BIOSYNTHETIC STUDIES OF OTTELIONE A AND THE STRUCTURAL RE-ANALYSIS OF THE "JONES ISOMERS"

THE STRUCTURAL REASSIGNMENT OF PHOMOPSICHALASIN TO THAT OF DIAPORTHICHALASIN

A DISSERTATION SUBMITTED TO THE FACULTY OF
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To my friends from the "consulate", thank you for making Minnesota my home away from home for the past several years.

Finally to my mother and father, Dothlyn and Albert, your unwavering love and support has enabled the completion of this thesis. Thank you for being devoted parents.

DEDICATION

To my mother and father, Dothlyn and Albert Brown.

ABSTRACT

Part I

Ottelione A, isolated from the fresh water plant *Ottelia alismoides*, is a cytotoxic agent at nanomolar levels against 60 human cancer cell lines. Among other compounds isolated were a group of novel 1,7-diarylheptanoids. We propose that one of these diarylheptanoids shares a biogenetic linkage with ottelione A. Namely, we hypothesize that a spontaneous (i.e., non-enzyme catalyzed) Cope rearrangement, almost entirely unprecedented in nature, is central to the biosynthesis of ottelione A. The successful synthesis of the hypothesized biologically relevant diarylheptanoid has now enabled us to probe its possible biogenetic linkage to ottelione A. During the course of our studies we have also performed the structure reanalysis of two related hydrienone compounds that share the exact same core as ottelione A.

Part II

Phomopsichalasin, a cytochalasin-like secondary metabolite, was isolated from an endophytic fungus *Phomopsis sp.* in 1995. Diporthichalasin, from the endophytic fungus *Diaporthe sp.* Bkk3, was isolated several years later in 2007. Both were assigned different structures and their spectroscopic characterization reported in two different solvents. By way of detailed NMR analysis and pertinent computational models we have demonstrated that the structure originally proposed for Phomopsichalasin was incorrect and is in fact that of the more recently isolated compound Diaporthichalasin.

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List of Abbreviations

Ac	Acetyl
AcCl	Acetyl chloride
AVE	Alyll vinyl ether
Ar	Aryl
9-BBN	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl ($C_6H_5CH_2$-)
Cald	Calculated
CSA	Camphor sulfonic acid
COD	Cyclooctadiene
DBU	Diaza(1,3)bicyclo[5.4.0]undecane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-Dicyanobenzoquinone
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Hünig's Base, Diisopropylethylamine
DMEDA	*N,N'*-Dimethyl-1,2-ethanediamine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	Dimethylsulfoxide
Dppf	1,1´-Bis(diphenylphosphino)ferrocene
Equiv	Equivalent
Et_2O	Diethyl ether

Et_3N	Triethylamine
EtOAc	Ethyl acetate
EVE	Ethyl vinyl ether
FVP	Flash vacuum pyrolysis
GC-MS	Gas chromatography-mass spectrometry
HR ESI-MS	High resolution electrospray ionization-mass spectrometry
HMBC	Hetero-nuclear multiple bond correlation
HMQC	Heteronuclear multiple quantum correhence
IMDA	Intramolecular Diels-Alder
IR	Infrared
J	Coupling constant (NMR)
Ph-H	Benzene
Ph-Me	Toluene
PPh_3	Triphenylphosphine
i-Pr	Isopropyl
LC-MS	Liquid chromatography-mass spectrometry
m-CPBA	*meta*-cholroperbenzoic acid
Me	Methyl
MeOH	Methanol
Mp	Melting point
MPLC	Medium-pressure liquid chromatography
MS	Molecular sieves
MTBE	Methyl *tert*-butyl ether

MVK	Methyl vinyl ketone
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
nOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect/enhancement spectroscopy
rt	Room temperature
SEM	Trimethylsilylethyloxymethyl
TBAF	Tetrabutyl ammonium fluoride
TFA	Trifluoroacetic acid
TIPS	Triisopropylsilyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography

PART I

CHAPTER I

A POTENTIAL ROLE FOR DIARYLHEPTANOIDS IN THE BIOSYNTHESIS OF OTTELIONE A.

I-A. INTRODUCTION AND BACKGROUND

I-A-1. *Isolation, structural characterization and biological activity of the otteliones.*

Ottelione A (**101**) and B (**102**, Figure I-1) were isolated from the fresh water plant *Ottelia alismoides*.[1] Structurally, the otteliones are a pair of diastereomeric 4-methylene-2-cyclohexenone compounds with four contiguous stereogenic centers and differ by the *cis* versus *trans* configuration of the 4-methylene-2-cyclohexenone ring fusion. The carbon framework of the otteliones is unprecedented among the >160,000[2] natural products that have been structurally characterized. Ottelione A was first isolated by Rhône-Poulenc Rorer (RPR) in 1996 along with its *p*-cresol tautomer RPR115781 (**103**, Figure I-1).[3] Later in 1998, Hoye and coworkers reported the isolation of *3a*-epimer, ottelione B.[4] In the isolation work by RPR the whole dried and powdered plant was extracted with MTBE and concentrated to dryness. The resultant gum was triturated, filtered, concentrated, and the bioactive fractions combined to give an enriched mixture.

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1 Leboul, J.; Provost, J. RP Rorer SA French patent WO 96/00205, 1996; *Chem. Abstr.* **1996**, *124*, 242296.

2 A Reaxys® search of 4-methylene-2-cyclohexenone fused ring core crossed with a search for isolated natural products (INP) on October 17, 2012 revealed the otteliones as the only isolated natural product with this structure.

3 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.

4 Ayyad, S.; Judd, A.; Shier, W.; Hoye, T. Otteliones A and B: Potently Cytotoxic 4-Methylene-2-Cyclohexenones from Ottelia Alismoides. *J. Org. Chem.* **1998**, *63*, 8102–8106.

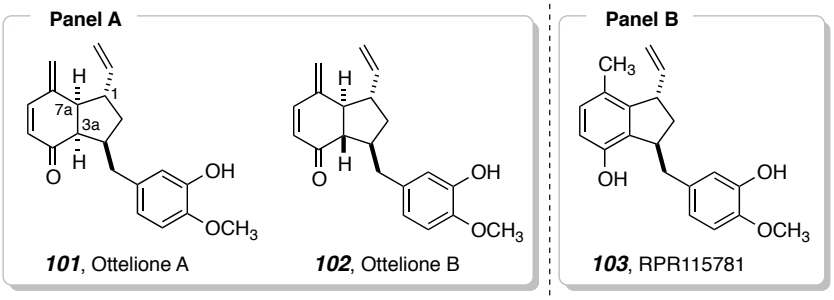

Figure I-1. *Panel A*: Structures of otteliones A and B; *Panel B*: p-cresol tautomer RPR115781.

Purification via concurrent centrifugal partition chromatography (CPC) provided compounds **101** and **103**. These structures were confirmed by ^{1}H NMR, ^{13}C NMR, COSY, HMQC, HMBC, NOE and NOESY. In the initial 1996 report only the constitution of **101** and **103** was deduced; the relative stereogenic information of **101** and **103** (as shown in Figure I-1) was unveiled in a later reported by RPR[3].

Hoye *et al.* hypothesized that ottelione A had the structure **104** or **105** (Panel A, Figure I-2)[4]. These proposed structures were ultimately overturned as a result of later total synthetic work on the otteliones. Moreover, Hoye also reported the isolation a

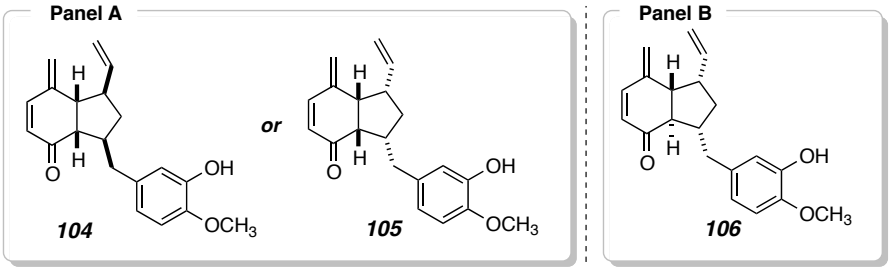

Figure I-2. *Panel A*. Hoye's first proposal of the structure for ottelione A (**101**) *Panel B*. Hoye's first proposal of the structure for ottelione B (**102**).

second compound, ottelione B. They proposed compound **106** (Panel B, Figure I-2) as a possible candidate structure. This structure was also amended to the now accepted structure **102** for ottelione B.

In addition to interesting structural features, the otteliones possess good biological activity against tublin polymerization into microtubules.[2] This mode of activity is of particular importance as microtubules are directly involved in various cell functions such as mitosis, intracellular movement, secretion, cell movement and maintenance of cell shape.[3] Thus a molecule that is capable of inhibiting microtubule formation has great

potential as an anticancer therapeutic. Compounds **101**, **102** and **103** were tested against various cancer cell lines. Otteliones A and B (**101** and **102**) were found to be more potent than the p-cresol derivative, **103**, presumably due to the addition of thiol groups to the 4-methylene-2-cyclohexenone core, resulting in irreversible tubulin binding. Compound **103** on the other hand was found to bind to tubulin reversibly through tublin binding assays, which accounts for **103**'s diminished cytotoxicity.[5]

Recent studies by the Sha group pin-pointed the portions of ottelione A that are necessary for activity by conducting structure active relationship studies (Figure I-3).[6] They uncovered that the C-1 vinyl group is not necessary for its cytotoxic activity. In comparison the C-7 exocyclic double bond is essential for the potency of ottelione A. It is thought that the exocyclic double bond in conjugation with the carbonyl might make it susceptible to nucleophilic addition, thus irreversibly binding with tubulin. The methoxy substituent on the aromatic ring cannot be interchanged with a hydroxyl or any other

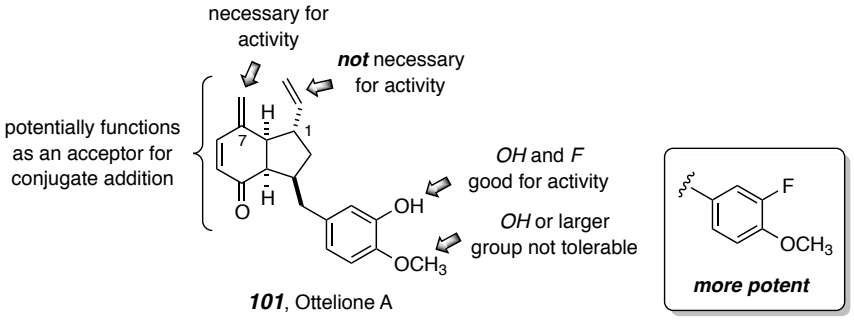

Figure I-3. Structure activity relationship of ottelione A.

larger groups such as a MOM group, *i.e.* only the methoxy group resulted in suitable cytotoxicity. Switching the phenolic OH group also resulted in enhanced potency. It should be explicitly stated that most of the emphasis will be given to the development of

[5] The RPR scientists evaluated the cytotoxicity of **101** and **102** on the human epidermoid KB cell line, **101** was found to have an IC_{50} value of 0.02 nM and **102**, IC_{50} = 0.17 μM; Hoye and coworkers submitted compounds **101** and **102** to the National Cancer Institute Developmental Therapeutics in vitro screening program again a panel of ~60 human tumor cell lines. Ottelione A was found to have a GI_{50} of <100 pM and ottelione B, <1 nM for most cell lines. The complete data from the NCI screening is presented in the supporting information of *ref.* 3.

[6] Chang, T. Y.; Tu, Y. P.; Wei, W.Y.; Chen, H. Y.; Chen, C. S.; Lee, Y. S.; Huang, J. J.; Sha, C. K. Synthesis and Antiproliferative Activities of Ottelione A Analogues. *ACS Med. Chem. Lett.* **2012**, *3*, 1075–1080.

the biosynthetic hypothesis of the otteliones (and in particular ottelione A) and not the total synthesis of these molecules that will be briefly addressed in section I-A-4.

I-A-2. *Biosynthetic hypothesis*

The quest for novel reactions remains of high importance in the field of organic chemistry. Of the many avenues for achieving this goal, the study of how nature constructs natural products is often productive, since evolutionary pressures typically favor biosynthetic pathways based on reactions that are both efficient and selective. Biosynthetic reactions described herein are those reactions that occur in a given organism or its immediate environment.[7] They include reactions that occur spontaneously and do not require enzyme catalysis.

What began as merely an isolation and structural elucidation project in the Hoye group, spurred musings about a possible biosynthetic hypothesis of the otteliones. The second attempt at isolation of these desired compounds (in the Hoye group) was met with disappointment as no compounds of interest were isolated.[8] Instead of the otteliones, they isolated and characterized a group of 1,7-diarylheptanoids (**109-112**, Figure I-4) as well as an oxidized analog of the otteliones (**113**).[9] In the case of compound **109**, there were four diastereomers isolated bringing the total number of novel diarylheptanoids to ten. The most revealing of the isolated compound for our current biosynthetic hypothesis was the 1,4-skipped diene **107**.

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

[8] Due to issues with the handling of the dried plant, it was left out in the sun for an extended period of time.

[9] (a) Lewis, H. J. Studies related to the ottelione family of natural products. Ph.D. Thesis, University of Minnesota, Minneapolis, MN, 2005. (b) Hoye, T. R.; Ayyad, S.-E.; Lewis, H. J.; Brown, S. G. New Diarylheptanoid and A Hydroxylated Ottelione from *Ottelia alismoides, Nat. Prod. Comm.* **2012**, ASAP.

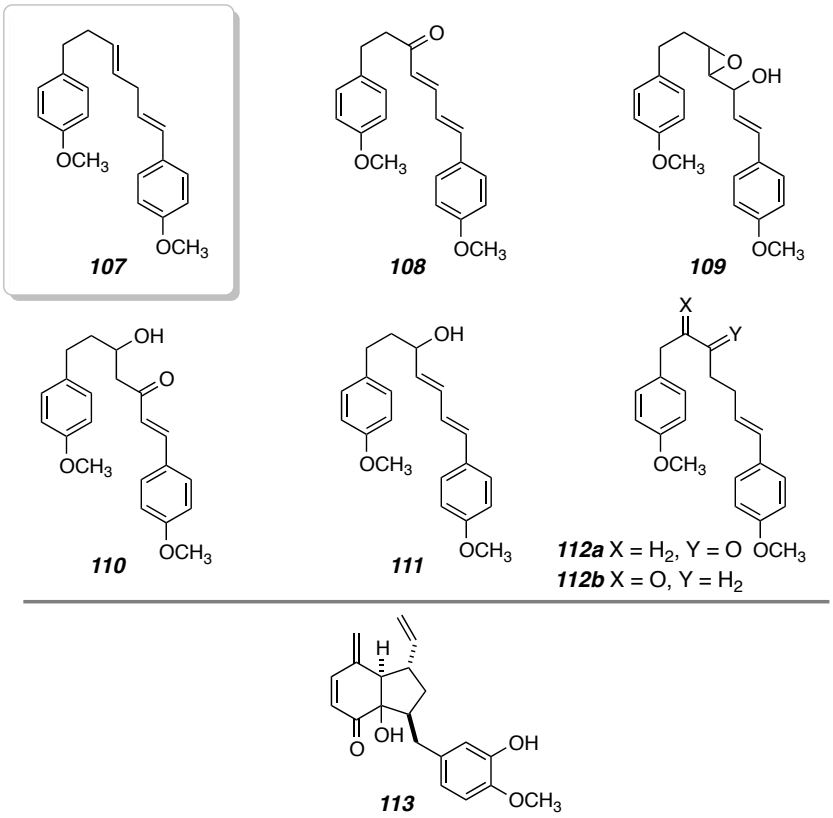


Figure I-4. Collection of diarylheptanoids isolated by Hoye and coworkers.

The skipped diene moiety in the structure **107** led us to wonder if there was a biosynthetic linkage between **107** and **101** (Figure I-5).

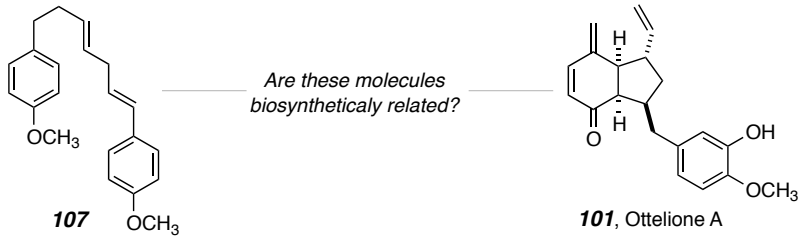
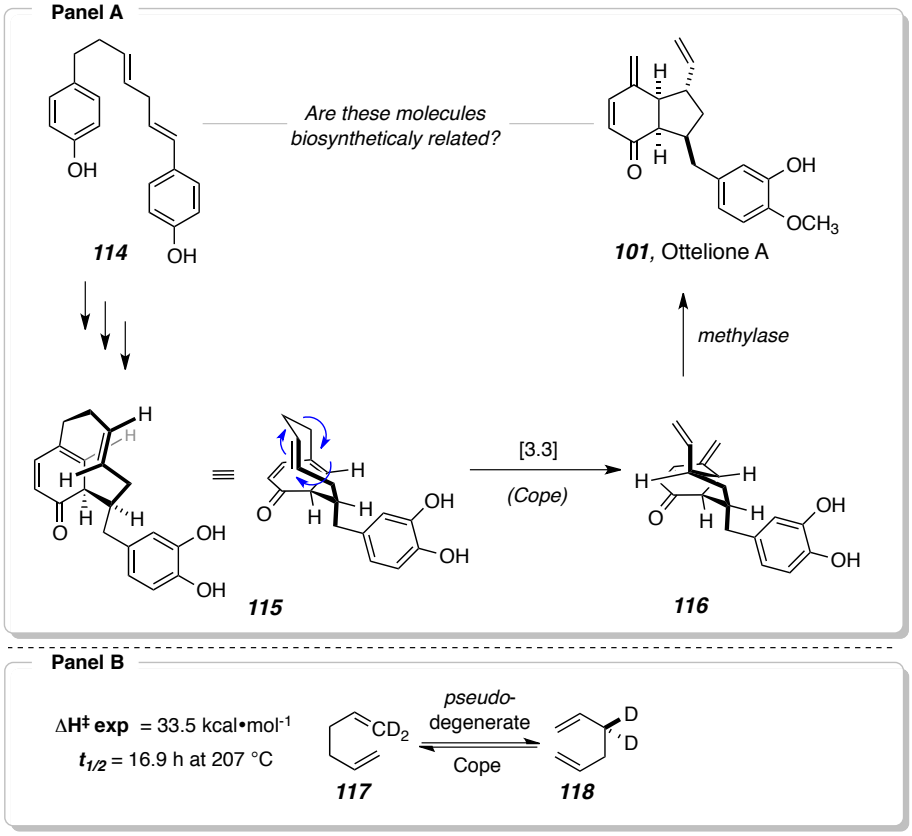


Figure I-5. Hoye and coworkers wonder if there was a biosynthetic linkage between compounds, **107** and **101**.

*We hypothesize that a Cope rearrangement within the strained [6]-metacyclophene derivative, (**115**, Panel A, Scheme I-1), is involved in the biosynthesis of ottelione A.*

Beginning with a series of transformations (soon to be discussed) from the bis-phenol **114**, **115** can undergo a [3.3]-sigmatropic rearrangement (a Cope rearrangement) to **116** that can be methylated to furnish ottelione A. The prototypical Cope rearrangement of

Scheme I-1. *Panel A*: Proposed biosynthetic hypothesis of ottelione A; *Panel B*: Cope rearrangement of 1,1-dideuteriohexa-1,5-diene.



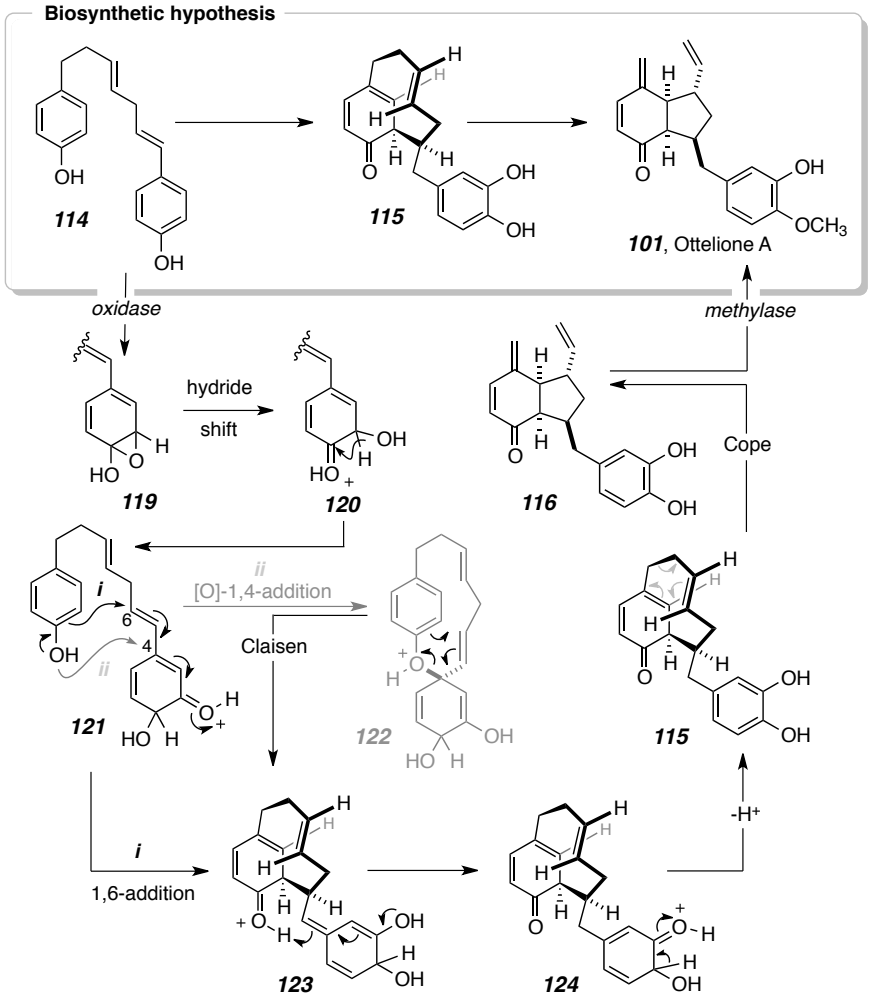
1,1-dideuteriohexa-1,5-diene (**117**, Panel B, Scheme I-1)[10] to **118** has been examined experimentally by Doering and coworkers. It was found to have an enthalpy of activation of 33.5 kcal•mol^{-1} as well as a half-life ($t_{1/2}$) of 16.9 h at 207 °C. The high enthalpy of activation of a standard Cope rearrangement precludes its ubiquity in biosynthetic pathways; there are very few incidents where the Cope rearrangements have been implicated in nature (see next section). However in this particular case, the Cope rearrangement is potentially operable due to the highly strained nature of the [6]-metacyclophene derivative **115**.

We envisioned that the biosynthesis of the proposed Cope precursor **115** could be accomplished by a series of proton shuffling events from the diarylhepatnoid **114**

[10] Doering, W. von E.; Toscano, V. G.; Beasley, G. H. Kinetics of the Cope Rearrangement of 1,1-Dideuteriohexa-1,5-Diene. *Tetrahedron* **1971**, *27*, 5299–5306.

(Scheme I-2). Beginning with the oxidation of **114** (by an oxidase such as tyrosine 3-monooxygenase) to **119,** protonation to **120**, followed by hydride shift provided the transient intermediate **121**. At this point we propose two possibilities with respect to the

Scheme I-2. Detailed description of the formal net-ene leading to Cope rearrangement precursor **115**



fate of **121**: *(i)* nucleophilic addition of the carbon *ortho* to the hydroxyl group to the C-6 position of the newly formed conjugated enone to form **123** *(ii)* nucleophilic addition of the oxygen atom to the C-4 position of the newly formed conjugated enone to form **122**. The protonated [9]-paracyclophene **122** could undergo a Claisen rearrangement to give rise to **123**. Protonation of the benzylic position along with concomitant deprotonation of the carbonyl can occur intramolecularly or in a two-step intermolecular fashion to yield intermediate **124**. This intermediate **124** is merely the protonated form of the Cope

precursor **115**, thus deprotonation and subsequent Cope rearrangement gives rise to **116** that can be methylated by a methylase such as catechol-*O*-methyl-transferase to give rise to ottelione A.

I-A-3. *Prior accounts of the Cope rearrangement in nature*

The scope of pericyclic reactions in nature has often been limited to variants of the well known Diels-Alder cycloaddition. Compounds such as lovastatin (**126**) (also known as mevinolin)[11], nargenicin (**127**)[12], and brevianamide A (**129**)[13], have all undergone extensive biosynthetic studies that point to the Diels-Alder cycloaddition as the key reaction in their respective biogenetic pathways[14] (Figure I-6). This ubiquity is however not the case with the Cope rearrangement due to the elevated temperatures typically necessary for it to occur. A few cases have been presented in the literature wherein the Cope rearrangement was implicated.

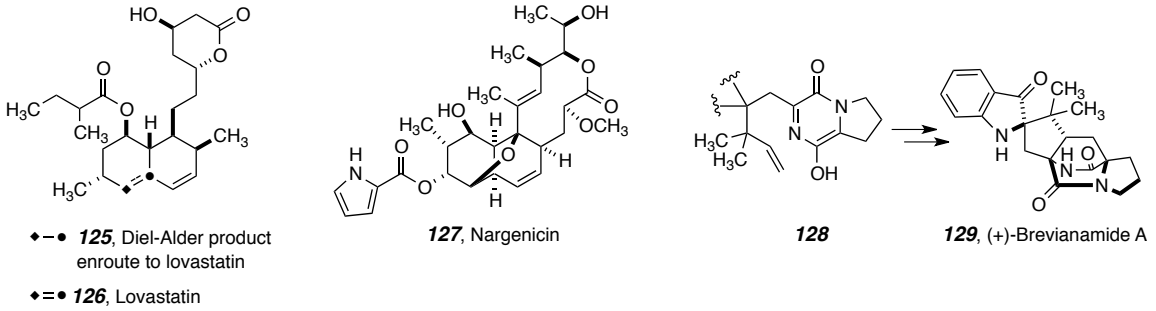


Figure I-6. A small representative sample of natural products derived from the Diels-Alder cycloaddition.

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[11] Moore, R. N.; Bigam, G.; Chan, J. K.; Hogg, A. M.; Nakashima, T. T.; Vederas, J. C. Biosynthesis of the Hypocholesterolemic Agent Mevinolin by *Aspergillus terreus*. Determination of the Origin of Carbon, Hydrogen, and Oxygen Atoms by Carbon-13 and Mass Spectrometry. *J. Am. Chem. Soc.* **1985**, *107*, 3694–3701.

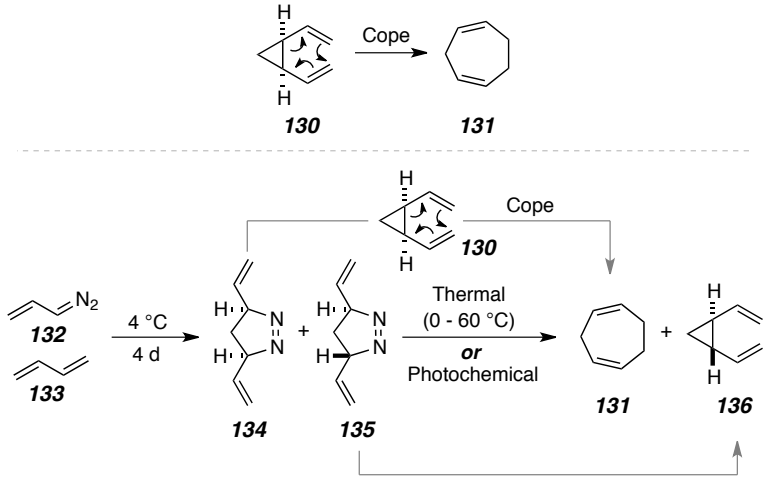
[12] Cane, D E; Yang, C C. Biosynthetic Origin of the Carbon Skeleton and Oxygen Atoms of Nargenicin A1. *J. Am. Chem. Soc.* **1984**, *106*, 784–787.

[13] Porter, A. E. A.; Sammes, P. G., A Diels–Alder Reaction of Possible Biosynthetic Importance. *J. Chem. Soc. D.* **1970**, *17*, 1103.

[14] For an extensive review of Diels-Alder accounts in nature see: Stocking, S.; Williams, R. M. Chemistry and Biology of Biosynthetic Diels-Alder Reactions. *Angew. Chem. Int. Ed.* **2003**, *42*, 3078–3115.

The Cope rearrangement can be accelerated when coupled with the release of strain energy. The quintessential example of this is in the case of the Cope rearrangement of *cis*-divinylcyclopropane (**130**, Scheme I-3) to yield 1,4-cycloheptadiene, **131**. In a 1975

Scheme I-3. The synthesis and Cope rearrangement of *cis*-divinylcyclopronae **130**



account by Schneider the synthesis of the *cis* and *trans*-divinyl-1-pyrazolines, compounds **134** and **135**, respectively, via the 1,3-dipolar cycloaddition of 3-diazo-1-propene (**132**) and 1,3-butadiene (**133**) was reported.[15,16] The thermal or photochemical degradation of these divinyl-1-pyrazolines gave **131** and the *trans*-divinylcyclopropane **136**. Using ^{1}H NMR spectroscopy, low temperature photolysis of the mixture of **134** and **135** provided only the compounds **130** and **136**. It was deduced from these experiments that **131** was formed as a result of the Cope rearrangement of **130**.

The first account of the isolation and structural characterization of **130** was reported by Brown *et al.* who also measured the $t_{1/2}$ of the Cope rearrangement of **130** to **131** to be 0.12 h at 20.4 °C.[17,18] Up until then all prior reports of the Cope rearrangement within

[15] Schneider, M. P. Low Temperature Thermal and Photochemical Formation of Diallylic 1,3-Diradicals. Cope Rearrangement Of cis-1,2-Divinylcyclopropane. *Angew. Chem. Int. Ed.* **1975**, *14*, 707–708.

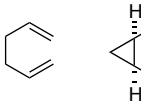
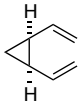
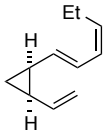
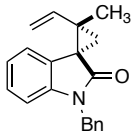
[16] Schneider, M. P.; Rau, P. Synthesis and Cope Rearrangement of *Cis*-1,2-Dialkenylcyclopropanes. *J. Amer. Chem. Soc.* **1979**, *101*, 4426–4427.

[17] Brown, J. M.; Golding, B. T.; Stofko, J. J. Isolation and Characterisation of Cis-Divinylcyclopropane. *J. Chem. Soc., Chem. Commun.* **1973**, 319b–320.

[18] Brown, J. M.; Golding, B. T.; Stofko, J. J. *Cis*-Divinylcyclopropane and the Hexafluoroacetylacetonatorhodium (I) Complexes of *Cis*-and *Trans*-Divinylcyclopropane. *J. Chem. Soc., Perkin Trans. 2* **1978**, 436–441.

130 were all on the basis of indirect methods detection as it had never been isolated. [19,20] In case of the *trans*-divinylcyclopropane **136**, due to the unfavorable molecular geometry the Cope rearrangement to **131** is not concerted and requires temperature on the order of 190 °C. The Cope rearrangement can be rendered more favorable if the entropy of activation ($\Delta S^{\neq}$) is made less negative by incorporating both vinyl groups into a ring (thereby bringing the ends of the 1,5-diene closer together) as is in the case of the bullvalene **138** (Table I-1).

Table I-1. Half-life, temperature, and enthalpy of activation (experimental and computational) of Cope rearrangement within 1,5-hexadiene (**137**)[10, 21], , *cis*-divinylcyclopropane (**130**)[17, 22], and bullvalene (**138**)[23, 24]; the known types of Cope rearrangement relevant to natural product biosynthesis [**139**[25] (pre-ectocarpene) to ectocarpene and **140**[26] (vis-à-vis welwitindolinones and dragmacidin E)]. [a]DFT B3LYP/6-31G. [b]SCF-MO (MIND0/2). [c]Our estimate based on reported NMR data. [d]Calculated using the estimated $t_{1/2}$ and the Arrhenius factor from the parent divinylcyclopropane **130**.

some relevant Cope sub-strates / *reaction parameters*	 ***137***	 ***130***	 ***138***	 ***139***	 ***140***
$t_{1/2}$	16.9 h	0.12 h	0.56 h	0.35 h	1 h [c]
temp	207 °C	20.4 °C	-10 °C	18 °C	60 °C
$\Delta H^{\ddagger}$ exp (kcal·mol^{-1})	33.5	19.4	13.3	15	23 [d]
$\Delta H^{\ddagger}$ comp (kcal·mol^{-1})	33.2 [a]	19.7 [a]	12.5 [b]	–	–

[19] Schröder, G.; Oth, J. F. M.; Merényi, R. Molecules Undergoing Fast, Reversible Valence-Bond Isomerization.(Molecules with Fluctuating Bonds). *Angew. Chem. Int. Ed.* **1965**, *14*, 752–761.

[20] Doering, W. E.; Roth, W. R. A Rapidly Reversible Degenerate Cope Rearrangement, Bicyclo[5.1.0]octa-2,5-diene. *Tetrahedron* **1963**, *19*, 715–737.

[21] Hrovat, D. A.; Chen, J.; Houk, K. N., Broden, W. T. Cooperative and Competitive Substituent Effects on the Cope Rearrangements of Phenyl-Substituted 1, 5-Hexadienes Elucidated by Becke3LYP/6-31G* Calculations. *J. Am. Chem. Soc.* **2000**, *122*, 7456–7460.

[22] Ozkan, I.; Zora, M. Transition Structures, Energetics, and Secondary Kinetic Isotope Effects for Cope Rearrangements of *cis*-1,2-Divinylcyclobutane and *cis*-1,2-divinylcyclopropane: A DFT Study. *J. Org. Chem.* **2003**, *68*, 9635–9642.

[23] Dewar, M. J. S.; Schoeller, W. W. Cope Rearrangements in the Bullvalene Series. *J. Am. Chem. Soc.* **1971**, *93*, 1481–1482.

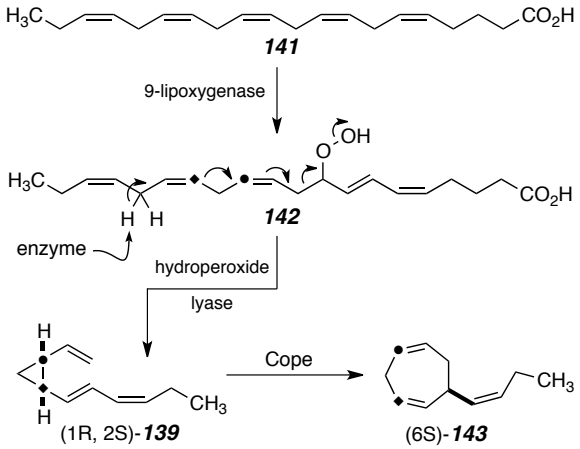
[24] Allerhand, A.; Gutowsky, H. S. Spin-Echo Nuclear Magnetic Resonance Studies of Chemical Exchange. VI. Rearrangment of Bullvalene and of Its Silver Nitrate Complex. *J. Am. Chem. Soc.* **1965**, *87*, 4092-4096.

[25] Pohnert. G.; Boland, W. Pericyclic Reactions in Nature: Synthesis and Cope Rearrangement of Thermolabile Bis-Alkenylcyclopropanes From Female Gametes of Marine Brown Algae (Phaeophyceae). *Tetrahedron* **1997**, *53*, 13681–13694.

[26] Schwarzer, D. D.; Gritsch, P. J.; Gaich, T. Mimicking Dimethylallyltryptophan Synthase: Experimental Evidence for a Biosynthetic Cope Rearrangement Process *Angew. Chem. Int. Ed.* **2012**, *51*, 11514–11516.

In studies by Boland *et al.* the feasibility of the Cope rearrangement was probed in the biosynthesis of the pheromone of the brown algae *Ectocarpus siliculosus,* ectocarpene (**143**, Scheme I-4).[27,28] Feeding studies with deuterium labeled *cis*-eicosa-5,8,11,14,17-pentaenic acid **141** proved that it serves as the precursor enroute to the natural product **143**.[29,30] The first step in this biosynthetic pathway involves oxidation to the 9-hydroperoxy fatty acid **142**, followed by cleavage of **142**, presumably by a hydroperoxide lyase to directly yield *(1R,2S)*-**139** and finally Cope rearrangement to *(6S)*-**143**. Boland later confirmed these feeding studies by independently synthesizing *(1R,2S)*-**139** and measuring the activation barrier and determined a $t_{1/2}$ of 0.35 h at 18 °C.[25, 31]

Scheme I-4. The proposed biosynthesis of ectocarpene **143** involving a Cope rearrangement of **139**.[25]



Wenkert and coworkers have also implicated the Cope rearrangement during the course of their studies on trytophan.[32] Here they propose a Cope rearrangement following the prenylation of tryptophan (**144**, Scheme I-5). They propose the prenylation of **144** at

[27] Boland, W.; Pohnert, G.; Maier, I. Pericyclic Reactions in Nature: Spontaneous Cope Rearrangement Inactivates Algae Pheromones. *Angew. Chem. Int. Ed.* **1995**, *34*, 1602–1604.

[28] Boland, W. The Chemistry of Gamete Attraction: Chemical Structures, Biosynthesis, and (a)Biotic Degradation of Algal Pheromones. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 37–43.

[29] Stratmann, K.; Boland, W.; Müller, D. G. Biosynthesis of Pheromones in Female Gametes of Marine Brown Algae (Phaeophyceae). *Tetrahedron* **1993**, *49*, 3755–3766.

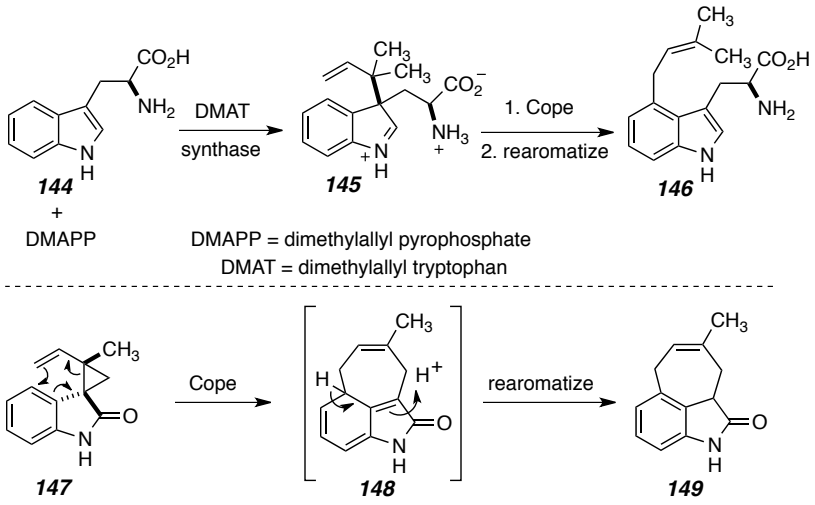
[30] Stratmann, K.; Boland, W.; Müller, D. G. Pheromones of Marine Brown Algae; a New Branch of the Eicosanoid Metabolism. *Angew. Chem. Int. Ed.* **1992**, *31*, 1246–1248.

[31] The Cope rearrangement of the *trans* analog of **37** was measured to have $t_{1/2}$ of 39 h at 70 °C: Moore, R. E.; Pettus, J. A. Isolation and Structure Determination of Dictyopterenes C' and D' From Dictyopteris. Stereospecificity in the Cope Rearrangement of Dictyopterenes A and B. *J. Amer. Chem. Soc.* **1971**, *93,* 3087–3088.

[32] Wenkert, E.; Sliwa, H. A Model Study of Ergot Alkaloid Biosynthesis. *Bioorg. Chem.* **1977**, *6*, 443–452.

C-3 with dimethylallyl pyrophosphate (DMAPP) would give rise to **145**. Cope rearrangement of **145** followed by rearomatization would yield the dimethylallyltryptophan **146**. In a recent report by Gaich, evidence for the Cope rearrangement of **147** to **148**, followed by rearomatization to furnished the tricycle **149**.[26]

Scheme I-5. A Biologically relevant Cope rearangement in the synthesis of alkaloids.



I-A-4. *Synthetic strategies toward otteliones A and B*.

To date there have numerous syntheses of the otteliones. The purpose of this dossier is not a total synthesis of otteliones A and B, thus the emphasis will not be placed on this topic. For convenience the references that detail past syntheses are provided herein.[33] Most of the syntheses involve the epimerization at C-3a of ottelione A (**101**, Figure I-7) to ottelione B (**102**). Early efforts employed DBU in hot benzene or *t*-BuOK in *t*-BuOH

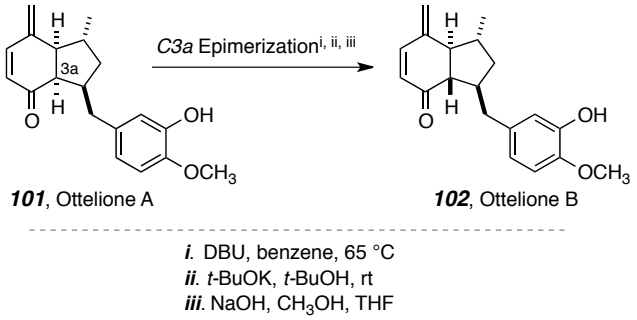


Figure I-7. Conditions used for the epimerization of ottelione A (**101**) to ottelione B (**102**).

[33] (a) Mehta, G.; Reddy, D. S. Synthetic Studies Directed Towards the Potent Cytotoxic Natural Product Ottelione A: Stereoselective Construction of the Complete Framework. *Chem. Commun.* **1999**, 2193–2194. (b) Kappe, C. O.; Murphree, S. S.; Padwa, A. Synthetic Applications of Furan Diels—Alder Chemistry. *Tetrahedron* **1997**, *53*, 14179–14233. (c) Trembleau, L.; Patiny, L.; Ghosez, L. Diels–Alder Reactions of Activated Furans to Cyclopentenone Derivatives: A Regiodivergent Diels–Alder Approach Towards Polyfunctionalised *cis*-Hydrindanones. *Tetrahedron Lett.* **2000**, *41*, 6377–6381. (d) Mehta, G; Islam, K. Total Synthesis of Epi-Otteliones. *Org. Lett.* **2002**, *4*, 2881–2884. (e) Mehta, G; Islam, K. Total Synthesis of (±)-Otteliones A and B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2396–2398. (f) Mehta, G; Islam, K. Enantioselective Total Syntheses of (+)- and (−)-Ottelione A and (+)- and (−)-Ottelione B. Absolute Configuration of the Novel, Biologically Active Natural Products. *Tetrahedron Lett.* **2003**, *35*, 6733–6736. (g) Araki, H.; Inoue, M.; Katoh, T. Total Synthesis and Absolute Configuration of Otteliones A and B, Novel and Potent Antitumor Agents From a Freshwater Plant. *Org. Lett.* **2003**, *5*, 3903–3906. (h) Araki, H.; Inoue, M.; Suzuki, T.; Yamori, T.; Kohno, M.; Watanabe, K.; Abe, H.; Katoh, T. Enantioselective Total Synthesis of (+)-Ottelione A, (−)-Ottelione B, (+)-3-Epi-Ottelione A and Preliminary Evaluation of Their Antitumor Activity. *Chem. Eur. J.* **2007**, *13,* 9866–9881. (i) Clive, D. L.; Fletcher, S. P. Synthesis of the Bicyclic Dienone Core of the Antitumor Agent Ottelione B. *Chem. Commun. (Camb.)* **2002**, *17*, 1940–1941. (j) Clive, D. L.; Liu, D. A Short Synthetic Route to the Core Structures of Otteliones A and B. *Tetrahedron Lett.* **2005***, 46*, 5305-5307. (k) Clive, D. L.; Liu, D. Synthesis of the Otteliones A and B: Use of a Cyclopropyl Group as Both a Steric Shield and a Vinyl Equivalent. *Angew. Chem. Int. Ed.* **2007**, *46*, 3738–3740. (l) Clive, D. L.; Liu, D. Synthesis of the Potent Anticancer Agents Ottelione A and Ottelione B in Both Racemic and Natural Optically Pure Forms. *J. Org. Chem.* **2008**, *73*, 3078–3087. (m) Lee, M. Y.; Kim, K. H.; Jiang, S.; Jung, Y. H.; Sim, J. Y.; Hwang, G.; Ryu, D. H. Enantioselective Formal Synthesis of Antitumor Agent (+)-Ottelione A. *Tetrahedron Lett.* **2008**, *49*, 1965–1967. (n) Chen, C. H.; Chen, Y. K.; Sha, C. Enantioselective Total Synthesis of Otteliones A and B. *Org. Lett.* **2010**, *12*, 1377–1379. (o) Suzuki, T.; Ghozati, K.; Zhou, D. Y.; Katoh, T.; Sasai, H. Formal Total Synthesis of Ottelione Using Iridium-Catalyzed Oxidative Desymmetrization. *Tetrahedron* **2010**, *66*, 7562–7568. (p) Betkekar, V. V.; Panda, S.; Kaliappan, K. P. A Tandem Enyne/Ring Closing Metathesis Approach to 4-Methylene-2-Cyclohexenols: An Efficient Entry to Otteliones and Loloanolides. *Org. Lett.* **2012**, *14*, 198–201.

to perform this transform. In the last report of the synthesis of the otteliones NaOH in THF/CH_3OH was found to be a superior set of conditions to achieve this transformation.

I-B. DIARYLHEPTANOIDS IN NATURE

I-B-1. *Introduction*

Diarylheptanoids are a group of secondary metabolites that consist of two aromatic rings connected by a seven carbon chain. They occur in both linear and cyclic forms and have been divided into five major groups on the basis of their chemical structures.[34, 35] Type I (**150**, Figure I-8) are non-phenolic linear diaylheptanoids, and their occurrence is limited to two of the ten plant families known to give rise to these compounds. In a report by Claeson *et al.* three of these diarylheptanoids isolated from the *Zingiberaceae* family, along with four new semi-synthetic derivatives, were evaluated as topical anti-inflammatory agents in ear edema.[36]

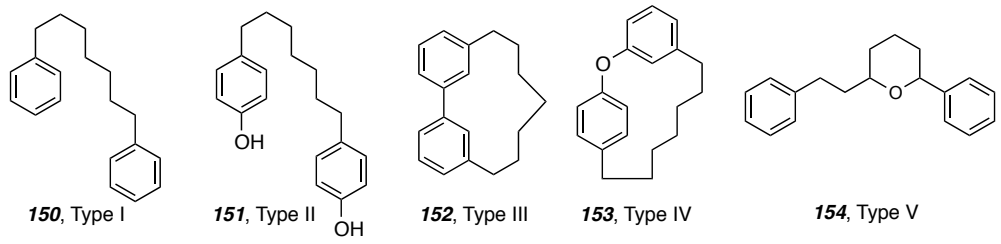


Figure I-8. The five types of 1,7-diarylheptanoids.

Phenolic linear diarylheptanoids (**151**, Type II), also known as curcuminoids (named after curcumin, the orange pigment of turmeric) represent the largest subset of diarlheptanoid compounds. Macrocyclic biarylheptanoids (**152**) are the third group of diarylheptanoids, but no biological activity has been reported for these compounds. Type IV (**153**) diarlheptanoids are described as macrocyclic diaryl ethers. Although no biological activity has been reported to date, antibacterial activity has been postulated based on the molecular mechanics and molecular orbital calculations for some of the

[34] Zhu, J.; Islas-Gonzalez, G.; Bois-Choussy, M. In *Recent Progress in Isolation, Bioactivity Evalutaion and Total Synthesis of Diarylheptanoids;* Organic Preparations and Procedures International; Organic Preparations and Procedures, Inc.: Newton Highlands, Mass., 2000; Vol. 32, pp 505–546.

[35] Claeson, P.; Claeson, U. P.; Tuchinda, P.; Reutrakul, V. In *Occurrence, Structure and Bioactivity of 1,7 Diarylheptanoids;* Atta-ur-Rahman, Ed.; Studies in Natural Products Chemistry: Bioactive Natural Product; Elsevier Science B.V.: Amsterdam, 2002; Vol. 26, pp 881.

[36] Claeson, P.; Pongprayoon, U; Sematong, T.; Tuchinda, P.; Reutrakul, V.; Soontorsaratune, P.; Taylor, W. C. Non-Phenolic Linear Diarylheptanoids from *Curcuma xanthorrhiza*: A Novel Type of Topical Anti-Inflammatory Agents: Structure-Activity Relationship. *Planta Med.* **1996**, *62*, 236–240.

isolated compounds.[37] The smallest group of the diarylhepatanoids, Type V, **154**, are cyclized within the C7-chain to form a pyran-like ring. Some of these compounds were found to inhibit nitric oxide (NO) production in lipopolysaccharide (LPS)-activated murine macrophages *in vitro*.[38]

Members of the class of diarylheptanoid natural products (Figure I-8) all contain an unbranched, seven-carbon chain substituted at C(1) and C(7) by oxygenated phenyl rings.[39] Well over 250 such natural products are known, but each of the ten newly isolated diarylheptanoids from *Ottelia alismoides* is a new structure and each contains an alkene conjugated with one of the aromatic rings (*i.e.*, each is styrenic) (Figure I-4). All known diarylheptanoids bear an oxygen substituent on at least one of the seven carbons of the heptanoid chain and the great majority of that oxygenation resides at C(1), C(3), C(5), and/or C(7), consistent with their polyacetate biosynthetic origin. Nearly fifty of the known diarylheptanoids contain an embedded styrene subunit. Related sets of ring-closed *bi*arylheptanoids (at least 66) and diaryletherheptanoids (at least 62) also exist (Figure I-9). The former all contain a biaryl bond having at least one flanking *ortho*-hydroxyl group. It is presumed that these biaryls and diarylethers are produced by phenolic oxidative coupling events from acyclic precursor *di*arylheptanoids.

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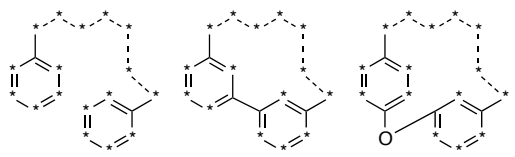
[37] Keserü, G. M.; Nógrádi, M. Prediction of Antibacterial Activity of Some Diarylheptanoids Isolated from *Garuga* Species by Molecular Mechanics and Molecular Orbital Calculations. *J. Mol. Struct. (Theochem)* **1993***, 286*, 259–265.

[38] Prasain, J. K.; Tezuka, Y.; Hase, K.; Basnet, P.; Dong, H.; Namba, T.; Kadota, S. Inhibitory Effect of Diarylheptanoids on Nitric Oxide Production in Activated Murine Macrophages. *Biol. Pharm. Bull.* **1998**, *21*, 371–374.

[39] We searched the Reaxys® database with substructures **ii-iv** [crossed with "INP" (isolated natural product)] to locate the structures summarized in Figure 3.



ii ***iii*** ***iv***

[with allowances for substitution at any atom and for any bond order in the seven carbon chain]

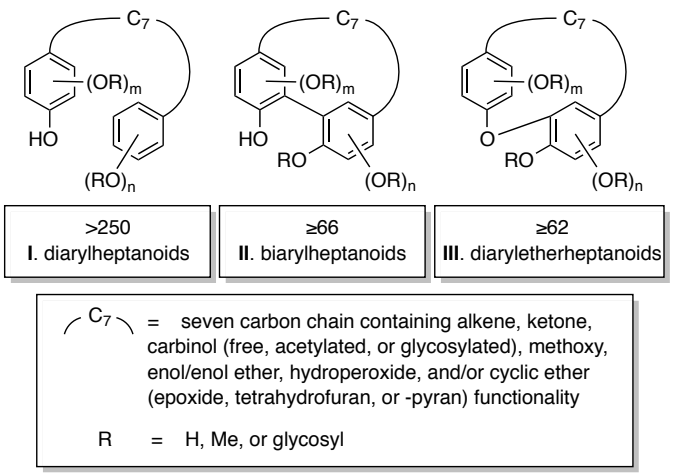
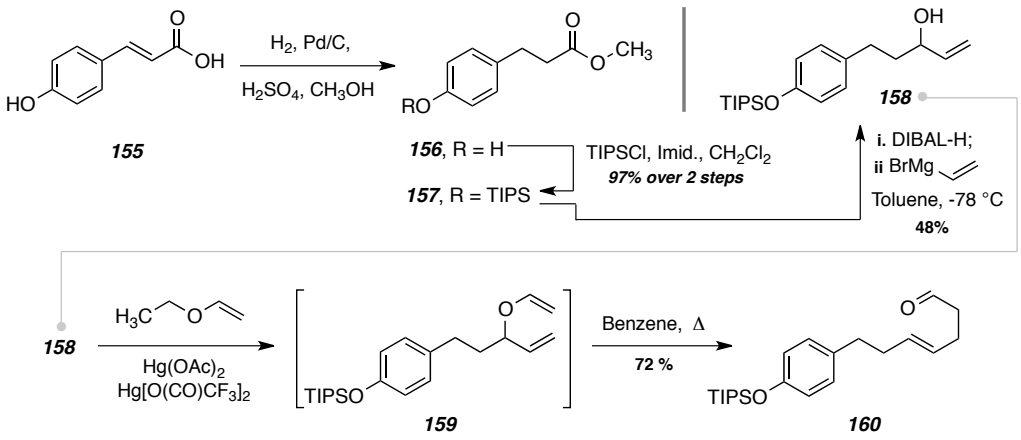


Figure I-9. Generic structures of families of diarylheptanoid (**I**), biarylheptanoid (**II**), and diaryletherheptanoid (**III**) natural products.

I-B-2. *Synthesis of 177 and 178*

Attempts at studying the series of transformations leading up to the Cope rearrangement in our outlined biosynthetic pathway (Scheme I-2) were expediently executed via the reliably scalable synthesis of the diarylhepatnoids **177** and **178**. Beginning with the one-pot methanolysis-hydrogenation of **155** to the dihydro-methyl coumarate ester **156** (Scheme I-6). The crude product from this transformation was protected as the TIPS ether under typical silylative conditions.[40, 41] The TIPS-protected

Scheme I-6. Synthesis of the aldehyde **160**.



phenol was then subjected to another one-pot transformation involving reduction of the ester to the aldehyde, followed by trapping of the liberated aldehyde with vinyl magnesium Grignard to provide the allylic alcohol **158** in a 48% yield. This one-pot procedure was developed by Hoye *et al.* during their studies of the bidirectional homologation of 1,n-diesters.[42] Here, they circumvented the problem associated with 1,n-dials, namely their tendency to form internal hydrates or nucleophilic addition to one of the aldehydes followed by cyclization. Thus, sequential low temperature addition of

[40] The TIPS protecting group was chosen due to its favorable stability toward acidic conditions (deprotection of an alkyl-TIPS ether is 100,000 times more difficult than a TMS ether under acidic conditions. Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*; John Wiley and Sons Inc: United States of America, 1999; Vol. 3, pp 779).

[41] As a general rule, aryl silyl ethers will favor deprotection under basic conditions: Crouch, R. D. Selective Monodeprotection of Bis-Silyl Ethers *Tetrahedron* **2004**, *60*, 5833–5871.

[42] Hoye, T. R.; Kopel, L.; Ryba, T. In Situ Generation and Nucleophilic Capture of 1,N-Dial Equivalents From 1,N-Dioates (α,ω-Diesters). *Synthesis* **2006**, *10*,1572–1574.

diisobutylaluminium hydride (DIBAL-H) and vinyl magnesium bromide afforded the allylic alcohol. DIBAL-H and vinyl-MgBr were titrated according to literature procedures).[43, 44]

With the allylic alcohol **158** in hand, our sights turned to the synthesis of the TIPS protected aldehyde **160**. We envisioned that this could be accomplished by a mercury catalyzed Claisen rearrangement.[45, 46, 47] Numerous Lewis acids (mostly metals) have been investigated as catalysts for both the Cope and Claisen rearrangement.[48, 49] While catalysts allow for the use of milder conditions in the Claisen rearrangement, thereby increasing the selectivity of the rearrangement, the use of some Lewis acids as catalyst has resulted in decreased regioselectivity *i.e.* [3,3] selectivity vs. [1,3]-selectivity (**164** and **165** respectively). In work by Rovis and Nasveschuk, it was suggested that the increased stability of the allyl cation (**163**) results in increased [1,3]-selectivity (Scheme I-7).[50] The allylic **158** alcohol was stirred overnight in ethyl vinyl ether along with a catalytic amount of mercuric(II)acetate. The following day a catalytic amount of mercuric(II)trifluoroacetate was added to the solution and stirred for an additional three hours. The addition of the more reactive mercuric(II)trifluoroacetate was thought to encourage the disproportionation of the 'acetal mercuric complex' thereby promoting formation of the allyl vinyl ether (**159**). Upon removal of the ethereal solvent, the adduct was immediately taken up in benzene and heated to 180 °C in a Teflon-caped culture tube for three hours. The enal **160** could be isolated in high yields with problems only

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[43] 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.

[44] Hoye, T. R.; Eklov, B. M.; Voloshin, M.; Yao, L. J. No-D NMR Spectroscopy as a Convenient Method for Titering Organolithium (RLi), RMgX, and LDA Solutions *Org. Lett*. **2004**, *6*, 2567–2570.

[45] Overman, L. E. Mercury(II)- and Palladium(II)-Catalyzed [3,3]-Sigmatropic Rearrangements [New Synthetic Methods (46)]. *Angew. Chem. Int. Edition in Ed.* **1984**, *23*, 579–586.

[46] Overman, L. E.; Renaldo, A. E. Catalyzed Sigmatropic Rearrangements. 10. Mechanism of the Palladium Dichloride Catalyzed Cope Rearrangement of Acyclic Dienes. A Substituent Effect Study. *J. Am. Chem. Soc.* **1990**, *112*, 3945–3949.

[47] Overman, L. E.; Knoll, F. M. Catalyzed Sigmatropic Rearrangements. 5. Palladium(II) Chloride Catalyzed Cope Rearrangements of Acyclic 1,5-Dienes. *J. Am. Chem. Soc.* **1980**, *102*, 865–867.

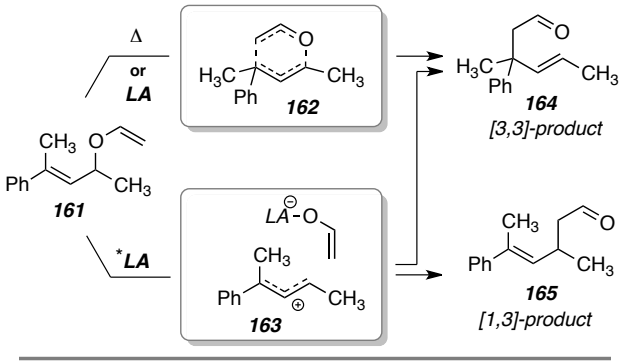
[48] Majumdar, K. C.; Alam, S.; Chattopadhyay, B. Catalysis of the Claisen Rearrangement. *Tetrahedron* **2008**, 64, 597–643.

[49] Lutz, R. P. Catalysis of the Cope and Claisen Rearrangements. *Chem. Rev.* **1984**, *84*, 205–247.

[50] Nasveschuk, C. G.; Rovis, T. Regioselective Lewis Acid-Mediated [1,3] Rearrangement of Allylvinyl Ethers *Org. Lett.* **2005**, *7*, 2173–2176.

encountered when **159** was not immediately carried over into the proceeding step.

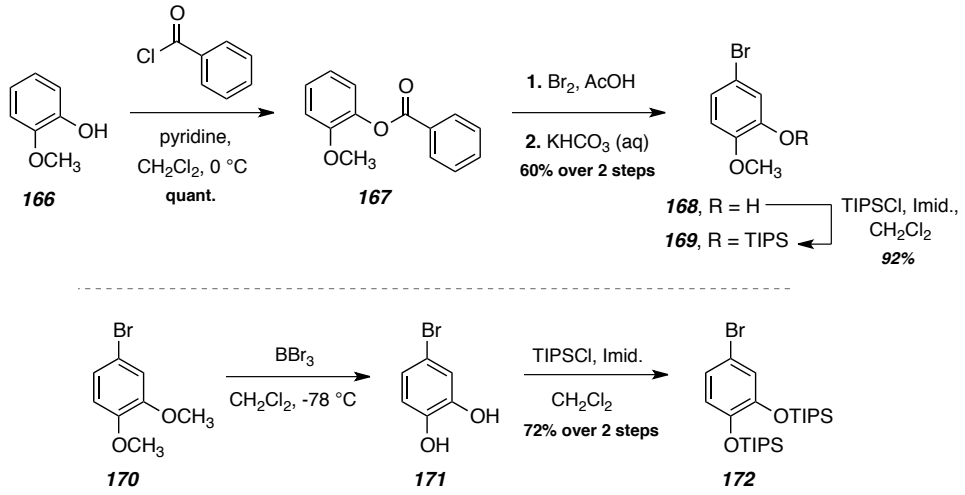
Scheme I-7. Competing pathway available in some cases depending on the use of Lewis acid (***LA***).



