fuchs protocol (Scheme II–32). I decided to first explore this chemistry with the iodoalkyne **2110**, since the product formed after it's hydroboration/esterification would be a far superior electrophile in the subsequent Negishi cross-coupling reaction. Thus, the dibromoolefin **2047** could be easily converted into the silyl enyne **2122** via treatment with 2.2 equivalents of *n*-BuLi and capture of the resulting lithium acetylide with TMSCl. The iodoalkyne **2110** was then generated by either of two methods. Treatment again of dibromoolefin **2047** with *n*-BuLi and trapping with iodine gave rise to both (*E*)- and (*Z*)-**2110** as a partially separable 4.6:1 mixture, a disappointing outcome that was compounded by the low yield. Similarly, a 3:1 mixture of (*E*)- and (*Z*)-**2110** was obtained when the silyl enyne **2122** was allowed to react with *N*-iodosuccinimide under the influence of catalytic $AgNO_3$.

Scheme II–32 | Synthesis of the iodoalkyne **2110** from either **2047** or **2122**.



(Trimethylsilyl)ethynyl Bromide. *Synthesis* **2006**, 1961–1970. In neither of these reports was the isolation of the intermediate (*Z*)-(1-halo-1-alkenyl)borane attempted.

The formation of iodoalkyne **2110** as a mixture of isomers was somewhat troubling, since a stereoselective hydroboration would be a moot point if the configuration of the other double bond could not be controlled. It was generally assumed that, although the (*E*)-**2110** may be formed initially in high isomeric purity, varying amounts of excess or *in situ* generated HI/I_2 were accelerating its interconversion with (*Z*)-**2110**. I then became aware of Michel and Rassat's one-pot protocol[116] wherein it was reported that the iodoalkyne of cinnamaldehyde could be prepared in 96% yield; at no point did the authors allude to complications arising from the instability of this product.[116]

According to the Michel and Rassat's prescribed conditions, PPh_3 (2.2 equiv), CHI_3 (2.1 equiv), and *t*-BuOK (2.0 equiv) were combined in THF to provide a brown suspension of diiodomethyltriphenylphosphorane (Scheme II–33). Addition of (*E*)-2-decenal (**2036**) to this mixture rapidly generated the intermediate diiodoalkyne, to which was added excess *t*-BuOK at –78 °C. This method very cleanly and efficiently delivered the iodoalkyne (*E*)-**2110** after silica gel chromatography. *However*, it was soon realized that the isomeric integrity of purified samples of this material was rapidly degraded at room temperature upon exposure to ambient light. For example, when a sample of (*E*)-**2110** was allowed to stand in $CDCl_3$ for a period of 24 h, a 1:1 mixture of (*E*)- and (*Z*)-isomers was obtained, as evidenced by analysis of the mixture by GC-MS and ^{1}H NMR spectroscopy. In contrast to **2110**, the *bromo*alkyne (*E*)-**2123**, which was prepared according to Grandjean's protocol[109] from the dibromoolefin **2047**, was found to be stable to prolonged exposure (48 h) to light in $CDCl_3$ solution. The above observations are consistent with the generation of I_2 upon photolytic decomposition of the **2110**, a phenomenon that has been studied previously for 1-iodo-1-hexyne.[117] The presence of

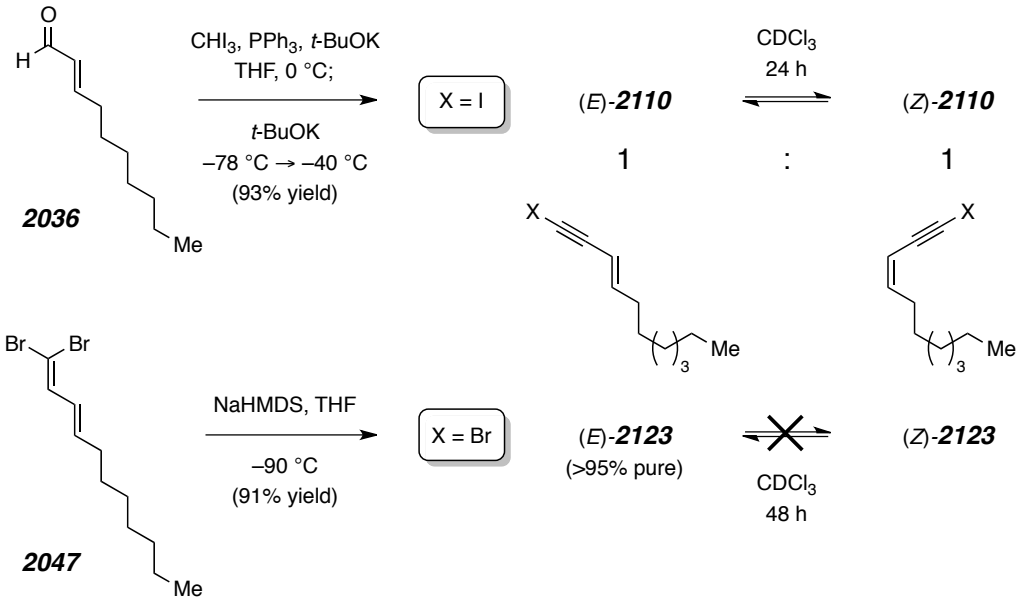
---

116 Michel, P.; Rassat, A. A One-Pot Procedure for the Synthesis of Iodoalkynes from Aldehydes. *Tetrahedron Lett.* **1999**, *40*, 8579–8581.

117 Inoue, Y.; Fukunaga, T.; Hakushi, T. Direct Photolysis of 1-Halo-1-Hexynes. Lack of Ionic Behavior. *J. Org. Chem.* **1983**, *48*, 1732–1737.

trace I_2 could then promote enyne isomerization[118] leading to the formation of (*E*)- and (*Z*)-**2110**, their ratio (1:1) presumably being under thermodynamic control.

Scheme II–33 | Preparation and relative stabilities of the 1-haloalkynes **2110** and **2123**.



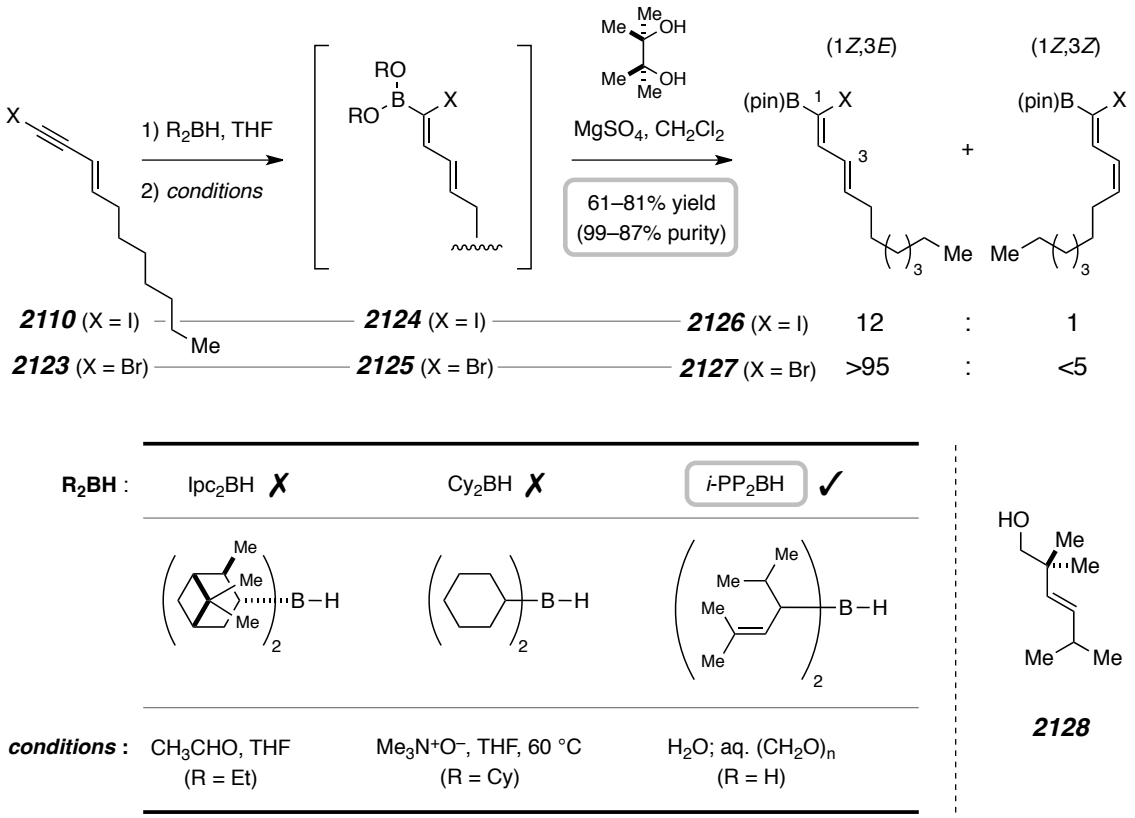
A series of experiments were next initiated in order to examine the efficiency with which **2110** and **2123** could be selectively reduced under a small sampling of hydroboration conditions. Although the iodoalkyne **2110** was eventually supplanted by the more stable bromoalkyne **2123**, the former compound was employed in these early studies purely out of necessity. I was guided to a considerable extent by the prior report from Suzuki and co-workers[114] (which was alluded to earlier) wherein they were able to establish that hydroboration of simple 1-iodoalkynes could be carried out with diisopinocampheylborane (Ipc_2BH). They further showed that the intermediate 1-alkenylboranes could be dealkylated with acetaldehyde and subsequently esterified with pinacol.

---

[118] See, e.g.: Haugan, J. A.; Englert, G.; Glinz, E.; Liaaen-Jensen, S. Algal Carotenoids. 48. Structural Assignments of Geometrical Isomers of Fucoxanthin. *Acta Chem. Scand.* **1992**, *46*, 389–395.

Three different hydroboration reagents were interrogated for the conversion of the iodoalkyne **2110** to the vinyl boronic ester **2126**–namely, Ipc_2BH, dicyclohexylborane (Cy_2BH), and *i*-PP_2BH[84] (Scheme II–34). When the iodoalkyne **2110** was exposed to Ipc_2BH, the first indication that the reactivity of 1-haloenynes towards this reagent would *not* parallel that reported for simple 1-haloalkynes was revealed. Surprisingly, after sequential treatment of the reaction mixture with acetaldehyde and pinacol, none of the desired product could be isolated. A complex reaction mixture was observed when analyzed by GC-MS prior to addition acetaldehyde, which suggests that the intermediate boronic ester **2124** (R = Et) was not being accessed under these conditions.

Scheme II–34 | Optimization of the 1-haloenyne hydroboration/esterification protocol.

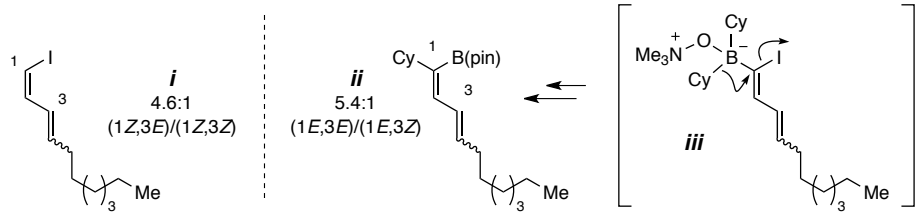


A slight improvement was achieved with Cy_2BH. Under the conditions reported by Hoffmann and Dresely,[119] trimethylamine *N*-oxide was employed to selectively oxidize the sp^3 carbon-boron bonds of the 1-alkenylborane that were generated by Cy_2BH hydroboration of terminal alkynes. First, preliminary studies indicated that the vinyl pinacol boronate derived from 1-undecyne could be cleanly produced under these conditions. However, when this method was extended to the hydroboration, oxidation, and transesterification of iodoalkyne **2110** (Scheme II–34) the desired product was indeed formed, but it was present among at least two other components.[120] Nevertheless,

---

119 (a) Vaultier, M.; Truchet, F.; Carboni, B.; Hoffmann, R. W.; Denne, I. Diels–Alder Reactions of 1,3-Dienylboronates as a New Route to Functionalized Carbocycles. *Tetrahedron Lett.* **1987**, *28*, 4169–4172. (b) Hoffmann, R. W.; Dresely, S. Preparation of 3-Substituted (*E*)-1-Alkenylboronic Esters. *Synthesis* **1988**, 103–106.

120 On the basis of ^{1}H NMR and GC-MS analyses, the vinyl iodide **i** and the vinyl boronic ester **ii** were identified as the two other major components produced along with **2126**. The ratio of **2126**:**i**:**ii** was estimated to be 1.0:0.45:0.52. Boronate **ii** most likely arises via sp^3 C–B bond migration with inversion at the alkenyl carbon (as suggested by intermediate **iii**). The configuration of the $\Delta^{1,2}$ alkene was not rigorously established. For analogous transformations, see ref 112a.



[*MJJ-IV-88*] Diagnostic ^{1}H NMR (500 MHz, $CDCl_3$) alkene resonances for each of these species are provided. (1*Z*,3*E*)-**i**: δ 6.68 (ddd, *J* = 0.5, 7.5, 9.5 Hz, 1H, ICH=C*H*CH=CH), 6.21 (ddddd, *J* = 1.5, 1.5, 1.5, 10.0, 15.5 Hz, 1H, ICH=CHC*H*=CH), 6.09 (ddddd, *J* = 1.0, 1.0, 1.0, 1.0, 7.5 Hz, 1H, IC*H*=CHCH=CH), and 6.00 (dddd, *J* = 1.0, 7.0, 7.0, 16.0 Hz, 1H, ICH=CHCH=C*H*) (cf. Stewart, S. K.; Whiting, A. Stereoselective Synthesis of Vinyl Iodides from Vinylboronate Pinacol Esters Using ICl. *Tetrahedron Lett.* **1995**, *36*, 3929–3932). (1*Z*,3*Z*)-**i**: δ 6.98 (ddd, *J* = 1.0, 7.5, 10.0 Hz, 1H, ICH=C*H*CH=CH), 6.28 (ddd, *J* = 1.5, 1.5, 7.5 Hz, 1H, IC*H*=CHCH=CH), *ca.* 6.11 (ddddd, *J* = 2.0, 2.0, 2.0, 10.5, 11.0 Hz, 1H, ICH=CHC*H*=CH), and 5.72 (ddddd, *J* = 1.5, 1.5, 7.5, 7.5, 11.0 Hz, 1H, ICH=CHCH=C*H*). (1*E*,3*E*)-**ii**: δ 6.68 {dddd, *J* = 1.5, 1.5, 11.0, 15.0 Hz, 1H, (Cy)[B(pin)]C=CH-C*H*=CH}, 6.48 {d, *J* = 11.0 Hz, 1H, (Cy)[B(pin)]C=C*H*CH=CH}, and 5.71 {ddd, *J* = 7.0, 7.0, 14.0 Hz, 1H, (Cy)[B(pin)]C=CHCH=C*H*}. (1*E*,3*Z*)-**ii**: δ 6.80 {d, *J* = 12.0 Hz, 1H, (Cy)[B(pin)]C=C*H*CH=CH}, 6.57 {dddd, *J* = 1.5, 1.5, 11.0, 11.0 Hz, 1H, (Cy)[B(pin)]C=CHC*H*=CH}, and 5.46 {ddd, *J* = 7.5, 7.5, 11.0 Hz, 1H, (Cy)[B(pin)]C=CHCH=C*H*}.

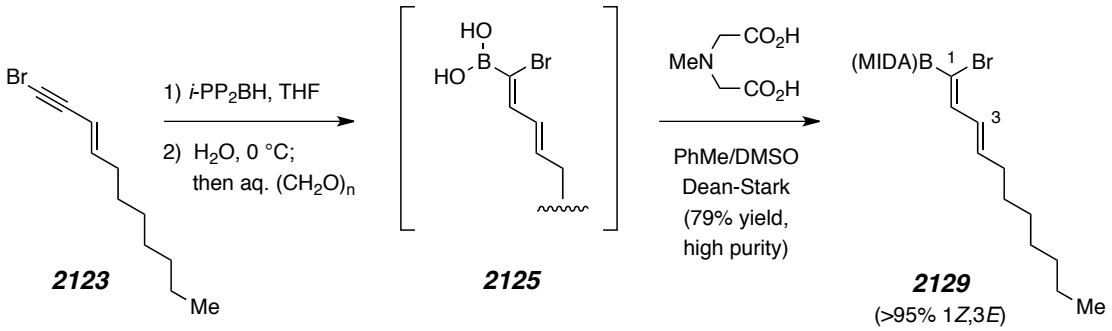
this was an encouraging first step toward the preparation of **2126**, and the search continued for a more suitable hydroboration reagent.

Given the success that was had during an earlier study that utilized *i*-PP_2BH, the iodoalkyne **2110** was exposed to this reagent. In the event, the iodoalkyne was rapidly consumed (even at 0 °C), and, after hydrolysis, work-up, and treatment with pinacol in the presence of excess $MgSO_4$, the vinyl boronic ester **2126** was *cleanly* formed in 81% isolated yield. As was mentioned previously, the stability of the iodoalkyne **2110** was problematic and its isomeric purity depended upon its prior handling (i.e., extent to which it had been exposed to ambient light). The isomeric purity of the vinyl pinacol boronate **2126** is therefore a reflection of this unfortunate fact [in this instance, it was produced as a 12:1 ratio of (1*Z*,3*E*)- and (1*Z*,3*Z*)-isomers, which, in my hands, has really been the best ratio obtainable]. It was therefore immensely important, having now identified a hydroboration reagent that could accomplish the job, to find that the bromoalkyne **2123** could be processed with comparable effectiveness to provide the analogous vinyl bromide **2127** in 61% isolated yield. Significantly, *this material was produced as essentially a single configurational isomer* (*dr* >95:5). The configuration of the $\Delta^{1,2}$ alkenes of **2126** and **2127**, though it could not be definitively established at this stage, is that expected [(1*Z*)] from a stereospecific *cis*-hydroboration, an outcome that is obviously not without precedent. On the other hand, the configuration of the $\Delta^{3,4}$ alkenes was trivially ascertained from analysis of $^3J_{H3,H4}$ coupling constant values.

The primary drawback that was discovered when *i*-PP_2BH was employed in the above sequence was that the allylative hydrolysis of formaldehyde that gives rise to the vinyl boronic esters **2124**/**2125** (R = H, Scheme II–34) also produces the alcohol **2128**. This substance partially co-eluted with the desired products, and although **2126**/**2127** could be obtained in sufficiently high purity through a rather tedious MPLC separation, the complete removal of **2128** was practically impossible on larger scales. The MIDA boronate **2129** (Scheme II–35) then became an attractive target because one would expect it to be highly polar compound (and also a versatile intermediate in it's own right). The

iodoalkyne **2110**, having served its purpose venerably, was by this time viewed as completely useless. Hence, hydroboration of the bromoalkyne **2123** under the optimized conditions delivered the boronic acid **2125**. Subjection of this material in crude form to Burke's general method[121] smoothly provided the MIDA boronate **2129** as an off-white solid in good yield. The mobility of this material on silica gel was sluggish at best in pure EtOAc. Therefore, the relatively non-polar impurities derived from the hydroboration chemistry were easily removed, and pure **2129** could be eluted with 1% CH_3CN in EtOAc.

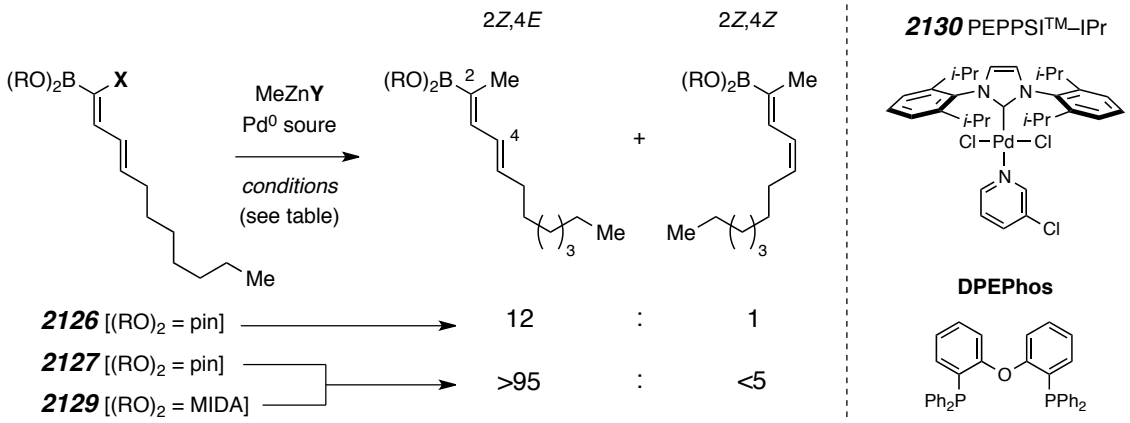
Scheme II–35 | Straightforward access to the more readily purified MIDA boronate **2129**.



With sufficient quantities of **2126**, **2127**, and **2129** now readily available, the final palladium(0)-catalyzed cross-coupling reaction was explored to forge the trisubstituted olefin within **2103** (and **2121**). When these studies were launched, the intent was to harness the power of the Negishi cross-coupling, a transformation for which there is ample precedent. Here again, Suzuki and co-workers[114] have provided several key examples wherein alkylzinc reagents were efficiently cross-coupled with (*Z*)-(1-iodo-1-alkenyl)boronic esters.

[121] Knapp, D. M.; Gillis, E. P.; Burke, M. D. A General Solution for Unstable Boronic Acids: Slow-Release Cross-Coupling from Air-Stable MIDA Boronates. *J. Am. Chem. Soc.* **2009**, *131*, 6961–6963.

Table II–6 | Optimization of the Negishi cross-coupling reaction for the preparation of the dienyl vinyl boronates **2103** and **2121**.



entry	SM #	X	Y	Pd^0 source	*conditions*	pdt (% yield)
1	***2126***	I	Me	$[Pd(dppf)Cl_2]CH_2Cl_2$ (7 mol%)	THF rt, 16 h	complex mixture
2	***2126***	I	Br	$[Pd(PPh_3)_4]$ (5 mol%)	THF rt, 18 h	***2103*** (75–90)
3	***2127***	Br	Br	$[Pd(PPh_3)_4]$ (5 mol%)	THF 50 °C, 40 h	***2103*** (48)
4	***2127***	Br	Br	$[Pd(DPEPhos)Cl_2]$ (5 mol%)	THF 50 °C, 24 h	***2103*** (34)
5	***2127***	Br	Br	***2130*** (1 mol%)	LiBr, THF/DMI rt, 4 h	***2103*** (73)
6	***2129***	Br	Br	***2130*** (1 mol%)	LiBr, THF rt, 18 h	***2121*** (72)

A series of experiments aimed at exploring this transformation were then initiated (Table II–6). Allowing the vinyl iodide **2126** to react with excess Me_2Zn in the presence of catalytic $[Pd(dppf)Cl_2]$ (entry 1) proceeded relatively cleanly at short (30 min) reaction

time. But as the reaction progressed over the course of 16 h, a complex mixture of products was observed by GC-MS analysis, which suggested that the product **2103** was inherently unstable toward Me_2Zn. A dramatically different outcome was observed when MeZnBr was employed in lieu of this reagent (entry 2). In the presence of 5 mol% [$Pd(PPh_3)_4$], this organozinc donor–freshly prepared from MeMgBr and dry $ZnBr_2$–smoothly converted **2126** [12:1 (1*Z*,3*E*)/(1*Z*,3*Z*)] into the vinyl boronate **2103** in excellent yield.

The vinyl bromide **2127**, however, proved to be a recalcitrant cross-coupling partner, and indeed this reactivity discrepancy vis-à-vis **2126** was anticipated. Whereas **2126** cleanly underwent Negishi cross-coupling at room temperature, the bromide **12127** required heating in THF for a period of 40 h under otherwise identical conditions (Table II–6, entry 3) and provided **2103** in disappointingly low yield. The superiority of the bidentate ligand DPEPhos in the Kumada–Tamao–Corriu cross-coupling has been demonstrated[122] and used to advantage by Negishi,[90] but in this specific setting the precatalyst [$Pd(DPEPhos)Cl_2$] offered no advantages over [$Pd(PPh_3)_4$] (entry 4).

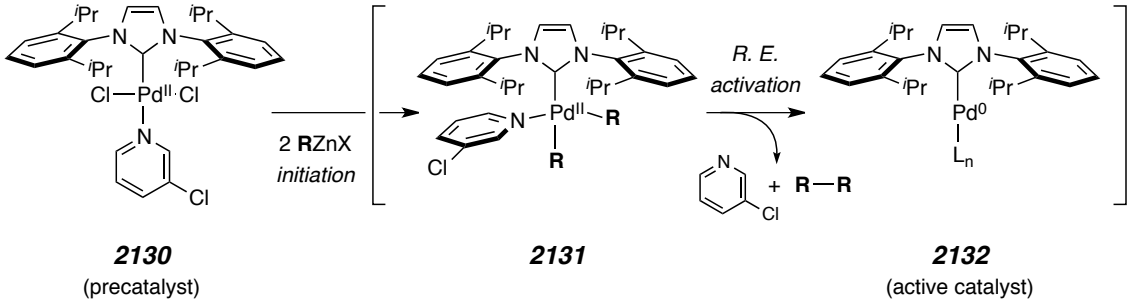
The examples presented in entries 3 and 4 are clearly an indication that the vinyl bromide **2127** undergoes oxidative addition at a substantially slower rate than does **2126**. What was being battled here was not simply an issue of reactivity, because GC-MS analysis of these reaction mixtures also revealed evidence for C–Br bond reduction, deborylation of **2103**, and, strangely, the 1,1-dimethylated analog of **2103**. Although the precise origin of this final by-product is unclear, a superior catalyst system was sorely needed. The high activity of palladium complexes of *N*-heterocyclic carbenes, and indeed complexes derived from many other transition metals as well,[123a] has become a well-

---

[122] Kranenburg, M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. The Effect of the Bite Angle of Diphosphane Ligands on Activity and Selectivity in Palladium-Catalyzed Cross-Coupling. *Eur. J. Inorg. Chem.* **1998**, 155–157.

recognized and synthetically useful phenomenon.[123b] Of particular note in this arena is the concept of PEPPSI (**P**yridine-**E**nhanced **P**recatalyst **P**reparation, **S**tabilization, and **I**nitiation) that has been introduced by Organ and co-workers.[93] These researchers were able to prepare air- and moisture-stable precatalysts–an example of which is the precatalyst PEPPSI™–IPr (**2130**, Scheme II–36)–and demonstrate their ability to cross-couple normally recalcitrant aryl and alkyl halides (and pseudohalides) in the Negishi reaction.[124] On the basis of computational and experimental studies, Organ and co-workers have proposed[93] that transmetalation of two equivalents of an organozinc donor (**R**ZnX) with precatalyst **2130**, reductive elimination from resulting Pd(II) species **2131**, and dissociation of the "throw away" 3-chlorpyridine ligand are the sequence of events that liberate the highly active NHC-ligated palladium(0) complex (**2132**).

Scheme II–36 | Activation of precatalyst **2130** in the presence of 2 equiv organozinc donor (**R**ZnX) to give rise to the active catalyst **2132** [adapted from ref 93].



123 (a) Herrmann, W. A. *N*-Heterocyclic Carbenes: A New Concept in Organometallic Catalysis. *Angew. Chem. Int. Ed.* **2002**, *41*, 1290–1309. (b) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. Palladium Complexes of *N*-Heterocyclic Carbenes as Catalysts for Cross-Coupling Reactions–A Synthetic Chemist's Perspective. *Angew. Chem. Int. Ed.* **2007**, *46*, 2768–2813.

124 Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Valente, C. A User-Friendly, All-Purpose Pd–NHC (NHC = *N*-Heterocyclic Carbene) Precatalyst for the Negishi Reaction: A Step Towards a Universal Cross-Coupling Catalyst. *Chem. Eur. J.* **2006**, *12*, 4749–4755.

Much to my delight, when the vinyl bromide **2127** was exposed to a premixed solution of **2130** (1 mol%), MeZnBr, and LiBr in THF/DMI at room temperature, a rapid and efficient reaction took place to give **2103** in a substantially improved yield (Table II–6, entry 5). Subsequent experimentation showed that not only was the MIDA boronate **2129** an equally competent substrate in this cross-coupling–giving rise to **2121** in 72% yield (entry 6)–but that the polar aprotic co-solvent DMI was completely unnecessary. The presence of DMI, which was reportedly required for certain substrates under Organ's protocol,[124] only served to complicate the purification of **2121**.

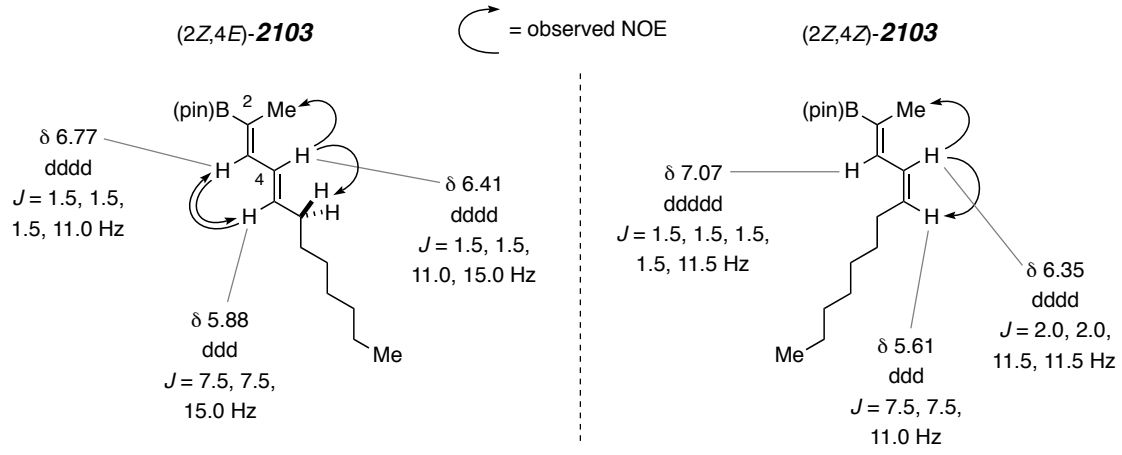


Figure II–3 | Key $^{3}J_{H,H}$, $^{4}J_{H,H}$, and chemical shift values for the isomeric dienyl boronates (2*Z*,4*E*)- and (2*Z*,4*Z*)-**2103**. The indicated NOE interactions permitted the unambiguous structural assignment of each isomer.

The constitution of each of (2*Z*,4*E*)- and (2*Z*,4*Z*)-**2103** could be readily ascertained from their respective $^{3}J_{H,H}$ and $^{4}J_{H,H}$ coupling values (Figure II–3). Moreover, the configuration of the $\Delta^{4,5}$ olefin within each of these isomers was evinced by the magnitude of the $^{3}J_{H,H}$ coupling constants (15.0 and 11.0–11.5 Hz, respectively). Gradient 1-D NOE (GOESY) experiments were conducted on the mixture of isomers (12:1) that was obtained from the conversion of **2126** to **2103** (cf. entry 2, Table II–6), wherein the olefinic ^{1}H resonances of the major and minor isomers were cleanly resolved.

Thus, irradiation of the resonance corresponding to H4 in the major [(2*Z*,4*E*)] isomer resulted in an enhancement of the resonances corresponding the allylic methyl (H1) and allylic methylene (H6). Irradiation of the same resonance in the minor [(2*Z*,3*Z*)] isomer likewise produced an enhancement in the upfield allylic methyl (H1) resonance, thereby firmly establishing the proposed structures. The structure of **2121**, which was formed as a single isomer, was unambiguously confirmed by its eventual conversion to **2103** (*vide infra*).

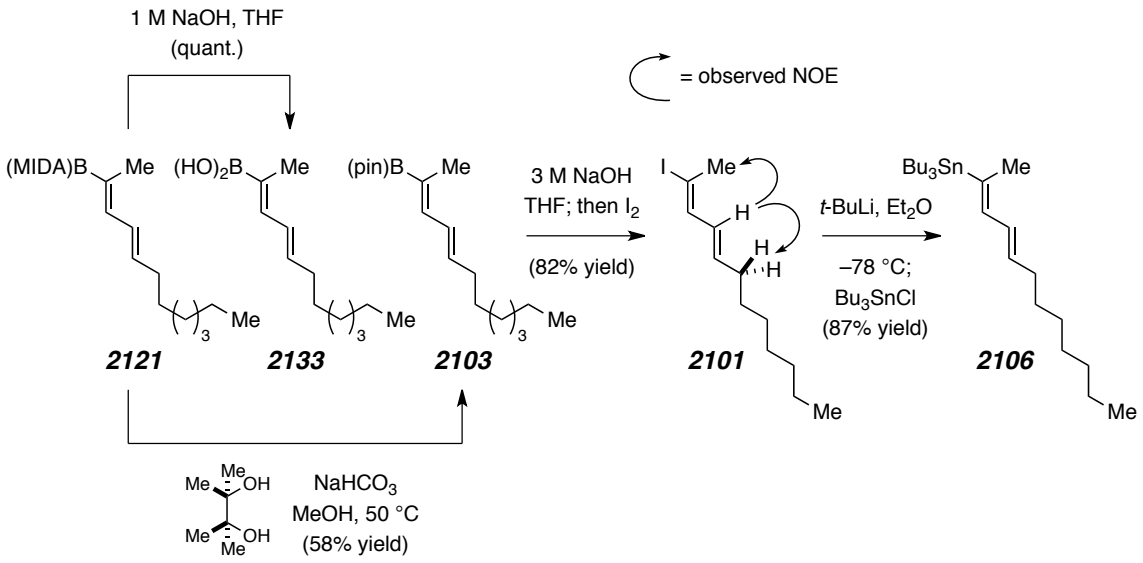
The vinyl pinacol boronate **2103** (and the boronic acid derived therefrom) is an obvious candidate for Suzuki–Miyaura cross-coupling; however, it can also serve as a precursor to other potentially useful intermediates (Scheme II–37). The ability of stable MIDA boronates such as **2121** to serve as surrogates to unstable boronic acids has been popularized by Burke and co-workers.[125] Thus, this compound could be readily converted to the boronic acid under mild conditions, which obviated the use of harsh oxidative conditions[126] that would have been required to produce **2133** from **2103**. Although an alternative means to access the pinacol boronate **2103** has been developed, it could also be conveniently generated from MIDA boronate **2121** by treatment with pinacol/$NaHCO_3$ in MeOH.[105] In turn, the dienyl iodide **2101** was smoothly produced by stereospecific iododeborylation[100] of **2103** and its configuration was confirmed by a gradient 1-D NOE experiment. Finally, treatment of the vinyl iodide **2101** with *t*-BuLi at low temperature and capture of the vinyl lithium species with Bu_3SnCl afforded the vinyl stannane **2106** in good yield.

---

125 Gillis, E. P.; Burke, M. D. A Simple and Modular Strategy for Small Molecule Synthesis: Iterative Suzuki–Miyaura Coupling of B-Protected Haloboronic Acid Building Blocks. *J. Am. Chem. Soc.* **2007**, *129*, 6716–6717.

126 Coutts, S. J.; Adams, J.; Krolikowski, D.; Snow, R. J. Two Efficient Methods for the Cleavage of Pinanediol Boronate Esters Yielding the Free Boronic Acids. *Tetrahedron Lett.* **1994**, *35*, 5109–5112.

Scheme II–37 | Production of **2133**, **2101**, and **2106** from either **2121** or **2103**.



G. NEW AVENUES OF DISCOVERY VIA THE π-ALLYL STILLE REACTION

G–1. IMPETUS AND REACTION SCOPE

The capricious and often low-yielding alkylation that was encountered in the preparation of the 2,2-dimethoxy ester **2078** (recall Table II–2) was, among other things (*vide supra*), a rather annoying bottleneck in the synthetic route. Moreover, it severely limited the types of strategies that could be used to access **2017**, which, until now, would have been limited to ester reduction. It was at this point that the π-allyl Stille reaction[127] of an allylic electrophile with an organostannane presented itself as a mild and selective alternative to the more violent conditions required for the enolate alkylation (Scheme II–38A). Inspired by two recent examples of the π-allyl Stille reaction in the arena of complex molecule synthesis,[128] it was proposed that a functionalized 1,4-diene such as **2134** could be prepared by the reaction of an appropriately substituted vinyl stannane with either of the allylic carbonates **2135** or **2136** under the action of catalytic palladium(0). Indeed, Castaño and Echavarren have disclosed the π-allyl Stille cross-coupling of allylic carbonates and found them to be superior substrates in both reaction rate and yield.[129a] If such an approach could be capitalized upon, then one could envision

---

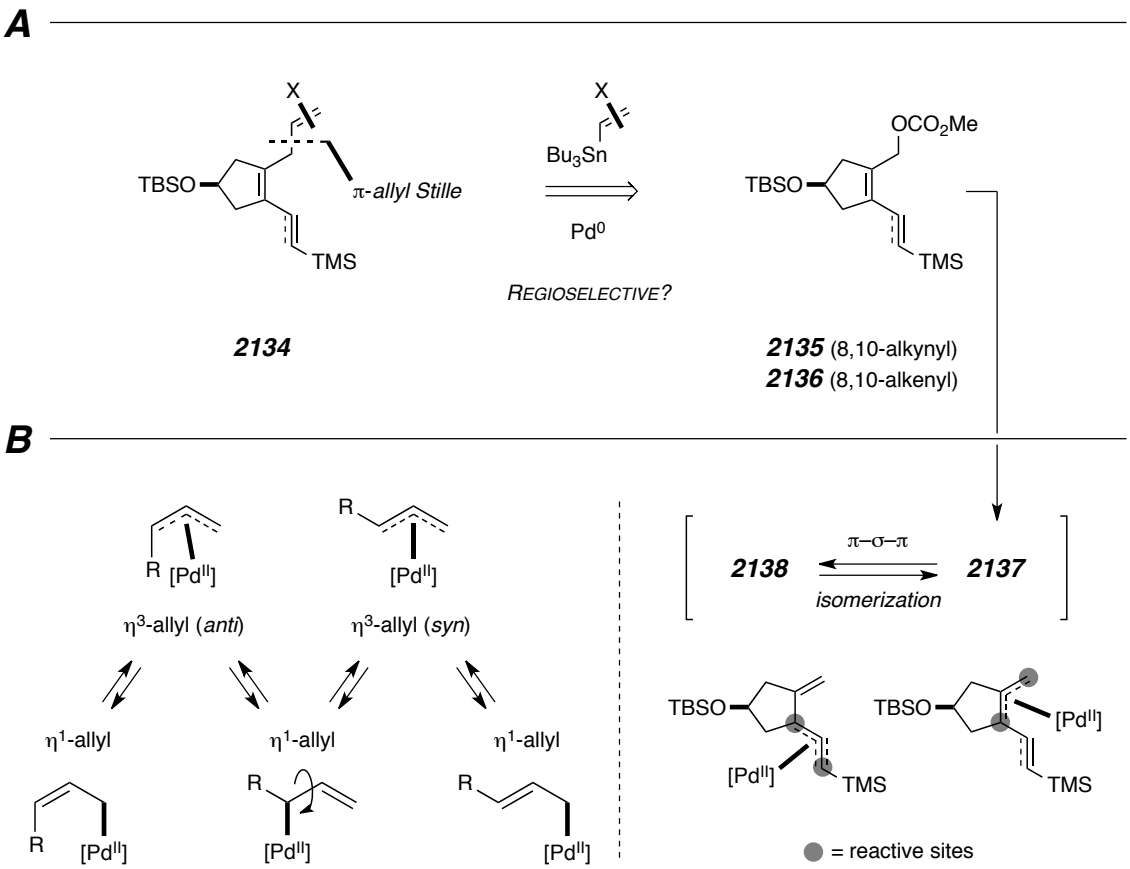
127 (a) Sheffy, F. K.; Stille, J. K. Palladium-Catalyzed Cross-Coupling of Allyl Halides with Organotins. *J. Am. Chem. Soc.* **1983**, *105*, 7173–7175. (b) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. Palladium-Catalyzed Cross-Coupling of Allyl Halides with Organotin Reagents: A Method of Joining Highly Functionalized Partners Regioselectively and Stereospecifically. *J. Am. Chem. Soc.* **1984**, *106*, 4833–4840. (c) Del Valle, L.; Stille, J. K.; Hegedus, L. S. Palladium-Catalyzed Coupling of Allylic Acetates with Aryl- and Vinylstannanes. *J. Org. Chem.* **1990**, *55*, 3019–3023.

128 (a) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. An Enantioselective Synthesis of FR182877 Provides a Chemical Rationalization of Its Structure and Affords Multigram Quantities of Its Direct Precursor. *J. Am. Chem. Soc.* **2003**, *125*, 5393–5407. (b) Shipe, W. D.; Sorensen, E. J. Convergent, Enantioselective Syntheses of Guanacastepenes A and E Featuring a Selective Cyclobutane Fragmentation. *J. Am. Chem. Soc.* **2006**, *128*, 7025–7035.

129 (a) Castaño, A. M.; Echavarren, A. M. Palladium-Catalyzed Cross-Coupling Reaction of Allyl Carbonates with Organostannanes. *Tetrahedron Lett.* **1996**, *37*, 6587–6590. (b) The studies carried out by Castaño and Echavarren regarding the qualitative relationship between reaction rate and the nucleofugality of the allylic electrophile suggested that oxidative insertion was the rate-limiting step.

the preparation of large number of potentially useful 1,4-diene intermediates (**2134**), their functionality being limited only by the nature of the vinyl stannane coupling partner.

Scheme II–38 | **A**: Retrosynthetic disconnection of the generic 1,4-diene **2134** via π-allyl Stille reactions of **2135** and **2136**. **B**: Potentially competing reaction manifolds via π–σ–π isomerization of the intermediate (η^3-allyl)palladium(II) complexes **2137** and **2138**.

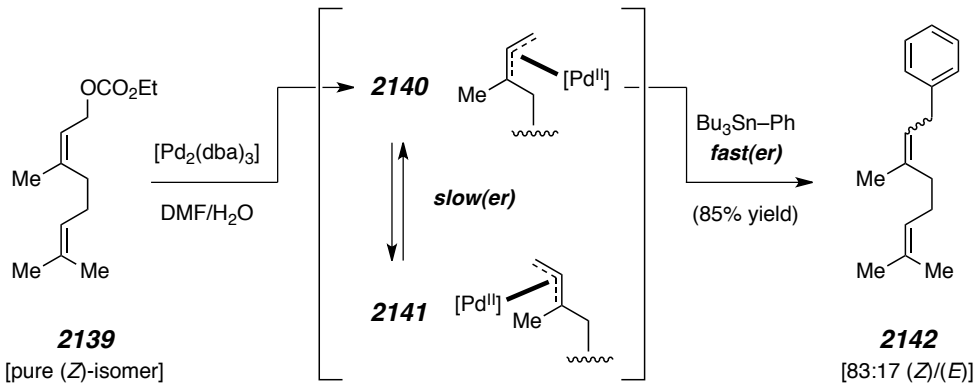


A potential caveat was recognized at the outset (Scheme II–38B). Namely, the (η^3-allyl)palladium(II) complex **2137** that would be generated upon oxidative insertion of palladium(0) into the allylic C–O bond of either **2135** or **2136** could be in equilibrium with the isomeric complex **2138**. This would be a consequence of the known π–σ–π isomerization[96] of (η^3-allyl)palladium(II) complexes through the intermediacy of their

(η^1-allyl)palladium(II) counterparts (cf. left portion of Scheme II–38B). Thus, within **2137** and **2138** there are three potential sites at which reductive elimination could occur and each pathway would give rise to a different, isomeric alkenyl (or allenyl) product.

The issues described above were addressed to an extent by the π-allyl Stille cross-coupling of nerol ethyl carbonate (**2139**) that was reported by Castaño and Echavarren[129a] (Scheme II–39). In their studies, isomerically pure **2139** was exposed to catalytic [$Pd_2(dba)_3$] in the presence of tri-*n*-butyl(phenyl)stannane to give rise to the benzylic diene **2142**. That the η^3-neryl (**2140**) and η^3-geranyl (**2141**) palladium(II) complexes were interconverting under the reaction conditions was implied by the isomeric purity of **2142**. However, the equilibrium ratio of **2140** and **2141** in solution is known to be *ca.* 1:1,[130] which suggests that the transmetalation and reductive elimination events occur at a comparable, if not slightly faster, rate than does π–σ–π isomerization (assuming that oxidative insertion is the rate-limiting step[129b]). It was therefore surmised that the η^3-allyl complex **2137** (Scheme II–38B) would be siphoned by transmetalation and subsequent reductive elimination at a rate faster than its interconversion with **2138**.

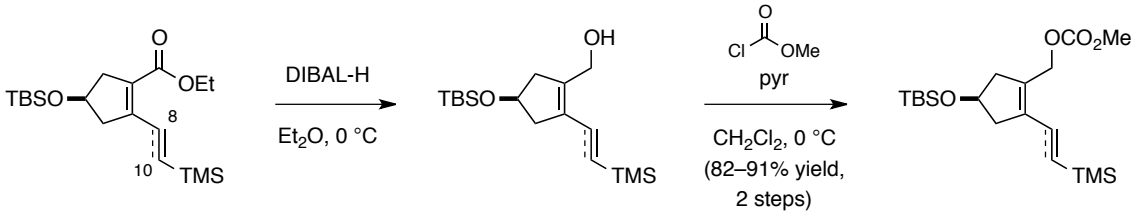
Scheme II–39 | A relevant π-allyl Stille cross-coupling reaction [adapted from ref 129a].



130 Åkermark, B.; Vitagliano, A. Reactivity and Syn–Anti Isomerization of (η^3-Geranyl)- and (η^3-Neryl)-palladium Complexes. Evidence for Electronic Control of the Regiochemistry of Nucleophilic Addition. *Organometallics* **1985**, *4*, 1275–1283.

The concerns discussed above would soon be laid to rest. But first the allylic carbonates **2135** and **2136** were prepared as shown in Scheme II–40. Reduction of either the Sonogashira (**2068**) or Heck (**2070**) cross-coupling products with DIBAL-H provided the allylic alcohols **2072** and **2143**, respectively. Exposure of each of these substances in crude form to methyl chloroformate/pyridine in CH_2Cl_2 afforded the allylic carbonates in 91% and 82% yield.

Scheme II–40 | Synthesis of the allylic carbonates **2135** and **2136** via reduction and acylation of the previously prepared ethyl esters **2068** and **2070**.



2068 (8,10-alkynyl)
2070 (8,10-alkenyl)

2072 (8,10-alkynyl)
2143 (8,10-alkenyl)

2135 (8,10-alkynyl)
2136 (8,10-alkenyl)

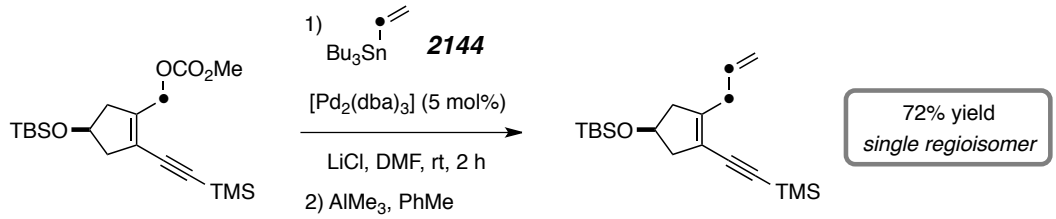
With multigram quantities of both of the allylic carbonates in hand, the π-allyl Stille cross-coupling of the enyne **2135** with commercially available tri-*n*-butyl(vinyl)-stannane (**2144**) was the first to be investigated (Scheme II–41A). In a slight modification of Castaño and Echavarren's procedure,[129a] these two species were sequentially added to a premixed, deep brown solution of LiCl and $[Pd_2(dba)_3]$ in DMF. Much to my delight, after a short reaction period clean conversion to a single product was observed by GC-MS. In order to remove the tin halide (Bu_3SnX) by-products, the crude material was subsequently treated with $AlMe_3$ in PhMe,[131] which generated the nonpolar, chromatographically separable Bu_3SnMe (a different solution to the tin halide problem was subsequently discovered and will be discussed shortly). The ^1H NMR spectrum of

[131] Renaud, P.; Lacôte, E.; Quaranta, L. Alternative and Mild Procedures for the Removal of Organotin Residues from Reaction Mixtures. *Tetrahedron Lett.* **1998**, *39*, 2123–2126.

the material that was isolated after this treatment was clearly consistent with the desired product (**2149**).

Scheme II–41 | **A**: First example of a successful π-allyl Stille reaction. **B**: Large-scale preparation of the oxygenated vinyl stannanes **2146** and **2148**.

A



2135 ***2149***

B

2145 ***2146*** ***2147*** ***2148***

Given that the terminal vinyl group within **2149** is of narrow synthetic utility, interest turned to the introduction of more highly oxidized functionality (e.g., enol ethers). The two oxygenated vinyl stannanes shown in Scheme II–41B were then synthesized. Neat 1,4-dioxene (**2145**)–prepared as a 74% w/w mixture with 1,4-dioxane[132]–was metalated with *t*-BuLi and the resulting vinyllithium species quenched

[132] Moss, R. D.; Paige, J. Improved Preparation of 2,3-Dihydro-*p*-dioxin (Dioxene). *J. Chem. Eng. Data* **1967**, *12*, 452–454.

with Bu_3SnCl to provide stannane **2146** in good yield.[133] Similarly, lithiation of ethyl vinyl ether (**2147**) according to Soderquist's protocol[134] (for methyl vinyl ether) and trapping with Bu_3SnCl afforded the stannyl enol ether **2148**.

The scope of the newly developed π-allyl Stille cross-coupling was then interrogated with each of the allylic carbonates **2135**/**2136** and four different organometallic donors (Table II–7). The cross-coupling of tri-*n*-butyl(vinyl)stannane (**2144**) proceeded equally well with **2136** as it did with **2135** to provide the skipped diene **2153** (entry 2, cf. entry 1). Similarly, the cross-coupling of stannylated 1,4-dioxene (**2146**) with either of the allylic carbonates proceeded uneventfully to give the potentially useful oxygenated 1,4-dienes **2150** and **2154**, respectively (entries 3 and 4).

The π-allyl Stille cross-coupling of stannane **2148** with either **2135** or **2136** was found to be very sluggish at room temperature, but simply heating these reaction mixtures to 50 °C smoothly affected the desired bond formation to yield the highly acid-sensitive enol ethers **2151** and **2155** (entries 5 and 6, Table II–7). Not unexpectedly, the hydrolytic lability of these compound presented a small challenge in that they were readily converted to the corresponding methyl ketones during SiO_2 chromatography. However, they could be isolated–*free from the majority of tin-containing residues*–when the SiO_2 was "deactivated" by addition of a few percent Et_3N to the mobile phase. Buffering one's mobile phase with Et_3N is a well-known and not particularly clever trick. But that most of the tin halide by-products were removed during this purification step, which greatly facilitated the studies described here, has scarcely been reported in the literature.[135]

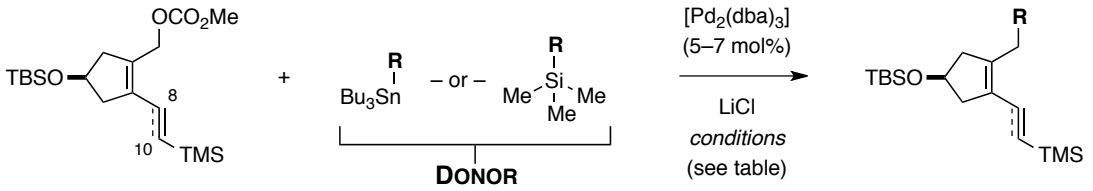
---

[133] Blanchot, V.; Fétizon, M.; Hanna, I. 2,3-Dihydro-1,4-dioxin in Organic Chemistry; Part II.1 Palladium-catalyzed Acylations of 5-Tributylstannyl-2,3-dihydro-1,4-dioxin: Preparation of 5-Acyl-2,3-dihydro-1,4-dioxins. *Synthesis* **1990**, 755–756.

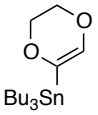
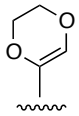
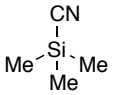
[134] Soderquist, J. A.; Ji-Ho Hsu, G. Pure, Unsolvated (α-Methoxyvinyl)lithium and Related Acyl Anion Equivalents via the Transmetalation of Organotin Compounds. *Organometallics* **1982**, *1*, 830–833.

[135] The difficulty associated with the removal of Bu_3SnX residues from relatively nonpolar products–such as those prepared in Table II–7–has been widely recognized in the literature. Several tactics have been reported that attempt to overcome this annoying problem, all of which have limitations. See ref 131 and references cited therein.

Table II–7 | Scope of the π-allyl Stille cross-coupling reactions of the allylic carbonates **2135**/**2136** with various organostannane (and organosilicon) donors.



2135 (8,10-alkynyl) ---------- ***2149–2152***
2136 (8,10-alkenyl) ---------- ***2153–2156***

entry	DONOR	SM #	LiCl (equiv)	*conditions*	R	pdt # (% yield)
1		***2135***	3.6	DMF rt, 1 h		***2149*** (96)
2	***2144***	***2136***	3.4	DMF rt, 0.5 h		***2153*** (91)
3		***2135***	3.3	DMF rt, 23 h		***2150*** (71)
4	***2146***	***2136***	3.3	DMF rt, 16 h		***2154*** (65)
5		***2135***	3.4	DMF 50 °C, 1 h		***2151*** (96)
6	***2148***	***2136***	4.1	DMF 50 °C, 1.5 h		***2155*** (94)
7[a]		***2135***	none	THF 60 °C, 17 h		***2152*** (46)
8[b]	***2157***	***2136***	none	THF 60 °C, 9 h		***2156*** (88)

[a] $[Pd(PPh_3)_4]$ (10 mol%) was used. [b] $[Pd(PPh_3)_4]$ (5 mol%) was used.

From a practical point of view, only in those reactions that employed the stannyl enol ether **2148** (entries 5 and 6, Table II–7) was "super dry" DMF required, as this hydrolytically unstable donor was decomposed at a rate that was competitive with its cross-coupling to provide the enol ethers **2151** and **2155** (which are themselves unstable toward prolonged heating in wet DMF). In the remaining cases (entries 1–4), off-the-shelf reagent grade DMF was more conveniently utilized, and in fact those reactions reached full conversion at a faster rate than was otherwise observed. Indeed, Castaño and Echavarren[129a] and others[136] have noted the beneficial effect that water can have on the rates and/or yields of palladium-catalyzed cross-coupling reactions.

The reactions shown in entries 7 and 8 of Table II–7, though not unrelated to the π-allyl Stille cross-coupling, employed the organometallic donor trimethylsilyl cyanide (**2157**) rather than an organostannane. This might seen like an odd way to prepare an allylic nitrile, but attempts to convert the alcohol **2072** into **2152** via traditional means (i.e., MsCl, Et_3N, CH_2Cl_2; NaCN, DMSO) resulted in complete decomposition of the intermediate mesylate. The procedure reported by Tsuji and co-workers[137] was found to be optimal, with the exception that conversion to the desired products was improved by the addition of an excess (5 equiv) of **2157**. Comparable results were obtained when these reactions were carried out in refluxing PhMe. Additionally, three other sets of conditions were explored for transforming **2135** into its allylic nitrile [$Pd(PPh_3)_4$ (cat.), with or without CuI (cat.), Bu_3SnCN, PhMe, 80 °C; [$Pd_2(dba)_3$ (cat.), LiCl, Bu_3SnCN, heat; $Pd(PPh_3)_4$ (cat.), $Zn(CN)_2$, DMF, 85 °C], all of which showed <5% conversion to the desired product (GC-MS). For reasons that are not entirely clear at present, the diene **2136** gave consistently higher yields in this transformation than did the enyne **2135**.

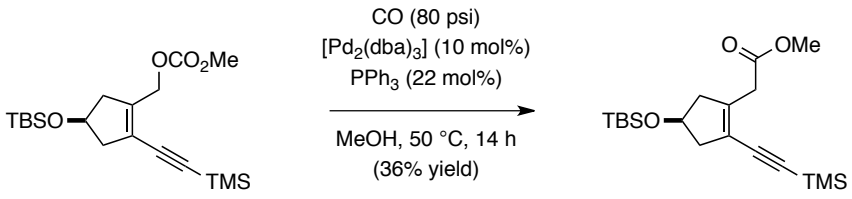
---

136 (a) Echavarren, A. M.; Tueting, D. R.; Stille, J. K. Palladium-Catalyzed Coupling of Vinyl Epoxides with Organostannanes. *J. Am. Chem. Soc.* **1988**, *110*, 4039–4041. (b) Tueting, D. R.; Echavarren, A. M.; Stille, J. K. Palladium Catalyzed Coupling of Organostannanes with Vinyl Epoxides. *Tetrahedron* **1989**, *45*, 979–992. (c) Zhang, H. –C.; Daves, Jr., G. D. Water Facilitation of Palladium-Mediated Coupling Reactions. *Organometallics* **1993**, *12*, 1499–1500.

137 Tsuji, Y.; Yamada, N.; Tanaka, S. Cyanation of Allylic Carbonates and Acetates Using Trimethylsilyl Cyanide Catalyzed by Palladium Complex. *J. Org. Chem.* **1993**, *58*, 16–17.

In addition to it's cross-coupling with organotin and organosilicon donors, the allylic carbonate **2135** was also subjected to palladium-catalyzed decarboxylation-carbonylation[138] with marginal success (Scheme II–42). In an unoptimized procedure, the methyl ester **2158**[139] could be prepared in exquisite purity, albeit in a meager 36% yield. Preliminary experimentation revealed that the addition of a trialkylamine (*i*-Pr_2NEt[140]) was severely detrimental to the reaction, giving **2158** in only 9% yield.

Scheme II–42 | Palladium(0)-catalyzed decarboxylation-carbonylation of **2135**.



2135 ***2158***

Finally, there is one additional aspect of the π-allyl Stille chemistry described here that merits brief discussion. In connection with a separate study, the simple allylic

---

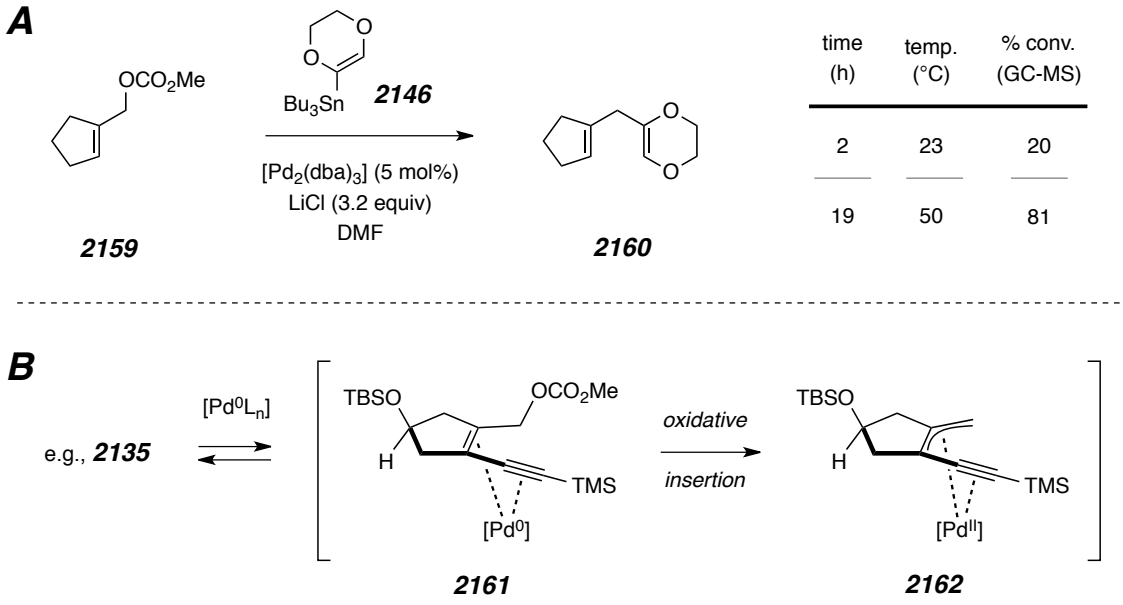
138 (a) Tsuji, J.; Sato, K.; Okumoto, H. Palladium-Catalyzed Decarboxylation-Carbonylation of Allylic Carbonates to Give β,γ-Unsaturated Esters Under Mild Conditions. *Tetrahedron Lett.* **1982**, *23*, 5189–5190. (b) Tsuji, J.; Sato, K.; Okumoto, H. Palladium-Catalyzed Decarboxylation-Carbonylation of Allylic Carbonates to Form β,γ-Unsaturated Esters. *J. Org. Chem.* **1984**, *49*, 1341–1344.

139 [*MJJ-V-62/72/75*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.49 [dddd, *J* = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.69 (s, 3H, $CH_2CO_2CH_3$), 3.34 (ABX_4, $\Delta\nu_{AB}$ = 60.3 Hz, J_{AB} = 16.5 Hz, J_{AX} = 1.0 Hz, J_{BX} = 1.5 Hz, 2H, $CH_2CO_2CH_3$), 2.78-2.71 [m, 2H, overlapping $CH_2CH(OTBS)CH_2$], 2.45 [dddddd, *J* = 2.0, 2.0, 2.0, 2.0, 3.5, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.39 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 4.0, 17.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 0.87 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.19 [s, 9H, $C{\equiv}CSi(CH_3)_3$], 0.05 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.04 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].
GC / LR EI-MS [5025015]: t_R 9.42 min; *m*/*z* (rel. int.) 366 (0.2, $M^{+\bullet}$), 351 (2, $M^{+\bullet}–CH_3^{\bullet}$), 309 [69, $M^{+\bullet}–C(CH_3)_3^{\bullet}$], 281 (100), 175 (31), 159 (10), 147 (8), and 89 (17).

140 Murahashi, S. –I.; Imada, Y.; Taniguchi, Y.; Higashiura, S. Palladium(0)-Catalyzed Carbonylation of Allyl Phosphates and Allyl Acetates. Selective Synthesis of β,γ-Unsaturated Esters. *Tetrahedron Lett.* **1988**, *29*, 4945–4948.

carbonate **2159** was prepared (Scheme II–43A). Whereas the cross-coupling of **2135** with stannane **2146** would usually reach full conversion in < 2 h at room temperature, the cross-coupling of **2159** with the same vinyl stannane had only reached 20% conversion to **2160**[141] under similar conditions.[142] Furthermore, even though heating the reaction mixture for a prolonged period (19 h) did improve the conversion (81%), the outcome was still far inferior to that obtained previously. Given that **2159** lacks the additional conjugated unsaturation that **2135** and **2136** each possess, these observations suggest that the type of internal coordination implied by complex **2161** (Scheme II–43B) might be essential. It may well be that coordination of the palladium(0) atom (and its associated ligand set) plays a dual role by first facilitating the oxidative insertion within **2161** and then cementing the resulting (η^3-allyl)palladium(II) complex **2162** into place.

Scheme II–43 | **A**: Qualitative reaction conversion data for the cross-coupling of **2159** with stannane **2146**. **B**: Does the type of coordination implied by **2161** facilitate oxidative insertion?



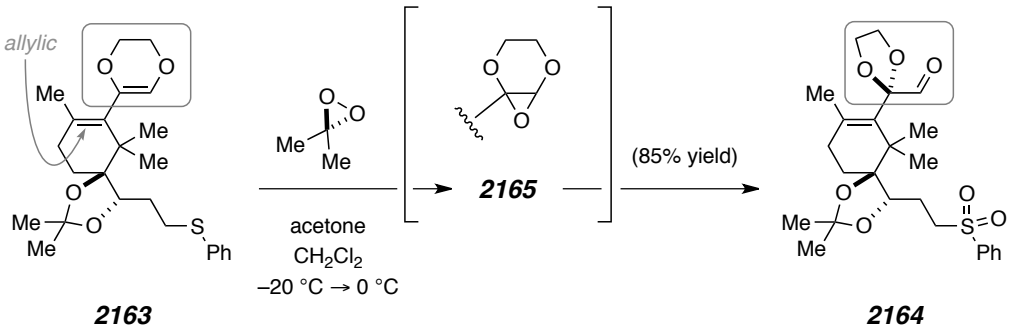
[141] [*MJJ-IV-94*] **GC / LR EI-MS** [5025015]: t_R 6.46 min; *m/z* (rel. int.) 166 (89, $M^{+\bullet}$) and 81 (100).

[142] The reaction times shown in Table II–7 are not necessarily the time *required* to reach full conversion.

G–2. REACTIVITY STUDIES OF 1,4-DIOXENYL EPOXIDES

What drove the studies presented in this section was the unearthing of the elegant work that has been reported by Fétizon and Hanna regarding the utility of 1,4-dioxene in organic synthesis.[143] Of particular note in this area is the generation and reactivity of epoxides derived from the 1,4-dioxene subunit, a representative example of which is shown in Scheme II–44. In work directed toward the synthesis of taxane diterpenoids, Hanna and co-workers[144b] reported the high-yielding production of the protected α-keto aldehyde **2164** by DMDO-mediated oxidation of the conjugated dioxenyl species **2163** (which was accompanied by sulfide oxidation). It is interesting to point out that this reaction, which presumably proceeded via spontaneous [1,2] C–O bond migration within the epoxydioxene **2165**, occurred *without* a Lewis acid catalyst.

Scheme II–44 | Spontaneous [1,2]-rearrangement of the epoxide (**2165**) derived from dioxenyl diene **2163** to provided the protected α-keto aldehyde **2164** [adapted from ref 144b].

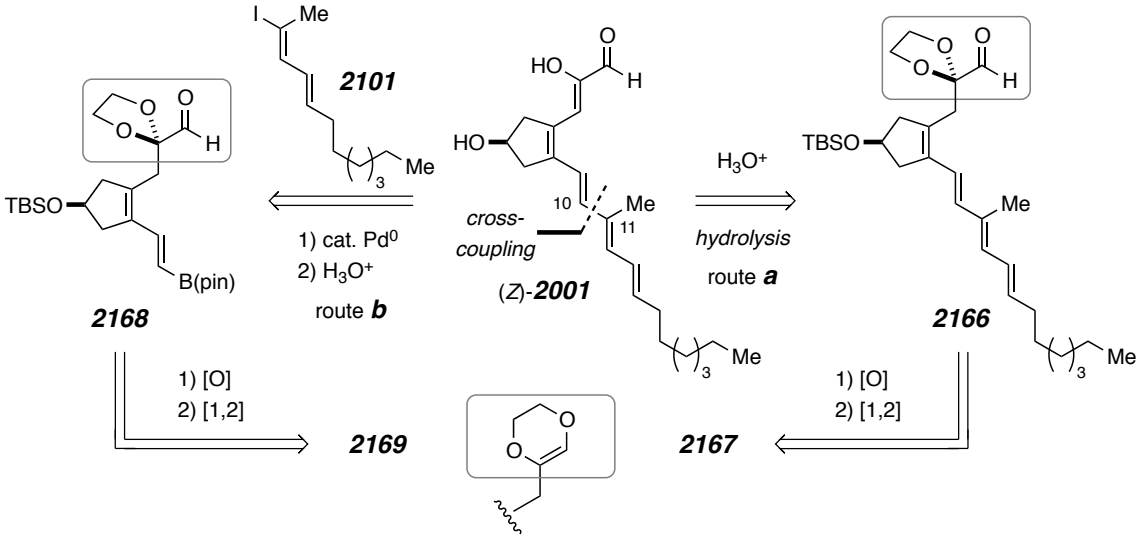


[143] For an early review, see: Fétizon, M.; Goulaouic, P.; Hanna, I. The Chemistry of 1,4-Dioxene (2,3-Dihydro-1,4-dioxin). Part VIII. *Heterocycles* **1989**, *28*, 521–527.

[144] (a) Baylon, C.; Hanna, I. 1,4-Dioxene in Organic Synthesis: Generation and Reactivity of Epoxydioxenes. *Tetrahedron Lett.* **1995**, *36*, 6475–6478. (b) Hanna, I.; Prangé, T.; Zeghdoudi, R. Synthesis of a Highly Functionalized AB Taxane Ring System Using 1,4-Dioxene. *Tetrahedron Lett.* **1996**, *37*, 7013–7016.

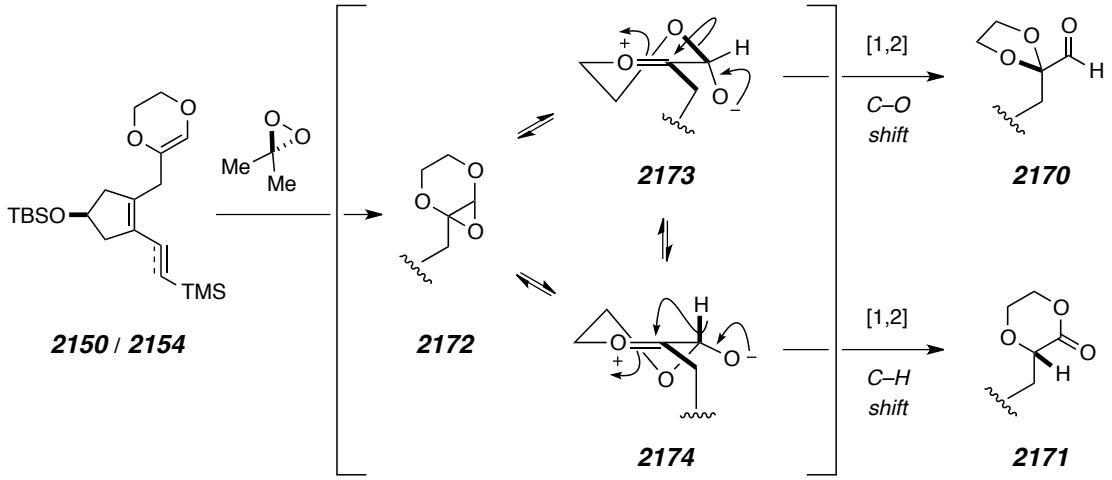
The reader should recognize that the highlighted region of the dioxolane protected α-keto aldehyde **2164** bears an uncanny resemblance to the 2,2-dimethoxy aldehyde subunit of **2017**, an intermediate whose preparation had been hampered by an enolate alkylation reaction that was, at best, reliably irreproducible. In light of the fact that the substituted 1,4-dioxenes **2150** and **2154** can now be easily accessed by the π-allyl Stille cross-coupling reaction (recall Table II–7, entries 3 and 4), the oxidative rearrangement chemistry developed by Hanna[144] could provide an alternative route to protected α-keto aldehydes such as **2166** and **2168** (Scheme II–45). Two potential routes can be envisioned to access the common pentaenol **2001**: **a**) hydrolysis of **2166**, which could in turn be prepared by oxidative rearrangement of dioxene **2167** with the C10–C11 bond having already been forged by cross-coupling, or **b**) oxidative rearrangement of the dienyl dioxene **2169** and *then* C10–C11 bond formation and subsequent hydrolysis. The latter of these two routes obviously provides a safety net should the selective oxidation of the dioxenyl polyene **2166** become problematic.

Scheme II–45 | Revised retrosynthetic analysis of the pentaenol **2001** via sequential oxidative rearrangement/cross-coupling (or vice versa) of the dioxenes **2169** and **2167**.



An important question that could not be addressed in Hanna and co-workers' studies was the partitioning of the reactive epoxydioxene intermediate into two competing reaction manifolds. Specifically, the thermal rearrangement of the epoxide (**2172**) that would be generated by treatment of either **2150** or **2154** with DMDO could evolve to generate the aldehyde **2170** or the dioxanone **2171** (or both) (Scheme II–46). A [1,2] C–*O* bond shift within the zwitterionic intermediate **2173** would provide the desired outcome (**2170**), whereas a [1,2] C–*H* bond shift within the alternative zwitterion **2174** would lead to **2171**. Interestingly, Hanna and co-workers did *not* observe the latter of these two pathways, but one example of such a process occurring in a related system has appeared in the literature.[145] Nevertheless, given the efficiency with which **2163** was converted into **2164** (see Scheme II–44), and also taking into account similar examples reported by Hanna,[144a] one could reasonably predict that the favored pathway in these systems is that of [1,2] C–O migration.

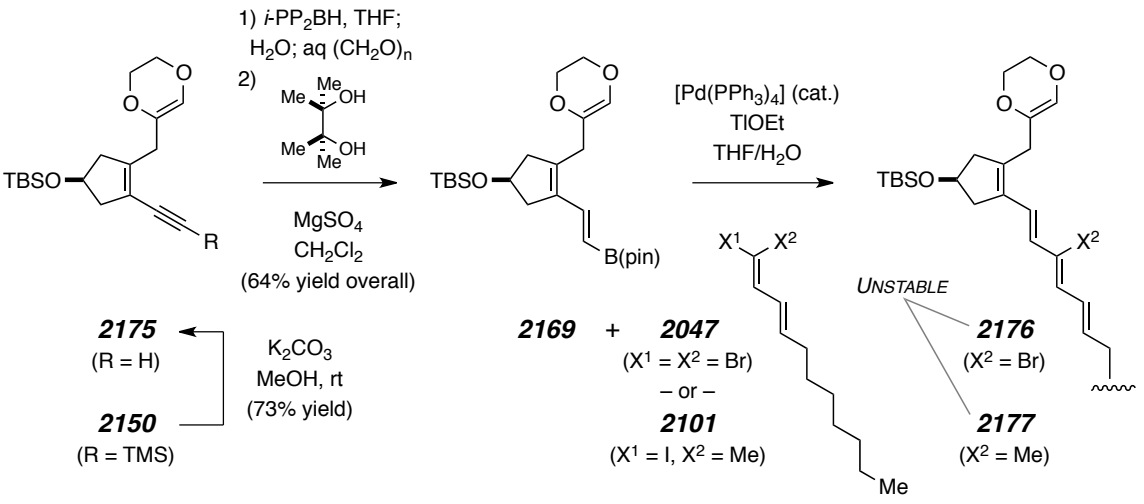
Scheme II–46 | Potentially competing modes of reactivity available to the epoxide **2172**.



[145] Adam, W.; Hadjiarapoglou, L.; Wang, X. Dimethyldioxirane Epoxidation of Alkenes Bearing Two Electron Donating Substituents. *Tetrahedron Lett.* **1991**, *32*, 1295–1298.

Of the two routes that have been proposed in the retrosynthetic analysis (see Scheme II–45), route **a** was the first to be explored. The intelligence that had been gathered from earlier studies suggested that the pinacol boronate **2169** should be readily accessible from the protected alkyne **2150** (Scheme II–47). Thus, exposure of the latter substrate to methanolic K_2CO_3 affected cleavage of the TMS protecting group to reveal the terminal alkyne **2175**. A sequence involving hydroboration of this substance with *i*-PP_2BH, hydrolysis, and esterification of the intermediate boronic acid with pinacol/ $MgSO_4$ provided the boronate **2169**.

Scheme II–47 | Synthesis and subsequent Suzuki cross-coupling of the boronate **2169**.



Earlier in this Chapter the synthesis of the polyene **2091** by the Suzuki cross-coupling of **2046** with **2047** was described. That product was prone to autoxidation and light-induced isomerization, but it could be isolated, purified, and handled when proper precautions were observed. When the boronate **2169** and either the 1,1-dibromoolefin **2047** or the vinyl iodide **2101** were reacted under Roush's conditions,[55b] the clean conversion to the polyenes **2176** and **2177** was inferred from TLC analysis (Scheme II–

47). However, it was somewhat disturbing to discover that, after reaction work-up and purification, both of these dioxenyl polyenes quickly decomposed at room temperature.

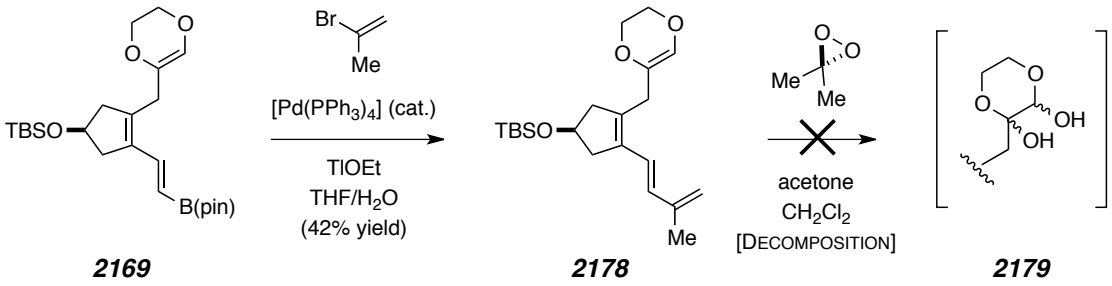
Even though it was now known that the polyenes **2176** and **2177** had very finite lifetimes, the possibility of selectively oxidizing the 1,4-dioxene subunit in the presence of an electron-rich polyene was still an enticing one. Fortunately, it was discovered that the dioxenyl triene **2178**[146] could be prepared by the cross-coupling of **2169** with 2-bromopropene (Scheme II–48), and this material was relatively more stable in comparison to the aforementioned intermediates. On the basis of studies that will be discussed shortly, it was expected that treatment of **2178** with a wet acetone solution of DMDO[147] would give rise to the diol **2179**, which should be readily identifiable by TLC and ^{1}H NMR analyses. However, carrying out the experiment as described resulted in extensive decomposition of the starting material. This unfortunate outcome in conjunction with the inherent instability of **2176** and **2177** made it obvious at this stage that further efforts in the route **a** lineage would be unproductive.

---

146 [*MJJ-IV-44*] **^{1}H NMR** (500 MHz, CD_2Cl_2): δ 6.48 [d, *J* = 16.0 Hz, 1H, C*H*=CHC(CH_3)=CH_2], 6.21 [d, *J* = 16.0 Hz, 1H, CH=C*H*C(CH_3)=CH_2], 5.81 (dd, *J* = 1.0, 1.0 Hz, 1H, CH_2C=C*H*), 4.98 [s, 1H, CH=CHC(CH_3)=CH_2], 4.96 [s, 1H, CH=CHC(CH_3)=CH_2], 4.48 [dddd, *J* = 3.5, 3.5, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 4.04-3.92 (AA'BB', 4H, OCH_2CH_2O), 2.88 [app s (ABq where $\Delta\nu_{AB}$ < 0.5 Hz), 2H, CH_2C=CH], 2.78 [dd, *J* = 7.0, 16.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.71 [dd, *J* = 6.5, 17.5 Hz, 1H, CH_2CH(OTBS)CH_2], 2.43 [dd, *J* = 3.0, 16.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.38 [dd, *J* = 3.0, 18.0 Hz, 1H, CH_2CH(OTBS)CH_2], 1.88 [s, 3H, CH=CHC(CH_3)=CH_2], 0.88 [s, 9H, (CH_3)$_3$CSi(CH_3)$_2$], 0.063 [s, 3H, (CH_3)$_3$CSi(CH_3)$_2$], and 0.059 [s, 3H, (CH_3)$_3$CSi(CH_3)$_2$].

147 Adam, W.; Hadjiarapoglou, L.; Jäger, V.; Klicić, J.; Seidel, B.; Wang, X. Epoxidation of Enol Silyl Ethers, Phosphates, Esters, and Lactones by Dimethyldioxirane. *Chem. Ber.* **1991**, *124*, 2361–2368.

Scheme II–48 | An attempt to selectively oxidize the triene **2178** was met with failure.

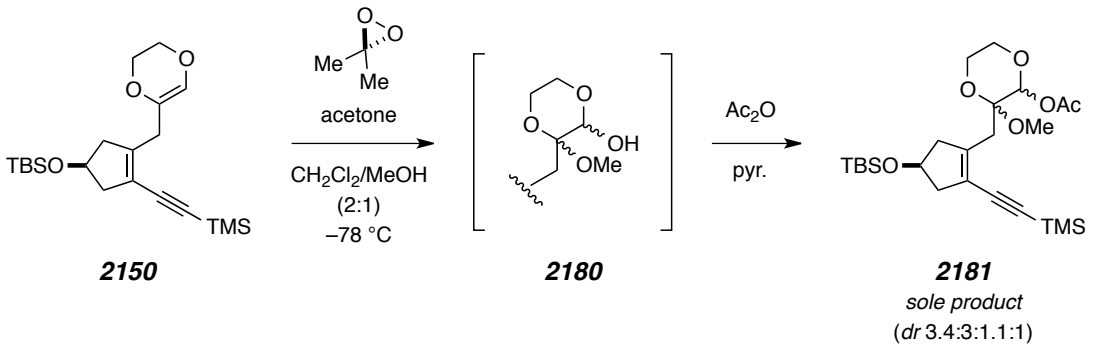


2169 ***2178*** ***2179***

At this juncture, attention necessarily turned to route **b**–namely, oxidative rearrangement of the 1,4-dioxene subunit prior to cross-coupling (cf. Scheme II–45). One could envision two approaches: i) direct oxidative rearrangement of the boronate **2169** or ii) oxidative rearrangement of the protected alkyne **2150** followed by 3-step introduction of the vinyl boronate. Because the attempted oxidation of the triene **2178** resulted only in starting material decomposition, it was impossible to decipher whether or not the epoxide-derived diol **2179** had indeed been produced. It therefore seemed prudent to determine the inherent selectivity of the DMDO oxidation by conducting the reaction with a more stable precursor. As it turned out, oxidation of the TMS alkyne **2150** with DMDO was a highly selective event. As expected, the intermediate oxidation product was quite moisture sensitive, and early studies indicated that analysis of this substance by ^{1}H NMR was not particularly informative. However, when the oxidation was carried out in a 2:1 CH_2Cl_2/MeOH solvent mixture (rather than pure CH_2Cl_2), the intermediate epoxide was rapidly trapped to provide an intermediate that was presumed to be the hemiacetal **2180** (Scheme II–49). Exposure of this material to Ac_2O/pyridine smoothly provided **2181**[148] as a mixture of all possible diastereomers, and, more importantly, as the major isolable product.

[148] [*MJJ-IV-145*] This material displayed the following diagnostic ^{1}H NMR resonances (500 MHz, $CDCl_3$): δ 5.57, 5.51, 5.46, and 5.37 [all s, 1H, C*H*(OAc)]; 4.47, 4.42, 4.41, and 4.39 [all dddd, J = 4.0,

Scheme II–49 | Oxidation of **2150** and derivatization of the resulting hemiacetal **2180**.



2150 ***2180*** ***2181***
sole product
(*dr* 3.4:3:1.1:1)

Emboldened by the successful oxidation/derivatization of **2150**, the [1,2] rearrangement of the intermediate epoxide was subsequently explored (Table II–8). It was quickly discovered that the epoxide **2182** does not, in contrast to Hanna's observations, rearrange under purely thermal conditions, as heating in both CH_2Cl_2 and PhMe produced no observable change (entries 1 and 2). In *all* of the examples reported by Hanna and co-workers (e.g., **2163** → **2164**, Scheme II–44) an additional double bond is conjugated with the 1,4-dixoene π-system. This feature is not enjoyed by **2150**, which suggests that the allylic nature of the intermediate oxocarbenium ion in Hanna's examples played a crucial role in lowering the barrier for epoxide ring opening.

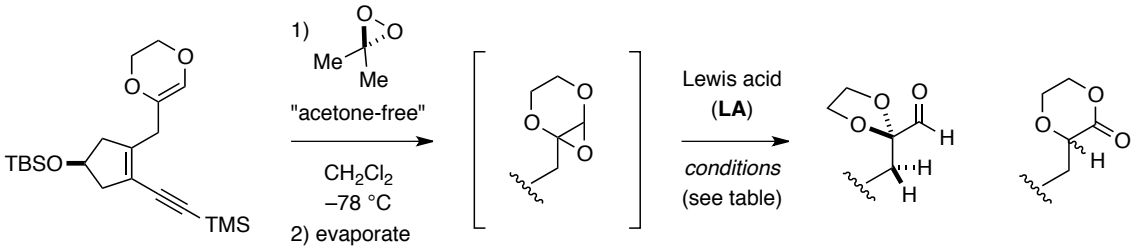
That the rearrangement of **2182** would require promotion by a Lewis acid was now unavoidable. A general procedure was thus developed that would allow for the sampling of several Lewis acid-catalysts. The procedure involved 1) oxidation of **2150** with "acetone free" DMDO[149] (*vide infra*) at low temperature, 2) removal of the solvent and excess DMDO under a stream of dry N_2, and, if necessary, 3) recharging the reaction flask with a different solvent/reagent combination. The extreme sensitivity of the

4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)]; 3.408, 3.406, 3.353, and 3.351 (all s, 3H, OC*H*$_3$); and 2.189, 2.185, 2.16, and 2.13 [all s, 3H, C(O)C*H*$_3$].

[149] Gibert, M.; Ferrer, M.; Sánchez-Baeza, F.; Messeguer, A. Availability and Reactivity of Concentrated Dimethyldioxirane Solutions in Solvents Other Than Acetone. *Tetrahedron* **1997**, *53*, 8643–8650.

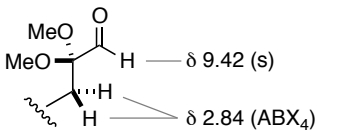
intermediate epoxide **2182** toward moisture necessitated the use of "acetone free" DMDO. According to the reported procedure,[149] solutions of DMDO in CH_2Cl_2 were prepared that could be more reliably dried than the corresponding acetone solutions.

Table II–8 | A sampling of thermal and Lewis acid-mediated conditions for the rearrangement of the *in situ* generated epoxy enyne **2182**.



2150 ***2182*** ***2170*** *VS.* ***2171***

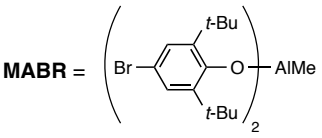
entry	**LA**	*conditions*	outcome
1	none	CH_2Cl_2, 60 °C	[NO REACTION]
2	none	PhMe, 110 °C	[NO REACTION]
3	$MgCl_2$	THF, 0 °C → rt	>1:20 ***2170*** / ***2171*** [86% yield, *dr* 1.3:1]
4	$ZnBr_2$	CH_2Cl_2, 50 °C	1:6.1 ***2170*** / ***2171*** [+ other components]
5	$Yb(OTf)_3$	CH_2Cl_2, 0 °C	1.1:1 ***2170*** / ***2171*** [+ other components]
6	MABR	CH_2Cl_2, –78 °C	***2170*** present [but mostly DECOMP.]
7	$Al(OC_6F_5)_3$	CH_2Cl_2, –78 °C	
8	$ZnI_2(Cl_2)$	CH_2Cl_2, 0 °C	



2183

1) DIBAL-H
CH_2Cl_2
–78 °C
2) EtOAc;
MeOH

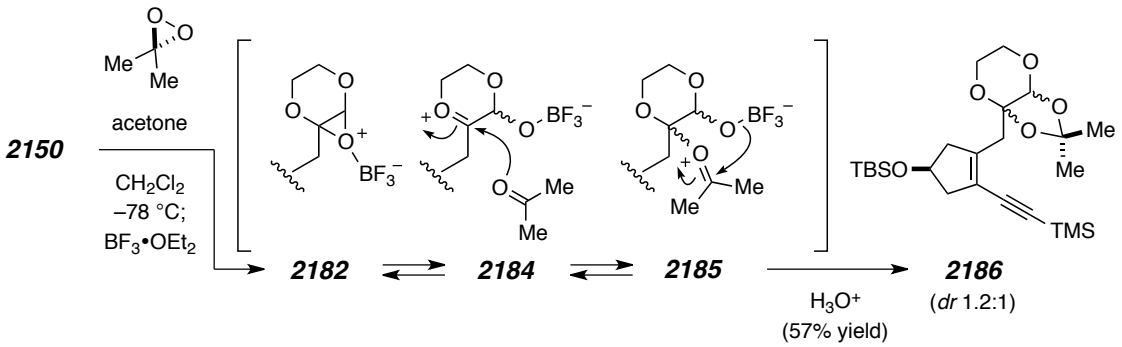
2178



Additionally, the final step in the aforementioned procedure was found to be essential when strong Lewis acids were employed because the acetone (produced upon DMDO oxidation) was capable of intercepting (**2184** → **2185**) the intermediate

oxocarbenium ion (Scheme II–50). Namely, early attempts to promote the rearrangement **2182** in the presence of BF_3•OEt_2 *without* solvent removal prior to reagent addition led to the clean formation of the 1,2-acetonide **2186**.

Scheme II–50 | Capture of the epoxide **2182** by acetone in the presence of BF_3•OEt_2.



Returning once again to Table II–8, it was discovered that the selective [1,2] rearrangement of the epoxide **2182** was, in practice, an ineffective means for generating **2170**. Among the salad of Lewis acids that were examined, only $MgCl_2$ gave rise to a single product–the dioxanone **2171** (entry 3)–that, unfortunately, arose via [1,2] C–H shift of the intermediate epoxide (cf. Scheme II–46). In addition to its formation with $MgCl_2$, the dioxanone **2171** was also observed with $ZnBr_2$ (entry 4) and $Yb(OTf)_3$ (entry 5), but in these instances it comprised an incrementally smaller portion of the overall product mixture and was co-produced with the desired aldehyde **2170**. Although the presence of **2170** could be inferred by ^{1}H NMR analysis of the crude reaction profiles obtained with the Lewis acids methylaluminum bis(4-bromo-2,6-di-*tert*-butyl-phenoxide)[150] (MABR, entry 6), aluminum tris(pentafluorophenoxide) (entry 7), and zinc

[150] Yamamoto and co-workers originally introduced MABR as a catalyst for the efficient rearrangement of various epoxides. See: (a) Maruoka, K.; Ooi, T.; Yamamoto, H. Organoaluminum-Promoted Rearrangement of Epoxy Silyl Ethers to β-Siloxy Aldehydes. *J. Am. Chem. Soc.* **1989**, *111*, 6431–6432. (b) Maruoka, K.; Ooi, T.; Nagahara, S.; Yamamoto, H. Organoaluminum-Catalyzed Rearrangement of Epoxides. A Facile Route to the Synthesis of Optically Active β-Siloxy Aldehydes.

iodide/chloride (entry 8), in all instances its formation was accompanied by extensive decomposition of the starting material and/or product(s). It should be mentioned that a pure sample of the aldehyde **2170** could not be prepared by the method described here. For comparison purposes, the similarly substituted 2,2-dimethoxy aldehyde **2183** was therefore prepared by DIBAL-H reduction of the corresponding ester **2078**. The diagnostic aldehyde [δ 9.37 (s)] and β-methylene [δ 2.83 (AB pattern)] resonances that were observed for **2170** in the experiments of Table II–8 are in good agreement with those assigned[151] for **2078** [δ 9.42 (s), and 2.84 (ABX_4 pattern), respectively].

Although the viability of the original retrosynthetic plan described at the beginning of this section had now been seriously compromised, related efforts pursuant to route **b** would not be abandoned just yet. In connection with the studies described in this section, the model cinnamyl-derived 1,4-dioxene **2189** was prepared and its reactivity briefly interrogated (Scheme II–51). Acylation of cinnamyl alcohol (**2187**) with methyl chloroformate provided the known[152] cinnamyl methyl carbonate **2188**.[153] A π-allyl Stille

---

Tetrahedron **1991**, *47*, 6983–6998. (c) Maruoka, K.; Bureau, R.; Ooi, T.; Yamamoto, H. Selective Rearrangement of Trisubstituted Epoxides to Aldehydes or Ketones. *Synlett* **1991**, 491–492.

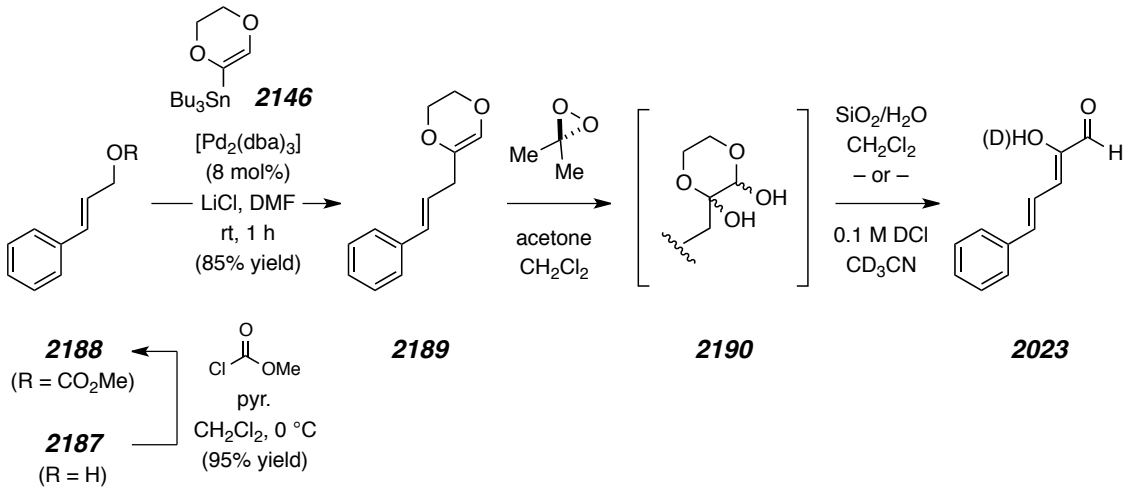
151 [*MJJ-III-31/39*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.42 (s, 1H, C*H*O), 4.41 [dddd, *J* = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.312 [s, 3H, $CH_2C(OCH_3)_2CHO$], 3.310 [s, 3H, $CH_2C(OCH_3)_2CHO$], 2.84 [ABX_4, $\Delta\nu_{AB}$ = 30.8 Hz, J_{AB} = 14.5 Hz, $J_{AX} = J_{BX}$ = 1.5 Hz, 2H, $CH_2C(OCH_3)_2CHO$], 2.66 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 7.0, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.59 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 7.0, 17.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.38 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 4.0, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.27 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 4.0, 17.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 0.87 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.19 [s, 9H, $C{\equiv}CSi(CH_3)_3$], and 0.03 [s, 6H, $(CH_3)_3CSi(CH_3)_2$].
GC / LR EI-MS [5029021]: t_R 11.76 min; *m/z* (rel. int.) 410 (1, $M^{+\bullet}$), 395 (1, $M^{+\bullet}–CH_3^{\bullet}$), 381 (72, $M^{+\bullet}–CHO^{\bullet}$), 353 [13 $M^{+\bullet}–C(CH_3)_3^{\bullet}$], 249 (4), 219 (4), 175 (13), 159 (6), 147 (11), and 103 {100, $[C(OCH_3)_2CHO]^+$}.

152 Lehmann, J.; Lloyd–Jones, G. C. Regiocontrol and Stereoselectivity in Tungsten-Bipyridine Catalysed Allylic Alkylation. *Tetrahedron* **1995**, *51*, 8863–8874.

153 [*MJJ-III-298*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41-7.38 (m, 2H, C_6H_5), 7.34-7.31 (m, 2H, C_6H_5), 7.29-7.25 (m, 1H, C_6H_5), 6.69 (ddd, *J* = 1.5, 1.5, 16.0 Hz, 1H, PhC*H*=CH), 6.30 (ddd, *J* = 6.5, 6.5, 16.0 Hz, 1H, PhCH=C*H*), 4.80 (dd, *J* = 1.5, 6.5 Hz, 1H, $CH_2OCO_2CH_3$), and 3.81 (s, 3H, OCO_2CH_3).
GC / LR EI-MS [5027016]: t_R 8.03 min; *m/z* (rel. int.) 192 (22, $M^{+\bullet}$), 133 (20, $M^{+\bullet}–C_2H_3O_2^{\bullet}$), 117 (71, $M^{+\bullet}–C_2H_3O_3^{\bullet}$), 115 (100, $M^{+\bullet}–C_6H_5^{\bullet}$), 105 (32), 91 [23, $(C_7H_7)^+$], and 77 [21, $(C_6H_5)^+$].

cross-coupling reaction of this material with stannane **2146** proceeded uneventfully to deliver **2189**[154] as a single regioisomer in commendable yield. Upon oxidation of this substance with DMDO/acetone, it was discovered, wholly serendipitously, that the putative intermediate **2190** smoothly hydrolyzed to the previously prepared dienol **2023** during SiO_2 chromatography. In practice, wet SiO_2 in CH_2Cl_2 was employed to more reliably accomplish this task.

Scheme II–51 | Regioselective preparation of the cinnamyl-derived 1,4-dioxene **2189** and its subsequent DMDO-mediated oxidation and hydrolysis.



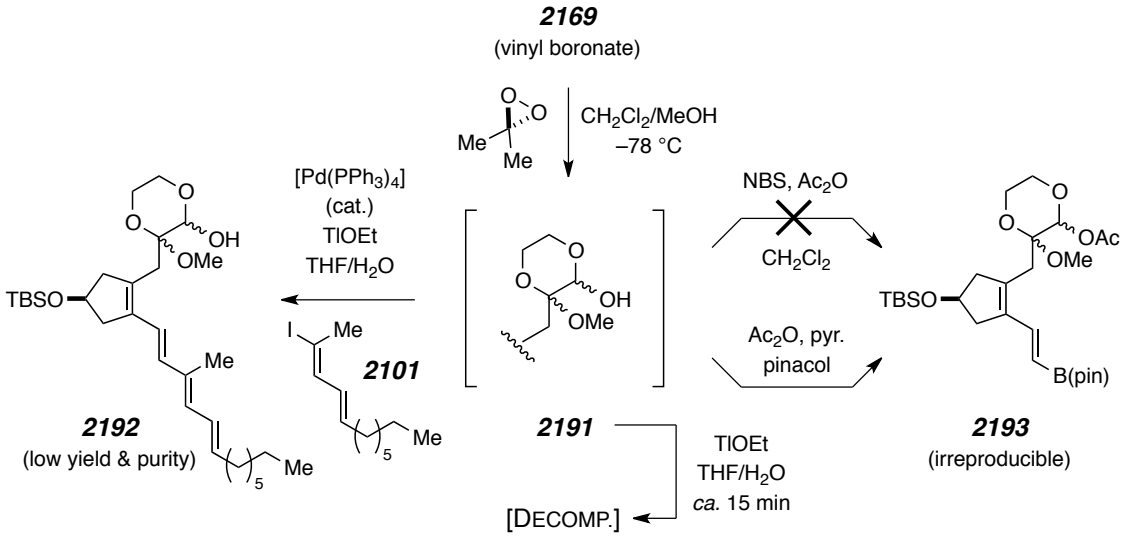
More interestingly, the fate of intermediate diol **2190** in 0.1 M DCl/CD_3CN could be monitored by ^1H NMR spectroscopy and, reassuringly, the same family of intermediates that were observed during the hydrolysis the 2,2-dimethoxy aldehyde **2020** (recall Figure II–1, Chapter II, Section C) were also detected under these conditions. The

---

154 [*MJJ-III-300/IV-68*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.37-7.35 (m, 2H, C_6H_5), 7.30 (dd, *J* = 7.0, 7.0 Hz, 2H, C_6H_5), 7.21 (dddd, *J* = 1.5, 1.5, 7.0, 7.0 Hz, 1H, C_6H_5), 6.46 (ddd, *J* = 1.5, 1.5, 16.0 Hz, 1H, PhC*H*=CH), 6.19 (ddd, *J* = 6.5, 6.5, 16.0 Hz, 1H, PhCH=C*H*), 5.90 (dd, *J* = 1.0, 1.0 Hz, 1H, CH_2C=C*H*), 4.12-4.00 (AA'BB', 4H, OCH_2CH_2O), and 2.87 (ddd, *J* = 1.0, 1.0, 6.5 Hz, 2H, CH_2).
GC / LR EI-MS [5027016]: t_R 9.07 min; *m/z* (rel. int.) 202 (100, $M^{+\bullet}$), 145 (29), 130 (20), 129 (27), 128 (16), 127 (27), 117 (74, $M^{+\bullet}$–$C_4H_5O_2^{\bullet}$), 115 (64), and 91 [27, $(C_7H_7)^+$].

results of these experiments raised the possibility that an oxidation/cross-coupling/ hydrolysis sequence involving the vinyl boronate **2169** could be carried out in a similar manner to access the α-keto aldehyde enol present in **2001**. When the DMDO-mediated oxidation of **2169** was carried out in CH_2Cl_2/MeOH at low temperature, selective oxidation of the dioxenyl moiety did indeed occur to give the hemiacetal **2191**. However, its subsequent *in situ* cross-coupling with the vinyl iodide **2101** was neither clean nor high yielding (Scheme II–52). Additionally, the diol derived from **2169** (i.e., from DMDO-mediated oxidation in pure CH_2Cl_2) suffered a similar fate. The reason for this became apparent when **2191** was exposed to TlOEt in THF/H_2O in the *absence* of **2101** and [$Pd(PPh_3)_4$], wherein decomposition occurred rapidly (≤ 15 min) at room temperature. Finally, attempts to prepare a more stable derivative of **2191** via acetylation (cf. **2150** → **2181**, Scheme II–49) were confounded by the base sensitivity of the vinyl pinacol boronate.

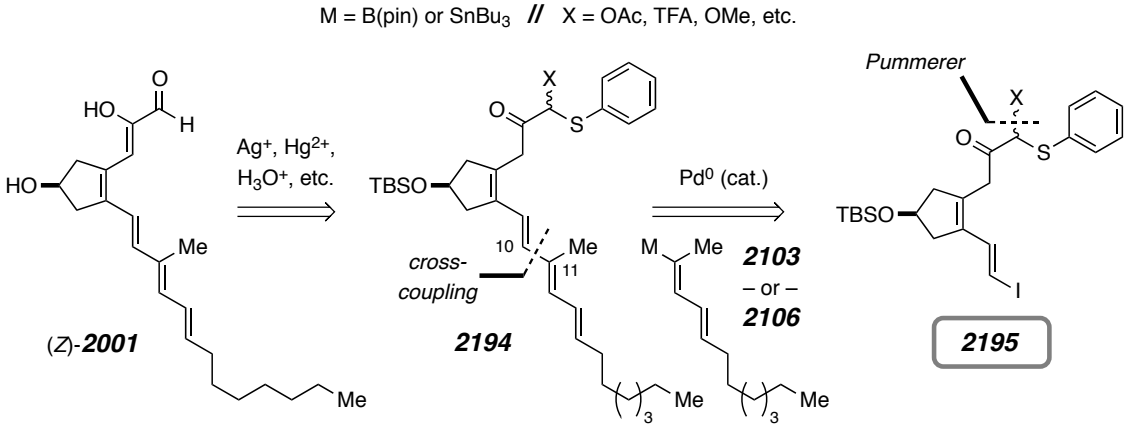
Scheme II–52 | Marginally productive reactions of the hemiacetal **2191**.



G–3. (OXIDATIVE) PUMMERER REARRANGEMENT STUDIES

The aftermath of the studies described in the previous section required that a fundamentally different tactic be pursued for the synthesis of the pentaenol **2001**. The anticipated fragility of the highly unsaturated framework of this intermediate was still viewed as a compelling incentive to generate this species at a late stage in the synthetic sequence, preferably during the penultimate step. As before, this requires that a suitably functionalized precursor be prepared from which **2001** could be liberated under mild hydrolytic reaction conditions. If we suppose for the moment that (*Z*)-**2001** could be generated by hydrolysis of the *O*,*S*-acetal within **2194** (Scheme II–53A), then the opportunity to employ a Pummerer rearrangement[155] becomes apparent. Retrosynthetic disconnection of the C10–C11 bond within this intermediate then reveals, as usual, a vinyl organometallic species (**2103** or **2106**) and the vinyl iodide **2195**. Their union would of course be affected by Stille/Suzuki cross-coupling reactions.

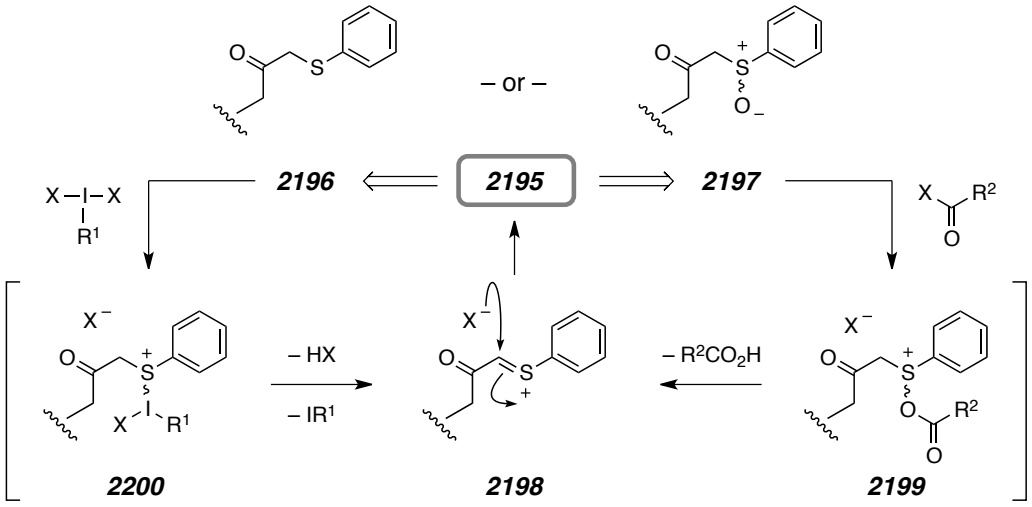
Scheme II–53 | Retrosynthetic analysis of **2001** via sequential cross-coupling and hydrolysis of the *O*,*S*-acetal **2195**.



[155] (a) Pummerer, R. Über Phenyl-sulfoxyessigsäure. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 2282–2291. (b) Pummerer, R.; Über Phenylsulfoxy-essigsäure (II). *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1401–1412.

It was envisioned that the *O*,*S*-acetal **2195** could arise via two distinct Pummerer processes that would emanate from either the β-keto sulfide **2196** or the β-keto sulfoxide **2197** (Scheme II–54). Whereas the β-keto sulfoxide **2197** would give rise to the thionium ion **2198** via the more traditional "non-oxidative" Pummerer intermediate **2199**, a distinct pathway, involving oxidative rearrangement of **2200** with a 10–I–3 iodane, would be available to **2196**. These two processes necessarily converge to the same thionium ion **2198**, the subsequent nucleophilic capture of which would deliver the *O*,*S*-acetal **2195**.

Scheme II–54 | Oxidative (**2196** → **2200**) and non-oxidative (**2197** → **2199**) Pummerer reactions to access **2195**, both of which converge to the same thionium ion (**2198**).



The generation and inter- and intramolecular capture of α-acyl thionium ions such as **2198** is a method that has found widespread use in the synthesis of carbo- and heterocyclic compounds.[156] Almost without exception, their formation is triggered by the action of Brønsted acids or carboxylic acid anhydrides on β-keto *sulfoxide* precursors.

[156] (a) Padwa, A.; Gunn, Jr., D. E.; Osterhout, M. H. Application of the Pummerer Reaction Toward the Synthesis of Complex Carbocycles and Heterocycles. *Synthesis* **1997**, 1353–1377. (b) Bur, S. K.; Padwa, A. The Pummerer Reaction: Methodology and Strategy for the Synthesis of Heterocyclic Compounds. *Chem. Rev.* **2004**, *104*, 2401–2432.

However, the hypervalent iodine(III)-triggered oxidative Pummerer rearrangements of β-keto *sulfide* precursors are relatively unexplored and have been relegated primarily to Friedel–Crafts alkylation of the intermediate thionium ions.[157]

Early attempts to assemble the sulfide **2201** and the sulfoxide **2223** revolved largely around the addition of organometallic species to either the nitrile **2152** or the methyl ester **2158** (Scheme II–55). Takeda and co-workers have reported the reaction of thioacetals and aliphatic nitriles in the presence of the low-valent titanocene(II) species $Cp_2Ti[P(OEt)_3]_2$.[158] Vinylimido complexes (cf. **2202**) are proposed to exist under these conditions, from which aliphatic ketones were produced in good yield upon hydrolysis (aq NaOH). In one instance, the use of tris(phenylthio)methane gave rise to a β-keto sulfide[158] (cf. **2201**). Unfortunately, when the allylic nitrile **2152** was exposed to these conditions, the starting material remained unchanged for an extended period of time.

Although nitriles are known to be excellent precursors to aldehydes, attempts to prepare **2205** by DIBAL-H reduction of **2152** resulted only in decomposition of the starting material and/or product (Scheme II–55). This result perhaps suggests that the aldehyde **2205** is inherently unstable, since, as it should be recalled, a DIBAL-H reduction is involved in the preparation of **2152**. Addition reactions of the lithium anion **2204**, which was prepared by deprotonation of methyl phenyl sulfoxide with LDA, were subsequently explored. Thus, addition of the allylic nitrile **2152** to a solution of **2204**– with or without addition of the potent activator HMPA–left the starting material

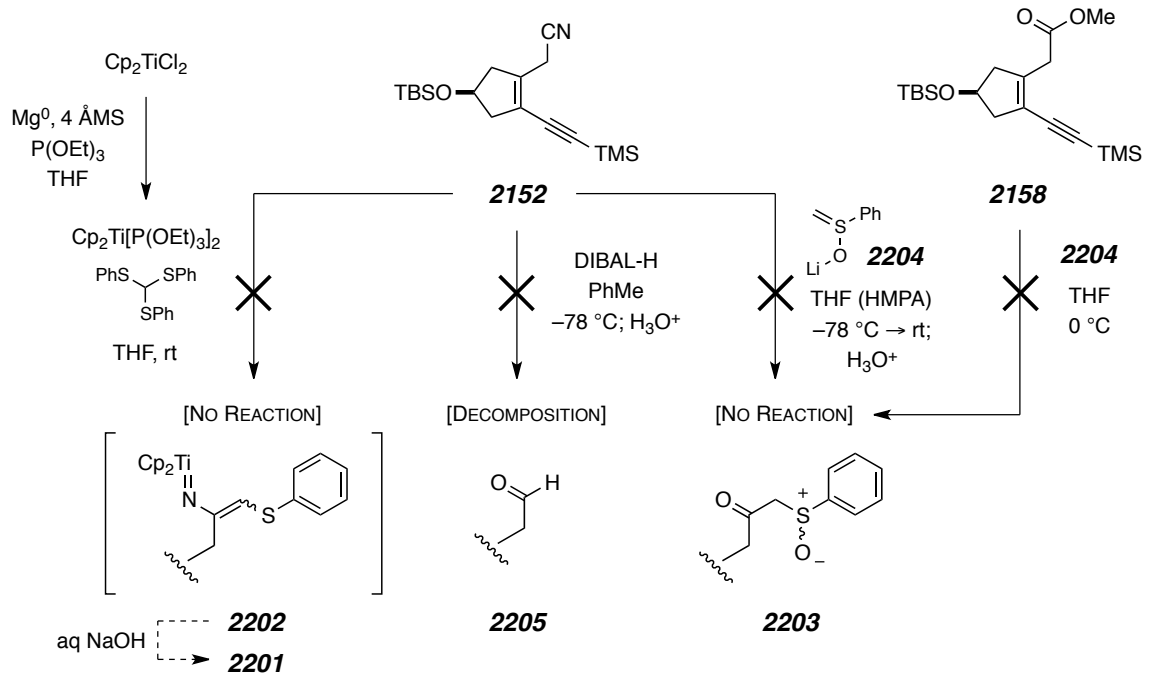
---

[157] (a) Tamura, Y.; Yakura, T.; Shirouchi, Y.; Haruta, J. Pummerer-Type Reaction of α-Acylsulfides Using Phenyl Iodosyl Bis(trifluoroacetate). *Chem. Pharm. Bull.* **1986**, *34*, 1061–1066. (b) Wang, H. –M; Lin, M. –C.; Chen, L. –C. Synthesis of 4*H*-Pyrrolo[2,1-*c*][1,4]benzothiazines and *N*-Methyl-1,3,4,5-tetrahydro-2*H*-3-Benzazepin-2-ones. *Heterocycles* **1994**, *38*, 1519–1526. (c) Lin, M. –L.; Wang, H. –M.; Kang, I. –J.; Chen, L. –C. Ene Reaction with Pummerer-Type Reaction Intermediate of α-(Methylthio)-*N*-methoxyl-*N*-methyl Acetamide: A New Synthesis of *N*-Methoxy-*N*-methyl-(*E*,*E*)-2,4-dienamides. *J. Chin. Chem. Soc.* **2000**, *47*, 1121–1124.

[158] Takeda, T.; Taguchi, H.; Fujiwara, T. Titanocene(II)-Promoted Desulfurizative Acylation of Thioacetals with Alkanenitriles. *Tetrahedron Lett.* **2000**, *41*, 65–68.

untouched. The attempted Claisen-like condensation of **2204** with the methyl ester **2158** was similarly unproductive.

Scheme II–55 | A survey of early, dead-end routes to prepare either **2201** or **2203**.

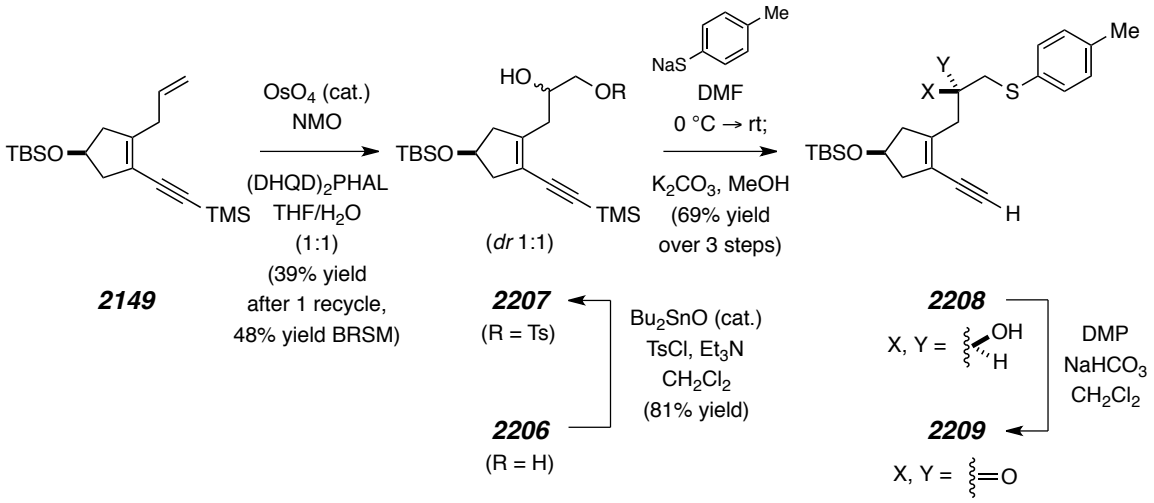


An alternative route was then pursued that relied upon chemoselective oxidation of the terminal olefin within **2149** (Scheme II–56). Because of their simplicity and ease of implementation, the Upjohn[159] dihydroxylation conditions [OsO_4 (cat.), NMO, acetone/H_2O (9:1)] were initially employed. However, the diol **2206** was formed in only 27% yield and was accompanied by a significant amount of over-oxidation (i.e., the tetraol derived from **2206**). A modest improvement was realized when, under otherwise similar conditions, the oxidation of **2149** was carried out in the presence of the

[159] VanRheenen, V.; Kelly, R. C.; Cha, D. Y. An Improved Catalytic OsO_4 Oxidation of Olefins to *cis*-1,2-Glycols Using Tertiary Amine Oxides as the Oxidant. *Tetrahedron Lett.* **1976**, *17*, 1973–1976.

phthalazine ligand $(DHQD)_2PHAL$.[160] Although this ligand did not, surprisingly, impact the diastereomeric ratio[161] of **2206**, it did appear to influence somewhat the selectivity for dihydroxylation of the terminal olefin. It should be emphasized that under the latter set of conditions the over-oxidation product was *always* observed at extended reaction periods; however, termination of the reaction, isolation of the unreacted starting material, and resubjection of this material did provide a means to upgrade the chemical yield.

Scheme II–56 | Regioselective sulfonylation of the diol derived from **2149** and nucleophilic displacement of the primary tosylate **2207** derived therefrom.



The diol was converted to the tosylate **2207** in a highly regioselective manner under the catalytic Bu_2SnO sulfonylation conditions that have been reported by Martinelli

---

160 Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. –S.; Kwong, H. –L.; Morikawa, K.; Wang, Z. –M.; Xu, D.; Zhang, X. –L. The Osmium-Catalyzed Asymmetric Dihydroxylation: A New Ligand Class and a Process Improvement. *J. Org. Chem.* **1992**, *57*, 2768–2771.

161 A similar dilemma has been encountered in the literature: Starr, J. T.; Koch, G.; Carreira, E. M. Enantioselective Synthesis of the Cyclopentyl Core of the Axinellamines. *J. Am. Chem. Soc.* **2000**, *122*, 8793–8794.

and co-workers[162] (Scheme II–56). With this material in hand, the most obvious course of action would be displacement of the primary tosylate with thiolate anion followed by oxidation of the resulting secondary alcohol. Indeed, when **2207** was allowed to react with sodium *p*-toluenethiolate–freshly prepared by the addition of the thiol to NaH in dry DMF–a reasonably clean reaction took place. The formation of the desired product was invariably accompanied by cleavage of the TMS alkyne protecting group. Thus, a second step was necessary (K_2CO_3, MeOH), which provided the free alkyne **2208** in good overall yield. Finally, oxidation of this material with the Dess–Martin periodinane[163] proceeded without incident to give the β-keto sulfide **2209**.

Although the route described in Scheme II–56 did provide access to the β-keto sulfide **2209**, the loss of the TMS protecting group during the displacement of **2207** coupled with superfluous redox/functional group manipulations detracted from its utility and certainly left something to be desired. It was at this stage that the first samples of the enol ethers **2151** and **2155** were being prepared by the robust and high yielding π-allyl Stille cross-coupling. Moreover, it was quickly recognized that the enol ethers within these substrates are excellent precursors to α-bromo ketones. In the event, hydrolytic bromination of **2151** with NBS in buffered, aqueous THF delivered **2210** in consistently high yield (Scheme II–57). The behavior of this substrate toward displacement with sodium *p*-toluenethiolate was somewhat more problematic and was crucially dependent upon stoichiometry. When **2210** was treated with *ca.* 1 equiv thiolate, the desired product **2201** could generally be isolated in good yield and purity. However, preliminary experiments indicated that excess thiolate (≥ 2 equiv), which was occasionally required to

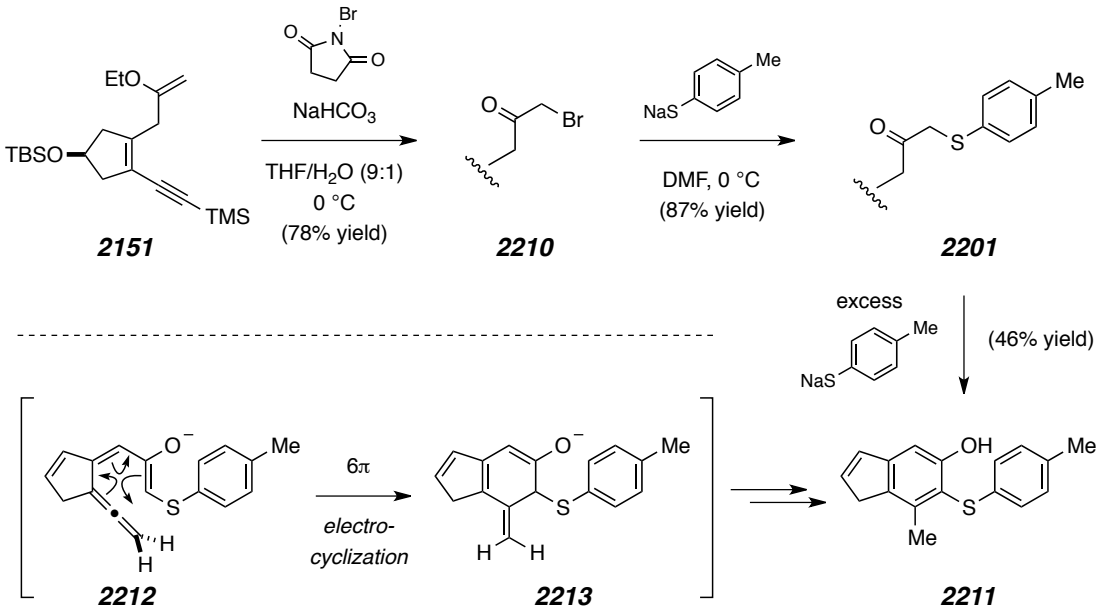
---

[162] (a) Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. Dibutyltin Oxide Catalyzed Selective Sulfonylation of α-Chelatable Primary Alcohols. *Org. Lett.* **1999**, *1*, 447–450. (b) Martinelli, M. J.; Vaidyanathan, R.; Pawlak, J. M.; Nayyar, N. K.; Dhokte, U. P.; Doecke, C. W.; Zollars, L. M. H.; Moher, E. D.; Khau, V. V.; Košmrlj, B. Catalytic Regioselective Sulfonylation of α-Chelatable Alcohols: Scope and Mechanistic Insight. *J. Am. Chem. Soc.* **2002**, *124*, 3578–3585.

[163] Dess, D. B.; Martin, J. C. Readily Accessible 12–I–5 Oxidant for the Conversion of Primary and Secondary Alcohols to Aldehydes and Ketones. *J. Org. Chem.* **1983**, *48*, 4155–4156.

drive the reaction to completion, not only caused loss of the TMS alkyne protecting group but also gave rise to an unusual product that was tentatively assigned structure **2211**.[164]

Scheme II–57 | A more efficient approach to the β-keto sulfide **2201** and the (presumably) base-catalyzed formation of the unusual by-product **2211**.



Since TMS deprotection was observed as a secondary event in the sulfenylation of **2207**, it seems reasonable that this is the first event to occur en route to **2211**. Base-catalyzed elimination of the *tert*-butyldimethylsiloxy group followed by alkyne isomerization could lead to **2212** (lower left of Scheme II–57). An "anionic oxy-6π"

---

164 [*MJJ-V-105*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.27 (br d, *J* = 8.0 Hz, 2H, $SC_6H_4CH_3$), 7.08 (br d, *J* = 8.0 Hz, 2H, $SC_6H_4CH_3$), 7.08 (dd, *J* = 3.0, 5.0 Hz, 1H, $CH_2CH{=}CHC{=}CH$), 6.76 (s, 1H, O*H*), 6.69 (ddd, *J* = 1.0, 1.0, 4.5 Hz, 1H, $CH_2CH{=}CHC{=}CH$), 6.32 (dd, *J* = 1.0, 2.5 Hz, 1H, $CH_2CH{=}CHC{=}CH$), 4.02 (s, 2H, $CH_2CH{=}CHC{=}CH$), 2.63 (s, 3H, CH_3), and 2.32 (s, 3H, $SC_6H_4CH_3$).
GC / LR EI-MS [5025015]: t_R 11.08 min; *m*/*z* (rel. int.) 268 (12, $M^{+\bullet}$) and 145 (100, $M^{+\bullet}–C_7H_7S^{\bullet}$).

electrocyclic ring closure[165] within this cross-conjugated allenyl enolate might be responsible for the formation of **2213**, rapid tautomerization within which would establish the aromatic character of **2211**. That the former electrocyclic process is driven by the formation of the (perhaps more stable) conjugated (rather than cross-conjugated) trienolate **2213** is an enticing mechanistic possibility.[166]

Preliminary efforts to oxidize **2201** with $CuCl_2$/CuO in acetone/H_2O,[167] the Dess–Martin periodinane in pyr/CH_2Cl_2,[168] or $NaIO_4$ in MeOH/H_2O invariably resulted in either decomposition of the starting material or no reaction. It was eventually discovered that the 10–I–3 iodanes [hydroxyl(tosyloxy)iodo]benzene[169] (**2214**, Koser's reagent a.k.a. HTIB) and [bis(trifluoroacetoxy)iodo]benzene[170] (**2217**, PIFA) both efficiently oxidized **2201**, and that the outcome of these processes was intimately linked to solvent composition (Scheme II–58). When HTIB was employed as the oxidant in CH_3CN/MeOH solvent, **2201** was rapidly (< 5 min) consumed at 0 °C and the formation of the *O*,*S*-acetal **2215** was inferred by TLC analysis. This product, which is presumably derived from oxidative Pummerer rearrangement and capture of the intermediate

---

165 A related process has been proposed by Paquette; see: Morwick, T. M.; Paquette, L. A. Combined Addition of Alkenyl and Allenic Anions to Squarate Esters. Direct Competition between Six-Ring and Eight-Ring Electrocyclization of 1,2,4,6,8-Cumulenic Pentaenes. *J. Org. Chem.* **1997**, *62*, 627–635.

166 Dramatic rate accelerations are observed in 6π electrocyclizations when electron-donating and electron-accepting groups are positioned at C3 and C2, respectively, of the 1,3,5-hexatriene subunit. The production of a more stable enolate product was proposed to rationalize the outcome. See: Magomedov, N. A.; Ruggiero, P. L.; Tang, Y. Remarkably Facile Hexatriene Electrocyclizations as a Route to Functionalized Cyclohexenones via Ring Expansion of Cyclobutenones. *J. Am. Chem. Soc.* **2004**, *126*, 1624–1625.

167 Carre, M. C.; Caubere, P. A Very Efficient Preparation of 1,2-Diketones. *Tetrahedron Lett.* **1985**, *26*, 3103–3106.

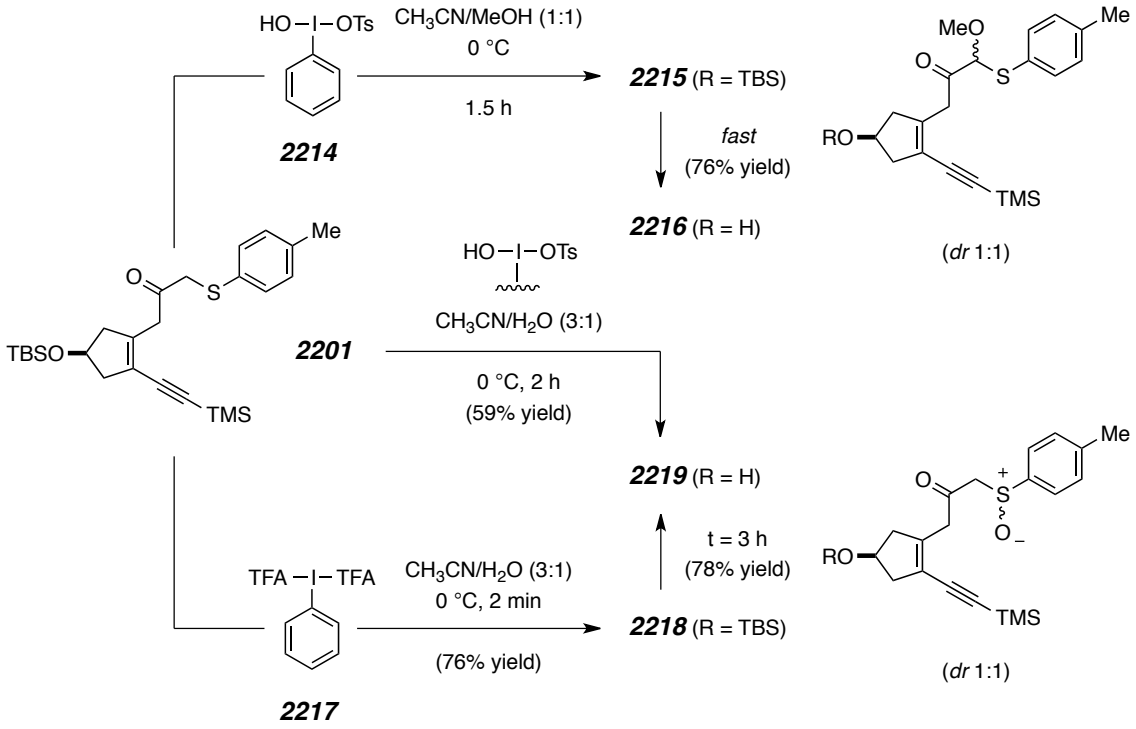
168 Linde II, R. G.; Jeroncic, L. O.; Danishefsky, S. J. Straightforward Synthesis of 1,2,3-Tricarbonyl Systems. *J. Org. Chem.* **1991**, *56*, 2534–2538.

169 Koser, G. F.; Wettach, R. H. Hypervalent Organoiodine. Reactions of Silver Arylsulfonates with Iodosobenzene Dichloride. *J. Org. Chem.* **1977**, *42*, 1476–1478.

170 Spyroudis, S.; Varvoglis, A. Dehydrogenations with Phenyliodine Ditrifluoroacetate. *Synthesis* **1975**, 445–447.

thionium ion with MeOH (cf. **2200** → **2198**, Scheme II–54), was too short lived to be isolated. Rather, the accumulation of *p*-TsOH during the course of the reaction swiftly induced TBS ether cleavage to provide the secondary alcohol **2216** in 76% yield.

Scheme II–58 | The 10–I–3 iodane-mediated oxidation reactions of **2201**.



A slightly different oxidative event occurred when aqueous CH_3CN was employed as the solvent (Scheme II–58). Specifically, exposure of the β-keto sulfide **2201** to HTIB under these conditions resulted in the smooth formation of the *sulfoxide* **2219**. Here again, TBS ether cleavage occurred at a rate that was competitive with oxidation. Although the oxidation of simple sulfides with HTIB has been reported,[171] **2219** is by far the most complex sulfoxide to have been prepared by this method.

[171] Xia, M.; Chen, X. –C. Hypervalent Iodine in Synthesis XXIII. Oxidation with [Hydroxy(tosyloxy)-iodo]benzene: Selective Oxidation of Sulfides to Sulfoxides. *Synth. Commun.* **1997**, *27*, 1315–1320.

Similarly, the reaction of **2201** with PIFA also gave rise to **2219** in 78% yield, but under these less strongly acidic conditions the intermediate TBS ether **2218** could also be isolated in 76% yield after a brief reaction period. As a few final notes with regard to this chemistry, the use of HTIB in the conversion of **2201** to **2216** generally provided superior results; however, both HTIB and PIFA could be used interchangeably in the conversion of **2201** to **2218**/**2219**. Furthermore, the use of these more powerful oxidants was found to be absolutely necessary; conducting these reactions in the presence of $PhI(OAc)_2$ under otherwise identical conditions resulted in no reaction.

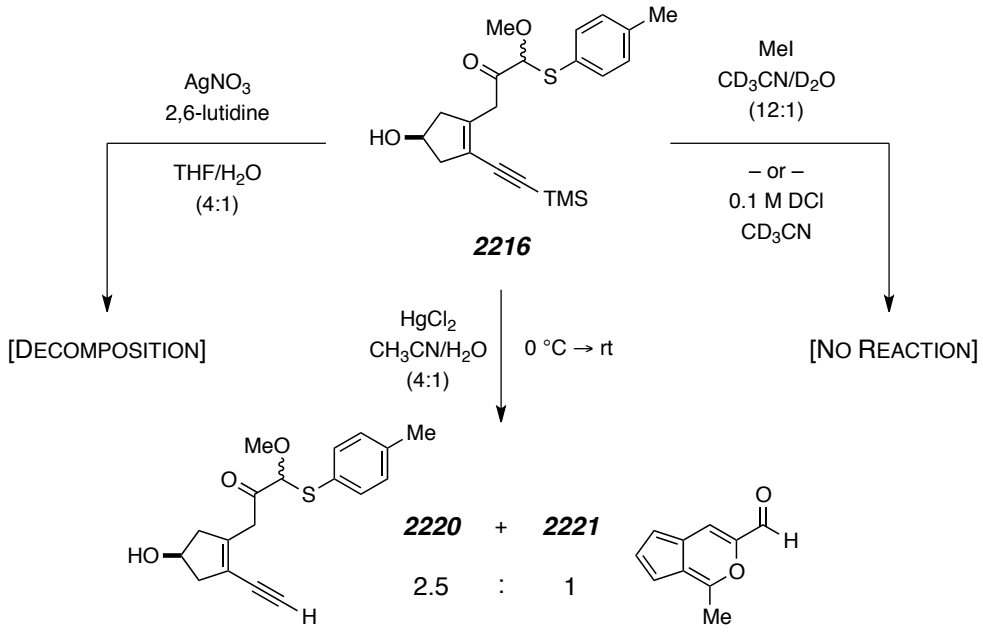
Because the *O*,*S*-acetal **2216** is simply a hydrolysis step away from an α-keto aldehyde, its reactivity was probed first. The small set of reaction conditions shown in Scheme II–59 are all relatively common methods for the hydrolysis of MTM ethers and di- and monothio acetals.[172] It was anticipated that some difficulty might be encountered in the attempted hydrolysis of the *O*,*S*-acetal within **2216**–after all, the carbonyl carbon is adjacent to the center that must accumulate carbocation character. The inconvenient truth of this prediction was realized when exposure of **2216** to $AgNO_3$, MeI, or aq DCl resulted in either decomposition of the starting material or no observable reaction. Moreover, when recourse was made to the harsher mercuric ion-mediated hydrolysis conditions (i.e., $HgCl_2$), the only isolable products were that of TMS alkyne cleavage (**2220**) and a rather unusual bicyclic structure from which all useful functionality had been stripped (**2221**[173]).

---

172 Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons, Inc.: New York, **1999**, pp 33–35 and 329–347.

173 [*MJJ-V-251*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.57 (s, 1H, C*H*O), 7.82 [s, 1H, C*H*=C(O)CHO], 7.31 [dd, *J* = 2.5, 4.5 Hz, 1H, (CH_3)C=CCH=C*H*CH=C], 7.08 [ddd, *J* = 1.0, 1.0, 4.5 Hz, 1H, (CH_3)C=C–C*H*=CHCH=C], 6.98 [dd, *J* = 1.0, 3.0 Hz, 1H, (CH_3)C=CCH=CHC*H*=C], and 2.83 (s, 3H, C*H*$_3$).
GC / LR EI-MS [5025015] t_R 7.07 min; *m*/*z* (rel. int.) 160 (100, $M^{+\bullet}$), 159 (13, $M^{+\bullet}$–H$^\bullet$), 132 (12), 131 (11, $M^{+\bullet}$–CHO$^\bullet$), 104 (6), 103 (37), 102 (10), 78 (10), and 77 (16).

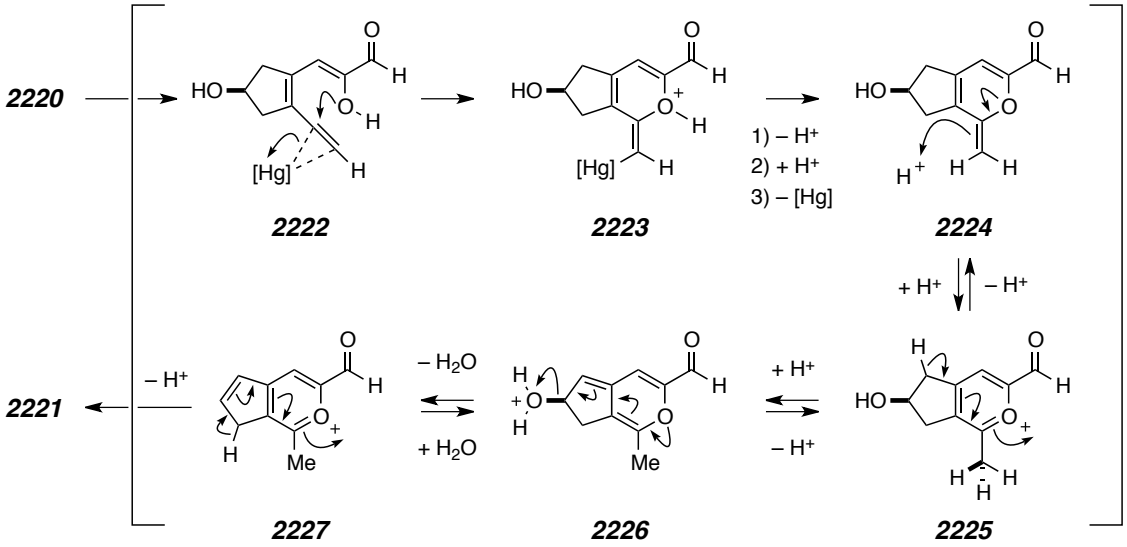
Scheme II–59 | The reactivity (or lack thereof) of the *O*,*S*-acetal **2216** under a small sampling of hydrolysis conditions.



A reasonable mechanism for the formation of the aldehyde **2221** has been offered in Scheme II–60. Were the *O*,*S*-acetal within **2220** to be hydrolyzed, it would most likely give rise to the α-keto aldehyde enol **2222**. A mercuric ion-mediated intramolecular "hydration"[174] of the terminal alkyne within this species would give rise to the vinyl mercurial **2223**, a formal protodemercuration of which would produce the enol ether **2224**. The oxocarbenium ion **2225**–produced via protonation of **2224**–could then lead to the formation of **2226** via proton loss. Finally, elimination of water from **2226** and tautomerization of **2227** would account for the formation of the observed product (**2221**).

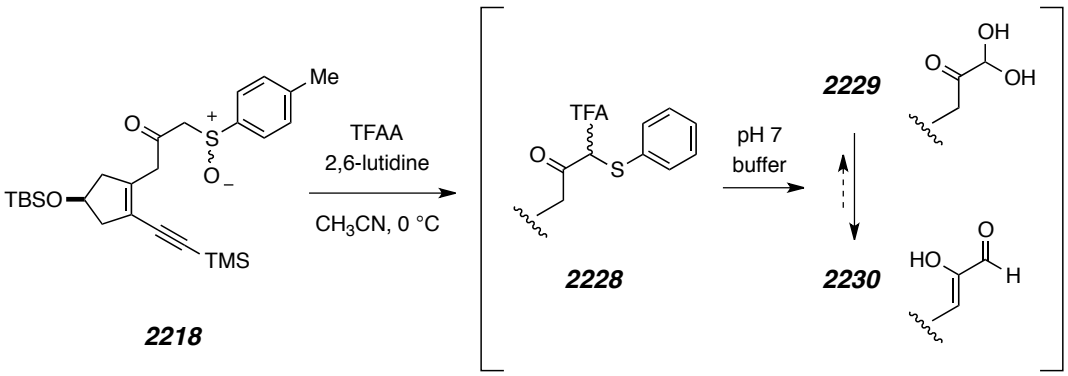
174 Smith, M. B.; March, J. Addition to Carbon–Carbon Multiple Bonds. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed.; John Wiley & Sons, Inc.: Hoboken, New Jersey, **2007**, pp 999–1250.

Scheme II–60 | A mechanistic rationalization for the production of **2221** under the mercuric ion-mediated hydrolysis of the *O*,*S*-acetal **2216** (via **2220**).



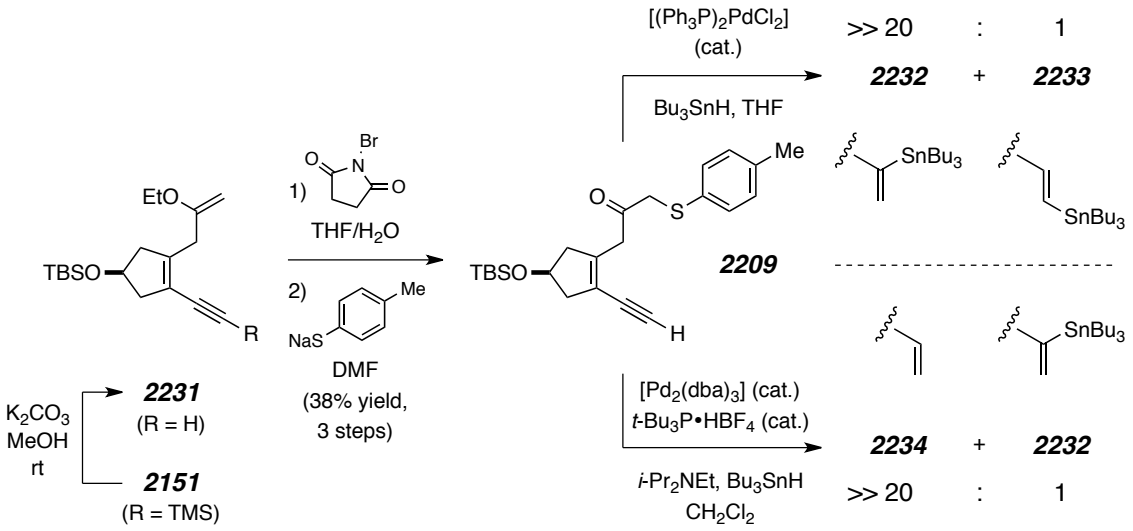
The recalcitrance of **2216** under the reaction conditions just described was not a particularly good omen for the hydrolysis of *O*,*S*-acetal in a more complex setting. As a result, the more traditional "non-oxidative" Pummerer rearrangement of the β-keto sulfoxide **2218** was briefly investigated (Scheme II–61). A very clean reaction took place upon treatment of this material with TFAA and 2,6-lutidine in CH_3CN, and the identity of the product was presumed to be that of the trifluoroacetate **2228**. Without further manipulation, the reaction mixture was treated directly with pH 7 buffer in order to induce hydrolytic cleavage of the trifluoroacetate within **2228**. Indeed, after product isolation and chromatographic purification, ^{1}H NMR and LC-MS analyses confirmed the presence of a mixture of the α-keto aldehyde hydrate **2229** and the enol **2230**. Although these two species were present in a *ca.* 1:4 ratio at the time of data collection, a previous model study (cf. Figure II–1) has established that the enol **2230** would be heavily favored at equilibrium.

Scheme II–61 | Traditional (non-oxidative) Pummerer rearrangement of the sulfoxide **2218**.



The ease and mildness of the conditions required to hydrolyze the trifluoroacetate **2228** was encouraging, and it immediately suggested the possibility that this chemistry could be conducted on an intermediate that already possessed the polyene (cf. **2194** where X = TFA in Scheme II–53). Thus, with the entire carbon skeleton in place, the TFAA-induced Pummerer rearrangement/*in situ* hydrolysis sequence could be used to generate the pentaenol **2001** without recourse to product isolation. A search was then initiated for a suitable organometallic cross-coupling partner (Scheme II–62). The TMS protected alkyne **2151** was exposed to methanolic K_2CO_3 to provide the free alkyne **2231**. Since it was realized that hydroboration *after* hydrolytic bromination and sulfenylation of **2231** might be thwarted by ketone reduction, the direct hydroboration of this material was first examined. Unfortunately, attempts at hydroboration with either catecholborane or *i*-PP_2BH followed by treatment with pinacol did not lead to the expected product; the hydrolytic lability this material is perhaps an explanation for these observations.

Scheme II–62 | Preparation of **2209** via **2231** and its subsequent hydrostannylation.



However, the enol ether within **2231**, as expected, smoothly underwent hydrolytic bromination in the presence of NBS to yield an intermediate α-bromo ketone that, after exposure to sodium *p*-toluenethiolate, gave rise to the β-keto sulfide **2209** in 38% yield over the 3 steps (Scheme II–62). With the hope of producing the (*E*)-1-stannylalkene **2222**, the alkyne **2209** was subjected to the previously employed hydrostannylation conditions of Zhang and co-workers[69] [$(Ph_3P)_2PdCl_2$ (cat.), Bu_3SnH]. In an outcome that was not entirely unexpected (cf. Scheme II–22), the near exclusive formation of the undesired, regioisomeric internal vinyl stannylalkene **2232** was evidenced by analysis of the crude reaction profile by ^1H NMR spectroscopy.[175] It has been demonstrated that the use of bulky trialkylphosphines in the hydrostannylation of 1-alkynes can have a beneficial impact of the regioisomeric composition of the resulting stannylalkene

[175] [*MJJ-V-127*] The following diagnostic ^1H NMR resonances for **2232** ($Bu_3SnC{=}CH_2$) and **2233** ($CH{=}CHSnBu_3$) were observed (500 MHz, $CDCl_3$): δ 6.81 (d, J = 19.0 Hz, 1H, C*H*=CHSnBu$_3$), 6.17 (d, J = 19.0 Hz, 1H, CH=C*H*SnBu$_3$), 5.59 (d, J = 3.5 Hz, 1H, $Bu_3SnC{=}CH_2$) and 5.25 (d, J = 3.5 Hz, 1H, $Bu_3SnC{=}CH_2$).

products.[176] The attempted hydrostannylation of **2209** in the presence of *t*-Bu_3P (liberated *in situ* from *t*-Bu_3P•HBF_4 and *i*-Pr_2NEt) resulted, once again, in the isolation of the undesired internal stannylalkene **2232**. However, under these conditions the major product was the reduced terminal alkene **2234**,[177] which presumably arose via protodestannylation of the desired regioisomeric stannylalkene **2233** under the reaction conditions.

Because the enol ether **2155** already exists in the proper oxidation state, it therefore became the next most viable intermediate (Scheme II–63). The potential difficulty that might be encountered during the hydrolytic bromination of this material, which possesses two electron-rich π-systems, was a clear and present danger. However, the enol ether would be predicted to be *far more* reactive; the reader will recall that the enol ether present within **2151** was unstable toward SiO_2. This prediction was indeed borne out experimentally, as the α-bromo ketone **2235** was efficiently produced upon exposure of **2155** to NBS in buffered aqueous THF. The use of as close to 1.0 equiv of NBS as possible is important–on one occasion, when the author did not closely regulate the reaction stoichiometry, the corresponding α-bromo ketone/vinyl bromide was a significant by-product that could not be removed chromatographically. Conversion of the vinyl silane **2235** to the vinyl iodide **2236** occurred stereoselectively under the influence of NIS in a $CH_3CN/ClCH_2CN$ solvent mixture.[99] At this stage a far more mild and effective protocol for α-bromo ketone sulfenylation was employed. Rather than using sodium *p*-toluenethiolate, wherein careful control of the reaction stoichiometry was previously required to avoid the formation of the by-product **2216** (see Scheme II–57),

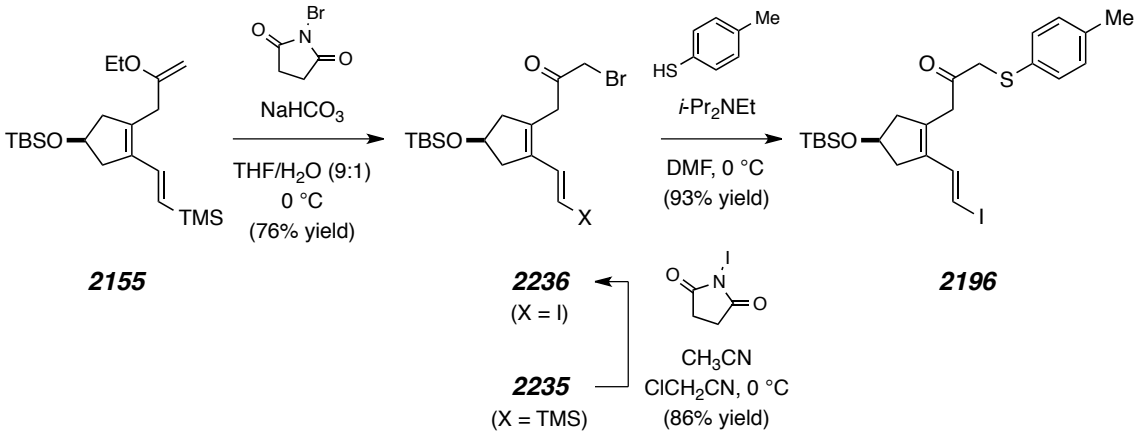
---

176 Darwish, A.; Lang, A.; Kim, T.; Chong, J. M. The Use of Phosphine Ligands to Control the Regiochemistry of Pd-Catalyzed Hydrostannations of 1-Alkynes: Synthesis of (*E*)-1-Tributylstannyl-1-alkenes. *Org. Lett.* **2008**, *10*, 861–864.

177 [*MJJ-V-128*] This material displayed the following diagnostic ^{1}H NMR resonances (500 MHz, $CDCl_3$): δ 6.52 (dd, *J* = 11.0, 17.0 Hz, 1H, C*H*=$CH_{trans}H_{cis}$), 5.12 (d, *J* = 10.5 Hz, 1H, CH=$CH_{trans}H_{cis}$), and 5.11 (d, *J* = 17.5 Hz, 1H, CH=C$H_{trans}H_{cis}$).

exposure of **2236** to *p*-toluene*thiol* in the presence of *i*-Pr_2NEt cleanly generated the β-keto sulfide **2196** as the sole product in excellent yield.

Scheme II–63 | Hydrolytic bromination, iododesilylation, and displacement of **2155** cleanly delivered the vinyl iodide **2196**.

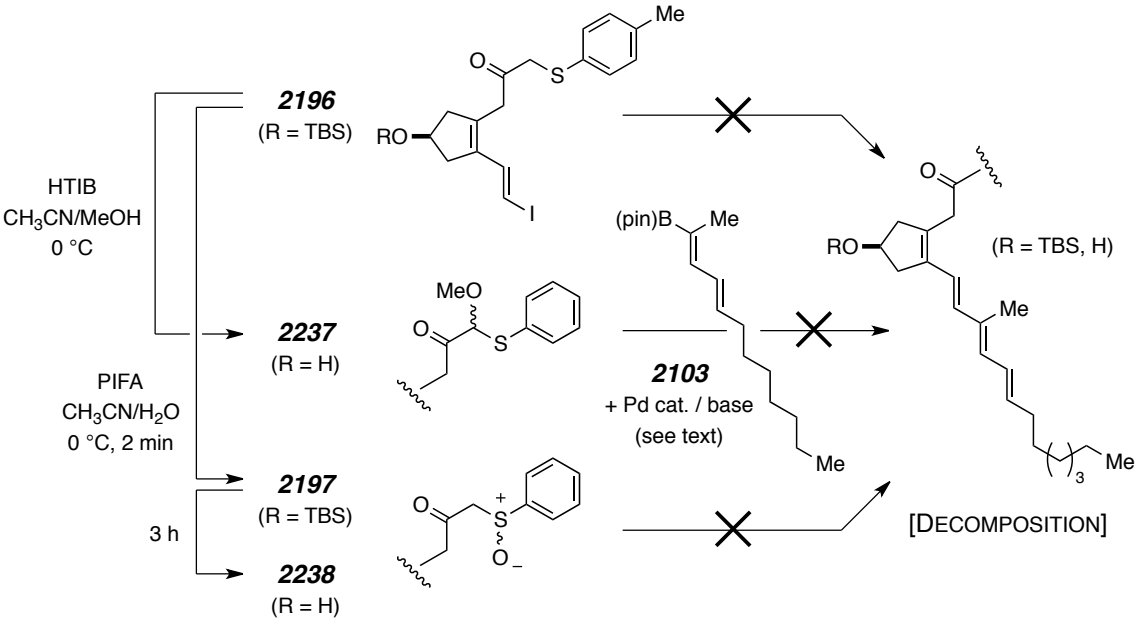


Now that a cross-coupling partner was available in the form of the vinyl iodide **2196**, the reactivity of this intermediate, as well as the oxidation products derived therefrom, were interrogated in their Suzuki reactions with the vinyl boronate **2103** (Scheme II–64). Thus, the *O*,*S*-acetal **2237** was prepared by the HTIB-mediated oxidation of **2196** in CH_2Cl_2/MeOH in a similar manner to that described previously. Oxidation of **2196** with PIFA in CH_3CN/H_2O was likewise employed to generate the TBS-protected sulfoxide **2197** and its deprotected congener **2238**. In a disappointing series of experiments, exposure of *any* of these intermediates to either Roush's Suzuki cross-coupling conditions[55] [$Pd(PPh_3)_4$ (cat.), TlOEt, THF/H_2O] or the catalyst/base pairing used by Nelson[178] {$[Pd(dppf)Cl_2]\bullet CH_2Cl_2$ (cat.), $Ba(OH)_2\bullet 8H_2O$, DMF} in a similar setting resulted in complete decomposition of the starting materials. That the failure of

[178] Gopalarathnam, A.; Nelson, S. G. Amphidinolide B: Asymmetric Synthesis of a C_7–C_{20} Synthon. *Org. Lett.* **2006**, *8*, 7–10.

these reactions was attributable to the base sensitivity of the vinyl iodide coupling partners was, in at least one instance, suggested by the recovery of the unreacted vinyl boronate **2103**.

Scheme II–64 | Unfruitful Suzuki cross-coupling reactions of four different vinyl iodides.

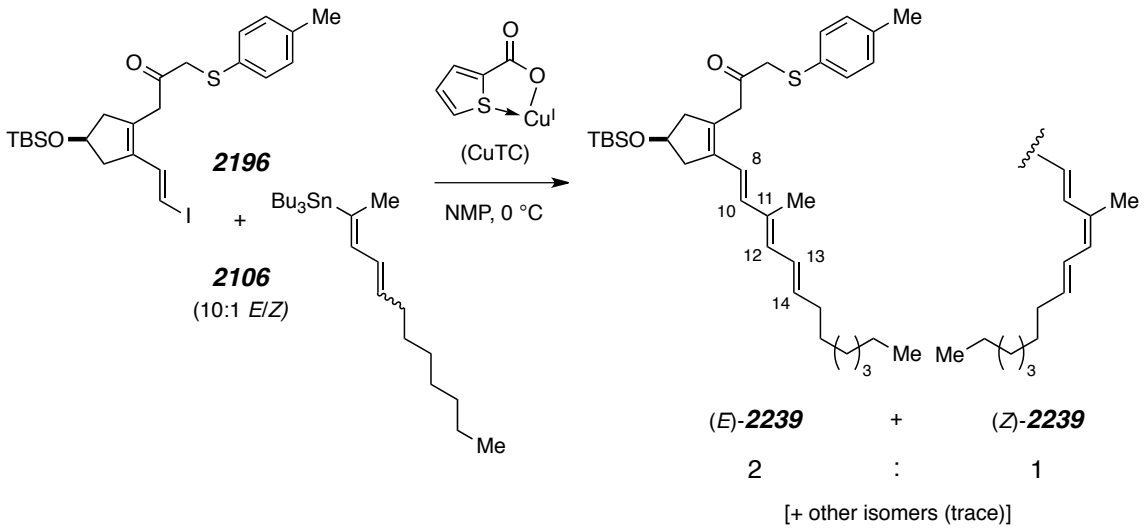


The basic conditions required to induce the Suzuki cross-coupling reaction are, generally speaking, quite mild, but the decomposition of the vinyl iodide substrates employed in Scheme II–64 would suggest otherwise. On the other hand, essentially neutral reaction conditions are often used to affect the Stille cross-coupling reaction. Thus, an attempt was made to bring about the union of the vinyl iodide **2196** with the vinyl stannane **2106** (Scheme II–65). Among the palladium(0)-catalyzed conditions that were studied first, both $[Pd(CH_3CN)_2Cl_2]$ in DMF (with our without added LiCl) and $[Pd(PhCN)_2Cl_2]$ together with the tin scavenger $[Ph_2PO_2]^-$ $[NBu_4]^+$[179] in DMF proved to

[179] Srogl, J.; Allred, G. D.; Liebeskind, L. S. Sulfonium Salts. Participants *par Excellence* in Metal-Catalyzed Carbon–Carbon Bond-Forming Reactions. *J. Am. Chem. Soc.* **1997**, *119*, 12376–12377.

be inferior with regard to reaction conversion. Similarly, no observable change occurred at room temperature when **2196** and **2106** were reacted in the presence of $[Pd_2(dba)_3]$ with the popular ligand $AsPh_3$[180] in NMP.

Scheme II–65 | The CuTC-mediated Stille–Liebeskind cross-coupling of **2196** with **2106**.



Once it was realized that this small sampling of palladium(0) precatalysts were relatively ineffective, the use of stoichiometric CuTC[74] was explored as an alternative method (Scheme II–65). When the vinyl iodide **2196** and stannane **2106** were exposed to excess (*ca.* 5 equiv) CuTC at 0 °C in NMP, the rapid reaction that ensued did indeed give rise to the expected Stille cross-coupling product **2239**. Unexpectedly, ^{1}H NMR analysis revealed this material to be a 2:1 mixture of $\Delta^{11,12}$ (*E*)- and (*Z*)-isomers[181] together with

---

180 Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. Palladium-Catalyzed Coupling of Arylstannanes with Organic Sulfonates: A Comprehensive Study. *J. Org. Chem.* **1993**, *58*, 5434–5444.

181 The configurations of the $\Delta^{8,10}$ and $\Delta^{13,14}$ olefins within (*E*)- and (*Z*)-**2239** could be easily ascertained by analysis of their respective $^3J_{H,H}$ and $^4J_{H,H}$ coupling constant values. The configuration of the $\Delta^{11,12}$ olefin, however, rests upon comparison of the chemical shift of the H12 resonances of each to those of (11*E*)- and (11*Z*)-**2094** (cf. Table II–5 and footnote 94). Diagnostic ^{1}H NMR (500 MHz, $CDCl_3$) resonances for the major (†) and minor (‡) isomers: δ 7.19† (d, *J* = 14.5 Hz, 1H, H8), 6.41‡ (d, *J* = 15.5

trace amounts of at least two other isomeric species. Although the use of less (1.2–3 equiv) CuTC did provide a more satisfactory outcome [(*E*)/(*Z*) 8:1], the reaction could not be driven to full conversion.

Since isomerically pure **2239** could not be prepared by the methods described here, the potential utility of this approach was dramatically reduced. Fortunately, more fruitful progress was being made contemporaneously on a different front.

G–4. DIRECT C9 OXIDATION AND FINAL ASSEMBLY OF (*Z*)-2001

A significant amount of experimental effort has now been exerted to prepare appropriately functionalized precursors (e.g., **2017**, **2166**, and **2194**) from which the key pentaenol **2001** might have been generated. These efforts have been congruent with the originally proposed synthesis plan (Chapter II, Section B). It is certainly true that some interesting and potentially useful chemistry has been unearthed, but, nevertheless, an efficient and stereoselective route to prepare *any* of the aforementioned intermediates has *not* been forthcoming. Upon reflection, it seemed that the original synthesis plan was perhaps too narrowly focused–in other words, there's more than one way to skin a cat.

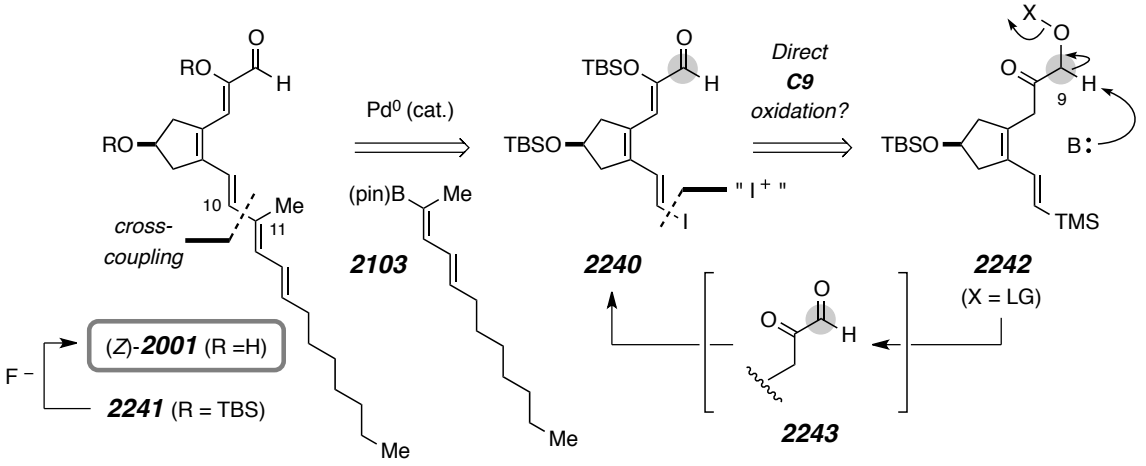
Were the fully protected α-keto aldehyde enol **2240** to be synthetically accessible, then its subsequent Suzuki cross-coupling with the vinyl boronate **2103** would deliver an intermediate (**2241**) that could give rise to **2001** by fluoride-induced deprotection (Scheme II–66). The stability and inherent reactivity of the highly conjugated penultimate intermediate **2241** was, rightly so, of some concern. But if we leave that issue aside for the moment, this approach has tremendous potential to permit one to *directly* access the pentaenol **2001**. In turn, it was envisioned that the keto tautomer **2243** would be transiently generated by elimination of HX from an activated intermediate such as **2242**.

Hz, 1H, H8), 6.39† (dddd, *J* = 1.5, 1.5, 11.5, 15.5 Hz, 1H, H13), 6.22† (d, *J* = 14.5 Hz, 1H, H10), 6.20‡ (d, *J* = 15.5 Hz, 1H, H10), 6.11† (d, *J* = 11.5 Hz, 1H, H12), 6.08‡ (dddd, *J* = 1.5, 1.5, 11.0, 14.5 Hz, 1H, H13), 5.91‡ (d, *J* = 11.0 Hz, 1H, H12), 5.77† (ddd, *J* = 7.0, 7.0, 14.5 Hz, 1H, H14), and 5.69‡ (ddd, *J* = 7.0, 7.0, 14.5 Hz, 1H, H14).

LR ESI-MS: $C_{35}H_{54}O_2SSi$ $[M+Na]^+$ requires 589.35; found 589.54.

On the basis of the author's previous experience, the α-keto aldehyde **2243** should rapidly collapse, via base-catalyzed tautomerization, to give the thermodynamically more stable enol tautomer. Preemptive silylation of this material would, after iododesilylation, give rise to the vinyl iodide **2240**, and this was projected to be a necessary step prior to the cross-coupling event. The base sensitivity of intermediates related to **2242** has already been documented in previous Sections of Chapter II. Thus, a method that would promote base-induced elimination within **2242** under *mild* conditions would need to be developed.

