Studies Toward the Total Synthesis of rac-Leuconolam, Modified Julia Olefination Approach to Access Functionalized Steroidal Side Chains, Proton-NMR Studies of Mosher-Like Esters, and Exploring a Non-Enzymatic Diels Alder Reaction to Account for the Methyl Sarcophytoate Core

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Dedication

I dedicate this Ph.D. thesis to my life partner and wife, Gulzade Ebru Izgu.

Abstract

This Ph.D. thesis is composed of five chapters, two of which are closely related and are presented at the begining. In Chapter-I, an extensive study toward the total synthesis of a plant natural product, namely leuconolam, will be discussed. In the course of this project, two different routes have been explored, where novel synthetic methods have been developed. In particular, some of the key bond-forming events such as Ireland-Claisen rearrangement, arene-alkene coupling (via either Stille reaction or C-H bond functionlization) and allylative ring closure are highlighted.

A side project that has emerged during my investigations in Chapter-I will be covered in Chapter-II. This work focuses on the synthesis of two new organometallic reagents and their utility in organopalladium mediated cross-couling reactions with various alkenyl and aryl halides.

Chapter-III encompasses the studies in the area of steroid chemistry, more specifically, in chemical construction of important steroid side chains. In order for a convergent strategy, a modified Julia olefination method has been performed on a common sulfone donor with a series of uselful aldehyde acceptors. Biologically relevant derivatives of alkyl and alkoxy branched side chains have been successfully synthesized.

In Chapter-IV, synthetic and spectroscopic studies in Mosher ester analysis technique will be discussed. This NMR based tool is critical in determining the absolute configuration of a stereogenic carbon center and is commonly used by organic chemists.

Finally, in Chapter-V, our efforts in generating a reactive pyrylium dienophile to facilitate a Diels-Alder reaction will be outlined.

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List of Abbreviations

Å	Angstrom
Ac	Acetyl
ATR	Attenuated Total Reflectance
Bn	Benzyl
Boc	tert-Butyloxycarbonyl
Br	Broad
BT	Benzothiazole
°C	Degrees Celsius
CDA	Chiral Derivatizing Agent
δ	Chemical Shift, in NMR Spectroscopy
d	Doublet, in NMR Spectroscopy
dba	Dibenzylideneacetone
DCC	*N*,*N*-Dicyclohexylcarbodiimide
DIAD	Diisopropyl azodicarboxylate
DIBAL or DIBAL-H	Diisobutylaluminum hydride
DMAP	*N*,*N*-Dimethyl-4-aminopyridine
DMP	Dess–Martin periodinane
DMF	Dimethylformamide
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide

dr	Diastereomeric ratio
EDCI	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
EE	Ethoxyethyl
ee	Enantiomeric Excess
equiv	Equivalent
ESI	Electrospray Ionization
Et	Ethyl
EWG	Electron Withdrawing Group
g	Gram(s)
HATU	*O*-(7-Azabenzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium hexafluorophosphate
HMPA	Hexamethylphosphoric triamide
HRMS	High-resolution Mass Spectrometry
HWE	Horner-Wadsworth-Emmons
Hz	Hertz (cycles per second)
IR	Infrared
i-Pr	Isopropyl
J	Coupling Constant (NMR)
KHMDS	Potassium *bis*(trimethylsilyl)amide
LA	Lewis Acid
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide

LiHMDS	Lithium *bis*(trimethylsilyl)amide
Me	Methyl
MHz	Megahertz
MJO	Modified Julia Olefination
mmol	MilliMole
mol	Mole(s)
MOM	Methoxymethyl
mp	Melting Point
MPLC	Medium Pressure Liquid Chromatography
NaHMDS	Sodium *bis*(trimethylsilyl)amide
nfom	Non First Order Multiplet
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect/Enhancement
ORIA	Open Ring Indole Alkaloid
PDC	Pyridinium dichromate
PEPPSI	Pyridine, Enhanced, Precatalyst, Preparation, Stabilization and Initiation
PG	Protecting Group
Ph	Phenyl
PMB	*para*-Methoxybenzyl
PMHS	Polymethylhydrosiloxane

ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonic acid
PT	1-Phenyl-1H-tetrazole
PTSA or *p*-TsOH	*p*-Toluenesulfonic acid monohydrate
q	Quartet, in NMR Spectroscopy
pyr	Pyridine
p	Pentet, in NMR Spectroscopy
R	Rectus (configurational)
RedAl	Sodium bis(2-methoxyethoxy)aluminium hydride
R_f	Ratio to Front
rt	Room Temperature
S	Sinister (configurational)
s	Singlet, in NMR Spectroscopy
t	Triplet, in NMR Spectroscopy
TBAF	Tetrabutylammonium fluoride
TBS	*tertiary*-Butyldimethylsilyl
TBSCl	*tertiary*-Butyldimethylsilyl chloride
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl or Tetramethylsilane

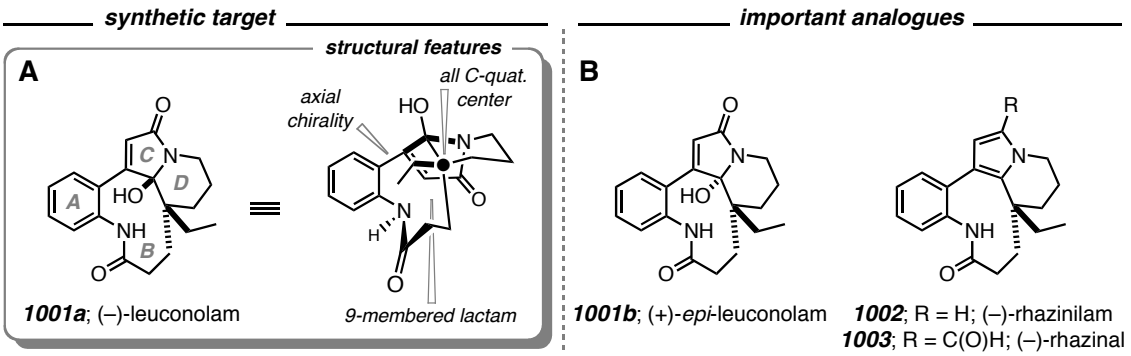
TMSCl	Trimethylsilyl chloride
Ts or *p*-Ts	*para*-Toluenesulfonyl

Chapter – I: Studies Toward the Total Synthesis of (±)-Leuconolam

I-A. Introduction and Background

(–)-Leuconolam (**1001a**) is a bis-lactam plant alkaloid, which has the complex molecular architecture shown in panel A of Figure I-1. This natural product can be found in two different *Leuconotis* plants located in Malaysia, *L. griffithii* and *L. eugenifolia*.[1] Goh and co-workers reported the first isolation and the structural assignment of **1001a**.[2] It belongs to a family of open-ring indole alkaloids (ORIAs),[3,4] and the most relevant analogues to leuconolam are shown in panel B.

Figure I-1. Structures of (–)-Leuconolam and Related Analogues.



Some of the key structural features of **1001a** are revealed by its single crystal X-ray structure.[3b] In particular, the styrenyl moiety and the acetanilide functional group are non co-planar with the benzenoid ring. Thus, the molecule is axially chiral around

1. In old Malayan medicine, these plants were used to treat dermatologic infections by applying topically on the infected skin.[3b]
2. Goh, S.H.; Wei, C.; Ali, A. R. M. *Tetrahedron Lett.* **1984**, *25*, 3483–3484.
3. (a) Goh, S.H.; Wei, C.; Ali, A. R. M. *Tetrahedron Lett.* **1986**, *27*, 2501–2504. (b) Goh, S. H.; Ali, R. M. A.; Wong, W. H. *Tetrahedron* **1989**, *45*, 7899–7920.
4. From here on, "ORIA" will be used to refer the molecules depicted in Figure I-1, even though the open-ring indole alkaloids encompass a significantly bigger group of compounds.

the arene-alkene C-C bond. Also the relative configuration between the pair of adjacent stereogenic quaternary carbon atoms presents an additional challenge in constructing such an alkaloid.

We have envisioned a bench-chemistry synthesis of **1001a** starting from commercially available and affordable chemicals. Our motivation stemmed from the intriguing molecular architecture of leuconolam, and from the anticipation of developing novel synthetic methodologies during the course of the synthetic endeavor. As the only researcher in this project, I have completed the total synthesis of racemic leuconolam **[(±)-1001a]**. My advisor Thomas R. Hoye and I are currently (Sep 2012) writing a manuscript about this study.

In 2006, Banwell and co-workers reported the only total synthesis of **1001a**,[5] which I will discuss in Section I-E. It is also noteworthy going over the syntheses of other analogues, **1002** and **1003** (Section I-D, just before the Banwell's synthesis of leuconolam). Later in this chapter, I will present my efforts in designing two different synthetic routes, and my most relevant progress toward the synthesis of leuconolam.

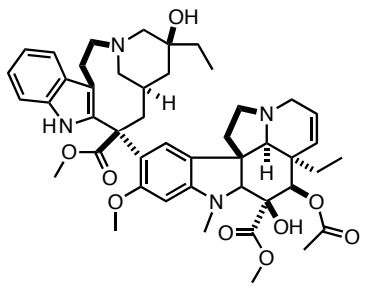
5. Banwell, M. G.; Beck, D. A. S.; Willis, A. C. *ARKIVOC* **2006**, 163–174.

I-B. Biological Activity of Leuconolam and Other Congeners

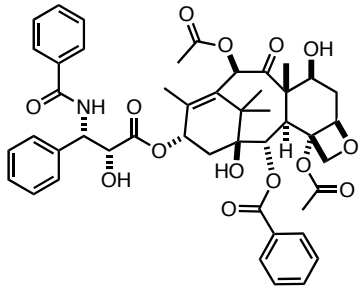
ORIAs (cf. Figure I-1) are reported as a new class of compounds having anti-mitotic (or spindle toxic) properties.[6] Their mode of action is described as a disruption of the tubulin-microtubule dynamics during the mitotic cell division. Tubulin, a protein involved in the formation of the mitotic spindles, is one of the main constituents of the microtubules, and is essential for cell replication.

Among ORIAs, (–)-rhazinilam (**1002**) is known to be the most potent.[7] Similar to the effect of vinblastine® (**1004**, Figure I-2), this alkaloid is able to induce a non-reversible assembly of tubulin. It also mimics the effect of paclitaxel (**1005**, the active ingredient of Taxol®) by inhibiting the disassembly of microtubules and inducing the formation of asters in mitotic cells and microtubule bundles in interphase cells.[6a,8a] More specifically, the required concentration of **1002** to inhibit 50% of the rate of microtubule assembly and disassembly (IC_{50} $value_{microtubule}$) has been reported as 18 and 2 μM,

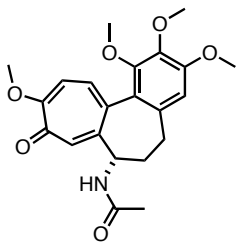
Figure I-2. Structures of Vinblastine®, Paclitaxel and Colchicine.



1004; vinblastine



1005; paclitaxel



1006; colchicine

6. (a) David, B.; Sévenet, T.; Morgat, M.; Guénard, D.; Moisand, A.; Tollon, Y.; Thoison, O.; Wright, M. *Cell Motil. Cytoskeleton* **1994**, *28*, 317–326. (b) Baudoin, O.; Guénard, D.; Gueritte, F. *Mini-Rev. Org. Chem*. **2004**, *1*, 333.
7. Décor, A.; Bellocq, D.; Thoison, O.; Lekieffre, N.; Chiaroni, A.; Ouazzani, J.; Cresteil, T.; Gueritte, F.; Baudoin, O. *Bioorg. Med. Chem*. **2006**, *14*, 1558–1564.
8. (a) David, B.; Sévenet, T.; Thoison, O.; Awang, K.; Païs, M.; Wright, M.; Guénard, D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2155–2158. (b) Thoison, O.; Guénard, D.; Sévenet ,T.; Kan-Fan, C.; Quirion, J. C.; Husson, H. P.; Deverre, J. R.; Chan, K. C.; Potier, *P. C. R. Acad. Sc., Paris* II **1987**, 157.

respectively. According to the same study, the required concentration of **1002** for 50% *in vitro* inhibition (IC_{50} value) of KB carcinoma cells is 0.7 μM.

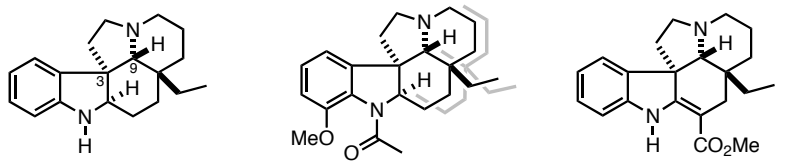
Bioactivity of (–)-rhazinal (**1003**) on tubulin is moderate compared to that of **1002**. The interaction of **1003** with tubulin has been observed at 2.0 μM, a concentration that is higher than what is observed for either **1004** or **1005**, yet similar to that for colchicine (**1006**, Figure I-2).[8a]

(–)-Leuconolam (**1001a**), on the other hand, has lower activity than other congeners. It has an IC_{50} value of minimum 100 μM against KB carcinoma cell line.[7] A hypothesis for the lack of potency is that the C-ring (cf. Figure I-1) is not aromatic.[8b]

I-C. Biosynthesis of Leuconolam

Leuconolam and other ORIAs shown in Figure I-1 share the structural complexity similar to that of the Aspidosperma alkaloids (related natural products are shown in Figure I-3).[9a-c] Those natural products exhibit a broad spectrum of bioactivity (from anti-cancer to anti-fungal), among which vinblastine (**1004**, cf. Figure I-2) is one of the most potent, and is currently in clinical use.[10]

Figure I-3. Related Aspidosperma Alkaloids.



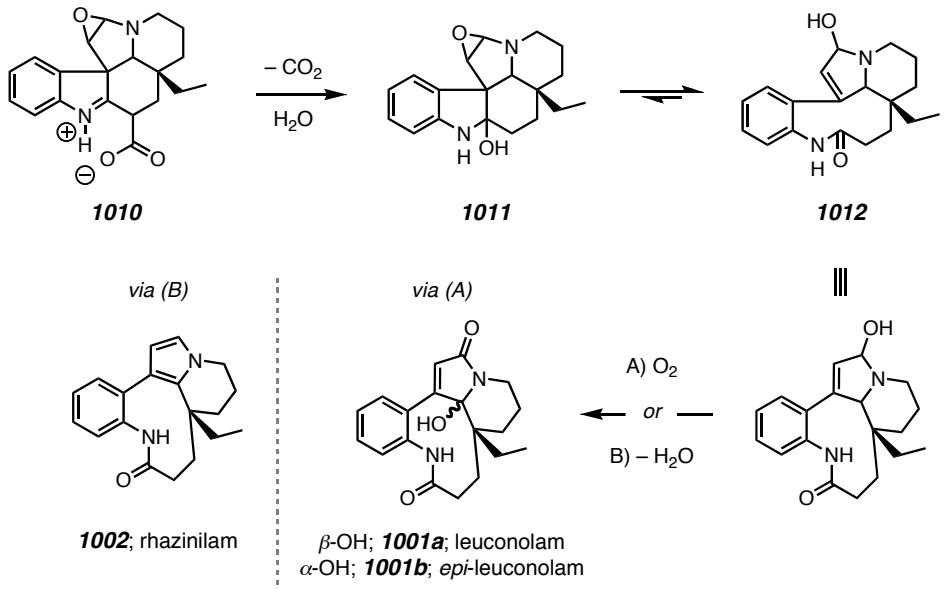
1007; aspidospermidine[9a] ***1008***; aspidospermine[9b] ***1009***; vincadifformine[9c]

To date, over 250 natural products belonging to this family have been reported.[11] All carbon quaternary centers (at the C3 and C9 positions, **1007**), as well as the monoterpenoid backbone (highlighted on **1008**) are the characteristics of most Aspidosperma alkaloids.

The biosynthesis of leuconolam (along with its epimer, **1001b**) has been hypothesized to occur starting from a related, proposed Aspidosperma alkaloid **1010** (Scheme I-1).[3a] Oxidation of the penultimate open-ring indole **1012** would then give **1001a-b** as well as rhazinilam (**1002**).

9. (a) Iyengar, R.; Schildknegt, K.; Morton, M.; Aube, J. *J. Org. Chem.* **2005**, *70*, 10645–10652. (b) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872–2973. (c) Djerassi, C.; Budzikiewicz, H.; Wilson, J.M.; Gosset., J.; Le Men, J.; Janot, M.-M. *Tetrahedron Lett.* **1962**, *3*, 235–239.
10. *The Alkaloids: Chemistry and Biology*; Brossi, A., Suffness, M., Eds.; Academic Press: San Diego, CA **1990**, *37*.
11. Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, **1998**, *51*, Chapter 1.

Scheme I-1. Proposed Biosynthesis of Three ORIAs, **1001a-b** and **1002**.



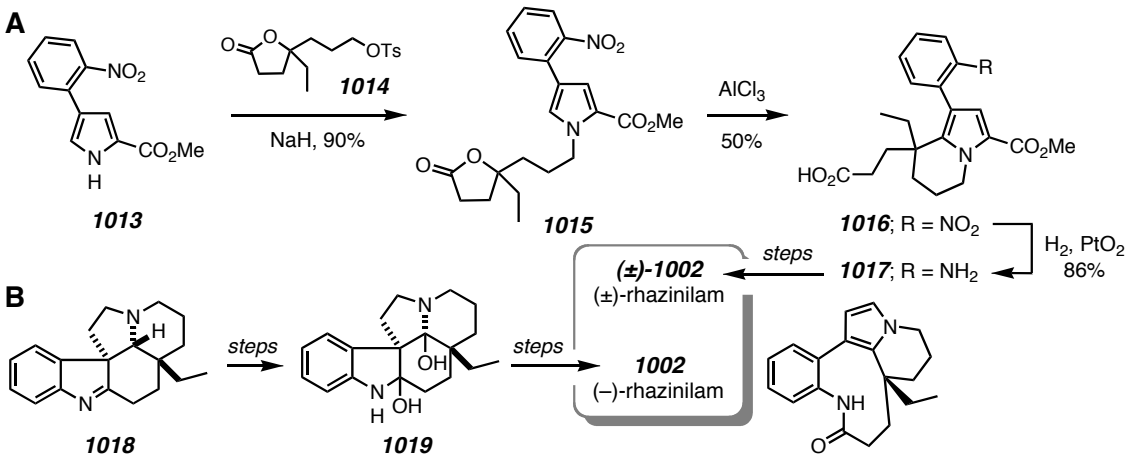
I-D. Total Syntheses Reported for the Analogues of (–)-Leuconolam

Since the early 2000's, there has been a great deal of interest in the synthetic community for developing elegant strategies to construct the carbon framework of the ORIAs (leuconolam congeners, cf. Figure I-1). Transition-metal-catalyzed C-C bond forming reactions (e.g., macrocyclizations) and C-H bond functionalizations[12] have been implemented in state-of-the art synthesis of the ORIAs, more specifically, (–)-rhazinilam (**1002**). After Smith's inaugural accomplishment,[13] **1002** has become the focus of several leading laboratories. Key transformations reported by these research groups for the total syntheses of **1002** as well as of **1003** (either in enantiomerically enriched or racemic form) will be discussed in chronological order.

I-D-1. Smith's Synthesis of (±)-Rhazinilam [(±)-1002].

In 1973, G. F. Smith and co-workers reported the first total synthesis of racemic rhazinilam [**(±)-1002**, Panel A in Scheme I-2].[13]

Scheme I-2. Highlights of the Smith's Total Synthesis of **(±)-1002** and Semi-Synthesis of **1002**.



12 For recent reviews about such strategies, see (a) Chen, D. Y.-K.; Youn, S. W. *Chem. Eur. J.* **2012**, *18*, 9452–9474. (b) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960–9009.

13. Ratcliffe, A. H.; Smith, G. F.; Smith, G. N. *Tetrahedron Lett.* **1973**, *14*, 5179–5184.

Their work also involved a semi-synthesis of **(–)-1002** from a related Aspidosperma alkaloid, (+)-1,2-dehydro-aspidospermidine (**1018**, and through the bis-hemiaminal **1019**, Panel B). They practiced oxidation-dehydration chemistry on this biomimetic precursor, which enabled them to obtain spectral information of the key intermediates also involved in their total synthesis.

An *N*-alkylation of the sodium salt of the starting pyrrole **1013** with the heptanoic acid γ-lactone **1014** gave **1015**. Subsequent Friedel-Crafts reaction of the $AlCl_3$ activated lactone, provided the piperidine **1016**. Following a four-step sequence [(i) reduction of nitro group; (ii) DCC mediated lactamization of the resulting amine; (iii) saponification of the methyl ester; and (iv) decarboxylation] provided the target alkaloid **(±)-1002**.

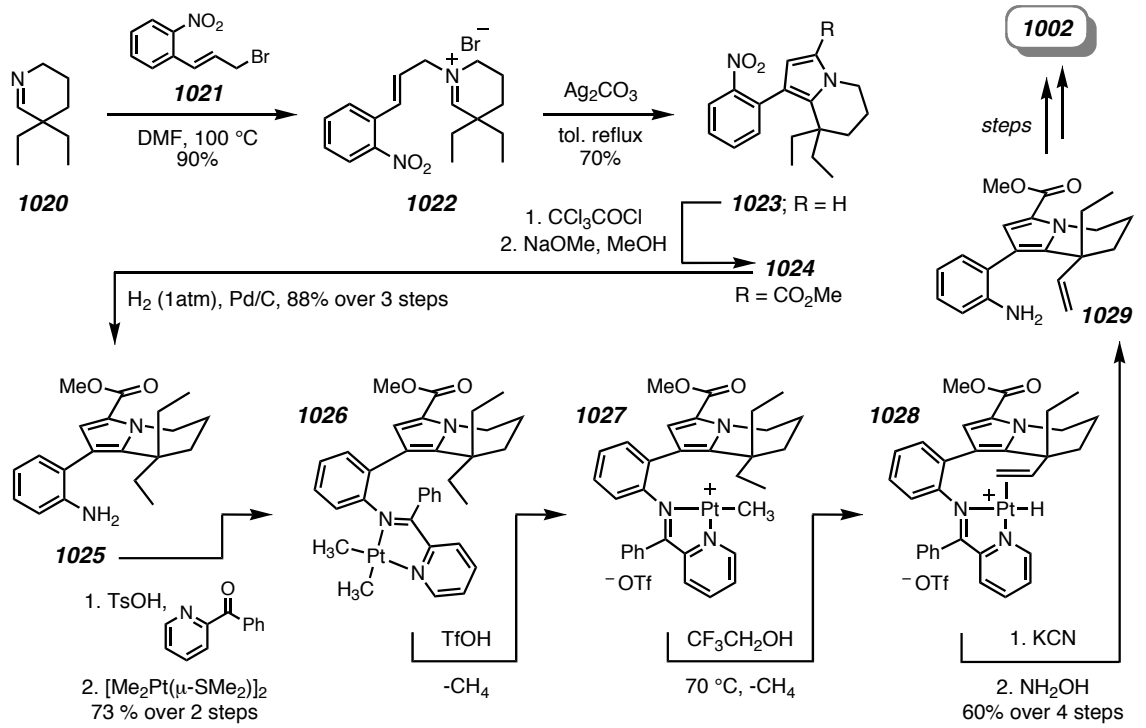
I-D-2. Sames's Synthesis of (–)-Rhazinilam (1002).

Sames and co-workers reported a synthesis of racemic **1002** in 2000, and disclosed an asymmetric version two years later. The key transformations in each study are Ag_2CO_3 mediated pyrrole synthesis and selective C-H bond oxidation of a pro-chiral ethyl group (Scheme I-3).[14] The asymmetric control during the oxidation chemistry was achieved using an oxazolinyl ketone auxiliary. The final carbon framework was then completed via a macrolactamization. Because the general approach for both racemic and asymmetric syntheses are the similar, here I will only be focusing on the highlights presented on the latter study.

The imine **1020** was first *N*-alkylated with nitrocinnamyl bromide (**1021**), and the resulting imminium bromide salt was treated with Ag_2CO_3 to form the pyrrole **1023**. Subsequent Firedel-Crafts acylation, methanolysis, and the reduction of the nitro group provided the aniline **1025**.

14. Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900–6903.

Scheme I-3. Highlights from the Sames's Synthesis of **1002**.



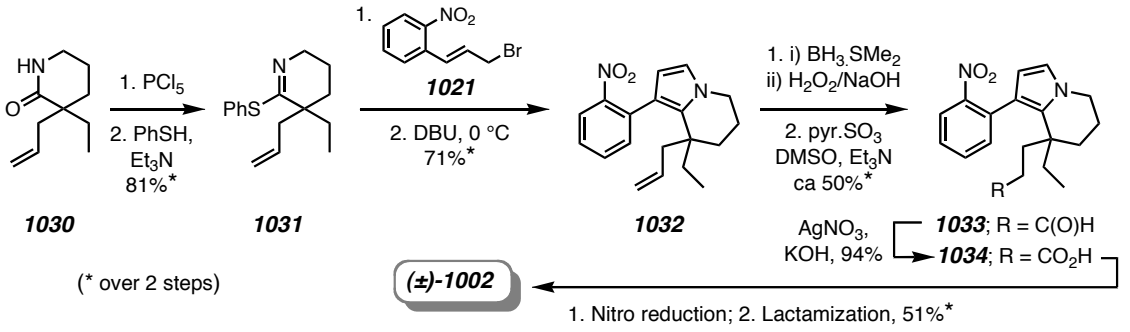
The key organoplatinum intermediate **1026** was synthesized from the aniline **1025** via the condensation with 2-benzoylpyridine and complexation of the resulting Schiff base with $[Me_2Pt(\mu\text{-}SMe_2)]_2$. Methane was liberated from **1026** upon treatment with 1 equiv of TfOH, and the triflate salt **1027** was isolated.

C-H bond oxidation to give intermediate **1028** was then achieved by another protic exclusion of a methane molecule from the complex, thereby converting the proximal (to aniline subunit) ethyl group to a vinyl group. Now the double bond functionality in hand (**1029**), The authors performed a one-carbon homologation through $OsO_4/NaIO_4$ oxidation and carbonylation. The subsequent amino acid derivative was then lactamized to afford enantio-enriched rhazinilam (**1002**).

I-D-3. Magnus's Synthesis of (±)-Rhazinilam (1002).

In 2001, Magnus and co-workers reported the total synthesis of racemic rhazinilam [**(±)-1002**] starting from the piperidinone **1030** (Scheme I-4).[15a]

Scheme I-4. Highlights from the Magnus's Synthesis of **(±)-1002**.



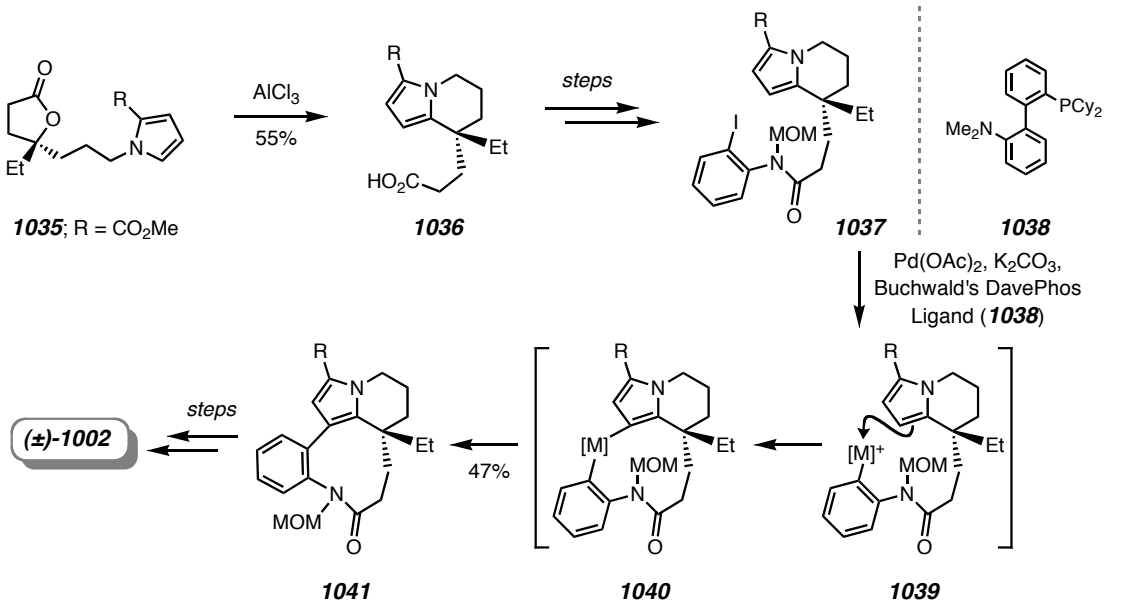
The key thiophenyl imino ether **1031**, which was obtained via a two-step protocol (1. PCl_5; 2. PhSH) from **1030**,[15b] was first allylated using **1021**, then, converted to the pyrrole **1032** under the basic conditions. Hydroboration on the allyl group followed by an oxidative work-up, and a Parikh-Doering oxidation of the resulting primary alcohol afforded the aldehyde **1033**, which was further oxidized to the carboxylic acid **1034**. Reduction of the nitro benzene and subsequent lactamization of the resulting aniline under Mukaiyama conditions completed the synthesis of **(±)-1002**.

I-D-4. Trauner's Approach to (±)-Rhazinilam (1002).

Trauner and co-workers reported the synthesis of (±)-rhazinilam [**(±)-1002**] via a palladium mediated C-H arylative macrocyclization on the protected anilide (**1037**, Scheme I-3).[16] A previously optimized route reported by Smith[13] provided the racemic lactone **1035** (after *N*-alkylation of **1014** cf. Scheme I-2), where the quaternary carbon center had been constructed. The pyrrole group underwent an $AlCl_3$-mediated intramolecular Friedel-

15. Magnus, P.; Rainey, T. *Tetrahedron* **2001**, *57*, 8647–8651.
16. Bowie, A. L.; Hughes, C. C.; Trauner, D. *Org. Lett.* **2005**, *7*, 5207–5209.

Scheme I-5. Highlights from the Trauner's Synthesis of **1002**.



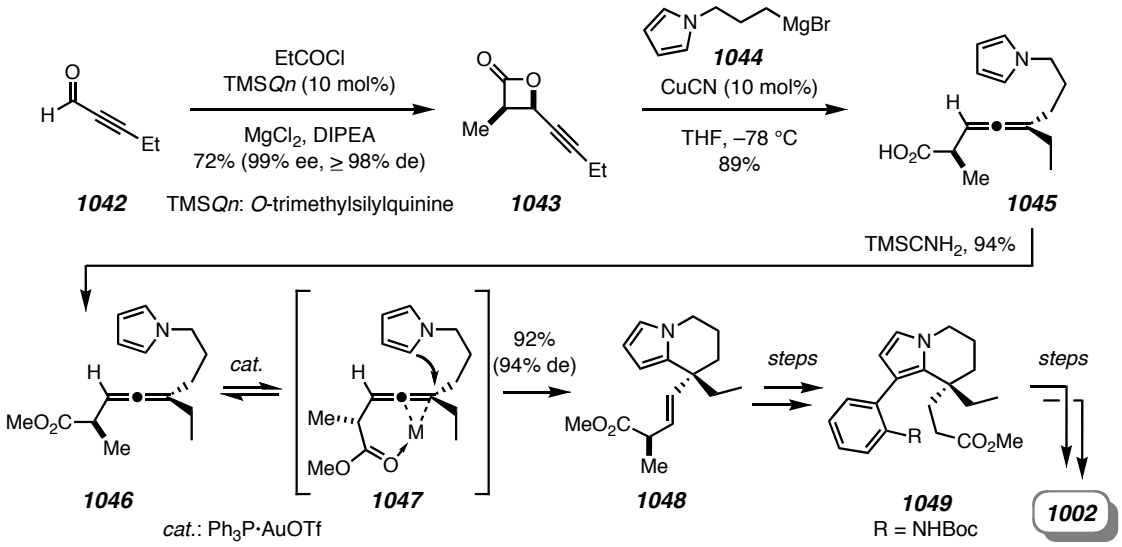
Crafts alkylation reaction affording the piperidine **1036**. Upon further decoration (amidation followed by *N*-MOM protection), the macrocyclization precursor **1037** was synthesized. After screening a number of Pd(II)-Pd(0) catalytic conditions, the researchers accomplished the desired aryl-aryl coupling under $Pd(OAc)_2/K_2CO_3$ in the presence of Buchwald's DavePhos ligand (**1038**, 10 mol %). The key cyclization mechanism was proposed to be an intramolecular C3-palladation of the pyrrole moiety in **1039**, followed by a reductive elimination on the intermediate **1040** to furnish the lactam **1041**. The authors also commented that the use of an electron-rich ligand like **1038** facilitated both a faster oxidative addition and a more reactive cationic Pd(II) species after a halide dissociation.

One important element to the synthesis reported by the Trauner group is that the MOM amide protecting group proved essential for the success of this cyclization. They observed only the deiodinated material with the free amide as the substrate.

I-D-5. Nelson's Approach to (–)-Rhazinilam (1002).

Nelson and co-workers reported the synthesis of enantio-enriched **1002** in 2006.[17] They successfully translated the allene chirality to the annulation event via a gold triflate catalyzed pyrrole-allene addition of the key tetrahydroindolizine **1045** (Scheme I-6).

Scheme I-6. Highlights from the Nelson's Synthesis of **1002**.



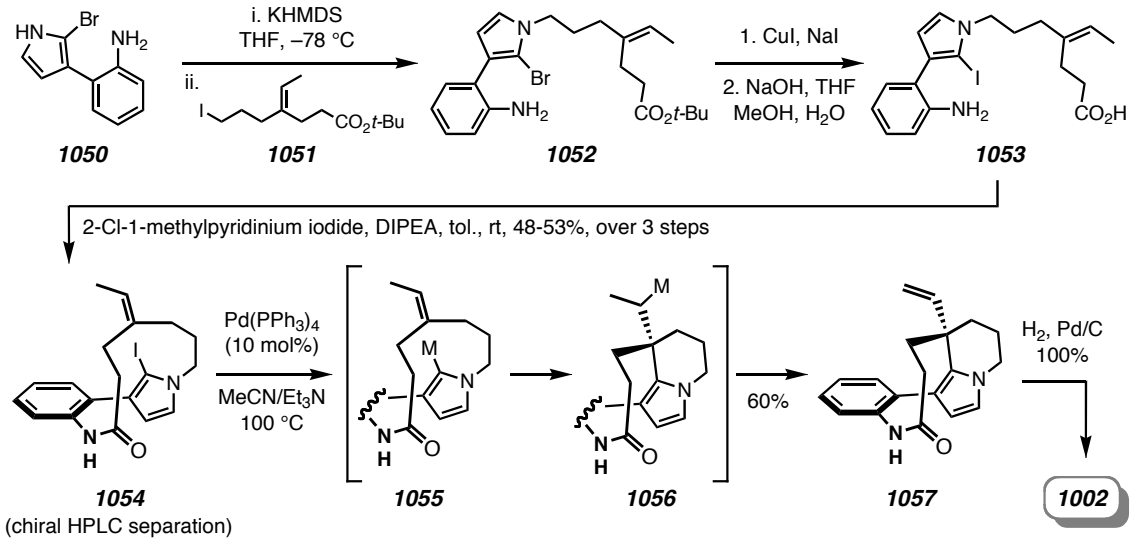
Starting with 2-pentynal (**1042**), a highly diastereo- and enantioselective [2+2] cycloaddition was realized by using a chiral alkaloid, *O*-TMS-quinine. The resulting disubstituted *β*-lactone **1043** was ring opened via a Cu(I) catalyzed S_N2' mechanism with the Grignard reagent **1044** to provide the allene **1045**. After searching among various gold catalysts, $Ph_3P{\cdot}AuOTf$ (5 mol%) found to be the optimal system and the difficult quaternary carbon center was established with high diastereoselectivity (94% de) in the piperidine **1048**. Further functional group transformations led to the amino ester **1049**. This was converted to the corresponding amino acid, which was subsequently cyclized to (–)-rhazinilam (**1002**).

17. Liu, Z.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc*. **2006**, *128*, 10352–10353.

I-D-6. Zakarian's Approach to (–)-Rhazinilam (1002).

Zakarian and co-workers have reported a synthesis of **1002**,[18] where they studied a bigger-to-smaller-ring-cyclization strategy (Scheme I-7).

Scheme I-7. Highlights from the Zakarian's Synthesis of **1002**.



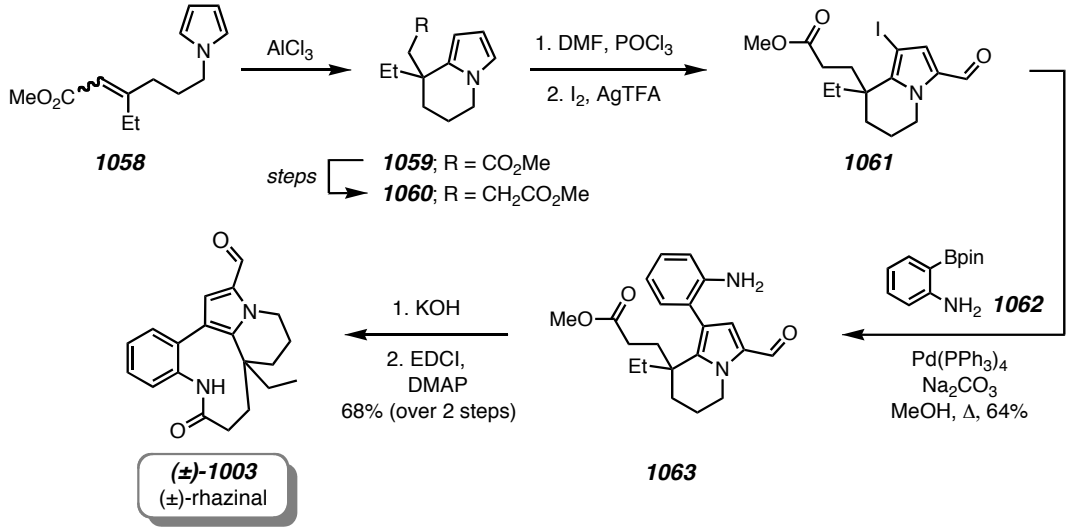
The synthesis of the 13-membered lactam **1054** began with an *N*-alkylation of the pyrrole **1050**, which was prepared by a regioselective bromination of the known protio analog.[19] The resulting bromide was transformed to the iodide using CuI/NaI, and the *tert*-butyl ester moiety was then saponified to the acid **1053**. Use of the Mukaiyama reagent (2-chloro-1-methylpyridinium salt) afforded the axially chiral macrolactam **1054**, and its desired enantiomeric content (*R*-isomer) was enriched by a chiral HPLC separation. With the enantioenriched iodide **1054** in hand, the authors performed a transannular Heck coupling under $Pd(PPh_3)_4$ catalysis to install the final carbon connectivity on **1057**. Reduction of the vinyl group under the standard hydrogenation conditions provided the title natural product (**1002**).

18. Gu, Z.; Zakarian, A. *Org. Lett.* **2010**, *12*, 4224–4227.
19. Morrison, M. D.; Hanthron, J. J.; Pratt, D. A. *Org. Lett.* **2009**, *11*, 1051–1054.

I-D-7. Banwell's Approach to (±)-Rhazinal [(±)-1003].

The research laboratory of Banwell has been studying the total syntheses of the ORIAs since the early 2000s. The group has reported[20] a synthesis of racemic rhazinal [**(±)-1003**] by highlighting a Michael addition strategy on the starting **1058** (Scheme I-8). Banwell presented the asymmetric version of this approach for the synthesis of other ORIAs, which I will discuss entirely in Section I-E.

Scheme I-8. Highlights from the Banwell's Synthesis of **(±)-1003**.



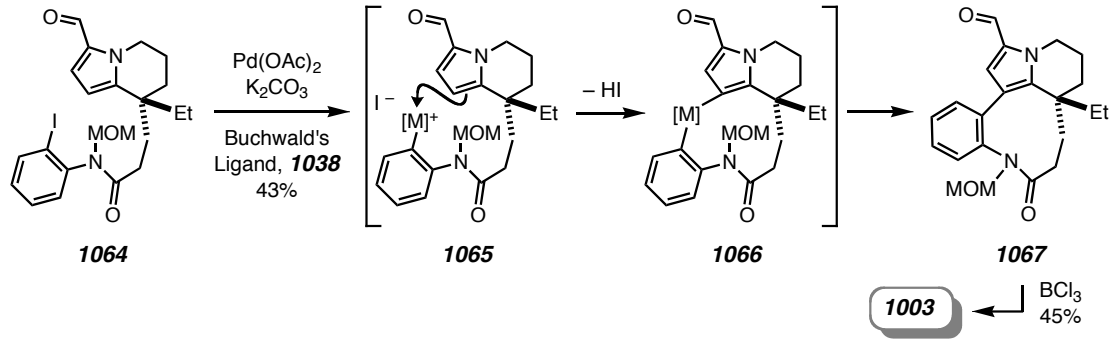
The Michael addition of the C2-pyrrole to the disubstituted acrylate under $AlCl_3$ activation afforded the racemic **1059**, which was then one-carbon homologated to **1060**. A Vilsmeier-Haack formylation and a subsequent regioselective iodination provided the amino ester precursor **1061**. The anilino functionality was constructed upon coupling with the organoboron species **1062** under the standard Suzuki cross-coupling reaction conditions. Finally, the target alkaloid **(±)-1003** was isolated in 68% yield from **1063**, after the KOH treatment and an EDCI mediated unimolecular amide bond formation.

20. Banwell, M. G.; Edwards, A. J.; Jolliffe, K. A.; Smith, J. A.; Hamel, E.; Verdier-Pinard, P. *Org. Biomol. Chem*. **2003**, *1*, 298–305.

I-D-8. Trauner's Approach to (–)-Rhazinal (1003).

Trauner and co-workers have reported the synthesis of (–)-rhazinal (**1003**), following a similar synthetic route to that designed for **1002**.[21a] C-H arylation of the pyrrole group was again the main highlight of the total synthesis of **1003** (Scheme I-9). This time, the cyclization precursor **1064**, the formylated analog of **1037** (cf. Scheme I-5), was transformed to the protected lactam **1067** in 43% yield.

Scheme I-9. Highlights from the Trauner's Synthesis of **1003**.

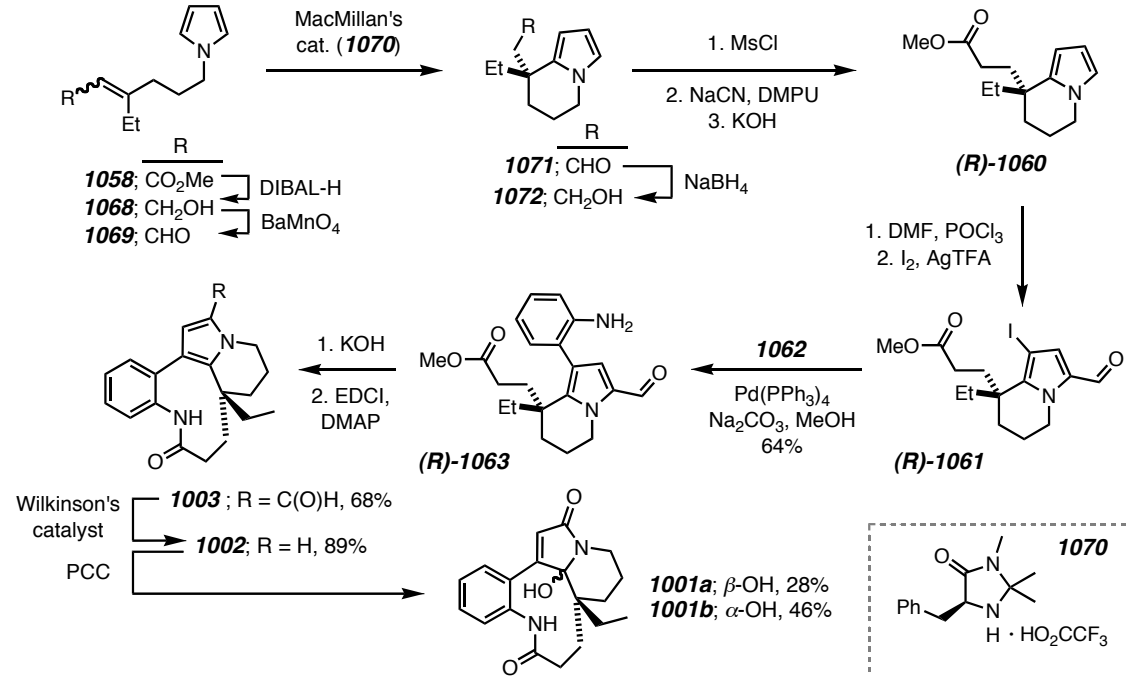


21. (a) Bowie, A. L. Jr.; Trauner, D. *J. Org. Chem.* **2009**, *74*, 1581–1586. (b) For arene-arene Heck type oxidative couplins, see Ref 21a.

I-E. Banwell's Synthesis of (–)-Leuconolam (1001a)

In 2006, Banwell and co-workers reported the first total synthesis of **1001a** (Scheme I-10).[5]

Scheme I-10. Banwell's Synthesis of (–)-Leuconolam (**1001a**, Part 1).

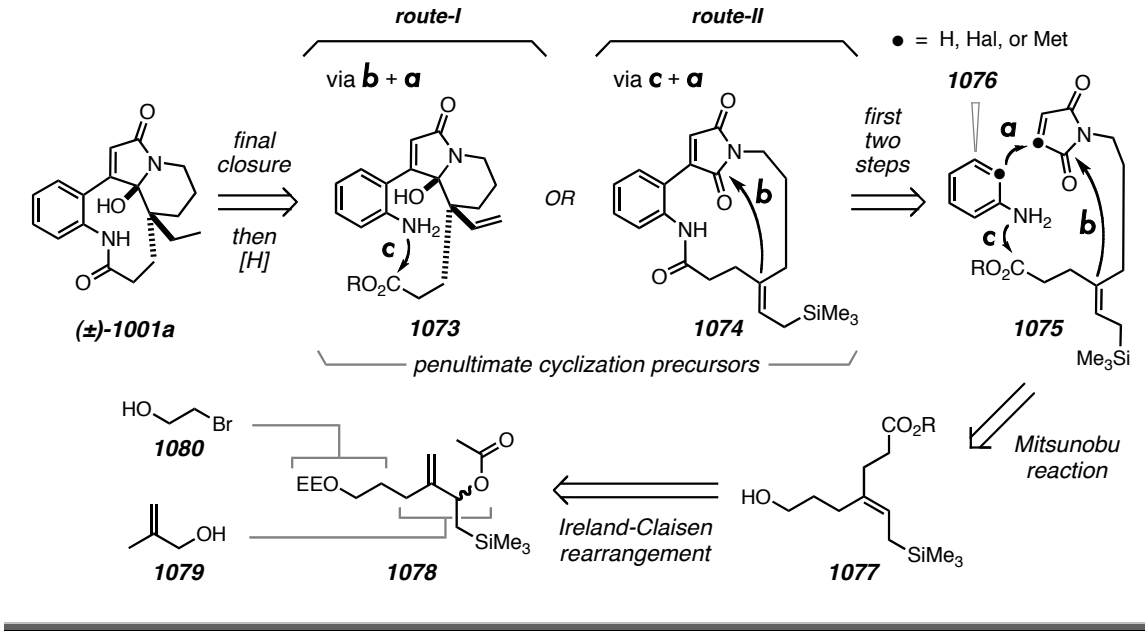


Banwell's approach toward leuconolam **1001a** is very similar to that of the previously reported **1003**. The asymmetric control during Michael addition step was achieved on **1069** using the MacMillan's organocatalyst **1070**. A series of functional group transformations for the desired one-carbon homologation gave ***(R)*-1060** (cf. Scheme I-8 for the preparation of the racemic analog). Subsequent formylation and iodination furnished the arene-alkene coupling precursor ***(R)*-1061**. The amide bond formation of the amino acid derived from ***(R)*-1063**, and removal of the formyl group afforded rhazinilam (**1002**). A final PCC oxidation of **1002** proceeded to give **1001a** in 28% yield along with its epimer, **1001b** (1:1.7 ratio).

I-F. Synthetic Design

Our synthetic design toward the molecular framework of leuconolam (**1001a**) encompasses three key bond-forming events, namely arene-alkene coupling (step **a** in Scheme I-11), intramolecular allylative cyclization (step **b**), and amide bond formation (step **c**) on a pivotal intermediate **1075**. Any two of these processes can be utilized to access the penultimate cyclization precursors, **1073** (via steps **b** + **a**) or **1074** (via steps **c** + **a**). Following two separate routes to get each precursor (through *route-I* or *route-II*), we envision a final ring closure (via step **c** or **b**, respectively) toward the target molecule **(±)-1001a**. The imide **1075** is obtained from the alcohol **1077** via a Mitsunobu reaction. The alcohol **1077** can be synthesized by an S_N2 displacement of the bromide **1080** with the allylic carbanion of methallyl alcohol (**1079**), followed by an Ireland-Claisen reaction of the resulting acetate allyl acetate **1078**.