* ***LA*** that predominately give [1,3]-products: $SnCl_4$, $TiCl_4$, $(CH_3)_2AlCl$, $EtAlCl_2$

In preparation for the addition of an aryl substituent to aldehyde **160**, the TIPS-protected bromo aryls **169** and **172** were synthesized (Scheme I-8).[51] Compound **166** was reacted with benzoyl chloride and provided the benzyl ester **167** in quantitative yield. Bromination followed by hydrolysis of the benzyl ester gave **168** in a 60% yield of over two steps. TIPS protection of the bromophenol **168** gave the silyl ether **169** in a 92 % yield. The synthesis of aryl bromide **172** was bit more streamlined as it involved two

Scheme I-8. Synthesis of the TIPS-protected bromoaryls **169** and **172**.

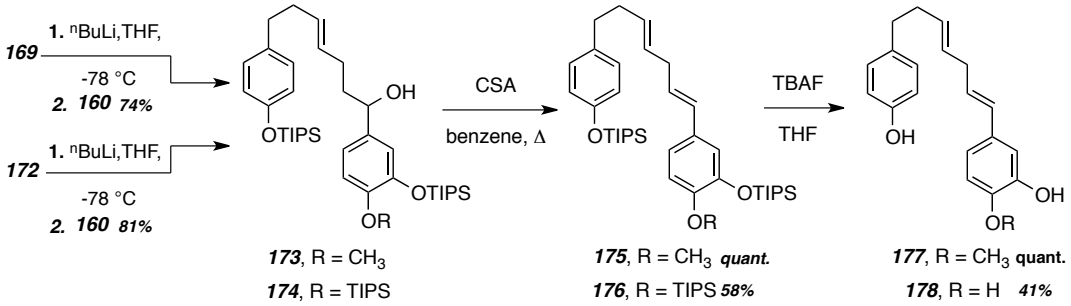


[51] The synthesis up until compounds **167** and **168** was conducted by a former Hoye group member, Dr. Gregory Hanson.

steps the first of which was the double demethylation of the commercially available dimethoxybenzene **170**. Double TIPS protection smoothly provided the desired bromo-aryl **172**.

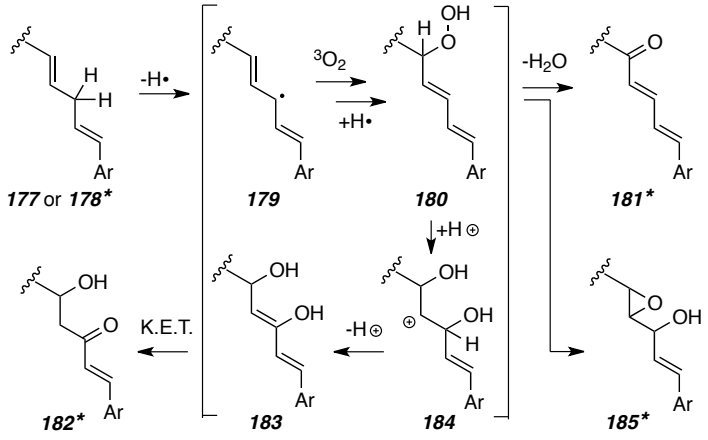
The end game strategy toward the synthesis of diarylheptanoids **177** and **178** proceeded smoothly (Scheme I-9). Lithiation of the bromo aryl compounds **169** and **172**, followed by addition to aldehyde **160** provided the benzylic alcohol **173** and **174** respectively. Dehydration of the alcohol with camphor sulfonic acid provided the styrenic olefins **175** and **176** in quantitative and 68% yields respectively. Global deprotection

Scheme I-9. End game synthesis of diarylheptanoids **177** and **178**.



with tetrabutyl ammonium fluoride gave the desired diarylheptanoids **177** and **178** in a quantitative and 41% yield respectively. The difference in yield for the global deprotection of **177** and **178** could be explained via a potential autooxdation pathway of skipped 1,4-dienes (Scheme I-10).

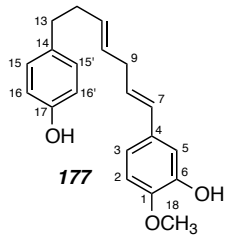
Scheme I-10. Hypothetical autooxidation pathway available to skipped 1,4-dienes. (adapted from ref. 9)



* Compare to isolated diarylheptanoids (***107***, ***108***, ***109***, ***110***) in Figure I-4

177 or ***178: 107*** ***181: 108*** ***182: 110*** ***185:109***

Table I-2 and Table I-3 details the proton and carbon assignments of **177** and **178** respectively (COSY, HMQC, HMBC were also helpful in deciphering some ^{1}H and ^{13}C resonances).



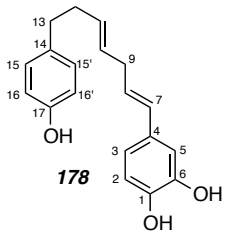


Table I-2. NMR spectral data for 4-((1*E*,4*E*)-7-(4-hydroxyphenyl)hepta-1,4-dien-1-yl)-2-methoxyphenol (**177**) in $CDCl_3$

Atom #	δ_H (mult, *J*, Hz)	Carbon
1	-	146.0
2	6.76 (d, *J* = 8.8 Hz)	115.4
3	6.86 (dd, *J* = 8.3, 1.9 Hz)	118.6
4	-	131.8
5	6.91 (d, *J* = 1.9 Hz)	111.9
6	-	145.6
7	6.2 (d, *J* = 15.8 Hz)	129.8
8	5.99 (dt, *J* = 15.8, 6.6 Hz)	127.9
9	2.83 (t, *J* = 6.1 Hz)	35.9
10	5.43 (dt, *J* = 15.4, 6.1 Hz)[a]	131.8
11	5.5 (dt, *J* = 15.5, 6.2 Hz) [b]	128.8
12	2.29 (q, *J* = 7.1 Hz)	34.5
13	2.62 (t, *J* = 7.3 Hz)	35.2
14	-	134.2
15/15'	7.03 (d, *J* = 8.4 Hz)	131.0
16/16'	6.76 (d, *J* = 8.4 Hz	110.8
17	-	153.8
18	3.86 (s, 3H)	56.2

[a, b] Chemical shifts from COSY

Table I-3. NMR spectral data for 4-((1*E*,4*E*)-7-(4-hydroxyphenyl)hepta-1,4-dien-1-yl)benzene-1,2-diol (**178**) in $CDCl_3$

Atom #	δ_H (mult, *J*, Hz)	Carbon
1	-	146.0
2	6.69 (d, *J* = 8.1 Hz)	119.0
3	6.74 (d, *J* = 8.2 Hz)	116.0*
4	-	131.0
5	6.89 (br s)	113.4
6	-	145.4
7	6.22 (d, *J* = 15.9 Hz)	131.1
8	5.91 (dt, *J* = 15.8, 6.6 Hz)	126.5
9	2.82 (t, *J* = 6.1 Hz)	36.5
10	5.48 (dt, *J* = 15.5, 5.7 Hz)[a]	131.5
11	5.54 (dt, *J* = 15.4, 5.5 Hz) [b]	129.5
12	2.27 (q, *J* = 7.5 Hz)	35.6
13	2.58 (t, *J* = 7.3 Hz)	35.8
14	-	133.5
15/15'	7.02 (d, *J* = 8.1 Hz)	130.1
16/16'	6.74 (d, *J* = 8.9 Hz	115.7*
17	-	156.3

[a, b] Chemical shifts from COSY

Interestingly, the products that can arise from this pathway **181**, **182**, and **185**, have the exact same substructure as isolated diarylheptanoids **108**, **110** and **109**, (respectively). This pathway is assumed to be available to the synthesized diarylheptanoids **177** and **178**. Therefore one explanation for the drastic difference in yields of the deprotection step is

that the rate of autooixdation of **178** is faster than **177**, leading to accelerated decomposition of the catechol derivative **178** and thus a low yield.

In an initial attempt to probe our biosynthetic hypothesis as well as the proposed autooxidation pathway we exposed both **177** and **178** (in separated reactions) varying concentrations of H_2SO_4 or TFA as well as varying degrees of heat and monitored the compounds via ^1H NMR. Over the course of hours we could observe a slow disappearance of the doubly allylic H(9) protons in **178** along with appearance of olefinic protons. The chemical shift of these protons were in accordance with enone both α and β protons of an enone. In the studies with **177** this phenomenon was not observed even after days of heating with either H_2SO_4 or TFA, only isomerization of the skipped diene to the conjugated diene was observed. These compounds were not isolated or further characterized as our attention turned to other more promising experiments in establishing our proposed biosynthetic hypothesis.

I-C. FUTURE STUDIES

The successful synthesis of the hypothesized 1,7-diarylheptanoid precursor to the otteliones opens the door to potential feedings studies with the *Ottelia alismoides* plant. By labeling compounds **177** and **178** and examining the molecules that can be isolated after a reasonable time, the incorporation of labeled fragments would help to uncover whether or not the 1,7-diarylheptanoids are precursors to the otteliones. Moreover feeding studies would also shed light on the biological pathways at play in the biosynthesis of the otteliones.

Biological testing is also a possibility with these newly synthesized compounds that can easily be explored given the ease of access to these compounds.

I-D. CONCLUDING REMARKS

The succinct, scalable synthesis of **177** and **178** facilitated the exploration of a possible connection of the 1,7-diarylheptanoids to the otteliones. The susceptibility of **178** to auto-oxidation suggested that our proposed pathway of the isolated **107** gave rise to the diarylheptanoids **108**, **110** and **109** could be operable, however the transformation of the synthesized diarylheptanoids to the otteliones (or compounds resembling the otteliones) was not observed. While we were hopeful this outcome was not terribly surprising, thus our attention focused on tractable experiments that would establish the Cope rearrangement in the biosynthesis of the otteliones.

CHAPTER II

THE COPE REARRANGEMENT WITHIN THE STRAINED [M]-CYCLOPHANE 204-PROX?[52]

II-A. BACKGROUND

II-A-1. *Introduction*

To gauge the feasibility of the Cope rearrangement occurring within the strained [m]-cyclophane **115** (Scheme I-1) to furnish ottelione A (**101**), early work in the Hoye group focused on the Cope rearrangement of the truncated analog (**201**) to nor-benzyl ottelione A **202-exo**[53] (Figure II-1).[54]The truncated Cope precursor **201** is the tautomer of the

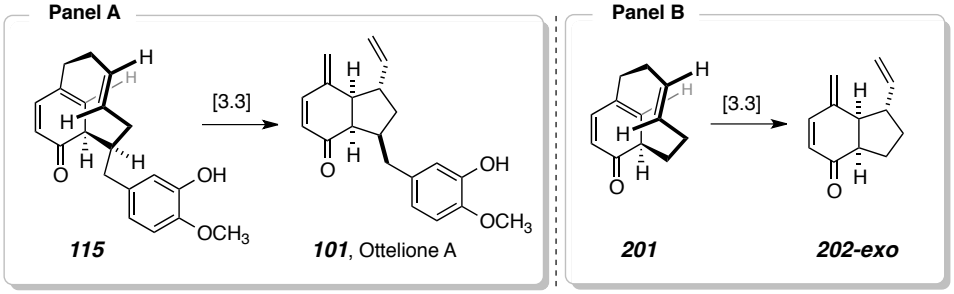
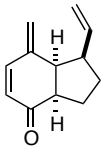


Figure II-1. *Panel A*: Proposed formation of ottelione A (**101**) from [m]-cyclophane **115** in the biosynthesis of **101**. *Panel B*: Truncated analogs of **101** (**202-exo**) and **115** (**201**) lacking the benzyl substituent.

[52] Hoye, T. R.; Kabrhel, J. E.; Brown, S. G.; Hanson, G. H. Biosynthesis of (+)-Ottelione A: Is a Cope Rearrangement Sufficiently Facile to be the Key Feature, Manuscript in Preparation

[53] The "exo" descriptor is affixed to **202-exo** as a comparison to the **202-endo** counterpart and will be addressed later in this chapter:



202-endo

[54] Kabrhel, J. Is a Cope Rearrangement Viable as the Key Feature in the Biosynthesis of (+)-Ottelione A? Ph.D. Thesis, University of Minnesota, MN, 2006.

phenolic [m]-cyclophane **203** (Figure II-2). Access to this strained [m]-cyclophane was achieved through the MOM-deprotection of phenol **204-prox**.[55] The energetics involved in the transformation of **203** to **202-exo**

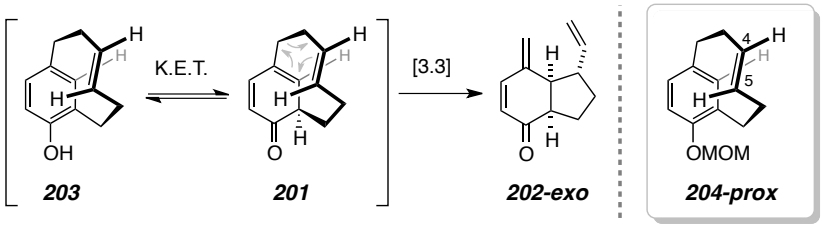
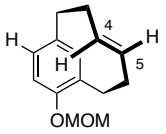


Figure II-2. Cope rearrangement with the strained compound **201** to **202-exo**. **201** can be accessed from the Keto-Enol-tautomerization (K.E.T.) from **203** that is made from the MOM-protected phenol **204-prox**.

were investigated through a computational study in the early stages of the synthetic efforts (Figure II-3). Specifically, phenol **203**, the cyclohexadienone tautomer **201** (nor-benzyl-**115**), the Cope rearranged isomer **202-exo** (nor-benzyl-**101**), and the transition structure **205** for the sigmatropic rearrangement converting **201** into **202-exo** were examined. The phenolic metacyclophene **203** was computed to be only 7.6 kcal mol^{-1} more stable than its dearomatized keto tautomer **201**, suggesting that **201** might be accessible experimentally via **203**. Most intriguingly, the activation barrier for the rearrangement of **201** to **202-exo** was only 14.1 kcal mol^{-1} (cf., E_{ACT} = 33.5 kcal•mol^{-1} for 1,5-hexadiene[56]). Presumably the cumulative effects of preorganization of the 1,5-diene into a chair-like geometry along with the strained (anti-Bredt) nature (cf., bullvalene family[57]) of **201** combine to render the rearrangement facile (cf., E_{ACT} = 15-18

[55] The descriptor 'prox', short for proximal, is affixed to **204-prox** to describe the orientation of the C(4)-C(5) double bond with respect to the MOM-protecting group on the aromatic ring. Namely, the highly shielded alkene proton (at C5) is closer to the MOM group in what we call here the proximal isomer and more remote (at C4) in the distal isomer (**204-dist**):



204-dist

[56] Dewar, M. J. S.; Wade, Jr. L. E. A Study of the Mechanism of the Cope Rearrangement *J. Am. Chem. Soc.* **1977**, *99*, 4417-4424.

[57] Williams, R. V.; Quast, H.; Borden, W. T. How Important Is Bishomoaromatic Stabilization in Determining the Relative Barrier Heights for the Degenerate Cope Rearrangements of Semibullvalene, Barbaralane, Bullvalene, and Dihydrobullvalene? *J. Org. Chem.* **2005**, *70*, 2627-2632.

kcal mol^{-1} for *cis*-1,2-divinylcyclopropane.[58] We then sought to explore this seemingly facile rearrangement in the laboratory.

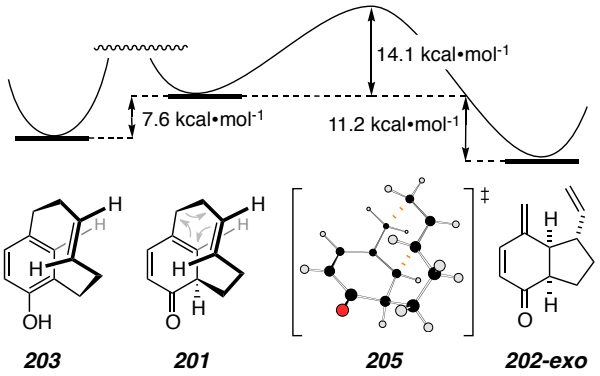


Figure II-3. Computed energetics of the Cope rearrangement [m]-cyclophane **203** to yield hydrinenone **202-exo** using DFT-B3LYP/6-31G* (adapted from ref 52).

II-A-2. *First generation synthesis of 204-prox.*[59]

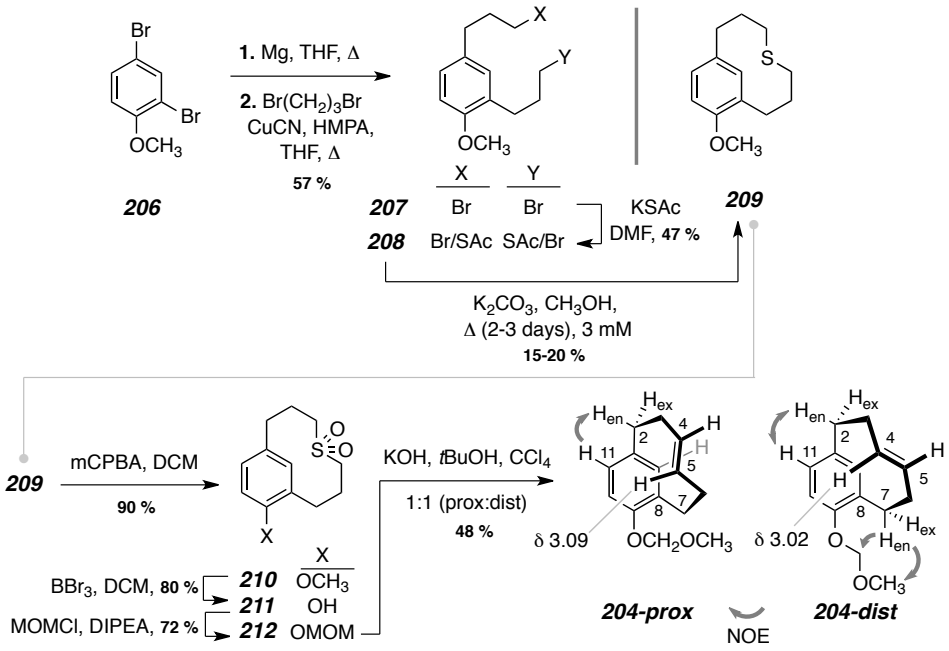
Summarized in Scheme II-1 is the synthesis of the [m]-cyclophane substrate **204-prox**, the MOM-protected version of phenol **203**. The first strategy employed in this synthesis was the Ramberg-Bäcklund reaction of the cyclic sulfone precursor **212,** which provided access to the strained alkene in the atropisomers **204-prox** and **204-dist**. The synthesis begins with the bis-alkylation of the 2,4-dibromoanisole (**206**) with 1,3-dibromopropane, which gave the dibromide **207**. Initial attempts to form the sulfide **209** involving a double S$_N$2 displacement of the bromides with Na_2S, gave only a 6-10% yield.

[58] A relatively low barrier especially after being compared to the activation barrier for the protypical Cope rearrangement of 1,5-hexadiene, 33.5 kcal•mol^{-1}.

[59] The synthesis of **204-prox** was accomplished and optimized by Dr. James Kabrhel and Dr. Gregory Hanson, both former members of the Hoye group.

Closer inspection of the product distribution revealed the dimer resulting from an

Scheme II-1. Synthesis of Cope precursor **204-prox.**



intermolecular double S_N2 displacement as the major product. Our efforts then turned to limiting the degree of dimerization by initial introduction of the sulfur atom followed by intramolecular S_N2 reaction. This was accomplished by first forming the mono-thioacetate **208** with a subsequent base-promoted intramolecular cyclization to give **209**.[60] Oxidation of the sulfide to the sulfone **210** followed by demethylation of the anisole and MOM-protection of the resultant phenol gave **212**.

Meyers modified Ramberg-Bäcklund conditions provided **204-prox** and **204-dist** that could be separated by HPLC with no sign of interconversion even under gas chromatographic analysis at elevated temperature.[61] Only the *E*-alkenes were observed (along with a minor chloroalkene byproduct) as the products of the Ramburg-Backlund olefination. The proper assignment of structure of each of these atropisomers was crucial, since the 1,5-diene subunit destined for probing the ease of the Cope rearrangement is rigidly held in a chair-like arrangement in **204-prox** but is boat-like in **204-dist**.

[60] The yields for this transformation were variable and the highest accomplished yield was 15-20%. This was the bottle-neck of the synthesis, and the issues encountered in this route will be discussed later.

[61] The cavity through which an alkene proton must pass to interconvert rotamers **204-prox** and **204-dist** is too small to permit that process.

Fortunately, all proton resonances in the ^{1}H NMR spectrum of the **204-dist** isomer were sufficiently resolved (in benzene-d_6) to permit full assignment, which was supported by complementary COSY, HMQC, and coupling constant data. The five-spin systems for protons attached to each of the contiguous C2-C4 and C5-C7 moieties in **204-dist** were fully identified.[62]

In the key experiment (Scheme II-2), a $CDCl_3$ solution of the proximal MOM ether **204-prox** and DMS (9 equiv) was treated with BF_3•OEt_2 (8 equiv) at ambient temperature. The initial ^{1}H NMR spectrum of this mixture was taken less than five minutes after addition of the Lewis acid. To our delight, no starting material remained and new resonances consistent with the 4-methylenecyclohex-2-en-1-one **202-exo** (as well as ca. one equivalent of the obligate $MeOCH_2(Me)_2S^+$ ion) were clearly evident in the spectrum. While the challenges associated with the synthesis of the strained substrate **204-prox** meant that we never had large quantities, this experiment was performed on at least eight separate occasions (on scales between 1 and 16 mg of the metacyclophene), and the product **202-exo** was formed in every instance. Yields of **202-exo** following chromatographic purification varied between 25-40%, and it was typically the major product.

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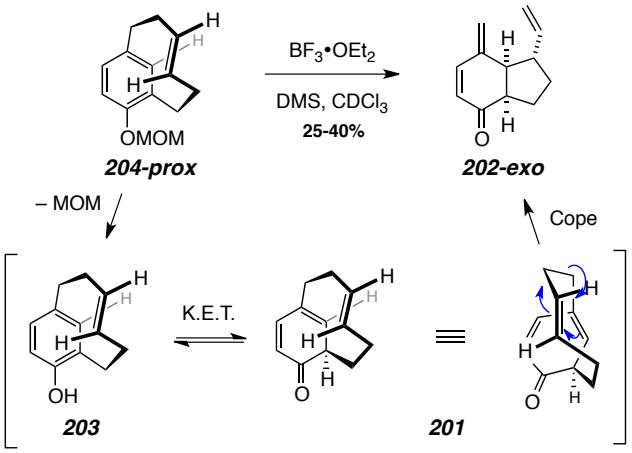
[62] The alkene proton H4 (δ 3.02) was shielded in **204-dist**. Importantly, H_{2en} showed mutual nuclear Overhauser enhancement (NOE) interactions with the aromatic proton H11 whereas $H7_{en}$ enhanced the methylene and methyl proton resonances arising from the MOM group. While several of the proton resonances in **204-prox** were partially overlapped, analysis of 2D spectra again allowed binning of the two sets of five protons at C2-C4 and, separately, C5-C7. Now, the highly shielded alkene proton (H5, δ 3.09) resides within the latter group. An NOE of H_{2en} upon irradiation of H11 confirmed the proper assignment of structures.

Scheme II-2. MOM-group removal of **204-prox** preempts the Cope rearrangement within **201** to **202-exo**.



We suggest that the phenol **203** tautomerizes to the dienone **201** in this acidic reaction medium and that a rapid Cope rearrangement ensues to give **202-exo**. Proper assignment of the relative configuration for the three stereocenters in **202-exo** is critical to the discussion if we are to offer this experimental outcome as the primary evidence to support our hypothesis that an analogous rearrangement (i.e., **115** to **101**, Scheme I-1) is the central element in ottelione A (**101**) biosynthesis. This amazing result was however muddied by an earlier account by Jones et. al,[63] wherein they reported the flash vacuum pyrolysis (FVP) of a spriocyclcictrienone to produce a mixture of hydrindenone compounds, one the C1-epimer of **202-exo**, namely, **202-endo**. A problem arises from the observation that two different structures have now been tentatively assigned to a substance having an identical ^{1}H NMR spectrum. We therefore took it upon ourselves to investigate the spectral properties of the compound originally reported as **202-endo**, by reproducing the FVP experiment (this will be presented in detail in Chapter III).

[63] Murray, D. F.; Baum, M. W.; Jones, 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.

II-B. EFFORTS TOWARD THE IMPROVED SYNTHESIS OF 204-PROX

II-B-1. *Synthesis of 209 – A chromatographic solution.*

As stated in the previous section, synthesis of cyclic sulfide **209** (Scheme II-1) proved to be the bottleneck of the synthetic plan *en route* to **204-prox**. In addition to attaining ample quantities of **209**, synthesis of the thioacetate-bromide **208** also proved to be problematic due to the difficulty in separating the starting dibromide **207**, the desired compound **208** and the dithioacetate **213** (Panel A, Figure II-4). This problem was circumvented by using a polar thioacetate analog such as in **214**. The synthesis of a

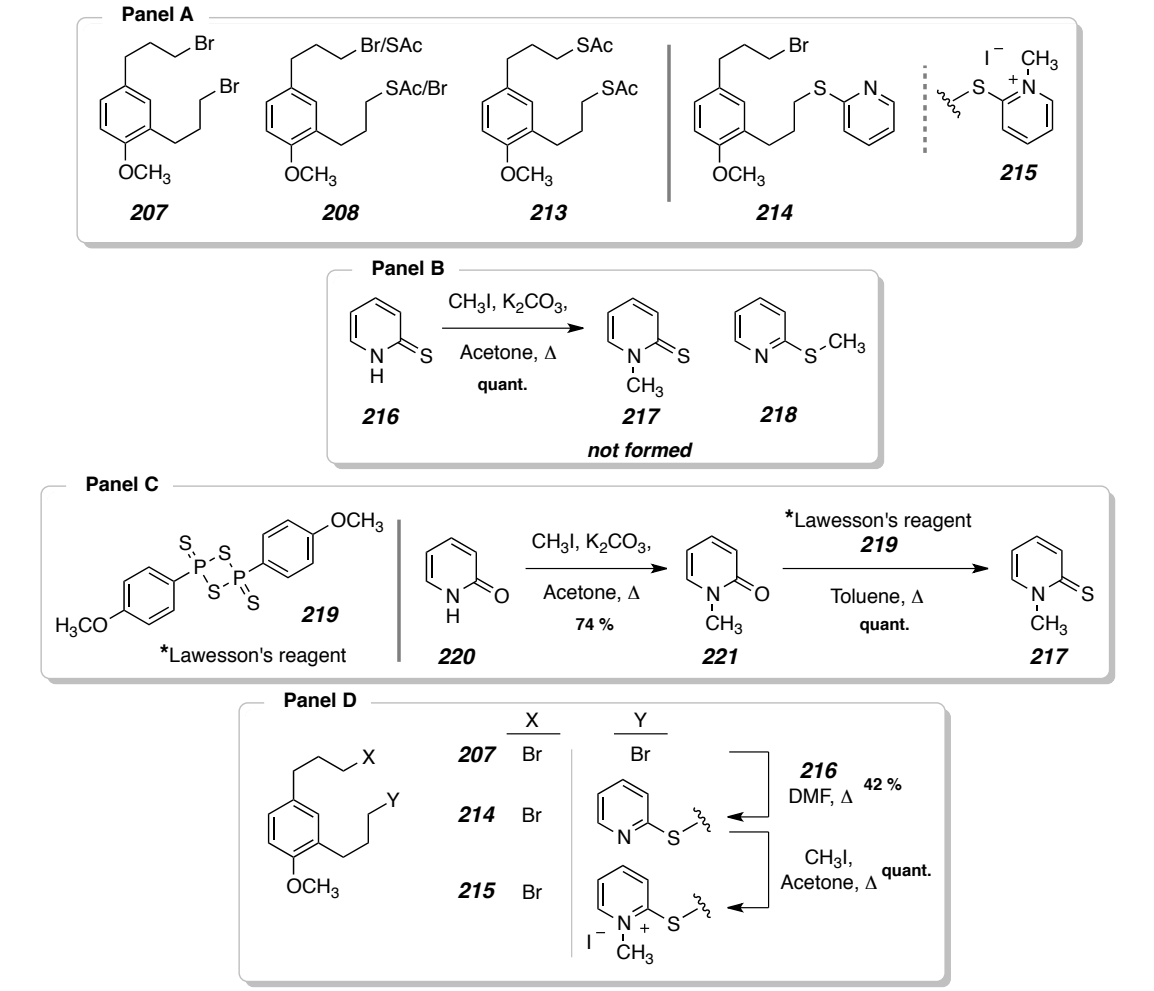


Figure II-4. Synthesis of intramolecular S_N2 precursor **208**

compound such as **214** would allow for the facile purification of a now more polar analog with a sulfur atom already incorporated in the desired position. Methylation of this compound to a pyridinium salt such as **215** would then allow for removal of the pyridine group to provide a free thiol (or the cyclic sulfide **209**).

We explored making the polar side chain by first synthesizing the 2-thio-pyridone (**217**). However, we isolated the *S*-methylated compound **218** in quantitative yield instead of the desired 2-thio-pyridone **216** (Panel B, Figure II-4). We then opted to make compound **217** by first methylating the commercially available 2-pyridone (**220**) to give compound **221** (Panel C, Figure II-4). This was then subjected to the thiolation step with Lawesson's reagent to provide compound **217** in a quantitative yield. When compound **217** was made to react with dibromide **207**, even after extensive heating to temperatures as high as 80 °C, no reaction was observed. Thus given the outcome in Panel B, Figure II-4 wherein methylation at the sulfur was preferred to that of methylation at the nitrogen we instead first reacted dibromide **207** with **216** (Panel D, Figure II-4) that successfully gave **214** along with the expected regioisomer.[64] Methylation provided compounds that could potentially be transformed to the cyclic sulfide **209**. However exploration of conditions used in the literature to invoke similar transformations[65] failed and in most cases provided the demethylated **214**. With these roadblocks encountered with the strategy of using the improved separation of starting materials in the intramolecular displacement, we switched our focus to completely changing the synthetic strategy employed to make **209**.

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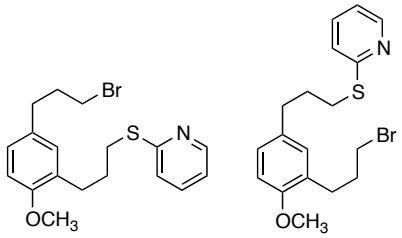
[64] These regioisomers could not be separated, however this was of no concern since both regioisomers could be taken forward to produce the desired cyclic sulfide **209** as in the case of the thioacetates mentioned in the previous section:



214 ***214'*** regioisomer

[65] NaOH in H_2O:THF at varying concentrations.

II-B-2. *A thiol-ene click strategy*

The thiol-ene reaction, herein described as the addition of a "S–H" bond across a double bond, has long been exploited as a means for hydrothiolation in the polymer and material science fields.[66, 67] The term 'click' was later added as the thiol-ene transformation has characteristics befitting the definition of a click reaction proposed by Sharpless in 2001.[68] Generally the thiol-ene reaction is performed under photochemically induced radical conditions (Figure II-5). Beginning with the formation of the thiyl radical, **II**, followed by addition of the radical across the double bond, **III**, to give an intermediate carbon centered radical, **IV**, and then lastly the chain transfer to a second molecule of RS–H to give the thiol-ene addition product, **V**. Specific to the synthesis of

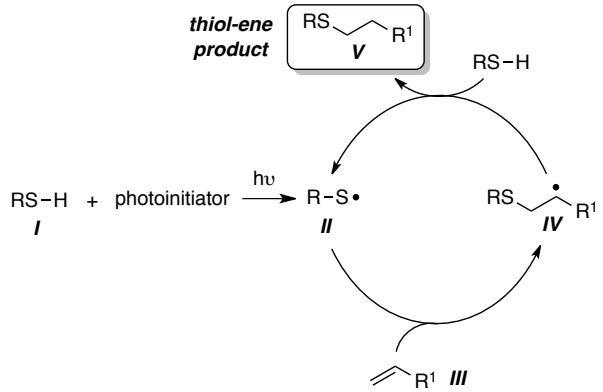


Figure II-5. Mechanism of a photoinitiated thiol-ene click reaction

209 we envisioned the intramolecular thiol-ene click reaction of **222** (Figure II-6). We then set out to synthesize compound **222** or a close analog that would give us the ability to probe this thiol-ene click transformation.

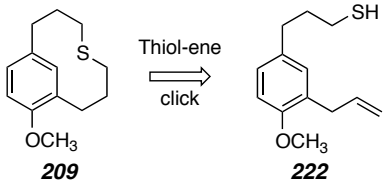


Figure II-6. Proposed thiol-ene click precursor, **222**, to form compound **209**.

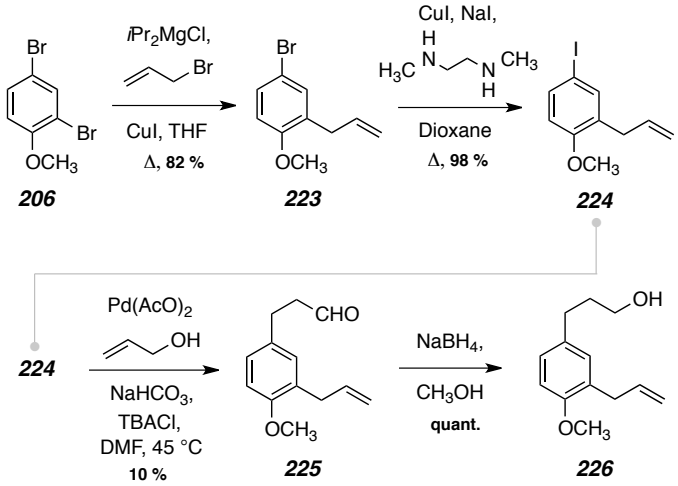
[66] Lowe, A. B. Thiol-Ene 'Click' Reactions and Recent Applications in Polymer and Materials Synthesis. *Polym. Chem.* **2010**, *1*, 17–36.

[67] Hoyle, C. E.; Lowe, A. B.; Bowman, C. N. Thiol-Click Chemistry: a Multifaceted Toolbox for Small Molecule and Polymer Synthesis. *Chem. Soc. Rev.* **2010**, *39*, 1355–1387.

[68] Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Click Chemistry: Diverse Chemical Function From a Few Good Reactions. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021.

Beginning with the allylation of the commercially available dibromide **206** via lithium-halogen exchange with *i*Pr_2MgCl in the presence of CuI provided the *ortho*-allyl anisole **223** in a 82% yield (Scheme II-3).[69] An "aromatic Finkelstein" reaction[70] provided the iodide **224**.[71] A formal Heck reaction to provide aldehyde **225** proceeded in a rather dismal yield of 10%.[72] The reduction to alcohol **226** proceeded in a quantitative yield. However, the low yield encourages us to consider other pathways that would improve the overall yield of the desired compound.

Scheme II-3. First generation synthesis of **222**, via synthesis of alcohol **226**.



Our second generation synthesis commenced with the quantitative Fischer esterification of the commercially available dihydro-*p*-coumaric acid **227** (Scheme II-4), followed by the *O*-allylation of the phenol to provide **229**. This allyl ether was then heated neat for 12 hours to yield the phenol **230**, by way of a Claisen rearrangement. At this point rather than methylating the phenol to **230** to access the anisole **222**, we opted to MOM-protect the phenol due to its successful removal under the key Cope rearrangement

[69] Nishiyama, H.; Isaka, K.; Itoh, K.; Ohno, K. Metal-Halogen Exchange Between Polybromoanisoles and aliphatic Grignard Reagents: A Synthesis of Cyclopenta [b] benzofurans. *J. Org. Chem.* **1992**, *57*, 407–410.

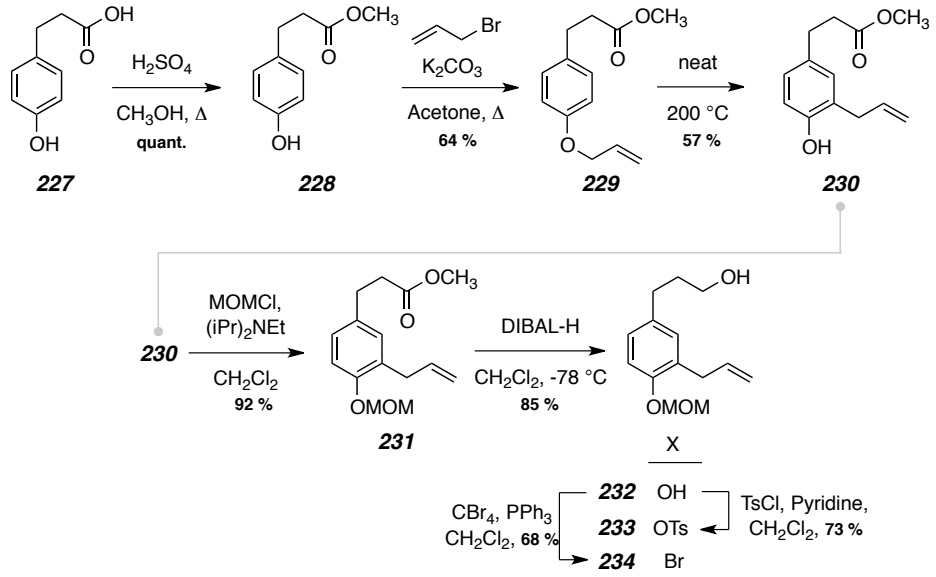
[70] Klapars, A.; Buchwald, S. L. Copper-Catalyzed Halogen Exchange in Aryl Halides: An Aromatic Finkelstein Reaction. *J. Am. Chem. Soc.* **2002**, *124*, 14844–14845.

[71] This transformation was conducted due to the failed subsequent reaction of the formal Heck reaction with the bromide **224** and allyl alcohol to provide aldehyde **226**.

[72] Jeffery, T. Palladium-Catalysed Arylation of Allylic Alcohols: Highly Selective Synthesis of β-Aromatic Carbonyl Compounds or β-Aromatic α, β-Unsaturated Alcohols. *Tetrahedron Lett.* **1991**, *32*, 2121–2124.

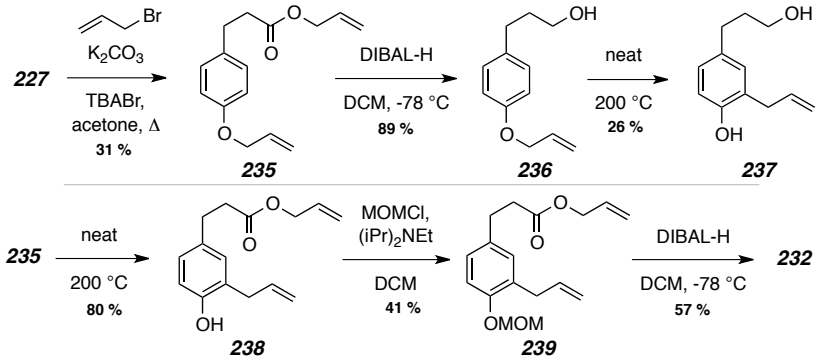
study (Scheme II-2). The MOM-protected phenol **231** was then reduced with DIBAL-H to the alcohol **232**.[73] In preparation for the displacement of the alcohol with a thiol-containing compound, **232** was tosylated to **233** or transformed to the bromide **234**.

Scheme II-4. Second generation synthesis of **222**, via the synthesis of **233** and **234**.



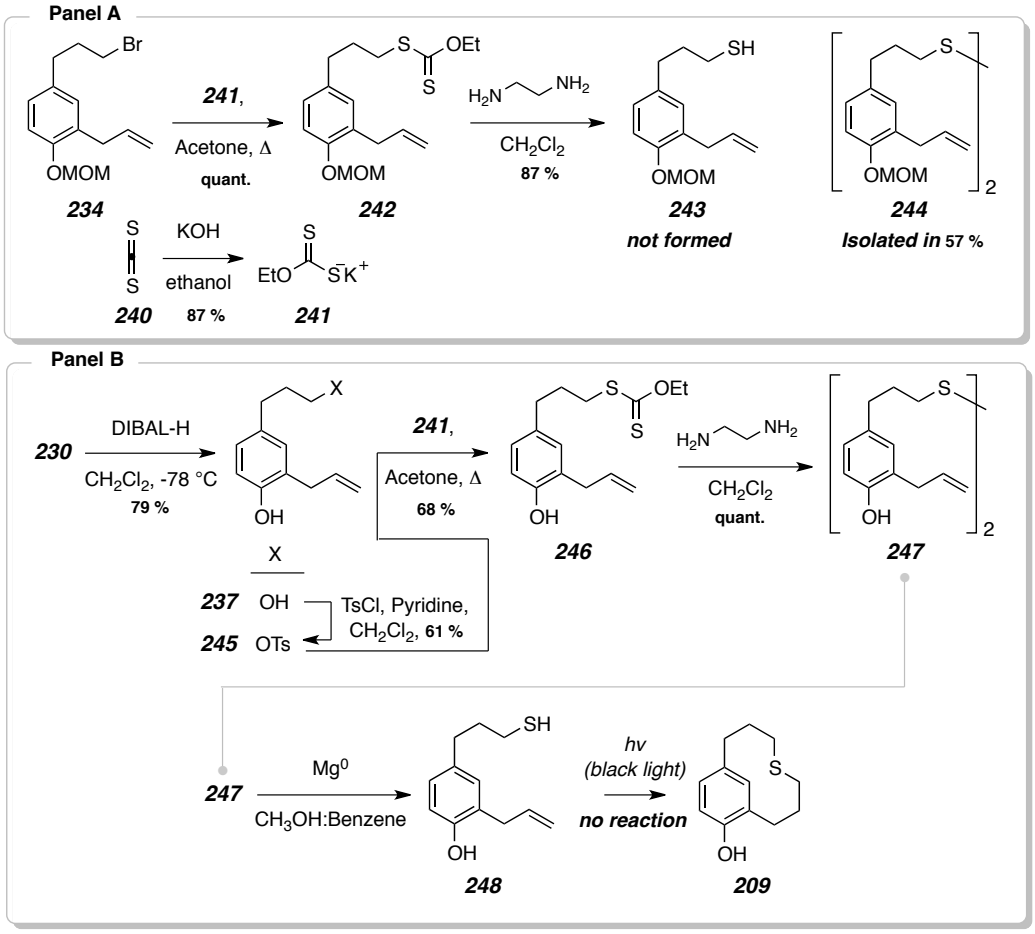
Both the tosylate **233** and bromide **234** were made to react with the xanthate potassium salt **241** to produce the xanthate **242** (Panel A, Scheme II-5). The xanthate potassium salt **241** was made by reaction of basified ethanol with carbon disulfide (**240**). The xanthate was decomposed in the presence of ethylene diamine, however instead of the free thiol **243** the dimer **244** was isolated. The free phenol was also synthesized

[73] Alternatively, **232** can be made by the route detailed below. Beginning with **227** allylation of both the phenol and carboxylic acid provided **235** that can then be reduced with DIBAL-H to provide **236**, followed by a Claisen rearrangement to **237** that can then be MOM-protected to give **232**. Conversely, from **235** and in this order Claisen rearrangement, MOM-protection and DIBAL-H reduction to **232.**



alongside the MOM-protected analog as a candidate for the thiol-ene click reaction and could be MOM-protected afterwards. From the post-Claisen phenol **230**, DIBAL-H

Scheme II-5. *Panel A:* Attempted synthesis of thiol **243**. *Panel B:* Synthesis of thiol **248**.



reduction of the ester provided the alcohol **237** (Panel B, Scheme II-5). The tosylate of alcohol **245** was then made to react with **241** to provide the xanthate **246** that was decomposed to again yield the undesired dimer **247**. However unlike the MOM-protected analog **244** reduction of the dimer **247** to free thiol **248** was accomplished by the action of magnesium turnings in a methanol/benzene mixture.[74] Although this reaction was incomplete some minute quantities of the desired thiol allowed for the exploration of thiol-ene click transformation.

[74] Reductions using dithiothreitol and $NaBH_4$ were attempted but were unsuccessful.

A rayonet reactor was employed as the source of the black light to invoke the desired transformation. After several hours of exposure to the light source only dimerization of the thiol was observed. With this result we again returned to the literature for more attractive and straightforward approaches to the cyclic sulfide **209**.

III-B-3. *Double β-alkyl Suzuki reaction*

Our next strategy involved the double β-alkyl Suzuki coupling reaction of a boronate derivative of diallyl sulfide such as **250** or **251** with a dihalide **206** or **249** (Figure II-7). This approach was attractive to us on a number of levels with the main reason being the direct access to the desired **209**. The β-alkyl Suzuki reaction has found prominence due

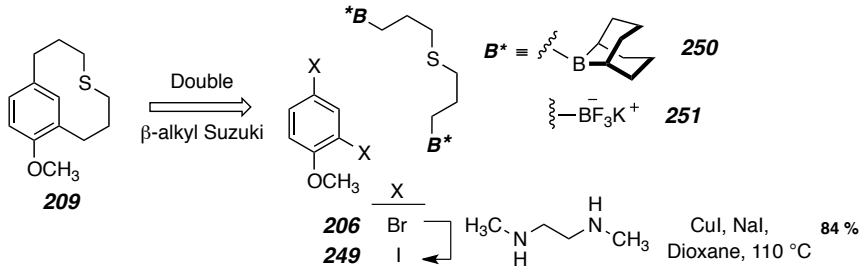


Figure II-7. Double *β*-alkyl Suzuki strategy.

to the mild and versatile conditions that can be used to forge C_{sp}^3–C_{sp}^2 bonds as compared to other methods such as the Negishi protocol.[75] We were enthralled by the possibility of directly forming the [m]-cyclophane in particular after coming across a report where the dimethyl diallyl silane **252** (Figure II-8) was first hydroborated with 9-BBN (**253**) and then subjected to the double β-allyl Suzuki reaction with the dibromobenzene **254** to give

[75] Trauner, D.; Danishefsky, S. J. The β-Alkyl Suzuki–Miyaura Cross-Coupling Reaction: Development, Mechanistic Study, and Applications in Natural Product Synthesis *Angew. Chem. Int. Ed.* **2001**, *57*, 553–563.

compound **255**.[76] Other [m]-cyclophanes synthesized using the β-alkyl Suzuki protocol also encouraged our foray into this method of stitching the molecule together.[77, 78] This reaction was successfully replicated and expanded to dibromoanisole **206** with reproducible yields.

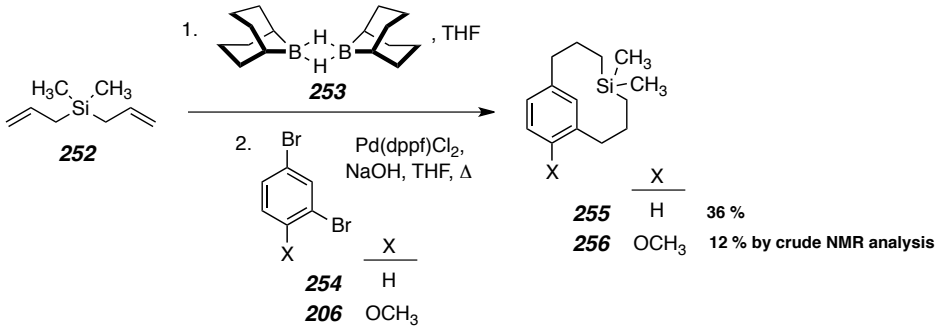


Figure II-8. Literature precedent of formation of [m]-cyclophane **255**.

We then investigated this reaction with more related substrates in the synthesis of **209**. Attempts at performing the double β-alkyl Suzuki with the actual substrates diallyl sulfide (**258**) and dibromoanisole **206** were all unsuccessful (Entries 1 and 4, Table II-1). Since we recovered ample quantities of the dibromide, we postulated that the initial oxidative addition step of the Pd-catalyst of **223** was slow and a more labile bond would aid in the transformation, which led to an attempted coupling of diiodoanisole **250** (Entry 2, Table II-1).[79] We even attempted the reaction with the dibromobenzene **254** in hopes that the less electron rich benzene would aid in the oxidation step (Entry 3, Table II-1). While we aware that macrocycle formation would be more difficult with the diallyl sulfide substrate than with the diallyl dimethyl silane, due to the shorter bond length of the C–S bond (1.81Å) compared to the C–Si bond (1.94 Å), we thought it was odd that not even the first bond forming event occurred. Consequently we investigated the simple

[76] Kwochka, W. R.; Damrauer, R.; Schmidt, M. W.; Gordon, M. S. Synthetic and Computational Studies of Silametacyclophanes: Macrocyclic Cage Compounds. *Organometallics* **1994**, *13*, 3728–3732.

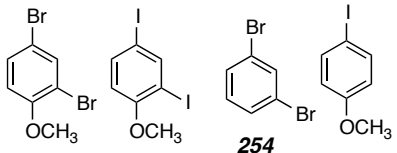
[77] Smith, B. B.; Kwochka, W. R.; Damrauer, R.; Swope, R. J.; Smyth, R. J. Synthesis of [6.6]Metacyclophane via the Suzuki Coupling. *J. Org. Chem.* **1997**, *62*, 8589–8590.

[78] Smith, B. B.; Hill, D. E.; Cropp, T. A.; Walsh, R. D.; Cartrette, D.; Hipps, S.; Shachter, A. M.; Pennington, W. T.; Kwochka, W. R. Synthesis of [n]- and [n.n]Cyclophanes by Using Suzuki−Miyaura Coupling. *J. Org. Chem.* **2002**, *67*, 5333–5337.

[79] It should be noted that the hydroboration step was not problematic as NMR study and subsequent oxidative workup with basic hydrogen peroxide proved that the hydroboration proceeded smoothly.

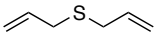
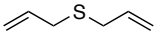
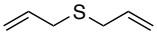
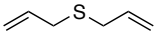
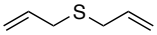
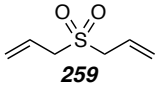
coupling with the diallyl sulfide **258** with two equivalents of 4-iodoanisole **257** (Entry 5, Table II-1). A Reaxys search of the β-alkyl coupling of a boron-derivative with an

Table II-1. Conditions screened in the quest of conducting the double *β*-alkyl Suzuki

*Halides: 

206 ***250*** ***254*** ***257***

Conditions: 1. Hydroboration: 9-BBN 2. Base: NaOH 3. Solvent: THF

Entry	*Halide	Alkene	Pd-catalyst
1	***206***	 ***258***	$Pd(PPh_3)_4$
2	***250***		$Pd(PPh_3)_4$
3	***254***		$Pd(PPh_3)_4$
4	***206***		$Pd(dppf)Cl_2$
5	***257*** (2 equiv)		$Pd(dppf)Cl_2$
6	***206***	 ***259***	$Pd(PPh_3)_4$

appropriately placed thioether, only yielded couplings with trifluoroboronate derivatives pioneered by the Molander laboratory.[80, 81, 82] In a last ditch effort to observe the double β-alkyl Suzuki coupling product we also tried the sulfone **259**[83] with the dibromoanisole **206** (Entry 6, Table II-1), only to recover **206** in appreciable yields.

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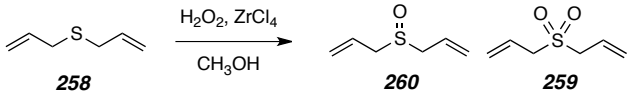
[80] Molander, G. A.; Yun, C. S.; Ribagorda, M.; Biolatto, B. β-Alkyl Suzuki-Miyaura Cross-Coupling Reactions with Air-Stable Potassium Alkyltrifluoroborates. *J. Org. Chem.* **2003**, *68*, 5534–5539.

[81] Molander, G. A.; Ito, T. Cross-Cupling Reactions of Potassium Alkyltrifluoroborates with Aryl and 1-Alkenyl Trifluoromethanesulfonates. *Org. Lett.* **2001**, *3*, 393–396.

[82] Molander, G. A.; Katona, B. W.; Machrouhi, F. Development of the Suzuki−Miyaura Cross-Coupling Reaction: Use of Air-Stable Potassium Alkynyltrifluoroborates in Aryl Alkynylations. *J. Org. Chem.* **2002**, *67*, 8416–8423.

[83] Bahrami, K. Selective Oxidation of Sulfides to Sulfoxides and Sulfones Using Hydrogen Peroxide (H_2O_2) in the Presence of Zirconium Tetrachloride. *Tetrahedron Lett.* **2006**, *47*, 2009–2012.



258 ***260*** ***259***

The promise of a potential Suzuki coupling with a thioether and various aryl derivatives enticed us to probe Molander's chemistry of the trifluoroboronates. However in an account by Molander (where they highlight improved conditions that promote the β-alkyl Suzuki reaction with aryl chlorides) they report a similar failed coupling of **262** with **263** (Figure II-9).[84] However we thought access to the diiodoanisole would enhance the likelihood of the coupling.[85]

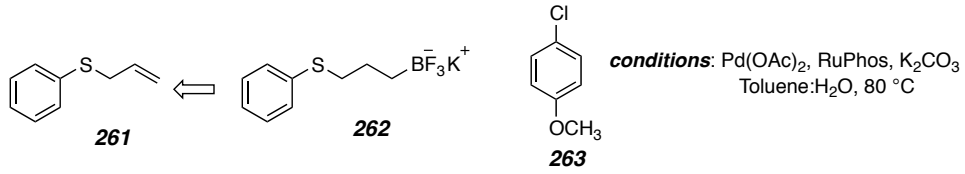


Figure II-9. Substrates and conditions attempted in the Molander laboratory that ultimately did not yield the desired compound.

We then turned to the synthesis of **262** (Scheme II-6). Allylation of benzenethiol **268** provided the allyl sulfide **261** that could be oxidized the sulfone **269** for later studies.[86] The allyl sulfide could also be subjected to first the hydroboration with $HBBr_2$•DMS followed by aqueous work-up, providing the boronic acid **270**, which could be recrystallized and used itself for Suzuki coupling. The acid was then made to react with potassium bifluoride (KHF_2) to produce the trifluoroboronate **262** that was also recrystallized and could be stored at ambient conditions. The Suzuki coupling of **262** with 4-iodoanisole **257** was attempted but was unsuccessful. Ultimately electron rich aryl halides proved problematic for the Molander group with a similar trifluoroboronic acid derivative.[80] The β-alkyl Suzuki coupling of **262** was successful with 4-acetylphenyltriflate. There is already inherent difficulty in the coupling of compounds

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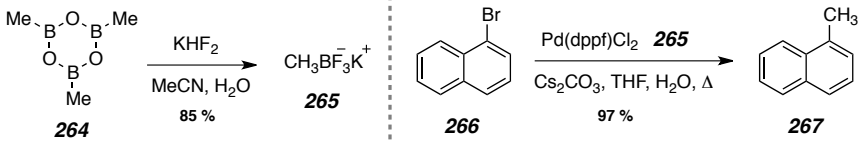
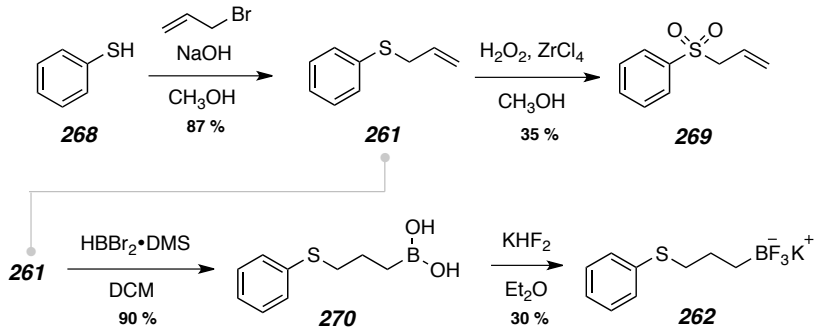
[84] Dreher, S. D.; Lim, S. E.; Sandrock, D. L.; Molander, G. A. Suzuki−Miyaura Cross-Coupling Reactions of Primary Alkyltrifluoroborates with Aryl Chlorides. *J. Org. Chem.* **2009**, *74*, 3626–3631.

[85] Synthesis of **265** according to literature protocol proceeded smoothly.[80] Deoxygenation was conducted using an argon balloon prior to the Suzuki coupling that proceed smoothly. When this was not conducted the reaction failed and yielded none of the desired compound:



[86] Formation of the tribfluoroboronic acid derivative was attempted, however this gave the desired compound in poor yields. Formation of **262** followed by oxidation with *m*CPBA however gave the sulfone tribfluoroboronic acid derivative.

Scheme II-6. Synthesis of the trifluoroboronate **262.**



with a leaving groups at the C-3 of alkylboranes such as 3-halopropylboranes. These compounds have been employed in the synthesis of cyclopropanes upon treatment with an appropriate base.[87, 88] While this innate difficulty was overcome with the synthesis of **262** (and only in the reaction with electron deficient aryl compounds) the fact remains that this could be a possible explanation why the reaction with **257** was unsuccessful. With this in mind we thought to make a thioether trifluoroboronate with a corresponding thiolate anion with a decreased propensity to act as a leaving group. So rather than a phenyl allyl thioether, an alkyl allyl thioether such as **272** could be more forgiving (Scheme II-7). Beginning with the allylation of **271** followed by the same two-step protocol applied in the previous scheme of hydroboration and reaction with potassium bifluoride, provided **274**. The trifluroboronate **274** was successfully coupled with 1-bromonaphthelene although in low yield to produce **275**.

We then turned our attention to the formation of the [m]-cyclophane. We first explored this chemistry with the dimethyl diallyl silane **252** given its success in the 9-BBN derivative coupling. Hydroboration of **258** to the boronic acid **278** and the subsequent reaction with potassium bifluoride to produced **279** (Scheme II-8). Dibromoanisole **206** was then made to react with **279** and after extended heating only compound **206** was recovered from the reaction mixture. We still opted to attempt the

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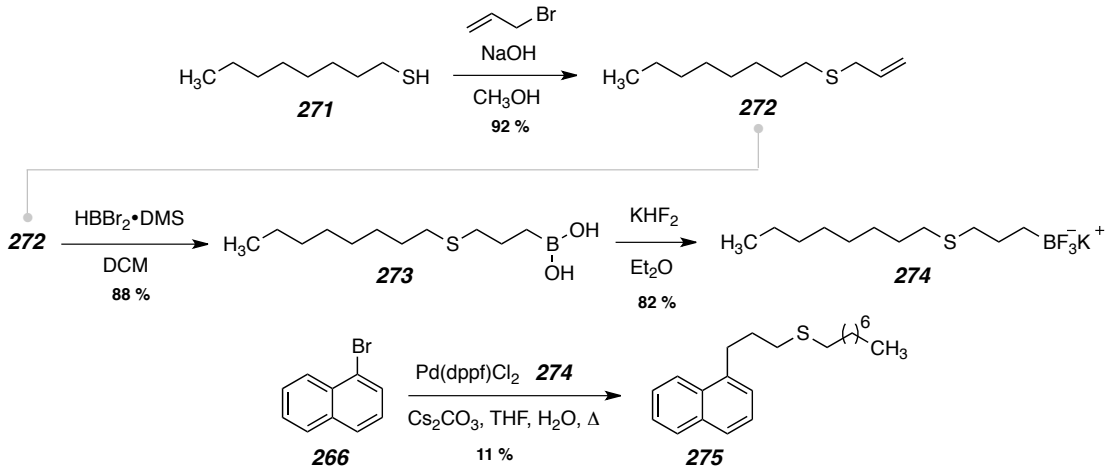
[87] Hawthorne, M. F.; Dupont, J. A. The Preparation and Reactions of β-Chloroethyl-and γ-Chloropropylborane Derivatives. *J. Am. Chem. Soc.* **1958***, 80*, 5830–5832.

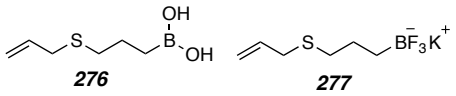
[88] Brown, H.C.; Rhodes, S. P. Synthesis of β-Cyclopropyl-and β-Cyclobutylbicyclo [3.3.1] Nonane via Ring Closure of Boron Intermediates. a Convenient Entry Into Cyclopropyl and Cyclobutyl Derivatives via Hydroboration. *J. Am. Chem. Soc.* **1969***, 91*, 2149–2150.