Scheme II–66 | Revised retrosynthetic analysis of the pentaenol **2001** via direct C9 oxidation of **2242**, Suzuki cross-coupling of **2240** and **2103**, and global deprotection of **2241**.



The high-yielding preparation of the α-bromo ketone **2235** was described earlier in Chapter II, and during those studies it was found to be a stable, storable intermediate. It is also an excellent candidate for oxidation under Kornblum-type conditions,[182] of

[182] (a) Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M. A New and Selective Method of Oxidation. *J. Am. Chem. Soc.* **1957**, *79*, 6562. (b) Kornblum, N.; Jones, W. J.; Anderson, G. J. A New and Selective Method of Oxidation. The Conversion of Alkyl Halides and Alkyl Tosylates to Aldehydes. *J. Am. Chem. Soc.* **1959**, *81*, 4113–4114.

which there are several different variants[183] that could be applied to the problem at hand. With the intent of accessing the enol **2244**, the α-bromo ketone **2235** was exposed to either Kornblum's original[182a] conditions (pure DMSO, 40 °C, 18 h) or Ganem's modified[183a] silver-assisted conditions (DMSO, $AgBF_4$, rt, 48; then NaOAc) (upper left of Scheme II–67). In both instances, the starting material was slowly and nonproductively consumed to give intractable, baseline (TLC analysis) product mixtures.

Godfrey and Ganem have shown[183b] that aldehydes are produced upon oxidation of primary halides with anhydrous[184] trimethylamine *N*-oxide (TMANO) in DMSO. When **2235** was allowed to react with excess (2.7 equiv) TMANO under these conditions, the enol **2244** was *not* produced (upper right of Scheme II–67). In a completely unexpected and rather bizarre turn of events, the terminal alkene **2247**[185] was instead isolated as essentially a single product. Moreover, the distinct yet related oxidation of **2235** with pyridine *N*-oxide ($NaHCO_3$, PhMe, heat), which are conditions

---

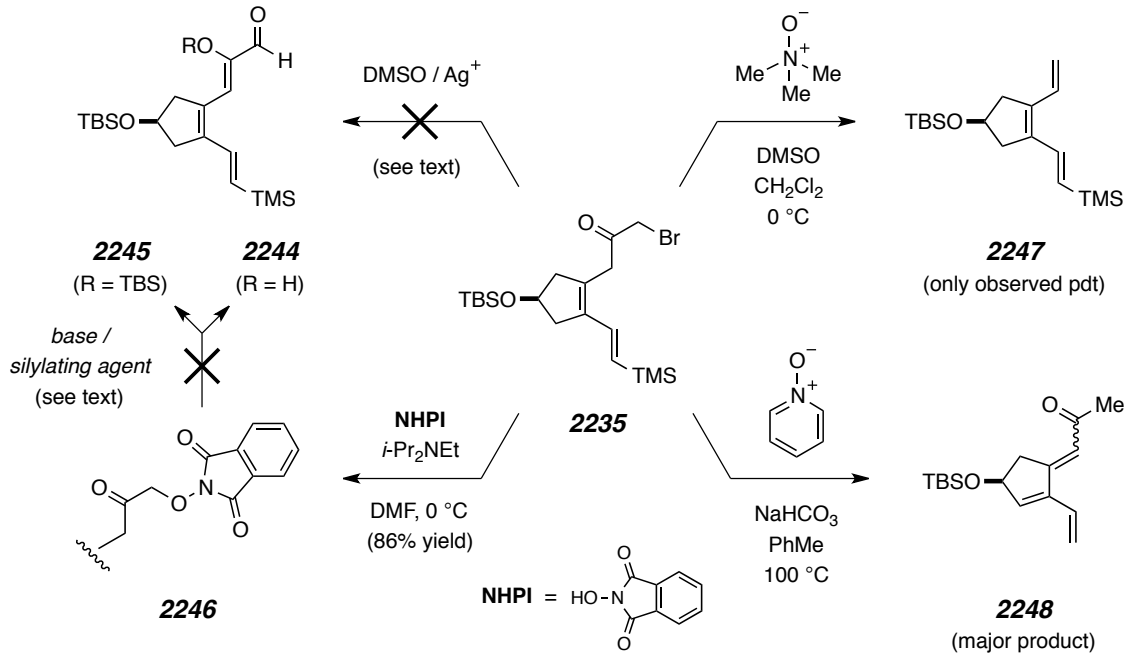
183 (a) Ganem, B.; Boeckman, Jr., R. K. Silver-Assisted Dimethylsulfoxide Oxidations; An Improved Synthesis of Aldehydes and Ketones. *Tetrahedron Lett.* **1974**, *15*, 917–920. (b) Godfrey, A. G.; Ganem, B. Ready Oxidation of Halides to Aldehydes Using Trimethylamine *N*-Oxide in Dimethylsulfoxide. *Tetrahedron Lett.* **1990**, *31*, 4825–4826. (c) Stowell, J. C. A Short Synthesis of the Sex Pheromone of the Pink Bollworm Moth. *J. Org. Chem.* **1970**, *35*, 244–245.

184 Soderquist, J. A.; Anderson, C. L. Crystalline Anhydrous Trimethylamine *N*-Oxide. *Tetrahedron Lett.* **1986**, *27*, 3961–3962.

185 [*MJJ-VI-128*] **^{1}H NMR** (500 MHz, CD_3CN): δ 7.09 [d, *J* = 19.0 Hz, 1H, C*H*=CHSi$(CH_3)_3$], 6.98 (dd, *J* = 10.5, 17.0 Hz, 1H, C*H*=C$H_{trans}H_{cis}$), 5.88 [d, *J* = 19.0 Hz, 1H, CH=C*H*Si$(CH_3)_3$], 5.19 (d, *J* = 17.5 Hz, 1H, CH=C$H_{trans}H_{cis}$), 5.18 (d, *J* = 10.5 Hz, 1H, CH=C$H_{trans}H_{cis}$), 4.53 [dddd, *J* = 3.0, 3.0, 6.5, 6.5 Hz, 1H, C*H*(OTBS)], 2.86 [dd, *J* = 6.5, 16.5 Hz, 1H, CH_2CH(OTBS)CH_2], 2.83 [dd, *J* = 6.5, 14.5 Hz, 1H, CH_2CH(OTBS)CH_2], 2.52-2.45 [m, 2H, overlapping CH_2CH(OTBS)CH_2], 0.88 [s, 9H, $(CH_3)_3$CSi$(CH_3)_2$], 0.10 [s, 9H, Si$(CH_3)_3$], and 0.08 [s, 6H, $(CH_3)_3$CSi$(CH_3)_2$].
GC / LR EI-MS [5025015]: t_R 8.71 min; *m/z* (rel. int.) 322 (19, $M^{+\bullet}$), 265 [100, $M^{+\bullet}$–C$(CH_3)_3^{\bullet}$], 191 (78), 147 (76), 117 (50), 75 (58), and 73 (61). This material partially decomposed upon entering the GC injection port, as evidenced by the presence of five additional, less intense peaks (t_R 8.56, 8.59, 8.83, 8.85, and 9.05 min).
TLC: R_f 0.85 (9:1 Hex/EtOAc).

that have been reported to provide an aldehyde from a primary alkyl bromide,[183c] proceeded to give yet another weird product–the cross conjugated trienone **2248**.[186]

Scheme II–67 | A sampling of dead-end routes emanating from the α-bromo ketone **2235**.



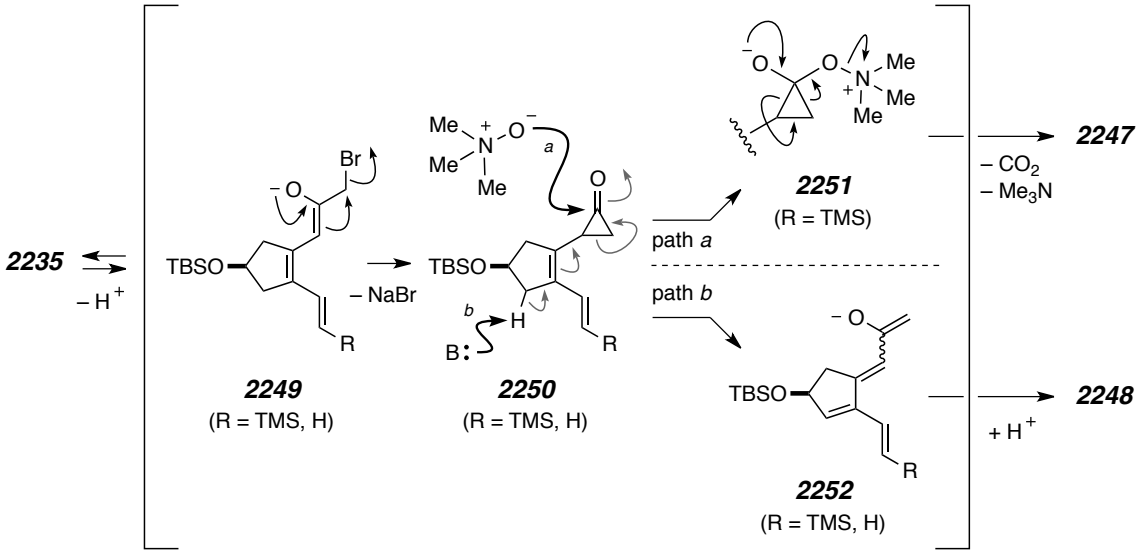
Reasonable mechanistic scenarios for the formation of **2247** and **2248** have been offered in Scheme II–68. The presence of trace quantities of Me_3N in TMANO could promote base-catalyzed enolization of **2235**. Intramolecular displacement within the

---

186 [*MJJ-VI-127*] **^{1}H NMR** (500 MHz, CD_3CN): δ 6.60 [d, *J* = 3.0 Hz, 1H, C=C*H*CH(OTBS)], 6.45 (dddd, *J* = 1.0, 1.0, 11.0, 17.5 Hz, 1H, C*H*=$CH_{trans}H_{cis}$), 6.33 [dd, *J* = 2.5, 2.5 Hz, 1H, C=C*H*C(O)CH_3], 5.71 (dd, *J* = 2.0, 18.0 Hz, 1H, CH=C$H_{trans}H_{cis}$), 5.37 (dd, *J* = 2.0, 11.5 Hz, 1H, CH=$CH_{trans}H_{cis}$), 4.96 [ddd, *J* = 3.0, 3.0, 5.5 Hz, 1H, C*H*(OTBS)], 3.44 (ddd, *J* = 2.5, 6.5, 19.5 Hz, 1H, CH_2), 2.66 (ddd, *J* = 2.5, 2.5, 19.5 Hz, 1H, CH_2), 2.19 [s, 3H, C(O)CH_3], 0.90 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.12 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.11 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].
GC / LR EI-MS [5025015]: t_R 8.59 min; *m*/*z* (rel. int.) 278 (37, $M^{+\bullet}$), 263 (54, $M^{+\bullet}–CH_3^{\bullet}$), 235 (37, $M^{+\bullet}–C_2H_3O^{\bullet}$), 221 [96, $M^{+\bullet}–C(CH_3)_3^{\bullet}$], 206 (26), 177 (19), 147 (14, $M^{+\bullet}–C_6H_{15}OSi^{\bullet}$), 129 (44), 117 (72), 105 (23), 103 (28), and 75 (100).
TLC: R_f 0.42 (9:1 Hex/EtOAc).

resulting enolate **2249** (R = TMS) would give rise to the cyclopropanone **2250** (R = TMS). Were this species to suffer 1,2-addition (path *a*) by TMANO, then oxidative excision of CO_2 and Me_3N from the tetrahedral intermediate thus obtained (**2251**) would account for the observed product (**2247**). With regard to the formation of **2248**, it appears likely that the cyclopropanone **2250** is also a viable intermediate. However, the point at which desilylation occurred during this transformation cannot be known with certainty. Under the mildly basic conditions employed (i.e., $NaHCO_3$), δ-deprotonation within **2250** (path *b*) would result in fragmentation of the cyclopropanone and formation of the cross-conjugated enolate **2252**. Protonation (or protonation and then desilylation) would then provide **2248**.

Scheme II–68 | Plausible mechanistic scenarios for the formation of the **2247** and **2248**.



Since the more traditional methods employed above had failed to give any products derived from direct C9 oxidation, the more exotic *N*-hydroxyphthalimide (NHPI) adduct **2246** was prepared by the reaction of **2235** with NHPI (*i*-Pr_2NEt, DMF) (lower left of Scheme II–67). Adducts of this type have been reported to undergo base-

catalyzed elimination to give glyoxals,[187] and thus the behavior of **2246** in the presence of various bases and silylating agents was investigated. In the presence of amine and amidine bases (i.e., Et_3N in DMF and CH_3CN, heat; DBU, CH_3CN) the formation of **2244** could be inferred by TLC analysis. The prolonged reaction times that were required to observe starting material consumption, however, caused extensive degradation of this material. Next, it was thought that perhaps **2246** could be activated toward elimination by silylation of the phthalimide moiety. But all of the reaction conditions that were surveyed (MTBSA, Et_3N, CH_3CN; TBSOTf, Et_3N, CH_2Cl_2; NaHMDS, THF, then TBSCl) were invariably accompanied by starting material decomposition or the formation of multiple unidentified components.

Much to my satisfaction, a solution to many of the difficulties described above came in the form of the Emmons–Kornblum protocol.[14] This method, which was employed by Snider and Liu during their **1-A** and **1-B** synthesis studies[7] (cf. Chapter I, Section B–1), involves the silver(I) nitrate-mediated generation of nitrate esters ($–ONO_2$) from α-halo (usually bromo) carbonyl compounds. The subsequent base-induced elimination of nitrite anion (NO_2^-) from these species gives rise to glyoxylates and glyoxals.[14] Indeed, the conversion of the α-bromo ketone **2235** into the corresponding nitrate ester **2254** was eventually realized, but this was by no means a straightforward endeavor (Scheme II–69). In the optimized procedure, a Finkelstein reaction of **2235** with sodium iodide delivered the corresponding α-iodo ketone **2253**. In crude form, this material was immediately exposed to $AgNO_3$ (3 equiv) and $Bu_4N^+ NO_3^-$ (3 equiv) in CH_3CN at room temperature for *ca.* 3 h to produce the nitrate ester **2254** in good yield. The use of $Bu_4N^+ NO_3^-$ was not called for in the original Kornblum[14a] report; however, in this setting it clearly had a beneficial influence on the reaction rate.[188] From **2254**, two

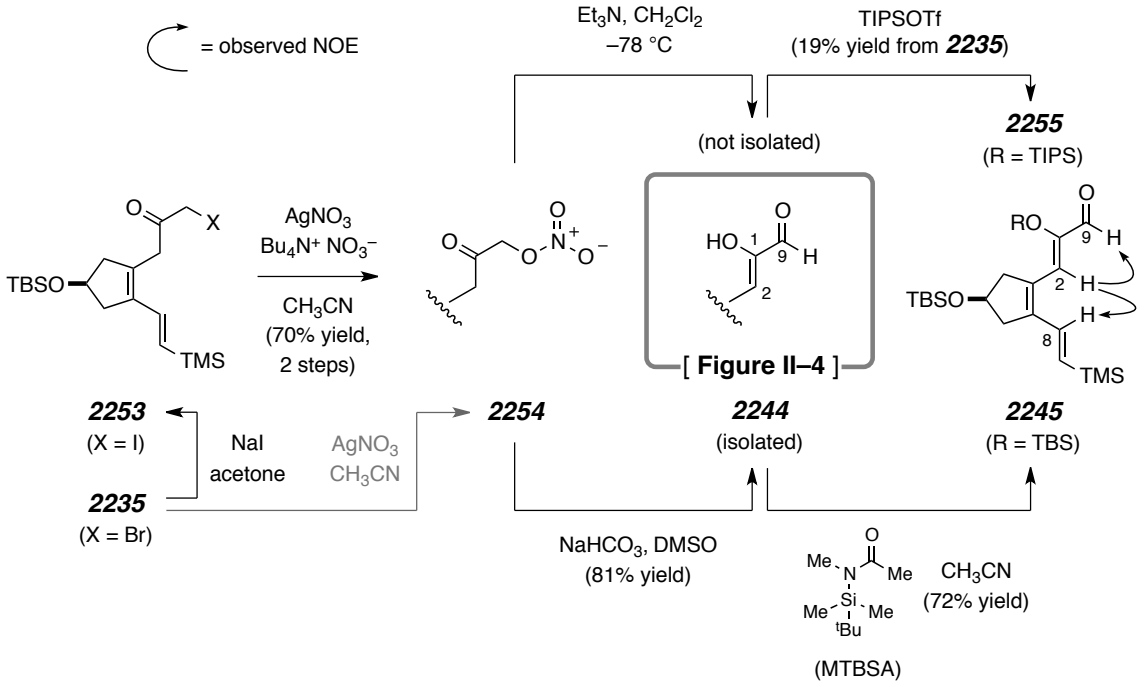
---

[187] Consonni, P.; Favara, D.; Omodei–Salé, A.; Bartolini, G.; Ricci, A. Reactivity of *N*-Phenacyloxy-carbamates and Related Systems in the Presence of Bases: Study of a New [1,2] Anionic Rearrangement. *J. Chem. Soc., Perkin Trans. 2* **1983**, 967–973.

[188] Cainelli, G.; Manescalchi, F.; Plessi, L. The Use of Nitrate Esters in the Synthesis of Di- and Tri-carbonyl Compounds. *Gazz. Chim. Ital.* **1986**, *116*, 163–164.

different routes were employed for its conversion to the silyl enol ethers **2245** and **2255**. The first of these, which was found to be quite inferior, involved the generation of **2244** with Et_3N in CH_2Cl_2 and its *in situ* capture by TIPSOTf to deliver the enol ether **2255** in disappointingly low overall yield (19% from **2235**). Although the TBS enol ether **2245** could be produced under these conditions by reaction of **2244** (generated with either Et_3N or imidazole) with TBSOTf, TBSCl, or *N*-methyl-*N*-(*tert*-butyldimethylsilyl)acetamide (MTBSA),[189] the isolated yields in these instances were equally poor (19–36%).

Scheme II–69 | Access to the silyl enol ethers **2245** and **2255** via the modified Emmons–Kornblum protocol.



Further experimentation revealed that $NaHCO_3$ in DMSO could be used to affect the elimination of nitrite anion from **2254** (Scheme II–69). Under these very mild

189 Mawhinney, T. P.; Madson, M. A. *N*-Methyl-*N*-(*tert*-butyldimethylsilyl)trifluoroacetamide and Related *N*-*tert*-Butyldimethylsilyl Amides as Protective Silyl Donors. *J. Org. Chem.* **1982**, *47*, 3336–3339.

conditions (*vide infra*), the free enol **2244** could be isolated as a bright yellow solid by rapid flash chromatography. That the newly formed $\Delta^{1,2}$ enol π-bond within **2244** possessed the (*Z*)-configuration was established at an early stage by a gradient 1-D NOE experiment. However, I was delighted to find that a crystalline sample of this substance could be obtained that was suitable for X-ray diffraction analysis. The crystal structure that resulted from this analysis is shown in Figure II–4, and, happily, both its constitution and configuration are uniformly congruent with those that had been deduced by alternative, spectroscopic means. Returning now to Scheme II–69, the enol oxygen of **2244** was, for reasons that will become apparent momentarily, silylated with MTBSA under the conditions of Mawhinney and Madson[189] to deliver the TBS enol ether **2245**. Although there would have been no reason to expect otherwise, the (*Z*)-configuration of the $\Delta^{1,2}$ enol ether π-bond of this product was nonetheless confirmed by a gradient 1-D NOE experiment.

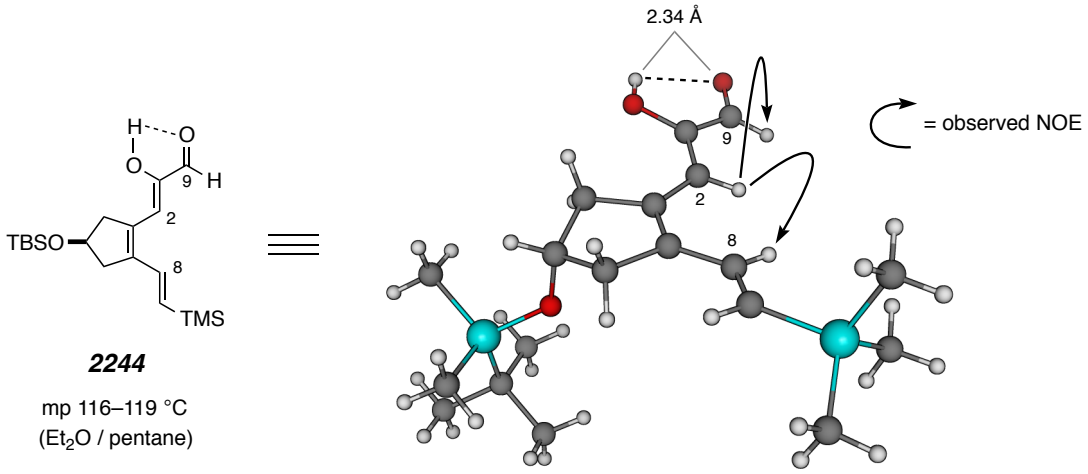


Figure II–4 | Three-dimensional rendering of **2244** from the single crystal X-ray structure coordinates and 1-D NOE interactions observed in CD_3CN solution.

There are a few points with regard to the chemistry shown in Scheme II–69 that should be mentioned: i) In accord with literature reports,[7,190] preemptive conversion of **2235** into the α-iodo ketone **2253** was found to have an immensely beneficial effect of the rate of the ensuing nitrate ester displacement; ii) when **2235** was allowed to react directly with $AgNO_3$ in CH_3CN, the prolonged reaction times (> 12 h) and harsh conditions (heating to 50 °C) that were necessary to drive the reaction to full conversion always resulted in extensive degradation of the desired product (**2254**); iii) reaction of **2235** with only $Bu_4N^+ NO_3^-$ in CH_3CN resulted in partial conversion to **2254**; iv) reaction of **2235** with catalytic $Bu_4N^+ NO_3^-$ and stoichiometric $AgNO_3$ did not noticeably influence the rate of the reaction; v) both the vinyl iodide (**2236**) and vinyl bromide derived from **2235** (via iodo- or bromodesilylation, respectively) were unproductively consumed in the presence of $AgNO_3$; and, finally, vi) the use of bases stronger than $NaHCO_3$ (i.e., Et_3N and NaOAc[7,14a]) for the elimination of nitrite ion from **2254** (which occurred spontaneously on certain occasions) frequently resulted in dark brown reaction mixtures from which **2244** was isolated in much lower yields.

With a reliable route to isomerically pure **2245** now in service, the cross-coupling/deprotection sequence could be investigated. It was tentatively planned that this substrate would, via iododesilylation, give rise to a vinyl iodide. There was some concern, however, that the electron rich, conjugated silyl enol ether within **2245** would react with an electrophilic iodine source faster than would the vinyl silane. In an unexpected and somewhat remarkable pair of transformations, both **2245** and **2255** *smoothly* underwent iododesilylation[191] with *N*-iodosuccinimide in CH_3CN at 0 °C

---

190 Tschaen, D. M.; Whittle, R. R.; Weinreb, S. M. Regiochemical Control by Nonbonded Interactions in an Intramolecular Nitrone Cycloaddition. *J. Org. Chem.* **1986**, *51*, 2604–2605.

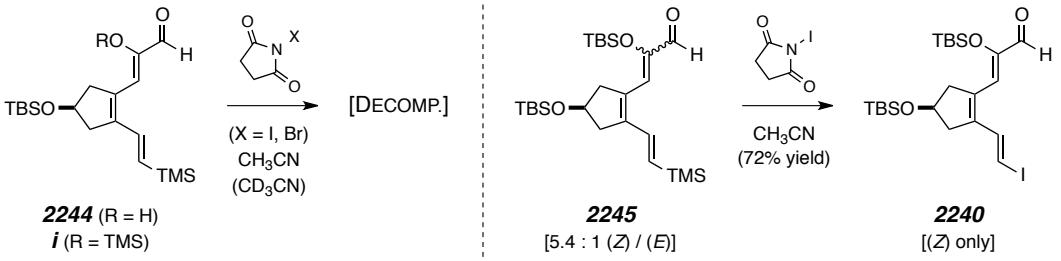
191 It should be recognized that protection of the enol **2244** as its corresponding TBS- or TIPS enol ether is absolutely essential for the success of the subsequent iododesilylation. For example, exposure of the free enol **2244** or the TMS enol ether **i** [prepared from **2235** (Et_3N, CH_2Cl_2; BSA)] to either bromo- or iododesilylative conditions gave an unidentified intermediate that quickly decomposed upon attempted product isolation. Interestingly, on one (and only one) occasion [*MJJ-VI-166*], the TBS enol ether **2245** was isolated as an isomeric mixture upon elimination and silylation [Et_3N, CH_2Cl_2; MTBSA (18%

(Scheme II–70). Simple solvent evaporation and direct purification of the crude residue by flash chromatography provided the vinyl iodides **2240** and **2256**[192] in reproducibly high yields. It was empirically determined that the use of $ClCH_2CN$[99] as a co-solvent was completely unnecessary to achieve a highly stereoselective outcome. Whereas a 1-D NOE experiment established that the $\Delta^{1,2}$ enol ether π-bond had retained its (*Z*)-configuration, the *trans* configuration of the monosubstituted vinyl iodide was trivially ascertained by analysis of the $^3J_{H8,H10}$ coupling values.

The opportunity to investigate the all-important Suzuki cross-coupling reaction was now at hand (Scheme II–70). It was eventually realized that the union of the vinyl iodide **2240** and the vinyl boronate **2103** could be affected by employing a modification of the conditions reported by Nelson.[178] In the event, a slight excess of **2103** was allowed to react with **2240** under the influence of $Ba(OH)_2 \cdot 8H_2O$ and the precatalyst derived from $Pd(OAc)_2$ (5 mol%) and Buchwald's dialkylbiaryl phosphine ligand SPhos[193] (10 mol%).

---

yield)] of the nitrate ester **2254**. Somewhat unexpectedly, the vinyl iodide **2240** emerged from the iododesilylation of this material as a single [(*Z*)] isomer. Taken together, these observations suggest that an intermediate iodonium ion is formed that rapidly and reversibly samples the entire conjugated π-system of **2245** (or **2244**/**i**). Presumably, desilylation (or proton loss) is the rate-determining step that leads to a productive (e.g., **2245**) or nonproductive (e.g. **2244** and **i**) outcome.

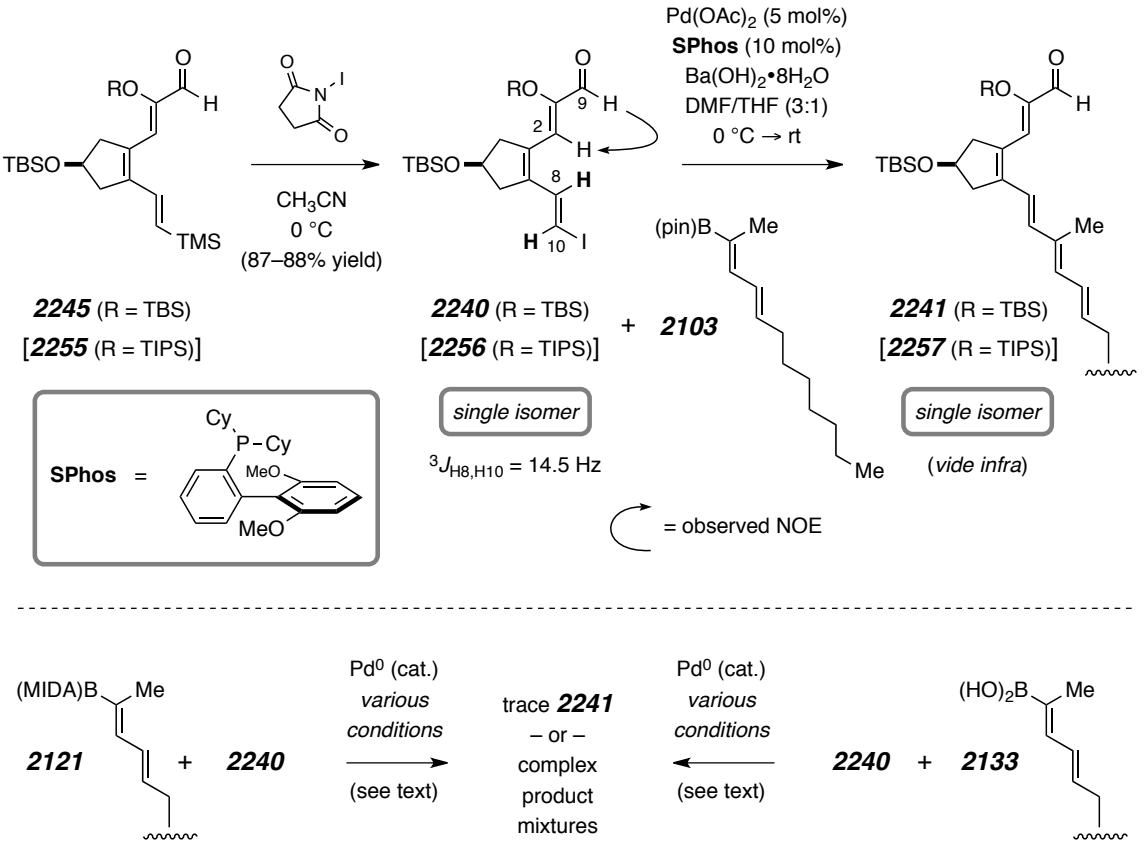


192 [*MJJ-VI-91/93*] **^{1}H NMR** (500 MHz, CD_3CN): δ 9.24 (s, 1H, C*H*O), 7.71 (d, *J* = 14.5 Hz, 1H, C*H*=CHI), 6.65 (d, *J* = 14.5 Hz, 1H, CH=C*H*I), 6.58 [s, 1H, C*H*=C(OTIPS)CHO], 4.55 [dddd, *J* = 2.5, 2.5, 6.0, 6.0 Hz, 1H, C*H*(OTBS)], 3.12 [dd, *J* = 6.5, 18.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.87 [br d, *J* = 18.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.82 [dd, *J* = 6.5, 17.5 Hz, 1H, CH_2CH(OTBS)CH_2], 2.47 [dd, *J* = 3.0, 17.5 Hz, 1H, CH_2CH(OTBS)CH_2], 1.32 {septet, *J* = 7.5 Hz, 3H, Si[C*H*$(CH_3)_2]_3$}, 1.057 {d, *J* = 7.5 Hz, 9H, Si[CH(C*H*$_3)_2]_3$}, 1.055 {d, *J* = 7.5 Hz, 9H, Si[CH(C*H*$_3)_2]_3$}, 0.87 [s, 9H, (C*H*$_3)_3$CSi$(CH_3)_2$], 0.064 [s, 3H, $(CH_3)_3$CSi(C*H*$_3)_2$], and 0.062 [s, 3H, $(CH_3)_3$CSi(C*H*$_3)_2$].

193 (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. Catalysts for Suzuki–Miyaura Coupling Processes: Scope and Studies of the Effect of Ligand Structure. *J. Am. Chem. Soc.* **2005**, *127*,

Under these conditions, the highly unsaturated (and highly colored) pentaenal **2241** could be isolated as essentially a single isomer (but only if isomerically pure **2103** was utilized). Because the unreacted vinyl boronate co-eluted on SiO_2, neither the isolated yield nor the configuration of **2241** was established at this stage (*vide infra*). In order to facilitate subsequent studies, the mixed TIPS/TBS ether **2257** was also prepared under very similar conditions, with the exception that $[Pd(dppf)Cl_2]\bullet CH_2Cl_2$ (8 mol%) was employed as the precatalyst.

Scheme II–70 | Iododesilylation of **2245** (and **2255**) and the subsequent Suzuki cross-coupling of the vinyl iodide **2240** (and **2256**).



4685–4696. (b) Martin, R.; Buchwald, S. L. Palladium-Catalyzed Suzuki–Miyaura Cross-Coupling Reactions Employing Dialkylbiaryl Phosphine Ligands. *Acc. Chem. Res.* **2008**, *41*, 1461–1473.

It was empirically observed during the course of this work that the vinyl pinacol boronate **2103** was a uniquely competent donor in these Suzuki cross-coupling reactions (lower portion of Scheme II–70). Specifically, attempts to bring about the union of the vinyl iodide **2240** and the MIDA boronate **2121** under a variety of conditions that mimicked the *in situ* slow release protocol of Burke and co-workers[105,121,194] [e.g., $Pd(OAc)_2$, SPhos, $Ba(OH)_2•8H_2O$, DMF/THF; $Pd(OAc)_2$, dppf, aq NaOH, THF/PhMe; $Pd(OAc)_2$, dppf, aq K_3PO_4, 1,4-dioxane; $Pd(OAc)_2$, SPhos, K_3PO_4, THF/H_2O] generally suffered from poor reaction conversion and/or the production of complex mixtures in which **2241** was but one product among *ca.* four other isomeric ones. A similar fate awaited the reactions between **2240** and the vinyl boronic acid **2133** {e.g., $[Pd(dppf)Cl_2]•CH_2Cl_2$, $Ba(OH)_2•8H_2O$, DMF/THF; $Pd(OAc)_2$, SPhos, K_3PO_4, THF/PhMe}, wherein only trace amounts of **2241** were observed by LC-MS analysis.

The relative stability of the secondary TBS ether within **2241** vis-à-vis the TBS enol ether toward a mild fluoride ion source was by no means obvious. It was primarily for this reason that the mixed TIPS/TBS substrate **2257** had been prepared, since the selective removal of either of these groups from this substrate could be more easily traced by ^{1}H NMR spectroscopy than would be the case for **2241**. Indeed, exposure of either **2241** or **2257** to the action of aq HF in CH_3CN/CH_2Cl_2[195] gave rise to the secondary alcohols **2258** and **2259**,[196] respectively (Scheme II–71). Note that the latter product

---

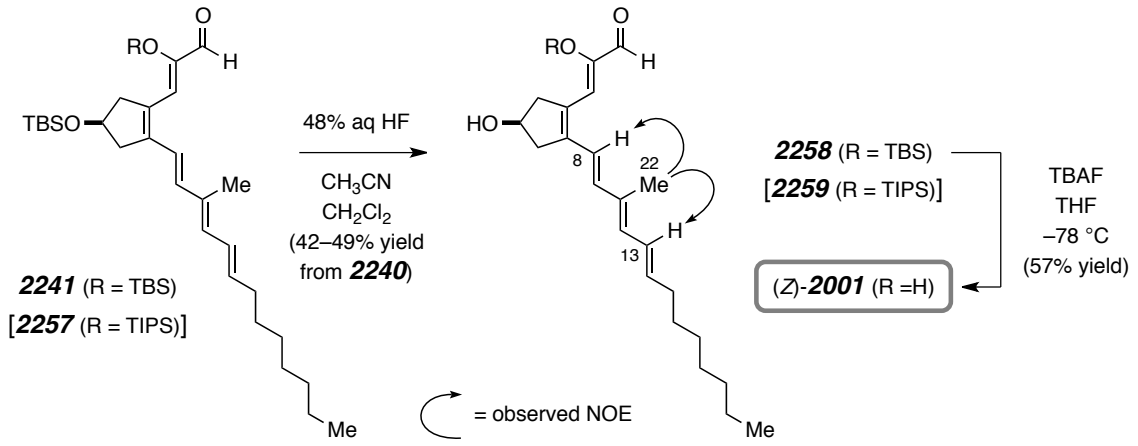
194 Lee, S. J.; Anderson, T. M.; Burke, S. D. A Simple and General Platform for Generating Stereochemically Complex Polyene Frameworks by Iterative Cross-Coupling. *Angew. Chem. Int. Ed.* **2010**, *49*, 8860–8863.

195 Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. An Excellent Reagent for the Removal of the *t*-Butyldimethylsilyl Protecting Group. *Tetrahedron Lett.* **1979**, *20*, 3981–3982.

196 [*MJJ-VI-94/95*] **^{1}H NMR** (500 MHz, CD_3CN): δ 9.26 (s, 1H, C*H*O), 6.84 [d, *J* = 15.5 Hz, 1H, C*H*=CHC(CH_3)=CHCH=CH], 6.71 [s, 1H, C*H*=C(OTIPS)CHO], 6.48 [d, *J* = 15.5 Hz, 1H CH=C*H*–C(CH_3)=CHCH=CH], 6.48 [dddd, *J* = 1.5, 1.5, 11.0, 14.5 Hz, 1H, CH=CHC(CH_3)=CHC*H*=CH], 6.23 [d, *J* = 11.5 Hz, 1H, CH=CHC(CH_3)=C*H*CH=CH], 5.85 [ddd, *J* = 7.0, 7.0, 14.5 Hz, 1H, CH=CH–C(CH_3)=CHCH=C*H*], 4.42 [ddddd, *J* = 2.5, 2.5, 4.5, 6.5, 6.5 Hz, 1H, C*H*(OH)], 3.19 [dd, *J* = 6.5, 18.0 Hz, 1H, C*H*$_2$CH(OH)CH_2], 2.94 [br d, *J* = 18.0 Hz, 1H, C*H*$_2$CH(OH)CH_2], 2.88 [d, *J* = 4.5 Hz, 1H, CH(O*H*)], 2.81 [dd, *J* = 6.5, 17.5 Hz, 1H, CH_2CH(OH)C*H*$_2$], 2.52 [br d, *J* = 17.5 Hz, 1H,

retained the TIPS enol ether. Moreover, on the basis of TLC analysis, prolonged exposure of **2258** to these reaction conditions did *not* provide the fully deprotected product (**2001**). Furthermore, attempts to affect cleavage of the TBS enol ether within **2258** with either $LiBF_4/CH_3CN$[197] or H_2SiF_6/CH_3CN[198] lead only recovered starting material (51% recovery in the latter instance). These observations clearly implicated the enol ether protecting group as the more stable of the two.

Scheme II–71 | Two-step deprotection of **2241** to give rise to the pentaenol (*Z*)-**2001**.



Nonetheless, the fact the **2258** (and thus **2241**) had been produced as essentially a single isomer was established by a GOESY experiment. Thus, irradiation of the C22 allylic methyl resonance resulted in an enhancement of the resonances corresponding to

$CH_2CH(OH)CH_2$], 2.16 [br ddd, *J* = 7.5, 7.5, 7.5 Hz, 2H, CH=CHCH_2], 1.95 [s, 3H, CH=CH–C(CH_3)=CHCH=CH], 1.44-1.38 [m, 2H, CH=CHCH_2CH_2(CH_2)$_4$$CH_3$], 1.33 {septet, *J* = 7.5 Hz, 3H, Si[CH(CH_3)$_2$]$_3$}, 1.33-1.27 [m, 8H, CH=CHCH_2CH_2(CH_2)$_4$$CH_3$], 1.071 {d, *J* = 7.5 Hz, 9H, Si[CH(CH_3)$_2$]$_3$}, 1.067 {d, *J* = 7.5 Hz, 9H, Si[CH(CH_3)$_2$]$_3$}, and 0.89 [t, *J* 7.0 Hz, 3H, CH=CHCH_2–CH_2(CH_2)$_4$CH_3].

197 Metcalf, B. W.; Burkhart, J. P.; Jund, K. Cleavage of *tert*-Butyldimethylsilyl Ethers by Tetrafluoroborate Salts. *Tetrahedron Lett.* **1980**, *21*, 35–36.

198 Pilcher, A. S.; Hill, D. K.; Shimshock, S. J.; Waltermire, R. E.; DeShong, P. Selective Deprotection of Trialkylsilyl Ethers Using Fluorosilicic Acid. *J. Org. Chem.* **1992**, *57*, 2492–2495.

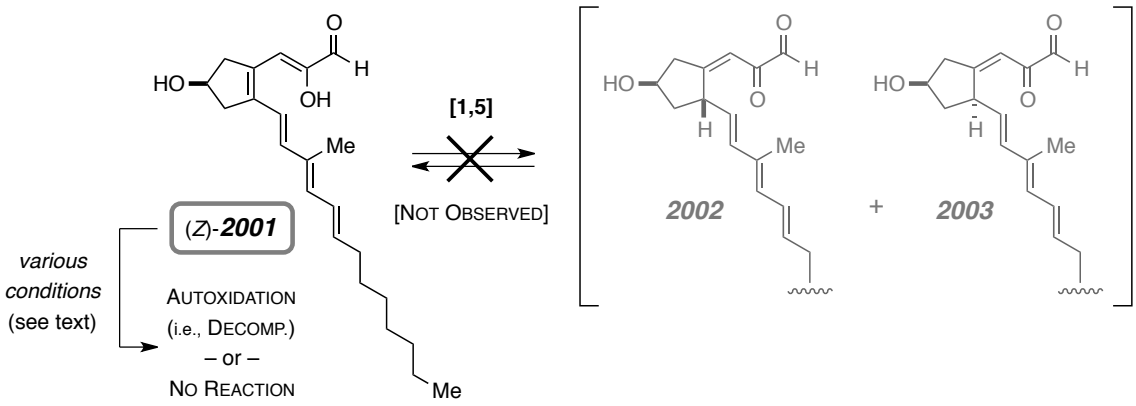
H8 and H13 (Scheme II–71). Since the mildly acidic conditions employed above failed to affect deprotection, it became clear that recourse would have to be made to more potent reagent–namely, TBAF. At first glance, the direct, global deprotection of **2241** would appear to be a more step economical method for preparing **2001**. However, when this intermediate as exposed to TBAF (2.6 equiv) in THF at 0 °C, complete destruction of the starting material occurred. With the intent of never making that mistake again, the deprotection of the polyenol **2258** was probed. Indeed, addition of *ca.* 1 equiv of TBAF to a low temperature (–78 °C) solution of **2258** in THF immediately produced a blood red solution (presumably, the intermediate tetra-*n*-butylammonium *penta*enolate) from which **2001** could be isolated in moderate yield (57%).

At long last, (*Z*)-**2001** was prepared in a *direct* and *highly stereoselective* fashion. The fact that this material could be isolated, purified by flash chromatography, and fully characterized was, in hindsight, an ominous signal of things to come. In Section A–1 of this Chapter, it was proposed that (*Z*)-**2001** would be in dynamic equilibrium, via spontaneous [1,5]-hydrogen atom shifts, with the diastereomeric α-keto aldehydes **2002** and **2003**. These latter two intermediates would then give rise to **1-A** (and 9-*epi*-**1-A**) and **1-B** (and 9-*epi*-**1-B**) through competitive, spontaneous intramolecular hetero-Diels–Alder (IMHDA) cycloaddition cascades.

To be quite blunt, of the *ca.* dozen samples of **2001** that have been independently prepared, none have been observed to enter into a tautomeric equilibrium of the type that has been proposed in the hypothesis for the biosynthesis of **1-A** and **1-B**. For example, when the stability of **2001** was probed in various aqueous organic solvent mixtures [i.e., pH 3 buffer/THF/*i*-PrOH, pH 7.4 buffer/THF/*i*-PrOH, and MeOH/H_2O], starting material consumption occurred fairly rapidly only to give intractable reaction mixtures (i.e., baseline material by TLC analysis and uninformative crude ^{1}H NMR spectra). Moreover, when monitored by ^{1}H NMR spectroscopy (in CD_3OD, CD_3CN, or DMSO-d_6; room temperature or heat), **2001** gradually decomposed (as evidenced by the broadening of the resonances throughout the spectrum) before giving rise to any discrete intermediates.

Perhaps not surprisingly, analysis of these samples by LC-MS strongly suggested that autoxidation of the conjugated (and electron-rich) polyene within **2001** was the primary event that initiated decomposition (see, for example, *MJJ-VI-208* and *VII-78*).

Scheme II–72 | Observations concerning the inherent reactivity of (*Z*)-**2001**.



Conversely, the pentaenol **2001** can be quite stable at room temperature, provided that oxygen is rigorously excluded (via freeze–pump–thaw cycles). For example, when **2001** was dissolved in CD_3CN/D_2O (9:1) and the ^1H NMR spectrum recorded at various time points, essentially no change was observed during the course of 21 h at room temperature. Unfortunately, this stability is not absolute, since mild heating (45 °C) of a solution of **2001** in degassed PhMe (inhibited with 250 ppm BHT) resulted in extensive decomposition of the starting material. In contrast to these observations, the mono-TBS polyene **2258** remained largely intact upon heating to 100 °C (C_6D_6, sealed NMR tube) for 18 h. Although the appearance at least two other (minor) isomeric components were observed during this final experiment, the olefinic resonances corresponding to **2258** nonetheless remained sharp and readily discernable.

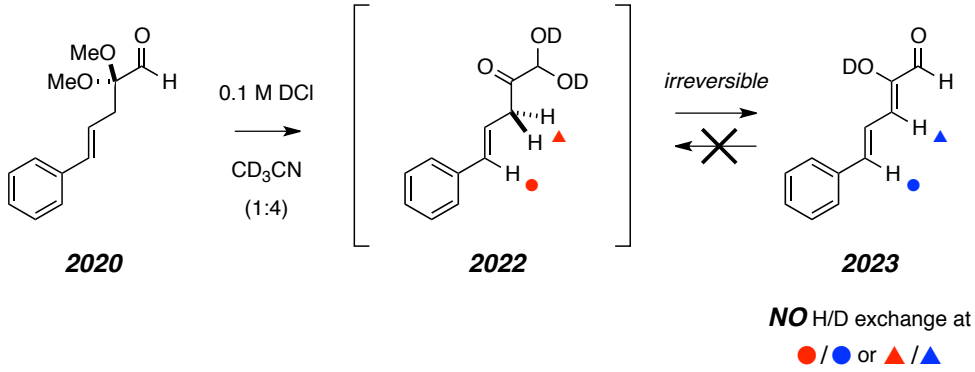
In retrospect, the observations that were made during the hydrolysis of the 2,2-dimethoxy aldehyde **2020** (Section C) might now provide some insight regarding the reluctance of **2001** to undergo tautomerization. During that model study, the formation of

the α-keto aldehyde hydrate **2022** was observed upon hydrolysis of **2020** in 0.1 M DCl/CD_3CN (Scheme II–73). The dienol **2023** was subsequently produced (and could be derivatized and characterized) upon collapse of this hydrate. Interestingly, very little deuterium incorporation (< 5%) was observed at those sites within **2023** that should have readily undergone H/D exchange (i.e., ▲ and ● vis-à-vis ▲ and ● in **2022**) under these deuterium-rich conditions. Moreover, if the enol **2023**, independently prepared and purified by an alternative method (see Scheme II–51), was subjected to the same hydrolysis conditions, again essentially no deuterium incorporation (< 5%) occurred.

It is now apparent that the explanation for these earlier observations regarding **2023** *and* the unwillingness of **2001** to undergo tautomerization are one in the same. Namely, the collapse of the α-keto aldehyde enol **2022** (Scheme II–73) is an *irreversible process*. In other words, **2023** and **2001** have fallen into thermodynamic wells, out from which they are unable to climb. It is somewhat unsettling (if not a bit amusing) to point out that the fate of **2001** was sealed five steps earlier in the synthetic sequence when the enol **2244** was prepared–at that time, a tremendous experimental victory.

Scheme II–73 | (Some of the) intermediates of Figure II–1 revisited.

[**Figure II–1**]



H. HYPOTHESIS FOR THE BIOSYNTHESIS OF PENOSTATINS A AND B REVISITED

REVISED HYPOTHESIS STATEMENT:

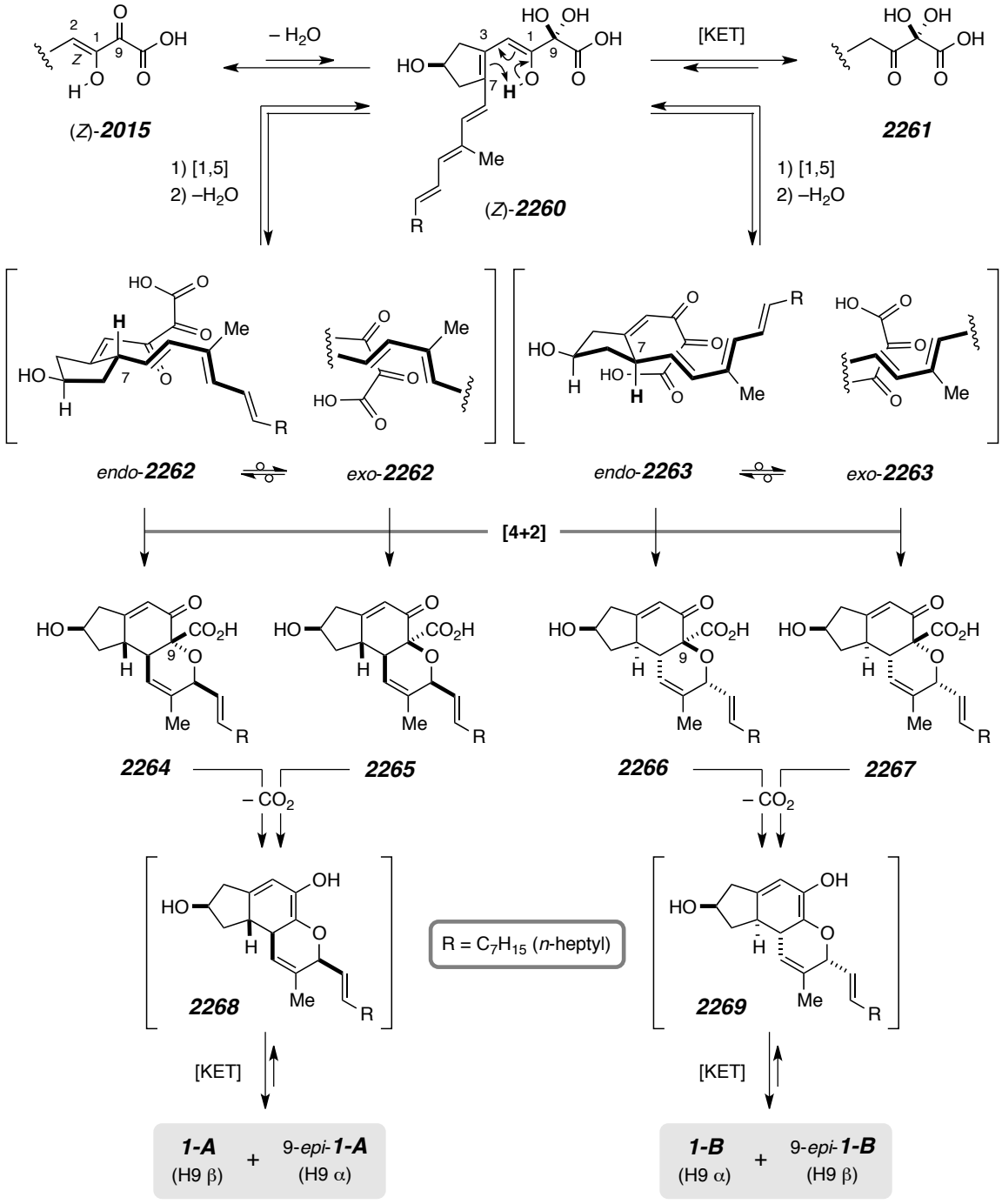
> *PENOSTATIN A (**1-A**) AND PENOSTATIN B (**1-B**) ARISE FROM A SINGLE (i.e., COMMON) BIOGENETIC INTERMEDIATE (e.g., **2015**) THAT DIVERGES INTO PARALLEL, DIASTEREOMERIC REACTION MANIFOLDS. THESE CASCADE, VIA COMPETITIVE SPONTANEOUS INTRAMOLECULAR HETERO-DIELS–ALDER, DECARBOXYLATION, AND TAUTOMERIZATION EVENTS, TO GIVE RISE TO THE NATURAL PRODUCTS.*

The observations that were made in the previous section regarding the recalcitrance of **2001** toward tautomerization compelled a reexamination of the hypothesis that was proposed at the beginning of Chapter II (recall Scheme II–1 in Section A–1). Leaving aside for the moment the propensity of **2001** to undergo autoxidation, we were intrigued by the kinetic and thermodynamic ramifications of an intermediate such as (*Z*)-**2260** (Scheme II–74). Specifically, via a pair of presumably rapid and reversible events, one might expect this intermediate to be in equilibrium with the β-keto acid hydrate **2261** and α-keto acid enol (*Z*)-**2015**. Indeed, vicinal tricarbonyl systems are notoriously susceptible to hydration at the central carbon to give intermediates such as **2261**.[199] Additionally, the existence of enol tautomers related to **2015** has been observed in 1,2,3-tricarbonyl amide subunits.[168] Importantly, this latter species is the $\Delta^{1,2}$ geometric isomer of (*E*)-**2015**, an intermediate that has already been proposed as a potential biosynthetic precursor of **2001** (via oxa-6π electrocyclization and decarboxylation of the enol **2014**; recall Scheme II–4 in Section A–2).

---

[199] (a) Rubin, M. B.; Gleiter, R. The Chemistry of Vicinal Polycarbonyl Compounds. *Chem. Rev.* **2000**, *100*, 1121–1164. (b) Wasserman, H. H.; Parr, J. The Chemistry of Vicinal Tricarbonyls and Related Systems. *Acc. Chem. Res.* **2004**, *37*, 687–701.

Scheme II–74 | Revised hypothesis for the biosynthetic origin of penostatin A (**1-A**) and B (**1-B**), and the co-production of 9-*epi*-penostatin A (9-*epi*-**1-A**) and B (9-*epi*-**1-B**).



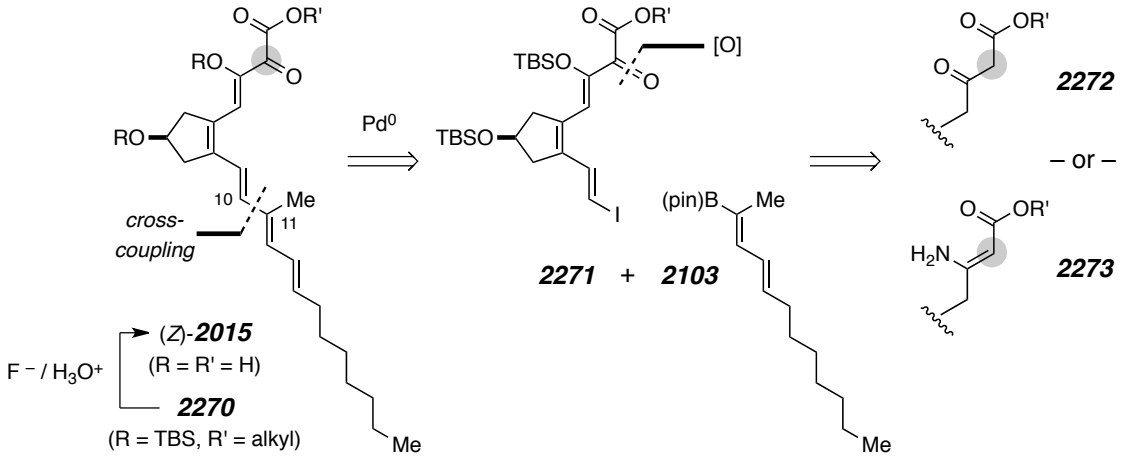
The bottom line with regard to the present discussion is that the inclusion of an electron withdrawing carboxyl group adjacent to the C9 carbonyl oxygen (as is present in **2015**, Scheme II–74) should result in a higher equilibrium concentration of the hydrate **2260**. Obviously, hydration at C9 would greatly diminish the carbonyl character at this center. It is therefore proposed that the ensuing pair of [1,5]-hydrogen atom shifts within (*Z*)-**2260**, which necessarily requires the build up of carbonyl character at C1, will be rendered far more energetically accessible than would otherwise have been the case for the α-keto aldehyde enol (*Z*)-**2001**.

In a similar manner to that described for the production of the α-keto aldehydes **2002** and **2003** (cf. Scheme II–1), internal delivery of a proton from the enol oxygen to either the β- or α-diastereoface of the $\Delta^{3,7}$ π-bond within (*Z*)-**2260** would result in the production of the diastereomeric tricarbonyl acids **2262** and **2263** (in equilibrium with the corresponding hydrates and carboxylates, of course). Were *endo*-**2262** and *endo*-**2263** to undergo IMHDA cycloaddition, they would give rise to the dihydropyrans **2264** and **2266**, respectively. Similarly, closure via *exo*-**2262** and *exo*-**2263** would generate **2265** and **2267**, respectively, which are the C9 epimers of the cycloadducts that were produced from the *endo*-IMHDA manifold. The common enol tautomers **2268** and **2269** that would be produced upon decarboxylation of **2264**/**2265** and **2266**/**2267**, respectively, would then give rise to **1-A**/9-*epi*-**1-A** and **1-B**/9-*epi*-**1-B** via tautomerization, a final event that would presumably be under thermodynamic control.

I. SYNTHESIS STRATEGIES TOWARD THE ENOL PYRUVATE (*Z*)-2015

Given that a relatively robust synthetic platform has already been developed for the preparation of (*Z*)-**2001**, the enol pyruvate (*Z*)-**2015** was identified as being the most logical access point to test the revised hypothesis. Thus, it was reasoned that if a fully protected intermediate such as **2270** could be prepared, then subsequent fluoride-ion-induced silyl ether cleavage and pyruvate ester hydrolysis should provide **2015** (Scheme II–75). The usual disconnection of the C10–C11 via Suzuki cross-coupling then reveals the vinyl iodide **2271** and the vinyl boronate **2103**. Since ample quantities of isomerically pure **2103** are already in hand, the synthetic crosshairs were now focused upon the preparation of **2271**. The most obvious starting point, it was believed, would be to consider either the direct or indirect α-oxidation of either a β-keto ester (**2272**) or an enamino ester (**2273**) since methods for the preparation of such species have already been described in Chapter II.

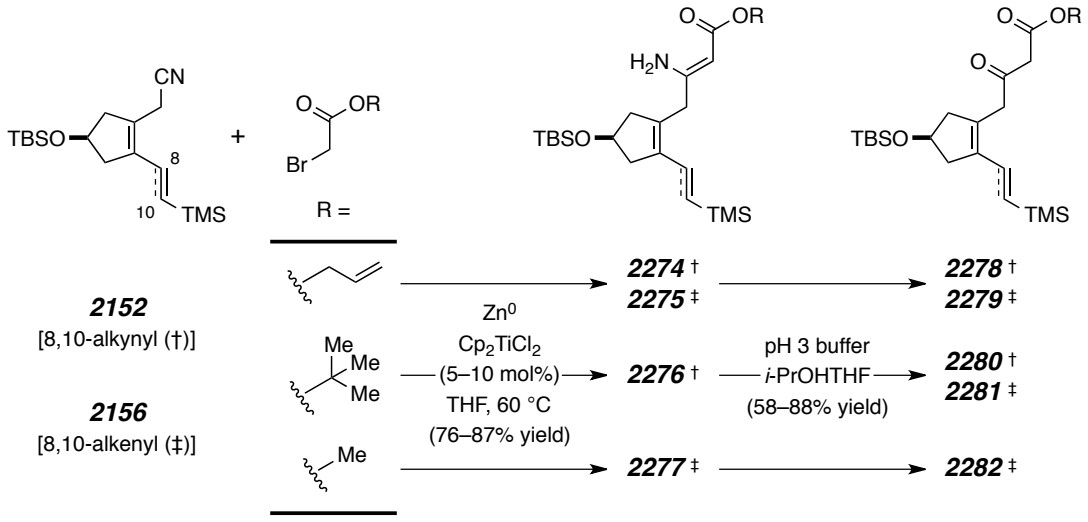
Scheme II–75 | Retrosynthetic analysis of the enol pyruvate (*Z*)-**2015**.



Since it could not be known at the outset what alkyl ester (i.e., the identity of R′ in the structures of Scheme II–75) would provide the best comprise between stability and

ease of hydrolysis, a small family of enamino- and β-keto esters were prepared (Scheme II–76). Reaction of the alkynyl- (**2152**) and alkenyl- (**2156**) allylic nitriles with the reagents derived from Zn^0/Cp_2TiCl_2[200] and either allyl-, *tert*-butyl-, or methyl bromoacetate under Hannick and Kishi's modification[201] of the Blaise homologation provided the enamino esters **2274**–**2277** in serviceable yields. Then, mild hydrolysis of these intermediates with pH 3 buffer in *i*-PrOH/THF efficiently delivered the β-keto esters **2278**–**2282**.

Scheme II–76 | Blaise homologation of the allylic nitriles **2152** and **2156** with allyl-, *tert*-butyl, and methyl bromoacetate.



At the time that these studies were initiated, the most abundant of the enamino- and β-keto esters were **2274** and **2278**, and therefore they were employed in a number of the exploratory studies (Scheme II–77). With the intent of isolating **2283** (R = H, Ac, or

[200] Ding, Y.; Zhao, G. One-Pot Preparation of β-Hydroxy Esters Catalyzed by a Bis(cyclopentadienyl)-titanium(IV) Dichloride–Zinc System. *J. Chem. Soc., Chem. Commun.* **1992**, 941–942.

[201] Hannick, S. M.; Kishi, Y. Improved Procedure for the Blaise Reaction: A Short, Practical Route to the Key Intermediates of the Saxitoxin Synthesis. *J. Org. Chem.* **1983**, *48*, 3833–3835.

Ts), the oxidation of **2274** was examined in the presence of some different hypervalent oxidants that are known to accomplish this transformation. Unfortunately, exposure of this species to a either $PhI(OAc)_2$[202] (DCE, 65 °C), PhI(OH)OTs[203] (CH_3CN, 65 °C), or IBX (DMSO and DMSO/H_2O) did not result in the expected outcome. Whereas complete decomposition of the starting material occurred with the latter two reagents, oxidation of **2274** with $PhI(OAc)_2$ gave evidence for the formation of the 2*H*-azirine **2285**.[204] This process, which perhaps proceeds via **2284**, has some precedent.[205]

The β-keto ester **2278** was similarly recalcitrant toward direct oxidation (Scheme II–77). For example, exposure of this substrate to DMP[206,207] (pyridine, CH_2Cl_2 or

---

202 Species related to **2283** (R = Ac) have been obtained from the $PhI(OAc)_2$-mediated oxidation of β-enamino ketones, see: Chen, Y.; Ju, T.; Wang, J.; Yu, W.; Du, Y.; Zhao, K. Concurrent α-Iodination and *N*-Arylation of Cyclic β-Enaminones. *Synlett* **2010**, 231–234.

203 For a report of the PhI(OH)OTs-mediated oxidation of methyl 3-aminocrotonate, see: Papoutsis, I.; Spyroudis, S.; Varvoglis, A. Reactivity of a New Alkenyl Phenyliodonium Tosylate Derived from Methyl 3-Aminocrotonate. *Tetrahedron* **1998**, *54*, 1005–1012.

204 [*MJJ-IV-230*] It must be said that this reaction was neither clean nor efficient, and thus a sample of **2285** could not be isolated in a high state of purity. However, the following diagnostic ^{1}H NMR (500 MHz, $CDCl_3$) resonances were evident: δ 3.84 [ABq (2x), $\Delta\nu_{AB}$ = 57 Hz, J_{AB} = 17.5 Hz, 4H, overlapping $CH_2C(=N)CHCO_2Allyl$], 2.51 [s, 1H, $CH_2C(=N)CHCO_2Allyl$], and 2.50 [s, 1H, $CH_2C(=N)CHCO_2Allyl$].
HR ESI-MS: $C_{23}H_{37}NO_3Si_2$ $[M+Na]^+$ requires 454.2204; found 454.2224.
TLC: R_f 0.52 (6:1 Hex/EtOAc).
The observed chemical shifts for the diastereomeric 2*H*-azirine methine protons that have been assigned to **2285** are reasonably consistent with literature values; see ref 205a and: Sakamoto, S.; Inokuma, T.; Takemoto, Y. Organocatalytic Asymmetric Neber Reaction for the Synthesis of 2*H*-Azirine Carboxylic Esters. *Org. Lett.* **2011**, *13*, 6374–6377.

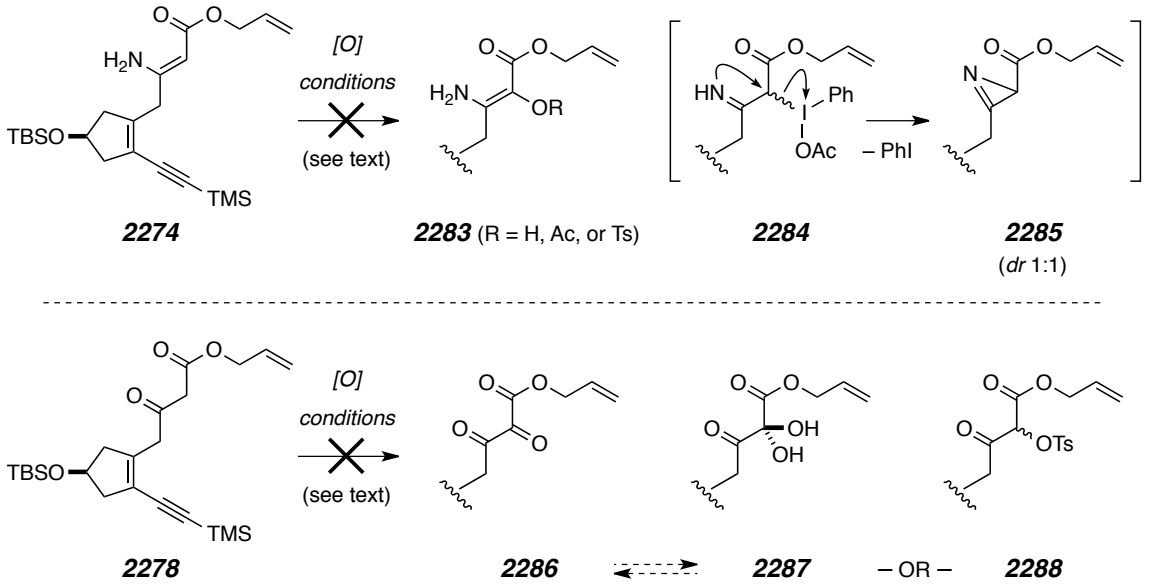
205 (a) Li, X.; Du, Y.; Liang, Z.; Li, X.; Pan, Y.; Zhao, K. Simple Conversion of Enamines to 2*H*-Azirines and Their Rearrangements under Thermal Conditions. *Org. Lett.* **2009**, *11*, 2643–2626. (b) Shimada, N.; Ashburn, B. O.; Basak, A. K.; Bow, W. F.; Vicic, D. A.; Tius, M. A. Organocatalytic Asymmetric aza-Nazarov Cyclization of an Azirine. *Chem. Commun.* **2010**, *46*, 3774–3775.

206 Batchelor, M. J.; Gillespie, R. J.; Golec, J. M. C.; Hedgecock, C. J. R. A Novel Application of the Dess–Martin Reagent to the Synthesis of an FK506 Analogue and other Tricarbonyl Compounds. *Tetrahedron Lett.* **1993**, *34*, 167–170.

207 Meyer, S. D.; Schreiber, S. L. Acceleration of the Dess-Martin Oxidation by Water. *J. Org. Chem.* **1994**, *59*, 7549–7552.

CH_2Cl_2/H_2O) or PhI(OH)OTs[208] (CH_3CN, 60–65 °C) gave intractable reaction mixtures from which neither **2286**/**2287** nor **2288** could be isolated. A comparable result was obtained upon the attempted Rubottom oxidation of the TBS enol ether derived from **2278** [i.e., TBSOTf, Et_3N, CH_2Cl_2; DMDO, CH_2Cl_2, –78 °C → 0 °C (≥ 5 components present on the basis of TLC analysis)].

Scheme II–77 | Attempted oxidation of either **2274** or **2278** under a variety of conditions did not give rise to the desired products (i.e., **2283** and **2286**/**2287**).

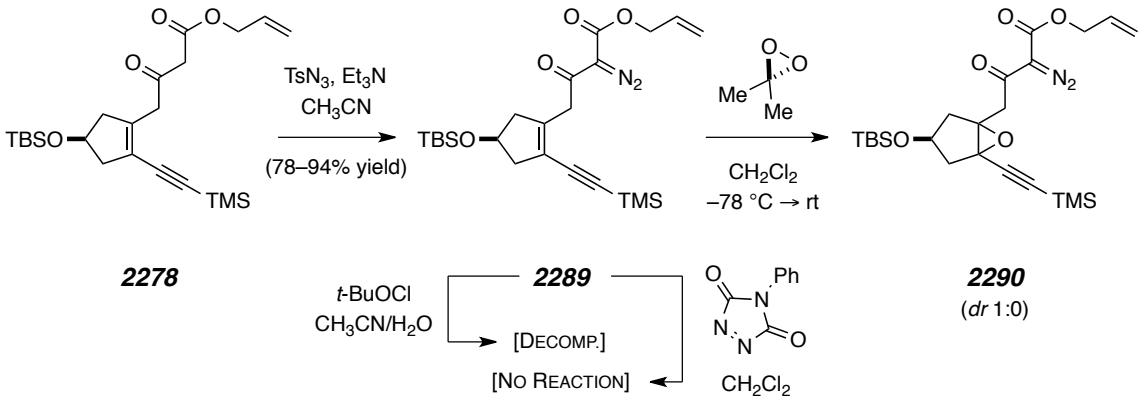


Due to their stability and ready availability via the Regitz transfer method, α-diazo β-dicarbonyl compounds have been widely used as precursors to *vic*-tricarbonyl systems. The tricarbonyl products are obtained upon oxidation of the α-diazo precursors,

[208] (a) Koser, G. F.; Relenyi, A. G.; Kalos, A. N.; Rebrovic, L.; Wettach, R. H. One-Step α-Tosyloxylation of Ketones with [Hydroxy(tosyloxy)iodo]benzene. *J. Org. Chem.* **1982**, *47*, 2487–2489. (b) Lodaya, J. S.; Koser, G. F. Direct α-Mesyloxylation of Ketones and β-Dicarbonyl Compounds with [Hydroxy(mesyloxy)iodo]benzene. *J. Org. Chem.* **1988**, *53*, 210–212.

a transformation that is most typically accomplished with *t*-BuOCl[199a] or DMDO.[209] In addition to this, Regitz himself has reported that triazolinedione ylides are produced upon reaction of diazo compounds with 4-phenyl-1,2,4-triazole-3,5-dione (PTAD).[210] These ylides were trapped with ethanol and subsequently hydrolyzed (HCl) to produce 1,2-dicarbonyl compounds.[211] With this in mind, the α-diazo β-keto ester **2289** was easily prepared by reaction of **2278** with TsN_3/Et_3N in CH_3N (Scheme II–78). Disappointingly, exposure of **2289** to *t*-BuOCl resulted in the nearly instantaneous destruction of the starting material; in stark contrast, absolutely no change was observed in the presence of PTAD. A clean transformation did finally occur when the DMDO-mediated oxidation of **2289** was carried out according to Saba's protocol,[209] but it *did not* yield the expected tricarbonyl product. Instead, epoxidation of the tetrasubstituted olefin occurred in a highly diastereoselective fashion to yield **2290** as the only isolable product.

Scheme II–78 | Preparation and preliminary reactivity studies of the α-diazo β-keto ester **2289**.



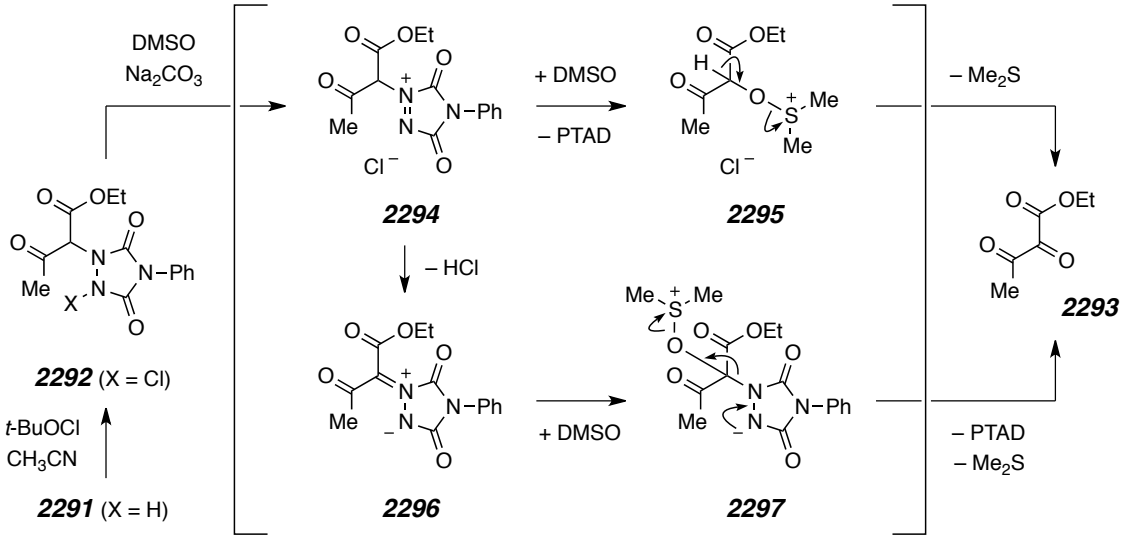
209 Saba, A. Synthesis of Vicinal Trioxo Compounds by Dimethyl Dioxirane Oxidation of 2-Diazo-1,3-dioxo Derivatives. *Synth. Commun.* **1994**, *24*, 695–699.

210 Bethäuser, W.; Regitz, M.; Theis, W. Über die Reaktivität von 4-Phenyl-1,2,4-triazolin-3,5-dion mit Diazoverbindungen. *Tetrahedron Lett.* **1981**, *22*, 2535–2538.

211 Theis, W.; Bethäuser, W.; Regitz, M. Untersuchungen an Diazoverbindungen und Aziden–LIII: Abfangreaktionen Instabiler Azomethinimin-dipole mit Ethanol. *Tetrahedron* **1985**, *41*, 1965–1971.

At this point, a fascinating pair of reports from Wilson and co-workers[212] caught my attention. These researchers discovered that PTAD readily reacted with ketones and β-diketones to provide α-urazolylcarbonyl adducts.[212a] These adducts then gave rise to di- and tricarbonyl products after *t*-BuOCl-mediated oxidation and subsequent treatment with DMSO/Na_2CO_3.[212b]

Scheme II–79 | Mechanistic proposal(s) by Wilson and co-workers for the formation of **2293** via the intermediacy of an acyltriazolinedione ylide (**2296**) [adapted from ref 212b].



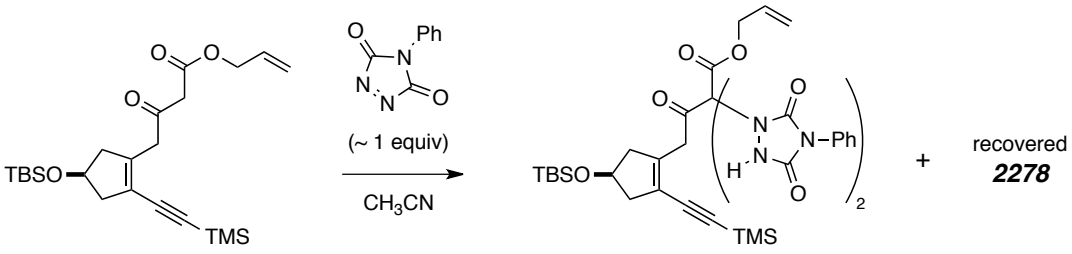
The mechanism that they proposed to account for the observed products invoked the intermediacy of acyltriazolinedione ylides of the type **2296** (Scheme II–79). Thus, oxidation of the PTAD adduct of ethyl acetoacetate (**2291**) presumably gave rise to the chlorinated α-urazolylcarbonyl intermediate (**2292**). Rapid elimination of HCl from the intermediate zwitterion **2294** in the presence of Na_2CO_3 might give rise to an ylide

212 (a) Wilson, R. M.; Hengge, A. C.; Ataei, A.; Chantarasiri, N. Addition of 4-Phenyltriazolinedione to Carbonyl Compounds: The Formation of α-Urazolylcarbonyl Compounds. *J. Org. Chem.* **1990**, *55*, 193–197. (b) Wilson, R. M.; Hengge, A. C. Synthesis and Chemistry of Acyltriazolinedione Ylides and Related Intermediates: New Methods for the Preparation of Di- and Tricarbonyl Compounds. *J. Org. Chem.* **1990**, *55*, 197–202.

(**2296**), from which the tricarbonyl **2293** would be generated upon reaction with DMSO (via **2297**). Alternatively, Wilson and Hengge[212b] also speculated that direct displacement of PTAD by DMSO within **2294** would produce a Swern-type intermediate (**2295**). Loss of Me_2S and HCl from this intermediate would then account for the formation of **2293**.

I was intrigued by the possibility that an adaptation of Wilson's chemistry might have some utility with regard to the synthesis of **2271** (cf. Scheme II–75). However, one of the most appealing aspects of this methodology–namely, the high reactivity and potently enophilic character of PTAD–is also one its primary drawbacks. Specifically, the reaction of PTAD with β-dicarbonyl compounds, which perhaps proceeds via a hetero Alder-ene reaction with the enol tautomer, tends to give rise to 2:1 PTAD:β-dicarbonyl adducts as a result of the enhanced enol content of the initially formed 1:1 adduct.[212a] This caveat is best illustrated by the reaction of **2278** with *ca.* 1 equiv of PTAD in CH_3CN at room temperature (Scheme II–80), wherein a mixture of the 2:1 adduct **2298** and unreacted **2278** was obtained (1:1 ratio on the basis of the crude ^{1}H NMR spectrum; the mass of **2298** was confirmed by LR ESI-MS analysis [*MJJ-IV-251*]). Although Wilson and co-workers overcame this problem by the using an excess of the (commercially available) β-dicarbonyl compound,[212a] this was clearly not a practical solution in the present case.

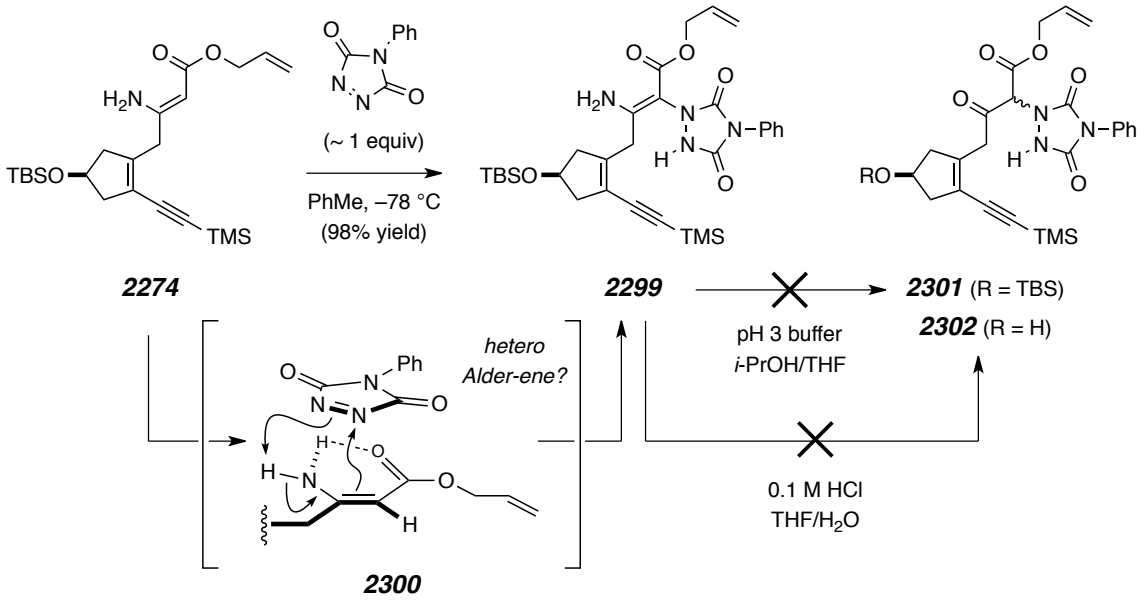
Scheme II–80 | Formation of a 2:1 PTAD adduct upon reaction of **2278** with 1 equiv PTAD.



2278 ***2298***

When an *enamino* ester was allowed to react with PTAD, however, a more workable solution to this problem was uncovered (Scheme II–81). In the event, treatment of **2274** with a PhMe solution of PTAD resulted in the rapid discharge of the characteristic blood red color of this reagent–*even at –78 °C*–whereupon the adduct **2299** was *cleanly* produced. On the basis of ^{1}H NMR analysis, this substance existed as a 5:1 mixture of isomeric species in CD_3CN solution.

Scheme II–81 | Formation and unproductive hydrolysis of the PTAD adduct **2299**.



Although related processes involving both PTAD[213] and diethyl azodicarboxylate (DEAD)[214] are known, to the author's knowledge this is one of the lowest temperatures

[213] (a) Wamhoff, H.; Wald, K.; Kirfel, A.; Farkas, L.; Samimi, N.; Will, G. Reaktionen von Uracilen, 5. Verbrückte 1,2,5,6-Tetrazocane mit Uracil- und Urazolbrücken durch Dimerisierung von 5-(1,2,4-Triazolidin-1-yl)uracilen. *Chem. Ber.* **1985**, *118*, 436–443. (b) Zhang, J. –H.; Wang, M. –X.; Huang, Z. –T. The Aza-ene Reaction of Heterocyclic Ketene Aminals with 4-Phenyl-1,2,4-triazoline-3,5-dione. *J. Chem. Res. (S)* **1998**, 486–487.

[214] (a) Taylor, E. C.; Martin, S. F. A New Synthesis of *as*-Triazines and Pyrimido[4,5-*e*]-*as*-triazines (6-Azapteridines). *J. Org. Chem.* **1970**, *35*, 3792–3795. (b) Huang, Z. –T.; Liu, Z. –R. Synthesis of 2-

ever recorded for such a transformation. A reasonable working mechanistic hypothesis invokes a 'hetero Alder-ene' reaction between PTAD and **2274** (Scheme II–81). Presumably, the initial pericyclic event is followed by rapid tautomerization to give rise to **2299**, but, admittedly, it is not clear at present precisely how this penultimate step occurs. It should be noted that the proposal of a hetero Alder-ene mechanism has some precedent in the reactions of ketonic 1,1-enediamines with PTAD.[213b]

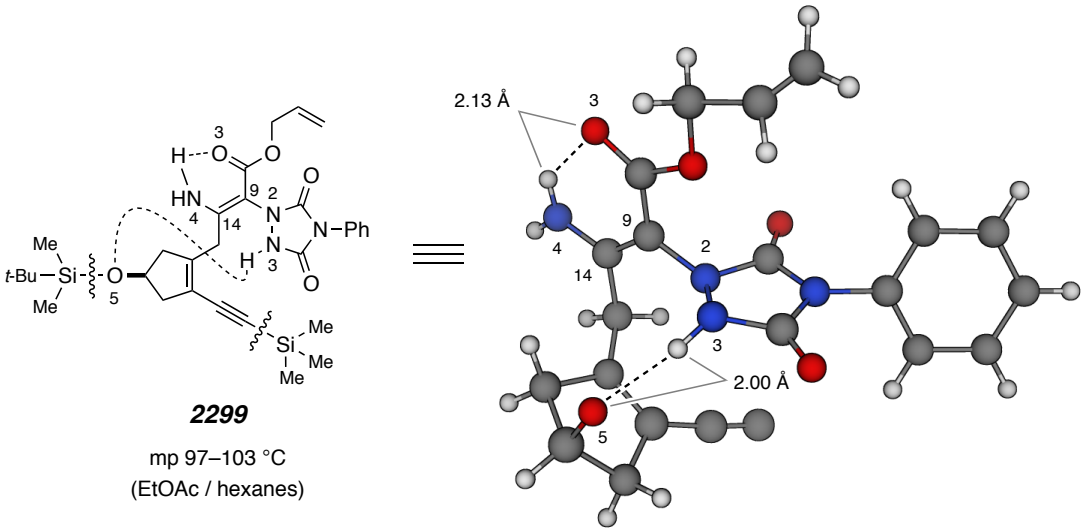


Figure II–5 | Three-dimensional rendering of **2299** from the single crystal X-ray structure coordinates. The Si, C, and H atoms of the TBS and TMS groups have been removed for clarity.

I was delighted to find that a crystalline sample of **2299** could be generated (EtOAc/Hex vapor diffusion) that was suitable for X-ray diffraction analysis, and the result of this experiment is shown in Figure II–5. Although both of the silicon-containing (i.e., TBS and TMS) groups were disordered (and thus have been removed for clarity),

(Benzoylmethylene)imidazolidines and -hexahydropyrimidines by Condensation of Ethyl Benzoylacetimidates with 1,2-Ethanediamine or 1,3-Propandiamine, and Some Addition Reactions. *Synthesis* **1987**, 357–362. (c) Cheng, Y.; Zhao, M.; Wang, M. –X.; Wang, L. –B.; Huang, Z. –T. Synthesis of Acetyl-Substituted Heterocyclic Enamines and Their Reaction with Diethyl Azodicarboxylate. *Synth. Commun.* **1995**, *25*, 1339–1351.

the most important, core elements of this structure unambiguously confirmed the proposed constitution of **2299**. Worthy of note is the presence of two internal hydrogen bonds: One between N4–H…O3 (2.13 Å) and another between N3–H…O5 (2.00 Å). In particular, this latter interaction suggests that the two isomeric species observed in CD_3CN solution correspond to C9–N3 rotamers (rather than a mixture of $\Delta^{9,14}$ geometric isomers) whose interconversion is relatively slow on the NMR timescale at 500 MHz. However, the NMR experiments that would be necessary to probe this point were not conducted.

With a simple and efficient method to prepare **2299** in hand, it was believed that its subsequent hydrolysis would provide a means to indirectly access the corresponding α-urazolyl β-keto ester (Scheme II–81). However, it was discovered that, contrary to the ready hydrolysis of the enamino ester **2274** with pH 3 buffer (*i*-PrOH/THF), the PTAD adduct was completely resistant to these conditions and thus it did not yield any of the expected product (**2301**). When recourse was made to more strongly acidic conditions (i.e., 0.1 M HCl), the secondary TBS ether was cleaved straightaway to generate the free alcohol (confirmed by ESI analysis[215]) but none of the hydrolysis product **2302** was observed.

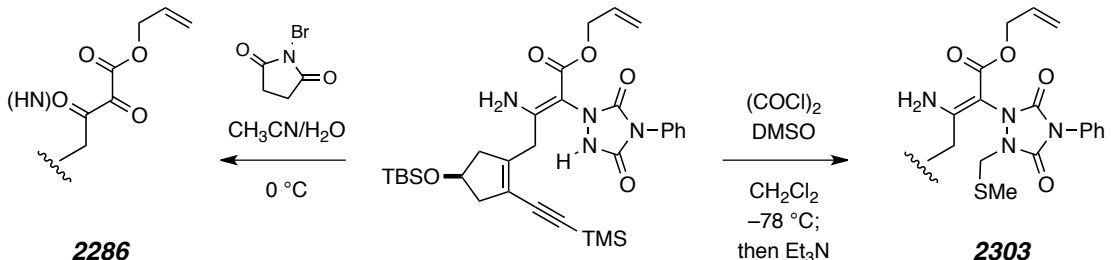
In light of the apparent inaccessibility of the α-urazolyl β-keto ester **2301** (or **2302**), it became clear that the oxidative chemistry of **2299** would have to be explored. In principle, a mechanistic scenario similar to that proposed by Wilson and co-workers (cf. Scheme II–79) could be invoked, with the exception that a hydrolysis step would be necessary so that the tricarbonyl product could be isolated. With this in mind, a variety of oxidative methods were explored for the generation of the acyltriazolinedione ylide derived from **2299**. Disappointingly, intractable reaction mixtures or starting material decomposition were observed under many of the conditions that were examined [i.e., i) $PhI(OAc)_2$, CH_3CN/H_2O; ii) NCS, CH_3CN; then Na_2CO_3/DMSO; iii) *t*-BuOCl, THF; iv) IBX, DMSO; v) DDQ, CH_3CN/pH 7 buffer or CH_2Cl_2/MeOH; vi) CAN,

---

215 [*MJJ-IV-247*] **HR ESI-MS**: $C_{25}H_{30}N_4O_5Si$ $[M+Na]^+$ requires 517.1878; found 517.1879.

CH_2Cl_2/MeOH; and vii) DMDO, CH_2Cl_2 or CH_2Cl_2/MeOH]. Treatment of **2299** with $PhI(OAc)_2$ in MeOH/CH_2Cl_2 (2:1) at 0 °C cleanly gave rise to a product formally derived from incorporation of formaldehyde into the starting material;[216] however, the constitution of this substance could not be established. Additionally, MTM protection[217] (to give **2303**[218]) occurred upon exposure of **2299** to Swern conditions (Scheme II–82).

Scheme II–82 | Some reactions of the α-urazolyl enamino ester **2299**.



2286
(observed by HR ESI-MS; could not be isolated)

2299

2303

---

216 [*MJJ-V-37*] **HR ESI-MS**: $C_{32}H_{44}N_4O_6Si_2$ $[M+Na]^+$ requires 659.2692; found 659.2771.

217 MTM ether formation has been observed to occur during the Swern oxidation; see: Williams, D. R.; Klingler, F. D.; Dabral, V. Synthesis of the Optically Active Hexahydrobenzofuran Nucleus of the Avermectins. *Tetrahedron Lett.* **1988**, *29*, 3415–3418.

218 [*MJJ-IV-258*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.49-7.45 (m, 8H, NC_6H_5), 7.40-7.36 (m, 2H, NC_6H_5), 5.90 (dddd, *J* = 5.0, 5.0, 11.0, 17.5 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.89 (dddd, *J* = 5.0, 5.0, 10.5, 17.5 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.40 (ABq, $\Delta\nu_{AB}$ = 33.9 Hz, J_{AB} = 12.0 Hz, 2H, NCH_2SCH_3), 5.40 (ABq, $\Delta\nu_{AB}$ = 11.7 Hz, J_{AB} = 11.5 Hz, 2H, NCH_2SCH_3), 5.289 (dddd, *J* = 2.0, 2.0, 2.0, 17.5 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.285 (dddd, *J* = 1.5, 1.5, 1.5, 17.0 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.147 (dddd, *J* = 1.5, 1.5, 1.5, 11.0 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.144 (dddd, *J* = 1.5, 1.5, 1.5, 11.0 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 4.63-4.61 (m, 4H, overlapping CH_2CH=$CH_{trans}H_{cis}$), 4.46 [dddd, *J* = 3.5, 3.5, 7.0, 7.0 Hz, 1H, CH(OTBS)], 4.44 [dddd, *J* = 3.0, 3.0, 6.5, 6.5 Hz, 1H, CH(OTBS)], 3.383 [ABq, $\Delta\nu_{AB}$ = 19.2 Hz, J_{AB} = 15.0 Hz, 2H, $CH_2C(NH_2)$], 3.377 [ABq, $\Delta\nu_{AB}$ = 45.5 Hz, J_{AB} = 15.0 Hz, 2H, $CH_2C(NH_2)$], 2.78-2.68 [m, 4H, overlapping $CH_2CH(OTBS)CH_2$], 2.48-2.34 [m, 4H, overlapping $CH_2CH(OTBS)CH_2$], 2.241 (s, 3H, NCH_2SCH_3), 2.239 (s, 3H, NCH_2SCH_3), 0.86 [s, 18H, 2x $(CH_3)_3CSi(CH_3)_2$], 0.19 [s, 18H, 2x $C{\equiv}CSi(CH_3)_3$], 0.04 [s, 6H, 2x $(CH_3)_3CSi(CH_3)_2$], and 0.03 [s, 6H, 2x $(CH_3)_3CSi(CH_3)_2$].
HR ESI-MS: $C_{33}H_{48}N_4O_5SSi_2$ $[M+Et_3NH]^+$ requires 770.4161; found 770.4190.

In only one instance was concrete circumstantial evidence for the production of the tricarbonyl/dicarbonyl imine **2286** obtained (Scheme II–82). Specifically, when a solution of **2299** in CH_3CN/H_2O was treated with NBS at 0 °C, the reaction mixture immediately developed a blood red color (indicative of PTAD formation). Although I was unable to isolate a discrete product after work-up and chromatography, direct HR ESI-MS analysis of the reaction mixture did suggest that **2286** had been formed under these conditions.[219] Presumably, an intermediate α-hydroxy β-keto/imino ester was produced [cf. Scheme II–79; note that displacement within **2294** could just as plausibly occur with water (rather than DMSO)] and swiftly oxidized[212b,220] by the PTAD that was liberated *in situ*. In spite of this promising observation, repeated attempts to optimize this reaction were wholly unfruitful.

---

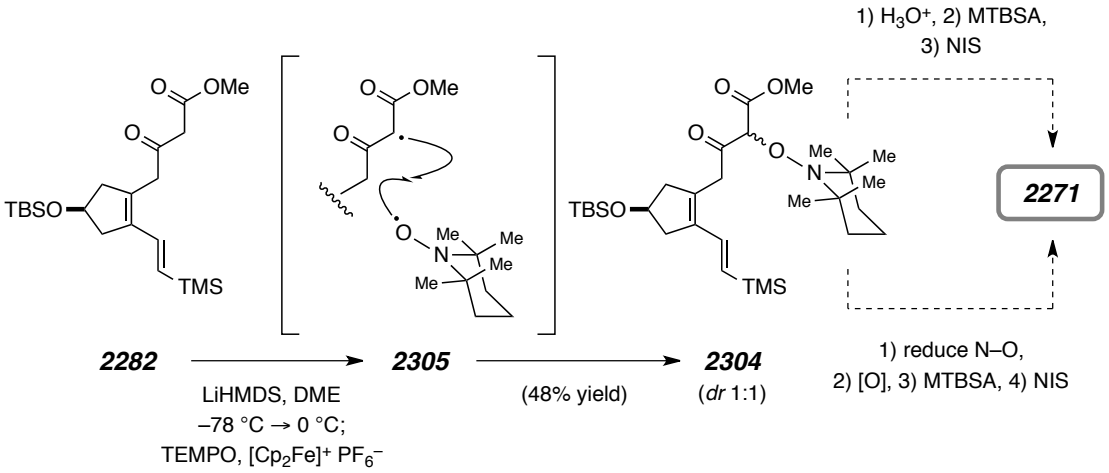
[219] [*MJJ-V-88*] **HR ESI-MS**: $C_{23}H_{36}O_5Si_2$–$C_{23}H_{37}NO_4Si_2$ $[2M+Na]^+$ requires 918.4255; found 918.4219. The principal ESI-MS peak that was observed for **2286** corresponded to the sodiated 1:1 α,β-diketo ester:α-keto β-imino ester adduct.

[220] Cookson, R. C.; Stevens, I. D. R.; Watts, C. T. A New Reagent for Oxidation of Alcohols to Ketones in Neutral Solution at Room Temperature. *Chem. Commun. (London)* **1966**, 744a.

J. FUTURE WORK

A series of more recent and promising results may provide the basis for a viable path toward the preparation of either **2271** or (*Z*)-**2015**. It was discovered that the α-oxygenated β-keto ester **2304** was produced (via the carbon-centered radical **2305**) in moderate (unoptimized) yield upon treatment of the lithium enolate derived from **2282** with TEMPO and $[Cp_2Fe]^+ PF_6^-$[221,222] (Scheme II–83).

Scheme II–83 | Functionalization of **2282** via oxidative enolate trapping with TEMPO.



With access to this material, two different routes could potentially be employed (Scheme II–83). The oxidation of ketones to α-diketones under the influence of oxoammonium salts (which proceed via the intermediacy of α-TEMPO adducts related to **2304**) is promoted by catalytic amounts of acid.[223] This raises the intriguing possibility

221 Jahn, U.; Hartmann, P.; Dix, I.; Jones, P. G. Oxidative Enolate Cyclizations of 6,8-Nonadienoates: Toward the Synthesis of Prostanes. *Eur. J. Org. Chem.* **2002**, 718–735.

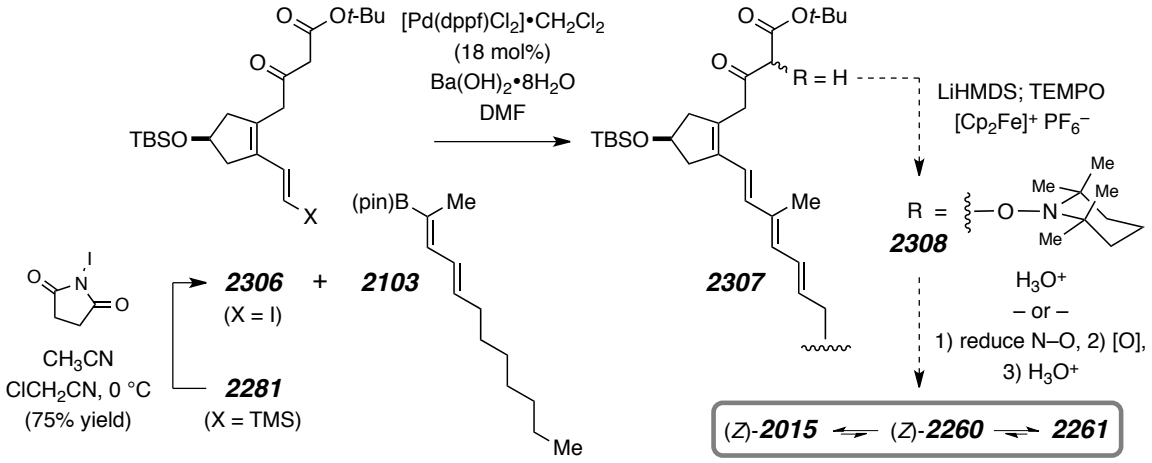
222 Xu, J.; Caro–Diaz, E. J. E.; Trzoss, L.; Theodorakis, E. A. Nature-Inspired Total Synthesis of (–)-Fusarisetin A. *J. Am. Chem. Soc.* **2012**, *134*, 5072–5075.

223 Hunter, D. H.; Barton, D. H. R.; Motherwell, W. J. Oxoammonium Salts as Oxidizing Agents: 2,2,6,6-Tetramethyl-1-oxopiperidinium Chloride. *Tetrahedron Lett.* **1984**, *25*, 603–606.

that the enolized *vic*-tricarbonyl system that is present in **2271** (cf. Scheme II–75) could be generated from **2304** under mildly acidic conditions. Subsequent silylation (with MTBSA, if necessary) and iododesilylation (NIS) would then deliver **2271**. Alternatively, a sequence of events involving 1) N–O bond reduction (e.g., Zn, AcOH/THF), 2) oxidation, 3) silylation, and 4) iododesilylation could also be deployed.

Should the handling of the intermediates leading to **2271** prove too difficult, the groundwork for a complementary approach has also been established (Scheme II–84). The vinyl iodide **2306** was generated upon exposure of the *tert*-butyl β-keto ester **2281** to (at least) 2 equivalents of NIS in $CH_3CN/ClCH_2CN$. A Suzuki cross-coupling reaction of this substance with the vinyl boronate **2103** was affected under Nelson's conditions[178] to give rise to **2307**, an intermediate that possesses the entire polyene scaffold present in (*Z*)-**2015**. With the precedent of Scheme II–83 in mind, oxidative trapping with TEMPO of the enolate derived from **2307** should provide **2308**. Then, (*Z*)-**2015** [in equilibrium with (*Z*)-**2260** and **2261**] could perhaps be observed under the conditions of its formation by acid-promoted elimination of TMP from **2308**. Here again, a potential fall back strategy would involve N–O bond scission, oxidation, and then hydrolysis.

Scheme II–84 | Suzuki cross-coupling of **2306** and **2103** produced the polyene **2307**.



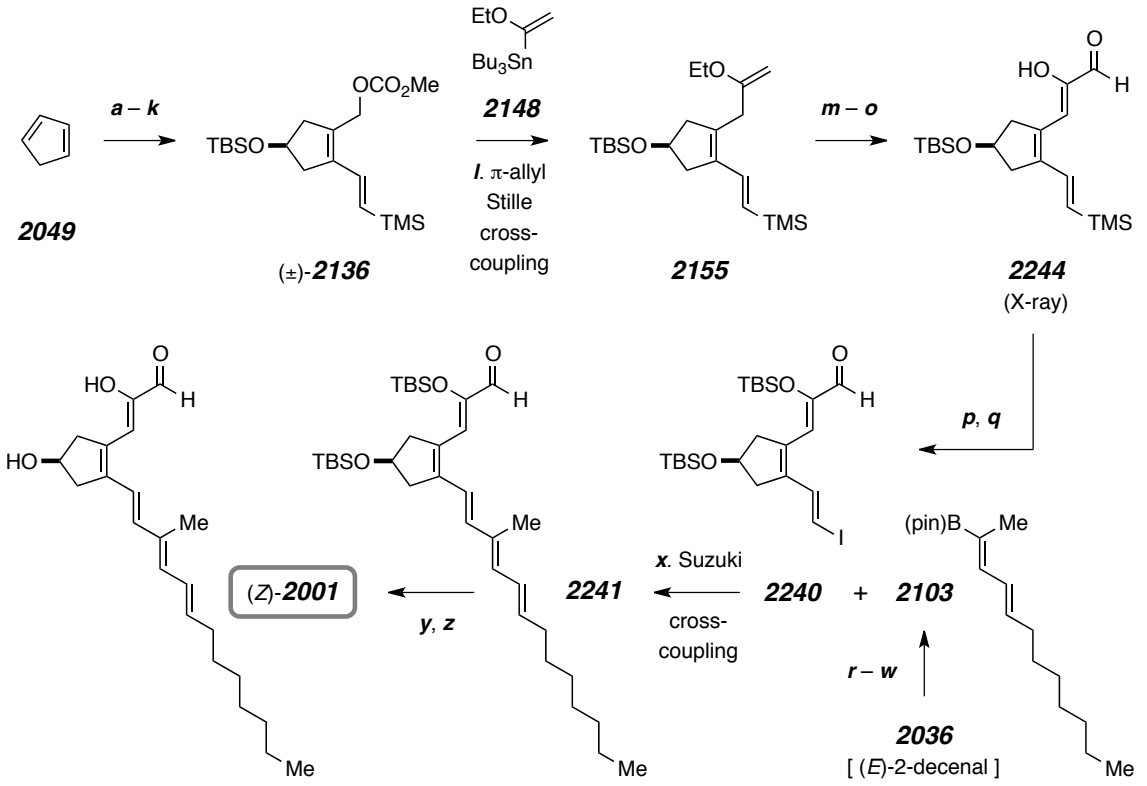
K. CONCLUSION

Chapter II was inaugurated with the hypothesis that penostatin A (**1-A**) and penostatin B (**1-B**) are biosynthetically derived, via competitive, spontaneous tautomerization and IMHDA events, from the common pentaenol (*Z*)-**2001** (recall Scheme II–1). In the face of several failures and roadblocks, the synthetic strategy slowly but surely evolved from one that intended to access the key pentaenol (*Z*)-**2001** via indirect means (i.e., hydrolysis of **2017**) to one that permitted its direct isolation. The culmination of these synthetic studies has been summarized in Scheme II–85.

Although this route has not yielded total syntheses of **1-A** or **1-B**, a substantial amount of interesting, and, arguably, useful chemistry has been unearthed. Highlights en route include: i) A practical and readily scalable route to the C2–C7 core structure **2048** (Section E–1), which provided gram quantities of this intermediate; ii) the development of a highly stereoselective synthesis of the C11–C22 diene fragment (**2103**) (Section F), which certainly has broader implications for the "H-to-T" preparation of a wide variety of conjugated, trisubstituted vinyl boronates from 1-bromoenynes; iii) the discovery and capitalization upon the mild and high-yielding π-allyl Stille cross-coupling reactions of the allylic carbonates **2135** and **2136** (Section G–1), which provided access to a family of intermediates that would have been difficult to prepare by alternative means; iv) *O*,*S*-acetal versus sulfoxide formation as a function of solvent composition in the oxidation of the β-keto sulfide **2201** (Section G–3); and v) the formation of the α-keto aldehyde enol **2244** via a new modification of the Emmons-Kornblum protocol[14] (Section G–4).

At least superficially, Chapter II has ended in a manner much the same as it began–with the proposal of a new hypothesis. Nevertheless, as any practitioner of the art knows well, progress in natural products total synthesis (or any discipline of science, for that matter) is measured just as much by its failures as it is by its successes. A revised hypothesis has thus been proposed (Scheme II–74, Section H) and a viable path forward toward the synthesis of (*Z*)-**2015** has been established (Sections I and J).

Scheme II–85 | Summary of the 26-step (20 longest linear) synthetic route that was developed to access the common pentaenol (*Z*)-**2001** from cyclopentadiene (**2049**).[a]



[a] Reagents and conditions: (**a**) CH_3CO_3H, NaOAc, CH_2Cl_2, 0 °C → rt (36% yield); (**b**) [$Pd(PPh_3)_4$] (0.2 mol%), AcOH, THF, 0 °C → rt (73% yield); (**c**) TBSCl, Et_3N, DMAP (10 mol%), CH_2Cl_2 0 °C → rt (98% yield); (**d**) K_2CO_3, MeOH, 0 °C → rt; (**e**) PCC, NaOAc, 4ÅMS, CH_2Cl_2 (85% yield over 2 steps); (**f**) $Pt(DVTMDS)_2$ (0.2 mol%), Et_3SiH (2.0 equiv), Et_2O, 0 °C → rt; (**g**) *n*-BuLi, THF, –78 °C → rt; then ethyl cyanoformate, –78 °C → rt (61% yield over 2 step); (**h**) Tf_2O, Et_3N, CH_2Cl_2, –78 °C (89% yield); (**i**) trimethyl(vinyl)silane, [$Pd(OAc)_2$] (1 mol%), Et_3N, DMSO, 50 °C (92% yield); (**j**) DIBAL-H, Et_2O, 0 °C; (**k**) methyl chloroformate, pyr, CH_2Cl_2, 0 °C (82% yield over 2 steps); (**l**) **2148**, [$Pd_2(dba)_3$] (5 mol%), LiCl, DMF, 50 °C (94% yield); (**m**) NBS, $NaHCO_3$, THF/H_2O, 0 °C (76% yield); (**n**) NaI, acetone; $AgNO_3$, Bu_4N^+ NO_3^-, CH_3CN (70% yield over 2 steps); (**o**) $NaHCO_3$, DMSO (81% yield); (**p**) MTBSA, CH_3CN (72% yield); (**q**) NIS, CH_3CN, 0 °C (87% yield); (**r**) CBr_4, PPh_3, CH_2Cl_2, 0 °C (95% yield); (**s**) NaHMDS, THF, –90 °C (91% yield); (**t**) *i*-PP_2BH, THF, 0 °C → rt; H_2O; aq $(CH_2O)_n$; (**u**) MIDA, PhMe/DMSO, Dean–Stark (79% yield over 2 steps); (**v**) PEPPSI^{TM}-IPr (1 mol%), MeZnBr, LiBr, THF (72% yield); (**w**) pinacol, $NaHCO_3$, MeOH, 50 °C (58% yield); (**x**) [$Pd(OAc)_2$] (5 mol%), SPhos (10 mol%), $Ba(OH)_2$•$8H_2O$, DMF/THF, 0 °C → rt; (**y**) 48% aq HF, CH_3CN/CH_2Cl_2 (49% yield over 2 steps); (**z**) TBAF, THF, –78 °C (57% yield).

CHAPTER III

PENOSTATIN I AND F

MODEL SYNTHESIS STUDIES

A. HYPOTHESIS FOR THE BIOSYNTHESIS OF PENOSTATINS I AND F

HYPOTHESIS STATEMENT:

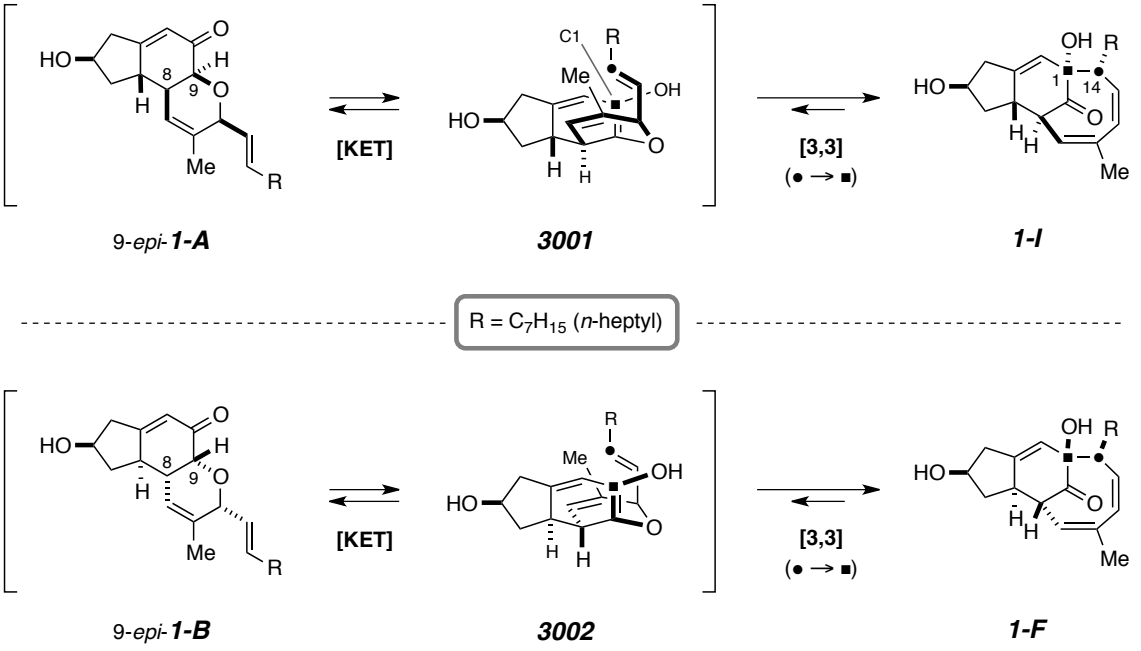
> *PENOSTATIN I (**1-I**) AND PENOSTATIN F (**1-F**) ARISE VIA SPONTANEOUS [3,3]-SIGMATROPIC (CLAISEN) REARRANGEMENTS OF THE ALLYL VINYL ETHERS **3001** AND **3002**, RESPECTIVELY. THESE LATTER SPECIES ARE GENERATED UPON TAUTOMERIZATION (OR ENOLIZATION) OF 9-epi-**1-A** AND 9-epi-**1-B**.*

It has been proposed in Chapter II of this thesis that penostatin A (**1-A**) and penostatin B (**1-B**) arise via spontaneous *exo*-IMHDA reactions of the diastereomeric α-keto aldehydes **2002** and **2003**, respectively. If the thermal cycloadditions of these latter species were not highly diastereoselective, then, it was postulated, that both 9-*epi*-penostatin A (9-*epi*-**1-A**) and 9-*epi*-penostatin B (9-*epi*-**1-B**) would be co-produced via the *endo*-IMHDA manifold. This Chapter will open by posing the following question: Could it be that both penostatin I (**1-I**) and penostatin F (**1-F**) are ultimately derived from these latter two metabolites (9-*epi*-**1-A** and 9-*epi*-**1-B**)?

Specifically, **1-A** and **1-B** each possesses a *trans* ring fusion across C8–C9. That these metabolites are stable under the conditions of their formation is self-evident. However, it is intriguing to note that 9-*epi*-**1-A** and 9-*epi*-**1-B**, which both possess a (less stable) *cis* ring fusion across C8–C9, are *absent* from the menu of natural products that

have been isolated from the fungus *Penicillium* sp. OUPS-79. This suggests that each is preferentially siphoned from the initial IMHDA product distribution, via keto-enol tautomerization ([KET]), to generate **3001** and **3002** (Scheme III–1). Embedded within these enol tautomers is an allyl vinyl ether (AVE) subunit that has a donor atom positioned at C1, a substitution pattern that is known to accelerate the rate of the Claisen rearrangement.[224] Spontaneous [3,3]-sigmatropic rearrangement of **3001** and **3002** would then *directly* generate the bicyclo[5.3.1]undecenone core of **1-I** and **1-F**, respectively.

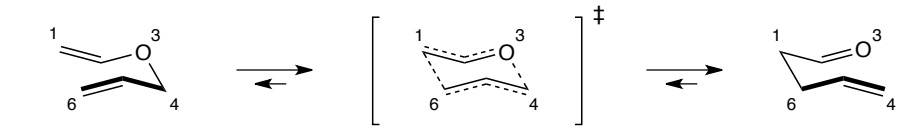
Scheme III–1 | Proposed biosynthetic origin of penostatin I (**1-I**) and penostatin F (**1-F**) via KET of 9-*epi*-**1-A** and 9-*epi*-**1-B** and subsequent spontaneous Claisen rearrangement of the allyl vinyl ethers **3001** and **3002**, respectively.



[224] (a) Burrows, C. J.; Carpenter, B. K. Substituent Effects on the Aliphatic Claisen Rearrangement. 1. Synthesis and Rearrangement of Cyano-Substituted Allyl Vinyl Ethers. *J. Am. Chem. Soc.* **1981**, *103*, 6983–6984. (b) Burrows, C. J.; Carpenter, B. K. Substituent Effects on the Aliphatic Claisen Rearrangement. 2. Theoretical Analysis. *J. Am. Chem. Soc.* **1981**, *103*, 6984–6986.

B. PREVIOUS STUDIES RELEVANT TO THE HYPOTHESIS

The proposal that a *spontaneous* aliphatic Claisen rearrangement of the type just described is operative in *any* biosynthetic pathway is, to the author's knowledge, unprecedented.[225] Just as would be predicted for the IMHDA events that give rise to **1-A** and **1-B**, the Claisen rearrangement–best exemplified by the conversion of AVE (**3003**) to 4-pentenal (**3004**)–is an exothermic process ($\Delta H° = -17$ kcal/mol)[226] (Figure III–1). Yet, it is a very sluggish reaction ($t_{1/2}$ *ca.* 60 h at 100 °C).[224,227]



3003
(3-oxa-1,5-hexadiene)

3004
(4-pentenal)

Figure III–1 | The prototypical Claisen rearrangement, a [3,3]-sigmatropic shift.

In light of the prototypical example provided above, it might seem imprudent to suggest that the Claisen rearrangement is a spontaneous biosynthetic transformation. *However, the high kinetic barrier associated with the conversion of **3003** to **3004** is the exception rather than the rule.* Indeed, both substituent and solvent effects have been invoked to explain the unanticipated facility with which some aliphatic Claisen

---

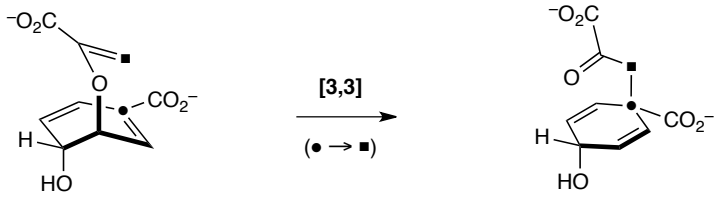
225 For a recent example where a spontaneous Claisen rearrangement of an *aryl* allyl ether has been shown to be operative in the biosynthesis of cyanobactin peptide natural products, see: McIntosh, J. A.; Donia, M. S.; Nair, S. K.; Schmidt, E. W. Enzymatic Basis of Ribosomal Peptide Prenylation in Cyanobacteria. *J. Am. Chem. Soc.* **2011**, *133*, 13698–13705.

226 Benson, S. W.; O'Neal, H. E. *Kinetic Data on Gas Phase Unimolecular Reactions*; U.S. Department of Commerce: Washington, DC, **1970**; NSRDS–NBS 21, p 363.

227 Gajewski, J. J.; Brichford, N. L. Secondary Deuterium Kinetic Isotope Effects in the Aqueous Claisen Rearrangement: Evidence Against an Ionic Transition State. *J. Am. Chem. Soc.* **1994**, *116*, 3165–3166.

rearrangements occur.[228] No more famous an example of this phenomenon exists than the transformation of chorismate (**3005**) to prephenate (**3006**) (Scheme III–2), key intermediates in the biosynthesis of tyrosine and phenylalanine.[229] This [3,3]-sigmatropic rearrangement, which is catalyzed *in vivo* by the enzyme chorismate mutase,[230] is one of the most heavily studied of its type and is often referred to as the only bona fide example of an enzyme-catalyzed pericyclic reaction.[231] Yet, astoundingly, when compared to the rate at which **3003** is converted to **3004** at 75 °C in di-*n*-butyl ether, the uncatalyzed rate of rearrangement of **3005** in water (pH 5) at the same temperature is approximately 4200 times faster![224a,231]

Scheme III–2 | The conversion of chorismate to prephenate in the shikimic acid pathway involves an enzyme-catalyzed [3,3]-sigmatropic (Claisen) rearrangement [adapted from ref 231].



3005
(chorismate)

3006
(prephenate)

---

228 Martín Castro, A. M. Claisen Rearrangement Over the Past Nine Decades. *Chem. Rev.* **2004**, *104*, 2939–3002.

229 Gibson, F.; Pittard, J. Pathways of Biosynthesis of Aromatic Amino Acids and Vitamins and Their Control in Microorganisms. *Bacteriol. Rev.* **1968**, *32*, 465–492.

230 (a) Andrews, P. R.; Smith, G. D.; Young, I. G. Transition-State Stabilization and Enzymatic Catalysis. Kinetic and Molecular Orbital Studies of the Rearrangement of Chorismate to Prephenate. *Biochemistry* **1973**, *12*, 3492–3498. (b) Gorisch, H. On the Mechanism of the Chorismate Mutase Reaction. *Biochemistry* **1978**, *17*, 3700–3705.

231 Ganem, B. The Mechanism of the Claisen Rearrangement: Déjà Vu All Over Again. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 936–945.

B–1. ON THE INFLUENCE OF C1 DONOR SUBSTITUENTS

The discovery of the chorismate mutase-catalyzed conversion of chorismate to prephenate ignited a renewed interest in the Claisen rearrangement, particularly as it pertained to natural products total synthesis.[232] Seminal contributions from the laboratories of Gajewski,[233] Carpenter,[224] Ireland,[234] Curran,[235] and others[236] forged the synthetic community's originally blunt understanding of the mechanistic underpinnings of this sigmatropic rearrangement into a razor sharp blade of broad synthetic utility. It was recognized[237] that, to the extent that one could establish a qualitative correlation between substitution patterns and reaction rates, then the Claisen rearrangement would be rendered far more synthetically valuable. In an effort to fill the void, theoretical models were developed that could be applied to thermal sigmatropic rearrangements *per se*,[238] and also for concerted pericyclic reactions in general.[237]

---

232 (a) Ziegler, F. E. Stereo- and Regiochemistry of the Claisen Rearrangement: Applications to Natural Products Synthesis. *Acc. Chem. Res.* **1977**, *10*, 227–232. (b) Bennett, G. B. The Claisen Rearrangement in Organic Synthesis; 1967 to January 1977. *Synthesis* **1977**, 589–606.

233 (a) Gajewski, J. J.; Conrad, N. D. Aliphatic Claisen Rearrangement Transition State Structure from Secondary α-Deuterium Isotope Effects. *J. Am. Chem. Soc.* **1979**, *101*, 2747–2748. (b) Gajewski, J. J.; Conrad, N. D. Variable Transition State Structure in 3,3-Sigmatropic Shifts from α-Secondary Deuterium Isotope Effects. *J. Am. Chem. Soc.* **1979**, *101*, 6693–6704.

234 Ireland, R. E.; Mueller, R. H.; Willard, A. K. The Ester Enolate Claisen Rearrangement. Stereochemical Control Through Stereoselective Enolate Formation. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877.

235 Curran, D. P.; Suh, Y. –G. Substituent Effects on the Claisen Rearrangement. The Accelerating Effect of a 6-Donor Substituent. *J. Am. Chem. Soc.* **1984**, *106*, 5002–5004.

236 (a) Castro, A. M. M. Claisen Rearrangement over the Past Nine Decades. *Chem. Rev.* **2004**, *104*, 2939–3002. (b) Rehbein, J.; Hiersemann, M. Mechanistic Aspects of the Aliphatic Claisen Rearrangement. In *The Claisen Rearrangement: Methods and Applications*, M. Hiersemann, U. Nubbemeyer, Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, **2007**, pp 525–557.

237 Carpenter, B. K. A Simple Model for Predicting the Effect of Substituents on the Rates of Thermal Pericyclic Reactions. *Tetrahedron* **1978**, *34*, 1877–1884.

238 Gajewski, J. J. Energy Surfaces of Sigmatropic Shifts. *Acc. Chem. Res.* **1980**, *13*, 142–148 and references therein.

In 1981, a theoretical treatment of the Claisen rearrangement by Carpenter and Burrows[224b] demonstrated that π-donor substituents positioned at C1 of simple allyl vinyl ethers should result in rate enhancement. Given the qualitative nature of their analysis,[237] and the (at that time) scant experimental data[239] regarding the impact of C1 donor substituents on the Claisen rearrangement, the authors could not estimate the relative magnitude of such a rate enhancement. Nevertheless, the prescience of Carpenter and Burrows' claims were soon realized when, in 1985, Koreeda and Luengo reported the discovery of the "anionic oxy-Claisen" rearrangement.[240] The authors observed drastic rate enhancements in the [3,3]-sigmatropic rearrangement of **3008**, an enolate that was formed upon treatment of α-(allyloxy)propiophenone (**3007**) with various metal hydrides (MH) in the presence of a large excess of methanol (Table III–1).

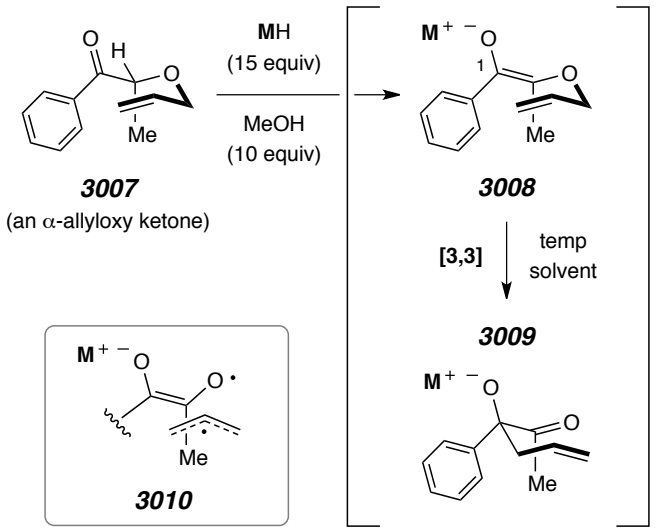
A cursory examination of Table III–1 reveals that this process was effected by both the nature of the counterion and the solvent employed. Whereas the potassium (entry 1) and sodium (entry 2) enolates of **3008** rapidly rearranged to the alkoxide **3009** in a coordinating solvent (THF) at shockingly low temperature ($t_{1/2}$ < 0.1 and 2.4 h at –23 °C, respectively), the lithium (entry 3) enolate was relatively slower reacting ($t_{1/2}$ 1.3 h at 67 °C). In fact, the potassium enolate of **3008** rearranged *even at –42 °C*–at that time, the lowest temperature recorded for *any* Claisen rearrangement.[240] These results stand in sharp contrast to those obtained in a non-coordinating solvent (PhMe), wherein the rate of sigmatropic rearrangement of the potassium (entry 4) enolate of **3008** was retarded ($t_{1/2}$ 3.3 h at –23 °C). The final entry in the table–namely, the silyl enol ether of **3008**–nicely contrasts the potassium enolate and highlights the important role of the donating ability of the C1 substituent in eliciting these rate enhancements.

---

239 (a) Lythgoe, B.; Milner, J. R.; Tideswell, J. Claisen Rearrangements of Allylic a-Phenylthioacetates: Applications in Synthesis. *Tetrahedron Lett.* **1975**, *16*, 2593–2596. (b) Kachinski, J. L. C.; Salomon, R. G. Allyloxy Ketone Enol Ether-Claisen Rearrangement. Regiospecific Synthesis of Allyl Ketones from Allyl Alcohols. *Tetrahedron Lett.* **1977**, *18*, 3235–3238.

240 Koreeda, M.; Luengo, J. I. Anionic Oxy-Claisen Rearrangement of Enolates of α-Allyloxy Ketones. A Remarkable Rate-Accelerating Effect Exhibited by the Nature of the Counterion. *J. Am. Chem. Soc.* **1985**, *107*, 5572–5573.

Table III–1 | The "anionic oxy-Claisen" rearrangement [adapted from ref 240].



entry	**M** =	solvent	temp. (°C)	$t_{1/2}$ (h)
1	K	THF	–23	< 0.1
2	Na	THF	–23	2.4
3	Li *	THF	67	1.3
4	K	PhMe	–23	3.3
5	$SiMe_3$	PhMe	71	0.5

* Comprised of ≤ 20% of the [2,3]-Wittig product.

An early transition state in the Claisen rearrangement of AVE (**3003**), with O3–C4 bond cleavage being more advanced than C1–C6 bond formation, has been established by secondary deuterium KIEs[241] and bolstered by theoretical investigations.[242] By extension, Koreeda and Luengo postulated[240] that a significant contribution from an oxy-oxaallyl radical anion/allyl radical pair (**3010**, lower left of Table III–1) could be exerted in the transition state, since the former is a stable semidione (produced by one-electron reduction of α-dicarbonyl compounds).[243] This mechanistic nuance, which is firmly supported by the empirical influence of a C1 oxygen donor atom, can just as easily be extended to the hypothesis presented in Scheme III–1. Specifically, might it be the

241 Gajewski, J. J. The Claisen Rearrangement. Response to Solvents and Substituents: The Case for both Hydrophobic and Hydrogen Bond Acceleration in Water and for a Variable Transition State. *Acc. Chem. Res.* **1997**, *30*, 219–225.

242 Vance, R. L.; Rondan, N. G.; Houk, K. N.; Jensen, F.; Borden, W. T.; Komornicki, A.; Wimmer, E. Transition Structures for the Claisen Rearrangement. *J. Am. Chem. Soc.* **1988**, *110*, 2314–2315.

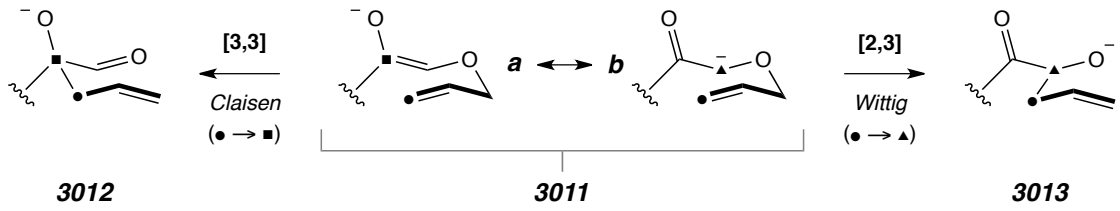
243 Carey, F. A.; Sundberg, R. J. Free-Radical Reactions. In *Advanced Organic Chemistry, Part A: Structure and Mechanisms*, 4TH ed.; Springer Publishing: New York, **2006**, pp 663–742.

case that the conjugate bases of **3001** and **3002** (i.e., the enolates of the α-allyloxy ketones 9-*epi*-**1-B** and 9-*epi*-**1-A**, respectively), present at small, but finite concentrations, undergo a pair of biosynthetic "anionic oxy-Claisen" rearrangements?

B–2. [3,3] VERSUS [2,3] ANIONIC-OXY SIGMATROPIC DICHOTOMY

Lurking beneath the superb efficiency of the anionic-oxy Claisen rearrangement is a mechanistic nuance that must not be ignored. The enolates of α-allyloxy ketones, a generic representation of which is **3011**, could in principle evolve to product(s) through two distinct sigmatropic processes (Scheme III–3). This dichotomy is most easily realized if one treats the two dominant resonance forms of the enolate–**3011a** and **3011b**–as distinct species. The former contributor is a 1-oxy-3-oxa-1,5-hexadiene that would decay through the [3,3]-sigmatropic (Claisen) manifold (**3011** → **3012**), whereas the latter species, which is formally an α-(allyloxy) α-carbanion, would give rise to the α-alkoxy ketone **13013** via the Wittig ([2,3]-sigmatropic) rearrangement.[240,244]

Scheme III–3 | Alternative sigmatropy for the enolates of α-allyloxy ketones (**3011**).

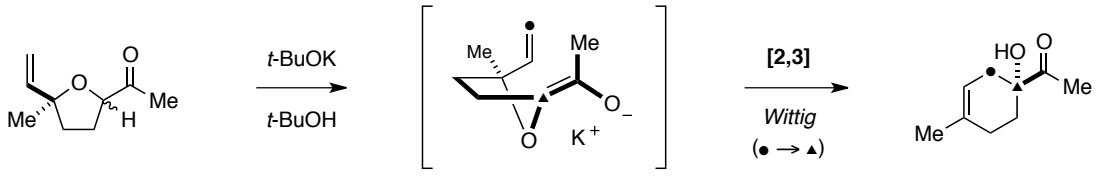


Of these two potential modes of reactivity, the [2,3]-sigmatropic rearrangement–at least as it pertains to α-allyloxy ketone- and ester-derived enolates–is by far the most

244 It should also be noted that a different Wittig rearrangement–namely, the [1,2] variant–could also be operative in these systems. See: Schöllkopf, U. Recent Results in Carbanion Chemistry. *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 763–773.

widely investigated.[245] Although these vast swathes of literature precedent cannot be adequately summarized here, Thomas and Dubini[246] were the first to demonstrate that such a transformation was feasible (Scheme III–4). In their report, treatment of the cyclic ketone **3104** with *t*-BuOK gave rise to the α-hydroxy ketone **3015** "*as the main product*"[246] that was clearly the result of [2,3]-Wittig rearrangement of the intermediate potassium enolate. The intervention of a [3,3]-sigmatropic pathway was, due to geometric constraints, precluded in this instance, but the authors further demonstrated that the [2,3]-Wittig process dominated with an acyclic ketone enolate, as well.[246]

Scheme III–4 | [2,3]-Wittig rearrangement of the potassium enolate of the cyclic ketone **3014** [adapted from ref 246].



3014 ***3015***

In contrast to the [2,3]-sigmatropic rearrangement, reports regarding the [3,3]-sigmatropic rearrangements of α-allyloxy ketone enolates are somewhat more difficult to locate. Among the most relevant examples, the rearrangement of the tricyclic ketone **3016** to the α-hydroxy ketone **3017** represents one of the first applications of the anionic oxy-Claisen rearrangement[247] (Scheme III–5A). Additionally, the [3,3]-sigmatropic

---

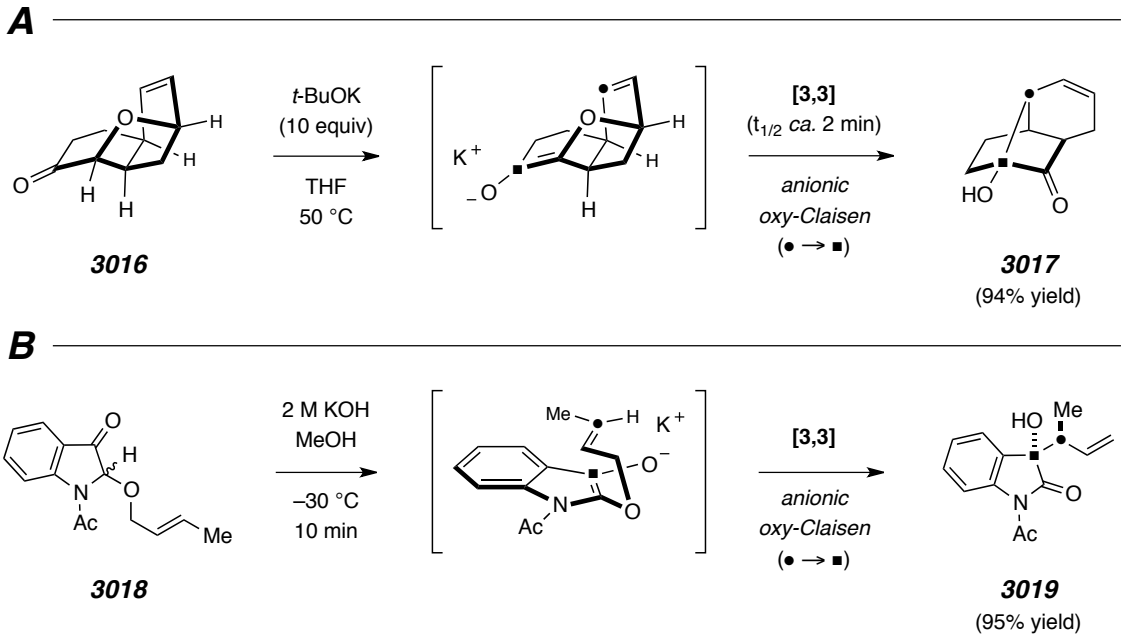
245 (a) Nakai, T.; Mikami, K. [2,3]-Wittig Sigmatropic Rearrangements in Organic Synthesis. *Chem. Rev.* **1986**, *86*, 885–902. (b) Mikami, K.; Nakai, T. Acyclic Stereocontrol via [2,3]-Wittig Sigmatropic Rearrangement. *Synthesis* **1991**, 594–604.

246 Thomas, A. F.; Dubini, R. 225. The [2,3] Sigmatropic Reaction of Acetonyl Allyl Ethers, a New Method for Preparing Certain 2-Hydroxyketones. *Helv. Chim. Acta* **1974**, *57*, 2084–2087.

247 Kirchner, J. J.; Pratt, D. V.; Hopkins, P. B. Anionic Oxy-Claisen Rearrangement of a Tricyclic α-Allyloxy Ketone. *Tetrahedron Lett.* **1988**, *29*, 4229–4232.

rearrangements of 2-allyloxyindolin-3-one enolates,[248] best exemplified by the diastereoselective conversion of **3018** into **3019** (Scheme III–5B), have been studied extensively.

Scheme III–5 | **A**: One of the first applications of the "anionic oxy-Claisen" rearrangement in the synthesis of the α-hydroxy ketone **3017** from **3016** [adapted from ref 247]. **B**: The [3,3]-sigmatropic rearrangements of the enolates of 2-allyloxyindolin-3-ones have been shown to occur under a number of different conditions [adapted from ref 248a].



[248] (a) Higuchi, K.; Saito, K.; Hirayama, T.; Watanabe, Y.; Kobayashi, E.; Kawasaki, T. Claisen Rearrangement through Enolization of 2-Allyloxyindolin-3-ones: Construction of Adjacent Carbon Stereocenters in 3-Hydroxyindolin-2-ones. *Synthesis* **2010**, 3609–3614. (b) Kawasaki, T.; Takamiya, W.; Okamoto, N.; Nagaoka, M.; Hirayama, T. Silyl-Enolization-Asymmetric Claisen Rearrangement of 2-Allyloxyindolin-3-one: Enantioselective Total Synthesis of 3a-Hydroxypyrrolo[2,3-*b*]indoline Alkaloid Alline. *Tetrahedron Lett.* **2006**, *47*, 5379–5382. (c) Kawasaki, T.; Nagaoka, M.; Satoh, T.; Okamoto, A.; Ukon, R.; Ogawa, A. Synthesis of 3-Hydroxyindolin-2-one Alkaloids, (±)-Donaxaridine and (±)-Convolutamydines A and E, through Enolization-Claisen Rearrangement of 2-Allyloxyindolin-3-ones. *Tetrahedron* **2004**, *60*, 3493–3503 and references therein. (d) Malapel-Andrieu, B.; Piroëlle, S.; Mérour, J. –Y. Claisen Rearrangement of 2-Allyloxyindolic Ketoester via a Decarboxylative Process. *J. Chem. Research (S)* **1998**, 594–595.

Notwithstanding the seminal report from Koreeda and Luengo,[240] the most frequently encountered systems are those involving the formation and subsequent thermal Claisen rearrangements of α-allyloxy ketone- or ester silyl enol ethers (i.e., 1-siloxy-3-oxa-1,5-hexadienes).[249] Certainly, either [2,3]- or [3,3]-sigmatropic processes (or both, competitively[249d]) are possible in the rearrangements of α-allyloxy ketone (or ester) enolates. As the brief literature survey presented above has verified, the ability to predict, *a priori*, which of these processes might prevail will depend upon a confluence of subtle factors that are unique to the system under study. Fortunately, the elegant work reported by Barriault and co-workers[15] (see Chapter I, Section C–2), and the thermal[250] and TRIBAL-catalyzed[251] ring-expansive Claisen technology developed by Paquette (Scheme III–6) both bear direct relevance to the hypothesis presented in Scheme III–1. What these two examples demonstrate is that an allyl vinyl ether subunit embedded within a six-membered ring is capable of giving rise to a cyclooctenone product via thermal Claisen

---

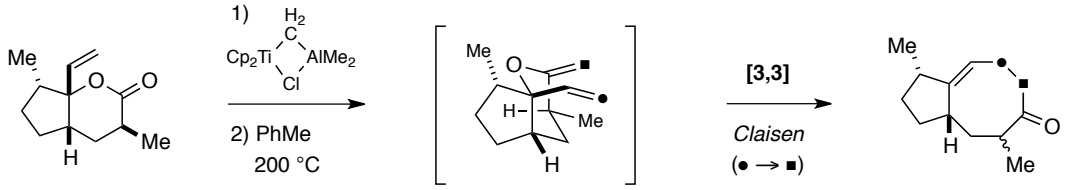
249 (a) Kachinski, J. L. C.; Salomon, R. G. Allyloxy Ketone Enol Ether-Claisen Rearrangement. Regiospecific Synthesis of Allyl Ketones from Allyl Alcohols. *Tetrahedron Lett.* **1977**, *18*, 3235–3238. (b) Kachinsky, J. L. C.; Salomon, R. G. Regiospecific Synthesis of β,γ-Unsaturated Ketones from Allylic Alcohols. Claisen Rearrangement of α-Allyloxy Ketone Enol Derivatives. *J. Org. Chem.* **1986**, *51*, 1393–1401. (c) Raucher, S.; Gustavson, L. M. [3,3]-Sigmatropic Rearrangement of Silyl Ketene Acetals of Methyl α-(Allyloxy)acetates. *Tetrahedron Lett.* **1986**, *27*, 1557–1560. (d) Takahashi, O.; Maeda, T.; Mikami, K.; Nakai, T. [3,3]-Claisen vs. [2,3]-Wittig Shift in Thermal and Fluoride Ion-Promoted Rearrangements of the *O*- and *C*-Silylated Forms of α-Allyloxy Esters. *Chem. Lett.* **1986**, 1355–1358.

250 (a) Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. Claisen Rearrangement of 6-Alkenyl-2-methylenetetrahydropyrans. A New Approach to Annulated 4-Cyclooctenones and a Stereospecific Synthesis of Precapnelladiene. *J. Am. Chem. Soc.* **1984**, *106*, 6868–6870. (b) Paquette, L. A.; Philippo, C. M. G.; Yo, N. H. Ring Expansion by Tandem Double Tebbe–Claisen Technology. *Can. J. Chem.* **1992**, *70*, 1356–1365 and references cited therein. (c) Paquette, L. A.; Wang, T. –Z.; Vo, N. H. Access to Naturally Occurring Cyclooctanoids by Two-Carbon Intercalation. Total Synthesis of (+)-Ceroplastol I. *J. Am. Chem. Soc.* **1993**, *115*, 1676–1683.

251 (a) Paquette, L. A.; Sun, L.; Friedrich, D.; Savage, P. B. Total Synthesis of (+)-Epoxydictymene. Application of Alkoxy-Directed Cyclization of Diterpenoid Construction. *J. Am. Chem. Soc.* **1997**, *119*, 8438–8450 and references cited therein. (b) Paquette, L. A.; Friedrich, D.; Rogers, R. D. Alkylaluminum-Catalyzed Claisen Expansion Reactions. Scope and Stereochemistry. *J. Org. Chem.* **1991**, *56*, 3841–3849.

rearrangement (e.g., **3021 → 3022**, Scheme III–6). Although heating to high temperatures was required to induce rearrangement in both instances, it has already been shown[240] that the precise nature of a C1 donor substituent (which **3021** lacks) will play a decisive role in eliciting the required rate enhancement.

Scheme III–6 | An early example of Paquette's tandem Tebbe olefination/Claisen rearrangement methodology for the synthesis of fused cyclooctenones [adapted from ref 250a].

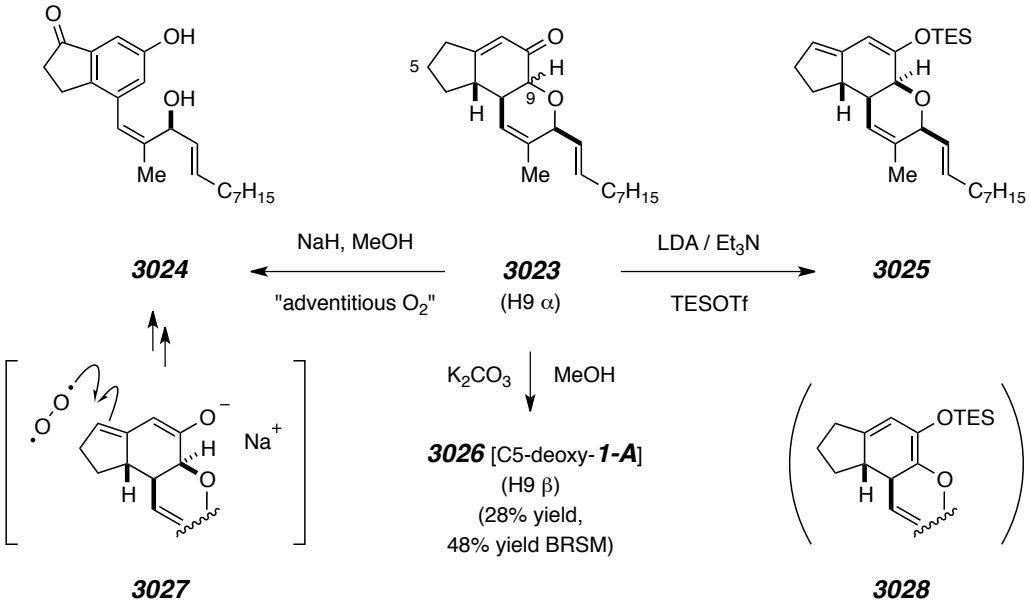


3020 ***3021*** ***3022***
(87-91% yield)

B–3. SNIDER'S REACTIVITY STUDIES OF C5-DEOXY-9-*epi*-PENOSTATIN A

During their **1-A** and **1-B** model synthesis studies, Snider and Liu reported a rather unusual trio of observations emanating from C5-deoxy-9-*epi*-**1-A** (**3023**) (Scheme III–7).[7a] Treatment of **3023** with NaH/MeOH under Koreeda and Luengo's conditions[240] resulted in the formation of the oxidized product **3024**, which they proposed arose via reaction of the dienolate **3027** with "adventitious oxygen" followed by base-catalyzed ring-opening of the pyran. Similarly, reaction of **3023** with TESOTf and either LDA or Et_3N resulted in the isolation of the conjugated dienyl TES enol ether **3025**, which would support the intermediacy of the dienolate **3027** in the production of **3024**. It is interesting to note that the cross-conjugated enol ether **3028** that is required for Claisen rearrangement was not observed under the latter pair of reaction conditions.

Scheme III–7 | Reported reactivity of C5-deoxy-9-*epi*-**1-A** (**3023**) under basic reaction conditions [adapted from ref 7a].

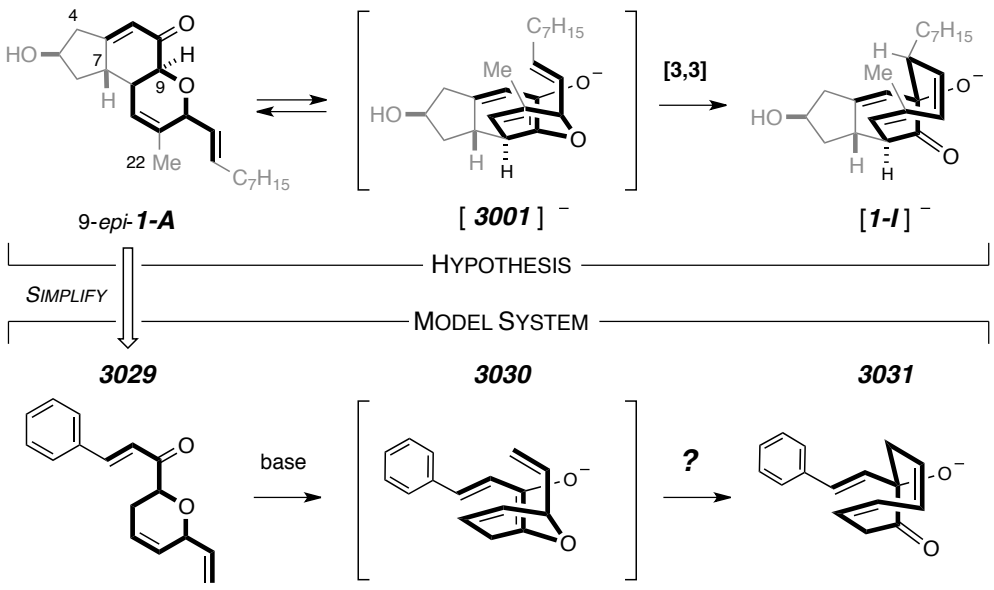


Finally, and most perplexing of all, **3023** could be partially isomerized to C5-deoxy-**1-A** (**3026**) in methanolic K_2CO_3. The ratio of **3023**/**3026** obtained after this treatment was *not* a thermodynamic one, since pure **3026** was left unchanged upon resubjection to identical reaction conditions.[7] It seems plausible that the β-methoxy ketone derived from **3023** (i.e., the product of methanol conjugate addition), which cannot give rise to the dienolate **3027**, was the active species under these conditions. But were the enolate derived from C9 deprotonation of **3023** to be accessed, one could, based upon previous discussions in this Section, have expected this intermediate to undergo an anionic oxy-Claisen rearrangement (or, perhaps, a [2,3]-Wittig rearrangement). Very much to the contrary, Snider and Liu stated that "…*isomerization of* ***24*** [**3023**] *for longer periods of time resulted in extensive decomposition*…"[7]

C. MODEL SUBSTRATE DESIGN

The studies described in the remaining sections of Chapter III have as their overarching goal the support (or refutation) of the hypothesis presented in Scheme III–1. Let us now revisit this hypothesis, where, for the sake of simplicity, only that pathway leading form 9-*epi*-**1-A** to **1-F** is shown (Scheme III–8). In light of the previous studies discussed in Section B, the most likely candidate for a spontaneous anionic oxy-Claisen rearrangement is the enolate derived from 9-*epi*-**1-A**, i.e., [**3001**]$^-$. It was reasoned that if a simplified version of 9-*epi*-**1-A** (or **1-A**) could be prepared and its reactivity investigated, then one might be able to glean some insightful details regarding this hypothesis. Ideally, the model compound would both retain the essential structural features of 9-*epi*-**1-A** and be more readily accessible than the parent structure. Of course, one's ability to extrapolate to the 'real' system observations made during the course of a model study is–by definition–limited, but this seemed a worthwhile endeavor.

Scheme III–8 | Model substrate design via simplification of 9-*epi*-**1-A** (and 9-*epi*-**1-B**).



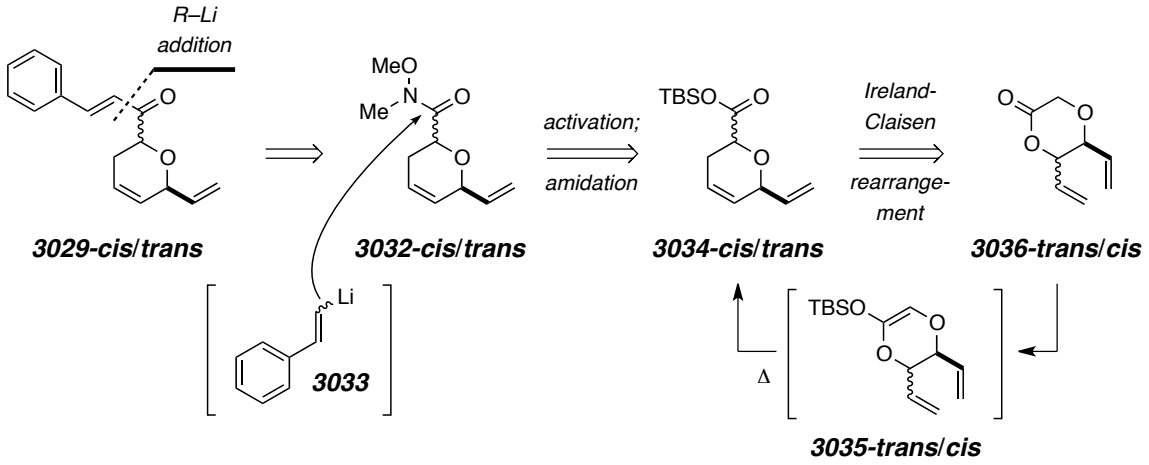
Excision of the hydroxycyclopentane (C4–C7), vinyl methyl (C22), and *n*-heptyl (C15–C21) carbon atoms within 9-*epi*-**1-A** revealed the dihydropyran **3029** as a substrate that possessed a reasonable level of complexity while maintaining several key structural attributes (Scheme III–8). If one makes the reasonable assumption that deprotonation of either the *cis* or *trans* isomers **3029** would occur at approximately the same rate, then either isomer will suffice because they both converge to the same (racemic) enolate, **3030**. Were this enolate to evolve to product through the [3,3]-sigmatropic reaction manifold, then, given the structural similarity between **3031** and [**1-I**]$^{-}$, one could be confident that the reaction course taken by [**3001**]$^{-}$ would proceed similarly.

D. SYNTHESIS AND REACTIVITY OF MODEL SUBSTRATES

D–1. RETROSYNTHETIC ANALYSIS

At this juncture, a short and efficient synthesis route to the model substrate(s), including both the *cis* (**3029-cis**) and *trans* (**3029-trans**) isomers, was devised (Scheme III–9). It was envisioned that the (*E*)-styrenyl appendage present in both of these isomers could be introduced *via* acylation of the organolithium reagent derived from β-bromostyrene (**3033**). The Weinreb amides **3032-cis**/**trans** (or functional equivalents thereof) then became obvious synthetic targets. These intermediates, in turn, should be accessible from the *tert*-butyldimethylsilyl esters **3034-cis**/**trans** through an activation/ amidation sequence.

Scheme III–9 | Retrosynthetic analyses of the Claisen model substrates **3029-cis/trans**.



Burke's well-established protocol[252] for the synthesis of substituted dihydropyrans from 6-alkenyl-1,4-dioxan-2-ones (e.g., **3036-trans**/**cis**) was viewed as an ideal method

[252] (a) Burke, S. D.; Armistead, D. M.; Schoenen, F. J. Polysubstituted Dihydropyrans via the Enolate Claisen Rearrangement. A Stereocontrolled Route to *C*-Pyranosides. *J. Org. Chem.* **1984**, *49*, 4320–4322. (b) Burke, S. D.; Armistead, D. M.; Fevig, J. M. Ionophore Synthesis. An Enantioselective

for the preparation of both the *cis* and *trans* isomers of silyl ester **3034**. Thus, it was anticipated that Ireland–Claisen rearrangement[253] of silyl enol ethers **3035-trans**/**cis**, themselves derived from *in situ* silylation of **3036-trans**/**cis**, would, depending on which lactone was employed, deliver either the *trans* (**3034-trans**) or *cis* (**3034-cis**) isomer.

D–2. SYNTHESIS STRATEGIES TOWARD 3029-cis/trans

The racemic dioxanones **3036-trans** and **3036-cis** were prepared as described in Scheme III–10. Hexa-1,5-diene-3,4-diol (**3038**) (1:1 *meso* + *d,l*), which was prepared on multi-gram scale from acrolein (**3037**) according to a straightforward, reliable procedure,[254] was reacted with di-*n*-butyltin oxide (Bu_2SnO) under Dean-Stark conditions. On the basis of the well-known reactivity of this reagent toward *vic*-diols,[255] the formation of the intermediate stannylene ketal **3039** is presumed; however, the

---

Route to the Left-Wing of Indanomycin (X-14547A). *Tetrahedron Lett.* **1985**, *26*, 1163–1166. (c) Burke, S. D.; Schoenen, F. J.; Murtiashaw, C. W. The Ester Enolate Claisen Rearrangement. Synthesis of a C(1)–C(6) Erythronolide Fragment. *Tetrahedron Lett.* **1986**, *27*, 449–452. (d) Burke, S. D.; Armistead, D. M.; Schoenen, F. J.; Fevig, J. M. An Enolate Claisen Route to *C*-Pyranosides–Development and Application to an Ionophore Synthon. *Tetrahedron Lett.* **1986**, *27*, 2787–2801. (e) Burke, S. D.; Schoenen, F. J.; Nair, M. S. The Dioxanone-to-Dihydropyran Claisen Rearrangement. Synthesis of C(7)–C(13) Fragments of Erythronolides A and B. *Tetrahedron Lett.* **1987**, *28*, 4143–4146. (f) Burke, S. D.; Lee, K. C.; Santafianos, D. Double Dioxanone-to-Dihydropyran Reorganization. Construction of a C(1)–C(13) Erythronolide Template. *Tetrahedron Lett.* **1991**, *32*, 3957–3960. (g) Burke, S. D.; Buchanan, J. L.; Rovin, J. D. Synthesis of a C(22) → C(34) Halichondrin Precursor via a Double Dioxanone-to-Dihydropyran Rearrangement. *Tetrahedron Lett.* **1991**, *32*, 3961–3964. (h) Burke, S. D.; Piscopio, A. D.; Kort, M. E.; Matulenko, M. A.; Parker, M. H.; Armistead, D. M.; Shankaran, K. Total Synthesis of Ionophore Antibiotic X-14547A (Indanomycin). *J. Org. Chem.* **1994**, *59*, 332–347.

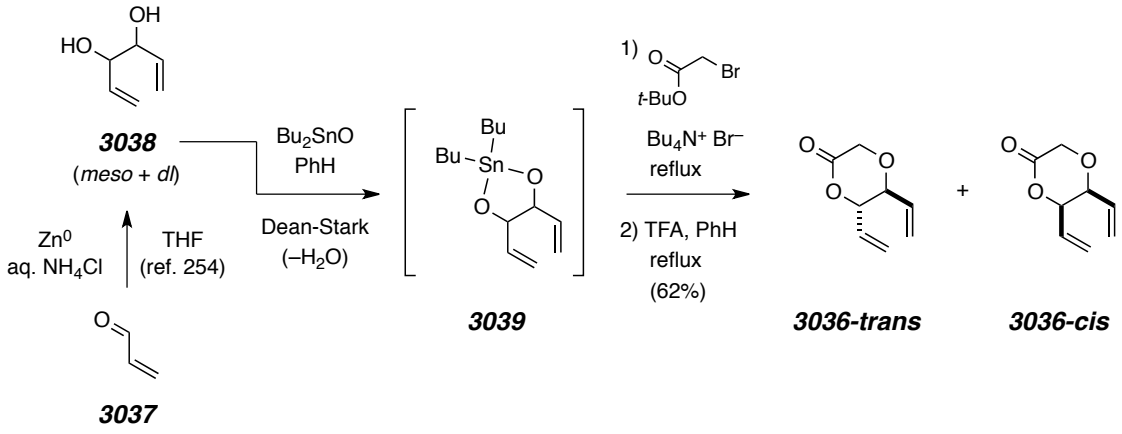
253 Ireland, R. E.; Mueller, R. H. The Claisen Rearrangement of Allyl Esters. *J. Am. Chem. Soc.* **1972**, *94*, 5897–5898.

254 (a) Hekmatshoar, R.; Yavari, I.; Beheshtiha, Y. S.; Heravi, M. M. Reductive Coupling of Carbonyl Compounds to Pinacols with Zinc in THF–Saturated Aqueous Ammonium Chloride. *Monatsh. Chem.* **2001**, *132*, 689–691. (b) Trost, B. M.; Aponick, A. Palladium-Catalyzed Asymmetric Allylic Alkylation of *meso*- and *dl*-1,2-Divinylethylene Carbonate. *J. Am. Chem. Soc.* **2006**, *128*, 3931–3933.

255 David, S.; Thieffry, A.; Veyrières, A. A Mild Procedure for the Regiospecific Benzylation and Allylation of Polyhydroxy-compounds *via* their Stannylene Derivatives in Non-polar Solvents. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1796–1801.

existence of a dimeric, pentacoordinate stannate structure cannot be discounted.[256] The solution that resulted from azeotropic removal of water was directly treated with *tert*-butyl bromoacetate and tetra-*n*-butylammonium bromide (or iodide) in refluxing benzene to deliver, after preliminary purification by flash chromatography, a mixture of the desired dioxanones (**3036-trans**/**cis**) together with their acyclic, hydroxy ester progenitors (not shown). This partially lactonized mixture was driven entirely to the desired products by subsequent treatment with TFA in refluxing benzene, which provided the isomeric lactones in 62% combined yield. It should be noted that ethyl (or methyl) bromoacetate could serve equally well as alkylating agents in the above sequence, and that under these conditions the intermediate hydroxyl esters typically were not isolated. However, the two-step procedure shown in Scheme III–10, which provided the dioxanones **3036-trans**/**cis** in a high state of purity, was the preferred method.

Scheme III–10 | Synthesis **3036-trans** and **3036-cis** via stannylene ketal alkylation.



Although the diastereomeric lactones were virtually indistinguishable by TLC analysis, they could be readily separated by MPLC. In this manner, the faster-eluting

[256] See, e.g.: Davies, A. G.; Price, A. J.; Dawes, H. M.; Hursthouse, M. B. Structure of 2,2-Dibutyl-1,3,2-dioxastannolane in the Solid State. *J. Chem. Soc., Dalton Trans.* **1986**, 297–302.

3036-trans was obtained in >95% purity whereas the slower-eluting **3036-cis** was typically 90% pure. It was mentioned earlier that these lactones could serve as ideal candidates for the Ireland–Claisen technology developed by Burke.[252] Dioxanone **3036-trans** was in fact an intermediate in recent total syntheses of KDO and 2-deoxy-β-KDO that were reported by Burke and Sametz;[257] however, characterization data was not provided. Moreover, dioxanone **3036-cis** had not been described in the literature prior to these studies. Full characterization of both isomers was thus undertaken, which led, *inter alia*, to the ^{1}H NMR chemical shifts and $^{3}J_{H,H}$ values shown in Figure III–2. Burke and co-workers have determined coupling constants for an assortment of *trans*- and *cis*-5,6-disubstituted 1,4-dioxan-2-ones.[252d] The reported ^{1}H–^{1}H $^{3}J_{trans}$ values, which range from 9.0–9.4 Hz, are clearly consistent with the 9.0 Hz value observed for **3036-trans**; likewise, the $^{3}J_{cis}$ value of 4.5 Hz for **3036-cis** also trends toward the reported values of 2.3–3.1 Hz.

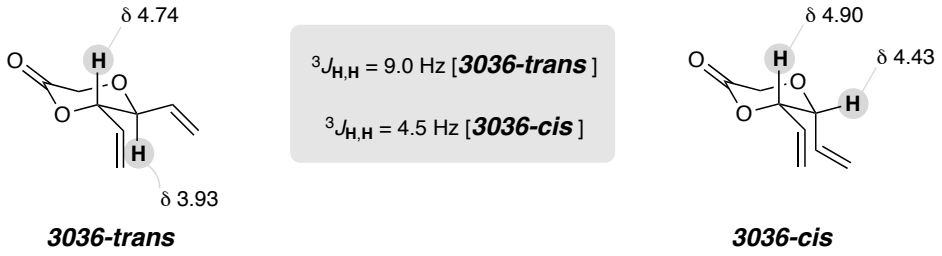
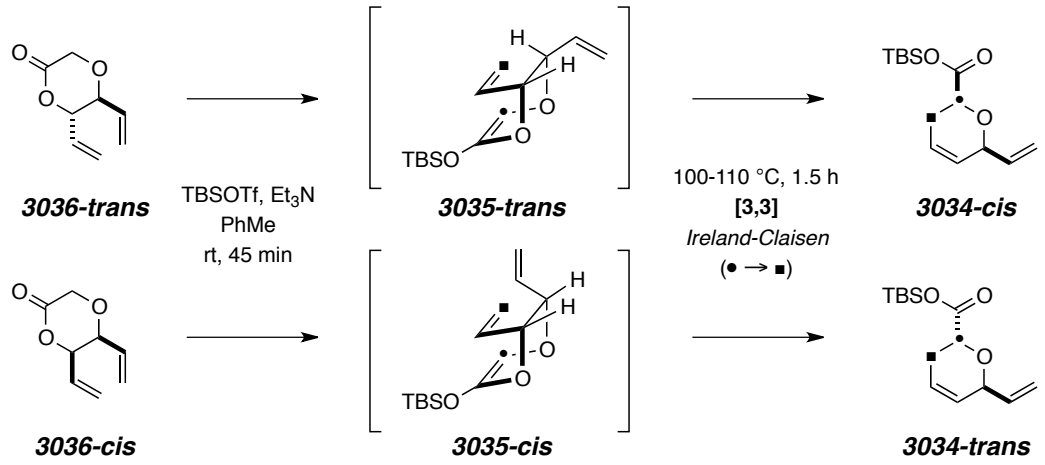


Figure III–2 | Select chemical shift and $^{3}J_{H,H}$ values for the isomeric dioxanones **3036-trans** and **3036-cis** determined in $CDCl_3$ at 500 MHz.