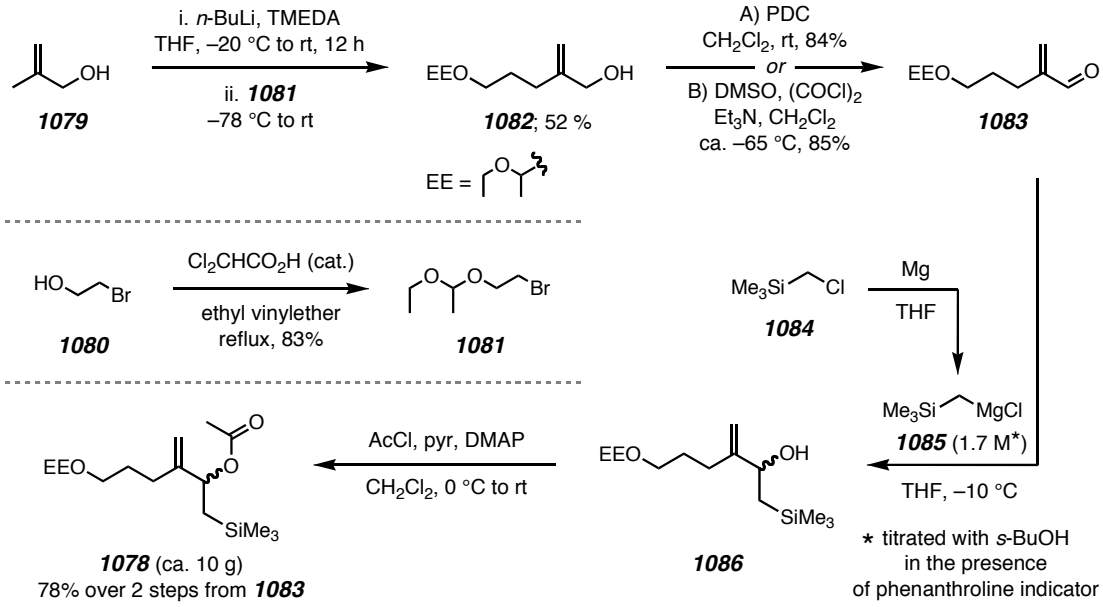
Scheme I-11. Retrosynthetic Analysis of Hoye's Approach Toward (–)-Leuconolam (**1001a**).



I-G-1. Results and Discussion (*Route-I*)

We started with the synthesis of the Ireland-Claisen rearrangement precursor **1078** by homologating the allylic carbon of commercially available methallyl alcohol (**1079**, Scheme I-12). Allylic C-alkylation of **1079** with **1085**[22] was achieved following a procedure reported by Trost,[23] where the alcohol was carefully treated with 2.2 equiv of *n*-BuLi in the presence of TMEDA. The alkylation occured at the more reactive allylic position (the C-terminus) affording the elongated alcohol **1082** in 52% isolated yield.

Scheme I-12. Synthesis of The Claisen-Ireland Rearrangement Precursor) **1078**.



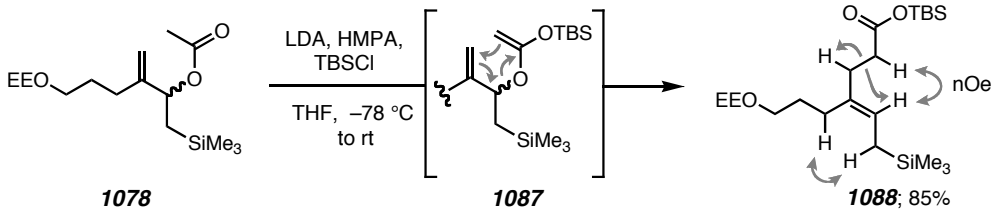
To functionalize the eastern side of **1082**, we performed a 3-step protocol: (i) Swern oxidation (preferred over the use of PDC for a large scale reaction setup); (ii) Grignard addition using ((trimethylsilyl)methyl)magnesium chloride (**1085**); and (iii) Acylation of the resulting allylic alcohol (**1086**)]. Pleasingly, the desired allylic ester **1078** was obtained in 78% yield from **1083** and in ca. 10-gram scale. The projected

22 (a) Vliet, M. J. van; Visscher, J.; Schwartz, Alan W, *Nucleosides & Nucleotides* **1994**, *13*, 2113–2124. (b) Boeckman, R. K.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997–4006.

23. Trost, B. M.; Shi, Y. *J. Am. Chem. Soc*. **1993**, *115*, 9421–9438.

Ireland-Claisen rearrangement installed the desired C=C double bond at the β-position of the silyl moiety. After screening various conditions, use of TBSCl[24a] as the silylating agent[24b] and HMPA led to a facile [3,3] sigmatropic rearrangement providing the TBS-ester **1088** in high yield (Scheme I-13). The stereochemistry of the alkene was determined via nOe experiment.

Scheme I-13. Ireland-Claisen Rearrangement of **1078**.

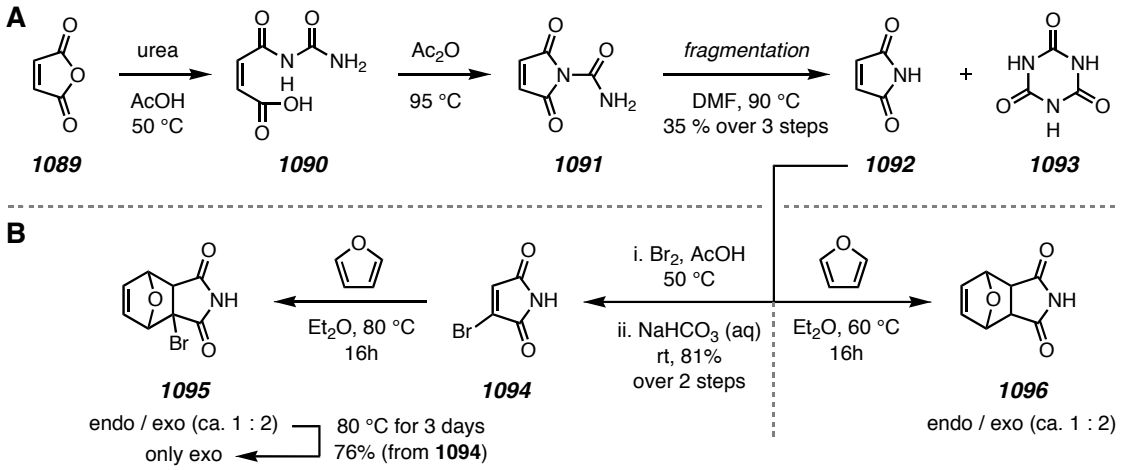


1078 ***1087*** ***1088***; 85%

Now the stage was set for operating on the western side of **1088**, more specifically, converting the OEE-ether to the *N*-alkyl maleimide (e.g., **1075**, cf. Scheme I-12). We determined to access the desired maleimide functionality via a Mitsunobu displacement using bromomaleimide (**1094**, Panel A in Scheme I-14). The bromination precursor, maleimide (**1092**), is an expensive chemical. Therefore, we decided to synthesize it (in large quantity) from readily available maleic anhydride (**1089**) following a three-step protocol.[25] Cyanuric acid (**1093**), the by-product formed by trimerization of the cleaved isocyanic acid, was easily removed as the DMF-insoluble material. Performing a dibromination-elimination sequence, we obtained bromo-maleimide (**1094**) in high yield (81%).

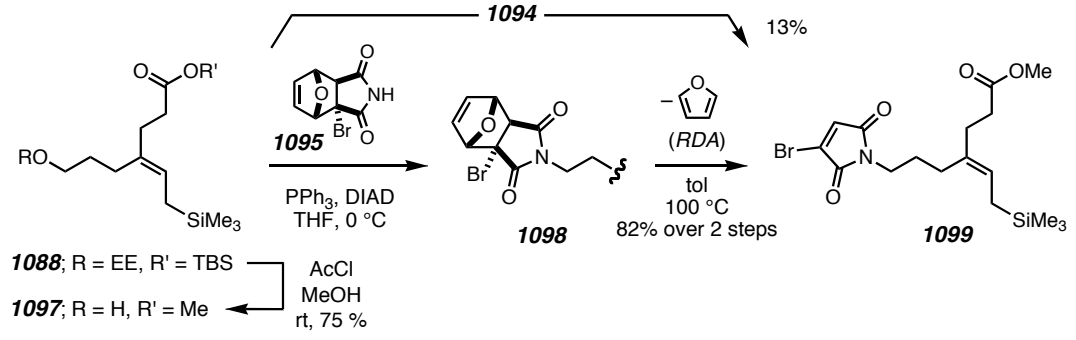
24. (a) Initial attempts using TMSCl resulted in essentially full recovery of the starting ester **1078** and trace amount of the alcohol **1086**. (b) Wilson, S. R.; Price, M. F. *J. Am. Chem. Soc*. **1982**, *104,* 1124–1126.
25. Tawney, P. O.; Snyder, R. H.; Bryan, C. E.; Conger, R. P.; Dovell, F. S.; Kelly, R. J.; Stiteler, C. H. *J. Org. Chem*. **1960**, *25*, 56–60.

Scheme I-14. Synthesis of the Mitsunobu Nucleophiles **1095** and **1096**.



Next, we opted to convert **1088** to a primary alcohol for the projected Mitsunobu reaction (Scheme I-15). We subjected the substrate to methanolic HCl [sub-stoichiometric amount of AcCl (0.3 equiv)]. Our TLC analysis revealed that the deprotection event occurred more rapidly than the esterification.

Scheme I-15. Synthesis of the Allylative Ring Closure Precursor, the Bromoimide **1094**.



Pleased with isolating **1097** in this one pot process, we attempted the Mitsunobu displacement using bromomaleimide (**1094**). Despite employing previously optimized

conditions for maleimide (**1092**),[26] we isolated the desired bromoimide **1094** in surprisingly low yield (13%). We noticed a considerable level of depletion of **1094** during the course of the reaction. That was also the case (yet to a lesser extend) when maleimide (**1094**) itself was used in a similar reaction setting. We hypothesized that **1094** was consumed through a major side reaction (likely polymerization) under the basic Mitsunobu conditions (PPh_3-DIAD). More specifically, a chain reaction could proceed via (self) conjugate addition of the deprotonated **1094**. To circumvent this problem, we masked its double bond of through a Diels-Alder (DA) reaction with furan (Panel B in Scheme I-14), and used the exo-adduct **1095** to displace the primary hydroxyl group (Scheme I-15). A toluene solution of the resulting imide **1098** was heated at 100 °C for 24 h to facilitate a retro-Diels-Alder (RDA) reaction that unmasked the double bond. Following this detour, we obtained the desired bromomaleimide **1099** in 82% overall yield from **1097**.

In order to test the feasibility of the allylative ring closure (or allylation), we synthesized a model compound **1100** (Table I-1) by a similar strategy using the known imide **1096**[27] (cf. Scheme I-14). With this symmetric imide, we intended to analyze the product outcome in the absence of a possible regioselectivity issue.

We screened a number of Lewis-Acids (LAs) to facilitate the key allylative ring closure (Table I-1). Many of the conditions proved to be ineffective to promote a nucleophilic attack to the carbonyl carbon providing the carbinolamide **1101**. The main obstacle we encountered was the formation of the terminal alkene **1102**; a by-product resulted from a proto-desilylation event. It is not obvious how a destructive proton source is generated. On the other hand, addition of the proton scavengers such as DIPEA, 2,6-lutidine or tetramethylsilane (TMS), did not lead to any conversion of the starting material. Gratifyingly, use of aluminum-based LAs ($MeAlCl_2$ or Me_2AlCl, entries 14 and 15, respectively) facilitated the ring closure smoothly. Furthermore, we did not detect the presence of **1102** in the crude reaction material.

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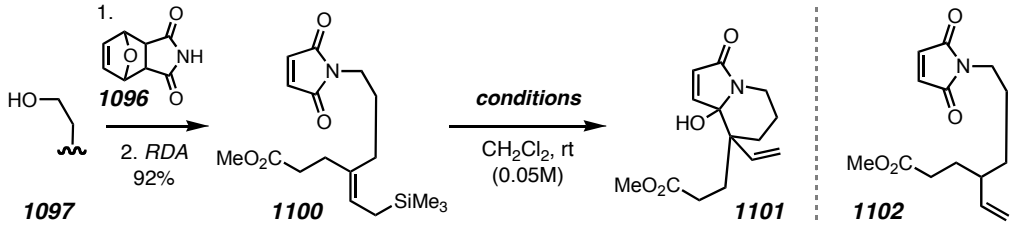
26. Walker, M. A. *J. Org. Chem.* **1995**, *60*, 5352–5355.
27. Zhu, J.; Kell, A. J.; Workenti, M. S. *Org. Lett.* **2006**, *8*, 4993–4996.

Table I-1. Exploring the LA Scope for the Key Allylative Cyclization.[a,b]

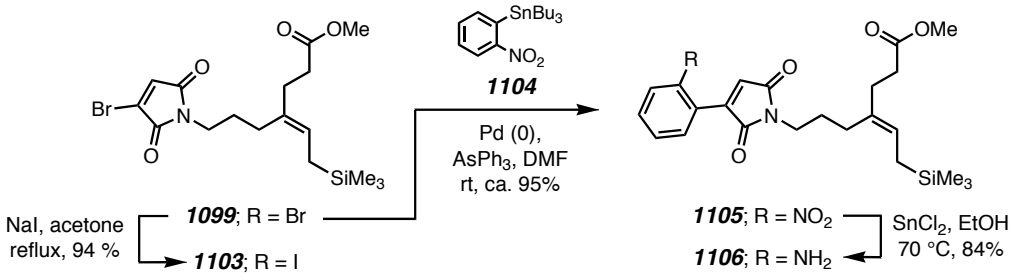


entry	Lewis acid	additive	**1100**[c]	**1101**[c]	**1102**[c]
1	TBSOTf	–	–	–	✔
2	TMSOTf	–	–	–	✔
3	TMSOTf	DIPEA	✔	–	–
4	TMSOTf	2,6-lutidine	✔	–	–
5	TMSOTf	TMS	✔	–	–
6	BF_3•OEt_2	–	–	–	✔
7	BF_3•OEt_2	DIPEA	✔	–	–
8	BF_3•OEt_2	2,6-lutidine	✔	–	–
9	BF_3•OEt_2	TMS	✔	–	–
10	pyrH+Br_3-	–	✔	–	–
11	Ti(Oi-pr)$_4$	–	✔	–	–
12	$TiCl_4$	–	–	–	✔
13	$TiCl_4$	DIPEA	✔	–	–
14	$MeAlCl_2$	–	–	✔	–
15	Me_2AlCl	–	–	✔	–

(a) Check mark indicates the isolated crude material after 10-60 min of reaction time, according to TLC analysis. (b) Reaction mixtures were quenched by addition of saturated NH_4Cl solution. (c) Yields were not determined. Only a qualitative analysis (by ^1H NMR of the crude samples) was made for each entry.

Once we discovered the proper LA activators (Me_2AlCl and $MeAlCl_2$[28]), we turned our attention to the same transformation with **1099**. Using other related analogues would also be critical in our synthetic route. Therefore, we derivatized the monobromo imide **1099** to a variety of cyclization precursors, such as the iodide **1103**, the nitro benzene **1105** and the aniline **1106** (Scheme I-16).

Scheme I-16. Synthesis of the Analogues of **1099**.

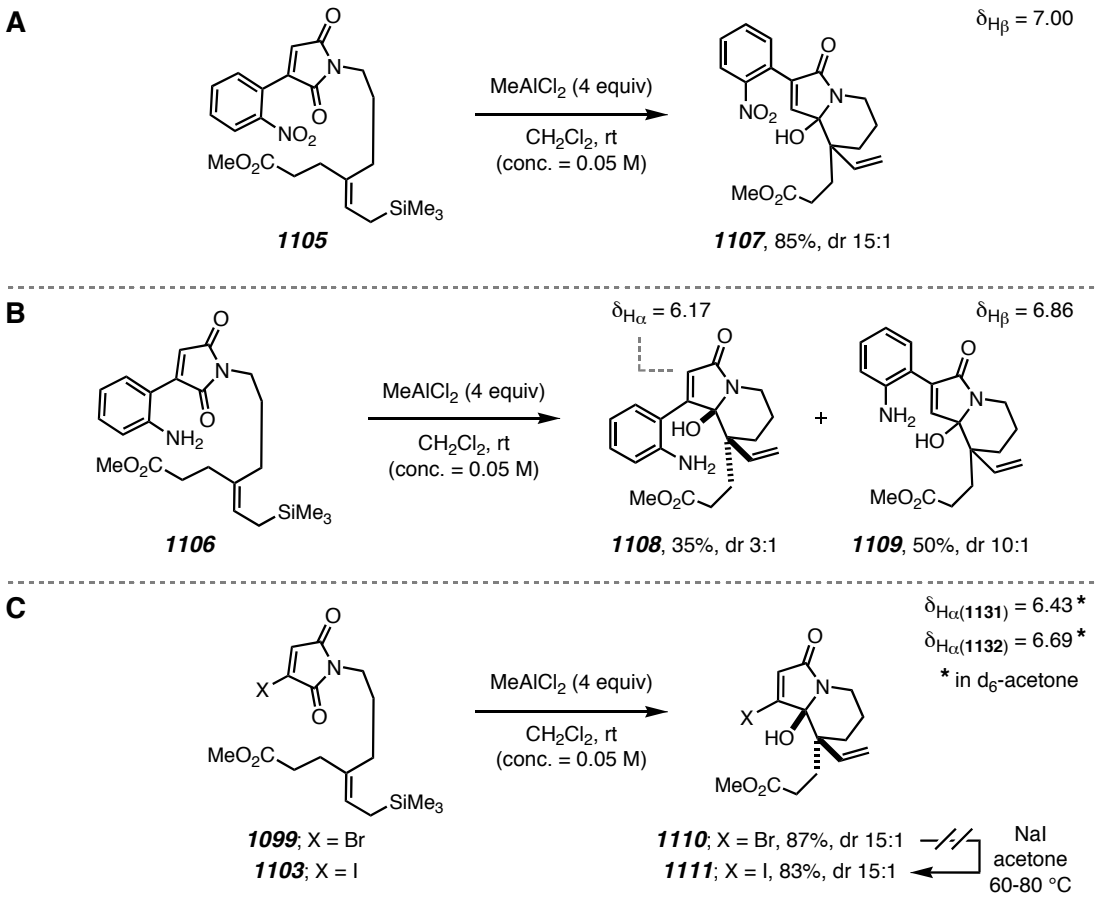


A Finkelstein reaction of **1099** with sodium idodide gave **1103**, which underwent a Stille cross-coupling with *o*-(tributylstannyl)-nitrobenzene (**1104**)[29] to provide **1105**. Reduction of the nitro group in **1105** was accomplished by $Sn(II)Cl_2$ in EtOH at elevated temperature to afford the anilino imide **1106**.

With a number of allylation precursors in hand, we began to explore their conversion to the corresponding carbinolamides using $MeAlCl_2$ (Scheme I-17). While the nitrophenyl imide **1105** (Panel A) exclusively produced the undesired regioisomeric carbinolamide **1107** with high diastereoselectivity (dr = 15:1), the aminophenyl counterpart **1106** (Panel B) provided a ca. 1:1.5 mixture of the desired and the undesired regioisomeric products **1108** and **1109**, respectively. One can propose that the aryl group in **1105** creates a steric bulk around the proximal carbonyl and against the alkyl

28. Because $MeAlCl_2$ was more readily available than Me_2AlCl in our laboratory, we chose to use the former reagent for the rest of the allylation experiments.
29. (a) *o*-(Tributylstannyl)-nitrobenzene (**1104**) was obtained in 83% yield form 2-iodo nitrobenzene according to a modification of the reported protocol by Kosugi, M.; Ohya, T.; Migita, T. *Bull. Chem. Soc. Jpn*. **1983**, *56*, 3855–3856. (b) See also Chapter II for the experimental details.

Scheme I-17. Allylative Allylation Reactions of Imides **1099**, **1103**, **1105** and **1106**.[a]



(a) Chemical shift values reported for measurements in $CDCl_3$ solvent unless otherwise indicated.

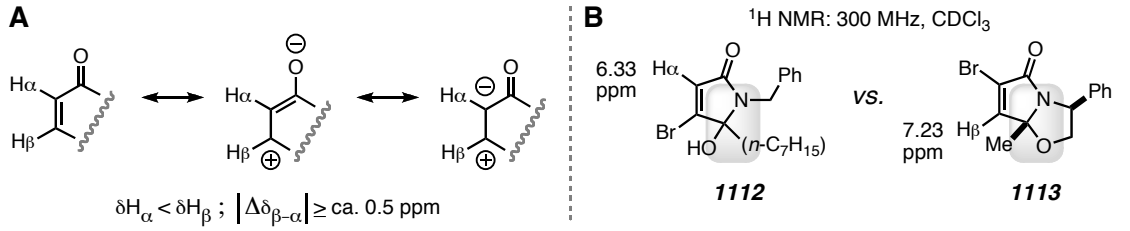
chain that needs to approach toward the carbonyl moiety. The electron-withdrawing nature of the nitro group increases the electrophilic character of the carbonyl center that is distant to the aromatic ring. Therefore, steric and electronic effects reinforce each other in directing the nucleophilic attack on the remote carbonyl. On the other hand, the free anilino-NH_2 in **1106** compromises that with its electron-donating nature. Furthermore, a possible chelation of the amino group with the aluminum center may activate the proximal carbonyl to some extent. However, the steric effect can still favors the attack on the distal reactive carbon. As a near future goal, we plan to run computational experiments to better ascertain the relative reactivity observed for each

mode of product formation.

To our delight, under the similar intramolecular allylation conditions, we exclusively obtained the desired regioisomers **1110** and **1111** from the halogenated (Br and I) imides **1099** and **1103**, respectively. Although it is not so clear, one rationale for that preference can be that each substituent can π-back-donate their unpaired electrons to the empty π∗ orbital of the C=C double bond of the imide. This will lower the electrophilicity of the distal carbonyl carbon, whereas the steric effect has minor impact.

Intramolecular allylation products **1107-1111** (cf. Scheme I-17) each give a singlet at 6-7 ppm region for their α-(amide)-protons in ^{1}H NMR spectrum. The chemical shift of the singlet is (to our convenience) the most diagnostic element in defining the regioisomers. There is generally a large chemical shift difference between H_α and H_β of the α,β-unsaturated carbonyls (Panel A in Figure I-4). Therefore, we expect the desired regioisomer, whose singlet peak originates from the proton that is on the C_α, has a significantly lower chemical shift value.

Figure I-4. Comparison of H_α *vs.* H_β Chemical Shifts of Generic (Panel A) and Specific (Panel B) α,β-Unsaturated Carbonyl Compounds.



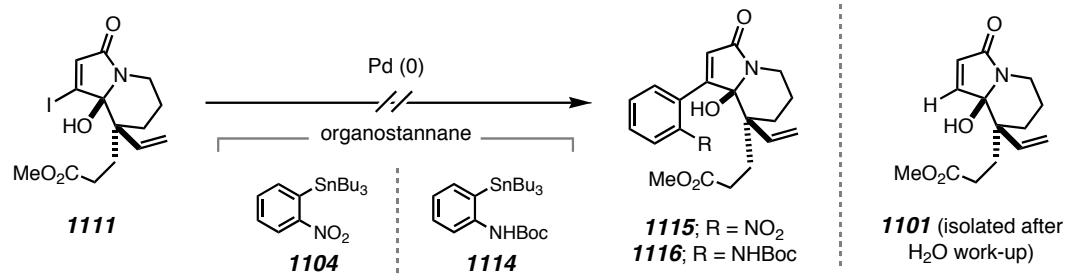
In addition, we found examples of structures that are closely related to the carbinolamides of our interest (with highlighted structural motifs in Panel B). The ^{1}H NMR chemical shifts of H_α in *N*-benzylated amide **1112**[30] and H_β in bicyclic lactam

30. Ma, S.; Xie, H. *Org. Lett.* **2000**, *2*, 3801–3803.

1113[31] have been reported to be 6.33 and 7.23 ppm. Spectral assignment of $CDCl_3$ solutions of each compound has been performed at 300-MHz field strength. Reported singlet chemical shifts of α- and β-protons are in agreement with what we observed for both the desired and undesired intramolecular allylation products (Scheme I-17).

Moving forward with our total synthesis, we next explored the Stille cross-couplings of the iodo carbinolamide **1111** with the aniline surrogates, **1104** and **1114** (Scheme I-18). Attempts of such a transformation with neither **1104** nor **1114** were successful. We instead isolated the proto-deiodinated amide **1101**, which was previously synthesized (cf. Table 1-I). We noticed that each organostannane were unreactive under our Stille coupling conditions.

Scheme I-18. Initial Efforts Toward an Arene-Alkene Coupling.



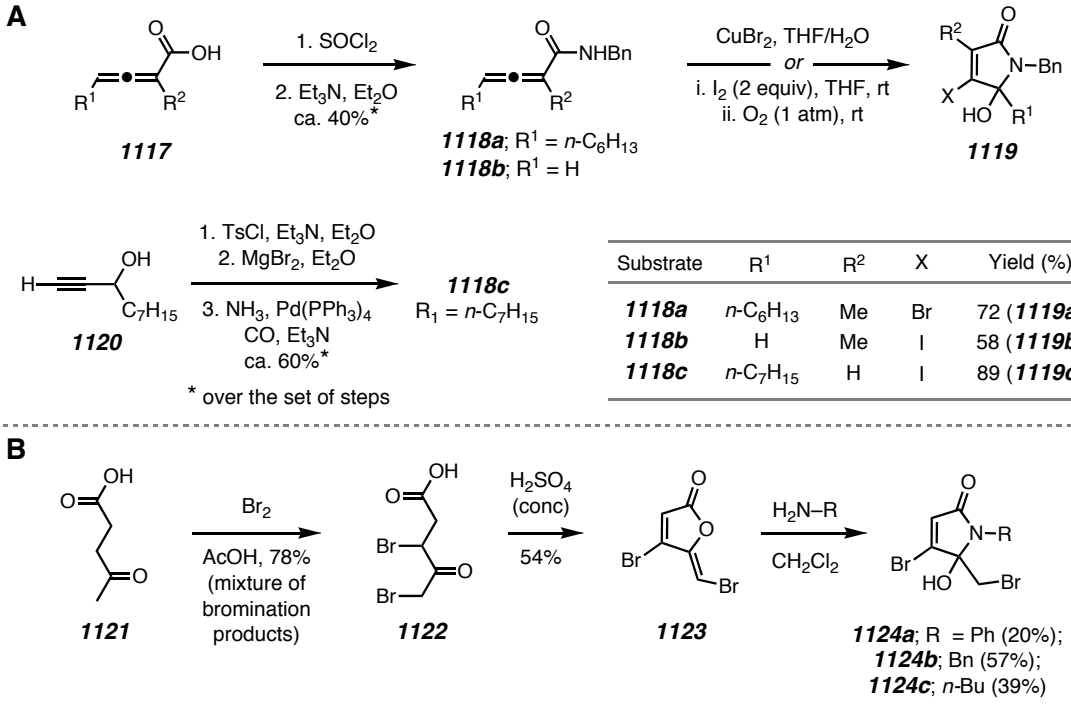
relative transmetalation aptitude of the electron deficient organostannanes (the nitrophenyl substituted **1104**, and the *N*-Boc protected **1114**) were slow as evident by their coupling with simple aryl or alkenyl halide.[32] After facing this roadblock, we turned our attention to construct a model substrate of the precious carbinolamide **1111** for a similar coupling reaction where we could test different organostannanes and/or reaction conditions (additives, solvent, etc.). However, access to such a model in our hands has proven to be difficult (e.g., a 1,2-addition of organolithium or organomagnesium species to an imide that generates the lactam motif in **1111**). In

31. Fray, A. H.; Meyers, A. I. *J. Org. Chem*. **1996**, *61*, 3362–3374.
32. Izgu. E. C.; Hoye, T. R. *Tetrahedron Lett*. **2012**, *53*, 4938–4941.

addition, there are only a handful of examples available for this purpose. The most relevant protocols are shown in Scheme I-20.

The Ma research group has extensively studied halolactamization-hydroxylation of 2,3-allenamides since early 2000's.[33] In a recent study,[33b] the group has reported the use of both CuX_2 and I_2/O_2 in forming the lactams **1119a-c** via γ-hydroxylation of allenamides **1118** (Panel A). They have prepared allenamide substrates **1118a-b** from the corresponding 2,3-allenilic acids **1117**, and **1118c** from the propargylic alcohols **1120** under previously optimized reaction conditions.[33a]

Scheme I-19. Protocols Reported to Synthesize γ-Hydroxy-γ-Alkyl Lactams.

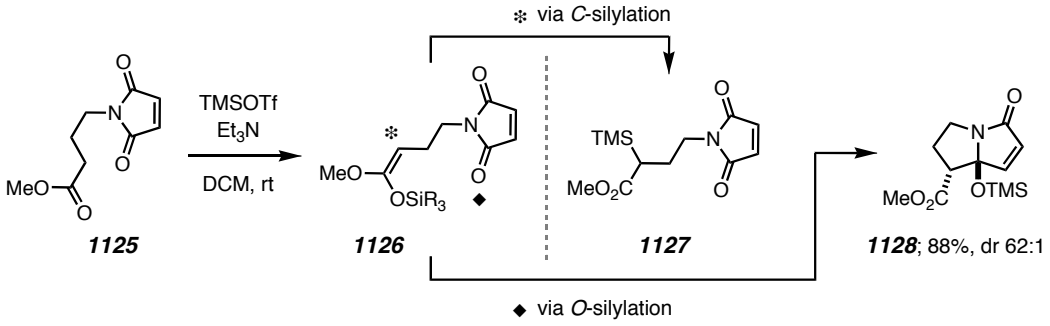


33. (a) Ma, S.; Xie, H. *J. Org. Chem.* **2002**, *67*, 6575–6578. (b) Ma, S.; Xie, H. *Tetrahedron* **2005**, *61*, 251–258.

In the late 1990's Steinberg reported the synthesis of biologically important fimbrolides including **1123** (Panel B)[34a] Later, Kumar studied the lactamizations of these fimbrolides, using alkyl or aryl amines.[34b] Heterocycles **1124** were obtained in modest to good yields via a lactone ring opening of **1123** followed by tautomerization.

In spite of the existing protocols for the synthesis of a bicyclic lactam, a more easily executed and efficient route was still desirable. On the other hand, our group studied the synthesis of the lactams like **1128** by a silylative-Dieckmann type cyclization (Scheme I-20).[35] The LA activated imide was trapped by the silyl ketene acetal (in **1126**) derived from soft enolization of the butanoate **1125**.

Scheme I-20. Hoye's Approach toward Bicyclic Carbinolamides like **1128**.

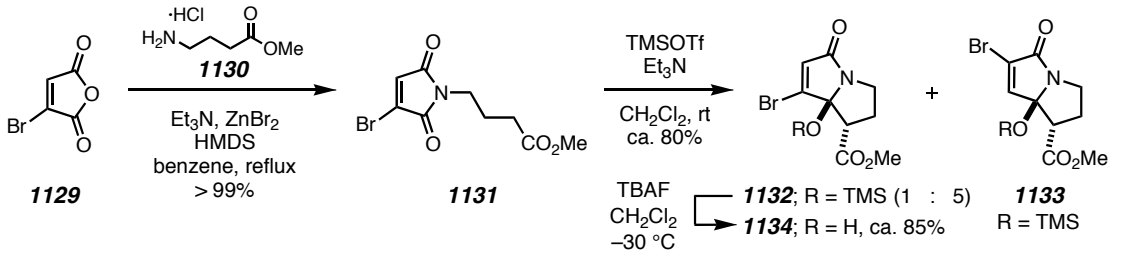


The LA activation occurred through the *O*-$SiMe_3$ formation (◆) to give **1128**, whereas, a competitive *C*-$SiMe_3$ etherification (✻) led to the maleimide **1148**. The key 5-membered cyclization was achieved under TMSOTf-Et_3N condition, and the use of other (and bulkier) silylating agents (e.g., TBSOTf) was also explored. Isolated yields of bicyclic pyrrolidines were comparable for each Lewis-acid condition. Also, the diastereomer in which the carbomethoxy and OTMS-ether are in a trans relationship were formed in these experiments.

34. (a) Manny, A. J.; Kjelleberg, S.; Kumar, N.; de Nys, R.; Read, R. W.; Steinberg, P. *Tetrahedron* **1997**, *53*, 15813–15826. (b) Goh, W. K.; Iskander, G.; Black, D. S.; Kumar, N. *Tetrahedron Lett.* **2007**, *48*, 2287–2290.
35. Hoye, T. R.; Dvornikovs, V.; Sizova, E. *Org. Lett.* **2006**, *8*, 5191–5194.

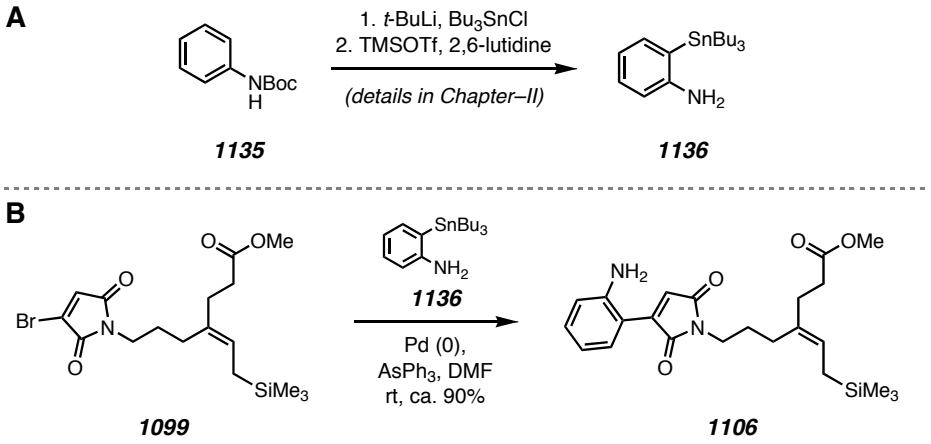
Motivated by these results, we proceeded to synthesize **1134** (Scheme I-21), the mono-halogenated analogues of **1128**. After a $ZnBr_2$ mediated condensation of bromomaleic anhydride (**1129**) with the amine **1130** (prepared from 4-aminobutyric acid[36]), we isolated the regioisomeric OTMS-ethers **1153** and **1154** in ca. 1:5 ratio.

Scheme I-21. Synthesis of the Model *β*-Bromo-Lactam **1134** via Hoye's Approach.



In one instance, we faced with the need to prepare the *ortho*-stannyl-aniline **1136** (Panel A in Scheme I-22) for an amide bond coupling. Later, we discovered that using this reagent, we were able to synthesize the allylative allylation substrate **1106** directly from the bromoimide **1099**. We were able to prepare this powerful cross-

Scheme I-22. Synthesis of *o*-(Tributylstannyl)aniline **1136** and Its Cross-Coupling with the Bromoimide **1099**.

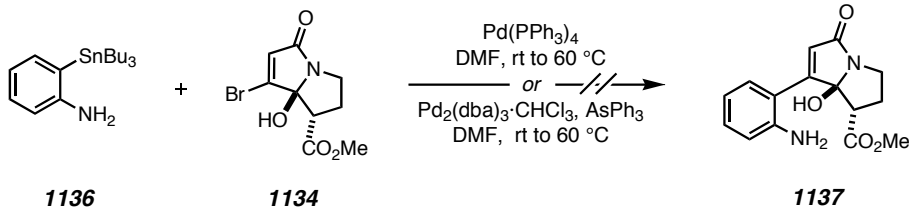


36. Moran, R. G.; Colman, P. D.; Forsch, R. A.; Rosowsky, A. *J. Med. Chem*. **1984**, *27*, 1263–1267.

coupling agent (**1136**) in two steps (1. *ortho*-stannylation; 2. *N*-Boc deprotection) from commercially available *N*-Boc aniline (**1135**).[32]

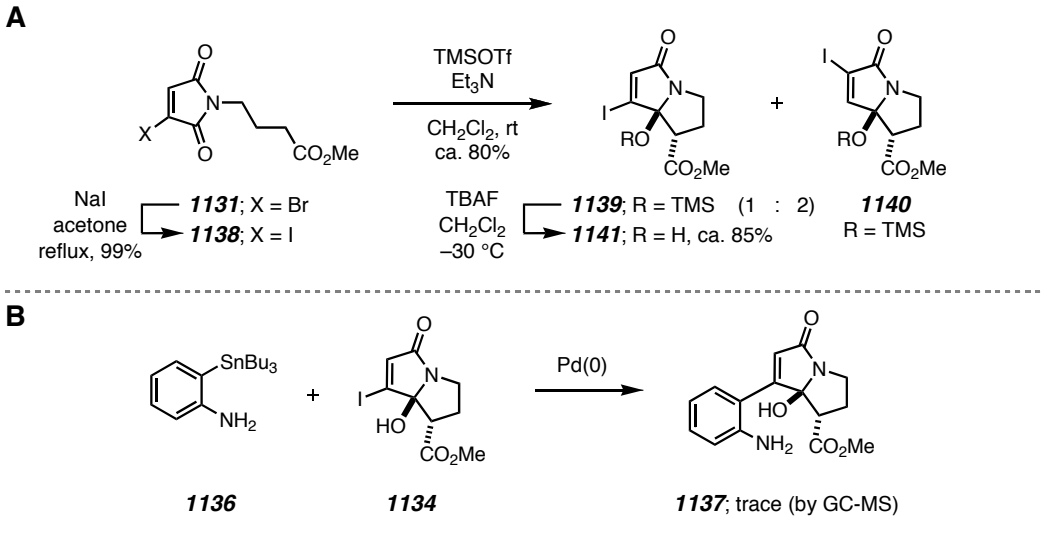
Our initial attempts toward the Stille coupling of **1136** with **1134** (Scheme I-23) were met with no success under our standard reaction conditions [A. $Pd(PPh_3)_4$ or B. $Pd_2(dba)_3{\cdot}CHCl_3/AsPh_3$].

Scheme I-23. Initial Trials of the Cross-Coupling of **1136** with **1134**.



These results intuitively led us to make the iodo anolog **1141** (Panel A in Scheme I-24), which is a more reactive alkenyl halide toward the oxidative addition by a low valent organometalic species.

Scheme I-24. Synthesis of the Model *β*-Iodo-Lactam **1141**.

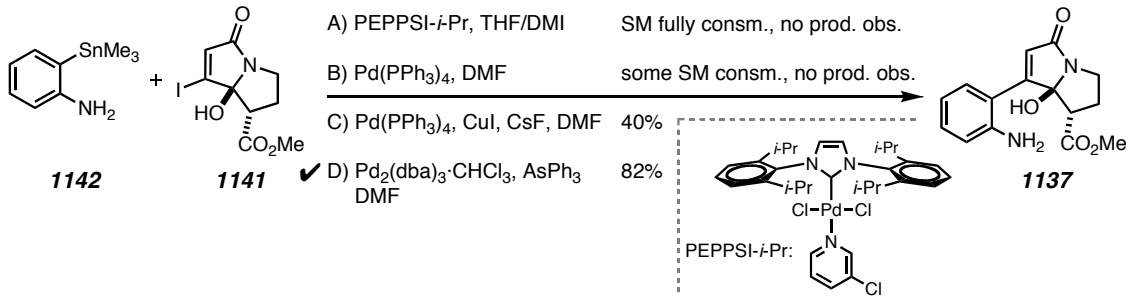


A Finkelstein reaction with NaI provided the required iodine functionality. Following a similar Dieckmann type cyclization and subsequent TMS removal afforded **1141**. Moreover, we were able to isolate this model compound in much higher quantity than that of the bromide **1134**. The regioselectivity in the cyclization event was higher (ca. 1:2) for the desired isomer.

To our disappointment, we observed only trace amount of the desired coupling product **1137** using the oranostannane **1136** and the alkenyl iodide **1134**. Both of the coupling partners were essentially recovered along with small amount of the proto-deiodinated by-product. Having experienced the difficulty in engaging **1136** in the complex iodide **1125**, we resorted to use the sterically less congested stannane **1142**[32,37] (Scheme I-25).

With this novel organostannane in hand, we focused on finding a proper reaction condition to engage—the most reactive Stille coupling partners that we had used so far—the stannane **1142** and the idodide **1141** (Scheme I-25).

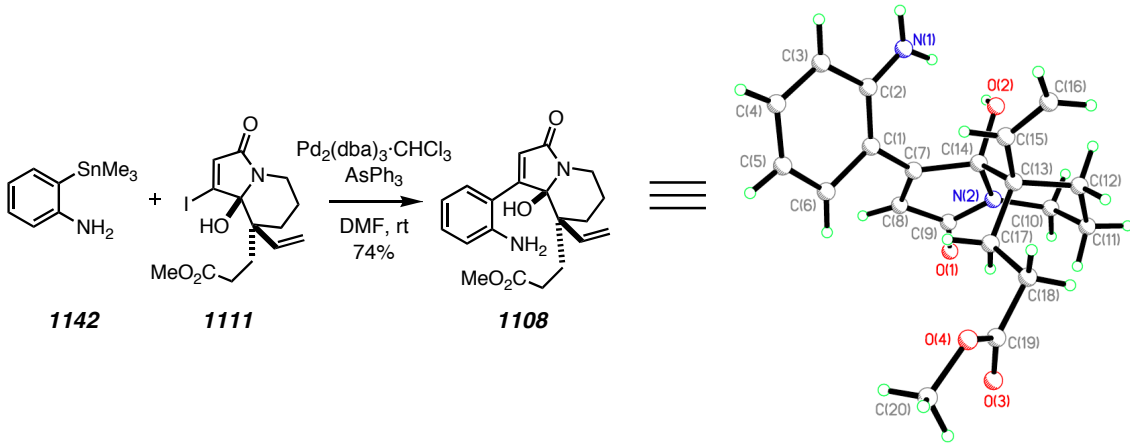
Scheme I-25. Union of the Stannane **1142** with the *β*-Iodo-Lactams **1141**.



After screening various Stille cross-coupling condition, we finally achieved the difficult arene-alkene coupling in 82% isolated yield using $Pd_2(dba)_3{\cdot}CHCl_3/AsPh_3$ (Method D).

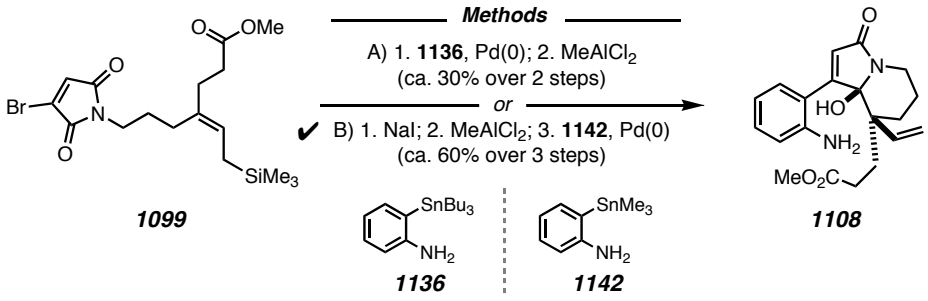
37. The organostannane **1142** was synthesized performing a similar two-step protocol developed for **1136** (cf. Panel A in Scheme I-22).

Scheme I-26. The Key Arene-Alkene Union of the Stannane **1142** with **1111**.



To our delight, the key arene-alkene coupling of **1111** (Scheme I-26) was successfully effected by the optimized Pd(0) condition [$Pd_2(dba)_3$·$CHCl_3$ and $AsPh_3$, Method D, cf. Scheme I-26] in 74% yield. Because this route was more efficient (Scheme I-29), we were not only able to scale up, but also grow samples of **1108** for X-ray structure analysis[38]

Scheme I-27. Overview of Two Different Methods to Access the Key Amino Ester **1108**.

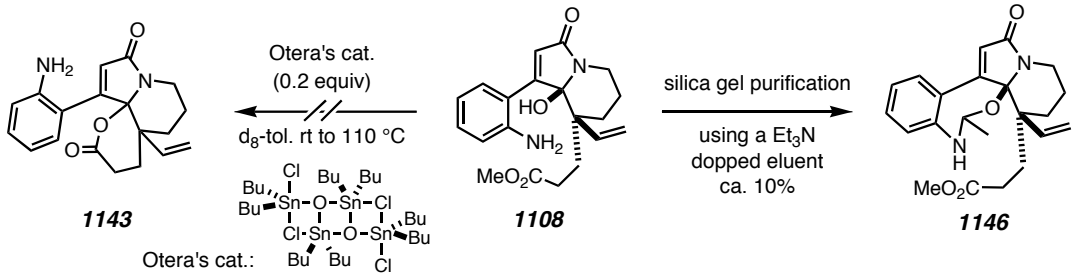


It is worth mentioning that we once attempted to lactonize **1108** (Scheme I-28) in

38. Re-crystallization of **1108** was done by slow gas-diffusion technique using EtOAc (solvent) and cyclohexane. The space group is P2(1)/n with cell constants a = 13.153(4) Å, b = 10.119(3) Å, c = 13.950(4) Å, beta = 102.627(4) deg., and V = 1811.6(10) Å.; Temperature: 173 K

by the action of Otera's catalyst—a mild activator for esters toward lactonization—before we obtained the X-ray crystallographic data of the molecule. Our intention was to explore the structure-reactivity relationship of **1108**, which would endow us with a better judgment about the allylation step (relative configurations of hydroxyl and vinyl groups). To our disappointment, we observed no conversion of the starting ester **1108** to a lactone like **1143**.

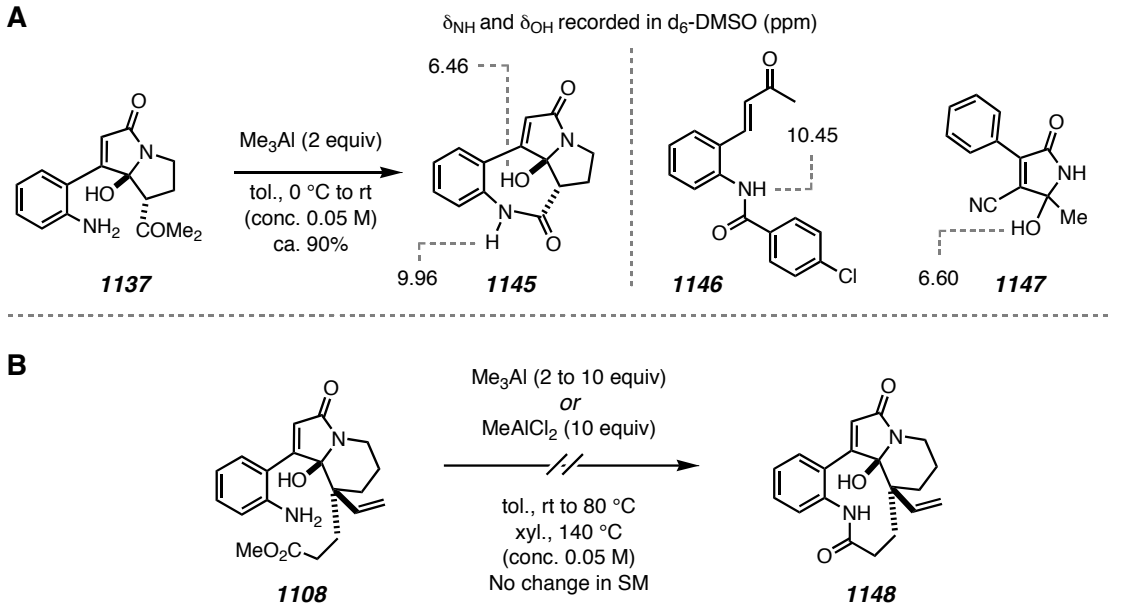
Scheme I-28. Attempt to Lactonize **1108**. Also Its Purification Artifact **1146**.



As a side note, we isolated the 7-membered bis-hemiaminal **1146** during an attempt to purify the crude amino ester **1108** by column chromatography. For a faster recovery of **1108**, we deactivated the dry-packed silica gel with ca. 5% Et_3N containing eluent. We believe that Et_3N underwent an auto-oxidation pathway through which it was converted into Et_2NH and acetaldehyde. The latter then reacted with the free amine of **1108** to generate an imine intermediate, which was trapped by γ-OH. Serendipitously, the isolation of **1146** encouraged us to believe that the aniline-NH_2 could indeed approach into the bicyclic core and reach out the ester for the desired lactam formation.

To sum up, the information gained in Scheme I-28 supported that there could be a condition for **1108** to eventually close the 9-membered lactam ring. Therefore, we explored a direct macrolactamization of the model compound **1137**, and later, of **1108** (Scheme I-29).

Scheme I-29. Efforts for the Direct Macrocyclization of Amino Esters **1137** and **1108**.



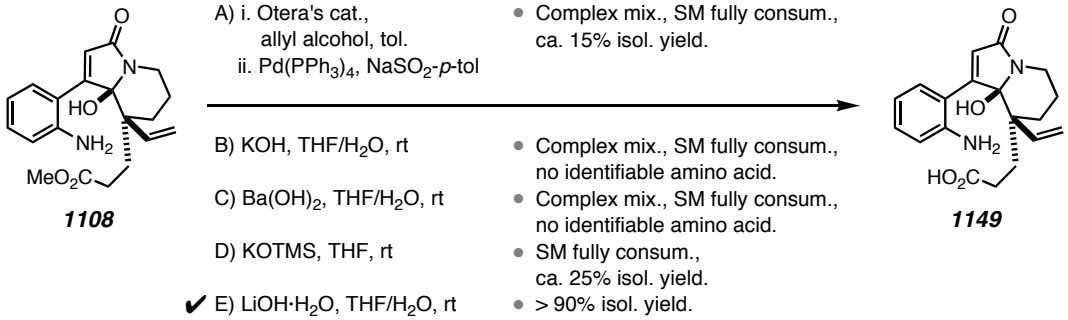
We observed an efficient lactamization of **1137** using Me_3Al (Panel A) at room temperature and in 0.05 M reaction concentration. The ^{1}H-NMR analysis (in d_6-DMSO for solubility purposes) of the reaction product indicated the desired amide bond formation. More specifically, we compared the proton chemical shifts of the amide-N*H* and *γ*-O*H* to those of reported molecules **1146**[39a] and **1147**.[39b] Each set of chemical shift values were comparable to one other [(in ppm) δ_{NH} = 9.96 *vs*. 10.45[39a]; and δ_{OH} = 6.46 *vs*. 6.60[39b]).