Scheme II-7. Synthesis of the trifluoroboronate **274.**

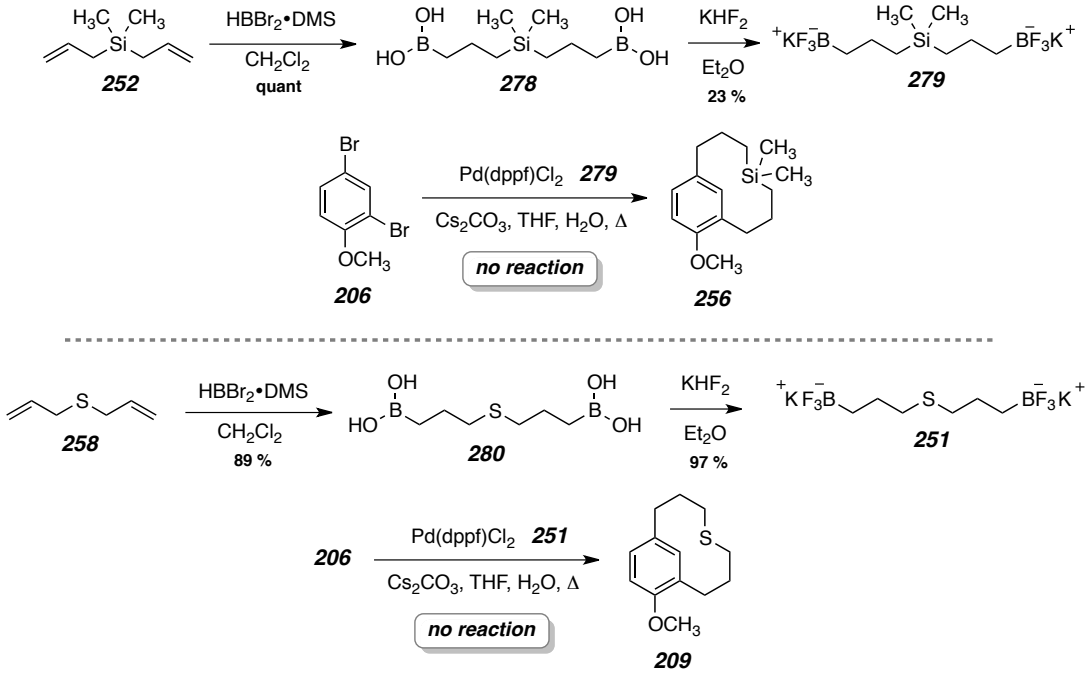


reaction with the actual substrate, and we prepared trifluoroboronate **251**. The yields of both the hydroboration and the reaction with the potassium bifluoride were low and in some cases the hydroboration did not go to completion.[89] As was suspected the reaction with the dibromoanisole **206** was not successful. Due to the struggles invoking the β-alkyl Suzuki coupling and moreover the difficulty in [m]-cyclophane formation, our efforts again turned to exploring an option were the problems encountered during [m]-cyclophane formation could be avoided.

[89] As a result of the incomplete hydroboration we were able to characterize compounds **276** and **277**:



Scheme II-8. Synthesis of **279** and **251**.



III-B-3. *Intramolecular displacement of allyl halides*

The final idea attempted in the synthesis of **209** was the double displacement of allylic halides (Figure II-10). Unlike the dibromide **207** used in the original synthesis of **209** (page 30, Scheme II-1), compound **282** or **283** would allow for greater proximity of the leaving groups thereby increasing the efficiency of the intramolecular displacement.

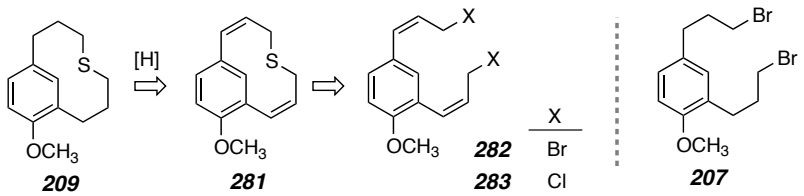
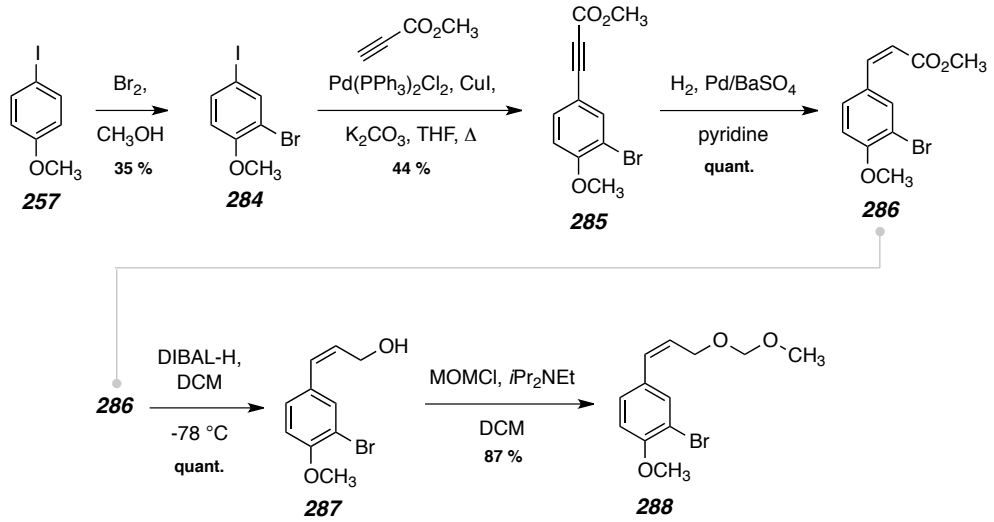


Figure II-10. Proposed formation of **281** en route to **209**.

Our original plan was to synthesize a compound that would allow for installment of different substituents at the C-2 and C-4 positions of the anisole, with one tether bearing an allylic leaving group and the other a thiol (or latent thiol, such as the thioacetate previously employed). Subsequent unveiling of the thiol would hopefully result in a facile intramolecular S_N2 displacement. Beginning with the bromination of the 4-iodoanisole **257**[90] to the iodo-bromo anisole **284** Sonogashira cross coupling with methyl propiolate,[91] gave the methyl ester **285** (Scheme II-9). Lindlar hydrogenation of **285** gave **286** that was then reduced to the allylic alcohol **287** followed by MOM-protection to yield **288**.

Scheme II-9. Synthesis of **288**.

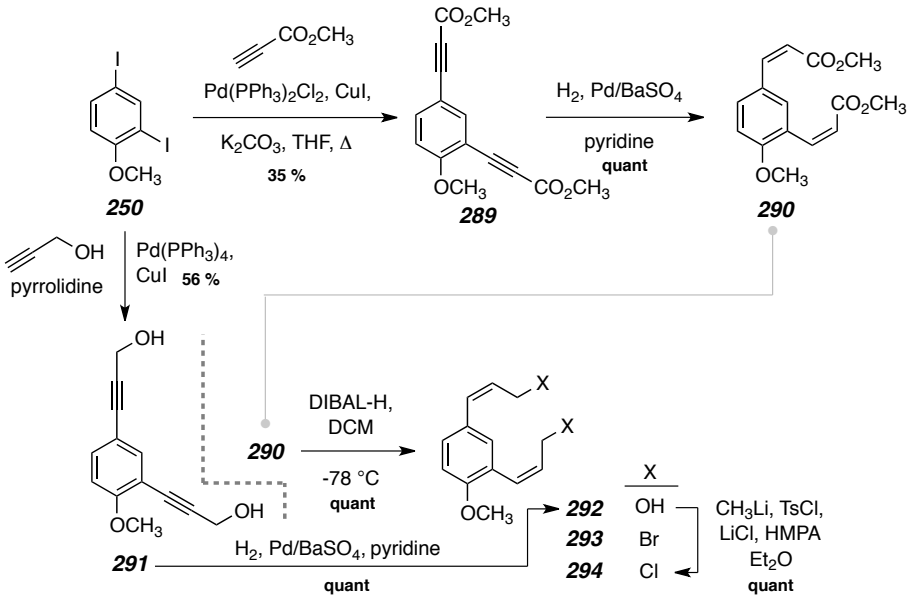


Ultimately this route was aborted due to the facility of another route that was being explored at the same time, in which we decided to synthesize a doubly allylic hailde that would allow for the displacement of both leaving groups. A double Sonogashira coupling of the diiodoanisole **250** with methyl propiolate provided **289** (Scheme II-10). Lindlar reduction yielded **290** that was reduced to the doubly allylic alcohol **292**. We later implemented a more straight-forward strategy employing a double Sonogashira reaction with propargyl alcohol to give the diol **291** followed by Lindlar reduction to **292**.

[90] Georgiades, S. N.; Clardy, J. Preparation of a Psammaplysene-Based Library. *Org. Lett.* **2006**, *8*, 4251–4254.

[91] Eckert, T.; Ipaktschi, J. A New Method for Synthesis of Methyl Arylpropiolates by Direct Heck Coupling of Aryl Iodide and Methyl Propiolate in Presence of K_2CO_3. *Syn. Commun.* **1998**, *28*, 327–335.

Scheme II-10. Synthesis of **294**.



Transformation to the dibromides **293** was attempted but was unsuccessful. On the other hand, chlorination of **292** yielded a mixture of the *cis-cis*, *cis-trans*, and *trans-trans*, di-chloro olefins **294**. These were not separated as we were of the opinion that all the diasteromers could react to form **209** if a S_N1 was operable under the reaction conditions.

We first reacted the mixture of dichlorides **294** with Na_2S in methanol under reflux (Figure II-11). This only resulted in the clean double displacement of the chloride with methanol to yield **295**. We then attempted to run the reaction in a polar non-nucleophilic solvent such as THF, however the solubility of Na_2S was problematic even at higher temperature as no sign of displacement of the chloride was observed, and only starting material was recovered.

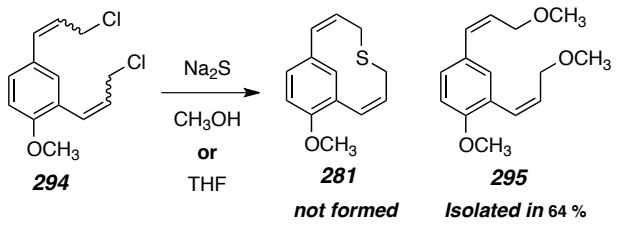


Figure II-11. Attempted cyclization conditions to produce **281**.

At this point we came to the conclusion that our initial synthesis of **209** was more attractive and would give a greater overall yield of the [m]-cyclophane than other routes explored. To this end our attention turned to exploring other interesting reaction manifolds within the context of the biosynthesis of the otteliones as well as the unambiguous proof of structure of **202-exo** versus **202-endo** (Chapter III).

II-C. PROGRESS TOWARD THE SYNTHESIS OF [9]-PARACYCLOPHANE **298**

II-C-1. *Synthesis of 2107 and attempted cyclization*

In order to probe the feasibility of the [9]-paracyclophane derivative **119** (Panel A, Figure II-12) in undergoing the tandem Claisen-Cope rearrangement in the biosynthetic pathway of the otteliones, we set out to synthesize simpler analogs in the form of the 9-paracyclophanes **296** (Cope-Cope rearrangement), **297** (Cope-Claisen rearrangement), and **298** (Claisen-Claisen rearrangement), (Panel B, Figure II-12).

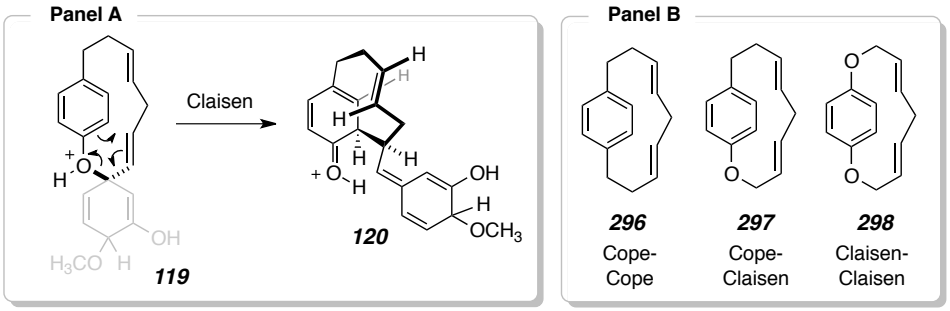
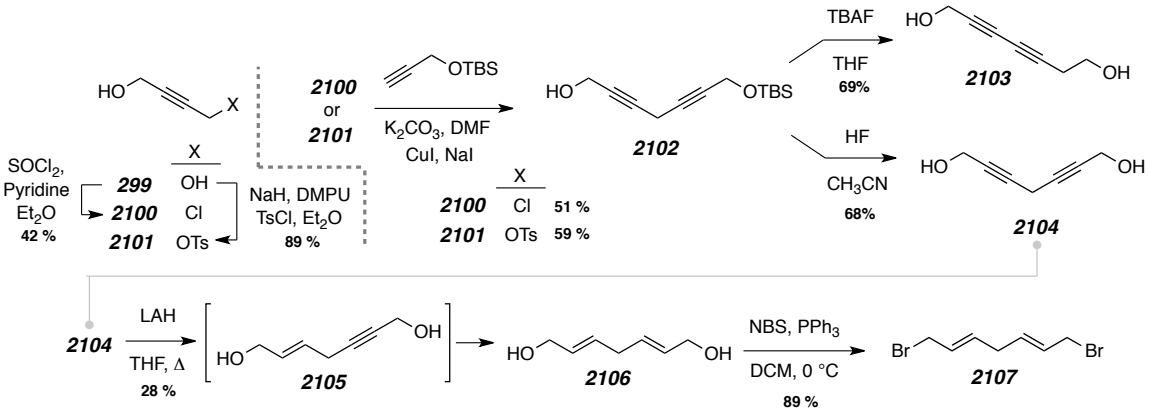


Figure II-12. [9]-Paracyclophane derivative **119** and simpler analogs **296**, **297**and **298**.

We opted to synthesize **298** due to a hopeful ease of construction with respect to the other substrates. Beginning with either the monochlorination[92] or the tosylation of butyn-diol **299**. Either the chloride **2100** or the tosylate **2101** when reacted with the TBS

Scheme II-11. Synthesis of **2107.**



[92] Qi, L.; Meijler, M. M.; Lee, S. -.; Sun, C.; Janda, K. D. Solid-Phase Synthesis of Anandamide Analogues. *Org. Lett.* **2004**, *6*, 1673–1675.

protected propargyl ether in the presence of CuI, NaI and K_2CO_3 provided alcohol **2102**.[93] Subsequent deprotection first with TBAF resulted in concomitant conjugation and gave **2103**. Whereas treatment of **2102** with HF successfully provided the desired diol **2104**. Reduction of the diol with $LiAlH_4$ provided the *trans*-alkene **2106**.[94] In some cases the ene-yne **2105** was isolated but could be re-subjected to the reaction conditions to provide **2106**. Successful formation of dibromide **2107** allowed for investigation of suitable reaction conditions to provide **298**. Unfortunately all attempts at a reaction with hydroquinone were met with disappointment, and thus our attention now primarily focused on the spectroscopic reassignment of the Cope rearrangement product from our key experiment.

[93] Lapitskaya, M. A.; Vasiljeva, L. L.; Pivnitsky, K. K. A Chemoselective Synthesis of Functionalized 1,4-Alkadiynes (Skipped Diacetylenes). *Synthesis* **1993**, 65–66.

[94] Hoffman R. W.; Kahrs, B. C.; Schiffer, J.; Fleischhauer, J. Flexible Molecules with Defined Shape. Part 3. Conformational Analysis of Bis(Tetrahydropyran-2-Yl)Methanes. *J. Chem. Soc. Perkin Trans. 2* **1996**, *11*, 2407–2414.

II-D. CONCLUDING REMARKS

The potential for improvements to the synthesis of [m]cyclophane **209** (and ultimately the Cope rearranged product **202-exo**) remains an area of interest. The ability to access substantial amounts of **202-exo** would have been ideal in unequivocally proving its structure. However given that prior attempts at scaling up this first generation pathway was not fruitful and the various attempted pathways discussed herein were unsuccessful, more effort could be put in developing a scalable synthesis of **209**.

Finally the exploration of the different reaction manifolds within the proposed biosynthetic pathway of the otteliones also remains an area where more effort is warranted. Synthesis of the 9-paracyclophanes **296**, **297**, and **298** would be a good start to this end. The successful synthesis of what has already set the stage for construction of **298** and potentially **297**. During the course of this synthesis, one should also be on the look out for the Cope and Claisen rearranged products that might be produced upon immediate formation of the paracyclophanes.

CHAPTER III

FLASH VACUUM PYROLYSIS EXPERIMENTS AND THE STRUCTURAL REASSIGNMENT OF THE JONES ISOMERS[52]

III-A. FLASH VACUUM PYROLYSIS

III-A-1. *Introduction*

"The ultimate goal of flash vacuum pyrolysis is the isolation of primary unimolecular decomposition or an early short sequence of unimolecular reactions. This is achieved by working at high temperature so that a short contact time will suffice for the primary reaction, at low pressures to inhibit secondary bimolecular reactions, with reactors and flows of carrier gas arranged to give short contact times and times of flight to cold collectors in which all reaction stop."[95]

Flash vacuum pyrolysis (hereafter referred to as FVP) is one of the pioneering experimental techniques employed by early chemists and alchemists and can be described as the "destructive distillation of mineral or organic materials".[96] FVP is characterized by its high pyrolytic temperatures and short contact time at low pressures[97] (also sometimes referred to interchangeably with FVT – flash vacuum thermolysis[98]). From as early as the fifteenth century, FVP was exploited in the laboratory as a method to synthesize sulfuric acid from ferrous sulfate. It was used as the primary method for investigating structural

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[95] Brown, R. F. C. Pyrolytic Methods in Organic Chemistry, Application of Flow and Flash Vacuum Pyrolytic Techniques.; Organic Chemistry; Academic Press: New York, 1980; Vol 4; p 39.

[96] Brown, R. F. C. Pyrolytic Methods in Organic Chemistry, Application of Flow and Flash Vacuum Pyrolytic Techniques.; Organic Chemistry; Academic Press: New York, 1980; Vol 4; p 1.

[97] Hedaya, E. Techniques of Flash Vacuum Pyrolysis. Cyclopentadienyl Radical and Its Dimer. *Acc. Chem. Res.* **1969**, *2*, 367–373.

[98] King, J. F.; De Mayo, P.; McIntosh, C. L.; Piers, K. Smith, D. J. H. Thermolysis of thiete l,l-Dioxide and Related Species. *Can. J. Chem.* **1970**, *48*, 3704–3715.

and chemical behavior due to the lack of sufficient knowledge on molecular formula and structural theory up until the nineteenth century. The broad spectrum of potential FVP experiments ranges from the mild thermal decomposition of malonic acid at 135 °C to the decomposition of methane in a porcelain tube at 1100 °C.[99]

The emergence of various high temperature and flow processes in the petroleum and petrochemical industry promoted the development of laboratory scale FVP techniques. It was during this period where the existence and chemical importance of alkyl radicals was established in his 1980 book on FVP, Brown details four major categories for the pyrolytic experiment.

> (*i*) the pyrolysis of compounds at atmospheric pressure (*ii*) pyrolysis of less volatile compounds at reduced pressure (1-30 Torr) (*iii*) Flash pyrolysis of liquids or solids in a moderate vacuum, (0.01-1 Torr) (*iv*) True flash vacuum pyrolysis (or very low pressure pyrolysis, VLPP[100]) at pressures of 0.001 Torr or less (with contact times on the order of milliseconds and usually with a short distance and time of flight before analysis or collection." [101]

Brown goes on to make the point that the distinction between the first three types of experiments are by no means sharp and are very "closely related". The fourth type of experiment is however different due to the very low pressures that are employed but that there is also gray area between types (iii) and (iv).[102]

Pyrolytic experiments typically include the operations detailed in Figure III-1. At each stage certain aspects can be adjusted to suit the experiment at hand. ***Stage 1*** – vaporization of the starting material can occur at varying temperatures and pressures. An inert carrier gas can also be used if a flash flow pyrolytic experiment is desired. In ***stage 2***, the vaporized starting material is passed through a hot tube reactor where it undergoes unimolecular rearrangements. Adjustment of the dimensions of the tube, the surface area (typically accomplished by packing the column), and the pressure is used to modulate the contact times of the molecule with the surface of the tube. In ***stage 3*** the rearranged

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[99] Hurd, C. D. The Pyrolysis of Carbon Compounds.; Chem. Catalog Co.: NewYork, 1929.

[100] Golden, D. M.; Spokes, G. N.; Benson, S. W. Very Low-Pressure Pyrolysis (VLPP); a Versatile Kinetic Tool. *Angew. Chem. Int. Ed.* **1973**, *12*, 534–546.

[101] Brown, R. F. C. Pyrolytic Methods in Organic Chemistry, Application of Flow and Flash Vacuum Pyrolytic Techniques.; Organic Chemistry; Academic Press: New York, 1980; Vol 4; p 21.

[102] Throughout the remainder of this dossier the term FVP experiments at pressures ranging from 45-70 mTorr.

compounds in the gas form are condensed at temperatures below the experiment (typically in a liquid nitrogen or dry ice/acetone trap). Finally the compounds can be

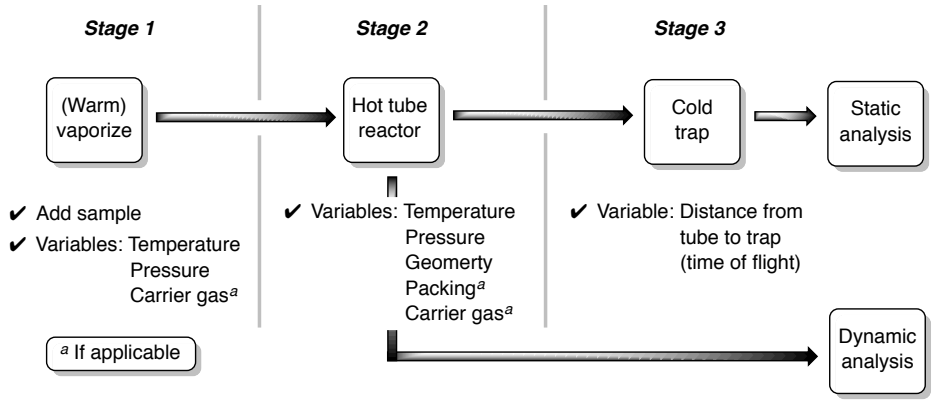


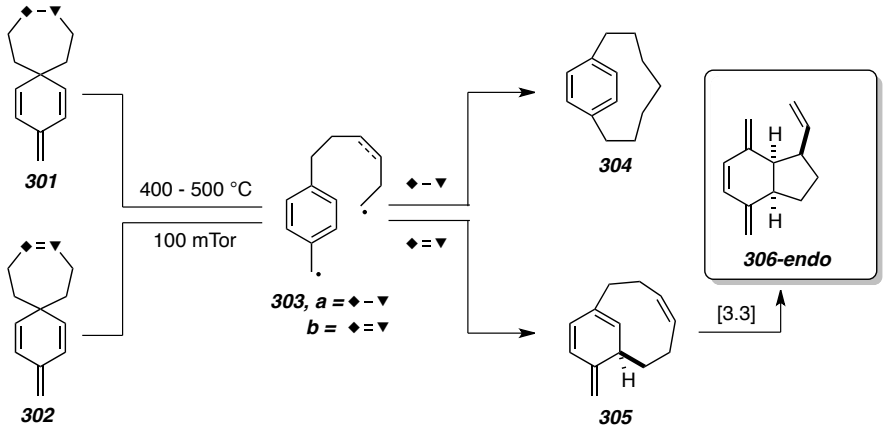
Figure III-1. Steps and variables in flow pyrolytic experiments (adapted in part from ref. 96)

analyzed by either static or dynamic methods. In static analysis, the pyrolyzed material is typically stable and can be subjected to chromatography or spectroscopic analysis. Dynamic methods analyze the emergent gas stream from the hot tube utilizing sensitive technique for species that are short-lived; for example microwave spectroscopy has been used for this purpose.

III-A-2. *Relevant FVP experiments*

The FVP of hydrocarbons was commonplace shortly after it was recognized as a reliable laboratory technique. In 1997 Van Straten and coworkers reported the FVP of the spriocyclic compound **301** to give the [7]-paracyclophane, **304**.[103,104] Here homolysis to the diradical (stabilized at one end in the benzylic position, **303a**) is followed by recombination to yield compound **304**. In an attempt to study the effect of placing a double bond at the ◆–▼ position (Scheme III-1), Jones *et al.* studied the FVP of the tetraene **302** and isolated compound **306-endo**.[63] Similar to compound **301**, **302** is believed to undergo homolysis to give a benzyl stabilized di-radical (**303b**) that then recombines to give the exo-methylene compound **305**. A [3.3]-sigmatropic rearrangement provides the hydrindene compound **306-endo**. This difference in reactivity between

Scheme III-1. Mechanism for the FVP of **301** and **302**.



301 and **302** was rationalized by Jones to occur due to the "shorter" length of the alkenyl side chain in **302**.[105] Another explanation is that the recombination of **303b** occurs reversibly to give the analogous paracyclophane whereas the recombination to give **305** immediately undergoes the irreversible rearrangement to give **306-endo**.

In 1985 Jenneskens reported the FVP of the spirocyclic-dienone **307** (Scheme III-

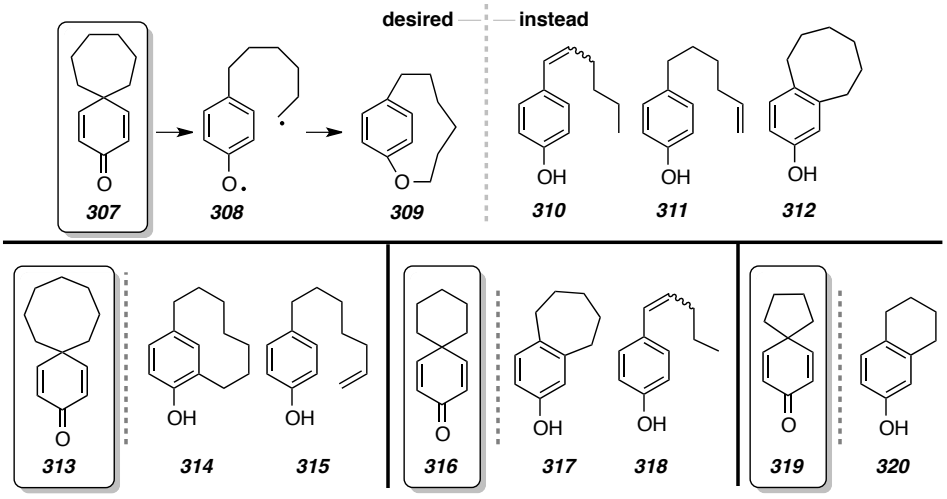
[103] Van Straten, J. W.; De Wolf, W. H.; Bickelhaupt, F. A Novel Synthesis of Short-Bridged [m]Paracyclophanes. *Rec. Trav. Chim. Pays-Bas*, **1977**, *96*, 88.

[104] Jenneskens, L. W.; De Wolf, W. H.; Bickelhaupt, F. Scope and Limitations of the Flash Vacuum Thermolysis Approach to Small [n]Paracyclophanes. *Tetrahedron* **1986**, *42*, 1561–1574.

[105] Due to the *Z*-alkene in **22** as opposed to the saturated side chain in **21**.

2).[106] This was done in an attempt to isolate the *O*-[7]paracyclophan-4-ene **309** (analogous to **304**, Scheme III-1), by way of diradical **308**. Instead they isolated compounds **310**, **311**, and **312** (Scheme III-2). They attributed this difference in reactivity to the high spin-density at the *ortho* and *para*-positions of phenoxy-stablized radicals.

Scheme III-2. FVP of **307**, **313**, **316**, and **319**.

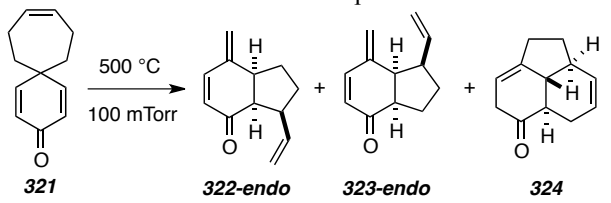


In the case of the terminal olefin **311**, the researchers hypothesize that after the initial bond homolysis to give the 1°-carbon-and-phenoxy stabilized diradical **308**, abstraction of the β-hydrogen atom of the primary radical by the *ortho*-stablized phenoxy radical, followed by tautomerization to the phenol. This only occurs in cases where the alkyl chain is long enough to permit this process. Similarly, recombination at the *ortho*-position to form *meta*-cyclophanes was only evident in cases where again the alkyl chain is long enough to facilitate this process. For example, FVP of **313** forms the *meta*-cyclophane **314** as well as the terminal alkene **315**. When the alkyl chain is too short to furnish a terminal alkene, abstraction of the β-hydrogen atom to the para-stablized radical facilitates the formation of styrenic olefin as is the case for **310** and **318**. Attack of the primary radical meta to the phenoxy radical was also evident in the FVP of **310**, **316**, and **319** (to give **312**, **317**, and **320,** respectively).

[106] Jenneskens, L .W.; Wolf, W. H.; Bickelhaupt, D. F. Flash Vacuum Thermolysis of Spirocyclohexadienones. *Tetrahedron* **1985**, 41, 3779–3784.

The key FVP experiment that spurred our efforts in exploring these types of chemistries was reported in 1986 by the Jones laboratory (Scheme III-3).[63] This study was undertaken in an attempt to explore the difference that incorporation of a double bond into the seven membered ring in the spirodieneone **307** (Scheme III-2) would make in the reactivity and products formed during the FVP reaction. Here the researchers conducted the FVP of spirotrienone **321** and they reported the isolation of the bicyclic compounds **322-endo** and **323-endo** and of the tricyclic compound **324**.

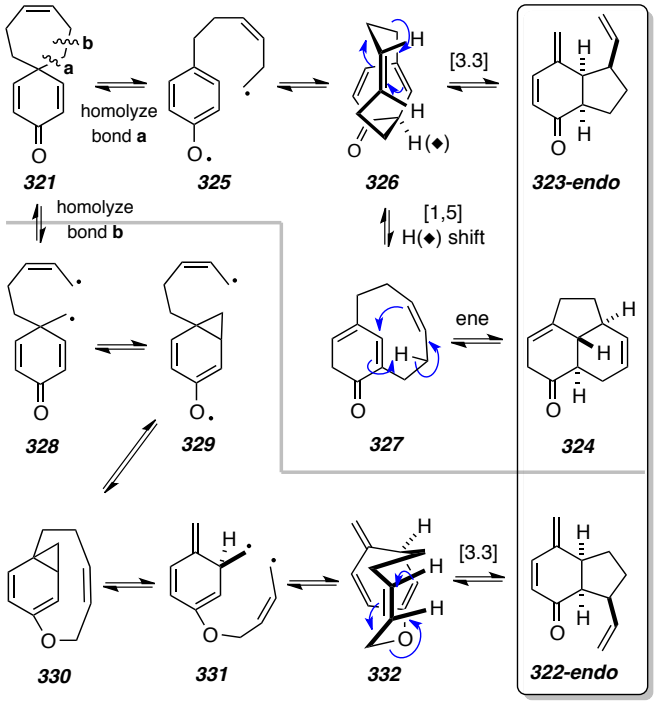
Scheme III-3. FVP of the spirotrieneone **321**.



321 ***322-endo*** ***323-endo*** ***324***

The proposed mechanism to account for the formation of these products is presented in Scheme III-4. Homolysis of bond *a* results in the homoallylic-phenoxy stabilized diradical **325** (a bond cleavage event very similar to that presented in the work by Jenneskens, **307** → **308** Scheme III-2). Recombination of **325** ortho to the *O*-radical would give rise to the meta-cyclophane **326**. Recall that the analogous *meta*-cyclophane in the case of **327** was not isolated, presumably due to the short length of the alkyl chain that was unable to recombine at the *ortho*-position. However these processes (such as the recombination at the *ortho*-position to form a *meta*-cyclophane) are thought to be reversible. The intermediate **326** can be siphoned off via a [3.3]-sigmatropic rearrangement (Cope rearrangement) to **323-endo**.

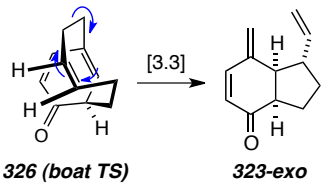
Scheme III-4. Proposed mechanism to account for the formation of **322-endo**, **323-endo**, and **324** in the FVP of **321**[63].



The pre-organized chair conformation shown in **326** would provide **323** as the sole product.[107] Intermediate **326** also has another escape route (other then its reversion to **325**) via a [1,5] H(◆)-shift to provide intermediate **327**. An ene reaction of the allylic hydrogen in the *meta*-cyclophane furnishes tricyclic compound **324.** Thus, this tricyclic dienone also arises as a result of initial homolysis of bond *a*.

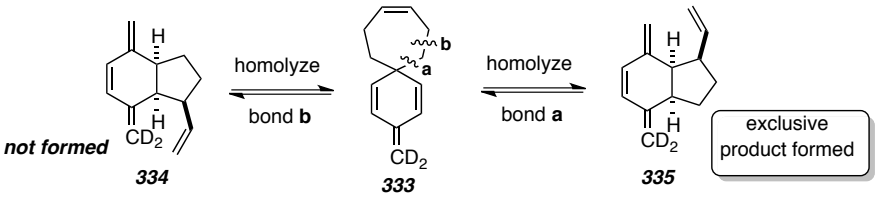
Homolysis of bond *b* in **321** forms the allylic-homoallylic diradical **328** that can collapse to the *O*-centered radical **329**. Recombination of **329** to the [6]-metacyclophene **330** followed by rearrangement gives the allyl vinyl ether **332**. This intermediate is then poised to undergo a [3.3]-sigmatropic rearrangement (Claisen rearrangement) to give the third reported compound from this FVP, **322-endo**. To answer the question of whether

[107] Cope rearrangement via the higher energy boat conformer in **326** would however give rise to the **323-exo** compound as shown below.



exclusive or competitive homolysis of bond *a* and/or *b* is at play, Jones *et al.* synthesized compound **333** (Scheme III-5). Following the mechanistic pathways outlined in, Scheme III-4 compound **334** should arise from homolysis of bond *b*, while compound

Scheme III-5. Deuteration studies conducted in order to probe the feasible of homolysis of bond *a* or *b*.



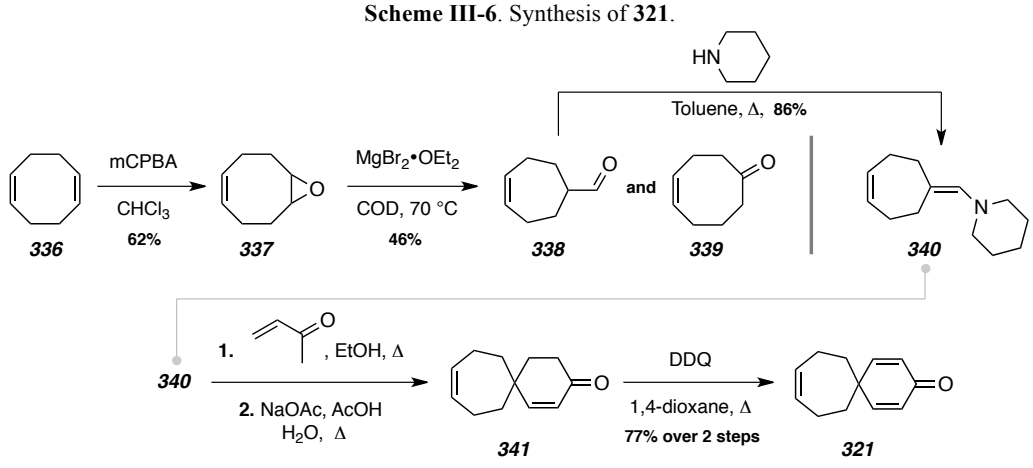
335 from bond *a*. Through NOE analysis the researchers determined that compound **335** was the only product formed, leading to the conclusion that only the pathway triggered by homolysis of bond *a* is operable. A similar deuteration study was not applicable in FVP of **321** and thus the validity of each pathway was not tested. The explanation that Jones offers for the difference in operable pathways in the FVP of **321** vs. **324** is due to the higher temperature that is required for the pyrolysis of the ketone **321** vs. the alkene **324**.

III-A-3. *Synthesis and FVP of 321*.

As briefly described in Chapter II, during the investigation of the Cope rearrangement within **201** we realized the compound isolated and characterized as **323-exo** was an exact match with the spectroscopic data presented for **323-endo** in an earlier report by Jones. A structural dilemma however arises then because the compound in the Jones study that matched with the **323-exo** had the opposite configuration at the vinyl-bearing carbon rendering it a diastereoisomer of **323-exo**. According to our spectroscopic analysis of the Cope product of [m]-cyclophane **204-prox** in conjunction with the highly preorganized nature of the Cope rearrangement, *we hypothesize that the compound isolated in the FVP studies by Jones et al. is not the compound **323-endo**, but its diastereomer, **323-exo***. To test this hypothesis we set out to recreate this FVP experiment, beginning with the synthesis of the spirotrienone **321 (**Scheme III-6).

The epoxidation of the commercially available 1,4-cyclooctadiene (**336**) smoothly provided the monoepoxide **337** along with some undesired diepoxide; these were separated by chromatography. This was followed by a Lewis acid-mediated ring contraction to provide the enal **338** accompanied by the undesired ketone **339**.[108] This transformation could be accomplished by the action of either LiBr or $MgBr_2 \bullet OEt_2$, the latter was employed preferentially due to the increase in reaction rate. Condensation of the isolated aldehyde with piperidine provided the enamine **340,** which was purified by

Scheme III-6. Synthesis of **321**.



[108] A relevant by-product of this reaction was the ketone **339** that was isolated in as high as c.a. 30% yield.

Kugelrohr distillation. Methyl vinyl ketone annulation of the enamine provided the spirodienone **341**, which was converted to the spirotrieneone **321** via a DDQ oxidation in 77% yield over two steps.[109]

Similar to the results reported in the Jones laboratory, the FVP of **321** proved to be reproducible at the array of temperatures investigated and provided three compounds that were separable by normal phase HPLC. The NMRs of these compounds were in accordance with those reported by Jones, leaving no doubt that we had the same compounds in hand. For the ease of the following discussion the compounds isolated from the FVP will often be referred to as Isomer I or Isomer II. Figure III-2 details the assignment that both Jones and this work presents. Tables III-1-9 details the ^{1}H and ^{13}C data for Isomers I and II for the structures proposed in this work.

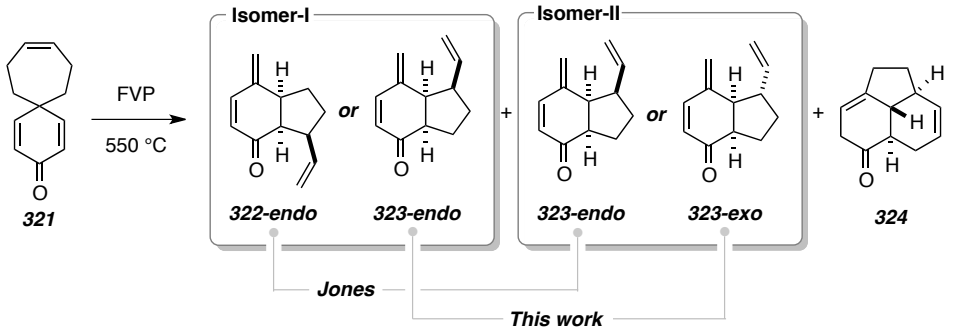
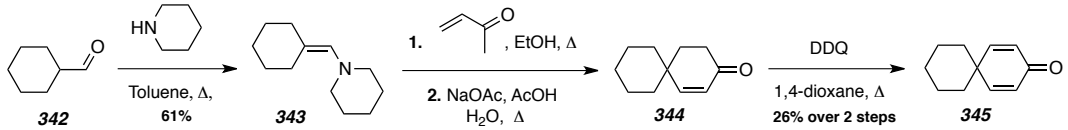


Figure III-2. Proposed structures for the FVP experiment from both Jones and Hoye.

Figure III-3 shows the apparatus constructed for the FVP experiments conducted. The oven used to vaporize the starting spirocyclic trienone **321** was held at 130 °C for all experiments, and the pressure of the closed system spanned 50-100 mTorr. The effect of varying the temperature of the hot tube reactor was explored by incrementally increasing the temperature and recording the yields and product distribution arising from the

[109] Prior to conducting the FVP of compound **321**, we opted to explore the synthesis (in addition to the FVP) of the model spirodienone **345**. In similar fashion to Scheme III-6, beginning with the condensation of the commercially available cyclohexanecarbaldehyde (**342**) with piperidine to provided the enamine **343** in 61% yield. Annulation with MVK gave the spirocyclic compound **344** followed by DDQ oxidation spirodienone **345** that was pyrolyzed to a mixture of predominately aromatic compounds, presumably those identified in studies by Jenneskens (Scheme III-2).



experiment. Figure III-4 details the results of varying the temperature of the hot tube reactor on the mass of the recovered, pyrolyzed material. At lower temperatures (510 and 520 °C) a significant portion of the starting material was recovered in the collecting flask. However at higher temperatures (610 and 620 °C) complete conversion of the starting spirotrienone was observed, although the yields of tractable material were lower. Mid-range temperatures provided the best yields of Isomer I and II and **324**. Purification by FCC followed by HPLC provided pristine samples of the FVP products. Complete assignment of all ^{1}H and ^{13}C resonances aided in the structural reassignment of the FVP products.

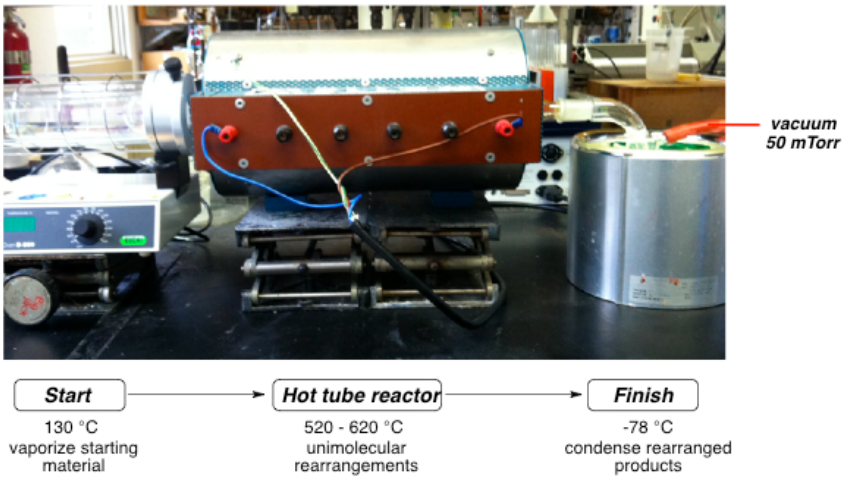


Figure III-3. Apparatus used for all runs of FVP.

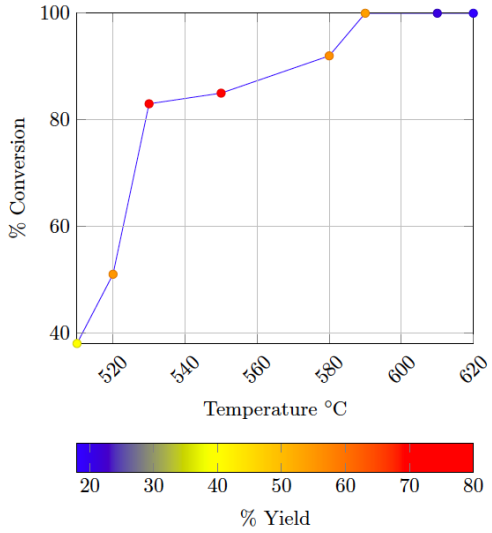
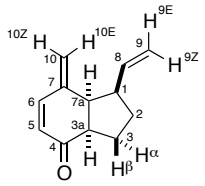


Figure III-4. Summary of FVP experimental results, %-Conversion vs. Temperature (°C) as well as the colorimetric scale indicating %-yield of the three compounds indicated in **Figure III-2**. All runs were conducted at pressures between 50-100 mTorr.

Figure III-5. Newly proposed structure for Isomer I: **323-endo**.



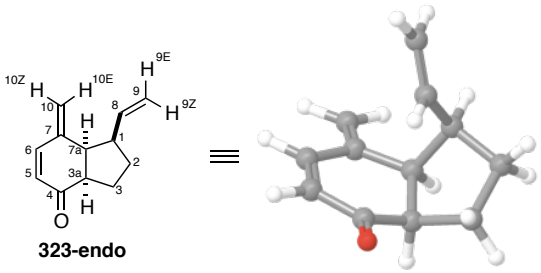
323-endo

Table III-1. NMR spectral data for the newly proposed structure for Isomer I: **323-endo** in $CDCl_3$.

Atom #	δ_H (mult, *J*, Hz)	COSY	Carbon	HMBC[a]
1	2.78 (br dddd, *J* = 9.8, 8.0, 8.0, 2.4 Hz)	H-2α, H-2β, H-7a, H-8	50.2	8, 7, 7a, 2, 9
2α	1.82 (dddd, *J* = 13.1, 9.7, 7.8, 6.8 Hz)	H-2β, H-3α, H-3β, H-1	26.0	8, 7a, 3, 2
2β	1.65 (ddddd, *J* = 13.4, 7.4, 5.2, 3.1, 0.8 Hz)	H-2α, H-3α, H-3β, H-1		8, 7a
3α	1.96 (dddd, *J* = 13.8, 9.4, 9.4, 4.7 Hz)	H-3α, H-2α, H-2β, H-3a	29.6	4, 3a
3β	2.41 (dddd, *J* = 13.3, 8.1, 8.1, 3.5 Hz)	H-3β, H-3a, H-2α, H-2β		4, 3a, 2
3a	2.81 (ddd, *J* = 9.5, 9.5, 3.5 Hz)	H-3α, H-3β, H-7a	47.3	8, 9, 7a, 3
4	-	-	200.8	-
5	5.93 (ddd, *J* = 10.1, 1.3, 0.8 Hz)	H-6, H-10E, H-10Z	127.9	3a, 7
6	6.98 (dddd, *J* = 10.0, 0.7, 0.7, 0.7 Hz)	H-5, H-10E, H-10Z	147.4	4, 7, 7a, 10
7	-	-	141.7	-
7a	3.25 (ddd, *J* = 8.4, 8.4, 0.9 Hz)	H-1, H-3a, H-6, H-10E, H-10Z	48.2	4, 7, 6, 8, 1
8	5.39 (ddd, *J* = 17.0, 10.1, 8.4 Hz)	H-1, H-9E, H-9Z	137.8	1, 2, 7a
9E	4.82 (ddd, *J* = 10.2, 1.8, 0.9 Hz)	H-1, H-9Z, H-8	115.3	1, 8
9Z	4.88 (ddd, *J* = 17.0, 1.9, 1.2 Hz)	H-1, H-8, H-9E		1, 8
10E	5.36 (ddd, *J* = 1.3, 1.3, 1.3 Hz)	H5, H6, H7a	121.9	6, 7, 7a
10Z	5.47 (dddd, *J* = 2.0, 1.0, 1.0, 1.0 Hz)	H5, H6, H7a		6, 7, 7a

[a] The numbers in the HMBC column correspond for each row entry (i.e., each proton) to those carbon atoms for which a cross-peak was detected in the HMBC spectrum.

Figure III-6. Newly proposed structure for Isomer I: **323-endo** as well as the lowest energy conformer found using MacroModel[110.111.112]



323-endo

Table III-2. NMR spectral data for the newly proposed structure for Isomer I: **323-endo** in methanol-d_4.

Atom #	δ_H (mult, *J*, Hz)	COSY	Carbon	HMBC[a]	Diff. NOE
1	2.80 (ddddd, *J* = 8, 8, 8, 2.9, 1.2, 1.2 Hz)	H-2α, H-2β, H-7a, H-8, H-9E, H-9Z	51.2	8, 7, 7a, 2, 9	
2α	1.85 (dddd, *J* = 12.9, 9.8, 7.9, 6.8 Hz)	H-1, H-2β, H-3α, H-3β	26.6	8, 7a, 3, 2	
2β	1.60 (ddddd, *J* = 13.1, 8.3, 4.7, 2.7, 0.8 Hz)	H-1, H-2α, H-3α, H-3β		8, 7a	H-2α
3α	1.96 (dddd, *J* = 13.6, 9.4, 9.4, 4.5 Hz)	H-2α, H-2β, H-3β, H-3a	30.2	4, 3a	H-3β
3β	2.34 (dddd, *J* = 13.5, 8.1, 8.1, 3.4 Hz)	H-3a, H-2α, H-2β, H-3α		4, 3a, 2	H-3α
3a	2.84 (dddd, *J* = 9.3, 9.3, 3.5, 0.7 Hz)	H-3α, H-3β, H-7a	48.3	8, 9, 7a, 3, 4	H-3α
4	-	-	203.1	-	-
5	5.88 (ddd, *J* = 9.9, 1.5, 0.9 Hz)	H-6, H-10E, H-10Z	128.1	3a, 7	H-6
6	7.12 (dddd, *J* = 9.9, 0.8, 0.8, 0.8 Hz)	H-5, H-7a, H-10E, H-10Z	149.4	4, 7, 7a, 10	H-5, H-10Z
7	-	-	142.9	-	-
7a	3.34 (ddd, *J* = 9.0, 7.8, 1.0 Hz)	H-6, H-1, H-3a, H-10E, H-10Z	49.1	4, 6, 7, 8, 1	H-1, H-3a, H-10E
8	5.39 (ddd, *J* = 17.0, 10.3, 8.4 Hz)	H-1, H-9E, H-9Z	139.0	1, 2, 7a	
9*E*	4.79 (ddd, *J* = 10.3, 2.0, 1.0 Hz)	H-1, H-8, H-9Z	115.4	1, 8	H-9Z
9*Z*	4.87 (ddd, *J* = 17.0, 1.9, 1.3 Hz)	H-1, H-8, H-9E		1, 8	H-9E
10*E*	5.46 (ddd, *J* = 1.5, 1.5, 1.5 Hz)	H-5, H-6, H-7a, H-10Z	123.1	6, 7, 7a	H-7a, H-10Z
10*Z*	5.56 (dddd, *J* = 1.8, 0.9, 0.9, 0.9 Hz)	H-5, H-6, H-7a, H-10E		6, 7, 7a	H-6, H-10E

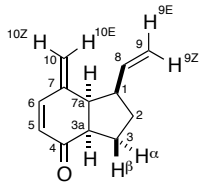
[a] The numbers in the HMBC column correspond for each row entry (i.e., each proton) to those carbon atoms for which a cross-peak was detected in the HMBC spectrum.

[110] MacroModel, version 9.7, Schrödinger , LCC, New York, NY, 2009.

[111] Maestro, version 9.3, Schrödinger , LCC, New York, NY, 2009.

[112] Chang, G.; Guida, W. C.; Still, W. C. An Internal-Coordinate Monte Carlo Method for Searching Conformational Space. *J. Amer. Chem. Soc.* **1989**, *111*, 4379-4386.

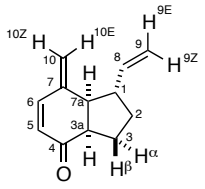
Table III-3. NMR spectral data for the newly proposed structure for Isomer I: **323-endo** in $CDCl_3$, methanol-d_4, and acetone-d_6.



323-endo

	^{1}H			^{13}C		
Atom #	**δ_H in $CDCl_3$**	**δ_H in methanol-d_4**	**δ_H in acetone-d_6**	**δ_C in $CDCl_3$**	**δ_C in methanol-d_4**	**δ_C in acetone-d_6**
1	2.78	2.80	2.79	50.2	51.2	50.7
2α	1.82	1.85	1.82	26.0	26.6	26.1
2β	1.65	1.60	1.54			
3α	1.96	1.96	1.88	29.6	30.2	30.0 (obsc by solvent)
3β	2.41	2.34	2.34			
3a	2.81	2.84	2.80	47.3	48.3	47.8
4	-	-		200.8	203.1	199.7
5	5.93	5.88	5.84	127.9	128.1	128.3
6	6.98	7.12	7.08	147.4	149.4	147.5
7	-	-		141.7	142.9	142.6
7a	3.25	3.34	3.34	48.2	49.1	48.8
8	5.39	5.39	5.36	137.8	139.0	138.9
9*E*	4.82	4.79	4.77	115.3	115.4	115.1
9*Z*	4.88	4.87	4.86			
10*E*	5.36	5.46	5.43	121.9	123.1	122.0
10*Z*	5.47	5.56	5.53			

Figure III-7. Newly proposed structure for Isomer II: **323-exo**.



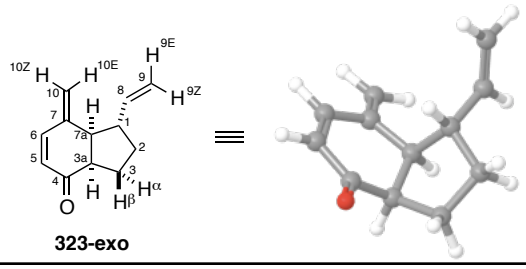
323-exo

Table III-4. NMR spectral data for (1*S*,3a*R*,7a*S*)-7-methylene-1-vinyl-3,3a,7,7a-tetrahydro-1*H*-inden-4(2*H*)-one (**323-exo**) in $CDCl_3$.

Atom #	δ_H (mult, *J*, Hz)	COSY	Carbon	HMBC[b]
1	2.20 (br dddd, *J* = 10.5, 9.9,[a] 8.2, 8.2 Hz)[a]	H-2α, H-2β, H-7a, H-8	49.8	8, 7, 7a, 2, 9
2α	1.49 (dddd, *J* = 13.1, 10.7, 9.8, 7.0 Hz)	H-2β, H-3α, H-3β, H-1	30.4	8, 7a, 3
2β	1.89 (dddd, *J* = 13.4, 8.6, 8.6, 4.9 Hz)	H-2α, H-3α, H-3β, H-1		8, 7a, 3
3α	1.95 (dddd, *J* = 13.5, 10.7, 8.6, 5.0 Hz)	H-2α, H-2β, H-3β, H-3a	26.0	4, 2, 3a
3β	2.38 (dddd, *J* = 13.5, 8.9, 7.0, 2.9 Hz)	H-2α, H-2β, H-3α, H-3a		4, 1, 2
3a	2.88 (ddd, *J* = 8.2, 8.2, 3.0 Hz)	H-3α, H-3β, H-7a	49.5	4, 1, 2, 3
4	-	-	200.6	-
5	5.92 (ddd, *J* = 9.9, 1.6, 0.9 Hz)	H-6, H-10E, H-10Z	126.5	4, 7
6	6.98 (dddd, *J* = 9.9, 1.2, 0.8, 0.8 Hz)	H-5, H-10E, H-10Z	146.0	4, 7, 7a
7	-	-	141.0	-
7a	2.64 (dd, *J* = 11.0, 7.7 Hz)	H-1, H-3a, H-6, H-10E, H-10Z	50.7	3a, 10, 7, 6, 4
8	5.65 (ddd, *J* = 17.0, 10.3, 8.2 Hz)	H-9E, H-9Z, H-1	140.7	1, 2
9*E*	5.01 (ddd, *J* = 10.2, 1.8, 0.8 Hz)	H-9Z, H-8, H-1	115.9	1, 8
9*Z*	4.89 (ddd, *J* = 17.0, 1.9, 0.9 Hz)	H-9E, H-8, H-1		1, 8
10*E*	5.22 (dddd, *J* = 1.5, 1.5, 0.8, 0.7 Hz)	H-6, H-5	121.7	6, 7, 7a
10*Z*	5.38 (dddd, *J* = 1.5, 0.8, 0.8, 0.8 Hz)	H-6, H-5		6, 7, 7a

[a] *J* values of 8.2, 8.2, and 10.5 can be identified (following line broadening analysis) within this multiplet, and the sum of all four *J*s (distance between the outermost lines of the resonance) is 36.8. The 9.9 value is deduced. [b] The numbers in the HMBC column correspond for each row entry (i.e., each proton) to those carbon atoms for which a cross-peak was detected in the HMBC spectrum.

Figure III-8. Newly proposed structure for Isomer II: **323-exo**, as well as the lowest energy conformer found using MacroModel.[110, 111, 112]



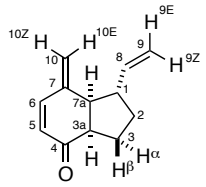
323-exo

Table III-5. NMR spectral data for the newly proposed structure for Isomer II: **323-exo** in methanol-d_4.

Atom #	δ_H (mult, *J*, Hz)	COSY	Carbon	HMBC[b]	Diff. NOE
1	2.21 (br dddd, *J* = 10.6, 9.4,[a] 8.6, 8.6 Hz)[a]	H-2α, H-2β, H-7a, H-8, H-9E, H-9Z	51.3	8, 7, 7a, 2, 9	H-8, H-9Z
2α	1.54 (dddd, *J* = 13.0, 10.7, 9.7, 6.7 Hz)	H-1, H-2β, H-3α, H-3β	31.3	8, 7a, 3	H-2β, H3α, H-8, H7a
2β	1.86 (dddd, *J* = 13.5, 8.7, 8.7, 5.0 Hz)	H-1, H-2α, H-3α, H-3β		8, 7a, 3	H-2α
3α	1.98 (dddd, *J* = 13.5, 10.7, 8.6, 5.0 Hz)	H-2α, H-2β, H-3β, H-3a	26.9	4, 2, 3a	H-3β
3β	2.31 (dddd, *J* = 13.4, 9.2, 6.6, 2.7 Hz)	H-3a, H-2α, H-2β, H-3α		4, 1, 2	H-3α
3a	2.89 (ddd, *J* = 8.6, 8.0, 2.9 Hz)	H-3α, H-3β, H-7a	50.7	4, 1, 2, 3	H-3α
4	-	-	202.8	-	-
5	5.89 (ddd, *J* = 9.9, 1.4,1.4 Hz)	H-6, H-10E, H-10Z	126.8	4, 7	H-6
6	7.12 (dddd, *J* = 9.8, 1.8, 0.7, 0.7 Hz)	H-5, H-7a, H-10E, H-10Z	147.9	4, 7, 7a	H-5, H-10Z
7	-	-	142.4	-	-
7a	2.72 (dd, *J* = 11.0, 7.8 Hz)	H-6, H-1, H-3a, H-10E, H-10Z	51.6	3a, 10, 7, 6, 4	H-2α, H8, H-10E
8	5.69 (ddd, *J* = 17.1, 10.2, 8.3 Hz)	H-1, H-9E, H-9Z	142.0	1, 2	H-1, H-2α, H-7a
9*E*	5.00 (ddd, *J* = 10.2, 2.0, 0.7 Hz)	H-1, H-8, H-9Z	116.1	1, 8	H-9Z
9*Z*	4.87 (ddd, *J* = 16.9, 2.0, 0.9 Hz)	H-1, H-8, H-9E		1, 8	H1, H-9E
10*E*	5.28 (dddd, *J* = 1.5, 1.5, 1.5, 0.6 Hz)	H-5, H-6, H-7a, H-10Z	122.8	6, 7, 7a	H-7a, H-10Z
10*Z*	5.46 (dddd, *J* = 1.6, 0.8, 0.8, 0.8 Hz)	H-5, H-6, H-7a, H-10E		6, 7, 7a	H-6, H-10E

[a] *J* values of 8.6, 8.6, and 10.6 can be identified (following line broadening analysis) within this multiplet, and the sum of all four *J*s (distance between the outermost lines of the resonance) is 37.2. The 9.4 value is deduced. [b] The numbers in the HMBC column correspond for each row entry (i.e., each proton) to those carbon atoms for which a cross-peak was detected in the HMBC spectrum.

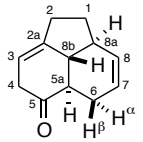
Table III-6. NMR spectral data for the newly proposed structure for Isomer II: **323-exo** in $CDCl_3$, methanol-d_4, and acetone-d_6.



323-exo

	^1H			^{13}C		
Atom #	**δ_H in $CDCl_3$**	**δ_H in methanol-d_4**	**δ_H in acetone-d_6**	**δ_C in $CDCl_3$**	**δ_C in methanol-d_4**	**δ_C in acetone-d_6**
1	2.20	2.21	2.15	49.8	51.3	50.5
2α	1.49	1.54	1.80	30.4	31.3	30.8
2β	1.89	1.86	1.49			
3α	1.95	1.98	1.87	26.0	26.9	26.1
3β	2.38	2.31	2.31			
3a	2.88	2.88	2.85	49.5	50.7	50.2
4	-	-	-	200.6	202.8	199.7
5	5.92	5.89	5.84	126.5	126.8	126.9
6	6.98	7.12	7.09	146.0	147.9	146.1
7	-	-	-	141.0	142.4	141.9
7a	2.64	2.72	2.70	50.7	51.6	51.4
8	5.65	5.69	5.7	140.7	142.0	142.1
9*E*	5.01	5.00	4.97	115.9	116.1	115.8
9*Z*	4.89	4.87	4.87			
10*E*	5.22	5.28	5.44	121.7	122.8	121.8
10*Z*	5.38	5.46	5.24			

Figure III-9. Tricyclic isomer **324**.