[257] Burke, S. D.; Sametz, G. M. Total Synthesis of 3-Deoxy-D-*manno*-2-octulosonic Acid (KDO) and 2-Deoxy-*β*-KDO. *Org. Lett.* **1999**, *1*, 71–74. A single enantiomer of **3036-trans**, which in this instance was prepared by a five-step sequence from D-mannitol, was used.

Purified samples of **3036-trans** and **3036-cis** were then independently subjected to Angel's modification[258] of the procedure of Burke,[252] conditions that are known to induce [3,3]-sigmatropic rearrangement in related systems (Scheme III–11). In the event, each of these dioxanones was allowed to react at room temperature with an excess of TBSOTf and Et_3N in toluene. Isolation of the presumed silyl enol ethers **3035-trans**/**cis** at this stage was never attempted; rather, their *in situ* generated solutions were directly heated to provide, after a short reaction period, the silyl esters **3034-cis** and **3034-trans**.

Scheme III–11 | Sigmatropic rearrangement of **3035-trans**/**cis**.



Early attempts to isolate these highly acid sensitive entities were frustratingly difficult. Perhaps not surprisingly, extensive decomposition of the desired products occurred when flash chromatography on silica gel was performed, a problem that was encountered even when the mobile phase was buffered with Et_3N. As a result, sequential

[258] Angle, S. R.; Breitenbucher, J. G.; Arnaiz, D. O. An Efficient Stereoselective Synthesis of $\Delta^{4,5}$-Pipecolic Esters. *J. Org. Chem.* **1992**, *57*, 5947–5955.

filtration through TMS-functionalized silica gel[259] was required to purify the silyl esters **3034-cis**/**trans**, which generally could be obtained in 80–85% purity [isolated yields were typically determined at a later stage when the products could be rigorously purified by silica gel chromatography (*vide infra*)].

The assignment of the relative configuration of these products rests entirely (and securely) on bountiful literature precedent. Studies conducted by Büchi,[260] Danishefsky,[261] and Burke[252] in related systems have established that, in contrast to the chair-like transition state orientation that is typically favored in the aliphatic Claisen rearrangement, the relative configuration of the newly created stereogenic centers within **3034-trans**/**cis** are consistent with a *boat-like* transition state orientation. As depicted in the bracketed structures **3035-trans** or **3035-cis** (Scheme III–11), the terminus of the ethenyl substituent that resides proximal to the silyl enol ether oxygen (●) engages the distal carbon of the silyl enol ether (■). The ensuing [3,3]-sigmatropic rearrangement of **3035-trans** gives rise to the *cis*-2,6-disubstituted dihydropyran **3034-cis**, whereas rearrangement through **3035-cis** produces the *trans* diastereomer **3034-trans**.

The focus of synthetic efforts now shifted to the identification of a method for the installation of the (*E*)-styrenyl appendage. The sequence of events delineated in the retrosynthetic analysis–namely, acylation of β-lithiostyrene (**3033**) with a Weinreb amide (**3032-cis**/**trans**)–was by no means the first plan of attack. Of paramount concern at this stage was the known instability of the free carboxylic acids derived from 2,6-dihydropyrans related to **3034-cis**/**trans**. For example, Burke and Sametz[257] have

---

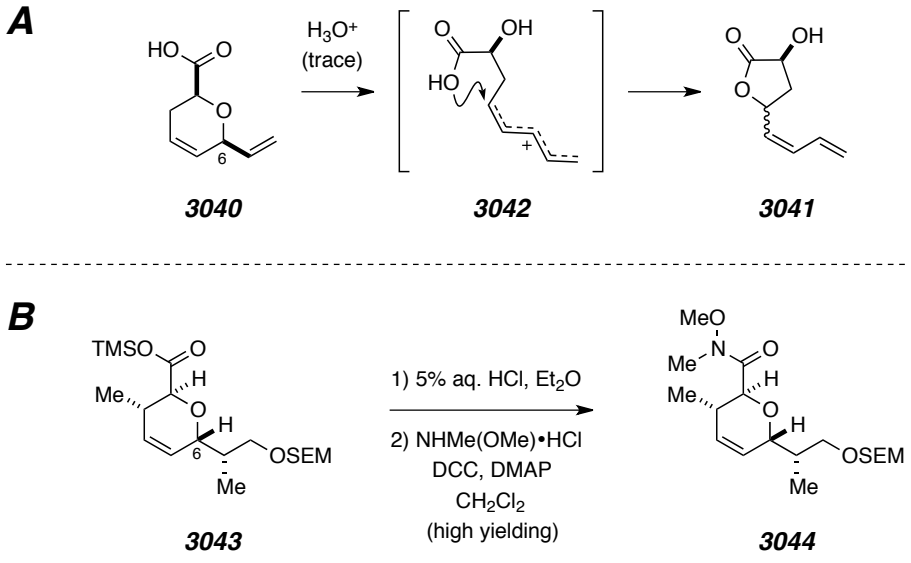
259 Such situations have been encountered in the literature; see ref 258 and Overman, L. E.; Angle, S. R. Synthesis Applications of Cationic Aza-Cope Rearrangements. Stereocontrolled Synthesis of Hexahydro-1*H*-pyrrolo[2,3-*d*]carbazoles. *J. Org. Chem.* **1985**, *50*, 4021–4028.

260 (a) Büchi, G.; Powell, Jr., J. E. A Structurally Selective Method for the Preparation of Certain Diels-Alder Adducts. *J. Am. Chem. Soc.* **1967**, *89*, 4559–4560. (b) Büchi, G.; Powell, Jr., J. E. The Claisen Rearrangement of 3,4-Dihydro-2*H*-pyranylethylenes. A New Method for the Synthesis of Cyclohexenes. *J. Am. Chem. Soc.* **1970**, *92*, 3126–3133.

261 Danishefsky, S.; Funk, R. L.; Kerwin, Jr., J. F. Claisen Rearrangement of Lactonic (Silyl) Enolates: A New Route to Functionalized Cycloalkenes. *J. Am. Chem. Soc.* **1980**, *102*, 6889–6891.

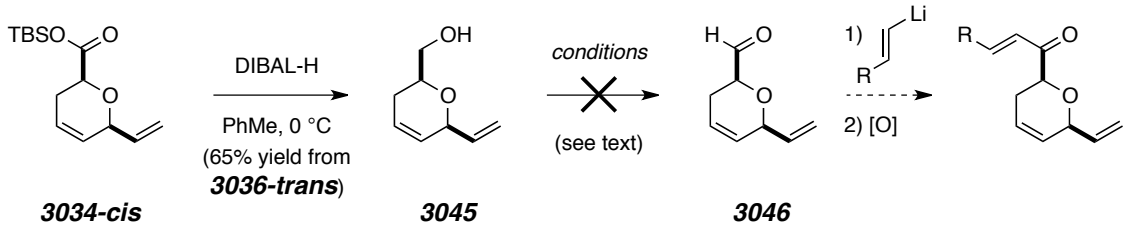
disclosed that production of the carboxylic acid **3040** (Scheme III–12A) by desilylation of **3034-cis** was accompanied by the formation hydroxy lactone **3041**. This process, which presumably proceeds by way of acid-catalyzed ring opening of **3040** to the pentadienyl cation **3042**, is apparently unique to compounds that bear an alkenyl substituent at C6 of the dihydropyran. This observation is to be contrasted with the reported behavior of dihydropyran **3043** (Scheme III–12B). Desilylation (5% aqueous HCl) and Weinreb amidation of this material, which now possesses a saturated alkyl substituent at C6, was uncomplicated by an acid-catalyzed rearrangement process and cleanly provided **3044**.[252h] It therefore became clear that any serious approach toward the synthesis of the model substrates **3029-cis**/**trans** must reckon with the observed sensitivity of **3040**.

Scheme III–12 | A: Rearrangement of **3040** to the hydroxy lactone **3041** via pentadienyl cation **3042** [adapted from ref 257]. **B**: High yielding production of **3044** via the carboxylic acid derived from **3043** [adapted from ref 252h].



A sequence involving reduction of the silyl ester **3034-cis** to the alcohol, oxidation to the aldehyde, organolithium addition, and oxidation of the incipient secondary allylic alcohol was, at first, an attractive means to circumvent the carboxylic acid. Reduction of **3034-cis** to the primary alcohol **3045**,[262] although unsuccessful with the more vicious reductant LAH, proceeded smoothly with DIBAL-H (Scheme III–13). However, subsequent manipulation of this material was unfruitful. Although the alcohol **3045** was completely consumed under all of the oxidative conditions [*MJJ-III-182/183*] that were explored [TPAP, NMO, 4Å MS, CH_2Cl_2;[32] TEMPO, $PhI(OAc)_2$, CH_3CN/pH 7 buffer;[263] SO_3•pyr, *i*-Pr_2NEt, CH_2Cl_2/DMSO[264]], in no case was the desired aldehyde **3046** detected by analysis of the crude reaction profiles by ^1H NMR spectroscopy.

Scheme III–13 | Reduction of the silyl ester **3034-cis** and attempted oxidation of **3045**.



3034-cis ***3045*** ***3046***

---

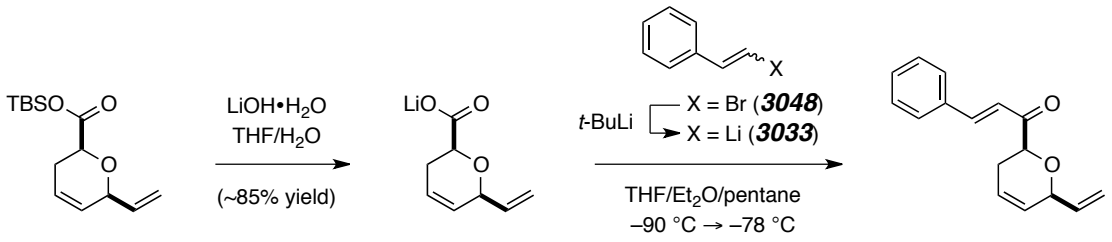
262 [*MJJ-III-180*] **^{1}H NMR** (500 MHz, $CDCl_3$): 5.86 (dddd, *J* = 2.0, 2.0, 5.5, 10.0 Hz, 1H, C*H*=CH), 5.83 (ddd, *J* = 7.0, 10.5, 17.5 Hz, 1H, C*H*=$CH_{trans}H_{cis}$), 5.65 (dddd, *J* = 1.5, 1.5, 3.0, 10.5 Hz, 1H, CH=C*H*), 5.32 (ddd, *J* = 1.5, 1.5, 17.0 Hz, 1H, CH=C$H_{trans}H_{cis}$), 5.19 (ddd, *J* = 1.5, 1.5, 10.5 Hz, 1H, CH=$CH_{trans}H_{cis}$), 4.66 [Σ (*J*s) = 20.5 Hz including 1.5, 1.5, and 6.5 Hz, 1H, CH=CHC*H*–CH=$CH_{trans}H_{cis}$), 3.78 (dddd, *J* = 3.0, 3.0, 7.5, 10.5 Hz, 1H, C*H*CH_2OH), 3.69 (ddd, *J* = 3.0, 8.0, 11.5 Hz, 1H, CHC*H*$_2$OH), 3.60 (ddd, *J* = 5.0, 7.5, 12.0 Hz, 1H, CHC*H*$_2$OH), 2.13 (dd, *J* = 5.0, 8.5 Hz, 1H, $CHCH_2O$*H*), 2.14-2.06 (m, 1H, C*H*$_2$), and 1.92-1.85 (m, 1H, C*H*$_2$).

263 De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. A Versatile and Highly Selective Hypervalent Iodine(III)/2,2,6,6-Tetramethyl-1-piperidinyloxyl-Mediated Oxidation of Alcohols to Carbonyl Compounds. *J. Org. Chem.* **1997**, *62*, 6974–6977.

264 Parikh, J. P.; Doering, W. E. Sulfur Trioxide in the Oxidation of Alcohols by Dimethyl Sulfoxide. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

Attention next turned to the synthesis of a species that could serve as a functional equivalent of a Weinreb amide. Since the addition of organolithium reagents to alkali metal carboxylates is well established,[265] this seemed like a worthwhile pursuit. The lithium carboxylate **3047** was prepared via aqueous LiOH-mediated desilylation of TBS silyl ester **3034-cis** (Scheme III–14). A sample of **3047** thus obtained was immediately allowed to react with β-lithiostyrene (**3033**), itself prepared by Br/Li–exchange of β-bromostyrene [**3048**, 8.3:1 (*E*)/(*Z*)] with *tert*-butyllithium.[266] Although small quantities of the desired product (**3029-cis**) could be isolated, the yield was unacceptably low. Additionally, this yield, albeit miniscule, could not be reproduced in separated runs of this reaction on slightly larger scale. It was surmised that poor solubility of the lithium carboxylate **3047**, which forms a suspension in THF, was the likely cause for the irreproducibility of this reaction.

Scheme III–14 | Addition of β-lithiostyrene (**3033**) to the lithium carboxylate **3047-cis** produced the desired product (**3029-cis**), but in disappointingly low isolated yield.



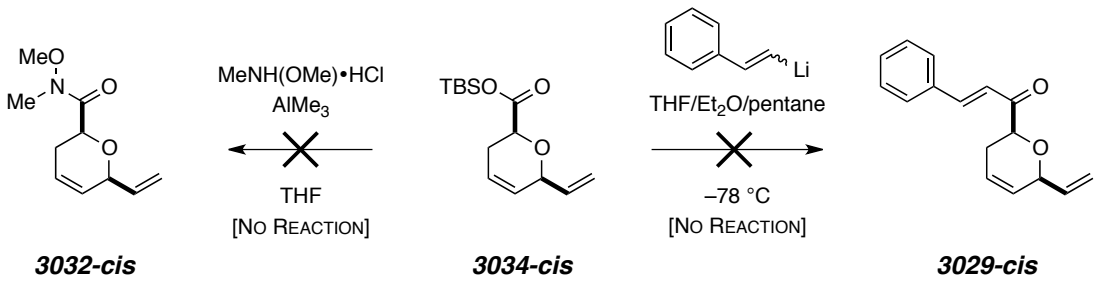
There exist very few reports of nucleophilic species being directly added to silyl esters, yet encouragement was drawn from a report that Et_2NAlMe_2 (Et_2NH + $AlMe_3$)

[265] Jorgenson, M. J. Preparation of Ketones from the Reaction of Organolithium Reagents with Carboxylic Acids. *Org. React.* **1970**, *18*, 1–97.

[266] Neumann, H.; Seebach, D. Stereospecific Preparation of Terminal Vinyllithium Derivatives by Br/Li-Exchange with *t*-Butyllithium. *Tetrahedron Lett.* **1976**, *17*, 4839–4842.

could be added directly to a TBS ester[267] and also from a well known method for Weinreb amide synthesis from carboxylic esters [NHMe(OMe)•HCl + $AlMe_3$]. Unfortunately, reaction of the silyl ester **3034-cis** with the aluminum species derived from this later reagent combination resulted no appreciable reaction (Scheme III–15). An attempt was also made to directly react **3034-cis** with β-lithiostyrene; however, a similar outcome was observed.

Scheme III–15 | Unsuccessful attempts at direct amidation/vinylation of ester **3034-cis**.



3032-cis ***3034-cis*** ***3029-cis***

The exploratory studies described previously, although largely unsuccessful, revealed the need to develop a route that incorporated the Weinreb amides **3032-cis**/**trans** as key intermediates. The 1978 report from Wissner and Grudzinskas[268] regarding the formation of acid chlorides directly from TBS esters revealed itself as a promising opportunity. In their reported procedure, which presumably involves *in situ* generation of the Vilsmeier reagent, a variety of simple aliphatic and aromatic TBS esters were reacted with stoichiometric $(COCl)_2$ in the presence of catalytic DMF. Subsequent treatment of the acid chlorides with EtOH/pyridine provided ethyl esters in high yields.[268]

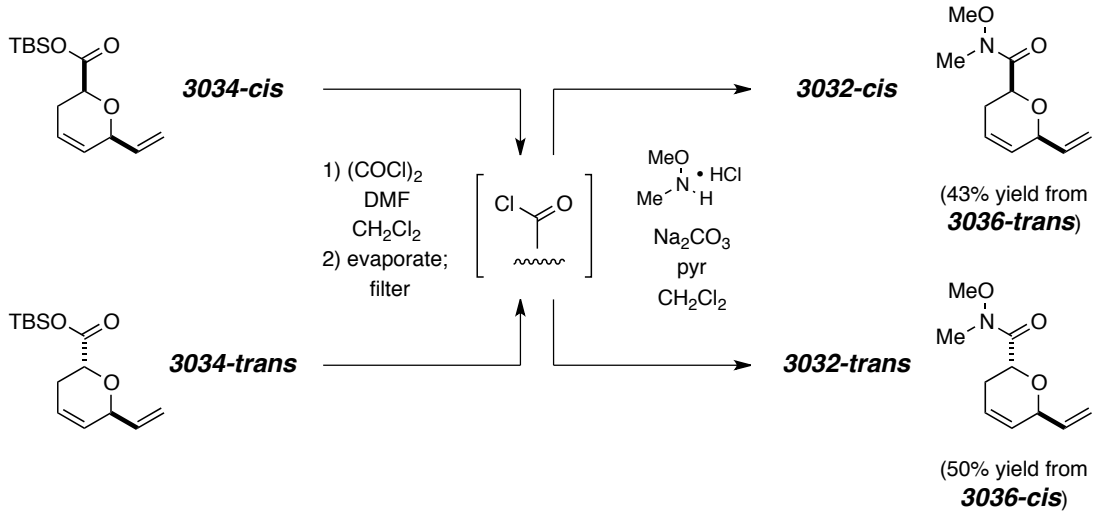
---

267 Sellès, P.; Lett, R. Convergent Stereospecific Synthesis of C292 (or LL-Z1640-2), and Hypothemycin. Part 1. *Tetrahedron Lett.* **2002**, *43*, 4621–4625.

268 Wissner, A.; Grudzinskas, C. V. Reaction of *tert*-Butyldimethylsilyl Ester with Oxalyl Chloride–Dimethylformamide: Preparation of Carboxylic Acid Chloride Under Neutral Conditions. *J. Org. Chem.* **1978**, *43*, 3972–3974.

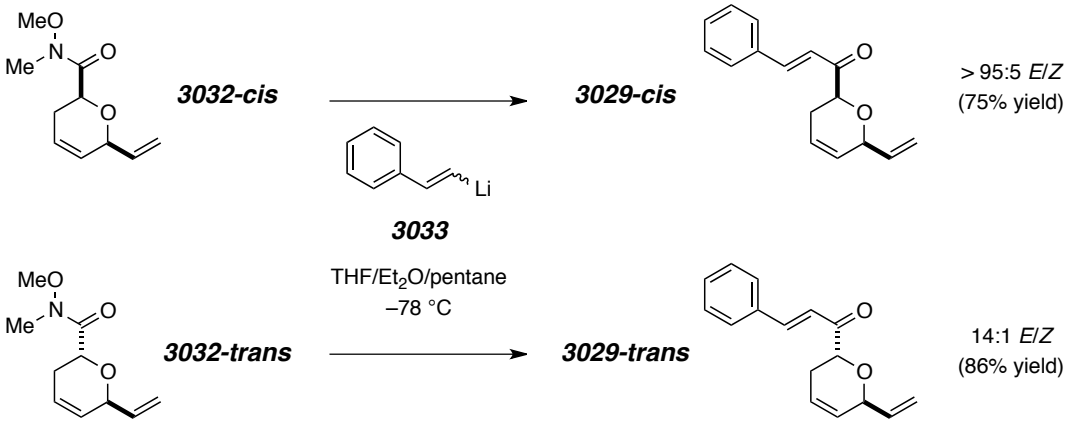
As shown in Scheme III–16, a modification of the Wissner/Grudzinskas protocol proved to be a satisfactory method for the generation of pure samples of **3032-cis**/**trans**. Early studies indicated that catalytic amounts of DMF were insufficient to drive these reactions to full conversion. For example, when the TBS esters **3034-cis**/**trans** were allowed to react with an excess of $(COCl)_2$ (*ca.* 2 equiv) and catalytic DMF in CH_2Cl_2 at 0 °C, only partial conversion to the intermediate acid chlorides were observed by TLC analysis. Surprisingly, this situation was not improved by heating of the reaction mixture for extended periods, or by simply adding an excess of DMF. However, full conversion to the intermediate acid chlorides could be achieved when **3034-cis**/**trans** were reacted with an excess (*ca.* 3 equiv) of the *preformed* Vilsmeier reagent. Since this modified procedure generated a heterogeneous reaction mixture, a filtration step was found to be necessary. Subsequent treatment of the intermediate acid chlorides thus obtained with *N*,*O*-dimethylhydroxylamine (free-based *in situ*) provided **3032-cis** and **3032-trans** in 43% and 50% overall yields from the dioxanones **3036-trans** and **3036-cis**, respectively.

Scheme III–16 | Synthesis of Weinreb amides **3032-cis**/**trans** from silyl esters **3034-cis**/**trans**.



Due to their relatively short shelf lives, the amides **3032-cis**/**trans**, once freshly prepared, were immediately utilized in the subsequent organometallic addition. Happily, addition of either of theses species to a preformed solution of β-lithiostyrene (**3033**) in the Trapp solvent mixture (4:4:1 THF/Et_2O/pentane) at –78 °C proceeded smoothly to provide the diastereomeric enones **3029-cis** and **3029-trans** in 75% and 86% yields, respectively (Scheme III–17). The isomeric purity of **3029-cis**, which is initially isolated as a *ca.* 14:1 mixture of (*E*)- and (*Z*)-isomers, could be upgraded to >95% (*E*)-isomer by MPLC purification. On the other hand, the (*E*)- and (*Z*)-isomers of **3029-trans** were chromatographically inseparable.

Scheme III–17 | Acylation of β-lithiostyrene (**3033**) with the Weinreb amides **3032-cis**/**trans**.



A final aspect of the reactions shown in Scheme III–17 deserves comment. That the dihydropyrans **3029-cis** and **3029-trans** were measurably enriched in the (*E*)-isomer vis-à-vis the isomeric composition [8.3:1 (*E*)/(*Z*)] of the β-bromostyrene from which **3033** was prepared suggests that (*E*)-β-lithiostyrene reacts with **3032-cis**/**trans** at a faster rate than does (*Z*)-β-lithiostyrene.[269] However, equilibration of the isomeric vinyllithium

[269] Seebach has demonstrated that (*E*)- and (*Z*)-β-lithiostyrene are configurationally stable in the –120 °C to –78 °C temperature regime. See ref 266.

species prior to addition of **3032-cis**/**trans** cannot be excluded as a possibility.[270] Nevertheless, this observation underscores the benefit and convenience of employing an excess (3 equiv) of this particular vinyllithium reagent.

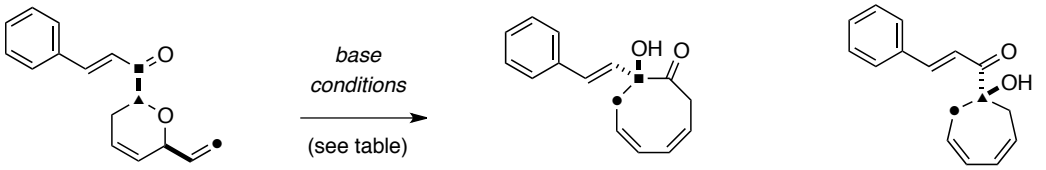
D–3. REACTIVITY STUDIES OF **3029-cis**/**trans** AND RELATED DERIVATIVES

Now that access to the model substrates **3029-cis**/**trans** had been made possible by a straightforward and relatively efficient synthetic route, their fate under a variety of basic reaction conditions was promptly investigated. As was discussed earlier in Chapter III, Koreeda and Luengo induced the [3,3]-sigmatropic rearrangement of the enolate derived from α-(allyloxy)propiophenone (**3007**) with high efficiency.[240] The conditions that they found to be optimal (i.e., excess KH/MeOH in THF) therefore seemed, at first glance, to be a reasonable starting point for these studies (Table III–2). When exposed to these conditions, however, the enone **3029-cis** was rapidly and nonproductively consumed; no evidence for the formation of the cyclooctadienone **3049** was obtained (entry 1). An identical outcome was observed in the absence of MeOH (entry 2). The deleterious nature of these strongly basic conditions is not unique to the present system. Indeed, Hopkins and co-workers made a similar observation during their anionic oxy-Claisen rearrangement studies of the bicyclic ketone **3016**[247] (see Scheme III–5A).

---

[270] Phenyl substituted vinyllithium and vinylmagnesium reagents are known to be less configurationally stable than their alkyl substituted counterparts. Their stability is, however, intimately related to solvent composition and temperature. See: Seyferth, D. Vinyl Compounds of Metals. In *Progress in Inorganic Chemistry* **1962**, *3*, 129–280. In particular, the reader is directed to pages 160–163 and 170.

Table III–2 | Preliminary reactivity studies of the model substrate **3029-cis**.



3029-cis ***3049*** *via* **[3,3]**-Claisen (● → ■) *VERSUS* ***3048*** *via* **[2,3]**-Wittig (● → ▲)

entry	base	*conditions*	observation(s)
1	KH (excess)	MeOH (excess), THF, 0 °C → rt	---[a]
2	KH (excess)	THF, 0 °C → rt	---[a]
3	Et_3N (4.0 equiv)	TBSOTf, C_6D_6, rt, 30 min	---[b]
4	K_2CO_3 (1.7 equiv)	MeOH, 60 °C, 1.5 h	***3048*** only product (50% yield)
5	$Bu_4N^+ {}^-OH$ (1.5 equiv)	*i*-PrOH / MeOH, rt, < 2 min	***3048*** only product (79% yield)

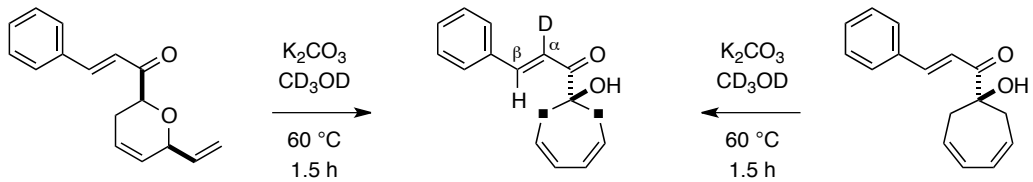
[a] Decomposition of the starting material. [b] No reaction.

In a search for milder conditions, **3029-cis** was exposed to TBSOTf in the presence of Et_3N (entry 3), but, unfortunately, no reaction took place. So surprising was this result that it had to be confirmed by *in situ* ^1H NMR monitoring (i.e., in C_6D_6). A clean transformation finally took place with the agency of K_2CO_3 in MeOH (entry 4). This transformation, which pretty cleanly gave rise to the *undesired* [2,3]-Wittig product **3048**, could be affected in 90 min at 60 °C or, alternatively, over the course of *ca.* 48 h at room temperature. The symmetrical nature of **3048** was strongly suggested by its ^1H NMR spectrum, which was considerably less complex than that corresponding to **3029-cis**. Moreover, the fact that the conjugated enone had been retained in this product was supported by the presence of a low-field ^1H NMR β-alkenyl resonance (δ 7.82 for **3048** vs. δ 7.77 for **3029-cis**). Finally, the [2,3]-Wittig product **3048** was again formed at the

exclusion of **3049** in the presence of $Bu_4N^+ {}^-OH$ (entry 5). Perhaps as a consequence of the non-coordinating nature of the Bu_4N^+ counterion, this rearrangement took place within minutes at room temperature.

During the course of these studies, the K_2CO_3-mediated rearrangement of **3029-cis** in CD_3OD was monitored by ^1H NMR spectroscopy (Scheme III–18). The fact that quantitative incorporation of deuterium had occurred at the α-position within **3048** under these conditions (via reversible CD_3O^- conjugate addition) was immediately apparent from the loss of the resonance corresponding to this proton [normally observed at δ 7.34 (d, J = 16.0 Hz)] and the collapse of the downfield β-enone resonance to a broad singlet (δ 7.81). A more detailed analysis of this material by ^1H NMR spectroscopy (i.e., relative signal intensity) and GC-MS[271] revealed that *ca.* 45–50% deuterium incorporation had occurred to an equal extent at the methylene carbon atoms (■) within **3048**-d_n (n = 1–5). Moreover, a similar observation was made when pure **3048** was exposed to K_2CO_3/CD_3OD, but in this instance the extent of deuterium incorporation was somewhat diminished (*ca.* 22–25%).[272]

Scheme III–18 | Deuterium incorporation studies of **3029-cis** and **3048**.



3029-cis ***3048***-d_n ***3048***

(*ca.* 22–55% D incorporation at ■)

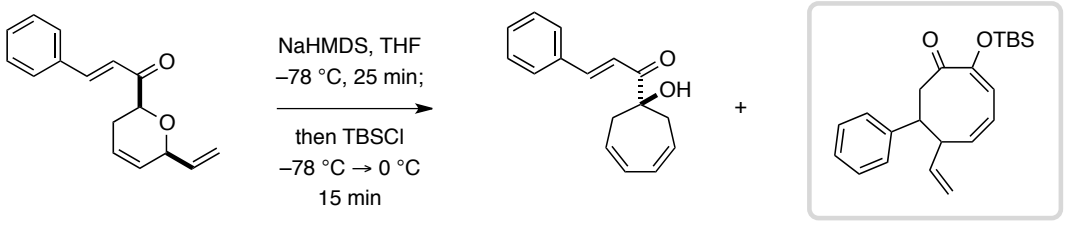
[271] [*MJJ-III-251*] **GC / LR EI-MS** [5027016]: t_R 10.69 min; *m/z* [rel. int. ($M^{+\bullet}$ region)] 245 (4.6, $M^{+\bullet}$-d_5), 244 (25.4, $M^{+\bullet}$-d_4), 243 (100, $M^{+\bullet}$-d_3), 242 (57.6, $M^{+\bullet}$-d_2), 241 (67.6, $M^{+\bullet}$-d_1), and 240 (1.1, $M^{+\bullet}$-d_0).

[272] [*MJJ-III-253*] **GC / LR EI-MS** [5027016]: t_R 10.69 min; *m/z* [rel. int. ($M^{+\bullet}$ region)] 245 (3.6, $M^{+\bullet}$-d_5), 244 (16.6, $M^{+\bullet}$-d_4), 243 (58.9, $M^{+\bullet}$-d_3), 242 (54.8, $M^{+\bullet}$-d_2), 241 (100, $M^{+\bullet}$-d_1), and 240 (1.7, $M^{+\bullet}$-d_0).

Although these deuterium incorporation studies suggested that something more intriguing might be at work here, I was nonetheless discouraged. At the time, the exclusive formation of **3048** seemed to indicate that the [2,3]-sigmatropic (Wittig) rearrangement was the kinetically favored pathway in this system, and thus these studies were placed on the backburner for quite some time.

With a renewed perspective, I revisited this chemistry several months later and began to explore the possibility that the enolates derived from **3029-cis**/**trans** could perhaps be isolated as their corresponding silyl enol ethers. Surely, I thought, these species would undergo thermal [3,3]-sigmatropic rearrangement, albeit at elevated temperatures (e.g., entry 5 in Table III–1). In order to probe this point, **3029-cis** was deprotonated with sodium bis(trimethylsilyl)amide (NaHMDS) in THF, and, after a short incubation period, the reaction mixture was treated with TBSCl and allowed to warm (Scheme III–19). That **3048** had been formed under these conditions was immediately recognized;[273] in most cases, it was the major component. However, with the aid of MPLC, I eventually fished out another product that most certainly *was not* the silyl enol ether derived from **3029-cis**, but rather the conjugated cyclooctadienone **3050**.

Scheme III–19 | Isolation of the [2,3]-Wittig product (**3048**) and an unexpected product (**3050**) upon deprotonation of **3029-cis**.

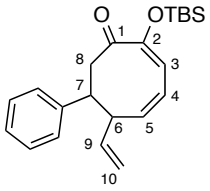


3029-cis ***3048*** (14–58% yield) ***3050*** *dr* > 95:5 (13–28% yield)

[273] The fact that **3048** was not silylated under these conditions can probably be attributed to the low nucleophilicity of the intermediate tertiary lithium alkoxide.

The constitution of this unusual and quite bewildering product was established after extensive 1-D (^{1}H and ^{13}C) and 2-D (^{1}H–^{1}H COSY, HMQC, and HMBC) NMR experiments; the results of these studies are tabulated in Table III–3. Although **3050** was formed as essentially a single diastereomer, its relative configuration could not be unambiguously established.

Table III–3 | Carbon (^{13}C) and proton (^{1}H) NMR spectroscopic data for **3050** in $CDCl_3$ at 75 and 500 MHz, respectively.[a]



3050

ATOM	CARBON	PROTON			COSY	HMBC
#	δ_C	δ_H	mult.	*J* [Hz]	(to ^{1}H-#)	(from ^{1}H → ^{13}C-#)
1	200.0	---	---	---	---	---
2	149.4	---	---	---	---	---
3	119.9	6.16	dddd	0.5, 0.5, 0.5, 6.5	4	1, 2, 4, 5
4	125.9	6.31	ddd	1.5, 6.5, 11.5	3, 5	2, 3, 6
5	137.5	6.00	ddd	0.5, 9.0, 11.5	4, 6	3, 9
6	47.4	3.36	dddddd	1.5, 1.5, 1.5, 5.0, 7.0, 8.5	5, 7, 9, 10	5, 7
7	59.3	3.65	ddd	3.5, 5.5, 13.0	6, 8_A, 8_B	none observed
8_A	45.0	3.57	dd	10.5, 13.5	7, 8_B	1, 7
8_B		2.44	dd	3.5, 10.5	7, 8_A	1, 2, 6, 7
9	139.1	5.46	ddd	7.0, 10.0, 17.5	6, 10	none observed
10_{trans}	116.2	4.97	ddd	1.5, 1.5, 17.5	9	9, 6
10_{cis}		4.94	ddd	1.5, 1.5, 10.5		

[a] The ^{13}C and ^{1}H NMR chemical shifts for the aromatic (C_6H_5) and silyl ether [$(CH_3)_3CSi(CH_3)_2$] atoms have been excluded. For a complete listing of all chemical shifts, see the EXPERIMENTAL SECTION.

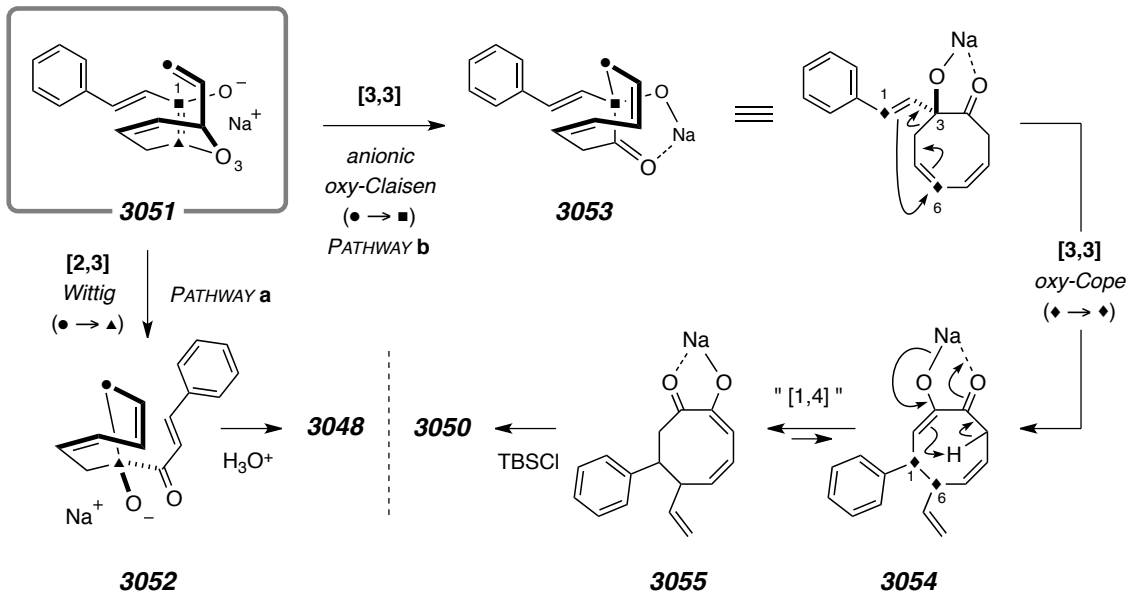
Intuitively, the structure of cyclooctadienone core of **3050** is clearly related to the product that one would expect to arise from [3,3]-sigmatropic rearrangement of the enolate derived from **3029-cis** (i.e., **3049**). However, the decoration of the 8-membered ring of **3050** with ethenyl and phenyl substituents was far less intuitive and, quite frankly, confusing. *What happened?* Well, as it turned out, the problem did not lie in the inherent reactivity of the enolate **3051**, but rather with the fortuitous positioning of the α,β-unsaturated ketone in the model substrate itself (Scheme III–20). The formation of **3048** under these conditions is now unexceptional and clearly the result of a [2,3]-Wittig rearrangement within **3051** (i.e., PATHWAY **a**). A considerably more interesting implication of these results, however, was that **3050** might ultimately be derived from an initial anionic oxy-Claisen rearrangement of the 1-alkoxy-3-oxa-1,5-hexadiene subunit within **3051**, an event that would give rise to the α-alkoxy cyclooctadienone **3053** (Scheme III–20, PATHWAY **b**). The unforeseen and completely overlooked consequence of incorporating the (*E*)-styrenyl appendage into the model substrates **3029-cis**/**trans** now became readily apparent. Namely, **3053** contains yet another (all-carbon) vicinal π,π-system. But this embedded 1,5-hexadiene is unique: It possesses an aromatic substituent at C1[274] and a highly donating alkoxide at C3,[275] two substitution patterns that are known to accelerate the rate of their [3,3]-sigmatropic rearrangements. Thus, were **3053** to undergo an anionic oxy-Cope rearrangement, then the 8-membered ring within this species would be simultaneously destroyed and then formed anew to provide a different cyclooctadienone (**3054**). Subsequent prototropic (formal [1,4]) shift to and silylation of the (more stable) dienolate **3055** would then give rise to the observed product (**3050**).

---

[274] Gentric, L.; Hanna, I.; Huboux, A.; Zaghdoudi, R. Rate Acceleration of Anionic Oxy-Cope Rearrangements Induced by an Additional Unsaturation. *Org. Lett.* **2003**, *5*, 3631–3634.

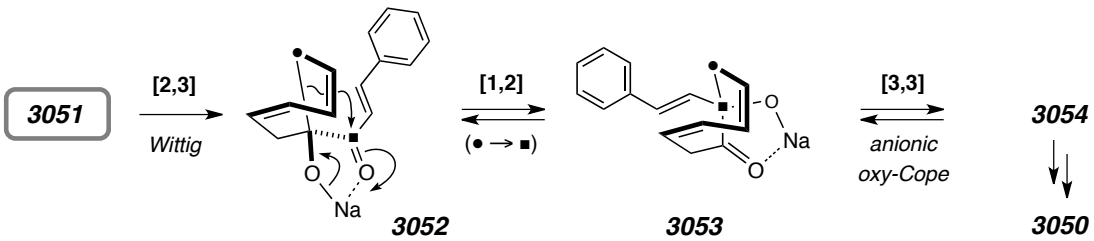
[275] Evans, D. A.; Golob, A. M. [3,3]Sigmatropic Rearrangements of 1,5-Diene Alkoxides. The Powerful Accelerating Effects of the Alkoxide Substituent. *J. Am. Chem. Soc.* **1975**, *97*, 4765–4766.

Scheme III–20 | Mechanistic hypotheses for the competitive formation of **3048** and **3050**.



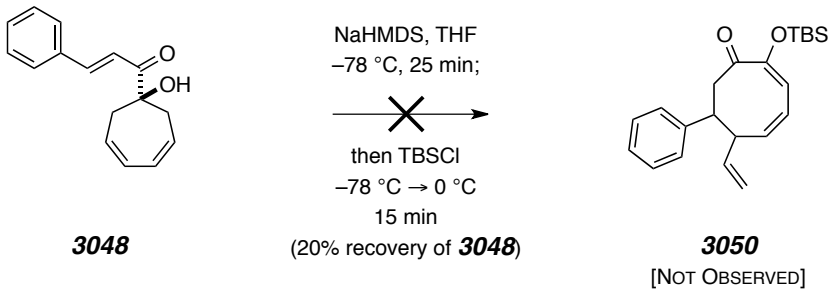
A different mechanistic proposal could be invoked that involves a more deep-seated rearrangement process (Scheme III–21). Specifically, it might be the case that the cyclooctadienone **3053** is *not* formed via anionic-oxy Claisen rearrangement, but rather through a [1,2]-rearrangement (C–C bond shift) within **3052**, the product derived from [2,3]-Wittig rearrangement of the enolate **3051**. This mechanistic possibility derives some support, albeit purely speculative in nature, from Hopkins' early study.[247]

Scheme III–21 | An alternative mechanistic rationalization for the formation of **3050**.



One experiment in particular did provide tentative support for the mechanistic scenario that has been proposed in Scheme III–20 for the formation of **3054**. If this intermediate did arise via reversible [1,2]-rearrangement of the sodium alkoxide **3052** (cf. Scheme III–21), then resubjection of purified **3048** to the same reaction conditions (i.e., NaHMDS, THF; then TBSCl) should give rise to some finite yield of the cyclooctadienone **3050**. When this reaction was carried out (Scheme III–22), the formation of **3050** was not detected. Although **3048** was only recovered in 20% yield,[276] this result nonetheless tentatively supported the initial proposal (Scheme III–20, PATHWAY **b**) that **3050** is ultimately derived from a pathway that involves sequential anionic oxy-Claisen- and anionic oxy-Cope rearrangements.

Scheme III–22 | Resubjection of **3048** to NaHMDS/TBSCl did not provide **3050**.



3048 (20% recovery of ***3048***) ***3050*** [NOT OBSERVED]

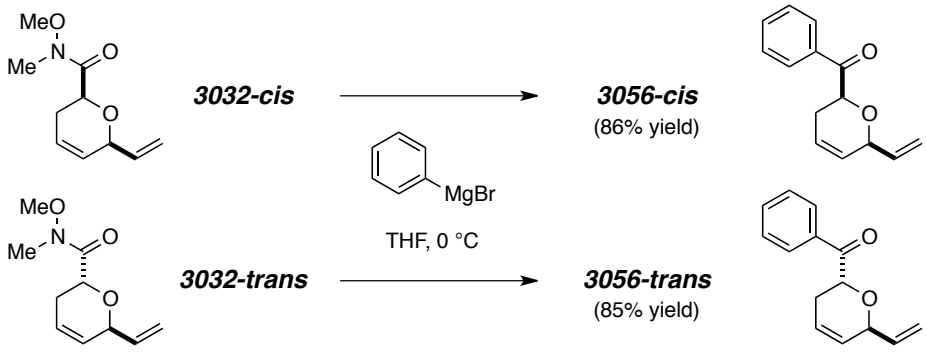
In light of the fact that **3048** *does not* give rise to **3050** upon deprotonation and treatment with TBSCl, the anomalous propensity of **3029-cis** and **3048** to undergo deuterium incorporation is somewhat puzzling (recall Scheme III–18). At the time that those observations were made, I speculated that deuterium was being incorporated into **3048**-d_n by a pathway involving the transient generation of and subsequent H–D exchange within the potassiated analog of **3053** (cf. Scheme III–21). But if the

[276] Evidence was also obtained [*MJJ-VII-127*] for the formation (in 19% yield) of a monosilylated dimeric by-product (**HR ESI-MS**: $C_{38}H_{46}O_4Si$ $[M+Na]^+$ requires 617.3058; found 617.3075). However, the structure of this compound was not fully delineated.

cyclooctadienone **3053** was being accessed reversibly under these conditions *and* it had a long enough lifetime to undergo partial deuterium incorporation, then why didn't it simply give rise to a product derived from an anionic oxy-Cope rearrangement (cf. Scheme III–20)? For the time being, these mechanistic issues will remain unresolved.

The realization that the cyclooctadienone alkoxide **3053** was an intermediate en route to **3050** was an exciting step forward. In particular, the tentative mechanistic proposal indicated that a product related to **3053** (via protonation) might be isolable were the offending unsaturation of the (*E*)-styrenyl appendage to be excised from the model substrates **3029-cis**/**trans**. Thus, in an effort to remove altogether the possibility of subsequent anionic oxy-Cope rearrangement within **3053**, a new model substrate was quickly identified and synthesized (Scheme III–23). Using the existing synthetic scaffold, the phenyl ketones **3056-cis**/**trans** were uneventfully produced upon exposure of the Weinreb amides **3032-cis**/**trans** to phenylmagnesium bromide in THF.

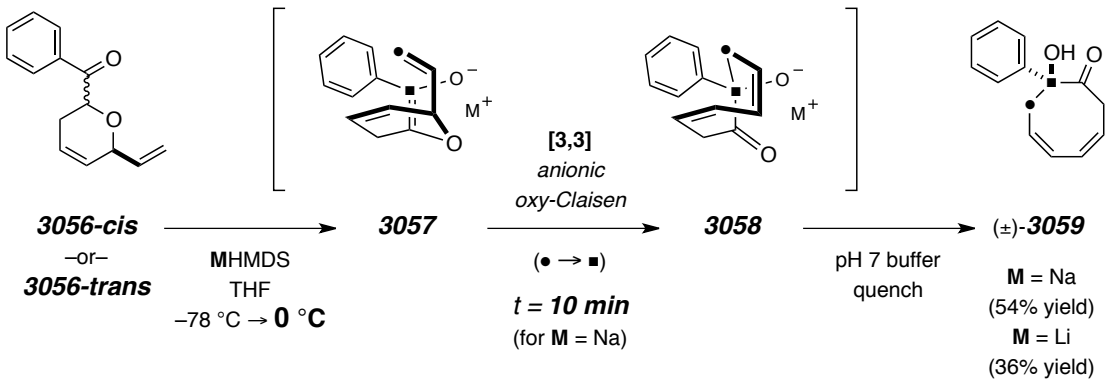
Scheme III–23 | High-yielding preparation of the phenyl ketones **3056-cis**/**trans**.



Gratifyingly, when a solution of **3056-cis** in THF was exposed to NaHMDS at low temperature (–78 °C) and the resulting enolate solution was allowed to warm (0 °C), the cyclooctadienone **3059** was isolated in decent yield (54%) after mild reaction quench (Scheme III–24). This was an exciting outcome indeed, since it implied that the enolate **3057** proceeded to generate the alkoxide **3058** via a rapid (t = 10 min at 0 °C!) anionic

oxy-Claisen rearrangement. Similarly, **3059** could be isolated, albeit in diminished yield (36%), after exposure of **3056-trans** to LiHMDS in THF under otherwise similar reaction conditions (i.e., –78 °C → 0 °C, 50 min). Clearly, the mass balance of these reactions was not perfect. But more importantly, the desired product (**3059**) was the major one.

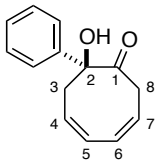
Scheme III–24 | Production of **3059** via anionic oxy-Claisen rearrangement of enolate **3057**.



A few observations regarding the reactions of Scheme III–24 are noteworthy. Analysis of the crude reaction mixtures by ^{1}H NMR revealed that at least two other minor, unidentified components were co-produced along with **3059** (which, incidentally, prevented the measurement of a meaningful half-life for the rearrangement). Present among then was *not* the product derived from [2,3]-Wittig rearrangement, as was evidenced by comparison with the ^{1}H NMR spectrum of an authentic sample of the (structurally related) product **3048**. Additionally, the cyclooctadienone **3059** could be isolated when **3056-trans** was treated with *t*-BuOK (THF, 0 °C, 15 min), but the crude product mixture was considerably more complex. In contrast, negligible (but observable) amounts of **3059** were produced when pure samples **3056-cis** or **3056-trans** were exposed to 1) $Bu_4N^+ {}^-OH$ (*i*-PrOH/MeOH, rt, 2 h), 2) 0.1 M NaOH [THF, rt, 20 d], and 3) DBU (CH_2Cl_2, rt, 27 h). The major product in all three cases was simply a 1:1 mixture of **3057-cis** and **3057-trans** (confirmed by ^{1}H NMR and GC-MS analyses).

The structure of **3059** rests upon firm ground. An arsenal of 1-D and 2-D NMR data have been collected and interpreted; these studies are summarized in Table III–4. As it turns out, the cyclooctadienone **3059** and a related analog that possesses a methyl group instead of a phenyl group are both known compounds.[277] However, no characterization data were provided for **3059**, and only IR bands were given for the latter derivative (ν = 3480 and 1710 cm^{-1}). Reassuringly, these values are in excellent agreement with those observed for **3059** (ν = 3465 and 1714 cm^{-1}).

Table III–4 | Carbon (^{13}C) and proton (^{1}H) NMR spectroscopic data for **3059** in C_6D_6 at 125 and 500 MHz, respectively.[a]



3059

ATOM	CARBON	PROTON			COSY	HMBC
#	δ_C	δ_H	mult.	*J* [Hz]	(→ ^{1}H-#)	(^{1}H → ^{13}C-#)
1	209.0	---	---	---	---	---
2	83.6	---	---	---	---	---
3_A	34.4	3.19	dd	9.0, 12.5	3_B, 4	1, 2, 4, 5
3_B		2.61	dd	7.0, 12.5	3_A, 4	1, 2, 4, δ 142.9
4	128.6	5.83	ddd	7.0, 9.0, 11.5	3_A, 3_B, 5	3, 5, 6, 7
5	127.8	5.69	ddddd	1.5, 1.5, 1.5, 5.0, 11.5	4, 6	2, 3, 4, 6, 7
6	125.7	5.51	dddd	2.0, 3.0, 5.0, 12.0	5, 7, 8_A, 8_B	4, 5, 7, 8
7	127.4	5.06	ddd	4.0, 6.5, 12.0	6, 8_A, 8_B	1, 5, 8
8_A	39.2	3.03	dddd	1.5, 3.0, 4.5, 16.5	6, 7, 8_B	1, 6, 7
8_B		2.41	br dd	6.0, 16.5	7, 8_A	1, 2, 6, 7
OH	---	4.87	s	---	---	1, 2, 3, 8, δ 142.9

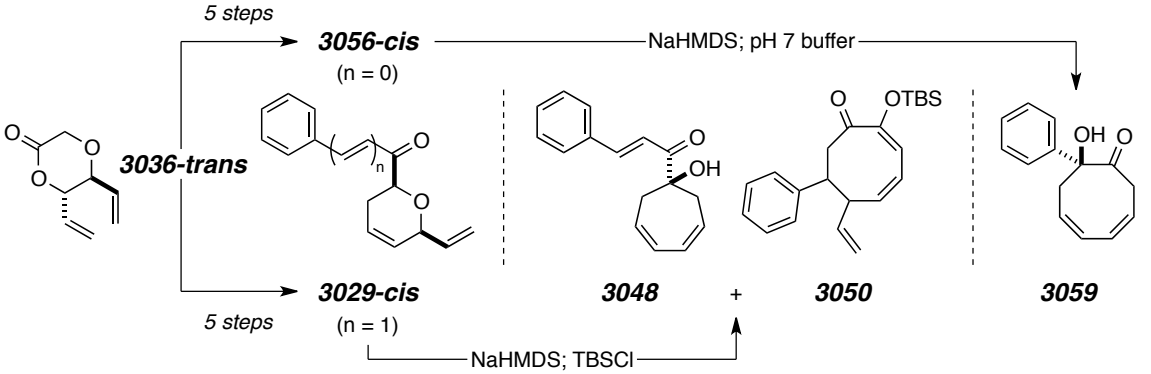
[a] The ^{1}H and ^{13}C resonances for the aromatic ring (C_6H_5) have been excluded for simplicity. A complete assignment has been provided in the EXPERIMENTAL SECTION.

277 Kitahara, Y.; Oda, M.; Miyakoshi, S.; Nakanishi, S. The Chemistry of 2-Hydroxy-2,4,6-cyclooctatrienone (1,7-π-Homotropolone). *Tetrahedron Lett.* **1976**, *17*, 2149–2152.

E. CONCLUSION

As part of a campaign designed to probe the hypothesis that penostatin F (**1-F**) and penostatin I (**1-I**) arise via spontaneous [3,3]-sigmatropic rearrangements, the homologous 2,6-disubstituted dihydropyran model substrates **3029-cis** and **3056-cis** were prepared by five-step synthetic sequences that emanated from the dioxanone **3036-trans** (Scheme III–24). Serendipity prevailed in the reactions of the enolate derived from **3029-cis**, wherein the unusual silyl enol ether **3050** emerged from two sequential [3,3]-sigmatropic events. On the basis of mechanistic considerations, the base-induced reactions of modified model substrates (**3057-cis**) eventuated in the isolation of **3059**.

Scheme III–24 | Summary of Chapter III achievements.



CHAPTER IV

PENOSTATIN G AND H

MODEL SYNTHESIS STUDIES

A. HYPOTHESIS FOR THE BIOSYNTHESIS OF PENOSTATINS G AND H

HYPOTHESIS STATEMENT:

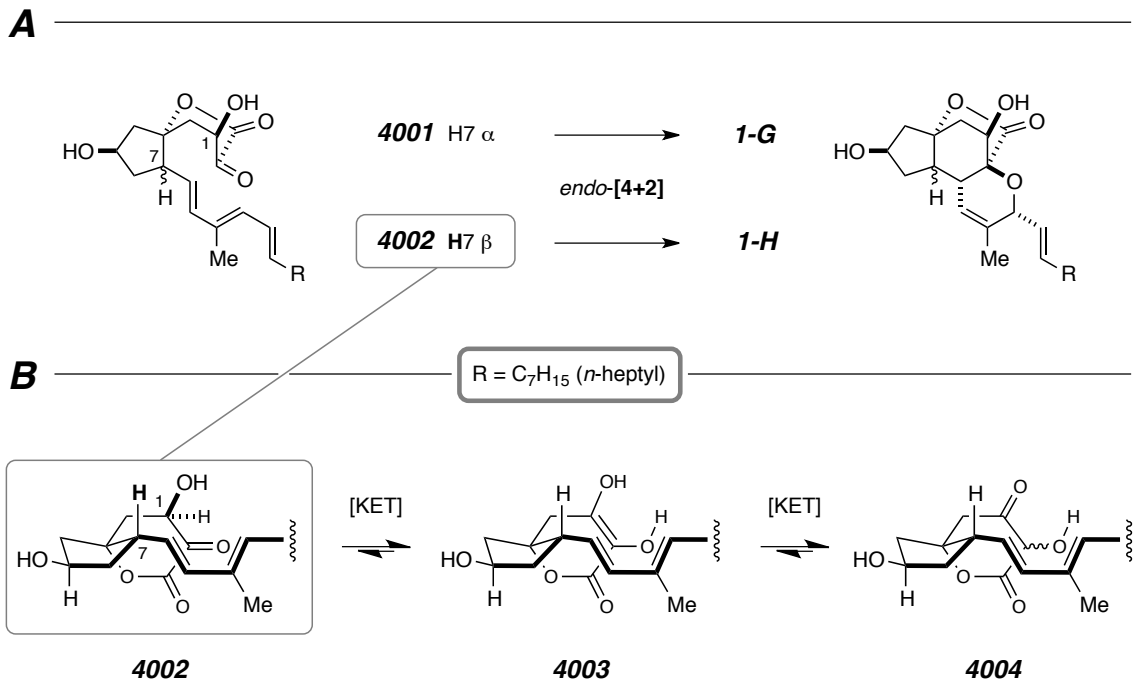
> *PENOSTATIN G (**1-G**) AND PENOSTATIN H (**1-H**) BOTH ARISE VIA SPONTANEOUS INTRAMOLECULAR HETERO-DIELS–ALDER REACTIONS OF THE C7 EPIMERIC β-HYDROXY α-KETO LACTONES **4001** AND **4002**, RESPECTIVELY.*

The rather unusual chemical structures of penostatin G (**1-G**) and penostatin H (**1-H**) set them apart from the other members of the penostatin family that have thus far been discussed. Of particular interest is the fact that these two metabolites, rather than sharing a tetraepimeric relationship as **1-A**/**1-B** and **1-I**/**1-F** do, are simply *epimeric* at C7. Moreover, **1-G** and **1-H** are *less* highly oxidized (by one H_2 equivalent). It is apparent, therefore, that there can be no direct comparison made here with those late stage biosynthetic intermediates (e.g., the pentaenol **2001**, Scheme II–1) that give rise to **1-A**, **-B**, **-I**, and **-F**. However, the reader will recall that, in Chapter II, Section A–2 of this Thesis, a pair of isomeric β-keto acids **2008** or **2009** were proposed as the ultimate starting point for C9 oxidation. It seems plausible that the terminal carboxyl groups of these linear precursors are manifest in **1-G** and **1-H** in the form of the β-hydroxy α-keto lactone.

Scheme IV–1 | Proposed biosynthetic origin of penostatin G (**1-G**) and penostatin (**1-H**).

A: IMHDA cycloadditions of the C7 epimeric spirocyclic γ-lactones **4001** and **4002**.

B: Generation of **4002** from the (more stable) tautomers **4003** and **4004**.



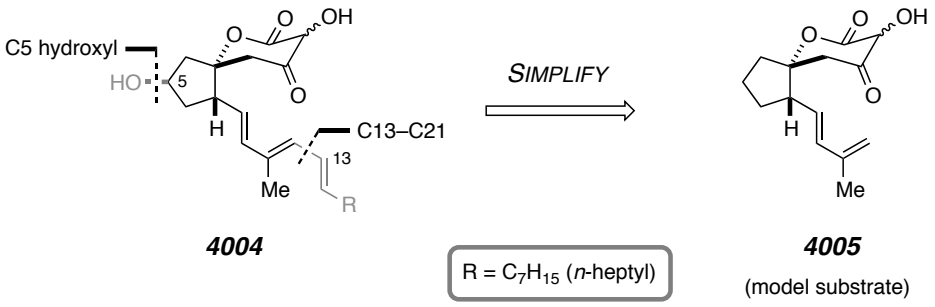
Were the C7 epimeric spirocyclic γ-lactones **4001** and **4002** to undergo IMHDA cycloaddition, they would give rise to **1-G** and **1-H**, respectively (Scheme IV–1A). The tautomeric series of intermediates **4002**–**4004**, which bear relevance to the formation of **1-H**, deserve further comment (Scheme IV–1B). Note that the stereoselective formation of **1-H** requires an *endo* approach of the diene with respect to the carbonyl dienophile (as depicted in **4002**) wherein cycloaddition must occur through the more sterically congested C1 hydroxyl epimer. Furthermore, among the manifold of equilibrating species, **4002** would actually be expected to be the *least* stable tautomer and, therefore, the least populated at equilibrium. However, in an aqueous biological medium, the interconversion between **4003** and **4002** would be arbitrated by an external water molecule (acting as a proton shuttle); thus, protonation from the more sterically

accessible α-diastereoface of the enediol (the back face as depicted in **4003**) would be anticipated and the C1 β-OH epimer should be formed more rapidly. The rate at which **4002** reverts to the enediol **4003** could be sufficiently slow relative to the IMHDA event, which would require this carbonyl dienophile to be exceedingly reactive.

B. MODEL SUBSTRATE DESIGN

Of the three intermediates depicted in Scheme IV–1B, the one most readily amenable to laboratory synthesis is the α-hydroxy β-keto lactone **4004**. In principle, this intermediate could be prepared through an adaptation of the synthetic route that was developed in Chapter II of this Thesis to access (*Z*)-**2001**. However, in Chapter III the proposed hypothesis for the biosynthetic origin of **1-I** and **1-F** was evaluated by the preparation and study of the reactivity of (the enolates derived from) simplified 9-*epi*-**1-A** (and **1-A**) analogs. In light of the success that was had during the course of that work, it was reasoned that a similar approach could be brought to bear on the hypothesis presented in Scheme IV–1 (Scheme IV–2). Specifically, the spirocyclic γ-lactone **4005** lacks both the C5 hydroxy group and the C13–C21 side chain that are present in **4004**, but retains all of the essential functionality that would be required for the proposed IMHDA reaction.

Scheme IV–2 | Identification of a simplified model for **4004** via removal of the C5 hydroxy group and the C13–C21 side chain.



4004 ***4005*** (model substrate)

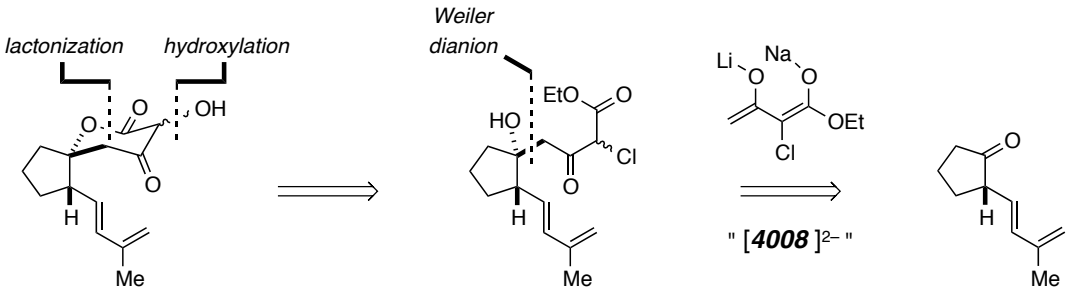
R = C_7H_{15} (*n*-heptyl)

C. SYNTHESIS STRATEGIES TOWARD THE SPIROCYCLIC γ-LACTONE **4005**

C–1. RETROSYNTHETIC ANALYSIS

It was anticipated that the α-hydroxy β-keto lactone **4005** would arise by treatment of an α-chloro β-keto lactone precursor with trimethylammonium acetate[278] (Scheme IV–3). The hydroxy ester **4006**, itself derived from addition of the chlorinated Weiler dianion[17,279] [**4008**]$^{2-}$ to the racemic homoallylic ketone **4007**, would in turn serve as a precursor to the requisite α-chloro intermediate via lactonization.

Scheme IV–3 | Retrosynthetic analysis of the model substrate **4005**.



Two distinct approaches were explored for the preparation of the deceptively simple homoallylic ketone **4007** (Scheme IV–4). In the first of these approaches, it was envisioned that dienylation[280] of the potassium enoxytriethylborate [**4009**–BEt_3]$^-$ with the

---

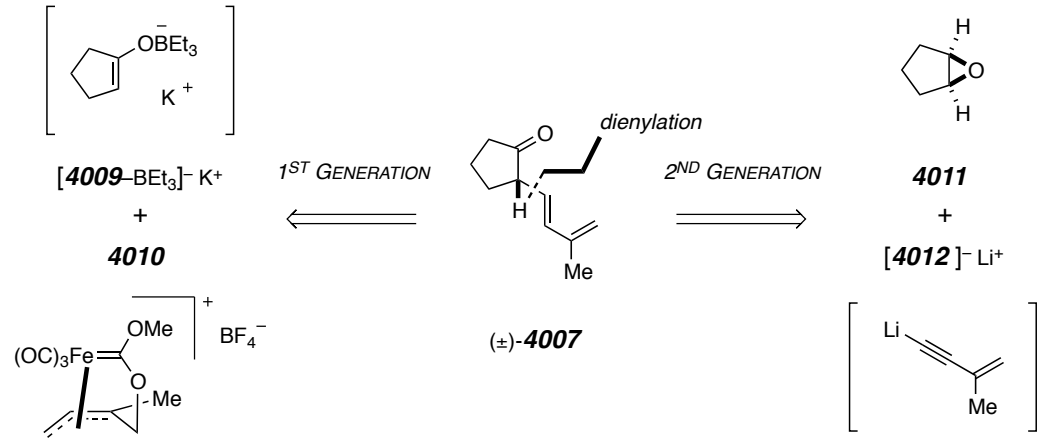
278 Ziegler, E.; Wittmann, H.; Sterk, H. Über Reaktionen mit Betain, 24. Mitt. [1]: Über Umsetzungen von Trimethylammoniumessigsäurebetain mit reaktiven Halogenverbindungen. *Monatsh. Chem.* **1989**, *120*, 907–912.

279 Snider, B. B.; Patricia, J. J. Manganese(III)-Based Oxidative Free-Radical Cyclizations. Oxidative Cyclization and Aromatization of 3-Oxo-6-heptenoate Esters. *J. Org. Chem.* **1989**, *54*, 38–46.

280 Böhmer, J.; Hampel, F.; Schobert, R. Regioselective Synthesis of Substituted (3*E*)-1,3-Dienes from Chelated Allyl–Ironcarbene Complexes and Potassium Enoxyborates. *Synthesis* **1997**, 661–667.

(η^3-allyl)tricarbonyliron carbene complex **4010** and subsequent demetalation[281] would provide a concise route to **4007**. As an alternative to this rather exotic 1ST generation route, it was anticipated that cyclopentene oxide (**4011**) could also serve as a precursor to **4007** via Yamaguchi alkynylation[282] with the lithium acetylide derived from 2-methylbut-1-en-3-yne (**4011**). Subsequent *trans* reduction[283] of the resulting homopropargylic alcohol and oxidation would allow one to arrive at the target molecule.

Scheme IV–4 | 1ST- and 2ND Generation approaches to the homoallylic ketone **4007**.



281 Böhmer, J.; Förtsch, W.; Schobert, R. Selective Demetalations of Iron Diene Complexes. Expidient Synthesis of Substituted (*Z*)-Allylalcohols. *Synlett* **1997**, 1073–1074.

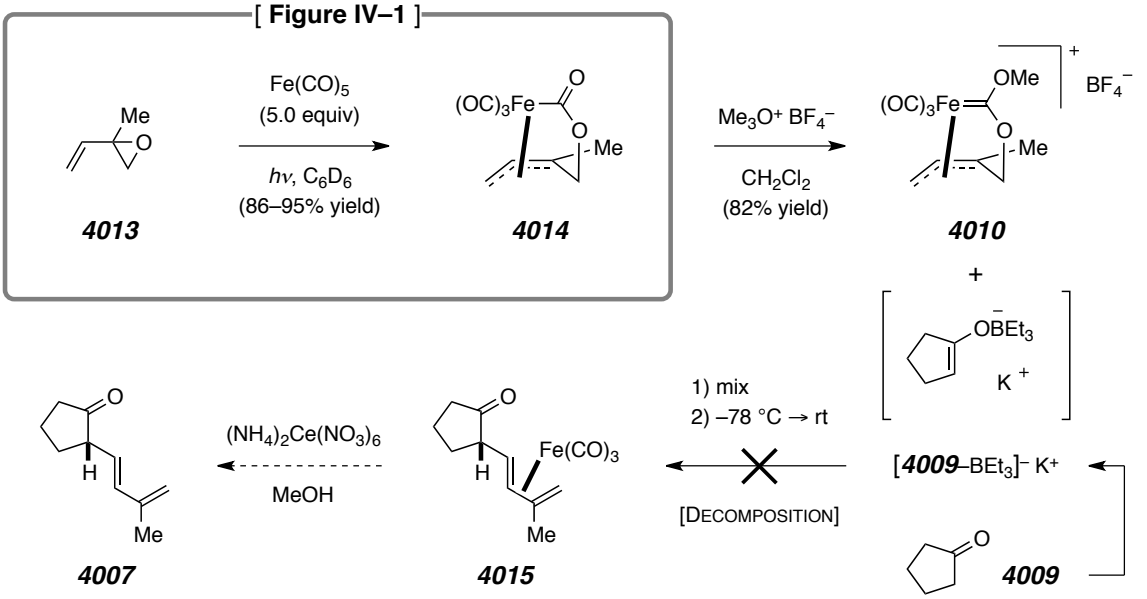
282 (a) Yamaguchi, M.; Hirao, I. An Efficient Method for the Alkynylation of Oxiranes Using Alkynyl Boranes. *Tetrahedron Lett.* **1983**, *24*, 391–394. (b) Aubrecht, K. B.; Winemiller, M. D.; Collum, D. B. BF_3-Mediated Addition of Lithium Phenylacetylide to an Imine: Correlations of Structures and Reactivities. BF_3•R_3N Derivatives as Substitutes for BF_3•OEt_2. *J. Am. Chem. Soc.* **2000**, *122*, 11084–11089.

283 Crousse, B.; Alami, M.; Linstrumelle, G. Stereoselective Reduction of Conjugated Homopropargylic Alcohols to (*E*)-Homoallylic Alcohols by Sodium Bis(2-methoxyethoxy) Aluminum Hydride. *Synlett* **1997**, 992–994.

C–2. 1ST GENERATION APPROACH

The preparation and subsequent reactivity of the (η^3-allyl)tricarbonyliron carbene complex **4010** is described in Scheme IV–5. Its direct precursor, the known (η^3-allyl)tricarbonyliron complex **4014**,[284] was prepared by irradiation (Rayonet reactor) of a C_6D_6 (or C_6H_6) solution of isoprene monoxide (**4013**) and excess iron pentacarbonyl [$Fe(CO)_5$]. This reaction could be easily monitored by ^1H NMR spectroscopy (Figure IV–1) wherein relatively clean conversion to the desired product was observed over the course of 69 h. It is interesting to note the substantial upfield shift of the resonances corresponding to the η^3-allyl fragment of **4014** (▲, ◆, and ●) in comparison to the more pedestrian location of the resonances for the same protons in **4013** (▲, ◆, and ●).

Scheme IV–5 | Synthesis and reactivity of the (η^3-allyl)tricarbonyliron carbene complex **4010**.



[284] (a) Aumann, R.; Ring, H.; Krüger, C.; Goddard, R. Untersuchungen zur Synthese ungesättigter δ-Lactone durch Cyclocarbonylierung von Vinyloxiranen mit Übergangsmetall-Komplexen. *Chem. Ber.* **1979**, *112*, 3644–3671. (b) Annis, G. D.; Ley, S. V.; Self, C. R.; Sivaramakrishnan, R. Preparation of Lactones *via* Tricarbonyliron–Lactone Complexes. *J. Chem. Soc., Perkin Trans. 1* **1981**, 270–277.

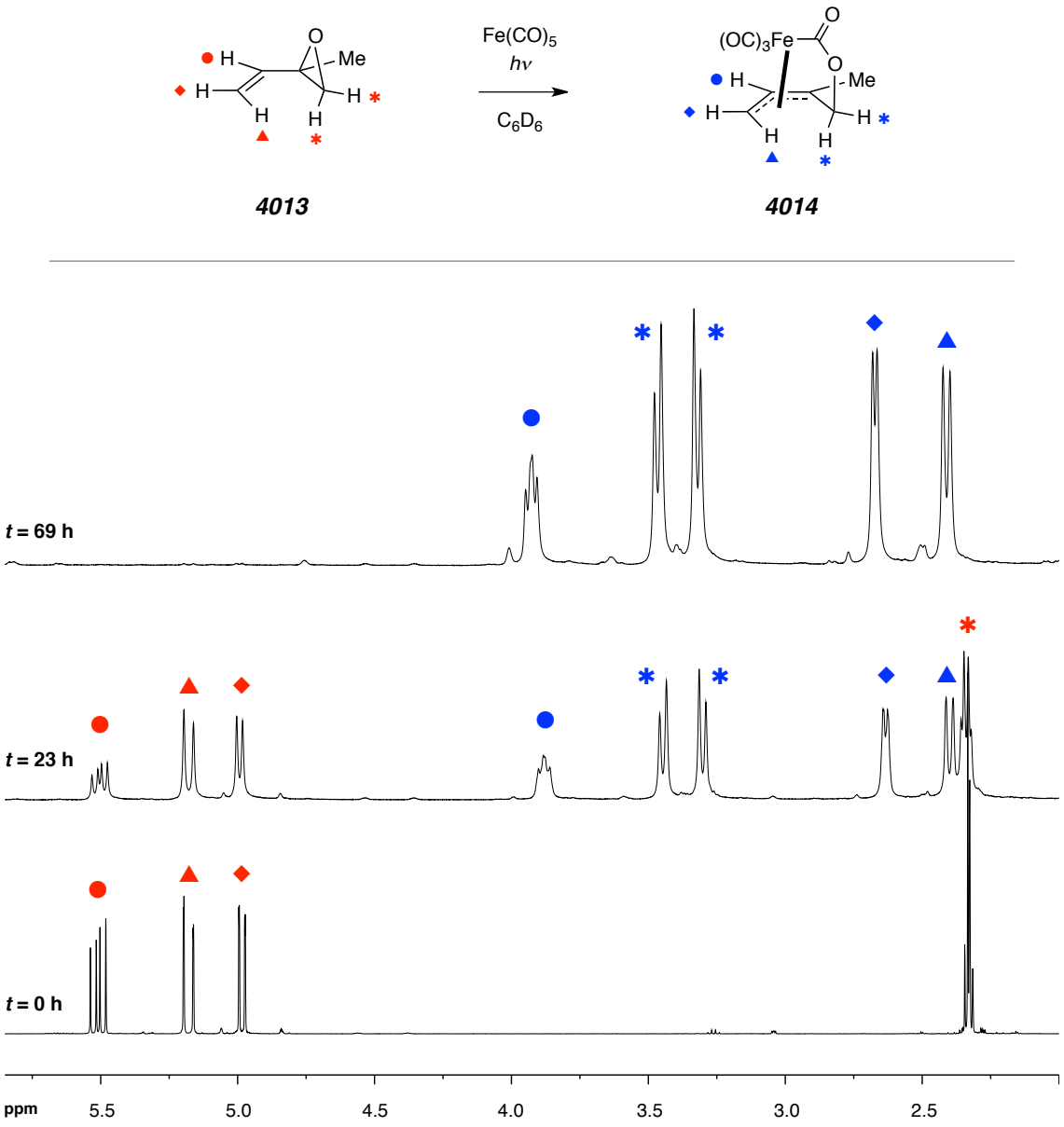


Figure IV–1 | Formation of the (η^3-allyl)tricarbonyliron complex **4014** from isoprene monoxide (**4013**) observed by ^{1}H NMR spectroscopy (500 MHz, C_6D_6).

The (η^3-allyl)tricarbonyliron lactone complex **4014** was subsequently exposed to trimethyloxonium tetrafluoroborate (Meerwein's salt) according to the procedure of

Schobert and co-workers[285] to provide the (η^3-allyl)tricarbonyliron carbene complex **4010** (Scheme IV–5). With this material in hand, the stage was now set to examine its subsequent use in the dienylation of cyclopentenone (**4009**). Although Negishi's original protocol[286] called for the use of potassium hydride (KH) it was discovered that KHMDS gave superior results, presumably because the titer of this latter reagent can be more reliably maintained. A preliminary experiment was conducted wherein the potassium enoxytriethylborate [**4009**–BEt_3]$^-$ was generated by 1) treatment of **4009** with KHMDS (–78 °C) and 2) addition of triethylborane in THF to the resulting enolate (–78 °C → rt), and then allowing this species to react with excess allyl bromide. Reassuringly, a relatively clean reaction took place (GC-MS analysis) to give α-allylated **4009**. However, when [**4009**–BEt_3]$^-$ was generated under otherwise identical conditions and then added to a slurry of **4010** in THF, the desired η^4-tricarbonyliron–diene complex **4015** could not be identified by examination of the crude reaction profile by ^{1}H NMR spectroscopy. Had **4015** been cleanly formed, its subsequent demetalation with CAN in MeOH would have afforded **4007**.

C–3. 2ND GENERATION APPROACH

The failure of the previous synthesis strategy to produce any of the ketone **4007** coupled with the rather exotic nature of the reagents employed (i.e., **4010**) required that a more practical strategy be developed. It was soon realized that this requirement could be fulfilled by a sequence emanating from cyclopentene oxide (**4011**) and 2-methylbut-1-en-3-yne (**4012**), since abundant quantities of both can be readily accessed by textbook reactions (Scheme IV–6). The union of these two fragments was accomplished by

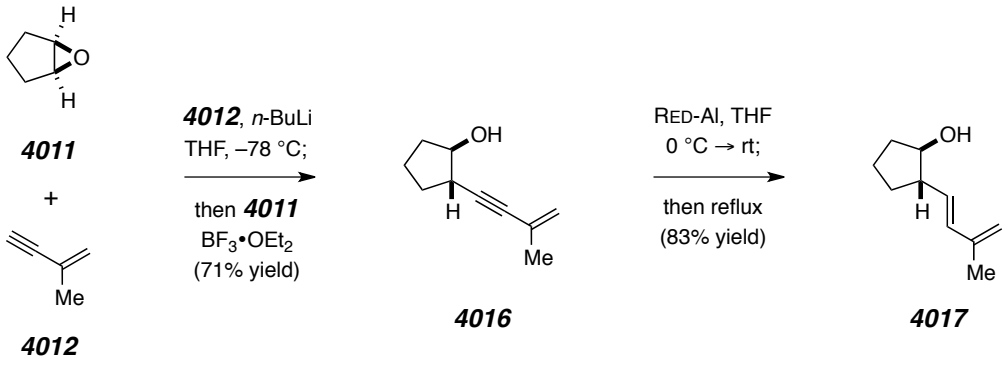
---

285 Förtsch, W.; Hampel, F.; Schobert, R. Synthese, Kristallstruktur und Reaktionen neuartiger metallacyclischer Dioxo- und Aminooxocarben-Komplexe des Eisens. *Chem. Ber.* **1994**, *127*, 711–715.

286 Negishi, E.; Idacavage, M. J. A Highly Selective Method for α-Alkylation of Ketones via Potassium Enoxytrialkylborates. *Tetrahedron Lett.* **1979**, *20*, 845–848.

Yamaguchi alkynylation[282] of **4011** with the acetylide derived from **4012**, which delivered the homopropargylic alcohol **4016** in commendable yield.

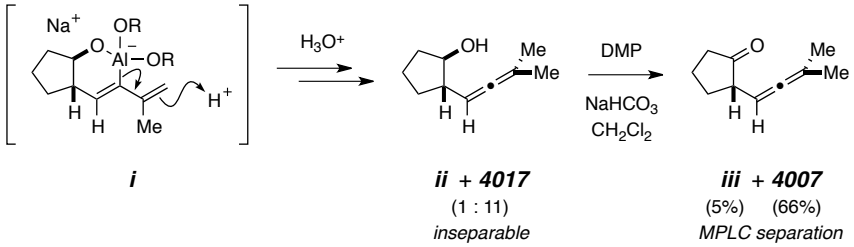
Scheme IV–6 | Synthesis of the homoallylic alcohol **4017** via Yamaguchi alkynylation of cyclopentene oxide (**4011**) and subsequent *trans*-hydrometalation of the enyne **4016**.



Exposure of **4016** to sodium bis(2-methoxyethoxy)aluminum hydride (RED-Al®) in refluxing THF affected intramolecular *trans*-hydrometalation[283] after which the (*E*)-1,3-dienol **4017**[287] was isolated as a single isomer ($^3J_{trans}$ = 15.5 Hz) (Scheme IV–6).

---

[287] Interestingly, under these hydroalumination conditions a small amount of the allene alcohol **ii** was also produced along with the (*E*)-1,3-diene **4017**. Although **ii** could not be removed chromatographically at this stage, its presence in purified samples of **4017** was evidenced by a characteristic downfield, seven-line pattern in the ^{1}H NMR spectrum {δ 4.97 [septet, J = 3.0 Hz, 1H, *H*C=C=C(CH$_3$)$_2$]}. It seems plausible that **ii** arose by vinylogous (rather than *ipso*) protonolysis of the sp^2-carbon–aluminum bond within the intermediate sodium alanate **i**.



It was subsequently discovered that the allenyl ketone **iii**, which was co-produced upon DMP- or IBX-mediated oxidation of the **ii**/**4017** mixture, ran slightly faster on SiO_2 and could be separated from the dienyl ketone **4007** by MPLC.

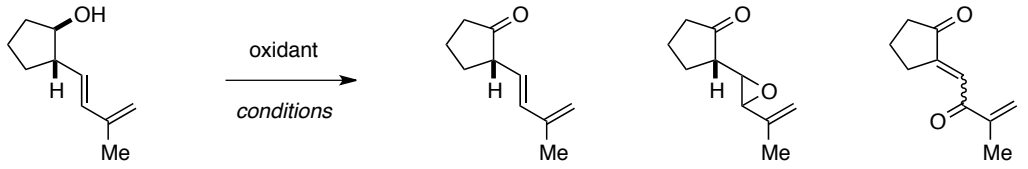
Now armed with a simple and straightforward method to prepare the homoallylic alcohol **4017**, the only obstacle that remained was its subsequent oxidation. It was initially assumed that this transformation could be trivially accomplished with any one of the most common sets of reaction conditions; but alas, such was not the case (Table IV–1). Among the "off-the-shelf" methods that were initially investigated, PDC (entry 1), the Swern oxidation (entry 2), TEMPO/PhI(OAc)$_2$[263] (entry 3), and the Parikh–Doering oxidation[264] (entry 4) all gave rise to complex product mixtures in which **4007** was a minor component (if it was present at all). In a completely unexpected turn of events, exposure of **4017** to TPAP/NMO (Ley oxidation,[32] entry 5) resulted in no observable reaction. Subsequent to this result it was discovered that Sharpless and co-workers have documented similar phenomenon in the $RuCl_2(PPh_3)_3$- and $Ru_3(CO)_{12}$-catalyzed oxidations of homoallylic alcohols.[288a] Based upon their observations, it seems plausible that the intermediate ruthenate ester that is generated upon reaction of TPAP with **4017** might form a stable olefin complex[288b] (**4020**, Scheme IV–7A) that inhibits catalyst turnover.

Data for **iii**: [*MJJ-I-210/254*] Diagnostic ^{1}H NMR (500 MHz, $CDCl_3$) resonances: δ 5.11 [septet, J = 2.5 Hz, 1H, *H*C=C=C(CH$_3$)$_2$], 2.76-2.71 [nfom, 1H, C(O)C*H*], 1.71 [d, J = 3.0 Hz, 3H, HC=C=C(C*H*$_3$)$_2$], and 1.69 [d, J = 2.5 Hz, 3H, HC=C=C(C*H*$_3$)$_2$].

GC / LR EI-MS [5025015]: t_R 6.88 min; *m*/*z* (rel. int.) 150 (3, $M^{+\bullet}$), 135 (18, $M^{+\bullet}$–$CH_3^{\bullet}$), 122 (100), 107 (76), 93 (15), 91 (23), 79 (65), and 77 (30). This material partially decomposed upon entering the GC injection port, as evidenced by the presence of three additional, slightly less intense peaks (t_R 7.89, 8.00, and 8.16 min).

288 (a) Sharpless, K. B.; Akashi, K.; Oshima, K. Ruthenium Catalyzed Oxidation of Alcohols to Aldehydes and Ketones by Amine-*N*-oxides. *Tetrahedron Lett.* **1976**, *17*, 2503–2506. (b) "*We speculate that certain homoallylic alcohols (note case 17 is an exception) form very stable alkoxyolefin complexes with ruthenium (II?) and thus tie up the catalyst…*" (ref 288a)

Table IV–1 | A survey of various alcohol oxidation conditions to convert **4017** into, among other products, the desired homoallylic ketone **4007**.



4017 ***4007*** ***4018*** (*dr* 1:1) ***4019*** (single isomer)

entry	oxidant	*conditions*	product(s) [% yield]
1	PDC	4Å MS, CH_2Cl_2, rt	---[a]
2	DMSO + $(COCl)_2$	Et_3N, CH_2Cl_2, –78 °C → rt	---[a]
3	TEMPO (cat.) + $PhI(OAc)_2$	CH_3CN / pH 7 buffer (1:1) (CH_2Cl_2)	---[a]
4	DMSO + SO_3•pyr	*i*-Pr_2NEt, CH_2Cl_2, 0 °C → rt	---[a]
5	TPAP (cat.) + NMO	4Å MS, CH_2Cl_2, rt	[NO REACTION]
6	DMP (2.3 equiv)	$NaHCO_3$, CH_2Cl_2 ($CDCl_3$), rt	***4018*** [53]
7	DMP (1.1 equiv)		***4007*** [71]
8	IBX (2.0 equiv)[b]	DMSO (DMSO-d_6), rt	***4007*** [36[d]] + ***4019*** [9[e]]
9	IBX (1.7 equiv)[c]		***4007*** [55] + ***4019*** [trace]

[a] A complex product mixture was obtained in which **4007** was *not* the major component. [b] IBX was added to a solution of the alcohol in DMSO (normal addition). [c] A solution of the alcohol in DMSO was added to a homogeneous solution of IBX in DMSO (inverse addition). [d] 39% yield based on recovered starting material (BRSM). [e] 10% yield BRSM.

Oxidation of **4017** with the venerable Dess–Martin periodinane,[163] which can be carried out under slightly acidic (or neutral, if buffered with $NaHCO_3$) reaction conditions, was viewed as the next most obvious alternative. When an excess of DMP (2.3 equiv) was employed (entry 6), the starting material was cleanly consumed over the course of 2.5 h and the formation of the ketone **4007** was presumed. However, upon

reaction work-up and purification, it was discovered that the epoxide **4018**[289] was the only isolable product. Although **4007** could be obtained (71% yield) as essentially a single product by careful control of the stoichiometry (entry 7), the mechanism by which **4018** was formed deserves further comment. As part of their exploitation of iodine(V) reagents in organic synthesis, Nicolaou and co-workers often observed the competitive epoxidation of anilides that contained a conjugated diene subunit.[290] They briefly interrogated[290b] the mechanism of these processes and discovered that Ac-IBX[291] (i.e., the hydrolysis product of DMP), rather than DMP itself, was the likely culprit responsible for diene epoxidation. The mechanism that was tentatively proposed for this transformation,[290b] which has been adapted here for the epoxidation of **4007** (Scheme IV–7B), invokes the (perhaps) concerted addition of the I–O bond of Ac-IBX onto the internal olefin of the conjugated diene within **4007**. Then, the type of rearrangement

---

289 [*MJJ-I-202*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.15 [dddd, *J* = 1.0, 1.0, 1.0, 1.0 Hz, 1H, $(CH_3)C{=}CH_2$], 5.14 [dddd, *J* = 1.0, 1.0, 1.0, 1.0 Hz, 1H, $(CH_3)C{=}CH_2$], 5.01 [dddd, *J* = 1.5, 1.5, 1.5, 1.5 Hz, 1H, $(CH_3)C{=}CH_2$], 5.00 [dddd, *J* = 1.5, 1.5, 1.5, 1.5 Hz, 1H, $(CH_3)C{=}CH_2$], 3.39 [d, *J* = 2.5 Hz, 1H, CHCH(O)C*H*], 3.23 [d, *J* = 2.5 Hz, 1H, CHCH(O)C*H*], 3.20 [dd, *J* = 2.5, 4.0 Hz, 1H, CHC*H*(O)CH], 3.06 [dd, *J* = 2.5, 4.0 Hz, 1H, CHC*H*(O)CH], 2.47 [ddd, *J* = 4.0, 8.5, 8.5 Hz, 1H, C*H*CH(O)CH], 2.38-2.27 [m, 3H, overlapping C*H*CH(O)CH and $C(O)CH_2CH_2CH_2$], 2.24-2.04 [m, 6H, overlapping $C(O)CH_2CH_2CH_2$], 1.91-1.73 [m, 4H, overlapping $C(O)CH_2CH_2CH_2$], 1.66 [dd, *J* = 1.0, 1.0 Hz, 3H, $(CH_3)C{=}CH_2$], and 1.64 [dd, *J* = 1.0, 1.0 Hz, 3H, $(CH_3)C{=}CH_2$].
HR ESI-MS: $C_{10}H_{14}O_2$ $[M+Na]^+$ requires 189.0886; found 189.0882.
GC / LR EI-MS [5025015]: t_R 7.60 and 7.66 min; *m*/*z* (rel. int.) 166 (1, $M^{+\bullet}$), 151 (4, $M^{+\bullet}–CH_3^{\bullet}$), 148 (3), 138 (5), 137 (6), 109 (23), 95 (90), 84 (100), 83 (73, $M^{+\bullet}–C_5H_7O^{\bullet}$), 82 (42), 81 (63), 79 (34), 68 (62), 67 (77), and 55 (62). This material partially decomposed upon entering the GC injection port, as evidenced by the presence of four other, slightly less intense peaks (t_R 7.03, 7.73, 7.81, and 8.61 min).

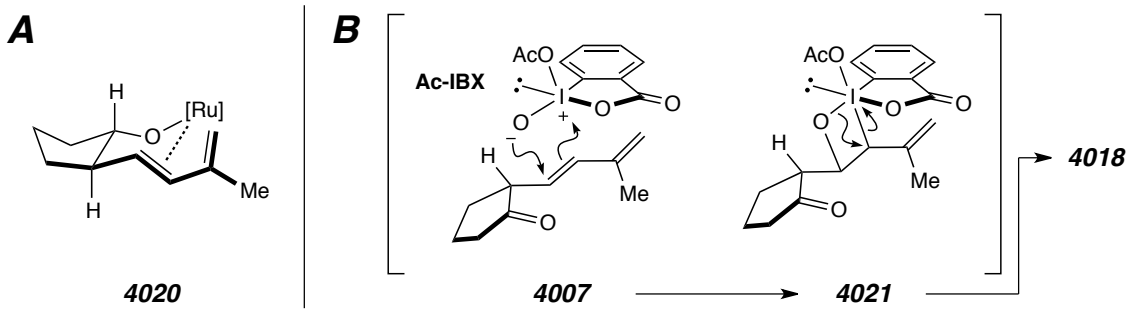
290 (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y. –L.; Sugita, K. Iodine(V) Reagents in Organic Synthesis. Part 1. Synthesis of Polycyclic Heterocycles via Dess–Martin Periodinane-Mediated Cascade Cyclization: Generality, Scope, and Mechanism of the Reaction. *J. Am. Chem. Soc.* **2002**, *124*, 2212–2220. (b) Nicolaou, K. C.; Sugita, K.; Baran, P. S.; Zhong, Y. –L. Iodine(V) Reagents in Organic Synthesis. Part 2. Access to Complex Molecular Architectures via Dess–Martin Periodinane-Generated *o*-Imidoquinones. *J. Am. Chem. Soc.* **2002**, *124*, 2221–2232.

291 Dess, D. B.; Martin, J. C. A Useful 12–I–5 Triacetoxyperiodinane (the Dess–Martin Periodinane) for the Selective Oxidation of Primary and Secondary Alcohols and a Variety of Related 12–I–5 Species. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

implied by the curly arrows within **4021** would account for the formation of the epoxide **4018**.

That the ketone **4007**, and not the alcohol **4017**, was the substrate for this epoxidation was established by an NMR experiment. When the oxidation of **4017** was carried out in $CDCl_3$ by the incremental addition of DMP (*ca.* 0.5 and 1.0 equiv) and the ^1H NMR spectrum collected after each addition, the clean formation of **4007** was observed and only a trace amount of **4018** could be detected. Only when an excess of DMP (2.6 equiv) was added could the formation of both **4018** and **4007** be observed.

Scheme IV–7 | **A**: A potential rationalization for the observation that **4017** was unreactive under Ley's TPAP/NMO system. **B**: Proposed mechanism for the formation of the epoxide **4018** by Ac-IBX-mediated oxidation of the homoallylic ketone **4007**.



The IBX-mediated oxidation[292] of **4017** was also explored (Table IV–1) and quite a different (and surprising) series of events took place. When a sample of the alcohol in DMSO was treated with this oxidant (2.0 equiv, entry 8), the desired ketone **4007** (36% yield) was indeed produced, but so too was the unusual enedione **4019**[293] (9% yield).

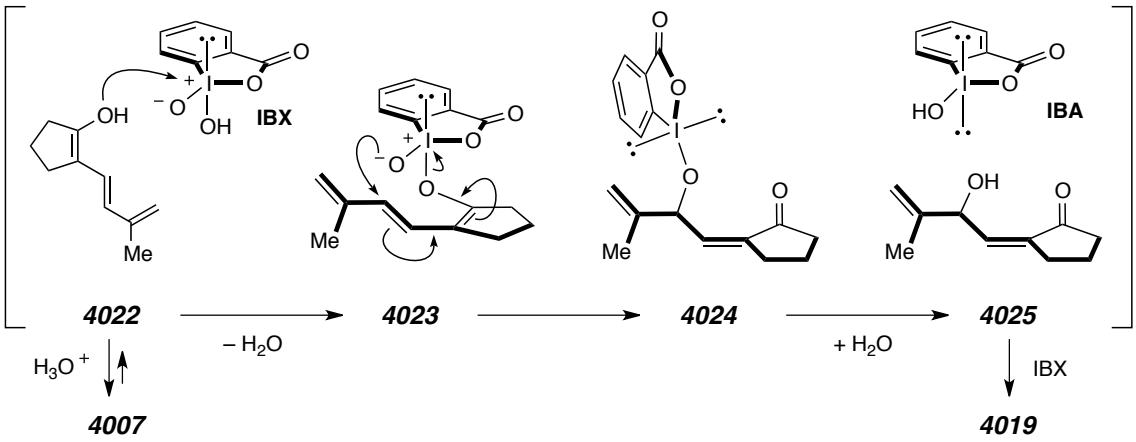
---

[292] Frigerio, M.; Santagostino, M. A Mild Oxidizing Reagent for Alcohols and 1,2-Diols: *o*-Iodoxybenzoic Acid (IBX) in DMSO. *Tetrahedron Lett.* **1994**, *35*, 8019–8022.

[293] [*MJJ-I-254*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.34 [dd, *J* = 3.0, 3.0 Hz, 1H, C(O)C=C*H*C(O)], 6.10 [ddd, *J* = 1.0, 1.0, 1.0 Hz, 1H, $(CH_3)C=CH_2$], 5.92 [ddd, *J* = 1.5, 1.5, 1.5 Hz, 1H, $(CH_3)C=CH_2$], 3.07 [ddd, *J* = 3.0, 7.5, 7.5 Hz, 2H, $C(O)CH_2CH_2CH_2C=CH$], 2.42 [dd, *J* = 8.0, 8.0 Hz, 2H, $C(O)CH_2CH_2$–

Although the configuration of this product could not be determined, it displayed a characteristic downfield ^{1}H NMR resonance [δ 7.34 (dd, J = 3.0, 3.0 Hz, 1H)] corresponding to the β-alkenyl proton of the enedione. Here again, the fact that **4007** was an intermediate in the pathway leading to **4019** was ascertained by monitoring the oxidation of **4017** with IBX (1.9 equiv) in DMSO-d_6 by ^{1}H NMR spectroscopy. In this experiment, the clean formation of the **4007** was observed after 4.5 h and only then did a significant quantity of **4019** build up.

Scheme IV–8 | Proposed mechanism for the formation of the enedione **4019**.



A reasonable mechanism for the formation of **4019** has been offered in Scheme IV–8. Water is one of the by-products of oxidation; in addition, IBX is quite acidic[294] (even in DMSO). The acid-catalyzed KET of **4007** would give the enol **4022**. Were this species to react with IBX, one might reasonably expect the **4023** to be produced, an

CH_2C=CH], 2.02 [dddd, J = 8.0, 8.0, 8.0, 8.0 Hz, 2H, C(O)CH_2CH_2C=CH], and 1.95 [dd, J = 1.5, 1.5 Hz, 3H, (CH_3)C=CH_2].

GC / LR EI-MS [5025015]: t_R 8.19 min; *m*/*z* (rel. int.) 164 (1, $M^{+\bullet}$), 136 (93), 121 (3), 95 (11, $M^{+\bullet}$–$C_4H_5O^{\bullet}$), and 69 (100, $M^{+\bullet}$–$C_6H_7O^{\bullet}$).

HR ESI-MS: $C_{10}H_{12}O_2$ $[M+Na]^+$ requires 187.0730; found 187.0716.

294 Gallen, M. J.; Goumont, R.; Clark, T.; Terrier, F.; Williams, C. M. *o*-Iodoxybenzoic Acid (IBX): pK_a and Proton-Affinity Analysis. *Angew. Chem. Int. Ed.* **2006**, *45*, 2929–2934.

oxidative rearrangement within which would then afford intermediate **4024**. Subsequent hydrolysis would liberate 2-iodosobenzoic acid (IBA) and, after oxidation of the alcohol **4025** by another equivalent of IBX, the observed enedione **4019**.

Finally, and for reasons that are unclear at present, it was empirically determined that the formation of **4019** could be largely suppressed when an "inverse addition" experimental protocol was employed (entry 9, Table IV–1), which gave rise to **4007** in good yield.

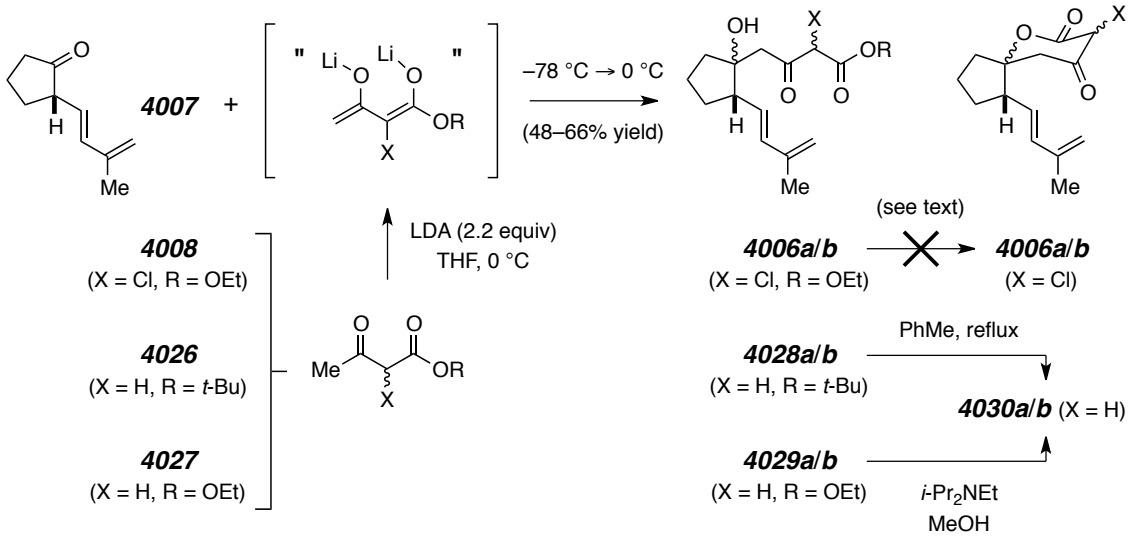
The oxidation studies just described, although unexpectedly difficult to resolve, did eventually deliver workable quantities of the homoallylic ketone **4007**, and thus the propensity of this material to undergo 1,2-addition in the presence of a Weiler dianion was subsequently investigated (Scheme IV–9). In accordance with the retrosynthetic strategy (see Scheme IV–3), the reaction of **4007** with the dianion derived from the α-chloro β-keto ester **4008** was among the first reactions to be explored. Most typically, Weiler dianions are generated by sequential treatment the β-keto ester with NaH and *n*-BuLi,[17] but, admittedly, I struggled with this chemistry for quite some time. For example, when the dianion derived from **4008** was generated under these standard conditions and allowed to react with **4007**, only decomposition of the starting homoallylic ketone was observed (presumably via base-catalyzed oligomerization). After a bit of experimentation, a clean reaction occurred only when the follow modifications were adhered to: i) Generation of the Weiler dianion (*ca.* 2 equiv with respect to **4007**) with slightly more than 2 equiv of LDA (with respect to **4008**) in THF and ii) maintaining a low concentration (*ca.* 10–20 mM) with respect to the homoallylic ketone **4007**. Under these conditions, a 55% combined yield of the separable diastereomeric aldol adducts **4006a** and **4006b** was obtained,[295] each of which existed as a 1:1 epimeric mixture of α-chloro β-keto esters. This victory was quickly rendered a moot point when the attempted

---

[295] The "**a**" and "**b**" numbering scheme (i.e., "**4006a**" and "**4006b**") is used here simply to indicate the order of elution on SiO_2 of the diastereomeric aldol adducts. Although the major product of these Weiler dianion reactions is presumably derived from 1,2-addition *trans* to the dienyl side chain within **4007**, no effort has been made to rigorously establish their relative configurations.

lactonization of these intermediates [i.e., *i*-Pr_2NEt, MeOH, rt; aq KOH, THF/MeOH/H_2O (2.5:1:1) then H_3O^+; Otera's catalyst,[296] PhMe, 60 °C] did not give any detectable amounts of the desired spirocyclic lactones **4006a**/**b**.

Scheme IV–9 | Weiler dianion addition to the homoallylic ketone **4007** and lactonization of the resulting aldol adducts **4028a**/**b** and **4029a**/**b**.



I speculated that the unwillingness of **4006a**/**b** to undergo lactonization was perhaps due in part to the presence of the α-chlorine atom within these hydroxy esters. Thus, under the previously described conditions for Weiler dianion generation, the analogous deschloro lactone precursors **4028a**/**b** and **4029a**/**b** were readily prepared by the reaction of **4007** with the dianions derived from either *tert*-butyl acetoacetate (**4026**) or ethyl acetoacetate (**4027**), respectively (Scheme IV–9). In contrast to **4006a**/**b**, the *tert*-butyl (**4028a**/**b**) and ethyl (**4029a**/**b**) β-keto esters could be lactonized in a reasonably efficient manner under either thermal (i.e., PhMe, reflux) or basic (i.e., *i*-Pr_2NEt, MeOH) reaction conditions.

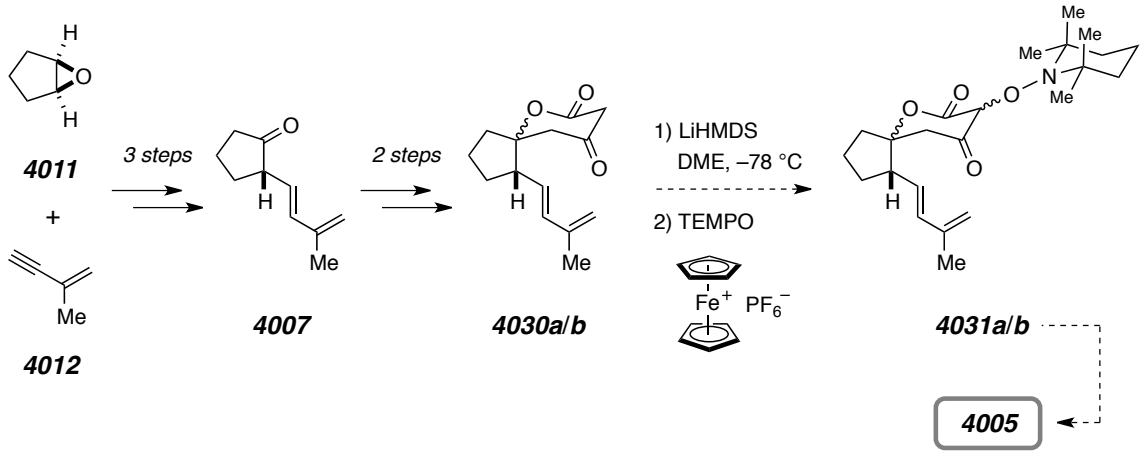
[296] Otera, J.; Dan-oh, N.; Nozaki, H. Novel Template Effects of Distannoxane Catalysts in Highly Efficient Transesterification and Esterification. *J. Org. Chem.* **1991**, *56*, 5307–5311.

D. CONCLUSION

What has been described in Chapter IV is the development of a straightforward five-step synthetic route for the preparation of the spirocyclic lactones **4030a**/**b** (Scheme IV–10). Highlights include: i) The use of simple and readily available starting materials (i.e., **4011** and **4012**), ii) the identification of two unusual by-products (**4018** and **4019**) that were formed during the oxidative preparation of the homoallylic ketone **4007**, and iii) the addition of various Weiler dianions to **4007** without serious complications from potentially competitive base-catalyzed decomposition pathways.

To be sure, this work has laid the groundwork for future efforts toward the model substrate **4005**. What remains to be seen, however, is whether or not α-oxidation of the lactones **4030a**/**b** will be a viable path forward. It is worthwhile to point out that in Chapter II of this Thesis, the successful α-oxygenation of a related β-keto ester substrate was described. Thus, it seems plausible that this method could be applied to the present system to generate **4031a**/**b**, from which the model substrate **4005** would be liberated by N–O bond reduction.

Scheme IV–10 | Summary of Chapter IV achievements and proposed strategy for α-oxygenation of the diastereomeric lactones **4030a**/**b**.



PART 2

FORAYS

IN

COMPUTATIONAL CHEMISTRY

CHAPTER V

INTRODUCTION AND BACKGROUND

A. RECENT CASES OF NATURAL PRODUCT STRUCTURE MISASSIGNMENT

Nuclear magnetic resonance (NMR) spectroscopy is the single most powerful and widely utilized tool for determining the three-dimensional structure (i.e., consisting of the constitution and relative configuration) of small organic molecules. Many of these molecules possess beneficial and potentially useful biological properties that are intimately linked to their three-dimensional structure. In particular, the structure elucidation of newly isolated natural products, once a tedious and time consuming exercise in chemical degradation and derivatization, has been made immeasurably more efficient by the advent of modern one- (1-D) and two-dimensional (2-D) NMR experiments,[297] in addition to a battery of other spectroscopic methods.

Yet the power of NMR spectroscopy to provide key insights regarding the constitution and/or relative configuration of an organic molecule is by no means absolute, particularly when that molecule is exceedingly complex (e.g., multiple stereogenic centers). Perhaps it is therefore not surprising–if not mildly alarming–that the natural products isolation literature over the past two decades has supplied a relatively steady flow of structural misassignments, *even when* the full battery of spectroscopic methods

---

[297] Claridge, T. D. W. *High-Resolution NMR Techniques in Organic Chemistry*, 1ST ed.; Baldwin, FRS, J. E., Williams, R. M., Eds.; Tetrahedron Organic Chemistry Series; Elsevier Science: New York, **1999**; Vol. 19.

have been employed.[298,299] This statement should not be misconstrued as a criticism of the natural products isolation community *per se*, but rather as a recognition that one's ability to fully (and correctly) interpret a set of 1-D and 2-D NMR spectroscopic data will be inversely related to the complexity and/or novelty of the system under study.

It is in these instances where total synthesis has historically played a critical role in not only identifying, but also swiftly cleansing the literature of these structural misassignments. In order to sharpen this point a bit, a few recent high profile examples are shown in Figure V–1. Brevenal, a polyether metabolite that was isolated from cultures of the red tide marine dinoflagellate *Karenia brevis*,[300] was initially assigned structure **5001**. Two separate total syntheses by Sasaki[301] identified 26-*epi*-**5001** as the true structure. Palmerolide A, a metabolite of the Antarctic circumpolar tunicate *Synoicum adareanum*, was given structure **5002** by Baker and co-workers.[302] No less than a year later, total syntheses by De Brabander and co-workers[303] led to a revision of its relative configuration to that of 7,10,11-*trisepi*-**5002**. Finally, structure **5003** was originally assigned to neopeltolide, an isolate of a deep-water sponge of the family

---

298 Nicolaou, K. C.; Snyder, S. A. Chasing Molecules That Were Never There: Misassigned Natural Products and the Role of Chemical Synthesis in Modern Structure Elucidation. *Angew. Chem. Int. Ed.* **2005**, *44*, 1012–1044.

299 Suyama, T. L.; Gerwick, W. H.; McPhail, K. L. Survey of Marine Natural Product Structure Revisions: A Synergy of Spectroscopy and Chemical Synthesis. *Bioorg. Med. Chem.* **2011**, *19*, 6675–6701.

300 Bourdelais, A. J.; Jacocks, H. M.; Wright, J. L. C.; Bigwarfe, Jr., P. M.; Baden, D. G. A New Polyether Ladder Compound Produced by the Dinoflagellate *Karenia brevis*. *J. Nat. Prod.* **2005**, *68*, 2–6.

301 Fuwa, H.; Ebine, M.; Bourdelais, A. J.; Baden, D. G.; Sasaki, M. Total Synthesis, Structure Revision, and Absolute Configuration of (–)-Brevenal. *J. Am. Chem. Soc.* **2006**, *128*, 16989–16999.

302 Diyabalanage, T.; Amsler, C. D.; McClintock, J. B.; Baker, B. J. Palmerolide A, a Cytotoxic Macrolide from the Antarctic Tunicate *Synoicum adareanum*. *J. Am. Chem. Soc.* **2006**, *128*, 5630–5631.

303 Jiang, X.; Liu, B.; Lebreton, S.; De Brabander, J. K. Total Synthesis and Structure Revision of the Marine Metabolite Palmerolide A. *J. Am. Chem. Soc.* **2007**, *129*, 6386–6387.

Neopeltidae.[304] As a result of synthetic work reported by the Panek[305] and Scheidt[306] groups, its relative configuration was revised in short order to that of 11,13-*bisepi*-**5003**.

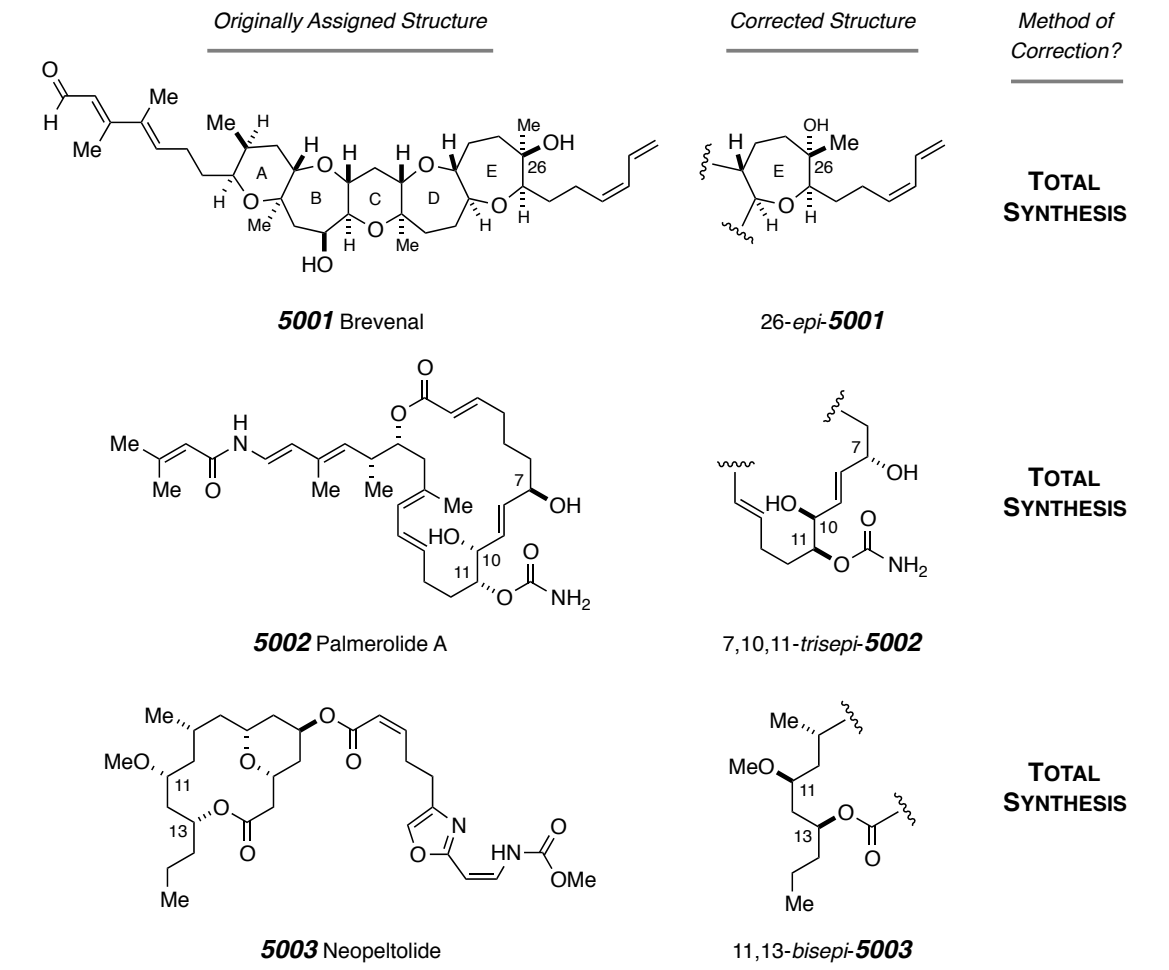


Figure V–1 | Recent cases of natural product structure misassignment (**5001**–**5003**).

304 Wright, A. E.; Botelho, J. C.; Guzmán, E.; Harmody, D.; Linley, P.; McCarthy, P. J.; Pitts, T. P.; Pomponi, S. A.; Reed, J. K. Neopeltolide, a Macrolide from a Lithistid Sponge of the Family Neopeltidae. *J. Nat. Prod.* **2007**, *70*, 412–416.

305 Youngsaye, W.; Lowe, J. T.; Pohlki, F.; Ralifo, P.; Panek, J. S. Total Synthesis and Stereochemical Reassignment of (+)-Neopeltolide. *Angew. Chem. Int. Ed.* **2007**, *46*, 9211–9214.

306 Custar, D. W.; Zabawa, T. P.; Scheidt, K. A. Total Synthesis and Structural Revision of the Marine Macrolide Neopeltolide. *J. Am. Chem. Soc.* **2008**, *130*, 804–805.

Undoubtedly, the examples shown above were impressive feats that represented important contributions to the synthetic community. They further underscore the indispensible and unarguable role of chemical synthesis in the structural reassignment of natural products. But each of these victories came at a high price–the devotion of many laboratory hours toward synthesizing the *wrong* structure. If a reliable method for the computation of NMR chemical shifts had existed at the time that each of the erroneous structures were reported, could these situations have been avoided? At the very least, might the discrepancy between computed and experimental NMR chemical shifts have caused these researchers to question the original assignments?

B. ROLE OF COMPUTED CHEMICAL SHIFTS IN STRUCTURE REVISION

The computation of NMR chemical shifts with quantum mechanical methods–density functional theory (DFT) in particular–is now widely recognized as a useful tool for small molecule structure elucidation, particularly as it pertains to the determination of relative configuration.[307] The list of natural substances that have been structurally characterized, at least in part, with the aid of DFT computed GIAO NMR chemical shifts continues to grow. This list, which includes viridiol,[308] aplidinones A–C,[309] kadlongilactones D and F,[310] artarborol,[311] maitotoxin,[312] gloriosaols A and B,[313] obtusallenes V–

---

307 (a) Bifulco, G.; Dambruoso, P.; Gomez–Paloma, L.; Riccio, R. Determination of Relative Configuration in Organic Compounds by NMR Spectroscopy and Computational Methods. *Chem. Rev.* **2007**, *107*, 3744–3779. (b) Di Micco, S.; Chini, M. G.; Riccio, R.; Bifulco, G. Quantum Mechanical Calculation of NMR Parameters in the Stereostructural Determination of Natural Products. *Eur. J. Org. Chem.* **2010**, 1411–1434. (c) Lodewyk, M. W.; Siebert, M. R.; Tantillo, D. J. Computational Prediction of ^{1}H and ^{13}C Chemical Shifts: A Useful Tool for Natural Product, Mechanistic, and Synthetic Organic Chemistry. *Chem. Rev.* **2012**, *112*, 1839–1862.

308 Wipf, P.; Kerekes, A. D. Structure Reassignment of the Fungal Metabolite TAEMC161 as the Phytotoxin Viridiol. *J. Nat. Prod.* **2003**, *66*, 716–718.

309 Aiello, A.; Fattorusso, E.; Luciano, P.; Mangoni, A.; Menna, M. Isolation and Structure Determination of Aplidinones A–C from the Mediterranean Ascidian *Aplidium conicum*: A Successful Regiochemistry Assignment by Quantum Mechanical ^{13}C NMR Chemical Shift Calculations. *Eur. J. Org. Chem.* **2005**, 5024–5030.

310 Pu, J. –X; Huang, S. –X.; Ren, J.; Xiao, W. –L.; Li, L. –M.; Li, R. –T.; Li, L. –B.; Liao, T. –G.; Lou, L. –G.; Zhu, H. –J.; Sun, H. –D. Isolation and Structure Elucidation of Kadlongilactones C–F from *Kadsura longipedunculata* by NMR Spectroscopy and DFT Computational Methods. *J. Nat. Prod.* **2007**, *70*, 1706–1711.

311 Fattorusso, C.; Stendardo, E.; Appendino, G.; Fattorusso, E.; Luciano, P.; Romano, A.; Taglialatela–Scafati, O. Artarborol, a *nor*-Caryophyllane Sesquiterpene Alcohol from *Artemisia arborescens*. Stereostructure Assignment through Concurrence of NMR Data and Computational Analysis. *Org. Lett.* **2007**, *9*, 2377–2380.

312 Nicolaou, K. C.; Frederick, M. O. On the Structure of Maitotoxin. *Angew. Chem. Int. Ed.* **2007**, *46*, 5278–5282.

313 Bassarello, C.; Bifulco, G.; Montoro, P.; Skhirtladze, A.; Kemertelidze, E.; Pizza, C.; Piacente, S. Gloriosaols A and B, Two Novel Phenolics from *Yucca gloriosa*: Structural Characterization and Configurational Assignment by a Combined NMR-Quantum Mechanical Strategy. *Tetrahedron* **2007**, *63*, 148–154.

VII,[314] elatenyne,[315] spiroleucettadine,[316] samoquasine A,[317] ketopelenolides C and D,[318] hypurticin,[319] and nobilistine A,[320] underscores the widespread acceptance of these techniques within the organic chemistry community. What follows in the remainder of this Section are two salient examples from the recent literature where computed NMR chemical shifts did play (or could have played) a decisive role in natural product structure elucidation. These examples will then serve as a backdrop to a concise summary of our group's own contributions to this area (Section C).

B–1. THE "HEXACYCLINOL DISPUTE"

To this day, the circumstances surrounding the structure revision of hexacyclinol remain a topic of considerable controversy. The dispute originated in 2002 when Gräfe and co-workers disclosed the isolation of hexacyclinol, a highly unusual antiproliferative

---

314 Braddock, D. C.; Rzepa, H. S. Structural Reassignment of Obtusallenes V, VI, and VII by GIAO-Based Density Functional Prediction. *J. Nat. Prod.* **2008**, *71*, 728–730.

315 Smith, S. G.; Paton, R. S.; Burton, J. W.; Goodman, J. M. Stereostructure Assignment of Flexible Five-Membered Rings by GIAO ^{13}C NMR Calculations: Prediction of the Stereochemistry of Elatenyne. *J. Org. Chem.* **2008**, *73*, 4053–4062.

316 White, K. N.; Amagata, T.; Oliver, A. G.; Tenney, K.; Wenzel, P. J.; Crews, P. Structure Revision of Spiroleucettadine, a Sponge Alkaloid with a Bicyclic Core Meager in H-Atoms. *J. Org. Chem.* **2008**, *73*, 8719–8722.

317 Timmons, C.; Wipf, P. Density Functional Theory Calculation of ^{13}C NMR Shifts of Diazaphenanthrene Alkaloids: Reinvestigation of the Structure of Samoquasine A. *J. Org. Chem.* **2008**, *73*, 9168–9170.

318 Fattorusso, E.; Luciano, P.; Romano, A.; Taglialatela–Scafati, O.; Appendino, G.; Borriello, M.; Fattorusso, C. Stereostructure Assignment of Medium-sized Rings through an NMR-Computational Combined Approach. Application to the New Germacranes Ketopelenolides C and D. *J. Nat. Prod.* **2008**, *71*, 1988–1992.

319 Mendoza–Espinoza, J. A.; López–Vallejo, F.; Fragoso–Serrano, M.; Pereda–Miranda, R.; Cerda–García–Rojas, C. M. Structural Reassignment, Absolute Configuration, and Conformation of Hypurticin, a Highly Flexible Polyacyloxy-6-heptenyl-5,6-dihydro-2*H*-pyran-2-one. *J. Nat. Prod.* **2009**, *72*, 700–708.

320 Lodewyk, M. W.; Tantillo, D. J. Prediction of the Structure of Nobilistine A Using Computed NMR Chemical Shifts. *J. Nat. Prod.* **2011**, *74*, 1339–1343.

secondary metabolite from cultures of the fungal strain *Panus rudis* HKI 0254.[321] Extensive 1-D and 2-D NMR spectroscopic experiments led to the assignment of structure **5004** (Figure V–2) for this natural product.

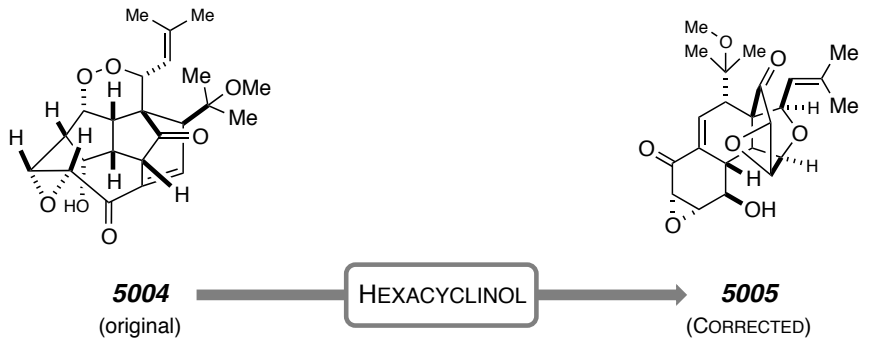


Figure V–2 | Originally proposed and revised structures of hexacyclinol.

Prompted by a highly "provocative"[322] total synthesis[323] of the proposed structure of hexacyclinol, Rychnovsky computed the carbon NMR chemical shifts for structure **5004** [at the mPW1PW91/6-31G(d,p)//HF/3-21G level of theory] and compared them to the experimentally observed values for the natural material. He found that the correlation between the computed and experimental data sets was quite unsatisfactory; as a result, an alternative structure was proposed for hexacyclinol (**5005**, Figure V–2), the computed carbon NMR chemical shifts of which were in much better agreement with the

[321] Schlegel, B.; Härtl, A.; Dahse, H. –M.; Gollmick, F. A.; Gräfe, U.; Dörfelt, H.; Kappes, B. Hexacyclinol, a New Antiproliferative Metabolite of *Panus rudis* HKI 0254. *J. Antibiot.* **2002**, *55*, 814–817.

[322] Rychnovsky, S. D. Predicting NMR Spectra by Computational Methods: Structure Revision of Hexacyclinol. *Org. Lett.* **2006**, *8*, 2895–2898.

[323] La Clair, J. J. Total Syntheses of Hexacyclinol, 5-*epi*-Hexacyclinol, and Desoxohexacyclinol Unveil an Antimalarial Prodrug Motif. *Angew. Chem. Int. Ed.* **2006**, *45*, 2769–2773.

experimental values.[322] Soon thereafter, Rychnovsky's proposal was confirmed by a total synthesis (and X-ray crystal structure) of **5005** that emerged from the Porco group.[324]

B–2. VANNUSAL B: EX-POST APPLICATION OF COMPUTED CHEMICAL SHIFTS

Vannusal B was isolated by Pietra and co-workers in 1999 and assigned structure **5006** (Figure V–3) on the basis of the usual battery of NMR experiments.[325] In a series of five publications beginning in 2008, the Nicolaou group[326] detailed their long and tumultuous campaign that eventually culminated in the reassignment of the originally proposed structure of vannusal B (**5006**) to that of the *octa*epimeric structure **5007**. During the course of these studies, they reported the total syntheses of eight (!) diastereomeric structures, of which the first and last to be prepared were obviously **5006** and **5007**, respectively.

The case of the true structure of vannusal B was subsequently reopened in 2011 when Bagno and co-workers examined the question via computational means.[327] They computed the carbon NMR chemical shifts [at the M06/pcS-2//B3LYP/6-31G(d,p) level

---

[324] Proco, Jr., J. A.; Su, S.; Lei, X.; Bardhan, S.; Rychnovsky, S. D. Total Synthesis and Structure Assignment of (+)-Hexacyclinol. *Angew. Chem. Int. Ed.* **2006**, *45*, 5790–5792.

[325] Guella, G.; Dini, F.; Pietra, F. Metabolites with a Novel C_{30} Backbone from Marine Ciliates. *Angew. Chem. Int. Ed.* **1999**, *38*, 1134–1136.

[326] (a) Nicolaou, K. C.; Zhang, H.; Ortiz, A.; Dagneau, P. Total Synthesis of the Originally Assigned Structure of Vannusal B. *Angew. Chem. Int. Ed.* **2008**, *47*, 8605–8610. (b) Nicolaou, K. C.; Zhang, H.; Ortiz, A. The True Structures of the Vannusals, Part 1: Initial Forays into Suspected Structures and Intelligence Gathering. *Angew. Chem. Int. Ed.* **2009**, *48*, 5642–5647. (c) Nicolaou, K. C.; Ortiz, A.; Zhang, H. The True Structures of the Vannusals, Part 2: Total Synthesis and Revised Structure of Vannusal B. *Angew. Chem. Int. Ed.* **2009**, *48*, 5648–5652. (d) Nicolaou, K. C.; Ortiz, A.; Zhang, H.; Dagneau, P.; Lanver, A.; Jennings, M. P.; Arseniyadis, S.; Faraoni, R.; Lizos, D. E. Total Synthesis and Structural Revision of Vannusals A and B: Synthesis of the Originally Assigned Structure of Vannusal B. *J. Am. Chem. Soc.* **2010**, *132*, 7138–7152. (e) Nicolaou, K. C.; Ortiz, A.; Zhang, H.; Guella, G. Total Synthesis and Structural Revision of Vannusals A and B: Synthesis of the True Structures of Vannusals A and B. *J. Am. Chem. Soc.* **2010**, *132*, 7153–7176.

[327] Saielli, G.; Nicolaou, K. C.; Ortiz, A.; Zhang, H.; Bagno, A. Addressing the Stereochemistry of Complex Organic Molecules by Density Functional Theory-NMR: Vannusal B in Retrospective. *J. Am. Chem. Soc.* **2011**, *133*, 6072–6077.

of theory] for all eight of the diastereomeric structures that had been independently prepared by total synthesis and then compared these data sets to those that had been determined experimentally. Indeed, the computed chemical shifts for structure **5007** showed a much better correlation with the experimental values for vannusal B. Moreover, the computed shifts for the originally assigned structure (**5006**) resulted in an error that was well over two times larger. Thus, these authors correctly concluded that "*…the structural revision of the originally assigned structure of vannusal B could have been greatly aided and simplified by a prior knowledge of the relevant NMR parameters, highlighting viable targets and, thereby, allowing synthetic efforts to be concentrated on the most likely structures*."[327]

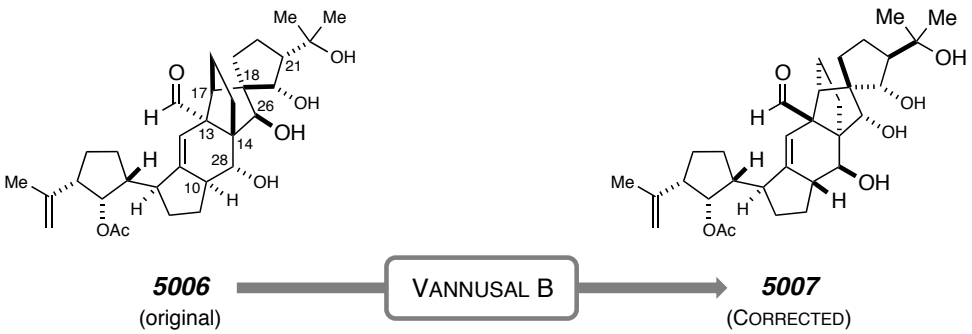


Figure V–3 | Originally proposed and revised structures of vannusal B.

C. PREVIOUS WORK FROM THE HOYE/CRAMER TEAM

The Hoye group has had a long-standing interest in the structure elucidation of complex natural products.[328] In particular, our approach to the determination of the relative[329] and absolute[328e] configurations of such stereochemically rich structures has relied upon chemical derivatization (e.g., Mosher ester) and analysis of experimental NMR spectroscopic parameters.[330]

More recently, we began to develop and exploit methodologies that involve the comparison of computed versus experimental NMR spectroscopic parameters. Among the fundamental observables in NMR spectroscopy, chemical shifts (δ) and scalar coupling constants (*J*) are the most diagnostic of three-dimensional structure–the bread and butter parameters, if you will. Our group has calculated the latter of these with molecular mechanics (MM) and employed them to confirm the relative configuration of

---

328 See, e.g.: (a) Efange, S. M. N.; Brun, R.; Wittlin, S.; Connolly, J. D.; Hoye, T. R.; McAkam, T.; Makolo, F. L.; Mbah, J. A.; Nelson, D. P.; Nyongbela, K. D.; Wirmum, C. K. Okundoperoxide, a Bicyclic Cyclofarnesylsesquiterpene Endoperoxide from *Scleria striatinux* with Antiplasmodial Activity. *J. Nat. Prod.* **2009**, *72*, 280–283. (b) Hoye, T. R.; Dvornikovs, V.; Fine, J. M.; Anderson, K. R.; Jeffrey, C. S.; Muddiman, D. C.; Shao, F.; Sorensen, P. W.; Wang, J. Details of the Structure Determination of the Sulfated Steroids PSDS and PADS: New Components of the Sea Lamprey (*Petromyzon marinus*) Migratory Pheromone. *J. Org. Chem.* **2007**, *72*, 7544–7550. (c) Sorensen, P. W.; Fine, J. M.; Dvornikovs, V.; Jeffrey, C. S.; Shao, F.; Wang, J.; Vrieze, L. A.; Anderson, K. R.; Hoye, T. R. Mixture of New Sulfated Steroids Functions as a Migratory Pheromone in the Sea Lamprey. *Nat. Chem. Biol.* **2005**, *1*, 324–328. (d) Ayyad, S. N.; Judd, A. S.; Shier, W. T.; Hoye, T. R. Otteliones A and B: Potently Cytotoxic 4-Methylene-2-cyclohexenones from *Ottelia alismoides*. *J. Org. Chem.* **1998**, *63*, 8102–8106. (e) Rieser, M. J.; Hui, Y.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. Determination of Absolute Configuration of Stereogenic Carbinol Centers in Annonaceous Acetogenins by ^{1}H- and ^{19}F-NMR Analysis of Mosher Ester Derivatives. *J. Am. Chem. Soc.* **1992**, *114*, 10203–10213.

329 E.g.: Hoye, T. R.; Hanson, P. R. Assigning the Relative Stereochemistry between C(2) and C(4) of the 2-Acetonyl-4-alkylbutyrolactone Substructures of the Appropriate Annonaceous Acetogenins. *J. Org. Chem.* **1991**, *56*, 5092–5095.

330 (a) Hoye, T. R.; Hanson, P. R.; Vyvyan, J. R. A Practical Guide to First-Order Multiplet Analysis in ^{1}H NMR Spectroscopy. *J. Org. Chem.* **1994**, *59*, 4096–4103. (b) Hoye, T. R.; Zhao, H. A Method for Easily Determining Coupling Constant Values: An Addendum to "A Practical Guide to First-Order Multiplet Analysis in ^{1}H NMR Spectroscopy." *J. Org. Chem.* **2002**, *67*, 4014–4016.

the natural product 16-*epi*-latrunculin B.[331] Subsequent to those investigations, a collaborative effort with Professor Christopher Cramer was initiated wherein we proposed to exploit the former–namely, computed NMR chemical shifts.

Under the guidance of Professors Hoye and Cramer, Keith Wiitala, a former graduate student, began to explore the use of more sophisticated DFT-based methods for the computation of proton and carbon NMR chemical shifts, the ultimate goal being to develop a method that would allow one to distinguish diastereomeric structures.[332] In 2006, these collaborative efforts culminated in the development of two new hybrid density functionals that were christened WP04 and WC04.[333] By employing a training set that spanned 43 molecules and covered a wide swath of chemical space, each of these functionals was empirically optimized for the computation of proton (WP04) and carbon (WC04) NMR chemical shifts. It was subsequently shown that WP04 and WC04 provided theoretical chemical shifts that were of comparable, if not superior, accuracy in comparison to those obtained from "off-the-shelf" functionals such as HF, B3LYP, PBE1, and *m*PW1PW91.[333,334]

With these new functionals in hand, a series of isomeric methylcyclohexanols (**5008c/t–5010c/t**, Table V–1) were then identified as ideal candidates with which to validate their utility.[334] In this study, Keith modeled each of the individual

---

331 Hoye, T. R.; Ayyad, S. N.; Eklov, B. M.; Hashish, N. E.; Shier, W. T.; El Sayed, K. A.; Hamann, M. T. Toward Computing Relative Configurations: 16-*epi*-Latrunculin B, a New Stereoisomer of the Actin Polymerization Inhibitor Latrunculin B. *J. Am. Chem. Soc.* **2002**, *124*, 7405–7410.

332 Wiitala, K. W. Modeling Proton and Carbon Chemical Shifts Using Density Functional Theory: Relevance to Determining Relative Configuration. Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2007**.

333 Wiitala, K. W.; Hoye, T. R.; Cramer, C. J. Hybrid Density Functional Methods Empirically Optimized for the Computation of ^{13}C and ^{1}H NMR Chemical Shifts in Chloroform Solution. *J. Chem. Theory Comput.* **2006**, *2*, 1085–1092.

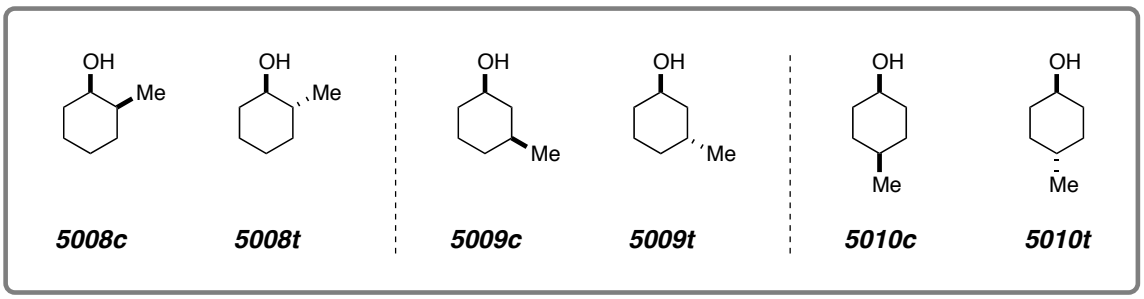
334 Wiitala, K. W.; Al-Rashid, Z. F.; Dvornikovs, V.; Hoye, T. R.; Cramer, C. J. Evaluation of Various DFT Protocols for Computing ^{1}H and ^{13}C Chemical Shifts to Distinguish Stereoisomers: Diastereomeric 2-, 3-, and 4-Methylcyclohexanols as a Test Set. *J. Phys. Org. Chem.* **2007**, *20*, 345–354.

methylcyclohexanol isomers as a family of conformers (i.e., hydroxyl rotamers and different chair forms). Each of these conformers was then optimized with DFT employing B3LYP/6-31G(d) and the integral equation formalism polarized continuum model (IEFPCM) for chloroform solvation effects. Single point gauge including atomic orbitals (GIAO) NMR calculations were then carried out with either the WP04 or WC04 functions in conjunction with the 6-311+G(2d,p) basis set, again employing IEFPCM (for chloroform). The computed proton and carbon NMR chemical shifts emerged for each isomer by referencing (to $SiMe_4$), Boltzmann-weighting, and linear correction procedures. As evidenced by the data in Table V–1A, the WP04 functional was fully capable of distinguishing among these isomeric structures by an impressive margin. With regard to the computed carbon NMR data, the WC04 functional performed with similarly outstanding effectiveness (Table V–1B).

During the course of these studies, Keith also examined the relative performance of the B3LYP and PBE1 functionals.[334] Notably, it was discovered that *all* of these functionals were able to discriminate among the isomeric methylcyclohexanols when computed *proton* data were examined; however, the WC04 and PBE1 functionals were unique in their ability to distinguish these isomers on the basis of computed *carbon* chemical shifts. Additionally, Keith was able to establish the following: i) Neither the WP04 nor the WC04 functional was particularly sensitive to the solvation model cavity employed in the GIAO NMR calculation (Bondi versus UA0); ii) in this particular setting, using *only* the global minimum energy conformer in the GIAO NMR calculation did not severely impact the conclusions drawn; and iii) a comparison of the relative ability of computed proton and carbon NMR chemical shifts to distinguish between the isomeric structures **5008c/t–5010c/t** revealed that proton nuclei were *ca.* twice as effective.[334]

Table V–1 | A: Correlation matrices of computed linearly corrected (WP04) vs. experimental ^{1}H NMR chemical shifts for **5008c/t–5010c/t** [adapted with permission from Table 9 in ref 334. Copyright © 2007 John Wiley & Sons, Ltd.].[a]

B: Correlation matrices of computed linearly corrected (WC04) vs. experimental ^{13}C NMR chemical shifts for **5008c/t–5010c/t** [adapted with permission from Table 13 in ref 334. Copyright © 2007 John Wiley & Sons, Ltd.].[a]



A. PROTON	5008			5009			5010	
	c CORR	*t* CORR		*c* CORR	*t* CORR		*c* CORR	*t* CORR
5008c EXP	***0.39***	2.50	**5009c** EXP	***0.88***	3.14	**5010c** EXP	***0.64***	2.42
5008t EXP	3.21	***0.79***	**5009t** EXP	2.64	***0.56***	**5010t** EXP	3.03	***0.70***

B. CARBON	5008			5009			5010	
	c CORR	*t* CORR		*c* CORR	*t* CORR		*c* CORR	*t* CORR
5008c EXP	***11.4***	23.1	**5009c** EXP	***9.0***	20.8	**5010c** EXP	***6.0***	18.5
5008c EXP	25.3	***11.8***	**5009t** EXP	17.1	***8.7***	**5010t** EXP	21.5	***7.6***

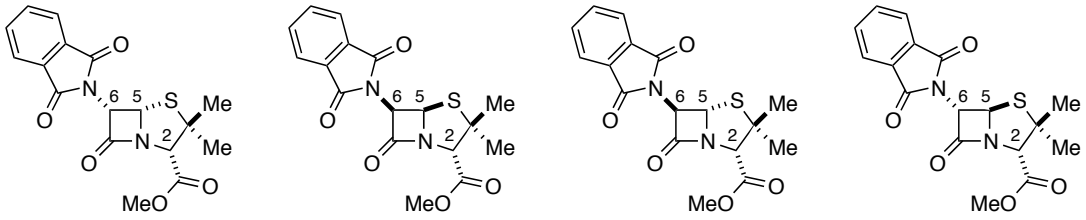
[a] Comparisons are expressed as the total absolute error between theoretical ("CORR") and experimental ("EXP") chemical shifts ($|\Delta\delta|_{T}$, ppm).

The lessons learned from the methylcyclohexanol study were subsequently extended to a more complex setting–namely, the penam β-lactams **5011**–**5014** (Table V–2).[335] Each of these structures was independently synthesized and the full compliment of ^{1}H and ^{13}C NMR spectral data were collected and interpreted in house (in addition to the carboxylic acids derived from **5012**–**5014**; however, they will not be discussed here). A very similar protocol was employed to generate computed proton NMR chemical shifts for penam β-lactam methyl esters as was described above. Here again, the WP04 functional was more than able to predict the relative configuration of these structures on the basis of comparison of the experimental ^{1}H NMR data to the computed proton chemical shifts (Table V–2). However, it was discovered that all of the functionals examined in this study (WC04, PBE1, and B3LYP) were *unable* to distinguish among **5011**–**5014** on the basis of computed *carbon* data, an outcome that was attributed to the presence of sulfur–carbon bonds in these molecules.[335] In accord with past form,[334] the comparison of computed versus experimental proton chemical shifts was the recommended approach.[335]

---

[335] Wiitala, K. W.; Cramer, C. J.; Hoye, T. R. Comparison of Various Density Functional Methods for Distinguishing Stereoisomers Based on Computed ^{1}H or ^{13}C NMR Chemical Shifts Using Diastereomeric Penam β-Lactams as a Test Set. *Magn. Reson. Chem.* **2007**, *45*, 819–829.

Table V–2 | Comparison of computed linearly corrected (WP04) vs. experimental ^{1}H NMR chemical shifts for **5011**–**5014** [adapted with permission from Table 4 in ref 335. Copyright © 2007 John Wiley & Sons, Ltd.].[a]



5011 (2*S*,5*S*,6*S*) ***5012*** (2*S*,5*R*,6*R*) ***5013*** (2*S*,5*S*,6*R*) ***5014*** (2*S*,5*R*,6*S*)

	5011 CORR	***5012*** CORR	***5013*** CORR	***5014*** CORR
5011 EXP	***0.95***	2.60	1.93	2.80
5012 EXP	1.88	***0.74***	2.83	1.46
5013 EXP	1.74	3.07	***0.85***	2.45
5014 EXP	1.98	1.14	2.19	***0.56***

[a] Comparisons are expressed as the total absolute error between theoretical ("CORR") and experimental ("EXP") chemical shifts ($|\Delta\delta|_T$, ppm).

In 2007, Keith completed his doctoral thesis research and headed off to greener pastures. It was at this time that I was handed the reigns of this project and charged with continuing what he had started. Guided largely by the tremendous amount of groundwork that had already been laid, I began to explore the application of computed NMR chemical shifts to structural issues that have emerged from concurrent natural product total synthesis endeavors in the Hoye group. These and related computational and experimental studies shall be the subject of Chapter VI.

CHAPTER VI

STRUCTURE DETERMINATION VIA COMPUTATION OF NMR CHEMICAL SHIFTS

A. COMPUTATIONAL REANALYSIS OF THE 'JONES ISOMERS'

HYPOTHESIS STATEMENT:

> *THE TWO ISOMERIC HYDRINDENONES THAT WERE ISOLATED BY JONES AND CO-WORKERS DURING THEIR 1986 FLASH VACUUM PYROLYSIS STUDIES HAVE BEEN INCORRECTLY ASSIGNED AS HAVING STRUCTURES **6006B** AND **6006D**.*

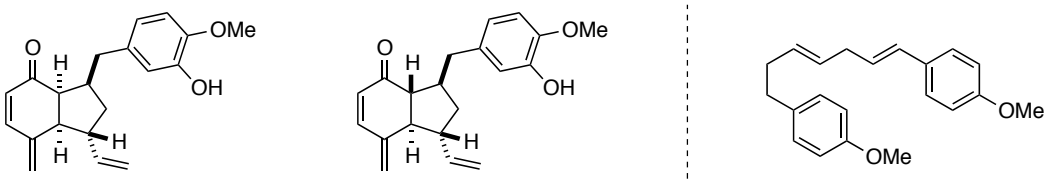
A–1. THE STRUCTURAL DILEMMA

In 1998, the Hoye and Shier groups reported the isolation and structural assignment of ottelione A (**6001**) and ottelione B (**6002**) (Figure VI–1), two new highly cytotoxic metabolites of the freshwater plant *Ottelia alismoides*.[328d] The initial tentative assignment of the relative configuration of **6001** was subsequently revised by a research group at Rhône-Poulenc Rorer in France[336] to that shown in Figure VI–1. Our group later reinvestigated the crude extracts of whole dried *O. alismoides*, wherein it was discovered that nine additional metabolites–a representative example of which is the diaryheptanoid

---

[336] Combeau, C.; Provost, J.; Lancelin, F.; Tournoux, Y.; Prod'homme, F.; Herman, F.; Lavelle, F.; Leboul, J.; Vuilhorgne, M. RPR112378 and RPR115781: Two Representatives of a New Family of Microtubule Assembly Inhibitors. *Mol. Pharmacol.* **2000**, *57*, 553–563.

6003 (Figure VI–1)–were also produced by the plant.[337] This finding revealed the enticing possibility that **6003** was perhaps the biosynthetic progenitor of **6001**, and consequently a provocative hypothesis that involved a spontaneous [3,3]-sigmatropic (Cope) rearrangement as a key step was proposed.[337]



6001 *ent*-Ottelione A ***6002*** *ent*-Ottelione B ***6003*** (a diarylheptanoid)

Figure VI–1 | Ottelione A (**6001**) and B (**6002**), and the diarylheptanoid **6003**, metabolites of the freshwater plant *Ottelia alismoides*.

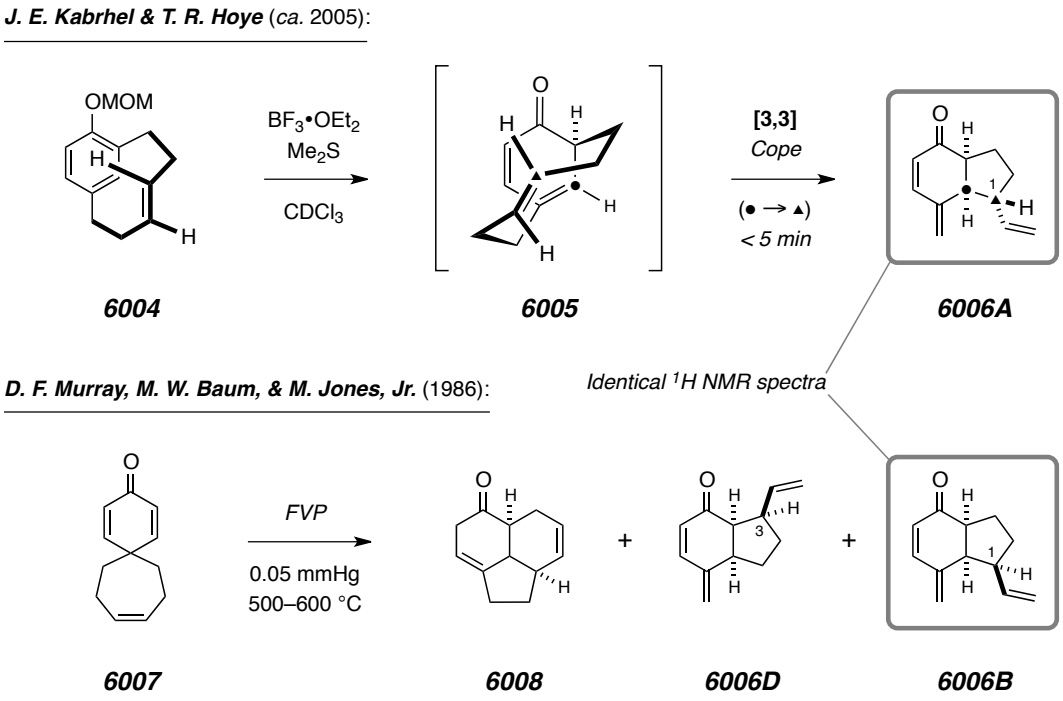
In connection with studies designed to test the hypothesis that **6001** arises via spontaneous Cope rearrangement, James E. Kabrhel, a former Hoye group member, had occasion to interrogate the reactivity of the strained [6]metacyclophane **6004**[338] (upper portion of Scheme VI–1). Exposure of this species to BF_3•OEt_3 and a large excess of Me_2S and subsequent collection of the ^{1}H NMR spectrum revealed that the hydrindenone **6006A** had been formed rapidly (< 5 min) at room temperature. In a very intriguing and impressive series of events, MOM ether cleavage within **6004** gave rise to a phenol that rapidly tautomerized to the cyclohexadienone **6005**. Spontaneous Cope rearrangement of this highly reactive intermediate then quickly gave birth to the observed product.

337 Lewis, H. J. Studies Related to the Ottelione Family of Natural Products. Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2005**.

338 Kabrhel, J. E. Part I: Is a Cope Rearrangement Viable as the Key Feature in the Biosynthesis of (+)-Ottelione A? Part II: The No-D Study of the n-BuLi Oxidation of 1,5-Cyclooctadiene. Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2006**.

During the course of an otherwise unrelated 1986 study, Maitland Jones, Jr. and co-workers[339] reported the flash vacuum pyrolysis (FVP) of the spirocyclic cyclohexadienone **6007** (lower portion of Scheme VI–1). They observed the formation of the tricycle **6008** and the constitutionally isomeric hydrindenones **6006D** and **6006B** and proposed a mechanistic scenario involving competitive Claisen and Cope rearrangement pathways.[339] These structures were assigned on the basis of their ^{1}H- [with/without Eu(fod)$_3$] and ^{13}C NMR spectra, IR absorptions, and a few key NOE experiments.

Scheme VI–1 | J. E. Kabrhel's initial observation that spontaneous Cope rearrangement of **6005** occurred upon deprotection of **6004** (upper portion) and the FVP of **6007** that was reported by Jones and co-workers (lower portion) [adapted from refs 338 and 339, respectively].



339 Murray, D. F.; Baum, M. W.; Jones, Jr., M. Thermal Rearrangement of 3-Methylenespiro[5.6]dodeca-1,4,9-triene and Spiro[5.6]dodeca-1,4,9-trien-3-one. *J. Org. Chem.* **1986**, *51*, 1–7.

A dilemma presented itself when it was discovered that the ^{1}H NMR spectrum that was assigned to **6006A**[338] was essentially identical to the spectrum reported by Jones and co-workers for **6006B**.[339] Note that relative asymmetric induction in the Cope rearrangement of **6005** must, *perforce*, give rise to the relative configuration of **6006A**. Moreover, certain aspects of the mechanistic proposal that Jones and co-workers set forth has led us to question[340] the assertion that **6006D** was correctly assigned.

A–2. COMPUTATIONAL STUDY OF THE HYDRINDENONES 6006A–6006D

In the interim, Ms. Susan G. Brown, a colleague of mine in the Hoye group, has synthesized the cyclohexadienone **6007** and subjected it to FVP. In accordance with Jones' observations, she isolated three compounds (HPLC), and collected and interpreted the full battery of 1-D (^{1}H, ^{13}C, and NOE) and 2-D (^{1}H–^{1}H COSY, HMQC, and HMBC) NMR spectroscopic data.[340] I was then kindly provided with a portion (^{1}H- and ^{13}C NMR spectra) of this data that corresponded to the hydrindenones that were originally assigned structures **6006A** and **6006D** by Jones and co-workers.

At this stage, I set out to resolve this structural issue via computational means. A subset of four diastereomeric candidate structures was identified (Figure VI–2), which, in addition to the three hydrindenone isomers already mentioned, included yet another structure (**6006C**) that is the C3 epimer of **6006D**. In light of the fact that an NOE was observed between H3a and H7a in each of the compounds isolated from the FVP experiment,[340] a *cis* relationship at the bicyclo[4.3.0]nonane ring fusion has been maintained in each of these candidate structures. With that structural restriction in place, the position (C1 vs. C3) and relative configuration [down (dn) vs. up] of the ethenyl group was then systematically varied.

---

340 Personal communication with Ms. Susan G. Brown (Hoye group); the full details of these (and related) studies will be published in due course.

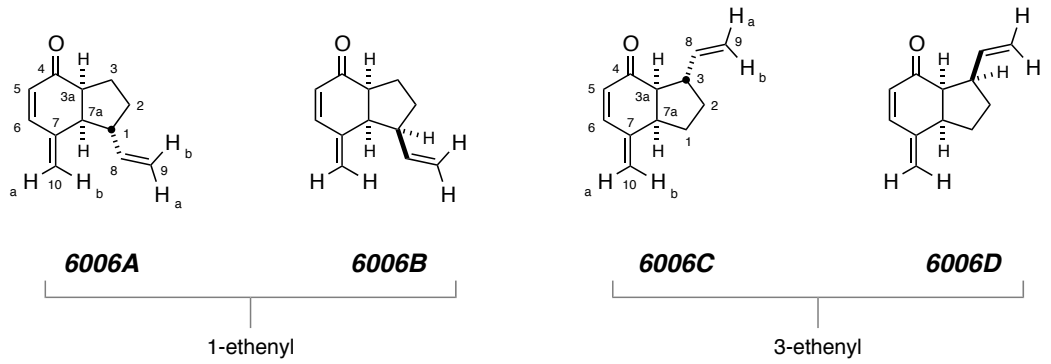


Figure VI–2 | Diastereomeric hydrindenone candidate structures (**6006A**–**6006D**) examined in the computational study of Section A.

Each of the candidate structures **6006A**–**6006D** was subjected to a preliminary molecular mechanics conformational search to yield four families of conformers. Further refinement of these conformers by DFT geometry optimization was then carried out with the M06-2X functional[341] wherein implicit solvation effects for chloroform were included. Finally, Boltzmann-weighted chemical shifts values were obtained from single-point GIAO NMR calculations that were carried out with the popular B3LYP functional (see Section A–3 for further details). The computed, Boltzmann-weighted proton and carbon chemical shifts (δ_{DFT}) for each of the isomeric hydrindenones **6006A**–**6006D** are compiled in Tables VI–1 and VI–2, respectively, as are the experimentally observed proton and carbon chemical shifts (δ_{EXP}) that have been assigned to structures **6006B** and **6006D**.

341 (a) Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-class Functionals and 12 Other Functionals. *Theor. Chem. Acc.* **2008**, *120*, 215–241. (b) Zhao, Y.; Truhlar, D. G. Density Functionals with Broad Applicability in Chemistry. *Acc. Chem. Res.* **2008**, *41*, 157–167.

Table VI–1 | Compilation of the computed (with chloroform solvation) proton NMR chemical shifts (δ_{DFT}) for the 1-ethenyl (**6006A**/**B**) and 3-ethenyl (**6006C**/**D**) hydrindenone isomers and the experimentally observed proton chemical shifts (δ_{EXP}) that have been assigned for structures **6006B** and **6006D** in $CDCl_3$.

[PROTON]	δ_{DFT} (1-ethenyl)			δ_{DFT} (3-ethenyl)		δ_{EXP}	
ATOM #	*6006A*	*6006B*	ATOM #	*6006C*	*6006D*	*"6006B"* [a]	*"6006D"* [b]
1	2.27	2.76	3	3.48	3.00	2.19	2.78
2_{dn}	1.92	1.81	2_{dn}	1.90	1.69	1.89	1.83
2_{up}	1.55	1.80	2_{up}	1.55	1.93	1.49	1.65
3_{dn}	2.75	2.62	1_{dn}	1.72	2.08	2.38	2.41
3_{up}	1.89	2.05	1_{up}	1.96	2.21	1.95	1.95
3a	3.06	2.90	3a	2.69	3.00	2.88	2.81
5	6.19	6.23	5	6.25	6.17	5.92	5.93
6	7.49	7.44	6	7.53	7.50	6.98	6.98
7a	2.75	3.42	7a	3.36	3.36	2.64	3.25
8	6.11	6.03	8	6.47	6.57	5.65	5.39
9a	5.35	5.08	9a	5.26	5.15	5.01	4.82
9b	5.14	5.20	9b	5.29	5.24	4.89	4.87
10a	5.93	5.91	10a	5.82	5.79	5.38	5.47
10b	5.62	5.83	10b	5.83	5.84	5.22	5.36

[a] **"6006B"** = "the ^{1}H NMR spectral data reported for **6006B**."

[b] **"6006D"** = "the ^{1}H NMR spectral data reported for **6006D**."

Table VI–2 | Compilation of the computed (with chloroform solvation) carbon NMR chemical shifts (δ_{DFT}) for the 1-ethenyl (**6006A**/**B**) and 3-ethenyl (**6006C**/**D**) hydrindenone isomers and the experimentally observed carbon chemical shifts (δ_{EXP}) that have been assigned for structures **6006B** and **6006D** in $CDCl_3$.

[CARBON]	δ_{DFT} (1-ethenyl)			δ_{DFT} (3-ethenyl)		δ_{EXP}	
ATOM #	*6006A*	*6006B*	ATOM #	*6006C*	*6006D*	*"6006B"* [a]	*"6006D"* [b]
1	51.9	54.1	3	47.9	52.7	49.8	50.3
2	29.6	27.7	2	29.2	29.9	30.4	26.1
3	23.4	23.8	1	33.1	31.7	26.0	30.0
3a	52.8	48.2	3a	57.3	56.9	49.5	47.4
4	205.3	205.7	4	204.7	205.2	200.6	200.9
5	126.0	128.8	5	127.1	128.6	126.5	128.0
6	149.7	150.6	6	149.8	150.8	146.0	147.5
7	146.3	147.8	7	149.5	151.5	141.0	141.7
7a	53.2	51.2	7a	45.4	44.7	50.7	48.3
8	147.3	143.1	8	148.4	146.4	140.7	137.9
9	114.4	113.7	9	110.8	111.9	115.9	115.4
10	123.6	122.3	10	122.0	121.0	121.7	122.1

[a] **"6006B"** = "the ^{13}C NMR spectral data reported for **6006B**."

[b] **"6006D"** = "the ^{13}C NMR spectral data reported for **6006D**."

In order to remove systematic error that may have accumulated during the DFT calculation process, the raw computed chemical shift values for **6006A–6006D** were further manipulated via linear scaling.[342] This process consisted of generating scatter plots for each of the computed proton and carbon data sets (*x* axis) versus the four

[342] E.g.: Rablen, P. R.; Pearlman, S. A.; Finkbiner, J. A Comparison of Density Functional Methods for the Estimation of Proton Chemical Shifts with Chemical Accuracy. *J. Phys. Chem. A* **1999**, *103*, 7357–7363.

different experimental proton and carbon data sets (*y* axis) that have been assigned to **6006B** and **6006D**. Thus, 16 unique plots were generated in this instance for the entire ensemble of computed versus experimental proton and carbon NMR data. With these plots in hand, regression analysis gave rise to a straight line from which the coefficient of determination (R^2), slope (*m*), and *y*-intercept (*b*) could be obtained. These latter two values were then used to calculate the scaled computed chemical shift (δ_{CORR}) for each unique proton or carbon nuclei in the individual candidate structures (see the Section A–3 for further information).

At this point it is important to address the logic by which computed chemical shifts will subsequently be compared to experimental values, since we are dealing here with experimental data sets that purportedly correspond to constitutionally isomeric structures. The order in which the various atom numbers appear in Tables VI–1 and VI–2 for the 1-ethenyl (**6006A** and **6006B**) and 3-ethenyl (**6006C** and **6006D**) isomeric hydrindenones have been purposefully arranged to reflect this logic. For example, the computed proton and carbon chemical shift values for atom 1 of the 1-ethenyl isomers will be compared with the experimental values that have been reported for atom 3 in structure **6006D**. Likewise, comparisons will be made between the computed values for atom 3 of the 3-ethenyl isomers with the experimental values that have been reported for atom 1 of structure **6006B**. The remaining atoms (2 and 3a–10) will simply be compared in a head-to-head fashion, regardless of which constitutional isomer is under consideration.

Three different criterions were employed to assess the 'goodness of fit' between the scaled computed and experimental chemical shifts–R^2, the total absolute error ($|\Delta\delta|_T$), and the corrected mean absolute error (CMAE)–and the results of these comparisons are complied in Tables VI–3A (proton) and VI–3B (carbon). With regard to the proton NMR spectral data assigned to "**6006B**", the computed values for **6006A** clearly show a better fit in both the total absolute error (1.04 ppm) and CMAE (0.04 ppm) criterion. Although a somewhat more satisfying value of R^2 (0.9857) was observed when

these experimental data are compared to the data computed for **6006B**, both the total absolute error (2.41 ppm) and CMAE (0.17 ppm) values are over twice as large. Finally, the experimental data reported for "**6006B**" vis-à-vis the computed shifts for both **6006C** and **6006D** reveal that these latter two structures are more or less equally poor fits.

Interestingly, comparison of the δ_{CORR} and δ_{EXP} values for the *carbon* NMR chemical shifts tells a somewhat different story (Table VI–3B). Namely, the δ_{CORR} values for the hydrindenone **6006B** show a noticeably superior match with *both* of the experimental data sets. However, it should be quickly pointed out that the computed shifts for **6006A** are also in good agreement (a close second place), particularly when one examines the total error (22.9 ppm) and CMAE (1.9 ppm) values versus δ_{EXP} for "**6006B**." Here again, the δ_{CORR} values for both **6006C** and **6006D** are poorer matches with both δ_{EXP} data sets by every metric of comparison. Notably, the total error is 1.2–2.3 times larger for these 3-ethenyl isomers than are those values for the alternative constitutional isomers **6006A** and **6006B**.

On the basis of the present computational study, it can be asserted with good confidence that Jones and co-workers did not isolate the 3-ethenyl hydrindenone **6006D** (or **6006C** for that matter) during their 1986 FVP studies.[339] Instead, it seems likely, particularly upon comparison of the computed versus experimental proton data sets, that the 1-ethenyl isomers **6006A** and **6006B** were the principal hydrindenone products of this chemistry. Furthermore, these results suggest that the experimental data that was originally assigned to structure **6006B** actually corresponds to **6006A**, the latter of which was isolated by J. E. Kabrhel[338] upon deprotection and Cope rearrangement of the [6]metacyclophane **6004** (Scheme VI–1).

Table VI–3 | Correlation matrices of scaled computed (δ_{CORR}) versus experimental (δ_{EXP}) data sets.[a] **A**: Comparison of computed (for **6006A**–**6006D**) and experimental (for "**6006B**" and "**6006D**") proton chemical shifts. **B**: Comparison of computed (for **6006A**–**6006D**) and experimental (for "**6006B**" and "**6006D**") carbon chemical shifts.