Having succeeded in direct lactamization of the model **1137**, we turned our attention to the same transformation of **1108** (Panel B). Using excess LA and/or applying heat did not provide any observable macrolactam **1148**. We almost fully recovered the starting amino ester **1108**, after quenching the reaction mixture with aqueous NH_4Cl.

39. (a) Bowman, W. R.; Fletcher, A. J.; Pedersen, J. M.; Lovell, P. J.; Elsegood, M. R. J.; López, E. H.; McKee, V.; Potts, G. B. S. *Tetrahedron* **2007**, *63*, 191–203. (b) Ciller, J. A.; Martín, N.; Seoane, C.; Soto, J. L *J. Chem. Soc., Perkin Trans. 1* **1985**, 2581–2584.

In our initial studies on *route-II* (Section I-E-2), we had successfully converted related esters to the carboxylic acids via an allyl alcohol esterification–deallylation protocol (Schemes I-35 and I-36). We expected that this two-step procedure would also be suitable for the transformation of **1108** to **1149** (Scheme I-30). However, this strategy [method A: (i) Esterification using Otera's catalyst in the presence of allyl alcohol; (ii) Pd(0) mediated deallylation] resulted in a complex reaction mixture with a low isolated yield of the amino acid **1149**.

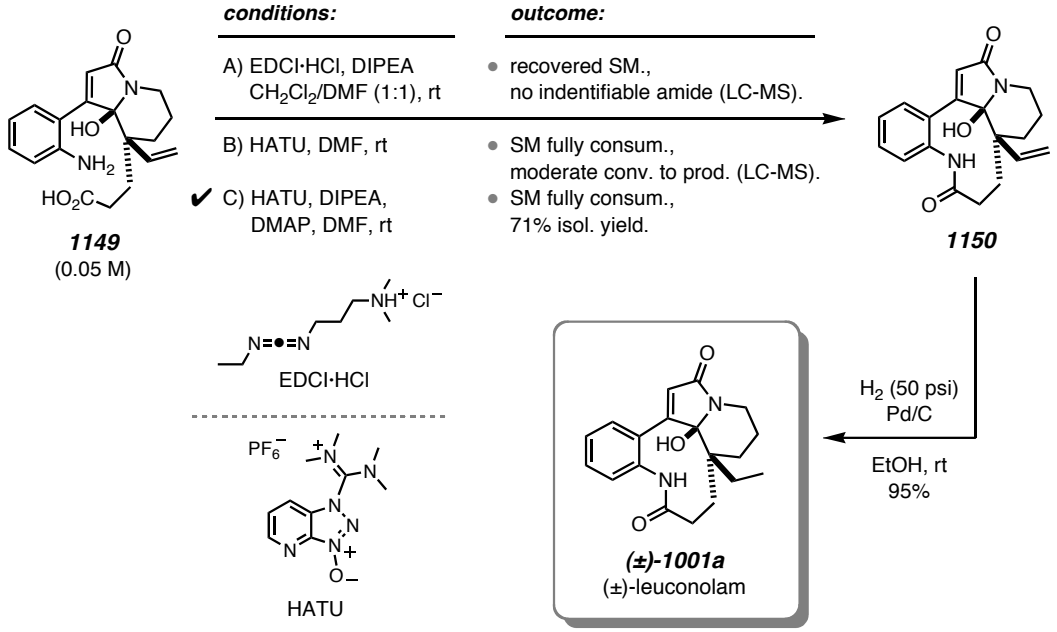
Scheme I-30. Synthesis of the Amino Acid **1149** from the Methyl Ester **1108**.



We then explored the conditions for direct saponification conditions, in which (methods B-D) we noticed the depletion of **1108** without the formation of **1149**. Under most conditions, ^{1}H-NMR analysis of the crude reaction samples indicated major changes in the integrity of the molecule (e.g., disappearance of the α-proton, and more generally, broadening of the previously identifiable proton resonances). The nature of the hydroxide-anion was apparently responsible for such destructive pathways. Gladly, LiOH-mono-hydrate (3 equiv, method E) served very effectively in our hands for the desired transformation. Immediately after observing the nearly full conversion of **1108** to the corresponding carboxylate (by LC-MS), the reaction mixture was neutralized at 10 °C by AcOH titration.

The stage was now open for the key macrolactamization to form the 9-membered leuconolam core.[40] We tested a standard carbodiimide mediated lactamization of **1149** using EDCI·HCl (1.5 equiv) in the presence of an organic buffer, such as DIPEA (Scheme I-31). Compared to using EDCI·HCl alone, addition of DIPEA led to a slightly less complex LC chromatogram of the crude reaction material. However, we did not observe a molecular mass (by LC-MS) that could be associated with a lactam.

Scheme I-31. Macrolactamization and Reduction to Access (±)-Leuconolam [**(±)-1001a**].



Gratifyingly, we detected the desired lactam formation when we treated a DMF solution (0.05 M) of the substrate with HATU (1.5 equiv). This new generation peptide bond forming agent is very robust, yet functional group tolerant.[41] Although the level of purity of the crude material was not satisfactory, we were motivated to run a similar experiment on a larger scale along with DIPEA and catalytic amount (0.1 equiv) of

40. Notice that the macrolactamizations reported by Banwell[5,20] involved amide bond coupling of a stereo-electronically more reactive aniline.
41. (a) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827–10852. (b) Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606–631.

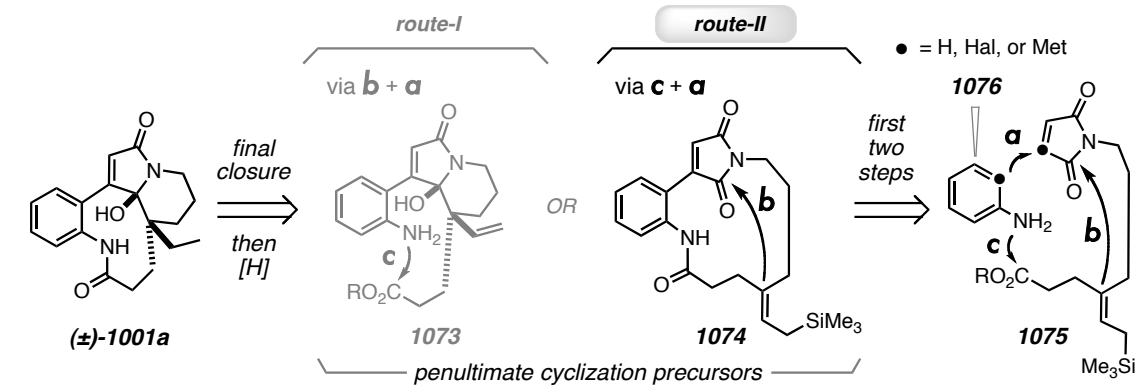
DMAP. This method was significantly more effective for the desired transformation (71% isolated yield). After silica-gel chromatography, we were able to bring up enough material to try the very final step, the hydrogenation of the vinyl group.

Subjecting **1150** to the standard reduction conditions (H_2 balloon/catalytic Pd on C) was not effective. We gradually increased the gas pressure and the palladium loading until we observed a good pace of the reduction. The purified material (by silica gel chromatography) provided the target alkaloid **(±)-1001a** in 95% yield as a white amorphous solid. Its ^{1}H-NMR spectrum was matching with the reported ones.[3b,5] The melting point (mp) of the solid was higher than 250 °C (which is the upper limit of the mp-apparatus; reported mp = 263-264 °C[3b]). Furthermore, the ESI-HRMS analysis showed the correct molecular mass with high accuracy (less than 5 ppm error).

I-G-2. Results and Discussion (*Route-II*)

During our efforts to achieve the molecular framework of leuconolam (**1001a**) via *route-I* (cf. Section I-E-1), we also explored the possibility of switching the order of the cyclization events. More specifically, we proposed *route-II* (Scheme I-32) in which a transannular cyclization of the acyclic substrate **1075** (via steps **c** + **a**) is followed by an allylation (step ***b***) on the resulting 13-membered lactam **1074** to construct the tetrafused ring system of **(±)-1001a**.

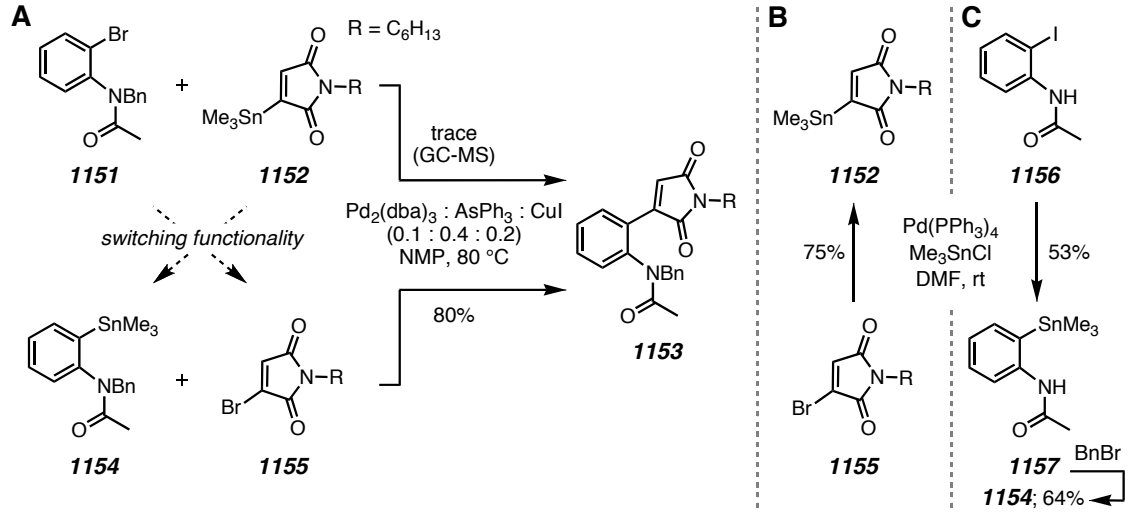
Scheme I-32. Overview of the Second Route to Leuconolam [**(±)-1001a**].



First, we opted to use the Stille cross-coupling reaction to construct a simplified model compound **1153** from the building blocks such as **1151** and **1152** (Panel A in Scheme I-33). The latter was prepared from the bromo maleimide **1155** via a Pd(0) mediated stannylation (Panel B). According to a recent report by Baldwin,[42] the reaction solvent (usually NMP or DMF) affects the role of copper metal, and a tin-copper trans-metalation event leads to a basic vinyl cuprate species. For our experiment, this basic species would likely derive from **1152** [in the form of X-Cu(II)-Csp^2]. Therefore, we determined to test the cross-coupling using an inert amide partner like **1151**, after removing the acidic amide proton.

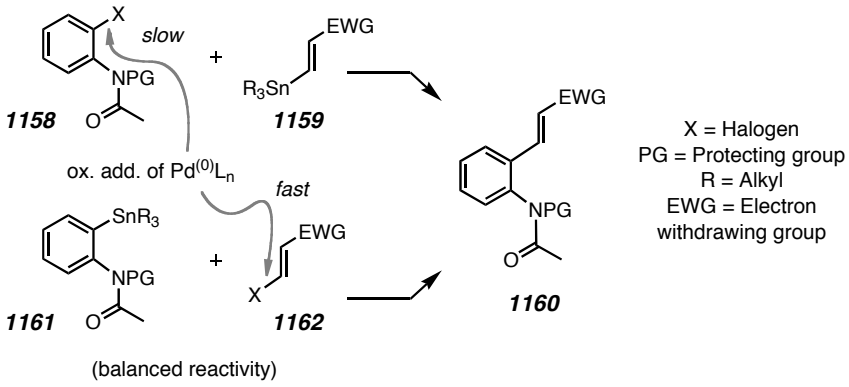
42. Mee, S. P. H.; Lee, V.; Baldwin, E. J. *Angew. Chem. Int. Ed.,* **2004**, *43*, 1132–1136.

Scheme I-33. Exploring the Arene-Alkene Coupling of Model Compounds via a Bimolecular Stille Coupling.



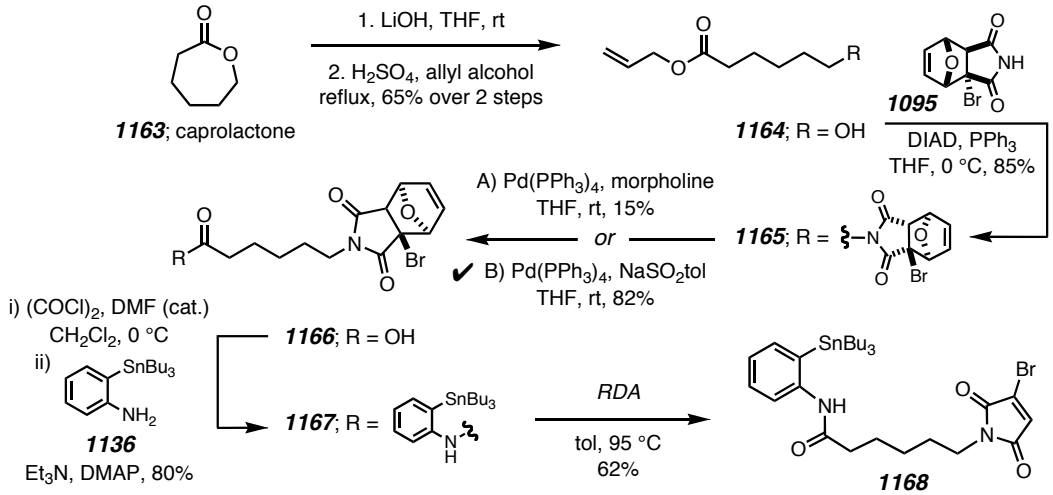
While no significant change in the amount of **1151** was observed (by GC-MS) during our Stille cross-coupling conditions [$Pd_2(dba)_3$·$CHCl_3$/$AsPh_3$/CuI], the organostannane **1152** was almost completely consumed. We also studied the coupling arene-alkene bonding between *o*-stannanyl-amide **1154** and the bromo imide **1155**. The former was synthesized from 2-iodo-acetanilide (**1156**) via a similar Pd(0) mediated stannylation, followed by benzylation (Panel C). Gratifyingly, this exchange in the carbon functionality significantly improved the feasibility of the reactants and afforded **1153** in 80% yield. We reasoned that because the aryl C-X bond of an amide like **1158** (Scheme I-35) is marginally electron deficient, it undergoes a slow oxidative addition by Pd(0). On the other hand, the electron rich C-Sn moiety is consumed by side reactions. A good balance in the relative reactivity of the partners (as in the case of **1161** and **1162**) leads to a higher coupling efficiency. More specifically, highly electron deficient alkenyl halide **1162** can undergo a relatively faster oxidative addition by Pd(0). This increases the concentration of the Pd(II) intermediate that can transmetallate with the organostannane portion.

Scheme I-34. Rationale for the Relative Reactivity of Stille Coupling Partners.



Resolving which carbon functionality is appropriate for an efficient bimolecular Stille coupling; we turned our attention to the unimolecular version (Scheme I-35). We elected **1168** as the model macrocyclization precursor, which did not need an allylic silyl functionality. Hence, we designed a 6-step route starting from readily available caprolactone (**1163**). A lactone ring opening with LiOH, followed by allyl alcohol esterification provided the Mitsunobu reaction precursor **1164** easily. Displacing the primary hydroxyl with the imide **1095**, and a deallylation of the resulting ester furnished

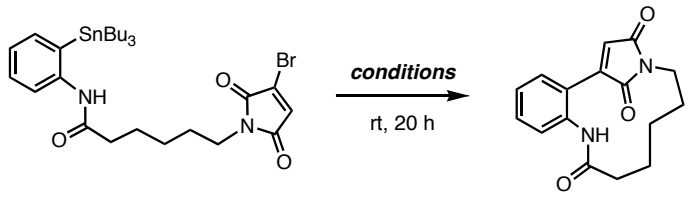
Scheme I-35. Model Study for Macrolactamization via Stille Coupling.



the carboxylic acid **1166**. An amide bond formation to install the required *o*-stannyl-anilino functionality was achieved by treating the freshly made acid chloride [via $(COCl)_2$ and DMF] with the organostannane **1136**. Use of Et_3N was critical to preserve the integrity of the acid labile **1136** (i.e. to prevent protodestannylation). Finally, a retro-Diels-Alder (RDA) reaction was performed to free the maleimide **1168**.

Because we were able to prepare **1168** in large enough quantity (ca. 300 mg), we could investigate a variety of unimolecular coupling conditions (Table I-2). We found that a big fraction of the organometalic catalyst systems (entries 1-4) including copper and palladium catalysts failed in being productive in the desired transformation. While the substrate **1168** was almost always consumed (except in entry 2), the macrocycle **1169** was formed in only trace amount (entries 1-4). Among the organopalladium pre-catalysts, the $Pd_2(dba)_3{\cdot}CHCl_3/AsPh_3$ system proved to be very powerful (82% isolated yield) and functional group tolerant (high product yield-to-substrate conversion ratio).

Table I-2. Macrocyclization of the Model Precursor **1168** via Stille Coupling.

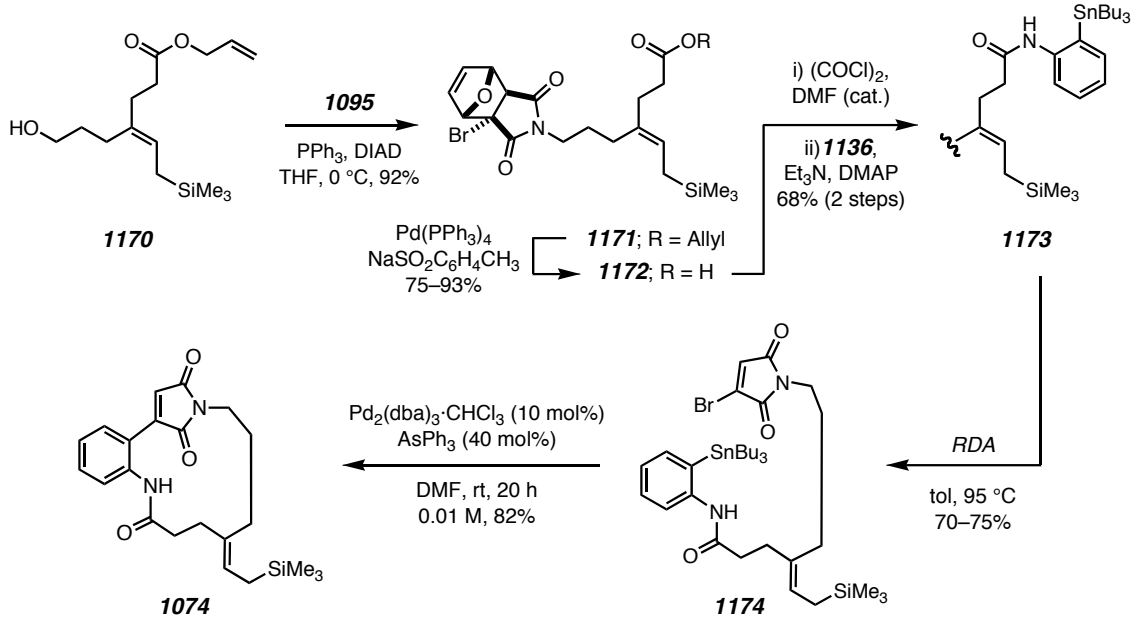


1168 (0.01M) ***1169***

entry	catalyst (equiv)	additive (equiv)	solvent	conv. of **1168** (%)	**1169**
1	CuTC (0.1)	–	NMP	~ 99	trace
2	$Pd(PPh_3)_4$ (0.1)	–	THF	20	trace
3	$Pd(PPh_3)_2Cl_2$ (0.1)	LiCl (2.0)	DMF	75	trace
4	$Pd_2(dba)_3{\cdot}CHCl_3$ (0.1)	–	NMP	~ 95	trace
5	$Pd_2(dba)_3{\cdot}CHCl_3$ (0.1)	$AsPh_4$ (0.4)	DMF	~ 99	82%
6	$Pd_2(dba)_3{\cdot}CHCl_3$ (0.1)	$AsPh_4$ (0.4); CuI (0.2)	DMF	~ 99	24%

Having found a robust Stille-macrocyclization method, we were set for the 13-membered cyclization that would assemble the arene-imide pieces of **1178** (Scheme I-36).

Scheme I-36. Synthesis of the Key Macrocycle **1074** via Stille Coupling.

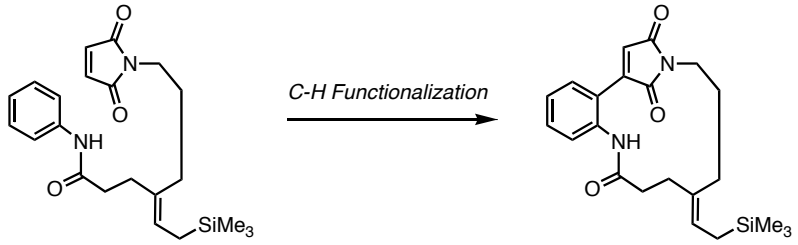


The primary alcohol **1170**, which was obtained by allyl alcohol esterification of the corresponding carboxylic acid, was displaced with **1095** under our standard Mitsunobu displacement conditions. A Pd(0) mediated deallylation of the resulting imide-ester **1171** afforded the carboxylic acid acid **1172** was. Subsequent amide bond formation, followed by a RDA reaction of the resulting *o*-stannyl-acetanilide **1173** furnished the macrocyclization substrate **1174** in good yield (ca. 50% over 3 steps). To our delight, the key unimolecular arene-alkene coupling to provide the 13-membered *o*-imido acetanilide **1074** was accomplished in 82% yield.

During our progress in a Stille coupling approach mentioned above, we were also exploring an alternative macrocyclization method. Having anilide and α,β-unsaturated carbonyl functionalities embedded in leuconolam (**1001a**), we opted to develop a

macrocyclization of the non-functionalized substrate (Scheme I-37). On much simpler molecular settings, Fagnou has reported pioneering studies in C-C bond forming reactions of non-functionalized indoles[43a] and acetanilides.[43b] However, to our knowledge, many of the arene-arene or arene-alkene couplings are limited to bimolecular reaction settings. A macrocyclization event that is related, yet for an arene-arene coupling is a long-lasting research project that Trauner has been focusing on.[21b]

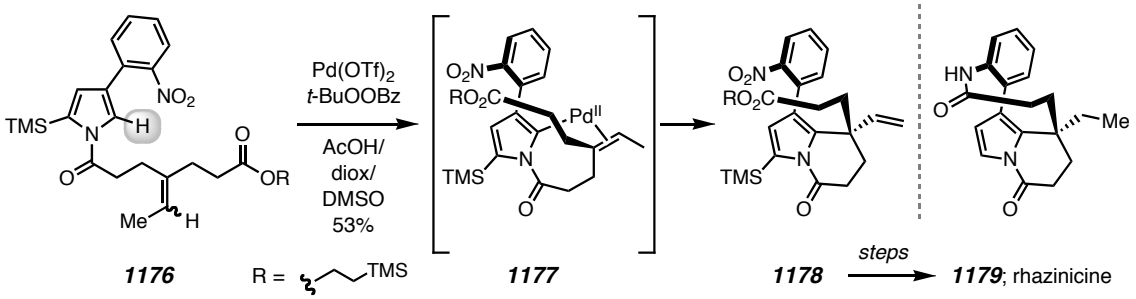
Scheme I-37. Envisioned Macrocyclization via C-H Bond Functionalization.



1175 ***1074***

More recently, Gaunt has reported macrocyclizations where arene-alkene C-C bonds have been formed by a C-H bond functionalization.[44] In the total synthesis of a

Scheme I-38. Reported Acetanilide-Acrylate Couplings via C-H Bond Functionalization.



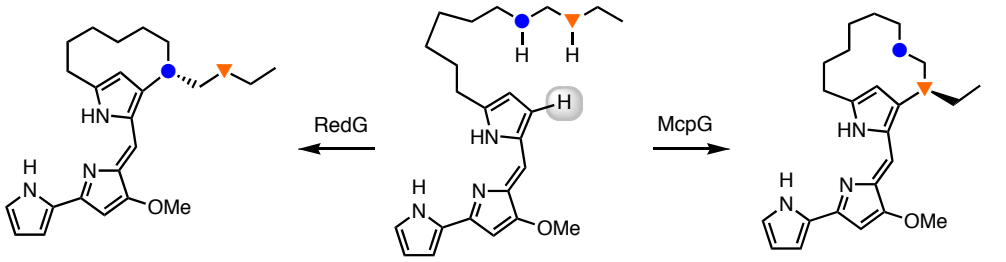
1176 R = TMS ***1177*** ***1178*** ***1179***; rhazinicine

43. (a) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172–1175. (b) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *131*, 18326–18339.
44. (a) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 3004–3007. (b) McMurray, L.; Beck, E. M.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2012**, *51*, ASAP.

related indole alkaloid, rhazinicine (**1179**, Scheme I-38), Gaunt has presented an elegant 6-membered ring formation (the piperidinone in **1178**) on the pyrrole **1176** under the acidic $Pd(OTf)_2$/*t*-BuO_2Bz conditions.

Other interesting cyclization event, yet to afford much larger carbocyclic rings, has recently been reported by Challis laboratory. The authors have showed some remarkable macrocyclizations through regio- and stereoselective C-H bond activations that are mediated by enzymes.[45a] Undecylprodigiosin (**1181**, Scheme I-39) is a biosynthetic precursor to certain prodiginines,[46a] streptorubin B (**1180**) and metacycloprodigiosin (**1182**). Under the enzymatic activity of RedG[46b] and McpG[46c] gene clusters, **1181** remarkably underwent 10- and 12-membered ring formations to provide **1180** and **1182**, respectively. RedG and McpG are Rieske oxygenase-like enzymes[46d] and are the first examples of such enzymes catalyzing oxidative carbocyclizations.

Scheme I-39. Macrocyclizations via C-H Bond Activation Reported in Biological Studies.



1180; streptorubin ***1181***; undecylprodigiosin ***1182***; metacycloprodigiosin

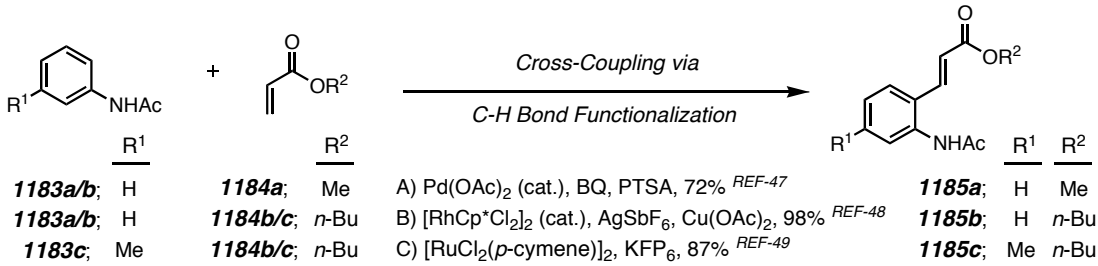
RedG and McpG are Rieske oxygenase-like enzymes

45. (a) Sydor, P. K.; Barry, S. M.; Odulate, O. M.; Barona–Gomez, F.; Haynes, S. W.; Corre, C.; Song, L.; Challis, G. L. *Nat. Chem.* **2011**, *3*, 388–392.

46. (a) Prodiginines are a class of biologically active molecules that disrupt protein-protein interactions in B-cells. (b) RedG is a specific portion of *red* gene cluster of *Streptomyces coelicolor* A3(2) that directs biosynthesis of streptorubin B (**1200**). (c) McpG is an orthologue of RedG and is produced by *S. longispororuber*. It mediates the biosynthesis of metacycloprodigiosin (**1202**). (d) Rieske enzymes are members of non-heme iron dependent oxygenases. They catalyze a variety of oxidation reactions such as *N*-oxidation of anilines to nitrobenzenes[46e] and *cis*-hydroxylation of aromatic compounds.[46f] (e) Gibson, D. T.; Parales, R. E. *Curr. Opin. Biotechnol.* **2000**, *11*, 236–243. (f) Lee. J.; Simurdiak, M.; Zhao, H. *J. Biol. Chem.* **2005**, *280*, 36719–36727.

As mentioned earlier, the arene-alkene couplings through oxidative Heck type C-H bond functionalizations are interesting and rarely reported. Although there are no reports for such transformations of the maleimides, alkyl acrylates have been shown to afford 2-substituted acetanilides **1185a-c** (Scheme I-40).

Scheme I-40. Reported Acetanilide-Acrylate Couplings via C-H Bond Functionalization.

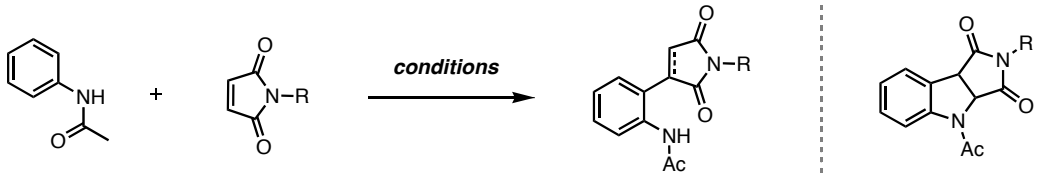


Three frontrunner laboratories, van Leeuwen, Glorius, and Ackermann research groups have extensively studied related acetanilide-acrylate couplings products (Scheme I-40). While the van Leeuwen group has focused their efforts on palladium chemistry,[47] the Glorius and the Ackermann laboratories have reported similar experiments utilizing with organorhodium[48] and organoruthenium[49] complexes, respectively.

Therefore, we turned our attention to find a method to achieve a similar coupling of non-functionalized partners, one of which would be the maleimide like **1186** (Table I-3) rather than an acrylate. After screening several conditions, we found that the Rh-based organometalic catalyst systems (entries 7-8) served the most effective. However, we observed not only the formation of the desired maleimide **1187**, but also the dihydro analog, the succinimide **1188**, and an isomer of **1187**, whose structure we assigned as the fused indolinone **1189**.

47. Boele, M. D. K.; van Strijdonck, G. P. F.; Vries, A. H. M.; Kamer, P. C. J.; Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587.
48. Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982–9983.
49. Ackermann, L.; Wang, L.; Wolfram, R.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 728–731.

Table I-3. Coupling of Acetanilides and α,β-Unsaturated Carbonyl Compounds via C-H Bond Functionalization.[a]



1183a/b ***1186*** R = $C_3H_6CO_2Me$ ***1187***; the maleimide ***1188***; the succinimide ***1189***

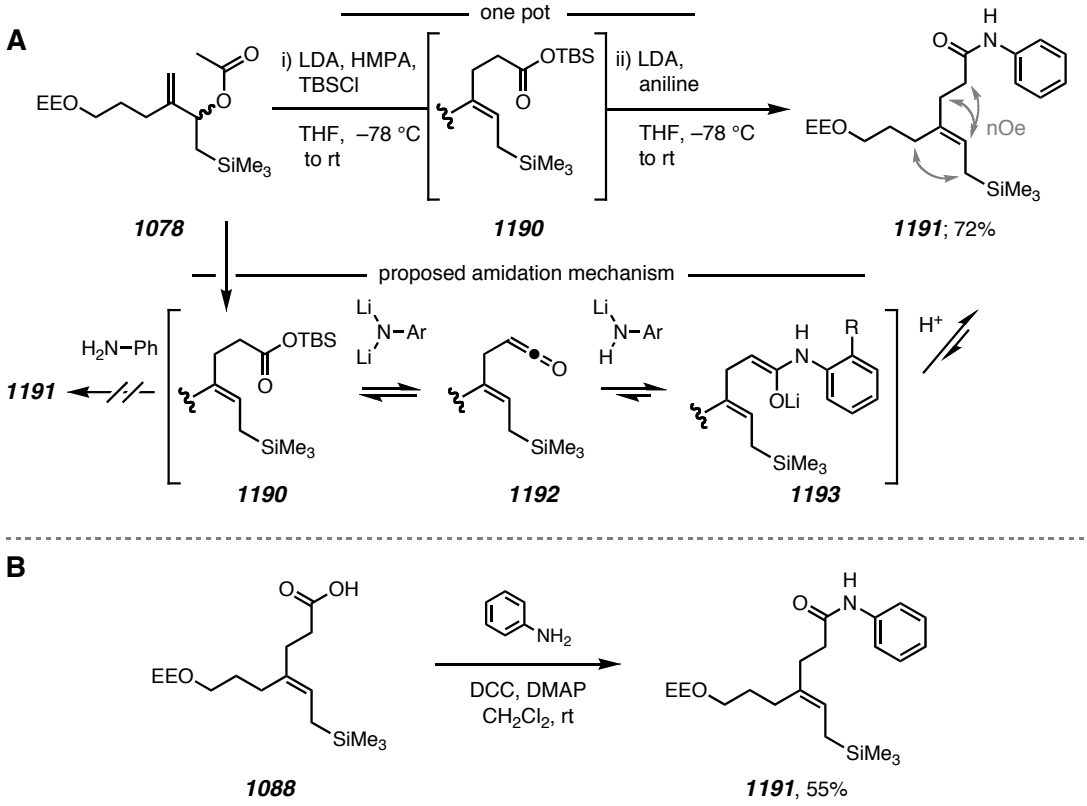
entry	cat. (equiv)[b]	additive (equiv)	solvent	**1187**[c]	**1188**[c]	**1189**[c]
1[d]	$PdCl_2$ (1.0)	AgOTf (2.0)	dioxane	35	–	–
2[d]	$Pd(OAc)_2$ (1.0)	BQ (1.0); PTSA (1.0)	AcOH/tol.	–	–	30
3[d]	[Ru] (0.1)	$AgBF_4$ (0.2); $Cu(OAc)_2$ (1.0)	*t*-amyl-OH	trace	trace	–
4[d]	[Ru] (0.1)	$AgBF_4$ (0.2); $Cu(OAc)_2$ (1.0)	*t*-amyl-OH/H_2O	–	–	–
5[d]	[Ru] (0.1)	KPF_6 (0.2); $Cu(OAc)_2$ (1.0)	*t*-amyl-OH/H_2O	–	–	–
6[d]	[Ru] (0.1)	KPF_6 (0.2); $Cu(OAc)_2$ (1.0)	H_2O	–	–	–
7[d]	[Rh] (0.1)	$AgSbF_6$ (0.2); $Cu(OAc)_2$ (2.0)	*t*-amyl-OH	40	20	20
8	[Rh] (0.1)	$AgBF_4$ (0.2); $Cu(OAc)_2$ (2.0)	*t*-amyl-OH	60	15	15
9	[Rh] (0.1)	$AgBF_4$ (0.2); $Cu(OAc)_2$ (2.0); NaOAc or $NaHCO_3$ (2.0)	*t*-amyl-OH	–	–	–

(a) Reaction temperature: 70 °C for entries 1-2 and 120 °C for entries 3-9. (b) Catalyst: [Ru] = $[RuCl_2(p\text{-cymene})]_2$; [Rh] = $[RhCp^*Cl_2]_2$. (c) Approximate % abundence of the species in the reaction aliquot taken after 16 h; (d) While some amount of **1183a/b** was left unreacted, almost all of **1186** was consumed.

The acetanilide carbonyl is likely the directing group for the *ortho*-metallation of the substrate. The C=C double of the imide can serve as a ligand around the cationic [Rh] center, which can undergo a carbometalation step. A β-hydride elimination (likely when π-allyl metal species allows the *cis* positioning of H-Met) leads to the desired imide **1187**. While a proto-metalation event, which results after the carbometalation across the imide doble bond, would account for the formation of the succinimide **1188**. On the other hand, the existence of the indolinone by-product **1189** shows that a potential conjugate addition of the **1187** anilide-*N* to the imide, or a N-Met-C complexation followed by a reductive amination step, which has also been hypothesized by Fagnou.[43b]

After these initial results, we proceeded to synthesize the key macrocyclization precursor **1175** (cf. Scheme I-37). We developed a one-pot Ireland-Claisen rearrangement-amidation protocol, where we were able to isolate the amide **1191** (Scheme I-41) directly from the allylic ester **1078**. In order to achieve such a one-pot transformation, we prepared, in a different reaction flask, a lithium dianion of aniline and slowly added to the silyl ester **1190** resulted from the [3,3] sigmatropic rearrangement of **1078**. One plausible explanation of the mechanism is that the dianionic amide can deprotonate the α-carbon of the silylester to give a ketene intermediate **1192**. The resulting monoanionic amide then can attack to the ketene to form **1193**, which upon protic quench and tautomerization leads to the acetanilide **1191**.

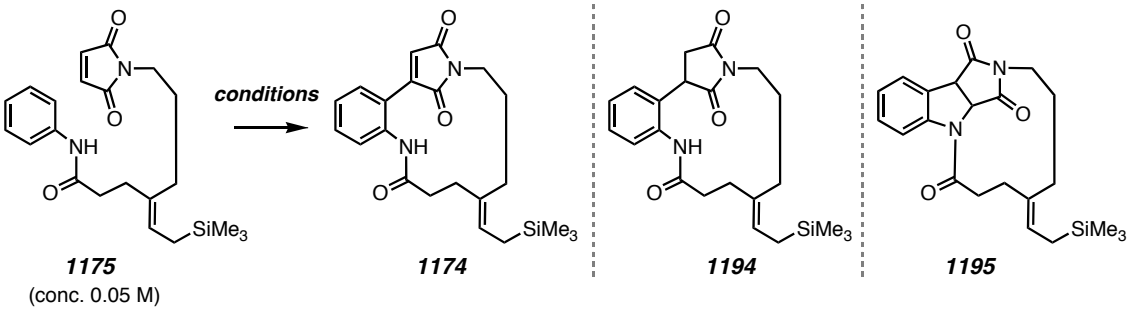
Scheme I-41. Ireland-Claisen Rearrangement Followed by Direct Amidation of **1078**.



After performing a standard EE-deprotection and a two-step Mitsunobu-RDA protocol, we isolated the macrocyclization precursor **1175** (Table I-4).

We subjected **1175** to a number of organorhodium catalyst systems, which we believed to be also suitable for the acid sensitive silyl group. In our earlier experiments with palladium species in the acidic solvents (e.g., AcOH/dioxane) or in the presence of acid additives (e.g., *p*-TsOH), we detected the loss of silyl moiety. The results shown in entries 2-3 (Table I-4) mirrored with the ones obtained in our model studies (entries 7-8 in Table I-3). As expected, we observed almost no conversion of the substrate **1175** when we used a stable (or relatively more highly ionic) silver salt like $AgNO_3$ (entry 1). In one experiment (entry 4), the succinimide product **1194** was produced almost exclusively using $AgSbF_6$ and AcOH (2 equiv). Surprisingly, AcOH did not lead

Table I-4. Efforts for Macrocyclization of **1175** via C-H Activation.[a]



entry	cat. (equiv)[b]	additive (equiv)	solvent	**1174**[c]	**1194**[c]	**1195**[c]
1	[Rh] (0.1)	$AgNO_3$ (0.2); $Cu(OAc)_2$ (4.0)	*t*-amyl-OH	–	–	–
2	[Ru] (0.1)	$AgBF_4$ (0.2); $Cu(OAc)_2$ (4.0)	*t*-amyl-OH	20	50	20
3	[Rh] (0.1)	$AgSbF_6$ (0.2); $Cu(OAc)_2$ (4.0)	*t*-amyl-OH	35	30	35
4	[Rh] (0.1)	$AgSbF_6$ (0.2); AcOH (2.0)	*t*-amyl-OH	–	70	–

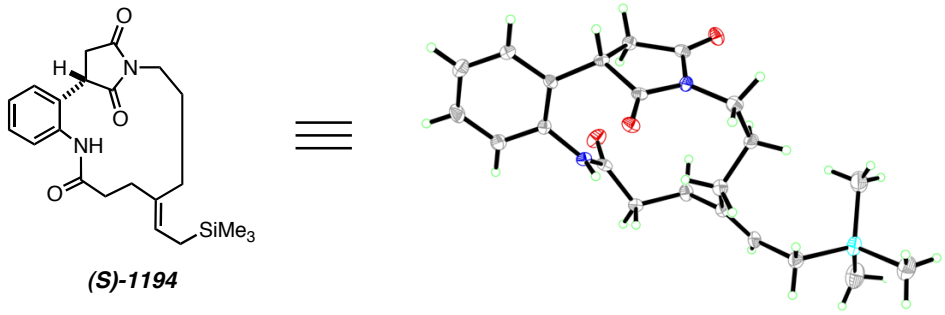
(a) Reaction temperature is 100-120 °C. (b) Catalyst: [Rh] = $[RhCp^*Cl_2]_2$. (c) Approximate % abundence of the species in the reaction aliquot taken after 16 h.

to any proto-desilylation, and it was compatible even at elevated reaction temperature (ca. 100-120 °C). We were able to isolate enough quantity of the imide **1194**, and obtained an X-ray structural information[50] (only the *S*-enantiomer is shown, Figure I-5).

We turned our attention to the key allylative cyclization on **1175**, that we obtained both from the Stille (cf. Scheme I-36) or the C-H functionalization (cf. Table I-4) reactions.

50. Re-crystallization of racemic **1194** was done by slow gas-diffusion technique using EtOAc (solvent) and cyclohexane. Bond precision: C-C = 0.0076 Å. The space group is P-1 with cell constants a = 16.364(3) Å, b = 17.753(4) Å, c = 17.754(4) Å; alpha = 108.124(3) deg., beta = 105.424(3) deg., gamma = 105.446(3) deg.; Temperature: 173 K.

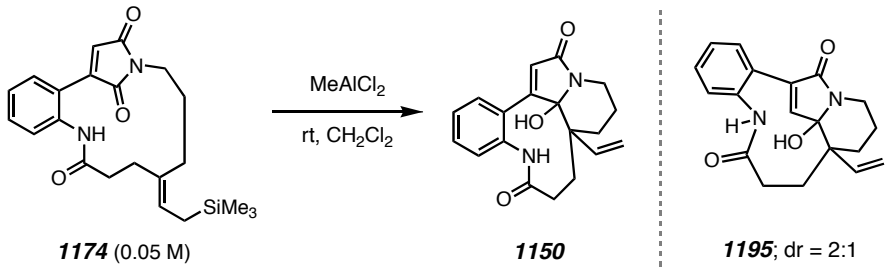
Figure I-5. X-ray Structure of **(*S*)-1194**.[a]



(a) Carbon in grey, oxygen in red, nitrogen in blue, and silicon in turquoise.

To our surprise, under our standard $MeAlCl_2$ LA-activation, we did not isolate any of the desired leuconolam precursor **1150**. Instead, we observed the formation of the undesired regioisomer **1195** as a 1:2 mixture of diastereomers.

Scheme I-42. Efforts Toward the Intarmolecular Allylation of **1174**.



I-H. Conclusion

We extensively studied novel approaches toward the synthesis of racemic leuconolam [**(±)-1001a**]. We highlighted the importance of planning more than one synthetic route toward a complex natural product. Our key bonding strategies involved arene-alkene coupling (step **a** in Scheme I-11), allylative cyclization (step **b**), and the amide bond formation (step **c**) on a pivotal intermediate **1075**.

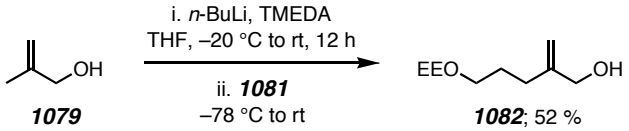
To our delight and excitement, we accomplished the total synthesis of the target alkaloid in 14-longest linear steps from methallyl alcohol (**1079**) following the *route-I*. In addition, we developed efficient syntheses of *o*–(trialkylstannyl)anilines **1136** and **1142**. Our efforts to synthesize these useful building blocks led us to explore some deeper aspects in Stille coupling chemistry. Eventually, our collective work evolved as a side-project, which I will thoroughly discuss in Chapter-II.

Regarding the *route-II*, we developed a one-pot Ireland–Claisen rearrangement–anilide formation to afford the key cyclization precursor **1175**. Furthermore, we achieved a 13–membered ring macrocyclization of linear precursors **1174** or **1175** via either C–H functionalization or a Stille coupling reaction.

I-I. Experimental Section

General Protocols. All reactions were performed under a dry nitrogen or argon atmosphere unless otherwise noted. All glassware was flame- and/or oven-dried before use. Tetrahydrofuran (THF), diethyl ether (Et_2O), and dichloromethane (CH_2Cl_2) were dried through Al_2O_3 columns; hexanes (Hex) and ethyl acetate (EtOAc) were used as received (reagent grade). All other reagents and solvents were used as received. Thin layer chromatography (TLC) was performed using TLC plastic sheets with F_{254} indicator and visualization via UV-light or staining with either potassium permanganate or anisaldehyde. Flash column purifications were performed using 40-63 μm silica gel or alumina (neutral, Brockman activity 1). Medium pressure liquid chromatography (MPLC) purifications were performed using glass columns, dry packed with 25-35 μm particle size silica gel. All NMR spectra were determined in $CDCl_3$. ^1H NMR spectra were acquired at 500 MHz ^1H. ^{13}C NMR spectra were acquired at 125 or 75 MHz. Chemical shifts (δ) for ^1H NMR spectra are referenced to TMS at δ = 0.00 ppm, and ^{13}C NMR spectra are referenced to $CDCl_3$ at δ = 77.23 ppm. The following abbreviations are used to describe NMR resonances: s (singlet), d (doublet), t (triplet), q (quartet), pentet (p), sext (sextet), m (multiplet), br (broad), and nfom (non-first order multiplet). Coupling constants (*J*) are reported in Hz. Infrared spectra were recorded on an FT-IR spectrometer. The most intense and/or diagnostic peaks are reported, and all spectra were collected in attenuated total reflectance (ATR) mode as thin films on a germanium window. Low-resolution GC-MS data (LRMS) were recorded at 70 eV. High-resolution mass spectra (HRMS) in the ESI mode were recorded on a time of flight instrument with 20,000 resolving power (FWHM) using PEG or PPG as internal standards/calibrants. High-resolution mass spectra (HRMS) in the CI or EI mode were recorded on a double focusing instrument with 4,000 resolving power (FWHM) using perfluorokerosene as the calibrant.

5-(1-Ethoxyethoxy)-2-methylenepentan-1-ol (1082).



1079 ***1082***; 52 %

To a 500 mL three-neck round bottom flask equipped with a mechanical stirrer, an addition funnel and a vacuum trap was added *n*-BuLi (2.5 M in hexanes, 200 mL, 2.2 equiv). The flask was placed in an ice bath and vaccum at 5 mmHg was applied to the system. Approximately 150 mL of hexane was collected in the vacuum trap over 30 min. The resulting thick yellow residue was carefully re-dissolved at 0 °C in dry Et2O by dropwise addition over 10 min. The solution was cooled to –78 °C and treated with TMEDA (xx mL, xx mmol, 2 equiv) and was stirred at –20 °C for 3 h. To this mixture was added a solution of methallyl alcohol (**1079**, xx mL, xx mmol, 1 equiv) in dry Et_2O (xx mL) at the same temperature. The resulting mixture was allowed to warm to room temperature at which it was stirred for 12 h, then treated with the bromoethanol **1081** at –78 °C. The resulting solution was stirred 0 °C for 12 h, quenched by addition of saturated aqueous NH_4Cl (100 mL) at the same temperature. The biphasic mixture was stirred for 1 h and extracted with EtOAc (3 x 1L). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel chromatography gave the monosubstitution product **1082** (15 g, 52%) as a light yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04 (s, 1H), 4.88 (s, 1H), 4.68 (q, *J* = 5.5, 1H), 4.07 (s, 2H), 3.65 (dq, *J* = 9.5, 7.0 Hz, 1H), 3.60 (dt, *J* = 9.5, 7.0 Hz, 1H), 3.49 (dq, *J* = 9.5, 7.0 Hz, 1H), 3.44 (dt, *J* = 9.5, 7.0 Hz, 1H), 2.34 (br s, 1H), 2.14 (t, *J* = 7.0, 2H), 1.75 (p, *J* = 7.0 Hz, 2H), 1.31 (d, *J* = 5.5 Hz, 3H), and 1.21 (t, *J* = 7.0 Hz, 3H).

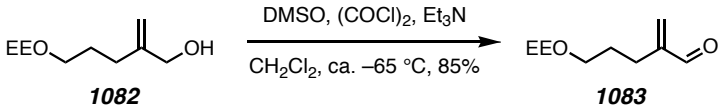
^{13}C NMR (125 MHz, $CDCl_3$) 148.1, 109.5, 99.6, 65.7, 64.8, 60.8, 29.5, 27.9, 19.8, and 15.3.

IR (neat): 3430, 3079, 2976, 2932, and 2875 cm^{-1}.

HRMS (ESI): calcd for $C_{10}H_{20}O_3 \bullet Na^+$ 211.1305, found 211.1304.

TLC R_f = 0.3 (Hex/EtOAc = 5:1).

5-(1-Ethoxyethoxy)-2-methylenepentanal (1083).