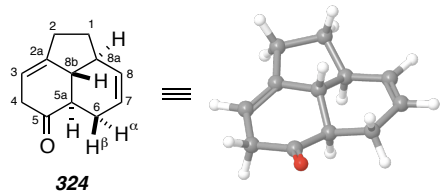
324

Table III-7. NMR spectral data for (5a*R*,8a*S*)-1,2a[1],4,5a,6,8a-hexahydroacenaphthylen-5(2*H*)-one in $CDCl_3$

Atom* #	δ_H (mult, *J*, Hz)	COSY	Carbon	HMBC
1α	1.97 (ddddd *J* = 12.6, 3.0, 2.2, 1.5, 0.7 Hz)	H-1dn, H-8a, H-2up, H-2dn	31.8	C-2, C-8b
1β	1.71 (dddd, *J* = 12.6, 2.4, 2.4, 1.2 Hz)	H-1dn, H-8a, H-2up, H-2dn		C-2, C-8, C-8b
2α	2.25-2.37[b] (m)	H-3, H-8a, H-1up, H-1dn	28.1	C-8a
2β	2.25-2.37[b](m)	H-3, H-8a, H-1up, H-1dn		C-8a
2a	-	-	143.7	-
3	5.53-5.57 (m, overlapped with H8)	H-8b, H-4	113.7	C-4, C-8b
4α	2.83-2.85 (m)	H-3, H-2	38.0	C-2a, C-3, C-5
4β	2.93-3.00 (m)	H-3, H-2		
5	-	-	214.4	-
5a	2.72 (ddd, *J* = 11.2, 6.8, 5.0 Hz)	H-6up, H-6dn	45.1	C-2a, C-5, C-6
6α	1.92 (dddd, *J* = 12.6, 11.2, 9.1, 7.1 Hz)	H-7	22.1	C-7
6β	2.03 (ddddd *J* = 13.51 3.5, 2.8, 2.2, 0.6 Hz)	H-5a, H-6up, H-8		C-1, C-2, C-7a
7	5.67 (dddd, *J* = 10.0, 4.9, 2.1, 2.1 Hz)	H-5a, H-6up, H-8b	125.3	C-6, C-8a, C-8
8	5.53-5.5 (m, overlapped with H3)	H-6up, H-6dn, H-8b	130.4	C-6, C-7
8a	2.76-2.80 (m)	H-8b, H-8	37.5	
8b	2.93-3.00 (m)	H-2up, H-2dn, H-5a, H-3	42.3	C-2a, C-3, C-5

* The assignment of α and β is not certain in this compound.

Figure III-10. Tricyclic isomer **324 a**nd the lowest energy conformer found using MacroModel.[110, 111, 112]



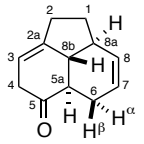
324

Table III-8. NMR spectral data for (5a*R*,8a*S*)-1,2a[1],4,5a,6,8a-hexahydroacenaphthylen-5(2*H*)-one in methanol-d_4

Atom* #	δ_H (mult, *J*, Hz)	COSY	Carbon	HMBC
1α	1.89 (ddddd *J* = 12.6, 3.0, 2.2, 1.5, 0.7 Hz	H-1dn, H-8a, H-2up, H-2dn	32.4	C-2, C-8b
1β	1.71 (dddd, *J* = 12.6, 2.4, 2.4, 1.2 Hz)	H-1dn, H-8a, H-2up, H-2dn		C-2, C-8, C-8b
2α	2.25-2.38 (m)	H-3, H-8a, H-1up, H-1dn	28.7	C-8a
2β	2.25-2.38 (m)	H-3, H-8a, H-1up, H-1dn		C-8a
2a	-	-	144.7	-
3	5.55-5.59 (m, overlapped with H8)	H-8b, H-4	114.5	C-4, C-8b
4α	2.82 (dddd, *J* = 22.7, 4.1, 3.5, 3.0, 2.4	H-3, H-2	38.6	C-2a, C-3, C-5
4β	2.93-3.00 (m)	H-3, H-2		
5	-	-	216.1	-
5a	2.65 (ddd, *J* = 11.2, 6.6, 4.8 Hz)	H-6up, H-6dn	46.1	C-2a, C-5, C-6
6α	1.95 (dddd, *J* = 12.6, 11.2, 9.1, 7.1 Hz)	H-7	22.8	C-7
6β	2.08 (ddddd *J* = 13.51 3.5, 2.8, 2.2, 0.6 Hz)	H-5a, H-6up, H-8		C-1, C-2, C-7a
7	5.67 (dddd, *J* = 10.0, 4.9, 2.1, 2.1 Hz)	H-5a, H-6up, H-8b	125.9	C-6, C-8a, C-8
8	5.55-5.59 (m, overlapped with H3)	H-6up, H-6dn, H-8b	131.2	C-6, C-7
8a	2.76-2.80 (m)	H-8b, H-8	38.4	
8b	2.94-3.00 (m)	H-2up, H-2dn, H-5a, H-3	43.1	C-2a, C-3, C-5

* The assignment of α vs. β is not certain in this compound/spectrum.

Table III-9. NMR spectral data for (5a*R*,8a*S*)-1,2a,4,5a,6,8a-hexahydroacenaphthylen-5(2*H*)-one in $CDCl_3$, methanol-d_4, and acetone-d_6



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	^{1}H			^{13}C		
Atom* #	**δ_H in $CDCl_3$**	**δ_H in methanol-d_4**	**δ_H in acetone-d_6**	**δ_C in $CDCl_3$**	**δ_C in methanol-d_4**	**δ_C in acetone-d_6**
1α	1.97	1.89	1.69	31.8	32.4	32.0
1β	1.71	1.71	1.87			
2α	2.25-2.37[b]	2.25-2.38[b]	2.21-2.34[b]	28.1	28.7	28.4
2β	2.25-2.37[b]	2.25-2.38[b]	2.21-2.34[b]			
2a	-	-	-	143.7	144.7	143.9
3	5.53-5.57[a]	5.55-5.59[a]	5.53-5.58[a]	113.7	114.5	114.6
4α	2.83-2.85	2.8	2.71	38.0	38.6	39.1
4β	2.93-3.00	2.93-3.00	2.92-3.00[c]			
5	-	-	-	214.4	216.1	212.1
5a	2.72	2.65	2.58	45.1	46.1	45.4
6α	1.92	1.95	1.92	22.1	22.8	22.3
6β	2.03	2.08	2.04			
7	5.67	5.67	5.66	125.3	125.9	125.8
8	5.53-5.57[a]	5.55-5.59[a]	5.53-5.58[a]	130.4	131.2	130.8
8a	2.76-2.80	2.76-2.80	2.75-2.80	37.5	38.4	38.0
8b	2.93-3.00	2.94-3.00	2.94-3.00	42.3	43.1	42.7

* The assignment of α vs. β is not certain in this compound/spectrum.
[a, b, c] Overlapping resonances; identity determined via COSY, HMQC and HMBC experiments.

III-B. EVIDENCE IN SUPPORT OF THE STRUCTURAL REASSIGNMENT OF **322-ENDO** TO **323-ENDO** AND **323-ENDO** TO **323-EXO**.

In the report by Jones *et al.* the ^{1}H NMR spectra for Isomer I, Isomer II, and **324** were all reported in $CDCl_3$ and their relative stereochemical configurations deduced via europium shift reagents.[113] Overlapped resonances in the spectrum of **324** in $CDCl_3$ were separated when the it was taken in a 1:1 mixture of $CDCl_3$ and C_6D_6. All spectra in the Jones report were recorded on a Perkin-Elmer R-32 90-MHz spectrometer, a JEOL FX90Q 90-MHz spectrometer, or a Bruker WM 250-MHz spectrometer. To the best of our knowledge no spectra were recorded on a 500-MHz instrument that would have been available, though not commonplace in 1986. Moreover, no two-dimensional NMR experiments (HMBC, HSQC etc.) were conducted. Presented in the following sections are the detailed spectroscopic analyses that ultimately led to the structural reassignment of **322-endo** and **323-endo** to that of **323-endo** and **323-exo** respectively (Figure III-11)[114].

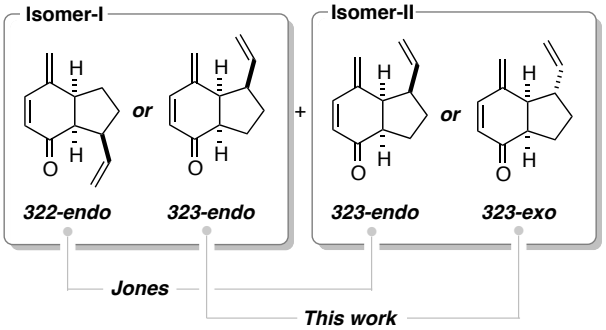


Figure III-11. Proposed reassignment of **322-endo** and **323-endo** to **323-endo** and **323-exo** respectively.

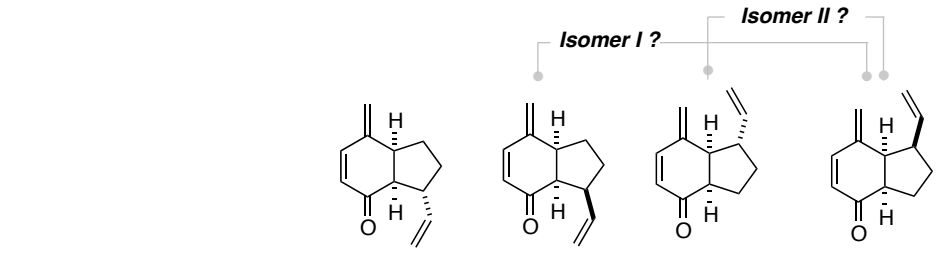
III-B-1. *Computational support*

In the course of gathering spectroscopic evidence to support the structural reassignment of isomers isolated for the FVP experiment, another graduate student in the

[113] 0.24 Equivalents of tris-(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium [$Eu(fod)_3$]

[114] The remainder of this dossier will only detail spectroscopic arguments pertaining to Isomer I and II, i.e. excluding the tricycle **324**.

Hoye group, Dr. Matthew Jansma, calculated the theoretical chemical shifts of compounds **322-endo**, **323-endo**, **323-exo,** and a forth isomer, **322-exo** (Figure III-12).[115]



Experimental ^1H NMR		322-exo	322-endo	323-exo	323-endo
structure originally assigned as ***322-endo***	$^a\lvert\Delta\delta\rvert_T$	2.61	2.37	2.57	***1.12***
structure originally assigned as ***323-endo***	$^a\lvert\Delta\delta\rvert_T$	3.89	3.49	***1.04***	2.41

$^a\lvert\Delta\delta\rvert_T$ (ppm), the total absolute error between corrected theoretical and experiemental chemical shifts.

Figure III-12. Comparison of the total mean absolute error of compounds **322-exo**, **322-endo**, **323-exo**, **323-endo**.

These values were then compared to the experimental chemical shift values of the FVP isomers. The total mean absolute error (MAE) between the theoretical and experimental chemical shifts values was determined and it was found that in the case of Isomer I, compound **323-endo** had the lowest MAE of the four isomers and in Isomer II, compound **323-exo** had the lowest MAE. While not conclusive this result gave us hope that exhaustive NMR analysis would resolve the structural ambiguity surrounding these isomers.

III-B-2. *Addressing the constitution of Isomer I: 322-endo vs. 323-endo*

The question of constitution is aptly addressed by HMBC experiments (in $CDCl_3$ as well as methanol-d_4) where both the presence and absence of distinguishable correlations was integral in establishing the structure of **323-endo**. One of the observable correlations that point to the structural reassignement of **322-endo** to **323-endo** is the cross-peak of H-

[115] Jansma, M. J. A Unified Strategy for Penostatin (Bio)synthesis and Forays in Computational Chemistry PhD Thesis, University of Minnesota, Minneapolis, MN, 2012.

7a[116] into C-1 (Figure III-13). This correlation, while consistent with **323-endo**, is also possible as a three-bond correlation in **322-endo**. H-7a also shows a two-bond correlation

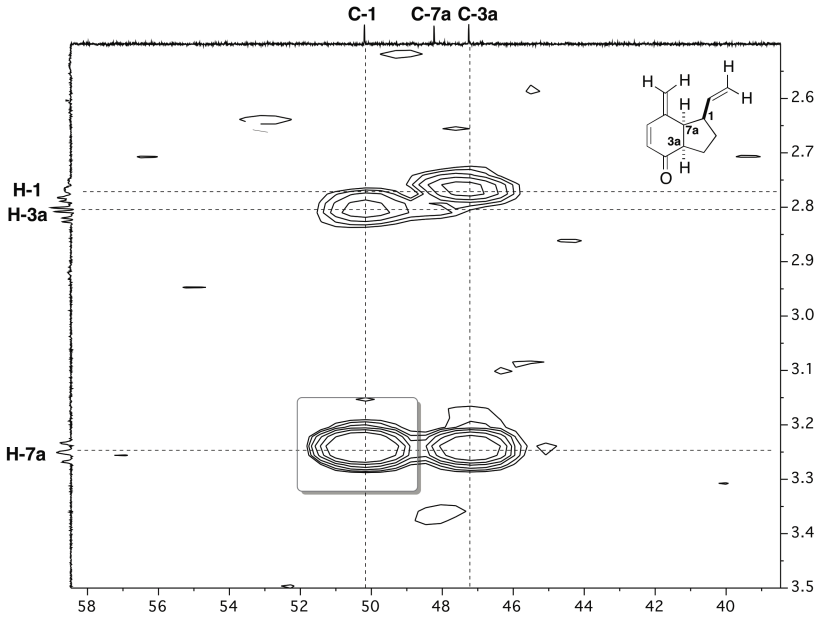


Figure III-13. HMBC snapshot showing the key correlation of H-7a into C-1 as well as other indicated cross-peaks.

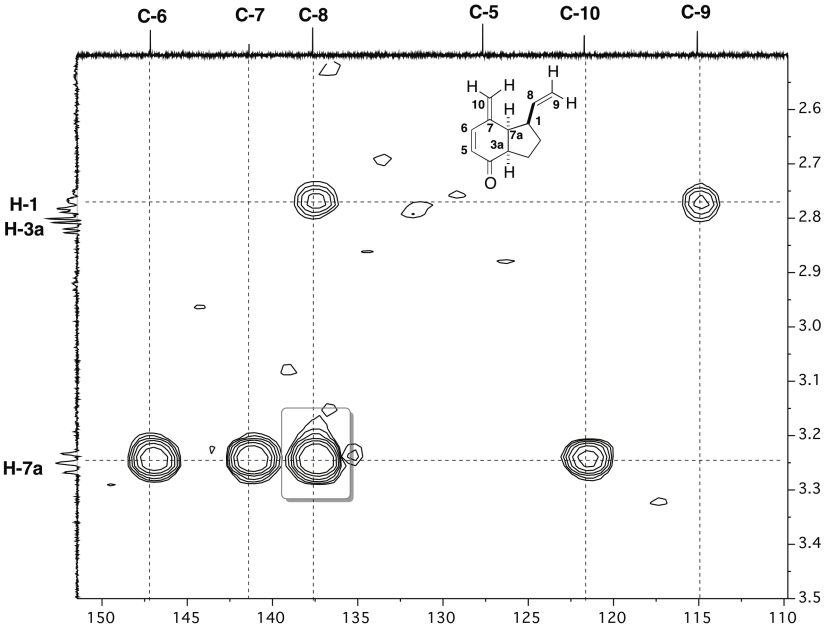


Figure III-14. HMBC snapshot showing the key correlation of H-7a into C-8 as well as other indicated cross-peaks.

[116] The identity of H-7a was confirmed by NOE analysis. Irradiation of H-10E resulted in an observed NOE to the resonance at 3.25 ppm, confirmed by COSY to be H-7a.

to C-3a. Figure III-12 also shows the HMBC correlation of H-3a to C-1 and analogously of H-1 to C-3a. A more convincing piece of evidence for the reassignment of the structure **322-endo** is the HMBC of H-7a into C-8 (Figure III-14). This is unequivocal proof for the constitutional reassignment of the compound first reported as **322-endo**. In the case of **322-endo**, H-7a and C-8 are four bonds away thus an HMBC cross peak is highly unlikely, whereas in **323-endo**, H-7a and C-8 are separated by three bonds thus a HMBC is expected. Other HMBC cross-peaks (indicated in Figure III-14) are: (*i*) the two-bond correlation of H-7a to C-7 (*ii*) the three-bond correlation of H-7a into C-6, and C-10 (*iii*) the two-bond coupling of H-1 into C-8 and (*iv*) H-1 into C-9.

Finally, there are two other observable HMBC peaks that also give credence to the structural reassignment of **322-endo** to **323-endo**. The methylene pair H-3α and H-3β have cross-peaks in the HMBC spectrum to C-4 (Figure III-15). This again would not be possible in the structure **322-endo**, thereby refuting its assignment. Confident in our reassignment of **322-endo** to **323-endo**, our attention now was focused on the structural reassignment of **323-endo** to **323-exo**.

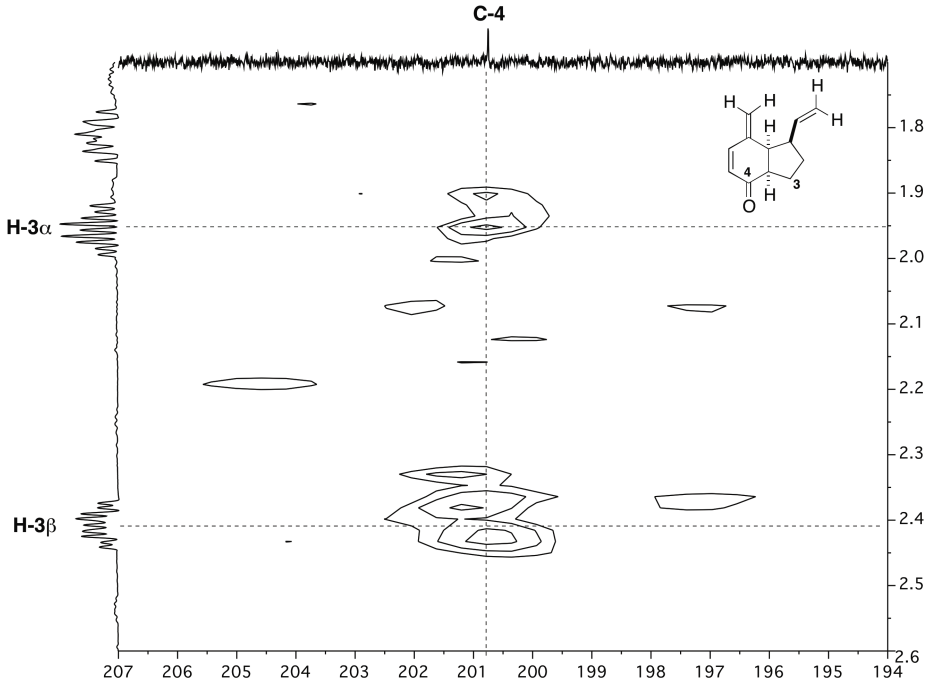


Figure III-15. HMBC snapshot showing the key correlation of the methylene pair H-3α and H3β into C-4.

III-B-3. *Relative configuration of Isomer II: 323-endo vs. 323-exo.*

Our attention turned to the unambiguous establishment of the relative configuration of the three stereocenters within each of Isomer I and Isomer II. We explored a number of strategies involving chemical modification of each isomer with the intent of differentiating the two on the basis of, for example, differing intramolecular cyclization behavior and/or accessing a crystalline derivative.

Oxidative Degradation studies

Inspired by the classical oxidative cleavage approach of the Ruff (or Ruff-Fenton degradation) reaction,[117] we opted to pursue the oxidative cleavage of all the olefins in each of compounds **323-exo** and **323-endo** to yield the tricarboxylic acids **348** and **349** respectively (Figure III-16). These acids can be easily differentiated based on their

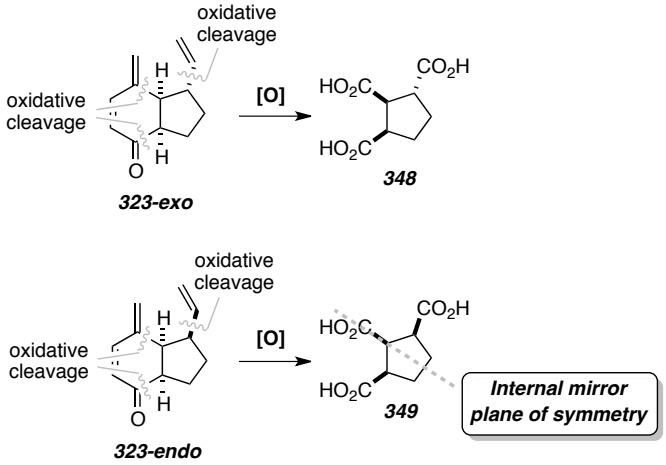
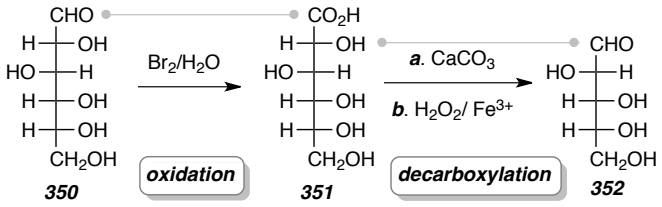


Figure III-16. Oxidative cleavage strategy.

[117] First reported in 1892, it was used in the structural determination of carbohydrates. As shown below it can be used to convert aldose (**350**) to arabinose (**351**) via first an oxidation to aldonic acid (**352**) followed by decarboxylation:

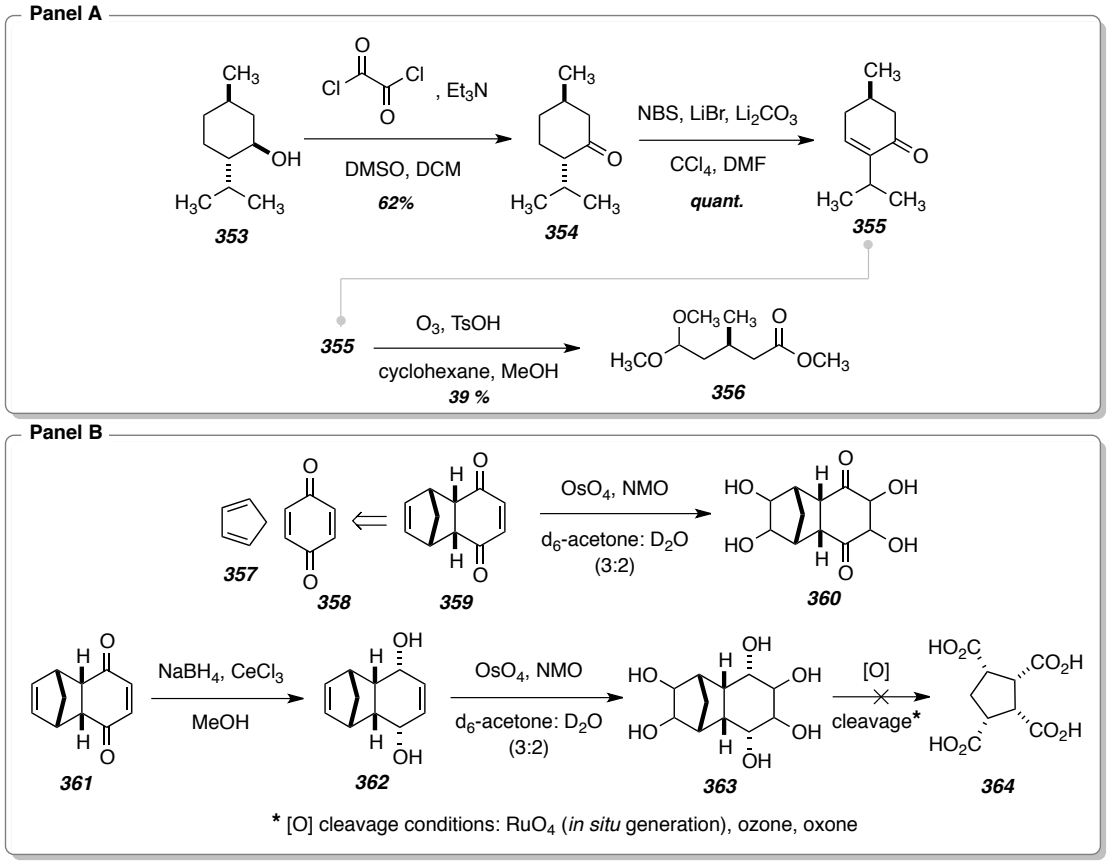


Wang, Z. *Ruff Degradation*, *Comprehensive Organic Name Reactions and Reagents* Hoboken, NJ, USA: John Wiley & Sons, Inc., 2010, 2446-2449.

expected ^{1}H and/or ^{13}C NMR spectral data, due to the internal mirror plane of symmetry of **349**. This would simplify the spectra of **349** as compared to **348**. Thus the relative configuration of the three stereogenic centers of the starting compounds could be inferred from the NMR spectra of the resultant tricarboxylic acids.

Various oxidative cleavage conditions were explored with particular emphasis on experiments that would allow for facile tractability of products. One such condition that was first explored on the model compound **355** was ozonolysis (Panel A, Scheme III-7). In quick fashion **355** was synthesized by the Swern oxidation of the commercially available menthol (**353**) to give the ketone **354**. This was converted to the dehydrocarvone **355**. Ozonlysis of **355** provided the expected oxidatively cleaved product **356**. When these conditions were explored on Isomer II from the FVP, only unidentifiable material was isolated.

Scheme III-7. Oxidative cleavage of model compounds.

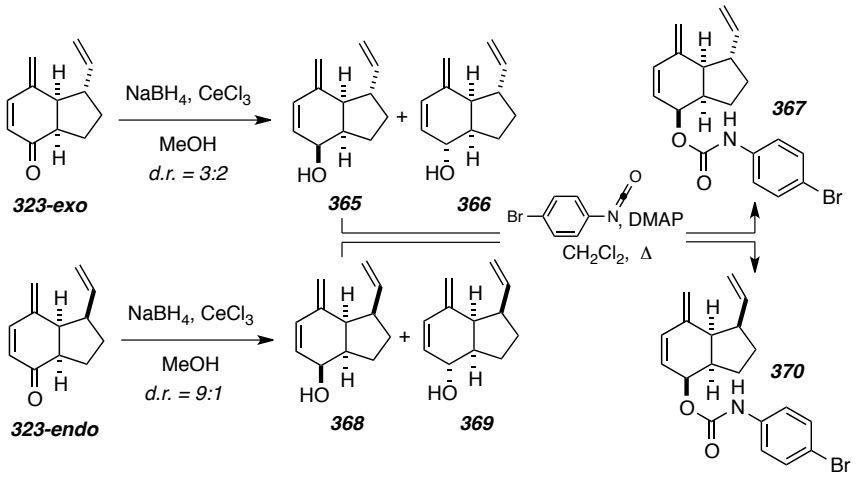


We then turned our attention to a more tractable method of oxidative cleavage. We opted to first completely dihydroxylate all the alkenes in a hydrindenone followed by cleavage of the diol to yield, directly, the carboxylic acid (Panel B, Scheme III-7).[118] Diels-Alder reaction of cyclopentadiene (**357**) and benzoquinone (**358**) provided compound **359**, which was exhaustively dihydroxylated to give, presumably, **360**. This posed a problem if applied to the actual substrate as in the test reactions with **359**, an aromatic compound presumably the phenol derivative of **359** was observed. Possible tautomerization conditions would not be ideal in a case where our goal is establishing relative configuration. This problem was circumvented by first conducting a Luche reduction of **359** to **361**. Dihydroxylation of **361** went smoothly, and when the polyol **362** was exposed to different diol cleavage conditions, no product corresponding to the tetra-carboxylic acid **364** was observed. Not withstanding the lack of success with this strategy, dihydroxylation followed by diol cleavage was attempted on substrate **363**, but, not surprisingly, was unsuccessful.

Formation of a suitable crystal for X-ray structural analysis was explored, but also to no avail. The preparation of hydrazone derivatives proved futile as well as sulfone derivatives (via the conjugate addition of sulfinate ions). We settled on the synthesis of carbamate derivatives of the major diastereomeric alcohols **365** and **368** arising from the Luche reduction of **323-exo** and **323-endo** respectively (Scheme III-8). Unfortunately, suitable crystals of carbamates **367** and **370** for single crystal X-ray analysis were not attainable. Thus, we turned to full analysis of the battery of 1D ^{1}H, COSY, HSQC, and extensive difference NOE NMR data for each isomer.

[118] These experiments were often monitored via ^{1}H NMR spectroscopy.

Scheme III-8. Pursuit of derivatives for X-ray structure analysis.



III-B-4. *Crucial NOE experiments*

Having now confirmed that the FVP experiment gave a diastereomic mixture of compounds **323-endo** and **323-exo** rather than a mixture of constitutional isomers, our attention now turned to determining the relative configuration of the isolated epimers. This was accomplished by (*i*) use of complementary deuterated solvents (*ii*) exhaustive coupling constant analysis, (iii) study of relevant computational models,[119] and (*iv*) crucial NOE experiments. The last of these was particularly informative in our structural reassignment.

All protons were irradiated and NOE data collected.[120] Several enhancements were integral in the reassignment of **323-endo** to **323-exo** (Figure III-17). The most relevant NOEs, revealing the relative configurations among C1/C3a/C7a, are indicated in black. Other NOEs, many of which guided or reinforced the assignment of the aliphatic proton resonances, are shown in gray.

[119] Molecular mechanics calculations for both **323-endo** and **323-exo** were carried out using MacroModel via Maestro as the graphical interface. A Monte Carlo conformation search using the MM3* force field gave six conformers for each compound within a 21.0 kJ•mol^{-1} (5.02 kcal•mol^{-1}).

[120] NOESY experiment in $CDCl_3$ were conducted, however we opted to use the results from difference NOE experiments as the basis of our structural analysis.

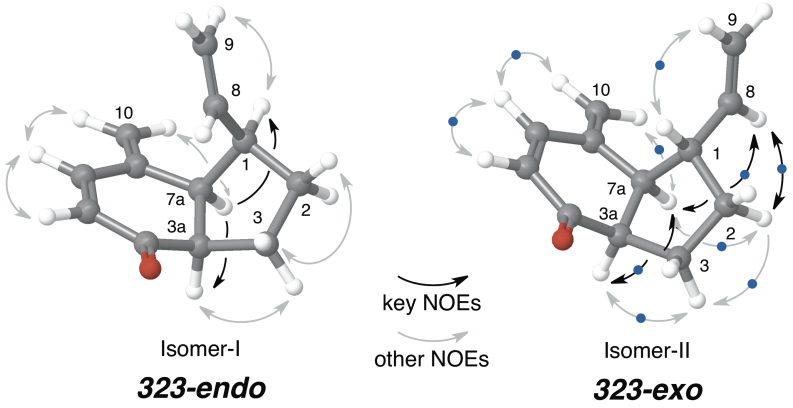


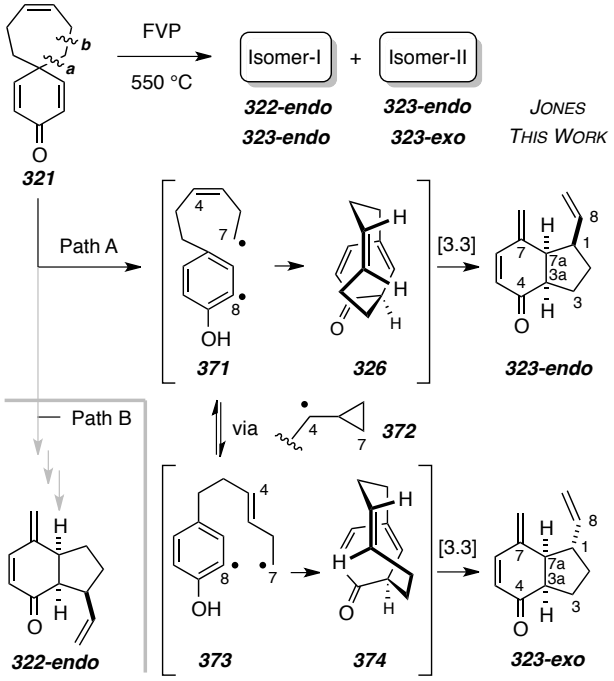
Figure III-17. Through-space enhancements observed through difference NOE experiments on Isomer I and Isomer II.

Most NOEs were observed in a bidirectional sense; single-headed arrows indicate that irradiation of the proton at the base of the arrow enhanced the one at the head. The blue dot (●) denotes analogous NOEs that were observed in ottelione A. We established that each compound possesses a *cis*-ring fusion within its bicyclic hydrindenone skeleton. The H3a/H7a coupling constant values for Isomers-I and -II (7.9 and 9.2 Hz) are consistent with *cis*- rather than *trans*-fused bicyclic structures. Strong NOEs between those bridgehead protons were evident in each Isomer. Thus, Isomers-I and -II are, indeed, epimeric at the vinyl-bearing C1. Analysis of additional key NOE interactions (black arrows) enabled definitive assignment of the configuration at C1 relative to the *cis*-oriented bridgehead protons. In Isomer-I NOEs between the H8/H7a and H8/H2α pairs clearly support the conclusion that the vinyl group has the exo-orientation of **323-exo**. These essential through-space relationships were also observed during extensive NOE studies of the natural sample of ottelione A (**1**) in the initial isolation studies by RPR. By contrast, Isomer-II, showed no NOE between H8/H7a or H8/H2α. Instead, a complementary NOE of H1 by H7a revealed the endo-nature of the vinyl substituent in **323-endo**. Thus, Isomer I is **323-endo** and Isomer II is **323-exo**.

III-C. CONCLUDING REMARKS

As a result of the successful structural reassignment of **322-endo** and **323-endo** to **323-endo** and **323-exo** respectively, an alternative mechanism is required to account for the formation of the newly proposed diastereomers (Scheme III-10). Intermediate **371**,

Scheme III-10. Alternative mechanism to account for the formation of newly proposed FVP products.



arising from bond "a" cleavage, is a homoallylic radical. As such, it is expected to interconvert with its trans-alkene isomer **373** via the cyclopropylcarbinyl radical **372**. Recombination of the C7-C8 centers in diradical **373** then gives **374**, the precursor to **323-exo**. In other words, we propose that both of Isomers-I and II arise via initial homolysis of bond "a" and that they have the diastereomeric structures **323-endo** and **323-exo** rather than the originally assigned (constitutional isomers) **322-endo** and **323-endo**, respectively. It should also be stated that the major ramification of this structural reassignment is that it directly supports our proposed hypothesis of the Cope rearrangement as the key feature in the biosynthesis of ottelione A.

PART II

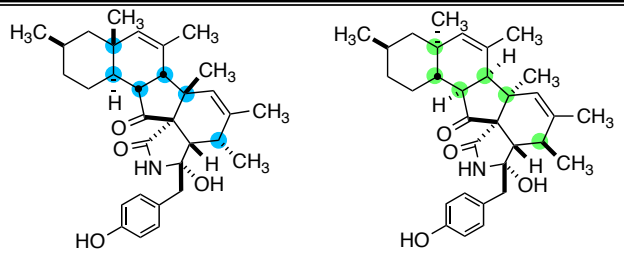
CHAPTER IV

THE HEXA-EPIMERS PHOMOPSICHALASIN AND DIAPORTHICHALASIN[121]

IV-A. BACKGROUND

IV-A-1. *Introduction*

Part I Chapter I highlighted the ubiquitous nature of reactions such as the Diels-Alder reaction in the biosynthesis of various natural products (page 9, Figure I-6). Over the past decade the Hoye group has investigated biologically relevant Diels-Alder reactions to form decalin ring systems. In the course of investigating several decalin containing compounds we came across the natural product phomopsichalasin **401** and shortly thereafter its hexa-epimer, diaporthichalasin **402** (Figure IV-1) [122, 123]



401 Phomopsichalasin ***402*** Diaporthichalasin

Figure IV-1. Structures of the natural products phomopsichalasin, **401**, and its hexa-epimer diaporthichalasin, **402**. These compounds differ at the highlighted stereogenic centers.

[121] Brown, S. G.; Jansma, M. J.; Hoye, T. R. Case Study of Empirical and Computational Chemical Shift Analyses: Reassignment of the Relative Configuration of Phomopsichalasin to That of Diaporthichalasin. *J. Nat. Prod.* **2012**, *75*, 1326–1331.

[122] 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.

[123] 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.

Other similar natural products that contain a decalin ring system as well as a lactam are oteromycin (**403**)[124], talaroconvolutin A (**404**)[125], talarconvolutin B (ZG-1494α (**405**)[126]), myceliothermophin A (**406**)[127] and codinaeopsin (**407**)[128] (Figure IV-2, all with the same relative configuration around the fused ring system)[129]. This work will focus on the two aforementioned natural products phomopsichalasin **401** and diaporthichalasin **402**. Phomopsichalasin was isolated from an endophytic fungus *Phomopsis sp* in 1995 by Horn and coworkers and was found to exhibit antibacterial activity in several disk

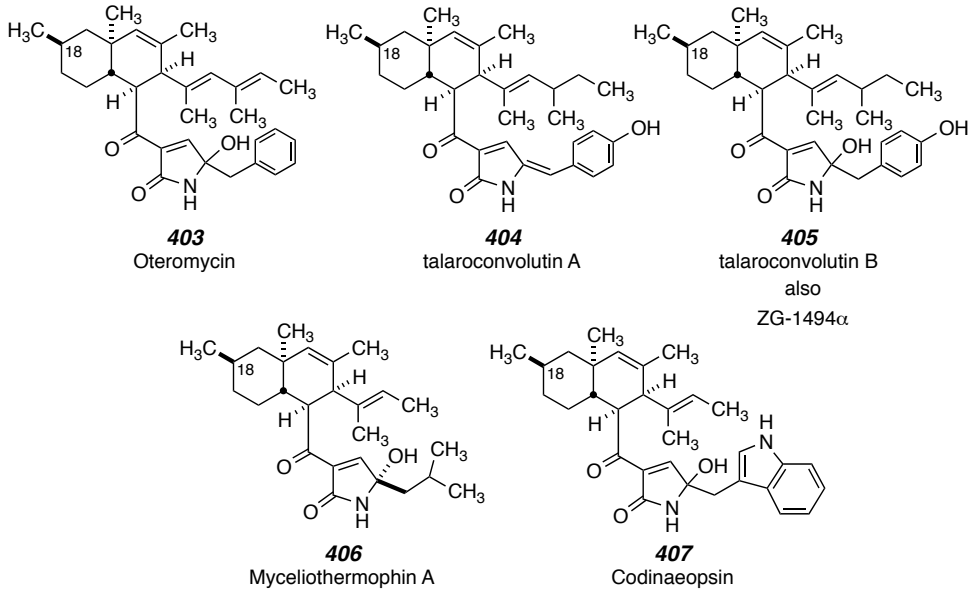


Figure IV-2. Structures of other lactam containing decalin natural products, namely oteromycin (**403**), talaroconvolutin A (**404**), talarconvolutin B (ZG-1494α) (**405**), myceliothermophin A (**406**) and codinaeopsin (**407**).

[124] Singh, S. B.; Goetz, M. A.; Jones, E. T.; Bills, G. F. Oteromycin: A Novel Antagonist of Endothelin Receptor *J. Org. Chem.* **1995**, *60*, 7040–7042.

[125] Suzuki, S.; Hosoe, T.; Nozawa, K.; Kawai, K.; Yaguchi, T.; Udagawa, S. Antifungal Substances Against Pathogenic Fungi, Talaroconvolutins, From *Talaromyces convolutus*. *J. Nat. Prod.* **2000**, *63*, 768–772.

[126] West, P. R.; v. Ness, J.; Varming, A.-M.; Rassing, B.; Biggs, S.; Gasper, S.; McKernan, P. A.; Piggot, J. A Novel Platelet-activating Factor Acetyltransferase Inhibitor from *Penicillium rubrum*, Isolation, Structure Elucidation and Biological Activity. *J. Antibiot*. **1996**, *49*, 967–973.

[127] Yang, Y.-L.; Lu, C.-P.; Chen, M.-Y.; Chen, K.-Y.; Wu, Y.-C.; Wu, S.-H. Cytotoxic Polyketides Containing Tetramic Acid Moieties Isolated From the Fungus *Myceliophthora thermophila*: Elucidation of the Relationship Between Cytotoxicity and Stereoconfiguration. *Chem*. *Eur*. *J*. **2007**, *13*, 6985–6991.

[128] Kontnik, R.; Clardy, J. Codinaeopsin, an Antimalarial Fungal Polyketide. *Org. Lett.* **2008**, *10*, 4149–4151.

[129] It should be noted at this point that phomopsichalasin does not share the same relative configuration as the other decalin containing natural products mentioned.

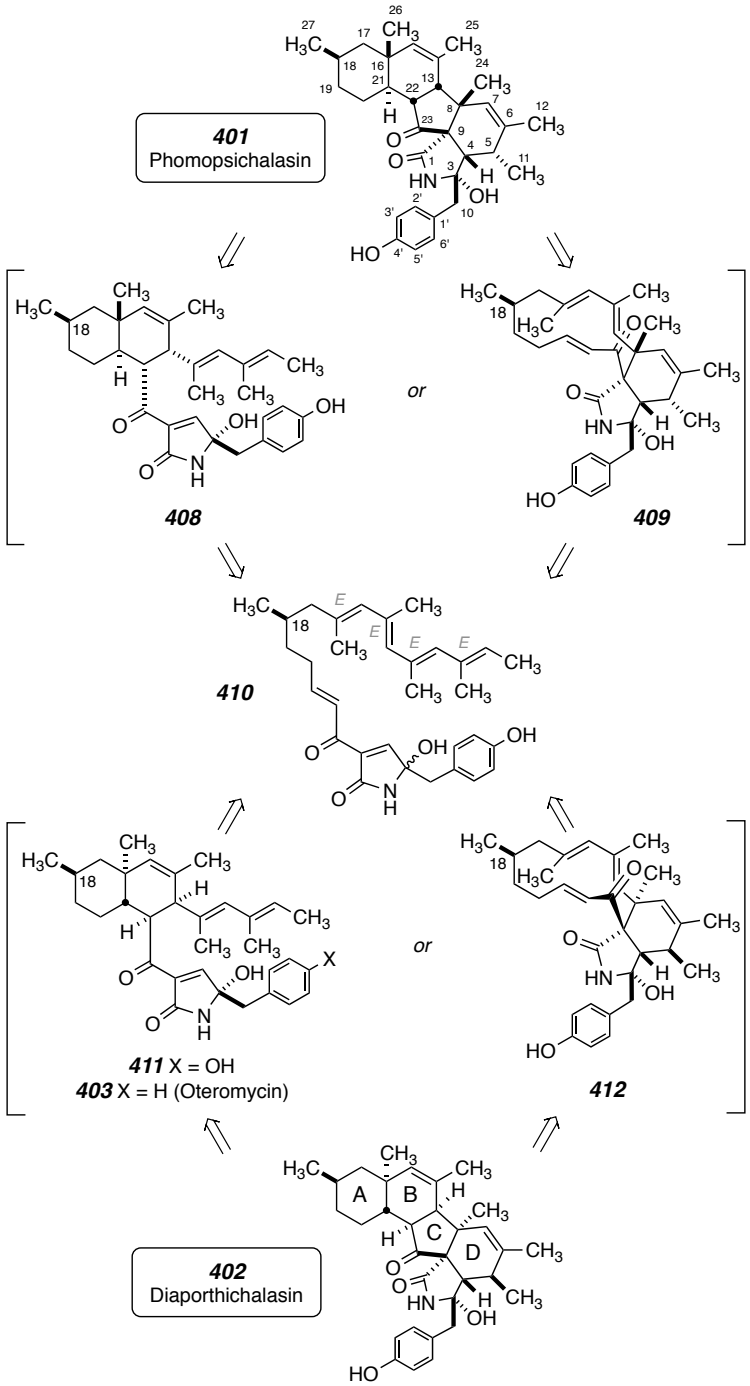
diffusion assays.[122] Several years later in 2007 diaporthichalasin was isolated from the endophytic fungus *Diaporthe sp. Bkk3*, and assigned the structure **402** on the basis of a battery of 1D and 2D NMR experiments and its structure was confirmed by the single crystal X-ray structure of **402**. After close inspection of the NMR data of **401** we noticed a few oddities that led us to call this structure into question. Adding to the confusion surrounding these two molecules, the published NMR data on which the analyses were performed that led to the assignments of **401** and **402** were recorded in two different solvents (methanol-d_4 and DMSO-d_6, respectively). In other words, our contention is that phomopsichalasin **401** and diaporthichalasin **402** are identical, *i.e.* both have structure **402**. Presented in the following sections are our arguments and experimental evidence to support this conjecture as well as additional aspects of NMR interpretation that provide guidance for avoiding some of the pitfalls that can lead to incorrect structure assignments. These recommendations/reminders include (i) the use of complementary solvents for acquiring NMR data that break accidental chemical shift degeneracy, (ii) the importance of assigning coupling constants as extensively as possible, and (iii) exercising caution when interpreting correlations in 2D spectra where overlapping resonances are involved.

IV-A-2. ***Biosynthetic hypothesis***

The structure of **401** attracted us because of the possibility that it might arise via a biosynthetic pathway involving a pair of (sequential) 4+2 net intramolecular Diels-Alder (IMDA) reactions beginning from the polyene precursor **410** (Scheme IV-1). This double-diene/double-dienophile is a very reasonable biosynthetic progenitor to **401** as it may potentially be made via ployketide synthase and non-ribosomal protein synthetase pathways. In principle, either of two IMDAs, leading either to octalin **408** or macrocycle **409**, could be the first to occur enroute from **410** to **401**.

We have further wondered if the IMDA reactions might occur in the absence of a specific enzymatic catalyst—that is, might one or both cycloadditions be sufficiently inherently fast to occur spontaneously? If so, then the relative configuration of the nine

Scheme IV-1. Biosynthetic considerations of the possible origin of structures **401** and **402**, assigned to phomopsichalsin and diaporthichalasin, respectively, point to the common intermediate hexa-ene **410**.



[a] For comparison purposes, the absolute configuration of C-18 is held constant in all structures. The absolute configuration of natural phomopsichalasin/diaporthichalasin (**402**) is unknown.

non-carbinolamide stereocenters in **401** would be established by the relative asymmetric induction originating from the C18 methyl-bearing stereocenter in **410**. Consequently, the relative configuration between C18 and C16 in **401** would seem odd, since the diaxial relationship between the methyl groups attached to those centers is destabilizing. In other words, the energy surface for the IMDA reaction leading from **410** to **408** (or **409** to **401**) would be destabilized by a growing syn-pentane interaction in the transition state geometry.

As previously mentioned, structure **402** shares the constitution of **401**, but differs in the relative configuration of several stereocenters. The differences between structures **402** and **401** bear directly on the question of possible spontaneity of the IMDA events. That is, **402** could arise from **411** or **412** either of which could be formed from **410**. Of course, this presents a quandary, because **410** is the same polyene precursor that we earlier identified by retrobiosynthetic analysis of structure **401**.

The uncatalyzed reaction of **410** would follow the same pathway(s) regardless of what organism may have produced that biosynthetic intermediate. This dichotomy could be construed as evidence that the cyclization chemistry of **410** is not spontaneous but, rather, is promoted by (Diels−Alderase-like) enzymes unique to each organism. We, however and in light of this information, returned to the question of the structure assigned to phomopsichalasin, i.e., **401**. In contrast to **401**, diaporthichalasin (**402**) contains (i) an equatorial methyl substituent at C-18; (ii) a relative configuration of the five stereocenters within its AB bicyclic octalin subunit that is entirely consistent with the geometry expected to arise from a concerted IMDA reaction and (iii) four stereocenters within its D-ring that would be anticipated from an IMDA cycloaddition in which the ketocarbonyl had been oriented endo to the C-5−C-8 diene (cf. **411** to **402** or **410** to **412**, Scheme IV-1) rather than the lactam carbonyl (cf. **408** to **401** or **410** to **409**)

IV-A-3. *Spectroscopic ambiguity surrounding the structure assigned to phomopsichalasin*

As intimated in the previous section, the growing syn-pentane interaction in the transition state geometry for the IMDA reaction leading from **410** to **408** (or **409** to **401**) renders the transition state horrendously high in energy. This dilemma prompted us to reexamine the data upon which the structural assignment of **401** was based. In particular, the ^{1}H NMR chemical shifts (methanol-d_4) of two protons first attracted our attention. Namely, the resonances for the axial protons at C-17 and C-19 in phomopsichalasin appear at 0.67 and 0.56 ppm, respectively. For the reasons discussed next, we surmised that these values were untenable for structure **401**.

Empirical interpretation of chemical shifts has been a mainstay of NMR analysis since the infancy of NMR spectroscopy. A methyl substituent on a cyclohexane ring is known to induce significant chemical shift perturbations on various other protons on that ring (Figure IV-3, panel A). The magnitude of some of these through-bond anisotropies is

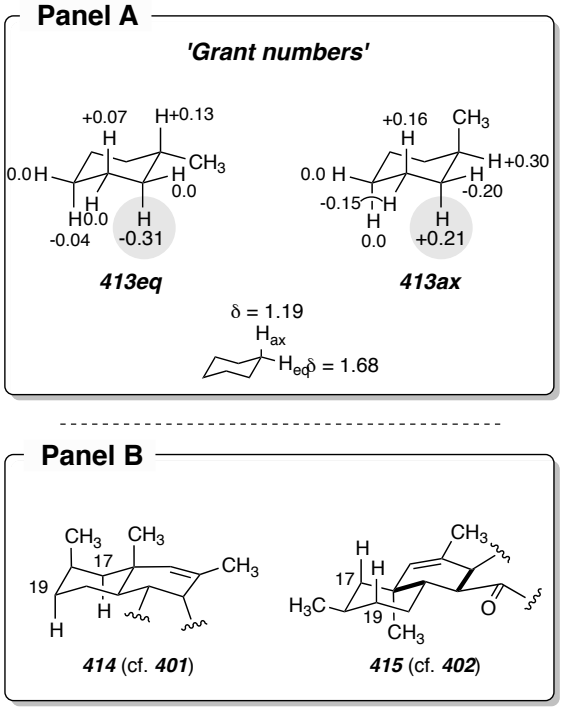


Figure IV-3. *Panel A*. Grant numbers: The incremental chemical shift perturbations imposed by a methyl substituent in the equatorial (cf. **413eq**) *vs* the axial (cf. **413ax**) position of a chairlike cyclohexane. Positive values refer to downfield (and negative upfield) changes in the chemical shift of the axial or equatorial protons of cyclohexane itself. *Panel B*. *trans*-Fused octalin subunit of structure **401** (**414**) *vs* its equatorial 18-CH_3 counterpart (**415**).

surprisingly large. These shift perturbations emerged from an insightful analysis of the (natural abundance deuterium) chemical shifts of numerous methyl-substituted cyclohexanes done in the Grant laboratory.[130] Hence, we refer to these as the "Grant numbers" and find them to be quite broadly applicable to the interpretation of chemical shift data in the context of a variety of structural settings. Quite relevant to the case of phomopsichalasin, the effect of an axially versus equatorially oriented methyl group on the axial proton at C-2 (see gray-highlighted data in each of structures **413eq** vs **413ax**) is particularly striking: H-2ax is perturbed by over 0.5 ppm simply depending upon the dihedral relationship (anti vs gauche) of its H−C-2 bond relative to the vicinal C-1−methyl bond! That is, when the methyl group is axial, the dihedral angle to H-2ax is ca. 180° and H-2ax is relatively deshielded, whereas when the methyl is equatorial, the dihedral is ca. 60° and H-2ax is shielded.

By applying the logic of a Grant analysis to structure **401**, we observed that the high-field nature of the chemical shift values for H-17ax and H-19ax is inconsistent with the axial orientation of the 18-methyl substituent (cf. substructure **414**, Figure 1V-A), which represents the geometry of the dominant conformer expected for the *trans*-fused AB bicyclic octalin skeleton of **401**. Instead, these shift values are much more compatible with an equatorial orientation for the 18-methyl group (cf. **415**). The diastereomeric relationship in **415** is a more reasonable stereochemical outcome for an IMDA reaction (forming the bold bonds in the cyclohexenyl B-ring in **415**) proceeding under control of relative internal asymmetric induction.

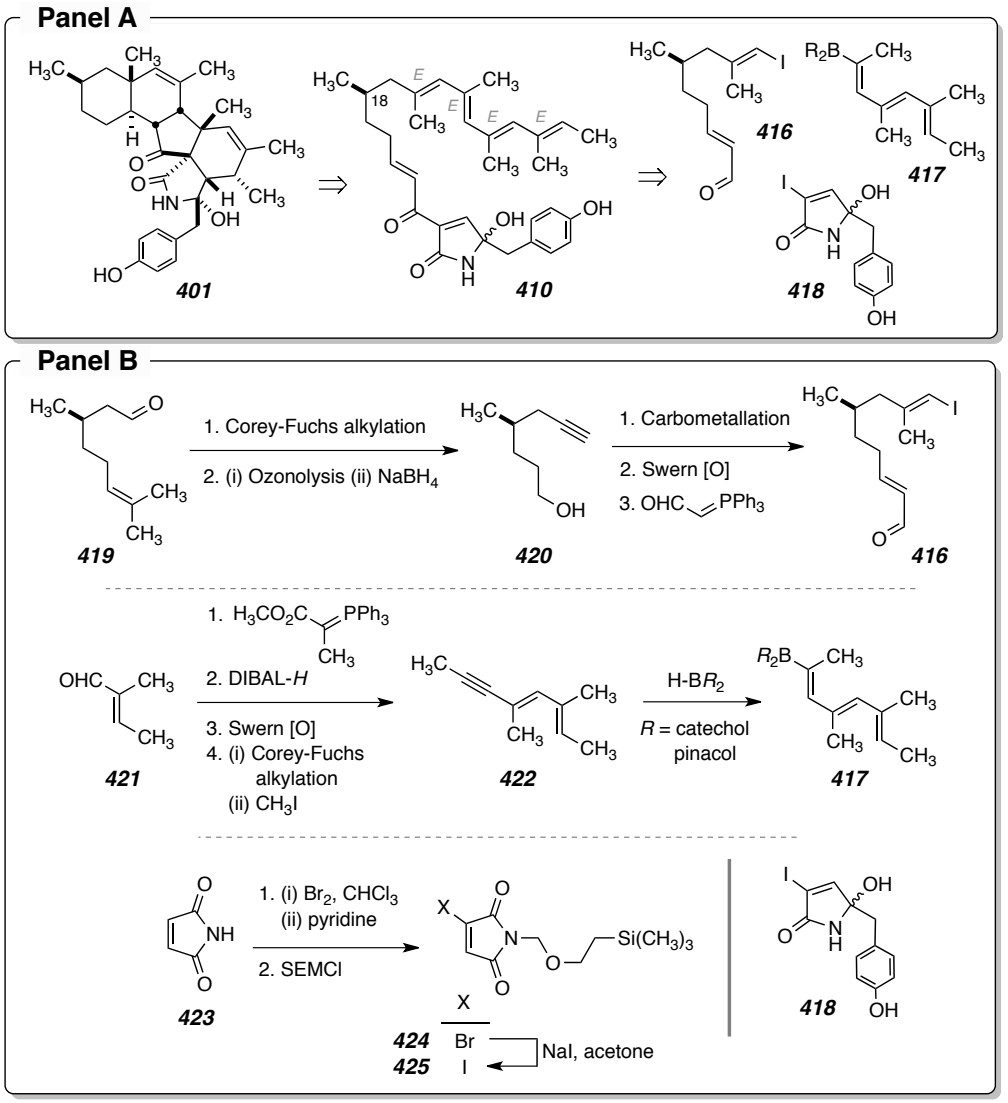
[130] Curtis, J.; Dalling, D. K.; Grant, D. M. Deuterium Chemical Shifts and Chemical Shift Parameters in Methylcyclohexanes *J. Org. Chem.* **1986**, *51*, 136−142.

IV-B. PREVIOUS SYNTHETIC EFFORTS

IV-B-1. *Progress towards the synthesis of 'phomopsichalasin' – Structure determination via synthesis*

Efforts towards the synthesis of the proposed structure of phomopsichalasin **401** began in the Hoye laboratory in 2008.[131] Since this thesis is not dedicated to the synthesis of phomoposichalasin, presented in Scheme IV-2 is the outline of the synthetic strategy employed. This work was pioneered by Dr. Elena Sizova[131], taken over by myself and

Scheme IV-2. *Panel A.* Retrosynthesis of the polyene precursor **410**. *Panel B.* Outline of synthetic strategy in the Hoye group.



[131] Sizova, E. P. Second Generation Synthesis of UCS1025A. Synthetic Efforts Toward Total Syntheses of CJ-16,264 and Phomopsichalasin PhD Thesis, University of Minnesota, Minneapolis, MN, 2009.

and then by a talented undergraduate student Julian Lo. The synthesis of **416**, begins with the commercially available *R*-cintronellal, **419**, that was converted to alcohol **420** by first conducting a Coery-Fuchs alkynation followed by ozonolysis coupled with a reductive work-up to furnish **420**. This alcohol was then carbonmetallated under standard Negishi $Al(CH_3)_3$-$ZrCp_2Cl_2$ mediated conditions. Swern oxidation followed by Wittig olefination provided the enal **416**. Compound **417** was synthesized by first reaction Wittig olefination of **422**, followed by DIBAl-H reduction to the alcohol, Swern oxidation to the aldehyde followed by Coery-Fuchs alkynation and methylation to provide **422**. Alkyne **421** was then hydroborated with catechol or pinacol borane to provide **417**. The Heterocycle **418** was a bit more challenging and installation of the benzyl substituent was problematic, to this end we accomplish the synthesis of the SEM-protected malimides **424** and **425**. All that remains is the addition of the benzylic substituent of **418** followed by the union of the three implicit compounds **416**, **417**, and **418**. Using a late-stage Suzuki cross coupling, the carbon-carbon bond was forged to furnish the conjugated tetraene, and a carbanion coupling to append the heterocycle to the polyene.

Recently, work employing this IMDA reation in the construction of a natural product similar to that of diaporthichalasin, fusarisetin A was reported.[132] Shortly thereafter, the Uchino group published work on the synthesis of the α-acyl-ϒ-hydroxylactams present in **401** and **402**[133], and this strategy was then applied in the first total synthesis of oteromycin, **403** that also utilized an IMDA to form the decalin ring system.[134] It should be noted that the second IMDA of carbinol-amide epimer of oteromycin did not proceed to provide the fused tetracyclic ring system even after refluxing in toluene. On the other hand, oteromycin reacted a second time to provide the tetracyclic compound, with the same relative configuration of diaporthichalasin **402**.

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[132] Deng, J.; Zhu, B.; Lu, Z.; Yu, H.; Li, A. Total Synthesis of (−)-Fusarisetin A and Reassignment of the Absolute Configuration of Its Natural Counterpart. *J. Am. Chem. Soc.* **2012**, *134*, 920–923.

[133] Uchiro, H.; Shionozaki, N.; Kobayakawa, Y.; Nakagawa, H.; Makino, K. A Novel Convergent Method for the Synthesis of α-Acyl-ϒ-Hydroxylactams and Its Application in the Total Synthesis of PI-090 and 091. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4765–4768.

[134] Uchiro, H.; Shionozaki, N.; Tanaka, R.; Kitano, H.; Iwamura, N.; Makino, K. First Total Synthesis of Oteromycin Utilizing One-Pot Four-Step Cascade Reaction Strategy. *Tetrahedron Lett.* **2013**, *54*, 506–511.

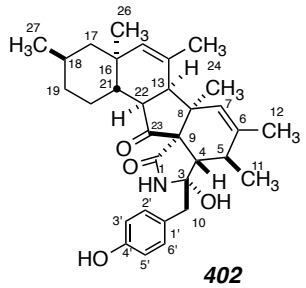
IV-C. A CASE FOR THE STRUCTURAL REASSIGNMENT OF PHOMOPSICHALASIN

IV-C-1. *Computational Support*

To further examine the hypothesis that structure **401** is an incorrect formulation for phomopsichalasin within (at least) the fused AB bicyclic subunit, we undertook a computational analysis. This work was conducted by former Hoye graduate student Dr. Matthew Jansma.[115] To make this study more tractable, we elected to examine two truncated structures that retained the ABC tricyclic substructure unit. Ultimately the most telling information were the computed (and Boltzmann-weighted) proton chemical shifts (δ_{DFT}) versus the experimental shifts reported for the analogous protons. The differences between the computed and experimental proton chemical shift values ($|\Delta\delta|$) along with the sum of the mean absolute errors ($|\Delta\delta_{AVE}|$) were calculated. The calculated probabilities indicated that the truncated structure for the "diaporthichalasin-like" stereoisomer) is a much better fit than the truncated structure for the "phomopsichalasin-like" stereoisomer with the spectroscopic data reported for phomopsichalasin with a >99.5% confidence interval.