A. PROTON

δ_{EXP}			δ_{CORR}			
			6006A	***6006B***	***6006C***	***6006D***
"6006B"		R^2	0.9758	***0.9857***	0.9704	0.9764
		$\lvert\Delta\delta\rvert_T$	***1.04***	2.41	3.89	3.49
		CMAE	***0.07***	0.17	0.28	0.25
"6006D"		R^2	0.9600	***0.9911***	0.9611	0.9687
		$\lvert\Delta\delta\rvert_T$	2.57	***1.12***	2.61	2.37
		CMAE	0.18	***0.08***	0.19	0.17

B. CARBON

δ_{EXP}			δ_{CORR}			
			6006A	***6006B***	***6006C***	***6006D***
"6006B"		R^2	0.9986	***0.9992***	0.9881	0.9830
		$\lvert\Delta\delta\rvert_T$	22.9	***20.5***	46.8	42.7
		CMAE	1.9	***1.7***	3.9	3.6
"6006D"		R^2	0.9958	***0.9987***	0.9892	0.9854
		$\lvert\Delta\delta\rvert_T$	36.0	***27.4***	46.7	40.2
		CMAE	3.0	***2.3***	3.9	3.4

[a] Comparisons are expressed as R^2 (unitless), the total absolute error between corrected theoretical (δ_{CORR}) and experimental (δ_{EXP}) chemical shifts ($\lvert\Delta\delta\rvert_T$, ppm),and the corrected mean absolute error (CMAE, ppm).

A–3. COMPUTATIONAL DETAILS

Molecular mechanics calculations were carried out using MacroModel[343] as implemented in the Maestro[344] graphical user interface. Each of the candidate structures was subjected to Monte Carlo Multiple Minimum (MCMM)[345] conformational searches where all minima within a 5.02 kcal/mol (21.0 kJ/mol) energetic window were retained. From this treatment, there was obtained a manageable number of conformers for **6006A** (11), **-B** (6), **-C** (11), and **-D** (11). Each of these conformations was optimized with PRCG (500 steps) employing the MMFFs force field and the GB/SA continuum solvation treatment for chloroform. The default values for all other parameters were retained.

The Gaussian 09 electronic structure-modeling platform[346] was employed for all density functional theory (DFT) calculations.

The conformational minima obtained as described above were fully optimized at the DFT level employing the hybrid meta-GGA functional M06-2X[341] in conjunction with the 6-31+G(d,p) basis set. The keyword 'integral(ultrafinegrid)' was specified in the route section for all DFT geometry optimizations. Frequency calculations conducted (by specifying the keyword 'freq = noraman' in the route section) at the same level of theory

---

343 MacroModel, version 9.7, Schrödinger, LCC, New York, NY, **2009**.

344 Maestro, version 9.0, Schrödinger, LCC, New York, NY, **2009**.

345 Chang, G.; Guida, W. C.; Still, W. C. An Internal Coordinate Monte Carlo Method for Searching Conformational Space. *J. Am. Chem. Soc.* **1989**, *111*, 4379-4386.

346 Gaussian 09, Revision A.1, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, **2009**.

provided the free energy values (i.e., 'Sum of electronic and thermal Free Energies') that were used to determine Boltzmann-weighted chemical shifts.[347] The inclusion of solvation effects for chloroform was accomplished by specifying the integral equation formalism polarized continuum model[348] wherein the solute cavities were constructed using united-atom radii[349] [i.e., keywords 'scrf = (IEFPCM, read, solvent = chloroform)' in the route section and 'radii = UA0' after the molecular coordinates section].

The optimized conformer geometries thus obtained for the isomeric hydrindenones **6006A**–**6006D** were subjected to single-point GIAO NMR calculations employing the B3LYP functional, the 6-311+G(2d,p) basis set, and the IEFPCM formalism for chloroform solvation. For these GIAO calculations, the solute cavities were constructed using Bondi radii[350] (i.e., by specifying the keyword 'radii = bondi' after the molecular coordinates section).

In order to determine the chemical shift [$\delta^{x}_{\mathrm{DFT}}$ (^{1}H)] for a particular proton nucleus within a candidate structure, the isotropic chemical shift for that nucleus (σ^{x}) was referenced to the isotropic chemical shift of the protons of tetramethylsilane (σ^{TMS}) according to equation 6.1:

$$\delta^{x}_{\mathrm{DFT}}(^{1}\mathrm{H}) = \left| \sigma^{\mathrm{TMS}} - \sigma^{x} \right| \qquad (6.1)$$

---

347 In this particular instance, a few of the conformers that were located by the molecular mechanics conformational search for **6006B** (1 of 6) **6006C** (2 of 11) and **6006D** (1 of 11) *did not* converge to a local minimum during the subsequent DFT optimizations, as evidenced by the presence of one low energy, imaginary (i.e., negative) frequency.

348 (a) Miertus, S.; Scrocco, E.; Tomasi, J. Electrostatic Interaction of a Solute with a Continuum. A Direct Utilization of Ab Initio Molecular Potentials for the Prevision of Solvent Effects. *Chem. Phys.* **1981**, *55*, 117-129. (b) Cancès, E.; Mennucci, B.; Tomasi, J. A New Integral Equation Formalism for the Polarizable Continuum Model: Theoretical Background and Applications to Isotropic and Anisotropic Dielectrics. *J. Chem. Phys.* **1997**, *107*, 3032-3041.

349 Barone, V.; Cossi, M.; Tomasi, J. A New Definition of Cavities for the Computation of Solvation Free Energies by the Polarizable Continuum Model. *J. Chem. Phys.* **1997**, *107*, 3210-3220.

350 Bondi, A. van der Waals Volumes and Radii. *J. Phys. Chem.* **1964**, *68*, 441-451.

The value computed for σ^{TMS} (31.86 ppm) was determined at the same level of theory. Isotropic chemical shifts for proton nuclei that were symmetry-related (i.e., methyl groups) were arithmetically averaged prior to being referenced.

The sp^2- and sp^3-hybridized carbon atoms were referenced to benzene and methanol, respectively, according to the multi-standard approach.[351] Thus, the computed chemical shift [δ^{x}_{DFT} (^{13}C)] for a particular carbon nucleus within a candidate structure was determined according to equation 6.2:

$$\delta^{x}_{DFT}(^{13}C) = \left| \sigma^{REF} - \sigma^{x} + \delta^{REF} \right| \tag{6.2}$$

where σ^{REF} is the isotropic chemical shift for the carbon(s) of either benzene (48.67 ppm) or methanol (128.96 ppm) that were computed at the same level of theory, σ^{x} is the computed isotropic chemical shift of the carbon nucleus of the candidate structure, and δ^{REF} is the experimentally observed chemical shift for either benzene (128.37 ppm) or methanol (50.41 ppm) in $CDCl_3$.[352]

The referenced chemical shifts thus obtained have been reported as a Boltzmann-weighted average across all conformers for a particular candidate structure according to equation 6.3:

$$\delta_i = \sum_i \left[\frac{\delta_i^{x} \, e^{(-\Delta E_i - RT)}}{\sum_j e^{(-\Delta E_j - RT)}} \right] \tag{6.3}$$

---

351 Sarotti, A. M.; Pellegrinet, S. C. A Multi-standard Approach for GIAO ^{13}C NMR Calculations. *J. Org. Chem.* **2009**, *74*, 7254–7260.

352 Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. NMR Chemical Shifts of Common Laboratory Solvents as Trace Impurities. *J. Org. Chem.* **1997**, *62*, 7512–7515.

where δ_i^x is the referenced chemical shift of nucleus x in conformer i, ΔE_i is the difference in free energy between the ith conformer and the most stable (global minimum) conformer, j runs across all conformers under consideration, R is the universal gas constant, and T = 298 K.

The Boltzmann-weighted proton and carbon δ_{DFT} values for **6006A–6006D** were further manipulated via linear correction. Each of the two experimental data sets (δ_{EXP}) for "**6006B**" and "**6006D**" were plotted against the computed data sets (i.e., **6006A** δ_{DFT} vs. "**6006B**" δ_{EXP}, **6006A** δ_{DFT} vs. "**6006D**" δ_{EXP}, and so on). Values for the coefficient of determination (R^2), slope (m), and y-intercept (b) were then obtained upon linear regression analysis of each of these scatter plots. Employing the latter two values, the corrected proton and carbon chemical shifts (δ_{CORR}) were calculated according to equation 6.4:

$$\delta_{CORR}^{x} = \frac{\delta_{DFT}^{x} - b}{m} \tag{6.4}$$

Finally, with these scaled chemical shifts in hand, the total absolute error ($|\Delta\delta|_T$) and the corrected mean absolute error (CMAE) were determined according to equations 6.5 and 6.6, respectively:

$$\left| \Delta\delta \right|_T = \sum_i \left| \delta_{CORR}^{i} - \delta_{EXP}^{i} \right| \tag{6.5}$$

$$\textbf{CMAE} = \frac{\sum_i^N \left| \delta_{CORR}^{i} - \delta_{EXP}^{i} \right|}{N} \tag{6.6}$$

where δ_{CORR}^{i} is the scaled computed chemical shift for nucleus i, δ_{EXP}^{x} is the experimentally observed chemical shift that has been assigned to nucleus i, and N is the total number of proton or carbon nuclei that are being compared.

B. CONCERNING THE RELATIVE CONFIGURATION OF THE AB RING SYSTEM OF PHOMOPSICHALASIN[353]

HYPOTHESIS STATEMENT:

*THE REATLIVE CONFIGURATION WITHIN (AT LEAST) THE AB RING SYSTEM OF THE CYCTOCHALASAN-LIKE SECONDARY METABOLITE PHOMOPSICHALASIN ("**6009**") WAS INCORRECTLY ASSIGNED.*

B–1. THE STRUCTURAL DILEMMA

In 1995, Horn and co-workers[354] reported the isolation of a new cytochalasan-like, hexacyclic secondary metabolite from the endophytic fungus *Phomopsis* sp. They named this compound phomopsichalasin and assigned it structure **6009** (Figure VI–3) on the basis of extensive 1-D and 2-D NMR experiments. Twelve years later, Pornpakakul and co-workers[355] disclosed the isolation and structure elucidation of diaporthichalasin (**6010**), a metabolite of the filamentous endophytic fungus *Diaporthe* sp. Bkk3. The constitution and relative configuration of **6010** were unambiguously established by a single crystal X-ray diffraction study.[355]

The structures of **6009** and **6010** piqued our group's interest for a number of reasons. Most alluring of all was the possibility that both of these hexaepimeric natural products might ultimately find their origin in the all-(*E*) tetraene **6011** (Figure VI–3).

---

353 Reproduced in part with permission from "Case Study of Empirical and Computational Chemical Shift Analyses: Reassignment of the Relative Configuration of Phomopsichalasin to that of Diaporthichalasin," Brown, S. G.; Jansma, M. J.; Hoye, T. R. *J. Nat. Prod.* **2012**, *ASAP* [Publication Date (Web): June 25, 2012]. Copyright © 2012 The American Chemical Society and American Society of Pharmacognosy.

354 Horn W. S.; Simmonds, M. S. J.; Schwartz, R. E.; Blaney, W. M. Phomopsichalasin, a Novel Antimicrobial Agent from an Endophytic *Phomopsis* sp. *Tetrahedron* **1995**, *51*, 3969–3978.

355 Pornpakakul, S.; Roengsumran, S.; Deechangvipart, S.; Petsom, A.; Muangsin, N.; Ngamrojnavanich, N.; Sriubolmas, N.; Chaichit, N.; Ohta, T. Diaporthichalasin, a Novel CYP3A4 Inhibitor from an Endophytic *Diaporthe* sp. *Tetrahedron Lett.* **2007**, *48*, 651–655.

Specifically, we have proposed[356] that a pair of *spontaneous* (i.e., non-enzyme catalyzed) intramolecular Diels–Alder (IMDA) cycloadditions are operative in the biosynthesis of these natural products. Yet, for reasons that have been discussed elsewhere,[356] the relative configuration of C16 and C18 that is present within the AB ring system of **6009** would be *unexpected* were it to arise via a thermal, substrate-controlled IMDA reaction of **6011**. On the other hand, the C16/C18 relative configuration of diaporthichalasin (**6010**) is entirely consistent with that expected from such a pericyclic event.

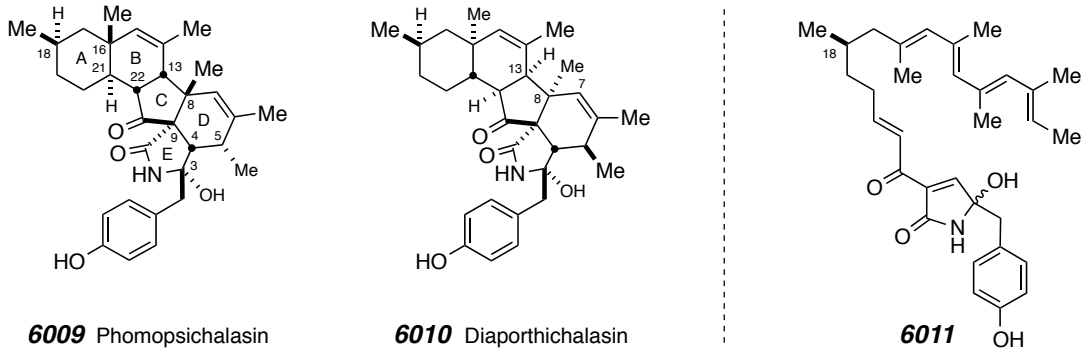


Figure VI–3 | Chemical structures that have been assigned to the diastereomeric, cytochalasan-like natural products phomopsichalasin (**6009**) and diaporthichalasin (**6010**).

Our skepticism regarding the relative configuration within the AB bicycle of **6009**, which, at this point, was founded entirely on hypothetical conjecture, nevertheless compelled us take a fresh look at the ^{1}H NMR spectral data that were reported by Horn and co-workers. One study in particular, which was reported in 1986 by Grant and co-workers,[357] bears direct relevance to the question at hand. Employing natural abundance, proton-decoupled ^{2}H NMR spectroscopy, these researchers revealed that a methyl

356 Sizova, E. P. Second Generation Synthesis of UCS1025A. Synthetic Efforts Toward Total Syntheses of CJ-16,264 and Phomopsichalasin. Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2009**.

357 Dalling, D. K.; Curtis, J.; Grant, D. M. Deuterium Chemical Shifts and Chemical Shift Parameters in Methylcyclohexanes. *J. Org. Chem.* **1986**, *51*, 136–142.

substituent on a cyclohexane ring alters the chemical shift (δ) of neighboring proton resonances to an unexpected and rather dramatic degree ('Grant numbers,' Figure VI–4). Astonishingly, an equatorially- (**6012**-Me_{eq}) versus axially- (**6012**-Me_{ax}) oriented methyl group induces a difference of *over 0.5 ppm* in the δ value of the vicinal $H2_{ax}$ proton (relative to the δ value of H_{ax} in cyclohexane itself).

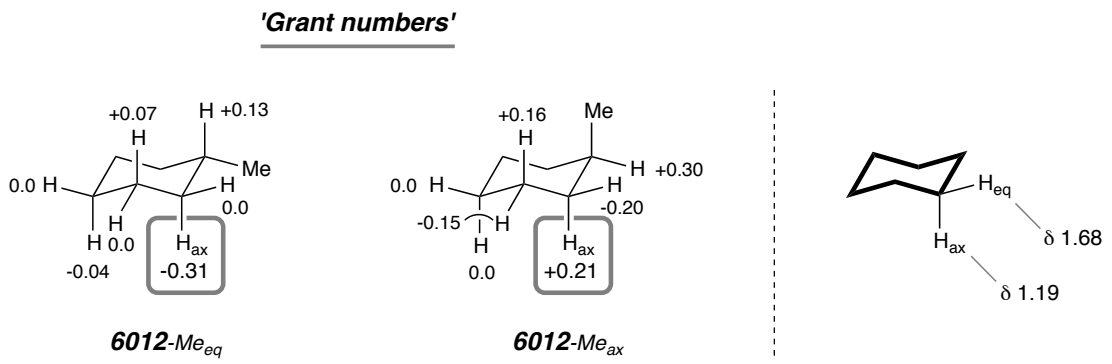


Figure VI–4 | Chemical shift perturbations of $H2_{ax}$ in methylcyclohexane that are induced by an equatorial (**6012**-Me_{eq}) vs. axial (**6012**-Me_{ax}) methyl group.

The two most revealing resonances in the ^1H NMR spectrum (collected in CD_3OD[354]) assigned to phomopsichalasin are $H17_{ax}$ and $H19_{ax}$ (Figure VI–5). Their high field δ values are, on the basis of the empirical analysis with the 'Grant numbers,' quite inconsistent with an axial orientation of the C27 methyl group. Furthermore, the δ values that have been assigned (in DMSO-d_6[355]) for $H17_{ax}$ and $H19_{ax}$ in the ^1H NMR spectrum of diaporthichalasin (**6010**), both of which are flanked by an equatorial methyl group, are in much better agreement with predicted values. It is also curious to note that, for two structures that are purportedly diastereomeric, the chemical shifts of $H17_{ax}$ and $H19_{ax}$ are remarkably similar. What then is the true structure of phomopsichalasin?

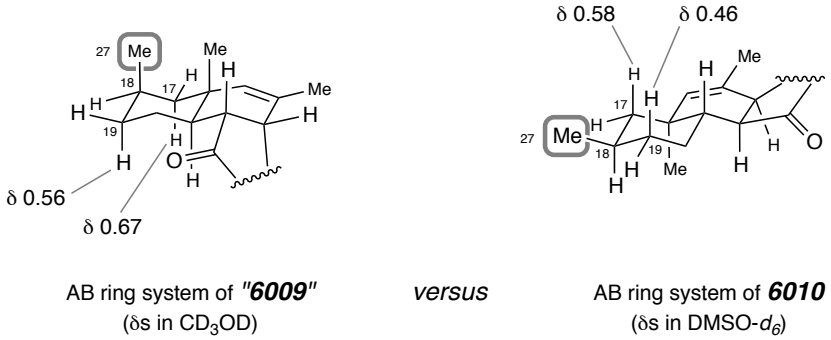


Figure VI–5 | Comparison of the reported δ values of $H17_{ax}$ and $H19_{ax}$ within the AB ring systems of phomopsichalasin ("**6009**") and diaporthichalasin (**6010**).

B–2. COMPUTATIONAL STUDY OF THE TRUNCATED ABC TRICYCLIC ISOMERS **6013A–6013D**

So that I could test the hypothesis that structure **6009** is an incorrect formulation for phomopsichalasin within (at least) the fused AB bicyclic subunit, a computational study was initiated. To make this study more tractable, four truncated structures were targeted that retained the ABC tricyclic substructure unit but lacked the additional complexity associated with the D- and E-rings and their substituents (Figure VI–6). Specifically, the proton and carbon NMR chemical shifts for the truncated substructures **6013A–6013D** were computed. Two of these substructures correspond to the ABC tricyclic skeleton common to both structures **6009** and **6010**. They are tetraepimeric at C16, C21, C22, and C13–i.e., truncated structure **6013A** has the same relative configuration within its A-ring as **6009** (i.e., "phomopsichalasin-like"), and **6013B** as **6010** ("diaporthichalasin-like"). For completeness, two additional structures were also interrogated–namely, **6013C** and **6013D**. In these latter two structures, the following structural elements were maintained: i) A *trans* orientation between H21 and H22 in light of the ~13 Hz $^3J_{H,H}$ value between these two protons,[354] and ii) a *cis* ring fusion across

C13/C22 based upon the observed[354] NOE and ~8 Hz $^{3}J_{H,H}$ value between protons H13 and H22 in the spectrum of phomopsichalasin.

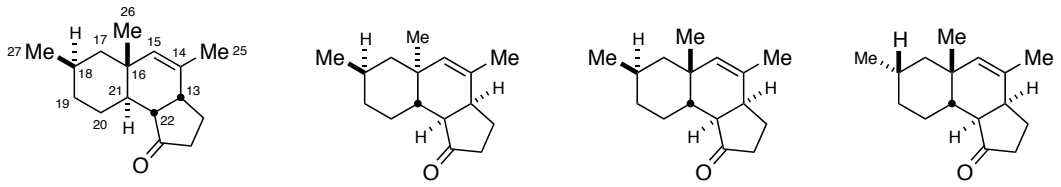


Figure VI–6 | Truncated ABC tricyclic isomers **6013A–6013D** that are the subject of the computational study of Section B.

Each of the structures **6013A–6013D** was subjected to an initial molecular mechanics conformational search, resulting in an easily manageable number of conformational minima (two for **6013A**, one for **6013B**, two for **6013C**, and three for **6013D**). As was the case in the previous section, DFT geometry optimizations were carried out with M06-2X[341] in conjunction with the 6-31+G(d,p) basis set. Finally, our WP04 and WC04 functionals[333] were employed in combination with the pcS-2 basis set[358] for single point GIAO NMR chemical shift calculations (implicit methanol solvation effects were included with IEFPCM).

The computed (and Boltzmann weighted) proton and carbon chemical shifts (δ_{DFT}) for **6013A–6013D** are listed in Tables VI–4 and VI–5, respectively, as are the experimental shifts reported for the analogous subset of nuclei in the ^{1}H and ^{13}C NMR spectra of phomopsichalasin (d_4-MeOH, δ_{EXP}). The differences between the computed and experimental shift values ($|\Delta\delta|$) are listed in the four rightmost columns. The bottom-line is presented as the mean absolute error (MAE) value for each of the

[358] Jensen, F. Basis Set Convergence of Nuclear Magnetic Shielding Constants Calculated by Density Functional Methods. *J. Chem. Theory Comput.* **2008**, *4*, 719–727.

comparisons of **6013A–6013D** vs. **"6009"** ("**6009**" is used here as a shorthand notation for "the spectral data reported for phomopsichalasin"). Using the full set of all 14 numbered protons (MAE_{FULL}, Table VI–4; cf. the structure of **6013A**, Figure VI–6), substructure **6013B** clearly shows a substantially better match between the calculated and experimental data sets than do any of the other structures (e.g., 0.11 ppm for **6013B** vs. 0.25, 0.20, and 0.25 ppm). Although this effect is less pronounced when one examines the computed versus experimental carbon data sets (Table VI–5), substructure **6013B** is still the best match (e.g., 4.8 ppm for **6013B** vs. 5.2, 5.8, and 6.7 ppm). If instead only the subset of proton nuclei that reside nearest to the point of difference in the relative configuration among **6013A–6013D** (i.e., atoms 17–19, 26, and 27) are compared, then the resulting "MAE_{LITE}" comparison favors substructure **6013B** to an even larger degree (Table VI–4, 0.11 ppm for **6013B** vs. 0.35, 0.21, and 0.27 ppm). If an identical type of comparison is made with the same subset of carbon nuclei, then the "MAE_{LITE}" values result in a similar conclusion (Table VI–5, 2.3 ppm for **6013B** vs. 3.2, 3.8, and 5.1 ppm).

Table VI–4 | Comparison of the computed (with methanol solvation) proton NMR chemical shifts (δ_{DFT}) for structures **6013A–6013D** with the experimentally observed shifts (δ_{EXP}) for the analogous subset of nuclei in the spectrum reported for phomopsichalasin (**"6009"**) in d_4-MeOH.

	δ_{DFT} (methanol)				δ_{EXP}	$\lvert\Delta\delta\rvert$ for δ_{DFT} *vs.* δ_{EXP}			
ATOM #	***6013A***	***6013B***	***6013C***	***6013D***	**"6009"** [a]	***6013A*** *vs.* **"6009"**	***6013B*** *vs.* **"6009"**	***6013C*** *vs.* **"6009"**	***6013D*** *vs.* **"6009"**
13	2.68	2.70	2.89	2.63	2.85	0.17	0.15	0.04	0.22
15	5.49	5.42	5.46	5.39	5.36	0.13	0.06	0.10	0.03
17_{eq}	1.41	1.40	1.33	1.24	1.45	0.04	0.05	0.12	0.21
17_{ax}	1.42	0.92	0.96	1.01	0.67	0.75	0.25	0.29	0.34
18	1.78	1.65	1.28	1.59	1.62	0.16	0.03	0.34	0.03
19_{eq}	1.38	1.58	1.42	1.31	1.64	0.26	0.06	0.22	0.33
19_{ax}	1.36	0.81	0.93	1.22	0.56	0.80	0.25	0.37	0.66
20_{eq}	1.45	1.55	1.38	1.67	1.50	0.05	0.05	0.12	0.17
20_{ax}	1.45	1.32	1.34	1.55	1.10	0.35	0.22	0.24	0.45
21	1.55	1.49	2.03	1.61	1.42	0.13	0.07	0.61	0.19
22	2.34	2.34	2.29	2.65	2.24	0.10	0.10	0.05	0.41
25	1.73	1.75	1.80	1.79	1.88	0.15	0.13	0.08	0.09
26	0.99	0.90	0.67	1.04	0.80	0.19	0.10	0.13	0.24
27	1.05	0.81	0.81	0.82	0.78	0.27	0.03	0.03	0.04
					MAE_{FULL} [b] **=**	***0.25***	***0.11***	***0.20***	***0.25***
					MAE_{LITE} [c] **=**	***0.35***	***0.11***	***0.21***	***0.27***
					DP4 probability [d] **=**	***<0.5%***	***>99.5%***	---	---

[a] **"6009"** = "the spectral data reported for phomopsichalasin." [b] Mean absolute error ($\lvert\Delta\delta_{AVE}\rvert$, ppm). Calculation includes all proton nuclei that are listed in the Table. [c] Including only the subset of proton nuclei 17–19, 26, and 27. [d] Scaled δ_{DFT} values derived from isotropic chemical shifts computed at the B3LYP/6-31G(d,p)//MMFF level of theory were employed (see ref 359).

Table VI–5 | Comparison of the computed (with methanol solvation) carbon NMR chemical shifts (δ_{DFT}) for structures **6013A–6013D** with the experimentally observed shifts (δ_{EXP}) for the analogous subset of nuclei in the spectrum reported for phomopsichalasin (**"6009"**) in d_4-MeOH.

	δ_{DFT} (methanol)				δ_{EXP}	$\lvert\Delta\delta\rvert$ for δ_{DFT} *vs.* δ_{EXP}			
ATOM #	***6013A***	***6013B***	***6013C***	***6013D***	**"6009"** [a]	***6013A*** *vs.* **"6009"**	***6013B*** *vs.* **"6009"**	***6013C*** *vs.* **"6009"**	***6013D*** *vs.* **"6009"**
13	40.1	40.2	35.9	39.9	52.0	11.9	11.8	16.1	12.1
14	138.5	139.9	138.5	138.7	129.5	9.0	10.4	9.0	9.2
15	136.8	135.3	134.6	134.8	139.7	2.9	4.4	5.1	4.9
16	28.6	28.6	29.5	28.9	37.0	8.4	8.4	7.5	8.1
17	45.5	47.7	48.7	42.5	49.4	3.9	1.7	0.7	6.9
18	28.4	26.8	28.4	27.4	28.4	0.0	1.6	0.0	1.0
19	32.0	36.1	35.6	30.0	36.9	4.9	0.8	1.3	6.9
20	20.2	24.3	31.8	21.2	24.5	4.3	0.2	7.3	3.3
21	36.3	35.8	36.8	31.4	42.2	5.9	6.4	5.4	10.8
22	44.7	44.8	49.0	41.6	50.8	6.1	6.0	1.8	9.2
23	230.9	230.9	231.0	230.8	221.3	9.6	9.6	9.7	9.5
25	21.3	21.4	21.4	21.6	25.5	4.2	4.1	4.1	3.9
26	23.1	19.9	32.5	26.9	23.1	0.0	0.0	9.4	3.8
27	22.2	24.1	23.8	24.0	19.9	2.3	1.0	3.9	4.1
					MAE_{FULL} [b] =	***5.2***	***4.8***	***5.8***	***6.7***
					MAE_{LITE} [c] =	***3.2***	***2.3***	***3.8***	***5.1***
					DP4 probability [d] =	***12.6%***	***87.4%***	---	---

[a] **"6009"** = "the spectral data reported for phomopsichalasin." [b] Mean absolute error ($\lvert\Delta\delta_{AVE}\rvert$, ppm). Calculation includes all proton nuclei that are listed in the Table. [c] Including only the subset of proton nuclei 17–19, 26, and 27. [d] Scaled δ_{DFT} values derived from isotropic chemical shifts computed at the B3LYP/6-31G(d,p)//MMFF level of theory were employed (see ref 359).

The MAE parameter that was employed in the above analysis is a straightforward and common method for judging the relative "goodness of fit" between computed and experimental NMR data sets.[314,317] Smith and Goodman recently introduced a more sophisticated, statistical analysis[359]–namely, the DP4 probability–that was developed for the specific instance where a single experimental NMR spectrum could be assigned to one of many possible diastereomeric candidate structures. Given the relative frequency with which this dilemma is encountered in natural product structure elucidation, it is perhaps no surprise that the DP4 probability has already found use in this arena.[360] The DP4 protocol specifies use of the MMFF force field to optimize conformer geometries, which are then subjected to single point DFT NMR calculations (with the B3LYP functional). The Boltzmann weighted chemical shifts thus generated are then used to calculate the DP4 probability for each candidate structure. This final step is aided by use of an online applet.[361] This analysis was applied to the computed proton and carbon data sets for each of **6013A** and **6013B** vs. the δ_{EXP} data sets. The DP4 probabilities also indicate that the truncated structure **6013B** (i.e., the "diaporthichalasin-like" stereoisomer) is a much better fit than **6013A** with the spectral data reported for phomopsichalasin with >99.5% (Table VI–4) and 87.4% (Table VI–5) confidence intervals.

In the interim, Professor Pornpakakul kindly provided our group with a generous sample of diaporthichalasin (**6010**). Ms. Susan G. Brown, the Hoye group NMR

---

359 Smith, S. G.; Goodman, J. M. Assigning Stereochemistry to Single Diastereomers by GIAO NMR Calculation: The DP4 Probability. *J. Am. Chem. Soc.* **2010**, *132*, 12946–12959.

360 For recent use of DP4 probability in the context of natural product structure elucidation, see: (a) Paterson, I.; Dalby, S. M.; Roberts, J. C.; Naylor, G. J.; Guzmán, E. A.; Isbrucker, R.; Pitts, T. P.; Linley, P.; Divlianska, D.; Reed, J. K.; Wright, A. E. Leiodermatolide, a Potent Antimitotic Macrolide from the Marine Sponge *Leiodermatium* sp. *Angew. Chem. Int. Ed.* **2011**, *50*, 3219–3223. (b) Lodewyk, M. W.; Tantillo, D. J. Prediction of the Structure of Nobilisitine A Using Computed NMR Chemical Shifts. *J. Nat. Prod.* **2011**, *74*, 1339–1343. (c) Wyche, T. P.; Hou, Y.; Braun, D.; Cohen, H. C.; Xiong, M. P.; Bugni, T. S. First Natural Analogs of the Cytotoxic Thiodepsipeptide Thiocoraline A from a Marine *Verrucosispora* sp. *J. Org. Chem.* **2011**, *76*, 6542–6547.

361 http://www-jmg.ch.cam.ac.uk/tools/nmr/DP4/

spectroscopy aficionado, recorded and interpreted a set of 1D and 2D NMR spectra in $CDCl_3$. She then provided me with a subset of this data (^1H and ^{13}C NMR spectra). The DFT computational analysis for **6013A–6013D** was repeated using PCM chloroform solvation. Comparison of these computed δ_{DFT} values with our experimental $CDCl_3$ data across the same subset of proton and carbon nuclei as before (Tables VI–6 and VI–7) resulted in MAE_{FULL}/MAE_{LITE} values and DP4 probabilities that once again show a far better match with the "diaporthichalasin-like" substructure **6013B**. In addition, the magnitudes of the MAE values for the methanol vs. the chloroform analyses are strikingly similar, which lends confidence that this methodology is applicable to a polar protic solvent.

The hypothesis that (at least) the AB ring system of phomopsichalasin was incorrectly assigned in 1995[354] has been strongly supported by the results of the present computational study. On the basis of comparison of the computed proton and carbon NMR chemical shifts for the candidate structures **6013A–6013D** with a subset of the experimental values that have been reported form phomopsichalasin, we are left to conclude that the proposed C16/C18 relative configuration (cf. substructure **6013A**) is actually *identical* to that found in the AB ring system of diaporthichalasin (cf. substructure **6013B**).

Table VI–6 | Comparison of the computed (with chloroform solvation) proton NMR chemical shifts (δ_{DFT}) for structures **6013A–6013D** with the experimentally observed shifts (δ_{EXP}) for the analogous subset of nuclei in the spectrum of diaporthichalasin (**6010**) in $CDCl_3$.

	δ_{DFT} (chloroform)				δ_{EXP}	$\lvert\Delta\delta\rvert$ for δ_{DFT} *vs.* δ_{EXP}			
ATOM #	***6013A***	***6013B***	***6013C***	***6013D***	**6010**	***6013A*** *vs.* **6010**	***6013B*** *vs.* **6010**	***6013C*** *vs.* **6010**	***6013D*** *vs.* **6010**
13	2.59	2.62	2.82	2.55	2.98	0.39	0.36	0.16	0.43
15	5.47	5.40	5.45	5.37	5.39	0.08	0.01	0.06	0.02
17_{eq}	1.39	1.38	1.31	1.23	1.45	0.06	0.07	0.14	0.22
17_{ax}	1.42	0.91	0.97	1.00	0.72	0.70	0.19	0.25	0.28
18	1.77	1.63	1.28	1.56	1.63	0.14	0.00	0.35	0.07
19_{eq}	1.39	1.60	1.42	1.32	1.72	0.33	0.12	0.30	0.40
19_{ax}	1.33	0.78	0.93	1.23	0.60	0.73	0.18	0.33	0.63
20_{eq}	1.56	1.66	1.36	1.79	1.64	0.08	0.02	0.28	0.15
20_{ax}	1.43	1.31	1.32	1.49	1.21	0.22	0.10	0.11	0.28
21	1.46	1.40	2.09	1.53	1.40	0.06	0.00	0.69	0.13
22	2.30	2.30	2.19	2.59	2.44	0.14	0.14	0.25	0.15
25	1.72	1.74	1.78	1.77	1.88	0.16	0.14	0.10	0.11
26	0.99	0.90	0.68	1.03	0.82	0.17	0.08	0.14	0.21
27	1.05	0.82	0.81	0.83	0.82	0.23	0.00	0.01	0.01
					MAE_{FULL}[a] =	***0.25***	***0.10***	***0.23***	***0.22***
					MAE_{LITE}[b] =	***0.34***	***0.09***	***0.22***	***0.26***
					DP4 probability[c] =	***<0.5%***	***>99.5%***	---	---

[a] Mean absolute error ($\lvert\Delta\delta_{AVE}\rvert$, ppm). Calculation includes all proton nuclei that are listed in the Table.

[b] Including only the subset of proton nuclei 17–19, 26, and 27.

[c] Scaled δ_{DFT} values derived from shielding tensors computed at the B3LYP/6-31G(d,p)//MMFF level of theory were employed (see ref 359).

Table VI–7 | Comparison of the computed (with chloroform solvation) carbon NMR chemical shifts (δ_{DFT}) for structures **6013A–6013D** with the experimentally observed shifts (δ_{EXP}) for the analogous subset of nuclei in the spectrum of diaporthichalasin (**6010**) in $CDCl_3$.

	δ_{DFT} (chloroform)				δ_{EXP}	$\lvert\Delta\delta\rvert$ for δ_{DFT} *vs.* δ_{EXP}			
ATOM #	***6013A***	***6013B***	***6013C***	***6013D***	**6010**	***6013A*** *vs.* **6010**	***6013B*** *vs.* **6010**	***6013C*** *vs.* **6010**	***6013D*** *vs.* **6010**
13	40.8	41.0	36.6	40.7	50.4	9.6	9.4	13.8	9.7
14	137.0	138.5	136.9	137.3	127.7	9.3	10.8	9.2	9.6
15	136.6	135.1	134.7	134.5	139.0	2.4	3.9	4.3	4.5
16	29.4	29.4	30.3	29.6	36.0	6.6	6.6	5.7	6.4
17	46.4	48.6	49.6	43.5	48.1	1.7	0.5	1.5	4.6
18	29.2	27.7	29.2	28.2	27.1	2.1	0.6	2.1	1.1
19	32.9	36.9	36.4	30.7	35.7	2.8	1.2	0.7	5.0
20	20.7	24.8	32.7	21.8	23.4	2.7	1.4	9.3	1.6
21	37.4	36.9	37.3	32.5	41.1	3.7	4.2	3.8	8.6
22	45.0	45.0	49.6	42.0	49.2	4.2	4.2	0.4	7.2
23	226.6	226.6	226.5	226.6	218.5	8.1	8.1	8.0	8.1
25	22.2	22.3	22.4	22.5	25.1	2.9	2.8	2.7	2.6
26	24.1	20.9	33.4	27.8	19.7	4.4	1.2	13.7	8.1
27	23.1	25.1	24.7	24.9	22.7	0.4	2.4	2.0	2.2
				MAE_{FULL}[a] =		***4.3***	***4.1***	***5.5***	***5.7***
				MAE_{LITE}[b] =		***3.0***	***2.1***	***4.3***	***4.6***
				DP4 probability[c] =		***3.2%***	***96.8%***	---	---

[a] Mean absolute error ($\lvert\Delta\delta_{AVE}\rvert$, ppm). Calculation includes all proton nuclei that are listed in the Table.

[b] Including only the subset of proton nuclei 17–19, 26, and 27.

[c] Scaled δ_{DFT} values derived from shielding tensors computed at the B3LYP/6-31G(d,p)//MMFF level of theory were employed (see ref 359).

On a final and somewhat tangential note, during the course of this study we noticed that the computed chemical shift of H13 in the "diaporthichalasin-like" truncated structure **6013B** (δ_{DFT} 2.70) was underestimated by 0.15 ppm in comparison to the experimentally observed (in CD_3OD[354]) value (δ_{EXP} 2.85) (left hand portion of Figure VI–7; *ent*-**6013B** was used because its three-dimensional structure can be more clearly depicted). Notice in the structure of diaporthichalasin (**6010**, see Figure VI–3) that there are two non-hydrogen substituents on the adjacent carbon (C8), one of which (C7) is *anti* to H13. On the basis of the 'Grant numbers' that were discussed previously (cf. Figure VI–4), one might expect H13 to be relatively deshielded by the presence of the C7 carbon substituent. In order to model this phenomenon without including the entire D-ring of diaporthichalasin, a derivative of **6013B** was constructed that possessed an *anti* methyl substituent at C8, the reasoning being that it would serve as a surrogate for C7 of **6010**. Indeed, the computed chemical shift for H13 (δ_{DFT} 2.88) in substructure *ent*-**6013B-Me** (right portion of Figure VI–7) is in much better agreement with the experimental value.

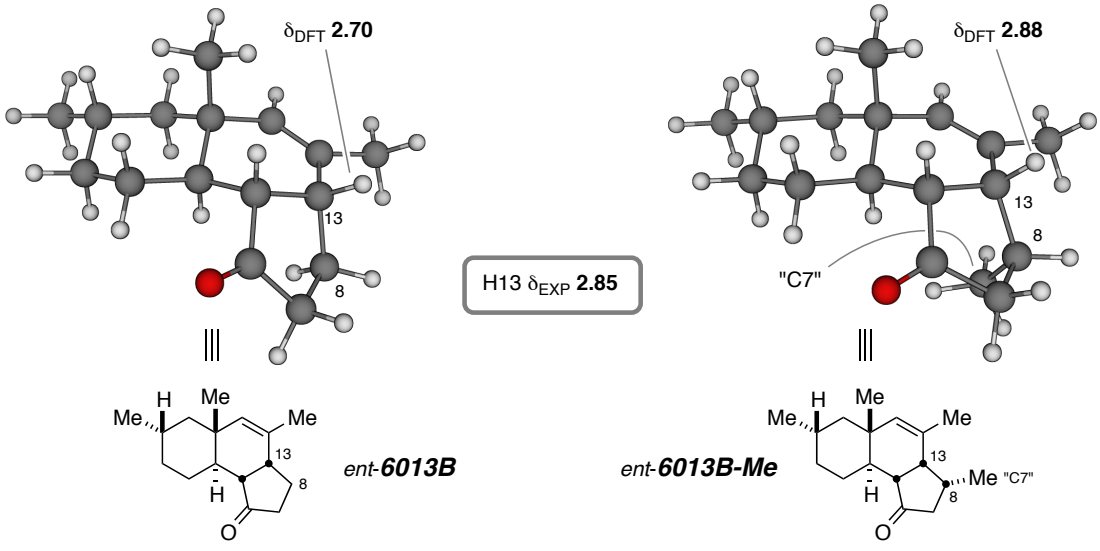


Figure VI–7 | A 'Grant effect' on the computed chemical shift (δ_{DFT}) for H13 in *ent*-**6013B** vis-à-vis δ_{DFT} in *ent*-**6013B-Me**. The H13–C13–C8–"C7" dihedral angle within *ent*-**6013B-Me** is computed to be *ca.* 160°.

B–3. COMPUTATIONAL DETAILS

Molecular mechanics conformational searches were carried out for each of the truncated ABC tricyclic isomers in a manner that was entirely analogous to that described in Section A–3. From these MCMM searches, 2 (**6013A**), 1 (**6013B**), 2 (**6013C**), and 3 (**6013D**) conformers were located within a 5.02 kcal/mol (21.0 kJ/mol) energetic window.

The conformational minima obtained as described above were fully optimized at the DFT level employing the hybrid meta-GGA functional M06-2X[341] in conjunction with the 6-31+G(d,p) basis set. Frequency calculations conducted at the same level of theory provided the free energy values that were used to determine Boltzmann-weighted chemical shifts. The inclusion of solvation effects for methanol and chloroform was accomplished by specifying the integral equation formalism polarized continuum model (IEFPCM)[348] wherein the solute cavities were constructed using united-atom radii.[349]

The optimized conformer geometries for **6013A**–**6013D** were subjected to single-point GIAO NMR calculations employing the hybrid GGA functionals WP04 (for proton) and WC04 (for carbon),[333] Jensen's pcS-2 basis set,[358] and the IEFPCM formalism for methanol and chloroform solvation. For all single-point GIAO NMR calculations, the solute cavities were constructed using Bondi radii.[350] [For a slightly more detailed discussion regarding the practical issues (i.e., keywords) associated with DFT geometry optimizations and GIAO NMR calculations, the reader is directed to Section A–3 of this Chapter.]

The isotropic chemical shift for a particular proton nucleus (σ^x) within a candidate structure was referenced to the isotropic chemical shift of the protons of tetramethylsilane (σ^{TMS}) in order to obtain the chemical shift [δ^x_{DFT} (^{1}H)] (see equation 6.1 in Section A–3). The values computed for σ^{TMS} (31.77 ppm and 31.78 ppm for methanol and chloroform IEFPCM solvation, respectively) were determined at the same level of theory. Isotropic

chemical shifts for proton nuclei that were symmetry-related (i.e., methyl groups) were arithmetically averaged prior to being referenced.

The multi-standard approach[351] (see equation 6.2 in Section A–3) was again employed to obtain the computed chemical shifts [$\delta^{x}_{\mathrm{DFT}}$ (^{13}C)] for the carbon nuclei in the candidate structures **6013A–6013D** by referencing the sp^2- and sp^3-hybridized carbon atoms to benzene and methanol, respectively. The isotropic chemical shift values (σ^{REF}) for the carbon(s) of either benzene (57.18 ppm and 57.40 ppm with methanol and chloroform IEFPCM solvation, respectively) or methanol (136.38 ppm and 136.63 ppm with methanol and chloroform IEFPCM solvation, respectively) were computed at the same level of theory. The experimentally observed chemical shifts (δ^{REF}) in these two solvents for either benzene [129.34 ppm (CD_3OD) and 128.37 ppm ($CDCl_3$)] or methanol [49.86 ppm (CD_3OD) and 50.41 ppm ($CDCl_3$)] were obtained from the literature.[352]

In situations were more than one low energy conformer was located for a particular candidate structure, the referenced proton and carbon chemical shifts have been expressed as a Boltzmann-weighed average across all conformers (see equation 6.3 in Section A–3). Finally, with these computed chemical shifts in hand, the mean absolute error (MAE) was determined according to equation 6.6:

$$\mathbf{MAE} = \frac{\sum_{i}^{N} \left| \delta^{i}_{\mathrm{DFT}} - \delta^{i}_{\mathrm{EXP}} \right|}{N} \tag{6.6}$$

where $\delta^{i}_{\mathrm{DFT}}$ is the computed chemical shift for nucleus *i*, $\delta^{x}_{\mathrm{EXP}}$ is the experimentally observed chemical shift that has been assigned to nucleus *i*, and *N* is the total number of proton or carbon nuclei that are being compared.

C. THE PATCHOULI ALCOHOL SAGA CONTINUES

HYPOTHESIS STATEMENT:

*THE CURRENTLY ACCEPTED ^{1}H NMR ASSIGNMENTS FOR PATCHOULI ALOCHOL (**6014**) ARE INCORRECT.*

C–1. CONDENSED HISTORY OF PATCHOULI ALCOHOL

Patchouli [*Pogostemon cablin* (Blanco) Benth.] is an herbaceous plant of the mint family that is native to tropical regions of Asia, particularly Indonesia, Malaysia, and the Philippines.[362] In the early 19th century, the maritime transit of fine cashmere wool from India to Europe brought with it the leaves of this plant, since, at that time, they were the most potent moth repellent known.[363] Unbeknownst to buyers of the period, the fragrant and fixative scent that persisted in these pieces of fine clothing was due to the essential oil of patchouli, a substance that is now widely employed as a naturally occurring base material in the perfumery industry.[362] Today, the cultivation of *Pogostemon cablin* has extended to areas of central Asia and South America, from which an estimated 1200 tons of the essential oil of patchouli are produced annually by steam distillation of the dried leaves of the plant.[363]

Of the bouquet of more than 20 sesquiterpenes that are known constituents of the essential oil of patchouli,[364] by far the most abundant (35–40%) is (–)-patchouli alcohol (a.k.a. 'patchoulol' or 'patchouli camphor'). Since the time of its initial isolation in

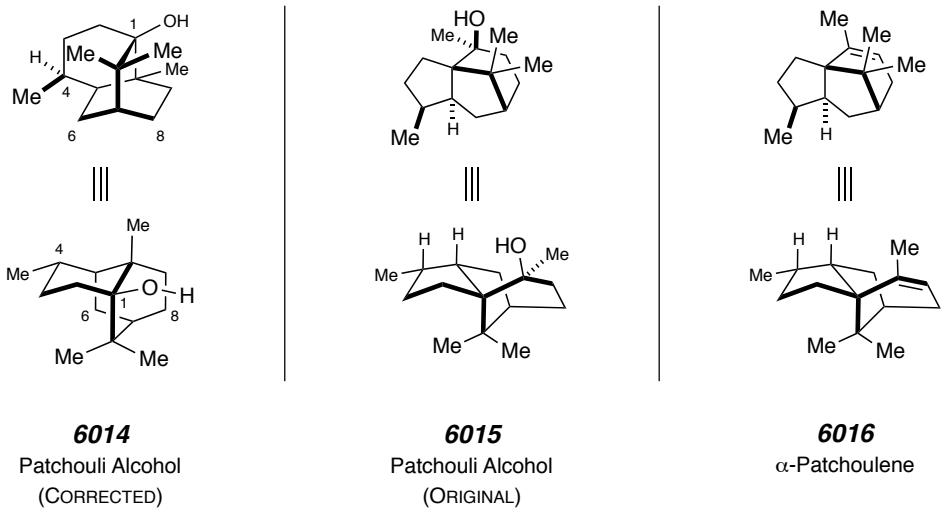
---

362 Akhila, A.; Tewari, R. Chemistry of Patchouli Oil: A Review. *CROMAP* **1984**, *6*, 38–54.

363 Kraft, P.; Weymuth, C.; Nussbaumer, C. Total Synthesis and Olfactory Evaluation of (1*R**,3*S**,6*S**,-7*S**,8*S**)-3-Hydroxy-6,8-dimethyltricyclo[5.3.1.$0^{3,8}$]undecan-2-one: A New Synthetic Route to the Patchoulol Skeleton. *Eur. J. Org. Chem.* **2006**, 1403–1412.

364 E.g.: (a) Buré, C. M.; Sellier, N. M. Analysis of the Essential Oil of Indonesian Patchouli (*Pogostemon cablin* Benth.) Using GC/MS (EI/CI). *J. Essent. Oil Res.* **2004**, *16*, 17–19. (b) Deguerry, F.; Pastore, L.; Wu, S.; Clark, A.; Chappell, J.; Schalk, M. The Diverse Sesquiterpene Profile of Patchouli, *Pogostemon cablin*, is Correlated with a Limited Number of Sesquiterpene Synthases. *Arch. Biochem. Biophys.* **2006**, *454*, 123–136.

crystalline form by Gal in 1869,[365] this tricyclic terpene alcohol has been the subject of considerable structural scrutiny. Although Gal had neither the means nor the theoretical basis to propose a structure for patchouli alcohol, several preliminary studies[366] appeared throughout the late 1800s that established its partial identity as a tertiary alcohol that possessed the molecular formula $C_{15}H_{26}O$. As a result of these and related studies, Treibs proposed a tentative structure for this natural product in 1949.[367] Soon thereafter, this initial assignment was revised when, in 1961, Büchi and co-workers reported an elegant series of synthetic and degradative studies that implicated **6015** as the true structure of patchouli alcohol[368] (Figure VI–8).



6014
Patchouli Alcohol
(CORRECTED)

6015
Patchouli Alcohol
(ORIGINAL)

6016
α-Patchoulene

Figure VI–8 | Chemical structures of patchouli alcohol (**6014**), its originally assigned structure (**6015**), and α-patchoulene (**6016**).

---

365 Gal, H. Ueber ein Homologes des Borneocamphers. *Justus Liebigs Ann. Chem.* **1869**, *150*, 374–376.

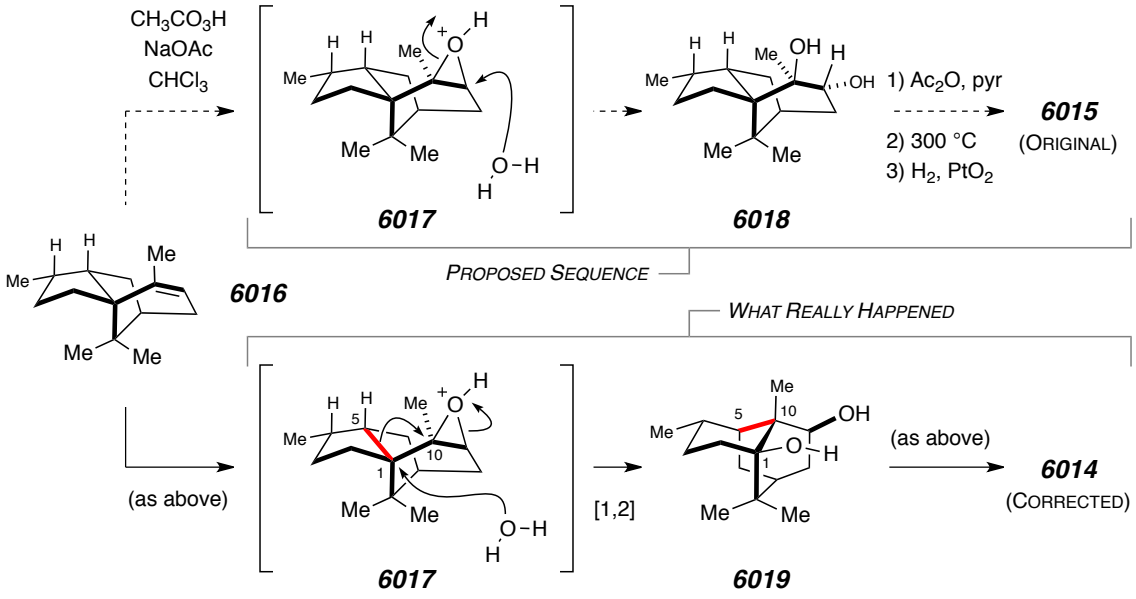
366 For a concise summary of these early studies, see: Simonsen, J.; Barton, D. H. R. Alcohols. *The Terpenes*, 2nd ed.; Cambridge University Press: London, **1952**; Vol. III, pp 175–178.

367 Treibs, W. Über bi- und polycyclische Azulene. III. Mitteil.: Der Patchouli-alkahol, ein tricyclischer Azulen-bildner. *Justus Leibigs Ann. Chem.* **1949**, *564*, 141–151.

368 Büchi, G.; Erickson, R. E.; Wakabayashi, N. Terpenes. XVI. Constitution of Patchouli Alcohol and Absolute Configuration of Cedrene. *J. Am. Chem. Soc.* **1961**, *83*, 927–938.

In an effort to definitively verify the constitution (and establish the absolute configuration) of patchouli alcohol, Büchi and co-workers subsequently embarked upon a total synthesis[369] of their proposed structure (**6015**) that commenced with (+)-camphor and proceeded by way of the sesquiterpene natural product α-patchoulene (**6016**) (Figure VI–8). With this latter, known substance in hand, a four-step synthetic sequence was employed that began by epoxidation of **6016** with peracetic acid followed by *in situ* oxirane ring opening with water to deliver the putative diol **6018** (top portion of Scheme VI–2). Acetylation, pyrolysis, and hydrogenation of this substance gave rise to a product that was identical to natural (–)-patchouli alcohol in all respects.[298,368,369]

Scheme VI–2 | Proposed (via **6018**) and actual (via **6019**) events en route to patchouli alcohol.



However, things changed quite suddenly when, in 1963, Dunitz and co-workers were able to obtain an X-ray crystal structure of the chromate diester derived from

369 Büchi, G.; MacLeod, Jr., W. D. Synthesis of Patchouli Alcohol. *J. Am. Chem. Soc.* **1962**, *84*, 3205–3206.

patchouli alcohol.[370] This analysis demonstrated that the true structure of patchouli alcohol was represented by **6014**, and it therefore became clear that the rationale that led Büchi and co-workers to propose structure **6015**, though mechanistically sound, was based upon an erroneous assumption.[371] Namely, the oxirane **6017** was indeed formed upon epoxidation of α-patchoulene (**6016**), but, unexpectedly, it evolved further through a [1,2] Wagner–Meerwein rearrangement manifold (i.e., migration of the C1–C5 bond, bottom portion of Scheme VI–2). Acetylation, pyrolysis, and hydrogenation of the constitutionally isomeric diol thus produced (**6019**) would then account for the formation of **6014**.

Since the initial reassignment of the structure of patchouli alcohol in 1963 by Dunitz and Büchi, a number of total[372] and formal[373] syntheses of this natural product have appeared in the literature.

---

370 Dobler, M.; Dunitz, J. D.; Gubler, B.; Weber, H. P.; Büchi, G.; Padilla O., J. The Structure of Patchouli Alcohol. *Proc. Chem. Soc.* **1963**, 383.

371 Büchi, G.; MacLeod, Jr., W. D.; Padilla O., J. Terpenes. XIX. Synthesis of Patchouli Alcohol. *J. Am. Chem. Soc.* **1964**, *86*, 4438–4444.

372 (a) Danishefsky, S.; Dumas, D. The Total Synthesis of Racemic Patchouli and *epi*-Patchouli Alcohol. *Chem. Commun. (London)* **1968**, 1287–1288. (b) Mirrington, R. N.; Schmalzl, K. J. Studies with Bicyclo[2.2.2]octenes. V. The Total Synthesis of (±)-Patchouli Alcohol. *J. Org. Chem.* **1972**, *37*, 2871–2877. (c) Näf, F.; Ohloff, G. A Short Stereoselective Total Synthesis of Racemic Patchouli Alcohol. *Helv. Chim. Acta.* **1974**, *57*, 1868–1870. (d) Yamada, K.; Kyotani, Y.; Manabe, S.; Suzuki, M. Total Synthesis of (±)-Patchouli Alcohol and (±)-Seychellene via a Common Homoisotwistane Intermediate. *Tetrahedron* **1979**, *35*, 293–298. (e) Bertrand, M.; Teisseire, P.; Pelerin, G. Sur une Solution de Rechange a la Cyclisation des ε-Halogenocetones–Application a la Synthese du (±)-Patchoulol. *Tetrahedron Lett.* **1980**, *21*, 2055–2056. (f) Näf, F.; Decorzant, R.; Giersch, W.; Ohloff, G. A Stereocontrolled Access to (±)-, (–)-, and (+)-Patchouli Alcohol. *Helv. Chim. Acta.* **1981**, *64*, 1387–1397. (g) Cory, R. M.; Bailey, M. D.; Tse, D. W. C. A Divergent Approach to Patchouli Sesquiterpenes: Synthesis of 3-Oxopatchouli Alcohol, 5-Oxo-7-hydroxy-13-norcycloseychellene, 6-Methoxy-4,12-dehydro-13-norcycloseychellene and Patchouli Alcohol. *Tetrahedron Lett.* **1990**, *31*, 6839–6842. (h) Magee, T. V.; Stork, G.; Fludzinski, P. A Total Synthesis of *rac*-Patchouli Alcohol. *Tetrahedron Lett.* **1995**, *36*, 7607–7610. (i) Srikrishna, A.; Satyanarayana, G. An Enantiospecific Total Synthesis of (–)-Patchouli Alcohol. *Tetrahedron: Asymmetry* **2005**, *16*, 3992–3997.

373 Kaliappan, K. P.; Subba Rao, G. S. R. Synthesis based on Cyclohexadienes. Part 22. Formal Syntheses of Patchouli Alcohol and Norpatchoulenol. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1385–1389.

C–2. REANALYSIS OF THE EXPERIMENTAL ^{1}H NMR CHEMICAL SHIFT ASSIGNMENTS FOR PATCHOULI ALCOHOL

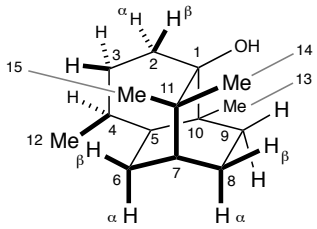
The calamitous series of events that eventually provided a concrete structural assignment for patchouli alcohol (**6014**) are legendary, and but one of many subtle reminders for organic chemists that even total synthesis has its limitations. Given the significance of **6014** in the annals of natural product structure misassignment,[298] we viewed its structure as an excellent test case for the computation of NMR chemical shifts with DFT. In collaboration with Ms. Ashley Garr, a graduate student in Prof. Christopher Cramer's group, we therefore set out to address the following question: If a reliable method for the computation of proton (and carbon) NMR chemical shifts had existed in 1961, could this classic case of structure misassignment have been avoided? A purely hypothetical proposition, to be sure, but nonetheless an interesting one.

Using methods that were similar to those described in earlier Sections of Chapter VI, Ashley Garr generated optimized geometries [at the M06-2X/6-31G(d) level of theory (IEFPCM chloroform solvation)] for the originally proposed (**6015**) and corrected (**6014**) structures and then computed their proton NMR chemical shifts [at the B3LYP/6-311+G(2d,p) level of theory (IEFPCM chloroform solvation)]. A portion of these computed data along with the experimental values[374] that have been assigned to **6014** are provided in Table VI–8. Upon examination of this data, one is immediately struck by how well the DFT-based method performs with regard to predicting the chemical shifts for **6014** (i.e., MAE–1 value of 0.08 ppm for δ_{DFT} versus δ_{EXP}). But getting to the heart of the question that was posed above, Ashley observed an MAE value that was almost twice as large (0.15 ppm) for the 'best fit' comparison between the computed values for the originally assigned structure **6015** and the experimental values (data not shown).

---

[374] Barton, D. H. R.; Belœil, J. –C.; Billion, A.; Boivin, J.; Lallemand, J. –Y.; Mergui, S. 30. Functionalisation of Saturated Hydrocarbons. Part 9. Oxidation of Patchouli Alcohol by the 'Gif System': Isolation and Organoleptic Properties of Three New Ketonic Derivatives. *Helv. Chim. Acta.* **1987**, *70*, 273–280.

Table VI–8 | Computed (DFT) and experimental ($CDCl_3$) ^{1}H NMR chemical shift data for patchouli alcohol (**6014**).



6014

ATOM #	δ_{DFT} [a]	δ_{EXP} (H6β/H8β original)	$\lvert\Delta\delta\rvert$	δ_{EXP} (H6β/H8β reversed)	$\lvert\Delta\delta\rvert$
	6014	***6014***[374]	δ_{DFT} *vs.* δ_{EXP}	***6014***	δ_{DFT} *vs.* δ_{EXP}
2	1.45	1.50	0.05	1.50	0.05
	1.67	1.70	0.03	1.70	0.03
3	1.39	1.34	0.05	1.34	0.05
	1.45	1.48	0.03	1.48	0.03
4	1.86	1.97	0.11	1.97	0.11
5	1.42	1.44	0.02	1.44	0.02
6α	1.21	1.26	0.05	1.26	0.05
6β	**1.47**	**1.85**	**0.38**	**1.48**	**0.01**
7	1.09	1.19	0.10	1.19	0.10
8α	1.28	1.26	0.02	1.26	0.02
8β	**1.85**	**1.48**	**0.37**	**1.85**	**0.00**
9	1.03	1.05	0.02	1.05	0.02
	1.83	1.85	0.02	1.85	0.02
12	0.80	0.78	0.02	0.78	0.02
13	0.80	0.84	0.04	0.84	0.04
14	1.02	1.05	0.03	1.05	0.03
15	1.01	1.07	0.06	1.07	0.06
			MAE–1[b] = 0.08		**MAE–2[b] = 0.04**

[a] The values for δ_{DFT} were computed and compiled by Ms. Ashley Garr (Cramer research group) and have been reproduced here for completeness. [b] Mean absolute error ($\lvert\Delta\delta_{AVE}\rvert$, ppm).

We soon recognized that the primary source of error that contributed to the value for MAE–1 was a result of two factors: A rather large underestimation of the chemical shift corresponding to $H6_{\beta}$ (i.e., | Δδ | of 0.38 ppm) and an equally large overestimation of the chemical shift corresponding to $H8_{\beta}$ (i.e., | Δδ | of 0.37 ppm). Interestingly, if we simply *reversed* the experimental assignments for $H6_{\beta}$ and $H8_{\beta}$, then the computed proton data were in much better agreement, giving rise to an MAE–2 value of 0.04 ppm (*half* of the original MAE–1 value). Could it be that the currently accepted ^{1}H NMR chemical shift assignments for patchouli alcohol (**6014**) are incorrect? This would be particularly surprising in light of the most recent report of a 'complete' ^{1}H NMR assignment of **6014**. Namely, in 2010 Coates and co-workers[375] collected a battery of high-field (600 MHz) NMR experiments for patchouli alcohol, claiming that their analysis had confirmed the ^{1}H NMR chemical shifts that were assigned for **6014** in 1987 by Barton and co-workers[374] (the latter of which are listed in Table VI–8).

At this stage, I was charged with testing the hypothesis that the chemical shifts for $H6_{\beta}$ and $H8_{\beta}$ within **6014** were incorrectly assigned, and thus my contributions to this project were entirely within the experimental realm. I collected and interpreted a battery of 1-D (^{1}H, ^{13}C, and DEPT) and 2-D (^{1}H–^{1}H COSY, NOESY, HSQC/HMQC, and HMBC) NMR spectroscopic data for **6014** in $CDCl_3$ and these data have been summarized in Table VI–9. As has been indicated in the table, the ^{1}H NMR spectrum of this compound is riddled with partially or severely overlapped multiplets, many of which displayed non-first order character. Acquisition of the ^{1}H NMR spectrum at 800 MHz did provide, as it must, greater chemical shift dispersion. However, contrary to earlier claims,[375] I was unable to discern any coupling constants for the resonances corresponding to $H6_{\beta}$, $H2_{\alpha}$, and $H3_{\alpha}$. Shown in Figure VI–9 are comparisons of the 500 MHz versus 800 MHz spectral data for **6014** as is a summary of the most informative COSY and NOESY interactions that were observed within this structure.

---

375 Faraldos, J. A.; Wu, S.; Chappell, J.; Coates, R. M. Doubly Deuterium-labeled Patchouli Alcohol from Cyclization of Singly-labeled [2-$^{2}H_1$]Farnesyl Diphosphate Catalyzed by Recombinant Patchoulol Synthase. *J. Am. Chem. Soc.* **2010**, *132*, 2998–3008.

Table VI–9 | Carbon (^{13}C) and proton (^{1}H) NMR spectroscopic data for patchouli alcohol (**6014**) in $CDCl_3$ at 125 and 500 MHz, respectively.

ATOM	CARBON	PROTON			COSY	NOESY [c]	HMBC
#	δ_C	δ_H	mult. [a]	*J* [Hz]	(→ ^{1}H-#)	(→ ^{1}H-#)	(^{1}H → ^{13}C-#)
1	75.6	---	---	---	---	---	---
2_β	32.7	1.72	dd (✓)	5.0, 12.5	2_α and 3_α or 3_β	3_β, 15	1, 4, 5, 10, 11
2_α		1.49 [b]	---	---	---	---	---
3_β	28.6	1.38 [b]	m (✗)	---	2_β, 4	2_β, 15	1, 2, 4, 12
3_α		1.47 [b]	---	---	---	---	---
4	28.1	1.97	dddddd (✓)	3.0, 6.5, 6.5, 6.5, 6.5, 12.0	3_β, 12	12, 13, and one of 2_α or 3_α	3, 6, 12
5	43.7	1.45 [b]	---	---	6_α	6_α	---
6_β	24.6	1.50 [b]	---	---	---	---	---
6_α		1.29	ddd (✓)	3.5, 10.5, 13.0	5, 6_β, [d] 7	5, 6_β, [d] 7	7, 11
7	39.1	1.20	m (✗)	Σ (*J*s) = 23 Hz	8_β	6_α	1, 5, 9, 14, 15
8_β	24.32	1.88 [b]	ddddd (✗)	2.0, 3.0, 4.5, 11.5, 11.5	8_α	7, 8_α	---
8_α		1.25 [b]	(✗)	---	8_β, 9_α, 9_β	8_β, 9_α	5, 7, 11 + 2–3 others
9_β	28.9	1.84 [b]	ddd (✗)	7.0, 11.5, 13.5	8_α, 9_α	9_α	1, 5, 8, 10
9_α		1.05	ddd (✓)	2.0, 14.0, 14.0	8_α, 9_β	9_β	5, 7, 10, 13
10	37.7	---	---	---	---	---	---
11	40.1	---	---	---	---	---	---
12	18.6	0.80	d (✓)	6.5	4	4 and 2_α, 3_α, or H6_β	3, 4, 5
13	20.6	0.85	s	---	n/o [e]	2_α or 3_α, 4, 9_α	1, 5, 9, 10
14	26.8	1.07	s	---	n/o [e]	n/o [e]	1, 7, 11, 15
15	24.30	1.09	s	---	n/o [e]	2_β, 3_β, 6_β, [d] 7	1, 7, 11, 14

[a] A "✓" indicates that the multiplet displayed first-order character whereas a "✗" indicates a significant amount of non-first-order character. In this latter case, the measurement of all possible *J*s for that resonance was usually not possible. [b] ^{1}H NMR chemical shift was ascertained from an HSQC experiment. [c] Data collected at 800 MHz. [d] Tentative assignment made by the process of elimination (i.e., of the three resonances in the 1.53-1.56 three proton multiplet, only one would be expected to show a cross-peak with the indicated proton resonance). [e] None observed.

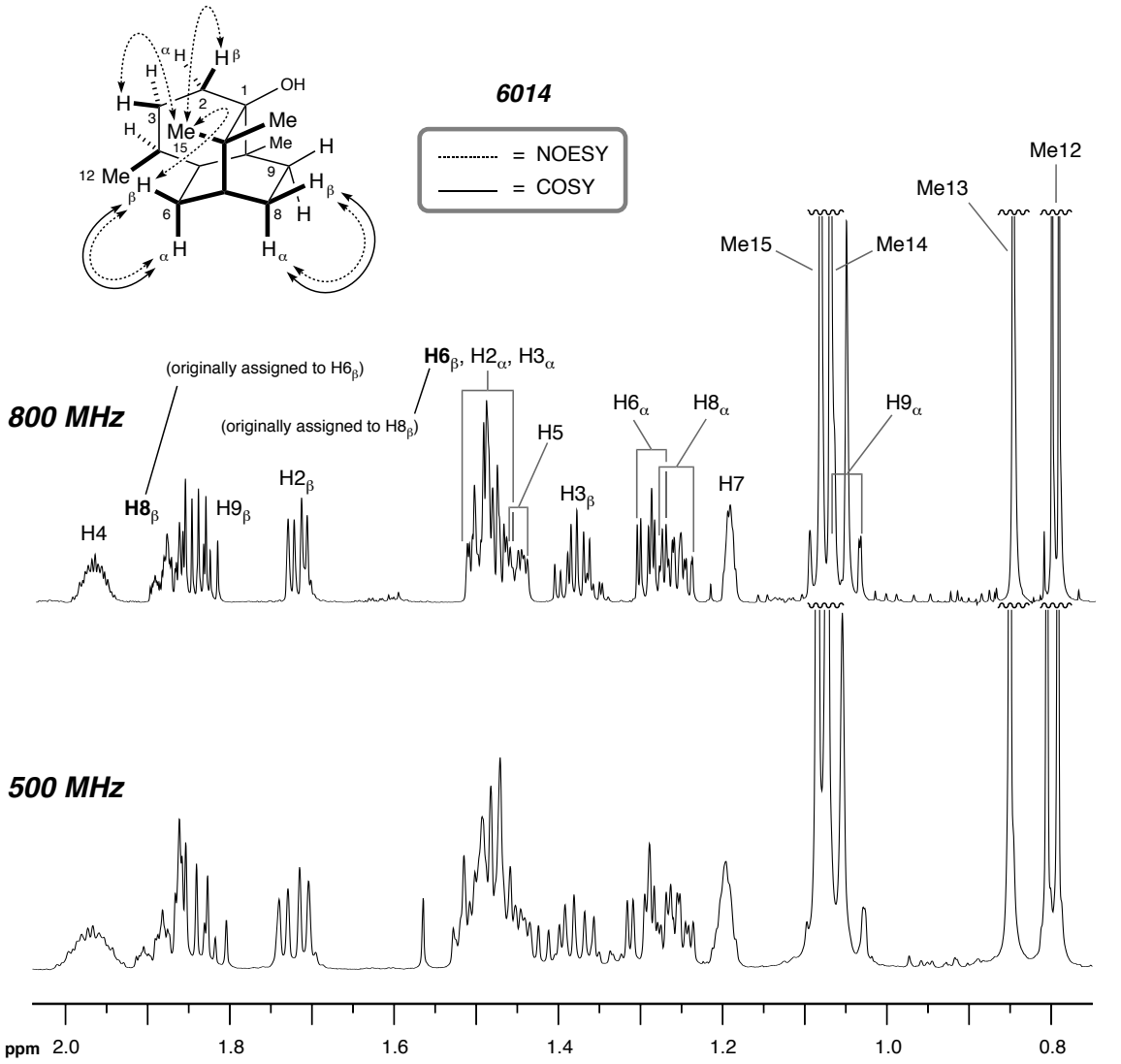


Figure VI–9 | ^{1}H NMR spectra of patchouli alcohol (**6014**) in $CDCl_3$ at 500 MHz (lower portion) and 800 MHz (upper portion), and key NOESY and COSY correlations.

For the most part, the analysis that led to the assignments shown in Table VI–9 has corroborated the earlier reports by both Barton[374] and Coates;[375] however, the agreement was not uniform. Several pieces of direct and circumstantial evidence has led

us to conclude that the ^{1}H NMR assignments for H6$_{\beta}$ and H8$_{\beta}$ should indeed be reversed. The most convincing lines of evidence are as follows (cf. Figure VI–9).

First of all, rather intense NOESY cross-peaks were observed between the C15 methyl group resonance and the resonances corresponding to H2$_{\beta}$ and H3$_{\beta}$. These latter two resonances are well resolved from neighboring protons (even at 500 MHz) and thus the assignment of the C15 methyl group rests upon firm ground. The C15 methyl group, in turn, displayed a NOESY crosspeak into the three-proton multiplet that was originally assigned to contain H8$_{\beta}$, H2$_{\alpha}$, and H3$_{\alpha}$. Since neither H2$_{\alpha}$ nor H3$_{\alpha}$ are in close spatial proximity to C15, we are left to conclude that the observed crosspeak is due to an NOE interaction with H8$_{\beta}$. However, this would be highly unusual since C15 resides on the *opposite* side of the bicyclo[2.2.2]octane ring system of **6014**, and thus an NOE interaction with H8$_{\beta}$ would be unexpected.

Furthermore, in the 2-D NOESY spectrum of **6014**, an intense crosspeak was observed between the resonance corresponding to H8$_{\alpha}$ and the resonance that was originally assigned to H6$_{\beta}$. A similarly intense correlation was observed between H6$_{\alpha}$ and the three-proton multiplet that purportedly corresponds to H8$_{\beta}$, H2$_{\alpha}$, and H3$_{\alpha}$. Here again, the interacting pairs of protons H8$_{\alpha}$/H6$_{\beta}$ and H6$_{\alpha}$/H8$_{\beta}$ are not is close spatial proximity. Importantly, the same sets of correlations that were observed in the NOESY spectrum are *also* observed in the ^{1}H–^{1}H COSY spectrum of **6014**. Why would such intense COSY correlations be observed for protons that are spaced four bonds apart, but no coupling whatsoever be observed with their geminal partners? These observations become reconcilable when it is realized that a large $^{2}J_{H,H}$ geminal coupling constant (and thus an intense COSY crosspeak) should be observed for protons attached to the same carbon atom. This is only possible if the currently accepted[374,375] chemical shift assignments for H6$_{\beta}$ and H8$_{\beta}$ are reversed. This reassignment is reflected in Table VI–9 and Figure VI–9.

C–3. EXPERIMENTAL DETAILS

^{1}H- and ^{13}C NMR spectra were recorded on Bruker Ascend™ 500 (500 and 125 MHz, respectively), Varian Inova 500 (500 and 125 MHz, respectively), and Varian Inova 800 (800 MHz) spectrometers. ^{1}H NMR chemical shifts in $CDCl_3$ are referenced to TMS (0.00 ppm). Non-first order multiplets are identified as "nfom". ^{13}C NMR chemical shifts in $CDCl_3$ are referenced to TMS (0.00 ppm). The following format was used to report ^{1}H NMR resonances: chemical shift (δ, in ppm) [multiplicity, coupling constant(s) in Hz, integral value, and assignment]. Coupling constant analysis was guided by methods we have described elsewhere.[330]

Patchouli oil was obtained from a commercial source [NOW® Personal Care, 100% Pure & Natural Patchouli Oil (from *Pogostemon cablin*); manufactured by NOW Foods, Bloomingdale, IL, USA; item # 7575] from which patchouli alcohol (**6014**) was isolated by chromatography. For example, purification of patchouli oil (201 mg) by medium pressure liquid chromatography (SiO_2, 30:1 Hex/EtOAc) provided pure **6014** as a clear, colorless oil (64 mg) that often solidified upon being placed under high vacuum (< 1 mmHg).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.97 (dddddd, J = 3.0, 6.5, 6.5, 6.5, 6.5, 12.0 Hz, 1H, H4), 1.88 (ddddd, J = 2.0, 3.0, 4.5, 11.5, 11.5 Hz, 1H, H8$_\beta$), 1.84 (ddd, J = 7.0, 11.5, 13.5 Hz, 1H, H9$_\beta$), 1.72 (dd, J = 5.0, 12.5 Hz, 1H, H2$_\beta$), 1.50, 1.49, 1.47 (m, 3H, H6$_\beta$, H2$_\alpha$, H3$_\alpha$), 1.45 (m, 1H, H5), 1.38 (nfom, 1H, H3$_\beta$), 1.29 (ddd, J = 3.5, 10.5, 13.0 Hz, 1H, H6$_\alpha$), 1.25 (nfom, 1H, H8$_\alpha$), 1.20 [nfom, Σ (Js) = 23 Hz, 1H, H7], 1.09 (s, 3H, Me15), 1.07 (s, 3H, Me14), 1.05 (ddd, J = 2.0, 14.0, 14.0 Hz, 1H, H9$_\alpha$), 0.85 (s, 3H, Me13), and 0.80 (d, J = 6.5 Hz, 3H, Me12).

^{1}H NMR (800 MHz, $CDCl_3$): δ 1.97 (dddddd, J = 2.4, 6.4, 6.4, 6.4, 6.4, 12.0 Hz, 1H, H4), 1.88 (ddddd, J = 1.6, 3.2, 4.8, 11.2, 11.2 Hz, 1H, H8$_\beta$), 1.84 (ddd, J = 7.2, 11.2, 13.6 Hz, 1H, H9$_\beta$), 1.72 (dd, J = 5.6, 12.8 Hz, 1H, H2$_\beta$), 1.52-1.44 (m, 4H, H6$_\beta$, H2$_\alpha$, H3$_\alpha$, H5), 1.38 [nfom, Σ (Js) = 46.4 Hz, 1H, H3$_\beta$], 1.29 (ddd, J = 3.2, 11.2, 13.6 Hz, 1H, H6$_\alpha$),

1.26 (nfom, 1H, H8$_\alpha$), 1.20 [nfom, Σ (*Js*) = 12.0 Hz, 1H, H7], 1.09 (s, 3H, Me15), 1.07 (s, 3H, Me14), 1.05 (ddd, *J* = 1.6, 13.6, 13.6 Hz, 1H, H9$_\alpha$), 0.85 (s, 3H, Me13), and 0.80 (d, *J* = 6.4 Hz, 3H, Me12).

^{13}C NMR (500 MHz, $CDCl_3$): 75.6 (C1), 43.7 (C5), 40.1 (C11), 39.1 (C7), 37.7 (C10), 32.7 (C2), 28.9 (C9), 28.6 (C3), 28.1 (C4), 26.8 (C14), 24.6 (C6), 24.32 (C8), 24.30 (C15), 20.6 (C13), and 18.6 (C12).

GC / LR EI-MS [5025015]: t_R 8.78 min; *m*/*z* (rel. int.) 222 (100, $M^{+\bullet}$), 207 (36), 189 (19), 179 (20), 161 (45), 138 (73), 125 (43), 109 (32), 98 (51), and 83 (54).

TLC: R_f 0.35 (8:1 Hex/EtOAc).

D. CONCLUSION

The studies described herein have demonstrated that the computation of proton and carbon NMR chemical shifts with DFT-based methods is a powerful and reliable strategy that is readily executed by an experimental organic chemist (after a sharp learning curve). Highlights from Chapter VI include (Figure VI–10): i) The ability to distinguish among a family of four diastereo- and constitutionally isomeric hydrindenones (**6006A–6006D**); ii) reassignment of the relative configuration within the AB ring system of phomopsichalasin to that present in **6013B**, which included an impressive application of the DP4 probability;[359] and iii) the validation through experimental spectroscopic means the computational prediction that the ^{1}H NMR chemical shift assignments for patchouli alcohol (**6014**) were in error.

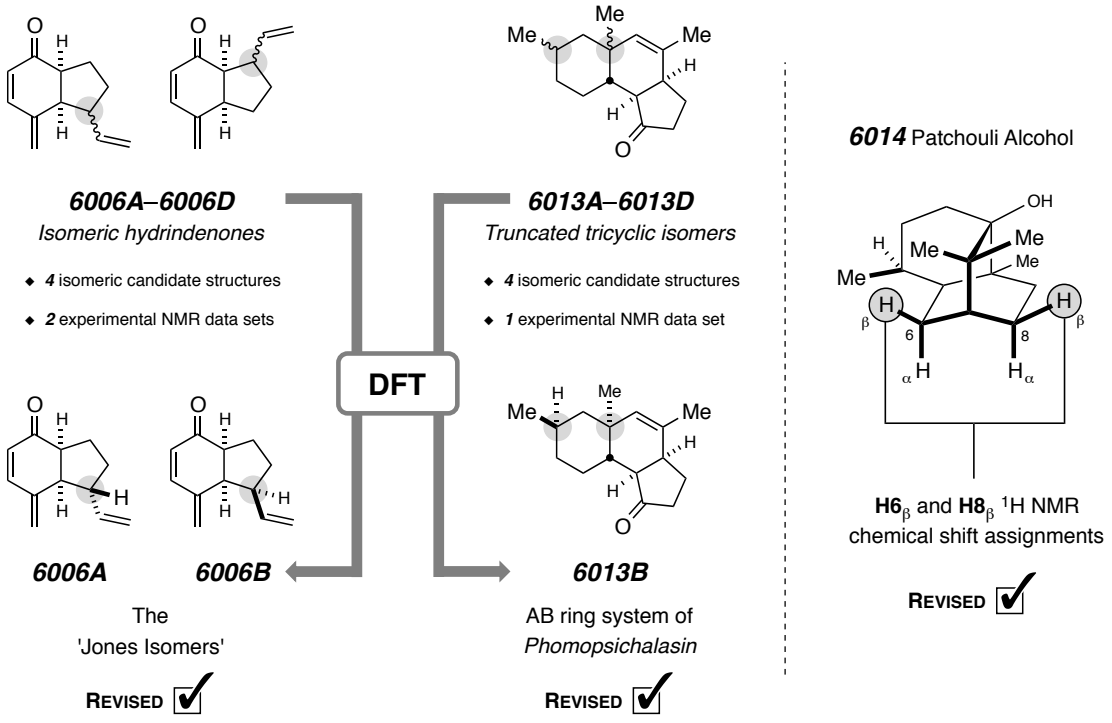


Figure VI–10 | Summary of Chapter VI computational and experimental studies.

EXPERIMENTAL SECTION

FOR

CHAPTERS II–IV

A. GENERAL EXPERIMENTAL PROTOCOLS

Unless stated to the contrary, all reactions were performed under an atmosphere of nitrogen or argon in oven- or flame-dried glassware. Most typically, reaction progress was monitored by analytical thin layer chromatography (TLC) using plastic-backed TLC plates that were fabricated with F_{254} indicator. Compounds were visualized with a UV lamp (254 nm) and/or with either *p*-anisaldehyde, ceric ammonium molybdate (CAM), or (less frequently) $KMnO_4$ TLC stains. Medium pressure liquid chromatography (25–200 psi) was performed using hand-packed columns of silica gel (average particle size: 18–32 μm; average pore size: 60Å), a Waters HPLC pump, and a Waters R401 differential refractive index detector. Flash chromatography was performed with E. Merck silica gel (average particle size: 40–60 μm; average pore size: 60Å) using standard methods.[376]

MATERIALS. Anhydrous THF, Et_2O, PhMe, and CH_2Cl_2 were tapped immediately prior to use after being passed through a column of activated alumina. Triethylamine (Et_3N), pyridine, diisopropylamine (*i*-Pr_2NH), and diisopropylethyl amine (*i*-Pr_2Net) were distilled from CaH_2 and stored over activated 3Å or 4Å MS. DMF and HMPA were distilled from CaH_2 at reduced pressure (*ca.* 25 and 1 mmHg, respectively) and then further dried by sequential storage over two batches of activated 3 Å MS (*ca.* 10% w/w). DMSO was stored over activated 3Å MS. Pentane was distilled from P_2O_5 and stored over activated 3Å MS. Trifluoromethanesulfonic anhydride (Tf_2O), which was prepared according to Stang's procedure,[377] was freshly distilled from a small quantity of P_2O_5 immediately prior to use. Residual water content in samples of pinacol was removed by co-evaporation with benzene (3 cycles) followed by drying under high vacuum immediately prior to use. Iodoform (CHI_3) was recrystallized from anhydrous MeOH (*ca.* 0.1 g/mL). Triphenylphosphine (PPh_3) was recrystallized from MeOH. Carbon

---

[376] Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923–2925.

[377] Stang, P. J.; Dueber, T. E. Preparation of Vinyl Trifluoromethanesulfonates: 3-Methyl-2-buten-2-yl Triflate. *Org. Synth.* **1974**, *54*, 79–83.

tetrabromide (CBr_4) and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) were periodically sublimed (50–60 °C @ *ca.* 1 mmHg). *N*-methyliminodiacetic acid (MIDA) was prepared [*MJJ-V-280*] on 100 g scale in 75% yield [mp 216–218 °C (dec)] according to Burke's reported procedure.[121] Solutions of DMDO in acetone were prepared on an as-needed basis according to Adam's method.[147] When necessary, the protocol of Messegeur and co-workers[149] was employed to obtain solutions of DMDO in CH_2Cl_2. Commercial zinc dust was activated by rapid washing with aq HCl according to the procedure of Newman and Evans.[378] Solutions of *n*-BuLi were titrated either by the method of Burchat, Chong, and Nielsen[379] or by No-D NMR spectroscopy.[380] The titer of solutions of DIBAL-H and RED-AL® (a.k.a. VITRIDE®) (both in PhMe) were determined by the "reaction titration" method previously described by our group.[381]

Solutions of pH 3 buffer were prepared by mixing 0.1 M citric acid (795 mL) and 0.2 M Na_2HPO_4 (205 mL). Solutions of DCl in D_2O (1 M and 0.1 M) were prepared according to the method of Brown and Groot.[382] Catecholborane was prepared from BH_3•SMe_2 according to the procedure of Brown and co-workers.[383] The 10–I–3 iodanes [hydroxyl(tosyloxy)iodo]benzene [*MJJ-IV-287*[169]] and [bis(trifluoroacetoxy)iodo]-benzene [*MJJ-V-82*[170]] were prepared according to literature procedures; likewise, the

---

378 Newman, M. S.; Evans, Jr., F. J. The Reformatsky Reaction: Effect of Alkyl Group in Alkyl α-Bromopropionates. *J. Am. Chem. Soc.* **1955**, *77*, 946–947.

379 Burchat, A. F.; Chong, J. M.; Nielsen, N. Titration of Alkyllithiums with a Simple Reagent to a Blue Endpoint. *J. Organomet. Chem.* **1997**, *542*, 281–283.

380 Hoye, T. R.; Eklov, B. M.; Voloshin, M. No-D NMR Spectroscopy as a Convenient Method for Titering Organolithium (RLi), RMgX, and LDA Solutions. *Org. Lett.* **2004**, *6*, 2567–2570.

381 Hoye, T. R.; Aspaas, A. W.; Eklov, B. M.; Ryba, T. D. Reaction Titration: A Convenient Method for Titering Reactive Hydride Agents (Red-Al, $LiAlH_4$, DIBALH, L-Selectride, NaH, and KH) by No-D NMR Spectroscopy. *Org. Lett.* **2005**, *7*, 2205–2208.

382 Brown, H. C.; Groot, C. A Convenient Procedure for the Preparation of Deuterium Chloride. *J. Am. Chem. Soc.* **1942**, *64*, 2223–2224.

383 Brown, H. C.; Mandal, A. K.; Kulkarni, S. U. Hydroboration. 45. New, Convenient Preparations of Representative Borane Reagents Utilizing Borane–Methyl Sulfide. *J. Org. Chem.* **1977**, *42*, 1392–1398.

10–I–4 iodinane oxide 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide[384] (IBX) and the 12–I–5 periodinane 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one[206,385] (DMP) were also prepared according to well established procedures.

Stock solutions of *i*-PP_2BH[84] were freshly prepared on an as-needed basis. The following procedure, which is a slight modification[386] of the originally reported protocol, is representative:

[*MJJ-V-211*] A 50-mL round-bottomed Schlenk flask was flame-dried under vacuum (< 1.0 mmHg), allowed to cool to rt, and placed under an atmosphere of N_2 by four evacuation-purge cycles. The flask was then charged with 2,5-dimethyl-2,4-hexadiene (1.9 mL, 1.47 g, 13.33 mmol, 2.2 equiv) and dry THF (6.0 mL), cooled to 0 °C, and treated by dropwise addition with neat BH_3•SMe_2 (0.60 mL, 6.00 mmol, 1.0 equiv). The Schlenk flask was sealed under N_2 and allowed to stir at 0 °C for 3 h to provide a solution that was 0.71 M [*i*-PP_2BH].

Hexa-1,5-diene-3,4-diol (**3038**, 1:1 *meso* + *d,l*) was prepared according to literature procedures.[254] Residual water content in samples of *N*,*O*-dimethylhydroxylamine hydrochloride was removed by co-evaporation with benzene (3 cycles) followed by drying under high vacuum immediately prior to use. Oxalyl chloride [$(COCl)_2$] was freshly distilled at atmospheric pressure under N_2 immediately prior to use. The TMS-functionalized silica gel that was required to purify the TBS esters **3034c** and **3034t** was prepared according to the following procedure:

---

384 Frigerio, M.; Santagostino, M.; Sputore, S. A User-Friendly Entry to 2-Iodoxybenzoic Acid (IBX). *J. Org. Chem.* **1999**, *64*, 4537–4538.

385 Ireland, R. E.; Liu, L. An Improved Procedure for the Preparation of the Dess-Martin Periodinane. *J. Org. Chem.* **1993**, *58*, 2899.

386 Molander, G. A.; Dehmel, F. Formal Total Synthesis of Oximidine II via a Suzuki-Type Cross-Coupling Macrocyclization Employing Potassium Organotrifluoroborates. *J. Am. Chem. Soc.* **2004**, *126*, 10313–10318. In this report, the more stable and easily handled BH_3•SMe_2 was employed instead of BH_3•THF.

[*MJJ-VI-135*] Freshly distilled TMSCl (20 mL, 17.1 g) was added in 4–5 mL portions over the course of 10 min to a slurry of SiO_2 (100 g, 40-60 μm, 60Å) and Et_3N (22 mL, 16.0 g) in dry CH_2Cl_2 (400 mL). The flask was then purged with dry N_2, fitted with a drying tube (DRIERITE®, 8 mesh), and stirred overnight at rt. The resulting mixture was filtered through a medium porosity frit and washed with dry CH_2Cl_2 (2 x 150 mL). Removal of the residual solvent at the rotary evaporator and then under high vacuum (< 1 mmHg) provided a free-flowing powder that was utilized without further processing.

Isoprene monoxide (**4013**) (bp 71–74 °C; lit.[387] bp 78–82 °C) was prepared according a literature protocol[387] by 1) formation of the bromohydrin of isoprene (NBS, H_2O) and 2) distillation of the crude isoprene bromohydrin from pulverized NaOH. The enyne **4012** (i.e., 2-methylbut-1-en-3-yne) was prepared by heating 2-methylbut-3-yn-2-ol in the presence of *p*-TsOH according to the procedure of Carothers and Coffman.[388]

INSTRUMENTATION/STRUCTURE ANALYSIS. ^{1}H- and ^{13}C NMR spectra were recorded on Bruker Ascend™ 500 (500 and 125 MHz, respectively), Varian Inova 500 (500 and 125 MHz, respectively) and Varian Inova 300 (300 and 75 MHz, respectively) spectrometers. ^{1}H NMR spectroscopic data are referenced to TMS (0.00 ppm) if collected in $CDCl_3$, acetonitrile (center line, 1.94 ppm) if collected in CD_3CN, or benzene (7.16 ppm) if collected in C_6D_6. Non-first order multiplets are identified as "nfom". ^{13}C NMR chemical shifts are referenced to chloroform (center line, 77.16 ppm) if collected in $CDCl_3$, acetonitrile (center line, 1.32 ppm) if collected in CD_3CN, or benzene (center line, 128.06) if collected in C_6D_6. Carbons being boron atoms were not observed (quadrupolar relaxation), and therefore are not reported. The following format was used to report ^{1}H NMR resonances: chemical shift (δ, in ppm) [multiplicity, coupling constant(s) in Hz, integral value, and assignment]. Coupling constant analysis was guided by methods we

---

387 Reist, E. J.; Junga, I. G.; Baker, B. R. Potential Anticancer Agents. XXXVII. Monofunctional Aziridines Related to Tetramin. *J. Org. Chem.* **1960**, *25*, 1673–1674.

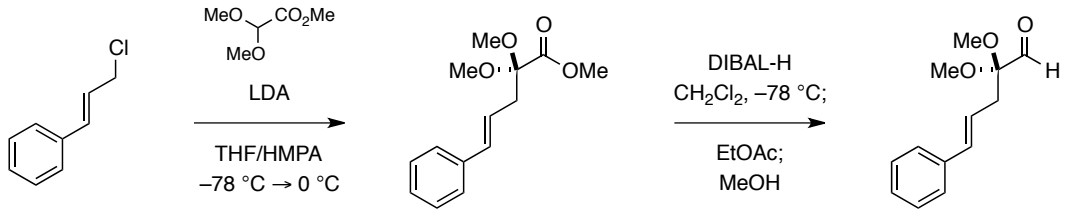
388 [*MJJ-I-191/212/III-262*] Carothers, W. H.; Coffman, D. D. Homologs of Chloroprene and Their Polymers (Second Paper on New Synthetic Rubbers). *J. Am. Chem. Soc.* **1932**, *54*, 4071–4076.

have described elsewhere.[330] Where applicable, the following convention has been adopted for reporting gradient 1-D NOE (GOESY) data: "→ HX" indicates that the resonances corresponding to proton number X was irradiated and "↑ HY" indicates that an enhancement in the resonance corresponding to proton number Y was observed. Infrared (IR) spectra were recorded on a Prospect MIDAC FT-IR spectrometer using a NaCl plate (neat) or ZnSe plate (ATR). Absorptions are reported in cm^{-1}. HR ESI-MS measurements were recorded on a Bruker BioTOF II instrument (reflectron ESI-TOF) using PEG (MW 200, 400, or 600) as an internal calibrant. GC-MS data were recorded on an Agilent 6890N GC interfaced with a 5975 inert XL MSD (EI, 70 eV). The methods used are noted parenthetically: e.g., 5025015 refers to 2 min initial hold time at 50 °C, a ramp to 250 °C at a rate of 20 °C min^{-1}, and a final hold time of 3 min (for a total run time of 15 min). A 30 m × 0.32 mm × 0.25 μm film thickness HP-5 capillary column was used. Reported melting points and boiling points are uncorrected. Dr. Victor G. Young, Jr. and Mr. Gregory Rohde of the Department of Chemistry at the University of Minnesota carried out the X-ray crystallographic analyses of compounds **2244** (see APPENDIX A) and **2299** (see APPENDIX B).

B. PREPARATION PROCEDURES AND CHARACTERIZATION DATA

B–1. CHAPTER II

(*E*)-2,2-DIMETHOXY-5-PHENYLPENT-4-ENAL (2020) via **(*E*)-METHYL 2,2-DIMETHOXY-5-PHENYLPENT-4-ENOATE (2019)**



2018 ***2019*** ***2020***

[*MJJ-III-138*] A solution of *n*-BuLi (850 μL, 2.05 mmol, 2.41 M in Hex) was added dropwise to a stirred solution of *i*-Pr_2NH (300 μL, 217 mg, 2.14 mmol) in dry THF (6.8 mL) at 0 °C. The resulting mixture was maintained at this temperature for 20 min, and was then cooled to –78 °C and stirred an additional 10 min. A solution of methyl dimethoxyacetate (261 mg, 1.95 mmol, 3.8 equiv) and HMPA (1.8 mL, 1.85 g, 10.30 mmol, 20 equiv) in dry THF (4.0 mL) was then added dropwise. Stirring was continued at –78 °C for 30 min, at which point a solution of cinnamyl chloride (**2018**) (79 mg, 0.52 mmol, 1.0 equiv) in dry THF (4.0 mL) was added dropwise. After having been stirred at –78 °C for 30 min, the reaction mixture was allowed to slowly warm to rt over the course of 90 min. The reaction mixture was quenched by the addition of satd aq NH_4Cl, the layers were shaken and separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic extracts were washed with 1:1 brine/H_2O (2x) and brine (1x), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 8:1 Hex/EtOAc) provided the 2,2-dimethoxy ester **2019** as a clear, colorless oil (102 mg, 0.41 mmol, 78% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (br d, *J* = 7.5 Hz, 2H, *o*-C_6H_5), 7.29 (dd, *J* = 7.5, 7.5 Hz, 2H, *m*-C_6H_5), 7.21 (dddd, *J* = 1.5, 1.5, 6.5, 6.5 Hz, 1H, *p*-C_6H_5), 6.45 [ddd, *J* = 1.5, 1.5, 15.5 Hz, 1H, (C_6H_5)C*H*=CH], 6.03 [ddd, *J* = 7.5, 7.5, 16.0 Hz, 1H, (C_6H_5)CH=C*H*], 3.77 (s, 3H, CO_2CH_3), 3.34 [s, 6H, $C(OCH_3)_2$], and 2.81 [dd, *J* = 1.5, 7.5 Hz, 2H, $CH_2C(OCH_3)_2$].

TLC: R_f 0.19 (6:1 Hex/EtOAc).

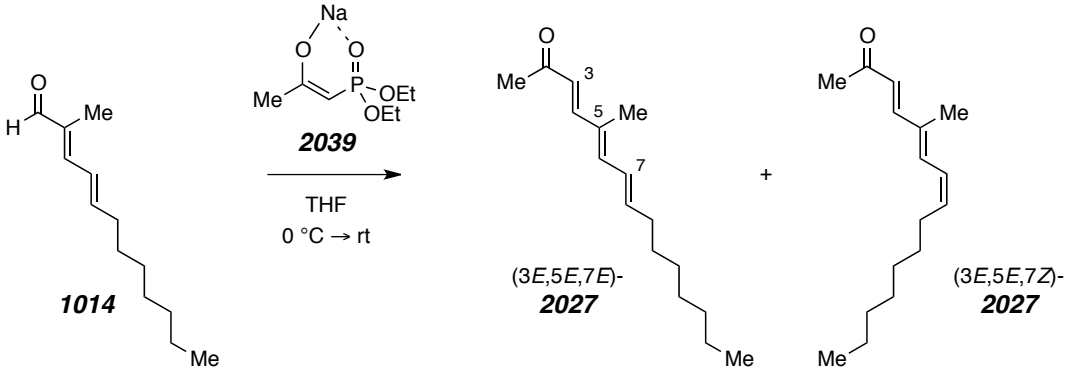
[*MJJ-III-133/141*] A solution of the above prepared 2,2-dimethoxy ester **2019** (100 mg, 0.40 mmol, 1.0 equiv) in dry CH_2Cl_2 (4.0 mL) was cooled to –78 °C and a solution of DIBAL-H (1.2 mL, 1.80 mmol, 4.5 equiv, 1.5 M in PhMe) was slowly added along the inner wall of the reaction vessel. After having been stirred for 15 min, excess DIBAL-H was destroyed by slow addition of EtOAc (0.5 mL). Stirring was continued for 10 min, at which point the reaction mixture was quenched by the addition of anhydrous MeOH (0.5 mL) and allowed to warm to rt. The resulting mixture was diluted with Et_2O and satd aq sodium potassium tartrate, and then 15% aq NaOH was added dropwise until two clear phases were evident. The layers were shaken and separated, the aqueous phase was extracted with EtOAc (3x), and the combined organic extracts were dried ($MgSO_4$) and filtered. Concentration of the filtrate *in vacuo* and purification of the crude residue by medium pressure liquid chromatography (SiO_2, 8:1 Hex/EtOAc) provided the title compound as a clear, colorless oil (79 mg, 0.36 mmol, 90% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.50 (s, 1H, C*H*O), 7.33-7.28 (m, 4H *o*/*m*-C_6H_5), 7.22 (dddd, *J* = 2.0, 2.0, 6.5, 6.5 Hz, 1H, *p*-C_6H_5), 6.44 [ddd, *J* = 1.5, 1.5, 15.5 Hz, 1H, (C_6H_5)C*H*=CH], 6.02 [ddd, *J* = 7.5, 7.5, 16.0 Hz, 1H, (C_6H_5)CH=C*H*], 3.36 [s, 6H, $CH_2C(OCH_3)_2$], and 2.74 [dd, *J* = 1.5, 7.5 Hz, 2H, $CH_2C(OCH_3)_2$].

GC / LR EI-MS [5025015]: t_R 8.79 min; *m*/*z* (rel. int.) 220 (1, $M^{+\bullet}$), 191 (57, $M^{+\bullet}$–CHO$^\bullet$), 159 (7), 144 (15), 129 (32), 117 (48, $M^{+\bullet}$–$C_4H_7O_3^\bullet$), 115 (49), 103 (100, $M^{+\bullet}$–$C_9H_9^\bullet$), and 91 (28).

TLC: R_f 0.25 (9:1 Hex/EtOAc).

(3*E*,5*E*,7*E*)-5-METHYLPENTADECA-3,5,7-TRIEN-2-ONE (2027)



[*MJJ-I-167*] Neat diethyl 2-oxopropylphosphonate (1.252 g, 6.45 mmol, 2.0 equiv) was added to a stirred suspension of NaH (225 mg, 5.63 mmol, 1.7 equiv, 60% dispersion in mineral oil) in dry THF (12 mL) at 0 °C, and, after a short induction period, vigorous H_2 evolution commenced and a clear, colorless solution of **2039** was obtained within 15 min. A solution of the dienal **1014** (628 mg, 3.23 mmol, 1.0 equiv) in dry THF (12 mL) was then added dropwise, and the resulting mixture was maintained with stirring for 60 min and then allowed to warm to rt. After having been stirred for 3 d, the reaction mixture was quenched by the addition of sat aq NH_4Cl (20 mL), the layers were shaken and separated, and the aqueous layer was extracted with Et_2O (4x). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 95:5 Hex/EtOAc) provided (3*E*,5*E*,7*Z*)-**2027** (31 mg, 0.13 mmol, 4% yield) followed by the title compound (290 mg, 1.24 mmol, 38% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 [d, *J* = 16.0 Hz, 1H, CH=CHCH=C(CH_3)C*H*=CH–C(O)CH_3], 6.44-6.38 [nfom, 2H, CH=C*H*C*H*=C(CH_3)CH=CHC(O)CH_3], 6.14 [d, *J* = 16.0 Hz, 1H, CH=CHCH=C(CH_3)CH=C*H*C(O)CH_3], 5.98 [ddd, *J* = 7.0, 7.0, 13.5 Hz,

1H, C*H*=CHCH=C(CH_3)CH=CH–C(O)CH_3], 2.30 [s, 3H C(O)C*H_3*], 2.19 [q, *J* = 7 Hz, 2H, CH=CHC*H_2*CH_2(CH_2)$_4$$CH_3$], 1.88 [s, 3H, CH=CHCH=C(C*H_3*)CH=CH–C(O)CH_3], 1.46-1.40 [m, 2H, CH=CHCH_2C*H_2*(CH_2)$_4$$CH_3$], 1.33-1.23 [m, 8H, CH=CHCH_2CH_2–(C*H_2*)$_4$$CH_3$] and 0.89 [t, *J* = 7 Hz, 3H, CH=CHCH_2CH_2(CH_2)$_4$C*H_3*].

IR (neat): 2956, 2926, 2855, 1668, 1599, 1580, 1256, and 973 cm^{-1}.

HR ESI-MS: $C_{16}H_{26}O$ $[M+Na]^+$ requires 257.1876; found 257.1878.

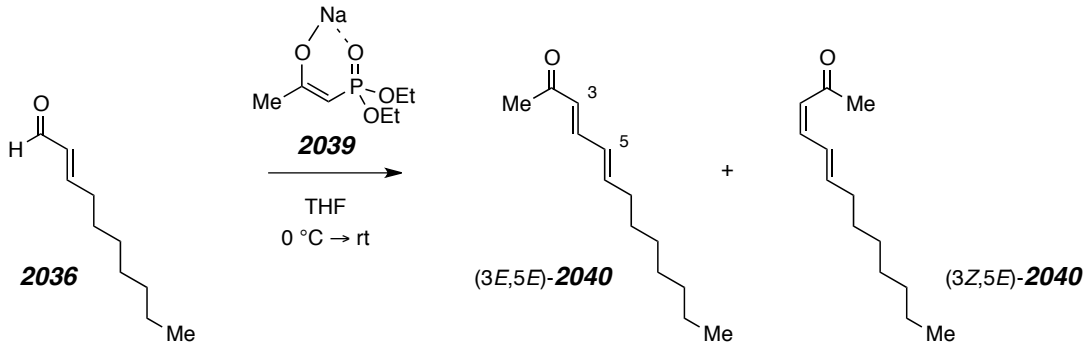
GC / LR EI-MS [5027016]: t_R 11.50 min; *m*/*z* (rel. int.) 234 (58, $M^{+\bullet}$), 219 (15, $M^{+\bullet}$–$CH_3^\bullet$), 191 (12, $M^{+\bullet}$–$C_2H_3O^\bullet$), 176 (6), 163 (6, $M^{+\bullet}$–$C_5H_{11}^\bullet$), 149 (100, $M^{+\bullet}$–$C_6H_{13}^\bullet$), 135 (34, $M^{+\bullet}$–$C_7H_{15}^\bullet$), 121 (36), 109 (34, $M^{+\bullet}$–$C_9H_{17}^\bullet$), 93 (51), and 91 (51).

TLC: R_f 0.32 (9:1 Hex/EtOAc).

Data for (3*E*,5*E*,7*Z*)-**2027**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 [d, *J* = 16.0 Hz, 1H, CH=CHCH=C(CH_3)C*H*=CH–C(O)CH_3], 6.72 [d, *J* = 12.0 Hz, 1H, CH=CHC*H*=C(CH_3)CH=CHC(O)CH_3], 6.36 [dddd, *J* = 1.5, 1.5, 11.0, 11.0 Hz, 1H, CH=C*H*CH=C(CH_3)CH=CHC(O)CH_3], 6.18 [d, *J* = 16.0 Hz, 1H, CH=CHCH=C(CH_3)CH=C*H*C(O)CH_3], 5.77 [ddd, *J* = 8.0, 8.0, 11.0 Hz, 1H, C*H*=CHCH=C(CH_3)CH=CHC(O)CH_3], 2.32 [s, 3H, C(O)C*H_3*], 2.27 [dddd, *J* = 1.5, 8.0, 8.0, 8.0 Hz, 2H, CH=CHC*H_2*CH_2(CH_2)$_4$$CH_3$], 1.89 [d, *J* = 1.5 Hz, 3H, CH=CHCH=C(C*H_3*)CH=CHC(O)CH_3], 1.45-1.39 [m, 2H, CH=CHCH_2C*H_2*(CH_2)$_4$$CH_3$], 1.35-1.23 [m, 8H, CH=CHCH_2CH_2(C*H_2*)$_4$$CH_3$], and 0.89 [t, *J* = 7.0 Hz, 3H, CH=CHCH_2CH_2(CH_2)$_4$C*H_3*].

(3*E*,5*E*)-TRIDECA-3,5-DIEN-2-ONE (2040)



[*MJJ-I-42/144*] Neat diethyl 2-oxopropylphosphonate (944 mg, 4.76 mmol, 1.2 equiv) was added to a stirred suspension of NaH (184 mg, 4.6 mmol, 1.1 equiv, 60% dispersion in mineral oil) in dry THF (12 mL). Once H_2 evolution had ceased, the resulting clear, colorless solution of **2039** was cooled to 0 °C and a solution of (*E*)-2-decenal (**2036**) (490 µL, 415 mg, 4.22 mmol, 1.0 equiv) in dry THF (12 mL) was added dropwise. After having been stirred at 0 °C for 10 min, the reaction mixture was allowed to warm to rt and was stirred an additional 22 h. The reaction mixture was quenched by the addition of sat aq NH_4Cl, the layers were shaken and separated, and the aqueous layer was extracted with Et_2O (3x). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 95:5 Hex/EtOAc) provided (3*Z*,5*E*)-**2040** (12 mg, 0.06 mmol, 1% yield) followed by the title compound (329 mg, 1.69 mmol, 36% yield).

^{1}H NMR[389] (500 MHz, $CDCl_3$): δ 7.10 [dd, *J* = 10.0, 15.5 Hz, 1H, CH=CHC*H*=CH–C(O)CH_3], 6.22-6.15 [nfom, 2H, C*H*=C*H*CH=CHC(O)CH_3], 6.06 [d, *J* = 15.5 Hz, 1H, CH=CHCH=C*H*C(O)CH_3], 2.27 [s, 3H, C(O)CH_3], 2.20-2.16 [m, 2H, CH=CHC$H_2$$CH_2$–$(CH_2)_4CH_3$], 1.46-1.40 [m, 2H, CH=CHCH_2C$H_2$$(CH_2)_4CH_3$], 1.34-1.22 [m, 8H CH=CH–

[389] Cf.: Molander, G. A.; Singaram, B.; Brown, H. C. Conjugate Addition–Elimination in the Reaction of *B*-1-Alkenyl-9-borabicyclo[3.3.1]nonanes with 4-Methoxy-3-buten-2-one. A Convenient New Route to Conjugated Dienones. *J. Org. Chem.* **1984**, *49*, 5024–5025.

$CH_2CH2(CH_2)_4CH_3$], and 0.88 [t, J = 7.0 Hz, 3H, $CH{=}CHCH_2CH_2(CH_2)_4CH_3$].

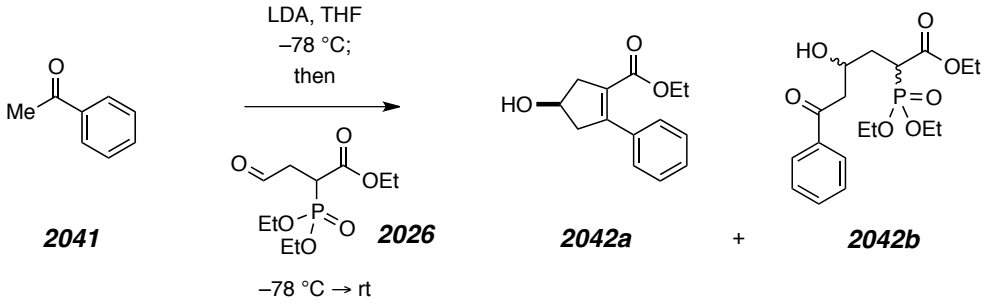
GC / LR EI-MS [5025015]: t_R 9.35 min; *m*/*z* (rel. int.) 194 (5, $M^{+\bullet}$), 179 (2, $M^{+\bullet}–CH_3^{\bullet}$), 151 (2, $M^{+\bullet}–C_2H_3O^{\bullet}$), 136 (2), 95 (100, $M^{+\bullet}–C_7H_{15}^{\bullet}$), 81 (23), and 67 (9).

TLC: R_f 0.25 (9:1 Hex/EtOAc).

Data for (3*Z*,5*E*)-**2040**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 [ddddd, J = 1.5, 1.5, 1.5, 11.5, 15.5 Hz, 1H, $CH{=}CHCH{=}CHC(O)CH_3$], 6.38 [dd, J = 11.5, 11.5 Hz, 1H, $CH{=}CHCH{=}CHC(O)CH_3$], 6.12 [ddd, J = 7.0, 7.0, 15.0 Hz, 1H, $CH{=}CHCH{=}CHC(O)CH_3$], 5.93 [d, J = 11.5 Hz, 1H, $CH{=}CHCH{=}CHC(O)CH_3$], 2.22 [s, 3H, $C(O)CH_3$], 2.20 [dddd, J = 1.5, 7.0, 7.0, 7.0 Hz, 2H, $CH{=}CHCH_2CH_2(CH_2)_4CH_3$], 1.46-1.40 [m, 2H,$CH_2CH_2(CH_2)_4CH_3$], 1.33-1.22 [m, 8H$CH_2CH_2(CH_2)_4CH_3$], and 0.88 [t, J = 7.0 Hz, 3H, $CH_2CH_2(CH_2)_4CH_3$].

(±)-ETHYL 4-HYDROXY-2-PHENYLCYCLOPENT-1-ENECARBOXYLATE and **ETHYL 2-(DIETHOXYPHOSPHORYL)-4-HYDROXY-6-OXO-6-PHENYLHEXANOATE (2042a/b)**



2041 ***2026*** ***2042a*** + ***2042b***

[*MJJ-I-88/110*] A solution of *n*-BuLi (950 μL, 2.26 mmol, 2.38 M in Hex) was added dropwise to a stirred solution of *i*-Pr_2NH (350 μL, 251 mg, 2.48 mmol) in dry THF (2.5 mL) at –78 ° and the resulting mixture was stirred for 40 min. A solution of acetophenone (**2041**) (220 μL, 227 mg, 1.89 mmol, 1.0 equiv) in dry THF (1.9 mL) was then added dropwise, and, after having been stirred for 1 h, this was followed by the dropwise

addition of a solution of the phosphonate aldehyde **2026** (458 mg, 1.72 mmol, 0.9 equiv) in dry THF (1.9 mL). Stirring was continued at –78 °C for 2 h, and then the reaction mixture was allowed to gradually warm to 0 °C over the course of 1 h and was quenched by the addition of satd aq NH_4Cl. The layers were shaken and separated, and the aqueous phase was extracted with EtOAc (2x). The combined organic material was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 3:1 Hex/EtOAc) provided the known cyclopentenoic ester **2042a**[43c] (26 mg, 0.11 mmol, 7% yield) followed by the title compound (86 mg, 0.22 mmol, 13% yield).

Data for the major (†) and minor (‡) diastereomers have been indicated (*dr* 1.7:1).

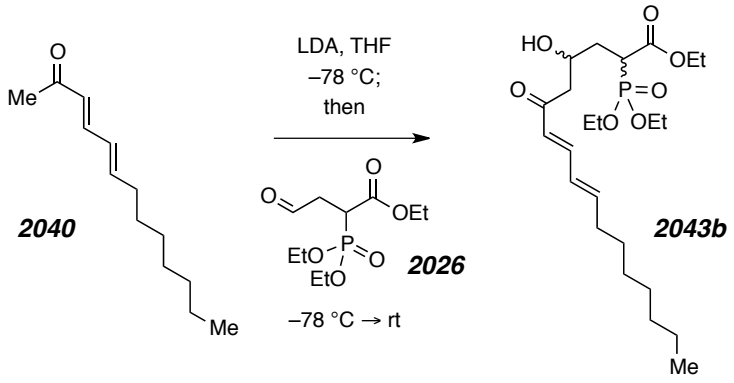
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49-7.41†‡ (m, 4H, C_6H_5), 7.37-7.30†‡ (m, 4H, C_6H_5), 7.28-7.25†‡ (m, 2H, C_6H_5), 5.17-5.08†‡ (m, 2H, C*H*OH), 4.49† (d, *J* = 2.0 Hz, 1H, CHO*H*), 4.25‡ (s, 1H, CHO*H*), 4.17-4.04†‡ [m, 12H, P(O)(OCH_2CH$_3$)$_2$ and $CO_2CH_2CH_3$], 3.48† [dd, *J* = 7.5, 12.5 Hz, 1H, $(CH_3CH_2O)_2P(O)CHCO_2Et$], 3.14‡ [dd, *J* = 8.0, 12.0 Hz, 1H, $(CH_3CH_2O)_2P(O)CHCO_2Et$], 2.73‡ (dd, *J* = 7.5, 13.5 Hz, 1H, CH_2), 2.64† (dd, *J* = 7.0, 14.5 Hz, 1H, CH_2), 2.63-2.56†‡ (m, 2H, CH_2), 2.46† (dd, *J* = 8.0, 14.0 Hz, 1H, CH_2), 2.39-2.37†‡ (m, 2H, CH_2), 2.21† (br dd, *J* = 4.5, 15.0 Hz, 1H, CH_2), 1.37-1.32†‡ [m, 12H, P(O)(OCH$_2$CH_3)$_2$], 1.16† (t, *J* = 7.0 Hz, 3H, $CO_2CH_2CH_3$), and 1.13‡ (t, *J* = 7.0 Hz, 3H, $CO_2CH_2CH_3$).

IR (neat): 3371, 2984, 2909, 1731, 1447, 1374, 1258, 1187, and 1035 cm^{-1}.

HR ESI-MS: $C_{18}H_{27}O_7P$ $[M+Na]^+$ requires 409.1387; found 409.1454.

TLC: R_f 0.36 (1:3 Hex/EtOAc).

(±)-(7*E*,9*E*)-ETHYL 2-(DIETHOXYPHOSPHORYL)-4-HYDROXY-6-OXOHEPTADECA-7,9-DIENOATE (2043b)



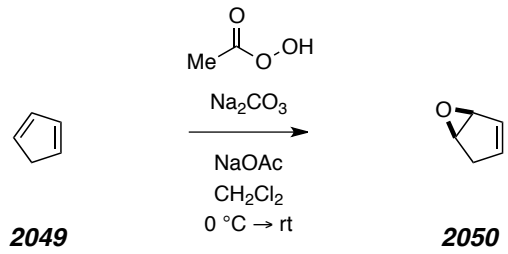
[*MJJ-I-102*] A solution of *n*-BuLi (100 μL, 0.24 mmol, 2.38 M in Hex) was added dropwise to a stirred solution of *i*-Pr_2NH (37 μL, 27 mg, 0.26 mmol) in dry THF (260 μL) at 0 °C, and the resulting mixture was cooled to –78 °C and stirred for 40 min. A solution of the trienone **2040** (36 mg, 0.20 mmol, 1.1 equiv) in dry THF (200 μL) was added dropwise and the light yellow solution that resulted was stirred for 1 h. The phosphonate aldehyde **2026** (45 mg, 0.17 mmol, 1.0 equiv) in dry THF (200 μL) was then added, stirring was continued at –78 °C for 2 h, and then the reaction mixture was allowed to gradually warm to –10 °C over the course of 1 h. The reaction mixture was quenched by the addition of satd aq NH_4Cl, the layers were shaken and separated, and the aqueous phase was extracted with EtOAc (2x). The combined organic material was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 3:1 Hex/EtOAc) provided the title compound (20 mg, 0.04 mmol, 26% yield).

Data for the major (†) and minor (‡) diastereomers have been indicated (*dr* 2.1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.32‡ [dd, *J* = 11.0, 15.0 Hz, 1H, CH=CHC*H*=CHC(O)], 6.31† [dd, *J* = 10.5, 15.0 Hz, 1H, CH=CHC*H*=CHC(O)], 6.02†‡ [dd, *J* = 11.0, 15.0 Hz,

2H, CH=C*H*CH=C*H*C(O)], 5.71†‡ [ddd, *J* = 7.0, 7.0, 14.5 Hz, 2H, C*H*=CH–CH=CHC(O)], 5.65† [d, *J* = 15.0 Hz, 1H, CH=CHCH=C*H*C(O)], 5.58‡ [d, *J* = 15.0 Hz, 1H, CH=CHCH=C*H*C(O)], 5.08-5.03† (m, 1H, C*H*OH), 5.00-4.94‡ (m, 1H, C*H*OH), 4.21-4.08†‡ [m, 12H, P(O)(OC*H*$_2$CH$_3$)$_2$ and CO$_2$C*H*$_2$CH$_3$], 3.81† (d, *J* = 1.5 Hz, 1H, CHO*H*), 3.65‡ (s, 1H, CHO*H*), 3.01† (dd, *J* = 8.0, 12.0 Hz, 1H, C*H*$_2$), 2.69‡ (dd, *J* = 8.0, 12.0 Hz, 1H, C*H*$_2$), 2.59-2.47‡ (m, 4H, C*H*$_2$), 2.39† (dd, *J* = 7.0, 15.0 Hz, 1H, C*H*$_2$), 2.30† (br dd, *J* = 8.0, 14.5 Hz, 1H, C*H*$_2$), 2.07†‡ [ddd, *J* = 7.0, 7.0, 7.0 Hz, 4H, CH=CHC*H*$_2$(CH$_2$)$_5$CH$_3$], 1.96† (dd, *J* = 5.0, 15.0 Hz, 1H, C*H*$_2$), 1.38-1.21†‡ [m, 38H, CH=CHCH$_2$(C*H*$_2$)$_5$CH$_3$, P(O)(OCH$_2$C*H*$_3$)$_2$, and CO$_2$CH$_2$C*H*$_3$], and 0.88†‡ [t, *J* = 7.0 Hz, 6H, CH=CHCH$_2$(CH$_2$)$_5$C*H*$_3$].

(±)-CYCLOPENTADIENE MONOEPOXIDE (2050)



2049 ***2050***

[*MJJ-IV-100*][56] A 1-L, 3-neck round-bottom flask equipped with an addition funnel and a thermocouple was charged with CH_2Cl_2 (500 mL), freshly distilled cyclopentadiene (**2049**) (71.0 mL, 55.8 g, 0.81 mol) and Na_2CO_3 (106.3 g, 1.00 mol), and the resulting heterogeneous mixture was cooled in an ice/H_2O bath. Meanwhile, the addition funnel was charged with a solution of peracetic acid [35.5% CH_3CO_3H (remainder composition: 40% CH_3CO_2H, 17% H_2O, 6.5% H_2O_2, and < 1% H_2SO_4), 77.0 mL, 90.3 g, 0.42 mol] containing NaOAc (2.1 g, 0.03 mol). This solution was then added dropwise with vigorous stirring at a rate such that the internal temperature did not exceed ca. 15 °C (the addition required 60 min). [*NOTE:* During the course of peracetic acid addition *and* the

first distillation (*vide infra*), a fiberglass blast shield was placed in front of the reaction/distillation apparatus.] At this point the reaction mixture was allowed to reach ambient temperature and stirring was continued for an additional 60 min. The reaction mixture was filtered through a medium porosity frit, the filter cake was washed with CH_2Cl_2 (3 x 75 mL), and most (but not all) of the CH_2Cl_2 was removed at the rotary evaporator. The residual solvent was then distilled at atmospheric pressure (bath temp. 55 °C) and then the pressure was reduced with a water aspirator (25–35 mmHg) while maintaining a constant bath temperature. This provided 34.2 g of a liquid that, on the basis of ^{1}H NMR analysis, was a 0.8:1 mixture of cyclopentadiene monoepoxide (**2050**) and CH_2Cl_2. Finally, redistillation of this material at water aspirator pressure–collecting material that boiled at 44–45 °C while maintaining a bath temperature of *ca.* 50–55 °C–provided the title compound as a clear, colorless liquid [13.4 g, 150 mmol, 36% yield based on peracetic acid (corrected for purity)] that was judged to be 92% (w/w) pure on the basis of ^{1}H NMR analysis. The two principal contaminants were 3-cyclopentenone[390] (4%) and (*Z*)-penta-2,4-dienal[391] (4%), both of which arise via thermal decomposition of cyclopentadiene monoepoxide. The chemical shift data that are provided below are in excellent agreement with reported values.[392]

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.15 (dddd, *J* = 1.0, 2.0, 2.0, 6.5 Hz, 1H, C*H*=CH), 5.99 (dddd, *J* = 2.5, 2.5, 2.5, 6.5 Hz, 1H, CH=C*H*), 3.92 [ddd, *J* = 2.0, 3.0, 3.5 Hz, 1H, CH=CHC*H*(O)CH], 3.83 [ddd, *J* = 2.0, 3.0, 3.0 Hz, 1H, CH_2C*H*(O)CH], 2.64 (dddd, *J* = 2.0, 2.0, 2.0, 19.0 Hz, 1H, CH_2), and 2.40 (dddd, *J* = 2.0, 2.0, 4.0, 19.0 Hz, 1H, CH_2).

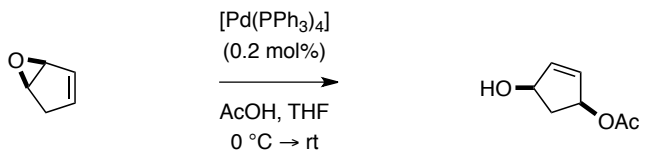
---

390 **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.09 [s, 4H, CH_2C(O)CH_2] and 2.88 (s, 2H, C*H*=C*H*).

391 **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.21 (d, *J* = 8.0 Hz, 1H, C*H*O), 7.32 (dddd, *J* = 1.5, 10.5, 12, 16.5 Hz, 1H, CH=CHC*H*=$CH_{trans}H_{cis}$), 6.96 (dddd, *J* = 1.0, 1.0, 11.0, 12.0 Hz, 1H, CH=C*H*CH=$CH_{trans}H_{cis}$), 5.91 (ddddd, *J* = 1.5, 1.5, 1.5, 8, 11.0 Hz, 1H, C*H*=CHCH=$CH_{trans}H_{cis}$), 5.66 (dddd, *J* = 1.0, 1.0, 2.0, 16.5 Hz, 1H, CH=CHCH=C$H_{trans}H_{cis}$), and 5.65 (dddd, *J* = 0.5, 0.5, 1.5, 10.5 Hz, 1H, CH=CHCH=$CH_{trans}H_{cis}$).

392 Hu, H.; Faraldos, J. A.; Coates, R. M. Scope and Mechanism of Intramolecular Aziridination of Cyclopent-3-enyl-methylamines to 1-Azatricyclo[2.2.1.$0^{2,6}$]heptanes with Lead Tetraacetate. *J. Am. Chem. Soc.* **2009**, *131*, 11998–12006.

(±)-*CIS*-3-ACETOXY-5-HYDROXYCYCLOPENT-1-ENE (2052)



2050 ***2052***

[*MJJ-III-160/IV-103*][57] To a solution of tetrakis(triphenylphosphine)palladium(0) (341 mg, 0.30 mmol, 0.2 mol%) in dry THF (120 mL) at 0 °C was added acetic acid (9.0 mL, 9.4 g, 157 mmol, 1.05 equiv). A solution of cyclopentadiene monoepoxide (**2050**) (92% purity, 13.4 g, 150 mmol, 1.0 equiv) in dry THF (15 mL) was then introduced via a pressure-equalizing addition funnel [quantitative transfer was achieved with additional THF (15 mL)]. The reaction mixture was then warmed to rt and, after having been stirred for 30 min, was concentrated *in vacuo*. The crude residue was filtered through SiO_2 (80 g) with the aid of Et_2O (800 mL) and the resulting cloudy yellow solution was filtered through a medium porosity frit containing a bed of $MgSO_4$ (60 g, Et_2O). Concentration of the filtrate *in vacuo* provided a bright yellow oil[393] that was purified by vacuum distillation (bp 86–88 °C @ 0.1–0.05 mmHg; lit.[57] 73–75 °C @ 0.15 mmHg) to provide the title compound as a clear, colorless oil (15.5 g, 108.8 mmol, 73% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.12 (ddd, *J* = 1.5, 2.5, 5.5 Hz, 1H, C*H*=CH), 5.99 (ddd, *J* = 1.0, 2.0, 5.5 Hz, 1H, CH=C*H*), 5.52-5.49 [m, 1H, C*H*OC(O)CH_3], 4.74-4.71 (m, 1H,

393 Analysis of the crude residue by ^{1}H NMR revealed that (*Z*)-penta-2,4-dienal, which was a minor contaminant present in **2050**, had been quantitatively converted to (*E*)-penta-2,4-dienal under the conditions of the palladium(0)-catalyzed acetoxylation. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.60 (d, *J* = 7.5 Hz, 1H, C*H*O), 7.11 (dddd, *J* = 0.5, 0.5, 11.0, 15.5 Hz, 1H, CH=C*H*CH=$CH_{trans}H_{cis}$), 6.60 (dddd, *J* = 0.5, 10.0, 11.0, 17.0 Hz, 1H, CH=CHC*H*=$CH_{trans}H_{cis}$), 6.19 (ddddd, *J* = 0.5, 0.5, 0.5, 7.5, 15.0 Hz, 1H, C*H*=CHCH=$CH_{trans}H_{cis}$), 5.76 (dddd, *J* = 1.0, 1.0, 1.0, 17.0 Hz, 1H, CH=CHCH=C$H_{trans}H_{cis}$), and 5.64 (ddddd, *J* = 0.5, 0.5, 0.5, 0.5, 10.0 Hz, 1H, CH=CHCH=$CH_{trans}H_{cis}$).

C*H*OH), 2.81 (ddd, *J* = 7.5, 7.5, 14.5 Hz, 1H, CH_2), 2.06 [s, 3H, OC(O)CH_3], 1.78 (br s, 1H, CHO*H*), and 1.66 (ddd, *J* = 4.0, 4.0, 15.0 Hz, 1H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 138.6, 132.5, 77.2, 74.8, 40.5, and 21.3.

IR (neat): 3426, 2942, 1733, 1363, 1240, 1089, 1059, 1018, 981, and 773 cm^{-1}.

GC / LR EI-MS [5025015]: t_R 4.30 min; *m*/*z* (rel. int.) 125 (4 $M^{+\bullet}$–$^{\bullet}$OH), 99 (7, $M^{+\bullet}$–$C_2H_3O^{\bullet}$), and 82 (100, $M^{+\bullet}$–CH_3CO_2H).

TLC: R_f 0.17 (2:1 Hex/EtOAc).

(±)-*CIS*-4-*TERT*-BUTYLDIMETHYLSILOXY-2-CYCLOPENTENYL ACETATE (2053)

2052 ***2053***

[*MJJ-III-162/IV-109*][58] A 2-L, 2-necked round bottom flask was charged with *cis*-3-acetoxy-5-hydroxycyclopent-1-ene (**2052**) (15.5 g, 109 mmol, 1.0 equiv), Et_3N (34.0 mL, 24.7 g, 244 mmol, 2.2 equiv), DMAP (1.4 g, 11 mmol, 10 mol%), and dry CH_2Cl_2 (350 mL), and the resulting mixture was cooled in an ice/H_2O bath. To this solution was added TBSCl (21.5 g, 143 mmol, 1.3 equiv) in two equal portions over the course of 10 min and, after the addition was complete, the reaction mixture was allowed to warm to ambient temperature. After having been stirred for 18 h, H_2O (400 mL) was added and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (200 mL) and brine (200 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was passed through a short pad of SiO_2 (4:1 Hex/EtOAc), concentrated, and purified by vacuum distillation (bp 98–107 °C

@ 0.05–0.025 mmHg, lit.[394] 155–165 °C @ 0.5 mmHg) to provide the title compound as a clear, colorless oil (27.2 g, 106 mmol, 98% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.98 (ddd, *J* = 2.0, 2.0, 6.0 Hz, 1H, C*H*=CH), 5.89 (ddd, *J* = 1.5, 1.5, 5.5 Hz, 1H, CH=C*H*), 5.48-5.45 [m, 1H, C*H*OC(O)CH_3], 4.73-4.70 [m, 1H, C*H*(OTBS)], 2.81 (ddd, *J* = 7.0, 7.0, 13.5 Hz, 1H, CH_2), 2.05 [s, 3H, OC(O)CH_3], 1.61 (ddd, *J* = 5.0, 5.0, 13.5 Hz, 1H, CH_2), 0.90 [s, 9H, (CH_3)$_3$CSi(CH_3)$_2$], 0.093 [s, 3H, (CH_3)$_3$CSi(CH_3)$_2$], and 0.087 [s, 3H, (CH_3)$_3$CSi(CH_3)$_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 139.0, 131.3, 77.1, 75.0, 41.3, 26.0, 21.3, 18.3, and -4.6.

IR (neat): 2954, 2932, 2888, 2858, 1738, 1368, 1240, 1104, 1049, 1021, 905, 838, and 776 cm^{-1}.

HR ESI-MS: $C_{13}H_{24}O_3Si$ $[M+Na]^+$ requires 279.1387; found 279.1393.

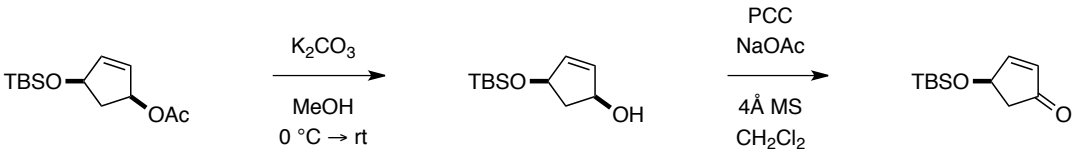
GC / LR EI-MS [5025015]: t_R 7.48 min; *m*/*z* (rel. int.) 197 (2, $M^{+\bullet}$–$CH_3CO_2^{\bullet}$), 196 (2, $M^{+\bullet}$–CH_3CO_2H), 159 (4), 139 (3), and 117 (100).

TLC: R_f 0.61 (6:1 Hex/EtOAc).

---

394 Kobayashi, Y.; Murugesh, M. G.; Nakano, M.; Takahisa, E.; Usmani, S. B.; Ainai, T. A New Method for Installation of Aryl and Alkenyl Groups onto a Cyclopentene Ring and Synthesis of Prostaglandins. *J. Org. Chem.* **2002**, *67*, 7110–7123.

(±)-4-*TERT*-BUTYLDIMETHYLSILOXY-2-CYCLOPENTEN-1-ONE (2055) via **(±)-*CIS*-4-*TERT*-BUTYLDIMETHYLSILOXYCLOPENT-2-ENOL (2054)**



2053 ***2054*** (±)-***2055***

[*MJJ-III-165/IV-110*][59] A solution of *cis*-4-*tert*-butyldimethylsiloxy-2-cyclopentenyl acetate (**2053**) (27.2 g, 106 mmol, 1.0 equiv) in anhydrous MeOH (500 mL) was cooled in an ice/H_2O bath. Solid K_2CO_3 (2.9 g, 21.3 mmol, 0.2 equiv) was then added in a single portion and, after 30 min, the reaction mixture was allowed to warm to rt. Stirring was continued for 4.5 h, at which point an additional portion of solid K_2CO_3 (1.5 g, 10.6 mmol, 0.1 equiv) was added. After having been stirred an additional 19 h at rt, the reaction mixture was concentrated to partial dryness at the rotavap. The evaporation residue was then re-dissolved in CH_2Cl_2 (600 mL) and washed successively with H_2O (2 x 300 mL) and brine (200 mL). The saline aqueous washes were back-extracted with CH_2Cl_2 (2 x 100 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting crude residue was passed through a short bed of SiO_2 (1:1 Hex/EtOAc) and the filtrate evaporated to dryness to provide a pale-yellow oil (25.1 g) that was used without further processing. The ^1H and ^{13}C NMR chemical shifts reported below were in close agreement with values reported in the literature.[395]

---

[395] ^1H NMR data: Ghosh, A. K.; Chapsal, B. D.; Baldridge, A.; Ide, K.; Koh, Y.; Mitsuya, H. Design and Synthesis of Stereochemically Defined Novel Spirocyclic P2-Ligands for HIV-1 Protease Inhibitors. *Org. Lett.* **2008**, *10*, 5135–5138. ^{13}C NMR data: Myers, A. G.; Glatthar, R.; Hammond, M.; Harrington, P. M.; Kuo, E. Y.; Liang, J.; Schaus, S. E.; Wu, Y.; Xiang, J. –N. Development of an Enantioselective Synthetic Route to Neocarzinostatin Chromophore and Its Use for Multiple Radioisotopic Incorporation. *J. Am. Chem. Soc.* **2002**, *124*, 5380–5401.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.95 (ddd, *J* = 1.5, 1.5, 5.5 Hz, 1H, C*H*=CH), 5.90 (ddd, *J* = 2.0, 2.0, 6.0 Hz, 1H, CH=C*H*), 4.66 [ddddd, *J* = 1.0, 1.0, 1.0, 4.5, 7.0 Hz, 1H, C*H*(OTBS)], 4.62-4.57 (m, 1H, C*H*OH), 2.69 (ddd, *J* = 7.0, 7.0, 14.0 Hz, 1H, CH_2), 1.62 (br s, 1H, CHO*H*), 1.51 (ddd, *J* = 4.5, 4.5, 13.5 Hz, 1H, CH_2), 0.90 [s, 9H, (CH_3)$_3$CSi(CH_3)$_2$], and 0.09 [s, 6H, (CH_3)$_3$CSi(CH_3)$_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 136.9, 135.8, 75.3, 75.2, 44.7, 26.0, 18.3, and -4.5.

IR (neat): 3350, 2954, 2931, 2886, 2857, 1364, 1256, 1127, 1098, 1070, 1020, 904, 838, and 774 cm^{-1}.

HR ESI-MS: $C_{11}H_{22}O_2Si$ $[M+Na]^+$ requires 237.1281; found 237.1284.

GC / LR EI-MS [5025015]: t_R 6.48 min; *m*/*z* (rel. int.) 213 (1, $M^{+\bullet}$–$H^{\bullet}$), 196 (1, $M^{+\bullet}$–H_2O), 157 [100, $M^{+\bullet}$–$C(CH_3)_3^{\bullet}$], 139 (14), and 111 (9).

TLC: R_f 0.25 (6:1 Hex/EtOAc).

[*MJJ-III-140/IV-147*][58] To a solution of the crude alcohol **2054** (106 mmol theoretical, 1.0 equiv) in dry CH_2Cl_2 (700 mL) was added activated, powdered 4Å MS (51 g) and anhydrous NaOAc (1.3 g, 15.8 mmol, 0.15 equiv). With vigorous stirring, the resulting suspension was treated with powdered PCC (34.5 g, 160 mmol, 1.5 equiv) in five equal portions over the course of 2-3 min. The dark brown suspension thus obtained was stirred for 4 h, at which point TLC analysis (6:1 Hex/EtOAc) of the reaction mixture indicated that the allylic alcohol had been consumed. The reaction mixture was then filtered (2x) through a bed of SiO_2 (Et_2O eluent) and the filtrate was evaporated to dryness. One additional filtration through SiO_2 (6:1 Hex/EtOAc) followed by concentration of the filtrate *in vacuo* provided a light yellow oil. Purification by vacuum distillation (bp 118–122 °C @ *ca*. 0.1 mmHg)–while cooling the receiving flask in an ice/H_2O bath–provided the title compound as a colorless, wet solid (19.2 g, 90.2 mmol, 85% yield over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (dd, *J* = 2.5, 5.5 Hz, 1H, *H*C=CHCO), 6.19 (dd, *J* = 1.0, 5.5 Hz, 1H, HC=C*H*CO), 4.99 {dddd, *J* = 1.5, 2.5, 2.5, 6.0, 1H, C*H*(OTBS)], 2.71 (dd, *J* = 5.5, 18.0 Hz, 1H, COCH_2), 2.25 (dd, *J* = 2.5, 18.5 Hz, 1H COCH_2), 0.91 [s, 9H, (CH_3)$_3$CSi(CH_3)$_2$], 0.14 [s, 3H, (CH_3)$_3$CSi(CH_3)$_2$], and 0.13 [s, 3H, (CH_3)$_3$CSi(CH_3)$_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 206.5, 163.9, 134.5, 71.0, 45.1, 25.9, 18.2, and -4.6.

IR (neat): 2954, 2931, 2887, 2858, 1723, 1356, 1255, 1182, 1109, 1071, 900, 836, and 780 cm^{-1}.

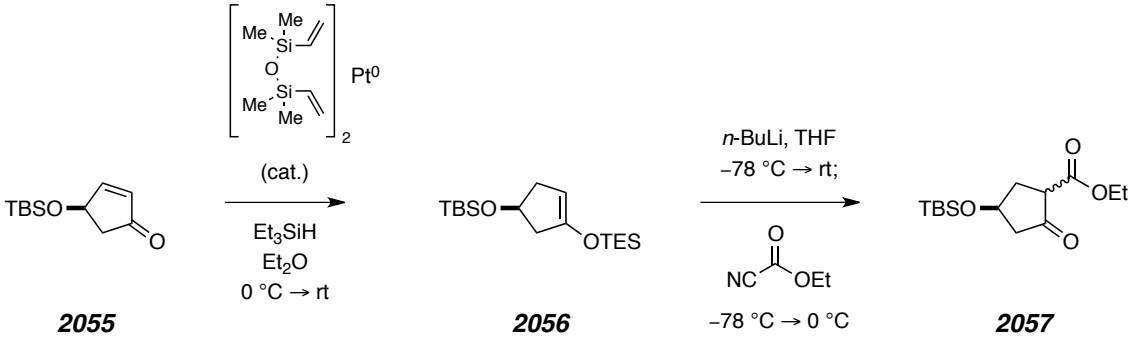
HR ESI-MS: $C_{11}H_{20}O_2Si$ $[M+Na]^+$ requires 235.1125; found 235.1126.

GC / LR EI-MS [5025015]: t_R 6.73 min; *m*/*z* (rel. int.) 197 (2, $M^{+\bullet}$–$CH_3^{\bullet}$), 155 [100, $M^{+\bullet}$–$C(CH_3)_3^{\bullet}$], 141 (2), 125 (8), 111 (12), and 81 (38).

MP: < 30 °C.

TLC: R_f 0.40 (6:1 Hex/EtOAc).

(±)-ETHYL 4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-OXOCYCLOPENTANE-CARBOXYLATE (2057) via **(±)-*TERT*-BUTYLDIMETHYL((3-(TRIETHYLSILOXY)-CYCLOPENT-3-EN-1-YL)OXY)SILANE (2056)**



[*MJJ-VI-214*][62] A 100-mL, 2-neck round-bottom flask was charged sequentially with freshly distilled triethylsilane (6.4 mL, 4.66 g, 40.07 mmol, 2.0 equiv) and a solution of

platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex (500 μL, *ca.* 2 wt% Pt in xylenes, *ca.* 0.2 mol% Pt), which immediately produced a light orange solution. After having been stirred for 10 min at rt, the mixture was cooled to 0 °C and a solution of the enone **2055** (4.23 g, 19.90 mmol, 1.0 equiv) in dry Et_2O (15 mL) was added via cannula over 5 min. Two additional portions of dry Et_2O (5 mL each) were used to rinse the transfer flask. The solution was stirred at 0 °C for 30 min and rt for 15 h, at which point GC-MS analysis of the reaction mixture indicated that the starting material had been consumed. The resulting light brown solution was concentrated *in vacuo* to leave a dark brown oil that was filtered through a 3.5 x 10 cm bed of SiO_2 (4% Et_3N/Hex eluent). Concentration of the filtrate *in vacuo* provided the title compound as a straw-colored oil (6.52 g, quantitative yield), which was used immediately without further purification. Select analytical data for **2056** [from *MJJ-V-35*] are provided below.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.51 [dddd, *J* = 2.0, 2.0, 2.0, 2.0 Hz, 1H, C*H*=C(OTES)], 4.45 [dddd, *J* = 5.0, 5.0, 7.5, 7.5 Hz, 1H, C*H*(OTBS)], 2.53 [dddd, *J* = 2.0, 2.0, 7.0, 15.0 Hz, 1H, C*H*$_2$CH(OTBS)CH$_2$], 2.49 [dddd, *J* = 2.0, 2.0, 7.5, 16.0 Hz, 1H, CH$_2$CH(OTBS)C*H*$_2$], 2.26 [ddddd, *J* = 2.0, 2.0, 2.0, 5.0, 16.0 Hz, 1H, CH$_2$CH(OTBS)C*H*$_2$], 2.19 [dddddd, *J* = 2.0, 2.0, 2.0, 2.0, 2.0, 15.0 Hz, 1H, C*H*$_2$CH(OTBS)CH$_2$], 0.97 [t, *J* = 8.0 Hz, 9H, Si(CH$_2$C*H*$_3$)$_3$], 0.88 [s, 9H, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$], 0.67 [q, 6H, Si(C*H*$_2$CH$_3$)$_3$], and 0.05 [s, 6H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ 152.0, 99.8, 70.9, 43.7, 39.5, 26.1, 18.3, 6.8, 4.9 and -4.6.

GC / LR EI-MS [5025015]: t_R 8.46 min; *m*/*z* (rel. int.) 328 (0.3, $M^{+\bullet}$), 327 (0.6, $M^{+\bullet}$–$H^{\bullet}$), 313 (3, $M^{+\bullet}$–$CH_3^{\bullet}$), 299 (3, $M^{+\bullet}$–$CH_2CH_3^{\bullet}$), 271 [100, $M^{+\bullet}$–$C(CH_3)_3^{\bullet}$], 189 (12), and 161 (29).

[*MJJ-VI-49/215*] A solution of the enol ether **2056** (6.52 g, 19.83 mmol, 1.0 equiv) in dry THF (130 mL) at –78 °C was treated with *n*-BuLi (8.7 mL, 21.75 mmol, 1.1 equiv, 2.5 M in Hex) dropwise over the course of 5 min. Once the addition was complete, the cooling

bath was removed and the reaction mixture was allowed to slowly warm to rt over 30 min. After having been stirred at this temperature for an additional 60 min, the reaction mixture was re-cooled to –78 °C and freshly distilled ethyl cyanoformate (2.2 mL, 2.21 g, 22.27 mmol, 1.1 equiv) was rapidly injected. The cloudy, pale yellow solution thus obtained was held at –78 °C for 30 min and was then allowed to warm to rt over the course of 30 min. After 20 min at rt, the cloudy, burgundy reaction mixture was quenched by the addition of satd aq NH_4Cl/H_2O (4:1, 200 mL). The layers were shaken and separated, and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with H_2O (100 mL) and brine (100 mL), dried ($MgSO_4$), and filtered. Concentration of the filtrate *in vacuo* and purification of the crude residue by flash chromatography (9:1 Hex/EtOAc) provided the β-keto ester **2057** as a slightly pink oil (3.49 g, 12.18 mmol, 61% yield over 2 steps).

^{1}H and ^{13}C NMR data corresponding to the major (†) and minor (‡) diastereomers has been indicated (*dr* 3.5:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.61-4.59† [nfom, 1H, C*H*(OTBS)], 4.42‡ [ddd, J = 6.0, 7.0, 13.5 Hz, 1H, C*H*(OTBS)], 4.21†‡ [ABX_3, $\Delta\nu_{AB}$ = 12.3 Hz, J_{AB} = 14.5, $J_{AX} = J_{BX}$ = 7.5 Hz, 2H, $CO_2CH_2CH_3$], 3.51-3.47† [nfom, 1H, C(O)C*H*$CO_2CH_2CH_3$], 3.16‡ [dd, J = 9.5, 9.5 Hz, 1H, C(O)C*H*$CO_2CH_2CH_3$], 2.49-2.42†‡ [m, 2H, CH_2CH(OTBS)CH_2], 2.33-2.28†‡ [m, 2H, CH_2CH(OTBS)CH_2], 1.29† (t, J = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 1.28‡ (t, J = 7.5 Hz, 3H, $CO_2CH_2CH_3$), 0.88‡ [s, 9H, $(CH_3)_3CSi(CH_3)_2$] 0.86† [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.09‡ [s, 3H, $(CH_3)_3CSi(CH_3)_2$], 0.08† [s, 3H, $(CH_3)_3CSi(CH_3)_2$], 0.07‡ [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.06† [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

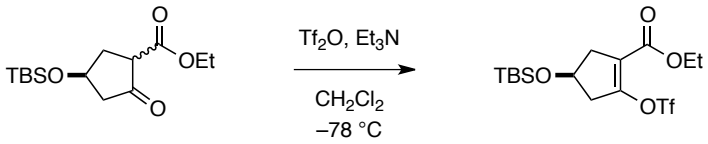
^{13}C NMR (75 MHz, $CDCl_3$): δ 210.6†, 208.9‡, 169.6†, 168.6‡, 68.3‡, 68.2†, 61.64‡, 61.60†, 54.2‡, 52.2†, 48.2†, 47.9‡, 37.2†, 36.7‡, 25.8†‡, 18.11‡, 18.05†, 14.30†, 14.27‡, -4.68‡, -4.73†‡, and -4.8†.

IR (neat): 2953, 2932, 2857, 1760, 1727, 1252, 1116, 1048, and 838 cm^{-1}.

HR ESI-MS: $C_{14}H_{26}O_4Si$ $[M+Na]^+$ requires 309.1493; found 309.1492.

TLC: R_f 0.37 (8:1 Hex/EtOAc).

(±)-ETHYL 4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-((TRIFLUOROMETHYLSULFONYL)OXY)-CYCLOPENT-1-ENECARBOXYLATE (2048)



2057 ***2048***

[*MJJ-VI-67/217*] To a solution of the β-keto ester **2057** (3.41 g, 11.90 mmol, 1.0 equiv) and Et_3N (2.5 mL, 1.82 g, 17.94 mmol, 1.5 equiv) in dry CH_2Cl_2 (100 mL) at –78 °C was added dropwise freshly distilled Tf_2O[377] (2.6 mL, 4.36 g, 15.45 mmol, 1.3 equiv) over the course of *ca.* 5 min. After having been stirred for 3 h at –78 °C, the still cold reaction mixture was poured into a separatory funnel that contained Et_2O (200 mL), H_2O (100 mL), and brine (100 mL). The resulting mixture was shaken and the layers separated, and the aqueous phase was extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), and then dried ($MgSO_4$) and filtered. Concentration of the filtrate *in vacuo* followed by purification of the crude residue by flash chromatography (30:1 → 20:1 Hex/EtOAc) provided the title compound as a clear, colorless oil (4.42 g, 10.55 mmol, 89% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.50 [dddd, J = 3.5, 3.5, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 4.26 (q, J = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 3.00 [dddd, J = 2.0, 2.0, 7.0, 18.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.96 [dddd, J = 2.0, 2.0, 7.0, 16.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.67 [dddd, J = 2.0, 2.0, 5.5, 18.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.63 [dddd, J = 2.0, 2.0, 5.5, 16.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 1.32 (t, J = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 0.88 [s,

9H, $(CH_3)_3CSi(CH_3)_2$], 0.073 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.069 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

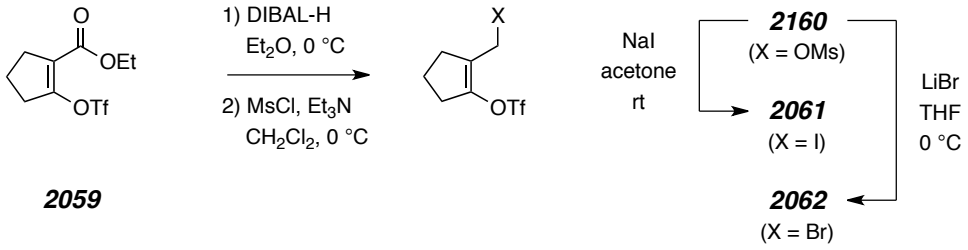
^{13}C NMR (75 MHz, $CDCl_3$): δ 162.2, 150.6, 121.2, 118.4 (q, $J_{^{13}C-^{19}F}$ = 318 Hz), 67.2, 61.4, 43.2, 40.2, 25.8, 18.1, 14.1, -4.7, and -4.8.

IR (neat): 2956, 2933, 2859, 1722, 1668, 1430, 1255, 1212, 1141, 1095, 1075, 985, and 847 cm^{-1}.

HR ESI-MS: $C_{15}H_{25}F_3O_6SSi$ $[M+Na]^+$ requires 441.0985; found 441.1001.

TLC: R_f 0.59 (8:1 Hex/EtOAc).

2-(IODOMETHYL)CYCLOPENT-1-EN-1-YL TRIFLUOROMETHANESULFONATE (2061) and **2-(BROMOMETHYL)CYCLOPENT-1-EN-1-YL TRIFLUOROMETHANESULFONATE (2062)**



[*MJJ-II-65/113*] A solution of DIBAL-H (6.0 mL, 9.0 mmol, 4.0 equiv, 1.5 M in PhMe) was added dropwise to a solution of the ethyl ester **2059** (645 mg, 2.24 mmol, 1.0 equiv) in dry Et_2O (18 mL) at 0 °C. After having been stirred at this temperature for 10 min, the reaction mixture was diluted with Et_2O and slowly quenched by the sequential addition of H_2O (0.4 mL) and 15% aq NaOH (0.4 mL). The resulting mixture was allowed to warm to rt and was then treated with H_2O (1.0 mL). Stirring was continued for 15 min at rt, after which time excess $MgSO_4$ was added and the resulting mixture was filtered through CELITE®. The filtrate was concentrated *in vacuo* and the crude residue thus obtained was purified by medium pressure liquid chromatography (SiO_2, 4:1 Hex/EtOAc) to provide the intermediate allylic alcohol (454 mg, 1.84 mmol, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.25 (ddddd, *J* = 1.5, 1.5, 1.5, 1.5, 6.0 Hz, 2H, C*H*$_2$OH), 2.67-2.62 (m, 2H, C*H*$_2$CH$_2$C*H*$_2$), 2.55-2.51 (m, 2H, C*H*$_2$CH$_2$C*H*$_2$), 2.02 (dddd, *J* = 8.0, 8.0, 8.0, 8.0 Hz, 2H, CH$_2$C*H*$_2$CH$_2$), and 1.47 (ddd, *J* = 2.0, 6.0, 6.0 Hz, 1H, CH$_2$O*H*).

GC / LR EI-MS [5025015]: t_R 6.52 min; *m*/*z* (rel. int.) 246 (9, $M^{+\bullet}$), 113 (33, $M^{+\bullet}$–$CF_3O_2S^{\bullet}$), 95 (21), 85 (30), 69 (47, CF_3^+), and 67 (100).

TLC: R_f 0.13 (9:1 Hex/EtOAc).

[*MJJ-II-98/103*] Methanesulfonyl chloride (30 μL, 44 mg, 0.39 mmol, 2.3 equiv) was added dropwise to a solution of the allylic alcohol (42 mg, 0.17 mmol, 1.0 equiv) and Et_3N (100 μL, 72 mg, 0.71 mmol, 4.2 equiv) in dry CH_2Cl_2 (1.5 mL) at 0 °C. The reaction mixture was allowed to stir at this temperature for 30 min and was then diluted with Et_2O and then poured onto H_2O. The layers were shaken and separated and the aqueous phase was extracted with Et_2O (1x). The combined organic extracts were washed with H_2O (1x) and brine (1x), dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude mesylate [**TLC**: R_f 0.26 (2:1 Hex/EtOAc)] that was used in the subsequent step without further purification.

Solid NaI (128 mg, 0.85 mmol, 5.0 equiv) was added to a solution of the crude mesylate (0.17 mmol theoretical) in reagent grade acetone (1.5 mL) and, after having been stirred for 10 min, the reaction mixture was partitioned between Et_2O and H_2O. The layers were separated and the aqueous phase was extracted with Et_2O (3x). The combined organic extracts were washed with satd aq $Na_2S_2O_3$ (1x) and brine (1x), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 98:2 Hex/EtOAc) provided the allylic iodide **2061** (39 mg, 0.11 mmol, 64% yield over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.91 (s, 2H, C*H*$_2$I), 2.59-2.53 (m, 4H, C*H*$_2$CH$_2$C*H*$_2$), and 2.04 (dddd, *J* = 8.0, 8.0, 8.0, 8.0 Hz, 2H, CH$_2$C*H*$_2$CH$_2$).

GC / LR EI-MS [5027016]: t_R 7.54 min; *m*/*z* (rel. int.) 229 (100, $M^{+\bullet}$–$I^{\bullet}$), 195 (1), 181 (2), 127 (4, I^+), 125 (5), 99 (12), 79 (32), and 69 (25, CF_3^+).

TLC: R_f 0.88 (2:1 Hex/EtOAc).

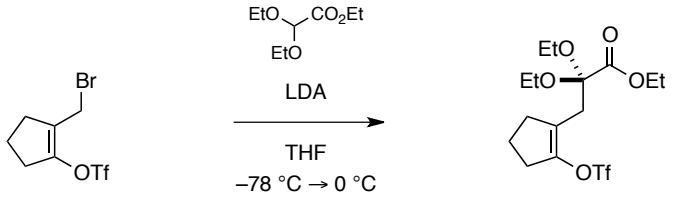
[*MJJ-II-69/122*] A sample of the crude mesylate was prepared as described above by treatment of a solution of the intermediate allylic alcohol (454 mg, 1.84 mmol, 1.0 equiv) and Et_3N (1.0 mL, 720 mg, 7.12 mmol, 3.9 equiv) in dry CH_2Cl_2 (18.0 mL) with MsCl (300 μL, 442 mg, 3.86 mmol, 2.1 equiv).

A solution of the crude mesylate (1.84 mmol theoretical) in dry THF (4.0 mL) was added dropwise to a solution of LiBr (1.73 g, 19.90 mmol, 10.8 equiv) in dry THF (14.0 mL) at 0 °C. After having been stirred at this temperature for 30 min, the reaction mixture was allowed to warm to rt and was maintained with stirring overnight. The reaction mixture was poured onto brine, H_2O was added to dissolve the inorganic salts that had precipitated, and the layers were shaken and separated. The aqueous phase was extracted with Et_2O (2x), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the crude residue by flash chromatography (98:2 Hex/EtOAc) provided the allylic bromide **2062** (524 mg, 1.70 mmol, 92% yield over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.00 (dddd, *J* = 1.5, 1.5, 1.5, 1.5 Hz, 2H, C*H*$_2$Br), 2.70-2.66 (m, 2H, C*H*$_2$CH$_2$C*H*$_2$), 2.57 -2.53 (m, 2H, C*H*$_2$CH$_2$C*H*$_2$), and 2.04 (dddd, *J* = 8.0, 8.0, 8.0, 8.0 Hz, 2H, CH$_2$C*H*$_2$CH$_2$).

TLC: R_f 0.83 (2:1 Hex/EtOAc).

ETHYL 2,2-DIETHOXY-3-(2-(((TRIFLUOROMETHYL)SULFONYL)OXY)CYCLOPENT-1-EN-1-YL)PROPANOATE (2064)



2062 ***2064***

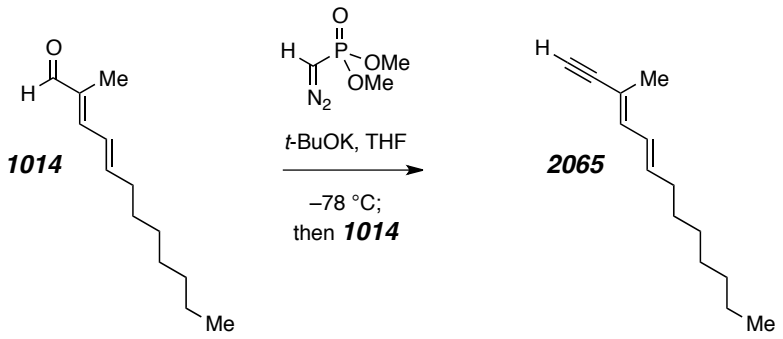
[*MJJ-II-111/124*] A solution of *n*-BuLi (1.6 mL, 3.66 mmol, 2.29 M in Hex) was added dropwise to a stirred solution of *i*-Pr_2NH (550 μL, 394 mg, 3.89 mmol) in dry THF (13.0 mL) at 0 °C. The resulting mixture was maintained at this temperature for 20 min, and was then cooled to –78 °C. Neat ethyl diethoxyacetate (600 μL, 593 mg, 3.36 mmol, 2.0 equiv) was added dropwise and the resulting mixture was warmed to 0 °C, stirred for 30 min, and then re-cooled to –78 °C. A solution of the allylic bromide **2062** (524 mg, 1.70 mmol, 1.0 equiv) in dry THF (5.0 mL) was added dropwise, and, after having been stirred at –78 °C for 30 min, the cooling bath was removed and the reaction mixture was allowed to warm to rt over the course of 30 min. At this point, the reaction mixture was partitioned between 1 M HCl and Et_2O, the layers were separated, and the aqueous phase was extracted with Et_2O (2x). The combined organic extracts were washed with sat aq $NaHCO_3$ (1x) and brine (1x), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by flash chromatography (95:5 Hex/EtOAc) provided the title compound (584 mg, 1.44 mmol, 85% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.22 (q, J = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 3.52 [ABX_3, $\Delta\nu_{AB}$ = 40.2 Hz, J_{AB} = 9.0 Hz, $J_{AX} = J_{BX}$ = 7.0 Hz, 4H, $C(OCH_2CH_3)_2$], 2.80 [dddd, J = 1.5, 1.5, 1.5, 1.5 Hz, 2H, $CH_2C(OCH_2CH_3)_2$], 2.60-2.55 (m, 2H, $CH_2CH_2CH_2$), 2.44-2.40 (m, 2H, $CH_2CH_2CH_2$), 1.93 (dddd, J = 8.0, 8.0, 8.0, 8.0 Hz, 2H, $CH_2CH_2CH_2$), 1.30 (t, J = 7.0 Hz, 3H, $CO_2CH_2CH_3$), and 1.23 [t, J = 7.0 Hz, 6H, $C(OCH_2CH_3)_2$].

GC / LR EI-MS [5029021]: t_R 9.66 min; *m*/*z* (rel. int.) 359 (8, $M^{+\bullet}$–$C_2H_5O^{\bullet}$), 331 (75, $M^{+\bullet}$–$C_3H_5O_2^{\bullet}$), 257 (7), 229 (37, $M^{+\bullet}$–$C_8H_{15}O_4^{\bullet}$), 175 (71, $M^{+\bullet}$–$C_7H_8F_3O_3S^{\bullet}$), 147 (89), 125 (100), and 119 (83).

TLC: R_f 0.46 (9:1 Hex/EtOAc).