1082 ***1083***

To a CH_2Cl_2 solution of $(COCl)_2$ (0.5 M, 1.2 equiv) at -78 °C was added DMSO (1.3 equiv) via a syringe pump, during which reaction the temperature was maintained at around –65 °C. After being stirred for 30 min at the same temperature, the reaction mixture was treated with a CH_2Cl_2 solution of the alcohol **1082** (1.0 M, 1.0 equiv) with a pace to keep the temperature, again, at around –65 °C. The resulting solution became inhomogenous after being stirred for 4 h, and neat Et_3N (3.0 equiv) was added dropwise. The reaction mixture was allowed to warm to 0 °C, where it was diluted with CH_2Cl_2 and quenched with saturated aqueous NH_4Cl solution. The organic layer was separated, washed with water and brine, and dried over Na_2SO_4. The combined organic layers were concentrated under reduced pressure. The resulting crude material was purified by distillation at 65-68 °C under ca. 1 mm Hg pressure to afford the title aldehyde **1083** in ca. 85% yield as a pale yellow oil. [Unorthodox to not have a spericied amount of reatants, solvent, etc.]

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (s, 1H), 6.29 (s, 1H), 6.03 (s, 1H), 4.68 (q, *J* = 5.5 Hz, 1H), 3.65 (dq, *J* = 9.5, 7.0 Hz, 1H), 3.59 (dt, *J* = 9.5, 6.5 Hz, 1H), 3.48 (dq, *J* = 9.5, 7.0 Hz, 1H), 3.45 (dt, *J* = 9.5, 6.5 Hz, 1H), 2.34 (t, *J* = 7.5 Hz, 2H), 1.74 (p, *J* = 6.5, 2H), 1.31 (d, *J* = 5.5 Hz, 3H), and 1.21 (t, *J* = 7.0 Hz, 3H).

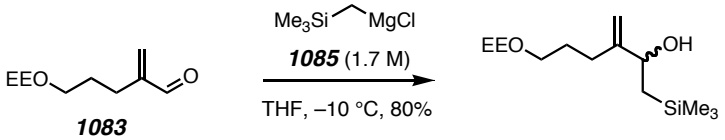
^{13}C NMR (125 MHz, $CDCl_3$) δ 194.6, 149.8, 134.2, 99.7, 64.4, 60.8, 27.9, 24.7, 19.9, and 15.3.

IR (neat): 2977, 2932, 2874, 1693, and 1379 cm^{-1}.

HRMS (ESI): calcd for $C_{10}H_{18}O_3 \bullet Na^+$ 209.1148, found 209.1146.

TLC R_f = 0.3 (Hex/EtOAc = 11:1).

6-(1-Ethoxyethoxy)-3-methylene-1-(trimethylsilyl)hexan-2-ol (1086).



1083 *1086*

(Chloromethyl)trimethylsilylmagnesium chloride (**1085**) was prepared in this manner: Commercially available (chloromethyl)trimethylsilane (2.23 mL, 16.0 mmol) was added to a stirred suspension of ground magnesium turnings (0.58 g, 24.0 mmol, 1.5 equiv) in Et_2O (38 mL) in a flame dried Schlenk flask. The mixture was boiled under reflux for 1 h and cooled to room temperature. The gray suspension was stirred at room temperature for 5 h. This silyl Grignard reagent (0.3 M, 8.62 mL, 2.60 mmol, 1.3 equiv) was added dropwise to a stirred solution of the aldehyde **1083** (0.37 g, 1.98 mmol) in Et_2O (1.30 mL) at –78 ^oC. The resulting mixture was warmed to room temperature over 2 h, stirred for an additional 3 h, quenched by the addition of saturated aqueous $NaHCO_3$ (1.00 mL), and extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with brine (2 x 5.00 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by MPLC (10:1 hex/EtOAc) gave the title compound **1086** (0.19 g, 80%) as a yellow oil.

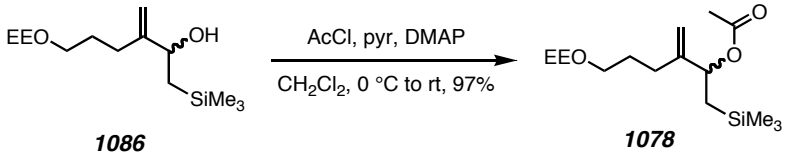
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.02 (s, 1H), 4.79 (s, 1H), 4.68 (q, *J* = 5.5 Hz, 1H), 4.29 (t, *J* = 7.5 Hz 1H), 3.68-3.60 (overlapped m, 2H), 3.52-3.44 (overlapped m, 2H), 2.21 (dt, *J* = 15.5, 8.0 Hz, 1H), 2.09 (dt, *J* = 15.5, 8.0 Hz, 1H), 1.79 (p, *J* = 7.0 Hz, 2H), 1.65 (br s, 1H), 1.32 (d, *J* = 5.5 Hz, 3H), 1.21 (t, *J* = 7.5 Hz, 3H), 0.97 (dd, *J* = 14.5, 6.5 Hz, 1H), 0.96 (dd, *J* = 14.5, 8.0 Hz, 1H), and 0.04 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 153.55, 153.51, 109.1, 99.8, 74.2, 65.24/65.1, 61.0/60.9, 28.5/28.4, 27.5/27.3, 24.69/24.68, 20.09/20.07, 15.5, and -0.7.

IR (neat): 2950, 2898, 1734, 1645, 1444, 1380 1248, 1132, 1091, 1054, and 859 cm^{-1}.

TLC R_f = 0.3 (Hex/EtOAc = 11:1).

6-(1-Ethoxyethoxy)-3-methylene-1-(trimethylsilyl)hexan-2-yl acetate (1078).



1086 ***1078***

To a solution of **1086** (1 equiv), pyridine (1.5 equiv), and DMAP (0.2 equiv) in MeOH (0.3 M) was added acetyl chloride at 0 ^oC. The reaction mixture was warmed to room temperature over 30 min and stirred overnight. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine and concentrated under reduced pressure. The resulting crude material was purified by silica gel chromatography (8:1 hex/EtOAc) to give the allylic ester **1078** (0.35 g, 97%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (br t, *J* = 8.5 Hz, 1H), 5.04 (s, 1H), 4.85 (s, 1H), 4.69 (q, *J* = 5.5 Hz, 1H), 3.66 (br dq, *J* = 10.0, 7.0 Hz, 1H), 3.60 (br dt, *J* = 10.5, 6.5 Hz, 1H), 3.50 (br dq, *J* = 10.0, 7.0 Hz, 1H), 3.45 (br dt, *J* = 10.5, 6.5 Hz, 1H), 2.12^+ (dt, *J* = 17, 8.5 Hz, 1H), 2.12^- (dt, *J* = 18, 6.5 Hz, 1H), 2.02 (s, 3H), 1.76^+ (dp, *J* = 13.5, 6.5 Hz, 1H), 1.76^- (dp, *J* = 13.5, 6.5 Hz, 1H), 1.31 (d, *J* = 5.5 Hz, 3H), 1.21 (t, *J* = 7.5 Hz, 3H), 1.09 (dd, *J* = 14.5, 8.5 Hz, 1H), 1.03 (dd, *J* = 14.5, 7.0 Hz, 1H), and 0.01 (s, 9H).

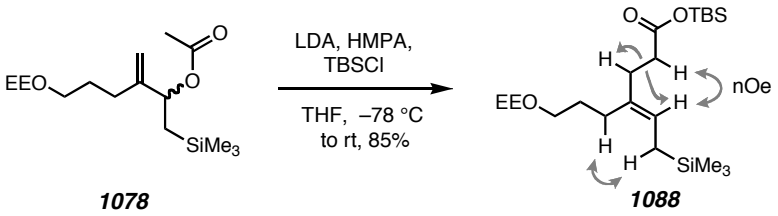
^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 149.0, 110,7, 99.6, 75.8, 64.9, 60.8, 27.9, 27.7, 22.2, 21.5, 19.9, 15.3, and -1.1.

IR (neat): 2975, 2952, 2897, 1740, 1370, and 1248 cm^{-1}.

HRMS (ESI): calcd for $C_{16}H_{32}O_4Si•Na^+$ 339.1962, found 339.1982.

TLC R_f = 0.4 (Hex/EtOAc = 10:1).

(*E*)-*tert*-Butyldimethylsilyl 7-(1-Ethoxyethoxy)-4-[2-(trimethylsilyl)ethylidene]heptanoate (1088).

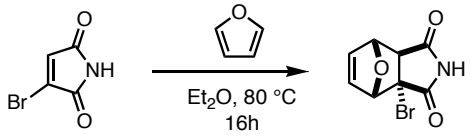


1078 ***1088***

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.21 (t, *J* = 8.5 Hz, 1H), 4.68 (q, *J* = 5.5 Hz, 1H), 3.65 (dq, *J* = 9.5, 7.0 Hz, 1H), 3.56 (dt, *J* = 9.5, 6.5 Hz, 1H), 3.49 (dq, *J* = 9.5, 7.0 Hz, 1H), 3.40 (dt, *J* = 9.5, 6.5 Hz, 1H), 2.40 (nfom, 2H), 2.30 (br t, *J* = 8 Hz, 2H), 2.07 (dt, *J* = 13.5, 7.5 Hz, 1H), 2.02 (dt, *J* = 13.5, 7.5 Hz, 1H), 1.63 (br p, *J* = 7, 2H), 1.41 (d, *J* = 8.5 Hz, 2H), 1.31 (d, *J* = 5.5 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 3H), 0.94 (s, 9H), 0.26 (s, 6H), and -0.02 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 174.2, 134.9, 121.7, 99.8, 65.4, 60.9, 35.6, 32.2, 28.6, 26.5, 25.8, 20.1, 18.6, 17.8, 15.6, and -1.51.

(±)-(3a*S*,4*S*,7*R*,7a*S*)-3a-Bromo-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindole-1,3(2*H*)-dione (1095)



1094 ***1095***

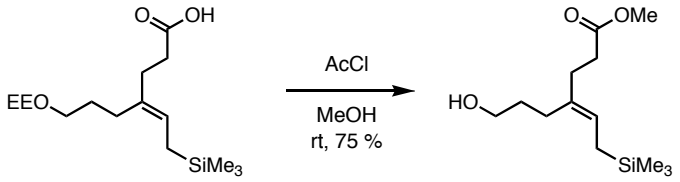
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (br s, 1H), 6.68-6.56 (nfom, 2H), 5.33 (dd *J* = 1.0, 1.0, 1H), 5.31 (dd *J* = 1.0, 1.0, 1H), and 2.89 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.95, 172.94, 136.8 136.7, 83.4, 82.8, 57.1, and 56.1.

IR (thin film): 3184, 3089, 1781, 1714, 1345, 1161, and 1032 cm^{-1}.

TLC: R_f 0.25 (2:1 Hex/EtOAc).

(*E*)-Methyl 7-Hydroxy-4-[2-(trimethylsilyl)ethylidene]heptanoate (1097).



1088 ***1097***

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.15 (t, *J* = 8.5 Hz, 1H), 3.59 (s, 3H), 3.58 (t, *J* = 6.5 Hz, 2H), 2.42-2.39 (m, 2H), 2.26 (br t, *J* = 7 Hz, 2H), 2.00 (br t, *J* = 8 Hz, 2H), 1.57 (br p, *J* = 7 Hz, 2H), 1.35 (d, *J* = 8.5 Hz, 2H), and -0.09 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 174.1, 134.6, 122.2, 63.1, 51.8, 33.7, 32.0, 31.2, 28.6, 27.5, 26.0, 20.8, 18.6, and -1.4.

IR (thin film): 3442, 2952, 2895, 2861, 1741, 1438, 1248, 1155, 1058, and 851 cm^{-1}.

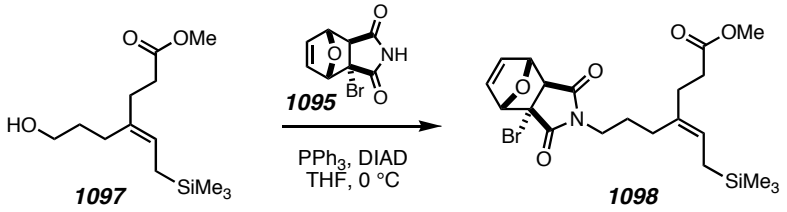
HRMS (ESI): calcd for $C_{13}H_{26}O_3Si{\bullet}Na^+$ 281.1543, found 281.1550.

TLC: R_f 0.40 (1:1 Hex/EtOAc).

General Procedure for a Mitsunobu Reaction

A solution of PPh_3 (1.5 equiv) in THF (0.3 M) at –10 °C was added a solution of the starting alcohol (1 quiv) in THF (0.3 M). The mixture was stirred for 5 min and treated with the imide (1.3 equiv). To the resulting solution was added DIAD (1.5 equiv) dropwise during which the color of the added DIAD (yellow) dissipated until the end point was reached. The reaction mixture was stirred at –10 °C over 30 min and quenched by addition of water. The organic phase was extracted with EtOAc, washed with brine and dried over Na_2SO_4. The organic liquid was concentrated under reduced pressure to give the crude material, which was purified by silica gel chromatography.

(±)-(*E*)-Methyl 7-((3a*S*,4*S*,7*R*,7a*S*)-3a-Bromo-1,3-dioxo-3a,4,7,7a-tetrahydro-1*H*-4,7-epoxyisoindol-2(3*H*)-yl)-4-[2-(trimethylsilyl)ethylidene]heptanoate (1098).



The imide **1098** was synthesized from the primary alcohol **1097** following the general Mitsunobu displacement procedure mentioned above.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.65 (br s, 2H), 5.27 (s, 1H), 5.26 (s, 1H), 5.20 (t, *J* = 8.5 Hz, 1H), 3.65 (s, 3H), 3.54 (t, *J* = 7.0 Hz, 2H), 2.85 (s, 1H), 2.40-2.36 (m, 2H), 2.29 (br t, *J* = 7.5 Hz, 2H), 1.96 (br t, *J* = 8 Hz, 2H), 1.65 (br p, *J* = 7 Hz, 2H), 1.37 (d, *J* = 8.5 Hz, 2H), and -0.04 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 174.0, 173.5, 173.4, 136.69, 136.68, 133.5, 122.7, 83.3, 82.7, 56.0, 55.4, 51.7, 40.0, 33.6, 31.8, 26.8, 26.0, 18.7, and -1.6.

IR (thin film): 2952, ca. 1730 (sh), 1711, 1163, and 855 cm^{-1}.

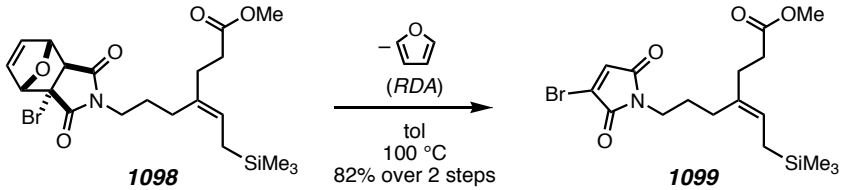
HRMS (ESI): calcd for $C_{21}H_{30}{}^{79}BrNO_5Si{\bullet}Na^+$ 506.0969, found 506.0960, and calcd for $C_{21}H_{30}{}^{81}BrNO_5Si{\bullet}Na^+$ 508.0949, found 508.0942.

TLC: R_f 0.55 (2:1 Hex/EtOAc).

General Procedure for the Retro-Diels-Alder (RDA) Reaction

A solution of the starting imide in toluene (0.05 M) was placed in a reaction culture tube. The solution was purged with Ar for 15 min, and the tube was quickly sealed which was then placed in a 100 °C oil bath. The reaction mixture was stirred until the TLC analysis showed the full conversion of the protected imide to the maleimide. The reaction mixture was allowed to cool down to room temperature, and diluted with EtOAc that helped the bulk toluene to be removed more easily under reduced pressure. The resulting residue was left under the high vacuum for 12 h. The crude material could be purified by column chromatography, however, in most cases the purity of the crude compound was high enough to be used in the following experiments.

(*E*)-Methyl 7-(3-Bromo-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-4-[2-(trimethylsilyl)ethylidene]heptanoate (1099).



1098 ***1099***

The maleimide **1099** was prepared from the protected imide **1098** following the general RDA procedure mentioned above.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86 (s, 1H), 5.22 (t, *J* = 8.5 Hz, 1H), 3.65 (s, 3H), 3.55 (br t, *J* = 7.5 Hz, 2H), 2.41-2.36 (m, 2H), 2.30 (br t, *J* = 7.5 Hz, 2H), 1.99 (br t, *J* = 8 Hz, 2H), 1.69-1.63 (br p, *J* = 7 Hz, 2H), 1.36 (d, *J* = 8.5 Hz, 2H), and -0.03 (s, 9H).

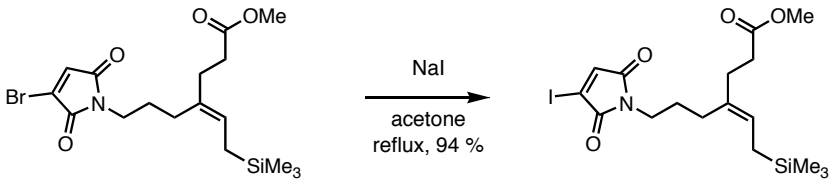
^{13}C NMR (125 MHz, $CDCl_3$): δ 173.9, 168.8, 165.5, 133.5, 132.0, 131.6, 122.7, 51.8, 39.1, 33.6, 31.7, 27.0 (br), 18.8, and -1.6.

IR (thin film): 2951, ca. 1730 (sh), 1715, 1398, 1245, 1155, and 851 cm^{-1}.

HRMS (ESI): calcd for $C_{17}H_{26}{}^{79}BrNO_4Si{\bullet}Na^+$ 438.0707, found 438.0713, and calcd for $C_{17}H_{26}{}^{81}BrNO_4Si{\bullet}Na^+$ 440.0687, found 440.0709.

TLC: R_f 0.65 (2:1 Hex/EtOAc).

(*E*)-Methyl 7-(3-Iodo-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-4-[2-(trimethylsilyl)ethylidene]heptanoate (1103).



1099 ***1103***

To a solution of the bromomaleimide **1099** (1 equiv) in acetone (0.5 M) was added NaI (10 equiv) at room temperature. The mixture was heated to reflux in a sealed culture tube, and was stirred for 24 h. The resulting mixture was cooled to room temperature and concentrated under reduced pressure. The acetone free residue was re-dissolved with EtOAc, washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford the iodide **1103**. The crude material was used in the next step without further purification.

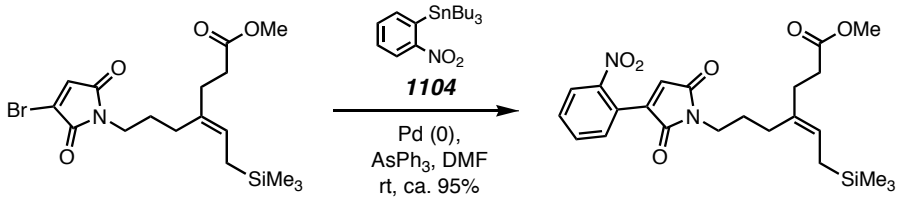
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (s, 1H), 5.22 (t, *J* = 8.5 Hz, 1H), 3.65 (s, 3H), 3.56 (br t, *J* = 7.5 Hz, 2H), 2.40-2.36 (m, 2H), 2.30 (br t, *J* = 7.5 Hz, 2H), 1.98 (br t, *J* = 8 Hz, 2H), 1.65 (br p, *J* = 7 Hz, 2H), 1.37 (d, *J* = 8.5 Hz, 2H), and -0.03 (s, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.9, 170.0, 166.9, 140.7, 133.5, 122.7, 107.5, 51.8, 39.3, 33.6, 31.7, 27.00, 26.97, 18.8, and -1.6.

IR (thin film): 2952, ca. 1730 (sh), 1711, 1440, 1398, 1247, 1155, and 853 cm^{-1}.

HRMS (ESI): calcd for $C_{17}H_{26}INO_4Si•Na^+$ 486.0568, found 486.0539.

(*E*)-Methyl 7-(3-(2-Nitrophenyl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-4-[2-(trimethylsilyl)ethylidene]heptanoate (1105).

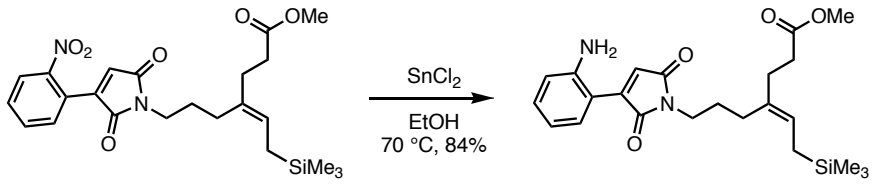


^{1}H NMR (500 MHz, $CDCl_3$): δ 8.18 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.74 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.67 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.47 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.68 (s, 1H), 5.22 (tt, *J* = 8.5, 1.0 Hz, 1H), 3.65 (s, 3H), 3.57 (t, *J* = 7.5 Hz, 2H), 2.41-2.37 (m, 2H), 2.32 (br tt, *J* = 8.0, 1.0 Hz, 2H), 2.01 (nfom, 2H), 1.69 (nfom, 2H), 1.40 (d, *J* = 8.5 Hz, 2H), and -0.04 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.9, 170.0, 168.8, 148.3, 145.6, 134.0, 133.6, 131.6, 131.5, 126.4, 125.2, 124.7, 122.5, 51.7, 38.6, 33.6, 31.8, 27.0, 26.9, 18.6, and -1.7.

IR (thin film): 2953, 1734, 1710, 1526, and 855cm^{-1}.

(*E*)-Methyl 7-[3-(2-Aminophenyl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl]-4-[2-(trimethylsilyl)ethylidene]heptanoate (1106).



1105 ***1106***

To a solution of **1105** (1 equiv) in EtOH (0.5 M) was added $SnCl_2$ (3 equiv) and the resulting mixture was heated to ca. 70 °C in a sealed culture tube. After 12 h, the reaction mixture was cooled to room temperature and was quenched by addition of brine. The organic phase was extracted with EtOAc, washed with water and brine. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the title anilino imide **1106** which was used later used without any purification.

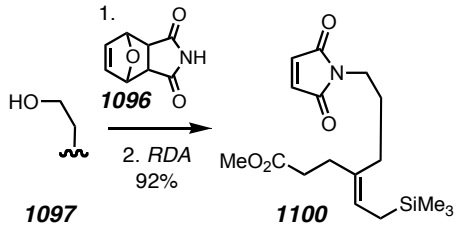
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.23 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H), 6.82 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1H), 6.76 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.73 (s, 1H), 5.22 (t, *J* = 8.5 Hz, 1H), 4.32 (br s, 2H), 3.65 (s, 3H), 3.57 (br t, *J* = 7.5 Hz, 2H), 2.42-2.38 (m, 2H), 2.32 (br t, *J* = 7.5 Hz, 2H), 2.02 (br t, *J* = 8 Hz, 2H), 1.71 (br p, *J* = 7 Hz, 2H), 1.39 (d, *J* = 8.5 Hz, 2H), and -0.03 (s, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 174.0, 171.4, 171.0, 146.5, 144.5, 133.7, 132.2, 131.4, 125.5, 122.5, 119.0, 117.3, 114.8, 51.7, 38.4, 33.6, 31.8, 27.1 (br), 18.7, and -1.6.

IR (thin film): 2952, 1737, 1702, 1626, 1441, 1404, 1248, 1156, and 854 cm^{-1}.

HRMS (ESI): calcd for $C_{23}H_{32}N_2O_4Si•Na^+$ 451.2096, found 451.2122.

(*E*)-Methyl 7-(2,5-Dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-4-[2-(trimethylsilyl)ethylidene]heptanoate (1100).



The primary alcohol **1097** was subjected to the Mitsunobu conditions with the protected imide nucleophile **1096** by performing the procedure mentioned above. The resulting intermediate was subjected to the RDA conditions as described above to afford the title symmetric maleimide **1100** in 92% overall yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.70 (s, 2H), 5.21 (t, *J* = 8.5 Hz, 1H), 3.65 (s, 3H), 3.51 (br t, *J* = 7.5 Hz, 2H), 2.39 (m, 2H), 2.31 (br t, *J* = 7.5 Hz, 2H), 1.98 (br t, *J* = 8 Hz, 2H), 1.64 (br p, *J* = 7 Hz, 2H), 1.37 (dt, *J* = 8.5, 1.0 Hz, 2H), and -0.03 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 174.0, 171.0, 134.3, 133.7, 122.5, 51.7, 38.1, 33.6, 31.8, 27.1, 27.07, 18.7, and -1.6.

IR (thin film): 2952, 1737, 1707, 1409, 1247, 1154, 855, and 838 cm^{-1}.

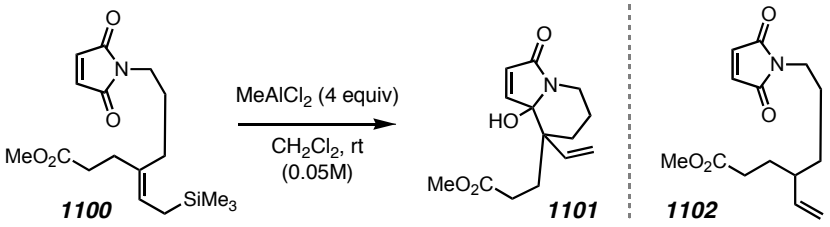
HRMS (ESI): calcd for $C_{17}H_{27}NO_4Si{\bullet}Na^+$ 360.1602, found 360.1586.

TLC: R_f 0.6 (2:1 Hex/EtOAc).

General Procedure for the Allylative Ring Closure

A solution of the allylation precursor imide (1 equiv) in CH_2Cl_2 (0.05 M) was treated with $MeAlCl_2$ (1.6 M) in hexane at room temperature. The resulting mixture was stirred at the same temperature for 10-60 min until TLC analysis showed the full conversion of the substrate. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude material was purified by trituration using 3:1 mixture of Hex/EtOAc. The product precipitated out as an amorphous solid that was in high enough purity to be used in the next experiments. The amino ester regioisomers were separated by silica gel chromatography using EtOAc as the eluent.

(±)-(8*R*,8a*R*)-Methyl 3-(8a-Hydroxy-3-oxo-8-vinyl-3,5,6,7,8,8a-hexahydroindolizin-8-yl)propanoate (1101).



The symmetric imide **1100** was subjected to the allylative ring closure conditions as described above to afford the carbinolamides **1101** and **1102**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (d, *J* = 6.0 Hz, 1H), 6.17 (d, *J* = 6.0 Hz, 1H), 5.87 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.40 (d, *J* = 11.0 Hz, 1H), 5.21 (d, *J* = 17.5 Hz, 1H), 4.07 (dd, *J* = 13.0, 5.5 Hz, 1H), 3.63 (s, 3H), 2.95 (ddd, *J* = 13.0, 13.0, 4.5 Hz, 1H), 2.54 (br s, 1H), 2.09 (dt, *J* = 15.5, 5.5 Hz, 1H), 2.09-2.02 (m, 2H), and 1.67-1.43 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8, 167.7, 146.9, 140.6, 128.6, 117.4, 91.9, 51.9,

46.2, 35.2, 28.7, 25.6, 24.3, and 20.1.

IR (thin film): 3330, 2950, 2926, 2873, 1736, 1684, 1433, 1172, 1057, and 913 cm^{-1}.

HRMS (ESI): calcd for $C_{14}H_{19}NO_4 \bullet Na^+$ 288.1206, found 288.1201.

TLC: R_f 0.2 (EtOAc).

Methyl 7-(2,5-Dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-4-vinylheptanoate (1102).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.69 (s, 1H), 5.43 (ddd, *J* = 17.0, 10.0, 9.0 Hz, 1H), 5.03 (dd, *J* = 10.0, 2.0 Hz, 1H), 4.98 (dd, *J* = 17.0, 2.0 Hz, 1H), 3.66 (s, 3H), 3.49 (t, *J* = 7.0 Hz, 2H), 2.32 (ddd, *J* = 16.0, 9.0, 5.5 Hz, 1H), 2.24 (ddd, *J* = 16.0, 9.0, 7.0 Hz, 1H), 1.93 (ddddd, *J* = 9.5, 9.5, 9.5, 4.5, 4.5 Hz, 1H), 1.71 (dddd, *J* = 13.5, 9.0, 7.0, 4.5 Hz, 1H), 1.68-1.46 (m, 4H), 1.36 (nfom, 1H), and 1.29-1.20 (nfom, 1H).

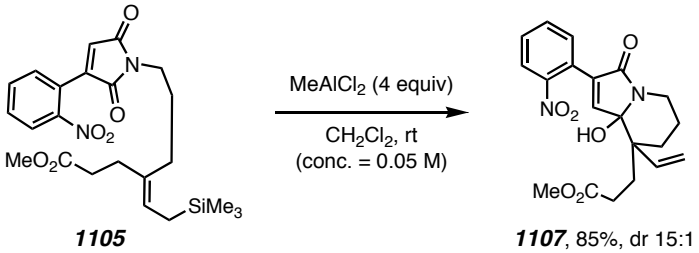
^{13}C NMR (125 MHz, $CDCl_3$): δ 174.4, 171.1, 141.5, 134.2, 116.4, 51.7, 43.7, 38.0, 32.10, 32.06, 30.0, and 26.4.

IR (thin film): 2927, 2852, 1734, 1706, 1409, 1254, 1172, 831, and 696 cm^{-1}.

HRMS (ESI): calcd for $C_{14}H_{19}NO_4 \bullet Na^+$ 288.1206, found 288.1217.

TLC: R_f 0.65 (2:1 Hex/EtOAc).

The Undesired Allylation Regioisomer of the Nitrophenyl 1107.



1105 ***1107***, 85%, dr 15:1

The nitrophenyl imide **1105** was subjected to the previously described allylative ring conditions affording the carbinolamide **1107**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.67 (td, *J* = 7.5, 1.5 Hz,

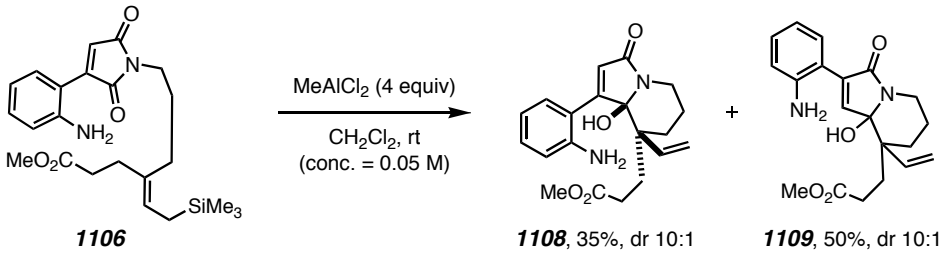
1H), 7.57 (td, *J* = 7.5, 1.5 Hz, 1H), 7.44 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.05 (s, 1H), 5.94 (dd, *J* = 17.5, 11.0, Hz, 1H), 5.36 (dd, *J* = 11.0, 1.0 Hz, 1H), 5.20 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.03 (dddd, *J* = 13.0, 5.5, 1.0, 1.0 Hz, 1H), 3.64 (s, 3H), 3.06 (ddd, *J* = 13.0, 13.0, 4.0 Hz, 1H), 2.19-1.09 (m, 3H), 1.82 (ddd, *J* = 15.0, 10.0, 6.5, 1H), and 1.76-1.55 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8, 165.0, 148.9, 140.6, 140.5, 138.6, 133.3, 131.8, 130.0, 126.8, 124.8, 117.2, 90.3, 51.9, 46.9, 35.8, 28.8, 25.5, 24.5, and 20.1.

IR (thin film): 2692, 2917, 2849, 1731, 1650, 1527, 1431, 1352, 1260, 1094, 1073, 1021, and 797 cm^{-1}.

HRMS (ESI): calcd for $C_{20}H_{22}N_2O_6 \bullet Na^+$ 409.1370, found 409.1388.

The Desired Allylation Regioisomer of the Amino Ester 1108.



1106 ***1108***, 35%, dr 10:1 ***1109***, 50%, dr 10:1

The anilino imide **1106** was subjected to the previously described allylative ring conditions affording the carbinolamides **1108** and **1109**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.19 (td, *J* = 7.5, 1.5 Hz, 1H), 6.83 (td, *J* = 7.5, 1.0 Hz, 1H), 6.74 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.17 (s, 1H), 5.36 (dd, *J* = 17.5, 11.0, Hz, 1H), 5.03 (dd, *J* = 11.0, 1.0 Hz, 1H), 4.98 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.60-4.20 (br s, N*H*$_2$), 4.11 (dddd, *J* = 13.0, 5.5, 1.5, 1.5 Hz, 1H), 3.61 (s, 3H), 2.99 (ddd, *J* = 13.0, 13.0, 4.0 Hz, 1H), 2.11 (m, 1H), 2.05-1.93 (m, 2H), and 1.67-1.43 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8, 167.3, 159.5, 143.8, 139.5, 130.7, 130.6, 127.4, 121.6, 119.8, 118.0, 117.6, 94.0, 51.9, 47.6, 35.6, 28.6, 25.5, 24.7, and 20.2.

IR (thin film): 3354 (br), 2949, 1734, 1676, 1672, 1434, 1419, 1289, 1202, 1172, 1048, 928, 841, 754, and 673 cm^{-1}.

LC-LRMS [ES + APCI, 50:50 to 0:100 (%) H_2O:MeOH, 10 min run]: t_R 3.30 min; 339.0 $(M–OH)^+$, and 677.3 $(2M–H_2O–OH)^+$.

HRMS (ESI): calcd for $C_{20}H_{24}N_2O_4•Na^+$ 379.1628, found 379.1636.

The Undesired Allylation Regioisomer of the Amino Ester 1109.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (ddd, *J* = 7.5, 1.5, 0.5 Hz, 1H), 7.14 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H), 6.86 (s, 1H), 6.76 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 6.67 (ddd, *J* = 8.0, 1.5, 0.5 Hz, 1H), 5.90 (dd, *J* = 17.5, 11.0, Hz, 1H), 5.34 (dd, *J* = 11.0, 1.0 Hz, 1H), 5.16 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.45-4.01 (br s, N*H*$_2$), 4.02 (ddd, *J* = 13.0, 5.5, 1.0 Hz, 1H), 3.60 (s, 3H), 2.93 (ddd, *J* = 13.0, 13.0, 4.0 Hz, 1H), 2.14-2.00 (m, 3H), and 1.65-1.45 (m, 5H).

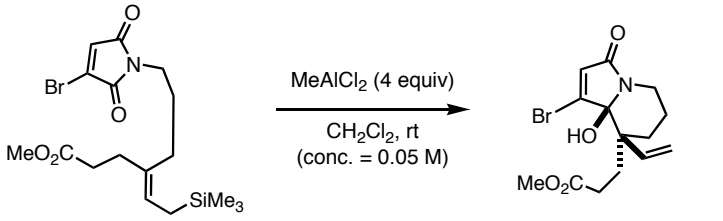
^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8, 167.2, 142.0, 140.7, 139.2, 131.0, 130.8, 130.4, 129.2, 125.6, 119.6, 117.0, 90.1, 51.9, 48.6, 35.6, 28.8, 25.6, 24.4, and 20.2.

IR (thin film): 2959, 1731, 1680, 1628, 1432, 1277, 1261, 763, and 753 cm^{-1}.

HRMS (ESI): calcd for $C_{20}H_{24}N_2O_4 \bullet Na^+$ 379.1628, found 379.1643.

TLC: R_f 0.6 (EtOAc).

The Desired Allylation Regioisomer of the Bromo Amide 1110.



1099; X = Br ***1110***; X = Br, 87%, dr 15:1

The bromoimide **1099** was subjected to the previously described allylative ring conditions to afford the carbinolamide **1110**.

^{1}H NMR (500 MHz, d_6-Acetone): δ 6.43 (s, 1H), 6.36 (dd, *J* = 17.5, 11.0, Hz, 1H), 5.36 (s, 1H), 5.25 (dd, *J* = 11.0, 1.0 Hz, 1H), 5.15 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.06 (dddd, *J* = 13.0, 5.5, 1.5, 1.5 Hz, 1H), 3.58 (s, 3H), 2.92 (td, *J* = 13.0, 4.0 Hz, 1H), 2.21-2.07 (m, 3H), and 1.64-1.53 (m, 5H).

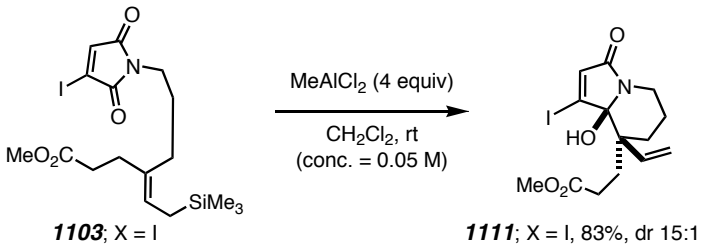
^{13}C NMR (125 MHz, d_6-Acetone): δ 174.0, 165.5, 143.9, 141.0, 130.4, 116.7, 93.0, 51.8, 47.4, 36.2, 29.0, 26.5, 26.0, and 20.7.

IR (thin film): 2919, 2848, 1736, 1711, 1673, 1268, and 847 cm^{-1}.

HRMS (ESI): calcd for $C_{14}H_{18}{}^{79}BrNO_4 \bullet Na^+$ 366.0311, found 366.0295, and calcd for $C_{14}H_{18}{}^{81}BrNO_4 \bullet Na^+$ 368.0291, found 368.0286 .

TLC: R_f 0.20 (EtOAc).

The Desired Allylation Regioisomer of the Iodo Amide 1111.



1103; X = I ***1111***; X = I, 83%, dr 15:1

The iodoimide **1103** was subjected to the previously described allylative ring conditions to afford the carbinolamide **1111**.

^{1}H NMR (500 MHz, d_6-Acetone): δ 6.69 (s, 1H), 6.46 (dd, *J* = 17.5, 11.0, Hz, 1H), 5.26 (dd, *J* = 11.0, 1.0 Hz, 1H), 5.18 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.07 (dddd, *J* = 13.0, 5.5, 1.5, 1.5 Hz, 1H), 3.58 (s, 3H), 2.95 (td, *J* = 13.0, 4.0 Hz, 1H), 2.20-2.13 (m, 3H), and 1.64-1.43 (m, 5H).

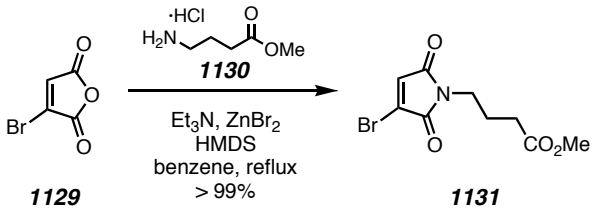
^{13}C NMR (125 MHz, d_6-Acetone): δ 173.1, 165.2, 141.1, 139.2, 122.7, 117.1, 51.8, 46.5, 36.5, 30.5, 29.0, 27.0, 25.9, and 20.6.

IR (thin film): 2948, 2918, 2850, 1730, 1699, 1672, 1434, 1419, 1245, 1202, 1170, 1053, and 914 cm^{-1}.

HRMS (ESI): calcd for $C_{14}H_{18}INO_4 \bullet Na^+$ 414.0173, found 414.0204.

TLC: R_f 0.25 (EtOAc).

Methyl 4-(3-Bromo-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)butanoate (1131).



To a solution of bromomaleimide (**1129**, 1 equiv) in benzene was treated with Et_3N (1.5 equiv), amine **1130** (1.5 equiv), and $ZnBr_2$ (1.5 equiv). The mixture was heated to reflux and stirred for 1 h. To the resulting mixture was added HMDS (2 equiv) dropwise. The reaction mixture was quenched by addition of aqueous HCl (15 % w/w) at room temperature. The insoluable material was collected trough vacuum filtration, and the filtrate was diluted with EtOAc. The organic liquid was washed with water and brine, and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the *N*-alkyl bromomaleimide **1131** in quantitative yield.

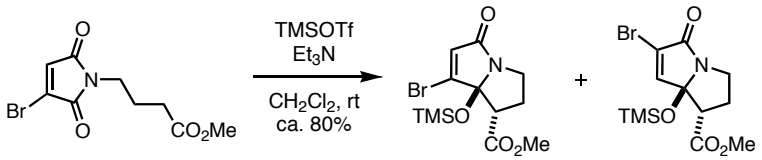
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.88 (s, 1H), 3.68 (s, 3H), 3.64 (t, J = 7.0 Hz, 2H), 2.34 (t, J = 7.0 Hz, 2H), and 1.95 (p, J = 7.0 Hz, 2H).

GC-LRMS [EI, 70 eV, m/z (rel. int.), 50-250 °C, 15 min run]: t_R 8.70 min; 347 (50), 349 (50), 332 (20), and 334 (20).

General Procedure for the Silylative Dieckman Cyclization

To a solution of the imide (1 equiv) in CH_2Cl_2 (0.1 M) was added Et_3N (3 equiv) and TMSOTf (2 equiv) at room temperature. The reaction mixture was stirred for 1 h and quenched by addition of saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure to give the cyclization products.

(±)-(1*S*,7a*S*)-Methyl-7-bromo-5-oxo-7a-(trimethylsilyloxy)-2,3,5,7a-tetrahydro-1*H*-pyrrolizine-1-carboxylate (1132).



1131 ***1132*** (1 : 5) ***1133***

The model bromomaleimide **1131** was subjected to the previously described silyltaive Dieckmann cyclization conditions affording the carbinolamides **1132** and **1133**.

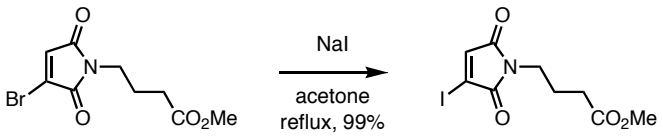
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.20 (s, 1H), 3.85 (ddd, *J* = 11.0, 9.0, 9.0 Hz, 1H), 3.61 (s, 3H), 3.32 (ddd, *J* = 11.0, 9.0, 2.0 Hz, 1H), 3.11 (ddd, *J* = 7.0, 1.0, 1.0 Hz, 1H), 2.62 (dddd, *J* = 13.0, 9.0, 9.0, 7.0 Hz, 1H), 2.44 (dddd, *J* = 13.0, 9.0, 2.0, 1.0 Hz, 1H), and 0.14 (s, 9H).

GC-LRMS [EI, 70 eV, m/z (rel. int.), 50-250 °C, 15 min run]: t_R 8.65 min; 347 (50), 349 (50), 332 (20), and 334 (20).

(±)-(1*S*,7a*S*)-methyl 6-bromo-5-oxo-7a-(trimethylsilyloxy)-2,3,5,7a-tetrahydro-1*H*-pyrrolizine-1-carboxylate (1133).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.07 (s, 1H), 3.80 (ddd, *J* = 11.0, 9.0, 9.0 Hz, 1H), 3.60 (s, 3H), 3.36 (ddd, *J* = 11.0, 9.0, 2.5 Hz, 1H), 3.15 (dd, *J* = 7.0, 2.0 Hz, 1H), 2.59 (dddd, *J* = 13.0, 9.0, 9.0, 7.0 Hz, 1H), 2.49 (dddd, *J* = 12.5, 8.5, 2.5, 2.0 Hz, 1H), and 0.11 (s, 9H).

Methyl 4-(3-iodo-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)butanoate (1138).

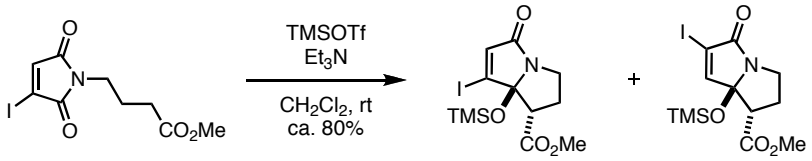


1131 ***1138***

To a solution of the bromomaleimide **1131** (1 equiv) in acetone (0.5 M) was added NaI (10 equiv) at room temperature. The mixture was heated to reflux in a sealed culture tube, and was stirred for 24 h. The resulting mixture was cooled to room temperature and concentrated under reduced pressure. The acetone free residue was re-dissolved with EtOAc, washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was used in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (s, 1H), 3.68 (s, 3H), 3.65 (t, J = 7.0 Hz, 2H), 2.35 (t, J = 7.0 Hz, 2H), and 1.93 (p, J = 7.0 Hz, 2H).

(±)-(1*S*,7a*S*)-methyl 7-iodo-5-oxo-7a-(trimethylsilyloxy)-2,3,5,7a-tetrahydro-1*H*-pyrrolizine-1-carboxylate (1139).



The model iodoomaleimide **1138** was subjected to the previously described silyltaive Dieckmann cyclization conditions affording the carbinolamides **1139** and **1140**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.45 (s, 1H), 3.86 (ddd, *J* = 11.0, 9.0, 9.0 Hz, 1H), 3.60 (s, 3H), 3.37 (ddd, *J* = 11.0, 9.0, 2.0 Hz, 1H), 3.08 (ddd, *J* = 7.0, 1.0, 1.0 Hz, 1H), 2.63 (dddd, *J* = 13.0, 9.0, 9.0, 7.0 Hz, 1H), 2.43 (dddd, *J* = 13.0, 9.0, 2.0, 1.0 Hz, 1H), and 0.15 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 171.0, 137.1, 119.5, 102.3, 52.1, 51.7, 43.1, 30.3, and 0.5.

IR (thin film): 2956, 2901, 1717, 1357, 1319, 1251, 1096, 901, and 846 cm^{-1}.

GC-LRMS [EI, 70 eV, m/z (rel. int.), 50-250 °C, 15 min run]: t_R 9.23 min; 395 (100), and 380 (30).

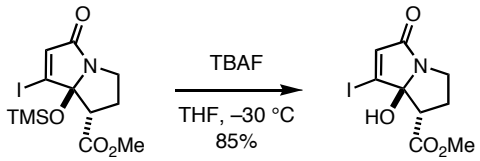
(±)-(1*S*,7a*S*)-Methyl 6-iodo-5-oxo-7a-(trimethylsilyloxy)-2,3,5,7a-tetrahydro-1*H*-pyrrolizine-1-carboxylate (1140).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (s, 1H), 3.80 (ddd, *J* = 11.0, 9.0, 9.0 Hz, 1H), 3.59 (s, 3H), 3.35 (ddd, *J* = 11.0, 9.0, 2.5 Hz, 1H), 3.13 (dd, *J* = 7.0, 1.5 Hz, 1H), 2.59 (dddd, *J* = 13.0, 9.0, 9.0, 7.0 Hz, 1H), 2.49 (dddd, *J* = 13.0, 9.0, 2.5, 1.5 Hz, 1H), and 0.10 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 171.2, 169.9, 153.6, 101.7, 95.4, 53.2, 52.4, 43.4, 30.8, and 1.1.

GC-LRMS [EI, 70 eV, m/z (rel. int.), 50-250 °C, 15 min run]: t_R 9.22 min; 395 (100), and 380 (20).

(±)-(1*S*,7a*S*)-Methyl 7a-hydroxy-7-iodo-5-oxo-2,3,5,7a-tetrahydro-1*H*-pyrrolizine-1-carboxylate (1141).



1139 ***1141***

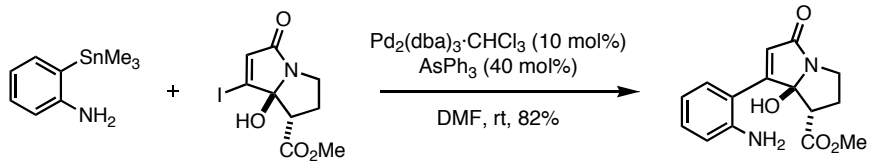
To a solution of the iodide **1139** (1 equiv) in THF (0.1 M) at –30 °C was added TBAF (1.0 M, 1.2 equiv) dropwise. The reaction mixture was stirred until TLC analysis showed full conversion of the substrate. The reaction mixture was quenched by addition of water. The organic material was extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was used in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.44 (s, 1H), 3.83 (ddd, *J* = 11.0, 9.0, 9.0 Hz, 1H), 3.63 (s, 3H), 3.45 (ddd, *J* = 11.0, 9.0, 2.0 Hz, 1H), 3.33 (m, O*H*), 3.21 (dd, *J* = 7.0, 1.5 Hz, 1H), 2.83 (ddd, *J* = 13.0, 9.0, 9.0, 7.0 Hz, 1H), and 2.45 (dddd, *J* = 13.0, 9.0, 2.5, 1.5 Hz, 1H).

IR (thin film): 3344 (br), 2957, 2928, 1730, 1961, 1438, 1361, 1200, and 1043 cm^{-1}.

GC-LRMS [EI, 70 eV, m/z (rel. int.), 50-250 °C, 15 min run]: t_R 8.90 min; 323 (100), and 306 (10).

The Model Stille Coupling Product: the Amino Ester 1137.



1142 ***1141*** ***1137***

A 0.2 M solution of **1142** (1 equiv) and **1141** (1 equiv) in DMF was purged with Ar for 10 min. To this solution was added $Pd_2(dba)_3{\cdot}CHCl_3$ (0.1 equiv) and $AsPh_3$ (0.4 equiv) and the resulting mixture was purged with Ar for 15 min. The reaction mixture was stirred for 6 h at room temperature and quenched by addition of brine. The organic products were extracted with EtOAc, washed with a half saturated brine [brine:H_2O (1:1)] three times, dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified using Hex/EtOAc (2:1) to give the title product in 82% yield.

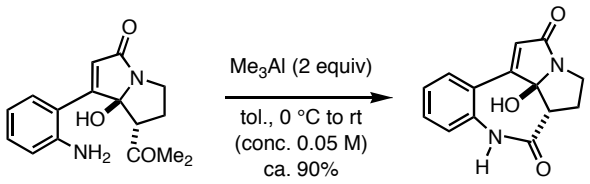
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.19 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1H), 6.83 (ddd, *J* = 8.5, 7.5, 1.0 Hz, 1H), 6.75 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.21 (s, 1H), 4.39 (br s, O*H*), 4.18 (br s, NH_2), 3.78 (ddd, *J* = 11.0, 9.0, 8.5 Hz, 1H), 3.46 (s, 3H), 3.35 (ddd, *J* = 11.0, 6.5, 1.5 Hz, 1H), 3.33 (dd, *J* = 9.0, 2.5 Hz, 1H), 2.82 (dddd, *J* = 13.0, 9.0, 9.0, 7.0 Hz, 1H), and 2.47 (dddd, *J* = 13.0, 8.5, 2.5, 1.5 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.2, 171.9, 156.4, 146.1, 131.2, 130.2, 123.9, 119.2, 117.7, 117.2, 101.3, 52.1, 50.8, 41.9, and 31.9.