IV-C-2. *Spectroscopic Support*

As mentioned previously, the published NMR data on which the analyses were performed that led to the assignments of **401** and **402** were recorded in two different solvents (methanol-d_4 and DMSO-d_6, respectively). We therefore also recorded spectra for the diaporthicahalasin (**402**) that was generously provided to us by Dr. Pornpakakul sample in each of these two solvents [Tables IV-1 (methanol-d_4) and IV-2 (DMSO-d_6)] and in $CDCl_3$ (Table IV-3), along with a figure of all observable HMBCs (Figure IV-5).



402

Figure IV-4. Labeled diagram of diaporthichalasin, **402**.

Table IV-1. NMR spectral data for diaporthichalasin **(402)** in d_4-methanol (UMN).

#	δ_H (mult, *J*, Hz) of "401"	δ_H (mult, *J*, Hz) of 402	COSY of 402 H → #	Carbon of "401"	Carbon of 402	HMBC of 402 (CD_3OD, $^1H \rightarrow ^{13}C$)
1	-	-	-	178.2	178.2	
2	-	-	-	-	-	
3	-	-	-	89.7	89.6	
4	2.73 (d, 1.7)	2.73 (d, 1.7)	5	52.4	52.4	3,5,6,8,9,11,23
5	2.09 (br q, 7.3)	2.09 (br q, 7.3)	4,7,11	30.7	30.7	3,4,6,7,9,11
6	-	-	-	136.6	136.6	
7	5.20 (br s)	5.21 (dq, 1.4, 1.4)	11,12,5	127.5	127.5	5,8,9,12,13
8	-	-	-	45.2	45.2	
9	-	-	-	66.1	66.1	
10	2.99 (br s)	3.0 (br s)	2'/6'	46.3	46.3	1′,2′/6′,3,4
11	0.81 (d, 7.4)	0.81 (d,7.3)		21	21.0	overlaps w/ 26 & 27
12	1.64 (br s)	1.65 (s)	7	22.7	22.7	*overlaps w/ 19 but can *ca.* 5,6,7,24
13	2.85 (br d, 8.0)	2.86 (d, 8)	15,22,25	52.0	51.9	7,8,14,15,21,22,24
14	-	-	-	129.5	129.5	
15	5.36 (br s)	5.37 (dq, 1.9, 1.9)	$13,20_{eq},25$	139.7	139.7	13,16,17,21,25
16	-	-	-	37.0	37.0	
17_{ax}	0.67 (dd, 12.2)	0.68 (dd, 12.4, 12.4)	17_{eq},18			
17_{eq}	1.45 (m)	1.45(ddd, 1.8, 3.8, 12.7)	17_{ax},20,22	49.4	49.5	16,18,21,26,27
18	1.62 obsc	1.62 (ddddq, 4.1, 4.1, 12.3, 12.3, 6.5)	17_{ax},27	28.4	28.4	overlaps w/ 12
19_{ax}	0.56 (dq, 3.7, 12.7)	0.57 (dddd, 4.3, 13.2, 13.2,13.2)				
19_{eq}	1.64 obsc	1.69 (dddd, Σ(*J*s) = 25.7 Hz including *J*s of 1.8 & 12.7)	18, 20_{ax},20_{eq}	36.9	36.9	16,21
20_{ax}	1.1 (dddd, 12.7, 2.2, 2.4)	1.1 (dddd, 4.3, 13.2, 13.2)	18, 19_{ax},21	24.5	24.5	
20_{eq}	1.5 (obsc)	1.51 (dddd, 3.3, 3.3, 3.3, 13.6)	15, 19_{ax}			
21	1.42 (m)	1.42 (ddd, 2.9, 12.7, 12.7)	17_{ax},20_{ax},22	42.2	42.2	overlaps w/ 17
22	2.24 (dd, 8.0, 12.7)	2.25 (dd, 8.1, 13.0)	$13,17_{eq}$	50.8	50.8	8,9,16,21,23
23	-	-	-	221.3	221.2	
24	1.52 (br s)	1.53 (s)		26.3	26.3	7,8,9,12,13
25	1.88 (br s)	1.89 (dd, 0.9, 1.3)	15	25.5	25.5	13,14,15,26
26	0.80 (s)	0.81 (s)		19.9	19.9	overlaps w/ 11,27
27	0.78 (d, 2.2)	0.81 (d, 6.5)		23.1	23.1	overlaps w/ 11,26
1′	-	-	-	128.0	128.0	
2′,6′	7.14 (d, 8.5)	7.15 (d, 8.5)	3'/5',10	132.8	132.7	1′,2′/6′,4′,3′/5′,10
3′,5′	6.74 (d, 8.5)	6.75 (d, 8.5)	2'/6'	116.1	116.1	1′,3′/5′,4′
4′	-	-	-	157.6	157.5	
OH	-	-	-	-	-	
OH	-	-	-	-	-	

Table IV-2. NMR spectral data for diaporthichalasin (**402**) in d_6-DMSO.

#	δ_H (mult, *J*, Hz) (2007)	δ_H (mult, *J*, Hz) (UMN)	Carbon (2007)	Carbon (UMN)
1	-		174.83	174.6
2	8.58 (s)	8.59 (s)	-	-
3	-	-	87.99	87.9
4	2.47 (s)	2.48 (d, 1.4)	49.27	49.2
5	2.03 (m)	2.03 (br q, 7.3)	28.82	28.7
6	-	-	134.77	134.7
7	5.08 (s)	5.08 (dq, 1.4, 1.5)	126.13	126.0
8	-	-	43.64	43.6
9	-	-	63.62	63.6
10	2.86 (s)	2.87 (d, 14.1) 2.85 (d, 14.1)	44.07	44.1
11	0.71 (d, 7.2)	0.71 (d, 7.4)	20.44	20.0
12	1.58 (s)	1.58 (dd, 0.8, 1.4)	22.44	22.3
13	2.72 (d, 8.0)	2.73 (d, 8.1)	50.14	50.0
14	-	-	128.13	128.8
15	5.36 (s)	5.32 (s)	137.95	137.8
16	-	-	35.56	35.5
17_{ax}	0.58 (dd, 12.4, 12.0)	0.58 (dd, 12.3, 12.3)	47.8	47.7
17_{eq}	1.41 (br d, 12.8)	1.41 (ddd, 1.7, 3.6, 12.6)		
18	1.54 (m)	1.55 (ddddq, 3.9, 3.9, 12.8, 12.8, 6.4)	26.72	26.6
19_{ax}	0.46 (br q, 12.4)	0.47 (dddd, 4.2, 12.9, 12.9, 12.9)	35.37	35.3
19_{eq}	1.62 (br d, 9.2)	1.62 (dddd, Σ(*J*s) = 24.7 Hz including *J*s of 1.2 & 12.2)		
20_{ax}	0.98 (br q, 12.4)	0.99 (dddd, 3.5, 13.4, 13.4, 13.4)	22.99	22.9
20_{eq}	1.37 (m)	1.37 (dddd, 3.4, 3.4, 3.4, 13.3)		
21	1.32 (dd, 12.8, 13.2)	1.32 (ddd, 2.9, 12.8, 12.8)	40.34	40.3
22	2.03 (dd, 12, 8.4)	2.04 (dd, 8.1, 12.9)	48.75	48.6
23	-	-	218.95	218.8
24	1.47 (s)	1.47 (s)	25.49	25.4
25	1.82 (s)	1.83 (dd, 0.8, 1.3)	24.98	24.9
26	0.74 (s)	0.74 (s)	19.52	19.9
27	0.75 (d, 7.6)	0.75 (d, 6.4)	22.66	22.6
1´	-	-	126.69	126.6
2´,6´	7.09 (d, 8.4)	7.09 (d, 8.4)	131.6	131.5
3´,5´	6.67 (d, 8.4)	6.67 (d, 8.5)	114.83	114.7
4´	-	-	155.93	155.9
OH	5.63 (s)	5.64 (br s)	-	-
OH	9.26(br s)	9.25 (br s)	-	-

Table IV-3. NMR spectral data for diaporthichalasin (**402**) in $CDCl_3$.

#	δ_H (mult, *J*, Hz)	COSY H→ #	Carbon	HMBC ($^1H \rightarrow {}^{13}C$)
1	-	-	175.1	
2	not assigned	-	-	
3	-	-	86.8	
4	2.91 (d, 2.1)	5	53.5	3,5,6,7,8,9,11,23
5	2.35 (ddqq, 2.1, 2.1, 0.9, 7.5)	4,7,11	29.4	3,4,6,11
6	-	-	135.3	
7	5.32 (dq, 1.6, 1.6)	5, 12	127.1	5,8,9,12
8	-	-	43.8	
9	-	-	64.8	
10	3.12 (d, 13.5) 2.98 (d, 13.4)	10 10	45.8	$1^{\prime}$,$2^{\prime}$/$6^{\prime}$, 3
11	1.01 (d, 7.4)	5	21.0	4,5,6
12	1.75 (dd, 0.9, 1.3)	5, 7	22.4	5,6,7
13	2.98 (d, 8.0)	15, 22, 25	50.4	8,15,21,22,24
14	-	-	127.7	
15	5.39 (dq, 1.9, 1.3)	13, 25	139.0	13,16,21,25
16	-	-	36.0	
17_{ax} **17_{eq}**	0.72 (dd, 12.4, 12.4) 1.45 (ddd, 1.9, 3.8, 13)	17_{eq},18 18,	48.1	16,27
18	1.63 (from COSY)	27	27.1	
19_{ax}	0.60 (dddd, 4.1, 13.1, 13.1, 13.1)	18,19_{eq}, 27	35.7	
19_{eq}	1.72 (from HMQC)	20_{ax}		
20_{ax} **20_{eq}**	1.21 (dddd, 3.5, 13, 13, 13) 1.64 (dddd, 3,3,3,13.5)	19_{eq} ,20_{eq},21 20_{ax}	23.4	
21	1.40 (ddd, 2.8, 12.7, 12.7)	22	41.1	
22	2.44 (dd, 8.3, 12.9)	13,21	49.2	8,21,16,23
23	-	-	218.5	
24	1.46 (s)	-	25.6	7,8,9,13
25	1.88 (dd, 0.9, 1.4)	13, 15	25.1	13,14,15
26	0.82 (s)	-	19.7	16,17,21
27	0.82 (d, 6.5)	18	22.7	17,18
1´	-	-	126.4	
2´,6´	7.15 (d, 8.5)	3´, 5´	131.2	$4^{\prime}$,$1^{\prime}$, $3^{\prime}$/$5^{\prime}$
3´,5´	6.84 (d, 8.5)	2´, 6´	116.2	$4^{\prime}$,$2^{\prime}$/$6^{\prime}$, 10
4´	-	-	155.5	
OH	5.49 (br s)	-	-	3,4,9
OH	6.07 (br s)	-	-	

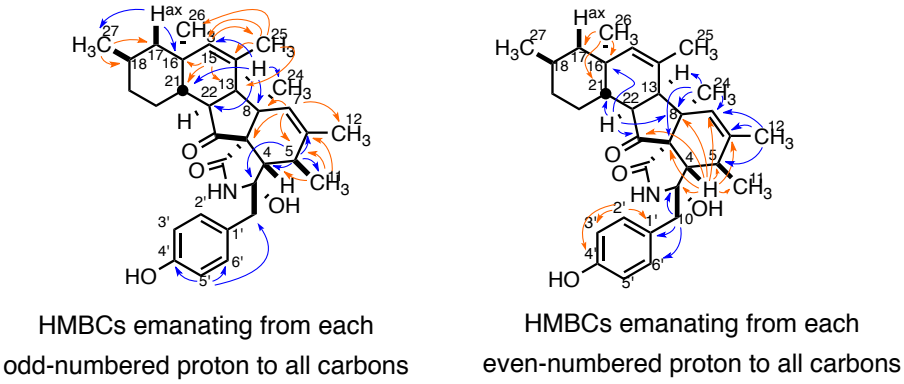


Figure IV-5. HMBC interactions observed for diaporthichalasin (**402**) in $CDCl_3$. Orange and blue arrows are used merely to help distinguish one set of correlations from another; they carry no additional specific meaning.

As we now suspected would be the case, the data for **402** in methanol-d_4 were essentially identical to those reported for the sample named phomopsichalasin (and incorrectly assigned structure **402**) in 1995. It is instructive to consider the analysis and logic that led to the incorrect assignment of the relative configuration of phomopsichalasin as **401**. The ^{1}H NMR spectrum for phomopsichalasin was reported in methanol-d_4 (and MeCN-d_3 in order to obtain a few additional J values). Three methylene or methine proton resonances (H-19eq, H- 20eq, H-18) were obscured by allylic methyl group resonances. In retrospect, dispersion of these resonances, in particular that of H-18, would have been helpful since H-18 is the methine proton at the stereogenic center whose relative configuration we now know to be incorrect. To reveal those overlapped resonances and extract essential coupling constants, we performed complementary experiments by (i) recording the spectrum of **402** in methanol-d_4 at a higher field strength (850 MHz) or (ii) performing an NMR titration with benzene-d_6 (into methanol-d_4). In the former, we could decipher all of the J values of H-18 (ddddq; J = 4.1, 4.1, 12.3, 12.3, and 6.5 Hz; Figure IV-6). This full coupling constant analysis was integral to "walking" the coupled protons around the A-ring of the transfused decalin system and to assigning the orientation of H-18 to be axial rather than equatorial (e.g., the H-18 resonance includes two trans-diaxial vicinal coupling constants).

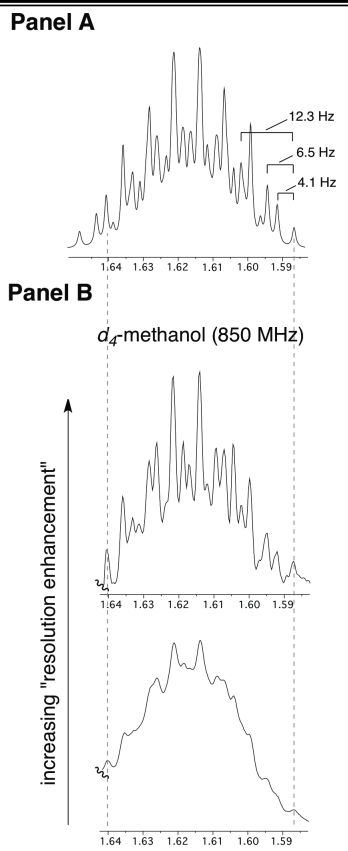


Figure IV-6. *Panel A.* Simulation spin-spin system of H-18 using iNMR. *Panel B.* In methanol-d_4 with increasing levels of "resolution enhancement", which confirmed these *J* values.

Another uncertainty was raised by the peculiar report of a doublet (δ = 0.78) with a coupling constant of 2.2 Hz for CH_3-27. This incorrect assignment resulted from overlapped resonances for CH_3-11, CH_3-26, and CH_3-27 at ca. 0.8 ppm. This was clarified as well by a benzene-d_6 titration (Figure IV-7, panel A), which cleanly resolved all three methyl groups and allowed us to observe the coupling constant for the doublet for CH_3-27 (*J* = 6.5 Hz), which was consistent with the *J* value in the multiplet assigned to H-18. However, in retrospect, even simpler solutions to this problem were available: (i) by straightforward line-broadening (resolution enhancement) analysis of the ^{1}H NMR data for the three methyl resonances partially overlapped at ca. 0.8 ppm in methanol-d_4 (d for CH_3-11, s for CH_3-26, and d for CH_3-27; Figure IV-7, panel B), we could deduce directly the correct coupling values for each of the doublets; (ii) upon recording the spectrum of **402** in $CDCl_3$, we observed that the resonance for CH_3-11 (assignment confirmed by COSY) was well resolved from the resonances CH_3-27 and CH_3-26; (iii)

finally, an unusual NOE was reported between CH_3-27 and H-4 in the methanol-d_4 spectrum of phomopsichalasin. Spatial proximity between these two protons appears to be inconsistent with either structure **401** or structure **402**. Again, this misinterpretation of the (NOESY) NMR data can be attributed to the three overlapping methyl resonances at ca. 0.8 ppm (cf. Figure IV-7), which introduces uncertainty in the interpretation of the NOESY correlation peak. In fact, an NOE between CH_3-11 and H-4 was reported in the Pornpakakul studies and that interaction is clearly consistent with **402** (and highly unlikely for structure **401**).

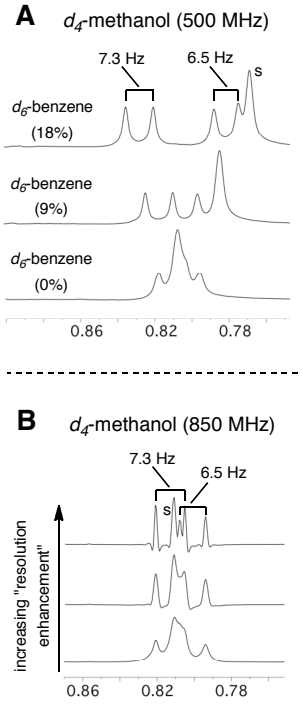
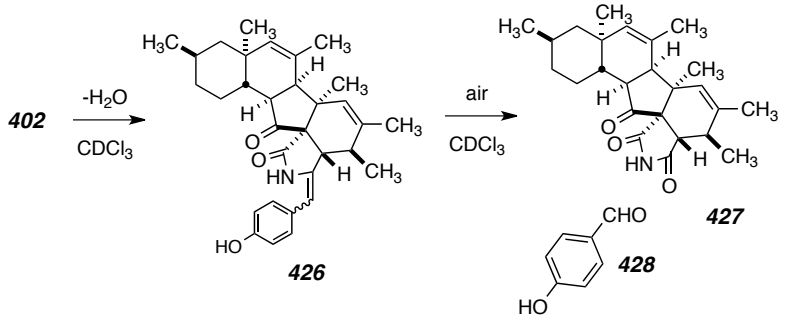


Figure IV-7. Insets of methyl regions of ^{1}H NMR spectra of **402** in various solvents. *Panel A*. In methanol-d_4 containing varying percentages of added benzene-d_6 in order verify the presence of two methyl doublets (with *J* values of 7.3 and 6.5 Hz). *Panel B*. In methanol-d_4 with increasing levels of "resolution enhancement", which confirmed these *J* values.

IV-C-3. *Miscellaneous observations – dehydration and oxidative degradation of 402*

We have also seen evidence for dehydrative and subsequent oxidative degradation events in samples of **402** upon prolonged storage in a solution of $CDCl_3$ (Scheme IV-3). More specifically, ^1H NMR resonances for the aromatic and benzylic protons in **402** diminished, and an intermediate species we suggest to be the enamide **426** was observed by LCMS and ^1H NMR spectroscopy ($CDCl_3$, new doublets at δ 7.06 and 6.81 for aromatic resonances and new singlets at δ 5.57, 5.42, and 5.35, which are consistent with H-10, H-15, and H-7 in **426**, respectively). Over additional time, resonances for the oxidative cleavage product, 4-hydroxybenzaldehyde (**428**), were observed (and confirmed by a doping experiment), and LCMS evidence for a new species having the mass of succinimide **427** was seen. Efficient aerobic cleavage of related enamides has been previously observed.[135, 136]

Scheme IV-3. Dehydration and subsequent oxidative degradation of **402**.



[135] Gunawan, S.; Nichol, G. S.; Chappeta, S.; Dietrich, J. Concise Preparation of Novel Tricyclic Chemotypes: Fused Hydantoin–Benzodiazepines. *Tetrahedron Lett.* **2010**, *51*, 4689–4692.

[136] Banfi, L.; Basso, A.; Casuscelli, F.; Guanti, G.; Synthesis of Novel Isochromene Derivatives by Tandem Ugi Reaction/Nucleophilic Substitution. *Synlett* **2010**, 85–88.

IV-D. CONCLUDING REMARKS

Through careful NMR spectroscopic analysis and pertinent computational models we were able to show that the proposed structure of **401**, phomopsichalasin, is that of the structure **402**, diaporthichalasin (Figure IV-8). As predicted, both the proton and carbon chemical shifts of an authentic sample of **402** (obtained in methanol-d_4) were a complete match to the reported chemical shifts of the structure formally known as **401**. By way of employing complementary solvents for acquiring NMR data we were able to assign all but two of the *J*-values for the protons of **402** (see Tables IV-1, IV-2 and IV-3 where we report two of the four *J*-values for $H19_{eq}$). This kind of meticulous analysis coupled with the use of appropriately chosen computational models has aided us in confidently reassigning the structure of "**401**" as **402**. It is our belief that when applied correctly, this analysis can also assist in avoiding the misinterpretation of spectral data of numerous complex natural products.

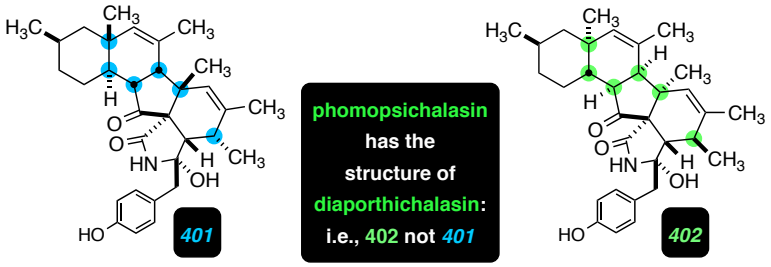


Figure IV-8. The proposed structure of **401**, phomopsichalasin, is that of the structure of **402**, diaporthichalasin.

EXPERIMENTAL SECTION

GENERAL METHODS

Reactions requiring anhydrous conditions were performed under an atmosphere of nitrogen or argon in flame-dried glassware cooled under a stream of nitrogen. Dried triethylamine was distilled from CaH_2; dried dimethylformamide was distilled from $MgSO_4$ and stored over 3Å MS. Anhydrous THF, diethyl ether, toluene, and methylene chloride were dried by being passed through a column of activated alumina. Pyridine was distilled from KOH prior to use.

^{n}BuLi, MeMgBr, Me_3Al, DIBAL-H were titrated with 1,4-cyclooctadiene by No-D NMR spectroscopy.

Medium pressure liquid chromatography (MPLC) refers to (25-60 psi) using handpacked columns of silica gel (18-32 μm, 60 Å), a Waters HPLC pump, and Waters R403 differential refractive index detector.

Analytical TLC was performed using TLC plastic and glass sheets with F_{254} indicator and detection was performed by UV-light or potassium permanganate or anisaldehyde staining.

^{1}H and ^{13}C NMR spectra were recorded on Bruker 850 (850 MHz), Bruker 500 (500 MHz), Varian Inova 500 (500 MHz), or Varian Inova 300 (300 MHz) instrument. ^{1}H NMR chemical shifts in $CDCl_3$ are referenced to TMS (0.00 ppm), in methanol-d_4 to 3.31 ppm (CHD_2OD), in acetone-d_6 to 2.05 ppm ($CD_2HC(O)CD_3$), in benzene-d_6 to 7.16 ppm (C_6D_5H), in water-d_2 to 4.80 ppm (HOD), and in DMSO-d_6 to 2.50 ppm (CHD_2SOCD_3). ^{13}C NMR chemical shifts in $CDCl_3$ are referenced to 77.16 ppm, in methanol-d_4 to 49.0 ppm, in acetone-d_6 to 29.84 ppm, in benzene-d_6 to 128.06 ppm and in DMSO-d_6 to 39.52 ppm. The following format was used to report ^{1}H NMR data: chemical shift in ppm (multiplicity, coupling constant(s) in Hz, integral value, and assignment). The following abbreviations are used to describe multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), pent (pentet), m (multiplet), nform (non-first order multiplet), and br (broad). ^{1}H NMR assignments are indicated by number (*e.g.*, H-3a), or structural characteristic (*e.g.*, CH_aH_b). The number refers to the corresponding atom

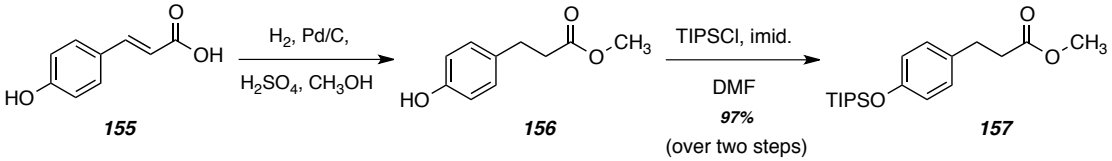
belonging to the longest segment of numbered carbons in the CAS name. Complex structures are also numbered in their structures in order to simplify proton assignment numbering and naming.

Infrared (IR) spectra were recorded on a Midac Corporation Prospect 4000 FT-IR spectrometer (only the most intense and/or diagnostic peaks are reported) using a NaCl plate (thin film). Absorptions are reported in cm^{-1}.

High-resolution mass spectra were recorded on a Bruker Biotof II (ESI-TOF) instrument using PEG or PPG as an internal calibrant. Tandem gas chromatography/low resolution mass spectroscopy (GC/MS) using electron impact ionization (EI) was performed at 70 eV on an Agilent Technologies 6890N series gas chromatograph equipped with an Agilent Technologies 5975 inert XL mass selective detector. Tandem liquid chromatography/low resolution mass spectroscopy (LC/MS) using multimode ESIAPCI ionization mode was performed on an Agilent Technologies 1100 series liquid chromatograph equipped with an Agilent Technologies G1956B LC/MSD SL mass selective detector.

Some compounds included in the experimental section are known in the literature.

Experiments



Methyl 3-(4-hydroxyphenyl)propanoate (156)

To a Fischer Porter tube equipped with a stir bar was added *p*-coumaric acid (2.0 g, 12.2 mmol, 1.0 equiv) dissolved in methanol (50 mL). To this solution 5% active Pd/C (0.26 g, 0.122 mmol, 0.01 equiv) was added, ensuring that there was no residual solid on the sides of the flask followed by three drops of sulfuric acid. The Fischer Porter tube was charged to 50 psi and vented, this charge-vent cycle was repeated three times and then finally the tube was charged once more with hydrogen and stirred at ambient temperature until the pressure dropped to 20 psi. At that point the tube was again charged to 50 psi with hydrogen. When the pressure held at 40 psi after 3 h of stirring, the tube was vented and neutralized with imidazole as indicated by pH paper. The suspension was then filtered through a celite pad and the solids washed thoroughly with EtOAc and the filtrate concentrated *in vacuo*. To this oily residue was added 10 mL of EtOAc and the resultant suspension was again filtered and concentrated via rotary evaporation to give 156 as a yellow oil that was used unpurified in the next step. (2.18 g, 12.1 mmol, 99%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (d, J = 8.3 Hz, 2H, ArH), 6.75 (d, J = 8.3 Hz, 2H, ArH), 3.67 (s, 3H, CO_2CH_3), 2.88 (t, J = 7.5 Hz, 2H, CH_2), and 2.60 (t, J = 7.9 Hz, 2H, CH_2).

Methyl 3-(4-((triisopropylsilyl)oxy)phenyl)propanoate (157)

To a solution of dihydro-methylcoumarate **156** (0.5 g, 2.77 mmol, 1.0 equiv) in DMF (6 mL) was added imidazole (0.38 g, 5.54 mmol, 2.0 equiv) followed by TIPSCl (0.89 mL, 4.16 mmol, 1.5 equiv). The solution was stirred at rt overnight. The following day H_2O (5 mL) was added and the layers separated. The aqueous layer was extracted with Et_2O (3 x 10 mL) that were then combined and washed with brine. This was dried over $MgSO_4$

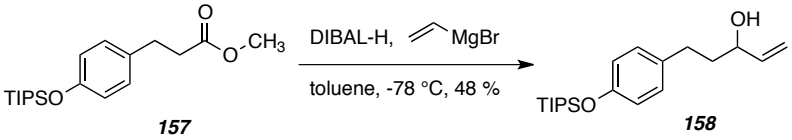
filtered and concentrated *in vacuo*. Purification by Kugelrohr distillation provided **157** as a pale yellow oil (0.924 g, 2.75 mmol, 97%).

^{1}H NMR (500 MHz, CD_3Cl): δ 7.03 (d, *J* = 8.3 Hz, 2H, ArH), 6.79 (d, *J* = 8.4 Hz, 2H. ArH), 3.65 (s, 3H, OC*H*$_3$), 2.87 (t, *J* = 7.7 Hz, 2H, CH_2), 2.59 (t, *J* = 7.9 Hz, 2H, CH_2), 1.22 (sep, *J* = 6.6 Hz, 1H, SiC*H*$(CH_3)_2$), and 1.19 (d, *J* = 6.9 Hz, 18H, SiCH(C*H*$_3)_2$).

^{13}C NMR (125 MHz, CD_3Cl): δ 173.7, 154.6, 133.0, 129.3, 120.0, 51.7, 36.2, 30.4, 17.8, and 12.8.

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 12.22 min; *m/z* 336 (45, M^+), 193 (100), 265 (40), 219 (50), 191 (25), and 107 (25).

5-(4-(Triisopropylsilyloxy)phenyl)pent-1-en-3-ol (158)



157 ***158***

To an oven dried round-bottomed flask fitted with an internal temperature probe was added ester **157** (0.25 g, 0.742 mmol, 1.0 equiv) and dry toluene (4 mL) under an N_2 atmosphere. The solution was cooled to -78 °C and DIBAL-H (0.811 mL, 0.817 mmol, 1.1 equiv, 1.007 M) was added slowly down the sides of the flask, ensuring that the solution temperature did not exceed -70 °C during the course of addition. The reaction mixture was stirred for 5 min at -78 °C, after which vinyl magnesium bromide (1.66 mL, 1.26 mmol, 1.7 equiv, 0.76 M) was added slowly down the sides of the flask, again ensuring that the temperature did not exceed -70 °C. The solution was then stirred for an additional 5 min at -78 °C, allowed to warm to ambient temperature and stirred for 3 hours. The reaction mixture was then cooled to 0 °C and an extractionless DIBAL-H work-up was employed. To the cooled reaction solution was added sequentially, 0.08 mL of H_2O, 0.07 mL of a 15% NaOH solution and by 0.2 mL of H_2O. This was stirred for 5 min at 0 °C, followed by 15 min of stirring at room temperature, after which a large portion of $MgSO_4$ was added and the slurry stirred overnight. This mixture was filtered

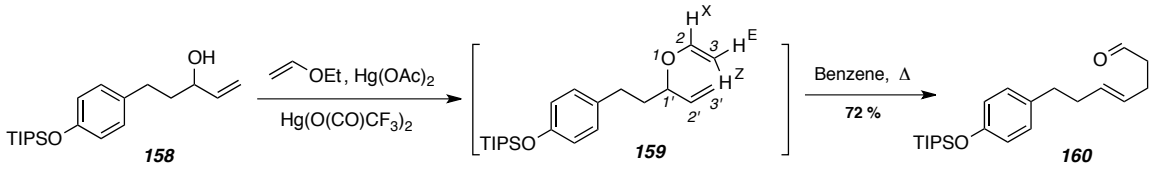
through a celite pad and rinsed with copious amount of toluene, and concentrated *in vacuo*. Purification by MPLC (4:1, Hexanes:EtOAc) furnished the desired compound **158** as a pale yellow oil (0.1184 g, 0.352 mmol, 48%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.03 (d, *J* = 8.3 Hz, 2H, ArH), 6.80 (d, *J* = 8.4 Hz, 2H, ArH), 5.98 (ddd, *J* = 16.6, 10.4, 6.2 Hz, 1H, C*H*=CH_2), 5.25 (d, *J* = 17.2, 1H, CH=C$H_{trans}H_{cis}$), 5.12 (d, *J* = 10.4 Hz, 1H, CH=$CH_{trans}H_{cis}$), 4.12 (apparent quartet, *J* = 6.9 Hz, 1H, C*H*OH), 2.63 (t, *J* = 6.7 Hz, 2H, CH_2), 2.04 (s, 1H, OH), 1.83 (dt, *J* = 6.9, 2.3 Hz, 1H, CH_2), 1.25 (sep, *J* = 7.6 Hz, 3H, SiC*H*$(CH_3)_2$), and 1.09 (d, *J* = 7.4 Hz, 18H, SiCH$(CH_3)_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 154.2, 141.1, 134.1, 129.2, 119.8, 114.8, 72.5, 38.7, 30.8, 18.0, and 12.7.

HR ESI-MS calcd for $C_{20}H_{34}O_2Si$ $[M + Na]^+$ 357.2227, found 357.2232.

IR (thin film**)**: 3380, 2943, 2866, 1741, 1609, 1510, 1262, and 917cm^{-1}.



Triisopropyl(4-(3-(vinyloxy)pent-4-en-1-yl)phenoxy)silane (**159**)

To a stirred solution of mercuric(II)acetate (0.02 g, 0.06 mmol, 0.1 equiv) in ethyl vinyl ether (8.12 mL) was added allyl alcohol **158** (0.218 g, 0.65 mmol, 1.0 equiv). The resulting solution was allowed to stir overnight. Mercuric(II)trifluoroacetate (0.017 g, 0.046 mmol, 0.007 equiv) was added and stirred for 3 hours. The mixture containing the allyl vinyl ether was concentrated under reduced pressure and taken into the next step.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.01 (d, *J* = 8.2 Hz, 2H, ArH), 6.79 (d, *J* = 8.4 Hz, 2H, ArH), 6.31 (dd, *J* = 14.1, 6.6 Hz, 1H, OCH_X=CH_2), 5.9 (ddd, *J* = 17.0, 10.2, 6.4 Hz, 1H, CH_X=CH_2), 5.23 (d, *J* = 17.2, 1H, CH=CH_ZH), 5.12 (d, *J* = 10.3 Hz, 1H, CH=$CH_{E'}H_{cis}$), 4.29 (d, *J* = 14.7, 1H, CH=CH_ZH), 4.11 (apparent quartet, *J* = 6.9 Hz, 1H, OC*H*CH=CH_2),

4.0 (d, J = 6.4 Hz, 1H, CH=CHH_E), 2.63 (t, J = 6.7 Hz, 2H, CH_2), 1.83 (dt, J = 2.3, 6.9 Hz, 1H, CH_2), 1.25 (sep, J = 7.6 Hz, 3H, SiCH(CH_3)$_2$), and 1.09 (d, J = 7.4 Hz, 18H, SiCH(CH_3)$_2$).

(*E*)-7-(4-(Triisopropylsilyloxy)phenyl)hept-4-enal (160)

A solution of allyl vinyl ether **159** was transferred to a culture tube with benzene (3.5 mL). The pale yellow solution was heated to 180 °C for 3 hours in a teflon lined screw cap culture tube. The reaction vessel was then cooled to room temperature and the benzene removed *in vacuo*. Purification by MPLC (98:2, Hexanes:EtOAc) provided the desired compound **160** as a pale yellow oil (0.17 g, 0.47 mmol, 72 %).

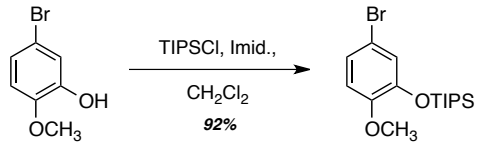
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.74 (s, 1H, COH), 6.98 (d, J = 8.2 Hz, 2H, ArH), 6.78 (d, J = 8.2 Hz , 2H, ArH), 5.47 (dt, J = 6.5, 15.3 Hz, 1H, CH), 5.38 (dt, J = 6.4, 15.3 Hz, 1H, CH), 2.58 (t, J = 7.4 Hz, 2H, CH_2CH$_2$), 2.47 (t, J = 7.1 Hz, 2H, CH_2CH$_2$), 2.32 (dt, J = 6.7, 13.7 Hz, 2H, CH_2CH$_2$), 2.26 (dt, J = 7.1, 14.6 Hz, 2H, CH$_2$CH_2), 1.24 (sep, J = 7.6 Hz, 3H, SiCH(CH_3)$_2$), and 1.09 (d, J = 7.4 Hz, 18H, SiCH(CH_3)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 202.37, 134.22, 131.08, 129.28, 128.37, 119.60, 113.63, 43.47, 35.04, 34.53, 25.15, 18.07, and 12.69.

HR ESI-MS calcd for $C_{23}H_{40}NaO_3Si$ $[M + NaMeOH]^+$ 415.2639, found 415.2644.

IR (thin film): 3027, 2942, 2865, 1728, 1608, 1509, 1262, and 914 cm^{-1}

(5-bromo-2-methoxyphenoxy)triisopropylsilane (169)



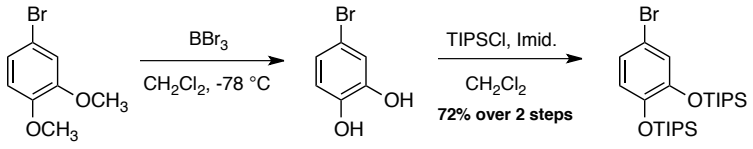
168 *169*

To a flask equipped with a stir bar was placed the bromo-aryl **168** (2.25 g, 11.1 mmol, 1.0 equiv) dissolved in DCM (23 mL), followed by imidazole (1.5 g, 22.2 mmol, 2.0 equiv). The flask was purged with nitrogen and TIPSCl (3.55 mL, 16.6 mmol, 1.5 equiv) was slowly added. The progress of the reaction was monitored by TLC and upon completion, H_2O (10 mL) and Et_2O (10 mL) was added to the reaction mixture, the aqueous layer extracted with Et_2O (3 x 10 mL), and organic layers combined and washed with brine. This was then dried over $MgSO_4$ and purified by FCC (9:1, Hexanes:EtOAc) furnished the desired compound **169** as a pale yellow oil (3.67 g, 10.2 mmol, 92 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.0 (m, 2H, ArH), 6.7 (d, *J* = 9.2 Hz, 1H, ArH), 6.66 (d, *J* = 8.6 Hz, 1H, ArH), 3.77 (s, 3H, OC*H*$_3$), 1.23 (septet, *J* = 7.5 Hz, 6H, C*H*$(CH_3)_2$), and 1.09 (d, *J* = 7.0 Hz, 18H, CH(C*H*$_3)_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 150.5, 146.2, 124.2, 123.7, 113.3, 112.4, 55.7, 18.1, and 13.0.

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 14.39 min; *m/z* 360 (5, M^+), 317 (90), 302 (100), 258 (20), 231 (40), and 216 (25).



170 *171* *172*

4-Bromocatechol (171)

To a flask equipped with a magnetic stir bar was added the 4-bromoveratrole (0.100 g, 0.46 mmol, 1.0 equiv) **170** dissolved in DCM (10 mL) and cooled to -78 °C. BBr_3 (0.109 mL, 1.15 mmol, 2.5 equiv) was slowly added and monitored via TLC. After 15 mins at 78 °C the yellow solution was warmed to rt. Upon completion via TLC, the solution was

quenched with $NaHCO_3$ (5 mL), extracted with EtAcO (3 x 10 mL) dried over $MgSO_4$, filtered and concentrated *in vacuo* and used unpurified in the next step.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.03 (d, *J* = 2.2 Hz, 1H, ArH), 6.92 (dd, *J* = 2.1, 8.5 Hz, 1H, ArH), 6.74 (d, *J* = 8.5 Hz, 1H, ArH), 5.81 (brs, 1H, OH), and 5.61 (brs, 1H, OH).

((4-bromo-1,2-phenylene)bis(oxy))bis(triisopropylsilane) (172)

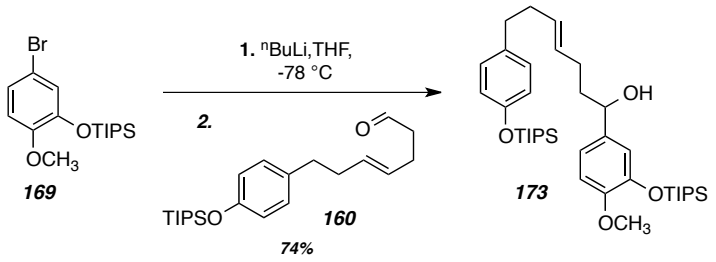
To a flask equipped with a stir bar place the bromocatechol (1.0 g, 5.29 mmol, 1.0 equiv) dissolved in DMF (15 mL), followed by imidazole (1.44 g, 21.1 mmol, 4.0 equiv). The flask was purged with nitrogen and TIPSCl (2.86 mL, 14.9 mmol, 3.0 equiv) was slowly added and monitored by TLC. Upon completion, H_2O (10 mL) and Et_2O (10 mL) was added to the reaction mixture, the aqueous layer extracted with Et_2O (3 x 10 mL), and organic layers combined and washed with brine. This was then dried over $MgSO_4$ and purified by kugelrohr distillation to furnished the desired compound **172** as a pale yellow oil (1.91 g, 0.22 mmol, 72%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.93 (d, *J* = 2.5 Hz, 1H, ArH), 6.86 (dd, *J* = 2.5, 8.5 Hz, 1H, ArH), 6.66 (d, *J* = 8.6 Hz, 1H, ArH), 1.28 (septet, *J* = 7.5 Hz, 6H, C*H*$(CH_3)_2$), 1.11 (d, *J* = 7.5 Hz, 18H, SiCH(C*H*$_3)_2$), and 1.09 (d, *J* = 7.5 Hz, 18H, SiCH(C*H*$_3)_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 148.1, 146.7, 123.8, 123.2, 121.1, 112.2, 18.1 [(SiCH(*C*$H_3)_2$, 2C overlapped] and 13.3 [(Si*C*H$(CH_3)_2$, 2C overlapped].

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 14.39 min; *m/z* 502 (30, M^+), 157 (100), 115 (65), 73 (35), and 59 (40).

(*E*)-1-(3-methoxy-4-((triisopropylsilyl)oxy)phenyl)-7-(4-((triisopropylsilyl)oxy)phenyl)hept-4-en-1-ol (173)



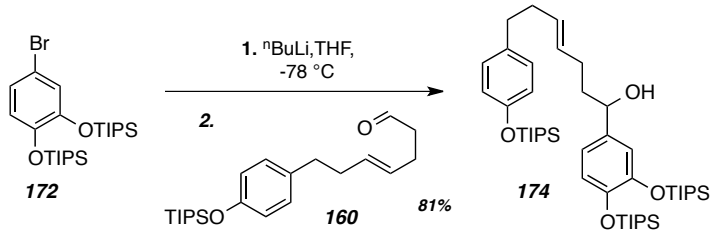
In an oven dried round-bottomed flask aryl bromide **169** (0.042 g, 0.117 mmol, 1.0 eqiuv) was dissolved in dry THF (1 mL). The flask was purged with nitrogen with vigorous stirring and cooled to -78 °C. To this solution was added 1.9 M *n*BuLi (0.117 mL, 0.235 mmol, 2.0 equiv) and the solution was stirred for 10 minutes at -78 °C. The aldehyde **160** (0.064 g, 0.176 mmol, 1.5 equiv) was dissolved in 1 mL of dry THF and slowly added to the reaction solution. The reaction mixture was warmed to room temperature and stirred overnight. Saturated aqueous NH_4Cl was added, the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The organic layers were then combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield a pale yellow oil. Purification by MPLC (95:5, Hexanes:EtOAc) furnished the desired compound **173** as a pale yellow oil (0.053 g, 0.087 mmol, 74 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.99 (d, *J* = 8.5 Hz, 2H, ArH), 6.87 (d, *J* = 2.0 Hz, 1H, ArH), 6.77 (d, *J* = 8.5 Hz, 2H, ArH), 6.75-6.80 (m, 3H, ArH), 5.44 (td, *J* = 5.9, 15.3 Hz, 1H, =CH), 5.40 (td, *J* = 5.6, 15.4 Hz, 1H,=CH), 4.53 (dd, *J* = 6.6, 6.6 Hz, 1H, C*H*OH), 3.79 (s, 3H, MeO), 2.58 (t, *J* = 7.4 Hz, 2H, CH_2Ar), 2.25 (dt, *J* = 6.1, 8.2 Hz, 2H, =CHCH_2CH$_2$), 1.98 (dt, m, 2H, CH_2CH) 1.81 (dddd, *J* = 6.9, 6.9, 6.9, 13.7 Hz, Hz, 1H, CH_AH$_B$CH$_2$), 1.69 (dddd, *J* = 6.3, 6.3, 8.8, 13.1 Hz, 1H, CH$_A$$H_BCH_2$), 1.24 (sep, *J* = 7.1 Hz, 6H, SiC*H*), 1.10 (d, *J* = 7.5 Hz, 18H, SiCH(CH_3)$_2$), and 1.08 (d, *J* = 7.3 Hz, 18H, SiCH(CH_3)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 137.16, 134.78, 130.75, 130.19, 130.10, 129.22, 129.20, 119.59, 118.90, 118.21, 113.90, 111.82, 73.56, 55.82, 38.53, 35.25, 34.68, 28.91, 28.85, 25.38, 12.93, and 12.67.

HR ESI-MS calcd for $C_{38}H_{64}O_4Si_2$ $[M + Na]^+$ 663.4241, found 663.4292.

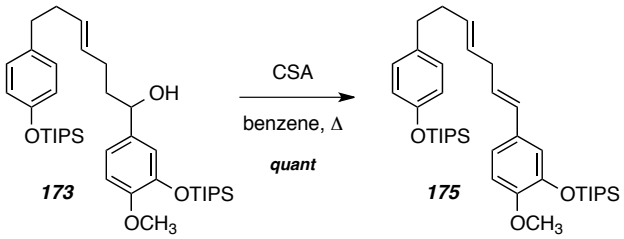
(E)-1-(3,4-bis((triisopropylsilyl)oxy)phenyl)-7-(4-((triisopropylsilyl)oxy)phenyl)hept-4-en-1-ol (**174**)



In an oven dried round-bottomed flask aryl bromide **172** (0.725 g, 1.45 mmol, 1.0 eqiuv) was dissolved in dry THF (10 mL). The flask was purged with nitrogen with vigorous stirring and cooled to -78 °C. This was added 1.9 M *n*BuLi (1.64 mL, 2.89 mmol, 2.0 equiv), and the solution was stirred for 10 minutes at -78 °C. The aldehyde **160** (0.521 g, 1.45 mmol, 1.0 equiv) was dissolved in 5 mL of dry THF and slowly added to the reaction solution. The reaction mixture was warmed to room temperature and stirred overnight. Saturated aqueous NH_4Cl was added, the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The organic layers were then combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by FCC (95:5 Hexanes: EtOAc) provided the desired compound **174** as a pale yellow oil (0.9246 g, 1.18 mmol, 81 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.99 (d, *J* = 8.4 Hz, 2H, ArH), 6.82 (d, *J* = 2.0 Hz, 1H, ArH), 6.78 (d, *J* = 8.2 Hz, 2H, ArH), 6.77 (d, *J* = 8.2 Hz, 1H, ArH), 6.69 (dd, *J* = 2.1, 8.2 Hz, 1H, ArH), 5.44 (dt, J = 5.8, 15.9 Hz, 1H, =CH), 5.40 (dt, J = 5.6, 15.1 Hz, 1H, =CH), 4.51 (dt, J = 3.2, 6.7 Hz, 1H, C*H*OH), 2.57 (t, *J* = 7.4 Hz, 2H, CH_2Ar), 2.25 (dt, *J* = 6.5, 8.1 Hz, 2H, =CHCH_2CH$_2$), 1.69-1.75 (m, 2H, CH_2), 1.63-1.59 (m, 2H, CH_2), 1.24-1.31 (m, 9H, SiC*H*$(CH_3)_2$), and 1.1 (brd, *J* = 8.6 Hz, 36H, Si(CHC$H_6)_3$).

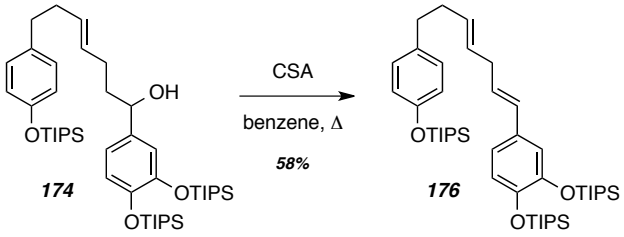
Triisopropyl(2-methoxy-4-((1*E*,4*E*)-7-(4-((triisopropylsilyl)oxy)phenyl)hepta-1,4-dien-1-yl)phenoxy)silane (175)



In a culture equipped with a magnetic stir bar place the diaryl alcohol **173** (0.043 g, 0.068 mmol, 1.0 equiv) dissolved in benzene (2 mL). Add the CSA (0.023 g, 0.102 mmol, 1.5 equiv) and reflux overnight. The following day the benzene was removed *in vacuo* and the compound purified by MPLC (95:5, Hexanes:EtOAc) provided the desired compound **175** as a pale yellow oil (0.044 g, 0.068 mmol, quant.)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.01 (d, *J* = 8.5 Hz, 2H, ArH), 6.90 (d, *J* = 1.9 Hz, 1H, ArH), 6.86 (dd, *J* = 2.0, 8.2 Hz, 1H, ArH), 6.78 (d, *J* = 8.8 Hz, 1H, ArH), 6.75 (d, *J* = 8.9 Hz, 1H, ArH), 6.24 (d, *J* = 15.9 Hz, 1H, ArC*H*=), 6.0 (dt, *J* = 6.8, 15.8 Hz, 1H, =CH), 5.55 (dt, *J* = 5.7, 15.6 Hx, 1H, =CH), 5.47 (dt, *J* = 5.5, 15.4 Hz, 1H, =CH), 3.79 (s, 3H, OCH_3), 2.85 (t, *J* = 5.6 Hz, 2H, CH_2), 2.61 (t, *J* = 7.3 Hz, 2H, CH_2), 2.30 (dt, *J* = 5.7, 6.5 Hz, 2H, CH_2), 1.31-1.71 (m, 6H, SiC*H*$(CH_3)_2$), 1.09 (d, *J* = 7.2 Hz, 18 H, Si(CHC$H_6)_3$), and 1.09 (d, *J* = 6.7 Hz, 18H, Si(CHC$H_6)_3$).

((4-((1*E*,4*E*)-7-(4-((triisopropylsilyl)oxy)phenyl)hepta-1,4-dien-1-yl)-1,2 phenylene)bis(oxy))bis(triisopropylsilane) (176)

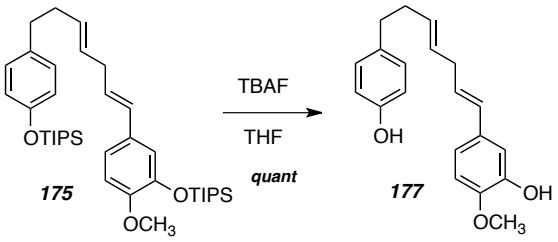


In a culture equipped with a magnetic stir bar place the diaryl alcohol **174** (0.925 g, 1.18 mmol, 1.0 equiv) dissolved in benzene (10 mL). Add the CSA (0.302 g, 1.3, 1.1 equiv) and reflux overnight. The following day the benzene was removed *in vacuo* and the

compound purified by FCC (98:2, Hexanes:EtOAc) provided the desired compound **176** as a pale yellow oil (0.528g, 0.69 mmol, 58 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.01 (d, *J* = 8.22 Hz, 2H, ArH), 6.84 (s, 1H, ArH), 6.79 (d, *J* = 8.4, 2H, ArH), 6.74 (m, 2H, ArH), 6.21 (d, *J* = 15.6 Hz, 1H, ArC*H*=), 5.96 (dt, *J* = 6.6, 15.8 Hz, 1H, =CH), 5.53 (dt, *J* = 6.3, 15.5 Hz, 1H, =CH), 5.48 (dt, *J* = 15.4, 5.82 Hz, 1H, =CH), 2.85 (t, *J* = 6.0, 2H, CH_2), 2.61 (t, *J* = 7.5 Hz, 2H, CH_2), 2.31 (dt, *J* = 6.8, 8.1 Hz, 2H, CH_2), 1.21-1.33 (m, 9H, SiC*H*$(CH_3)_2$), and 1.08-1.21 (m, 18, SiCH$(CH_3)_2$).

4-((1*E*,4*E*)-7-(4-hydroxyphenyl)hepta-1,4-dien-1-yl)-2-methoxyphenol (**177**)



To a flask equipped with a magnetic stir bar was added diaryl compound **175** (0.05 g, 0.08 mmol, 1.0 equiv) dissolved in THF (2 mL) followed by the dropwise addition of a 1M TBAF solution (0.16 mL, 0.16 mmol, 2.0 equiv) and stir at ambient temperature. When complete by TLC the reaction was concentrated *in vacuo* and purified by MPLC (9:1, Hexanes:EtOAc) to afford the diaryl compound **177** as an orange solid (32 mg, 0.08 mmol, quant.)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.03 (d, *J* = 8.4 Hz, 2H, ArH), 6.91 (d, *J* = 1.9 Hz, 1H, ArH), 6.79 (dd, *J* = 8.3, 1.9 Hz, 1H, ArH), 6.76 (d, *J* = 8.8 Hz, 1H, ArH), 6.76 (d, *J* = 8.4 Hz, 2H, ArH), 6.2 (d, *J* = 15.8 Hz, 1H, =CH), 5.99 (dt, *J* = 15.8, 6.63 Hz, 1H, =CH), 5.5 (dt, *J* = 15. 5, 6.2 Hz, 1H, =CH), 5.43 (dt, *J* = 15. 4, 6.1 Hz, 1H, =CH), 3.86 (s, 3H, OCH_3), 2.83 (t, *J* = 6.1 Hz, 2H, CH_2), 2.62 (t, *J* = 7.3 Hz, 2H, CH_2), and 2.29 (q, *J* = 7.1 Hz, 2H, CH_2).

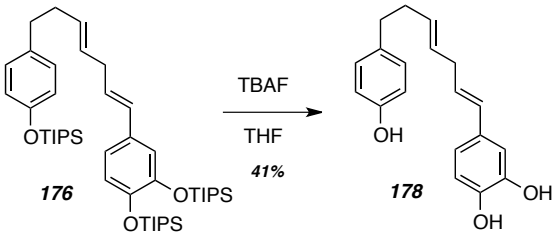
^{13}C NMR (125 MHz, $CDCl_3$): δ 153.8, 146.0, 145.6, 134.2, 131.8, 131.0, 129.8, 129.7, 128.8, 127.9, 118.6, 115.4, 111.9, 110.8, 56.2, 35.9, 35.2, and 34.5.

IR (thin film**)**: 3401, 2924, 1511.9, and 1269.4.

LC-LRMS [ES /AP −/+, 50:50 to 0:100 (%) H_2O:MeOH]: t_R = 8.64 min; 309.2 ($M\text{-}H^+$)

HR ESI-MS calcd for $C_{38}H_{64}O_4Si_2$ $[M + Na]^+$ 333.1461 found 333.1470.

4-((1*E*,4*E*)-7-(4-hydroxyphenyl)hepta-1,4-dien-1-yl)benzene-1,2-diol (178)



To a flask equipped with a magnetic stir bar was added diaryl compound **176** (0.528 g, 0.69 mmol, 1.0 equiv) dissolved in THF (15 mL) followed by the dropwise addition of a 1M TBAF solution (0.61 mL, 2.07 mmol, 3.0 equiv) and stir at ambient temperature. When complete by TLC the reaction was concentrated *in vacuo* and purified by FCC (8:1:1, Hexanes:EtOAc:MeOH) to afford the diaryl compound **178** as an orange solid (0.085 g, 0.285 mmol, 41 %).

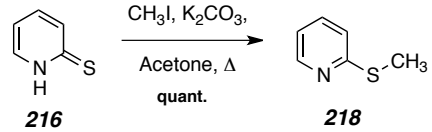
^{1}H NMR (500 MHz, acetone-d_6): δ 7.02 (d, J = 8.1 Hz, 2H, ArH), 6.89 (br s, 1H, ArH), 6.74 (d, J = 8.9 Hz, 1H ArH), 6.74 (d, J = 8.2 Hz, 1H ArH), 6.69 (d, J = 8.1 Hz, 1H, ArH), 6.22 (d, J = 15.9 Hz, 1H, ArC*H*=), 5.91 (dt, J = 15.8, 6.6 Hz, 1H, =CH), 5.54 (dt, J = 15.4, 5.5 Hz, 1H, =CH), 5.48 (dt, J = 15.5, 5.7 Hz, 1H, =CH), 2.82 (t, J = 6.1 Hz, 2H, CH_2), 2.58 (t, J = 7.3 Hz, 2H, CH_2), and 2.27 (q, J = 7.5 Hz, 2H, CH_2).

^{13}C NMR (125 MHz, acetone-d_6): δ 156.3, 146.0, 145.4, 133.5, 131.5, 131.1, 131.0, 130.1, 129.5, 126.5, 119.0, 116.0, 115.7, 113.4, 36.5, 35.8, and 35.6.

IR (thin film**)**: 3379, 2925, 1513.2, and 1233.2 cm^{-1}

HR ESI-MS calcd for $C_{38}H_{64}O_4Si_2$ $[M + Na]^+$ 319.1305 found 319.1317.

2-(methylthio)pyridine (218)

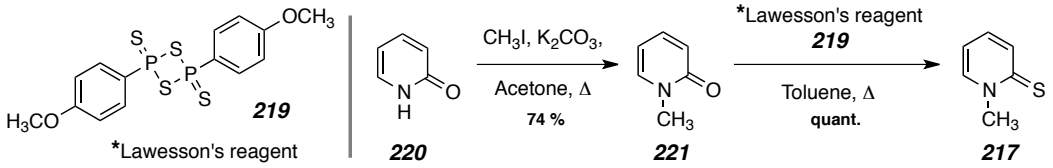


216 ***218***

In a culture tube equipped with a magnetic stir bar was added 2-mercaptopyridine (0.100 g, 0.899 mmol, 1.0 equiv) dissolved in acetone (10 mL). K_2CO_3 (0.435 g, 3.15 mmol, 3.5 equiv) followed by methyl iodide (0.20 mL, 3.15 mmol, 3.5 equiv), were added to the reaction and stirred overnight at rt. The following day the residue was taken up in water, extracted with $CHCl_3$, rinsed with brine, dried over $MgSO_4$, filtered and the solvent removed by rotary evaporation to provide **218** as the only product in a quantitative yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (d, *J* = 5.1 Hz, 1H), 7.48 (dt, *J* = 7.9, 1.8 Hz, 1H), 7.18 (d, *J* = 8.1 Hz, 1H), 6.97 (dd, *J* = 7.3, 4.9 Hz, 1H), and 2.57 (s, 3H, CH_3).

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 8.58 min; 125 (M^+, 100), 97 (15), 81 (45), 65 (15), and 51 (15).



220 ***221*** ***217***

1-methylpyridin-2(1*H*)-one (221)

In a culture tube equipped with a magnetic stir bar was added 2-pyridone (1.00 g, 10.5 mmol, 1.0 equiv) dissolved in acetone (50 mL). K_2CO_3 (5.1 g, 36.8 mmol, 3.5 equiv) followed by methyl iodide (2.3 mL, 36.8 mmol, 3.5 equiv) were added to the reaction and stirred overnight at rt. The following day the residue was taken up in water and extracted with $CHCl_3$, rinsed with brine, dried over $MgSO_4$, filtered and the solvent removed by rotary evaporation to provide **221** as a white solid (0.849 g, 7.77 mmol, 74 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (ddd, *J* = 8.9, 6.6, 2.1 Hz, 1H), 7.28 (dd, *J* = 6.7, 2.0 Hz, 1H), 6.58 (d, *J* = 9.1 Hz, 1H), 6.15 (t, *J* = 6.7 Hz, 1H), and 3.55 (s, 3H, CH_3).

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 6.81 min; 109 (M^+, 100), 81 (65), and 53 (17).

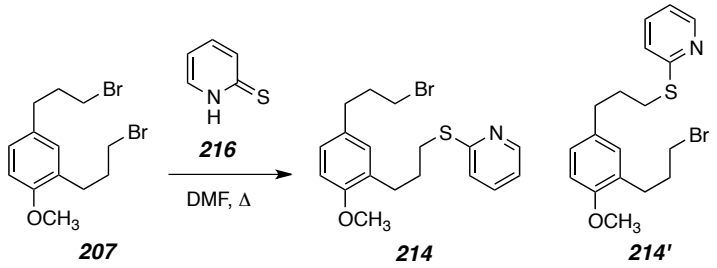
1-methylpyridine-2(1*H*)-thione (**217**)

In a culture tube equipped with a stir bar the methylated thione (0.749 g, 6.86 mmol, 1.0 equiv) was dissolved in toluene (6 mL) and Lawesson's reagent (1.5 g, 3.77 mmol, 0.55 equiv) was added to this reaction mixture. The resultant solution was refluxed for ½ hr, after which it was filtered and concentrated *in vacuo* to provide **217** in a quantitative yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.6 Hz, 1H), 7.67 (d, *J* = 6.5 Hz, 1H), 7.21 (ddd, *J* = 8.6, 6.9, 1.6 Hz, 1H), 6.65 (dt, *J* = 6.8, 1.3 Hz, 1H), and 4.0 (s, 3H, CH_3).