(3*E*,5*E*)-3-METHYLTRIDECA-3,5-DIEN-1-YNE (2065)



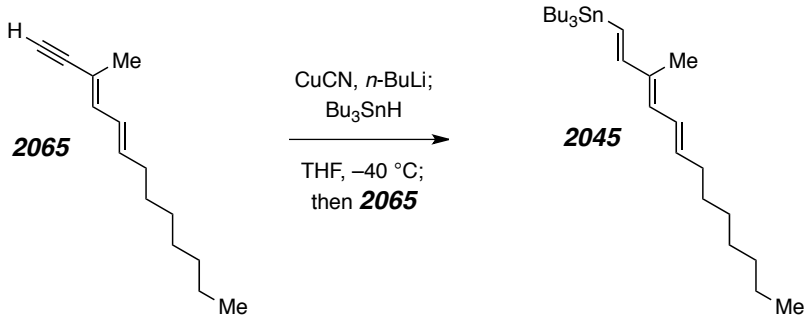
[*MJJ-II-116*] A solution of dimethyl (diazomethyl)phosphonate (162 mg, 1.08 mmol, 2.1 equiv) in dry THF (2.0 mL) was added dropwise to a mixture of *t*-BuOK (131 mg, 1.17 mmol, 2.3 equiv) in dry THF (3.0 mL) at –78 °C. The resulting bright yellow solution was maintained with stirring for 15 min and then a solution of the dienal **1014** (98 mg, 0.50 mmol, 1.0 equiv) in dry THF (2.0 mL) was added dropwise. After having been stirred at –78 °C for 2.5 h, the reaction mixture was allowed to warm to rt and was maintained with stirring overnight. At this point, TLC analysis of the reaction mixture revealed that **1014** [**TLC**: R_f 0.16 (95:5 Hex/EtOAc)] had been consumed. The reaction mixture was quenched by the addition of satd aq NH_4Cl (10 mL) and H_2O was added to dissolve the inorganic salts that had precipitated. The layers were shaken and separated, the aqueous phase was extracted with Et_2O (3x), and the combined organic extracts were washed with brine (1x), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by flash chromatography (100% Hex) provided the title compound (22 mg, 0.12 mmol, 23% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.42 [d, *J* = 11.0 Hz, 1H, CH=CHC*H*=C(CH_3)C≡CH], 6.25 [dddd, *J* = 1.5, 1.5, 11.0, 15.0 Hz, 1H, CH=C*H*CH=C(CH_3)C≡CH], 5.79 [ddd, *J* = 7.0, 7.0, 15.0 Hz, 1H, C*H*=CHCH=C(CH_3)C≡CH], 2.90 (s, 1H, C≡C*H*), 2.12 [dddd, *J* = 1.5, 7.0, 7.0, 7.0 Hz, 2H, CH=CHC*H*$_2$$CH_2$($CH_2$)$_4$$CH_3$], 1.89 [d, *J* = 1.5 Hz, 3H, CH=CHCH=C(C*H*$_3$)C≡CH], 1.43-1.37 [m, 2H, CH=CHCH_2C*H*$_2$(CH_2)$_4$$CH_3$], 1.33-1.23 [m, 8H, CH=CHCH_2CH_2(C*H*$_2$)$_4$$CH_3$], and 0.88 [t, *J* = 7.0 Hz, 3H CH=CHCH_2CH_2(CH_2)$_4$C*H*$_3$].

GC / LR EI-MS [5029021]: t_R 8.31 min; *m*/*z* (rel. int.) 190 (21, $M^{+\bullet}$) and 105 (100, $M^{+\bullet}$–$C_6H_{13}^{\bullet}$).

TLC: R_f 0.31 (100% Hex).

TRI-*n*-BUTYL((1*E*,3*E*,5*E*)-3-METHYLTRIDECA-1,3,5-TRIEN-1-YL)STANNANE (2045)



[*MJJ-II-117*] A solution of *n*-BuLi (150 μL, 0.34 mmol, 2.15 equiv, 2.29 M in Hex) was added dropwise to a suspension of CuCN (14.2 mg, 0.16 mmol, 1.0 equiv) in dry THF (500 μL) at *ca.* –40 °C (CH_3CN/dry ice). After having been stirred at this temperature for 10 min, the homogeneous solution that had formed was treated with neat Bu_3SnH (90 μL, 97 mg, 0.33 mmol, 2.1 equiv). This immediately induced H_2 evolution and the formation of a bright yellow solution to which was added, after having been stirred an additional 20 min, a solution of the dienyne **2065** (22 mg, 0.12 mmol, 0.72 equiv) in THF (500 μL). Stirring was continued at –40 °C for 20 min, at which point the reaction mixture was

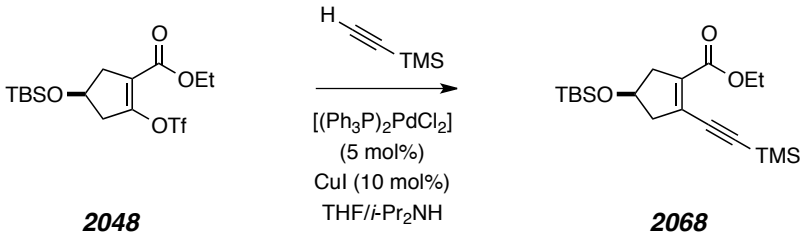
slowly quenched with MeOH/satd aq NH_4Cl (1:1, 5 mL) and was diluted with hexanes. The layers were shaken and separated, the aqueous phase was extracted with hexanes (3x), and the combined organic extracts were washed with brine (1x) and dried (Na_2SO_4). The oil (quantitative mass recovery) that was left after filtration and solvent evaporation was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.56 (d, *J* = 19.0 Hz, 1H, $Bu_3SnCH=CH$), 6.38 [dddd, *J* = 1.5, 1.5, 11.0, 15.0 Hz, 1H, $(CH_3)C=CHCH=CH$], 6.19 (d, *J* = 19.0 Hz, 1H, $Bu_3SnCH=CH$), 6.03 [d, *J* = 11.0 Hz, 1H, $(CH_3)C=CHCH=CH$], 5.76 [ddd, *J* = 7.0, 7.0, 15.0 Hz, 1H, $(CH_3)C=CHCH=CH$], 2.14 [dddd, *J* = 1.5, 7.0, 7.0, 7.0 Hz, 2H, $CH=CHCH_2CH_2(CH_2)_4CH_3$], 1.84 [d, *J* = 1.0 Hz, 3H, $(CH_3)C=CHCH=CH$], 1.55-1.37 [m, 8H, overlapping $Sn(CH_2CH_2CH_2CH_3)_3$ and $CH=CHCH_2CH_2(CH_2)_4CH_3$], 1.35-1.25 [m, 14H, overlapping $Sn(CH_2CH_2CH_2CH_3)_3$ and $CH=CHCH_2CH_2(CH_2)_4CH_3$], 0.92-0.87 [m, 12H, overlapping $Sn(CH_2CH_2CH_2CH_3)_3$ and $CH=CHCH_2CH_2(CH_2)_4CH_3$], and 0.82-0.78 [m, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$].

GC / LR EI-MS [5029021]: t_R 13.61 min; *m*/*z* (rel. int.) 425 [116722, $M^{+\bullet}(^{120}Sn)–C_4H_9^{\bullet}$], 423 [76, $M^{+\bullet}(^{118}Sn)–C_4H_9^{\bullet}$], 421 [42, $M^{+\bullet}(^{116}Sn)–C_4H_9^{\bullet}$], 311 (21), 309 (16), 307 (8), 291 [44, $(^{120}SnBu_3)^+$], 289 [33, $(^{118}SnBu_3)^+$], 287 [19, $(^{116}SnBu_3)^+$], 235 (77), 233 (57), 231 (35), 177 (86), 175 (57), and 173 (17).

TLC: R_f 0.79 (100% Hex).

(±)-ETHYL 4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(TRIMETHYLSILYLETHYNYL)-CYCLOPENT-1-ENECARBOXYLATE (2068)



2048 ***2068***

[*MJJ-IV-189/260/VII-41*] A solution of the enol triflate **2048** (1.73 g, 4.13 mmol, 1.0 equiv) in dry THF (10 mL) was added dropwise to a turbid solution of $(Ph_3P)_2PdCl_2$ (144 mg, 0.21 mmol, 5 mol%) and CuI (79 mg, 0.41 mmol, 10 mol%) in dry THF (20 mL). The resulting mixture was treated sequentially with (trimethylsilyl)acetylene (880 μL, 612 mg, 0.23 mmol, 1.5 equiv) and distilled *i*-Pr_2NH (10 mL) and, within 5 min, the color of the reaction mixture evolved from light yellow to orange, and then finally to dark brown. After having been stirred at rt overnight, the reaction mixture was diluted with Et_2O (100 mL) and filtered through a bed of CELITE®. The filtrate was washed with satd aq NH_4Cl/H_2O (2:1, 75 mL), the aqueous layer was extracted with Et_2O (2 x 50 mL), and the combined organic extracts were washed with H_2O (50 mL) and brine (50 mL). The organic material was dried (Na_2SO_4), filtered, and concentrated at reduced pressure. Purification of the crude residue by flash chromatography (40:1 Hex/EtOAc) provided the title compound as a light yellow oil (1.33 g, 3.64 mmol, 88% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.46 [dddd, *J* = 3.5, 3.5, 6.5, 6.5 Hz, 1H, C*H*(OTBS)], 4.23 (q, *J* = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 2.93 [dddd, *J* = 2.0, 2.0, 7.0, 18.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.88 [dddd, *J* = 1.5, 1.5, 7.0, 17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.64 [ddddd, *J* = 2.0, 2.0, 3.5, 17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.61 [dddd, *J* = 2.0, 2.0, 4.0, 17.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 1.33 (t, *J* = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 0.87 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.23 [s, 9H, $C{\equiv}CSi(CH_3)_3$], and 0.05 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

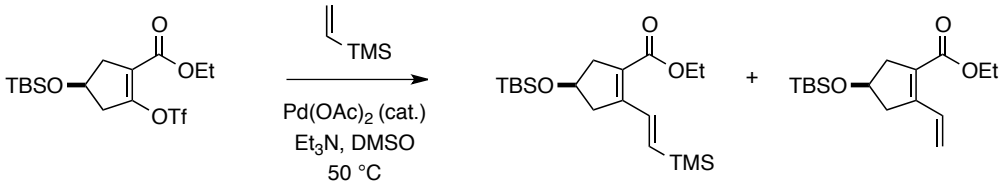
^{13}C NMR (125 MHz, $CDCl_3$): δ 164.3, 136.6, 131.2, 105.9, 100.5, 70.3, 60.6, 49.2, 43.4, 26.0, 18.3, 14.4, -0.1, and -4.7.

IR (neat): 2956, 2931, 2900, 2857, 2144, 1704, 1249, 1221, 1098, 1067, 842, and 775 cm^{-1}.

HR ESI-MS: $C_{19}H_{34}O_3Si_2$ $[M+Na]^+$ requires 389.1939; found 389.1951.

TLC: R_f 0.53 (8:1 Hex/EtOAc).

(±)-(*E*)-ETHYL-4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(2-TRIMETHYLSILYLVINYL)-CYCLOPENT-1-ENE-CARBOXYLATE (2070)



2048 ***2070*** ***2071***

[*MJJ-VI-218*] To a solution of the enol triflate **2048** (4.31 g, 10.30 mmol, 1.0 equiv) and Et_3N (4.3 mL, 3.12 g, 30.85 mmol, 3.0 equiv) in DMSO (100 mL) were added sequentially $Pd(OAc)_2$ (23 mg, 0.102 mmol, 1.0 mol%) and trimethyl(vinyl)silane (4.5 mL, 3.08 g, 30.71 mmol, 3.0 equiv). The reaction flask was then immersed in a pre-heated (50 °C) oil bath and, after having been stirred at this temperature for 60 min, the solution rapidly changed color from light brown (tan) to dark brown. At this point, GC-MS analysis of the reaction mixture indicated that the starting material had been consumed. The reaction mixture was then filtered through a bed of CELITE® (Et_2O eluent) and the filtrate was poured into a separatory funnel that contained Et_2O (200 mL) and 1:1 brine/H_2O (400 mL). This mixture was shaken and the layers separated, and the aqueous phase was extracted with Et_2O (3 x 150 mL). The combined organic extracts were washed with H_2O (2 x 100 mL) and brine (100 mL), dried ($MgSO_4$), and filtered.

Evaporation of the solvent *in vacuo* followed by purification of the crude residue by flash chromatography (98:2 → 20:1 Hex/EtOAc) provided the title compound as a light yellow oil (3.74 g, 9.43 mmol, 92% yield corrected for purity) that was judged to be 93% (w/w) pure on the basis of ^{1}H NMR analysis. The only contaminant was the reduced terminal alkene **2071**,[396] which was chromatographically inseparable at this stage.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 [d, *J* = 19.5 Hz, 1H, C*H*=CHSi$(CH_3)_3$], 6.13 [d, *J* = 19.0 Hz, 1H, CH=C*H*Si$(CH_3)_3$], 4.46 [dddd, *J* = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 4.22 (q, *J* = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 2.98 [dd, *J* = 6.5, 17.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.93 [dd, *J* = 7.0, 17.5 Hz, 1H, CH_2CH(OTBS)C*H*$_2$], 2.69 [dd, *J* = 4.5, 17.5 Hz, 1H, C*H*$_2$CH(OTBS)CH_2], 2.63 [dd, *J* = 4.5, 17.5 Hz, 1H, CH_2CH(OTBS)C*H*$_2$], 1.32 (t, *J* = 7.5 Hz, 3H, $CO_2CH_2CH_3$), 0.89 [s, 9H, $(CH_3)_3$CSi$(CH_3)_2$], 0.12 [s, 9H, Si$(CH_3)_3$], and 0.07 [s, 6H, $(CH_3)_3$CSi$(CH_3)_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 150.2, 138.7, 138.5, 126.8, 69.9, 60.2, 44.6, 43.9, 26.0, 18.4, 14.5, -1.3, and -4.6.

IR (neat): 2955, 2930, 2901, 2857, 1707, 1247, 1214, 1089, 1067, 863, and 839 cm^{-1}.

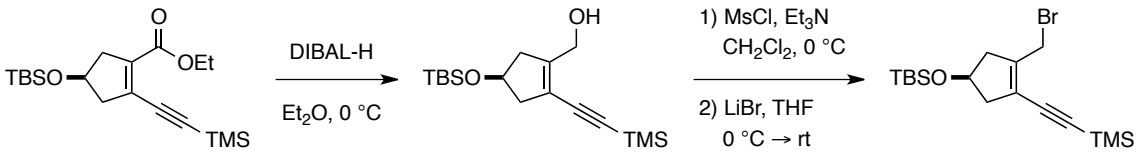
HR ESI-MS: $C_{19}H_{36}O_3Si_2$ $[M+Na]^+$ requires 391.2095; found 391.2108.

TLC: R_f 0.62 for **2070** (major); R_f 0.58 for **2071** (minor) (8:1 Hex/EtOAc).

---

[396] The following diagnostic ^{1}H NMR resonances were observed for **2071** (500 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 11.5, 17.5 Hz, 1H, C*H*=CH$_{trans}$H$_{cis}$), 5.41 (d, *J* = 17.5 Hz, 1H, CH=C*H*$_{trans}$H$_{cis}$), and 5.40 (d, *J* = 11.5 Hz, 1H, CH=CH$_{trans}$*H*$_{cis}$). Since the major product (**2070**) obscured the remaining resonances of **2071**, a complete chemical shift assignment was precluded at this stage.

(±)-((2-(BROMOMETHYL)-4-(*TERT*-BUTYLDIMETHYLSILOXY)CYCLOPENT-1-EN-1-YL)ETHYNYL)TRIMETHYLSILANE (2074) via **(±)-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(TRIMETHYLSILYLETHYNYL)CYCLOPENT-1-EN-1-YL)METHANOL (2072)**



2068 ***2072*** ***2074***

[*MJJ-II-285/III-47*] A solution of DIBAL-H (3.8 mL, 5.70 mmol, 3.0 equiv, 1.5 M in PhMe) was added dropwise to a solution of the ethyl ester **2068** (693 mg, 1.89 mmol, 1.0 equiv) in dry Et_2O (20 mL) at 0 °C. After having been stirred for 10 min at this temperature, the reaction mixture was *slowly* quenched by dropwise addition of H_2O. Once H_2 evolution had ceased, the resulting mixture was warmed to rt and treated with satd aq potassium sodium tartrate. Dilute (1 M) HCl was then added until a clear, two-phase mixture was obtained. The phases were separated and the aqueous phase was extracted with Et_2O (3x). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to leave a light brown oil (603 mg) that was used in the subsequent procedure without further purification. Select analytical data [from *MJJ-II-285*] for material that was purified by medium pressure liquid chromatography (SiO_2, 14:1 Hex/EtOAc) are provided below.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.49 [dddd, *J* = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 4.35 (ddddd, *J* = 1.5, 1.5, 1.5, 1.5, 6.5 Hz, 2H, CH_2OH), 2.78-2.72 [m, 2H, CH_2CH(OTBS)CH_2], 2.46 [dddddd, *J* = 2.0, 2.0, 2.0, 2.0, 3.5, 16.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.45-2.40 [m, 1H, CH_2CH(OTBS)CH_2], 1.69 (t, *J* = 6.0 Hz, 1H, CH_2O*H*), 0.88 [s, 9H, (CH_3)$_3$CSi(CH_3)$_2$], 0.19 [s, 9H, Si(CH_3)$_3$], 0.055 [s, 3H, (CH_3)$_3$CSi(CH_3)$_2$], and 0.052 [s, 3H, (CH_3)$_3$CSi(CH_3)$_2$].

TLC: R_f 0.30 (9:1 Hex/EtOAc).

[*MJJ-III-48/93/269*] Methanesulfonyl chloride (200 μL, 295 mg, 2.57 mmol, 1.4 equiv) was added dropwise to a solution of the crude allylic alcohol **2072** (1.89 mmol theoretical) and Et_3N (550 μL, 394 mg, 3.89 mmol, 2.1 equiv) in dry CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was allowed to stir at this temperature for 40 min, at which point it was diluted with Et_2O (40 mL) and then poured onto H_2O (30 mL). The layers were shaken and separated, the aqueous phase was extracted with Et_2O (2 x 30 mL), and the combined organic extracts were washed with H_2O (20 mL) and brine (1x). Drying ($MgSO_4$), filtration, and evaporation of the solvent at reduced pressure proved the crude mesylate that was used in the subsequent step without further purification.

A sample of LiBr (861 mg, 9.91 mmol, 5.2 equiv) was flame-dried under a stream of dry N_2. After having been cooled to rt, dry THF (15.0 mL) was added and, once the LiBr was completely solubilized, the solution was cooled to 0 °C. A solution of the crude mesylate (1.89 mmol theoretical) in dry THF (5.0 mL) was added dropwise, the cooling bath was removed, and the resulting mixture allowed to warm to rt. After having been stirred at this temperature overnight, the reaction mixture was diluted pentane and then poured onto brine/H_2O (5:1, 30 mL). The layers were shaken and separated, the aqueous layer was extracted with pentane (3x), and the combined organic extracts were washed with brine (1x), dried (Na_2SO_4), and filtered. Concentration of the filtrate *in vacuo* and purification of the crude residue by flash chromatography (99:1 → 98:2 Hex/EtOAc) provided the title compound as a yellow oil (577 mg, 1.50 mmol, 79% yield over 3 steps). This oil solidified upon storage at –20 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.49 [dddd, J = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 4.19 (ABq, $\Delta\nu_{AB}$ = 50.5 Hz, J_{AB} = 10.0 Hz, 2H, CH_2Br), 2.84 [dd, J = 7.0, 17.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.76 [dd, J = 7.0, 16.5 Hz, 1H, CH_2CH(OTBS)CH_2], 2.49-2.43 [m, 2H, overlapping CH_2CH(OTBS)CH_2], 0.88 [s, 9H, (CH_3)$_3$CSi(CH_3)$_2$], 0.21 [s, 9H, Si(CH_3)$_3$ and 0.06 [s, 6H, (CH_3)$_3$CSi(CH_3)$_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 144.2, 121.4, 101.8, 99.8, 70.9, 46.9, 44.2, 29.3, 26.0, 18.3, 0.1, and -4.6.

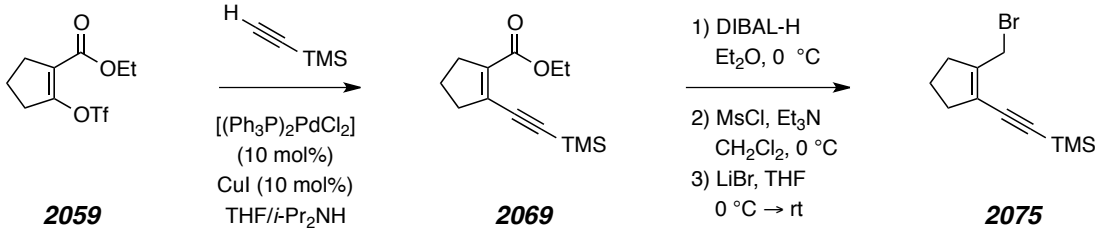
IR (thin film): 2956, 2930, 2898, 2857, 2143, 1252, 1101, 1067, 843, 778, and 763 cm^{-1}.

GC / LR EI-MS [5025015]: t_R 9.27 min; *m/z* (rel. int.) 373 [3, $M^{+\bullet}(^{81}Br)–CH_3^{\bullet}$], 371 [2, $M^{+\bullet}(^{79}Br)–CH_3^{\bullet}$], 331 [34, $M^{+\bullet}(^{81}Br)–C(CH_3)_3^{\bullet}$], 329 [29, $M^{+\bullet}(^{79}Br)–C(CH_3)_3^{\bullet}$], 307 (18, $M^{+\bullet}–Br^{\bullet}$), 251 (57) 213 (40), 211 (38), 175 (78), 161 (43), 159 (46), and 147 (100). This material partially decomposed upon entering the GC injection port, as evidenced by the presence of three additional, slightly less intense peaks (t_R 7.90, 8.15, and 8.89 min).

MP: 42–44 °C.

TLC: R_f 0.79 (9:1 Hex/EtOAc).

((2-(BROMOMETHYL)CYCLOPENT-1-EN-1-YL)ETHYNYL)TRIMETHYLSILANE (2075) via **ETHYL 2-(TRIMETHYLSILYLETHYNYL)CYCLOPENT-1-ENECARBOXYLATE (2069)**



2059 ***2069*** ***2075***

[*MJJ-II-135/158*] In a procedure that was analogous to that described for the preparation of the ynoate **2068**, the enol triflate **2059** [**TLC**: R_f 0.46 (9:1 Hex/EtOAc)] (1.13 g, 3.91 mmol, 1.0 equiv) was allowed to react with (trimethylsilyl)acetylene (2.8 mL, 1.93 g, 19.67 mmol, 5.0 equiv) in the presence of $(Ph_3P)_2PdCl_2$ (274 mg, 0.39 mmol, 10 mol%) and CuI (76 mg, 0.40 mmol, 10 mol%) in dry THF/*i*-Pr_2NH (3:1, 40 mL). After having been stirred overnight at rt, the reaction mixture was diluted with Et_2O and H_2O, the layers were shaken and separated, and the aqueous phase was extracted with Et_2O (3x). The combined organic extracts were washed with brine (1x), dried ($MgSO_4$), filtered, and

evaporated to dryness. Purification of the crude residue by flash chromatography (100% Hex → 95:5 Hex/EtOAc) provided the ynoate **2069** (843 mg, 3.57 mmol, 91% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.24 (q, *J* = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 2.72-2.64 (m, 4H, $CH_2CH_2CH_2$), 1.90 (dddd, *J* = 8.0, 8.0, 8.0, 8.0 Hz, 2H, $CH_2CH_2CH_2$), 1.33 (t, *J* = 7.0 Hz, 3H, $CO_2CH_2CH_3$), and 0.23 [s, 9H, $C{\equiv}CSi(CH_3)_3$].

TLC: R_f 0.56 (9:1 Hex/EtOAc).

[*MJJ-II-137/160*] In a procedure that was analogous to that described for the preparation of the allylic alcohol **2072**, a solution of the ethyl ester **2069** (376 mg, 1.59 mmol, 1.0 equiv) in dry Et_2O (12.0 mL) at 0 °C was treated dropwise with a solution of DIBAL-H (4.2 mL, 6.30 mmol, 4.0 equiv, 1.5 M in PhMe). After having been stirred at this temperature for 30 min, the reaction mixture was quenched and processed as described previously (i.e., H_2O quench, addition of 1 M HCl, and Et_2O extraction). Purification of the crude residue by flash chromatography (8:1 Hex/EtOAc) provided the allylic alcohol **2073** (259 mg, 1.33 mmol, 84% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.37 (ddddd, *J* = 1.5, 1.5, 1.5, 1.5, 5.5 Hz, 2H, CH_2OH), 2.54-2.46 (m, 4H, $CH_2CH_2CH_2$), 1.89 (dddd, *J* = 8.0, 8.0, 8.0, 8.0 Hz, 2H, $CH_2CH_2CH_2$), 1.75 (t, *J* = 6.0 Hz, 1H, CH_2OH), and 0.20 [s, 9H, $C{\equiv}CSi(CH_3)_3$].

GC / LR EI-MS [5027016]: t_R 7.93 min; *m*/*z* (rel. int.) 194 (16, $M^{+\bullet}$), 179 (66 $M^{+\bullet}$–$CH_3^{\bullet}$), 161 (18), 151 (18), 99 (34), 75 (100), and 73 (91).

TLC: R_f 0.08 (9:1 Hex/EtOAc).

[*MJJ-II-138/161*] In a procedure that was analogous to that described for the mesylation of **2072**, the allylic alcohol **2073** (259 mg, 1.33 mmol, 1.0 equiv) was allowed to react with MsCl (200 μL, 295 mg, 2.57 mmol, 2.0 equiv) and Et_3N (750 μL, 540 mg, 5.34 mmol, 4.0 equiv) in dry CH_2Cl_2 (12.0 mL) for 60 min at 0 °C. The reaction mixture was

then processed as detailed previously to provide the crude mesylate that was used immediately in the next step without further purification.

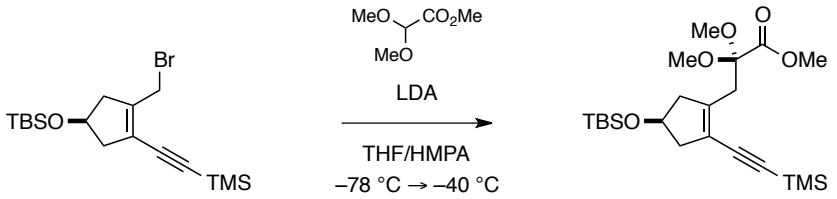
A solution of the crude mesylate (1.33 mmol theoretical) in dry THF (3.0 mL) was added dropwise to a solution of flame-dried LiBr (1.06 g, 12.3 mmol, 9.2 equiv) in dry THF (9.0 mL) at 0 °C. After having been stirred for 45 min, the reaction mixture was warmed to rt, stirred for 30 min, diluted with Et_2O, and then poured onto brine/H_2O. The layers were shaken and separated, the aqueous phase was extracted with Et_2O (2x), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the crude residue by flash chromatography (100% Hex) provided the allylic bromide **2075** (252 mg, 0.98 mmol, 74% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.21 (dddd, *J* = 1.0, 1.0, 1.0, 1.0 Hz, 2H, C*H*$_2$Br), 2.58-2.49 (m, 4H, C*H*$_2$CH$_2$C*H*$_2$), 1.91 (dddd, *J* = 8.0, 8.0, 8.0, 8.0 Hz, 2H, CH$_2$C*H*$_2$CH$_2$), and 0.21 [s, 9H, Si(C*H*$_3$)$_3$].

GC / LR EI-MS [5027016]: t_R 8.26 min; *m*/*z* (rel. int.) 258 [9, $M^{+\bullet}$(^{81}Br)], 256 [8, $M^{+\bullet}$(^{79}Br)], 177 (100, $M^{+\bullet}$–Br$^\bullet$), 161 (23), 149 (14), 137 (13), 117 (10), and 97 (51).

TLC: R_f 0.49 (98:2 Hex/EtOAc).

(±)-METHYL 3-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(TRIMETHYLSILYLETHYNYL)-CYCLOPENT-1-EN-1-YL)-2,2-DIMETHOXYPROPANOATE (2078)



2074 ***2078***

Methyl dimethoxyacetate. [*MJJ-III-259*] A 250-mL round-bottom flask was charged with glyoxylic acid monohydrate (16.8 g, 183 mmol, 1.0 equiv), trimethylorthoformate (100 mL, 97.0 g, 914 mmol, 5.0 equiv), and *p*-toluenesulfonic acid monohydrate (3.5 g, 18.3 mmol, 10 mol%). The resulting mixture was allowed to stir overnight at rt and then anhydrous K_2CO_3 (4.0 g, 29.0 mmol) was added in a single portion. The reaction flask was fitted with a single-piece, vacuum jacketed fractional distillation apparatus and the contents were distilled at reduced pressure (bp 65 °C @ ~25 mmHg; lit.[397] 64–67 °C @ 20 mmHg) to provide the title compound as a clear, colorless liquid (17.1 g, 127 mmol, 70% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.83 [s, 1H, $(CH_3O)_2CHCO_2CH_3$], 3.81 [s, 3H, $(CH_3O)_2CHCO_2CH_3$], and 3.43 [s, 6H, $(CH_3O)_2CHCO_2CH_3$].

[*MJJ-III-99/220/VII-86*] A solution of *n*-BuLi (650 μL, 1.64 mmol, 2.53 M in Hex) was added dropwise to a stirred solution of *i*-Pr_2NH (250 μL, 181 mg, 1.78 mmol) in dry THF (8.2 mL) at 0 °C. The resulting mixture was maintained at this temperature for 20 min, and was then cooled to –78 °C and stirred an additional 10 min. A solution of methyl

---

397 Cameron, A. G.; Hewson, A. T. Synthesis of 1-Alkylthiovinyl- and 1-Arylthiovinyl-phosphonium Salts and Their Use in the Formation of Cyclopentanes. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2979–2982.

dimethoxyacetate (206 mg, 1.54 mmol, 10 equiv) and HMPA (2.7 mL, 2.78 g, 15.52 mmol, 100 equiv) in dry THF (6.0 mL) was then added dropwise. Stirring was continued at –78 °C for 30 min, at which point a light yellow, cloudy solution had developed. The allylic bromide **2074** (60 mg, 0.15 mmol, 1.0 equiv) was then added dropwise as a solution in dry THF (6.0 mL) and, after having been stirred at –78 °C for 40 min, the cooling bath was removed and the reaction mixture was quenched by the addition of satd aq NH_4Cl (30 mL). The resulting mixture was poured into a separatory funnel with the aid of EtOAc, the layers were shaken and separated, and the aqueous phase was extracted with EtOAc (3x). The combined organic extracts were washed with 1:1 brine/H_2O (2x) and brine (1x), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was filtered through a short bed of SiO_2 (1:1 Hex/EtOAc), concentrated *in vacuo*, and purified by medium pressure liquid chromatography (SiO_2, 14:1 Hex/EtOAc) to provide the title compound as a light yellow oil (49 mg, 0.11 mmol, 72% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.41 [dddd, J = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.78 [s, 3H, $CH_2C(OCH_3)_2CO_2CH_3$], 3.303 [s, 3H, $CH_2C(OCH_3)_2CO_2CH_3$], 3.30 [s, 3H, $CH_2C(OCH_3)_2CO_2CH_3$], 2.94 [ABq, $\Delta\nu_{AB}$ = 63.9 Hz, J_{AB} = 14.5 Hz, 2H, $CH_2C(OCH_3)_2CO_2CH_3$], 2.68-2.63 [m, 2H, overlapping $CH_2CH(OTBS)CH_2$], 2.38 [br d, J = 17.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.27 [br d, J = 17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 0.87 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.18 [s, 9H, $Si(CH_3)_3$], and 0.03 [s, 6H, $(CH_3)_3CSi(CH_3)_2$].

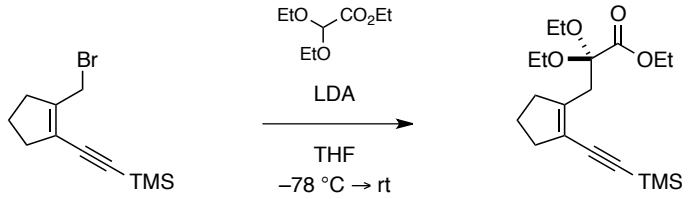
^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 143.1, 120.3, 101.7, 101.3, 98.9, 71.5, 52.7, 50.2, 46.1, 45.3, 35.8, 26.0, 18.3, 0.2, -4.63, and -4.64.

IR (neat): 2954, 2901, 2857, 2141, 1754, 1251, 1200, 1136, 1095, 1066, 855, 842, and 776 cm^{-1}.

HR ESI-MS: $C_{22}H_{40}O_5Si_2$ $[M+Na]^+$ requires 463.2306; found 463.2323.

TLC: R_f 0.34 (9:1 Hex/EtOAc).

ETHYL 2,2-DIETHOXY-3-(2-(TRIMETHYLSILYLETHYNYL)CYCLOPENT-1-EN-1-YL)-PROPANOATE (2080)



2075 ***2080***

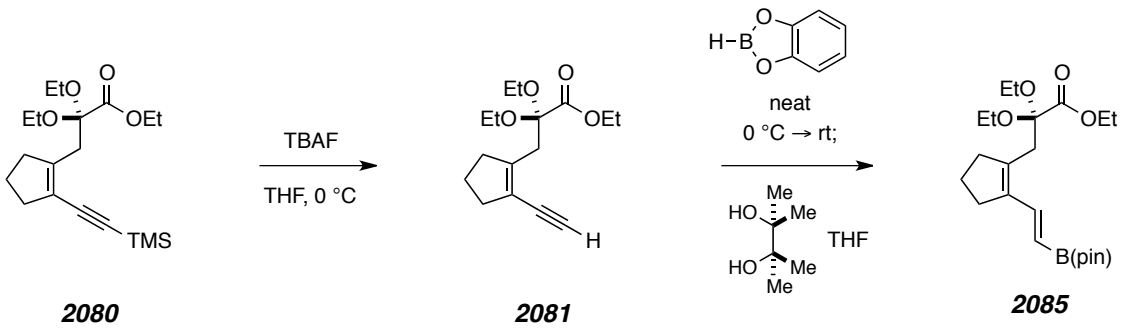
[*MJJ-II-132/139*] A solution of *n*-BuLi (300 μL, 0.69 mmol, 2.29 M in Hex) was added dropwise to a stirred solution of *i*-Pr_2NH (100 μL, 71.6 mg, 0.71 mmol) in dry THF (2.4 mL) at 0 °C. The resulting mixture was maintained at this temperature for 20 min, and was then cooled to –78 °C. Neat ethyl diethoxyacetate (120 μL, 119 mg, 0.67 mmol, 5.6 equiv) was added dropwise and the resulting mixture was warmed to 0 °C, stirred for 30 min, and then re-cooled to –78 °C. A solution of the allylic bromide **2075** (32 mg, 0.12 mmol, 1.0 equiv) in dry THF (1.0 mL) was added dropwise, and, after having been stirred at –78 °C for 60 min, the reaction mixture was allowed to warm to 0 °C. Stirring was continued at this temperature for 45 min and then at rt for 15 min. The reaction mixture was partitioned between 1 M HCl and Et_2O, the layers were separated, and the aqueous phase was extracted with Et_2O (2x). The combined organic extracts were washed with sat aq $NaHCO_3$ (1x) and brine (1x), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (20:1 Hex/EtOAc) provided the title compound (32 mg, 0.09 mmol, 76% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.23 (q, J = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 3.55 [ABX_3, $\Delta\nu_{AB}$ = 91.6 Hz, J_{AB} = 9.0 Hz, $J_{AX} = J_{BX}$ = 7.0 Hz, 4H, $C(OCH_2CH_3)_2$], 2.98 [dddd, J = 1.5, 1.5, 1.5, 1.5 Hz, 2H, $CH_2C(OCH_2CH_3)_2$], 2.44-2.35 (m, 4H, $CH_2CH_2CH_2$), 1.80 (dddd, J = 8.0, 8.0, 8.0, 8.0 Hz, 2H, $CH_2CH_2CH_2$), 1.31 (t, J = 7.0 Hz, 3H, $CO_2CH_2CH_3$), 1.23 [t, J = 7.0 Hz, 6H, $C(OCH_2CH_3)_2$], and 0.19 [s, 9H, $C{\equiv}CSi(CH_3)_3$].

GC / LR EI-MS [5027016]: t_R 10.59 min; *m*/*z* (rel. int.) 306 (1), 279 (43, $M^{+\bullet}$–$C_3H_5O^{\bullet}$), 263 (6), 175 [100, $(C_8H_{15}O_4)^+$], 147 (96), 133 (15), 119 (79), 105 (20), 91 (29), and 73 (44).

TLC: R_f 0.15 (98:2 Hex/EtOAc).

(*E*)-ETHYL 2,2-DIETHOXY-3-(2-(2-(4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)VINYL)CYCLOPENT-1-EN-1-YL)PROPANOATE (2085) via **ETHYL 2,2-DIETHOXY-3-(2-ETHYNYLCYCLOPENT-1-EN-1-YL)PROPANOATE (2081)**



2080 ***2081*** ***2085***

[*MJJ-II-217*] A solution of tetra-*n*-butylammonium fluoride (700 µL, 0.70 mmol, 1.5 equiv, 1.0 M in THF) was added dropwise to a solution of the TMS alkyne **2080** (165 mg, 0.47 mmol, 1.0 equiv) in dry THF (5.0 mL) at 0 °C. After having been stirred at this temperature for 5 min, GC-MS analysis of a reaction mixture aliquot revealed that the starting material had been consumed. The reaction mixture was diluted with Et_2O and quenched by the addition of satd aq NH_4Cl. The layers were shaken and separated, the aqueous phase was extracted with Et_2O (2x), and the combined organic extracts were washed with brine (1x), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 20:1 Hex/EtOAc) provided the alkyne **2081** (119 mg, 0.42 mmol, 90% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.22 (q, J = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 3.55 [ABX_3, $\Delta\nu_{AB}$ = 68.9 Hz, J_{AB} = 9.0 Hz, $J_{AX} = J_{BX}$ = 7.0 Hz, 4H, $C(OCH_2CH_3)_2$], 3.12 (s, 1H, C≡C*H*),

2.98 [s, 2H, C*H*$_2$C(OCH$_2$CH$_3$)$_2$], 2.43 (dd, *J* = 7.5, 7.5 Hz, 4H, C*H*$_2$CH$_2$C*H*$_2$), 1.83 (dddd, *J* = 7.5, 7.5, 7.5, 7.5 Hz, 2H, CH$_2$C*H*$_2$CH$_2$], 1.30 (t, *J* = 7.0 Hz, 3H, CO$_2$CH$_2$C*H*$_3$), and 1.23 [t, *J* = 7.0 Hz, 6H, C(OCH$_2$C*H*$_3$)$_2$].

GC / LR EI-MS [5027016]: t_R 9.53 min; *m*/*z* (rel. int.) 207 (84, $M^{+\bullet}$–$C_3H_5O_2^{\bullet}$), 175 [100, $(C_8H_{15}O_4)^+$], 147 (90), 133 (23), 119 (94), 105 [87, $(C_8H_9)^+$], 91 [67, $(C_7H_7)^+$], 79 (31), and 77 (34).

TLC: R_f 0.54 (8:1 Hex/EtOAc).

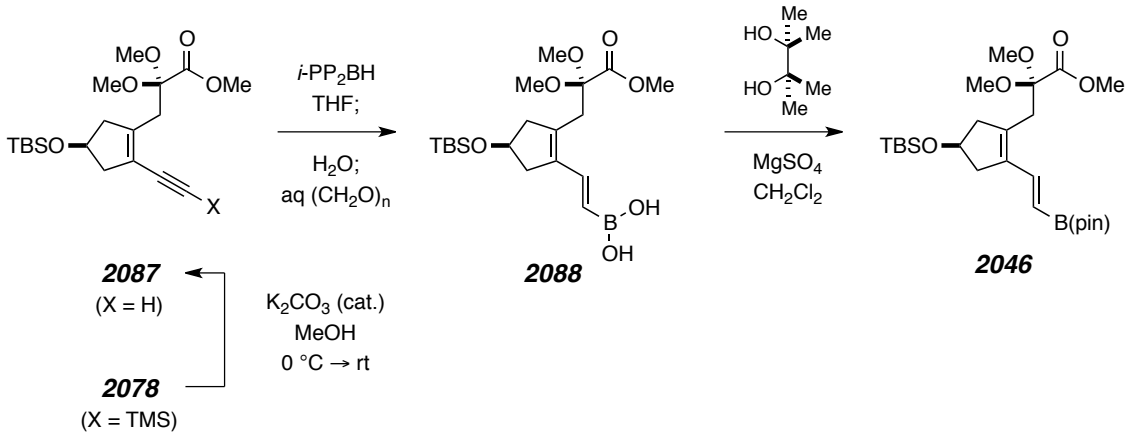
[*MJJ-II-218/241*] A dry 13 x 100 mm culture tube was charged with the alkyne **2081** (100 mg, 0.36 mmol, 1.0 equiv) and then cooled to 0 °C. Neat catecholborane (60 μL, 68 mg, 0.56 mmol, 1.6 equiv) was then added and the resulting mixture was allowed to warm to rt and was maintained at this temperature for 15 h. The yellow solid residue that had formed was dissolved in dry THF (400 μL), and the resulting solution was cooled to 0 °C and treated with pinacol (87 mg, 0.74 mmol, 2.0 equiv). The cooling bath was removed and, after having been stirred at rt for 5 h, the reaction mixture was treated with another portion of pinacol (51 mg). Stirring was continued for an additional 5 h at rt, at which point the reaction mixture was concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 9:1 Hex/EtOAc) provided the vinyl pinacol boronate **2085** (113 mg, 0.28 mmol, 77% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 [d, *J* = 18.0 Hz, 1H, C*H*=CHB(pin)], 5.41 [d, *J* = 18.0 Hz, 1H, CH=C*H*B(pin)], 4.10 (q, *J* = 7.0 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 3.55 [ABX$_3$, $\Delta\nu_{AB}$ = 53.7 Hz, J_{AB} = 9.5 Hz, J_{AX} = J_{BX} = 7.0 Hz, 4H, C(OC*H*$_2$CH$_3$)$_2$], 2.93 [s, 2H, C*H*$_2$C(OCH$_2$CH$_3$)$_2$], 2.55 (dd, *J* = 7.5, 7.5 Hz, 2H, C*H*$_2$CH$_2$C*H*$_2$), 2.43 (dd, *J* = 7.5, 7.5 Hz, 2H, C*H*$_2$CH$_2$C*H*$_2$), 1.78 (dddd, *J* = 7.5, 7.5, 7.5, 7.5 Hz, 2H, CH$_2$C*H*$_2$CH$_2$), 1.27 [s, 12H, OC(C*H*$_3$)$_2$C(C*H*$_3$)$_2$O], 1.26 (t, *J* = 7.0 Hz, 3H, CO$_2$CH$_2$C*H*$_3$), and 1.25 [t, *J* = 7.0 Hz, 6H, C(OCH$_2$C*H*$_3$)$_2$].

GC / LR EI-MS [5027016]: t_R 14.51 min; *m*/*z* (rel. int.) 335 [6, $M^{+\bullet}(^{11}B)–C_3H_5O_2^{\bullet}$], 334 [1, $M^{+\bullet}(^{10}B)–C_3H_5O_2^{\bullet}$], 207 (4), 191 (5), 175 [95, $(C_8H_{15}O_4)^+$], 163 (38), 147 (100), 133 (14), 119 (74), 105 [17, $(C_8H_9)^+$], and 91 [30, $(C_7H_7)^+$].

TLC: R_f 0.29 (9:1 Hex/EtOAc).

(±)-(*E*)-METHYL 3-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(2-(4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)VINYL)CYCLOPENT-1-EN-1-YL)-2,2-DIMETHOXYPROPANOATE (2046) via **(±)-METHYL 3-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-ETHYNYL-CYCLOPENT-1-EN-1-YL)-2,2-DIMETHOXYPROPANOATE (2087)**



[*MJJ-III-101/VII-89*] To a solution of the TMS alkyne **2078** (63 mg, 0.14 mmol, 1.0 equiv) in anhydrous MeOH (1.5 mL) at 0 °C was added K_2CO_3 (3.8 mg, 28 μmol, 20 mol%). The cooling bath was removed and the reaction mixture was allowed to warm to rt. After having been stirred at this temperature for 7 h, the reaction mixture was concentrated to partial dryness at the rotavap. The evaporation residue was taken up in Et_2O (20 mL) and washed with 1:1 brine/H_2O (20 mL). The aqueous layer was extracted with Et_2O (1x) and EtOAc (2x), and then the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by

medium pressure liquid chromatography (SiO_2, 9:1 Hex/EtOAc) provided the title compound as a light yellow oil (47 mg, 0.13 mmol, 89% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.44 [dddd, J = 4.5, 4.5, 7.5, 7.5 Hz, 1H, C*H*(OTBS)], 3.78 [s, 3H, $CH_2C(OCH_3)_2CO_2CH_3$], 3.31 [s, 6H, $CH_2C(OCH_3)_2CO_2CH_3$], 3.11 (s, 1H, C≡C*H*), 2.95 [ABq, $\Delta\nu_{AB}$ = 60.8 Hz, J_{AB} = 14.5 Hz, 2H, $CH_2C(OCH_3)_2CO_2CH_3$], 2.71 [dd, J = 7.5, 19.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.68 [dd, J = 7.0, 17.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.39 [br dd, J = 3.5, 16.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.30 [br dd, J = 4.0, 18.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 0.87 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], and 0.04 [s, 6H, $(CH_3)_3CSi(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 143.9, 119.2, 101.9, 81.7, 79.8, 71.4, 52.7, 50.22, 50.21, 46.1, 45.4, 35.6, 26.0, 18.3, and -4.6.

IR (neat): 3276, 2952, 2933, 2856, 2094, 1753, 1255, 1230, 1198, 1137, 1094, 1063, 837, and 777 cm^{-1}.

HR ESI-MS: $C_{19}H_{32}O_5Si$ $[M+Na]^+$ requires 391.1911; found 391.1925.

TLC: R_f 0.23 (9:1 Hex/EtOAc).

[*MJJ-III-252/VII-90*] A stock solution of *i*-PP_2BH (0.71 M in THF) was prepared as described previously. An aliquot of this stock solution (200 μL, ~142 μmol, ~1.4 equiv) was added dropwise to a solution of the alkyne **2087** (36.4 mg, 99 μmol, 1.0 equiv) in dry THF (500 μL) at 0 °C and, after the addition was complete, the reaction mixture was allowed to reach rt over 30 min. After having been stirred at this temperature for 2 h, TLC analysis of the reaction mixture indicated that the starting material had been consumed. The reaction mixture was cooled to 0 °C, slowly quenched by the addition of H_2O (50 μL), and then allowed to warm to rt. Stirring was continued for 2.5 h, at which point the reaction mixture was treated with paraformaldehyde (500 μL, 37 wt% in H_2O). After having been stirred at rt overnight, the reaction mixture was diluted with EtOAc

and poured onto brine (10 mL). The layers were shaken and separated, and the aqueous layer was extracted with EtOAc (1x) and CH_2Cl_2 (2x). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo* to leave a yellow oil that was used immediately without further purification.

In separate experiments [*MJJ-III-104/121*] the intermediate boronic acid (**2088**), which in these instances was produced by catecholborane hydroboration followed by *in situ* hydrolysis, could be purified by flash chromatography (1:1 Hex/EtOAc → 99:1 EtOAc/MeOH). Analysis of these samples by ^{1}H NMR revealed the presence of at least 4 (discrete) components, and therefore the spectral data were not readily amendable to full interpretation. Select analytical data have been provided below.

HR ESI-MS: $C_{19}H_{35}BO_7Si$ $[M\text{-}2H_2O\text{+}2MeOH\text{+}Na]^+$ requires 465.2450; found 465.2448.

TLC: R_f 0.56 (99:1 EtOAc/MeOH).

[*MJJ-III-254/VII-90*] A solution of the crude boronic acid (99 μmol theoretical) in CH_2Cl_2 (1.0 mL) was treated sequentially with pinacol (14.5 mg, 123 μmol, 1.2 equiv) and anhydrous $MgSO_4$ (excess), and the resulting suspension was maintained with stirring for a period of 6 h. The reaction mixture was then diluted with CH_2Cl_2, filtered through a short pad of CELITE®, and the filtrate was concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 6:1 Hex/EtOAc) provided the title compound (**2046**) as a yellow oil [35.2 mg, 65.2 μmol, 66% yield over 2 steps (corrected for purity)] that was judged to be 92% pure on the basis of ^{1}H NMR analysis. The primary contaminant was (*E*)-2,2,5-trimethylhex-3-en-1-ol,[398] a by-product that is formed after allylative hydrolysis of the intermediate boronic half-acid.

---

[398] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.44 [dd, *J* = 7.0, 16.0 Hz, 1H, $(CH_3)_2CCH{=}CHCH(CH_3)_2$], 5.27 [dd, *J* = 1.0, 16.0 Hz, 1H, $(CH_3)_2CCH{=}CHCH(CH_3)_2$], 3.28 (d, *J* = 6.0 Hz, 2H, CH_2OH), 2.34-2.22 (m, 1H, $CH{=}CHCH(CH_3)_2$], 0.99 [s, 6H, $(CH_3)_2CCH{=}CH$], and 0.98 [d, *J* = 7.0 Hz, 6H, $CH{=}CHCH(CH_3)_2$]. **^{13}C NMR** (125 MHz, $CDCl_3$): δ 137.2, 133.5, 71.7, 38.2, 31.4, 24.2, and 22.9.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 [d, *J* = 18.0 Hz, 1H, C*H*=CHB(pin)], 5.41 [d, *J* = 18.0 Hz, 1H, CH=C*H*B(pin)], 4.42 [dddd, *J* = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.68 [s, 3H, $CH_2C(OCH_3)_2CO_2CH_3$], 3.32 [s, 3H, $CH_2C(OCH_3)_2CO_2CH_3$], 3.30 [s, 3H, $CH_2C(OCH_3)_2CO_2CH_3$], 2.90 [ABq, $\Delta\nu_{AB}$ = 62.5 Hz, J_{AB} = 14.0 Hz, 2H, $CH_2C(OCH_3)_2CO_2CH_3$], 2.85 [dd, *J* = 7.0, 18.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.69 [dd, *J* = 7.0, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.42 [dd, *J* = 3.5, 18.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.37 [dd, *J* = 3.5, 15.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 1.26 [s, 12H, $OC(CH_3)_2C(CH_3)_2O$], 0.87 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.042 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.039 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

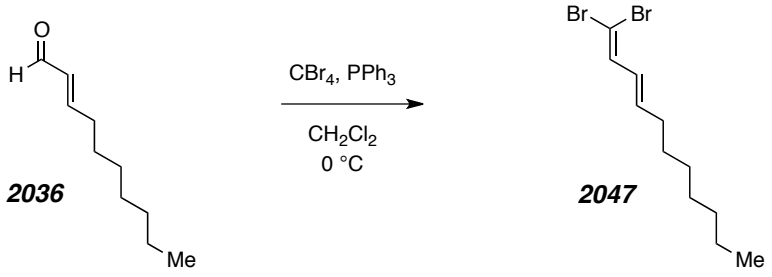
^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6, 142.4, 137.5, 136.2, 102.6, 83.2, 70.8, 52.5, 50.3, 50.1, 47.5, 42.3, 33.6, 26.1, 25.0, 24.9, 18.3, and -4.6.

IR (neat): 2952, 2932, 2856, 1757, 1627, 1596, 1382, 1346, 1323, 1197, 1143, 1094, 1063, 838, and 777 cm^{-1}.

HR ESI-MS: $C_{25}H_{45}BO_7Si$ $[M+Na]^+$ requires 519.2920; found 519.2927.

TLC: R_f 0.28 (6:1 Hex/EtOAc).

(*E*)-1,1-DIBROMOUNDECA-1,3-DIENE (2047)



[*MJJ-VI-108/239/VII-24*] To a solution of sublimed CBr_4 (4.35 g, 13.11 mmol, 2.0 equiv) in dry CH_2Cl_2 (60 mL) at 0 °C was added portionwise PPh_3 (6.87 g, 26.20 mmol, 4.0 equiv) via a powder funnel over a *ca.* 45 s period. The resulting bright orange solution

was stirred at 0 °C for 10 min, and then neat (*E*)-2-decenal (**2036**) (1.2 mL, 1.01 g, 6.54 mmol, 1.0 equiv) was added dropwise over 30 s. The color of the solution deepened to dark red during the addition of the enal and, after 2 min, TLC analysis of the reaction mixture indicated that the starting material had been consumed. The reaction mixture was diluted with hexanes (150 mL), stirred an additional 2 min, and filtered through a 4 cm x 10 cm bed of SiO_2 with the aid of additional hexanes (200 mL) to provide a clear, colorless filtrate. Removal of the solvent *in vacuo* and purification of the crude residue by flash chromatography (100% Hex) provided the title compound as a light yellow oil (1.92 g, 6.20 mmol, 95% yield).

[*NOTE:* Prolonged reaction times (> 30 min @ 0 °C) resulted in extensive decomposition of the dibromoolefin **2047**. It also decomposed rapidly (< 10 h) when stored neat at rt, and thus was typically prepared as needed on scales smaller (0.2-0.3 mmol; e.g., *MJJ-II-164/187*) than that described above. In those instances, the second chromatographic step was unnecessary; simple dilution of the reaction mixture with Hex (~10 vol) followed by SiO_2 filtration was sufficient to provide **2047** in a high state of purity.]

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.89 (d, *J* = 10.0 Hz, 1H, Br_2C=C*H*CH=CH), 6.08 (dddd, *J* = 1.5, 1.5, 10.0, 15.5 Hz, 1H, Br_2C=CHC*H*=CH), 5.91 (ddd, *J* = 7.0, 7.0, 14.5 Hz, 1H, Br_2C=CHCH=C*H*), 2.09 [dddd, *J* = 2.0, 7.5, 7.5, 7.5 Hz, 2H, CH=CHC$H_2$$CH_2$–$(CH_2)_4CH_3$], 1.43-1.37 [m, 2H, CH=CHCH$_2$C$H_2$$(CH_2)_4CH_3$], 1.33-1.23 [m, 8H, CH=CHCH$_2$CH$_2$$(CH_2)_4CH_3$], and 0.88 [t, *J* = 7.0 Hz, 3H, CH=CHCH$_2$CH$_2$$(CH_2)_4CH_3$].

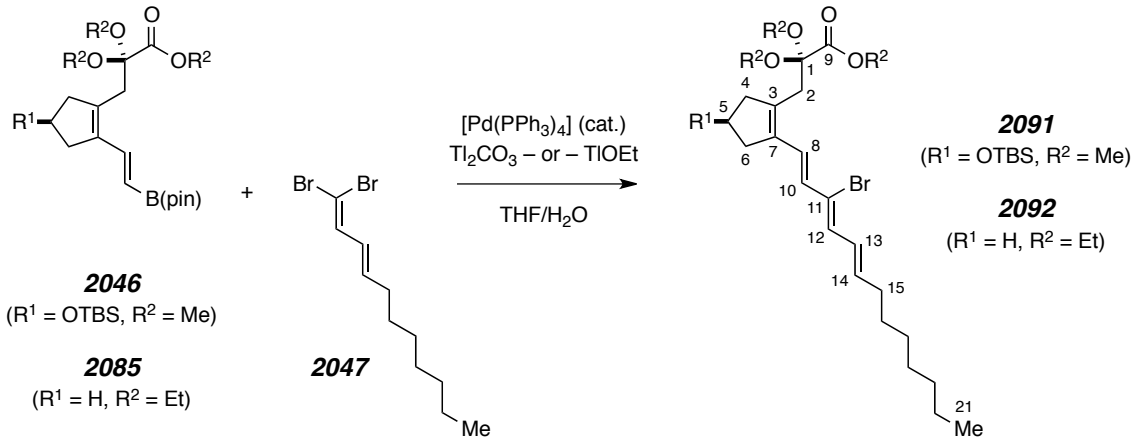
^{13}C NMR (75 MHz, $CDCl_3$): δ 139.9, 137.3, 127.2, 88.4, 33.1, 31.9, 29.3, 29.0, 22.8, and 14.3.

IR (neat): 2953, 2925, 2855, 1768, 1620, 1461, 1078, 1005, 968, and 804 cm^{-1}.

GC / LR EI-MS [5025015]: t_R 8.12 min; *m*/*z* (rel. int.) 312 [13, $M^{+\bullet}$(^{81}Br/^{81}Br)], 310 [25, $M^{+\bullet}$(^{79}Br/^{81}Br)], 308 [13, $M^{+\bullet}$(^{79}Br/^{79}Br)], 214 (50), 212 (100), 210 (51), 146 (14), 144 (14), 133 (7), 131 (7), 119 (4), and 117 (3).

TLC: R_f 0.72 (100% Hex).

1,1-DIBROMOOLEFIN SUZUKI CROSS-COUPLING: PREPARATION OF (±)-METHYL 3-(2-((1*E*,3*Z*,5*E*)-3-BROMOTRIDECA-1,3,5-TRIEN-1-YL)-4-(*TERT*-BUTYLDIMETHYLSILOXY)-CYCLOPENT-1-EN-1-YL)-2,2-DIMETHOXYPROPANOATE (2091) and **ETHYL 3-(2-((1*E*,3*Z*,5*E*)-3-BROMOTRIDECA-1,3,5-TRIEN-1-YL)CYCLOPENT-1-EN-1-YL)-2,2-DIETHOXYPROPANOATE (2092)**



2091 (R^1 = OTBS, R^2 = Me). [*MJJ-III-58/63/86/VII-100*] A 5-mL pear-shaped flask was charged with the pinacol boronic ester **2046** (16.2 mg, 32.6 μmol, 1.0 equiv), dibromoolefin **2047** (24.8 mg, 80.0 μmol, 2.5 equiv), THF (450 μL), and distilled H_2O (150 μL). The reaction flask was then fitted with a 2-neck vacuum adapter and the contents were degassed by freeze-pump-thaw (4 cycles), after which the vacuum adapter was replaced with a septum/N_2 inlet. A catalytic amount of tetrakis(triphenylphosphine)-palladium(0) (8.6 mg, 7.4 μmol, 23 mol%) was added, which produced a bright yellow solution. After having been stirred for 5 min at rt, solid Tl_2CO_3 (43 mg, 91.7 μmol, 2.8 equiv) was added. The appearance of a finely divided, pale yellow precipitate was observed shortly thereafter, and stirring was continued for 1.5 at rt. At this point, TLC analysis of the reaction mixture revealed that the starting material had been consumed. The reaction mixture was diluted with Et_2O (~10 vol) and then quenched by the addition of 1 M $NaHSO_4$ (~10 vol). After having been stirred for 10 min, the resulting suspension

was filtered through CELITE® with the aid of additional Et_2O. The layers were separated, and the organic layer was washed with H_2O (1x) and brine (1x). The organic material was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 14:1 Hex/EtOAc) provided the title compound as an off-white solid (11.7 mg, 19.5 μmol, 60% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.83 (d, J = 14.5 Hz, 1H, H8), 6.51 (dddd, J = 1.5, 1.5, 10.5, 14.0 Hz, 1H, H13), 6.47 (d, J = 10.0 Hz, 1H, H12), 6.10 (d, J = 14.5 Hz, 1H, H10), 5.95 (ddd, J = 6.5, 6.5, 14.5 Hz, 1H, H14), 4.45 (dddd, J = 4.5, 4.5, 7.0, 7.0 Hz, 1H, H5), 3.67 [s, 3H, $(CH_3O)_2CCO_2CH_3$], 3.33 [s, 3H, $(CH_3O)_2CCO_2CH_3$], 3.31 [s, 3H, $CH_2(CH_3O)_2CCO_2CH_3$], 2.90 (ABq, $\Delta\nu_{AB}$ = 59.2 Hz, J_{AB} = 14.0 Hz, 2H, $H2_A/H2_B$), 2.86 (dd, J = 6.5, 18.0 Hz, 1H, H4), 2.70 (dd, J = 7.5, 15.5 Hz, 1H, H6), 2.42 (dd, J = 4.0, 18.0 Hz, 1H, H4), 2.38 (dd, J = 4.0, 16.0 Hz, 1H, H6), 2.16 (dddd, J = 1.5, 7.5, 7.5, 7.5 Hz, 2H, H15), 1.45-1.39 (m, 2H, H16), 1.34-1.23 (m, 8H, H17–H20), 0.88 (t, J = 6.5 Hz, 3H, H21), 0.88 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], and 0.06 [s, 6H, $(CH_3)_3CSi(CH_3)_2$].

^{1}H NMR (500 MHz, C_6D_6): δ 7.24 (d, J = 15.0 Hz, 1H, H8), 6.79 (dddd, J = 1.5, 1.5, 10.0, 15.0 Hz, 1H, H13), 6.27 (d, J = 10.0 Hz, 1H, H12), 6.15 (d, J = 14.5 Hz, 1H, H10), 5.79 (ddd, J = 7.0, 7.0, 14.5 Hz, 1H, H14), 4.43 (dddd, J = 4.0, 4.0, 7.0, 7.0 Hz, 1H, H5), 3.43 [s, 3H, $(CH_3O)_2CCO_2CH_3$], 3.14 [s, 3H, $(CH_3O)_2CCO_2CH_3$], 3.08 [s, 3H, $(CH_3O)_2CCO_2CH_3$], 3.06 [dd, J = 7.0, 18.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.89 (ABq, $\Delta\nu_{AB}$ = 82.8 Hz, J_{AB} = 14.0 Hz, 2H, H2), 2.71 [dd, J = 7.0, 15.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.70 [dd, J = 4.0, 18.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.59 [dd, J = 4.0, 15.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.00 (dddd, J = 1.5, 7.5, 7.5, 7.5 Hz, 2H, H15), 1.33-1.19 (m, 10H, H16–H20), 1.00 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.90 (t, J = 7.0 Hz, 3H, H21), 0.11 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.10 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

GOESY (C_6D_6, 500 MHz): ➝ H12, ↑ H10 and ↑ H14; ➝ H10, ↑ H12.

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.8 (C9), 140.2 (C14), 135.4 (C7), 134.8 (C3), 132.1 (C12), 129.0 (C10), 128.7 (C13), 126.7 (C8), 123.2 (C11), 102.6 (C1), 71.0 (C5), 52.7

(CO_2CH_3), 50.3 [$C(OCH_3)_2$], 50.1 [$C(OCH_3)_2$], 47.4 (C4), 43.1 (C6), 33.7 (C2), 33.5 (C15), 31.9 (C16–C20), 29.35 (C16–C20), 29.29 (C16–C20), 29.24 (C16–C20), 26.1, 22.8 (C16–C20), 18.4, 14.2 (C21), and -4.5.

IR (thin film): 2952, 2927, 2855, 1756, 1252, 1225, 1198, 1171, 1136, 1093, 1063, 969, 941, 836, and 777 cm^{-1}.

HR ESI-MS: $C_{30}H_{51}BrO_5Si$ $[M+NH_4]^+$ requires 616.3027; found 616.3033.

MP: 87–90 °C.

TLC: R_f 0.50 (6:1 Hex/EtOAc); R_f 0.40 (8:1 Hex/EtOAc).

2092 (R^1 = H, R^2 = Et). [*MJJ-II-191/232*] A 10-mL round bottom flask was charged with the pinacol boronic ester **2085** (48 mg, 0.12 mmol, 1.0 equiv), dibromoolefin **2047** (46 mg, 0.15 mmol, 1.25 equiv), THF (1.5 mL), and distilled H_2O (0.5 mL). The reaction flask was then fitted with a 2-neck vacuum adapter and the contents were degassed by freeze-pump-thaw (4 cycles), after which the vacuum adapter was replaced with a septum/N_2 inlet. A catalytic amount of tetrakis(triphenylphosphine)palladium(0) (14.3 mg, 12.4 μmol, 10 mol%) was added and, after having been stirred for 5 min at rt, neat TlOEt (15 μL, 53 mg, 0.21 mmol, 1.8 equiv) was added via WIRETROL®. Stirring was continued at rt for 20 min, at which point the reaction mixture was diluted with an equal volume of Et_2O and quenched by the addition of 1 M $NaHSO_4$ (10 mL). Five min later, the resulting mixture was filtered through CELITE® with the aid of additional Et_2O, the layers were shaken and separated, and the organic layer was washed with H_2O (1x) and brine (1x). Concentration of the organic material *in vacuo* and purification of the crude residue by medium pressure liquid chromatography (SiO_2, 20:1 Hex/EtOAc) provided the title compound (34 mg, 66.5 μmol, 55% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.88 (d, *J* = 15.0 Hz, 1H, H8), 6.51 (dddd, *J* = 1.5, 1.5, 10.0, 14.5 Hz, 1H, H13), 6.45 (d, *J* = 10.0 Hz, 1H, H12), 6.11 (d, *J* = 14.5 Hz, 1H, H10), 5.94 (ddd, *J* = 7.0, 7.0, 14.5 Hz, 1H, H14), 4.11 (q, *J* = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 3.55

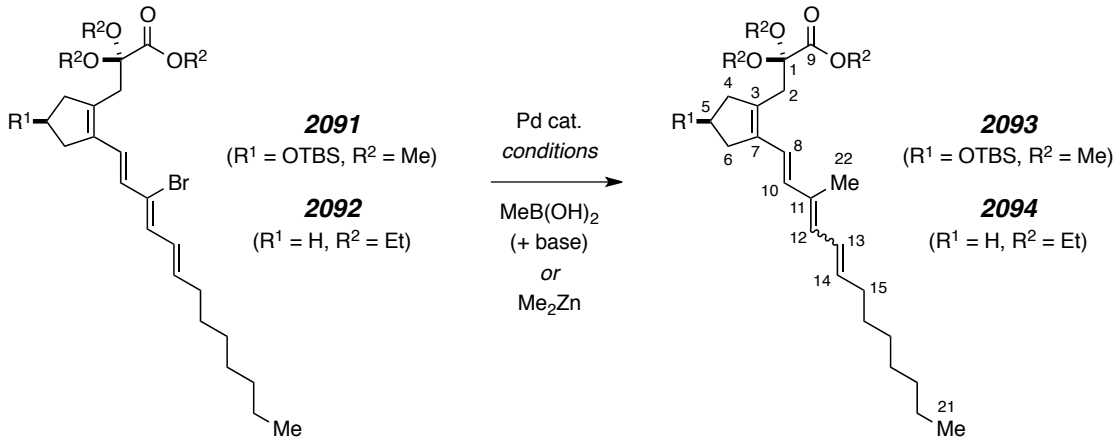
[ABX_3, $\Delta\nu_{AB}$ = 54.3 Hz, J_{AB} = 9.0 Hz, $J_{AX} = J_{BX}$ = 7.0 Hz, 4H, $C(OCH_2CH_3)_2$], 2.92 (s, 2H, H2), 2.54 (dd, *J* = 7.5, 7.5 Hz, 2H, H4), 2.44 (dd, *J* = 7.5, 7.5 Hz, 2H, H6), 2.16 (dddd, *J* = 1.5, 7.0, 7.0, 7.0 Hz, 2H, H15), 1.81 (dddd, *J* = 7.5, 7.5, 7.5, 7.5 Hz, 2H, H5), 1.45-1.38 [m, 2H, $CH{=}CHCH_2CH_2(CH_2)_4CH_3$], 1.33-1.22 [m, 8H, $CH{=}CHCH_2{-}CH_2(CH_2)_4CH_3$], 1.245 [t, *J* = 7.0 Hz, 6H, $C(OCH_2CH_3)_2$], 1.239 (t, *J* = 7.0 Hz, 3H, $CO_2CH_2CH_3$), and 0.88 [t, *J* = 7.0 Hz, 3H, $CH{=}CHCH_2CH_2(CH_2)_4CH_3$].

GOESY ($CDCl_3$, 500 MHz): ➞ H8, ↟ H2.

LR ESI-MS: $C_{27}H_{43}BrO_4$ $[M+Na]^+$ requires 533.22; found 533.19.

TLC: R_f 0.47 (9:1 Hex/EtOAc).

PALLADIUM(0)-CATALYZED VINYL BROMIDE METHYLATION: PREPARATION OF (±)-METHYL 3-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-((1*E*,3*E*,5*E*)-3-METHYLTRIDECA-1,3,5-TRIEN-1-YL)CYCLOPENT-1-EN-1-YL)-2,2-DIMETHOXYPROPANOATE (2093) and **ETHYL 2,2-DIETHOXY-3-(2-((1*E*,3*E*,5*E*)-3-METHYLTRIDECA-1,3,5-TRIEN-1-YL)-CYCLOPENT-1-EN-1-YL)PROPANOATE (2094)**



2093 (R^1 = OTBS, R^2 = Me) from **$Pd(dppf)Cl_2$/$C_3H_9B_3O_3$/Cs_2CO_3**. [*MJJ-III-78*] A 13 x 100 mm culture tube was charged with the vinyl bromide **2091** (10.8 mg, 18.0 μmol, 1.0

equiv), $[Pd(dppf)Cl_2]•CH_2Cl_2$ (1.0 mg, 1.4 μmol, 8 mol%), and DMF (800 μL). To this mixture was added a solution of Cs_2CO_3 (173 mg, 529 μmol, 29 equiv) and trimethylboroxine (25 μL, 23 mg, 180 μmol, 10 equiv) in distilled H_2O (400 μL). The resulting orange, heterogeneous mixture was then immersed in an oil bath that had been pre-heated to *ca.* 80 °C. The reaction mixture was maintained with stirring at this temperature for a period of 30 min. The dark brown mixture that resulted was cooled to rt, diluted with Et_2O, and poured onto 1:1 brine/H_2O. The layers were shaken and separated, and the aqueous phase was extracted with Et_2O (4x). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was filtered through a short plug of SiO_2 (1:1 Hex/EtOAc) and then concentrated *in vacuo* (2x). Purification of the crude residue by two cycles of medium pressure liquid chromatography (SiO_2, 9:1 Hex/EtOAc then 14:1 Hex/EtOAc) provided the unreacted vinyl bromide **2091** (3.4 mg, 5.7 μmol, 31% recovery) followed by the title compound (4.4 mg, 8.2 μmol, 46% yield, 67% yield based on recovered starting material). On the basis of ^{1}H NMR analysis, **2093** existed as an inseparable 7:1 mixture of (11*E*)- and (11*Z*)-isomers.

2093 (R^1 = OTBS, R^2 = Me) from **Pd[P(*t*-Bu)$_3$]$_2$/Me$_2$Zn**. [*MJJ-III-117*] A solution of the vinyl bromide **2091** (9.1 mg, 15.2 μmol, 1.0 equiv) in dry THF (500 μL) at 0 °C was treated successively with bis(tri-*tert*-butylphosphine)palladium(0) (1.5 mg, 2.9 μmol, 19 mol%) and a solution of Me_2Zn (16 μL, 32 μmol, 2.1 equiv, 2.0 M in PhMe). The resulting light orange solution was stirred for 5 min at 0 °C and then the cooling bath was removed. Soon thereafter, the reaction mixture was quenched by the addition of 20% aq NH_4Cl (5 mL), diluted with EtOAc, and the layers were shaken and separated. The aqueous layer was extracted with EtOAc (2x), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 9:1 Hex/EtOAc) provided the title

compound (7.0 mg, 13.1 μmol, 86% yield) that, on the basis of ^{1}H NMR analysis, was judged to be an inseparable 15:1 mixture of (11*E*)- and (11*Z*)-isomers.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.42 (d, *J* = 15.5 Hz, 1H, H8), 6.38 (dddd, *J* = 1.5, 1.5, 11.0, 14.5 Hz, 1H, H13), 6.16 (d, *J* = 15.5 Hz, 1H, H10), 6.08 (d, *J* = 11.0 Hz, 1H, H12), 5.75 (ddd, *J* = 7.5, 7.5, 14.5 Hz, 1H, H14), 4.44 (dddd, *J* = 4.5, 4.5, 7.0, 7.0 Hz, 1H, H5), 3.63 [s, 3H, $(CH_3O)_2CCO_2CH_3$], 3.32 [s, 3H, $(CH_3O)_2CCO_2CH_3$], 3.30 [s, 3H, $(CH_3O)_2CCO_2CH_3$], 2.86 (ABq, $\Delta\nu_{AB}$ = 47.0 Hz, J_{AB} = 14.0 Hz, 2H, H2), 2.82 [dd, *J* = 7.0, 17.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.72 [dd, *J* = 7.0, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.44-2.35 [m, 2H, overlapping $CH_2CH(OTBS)CH_2$], 2.14 [br ddd, *J* = 7.0, 7.0, 7.0 Hz, 2H, $CH=CHCH_2CH_2(CH_2)_4CH_3$], 1.90 (s, 3H, H22), 1.43-1.37 [m, 2H, $CH=CHCH_2CH_2(CH_2)_4CH_3$], 1.33-1.22 [m, 8H, $CH=CHCH_2CH_2(CH_2)_4CH_3$], 0.89 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.88 [t, *J* = 6.5 Hz, 3H, $CH=CHCH_2CH_2(CH_2)_4CH_3$], and 0.60 [s, 6H, $(CH_3)_3CSi(CH_3)_2$].

^{1}H NMR (500 MHz, C_6D_6): δ 6.69 (d, *J* = 16.5 Hz, 1H, H8), 6.50 (dddd, *J* = 1.5, 1.5, 11.0, 14.5 Hz, 1H, H13), 6.39 (d, *J* = 15.5 Hz, 1H, H10), 6.20 (d, *J* = 11.5 Hz, 1H, H12), 5.75 (ddd, *J* = 7.0, 7.0, 14.5 Hz, 1H, H14), 4.56 (dddd, *J* = 4.0, 4.0, 7.0, 7.0 Hz, 1H, H5), 3.33 [s, 3H, $(CH_3O)_2CCO_2CH_3$], 3.15 [s, 3H, $(CH_3O)_2CCO_2CH_3$], 3.10 [s, 3H, $(CH_3O)_2CCO_2CH_3$], 3.04 [dd, *J* = 6.5, 17.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.92 (ABq, $\Delta\nu_{AB}$ = 57.8 Hz, J_{AB} = 14.0 Hz, 2H, H2), 2.82 [dd, *J* = 7.0, 15.5 Hz, 1H, $CH_2CH(OTBS)–CH_2$], 2.72 [dd, *J* = 3.5, 17.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.67 [dd, *J* = 4.0, 15.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.10 [br ddd, *J* = 7.0, 7.0, 7.0 Hz, 2H, $CH=CHCH_2(CH_2)_5–CH_3$], 1.88 (d, *J* = 1.0 Hz, 3H, H22), 1.40-1.21 [m, 10H, $CH=CHCH_2(CH_2)_5CH_3$], 1.00 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.90 [t, *J* = 7.0 Hz, 3H, $CH=CHCH_2(CH_2)_5CH_3$], 0.11 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.10 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 136.4, 136.3, 134.9, 133.5, 131.9, 131.4, 127.0, 120.9, 102.8, 71.1, 52.6, 50.3, 50.1, 47.2, 42.9, 33.6, 33.4, 32.0, 29.6, 29.4, 29.3, 26.1, 22.8, 18.4, 14.3, 12.8, and -4.5.

IR (neat): 2952, 2928, 2855, 1753, 1462, 1439, 1253, 1209, 1137, 1094, 1066, 837, and 771 cm^{-1}.

HR ESI-MS: $C_{31}H_{54}O_5Si$ $[M+NH_4]^+$ requires 552.4079; found 552.4086.

TLC: R_f 0.37 (8:1 Hex/EtOAc).

2094 (R^1 = H, R^2 = Et) from **Pd(dppf)Cl_2/$C_3H_9B_3O_3$/Cs_2CO_3**. [*MJJ-II-224/225/234/246*] A 13 x 100 mm culture tube was charged with the vinyl bromide **2092** (13.0 mg, 25.4 μmol, 1.0 equiv), DMF (1.0 mL), and H_2O (0.2 mL), and the resulting solution was degassed by freeze-pump-thaw (3 cycles). Trimethylboroxine (20 μL, 18.0 mg, 143 μmol, 5.6 equiv), [Pd(dppf)Cl_2]•CH_2Cl_2 (4.3 mg, 5.9 μmol, 23 mol%), and Cs_2CO_3 (231 mg, 709 μmol, 28 equiv) were then added sequentially, and the orange, heterogeneous mixture was immersed in an oil bath that had been pre-heated to *ca.* 80 °C. After having been stirred at this temperature for 2.5 h, the resulting dark brown mixture was cooled to rt and diluted with Et_2O and H_2O. The layers were shaken and separated, and the aqueous phase was extracted with Et_2O (2x). The combined organic extracts were washed with brine (1x), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 20:1 Hex/EtOAc) provided the title compound (6.0 mg, 13.4 μmol, 53% yield) that, on the basis of ^{1}H NMR analysis, was an inseparable 3.8:1 mixture of (11*E*)- and (11*Z*)-isomers.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.48 (d, *J* = 15.5 Hz, 1H, H8), 6.39 (dddd, *J* = 1.5, 1.5, 11.0, 15.0 Hz, 1H, H13), 6.17 (d, *J* = 15.5 Hz, 1H, H10), 6.07 (d, *J* = 11.0 Hz, 1H, H12), 5.74 (ddd, *J* = 7.0, 7.0, 15.0 Hz, 1H, H14), 4.07 (q, *J* = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 3.55 [ABX_3, $\Delta\nu_{AB}$ = 56.5 Hz, J_{AB} = 9.5 Hz, $J_{AX} = J_{BX}$ = 7.0 Hz, 4H, $C(OCH_2CH_3)_2$], 2.88 (dd, *J* = 1.5, 1.5 Hz, 2H, H2), 2.51 (dd, *J* = 7.0, 7.0 Hz, 2H, H4), 2.45 (dd, *J* = 7.5, 7.5 Hz, 2H, H6), 2.14 (br ddd, *J* = 7.5, 7.5, 7.5 Hz, 2H, H15), 1.91 (d, *J* = 1.0 Hz, 3H, H22), 1.79 (dddd, *J* = 7.5, 7.5, 7.5, 7.5 Hz, 2H, H5), 1.43-1.37 [m, 2H, $CH{=}CHCH_2CH_2(CH_2)_4CH_3$], 1.33-1.25 [m, 8H, $CH{=}CHCH_2CH_2(CH_2)_4CH_3$], 1.24 [t, *J* = 7.0 Hz, 6H, $C(OCH_2CH_3)_2$],

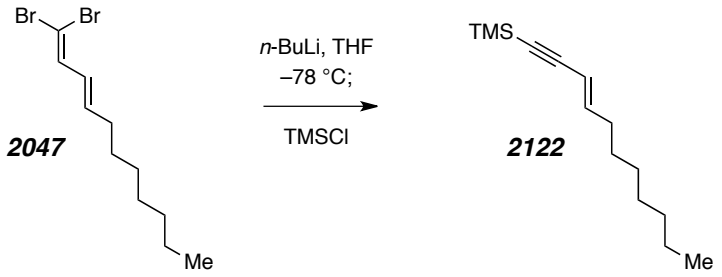
1.20 (t, J = 7.0 Hz, 3H, $CO_2CH_2CH_3$), and 0.88 [t, J = 7.0 Hz, 3H, $CH{=}CHCH_2CH_2(CH_2)_4CH_3$].

GOESY ($CDCl_3$, 500 MHz): ➞ H12, ↑ H10 and ↑ H14.

^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1 (C9), 138.2 (C7), 136.0 (C14), 135.2 (C3), 134.3 (C10), 133.7 (C11), 131.4 (C12), 127.1 (C13), 121.4 (C8), 102.0 (C1), 61.5 ($CO_2CH_2CH_3$), 58.0 [$C(OCH_2CH_3)_2$], 37.2 (C4), 34.5 (C2), 33.4 (C15), 32.9 (C6), 32.0, 29.6, 29.4, 29.3, 22.8 (C16–C20), 22.0 (C5), 15.3 [$CO_2CH_2CH_3$ and $C(OCH_2CH_3)_2$], 14.2 (C21), and 12.9 (C22).

HR ESI-MS: $C_{28}H_{46}O_4$ $[M+Na]^+$ requires 469.3288; found 469.3283.

(*E*)-TRIMETHYL(UNDEC-3-EN-1-YN-1-YL)SILANE (2122)



[*MJJ-IV-39/49*] To a solution of the 1,1-dibromoolefin **2047** (875 mg, 2.82 mmol, 1.0 equiv) in dry THF (35 mL) at –78 °C was added dropwise a solution of *n*-BuLi (2.7 mL, 6.16 mmol, 2.2 equiv, 2.28 M in Hex). The initially formed bright yellow solution was maintained with stirring at –78 °C for 20 min and was then warmed to –40 °C and stirred an additional 40 min, at which point the solution had become light orange in color. The reaction mixture was then re-cooled to –78 °C and treated with freshly distilled TMSCl (420 μL, 340 mg, 3.31 mmol, 1.2 equiv). The cooling bath was removed and the reaction mixture was allowed to warm to rt, at which point it was quenched by the addition of satd aq NH_4Cl. The layers were shaken and separated, and the aqueous phase was extracted

with pentane (3x). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by flash chromatography (100% Hex) provided the title compound as a clear, colorless oil (528 mg, 2.37 mmol, 84% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.22 [ddd, J = 7.5, 7.5, 16.0 Hz, 1H, CH_2CH=CH–C≡CSi(CH_3)$_3$], 5.50 [ddd, J = 2.0, 2.0, 16.0 Hz, 1H, CH_2CH=CHC≡CSi(CH_3)$_3$], 2.09 [dddd, J = 1.5, 7.0, 7.0, 7.0 Hz, 2H, CH=CHCH_2CH$_2$(CH$_2$)$_4$CH$_3$], 1.41-1.35 [m, 2H, CH=CHCH$_2$CH_2(CH$_2$)$_4$CH$_3$], 1.32-1.22 [m, 8H, CH=CHCH$_2$CH$_2$(CH_2)$_4$CH$_3$], 0.88 [t, J = 7.0 Hz, 3H, CH=CHCH$_2$CH$_2$(CH$_2$)$_4$CH_3], and 0.18 [s, 9H, Si(CH_3)$_3$].

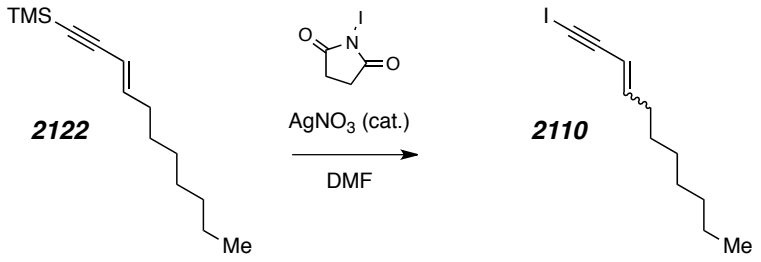
^{13}C NMR (75 MHz, $CDCl_3$): δ 146.6, 109.6, 104.3, 92.6, 33.2, 31.9, 29.3, 29.2, 28.8, 22.8, 14.2, and 0.2.

IR (neat): 2957, 2926, 2856, 2176, 2135, 1250, 846, and 761 cm^{-1}.

GC / LR EI-MS [5025015]: t_R 7.60 min; *m*/*z* (rel. int.) 222 (7, $M^{+\bullet}$), 207 (100, $M^{+\bullet}$–$CH_3^{\bullet}$), 179 (1, $M^{+\bullet}$–$C_3H_7^{\bullet}$), 165 (2, $M^{+\bullet}$–$C_4H_9^{\bullet}$), 148 (3), 135 (4), 122 (4), and 109 (14).

TLC: R_f 0.38 (100% Hex).

(*E*)-1-IODOUNDEC-3-EN-1-YNE (2110) [from **(*E*)-TRIMETHYL(UNDEC-3-EN-1-YN-1-YL)SILANE (2122)]**



[*MJJ-IV-54/58*] Solid $AgNO_3$ (12.2 mg, 0.07 mmol, 30 mol%) was added to a solution of the TMS alkyne **2122** (54 mg, 0.24 mmol, 1.0 equiv) and *N*-iodosuccinimide (65 mg,

0.29 mmol, 1.2 equiv) in dry DMF (2.0 mL). The flask was wrapped with aluminum foil and the reaction mixture was stirred overnight in the dark. The reaction mixture was then quenched with H_2O (20 mL) and diluted with EtOAc, and the resulting mixture was filtered through CELITE®. The layers were shaken and separated, the aqueous phase was extracted with EtOAc (2x), and the combined organic extracts were washed with H_2O (2x) and brine (1x). After having been dried ($MgSO_4$) and filtered, the organic material was evaporated to dryness. Purification of the crude residue by flash chromatography (100% Hex) provided the title compound (38 mg, 0.14 mmol, 57% yield) as a 3:1 *E*/*Z* mixture of isomers [measured ratio from *MJJ-IV-54*].

Data for the (*E*)-isomer [from *MJJ-IV-58/86*]:

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.20 (ddd, *J* = 7.5, 7.5, 16.0 Hz, 1H, CH_2CH=CH–C≡C–I), 5.57 (ddd, *J* = 2.0, 2.0, 16.0 Hz, 1H, CH_2CH=C*H*C≡C–I), 2.10 [dddd, *J* = 1.5, 7.0, 7.0, 7.0 Hz, 2H, CH=CHC$H_2CH_2(CH_2)_4CH_3$], 1.40-1.34 [m, 2H, CH=CHC$H_2CH_2(CH_2)_4CH_3$], 1.32-1.21 [m, 8H, CH=CHC$H_2CH_2(CH_2)_4CH_3$], and 0.88 [t, *J* = 7.0 Hz, 3H, CH=CHC$H_2CH_2(CH_2)_4CH_3$].

GC / LR EI-MS [5025015]: t_R 8.27 min; *m*/*z* (rel. int.) 276 (53, $M^{+\bullet}$), 191 (30, $M^{+\bullet}$–$C_6H_{13}^{\bullet}$), and 178 (100, $M^{+\bullet}$–$C_7H_{14}^{\bullet}$).

TLC: R_f 0.68 (100% Hex).

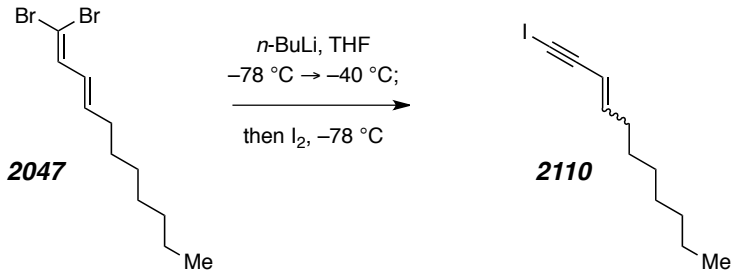
Data for the (*Z*)-isomer [from *MJJ-IV-58/86*]:

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.90 (ddd, *J* = 7.5, 7.5, 11.0 Hz, 1H, CH_2CH=CH–C≡C–I), 5.56 (ddd, *J* = 1.5, 1.5, 11.0 Hz, 1H, CH_2CH=C*H*C≡C–I), 2.32 [dddd, *J* = 1.5, 7.5, 7.5, 7.5 Hz, 2H, CH=CHC$H_2CH_2(CH_2)_4CH_3$], 1.43-1.36 [m, 2H, CH=CHC$H_2CH_2(CH_2)_4CH_3$], 1.33-1.22 [m, 8H, CH=CHC$H_2CH_2(CH_2)_4CH_3$], and 0.89 [t, *J* = 7.0 Hz, 3H, CH=CHC$H_2CH_2(CH_2)_4CH_3$].

GC / LR EI-MS [5025015]: t_R 7.76 min; *m*/*z* (rel. int.) 276 (24, $M^{+\bullet}$), 191 (20, $M^{+\bullet}$–$C_6H_{13}^{\bullet}$), and 178 (100, M^{+}–$C_7H_{14}^{\bullet}$).

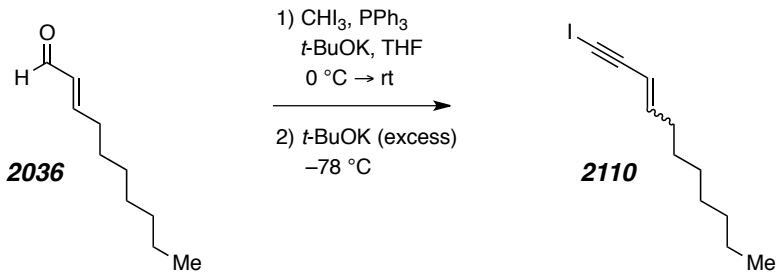
(*E*)-1-IODOUNDEC-3-EN-1-YNE (2110)

[from **(*E*)-1,1-DIBROMOUNDECA-1,3-DIENE (2047)]**



[*MJJ-IV-86*] A solution of *n*-BuLi (1.35 mL, 3.38 mmol, 2.2 equiv) was added dropwise to a solution of the dibromoolefin **2047** (476 mg, 1.54 mmol, 1.0 equiv) in dry THF (8.0 mL) at –78 °C. After having been stirred at this temperature for 20 min, the reaction mixture was allowed to warm to –40 °C and was held at this temperature for 45 min. The reaction mixture was then re-cooled to –78 °C and was treated by dropwise addition with a solution of I_2 (548 mg, 2.16 mmol, 1.4 equiv) in dry THF (4.0 mL). After having been warmed to rt, the reaction mixture was quenched by the addition of 0.1 M $Na_2S_2O_3$ until a light yellow color persisted. The layers were shaken and separated and the aqueous phase was extracted with pentane (3x). The combined organic extracts were washed with 0.1 M $Na_2S_2O_3$ (1x) and brine (1x), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by flash chromatography (100% Hex) provided a 1:1 mixture of (*E*)- and (*Z*)-**2110** (55 mg, 0.20 mmol, 13% yield) followed by a > 20:1 mixture of (*E*)- and (*Z*)-**2110** (113 mg, 0.41 mmol, 27% yield). The ^{1}H NMR spectra of these mixtures were identical to a sample of (*E*)- and (*Z*)-**2110** that had been obtained from an alternative procedure.

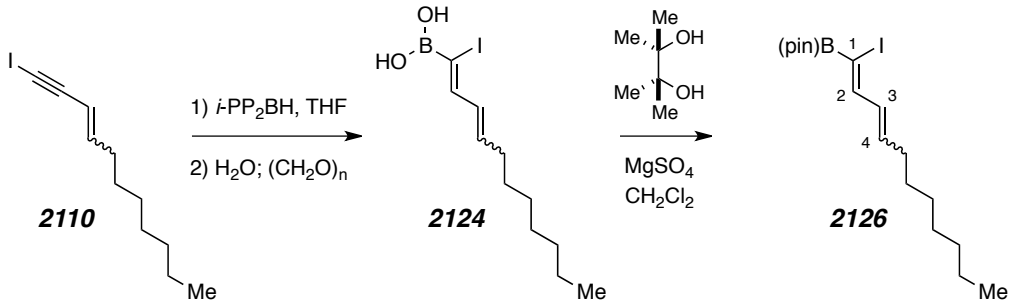
(*E*)-1-IODOUNDEC-3-EN-1-YNE (2110) [from **(*E*)-2-DECENAL (2036)]**



[*MJJ-IV-120*] A 100-mL, 3-neck round bottom flask was charged with PPh_3 (1.104 g, 4.21 mmol, 2.2 equiv), freshly recrystallized CHI_3 (1.576 g, 4.00 mmol, 2.1 equiv), and *t*-BuOK (423 mg, 3.77 mmol, 2.0 equiv). Dry THF (20 mL) was injected and the resulting mixture was cooled to 0 °C and allowed to stir for 5 min. Neat (*E*)-2-decenal (**2036**) (350 μL, 294 mg, 1.91 mmol, 1.0 equiv) was then added dropwise and stirring was continued for 5 min, at which point the reaction mixture was allowed to warm to rt. After having been stirred at this temperature for 10 min, the reaction mixture was cooled to –78 °C and solid *t*-BuOK (1.064 g, 9.48 mmol, 5.0 equiv) was added in a single portion. The reaction mixture was held at –78 °C for 30 min, and was then warmed to –40 °C and stirred an additional 10 min. At this point, complete consumption of the intermediate diiodoalkyne [**TLC**: R_f 0.86 (100% Hex)] was observed by TLC analysis. The reaction mixture was quenched at –40 °C by the addition of brine (20 mL) and, after having been warmed to rt, the resulting mixture was filtered through CELITE® (Hex). The layers were shaken and separated, and the aqueous layer was extracted with Hex (1x). The combined organic extracts were then filtered through a short bed of SiO_2 (Hex eluent) and concentrated *in vacuo*. Purification of the crude residue by flash chromatography (100% Hex) provided the title compound as a light yellow oil (488 mg, 1.78 mmol, 93% yield), the ^{1}H NMR spectrum of which was identical to that obtained from the alternative procedure described above.

In a separate experiment [*MJJ-V-209*], a sample of the purified iodoalkyne **2110** was allowed to stand in $CDCl_3$ exposed to ambient lab light for 24 h. On the basis of ^1H NMR and GC-MS analyses, a 1:1 mixture of (*E*)- and (*Z*)-isomers was present. However, empirical experience has suggested that rapid (< 1 h) and significant loss in the isomeric purity of **2110** will occur if freshly prepared samples are not protected from light.

2-((1*Z*,3*E*)-1-IODOUNDECA-1,3-DIEN-1-YL)-4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLANE (2126)



[*MJJ-V-211*] A stock solution of *i*-PP_2BH (0.71 M in THF) was prepared as described previously. An aliquot of this stock solution (5.4 mL, ~3.83 mmol, ~1.1 equiv) was added dropwise to a solution of the iodoalkyne **2110** (983 mg, 3.56 mmol, 1.0 equiv) in dry THF (7.0 mL) at 0 °C and, after the addition was complete, the reaction mixture was allowed to reach rt over 2.5 h. At this point TLC analysis indicated that the starting material had been consumed, and the reaction mixture was then recooled to 0 °C and quenched slowly with H_2O (0.50 mL). Gas evolution had subsided within 5 min, at which point the solution was allowed to gradually warm to rt over 30 min and was then treated with paraformaldehyde (2.0 mL, 37 wt% in H_2O). After having been stirred overnight at rt, the reaction mixture was poured onto brine (20 mL), the layers were shaken and separated, and the aqueous layer was extracted with EtOAc (1x) and CH_2Cl_2 (2x). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo* to leave behind an oil that was used immediately without further purification.

The crude boronic acid (3.56 mmol theoretical) was dissolved in CH_2Cl_2 (10 mL) and treated sequentially with pinacol (543 mg, 4.60 mmol, 1.3 equiv) and $MgSO_4$ (4.8 g). After having been stirred overnight at rt, the reaction mixture was diluted with Hex/EtOAc (6:1), filtered through a pad of SiO_2, and the filtrate was evaporated *in vacuo*. Purification of the crude residue by flash chromatography (100% Hex → 98:2 → 40:1 Hex/EtOAc) provided the title compound as a yellow oil (1.16 g, 2.87 mmol, 81% yield over 2 steps) that, on the basis of ^{1}H NMR analysis, was an inseparable 12:1 mixture of isomers. A trace amount (< 1% w/w) of (*E*)-2,2,5-trimethylhex-3-en-1-ol[398] was present.

Select analytical data for the major isomer [(1*Z*,3*E*)-**2126** assumed]:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (d, *J* = 9.5 Hz, 1H, H2), 6.38 (dddd, *J* = 1.5, 1.5, 9.5, 15.0 Hz, 1H, H3), 6.21 (ddd, *J* = 7.0, 7.0, 14.5 Hz, 1H, H4), 2.16 [dddd, *J* = 1.0, 7.0, 7.0, 7.0 Hz, 2H, CH=CHC*H*$_2$CH$_2$(CH$_2$)$_4$CH$_3$], 1.45-1.40 [m, 2H, CH=CHCH$_2$C*H*$_2$–(CH$_2$)$_4$CH$_3$], 1.29 [s, 12H, OC(C*H*$_3$)$_2$C(C*H*$_3$)$_2$O], 1.33-1.23 [m, 8H, CH=CHCH$_2$CH$_2$(C*H*$_2$)$_4$CH$_3$], and 0.88 [t, *J* = 7.0 Hz, 3H, CH=CHCH$_2$CH$_2$(CH$_2$)$_4$C*H*$_3$].

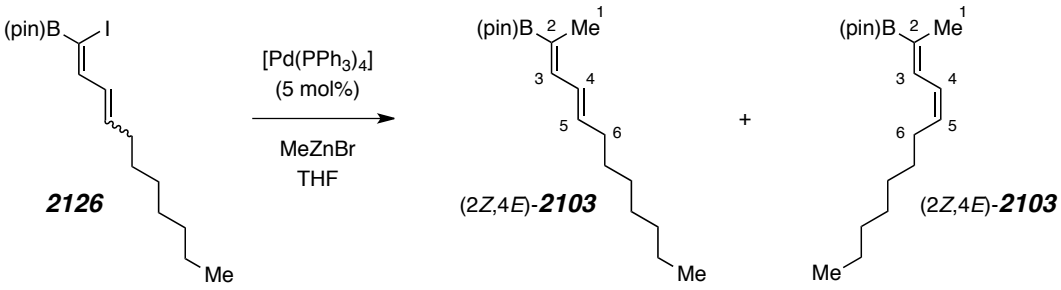
GC / LR EI-MS [5025015]: t_R 10.81 min; *m*/*z* (rel. int.) 404 [842160, $M^{+\bullet}$(^{11}B)], 403 [25, $M^{+\bullet}$(^{10}B)], 389 (6, $M^{+\bullet}$–$CH_3^{\bullet}$), 306 (24), 305 (35, $M^{+\bullet}$–$C_7H_{15}^{\bullet}$), 304 (31), 233 (13), 191 (12), 177 (29), 149 (11), 135 (15), 121 (12), and 101 (41).

Select analytical data for the minor isomer [(1*Z*,3*Z*)-**2126** assumed]:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 1.0, 10.0 Hz, 1H, H2), 6.27 (dddd, *J* = 1.5, 1.5, 10.5, 10.5 Hz, 1H, H3), 5.84 (ddd, *J* = 1.0, 7.5, 7.5, 11.0 Hz, 1H, H4), 2.29 [dddd, *J* = 1.5, 7.0, 7.0, 7.0 Hz, 2H, CH=CHC*H*$_2$CH$_2$(CH$_2$)$_4$CH$_3$], 1.45-1.40 [m, 2H, CH=CHCH$_2$C*H*$_2$(CH$_2$)$_4$CH$_3$], 1.29 [s, 12H, OC(C*H*$_3$)$_2$C(C*H*$_3$)$_2$O], 1.33-1.23 [m, 8H, CH=CHCH$_2$CH$_2$(C*H*$_2$)$_4$CH$_3$], and 0.88 [t, *J* = 7.0 Hz, 3H, CH=CHCH$_2$CH$_2$(CH$_2$)$_4$C*H*$_3$].

GC / LR EI-MS [5025015]: t_R 10.45 min; *m*/*z* (rel. int.) 404 [90722, $M^{+\bullet}(^{11}B)$], 403 [24, $M^{+\bullet}(^{10}B)$], 389 (6, $M^{+\bullet}–CH_3^{\bullet}$), 358 (6), 357 (1), 306 (28), 305 (42, $M^{+\bullet}–C_7H_{15}^{\bullet}$), 304 (35), 233 (20), 191 (18), 177 (39), 149 (17), 135 (23), 121 (19), and 101 (61).

2-((2*Z*,4*E*)-DODECA-2,4-DIEN-2-YL)-4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLANE (2103)



[*MJJ-V-214*] A sample of $ZnBr_2$ (4.20 g, 18.66 mmol) was flame dried under a stream of dry N_2 until a white, free-flowing powder was obtained. After having been cooled to rt, the flask was charged with dry THF (40 mL) and, once the $ZnBr_2$ had completely dissolved, the resulting clear, colorless solution was cooled to 0 °C. To this solution was added dropwise MeMgBr (4.4 mL, 18.39 mmol, 4.18 M in Et_2O), which immediately produced a heavy white precipitate. The heterogeneous mixture thus obtained was vigorously stirred at 0 °C for 20 min to provide a solution that was *ca.* 0.41 M [MeZnBr]. Meanwhile, a solution of the vinyl iodide **2126** (1.16 g, 2.86 mmol, 1.0 equiv) in dry THF (20 mL) was cooled to 0 °C with stirring, and was treated with tetrakis(triphenyl-phosphine)palladium(0) (166 mg, 0.144 mmol, 5 mol%) to provide a homogeneous, pale yellow mixture. Approximately ⅔ the total volume of the MeZnBr stock solution (~ 12.1 mmol, ~ 4 equiv) was then transferred to the reaction flask via cannula. The cooling bath was removed, the flask was wrapped with aluminum foil, and the reaction mixture was maintained with stirring in a subdued light environment for a period of 18 h at rt. The reaction mixture was then cooled to 0 °C and *slowly* quenched by the addition of satd aq

NH_4Cl (~ 5 mL). The resulting two-phase mixture was poured onto H_2O (25 mL), the layers were shaken and separated, and the aqueous phase was extracted with Et_2O (2x). The combined organic extracts were washed with H_2O (1x) and brine (1x), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by flash chromatography (98:2 Hex/EtOAc) provided the title compound as a light yellow oil (624 mg, 2.14 mmol, 75% yield) that, on the basis of ^{1}H NMR analysis, was an inseparable 12:1 mixture of (2*Z*,4*E*)- and (2*Z*,4*Z*)-isomers. The configuration of each of these isomers was unambiguously established by gradient 1-D NOE (GOESY) experiments.

Data for the major isomer [(2*Z*,4*E*)-**2103**] (^{13}C NMR and IR data from *MJJ-VII-70*):

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.77 (dddd, *J* = 1.5, 1.5, 1.5, 11.0 Hz, 1H, H3), 6.41 (dddd, *J* = 1.5, 1.5, 11.0, 15.0 Hz, 1H, H4), 5.88 (ddd, *J* = 7.5, 7.5, 15.0 Hz, 1H, H5), 2.13 (dddd, *J* = 1.0, 7.0, 7.0, 7.0 Hz, 2H, H6), 1.80 (d, *J* = 1.5 Hz, 3H, H1), 1.42-1.36 [m, 2H, $CH{=}CHCH_2CH_2(CH_2)_4CH_3$], 1.33-1.22 [m, 8H, $CH{=}CHCH_2CH_2(CH_2)_4CH_3$], 1.26 [s, 12H, $OC(CH_3)_2C(CH_3)_2O$], and 0.88 [t, *J* = 7.0 Hz, 3H, $CH{=}CHCH_2CH_2(CH_2)_4CH_3$].

GOESY ($CDCl_3$, 500 MHz): ➞ H4; ↑ H1 and ↑ H6.

GC / LR EI-MS [5025015]: t_R 9.41 min; *m*/*z* (rel. int.) 292 [91, $M^{+\bullet}(^{11}B)$], 291 [23, $M^{+\bullet}(^{10}B)$], 277 [19, $M^{+\bullet}(^{11}B)–CH_3^\bullet$], 276 [5, $M^{+\bullet}(^{10}B)–CH_3^\bullet$], 235 (20, $M^{+\bullet}–C_4H_9^\bullet$), 207 (8, $M^{+\bullet}–C_9H_{13}^\bullet$), 194 (23), 193 (73, $M^{+\bullet}–C_7H_{15}^\bullet$), 192 (100), 191 (37), 179 (25), 163 (23), 149 (15), 135 (23), 122 (43), 107 (50), 101 (72), 93 (28), and 83 (37).

^{13}C NMR (125 MHz, $CDCl_3$): δ 142.8, 139.1, 126.5, 83.3, 33.2, 32.0, 29.4, 29.3, 24.9, 22.8, 14.3, and 14.2.

IR (neat): 2977, 2959, 2926, 2856, 1371, 1304, 1146, and 1095 cm^{-1}.

TLC: R_f 0.53 (15:1 Hex/EtOAc).

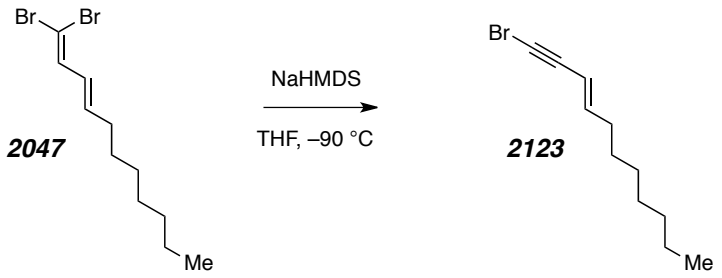
Select analytical data for the minor isomer [(2*Z*,4*Z*)-**2103**]:

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.07 (ddddd, *J* = 1.5, 1.5, 1.5, 1.5, 11.5 Hz, 1H, H3), 6.35 (dddd, *J* = 2.0, 2.0, 11.5, 11.5 Hz, 1H, H4), 5.61 (ddd, *J* = 7.5, 7.5, 11.0 Hz, 1H, H5), 2.28 [dddd, *J* = 2.0, 7.5, 7.5, 7.5 Hz, 2H, H6], 1.81 (d, *J* = 2.0 Hz, 3H, H1), 1.42-1.36 [m, 2H, $CH{=}CHCH_2CH_2(CH_2)_4CH_3$], 1.33-1.22 [m, 8H, $CH{=}CHCH_2CH_2(CH_2)_4CH_3$], 1.26 [s, 12H, $OC(CH_3)_2C(CH_3)_2O$], and 0.88 [t, *J* = 7.0 Hz, 3H, $CH{=}CHCH_2CH_2(CH_2)_4CH_3$].

GOESY ($CDCl_3$, 500 MHz): ➞ H4; ↑ H1 and ↑ H5.

GC / LR EI-MS [5025015]: t_R 8.96 min; *m*/*z* (rel. int.) 292 [96, $M^{+\bullet}(^{11}B)$], 291 [25, $M^{+\bullet}(^{10}B)$], 277 [24, $M^{+\bullet}(^{11}B)–CH_3^{\bullet}$], 276 [5, $M^{+\bullet}(^{10}B)–CH_3^{\bullet}$], 235 (27, $M^{+\bullet}–C_4H_9^{\bullet}$), 207 (11, $M^{+\bullet}–C_9H_{13}^{\bullet}$), 194 (25), 193 (70, $M^{+\bullet}–C_7H_{15}^{\bullet}$), 192 (31456), 191 (41), 179 (30), 163 (24), 149 (20), 137 (19), 136 (20), 135 (27), 122 (48), 107 (52), 101 (82), 93 (32), and 83 (40).

(*E*)-1-BROMOUNDEC-3-EN-1-YNE (2123)



2047 ***2123***

[*MJJ-VI-109/240/VII-25*] A solution of the dibromoolefin **2047** (852 mg, 2.748 mmol, 1.0 equiv) in dry THF (20 mL) was cooled to –90 °C (Et_2O/dry ice bath). To this solution was added dropwise sodium bis(trimethylsilyl)amide (NaHMDS) (1.8 mL, 3.60 mmol, 2.0 M in THF, 1.3 equiv) and the resulting light brown mixture was stirred at –90 °C for 30 min. The reaction mixture was quenched at –90 °C with satd aq NH_4Cl (40 mL), allowed to warm to rt over 30 min, and treated with H_2O until a clear, two-phase mixture

was obtained. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a brown residue that was purified by flash chromatography (100% Hex) to yield the title compound as a clear, colorless oil (572 mg, 2.496 mmol, 91% yield), which was judged to be >95% pure *E*-isomer on the basis of ^{1}H NMR analysis.

A sample of the bromoalkyne **2123** [from *MJJ-VI-109*] was allowed to stand in $CDCl_3$ exposed to ambient lab light for a period of 48 h. In stark contrast to the sensitive iodoalkyne **2110**, no deterioration in the isomeric purity of **2123** was observed.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.21 (ddd, *J* = 7.0, 7.0, 15.5 Hz, 1H, C*H*=CHC≡CBr), 5.43 (dddd, *J* = 0.5, 1.5, 1.5, 16.0 Hz, 1H, CH=C*H*C≡CBr), 2.09 [ddddd, *J* = 0.5, 1.5, 7.0, 7.0, 7.0 Hz, 2H, CH=CHCH_2CH$_2$(CH$_2$)$_4$CH$_3$], 1.40-1.35 [m, 2H, CH=CHCH$_2$CH_2(CH$_2$)$_4$CH$_3$], 1.32-1.22 [m, 8H, CH=CHCH$_2$CH$_2$(CH_2)$_4$CH$_3$], and 0.88 [t, *J* = 7.0 Hz, 3H, CH=CHCH$_2$CH$_2$(CH$_2$)$_4$CH_3].

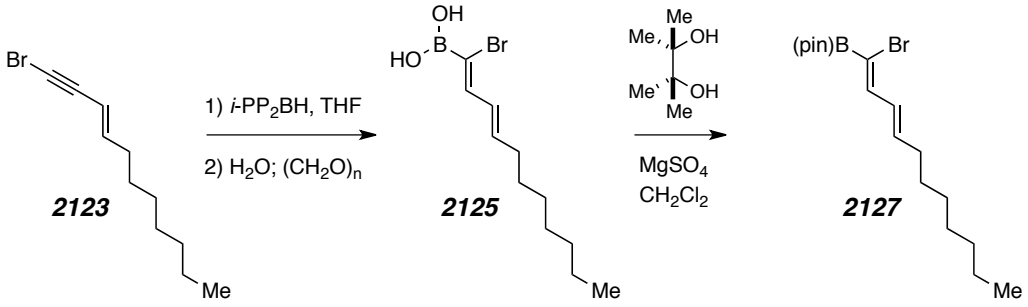
^{13}C NMR (125 MHz, $CDCl_3$): δ 147.0, 109.1, 79.1, 47.3, 33.1, 31.9, 29.24, 29.19, 28.7, 22.8, and 14.2.

IR (neat): 2955, 2925, 2855, 1461, and 954 cm^{-1}.

GC / LR EI-MS [5025015]: t_R 6.73 min; *m*/*z* (rel. int.) 230 [57, $M^{+\bullet}$(^{81}Br)], 228 [60, $M^{+\bullet}$(^{79}Br)], 145 [58, $M^{+\bullet}$(^{81}Br)–$C_6H_{13}^{\bullet}$], 143 [59, $M^{+\bullet}$(^{79}Br)–$C_6H_{13}^{\bullet}$], 132 (62), 130 (73), 119 (46), 107 (53), 93 (88), and 79 (100).

TLC: R_f 0.69 (100% Hex).

2-((1*Z*,3*E*)-1-BROMOUNDECA-1,3-DIEN-1-YL)-4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLANE (2127)



[*MJJ-VI-111*] A stock solution of *i*-PP$_2$BH (0.71 M in THF) was prepared as described previously. An aliquot of this stock solution (3.7 mL, ~2.63 mmol, ~1.1 equiv) was added dropwise to a solution of the bromoalkyne **2123** (542 mg, 2.37 mmol, 1.0 equiv) in dry THF (20 mL) at 0 °C and, after the addition was complete, the reaction mixture was allowed to reach rt over 30 min. At this point TLC analysis indicated that the starting material had been consumed, and the reaction mixture was then re-cooled to 0 °C and quenched slowly with H$_2$O (0.50 mL). Gas evolution had subsided within 5 min, at which point the solution was allowed to gradually warm to rt and was treated with paraformaldehyde (2.1 mL, 37 wt% in H$_2$O). After having been stirred at rt for 13 h, the reaction mixture was poured onto brine (50 mL), the layers were shaken and separated, and the aqueous layer was extracted with EtOAc (1x) and CH$_2$Cl$_2$ (2x). The combined organic layers were dried (MgSO$_4$), filtered, concentrated *in vacuo* to leave behind an oil that was used immediately without further purification.

[*MJJ-VI-112/246*] The crude boronic acid (2.37 mmol theoretical) was dissolved in CH$_2$Cl$_2$ (20 mL) and treated sequentially with pinacol (435 mg, 3.68 mmol, 1.6 equiv) and MgSO$_4$ (excess). After having been stirred at rt for 24 h, the reaction mixture was filtered through a pad of CELITE® with the aid of additional CH$_2$Cl$_2$, and the solvent was

removed *in vacuo*. Purification of the crude residue by flash chromatography (100% Hex → 98:2 → 40:1 Hex/EtOAc) provided the title compound as a yellow oil [588 mg, 1.43 mmol, 61% yield over 2 steps (corrected for purity)] that was judged to be 87% pure on the basis of ^{1}H NMR analysis [contaminated with (*E*)-2,2,5-trimethylhex-3-en-1-ol[398]].

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 {d, *J* = 10.0 Hz, 1H, [B(pin)](Br)C=C*H*CH=CH}, 6.53 {dddd, *J* = 1.5, 1.5, 10.5, 15.5 Hz, 1H, [B(pin)](Br)C=CHC*H*=CH}, 6.14 {ddd, *J* = 7.0, 7.0, 14.5 Hz, 1H, [B(pin)](Br)C=CHCH=C*H*}, 2.16 [dddd, *J* = 1.5, 1.5, 1.5, 7.0 Hz, 2H, CH=CHCH_2CH$_2$(CH$_2$)$_4$CH$_3$], 1.45-1.39 [m, 2H, CH=CHCH$_2$CH_2(CH$_2$)$_4$CH$_3$], 1.33-1.22 [m, 8H, CH=CHCH$_2$CH$_2$(CH_2)$_4$CH$_3$], 1.30 [s, 12H, OC(CH_3)$_2$C(CH_3)$_2$O], and 0.88 [t, *J* = 7.0 Hz, 3H, CH=CHCH$_2$CH$_2$(CH$_2$)$_4$CH_3].

^{13}C NMR (125 MHz, $CDCl_3$): δ 145.0, 144.1, 128.2, 84.8, 33.3, 31.9, 29.28, 29.26, 28.9, 24.9, 22.8, and 14.2.

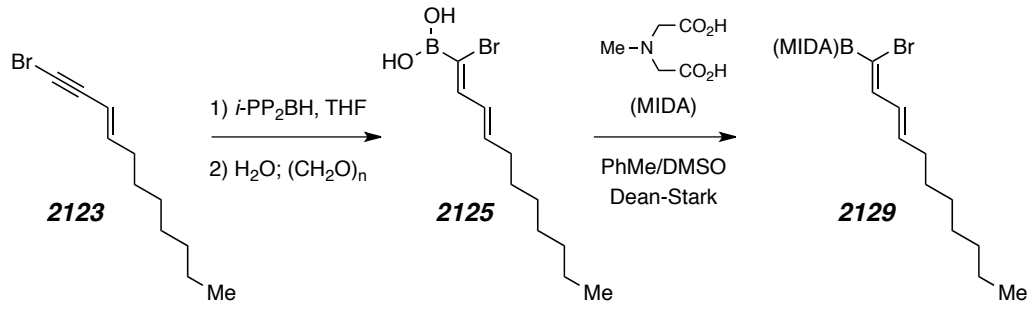
IR (neat): 2978, 2956, 2926, 2855, 1635, 1592, 1462, 1355, 1328, 1143, 974, and 851 cm^{-1}.

LR ESI-MS: $C_{17}H_{30}BBrO_2$ $[M+Na]^+$ requires 379.14; found 379.14.

GC / LR EI-MS [5025015]: t_R 10.45 min; *m*/*z* (rel. int.) 358 [60, $M^{+\bullet}$(^{81}Br)], 356 [61, $M^{+\bullet}$(^{79}Br)], 355 [14, $M^{+\bullet}$(^{10}B)], 343 [5, $M^{+\bullet}$(^{81}Br)–$CH_3^{\bullet}$], 341 [5, $M^{+\bullet}$(^{79}Br)–$CH_3^{\bullet}$], 340 [1, $M^{+\bullet}$(^{10}B)–$CH_3^{\bullet}$], 260 (34), 259 [41, $M^{+\bullet}$(^{79}Br)–$C_7H_{15}^{\bullet}$], 258 (54), 257 [43, $M^{+\bullet}$(^{79}Br)–$C_7H_{15}^{\bullet}$], 256 (21), 233 (27), 191 (53), 179 (27), 177 (36), 149 (17), 135 (27), 121 (21), 101 (100), 93 (56), and 83 (49).

TLC: R_f 0.47 (15:1 Hex/EtOAc).

2-((1*Z*,3*E*)-1-BROMOUNDECA-1,3-DIEN-1-YL)-6-METHYL-1,3,6,2-DIOXAZABOROCANE-4,8-DIONE (2129)



[*MJJ-VII-26*] A stock solution of *i*-PP$_2$BH (0.71 M in THF) was prepared as described previously. An aliquot of this stock solution (4.0 mL, ~2.84 mmol, ~1.1 equiv) was added dropwise to a solution of the bromoalkyne **2123** (589 mg, 2.57 mmol, 1.0 equiv) in dry THF (20 mL) at 0 °C and, after the addition was complete, the reaction mixture was allowed to reach rt over 15 min. At this point TLC analysis indicated that the starting material had been consumed, and the reaction mixture was then cooled to 0 °C and quenched slowly with H_2O (0.50 mL). Gas evolution had subsided within 5 min, at which point the solution was allowed to gradually warm to rt over 1.5 h, and was then treated with paraformaldehyde (3.0 mL, 37 wt% in H_2O). After having been stirred at rt for 16 h, the reaction mixture was poured onto brine (50 mL), the layers were shaken and separated, and the aqueous layer was extracted with EtOAc (1x) and CH_2Cl_2 (2x). The combined organic material was dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo* to provide the crude boronic acid that was used immediately without further purification.

[*MJJ-VII-27*] A 25-mL round-bottom flask that contained the crude boronic acid (2.57 mmol theoretical) was charged with PhMe (2.5 mL), DMSO (1.0 mL), and MIDA (423 mg, 2.88 mmol, 1.1 equiv). The reaction flask was then fitted with a 10-mL Dean-Stark

trap to which was connected a West condenser that was vented to ambient atmosphere. The Dean-Stark trap was filled with PhMe and the reaction mixture was heated to reflux for 30 min. After having been cooled to rt, the reaction mixture was poured into a separatory funnel that contained brine (20 mL) and H_2O (20 mL). The resulting mixture was diluted with EtOAc, the layers were shaken and separated, and the aqueous phase was extracted with EtOAc (2x). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the resulting orange, solid residue by flash chromatography (1:1 Hex/EtOAc → 99:1 EtOAc/CH_3CN) provided the title compound as an off-white solid (781 mg, 2.02 mmol, 79% yield).

^{1}H NMR (500 MHz, CD_3CN): δ 6.97 {d, J = 10.0 Hz, 1H, [B(MIDA)](Br)-C=C*H*CH=CH}, 6.46 {dddd, J = 1.5, 1.5, 10.0, 15.5 Hz, 1H, [B(MIDA)](Br)-C=CHC*H*=CH}, 6.14 {dddd, J = 1.0, 7.0, 7.0, 16.0 Hz, 1H, [B(MIDA)](Br)-C=CHCH=C*H*}, 3.98 [ABq, $\Delta\nu_{AB}$ = 59.6 Hz, J_{AB} = 17.0 Hz, 4H, $O_2CCH_2N(CH_3)CH_2CO_2$], 2.87 [s, 3H, $O_2CCH_2N(CH_3)CH_2CO_2$], 2.16 [dddd, J = 1.5, 7.0, 7.0, 7.0 Hz, 2H, $CH{=}CHCH_2CH_2(CH_2)_4CH_3$], 1.45-1.39 [m, 2H, $CH{=}CHCH_2CH_2(CH_2)_4CH_3$], 1.34-1.26 [m, 8H, $CH{=}CHCH_2CH_2(CH_2)_4CH_3$], and 0.89 [t, J = 6.5 Hz, 3H, $CH{=}CHCH_2CH_2(CH_2)_4CH_3$].

^{13}C NMR (125 MHz, CD_3CN): δ 168.8, 142.9, 139.6, 128.5, 63.5, 47.5, 33.6, 32.5, 29.9, 29.8, 29.6, 23.4, and 14.4.

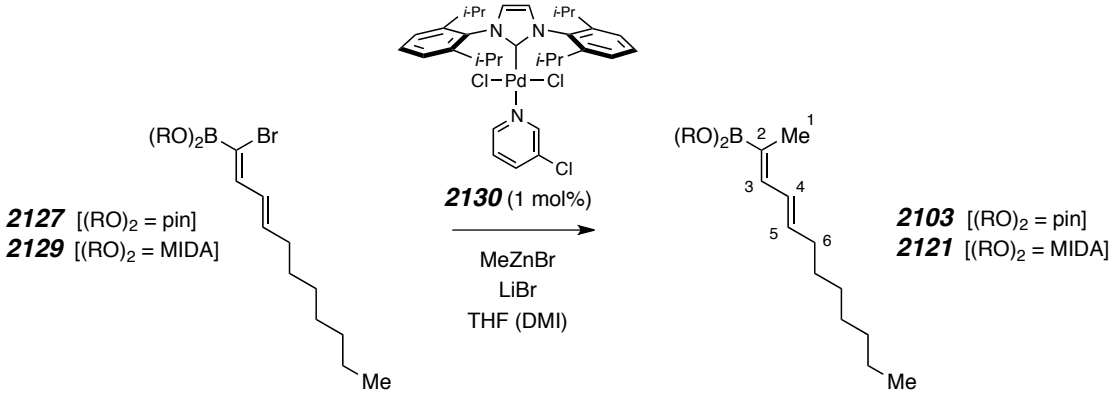
IR (thin film): 2956, 2925, 2855, 1767, 1284, 1036, and 967 cm^{-1}.

HR ESI-MS: $C_{16}H_{25}BBrNO_4$ $[M\text{-}H]^-$ requires 384.0987; found 384.0989.

MP: 106–110 °C.

TLC: R_f 0.45 (99:1 EtOAc/CH_3CN).

2-((2*Z*,4*E*)-DODECA-2,4-DIEN-2-YL)-4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLANE (2103) and **2-((2*Z*,4*E*)-DODECA-2,4-DIEN-2-YL)-6-METHYL-1,3,6,2-DIOXAZABOROCANE-4,8-DIONE (2121)**



$(RO)_2$ = pin (2103). [*MJJ-VI-253*] A 0.56 M stock solution of MeZnBr was prepared in an analogous fashion to that described in the conversion of **2126** to **2103** from flame-dried $ZnBr_2$ (775 mg, 3.44 mmol) and MeMgBr (1.3 mL, 3.39 mmol, 2.61 M in Et_2O) in dry THF (4.8 mL). A sample of LiBr (44.4 mg, 0.51 mmol, 3.5 equiv) was placed in a 13 x 100 mm culture tube and flame-dried under a stream of dry N_2. The flask was cooled to rt and charged with dry THF (0.5 mL), dry DMI (0.5 mL), and PEPPSI^{TM}-IPr (**2130**) (1.2 mg, 2.0 μmol, 1 mol%). To the resulting mixture was added dropwise an aliquot of the MeZnBr stock solution (~0.5 mL, ~0.28 mmol, 2 equiv). Stirring was continued for 5 min, at which point the neat vinyl bromide **2127** (52.8 mg, 0.15 mmol, 1.0 equiv) was delivered to the reaction mixture via a 100-μL WIRETROL®. After having been stirred at rt for 4 h, GC-MS analysis of the reaction mixture revealed that the starting material had been consumed. The reaction mixture was diluted with Et_2O and washed with 1 M Na_3EDTA (1x). The aqueous material was back-extracted with Et_2O (1x), and the combined organic extracts were washed with brine (1x), dried ($MgSO_4$), and filtered. Evaporation of the solvent *in vacuo* and purification of the crude residue by flash chromatography (100% Hex → 30:1 Hex/EtOAc) provided the title compound (31.5 mg,

0.11 mmol, 73% yield). The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of this material was identical to an authentic sample of (2*Z*,4*E*)-**2103** (configuration ascertained from the mixture of isomers; *vide supra*).

(RO)$_2$ = MIDA (2121). [*MJJ-VII-31/37*] A 0.85 M stock solution of MeZnBr was prepared (*vide supra*) from flame-dried $ZnBr_2$ (1.68 g, 7.45 mmol) and MeMgBr (3.0 mL, 7.29 mmol, 2.43 M in Et_2O) in dry THF (5.6 mL). A sample of LiBr (226 mg, 2.60 mmol, 3.0 equiv) was placed in a 25-mL round-bottom flask and flame-dried under a stream of dry N_2. The flask was cooled to rt and charged with dry THF (3.5 mL) and PEPPSI^{TM}-IPr (**2130**) (6.2 mg, 9.1 μmol, 1 mol%). To the resulting mixture was added dropwise an aliquot of the MeZnBr stock solution (~3 mL, ~2.6 mmol, 3.0 equiv), which immediately produced an orange, homogeneous solution. Stirring was continued for 5 min, at which point a solution the vinyl bromide **2129** (330 mg, 0.86 mmol, 1.0 equiv) in dry THF (3.5 mL) was added dropwise. After having been stirred at rt for 18 h, LC-MS analysis of the reaction mixture revealed that the starting material had been consumed. The reaction mixture was quenched by the addition of satd aq NH_4Cl/H_2O, diluted with EtOAc, and the layers were shaken and separated. The aqueous layer was extracted with EtOAc (2x), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by flash chromatography (1:1 Hex/EtOAc → 99:1 EtOAc/CH_3CN) provided the title compound as an off-white solid (198 mg, 0.62 mmol, 72% yield).

^{1}H NMR (500 MHz, CD_3CN): δ 6.45 {dddd, *J* = 1.5, 1.5, 11.0, 15.0 Hz, 1H, [B(MIDA)](CH$_3$)C=CHC*H*=CH}, 6.29 {dddd, *J* = 1.5, 1.5, 1.5, 11.0 Hz, 1H, [B(MIDA)](CH$_3$)C=C*H*CH=CH}, 5.79 {ddd, *J* = 7.5, 7.5, 15.0 Hz, 1H, [B(MIDA)](CH$_3$)C=CHCH=C*H*}, 3.86 [ABq, $\Delta\nu_{AB}$ = 71.0 Hz, J_{AB} = 17.0 Hz, 4H, $O_2CCH_2N(CH_3)CH_2CO_2$], 2.72 [s, 3H, $O_2CCH_2N(CH_3)CH_2CO_2$], 2.13 [dddd, *J* = 1.5, 7.5, 7.5, 7.5 Hz, 2H, CH=CHCH_2CH$_2$(CH$_2$)$_4$CH$_3$], 1.70 {d, *J* = 1.5 Hz, 3H,

[B(MIDA)](C*H*$_3$)C=CHCH=CH}, 1.43-1.37 [m, 2H, CH=CHCH$_2$C*H*$_2$(CH$_2$)$_4$CH$_3$], 1.34-1.26 [m, 8H CH=CHCH$_2$CH$_2$(C*H*$_2$)$_4$CH$_3$], and 0.88 [t, *J* = 7.0 Hz, 3H CH=CHCH$_2$CH$_2$(CH$_2$)$_4$C*H*$_3$].

^{13}C NMR (125 MHz, CD_3CN): δ 169.5, 137.8, 137.4, 127.4, 62.7, 47.3, 33.6, 32.5, 30.1, 29.9, 29.8, 23.3, 15.0, and 14.4.

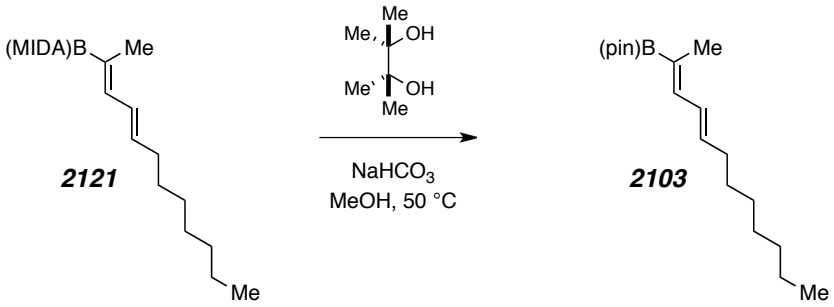
IR (thin film): 2957, 2925, 2855, 1757, 1294, 1029, 1006, and 966 cm^{-1}.

HR ESI-MS: $C_{17}H_{28}BNO_4$ $[M-H]^-$ requires 320.2039; found 320.2036.

MP: 86–90 °C.

TLC: R_f 0.37 (99:1 EtOAc/CH_3CN).

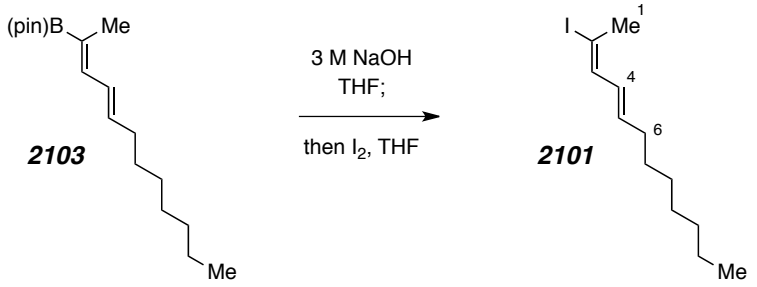
2-((2*Z*,4*E*)-DODECA-2,4-DIEN-2-YL)-4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLANE (2103) [via **2-((2*Z*,4*E*)-DODECA-2,4-DIEN-2-YL)-6-METHYL-1,3,6,2-DIOXAZABOROCANE-4,8-DIONE (2121)]**



[*MJJ-VII-70/120*] A 16 x 125 mm culture tube was charged with the MIDA boronate **2121** (53 mg, 0.17 mmol, 1.0 equiv), anhydrous pinacol (40 mg, 0.34 mmol, 2.0 equiv), $NaHCO_3$ (73 mg, 0.87 mmol, 5.2 equiv), and MeOH (1.7 mL). The culture tube was sealed with a TEFLON®-lined cap, wrapped with aluminum foil, and immersed in an oil bath that had been preheated to 50 °C. After having been stirred in a subdued light environment for 2 h 15 min at this temperature, the reaction mixture was cooled to rt,

diluted with a copious volume of EtOAc, and filtered through CELITE®. The filtrate was concentrated *in vacuo* and filtered through a short pad of SiO_2 (8:1 Hex/EtOAc). Evaporation of the filtrate to dryness and purification of the crude residue by medium pressure liquid chromatography (SiO_2, 98:2 Hex/EtOAc) provided the title compound as a clear, colorless oil (28 mg, 0.10 mmol, 58% yield). The ^{1}H NMR spectrum of **2103** prepared here was indistinguishable from an authentic sample that was arrived at from the vinyl iodide **2126** (*vide supra*), with the exception that this time it was isolated as a single [(2*Z*,4*E*)] isomer. The ^{13}C NMR and IR spectra for this higher purity material were collected, but for completeness these data were included in the earlier procedure.

(2*E*,4*E*)-2-IODODODECA-2,4-DIENE (2101)



[*MJJ-IV-119/V-210/223*] A solution of the vinyl pinacol boronate **2103** (101 mg, 0.35 mmol, 1.0 equiv) in THF (2.0 mL) at 0 °C in a flask open to air was treated with 3 M NaOH (350 μL, 1.05 mmol, 3.0 equiv). The resulting mixture was stirred for 5 min and then a solution of I_2 (181 mg, 0.71 mmol, 2.1 equiv) in THF (1.5 mL) was added. After having been stirred for 30 min at 0 °C, the reaction mixture was quenched by the addition of 0.1 M $Na_2S_2O_3$. The layers were shaken and separated, the aqueous phase was extracted with Et_2O (2x), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by flash chromatography (100% Hex) provided the title compound (83 mg, 0.28 mmol, 82% yield). Since the starting material (**2101**) was ultimately derived from a precursor (the

vinyl iodide **2126**) that could not be prepared in isomerically pure form, in this instance **2101** was isolated as an inseparable 7:1 mixture of (2*E*,4*E*)- and (2*E*,4*Z*)[399]-isomers. Data for the former, major product have been provided.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.71 (ddddd, *J* = 1.5, 1.5, 1.5, 1.5, 11.0 Hz, 1H, H3), 6.11 (dddd, *J* = 1.5, 1.5, 11.0, 15.0 Hz, 1H, H4), 5.66 (ddd, *J* = 7.0, 7.0, 14.5 Hz, 1H, H5), 2.48 (d, *J* = 1.5 Hz, 3H, H1), 2.06 (dddd, *J* = 1.5, 7.5, 7.5, 7.5 Hz, 2H, H6), 1.40-1.35 [m, 2H, $CH{=}CHCH_2CH_2(CH_2)_4CH_3$], 1.33-1.23 [m, 8H, $CH{=}CHCH_2CH_2(CH_2)_4CH_3$], and 0.88 [t, *J* = 7.0 Hz, 3H, $CH{=}CHCH_2CH_2(CH_2)_4CH_3$].

GOESY (500 MHz, $CDCl_3$): ➞ H4; ↑ H1 and ↑ H6.

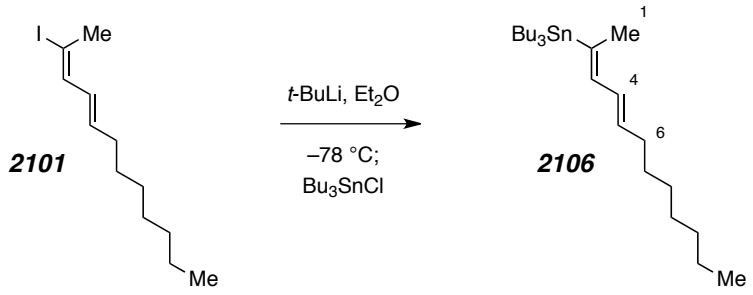
GC / LR EI-MS [5025015]: t_R 7.95 min; *m*/*z* (rel. int.) 292 (99, $M^{+\bullet}$), 207 (10, $M^{+\bullet}$–$C_6H_{13}^{\bullet}$), 194 (100), 109 (8), 95 (14), and 80 (41).

TLC: R_f 0.89 (20:1 Hex/EtOAc).

---

399 (2*E*,4*Z*)-**2101** displayed the following diagnostic ^{1}H NMR resonances: δ 7.00 (ddddd, *J* = 1.5, 1.5, 1.5, 1.5, 11.5 Hz, 1H, H3), 6.05 (dddd, *J* = 2.0, 2.0, 11.5, 11.5 Hz, 1H, H4), 5.42 (ddd, *J* = 7.5, 7.5, 11.0 Hz, 1H, H5), 2.51 (d, *J* = 1.5 Hz, 3H, H1), and 2.11 (dddd, *J* = 2.0, 7.5, 7.5, 7.5 Hz, 2H, H6).

TRI-*n*-BUTYL((2*E*,4*E*)-DODECA-2,4-DIEN-2-YL)STANNANE (2106)



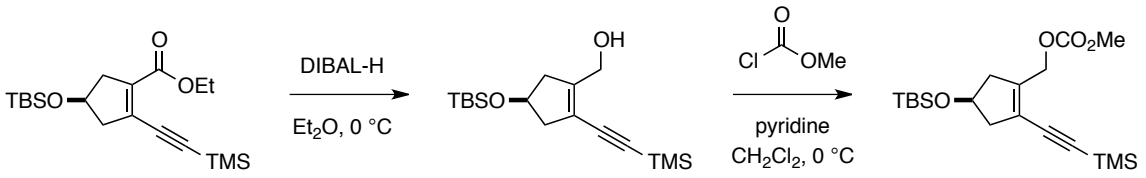
[*MJJ-V-212/224*] A solution of *t*-BuLi (180 μL, 0.31 mmol, 1.8 equiv, 1.7 M in pentane) was added dropwise to a solution of the vinyl iodide **2101** (50 mg 0.17 mmol, 1.0 equiv) in dry Et_2O (1.7 mL) at –78 °C. After having been stirred for 40 min at this temperature, neat Bu_3SnCl (50 μL, 60 mg, 0.184 mmol, 1.1 equiv) was added dropwise. The reaction mixture was then allowed to warm to 0 °C and was held at that temperature for 30 min before being quenched by the addition of satd aq NH_4Cl/NH_4OH (9:1, 10 mL). The layers were shaken and separated and the aqueous phase was extracted with Et_2O (2x). The combined organic extracts were washed with brine (1x), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the crude residue by flash chromatography (4% Et_3N/Hex) provided the title compound (68 mg, 0.15 mmol, 87% yield). This material was isolated as a 7:1 mixture of (2*E*,4*E*)- and (2*E*,4*Z*)-isomers.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.42 [dddd, *J* = 2.0, 2.0, 10.5, 15.5 Hz, 1H, $(Bu_3Sn)(CH_3)C=CHC\mathit{H}=CH$], 6.14 [dddd, *J* = 2.0, 2.0, 2.0, 10.5 Hz, 1H, $(Bu_3Sn)(CH_3)C=C\mathit{H}CH=CH$], 5.65 [ddd, *J* = 7.0, 7.0, 15.5 Hz, 1H, $(Bu_3Sn)(CH_3)C=CH–CH=C\mathit{H}$], 2.11 [dddd, *J* = 1.5, 7.0, 7.0, 7.0 Hz, 2H, $CH=CHC\mathit{H}_2CH_2(CH_2)_4CH_3$], 1.97 [d, *J* = 2.0 Hz, 3H, $(Bu_3Sn)(C\mathit{H}_3)C=CHCH=CH$], 1.54-1.46 [m, 6H, $Sn(CH_2C\mathit{H}_2CH_2CH_3)_3$], 1.42-1.37 [m, 2H, $CH=CHCH_2C\mathit{H}_2(CH_2)_4CH_3$], 1.35-1.25 [m, 14H, overlapping $CH=CHCH_2CH_2(C\mathit{H}_2)_4CH_3$ and $Sn(CH_2CH_2C\mathit{H}_2CH_3)_3$], 0.88 [t, *J* = 7.0 Hz, 9H,

$Sn(CH_2CH_2CH_2C\mathit{H_3})_3$], and 0.92-0.87 [m, 9H, overlapping $CH{=}CHCH_2CH_2(CH_2)_4C\mathit{H_3}$ and $Sn(C\mathit{H_2}CH_2CH_2CH_3)_3$].

GC / LR EI-MS [5025015]: t_R 11.52 min; *m*/*z* (rel. int.) 399 [100, $M^{+\bullet}(^{120}Sn)–C_4H_9^{\bullet}$], 397 [76, $M^{+\bullet}(^{118}Sn)–C_4H_9^{\bullet}$], 395 [42, $M^{+\bullet}(^{116}Sn)–C_4H_9^{\bullet}$], 343 (53), 341 (41), 339 (23), 287 (44), 285 (33), and 283 (24).

(±)-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(TRIMETHYLSILYLETHYNYL)CYCLOPENT-1-EN-1-YL)METHYL METHYL CARBONATE (2135) via **(±)-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(TRIMETHYLSILYLETHYNYL)CYCLOPENT-1-EN-1-YL)METHANOL (2072)**



2068 ***2072*** ***2135***

[*MJJ-IV-104/192*] To a solution of the ethyl ester **2068** (1.33 g, 3.63 mmol, 1.0 equiv) in dry Et_2O (35 mL) at 0 °C was added dropwise a solution of DIBAL-H (6.0 mL, 9.0 mmol, 2.5 equiv, 1.5 M in PhMe) over the course of 10 min. After having been stirred for 10 min at 0 °C, the reaction mixture was *slowly* quenched by dropwise addition of 1 M HCl. Once H_2 evolution had ceased, the resulting mixture was diluted with Et_2O (40 mL) and H_2O (50 mL) and allowed to warm to rt, at which point a milky white suspension had developed. Dilute HCl was then added until two clear, colorless phases were evident. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to leave an oil (1.26 g) that was used in the subsequent procedure without further purification.

In a separate experiment [*MJJ-V-59*], the ethyl ester **2068** (3.79 g, 10.33 mmol, 1.0 equiv) in Et_2O (100 mL) was reduced with DIBAL-H (14.5 mL, 21.75 mmol, 2.1 equiv,

1.5 M in PhMe). The reaction was processed as described above, but this time the intermediate allylic alcohol was purified by flash chromatography (15:1 → 8:1 → 6:1 Hex/EtOAc) to provide 3.27 g (98% yield).

[*MJJ-IV-195/V-255*] To a solution of the crude allylic alcohol **2072** (3.63 mmol theoretical, 1.0 equiv) and pyridine (440 μL, 430 mg, 5.44 mmol, 1.5 equiv) in dry CH_2Cl_2 (20 mL) at 0 °C was added dropwise methyl chloroformate (340 μL, 416 mg, 4.40 mmol, 1.2 equiv). After having been stirred for 60 min at 0 °C, an additional portion of pyridine (60 μL, 59 mg, 0.74 mmol, 0.2 equiv) and methyl chloroformate (100 μL, 122 mg, 1.29 mmol, 0.4 equiv) were added. The reaction mixture was allowed to stir an additional 30 min at 0 °C, at which point it was quenched by the addition of 2:1 satd aq NH_4Cl/H_2O (60 mL). The resulting mixture was diluted with Et_2O (20 mL), the layers were shaken and separated, and the aqueous phase was extracted with Et_2O (2 x 30 mL). The combined organic extracts were washed with brine (1x), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (99:1 → 20:1 Hex/EtOAc) to provide the title compound as a light yellow oil (1.27 g, 3.31 mmol, 91% yield over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.86 (ABX_4, $\Delta\nu_{AB}$ = 28.9 Hz, J_{AB} = 12.5 Hz, $J_{AX} = J_{BX}$ = 1.5 Hz, 2H, $CH_2OCO_2CH_3$), 4.49 [dddd, J = 4.0, 4.0, 7.0, 7.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 3.80 (s, 3H, $CH_2OCO_2CH_3$), 2.79-2.71 [m, 2H, overlapping $CH_2CH(OTBS)CH_2$], 2.47 [dddddd, J = 2.0, 2.0, 2.0, 2.0, 3.5, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.40 [dddddd, J = 2.0, 2.0, 2.0, 2.0, 3.5, 18.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 0.87 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.19 [s, 9H, $Si(CH_3)_3$], 0.05 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.04 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

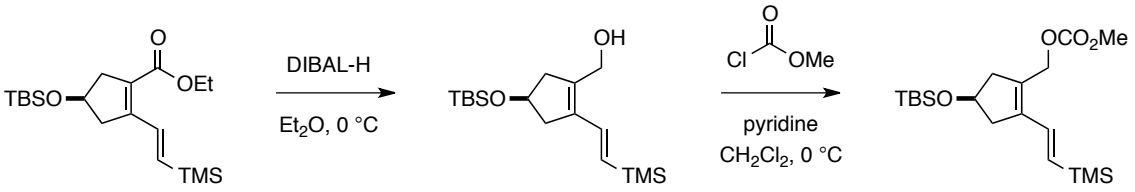
^{13}C NMR (75 MHz, $CDCl_3$): δ 155.8, 142.6, 121.1, 100.6, 99.7, 71.1, 65.3, 55.0, 46.7, 43.7, 26.0, 18.3, 0.1, and -4.7.

IR (neat): 2955, 2931, 2898, 2857, 2146, 1753, 1255, and 843 cm^{-1}.

HR ESI-MS: $C_{19}H_{34}O_4Si_2$ $[M+Na]^+$ requires 405.1888; found 405.1901.

TLC: R_f 0.42 (15:1 Hex/EtOAc).

(±)-(*E*)-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(2-TRIMETHYLSILYLVINYL)-CYCLOPENT-1-EN-1-YL)METHYL METHYL CARBONATE (2136) via **(±)-(*E*)-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(2-TRIMETHYLSILYLVINYL)-CYCLOPENT-1-EN-1-YL)-METHANOL (2143)**



2070 ***2143*** ***2136***

[*MJJ-VI-220*] To a solution of the ethyl ester **2070** (3.64 g, 9.88 mmol, 1.0 equiv) in dry Et_2O (100 mL) at 0 °C was added dropwise a solution of DIBAL-H (24.0 mL, 20.16 mmol, 2.0 equiv, 0.84 M in PhMe) over the course of 10 min. After having been stirred for 5 min at 0 °C, the reaction mixture was *slowly* quenched by dropwise addition of H_2O (*ca.* 5 mL). Once H_2 evolution had ceased, the resulting mixture was diluted with Et_2O (20 mL) and allowed to warm to rt, at which point a milky white suspension developed. Dilute HCl (1 M, 100 mL) was then added until two clear, colorless phases were evident. The phases were separated, the aqueous phase was extracted with Et_2O (3 x 75 mL), and the combined organic extracts were washed with satd aq $NaHCO_3$ (50 mL) and brine (50 mL). Drying ($MgSO_4$), filtration, and concentration of the combined organics *in vacuo*, followed by filtration of the crude residue through a short bed of SiO_2 (1:1 Hex/EtOAc) provided the crude allylic alcohol (3.41 g). This material was used in the subsequent procedure without further purification. Select analytical [from *MJJ-V-137*] are provided below.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 [d, *J* = 19.0 Hz, 1H, C*H*=CHSi$(CH_3)_3$], 5.78 [d, *J* = 19.0 Hz, 1H, CH=C*H*Si$(CH_3)_3$], 4.51 [dddd, *J* = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 4.35 (br d, *J* = 4.0 Hz, 2H, CH_2OH), 2.87 [dd, *J* = 6.0, 17.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.80 [dd, *J* = 7.0, 16.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.54 [dd, *J* = 3.0, 18.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.48 [dd, *J* = 4.0, 17.0 Hz, 1H, CH_2CH(OTBS)CH_2], 0.89 [s, 9H, (CH_3)$_3$CSi$(CH_3)_2$], 0.09 [s, 9H, Si(CH_3)$_3$], and 0.08 [s, 6H, $(CH_3)_3$CSi(CH_3)$_2$].

[*MJJ-VI-221*] To a solution of the crude alcohol **2143** (9.88 mmol theoretical) and pyridine (1.3 mL, 1.28 g, 16.14 mmol, 1.6 equiv) in dry CH_2Cl_2 (100 mL) at 0 °C was added dropwise freshly distilled methyl chloroformate (1.15 mL, 1.41 g, 14.88 mmol, 1.5 equiv). After having been stirred at 0 °C for 30 min, the reaction mixture was poured into a separatory funnel that contained Et_2O (100 mL) and 3:1 satd aq NH_4Cl/H_2O (200 mL). The resulting mixture was shaken and the layers separated, and the aqueous phase was extracted with Et_2O (2 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (98:2 → 40:1 Hex/EtOAc) to provide the title compound as a turbid, light yellow oil (3.13 g, 8.14 mmol, 82% yield over 2 steps). At this stage, the desilylated analog of **2136**, which was co-produced by reduction and acylation of the terminal olefin contaminant **2071**, ran slightly slower on SiO_2 and could be removed chromatographically.[400]

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.83 [d, *J* = 18.5 Hz, 1H, C*H*=CHSi$(CH_3)_3$], 5.84 [d, *J* = 19.0 Hz, 1H, CH=C*H*Si$(CH_3)_3$], 4.85 (ABq, $\Delta\nu_{AB}$ = 50.0 Hz, J_{AB} = 12.5 Hz, 2H, CH_2OCO_2CH_3), 4.50 [dddd, *J* = 4.0, 4.0, 7.0, 7.0 Hz, 1H C*H*(OTBS)], 3.79 (s, 3H,

---

[400] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.69 (dd, *J* = 10.5, 17.0 Hz, 1H, C*H*=$CH_{trans}H_{cis}$), 5.19 (dd, *J* = 1.5, 11.0 Hz, 1H, CH=$CH_{trans}H_{cis}$), 5.16 (dd, *J* = 1.5, 17.5 Hz, 1H, CH=C$H_{trans}H_{cis}$), 4.81 (ABq, $\Delta\nu_{AB}$ = 48.2 Hz, J_{AB} = 12.5 Hz, 1H, CH_2OCO_2CH_3), 4.53 [dddd, *J* = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.78 (s, 3H, $CH_2OCO_2CH_3$), 2.85-2.77 [m, 2H, overlapping CH_2CH(OTBS)CH_2], 2.49-2.45 [m, 2H, overlapping CH_2CH(OTBS)CH_2], 0.89 [s, 9H, (CH_3)$_3$CSi$(CH_3)_2$], 0.068 [s, 3H, $(CH_3)_3$CSi(CH_3)$_2$], and 0.066 [s, 3H, $(CH_3)_3$CSi(CH_3)$_2$].

$CH_2OCO_2CH_3$), 2.83 [dd, J = 7.0, 17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.81 [dd, J = 6.5, 16.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.51-2.49 [m, 1H, $CH_2CH(OTBS)CH_2$], 2.48-2.46 [m, 1H, $CH_2CH(OTBS)CH_2$], 0.87 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.10 [s, 9H, $Si(CH_3)_3$], 0.07 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.06 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

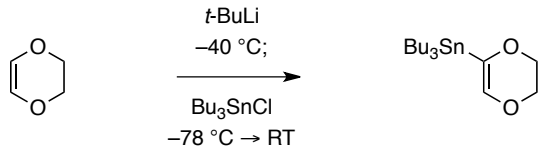
^{13}C NMR (75 MHz, $CDCl_3$): δ 156.0, 139.2, 136.2, 133.1, 131.6, 70.6, 63.7, 55.0, 45.5, 43.0, 26.1, 18.4, -1.1, and -4.6.

IR (neat): 2954, 2931, 2898, 2856, 1750, 1249, 863, and 839 cm^{-1}.

HR ESI-MS: $C_{19}H_{36}O_4Si_2$ $[M+Na]^+$ requires 407.2044; found 407.2050.

TLC: R_f 0.42 (15:1 Hex/EtOAc).

5-TRI-*n*-BUTYLSTANNYL-2,3-DIHYDRO-1,4-DIOXIN (2146)



2145 ***2146***

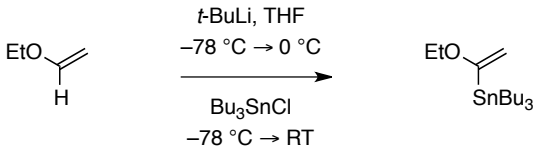
[*MJJ-IV-143*][133] A 3-neck, 250-mL round bottom flask equipped with a 125-mL pressure equalizing addition funnel was charged with neat 1,4-dioxene[132] (**2145**) (19.06 g, 164 mmol, 74% w/w mixture with 1,4-dioxane, 1.0 equiv) and cooled to –40 °C (acetonitrile/dry ice bath). While being vigorously stirred, a solution of *t*-BuLi (95 mL, 162 mmol, 1.7 M in pentane, 1.0 equiv) was added dropwise via the addition funnel over the course of 40 min. After having been stirred at this temperature for an additional 60 min, the reaction mixture was then cooled to –78 °C and a solution of Bu_3SnCl (22.5 mL, 27.0 g, 83 mmol, 0.5 equiv) in dry THF (*ca.* 30 mL) was added dropwise via a hypodermic syringe. Once the addition was complete, the reaction mixture was allowed to warm to rt over the course of 30 min and was then slowly quenched by the addition of satd aq NH_4Cl (25 mL). A small portion of H_2O was added to dissolve any precipitated

solids and then the layers were shaken and separated. The aqueous phase was extracted with Et_2O (2 x 75 mL), the combined organic extracts were washed with H_2O (1x) and brine (1x), dried (Na_2SO_4), and filtered. Evaporation of the filtrate *in vacuo* followed by purification of the crude residue by Kugelrohr distillation (oven temp. *ca.* 180 °C @ 0.025 mmHg) provided the title compound as a light yellow oil (26.8 g, 71.4 mmol, 86% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.69 [s, 1H, (Sn)OC=C*H*O], 4.11-4.01 (AA'BB', 4H, OCH_2CH_2O), 1.55-1.45 [m, 6H, Sn($CH_2CH_2CH_2CH_3$)$_3$], 1.36-1.27 [m, 6H, Sn($CH_2CH_2CH_2CH_3$)$_3$], 0.94-0.91 [m, 6H, Sn($CH_2CH_2CH_2CH_3$)$_3$], and 0.90 [t, J = 7.0 Hz, 9H Sn($CH_2CH_2CH_2CH_3$)$_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ 140.3, 132.7, 65.5, 31.0, 29.6, 29.1, 27.9, 27.4, 13.9, 9.6, and 8.0.

(α-ETHOXYVINYL)TRI-*n*-BUTYLTIN (2148)



2147 ***2148***

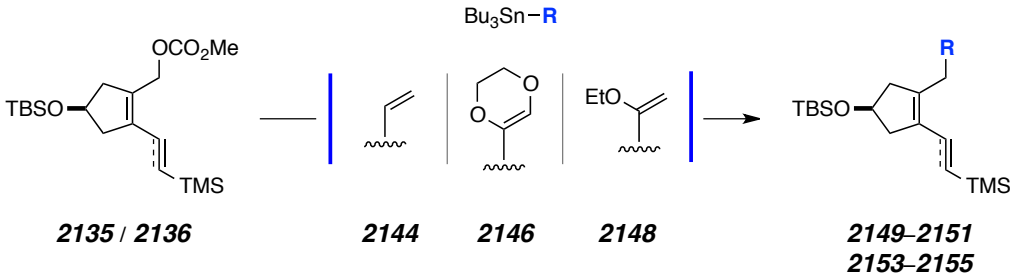
[*MJJ-V-97*][134] A 3-neck, 500-mL round bottom flask equipped with a 125-mL pressure equalizing addition funnel was charged with dry THF (50 mL) and freshly distilled ethyl vinyl ether (**2147**) (13.0 mL, 9.79 g, 136 mmol, 1.0 equiv). To the addition funnel was added *t*-BuLi (60.0 mL, 102 mmol, 0.75 equiv, 1.7 M solution in pentane), after which the reaction mixture was cooled to –78 °C. The organolithium solution was then added dropwise over the course of 40 min, which immediately produced a bright yellow, heterogeneous mixture (an additional 10 mL rinse with dry pentane was used for quantitative transfer). Upon warming to 0 °C, the reaction mixture gradually became

homogeneous and deep orange in color, then finally evolving to a very pale yellow (almost colorless) solution. After having been stirred at 0 °C for an additional 30 min, the reaction mixture was re-cooled to –78 °C and a solution of Bu_3SnCl (19.0 mL, 22.8 g, 70 mmol, 0.5 equiv) in dry THF (10 mL) was added dropwise over 15 min via the addition funnel (10 mL dry THF rinse used for quantitative transfer). The resulting milky white solution was then allowed to warm to rt and was held at this temperature for 30 min. At this point, the reaction mixture was quenched by addition of satd aq NH_4Cl (100 mL). The layers were separated, the aqueous phase was extracted with Et_2O (2 x 100 mL), and the combined organic extracts were washed with H_2O (50 mL) and brine (50 mL). After the organic material was dried (Na_2SO_4) and filtered, evaporation of the solvent *in vacuo* left a residue that was purified by Kugelrohr distillation (oven temp. *ca.* 155-170 °C @ 0.08-0.1 mmHg) to provide the title compound as a clear, colorless oil (20.3 g, 56.1 mmol, 80% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.67 [d, *J* = 1.5 Hz, 1H, $(CH_3CH_2O)C{=}CH_2$], 4.04 [d, *J* = 2.0 Hz, 1H, $(CH_3CH_2O)C{=}CH_2$], 3.70 [q, *J* = 7.0 Hz, 2H, $(CH_3CH_2O)C{=}CH_2$], 1.56-1.50 [m, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$], 1.32 [ddddd, *J* = 7.5, 7.5, 7.5, 7.5, 7.5 Hz, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$], 1.25 [t, *J* = 7.0 Hz, 3H, $(CH_3CH_2O)C{=}CH_2$], 0.95-0.92 [m, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$], and 0.89 [t, *J* = 7.0 Hz, 9H, $Sn(CH_2CH_2CH_2CH_3)_3$].

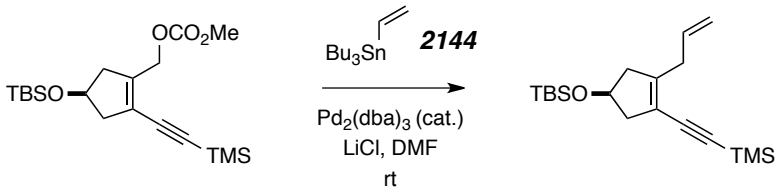
^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 95.5, 62.2, 29.1, 27.4, 14.7, 13.9, and 9.9.

PALLADIUM(0)-CATALYZED π-ALLYL STILLE CROSS-COUPLING: GENERAL PROCEDURE



A sample of LiCl (3.3-3.6 equiv) was flame-dried under a continuous stream of dry N_2, and, after having been cooled to rt, the reaction flask was charged with tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$, 5–10 mol%] and dry DMF (~0.1 M). To this solution was added the requisite allylic carbonate (**2135**/**2136**) (1.0 equiv) as a solution in DMF and, after having been stirred for 5 min at rt, the appropriate vinyl stannane (**2144**, **2146**, or **2148**) (1.2–2.0 equiv). Then, the reaction mixture was either held at rt or immersed in a preheated (50 °C) oil bath and allowed to stir under N_2 for the indicated time period. Once the starting material had been consumed (as revealed by GC-MS analysis), the reaction mixture was cooled to rt, diluted with EtOAc (~ 3 volumes), and filtered through CELITE® directly into a separatory funnel that contained brine/H_2O (1:1). The layers were shaken and separated, the organic phase was washed with brine/H_2O (1:1), and the combined aqueous washings were back-extracted with EtOAc (1x). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to leave a residue that was purified by either flash chromatography or medium pressure liquid chromatography (SiO_2).

(±)-((2-ALLYL-4-(*TERT*-BUTYLDIMETHYLSILOXY)CYCLOPENT-1-EN-1-YL)ETHYNYL)-TRIMETHYLSILANE (2149)



2135 ***2149***

[*MJJ-VII-36*] According to the GENERAL PROCEDURE, the allylic carbonate **2135** (103 mg, 0.270 mmol, 1.0 equiv) and tri-*n*-butyl(vinyl)tin (**2144**) (110 mg, 0.345 mmol, 1.3 equiv) in reagent grade DMF (2.6 mL) were reacted in the presence of LiCl (40.8 mg, 0.962 mmol, 3.6 equiv) and $Pd_2(dba)_3$ (16.4 mg, 0.018 mmol, 7 mol%) for 1 h at rt. The dark brown residue obtained after work-up was purified by flash chromatography (4% Et_3N/Hex) to provide the title compound as a light brown oil (86 mg, 0.258 mmol, 96% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.76 (dddd, J = 7.0, 7.0, 10.0, 17.0 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.08 (dddd, J = 1.5, 1.5, 1.5, 17.0 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.02 (dddd, J = 1.5, 1.5, 1.5, 10.0 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 4.44 [dddd, J = 4.5, 4.5, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.02 (br d, J = 6.5 Hz, 2H, CH_2CH=$CH_{trans}H_{cis}$), 2.72 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 7.0, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.64 [ddddd, J = 1.0, 1.0, 2.5, 7.0, 17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.44 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 5.0, 15.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.30 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 4.5, 17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 0.87 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.19 [s, 9H, $Si(CH_3)_3$], 0.042 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.037 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

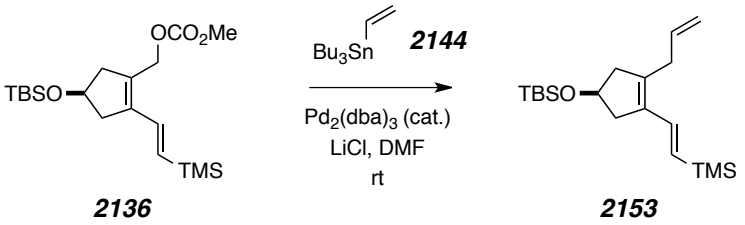
^{13}C NMR (125 MHz, $CDCl_3$): δ 148.5, 134.9, 116.40, 116.36, 101.8, 98.0, 71.4, 46.4, 45.3, 35.2, 26.0, 18.3, 0.3, and -4.6.

IR (neat): 2954, 2929, 2898, 2856, 2141, 1248, 1097, 1065, 854, and 839 cm^{-1}.

GC / LR EI-MS [5025015]: t_R 8.46 min; *m*/*z* (rel. int.) 334 (0.2, $M^{+\bullet}$), 319 (7, $M^{+\bullet}$–$CH_3^{\bullet}$), 277 [100, $M^{+\bullet}$–$C(CH_3)_3^{\bullet}$], 203 {5, $M^{+\bullet}$–$O[(CH_3)_3CSi(CH_3)_2]^{\bullet}$}, 187 (9), 159 (12), 147 (87), and 133 (12).

TLC: R_f 0.75 (15:1 Hex/EtOAc).

(±)-(*E*)-(2-(2-ALLYL-4-(*TERT*-BUTYLDIMETHYLSILOXY)CYCLOPENT-1-EN-1-YL)VINYL)-TRIMETHYLSILANE (2153)



[*MJJ-VII-49*] According to the GENERAL PROCEDURE, the allylic carbonate **2136** (99 mg, 0.258 mmol, 1.0 equiv) and tri-*n*-butyl(vinyl)tin (**2144**) (108 mg, 0.340 mmol, 1.3 equiv) in reagent grade DMF (2.6 mL) were reacted in the presence of LiCl (37.0 mg, 0.873 mmol, 3.4 equiv) and $Pd_2(dba)_3$ (13.0 mg, 0.014 mmol, 5 mol%) for 30 min at rt. The dark brown residue obtained after work-up was purified by flash chromatography (4% Et_3N/Hex) to provide the title compound as a light yellow oil (79 mg, 0.235 mmol, 91% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.82 [d, *J* = 18.5 Hz, 1H, C*H*=CHSi$(CH_3)_3$], 5.75 (dddd, *J* = 6.5, 6.5, 10.0, 16.5 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.68 [d, *J* = 19.0 Hz, 1H, CH=C*H*Si$(CH_3)_3$], 5.05 (dddd, *J* = 2.0, 2.0, 2.0, 17.0 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.01 (dddd, *J* = 1.5, 1.5, 1.5, 10.0 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 4.47 [dddd, *J* = 4.5, 4.5, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 2.98 (dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 1.5, 6.5 Hz, 2H, CH_2CH=$CH_{trans}H_{cis}$), 2.77 [ddddddd, *J* = 1.5, 1.5, 1.5, 1.5, 1.5, 7.0, 15.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.68 [ddddddd, *J* = 1.0, 1.0, 1.0, 1.0, 1.0, 7.0, 18.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.46-2.37 [m, 2H, overlapping $CH_2CH(OTBS)CH_2$], 0.89 [s, 9H,

($C\mathit{H}_3$)$_3$CSi(CH_3)$_2$], 0.09 [s, 9H, Si($C\mathit{H}_3$)$_3$], 0.064 [s, 3H, (CH_3)$_3$CSi($C\mathit{H}_3$)$_2$], and 0.058 [s, 3H, (CH_3)$_3$CSi($C\mathit{H}_3$)$_2$].