IR (thin film): 3354, 2959, 1730, 1684, 1628, 1449, 1363, 1045, and 759 cm^{-1}.

HRMS (ESI): calcd for $C_{15}H_{16}N_2O_4{\bullet}Na^+$ 311.1002, found 311.1036.

The Model Amidation Product 1145.

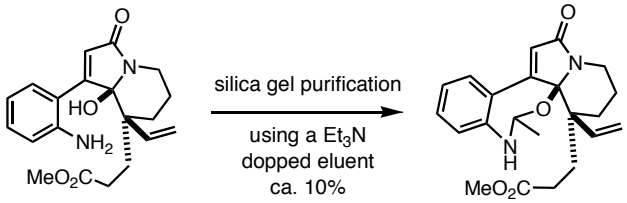


1137 ***1145***

To a solution of **1137** (1 equiv) in toluene (0.05 M) was added Me_3Al (2 equiv) drop-wise at 0 °C. The reaction mixture was stirred for 4 h and quenched at the same temperature by addition of saturated aqueous $NaHCO_3$. The organic phase was extracted with EtOAc, washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel chromatography using EtOAc/Hex (5:1).

^{1}H NMR (500 MHz, d_6-DMSO): δ 9.96 (br s, N*H*), 7.39 (ddd, *J* = 9.0, 7.5, 1.5 Hz, 1H), 7.29 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.16 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1H), 7.08 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.46 (br s, O*H*), 6.03 (s, 1H), 3.46 (ddd, *J* = 11.0, 7.0, 6.5 Hz, 1H), 3.21 (dd, *J* = 7.0, 7.0 Hz, 1H), 3.17 (ddd, *J* = 11.0, 7.0, 7.0 Hz, 1H), 2.38 (dd, *J* = 7.0, 7.0 Hz, 1H), and 2.37 (dd, *J* = 7.0, 7.0 Hz, 1H).

The Purification By-Product, the Bis-hemiaminal 1146.



1108 ***1146***

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (d, *J* = 7.0, 1H), 7.18 (td, *J* = 8.0, 1.5 Hz, 1H), 6.81 (td, *J* = 7.5, 1.0 Hz, 1H), 6.54 (dd, *J* = 8.5, 1.0 Hz, 1H), 6.28 (s, 1H), 5.37 (dd, *J* = 17.5, 11.0, Hz, 1H), 5.09 (dq, 8.0, 5.5 Hz, 1H), 4.85 (dd, *J* = 11.0, 1.0 Hz, 1H), 4.79 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.15 (dddd, 13.0, 5.5, 1.5, 1.5 Hz, 1H), 3.61 (s, 3H), 2.99 (td, *J* =

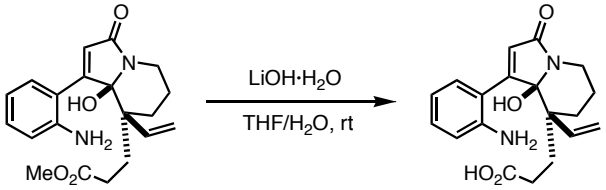
13.0, 4.0 Hz, 1H), 2.10 (m, 1H), 1.98 (dd, *J* = 10.0, 8.0 Hz, 2H), and 1.53-1.41 (m, 2H), and 1.38 (d, *J* = 5.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.9, 167.1, 160.3, 144.3, 139.3, 131.0, 129.2, 125.8, 119.64, 119.61. 116.5, 115.9, 100.0, 78.6, 51.8, 48.1, 35.7, 28.7, 25.4, 25.2, 21.9, and 20.1.

IR (thin film): 3318 (br), 2948, 1737, 1676, 1487, 1169, 1048, and 757 cm^{-1}.

HRMS (ESI): calcd for $C_{22}H_{26}N_2O_4 \bullet Na^+$ 405.1785, found 405.1807.

The Amino Acid 1149.

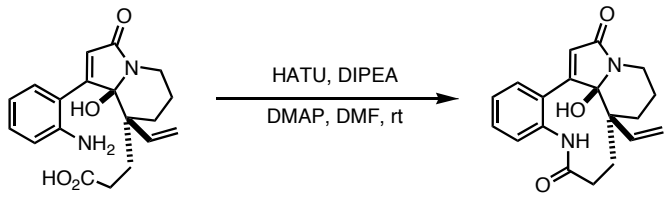


1108 ***1149***

To a 0.1 M solution of the amino ester **1108** (1 equiv) in THF/H_2O (3:1) was added LiOH·H_2O (3 equiv) at room temperature. The reaction solution was stirred for 6 h and diluted with EtOAc. The resulting mixture was treated with AcOH dropwise until the pH reached down to neutrality. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was used in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (br d, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.25 (s, 1H), 5.34 (dd, *J* = 17.0, 11.0, Hz, 1H), 5.03 (d, *J* = 11.5 Hz, 1H), 5.01 (d, *J* = 18.0 Hz, 1H), 4.16 (br dd, *J* = 13.5, 5.0 Hz, 1H), 3.02 (td, *J* = 13.5, 5.0 Hz, 1H), 2.14-1.95 (m, 3H), and 1.70-1.14 (m, 5H).

The Hydrogenation Precursor, Dehydro-Leuconolam 1150.



1149 (0.05 M) ***1150***

To a solution of the amino acid **1149** (1 equiv) in DMF (0.05 M) was added DIPEA (1.5 equiv), DMAP (0.2 equiv) and HATU (1.5 equiv) at room temperature. The reaction solution was stirred for 6 h and quenched by addition of water. The resulting mixture was extracted with EtOAc, washed with brine, and concentrated under reduced pressure. The crude material was purified by silica gel chromatography with 10:1 EtOAc/MeOH.

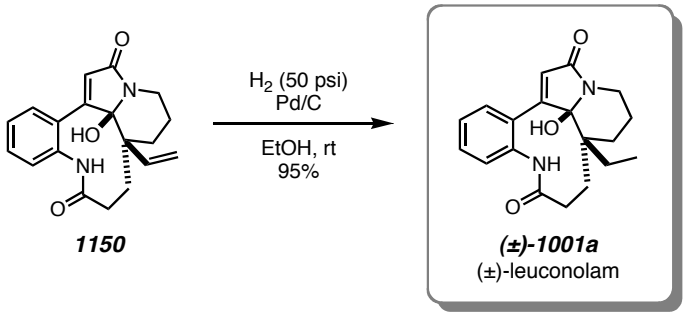
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.0 Hz, 1H), 7.41 (app t, *J* = 7.0 Hz, 1H), 7.35 (app t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 6.17 (dd, *J* = 18.0, 11.5, Hz, 1H), 5.95 (s, 1H), 4.98 (d, *J* = 11.5 Hz, 1H), 4.85 (d, *J* = 18.0 Hz, 1H), 4.00 (br m, 1H), 2.91 (br m, 1H), 2.36 (dd, *J* = 14.5, 8.0 Hz, 1H), 2.19-2.13 (m, 1H), 2.02-1.91 (m, 2H), and 1.63-1.49 (m, 3H), and 1.43 (br d, *J* = 13.0 Hz, 1H).

IR (thin film): 3257 (br), 2929, 2888, 1678, 1441, 1040, and 1026 cm^{-1}.

LC-LRMS [ES + APCI, 50:50 to 0:100 (%) H_2O:MeOH, 10 min run]: t_R 3.61 min; 325.0 $(M–OH)^+$, and 357.0 $(M–OH+MeOH)^+$.

HRMS (ESI): calcd for $C_{19}H_{20}N_2O_3•Na^+$ 347.1366, found 347.1361.

Synthetic (±)-Leuconolam [(±)-1001a].



The dehydro-macrolactam **1150** (1 equiv) was dissolved in EtOH (0.1 M) and the solution was placed in a high-pressure glass reactor equipped with a pressure gauge. Pd/C (1 equiv) was added into the solution and the reactor was sealed. To the vessel was introduced H_2 gas (50 psi) and the mixture was stirred at room temperature for 5 h. The pressure was released and resulting suspension was filtered through a plug of Celite. The ethanolic filtrate was concentrated under reduced pressure and the crude material was purified by silica gel chromatography with EtOAc/MeOH (10:2) to give the natural alkaloid racemic leuconolam [**(±)-1001a**] in 95% yield.

mp: ≥ 250 °C.

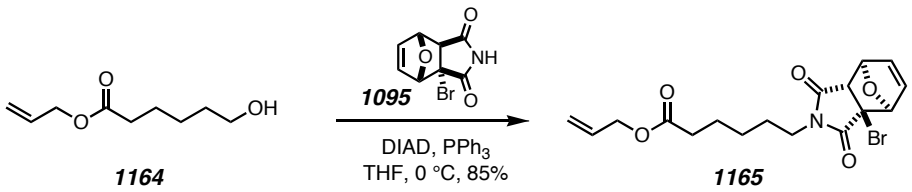
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.42 (td, *J* = 7.5, 1.5 Hz, 1H), 7.36 (td, *J* = 7.5, 1.5 Hz, 1H), 7.19 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.19 (br s, N*H*), 5.86 (s, 1H), 4.05 (br d, *J* = 12.0 Hz 1H), 3.58-3.49 (br s, O*H*), 2.90 (ddd, *J* = 13.0, 9.5, 7.0 Hz, 1H), 2.17 (br dd, *J* = 14.5, 7.5 Hz, 1H), 2.04 (br dd, *J* = 13.5, 13.5 Hz, 1H), 1.80-1.69 (m, 2H), 1.63-1.44 (m, 4H), 1.32-1.24 (m, 2H), and 0.58 (t, *J* = 7.5 Hz, 3H).

IR (thin film): 3227 (br), 2889, 1681, 1438, 1040, 1026, and 761 cm^{-1}.

LC-LRMS [ES + APCI, 50:50 to 0:100 (%) H_2O:MeOH, 10min run]: t_R 3.84 min; 327.0 $(M–OH)^+$, 359.0 $(M–OH+MeOH)^+$, and 653.3 $(2M–H_2O–OH)^+$.

HRMS (ESI, PPG calibrant): calcd for $C_{19}H_{22}N_2O_3•Na^+$ 349.1523, found 349.1539.

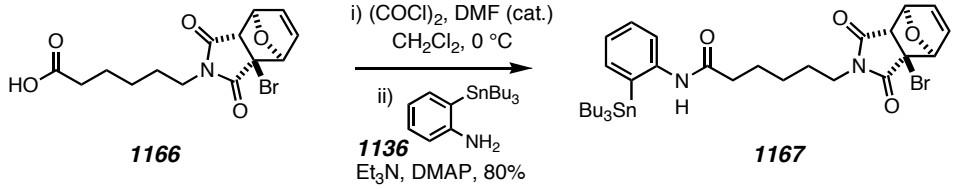
The Model Mitsunobu Displacement Product: the Allyl Ester 1165.



The primary alcohol **1164** was subjected to the Mitsunobu conditions with the protected imide nucleophile **1095** by following the procedure mentioned above.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (br s, 2H), 5.86 (ddt, *J* = 17.0, 10.0, 5.5 Hz, 1H), 5.32-5.21 (m, 5 x 1H overlap, 5H), 4.58 (d, *J* = 5.5 Hz, 2H), 3.55 (dd, *J* = 7.0, 7.0 Hz, 2H), 2.83 (s, 1H), 2.33 (t, *J* = 8.0 Hz, 2H), 1.64 (tt, *J* = 8.0, 7.5 Hz, 2H), 1.60 (p, *J* = 7.5 Hz, 2H), 1.32 (m, 2H).

The Model-RDA precursor: the Amide 1167.



To a solution of the carboxylic acid **1166** (1 equiv) in CH_2Cl_2 (0.3 M) was added catalytic amount of DMF and oxallyl chloride (1.2 equiv) at 0 °C. The reaction mixture was stirred for 30 min and the volatiles were removed under gentle vacuum to give the residual acil chloride intermediate. This material was re-dissolved with CH_2Cl_2 (0.3 M) and immediately subjected to Et_3N (1.5 equiv), DMAP (0.2 equiv) and the organostanne **1136** (1.5 equiv). The resulting mixture was stirred at room temperature for 6 h and quenched by addition of saturated aqueous $NaHCO_3$. The organic materials were extracted with EtOAc, washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel chromatography using Hex/EtOAc/Et_3N (10:5:1) pre-packed column and eluted with

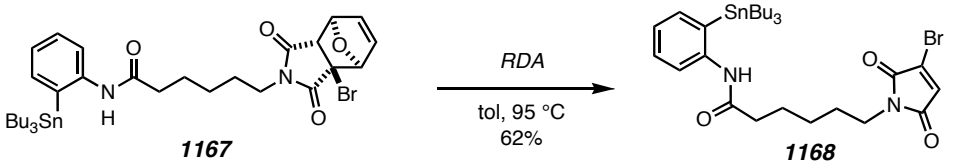
Hex/EtOAc (2:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.36 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.32 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.12 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.97 (br s, N*H*), 6.65 (dd, *J* = 1.5, 1.5 Hz, 1H), 6.64 (dd, *J* = 1.5, 1.5 Hz, 1H), 5.25 (dd, *J* = 1.5, 1.5 Hz, 1H), 5.24 (dd, *J* = 1.5, 1.5 Hz, 1H), 3.56 (dd, *J* = 7.5, 7.0 Hz, 2H), 2.84 (s, 1H), 2.31 (dd, *J* = 7.5, 7.5 Hz, 2H), 1.75 (tt, *J* = 7.5, 7.0 Hz, 2H), 1.62 (tt, *J* = 7.5, 7.0 Hz, 2H), 1.52 (m, 6H), 1.40 (m, 2H), 1.33 (tq, *J* = 7.5, 7.5 Hz, 6H), 1.10 (dd, *J* = 8.0, 7.0 Hz, 6H), and 0.90 (t, *J* = 7.5 Hz, 9H).

LC-LRMS [ES + APCI, 50:50 to 0:100 (%) H_2O:MeOH, 15 min run]: t_R 12.21 min; 723.0 $(M+1)^+$.

TLC: R_f 0.7 (1:1 Hex/EtOAc).

6-(3-Bromo-2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-(2-(tributylstannyl)phenyl)hexanamide (1168).



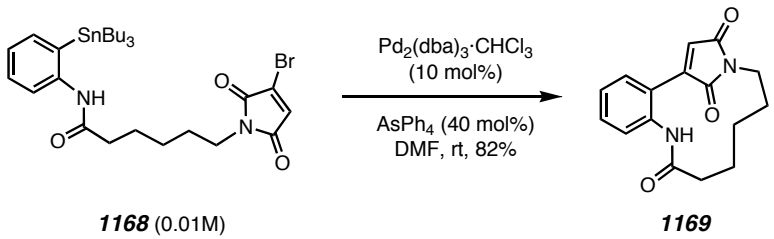
The imide **1167** was subjected to the RDA conditions as described above to afford the model bromo maleimide **1168** in 62% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.38 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.33 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H), 7.12 (ddd, *J* = 7.5, 7.0, 1.0 Hz, 1H), 6.98 (br s, N*H*), 6.84 (s, 1H), 3.58 (dd, *J* = 7.5, 7.5 Hz, 2H), 2.40 (dd, *J* = 7.5, 7.5 Hz, 2H), 1.78 (tt, *J* = 7.5, 7.0 Hz, 2H), 1.62 (tt, *J* = 7.5, 7.0 Hz, 2H), 1.54 (m, 6H), 1.37 (tq, 7.5, 7.5 Hz, 6H), 1.38 (m, 2H), 1.11 (dd, 8.0, 7.0 Hz, 6H), and 0.89 (t, *J* = 7.5 Hz, 9H).

LC-LRMS [ES + APCI, 50:50 to 0:100 (%) H_2O:MeOH, 15 min run]: t_R 12.17 min; 653.0 $(M+1)^+$.

TLC: R_f 0.4 (2:1 Hex/EtOAc).

The Model Stille Macrocyclization Product 1169.

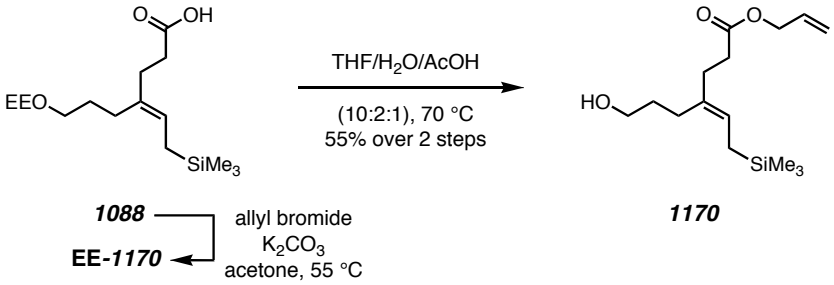


^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (ddd, *J* = 7.5, 7.5, 2.0 Hz, 1H), 7.46 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.43 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 7.29 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.63 (br s, N*H*), 3.89 (ddd, *J* = 14.0, 10.0, 5.5 Hz, 1H), 3.72 (ddd, *J* = 14.0, 6.0, 4.0 Hz, 1H), 2.48 (ddd, *J* = 14.0, 6.5, 3.5 Hz, 1H), 2.22 (ddd, *J* = 14.0, 10.0, 4.0 Hz, 1H), 1.98 (m, 1H), 1.72-1.58 (m, 2H), 1.51 (ddddd, 15.0, 10.0, 10.0, 5.0, 5.0 Hz, 1H), and 1.02 (ddddd, 15.0, 10.0, 10.0, 5.0, 5.0 Hz, 1H).

LC-LRMS [ES + APCI, 50:50 to 0:100 (%) H_2O:MeOH, 15 min run]: t_R 8.06 min; 285.0 $(M+1)^+$.

TLC: R_f 0.25 (1:2 Hex/EtOAc).

(*E*)-allyl 7-hydroxy-4-[2-(trimethylsilyl)ethylidene]heptanoate (1170).



(*E*)-Allyl 7-(1-ethoxyethoxy)-4-[2-(trimethylsilyl)ethylidene]heptanoate (EE-1170).

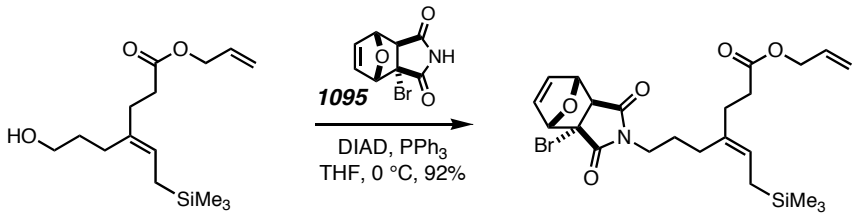
^{1}H NMR (500 MHz, $CDCl_3$): 5.91 (ddt, *J* = 17.0, 10.5, 6.0 Hz, 1H), 5.33 (ddt, *J* = 17.0,

1.5, 1.5 Hz, 1H), 5.24 (ddt, *J* = 10.5, 1.5, 1.5 Hz, 1H), 5.21 (t, *J* = 8.5 Hz, 1H), 4.69 (dt, *J* = 6.0, 1.5 Hz, 1H), 4.56 (dt, *J* = 6.0, 1.5 Hz, 2H), 3.64 (dq, *J* = 9.5, 7.0 Hz, 1H), 3.55 (dt, *J* = 9.5, 6.5 Hz, 1H), 3.48 (dq, *J* = 9.5, 7.0 Hz, 1H), 3.39 (dq, *J* = 9.5, 6.5 Hz, 1H), 2,41 (nfom, 2H), 2.31 (dd, *J* = 8.5, 7.5 Hz, 2H), 2.05 (m, 2H), 1.64 (tt, *J* = 8.0, 7.5 Hz, 2H), 1.41 (d, *J* = 8.5 Hz, 2H), 1.31 (d, *J* = 5.5 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 3H), and -0.02 (s, 9H).

The Spectral Data of 1170:

^{1}H NMR (500 MHz, $CDCl_3$): 5.92 (ddt, *J* = 17.0, 10.5, 6.0 Hz, 1H), 5.32 (ddt, *J* = 17.0, 1.5, 1.5 Hz, 1H), 5.24 (ddt, *J* = 10.5, 1.5, 1.5 Hz, 1H), 4.57 (dt, *J* = 6.0, 1.5 Hz, 1H), 3.65 (t, *J* = 5.5 Hz, 2H), 2,44 (nfom, 2H), 2.34 (dd, *J* = 8.0, 7.0 Hz, 2H), 2.06 (m, 2H), 1.65 (tt, *J* = 8.0, 7.5 Hz, 2H), 1.43 (d, *J* = 8.5 Hz, 2H), and -0.02 (s, 9H).

The Mitsunobu Displacement Product, Allyl Ester 1171.

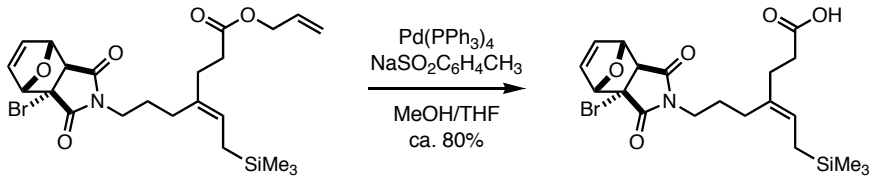


1170 ***1171***

The primary alcohol **1170** was subjected to the Mitsunobu conditions with the protected imide nucleophile **1095** by following the previously described procedure to afford the imide **1171** in 92% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.65 (br s, 2H), 5.88 (ddt, *J* = 17.0, 10.0, 5.5 Hz, 1H), 5.35-5.20 (m, 5 x 1H overlap, 5H), 4.56 (d, *J* = 5.5 Hz, 2H), 3.57 (dd, *J* = 7.0, 7.0 Hz, 2H), 2.86 (s, 1H), 2.40 (dd, *J* = 8.5, 8.0 Hz, 2H), 2.30 (dd, *J* = 8.5, 8.0 Hz, 2H), 1.96 (m, 2H), 1.65 (tt, *J* = 8.0, 7.5 Hz, 2H), 1.31 (d, *J* = 8.5, 2H), and -0.04 (s, 9H).

The Amidation Precursor Acid 1172.

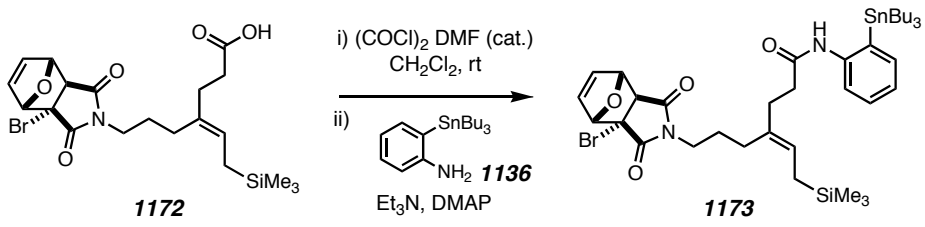


1171 ***1172***

To a solution of allyl ester **1171** (1 equiv) in THF (0.3 M) was added $Pd(PPh_3)_4$ (0.2 equiv) and a solution of $NaSO_2C_6H_4CH_3$ (1.5 equiv) in MeOH (1 M) at room temperature. The reaction mixture was stirred for 6 h and quenched by addition of water. The organic materials were extracted with EtOAc, washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel chromatography using Hex/EtOAc (2:1) to afford the carboxylic acid **1172** in ca. 80% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ No observable acid proton, 6.66 (d, *J* = 1.5 Hz, 1H), 6.65 (d, *J* = 1.5 Hz, 1H), 5.28 (d, *J* = 1.5 Hz, 1H), 5.26 (d, *J* = 1.5 Hz, 1H), 5.23 (t, *J* = 8.5 Hz, 1H), 3.57 (dd, *J* = 7.0, 7.0 Hz, 2H), 2.86 (s, 1H), 2.42 (dd, *J* = 8.5, 8.0 Hz, 2H), 2.31 (dd, *J* = 8.5, 8.0 Hz, 2H), 1.98 (m, 2H), 1.66 (tt, *J* = 8.0, 7.5 Hz, 2H), 1.38 (d, *J* = 8.5, 2H), and -0.04 (s, 9H).

***o*-Stannyl-Anilide RDA Precursor 1173.**

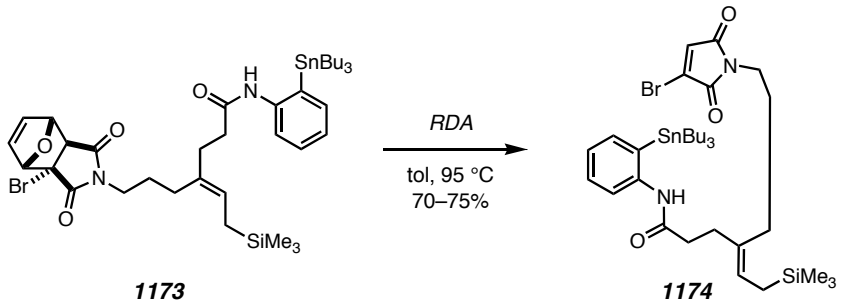


1172 ***1136*** ***1173***

The acid **1172** was subjected to the two-step acid chloride formation-amidation procedure condition as described above to afford the amide **1173** in ca. 70% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.37 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.32 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.13 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 7.02 (br s, N*H*), 6.65 (dd, *J* = 1.5, 1.5 Hz, 1H), 6.64 (dd, *J* = 1.5, 1.5 Hz, 1H), 5.28 (t, *J* = 8.5 Hz, 1H), 5.26 (dd, *J* = 1.5, 1.5 Hz, 1H), 5.25 (dd, *J* = 1.5, 1.5 Hz, 1H), 3.57 (dd, *J* = 7.0, 7.0 Hz, 2H), 2.85 (s, 1H), 2.45-2.35 (m, 2 x 2H overlap, 4H), 2.03 (m, 2H), 1.70 (tt, *J* = 7.5, 6.5 Hz, 2H), 1.53 (m, 6H), 1.40 (d, *J* = 8.5, 2H), 1.33 (tq, *J* = 7.5, 7.5 Hz, 6H), 1.10 (dd, *J* = 8.0, 7.5 Hz, 6H), and 0.90 (t, *J* = 7.5 Hz, 9H).

(*E*)-7-(3-Bromo-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)-N-(2-(tributylstannyl)-phenyl)-4-[2-(trimethylsilyl)ethylidene]heptanamide (1174).

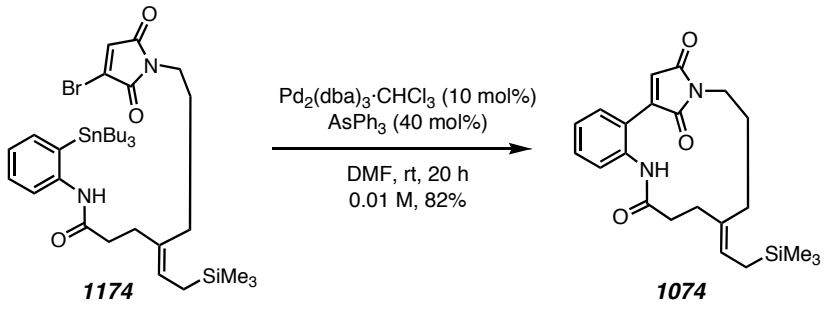


1173 ***1174***

The imide **1173** was subjected to the RDA conditions as described above to afford the bromo maleimide **1174** in ca. 75% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.36 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.32 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 1H), 7.12 (ddd, *J* = 7.5, 7.0, 1.0 Hz, 1H), 7.02 (br s, N*H*), 6.86 (s, 1H), 5.30 (t, *J* = 8.5 Hz, 1H), 3.57 (dd, *J* = 7.5, 7.5 Hz, 2H), 2.43-2.37 (nfom, 2 x 2H overlap, 4H), 2.00 (dd, *J* = 8.0, 8.0 Hz, 2H), 1.71 (tt, *J* = 8.0, 7.5 Hz, 2H), 1.52 (m, 6H), 1.39 (d, 8.5 Hz, 2H), 1.33 (sex, 7.5 Hz, 6H), 1.10 (dd, 8.5, 8.0 Hz, 6H), 0.89 (t, *J* = 7.5 Hz, 9H), and -0.02 (s, 9H).

The Stille Macrocyclization Product 1074.



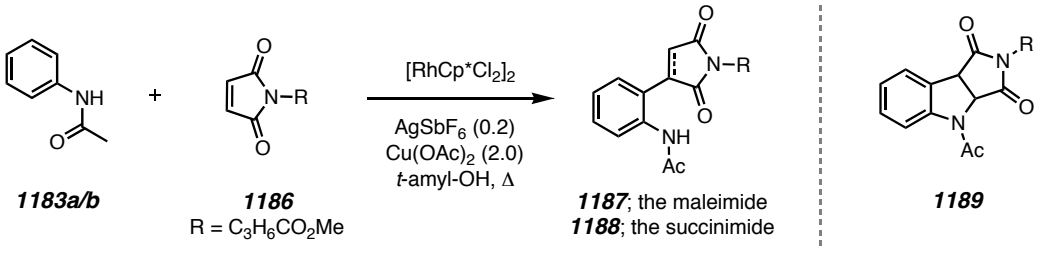
1174 ***1074***

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 (br s, N*H*), 7.58 (ddd, *J* = 7.5, 1.5, 0.5 Hz, 1H), 7.52 (ddd, *J* = 7.0, 7.0, 1.0 Hz, 1H), 7.30 (ddd, *J* = 7.0, 7.0, 1.5 Hz, 1H), 7.34 (ddd, *J* = 7.5, 1.5, 0.5 Hz, 1H), 6.52 (s, 1H), 5.14 (dddd, *J* = 11.5, 6.0, 3.5, 1.5 Hz, 1H), 3.98 (ddd, *J* = 14.0, 12.5, 4.0 Hz, 1H), 3.51 (ddd, *J* = 14.0, 4.0, 2.5 Hz, 1H), 2.73 (ddd, *J* = 16.0, 8.0, 3.0 Hz, 1H), 2.65-2.60 (m, 2H), 2.53 (ddd, *J* = 13.0, 2.5, 2.5 Hz, 1H), 2.49 (ddd, *J* = 13.0, 3.0, 3.0 Hz, 1H), 2.14 (d, *J* = 8.0 Hz, 1H), 1.93 (dd, *J* = 15.0, 7.0 Hz, 1H), 1.72 (ddddd, 14.5, 9.0, 4.5, 2.0, 2.0 Hz, 1H), and 1.47 (dd, *J* = 13.5, 11.5 Hz, 1H), 0.93 (ddddd, 13.0, 6.0, 2.5, 1.5, 1.5 Hz, 1H), and -0.10 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 172.7, 171.7, 170.0, 146.6, 134.9, 132.3, 131.7, 130.0, 128.6, 128.1, 127.1, 125.5, 122.3, 39.5, 34.8, 30.1, 29.6, 21.8, 19.9, and -1.4.

HRMS (ESI): calcd for $C_{22}H_{28}N_2O_3Si•Na^+$ 419.1761, found 419.1760.

The Model C-H Functionalization Product: the Maleimide 1187.



1183a/b ***1186*** R = $C_3H_6CO_2Me$ ***1187***; the maleimide ***1188***; the succinimide ***1189***

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.98 (br s, N*H*), 7.92 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.50 (dd,

J = 7.0, 1.5, 1.5 Hz, 1H), 7.48 (ddd, *J* = 8.0, 7.0 Hz, 1H), 7.22 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 6.65 (s, 1H), 3.69 (t, *J* = 6.5 Hz, 1H), 3.66 (s, 3H), 2.39 (t, *J* = 7.0 Hz, 2H), 2.17 (s, 3H), and 2.01 (tt, *J* = 7.0, 6.5 Hz, 2H).

GC-LRMS [EI, 70 eV, m/z (rel. int.) 50-290 °C, 21 min run]: t_R 12.55 min; 330 (70), 288 (50), and 257 (50).

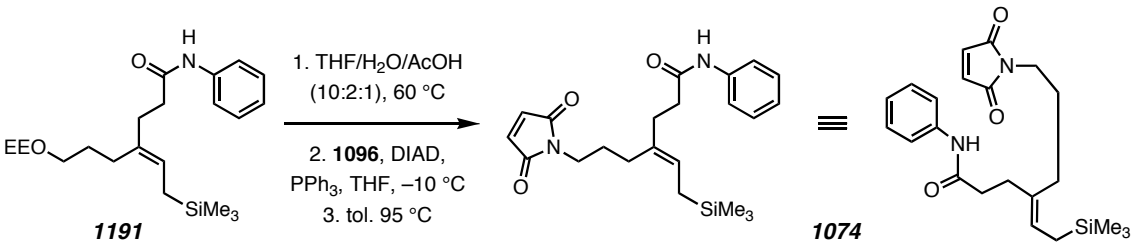
HRMS (ESI): calcd for $C_{17}H_{18}N_2O_5 \bullet Na^+$ 353.1108, found 353.1165.

The Model C-H Functionalization Product, the Succinimide 1188.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (br s, N*H*), 7.64 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.35 (td, *J* = 8.0, 1.5 Hz, 1H), 7.23 (td, *J* = 8.0, 1.5 Hz, 1H), 7.15 (dd, *J* = 8.0, 1.5 Hz, 1H), 4.33 (dd, *J* = 8.5, 5.5 Hz, 1H), 3.64 (s, 3H), 3.56 (dd, *J* = 7.0, 2.0 Hz, 2H), 3.11 (d, *J* = 8.5 Hz, 1H), 3.10 (d, *J* = 5.5 Hz, 1H), 2.33 (dd, *J* = 7.0, 7.0 Hz, 2H), 2.22 (s, 3H), 1.94 (td, *J* = 11.5, 7.0 Hz, 1H), and 1.90 (td, *J* = 11.5, 7.0 Hz, 1H).

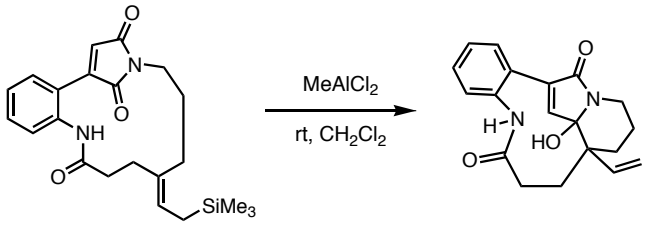
HRMS (ESI): calcd for $C_{17}H_{20}N_2O_5 \bullet Na^+$ 355.1264, found 355.1262.

(*E*)-7-(2,5-Dioxo-2,5-dihydro-1H-pyrrol-1-yl)-N-phenyl-4-[2-(trimethylsilyl)-ethylidene]heptanamide (1074).



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.45 (br s, N*H*), 7.31 (dd, *J* = 8.5, 7.5 Hz, 2H), 7.09 (td, *J* = 7.5, 1.0 Hz, 1H), 6.71 (s, 2H), 5.33 (t, *J* = 8.5 Hz, 1H), 3.52 (dd, *J* = 7.5, 7.5 Hz, 2H), 2.44 (br s, 2H+2H overlap, 4H), 2.04 (dd, *J* = 7.5, 7.5 Hz, 2H), 1.70 (dddd, *J* = 12.5, 7.5, 6.0, 6.0 Hz, 2H), 1.39 (d, *J* = 8.5 Hz, 2H), and -0.03 (s, 9H).

The Undesired Allylation Regioisomer 1195.



1174 (0.05 M) ***1195***; dr = 2:1

The macrocycle **1174** was subjected to the previously described allylative ring conditions affording the carbinolamide **1195** as a mixture of diastereomers (ca. 2:1).

The most diagnostic proton resonances for the ***major*** isomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (br s, N*H*), 7.43-7.38 (m, 2H), 7.35-7.31 (m, 2H), 7.07 (s, 1H), 6.27 (dd, *J* = 17.5, 11.0 Hz, 1H), 4.08-4.01 (m, 1H), and 3.11 (ddd, *J* = 12.5, 8.5, 8.5 Hz, 1H).

The most diagnostic proton resonances for the ***minor*** isomer:

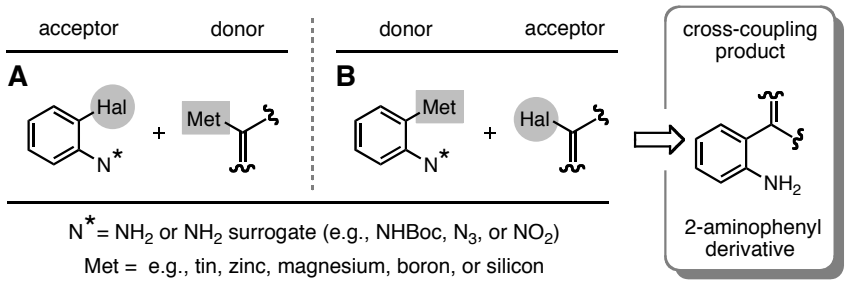
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (br s, N*H*), 7.12 (s, 1H), 6.34 (dd, *J* = 18.0, 11.0 Hz, 1H), 4.08-4.01 (m, 1H), and 3.02 (ddd, *J* = 12.5, 12.5, 5.0 Hz, 1H).

Chapter – II: *o*-(Trialkylstannyl)anilines and Their Utility in Migita-Kosugi-Stille Cross-Coupling: Direct Introduction of the 2-Aminophenyl Substituent

II-A. Introduction and Background

The 2-aminophenyl substituent is an important structural entity in organic[51a-e] and medicinal chemistry.[51f-i] The essential features of cross-coupling partners suitable for installation of such a moiety are shown in Figure II-1. In principle, the 2-aminophenyl partner can be either the acceptor (panel A) or donor (panel B) and the most direct

Figure II-1. Cross-coupling Strategies for Preparation of 2-Aminophenyl Derivatives.

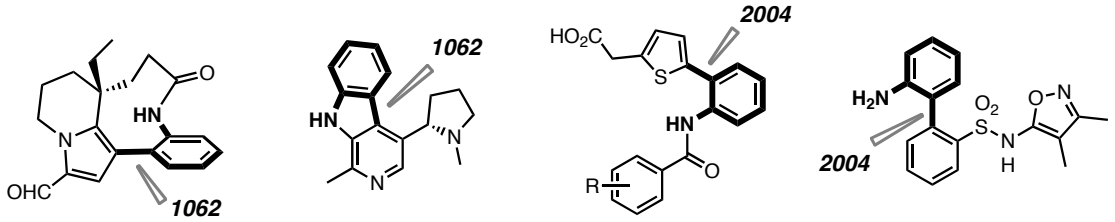


51. (a) Baudoin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem*. **2000**, *65*, 9268–9271. (b) Baudoin, O.; Cesario, M.; Guénard, D.; Guéritte, F. *J. Org. Chem*. **2002**, *67*, 1199–1207. (c) Banwell, M. G.; Edwards, A. J.; Jolliffe, K. A.; Smith, J. A.; Hamel, E.; Verdier-Pinard, P. *Org. Biomol. Chem*. **2003**, *1*, 296–305. (d) Wagner, F. F.; Comins, D. L. *Org. Lett*. **2006**, *8*, 3549–3552. (e) Zhang, J.; Ciufolini, M. A. *Org. Lett.* **2011**, *13*, 390–393. (f) Murugesan, N.; Gu, Z.; Stein, P. D.; Bisaha, S.; Spergel, S.; Girotra, R.; Lee, V. G.; Lloyd, J.; Misra, N. R.; Schmidt, J.; Mathur, A.; Stratton, L.; Kelly, Y. F.; Bird, E.; Waldron, T.; Liu, E. C.-K.; Zhang, R.; Lee, H.; Serafino, R.; Abboa-Offei, B.; Mathers, P.; Giancarli, M.; Seymour, A. A.; Webb, M. L.; Moreland, S.; Barrish, J. C.; Hunt, J. T. *J. Med. Chem*. **1998**, *41*, 5198–5218. (g) Baudoin, O.; Claveau, F.; Thoret, S.; Herrbach, A.; Guénard, D.; Guéritte, F. *Bioorg. Med. Chem*. **2002**, *10*, 3395–3400. (h) Kranich, R.; Busemann, A. S.; Bock, D.; Schroeter-Maas, S.; Beyer, D.; Heinemann, B.; Meyer, M.; Schierhorn, K.; Zahlten, R.; Wolff, G.; Aydt, E. M.; *J. Med. Chem*. **2007**, *50*, 1101–1115. (i) Ganesh, T.; Thepchatri, P.; Li, L.; Du, Y.; Fu, H.; Snyder, J. P.; Sun, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4982–4987.

access to the desired anilino cross-coupling product is when the nitrogen functionality in these reactants is the free amino ($–NH_2$) group.

Some of the medicinally important compounds containing an embedded 2-aminoarene subunit are shown in Figure II-2 (highlighted in bold). In the synthesis of each of these molecules, the 2-aminophenyl units were installed by an aryl-aryl cross-coupling reaction.[51c,d,h,f]

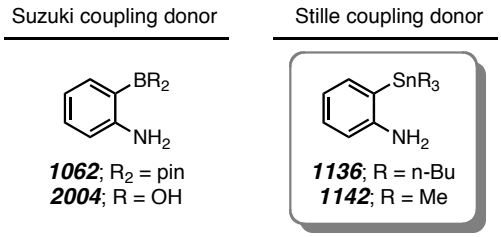
Figure II-2. Examples of Biologically Relevant Compounds Synthesized via a 2-Amino-phenylation Cross-coupling Reaction.



rhazinal (***1003***)[51c] brevicolline (***2001***)[51d] selectin antagonists (***2002***)[51h] endothelin antagonists (***2003***)[51f]

The twisted pyrrole-anilide bond in axially chiral rhazinal (**1003**, cf. Chapter-I) and the pyridine-indole fusion of nicotine derived brevicolline have both been constructed through a palladium mediated *o*-(metallo)aniline and aryl halide cross-coupling. Biologically relevant compounds that are synthesized by this strategy are not limited to natural alkoloids; several medicinal chemistry groups have reported the preparation of polyaromatic molecule libraries for the discovery of protein inhibitors. In particular, selectin (a transmembrane glycoprotein) antagonists **2002** and endothelin (an endothelium protein responsible for hypertension) antagonists **2003** have been prepared via direct thiophine-anilide and sulfonylbenzene-aniline bonding, respectively. The key *o*-(metallo)aniline reagent for these transformations (see the corresponding C-C connections indicated in each structure in Figure II-2) was the Suzuki cross-coupling donors, either the pinacolate ester **1062** or the boronic acid **2004** (Figure II-3). These are commercially available but relatively expensive (ca. $100/g). Their preparation via

Figure II-3. Free Anilino Cross-coupling Building Blocks: Known Boron Reagents[52] (**1062** and **2004**) and New Tin Reagents (**1136** and **1142**).



borylation with $(RO)_2B\text{-}B(OR)_2$[52a,b] or $(RO)_2B\text{-}H$[51a,d] uses rather exotic reagents, ligands, and/or conditions.[53]

Faced with the need to achieve introduction of a 2-aminophenyl substituent in our leuconolam (**1001a**) synthesis project (cf. Chapter-I), we had occasion to explore a new class of reagents—namely the 2-aminophenylstannanes **1136** and **1142** (Figure II-3). We viewed **1136** and **1142** as potentially general and valuable synthons for Migita-Kosugi-Stille cross-coupling[54] reactions. We developed a high-yielding, multigram synthesis of each reagent. These organostannanes proved to be robust (shelf- and air-stable) and, in our hands, additionally advantageous compared to the boron-based analogs **1062** and **2004**. They can be coupled with alkenyl and aryl halides under neutral conditions, a feature that is often advantageous in complex molecule settings. Therefore, in this chapter, I will discuss our efforts to establish a convenient methodology to synthesize **1136** and **1142**, and present their utility in palladium mediated cross-coupling reactions with selected alkenyl and aryl halides/triflates.

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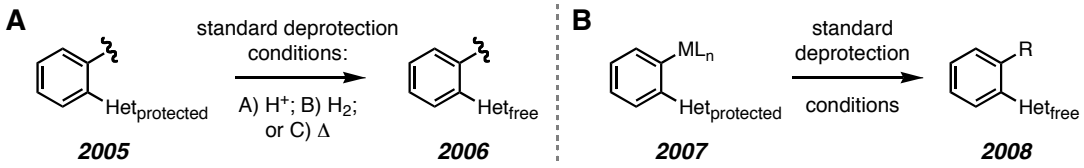
52. (a) Appukkuttan, P.; Van der Eycken, E.; Dehae, W. *Synlett.* **2003**, 1204–1206. (b) Yamamoto, T.; Morita, T.; Takagi, J.; Yamakawa, T. *Org. Lett.* **2011**, *13*, 5766-5769.
53. Earlier reports for the synthesis of **10yya** involved nitration of phenylboronic acid followed by catalytic hydrogenation; (a) Verbit, L.; Levy, J. S.; Rabitz, H.; Kwalwasser, W. *Tetrahedron Lett.* **1966**, *10*, 1053–1055. (b) Groziak, M. P.; Ganguly, A. D.; Robinson, P. D. *J. Am. Chem. Soc*. **1994**, *116*, 7597–7605.
54. (a) Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press, London, UK., **2005**, pp 438–439. (b) From here on, I will be referring to "Migita-Kosugi-Stille" as "Stille" for convenience.

II-B. Results and Discussion

Derivatizations of heteroatom bearing aromatic molecules (e.g., anilines, thiols, phenols) can be a challenging task, especially when the process is a metalation. The heteroatom (e.g., N or O) that is protected prior to the metallation (**2005**), will need to be deprotected afterwards (**2006**). Deprotection protocols often rely on using non-neutral reaction medium (for the sake of discussion, an acid treatment), hydrogenation or heating (Panel A in Scheme II-1). However, (semi)metal-carbon bonds can be labile toward protolysis (or, in general, cleavage by an electrophile) or homolysis (conversion of **2007** to **2008**, Panel B). The C-Sn bond is one of such labile chemical bonds, and it is prone to be readily cleaved under the deprotection conditions mentioned above (and shown in Scheme II-1). The area of organostannes is not as well explored as the boron analogues (admittedly, also because organostannanes are more toxic).

Scheme II-1. Generic Heteroatom Deprotection Event (Panel A) and a Potential Obstacle in the Aftermath of Metalation (Panel B).

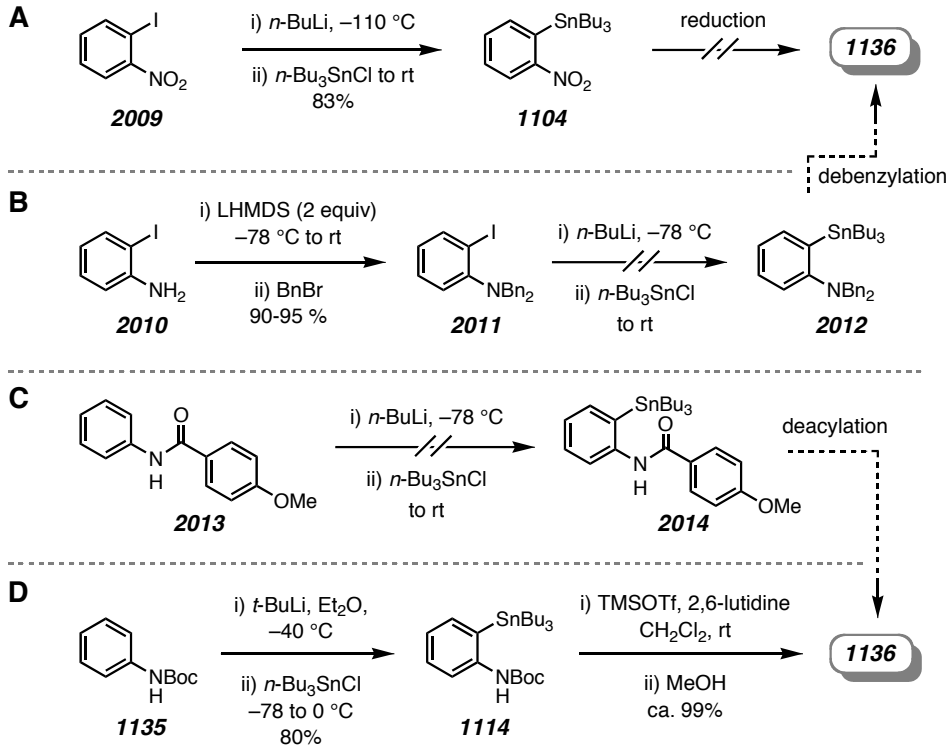


Het = heteroatom; M = (semi)metal; L_n = ligand(s); R = atom other than M (e.g., H)

Our investigations into the synthesis of **1136** (Figure II-3) are summarized in Scheme II-2. First, we explored reduction of *o*-(tributylstannyl)-nitrobenzene (**1104**[55], Panel A) with Sn(II)Cl_2/EtOH, Fe(0)/EtOH, or Pd/C, H_2 (1 atm)/DCM or EtOH. We recovered starting material using the first two conditions, and we observed only the formation of nitrobenzene with the last. Next, we considered di-debenzylation[56] of *N*,*N*-

55. Kosugi, M.; Ohya, T.; Migita, T. *Bull. Chem. Soc. Jpn*. **1983**, *56*, 3855–3856.
56. (a) Gonzáles-Morales, A.; Díaz-Countiño, D.; Fernandez-Zertuche, M.; García-Barradas, O.; Ordóñez, M. *Tetrahedron: Asymmetry* **2004**, *15*, 457–463. (b) Theodora, W.; Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; 3rd Ed.; J. Wiley & Sons, Inc.: New York, NY., **1999**, p 579.