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 8.72 min; 125 (M^+, 100), 97 (15), 81 (45), 65 (15), and 51 (15).

2-((3-(3-(3-bromopropyl)-4-methoxyphenyl)propyl)thio)pyridine (**214**) and **2-((5-(3-bromopropyl)-2-methoxyphenethyl)thio)pyridine** (**214'**)



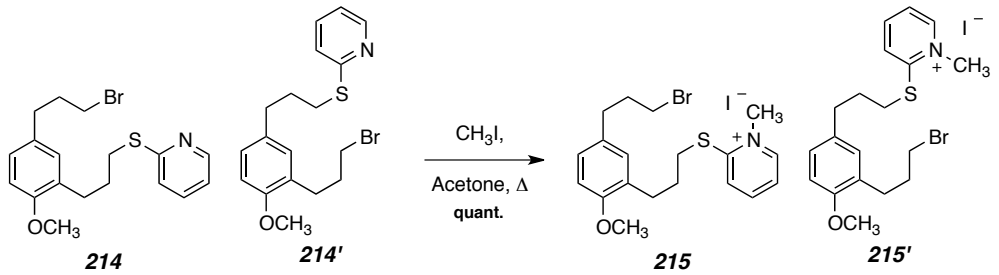
207 ***214*** ***214'***

In a culture tube equipped with a stir bar was added the dihalide **207** (0.100 g, 0.296 mmol, 1.0 equiv) dissolved in DMF (5 mL) followed by 2-mercaptopyridine (0.033g, 0.296 mmol, 1.0 equiv). This was then heated to 150 °C overnight. Upon completion, the reaction was concentrated *in vacuo*. And purified by FCC (8:2, Hexanes:EtAcO) to yield **214** and **214'** as a yellow oil (0.047 g, 0.124 mmol, 42 %)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.41 (d, *J* = 4.9 Hz, 2H, ArH), 7.45 (dd, *J* = 7.8, 7.8 Hz, 2H, ArH), 7.15 (d, *J* = 8.0 Hz, 2H, ArH), 7.08-6.95 (m, 6H, ArH), 6.76 (d, *J* = 8.2 Hz, 2H, ArH), 3.78 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.40 (d, *J* = 6.8 Hz, 2H, CH_2), 3.38 (t, *J* =

6.8 Hz, 2H, CH_2), 3.17 (t, *J* = 7.3 Hz, 2H, CH_2), 3.17 (t, *J* = 7.2 Hz, 2H, CH_2), 2.67-2.77 (m, 8H, CH_2), 2.12 (pent, *J* = 7.0 Hz, 4H, CH_2), and 2.00 (pent, *J* = 7.5 Hz, 4H, CH_2).

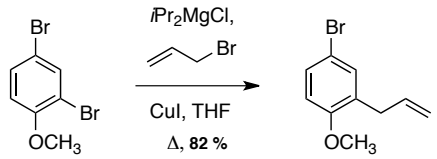
2-((5-(3-bromopropyl)-2-methoxyphenethyl)thio)-1-methylpyridin-1-ium iodide (215) and **2-((3-(3-(3-bromopropyl)-4-methoxyphenyl)propyl)thio)-1-methylpyridin-1-ium iodide (215')**



To a culture tube equipped with a stir bar was added **214** and **214'** (0.199 g, 0.523 mmol, 1.0 equiv) dissolved in acetone (5 mL) followed by the addition of MeI (0.13 mL, 2.09 mmol, 4.0 equiv). The reaction was heated overnight and the following day the reaction was allowed to stand at rt, where the solid **215** and **215'** precipitated, and filtration provided a gummy solid (0.281 g, 0.523 mmol, quant).

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.66 (d, *J* = 6.6 Hz, 1H, ArH), 9.61 (d, *J* = 6.5 Hz, 2H, ArH), 8.25 (dd, *J* = 8.3 Hz, 1H, ArH), 8.24 (dd, *J* = 8.4 Hz, 1H, ArH), 7.72 (d, *J* = 6.7 Hz, 1H, ArH), 7.69 (d, *J* = 8.4 Hz, 1H, ArH), 6.82 (d, *J* = 8.2 Hz, 1H, ArH), 6.81 (d, *J* = 8.2 Hz, 1H, ArH), 6.98-7.08 (m, 6H, ArH), 4.42 (s, 3H, NCH_3), 4.41 (s, 3H, NCH_3), 3.83 (s, 6H, OCH_3), 3.28 (t, *J* = 7.2 Hz, 4H, CH_2), 3.17 (t, *J* = 7.3 Hz, 2H, CH_2), 3.15 (t, *J* = 7.2 Hz, 2H, CH_2), 2.82 (t, *J* = 7.0 Hz, 2H, CH_2), 2.79 (t, *J* = 7.1 Hz, 2H, CH_2), 2.70 (t, *J* = 7.3 Hz, 2H, CH_2), 2.66 (t, *J* = 7.5 Hz, 2H, CH_2), 2.16 (pent, *J* = 5.5 Hz, 2H, CH_2), and (pent, *J* = 7.4 Hz, 2H, CH_2).

2-allyl-4-bromo-1-methoxybenzene (223)



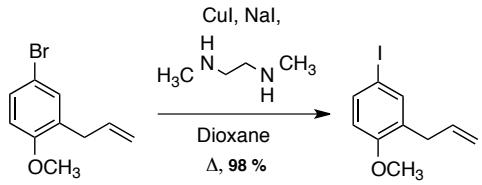
206 ***223***

In a culture tube equipped with a stir bar was added dibromoanisole **206** (5.0 g, 18.8 mmol, 1.0 equiv) dissolved in THF (47 mL) followed by *i*Pr_2MgCl (23.5 mL, 47.0 mmol, 2.5 equiv, 2.0 M). This was then heated at 40 °C for 5 hours after which the reaction was cooled to 0 °C then CuI (0.36 g, 1.88 mmol, 0.1 equiv) and allyl bromide (2.44 mL, 28.2 mmol, 1.5 equiv) was then added and stirred at room temperature for 2 hours. This was then quenched with water, extracted with Et_2O (3 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by FCC 9:1 (Hexanes:EtAcO) to yield **223** as a yellow oil (3.5 g, 15.4 mmol, 82 %)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (dd, *J* = 8.6, 2.6 Hz, 1H, Ar*H*), 7.24 (d, *J* = 2.6 Hz, 1H, Ar*H*), 6.71 (d, *J* = 8.6 Hz, 1H, Ar*H*), 5.94 (ddt, *J* = 17.3, 10.7, 6.6 Hz, 1H, C*H*=CH_2), 5.04-5.08 (m, 2H, =CH_2), 3.80 (s, 3H, OCH_3), and 3.34 (ddd, *J* = 6.7, 1.6, 1.6 Hz, 2H, CH_2).

GC/MS [EI, 70 eV, m/z (rel. int.), 50-250 °C, 25 min run]: t_r = 9.77 min; 226 (M^+), 147 (48), 132 (100), 115 (50), 103 (27), 91 (30) and 77 (28).

2-allyl-4-iodo-1-methoxybenzene (224)



223 ***224***

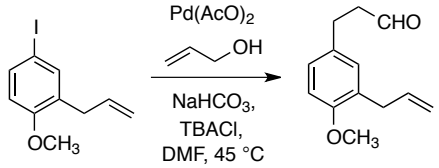
In a culture tube equipped with a stir bar was added CuI (0.021 g, 0.11 mmol, 0.05 equiv), DMEDA (24 μL, 0.22 mmol, 0.1 equiv), followed by NaI (0.66 g, 4.4 mmol, 2.0 equiv) in 10 mL of 1,4-dioxane. This was purged with argon and DMEDA (24 μL, 0.22 mmol, 0.1 equiv) added once more followed by **223** (0.5 g, 2.2 mmol, 1.0 equiv). The tube was

then capped and heated at reflux for 2 days and monitored by GC/MS. When complete, the reaction was quenched with 30 % $NH_{3\,(l)}$, poured unto H_2O and extracted with DCM (4 x 15 mL) dried over $MgSO_4$, filtered and concentrated to provide **224** as a brown solid (0.589 g, 2.15 mmol, 98 %)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (dd, *J* = 8.6, 2.6 Hz, 1H, Ar*H*), 7.24 (d, *J* = 2.7 Hz, 1H, Ar*H*), 6.72 (d, *J* = 8.7 Hz, 1H, Ar*H*), 5.94 (ddt, *J* = 15.3, 10.7, 6.6 Hz, 1H, C*H*=CH_2), 5.04-5.08 (m, 2H, =CH_2), 3.71 (s, 3H, OCH_3), and 3.34 (dt, *J* = 6.7, 1.6 Hz, 2H, CH_2).

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 8.09 min; 274 (M^+), 147 (48), 132 (100), 115 (50), 103 (27), 91 (30) and 77 (28).

3-(3-allyl-4-methoxyphenyl)propanal (**225**)



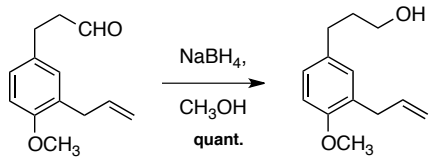
224 **10 %** ***225***

In a culture tube equipped with a stir bar was added iodoanisole **224** (0.589 g, 2.14 mmol, 1.0 equiv) dissolved in DMF (2 mL). To this was added $Pd(OAc)_2$ (0.014 g, 0.064 mmol, 0.03 equiv), $NaHCO_3$ (0.449 g, 5.35 mmol, 2.5 equiv), TBACl (0.594 g, 2.14 mmol, 1.0 eequiv) and allyl alcohol (0.364 mL, 5.4 mmol, 2.5 equiv). This was heated to 45 °C for 24 hours. Upon completion the reaction was quenched with NH_4Cl and extracted with Et_2O (3 x 5 mL) and dried with brine and $MgSO_4$, filtered, concentrated in vacuo. Purification by FCC in 9:1 (Hexanes:EtAcO) yielded compound **225** as a brown oil (0.046 g, 0.223 mmol, 10 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.81 (t, *J* = 1.6 Hz, 1H, C*H*O), 7.01 (dd, *J* = 8.2, 2.4 Hz, 1H, Ar*H*), 6.96 (d, *J* = 2.4 Hz, 1H, Ar*H*), 6.78 (d, *J* = 8.3 Hz, 1H, Ar*H*), 5.94 (ddt, *J* = 15.3, 10.7, 6.6 Hz, 1H, C*H*=CH_2), 5.05 (ddt, *J* = 15.3, 10.7, 6.6 Hz, 1H, C*H*=CH_2), 5.03-5.07 (m, 2H, =CH_2), 3.81 (s, 3H, OCH_3), 3.35 (dt, *J* = 6.6, 1.6 Hz, 2H, CH_2), 2.89 (t, *J* = 7.7 Hz, 2H, CH_2), and 2.74 (dt, *J* = 8.0, 1.7 Hz, 2H, CH_2CHO).

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 8.55 min; 204 (M^+), 161 (100), 48 (20), 115 (17), and 91 (18).

3-(3-allyl-4-methoxyphenyl)propan-1-ol (226)

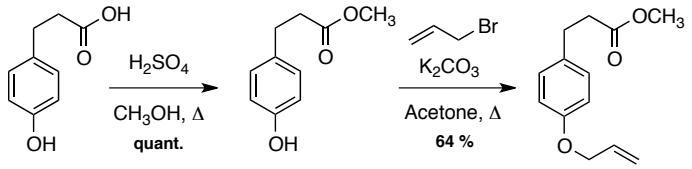


225 ***226***

In a 10 mL round bottomed flask equipped with a stir bar was added **225** (0.046, 0.223 mmol, 1.0 equiv) dissolved in MeOH (2 mL) followed by portion-wise addition of $NaBH_4$ (0.013 g, 0.336 mmol, 1.5 equiv) and stirred overnight. The following day the reaction was concentrated *in vacuo* and purified by FCC 8:2 (Hexanes:EtAcO) to provide **226** as a yellow oil (0.046, 0.223, quant.).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.01 (dd, *J* = 8.2, 2.4 Hz, 1H, Ar*H*), 6.97 (d, *J* = 2.4 Hz, 1H, Ar*H*), 6.78 (d, *J* = 8.3 Hz, 1H, Ar*H*), 5.99 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H, C*H*=CH_2), 5.02-5.07 (m, 2H, =CH_2), 3.81 (s, 3H, OCH_3), 3.67 (t, *J* = 6.4 Hz, 2H, CH_2OH), 3.36 (dt, *J* = 6.6, 1.5 Hz, 2H, CH_2), 2.63 (t, *J* = 7.4 Hz, 2H, CH_2), and 1.86 (pent, *J* = 6.5 Hz, 2H, CH_2).

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 8.89 min; 206 (M^+), 161 (100), 147 (10), 121 (11), and 91 (12).



227 ***228*** ***229***

methyl 3-(4-hydroxyphenyl)propanoate (228)

In culture tube equipped with a stir bar was added acid **227** (1.0 g, 6.0 mmol) dissolved in 15 mL of MeOH followed by 3 drops of H_2SO_4. This was refluxed for 3hrs and when complete by TLC was neutralized with $NaHCO_3$, extracted with EtAcO (3 x 10 mL), dried with brine and $MgSO_4$, filtered and concentrated *in vacuo* to provide the methyl ester as a yellow oil (1.07 g, 6.0 mmol, quant.)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (d, *J* = 8.3 Hz, 2H, ArH), 6.75 (d, *J* = 8.3 Hz, 2H, ArH), 3.67 (s, 3H, CO_2CH_3), 2.88 (t, *J* = 7.5 Hz, 2H, CH_2), and 2.60 (t, *J* = 7.9 Hz, 2H, CH_2).

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methyl 3-(4-(allyloxy)phenyl)propanoate (229)

In a culture tube equipped with a stir bar was added methyl ester **228** (1.07 g, 6.0 mmol, 1.0 equiv) dissolved in acetone (11 mL). To this was added K_2CO_3 (1.7 g, 12.3 mmol, 2.0 equiv) and allyl bromide (0.784 mL, 9.27 mmol, 1.5 equiv) and heated overnight. The following day the reaction was quenched with water and concentrated in vacuo, extracted with Et_2O (3 x 10 mL), washed with brine, dried over $MgSO_4$, filtered and concentrated by rotatory evaporation to provide the allyl ether as a yellow oil (0.849 g, 3.85 mmol, 64 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.84 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.05 (ddt, *J* = 15.3, 10.6, 5.3 Hz, 2H, C*H*=CH_2), 5.40 (ddt, *J* = 17.2, 10.5, 1.6 Hz, 1H. =CH_2), 5.28 (ddt, *J* = 10.5, 5.3, 1.4 Hz, 1H, CH_2), 4.51 (dt, *J* = 5.3, 1.5 Hz, 2H, OCH_2), 3.66 (s, 3H, CO_2CH_3), 2.89 (t, *J* = 7.6 Hz, 2H, CH_2), and 2.60 (t, *J* = 7.9 Hz, 2H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.4, 157.2, 133.5, 132.8, 129.3, 117.5, 114.8, 68.9, 51.6, 36.0, and 30.2.

IR: 2949, 1737, 1241, and 1176 cm^{-1}.

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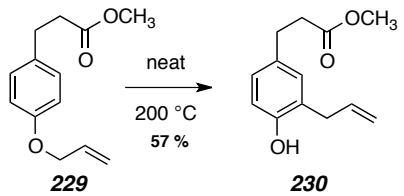
methyl 3-(3-allyl-4-hydroxyphenyl)propanoate (230)



229 ***230***

In culture tube equipped with a stir bar was added allyl ether **229** (1.34 g, 6.08 mmol) that was then heated overnight neat at 200 °C. The following day the reaction was

purified by FCC 8:2 (Hexanes:EtAcO) to provide **230** as a clear yellow oil (0.77 g, 3.5 mmol, 57 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.95 (dd, *J* = 8.0, 2.4 Hz, 1H, Ar*H*), 6.93 (d, *J* = 2.2 Hz, 1H, Ar*H*), 6.73 (d, *J* = 8.0 Hz, 1H, Ar*H*), 6.00 (dt, *J* = 16.0, 6.4 Hz, 1H, Ar*H*), 5.13-5.18 (m, 2H, =CH_2), 4.93 (s, 1H, ArO*H*), 3.67 (s, 3H, CO_2CH_3), 3.38 (dt, *J* = 6.4, 1.7 Hz, 2H, CH_2), 2.86 (t, *J* = 7.6 Hz, 2H, CH_2), and 2.59 (t, *J* = 8.2 Hz, 2H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8, 152.6, 136.5, 132.7, 130.2, 127.4, 125.6, 116.3, 115.7, 51.7, 36.1, 35.0, and 30.2.

IR: 3433, 1713, 1509, 1352, 1263, 1202 and 820 cm^{-1}.

HR ESI-MS calcd for $C_{13}H_{16}O_3$ $[M + Na]^+$ 243.0992, found 243.0998.

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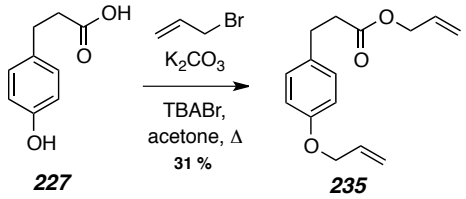
allyl 3-(4-(allyloxy)phenyl)propanoate (235)



227 ***235***

In a culture tube quipped with a stir bar was added **227** (5.0 g, 30 mmol, 1.0 equiv) dissolved in acetone (20 mL). To this was added K_2CO_3 (12.4 g, 90 mmol, 3.0 equiv) and allyl bromide (7.8 mL, 90 mmol, 3.0 equiv) and heated overnight. The following day, TBABr was added (19.34 g, 60 mmol, 2.0 equiv) and the resultant suspension heated for 24 h. Upon completion, the reaction was quenched with water and concentrated in vacuo, extracted with Et_2O (3 x 20 mL), washed with brine, dried over $MgSO_4$, filtered and concentrated by rotatory evaporation. Purification by FCC in 8:2 (Hexanes:EtAcO) yielded compound **235** as the allyl ether as a yellow oil (2.29 g, 9.31 mmol, 31 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.84 (d, *J* = 8.8, 2H, Ar*H*), 6.05 (ddt, *J* = 15.8, 10.6, 5.3 Hz, 1H, C*H*=CH_2), 5.89 (ddt, *J* = 16.2, 10.4, 5.7 Hz, 1H, C*H*=CH_2), 5.41 (ddt, *J* = 17.2, 3.2, 1.6 Hz, 1H, =CH_2), 5.28 (ddt, *J* = 15.9, 3.04, 1.5 Hz, 1H, =CH_2), 5.28 (ddt, *J* = 12.0, 3.0, 1.5 Hz, 1H, =CH_2), 5.22 (ddt, *J* = 10.5, 2.6, 1.3 Hz,

1H, =C*H*$_2$), 4.57 (dt, *J* = 5.7, 1.4 Hz, 2H, OC*H*$_2$), 4.51 (dt, *J* = 5.3, 1.5 Hz, 2H, OC*H*$_2$), 2.90 (t, *J* = 7.6 Hz, 2H, C*H*$_2$), and 2.63 (t, *J* = 7.5 Hz, 2H, C*H*$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.7, 157.3, 133.5, 132.9, 132.4, 129.4, 114.9, 118.3, 117.7, 69.0, 65.3, 36.3, and 30.3.

IR: 2927, 1734, 1511, 1241, and 1153 cm^{-1}.

HR ESI-MS calcd for $C_{15}H_{18}O_3$ $[M + Na]^+$ 269.1148, found 269.1143.

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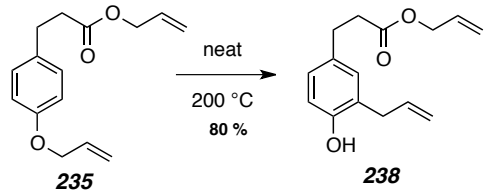
allyl 3-(3-allyl-4-hydroxyphenyl)propanoate (238)



235 ***238***

In culture tube equipped with a stir bar was added **235** (0.729 g, 2.96 mmol) that was then heated overnight at 200 °C neat. The following day the reaction was purified by FCC 9:1 (Hexanes:EtAcO) to provide **238** as a clear yellow oil (0.5816 g, 2.36 mmol, 80 %).

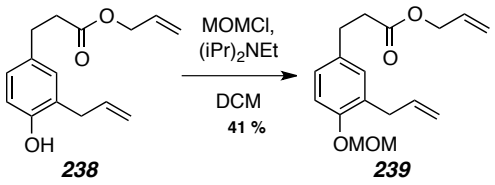
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.93 (m, 2H, Ar*H*), 6.72 (d, *J* = 8.6, 1H, Ar*H*), 5.99 (ddt, *J* = 15.9, 11.6, 6.5 Hz, 1H, C*H*=CH$_2$), 5.89 (ddt, *J* = 16.2, 10.5, 5.7 Hz, 1H, C*H*=CH$_2$), 5.57 (brs, 1H, OH), 5.28 (d, *J* = 17.2 Hz, 1H, =C*H*$_2$), 5.22 (d, *J* = 10.2, 3.04, 1.5 Hz, 1H, =C*H*$_2$), 5.10-5.14 (m, 2H), 4.57 (d, *J* = 5.7, 2H, OC*H*$_2$), 3.37 (d, *J* = 6.4, 2H, OC*H*$_2$), 2.87 (t, *J* = 7.7 Hz, 2H, C*H*$_2$), and 2.63 (t, *J* = 8.0 Hz, 2H, C*H*$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.1, 152.8, 136.7, 132.7, 132.3, 130.4, 127.6, 125.8, 118.4, 116.4, 115.9, 65.4, 36.4, 35.1, 30.3, and 30.3.

IR: 3421, 1707, 1516, 1442, 1260, 1181, and 1157 cm^{-1}.

HR ESI-MS calcd for $C_{15}H_{18}O_3$ $[M + Na]^+$ 269.1148, found 269.1154.

allyl 3-(3-allyl-4-(methoxymethoxy)phenyl)propanoate (**239**):



238 ***239***

In a round bottomed flask equipped with a stir bar was added methyl ester **238** (300 mg, 1.22 mmol, 1.0 equiv) dissolved in DCM (10 mL). This was cooled to 0 °C to this was added Huing's base (0.3 mL, 1.67 mmol, 1.37 equiv) and MOMCl (0.35 mL, 2.12 mmol, 1.74 equiv, 6.0 M) and stirred at rt for 5 hrs. When completed the reaction was poured unto water and the organic layer washed with brine (15 mL), dried over $MgSO_4$, filter and concentrated *in vacuo*. Purification by FCC in 9:1 (Hexanes:EtAcO) provided compound **239** as a clear colorless oil (0.147 g, 0.51 mmol, 41 %).

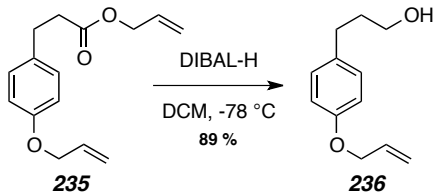
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.99 (br s, 3H, Ar*H*), 5.98 (ddt, *J* = 15.9, 11.6, 6.5 Hz, 1H, C*H*=CH_2), 5.90 (ddt, *J* = 16.2, 10.5, 5.7 Hz, 1H, C*H*=CH_2), 5.28 (d, *J* = 17.2 Hz, 1H, =CH_2), 5.22 (d, *J* = 10.2, 3.04, 1.5 Hz, 1H, =CH_2), 5.16 (brs, 2H, OCH_2O), 5.02-5.06 (m, 2H), 4.57 (d, *J* = 5.7, 2H, OCH_2), 3.47 (brs, 3H, OCH_3), 3.37 (d, *J* = 6.5, 2H, OCH_2), 2.88 (t, *J* = 7.7 Hz, 2H, CH_2), and 2.62 (t, *J* = 8.0 Hz, 2H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.8, 153.6, 137.1, 133.9, 132.4, 130.1, 129.5, 127.1, 118.4, 115.6, 114.3, 94.7, 65.3, 56.2, 36.2, 34.6, and 30.3.

IR: 2930, 1736, 1499, 1243, 1151, and 1002 cm^{-1}.

HR ESI-MS calcd for $C_{17}H_{22}O_4$ $[M + Na]^+$ 313.1410, found 313.1415.

3-(4-(allyloxy)phenyl)propan-1-ol (**236**):

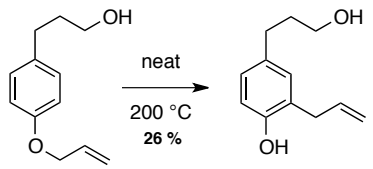


235 ***236***

To an oven dried round-bottomed flask equipped with a stir bar was added ester **235** (2.29 g, 9.33 mmol, 1.0 equiv) dissolved in DCM (120 mL) under an N_2 atmosphere. The solution was cooled to -78 °C and DIBAL-H (18.66 mL, 27.99 mmol, 3.0 equiv, 1.5 M) was added slowly the reaction warmed to rt and allowed to stir until complete by TLC. When complete quench with MeOH followed by Rochelle's salt and stirred at rt until homogenous. This was then poured unto to H_2O and extracted with Et_2O (3 x 30 mL), dried with brine and $MgSO_4$, filtered and concentrated *in vacuo.* Purification by FCC in 8:2 (Hexanes:EtAcO) yielded compound **236** as the alcohol as a yellow oil (1.59 g, 8.28 mmol, 89 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.85 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.05 (ddt, *J* = 17.4, 10.6, 5.3 Hz, 1H, C*H*=CH_2), 5.41 (ddt, *J* = 17.2, 4.0, 1.7 Hz, 1H, =CH_2), 5.28 (ddt, *J* = 10.5, 3.0, 1.5 Hz, 1H, =CH_2), 4.50 (dt, *J* = 5.3, 1.6 Hz, 2H, OCH_2), 3.66 (t, *J* = 6.4 Hz, 2H, CH_2OH), 2.65 (t, *J* = 7.4 Hz, 2H, CH_2), and 1.85 (pent, *J* = 6.5 Hz, 2H, CH_2).

2-allyl-4-(3-hydroxypropyl)phenol (**237**)



236 ***237***

In a culture tube equipped with a stir bar was added **236** (1.59 g, 8.28 mmol) that was then heated overnight at 200 °C neat. The following day the reaction was purified by FCC 8:2 (Hexanes:EtAcO) to provide **237** as a clear yellow oil (0.409 g, 2.13 mmol, 26 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.95 (dd, *J* = 8.0, 2.4 Hz, 1H, Ar*H*), 6.93 (d, *J* = 2.2 Hz, 1H, Ar*H*), 6.73 (d, *J* = 8.0 Hz, 1H, Ar*H*), 6.01 (dt, *J* = 15.6, 6.4 Hz, 1H, Ar*H*), 5.13-5.18 (m, 2H, =CH_2), 3.67 (t, *J* = 6.4 Hz, 2H, CH_2OH), 3.39 (dt, *J* = 6.3, 1.7 Hz, 2H, CH_2), 2.62 (t, *J* = 7.5 Hz, 2H, CH_2), and 1.85 (pent, *J* = 6.5 Hz, 2H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ 152.5, 136.7, 134.1, 130.5, 127.7, 125.6, 116.4, 115.9, 62.6, 35.2, 34.6, and 31.4.

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 9.109 min; 192 (M^+), 147 (100), 133 (12), 119 (13), 107 (13), and 91 (17).

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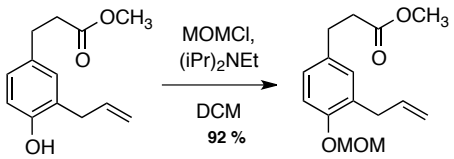
methyl 3-(3-allyl-4-(methoxymethoxy)phenyl)propanoate (231)



230 ***231***

In a round bottomed flask equipped with a stir bar was added methyl ester **230** (1.53 g, 6.96 mmol, 1.0 equiv) dissolved in DCM (30 mL). This was cooled to 0 °C to this was added Huing's base (1.67 mL, 9.53 mmol, 1.37 equiv) and MOMCl (1.38 mL, 8.62 mmol, 1.74 equiv, 6.23 M) and stirred at rt for 5 hrs. When completed the reaction was poured unto water and the organic layer washed with brine (15 mL), dried over $MgSO_4$, filter and concentrated *in vacuo*. Purification by FCC in 9:1 (Hexanes:EtAcO) provided compound **231** as a clear colorless oil (1.7 g, 6.4 mmol, 92 %).

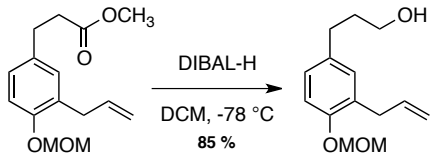
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.96 (m, 1H, Ar*H*), 6.93 (m, 1H, Ar*H*), 6.73 (d, *J* = 8.0 Hz, 1H, Ar*H*), 6.00 (ddt, *J* = 16.0, 9.8, 6.4 Hz, 1H, C*H*=CH_2), 5.17 (s, 2H, OCH_2O), 5.16 (m, 1H, =C*H*), 5.13 (m, 1H, =C*H*), 3.67 (s, 3H, OCH_3), 3.38 (d, *J* = 6.3 Hz, 2H, CH_2), 2.86 (t, *J* = 7.7 Hz, 2H, CH_2), and 2.59 (t, *J* = 8.0 Hz, 2H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.6, 153.6, 137.1, 133.9, 130.1, 129.5, 127.1, 115.6, 114.3, 94.7, 56.2, 51.8, 36.2, 34.6, and 30.3.

IR: 2955, 1737, 1500, 1437, 1244, 1198, 1152, 1076 and 1003 cm^{-1}.

HR ESI-MS calcd for $C_{15}H_{20}O_4$ $[M + Na]^+$ 287.1254, found 269.1271.

3-(3-allyl-4-(methoxymethoxy)phenyl)propan-1-ol (**232**)



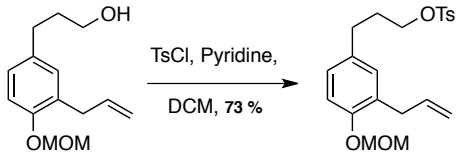
231 ***232***

To an oven dried round-bottomed flask equipped with a stir bar was added ester **231** (0.771 g, 3.4 mmol, 1.0 equiv) dissolved in DCM (20 mL) under an N_2 atmosphere. The solution was cooled to -78 °C and DIBAL-H (8.1 mL, 10.49 mmol, 3.0 eqiv, 1.3 M) was added slowly the reaction warmed to rt and allowed to stir until complete by TLC. When complete quench with MeOH followed by Rochelle's salt and stirred at rt until homogenous. This was then poured unto to H_2O and extracted with Et_2O (3 x 15 mL), dried with brine and $MgSO_4$, filtered and concentrated *in vacuo* furnished the alcohol **232** as a yellow oil (0.553 g, 2.88 mmol, 85 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.98 (br s, 3H, Ar*H*), 6.00 (ddt, *J* = 16.0, 9.8, 6.4 Hz, 1H, C*H*=CH_2), 5.17 (s, 2H, OCH_2O) 5.16 (m, 1H, =C*H*), 5.13 (m, 1H, =C*H*), 3.67 (t, *J* = 6.3 Hz, 2H, CH_2OH), 3.47 (s, 3H, OCH_3), 3.38 (dd, *J* = 6.3, 1.6 Hz, 2H, CH_2), 2.61-2.65 (m, 2H, CH_2), and 1.85 (pent, *J* = 6.7 Hz, 2H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.3, 137.2, 135.3, 130.2, 129.4, 127.2, 115.6, 114.3, 94.8, 62.5, 56.2, 36.2, 34.6, and 31.5.

3-(3-allyl-4-(methoxymethoxy)phenyl)propyl 4-methylbenzenesulfonate (233)



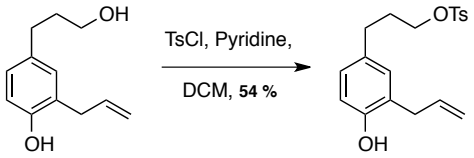
232 ***233***

To a round bottomed flask equipped with a stir bar was placed alcohol **232** (1.48 g, 5.58 mmol, 1.0 eqiuv) dissolved in DCM (50 mL). To this solution was added pyridine (0.67 mL, 8.37 mmol, 1.5 equiv) followed by TsCl (1.17 g, 6.14 mmol, 1.1 equiv) at 0 °C and stirred at ambient temperature until complete by TLC. This was then poured unto to H_2O, acidified with HCl, extracted with Et_2O, dried with brine then $MgSO_4$, filtered and concentrated *in vacuo*. Purification by FCC in 95:5 (Hexanes:EtAcO) provided compound **233** as a clear colorless oil (1.59 g, 4.07 mmol, 73 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.34 (d, *J* = 8.0 Hz, 2H, Ar*H*), 6.93 (d, *J* = 8.3 Hz, 1H, Ar*H*), 6.88 (d, *J* = 2.3 Hz, 1H, Ar*H*), 6.85 (dd, *J* = 8.2, 2.4 Hz, 1H, Ar*H*), 5.95 (ddt, *J* =16.1, 9.5, 6.6 Hz, 1H, C*H*=CH_2), 5.15 (s, 2H, OCH_2O), 5.01-5.05 (m, 2H, =CH_2), 4.02 (t, *J* = 6.2 Hz, 2H, CH_2O), 3.47 (s, 3H, OCH_3), 3.35 (dt, *J* = 6.6, 1.5 Hz, 2H, CH_2), 2.65 (t, *J* = 7.4 Hz, 2H, CH_2), 2.46 (s, 3H, CH_3), 1.93 (pent, *J* = 7.3 Hz, 2H, CH_2), and 1.26 (t, *J* = 7.1 Hz, 2H, CH_2).

GC/MS [EI, 70 eV, m/z (rel. int.), 50-250 °C, 20 min run]: t_r = 9.585 min; 254 (M^+), 209 (100), 191 (34), 159 (36), 145 (52), 131 (21), and 115 (17).

3-(3-allyl-4-hydroxyphenyl)propyl 4-methylbenzenesulfonate (254):

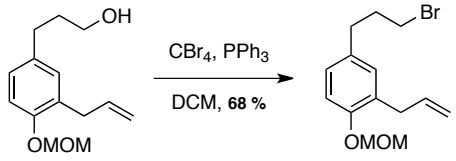


237 ***245***

To a round bottomed flask equipped with a stir bar was placed diol **237** (0.409 g, 2.13 mmol, 1.0 eqiuv) dissolved in DCM (50 mL). To this solution was added pyridine (0.256 mL, 3.2 mmol, 1.5 equiv) followed by TsCl (0.445 g, 2.34 mmol, 1.1 equiv) at 0 °C. This was stirred at ambient temperature until complete by TLC. This was then poured unto to H_2O, acidified with HCl, extracted with Et_2O, dried with brine then $MgSO_4$, filtered and concentrated in vacuo. Purification by FCC in 7:3 (Hexanes:EtAcO) provided compound **245** as a clear colorless oil (0.399 g, 1.15 mmol, 54 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.2 Hz, 2H, Ar*H*), 7.34 (d, *J* = 7.9 Hz, 2H, Ar*H*), 6.82 (d, *J* = 8.8 Hz, 1H, Ar*H*), 6.82 (dd, *J* = 8.8, 2.1 Hz, 1H, Ar*H*), 6.69 (d, *J* = 8.7 Hz, 1H, Ar*H*), 5.98 (ddt, *J* = 15.7, 10.8, 6.4 Hz, 1H, C*H*=CH_2), 5.12-5.16 (m, 2H, =CH_2), 4.83 (s, 1H, O*H*), 4.02 (t, *J* = 6.2 Hz, 2H, CH_2O), 3.35 (dt, *J* = 6.3, 1.7 Hz, 2H, CH_2), 2.56 (t, *J* = 7.8, 2H, CH_2), 2.46 (s, 3H, CH_3), 1.91 (pent, *J* = 6.3 Hz, 2H, CH_2), and 1.26 (t, *J* = 7.2 Hz, 2H, CH_2).

2-allyl-4-(3-bromopropyl)-1-(methoxymethoxy)benzene (234)



232 ***234***

To a round bottomed flask cooled to 0 °C was added the alcohol ## (80 mg, 0.34 mmol, 1.0 equiv), dissolved in DCM (1 mL) followed by CBr_4 (134 mg, 0.4 mmol, 1.2 equiv) and PPh_3 (10 mg, 0.40 mmol, 1.2 equiv). When complete by TLC, the reaction was

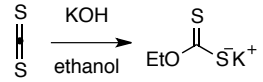
quenched with H_2O, extracted with Et_2O, washed with brine and dried over $MgSO_4$. Filtration and concentration by rotary evaporation, followed by purification via FCC (9:1, Hexanes:EtAcO).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97-6.98 (m, 3H, Ar*H*), 5.98 (ddt, *J* = 16.8, 10.8, 6.6 Hz, 1H, C*H*=CH_2), 5.16 (s, 2H, OCH_2O), 5.12-5.16 (m, 2H, =CH_2), 3.47 (s, 3H, OCH_3), 3.36-3.39 (overlapping m, 4H, CH_2C=, CH_2Br), 2.69 (t, *J* = 7.2 Hz, 2H, CH_2), and 2.12 (pent, *J* = 6.8 Hz, 2H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.5, 137.1, 133.9, 130.3, 129.4, 127.4, 115.6, 114.3, 94.7, 56.2, 34.6, 34.5 and 33.3 (2 overlapped).

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 9.247 min; 230 (M^{+2}, 73), 298 (M^+, 73), 255 (100), 253 (100), 191 (83), 159 (74), 145 (74) and 131 (34).

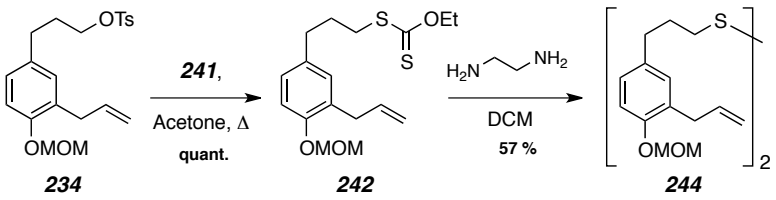
Potassium ethyl xanthate (241)



240 **87 %** ***241***

To a culture tube equipped with a magnetic stir bar was added KOH (14 g, 249 mmol, 1.6 equiv) dissolved in EtOH (50 mL) and the solution cooled to 0 °C. To this was added carbon disulfide (15 mL, 156 mmol, 1.0 equiv) and the resultant solution stirred overnight. The following day the solution was concentrated to provide **241** as a peach colored solid (23.4 g, 14.7 mmol, 94 %).

^{1}H NMR (500 MHz, DMSO-d_3): δ 4.21 (q, *J* = 7.1 Hz, 2H, CH_2), and 1.17 (t, *J* = 7.1 Hz, 3H, CH_3).



***S*-(3-(3-allyl-4-(methoxymethoxy)phenyl)propyl) *O*-ethyl carbonodithioate (242)**

To a culture tube equipped with a magnetic stir bar was added xanthate **241** (12.3 mg, 0.08 mmol, 1.5 equiv) in acetone (0.3 mL) followed by tosylate **234** (20 mg, 0.051 mmol, 1.0 equiv). The resultant solution was then refluxed for 30 mins and monitored by TLC. Upon completion, the tube was cooled to rt, the potassium salt filter and the solvent removed by rotary evaporation. The residue was then taken up in $CHCl_3$ (2 mL) washed with brine (2 mL) and dried over $MgSO_4$, filtered and concentrated in vacuo and taken on crude into the next step.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (m, 3H, Ar*H*), 5.98 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H, C*H*=CH_2), 5.17 (s, 2H, OCH_2O), 5.05 (ddt, *J* = 16.9, 1.8, 1.8 Hz, 1H, =CH_2), 5.04 (ddt, *J* = 10.2, 1.4, 1.4 Hz, 1H, =CH_2), 4.64 (q, *J* = 7.1 Hz, 2H, OC$H_2$$CH_3$), 3.47 (s, 3H, OC$H_3$), 3.38 (ddd, *J* = 6.6, 1.6, 1.6 Hz, 2H, CH_2CH=), 3.11 (t, *J* = 7.3 Hz, 2H, CH_2), 2.65 (t, *J* = 7.4 Hz, 2H, CH_2), 1.98 (pent, *J* = 7.6 Hz, 2H, CH_2), and 1.41 (t, *J* = 7.1 Hz, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 215.1, 153.4, 137.2, 134.4, 130.3, 129.4, 127.3, 115.6, 114.3, 94.7, 70.0, 56.2, 35.4, 34.6, 34.3, 30.4, and 14.0.

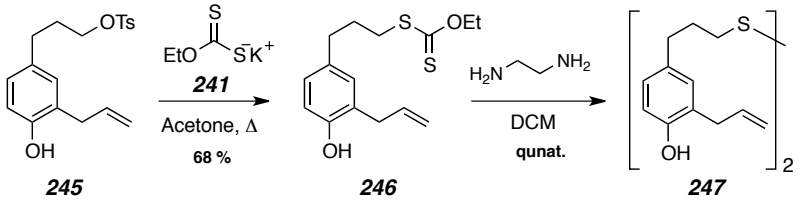
GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 12.8 min; 340 (M^+), 307 (100), 247 (15), 173 (7), and 145 (24).

DIMER (244)

Xanthogenic ester **242** was decomposed with ethylenediamine (0.05 mL, 0.748 mmol, 14.6 equiv) for 30 mins at rt. This was acidified with 0.1 M HCl, extracted with hexanes, washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (m, 3H, ArH), 5.98 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H, C*H*=CH_2), 5.17 (s, 2H, OCH_2O), 5.05 (ddt, *J* = 16.9, 1.8, 1.8 Hz, 1H, =CH_2), 5.04 (ddt, *J* = 10.2, 1.4, 1.4 Hz, 1H, =CH_2), 3.47 (s, 3H, OCH_3), 3.38 (ddd, *J* = 6.6, 1.5, 1.5 Hz, 2H, CH_2CH=), 2.67 (t, *J* = 7.2 Hz, 2H, CH_2), 2.63 (t, *J* = 7.3 Hz, 2H, CH_2), and 1.96 (pent, *J* = 7.5 Hz, 2H, CH_2).

LC-LRMS [ES /AP −/+, 50:50 to 0:100 (%) H_2O:MeOH]: t_R = 15.53 min; 520 ($M+NH_4^+$)



***S*-(3-(3-allyl-4-hydroxyphenyl)propyl) *O*-ethyl carbonodithioate (246)**

To a culture tube equipped with a magnetic stir bar was added xanthate **241** (12.3 mg, 0.08 mmol, 1.5 equiv) in acetone (0.3 mL) followed by tosylate **245** (20 mg, 0.051 mmol, 1.0 equiv). The resultant solution was then refluxed for 30 mins and monitored by TLC. Upon completion, the tube was cooled to rt, the potassium salt filter and the solvent removed by rotary evaporation. The residue was then taken up in $CHCl_3$ (2 mL) washed with brine (2 mL) and dried over $MgSO_4$, filtered and concentrated *in vacuo* and taken on crude into the next step.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (m, 3H, Ar*H*), 6.01 (ddt, *J* = 16.8, 10.2, 6.4 Hz, 1H, C*H*=CH_2), 5.17 (s, 2H, OCH_2O), 5.05 (ddt, *J* = 16.9, 1.8, 1.8 Hz, 1H, =CH_2), 5.04 (ddt, *J* = 10.2, 1.4, 1.4 Hz, 1H, =CH_2), 3.39 (ddd, *J* = 6.6, 1.6, 1.6 Hz, 2H, CH_2CH=), 3.11 (t, *J* = 7.3 Hz, 2H, CH_2), 2.65 (t, *J* = 7.4 Hz, 2H, CH_2), 1.98 (pent, *J* = 7.6 Hz, 2H, CH_2), and 1.41 (t, *J* = 7.1 Hz, 3H, CH_3).

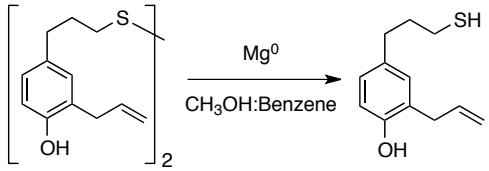
DIMER (244)

Xanthogenic ester **246** was decomposed with ethylenediamine (0.05 mL, 0.748 mmol, 14.6 equiv) for 30 mins at rt. This was acidified with 0.1 M HCl, extracted with hexanes, washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (m, 2H, ArH), 6.72 (d, *J* = 8.8 Hz, 1H, Ar*H*), 6.01 (ddt, *J* = 16.8, 10.2, 6.8 Hz, 1H, C*H*=CH_2), 5.05 (ddt, *J* = 16.9, 1.8, 1.8 Hz, 1H, =CH_2), 5.04 (ddt, *J* = 10.2, 1.4, 1.4 Hz, 1H, =CH_2), 3.38 (ddd, *J* = 6.6, 1.5, 1.5 Hz, 2H, CH_2CH=), 2.66 (t, *J* = 7.2 Hz, 2H, CH_2), 2.62 (t, *J* = 7.3 Hz, 2H, CH_2), and 1.96 (pent, *J* = 7.5 Hz, 2H, CH_2).

LC-LRMS [ES /AP −/+, 50:50 to 0:100 (%) H_2O:MeOH]: t_R = 15.84 min; 413 ($M\text{-}H^+$)

2-allyl-4-(3-mercaptopropyl)phenol (**248**)



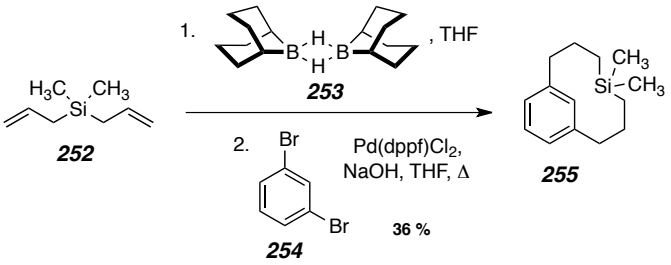
247 ***248***

In a culture tube equipped with a stir bar was added disulfide **247** (0.012 g, 0.03 mmol, 1.0 equiv) dissolved in methanol and benzene (1.0 and 0.1 mL) under nitrogen. To the culture tube was placed magnesium flings (0.0024 g, 0.1 mmol, 3.3 equiv) and under the solution fresh surface of the surface of the magnesium was exposed. The reaction was stirred at rt and monitored by TLC. When complete, the reaction was filtered and concentrated via rotary evaporation. The residue was taken up in $HCl_{(aq)}$, extracted with Et_2O (3 x 5 mL), dried over Na_2SO_4, filtered and concentrated to provide a 6:1 ratio of **247**:**248**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (m, 2H, ArH), 6.72 (d, *J* = 8.8 Hz, 1H, Ar*H*), 6.01 (ddt, *J* = 16.8, 10.2, 6.8 Hz, 1H, C*H*=CH_2), 5.05 (m, 1H, =CH_2), 5.04 (m, 1H, =CH_2),

3.38 (ddd, *J* = 6.6, 1.5, 1.5 Hz, 2H, C*H*$_2$CH=), 2.66 (t, *J* = 7.2 Hz, 2H, CH$_2$), 2.53 (q, *J* = 7.2 Hz, 2H, C*H*$_2$), and 1.89 (pent, *J* = 7.5 Hz, 2H, C*H*$_2$), and 1.35 (t, *J* = 7.9 Hz, 1H, SH).

4,4-Dimethyl-4-sila[7]metacyclophane (255)



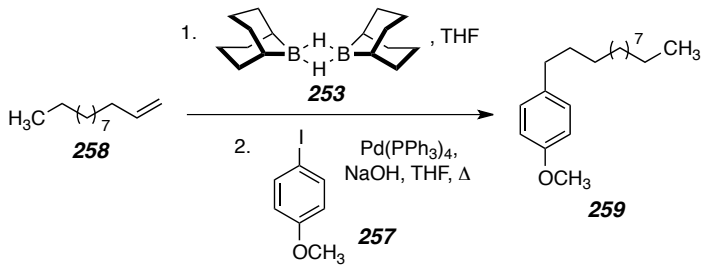
In a pear shaped flask equipped with a magnetic stir bar was added 9-BBN (0.378 g, 2.85 mmol, 4.0 equiv) under an argon atmosphere followed THF (10 mL) that was stirred for 5 mins at rt. To this was added the allyl silane **252** (0.13 mL, 0.712 mmol, 1.0 equiv) that was allowed to react for 5 h. In a culture tube equipped with a magnetic stir bar was added Pd(dppf)Cl$_2$ (17 mg, 0.021 mmol, 0.03 equiv), NaOH (57 mg, 1.42 mmol, 2.5 equiv), **254** (0.085 mL, 0.712 mmol, 1.0 equiv) in THF (30 mL), to this culture was added the dialkyl borane solution via slow syringe addition and was refluxed overnight. The following day the reaction was poured unto 12 mL of hexanes, washed with 1.0 M HCl (5 mL), sat. NaHCO$_3$ (5 mL), brine (5 mL), dried over MgSO$_4$, filtered and concentrated *in vacuo*. Purification via FCC in Hexanes afforded the desired compound **255** clear oil (0.056 g, 0.257 mmol, 36 %).

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.23 (d, *J* = 7.51 Hz, 1H, Ar*H*), 7.19 (d, *J* = 1.95 Hz, 1H, Ar*H*), 6.95 (dd, *J* = 7.47,1.85 Hz, 1H, Ar*H*), 2.64 (t, *J* = 5.97 Hz, 4H, C*H*$_2$), 1.73 (pent, J = 6.08 Hz, 4H, CH$_2$), 0.80 (nfo), and - 0.72 (s, 6H, CH$_3$).

^{13}C NMR (125 MHz, CDCl$_3$): 141.9, 129.8, 129.5, 125.7, 38.0, 26.9, 16.7, and -0.7.

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 8.2 min; 218 (M^+), 203 (100), 188 (80), 162 (31), 147 (15), and 59 (20).

1-dodecyl-4-methoxybenzene (**259**):

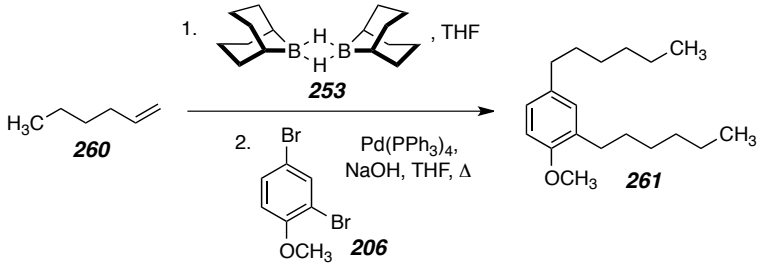


In a pear shaped flask equipped with a magnetic stir bar was added 9-BBN (0.043 g, 0.178 mmol, 1.5 equiv) under an argon atmosphere followed THF (0.5 mL) which was stirred for 5 mins at rt. To this was added the 1-dodecene **258** (26 μL, 0.119 mmol, 1.0 equiv) that was allowed to react for 5 h. In a culture tube equipped with a magnetic stir bar was added $Pd(PPh_3)_4$ (2.1 mg, 0.002 mmol, 0.015 equiv), NaOH (12 mg, 0.312 mmol, 2.6 equiv), 4-Iodoanisole (28 mg, 0.119 mmol, 1.0 equiv) in THF (5 mL), to this culture was added the dialkyl borane solution via slow syringe addition and was refluxed overnight. The following day the reaction was poured unto 12 mL of hexanes, washed with 1.0 M HCl (5 mL), sat. $NaHCO_3$ (5 mL), brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09 (d, *J* = 8.7 Hz, 2H, Ar*H*), 6.82 (d, *J* = 8.7 Hz, 2H, Ar*H*), 3.79 (s, 3H, OCH_3), 2.54 (t, *J* = 7.6 Hz, 2H, ArCH_2), 1.4-1.9 (m, 20H, CH_2), and 0.88 (t, *J* = 7.1, 3H, CH_2CH_3).

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 10.81 min; 276 (M^+), 121 (100), and 91 (9).

2,4-dihexyl-1-methoxybenzene (**261**):

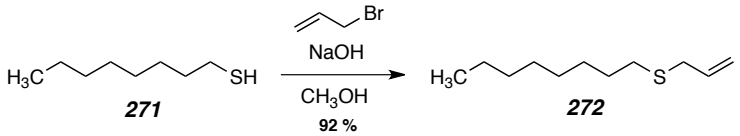


In a pear shaped flask equipped with a magnetic stir bar was added 9-BBN (0.087 g, 0.357 mmol, 3.0 equiv) under an argon atmosphere followed THF (0.5 mL) which was stirred for 5 mins at rt. To this was added the 1-dodecene **260** (30 μL, 0.238 mmol, 2.0 equiv) that was allowed to react for 5 h. In a culture tube equipped with a magnetic stir bar was added $Pd(PPh_3)_4$ (4 mg, 0.004 mmol, 0.03 equiv), NaOH (25 mg, 0.625 mmol, 5.25 equiv), **206** (32 mg, 0.119 mmol, 1.0 equiv) in THF (5 mL), to this culture was added the dialkyl borane solution via slow syringe addition and was refluxed overnight. The following day the reaction was poured unto 12 mL of hexanes, washed with 1.0 M HCl (5 mL), sat. $NaHCO_3$ (5 mL), brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*.

^{1}H NMR (500 MHz, $CDCl_3$): 6.95 (dd, *J* = 7.9, 2.2 Hz, 1H, Ar*H*), 6.93 (d, *J* = 2.1 Hz, 1H, Ar*H*), 6.74 (d, *J* = 8.o Hz, 1H, Ar*H*), 3.79 (s, 3H, OCH_3), 2.49-2.61 (m, 4H, ArCH_2), 1.4-1.9 (m, 16H, CH_2), and 0.88 (m, 6H, CH_2CH_3).

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 10.13 min; 276 (M^+), 205 (100), 105 (25), and 55 (8).

allyl(octyl)sulfide (**272**)



To a culture tube equipped with a stir bar was added NaOH (1.37 g, 34.2mmol, 1.0 equiv) dissolved in MeOH (30 mL). To this solution was added **271** (5.95 mL, 34.2 mmol,

1.0 equiv), followed by allyl bromide (3.57 mL, 41.04 mmol, 1.2 equiv) that was stirred at rt overnight. The following day was added H_2O (10 mL) and extracted with Et_2O (3 x 15 mL), washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide **272** as a clear colorless oil (5.81 g, 31.2 mmol, 92 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.79 (ddt, *J* = 17.5, 10.5, 7.2 Hz, 1H, C*H*=CH_2), 5.07-5.1 (m, 2H, =CH_2), 3.13 (dt, *J* = 7.2, 1.1 Hz, 2H, CH_2), 2.45 (t, *J* = 7.5 Hz, 2H, CH_2), 1.56 (pent, *J* = 7.0 Hz, 2H, CH_2), 1.27-1.39 (m, 10H, CH_2), and 0.88 (t, *J* = 7.1, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 134.7, 116.8, 34.9, 32.0, 30.8, 29.5, 29.4, 29.3, 29.0, 22.8, and 14.2.

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 6.7 min; 186 (M^+), 145 (100), 87 (17), 69 (52), and 55 (20).

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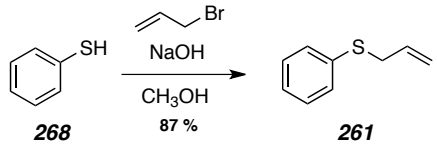
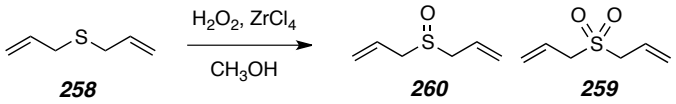
allyl(phenyl)sulfide (261)



To a culture tube equipped with a stir bar was added NaOH (1.8 g, 45.4 mmol, 1.0 equiv) dissolved in MeOH (30 mL). To this solution was added the phenylthiol (4.63 mL, 45.4 mmol, 1.0 equiv), followed by allyl bromide (4.15 mL, 54.5 mmol, 1.2 equiv) that was stirred at rt overnight. The following day was added H_2O and extracte with Et_2O, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide the allyl sulfide as a clear colorless oil (5.93 g, 39.5 mmol, 87 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16-7.36 (m, 5H, Ar*H*), 5.88 (ddt, *J* = 16.9, 10.0, 6.9 Hz, 1H, C*H*=CH_2), 5.14 (ddt, *J* = 16.9, 1.4, 1.4 Hz, 1H, =CH), 5.07 (ddt, *J* = 10.0, 1.0, 1.0 Hz, 1H, =CH), and 3.48 (dt, *J* = 6.8, 1.2 Hz, 2H, CH).

^{13}C NMR (125 MHz, $CDCl_3$): δ 136.0, 133.7, 129.9, 128.9, 126.3, 117.7, and 37.2.



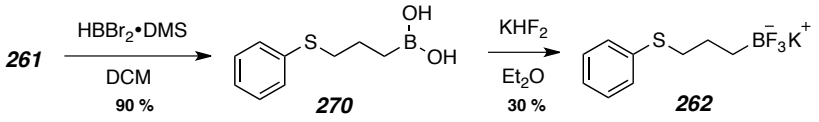
To an oven dried flask was added diallyl sulfide (0.26 mL, 2.0 mmol, 1.0 equiv) dissolved in methanol (15 mL). To this solution was added $ZrCl_4$ (1.16 g, 5.0 mmol, 2.5 equiv) followed by H_2O_2 (2 mL, 20 mmol, 10.0 equiv) which was stirred at rt unitl complete by TLC. This was then quenched with H_2O (15 mL), extracted with $CHCl_3$ (4 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification via FCC in Hexanes:EtAcO (7:3) afforded both **259** and **260**.

3-(allylsulfinyl)prop-1-ene (**260**)

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.9 (ddt, *J* = 17.4, 10.3, 7.4 Hz, 2H, C*H*=CH_2), 5.47 (dd, *J* = 10.2, 1.0 Hz, 2H, =CH), 5.4 (dd, *J* = 17.1, 1.3 Hz, 2H, =CH), 3.54 (dd, 12.9, 7.3 Hz, 2H, CH), and 3.41 (dd, 13, 7.6 Hz, 2H, CH).

3-(allylsulfonyl)prop-1-ene (**259**)

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.93 (ddt, *J* = 17.5, 10.2, 7.4 Hz, 2H, C*H*=CH_2), 5.53 (ddt, *J* = 10.2, 0.95, 0.95 Hz, 2H, =C*H*), 5.44 (ddt, *J* = 17.1, 1.1, 1.1 Hz, 2H, =C*H*), and 3.72 (dt, *J* = 7.2, 0.8 Hz, 4H, CH_2).



(3-(phenylthio)propyl)boronic acid (**270**):

To a culture tube equipped with a stir bar was placed **261** (2.0 g, 13.3 mmol, 1.0 equiv) followed by a 1.0 M $HBBr_2$•DMS in DCM (26.6 mL, 26.6 mmol, 2.0 equiv). The resultant solution was heated overnight. The following day the reaction was diluted with Et_2O (10 mL) and quenched with H_2O (10 mL). This was stirred for 30 mins and rt and extracted with Et_2O (3 x 10 mL), dried over $MgSO_4$, filtered, concentrated by rotary evaporation and recrystallized from Et_2O/ hexanes to yield **270** as an off-white solid (2.34 g, 11.9 mmol, 90%).

^{1}H NMR (500 MHz, acetone-d_6): δ 7.33 (d, J = 8.0 Hz, 2H, ArH), 7.29 (d, J = 7.5 Hz, 2H, ArH), 7.15 (t, J = 7.2 Hz, 1H, ArH), 2.95 (t, J = 7.7 Hz, 2H, CH_2), 1.75 (pent, J = 7.7 Hz, 2H, CH_2), and 0.88 (t, J = 7.8 Hz, 2H, CH_2).

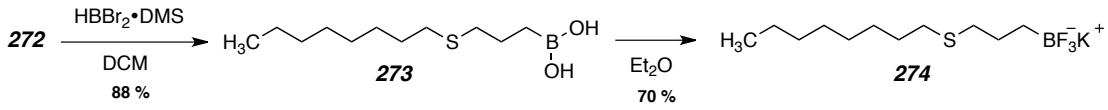
^{13}C NMR (125 MHz, acetone-d_6): δ 137.5, 128.8, 128.2, 125.3, 35.2, 26.3, and 24.4.

Potassium(3-(phenylthio)propyl)trifluoroborate (**262**):

To a culture tube equipped with a stir bar was placed boronic acid **270** (2.34 g, 11.9 mmol 1.0 equiv) dissolved in Et_2O (61.6 mL). To this was added KHF_2 (2.79 g, 35.7 mmol, 30 equiv) followed by slow addition of H_2O (2.74 mL) over the course of 1 h. This was then extracted with acetone and dried over $MgSO_4$, filtered and concentrated in vacuo. Recrystallization with hot acetone and Et_2O gave the trifluroboronate **262** as a white solid (0.93 g, 3.61 mmol, 35%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 7.29-7.23 (m, 4H, ArH), 7.13-7.10 (m, 1H, ArH), 2.83 (t, J = 7.9 Hz, 2H, CH_2), 1.49-1.42 (m, 2H, CH_2), and 0.07 (brs).