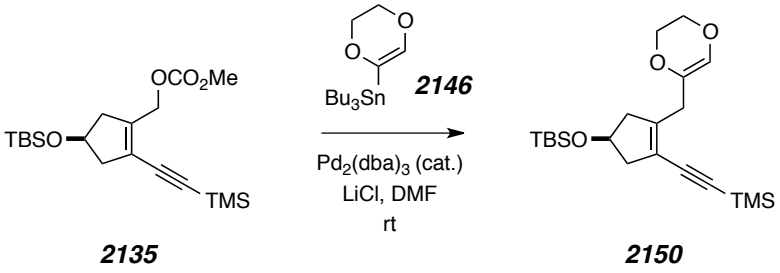
^{13}C NMR (125 MHz, $CDCl_3$): δ 137.5, 137.4, 135.5, 134.3, 129.6, 115.9, 70.9, 47.1, 42.8, 33.0, 26.1, 18.4, -1.0, and -4.5.

IR (neat): 2954, 2929, 2856, 1249, 1096, 1065, 863, 838, and 774 cm^{-1}.

GC / LR EI-MS [5025015]: t_R 8.66 min; *m*/*z* (rel. int.) 336 ($M^{+\bullet}$, 2), 321 (2, $M^{+\bullet}$–$CH_3^{\bullet}$), 279 [44, $M^{+\bullet}$–$C(CH_3)_3^{\bullet}$], 205 {16, $M^{+\bullet}$–O[$(CH_3)_3CSi(CH_3)_2]^{\bullet}$}, 203 (13), 191 (13), 189 (15), 187 (22), 147 (100), and 131 (16).

TLC: R_f 0.69 (15:1 Hex/EtOAc).

(±)-*TERT*-BUTYL((3-((5,6-DIHYDRO-1,4-DIOXIN-2-YL)METHYL)-4-(TRIMETHYLSILYL-ETHYNYL)CYCLOPENT-3-EN-1-YL)OXY)DIMETHYLSILANE (2150)



[*MJJ-VII-52*] According to the GENERAL PROCEDURE, the allylic carbonate **2135** (101 mg, 0.264 mmol, 1.0 equiv) and 5-tri-*n*-butylstannyl-2,3-dihydro-1,4-dioxin (**2146**) (196 mg, 0.522 mmol, 2.0 equiv) in dry DMF (2.6 mL) were reacted in the presence of LiCl (37.1 mg, 0.875 mmol, 3.3 equiv) and $Pd_2(dba)_3$ (11.5 mg, 0.013 mmol, 5 mol%) for 23 h at rt. The dark brown residue obtained after work-up was purified by flash chromatography (4% Et_3N/Hex) and then medium pressure liquid chromatography (SiO_2, 99:1 Hex/EtOAc) to provide the title compound as a light yellow oil (74 mg, 0.188 mmol, 71% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86 (s, 1H, $CH_2C{=}CH$), 4.45 [dddd, J = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 4.06-3.97 (AA'BB', 4H, OCH_2CH_2O), 2.93 (ABq, $\Delta\nu_{AB}$ = 13.5 Hz, J_{AB} = 15.5 Hz, 2H, $CH_2C{=}CH$), 2.73 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 7.0, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.64 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 7.0, 18.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.44 [dddddd, J = 2.0, 2.0, 2.0, 2.0, 4.0, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.34 [dddddd, J = 2.0, 2.0, 2.0, 2.0, 4.5, 17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 0.87 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.19 [s, 9H, $Si(CH_3)_3$], 0.045 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.044 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 147.3, 135.2, 123.0, 117.4, 101.6, 98.4, 71.3, 64.8, 64.0, 46.4, 45.3, 31.8, 26.0, 18.3, 0.3, and -4.6.

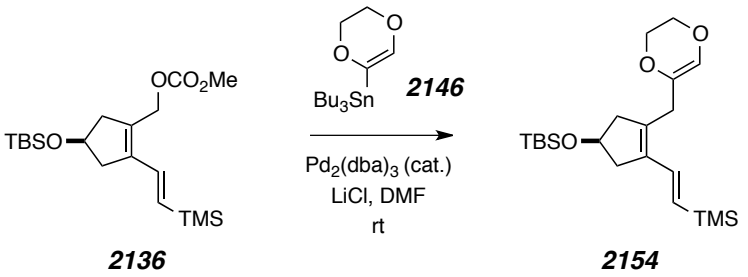
IR (neat): 2955, 2929, 2857, 2140, 1685, 1250, 1092, 1065, 842, and 777 cm^{-1}.

GC / LR EI-MS [5025015]: t_R 10.51 min; *m*/*z* (rel. int.) 392 (46, $M^{+\bullet}$), 377 (6, $M^{+\bullet}–CH_3^{\bullet}$), 335 [100, $M^{+\bullet}–C(CH_3)_3^{\bullet}$], 307 (13, $M^{+\bullet}–C_4H_5O_2^{\bullet}$), 291 (6), 279 (14), 260 (12), 217 (14), 175 (26), 147 (41), and 73 (42).

HR ESI-MS: $C_{21}H_{36}O_3Si_2$ $[M+Na]^+$ requires 415.2095; found 415.2122.

TLC: R_f 0.48 (15:1 Hex/EtOAc).

(±)-(*E*)-*TERT*-BUTYL((3-((5,6-DIHYDRO-1,4-DIOXIN-2-YL)METHYL)-4-(2-TRIMETHYLSILYLVINYL)CYCLOPENT-3-EN-1-YL)OXY)DIMETHYLSILANE (2154)



[*MJJ-VII-39*] According to the GENERAL PROCEDURE, the allylic carbonate **2136** (101 mg, 0.263 mmol, 1.0 equiv) and 5-tri-*n*-butylstannyl-2,3-dihydro-1,4-dioxin (**2146**) (169 mg, 0.451 mmol, 1.7 equiv) in dry DMF (2.6 mL) were reacted in the presence of LiCl (36.4 mg, 0.859 mmol, 3.3 equiv) and $Pd_2(dba)_3$ (11.7 mg, 0.013 mmol, 5 mol%) for 16 h at rt. The dark brown residue obtained after work-up was purified by flash chromatography (4% Et_3N/Hex) and then medium pressure liquid chromatography (SiO_2, 99:1 Hex/EtOAc) to provide the title compound as a light yellow oil (67 mg, 0.171 mmol, 65% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.82 [d, J = 19.0 Hz, 1H, C*H*=CHSi$(CH_3)_3$], 5.83 (s, 1H, CH_2C=C*H*), 5.70 [d, J = 19.0 Hz, 1H, CH=C*H*Si$(CH_3)_3$], 4.47 [dddd, J = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 4.07-3.97 (AA'BB', 4H, OCH_2CH_2O), 2.90 (ABq, $\Delta\nu_{AB}$ = 19.0 Hz, J_{AB} = 15.5 Hz, 2H, CH_2C=CH), 2.77 [br dd, J = 7.5, 16.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.72 [br dd, J = 7.5, 18.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.46-2.40 [m, 2H, overlapping CH_2CH(OTBS)CH_2], 0.89 [s, 9H, (CH_3)$_3$CSi$(CH_3)_2$], 0.09 [s, 9H, Si(CH_3)$_3$], 0.07 [s, 3H, $(CH_3)_3$CSi(CH_3)$_2$], and 0.06 [s, 3H, $(CH_3)_3$CSi(CH_3)$_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ 137.3, 135.7, 135.5, 135.3, 130.0, 122.9, 70.8, 64.8, 64.0, 47.0, 42.9, 29.7, 26.1, 18.4, -1.0, and -4.5.

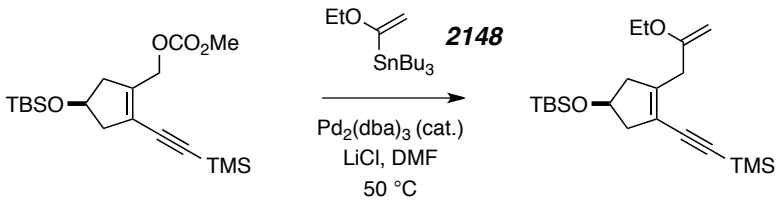
IR (neat): 2953, 2929, 2856, 1248, 1090, 1065, 864, 838, and 776 cm^{-1}.

GC / LR EI-MS [5025015]: t_R 10.68 min; *m*/*z* (rel. int.) 394 (20, $M^{+\bullet}$), 337 [11, $M^{+\bullet}$–$C(CH_3)_3^{\bullet}$], 293 (9), 247 (19), 219 (50), 203 (19), 189 (32), 147 (52), 129 (42), 117 (35), 99 (21), and 73 (100).

HR ESI-MS: $C_{21}H_{38}O_3Si_2$ $[M+Na]^+$ requires 417.2252; found 417.2281.

TLC: R_f 0.47 (15:1 Hex/EtOAc).

(±)-*TERT*-BUTYL((3-(2-ETHOXYALLYL)-4-(TRIMETHYLSILYLETHYNYL)CYCLOPENT-3-EN-1-YL)OXY)DIMETHYLSILANE (2151)



2135 ***2151***

[*MJJ-VII-58*] According to the GENERAL PROCEDURE, the allylic carbonate **2135** (102 mg, 0.267 mmol, 1.0 equiv) and (α-ethoxyvinyl)tri-*n*-butyltin (**2148**) (117 mg, 0.324 mmol, 1.2 equiv) in dry DMF (2.6 mL) were reacted in the presence of LiCl (38.5 mg, 0.908 mmol, 3.4 equiv) and $Pd_2(dba)_3$ (12.4 mg, 0.014 mmol, 5 mol%) for 1 h at 50 °C. The dark brown residue obtained after work-up was purified by flash chromatography (4% Et_3N/Hex) to provide the title compound as a light yellow oil (97 mg, 0.256 mmol, 96% yield).

[*NOTE:* The enol ether **2151** readily hydrolyzed to the methyl ketone during purification if the SiO_2 was not pretreated with a small percentage (*ca.* 2–4%) of Et_3N.]

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.44 [dddd, *J* = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.87 [d, *J* = 2.0 Hz, 1H, $(CH_3CH_2O)C=CH_2$], 3.86 [d, *J* = 2.0 Hz, 1H, $(CH_3CH_2O)C=CH_2$], 3.71 [q, *J* = 7.0 Hz, 2H, $(CH_3CH_2O)C=CH_2$], 3.06 [dddd, *J* = 1.5,

1.5, 1.5, 1.5 Hz, 2H, C*H*$_2$(CH$_3$CH$_2$O)C=CH$_2$], 2.72 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 6.5, 15.5 Hz, 1H, C*H*$_2$CH(OTBS)CH$_2$], 2.65 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 7.0, 17.5 Hz, 1H, CH$_2$CH(OTBS)C*H*$_2$], 2.44 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 3.5, 16.0 Hz, 1H, C*H*$_2$CH(OTBS)CH$_2$], 2.36 [dddddd, *J* = 2.0, 2.0, 2.0, 2.0, 3.5, 18.0 Hz, 1H, CH$_2$CH(OTBS)C*H*$_2$], 1.29 [t, *J* = 7.0 Hz, 3H, (C*H*$_3$CH$_2$O)C=CH$_2$], 0.87 [s, 9H, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$], 0.19 [s, 9H, Si(C*H*$_3$)$_3$], 0.042 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$], and 0.037 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$].

^{13}C NMR (125 MHz, CDCl$_3$): δ 160.5, 147.6, 117.3, 101.8, 98.0, 81.9, 71.4, 62.9, 46.3, 45.6, 36.4, 26.0, 18.3, 14.6, 0.3, and -4.6.

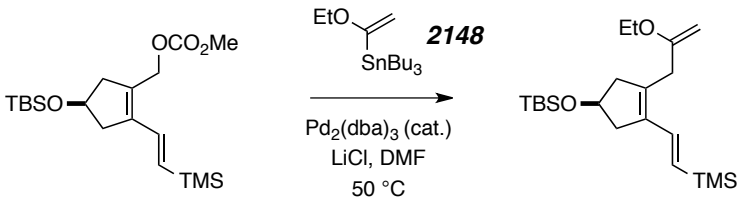
IR (neat): 2956, 2929, 2857, 2142, 1654, 1251, 1096, 1067, 855, 841, 774, and 761 cm^{-1}.

GC / LR EI-MS [5025015]: t$_R$ 9.44, 10.02, and 10.13 min; *m*/*z* for t$_R$ 9.44 min (rel. int.) 378 (13, M$^{+\bullet}$), 321 [100, M$^{+\bullet}$–C(CH$_3$)$_3^\bullet$], 293 (49, M$^{+\bullet}$–C$_5$H$_9$O$^\bullet$), 219 (38), 203 (28), 147 (56), and 73 (58).

HR ESI-MS: C$_{21}$H$_{38}$O$_2$Si$_2$ [M+Na]$^+$ requires 401.2303; found 401.2335.

TLC: R$_f$ (**2151**) 0.69; R$_f$ (methyl ketone) 0.39 (15:1 Hex/EtOAc).

(±)-(*E*)-*TERT*-BUTYL((3-(2-ETHOXYALLYL)-4-(2-TRIMETHYLSILYLVINYL)CYCLOPENT-3-EN-1-YL)OXY)DIMETHYLSILANE (2155)



2136 ***2155***

[*MJJ-VI-80/104/VII-38*] According to the GENERAL PROCEDURE, the allylic carbonate **2136** (101 mg, 0.264 mmol, 1.0 equiv) and (α-ethoxyvinyl)tri-*n*-butyltin (**2148**) (126 mg, 0.349 mmol, 1.3 equiv) in dry DMF (2.6 mL) were reacted in the presence of LiCl (46.2

mg, 1.090 mmol, 4.1 equiv) and $Pd_2(dba)_3$ (11.9 mg, 0.013 mmol, 5 mol%) for 1.5 h at 50 °C. The dark brown residue obtained after work-up was purified by flash chromatography (4% Et_3N/Hex) to provide the title compound as a light yellow oil (94 mg, 0.247 mmol, 94% yield). The reader is directed to the *NOTE* above regarding the purification of this acid-sensitive ethyl enol ether.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.83 [d, *J* = 19.0 Hz, 1H, C*H*=CHSi$(CH_3)_3$], 5.68 [d, *J* = 18.5 Hz, 1H, CH=C*H*Si$(CH_3)_3$], 4.46 [dddd, *J* = 4.5, 4.5, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.86 [d, *J* = 2.0 Hz, 1H, $(CH_3CH_2O)C=CH_2$], 3.83 [d, *J* = 2.0 Hz, 1H, $(CH_3CH_2O)C=CH_2$], 3.71 [q, *J* = 7.0 Hz, 2H, $(CH_3CH_2O)C=CH_2$], 3.00 [ABq, $\Delta\nu_{AB}$ < 0.5 Hz, J_{AB} = 15.5 Hz, 2H, $CH_2(CH_3CH_2O)C=CH_2$], 2.79-2.70 [m, 2H, overlapping $CH_2CH(OTBS)CH_2$], 2.47-2.42 [m, 2H, overlapping $CH_2CH(OTBS)CH_2$], 1.28 [t, *J* = 7.0 Hz, 3H, $(CH_3CH_2O)C=CH_2$], 0.89 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.09 [s, 9H, $Si(CH_3)_3$], 0.064 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.058 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ 160.8, 137.8, 136.1, 135.3, 129.5, 81.7, 70.9, 62.9, 47.4, 42.7, 34.3, 26.1, 18.4, 14.6, -1.0, and -4.5.

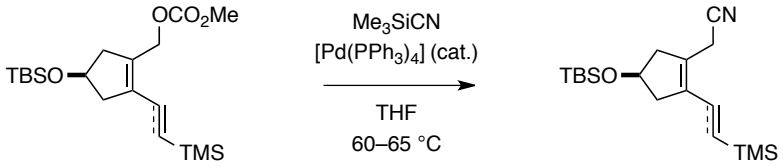
IR (neat): 2954, 2929, 2902, 2856, 1653, 1633, 1572, 1248, 1231, 1094, 1068, 863, and 838 cm^{-1}.

GC / LR EI-MS [5025015]: t_R 9.62, 9.95, and 10.13 min; *m*/*z* for t_R 9.62 min (rel. int.) 380 (15, $M^{+\bullet}$), 365 (4, $M^{+\bullet}–CH_3^\bullet$), 351 (11, $M^{+\bullet}–C_2H_5^\bullet$), 323 [10, $M^{+\bullet}–C(CH_3)_3^\bullet$], 277 (39), 261 (9), 249 {16, $M^{+\bullet}–[(CH_3)_3CSi(CH_3)_2]O^\bullet$}, 219 (79), 205 (86), 187 (19), 175 (27), 147 (60), 130 (59), and 73 (100).

HR ESI-MS: $C_{21}H_{40}O_2Si_2$ $[M+Na]^+$ requires 403.2459; found 403.2472.

TLC: R_f (**2155**) 0.73; R_f (methyl ketone) 0.39 (15:1 Hex/EtOAc).

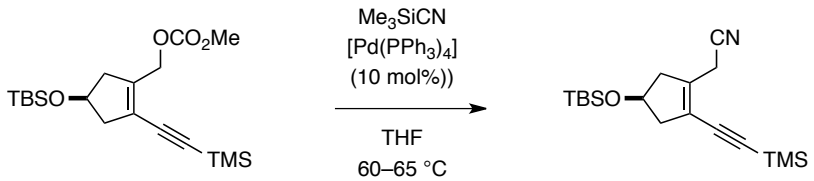
PALLADIUM(0)-CATALYZED ALLYLIC CYANATION: GENERAL PROCEDURE



2135 / ***2136*** ***2152*** / ***2156***

A flame-dried culture tube (25 x 150 mm) was fitted with a rubber septum and charged with the allylic carbonate (**2135**/**2136**) (1.0 equiv), dry THF (10.0 mL), and $Pd(PPh_3)_4$ (5-10 mol%). Neat trimethylsilyl cyanide (5 equiv) was injected, the rubber septum was replaced with a Teflon-lined cap, and the reaction mixture was immersed in an oil bath that had been preheated to 60–65 °C. After having been stirred at this temperature for the indicated period, the reaction mixture was cooled to rt, diluted with Hex/EtOAc (6:1), and filtered through a short pad of SiO_2. Concentration *in vacuo* provided a crude residue that was purified by medium pressure liquid chromatography (SiO_2, Hex/EtOAc).

(±)-2-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(TRIMETHYLSILYLETHYNYL)CYCLOPENT-1-EN-1-YL)ACETONITRILE (2152)



2135 ***2152***

[*MJJ-VI-287*] According to the GENERAL PROCEDURE, the allylic carbonate **2135** (390 mg, 1.02 mmol, 1.0 equiv) and neat trimethylsilyl cyanide (650 μL, 5.20 mmol, 5.1 equiv) in dry THF (10.0 mL) were allowed to react in the presence of $Pd(PPh_3)_4$ (114 mg,

0.100 mmol, 10 mol%) for 17 h. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 99:1 Hex/EtOAc) provided the title compound as a white solid (156 mg, 0.47 mmol, 46% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.52 [dddd, J = 3.5, 3.5, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.37 (ABX_4, $\Delta\nu_{AB}$ = 54.1 Hz, J_{AB} = 18.0 Hz, $J_{AX} = J_{BX}$ = 1.5 Hz, 2H, CH_2C≡N), 2.85-2.74 [m, 2H, overlapping CH_2CH(OTBS)CH_2], 2.49-2.43 [m, 2H, overlapping CH_2CH(OTBS)CH_2], 0.88 [s, 9H, (CH_3)$_3$CSi(CH$_3$)$_2$], 0.20 [s, 9H, Si(CH_3)$_3$], and 0.06 [s, 6H, (CH$_3$)$_3$CSi(CH_3)$_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ 136.4, 121.7, 116.6, 101.4, 99.3, 70.6, 46.6, 45.1, 26.0, 19.0, 18.3, 0.1, and -4.7

IR (thin film): 2953, 2929, 2900, 2857, 2250, 2147, 1250, 1077, and 840 cm^{-1}.

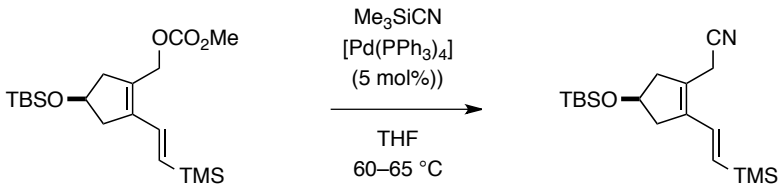
GC / LR EI-MS [5025015]: t_R 9.35 min; *m*/*z* (rel. int.) 318 (5, $M^{+\bullet}$–$CH_3^{\bullet}$), 276 [100, $M^{+\bullet}$–$C(CH_3)_3^{\bullet}$], 249 (4), 186 (4), 177 (9), 175 (8), 159 (17), and 147 (22).

HR ESI-MS: $C_{18}H_{31}NOSi_2$ $[M+Na]^+$ requires 356.1836; found 356.1829.

MP: 77–79 °C.

TLC: R_f 0.44 (15:1 Hex/EtOAc).

(±)-(*E*)-2-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(2-TRIMETHYLSILYLVINYL)-CYCLOPENT-1-EN-1-YL)ACETONITRILE (2156)



2136 ***2156***

[*MJJ-V-152/VI-84/212/VII-42*] According to the GENERAL PROCEDURE, the allylic carbonate **2136** (459 mg, 1.19 mmol, 1.0 equiv) and neat trimethylsilyl cyanide (750 μL, 6.00 mmol, 5.0 equiv) in dry THF (10.0 mL) were allowed to react in the presence of $Pd(PPh_3)_4$ (70 mg, 0.061 mmol, 5 mol%) for 9 h. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 99:1 Hex/EtOAc) provided the title compound as a white solid (354 mg, 1.06 mmol, 88% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.64 [d, J = 18.5 Hz, 1H, C*H*=CHSi$(CH_3)_3$], 5.86 [d, J = 18.5 Hz, 1H, CH=C*H*Si$(CH_3)_3$], 4.53 [dddd, J = 3.5, 3.5, 7.5, 7.5 Hz, 1H, C*H*(OTBS)], 3.32 [ABX$_4$, $\Delta\nu_{AB}$ = 54.6 Hz, J_{AB} =18.0 Hz, $J_{AX} = J_{BX}$ = 1.5 Hz, 2H, CH_2C≡N], 2.89 [dd, J = 7.0, 17.5 Hz, 1H, CH_2CH(OTBS)CH_2], 2.81 [dd, J = 7.0, 16.5 Hz, 1H CH_2CH(OTBS)CH_2], 2.53 [dd, J = 3.0, 17.5 Hz, 1H CH_2CH(OTBS)CH_2], 2.47 [dd, J = 3.5, 16.0 Hz, 1H CH_2CH(OTBS)CH_2], 0.89 [s, 9H, (CH_3)$_3$CSi$(CH_3)_2$], 0.11 [s, 9H, Si(CH_3)$_3$], and 0.08 [s, 6H, $(CH_3)_3$CSi(CH_3)$_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 138.2, 135.3, 133.9, 125.3, 117.0, 70.1, 46.9, 43.1, 26.0, 18.3, 17.1, -1.2, and -4.6.

IR (thin film): 2953, 2929, 2856, 2248, 1250, 1070, 989, 863, 838, and 776 cm^{-1}.

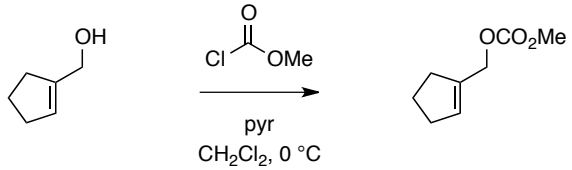
GC / LR EI-MS [5025015]: t_R 9.65 min; *m*/*z* (rel. int.) 320 (5, $M^{+\bullet}$–$CH_3^{\bullet}$), 278 [100, $M^{+\bullet}$–$C(CH_3)_3^{\bullet}$], 188 (18), 179 (26), and 147 (43).

HR ESI-MS: $C_{18}H_{33}NOSi_2$ $[M+Na]^+$ requires 358.1993; found 358.2003.

MP: 100–102 °C.

TLC: R_f 0.35 (15:1 Hex/EtOAc).

1-(HYDROXYMETHYL)CYCLOPENTENE METHYL CARBONATE (2159)



2309 ***2159***

[*MJJ-IV-92*] A solution of 1-(hydroxymethyl)cyclopentene[401,402] (**2309**) (4.09 g, 41.7 mmol, 1.0 equiv) in CH_2Cl_2 (150 mL) was cooled to 0 °C and treated sequentially with pyridine (5.1 mL, 4.99 g, 63.1 mmol, 1.5 equiv) and methyl chloroformate (4.3 mL, 5.26 g, 55.6 mmol, 1.3 equiv). After having been stirred at 0 C for 1.5 h, the reaction mixture was quenched by the addition of satd aq NH_4Cl (100 mL) and diluted with Et_2O (100 mL). The layers were shaken and separated, the aqueous phase was extracted with Et_2O (2x), and the combined organic extracts were washed with brine (1x), dried ($MgSO_4$), and filtered. The filtrate was concentrated to partial dryness at the rotavap, the flask was fitted with a short-path distillation apparatus, and the remaining solvent was removed by distillation at atmospheric pressure. Purification of the crude residue thus obtained by

---

401 Prepared according to the literature procedure [*MJJ-IV-91*]: Pal, P. R.; Skinner, C. G.; Dennis, R. L.; Shive, W. Cyclopentanealanine and 1-Cyclopentene-1-alanine, Inhibitory Analogs of Leucine and Phenylalanine. *J. Am. Chem. Soc.* **1956**, *78*, 5116–5118.

402 **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.62 (dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 1.5, 3.5 Hz, 1H, C=C*H*), 4.20 (ddddddd, *J* = 1.0, 1.0, 1.0, 1.0, 1.0, 1.0, 7.5 Hz, 2H, CH_2OH), 2.38-2.30 (m, 4H, CH_2CH$_2$CH_2), 1.95-1.89 (m, 2H, CH$_2$CH_2CH$_2$), and 1.37 (ddd, *J* = 1.0, 6.0, 6.0 Hz, 1H, CH$_2$O*H*).
TLC: R_f 0.09 (6:1 Hex/EtOAc).
BP: 89–90 °C @ 25 mmHg (lit.[401] 75 °C @ 20 mmHg).

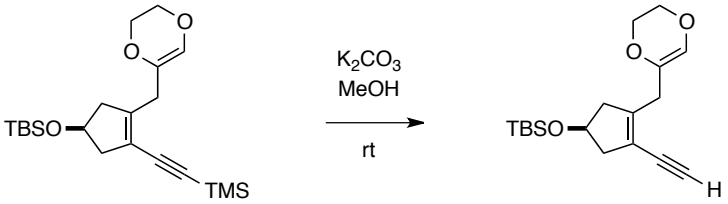
vacuum distillation (bp 94–96 °C @ 16 mmHg) provided the title compound as a clear, colorless liquid (6.21 g, 39.8 mmol, 95% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.73-5.70 (nfom, 1H, C=C*H*), 4.71-4.69 (nfom, 2H, $CH_2OCO_2CH_3$), 3.79 (s, 3H, $CH_2OCO_2CH_3$), 2.39-2.30 (m, 4H, $CH_2CH_2CH_2$), and 1.97-1.87 (m, 2H, $CH_2CH_2CH_2$).

GC / LR EI-MS [5025015]: t_R 5.30 min; *m*/*z* (rel. int.) 156 (0.4, $M^{+\bullet}$), 111 (4), 97 (6, $M^{+\bullet}$–$CO_2CH_3^{\bullet}$), 81 (35, $M^{+\bullet}$–$OCO_2CH_3^{\bullet}$), 80 (86), 79 (100), 77 (21), 67 (11, $M^{+\bullet}$–$CH_2OCO_2CH_3^{\bullet}$), and 59 (7).

TLC: R_f 0.43 (6:1 Hex/EtOAc).

(±)-*TERT*-BUTYL((3-((5,6-DIHYDRO-1,4-DIOXIN-2-YL)METHYL)-4-ETHYNYLCYCLO-PENT-3-EN-1-YL)OXY)DIMETHYLSILANE (2175)



2150 ***2175***

[*MJJ-IV-24/25111/VII-113*] Solid K_2CO_3 (123 mg, 0.89 mmol, 1.4 equiv) was added in a single portion to a solution of the TMS alkyne **2150** (249 mg, 0.63 mmol, 1.0 equiv) in anhydrous MeOH (5.0 mL). After having been stirred at rt overnight, the reaction mixture was concentrated *in vacuo*, suspended in Et_2O, and poured onto brine (15 mL). The layers were shaken and separated, the aqueous phase was extracted with Et_2O (3x), and the combined organic extracts were dried ($MgSO_4$) and filtered. Evaporation of the filtrate to dryness and purification of the crude residue by medium pressure liquid chromatography (SiO_2, 98:2 Hex/EtOAc) provided the title compound (149 mg, 0.46 mmol, 73% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.87 (dd, *J* = 1.0, 1.0 Hz, 1H, CH_2C=C*H*), 4.48 [dddd, *J* = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 4.08-3.97 (AA'BB', 4H, OCH_2CH_2O), 3.11 (s, 1H, C≡C*H*), 2.94 (ABq, $\Delta\nu_{AB}$ = 15.0 Hz, J_{AB} = 16.5 Hz, 2H, CH_2C=CH), 2.75 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 6.5, 16.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.66 [ddddddd, *J* = 1.5, 1.5, 1.5, 1.5, 1.5, 7.0, 17.5 Hz, 1H, CH_2CH(OTBS)CH_2], 2.45 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 4.0, 16.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.35 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 4.0, 17.5 Hz, 1H, CH_2CH(OTBS)CH_2], 0.88 [s, 9H, (CH_3)$_3$CSi$(CH_3)_2$], and 0.05 [s, 6H, $(CH_3)_3$CSi(CH_3)$_2$].

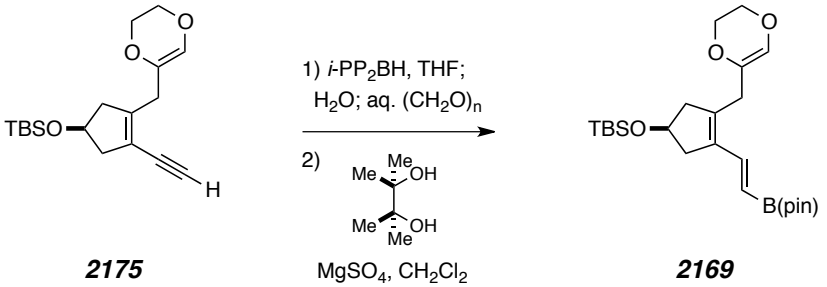
^{13}C NMR (125 MHz, $CDCl_3$): δ 147.5, 135.0, 123.1, 116.5, 81.1, 80.2, 71.2, 64.8, 64.0, 46.4, 45.2, 31.7, 26.0, 18.3, -4.60, and -4.62.

IR (neat): 3311, 3288, 2953, 2929, 2857, 2094, 1685, 1252, 1196, 1147, 1090, 1066, 896, 837, and 777 cm^{-1}.

HR ESI-MS: $C_{18}H_{28}O_3Si$ $[M+Na]^+$ requires 343.1700; found 343.1758.

TLC: R_f 0.56 (6:1 Hex/EtOAc).

(±)-(*E*)-*TERT*-BUTYL((3-((5,6-DIHYDRO-1,4-DIOXIN-2-YL)METHYL)-4-(2-(4,4,5,5-TETRAMETHYL-1,3,2-DIOXABOROLAN-2-YL)VINYL)CYCLOPENT-3-EN-1-YL)OXY)-DIMETHYLSILANE (2169)



2175 ***2169***

[*MJJ-IV-26/53/VII-117*] A stock solution of *i*-PP_2BH (0.71 M in THF) was prepared as described previously. An aliquot of this stock solution (320 μL, ~0.227 mmol, ~1.3

equiv) was added dropwise to a solution of the alkyne **2175** (55 mg, 0.172 mmol, 1.0 equiv) in dry THF (600 μL) at 0 °C and, after the addition was complete, the reaction mixture was allowed to reach rt. After having been stirred at this temperature for 10 min, TLC analysis of the reaction mixture indicated that the starting material had been consumed. The reaction mixture was cooled to 0 °C, slowly quenched by the addition of H_2O (100 μL), and then allowed to warm to rt. Stirring was continued for 1.5 h, at which point the reaction mixture was treated with paraformaldehyde (500 μL, 37 wt% in H_2O). After having been stirred at rt overnight, the reaction mixture was diluted with EtOAc and poured onto brine (15 mL). The layers were shaken and separated, and the aqueous layer was extracted with EtOAc (2x) and CH_2Cl_2 (2x). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed *in vacuo* to leave a yellow oil that was used immediately without further purification.

[*MJJ-IV-27/55/VII-117*] A solution of the crude boronic acid (0.172 mmol theoretical) in CH_2Cl_2 (3.0 mL) was treated sequentially with pinacol (27.5 mg, 0.23 mmol, 1.3 equiv) and anhydrous $MgSO_4$ (excess), and the resulting suspension was maintained overnight with stirring. The reaction mixture was diluted with CH_2Cl_2, filtered through a short pad of CELITE®, and the filtrate was concentrated *in vacuo*. The residue thus obtained was filtered through SiO_2 and concentrated *in vacuo* (2x, 1:1 Hex/EtOAc then 8:1 Hex/EtOAc). Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 9:1 Hex/EtOAc) provided the title compound (49 mg, 0.109 mmol, 64% yield over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 [d, J = 18.0 Hz, 1H, C*H*=CHB(pin)], 5.82 (s, 1H, CH_2C=C*H*), 5.42 [d, J = 18.0 Hz, 1H, CH=C*H*B(pin)], 4.46 [dddd, J = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 4.06-3.96 (AA'BB', 4H, OCH_2CH_2O), 2.95 (ABq, $\Delta\nu_{AB} < 0.5$ Hz, J_{AB} = 16.5 Hz, 2H, CH_2C=CH), 2.77 [dd, J = 7.0, 16.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.73 [dd, J = 7.0, 18.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.47-2.41 [m, 2H, overlapping

C*H*$_2$CH(OTBS)C*H*$_2$], 1.28 [s, 12H, OC(C*H*$_3$)$_2$C(C*H*$_3$)$_2$O], 0.88 [s, 9H, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$], and 0.05 [s, 6H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$].

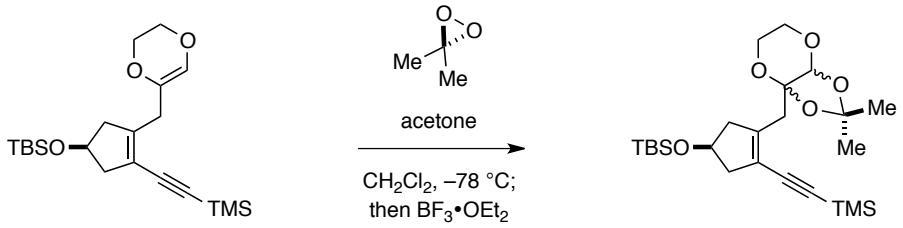
^{13}C NMR (125 MHz, $CDCl_3$): δ 142.7, 139.6, 135.4, 135.1, 123.1, 83.2, 70.7, 64.8, 64.0, 47.1, 42.7, 29.9, 26.1, 25.0, 24.9, 18.3, -4.5, and -4.6.

IR (neat): 2976, 2954, 2929, 2857, 1685, 1632, 1599, 1381, 1346, 1321, 1252, 1194, 1144, 1090, 1064, 838, and 777 cm^{-1}.

HR ESI-MS: $C_{24}H_{41}BO_5Si$ $[M+Na]^+$ requires 471.2709; found 471.2764.

TLC: R_f 0.37 (6:1 Hex/EtOAc).

(±)-*TERT*-BUTYL((3-((2,2-DIMETHYLTETRAHYDRO-[1,3]DIOXOLO[4,5-*b*][1,4]DIOXIN-3A-YL)METHYL)-4-(TRIMETHYLSILYLETHYNYL)CYCLOPENT-3-EN-1-YL)OXY)DIMETHYL-SILANE (2186)



2150 ***2186***

[*MJJ-IV-157*] A pre-dried (activated 4Å MS) solution of DMDO (400 µL, 39 µmol, 1.4 equiv, 0.097 M in acetone) was added dropwise to a solution of **2150** (11.1 mg, 28 µmol, 1.0 equiv) in dry CH_2Cl_2 (300 µL) at –78 °C, and the resulting mixture was allowed to stir at this temperature for 5 min. An aliquot of a stock solution of freshly distilled BF_3•OEt_2 (100 µL, 30 µmol, 1.1 equiv, 0.3 M in CH_2Cl_2) was then introduced and, after having been stirred for 30 min, the reaction mixture was quenched at –78 °C by the addition of satd aq NH_4Cl. The resulting mixture was warmed to rt, filtered through CELITE®, and the layers were shaken and separated. The aqueous phase was extracted

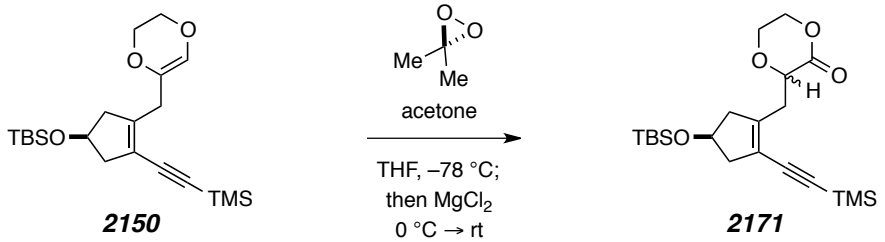
with CH_2Cl_2 (3x), and the combined organic extracts were dried ($MgSO_4$) and filtered. Concentration of the filtrate under reduced pressure and purification of the crude residue by medium pressure liquid chromatography (SiO_2, 20:1 Hex/EtOAc) provided the title compound (7.4 mg, 15.8 μmol, 57% yield, *dr* 1.2:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.163 (s, 1H), 5.157 (s, 1H), 4.45 [dddd, J = 4.0, 4.0, 7.5, 7.5 Hz, 1H, C*H*(OTBS)], 4.43 [dddd, J = 4.0, 4.0, 6.5, 6.5 Hz, 1H, C*H*(OTBS)], 3.98-3.88 (m, 4H, OCH_2CH_2O), 3.81-3.76 (m, 1H, OCH_2CH_2O), 3.74-3.70 (m, 1H, OCH_2CH_2O), 3.66-3.56 (m, 2H, OCH_2CH_2O), 2.79 [ABq, $\Delta\nu_{AB}$ = 90.8 Hz, J_{AB} = 14.0 Hz, 2H, CH_2C(O$_2$)C], 2.75 [ABq, $\Delta\nu_{AB}$ = 46.4 Hz, J_{AB} = 14.0 Hz, 2H, CH_2C(O$_2$)C], 2.85-2.66 [m, 4H, overlapping CH_2CH(OTBS)CH_2], 2.53-2.41 [m, 4H, overlapping CH_2CH(OTBS)CH_2], 1.613 [s, 3H, OC(CH_3)$_2$O], 1.606 [s, 3H, OC(CH_3)$_2$O], 1.44 [s, 3H, OC(CH_3)$_2$O], 1.43 [s, 3H, OC(CH_3)$_2$O], 0.873 [s, 9H, (CH_3)$_3$CSi(CH$_3$)$_2$], 0.870 [s, 9H, (CH_3)$_3$CSi(CH$_3$)$_2$], 0.18 [s, 18H, overlapping C≡CSi(CH_3)$_3$], 0.045 [s, 3H, (CH$_3$)$_3$CSi(CH_3)$_2$], 0.041 [s, 6H, (CH$_3$)$_3$CSi(CH_3)$_2$], and 0.038 [s, 3H, (CH$_3$)$_3$CSi(CH_3)$_2$].

HR ESI-MS: $C_{24}H_{42}O_5Si_2$ $[M+Na]^+$ requires 489.2463; found 489.2464.

TLC: R_f 0.62 (4:1 Hex/EtOAc).

(±)-3-((4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(TRIMETHYLSILYLETHYNYL)CYCLOPENT-1-EN-1-YL)METHYL)-1,4-DIOXAN-2-ONE (2171)



[*MJJ-IV-154*] Activated, powdered 4Å MS (~2 spatula tips) was added to a solution of **2150** (5.1 mg, 13 μmol, 1.0 equiv) in dry THF (500 μL), and resulting suspension was

stirred at rt for 15 min. After having been cooled to –78 °C, a pre-dried (activated 4Å MS) solution of DMDO (150 μL, 15 μmol, 1.2 equiv, 0.097 M in acetone) was slowly added dropwise and, after having been stirred for 2 min, TLC analysis indicated the clean formation of a new material [R_f 0.19 (4:1 Hex/EtOAc)] that was presumed to be the hydrolysis (on SiO_2) product of the intermediate epoxide. The reaction mixture was allowed to warm to 0 °C and was treated with anhydrous $MgCl_2$ (16.5 mg, 173 μmol, 13 equiv). Stirring was continued at this temperature for 5 min and then at rt for 1 h 15 min, at which point the formation of a new, slightly less polar material was observed by TLC analysis. The reaction mixture was diluted with THF, filtered through CELITE®, concentrated *in vacuo*, and filtered once again, this time through SiO_2 (1:1 Hex/EtOAc). Evaporation of the filtrate to dryness and purification of the crude residue by medium pressure liquid chromatography (SiO_2, 5:1 Hex/EtOAc) provided the title compound (6.5 mg, 11.1 μmol, 86% yield corrected for purity, *dr* 1.3:1) that, on the basis of ^{1}H NMR and GC-MS analyses, was contaminated with a single Bu_3SnX species (residual from the preceding π-allyl Stille cross-coupling reaction). Assuming that Bu_3SnCl was the principal contaminant, then the desired product was judged to be *ca.* 70% pure.

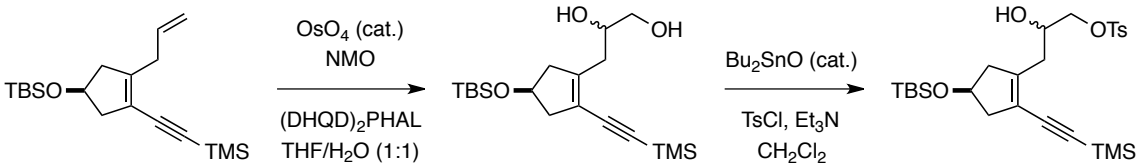
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.55-4.40 [m, 8H, overlapping C*H*(OTBS) and $CH_2CHCO_2CH_2CH_2O$], 4.02-3.98 (m, 2H, $CH_2CHCO_2CH_2CH_2O$), 3.83-3.77 (m, 2H, $CH_2CHCO_2CH_2CH_2O$), 2.94-2.88 (m, 4H, $CH_2CHCO_2CH_2CH_2O$), 2.77-2.62 [m, 4H, overlapping $CH_2CH(OTBS)CH_2$], 2.49-2.32 [m, 4H, overlapping $CH_2CH(OTBS)CH_2$], 0.874 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.873 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.19 [s, 18H, $Si(CH_3)_3$], 0.048 [s, 6H, $(CH_3)_3CSi(CH_3)_2$], and 0.045 [s, 6H, $(CH_3)_3CSi(CH_3)_2$].

GC / LR EI-MS [5025015]: t_R 12.08 min; *m*/*z* (rel. int.) 351 [33, $M^{+\bullet}$–$C(CH_3)_3^{\bullet}$], 307 (2, $M^{+\bullet}$–$C_4H_5O_3^{\bullet}$), 279 (10), 205 (8), 189 (9), 175 (9), 159 (6), 147 (17), 133 (6), 131 (5), 115 (8), 103 (6), 75 (100), 73 (69), and 57 (47).

HR ESI-MS: $C_{21}H_{36}O_4Si_2$ $[M+Na]^+$ requires 431.2044; found 431.2043.

TLC: R_f 0.29 (4:1 Hex/EtOAc).

(±)-3-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(TRIMETHYLSILYLETHYNYL)CYCLOPENT-1-EN-1-YL)-2-HYDROXYPROPYL 4-METHYLBENZENESULFONATE (2207) via **(±)-3-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(TRIMETHYLSILYLETHYNYL)CYCLOPENT-1-EN-1-YL)PROPANE-1,2-DIOL (2206)**



2149 ***2206*** ***2207***

[*MJJ-V-89/92*] A solution of OsO_4 (100 µL, 0.014 mmol, 3.5 mol% 0.135 M in H_2O) was added via WIRETROL® to a mixture of the 1,4-diene **2149** (129 mg, 0.39 mmol, 1.0 equiv), $(DHQD)_2PHAL$ (20.5 mg, 0.026 mmol, 7.0 mol%), and NMO (45.4 mg, 0.39 mmol, 1.0 equiv) in THF/H_2O (1:1, 4.0 mL). After having been stirred overnight at rt, the reaction mixture was diluted with EtOAc and quenched by the addition of satd aq $Na_2S_2O_3$. The layers were shaken and separated, the aqueous phase was extracted with EtOAc (3x), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 35% EtOAc/Hex) provided unreacted **2149** (52 mg, 0.16 mmol) followed by the diol **2206** (39 mg, 0.11 mmol, *dr* 1:1).

Unreacted **2149** was processed in a similar manner to that described above by reaction with OsO_4 (50 µL, 6.8 µmol, 4.0 mol%, 0.135 M in H_2O), $(DHQD)_2PHAL$ (10.0 mg, 12.8 µmol, 8.0 mol%), and NMO (18.2 mg, 0.16 mmol, 1.0 equiv) in THF/H_2O (2:1, 3 mL). Reaction work-up provided a crude residue that was purified by two rounds of medium pressure liquid chromatography (SiO_2, 35% EtOAc/Hex then 0.1% EtOAc/Hex) to provide the diol **2206** (16 mg, 0.04 mmol, *dr* 1:1) and then unreacted **2149** (25 mg, 0.07 mmol). The combined isolated yield of **2206** after one recycle was 39% (48% based on recovered **2149**).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.413 [dddd, *J* = 4.0, 4.0, 7.5, 7.5 Hz, 1H, C*H*(OTBS)], 4.406 [dddd, *J* = 3.5, 3.5, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.89-3.82 [m, 2H, $CH_2CH(OH)CH_2OH$], 3.62-3.45 [overlapping ABXY patterns, 2H, $CH_2CH(OH)–CH_2OH$], 2.72-2.58 [m, 4H, $CH_2CH(OH)CH_2OH$], 2.52-2.47 [m, 2H, $CH_2CH(OTBS)CH_2$], 2.45-2.27 [m, 6H, $CH_2CH(OTBS)CH_2$], 2.16 [d, *J* = 5.0 Hz, 1H, CH(O*H*)], 2.12 [d, *J* = 5.5 Hz, 1H, CH(O*H*)], 1.98 (dd, *J* = 5.0, 7.5 Hz, 1H, CH_2OH), 1.95 (dd, *J* = 5.0, 7.5 Hz, 1H, CH_2OH), 0.832 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.827 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.157 [s, 9H, $Si(CH_3)_3$], 0.155 [s, 9H, $Si(CH_3)_3$], 0.008 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], 0.005 [s, 6H, $(CH_3)_3CSi(CH_3)_2$], and 0.000 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

TLC: R_f 0.44 (1:1 Hex/EtOAc).

[*MJJ-V-73/95*] A solution of *p*-toluenesulfonyl chloride (TsCl) was prepared by dissolving the reagent (63.4 mg, 0.33 mmol) in dry CH_2Cl_2 (0.73 mL). The resulting stock solution, which was 0.46 M [TsCl], was used immediately in the following procedure.

An aliquot of the TsCl stock solution (100 μL, 45.6 μmol, 1.0 equiv) was added to a mixture of the diol **2206** (16.1 mg, 43.7 μmol, 1.0 equiv), Et_3N (5.8 mg, 57.3 μmol, 1.3 equiv), and Bu_2SnO (1.8 mg, 7.2 μmol, 17 mol%) in dry CH_2Cl_2 (0.5 mL). Two additional aliquots of the TsCl stock solution were added after 3.0 h (10 μL) and 3.5 h (10 μL), at which point the reaction had reached full conversion. The reaction mixture was diluted with 1:1 Hex/EtOAc and was flushed through a short bed of SiO_2. The filtrate was evaporated to dryness and again filtered through SiO_2 (1:1 Hex/EtOAc). After removal of the solvent *in vacuo*, the resulting crude residue was purified by medium pressure liquid chromatography (SiO_2, 8:1 Hex/EtOAc) to provide the primary tosylate **2207** (18.4 mg, 35.2 μmol, 81% yield, *dr* 1:1).

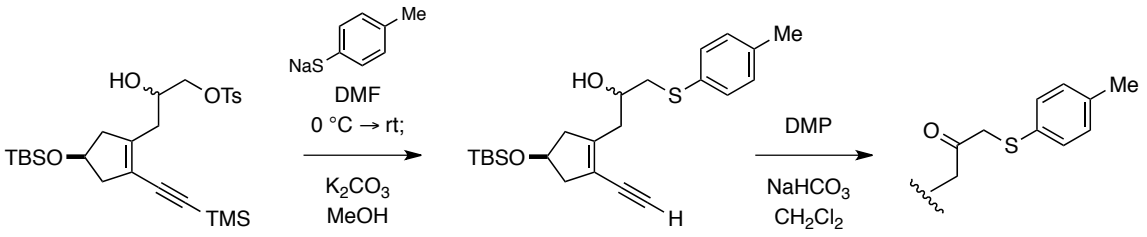
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82-7.79 (m, 4H, $OSO_2C_6H_4CH_3$), 7.35 (app d, *J* = 8.5 Hz, 4H, $OSO_2C_6H_4CH_3$), 4.43 [dddd, *J* = 3.5, 3.5, 7.5, 7.5 Hz, 1H, C*H*(OTBS)], 4.42

[dddd, J = 4.0, 4.0, 7.5, 7.5 Hz, 1H, C*H*(OTBS)], 4.09-4.03 [m, 4H, CH_2CH(OH)–CH_2OTs], 3.94-3.90 [m, 2H, CH_2CH(OH)CH_2OTs], 2.73-2.59 [m, 4H, CH_2CH(OH)–CH_2OTs], 2.45 (s, 6H, $OSO_2C_6H_4CH_3$), 2.47-2.37 [m, 6H, CH_2CH(OTBS)CH_2], 2.36-2.28 [m, 2H, CH_2CH(OTBS)CH_2], 0.86 [s, 18H, $(CH_3)_3CSi(CH_3)_2$], 0.17 [s, 18H, $C{\equiv}CSi(CH_3)_3$], 0.04 [s, 6H, $(CH_3)_2CSi(CH_3)_2$], and 0.03 [s, 6H, $(CH_3)_2CSi(CH_3)_2$].

HR ESI-MS: $C_{26}H_{42}O_5SSi_2$ $[M+Na]^+$ requires 545.2184; found 545.2207.

TLC: R_f 0.68 (40% EtOAc/Hex).

(±)-1-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-ETHYNYLCYCLOPENT-1-EN-1-YL)-3-(*P*-TOLYLTHIO)PROPAN-2-ONE (2209) via **(±)-1-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-ETHYNYLCYCLOPENT-1-EN-1-YL)-3-(*P*-TOLYLTHIO)PROPAN-2-OL (2208)**



2207 ***2208*** ***2209***

[*MJJ-V-91*] A stock solution of sodium 4-methylbenzenethiolate (*p*-TolSNa) was prepared in the following manner. An arbitrary amount of wet NaH (60% dispersion in mineral oil) was quickly added to a round-bottom flask that had previously been flame-dried and tared. The solid was then washed with dry pentane (3 x ~5 mL) and the residual solvent was removed under a stream of dry N_2 to leave behind dry NaH (214 mg, 8.92 mmol). The round-bottom flask was charged with dry DMF (15.0 mL) and cooled to 0 °C. With vigorous stirring, a solution of *p*-TolSH (1.29 g, 10.41 mmol) in dry DMF (5.0 mL) was added dropwise such that H_2 evolution occurred at a continuous, but controlled, rate. Once gas evolution ceased, the cooling bath was removed and the

reaction mixture was stirred briefly at rt. This solution, which was 0.45 M [*p*-TolSNa], was utilized in the following procedure.

A crude sample of the tosylate **2207** (100 μmol theoretical) that had been prepared in a separate experiment [*MJJ-V-90*] was dissolved in dry DMF (1.0 mL) and treated with an aliquot of the *p*-TolSNa stock solution (650 μL, 0.29 mmol, 2.9 equiv). After having been stirred for 15 h at rt, another portion of *p*-TolSNa (650 μL, 0.29 mmol, 5.8 equiv total) was added and stirring was continued an additional 3 h. The reaction mixture was diluted with EtOAc, washed with 1:1 brine/H_2O (2x), and the combined aqueous washings were back-extracted with EtOAc (1x). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 15:1 Hex/EtOAc) provided material (35 mg) that, on the basis of LC-MS analysis, was a mixture of silylated and desilylated alkynes.

[*MJJ-V-93*] Solid, anhydrous K_2CO_3 (3.9 mg, 28.2 μmol) was added to a solution of the above prepared mixture of products in anhydrous MeOH (2.0 mL). After having been stirred overnight at rt, the reaction mixture was evaporated to partial dryness at the rotavap. The resulting residue was suspended in EtOAc, poured onto brine, and the layers were shaken and separated. The aqueous phase was extracted with EtOAc (2x), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography provided the desilylated sulfenyl alcohol **2208** (28 mg, 69.5 μmol, 69% yield over 3 steps from the diol **2206**, *dr* 1:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.28 (m, 4H, $SC_6H_4CH_3$), 7.12-7.09 (m, 4H, $SC_6H_4CH_3$), 4.46 [dddd, *J* = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 4.44 [dddd, *J* = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.86-3.78 [m, 2H, C*H*(OH)], 3.11 (dd, *J* = 4.0, 14.0 Hz, 1H, $CH_2SC_6H_4CH_3$), *ca.* 3.10 [2H, C≡C*H* (obscured by resonances at δ 3.11 and 3.09)], 3.09 (dd, *J* = 4.0, 14.0 Hz, 1H, $CH_2SC_6H_4CH_3$), 2.86 (dd, *J* = 8.5, 14.0 Hz, 1H, $CH_2SC_6H_4CH_3$), 2.83 (dd, *J* = 8.5, 14.0 Hz, 1H, $CH_2SC_6H_4CH_3$), 2.76-2.54 [m, 8H, overlapping CH_2CH(OH) and CH_2CH(OTBS)CH_2], 2.46 [d, *J* = 3.5 Hz, 1H, CH(O*H*)],

2.44 [d, J = 3.0 Hz, 1H, CH(O*H*)], 2.45-2.27 [m, 4H, C*H*$_2$CH(OTBS)C*H*$_2$], 2.32 (s, 6H, SC$_6$H$_4$C*H*$_3$), 0.871 [s, 9H, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$], 0.865 [s, 9H, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$], 0.045 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$], 0.042 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$], 0.038 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$], and 0.035 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$].

GC / LR EI-MS [5025015]: t_R 13.11 min; *m*/*z* (rel. int.) 402 (8, $M^{+\bullet}$), 345 [15, $M^{+\bullet}$–C(CH$_3$)$_3^{\bullet}$], 270 {31, $M^{+\bullet}$–[(CH$_3$)$_3$CSi(CH$_3$)$_2$]OH}, 265 (47, $M^{+\bullet}$–C$_8$H$_9$S$^{\bullet}$), 253 (21), 238 (11), 237 (14), 236 (14), 226 (22), 221 (30, $M^{+\bullet}$–C$_{10}$H$_{13}$OS$^{\bullet}$), 219 (28), 179 (15), 166 (29), 149 (66), 137 (100), 129 (64), 123 (37), 105 (35), 104 (44), 103 (31), 91 (38), and 75 (97).

[*MJJ-V-81*] A solution of the Dess–Martin periodinane (DMP) was prepared by dissolving the reagent (47.4 mg, 0.122 mmol) in dry CH_2Cl_2 (1.0 mL). The resulting stock solution, which was 0.11 M [DMP], was utilized immediately in the following procedure.

A sample of the purified alcohol **2208** (10.7 μmol theoretical) that had been prepared in a separate experiment [*MJJ-V-80*] was dissolved in dry CH_2Cl_2 (300 μL) and cooled to 0 °C. Then, solid $NaHCO_3$ (spatula tip) and an aliquot of the DMP stock solution (100 μL, 11.2 μmol, 1.0 equiv) were sequentially added. After having been stirred at 0 °C for 2 h, the reaction mixture was quenched by the addition of solid $Na_2S_2O_3$ and $NaHCO_3$. Water was then added until a clear, two-phase system was produced. The layers were shaken and separated, the aqueous phase was extracted with CH_2Cl_2 (2x), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the crude residue by flash chromatography (98:2 Hex/EtOAc) provided a sample of the β-keto sulfide **2209** (5.4 mg) that was judged to be > 80% pure on the basis of ^{1}H NMR and GC-MS analyses.

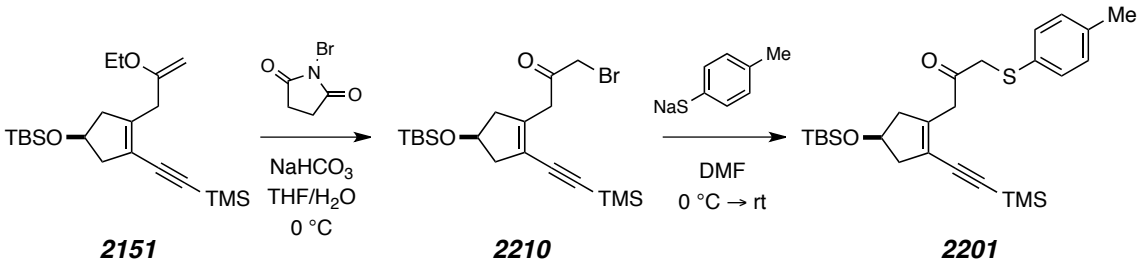
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, J = 8.5 Hz, 2H, SC$_6$*H*$_4$CH$_3$), 7.10 (d, J = 8.5 Hz, 2H, SC$_6$*H*$_4$CH$_3$), 4.45 [dddd, J = 4.0, 4.0, 7.5, 7.5 Hz, 1H, C*H*(OTBS)], 3.67 [ABq, $\Delta\nu_{AB}$

= 18.7 Hz, J_{AB} = 15.0 Hz, 2H, $CH_2C(O)CH_2SC_6H_4CH_3$], 3.56 [ABX_4, $\Delta\nu_{AB}$ = 36.7 Hz, J_{AB} = 15.5 Hz, $J_{AX} = J_{BX}$ = 1.5 Hz, 2H, $CH_2C(O)CH_2SC_6H_4CH_3$], 3.14 (s, 1H, C≡C*H*), 2.74 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 7.0, 18.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.62 [ddddddd, *J* = 1.5, 1.5, 1.5, 1.5, 1.5, 7.0, 17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.44 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 4.5, 17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.31 (s, 3H, $SC_6H_4CH_3$), 2.26 [br dd, *J* = 3.5, 17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 0.86 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.04 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.03 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

GC / LR EI-MS [5029021]: t_R 11.08 min; *m*/*z* (rel. int.) 268 {13, $M^{+\bullet}$–$[(CH_3)_3CSi(CH_3)_2]OH$}, 145 (100), 115 (12), and 91 (7).

TLC: R_f *ca.* 0.33 (20:1 EtOAc/Hex).

(±)-1-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(TRIMETHYLSILYLETHYNYL)CYCLOPENT-1-EN-1-YL)-3-(*P*-TOLYLTHIO)PROPAN-2-ONE (2201) via **(±)-1-BROMO-3-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(TRIMETHYLSILYL-ETHYNYL)CYCLOPENT-1-EN-1-YL)PROPAN-2-ONE (2210)**



2151 ***2210*** ***2201***

[*MJJ-V-101/166/VII-94*] To a solution of the enol ether **2151** (177 mg, 0.47 mmol, 1.0 equiv) in THF/H_2O (9:1, 5.0 mL) at 0 °C were added sequentially $NaHCO_3$ (118 mg, 1.41 mmol, 3.0 equiv) and recrystallized *N*-bromosuccinimide (85 mg, 0.48 mmol, 1.0 equiv). After having been stirred at 0 °C for 50 min, the reaction mixture was diluted with Et_2O and poured onto H_2O (20 mL). A small volume of brine was added, the layers were shaken and separated, and the aqueous layer was extracted with Et_2O (2x). The

combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 98:2 Hex/EtOAc) provided the α-bromo ketone **2210** as a yellow oil (156 mg, 0.36 mmol, 78% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.47 [dddd, J = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.99 [ABq, $\Delta\nu_{AB}$ = 8.4 Hz, J_{AB} = 13.0 Hz, 2H, $CH_2C(O)CH_2Br$], 3.58 [ABX_4 (app dddd), $\Delta\nu_{AB}$ < 0.5 Hz, J = 1.5, 1.5, 1.5, 1.5 Hz, 2H, $CH_2C(O)CH_2Br$], 2.76 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 6.5, 16.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.69 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 6.5, 17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.46 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 3.5, 16.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.32 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 4.0, 17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 0.87 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.21 [s, 9H, $Si(CH_3)_3$], 0.05 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.04 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 198.1, 141.5, 121.1, 100.7, 100.4, 71.1, 46.4, 45.9, 42.2, 34.2, 26.0, 18.3, 0.2, and -4.7.

IR (neat): 2956, 2930, 2898, 2857, 2142, 1719, 1251, 1097, 1063, 842, and 777 cm^{-1}.

HR ESI-MS: $C_{19}H_{33}BrO_2Si_2$ $[M+H]^+$ requires 429.1275; found 429.1291.

TLC: R_f 0.33 (20:1 Hex/EtOAc).

[*MJJ-V-157/160/170*] A stock solution of *p*-TolSNa was prepared as just described from dry NaH (167 mg, 6.96 mmol) and *p*-TolSH (1.03 g, 8.25 mmol) in dry DMF (17.0 mL total volume). The resulting solution was 0.41 M [*p*-TolSNa].

An aliquot of the *p*-TolSNa solution (1.1 mL, 0.451 mmol, 1.4 equiv) was added dropwise to a 0 °C solution of the α-bromo ketone **2210** (138 mg, 0.32 mmol, 1.0 equiv) in dry DMF (3.0 mL). Once starting material consumption was observed by LC-MS analysis, the reaction mixture diluted with EtOAc and poured onto 1:1 brine/H_2O. The layers were shaken and separated, and the organic layer was washed again with 1:1

brine/H_2O. The combined aqueous washings were then back-extracted with EtOAc (1x), and then the combined organic extracts were washed with brine (1x). The organic material was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 98:2 Hex/EtOAc) provided the β-keto sulfide **2201** as a clear, colorless oil (132 mg, 0.28 mmol, 87% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (br d, J = 8.0 Hz, 2H, $SC_6H_4CH_3$), 7.09 (br d, J = 8.0 Hz, 2H, $SC_6H_4CH_3$), 4.43 [dddd, J = 4.0, 4.0, 7.0, 7.0 Hz, 1H C*H*(OTBS)], 3.67 [ABq, $\Delta\nu_{AB}$ = 21.2 Hz, J_{AB} = 15.0 Hz, 2H, $CH_2C(O)CH_2SC_6H_4CH_3$], 3.55 [ABq, $\Delta\nu_{AB}$ = 35.3 Hz, J_{AB} = 14.5 Hz, 2H, $CH_2C(O)CH_2SC_6H_4CH_3$], 2.73 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 7.0, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.61 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 6.5, 17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.44 [ddddd, J = 2.0, 2.0, 2.0, 3.5, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.31 (s, 3H, $SC_6H_4CH_3$), 2.26 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 4.0, 18.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 0.86 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.20 [s, 9H, $Si(CH_3)_3$], 0.03 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.02 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

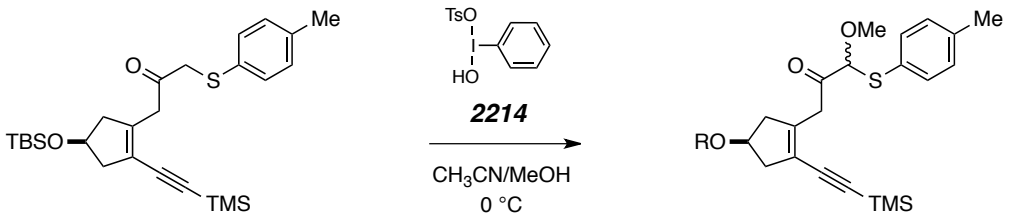
^{13}C NMR (125 MHz, $CDCl_3$): δ 201.6, 142.3, 137.4, 130.94, 130.90, 130.0, 120.4, 101.1, 99.8, 71.2, 46.3, 45.9, 44.4, 42.9, 26.0, 21.2, 18.3, 0.2, and -4.7.

IR (neat): 2955, 2929, 2898, 2856, 2141, 1714, 1250, 1093, 1062, and 842 cm^{-1}.

HR ESI-MS: $C_{26}H_{40}O_2SSi_2$ $[M+H]^+$ requires 473.2360; found 473.2370.

TLC: R_f 0.42 (15:1 Hex/EtOAc).

(±)-3-(4-HYDROXY-2-(TRIMETHYLSILYLETHYNYL)CYCLOPENT-1-EN-1-YL)-1-METHOXY-1-(*P*-TOLYLTHIO)PROPAN-2-ONE (2216)



2201 ***2215*** (R = TBS)
2216 (R = H)

[*MJJ-V-182/192/VII-96*] A flame dried 13 x 100 mm culture tube was charged with dry CH_3CN (350 μL), dry MeOH (350 μL), and the β-keto sulfide **2201** (32.1 mg, 67.9 μmol, 1.0 equiv). After having been cooled to 0 °C, the resulting solution was treated with PhI(OH)OTs (28.9 mg, 73.7 μmol, 1.1 equiv). The reaction mixture was maintained with stirring at 0 °C for a period of 50 min, during which time the formation of the intermediate TBS ether **2215** and its rapid conversion to **2216** was observed by TLC analysis. At this point, the reaction mixture was diluted with EtOAc and quenched by the addition of 1:1 satd aq $NaHCO_3$/satd aq $Na_2S_2O_3$. The resulting mixture was warmed to rt, stirred vigorously for 30 min, and then poured onto brine. The layers were shaken and separated, the aqueous phase was extracted with EtOAc (2x), and the combined organic extracts were washed with brine (1x), dried ($MgSO_4$), and filtered. Concentration of the filtrate *in vacuo* and purification of the crude residue by medium pressure liquid chromatography (SiO_2, 2:1 Hex/EtOAc) provided the title compound as a yellow oil (25 mg, 51.4 μmol, 76% yield corrected for purity, *dr* 1:1) from which trace amounts of EtOAc were difficult to remove.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, J = 8.0 Hz, 4H, overlapping $SC_6H_4CH_3$), 7.11 (br d, J = 7.5 Hz, 4H, overlapping $SC_6H_4CH_3$), 5.09 [s, 1H, $CH_2C(O)CH(OCH_3)SAr$], 5.07 [s, 1H, $CH_2C(O)CH(OCH_3)SAr$], 4.47-4.39 [m, 2H, overlapping $CH(OH)$], 3.611 (s, 3H,

OC*H*$_3$), 3.609 (s, 3H, OC*H*$_3$), 3.56 [ABq (app br s), 2H, C*H*$_2$C(O)CH(OCH$_3$)SAr], 3.55 [ABq, $\Delta\nu_{AB}$ = 57.1 Hz, J_{AB} = 16.0 Hz, 2H, C*H*$_2$C(O)CH(OCH$_3$)SAr], 3.43 (d, *J* = 3.5 Hz, 1H, O*H*), 2.86-2.74 [m, 3H, overlapping C*H*$_2$CH(OH)C*H*$_2$], 2.67 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 6.0, 18.5 Hz, 1H, C*H*$_2$CH(OH)CH$_2$], 2.46 [d, *J* = 17.0 Hz, 1H, CH$_2$CH(OH)C*H*$_2$], 2.45 [d, *J* = 17.0 Hz, 1H, C*H*$_2$CH(OH)CH$_2$], 2.34 [d, *J* = 16.5 Hz, 1H, CH$_2$CH(OH)C*H*$_2$], 2.32 (s, 6H, overlapping SC$_6$H$_4$C*H*$_3$), 2.23 [d, *J* = 18.0 Hz, 1H, C*H*$_2$CH(OH)CH$_2$], 1.64 (d, *J* = 6.5 Hz, O*H*), 0.218 [s, 9H, C≡CSi(C*H*$_3$)$_3$], and 0.215 [s, 9H, C≡CSi(C*H*$_3$)$_3$].

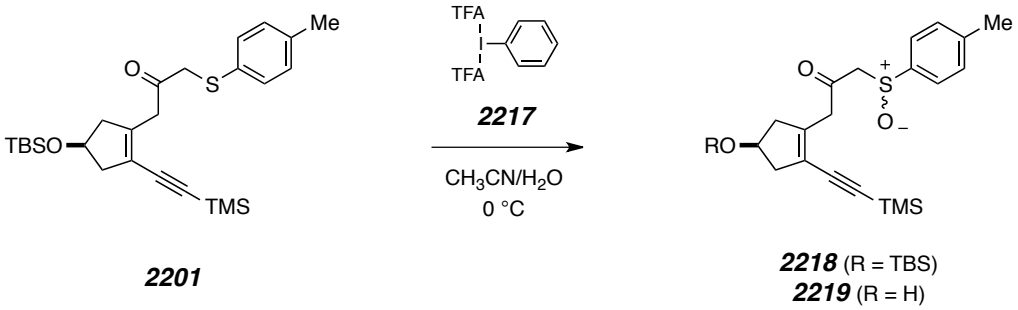
^{13}C NMR (125 MHz, $CDCl_3$): δ 198.2, 197.9, 142.5, 142.4, 139.3, 139.2, 134.72, 134.69, 131.0, 130.1, 130.04, 130.03, 126.8, 126.6, 120.4, 120.3, 101.0, 100.0, 99.9, 91.65, 91.58, 70.84, 70.82, 56.4, 46.4, 46.3, 45.94, 45.87, 40.3, 21.4, and 0.2.

IR (neat): 3448, 2956, 2925, 2830, 2139, 1721, 1249, 1078, and 855 cm^{-1}.

HR ESI-MS: $C_{21}H_{28}O_3SSi$ $[M\text{-}OCH_3]^+$ requires 357.1339; found 357.1345.

TLC: R_f (**2215**) 0.38 (9:1 Hex/EtOAc); R_f (**2216**) 0.46 (1:1 Hex/EtOAc).

(±)-1-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(TRIMETHYLSILYLETHYNYL)CYCLOPENT-1-EN-1-YL)-3-(*P*-TOLYLSULFINYL)PROPAN-2-ONE (2218)



2201 ***2218*** (R = TBS) ***2219*** (R = H)

[*MJJ-V-180/VII-115*] A room temperature solution of PIFA was prepared by dissolution of the reagent (76.3 mg, 0.177 mmol) in CH_3CN (1.0 mL) and the resulting stock solution, which was 0.177 M [PIFA], was utilized in the following procedure.

A solution of the β-keto sulfide **2201** (7.4 mg, 15.7 μmol, 1.0 equiv) in CH_3CN/H_2O (3:1, 200 μL) in a 13 x 100 mm culture tube open to air was cooled to 0 °C and treated with an aliquot of the above prepared PIFA stock solution (100 μL, 17.7 μmol, 1.1 equiv). After having been stirred at 0 °C for *ca.* 2 min, the reaction mixture was quenched by the sequential addition of satd aq $NaHCO_3$ and satd aq $Na_2S_2O_3$. The resulting mixture was diluted with EtOAc and allowed to warm to rt. The layers were separated, the aqueous phase was extracted with EtOAc (2x), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by flash chromatography (6:1 → 3:1 Hex/EtOAc) provided the title compound as a light yellow oil (5.8 mg, 11.9 μmol, 76% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 [br d, J = 8.5 Hz, 2H, S(O)$C_6H_4CH_3$], 7.55 [br d, J = 8.0 Hz, 2H, S(O)$C_6H_4CH_3$], 7.34-7.32 [m, 4H, overlapping S(O)$C_6H_4CH_3$], 4.44 [dddd, J = 3.5, 3.5, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 4.40 [dddd, J = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.89 [ABq, $\Delta\nu_{AB}$ = 7.7 Hz, J_{AB} = 14.0 Hz, 2H, $CH_2C(O)CH_2S(O)Ar$], 3.88 [ABq, $\Delta\nu_{AB}$ = 77.2 Hz, J_{AB} = 14.0 Hz, 2H, $CH_2C(O)CH_2S(O)Ar$], 3.43 [ABq, $\Delta\nu_{AB}$ = 29.7 Hz, J_{AB} = 15.5 Hz, 2H, $CH_2C(O)CH_2S(O)Ar$], 3.42 [ABq, $\Delta\nu_{AB}$ = 36.7 Hz, J_{AB} = 15.5 Hz, 2H, $CH_2C(O)CH_2S(O)Ar$], 2.74 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 7.0, 15.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.71 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 7.0, 14.5 Hz, 1H, CH_2CH–(OTBS)CH_2], 2.61 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 7.0, 18.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.54 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 7.0, 18.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.45-2.39 [m, 2H, $CH_2CH(OTBS)CH_2$ overlapping with S(O)$C_6H_4CH_3$], 2.42 [s, 6H, overlapping S(O)$C_6H_4CH_3$], 2.26-2.19 [m, 2H, overlapping $CH_2CH(OTBS)CH_2$], 0.86 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.85 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.19 [s, 9H, $C{\equiv}CSi(CH_3)_3$], 0.17 [s, 9H, $C{\equiv}CSi(CH_3)_3$], 0.029 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], 0.026 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], 0.025 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.017 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 198.3, 198.2, 142.33, 142.31, 140.8, 140.7, 140.14, 140.07, 130.3, 130.2, 124.41, 124.36, 121.3, 121.2, 100.8, 100.33, 100.28, 71.13, 71.08,

68.10, 68.05, 46.7, 46.6, 46.5, 46.4, 46.0, 45.9, 26.01, 25.99, 21.6, 18.28, 18.27, 0.15, 0.14, and -4.7.

IR (neat): 2955, 2929, 2899, 2856, 2141, 1715, 1251, 1090, 1059, and 843 cm^{-1}.

HR ESI-MS: $C_{26}H_{40}O_3SSi_2$ $[M+Na]^+$ requires 511.2129; found 511.2172.

TLC: R_f 0.35 (3:1 Hex/EtOAc).

(±)-1-(4-HYDROXY-2-(TRIMETHYLSILYLETHYNYL)CYCLOPENT-1-EN-1-YL)-3-(*P*-TOLYLSULFINYL)PROPAN-2-ONE (2219)

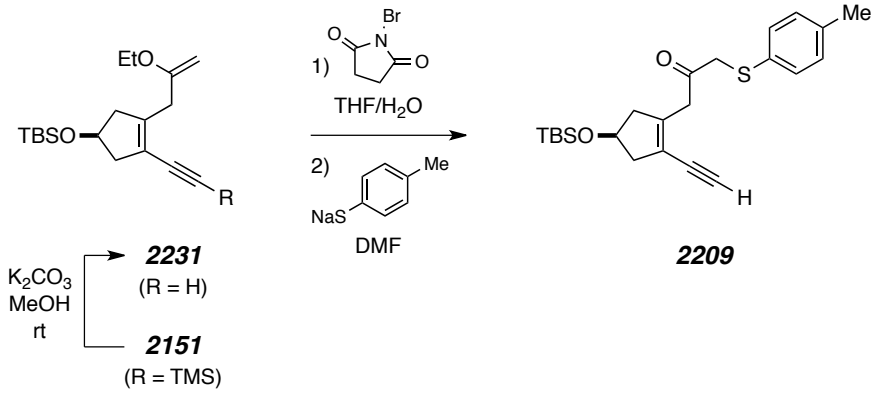
In a separate experiment [*MJJ-V-178*], the secondary alcohol **2219** was prepared by treatment of a 0 °C solution of the β-keto sulfide **2201** (7.3 mg, 15.4 μmol, 1.0 equiv) in CH_3CN/H_2O (3:1, 200 μL) with a PIFA stock solution (100 μL, 17.4 μmol, 1.1 equiv, 0.174 M in CH_3CN). After having been stirred at 0 °C for 3 h 45 min, the reaction mixture was quenched by the addition of 10% aq $NaHCO_3$, and the resulting mixture was diluted with EtOAc and poured onto brine. The layers were shaken and separated, the aqueous phase was extracted with EtOAc (1x), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by flash chromatography (1:1 Hex/EtOAc → 100% EtOAc) provided the title compound as a light yellow oil (4.5 mg, 12.0 μmol, 78% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 [br d, J = 8.0 Hz, 2H, S(O)C$_6$*H*$_4$CH$_3$], 7.54 [br d, J = 8.0 Hz, 2H, S(O)C$_6$*H*$_4$CH$_3$], 7.341 [br d, J = 8.0 Hz, 2H, S(O)C$_6$*H*$_4$CH$_3$], 7.337 [br d, J = 8.0 Hz, 2H, S(O)C$_6$*H*$_4$CH$_3$], 4.46-4.41 [m, 1H, C*H*(OH)], 4.40-4.36 [m, 1H, C*H*(OH)], 3.90 [ABq, $\Delta\nu_{AB}$ = 324 Hz, J_{AB} = 13.5 Hz, 2H, CH$_2$C(O)C*H*$_2$S(O)Ar], 3.89 [ABq, $\Delta\nu_{AB}$ = 35.5 Hz, J_{AB} = 13.5 Hz, 2H, CH$_2$C(O)C*H*$_2$S(O)Ar], 3.74 (br s, 1H, O*H*), 3.49 [ABq, $\Delta\nu_{AB}$ = 206 Hz, J_{AB} = 14.0 Hz, 2H, C*H*$_2$C(O)CH$_2$S(O)Ar], 3.49 [ABq, $\Delta\nu_{AB}$ = 74.0 Hz, J_{AB} = 15.0 Hz, 2H, CH$_2$C(O)CH$_2$S(O)Ar], 3.11 (br d, J = 7.5 Hz, 1H, O*H*), 2.89-2.82 [m, 2H, overlapping C*H*$_2$CH(OH)CH$_2$], 2.72 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 6.0, 18.0 Hz, 1H,

C*H*$_2$CH(OH)CH$_2$], 2.70-2.64 [m, 1H, C*H*$_2$CH(OH)CH$_2$], 2.57 [dddd, *J* = 1.5, 1.5, 1.5, 17.0 Hz, 1H, CH$_2$CH(OH)C*H*$_2$], 2.49 [dddd, *J* = 1.5, 1.5, 1.5, 17.0 Hz, 1H, CH$_2$CH(OH)C*H*$_2$], 2.42 [s, 6H, overlapping, S(O)C$_6$H$_4$C*H*$_3$], 2.34 [dddd, *J* = 1.0, 1.0, 1.0, 18.5 Hz, 1H, CH$_2$CH(OH)C*H*$_2$], 2.31 [br d, *J* = 18.0 Hz, 1H, CH$_2$CH(OH)C*H*$_2$], 0.19 [s, 9H, Si(C*H*$_3$)$_3$], and 0.14 [s, 9H, Si(C*H*$_3$)$_3$].

TLC: R_f 0.15 (1:1 Hex/EtOAc)

(±)-1-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-ETHYNYLCYCLOPENT-1-EN-1-YL)-3-(*P*-TOLYLTHIO)PROPAN-2-ONE (2209) via **(±)-*TERT*-BUTYL((3-(2-ETHOXYALLYL)-4-ETHYNYLCYCLOPENT-3-EN-1-YL)OXY)DIMETHYLSILANE (2231)**



[*MJJ-V-122*] Solid, anhydrous K_2CO_3 (2.5 mg, 0.018 mmol, 15 mol%) was added to a solution of the enol ether **2151** (45.3 mg, 0.12 mmol, 1.0 equiv) in MeOH (2.0 mL). After having been stirred overnight at right, the reaction mixture was concentrated *in vacuo*. Purification of the crude residue by flash chromatography (2% Et_3N/Hex) provided the alkyne **2231** (33.2 mg, 0.11 mmol, 90% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.47 [dddd, *J* = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.87 [s, 2H, (CH$_3$CH$_2$O)C=C*H*$_2$], 3.71 [q, *J* = 7.0 Hz, 2H, (CH$_3$C*H*$_2$O)C=CH$_2$], 3.09 (s, 1H, C≡C*H*), 3.07 [ABX$_4$, $\Delta\nu_{AB} < 0.5$ Hz, J_{AB} = 17.0 Hz, $J_{AX} = J_{BX}$ = 1.5 Hz, 2H,

C*H*$_2$(CH$_3$CH$_2$O)C=CH$_2$], 2.74 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 6.5, 16.0 Hz, 1H, C*H*$_2$CH(OTBS)CH$_2$], 2.66 [ddddddd, *J* = 1.5, 1.5, 1.5, 1.5, 1.5, 7.0, 17.5 Hz, 1H, CH$_2$CH(OTBS)C*H*$_2$], 2.45 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 3.5, 16.0 Hz, 1H, C*H*$_2$CH(OTBS)CH$_2$], 2.37 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 4.0, 17.5 Hz, 1H, CH$_2$CH(OTBS)C*H*$_2$], 1.29 [t, *J* = 7.0 Hz, 3H, (C*H*$_3$CH$_2$O)C=CH$_2$], 0.88 [s, 9H, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$], 0.050 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$], and 0.046 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$].

GC / LR EI-MS [5025015]: t_R 8.32, 8.99, and 9.09 min; *m*/*z* for t_R 8.32 min (rel. int.) 306 (16, $M^{+\bullet}$), 249 [79, $M^{+\bullet}$–C(CH$_3$)$_3^{\bullet}$], 221 (100, $M^{+\bullet}$–C$_5$H$_9$O$^{\bullet}$), 205 (14), 203 (13), 177 (15), 175 {16, $M^{+\bullet}$–[(CH$_3$)$_3$CSi(CH$_3$)$_2$]O$^{\bullet}$}, 147 (13), 146 (10), 145 (12), 129 (31), 117 (12), 115 (11), 103 (15), and 75 (51).

[*MJJ-V-124*] A solution of *N*-bromosuccinimide was prepared by dissolving the recrystallized reagent (94.1 mg, 0.53 mmol) in THF (2.0 mL). The resulting stock solution, which was 0.26 M [NBS], was utilized immediately in the following procedure.

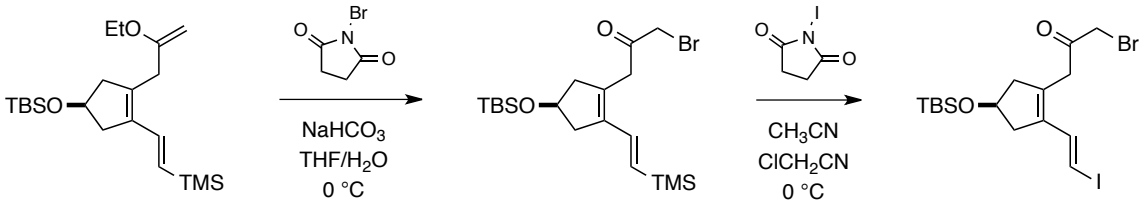
A room temperature solution of the enol ether **2231** (29.4 mg, 95.9 μmol, 1.0 equiv) in THF/H$_2$O (9:1, 1.0 mL) in a flask open to air was treated with an aliquot of the NBS stock solution (450 μL, 119 μmol, 1.2 equiv). After having been stirred for 40 min, the reaction mixture was diluted with Et$_2$O and poured onto brine (10 mL). The layers were shaken and separated, the aqueous phase was extracted with Et$_2$O (2x), and the combined organic extracts were dried (Na$_2$SO$_4$), filtered, and concentrated *in vacuo*. The crude residue was filtered through SiO$_2$ (8:1 Hex/EtOAc), evaporated to dryness, and used immediately in the subsequent step without further purification.

TLC: R_f 0.33 (20:1 Hex/EtOAc).

[*MJJ-V-81/126*] A stock solution of *p*-TolSNa was prepared as just described from dry NaH (71 mg, 2.96 mmol) and *p*-TolSH (442 mg, 3.56 mmol) in dry DMF (10.0 mL total volume). The resulting solution was 0.30 M [*p*-TolSNa].

An aliquot of the *p*-TolSNa stock solution (330 μL, 99.0 μmol, 1.0 equiv) was added dropwise to a 0 °C solution of the crude α-bromo ketone (95.9 μmol theoretical) in dry DMF (1.0 mL). Once starting material consumption was observed, the reaction mixture was diluted with EtOAc and washed with 1:1 brine/H_2O (2x). The combined aqueous washings were back-extracted with EtOAc (1x), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 98:2 Hex/EtOAc) provided the β-keto sulfide **2209** (16.1 mg, 40.2 μmol, 42% yield). The ^{1}H NMR spectrum of this material was identical to an authentic sample that had been prepared earlier (*vide supra*).

(±)-(*E*)-1-BROMO-3-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(2-IODOVINYL)CYCLOPENT-1-EN-1-YL)PROPAN-2-ONE (2236) via **(±)-(*E*)-1-BROMO-3-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(2-TRIMETHYLSILYLVINYL)-CYCLOPENT-1-EN-1-YL)PROPAN-2-ONE (2235)**



2155 ***2235*** ***2236***

[*MJJ-VI-260/VII-40*] To a solution of the enol ether **2155** (468 mg, 1.23 mmol, 1.0 equiv) in THF (10.8 mL) at 0 °C was added $NaHCO_3$ (313 mg, 3.73 mmol, 3.0 equiv). This mixture was then treated successively with H_2O (1.2 mL) and *N*-bromosuccinimide (219 mg, 1.23 mmol, 1.0 equiv). After having been stirred at 0 °C for 30 min, the reaction mixture was diluted with Et_2O/H_2O and poured onto satd aq $NaHCO_3$ (50 mL). The layers were shaken and separated, and the aqueous layer was extracted with Et_2O (2 x 25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid

chromatography (SiO_2, 99:1 Hex/EtOAc) provided the α-bromo ketone **2235** as a yellow oil (406 mg, 0.94 mmol, 76% yield). This oil solidified upon storage at –20 °C and could be stored at this temperature (excluding light) indefinitely without decomposition.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.77 [d, *J* = 18.5 Hz, 1H, C*H*=CHSi$(CH_3)_3$], 5.83 [d, *J* = 18.5 Hz, 1H, CH=C*H*Si$(CH_3)_3$], 4.48 [dddd, *J* = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.90 [ABq, $\Delta\nu_{AB}$ = 6.3 Hz, J_{AB} = 12.5 Hz, 2H, $CH_2C(O)CH_2Br$], 3.57 [ABq, $\Delta\nu_{AB}$ = 21.5 Hz, J_{AB} = 15.5 Hz, 2H, $CH_2C(O)CH_2Br$], 2.78 [dd, *J* = 7.0, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.73 [dd, *J* = 6.5, 17.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.47 [dd, *J* = 3.0, 16.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.38 [dd, *J* = 3.5, 18.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 0.88 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.11 [s, 9H, $Si(CH_3)_3$], 0.063 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.056 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ 199.0, 138.3, 136.3, 132.6, 130.1, 70.5, 47.5, 42.8, 40.1, 33.6, 26.0, 18.3, -1.1, and -4.6.

IR (thin film): 2953, 2929, 2897, 2856, 1716, 1249, 1094, 1061, 863, and 839 cm^{-1}.

HR ESI-MS: $C_{19}H_{35}BrO_2Si_2$ $[M+Na]^+$ requires 453.1251; found 453.1253.

MP: 31–32 °C.

TLC: R_f 0.21 (20:1 Hex/EtOAc).

[*MJJ-V-194/VII-116*] Solid *N*-iodosuccinimide (46.2 mg, 0.205 mmol, 1.2 equiv) was added in a single portion to a stirred solution of the vinyl silane **2235** (74.2 mg, 0.172 mmol, 1.0 equiv) in $CH_3CN/ClCH_2CN$ (9:1, 2.0 mL) at 0 °C. After having been stirred at this temperature for 3 h, LC-MS analysis of the reaction mixture revealed that the starting material had been consumed. The reaction mixture was diluted with Et_2O and then poured on satd aq $NaHCO_3$. The layers were shaken and separated, and the aqueous phase was extracted with Et_2O (2x). The combined organic extracts were washed with brine (1x), dried ($MgSO_4$), filtered, and evaporated to dryness. Purification of the crude

residue by medium pressure liquid chromatography (SiO_2, 40:1 Hex/EtOAc) provided the vinyl iodide **2236** as a yellow oil (71.7 mg, 0.148 mmol, 86% yield) that solidified upon being placed under high vacuum (< 1 mmHg).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 [d, J = 14.5 Hz, 1H, C*H*=CHI], 6.31 [d, J = 14.5 Hz, 1H, CH=C*H*I], 4.49 [dddd, J = 3.5, 3.5, 6.5, 6.5 Hz, 1H, C*H*(OTBS)], 3.91 [ABq, $\Delta\nu_{AB}$ = 4.2 Hz, J_{AB} = 12.5 Hz, 2H, $CH_2C(O)CH_2Br$], 3.52 [ABq, $\Delta\nu_{AB}$ = 17.9 Hz, J_{AB} = 16.0 Hz, 2H, $CH_2C(O)CH_2Br$], 2.76 [dd, J = 7.0, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.67 [dd, J = 6.5, 17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.45 [dd, J = 3.0, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.29 [dd, J = 3.5, 18.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 0.87 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.06 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.05 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ 198.4, 138.6, 136.7, 131.1, 79.2, 70.3, 47.1, 42.5, 40.1, 33.7, 26.0, 18.3, and -4.6.

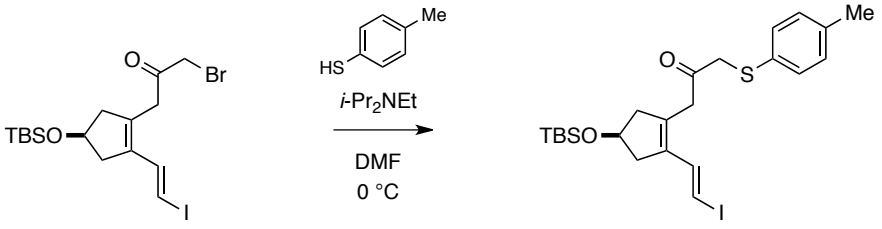
IR (thin film): 2952, 2929, 2896, 2855, 1717, 1253, 1061, 979, 939, 908, 937, and 777 cm^{-1}.

HR ESI-MS: $C_{16}H_{26}BrIO_2Si$ $[M+Na]^+$ requires 506.9822; found 506.9840.

MP: 67–69 °C.

TLC: R_f 0.34 (8:1 Hex/EtOAc).

(±)-(*E*)-1-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(2-IODOVINYL)CYCLOPENT-1-EN-1-YL)-3-(*P*-TOLYLTHIO)PROPAN-2-ONE (2196)



2236 ***2196***

[*MJJ-V-196*] A stock solution of 4-methylbenzenethiol (*p*-TolSH) was prepared by dissolving the neat compound (87.4 mg, 0.704 mmol) in dry DMF (2.3 mL). The resulting solution, which was 0.31 M [*p*-TolSH], was utilized in the following procedure.

A solution of the α-bromo ketone **2236** (70.2 mg, 0.145 mmol, 1.0 equiv) in dry DMF (2.0 mL) was cooled to 0 °C and treated sequentially with an aliquot of the *p*-TolSH stock solution (0.5 mL, 0.153 mmol, 1.1 equiv) and neat *i*-Pr_2NEt (20.5 mg, 0.159 mmol, 1.1 equiv). Stirring was continued at 0 °C for 50 min, at which point LC-MS analysis of the reaction mixture revealed that the starting material had been consumed. The reaction mixture was diluted with EtOAc and then poured onto 1:1 brine/H_2O. The layers were shaken and separated, and the organic phase was washed with 1:1 brine/H_2O. The combined aqueous washings were then back-extracted with EtOAc (1x). Finally, the combined organic extracts were washed with brine (1x), dried ($MgSO_4$), filtered, and concentrated at reduced pressure. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 40:1 Hex/EtOAc) provided the title compound (71.3 mg, 0.135 mmol, 93% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.25 (m, 2H, $SC_6H_4CH_3$), 7.19 [d, J = 14.5 Hz, 1H, C*H*=CHI], 7.14-7.11 (m, 2H, $SC_6H_4CH_3$), 6.22 [d, J = 14.5 Hz, 1H, CH=C*H*I], 4.44 [dddd, J = 3.5, 3.5, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.60 [ABq, $\Delta\nu_{AB}$ = 13.8 Hz, J_{AB} = 14.5

Hz, 2H, $CH_2C(O)CH_2SC_6H_4CH_3$], 3.43 [ABq, $\Delta\nu_{AB}$ = 11.1 Hz, J_{AB} = 16.0 Hz, 2H, $CH_2C(O)CH_2SC_6H_4CH_3$], 2.71 [dd, J = 7.0, 15.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.58 [dd, J = 7.0, 18.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.40 [dd, J = 3.5, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.32 (s, 3H, $SC_6H_4CH_3$) 2.22 [dd, J = 3.0, 17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 0.86 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.04 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.03 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

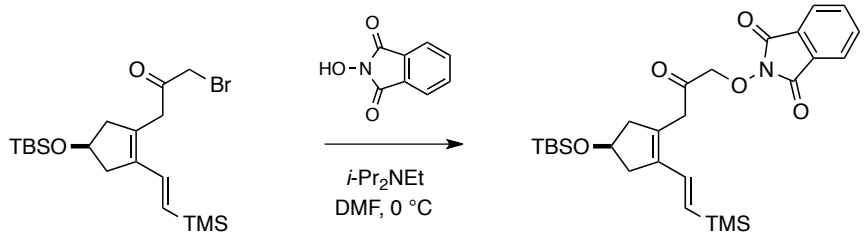
^{13}C NMR (125 MHz, $CDCl_3$): δ 201.9, 138.9, 137.6, 136.1, 131.9, 130.8, 130.6, 130.2, 78.4, 70.4, 47.1, 44.0, 42.4, 40.8, 26.0, 21.2, 18.3, -4.61, and -4.64.

IR (neat): 2952, 2928, 2857, 1711, 1253, 1091, 1061, 837, 807, and 778 cm^{-1}.

HR ESI-MS: $C_{23}H_{33}IO_2SSi$ $[M+Na]^+$ requires 551.0907; found 551.0967.

TLC: R_f 0.43 (8:1 Hex/EtOAc).

(±)-(*E*)-2-(3-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(2-TRIMETHYLSILYLVINYL)-CYCLOPENT-1-EN-1-YL)-2-OXOPROPOXY)ISOINDOLINE-1,3-DIONE (2246)



2235 ***2246***

[*MJJ-VI-154*] A solution of *i*-Pr_2NEt was prepared by dissolving the reagent (50 μL, 0.287 mmol) in dry DMF (480 μL). The resulting stock solution, which was 0.54 M [*i*-Pr_2NEt], was utilized immediately in the following procedure.

A solution of the α-bromo ketone **2235** (9.7 mg, 22.5 μmol, 1.0 equiv) in dry DMF (200 μL) at 0 °C was treated sequentially with solid *N*-hydroxyphthalimide (4.4 mg, 27.0

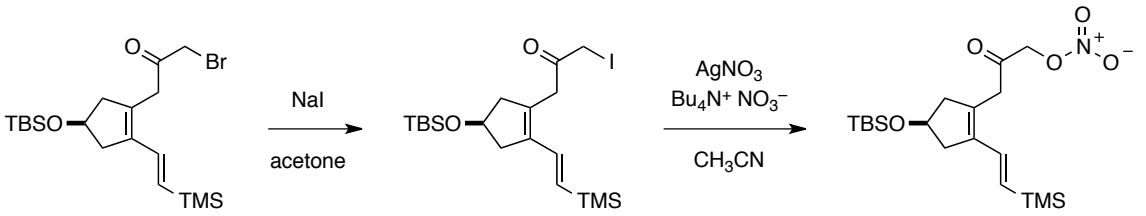
μmol, 1.2 equiv) and an aliquot of the *i*-Pr_2NEt stock solution (50 μL, 27.1 μmol, 1.2 equiv). After having been stirred at 0 °C for 15 min, the reaction mixture was allowed to warm to rt and was held at this temperature for 5 min. The reaction mixture was diluted with EtOAc and poured onto 1:1 brine/H_2O. The layers were shaken and separated, and the organic material was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 9:1 Hex/EtOAc) provided the title compound (9.9 mg, 19.3 μmol, 86% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86-7.77 (AA'BB', 4H, phthalimide C_6H_4), 6.80 [d, J = 19.0 Hz, 1H, C*H*=CHSi$(CH_3)_3$], 5.79 [d, J = 19.0 Hz, 1H, CH=C*H*Si$(CH_3)_3$], 4.76 [ABq, $\Delta\nu_{AB}$ = 11.7 Hz, J_{AB} = 16.0 Hz, 2H, C(O)CH_2O–phthalimide], 4.51 [dddd, J = 4.5, 4.5, 7.5, 7.5 Hz, 1H, C*H*(OTBS)], 3.70 [ABq, $\Delta\nu_{AB}$ = 37.3 Hz, J_{AB} = 16.0 Hz, 2H, CH_2C(O)CH_2O–phthalimide], 2.82-2.76 [m, 2H, CH_2CH(OTBS)CH_2], 2.47 [dd, J = 4.0, 16.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.43 [dd, J = 4.0, 17.0 Hz, 1H, CH_2CH(OTBS)CH_2], 0.88 [s, 9H, (CH_3)$_3$CSi$(CH_3)_2$], 0.09 [s, 9H, Si(CH_3)$_3$], 0.064 [s, 3H, $(CH_3)_3$CSi(CH_3)$_2$], and 0.058 [s, 3H, $(CH_3)_3$CSi(CH_3)$_2$].

LC / LR ES+APCI-MS [Symmetry® C_8, 3.9 x 150 mm, 5 μm, 100% MeOH/H_2O (98:2)]: t_R 4.80 min; *m*/*z* $[M+NH_4]^+$ 531.

TLC: R_f 0.14 (9:1 Hex/EtOAc).

(±)-(*E*)-3-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(2-TRIMETHYLSILYLVINYL)-CYCLOPENT-1-EN-1-YL)-2-OXOPROPYL NITRATE (2254) via **(±)-(*E*)-1-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(2-TRIMETHYLSILYLVINYL)CYCLOPENT-1-EN-1-YL)-3-IODOPROPAN-2-ONE (2253)**



2235 ***2253*** ***2254***

[*MJJ-VI-298*] Solid NaI (60.6 mg, 0.404 mmol, 1.5 equiv) was added in a single portion to a stirred solution of the α-bromo ketone **2235** (116.7 mg, 0.270 mmol, 1.0 equiv) in acetone (2.5 mL) in a flask open to air, which immediately produced a light yellow precipitate. The reaction flask was wrapped with aluminum foil and the resulting heterogeneous mixture was stirred in a subdued-light environment for 2.5 h. The reaction mixture was diluted with CH_2Cl_2, filtered through a bed of CELITE®, and the yellow filtrate was washed with 10% aq $NaHSO_3$ (35 mL). The aqueous wash was extracted once with CH_2Cl_2 (15 mL) and the combined organic extracts were washed with brine (25 mL) and dried ($MgSO_4$). Filtration, concentration *in vacuo*, and azeotropic removal of residual water with benzene (2 cycles) provided a light brown oil (136 mg) that was used immediately without further purification. Select analytical data [from *MJJ-VI-266*] for the intermediate α-iodo ketone (**2253**) are provided below.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.80 [d, J = 19.0 Hz, 1H, C*H*=CHSi$(CH_3)_3$], 5.83 [d, J = 19.0 Hz, 1H, CH=C*H*Si$(CH_3)_3$], 4.49 [dddd, J = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.81 [ABq, $\Delta\nu_{AB}$ = 22.4 Hz, J_{AB} = 10.0 Hz, 2H, $CH_2C(O)CH_2I$], 3.62 [ABq, $\Delta\nu_{AB}$ = 25.5 Hz, J_{AB} = 15.0 Hz, 2H, $CH_2C(O)CH_2I$], 2.78 [dd, J = 6.5, 16.0 Hz, 1H,

C*H*$_2$CH(OTBS)CH$_2$], 2.74 [dd, *J* = 6.5, 17.0 Hz, 1H, CH$_2$CH(OTBS)C*H*$_2$], 2.47 [dd, *J* = 3.5, 16.5 Hz, 1H, C*H*$_2$CH(OTBS)CH$_2$], 2.38 [dd, *J* = 4.0, 17.5 Hz, 1H, CH$_2$CH(OTBS)C*H*$_2$], 0.88 [s, 9H, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$], 0.11 [s, 9H, Si(C*H*$_3$)$_3$], 0.063 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$], and 0.055 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$].

TLC: R_f 0.21 (20:1 Hex/EtOAc).

Tetra-*n*-butylammonium nitrate ($Bu_4N^+NO_3^-$). [*MJJ-VI-262*] To a solution of tetra-*n*-butylammonium bromide (8.05 g, 24.98 mmol, 1.0 equiv) in absolute EtOH (40 mL) was added $AgNO_3$ (4.26 g, 25.08 mmol, 1.0 equiv). A finely divided pale green precipitate slowly formed over the course of *ca.* 3 h, and stirring was continued for 19 h at rt. The reaction mixture was then filtered through a bed of CELITE® (absolute EtOH eluent), the filtrate was concentrated *in vacuo*, and the resulting wet solid was recrystallized from boiling EtOAc. The product was collected by vacuum filtration, washed with anhydrous Et_2O, and dried under high vacuum to provide the title compound as a white crystalline solid (6.73 g, 22.10 mmol, 88% yield).

MP: 121–122 °C (lit.[403] 120–121 °C)

[*MJJ-VI-298* continued/*V-273*] To a solution of the crude α-iodo ketone **2253** (0.270 mmol theoretical) in dry CH_3CN (2.5 mL) were added sequentially $AgNO_3$ (143.0 mg, 0.842 mmol, 3.1 equiv) and Bu_4N^+ NO_3^- (248.6 mg, 0.817 mmol, 3.0 equiv). Prior to wrapping the reaction flask with aluminum foil, the formation of a finely divided yellow precipitate was observed immediately after the addition of the silver salt. After having been stirred in the dark for 3 h, the reaction mixture was diluted with Et_2O (*ca.* 40 mL) and the solids that precipitated were removed by filtration through a bed of CELITE®. The filtrate was washed with H_2O (20 mL), the aqueous layer was extracted with Et_2O (2x),

---

[403] Buckles, R. E.; Harris, L. The Kinetics of the Reactions of Quaternary Ammonium Tribromides with Crotonic Acid in Ethylene Chloride. *J. Am. Chem. Soc.* **1957**, *79*, 886–889.

and the combined organic extracts were washed with brine (1x) and dried ($MgSO_4$). After filtration and removal of the solvent *in vacuo*, the crude residue was purified by flash chromatography (Hex → 40:1 → 8:1 Hex/EtOAc) to provide the title compound as a bright yellow oil (78.2 mg, 0.189 mmol, 70% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.73 [d, *J* = 18.5 Hz, 1H, C*H*=CHSi$(CH_3)_3$], 5.88 [d, *J* = 18.5 Hz, 1H, CH=C*H*Si$(CH_3)_3$], 4.97 [ABq, $\Delta\nu_{AB}$ = 7.5 Hz, J_{AB} = 18.0 Hz, 2H, $CH_2C(O)CH_2ONO_2$], 4.48 [dddd, *J* = 3.5, 3.5, 6.5, 6.5 Hz, 1H, C*H*(OTBS)], 3.41 [ABq, $\Delta\nu_{AB}$ = 42.2 Hz, J_{AB} = 15.5 Hz, 2H, $CH_2C(O)CH_2ONO_2$], 2.78 [dd, *J* = 6.5, 17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.74 [dd, *J* = 6.5, 18.5 Hz, 1H $CH_2CH(OTBS)CH_2$], 2.49 [dd, *J* = 3.0, 16.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.37 [dd, *J* = 3.0, 18.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 0.88 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.11 [s, 9H, $Si(CH_3)_3$], 0.07 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.06 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

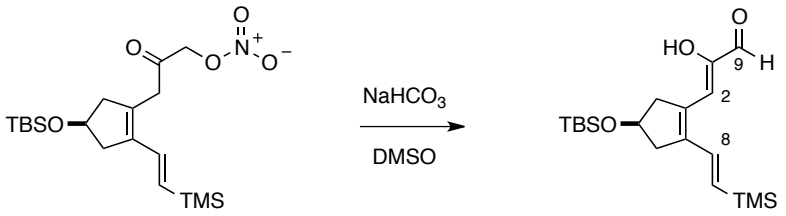
^{13}C NMR (75 MHz, $CDCl_3$): δ 198.6, 138.8, 135.8, 133.5, 128.7, 73.5, 70.4, 47.7, 42.9, 40.0, 26.0, 18.3, -1.1, and -4.6.

IR (neat): 2953, 2929, 2856, 1738, 1653, 1285, 1248, and 843 cm^{-1}.

HR ESI-MS: $C_{19}H_{35}NO_5Si_2$ $[M+Na]^+$ requires 436.1946; found 436.1963.

TLC: R_f 0.64 (6:1 Hex/EtOAc).

(±)-(*Z*)-3-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-((*E*)-2-TRIMETHYLSILYLVINYL)-CYCLOPENT-1-EN-1-YL)-2-HYDROXYACRYLALDEHYDE (2244)



2254 ***2244***

[*MJJ-VII-21*] To a solution of the nitrate ester **2254** (74.9 mg, 0.181 mmol, 1.0 equiv) in DMSO (2.0 mL) in a flask open to air was added solid $NaHCO_3$ (16.8 mg, 0.200 mmol, 1.1 equiv). The flask was sealed with a plastic caplug and stirred at rt for 80 min. The reaction mixture was then diluted with Et_2O (*ca.* 10 volumes) and poured into a separatory funnel that contained brine (20 mL) and H_2O (20 mL). The layers were shaken and separated, and the aqueous phase was extracted with Et_2O (2x). The combined organic extracts were washed with H_2O (15 mL) and brine (15 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting solid residue was purified by rapid flash chromatography (30:1 → 8:1 Hex/EtOAc) to provide the title compound as a yellow solid (53.9 mg, 0.147 mmol, 81% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.21 (d, *J* = 1.0 Hz, 1H, C*H*O), 7.00 [d, *J* = 18.5 Hz, 1H, C*H*=CHSi$(CH_3)_3$], 6.31 [br ddd (app q), *J* = 1.0, 1.0, 1.0 Hz, 1H, C*H*=C(OH)CHO], 6.15 [dd (app t), *J* = 1.5, 1.5 Hz, 1H, CH=C(O*H*)CHO], 6.02 [d, *J* = 18.5 Hz, 1H, CH=C*H*Si$(CH_3)_3$], 4.53 [dddd, *J* = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.29 [dddd, *J* = 1.0, 1.0, 6.5, 17.5 Hz, 1H, CH_2CH(OTBS)CH_2], 2.98 [dd, *J* = 4.0, 17.5 Hz, 1H, CH_2CH(OTBS)CH_2], 2.84 [dddd, *J* = 1.0, 1.0, 7.0, 17.5 Hz, 1H, CH_2CH(OTBS)CH_2], 2.54 [dd, *J* = 4.5, 17.5 Hz, 1H, CH_2CH(OTBS)CH_2], 0.90 [s, 9H, (CH_3)$_3$CSi$(CH_3)_2$], 0.14 [s, 9H, Si(CH_3)$_3$], 0.089 [s, 3H, $(CH_3)_3$CSi(CH_3)$_2$], and 0.087 [s, 3H, $(CH_3)_3$CSi(CH_3)$_2$].

GOESY (500 MHz, CD_3CN): ➞ H2, ↑ H8 and ↑ H9.

^{13}C NMR (125 MHz, $CDCl_3$): δ 188.2, 148.3, 144.4, 136.1, 135.3, 133.1, 116.5, 70.9, 46.0, 42.9, 26.1, 18.4, -1.1, and -4.5.

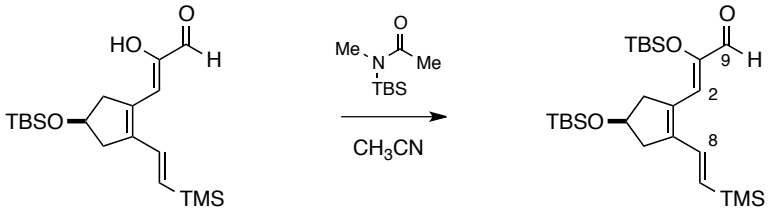
IR (thin film): 3379, 2954, 2929, 2898, 2857, 1657, 1618, 1412, 1364, 1305, 1248, and 843 cm^{-1}.

HR ESI-MS: $C_{19}H_{34}O_3Si_2$ $[M-H]^-$ requires 365.1974; found 365.1957.

TLC: R_f 0.14 (20:1 Hex/EtOAc).

A crystalline sample of the enol **2244** suitable for X-ray analysis (see Figure II–4 and APPENDIX A) was generated using vial-in-a-vial vapor diffusion crystallization. A sample of the purified enol (2.8 mg) in a 2-mL inner vial was dissolved in dry Et_2O (100 μL) and a shallow layer of pentane was added to the outer vial. The outer vial was capped and stored at –20 °C for one week, at which point yellow, block-like crystals had formed on the wall of the inner vial (**MP**: 116–119 °C).

(±)-(*Z*)-2-(*TERT*-BUTYLDIMETHYLSILOXY)-3-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-((*E*)-2-TRIMETHYLSILYLVINYL)CYCLOPENT-1-EN-1-YL)ACRYLALDEHYDE (2245)



2244 ***2245***

***N*-Methyl-*N*-(*tert*-butyldimethylsilyl)acetamide (MTBSA).**[189] [*MJJ-VI-150*] To a solution of *N*-methylacetamide (5.5 mL, 5.26 g, 72.0 mmol, 1.0 equiv) in Et_3N (100 mL) was added TBSCl (14.16 g, 93.9 mmol, 1.3 equiv). The reaction flask was purged with dry N_2, fitted with a drying tube (DRIERITE®, 8 mesh), and stirred vigorously at rt for 60

h. The reaction mixture was then filtered through a bed of CELITE® that had been flamed dried under a stream of dry air, and the filter cake was washed with additional Et_3N. The filtrate was then concentrated at reduced pressure and the resulting straw colored oil was gravity filtered into a 100-mL round-bottom flask. Removal of the residual Et_3N by distillation at ambient pressure followed by vacuum distillation (bp 45–46 °C @ 1.0 mmHg; lit.[189] bp 57–59 °C @ 1.0 mmHg) provided the title compound as a clear, colorless oil (9.09 g, 94% pure, 45.6 mmol, 63% yield corrected for purity) that solidified upon cooling the collection flask in an ice/H_2O bath. On the basis of ^{1}H NMR analysis, this material was contaminated with 6% (w/w) of unreacted *N*-methylacetamide.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.82 [s, 3H, C(O)C*H*$_3$], 2.09 [br s, 3H, NC*H*$_3$(TBS)], 0.94 [br s, 9H, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$], and 0.24 [br s, 6H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$].

[*MJJ-VII-23*] A sample of the enol **2244** (51.1 mg, 0.139 mmol, 1.0 equiv) was suspended in dry CH_3CN (1.4 mL) and the mixture was gently heated (heat gun) to completely solubilize the starting material. After having been cooled to rt, the resulting yellow solution was treated dropwise with freshly distilled MTBSA (580 μL, 522 mg, 2.785 mmol, 20 equiv) (a slight deepening of the yellow color was observed). Stirring was continued for 16 h at rt, at which point TLC and LC-MS analysis of the reaction mixture revealed that the starting material had been consumed. The solvent was removed at the rotavap to leave an orange oil, from which most of the excess silylating agent was sublimed by gentle heating (50 °C) at reduced pressure (*ca.* 2 mmHg). Purification of the crude residue thus obtained by flash chromatography (Hex → 40:1 Hex/EtOAc) provided the title compound as an orange gum (48.2 mg, 0.100 mmol, 72% yield).

[*NOTE:* Although the neat silyl enol ether **2245** was prone to decomposition at rt, its integrity could be maintained by storage at –20 °C as a dilute solution in EtOAc.]

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.22 (s, 1H, C*H*O), 6.99 [d, *J* = 19.0 Hz, 1H, C*H*=CHSi$(CH_3)_3$], 6.48 [s, 1H, C*H*=C(OTBS)CHO], 6.00 [d, *J* = 19.0 Hz, 1H, CH=C*H*Si$(CH_3)_3$], 4.51 [dddd, *J* = 4.5, 4.5, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.25 [dd, *J* = 6.5, 17.5 Hz, 1H, CH_2CH(OTBS)CH_2], 2.95 [br dd, *J* = 3.5, 17.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.83 [dd, *J* = 7.5, 17.5 Hz, 1H, CH_2CH(OTBS)CH_2], 2.52 [br dd, *J* = 4.0, 17.5 Hz, 1H, CH_2CH(OTBS)CH_2], 0.95 [s, 9H, (CH_3)$_3$CSi$(CH_3)_2$], 0.90 [s, 9H, (CH_3)$_3$CSi$(CH_3)_2$], 0.23 [s, 6H, $(CH_3)_3$CSi(CH_3)$_2$], 0.13 [s, 9H, Si(CH_3)$_3$], 0.079 [s, 3H, $(CH_3)_3$CSi(CH_3)$_2$], and 0.077 [s, 3H, $(CH_3)_3$CSi(CH_3)$_2$].

GOESY (500 MHz, CD_3CN): ➞ H2, ↑ H8 and ↑ H9.

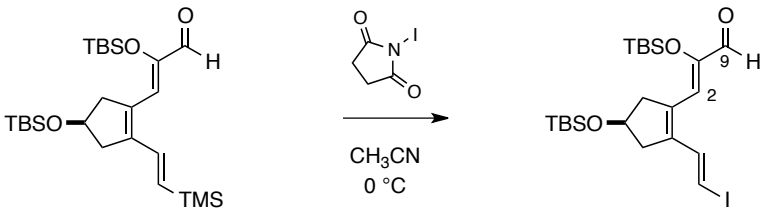
^{13}C NMR (125 MHz, $CDCl_3$): δ 189.5, 149.6, 143.9, 136.2, 135.0, 133.0, 124.4, 70.9, 46.5, 42.7, 26.2, 26.1, 19.1, 18.4, -1.1, -2.97, -3.01, -4.62, and -4.65.

IR (neat): 2953, 2930, 2896, 2857, 1686, 1411, 1364, 1250, 1232, 863, 837, and 781 cm^{-1}.

HR ESI-MS: $C_{25}H_{48}O_3Si_3$ $[M+Na]^+$ requires 503.2803; found 503.2809.

TLC: R_f 0.57 (15:1 Hex/EtOAc).

(±)-(*Z*)-2-(*TERT*-BUTYLDIMETHYLSILOXY)-3-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-((*E*)-2-IODOVINYL)CYCLOPENT-1-EN-1-YL)ACRYLALDEHYDE (2240)



2245 ***2240***

[*MJJ-VII-71*] Recrystallized *N*-iodosuccinimide (12.8 mg, 56.9 μmol, 1.3 equiv) was added in a single portion to a stirred solution of the vinyl silane **2245** (21.3 mg, 44.3

μmol, 1.0 equiv) in dry CH_3CN (0.5 mL) at 0 °C. The color of the reaction mixture gradually changed from yellow to orange and, after having been stirred at 0 °C for 50 min, LC-MS analysis of a reaction aliquot revealed that the starting material had been consumed. The reaction mixture was then concentrated at the rotavap to leave a red oil that was directly purified by flash chromatography (Hex → 40:1 Hex/EtOAc) to provide the title compound as a bright yellow oil (21.0 mg, 39.3 μmol, 87% yield). The reader should refer to the *NOTE* above regarding the storage of the vinyl silane **2245**. However, the product of the present procedure (**2240**) was considerably more prone to light-induced and thermal decomposition, and was typically prepared in relatively small quantities on an as-needed basis.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.22 (s, 1H, C*H*O), 7.53 (d, *J* = 14.5 Hz, 1H, C*H*=CHI), 6.47 (d, *J* = 14.5 Hz, 1H, CH=C*H*I), 6.34 [s, 1H, C*H*=C(OTBS)CHO], 4.52 [dddd, *J* = 4.0, 4.0, 7.5, 7.5 Hz, 1H, C*H*(OTBS)], 3.14 [dd, *J* = 6.5, 17.5 Hz, 1H, C*H*$_2$CH(OTBS)CH$_2$], 2.85 [dd, *J* = 3.5, 17.5 Hz, 1H, C*H*$_2$CH(OTBS)CH$_2$], 2.80 [dd, *J* = 7.0, 17.5 Hz, 1H, CH$_2$CH(OTBS)C*H*$_2$], 2.50 [dd, *J* = 4.0, 17.5 Hz, 1H, CH$_2$CH(OTBS)C*H*$_2$], 0.95 [s, 9H, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$], 0.89 [s, 9H, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$], 0.23 [s, 6H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$], and 0.07 [s, 6H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$].

GOESY (500 MHZ, CD_3CN): ➔ H9, ↑ H2.

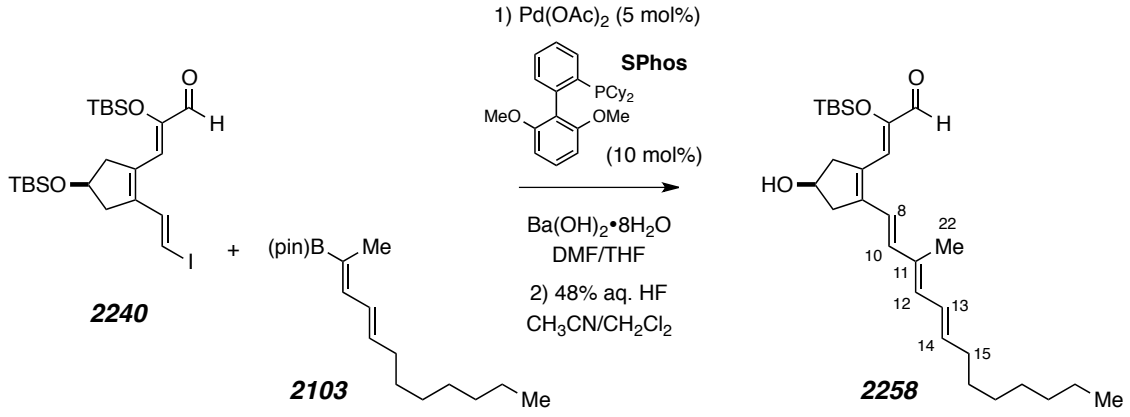
^{13}C NMR (125 MHz, $CDCl_3$): δ 189.5, 150.1, 141.3, 138.9, 133.4, 123.5, 81.1, 70.7, 46.0, 42.3, 26.2, 26.0, 19.1, 18.4, -2.99, -3.02, -4.63, and -4.66.

IR (neat): 2953, 2929, 2895, 2856, 1685, 1413, 1363, 1251, 1236, 1167, and 838 cm^{-1}.

HR ESI-MS: $C_{22}H_{39}IO_3Si_2$ $[M+Na]^+$ requires 557.1375; found 557.1381.

TLC: R_f 0.54 (15:1 Hex/EtOAc).

(±)-(*Z*)-2-(*TERT*-BUTYLDIMETHYLSILOXY)-3-(4-HYDROXY-2-((1*E*,3*E*,5*E*)-3-METHYL-TRIDECA-1,3,5-TRIEN-1-YL)CYCLOPENT-1-EN-1-YL)ACRYLALDEHYDE (2258) via **(±)- (*Z*)-2-(*TERT*-BUTYLDIMETHYLSILOXY)-3-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-((1*E*,3*E*,5*E*)-3-METHYLTRIDECA-1,3,5-TRIEN-1-YL)CYCLOPENT-1-EN-1-YL)ACRYL-ALDEHYDE (2241)**



[*MJJ-VII-79*] A stock solution of the palladium pre-catalyst was prepared in the following manner: A solution of $Pd(OAc)_2$ (4.1 mg, 18.3 μmol, 1.0 equiv) in THF (1.2 mL) was treated with 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (**SPhos**) (15.4 mg, 37.5 μmol, 2.0 equiv). The resulting homogeneous mixture was stirred at rt for 30 min to produce an orange catalyst solution that was 0.015 M [Pd].

A 13 x 100 mm culture tube was charged with the vinyl iodide **2240** (16.8 mg, 31.4 μmol, 1.0 equiv), DMF (300 μL), and the vinyl boronic ester **2103** (13.8 mg, 47.2 μmol, 1.5 equiv). An aliquot (100 μL, 1.5 μmol, 5 mol% Pd, 10 mol% **SPhos**) of the pre-catalyst stock solution was delivered to the reaction mixture via a 100-μL WIRETROL® and the resulting mixture was cooled to 0 °C. Solid $Ba(OH)_2•8H_2O$ (11.0 mg, 34.9 μmol, 1.1 equiv) was added, the culture tube was wrapped with aluminum foil, and the reaction mixture was maintained with stirring in a subdued-light environment at 0 °C for 45 min and at rt for 30 min. The reaction mixture, which had now developed a deep red color,

was diluted with EtOAc (2 mL) and then 1:1 H_2O/brine (3 mL) was added. The layers were separated and the aqueous phase was extracted with EtOAc (3 x 2 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to leave a dark red oil that was utilized in the next step without further processing. Select analytical data for the intermediate bis-TBS ether **2241** [from *MJJ-VI-223*] are provided below.

^{1}H NMR (500 MHz, CD_3CN): δ 9.23 (s, 1H, C*H*O), 6.82 (d, *J* = 16.0 Hz, 1H, H8), 6.73 [s, 1H, C*H*=C(OTBS)CHO], 6.47 (dddd, *J* = 1.5, 1.5, 11.5, 15.0 Hz, 1H, H13), 6.47 (d, *J* = 15.5 Hz, 1H, H10), 6.23 (d, *J* = 11.0 Hz, 1H, H12), 5.85 (ddd, *J* = 7.0, 7.0, 14.5 Hz, 1H, H14), 4.56 [dddd, *J* = 3.0, 3.0, 6.5, 6.5 Hz, 1H, C*H*(OTBS)], 3.19 [dd, *J* = 6.5, 17.5 Hz, 1H, C*H*$_2$CH(OTBS)CH_2], 2.93 [dd, *J* = 2.5, 18.0 Hz, 1H, C*H*$_2$CH(OTBS)CH_2], 2.85 [dd, *J* = 6.0, 17.5 Hz, 1H, CH_2CH(OTBS)C*H*$_2$], 2.52 [dd, *J* = 2.5, 17.0 Hz, 1H, CH_2CH(OTBS)C*H*$_2$], 2.16 [br ddd, *J* = 7.0, 7.0, 7.0 Hz, 2H, CH=CHC*H*$_2$$CH_2$–$(CH_2)_4CH_3$], 1.95 (s, 3H, H22), 1.44-1.37 [m, 2H, CH=CHCH_2C*H*$_2$$(CH_2)_4CH_3$], 1.34-1.26 [m, 8H, CH=CHCH_2CH_2(C*H*$_2$)$_4$$CH_3$], 0.95 [s, 9H, (C*H*$_3$)$_3CSi(CH_3)_2$], 0.89 [t, *J* = 7.0 Hz, 3H, CH=CH$CH_2CH_2(CH_2)_4$C*H*$_3$], 0.88 [s, 9H, (C*H*$_3$)$_3$CSi$(CH_3)_2$], 0.211 [s, 3H, $(CH_3)_3$CSi(C*H*$_3$)$_2$], 0.207 [s, 3H, $(CH_3)_3$CSi(C*H*$_3$)$_2$], and 0.08 [s, 6H, $(CH_3)_3$CSi(C*H*$_3$)$_2$].

TLC: R_f 0.53 (15:1 Hex/EtOAc).

[*MJJ-VII-80*] With the aid of a small amount of Et_2O, the crude bis-TBS ether **2241** (31.4 μmol theoretical) was transferred to a 2-mL polypropylene cryogenic vial that was wrapped with aluminum foil. The transfer solvent was removed under a gentle stream of N_2, and then the vial was charged with CH_2Cl_2 (300 μL) and CH_3CN (300 μL). After having been cooled to 0 °C, the reaction mixture was treated with 48% aq HF (50 μL). Stirring was continued at 0 °C for 30 min, at which point another portion of 48% aq HF (50 μL) was added. An additional 30 min of stirring at 0 °C was required to observe starting material consumption by TLC. The reaction mixture was diluted with EtOAc (2

mL) and was cautiously added to satd aq $NaHCO_3$ (3 mL). Once gas evolution had ceased, the layers were separated, the aqueous phase was extracted with EtOAc (3 x 2 mL), and the combined organic extracts were dried ($MgSO_4$). Concentration of the filtrate *in vacuo* and purification of the crude residue by medium pressure liquid chromatography (SiO_2, 8:1 Hex/EtOAc) provided the mono-TBS enol ether **2258** as an orange solid (7.0 mg, 15.3 μmol, 49% yield over 2 steps).

^{1}H NMR (500 MHz, CD_3CN): δ 9.24 (s, 1H, C*H*O), 6.82 (d, *J* = 15.5 Hz, 1H, H8), 6.74 [dd, *J* = 0.5, 0.5 Hz, 1H, C*H*=C(OTBS)CHO], 6.48 (d, *J* = 15.5 Hz, 1H, H10), 6.47 (dddd, *J* = 1.5, 1.5, 11.0, 14.5 Hz, 1H, H13), 6.23 (d, *J* = 11.5 Hz, 1H, H12), 5.85 (ddd, *J* = 7.5, 7.5, 15.0 Hz, 1H, H14), 4.41 [ddddd, *J* = 2.5, 2.5, 4.0, 6.0, 7.0 Hz, C*H*(OH)], 3.14 [dd, *J* = 6.0, 17.5 Hz, 1H, C*H*$_2$CH(OH)CH$_2$], 2.91 [br d, *J* = 18.0 Hz, 1H, CH$_2$CH(OH)C*H*$_2$], 2.88 [d, *J* = 4.5 Hz, 1H, CH(O*H*)], 2.80 [dd, *J* = 6.5, 18.0 Hz, 1H, CH$_2$CH(OH)C*H*$_2$], 2.51 [dd, *J* = 2.0, 17.5 Hz, 1H, C*H*$_2$CH(OH)CH$_2$], 2.16 [dddd, *J* = 1.5, 7.5, 7.5, 7.5 Hz, 2H, CH=CHC*H*$_2$CH$_2$(CH$_2$)$_4$CH$_3$], 1.95 (s, 3H, H22), 1.44-1.38 [m, 2H, CH=CHCH$_2$C*H*$_2$(CH$_2$)$_4$CH$_3$], 1.34-1.26 [m, 8H, CH=CHCH$_2$CH$_2$(C*H*$_2$)$_4$CH$_3$)], 0.96 [s, 9H, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$], 0.89 [t, *J* = 7.0 Hz, 3H, CH=CHCH$_2$CH$_2$(CH$_2$)$_4$C*H*$_3$], 0.22 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$], and 0.20 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$].

GOESY (500 MHz, CD_3CN): ➞ H22, ↑ H8 and ↑ H13.

^{13}C NMR (125 MHz, CD_3CN): δ 190.7, 150.0, 145.1, 138.6, 138.5, 134.8, 134.6, 133.4, 128.0, 126.1, 121.5, 70.3, 46.6, 43.1, 33.8, 32.6, 30.1, 29.92, 29.87, 26.5, 23.4, 19.6, 14.4, 12.8, -2.8, and -2.9.

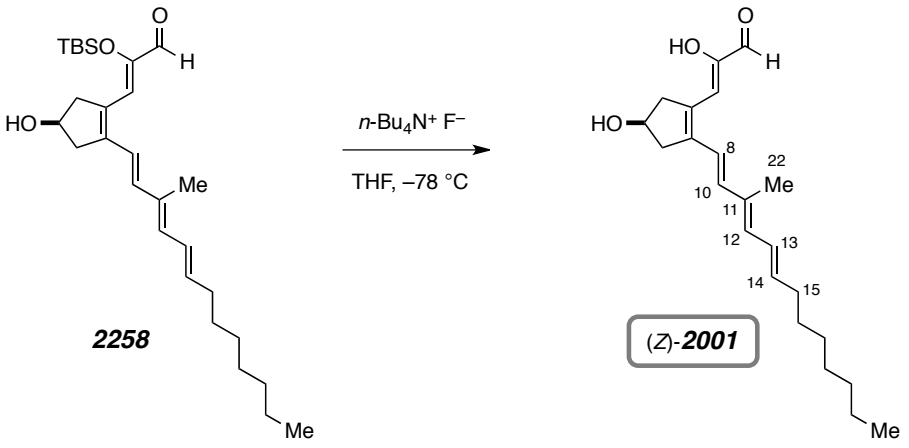
IR (thin film): 3358, 2953, 2926, 2855, 1679, 1413, 1368, 1252, 1234, 1170, 1026, 962, 840, 827, and 785 cm^{-1}.

HR ESI-MS: $C_{28}H_{46}O_3Si$ $[M\text{-}TBS]^-$ requires 343.2279; found 343.2286.

MP: 89–93 °C.

TLC: R_f 0.21 (8:1 Hex/EtOAc).

(±)-(*Z*)-2-HYDROXY-3-(4-HYDROXY-2-((1*E*,3*E*,5*E*)-3-METHYLTRIDECA-1,3,5-TRIEN-1-YL)CYCLOPENT-1-EN-1-YL)ACRYLALDEHYDE [(*Z*)-2001]



[*MJJ-VII-81*] A solution of TBAF was prepared by diluting a 1.0 M solution of the reagent (200 μL, 0.200 mmol) with dry THF (1.1 mL). This stock solution, which was 0.154 M [TBAF], was utilized immediately in the following procedure.

A 13 x 100 mm culture tube was charged with the mono-TBS enol ether **2258** (6.3 mg, 13.7 μmol, 1.0 equiv) and dry THF (500 μL). After having been cooled to –78 °C, the resulting bright yellow solution was treated dropwise with an aliquot of the TBAF stock solution (100 μL, 15.4 μmol, 1.1 equiv). The color of the reaction mixture gradually evolved from yellow to blood red during the course of the addition and, after having been stirred for 5 min, TLC analysis of the reaction mixture revealed that the starting material had been consumed. The cooling bath was removed and the reaction mixture was immediately quenched by the addition of satd aq NH_4Cl (2 mL), after which the blood red color of the reaction mixture was discharged upon warming. The reaction mixture was diluted with EtOAc (2 mL) and the inorganic salts that had precipitated were dissolved by the addition of H_2O (~1 mL). The layers were separated, the aqueous phase was extracted with EtOAc (3 x 1 mL), and the combined organic extracts were dried ($MgSO_4$) and filtered. Concentration of the filtrate *in vacuo* and rapid purification of the

crude residue by flash chromatography (8:1 → 1:1 Hex/EtOAc) provided the title compound as an orange solid (2.7 mg, 7.8 μmol, 57% yield).

^{1}H NMR (500 MHz, CD_3CN): δ 9.22 [d, *J* = 0.5 Hz, 1H, C*H*O], 6.83 (d, *J* = 16.0 Hz, 1H, H8), 6.76 [dd, *J* = 1.0, 1.0 Hz, 1H, C*H*=C(OH)CHO], 6.51 [s, 1H, CH=C(O*H*)CHO], 6.48 (dddd, *J* = 1.5, 1.5, 11.0, 14.5 Hz, 1H, H13), 6.47 (d, *J* = 16.0 Hz, 1H, H10), 6.23 (d, *J* = 11.5 Hz, 1H, H12), 5.85 (ddd, *J* = 7.5, 7.5, 14.5 Hz, 1H, H14), 4.42 [ddddd, *J* = 2.5, 2.5, 4.5, 6.5, 6.5 Hz, C*H*(OH)], 3.15 [dd, *J* = 6.0, 18.0 Hz, 1H, C*H*$_2$CH(OH)CH$_2$], 2.91 [br d, *J* = 18.0 Hz, 1H, C*H*$_2$CH(OH)CH$_2$], 2.83 [d, *J* = 4.5 Hz, 1H, CH(O*H*)], 2.81 [dd, *J* = 6.5, 17.5 Hz, 1H, CH$_2$CH(OH)C*H*$_2$], 2.52 [br d, *J* = 17.5 Hz, 1H, CH$_2$CH(OH)C*H*$_2$], 2.16 [dddd, *J* = 1.5, 7.5, 7.5, 7.5 Hz, 2H, CH=CHC*H*$_2$CH$_2$(CH$_2$)$_4$CH$_3$], 1.96 (s, 3H, H22), 1.44-1.39 [m, 2H, CH=CHCH$_2$C*H*$_2$(CH$_2$)$_4$CH$_3$], 1.34-1.26 [m, 8H, CH=CHCH$_2$CH$_2$–(C*H*$_2$)$_4$CH$_3$)], and 0.87 [t, *J* = 7.0 Hz, 3H, CH=CHCH$_2$CH$_2$(CH$_2$)$_4$C*H*$_3$].

^{13}C NMR (125 MHz, CD_3CN): δ 189.4, 149.8, 144.5, 138.41, 138.38, 134.6, 133.8, 128.0, 121.5, 117.7, 70.2, 46.3, 43.2, 33.8, 32.6, 30.1, 29.91, 29.87, 23.4, 14.4, and 12.7.

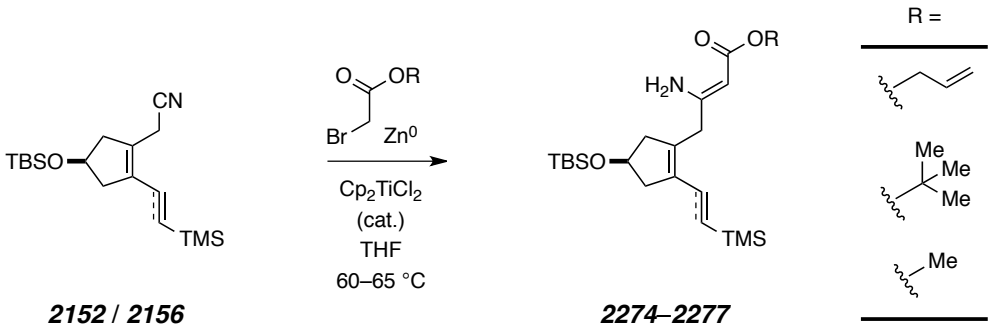
IR (thin film): 3417, 2922, 2853, 1653, 1614, 1421, and 958 cm^{-1}.

HR ESI-MS: $C_{22}H_{32}O_3$ $[M-H]^-$ requires 343.2279; found 343.2285.

MP: 94–102 °C (dec).

TLC: R_f 0.49 (1:1 Hex/EtOAc).

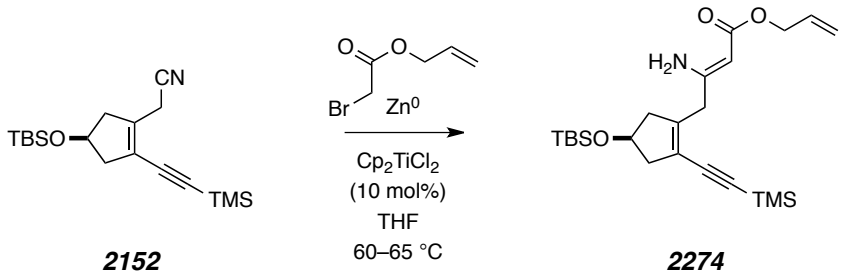
BLAISE HOMOLOGATION OF ALLYLIC NITRILES: GENERAL PROCEDURE



2152* / *2156 ***2274–2277***

Activated, finely ground Zn dust (*ca.* 20 equiv), titanocene dichloride (Cp_2TiCl_2) (5–10 mol%), and the appropriate alkyl bromoacetate (2-5 drops) were sequentially added to a solution of the allylic nitriles (**2152**/**2156**) (1.0 equiv) in dry THF (~0.1 M). The reaction flask was then immersed in a pre-heated (60–65 °C) oil bath and a solution of the alkyl bromoacetate (*ca.* 10 equiv) in dry THF was added via syringe pump during the indicated time period. Reaction progress was monitored by TLC analysis, wherein the more polar enamino ester product was clearly resolved from the less polar allylic nitrile. Once the starting material had been consumed, the reaction mixture was diluted with Hex/EtOAc (6:1), passed through a short bed of SiO_2, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2) provided the enamino esters (**2274**–**2277**) as light yellow, viscous oils, from which trace amounts of EtOAc were difficult to remove. Since the neat compounds were prone to decomposition, it is recommended that they be stored as dilute solutions (e.g., in EtOAc).

(±)-(*Z*)-ALLYL 3-AMINO-4-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(TRIMETHYLSILYL-ETHYNYL)CYCLOPENT-1-EN-1-YL)BUT-2-ENOATE (2274)



2152 ***2274***

[*MJJ-IV-215*] According to the GENERAL PROCEDURE, a solution of allyl bromoacetate (700 mg, 3.91 mmol, 10 equiv) in dry THF (2.0 mL) was added over the course of 4 h to a mixture of the allylic nitrile **2152** (128 mg, 0.39 mmol, 1.0 equiv), Zn^0 (517 mg, 7.91 mmol, 21 equiv), and Cp_2TiCl_2 (9.5 mg, 0.038 mmol, 10 mol%) in dry THF (4.0 mL). In this instance, full consumption of the starting material was observed when ~⅔ the total volume of the allyl bromoacetate solution had been added; the reaction was stopped at this point. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 20:1 Hex/EtOAc) provided the title compound (149 mg, 0.33 mmol, 85% yield corrected for purity).

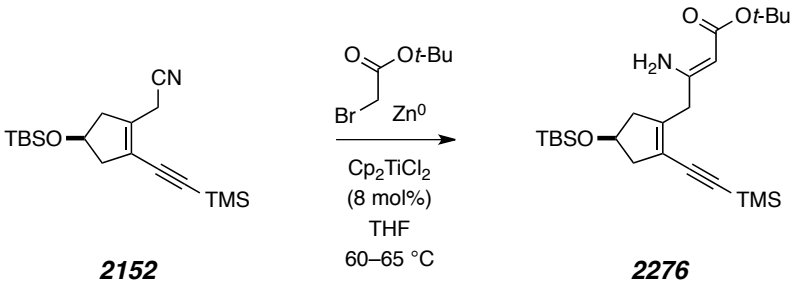
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 [br s, 1H, (H_2N)C=CH], 5.96 (dddd, J = 5.5, 5.5, 10.5, 17.0 Hz, 1H, CO_2CH_2CH=$CH_{trans}H_{cis}$), 5.32 (dddd, J = 1.5, 1.5, 1.5, 17.5 Hz, 1H, CO_2CH_2CH=$CH_{trans}H_{cis}$), 5.21 (dddd, J = 1.5, 1.5, 1.5, 10.5 Hz, 1H, CO_2CH_2CH=$CH_{trans}H_{cis}$), 4.85 [br s, 1H, (H_2N)C=CH], 4.59 [s, 1H, (H_2N)C=CH], 4.58 (ddd, J = 1.0, 1.0, 5.5 Hz, 2H, CO_2CH_2CH=$CH_{trans}H_{cis}$), 4.45 [dddd, J = 4.0, 4.0, 7.0, 7.0 Hz, 1H, CH(OTBS)], 3.11 [ABq, $\Delta\nu_{AB}$ < 0.5 Hz, J_{AB} = 15.0 Hz, 2H, CH_2(H_2N)C=CH], 2.75 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 6.5, 16.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.62 [dddddd, J = 1.0, 1.0, 1.0, 1.0, 6.5, 17.5 Hz, 1H, CH_2CH(OTBS)CH_2], 2.46 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 4.5, 16.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.30 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 4.0,

17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 0.86 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.20 [s, 9H, $Si(CH_3)_3$], 0.04 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.03 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

HR ESI-MS: $C_{23}H_{39}NO_3Si_2$ $[M+Na]^+$ requires 456.2361; found 456.2351.

TLC: R_f 0.44 (9:1 Hex/EtOAc).

(±)-(*Z*)-*TERT*-BUTYL 3-AMINO-4-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(TRIMETHYLSILYLETHYNYL)CYCLOPENT-1-EN-1-YL)BUT-2-ENOATE (2276)



2152 ***2276***

[*MJJ-V-47/VI-289*] According to the GENERAL PROCEDURE, a solution of *tert*-butyl bromoacetate (575 mg, 2.948 mmol, 10 equiv) in dry THF (1.0 mL) was added over the course of 60 min to a mixture of the allylic nitrile **2152** (94.9 mg, 0.28 mmol, 1.0 equiv), Zn^0 (375 mg, 5.73 mmol, 20 equiv), and Cp_2TiCl_2 (5.7 mg, 0.023 mmol, 8 mol%) in dry THF (2.0 mL). Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 99:1 Hex/EtOAc) provided the title compound (111 mg, 0.25 mmol, 87% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 [br s, 1H, $(H_2N)C=CH$], 4.17 [br s, 1H, $(H_2N)C=CH$], 4.48 [s, 1H, $(H_2N)C=CH$], 4.45 [dddd, J = 3.5, 3.5, 7.0, 7.0 Hz, 1H, $CH(OTBS)$], 3.06 [ABq (app s), $\Delta\nu_{AB} < 0.5$ Hz, 2H, $CH_2(H_2N)C=CH$], 2.74 [dd, J = 6.5, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.62 [dd, J = 7.0, 17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.45 [dd, J = 3.5, 16.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.31 [dd, J = 3.0, 17.5 Hz, 1H,

$CH_2CH(OTBS)CH_2$], 1.47 [s, 9H, $CO_2C(CH_3)_3$], 0.86 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.19 [s, 9H, $Si(CH_3)_3$], 0.04 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.03 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

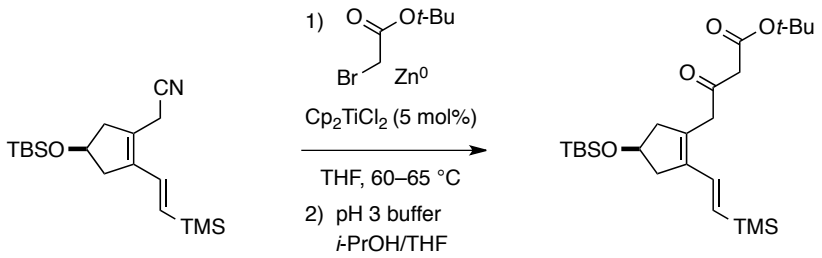
^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 159.4, 145.7, 119.9, 101.2, 99.2, 86.2, 78.5, 71.2, 46.4, 45.2, 37.3, 28.7, 26.0, 18.3, 0.2, and -4.6.

IR (neat): 3476, 3332, 2956, 2930, 2857, 2141, 1667, 1615, 1555, 1251, 1147, and 843 cm^{-1}.

HR ESI-MS: $C_{24}H_{43}NO_3Si_2$ $[M+Na]^+$ requires 472.2674; found 472.2652.

TLC: R_f 0.37 (15:1 Hex/EtOAc).

(±)-(*E*)-*TERT*-BUTYL 4-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(2-TRIMETHYLSILYL-VINYL)CYCLOPENT-1-EN-1-YL)-3-OXOBUTANOATE (2281)



2156 ***2281***

[*MJJ-V-168/175/VII-114/118*] According to the GENERAL PROCEDURE, a solution of *tert*-butyl bromoacetate (578 mg, 2.96 mmol, 10 equiv) in dry THF (1.0 mL) was added over the course of 3 h to a mixture of the allylic nitrile **2156** (99 mg, 0.29 mmol, 1.0 equiv), Zn^0 (383 mg, 5.86 mmol, 20 equiv), and Cp_2TiCl_2 (3.2 mg, 0.013 mmol, 4 mol%) in dry THF (2.5 mL). Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 98:2 Hex/EtOAc) provided material that, on the basis of ESI-MS analysis, was a mixture of the intermediate enamino ester and the hydrolyzed β-keto ester. According to the GENERAL PROCEDURE for enamino ester hydrolysis (*vide infra*), this mixture was dissolved in *i*-PrOH (3.0 mL), pH 3 buffer (3.0 mL), and THF (2.0 mL)

and the resulting solution was stirred rt overnight. Purification of the crude reside that was obtained after reaction work-up by medium pressure liquid chromatograph (SiO_2, 98:2 Hex/EtOAc) provided the β-keto ester **2281** as a light yellow oil (70 mg, 0.15 mmol, 53% yield over 2 steps). On the basis of ^{1}H NMR analysis, this material contained *ca.* 9% of the corresponding enol tautomer.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.74 [d, J = 19.0 Hz, 1H, C*H*=CHSi$(CH_3)_3$], 5.80 [d, J = 19.0 Hz, 1H, CH=C*H*Si$(CH_3)_3$], 4.49 [dddd, J = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.45 [app dddd, J = 1.5, 1.5, 1.5, 1.5, 2H, CH_2C(O)CH_2CO_2t-Bu], 3.35 [ABq, $\Delta\nu_{AB}$ = 12.3 Hz, J_{AB} = 15.5 Hz, 2H, CH_2C(O)CH_2CO_2t-Bu], 2.78 [dd, J = 7.0, 16.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.73 [dd, J = 7.0, 18.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.46 [dd, J = 3.5, 16.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.37 [dd, J = 4.0, 18.5 Hz, 1H, CH_2CH(OTBS)CH_2], 1.46 [s, 9H, CO_2C(CH_3)$_3$], 0.88 [s, 9H, (CH_3)$_3$CSi$(CH_3)_2$], 0.10 [s, 9H, CH=CHSi(CH_3)$_3$], 0.06 [s, 3H, $(CH_3)_3$CSi(CH_3)$_2$], and 0.05 [s, 3H, $(CH_3)_3$CSi(CH_3)$_2$].

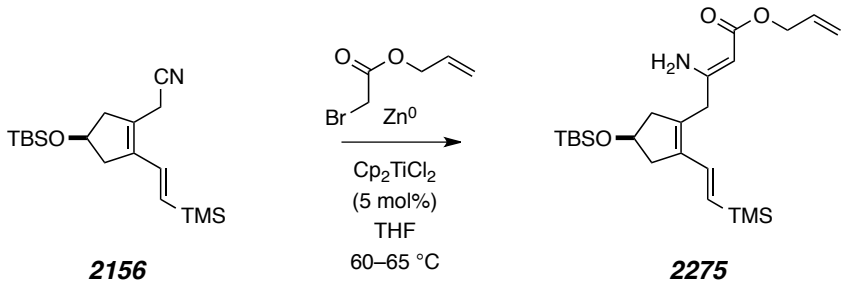
^{13}C NMR (125 MHz, $CDCl_3$): δ 200.6, 166.4, 137.9, 136.6, 132.1, 130.7, 82.1, 70.6, 49.6, 47.6, 43.2, 42.8, 28.1, 26.0, 18.3, -1.1, -4.59, and -4.61.

IR (neat): 2955, 2930, 2900, 2857, 1719, 1250, 1148, 1095, 1063, 863, 839, and 777 cm^{-1}.

HR ESI-MS: $C_{24}H_{44}O_4Si_2$ $[M+Na]^+$ requires 475.2670; found 475.2672.

TLC: R_f 0.49 (8:1 Hex/EtOAc).

(±)-(*Z*)-ALLYL 3-AMINO-4-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-((*E*)-2-TRIMETHYLSILYLVINYL)CYCLOPENT-1-EN-1-YL)BUT-2-ENOATE (2275)

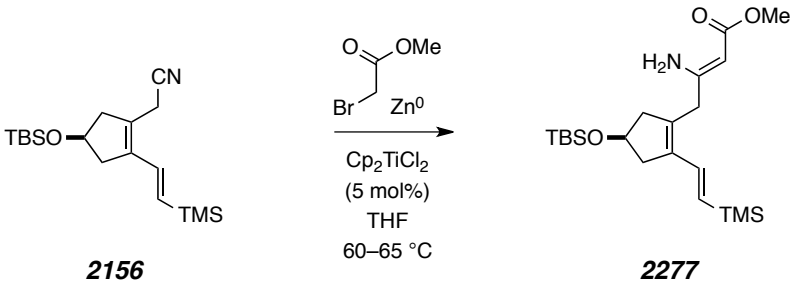


[*MJJ-V-154/VI-54*] According to the GENERAL PROCEDURE, a solution of allyl bromoacetate (222 mg, 1.24 mmol, 10 equiv) in dry THF (0.5 mL) was added over the course of 5 h to a mixture of the allylic nitrile **2156** (41 mg, 0.12 mmol, 1.0 equiv), Zn^0 (160 mg, 2.44 mmol, 20 equiv), and Cp_2TiCl_2 (1.6 mg, 6.4 μmol, 5 mol%) in dry THF (1.2 mL). Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 20:1 Hex/EtOAc) provided the title compound (40 mg, 0.09 mmol, 76% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 [br s, 1H, (H_2N)C=CH], 6.77 [d, J = 18.5Hz, 1H, C*H*=CHSi(CH_3)$_3$], 5.96 (dddd, J = 6.0, 6.0, 10.5, 17.5 Hz, 1H, CO_2CH_2CH=$CH_{trans}H_{cis}$), 5.82 [d, J = 18.5 Hz, 1H, CH=C*H*Si(CH_3)$_3$], 5.32 (dddd, J = 2.0, 2.0, 2.0, 17.5 Hz, 1H, CO_2CH_2CH=C$H_{trans}H_{cis}$), 5.21 (dddd, J = 1.5, 1.5, 1.5, 10.5 Hz, 1H, CO_2CH_2CH=$CH_{trans}H_{cis}$), 4.67 [br s, 1H, (H_2N)C=CH], 4.61 [s, 1H, (H_2N)C=C*H*], 4.58 (ddd, J = 1.5, 1.5, 5.5 Hz, 2H, CO_2CH_2CH=$CH_{trans}H_{cis}$), 4.46 [dddd, J = 3.5, 3.5, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.12 [ABq, $\Delta\nu_{AB}$ = 39.4 Hz, J_{AB} = 15.0 Hz, 2H, CH_2(H_2N)C=CH], 2.78 [dd, J = 6.5, 16.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.66 [dd, J = 6.5, 17.5 Hz, 1H, CH_2CH(OTBS)CH_2], 2.48 [dd, J = 3.0, 16.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.36 [dd, J = 3.0, 17.5 Hz, 1H, CH_2CH(OTBS)CH_2], 0.87 [s, 9H, (CH_3)$_3$CSi(CH_3)$_2$], 0.10 [s, 9H, Si(CH_3)$_3$], 0.06 [s, 3H, (CH_3)$_3$CSi(CH_3)$_2$], and 0.05 [s, 3H, (CH_3)$_3$CSi(CH_3)$_2$].

LC / LR APCI-MS [Symmetry® C_8, 3.9 x 150 mm, 5 μm, 50 → 100% MeOH/H_2O (98:2)]: t_R 18.4 min; *m*/*z* $[M+H]^+$ 436.

(±)-(*Z*)-METHYL 3-AMINO-4-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-((*E*)-2-TRIMETHYLSILYLVINYL)CYCLOPENT-1-EN-1-YL)BUT-2-ENOATE (2277)



2156 ***2277***

[*MJJ-VII-91*] According to the GENERAL PROCEDURE, a solution of distilled methyl bromoacetate (512 mg, 3.35 mmol, 10 equiv) in dry THF (1.0 mL) was added over the course of 2.5 h to a mixture of the allylic nitrile **2156** (111 mg, 0.33 mmol, 1.0 equiv), Zn^0 (431 mg, 6.59 mmol, 20 equiv), and Cp_2TiCl_2 (4.2 mg, 0.017 mmol, 5 mol%) in dry THF (3.0 mL). Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 15:1 Hex/EtOAc) provided the title compound (114 mg, 0.27 mmol, 83% yield corrected for purity).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 [br s, 1H, (*H*$_2$N)C=CH], 6.78 [d, *J* = 18.5 Hz, 1H, C*H*=CHSi(CH$_3$)$_3$], 5.82 [d, *J* = 19.0 Hz, 1H, CH=C*H*Si(CH$_3$)$_3$], 4.65 [br s, 1H, (*H*$_2$N)C=CH], 4.58 [s, 1H, (H$_2$N)C=C*H*CO$_2$CH$_3$], 4.46 [dddd, *J* = 3.5, 3.5, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.65 (s, 3H, CO$_2$C*H*$_3$), 3.11 [ABq, $\Delta\nu_{AB}$ = 38.3 Hz, J_{AB} = 15.5 Hz, 2H, C*H*$_2$(H$_2$N)C=CH], 2.78 [dd, *J* = 6.5, 16.0 Hz, 1H, C*H*$_2$CH(OTBS)CH$_2$], 2.66 [dd, *J* = 7.0, 17.5 Hz, 1H, CH$_2$CH(OTBS)C*H*$_2$], 2.48 [dd, *J* = 3.0, 16.0 Hz, 1H, C*H*$_2$CH(OTBS)CH$_2$], 2.36 [dd, *J* = 3.5, 17.5 Hz, 1H, CH$_2$CH(OTBS)C*H*$_2$], 0.87 [s, 9H, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$], 0.10 [s, 9H, Si(C*H*$_3$)$_3$], 0.06 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$], and 0.05 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$].

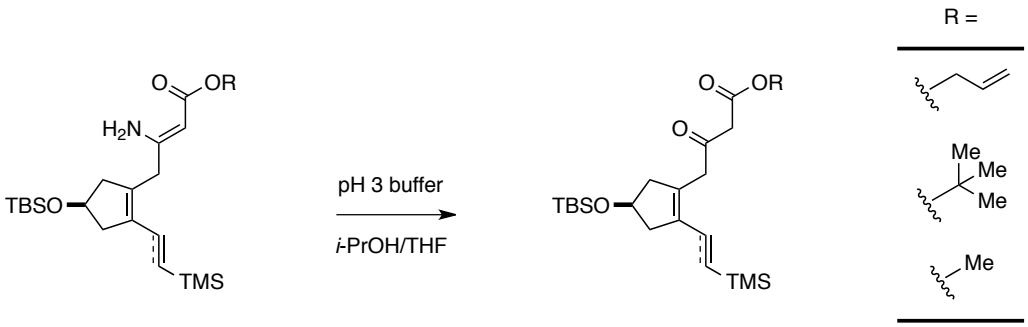
^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 160.6, 138.2, 136.3, 133.4, 132.2, 84.0, 70.6, 50.3, 46.8, 42.9, 34.8, 26.0, 18.3, -1.1, -4.58, and -4.62.

IR (neat): 3446, 3334, 2952, 2931, 2899, 2856, 1672, 1618, 1558, 1250, 1164, 863, 839, and 778 cm^{-1}.

HR ESI-MS: $C_{21}H_{39}NO_3Si_2$ $[M+H]^+$ requires 410.2541; found 410.2559.

TLC: R_f 0.28 (9:1 Hex/EtOAc).

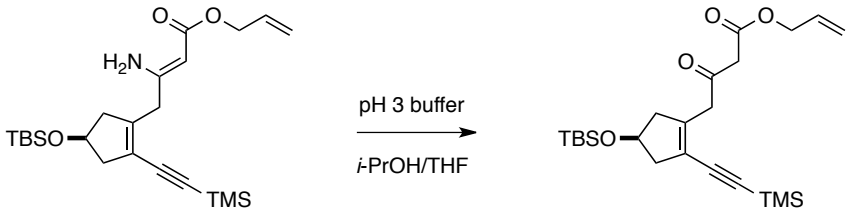
ENAMINO ESTER HYDROLYSIS: GENERAL PROCEDURE



2274–2277 ***2278–2280/2282***

A sample of the respective enamino ester (**2274**–**2277**) was dissolved in *i*-PrOH (or *i*-PrOH/H_2O) and then pH 3 buffer was added at rt. The resulting cloudy mixture that inevitably formed was made homogeneous by the dropwise addition of THF. The reaction mixture was allowed to stir for the indicated period of time while monitoring conversion by LC-MS analysis. Unless stated otherwise, the reaction mixture was processed in the following manner: It was diluted with EtOAc, poured onto brine, and the layers were shaken and separated. The aqueous phase was extracted with EtOAc (2–3x), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue was then purified by medium pressure liquid chromatography (SiO_2) to provide the corresponding β-keto esters **2278**–**2280**/**2282** (for the preparation of **2281**, consult the previous section).

(±)-ALLYL 4-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(TRIMETHYLSILYLETHYNYL)-CYCLOPENT-1-EN-1-YL)-3-OXOBUTANOATE (2278)



2274 ***2278***

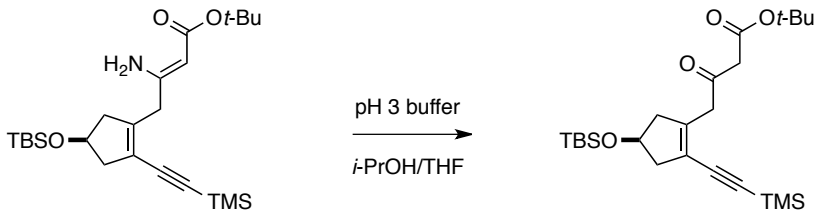
[*MJJ-IV-206/286*] According to the GENERAL PROCEDURE, a solution of the enamino allyl ester **2274** (100 mg, 0.23 mmol) in *i*-PrOH/THF/H_2O (8:4:1, 2.6 mL) was treated with pH 3 buffer (1.6 mL). After having been stirred for 2 d at rt, reaction mixture was diluted with EtOAc, poured onto 1:1 satd aq $NaHCO_3/H_2O$, and the layers were shaken and separated. The aqueous phase was extracted with EtOAc (3x), and the combined organic extracts were washed with brine (1x), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 40:1 Hex/EtOAc) provided the title compound (88 mg, 0.20 mmol, 88% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.91 (dddd, J = 6.0, 6.0, 10.5, 16.5 Hz, 1H, CH_2–C*H*=$CH_{trans}H_{cis}$), 5.34 (dddd, J = 1.5, 1.5, 1.5, 17.0 Hz, 1H, CH_2CH=C$H_{trans}H_{cis}$), 5.26 (dddd, J = 1.5, 1.5, 1.5, 10.5 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 4.64 (ddd, J = 1.5, 1.5, 6.0 Hz, 2H, CH_2CH=$CH_{trans}H_{cis}$), 4.47 [dddd, J = 3.5, 3.5, 6.5, 6.5 Hz, 1H, C*H*(OTBS)], 3.54 [ABq, $\Delta\nu_{AB}$ = 10.8 Hz, J_{AB} = 16.0 Hz, 2H, $CH_2C(O)CH_2CO_2$Allyl], 3.48 [ABX_4, $\Delta\nu_{AB}$ = 10.1 Hz, J_{AB} =15.0 Hz, J_{AX} = J_{BX} = 1.5 Hz, 2H, CH_2C(O)CH_2CO_2Allyl], 2.76 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 6.5, 16.5 Hz, 1H, CH_2CH(OTBS)CH_2], 2.68 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 7.0, 17.5 Hz, 1H, CH_2CH(OTBS)CH_2], 2.45 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 3.0, 16.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.31 [dddddd, J = 1.0, 1.0, 1.0, 1.0, 4.0, 18.0 Hz, 1H, CH_2CH(OTBS)CH_2], 0.87 [s, 9H, (CH_3)$_3$CSi$(CH_3)_2$], 0.20 [s, 9H, C≡CSi$(CH_3)_3$], 0.043 [s, 3H, $(CH_3)_3$CSi(CH_3)$_2$], and 0.036 [s, 3H, $(CH_3)_3$CSi(CH_3)$_2$].

LC / LR ESI-MS [Symmetry® C_8, 3.9 x 150 mm, 5 μm, 50 → 100% MeOH/H_2O (98:2)]: t_R 17.1 min; *m*/*z* $[M+NH_4]^+$ 452.

TLC: R_f 0.74 (4:1 Hex/EtOAc).

(±)-*TERT*-BUTYL 4-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(TRIMETHYLSILYLETHYNYL)-CYCLOPENT-1-EN-1-YL)-3-OXOBUTANOATE (2280)



2276 ***2280***

[*MJJ-VI-290*] According to the GENERAL PROCEDURE, a solution of the enamino *tert*-butyl ester **2276** (67.8 mg, 0.151 mmol) in *i*-PrOH (1.5 mL) was treated with pH 3 buffer (1.5 mL) and then THF (1.0 mL). After having been stirred for 22 h at rt, reaction work-up provided a crude residue that was purified by medium pressure liquid chromatography (SiO_2, 40:1 Hex/EtOAc) to provide the title compound as a light yellow oil (55.2 mg, 0.122 mmol, 81% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.47 [dddd, J = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.47 [ABX_4, $\Delta\nu_{AB}$ = 23.8 Hz, J_{AB} = 15.5 Hz, J_{AX} = J_{BX} = 1.5 Hz, 2H], 3.41 [ABq, $\Delta\nu_{AB}$ = 7.1 Hz, J_{AB} = 16.0 Hz, 2H], 2.75 [dddddd, J = 2.0, 2.0, 2.0, 2.0, 6.5, 16.5 Hz, 1H, CH_2CH(OTBS)CH_2], 2.69 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 7.0, 17.5 Hz, 1H, CH_2CH(OTBS)CH_2], 2.45 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 4.5, 16.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.31 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 4.0, 18.0 Hz, 1H, CH_2CH(OTBS)CH_2], 1.47 [s, 9H, $CO_2C(CH_3)_3$], 0.87 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.20 [s, 9H, $Si(CH_3)_3$], 0.042 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.036 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

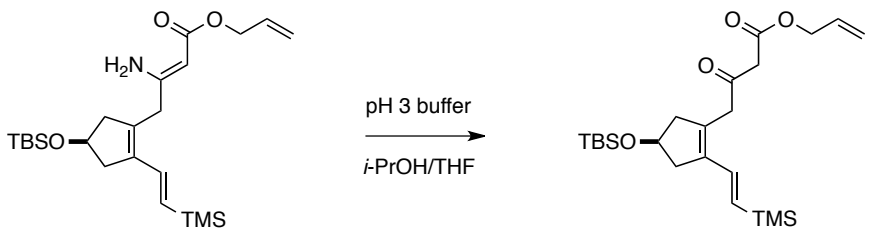
^{13}C NMR (75 MHz, $CDCl_3$): δ 200.1, 166.4, 141.8, 120.7, 100.9, 99.7, 82.0, 71.2, 50.0, 46.3, 45.8, 45.2, 28.1, 26.0, 18.3, 0.2, and -4.7.