Scheme II-2. Synthesis of *o*-(Tributylstannyl)aniline (**1136**).

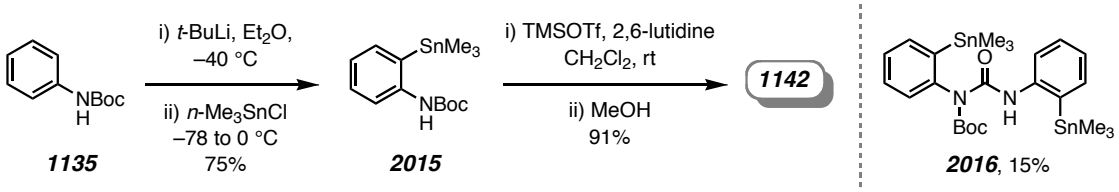


dibenzyl-2-(tributylstannyl)aniline (**2012**, Panel B). However, stannylation of the iodo precursor **2011** via lithium halogen exchange with *n*-BuLi gave *N*,*N*-dibenzyl-2-butylaniline as the only identifiable product. We then examined directed-ortho-metallation[57] of the anilide, 4-methoxy-*N*-phenylbenzamide (**2013**, Panel C). However, stannylation occurred, instead, primarily at the 2-position of the 4-methoxyphenyl moiety of the starting anilide **2013**. Finally, we explored lithiation[58] and stannylation of *N*-Boc aniline (**1135**, Panel D). We found Stanetty's protocol for the lithiation (*t*-BuLi, Et_2O, –40 °C)[58b] to be more serviceable[59] for the efficient preparation of the desired

57. (a) Snieckus, V. *Heterocycles* **1980**, *14*, 1649–1676. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933 and references cited therein.
58. (a) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798–4801. (b) Stanetty, P.; Koller, H.; Mihovilovic, M. *J. Org. Chem.* **1992**, *57*, 6833–6837.
59. In our hands performing the lithiation and quenching sequence in THF at –78 °C[Error! Bookmark not defined.a,60] resulted in variable yields (ca. 20–55%).

aniline precursor **1114**,[60] following quenching with *n*-Bu_3SnCl. We explored a number of conditions for removal of the Boc group in **1114**. Purification of **1136** on either silica gel or alumina (basic or neutral) was problematic. Gratifyingly, the TMSOTf-mediated Boc-cleavage developed by Sakaitani and Ofune[61] smoothly provided *o*-(tributylstannyl)aniline (**1136**) with excellent yield and in a high state of purity. This material (oil) has been stored on the benchtop with no protection from light, air, or moisture for over a year, and no significant deterioration is observable in its ^{1}H-NMR spectrum.

Scheme II-3. Synthesis of *o*-(trimethylstannyl)aniline (**1142**).



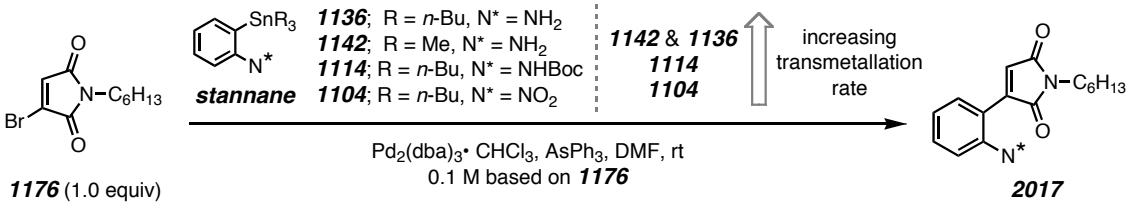
Access to **1142** involves a similar protocol from **1135** (Me_3SnCl was used to quench the initial lithiated *N*-Boc aniline) and proceeds with similar overall yield (Scheme II-3). We occasionally (ca. 3 out of 5 trials regardless of the reaction scale) observed a small amount (15%) of by-product formed during the stannylation process. By detailed NMR and MS analyses, we assigned its structure as **2016**. This compound is easily separated from **2015** by silica gel chromatography, and it is somewhat less acid sensitive (e.g., no deactivation of silica gel is needed for the purification).

We then studied the performance of **1136** and **1142** compared with the known 2-*N*-Boc- and 2-nitro-phenylstannanes (**1114** and **1104**) in coupling reactions with *N*-alkyl bromomaleimide (**1176**) as the alkenyl halide. To test the relative efficiency and reactivity of Stille cross-couplings with organotin reagents containing different

60. (a) Salituro, F. G.; McDonald, I. A. *J. Org. Chem*. **1988**, *53*, 6138–6139. (b) Iwao, M.; Takehara, H.; Furukawa, S.; Watanabe, M. *Heterocycles* **1993**, *36*, 1483–1488.
61. Sakaitani, M.; Ohfune, Y. *J. Org. Chem*. **1990**, *55*, 870–876.

nitrogen-based functional groups, we studied the reactions of **1104**, **1114**, **1136**, and **1142** (Table II-1, graphic) with *N*-hexyl bromomaleimide (**1176**) as the halide partner. This alkenyl halide was also a model compound for the organometal catalyzed aryl-alkenyl coupling studies we carried out in Chapter–I. The results of our feasibility studies for **1104**, **1114**, **1136**, and **1142** are presented in entries 1-6 of Table II-1.

Table II-1. Stille Cross-Couplings of Stannanes with the Imide **1176**.[a]



entry[b]	stannane	equiv	time (h)	conv. of **1176** (%)	**2017**, yield[c]
1	**1136**	1.1	12.0	90	**2017a/b**, 82 %
2	**1142**	1.1	12.0	90	**20187a/b**, 85 %
3	**1136**	1.1	0.5	> 99	**2017a/b**, 94 %
4	**1114**	1.1	12.0	> 99	**2017c**, 91%
5	**1104**	1.1	24.0	20	**2017d**, 13 %
6[d]	**1104**	1.1	24.0	> 99	**2017d**, 85%
7	**1136** + **1114**	10.0	0.5	> 99	**2017a/b**[e]
8	**1136** + **1104**	10.0	0.5	> 99	**2017a/b**[e]
9	**1114** + **1104**	10.0	12.0	> 99	**2017c**[e]

[a]One-hundred mg of **1176** was used in the experiments reported in entries 1-6; ten mg in entries 7-9. [b]$Pd_2(dba)_3$•$CHCl_3$ (1 mol%), $AsPh_3$ (4 mol%) in entries 1-2, $Pd_2(dba)_3$•$CHCl_3$ (5 mol%), $AsPh_3$ (20 mol%) in entries 3-9. [c]Isolated yields for entries 1-6. [d]CuI (10 mol%) was added. [e]Only product that was observed by GC-MS analysis; yield was not determined.

Our initial screening of catalysts and additives for the coupling of **1136** or **1142** with imide **1176** showed that $Pd_2(dba)_3$•$CHCl_3$/$AsPh_3$ was superior to $Pd(PPh_3)_4$,

$Pd(PPh_3)_2Cl_2$/LiCl, or $Pd_2(dba)_3$•$CHCl_3$/PPh_3.

The isolated yields were excellent even when using a nearly 1:1 stoichiometric ratio. Although the nitro compound **1104** reacted somewhat sluggishly under our standard conditions (entry 5), addition of CuI led to a significant improvement (entry 6).[62] We also performed a series of competition studies[63] designed to determine the relative reactivity of **1136**, **1114**, and **1104** (entries 7-9, Table II-1). When imide **1176** was treated simultaneously with an excess of **1136** and the nitro compound **1104** (10 equiv each, entry 7), anilinoimide **2017a/b** (**2017a** = **2017b**; **2017**, N* = NH_2) was observed as the sole coupling product, imide **1176** was fully consumed, and **1136** was ca. 10% consumed (GC/MS integration). The reactivity of **1136** was also compared to that of the *N*-Boc protected derivative **1114** (entry 8). Again, anilinoimide **2017a/b** was the exclusive product. These results show that **1136** is very effective in this additive-free Stille cross-coupling reaction and is more reactive than either **1114** or **1104**. Although other explanations are possible, these observations are consistent with a more rapid transmetalation to the RPd(II)Br species by the amine-bearing organostannane **1136**. A similar explanation has been invoked in an earlier study by Farina.[64]

Next, we explored the scope of the cross-coupling of **1136** using various alkenyl and aryl halides (Table II-2). We performed all reactions in DMF (purged with Ar for ca. 10 min prior to addition of the catalyst and additives) at room temperature and after 24 hours, we quenched the reaction mixtures with saturated aqueous NaCl solution.

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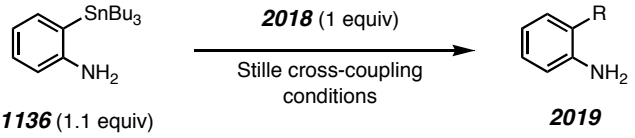
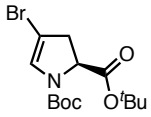
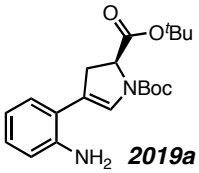
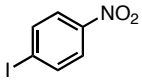
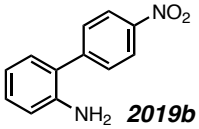
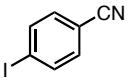
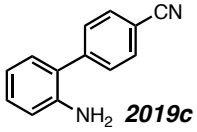
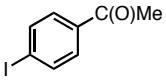
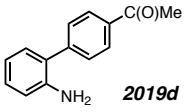
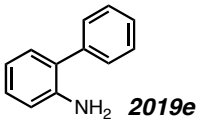
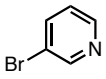
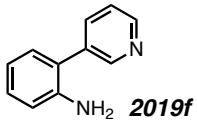
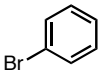
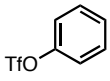
62. Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem*. **1994**, *59*, 5905–5911.
63. Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books, Sausalito, CA., **2006**, pp 473–474.
64. Farina, V. *Pure. Appl. Chem.* **1996**, *68*, 73–78.

Table II-2. Stille Cross-Couplings of **1136** with Alkenyl and Aryl Halides **2018**.[a]

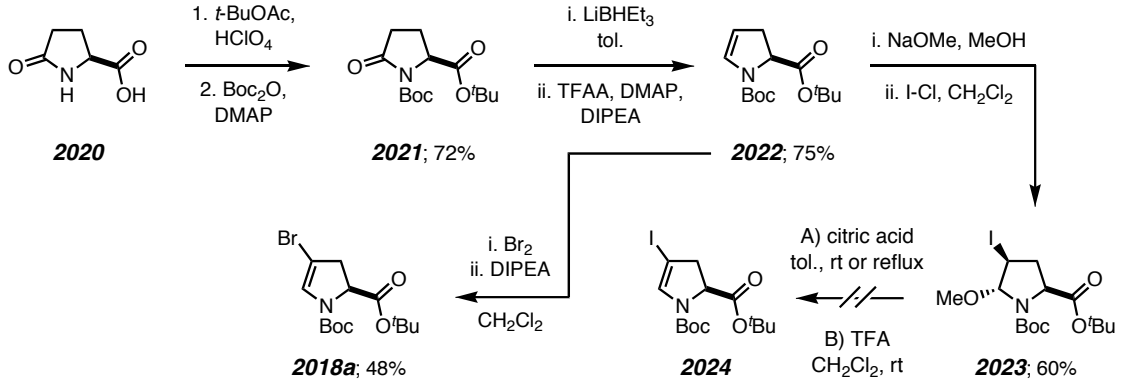


1136 (1.1 equiv) ***2019***

entry	**2018**	catalyst (mol%)	additives (equiv)	**2019**	yield (%)
1	 ***2018a***	$Pd(PPh_3)_4$ (5)	CuI (0.1). CsF (2.0)	 ***2019a***	62
2	 ***2018b***	$Pd_2(dba)_3{\cdot}CHCl_3$ (5)	$AsPh_3$ (0.2)	 ***2019b***	86
3	 ***2018c***	$Pd_2(dba)_3{\cdot}CHCl_3$ (5)	$AsPh_3$ (0.2)	 ***2019c***	84
4	 ***2018d***	$Pd_2(dba)_3{\cdot}CHCl_3$ (5)	$AsPh_3$ (0.2)	 ***2019d***	73
5	 ***2018e***	$Pd(PPh_3)_4$ (10)	CuI (0.2). CsF (2.0)	 ***2019e***	82
6	 ***2018f***	$Pd(PPh_3)_4$ (10)	CuI (0.2). CsF (2.0)	 ***2019f***	66
7	 ***2018g***	$Pd(PPh_3)_4$ (10)	CuI (0.2). CsF (2.0)	***2019e***	63
8	 ***2018h***	$Pd(PPh_3)_4$ (10)	CuI (0.2). CsF (2.0)	***2019e***	80

Use of the Stille cross-coupling conditions championed by Baldwin and co-workers,[65] namely, $Pd(PPh_3)_4$–CuI–CsF in DMF, provided significantly higher product yields for substrates exhibiting low reactivity (**2018a** in entry 1, and **2018e-h** in entries 5-8) under typical conditions. Coupling of **1136** with the (multifunctional) bromodihydropyrrole **2018a** (Scheme II-4) provided the 2-(aminophenyl)-dihydropyrrole **2019a** in 62% yield (entry 1). While aryl iodides **2013b-e** (entries 2-5) underwent cross-coupling reactions efficiently, aryl bromides **2018f** and **2018g** gave 2-(aryl)anilines **2019f** and **2019e** in somewhat lower yields (ca. 65%, entries 6-7, respectively). Similar to the case of **2018a**, phenyl triflate (**2018h**) was unreactive under the $Pd_2(dba)_3$•$CHCl_3$–$AsPh_3$ (with or without CuI additive) condition. The coupling efficiency with this partner significantly increased, again, using Baldwin's conditions, which resulted in 80% isolated yield of 2-(phenyl)aniline (entry 8).

Scheme II-4. Synthesis of Bromoenecarbamate (**2018a**).



We prepared the bromoenecarbamate **2018a** following a 6-step/4-pot route from commercially available L-pyroglutamic acid. Although the synthesis of alkene **2022** was straightforward and easily scalable following Bräse's protocol,[66] halogenation-elimination to provide a halo-alkene was a difficult and low yielding transformation in general. Our initial attempts to obtain the iodoenecarbamate **2024** from **2022** using (i)

65. Mee, S. P.; Lee, V.; Baldwin, J. E. *Angew. Chem. Int. Ed*. **2004**, *43*, 1132–1136.
66. Gross, U.; Nieger, M.; Bräse, S. *Org. Lett.* **2009**, *11*, 4740–4742.

iodine monochloride in the presence of NaOMe in MeOH/CH_2Cl_2,[67] and (ii) acid mediated methanol elimination proved unsuccessful. This was mainly due to the lack of reactivity of the iodo ether **2023** in acidic conditions. On the other hand, utilizing harsher reagents (e.g., TFA) caused formation of a number of degradation products (major of which was the Boc deprotection product observed by LC-MS analysis). Therefore, we prepared the bromo analog **2018a** via a one-pot bromination-elimination procedure from **2022**. Although in moderate yield (48%), we were able to obtain **2018a** by sequential addition of Br_2 (1.05 equiv) and DIPEA (1.1 equiv) at low temperature. Excess Br_2, which could potentially cause side reactions, was scavenged by addition (prior to DIPEA) of trace amount of 1-octene as reported by Ojima.[68]

67. Zhang, H.; Curran, D. P. *J. Am. Chem. Soc.* **2011**, *133*, 10376–10378.
68. Chiou, W.-H.; Schoenfelder, A.; Sun, L.; Mann, A.; Ojima, I. *J. Org. Chem*. **2007**, *72*, 9418–9425.

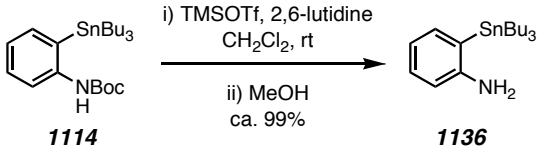
II-C. Conclusion

In conclusion, we have shown that the *o*-anilinostannanes **1136** and **1142** are facile participants in Stille cross-coupling reactions. Each was efficiently synthesized on multigram scale. Their cross-coupling reactivity toward *N*-hexyl bromomaleimide (**1176**) is greater than that of either the *N*-Boc or nitro analog **1114** or **1104**, respectively. The efficient preparations of **1136** and **1142** and their wide substrate scope in Stille cross-couplings make these organostannanes important and practical building blocks for general use in organic synthesis.

II-D. Experimental Section

All reactions were performed under a dry nitrogen or argon atmosphere unless otherwise noted. All glassware was flame- and/or oven-dried before use. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were dried through Al_2O_3 columns; hexanes (Hex) and ethyl acetate (EtOAc) were used as received (reagent grade). All other reagents and solvents were used as received. Thin layer chromatography (TLC) was performed using TLC plastic sheets with F_{254} indicator and visualization via UV-light or staining with either potassium permanganate or anisaldehyde. Flash column purifications were performed using 40-63 mm silica gel or alumina (neutral, Brockman activity 1). Medium pressure liquid chromatography (MPLC) purifications were performed using glass columns, dry packed with ca. 25-35 mm particle size silica gel. The MPLC apparatus was outfitted with an HPLC pump and refractive index detector. All NMR spectra were determined in $CDCl_3$. ^1H NMR spectra were acquired at 500 MHz ^1H. ^{13}C NMR spectra were acquired at 125 or 75 MHz. Chemical shifts (δ) for ^1H NMR spectra are referenced to TMS at δ = 0.00 ppm, and ^{13}C NMR spectra are referenced to $CDCl_3$ at δ = 77.16 ppm. The following abbreviations are used to describe NMR resonances: s (singlet), d (doublet), t (triplet), q (quartet), sext (sextet), m (multiplet), br (broad), nfom (non-first order multiplet), and nfod (non-first order doublet). Coupling constants (*J*) are reported in Hz. Infrared spectra were recorded on an FT-IR spectrometer. The most intense and/or diagnostic peaks are reported, and all spectra were collected in attenuated total reflectance (ATR) mode as thin films on a germanium window. Optical rotation data were recorded on a Perkin-Elmer-241 polarimeter using a 3.5x50 mm or 100 mm cell. Low-resolution GC-MS data (LRMS) were recorded at 70 eV. High-resolution mass spectra (HRMS) in the ESI mode were recorded on a time of flight instrument with 20,000 resolving power (FWHM) using PEG as an internal standard/calibrant. High-resolution mass spectra (HRMS) in the CI or EI mode were recorded on a double focusing instrument with 4,000 resolving power (FWHM) using perfluorokerosene calibrant.

***o*-(Tributylstannyl)aniline (1114).**



1114 ***1136***

To a solution of **1114** (10.0 g, 20.7 mmol, 1.0 equiv) and 2,6-lutidine (14.5 mL, 124.2 mmol, 6.0 equiv) in 105 mL of dry CH_2Cl_2 was added TMSOTf (11.2 mL, 62.1 mmol, 3.0 equiv) at rt and under an Ar atmosphere. After being stirred for 1 h, the reaction mixture was treated with MeOH (35 mL) and stirred for an additional 30 min, and water (30 mL) was added. The resulting mixture was diluted with CH_2Cl_2 (200 mL) and stirred vigorously for 15 min. The organic layer was washed with water (100 mL x 3) and brine (100 mL), dried over Na_2SO_4, concentrated on a rotary evaporator, and placed on a high vacuum pump line for 24 h to give **1136** (7.9 g, ca. 99%) as a pale yellow oil. This material was sufficiently pure for use in subsequent coupling reactions.

^{1}**H NMR** (500 MHz, $CDCl_3$): δ 7.23 (dd, *J* = 8.5, 1.0, 1H), 7.13 (ddd, *J* = 7.5, 7.5, 1.0, 1H), 6.76 (ddd, *J* = 8.5, 7.5, 1.5, 1H), 6.67 (dd, *J* = 7.5, 1.5, 1H), 3.61 (br s, 2H), 1.52 (nfom, 6H), 1.33 (sext, *J* = 7.5, 6H), 1.10 (nfom, 6H), and 0.89 (t, *J* = 7.5, 9H).

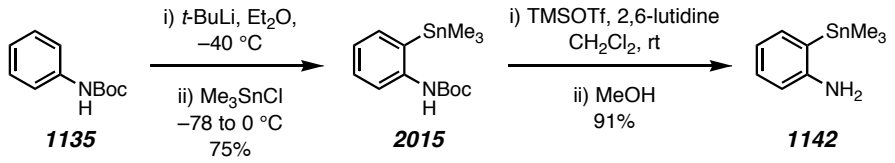
^{13}**C NMR** ($CDCl_3$, 75 MHz) δ 152.2, 137.5, 129.6, 126.0, 118.9, 114.9, 29.3, 27.5, 13.8, and 9.7.

IR (thin film): 2956, 2925, 2871, 2853, 1616, 1464, and 1436 cm^{-1}.

GC-LRMS [EI, 70 eV, m/z (rel. int.)] 383 (1, M^+), 352 (3), 326 (100), 270 (10), and 212 (90).

HRMS (CI, 4% NH_3 in CH_4) calcd for $C_{18}H_{33}NSn•H^+$ 384.1708, found 384.1698.

***o*-(Trimethylstannyl)aniline (1142).**



1135 ***2015*** ***1142***

N-Boc-aniline (**1035**, 5.0 g, 26 mmol, 1.0 equiv) was placed in an oven dried 250 mL round bottomed-flask and dissolved in 100 mL of dry Et_2O. The solution was cooled to –40 °C under an Ar atmosphere. *t*-BuLi (1.6 M in pentane, 36.0 mL, 57 mmol, 2.2 equiv) was added via a syringe pump over 30 min, during which time the mixture became homogenous, and the resulting solution was stirred at 0 °C for 3 h. The reaction mixture was cooled to –78 °C, treated with Me_3SnCl (5.2 g, 26 mmol, 1.0 equiv), and stirred at 0 °C for 6 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (50 mL) at 0 °C. The organics were extracted with Et_2O (300 mL x 2) and washed with brine (50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography [either on silica gel, dry packed and pre-washed with a 10:1:1 mixture of Hex/Et_3N/EtOAc, eluted with 20:1 mixture of Hex/EtOAc or on neutral alumina (Brockman activity 1), dry packed and pre-washed with a 40:4:1 mixture of Hex/Et_3N/EtOAc, eluted with 20:1 mixture of Hex/EtOAc] provided *N*-(*tert*-Butoxycarbonyl)-2-(trimethylstannyl)aniline[69a] (**2015**, 6.9 g, 19 mmol, 75%) as an off-white solid and a more slowly eluting byproduct, the bis-stannane **2016** (2.5 g, 15%) as a colorless oil. The spectral data for **2015** were consistent with those previously reported.[69a]

The *N*-Boc stannane **2015** (5.20 g, 14.6 mmol, 1.0 equiv) and 2,6-lutidine (10.2 mL, 87.6 mmol, 6.0 equiv) in 50 mL of dry CH_2Cl_2 were treated with TMSOTf (7.90 mL, 43.8 mmol, 3.0 equiv) at rt and under an Ar atmosphere. After being stirred for 1 h, the reaction mixture was treated with MeOH (20 mL) and stirred for an additional 30

69. (a) Salituro, F. G.; McDonald, I. A. *J. Org. Chem*. **1988**, *53*, 6138–6139. (b) Iwao, M.; Takehara, H.; Furukawa, S.; Watanabe, M. *Heterocycles* **1993**, *36*, 1483–1488.

min, and water (10 mL) was added. The resulting mixture was diluted with CH_2Cl_2 (100 mL) and stirred vigorously for 15 min. The organic layer was washed with water (50 mL x 3) and brine (50 mL), dried over Na_2SO_4, concentrated on a rotary evaporator, and placed on a high vacuum pump line for 24 h to give **1142** (3.40 g, 13.2 mmol, 91%) as a pale yellow oil. This material was sufficiently pure for use in subsequent coupling reactions. Upon extended storage, this material darkened in color, but analysis by ^{1}H NMR spectroscopy indicated that the integrity was largely unchanged and such samples continued to perform well when used in subsequent coupling experiments.

^{1}H NMR (500 MHz, $CDCl_3$): 7.23 (dd, *J* = 8.5, 1.0, 1H), 7.14 (ddd, *J* = 7.5, 7.5, 1.0, 1H), 6.80 (ddd, *J* = 8.5, 7.5, 1.5, 1H), 6.67 (dd, *J* = 8.0, 1.0, 1H), and 0.33 (s, 9H).

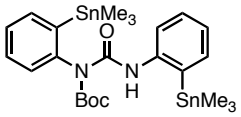
^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.1, 136.9, 130.0, 126.0, 118.9, 115.1, and –9.7.

IR (thin film): 3367, 3057, 2979, 2912, 1618, 1472, 1436, 1309, and 1290 cm^{-1}.

GC-LRMS [EI, 70 eV, m/z (rel. int.)] 257 (10, M^+), 242 (100), and 212 (70).

HRMS (EI, 70 eV) calcd for $C_9H_{15}NSn^+$ 257.0221, found 257.0242.

***tert*-Butyl 2-(trimethylstannyl)phenyl(2-(trimethylstannyl)phenylcarbamoyl)-carbamate (2016).**



2016

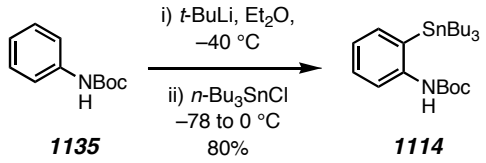
^{1}H NMR (500 MHz, $CDCl_3$): 10.66 (s, br, 1H), 7.52 (dd, *J* = 7.5, 2.0, 1H), 7.44 (dd, *J* = 7.5, 1.5, 1H), 7.35 (ddd, *J* = 9.0, 7.5, 1.5, 1H), 7.13 (ddd, *J* = 8.5, 7.5, 1.5, 1H), 7.10 (dd, 8.5, 1.0, 1H), 1.37 (s, 9H), 0.40 (s, 9H), and 0.30 (s, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.4, 153.0, 144.4,143.3, 142.6, 136.5, 136.5, 135.3, 129.5, 129.3, 128.6, 127.4, 124.8, 123.5, 84.0, 28.1, –9.3, and –9.4.

IR (thin film): 3280, 3054, 2979, 2915, 1726, 1688, 1526, 1369, 1321, and 1150 cm^{-1}.

HRMS (ESI) calcd for $C_{24}H_{36}N_2O_3{}^{120}Sn_2 \bullet H^+$ 641.0843, found 641.084.

***tert*-Butyl *N*-(2-tributylstannyl)phenylcarbamate (1114).**



1135 ***1114***

N-Boc-aniline (**1135**, 5.00 g, 25.9 mmol, 1.0 equiv) was placed in an oven dried 250 mL round bottomed-flask and dissolved in 52 mL of dry Et_2O. The solution was cooled to –40 °C under an Ar atmosphere. *t*-BuLi (1.6 M in pentane, 34.0 mL, 54.4 mmol, 2.1 equiv) was added via a syringe pump over 30 min, during which the mixture became homogenous, and the resulting solution was stirred at 0 °C for 3 h. The reaction mixture was further cooled to –78 °C, treated with Bu_3SnCl (6.8 mL, 25.1 mmol, 1.0 equiv), and stirred at 0 °C for 6 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (50 mL) at 0 °C. The organics were extracted with Et_2O (300 mL x 2) and washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography using neutral alumina (Brockman activity 1, dry packed and pre-washed with a 40:4:1 mixture of Hex/Et_3N/EtOAc, eluted with 20:1 mixture of Hex/EtOAc) gave **1114**[69b] (10.0 g, 80%) as a colorless oil.

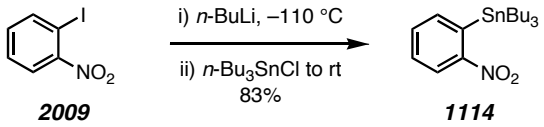
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (br s, 1H), 7.34 (dd, *J* = 7.5, 1.5, 1H), 7.32 (ddd, *J* = 7.5, 7.0, 1.5, 1H), 7.07 (ddd, *J* = 7.5, 6.5, 1.0, 1H), 6.30 (br s, 1H), 1.52 (nfom, 6H), 1.51 (s, 9H), 1.34 (sext, *J* = 7.5, 6H), 1.10 (nfom, 6H), and 0.89 (t, *J* = 7.5, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.5, 143.6, 137.0, 129.3, 124.2, 122.0 (br), 80.3, 29.1, 28.5, 27.4, 13.7, and 10.1.

IR (thin film): 3440, 2956, 2926, 2871, 2853, 1737, and 1507 cm^{-1}.

HRMS (ESI) calcd for $C_{23}H_{41}NO_2Sn \bullet Na^+$ 506.2051, found 506.2078.

Tributyl-(2-nitrophenyl)stannane (1104).



2009 ***1114***

1-Iodo-2-nitrobenzene (**2009**, 2.0 g, 8.0 mmol, 1.0 equiv) was placed in a flame-dried 250 mL round bottomed-flask and dissolved in 75 mL of dry THF. The solution was cooled to –100 °C under an Ar atmosphere. To this solution was added *n*-BuLi (2.4 M in hexane, 3.4 mL, 8.0 mmol, 1.0 equiv) via a syringe pump over 10 min. The solution was stirred at the same temperature for 3 min, after which Bu_3SnCl (2.2 mL, 8.0 mmol, 1.0 equiv) was added dropwise. The resulting reaction mixture was allowed to warm to rt and stirred for 1 h before being diluted with a 2:1 mixture of Hex/Et_2O (150 mL) and poured into ice-water (ca. 50 mL). The organic phase was extracted and washed with brine (50 mL x 2). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give the crude material. Column chromatography using silica gel (dry packed, pre-washed with 1:4 mixture of Et_3N/EtOAc and, eluted with 50:1 mixture of Hex/EtOAc), gave **1104**[70] (2.7 g, 83%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (dd, *J* = 8.5, 1.0, 1H), 7.68 (dd, *J* = 7.5, 1.5, 1H), 7.62 (ddd, *J* = 7.5, 7.5, 1.0, 1H), 7.49 (ddd, *J* = 8.5, 7.5, 1.5, 1H), 1.50 (nfom, 6H), 1.31 (sext, *J* = 7.5, 6H), 1.12 (nfom, 6H), and 0.87 (t, *J* = 7.5, 9H).

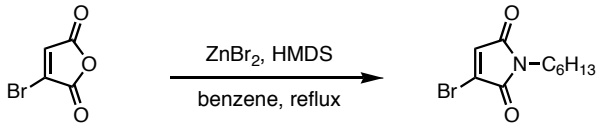
^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.7, 140.4, 137.8, 133.6, 129.3, 124.2, 28.8, 27.4, 13.8, and 11.1.

IR (thin film): 2955, 2922, 2853, 1339, 1270, 1262, and 870 cm^{-1}.

LRMS [EI, 70 eV, m/z (rel. int.)] 413 (1, M^+), 356 (100), 300 (10), and 242 (30).

70. Kosugi, M.; Ohya, T.; Migita, T. *Bull. Chem. Soc. Jpn*. **1983**, *56*, 3855–3856.

3-Bromo-(*N*-hexyl)maleimide (1176).



S-1 ***1176***

To a suspension of bromomaleic anhydride[71] (**S-1**, 3.2 g, 18.0 mmol, 1.0 equiv) in benzene (120 mL) was added a solution of *n*-hexylamine (2.4 mL, 18.0 mmol, 1.0 equiv) in benzene (60 mL). The resulting mixture was stirred at rt for 1 h, and $ZnBr_2$[72] (4.5 g, 19.8 mmol, 1.1 equiv) was introduced in one portion. The reaction mixture was heated to reflux temperature after which a solution of HMDS (5.6 mL, 27 mmol, 1.5 equiv) in benzene (50 mL) was slowly added. After being stirred for 1 h, an additional 1.0 mL of HMDS (neat) was added, and the mixture was stirred at the same temperature for 3 h. The resulting reaction mixture was cooled to rt, poured into 0.5 N HCl (100 mL), and extracted with Et_2O (250 mL x 2). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (6:1 Hex/EtOAc) of the crude material gave **1176** (3.9 g, 84%) as a red oil. R_f = 0.5 (6:1 Hex/EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.86 (s, 1H), 3.55 (dd, *J* = 7.5, 7.0, 2H), 1.59 (br p, *J* = 7.0, 2H), 1.28 (br s, 6H), 0.88 (br t, *J* = 7.0, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.8, 165.5, 131.9, 131.4, 39.1, 31.4, 28.5, 26.5, 22.6, and 14.1. IR (thin film): 2955, 2929, 2858, 1716, 1589, 1399, and 1368 cm^{-1}.

GC-LRMS [EI, 70 eV, m/z (rel. int.)] 259-261 (40, M^+), 190-188 (80), 152 (100).

HRMS (EI, 70 eV) calcd for $C_{10}H_{14}{}^{79}BrNO_2^+$ 259.0202, found 259.0201 and calcd for $C_{10}H_{14}{}^{81}BrNO_2^+$ 261.0182, found 261.0190.

71. Gortinskaya, T. V.; Nyrkova, V. G.; Savitskaya, N. V.; Shchukina, M. N.; Klimonova, Z. M.; Potapova, V. G.; Gorodetskii, L. S.; Volzhina, O. N. *Pharm. Chem. J.* **1973**, *7*, 353–355.
72. Reddy, P. Y.; Kondo, S.; Toru, T.; Ueno, Y. *J. Org. Chem.* **1997**, *62*, 2652–2654.

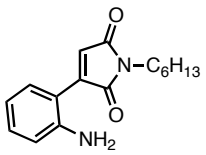
General Procedure for the Stille Cross-Coupling of Imide 1176 with Arylstannanes to Produce Adducts 2017 (Entries 1-6 in Table II-1):

A mixture of imide **1176** (100 mg, 0.38 mmol, 1.0 equiv) and arylstannane **2** (1.0 equiv) in dry DMF (4.0 mL) was purged with Ar for 15 min and treated with $Pd_2(dba)_3$•$CHCl_3$ (0.01 equiv for entries 1-2, or 0.05 equiv for entries 3-6 in Table 1) and $AsPh_3$ (0.04 equiv for entries 1-2, or 0.2 equiv for entries 3-6 in Table 1). The reaction mixture was purged with Ar for an additional 15 min and stirred at rt until the TLC analysis showed no evidence of imide **1176**. The solution was diluted with brine (20 mL) and EtOAc (100 mL), and the organic phase was washed with a 1:1 mixture of water and brine (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude reaction products **2017a/b**, **2017c**, or **2017d** were purified by flash chromatography.

General Procedure for the Competitive Stille Cross-Coupling of Imide 1176 with Arylstannanes (Entries 7-9 in Table 1):

A mixture of imide **1176** (10 mg, 0.040 mmol, 1.0 equiv) and each of two arylstannanes **1136** and **1142** (10.0 equiv of each) in dry DMF (0.2 mL) was purged with Ar for 15 min and treated with $Pd_2(dba)_3$•$CHCl_3$ (3 mg, 0.003 mmol, 0.1 equiv) and $AsPh_3$ (3 mg, 0.010 mmol, 0.4 equiv). The reaction mixture was purged with Ar for an additional 15 min and stirred at rt until the TLC analysis showed no evidence of imide **1176**. The solution was diluted with brine (2 mL) and EtOAc (10 mL), and the organic phase was washed with a 1:1 mixture of water and brine (3 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to provide coupling products **2017a/b, 2017c, and 2017d**.

3-(2-Aminophenyl)-*N*-hexylmaleimide (2017a/b).



2017a/b

Using the general procedure mentioned above (also see entry 3 in Table II-1) 106 mg (94%) of **2017a/b** was isolated as a red oil.

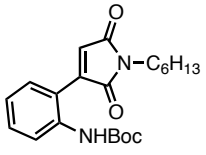
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (dd, *J* = 7.5, 1.5, 1H), 7.23 (ddd, *J* = 8.0, 7.5, 1.5, 1H), 6.82 (ddd, *J* = 8.0, 7.5, 1.5 1H), 6.74 (dd, *J* = 7.5, 1.0, 1H), 6.71 (s, 1H), 4.31 (br s, 2H), 3.57 (dd, *J* = 7.5, 7.0, 2H), 1.62 (nfom, 2H), 1.31 (m, 6H), and 0.88 (br t, *J* = 7, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.5, 171.0, 146.4, 144.3, 132.1, 131.3, 125.4, 119.0, 117.3, 114.7, 38.3, 31.4, 28.6, 26.5, 22.6 and 14.1.

IR (thin film): 3370, 3451, 2963, 2931, 2858, 1697, 1624, 1448, and 1405 cm^{-1}.

HRMS (ESI) calcd for $C_{16}H_{20}N_2O_2 \bullet Na^+$ 295.1417, found 295.1415.

***tert*-Butyl-2-(*N*-hexylmaleimid-3-yl)phenylcarbamate (2017c).**



2017c

Using the general procedure mentioned above (also see entry 4 in Table II-1) 137 mg (91%) of **2017c** was isolated as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (dd, *J* = 8.5, 1.0, 1H), 7.55 (br s, 1H), 7.45 (ddd, *J*

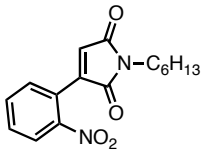
= 8.0, 8.0, 1.0, 1H), 7.41 (dd, *J* = 8.0, 1.0, 1H), 7.17 (ddd, *J* = 8.0, 8.0, 1.0, 1H), 6.66 (s, 1H), 3.61 (dd, *J* = 7.5, 7.0, 2H), 1.64 (br p, *J* = 7.0, 2H), 1.50 (br s, 9H), 1.32 (m, 8H), and 0.89 (br t, *J* = 7, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.6, 170.3, 153.4, 145.2, 136.6, 131.8, 130.8, 127.9, 124.5, 124.0, 121.3, 80.9, 38.5, 31.4, 28.5, 28.4, 26.5, 22.6, and 14.1.

IR (thin film): 2955, 2931, 2859, 1702, 1515, 1445, 1405, 1367, 1228, and 1158 cm^{-1}.

HRMS (ESI) calcd for $C_{21}H_{28}N_2O_4 \bullet Na^+$ 395.1941, found 395.1937.

3-(2-Nitrophenyl)-*N*-hexylmaleimide (2017d).



2017d

Using the general procedure mentioned above (also see entry 6 in Table II-1) 105 mg (85%) of **2017d** was isolated as a yellow oil.

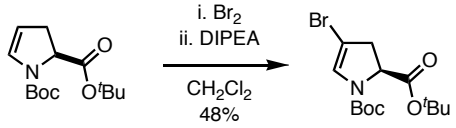
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (dd, *J* = 7.5, 1.5, 1H), 7.74 (ddd, *J* = 8.5, 7.5, 1.0, 1H), 7.67 (ddd, *J* = 9.0, 8.0, 1.0, 1H), 7.48 (dd, *J* = 7.5, 1.5, 1H), 6.68 (s, 1H), 3.57 (dd, *J* = 7.5, 7.0, 2H), 1.62 (nfom, 2H), 1.31 (m, 6H), and 0.88 (br t, *J* = 7, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.2, 168.9, 148.3, 145.5, 134.0, 131.6, 131.5, 126.4, 125.3, 124.7, 38.6, 31.3, 28.5, 26.4, 22.6 and 14.1.

IR (thin film): 2957, 2930, 2859, 1708, 1527, 1403, and 1350 cm^{-1}.

HRMS (ESI) calcd for $C_{16}H_{18}N_2O_4 \bullet Na^+$ 325.1159, found 325.1182.

(*S*)-Di-tert-butyl 4-bromo-2,3-dihydro-1H-pyrrole-1,2-dicarboxylate (2018a).



2022 ***2018a***

To a solution of enecarbamate **2022**[66] (300 mg, 1.1 mmol, 1 equiv) in CH_2Cl_2 (11 mL) at –78 °C was slowly added Br_2 (60 μL, 1.2 mmol, 1.1 equiv). After the starting material **16** was fully consumed, 1-octene (15 μL, 0.1 mmol, 0.2 equiv) was added to scavenge the excess Br_2. To the resulting solution was slowly added diisopropyl ethylamine (210 μL, 1.2 mmol, 1.1 equiv), and the resulting mixture was allowed to warm to rt, at which it was stirred for 1 hour. The reaction mixture was poured into a saturated aqueous solution of $Na_2S_2O_3$ (ca. 50 mL) and extracted with CH_2Cl_2 (2 x 100 mL). Combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the crude material. MPLC separation using 5:1 (Hex:EtOAc) provided 195 mg of the bromo-alkene **2018a** (48 %) as a yellow oil. $[\alpha]_D$ –51.4 (c 0.017 g/mL, $CHCl_3$).

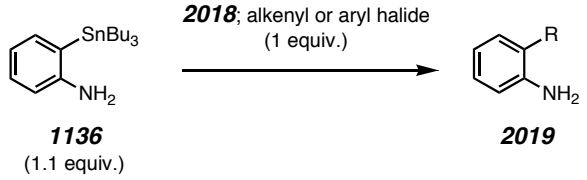
^{1}**H NMR** (500 MHz, $CDCl_3$, two rotamers ca. 1:1): δ 6.75 (s, 0.5H), 6.62 (s, 0.5H), 4.57 (dd, *J* = 12.0, 4.5 Hz, 0.5H), 4.50 (dd, *J* = 12.0, 4.5 Hz, 0.5H), 3.26 (dd, *J* = 12, 14 Hz, 0.5H), 3.23 (dd, *J* = 12, 14 Hz, 0.5H), 2.81–2.75 (m, 1H), 1.49, 1.479, 1.475, and 1.45 (four s, 4.5H eacH).

^{13}**C NMR** ($CDCl_3$, 75 MHz) δ 169.9, 169.8, 150.8, 150.6, 130.0, 97.10, 97.06, 82.2, 82.1, 81.6, 81.5, 59.5, 59.2, 41.6, 40.5, 28.4, 28.3, and 28.1.

IR (thin film): 2979, 1746, 1710, 1394, 1369, 1222, 1152, and 1140 cm^{-1}.

HRMS (ESI) calcd for $C_{14}H_{22}NO_4{}^{79}Br{\bullet}Na^+$ 370.0630, found 370.0625 and calcd for $C_{14}H_{22}NO_4{}^{81}Br{\bullet}Na^+$ 372.0609, found 372.0607.

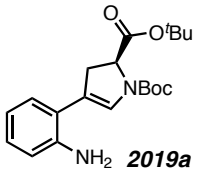
General Procedure for the Stille Cross-Coupling of 1136 with Alkenyl or Aryl Halides 2018.



1136 (1.1 equiv.) ***2019***

A mixture of **1136** (60 mg, 0.16 mmol, 1.1 equiv) and the halide **2018** (see Table 2; 0.14 mmol, 1 equiv) in dry DMF (1.4 mL) was purged with Ar for 10 min. To this solution was added either $Pd_2(dba)_3$•$CHCl_3$ (10 mg, 0.014 mmol, 0.1 equiv) and $AsPh_3$ (12 mg, 0.06 mmol, 0.4 equiv) simultaneously (entries 2-4 in Table 2), or first CsF (40 mg, 0.28 mmol, 2 equiv) then $Pd(PPh_3)_4$ (8 mg, 0.014 mmol, 0.1 equiv) and CuI (4 mg, 0.03 mmol, 0.2 equiv, entries 1, 5-8). The mixture was purged with Ar for an additional 10 min and stirred at rt for 16 h. The resulting mixture was diluted with brine (1 mL) and EtOAc (10 mL), and the organic phase was washed with a 1:1 mixture of water and brine (3 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give crude coupling products **2019**.

(*S*)-Di-tert-butyl 4-aminophenyl-2,3-dihydro-1H-pyrrole-1,2-dicarboxylate (2019a).



2019a

Table II-2, entry 1: Isolated in 62% yield as a pale yellow oil. $[\alpha]_D$ –38.7 (c 0.015 g/mL, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$ two rotamers ca. 2:1): *major* δ 7.14 (s, 1H), 7.03-6.99 (m, 2H), 6.77-6.71 (m, 2H), 4.55 (dd, *J* = 12.0, 4.5 Hz, 1H). 3.88 (br s, 2H), 3.50 (dd, *J* = 15.0, 14.0 Hz, 1H), 2.93 (dd, *J* = 16.0, 4.5 Hz, 1H), 1.491 (s, 9H), and 1.486 (s, 9H).

minor δ 6.95 (s, 1H), 7.03-6.99 (m, 2H), 6.78-6.71 (m, 2H), 4.63 (dd, *J* = 12.0, 4.5 Hz, 1H). 3.88 (br s, 2H), 3.43 (dd, *J* = 15.0, 13.5 Hz, 1H), 2.89 (dd, *J* = 16.0, 4.5 Hz, 1H), 1.51 (s, 9H), and 1.49 (s, 9H).

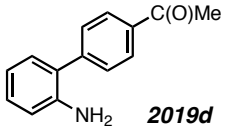
^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.84, 170.78, 151.7, 151.4, 144.3, 144.1, 127.6, 127.5, 127.3, 127.1, 126.9, 120.8, 120.5, 119.0, 118.7, 116.4, 116.3, 81.8, 81.7, 81.2, 81.1, 58.4, 58.2, 38.2, 37.1, 37.0, 28.5, 28.4, 28.2, and 28.1.

IR (thin film): 2977, 1741, 1702, 1620, 1453, 1406, 1275, 1256, and 1155 cm^{-1}.

GC-LRMS [EI, 70 eV, m/z (rel. int.)] 360 (30, M^+), 260 (40), 204 (50), 159 (100), and 130 (90).

HRMS (ESI) calcd for $C_{20}H_{28}N_2O_4 \bullet Na^+$ 383.1941, found 383.1982.

2-(4-Acetylphenyl)aniline (2019d).



2019d

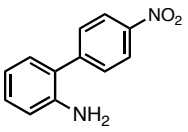
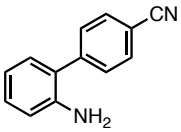
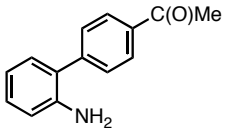
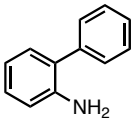
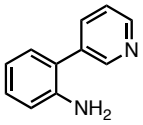
Table II-2, entry 4: Isolated in 73% yield as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (nfod, *J* = 8.5, 2H), 7.59 (nfod, *J* = 8.5, 2H), 7.20 (ddd, *J* = 9.0, 8.0, 1.0, 1H), 7.14 (dd, *J* = 7.5, 1.5, 1H), 6.86 (ddd, *J* = 9.0, 7.5, 1.5, 1H), 6.79 (dd, *J* = 8.0, 1.0, 1H), 3.78 (br s, 2H), and 2.66 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.0, 144.8, 143.6, 135.9, 130.4, 129.41, 129.38, 129.1, 126.4, 119.0, 116.0, and 26.8.

IR (thin film): 1678, 1604, 1468, 1402, 1357, and 1269 cm^{-1}.

HRMS (ESI) calcd for $C_{14}H_{13}NO{\bullet}H^+$ 212.1070, found 212.1088.

2-(4-nitrophenyl)aniline (2019b)[73] 	**2-(4-cyanophenyl)aniline (2019c)**[73] 	**2-(4-acetylphenyl)aniline (2019d)**[74] 
2-(phenyl)aniline (2019e)[75] 	**2-(pyridin-3-yl)aniline (2019f)**[76] 	

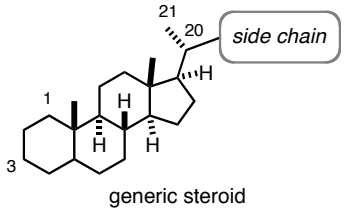
73. Stokes, B. J.; Jovanovic, B.; Dong, H.; Richert, K. J.; Riell, R. D.; Driver, T. G. *J. Org. Chem.* **2009**, *74*, 3225-3228.
74. Dell 'Erba, C.; Garbarino, G.; Guanti, G. *Tetrahedron* **1971**, *27*, 113–121.
75. Baghbanzadeh, M.; Pilger, C.; C. O. Kappe *J. Org. Chem.* **2011**, *76*, 1507–1510.
76. Dong, H.; Latka, R. T.; Driver, T. G. *Org. Lett.* **2011**, *13*, 2726–2729.

Part – III: Access to Functionalized Steroid Side Chains via Modified Julia Olefination

III-A. Introduction and Background

Steroids are biologically important and complex molecules sharing common structural features as shown in Figure III-1 (Tetrafused hydrocarbon backbone usually containing a side chain at C22). They belong to a rich family of organic compounds such as cholesterols, pheromones and sex hormones.

Figure III-1. Generic Steroid Structure with Highlighted Side Chain.