^{13}C NMR (125 MHz, acetone-d_6): δ 138.3, 129.3, 127.7, 125.3, 35.9, 26.3, and 26.3.



(3-(octylthio)propyl)boronic acid (**273**)

To a culture tube equipped with a stir bar was placed allyl sulfide **272** (2.0 g, 10.7 mmol, 1.0 equiv) followed by a 1.0 M $HBBr_2$•DMS in DCM (21.4 mL, 21.4 mmol, 2.0 equiv). The resultant solution was heated overnight. The following day the reaction was diluted with Et_2O (10 mL) and quenched with H_2O (10 mL). This was stirred for 30 mins and rt and extracted with Et_2O (3 x 10 mL), dried over $MgSO_4$, filtered, concentrated by rotary evaporation and recrystallized from Et_2O/ hexanes to yield **273** as an off-white solid (2.21 g, 9.52 mmol 88%).

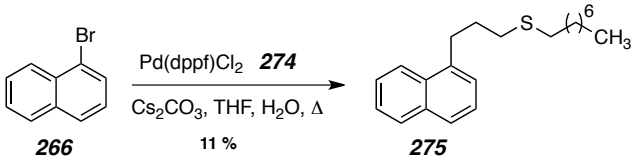
^{1}H NMR (500 MHz, $CDCl_3$): δ 2.55 (t, *J* = 7.0 Hz, 2H, C*H*$_2$S), 2.53 (t, *J* = 7.5 Hz, 2H, CH_2), 2.48 (m, 2H, CH_2), 1.76 (m, 2H, CH_2), 1.72 (m, 2H, CH_2), 1.57 (pent, *J* = 7.0 Hz, 2H, CH_2), 1.25-1.31 (m, 8H), 0.88 (t, *J* = 7.1 Hz, 3H, C*H*$_3$).

Potassium(3-(octylthio)propyl)trifluoroborate (274)

To a culture tube equipped with a stir bar was placed boronic acid **273** (2.21 g, 9.52 mmol, 1.0 equiv) dissolved in Et_2O (45.1 mL). To this was added KHF_2 (2.04 g, 26.2 mmol, 30 equiv) followed by slow addition of H_2O (2 mL) over the course of 1 h. This was then extracted with acetone and dried over $MgSO_4$, filtered and concentrated in vacuo. Recrystallization with hot acetone and Et_2O gave **274** as a white solid (2.04 g, 6.93 mmol, 70%).

^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 2.4 (t, *J* = 7.3 Hz, 2H, CH_2S), 2.34 (t, *J* = 7.8 Hz, 2H, CH_2S), 1.47 (pent, *J* = 7.5 Hz, 2H, CH_2), 1.38-1.24 (m, 12H, CH_2), 0.85 (t, *J* = 7.0 Hz, 3H, CH_3) and -0.02 (apparent sexet, *J* = 7.1, 2H, CH_2).

(3-(naphthalen-1-yl)propyl)(octyl)sulfane (275)

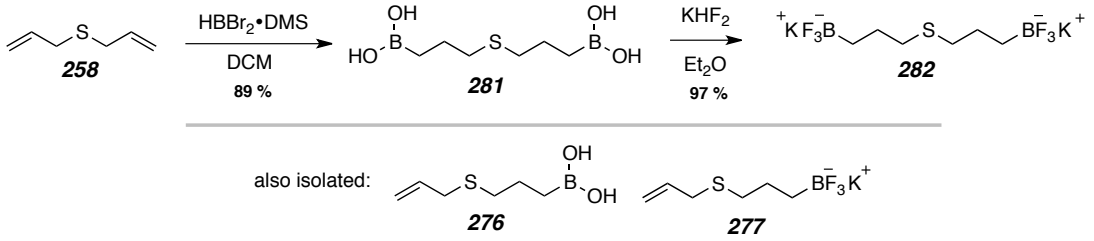


266 *275*

In a culture tube equipped with a stir bar was added **274** (0.100 g, 0.340 mmol, 1.0 equiv) along with Cs_2CO_3 (0.332 g, 1.01 mmol. 3.0 equiv), Pd(dppf)Cl_2•DCM (0.028 mg, 0.034 mmol, 0.1 equiv) and bromonaphthalene (0.077 mg, 0.473 mmol, 1.1 equiv) in degassed THF (4.1 mL) and H_2O (0.4 mL). This was then heated overnight. The following day the reaction was diluted with H_2O, the layers separated and extracted with Et_2O . The organic layers were combined, washed with $HCl_{(aq)}$ and dried over $MgSO_4$, filtered and concentrated to give **267**. (0.012 mg, 0.037 mmol, 11%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.5 Hz, 1H, ArH), 7.95 (d, *J* = 8.2 Hz, 1H, ArH), 7.72 (d, *J* = 8.7 Hz, 1H, ArH), 7.52 (dd, *J* = 6.7, 6.7 Hz, 1H, ArH), 7.48 (dd, *J* = 7.5, 7.5 Hz, 1H, ArH), 7.34 (dd, *J* = 7.4 7.4 Hz, 1H, ArH), 7.32 (d, *J* = 6.8 Hz, 1H, ArH),

3.19 (t, J = 7.8 Hz, 2H, CH_2), 2.98 (t, J = 7.4 Hz, 2H, CH_2), 1.52-1.79 (m, 16H, CH_2), and 0.99 (t, J = 7.4 Hz, 3H, CH_3)



(thiobis(propane-3,1-diyl))diboronic acid (281)

To a culture tube equipped with a stir bar was placed bisallyl sulfide **258** (0.5 g, 4.37 mmol, 1.0 equiv) followed by a 1.0 M $HBBr_2$•DMS in DCM (17.3 mL, 17.5 mmol, 4.0 equiv). The resultant solution was heated overnight. The following day the reaction was diluted with Et_2O (5 mL) and quenched with H_2O (5 mL). This was stirred for 30 mins and rt and extracted with Et_2O (3 x 5 mL), dried over $MgSO_4$, filtered, concentrated by rotary evaporation and recrystallized from Et_2O/ hexanes to yield **281** as an off-white solid (2.34 g, 11.9 mmol 89%).

^{1}H NMR (500 MHz, DMSO-d_6): δ δ 2.39 (t, J = 7.4 Hz, 2H, CH_2), 1.53 (pent, J = 7.6 Hz, 2H, CH_2), and 0.65 (t, J = 8.2 Hz, 2H, CH_2).

Potassuium(thiobis(propane-3,1-diyl))di-trifluoroborate (282)

To a culture tube equipped with a stir bar was placed boronic acid **281** (24.8 g, 0.12 mmol 1.0 equiv) dissolved in Et_2O (0.6 mL). To this was added KHF_2 (56 mg, 0.722 mmol, 6 equiv) followed by slow addition of H_2O (0.05 mL) over the course of 1 h. This was then extracted with acetone and dried over $MgSO_4$, filtered and concentrated in vacuo. Recrystallization with hot acetone and Et_2O gave the trifluroboronate **282** as a white solid (38.2 mg, 0.116 mmol, 97%).

^{1}H NMR (500 MHz, DMSO-d_6): δ 2.3 (t, J = 7.8 Hz, 2H, CH_2), 1.3 (pent, J = 8.0 Hz, 2H, CH_2), and -0.04 – 0.00 (m, 2H, CH_2).

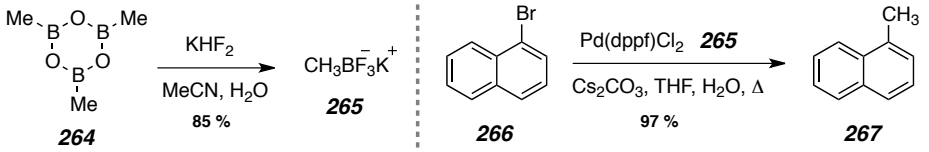
^{13}C NMR (125 MHz, DMSO-d_6): δ 35.2, 30.7, and 26.6.

(3-(allylthio)propyl)boronic acid (**276**):

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.83-5.7 (m, 1H, =CH), 5.12-5.07 (m, 2H, $=CH_2$), 3.10 – 3.14 (m, 2H, CH_2), 2.48 – 2.51 (m, 2H, CH_2), 1.68 – 1.78 (m, 2H, CH_2), and 0.94 – 1.02 (m, 2H, CH_2).

Potassium(3-(allylthio)propyl)trifluoroborate (**277**):

^{1}H NMR (500 MHz, DMSO-d_6): δ 5.7 (ddt, J = 17.0, 10.0, 7.1 Hz, 1H, =CH), 5.06 (dd, J = 17.0, 1.6 Hz, 1H, =CH), 5.02 (dd, J = 9.9 Hz, 1H, =CH), 3.06 (d, J = 9.5 Hz, 2H, CH_2), 2.31 (t, J = 7.8 Hz, 2H, CH_2), 1.31-1.37 (m, 2H, CH_2), and -0.06 – 0.0 (m, 2H, CH_2).



Potassium methyltrifluoroborate (**265**)

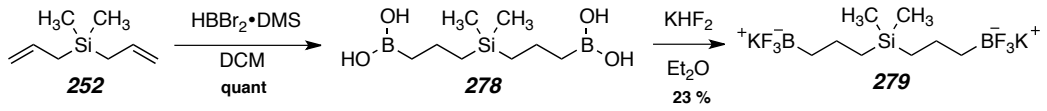
In a round bottomed flask equipped with a stir bar was added KHF_2 (9.59 g, 122.8 mmol, 6.0 equiv), dissolved in CH_3CN. To this solution was added trimethylboroxine (2.57 g, 20.5 mmol, 1.0 equiv) and the mixture cooled to 0 °C and stirred for 30 mins. H_2O (2.25 mL) was added the mixture stirred for 3 h. The resultant solid was filtered, dried under vacuum and triturated with acetone/methanol 1:1 mixture (50 mL). This was filtered, washed with acetone/methanol 1:1 mixture (50 mL) and once with acetone/methanol 1:2 mixture (50 mL) to give a white solid (2.12 g, 17.4 mmol, 85%).

^{1}H NMR (500 MHz, D_2O): δ 0.32.

1-methylnaphthalene (**267**)

In a culture tube equipped with a stir bar was added **265** (0.05 g, 0.41 mmol, 1.0 equiv) along with Cs_2CO_3 (0.4 g, 1.23 mmol. 3.0 equiv), Pd(dppf)Cl_2•DCM (33 mg, 0.041 mmol, 0.1 equiv) and bromonaphthalene (93.1 mg, 0.45 mmol, 1.1 equiv) in degassed THF (4.1 mL) and H_2O (0.4 mL). This was then heated overnight. The following day the reaction was diluted with H_2O, the layers separated and extracted with Et_2O . The organic layers were combined, washed with $HCl_{(aq)}$ and dried over $MgSO_4$, filtered and concentrated to give **267**. (60 mg, 0.39 mmol, 96%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.2 Hz, 1H, ArH), 7.45 (d, *J* = 7.8 Hz, 1H, ArH), 7.71 (d, *J* = 8.2 Hz, 1H, ArH), 7.52 (dd, *J* = 6.7, 6.7 Hz, 1H, ArH), 7.48 (dd, *J* = 7.5, 7.5 Hz, 1H, ArH), 7.34 (dd, *J* = 7.4 7.4 Hz, 1H, ArH), 7.32 (d, *J* = 6.8 Hz, 1H, ArH), and 2.70 (s, 3H, CH_3).



((dimethylsilanediyl)bis(propane-3,1-diyl))diboronic acid (**279**)

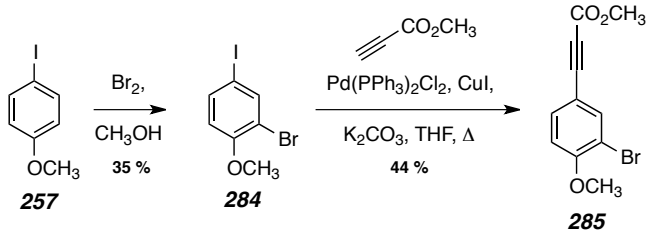
To a culture tube equipped with a stir bar was placed diallyl silane **253** (0.5 g, 3.56 mmol, 1.0 equiv) followed by a 1.0 M $HBBr_2$•DMS in DCM (14.3 mL, 14.3 mmol, 4.0 equiv). The resultant solution was heated overnight. The following day the reaction was diluted with Et_2O (5 mL) and quenched with H_2O (5 mL). This was stirred for 30 mins and rt and extracted with Et_2O (3 x 5 mL), dried over $MgSO_4$, filtered, concentrated by rotary evaporation and recrystallized from Et_2O/ hexanes to yield **280** as an off-white solid (0.821 g, 3.56 mmol, quant).

^{1}H NMR (500 MHz, DMSO-d_6): δ 1.33 (pent, *J* = 7.9 Hz, 2H, CH_2), 0.62 (t, *J* = 7.8 Hz, 2H, CH_2), 0.44 (t, *J* = 8.5 Hz, 2H, CH_2), and -0.08 (s, 6H, CH_3).

Potassium((dimethylsilanediyl)bis(propane-3,1-diyl))di-trifluoroborate (280)

To a culture tube equipped with a stir bar was placed boronic acid **279** (0.3 g, 1.29 mmol 1.0 equiv) dissolved in Et_2O (7.0 mL). To this was added KHF_2 (0.3 mg, 3.88 mmol, 3 equiv) followed by slow addition of H_2O (0.07 mL) over the course of 1 h. This was then extracted with acetone and dried over $MgSO_4$, filtered and concentrated *in vacuo*. Recrystallization with hot acetone and Et_2O gave the trifluroboronate **280** as a white solid (196.1 mg, 0.841 mmol, 23%).

^{1}H NMR (500 MHz, DMSO-d_6): δ 1.14-1.07 (m, 2H, CH_2), 0.36 (t, J = 8.2 Hz, 2H, CH_2), and 0.00 – -0.05 (m, 2H, CH_2).



2-bromo-4-iodo-1-methoxybenzene (284)

To a round bottomed flask equipped with a stir bar was added 4-Iodophenol (10.0 g, 42.7 mmol, 1.0 equiv) dissolved in MeOH (60 mL) and cooled to 0 °C under a nitrogen atmosphere. This was followed by dropwise addition of bromine (7.5g, 47.0 mmol, 1.1 equiv) and monitored by TLC until complete. Upon completion a $Na_2S_2O_3$ solution was added and the resultant mixture extracted with Et_2O (2 x 20 mL), washed with brine (20 mL), H_2O (20 mL) and dried over $MgSO_4$. This was then filtered and concentrated *in vacuo*. Purification by FCC (9:1, Hexanes:EtOAc) furnished the desired compound **284** as a white solid (4.6 g, 14.7 mmol, 35%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, J = 2.05 Hz, 1H, Ar*H*), 7.55 (dd, J = 8.60, 2.04 Hz, 1H, Ar*H*), 6.66 (d, J = 8.64 Hz, 1H), and 3.87 (s, 3H, OCH_3).

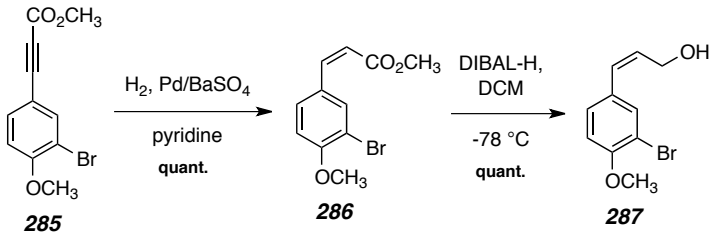
GC/MS [EI, 70 eV, m/z (rel. int.), 50-250 °C, 15 min run]: t_r = 7.53 min; 312 (M^+, 100), 297 (46), 269 (20), 172 (7), and 63 (11).

methyl 3-(3-bromo-4-methoxyphenyl)propiolate (**285**)

In a culture tube equipped with a stir bar was added284 (2.0 g, 6.39 mmol, 1.0 equiv) dissolved in THF (20 mL) under a nitrogen atmosphere. $Pd(PPh_3)_2Cl_2$ (0.09 g, 0.128 mmol, 0.02 equiv), CuI (0.049 g, 0.256 mmol, 0.04 equiv), K_2CO_3 (1.77 g, 12.78 mmol, 2.0 equiv) was then added to the culture tube and the resultant slurry refluxed overnight. The following day H_2O (10 mL) was added, the layers separated and the aqueous layer extracted with Et_2O (3 x 10 mL). The organic layers were combined, washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated by rotary evaporation. Purification by FCC (9:1, Hexanes:EtOAc) furnished the desired compound **285** as a yellow solid (0.62 g, 2.23 mmol, 44%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 2.01 Hz, 1H, Ar*H*), 7.53 (dd, *J* = 8.53, 2.03 Hz, 1H, Ar*H*), 6.88 (d, *J* = 8.58 Hz, 1H, Ar*H*), 3.93 (s, 3H, CO_2CH_3), and 3.83 (s, 3H, OCH_3).

GC/MS [EI, 70 eV, m/z (rel. int.), 50-250 °C, 15 min run]: t_r = 9.36 min; 268 (M^+), 239 (92), 212 (100), 197 (10), 166 (10), and 87 (17).



(*Z*)-methyl 3-(3-bromo-4-methoxyphenyl)acrylate (**286**)

In small vial equipped with a stir bar and fitted septum was added **285** (0.112 g, 0.416 mmol, 1.0 equiv) dissolved in pyridine (5 mL), followed by $Pd/BaSO_4$ (0.082 g, 0.041 mmol, 0.1 equiv). A balloon filled with hydrogen was the allowed to bubble through the reaction mixture for 20 minutes after which the palladium catalyst was removed via filtration through a bed of celite. Concentration by way of rotary evaporation provide the desired compound **287** as a yellow oil (0.113 g, 0.416 mmol, quant.).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, *J* = 2.16 Hz, 1H. Ar*H*), 7.69 (dd, *J* = 8.62, 2.19 Hz, 1H, Ar*H*), 6.88 (d, J = 8.60 Hz, 1H, ArH), 6.80 (d, *J* = 12.70 Hz, 1H, =C*H*), 5.88 (d, *J* = 12.70 Hz, 1H, =C*H*), 3.93 (s, 3H, CO_2CH_3), and 3.74 (s, 3H, OCH_3).

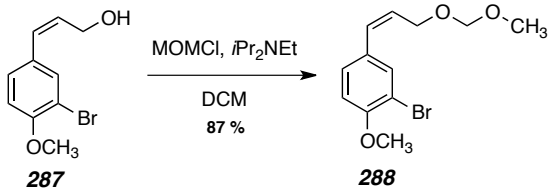
GC/MS [EI, 70 eV, m/z (rel. int.), 50-250 °C, 15 min run]: t_r = 9.36 min; 270 (M^+), 212 (48), 199 (100), 134 (10), and 77 (12).

(*Z*)-3-(3-bromo-4-methoxyphenyl)prop-2-en-1-ol (**287**)

To an oven dried round-bottomed flask equipped with a stir bar was added ester **286** (0.113 g, 0.416 mmol, 1.0 equiv) dissolved in DCM (5 mL) under an N_2 atmosphere. The solution was cooled to -78 °C and DIBAL-H (0.93 mL, 1.4 mmol, 3.0 eqiv, 1.5 M) was added slowly the reaction warmed to rt and allowed to stir until complete by TLC. When complete quench with MeOH followed by Rochelle's salt and stirred at rt until homogenous. This was then poured unto to H_2O and extracted with Et_2O (3 x 10 mL), dried with brine and $MgSO_4$, filtered and concentrated *in vacuo* furnished the alcohol **287** as a yellow oil (0.101 g, 0.416 mmol, quant.).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, *J* = 2.14 Hz, 1H. Ar*H*), 7.14 (dd, *J* = 8.56, 2.33 Hz, 1H, Ar*H*), 6.87 (d, *J* = 8.46 Hz, 1H, Ar*H*), 6.45 (dt, *J* = 11.68, 1.79 Hz, 1H, =C*H*), 5.83 (dt, *J* = 11.64, 6.46 Hz, 1H, =C*H*), 4.42 (dd, J = 6.47, 1.74 Hz, 2H, CH_2OH), and 3.91 (s, 3H, OCH_3).

(*Z*)-2-bromo-1-methoxy-4-(3-(methoxymethoxy)prop-1-en-1-yl)benzene (**288**)

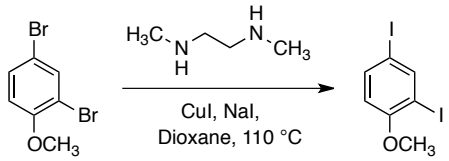


287 ***288***

In a round bottomed flask equipped with a magnetic stir bar was added the alcohol **287** (0.114 g, 0.469 mmol, 1.0 equiv) dissolved in DCM (2 mL) and cooled to 0 °C. To this was added *i*Pr_2Nt (0.081 g, 0.628 mmol, 1.34 equiv) followed by MOMCl (0.1 mL, 0.581 mmol, 1.24 equiv, 6.23 M) and stirred overnight at ambient temperature. The following

day the reaction was quenched with H_2O (5 mL), washed with brine and dried over $MgSO_4$ to give the MOM-protected alcohol **288** (0.117 g, 0.407 mmol, 87 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 2.24 Hz, 1H, Ar*H*), 7.15 (dd, *J* = 8.45, 2.25 Hz, 1H, Ar*H*), 6.87 (d, *J* = 8.47 Hz, 1H, Ar*H*), 6.49 (dt, *J* = 11.74, 1.76 Hz, 1H, =C*H*), 5.81 (dt, *J* = 11.73, 6.48 Hz, 1H, =C*H*), 4.69 (s, 2H, OCH_2O), 4.31(dd, J = 6.48, 1.77 Hz, 2H, =CHCH_2O) 3.91 (s, 3H, ArOCH_3), and 3.40 (s, 3H, OCH_3).



206 ***249***

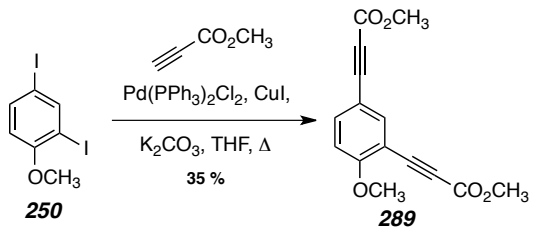
2,4-diiodo-1-methoxybenzene (**249**)

In a culture tube equipped with a stir bar was added CuI (0.036 g, 0.188 mmol, 0.05 equiv), DMEDA (0.033 g, 0.376 mmol, 0.1 equiv), followed by NaI (1.13 g, 7.52 mmol, 2.0 equiv) in 10 mL of 1,4-dioxane. This was purged with argon and DMEDA (0.033 g, 0.376 mmol, 0.1 equiv) added once more followed by dibromoanisole (1.0 g, 3.76 mmol, 1.0 equiv). The tube was then capped and heated at reflux for 2days and monitored by GC/MS. When complete, the reaction was quenched with 30 % $NH_{3\,(l)}$, poured unto H_2O and extracted with DCM (4 x 15 mL) dried over $MgSO_4$, filtered and concentrated to provide **249** as a brown solid (1.14 g, 3.15 mmol, 84 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, *J* = 2.11 Hz, 1H, Ar*H*), 7.58 (dd, *J* = 8.61, 2.10 Hz, 1H, Ar*H*), 6.58 (d, *J* = 8.63 Hz, 1H, Ar*H*), and 3.86 (s, 3H, OCH_3).

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 8.25 min; 360 (M^+, 100), 345 (41), 317 (10), 218 (18), and 63 (10).

dimethyl 3,3'-(4-methoxy-1,3-phenylene)dipropiolate (**289**)

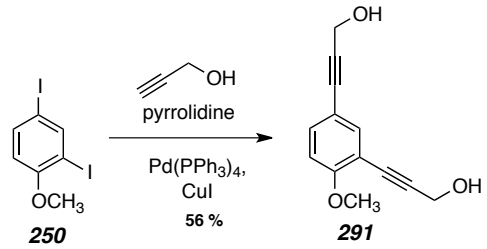


In a culture tube equipped with a stir bar was added **250** (0.214 g, 0.59 mmol, 1.0 equiv) dissolved in THF (7.0 mL) under a nitrogen atmosphere. $Pd(PPh_3)_2Cl_2$ (0.021 g, 0.0295 mmol, 0.05 equiv), CuI (0.009 g, 0.047 mmol, 0.08 equiv), K_2CO_3 (0.329 g, 2.38 mmol, 4.0 equiv), methyl propiolate (0.2 g, 2.38 mmol, 4.0 equiv) was then added to the culture tube and the resultant slurry refluxed overnight. The following day H_2O (10 mL) was added, the layers separated and the aqueous layer extracted with Et_2O (3 x 10 mL). The organic layers were combined, washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated by rotary evaporation. Purification by FCC (9:1, Hexanes:EtOAc) furnished the desired compound **289** as a yellow solid (0.056 g, 0.041 mmol, 35%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 2.1 Hz, 1H, Ar*H*), 7.64 (dd, *J* = 8.7, 2.1 Hz, 1H, Ar*H*), 6.91 (d, *J* = 8.8 Hz, 1H, Ar*H*), 3.94 (s, 3H, CO_2CH_3), 3.84 (s, 3H, OCH_3), and 3.84 (s, 3H, CO_2CH_3).

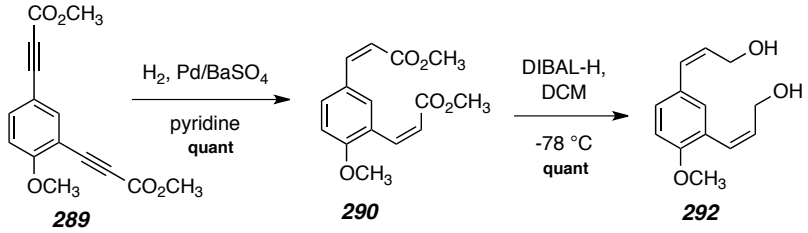
GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 11.2 min; 272 (M^+, 100), 241 (88), 214 (35), 155 (22), and 126 (11).

3,3'-(4-methoxy-1,3-phenylene)bis(prop-2-yn-1-ol) (**291**):



In a culture tube equipped with a stir bar was added **250** (0.30 g, 0.694 mmol, 1.0 equiv) dissolved in pyrrolidine (0.45 mL) under a nitrogen atmosphere. $Pd(PPh_3)_4$ (0.096 g, 0.0694 mmol, 0.01 equiv), CuI (0.031g, 0.139 mmol, 0.2 equiv), propargyl alcohol (0.187 g, 2.78 mmol, 4.0 equiv) was then added to the culture tube and the resultant slurry refluxed overnight. The following day H_2O (10 mL) was added, the layers separated and the aqueous layer extracted with Et_2O (3 x 10 mL). The organic layers were combined, washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated by rotary evaporation. Purification by FCC (8:2, Hexanes:EtOAc) furnished the desired compound **291** as a dark red oil (0.084 g, 0.388 mmol, 56%)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, *J* = 2.2 Hz, 1H, Ar*H*), 7.37 (dd, *J* = 8.6, 2.2 Hz, 1H, Ar*H*), 6.81 (d, *J* = 8.6 Hz, 1H, Ar*H*), 4.52 (s, 3H, C*H*$_2$OH), 4.47 (s, 3H, C*H*$_2$OH), and 3.89 (s, 3H, OC*H*$_3$).



(2*Z*,2'*Z*)-dimethyl 3,3'-(4-methoxy-1,3-phenylene)diacrylate (**290**)

In small vial equipped with a stir bar and fitted septum was added **289** (0.0056 g, 0.02 mmol, 1.0 equiv) dissolved in pyridine (0.3 mL), followed by $Pd/BaSO_4$ (0.004 g, 0.002 mmol, 0.1 equiv). A balloon filled with hydrogen was the allowed to bubble through the reaction mixture for 20 minutes after which the palladium catalyst was removed via

filtration through a bed of celite. Concentration by way of rotary evaporation provide the desired compound **290** as a yellow oil (0.006 g, 0.02 mmol, quant.).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (dd, *J* = 8.67, 2.38 Hz, 1H, Ar*H*), 7.82 (d, *J* = 2.40 Hz, 1H, Ar*H*), 7.12 (d, *J* = 12.44 Hz, 1H, =C*H*), 6.87 (d, *J* = 8.68 Hz, 1H, Ar*H*), 6.86 (d, *J* = 12.75 Hz, 1H, =C*H*), 6.00 (d, *J* = 12.44 Hz, 1H, =CH), 5.85 (d, *J* = 12.75 Hz, 1H, =C*H*), 3.86 (s, 3H, OCH_3), 3.72 (s, 3H, CO_2CH_3), and 3.67 (s, 3H, CO_2CH_3).

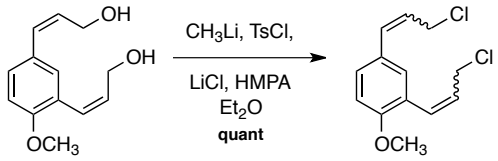
GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 10.2 min; 276 (M^+), 245 (100), 213 (24), 185 (22), and 115 (13).

(2*Z*,2'*Z*)-3,3'-(4-methoxy-1,3-phenylene)bis(prop-2-en-1-ol) (292)

To an oven dried round-bottomed flask equipped with a stir bar was added ester **290** (0.006 g, 0.02 mmol, 1.0 equiv) dissolved in DCM (0.3 mL) under an N_2 atmosphere. The solution was cooled to -78 °C and DIBAL-H (0.128 mL, 1.28 mmol, 6.0 eqiv, 1.0 M) was added slowly the reaction warmed to rt and allowed to stir until complete by TLC. When complete quench with MeOH followed by Rochelle's salt and stirred at rt until homogenous. This was then poured unto to H_2O and extracted with Et_2O (3 x 5 mL), dried with brine and $MgSO_4$, filtered and concentrated *in vacuo* furnished the alcohol **292** as a yellow oil (0.003 g, 0.0015 mmol, 75 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (d, *J* = 2.3 Hz, 1H, Ar*H*), 7.13 (dd, *J* = 8.4, 2.3 Hz, 1H. Ar*H*), 6.86 (d, *J* = 8.4 Hz, 1H, Ar*H*), 6.71 (d, *J* = 11.5 Hz, 1H, =CH), 6.54 (d, *J* = 11.6 Hz, 1H, =CH), 5.97 (dt, *J* = 11.6, 7.1 Hz, 1H, =C*H*), 5.83 (dt, *J* = 11.6, 6.9 Hz, 1H, =C*H*), 4.41 (dd, *J* = 6.9, 1.5 Hz, 2H, CH_2OH), 4.32 (dd, *J* = 7.1, 1.4 Hz, 2H, CH_2OH), and 3.85 (s, 3H, OCH_3).

2,4-bis(3-chloroprop-1-en-1-yl)-1-methoxybenzene (294)

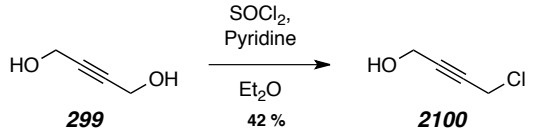


292 ***294***

In a culture tube equipped with a stir bar was added the diol **292** (0.050 g, 0.227 mmol, 1.0 equiv) dissolved in diethyl ether (0.1 mL) and HMPA (0.08 mL) at 0 °C followed by CH_3Li (0.28 mL, 0.454 mmol, 2.0 equiv). In another flask was added TsCl (0.091 g, 0.477 mmol, 2.1 equiv) dissolved in Et_2O (0.1 mL) this solution was then added to the first flask followed by LiCl (0.019 g, 0.454, 2.0 equiv). The culture tube was capped and stirred overnight. The following day the solution was diluted with ether and water, the layers separated, and the organic phase washed with water, brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*. FCC in 6:4 (Hexanes:EtAcO) provided a mixture of dichlorides (shown below is the characterization data for the Z,Z-dialkene) in a quantitive yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.4, 2.3 Hz, 1H, Ar*H*), 7.15 (dd, *J* = 2.2 Hz, 1H. Ar*H*), 6.90 (d, *J* = 8.4 Hz, 1H, Ar*H*), 6.72 (d, *J* = 11.5 Hz, 1H, =CH), 6.5 (d, *J* = 11.6 Hz, 1H, =CH), 5.94 (dt, *J* = 11.6, 7.1 Hz, 1H, =C*H*), 5.84 (dt, *J* = 11.6, 6.9 Hz, 1H, =C*H*), 4.30 (dd, *J* = 8.4, 1.0 Hz, 2H, CH_2Cl), 4.22 (dd, *J* = 7.9, 1.0 Hz, 2H, CH_2Cl), and 3.86 (s, 3H, OCH_3).

4-Chloro-but-2-yn-1ol (2100)

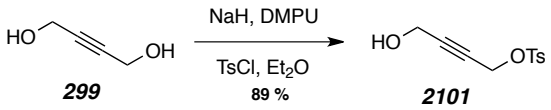


To a stirred solution of 1,4-but-2-yndiol (10.0 g, 116.2 mmol, 1.0 equiv) in Et_2O (11.4 mL) was added at pyridine (10.34 mL, 127.8 mmol, 1.1 equiv). This was then cooled in an ice-salt bath followed by drop wise addition of thionyl chloride (9.33 mL, 127.8 mmol, 1.1 equiv) and stirred overnight at rt. The following day the reaction was added to cold water and the layers separated. The aqueous layer was then extracted with Et_2O (4 x 20 mL), the organic layers were combined and washed with $NaHCO_3$ (sat.), D.I. H_2O and brine. The solution was dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by FCC (1:1, Hexanes:Et_2O) to provide the chlorobutynol as a pale yellow oil (5.12 g, 49.0 mmol, 42 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.33 (dt, *J* = 6.2, 2.1 Hz, 2H, C*H*$_2$OH), 4.20 (t, *J* = 2.1, 2H, C*H*$_2$Cl), and 2.40 (t, *J* = 6.1, 1H, O*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ 84.84, 80.63, 51.11, and 30.57.

4-hydroxybut-2-yn-1-yl 4-methylbenzenesulfonate (2101)



In a round bottomed flask equipped with a magnetic stir bar was added NaH (2.32 g, 58.08 mmol, 1.0 equiv, 60 % dispersion) followed by THF (93 mL) and a solution of 1,4-but-2-yndiol (5.0 g, 58.1 mmol, 1.0 equiv) in DMPU (23.3 mL). In another flask the TsCl (11.07 g, 58.08 mmol, 1.0 equiv) was dissolved in THF (93 mL) and then added slowly to the round bottomed flask containing the butyndiol. This was stirred for 5 h at rt and then filtered through a plug of silica and eluted with Et_2O. The ethereal solution was washed with H_2O, dried over $MgSO_4$, filtered and the solvent removed by rotary

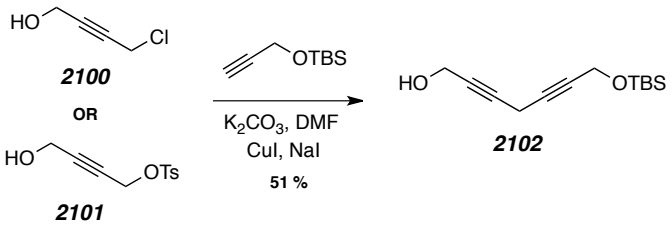
evaporation. Purification by FCC (3:2, Hexanes:EtOAc) afforded the tosylate as a pale yellow oil (12.4 g, 51.7 mmol, 89 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.4 Hz, 2H, =C*H*), 7.37 (d, *J* = 8.5 Hz, 2H, =C*H*), 4.73 (t, *J* = 1.8 Hz, 2H, CH_2), 4.17 (t, *J* = 1.8, Hz, 2H, CH_2), and 2.46 (s, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 145.5, 133.0, 130.0, 128.3, 87.9, 77.5, 58.1, 50.9, and 21.8.

HR ESI-MS calcd for $C_{11}H_{12}O_4S$ $[M + Na]^+$ 263.0349, found 262.0353

7-((*tert*-butyldimethylsilyl)oxy)hepta-2,5-diyn-1-ol (2102)



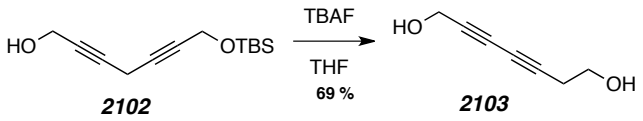
To a round bottomed flask equipped with a magnetic stir was added CuI (1.55 g, 8.12 mmol, 1.0 equiv), NaI (2.43 g, 16.25 mmol, 2.0 equiv), K_2CO_3 (2.25 g, 16.25 mmol, 2.0 equiv) and DMF (19.4 mL). To this suspension was added the TBS protected propargyl alcohol (2.77 g, 16.25 mmol, 2.0 equiv) followed by the chlorobutynol **2100** (0.85 g, 8.12 mmol, 1.0 equiv). This was stirred overnight at ambient temperature and the following day quenched with NH_4Cl (10 mL), extracted with DCM (3 x 15 mL), organic layers combined and washed with D.I. H_2O, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by FCC (8:2, Hexanes:EtAO) provided **2102** as an orange oil (0.984 g, 4.13 mmol, 51 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.31 (t, *J* = 2.2 Hz, 2H, CH_2), 4.26 (t, *J* = 2.2 Hz, 2H, CH_2), 3.24 (pent, *J* = 2.2 Hz, 2H, CH_2), 0.91 (s, 9H, CH_3), and 0.12 (s, 6H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 80.05, 79.51, 78.98, 78.67, 52.04, 51.43, 26.06, 18.55, 10.19, and -4.93.

HR ESI-MS calcd for $C_{13}H_{22}O_2Si$ $[M + Na]^+$ 261.1281, found 261.1288.

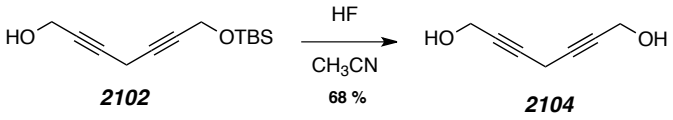
Hepta-2,4-diyne-1,7-diol (2103)



To a round bottomed flask equipped with a magnetic stir was added the TBS-protected hepta-2,5-diyn-1-ol **2102** (0.108 g, 0.453 mmol, 1.0 equiv) dissolved in THF (5 mL) followed by the dropwise addition of a 1 M TBAF solution (0.493 mL, 0.493 mmol, 1.1 equiv). This was stirred overnight at ambient temperature and the following day quenched with H_2O (3 mL), extracted with EtAcO (3 x 5 mL), organic layers combined and washed with D.I. H_2O, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide **2103** as an orange oil (0.035 g, 0.282 mmol, 69 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.33 (dt, *J* = 6.3, 1.1 Hz, 2H, CC*H*$_2$OH), 3.77 (dt, *J* = 6.2, 6.2 Hz, 2H, CH_2C*H*$_2$OH), 2.57 (tt, *J* = 1.1, 6.3 Hz, 2H, CC*H*$_2$$CH_2$), 1.80 (t, *J* = 6.3 Hz, 1H, O*H*), and 1.71 (t, *J* = 6.3 Hz, 1H, O*H*).

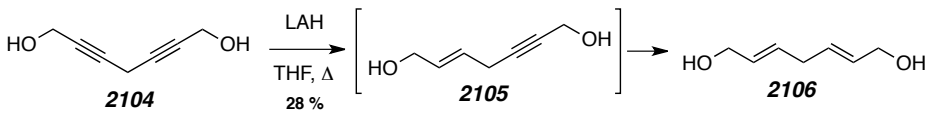
Hepta-2,5-diyne-1,7-diol (2104)



To a plastic culture tube equipped with a stir bar place the TBS-protected hepta-2,5-diyn-1-ol **2102** (0.341 g, 1.43 mmol, 1.0 equiv) dissolved in CH_3CN (3.4 mL) cooled to 0 °C followed by dropwise addition of a 48 % HF solution in water (0.68 mL) dissolved in 3.4 mL of CH_3CN. This was stirred at 0 °C for 2 h and monitored by TLC. When completed it was quenched with aqueous $NaHCO_3$ (added until reaction was neutral), extracted with EtAcO (3 x 4 mL), washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to provide **2104** as an orange solid (0.121 g, 0.975 mmol, 68 %).

^{1}H NMR (500 MHz, acetone-d_6): δ 4.15 (t, *J* = 2.2 *Hz*, 4H, C*H*$_2$OH), and 3.25 (pent, *J* = 2.2 Hz, 2H, CH_2).

^{13}C NMR (125 MHz, acetone-d_6): δ 80.6, 79.1, 50.6, and 9.8.



(2*E*, 5*E*)-hepta-2,5-diene-1,7-diol (2106)

To a culture tube equipped with a magnetic stir bar was added $LiAlH_4$ (0.158g, 4.17 mmol, 3.0 equiv) suspended in THF (0.4 mL) followed by dropwise additon of the diol **2104** (0.172 g, 1.39 mmol, 1.0 equiv) dissolved in THF (0.4 mL). This was refluxed overnight and the following day was quenched with a 1 M HCl solution, extracted with EtAcO (3 x 2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification in EtAcO provided **2106** as a pale yellow oil (0.050 g, 0.389 mmol, 28 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.72 (dt, *J* = 15.5, 5.6 Hz, 2H, =C*H*), 5.67 (dt, *J* = 15.5, 4.9 Hz, 2H, =C*H*), 4.12 (t, *J* = 4.8, 4H, CH_2OH), and 2.81 (t, *J* = 5.1, 2H, CH_2).

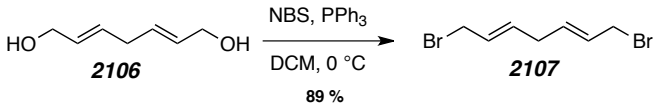
^{13}C NMR (125 MHz, $CDCl_3$): δ 130.6, 130.4, 63.8, and 35.0.

(2*E*)-hepta-2-ene-5-yn-1,7-diol (2105)

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.92 (dtt, *J* = 15.3, 5.7, 1.8 Hz, 1H, =C*H*), 5.70 (dtt, *J* = 15.3, 5.5, 1.6 Hz, 1H, =C*H*), 4.29 (dt, *J* = 5.7, 2.2 Hz, 2H, CH_2OH), 4.15 (t, *J* = 4.5 Hz, 2H, CH_2OH), and 3.01 (ddt, *J* = 5.5, 3.7, 1.9, 2H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ 131.1, 126.2, 83.2, 80.8, 63.3, 51.5, and 21.9.

(2*E*,5*E*)-1,7-dibromohepta-2,5-diene (2107)



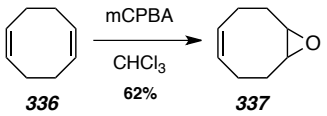
2106 **89 %** ***2107***

In a small vial equipped with a stir bar was added the diol **2106** (0.005 g, 0.039 mmol, 1.0 equiv) dissolved in DCM (0.3 mL) cooled to 0 °C. To this flask was added NBS (0.015 g, 0.086 mmol, 2.2 equiv) followed by PPh_3 (0.023 g, 0.086 mmol, 2.2 equiv). This was stirred at rt until complete by TLC, it was washed with H_2O, and dried over $MgSO_4$. Purification by FCC (pentanes) provided the desired dibromide as a clear oil (0.009 g, 0.035 mmol, 89 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.78 (dt, J = 15.2, 5.7 Hz, 1H, =C*H*), 5.72 (dt, *J* = 15.3, 6.4, 1.6 Hz, 1H, =C*H*), 3.95 (d, *J* = 6.4 Hz, 2H, CH_2Br), and 2.85 (t, *J* = 5.2 Hz, 2H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ 133.07, 128.16, 34.54, and 33.01.

(*Z*)-9-Oxabicyclo[6.1.0]non-4-ene (337)

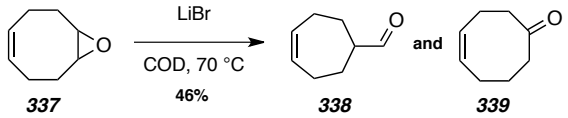


To a slurry of *m*-CPBA (9.0 g, 50 mmol, 1.0 equiv) in chloroform (40 mL) at 0 °C, cycloocta-1,5-diene (COD, **336**, 6.6 mL, 50 mmol, 1.0 equiv) in chloroform (20 mL) was added rapidly with stirring. The mixture was stirred at ambient temperature for 30 h, after which 10% $NaOH_{(aq)}$ (20 mL) was added. The organic layer was washed 3 x 100 mL H_2O (or until the washing was neutral). The resultant solution was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by FCC (4:1, Hexanes: EtAcO) provided **337** as a colorless oil (3.9 g, 31 mmol, 63 %). In other cases, the crude mixture following concentration, which contained an ca. 0.25:1.0:0.075 ratio of COD (**336**):mono-epoxide **337**:diepoxide, as judged by analysis of the ^{1}H NMR spectrum, was only partially fractionated by FCC in a fashion such that the resulting epoxide contained unreacted COD.

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.57 (br t, *J* = 4 Hz, 2H, =CH), 3.06-3.03 (nfom, 2H, CH), 2.42-2.47 (nfom, 2H, CH), 2.12-2.17 (nfom, CH_2, 2H), 2.07-2.04 (nfom, CH_2, 2H), and 2.03-2.00 (m, CH_2, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 128.8, 56.7, 28.1, and 23.7.

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 4.27 min; 123 (M^+-H), 108 (10), 80 (75), 67 (100), and 54 (98).



Lithium bromide (anhydrous, 2.3 g, 27 mmol, 1.0 equiv) was added to 9-oxabicyclo[6.1.0]non-4-ene (3.4 g, 28 mmol, 1.0 equiv), still containing some COD from the previous step. The solution was refluxed at 170 °C for 3 days, at which point, two

more equivalents of lithium bromide were added. The resulting viscous solution was stirred for 4 more days until GC/MS analysis indicate full consumption of epoxide **337** (6.67 min t_R). The COD was removed with a hexanes flush via flash chromatography. Elution with 3:1 pentane:ether removed the rest of the organic material from the column, which was concentrated under reduced pressure. This partially purified material was further fractionated by MPLC (4:1 pentane:Et_2O) to give, in order of elution, cyclohept-4-enecarbaldehyde (**338**, 2.2 g, 17 mmol, 63 % yield) along with the cyclooctenone **339**.

Cyclohept-4-enecarbaldehyde (**338**)

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.68 (br s, C*H*O, 1H), 5.79 (br s, *H*C=C*H*, 2H), 2.46 (br s, 1H, C*H*CHO), 2.31-2.28 (nfom, CH_2, 2H), 2.12 (m, CH_2, 2H), 2.05-2.04 (nfom, CH_2, 2H), and 1.53 (m, CH_2, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 204.4, 131.7, 54.3, 26.6, and 26.3.

IR: 3019, 2939, 2844, 2710, 1726, 1685, 1444, 911, and 731 cm^{-1}.

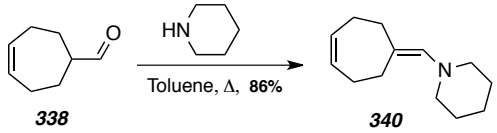
GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 7.05 min; 124 (M^+), 99 (47), 96 (100), 67 (90), and 52 (47).

(*Z*)-Cyclooct-4-enone (**339**)

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.66 (m, 2H), 2.43 (m, 6H), 2.13 (m, 2H), and 1.56 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 215.0, 130.9, 130.4, 47.4, 40.5, 26.5, 24.1, and 22.0.

1-(Cyclohept-4-en-1-ylidenemethyl)piperidine (340)



338 *340*

Cyclohept-4-enecarbaldehyde (**338**, 1.5 g, 12 mmol) was dissolved in toluene (17 mL). Piperidine (1.3 mL, 13 mmol) was added and the solution was heated in a 110 °C bath in a teflon-capped glass tube for six hours. Analysis by GC/MS revealed the reaction to be complete by disappearance of the starting aldehyde **338** (7.05 min t_R). The solution was distilled in a Kugelrohr apparatus to give 1-(cyclohept-4- enylidenemethyl)piperidine (**340**, 2.1 g, 11 mmol, 92 % yield) as a clear oil.

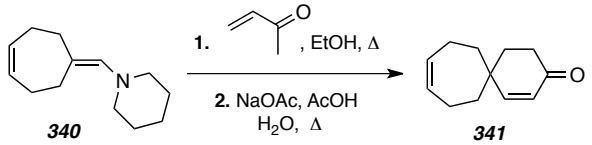
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.82-5.73 (m, 2H, *H*C=C*H*), 5.39 (br s, 1H, =C*H*N), 2.55 (t, *J* = 5.3 Hz, 4H, NC*H*$_2$), 2.40 (t, *J* = 5.7 Hz, 2H, CH_2), 2.19-2.15 (m, 6H), 1.58 (m, 4H), and 1.43 (br pent, *J* = 6.0 Hz, 2H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ 136.0, 131.8, 131.6, 131.5, 54.8, 34.2, 30.3, 29.4, 27.6, 26.0, and 24.4.

IR: 3015, 2945, 2851, 2788, 1654, 1441, 1128, and 715 cm^{-1}.

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 7.72 min; 179 (M^+), 164 (9), 150 (72), 136 (79), 122 (100), 110 (48) and 84 (16).

Spiro[5.6]dodeca-1,9-dien-3-one (341)



340 *341*

Enamine **340** (1.8 g, 8.9 mmol, 1.0 equiv) was dissolved in absolute ethanol (33 mL) in a three-necked 100 mL round-bottomed flask (under nitrogen) equipped with a stirring bar and condenser. After the solution has been stirred for 5 min, methyl vinyl ketone (0.48 mL, 10.2 mmol, 1.1 equiv) was added dropwise. The solution was refluxed for 20 h, after

which the mixture was cooled and anhydrous sodium acetate (1.7 g), acetic acid (2.8 mL), and water (4.8 mL) were added. The mixture was again brought to reflux for 8 h. The solution was cooled with ice water, and aqueous 15% sodium hydroxide was added until the pH reached 9–10. The solution was refluxed for another 15 h. The cooled reaction mixture was diluted with 100 mL of ice cold water and extracted with ether (3 x 20 mL). The ethereal layer was washed with 5% HCl (15 mL) and brine (3 x 15 mL), dried over magnesium sulfate, filtered, and concentrated to afford an orange oil that was purified by FCC (9:1, Hexanes:EtAcO) to give enone **341** (0.6 g, 3.4 mmol, 38 %) or in most cases used unpurified in the following step.

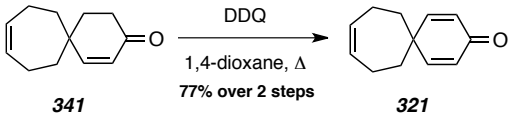
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.87 (d, *J* = 10.2 Hz, 1H, =C$_\beta$*H*), 5.88 (d, *J* = 10.2 Hz, 1H, =C$_\alpha$*H*), 5.71 (br t, *J* = 2.8 Hz, 2H, *H*C=C*H*), 2.44 (t, *J* = 6.6 Hz, 2H, CH_2), 2.26-2.16 (m, 4H), 1.94 (br t, *J* = 6.8 Hz, 2H, CH_2), 1.77-1.72 (m, 2H, CH_2), and 1.71-1.66 (m, 2H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ 199.9, 158.3, 131.1, 126.9, 38.4, 36.3, 34.1, 32.4, and 24.1.

IR: 3017, 2919, 1682, and 861cm^{-1}.

HRMS: calcd for $C_{12}H_{16}ONa$ (M•Na$^+$) 199.1093, found 199.1084.

Spiro[5.6]dodeca-1,4,9-trien-3-one (321)



341 *321*

Spiro[5.6]dodeca-1,9-dien-3-one (**341**, 0.522 g, 2.970 mmol) was dissolved in dioxane (9.9 mL). 2,3-Dichloro-5,6-dicyanobenzoquinone (1.3 g, 5.9 mmol) was added to the solution, which was magnetically stirred in a teflon-capped glass tube at 120 °C overnight. The reaction was deemed complete by GC/MS by full consumption of the starting enone **341** (9.52 min t_R). The solution was transferred to a round-bottomed flask and concentrated to give a dark brown solid (86 % crude). The solid was taken up in ether and washed with DI water (3 x 10 mL). The water layers were combined and back-

extracted with ether (3 x 10 mL). The organic layers were combined, rinsed with brine (3 x 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the crude product as a yellow oil. This residue was purified via MPLC (9:1 Hexanes:EtOAc) to give spiro[5.6]dodeca-1,4,9-trien-3-one (**321**) as a clear oil (0.34 g, 1.9 mmol, 66 %).

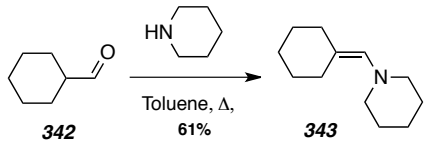
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (d, *J* = 10.0 Hz, 2H, $=C_\beta H$), 6.24 (d, *J* = 10.0 Hz, 2H, $=C_\alpha H$), 5.75 (t, *J* = 3.2 Hz, 2H, *H*C=C*H*), 2.34-2.30 (m, 4H, CH_2), and 1.79-1.76 (m, 4H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ 186.1, 155.3, 131.0, 127.7, 43.4, 36.1, and 24.6.

IR (thin film): 3017, 2921, 2853, 1663, and 873 cm^{-1}.

HRMS: calcd for $C_{12}H_{14}ONa$ ($M•Na^+$) 197.0937, found 197.0942.

1-(cyclohexylidenemethyl)piperidine (**343**)

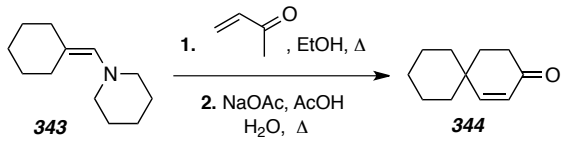


Cyclohexanecarbaldehyde (5.0 g, 44.6 mmol, 1.0 equiv) was dissolved in toluene (58 mL) followed by addition of piperidine (4.17 mL, 49.0 mmol, 1.1 equiv) was added and the solution was heated at 110 °C in a teflon-capped glass tube for six hours. Analysis by GC/MS revealed the reaction to be complete (8.748 ret.). The solution was Kugelrohr distilled to give **343** as a clear oil (4.89 g, 27.2 mmol, 61%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.32 (br s, 1H, =CH), 2.53 (t, *J* = 5.4 Hz, 4H, CH_2), 2.44 (t, *J* = 5.9 Hz, 2H, CH_2), 1.98 (t, *J* = 5.9 Hz, 2H, CH_2), 1.57 (pent, *J* = 5.9 Hz, 4H, CH_2), 1.47-1.54 (m, 6H, CH_2), and 1.42 (pent, *J* = 5.2, 2H, CH_2).

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 7.74 min; 179 (M^+, 100), 150 (175), 136 (80), 122 (95), 110 (50), and 84 (25).

Spiro[5.5]undec-1-en-3-one (344)



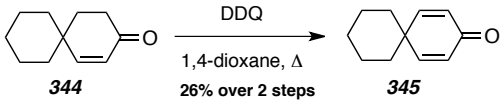
To a three neck 100 mL round bottomed flask (under nitrogen) equipped with a stirring bar and condenser, add the enamine **343** (1.16 g, 6.47 mmol, 1.0 equiv) and dissolve in absolute ethanol (30 mmL). After the solution has been stirred for 5 min, methyl vinyl ketone (0.58 mL, 7.12 mmol, 1.1 equiv) is added dropwise. The solution is refluxed for 20 h after which the mixture is cooled and anhydrous sodium acetate (1.15 g), acetic acid (2.0 mL), water (3.5 mL) were added and the mixture is once again reflux for 8h. The heat is removed and the solution is cooled with ice water, aqueous 15% sodium hydroxide is added until pH 9–10. The solution is refluxed for another 15 h; at the end of this period the reaction mixture is cooled. The reaction mixture is then diluted with 10 mL ice cold water and extracted with ether (3 x 10 mL). The ethereal layer is then washed with 5% HCl (5 mL), brine (3 x 10 mL) and dried over magnesium sulfate and filtered. The ether is then removed by rotary evaporation to afford **344** as an orange oil that was carried crude into the following step.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.84 (d, *J* = 10.26 Hz, 1H, =CH), 5.89 (d, *J* = 10.23 Hz, 1H, =CH), 2.43 (t, J = 6.69 Hz, 2H, CH_2), 1.91 (t, J = 6.78 Hz, 2H, CH_2), and 1.57- 1.47 (m, 10H, CH_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.3, 159.3, 127.4, 36.0, 35.6, 33.9, 32.9, 26.0, and 21.8.

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 8.32 min; 164 (M^+), 136 (75), 122 (100), 107 (82), 93 (30), and 79 (75).

Spiro[5.5]undeca-1,4-dien-3-one (345)



Spiro[5.5]undec-1-en-3-one (0.451 g, 2.75 mmol, 1.0 equiv) was solvated with dioxane (8 mL) and to this solution was added 2,3-dichloro-5,6-dicyanobenzoquinone (1.29 g, 5.68 mmol, 2.07 equiv), which was magnetically stirred in a teflon-capped glass tube at 120 °C overnight. The following day, the solution was concentrated and the solid was taken up in ether and washed with DI water (3 x 8 mL). The water layers were combined and back-extracted with ether (3 x 8 mL). The organic layers were combined, rinsed with brine (3 x 8 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the crude product as a yellow oil. The product was purified via medium performance liquid chromatography (9:1 Hexanes:EtAcO) to give **345** as a clear oil (0.115 g, 0.71 mmol, 26 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09 (d, *J* = 9.9 Hz, 2H, =CH), 6.4 (d, *J* = 10 Hz, 2H, =CH), and 1.54-1.68 (m, 10H).

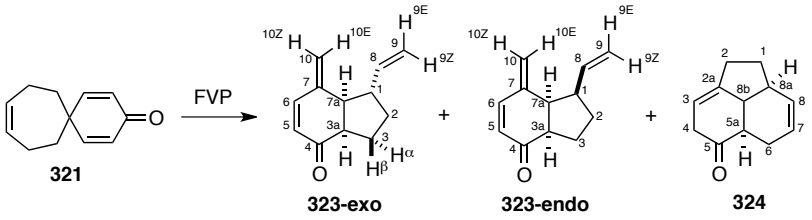
^{13}C NMR (125 MHz, $CDCl_3$): δ 186.4, 155.8, 128.1, 41.0, 35.5, 25.6, and 21.7.

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 8.61 min; 162 (M^+), 134 (75), 119 (50), 105 (45), 91 (100), and 78 (80).

General procedure for the flash vacuum pyrolysis (FVP) experiments

The spiro[5.6]dodeca-1,4,9-trien-3-one (**321**, typically 200-300 mg) was placed in a 50 mL round-bottomed flask (24/40 neck). Care was taken to ensure that the sample was completely devoid of any traces of solvent. The FVP oven was allowed to equilibrate to the desired temperature ranging between 500-600 °C (as measured by a thermocouple inserted ca. halfway into the oven chamber and alongside the quartz tube (ca. 500 cm long) extending through the oven. A dry-ice acetone cold bath and trap were placed on the exit port of the oven tube. The entire apparatus was placed under vacuum (ca. 50±20

mtorr) and heated with a Kugelrohr oven to 127 °C to facilitate vaporization of the sample. It typically required ca. 1 h for all of the trienone **321** to exit the round-bottomed flask. The system was vented and the condensed product was rinsed with EtOAc and transferred to a tared flask. Concentration via rotary evaporation followed by FCC in 9:1 (Hexanes:EtOAc) gave the mixture of the three isomeric FVP products. HPLC purification in 99:1 (Hexanes:EtOAc) gave, in order of elution, compounds **324**, **323-exo**, and **323-endo** in varying ratios depending on the temperature of the FVP experiment.



(1*S*,3a*R*,7a*S*)-7-methylene-1-vinyl-3,3a,7,7a-tetrahydro-1*H*-inden-4(2*H*)-one (323-exo)

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.98 (dddd, *J* = 9.9, 1.2, 0.8, 0.8 Hz, 1H, H6), 5.92 (ddd, *J* = 9.9, 1.6, 0.9 Hz, 1H, H5), 5.65 (ddd, *J* = 17.0, 10.3, 8.2 Hz, 1H, H8), 5.38 (dddd, *J* = 1.5, 0.8, 0.8, 0.8 Hz, 1H, H10Z), 5.22 (dddd, *J* = 1.5, 1.5, 0.8, 0.7 Hz, 1H, H10E), 5.01 (ddd, *J* = 10.2, 1.8, 0.8 Hz, 1H, H9E), 4.89 (ddd, *J* = 17.0, 1.9, 0.8 Hz, 1H, H9Z), 2.88 (ddd, *J* = 8.2, 8.2, 3.0 Hz, 1H, H3a), 2.64 (dd, *J* = 11.0, 7.7 Hz, 1H, H7a), 2.38 (dddd, *J* = 13.5, 8.9, 7.0, 2.9 Hz, 1H, H3β), 2.20 (br dddd, *J* = 10.5, 9.9, 8.2, 8.2 Hz, 1H, H1), 1.95 (dddd, *J* = 13.5, 10.7, 8.6, 5.0 Hz, 1H, H3α), 1.89 (dddd, *J* = 13.4, 8.6, 8.6, 4.9 Hz, 1H, H2β), and 1.49 (dddd, *J* = 13.1, 10.7, 9.8, 7.0 Hz, 1H, H2α).