IR (neat): 2956, 2931, 2857, 2142, 1740, 1720, 1251, and 842 cm^{-1}

HR ESI-MS: $C_{24}H_{42}O_4Si_2$ $[M+Na]^+$ requires 473.2514; found 473.2533.

TLC: R_f 0.33 (15:1 Hex/EtOAc).

(±)-(*E*)-ALLYL 4-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(2-TRIMETHYLSILYLVINYL)-CYCLOPENT-1-EN-1-YL)-3-OXOBUTANOATE (2279)



2275 ***2279***

[*MJJ-V-158/VI-56/59*] According to the GENERAL PROCEDURE, a solution of the enamino allyl ester **2275** (29 mg, 66.3 μmol) in *i*-PrOH/THF/H_2O (8:8:1, 0.85 mL) was treated with pH 3 buffer (1.0 mL). After having been stirred for 18 h at rt, reaction mixture was diluted with EtOAc, poured onto 1:1 brine/H_2O, and the layers were shaken and separated. The aqueous phase was extracted with EtOAc (2x), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 20:1 Hex/EtOAc) provided the title compound (23 mg, 52.7 μmol, 80% yield, 91% yield based on recovered starting material) followed by unreacted **2275** (3.4 mg, 7.8 μmol, 12% yield).

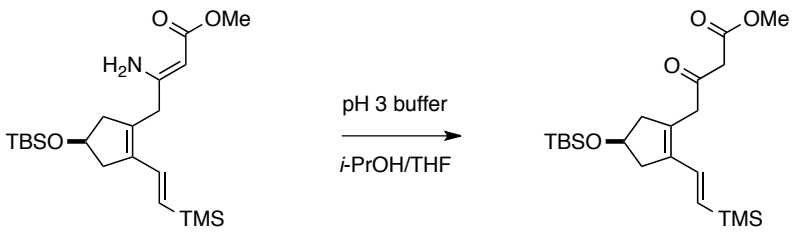
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.73 [d, J = 19.0 Hz, 1H, C*H*=CHSi$(CH_3)_3$], 5.90 (dddd, J = 6.0, 6.0, 10.5, 17.5 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.81 [d, J = 19.0 Hz, 1H, CH=C*H*Si$(CH_3)_3$], 5.33 (dddd, J = 2.0, 2.0, 2.0, 17.5 Hz, 1H, CH_2CH=C$H_{trans}H_{cis}$), 5.25

(dddd, J = 1.5, 1.5, 1.5, 10.5 Hz, 1H, $CH_2CH{=}CH_{trans}H_{cis}$), 4.63 (ddd, J = 1.5, 1.5, 6.0 Hz, 2H, $CH_2CH{=}CH_{trans}H_{cis}$), 4.48 [dddd, J = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.47 [ABq, $\Delta\nu_{AB}$ = 11.3 Hz, J_{AB} = 15.5 Hz, 2H, $CH_2C(O)CH_2CO_2$Allyl], 3.46 [ABX_4, $\Delta\nu_{AB}$ = 9.6 Hz, J_{AB} = 15.5 Hz, $J_{AX} = J_{BX}$ = 1.5 Hz, 2H, $CH_2C(O)CH_2CO_2$Allyl], 2.78 [dd, J = 6.5, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.73 [dd, J = 7.5, 18.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.46 [dd, J = 3.5, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.37 [dd, J = 3.5, 17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 0.88 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.10, [s, 9H, $CH{=}CHSi(CH_3)_3$], 0.06 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.05 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

LC / LR ES+APCI-MS [Zorbax SB-C_{18}, 2.1 x 30 mm, 3.5 µm, 50 → 100% MeOH/H_2O (98:2)]: t_R 7.08 min; m/z $[M\text{-}H]^-$ 435.

TLC: R_f 0.46 (9:1 Hex/EtOAc).

(±)-(*E*)-METHYL 4-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(2-TRIMETHYLSILYL-VINYL)CYCLOPENT-1-EN-1-YL)-3-OXOBUTANOATE (2282)



2277 ***2282***

[*MJJ-VII-92*] According to the GENERAL PROCEDURE, a solution of the enamino methyl ester **2277** (65 mg, 0.16 mmol) in *i*-PrOH (1.6 mL) was treated with pH 3 buffer (1.6 mL) and then THF (1.0 mL). After having been stirred for 27 h at rt, reaction work-up provided a crude residue that was purified by medium pressure liquid chromatography (SiO_2, 20:1 Hex/EtOAc) to provide the title compound as a light yellow oil (38 mg, 0.09 mmol, 58% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.74 [d, *J* = 18.5 Hz, 1H, C*H*=CHSi$(CH_3)_3$], 5.82 [d, *J* = 18.5 Hz, 1H, CH=C*H*Si$(CH_3)_3$], 4.48 [dddd, *J* = 3.5, 3.5, 6.5, 6.5 Hz, 1H, C*H*(OTBS)], 3.73 (s, 3H, CO_2CH_3), 3.45 [ABq, $\Delta\nu_{AB}$ = 9.6 Hz, J_{AB} = 16.0 Hz, 2H, $CH_2C(O)CH_2$–CO_2CH_3], 3.45 [app s (ABq where $\Delta\nu_{AB}$ << 0.5 Hz), 2H, $CH_2C(O)CH_2CO_2CH_3$], 2.78 [dd, *J* = 7.0, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.72 [dd, *J* = 7.0, 17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.47 [br dd, *J* = 3.5, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.37 [dd, *J* = 4.0, 18.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 0.88 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.10 [s, 9H, CH=CHSi$(CH_3)_3$], 0.062 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.055 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

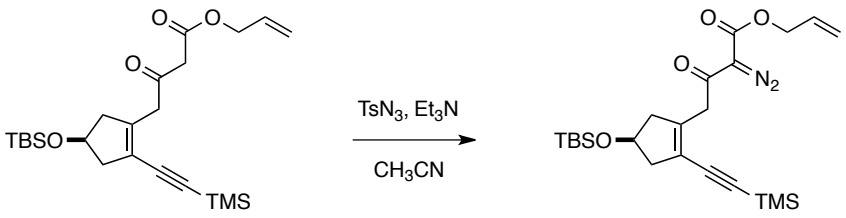
^{13}C NMR (125 MHz, $CDCl_3$): δ 200.2, 167.6, 138.1, 136.4, 132.4, 130.4, 70.5, 52.4, 48.0, 47.6, 43.4, 42.8, 26.0, 18.3, -1.1, and -4.6.

IR (neat): 2954, 2930, 2898, 2856, 1750, 1721, 1248, 1094, 1063, 864, and 839 cm^{-1}.

HR ESI-MS: $C_{21}H_{38}O_4Si_2$ $[M+H]^+$ requires 411.2381; found 411.2385.

TLC: R_f 0.34 (9:1 Hex/EtOAc).

(±)-ALLYL 4-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(TRIMETHYLSILYLETHYNYL)-CYCLOPENT-1-EN-1-YL)-2-DIAZO-3-OXOBUTANOATE (2289)



2278 ***2289***

[*MJJ-IV-222/V-23*] A solution of *p*-toluenesulfonyl azide (TsN_3) was prepared by dissolving the neat reagent (130 mg, 0.66 mmol) in dry CH_3CN (1.2 mL). The resulting stock solution, which was 0.55 M [TsN_3], was utilized immediately in the following procedure.

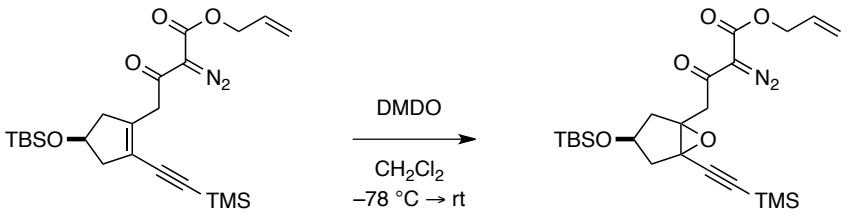
An aliquot of the TsN_3 stock solution (50 μL, 27.6 μmol, 1.1 equiv) and Et_3N (6.0 mg, 59.3 μmol, 2.5 equiv) were sequentially added via WIRETROL® to a solution of the β-keto ester **2278** (10.5 mg, 24.2 μmol, 1.0 equiv) in dry CH_3CN (300 μL). After having been stirred at rt for 45 min, an additional portion of the TsN_3 stock solution (25 μL, 13.8 μmol, 0.6 equiv) was added. Stirring was continued for 1 h 45 min, at which point the reaction mixture was concentrated *in vacuo*. Purification of the crude residue by flash chromatography (99:1 Hex/EtOAc) provided the title compound (8.7 mg, 18.9 μmol, 78% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.95 (dddd, J = 5.5, 5.5, 10.5, 17.0 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.36 (dddd, J = 1.5, 1.5, 1.5, 17.0 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.30 (dddd, J = 1.5, 1.5, 1.5, 10.5 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 4.75 (ddd, J = 1.5, 1.5, 5.5 Hz, 2H, CH_2CH=$CH_{trans}H_{cis}$), 4.50 [dddd, J = 4.5, 4.5, 7.0, 7.0 Hz, 1H, CH(OTBS)], 3.86 [ABq, $\Delta\nu_{AB}$ = 51.4 Hz, J_{AB} = 17.0 Hz, 2H, $CH_2C(O)C(N_2)CO_2$Allyl], 2.77-2.71 [m, 2H, overlapping $CH_2CH(OTBS)CH_2$], 2.46 [br dd, J = 4.0, 16.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.36 [br dd, J = 4.5, 17.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 0.87 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.18 [s, 9H, $C{\equiv}CSi(CH_3)_3$], 0.041 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.036 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

LR ESI-MS: $C_{23}H_{36}N_2O_4Si_2$ $[M+Na]^+$ requires 483.21; found 483.22.

TLC: R_f 0.32 (9:1 Hex/EtOAc).

(±)-ALLYL 4-(3-(*TERT*-BUTYLDIMETHYLSILOXY)-5-(TRIMETHYLSILYLETHYNYL)-6-OXABICYCLO[3.1.0]HEXAN-1-YL)-2-DIAZO-3-OXOBUTANOATE (2290)



2289 ***2290***

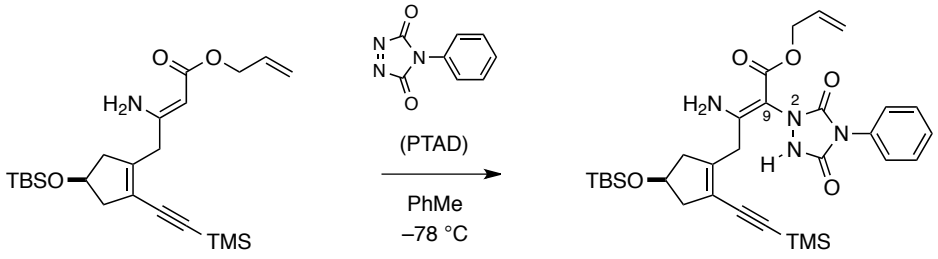
[*MJJ-IV-223*] An acetone solution of DMDO (400 μL, 44 μmol, 2.7 equiv, 0.11 M) was added to a solution of the α-diazo β-keto ester **2289** (7.6 mg, 16.5 μmol, 1.0 equiv) in CH_2Cl_2 (300 μL) at –78 °C. No observable reaction occurred at this temperature, and thus the reaction mixture was allowed to warm to 0 °C. After having been maintained with stirring for 2 h at 0 °C, the appearance of a single new, slightly more polar component was observed by TLC analysis (6:1 Hex/EtOAc). The reaction mixture was then allowed to warm to rt, held at this temperature for an additional 2.5 h, and concentrated *in vacuo* to provide the title compound (quantitative yield assumed). On the basis of ^{1}H NMR analysis, **2290** was cleanly formed as essentially a single diastereomer of unknown relative configuration.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.95 (dddd, J = 5.5, 5.5, 10.0, 17.0 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.36 (dddd, J = 1.5, 1.5, 1.5, 17.0 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.31 (dddd, J = 1.5, 1.5, 1.5, 10.5 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 4.74 (ddd, J = 1.5, 1.5, 6.0 Hz, 2H, CH_2CH=$CH_{trans}H_{cis}$), 4.03 [dddd, J = 7.5, 7.5, 7.5, 7.5, 1H, C*H*(OTBS)], 3.37 [ABq, $\Delta\nu_{AB}$ = 54.8 Hz, J_{AB} = 18.0 Hz, 2H, $CH_2C(O)C(N_2)CO_2$Allyl], 2.59 [dd, J = 7.0, 13.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.56 [dd, J = 7.5, 13.5 Hz, 1H, $CH_2CH(OTBS)CH_2$], 1.94 [dd, J = 7.0, 14.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 1.78 [dd, J = 7.5, 14.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 0.85 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.17 [s, 9H, $C{\equiv}CSi(CH_3)_3$], and 0.01 [s, 6H, $(CH_3)_3CSi(CH_3)_2$].

HR ESI-MS: $C_{23}H_{36}N_2O_5Si_2$ $[M+Na]^+$ requires 499.2055; found 499.2049.

TLC: R_f 0.38 (6:1 Hex/EtOAc).

(±)-(*E*)-ALLYL 3-AMINO-4-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(TRIMETHYLSILYLETHYNYL)CYCLOPENT-1-EN-1-YL)-2-(3,5-DIOXO-4-PHENYL-1,2,4-TRIAZOLIDIN-1-YL)BUT-2-ENOATE (2299)



2274 ***2299***

[*MJJ-IV-282/V-25/34*] A solution of 4-phenyl-1,2,4-triazole-3,5-dione (PTAD) was prepared by dissolving the sublimed reagent (13.3 mg, 75.9 μmol) in dry PhMe (1.5 mL) (occasionally, heating was required to obtain a homogenous, blood red solution). The resulting stock solution, which was 0.05 M [PTAD], was utilized immediately in the following procedure.

A vigorously stirred solution of the allyl enamino ester **2274** (15.5 mg, 35.7 μmol, 1.0 equiv) in dry PhMe (100 μL) at –78 °C was treated dropwise with an aliquot (700 μL, 35.7 μmol, 1.0 equiv) of the PTAD stock solution. As each drop of this solution hit the reaction mixture, the deep red PTAD color was quickly (< 1 s) discharged. Once *ca.* 0.8 equiv PTAD had been added, the time required for discharge of the red color began to lengthen somewhat (~ 2–5 s). Full consumption of the starting material was signaled when the addition of 1 more drop of the PTAD stock solution resulted in a color change in the reaction mixture from colorless to light pink. At this point, reaction completion was confirmed by TLC analysis. The reaction mixture was allowed to warm to rt and was

concentrated *in vacuo*. Purification of the crude residue by flash chromatography (3:1 → 1:1 Hex/EtOAc) provided the title compound as a light yellow oil (21.2 mg, 34.8 μmol, 98% yield) that usually solidified upon being placed under high vacuum (< 1 mmHg). On the basis of ^{1}H NMR analysis, this material existed at a 5:1 mixture of isomeric species that are assumed to be C9–N2 rotamers.

The major (†) and minor (‡) isomers have been indicated

^{1}H NMR (500 MHz, CD_3CN): δ 8.45† (br s, 1H, N*H*), 8.32† (br s, 1H, N*H*), 8.27‡ (br s, 1H, N*H*), 8.12‡ (br s, 1H, N*H*), 7.51-7.37 (m, 10H, NC_6H_5) 6.34† (br s, 1H, N*H*), 6.04‡ (br s, 1H, N*H*), 5.89‡ (dddd, *J* = 5.0, 5.0, 10.5, 17.5 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.87† (dddd, *J* = 5.0, 5.0, 10.5, 17.0 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.26‡ (dddd, *J* = 2.0, 2.0, 2.0, 17.5 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.25† (dddd, *J* = 2.0, 2.0, 2.0, 17.0 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.15‡ (dddd, *J* = 1.5, 1.5, 1.5, 10.5 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.12† (dddd, *J* = 2.0, 2.0, 2.0, 11.0 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 4.59‡ (ddd, *J* = 2.0, 2.0, 5.5 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 4.56† (ddd, *J* = 1.5, 1.5, 5.0 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 4.51†‡ [dddd, *J* = 1.0, 1.0, 5.5, 5.5 Hz, 2H, overlapping C*H*(OTBS)], 3.44‡ [ABq, $\Delta\nu_{AB}$ = 135 Hz, J_{AB} = 14.5 Hz, 2H, $CH_2C(NH_2)$], 3.38† [ABq, $\Delta\nu_{AB}$ = 295 Hz, J_{AB} = 14.0 Hz, 2H, $CH_2C(NH_2)$], 2.81-2.66†‡ [m, 4H, overlapping $CH_2CH(OTBS)CH_2$], 2.34†‡ [dddd, *J* = 1.0, 1.0, 1.0, 16.0 Hz, 2H, overlapping $CH_2CH(OTBS)CH_2$], 2.24†‡ [dddd, *J* = 1.0, 1.0, 1.0, 17.5 Hz, 2H, overlapping $CH_2CH(OTBS)CH_2$], 0.88† [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.87‡ [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.13‡ [s, 6H, $(CH_3)_3CSi(CH_3)_2$], 0.12† [s, 3H, $(CH_3)_3CSi(CH_3)_2$], 0.08† [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.05†‡ [s, 18H, $Si(CH_3)_3$].

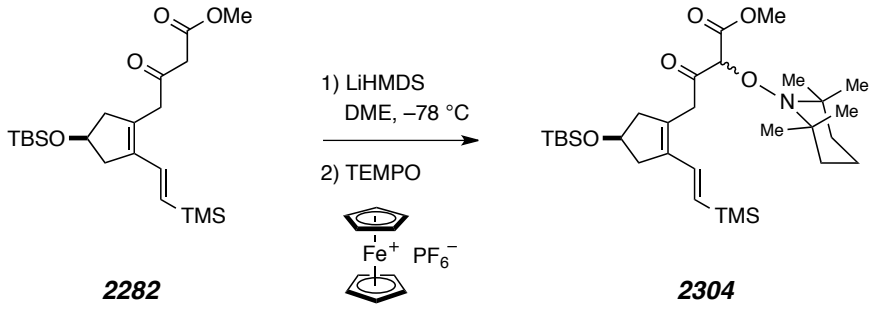
HR ESI-MS: $C_{31}H_{44}N_4O_5Si_2$ $[M+H]^+$ requires 609.2923; found 609.2984.

TLC: R_f 0.40 and 0.23 (2:1 Hex/EtOAc).

Crystalline samples of **2299** were generated by either of two methods. In the first, a small amount of purified **2299** (*ca.* 4 mg) was dissolved in a minimum amount of 1:1

Hex/EtOAc at rt. The resulting solution was stored at –20 °C for 48 h, at which point needle-like crystals had formed {**MP**: 176–178 °C [solvent loss (i.e., bubbling) observed at 171–172 °C]}. Alternatively, vial-in-a-vial vapor diffusion crystallization was used to generate material that was suitable for X-ray analysis (see Figure II–5 and APPENDIX B). A sample of purified **2299** (43 mg) in a 2-mL vial was suspended in EtOAc (300 μL) and the resulting mixture was gently heated (50–55 °C) until a homogeneous solution was obtained. This vial was then placed within a larger, outer vial that contained a shallow layer of hexanes. The outer vial was capped and stored at –20 °C for several weeks, at which point light yellow plates had formed (**MP**: 97–103 °C).

(±)-METHYL 4-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-((*E*)-2-TRIMETHYLSILYL-VINYL)CYCLOPENT-1-EN-1-YL)-3-OXO-2-((2,2,6,6-TETRAMETHYLPIPERIDIN-1-YL)OXY)BUTANOATE (2304)



2282 ***2304***

[*MJJ-VII-106*] A solution LiHMDS was prepared by the dropwise addition of *n*-BuLi (350 μL, 0.88 mmol, 2.5 M in Hex) to a solution of HMDS (200 μL, 155 mg, 0.96 mmol) in dry DME (3.45 mL) at –78 °C, and the resulting mixture was allowed to stir for 30 min. This stock solution, which was 0.22 M [LiHMDS], was utilized immediately in the following procedure.

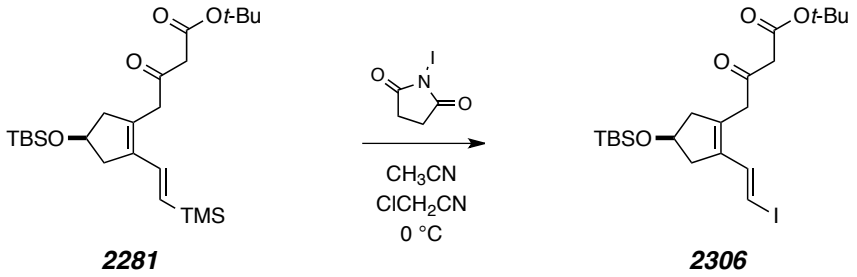
A flame-dried 13 x 100 mm culture tube was charged with dry DME (300 μL) and the methyl β-keto ester **2282** (15.2 mg, 37.0 μmol, 1.0 equiv), and the resulting solution was

cooled to –78 °C. An aliquot of the LiHMDS stock solution (200 μL, 43.8 μmol, 1.2 equiv) was then added dropwise, after which the resulting bright yellow solution was warmed slightly to *ca.* –65 °C ($CHCl_3$/dry ice bath) and stirred 25 min. After having been warmed further to 0 °C, the reaction mixture was treated with freshly sublimed TEMPO (6.4 mg, 41.0 μmol, 1.1 equiv), and, 5 min later, with $[Cp_2Fe]^+ PF_6^-$ (17.4 mg, 52.6 μmol, 1.4 equiv). Stirring was continued at 0 °C for 15 min, at which point the reaction mixture was quenched by the addition of satd aq NH_4Cl, diluted with Et_2O, and filtered through a short pad of SiO_2 (Et_2O). The filtrate was concentrated under reduced pressure and the resulting residue was purified by medium pressure liquid chromatography (SiO_2, 30:1 Hex/EtOAc) to provide the title compound (10.0 mg, 17.7 μmol, 48% yield). On the basis of ^{1}H NMR analysis, **2304** was formed as an inseparable 1:1 mixture of diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.73 [d, J = 18.5 Hz, 1H, CH=C*H*Si$(CH_3)_3$], 6.72 [d, J = 18.5 Hz, 1H, CH=C*H*Si$(CH_3)_3$], 5.76 [d, J = 18.5 Hz, 1H, C*H*=CHSi$(CH_3)_3$], 5.75 [d, J = 18.5 Hz, 1H, C*H*=CHSi$(CH_3)_3$], 4.91 [s, 1H, C(O)C*H*(O–N)CO_2CH_3], 4.88 [s, 1H, C(O)C*H*(O–N)CO_2CH_3], 4.50 [dddd, J = 4.5, 4.5, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 4.47 [dddd, J = 4.5, 4.5, 7.5, 7.5 Hz, 1H, C*H*(OTBS)], 3.734 (s, 3H, CO_2CH_3), 3.730 (s, 3H, CO_2CH_3), 3.62 [ABq, $\Delta\nu_{AB}$ = 132 Hz, J_{AB} = 16.0 Hz, 2H, CH_2C(O)C*H*(O–N)CO_2CH_3], 3.64 [ABq, $\Delta\nu_{AB}$ = 48 Hz, J_{AB} = 17.0 Hz, 2H, CH_2C(O)C*H*(O–N)CO_2CH_3], 2.80-2.70 [m, 4H, overlapping CH_2CH(OTBS)CH_2], 2.46-2.35 [m, 4H, overlapping CH_2CH(OTBS)CH_2], 1.58-0.97 [m, 36H, $(CH_3)_2CCH_2CH_2CH_2C(CH_3)_2$], 0.88 [s, 18H, $(CH_3)_3CSi(CH_3)_2$], 0.10 [s, 9H, Si$(CH_3)_3$], 0.09 [s, 9H, Si$(CH_3)_3$], 0.06 [s, 6H, $(CH_3)_3CSi(CH_3)_2$], and 0.05 [s, 6H, $(CH_3)_3CSi(CH_3)_2$].

HR ESI-MS: $C_{30}H_{55}NO_5Si_2$ $[M+Na]^+$ requires 588.3511; found 588.3524.

(±)-(*E*)-*TERT*-BUTYL 4-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-(2-IODOVINYL)-CYCLOPENT-1-EN-1-YL)-3-OXOBUTANOATE (2306)



2281 ***2306***

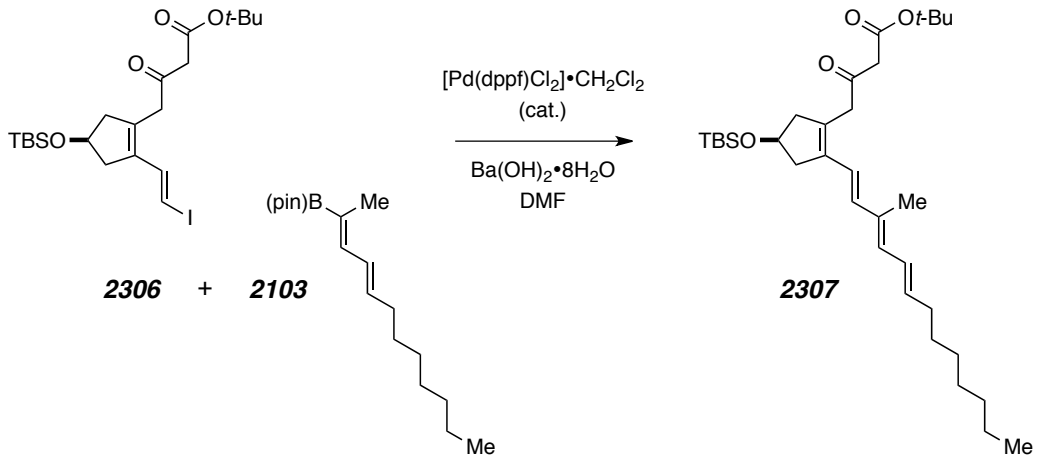
[*MJJ-V-190*] Recrystallized *N*-iodosuccinimide (42.3 mg, 188 μmol, 2.2 equiv) was added in a single portion to a stirred solution of the β-keto ester **2281** (39.0 mg, 86.1 μmol, 1.0 equiv) in $CH_3CN/ClCH_2CN$ (9:1, 1.0 mL) at 0 °C. After having been stirred at this temperature for 1.5 h, LC-MS analysis of the reaction mixture revealed that the starting material had been consumed. The reaction mixture was diluted with Et_2O and quenched by the addition of satd aq $Na_2S_2O_3$, and the resulting mixture was allowed to warm to rt. After 3 h, the reaction mixture was poured onto brine, the layers were shaken and separated, and the aqueous phase was extracted with Et_2O (3x). The combined organic extracts were washed with brine (1x), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 40:1 Hex/EtOAc) provided the title compound (32.8 mg, 64.8 μmol, 75% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, J = 14.0 Hz, 1H, C*H*=CHI), 6.27 (d, J = 14.5 Hz, 1H, CH=C*H*I), 4.49 [dddd, J = 3.5, 3.5, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.40 [ABq (app s) where $\Delta\nu_{AB}$ < 0.5 Hz, 2H, C*H*$_2$C(O)CH$_2$CO$_2$*t*-Bu], 3.35 [ABq, $\Delta\nu_{AB}$ = 17 Hz, J_{AB} = 15.5 Hz, 2H, CH$_2$C(O)C*H*$_2$CO$_2$*t*-Bu], 2.76 [dd, J = 7.0, 16.0 Hz, 1H, C*H*$_2$CH(OTBS)CH$_2$], 2.66 [dd, J = 7.0, 18.0 Hz, 1H, CH$_2$CH(OTBS)C*H*$_2$], 2.44 [br dd, J = 3.5, 15.5 Hz, 1H, C*H*$_2$CH(OTBS)CH$_2$], 2.27 [br dd, J = 3.0, 17.5 Hz, 1H, CH$_2$CH(OTBS)C*H*$_2$], 1.48 [s, 9H, CO$_2$C(C*H*$_3$)$_3$], 0.87 [s, 9H, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$], 0.053 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$], and 0.047 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$].

LC / LR ES+APCI-MS [Zorbax SB-C_{18}, 2.1 x 30 mm, 3.5 μm, 50 → 100% MeOH/H_2O (98:2)]: t_R 6.69 min; *m/z* $[M+H]^+$ 505.

TLC: R_f 0.44 (9:1 Hex/EtOAc).

(±)-*TERT*-BUTYL 4-(4-(*TERT*-BUTYLDIMETHYLSILOXY)-2-((1*E*,3*E*,5*E*)-3-METHYL-TRIDECA-1,3,5-TRIEN-1-YL)CYCLOPENT-1-EN-1-YL)-3-OXOBUTANOATE (2307)



[*MJJ-V-195*] A 13 x 100 mm culture tube was charged sequentially with DMF (200 μL), the vinyl iodide **2306** (6.5 mg, 12.8 μmol, 1.0 equiv), the vinyl boronate **2103** (4.9 mg, 16.8 μmol, 1.3 equiv), $[Pd(dppf)Cl_2]•CH_2Cl_2$ (1.7 mg, 2.3 μmol, 18 mol%), and $Ba(OH)_2•8H_2O$ (11.5 mg, 36.5 μmol, 2.8 equiv). After having been stirred at rt for 1.5 h, the reaction mixture was diluted with EtOAc and quenched by the addition of satd aq NH_4Cl. The layers were shaken and separated, the aqueous phase was extracted with EtOAc (2x), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 40:1 Hex/EtOAc) provided the title compound. On the basis of ^1H NMR analysis, **2307** had been cleanly formed (enol content *ca.* 5%).

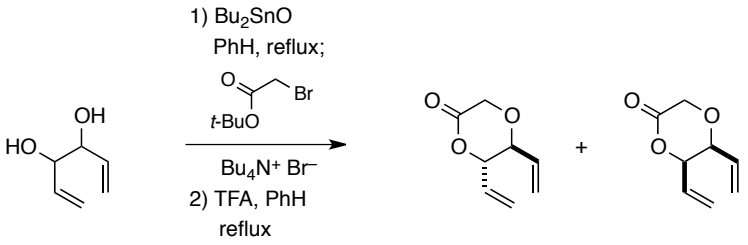
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.40 [d, *J* = 15.5 Hz, 1H, C*H*=CHC(CH_3)=CHCH=CH], 6.39 [dddd, *J* = 1.5, 1.5, 11.0, 15.0 Hz, 1H, CH=CHC(CH_3)=CHC*H*=CH], 6.23 [d, *J* = 15.5 Hz, 1H, CH=C*H*C(CH_3)=CHCH=CH], 6.12 [d, *J* = 11.0 Hz, 1H, CH=CH–C(CH_3)=C*H*CH=CH], 5.77 [ddd, *J* = 7.0, 7.0, 14.5 Hz, 1H, CH=CHC(CH_3)=CH–CH=C*H*], 4.51 [dddd, *J* = 3.5, 3.5, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.43 [ABq, $\Delta\nu_{AB}$ = 9.3 Hz, J_{AB} = 16.0 Hz, 2H, C*H*$_2$C(O)CH_2CO_2*t*-Bu], 3.35 [ABq, $\Delta\nu_{AB}$ = 13 Hz, J_{AB} = 15.5 Hz, 2H, CH_2C(O)C*H*$_2$$CO_2$*t*-Bu], 2.81 [dd, *J* = 7.0, 15.5 Hz, 1H, C*H*$_2$CH(OTBS)CH_2], 2.73 [dd, *J* = 6.5, 17.5 Hz, 1H, CH_2CH(OTBS)C*H*$_2$], 2.50 [dd, *J* = 3.5, 16.0 Hz, 1H, C*H*$_2$CH(OTBS)CH_2], 2.36 [dd, *J* = 3.0, 17.5 Hz, 1H, CH_2CH(OTBS)C*H*$_2$], 2.14 [ddd, *J* = 7.0, 7.0, 7.0 Hz, 2H, CH=CHC*H*$_2$$CH_2$($CH_2$)$_4$$CH_3$], 1.89 [s, 3H, C*H*=CHC(C*H*$_3$)=CH–CH=CH], 1.46 [s, 9H, CO_2C(C*H*$_3$)$_3$], 1.43-1.36 [m, 2H, CH=CHCH$_2$C*H*$_2$(CH_2)$_4$$CH_3$], 1.33-1.25 [m, 8H, CH=CHCH$_2$$CH_2$(C*H*$_2$)$_4$$CH_3$], 0.88 [s, 9H, (C*H*$_3$)$_3$CSi($CH_3$)$_2$], 0.07 [s, 3H, ($CH_3$)$_3$CSi(C*H*$_3$)$_2$], and 0.06 [s, 3H, ($CH_3$)$_3$CSi(C*H*$_3$)$_2$].

LR ESI-MS: $C_{33}H_{56}O_4Si$ $[M+Na]^+$ requires 567.38; found 567.52.

TLC: R_f 0.32 (20:1 Hex/EtOAc).

B–2. CHAPTER III

(±)-*TRANS*- and (±)-*CIS*-5,6-DIVINYL-1,4-DIOXAN-2-ONE (3036-trans/3036-cis)



3038 ***3036-trans*** ***3036-cis***

[*MJJ-VI-264*] To a solution of hexa-1,5-diene-3,4-diol as a mixture of diastereomers (**3038**) (518 mg, 4.54 mmol, 1.0 equiv) in benzene (~85 mL) was added Bu_2SnO (1.24 g, 4.99 mmol, 1.1 equiv). The flask was fitted with a Dean–Stark trap and a West condenser, and the reaction mixture was refluxed for 2 h with azeotropic removal of H_2O (approximately 40 mL of benzene was also removed via a stopcock on the Dean–Stark trap). The reaction mixture was then cooled to rt and treated sequentially with *tert*-butyl bromoacetate (740 μL, 978 mg, 5.01 mmol, 1.1 equiv) and $Bu_4N^+ Br^-$ (1.65 g, 5.12 mmol, 1.1 equiv). The flask was fitted with a West condenser and the reaction mixture was again heated to reflux and maintained at this temperature for 42 h. After having been cooled to rt, the reaction mixture was filtered through CELITE® and concentrated *in vacuo*. This residue was passed through a short bed of SiO_2 (EtOAc eluent) and the filtrate was evaporated to dryness. Purification of the crude residue by flash chromatography (20:1 → 6:1 → 4:1 Hex/EtOAc) provided a mixture of **3036-trans** and **3036-cis** (contaminated by their hydroxy esters precursors). This mixture was dissolved in benzene (40 mL) and treated with TFA (100 μL, 149 mg, 1.31 mmol). After having been refluxed for 18 h, the reaction mixture was cooled to rt and concentrated *in vacuo*. Filtration through SiO_2 (EtOAc eluent), evaporation to dryness, and purification of the crude residue (which contained the partially co-eluting mixture of **3036-trans** and **3036-cis**) by medium

pressure liquid chromatography (SiO_2, 6:1 Hex/EtOAc) provided >95% pure **3036-trans** (174 mg, 1.13 mmol) followed by 90% pure **3036-cis** (260 mg, 1.69 mmol). On the basis of ^{1}H NMR analysis, this latter fraction was a 9.5:1 mixture **3036-cis** and **3036-trans**. The combined yield of **3036-trans**/**3036-cis** was 62%.

HR ESI-MS [ascertained from a mixture of **3036-trans** and **3036-cis**]:
$C_8H_{10}O_3$ $[M+MeOH+Na]^+$ requires 209.0784; found 209.0784.

Analytical data for **3036-trans**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.79 (ddd, *J* = 6.5, 11.0, 17.0 Hz, 1H, C*H*=$CH_{trans}H_{cis}$), 5.77 (ddd, *J* = 5.5, 11.0, 17.0 Hz, 1H, C*H*=$CH_{trans}H_{cis}$), 5.50 (ddd, *J* = 1.0, 1.0, 17.0 Hz, 1H, CH=C*H*$_{trans}$H$_{cis}$), 5.49 (ddd, *J* = 1.5, 1.5, 17.5 Hz, 1H, CH=C*H*$_{trans}$H$_{cis}$), 5.41 (ddd, *J* = 1.0, 1.0, 11.0 Hz, 1H, CH=CH$_{trans}$*H*$_{cis}$), 5.40 (ddd, *J* = 1.5, 1.5, 10.5 Hz, 1H, CH=CH$_{trans}$*H*$_{cis}$), 4.74 [dddd, *J* = 1.5, 1.5, 6.5, 9.0 Hz, 1H, *H*COC(O)CH_2OCH], 4.44 [ABq, $\Delta\nu_{AB}$ = 109.8 Hz, J_{AB} = 18.0 Hz, 2H, OC(O)C*H*$_2$O], and 3.93 [dddd, *J* = 1.5, 1.5, 6.0, 8.5 Hz, 1H, HCOC(O)CH_2OC*H*].

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 131.3, 131.1, 120.8, 120.6, 83.1, 76.8, and 65.3.

IR (neat): 1750, 1260, 1226, 1008, 989, and 939 cm^{-1}.

GC / LR EI-MS [5025015]: t_R 4.94 min; *m*/*z* (rel. int.) 98 (94), 96 (26), 79 (55), 77 (37), 70 (100), 69 (44), and 55 (35).

TLC: R_f 0.34 (4:1 Hex/EtOAc).

Analytical data for **3036-cis**:

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.95 (ddd, *J* = 6.5, 10.5, 17.0 Hz, 1H, C*H*=CH_2), 5.74 (ddd, *J* = 5.5, 11.0, 17.5 Hz, 1H, C*H*=CH_2), 5.45 (ddd, *J* = 1.5, 1.5, 17.0 Hz, 1H, CH=C*H*$_{trans}$H$_{cis}$), 5.44 (ddd, *J* = 1.5, 1.5, 10.5 Hz, 1H, CH=CH$_{trans}$*H*$_{cis}$), 5.42 (ddd, *J* = 1.5, 1.5, 17.0 Hz, 1H, CH=C*H*$_{trans}$H$_{cis}$), 5.39 (ddd, *J* = 1.5, 1.5, 11.0 Hz, 1H, CH=CH$_{trans}$*H*$_{cis}$), 4.90 [dddd, *J* = 1.5, 1.5, 4.5, 4.5 Hz, 1H, *H*COC(O)CH_2COCH], 4.47

[ABq, $\Delta\nu_{AB}$ = 51.8 Hz, J_{AB} = 17.5 Hz, 2H, HCOC(O)C*H*$_2$OCH], and 4.43 [dddd, *J* = 1.5, 1.5, 4.5, 4.5 Hz, 1H, HCOC(O)CH$_2$OC*H*].

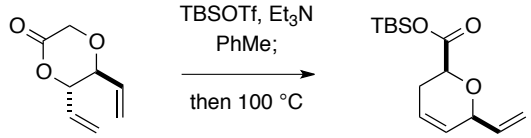
^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 131.0, 130.9, 120.9, 119.9, 81.7, 75.0, and 65.2.

IR (neat): 1747, 1218, 1006, 989, and 936 cm^{-1}.

GC / LR EI-MS [5025015]: t_R 5.06 min; *m*/*z* (rel. int.) 98 (98), 96 (27), 79 (53), 77 (37), 70 (100), 69 (48), and 55 (36).

TLC: R_f 0.32 (4:1 Hex/EtOAc).

(±)-*CIS*-*TERT*-BUTYLDIMETHYLSILYL 6-VINYL-3,6-DIHYDRO-2*H*-PYRAN-2-CARBOXYLATE (3034-cis)



3036-trans ***3034-cis***

[*MJJ-III-192/VI-265/VII-54*] A flame-dried culture tube (25 x 150 mm) was fitted with a rubber septum and charged with **3036-trans** (119 mg, 0.77 mmol, 1.0 equiv), dry PhMe (7.0 mL), and Et_3N (430 μL, 312 mg, 3.09 mmol, 4.0 equiv). Neat, freshly distilled TBSOTf (360 μL, 414 mg, 1.57 mmol, 2.0 equiv) was added dropwise, which produced a cloudy, tan colored solution. The rubber septum was then replaced with a TEFLON®-lined cap, and the reaction mixture was maintained at rt with stirring for 45 min. At this point, the reaction mixture was immersed in an oil bath that had been preheated to 100–110 °C and, after having been stirred at this temperature for 1.5 h, analysis of the reaction mixture by TLC and GC-MS indicated that the starting material had been consumed. The reaction mixture was cooled to rt and filtered through TMS-functionalized SiO_2 (PhMe eluent, see General Experimental Protocols). Concentration *in vacuo*, filtration through

TMS-functionalized SiO_2 (pentane eluent), and solvent evaporation provided the TBS ester **3034-cis** as a light yellow oil (179 mg, 0.67 mmol). The lability of this compound was apparent from the fact that multiple components were observed by TLC analysis upon chromatography on normal SiO_2 (even when deactivated with Et_3N-doped eluents). Moreover, neat samples of **3034-cis** decomposed within several hours upon storage at rt. Consequently, it was prepared immediately before use in the following reaction.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.89-5.85 (m, 1H, C*H*=CH), 5.87 (ddd, *J* = 6.5, 10.5, 17.0 Hz, 1H, C*H*=CH$_{trans}$H$_{cis}$), 5.67 (dddd, *J* = 2.0, 2.0, 2.0, 10.0 Hz, 1H, CH=C*H*), 5.35 (ddd, *J* = 1.5, 1.5, 17.0 Hz, 1H, CH=C*H*$_{trans}$H$_{cis}$), 5.18 (ddd, *J* = 1.5, 1.5, 10.5 Hz, 1H, CH=CH$_{trans}$*H*$_{cis}$), 4.70 (dddddd, *J* = 1.0, 1.0, 3.5, 3.5, 5, 6 Hz, 1H, CH=CHC*H*–CH=CH$_{trans}$H$_{cis}$), 4.25-4.22 (nfom, 1H, C*H*CO$_2$TBS), 2.35-2.31 (m, 2H, C*H*$_2$), 0.94 [s, 9H, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$], 0.30 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$], and 0.29 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 137.0, 129.0, 123.9, 116.6, 76.5, 72.9, 28.0, 25.6, and -4.8.

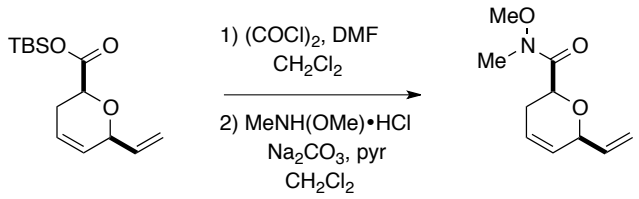
IR (neat): 2955, 2933, 2891, 2860, 2361, 2340, 1745, 1722, 1255, 1219, 1185, 1103, 843, and 793 cm^{-1}.

HR ESI-MS: $C_{14}H_{24}O_3Si$ $[M+Na]^+$ requires 291.1387; found 291.1387.

GC / LR EI-MS [5025015]: t_R 7.22 min; *m*/*z* (rel. int.) 268 (1, $M^{+\bullet}$), 211 [83, $M^{+\bullet}$–C(CH$_3$)$_3^{\bullet}$], 193 (30), 183 (17), 167 (15), 149 (16), 131 (54, $TBSO^+$), 75 (100), and 73 (45).

TLC: R_f 0.28 (15:1 Hex/EtOAc).

(±)-*CIS*-*N*-METHOXY-*N*-METHYL-6-VINYL-3,6-DIHYDRO-2*H*-PYRAN-2-CARBOXAMIDE (3032-cis)



3034-cis ***3032-cis***

[*MJJ-VII-56*] The *tert*-butyldimethylsilyl ester **3034-cis** (179 mg, 0.67 mmol, 1.0 equiv) was transferred to a 25-mL round bottom flask and the residual water was co-evaporated with PhH (~3 mL, 2 cycles). The reaction flask was then charged with CH_2Cl_2 (4.0 mL) and dry DMF (160 μL, 151 mg, 2.07 mmol, 3.1 equiv). The resulting solution was cooled to 0 °C and treated dropwise with freshly distilled oxalyl chloride (170 μL, 247 mg, 1.95 mmol, 2.9 equiv). Vigorous gas evolution ensued after a short (*ca.* 2 s) induction period, at which point the initial clear, colorless reaction solution became a pale yellow foam. Once gas evolution had ceased, the cooling bath was removed and an additional amount of CH_2Cl_2 (1.0 mL) was added to aid stirring. After having been stirred at rt for 9 h, most of the CH_2Cl_2 was removed at the rotavap, and the solid, orange residue that remained was suspended in pentane and filtered through a bed of pre-dried CELITE®. The light yellow, cloudy oil obtained after concentration of the filtrate was redissolved in PhH, the solution was evaporated to dryness, and the crude acid chloride thus obtained was used in the following procedure without further processing.

A suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (164 mg, 1.68 mmol, 2.5 equiv) and anhydrous Na_2CO_3 (359 mg, 3.39 mmol, 5.1 equiv) in dry CH_2Cl_2 (3.0 mL) was cooled to 0 °C. To this mixture was added pyridine (2 drops) followed by the crude acid chloride (0.67 mmol theoretical, 1.0 equiv) as a solution in dry CH_2Cl_2 (3.0 mL). The resulting heterogeneous mixture was stirred at 0 °C for 30 min, at which point the

cooling bath was removed. After having been stirred at rt for 12 h, the reaction mixture was diluted with EtOAc and poured onto brine/H_2O (1:1, 30 mL). The layers were shaken (not stirred) and separated, and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 2:1 Hex/EtOAc) provided the title compound as a clear, colorless oil (65 mg, 0.33 mmol, 43% yield over 3 steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.91 (dddd, J = 2.0, 2.0, 6.0, 10.5 Hz, 1H, CH=C*H*), 5.87 (ddd, J = 7.0, 10.5, 17.0 Hz, 1H, C*H*=$CH_{trans}H_{cis}$), 5.65 (dddd, J = 1.5, 1.5, 3.0, 10.0 Hz, 1H, C*H*=CH), 5.32 (ddd, J = 1.0, 1.0, 17.0 Hz, 1H, CH=C$H_{trans}H_{cis}$), 5.18 (ddd, J = 1.0, 1.0, 10.0 Hz, 1H, CH=$CH_{trans}H_{cis}$), 4.73-4.62 (m, 1H, CH=CHC*H*CH=$CH_{trans}H_{cis}$), 4.63-4.55 [br m, 1H, C*H*C(O)N(OCH_3)CH_3], 3.76 [s, 3H, N(OCH_3)CH_3], 3.23 [br s, 3H, N(OCH_3)CH_3], 2.56 (ddddd, J = 2.0, 3.0, 4.0, 10.5, 17.0 Hz, 1H, CH_2), and 2.07 (ddddd, J = 1.5, 3.0, 3.0, 6.5, 17.5 Hz, 1H, CH_2).

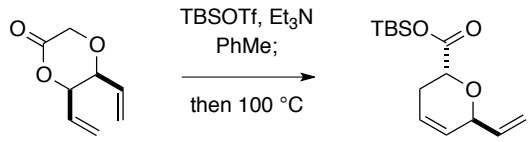
^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 137.3, 128.5, 124.5, 116.7, 77.1, 71.0, 61.7, 32.3, and 26.6.

IR (neat): 2974, 2935, 1671, 1182, 1074, 990, and 853 cm^{-1}.

HR ESI-MS: $C_{10}H_{15}NO_3$ $[M+Na]^+$ requires 220.0944; found 220.0947.

TLC: R_f 0.26 (2:1 Hex/EtOAc).

(±)-*TRANS*-*TERT*-BUTYLDIMETHYLSILYL 6-VINYL-3,6-DIHYDRO-2*H*-PYRAN-2-CARBOXYLATE (3034-trans)



3036-cis ***3034-trans***

[*MJJ-III-192/VII-55/65*] In a procedure entirely analogous to that described for the formation of **3034-cis**, a solution of **3036-cis** (138 mg, 0.90 mmol, 1.0 equiv) and Et_3N (500 μL, 363 mg, 3.59 mmol, 4.0 equiv) in dry PhMe (8.0 mL) was treated with neat, freshly distilled TBSOTf (420 μL, 483 mg, 1.83 mmol, 2.0 equiv). After having been stirred for 45 min at rt and 1.5 h at 100–110 °C, the crude reaction mixture was processed as described above for the preparation of **3034-cis** to provide the TBS ester **3034-trans** as a light yellow oil (188 mg, 0.70 mmol). This somewhat labile silyl ester was immediately taken forward in the preparation of **3032-trans**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.92-5.89 (m, 1H, C*H*=CH), 5.91 (ddd, *J* = 5.5, 10.5, 17.0 Hz, 1H, C*H*=CH$_{trans}$H$_{cis}$), 5.75 (dddd, *J* = 2.0, 2.0, 2.0, 10.0 Hz, 1H, CH=C*H*), 5.26 (ddd, *J* = 1.5, 1.5, 17.5 Hz, 1H, CH=C*H*$_{trans}$H$_{cis}$), 5.25 (ddd, *J* = 1.0, 1.0, 10.5 Hz, 1H, CH=CH$_{trans}$*H*$_{cis}$), 4.93-4.90 (m, 1H, CH=CHC*H*CH=CH$_{trans}$H$_{cis}$), 4.32 (dd, *J* = 5.5, 8.0 Hz, 1H, C*H*CO$_2$TBS), 2.38-2.35 (m, 2H, C*H*$_2$), 0.94 [s, 9H, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$], and 0.29 [s, 6H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 136.7, 127.8, 123.8, 117.6, 73.2, 68.6, 27.6, 25.6, 17.8, -4.8.

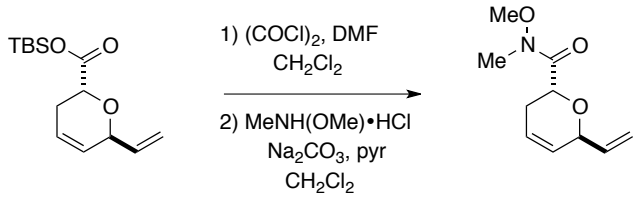
IR (neat): 2954, 2933, 2890, 2860, 1726, 1296, 1255, 1221, 1183, 1102, 842, and 792 cm^{-1}.

HR ESI-MS: $C_{14}H_{24}O_3Si$ $[M+Na]^+$ requires 291.1387; found 291.1363.

GC / LR EI-MS [5025015]: t_R 7.28 min; *m*/*z* (rel. int.) 268 (1, $M^{+\bullet}$), 211 [100, $M^{+\bullet}$–$C(CH_3)_3^{\bullet}$], 193 (25), 183 (12), 167 (12), 149 (12), 131 (40, $TBSO^+$), 75 (80), and 73 (43).

TLC: R_f 0.26 (15:1 Hex/EtOAc).

(±)-*TRANS*-*N*-METHOXY-*N*-METHYL-6-VINYL-3,6-DIHYDRO-2H-PYRAN-2-CARBOXAMIDE (3032-trans)



3034-trans ***3032-trans***

[*MJJ-VII-57/67*] In a procedure entirely analogous to that described for the formation of **3032-cis**, a solution of the *tert*-butyldimethylsilyl ester **3034-trans** (188 mg, 0.70 mmol, 1.0 equiv) and dry DMF (160 μL, 151 mg, 2.07 mmol, 3.0 equiv) in CH_2Cl_2 (4.4 mL) at 0 °C was treated with freshly distilled oxalyl chloride (170 μL, 251 mg, 1.98 mmol, 2.8 equiv). Additional CH_2Cl_2 (3.0 mL) was added to the resulting heterogeneous mixture and, after having been stirred at rt for 18 h, the reaction mixture was processed as described for the preparation of **3032-cis**.

The crude acid chloride thus obtained (0.70 mmol theoretical) in dry CH_2Cl_2 (3.0 mL) was added dropwise to a 0 °C suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (172 mg, 1.76 mmol, 2.5 equiv) and anhydrous Na_2CO_3 (371 mg, 3.50 mmol, 5.0 equiv) in dry CH_2Cl_2 (4.0 mL) that contained pyridine (2 drops). The reaction mixture was stirred for 30 min at 0 °C and 4 h at rt. Reaction work-up as previously described and purification by medium pressure liquid chromatography (SiO_2, 2:1 Hex/EtOAc) provided the title compound as a clear, colorless oil (89 mg, 0.45 mmol, 50% yield over 3 steps).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.98-5.94 (m, 1H, C*H*=CH), 5.97 (ddd, *J* = 5.5, 10.5, 17.0 Hz, 1H, C*H*=$CH_{trans}H_{cis}$), 5.76 (dddd, *J* = 1.5, 3.0, 3.0, 10.5 Hz, 1H, CH=C*H*), 5.28 (ddd, *J* = 1.5, 1.5, 10.5 Hz, 1H, CH=$CH_{trans}H_{cis}$), 5.26 (ddd, *J* = 2.0, 2.0, 17.5 Hz, 1H, CH=C$H_{trans}H_{cis}$), 4.84 (br s, 1H, CH=CHC*H*CH=$CH_{trans}H_{cis}$), 4.64 [br s, 1H, C*H*C(O)N(OCH_3)CH_3], 3.71 [s, 3H, N(OCH_3)CH_3], 3.22 [br s, 3H, N(OCH_3)CH_3], 2.50-2.45 (br m, 1H, CH_2), and 2.13 (ddddd, *J* = 1.5, 1.5, 4.0, 5.5, 17.5 Hz, 1H, CH_2).

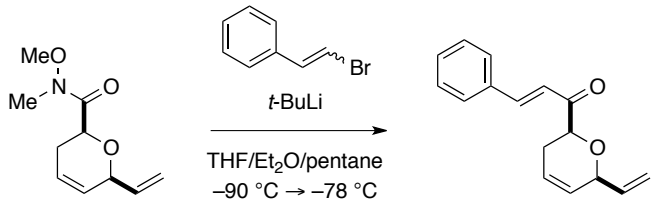
^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 136.6, 126.9, 124.7, 117.9, 73.5, 65.5, 61.7, 32.4, and 26.7.

IR (neat): 2975, 2936, 1671, 1182, 1068, and 991 cm^{-1}.

HR ESI-MS: $C_{10}H_{15}NO_3$ $[M+Na]^+$ requires 220.0944; found 220.0934.

TLC: R_f 0.20 (2:1 Hex/EtOAc).

(±)-(*E*)-3-PHENYL-1-(*CIS*-6-VINYL-3,6-DIHYDRO-2*H*-PYRAN-2-YL)-PROP-2-EN-1-ONE (3029-cis)



3032-cis ***3029-cis***

[*MJJ-VII-64*] A room temperature solution of *tert*-butyllithium (600 μL, 1.02 mmol, 1.7 M solution in pentane) was added dropwise to a cold (–90 °C, Et_2O/dry ice bath) solution of distilled β-bromostyrene [67 μL, 95 mg, 0.52 mmol, 3.0 equiv; 8.3:1 mixture of (*E*)- and (*Z*)-isomers] in THF/Et_2O/pentane (4:4:1, 4.95 mL). The resulting bright yellow solution was maintained with stirring at –90 °C for 30 min, warmed to –78 °C, and stirred an additional 30 min to provide an orange solution of β-lithiostyrene. The Weinreb amide

3032-cis (34 mg, 0.17 mmol, 1.0 equiv) was then added dropwise as a solution in dry THF (1.5 mL), during which time the reaction mixture slowly evolved in color from orange to pale yellow. After having been stirred at –78 °C for 50 min, the cooling bath was removed and the reaction mixture was immediately quenched by the addition of dilute aq $NaHSO_4$ (0.01 M, 20 mL). The resulting mixture was warmed to rt and diluted with Et_2O, and the layers were shaken and separated. The aqueous phase was extracted with Et_2O (2 x 15 mL), and the combined organic extracts were washed with 0.01 M $NaHSO_4$ (10 mL) and brine. The organic material was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 30:1 Hex/EtOAc) provided the (*Z*)-isomer [~1 mg, **TLC**: R_f 0.25 (15:1 Hex/EtOAc)] followed by the title compound as a pale yellow oil (31 mg, 0.13 mmol, 75% yield). This material was judged to be >95% pure (*E*)-isomer on the basis of ^{1}H NMR analysis.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 [d, *J* = 16.0 Hz, 1H, C(O)CH=C*H*C_6H_5], 7.63-7.59 (m, 2H, C_6H_5), 7.41-7.38 (m, 3H, C_6H_5), 7.30 [d, *J* = 16.0 Hz, 1H, C(O)C*H*=CHC_6H_5], 5.95-5.91 (m, 1H, C*H*=CH), 5.92 (ddd, *J* = 6.5, 10.5, 17.0 Hz, 1H, C*H*=CH$_{trans}$H$_{cis}$), 5.70 (dddd, *J* = 2.0, 2.0, 2.0, 10.0 Hz, 1H, CH=C*H*), 5.40 (ddd, *J* = 1.5, 1.5, 17.5 Hz, 1H, CH=C*H*$_{trans}$H$_{cis}$), 5.24 (ddd, *J* = 1.5, 1.5, 10.5 Hz, 1H, CH=CH$_{trans}$*H*$_{cis}$), 4.79 [ddddd, *J* = 1.5, 1.5, 3.5, 6.5, 6.5 Hz, 1H, CH=CHC*H*CH=CH$_{trans}$H$_{cis}$], 4.34-4.31 [nfom, 1H, C(O)C*H*CH_2], and 2.37-2.26 (m, 2H, C*H*$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 198.4, 144.3, 137.3, 134.8, 130.7, 129.0, 128.9, 128.7, 124.2, 120.8, 116.5, 78.4, 76.6, and 27.3.

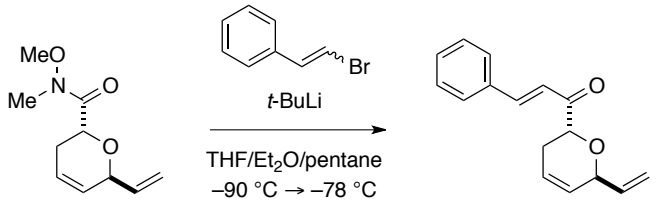
IR (neat): 3034, 2895, 2830, 1687, 1606, 1330, 1071, 986, and 928 cm^{-1}.

HR ESI-MS: $C_{16}H_{16}O_2$ $[M+Na]^+$ requires 263.1043; found 263.1044.

GC / LR EI-MS [5027016]: t_R 10.44 min; *m*/*z* (rel. int.) 240 (1, $M^{+\bullet}$), 131 (100, $M^{+\bullet}$–$C_7H_9O^{\bullet}$), and 103 (34, $M^{+\bullet}$–$C_8H_9O_2^{\bullet}$).

TLC: R_f 0.21 (15:1 Hex/EtOAc).

(±)-(*E*)-3-PHENYL-1-(TRANS-6-VINYL-3,6-DIHYDRO-2*H*-PYRAN-2-YL)-PROP-2-EN-1-ONE (3029-trans)



3032-trans ***3029-trans***

[*MJJ-VII-62*] In a procedure entirely analogous to that described for the formation of **3029-cis**, a solution of β-lithiostyrene was prepared by dropwise addition of a solution of *tert*-butyllithium (680 μL, 1.156 mmol, 1.7 M solution in pentane) to a cold solution of distilled β-bromostyrene [76 μL, 108 mg, 0.590 mmol, 3.0 equiv; 8.3:1 mixture of (*E*)- and (*Z*)-isomers] in THF/Et_2O/pentane (4:4:1, 5.85 mL). After addition of the Weinreb amide **3032-trans** (39 mg, 0.198 mmol, 1.0 equiv) as a solution in dry THF (1.5 mL), the reaction mixture was allowed to stir at –78 °C for 45 min. Reaction work-up and purification as described above provided the title compound as a pale yellow oil (41 mg, 0.171 mmol, 86% yield). This material was an inseparable mixture of (*E*)- (major) and (*Z*)- (minor) isomers (*ca.* 14:1 on the basis of ^{1}H NMR analysis).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 [d, *J* = 16.0 Hz, 1H, C(O)CH=C*H*C_6H_5], 7.62-7.60 (m, 2H, C_6H_5), 7.41-7.39 (m, 3H, C_6H_5), 7.22 [d, *J* = 16.0 Hz, 1H, C(O)C*H*=CHC_6H_5], 6.00-5.96 (m, 1H, C*H*=CH), 5.98 (ddd, *J* = 5.0, 10.5, 17.5 Hz, C*H*=$CH_{trans}H_{cis}$), 5.79 (dddd, *J* = 2.0, 2.0, 4.0, 10.5 Hz, 1H, CH=C*H*), 5.31 (ddd, *J* = 1.5, 1.5, 11.0 Hz, 1H, CH=$CH_{trans}H_{cis}$), 5.28 (ddd, *J* = 1.5, 1.5, 17.5 Hz, 1H, CH=C$H_{trans}H_{cis}$), 4.87 [Σ (*J*s) = 18.0 Hz including 2.0, 2.0, and 5.0 Hz, 1H, CH=CHC*H*CH=$CH_{trans}H_{cis}$), 4.40 [dd, *J* = 5.5, 8.5 Hz, 1H, C(O)C*H*CH_2], and 2.35-2.32 (m, 2H, CH_2).

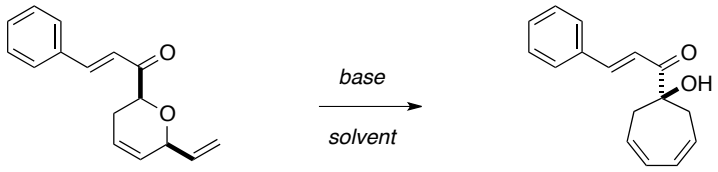
^{13}C NMR (125 MHz, $CDCl_3$): δ 198.6, 144.2, 136.5, 134.8, 130.7, 129.0, 128.7, 127.3, 124.7, 121.1, 118.1, 73.6, 73.2, and 26.8.

IR (neat): 3036, 2896, 1688, 1607, 1329, 1309, 1201, 1182, 1070, 989, and 930 cm^{-1}.

HR ESI-MS: $C_{16}H_{16}O_2$ $[M+Na]^+$ requires 263.1043; found 263.1048.

TLC: R_f 0.23 (15:1 Hex/EtOAc).

(±)-(*E*)-1-(1-HYDROXYCYCLOHEPTA-3,5-DIEN-1-YL)-3-PHENYLPROP-2-EN-1-ONE (3048)



3029-cis ***3048***

K_2CO_3/MeOH. [*MJJ-III-250*] A 13 x 100 mm culture tube was charged with CH_3OH (1.0 mL), the enone **3029-cis** (10.3 mg, 43 μmol, 1.0 equiv) and anhydrous K_2CO_3 (10.2 mg, 74 μmol, 1.7 equiv). The culture tube was then sealed with a TEFLON®-lined cap and the reaction mixture was immersed in an oil bath that had been preheated to 60 °C. After having been vigorously stirred at this temperature for 90 min, the reaction mixture was cooled to rt, diluted with EtOAc, and poured onto 1:1 brine/H_2O. The layers were shaken and separated, the aqueous phase was extracted with EtOAc (2x), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 9:1 Hex/EtOAc) provided the title compound (5.1 mg, 21.2 μmol, 50% yield).

$Bu_4N^+ {}^-OH$/MeOH/*i*-PrOH. [*MJJ-V-245/VII-66*] With the aid of a 50 μL WIRETROL®, a sample of the neat enone **3029-cis** (4.8 mg, 20.0 μmol, 1.0 equiv) was added to a stirred solution of tetra-*n*-butylammonium hydroxide ($Bu_4N^+ {}^-OH$) (300 μL, 30 μmol, 0.1 M in MeOH/*i*-PrOH, 1.5 equiv) at rt. Within the space of 30–60 s, the color of the reaction mixture evolved from light yellow to red to deep purple. After having been stirred for 10 min, the reaction mixture was diluted with EtOAc and poured onto satd aq NH_4Cl, at which point the deep purple color was immediately discharged to give rise to a light yellow organic phase. The layers were shaken and separated, the aqueous phase was extracted with EtOAc (1x), and the combined organic material was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by flash chromatography (8:1 Hex/EtOAc) provided the title compound (3.8 mg, 15.8 μmol, 79% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 [d, *J* = 16.0 Hz, 1H, C(O)CH=C*H*C_6H_5], 7.63-7.59 (m, 2H, C_6H_5), 7.43-7.40 (m, 3H, C_6H_5), 7.34 [d, *J* = 16.0 Hz, 1H, C(O)C*H*=CHC_6H_5], 6.14-6.10 (nfom, 2H, sp^2-C*H*), 5.88 (ddd, *J* = 3.5, 6.0, 12.0 Hz, 2H, sp^2-C*H*), 3.40 (s, 1H, O*H*), 2.78-2.72 (nfom, 2H, CH_2), and 2.46 (dd, *J* = 6.5, 15.5 Hz, 2H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ 201.6, 145.5, 134.7, 131.0, 129.3, 129.1, 128.8, 127.7, 119.4, 80.5, and 39.6.

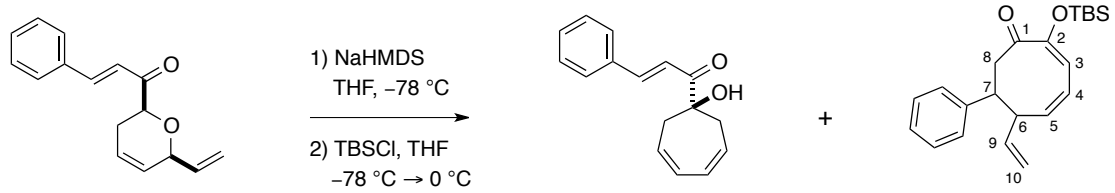
IR (neat): 3449, 3025, 2918, 1680, 1605, 1575, 1330, 1098, 1067, 983, and 761 cm^{-1}.

HR ESI-MS: $C_{16}H_{16}O_2$ $[M+Na]^+$ requires 263.1043; found 263.1049.

GC / LR EI-MS [5027016]: t_R 10.69 min; *m*/*z* (rel. int.) 240 (70, $M^{+\bullet}$), 212 (19), 170 (19), 155 (29), 131 (100, $M^{+\bullet}$–$C_7H_9O^\bullet$), 121 (21), 115 (23), 103 (24, $M^{+\bullet}$–$C_8H_9O_2^\bullet$), 91 (34), and 77 (26).

TLC: R_f 0.21 (9:1 Hex/EtOAc).

(*E*)-1-(1-HYDROXYCYCLOHEPTA-3,5-DIEN-1-YL)-3-PHENYLPROP-2-EN-1-ONE (3048) and **(±)-(2*E*,4*Z*)-2-(*TERT*-BUTYLDIMETHYLSILOXY)-7-PHENYL-6-VINYLCYCLOOCTA-2,4-DIENONE (3050)**



3029-cis ***3048*** ***3050***

[*MJJ-VI-171/248*] A 0.74 M solution of NaHMDS was prepared by diluting the commercial reagent (200 μL, 0.40 mmol, 2.0 M in THF) with dry THF (340 μL). Also, a 0.75 M solution of TBSCl was prepared by dissolving the reagent (112 mg, 0.75 mmol) in dry THF (1.0 mL). Both of these stock solutions were utilized immediately in the following procedure.

An aliquot of the NaHMDS stock solution (200 μL, 0.148 mmol, 1.06 equiv) was added dropwise to a stirred solution of the enone **3029-cis** (33.4 mg, 0.14 mmol, 1.0 equiv) in dry THF (700 μL) at –78 °C, which immediately induced the formation of a light brown color. After having been stirred for 25 min, an aliquot of the TBSCl stock solution (200 μL, 0.149 mmol, 1.06 equiv) was added dropwise, and, a short period later, the reaction mixture was allowed to warm to 0 °C. Stirring was continued at this temperature for 15 min, at which point the reaction mixture was quenched by the addition of 10% aq $NaHCO_3$ and diluted with Et_2O. The resulting mixture was poured onto 10% aq $NaHCO_3$ (20 mL), the layers were shaken and separated, and the aqueous phase was extracted with Et_2O (2x). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Preliminary purification of the crude residue by flash chromatography (100% Hex → 99:1 → 9:1 Hex/EtOAc) provided two fractions. The more polar of these two fractions was subjected to medium pressure liquid chromatography (SiO_2, 8:1

Hex/EtOAc) to provide the [2,3]-Wittig product **3048** (4.6 mg, 19.1 μmol, 14% yield), the ^{1}H NMR spectrum of which was identical to a sample that had been prepared by alternative means. Purification of the less polar fraction by MPLC (99:1 Hex/EtOAc) then provided the title compound (6.7 mg, 18.9 μmol, 13% yield).

In a separate experiment [*MJJ-V-246*], the enone **3029-cis** (10.0 mg, 41.6 μmol, 1.0 equiv) was treated with NaHMDS (200 μL, 60.0 μmol, 1.4 equiv, 0.3 M in THF) at –78 °C and then TBSCl (200 μL, 60 μmol, 1.4 equiv, 0.3 M in THF) (–78 °C → 0 °C) in an identical manner to that described above. The reaction mixture was quenched by the addition of 10% aq $NaHCO_3$, diluted with Et_2O, and poured onto 1:1 brine/H_2O. The layers were shaken and separated, the aqueous phase was extracted with Et_2O (1x), and the combined organic material was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Preliminary purification of the crude residue by flash chromatography (9:1 Hex/EtOAc) provided a faster running fraction (9.8 mg) followed by a clean sample of the [2,3]-Wittig product **3048** (5.8 mg, 24.1 μmol, 58% yield). Subjection of the less polar fraction to medium pressure liquid chromatography (SiO_2, 40:1 Hex/EtOAc) provided the title compound (4.2 mg, 11.8 μmol, 28% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29-7.22 (m, 3H, C_6H_5), 7.18-7.16 (m, 2H, C_6H_5), 6.31 (ddd, J = 1.5, 6.5, 11.5 Hz, 1H, H4), 6.16 (ddd, J = 0.5, 0.5, 0.5, 6.5 Hz, 1H, H3), 6.00 (ddd, J = 0.5, 9.0, 11.5 Hz, 1H, H5), 5.46 (ddd, J = 7.0, 10.0, 17.5 Hz, 1H, H9), 4.97 (ddd, J = 1.5, 1.5, 17.5 Hz, 1H, $H10_{trans}$), 4.94 (ddd, J = 1.5, 1.5, 10.5 Hz, 1H, $H10_{cis}$), 3.65 (ddd, J = 3.5, 5.5, 13.0 Hz, 1H, H7), 3.57 (dd, J = 10.5, 13.5 Hz, 1H, $H8_A$), 3.36 (dddddd, J = 1.5, 1.5, 1.5, 5.0, 7.0, 8.5 Hz, 1H, H6), 2.44 (dd, J = 3.5, 10.5 Hz, 1H, $H8_B$), 0.97 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.22 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.18 [s, 3H, $(CH_3)_3CSi(CH_3)_2$].

^{13}C NMR (75 MHz, $CDCl_3$): δ 200.0 (C1), 149.4 (C2), 139.7 (C_6H_5), 139.1 (C9), 137.5 (C5), 128.4 (C_6H_5), 128.2 (C_6H_5), 127.3 (C_6H_5), 125.9 (C4), 119.9 (C3), 116.2 (C10),

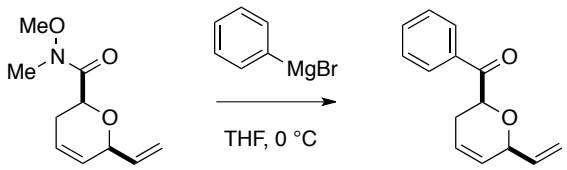
59.3 (C7), 47.4 (C6), 45.0 (C8), 25.9 [$(CH_3)_3CSi(CH_3)_2$], 18.7 [$(CH_3)_3CSi(CH_3)_2$], and -4.5 [$(CH_3)_3CSi(CH_3)_2$].

IR (neat): 2954, 2930, 2856, 1670, 1254, 1206, 1108, 850, and 785 cm^{-1}.

HR ESI-MS: $C_{22}H_{30}O_2Si$ $[M+Na]^+$ requires 377.1907; found 377.1924.

TLC: R_f 0.48 (15:1 Hex/EtOAc).

(±)-PHENYL(*CIS*-6-VINYL-3,6-DIHYDRO-2*H*-PYRAN-2-YL)METHANONE (3056-cis)



3032-cis ***3056-cis***

[*MJJ-VII-63*] To a solution of the Weinreb amide **3032-cis** (30 mg, 0.15 mmol, 1.0 equiv) in dry THF (1.5 mL) at 0 °C was added dropwise PhMgBr (170 µL, 0.17 mmol, 1.1 equiv, 1 M solution in THF). After having been stirred for 15 min, the reaction mixture was quenched at 0 °C by the addition of satd aq NH_4Cl (15 mL) and then diluted with Et_2O. The layers were shaken and separated, and the aqueous phase was extracted with Et_2O (2 x 15 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 30:1 Hex/EtOAc) provided the title compound as a clear, colorless oil (28 mg, 0.13 mmol, 86% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05-8.02 [m, 2H, C(O)C_6H_5], 7.57 [tt, J = 1.5, 7.0 Hz, 1H, C(O)C_6H_5], 7.46 [tt, J = 1.5, 8.0 Hz, 2H, C(O)C_6H_5], 5.96 (dddd, J = 2.0, 2.0, 5.5, 10.0 Hz, 1H, C*H*=CH), 5.89 (ddd, J = 6.5, 10.5, 17.0 Hz, 1H, C*H*=$CH_{trans}H_{cis}$), 5.74 (dddd, J = 1.5, 1.5, 3.0, 10.0 Hz, 1H, CH=C*H*), 5.35 (ddd, J = 1.5, 1.5, 17.0 Hz, 1H, CH=C$H_{trans}H_{cis}$), 5.20 (ddd, J = 1.5, 1.5, 10.5 Hz, 1H, CH=$CH_{trans}H_{cis}$), 4.94 [dd, J = 3.5,

11.0 Hz, 1H, C*H*C(O)C_6H_5], 4.86 [Σ (*J*s) = 20 Hz including 1.5, 1.5, and 6.5 Hz, 1H, CH=CHC*H*CH=$CH_{trans}H_{cis}$), 2.55 (ddddd, *J* = 2.0, 3.0, 4.0, 11.0, 17.5 Hz, 1H, CH_2), and 2.25 (ddddd, *J* = 1.5, 3.5, 3.5, 6.0, 17.5 Hz, 1H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ 197.4, 137.1, 135.2, 133.4, 129.3, 128.8, 128.6, 124.3, 116.8, 77.0, 76.4, and 27.4.

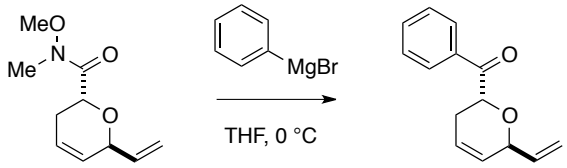
IR (neat): 3038, 2923, 2838, 1691, 1232, 1181, 1094, 1071, 928, and 858 cm^{-1}.

HR ESI-MS: $C_{14}H_{14}O_2$ $[M+Na]^+$ requires 237.0886; found 237.0889.

GC / LR EI-MS [5025015]: t_R 8.09 min; *m*/*z* (rel. int.) 214 (2, $M^{+\bullet}$), 144 (3), 105 (100, $M^{+\bullet}$–$C_7H_9O^{\bullet}$), 79 (13), and 77 (41).

TLC: R_f 0.35 (15:1 Hex/EtOAc).

(±)-PHENYL(*TRANS*-6-VINYL-3,6-DIHYDRO-2*H*-PYRAN-2-YL)METHANONE (3036-trans)



3032-trans ***3056-trans***

[*MJJ-VII-51*] In a procedure entirely analogous to that described for the formation of **3056-cis**, the Weinreb amide **3032-trans** (74 mg, 0.38 mmol, 1.0 equiv) in dry THF (3.5 mL) was allowed to react with PhMgBr (400 μL, 0.40 mmol, 1.1 equiv, 1 M solution in THF) at 0 °C for 20 min. Reaction work-up and purification as described provided the title compound as a clear, colorless oil (68 mg, 0.32 mmol, 85% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02-7.99 [m, 2H, C(O)C_6H_5], 7.57 [tt, *J* = 1.5, 7.0 Hz, 1H, C(O)C_6H_5], 7.46 [tt, *J* = 1.5, 8.5 Hz, 2H, C(O)C_6H_5], 6.04 (ddd, *J* = 5.5, 10.5, 17.5 Hz, 1H, C*H*=$CH_{trans}H_{cis}$), 6.01 (dddd, *J* = 2.5, 2.5, 5.0, 10.0 Hz, 1H, C*H*=CH), 5.80

(dddd, J = 1.5, 2.5, 3.0, 10.0 Hz, 1H, CH=C*H*), 5.37 (ddd, J = 1.0, 1.0, 10.0 Hz, 1H, CH=CH$_{trans}$*H*$_{cis}$), 5.30 (ddd, J = 1.5, 1.5, 17.5 Hz, 1H, CH=C*H*$_{trans}$H$_{cis}$), 5.04 [dd, J = 4.0, 9.5 Hz, 1H, C*H*C(O)C$_6$H$_5$], 4.84 [Σ (Js) = 18.0 Hz including 1.5, 1.5, and 5.5 Hz, 1H, CH=CHC*H*CH=CH$_{trans}$H$_{cis}$], 2.53 (ddddd, J = 2.5, 2.5, 2.5, 9.0, 17.5 Hz, 1H, C*H*$_2$), and 2.29 (ddddd, J = 1.5, 1.5, 4.0, 5.0, 17.5 Hz, 2H, C*H*$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 198.1, 136.4, 135.3, 133.4, 129.1, 128.6, 127.0, 124.7, 118.8, 73.6, 70.6, and 27.0.

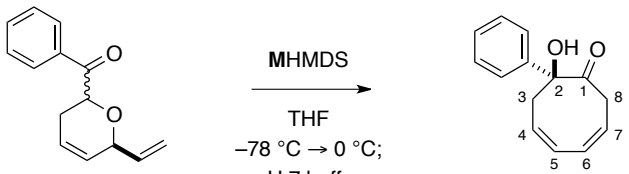
IR (neat): 3038, 2910, 1690, 1231, 1181, 1051, and 933 cm^{-1}.

HR ESI-MS: $C_{14}H_{14}O_2$ $[M+Na]^+$ requires 237.0886; found 237.0893.

GC / LR EI-MS [5025015]: t_R 8.18 min; *m*/*z* (rel. int.) 214 (3, $M^{+\bullet}$), 159 (5), 105 (100, $M^{+\bullet}$–$C_7H_9O^{\bullet}$), 79 (12), and 77 (41).

TLC: R_f 0.31 (15:1 Hex/EtOAc).

(±)-(3*Z*,5*Z*)-8-HYDROXY-8-PHENYLCYCLOOCTA-3,5-DIENONE (3059)



3056-cis
–or–
3056-trans

3059

M = Na. [*MJJ-VI-160/250*] A solution of NaHMDS was prepared by diluting a precise volume of the commercial reagent (400 μL, 0.80 mmol, 2.0 M in THF) with dry THF (2.1 mL). The resulting stock solution, which was 0.32 M [NaHMDS], was utilized immediately in the following procedure.

An aliquot of the NaHMDS stock solution (400 μL, 0.128 mmol, 1.1 equiv) was added dropwise to a solution of the phenyl ketone **3056-cis** (25.2 mg, 0.118 mmol, 1.0 equiv) in dry THF (800 μL) at –78 °C, which immediately produced a light yellow reaction mixture. After having been stirred for 20 min, the reaction mixture was allowed to warm to 0 °C. During this time, the color of the reaction mixture evolved from light yellow to deep red. Stirring was continued for 10 min at 0 °C, at which point the reaction mixture was quenched by the addition of pH 7 buffer and the deep red color was immediately discharged. The reaction mixture was diluted with Et_2O, poured onto pH 7 buffer (20 mL), and the layers were shaken and separated. The aqueous phase was extracted with Et_2O (2x) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Preliminary purification of the crude residue by medium pressure liquid chromatography (SiO_2, 20:1 Hex/EtOAc) provided two fractions. Resubjection of the more polar fraction to MPLC (SiO_2, 15:1 Hex/EtOAc) provided the title compound as a clear, colorless oil (13.5 mg, 63.0 μmol, 54% yield).

M = Li. [*MJJ-VII-109*] A solution of *n*-BuLi (450 μL, 1.125 mmol, 2.5 M in Hex) was added dropwise to a solution of distilled (CaH_2) HMDS (250 μL, 194 mg, 1.199 mmol) in dry THF (1.4 mL) at 0 °C. The resulting mixture was allowed to stir for 20 min to provide a stock solution that was 0.54 M [LiHMDS].

An aliquot of the LiHMDS stock solution (200 μL, 0.107 mmol, 1.1 equiv) was added dropwise to a solution of the phenyl ketone **3056-trans** (21.0 mg, 98.0 μmol, 1.0 equiv) in dry THF (800 μL) at –78 °C, which immediately produced a light yellow reaction mixture. After having been stirred for 20 min, the reaction mixture was allowed to warm to 0 °C and was held at this temperature for 50 min (the observations noted above regarding the color of the reaction mixture were essentially identical in the present case). The reaction mixture was diluted with Et_2O, poured onto pH 7 buffer (15 mL), and the layers were shaken and separated. The aqueous phase was extracted with Et_2O (2x) and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*.

The crude residue was filtered through short pad of SiO_2 (6:1 Hex/EtOAc) and concentrated *in vacuo* prior to being purified by medium pressure liquid chromatography (SiO_2, 15:1 Hex/EtOAc, 2 cycles) to provide the title compound as a clear, colorless oil (7.6 mg, 35.5 μmol, 36% yield).

^{1}H NMR (500 MHz, C_6D_6): δ 7.30-7.28 (m, 2H, C_6H_5), 7.09-7.03 (m, 3H, C_6H_5), 5.83 (ddd, *J* = 7.0, 9.0, 11.5 Hz, 1H, H4), 5.69 (ddddd, *J* = 1.5, 1.5, 1.5, 5.0, 11.5 Hz, 1H, H5), 5.51 (dddd, *J* = 2.0, 3.0, 5.0, 12.0 Hz, 1H, H6), 5.06 (ddd, *J* = 4.0, 6.5, 12.0 Hz, 1H, H7), 4.87 (s, 1H, O*H*), 3.19 (dd, *J* = 9.0, 12.5 Hz, 1H, $H3_A$), 3.03 (dddd, *J* = 1.5, 3.0, 4.5, 16.5 Hz, 1H, $H8_A$), 2.61 (dd, *J* = 7.0, 12.5 Hz, 1H, $H3_B$), and 2.41 (br dd, *J* = 6.0, 16.5 Hz, 1H, $H8_B$).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (br d, *J* = 7.5 Hz, 2H, C_6H_5), 7.38 (br dd, *J* = 7.0, 7.0 Hz, 2H, C_6H_5), 7.33 (br d, *J* = 7.5 Hz, 1H, C_6H_5), 5.96-5.84 (m, 3H, C*H*=C*H*–C*H*=CH), 5.63 (ddd, *J* = 4.0, 6.5, 12.0 Hz, 1H, CH=CHCH=C*H*), 4.70 (s, 1H, O*H*), 3.48-3.42 [m, 2H, 2x CH_2], 2.83 (br dd, *J* = 2.0, 16.5 Hz, 1H, CH_2), and 2.82 (dd, *J* = 6.5, 12.5 Hz, 1H, CH_2).

^{13}C NMR (125 MHz, C_6D_6): δ 209.0 (C1), 142.9 (C_6H_5), 128.8 (C_6H_5), 128.6 (C4), 128.3 (C_6H_5), 127.8 (C5), 127.4 (C7), 126.3 (C_6H_5), 125.7 (C6), 83.6 (C2), 39.2 (C8), and 34.4 (C3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 209.8, 141.9, 128.9, 128.6, 128.2, 127.9, 127.2, 125.9, 83.6, 39.4, and 34.0.

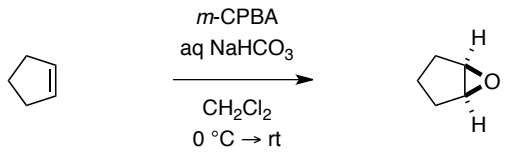
IR (neat): 3465, 3059, 3026, 2926, 2851, 1714, 1097, 1071, 766, and 741 cm^{-1}.

HR ESI-MS: $C_{14}H_{14}O_2$ $[M+Na]^+$ requires 237.0886; found 237.0894.

TLC: R_f 0.29 (8:1 Hex/EtOAc).

B–3. CHAPTER IV

CYCLOPENTENE OXIDE (4011)



4032 ***4011***

[*MJJ-III-263*] A vigorously stirred biphasic mixture of cyclopentene (**4032**) (25.2 mL, 19.43 g, 285 mmol, 1.0 equiv), CH_2Cl_2 (170 mL) and satd aq $NaHCO_3$ (170 mL) was cooled in an ice/H_2O bath and solid 3-chloroperoxybenzoic acid (*m*-CPBA) (53.7 g, 240 mmol, 0.8 equiv, 77 wt% assumed) was added in five approximately equal portions over the course of *ca.* 3 h. Shortly after the final addition, the reaction mixture was allowed to warm to rt and stir overnight, at which point a negative starch–iodide test was obtained. The reaction mixture was diluted with H_2O until a clear, two-phase system was obtained. The layers were shaken and separated, the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL), and the combined organic extracts were washed with satd aq $NaHCO_3$ (1x) and brine (1x). The organic material was reduced to a volume of 150–175 mL at the rotavap, and then most of the remaining CH_2Cl_2 and unreacted cyclopentene were removed by distillation at atmospheric pressure (bath temp. 50–55 °C, bp *ca.* 45 °C). The pressure within the distillation apparatus was reduced to *ca.* 85 mmHg while maintaining a constant bath temp. and, after collecting a forecut (18.9 g), there was obtained a fraction of material (27.5 g) that was mostly **4011**. Redistillation of this latter fraction at atmospheric pressure (bp 97–100 °C; lit.[404] 98–100 °C @ 750 mmHg) provided the title compound as a clear, colorless liquid (11.2 g, 133 mmol, 56% yield).

---

[404] Emmons, W. D.; Pagano, A. S. Peroxytrifluoroacetic Acid. IV. The Epoxidation of Olefins. *J. Am. Chem. Soc.* **1955**, *77*, 89–92.

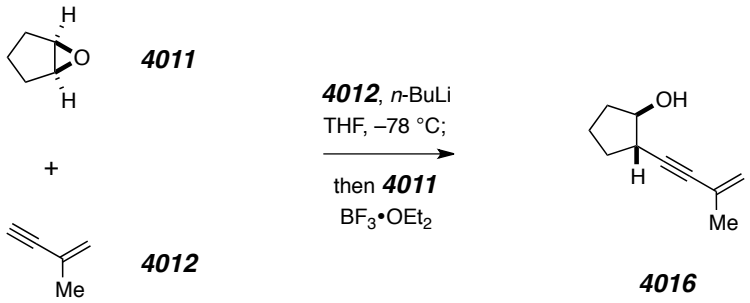
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.46 [s, 2H, $CH_2CH(O)CHCH_2$], 2.04-1.98 (m, 2H, $CH_2CH_2CH_2$), 1.60-1.52 (m, 3H, $CH_2CH_2CH_2$), and 1.41-1.30 (m, 1H, $CH_2CH_2CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 57.2, 27.2, and 18.3.

IR (neat): 3026, 2956, 2854, 1439, 1392, 1298, 935, 921, and 839 cm^{-1}.

TLC: R_f 0.43 (6:1 Hex/EtOAc).

(±)-*TRANS*-2-2-(3-METHYLBUT-3-EN-1-YN-1-YL)CYCLOPENTANOL (4016)



[*MJJ-I-193/270/VII-85*] A solution of *n*-BuLi (12.6 mL, 31.5 mmol, 2.5 M in Hex) was added dropwise to a solution of the enyne **4012** (3.0 mL, 2.09 g, 31.5 mmol, 1.0 equiv) in dry THF (100 mL) at –78 °C. After having been stirred at this temperature for 30 min, neat cyclopentene oxide (**4011**) (3.04 g, 36.1 mmol, 1.1 equiv) and BF_3•OEt_2 (5.2 mL, 5.82 g, 41.0 mmol, 1.3 equiv) were added in rapid succession. Stirring was continued at –78 °C for a period of 60 min, at which point the cooling bath was removed and the reaction mixture was immediately quenched by the addition of satd aq NH_4Cl (75 mL). Once the resulting mixture had warmed to rt, the layers were shaken and separated, the aqueous phase was extracted with EtOAc (3x), and the combined organic extracts were washed with H_2O (1x) and brine (1x). The organic material was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the crude residue by flash chromatography (6:1 Hex/EtOAc) provided the title compound as a light yellow oil (3.36 g, 22.4 mmol, 71% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.21 [dddd, *J* = 1.0, 1.0, 1.0, 1.0 Hz, 1H, $(CH_3)C=CH_2$], 5.16 [dddd, *J* = 1.5, 1.5, 1.5, 1.5 Hz, 1H, $(CH_3)C=CH_2$], 4.20 [ddd, *J* = 6.0, 6.0, 6.0 Hz, 1H, C*H*(OH)], 2.67 (ddd, *J* = 5.5, 8.0, 8.0 Hz, 1H, C*H*C C), 2.10 (dddd, *J* = 3.5, 3.5, 8.0, 8.0 Hz, 1H, CH_2), 2.04 (dddd, *J* = 6.0, 8.5, 8.5, 15.0 Hz, 1H, CH_2), 1.87 [dd, *J* = 1.5, 1.5 Hz, 3H, $(CH_3)C=CH_2$], 1.79-1.64 (m, 3H, overlapping CH_2), and 1.58 (dddd, *J* = 6.0, 6.0, 6.0, 15.0 Hz, 1H, CH_2).

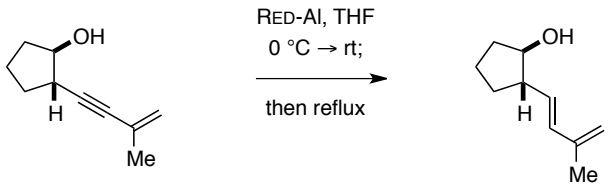
^{13}C NMR (125 MHz, $CDCl_3$): δ 127.2, 120.9, 90.8, 83.2, 79.4, 40.2, 33.5, 31.1, 23.9, and 21.8.

IR (neat): 3350, 2960, 2922, 2876, 2221, 1614, 1332, 1301, 1090, 987, and 892 cm^{-1}.

GC / LR EI-MS [5025015]: t_R 6.84 min; *m*/*z* (rel. int.) 150 (5, $M^{+\bullet}$), 149 (9, $M^{+\bullet}–H^{\bullet}$), 135 (35, $M^{+\bullet}–CH_3^{\bullet}$), 122 (52), 107 (41), 93 (39), 91 (100), 79 (91), and 77 (53).

TLC: R_f 0.17 (6:1 Hex/EtOAc).

(±)-*TRANS*-2-((*E*)-3-METHYLBUTA-1,3-DIEN-1-YL)CYCLOPENTANOL (4017)



4016 ***4017***

[*MJJ-I-205/281*] A solution of the alkynol **4016** (906 mg, 6.03 mmol, 1.0 equiv) in dry THF (3.0 mL) was added dropwise to a solution of sodium bis(2-methoxyethoxy)-aluminum hydride (RED-Al®) (9.0 mL, 28.8 mmol, 3.2 M in PhMe) in dry THF (60 mL) at 0 °C at a rate such that H_2 evolution occurred in a constant, controlled manner. Once gas evolution had ceased, the cooling bath was removed and the reaction mixture was allowed to slowly reach rt. At this point, the reaction flask was fitted with a West condenser and was immersed in an oil bath that had been preheated to 60–70 °C. After

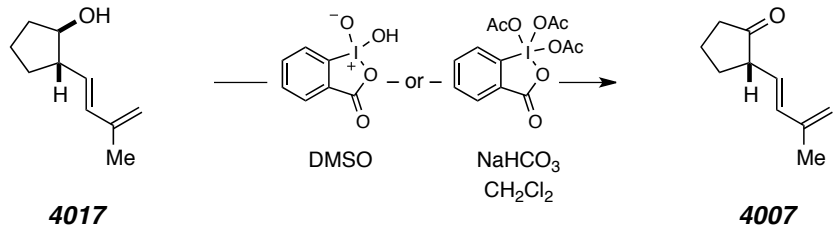
having been stirred at this temperature for a period of 19 h, GC-MS analysis of a reaction mixture aliquot revealed that the starting material had been consumed. The reaction mixture was re-cooled to 0 °C and was then *slowly* quenched by the dropwise addition of 1 M HCl (25 mL). The resulting mixture was filtered through CELITE® with the aid of EtOAc, and the layers of the filtrate were shaken and separated. The aqueous phase was extracted with EtOAc (2x) and the combined organic extracts were washed with satd aq $NaHCO_3$ (1x) and brine (1x), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the crude residue by flash chromatography (4:1 Hex/EtOAc) provided the title compound (761 mg, 5.00 mmol, 83% yield) that, on the basis of ^{1}H NMR analysis, was contaminated with *ca.* 8% w/w of the corresponding allene by-product (see footnote 287).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.23 [d, *J* = 15.5 Hz, 1H, CH=C*H*(CH_3)C=CH_2], 5.57 [dd, *J* = 8.0, 15.5 Hz, 1H, C*H*=CH(CH_3)C=CH_2], 4.91 [br s, 2H, CH=CH(CH_3)C=CH_2], 3.89 [dddd, *J* = 3.5, 7.0, 7.0, 7.0 Hz, 1H, C*H*(OH)], 2.37 [dddd, *J* = 8.0, 8.0, 8.0 Hz, 1H, C*H*CH=CH], 2.01 (dddd, *J* = 5.5, 7.0, 8.5, 12.5 Hz, 1H, CH_2), 1.94 (dddd, *J* = 3.5, 8.0, 8.0, 16.5 Hz, 1H, CH_2), 1.85 [dd, *J* = 1.0, 1.0, 3H, CH=CH(CH_3)C=CH_2], 1.81-1.72 (m, 1H, CH_2), 1.70-1.55 (m, 3H, overlapping CH_2 and O*H*), and 1.45 (*J* = 8.0, 9.5, 9.5, 13.0 Hz, 1H, CH_2).

GC / LR EI-MS [5025015]: t_R 6.97 min; *m*/*z* (rel. int.) 152 (43, $M^{+\bullet}$), 137 (22, $M^{+\bullet}$–$CH_3^{\bullet}$), 123 (13), 119 (13), 109 (65), 95 (33), 93 (100), 91 (56), 84 (48), 81 (42), 79 (73), and 77 (51).

TLC: R_f 0.18 (4:1 Hex/EtOAc).

(±)-(*E*)-2-(3-METHYLBUTA-1,3-DIEN-1-YL)CYCLOPENTANONE (4007)



IBX. [*MJJ-III-282*] A sample of IBX (658 mg, 2.35 mmol, 1.7 equiv) was added to reagent grade DMSO (10.0 mL) in a flask that had been wrapped with aluminum foil but was open to air. The resulting mixture was stirred at rt until complete dissolution of IBX had occurred (20–30 min), at which point a solution of the homoallylic alcohol **4017** (205 mg, 1.35 mmol, 1.0 equiv) in DMSO (3.0 mL) was added dropwise. The flask was sealed with a plastic caplug and the contents stirred at rt for 2 h. The reaction mixture was then cooled to 0 °C, H_2O (20 mL) was slowly added and, after having been stirred for 20 min, the resulting cloudy mixture was filtered through CELITE® (pentane eluent). The layers were shaken and separated, the aqueous phase was extracted with pentane (3x) and Et_2O (2x), and the combined organic extracts were washed sequentially with 0.1 M $Na_2S_2O_3$ (2x), satd aq $NaHCO_3$ (1x), and brine (1x). After having been dried ($MgSO_4$) and filtered, the organic material was concentrated under reduced pressure to leave a residue that was purified by medium pressure liquid chromatography (SiO_2, 9:1 Hex/EtOAc) to provide the title compound (111 mg, 0.74 mmol, 55% yield).

DMP. [*MJJ-I-209/210*] To a mixture of the homoallylic alcohol **4017** (501 mg, 3.29 mmol, 1.0 equiv) and solid $NaHCO_3$ (929 mg, 11.06 mmol, 3.4 equiv) in dry CH_2Cl_2 (20 mL) was added the Dess–Martin periodinane (1.41 g, 3.31 mmol, 1.0 equiv) in a single portion. After having been stirred at rt for 30 min, TLC analysis of the reaction mixture revealed that the starting material had been consumed. The reaction mixture was cooled to 0 °C, quenched by the addition of satd aq $NaHCO_3$/20% aq $Na_2S_2O_3$ (1:1, 10 mL), and was allowed to warm to rt with vigorous stirring over the course of 30 min. The layers

were shaken and separated, the aqueous phase was extracted with CH_2Cl_2 (2x), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 8:1 Hex/EtOAc) provided the title compound (324 mg, 2.16 mmol, 66% yield).

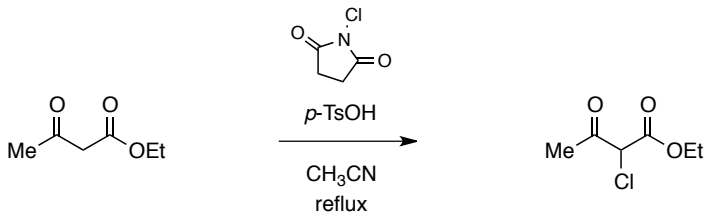
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.22 [dd, J = 1.5, 15.5 Hz, 1H, CH=C*H*(CH_3)C=CH_2], 5.67 [dd, J = 6.5, 16.0 Hz, 1H, C*H*=CH(CH_3)C=CH_2], 4.95-4.94 [nfom, 2H, CH=CH–(CH_3)C=C*H*$_2$], 2.88-2.84 [nfom, 1H, C(O)$CH_2CH_2CH_2$C*H*], 2.39-2.28 [m, 2H, C(O)C*H*$_2$$CH_2CH_2CH$], 2.18 [dddd, J = 9.0, 9.0, 9.0, 9.0 Hz, 1H, C(O)CH_2CH_2C*H*$_2$CH], 2.10-2.05 [m, 1H, C(O)CH_2CH_2C*H*$_2$CH], 1.91-1.79 [m, 2H, C(O)CH_2C*H*$_2$$CH_2$CH], and 1.85 [br s, 3H, CH=CH(C*H*$_3$)C=CH_2].

HR ESI-MS: $C_{10}H_{14}O$ $[M+Na]^+$ requires 173.0937; found 173.0925.

GC / LR EI-MS [5025015]: t_R 6.97 min; *m*/*z* (rel. int.) 150 (30, $M^{+\bullet}$), 135 (47, $M^{+\bullet}$–$CH_3^{\bullet}$), 122 (8), 107 (16), 106 (11), 94 (30), 93 (33), 91 (28), 79 (100), and 77 (31). This material partially decomposed upon entering the GC injection port, as evidenced by the presence of three additional, slightly less intense peaks (t_R 7.89, 8.00, and 8.16 min).

TLC: R_f 0.39 (4:1 Hex/EtOAc).

ETHYL 2-CHLORO-3-OXOBUTANOATE (4008)



4027 ***4008***

[*MJJ-I-185*] Recrystallized *N*-chlorosuccinimide (3.76 g, 28.2 mmol, 1.1 equiv) was added to a stirred solution of ethyl acetoacetate (**4027**) (3.2 mL, 3.29 g, 25.3 mmol, 1.0

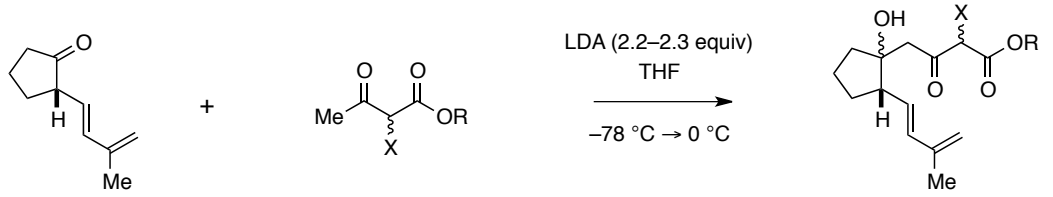
equiv) and *p*-toluenesulfonic acid hydrate (7.34 g, 38.6 mmol, 1.5 equiv) in CH_3CN (250 mL). The reaction mixture was heated to reflux and monitored by TLC (6:1 Hex/EtOAc). After having been stirred for 1 h, the volatile material was removed at the rotavap and the resulting residue was dissolved in CH_2Cl_2 (40 mL). The organic layer was washed with H_2O (2x), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by flash chromatography (8:1 Hex/EtOAc) provided the title compounds as a yellow oil (3.96 g, 24.1 mmol, 95% yield) that existed as a 1.2:1 mixture of enol/keto tautomers. Also, on the basis of ^{1}H NMR analysis, **4008** was contaminated with *ca.* 7% (w/w) of ethyl 2,2-dichloro-3-oxobutanoate [δ 4.38 (q, J = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 2.50 (s, 3H, CH_3), and 1.357 (t, J = 7.0 Hz, 3H, $CO_2CH_2CH_3$)].

The keto (†) and enol (‡) tautomers have been indicated.

^{1}H NMR (500 MHz, $CDCl_3$): δ 12.35‡ (s, 1H, O*H*), 4.76† [s, 1H, $CH_3C(O)CH(Cl)$–CO_2Et], 4.305† (t, J = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 4.302‡ (t, J = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 2.39† [s, 3H, $CH_3C(O)$], 2.19‡ [s, 3H, $CH_3C(OH)$], 1.363‡ (t, J = 7.0 Hz, 3H, $CO_2CH_2CH_3$), and 1.33† (t, J = 7.0 Hz, 3H, $CO_2CH_2CH_3$).

TLC: R_f 0.45 (4:1 Hex/EtOAc).

(±)-(*E*)-ETHYL 2-CHLORO-4-(1-HYDROXY-2-(3-METHYLBUTA-1,3-DIEN-1-YL)CYCLOPENTYL)-3-OXOBUTANOATE (4006a/b), **(±)-(*E*)-*TERT*-BUTYL 4-(1-HYDROXY-2-(3-METHYLBUTA-1,3-DIEN-1-YL)CYCLOPENTYL)-3-OXOBUTANOATE (4028a/b)**, and **(±)-(*E*)-ETHYL 4-(1-HYDROXY-2-(3-METHYLBUTA-1,3-DIEN-1-YL)CYCLOPENTYL)-3-OXOBUTANOATE (4029a/b)**



4007

4008 (X = Cl, R = OEt)
4026 (X = H, R = *t*-Bu)
4027 (X = H, R = OEt)

4006 (X = Cl, R = OEt)
4028 (X = H, R = *t*-Bu)
4029 (X = H, R = OEt)

4006. [*MJJ-I-280*] A solution of *i*-Pr_2NH (150 μL, 107 mg, 1.06 mmol, 2.3 equiv) in dry THF (12.0 mL) at 0 °C was treated dropwise with a solution of *n*-BuLi (400 μL, 0.97 mmol, 2.2 equiv, 2.42 M in Hex). After having been stirred for 20 min, the reaction mixture was treated with a solution of the α-chloro β-keto ester **4008** (73 mg, 0.44 mmol, 1.0 equiv) in dry THF (2.0 mL). The resulting dark yellow (almost orange) dianion solution was maintained with stirring for a period of 60 min and then cooled to –78 °C. A solution of the dienyl ketone **4007** (30.3 mg, 0.20 mmol, 0.5 equiv) in dry THF (2.0 mL) was then added dropwise, which did not result in a significant color change. Stirring was continued for 2.5 h at –78 °C and then the reaction mixture was allowed to gradually warm to 0 °C. During this time, the color of the reaction mixture evolved from dark yellow to dark green/brown. After 60 min, the reaction mixture was quenched by the addition of satd aq NH_4Cl/H_2O (2:1, 15 mL). The layers were shaken and separated, the aqueous phase was extracted with EtOAc (4x), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated at reduced pressure. Purification of the crude residue by medium pressure liquid chromatography (SiO_2, 6:1 Hex/EtOAc) provided a less polar diastereomer (**4006a**) (27 mg, 0.07 mmol, 35% yield corrected for purity)

followed by a more polar one (**4006b**) (13 mg, 0.04 mmol, 20% yield). On the basis of ^{1}H NMR analysis, **4006a** was contaminated with 18% (w/w) of unreacted α-chloro β-keto ester (**4008**), whereas **4006b** was contaminated with 9% (w/w) of **4006a**.

Data for **4006a** [mixture of α-chloro β-keto ester epimers (*dr* 1:1), *ca.* 18% enol content]:

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.19 [d, *J* = 15.5 Hz, 1H, CH=C*H*(CH_3)C=CH_2], 6.18 [d, *J* = 15.5 Hz, 1H, CH=C*H*(CH_3)C=CH_2], 5.69 [dd, *J* = 9.0, 15.5 Hz, 1H, C*H*=CH(CH_3)C=CH_2], 5.68 [dd, *J* = 9.0, 15.5 Hz, 1H, C*H*=CH(CH_3)C=CH_2], 4.95-4.88 [m, 4H, CH=CH(CH_3)C=CH_2], 4.85 [s, 1H, C(O)C*H*(Cl)CO_2], 4.81 [s, 1H, C(O)C*H*(Cl)CO_2], 4.33-4.26 (m, 4H, $CO_2CH_2CH_3$), 2.93 [ABq, $\Delta\nu_{AB}$ = 153 Hz, J_{AB} = 17.5 Hz, 2H, CH_2C(O)], 2.89 [ABq, $\Delta\nu_{AB}$ = 94.4 Hz, J_{AB} = 17.5 Hz, 2H, CH_2C(O)], 2.79 (d, *J* = 1.0 Hz, 1H, O*H*), 2.75 (d, *J* = 1.5 Hz, 1H, O*H*), 2.22 (ddd, *J* = 9.0, 9.0, 9.0 Hz, 2H, C*H*CH=CH), 1.86 [br s, 6H, CH=CH(CH_3)C=CH_2], 1.98-1.78 (m, 8H, CH_2CH_2CH_2), 1.72-1.63 (m, 4H, CH_2CH_2CH_2), 1.311 (t, *J* = 7.0 Hz, $CO_2CH_2CH_3$), and 1.308 (t, *J* = 7.0 Hz, $CO_2CH_2CH_3$).

TLC: R_f 0.38 (4:1 Hex/EtOAc).

Data for **4006b** [mixture of α-chloro β-keto ester epimers (*dr* 1:1), *ca.* 14% enol content]:

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.11 [d, *J* = 15.5 Hz, 1H, CH=C*H*(CH_3)C=CH_2], 6.10 [d, *J* = 15.5 Hz, 1H, CH=C*H*(CH_3)C=CH_2], 5.40 [dd, *J* = 9.0, 15.5 Hz, 1H, C*H*=CH(CH_3)C=CH_2], 5.39 [dd, *J* = 9.0, 15.5 Hz, 1H, C*H*=CH(CH_3)C=CH_2], 4.94-4.90 [m, 4H, CH=CH(CH_3)C=CH_2], 4.80 [s, 1H, C(O)C*H*(Cl)CO_2], 4.72 [s, 1H, C(O)C*H*(Cl)CO_2], 4.29 (q, *J* = 7.0 Hz, $CO_2CH_2CH_3$), 4.27 (q, *J* = 7.0 Hz, $CO_2CH_2CH_3$), 3.27 (d, *J* = 1.0 Hz, 1H, O*H*), 3.24 (d, *J* = 1.0 Hz, 1H, O*H*), 2.91 [ABq, $\Delta\nu_{AB}$ = 44.3 Hz, J_{AB} = 18.5 Hz, 2H, CH_2C(O)], 2.87 [app s (ABq where $\Delta\nu_{AB} << 0.5$ Hz), 2H, CH_2C(O)], 2.72-2.67 (m, 2H, C*H*CH=CH), 2.19-2.12 (m, 2H, CH_2), 1.82 [br s, 6H, CH=CH(CH_3)C=CH_2], 1.89-1.61 (m, 8H, CH_2), 1.55-1.48 (m, 2H, CH_2), 1.31 (t, *J* = 7.0 Hz, $CO_2CH_2CH_3$), and 1.30 (t, *J* = 7.0 Hz, $CO_2CH_2CH_3$).

TLC: R_f 0.33 (4:1 Hex/EtOAc).

4028. [*MJJ-I-255*] A solution of LDA was prepared as described above from *i*-Pr_2NH (200 μL, 143 mg, 1.42 mmol, 2.36 equiv) and a solution of *n*-BuLi (550 μL, 1.35 mmol, 2.25 equiv, 2.45 M in Hex) in dry THF (10.0 mL) at 0 °C. Neat *tert*-butyl acetoacetate (**4026**) (100 μL, 95 mg, 0.60 mmol, 1.0 equiv) was then added dropwise. The resulting bright yellow solution was stirred for 60 min at 0 °C and then cooled to –78 °C. A solution of the dienyl ketone **4007** (48 mg, 0.32 mmol, 0.5 equiv) in dry THF (3.0 mL) was added dropwise, and, after having been stirred for 3.5 h, the reaction mixture was allowed to warm to 0 °C. After 1 h at this temperature, the reaction mixture was quenched by the addition of sat aq NH_4Cl and the layers were shaken and separated. The aqueous phase was extracted with EtOAc (3x), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by two cycles of medium pressure liquid chromatography (SiO_2, 6:1 Hex/EtOAc then 9:1 Hex/EtOAc) provided the less polar diastereomer **4028a** (34 mg, 0.08 mmol, 24% yield corrected for purity) followed by the more polar diastereomer **4028b** (24 mg, 0.08 mmol, 24% yield). On the basis of ^{1}H NMR analysis, **4028a** was contaminated with 29% (w/w) with unreacted **4026**. However, in a separate experiment [*MJJ-III-273*] each of these diastereomers could be isolated in high purity (> 90%).

Data for **4028a** (*ca.* 6% enol content):

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.16 [d, J = 15.5 Hz, 1H, CH=C*H*(CH_3)C=CH_2], 5.70 [dd, J = 9.0, 15.5 Hz, 1H, C*H*=CH(CH_3)C=CH_2], 4.92-4.89 [m, 2H, CH=CH–(CH_3)C=C*H*$_2$], 3.36 [ABq, $\Delta\nu_{AB}$ = 14.9 Hz, J_{AB} = 15.5 Hz, 2H, C(O)C*H*$_2$CO_2*t*-Bu], 3.12 (d, J = 1.5 Hz, 1H, O*H*), 2.75 [ABq, $\Delta\nu_{AB}$ = 144 Hz, J_{AB} = 17.5 Hz, 2H, C*H*$_2$C(O)CH_2–CO_2*t*-Bu], 2.16 (ddd, J = 9.0, 9.0, 9.0 Hz, 1H, C*H*CH=CH), 2.04-1.98 (m, 1H, C*H*$_2$), 1.93-1.78 (m, 3H, C*H*$_2$), 1.86 [s, 3H, CH=CH(C*H*$_3$)C=CH_2], 1.69-1.59 (m, 2H, C*H*$_2$), and 1.46 [s, 9H, $CO_2C(CH_3)_3$].

TLC: R_f 0.34 (4:1 Hex/EtOAc).

Data for **4028b** (*ca.* 6% enol content):

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.11 [d, *J* = 15.5 Hz, 1H, CH=C*H*(CH_3)C=CH_2], 5.41 [dd, *J* = 9.0, 15.5 Hz, 1H, C*H*=CH(CH_3)C=CH_2], 4.92 [br s, 2H, CH=CH(CH_3)C=CH_2], 3.70 (d, *J* = 1.0 Hz, 1H, O*H*), 3.30 [ABq, $\Delta\nu_{AB}$ = 28.0 Hz, J_{AB} = 15.5 Hz, 2H, C(O)CH_2CO_2*t*-Bu], 2.70 [ABq, $\Delta\nu_{AB}$ = 10.7 Hz, J_{AB} = 17.5 Hz, 2H, CH_2C(O)CH_2–CO_2*t*-Bu], 2.67 (ddd, *J* = 5.5, 8.5, 8.5 Hz, 1H, C*H*CH=CH), 2.18-2.09 (m, 1H, CH_2), 1.90-1.81 (m, 2H, CH_2), 1.82 [s, 3H, CH=CH(CH_3)C=CH_2], 1.75-1.67 (m, 1H, CH_2), 1.65-1.59 (m, 1H, CH_2), 1.52-1.48 (m, 1H, CH_2), and 1.46 [s, 9H, CO_2C(CH_3)$_3$].

TLC: R_f 0.25 (4:1 Hex/EtOAc).

4029. [*MJJ-I-296*] A solution of LDA was prepared as described above from *i*-Pr_2NH (400 μL, 286 mg, 2.83 mmol, 2.4 equiv) and a solution of *n*-BuLi (1.05 mL, 2.63 mmol, 2.2 equiv, 2.50 M in Hex) in dry THF (25.0 mL) at 0 °C. Neat ethyl acetoacetate (**4027**) (150 μL, 153 mg, 1.18 mmol, 1.0 equiv) was then added dropwise. The resulting light yellow solution was stirred for 60 min at 0 °C and then cooled to –78 °C. A solution of the dienyl ketone **4007** (85 mg, 0.56 mmol, 0.5 equiv) in dry THF (5.0 mL) was added dropwise, and, after having been stirred for 3 h, the reaction mixture was allowed to warm to 0 °C. After 2.5 h at this temperature, the reaction mixture was quenched at 0 °C by the addition of sat aq NH_4Cl (25 mL). The layers were shaken and separated, the aqueous phase was extracted with EtOAc (3x), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification of the crude residue by two cycles of medium pressure liquid chromatography (SiO_2, 4:1 Hex/EtOAc) provided the less polar diastereomer **4029a** (79 mg, 0.22 mmol, 39% yield corrected for purity) followed by the more polar diastereomer **4029b** (42 mg, 0.15 mmol, 27% yield). On the basis of ^{1}H NMR analysis, **4029a** was contaminated with 23% (w/w) with unreacted

4027. Additionally, both of these fractions were contaminated with a small amount of a common, unknown impurity.

Data for **4029a** (*ca.* 7% enol content):

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.17 [d, *J* = 15.5 Hz, 1H, CH=C*H*(CH_3)C=CH_2], 5.69 [dd, *J* = 9.0, 15.5 Hz, 1H, C*H*=CH(CH_3)C=CH_2], 4.91-4.89 [m, 2H, CH=CH–(CH_3)C=C*H*$_2$], 4.21 (q, *J* = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 3.46 [ABq, $\Delta\nu_{AB}$ = 16.8 Hz, J_{AB} = 15.5 Hz, 2H, C(O)C*H*$_2$$CO_2$Et], 3.05 (s, 1H, O*H*), 2.76 [ABq, $\Delta\nu_{AB}$ = 134 Hz, J_{AB} = 17.0 Hz, 2H, C*H*$_2$C(O)CH_2CO_2Et], 2.17 (ddd, *J* = 9.0, 9.0, 9.0 Hz, 1H, C*H*CH=CH), 2.02-1.93 (m, 1H, C*H*$_2$), 1.89-1.78 (m, 3H, C*H*$_2$), 1.86 [s, 3H, CH=CH(C*H*$_3$)C=CH_2], 1.68-1.61 (m, 2H, C*H*$_2$), and 1.28 (t, *J* = 7.0 Hz, 3H, CO_2CH_2C*H*$_3$).

HR ESI-MS: $C_{16}H_{24}O_4$ $[M+Na]^+$ requires 303.1567; found 303.1557.

TLC: R_f 0.30 (4:1 Hex/EtOAc).

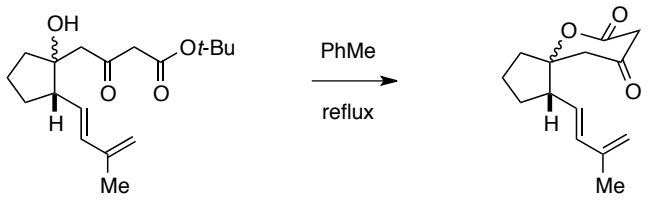
Data for **4029b** (*ca.* 7% enol content):

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.10 [d, *J* = 15.5 Hz, 1H, CH=C*H*(CH_3)C=CH_2], 5.40 [dd, *J* = 9.0, 15.5 Hz, 1H, C*H*=CH(CH_3)C=CH_2], 4.92 [br s, 2H, CH=CH(CH_3)C=C*H*$_2$], 4.18 (q, *J* = 7.0 Hz, 2H, $CO_2CH_2CH_3$), 3.62 (s, 1H, O*H*), 3.39 [ABq, $\Delta\nu_{AB}$ = 24.8 Hz, J_{AB} = 15.5 Hz, 2H, C(O)C*H*$_2$$CO_2$Et], 2.73 [ABq, $\Delta\nu_{AB}$ = 17.9 Hz, J_{AB} = 17.5 Hz, 2H, C*H*$_2$C(O)CH_2CO_2Et], 2.68 (ddd, *J* = 5.0, 8.5, 8.5 Hz, 1H, C*H*CH=CH), 2.16-2.11 (m, 1H, C*H*$_2$), 1.90-1.81 (m, 2H, C*H*$_2$), 1.82 [s, 3H, CH=CH(C*H*$_3$)C=CH_2], 1.75-1.69 (m, 1H, C*H*$_2$), 1.63-1.58 (m, 1H, C*H*$_2$), 1.53-1.46 (m, 1H, C*H*$_2$), and 1.27 (t, *J* = 7.0 Hz, 3H, CO_2CH_2C*H*$_3$).

HR ESI-MS: $C_{16}H_{24}O_4$ $[M+Na]^+$ requires 303.1567; found 303.1568.

TLC: R_f 0.21 (4:1 Hex/EtOAc).

(±)-(*E*)-1-(3-METHYLBUTA-1,3-DIEN-1-YL)-6-OXASPIRO[4.5]DECANE-7,9-DIONE (4030a/b)



4028a ***4030a***

[*MJJ-II-50/55/III-277*] The following procedure, which describes the formation of **4030a** from **4028a**, is representative. A dry round bottom flask was charged with the *tert*-butyl β-keto ester **4028a** (17.2 mg, 55.8 μmol) and dry PhMe (3.2 mL). The reaction flask was fitted with a West condenser and the contents were heated to reflux under N_2 for a period of *ca.* 18 h. After having been cooled to rt, the reaction mixture was evaporated *in vacuo* and the crude residue was purified by medium pressure liquid chromatography (SiO_2, 2:1 Hex/EtOAc) to provide the title compound (8.0 mg, 34.1 μmol, 61% yield).

Data for **4030a** (derived from **4028a**) [*MJJ-II-55*]:

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.20 [d, J = 15.5 Hz, 1H, CH=C*H*(CH_3)C=CH_2], 5.60 [dd, J = 9.0, 15.5 Hz, 1H, C*H*=CH(CH_3)C=CH_2], 4.98 [dddd, J = 2.0, 2.0, 2.0, 2.0 Hz, 1H, CH=CH(CH_3)C=CH_2], 4.94 [dddd, J = 1.0, 1.0, 1.0, 2.5 Hz, 1H, CH=CH(CH_3)C=CH_2], 3.36 [ABq, $\Delta\nu_{AB}$ = 27.4 Hz, J_{AB} = 21.0 Hz, 2H, CH_2C(O)C$H_2$$CO_2$], 2.70 [ABq, $\Delta\nu_{AB}$ = 107 Hz, J_{AB} = 16.5 Hz, 2H, CH_2C(O)CH_2CO_2], 2.41 (ddd, J = 9.0, 9.0, 9.0 Hz, 1H, C*H*CH=CH), 2.11-1.95 (m, 3H, CH_2), 1.89-1.75 (m, 3H, CH_2), and 1.83 [dd, J = 0.5, 1.5 Hz, 3H, CH=CH(CH_3)C=CH_2].

TLC: R_f 0.20 (2:1 Hex/EtOAc).

Data for **4030b** (derived from **4028b**) [*MJJ-II-50*]:

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.22 [d, *J* = 15.5 Hz, 1H, CH=C*H*(CH_3)C=CH_2], 5.37 [dd, *J* = 9.0, 15.5 Hz, 1H, C*H*=CH(CH_3)C=CH_2], 4.99 [dddd, *J* = 2.0, 2.0, 2.0, 2.0 Hz, 1H, CH=CH(CH_3)C=C*H*$_2$], 4.94 [dddd, *J* = 0.5, 0.5, 0.5, 2.0 Hz, 1H, CH=CH–(CH_3)C=C*H*$_2$], 3.39 [app s (ABq where $\Delta\nu_{AB}$ << 0.5 Hz), 2H, CH_2C(O)C*H*$_2$$CO_2$], 2.93 (ddd, *J* = 8.5, 8.5, 8.5 Hz, 1H, C*H*CH=CH), 2.64 [ABq, $\Delta\nu_{AB}$ = 87.4 Hz, J_{AB} = 17.0 Hz, 2H, C*H*$_2$C(O)CH_2CO_2], 2.20-2.09 (m, 2H, C*H*$_2$), 1.99-1.90 (m, 1H, C*H*$_2$), 1.87-1.82 (m, 1H, C*H*$_2$), 1.63-1.55 (m, 2H, C*H*$_2$), and 1.80 [dd, *J* = 1.0, 1.5 Hz, 3H, CH=CH(C*H*$_3$)C=CH_2].

NOTES FOR CHAPTERS II–IV & VI

[41] [*MJJ-III-157*] Diagnostic ^{1}H NMR resonances for the two principal species (**2021** and **2022**) observed during the hydrolysis of **2020**, including the final product **2023**, are provided [500 MHz, CD_3CN/0.1 M DCl (4:1)]. (a) **2021**: δ 6.43 (ddd, J = 1.5, 1.5, 16.0 Hz, 1H, PhC*H*=CHCH$_2$), 6.29 (ddd, J = 7.0, 7.0, 16.0 Hz, 1H, PhCH=C*H*CH$_2$), 4.89 [s, 1H, C*H*(OD)$_2$], and 2.59 (dd, J = 1.5, 7.0 Hz, 2H, PhCH=CHC*H*$_2$). (b) **2022**: δ 6.48 (ddd, J = 1.5, 1.5, 16.0 Hz, 1H, PhC*H*=CHCH$_2$), 6.31 (ddd, J = 7.0, 7.0, 16.0 Hz, 1H, PhCH=C*H*CH$_2$), 5.11 [s, 1H, C*H*(OD)$_2$], and 3.53 (dd, J = 1.5, 7.0 Hz, 2H, PhCH=CHC*H*$_2$). (c) **2023**: δ 9.13 (s, 1H, C*H*O), 7.55-7.52 (m, 2H, *ortho*-C$_6$*H*$_5$), 6.94 (dd, J = 1.0, 16.0 Hz, 1H, PhC*H*=CHCH), and 6.26 (dd, J = 1.0, 11.0 Hz, 1H, PhCH=CHC*H*).

[42] [*MJJ-III-147*] **^{1}H NMR** (500 MHz, CD_3CN): δ 9.23 (s, C*H*O), 7.54-7.51 (nfom, 2H, *o*-C$_6$*H*$_5$), 7.41-7.31 (m, 3H, *m*- and *p*-C$_6$*H*$_5$), 7.35 [dd, J = 11.0, 16.0 Hz, 1H, CH=C*H*CH=C(OTBS)CHO], 7.00 [d, J = 15.5 Hz, 1H, C*H*=CHCH=C(OTBS)–CHO], 6.58 [dd, J = 1.0, 11.5 Hz, 1H, CH=CHC*H*=C(OTBS)CHO], 1.03 [s, 9H, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$], and 0.20 [s, 6H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$].

[70] The following diagnostic ^{1}H NMR (500 MHz, $CDCl_3$) resonances were observed for **2066**: δ 5.89 [d, J = 2.0 Hz, 1H, (Bu$_3$Sn)C=C*H*$_2$] and 5.21 [d, J = 2.0 Hz, 1H, (Bu$_3$Sn)C=C*H*$_2$].

[71] In addition to **2045** and **2066**, the reduced terminal olefin, which was presumably derived from protodestannylation of **2045**, was also observed (relative ratio *ca.* 2). Diagnostic ^{1}H NMR (500 MHz, $CDCl_3$) resonances for this species: δ 6.39 (dd, J = 10.5, 17.5 Hz, 1H, C*H*=CH$_{trans}$H$_{cis}$), 5.16 (d, J = 17.0 Hz, 1H, CH=C*H*$_{trans}$H$_{cis}$), and 5.00 (d, J = 11.0 Hz, 1H, CH=CH$_{trans}$*H*$_{cis}$).

[79] The diagnostic ^{1}H NMR (500 MHz, $CDCl_3$) resonances that were observed for each of these species are provided. (a) **2083**: δ 5.63 [d, J = 3.0 Hz, 1H, (Bu$_3$Sn)C=C*H*$_2$] and 5.28 [d, J = 3.5 Hz, 1H, (Bu$_3$Sn)C=C*H*$_2$]. (b) **2084**: δ 6.83 (d, J = 19.0 Hz, 1H Bu$_3$SnCH=C*H*) and 6.07 (d, J = 19.0 Hz, 1H, Bu$_3$SnC*H*=CH).

[82] The following diagnostic ^{1}H NMR (500 MHz, $CDCl_3$) resonances were observed for **2086**: δ 5.85 [d, J = 3.5 Hz, 1H, (Bpin)C=C*H*$_2$] and 5.61 [d, J = 3.5 Hz, 1H, (Bpin)C=C*H*$_2$].

[94] Diagnostic ^{1}H NMR (500 MHz, $CDCl_3$) resonances for (11*Z*)-**2094** and (11*Z*)-**2093** are provided. (a) (11*Z*)-**2094**: δ 6.67 (d, *J* = 15.5 Hz, 1H, H8), 6.50 (d, *J* = 15.5 Hz, 1H, H10), 6.50 (dddd, *J* = 1.5, 1.5, 11.0, 15.0 Hz, 1H, H13), 5.93 (d, *J* = 11.5 Hz, 1H, H12), 5.67 (ddd, *J* = 7.5, 7.5, 15.0 Hz, 1H, H14), and 1.92 (s, 3H, H22). (b) (11*Z*)-**2093**: δ 6.65 (d, *J* = 16.5 Hz, 1H, H8), 6.50 (dddd, *J* = 1.5, 1.5, 11.0, 15.0 Hz, 1H, H13), 5.95 (d, *J* = 11.0 Hz, 1H, H12), 5.68 (ddd, *J* = 7.0, 7.0, 14.5 Hz, 1H, H14), and 1.91 (s, 3H, H22). (c) In both instances, the remaining ^{1}H NMR resonances were obscured by the major components, (11*E*)-**2094** and (11*E*)-**2093**, respectively.

[107] [*MJJ-V-284/294*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.39 [dd, *J* = 7.0, 7.0 Hz, 1H, $(Br)_2C{=}CH$], 2.09 [ddd, *J* = 7.0, 7.0, 7.0 Hz, 2H, $(Br)_2C{=}CHCH_2$], 1.46-1.39 [m, 2H, $CH_2CH_2(CH_2)_4CH_3$], 1.34-1.23 [m, 8H, $CH_2CH_2(CH_2)_4CH_3$], and 0.89 [t, *J* = 7.0 Hz, 3H, $CH_2CH_2(CH_2)_4CH_3$].
GC / LR EI-MS [5025015]: t_R 6.49 min; *m/z* (rel. int.) 286 [12, $M^{+\bullet}(^{81}Br/^{81}Br)$], 284 [23, $M^{+\bullet}(^{79}Br/^{81}Br)$], 282 [17, $M^{+\bullet}(^{79}Br/^{79}Br)$], 201 [31, $M^{+\bullet}(^{81}Br/^{81}Br)–C_6H_{13}^{\bullet}$], 199 [64, $M^{+\bullet}(^{79}Br/^{81}Br)–C_6H_{13}^{\bullet}$], 197 [31, $M^{+\bullet}(^{79}Br/^{79}Br)–C_6H_{13}^{\bullet}$], 123 (85), and 81 (100).

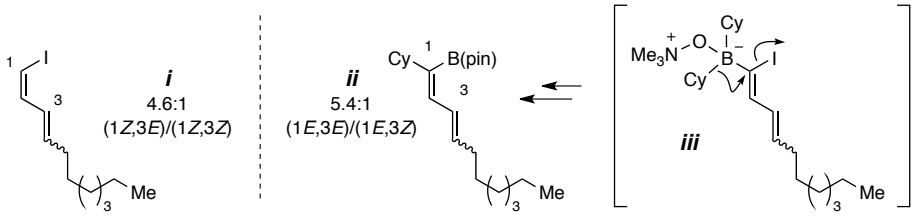
[108] [*MJJ-V-286/296*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.20 (dd, *J* = 7.0, 7.0 Hz, 2H, $BrC{\equiv}CCH_2CH_2$), 1.51 (dddd, *J* = 1.0, 7.0, 7.0, 16.0 Hz, 2H, $BrC{\equiv}CCH_2CH_2$), 1.39-1.34 [m, 2H, $BrC{\equiv}CCH_2CH_2CH_2$-$(CH_2)_3CH_3$], 1.32-1.24 [m, 6H, $BrC{\equiv}CCH_2CH_2CH_2(CH_2)_3CH_3$], and 0.89 [t, *J* = 7.0 Hz, 3H, $BrC{\equiv}CCH_2$–$CH_2CH_2(CH_2)_3CH_3$].
GC / LR EI-MS [5025015]: t_R 4.97 min; *m/z* (rel. int.) 161 [7, $M^{+\bullet}(^{81}Br)–C_3H_7^{\bullet}$], 159 [7, $M^{+\bullet}(^{79}Br)–C_3H_7^{\bullet}$], 147 [7, $M^{+\bullet}(^{81}Br)–C_4H_9^{\bullet}$], 145 [7, $M^{+\bullet}(^{79}Br)–C_4H_9^{\bullet}$], 134 (13), 132 (14), 119 [24, $M^{+\bullet}(^{81}Br)–C_6H_{13}^{\bullet}$], 117 [22, $M^{+\bullet}(^{79}Br)–C_6H_{13}^{\bullet}$], 81 (100), and 79 (71).

[110] [*MJJ-VI-21*] The *E* (†) and *Z* (‡) isomers have been indicated. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.51‡ (ddd, *J* = 7.0, 7.0, 12.0 Hz, 1H, $Bu_3SnCH{=}CH$), 5.94† (ddd, *J* = 6.0, 6.0, 19.0 Hz, 1H, $Bu_3SnCH{=}CH$), 5.85† (ddd, *J* = 1.0, 1.0, 19.0 Hz, 1H, $Bu_3SnCH{=}CH$), 5.77‡ (ddd, *J* = 1.0, 1.0, 12.0 Hz, 1H, $Bu_3SnCH{=}CH$), 2.12† (dddd, *J* = 1.0, 6.5, 7.0, 7.0 Hz, 2H, $Bu_3SnCH{=}CHCH_2$), 2.01‡ (dddd, *J* = 1.0, 7.0, 7.0, 7.0 Hz, 2H, $Bu_3SnCH{=}CHCH_2$), 1.54-1.43†‡ [m, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$], 1.42-1.36†‡ [m, 2H, $CH_2CH_2(CH_2)_4CH_3$], 1.34-1.25†‡ [m, 14H, overlapping $CH_2CH_2(CH_2)_4CH_3$ and $Sn(CH_2CH_2CH_2CH_3)_3$], 0.89†‡ [t, *J* = 7.5 Hz, 12H, overlapping $CH_2CH_2(CH_2)_4CH_3$ and $Sn(CH_2CH_2CH_2CH_3)_3$], and 0.88-0.84†‡ [m, 6H, $Sn(CH_2CH_2CH_2CH_3)_3$].

GC / LR EI-MS [5025015]: t_R 10.09 min (*E* isomer) and 10.05 min (*Z* isomer); *m*/*z* (rel. int.) 359 [100, $M^{+\bullet}(^{120}Sn)–C_4H_9^{\bullet}$], 357 [75, $M^{+\bullet}(^{118}Sn)–C_4H_9^{\bullet}$], 355 [41, $M^{+\bullet}(^{116}Sn)–C_4H_9^{\bullet}$], 303 (58), 301 (44), 299 (25), 247 (59), 245 (47), and 243 (28). The LR EI-MS fragmentation patterns for the (*E*)- and (*Z*)-isomers were indistinguishable.

[111] In contrast to the isomeric purity of **2109**, the *E*/*Z* ratios for the product vinyl stannanes in Pattenden's report always exceeded 95:5; see ref 80.

[120] On the basis of ^{1}H NMR and GC-MS analyses, the vinyl iodide **i** and the vinyl boronic ester **ii** were identified as the two other major components produced along with **2126**. The ratio of **2126**:**i**:**ii** was estimated to be 1.0:0.45:0.52. Boronate **ii** most likely arises via sp^3 C–B bond migration with inversion at the alkenyl carbon (as suggested by intermediate **iii**). The configuration of the $\Delta^{1,2}$ alkene was not rigorously established. For analogous transformations, see ref 112a.



[*MJJ-IV-88*] Diagnostic ^{1}H NMR (500 MHz, $CDCl_3$) alkene resonances for each of these species are provided. (1*Z*,3*E*)-**i**: δ 6.68 (ddd, *J* = 0.5, 7.5, 9.5 Hz, 1H, ICH=C*H*CH=CH), 6.21 (ddddd, *J* = 1.5, 1.5, 1.5, 10.0, 15.5 Hz, 1H, ICH=CH–C*H*=CH), 6.09 (ddddd, *J* = 1.0, 1.0, 1.0, 1.0, 7.5 Hz, 1H, IC*H*=CHCH=CH), and 6.00 (dddd, *J* = 1.0, 7.0, 7.0, 16.0 Hz, 1H, ICH=CHCH=C*H*) (cf. Stewart, S. K.; Whiting, A. Stereoselective Synthesis of Vinyl Iodides from Vinylboronate Pinacol Esters Using ICl. *Tetrahedron Lett.* **1995**, *36*, 3929–3932). (1*Z*,3*Z*)-**i**: δ 6.98 (ddd, *J* = 1.0, 7.5, 10.0 Hz, 1H, ICH=C*H*CH=CH), 6.28 (ddd, *J* = 1.5, 1.5, 7.5 Hz, 1H, IC*H*=CHCH=CH), *ca.* 6.11 (ddddd, *J* = 2.0, 2.0, 2.0, 10.5, 11.0 Hz, 1H, ICH=CHC*H*=CH), and 5.72 (ddddd, *J* = 1.5, 1.5, 7.5, 7.5, 11.0 Hz, 1H, ICH=CHCH=C*H*). (1*E*,3*E*)-**ii**: δ 6.68 {dddd, *J* = 1.5, 1.5, 11.0, 15.0 Hz, 1H, (Cy)[B(pin)]C=CHC*H*=CH}, 6.48 {d, *J* = 11.0 Hz, 1H, (Cy)[B(pin)]C=C*H*–CH=CH}, and 5.71 {ddd, *J* = 7.0, 7.0, 14.0 Hz, 1H, (Cy)[B(pin)]C=CHCH=C*H*}. (1*E*,3*Z*)-**ii**: δ 6.80 {d, *J* = 12.0 Hz, 1H, (Cy)[B(pin)]C=C*H*CH=CH}, 6.57 {dddd, *J* = 1.5, 1.5, 11.0, 11.0 Hz, 1H, (Cy)[B(pin)]C=CHC*H*=CH}, and 5.46 {ddd, *J* = 7.5, 7.5, 11.0 Hz, 1H, (Cy)[B(pin)]C=CHCH=C*H*}.

[135] The difficulty associated with the removal of Bu_3SnX residues from relatively nonpolar products–such as those prepared in Table II–7–has been widely recognized in the literature. Several tactics have been reported that attempt to overcome this annoying problem, all of which have limitations. See ref 131 and references cited therein.

[139] [*MJJ-V-62/72/75*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.49 [dddd, J = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.69 (s, 3H, $CH_2CO_2CH_3$), 3.34 (ABX_4, $\Delta\nu_{AB}$ = 60.3 Hz, J_{AB} = 16.5 Hz, J_{AX} = 1.0 Hz, J_{BX} = 1.5 Hz, 2H, $CH_2CO_2CH_3$), 2.78-2.71 [m, 2H, overlapping $CH_2CH(OTBS)CH_2$], 2.45 [dddddd, J = 2.0, 2.0, 2.0, 2.0, 3.5, 16.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 2.39 [dddddd, J = 1.5, 1.5, 1.5, 1.5, 4.0, 17.0 Hz, 1H, $CH_2CH(OTBS)CH_2$], 0.87 [s, 9H, $(CH_3)_3CSi(CH_3)_2$], 0.19 [s, 9H, $C{\equiv}CSi(CH_3)_3$], 0.05 [s, 3H, $(CH_3)_3CSi(CH_3)_2$], and 0.04 [s, 3H, $(CH_3)_3C–Si(CH_3)_2$].

GC / LR EI-MS [5025015]: t_R 9.42 min; *m*/*z* (rel. int.) 366 (0.2, $M^{+\bullet}$), 351 (2, $M^{+\bullet}–CH_3^{\bullet}$), 309 [69, $M^{+\bullet}–C(CH_3)_3^{\bullet}$], 281 (100), 175 (31), 159 (10), 147 (8), and 89 (17).

[141] [*MJJ-IV-94*] **GC / LR EI-MS** [5025015]: t_R 6.46 min; *m*/*z* (rel. int.) 166 (89, $M^{+\bullet}$) and 81 (100).

[142] The reaction times shown in Table II–7 are not necessarily the time *required* to reach full conversion.

[146] [*MJJ-IV-44*] **^{1}H NMR** (500 MHz, CD_2Cl_2): δ 6.48 [d, J = 16.0 Hz, 1H, C*H*=CHC(CH$_3$)=CH$_2$], 6.21 [d, J = 16.0 Hz, 1H, CH=C*H*C(CH$_3$)=CH$_2$], 5.81 (dd, J = 1.0, 1.0 Hz, 1H, CH$_2$C=C*H*), 4.98 [s, 1H, CH=CHC(CH$_3$)=C*H*$_2$], 4.96 [s, 1H, CH=CHC(CH$_3$)=C*H*$_2$], 4.48 [dddd, J = 3.5, 3.5, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 4.04-3.92 (AA'BB', 4H, OC*H*$_2$C*H*$_2$O), 2.88 [app s (ABq where $\Delta\nu_{AB}$ < 0.5 Hz), 2H, C*H*$_2$C=CH], 2.78 [dd, J = 7.0, 16.0 Hz, 1H, C*H*$_2$CH(OTBS)CH$_2$], 2.71 [dd, J = 6.5, 17.5 Hz, 1H, CH$_2$CH(OTBS)C*H*$_2$], 2.43 [dd, J = 3.0, 16.0 Hz, 1H, C*H*$_2$CH(OTBS)CH$_2$], 2.38 [dd, J = 3.0, 18.0 Hz, 1H, CH$_2$CH(OTBS)C*H*$_2$], 1.88 [s, 3H, CH=CHC(C*H*$_3$)=CH$_2$], 0.88 [s, 9H, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$], 0.063 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$], and 0.059 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$].

[148] [*MJJ-IV-145*] This material displayed the following diagnostic ^{1}H NMR resonances (500 MHz, $CDCl_3$): δ 5.57, 5.51, 5.46, and 5.37 [all s, 1H, C*H*(OAc)]; 4.47, 4.42, 4.41, and 4.39 [all dddd, J = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)]; 3.408, 3.406, 3.353, and 3.351 (all s, 3H, OC*H*$_3$); and 2.189, 2.185, 2.16, and 2.13 [all s, 3H, C(O)C*H*$_3$].

[151] [*MJJ-III-31/39*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.42 (s, 1H, C*H*O), 4.41 [dddd, *J* = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.312 [s, 3H, $CH_2C(OC\mathit{H_3})_2CHO$], 3.310 [s, 3H, $CH_2C(OC\mathit{H_3})_2CHO$], 2.84 [$ABX_4$, $\Delta\nu_{AB}$ = 30.8 Hz, J_{AB} = 14.5 Hz, $J_{AX} = J_{BX}$ = 1.5 Hz, 2H, $C\mathit{H_2}C(OCH_3)_2CHO$], 2.66 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 7.0, 16.0 Hz, 1H, $C\mathit{H_2}CH(OTBS)CH_2$], 2.59 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 7.0, 17.0 Hz, 1H, $CH_2CH(OTBS)C\mathit{H_2}$], 2.38 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 4.0, 16.0 Hz, 1H, $C\mathit{H_2}CH(OTBS)CH_2$], 2.27 [dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 4.0, 17.0 Hz, 1H, $CH_2CH(OTBS)C\mathit{H_2}$], 0.87 [s, 9H, $(C\mathit{H_3})_3CSi(CH_3)_2$], 0.19 [s, 9H, C≡C–$Si(C\mathit{H_3})_3$], and 0.03 [s, 6H, $(CH_3)_3CSi(C\mathit{H_3})_2$].
GC / LR EI-MS [5029021]: t_R 11.76 min; *m*/*z* (rel. int.) 410 (1, $M^{+\bullet}$), 395 (1, $M^{+\bullet}–CH_3^{\bullet}$), 381 (72, $M^{+\bullet}–CHO^{\bullet}$), 353 [13 $M^{+\bullet}–C(CH_3)_3^{\bullet}$], 249 (4), 219 (4), 175 (13), 159 (6), 147 (11), and 103 {100, $[C(OCH_3)_2CHO]^+$}.

[153] [*MJJ-III-298*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.41-7.38 (m, 2H, $C_6\mathit{H_5}$), 7.34-7.31 (m, 2H, $C_6\mathit{H_5}$), 7.29-7.25 (m, 1H, $C_6\mathit{H_5}$), 6.69 (ddd, *J* = 1.5, 1.5, 16.0 Hz, 1H, PhC*H*=CH), 6.30 (ddd, *J* = 6.5, 6.5, 16.0 Hz, 1H, PhCH=C*H*), 4.80 (dd, *J* = 1.5, 6.5 Hz, 1H, $C\mathit{H_2}OCO_2CH_3$), and 3.81 (s, 3H, $OCO_2C\mathit{H_3}$).
GC / LR EI-MS [5027016]: t_R 8.03 min; *m*/*z* (rel. int.) 192 (22, $M^{+\bullet}$), 133 (20, $M^{+\bullet}–C_2H_3O_2^{\bullet}$), 117 (71, $M^{+\bullet}–C_2H_3O_3^{\bullet}$), 115 (100, $M^{+\bullet}–C_6H_5^{\bullet}$), 105 (32), 91 [23, $(C_7H_7)^+$], and 77 [21, $(C_6H_5)^+$].

[154] [*MJJ-III-300/IV-68*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.37-7.35 (m, 2H, $C_6\mathit{H_5}$), 7.30 (dd, *J* = 7.0, 7.0 Hz, 2H, $C_6\mathit{H_5}$), 7.21 (dddd, *J* = 1.5, 1.5, 7.0, 7.0 Hz, 1H, $C_6\mathit{H_5}$), 6.46 (ddd, *J* = 1.5, 1.5, 16.0 Hz, 1H, PhC*H*=CH), 6.19 (ddd, *J* = 6.5, 6.5, 16.0 Hz, 1H, PhCH=C*H*), 5.90 (dd, *J* = 1.0, 1.0 Hz, 1H, $CH_2C=C\mathit{H}$), 4.12-4.00 (AA'BB', 4H, $OC\mathit{H_2}C\mathit{H_2}O$), and 2.87 (ddd, *J* = 1.0, 1.0, 6.5 Hz, 2H, $C\mathit{H_2}$).
GC / LR EI-MS [5027016]: t_R 9.07 min; *m*/*z* (rel. int.) 202 (100, $M^{+\bullet}$), 145 (29), 130 (20), 129 (27), 128 (16), 127 (27), 117 (74, $M^{+\bullet}–C_4H_5O_2^{\bullet}$), 115 (64), and 91 [27, $(C_7H_7)^+$].

[164] [*MJJ-V-105*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.27 (br d, *J* = 8.0 Hz, 2H, $SC_6\mathit{H_4}CH_3$), 7.08 (br d, *J* = 8.0 Hz, 2H, $SC_6\mathit{H_4}CH_3$), 7.08 (dd, *J* = 3.0, 5.0 Hz, 1H, $CH_2CH=C\mathit{H}C=CH$), 6.76 (s, 1H, O*H*), 6.69 (ddd, *J* = 1.0, 1.0, 4.5 Hz, 1H, $CH_2C\mathit{H}=CHC=CH$), 6.32 (dd, *J* = 1.0, 2.5 Hz, 1H, $CH_2CH=CHC=C\mathit{H}$), 4.02 (s, 2H, $C\mathit{H_2}CH=CHC=CH$), 2.63 (s, 3H, $C\mathit{H_3}$), and 2.32 (s, 3H, $SC_6H_4C\mathit{H_3}$).
GC / LR EI-MS [5025015]: t_R 11.08 min; *m*/*z* (rel. int.) 268 (12, $M^{+\bullet}$) and 145 (100, $M^{+\bullet}–C_7H_7S^{\bullet}$).

[173] [*MJJ-V-251*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.57 (s, 1H, C*H*O), 7.82 [s, 1H, C*H*=C(O)CHO], 7.31 [dd, *J* = 2.5, 4.5 Hz, 1H, (CH_3)C=CCH=C*H*CH=C], 7.08 [ddd, *J* = 1.0, 1.0, 4.5 Hz, 1H, (CH_3)C=CC*H*=CHCH=C], 6.98 [dd, *J* = 1.0, 3.0 Hz, 1H, (CH_3)C=CCH=CHC*H*=C], and 2.83 (s, 3H, C*H*$_3$).
GC / LR EI-MS [5025015] t_R 7.07 min; *m*/*z* (rel. int.) 160 (100, $M^{+\bullet}$), 159 (13, $M^{+\bullet}$–H$^\bullet$), 132 (12), 131 (11, $M^{+\bullet}$–CHO$^\bullet$), 104 (6), 103 (37), 102 (10), 78 (10), and 77 (16).

[175] [*MJJ-V-127*] The following diagnostic ^{1}H NMR resonances for **2232** ($Bu_3SnC=CH_2$) and **2233** (CH=CHSnBu_3) were observed (500 MHz, $CDCl_3$): δ 6.81 (d, *J* = 19.0 Hz, 1H, C*H*=CHSnBu_3), 6.17 (d, *J* = 19.0 Hz, 1H, CH=C*H*SnBu_3), 5.59 (d, *J* = 3.5 Hz, 1H, $Bu_3SnC=CH_2$) and 5.25 (d, *J* = 3.5 Hz, 1H, $Bu_3SnC=CH_2$).

[177] [*MJJ-V-128*] This material displayed the following diagnostic ^{1}H NMR resonances (500 MHz, $CDCl_3$): δ 6.52 (dd, *J* = 11.0, 17.0 Hz, 1H, C*H*=CH$_{trans}$H$_{cis}$), 5.12 (d, *J* = 10.5 Hz, 1H, CH=CH$_{trans}$*H*$_{cis}$), and 5.11 (d, *J* = 17.5 Hz, 1H, CH=C*H*$_{trans}$H$_{cis}$).

[181] The configurations of the $\Delta^{8,10}$ and $\Delta^{13,14}$ olefins within (*E*)- and (*Z*)-**2239** could be easily ascertained by analysis of their respective $^3J_{H,H}$ and $^4J_{H,H}$ coupling constant values. The configuration of the $\Delta^{11,12}$ olefin, however, rests upon comparison of the chemical shift of the H12 resonances of each to those of (11*E*)- and (11*Z*)-**2094** (cf. Table II–5 and footnote 94). Diagnostic ^{1}H NMR (500 MHz, $CDCl_3$) resonances for the major (†) and minor (‡) isomers: δ 7.19† (d, *J* = 14.5 Hz, 1H, H8), 6.41‡ (d, *J* = 15.5 Hz, 1H, H8), 6.39† (dddd, *J* = 1.5, 1.5, 11.5, 15.5 Hz, 1H, H13), 6.22† (d, *J* = 14.5 Hz, 1H, H10), 6.20‡ (d, *J* = 15.5 Hz, 1H, H10), 6.11† (d, *J* = 11.5 Hz, 1H, H12), 6.08‡ (dddd, *J* = 1.5, 1.5, 11.0, 14.5 Hz, 1H, H13), 5.91‡ (d, *J* = 11.0 Hz, 1H, H12), 5.77† (ddd, *J* = 7.0, 7.0, 14.5 Hz, 1H, H14), and 5.69‡ (ddd, *J* = 7.0, 7.0, 14.5 Hz, 1H, H14).
LR ESI-MS: $C_{35}H_{54}O_2SSi$ $[M+Na]^+$ requires 589.35; found 589.54.

[185] [*MJJ-VI-128*] **^{1}H NMR** (500 MHz, CD_3CN): δ 7.09 [d, *J* = 19.0 Hz, 1H, C*H*=CHSi$(CH_3)_3$], 6.98 (dd, *J* = 10.5, 17.0 Hz, 1H, C*H*=CH$_{trans}$H$_{cis}$), 5.88 [d, *J* = 19.0 Hz, 1H, CH=C*H*Si$(CH_3)_3$], 5.19 (d, *J* = 17.5 Hz, 1H, CH=C*H*$_{trans}$H$_{cis}$), 5.18 (d, *J* = 10.5 Hz, 1H, CH=CH$_{trans}$*H*$_{cis}$), 4.53 [dddd, *J* = 3.0, 3.0, 6.5, 6.5 Hz, 1H, C*H*(OTBS)], 2.86 [dd, *J* = 6.5, 16.5 Hz, 1H, C*H*$_2$CH(OTBS)CH$_2$], 2.83 [dd, *J* = 6.5, 14.5 Hz, 1H, CH$_2$CH(OTBS)C*H*$_2$], 2.52-2.45 [m, 2H, overlapping

C*H*$_2$CH(OTBS)C*H*$_2$], 0.88 [s, 9H, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$], 0.10 [s, 9H, Si(C*H*$_3$)$_3$], and 0.08 [s, 6H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$].

GC / LR EI-MS [5025015]: t_R 8.71 min; *m*/*z* (rel. int.) 322 (19, $M^{+\bullet}$), 265 [100, $M^{+\bullet}$–C(CH$_3$)$_3^{\bullet}$], 191 (78), 147 (76), 117 (50), 75 (58), and 73 (61). This material partially decomposed upon entering the GC injection port, as evidenced by the presence of five additional, less intense peaks (t_R 8.56, 8.59, 8.83, 8.85, and 9.05 min).

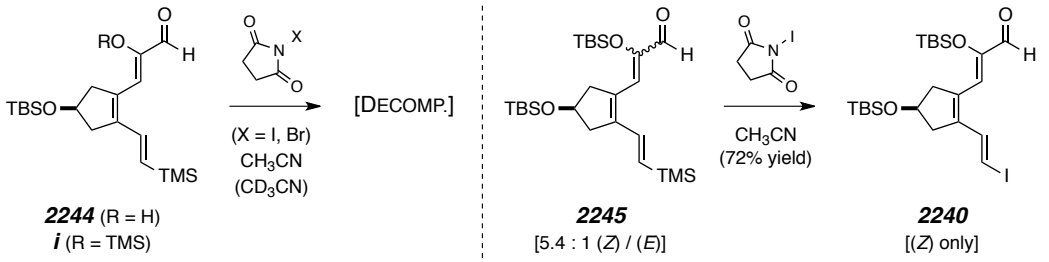
TLC: R_f 0.85 (9:1 Hex/EtOAc).

[186] [*MJJ-VI-127*] **^{1}H NMR** (500 MHz, CD$_3$CN): δ 6.60 [d, *J* = 3.0 Hz, 1H, C=C*H*CH(OTBS)], 6.45 (dddd, *J* = 1.0, 1.0, 11.0, 17.5 Hz, 1H, C*H*=CH$_{trans}$H$_{cis}$), 6.33 [dd, *J* = 2.5, 2.5 Hz, 1H, C=C*H*C(O)CH$_3$], 5.71 (dd, *J* = 2.0, 18.0 Hz, 1H, CH=C*H*$_{trans}$H$_{cis}$), 5.37 (dd, *J* = 2.0, 11.5 Hz, 1H, CH=CH$_{trans}$*H*$_{cis}$), 4.96 [ddd, *J* = 3.0, 3.0, 5.5 Hz, 1H, C*H*(OTBS)], 3.44 (ddd, *J* = 2.5, 6.5, 19.5 Hz, 1H, C*H*$_2$), 2.66 (ddd, *J* = 2.5, 2.5, 19.5 Hz, 1H, C*H*$_2$), 2.19 [s, 3H, C(O)C*H*$_3$], 0.90 [s, 9H, (C*H*$_3$)$_3$CSi(CH$_3$)$_2$], 0.12 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$], and 0.11 [s, 3H, (CH$_3$)$_3$CSi(C*H*$_3$)$_2$].

GC / LR EI-MS [5025015]: t_R 8.59 min; *m*/*z* (rel. int.) 278 (37, $M^{+\bullet}$), 263 (54, $M^{+\bullet}$–$CH_3^{\bullet}$), 235 (37, $M^{+\bullet}$–$C_2H_3O^{\bullet}$), 221 [96, $M^{+\bullet}$–C(CH$_3$)$_3^{\bullet}$], 206 (26), 177 (19), 147 (14, $M^{+\bullet}$–$C_6H_{15}OSi^{\bullet}$), 129 (44), 117 (72), 105 (23), 103 (28), and 75 (100).

TLC: R_f 0.42 (9:1 Hex/EtOAc).

[191] It should be recognized that protection of the enol **2244** as its corresponding TBS- or TIPS enol ether is absolutely essential for the success of the subsequent iododesilylation. For example, exposure of the free enol **2244** or the TMS enol ether **i** [prepared from **2235** (Et_3N, CH_2Cl_2; BSA)] to either bromo- or iododesilylative conditions gave an unidentified intermediate that quickly decomposed upon attempted product isolation. Interestingly, on one (and only one) occasion [*MJJ-VI-166*], the TBS enol ether **2245** was isolated as an isomeric mixture upon elimination and silylation [Et_3N, CH_2Cl_2; MTBSA (18% yield)] of the nitrate ester **2254**. Somewhat unexpectedly, the vinyl iodide **2240** emerged from the iododesilylation of this material as a single [(*Z*)] isomer. Taken together, these observations suggest that an intermediate iodonium ion is formed that rapidly and reversibly samples the entire conjugated π-system of **2245** (or **2244**/**i**). Presumably, desilylation (or proton loss) is the rate-determining step that leads to a productive (e.g., **2245**) or nonproductive (e.g. **2244** and **i**) outcome.



2244 (R = H)
i (R = TMS)

2245
[5.4 : 1 (*Z*) / (*E*)]

2240
[(*Z*) only]

[192] [*MJJ-VI-91/93*] **^{1}H NMR** (500 MHz, CD_3CN): δ 9.24 (s, 1H, C*H*O), 7.71 (d, *J* = 14.5 Hz, 1H, C*H*=CHI), 6.65 (d, *J* = 14.5 Hz, 1H, CH=C*H*I), 6.58 [s, 1H, C*H*=C(OTIPS)CHO], 4.55 [dddd, *J* = 2.5, 2.5, 6.0, 6.0 Hz, 1H, C*H*(OTBS)], 3.12 [dd, *J* = 6.5, 18.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.87 [br d, *J* = 18.0 Hz, 1H, CH_2CH(OTBS)CH_2], 2.82 [dd, *J* = 6.5, 17.5 Hz, 1H, CH_2CH(OTBS)CH_2], 2.47 [dd, *J* = 3.0, 17.5 Hz, 1H, CH_2CH(OTBS)CH_2], 1.32 {septet, *J* = 7.5 Hz, 3H, Si[C*H*(CH_3)$_2$]$_3$}, 1.057 {d, *J* = 7.5 Hz, 9H, Si[CH(CH_3)$_2$]$_3$}, 1.055 {d, *J* = 7.5 Hz, 9H, Si[CH(CH_3)$_2$]$_3$}, 0.87 [s, 9H, (CH_3)$_3$CSi(CH_3)$_2$], 0.064 [s, 3H, (CH_3)$_3$C–Si(CH_3)$_2$], and 0.062 [s, 3H, (CH_3)$_3$CSi(CH_3)$_2$].

[196] [*MJJ-VI-94/95*] **^{1}H NMR** (500 MHz, CD_3CN): δ 9.26 (s, 1H, C*H*O), 6.84 [d, *J* = 15.5 Hz, 1H, C*H*=CHC(CH_3)=CHCH=CH], 6.71 [s, 1H, C*H*=C(OTIPS)–CHO], 6.48 [d, *J* = 15.5 Hz, 1H CH=C*H*C(CH_3)=CHCH=CH], 6.48 [dddd, *J* = 1.5, 1.5, 11.0, 14.5 Hz, 1H, CH=CHC(CH_3)=CHC*H*=CH], 6.23 [d, *J* = 11.5 Hz, 1H, CH=CHC(CH_3)=C*H*CH=CH], 5.85 [ddd, *J* = 7.0, 7.0, 14.5 Hz, 1H, CH=CHC(CH_3)=CHCH=C*H*], 4.42 [ddddd, *J* = 2.5, 2.5, 4.5, 6.5, 6.5 Hz, 1H, C*H*(OH)], 3.19 [dd, *J* = 6.5, 18.0 Hz, 1H, CH_2CH(OH)CH_2], 2.94 [br d, *J* = 18.0 Hz, 1H, CH_2CH(OH)CH_2], 2.88 [d, *J* = 4.5 Hz, 1H, CH(O*H*)], 2.81 [dd, *J* = 6.5, 17.5 Hz, 1H, CH_2CH(OH)CH_2], 2.52 [br d, *J* = 17.5 Hz, 1H, CH_2CH(OH)CH_2], 2.16 [br ddd, *J* = 7.5, 7.5, 7.5 Hz, 2H, CH=CHCH_2], 1.95 [s, 3H, CH=CH–C(CH_3)=CHCH=CH], 1.44-1.38 [m, 2H, CH=CHCH_2CH_2(CH_2)$_4$$CH_3$], 1.33 {septet, *J* = 7.5 Hz, 3H, Si[C*H*(CH_3)$_2$]$_3$}, 1.33-1.27 [m, 8H, CH=CHCH_2CH_2–(CH_2)$_4$$CH_3$], 1.071 {d, *J* = 7.5 Hz, 9H, Si[CH(CH_3)$_2$]$_3$}, 1.067 {d, *J* = 7.5 Hz, 9H, Si[CH(CH_3)$_2$]$_3$}, and 0.89 [t, *J* 7.0 Hz, 3H, CH=CHCH_2CH_2(CH_2)$_4$CH_3].

[204] [*MJJ-IV-230*] It must be said that this reaction was neither clean nor efficient, and thus a sample of **2285** could not be isolated in a high state of purity. However, the following diagnostic ^{1}H NMR (500 MHz, $CDCl_3$) resonances were evident: δ 3.84 [ABq (2x), $\Delta\nu_{AB}$ = 57 Hz, J_{AB} = 17.5 Hz, 4H, overlapping CH_2C(=N)CH–CO_2Allyl], 2.51 [s, 1H, CH_2C(=N)C*H*CO_2Allyl], and 2.50 [s, 1H, CH_2C(=N)C*H*–CO_2Allyl].

HR ESI-MS: $C_{23}H_{37}NO_3Si_2$ $[M+Na]^+$ requires 454.2204; found 454.2224.

TLC: R_f 0.52 (6:1 Hex/EtOAc).

The observed chemical shifts for the diastereomeric 2*H*-azirine methine protons that have been assigned to **2285** are reasonably consistent with literature values; see ref 205a and: Sakamoto, S.; Inokuma, T.; Takemoto, Y. Organocatalytic Asymmetric Neber Reaction for the Synthesis of 2*H*-Azirine Carboxylic Esters. *Org. Lett.* **2011**, *13*, 6374–6377.

[215] [*MJJ-IV-247*] **HR ESI-MS**: $C_{25}H_{30}N_4O_5Si$ $[M+Na]^+$ requires 517.1878; found 517.1879.

[216] [*MJJ-V-37*] **HR ESI-MS**: $C_{32}H_{44}N_4O_6Si_2$ $[M+Na]^+$ requires 659.2692; found 659.2771.