Studying pharmacological properties of steroidal compounds can be difficult because they may exist in micro gram scale per gram quantity of aquatic organism tissue.[77] While biochemical studies suffer from the isolation inadequacy, there have been efforts for organic synthesis of potent steroids.[78] Steroid-based starting materials are commercially available, however, many of the targets require multi-step synthesis (also including enzymatic transformations). One major reason why steroids are made via lengthy synthetic routes is that, regio- and stereospecific side chain modifications are challenging. The side chain of a steroid is a highly crucial part of the molecule,

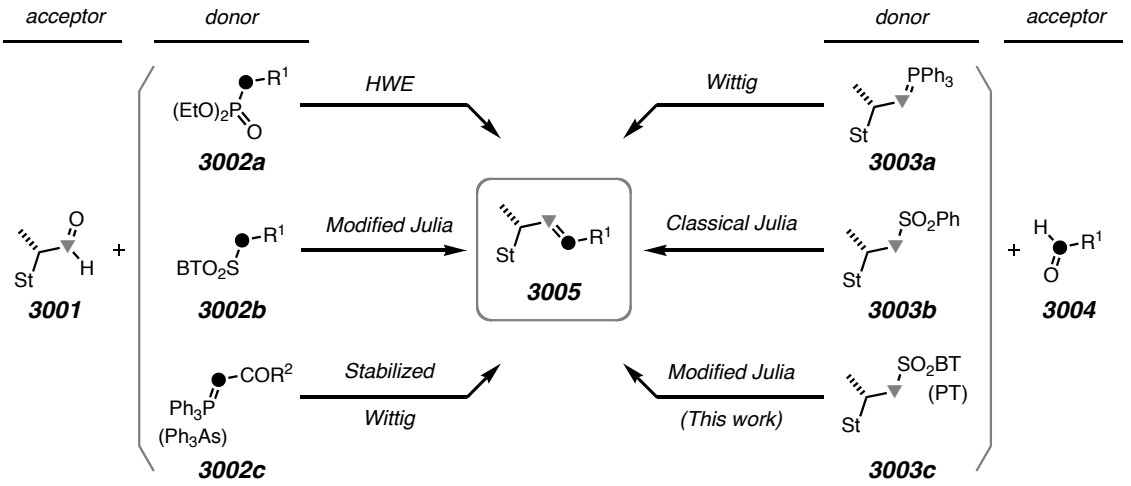
77. Brunel, M. J.; Salmi, C.; Loncle, C.; Vidal, N.; Letourneoux, Y. *Current Cancer Drug Targets* **2005**, *5*, 267–272.
78. (a) Antonchick, A. P.; Schneider, B.; Zhabinskii, V. N.; Khripach, V. A. *Steroids* **2004**, 617–628. (b) Matsuo, J.-I.; Kozai, T.; Nishikawa, O.; Hattori, Y.; Ishibashi, H. *J. Org. Chem.* **2008**, *73*, 6902–6904.

because it plays a key role in affecting the steroid's activity.

A commonly used method to access steroidal compounds with diverged side chains is the coupling of a steroidal unit and a partner containing the side chain carbon backbone. The overview of such reported approaches are laid out in Scheme III-1.

Being an electrophilic acceptor, steroidal aldehydes **3001** have been used in Horner-Wadsworth-Emmons (HWE, **3002a**),[79a-f] modified Julia (**3002b**),[80] and Wittig

Scheme III-1. Overview of the Coupling Strategies to Construct Functionalized Steroidal Side Chains.[a]



[a] St = generic steroid nucleus; BT = benzothiazolyl; PT = 1-phenyl-1*H*-tetrazol-5-yl.

(with stabilized ylides, **3002c**)[81] olefination reactions to forge the C22-C23 alkene in

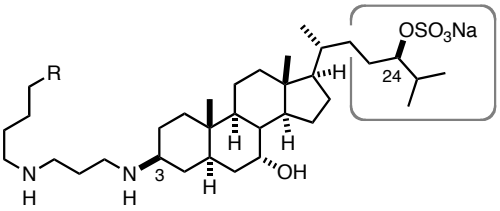
79. (a) Giroux, S.; Corey, E. J. *J. Am. Chem. Soc*. **2007**, *129*, 9866–9867. (b) Yamamoto, S.; Watanabe, B.; Otsuki, J.; Nakagawa, Y.; Akamatsu, M.; Miyagawa, H. *Bio. & Med. Chem*. **2006**, *14*, 1761–1770. (c) Tochtrop, G. P.; DeKoster, G. T.; Cistola, D. P.; Covey, D. F. *Bio. & Med. Chem. Lett*. **2002**, *12*, 433–435. (d) Kinney, W. A.; Zhang, X.; Williams, J. I.; Johnston, S.; Michalak, R. S.; Deshpande, M.; Dostal, L.; Rosazza, J. P. N. *Org. Lett*. **2000**, *2*, 2921–2922. (e) Jones, S. R.; Selinsky, B. S.; Rao, M. N.; Zhang, X.; Kinney, W. A.; Tham, F. S. *J. Org. Chem*. **1998**, *63*, 3786–3789. (f) Koch, P.; Nakatani, Y.; Luu, B.; Ourisson, G. *Bull. Soc. Chim. Fr*. **1983**, 189–194.

80. Jiang, B.; Shi, H.; Xu, M.; Wang, W.; Zhou, W. *Tetrahedron* **2008**, *64*, 9738–9744.

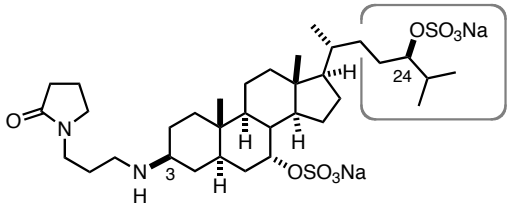
81. Shingate, B. B.; Hazra, B. G.; Pore, V. S.; Gonnade, R. G.; Bhadbhade, M. M. *Tetrahedron* **2007**, *65*, 5622–5635. (h) Shu, Y.; Jones, S. R.; Kinney, W. A.; Selinsky, B. S. *Steroids* **2002**, *67*, 291–304. (i) Rao, M. N.; McGuigan, M. A.; Zhang, X.; Shaked, Z.; Kinney, W. A.; Bulliard, M.;

products **3005**. Alternatively, steroidal phosphonium ylide (**3003a**) and phenylsulfonyl (**3003b**) donors were coupled with aldehyde acceptors **3004** via Wittig[82] and classical Julia[83] olefination reactions, respectively.

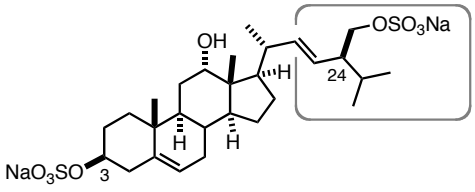
Figure III-2. Some of the Related Potent Steroids with C-24 Functionalized Side Chains (**3006**[84a], **3007**[84b], **3008**[84c], **3009**[84c], and **3010**[84d]).



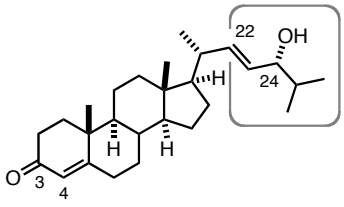
3006; squalamine (R = NH_2)
3007; MSI-1436 [R = $(CH_2)_3NH_2$]



3008; Petromyzonamine disulfate (PADS)



3009; Petromyzosterol disulfate (PSDS)



3010; (22*E*, 24*R*)-24-Hydroxycholest-4,22-dien-3-one

Our Research Group has been studying the synthesis of analogs of sea lamprey pheromone components with C24 oxygenated side chain (e.g., **3008**[84c] in Figure III-2).

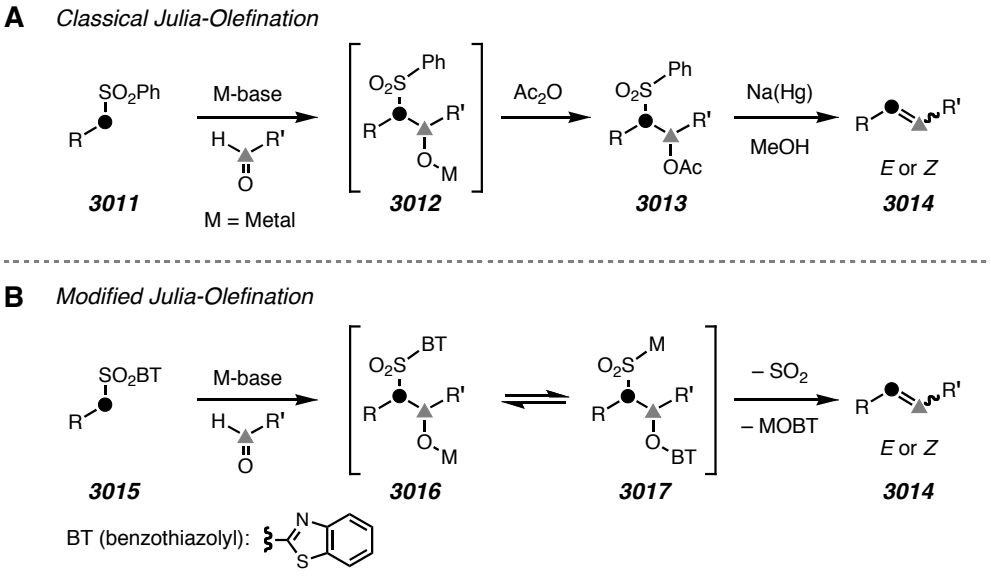
Laboue, B.; Lee, N. E. *J. Org. Chem*. **1997**, *62*, 4541–4545. (j) Okamoto, M.; Tabe, M.; Fuji, T.; Tanaka, T. *Tetrahedron: Asymmetry* **1995**, *6*, 767–768. (k) Wei-Shan, Z.; Hui-Qiang, Z.; Zhi-Qin, W. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2281–2286. (l) Wei-Shan, Z.; Biao, J.; Xin-fu, P. *Tetrahedron* **1990**, *46*, 3173–3188. (m) Zheng-Wu, S.; Wei-Shan, Z. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1765–1767.

82. Harney, D. W.; Macrides, T. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1353–1356.
83. D'Ambra, T. E.; Javitt, N. B.; Lacy, J.; Srinivasan, P.; Warchol, T. *Steroids* **2000**, *65*, 401–407.;
84. (a) Moore, K. S.; Wehrli, S.; Roder, M.; Forrest, J. N. Jr.; McCrimmon, D.; Zasloff, M. *Proc. Natl. Acad. Sci. U.S.A* **1993**, *90*, 1354–1358. (b) Rao, M. N.; Shinnar, A. E.; Noecker, L. A.; Chao, T. L.; Feibush, B.; Snyder, B.; Sharkansky, I.; Sarkahian, A.; Zhang, X.; Jones, S. R.; Kinney, W. A.; Zasloff, M. *J. Nat. Prod*. **2000**, *63*, 631–635. (c) Sorensen, P. W.; Fine, J. M.; Dvornikovs, V.; Jeffrey, C. S.; Shao, F.; Wang, J.; Vrieze, L. A.; Anderson, K. R.; Hoye, T. R. *Nat. Chem. Biol.* **2005**, *1*, 324–328. (d) Mellado, G. G.; Zubìa, E.; Ortega, M. J.; Lòpez-Gonzàlez, P. J. *Steroids* **2004**, *69*, 291–299.

Aiming to develop a convergent method in which a common intermediate could be used to install various side chains, we have established a modified Julia olefination[85] (MJO) strategy using donors **3003c** (Scheme III-1), primarily with the benzothiazolyl (BT) sulfone, and a variety of acceptor aldehydes **3004**. We have also compared the reactivity of BT-sulfone to that of the 1-phenyl-1*H*-tetrazol-5-yl (PT) sulfone counterpart.

Julia olefination (named after French chemist Marc Julia, who disclosed this transformation first in the early 1970's in collaboration with Jean-Marc Paris[86]) is a reaction of a sulfone donor with an aldehyde acceptor (also, but rarely, with a ketone) to form an alkene (Scheme III-2). The proposed reaction mechanisms of the classical Julia

Scheme III-2. Classical *vs* Modified Julia Olefination Reactions (MJOs).



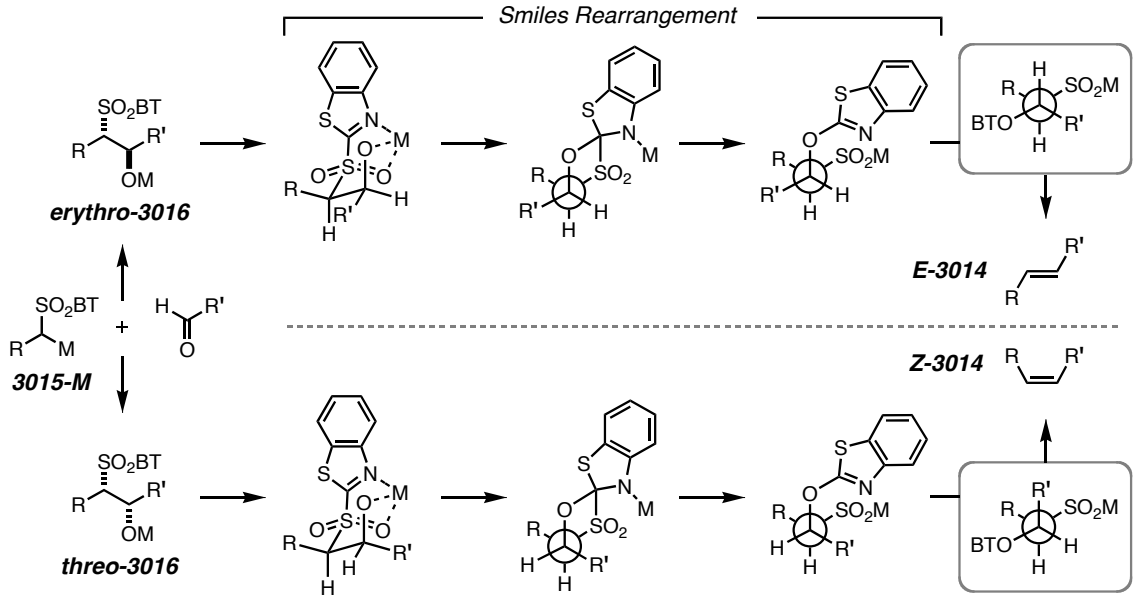
olefination and the modified version (our approach) are shown in Panel A and B of Scheme III-2, respectively.

85. (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O., A. *Tetrahedron Lett*. **1991**, *32*, 1175–1178. (b) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J. Morley, A. *Synlett* **1998**, 26–28. (c) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585.

86. Julia, M.; Paris, J.-M. *Tetrahedron Lett*. **1973**, *14*, 4833–4836.

In the classical version, α-C of the sulfone **3011** is deprotonated by a base (e.g., *n*-BuLi) and the resulting carbanion attacks an aldehyde to generate **3012** intermediate, which is then generally acylated *in situ*. Ester **3013** is reduced upon treatment with sodium amalgam (also sometimes with SmI_2) to accomplish the sulfone elimination and provide the alkene product. The modified Julia olefination (MJO) has an advantage over the classical version in the sense that the overall transformation can be done in one-pot.

Scheme III-3. Smiles Rearrangement and the Product Outcome in MJO.



More specifically, sulfone **3015** can be converted into the alkenes **3014** via *Smiles rearrangement*,[87] where an intramolecular nucleophilic aromatic susbtitution occurs facilitating the benzathiazolyl group migration from sulfone to alkoxide (Scheme III-3). Nucleophilic addition of **3015-M** (M = Li, Na, or K, depending on the base used to deprotonate **3015**) to an aldehyde can produce two isomeric intermediates, the anti addition alkoxide **erythro-3016** and the syn addition alkoxide **threo-3016**. Each undergoes structural orientations in which sulfonyl oxygen and heteroatom (e.g.,

87. Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press, London, UK., **2005**, pp 416–417.

nitrogen) of the sulfone-activated aromatic ring can coordinate to the alkoxide metal. These orientations bring the nucleophilic oxide and the electrophilic benzothiazolyl carbon to close proximity. An addition-elimination process occurs, where *ipso* attack by the nucleophile forms a five-membered transition state that affords the corresponding alkene product after the BT-oxide elimination.

III-B. Results and Discussion

Our design involved a C22-sulfonyl steroid as the common intermediate, which could serve for the anionic donor partner. Expecting that the feasibility of phenyltetrazolyl sulfone donors are generally more effective,[85b] we directed our attention toward a synthesis of a steroidal PT-sulfone. In this regard, we prepared **PT-3022** as outlined in Scheme III-4 from β-stigmasterol (**3018**). Stigmasterol is an unsaturated plant sterol isolated from soybean and herbs, and is an affordable steroid-based starting material.

Tosylation of the C3 hydroxyl of **3018** and subsequent protective etherification[88] provided the base-stable intermediate, *i*-stigmasteryl methyl ether (**3019**, 74% yield over two steps). This two-step protocol is versatile in protecting both C3 hydroxyl and C5-C6 double bond (in particular from oxidative bond cleavage or hydrogenation). Ozonolysis (and reductive workup with $NaBH_4$) of the disubstituted olefin smoothly provided the primary alcohol **3020** [and (*S*)-2-ethyl-3-methylbutan-1-ol]. It is worth noting that a major problem associated with the ozonolysis of *i*-steroids, namely undesired oxidation of the methine C–H bond at the C6-ether,[89] was avoided by using the unconventional solvent tetrahydrofuran as major component of the reaction medium (THF/MeOH; 10:1). The resulting alcohol **3020** was formed in high yield (86%), and butyrolactone was isolated as a byproduct, its amount increasing with increased reaction time. We believe that THF effectively buffers the ozonolysis reaction by acting as a sacrificial reductant and preventing over-oxidation of **3019** and its derived products. The thioether **PT-3021** was prepared from **3020** using the Mitsunobu protocol (PTSH, DIAD, PPh_3) and subsequently oxidized to the sulfone **PT-3022** (ammonium paramolybdate, H_2O_2).

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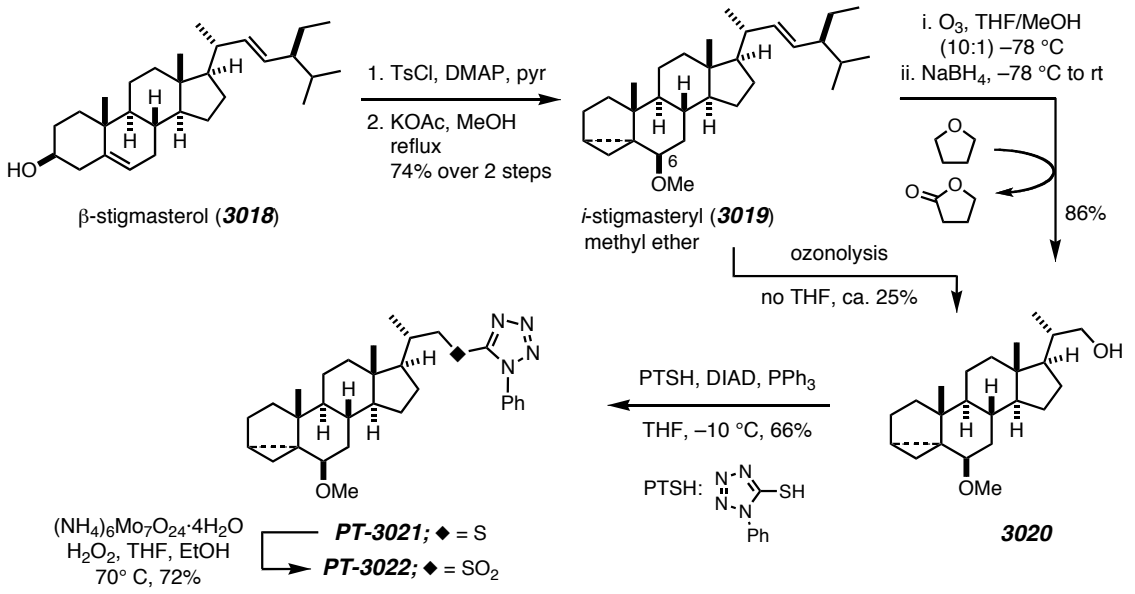
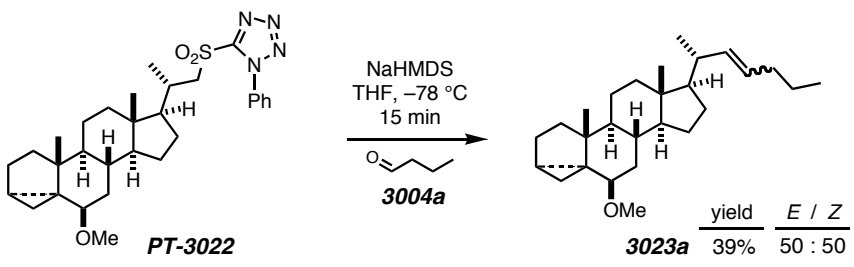
88. Fernholz, E.; Ruigh, W. L. *J. Am. Chem. Soc.* **1940**, *62*, 3346–3348.
89. Spencer, T. A.; Li, D.; Russel, J. S.; Tomkinson, N. C. O.; Willson, T. M. *J. Org. Chem.* **2000**, 65, 1919–1923.

Scheme III-4. Synthesis of the MJO Donor **PT-3022**.



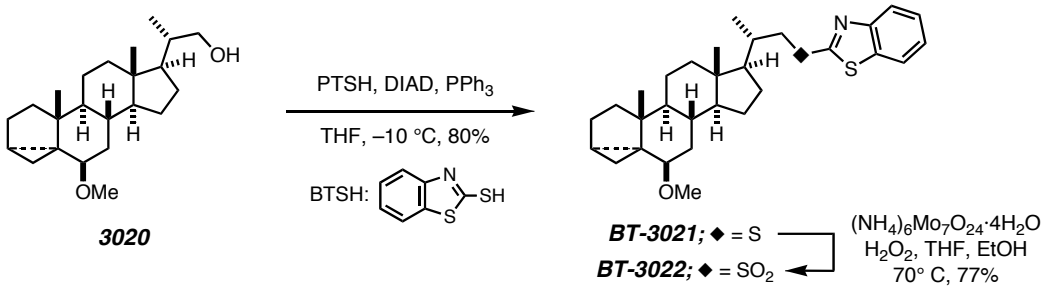
Sodium anion of the corresponding sulfone **PT-3022** (generated via NaHMDS, THF, –78 °C) properly served as the olefination donor, while the potassium counterpart (generated via KHMDS, THF, –78 °C) essentially failed in providing the desired olefination product [e.g., reaction with butyraldehyde (**3004a**)]. Our initial MJO attempt with **PT-3022** using **3004a** gave the alkene **3023a** in surprisingly low yield (39%, Scheme III-5). The ^{1}H NMR spectrum of the crude organic material indicated essentially equal amounts of each *E* and *Z* alkenes **3023a**.

Scheme III-5. MJO of **PT-3022** with Butyraldehyde (**3004a**).



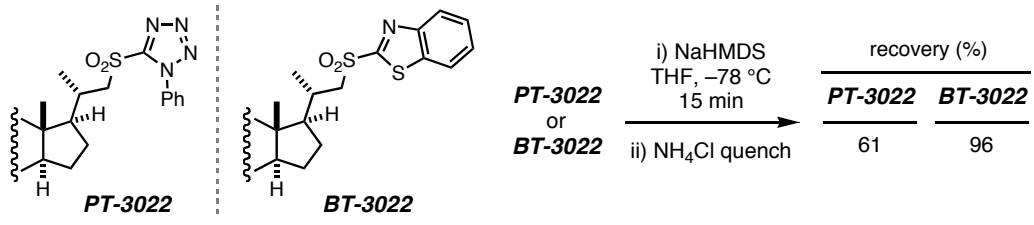
We then turned our attention to synthesize an alternative sulfone donor, namely the benzothiazolyl (BT) sulfone **BT-3022**. We followed a similar approach (Scheme III-7) where we, this time, used 2-mercaptobenzothiazole (BTSH) as the Mitsunobu nucleophile to displace the activated hydroxyl of **3020**. Subsequent sulfide oxidation under Mo(VI)/H_2O_2 conditions smoothly provided **BT-3022** (62% yield from **3020**).

Scheme III-6. Synthesis of the Alternative MJO Donor **BT-3022**.[a]



Our investigations, which were conducted for sodium anions, showed that the anion of **BT-3022** was more stable than that of **PT-3022**. We quenched each sulfonyl anion with saturated NH_4Cl solution 15 minutes after addition of base. We then re-isolated the starting sulfones by silica gel chromatography (using MPLC) with 61 vs 96% recovery efficiency, respectively (Scheme III-7).

Scheme III-7. Recovery/Stability of the Sulfone Anions.[a]

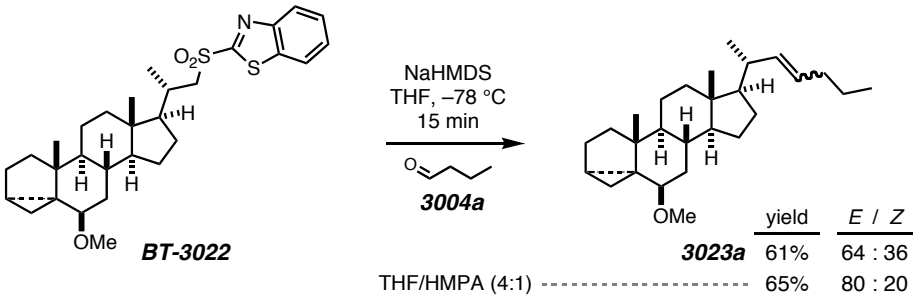


[a]Stoichiometric ratio of sulfone/NaHMDS was 1:1.2.

In agreement with the stability studies, the sodium anion of **BT-3022** was also observed to be more effective to achieve olefination using **3004a** (Scheme III-8). The

isolated yield of the MJO product using butyraldehyde (1:1:1.2 stoichiometric ratio of sulfone/butyraldehyde/NaHMDS) was higher (61 *vs.* 39%) when the benzothiazolyl sulfone **BT-3022** was used. Moreover (and as Liu and Jacobsen have described[90]), the use of HMPA as an additive improved the ***E*-3023a**/***Z*-3023a** product ratio.

Scheme III-8. MJO of **BT-3022** with Butyraldehyde (**3004a**).

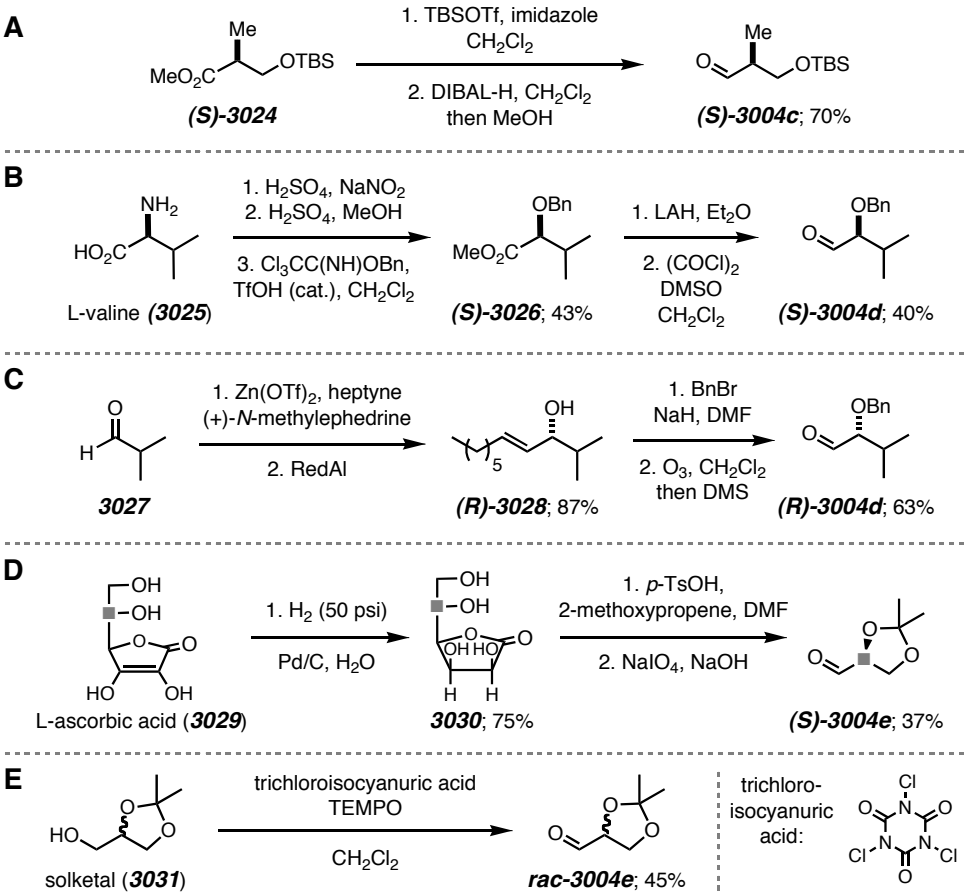


Having a robust sulfone donor with an optimized olefination condition in hand, the platform was opened for the synthesis of various α-substituted aldehydes **3004c-e** (**3004a-b** are commercially available aldehydes, Scheme III-9).

In a straightforward fashion, we obtained the α-methyl aldehyde **(*S*)-3004c** from the known methylpropanoate **(*S*)-3024**[91] via a TBS protection of the primary hydroxyl followed by a DIBAL-H reduction of the ester (Panel A in Scheme III-9). We determined that the aldehydes **(*R*)-3004d** and **(*S*)-3004d** would be proper building blocks in synthesizing the targets like **3006-3008** and **3010**, respectively. Following a 4-step sequence[92] [Panel B, 1. deazotization-double inversion; 2. Benzylation of the α-OH; 3. LAH reduction of the ester; 4. Swern oxidation of the resulting alcohol to the aldehyde] provided **(*R*)-3004d** in 17% overall yield starting from L-valine (**3025**). Another 4-step procedure [Panel C, 1. enantioselective alkyne addition to isobutyraldehyde (**3027**); 2. RedAl reduction of the triple bond to the *E*-double bond;

90. Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123,* 10772–10773.
91. Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc., Perkin Trans 1* **1989**, 507–518.
92. Li, W.-R.; Ewing, W. R.; Harris, B. D.; Joullie, M. M. *J. Am. Chem. Soc.* **1990**, *112*, 7659–7672.

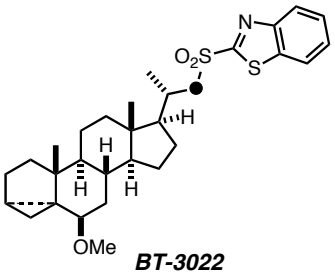
Scheme III-9. Preparation of Aldehydes **3004c-e**.



3. Benzylation of the α-OH; and 4. Ozonolysis of the double bond followed by a reductive work-up] gave **(*S*)-3004d**, the enantiomer that would lead to the side chain of **3010**. For additional modifications on steroidal side chains that can potentially be performed, we opted to use a poly-oxygenated building block like **(*S*)-3004e** (Panel D). We reduced (by hydrogenation) L-ascorbic acid and protected the more spatially available diols (designated by the dot on **3030**). An oxidative cleavage (by $NaIO_4$/NaOH) of the α- and β-OHs, provided the aldehyde **(*S*)-3004e**. Finally, the racemate ***rac*-3004** (Panel E) was prepared with an oxidation of the readily available solketal (**3031**).

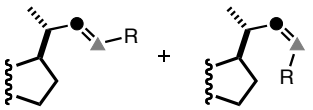
We then studied the olefination reactions of a series of aldehydes **3008** with **BT-3005** as the sulfone donor (Table III-1). The aldehydes contain α-methyl or α-alkoxy branching. The results demonstrate the effectiveness of this process to instal functional side chains similar to those embedded in **3006-3010** (cf. Figure III-2)

Table III-1. Synthesis of Alkenes **3023** via the Modified Julia Olefination (MJO).[a]

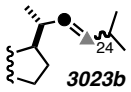
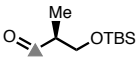
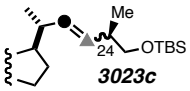
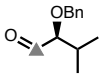
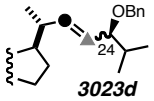
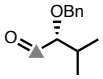
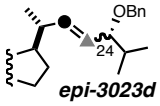
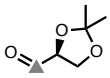
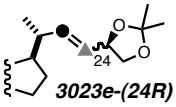
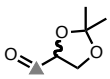
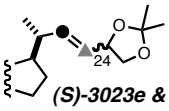


BT-3022

i. NaHMDS
THF/HMPA (4:1)
–78 °C
ii. aldehyde



E-3023 ***Z-3023***

entry	aldehyde	alkenes	yield (%)	*E* / *Z*
1	 ***3004b***	 ***3023b***	90	75:25
2	 ***(S)-3004c***	 ***3023c***	60	85:15
3	 ***(S)-3004d***	 ***3023d***	82	94:6
4	 ***(R)-3004d***	 ***epi-3023d***	80	82:18
5	 ***(S)-3004e***	 ***3023e-(24R)***	81	90:10
6	 ***rac-3004e***	 ***(S)-3023e & (R)-3023e***	60	65:35 [from ***3023e-(24S)***]

[a]E/Z ratios were determined by ^{1}H NMR analysis of product mixtures.

Aldehyde **(*S*)-3004d** provided **3023d** both in high yield and with excellent *E/Z*-selectivity (entry 3). Use of the enantiomeric aldehyde **(*R*)-3004d** gave the C24-epimer in 80% yield and with 82:18 *E/Z*-selectivity (entry 4). Entries 5-6 demonstrate

additional scope of the method. Aldehyde (***S*)-3004e**[93] again showed a high *E/Z*-selectivity. Use of the racemate ***rac*-3004e** (2 equiv) produced similar amounts of C24-epimers. While the *E/Z*-selectivity in product **3023e-(24*R*)** was similar to that observed in entry 5 (i.e., 90:10), the epimeric mixture of alkenes **3023e-(24*S*)** was formed with reduced selectivity for alkene geometry (i.e., 65:35). Thus, the degree of matching/mis-matching for the substrates in either of the pairs of entries 1/2 or 5/6 is small.

93. Hubschwerlen, C.; Specklin, J. L.; Higelin, J. *Org. Synth., Coll. Vol. 9*, **1998**, 454–457.

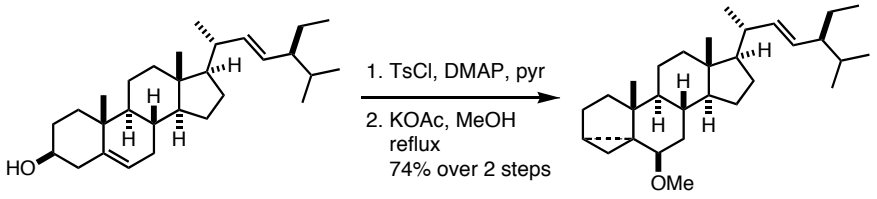
III-C. Conclusion

In summary, we have demonstrated the utility of a modified Julia olefination strategy for providing easy access to steroidal products containing a variety of functionalized side chains. The steric demand of both α-branched coupling partners that participate in this transformation is noteworthy. Contrary to the general trend observed for modified Julia reaction using less hindered pairs of substrates, we here found that the olefination efficiency and alkene diastereoselectivity of the steroidal BT-sulfonyl donor to be superior to the PT-sulfonyl version.[94] This is likely a result of greater lability of the metallated PT-sulfone anion. Our additional noteworthy observations are i) the use of THF as the bulk solvent to improve the ozonolysis of cyclopropyl-containing substrate **3019**. This protocol may be useful for chemoselective transformation of other complex substrates bearing functionality sensitive to oxidation.

94. (a) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585. (b) Aissa, C. *Eur. J. Org. Chem.* **2009**, 1831–1844.

III-D. Experimental Section

All reactions were performed under a dry nitrogen or argon atmosphere unless otherwise noted. All glassware was flame- and/or oven-dried before use. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were dried through Al_2O_3 columns; hexanes (Hex) and ethyl acetate (EtOAc) were used as received (reagent grade). All other reagents and solvents were used as received. Thin layer chromatography (TLC) was performed using TLC plastic sheets with F_{254} indicator and visualization via UV-light or staining with either potassium permanganate or anisaldehyde. Flash column purifications were performed using 40-63 μm silica gel. Medium pressure liquid chromatography (MPLC) purifications were performed using Michel-Miller columns, dry packed with ca. 25-35 μm silica gel. The MPLC apparatus was outfitted with a Waters HPLC pump and refractive index detector. All NMR spectra were determined in $CDCl_3$. ^1H NMR spectra were acquired on a Varian VI-500 (500 MHz ^1H). ^{13}C NMR spectra were acquired on a Varian VI-500 (125 MHz ^{13}C) using $CDCl_3$ solvent. Chemical shifts (δ) for ^1H NMR spectra are referenced to TMS at δ = 0.00 ppm, and ^{13}C NMR spectra are referenced to $CDCl_3$ at δ = 77.0 ppm. The following abbreviations are used to describe NMR signals: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), sept (septet), m (multiplet), br (broad), app (apparent), and nfom (non-first order multiplet). Coupling constants (*J*) are reported in Hz. Infrared spectra were recorded on a Midac Corporation Prospect 4000 FT-IR spectrometer. The most intense and/or diagnostic peaks are reported, and all samples were collected in attenuated total reflectance (ATR) mode as thin films on a germanium window. Optical rotation data were recorded on a Perkin-Elmer-241 polarimeter using a 3.5x50 mm or 100 mm cell. Melting point data were collected on a Köfler hot stage and are uncorrected. Low-resolution GC-MS data were recorded at 70 eV on an Agilent 5975 GC-MSD. High-resolution mass spectra were recorded on a Bruker BioTOF II (ESI-TOF) instrument using PEG as an internal standard/calibrant.



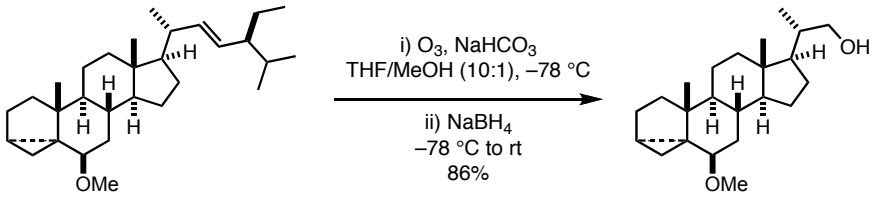
3018; β-stigmasterol ***3019***; *i*-stigmasteryl methyl ether

_i_-Stigmasteryl methyl ether (3019).

To a solution of *p*-toluenesulfonyl chloride (9.72 g, 51.0 mmol, 2.1 equiv) and 4-dimethylaminopyridine (296 mg, 2.43 mmol, 0.1 equiv) in 120 mL of pyridine was added stigmasterol (10.0 g, 24.3 mmol, 1.0 equiv). The resultant mixture was allowed to stir for 12 h at room temperature, at which time the solution was poured into saturated aqueous sodium bicarbonate (500 mL) and filtered to provide a crude solid. Recrystallization from acetone provided the intermediate tosylate ester (10.3 g, 75%) as a white amorphous solid. R_f 0.67 (6:1 hexanes/ethyl acetate); $[\alpha]_D$ -43.5 (c 2.8, $CHCl_3$); mp 137–140 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.5 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 5.30 (ddd, *J* = 5.5, 2.0, 2.0 Hz, 1H), 5.14 (dd, *J* = 15.5, 9.0 Hz, 1H), 5.01 (dd, *J* = 15.5, 9.0 Hz, 1H), 4.32 (dddd, *J* = 11.5, 11.5, 4.5, 4.5 Hz, 1H), 2.47–2.41 (m, 4H), 2.27 (dd, *J* = 13.0, 3.5 Hz, 1H), 2.07–1.90 (m, 3H), 1.84–1.79 (m, 2H), 1.74–1.66 (m, 2H), 1.57–1.38 (m, 10H), 1.28–1.11 (m, 4H), 1.06–1.02 (m, 1H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.97 (s, 3H), 0.89 (dddd, *J* = 6.0, 6.0, 6.0, 6.0 Hz, 1H), 0.84 (d, *J* = 6.5 Hz, 3H), 0.80 (dd, *J* = 8.5, 8.5 Hz, 3H), 0.79 (d, *J* = 8.0 Hz, 3H), and 0.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.4, 138.9, 138.3, 134.7, 129.8, 129.3, 127.7, 123.5, 82.4, 56.7, 55.9, 51.3, 49.9, 42.2, 40.5, 39.6, 38.9, 36.9, 36.4, 31.90, 31.85, 31.8, 28.9, 28.7, 25.4, 24.3, 21.7, 21.2, 21.12, 21.10 19.2, 19.0, 12.3, and 12.0.

To a solution of the tosylate (10.0 g, 17.7 mmol, 1.0 equiv) in 440 mL of methanol was added potassium acetate (9.5 g, 97.2 mmol, 5.5 equiv). The resultant solution was heated to reflux and maintained at this temperature for 3 h. The solution was cooled to room temperature, concentrated in vacuo, and diluted with 150 mL of water. The aqueous layer was extracted with ethyl acetate (200 mL x 3) and the

combined organic layer was washed with brine and dried over anhydrous sodium sulfate prior to concentration in vacuo to provide the crude material. Purification by flash chromatography provided *i*-stigmasteryl methyl ether (**3019**)[95] (7.34 g, 98%) as a white amorphous solid. R_f 0.70 (10:1, hexanes/ethyl acetate); $[\alpha]_D$ +16.0 (c 4.1, $CHCl_3$); mp 55–57 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.15 (dd, *J* = 15.0, 8.5 Hz, 1H), 5.02 (dd, *J* = 15.0, 8.5 Hz, 1H), 3.33 (s, 3H), 2.77 (dd, *J* = 2.5, 2.5 Hz, 1H), 0.74 (s, 3H), 0.65 (dd, *J* = 4.5, 4.5 Hz, 1H), and 0.44 (dd, *J* = 8.0, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.4, 129.2, 82,4, 56.7, 56.6, 56.1, 51.3, 48.1, 43.4, 42.7, 40.6, 40.2, 35.3, 35.0, 33.4, 31.9, 30.5, 29.1, 25.4, 25.0, 24.3, 22.8, 21.5, 21.2, 21.1, 19.3, 19.0, 13.1, 12.5, and 12.3.



3019; *i*-stigmasteryl methyl ether

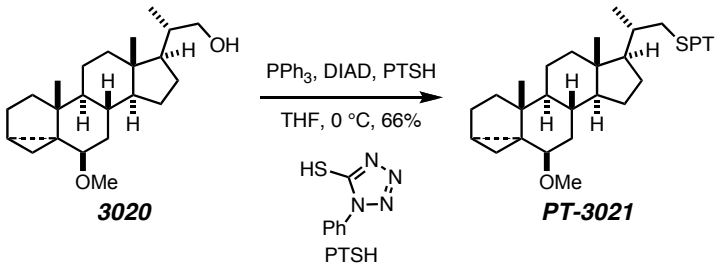
3020

6β-Methoxy-3α,5-cyclo-5α-23,24-bisnorcholan-22-ol (3020).

To a solution of *i*-stigmasteryl methyl ether (**3019**) (7.30 g, 17.1 mmol, 1.0 equiv) and sodium bicarbonate (7.30 g, 87.0 mmol, 5.1 equiv) in 360 mL of THF and 36 mL of methanol at –78 °C was passed ozone until TLC analysis indicated consumption of the starting material (ca. 15 min). Oxygen was passed through the solution for an additional 5 min at which time sodium borohydride (3.9 g, 102.6 mmol, 6.0 equiv) was added in one portion and the solution was allowed to reach room temperature over 1 h. The reaction mixture was quenched by the slow addition of saturated ammonium chloride. The resulting suspension was concentrated to remove most of the organic solvent and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material

95. Fernholz, E.; Ruigh, W. L. *J. Am. Chem. Soc.* **1940**, *62*, 3346–3348.

was purified by flash chromatography to provide **3020**[96] (5.1 g, 83%) as a white amorphous solid. R_f 0.40 (3:1 hexanes/ethyl acetate); $[\alpha]_D$ +29.3 (c 3.9, $CHCl_3$); mp 74–76 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.64 (dd, *J* = 10.5, 3.5 Hz, 1H), 3.37 (dd, *J* = 10.5, 6.5 Hz, 1H), 3.33 (s, 3H), 2.78 (dd, *J* = 3.0, 3.0 Hz, 1H), 1.98 (ddd, *J* = 12.0, 3.0, 3.0 Hz, 1H), 1.89 (ddd, *J* = 13.5, 3.0, 3.0 Hz, 1H), 1.85–0.97 (m, 15H), 1.05 (d, *J* = 6.5 Hz, 3H), 0.95–0.77 (m, 4H), 0.74 (s, 3H), 0.65 (dd, *J* = 5.0, 5.0 Hz, 1H), and 0.43 (dd, *J* = 8.0, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 82.4, 68.0, 56.6, 56.3, 55.6, 48.0, 43.4, 42.9, 40.1, 38.8, 35.3, 35.1, 33.4, 30.5, 27.8, 25.0, 24.3, 22.8, 21.5, 19.3, 16.8, 13.1, and 12.3.

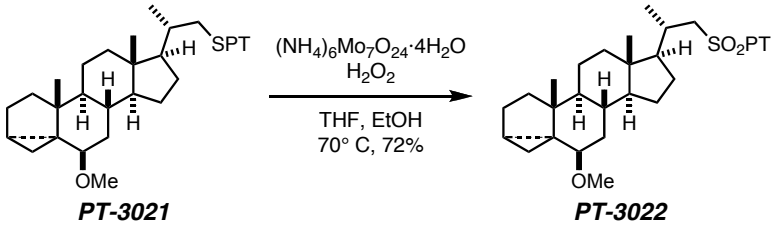


5-(((*S*)-2-((1a*R*,3a*R*,3b*S*,5a*S*,6*R*,8a*S*,8b*S*,10*R*,10a*R*)-10-Methoxy-3a,5a-dimethylhexadecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)propyl)thio)-1-phenyl-1*H*-tetrazole (PT-3021).

To a solution of alcohol **3020** (500 mg, 1.45 mmol, 1.0 equiv), phenyl-1H-tetrazole-5-thiol (340 mg, 1.88 mmol, 1.3 equiv), and triphenylphosphine (490 mg, 1.88 mmol, 1.3 equiv) in 14.0 mL of THF was added diisopropyl azodicarboxylate (370 μL, 1.88 mmol, 1.3 equiv) dropwise at 0 °C. The solution was allowed to stir at this temperature for an additional hour. The volatiles were removed in vacuo to provide the crude material, which was purified by flash chromatography to provide sulfide **PT-3021** (484 mg, 66%) as a white amorphous solid. R_f 0.45 (6:1 hexanes/ethyl acetate); $[\alpha]_D$

96. Spencer, T. A.; Li, D.; Russel, J. S.; Tomkinson, N. C. O.; Willson, T. M. *J. Org. Chem.* **2000**, 65, 1919–1923.

+30.5 (c 4.2, $CHCl_3$); mp 41–44 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61–7.55 (m, 5H), 3.73 (dd, *J* = 12.5, 2.5 Hz, 1H), 3.33 (s, 3H), 3.13 (dd, *J* = 12.5, 8.5 Hz, 1H), 2.77 (dd, *J* = 2.5, 2.5 Hz, 1H), 1.98–1.88 (m, 4H), 1.78–1.71 (m, 2H), 1.68–1.62 (m, 1H), 1.55–0.96 (m, 10H), 1.10 (d, *J* = 6.5 Hz, 3H), 0.91–0.79 (m, 3H), 0.65 (dd, *J* = 5.0, 5.0 Hz, 1H), and 0.44 (dd, *J* = 8.0, 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.9, 133.8, 130.0, 129.8 (2C), 123.9 (2C), 82.4, 56.6, 56.3, 55.4, 47.9, 43.4, 43.2, 41.0, 40.1, 36.2, 35.3, 35.0, 33.4, 30.5, 28.0, 24.9, 24.2, 22.8, 21.5, 19.3, 18.8, 13.1, and 12.4; IR (thin film): 2933, 2868, 1500, 1383, 1097, and 761 cm^{-1}; HRMS calculated 529.2972 ($C_{30}H_{42}N_4OSNa^+$), observed 529.2968.

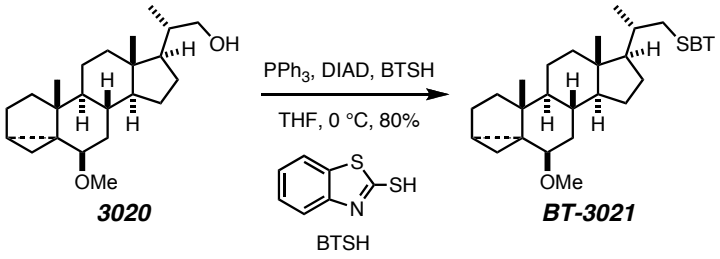


PT-3021 ***PT-3022***

5-(((*S*)-2-((1a*R*,3a*R*,3b*S*,5a*S*,6*R*,8a*S*,8b*S*,10*R*,10a*R*)-10-Methoxy-3a,5a-dimethylhexadecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)propyl)sulfonyl)-1-phenyl-1*H*-tetrazole (PT-3022).