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.6, 146.0, 141.0, 140.7, 126.5, 121.7, 115.9, 50.7, 49.8, 49.5, 30.4, and 26.0.

IR (thin film): 2956, 2927, 1671, and 1261 cm^{-1}

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 5.72 min; 174 (M^+), 147 (57), 133 (81), 107 (100), and 91 (89).

^{1}H NMR (500 MHz, methanol−d_4): δ 7.12 (dddd, J = 9.8, 1.8, 0.7, 0.7 Hz, 1H, H6), 5.89 (ddd, J = 9.9, 1.4, 1.4 Hz, 1H, H5), 5.69 (ddd, J = 17.1, 10.2, 8.3 Hz, 1H, H8), 5.46 (dddd, J = 1.6, 0.8, 0.8, 0.8 Hz, 1H, H10Z), 5.28 (dddd, J = 1.5, 1.5, 1.5, 0.6 Hz, 1H, H10E), 5.00 (ddd, J = 10.2, 2.0, 0.9 Hz, 1H, H9Z), 4.87 (ddd, J = 16.9, 2.0, 0.9 Hz, 1H, H9Z), 2.89 (ddd, J = 8.6, 8.0, 2.9 Hz, 1H, H3a), 2.72 (dd, J = 11.0, 7.8 Hz, 1H, H7a), 2.31 (dddd, J = 13.4, 9.2, 6.6, 2.7 Hz, 1H, H3β), 2.21 (br dddd, J = 10.6, 9.4, 8.6, 8.6 Hz, 1H, H1), 1.98 (dddd, J = 13.5, 10.7, 8.6, 5.0 Hz, 1H, H3α), 1.86 (dddd, J = 13.5, 8.7, 8.7, 5.0 Hz, 1H, H2β), and 1.54 (dddd, J = 13.0, 10.7, 9.7, 6.7 Hz, 1H, H2α).

^{13}C NMR (125 MHz, methanol−d_4): δ 202.8, 147.9, 142.4, 142.0, 126.8, 122.8, 116.1, 51.6, 51.3, 50.7, 31.3, and 26.9.

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^{1}H NMR (500 MHz, acetone−d_6): δ 7.09 (dddd, J = 9.8, 1.8, 0.7, 0.7 Hz, 1H, H6), 5.84 (ddd, J = 9.9, 1.4, 1.4 Hz, 1H, H5), 5.70 (ddd, J = 17.1, 10.2, 8.3 Hz, 1H, H8), 5.44 (dddd, J = 1.6, 0.8, 0.8, 0.8 Hz, 1H, H10a), 5.24 (dddd, J = 1.5, 1.5, 1.5, 0.6 Hz, 1H, 10b), 4.97 (ddd, J = 10.2, 2.0, 0.9 Hz, 1H, H9a), 4.87 (ddd, J = 16.9, 2.0, 0.9 Hz, 1H, H9b), 2.85 (ddd, J = 8.2, 8.2, 2.0 Hz, 1H, H3a), 2.70 (dd, J = 10.9, 7.7 Hz, 1H, H7a), 2.31 (dddd, J = 13.4, 9.2, 6.6, 2.7 Hz, 1H, H3β), 2.15 (br dddd, J = 10.6, 9.4, 8.6, 8.6 Hz, 1H, H1), 1.87 (dddd, J = 13.5, 10.7, 8.6, 5.0 Hz, 1H, H3α), 1.80 (dddd, J = 13.5, 8.7, 8.7, 5.0 Hz, 1H, H2β), and 1.49 (dddd, J = 12.9, 10.9, 9.6, 6.6 Hz, 1H, H2α).

^{13}C NMR (125 MHz, acetone−d_6): δ 199.7, 146.0, 142.1, 141.9, 126.9, 121.8, 115.8, 51.4, 50.5, 50.2, 30.8, and 26.1.

(1*R*,3a*R*,7a*S*)-7-methylene-1-vinyl-3,3a,7,7a-tetrahydro-1*H*-inden-4(2*H*)-one (323-endo)

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.98 (dddd, J = 10.0, 0.7, 0.7, 0.7 Hz, 1H, H6), 5.93 (ddd, J = 10.1, 1.3, 0.8 Hz, 1H, H5), 5.47 (dddd, J = 2.0, 1.0, 1.0, 1.0 Hz, 1H, H10Z), 5.39 (ddd, J = 17.0, 10.1, 8.4 Hz, 1H, H8), 5.36 (ddd, J = 1.3, 1.3, 1.3 Hz, 1H, H10E),

4.88 (ddd, *J* = 17.0, 1.9, 1.2 Hz, 1H, H9Z), 4.82 (ddd, *J* = 10.2, 1.8, 0.9 Hz, 1H, H9E), 3.25 (ddd, *J* = 8.4, 8.4, 0.9 Hz, 1H, H7a), 2.81 (ddd, *J* = 9.5, 9.5, 3.5 Hz, 1H, H3a), 2.78 (br dddd, *J* = 9.8, 8.0, 8.0, 2.4 Hz, 1H, H1), 2.41 (dddd, *J* = 13.8, 8.1, 8.1, 3.5 Hz, 1H, H3β), 1.96 (dddd, *J* = 13.8, 9.4, 9.4, 4.7 Hz, 1H, H3α), 1.82 (dddd, *J* = 13.1, 9.7, 7.8, 6.8 Hz, 1H, H2α), and 1.65 (ddddd, *J* = 13.4, 7.4, 5.2, 3.1, 0.8 Hz, 1H, H2β).

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.8, 147.4, 141.7, 137.8, 127.9, 121.9, 115.3, 50.2, 48.2, 47.3, 29.6, and 26.0.

IR (thin film): 2958, 2927, 2856, 1674, 1261 cm^{-1}

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 5.79 min; 174 (M^+), 147 (61), 133 (83), 107 (100), and 91 (81).

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^{1}H NMR (500 MHz, methanol−*d*$_4$): δ 7.12 (dddd, *J* = 9.9, 0.8, 0.8, 0.8 Hz, 1H, H6), 5.88 (ddd, *J* = 9.9, 1.5, 0.9 Hz, 1H, H5), 5.56 (dddd, *J* = 1.8, 0.9, 0.9, 0.9 Hz, 1H, H10Z), 5.46 (ddd, *J* = 1.5, 1.5, 1.5 Hz, 1H, H10E), 5.39 (ddd, *J* = 17.0, 10.3, 8.4 Hz, 1H, H8), 4.87 (ddd, *J* = 17.0, 1.9, 1.3 Hz, 1H, H9Z), 4.79 (ddd, *J* = 10.3, 2.0, 1.0 Hz, 1H, H9E), 3.34 (ddd, *J* = 9.0, 7.8, 1.0 Hz, 1H, H7a), 2.84 (dddd, *J* = 9.3, 9.3, 3.5, 0.7 Hz, 1H, H3a), 2.80 (dddddd, *J* = 8, 8, 8, 2.9, 1.2, 1.2 Hz, 1H, H1), 2.34 (dddd, *J* = 13.5, 8.1, 8.1, 3.4 Hz, 1H, H3β), 1.96 (dddd, *J* = 13.6, 9.4, 9.4, 4.5 Hz, 1H, H3α), 1.85 (dddd, *J* = 12.9, 9.8, 7.9, 6.8 Hz, 1H, H2α), and 1.60 (ddddd, *J* = 13.1, 8.3, 4.7, 2.7, 0.8 Hz, 1H, H2β).

^{13}C NMR (125 MHz, methanol−*d*$_4$): δ 203.1, 149.4, 142.9, 139.0, 128.1, 123.1, 115.4, 51.2, 49.1, 48.3, 30.2, and 26.6.

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^{1}H NMR (500 MHz, acetone−*d*$_6$): δ 7.08 (d, *J* = 10.0 Hz, 1H, H6), 5.84 (d, *J* = 9.9 Hz, 1H, H5), 5.53 (br s, 1H, H10Z), 5.43 (ddd, *J* = 17.0, 10.0, 8.5 Hz, 1H, H8) 5.36 (br s, 1H, H10E), 4.86 (ddd, *J* = 17.0, 2.0, 1.0, 1H, H9Z), 4.77 (ddd, *J* = 10.0, 2.0, 1.0 Hz, 1H, H9E), 3.34 (dd, *J* = 8.4, 8.4 Hz, 1H, H7a), 2.80 (dddd, *J* = 7.0, 8.0, 9.0, 13.0 Hz, 1H, H3a), 2.79 (dddd, *J* = 2.4, 8.0, 8.0, 9.8 Hz, 1H, H1), 2.34 (dddd, J = 3.5, 8.0, 8.0, 13.5 Hz,

1H, H3α), 1.88 (dddd, J = 4.5, 9.5, 9.5, 14.0 Hz, 1H, H3β), 1.82 (dddd, J = 7.0, 8.0, 9.0, 13.0 Hz, 1H, H2α), and 1.54 (dddd, J = 2.5, 4.5, 7.5, 13.0 Hz, 1H, H2β).

^{13}C NMR (125 MHz, acetone−d_6): δ 199.7, 147.5, 142.6, 138.9, 128.3, 122.0, 115.1, 50.7, 48.8, 47.8, 30.0, and 26.1.

(5a*R*,8a*S*)-1,2a^{1},4,5a,6,8a-hexahydroacenaphthylen-5(2*H*)-one (324)

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.67 (dddd, *J* = 10.0, 4.9, 2.1, 2.1 Hz, 1H, H7), 5.53-5.57 (m, 2H, H3 and H8), 2.93-3.00 (m, 2H, H4β and H8b), 2.83-2.85 (m, 1H, 4α), 2.76-2.80 (m, 1H, H8b), 2.72 (ddd, *J* = 11.2, 6.8, 5.0 Hz, 1H, H5a), 2.25-2.37 (m, 2H, H2α and H2β), 2.03 (ddddd, *J* = 13.5, 3.5, 2.8, 2.2, 0.6 Hz, 1H, H6α),1.97 (ddddd, *J* = 12.6, 3.0, 2.2, 1.5, 0.7 Hz, 1H, H1α), 1.92 (dddd, *J* = 12.6, 11.2, 9.1, 7.1 Hz, 1H, H6α), and 1.71 (dddd, *J* = 12.6, 2.4, 2.4, 1.2 Hz, 1H, H1β).

^{13}C NMR (125 MHz, $CDCl_3$): δ 214.4, 143.7, 130.4, 125.3, 113.7, 45.1, 42.3, 38.0, 37.5, 31.8, 28.1, and 22.1.

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 5.73 min; 174 (M^+), 147 (51), 133 (89), 107 (100), and 91 (78).

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^{1}H NMR (500 MHz, methanol−d_4): δ 5.67 (dddd, *J* = 10.0, 4.9, 2.1, 2.1 Hz, 1H, H7), 5.55-5.59 (m, 2H, H3 and H8), 2.94-3.00 (m, 1H, H8b), 2.93-3.00 (m, 1H, H4β), 2.82 (ddddd, *J* = 22.7, 4.1, 3.5, 3.0, 2.4 1H, 4α), 2.76-2.80 (m, 1H, H8a), 2.65 (ddd, *J* = 11.2, 6.6, 4.8 Hz, 1H, H5a), 2.25-2.38 (m, 2H, H2α and H2β), 2.08 (ddddd, *J* = 13.5, 3.5, 2.8, 2.2, 0.6 Hz, 1H, H6β), 1.95 (dddd, *J* = 12.6, 11.2, 9.1, 7.1 Hz, 1H, H6α), 1.89 (ddddd, *J* = 12.6, 3.0, 2.2, 2.5, 0.7 Hz, 1H, H1α), and 1.71 (dddd, *J* = 12.6, 2.4, 2.4, 1.2 Hz, 1H, H1β).

^{13}C NMR (125 MHz, $CDCl_3$): δ 216.1, 144.7, 131.2, 125.9, 114.5, 46.1, 43.1, 38.6, 38.4, 32.4, 28.7, and 22.8.

^{1}H NMR (500 MHz, acetone−d_6): δ): δ 5.66 (dddd, J = 10.0, 4.9, 2.1, 2.1 Hz, 1H, H7), 5.53-5.58 (m, 2H, H3 and H8), 2.93-3.00 (m, 1H, H8b and H4β), 2.76-2.80 (m, 1H, H8a), 2.71 (ddddd, J = 22.7, 4.1, 3.5, 3.0, 2.4 1H, 4α), 2.58 (ddd, J = 11.2, 6.6, 4.8 Hz, 1H, H5a), 2.21-2.34 (m, 2H, H2α and H2β), 2.04 (ddddd, J = 13.5, 3.5, 2.8, 2.2, 0.6 Hz, 1H, H6β), 1.92 (dddd, J = 12.6, 11.2, 9.1, 7.1 Hz, 1H, H6α), 1.87 (ddddd, J = 12.6, 3.0, 2.2, 2.5, 0.7 Hz, 1H, H1α), and 1.69 (dddd, J = 12.6, 2.4, 2.4, 1.2 Hz, 1H, H1β).

^{13}C NMR (125 MHz, $CDCl_3$): δ 212.1, 143.9, 130.8, 125.8, 114.6, 45.4, 42.7, 39.1, 38.0, 32.0, 28.4, and 22.3.

Molecular mechanics calculations for both **323-endo** and **323-exo** were carried out using MacroModel via Maestro as the graphical interface. A Monte Carlo conformation search using the MM3* force field gave six conformers for each compound (Figure S1) within a 21.0 kJ•mol^{-1} (5.02 kcal•mol^{-1}).

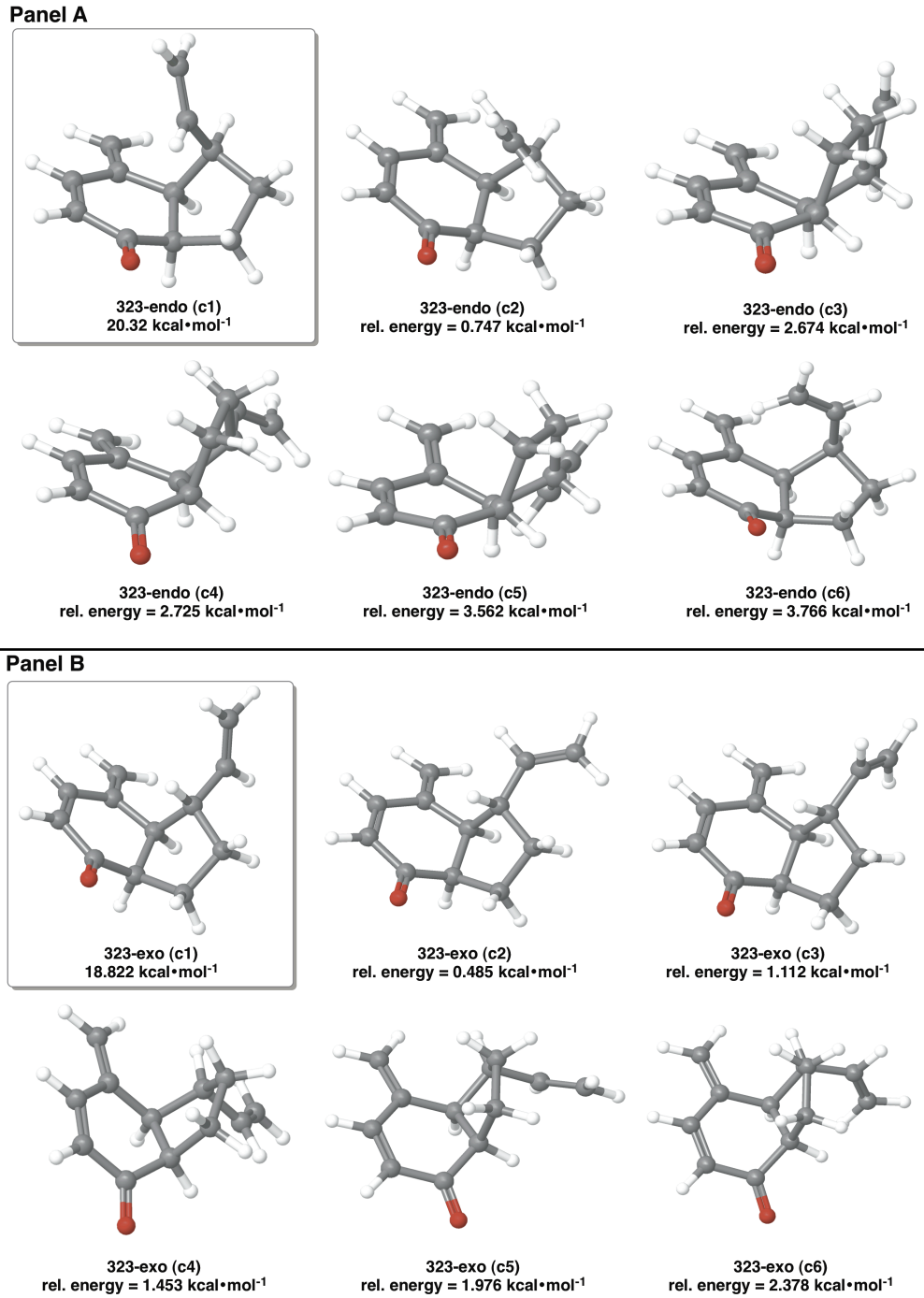


Figure S1. Panel A: Conformers of **323-endo** Panel B: Conformers of **323-exo**.

(i). ^{1}H NMR – The use of complementary deuterated solvents

Reliable NOE data hinges on distinct resonances that can be irradiated in order to observe the corresponding NOE. The initial account by Jones reported the protons labeled H-3β and H-1 in close proximity, moreover protons H-3α and H-2β were overlapped at ca. 1.9 ppm. This would not allow for unambiguous NOE analysis, thus the spectra of **323-endo** was recorded in methanol–d_4 and acetone–d_6 in hopes of separating these resonances (Figure S2). This turned out to work quite well at separating and consequently NOE and exhaustive coupling constant analysis could be done. The remaining resonances were isolated enough to conduct NOE experiments.

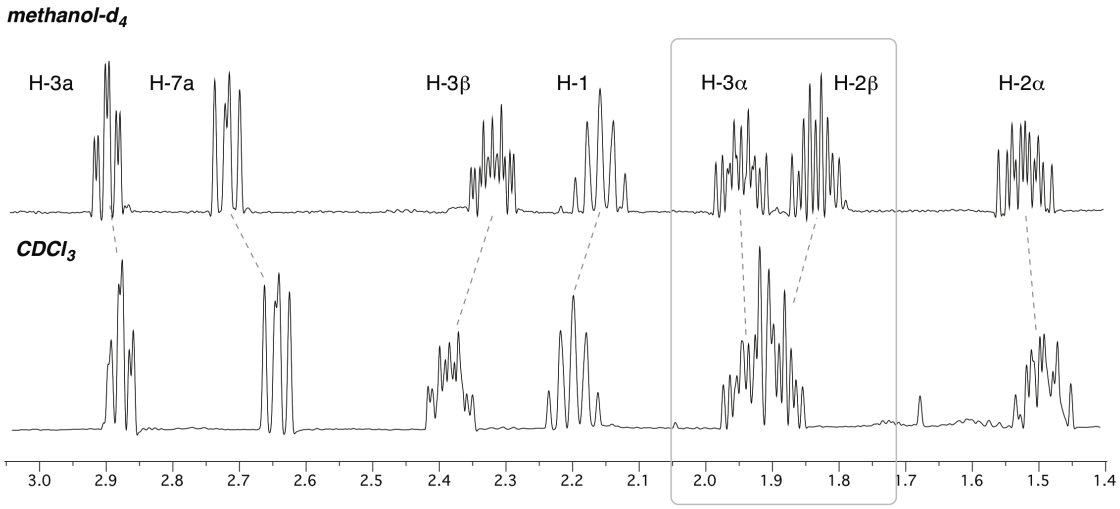


Figure S2. The use of complementary solvents to separate H-3α and H-2β in Isomer II.

Not only can convincing NOEs be obtained, but the HSQC and HMBC data is put on even firmer ground now that H-3α and H-2β were separated.

(ii) ^{1}H NMR – Exhaustive coupling constant analysis and relevant computational models

Coupling constant analysis is at the heart of interpretation of ^{1}H NMR spectra. In particular the ability to 'match' the coupling constants of protons in a ring is integral to reliably determining the relative configuration of organic molecules. In the work by Jones *et al.* the *J*-values for the compound first reported as **323-endo** (what we propose to be **323-exo**) has H-1 as well as the methylene pairs H-2 and H-3 were reported as multiplets

(i.e. no *J*-values were deduced or reported). Using methanol–d_4 all resonances that were first reported as multiplets by Jones were extracted. In the case of H3β the multiplicity was deduced to be a 'dddd' pattern with *J*s of 13.4, 9.2, 6.6, and 2.7 Hz after the spectra was recorded in methanol–d_4, as well as resolution enhanced (Figure S3). This was assigned as H3β as the resonance easily assigned as H3a was deduced to be a 'ddd' with *J*s of 8.6, 8.0, and 2.9 Hz, with the *J*-value of 8.0 Hz arising from coupling to H7a. The only 'match' to the *J*-value of 2.9 Hz of H3a is the *J*-value of 2.7 Hz of H3β, therefore

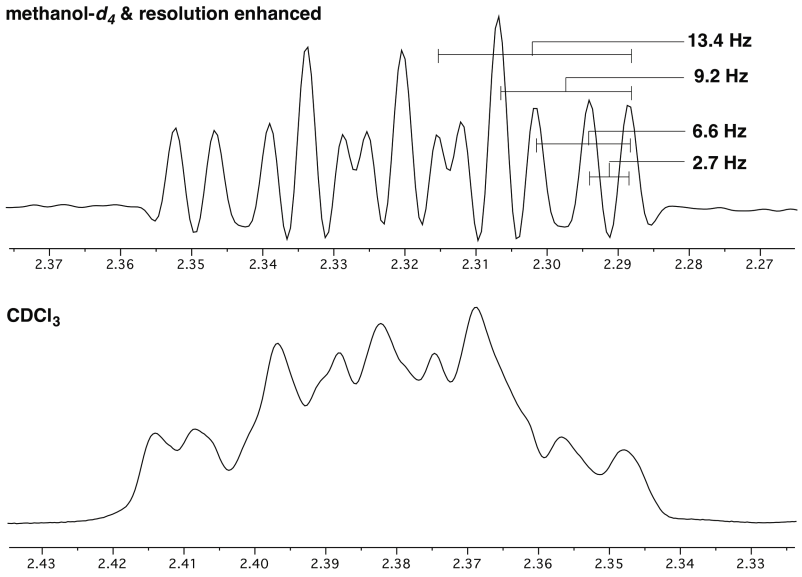


Figure S3. Snapshot of the proton labeled as H3β recorded in $CDCl_3$ and "resolution enhanced" in methanol–d_4 with extracted coupling constants.

the remaining 8.6 Hz *J*-value arises from coupling to H3α. Simply stated the coupling constants of 8.6 and 2.7 Hz corresponds to H3α and H3β respectively. The magnitude of these coupling constants is corroborated by the dihedral angles calculated from the lowest energy conformer of **323-exo** (Figure S4). The dihedral angle between H3a and H3α was found to be 17 °, appropriate for a *J*-value of 8.6 Hz, while the dihedral angle between H3a and H3β was fond to be 103 °, appropriate for a *J*-value of 2.7 Hz, (Table S1).

Figure S4. Lowest energy conformer of **323-exo**

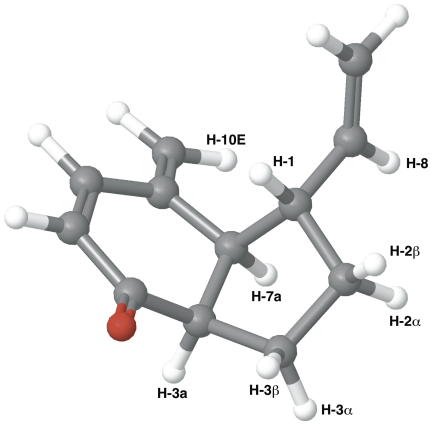


Table S1. Key coupling constants, dihedral angles, NOEs and atomic distances for the lowest energy conformer of **323-exo** (Figure S4)

Atom #	*J* (Hz)[a]	∠ (°)	Distance (Å)	NOE[a]
1–7a	10.8	117	3.09	-
1–2α	9.5	161	3.07	-
1–2β	8.7	41	2.42	-
1–8	8.5	180	3.13	✔ H1 ↔ H8
2α–3α	10.7	11	2.32	✔ H2α ↔ H2β
2α–3β	6.7	129	2.99	-
2β–3α	5.0	109	2.90	-
2β–3β	9.0	9	2.37	-
3α–3a	8.6	17	2.35	✔ H3α ↔ H3a
3β–3a	2.8	103	2.87	-
3a–7a	7.9	42	2.40	✔ H3a ↔ H7a
7a-10E	1.5	n.a.	2.43	✔ H7a ↔ H10E
7a-8	0	n.a.	2.67	✔ H7a ↔ H8
2α–8	0	n.a.	2.57	✔ H2α ↔ H8
1-3α	0	n.a.	3.88	-

[a] *J*-values are the average of those deduced from the multiplet of each proton. E.g., for $J_{1\text{-}7a}$, H1 includes a measured 10.6 and H7a a 11.0 Hz coupling constant; hence, 10.8 is recorded as the average value.
[b] Dihedral angles and interatomic distances were measured from the lowest energy conformer of **323-exo** that was identified by a Monte Carlo conformation search using the MM3* force field in MacroModel.
[c] Key (difference) NOEs were extracted from ^{1}H NMR spectra recorded in methanol–d_4.

The coupling constants of the formerly overlapped resonances H3α and H2β were also extracted from the resolution enhanced spectrum in methanol–d_4. Both H3α and H2β were determined to be ‘dddd’. This differentiation is particularly important as H2β is one of the protons adjacent to the stereogenic center in question (C-1). Here the *J*s of H2β

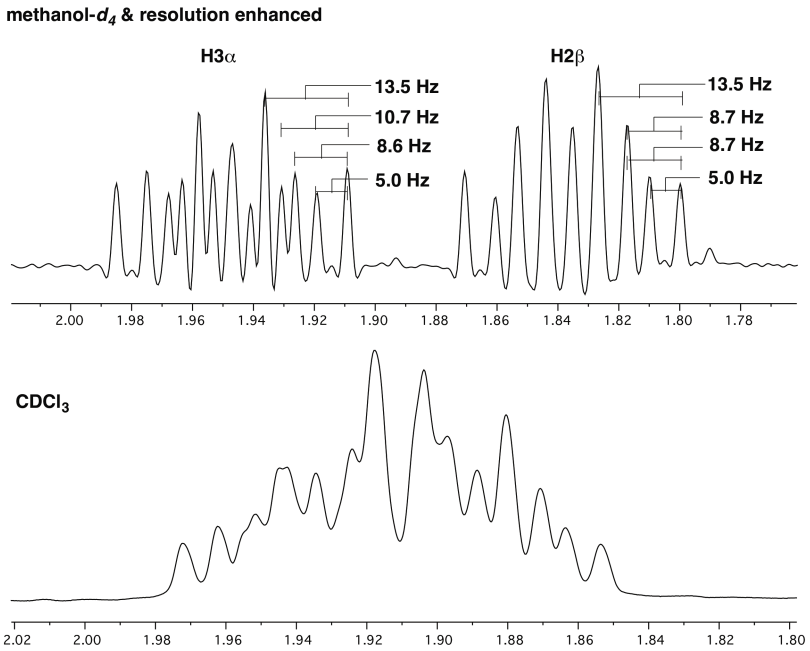


Figure S2. Snapshot of the protons labeled as H3α (to the left) and H2β (on the right) recorded in $CDCl_3$ and "resolution enhanced" in methanol–d_4 with extracted coupling constants.

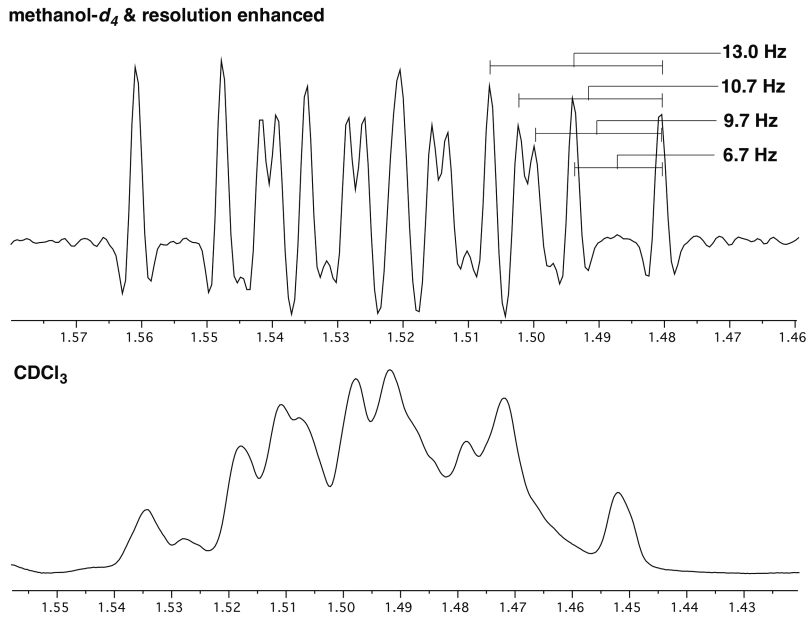


Figure S5. Snapshot of the protons labeled as H2α recorded in $CDCl_3$ and "resolution enhanced" in methanol–d_4 with extracted coupling constants.

were determined to be 13.5, 8.7, 8.7, and 5.0 Hz (coupling to: H2α, H1, H3β, and H3α respectively). Once again the magnitude of the *J*-value (in particular the coupling to H-1) is validated by the calculated dihedral angles in the lowest energy conformer of **323-exo**.

Those that were not, was presumably due non-first order nature of the signals. Here, taking the spectra of the compound in methanol-d_4 was helpful in breaking this occurrence thus complete coupling constant analysis could be conducted.

Figure S6. Lowest energy conformer of **323-endo.**

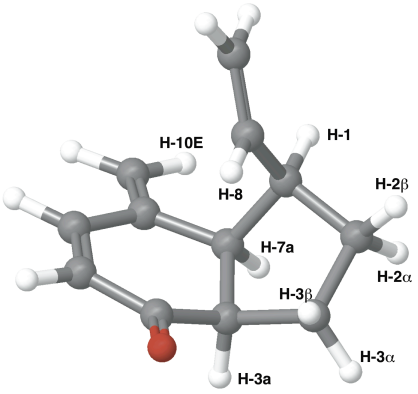


Table S2. Key coupling constants, dihedral angles, NOEs and atomic distances for the lowest energy conformer **323**-endo (Figure –S6).

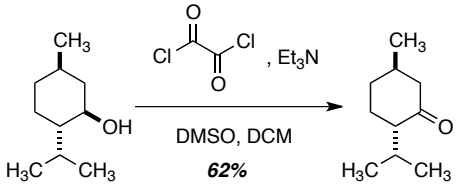
Atom #	*J* (Hz) [a]	∠ (°) [b]	Distance (Å) [b]	NOE [c]
1–7a	7.9	48	2.41	✔ H1 ↼ H7a
1–2α	7.4	39	2.42	-
1–2β	2.8	81	2.72	-
1–8	8.2	171	3.14	-
2α–3α	9.6	25	2.36	-
2α–3β	8.0	143	3.04	-
2β–3α	4.6	95	2.82	-
2β–3β	8.2	23	2.39	-
3α–3a	9.4	1	2.34	✔ H3a ↔ H3α
3β–3a	3.4	118	2.95	-
3a–7a	9.2	34	2.32	✔ H3a ↼ H7a
7a-10E	1.5	n.a.	2.46	✔ H7a ↔ H10E
3α-3β	13.6	n.a.	1.79	✔ H3α ↔ H3β
7a-8	0	n.a.	3.97	-
2α–8	0	n.a.	3.86	-
1-3α	0	n.a.	4.10	-

[a] *J*-values are the average of those deduced from the multiplet of each proton. E.g., for $J_{1\text{-}2\beta}$, H1 includes a measured 2.7 and H2β a 2.9 Hz coupling constant; hence, 2.8 is recorded as the average value.
[b] Dihedral angles and interatomic distances were measured from the lowest energy conformer of **323-endo** that was identified by a Monte Carlo conformation search using the MM3* force field in MacroModel.
[c] Key (difference) NOEs were extracted from ^{1}H NMR spectra recorded in methanol–d_4.

In **323-exo**, the large *J*-value between H-1 and H-7a (10.6/11 Hz) would hint at a trans relationship between the two protons thus the vinyl substituent is on the same side as H-

7a. The dihedral angle between these two protons is 176.7°. Matching the *J*-values presented in table S2 aids in determining the α and β protons of the methylene protons on C-2 and C-3. Whereas the J-value between H-1 and H-7a **323-endo** is 8/7.8 Hz with a dihedral angle of 47.4°.

(2*S*,5*R*)-2-isopropyl-5-methylcyclohexanone (354)

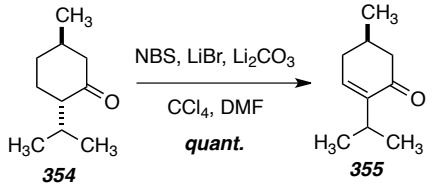


To a round bottomed flask equipped with a stir bar was added oxayl chloride (0.89 g, 7.04 mmol, 1.1 equiv) dissolved in 3.13 mL of DCM. The mixture was cooled to -78 °C, and DMSO (1.1 g, 14.1 mmol, 2.2 equiv) dissolved in DCM (9.4 mL) and added to the original flask. The mixture was stirred for ½ h at -78 °C. To the original flask alcohol **253** (1.0 g, 6.4 mmol, 1.0 equiv) dissolved in DCM (1.7 mL) was added and the resultant solution was stirred for 1 h. Et_3N (2.98 g, 29.4 mmol, 4.6 equiv) was added and the solution warmed to rt an stirred for an additional hour, after which the mixture was poured unto $NH_4Cl_{sat.}$, extracted with DCM, washed with brine and dried over Na_2SO_4. Filtration and rotatory evaporation gave the ketone **354** in a 62 % yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.35 (ddd, *J* = 12.9, 4.0, 2.1 Hz, 1H, CH), 2.14 (m, 1H, CH), 1.99 (ddd, *J* = 12.4, 12.4, 1.1 Hz, 1H, CH), 2.02-2.08 (m, 2H, CH), 1.82-1.92 (m, 2H, CH), 1.30-1.42 (m, 2H, CH), 1.01 (d, *J* = 6.4 Hz, 3H, CH_3), 0.91 (d, *J* = 6.8 Hz, 3H, CH_3), and 0.85 (d, *J* = 6.8 Hz, 3H, CH_3).

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 5.33 min; 154 (M^+), 139 (60), 112 (100), 97 (26), 69 (71), and 55 (27).

(*R*)-2-isopropyl-5-methylcyclohex-2-enone (355)



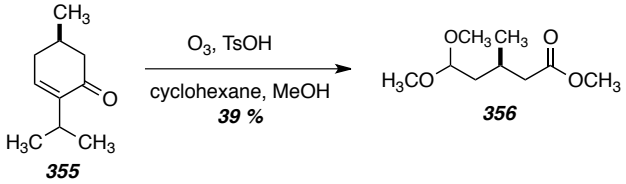
354 ***355***

To a culture tube equipped with a stir bar was placed the methone (0.2 g, 1.3 mmol 1.0 equiv) dissolved in CCl_4 (6.5 mL) followed by NBS (0.23 g, 1.3 mmol, 1.0 equiv). The resultant solution was refluxed for 2 h. The reaction was cooled to rt and aniline (0.12 g, 1.3 mmol, 1.0 equiv) was added and allowd to stir overnight. The following day, the solution was washed with 5% HCl, $NaHCO_3$, and dried over Na_2SO_4. Filtration followed by rotatory evaporation gave the ketone **355** in a quantitative yield.

[sgb_2_269f1] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.64 (ddd, *J* = 5.8, 2.8, 1.1 Hz, 1H, CH), 2.86 (septet, *J* = 6.9 Hz, 1H, CH), 2.49 (ddd, *J* = 15.1, 3.1, 1.8 Hz, 1H, CH), 2.42 (ddd, *J* = 18.2, 5.2, 5.2 Hz, 1H, CH), 1.98-2.19 (m, 4H, CH), 1.04 (d, *J* = 6.4 Hz, 3H, CH_3), 1.0 (d, *J* = 6.4 Hz, 3H, CH_3), and 1.00 (d, *J* = 6.8 Hz, 3H, CH_3).

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 5.49 min; 152 (M^+), 137 (49), 110 (100), 95 (90), 81 (22), and 67 (63).

(*R*)-methyl 5,5-dimethoxy-3-methylpentanoate (356)



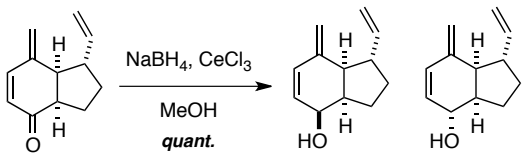
355 ***356***

To a round bottomed flask equipped with a magnetic stir bar was added the enone **355** (1.49 g, 3.24 mmol, 1.0 equiv) dissolved in cyclohexane:methanol (3.5:0.3 mL) followed by TsOH (0.616 g, 3.24 mmol, 1.0 equiv) and the reaction mixture oxonized to produce **356** as a yellow oil (0.239 g, 1.23 mmol, 39%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.46 (dd, *J* = 6.6, 5.0 Hz, 1H, CH), 3.67 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 3.31 (s, 3H, OCH_3), 2.36 (dd, *J* = 14.9, 9.0 Hz, 1H, CH), 2.10-2.10

(m, 2H, CH), 1.67 (ddd, *J* = 5.9, 6.8, 12.6 Hz, 1H, CH), 1.47 (ddd, *J* = 5.0, 7.7, 12.7 Hz, 1H, CH), and 0.99 (d, *J* = 6.6 Hz, 3H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2, 102.7, 52.7, 52.1, 51.3, 41.4, 38.8, 26.6, and 20.0.



323-exo *365* *366*

In a round bottomed flask equipped with a stir bar was added the enone **323-exo** (0.006 g, 0.034 mmol, 1.0 equiv) dissolved in methanol (0.5 mL) and the flask cooled to 0 °C. To this soultion was added $CeCl_3$ (0.009 g, 0.037 mmol, 1.1 equiv) followed by $NaBH_4$ (0.001 g, 0.034 mmol, 1.0 equiv). When complete via TLC, acetone was added to quench any residual $NaBH_4$, the reaction diluted with DCM (2 mL) and washed with H_2O. The aqueous layer was then extracted with DCM (2 mL), the organic layers combined and washed with brine and dried over $MgSO_4$. Filtration and concentration via rotary evaporation and purification via FCC (8:2, Hexanes:EtAcO) provided both **365** and **366** in a 3:2 ratio by crude NMR.

(1S,3aR,4S,7aS)-7-methylene-1-vinyl-2,3,3a,4,7,7a-hexahydro-1H-inden-4-ol (**365**)

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.17 (dd, *J* = 10.0, 2.4, 1H, =CH), 5.78 (d, *J* = 10.2 Hz, 1H, =CH), 5.76 (ddd, *J* = 17.6, 10.4, 7.9 Hz, 1H, =CH), 5.03 (br s, Hz, 1H, =CH), 4.96 (ddd, *J* = 10.3 Hz, 1H, =CH), 4.95 (ddd, *J* = 17.1, 1H, =CH), 4.35 (br s, 1H, C*H*OH), 2.62 (apparent pent, *J* = 7.8 Hz, 1H, CH), 2.48 (dddd *J* = 8.6, 7.1, 1.6, 1.6 Hz, 1H, CH), 2.41 (apparent pent, *J* = 6.7 Hz, 1H, CH), 1.99 (dddd, *J* = 13.3, 9.3, 8.6, 5.0 Hz, 1H, CH), 1.84 (dddd, *J* = 12.8, 10.1, 7.6, 4.9 Hz, 1H, CH), 1.77 (ddd, *J* = 12.7, 9.5, 6.8, 3.4 Hz, 1H, CH), and 1.51 (dddd, *J* = 13.2, 10.1, 7.2, 6.4 Hz, 1H, CH).

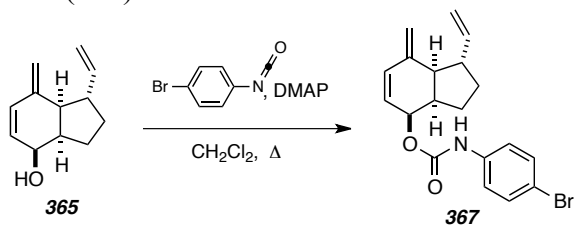
GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 6.54 min; 176 (M^+), 147 (88), 133 (82), 107 (100), and 91 (94).

(1S,3aR,4R,7aS)-7-methylene-1-vinyl-2,3,3a,4,7,7a-hexahydro-1H-inden-4-ol (366)

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.17 (dd, *J* = 10.0, 2.4, 1H, =CH), 5.76 (ddd, *J* = 10.0, 1.9, 1.9 Hz, 1H, =CH), 5.65 (ddd, *J* = 8.3, 10.2, 16.7 Hz, 1H, =CH), 5.00 (ddd, *J* = 0.8, 0.8, 0.9 Hz, 1H, =CH), 4.96 (ddd, *J* = 10.0, 1.9, 1.2 Hz, 1H, =CH), 4.95 (ddd, *J* = 17.0, 2.6, 1.6 Hz, 1H, =CH), 4.77 (dddd, *J* = 2.0, 1.0, 1.0, 1.0 Hz, 1H, =CH), 4.00 (br d, *J* = 8.4 Hz, 1H, C*H*OH), 2.36 (dd, *J* = 11.0, 6.2 Hz, 1H, CH), 2.18-2.26 (m, 1H, CH), 2.00-2.07 (m, 2H, CH), 1.82-1.95 (m, 1H, CH), and 1.61 (dddd, *J* = 13.2, 10.8, 8.3, 4.7 Hz, 1H, CH).

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 6.59 min; 176 (M^+), 147 (61), 130 (100), 107 (90), 91 (92), and 77 (51).

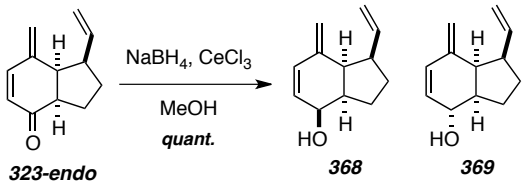
(1*S*,3a*R*,4*S*,7a*S*)-7-methylene-1-vinyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-4-yl (4-bromophenyl)carbamate (367)



In a small vial equipped with a stir bar was placed the alcohol **365** (1.1 mg, 0.006 mmol, 1.0 equiv) dissolved in DCM (0.2 mL). To this was placed bromophenyl isocyanate (3.7 mg, 0.018 mmol, 3.0 equiv) followed by DMAP (2.3 mg, 0.019 mmol, 3.1 equiv) and then the solution was heated to 60 °C and stirred until complete via TLC. When complete, the reaction was concentrated via rotary evaporation and purified by FCC to provide the carbamate **367** (2.2 mg, 0.006, quant).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.8 Hz, 2H, =CH), 7.30 (d, *J* = 8.5 Hz, 2H, =CH), 6.61 (br s, 1H, NH), 6.19 (dd, *J* = 10.0, 2.2 Hz, 1H, =CH), 5.71 (ddd, *J* = 9.9, 1.9, 1.9 Hz, 1H, =CH), 5.67 (ddd, *J* = 16.9, 10.1, 8.1 Hz, 1H, =CH), 5.21 (br d, *J* = 8.7 Hz, 1H, =CH), 5.05 (br s, 1H, =CH), 4.98 (dd, *J* = 10.1, 2.2 Hz, 1H, =CH), 4.9 (dd, *J* = 16.9, 1.9 Hz, 1H, =CH), 4.84 (br s, 1H, =CH), 2.42 (dd, *J* = 10.8, 6.2 Hz, 1H, CH), 2.35

(apparent pent, *J* = 9.3 Hz, 1H, CH), 2.3 (dddd, *J* = 14.5, 11.5, 6.0, 2.3 Hz, 1H, CH), 2.03 (dddd, *J* = 13.4, 9.0, 9.0, 7.1 Hz, 1H, CH), 1.78-1.83 (m, 1H, CH), and 1.61 (dddd, *J* = 13.3, 9.9, 7.8, 5.3 Hz, 1H, CH).



323-endo ***368*** ***369***

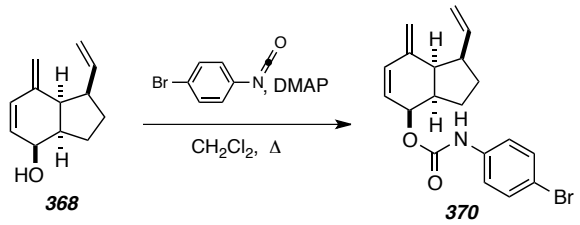
In a round bottomed flask equipped with a stir bar was added the enone **323-endo** (0.008 g, 0.045 mmol, 1.0 equiv) dissolved in methanol (0.7 mL) and the flask cooled to 0 °C. To this soultion was added $CeCl_3$ (0.012 g, 0.049 mmol, 1.1 equiv) followed by $NaBH_4$ (0.002 g, 0.045 mmol, 1.0 equiv). When complete via TLC, acetone was added to quench any residual $NaBH_4$, the reaction diluted with DCM (2 mL) and washed with H_2O. The aqueous layer was then extracted with DCM (2 mL), the organic layers combined and washed with brine and dried over $MgSO_4$. Filtration and concentration via rotary evaporation and purification via FCC (9:21, Hexanes:EtAcO) provided both **368** and **369** in a 9:1 ratio by crude NMR. Due to the scale and ratio of the alcohols, no ^{1}H NMR of **369** was taken.

(1*R*,3a*R*,4*S*,7a*S*)-7-methylene-1-vinyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-4-ol (**368**)

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.15 (dd, *J* = 9.9, 2.0 Hz, 1H, =CH), 5.96 (ddd, 5.71 (dd, *J* = 9.9, 3.7 Hz, 1H, =CH), 5.71 (ddd, *J* = 9.9, 2.9, 1.5 Hz, 1H, =CH), 5.07 (br s, 1H, =CH), 5.01-5.05 (m, 2H, =CH), 4.99 (br s, 1H, =CH), 4.39 (br s, 1H, CHO), 2.99 (t, *J* = 7.1 Hz, 1H, CH), 2.81 (apparent pent, *J* = 6.9 Hz, 1H, CH), 2.53 (apparent pent, *J* = 7.1 Hz, 1H, CH), and 1.56-1.81 (m, 3H, CH).

GC/MS [EI, 70 eV, m/z (rel. int.), 50-270 °C, 16 min run]: t_r = 6.72 min; 176 (M^+), 147 (87), 130 (91), 107 (92), 91 (100), and 77 (51).

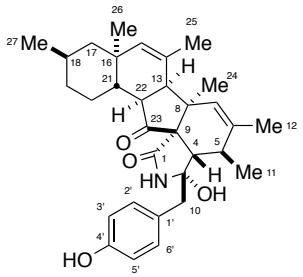
(1*R*,3a*R*,4*S*,7a*S*)-7-methylene-1-vinyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-4-yl (4-bromophenyl)carbamate (370)



In a small vial equipped with a stir bar was placed the alcohol **368** (0.005 mg, 0.030 mmol, 1.0 equiv) dissolved in DCM (1.0 mL). To this was placed bromophenyl isocyanate (0.018 g, 0.090 mmol, 3.0 equiv) followed by DMAP (0.011 g, 0.093 mmol, 3.1 equiv) and then the solution was heated to 60 °C and stirred until complete via TLC. When complete, the reaction was concentrated via rotary evaporation and purified by FCC to provide the carbamate **370** (0.011 g, 0.030, quant).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, *J* = 8.8 Hz, 2H, =CH), 7.30 (d, *J* = 8.5 Hz, 2H, =CH), 6.57 (br s, 1H, NH), 6.23 (dd, *J* = 10.0, 2.0 Hz, 1H, =CH), 5.96 (ddd, *J* = 17.5, 11.5, 7.7 Hz, 1H, =CH), 5.65 (d, *J* = 10.1 Hz, 1H, =CH), 5.54-5.57 (m, 1H, =CH), 5.10 (br s, 1H, =CH), 5.04 (br s, 1H, =CH), 4.97-5.01 (m, 2H, =CH), 3.03 (dd, *J* = 6.7, 6.7 Hz, 1H, CH), 2.80 (apparent pent, *J* = 7.2 Hz, 1H, CH), 2.73 (apparent pent, *J* = 6.7 Hz, 1H, CH), and 1.66-1.84 (m, 3H, CH).

NMR Spectroscopic Data for Diaporthichalasin (402)



Diaporthichalasin (***402***)

atom numbering

^{1}H NMR (850 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.5 Hz, 2H, *H2′/6′*), 6.84 (d, *J* = 8.5 Hz, 2H, *H3′/5′*), 6.07 (br s, 1H, O*H*), 5.49 (br s, 1H, O*H*), 5.39 (dq, *J* = 1.9, 1.3 Hz, 1H, *H15*), 5.32 (dq, *J* = 1.6, 1.6, 1H, *H7*), 3.12 (d, *J* = 13.5 Hz, 1H, *H10*), 2.98 (d, *J* = 13.4 Hz, 1H, *H10*), 2.98 (d, *J* = 8.0 Hz, 1H, *H13*), 2.91 (d, *J* = 2.1 Hz, 1H, *H4*), 2.44 (dd, *J* = 8.3, 12.9 Hz, 1H, *H22*), 2.35 (s, 1H, N*H*), 2.35 (ddqq, *J* = 2.1, 2.1, 0.9, 7.5 Hz, 1H, *H5*), 1.88 (dd, *J* = 0.9, 1.4 Hz, 3H, *H25*), 1.75 (dd, *J* = 0.9, 1.3 Hz, 3H, *H12*), 1.72 (from HMQC, 1H, *H19eq*), 1.64 (dddd, *J* = 3, 3, 3, 13.5 Hz, 1H, *H20eq*), 1.63 (from COSY, 1H, *H18*), 1.46 (s, 3H, *H24*), 1.45 (ddd, *J* = 1.9, 3.8, 13 Hz, 1H, *H17eq*), 1.40 (ddd, *J* = 2.8, 12.7, 12.7 Hz, 1H, *H21*), 1.21 (dddd, *J* = 3.5, 13, 13, 13 Hz, 1H, *H20ax*), 1.01 (d, *J* = 7.4 Hz, 3H, *H11*), 0.82 (s, 3H, *H26*), 0.82 (d, *J* = 6.5 Hz, 3H, *H27*), 0.72 (dd, *J* = 12.4, 12.4 Hz, 1H, *H17ax*), and 0.60 (dddd, *J* = 4.1, 13.1, 13.1, 13.1 Hz, 1H, *H19ax*).

^{13}C NMR (125 MHz, $CDCl_3$) δ 218.5, 175.1, 155.5, 139.0, 135.3, 131.2, 127.7, 127.1, 126.4, 116.2, 86.8, 64.8, 53.5, 50.4, 49.2, 48.1, 45.8, 43.8, 41.1, 36.0, 35.7, 29.4, 27.1, 25.6, 25.1, 23.4, 22.7, 22.4, 21.0 and 19.7.

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^{1}H NMR (850 MHz, methanol-d_4) δ 7.15 (d, *J* = 8.5 Hz, 2H, *H2′/6′*), 6.75 (d, *J* = 8.5 Hz, 2H, *H3′/5′*), 5.37 (dq, *J* = 1.9, 1.9 Hz, 1H, *H15*), 5.21 (dq, *J* = 1.4, 1.4, 1H, *H7*), 3.0 (br s, *2*H, *H10*), 2.86 (d, *J* = 8.0 Hz, 1H, *H13*), 2.73 (d, *J* = 1.7 Hz, 1H, *H4*), 2.25 (dd, *J* = 8.1, 13.0 Hz, 1H, *H22*), 2.09 (br q, *J* = 7.3 Hz, 1H, *H5*), 1.89 (dd, *J* = 0.9, 1.3 Hz, 3H, *H25*), 1.69 (dddd, Σ(*J*s) = 25.7 Hz including *J*s of 1.8 & 12.7 Hz, *H19eq*), 1.65 (s, 3H, *H12*), 1.62 (ddddq, *J* = 4.1, 4.1, 12.3, 12.3, 6.5 Hz, 1H, *H18*), 1.53 (s, 3H, *H24*), 1.52 (dddd, *J* =

3.3, 3.3, 3.3, 13.6 Hz, 1H, *H20eq*), 1.45 (ddd, *J* = 1.8, 3.8, 12.7 Hz, 1H, *H17eq*), 1.45 (ddd, *J* = 2.9, 12.7, 12.7 Hz, 1H, *H21*), 1.1 (dddd, *J* = 4.3, 13.2, 13.2, 13.2 Hz, 1H, *H20ax*), 0.81 (s, 3H, *H26*), 0.81 (d, *J* = 6.5 Hz, 3H, *H27*), 0.81 (d, *J* = 7.3 Hz, *3H*, *H11*), 0.68 (dd, *J* = 12.4, 12.4 Hz, 1H, *H17ax*), and 0.57 (dddd, *J* = 4.3, 13.2, 13.2, 13.2 Hz, 1H, *H19ax*).

^{13}C NMR (125 MHz, methanol-d_4) δ 221.2, 178.2, 157.5, 139.7, 136.6, 132.7, 129.5, 128.0, 127.5, 116.1, 89.6, 66.1, 52.4, 51.9, 50.8, 49.5, 46.3, 45.2, 42.2, 37.0, 36.9, 30.7, 28.4, 26.3, 25.5, 24.5, 23.1, 22.7, 21.0 and 19.9.

^{1}H NMR (850 MHz, DMSO-d_6) δ 9.25 (br s, 1H, O*H*), 8.59 (br s, 1H, N*H*), 7.09 (d, *J* = 8.4 Hz, 2H, *H2'/6'*), 6.67 (d, *J* = 8.5 Hz, 2H, *H3'/5'*), 5.64 (br s, 1H, O*H*), 5.32 (s, 1H, *H15*), 5.08 (dq, *J* = 1.4, 1.5 Hz, 1H, *H7*), 2.87 (d, *J* = 14.1 Hz, 1H, *H10*), 2.85 (d, *J* = 14.1 Hz, 1H, *H10*), 2.73 (d, *J* = 8.1 Hz, 1H, *H13*), 2.48 (d, *J* = 1.4 Hz, 1H, *H4*), 2.04 (dd, *J* = 8.1, 12.9 Hz, 1H, *H22*), 2.03 (br q, *J* = 7.3 Hz, 1H, *H5*), 1.83 (dd, *J* = 0.8, 1.3 Hz, 3H, *H25*), 1.62 (dddd, Σ(Js) = 24.7 Hz including *J*s of 1.2 & 12.2 Hz, *H19eq*), 1.58 (dd, *J* = 0.8, 1.4 Hz, 3H, *H12*), 1.55 (ddddq, *J* = 3.9, 3.9, 12.8, 12.8, 6.4 Hz, 1H, *H18*), 1.47 (s, 3H, *H24*), 1.41 (ddd, *J* = 1.7, 3.6, 12.6 Hz, 1H, *H17eq*), 1.37 (dddd, *J* = 3.4, 3.4, 3.4, 13.3 Hz, 1H, *H20eq*), 1.32 (ddd, *J* = 2.9, 12.8, 12.8 Hz, 1H, *H21*), 0.99 (dddd, *J* = 3.5, 13.4, 13.4, 13.4 Hz, 1H, *H20ax*), 0.75 (d, *J* = 6.4 Hz, 3H, *H27*), 0.74 (s, 3H, *H26*), 0.71 (d, *J* = 7.4 Hz, 3H, *H11*), 0.58 (dd, *J* = 12.3, 12.3 Hz, 1H, *H17ax*), and 0.47 (dddd, *J* = 4.2, 12.9, 12.9, 12.9 Hz, 1H, *H19ax*).

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^{13}C NMR (125 MHz, DMSO-d_6) δ 218.8, 174.7, 155.9, 137.9, 134.7, 131.5, 128.8, 126.6, 126.1, 114.7, 87.9, 63.6, 50.0, 49.2, 48.6, 47.7, 44.1, 43.6, 40.3, 35.5, 35.3, 28.7, 26.6, 25.4, 24.9, 22.9, 22.6, 22.3, 20.0 and 19.9.

HRMS (ESI-TOF): Calcd for $(C_{32}H_{41}NO_4Na)^+$ 526.2928. Found 526.2948.

Table S3. Summary of reported and recollected proton (left half) and carbon (right half) NMR chemical shift data for phomopsichalasin (once known as **401**) and diaporthichalasin (**402**) in three different solvents.

Nucleus	**δ ^{1}H**					**δ ^{13}C**				
Sample	**Diap.** $CDCl_3$-*UMN*	**Phom.** MeOH-*1995*	**Diap.** MeOH-*UMN*	**Diap.** DMSO-*2007*	**Diap.** DMSO-*UMN*	**Diap.** $CDCl_3$-*UMN*	**Phom.** MeOH-*1995*	**Diap.** MeOH-*UMN*	**Diap.** DMSO-*2007*	**Diap.** DMSO-*UMN*
Atom #										
1	-	-	-	-	-	175.1	178.2	178.2	174.83	174.65
2	n/a[a]	-	n/a[a]	8.58	8.59	-	-	-	-	-
3	-	-	-	-	-	86.8	89.7	89.6	87.99	87.86
4	2.91	2.73	2.73	2.47	2.48	53.5	52.4	52.4	49.27	49.21
5	2.35	2.09	2.09	2.03	2.03	29.4	30.7	30.7	28.82	28.74
6	-	-	-	-	-	135.3	136.6	136.6	134.77	134.68
7	5.32	5.20	5.21	5.08	5.08	127.1	127.5	127.5	126.13	126.05
8	-	-	-	-	-	43.8	45.2	45.2	43.64	43.57
9	-	-	-	-	-	64.8	66.1	66.1	63.62	63.57
10a **10b**	3.12 2.98	2.99	3.00	2.86	2.87 2.85	45.8	46.3	46.3	44.07	44.06
11	1.01	0.81	0.81	0.71	0.71	21.0	21.0	21.0	20.44	19.95
12	1.75	1.64	1.65	1.58	1.58	22.4	22.7	22.7	22.44	22.33
13	2.98	2.85	2.86	2.72	2.73	50.4	52.0	51.9	50.14	50.02
14	-	-	-	-	-	127.7	129.5	129.5	128.13	128.79
15	5.39	5.36	5.37	5.36	5.32	139.0	139.7	139.7	137.95	137.85
16	-	-	-	-	-	36.0	37.0	37.0	35.56	35.48
17_{ax} **17_{eq}**	0.72 1.45	0.67 1.45	0.68 1.45	0.58 1.41	0.58 1.41	48.1	49.4	49.5	47.8	47.73
18	1.63	1.62	1.62	1.54	1.55	27.1	28.4	28.4	26.72	26.63
19_{ax} **19_{eq}**	0.60 1.72	0.56 1.64	0.57 1.69	0.46 1.62	0.47 1.62	35.7	36.9	36.9	35.37	35.29
20_{ax} **20_{eq}**	1.21 1.64	1.10 1.50	1.10 1.52	0.98 1.37	0.99 1.37	23.4	24.5	24.5	22.99	22.91
21	1.40	1.42	1.45	1.32	1.32	41.1	42.2	42.2	40.34	40.26
22	2.44	2.24	2.25	2.03	2.04	49.2	50.8	50.8	48.75	48.63
23	-	-	-	-	-	218.5	221.3	221.2	218.95	218.75
24	1.46	1.52	1.53	1.47	1.47	25.6	26.3	26.3	25.49	25.39
25	1.88	1.88	1.89	1.82	1.83	25.1	25.5	25.5	24.98	24.87
26	0.82	0.80	0.81	0.74	0.74	19.7	19.9	19.9	19.52	19.94
27	0.82	0.78	0.81	0.75	0.75	22.7	23.1	23.1	22.66	22.56
1′	-	-	-	-	-	126.4	128.0	128.0	126.69	126.59
2′/6′	7.15	7.14	7.15	7.09	7.09	131.2	132.8	132.7	131.6	131.48
3′/5′	6.84	6.74	6.75	6.67	6.67	116.2	116.1	116.1	114.83	114.72
4′	-	-	-	-	-	155.5	157.6	157.5	155.93	155.86
OH	5.49			5.63	5.64	-	-	-	-	-
OH	6.07			9.26	9.25	-	-	-	-	-

[a] n/a = not assigned.

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