[218] [*MJJ-IV-258*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.49-7.45 (m, 8H, NC_6H_5), 7.40-7.36 (m, 2H, NC_6H_5), 5.90 (dddd, J = 5.0, 5.0, 11.0, 17.5 Hz, 1H, CH_2–CH=$CH_{trans}H_{cis}$), 5.89 (dddd, J = 5.0, 5.0, 10.5, 17.5 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.40 (ABq, $\Delta\nu_{AB}$ = 33.9 Hz, J_{AB} = 12.0 Hz, 2H, NCH_2SCH_3), 5.40 (ABq, $\Delta\nu_{AB}$ = 11.7 Hz, J_{AB} = 11.5 Hz, 2H, NCH_2SCH_3), 5.289 (dddd, J = 2.0, 2.0, 2.0, 17.5 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.285 (dddd, J = 1.5, 1.5, 1.5, 17.0 Hz, 1H, CH_2–CH=$CH_{trans}H_{cis}$), 5.147 (dddd, J = 1.5, 1.5, 1.5, 11.0 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 5.144 (dddd, J = 1.5, 1.5, 1.5, 11.0 Hz, 1H, CH_2CH=$CH_{trans}H_{cis}$), 4.63-4.61 (m, 4H, overlapping CH_2CH=$CH_{trans}H_{cis}$), 4.46 [dddd, J = 3.5, 3.5, 7.0, 7.0 Hz, 1H, CH(OTBS)], 4.44 [dddd, J = 3.0, 3.0, 6.5, 6.5 Hz, 1H, CH(OTBS)], 3.383 [ABq, $\Delta\nu_{AB}$ = 19.2 Hz, J_{AB} = 15.0 Hz, 2H, $CH_2C(NH_2)$], 3.377 [ABq, $\Delta\nu_{AB}$ = 45.5 Hz, J_{AB} = 15.0 Hz, 2H, $CH_2C(NH_2)$], 2.78-2.68 [m, 4H, overlapping CH_2CH(OTBS)–CH_2], 2.48-2.34 [m, 4H, overlapping CH_2CH(OTBS)CH_2], 2.241 (s, 3H, NCH_2SCH_3), 2.239 (s, 3H, NCH_2SCH_3), 0.86 [s, 18H, 2x $(CH_3)_3CSi(CH_3)_2$], 0.19 [s, 18H, 2x $C{\equiv}CSi(CH_3)_3$], 0.04 [s, 6H, 2x $(CH_3)_3CSi(CH_3)_2$], and 0.03 [s, 6H, 2x $(CH_3)_3CSi(CH_3)_2$].

HR ESI-MS: $C_{33}H_{48}N_4O_5SSi_2$ $[M+Et_3NH]^+$ requires 770.4161; found 770.4190.

[219] [*MJJ-V-88*] **HR ESI-MS**: $C_{23}H_{36}O_5Si_2$–$C_{23}H_{37}NO_4Si_2$ $[2M+Na]^+$ requires 918.4255; found 918.4219. The principal ESI-MS peak that was observed for **2286** corresponded to the sodiated 1:1 α,β-diketo ester:α-keto β-imino ester adduct.

[244] It should also be noted that a different Wittig rearrangement–namely, the [1,2] variant–could also be operative in these systems. See: Schöllkopf, U. Recent Results in Carbanion Chemistry. *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 763–773.

[262] [*MJJ-III-180*] **^{1}H NMR** (500 MHz, $CDCl_3$): 5.86 (dddd, *J* = 2.0, 2.0, 5.5, 10.0 Hz, 1H, C*H*=CH), 5.83 (ddd, *J* = 7.0, 10.5, 17.5 Hz, 1H, C*H*=$CH_{trans}H_{cis}$), 5.65 (dddd, *J* = 1.5, 1.5, 3.0, 10.5 Hz, 1H, CH=C*H*), 5.32 (ddd, *J* = 1.5, 1.5, 17.0 Hz, 1H, CH=C$H_{trans}H_{cis}$), 5.19 (ddd, *J* = 1.5, 1.5, 10.5 Hz, 1H, CH=$CH_{trans}H_{cis}$), 4.66 [Σ (*J*s) = 20.5 Hz including 1.5, 1.5, and 6.5 Hz, 1H, CH=CHC*H*–CH=$CH_{trans}H_{cis}$), 3.78 (dddd, *J* = 3.0, 3.0, 7.5, 10.5 Hz, 1H, C*H*CH_2OH), 3.69 (ddd, *J* = 3.0, 8.0, 11.5 Hz, 1H, CHC*H*$_2$OH), 3.60 (ddd, *J* = 5.0, 7.5, 12.0 Hz, 1H, CHC*H*$_2$OH), 2.13 (dd, *J* = 5.0, 8.5 Hz, 1H, $CHCH_2O$*H*), 2.14-2.06 (m, 1H, C*H*$_2$), and 1.92-1.85 (m, 1H, C*H*$_2$).

[269] Seebach has demonstrated that (*E*)- and (*Z*)-β-lithiostyrene are configurationally stable in the –120 °C to –78 °C temperature regime. See ref 266.

[270] Phenyl substituted vinyllithium and vinylmagnesium reagents are known to be less configurationally stable than their alkyl substituted counterparts. Their stability is, however, intimately related to solvent composition and temperature. See: Seyferth, D. Vinyl Compounds of Metals. In *Progress in Inorganic Chemistry* **1962**, *3*, 129–280. In particular, the reader is directed to pages 160–163 and 170.

[271] [*MJJ-III-251*] **GC / LR EI-MS** [5027016]: t_R 10.69 min; *m*/*z* [rel. int. ($M^{+\bullet}$ region)] 245 (4.6, $M^{+\bullet}$-*d*$_5$), 244 (25.4, $M^{+\bullet}$-*d*$_4$), 243 (100, $M^{+\bullet}$-*d*$_3$), 242 (57.6, $M^{+\bullet}$-*d*$_2$), 241 (67.6, $M^{+\bullet}$-*d*$_1$), and 240 (1.1, $M^{+\bullet}$-*d*$_0$).

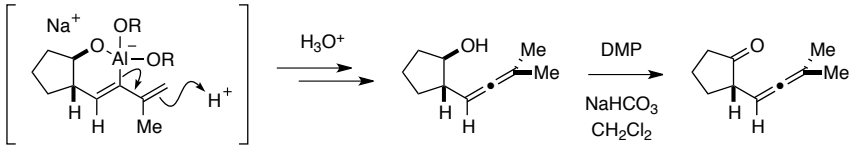
[272] [*MJJ-III-253*] **GC / LR EI-MS** [5027016]: t_R 10.69 min; *m*/*z* [rel. int. ($M^{+\bullet}$ region)] 245 (3.6, $M^{+\bullet}$-*d*$_5$), 244 (16.6, $M^{+\bullet}$-*d*$_4$), 243 (58.9, $M^{+\bullet}$-*d*$_3$), 242 (54.8, $M^{+\bullet}$-*d*$_2$), 241 (100, $M^{+\bullet}$-*d*$_1$), and 240 (1.7, $M^{+\bullet}$-*d*$_0$).

[273] The fact that **3048** was not silylated under these conditions can probably be attributed to the low nucleophilicity of the intermediate tertiary lithium alkoxide.

[276] Evidence was also obtained [*MJJ-VII-127*] for the formation (in 19% yield) of a monosilylated dimeric by-product (**HR ESI-MS**: $C_{38}H_{46}O_4Si$ $[M+Na]^+$ requires 617.3058; found 617.3075). However, the structure of this compound was not fully delineated.

[287] Interestingly, under these hydroalumination conditions a small amount of the allene alcohol **ii** was also produced along with the (*E*)-1,3-diene **4017**. Although **ii** could not be removed chromatographically at this stage, its presence in purified samples of **4017** was evidenced by a characteristic downfield, seven-line pattern in the ^{1}H NMR spectrum {δ 4.97 [septet, *J* = 3.0 Hz, 1H, *H*C=C=C$(CH_3)_2$]}. It

seems plausible that **ii** arose by vinylogous (rather than *ipso*) protonolysis of the sp^2-carbon–aluminum bond within the intermediate sodium alanate **i**.



i ***ii* + 4017** (1 : 11) *inseparable* ***iii* + 4007** (5%) (66%) *MPLC separation*

It was subsequently discovered that the allenyl ketone **iii**, which was co-produced upon DMP- or IBX-mediated oxidation of the **ii**/**4017** mixture, ran slightly faster on SiO_2 and could be separated from the dienyl ketone **4007** by MPLC.

Data for **iii**: [*MJJ-I-210/254*] Diagnostic ^{1}H NMR (500 MHz, $CDCl_3$) resonances: δ 5.11 [septet, J = 2.5 Hz, 1H, *H*C=C=C(CH$_3$)$_2$], 2.76-2.71 [nfom, 1H, C(O)C*H*], 1.71 [d, J = 3.0 Hz, 3H, HC=C=C(C*H*$_3$)$_2$], and 1.69 [d, J = 2.5 Hz, 3H, HC=C=C(C*H*$_3$)$_2$].

GC / LR EI-MS [5025015]: t_R 6.88 min; *m*/*z* (rel. int.) 150 (3, $M^{+\bullet}$), 135 (18, $M^{+\bullet}$–$CH_3^\bullet$), 122 (100), 107 (76), 93 (15), 91 (23), 79 (65), and 77 (30). This material partially decomposed upon entering the GC injection port, as evidenced by the presence of three additional, slightly less intense peaks (t_R 7.89, 8.00, and 8.16 min).

[289] [*MJJ-I-202*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.15 [dddd, J = 1.0, 1.0, 1.0, 1.0 Hz, 1H, (CH$_3$)C=C*H*$_2$], 5.14 [dddd, J = 1.0, 1.0, 1.0, 1.0 Hz, 1H, (CH$_3$)C=C*H*$_2$], 5.01 [dddd, J = 1.5, 1.5, 1.5, 1.5 Hz, 1H, (CH$_3$)C=C*H*$_2$], 5.00 [dddd, J = 1.5, 1.5, 1.5, 1.5 Hz, 1H, (CH$_3$)C=C*H*$_2$], 3.39 [d, J = 2.5 Hz, 1H, CHCH(O)C*H*], 3.23 [d, J = 2.5 Hz, 1H, CHCH(O)C*H*], 3.20 [dd, J = 2.5, 4.0 Hz, 1H, CHC*H*(O)CH], 3.06 [dd, J = 2.5, 4.0 Hz, 1H, CHC*H*(O)CH], 2.47 [ddd, J = 4.0, 8.5, 8.5 Hz, 1H, C*H*CH(O)CH], 2.38-2.27 [m, 3H, overlapping C*H*CH(O)CH and C(O)C*H*$_2$CH$_2$–CH$_2$], 2.24-2.04 [m, 6H, overlapping C(O)C*H*$_2$CH$_2$C*H*$_2$], 1.91-1.73 [m, 4H, overlapping C(O)CH$_2$C*H*$_2$CH$_2$], 1.66 [dd, J = 1.0, 1.0 Hz, 3H, (C*H*$_3$)C=CH$_2$], and 1.64 [dd, J = 1.0, 1.0 Hz, 3H, (C*H*$_3$)C=CH$_2$].

HR ESI-MS: $C_{10}H_{14}O_2$ $[M+Na]^+$ requires 189.0886; found 189.0882.

GC / LR EI-MS [5025015]: t_R 7.60 and 7.66 min; *m*/*z* (rel. int.) 166 (1, $M^{+\bullet}$), 151 (4, $M^{+\bullet}$–$CH_3^\bullet$), 148 (3), 138 (5), 137 (6), 109 (23), 95 (90), 84 (100), 83 (73, $M^{+\bullet}$–$C_5H_7O^\bullet$), 82 (42), 81 (63), 79 (34), 68 (62), 67 (77), and 55 (62). This material partially decomposed upon entering the GC injection port, as evidenced by the

presence of four other, slightly less intense peaks (t_R 7.03, 7.73, 7.81, and 8.61 min).

[293] [*MJJ-I-254*] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.34 [dd, *J* = 3.0, 3.0 Hz, 1H, C(O)C=C*H*C(O)], 6.10 [ddd, *J* = 1.0, 1.0, 1.0 Hz, 1H, $(CH_3)C=CH_2$], 5.92 [ddd, *J* = 1.5, 1.5, 1.5 Hz, 1H, $(CH_3)C=CH_2$], 3.07 [ddd, *J* = 3.0, 7.5, 7.5 Hz, 2H, $C(O)CH_2CH_2CH_2C=CH$], 2.42 [dd, *J* = 8.0, 8.0 Hz, 2H, $C(O)CH_2CH_2CH_2$–C=CH], 2.02 [dddd, *J* = 8.0, 8.0, 8.0, 8.0 Hz, 2H, $C(O)CH_2CH_2CH_2C=CH$], and 1.95 [dd, *J* = 1.5, 1.5 Hz, 3H, $(CH_3)C=CH_2$].
GC / LR EI-MS [5025015]: t_R 8.19 min; *m*/*z* (rel. int.) 164 (1, $M^{+\bullet}$), 136 (93), 121 (3), 95 (11, $M^{+\bullet}$–$C_4H_5O^{\bullet}$), and 69 (100, $M^{+\bullet}$–$C_6H_7O^{\bullet}$).
HR ESI-MS: $C_{10}H_{12}O_2$ $[M+Na]^+$ requires 187.0730; found 187.0716.

[295] The "**a**" and "**b**" numbering scheme (i.e., "**4006a**" and "**4006b**") is used here simply to indicate the order of elution on SiO_2 of the diastereomeric aldol adducts. Although the major product of these Weiler dianion reactions is presumably derived from 1,2-addition *trans* to the dienyl side chain within **4007**, no effort has been made to rigorously establish their relative configurations.

[340] Personal communication with Ms. Susan G. Brown (Hoye group); the full details of these (and related) studies will be published in due course.

[347] In this particular instance, a few of the conformers that were located by the molecular mechanics conformational search for **6006B** (1 of 6) **6006C** (2 of 11) and **6006D** (1 of 11) *did not* converge to a local minimum during the subsequent DFT optimizations, as evidenced by the presence of one low energy, imaginary (i.e., negative) frequency.

[390] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.09 [s, 4H, $CH_2C(O)CH_2$] and 2.88 (s, 2H, C*H*=C*H*).

[391] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.21 (d, *J* = 8.0 Hz, 1H, C*H*O), 7.32 (dddd, *J* = 1.5, 10.5, 12, 16.5 Hz, 1H, CH=CHC*H*=$CH_{trans}H_{cis}$), 6.96 (dddd, *J* = 1.0, 1.0, 11.0, 12.0 Hz, 1H, CH=C*H*CH=$CH_{trans}H_{cis}$), 5.91 (ddddd, *J* = 1.5, 1.5, 1.5, 8, 11.0 Hz, 1H, C*H*=CHCH=$CH_{trans}H_{cis}$), 5.66 (dddd, *J* = 1.0, 1.0, 2.0, 16.5 Hz, 1H, CH=CHCH=C$H_{trans}H_{cis}$), and 5.65 (dddd, *J* = 0.5, 0.5, 1.5, 10.5 Hz, 1H, CH=CHCH=$CH_{trans}H_{cis}$).

[393] Analysis of the crude residue by ^{1}H NMR revealed that (*Z*)-penta-2,4-dienal, which was a minor contaminant present in **2050**, had been quantitatively converted to (*E*)-penta-2,4-dienal under the conditions of the palladium(0)-

catalyzed acetoxylation. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.60 (d, *J* = 7.5 Hz, 1H, C*H*O), 7.11 (dddd, *J* = 0.5, 0.5, 11.0, 15.5 Hz, 1H, CH=C*H*CH=$CH_{trans}H_{cis}$), 6.60 (dddd, *J* = 0.5, 10.0, 11.0, 17.0 Hz, 1H, CH=CHC*H*=$CH_{trans}H_{cis}$), 6.19 (ddddd, *J* = 0.5, 0.5, 0.5, 7.5, 15.0 Hz, 1H, C*H*=CHCH=$CH_{trans}H_{cis}$), 5.76 (dddd, *J* = 1.0, 1.0, 1.0, 17.0 Hz, 1H, CH=CHCH=C$H_{trans}H_{cis}$), and 5.64 (ddddd, *J* = 0.5, 0.5, 0.5, 0.5, 10.0 Hz, 1H, CH=CHCH=$CH_{trans}H_{cis}$).

[396] The following diagnostic ^{1}H NMR resonances were observed for **2071** (500 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 11.5, 17.5 Hz, 1H, C*H*=$CH_{trans}H_{cis}$), 5.41 (d, *J* = 17.5 Hz, 1H, CH=C$H_{trans}H_{cis}$), and 5.40 (d, *J* = 11.5 Hz, 1H, CH=$CH_{trans}H_{cis}$). Since the major product (**2070**) obscured the remaining resonances of **2071**, a complete chemical shift assignment was precluded at this stage.

[398] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.44 [dd, *J* = 7.0, 16.0 Hz, 1H, $(CH_3)_2$CCH=C*H*–$CH(CH_3)_2$], 5.27 [dd, *J* = 1.0, 16.0 Hz, 1H, $(CH_3)_2$CC*H*=CHCH$(CH_3)_2$], 3.28 (d, *J* = 6.0 Hz, 2H, CH_2OH), 2.34-2.22 (m, 1H, CH=CHC*H*$(CH_3)_2$], 0.99 [s, 6H, $(CH_3)_2$CCH=CH], and 0.98 [d, *J* = 7.0 Hz, 6H, CH=CHCH$(CH_3)_2$].
^{13}C NMR (125 MHz, $CDCl_3$): δ 137.2, 133.5, 71.7, 38.2, 31.4, 24.2, and 22.9.

[399] (2*E*,4*Z*)-**2101** displayed the following diagnostic ^{1}H NMR resonances: δ 7.00 (ddddd, *J* = 1.5, 1.5, 1.5, 1.5, 11.5 Hz, 1H, H3), 6.05 (dddd, *J* = 2.0, 2.0, 11.5, 11.5 Hz, 1H, H4), 5.42 (ddd, *J* = 7.5, 7.5, 11.0 Hz, 1H, H5), 2.51 (d, *J* = 1.5 Hz, 3H, H1), and 2.11 (dddd, *J* = 2.0, 7.5, 7.5, 7.5 Hz, 2H, H6).

[400] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.69 (dd, *J* = 10.5, 17.0 Hz, 1H, C*H*=$CH_{trans}H_{cis}$), 5.19 (dd, *J* = 1.5, 11.0 Hz, 1H, CH=$CH_{trans}H_{cis}$), 5.16 (dd, *J* = 1.5, 17.5 Hz, 1H, CH=C$H_{trans}H_{cis}$), 4.81 (ABq, $\Delta\nu_{AB}$ = 48.2 Hz, J_{AB} = 12.5 Hz, 1H, CH_2OCO_2CH_3), 4.53 [dddd, *J* = 4.0, 4.0, 7.0, 7.0 Hz, 1H, C*H*(OTBS)], 3.78 (s, 3H, $CH_2OCO_2CH_3$), 2.85-2.77 [m, 2H, overlapping CH_2CH(OTBS)CH_2], 2.49-2.45 [m, 2H, overlapping CH_2CH(OTBS)CH_2], 0.89 [s, 9H, $(CH_3)_3$CSi$(CH_3)_2$], 0.068 [s, 3H, $(CH_3)_3$CSi(CH_3)$_2$], and 0.066 [s, 3H, $(CH_3)_3$CSi(CH_3)$_2$].

[402] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.62 (dddddd, *J* = 1.5, 1.5, 1.5, 1.5, 1.5, 3.5 Hz, 1H, C=C*H*), 4.20 (ddddddd, *J* = 1.0, 1.0, 1.0, 1.0, 1.0, 1.0, 7.5 Hz, 2H, CH_2OH), 2.38-2.30 (m, 4H, C$H_2CH_2CH_2$), 1.95-1.89 (m, 2H, $CH_2CH_2CH_2$), and 1.37 (ddd, *J* = 1.0, 6.0, 6.0 Hz, 1H, CH_2OH).
TLC: R_f 0.09 (6:1 Hex/EtOAc).
BP: 89–90 °C @ 25 mmHg (lit.[401] 75 °C @ 20 mmHg).

BIBLIOGRAPHY

[1] (a) Takahashi, C.; Numata, A.; Yamada, T.; Minoura, K.; Enomoto, S.; Konishi, K.; Nakai, M.; Matsuda, C.; Nomoto, K. Penostatins, Novel Cytotoxic Metabolites from a *Penicillium* Species Separated from a Green Alga. *Tetrahedron Lett.* **1996**, *37*, 655–658. (b) Iwamoto, C.; Minoura, K.; Hagishita, S.; Nomoto, K.; Numata, A. Penostatins F–I, Novel Cytotoxic Metabolites from a *Penicillium* Species Separated from an *Enteromorpha* Marine Alga. *J. Chem. Soc., Perkin Trans. 1* **1998**, 449–456. (c) Iwamoto, C.; Minoura, K.; Oka, T.; Ohta, T.; Hagishita, S.; Numata, A. Absolute Stereostructures of Novel Cytotoxic Metabolites, Penostatins A–E, from a *Penicillium* Species Separated from an *Enteromorpha* Alga. *Tetrahedron* **1999**, *55*, 14353–14368.

[2] Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Ito, Y.; Hasegawa, T. Communesins, Cytotoxic Metabolites of a Fungus Isolated from a Marine Alga. *Tetrahedron Lett.* **1993**, *34*, 2355–2358.

[3] Numata, A.; Takahashi, C.; Ito, Y.; Minoura, K.; Yamada, T.; Matsuda, C.; Nomoto, K. Penochalasins, a Novel Class of Cytotoxic Cytochalasans from a *Penicillium* Species Separated from a Marine Alga: Structure Determination of Solution Conformation. *J. Chem. Soc., Perkin Trans. 1* **1996**, 239–245.

[4] Iwamoto, C.; Yamada, T.; Ito, Y.; Minoura, K.; Numata, A. Cytotoxic Cytochalasans from a *Penicillium* Species Separated from a Marine Alga. *Tetrahedron* **2001**, *57*, 2997–3004.

[5] (a) Karplus, M. Contact Electron-Spin Coupling of Nuclear Magnetic Moments. *J. Chem. Phys.* **1959**, *30*, 11–15. (b) Abraham, R. J.; Holker, J. S. E. 150. An Investigation by Proton Magnetic Resonance of the Conformation of Ring A in Some 2-Bromo-3-oxo-steroids. *J. Chem. Soc.* **1963**, 806–811.

[6] (a) Kusumi, T.; Ohtani, I.; Inouye, Y.; Kakisawa, H. Absolute Configurations of Cytotoxic Marine Cembranolides; Consideration of Mosher's Method. *Tetrahedron Lett.* **1988**, *29*, 4731–4734. (b) Ohtani, I.; Kusumi, T.; Ishitsuka, M. O.; Kakisawa, H. Absolute Configurations of Marine Diterpenes Possessing a Xenicane Skeleton. An Application of an Advanced Mosher's Method.

Tetrahedron Lett. **1989**, *30*, 3147–3150. (c) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. High-Field FT NMR Application of Mosher's Method. The Absolute Configurations of Marine Terpenoids. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.

[7] (a) Snider, B. B.; Liu, T. Total Synthesis of (±)-Deoxypenostatin A. *J. Org. Chem.* **1999**, *64*, 1088–1089. (b) Snider, B. B.; Liu, T. Total Synthesis of (±)-Deoxypenostatin A. Approaches to the Syntheses of Penostatins A and B. *J. Org. Chem.* **2000**, *65*, 8490–8498.

[8] (a) Corey, E. J.; Kang, J. α-Lithiomethylenetriphenylphosphorane, a Highly Reactive Ylide Equi-valent. *J. Am. Chem. Soc.* **1982**, *104*, 4724–4725. (b) Corey, E. J.; Kang, J.; Kyler, K. Activation of Methylenetriphenylphosphorane by Reaction with *t*-Butyl- or *sec*-Butyllithium. *Tetrahedron Lett.* **1985**, *26*, 555–558.

[9] Qian, C.; Huang, T. Glyoxylate-Ene Reaction Catalyzed by $Ln(OTf)_3$. *Tetrahedron Lett.* **1997**, *38*, 6721–6724.

[10] (a) Larson, E. R.; Danishefsky, S. On the Mechanism of the Lewis Acid Catalyzed Cyclocondensation of Aldehydes with Siloxydienes. *Tetrahedron Lett.* **1982**, *23*, 1975–1978. (b) Danishefsky, S.; Kerwin, J. F.; Kobayashi, S. Lewis Acid Catalyzed Cyclocondensations of Functionalized Dienes with Aldehydes. *J. Am. Chem. Soc.* **1982**, *104*, 358–360. (c) Larson, E. R.; Danishefsky, S. Mechanistic Variations in the Lewis Acid Catalyzed Cyclocondensation of Siloxydienes with Aldehydes. *J. Am. Chem. Soc.* **1982**, *104*, 6458–6460. (d) Danishefsky, S. J.; Larson, E.; Askin, D.; Kato, N. On the Scope, Mechanism, and Stereoselectivity of the Lewis Acid Catalyzed Cyclocondensation of Activated Dienes with Aldehydes: An Application to the Erythronolide Problem. *J. Am. Chem. Soc.* **1985**, *107*, 1246–1255.

[11] Terada, M.; Mikami, K.; Nakai, T. Enantioselective Hetero-Diels–Alder Reaction with Glyoxylate Catalyzed by Chiral Titanium Complex: Asymmetric Synthesis of the Lactone Portion of Mevinolin and Compactin. *Tetrahedron Lett.* **1991**, *32*, 935–938.

[12] Jørgensen, K. A. Catalytic Asymmetric Hetero-Diels–Alder Reactions of Carbonyl Compounds and Imines. *Angew. Chem. Int. Ed.* **2000**, *39*, 3558–3588.

[13] Jurczak, J.; Gołębiowski, A.; Rahm, A. High-Pressure [4+2] Cycloaddition of 1-Methoxy-3-trialkylsilyloxybuta-1,3-dienes to Butyl Glyoxylate. Isolation of Primary Cycloadducts. *Tetrahedron Lett.* **1986**, *27*, 853–856.

[14] (a) Kornblum, N.; Frazier, H. W. A New and Convenient Synthesis of Glyoxals, Glyoxalate Esters, and α-Diketones. *J. Am. Chem. Soc.* **1966**, *88*, 865–866. (b) Emmons, W. D.; Freeman, J. P. The Synthesis of Diketones from Nitratoketones. *J. Am. Chem. Soc.* **1955**, *77*, 4415–4416.

[15] Barriault, L.; Ang, P. J. A.; Lavigne, R. M. A. Rapid Assembly of the Bicyclo[5.3.1]undecenone Core of Penostatin F: A Successive Diels–Alder/Claisen Reaction Strategy with an Efficient Stereochemical Relay. *Org. Lett.* **2004**, *6*, 1317–1319.

[16] Barriault, L.; Thomas, J. D. O.; Clément, R. Highly Stereoselective Hydroxy-Directed Diels–Alder Reaction. *J. Org. Chem.* **2003**, *68*, 2317–2323.

[17] Huckin, S. N.; Weiler, L. Alkylation of Dianions of β-Keto Esters. *J. Am. Chem. Soc.* **1974**, *96*, 1082–1087.

[18] Evans, D. A.; Chapman, K. T.; Carreira, E. M. Directed Reduction of β-Hydroxy Ketones Employing Tetramethylammonium Triacetoxyborohydride. *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.

[19] Vedejs, E.; Daugulis, O. Dual Activation in the Esterification of Hindered Alcohols with Anhydrides using $MgBr_2$ and a Tertiary Amine. *J. Org. Chem.* **1996**, *61*, 5702–5703.

[20] Ward, D. E.; Abaee, M. S. Intramolecular Diels–Alder Reaction by Self-Assembly of the Components on a Lewis Acid Template. *Org. Lett.* **2000**, *2*, 3937–3940.

[21] Fujioka, K.; Yokoe, H.; Yoshida, M.; Shishido, K. Total Synthesis of Penostatin B. *Org. Lett.* **2012**, *14*, 244–247.

[22] (a) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. Relay Ring-Closing Metathesis (RRCM): A Strategy for Directing Metal Movement Throughout Olefin Metathesis Sequences. *J. Am. Chem. Soc.* **2004**, *126*, 10210–10211. (b) Hoye, T. R.; Danielson, M. E.; May, A. E.; Zhao, H. Total Synthesis of (–)-Callipeltoside A. *J. Org. Chem.* **2010**, *75*, 7052–7060.

[23] Nishigaichi, Y.; Hanano, Y.; Takuwa, A. Simultaneous Control of Regio- and Stereochemistries in the Reaction between α-Alkoxyaldehydes and Pentadienyltin. Selective Preparations of the Four Regio- and Diastereomers. *Chem. Lett.* **1998**, 33–34.

[24] Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. Organocobalt Complexes. Part II. Reaction of Acetylenehexacarbonyldicobalt Complexes, $(R^1C_2R^2)Co_2(CO)_6$, with Norbornene and its Derivatives. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977–981.

[25] Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *N*-Oxide Promoted Pauson–Khand Cyclizations at Room Temperature. *Tetrahedron Lett.* **1990**, *31*, 5289–5292.

[26] Tsuda, T.; Hayashi, T.; Satomi, H.; Kawamoto, T.; Saegusa, T. Methylcopper(I)-Catalyzed Selective Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds by Diisobutylaluminum Hydride in the Presence of Hexamethyl-phosphoric Triamide. *J. Org. Chem.* **1986**, *51*, 537–540.

[27] Shiina, I.; Ibuka, R.; Kubota, M. A New Condensation Reaction for the Synthesis of Carboxylic Esters from Nearly Equimolar Amounts of Carboxylic Acids and Alcohols using 2-Methyl-6-nitrobenzoic Anhydride. *Chem. Lett.* **2002**, 286–287.

[28] Cossy, J.; Bauer, D.; Bellosta, V. A Short Synthesis of the C1–C7 Fragment of Methymycin by Ring-Closing Olefin Metathesis. *Tetrahedron Lett.* **1999**, *40*, 4187–4188.

[29] Fürstner, A.; Langemann, K. Total Synthesis of (+)-Ricinelaidic Acid Lactone and of (–)-Gloeosporone Based on Transition-Metal-Catalyzed C–C Bond Formations. *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136.

[30] Ghosh, A. K.; Cappiello, J.; Shin, D. Ring-Closing Metathesis Strategy to Unsaturated γ- and δ-Lactones: Synthesis of Hydroxyethylene Isostere for Protease Inhibitors. *Tetrahedron Lett.* **1998**, *39*, 4651–4654.

[31] Fukuda, K.; Miyashita, M.; Tanino, K. Practical Synthesis of (*E*)- and (*Z*)-2-Silyl-3-penten-1-ols with High Enantiopurity. *Tetrahedron Lett.* **2010**, *51*, 4523–4525.

[32] Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. Tetrapropylammonium Perruthenate, $Pr_4N^+RuO_4^-$, TPAP: A Catalytic Oxidant for Organic Synthesis. *Synthesis* **1994**, 639–666.

[33] Ito, Y.; Hirao, T.; Saegusa, T. Synthesis of α,β-Unsaturated Carbonyl Compounds by Palladium(II)-Catalyzed Dehydrosilylation of Silyl Enol Ethers. *J. Org. Chem.* **1978**, *43*, 1011–1013.

[34] Weinreb, S. M. Heterodienophile Additions to Dienes. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: New York, **1991**; Vol. 5, pp 401–449.

[35] Lubineau, A.; Augé, J.; Grand, E.; Lubin, N. Aqueous Hetero Diels–Alder Reactions: The Carbonyl Case. *Tetrahedron* **1994**, *50*, 10265–10276.

[36] (a) Rideout, D. C.; Breslow, R. Hydrophobic Acceleration of Diels–Alder Reactions. *J. Am. Chem. Soc.* **1980**, *102*, 7816–7817. (b) Grieco, P. A.; Garner, P.; He, Z. "Micellar" Catalysis in the Aqueous Intermolecular Diels–Alder Reaction: Rate Acceleration and Enhanced Selectivity. *Tetrahedron Lett.* **1983**, *24*, 1897–1900. (c) Otto, S.; Engberts, J. B. F. N. Diels–Alder Reactions in Water. *Pure Appl. Chem.* **2000**, *72*, 1365–1372.

[37] (a) Staunton, J.; Weissman, K. J. Polyketide Biosynthesis: A Millennium Review. *Nat. Prod. Rep.* **2001**, *18*, 380–416. (b) Fischbach, M. A.; Walsh, C. T. Assembly-Line Enzymology for Polyketide and Nonribosomal Peptide Antibiotics: Logic, Machinery, and Mechanisms. *Chem. Rev.* **2006**, *106*, 3468–3496. (c) Hertweck, C. The Biosynthetic Logic of Polyketide Diversity. *Angew. Chem. Int. Ed.* **2009**, *48*, 4688–4716.

[38] The activation barrier and enthalpy of reaction for the valence isomerization of (*Z*)-penta-2,4-dienal to 2*H*-pyran have been computed to be 22–25 kcal/mol and ≈ 0 kcal/mol, respectively; see: Rodríguez–Otero, J. Study of the Electrocyclization of (*Z*)-Hexa-1,3,5-triene and Its Heterosubstituted Analogues Based on Ab Initio and DFT Calculations. *J. Org. Chem.* **1999**, *64*, 6842-6848.

[39] Beaudry, C. M.; Malerich, J. P.; Trauner, D. Biosynthetic and Biomimetic Electrocyclizations. *Chem. Rev.* **2005**, *105*, 4757–4778.

[40] Huet, F.; Pellet, M.; Conia, J. M. Preparation of Acetals of Substituted Glyoxylic Esters (Methyl 2,2-Dimethoxylalkanoates). *Synthesis* **1979**, 33–34.

[43] (a) Kraus, G. A.; Jones, C. The Reaction of Ketone Enolates with a δ-Oxo Phosphonate: A Carbanion-Based [4+2] Annulation. *Synlett* **2001**, 793–794. (b) Kraus, G. A.; Choudhury, P. K. Phosphonate Aldehyde Annulation. A One-Pot Synthesis of δ-Hydroxy Cyclopentenoic Esters. *Org. Lett.* **2002**, *4*, 2033–2034. (c) Kraus, G. A.; Choudhury, P. K. Phosphonate Aldehyde Annulation – A One-Pot Synthesis of Hydroxycycloalkenoic Esters–Application to Analogs of Glycinoeclepin A. *Eur. J. Org. Chem.* **2004**, 2193–2197.

[44] Minami, T.; Hirakawa, K.; Koyanagi, S.; Nakamura, S.; Yamaguchi, M. A New Synthesis of α-Methylene Lactones. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2385–2390.

[45] Kirschleger, B.; Queignec, R. Heterogeneous Mediated Alkylation of Ethyl Diethylphosphonoacetate. A "One-Pot" Access to α-Alkylated Acrylic Esters. *Synthesis* **1986**, 926-928.

[46] Wittig, G.; Hesse, A. Directed Aldol Condensations: β-Phenylcinnamaldehyde. *Org. Synth.* **1970**, *50*, 66.

[47] Bialke, A. L.; Izgu, E. C.; Jansma, M. J.; Jeon, J.; May, A. E.; Sizova, E. P.; Hoye, T. R. Gallery I of No-D ^{1}H NMR Snapshots of Carbanionic Species. *Proceedings of the 8th International Symposium on Carbanion Chemistry (ISCC-8)*, Madison, WI, June 6-10, **2007**, P-15.

[48] Hoye, T. R.; Eklov, B. M.; Ryba, T. D.; Voloshin, M.; Yao, L. J. No-D NMR (No-Deuterium Proton NMR) Spectroscopy: A Simple Yet Powerful Method for Analyzing Reaction and Reagent Solutions. *Org. Lett.* **2004**, *6*, 953–956.

[49] Hoye, T. R.; Kabrhel, J. E.; Hoye, R. C. No-D NMR Study of the Pathway for *n*-BuLi "Oxidation" of 1,5-Cyclooctadiene to Dilithium Cyclooctatetraene Dianion [Li_2COT^{2-}]. *Org. Lett.* **2005**, *7*, 275-277.

[50] (a) Wadsworth, Jr., W. S.; Emmons, W. D. The Utility of Phosphonate Carbanions in Olefin Synthesis. *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738. (b) Spino, C.; Crawford, J.; Bishop, J. Sequential Diels–Alder Reactions on a 1,3,7,9-Tetraene: An Efficient and Stereoselective Route to the Perhydrophenanthrene Skeleton. *J. Org. Chem.* **1995**, *60*, 844-851.

[51] Kitamura, M.; Tokunaga, M.; Noyori, R. Asymmetric Hydrogenation of β-Keto Phosphonates: A Practical Way to Fosfomycin. *J. Am. Chem. Soc.* **1995**, *117*, 2931-2932. The phosphonate **2039** was prepared according to the procedure described in footnote 7 of this report.

[52] Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457–2483.

[53] (a) Stille, J. K. The Palladium-Catalyzed Cross-Coupling Reactions of Organotin Reagents with Organic Electrophiles. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. The Stille Reaction. *Org. React.* **1997**, *50*, 1–652.

[54] Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Palladium-Catalyzed Cross-Coupling Reactions in Total Synthesis. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489.

[55] (a) Roush, W. R.; Moriarty, K. J.; Brown, B. B. Stereoselective Synthesis of (*Z*,*E*)-2-Bromo-1,3-dienes via the Palladium(0) Catalyzed Cross Coupling Reactions of 1,1-Dibromoolefins and Vinylboronic Acids. *Tetrahedron Lett.* **1990**, *31*, 6509–6512. (b) Frank, S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. Use of Thallium(I) Ethoxide in Suzuki Cross Coupling Reactions. *Org. Lett.* **2000**, *2*, 2691–2694.

[56] Korach, M.; Nielsen, D. R.; Rideout, W. H. Dihydroxycyclopentene. *Org. Synth.* **1962**, *42*, 50–54.

[57] Deardorff, D. R.; Myles, D. C. Palladium(0)-catalyzed *syn*-1,4-Addition of Carboxylic Acids to Cyclopentadiene Monoepoxide: *cis*-3-Acetoxy-5-hydroxy-cyclopent-1-ene. *Org. Synth.* **1989**, *67*, 114–117.

[58] An adaptation of the reported procedure: Paquette, L. A.; Earle, M. J.; Smith, G. F. (4*R*)-(+)-*tert*-Butyl-dimethylsiloxy-2-cyclopenten-1-one. *Org. Synth.* **1996**, *73*, 36–40.

[59] Slight modification of the reported procedure: Shizuka, M.; Snapper, M. L. Selective Synthesis of *ent*-15-*epi*-F_{2t}-Isoprostane and a Deuterated Derivative. *Synthesis* **2007**, 2397–2403.

[60] (a) Stork, G.; Hudrlik, P. F. Generation, Nuclear Magnetic Resonance Spectra, and Alkylation of Enolates from Trialkylsilyl Enol Ethers. *J. Am. Chem. Soc.* **1968**, *90*, 4464–4465. (b) Brown, M. K.; Hoveyda, A. H. Enantioselective Total Synthesis of Clavirolide C. Applications of Cu-Catalyzed Asymmetric Conjugate Additions and Ru-Catalyzed Ring-Closing Metathesis. *J. Am. Chem. Soc.* **2008**, *130*, 12904–12906.

[61] (a) Ojima, I.; Nihonyanagi, M.; Kogure, T.; Kumagai, M.; Horiuchi, S.; Nakatsugawa, K. Reduction of Carbonyl Compounds via Hydrosilylation. I. Hydrosilylation of Carbonyl Compounds Catalyzed by Tris(triphenylphosphine)-chlororhodium. *J. Organomet. Chem.* **1975**, *94*, 449–461. (b) Corey, E. J.; Su, W. Identification of a Crucial Substructural Unit for Thromboxane A_2 Receptor Binding. *Tetrahedron Lett.* **1990**, *31*, 2677–2680.

[62] Johnson, C. R.; Raheja, R. K. Hydrosilylation of Enones: Platinum Divinyl-tetramethyldisiloxane Complex in the Preparation of Triisopropylsilyl and Triphenylsilyl Enol Ethers. *J. Org. Chem.* **1994**, *59*, 2287–2288.

[63] Mander, L. N.; Sethi, S. P. Regioselective Synthesis of β-Ketoesters from Lithium Enolates and Methyl Cyanoformate. *Tetrahedron Lett.* **1983**, *24*, 5425–5428.

[64] Ohe, T.; Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds with Organic Triflates. *J. Org. Chem.* **1993**, *58*, 2201–2208.

[65] Utimoto, K.; Wakabayashi, Y.; Shishiyama, Y.; Inoue, M.; Nozaki, H. 2-Alkoxy and 2,2-Dialkoxy Nitriles from Acetals and Orthoesters–Exchange of Alkoxy into Cyano Group by Means of Cyanotrimethylsilane. *Tetrahedron Lett.* **1981**, *22*, 4279–4280.

[66] Babler, J. H. An Expeditious Route to Monoprotected α-Keto Aldehydes with Control of Regiochemistry. *Synth. Commun.* **1989**, *19*, 355–358.

[67] (a) Seyferth, D.; Marmor, R. S.; Hilbert, P. Some Reactions of Dimethylphosphono-Substituted Diazoalkanes. $(MeO)_2P(O)CR$ Transfer to Olefins and 1,3-Dipolar Additions of $(MeO)_2P(O)C(N_2)R^1$. *J. Org. Chem.* **1971**, *36*, 1379–1386. (b) Gilbert, J. C.; Weerasooriya, U. Diazoethenes: Their Attempted Synthesis from Aldehydes and Aromatic Ketones by Way of the Horner–Emmons Modification of the Wittig Reaction. A Facile Synthesis of Alkynes. *J. Org. Chem.* **1982**, *47*, 1837–1845.

[68] Brown, D. G.; Velthuisen, E. J.; Commerford, J. R.; Brisbois, R. G.; Hoye, T. R. A Convenient Synthesis of Dimethyl (Diazomethyl)phosphonate (Seyferth/Gilbert Reagent). *J. Org. Chem.* **1996**, *61*, 2540–2541.

[69] Zhang, H. X.; Guibé, F.; Balavoine, G. Palladium- and Molybdenum-Catalyzed Hydrostannation of Alkynes. A Novel Access to Regio- and Stereodefined Vinylstannanes. *J. Org. Chem.* **1990**, *55*, 1857–1867.

[72] Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. Transmetalation Reactions of Higher Order Cyanocuprates: Direct Formation of Trialkyltin Cuprates from Tin Hydrides which Bypasses Organolithium Intermediates. *Tetrahedron Lett.* **1989**, *30*, 2065–2068.

[73] The regio- and stereoselectivity of $(Bu_3Sn)(n\text{-Bu})Cu(CN)Li_2$-mediated stannylcupration of enynes has been studied. See: Le Ménez, P.; Berque, I.; Fargeas, V.; Ardisson, J.; Pancrazi, A. New Synthetic Approach to the Western Part C_{10}–C_{15} of (±)-Des-Epoxy-Rosaramycin. *Synlett* **1994**, 998–1000.

[74] Allred, G. D.; Liebeskind, L. S. Copper-Mediated Cross-Coupling of Organostannanes with Organic Iodides at or Below Room Temperature. *J. Am. Chem. Soc.* **1996**, *118*, 2748–2749.

[75] Fürstner, A.; Funel, J. –A.; Tremblay, M.; Bouchez, L. C.; Nevado, C.; Waser, M.; Ackerstaff, J.; Stimson, C. C. A Versatile Protocol for Stille–Migita Cross Coupling Reactions. *Chem. Commun.* **2008**, 2873–2875.

[76] Gebauer, O.; Brückner, R. β-Alkoxycarbonyl Enol Triflates as Precursors to Stereopure 3-Ene-1,5-diyne Building Blocks for the Chromophores of Neocarzinostatin, C-1027, Kedarcidin, Maduropeptin, and N1999A2. *Synthesis* **2000**, 588–602.

[77] Karabelas, K.; Hallberg, A. Synthesis of 1-Trimethylsilyl 1,3-Dienes by the Palladium-Catalyzed Reaction of Trimethylvinylsilane with Vinyl Iodides/Silver Nitrate or Vinyl Triflates. *J. Org. Chem.* **1988**, *53*, 4909–4914.

[78] Shen, W.; Wang, L. The Stille Reaction of 1,1-Dibromo-1-alkenes: Preparation of Trisubstituted Alkenes and Internal Alkynes. *J. Org. Chem.* **1999**, *64*, 8873–8879.

[80] Boden, C. D. J.; Pattenden, G.; Ye, T. Palladium-Catalyzed Hydrostannylations of 1-Bromoalkynes. A Practical Synthesis of (*E*)-1-Stannylalk-1-enes. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2417–2419.

[81] Tucker, C. E.; Davidson, J.; Knochel, P. Mild and Stereoselective Hydroborations of Functionalized Alkynes and Alkenes Using Pinacolborane. *J. Org. Chem.* **1992**, *57*, 3482–3485.

[83] Brown, H. C.; Gupta, S. K. Hydroboration. XXXIX. 1,3,2-Benzodioxaborole (Catecholborane) as a New Hydroboration Reagent for Alkenes and Alkynes. A General Synthesis of Alkane- and Alkeneboronic Acids and Esters via Hydroboration. Directive Effects in the Hydroboration of Alkenes and Alkynes with Catecholborane. *J. Am. Chem. Soc.* **1975**, *97*, 5249–5255.

[84] Kalinin, A. V.; Scherer, S.; Snieckus, V. Di(isopropylprenyl)borane: A New Hydroboration Reagent for the Synthesis of Alkyl and Alkenyl Boronic Acids. *Angew. Chem. Int. Ed.* **2003**, *42*, 3399–3404.

[85] Uenishi, J.; Beau, J. –M.; Armstrong, R. W.; Kishi, Y. Dramatic Rate Enhancement of Suzuki Diene Synthesis: Its Application to Palytoxin Synthesis. *J. Am. Chem. Soc.* **1987**, *109*, 4756–4758.

[86] Markó, I. E.; Murphy, F.; Dolan, S. Efficient Synthesis of the Left-Hand Subunit of Milbemycin β3 Using a Suzuki Coupling Reaction. *Tetrahedron Lett.* **1996**, *37*, 2507–2510.

[87] Evans, D. A.; Starr, J. T. A Cycloaddition Cascade Approach to the Total Synthesis of (–)-FR182877. *J. Am. Chem. Soc.* **2003**, *125*, 13531–13540.

[88] Corey, E. J.; Fuchs, P. L. A Synthetic Method for Formyl → Ethynyl Conversion (RCHO → RC≡CH or RC≡CR′). *Tetrahedron Lett.* **1972**, *13*, 3769–3772.

[89] Gray, M.; Andrews, I. P.; Hook, D. F.; Kitteringham, J.; Voyle, M. Practical Methylation of Aryl Halides by Suzuki–Miyaura Coupling. *Tetrahedron Lett.* **2000**, *41*, 6237–6240.

[90] Zeng, X.; Hu, Q.; Qian, M.; Negishi, E. Clean Inversion of Configuration in the Pd-Catalyzed Cross-Coupling of 2-Bromo-1,3-dienes. *J. Am. Chem. Soc.* **2003**, *125*, 13636–13637.

[91] Dai, C.; Fu, G. C. The First General Method for Palladium-Catalyzed Negishi Cross-Coupling of Aryl and Vinyl Chlorides: Use of Commercially Available $Pd(P(t\text{-}Bu)_3)_2$ as a Catalyst. *J. Am. Chem. Soc.* **2001**, *123*, 2719–2724.

[92] Zeng, X.; Qian, M.; Hu, Q.; Negishi, E. Highly Stereoselective Synthesis of (1*E*)-2-Methyl-1,3-dienes by Palladium-Catalyzed *trans*-Selective Cross-Coupling of 1,1-Dibromo-1-alkenes with Alkenylzinc Reagents. *Angew. Chem. Int. Ed.* **2004**, *43*, 2259–2263.

[93] O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. Easily Prepared Air- and Moisture-Stable Pd–NHC (NHC = *N*-Heterocyclic Carbene) Complexes: A Reliable, User-Friendly, Highly Active Palladium Precatalyst for the Suzuki–Miyaura Reaction. *Chem. Eur. J.* **2006**, *12*, 4743–4748.

[95] (a) Ogasawara, M.; Okada, A.; Watanabe, S.; Fan, L.; Uetake, K.; Nakajima, K.; Takahashi, T. Synthesis, Structure, and Reactivity of (1,2,3-η^3-Butadien-3-yl)palladium Complexes. *Organometallics* **2007**, *26*, 5025–5029. (b) Ogasawara, M.; Fan, L.; Ge, Y.; Takahashi, T. Palladium-Catalyzed Preparation of Vinylallenes from 2-Bromo-1,3,5-trienes via an Alkylidene-π-allylpalladium-Mediated Formal S_N2'' Pathway. *Org. Lett.* **2006**, *8*, 5409–5412.

[96] E.g.: Tsuji, J. Pd(0)-Catalyzed Reactions of Allylic Compounds via π-Allylpalladium Complexes. In *Palladium Reagents and Catalysts: New Perspectives for the 21ST Century*. 2ND ed; John Wiley & Sons: Hoboken, NJ, **2004**; pp 431–517.

[97] Granberg, K. L.; Bäckvall, J. –E. Isomerization of (π-Allyl)palladium Complexes via Nucleophilic Displacement by Palladium(0). A Common Mechanism in

Palladium(0)-Catalyzed Allylic Substitution. *J. Am. Chem. Soc.* **1992**, *114*, 6858–6863.

[98] (a) Takahashi, T.; Jinbo, Y.; Kitamura, K.; Tsuji, J. Chirality Transfer from C–O to C–C in the Palladium Catalyzed ScN′ Reaction of (*E*)- and (*Z*)-Allylic Carbonates with Carbonucleophile. *Tetrahedron Lett.* **1984**, *25*, 5921–5924. (b) Mackenzie, P. B.; Whelan, J.; Bosnich, B. Asymmetric Synthesis. Mechanism of Asymmetric Catalytic Allylation. *J. Am. Chem. Soc.* **1985**, *107*, 2046–2054.

[99] Stamos, D. P.; Taylor, A. G.; Kishi, Y. A Mild Preparation of Vinyliodides from Vinylsilanes. *Tetrahedron Lett.* **1996**, *37*, 8647–8650.

[100] Brown, H. C.; Hamaoka, T.; Ravindran, N. Reaction of Alkenylboronic Acids with Iodine Under the Influence of Base. Simple Procedure for the Stereospecific Conversion of Terminal Alkynes into *trans*-1-Alkenyl Iodides via Hydroboration. *J. Am. Chem. Soc.* **1973**, *95*, 5786–5788.

[101] For a description of the "H-to-T" and "T-to-H" nomenclature as it applies to trisubstituted olefin synthesis, see: (a) Negishi, E.; Liou, S.; Xu, C.; Huo, S. A Novel, Highly Selective, and General Methodology for the Synthesis of 1,5-Diene-Containing Oligoisoprenoids of All Possible Geometrical Combinations Exemplified by an Iterative and Convergent Synthesis of Coenzyme Q_{10}. *Org. Lett.* **2002**, *4*, 261–264. (b) Negishi, E.; Wang, G.; Rao, H.; Xu, Z. Alkyne Elementometalation–Pd-Catalyzed Cross-Coupling. Toward Synthesis of All Conceivable Types of Acyclic Alkenes in High Yields, Efficiently, Selectively, Economically, and Safely: "Green" Way. *J. Org. Chem.* **2010**, *75*, 3151–3182.

[102] Trost, B. M.; Ball, Z. T. Addition of Metalloid Hydrides to Alkynes: Hydrometallation with Boron, Silicon, and Tin. *Synthesis* **2005**, 853–887.

[103] Hyla–Kryspin, I.; Gleiter, R.; Kureger, C.; Zwettler, R.; Erker, G. Formation of β-CH Agostic Alkenyl-zirconocene Complexes. *Organomettalics* **1990**, *9*, 517–523.

[104] Van Horn, D. E.; Negishi, E. Controlled Carbometalation. Reaction of Acetylenes with Organoalane–Zirconocene Dichloride Complexes as a Route to Stereo- and Regio-Defined Trisubstituted Olefins. *J. Am. Chem. Soc.* **1978**, *100*, 2252–2254.

[105] Woerly, E. M.; Cherney, A. H.; Davis, E. K.; Burke, M. D. Stereoretentive Suzuki-Miyaura Coupling of Haloallenes Enables Fully Stereocontrolled Access to (–)-Peridinin. *J. Am. Chem. Soc.* **2010**, *132*, 6941–6943.

[106] Zhang, H. X.; Guibé, F.; Balavoine, G. Palladium- and Molybdenum-Catalyzed Hydrostannation of Alkynes. A Novel Access to Regio- and Stereodefined Vinylstannanes. *J. Org. Chem.* **1990**, *55*, 1857–1867.

[109] Grandjean, D.; Pale, P.; Chuche, J. An Improved Procedure for Aldehyde-to-Alkyne Homologation via 1,1-Dibromoalkenes; Synthesis of 1-Bromoalkynes. *Tetrahedron Lett.* **1994**, *35*, 3529–3530.

[112] For key examples, see: (a) Zweifel, G.; Arzoumanian, H. α-Halovinylboranes. Their Preparation and Conversion into *cis*-Vinylhalides, *trans*-Olefins, Ketones, and *trans*-Vinylboranes. *J. Am. Chem. Soc.* **1967**, *89*, 5086–5088. (b) Negishi, E.; Williams, R. M.; Lew, G.; Yoshida, T. A Stereoselective Synthesis of *cis*-Alkenylboranes. *J. Organomet. Chem.* **1975**, *92*, C4–C6. (c) Campbell, J. B.; Molander, G. A. An Improved Synthesis of *cis*-Alkenylboranes. *J. Organomet. Chem.* **1978**, *156*, 71–79. (d) Brown, H. C.; Imai, T. Organoboranes. 37. Synthesis and Properties of (*Z*)-1-Alkenylboronic Esters. *Organometallics* **1984**, *3*, 1392–1395 and references therein. (e) Kamabuchi, A.; Moriya, T.; Miyaura, N.; Suzuki, A. Synthesis of Functionalized 1-Alkenylboronates via Hydroboration-Dealkylation of Alkynes with Diisopinocampheylborane. *Synth. Commun.* **1993**, *23*, 2851–2859.

[113] Xu, S.; Lee, C. –T.; Rao, H.; Negishi, E. Highly (≥98%) Stereo- and Regioselective Trisubstituted Alkene Synthesis of Wide Applicability *via* 1-Halo-1-alkyne Hydroboration-Tandem Negishi-Suzuki Coupling or Organoborate Migratory Insertion. *Adv. Synth. Catal.* **2011**, *353*, 2981–2987. It should be noted that the studies described in this section were well underway at the time of this publication's appearance.

[114] Suzuki and co-workers were the first to demonstrate the feasibility of this approach: Moriya, T.; Miyaura, N.; Suzuki, A. Stereoselective Synthesis of (*Z*)-(1-Organo-1-alkenyl)boronic Esters by the Palladium-Catalyzed Cross-Coupling Reaction of (*Z*)-(1-Iodo-1-alkenyl)boronic esters with Organozinc Reagents. *Chem. Lett.* **1993**, 1429–1432.

[115] Only two examples of the hydroboration of 1-haloenynes can be located: (a) Jeon, S. –J.; Fisher, E. L.; Carroll, P. J.; Walsh, P. J. Direct Stereospecific Generation of (*Z*)-Disubstituted Allylic Alcohols. *J. Am. Chem. Soc.* **2006**, *128*, 9618–9619. (b) Hoshi, M.; Kawamura, N.; Shirakawa, K. Construction of Terminal Conjugated Enynes: Cu-Mediated Cross-Coupling Reaction of Alkenyldialkylborane with (Trimethylsilyl)ethynyl Bromide. *Synthesis* **2006**, 1961–1970. In

neither of these reports was the isolation of the intermediate (*Z*)-(1-halo-1-alkenyl)borane attempted.

[116] Michel, P.; Rassat, A. A One-Pot Procedure for the Synthesis of Iodoalkynes from Aldehydes. *Tetrahedron Lett.* **1999**, *40*, 8579–8581.

[117] Inoue, Y.; Fukunaga, T.; Hakushi, T. Direct Photolysis of 1-Halo-1-Hexynes. Lack of Ionic Behavior. *J. Org. Chem.* **1983**, *48*, 1732–1737.

[118] See, e.g.: Haugan, J. A.; Englert, G.; Glinz, E.; Liaaen-Jensen, S. Algal Carotenoids. 48. Structural Assignments of Geometrical Isomers of Fucoxanthin. *Acta Chem. Scand.* **1992**, *46*, 389–395.

[119] (a) Vaultier, M.; Truchet, F.; Carboni, B.; Hoffmann, R. W.; Denne, I. Diels–Alder Reactions of 1,3-Dienylboronates as a New Route to Functionalized Carbocycles. *Tetrahedron Lett.* **1987**, *28*, 4169–4172. (b) Hoffmann, R. W.; Dresely, S. Preparation of 3-Substituted (*E*)-1-Alkenylboronic Esters. *Synthesis* **1988**, 103–106.

[121] Knapp, D. M.; Gillis, E. P.; Burke, M. D. A General Solution for Unstable Boronic Acids: Slow-Release Cross-Coupling from Air-Stable MIDA Boronates. *J. Am. Chem. Soc.* **2009**, *131*, 6961–6963.

[122] Kranenburg, M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. The Effect of the Bite Angle of Diphosphane Ligands on Activity and Selectivity in Palladium-Catalyzed Cross-Coupling. *Eur. J. Inorg. Chem.* **1998**, 155–157.

[123] (a) Herrmann, W. A. *N*-Heterocyclic Carbenes: A New Concept in Organometallic Catalysis. *Angew. Chem. Int. Ed.* **2002**, *41*, 1290–1309. (b) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. Palladium Complexes of *N*-Heterocyclic Carbenes as Catalysts for Cross-Coupling Reactions–A Synthetic Chemist's Perspective. *Angew. Chem. Int. Ed.* **2007**, *46*, 2768–2813.

[124] Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Valente, C. A User-Friendly, All-Purpose Pd–NHC (NHC = *N*-Heterocyclic Carbene) Precatalyst for the Negishi Reaction: A Step Towards a Universal Cross-Coupling Catalyst. *Chem. Eur. J.* **2006**, *12*, 4749–4755.

[125] Gillis, E. P.; Burke, M. D. A Simple and Modular Strategy for Small Molecule Synthesis: Iterative Suzuki–Miyaura Coupling of B-Protected Haloboronic Acid Building Blocks. *J. Am. Chem. Soc.* **2007**, *129*, 6716–6717.

[126] Coutts, S. J.; Adams, J.; Krolikowski, D.; Snow, R. J. Two Efficient Methods for the Cleavage of Pinanediol Boronate Esters Yielding the Free Boronic Acids. *Tetrahedron Lett.* **1994**, *35*, 5109–5112.

[127] (a) Sheffy, F. K.; Stille, J. K. Palladium-Catalyzed Cross-Coupling of Allyl Halides with Organotins. *J. Am. Chem. Soc.* **1983**, *105*, 7173–7175. (b) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. Palladium-Catalyzed Cross-Coupling of Allyl Halides with Organotin Reagents: A Method of Joining Highly Functionalized Partners Regioselectively and Stereospecifically. *J. Am. Chem. Soc.* **1984**, *106*, 4833–4840. (c) Del Valle, L.; Stille, J. K.; Hegedus, L. S. Palladium-Catalyzed Coupling of Allylic Acetates with Aryl- and Vinylstannanes. *J. Org. Chem.* **1990**, *55*, 3019–3023.

[128] (a) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. An Enantioselective Synthesis of FR182877 Provides a Chemical Rationalization of Its Structure and Affords Multigram Quantities of Its Direct Precursor. *J. Am. Chem. Soc.* **2003**, *125*, 5393–5407. (b) Shipe, W. D.; Sorensen, E. J. Convergent, Enantioselective Syntheses of Guanacastepenes A and E Featuring a Selective Cyclobutane Fragmentation. *J. Am. Chem. Soc.* **2006**, *128*, 7025–7035.

[129] (a) Castaño, A. M.; Echavarren, A. M. Palladium-Catalyzed Cross-Coupling Reaction of Allyl Carbonates with Organostannanes. *Tetrahedron Lett.* **1996**, *37*, 6587–6590. (b) The studies carried out by Castaño and Echavarren regarding the qualitative relationship between reaction rate and the nucleofugality of the allylic electrophile suggested that oxidative insertion was the rate-limiting step.

[130] Åkermark, B.; Vitagliano, A. Reactivity and Syn–Anti Isomerization of (η^3-Geranyl)- and (η^3-Neryl)-palladium Complexes. Evidence for Electronic Control of the Regiochemistry of Nucleophilic Addition. *Organometallics* **1985**, *4*, 1275–1283.

[131] Renaud, P.; Lacôte, E.; Quaranta, L. Alternative and Mild Procedures for the Removal of Organotin Residues from Reaction Mixtures. *Tetrahedron Lett.* **1998**, *39*, 2123–2126.

[132] Moss, R. D.; Paige, J. Improved Preparation of 2,3-Dihydro-*p*-dioxin (Dioxene). *J. Chem. Eng. Data* **1967**, *12*, 452–454.

[133] Blanchot, V.; Fétizon, M.; Hanna, I. 2,3-Dihydro-1,4-dioxin in Organic Chemistry; Part II.1 Palladium-catalyzed Acylations of 5-Tributylstannyl-2,3-

dihydro-1,4-dioxin: Preparation of 5-Acyl-2,3-dihydro-1,4-dioxins. *Synthesis* **1990**, 755–756.

[134] Soderquist, J. A.; Ji-Ho Hsu, G. Pure, Unsolvated (α-Methoxyvinyl)lithium and Related Acyl Anion Equivalents via the Transmetalation of Organotin Compounds. *Organometallics* **1982**, *1*, 830–833.

[136] (a) Echavarren, A. M.; Tueting, D. R.; Stille, J. K. Palladium-Catalyzed Coupling of Vinyl Epoxides with Organostannanes. *J. Am. Chem. Soc.* **1988**, *110*, 4039–4041. (b) Tueting, D. R.; Echavarren, A. M.; Stille, J. K. Palladium Catalyzed Coupling of Organostannanes with Vinyl Epoxides. *Tetrahedron* **1989**, *45*, 979–992. (c) Zhang, H. –C.; Daves, Jr., G. D. Water Facilitation of Palladium-Mediated Coupling Reactions. *Organometallics* **1993**, *12*, 1499–1500.

[137] Tsuji, Y.; Yamada, N.; Tanaka, S. Cyanation of Allylic Carbonates and Acetates Using Trimethylsilyl Cyanide Catalyzed by Palladium Complex. *J. Org. Chem.* **1993**, *58*, 16–17.

[138] (a) Tsuji, J.; Sato, K.; Okumoto, H. Palladium-Catalyzed Decarboxylation-Carbonylation of Allylic Carbonates to Give β,γ-Unsaturated Esters Under Mild Conditions. *Tetrahedron Lett.* **1982**, *23*, 5189–5190. (b) Tsuji, J.; Sato, K.; Okumoto, H. Palladium-Catalyzed Decarboxylation-Carbonylation of Allylic Carbonates to Form β,γ-Unsaturated Esters. *J. Org. Chem.* **1984**, *49*, 1341–1344.

[140] Murahashi, S. –I.; Imada, Y.; Taniguchi, Y.; Higashiura, S. Palladium(0)-Catalyzed Carbonylation of Allyl Phosphates and Allyl Acetates. Selective Synthesis of β,γ-Unsaturated Esters. *Tetrahedron Lett.* **1988**, *29*, 4945–4948.

[143] For an early review, see: Fétizon, M.; Goulaouic, P.; Hanna, I. The Chemistry of 1,4-Dioxene (2,3-Dihydro-1,4-dioxin). Part VIII. *Heterocycles* **1989**, *28*, 521–527.

[144] (a) Baylon, C.; Hanna, I. 1,4-Dioxene in Organic Synthesis: Generation and Reactivity of Epoxydioxenes. *Tetrahedron Lett.* **1995**, *36*, 6475–6478. (b) Hanna, I.; Prangé, T.; Zeghdoudi, R. Synthesis of a Highly Functionalized AB Taxane Ring System Using 1,4-Dioxene. *Tetrahedron Lett.* **1996**, *37*, 7013–7016.

[145] Adam, W.; Hadjiarapoglou, L.; Wang, X. Dimethyldioxirane Epoxidation of Alkenes Bearing Two Electron Donating Substituents. *Tetrahedron Lett.* **1991**, *32*, 1295–1298.

[147] Adam, W.; Hadjiarapoglou, L.; Jäger, V.; Klicić, J.; Seidel, B.; Wang, X. Epoxidation of Enol Silyl Ethers, Phosphates, Esters, and Lactones by Dimethyldioxirane. *Chem. Ber.* **1991**, *124*, 2361–2368.

[149] Gibert, M.; Ferrer, M.; Sánchez-Baeza, F.; Messeguer, A. Availability and Reactivity of Concentrated Dimethyldioxirane Solutions in Solvents Other Than Acetone. *Tetrahedron* **1997**, *53*, 8643–8650.

[150] Yamamoto and co-workers originally introduced MABR as a catalyst for the efficient rearrangement of various epoxides. See: (a) Maruoka, K.; Ooi, T.; Yamamoto, H. Organoaluminum-Promoted Rearrangement of Epoxy Silyl Ethers to β-Siloxy Aldehydes. *J. Am. Chem. Soc.* **1989**, *111*, 6431–6432. (b) Maruoka, K.; Ooi, T.; Nagahara, S.; Yamamoto, H. Organoaluminum-Catalyzed Rearrangement of Epoxides. A Facile Route to the Synthesis of Optically Active β-Siloxy Aldehydes. *Tetrahedron* **1991**, *47*, 6983–6998. (c) Maruoka, K.; Bureau, R.; Ooi, T.; Yamamoto, H. Selective Rearrangement of Trisubstituted Epoxides to Aldehydes or Ketones. *Synlett* **1991**, 491–492.

[152] Lehmann, J.; Lloyd–Jones, G. C. Regiocontrol and Stereoselectivity in Tungsten-Bipyridine Catalysed Allylic Alkylation. *Tetrahedron* **1995**, *51*, 8863–8874.

[155] (a) Pummerer, R. Über Phenyl-sulfoxyessigsäure. *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 2282–2291. (b) Pummerer, R.; Über Phenylsulfoxyessigsäure (II). *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1401–1412.

[156] (a) Padwa, A.; Gunn, Jr., D. E.; Osterhout, M. H. Application of the Pummerer Reaction Toward the Synthesis of Complex Carbocycles and Heterocycles. *Synthesis* **1997**, 1353–1377. (b) Bur, S. K.; Padwa, A. The Pummerer Reaction: Methodology and Strategy for the Synthesis of Heterocyclic Compounds. *Chem. Rev.* **2004**, *104*, 2401–2432.

[157] (a) Tamura, Y.; Yakura, T.; Shirouchi, Y.; Haruta, J. Pummerer-Type Reaction of α-Acylsulfides Using Phenyl Iodosyl Bis(trifluoroacetate). *Chem. Pharm. Bull.* **1986**, *34*, 1061–1066. (b) Wang, H. –M; Lin, M. –C.; Chen, L. –C. Synthesis of 4*H*-Pyrrolo[2,1-*c*][1,4]benzothiazines and *N*-Methyl-1,3,4,5-tetrahydro-2*H*-3-Benzazepin-2-ones. *Heterocycles* **1994**, *38*, 1519–1526. (c) Lin, M. –L.; Wang, H. –M.; Kang, I. –J.; Chen, L. –C. Ene Reaction with Pummerer-Type Reaction Intermediate of α-(Methylthio)-*N*-methoxyl-*N*-methyl Acetamide: A New Synthesis of *N*-Methoxy-*N*-methyl-(*E*,*E*)-2,4-dienamides. *J. Chin. Chem. Soc.* **2000**, *47*, 1121–1124.

[158] Takeda, T.; Taguchi, H.; Fujiwara, T. Titanocene(II)-Promoted Desulfurizative Acylation of Thioacetals with Alkanenitriles. *Tetrahedron Lett.* **2000**, *41*, 65–68.

[159] VanRheenen, V.; Kelly, R. C.; Cha, D. Y. An Improved Catalytic OsO_4 Oxidation of Olefins to *cis*-1,2-Glycols Using Tertiary Amine Oxides as the Oxidant. *Tetrahedron Lett.* **1976**, *17*, 1973–1976.

[160] Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. –S.; Kwong, H. –L.; Morikawa, K.; Wang, Z. –M.; Xu, D.; Zhang, X. –L. The Osmium-Catalyzed Asymmetric Dihydroxylation: A New Ligand Class and a Process Improvement. *J. Org. Chem.* **1992**, *57*, 2768–2771.

[161] A similar dilemma has been encountered in the literature: Starr, J. T.; Koch, G.; Carreira, E. M. Enantioselective Synthesis of the Cyclopentyl Core of the Axinellamines. *J. Am. Chem. Soc.* **2000**, *122*, 8793–8794.

[162] (a) Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. Dibutyltin Oxide Catalyzed Selective Sulfonylation of α-Chelatable Primary Alcohols. *Org. Lett.* **1999**, *1*, 447–450. (b) Martinelli, M. J.; Vaidyanathan, R.; Pawlak, J. M.; Nayyar, N. K.; Dhokte, U. P.; Doecke, C. W.; Zollars, L. M. H.; Moher, E. D.; Khau, V. V.; Košmrlj, B. Catalytic Regioselective Sulfonylation of α-Chelatable Alcohols: Scope and Mechanistic Insight. *J. Am. Chem. Soc.* **2002**, *124*, 3578–3585.

[163] Dess, D. B.; Martin, J. C. Readily Accessible 12–I–5 Oxidant for the Conversion of Primary and Secondary Alcohols to Aldehydes and Ketones. *J. Org. Chem.* **1983**, *48*, 4155–4156.

[165] A related process has been proposed by Paquette; see: Morwick, T. M.; Paquette, L. A. Combined Addition of Alkenyl and Allenic Anions to Squarate Esters. Direct Competition between Six-Ring and Eight-Ring Electrocyclization of 1,2,4,6,8-Cumulenic Pentaenes. *J. Org. Chem.* **1997**, *62*, 627–635.

[166] Dramatic rate accelerations are observed in 6π electrocyclizations when electron-donating and electron-accepting groups are positioned at C3 and C2, respectively, of the 1,3,5-hexatriene subunit. The production of a more stable enolate product was proposed to rationalize the outcome. See: Magomedov, N. A.; Ruggiero, P. L.; Tang, Y. Remarkably Facile Hexatriene Electrocyclizations as a Route to Functionalized Cyclohexenones via Ring Expansion of Cyclobutenones. *J. Am. Chem. Soc.* **2004**, *126*, 1624–1625.

[167] Carre, M. C.; Caubere, P. A Very Efficient Preparation of 1,2-Diketones. *Tetrahedron Lett.* **1985**, *26*, 3103–3106.

[168] Linde II, R. G.; Jeroncic, L. O.; Danishefsky, S. J. Straightforward Synthesis of 1,2,3-Tricarbonyl Systems. *J. Org. Chem.* **1991**, *56*, 2534–2538.

[169] Koser, G. F.; Wettach, R. H. Hypervalent Organoiodine. Reactions of Silver Aryl-sulfonates with Iodosobenzene Dichloride. *J. Org. Chem.* **1977**, *42*, 1476–1478.

[170] Spyroudis, S.; Varvoglis, A. Dehydrogenations with Phenyliodine Ditrifluoro-acetate. *Synthesis* **1975**, 445–447.

[171] Xia, M.; Chen, X. –C. Hypervalent Iodine in Synthesis XXIII. Oxidation with [Hydroxy(tosyloxy)iodo]benzene: Selective Oxidation of Sulfides to Sulfoxides. *Synth. Commun.* **1997**, *27*, 1315–1320.

[172] Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons, Inc.: New York, **1999**, pp 33–35 and 329–347.

[174] Smith, M. B.; March, J. Addition to Carbon–Carbon Multiple Bonds. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed.; John Wiley & Sons, Inc.: Hoboken, New Jersey, **2007**, pp 999–1250.

[176] Darwish, A.; Lang, A.; Kim, T.; Chong, J. M. The Use of Phosphine Ligands to Control the Regiochemistry of Pd-Catalyzed Hydrostannations of 1-Alkynes: Synthesis of (*E*)-1-Tributylstannyl-1-alkenes. *Org. Lett.* **2008**, *10*, 861–864.

[178] Gopalarathnam, A.; Nelson, S. G. Amphidinolide B: Asymmetric Synthesis of a C_7–C_{20} Synthon. *Org. Lett.* **2006**, *8*, 7–10.

[179] Srogl, J.; Allred, G. D.; Liebeskind, L. S. Sulfonium Salts. Participants *par Excellence* in Metal-Catalyzed Carbon–Carbon Bond-Forming Reactions. *J. Am. Chem. Soc.* **1997**, *119*, 12376–12377.

[180] Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. Palladium-Catalyzed Coupling of Arylstannanes with Organic Sulfonates: A Comprehensive Study. *J. Org. Chem.* **1993**, *58*, 5434–5444.

[182] (a) Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M. A New and Selective Method of Oxidation. *J. Am. Chem. Soc.* **1957**, *79*, 6562. (b) Kornblum, N.; Jones, W. J.; Anderson, G. J. A New and Selective Method of Oxidation. The Conversion of Alkyl Halides and Alkyl Tosylates to Aldehydes. *J. Am. Chem. Soc.* **1959**, *81*, 4113–4114.

[183] (a) Ganem, B.; Boeckman, Jr., R. K. Silver-Assisted Dimethylsulfoxide Oxidations; An Improved Synthesis of Aldehydes and Ketones. *Tetrahedron Lett.* **1974**, *15*, 917–920. (b) Godfrey, A. G.; Ganem, B. Ready Oxidation of Halides to Aldehydes Using Trimethylamine *N*-Oxide in Dimethylsulfoxide. *Tetrahedron Lett.* **1990**, *31*, 4825–4826. (c) Stowell, J. C. A Short Synthesis of the Sex Pheromone of the Pink Bollworm Moth. *J. Org. Chem.* **1970**, *35*, 244–245.

[184] Soderquist, J. A.; Anderson, C. L. Crystalline Anhydrous Trimethylamine *N*-Oxide. *Tetrahedron Lett.* **1986**, *27*, 3961–3962.

[187] Consonni, P.; Favara, D.; Omodei–Salé, A.; Bartolini, G.; Ricci, A. Reactivity of *N*-Phenacyloxycarbamates and Related Systems in the Presence of Bases: Study of a New [1,2] Anionic Rearrangement. *J. Chem. Soc., Perkin Trans. 2* **1983**, 967–973.

[188] Cainelli, G.; Manescalchi, F.; Plessi, L. The Use of Nitrate Esters in the Synthesis of Di- and Tri-carbonyl Compounds. *Gazz. Chim. Ital.* **1986**, *116*, 163–164.

[189] Mawhinney, T. P.; Madson, M. A. *N*-Methyl-*N*-(*tert*-butyldimethylsilyl)trifluoro–acetamide and Related *N*-*tert*-Butyldimethylsilyl Amides as Protective Silyl Donors. *J. Org. Chem.* **1982**, *47*, 3336–3339.

[190] Tschaen, D. M.; Whittle, R. R.; Weinreb, S. M. Regiochemical Control by Nonbonded Interactions in an Intramolecular Nitrone Cycloaddition. *J. Org. Chem.* **1986**, *51*, 2604–2605.

[193] (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. Catalysts for Suzuki–Miyaura Coupling Processes: Scope and Studies of the Effect of Ligand Structure. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696. (b) Martin, R.; Buchwald, S. L. Palladium-Catalyzed Suzuki–Miyaura Cross-Coupling Reactions Employing Dialkylbiaryl Phosphine Ligands. *Acc. Chem. Res.* **2008**, *41*, 1461–1473.

[194] Lee, S. J.; Anderson, T. M.; Burke, S. D. A Simple and General Platform for Generating Stereochemically Complex Polyene Frameworks by Iterative Cross-Coupling. *Angew. Chem. Int. Ed.* **2010**, *49*, 8860–8863.

[195] Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. An Excellent Reagent for the Removal of the *t*-Butyldimethylsilyl Protecting Group. *Tetrahedron Lett.* **1979**, *20*, 3981–3982.

[197] Metcalf, B. W.; Burkhart, J. P.; Jund, K. Cleavage of *tert*-Butyldimethylsilyl Ethers by Tetrafluoro-borate Salts. *Tetrahedron Lett.* **1980**, *21*, 35–36.

[198] Pilcher, A. S.; Hill, D. K.; Shimshock, S. J.; Waltermire, R. E.; DeShong, P. Selective Deprotection of Trialkylsilyl Ethers Using Fluorosilicic Acid. *J. Org. Chem.* **1992**, *57*, 2492–2495.

[199] (a) Rubin, M. B.; Gleiter, R. The Chemistry of Vicinal Polycarbonyl Compounds. *Chem. Rev.* **2000**, *100*, 1121–1164. (b) Wasserman, H. H.; Parr, J. The Chemistry of Vicinal Tricarbonyls and Related Systems. *Acc. Chem. Res.* **2004**, *37*, 687–701.

[200] Ding, Y.; Zhao, G. One-Pot Preparation of β-Hydroxy Esters Catalyzed by a Bis(cyclopentadienyl)-titanium(IV) Dichloride–Zinc System. *J. Chem. Soc., Chem. Commun.* **1992**, 941–942.

[201] Hannick, S. M.; Kishi, Y. Improved Procedure for the Blaise Reaction: A Short, Practical Route to the Key Intermediates of the Saxitoxin Synthesis. *J. Org. Chem.* **1983**, *48*, 3833–3835.

[202] Species related to **2283** (R = Ac) have been obtained from the $PhI(OAc)_2$-mediated oxidation of β-enamino ketones, see: Chen, Y.; Ju, T.; Wang, J.; Yu, W.; Du, Y.; Zhao, K. Concurrent α-Iodination and *N*-Arylation of Cyclic β-Enaminones. *Synlett* **2010**, 231–234.

[203] For a report of the PhI(OH)OTs-mediated oxidation of methyl 3-aminocrotonate, see: Papoutsis, I.; Spyroudis, S.; Varvoglis, A. Reactivity of a New Alkenyl Phenyliodonium Tosylate Derived from Methyl 3-Aminocrotonate. *Tetrahedron* **1998**, *54*, 1005–1012.

[205] (a) Li, X.; Du, Y.; Liang, Z.; Li, X.; Pan, Y.; Zhao, K. Simple Conversion of Enamines to 2*H*-Azirines and Their Rearrangements under Thermal Conditions. *Org. Lett.* **2009**, *11*, 2643–2626. (b) Shimada, N.; Ashburn, B. O.; Basak, A. K.; Bow, W. F.; Vicic, D. A.; Tius, M. A. Organocatalytic Asymmetric aza-Nazarov Cyclization of an Azirine. *Chem. Commun.* **2010**, *46*, 3774–3775.

[206] Batchelor, M. J.; Gillespie, R. J.; Golec, J. M. C.; Hedgecock, C. J. R. A Novel Application of the Dess–Martin Reagent to the Synthesis of an FK506 Analogue and other Tricarbonyl Compounds. *Tetrahedron Lett.* **1993**, *34*, 167–170.

[207] Meyer, S. D.; Schreiber, S. L. Acceleration of the Dess-Martin Oxidation by Water. *J. Org. Chem.* **1994**, *59*, 7549–7552.

[208] (a) Koser, G. F.; Relenyi, A. G.; Kalos, A. N.; Rebrovic, L.; Wettach, R. H. One-Step α-Tosyloxylation of Ketones with [Hydroxy(tosyloxy)iodo]benzene. *J. Org. Chem.* **1982**, *47*, 2487–2489. (b) Lodaya, J. S.; Koser, G. F. Direct α-

Mesyloxylation of Ketones and β-Dicarbonyl Compounds with [Hydroxy-(mesyloxy)iodo]benzene. *J. Org. Chem.* **1988**, *53*, 210–212.

[209] Saba, A. Synthesis of Vicinal Trioxo Compounds by Dimethyl Dioxirane Oxidation of 2-Diazo-1,3-dioxo Derivatives. *Synth. Commun.* **1994**, *24*, 695–699.

[210] Bethäuser, W.; Regitz, M.; Theis, W. Über die Reaktivität von 4-Phenyl-1,2,4-triazolin-3,5-dion mit Diazoverbindungen. *Tetrahedron Lett.* **1981**, *22*, 2535–2538.

[211] Theis, W.; Bethäuser, W.; Regitz, M. Untersuchungen an Diazoverbindungen und Aziden–LIII: Abfangreaktionen Instabiler Azomethinimin-dipole mit Ethanol. *Tetrahedron* **1985**, *41*, 1965–1971.

[212] (a) Wilson, R. M.; Hengge, A. C.; Ataei, A.; Chantarasiri, N. Addition of 4-Phenyltriazolinedione to Carbonyl Compounds: The Formation of α-Urazolylcarbonyl Compounds. *J. Org. Chem.* **1990**, *55*, 193–197. (b) Wilson, R. M.; Hengge, A. C. Synthesis and Chemistry of Acyltriazolinedione Ylides and Related Intermediates: New Methods for the Preparation of Di- and Tricarbonyl Compounds. *J. Org. Chem.* **1990**, *55*, 197–202.

[213] (a) Wamhoff, H.; Wald, K.; Kirfel, A.; Farkas, L.; Samimi, N.; Will, G. Reaktionen von Uracilen, 5. Verbrückte 1,2,5,6-Tetrazocane mit Uracil- und Urazolbrücken durch Dimerisierung von 5-(1,2,4-Triazolidin-1-yl)uracilen. *Chem. Ber.* **1985**, *118*, 436–443. (b) Zhang, J. –H.; Wang, M. –X.; Huang, Z. –T. The Aza-ene Reaction of Heterocyclic Ketene Aminals with 4-Phenyl-1,2,4-triazoline-3,5-dione. *J. Chem. Res. (S)* **1998**, 486–487.

[214] (a) Taylor, E. C.; Martin, S. F. A New Synthesis of *as*-Triazines and Pyrimido[4,5-*e*]-*as*-triazines (6-Azapteridines). *J. Org. Chem.* **1970**, *35*, 3792–3795. (b) Huang, Z. –T.; Liu, Z. –R. Synthesis of 2-(Benzoylmethylene)-imidazolidines and -hexahydropyrimidines by Condensation of Ethyl Benzoyl-acetimidates with 1,2-Ethanediamine or 1,3-Propandiamine, and Some Addition Reactions. *Synthesis* **1987**, 357–362. (c) Cheng, Y.; Zhao, M.; Wang, M. –X.; Wang, L. –B.; Huang, Z. –T. Synthesis of Acetyl-Substituted Heterocyclic Enamines and Their Reaction with Diethyl Azodicarboxylate. *Synth. Commun.* **1995**, *25*, 1339–1351.

[217] MTM ether formation has been observed to occur during the Swern oxidation; see: Williams, D. R.; Klingler, F. D.; Dabral, V. Synthesis of the Optically Active

Hexahydrobenzofuran Nucleus of the Avermectins. *Tetrahedron Lett.* **1988**, *29*, 3415–3418.

[220] Cookson, R. C.; Stevens, I. D. R.; Watts, C. T. A New Reagent for Oxidation of Alcohols to Ketones in Neutral Solution at Room Temperature. *Chem. Commun. (London)* **1966**, 744a.

[221] Jahn, U.; Hartmann, P.; Dix, I.; Jones, P. G. Oxidative Enolate Cyclizations of 6,8-Nonadienoates: Toward the Synthesis of Prostanes. *Eur. J. Org. Chem.* **2002**, 718–735.

[222] Xu, J.; Caro–Diaz, E. J. E.; Trzoss, L.; Theodorakis, E. A. Nature-Inspired Total Synthesis of (–)-Fusarisetin A. *J. Am. Chem. Soc.* **2012**, *134*, 5072–5075.

[223] Hunter, D. H.; Barton, D. H. R.; Motherwell, W. J. Oxoammonium Salts as Oxidizing Agents: 2,2,6,6-Tetramethyl-1-oxopiperidinium Chloride. *Tetrahedron Lett.* **1984**, *25*, 603–606.

[224] (a) Burrows, C. J.; Carpenter, B. K. Substituent Effects on the Aliphatic Claisen Rearrangement. 1. Synthesis and Rearrangement of Cyano-Substituted Allyl Vinyl Ethers. *J. Am. Chem. Soc.* **1981**, *103*, 6983–6984. (b) Burrows, C. J.; Carpenter, B. K. Substituent Effects on the Aliphatic Claisen Rearrangement. 2. Theoretical Analysis. *J. Am. Chem. Soc.* **1981**, *103*, 6984–6986.

[225] For a recent example where a spontaneous Claisen rearrangement of an *aryl* allyl ether has been shown to be operative in the biosynthesis of cyanobactin peptide natural products, see: McIntosh, J. A.; Donia, M. S.; Nair, S. K.; Schmidt, E. W. Enzymatic Basis of Ribosomal Peptide Prenylation in Cyanobacteria. *J. Am. Chem. Soc.* **2011**, *133*, 13698–13705.

[226] Benson, S. W.; O'Neal, H. E. *Kinetic Data on Gas Phase Unimolecular Reactions*; U.S. Department of Commerce: Washington, DC, **1970**; NSRDS–NBS 21, p 363.

[227] Gajewski, J. J.; Brichford, N. L. Secondary Deuterium Kinetic Isotope Effects in the Aqueous Claisen Rearrangement: Evidence Against an Ionic Transition State. *J. Am. Chem. Soc.* **1994**, *116*, 3165–3166.

[228] Martín Castro, A. M. Claisen Rearrangement Over the Past Nine Decades. *Chem. Rev.* **2004**, *104*, 2939–3002.

[229] Gibson, F.; Pittard, J. Pathways of Biosynthesis of Aromatic Amino Acids and Vitamins and Their Control in Microorganisms. *Bacteriol. Rev.* **1968**, *32*, 465–492.

[230] (a) Andrews, P. R.; Smith, G. D.; Young, I. G. Transition-State Stabilization and Enzymatic Catalysis. Kinetic and Molecular Orbital Studies of the Rearrangement of Chorismate to Prephenate. *Biochemistry* **1973**, *12*, 3492–3498. (b) Gorisch, H. On the Mechanism of the Chorismate Mutase Reaction. *Biochemistry* **1978**, *17*, 3700–3705.

[231] Ganem, B. The Mechanism of the Claisen Rearrangement: Déjà Vu All Over Again. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 936–945.

[232] (a) Ziegler, F. E. Stereo- and Regiochemistry of the Claisen Rearrangement: Applications to Natural Products Synthesis. *Acc. Chem. Res.* **1977**, *10*, 227–232. (b) Bennett, G. B. The Claisen Rearrangement in Organic Synthesis; 1967 to January 1977. *Synthesis* **1977**, 589–606.

[233] (a) Gajewski, J. J.; Conrad, N. D. Aliphatic Claisen Rearrangement Transition State Structure from Secondary α-Deuterium Isotope Effects. *J. Am. Chem. Soc.* **1979**, *101*, 2747–2748. (b) Gajewski, J. J.; Conrad, N. D. Variable Transition State Structure in 3,3-Sigmatropic Shifts from α-Secondary Deuterium Isotope Effects. *J. Am. Chem. Soc.* **1979**, *101*, 6693–6704.

[234] Ireland, R. E.; Mueller, R. H.; Willard, A. K. The Ester Enolate Claisen Rearrangement. Stereochemical Control Through Stereoselective Enolate Formation. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877.

[235] Curran, D. P.; Suh, Y. –G. Substituent Effects on the Claisen Rearrangement. The Accelerating Effect of a 6-Donor Substituent. *J. Am. Chem. Soc.* **1984**, *106*, 5002–5004.

[236] (a) Castro, A. M. M. Claisen Rearrangement over the Past Nine Decades. *Chem. Rev.* **2004**, *104*, 2939–3002. (b) Rehbein, J.; Hiersemann, M. Mechanistic Aspects of the Aliphatic Claisen Rearrangement. In *The Claisen Rearrangement: Methods and Applications*, M. Hiersemann, U. Nubbemeyer, Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, **2007**, pp 525–557.

[237] Carpenter, B. K. A Simple Model for Predicting the Effect of Substituents on the Rates of Thermal Pericyclic Reactions. *Tetrahedron* **1978**, *34*, 1877–1884.

[238] Gajewski, J. J. Energy Surfaces of Sigmatropic Shifts. *Acc. Chem. Res.* **1980**, *13*, 142–148 and references therein.

[239] (a) Lythgoe, B.; Milner, J. R.; Tideswell, J. Claisen Rearrangements of Allylic a-Phenylthioacetates: Applications in Synthesis. *Tetrahedron Lett.* **1975**, *16*, 2593–2596. (b) Kachinski, J. L. C.; Salomon, R. G. Allyloxy Ketone Enol Ether-Claisen Rearrangement. Regiospecific Synthesis of Allyl Ketones from Allyl Alcohols. *Tetrahedron Lett.* **1977**, *18*, 3235–3238.

[240] Koreeda, M.; Luengo, J. I. Anionic Oxy-Claisen Rearrangement of Enolates of α-Allyloxy Ketones. A Remarkable Rate-Accelerating Effect Exhibited by the Nature of the Counterion. *J. Am. Chem. Soc.* **1985**, *107*, 5572–5573.

[241] Gajewski, J. J. The Claisen Rearrangement. Response to Solvents and Substituents: The Case for both Hydrophobic and Hydrogen Bond Acceleration in Water and for a Variable Transition State. *Acc. Chem. Res.* **1997**, *30*, 219–225.

[242] Vance, R. L.; Rondan, N. G.; Houk, K. N.; Jensen, F.; Borden, W. T.; Komornicki, A.; Wimmer, E. Transition Structures for the Claisen Rearrangement. *J. Am. Chem. Soc.* **1988**, *110*, 2314–2315.

[243] Carey, F. A.; Sundberg, R. J. Free-Radical Reactions. In *Advanced Organic Chemistry, Part A: Structure and Mechanisms*, 4TH ed.; Springer Publishing: New York, **2006**, pp 663–742.

[245] (a) Nakai, T.; Mikami, K. [2,3]-Wittig Sigmatropic Rearrangements in Organic Synthesis. *Chem. Rev.* **1986**, *86*, 885–902. (b) Mikami, K.; Nakai, T. Acyclic Stereocontrol via [2,3]-Wittig Sigmatropic Rearrangement. *Synthesis* **1991**, 594–604.

[246] Thomas, A. F.; Dubini, R. 225. The [2,3] Sigmatropic Reaction of Acetonyl Allyl Ethers, a New Method for Preparing Certain 2-Hydroxyketones. *Helv. Chim. Acta* **1974**, *57*, 2084–2087.

[247] Kirchner, J. J.; Pratt, D. V.; Hopkins, P. B. Anionic Oxy-Claisen Rearrangement of a Tricyclic α-Allyloxy Ketone. *Tetrahedron Lett.* **1988**, *29*, 4229–4232.

[248] (a) Higuchi, K.; Saito, K.; Hirayama, T.; Watanabe, Y.; Kobayashi, E.; Kawasaki, T. Claisen Rearrangement through Enolization of 2-Allyloxyindolin-3-ones: Construction of Adjacent Carbon Stereocenters in 3-Hydroxyindolin-2-ones. *Synthesis* **2010**, 3609–3614. (b) Kawasaki, T.; Takamiya, W.; Okamoto, N.; Nagaoka, M.; Hirayama, T. Silyl-Enolization-Asymmetric Claisen Rearrangement of 2-Allyloxyindolin-3-one: Enantioselective Total Synthesis of 3a-Hydroxypyrrolo[2,3-*b*]indoline Alkaloid Alline. *Tetrahedron Lett.* **2006**, *47*, 5379–5382. (c) Kawasaki, T.; Nagaoka, M.; Satoh, T.; Okamoto, A.; Ukon, R.;

Ogawa, A. Synthesis of 3-Hydroxyindolin-2-one Alkaloids, (±)-Donaxaridine and (±)-Convolutamydines A and E, through Enolization-Claisen Rearrangement of 2-Allyloxyindolin-3-ones. *Tetrahedron* **2004**, *60*, 3493–3503 and references therein. (d) Malapel-Andrieu, B.; Piroëlle, S.; Mérour, J. –Y. Claisen Rearrangement of 2-Allyloxyindolic Ketoester via a Decarboxylative Process. *J. Chem. Research (S)* **1998**, 594–595.

[249] (a) Kachinski, J. L. C.; Salomon, R. G. Allyloxy Ketone Enol Ether-Claisen Rearrangement. Regiospecific Synthesis of Allyl Ketones from Allyl Alcohols. *Tetrahedron Lett.* **1977**, *18*, 3235–3238. (b) Kachinsky, J. L. C.; Salomon, R. G. Regiospecific Synthesis of β,γ-Unsaturated Ketones from Allylic Alcohols. Claisen Rearrangement of α-Allyloxy Ketone Enol Derivatives. *J. Org. Chem.* **1986**, *51*, 1393–1401. (c) Raucher, S.; Gustavson, L. M. [3,3]-Sigmatropic Rearrangement of Silyl Ketene Acetals of Methyl α-(Allyloxy)acetates. *Tetrahedron Lett.* **1986**, *27*, 1557–1560. (d) Takahashi, O.; Maeda, T.; Mikami, K.; Nakai, T. [3,3]-Claisen vs. [2,3]-Wittig Shift in Thermal and Fluoride Ion-Promoted Rearrangements of the *O*- and *C*-Silylated Forms of α-Allyloxy Esters. *Chem. Lett.* **1986**, 1355–1358.

[250] (a) Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. Claisen Rearrangement of 6-Alkenyl-2-methylenetetrahydropyrans. A New Approach to Annulated 4-Cyclooctenones and a Stereospecific Synthesis of Precapnelladiene. *J. Am. Chem. Soc.* **1984**, *106*, 6868–6870. (b) Paquette, L. A.; Philippo, C. M. G.; Yo, N. H. Ring Expansion by Tandem Double Tebbe–Claisen Technology. *Can. J. Chem.* **1992**, *70*, 1356–1365 and references cited therein. (c) Paquette, L. A.; Wang, T. –Z.; Vo, N. H. Access to Naturally Occurring Cyclooctanoids by Two-Carbon Intercalation. Total Synthesis of (+)-Ceroplastol I. *J. Am. Chem. Soc.* **1993**, *115*, 1676–1683.

[251] (a) Paquette, L. A.; Sun, L.; Friedrich, D.; Savage, P. B. Total Synthesis of (+)-Epoxydictymene. Application of Alkoxy-Directed Cyclization of Diterpenoid Construction. *J. Am. Chem. Soc.* **1997**, *119*, 8438–8450 and references cited therein. (b) Paquette, L. A.; Friedrich, D.; Rogers, R. D. Alkylaluminum-Catalyzed Claisen Expansion Reactions. Scope and Stereochemistry. *J. Org. Chem.* **1991**, *56*, 3841–3849.

[252] (a) Burke, S. D.; Armistead, D. M.; Schoenen, F. J. Polysubstituted Dihydropyrans via the Enolate Claisen Rearrangement. A Stereocontrolled Route to *C*-Pyranosides. *J. Org. Chem.* **1984**, *49*, 4320–4322. (b) Burke, S. D.;

Armistead, D. M.; Fevig, J. M. Ionophore Synthesis. An Enantioselective Route to the Left-Wing of Indanomycin (X-14547A). *Tetrahedron Lett.* **1985**, *26*, 1163–1166. (c) Burke, S. D.; Schoenen, F. J.; Murtiashaw, C. W. The Ester Enolate Claisen Rearrangement. Synthesis of a C(1)–C(6) Erythronolide Fragment. *Tetrahedron Lett.* **1986**, *27*, 449–452. (d) Burke, S. D.; Armistead, D. M.; Schoenen, F. J.; Fevig, J. M. An Enolate Claisen Route to *C*-Pyranosides–Development and Application to an Ionophore Synthon. *Tetrahedron Lett.* **1986**, *27*, 2787–2801. (e) Burke, S. D.; Schoenen, F. J.; Nair, M. S. The Dioxanone-to-Dihydropyran Claisen Rearrangement. Synthesis of C(7)–C(13) Fragments of Erythronolides A and B. *Tetrahedron Lett.* **1987**, *28*, 4143–4146. (f) Burke, S. D.; Lee, K. C.; Santafianos, D. Double Dioxanone-to-Dihydropyran Reorganization. Construction of a C(1)–C(13) Erythronolide Template. *Tetrahedron Lett.* **1991**, *32*, 3957–3960. (g) Burke, S. D.; Buchanan, J. L.; Rovin, J. D. Synthesis of a C(22) → C(34) Halichondrin Precursor via a Double Dioxanone-to-Dihydropyran Rearrangement. *Tetrahedron Lett.* **1991**, *32*, 3961–3964. (h) Burke, S. D.; Piscopio, A. D.; Kort, M. E.; Matulenko, M. A.; Parker, M. H.; Armistead, D. M.; Shankaran, K. Total Synthesis of Ionophore Antibiotic X-14547A (Indanomycin). *J. Org. Chem.* **1994**, *59*, 332–347.

[253] Ireland, R. E.; Mueller, R. H. The Claisen Rearrangement of Allyl Esters. *J. Am. Chem. Soc.* **1972**, *94*, 5897–5898.

[254] (a) Hekmatshoar, R.; Yavari, I.; Beheshtiha, Y. S.; Heravi, M. M. Reductive Coupling of Carbonyl Compounds to Pinacols with Zinc in THF–Saturated Aqueous Ammonium Chloride. *Monatsh. Chem.* **2001**, *132*, 689–691. (b) Trost, B. M.; Aponick, A. Palladium-Catalyzed Asymmetric Allylic Alkylation of *meso*- and *dl*-1,2-Divinylethylene Carbonate. *J. Am. Chem. Soc.* **2006**, *128*, 3931–3933.

[255] David, S.; Thieffry, A.; Veyrières, A. A Mild Procedure for the Regiospecific Benzylation and Allylation of Polyhydroxy-compounds *via* their Stannylene Derivatives in Non-polar Solvents. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1796–1801.

[256] See, e.g.: Davies, A. G.; Price, A. J.; Dawes, H. M.; Hursthouse, M. B. Structure of 2,2-Dibutyl-1,3,2-dioxastannolane in the Solid State. *J. Chem. Soc., Dalton Trans.* **1986**, 297–302.

[257] Burke, S. D.; Sametz, G. M. Total Synthesis of 3-Deoxy-D-*manno*-2-octulosonic Acid (KDO) and 2-Deoxy-*β*-KDO. *Org. Lett.* **1999**, *1*, 71–74. A single

enantiomer of **3036-trans**, which in this instance was prepared by a five-step sequence from D-mannitol, was used.

[258] Angle, S. R.; Breitenbucher, J. G.; Arnaiz, D. O. An Efficient Stereoselective Synthesis of $\Delta^{4,5}$-Pipecolic Esters. *J. Org. Chem.* **1992**, *57*, 5947–5955.

[259] Such situations have been encountered in the literature; see ref 258 and Overman, L. E.; Angle, S. R. Synthesis Applications of Cationic Aza-Cope Rearrangements. Stereocontrolled Synthesis of Hexahydro-1*H*-pyrrolo[2,3-*d*]carbazoles. *J. Org. Chem.* **1985**, *50*, 4021–4028.

[260] (a) Büchi, G.; Powell, Jr., J. E. A Structurally Selective Method for the Preparation of Certain Diels-Alder Adducts. *J. Am. Chem. Soc.* **1967**, *89*, 4559–4560. (b) Büchi, G.; Powell, Jr., J. E. The Claisen Rearrangement of 3,4-Dihydro-2*H*-pyranylethylenes. A New Method for the Synthesis of Cyclohexenes. *J. Am. Chem. Soc.* **1970**, *92*, 3126–3133.

[261] Danishefsky, S.; Funk, R. L.; Kerwin, Jr., J. F. Claisen Rearrangement of Lactonic (Silyl) Enolates: A New Route to Functionalized Cycloalkenes. *J. Am. Chem. Soc.* **1980**, *102*, 6889–6891.

[263] De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. A Versatile and Highly Selective Hypervalent Iodine(III)/2,2,6,6-Tetramethyl-1-piperidinyloxyl-Mediated Oxidation of Alcohols to Carbonyl Compounds. *J. Org. Chem.* **1997**, *62*, 6974–6977.

[264] Parikh, J. P.; Doering, W. E. Sulfur Trioxide in the Oxidation of Alcohols by Dimethyl Sulfoxide. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.

[265] Jorgenson, M. J. Preparation of Ketones from the Reaction of Organolithium Reagents with Carboxylic Acids. *Org. React.* **1970**, *18*, 1–97.

[266] Neumann, H.; Seebach, D. Stereospecific Preparation of Terminal Vinyllithium Derivatives by Br/Li-Exchange with *t*-Butyllithium. *Tetrahedron Lett.* **1976**, *17*, 4839–4842.

[267] Sellès, P.; Lett, R. Convergent Stereospecific Synthesis of C292 (or LL-Z1640-2), and Hypothemycin. Part 1. *Tetrahedron Lett.* **2002**, *43*, 4621–4625.

[268] Wissner, A.; Grudzinskas, C. V. Reaction of *tert*-Butyldimethylsilyl Ester with Oxalyl Chloride–Dimethylformamide: Preparation of Carboxylic Acid Chloride Under Neutral Conditions. *J. Org. Chem.* **1978**, *43*, 3972–3974.

[274] Gentric, L.; Hanna, I.; Huboux, A.; Zaghdoudi, R. Rate Acceleration of Anionic Oxy-Cope Rearrangements Induced by an Additional Unsaturation. *Org. Lett.* **2003**, *5*, 3631–3634.

[275] Evans, D. A.; Golob, A. M. [3,3]Sigmatropic Rearrangements of 1,5-Diene Alkoxides. The Powerful Accelerating Effects of the Alkoxide Substituent. *J. Am. Chem. Soc.* **1975**, *97*, 4765–4766.

[277] Kitahara, Y.; Oda, M.; Miyakoshi, S.; Nakanishi, S. The Chemistry of 2-Hydroxy-2,4,6-cyclooctatrienone (1,7-π-Homotropolone). *Tetrahedron Lett.* **1976**, *17*, 2149–2152.

[278] Ziegler, E.; Wittmann, H.; Sterk, H. Über Reaktionen mit Betain, 24. Mitt. [1]: Über Umsetzungen von Trimethylammoniumessigsäurebetain mit reaktiven Halogen-verbindungen. *Monatsh. Chem.* **1989**, *120*, 907–912.

[279] Snider, B. B.; Patricia, J. J. Manganese(III)-Based Oxidative Free-Radical Cyclizations. Oxidative Cyclization and Aromatization of 3-Oxo-6-heptenoate Esters. *J. Org. Chem.* **1989**, *54*, 38–46.

[280] Böhmer, J.; Hampel, F.; Schobert, R. Regioselective Synthesis of Substituted (3*E*)-1,3-Dienes from Chelated Allyl–Ironcarbene Complexes and Potassium Enoxyborates. *Synthesis* **1997**, 661–667.

[281] Böhmer, J.; Förtsch, W.; Schobert, R. Selective Demetalations of Iron Diene Complexes. Expidient Synthesis of Substituted (*Z*)-Allylalcohols. *Synlett* **1997**, 1073–1074.

[282] (a) Yamaguchi, M.; Hirao, I. An Efficient Method for the Alkynylation of Oxiranes Using Alkynyl Boranes. *Tetrahedron Lett.* **1983**, *24*, 391–394. (b) Aubrecht, K. B.; Winemiller, M. D.; Collum, D. B. BF_3-Mediated Addition of Lithium Phenylacetylide to an Imine: Correlations of Structures and Reactivities. BF_3•R_3N Derivatives as Substitutes for BF_3•OEt_2. *J. Am. Chem. Soc.* **2000**, *122*, 11084–11089.

[283] Crousse, B.; Alami, M.; Linstrumelle, G. Stereoselective Reduction of Conjugated Homopropargylic Alcohols to (*E*)-Homoallylic Alcohols by Sodium Bis(2-methoxyethoxy) Aluminum Hydride. *Synlett* **1997**, 992–994.

[284] (a) Aumann, R.; Ring, H.; Krüger, C.; Goddard, R. Untersuchungen zur Synthese ungesättigter δ-Lactone durch Cyclocarbonylierung von Vinyloxiranen mit Übergangsmetall-Komplexen. *Chem. Ber.* **1979**, *112*, 3644–3671. (b) Annis, G. D.; Ley, S. V.; Self, C. R.; Sivaramakrishnan, R. Preparation of Lactones *via*

Tricarbonyliron–Lactone Complexes. *J. Chem. Soc., Perkin Trans. 1* **1981**, 270–277.

[285] Förtsch, W.; Hampel, F.; Schobert, R. Synthese, Kristallstruktur und Reaktionen neuartiger metallacyclischer Dioxo- und Aminooxocarben-Komplexe des Eisens. *Chem. Ber.* **1994**, *127*, 711–715.

[286] Negishi, E.; Idacavage, M. J. A Highly Selective Method for α-Alkylation of Ketones via Potassium Enoxytrialkylborates. *Tetrahedron Lett.* **1979**, *20*, 845–848.

[288] (a) Sharpless, K. B.; Akashi, K.; Oshima, K. Ruthenium Catalyzed Oxidation of Alcohols to Aldehydes and Ketones by Amine-N-oxides. *Tetrahedron Lett.* **1976**, *17*, 2503–2506. (b) "*We speculate that certain homoallylic alcohols (note case 17 is an exception) form very stable alkoxyolefin complexes with ruthenium (II?) and thus tie up the catalyst*…" (ref 288a)

[290] (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y. –L.; Sugita, K. Iodine(V) Reagents in Organic Synthesis. Part 1. Synthesis of Polycyclic Heterocycles via Dess–Martin Periodinane-Mediated Cascade Cyclization: Generality, Scope, and Mechanism of the Reaction. *J. Am. Chem. Soc.* **2002**, *124*, 2212–2220. (b) Nicolaou, K. C.; Sugita, K.; Baran, P. S.; Zhong, Y. –L. Iodine(V) Reagents in Organic Synthesis. Part 2. Access to Complex Molecular Architectures via Dess–Martin Periodinane-Generated *o*-Imidoquinones. *J. Am. Chem. Soc.* **2002**, *124*, 2221–2232.

[291] Dess, D. B.; Martin, J. C. A Useful 12–I–5 Triacetoxyperiodinane (the Dess–Martin Periodinane) for the Selective Oxidation of Primary and Secondary Alcohols and a Variety of Related 12–I–5 Species. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

[292] Frigerio, M.; Santagostino, M. A Mild Oxidizing Reagent for Alcohols and 1,2-Diols: *o*-Iodoxybenzoic Acid (IBX) in DMSO. *Tetrahedron Lett.* **1994**, *35*, 8019–8022.

[294] Gallen, M. J.; Goumont, R.; Clark, T.; Terrier, F.; Williams, C. M. *o*-Iodoxybenzoic Acid (IBX): pK_a and Proton-Affinity Analysis. *Angew. Chem. Int. Ed.* **2006**, *45*, 2929–2934.

[296] Otera, J.; Dan-oh, N.; Nozaki, H. Novel Template Effects of Distannoxane Catalysts in Highly Efficient Transesterification and Esterification. *J. Org. Chem.* **1991**, *56*, 5307–5311.

[297] Claridge, T. D. W. *High-Resolution NMR Techniques in Organic Chemistry*, 1ST ed.; Baldwin, FRS, J. E., Williams, R. M., Eds.; Tetrahedron Organic Chemistry Series; Elsevier Science: New York, **1999**; Vol. 19.

[298] Nicolaou, K. C.; Snyder, S. A. Chasing Molecules That Were Never There: Misassigned Natural Products and the Role of Chemical Synthesis in Modern Structure Elucidation. *Angew. Chem. Int. Ed.* **2005**, *44*, 1012–1044.

[299] Suyama, T. L.; Gerwick, W. H.; McPhail, K. L. Survey of Marine Natural Product Structure Revisions: A Synergy of Spectroscopy and Chemical Synthesis. *Bioorg. Med. Chem.* **2011**, *19*, 6675–6701.

[300] Bourdelais, A. J.; Jacocks, H. M.; Wright, J. L. C.; Bigwarfe, Jr., P. M.; Baden, D. G. A New Polyether Ladder Compound Produced by the Dinoflagellate *Karenia brevis*. *J. Nat. Prod.* **2005**, *68*, 2–6.

[301] Fuwa, H.; Ebine, M.; Bourdelais, A. J.; Baden, D. G.; Sasaki, M. Total Synthesis, Structure Revision, and Absolute Configuration of (–)-Brevenal. *J. Am. Chem. Soc.* **2006**, *128*, 16989–16999.

[302] Diyabalanage, T.; Amsler, C. D.; McClintock, J. B.; Baker, B. J. Palmerolide A, a Cytotoxic Macrolide from the Antarctic Tunicate *Synoicum adareanum*. *J. Am. Chem. Soc.* **2006**, *128*, 5630–5631.

[303] Jiang, X.; Liu, B.; Lebreton, S.; De Brabander, J. K. Total Synthesis and Structure Revision of the Marine Metabolite Palmerolide A. *J. Am. Chem. Soc.* **2007**, *129*, 6386–6387.

[304] Wright, A. E.; Botelho, J. C.; Guzmán, E.; Harmody, D.; Linley, P.; McCarthy, P. J.; Pitts, T. P.; Pomponi, S. A.; Reed, J. K. Neopeltolide, a Macrolide from a Lithistid Sponge of the Family Neopeltidae. *J. Nat. Prod.* **2007**, *70*, 412–416.

[305] Youngsaye, W.; Lowe, J. T.; Pohlki, F.; Ralifo, P.; Panek, J. S. Total Synthesis and Stereochemical Reassignment of (+)-Neopeltolide. *Angew. Chem. Int. Ed.* **2007**, *46*, 9211–9214.

[306] Custar, D. W.; Zabawa, T. P.; Scheidt, K. A. Total Synthesis and Structural Revision of the Marine Macrolide Neopeltolide. *J. Am. Chem. Soc.* **2008**, *130*, 804–805.

[307] (a) Bifulco, G.; Dambruoso, P.; Gomez–Paloma, L.; Riccio, R. Determination of Relative Configuration in Organic Compounds by NMR Spectroscopy and Computational Methods. *Chem. Rev.* **2007**, *107*, 3744–3779. (b) Di Micco, S.;

Chini, M. G.; Riccio, R.; Bifulco, G. Quantum Mechanical Calculation of NMR Parameters in the Stereostructural Determination of Natural Products. *Eur. J. Org. Chem.* **2010**, 1411–1434. (c) Lodewyk, M. W.; Siebert, M. R.; Tantillo, D. J. Computational Prediction of ^{1}H and ^{13}C Chemical Shifts: A Useful Tool for Natural Product, Mechanistic, and Synthetic Organic Chemistry. *Chem. Rev.* **2012**, *112*, 1839–1862.

[308] Wipf, P.; Kerekes, A. D. Structure Reassignment of the Fungal Metabolite TAEMC161 as the Phytotoxin Viridiol. *J. Nat. Prod.* **2003**, *66*, 716–718.

[309] Aiello, A.; Fattorusso, E.; Luciano, P.; Mangoni, A.; Menna, M. Isolation and Structure Determination of Aplidinones A–C from the Mediterranean Ascidian *Aplidium conicum*: A Successful Regio-chemistry Assignment by Quantum Mechanical ^{13}C NMR Chemical Shift Calculations. *Eur. J. Org. Chem.* **2005**, 5024–5030.

[310] Pu, J. –X; Huang, S. –X.; Ren, J.; Xiao, W. –L.; Li, L. –M.; Li, R. –T.; Li, L. –B.; Liao, T. –G.; Lou, L. –G.; Zhu, H. –J.; Sun, H. –D. Isolation and Structure Elucidation of Kadlongilactones C–F from *Kadsura longipedunculata* by NMR Spectroscopy and DFT Computational Methods. *J. Nat. Prod.* **2007**, *70*, 1706–1711.

[311] Fattorusso, C.; Stendardo, E.; Appendino, G.; Fattorusso, E.; Luciano, P.; Romano, A.; Taglialatela–Scafati, O. Artarborol, a *nor*-Caryophyllane Sesquiterpene Alcohol from *Artemisia arborescens*. Stereostructure Assignment through Concurrence of NMR Data and Computational Analysis. *Org. Lett.* **2007**, *9*, 2377–2380.

[312] Nicolaou, K. C.; Frederick, M. O. On the Structure of Maitotoxin. *Angew. Chem. Int. Ed.* **2007**, *46*, 5278–5282.

[313] Bassarello, C.; Bifulco, G.; Montoro, P.; Skhirtladze, A.; Kemertelidze, E.; Pizza, C.; Piacente, S. Gloriosaols A and B, Two Novel Phenolics from *Yucca gloriosa*: Structural Characterization and Configurational Assignment by a Combined NMR-Quantum Mechanical Strategy. *Tetrahedron* **2007**, *63*, 148–154.

[314] Braddock, D. C.; Rzepa, H. S. Structural Reassignment of Obtusallenes V, VI, and VII by GIAO-Based Density Functional Prediction. *J. Nat. Prod.* **2008**, *71*, 728–730.

[315] Smith, S. G.; Paton, R. S.; Burton, J. W.; Goodman, J. M. Stereostructure Assignment of Flexible Five-Membered Rings by GIAO ^{13}C NMR Calculations:

Prediction of the Stereochemistry of Elatenyne. *J. Org. Chem.* **2008**, *73*, 4053–4062.

[316] White, K. N.; Amagata, T.; Oliver, A. G.; Tenney, K.; Wenzel, P. J.; Crews, P. Structure Revision of Spiroleucettadine, a Sponge Alkaloid with a Bicyclic Core Meager in H-Atoms. *J. Org. Chem.* **2008**, *73*, 8719–8722.

[317] Timmons, C.; Wipf, P. Density Functional Theory Calculation of ^{13}C NMR Shifts of Diazaphenanthrene Alkaloids: Reinvestigation of the Structure of Samoquasine A. *J. Org. Chem.* **2008**, *73*, 9168–9170.

[318] Fattorusso, E.; Luciano, P.; Romano, A.; Taglialatela–Scafati, O.; Appendino, G.; Borriello, M.; Fattorusso, C. Stereostructure Assignment of Medium-sized Rings through an NMR-Computational Combined Approach. Application to the New Germacranes Ketopelenolides C and D. *J. Nat. Prod.* **2008**, *71*, 1988–1992.

[319] Mendoza–Espinoza, J. A.; López–Vallejo, F.; Fragoso–Serrano, M.; Pereda–Miranda, R.; Cerda–García–Rojas, C. M. Structural Reassignment, Absolute Configuration, and Conformation of Hypurticin, a Highly Flexible Polyacyloxy-6-heptenyl-5,6-dihydro-2*H*-pyran-2-one. *J. Nat. Prod.* **2009**, *72*, 700–708.

[320] Lodewyk, M. W.; Tantillo, D. J. Prediction of the Structure of Nobilistine A Using Computed NMR Chemical Shifts. *J. Nat. Prod.* **2011**, *74*, 1339–1343.

[321] Schlegel, B.; Härtl, A.; Dahse, H. –M.; Gollmick, F. A.; Gräfe, U.; Dörfelt, H.; Kappes, B. Hexacyclinol, a New Antiproliferative Metabolite of *Panus rudis* HKI 0254. *J. Antibiot.* **2002**, *55*, 814–817.

[322] Rychnovsky, S. D. Predicting NMR Spectra by Computational Methods: Structure Revision of Hexacyclinol. *Org. Lett.* **2006**, *8*, 2895–2898.

[323] La Clair, J. J. Total Syntheses of Hexacyclinol, 5-*epi*-Hexacyclinol, and Desoxohexacyclinol Unveil an Antimalarial Prodrug Motif. *Angew. Chem. Int. Ed.* **2006**, *45*, 2769–2773.

[324] Proco, Jr., J. A.; Su, S.; Lei, X.; Bardhan, S.; Rychnovsky, S. D. Total Synthesis and Structure Assignment of (+)-Hexacyclinol. *Angew. Chem. Int. Ed.* **2006**, *45*, 5790–5792.

[325] Guella, G.; Dini, F.; Pietra, F. Metabolites with a Novel C_{30} Backbone from Marine Ciliates. *Angew. Chem. Int. Ed.* **1999**, *38*, 1134–1136.

[326] (a) Nicolaou, K. C.; Zhang, H.; Ortiz, A.; Dagneau, P. Total Synthesis of the Originally Assigned Structure of Vannusal B. *Angew. Chem. Int. Ed.* **2008**, *47*,

8605–8610. (b) Nicolaou, K. C.; Zhang, H.; Ortiz, A. The True Structures of the Vannusals, Part 1: Initial Forays into Suspected Structures and Intelligence Gathering. *Angew. Chem. Int. Ed.* **2009**, *48*, 5642–5647. (c) Nicolaou, K. C.; Ortiz, A.; Zhang, H. The True Structures of the Vannusals, Part 2: Total Synthesis and Revised Structure of Vannusal B. *Angew. Chem. Int. Ed.* **2009**, *48*, 5648–5652. (d) Nicolaou, K. C.; Ortiz, A.; Zhang, H.; Dagneau, P.; Lanver, A.; Jennings, M. P.; Arseniyadis, S.; Faraoni, R.; Lizos, D. E. Total Synthesis and Structural Revision of Vannusals A and B: Synthesis of the Originally Assigned Structure of Vannusal B. *J. Am. Chem. Soc.* **2010**, *132*, 7138–7152. (e) Nicolaou, K. C.; Ortiz, A.; Zhang, H.; Guella, G. Total Synthesis and Structural Revision of Vannusals A and B: Synthesis of the True Structures of Vannusals A and B. *J. Am. Chem. Soc.* **2010**, *132*, 7153–7176.

[327] Saielli, G.; Nicolaou, K. C.; Ortiz, A.; Zhang, H.; Bagno, A. Addressing the Stereochemistry of Complex Organic Molecules by Density Functional Theory-NMR: Vannusal B in Retrospective. *J. Am. Chem. Soc.* **2011**, *133*, 6072–6077.

[328] See, e.g.: (a) Efange, S. M. N.; Brun, R.; Wittlin, S.; Connolly, J. D.; Hoye, T. R.; McAkam, T.; Makolo, F. L.; Mbah, J. A.; Nelson, D. P.; Nyongbela, K. D.; Wirmum, C. K. Okundoperoxide, a Bicyclic Cyclofarnesylsesquiterpene Endoperoxide from *Scleria striatinux* with Antiplasmodial Activity. *J. Nat. Prod.* **2009**, *72*, 280–283. (b) Hoye, T. R.; Dvornikovs, V.; Fine, J. M.; Anderson, K. R.; Jeffrey, C. S.; Muddiman, D. C.; Shao, F.; Sorensen, P. W.; Wang, J. Details of the Structure Determination of the Sulfated Steroids PSDS and PADS: New Components of the Sea Lamprey (*Petromyzon marinus*) Migratory Pheromone. *J. Org. Chem.* **2007**, *72*, 7544–7550. (c) Sorensen, P. W.; Fine, J. M.; Dvornikovs, V.; Jeffrey, C. S.; Shao, F.; Wang, J.; Vrieze, L. A.; Anderson, K. R.; Hoye, T. R. Mixture of New Sulfated Steroids Functions as a Migratory Pheromone in the Sea Lamprey. *Nat. Chem. Biol.* **2005**, *1*, 324–328. (d) Ayyad, S. N.; Judd, A. S.; Shier, W. T.; Hoye, T. R. Otteliones A and B: Potently Cytotoxic 4-Methylene-2-cyclohexenones from *Ottelia alismoides*. *J. Org. Chem.* **1998**, *63*, 8102–8106. (e) Rieser, M. J.; Hui, Y.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. Determination of Absolute Configuration of Stereogenic Carbinol Centers in Annonaceous Acetogenins by ^{1}H- and ^{19}F-NMR Analysis of Mosher Ester Derivatives. *J. Am. Chem. Soc.* **1992**, *114*, 10203–10213.

[329] E.g.: Hoye, T. R.; Hanson, P. R. Assigning the Relative Stereochemistry between C(2) and C(4) of the 2-Acetonyl-4-alkylbutyrolactone Substructures of the Appropriate Annonaceous Acetogenins. *J. Org. Chem.* **1991**, *56*, 5092–5095.

[330] (a) Hoye, T. R.; Hanson, P. R.; Vyvyan, J. R. A Practical Guide to First-Order Multiplet Analysis in ^{1}H NMR Spectroscopy. *J. Org. Chem.* **1994**, *59*, 4096–4103. (b) Hoye, T. R.; Zhao, H. A Method for Easily Determining Coupling Constant Values: An Addendum to "A Practical Guide to First-Order Multiplet Analysis in ^{1}H NMR Spectroscopy." *J. Org. Chem.* **2002**, *67*, 4014–4016.

[331] Hoye, T. R.; Ayyad, S. N.; Eklov, B. M.; Hashish, N. E.; Shier, W. T.; El Sayed, K. A.; Hamann, M. T. Toward Computing Relative Configurations: 16-*epi*-Latrunculin B, a New Stereoisomer of the Actin Polymerization Inhibitor Latrunculin B. *J. Am. Chem. Soc.* **2002**, *124*, 7405–7410.

[332] Wiitala, K. W. Modeling Proton and Carbon Chemical Shifts Using Density Functional Theory: Relevance to Determining Relative Configuration. Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2007**.

[333] Wiitala, K. W.; Hoye, T. R.; Cramer, C. J. Hybrid Density Functional Methods Empirically Optimized for the Computation of ^{13}C and ^{1}H NMR Chemical Shifts in Chloroform Solution. *J. Chem. Theory Comput.* **2006**, *2*, 1085–1092.

[334] Wiitala, K. W.; Al-Rashid, Z. F.; Dvornikovs, V.; Hoye, T. R.; Cramer, C. J. Evaluation of Various DFT Protocols for Computing ^{1}H and ^{13}C Chemical Shifts to Distinguish Stereoisomers: Diastereomeric 2-, 3-, and 4-Methylcyclohexanols as a Test Set. *J. Phys. Org. Chem.* **2007**, *20*, 345–354.

[335] Wiitala, K. W.; Cramer, C. J.; Hoye, T. R. Comparison of Various Density Functional Methods for Distinguishing Stereoisomers Based on Computed ^{1}H or ^{13}C NMR Chemical Shifts Using Diastereomeric Penam β-Lactams as a Test Set. *Magn. Reson. Chem.* **2007**, *45*, 819–829.

[336] Combeau, C.; Provost, J.; Lancelin, F.; Tournoux, Y.; Prod'homme, F.; Herman, F.; Lavelle, F.; Leboul, J.; Vuilhorgne, M. RPR112378 and RPR115781: Two Representatives of a New Family of Microtubule Assembly Inhibitors. *Mol. Pharmacol.* **2000**, *57*, 553–563.

[337] Lewis, H. J. Studies Related to the Ottelione Family of Natural Products. Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2005**.

[338] Kabrhel, J. E. Part I: Is a Cope Rearrangement Viable as the Key Feature in the Biosynthesis of (+)-Ottelione A? Part II: The No-D Study of the n-BuLi

Oxidation of 1,5-Cyclooctadiene. Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2006**.

[339] Murray, D. F.; Baum, M. W.; Jones, Jr., M. Thermal Rearrangement of 3-Methylenespiro[5.6]dodeca-1,4,9-triene and Spiro[5.6]dodeca-1,4,9-trien-3-one. *J. Org. Chem.* **1986**, *51*, 1–7.

[341] (a) Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-class Functionals and 12 Other Functionals. *Theor. Chem. Acc.* **2008**, *120*, 215–241. (b) Zhao, Y.; Truhlar, D. G. Density Functionals with Broad Applicability in Chemistry. *Acc. Chem. Res.* **2008**, *41*, 157–167.

[342] E.g.: Rablen, P. R.; Pearlman, S. A.; Finkbiner, J. A Comparison of Density Functional Methods for the Estimation of Proton Chemical Shifts with Chemical Accuracy. *J. Phys. Chem. A* **1999**, *103*, 7357–7363.

[343] MacroModel, version 9.7, Schrödinger, LCC, New York, NY, **2009**.

[344] Maestro, version 9.0, Schrödinger, LCC, New York, NY, **2009**.

[345] Chang, G.; Guida, W. C.; Still, W. C. An Internal Coordinate Monte Carlo Method for Searching Conformational Space. *J. Am. Chem. Soc.* **1989**, *111*, 4379-4386.

[346] Gaussian 09, Revision A.1, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, **2009**.

[348] (a) Miertus, S.; Scrocco, E.; Tomasi, J. Electrostatic Interaction of a Solute with a Continuum. A Direct Utilization of Ab Initio Molecular Potentials for the Prevision of Solvent Effects. *Chem. Phys.* **1981**, *55*, 117-129. (b) Cancès, E.; Mennucci, B.; Tomasi, J. A New Integral Equation Formalism for the Polarizable Continuum Model: Theoretical Background and Applications to Isotropic and Anisotropic Dielectrics. *J. Chem. Phys.* **1997**, *107*, 3032-3041.

[349] Barone, V.; Cossi, M.; Tomasi, J. A New Definition of Cavities for the Computation of Solvation Free Energies by the Polarizable Continuum Model. *J. Chem. Phys.* **1997**, *107*, 3210-3220.

[350] Bondi, A. van der Waals Volumes and Radii. *J. Phys. Chem.* **1964**, *68*, 441-451.

[351] Sarotti, A. M.; Pellegrinet, S. C. A Multi-standard Approach for GIAO ^{13}C NMR Calculations. *J. Org. Chem.* **2009**, *74*, 7254–7260.

[352] Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. NMR Chemical Shifts of Common Laboratory Solvents as Trace Impurities. *J. Org. Chem.* **1997**, *62*, 7512–7515.

[353] Reproduced in part with permission from "Case Study of Empirical and Computational Chemical Shift Analyses: Reassignment of the Relative Configuration of Phomopsichalasin to that of Diaporthichalasin," Brown, S. G.; Jansma, M. J.; Hoye, T. R. *J. Nat. Prod.* **2012**, *ASAP* [Publication Date (Web): June 25, 2012]. Copyright © 2012 The American Chemical Society and American Society of Pharmacognosy.

[354] Horn W. S.; Simmonds, M. S. J.; Schwartz, R. E.; Blaney, W. M. Phomopsichalasin, a Novel Antimicrobial Agent from an Endophytic *Phomopsis* sp. *Tetrahedron* **1995**, *51*, 3969–3978.

[355] Pornpakakul, S.; Roengsumran, S.; Deechangvipart, S.; Petsom, A.; Muangsin, N.; Ngamrojnavanich, N.; Sriubolmas, N.; Chaichit, N.; Ohta, T. Diaporthichalasin, a Novel CYP3A4 Inhibitor from an Endophytic *Diaporthe* sp. *Tetrahedron Lett.* **2007**, *48*, 651–655.

[356] Sizova, E. P. Second Generation Synthesis of UCS1025A. Synthetic Efforts Toward Total Syntheses of CJ-16,264 and Phomopsichalasin. Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2009**.

[357] Dalling, D. K.; Curtis, J.; Grant, D. M. Deuterium Chemical Shifts and Chemical Shift Parameters in Methylcyclohexanes. *J. Org. Chem.* **1986**, *51*, 136–142.

[358] Jensen, F. Basis Set Convergence of Nuclear Magnetic Shielding Constants Calculated by Density Functional Methods. *J. Chem. Theory Comput.* **2008**, *4*, 719–727.

[359] Smith, S. G.; Goodman, J. M. Assigning Stereochemistry to Single Diastereomers by GIAO NMR Calculation: The DP4 Probability. *J. Am. Chem. Soc.* **2010**, *132*, 12946–12959.

[360] For recent use of DP4 probability in the context of natural product structure elucidation, see: (a) Paterson, I.; Dalby, S. M.; Roberts, J. C.; Naylor, G. J.; Guzmán, E. A.; Isbrucker, R.; Pitts, T. P.; Linley, P.; Divlianska, D.; Reed, J. K.; Wright, A. E. Leiodermatolide, a Potent Antimitotic Macrolide from the Marine Sponge *Leiodermatium* sp. *Angew. Chem. Int. Ed.* **2011**, *50*, 3219–3223. (b) Lodewyk, M. W.; Tantillo, D. J. Prediction of the Structure of Nobilisitine A Using Computed NMR Chemical Shifts. *J. Nat. Prod.* **2011**, *74*, 1339–1343. (c) Wyche, T. P.; Hou, Y.; Braun, D.; Cohen, H. C.; Xiong, M. P.; Bugni, T. S. First Natural Analogs of the Cytotoxic Thiodepsipeptide Thiocoraline A from a Marine *Verrucosispora* sp. *J. Org. Chem.* **2011**, *76*, 6542–6547.

[361] http://www-jmg.ch.cam.ac.uk/tools/nmr/DP4/

[362] Akhila, A.; Tewari, R. Chemistry of Patchouli Oil: A Review. *CROMAP* **1984**, *6*, 38–54.

[363] Kraft, P.; Weymuth, C.; Nussbaumer, C. Total Synthesis and Olfactory Evaluation of (1*R**,3*S**,6*S**,7*S**,8*S**)-3-Hydroxy-6,8-dimethyltricyclo[5.3.1.$0^{3,8}$]-undecan-2-one: A New Synthetic Route to the Patchoulol Skeleton. *Eur. J. Org. Chem.* **2006**, 1403–1412.

[364] E.g.: (a) Buré, C. M.; Sellier, N. M. Analysis of the Essential Oil of Indonesian Patchouli (*Pogostemon cablin* Benth.) Using GC/MS (EI/CI). *J. Essent. Oil Res.* **2004**, *16*, 17–19. (b) Deguerry, F.; Pastore, L.; Wu, S.; Clark, A.; Chappell, J.; Schalk, M. The Diverse Sesquiterpene Profile of Patchouli, *Pogostemon cablin*, is Correlated with a Limited Number of Sesquiterpene Synthases. *Arch. Biochem. Biophys.* **2006**, *454*, 123–136.

[365] Gal, H. Ueber ein Homologes des Borneocamphers. *Justus Liebigs Ann. Chem.* **1869**, *150*, 374–376.

[366] For a concise summary of these early studies, see: Simonsen, J.; Barton, D. H. R. Alcohols. *The Terpenes*, 2nd ed.; Cambridge University Press: London, **1952**; Vol. III, pp 175–178.

[367] Treibs, W. Über bi- und polycyclische Azulene. III. Mitteil.: Der Patchouli-alkahol, ein tricyclischer Azulen-bildner. *Justus Leibigs Ann. Chem.* **1949**, *564*, 141–151.

[368] Büchi, G.; Erickson, R. E.; Wakabayashi, N. Terpenes. XVI. Constitution of Patchouli Alcohol and Absolute Configuration of Cedrene. *J. Am. Chem. Soc.* **1961**, *83*, 927–938.

[369] Büchi, G.; MacLeod, Jr., W. D. Synthesis of Patchouli Alcohol. *J. Am. Chem. Soc.* **1962**, *84*, 3205–3206.

[370] Dobler, M.; Dunitz, J. D.; Gubler, B.; Weber, H. P.; Büchi, G.; Padilla O., J. The Structure of Patchouli Alcohol. *Proc. Chem. Soc.* **1963**, 383.

[371] Büchi, G.; MacLeod, Jr., W. D.; Padilla O., J. Terpenes. XIX. Synthesis of Patchouli Alcohol. *J. Am. Chem. Soc.* **1964**, *86*, 4438–4444.

[372] (a) Danishefsky, S.; Dumas, D. The Total Synthesis of Racemic Patchouli and *epi*-Patchouli Alcohol. *Chem. Commun. (London)* **1968**, 1287–1288. (b) Mirrington, R. N.; Schmalzl, K. J. Studies with Bicyclo[2.2.2]octenes. V. The Total Synthesis of (±)-Patchouli Alcohol. *J. Org. Chem.* **1972**, *37*, 2871–2877. (c) Näf, F.; Ohloff, G. A Short Stereoselective Total Synthesis of Racemic Patchouli Alcohol. *Helv. Chim. Acta.* **1974**, *57*, 1868–1870. (d) Yamada, K.; Kyotani, Y.; Manabe, S.; Suzuki, M. Total Synthesis of (±)-Patchouli Alcohol and (±)-Seychellene via a Common Homoisotwistane Intermediate. *Tetrahedron* **1979**, *35*, 293–298. (e) Bertrand, M.; Teisseire, P.; Pelerin, G. Sur une Solution de Rechange a la Cyclisation des ε-Halogenocetones–Application a la Synthese du (±)-Patchoulol. *Tetrahedron Lett.* **1980**, *21*, 2055–2056. (f) Näf, F.; Decorzant, R.; Giersch, W.; Ohloff, G. A Stereocontrolled Access to (±)-, (–)-, and (+)-Patchouli Alcohol. *Helv. Chim. Acta.* **1981**, *64*, 1387–1397. (g) Cory, R. M.; Bailey, M. D.; Tse, D. W. C. A Divergent Approach to Patchouli Sesquiterpenes: Synthesis of 3-Oxopatchouli Alcohol, 5-Oxo-7-hydroxy-13-norcycloseychellene, 6-Methoxy-4,12-dehydro-13-norcycloseychellene and Patchouli Alcohol. *Tetrahedron Lett.* **1990**, *31*, 6839–6842. (h) Magee, T. V.; Stork, G.; Fludzinski, P. A Total Synthesis of *rac*-Patchouli Alcohol. *Tetrahedron Lett.* **1995**, *36*, 7607–7610. (i) Srikrishna, A.; Satyanarayana, G. An Enantiospecific Total Synthesis of (–)-Patchouli Alcohol. *Tetrahedron: Asymmetry* **2005**, *16*, 3992–3997.

[373] Kaliappan, K. P.; Subba Rao, G. S. R. Synthesis based on Cyclohexadienes. Part 22. Formal Syntheses of Patchouli Alcohol and Norpatchoulenol. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1385–1389.

[374] Barton, D. H. R.; Belœil, J. –C.; Billion, A.; Boivin, J.; Lallemand, J. –Y.; Mergui, S. 30. Functionalisation of Saturated Hydrocarbons. Part 9. Oxidation of Patchouli Alcohol by the 'Gif System': Isolation and Organoleptic Properties of Three New Ketonic Derivatives. *Helv. Chim. Acta.* **1987**, *70*, 273–280.

[375] Faraldos, J. A.; Wu, S.; Chappell, J.; Coates, R. M. Doubly Deuterium-labeled Patchouli Alcohol from Cyclization of Singly-labeled [2-$^{2}H_{1}$]Farnesyl Diphosphate Catalyzed by Recombinant Patchoulol Synthase. *J. Am. Chem. Soc.* **2010**, *132*, 2998–3008.

[376] Still, W. C.; Kahn, M.; Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *J. Org. Chem.* **1978**, *43*, 2923–2925.

[377] Stang, P. J.; Dueber, T. E. Preparation of Vinyl Trifluoromethanesulfonates: 3-Methyl-2-buten-2-yl Triflate. *Org. Synth.* **1974**, *54*, 79–83.

[378] Newman, M. S.; Evans, Jr., F. J. The Reformatsky Reaction: Effect of Alkyl Group in Alkyl α-Bromopropionates. *J. Am. Chem. Soc.* **1955**, *77*, 946–947.

[379] Burchat, A. F.; Chong, J. M.; Nielsen, N. Titration of Alkyllithiums with a Simple Reagent to a Blue Endpoint. *J. Organomet. Chem.* **1997**, *542*, 281–283.

[380] Hoye, T. R.; Eklov, B. M.; Voloshin, M. No-D NMR Spectroscopy as a Convenient Method for Titering Organolithium (RLi), RMgX, and LDA Solutions. *Org. Lett.* **2004**, *6*, 2567–2570.

[381] Hoye, T. R.; Aspaas, A. W.; Eklov, B. M.; Ryba, T. D. Reaction Titration: A Convenient Method for Titering Reactive Hydride Agents (Red-Al, $LiAlH_4$, DIBALH, L-Selectride, NaH, and KH) by No-D NMR Spectroscopy. *Org. Lett.* **2005**, *7*, 2205–2208.

[382] Brown, H. C.; Groot, C. A Convenient Procedure for the Preparation of Deuterium Chloride. *J. Am. Chem. Soc.* **1942**, *64*, 2223–2224.

[383] Brown, H. C.; Mandal, A. K.; Kulkarni, S. U. Hydroboration. 45. New, Convenient Preparations of Representative Borane Reagents Utilizing Borane–Methyl Sulfide. *J. Org. Chem.* **1977**, *42*, 1392–1398.

[384] Frigerio, M.; Santagostino, M.; Sputore, S. A User-Friendly Entry to 2-Iodoxybenzoic Acid (IBX). *J. Org. Chem.* **1999**, *64*, 4537–4538.

[385] Ireland, R. E.; Liu, L. An Improved Procedure for the Preparation of the Dess-Martin Periodinane. *J. Org. Chem.* **1993**, *58*, 2899.

[386] Molander, G. A.; Dehmel, F. Formal Total Synthesis of Oximidine II via a Suzuki-Type Cross-Coupling Macrocyclization Employing Potassium Organotrifluoroborates. *J. Am. Chem. Soc.* **2004**, *126*, 10313–10318. In this report, the more stable and easily handled BH_3•SMe_2 was employed instead of BH_3•THF.

[387] Reist, E. J.; Junga, I. G.; Baker, B. R. Potential Anticancer Agents. XXXVII. Monofunctional Aziridines Related to Tetramin. *J. Org. Chem.* **1960**, *25*, 1673–1674.

[388] [*MJJ-I-191/212/III-262*] Carothers, W. H.; Coffman, D. D. Homologs of Chloroprene and Their Polymers (Second Paper on New Synthetic Rubbers). *J. Am. Chem. Soc.* **1932**, *54*, 4071–4076.

[389] Cf.: Molander, G. A.; Singaram, B.; Brown, H. C. Conjugate Addition–Elimination in the Reaction of *B*-1-Alkenyl-9-borabicyclo[3.3.1]nonanes with 4-Methoxy-3-buten-2-one. A Convenient New Route to Conjugated Dienones. *J. Org. Chem.* **1984**, *49*, 5024–5025.

[392] Hu, H.; Faraldos, J. A.; Coates, R. M. Scope and Mechanism of Intramolecular Aziridination of Cyclopent-3-enyl-methylamines to 1-Azatricyclo[2.2.1.$0^{2,6}$]heptanes with Lead Tetraacetate. *J. Am. Chem. Soc.* **2009**, *131*, 11998–12006.

[394] Kobayashi, Y.; Murugesh, M. G.; Nakano, M.; Takahisa, E.; Usmani, S. B.; Ainai, T. A New Method for Installation of Aryl and Alkenyl Groups onto a Cyclopentene Ring and Synthesis of Prostaglandins. *J. Org. Chem.* **2002**, *67*, 7110–7123.

[395] ^{1}H NMR data: Ghosh, A. K.; Chapsal, B. D.; Baldridge, A.; Ide, K.; Koh, Y.; Mitsuya, H. Design and Synthesis of Stereochemically Defined Novel Spirocyclic P2-Ligands for HIV-1 Protease Inhibitors. *Org. Lett.* **2008**, *10*, 5135–5138. ^{13}C NMR data: Myers, A. G.; Glatthar, R.; Hammond, M.; Harrington, P. M.; Kuo, E. Y.; Liang, J.; Schaus, S. E.; Wu, Y.; Xiang, J. –N. Development of an Enantioselective Synthetic Route to Neocarzinostatin Chromophore and Its Use for Multiple Radioisotopic Incorporation. *J. Am. Chem. Soc.* **2002**, *124*, 5380–5401.

[397] Cameron, A. G.; Hewson, A. T. Synthesis of 1-Alkylthiovinyl- and 1-Arylthiovinyl-phosphonium Salts and Their Use in the Formation of Cyclopentanes. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2979–2982.

[401] Prepared according to the literature procedure [*MJJ-IV-91*]: Pal, P. R.; Skinner, C. G.; Dennis, R. L.; Shive, W. Cyclopentanealanine and 1-Cyclopentene-1-alanine,

Inhibitory Analogs of Leucine and Phenylalanine. *J. Am. Chem. Soc.* **1956**, *78*, 5116–5118.

[403] Buckles, R. E.; Harris, L. The Kinetics of the Reactions of Quaternary Ammonium Tribromides with Crotonic Acid in Ethylene Chloride. *J. Am. Chem. Soc.* **1957**, *79*, 886–889.

[404] Emmons, W. D.; Pagano, A. S. Peroxytrifluoroacetic Acid. IV. The Epoxidation of Olefins. *J. Am. Chem. Soc.* **1955**, *77*, 89–92.

[405] SMART V5.054, Bruker Analytical X-Ray Systems, Madison, WI (2001).

[406] Blessing, R. An Empirical Correction for Absorption Anisotropy. *Acta Cryst.* **1995**, *A51*, 33–38.

[407] SAINT+ V6.45, Bruker Analytical X-Ray Systems, Madison, WI (2003).

[408] SHELXTL V6.14, Bruker Analytical X-Ray Systems, Madison, WI (2000).

[409] APEX-II, Bruker Analytical X-Ray Systems, Madison, WI (2008).

[410] SAINT+ V7.68, Bruker Analytical X-Ray Systems, Madison, WI (2003).

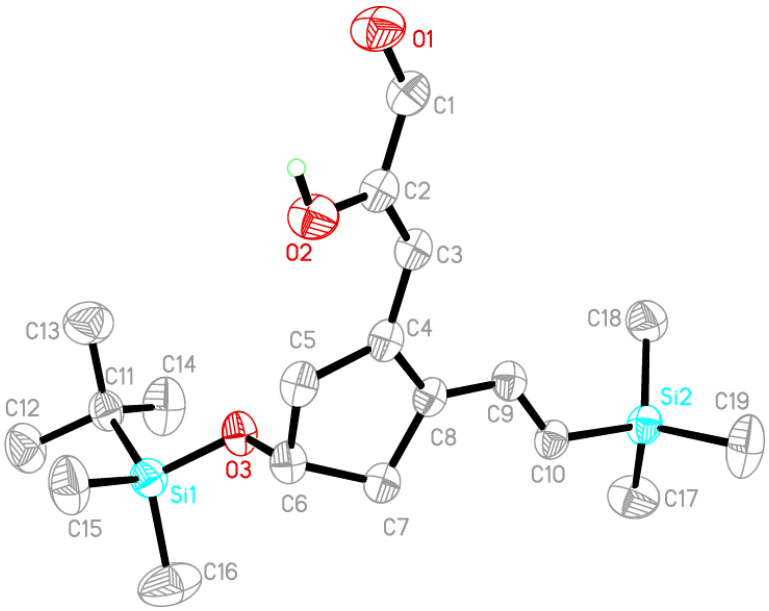
[411] SHELXTL V2008/4, Bruker Analytical X-Ray Systems, Madison, WI (2000).

* * * * * *

APPENDIX A:

CRYSTAL STRUCTURE DATA FOR **2244**

$C_{19}\ H_{34}\ O_3\ Si_2$



Report generated February 1, 2012

[REFERENCE NUMBER: 12016_0m]

X-Ray Crystallographic Laboratory
Department of Chemistry
University of Minnesota
207 Pleasant Street SE
Minneapolis, MN 55455

DATA COLLECTION: A crystal (approximate dimensions 0.40 x 0.17 x 0.09 mm^3) was placed onto the tip of a 0.1 mm diameter glass capillary and mounted on a Bruker APEX-II CCD diffractometer for a data collection at 173(2) K.[405] A preliminary set of cell constants was calculated from reflections harvested from three sets of 20 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed. This produced initial orientation matrices determined from 109 reflections. The data collection was carried out using MoKα radiation (graphite monochromator) with a frame time of 90 seconds and a detector distance of 6.0 cm. A randomly oriented region of reciprocal space was surveyed to the extent of one sphere and to a resolution of 0.79 Å. Four major sections of frames were collected with 0.50° steps in ω at four different ϕ settings and a detector position of –28° in 2θ. The intensity data were corrected for absorption and decay (SADABS).[406] Final cell constants were calculated from the xyz centroids of 4355 strong reflections from the actual data collection after integration (SAINT).[407] Refer to Table A–1 for additional crystal and refinement information.

STRUCTURE SOLUTION AND REFINEMENT: The structure was solved using SHELXS-97 (Sheldrick, 1990)[408] and refined using SHELXL-97 (Sheldrick, 1997).[408] The space group P-1 was determined based on systematic absences and intensity statistics. A direct-methods solution was calculated which provided most non-hydrogen atoms from the E-map. Full-matrix least squares / difference Fourier cycles were performed which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms not involved in hydrogen bonging were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. H2 was located on an E-map and was refined with isotropic displacement parameters. The final full matrix least squares refinement converged to $R1 = 0.0439$ and $wR2 = 0.1370$ (F^2, all data).

STRUCTURE DESCRIPTION: The structure is the one suggested. Both enantiomers are present in the centrosymmetric cell (space group P-1). The α-hydroxy aldehyde moiety forms a hydrogen bonded ring with another molecule in an adjacent unit cell. The two molecules involved in the hydrogen bonding are related by an inversion center.

Data collection and structure solution were conducted at the X-Ray Crystallographic Laboratory, S146 Kolthoff Hall, Department of Chemistry, University of Minnesota. All calculations were performed using Pentium computers using the current SHELXTL suite of programs.

---

[405] SMART V5.054, Bruker Analytical X-Ray Systems, Madison, WI (2001).

[406] Blessing, R. An Empirical Correction for Absorption Anisotropy. *Acta Cryst.* **1995**, *A51*, 33–38.

[407] SAINT+ V6.45, Bruker Analytical X-Ray Systems, Madison, WI (2003).

[408] SHELXTL V6.14, Bruker Analytical X-Ray Systems, Madison, WI (2000).

Table A–1 | Crystal data and structure refinement for 12016_0m.

Identification code	12016_0m	
Empirical formula	$C_{19}\ H_{34}\ O_3\ Si_2$	
Formula weight	366.64	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.6142(18) Å	α = 76.673(3)°
	b = 10.880(3) Å	β = 88.242(3)°
	c = 13.819(3) Å	γ = 80.758(3)°
Volume	1099.5(4) Å^3	
Z	2	
Density (calculated)	1.107 Mg/m^3	
Absorption coefficient	0.174 mm^{-1}	
F(000)	400	
Crystal color, morphology	yellow, Block	
Crystal size	0.40 x 0.17 x 0.09 mm^3	
Theta range for data collection	1.51 to 26.73°	
Index ranges	$-9 \le h \le 9$, $-13 \le k \le 13$, $-17 \le l \le 17$	
Reflections collected	11677	
Independent reflections	4633 [R(int) = 0.0395]	
Observed reflections	3121	
Completeness to theta = 26.73°	98.8%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9852 and 0.9330	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4633 / 0 / 229	
Goodness-of-fit on F^2	1.034	
Final R indices [I>2sigma(I)]	R1 = 0.0439, wR2 = 0.1127	
R indices (all data)	R1 = 0.0782, wR2 = 0.1372	
Largest diff. peak and hole	0.350 and –0.374 e.Å^{-3}	

Table A–2 | Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 12016_0m. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
Si2	3687(1)	1968(1)	3037(1)	37(1)
Si1	1515(1)	2873(1)	8625(1)	36(1)
O1	–825(2)	9578(1)	4101(1)	48(1)
O2	1477(2)	8017(2)	5536(1)	42(1)
O3	1669(2)	3445(1)	7422(1)	36(1)
C1	–331(3)	8463(2)	4075(2)	37(1)
C2	866(3)	7582(2)	4794(2)	32(1)
C3	1290(3)	6355(2)	4716(2)	32(1)
C4	2279(3)	5311(2)	5419(2)	30(1)
C5	2682(3)	5356(2)	6471(2)	35(1)
C6	3214(3)	3961(2)	6992(2)	33(1)
C7	3929(3)	3312(2)	6159(2)	34(1)
C8	2963(3)	4145(2)	5245(2)	29(1)
C9	2856(3)	3711(2)	4337(2)	32(1)
C10	3761(3)	2625(2)	4160(2)	34(1)
C11	–846(3)	2600(2)	8875(2)	39(1)
C12	–1055(4)	2079(3)	10000(2)	59(1)
C13	–2134(4)	3849(3)	8571(2)	61(1)
C14	–1360(4)	1639(3)	8332(2)	67(1)
C15	2069(4)	4053(3)	9301(2)	60(1)
C16	3091(4)	1364(3)	9000(3)	80(1)
C17	4114(4)	201(2)	3463(2)	61(1)
C18	1483(4)	2491(3)	2407(2)	54(1)
C19	5442(4)	2493(3)	2149(2)	68(1)

Table A–3 | Selected bond lengths [Å] and angles [°] for 12016_0m.

O(1)–C(1)	1.219(3)	C(4)–C(8)	1.363(3)
O(2)–C(2)	1.347(2)	C(9)–C(10)	1.338(3)
O(2)–H(2)	0.82(3)	C(2)–O(2)–H(2)	110.2(19)

Table A–4 | Selected torsion angles [°] for 12016_0m.

O1–C1–C2–O2	–0.2(3)	O3–C6–C7–C8	90.18(19)
O1–C1–C2–C3	178.0(2)	C5–C6–C7–C8	–27.1(2)
O2–C2–C3–C4	6.1(3)	C3–C4–C8–C9	0.2(3)
C1–C2–C3–C4	–172.0(2)	C5–C4–C8–C9	179.44(18)
C2–C3–C4–C8	–167.3(2)	C3–C4–C8–C7	179.41(18)
C2–C3–C4–C5	13.6(3)	C5–C4–C8–C7	–1.4(2)
C8–C4–C5–C6	–16.1(2)	C6–C7–C8–C4	18.1(2)
C3–C4–C5–C6	163.14(18)	C6–C7–C8–C9	–162.63(17)
C4–C5–C6–O3	–90.95(19)	C4–C8–C9–C10	170.0(2)
C4–C5–C6–C7	26.3(2)	C7–C8–C9–C10	–9.1(3)

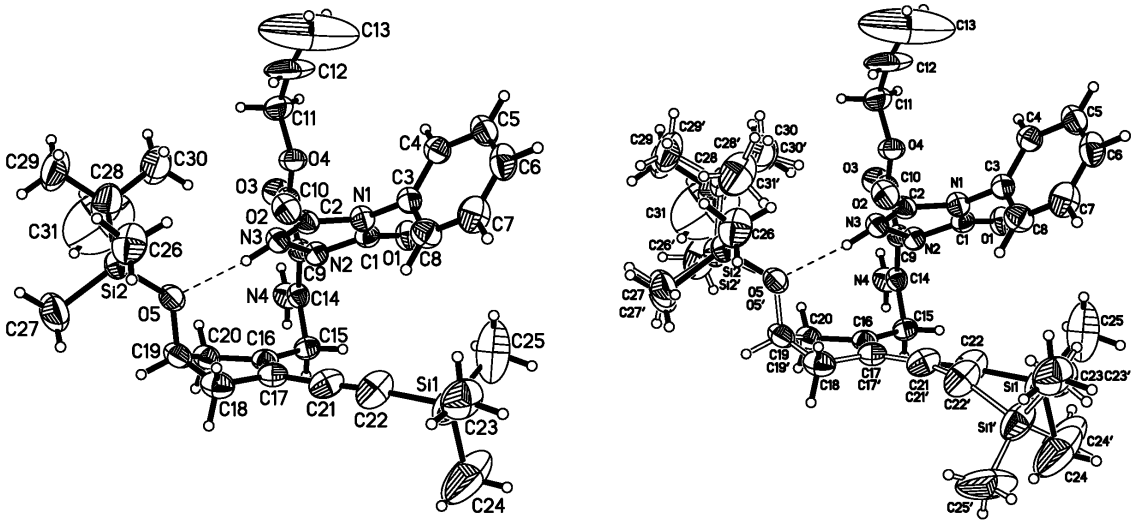
Table A–5 | Hydrogen bonds for 12016_0m [Å and °].

D–H	d(D–H)	d(H…A)	d(D…A)	<(DHA)	A
O2–H2	0.82(3)	2.34(3)	2.756(2)	112(2)	O1
O2–H2	0.82(3)	1.99(3)	2.742(2)	153(3)	O1 [–x,–y+2,–z+1]

APPENDIX B:

CRYSTAL STRUCTURE DATA FOR **2299**

$C_{31}\ H_{44}\ N_4\ O_5\ Si_2$



Report generated June 29, 2012

[REFERENCE NUMBER: 12114c]

X-Ray Crystallographic Laboratory
Department of Chemistry
University of Minnesota
207 Pleasant Street SE
Minneapolis, MN 55455

DATA COLLECTION: A crystal (approximate dimensions 0.40 x 0.35 x 0.09 mm^3) was placed onto the tip of a 0.1 mm diameter glass capillary and mounted on a Bruker APEX-II CCD diffractometer for a data collection at 173(2) K.[409] A preliminary set of cell constants was calculated from reflections harvested from three sets of 20 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed. This produced initial orientation matrices determined from 73 reflections. The data collection was carried out using MoKα radiation (graphite monochromator) with a frame time of 60 seconds and a detector distance of 6.0 cm. A randomly oriented region of reciprocal space was surveyed to the extent of one sphere and to a resolution of 0.84 Å. Four major sections of frames were collected with 0.30° steps in ω at four different ϕ settings and a detector position of –28° in 2θ. The intensity data were corrected for absorption and decay (SADABS).[406] Final cell constants were calculated from 2994 strong reflections from the actual data collection after integration (SAINT).[410] Refer to Table B–1 for additional crystal and refinement information.

STRUCTURE SOLUTION AND REFINEMENT: The structure was solved using SHELXS-97 (Sheldrick, 1990)[411] and refined using SHELXL-97 (Sheldrick, 1997).[411] The space group $P2_1/n$ was determined based on systematic absences and intensity statistics. A direct-methods solution was calculated which provided most non-hydrogen atoms from the E-map. Full-matrix least squares / difference Fourier cycles were performed which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. The final full matrix least squares refinement converged to $R1 = 0.0540$ and $wR2 = 0.1579$ (F^2, all data).

STRUCTURE DESCRIPTION: The structure is the one suggested. Both Si groups are disordered. Copious restraints and constraints were applied in order to arrive to a reasonable result. The pivot atoms of the disordered groups were C21 and O5, respectively. Each had a major and minor disorder component. One drawing is provided showing the major components without minor components. Another shows all disorder together. This structure result essentially demonstrates the point of concept for this material. If this result is published, then do be cautious to present it accordingly.

Data collection and structure solution were conducted at the X-Ray Crystallographic Laboratory, 192 Kolthoff Hall, Department of Chemistry, University of Minnesota. All calculations were performed using Pentium computers using the current SHELXTL suite of programs.

---

[409] APEX-II, Bruker Analytical X-Ray Systems, Madison, WI (2008).

[410] SAINT+ V7.68, Bruker Analytical X-Ray Systems, Madison, WI (2003).

[411] SHELXTL V2008/4, Bruker Analytical X-Ray Systems, Madison, WI (2000).

Table B–1 | Crystal data and structure refinement for 12114c.

Identification code	12114c	
Empirical formula	$C_{31}\ H_{44}\ N_4\ O_5\ Si_2$	
Formula weight	608.88	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 13.7551(14) Å	a = 90°
	b = 16.1198(17) Å	b = 109.370(1)°
	c = 16.9803(18) Å	g = 90°
Volume	3551.9(6) Å^3	
Z	4	
Density (calculated)	1.139 Mg/m^3	
Absorption coefficient	0.140 mm^{-1}	
F(000)	1304	
Crystal color, morphology	Colorless, Plate	
Crystal size	0.40 x 0.35 x 0.09 mm^3	
Theta range for data collection	1.79 to 26.37°	
Index ranges	$-17 \le h \le 16$, $0 \le k \le 20$, $0 \le l \le 21$	
Reflections collected	41262	
Independent reflections	7264 [R(int) = 0.0404]	
Observed reflections	5114	
Completeness to theta = 26.37°	100.0%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9875 and 0.9461	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7264 / 144 / 471	
Goodness-of-fit on F^2	1.037	
Final R indices [I>2sigma(I)]	R1 = 0.0540, wR2 = 0.1375	
R indices (all data)	R1 = 0.0813, wR2 = 0.1579	
Largest diff. peak and hole	0.601 and –0.396 e.Å^{-3}	

Table B–2 | Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 12114c. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
N1	595(1)	1958(1)	222(1)	36(1)
C1	1179(2)	1610(1)	980(1)	34(1)
O1	1620(1)	949(1)	1094(1)	44(1)
N2	1157(1)	2181(1)	1576(1)	34(1)
N3	438(1)	2811(1)	1174(1)	36(1)
C2	146(2)	2703(1)	339(1)	36(1)
O2	–406(1)	3150(1)	–207(1)	46(1)
C3	480(2)	1613(1)	–581(1)	35(1)
C4	–53(2)	879(1)	–824(1)	40(1)
C5	–171(2)	564(2)	–1609(2)	49(1)
C6	229(2)	978(2)	–2138(2)	53(1)
C7	760(2)	1710(2)	–1888(2)	57(1)
C8	890(2)	2029(2)	–1105(2)	47(1)
C9	1242(2)	1934(1)	2399(1)	35(1)
C10	381(2)	1511(1)	2527(1)	40(1)
O3	358(1)	1243(1)	3190(1)	52(1)
O4	–420(1)	1442(1)	1807(1)	44(1)
C11	–1362(2)	1088(2)	1862(2)	56(1)
C12	–2088(3)	1046(3)	984(3)	117(2)
C13	–2587(6)	643(7)	559(5)	299(7)
C14	2156(2)	2089(1)	3024(1)	37(1)
N4	2351(2)	1842(1)	3811(1)	47(1)
C15	2978(2)	2592(1)	2837(1)	40(1)
C16	2596(2)	3449(1)	2558(1)	38(1)
C18	2162(2)	4691(2)	1794(2)	52(1)
C20	2152(2)	4010(1)	3057(1)	43(1)
C17	2595(2)	3826(2)	1854(1)	43(1)
C21	3000(2)	3472(2)	1258(2)	54(1)
C22	3348(4)	3123(3)	775(3)	69(1)
Si1	3998(1)	2593(1)	123(1)	79(1)
C23	3485(4)	3001(3)	–949(2)	85(1)
C24	5391(3)	2797(4)	589(4)	174(3)
C25	3728(4)	1471(2)	143(3)	126(2)
C17'	2595(2)	3826(2)	1854(1)	43(1)
C21'	3000(2)	3472(2)	1258(2)	54(1)
C22'	3396(12)	3368(9)	720(9)	69(1)

Si1'	4285(3)	3323(3)	114(2)	79(1)
C23'	3559(12)	2951(10)	–946(4)	85(1)
C24'	5333(9)	2595(9)	647(13)	174(3)
C25'	4800(12)	4375(6)	77(9)	143(10)
C19	1593(2)	4674(1)	2421(2)	47(1)
O5	548(1)	4397(1)	2016(1)	47(1)
Si2	–535(1)	4942(1)	1770(1)	40(1)
C26	–1061(3)	5095(3)	629(2)	71(1)
C27	–265(4)	5972(2)	2281(6)	84(1)
C28	–1426(3)	4335(3)	2164(3)	86(2)
C29	–2445(3)	4790(5)	2003(5)	109(2)
C30	–1663(6)	3486(3)	1756(5)	140(2)
C31	–960(6)	4202(5)	3104(3)	225(7)
C19'	1593(2)	4674(1)	2421(2)	47(1)
O5'	548(1)	4397(1)	2016(1)	47(1)
Si2'	–386(2)	4829(1)	2326(2)	48(1)
C26'	–127(6)	4619(6)	3447(3)	85(4)
C27'	–381(8)	5964(2)	2171(10)	84(1)
C28'	–1615(4)	4350(5)	1676(4)	69(4)
C29'	–2524(4)	4708(10)	1887(8)	109(2)
C30'	–1614(10)	3416(5)	1812(9)	140(2)
C31'	–1818(6)	4502(7)	750(3)	105(5)

Table B–3 | Selected bond lengths [Å] for 12114c.

N(2)–C(9)	1.419(3)	C(9)–C(10)	1.444(3)
N(2)–N(3)	1.423(2)	C(14)–N(4)	1.333(3)
N(3)–C(2)	1.350(3)	N(4)–H(4B)	0.8800
N(3)–H(3A)	0.910(3)	C(16)–C(17)	1.340(3)
C(9)–C(14)	1.373(3)		

Table B–4 | Selected torsion angles [°] for 12114c.

O1–C1–N2–C9	–29.3(3)	C14–C9–C10–O3	0.0(4)
N1–C1–N2–C9	151.05(18)	N2–C9–C14–N4	–175.82(19)
C9–N2–N3–C2	–153.11(18)	C10–C9–C14–N4	1.9(3)
N2–N3–C2–O2	–174.8(2)	N2–C9–C14–C15	6.8(3)
N1–C3–C4–C5	178.81(19)	N4–C14–C15–C16	–115.9(2)
C1–N2–C9–C14	106.1(2)	C9–C14–C15–C16	61.6(3)
N3–N2–C9–C14	–115.0(2)		

Table B–5 | Hydrogen bonds for 12114c [Å and °].

D–H	d(D–H)	d(H…A)	d(D…A)	<(DHA)	A
N3–H3A	0.910(3)	2.004(5)	2.909(2)	173(2)	O5
N3–H3A	0.910(3)	2.004(5)	2.909(2)	173(2)	O5'
N4–H4B	0.88	2.13	2.765(3)	128.5	O3
N4–H4C	0.88	2.16	2.981(3)	155.4	O2 [x+1/2,–y+1/2,–z+1/2]