A solution of **PT-3021** (300 mg, 0.60 mmol, 1.0 equiv), ammonium paramolybdate tetrahydrate (148 mg, 0.12 mmol, 0.2 equiv), and 30% hydrogen peroxide (410 mL, 7.12 mmol, 12.0 equiv) in 4.7 mL ethanol and 2.4 mL of tetrahydrofuran was heated at 70 °C for 2 h. The reaction mixture was cooled to room temperature, diluted with 5 mL of water, and extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous sodium thiosulfate and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography to provide **PT-3022** (232 mg, 72%) as a white amorphous solid. R_f 0.35 (6:1 hexanes/ethyl acetate); $[\alpha]_D$ +19.4 (c 1.5, $CHCl_3$); mp 47–49 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69–7.60 (m, 5H), 3.95 (dd, *J* =

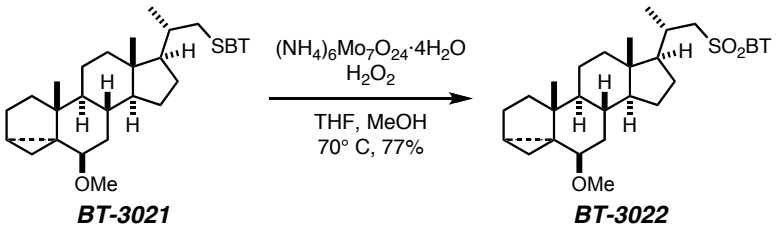
14.5, 2.0 Hz, 1H), 3.50 (dd, *J* = 14.5, 10.0 Hz, 1H), 3.33 (s, 3H), 2.78 (dd, *J* = 2.5, 2.5 Hz, 1H), 2.39–2.31 (m, 1H), 1.97 (ddd, *J* = 12.5, 3.0, 3.0 Hz, 1H), 1.93–1.85 (m, 2H), 1.79–1.72 (m, 2H), 1.67–1.63 (m, 1H), 1.53 (dd, *J* = 12.5, 5.0 Hz, 1H), 1.49 (dd, *J* = 12.5, 8.0 Hz, 1H), 1.46–1.31 (m, 4H), 1.26 (d, *J* = 6.5 Hz, 3H), 1.24–1.15 (m, 2H), 1.13–1.05 (m, 2H), 1.02 (s, 3H), 0.92–0.79 (m, 3H), 0.77 (s, 3H), 0.66 (dd, *J* = 5.0, 5.0 Hz, 1H), and 0.45 (dd, *J* = 8.0, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.3, 133.1, 131.4, 129.7, 125.2, 80.3, 61.6, 56.6, 56.5, 55.5, 47.8, 43.4, 43.3, 40.1, 35.2, 35.0, 33.6, 32.0, 30.5, 28.2, 25.0, 24.0, 22.7, 21.5, 20.0, 19.3, 13.1, and 12.1; IR (thin film): 2931, 2868, 1498, 1344, 1153, 1098 and 762 cm^{-1}; HRMS calculated 561.2870 ($C_{30}H_{42}N_4O_3SNa^+$), observed 561.2880.



2-(((*S*)-2-((1a*R*,3a*R*,3b*S*,5a*S*,6*R*,8a*S*,8b*S*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethylhexadecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)propyl)thio)benzo[*d*]thiazole (BT-3021).

To a solution of **3020** (5.00 g, 14.5 mmol, 1.0 equiv), triphenylphosphine (4.94 g, 18.9 mmol, 1.3 equiv), and 2-mercaptobenzothiazole (3.15 g, 18.9 mmol, 1.3 equiv) in 140 mL of tetrahydrofuran at 0 °C was added dropwise diisopropyl azodicarboxylate (4.30 mL, 21.8 mmol, 1.5 equiv). The resultant solution was allowed to stir at 0 °C for an additional 5 h, at which time the reaction mixture was concentrated in vacuo and purified by recrystallization from acetone to give the BT-thioether **BT-3021** (5.74 g, 80%) as a white amorphous solid. R_f 0.62 (3:1 hexanes/ethyl acetate); $[\alpha]_D$ +48.8 (c 1.2, $CHCl_3$); mp 125–126 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (ddd, *J* = 8.0, 0.5, 0.5

Hz, 1H), 7.75 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 1H), 7.41 (ddd, *J* = 8.5, 8.5, 1.5 Hz, 1H), 7.29 (ddd, *J* = 8.0, 8.0, 1.0 Hz, 1H), 3.65 (dd, *J* = 12.5, 2.5 Hz, 1H), 3.33 (s, 3H), 3.07 (dd, *J* = 12.5, 8.5 Hz, 1H), 2.78 (dd, *J* = 3.0, 2.5 Hz, 1H), 2.02–1.89 (m, 4H), 1.80–1.72 (m, 2H), 1.67 (dddd, *J* = 12.0, 9.0, 9.0, 3.5 Hz, 1H), 1.56–1.48 (m, 3H), 1.46–1.36 (m, 2H), 1.31 (ddd, *J* = 9.5, 9.5, 9.5 Hz, 1H), 1.25–1.06 (m, 7H), 1.03 (s, 3H), 0.92–0.81 (m, 3H), 0.75 (s, 3H), 0.66 (dd, *J* = 4.5, 4.5 Hz, 1H), and 0.44 (dd, *J* = 8.0, 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.0, 153.3, 135.1, 126.0, 124.1, 121.4, 120.9, 82.4, 56.6, 56.4, 55.5, 48.0, 43.4, 43.2, 41.1, 40.8, 36.5, 35.3, 35.1, 33.4, 30.5, 28.1, 25.0, 24.2, 22.8, 21.5, 18.9, 19.3, 13.1, and 12.4; IR (thin film): 2932, 2866, 1457, 1428, 1098, 995, and 756 cm^{-1}; HRMS calculated 496.2702 ($C_{30}H_{41}NOS_2 + H^+$), observed 496.2697.

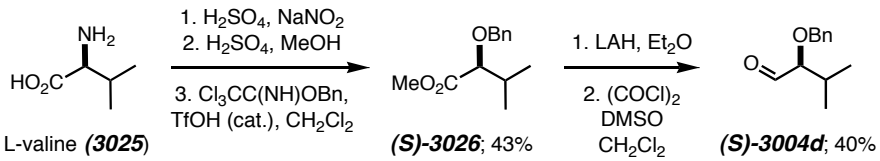


BT-3021 ***BT-3022***

2-(((*S*)-2-((1a*R*,3a*R*,3b*S*,5a*S*,6*R*,8a*S*,8b*S*,10*R*,10a*R*)-10-methoxy-3a,5a-dimethylhexadecahydrocyclopenta[*a*]cyclopropa[2,3]cyclopenta[1,2-*f*]naphthalen-6-yl)propyl)sulfonyl)benzo[*d*]thiazole (BT-3022).

A solution of the BT-thioether **BT-3021** (6.0 g, 12.1 mmol, 1.0 equiv), ammonium paramolybdate tetrahydrate (3.0 g, 2.4 mmol, 0.2 equiv), and 30% hydrogen peroxide (16.8 mL, 145.6 mmol, 12.0 equiv) in 180 mL of tetrahydrofuran and 60 mL methanol was heated to 70 °C for 2 h. The reaction mixture was cooled to room temperature, diluted with 50 mL of water, and extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous sodium thiosulfate and brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography to give the sulfone **BT-3022** (4.9 g, 77%) as a white amorphous solid. R_f 0.5 (3:1 hexanes/ethyl acetate); $[\alpha]_D$ +39.9 (c 2.9, $CHCl_3$); mp 64–

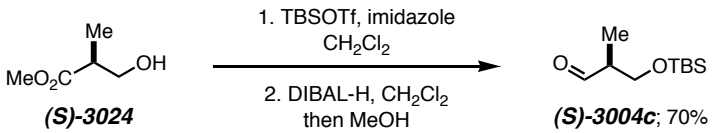
68 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.64 (ddd, *J* = 8.0, 8.0, 1.0 Hz, 1H), 7.59 (ddd, *J* = 8.0, 8.0, 1.0 Hz, 1H), 3.64 (dd, *J* = 14.0, 1.0 Hz, 1H), 3.31 (s, 3H), 3.26 (dd, *J* = 14.5, 10.0 Hz, 1H), 2.76 (dd, *J* = 2.0, 2.0 Hz, 1H), 2.36–2.27 (m, 1H), 1.97 (ddd, *J* = 12.5, 3.0, 3.0 Hz, 1H), 1.89–1.66 (m, 4H), 1.65–1.57 (m, 1H), 1.56–1.21 (m, 6H), 1.24 (d, *J* = 6.5 Hz, 3H), 1.19–1.00 (m, 3H), 0.94 (s, 3H), 0.88–0.76 (m, 4H), 0.72 (s, 3H), 0.63 (dd, *J* = 4.5, 4.5 Hz, 1H), and 0.42 (dd, *J* = 8.0, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.0, 152.7, 136.7, 128.0, 127.7, 125.4, 122.4, 82.3, 60.5, 56.6, 56.5, 55.6, 47.9, 43.4, 43.2, 40.0, 35.2, 35.0, 33.4, 32.4, 30.5, 28.6, 25.0, 24.0, 22.7, 21.5, 20.1, 19.3, 13.1, and 12.2; IR (thin film): 2934, 2869, 1472, 1320, 1146, 1097, and 761 cm^{-1}; HRMS calculated 550.2420 ($C_{30}H_{41}NO_3S_2Na^+$), observed 550.2446.



L-valine ***(3025)*** ***(S)-3026***; 43% ***(S)-3004d***; 40%

(*S*)-2-(Benzyloxy)-3-methylbutanal [(*S*)-3004d].

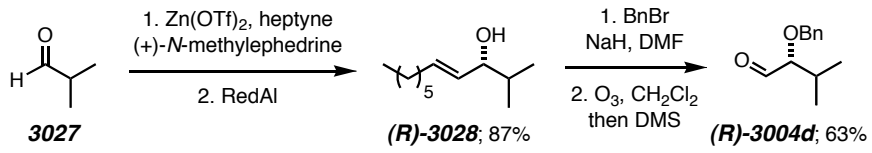
Aldehyde **(*S*)-3004d** was prepared in 5 steps and 17% overall yield, mostly according to literature procedures;[92] we used a Swern rather than Parikh-Doering oxidation for step 5. The ^{1}H NMR spectrum of the product was entirely consistent with that of the reported data.



(S)-3024 ***(S)-3004c***; 70%

(*S*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropanal [(*S*)-3004c].

To a solution of **(*S*)-3024** (1 equiv) in CH_2Cl_2 (0.5 M) and imidazole (2 equiv) was added TBSOTf (1.5 equiv) at room temperature, and the resulting mixture was stirred for 6 h. Upon quenching by addition of a saturated aqueous solution of NH_4Cl, the OTBS-ether was isolated in ca. 90% as the crude reaction product. This material was directly used in the next step without purification. The OTBS-ether (500 mg, 2.16 mmol, 1.0 equiv) in methylene chloride (7.6 mL) at –78 °C was added DIBAL-H (1.5 M, 1.60 mL, 2.37 mmol, 1.1 equiv) dropwise over 15 min. After being stirred for an additional 4 h at –78 °C, the mixture was quenched by slow addition of MeOH (0.5 mL). The resulting mixture was allowed to warm to room temperature and poured into a saturated aqueous potassium sodium tartrate solution (5.0 mL). The mixture was stirred vigorously until the phase separation occurred. The aqueous layer was extracted with methylene chloride and the combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. Purification of the crude material by flash chromatography provided **(*S*)-3004c**[97] (305 mg, 70%) as a colorless oil. R_f 0.70 (3:1 hexanes/ethyl acetate). %). $[\alpha]_D$ +32.5 (c 1.0, $CHCl_3$) [lit[97] $[\alpha]_D$ +37.8 (c 1.2, $CHCl_3$)]; the ^1H NMR spectrum of the product was entirely consistent with that of the reported data.



3027 ***(R)-3028***; 87% ***(R)-3004d***; 63%

(*R*)-2-Methyldec-4-yn-3-ol (S2).

A 25 mL round bottom flask was charged with $Zn(OTf)_2$ (800 mg, 2.20 mmol, 0.2 equiv) and heated to 125 °C at which point vacuum (0.6 mmHg) was applied for 4 h. The flask was allowed to cool to room temperature, (+)-*N*-methylephedrine (440 mg, 2.45 mmol, 0.22 equiv) was introduced, and vacuum was applied for 30 min. The flask

97. Ito, Y.; Kimura, Y.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3337–3340.

was purged with argon, and toluene (7.5 mL) and triethyl amine (770 μL, 5.57 mmol, 0.5 equiv) were added. The resulting mixture was stirred for 2 h at room temperature, and 1-heptyne (1.75 mL, 13.3 mmol, 1.2 equiv) was added in one portion. After being stirred for 15 min, the mixture was treated with isobutyraldehyde (**3027**, 1.03 mL, 11.1 mmol, 1.0 equiv) in one portion, and the flask was heated to 60 °C for 12 h. The reaction was quenched by addition of saturated NH_4Cl (10 mL), extracted with diethyl ether, washed with water and brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the crude propargylic alcohol **S2** (1.80 g, 95%) as a colorless oil, which was used in the next step without purification. R_f 0.30 (10:1 hexanes/ethyl acetate); $[\alpha]_D$ +1.5 (c 8.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.16 (m, 1H), 2.21 (td, *J* = 7.5, 2.0 Hz, 2H), 1.84 (d sept, *J* = 6.5, 6.5 Hz, 1H), 1.74 (m, 1H, OH), 1.51 (app pent, *J* = 7.5, Hz, 2H), 1.28-1.40 (m, 4H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 86.3, 79.8, 68.2, 34.7, 31.0, 28.4, 22.2, 18.7, 18.1, 17.4, and 14.0; IR (thin film): 3387, 2959, 2932, 2872, 2230, 1467, 1145, and 1027 cm^{-1}; LR-EIMS [70 eV, m/z (rel. int.)] 168 (1, M^+), 153 (8, M^+-CH_3•), 139 (10, M^+-C_2H_5•), 125 (100, M^+-C_3H_7•), 111 (40, M^+-C_4H_9•), and 97 (45, M^+-C_5H_{11}•).

(*E,R*)-2-Methyldec-4-en-3-ol (S3).

To a solution of **S2** (1.8 g, 10.7 mmol, 1.0 equiv) in diethyl ether (27 mL) at 0 °C was added Red-Al (6.5 mL, 65 %w, 21.4 mmol, 2.0 equiv), and the reaction mixture was allowed to reach room temperature. The septum of the reaction flask was replaced with a condenser, and the mixture was refluxed at 40 °C for 72 h. The reaction was quenched at 0 °C by dropwise addition of a saturated aqueous solution of sodium potassium tartrate, and the mixture was stirred at rt for 1 h. The mixture was extracted with diethyl ether, washed with water and brine, dried over anhydrous sodium sulfate, and concentrated to give 1.7 g of the crude *E*-alkene **S3** (~92%) as a colorless oil, which was used in the next step without purification. R_f 0.30 (10:1 hexanes/ethyl acetate);

$[\alpha]_D$ +6.1 (c 2.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.63 (dtd, *J* = 15.5, 6.5, 1.0 Hz, 1H), 5.45 (ddt, *J* = 15.5, 7.5, 1.5 Hz, 1H), 3.78 (br dd, *J* = 6.5, 6.5 Hz, 1H), 2.04 (dtdd, *J* = 7.0, 7.0, 1.5, 1.5 Hz, 2H), 1.70 (d sept, *J* = 7.0, 7.0 Hz, 1H), 1.29 (app pent, *J* = 7.0 Hz, 2H), 1.24-1.33 (m, 4H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.2, 131.1, 78.4, 33.8, 32.3, 31.4, 28.9, 22.5, 18.24, 18.19, and 14.1; IR (thin film): 3387, 2957, 2926, 2872, 1671, 1466, 1381, 1013, and 971 cm^{-1}; LR-EIMS [70 eV, m/z (rel. int.)] 170 (10, M^+), 152 (8, M^+-H_2O), and 127 (80, M^+-C_3H_7•).

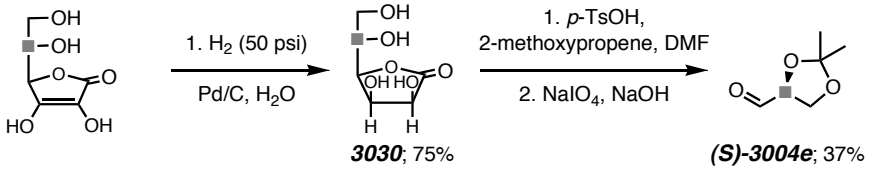
(*E*,*R*)-[(2-Methyldec-4-en-3-yloxy)methyl]benzene (S4).

To a solution of **S3** (900 mg, 5.30 mmol, 1.0 equiv) in dimethyl formamide (15 mL) at 0 °C was added sodium hydride (150 mg, 6.35 mmol, 1.2 equiv) in one portion and the mixture was stirred for 20 min at which time benzyl bromide (950 μL, 7.94 mmol, 1.5 equiv) and tetrabutylammonium bromide (196 mg, 0.53 mmol, 0.1 equiv) were added consecutively. The resulting solution was allowed to reach room temperature and stirred for 72 h. The mixture was poured into saturated NH_4Cl solution and extracted with ethyl acetate (250 mL). The organic layer was washed with water (100 mL x 3) and brine, dried over sodium sulfate, and concentrated under reduced pressure to give 1.2 g of the crude benzyl ether **S4** (~90 %) as a colorless oil, which was used in the next step without purification. R_f 0.70 (12:1 hexanes/ethyl acetate); $[\alpha]_D$ +43.5 (c 3.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.33–7.26 (m, 5H), 5.57 (dtd, *J* = 15.5, 6.5, 0.5 Hz, 1H), 5.32 (ddt, *J* = 15.5, 8.5, 1.5 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.31 (d, *J* = 12.0 Hz, 1H), 3.34 (ddd, *J* = 8.5, 7.0, 0.5 Hz, 1H), 2.08$^+$ (dtdd, *J* = 14.0, 7.0, 7.0, 1.5 Hz, 1H), 2.08$^-$ (dtdd, *J* = 14.0, 7.0, 7.0, 1.5 Hz, 1H), 1.77 (d sept, *J* = 7.0, 7.0 Hz, 1H), 1.41 (app pent, *J* = 7.0 Hz, 2H), 1.34–1.26 (m, 4H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.3, 135.4, 130.0, 128.4, 127.7, 127.2, 85.6, 69.7, 32.9, 32.3, 31.4, 29.1, 22.5, 19.0, 18.6, and 14.1; IR (thin film): 2988, 2979, 2957, 2930, 2870, 1453, 1381, 1142, 1068, 974,

734, and 697 cm^{-1}; HRMS calculated 283.2032 ($C_{18}H_{28}ONa^{+}$), observed 283.2049.

(*R*)-2-(Benzyloxy)-3-methylbutanal [(*R*)-3004d].

To a solution of **S4** (500 mg, 1.92 mmol, 1.0 equiv) in methylene chloride (60 mL) and (3 mL) methanol at −78 °C was passed ozone until a blue color appeared. Oxygen was passed through the solution for an additional 5 min, at which time dimethyl sulfide (1.1 mL, 15.4 mmol, 8.0 equiv) was added and the solution was allowed to reach room temperature. The reaction mixture was stirred for an additional 12 h, and the bulk of the solvent was removed under reduced pressure. The residue was purified by flash chromatography [R_f 0.7 (6:1 hexanes/ethyl acetate)] to provide the aldehyde **(*R*)-3004d** (260 mg, 70%). $[\alpha]_D$ +67.0 (c 8.4, $CHCl_3$). The ^1H NMR spectrum of the product was essentially identical to that of **(*S*)-3004d**.

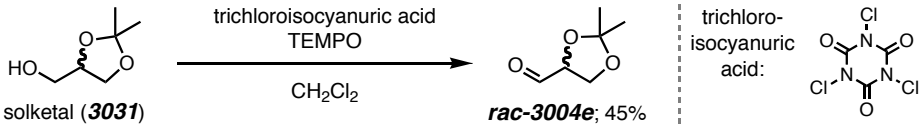


L-(*S*)-Glyceraldehyde acetonide [(*S*)-3004e].

Aldehyde **(*S*)-3004e** was prepared in 28% overall yield according to literature procedures.[98a-c]

$[\alpha]_D$ -54.9 (c 3.4, $CHCl_3$) [lit[98c] $[\alpha]_D$ -75.4 (c 8, benzene)]; The ^1H NMR spectrum of the product was entirely consistent with that of the reported data.

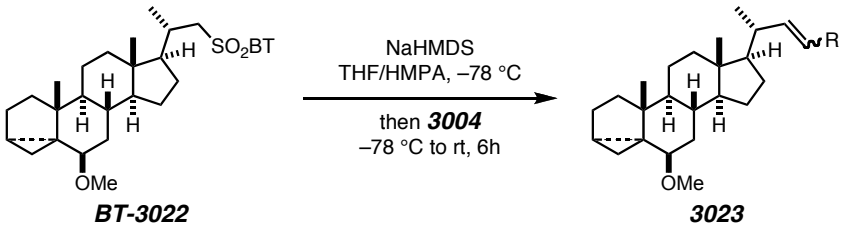
98. (a) Andrews, G. C.; Crawford, T. C.; Bacon, B. E. *J. Org. Chem.* **1981**, *46*, 2976–2977. (b) Hubschwerlen, C. *Synthesis* **1986**, 962. (c) Hubschwerlen, C.; Specklin, J. L.; Higelin, J. *Org. Synth., Coll. Vol. 9*, **1998**, 454–457.



(±)-Glyceraldehyde acetonide (*rac*-3004e).

Racemic aldehyde ***rac*-3004e**[99] was prepared in 45% yield mostly according to literature procedure;[100] the reaction mixture was stirred for 10 min, and the crude material was purified by distillation (bp temp 53 °C at 300 torr). The ^{1}H NMR spectrum of ***rac*-3004e** was essentially identical to that of **(*S*)-3004e**.

General procedure for the Modified-Julia Olefination:



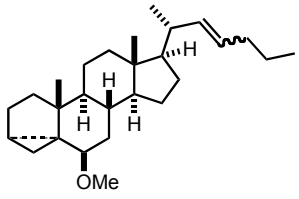
BT-3022 ***3023***

To a stirred solution of **BT-3022** (150 mg, 0.28 mmol, 1.0 equiv) in THF (3.2 mL) and hexamethylphosphoramide (0.8 mL) at –78 °C was added sodium *bis*(trimethylsilyl)amide (1.90 M in THF, 0.180 mL, 0.34 mmol, 1.2 equiv). The resultant solution was allowed to stir at –78 °C for 15 min followed by the rapid addition of aldehyde (0.28 mmol, 1.0 equiv in 0.5 mL THF). The mixture was allowed to reach room temperature and stirred for an additional 6 h, at which time the reaction was quenched by the addition of saturated ammonium chloride. The aqueous layer was extracted with ethyl acetate and the combined organic layer was washed with saturated sodium bicarbonate and brine and dried over anhydrous sodium sulfate. The crude

99. Compound was reported as trimer: Kimura, M.; Shimizu, M.; Tanaka, S.; Tamaru, Y. *Tetrahedron* **2005**, *61*, 3709–3718.

100. De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041–3043.

material was purified by flash chromatography (or MPLC) on silica gel to provide the alkene products **3023**.



3023a

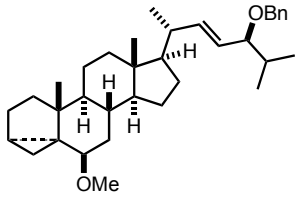
The mixture of E/Z-alkenes (ratio 80:20) was not separable by MPLC (SiO_2) and was characterized as the mixture.

(3α,5*R*,6β,22*E*)-6-Methoxy-3,5-cyclo-27-norcholest-22-ene (3023a-*E*).

R_f 0.65 (10:1 hexanes/ethyl acetate); $[\alpha]_D$ +20.9 (c 6.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): 5.29 (dt, *J* = 15.5, 6.5, 1H), 5.22 (ddd, *J* = 15.0, 8.0, 1.0 Hz, 1H) , 3.32 (s, 3H), 2.77 (dd, *J* = 2.5, 2.5 Hz, 1H), 2.06-1.88 (m, 3H), 1.97 (ddd, *J* = 12.5, 3.5, 3.5 Hz, 1H), 1.89 (ddd, *J* = 13.5, 3.0, 3.0 Hz, 1H), 1.78–1.61 (m, 3H), 1.59-0.80 (m, 16H), 1.02 (s, 3H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.89 (t, *J* = 7.5, 3H), 0.73 (s, 3H), 0.65 (dd, *J* = 4.5, 4.5 Hz, 1H), and 0.43 (dd, *J* = 8.0, 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.2, 127.3, 82.4, 56.63, 56.59, 56.1, 48.1, 43.4, 42.7, 40.2, 40.1, 35.3, 35.1, 34.6, 33.4, 30.5, 28.7, 25.0, 24.2, 22.82, 22.79, 21.5, 20.8, 19.3, 13.7, 13.1, and 12.5; IR (thin film): 2954, 2930, 2868, 2849, 1456, 1098, and 967 cm^{-1}; LR-EIMS [70 eV, m/z (rel. int.)] 384 (30, M^+), and 369 (80, M^+-CH_3•).

(3α,5*R*,6β,22*Z*)-6-Methoxy-3,5-cyclo-27-norcholest-22-ene (3023a-*Z*).

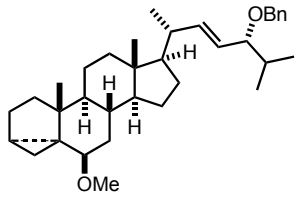
^{1}H NMR (500 MHz, $CDCl_3$), identifiable, distinguishable, and diagnostic peaks of the *Z*-alkene: δ 5.13 (dd, *J* = 10.0, 3.0, 1H), and 2.44 (m, 1H).



3023d-E

(3α,5*R*,6β,22*E*,24*S*)-24-Benzyloxy-6-methoxy-3,5-cyclocholest-22-ene (3023d-*E*).

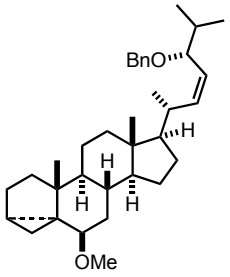
R_f 0.55 (10:1 hexanes/ethyl acetate); $[\alpha]_D$ -1.0 (c 3.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.32–7.28 (m, 5H), 5.41 (dd, *J* = 15.5, 9.0 Hz, 1H), 5.23 (dd, *J* = 15.0, 8.5 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.31 (d, *J* = 12.0 Hz, 1H), 3.33 (s, 3H), 3.30 (dd, *J* = 8.5, 7.0 Hz, 1H), 2.78 (dd, *J* = 2.5, 2.5 Hz, 1H), 2.20–2.10 (m, 1H), 1.99 (ddd, *J* = 12.5, 3.5, 3.5 Hz, 1H), 1.89 (ddd, *J* = 13.5, 3.0, 3.0 Hz, 1H), 1.81–1.62 (m, 3H), 1.61–1.50 (m, 3H), 1.43–1.40 (m, 2H), 1.35–0.80 (m, 10H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.03 (s, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.75 (s, 3H), 0.65 (dd, *J* = 5.0, 5.0 Hz, 1H), and 0.43 (dd, *J* = 7.5, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.1, 139.5, 128.2, 127.7, 127.2, 126.2, 85.6, 82.4, 69.6, 56.6 (2C), 55.8, 48.1, 43.4, 42.8, 40.25, 40.22, 35.3, 35.1, 33.4, 33.0, 30.5, 28.9, 25.0, 24.3, 22.8, 21.5, 21.0, 19.3, 19.2, 18.6, 13.1, and 12.5; IR (thin film): 2951, 2933, 2868, 1454, 1381, 1097, 1068, and 975 cm^{-1}; LR-EIMS [70 eV, m/z (rel. int.)] 504 (1, M^+), 489 (5, M^+-CH_3•), and 461 (40, M^+-C_3H_7•).



epi-3023d-E

(3α,5*R*,6β,22*E*,24*R*)-24-Benzyloxy-6-methoxy-3,5-cyclocholest-22-ene (*epi*-3023d-*E*).

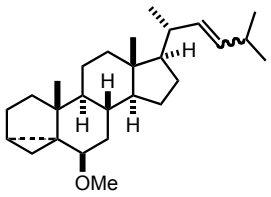
R_f 0.40 (15:1 hexanes/ethyl acetate); $[\alpha]_D$ +48.4 (c = 2.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.32–7.29 (m, 5H), 5.43 (dd, *J* = 15.5, 9.0 Hz, 1H), 5.24 (dd, *J* = 15.5, 8.5 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.30 (d, *J* = 12.0 Hz, 1H), 3.33 (s, 3H), 3.30 (dd, *J* = 8.5, 7.0 Hz, 1H), 2.78 (dd, *J* = 2.5, 2.5 Hz, 1H), 2.20–2.10 (m, 1H), 1.99 (ddd, *J* = 12.5, 3.5, 3.5 Hz, 1H), 1.89 (ddd, *J* = 13.5, 3.0, 3.0 Hz, 1H), 1.81–1.62 (m, 3H), 1.61–1.50 (m, 3H), 1.43–1.40 (m, 2H), 1.35–0.80 (m, 10H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.03 (s, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.75 (s, 3H), 0.65 (dd, *J* = 5.0, 5.0 Hz, 1H), and 0.43 (dd, *J* = 7.5, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.8, 139.3, 128.2, 127.7, 127.2, 126.6, 85.6, 82.4, 69.7, 56.6 (2C), 55.8, 48.1, 43.4, 42.8, 40.2, 40.1, 35.3, 35.1, 33.4, 33.0, 30.5, 28.9, 25.0, 24.3, 22.8, 21.5, 20.8, 19.3, 19.1, 18.6, 13.1, and 12.5; IR (thin film): 2953, 2933, 2868, 1455, 1097, 1068, 1027, 1017, 970, and 804 cm^{-1}; LR-EIMS [70 eV, m/z (rel. int.)] 504 (1, M^+), 489 (3, M^+-CH_3•), and 461 (45, M^+-C_3H_7•).



epi-3023d-Z

(3α,5*R*,6β,22*Z*,24*R*)-24-Benzyloxy-6-methoxy-3,5-cyclocholest-22-ene (*epi*-3023d-*Z*).

R_f 0.45 (15:1 hexanes/ethyl acetate); $[\alpha]_D$ -1.7 (c 0.7 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.37–7.33 (m, 5H), 5.46 (dd, *J* = 10.5, 10.5 Hz, 1H), 5.18 (dd, *J* = 10.5, 10.5 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.30 (d, *J* = 12.0 Hz, 1H), 3.48 (dd, *J* = 10.0, 6.5 Hz, 1H), 3.32 (s, 3H), 2.77 (dd, *J* = 3.0, 3.0 Hz, 1H), 2.46–2.38 (m, 1H), 1.96 (ddd, *J* = 13.0, 3.5, 3.5 Hz, 1H), 1.88 (ddd, *J* = 14.0, 3.0, 3.0 Hz, 1H), 1.81–1.62 (m, 3H), 1.61–1.50 (m, 3H), 1.43–1.40 (m, 2H), 1.35–0.80 (m, 10H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.03 (s, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.75 (s, 3H), 0.65 (dd, *J* = 4.5, 4.5 Hz, 1H), and 0.43 (dd, *J* = 8.0, 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.1, 139.4, 128.2, 127.5, 127.2, 126.0, 82.4, 79.5, 69.9, 56.6, 56.5, 56.3, 48.1, 43.4, 42.9, 40.3, 35.3, 35.0, 34.7, 33.356, 33.359, 30.5, 28.6, 25.0, 24.2, 22.8, 21.6, 21.0, 19.3, 19.1, 18.7, 13.1, and 12.6; IR (thin film): 2953, 2930, 2867, 1723, 1454, 1097, 1068, 1027, 1016, and 697 cm^{-1}; LR-EIMS [70 eV, m/z (rel. int.)] 504 (1, M^+), 489 (5, M^+-CH_3•), and 461 (55, M^+-C_3H_7•).



3023b

The mixture of *E/Z*-alkenes (ratio 75:25) was not separable by MPLC (SiO_2) and was characterized as the mixture.

(3α,5*R*,6β,22*E*)-6-Methoxy-3,5-cyclo-26,27-dinorergost-22-ene (3023b-*E*).[101]

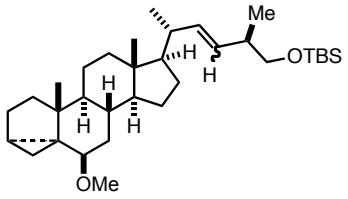
R_f 0.65 (10:1 hexanes/ethyl acetate); $[\alpha]_D$ +25.0 (c 4.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.26 (dd, *J* = 15.5, 6.5 Hz, 1H), 5.16 (ddd, *J* = 15.5, 8.5, 1.0 Hz, 1H), 3.32 (s, 3H), 2.77 (dd, *J* = 2.5, 2.5 Hz, 1H), 2.19 (ddqq, *J* = 7.0, 1.0, 7.0, 7.0 Hz, 1H), 2.10–2.00 (m, 1H), 1.97 (ddd, *J* = 12.5, 3.5, 3.5 Hz, 1H), 1.89 (ddd, *J* = 13.5, 3.0, 3.0 Hz, 1H), 1.80–1.65 (m, 2H), 1.60–1.48 (m, 3H), 1.46–1.38 (m, 2H), 1.34–0.78 (m, 10H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.04 (s, 3H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 8.0 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.75 (s, 3H), 0.65 (dd, *J* = 5.0, 5.0 Hz, 1H), and 0.43 (dd, *J* = 7.5, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 134.8, 133.7, 82.4, 56.64, 56.59, 56.17, 48.08, 43.2, 42.7, 40.2, 40.0, 35.3, 35.08, 33.4, 31.0, 30.5, 28.6, 25.0, 24.1, 22.83, 22.81, 22.79, 21.51, 20.8, 19.3, 13.1, and 12.49; IR (thin film): 2954, 2932, 2867, 1458, 1380, 1096, and 969 cm^{-1}; LR-EIMS [70 eV, m/z (rel. int.)] 384 (50, M^+), 369 (70, M^+-CH_3•), and 352 (72, M^+-MeOH).

(3α,5*R*,6β,22*Z*)-6-Methoxy-3,5-cyclo-26,27-dinorergost-22-ene (3023b-*Z*).

^{1}H NMR (500 MHz, $CDCl_3$), identifiable, distinguishable, and diagnostic peaks of the *Z*-alkene: δ 5.00 (dd, *J* = 10.5, 3.5 Hz, 1H), 4.99 (dd, *J* = 10.5, 3.5, 1.0 Hz, 1H), 2.77 (dd, *J* = 2.5, 2.5 Hz, 1H), 2.61 (m, 1H), and 2.42–2.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 134.2, 134.1, 82.4, 56.64, 56.59, 56.20, 48.10, 43.2, 42.7, 40.3, 40.0, 35.05,

101. Tyrlik-Kurek, A.; Marczak, S.; Michalak, K.; Wilcha, J.; Zarecki, A. *J. Org. Chem.* **2001**, *66*, 6994–7001.

34.6, 33.4, 31.0, 30.5, 28.5, 26.8, 24.2, 22.6, 22.2, 22.79, 21.53, 20.8, 19.3, 13.1, and 12.58.



3023c

The mixture of *E/Z*-alkenes (ratio 85:15) was not separable by MPLC (SiO_2) and was characterized as the mixture.

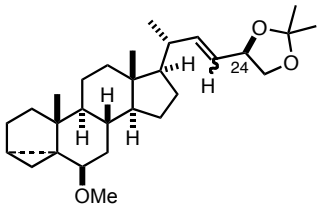
(1,1-Dimethylethyl)[[(3α,5*R*,6β,22*E*,24*R*)-6-methoxy-3,5-cyclo-27,28-bisnorergost-22-en-25-yl]oxy]dimethylsilane (3023c-*E*).

R_f 0.45 (20:1 hexanes/ethyl acetate); $[\alpha]_D$ +21.0 (c 1.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 5.26 (dd, *J* = 15.5, 8.0 Hz, 1H), 5.20 (dd, *J* = 15.5, 6.5 Hz, 1H), 3.47 (dd, *J* = 9.0, 5.5 Hz, 1H), 3.32 (dd, *J* = 8.5, 8.5 Hz, 1H), 3.32 (s, 3H), 3.30 (dd, *J* = 8.5, 7.0 Hz, 1H), 2.77 (dd, *J* = 2.5, 2.5 Hz, 1H), 2.22 (sept, *J* = 6.5 Hz, 1H), 2.05–1.98 (m, 1H), 1.96 (ddd, *J* = 12.5, 3.5, 3.5 Hz, 1H), 1.89 (ddd, *J* = 13.5, 3.0, 3.0 Hz, 1H), 1.81–0.76 (m, 16H), 1.02 (s, 3H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 9H), 0.72 (s, 3H), 0.65 (dd, *J* = 4.5, 4.5 Hz, 1H), 0.43 (dd, *J* = 8.0, 5.0 Hz, 1H), and 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.6, 130.0, 82.4, 68.5, 56.63, 56.59, 56.0, 48.1, 43.4, 42.7, 40.2, 40.1, 39.3, 35.3, 35.0, 33.4, 30.5, 28.7, 26.04, 26.0, 25.9 (2C), 25.0, 24.1, 22.8, 21.6, 20.7, 19.3, 17.0, 13.1, 12.5, -5.25, -5.30; IR (thin film): 2989, 2979, 2954, 2933, 2869, 1257, 1142, 1098, 1017, 836, 807, and 776 cm^{-1}; HRMS calculated 537.4098 ($C_{33}H_{58}O_2SiNa^+$), observed 537.4074.

(1,1-Dimethylethyl)[[(3α,5*R*,6β,22*Z*,24*R*)-6-methoxy-3,5-cyclo-27,28-bisnorergost-22-en-25-yl]oxy]dimethylsilane (3023c-*Z*).

^1H NMR (500 MHz, $CDCl_3$), identifiable, distinguishable, and diagnostic peaks of

the *Z*-alkene: δ 5.14 (dd, *J* = 10.5, 10.5, 1H), 4.92 (dd, *J* = 10.5, 10.5, 1H), 3.44 (dd, *J* = 10.0, 6.0, 1H), 2.64 (m, 1H), and 2.43 (m, 1H).



3023e-(24R)

The mixture of *E/Z*-alkenes (ratio 90:10) was not separable by MPLC (SiO_2) and was characterized as the mixture.[102]

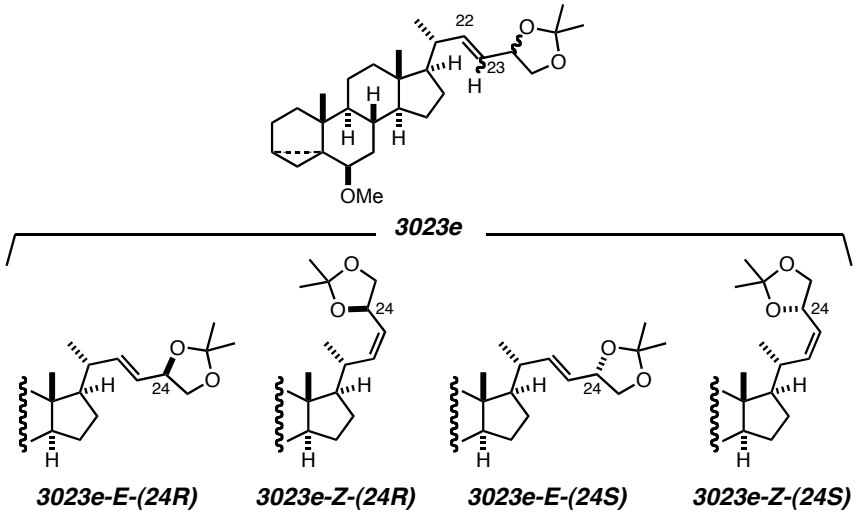
(3β,5*R*,6β,22*E*,24*R*)-6-Methoxy-3,5-cyclo-26,27-dinorcholest-22-ene-24,25-diol, cyclic 1-methylethylidene acetal 3023e-*E*-(24*R*).

R_f 0.40 (10:1 hexanes/ethyl acetate); $[\alpha]_D$ +12.0 (c 4.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.62 (dd, *J* = 15.0, 8.5 Hz, 1H), 5.34 (dd, *J* = 15.5, 8.0 Hz, 1H), 4.43 (td, *J* = 8.0, 6.0 Hz, 1H), 4.04 (dd, *J* = 8.5, 6.5 Hz, 1H), 3.54 (t, *J* = 8.0 Hz, 1H), 3.24 (s, 3H), 2.77 (dd, *J* = 2.5, 2.5 Hz, 1H), 2.17–2.07 (m, 1H), 1.97 (ddd, *J* = 12.5, 3.5, 3.5 Hz, 1H), 1.87 (ddd, *J* = 13.5, 3.0, 3.0 Hz, 1H), 1.81–1.64 (m, 2H), 1.62–1.48 (m, 3H), 1.46–0.78 (m, 12H), 1.42 (s, 3H), 1.39 (s, 3H), 1.05 (d, *J* = 6.5 Hz, 3H), 1.02 (s, 3H), 0.73 (s, 3H), 0.65 (dd, *J* = 5.0, 5.0 Hz, 1H), and 0.43 (dd, *J* = 7.5, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.0, 124.7, 109.0, 82.4, 77.6, 69.59, 56.6, 56.5, 55.5, 48.0, 43.4, 42.83, 40.2, 39.8, 35.2, 35.1, 33.4, 30.5, 28.5, 26.8, 26.0, 25.0, 24.1, 22.8, 21.8, 19.9, 19.3, 13.1 and 12.4; IR (thin film): 2989, 2980, 2944, 2869, 1453, 1379, 1142, 1098, 1061, and 969 cm^{-1}; LR-EIMS [70 eV, m/z (rel. int.)] 442 (40, M^+), 427 (70, M^+-CH_3•), and 410 (50, M^+-MeOH).

102. Fuerst, A.; Labler, L.; Meier, W. *Proceedings of the Sixth Workshop on Vitamin D;* Walter De Gruyter-Berlin-New York, **1985**, 733–738.

(3β,5*R*,6β,22*Z*,24*R*)-6-Methoxy-3,5-cyclo-26,27-dinorcholest-22-ene-24,25-diol, cyclic 1-methylethylidene acetal 3023e-*Z*-(24*R*).

^{1}H NMR (500 MHz, $CDCl_3$), identifiable, distinguishable, and diagnostic peaks: δ 5.40 (dd, *J* = 11.0, 7.5 Hz, 1H), and 5.26 (dd, *J* = 11.0, 9.0 Hz, 1H), 4.86 (tdd, *J* = 8.0, 6.0, 1.0 Hz, 1H), 4.08 (dd, *J* = 8.0, 6.0 Hz, 1H), 3.49 (t, *J* = 8.0 Hz, 1H), 3.34 (s, 3H), 3.30 (dd, *J* = 8.5, 7.0 Hz, 1H), and 2.48–2.40 (m, 1H).



The mixture of these four isomers was not separable by MPLC (SiO_2) and was characterized as the mixture.

R_f 0.40 (10:1 hexanes/ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$), diagnostic peaks for the alkene protons attached to C22 and C23: **3023e-*E*-(24*R*):** δ 5.62 (dd, *J* = 15.0, 8.5 Hz, 1H), and 5.341 (dd, *J* = 15.5, 8.0 Hz, 1H); **3023e-*Z*-(24*R*):** δ 5.40 (dd, *J* = 11.0, 7.5 Hz, 1H), and 5.26 (dd, *J* = 11.0, 9.0 Hz, 1H); **3023e-*E*-(24*S*):** δ 5.64 (dd, *J* = 15.5, 8.5 Hz, 1H), 5.344 (dd, *J* = 15.5, 8.0 Hz, 1H); **3023e-*Z*-(24*S*):** δ 5.38 (dd, *J* = 11.0, 7.5 Hz, 1H), 5.22 (dd, *J* = 11.0, 9.0 Hz, 1H).

Part – IV: Long-range Shielding Effects in the ^{1}H NMR Spectra of Mosher-like Ester Derivatives

IV-A. Introduction and Background

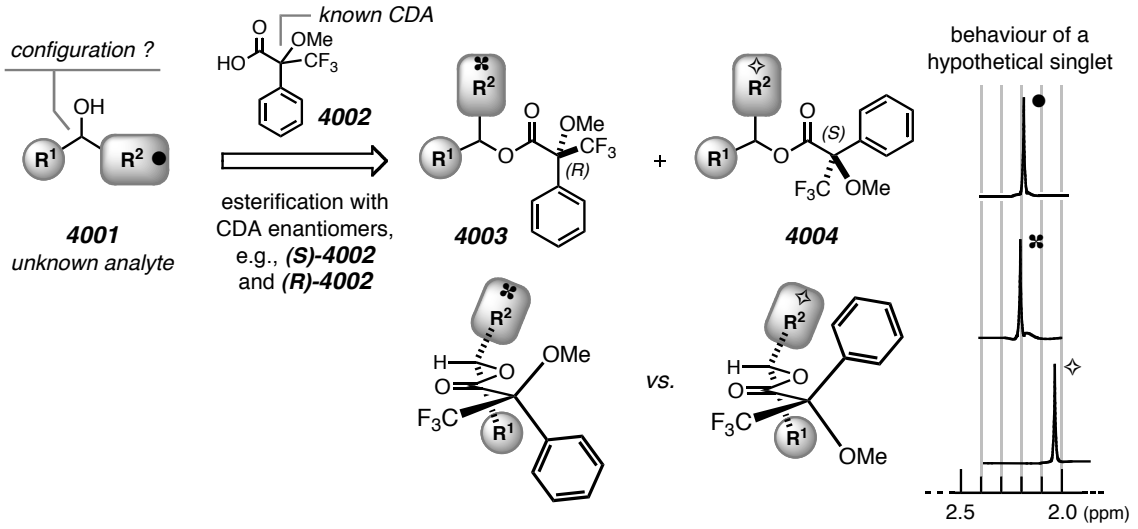
Determining the absolute configuration of stereogenic carbinol and amino centers is a challenging task in chemistry. The accuracy of the assignment is not only important for synthesis purposes,[103a] but also critical for medicinal chemistry and drug development.[103b]

Mosher ester/amide analysis[104] is a powerful and widely used NMR based method[105] for assignment of seterogenic carbinol/amino centers. The analysis requires a modification of the molecule, which will make a spectral differentiation possible by various NMR techniques.[106a] The most widely used Mosher ester/amide analysis technique[106b] involves two fundamental stages. First, the analyte of interest is derivatized with a chiral derivatizing agent (CDA), whose stereochemical information is known. In general, one makes a complementary pair of diastereomeric derivatives of the analyte using enantiomerically enriched samples of each antipode of the CDA (Figure IV-1). The CDA moiety introduces a local magnetic anisotropy, which selectively influences (or using Mosher terminology, "discriminates") diastereotopic protons. Therefore, the analyte is affected differently by two different CDAs. Second, the configuration of the parent alcohol/amine is deduced by comparing the sets of differential chemical shifts ($\Delta\delta$s) for analogous proton resonances in the spectrum of

103. (a) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley-Interscience Inc.: Hoboken, NJ, **1994**. (b) Francotte, E.; Linder, W. *Chirality in Drug Research*; *Wiley*/VCH, Weinheim, Germany, **2006**.
104. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
105 Thomas J. Wenzel, *Discrimination of Chiral Compounds Using NMR Spectroscopy*; J. Wiley & Sons, Inc.: Hoboken, NJ, **2007**.
106. (a) Seco, M. J.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17–117. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.

each diastereomer.

Figure IV-1. Basics of Mosher Ester Analysis for a Carbinol **4001**.



When a Mosher ester analysis is employed for an analyte (e.g., **4001** in Figure IV-1), a pair of diastereomeric esters (**4003** and **4004**) is formed using the known enantiomeric CDA-acids **4002**. For the sake of the argument, let's say a particular proton of the analyte **4001** appears as a singlet on the ^{1}H-NMR spectrum (Figure IV-1). This singlet may stay almost at the same position (say for **4003**) or shift to upfield (say for **4004**) on the spectrum. Based on our imagination, the chemical shift difference ($\Delta\delta = \delta_{4003} - \delta_{4004}$) equals to 0.17 ppm. This is a positive number, and the proton in question should locate in the anisotropic cone of the CDA-aromatic ring. This information tells us that the proton is shielded by the phenyl ring of the CDA, and because we know which substituent (R^1 or R^2) accomodates this proton, we can ascertain the configurations of each diastereomer. is In the case of a hypothetical These empirical methods rely on an understanding of the dominant conformation adopted by the ester/amide derivative.

One important aspect of Mosher analysis is the distance over which the anisotropic differential shielding effects exert themselves. Therefore, following up the

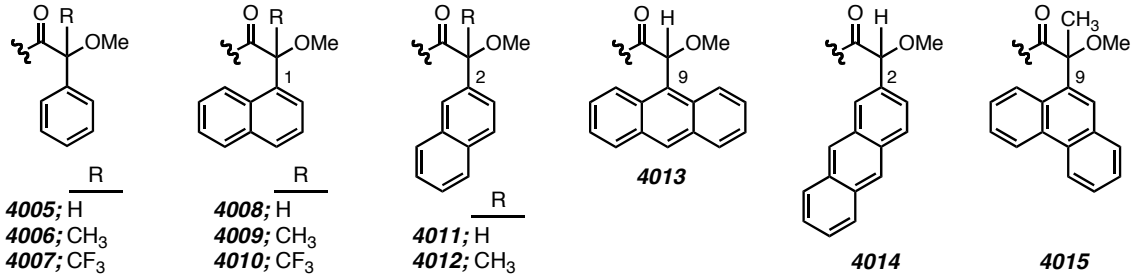
pivotal initial studies of former Hoye Group members,[107a] Christopher R. H. Hale (my undergraduate mentoree) and I studied the inherent nature of the carbinol analytes and the CDAs. I was involved in the synthesis of the details about the earlier investigations on this project are not presented here, yet they can be found in the corresponding Ph.D. theses.[107b]

107. (a) Michael J. Mayer, Matthew K. Renner (graduate students), Sara E. Erickson, Sherrie L. Erickson-Birkedahl, and Patrick K. Notz (undergraduate students). (b) Mayer, M. J. Ph.D. Thesis, University of Minnesota, **1998**. (c) Renner, M. K. Ph.D. Theses, University of Minnesota, **1995**.

IV-B. Results and Discussion

With the need for preparing powerful CDAs, we focused on synthesizing a naphthyl derivative of the phenylacetyl reagents **4005-4007** (Table IV-1), namely α-methoxy-α-trifluoromethyl-1-naphthylacetyl [$MTN_{(1)}A$, **4010**]. *For the convenience of the reader, the synthetic route both to the acid **4010-OH** and the derivatized menthols [**(R)-** and **(S)-4010-m**] are shown after Table IV-1 in Scheme IV-1. This table presents detailed comparative analyses of the proton chemical shift values for CDAs in Figure IV-2.*

Figure IV-2. Known Mosher-like Chiral Derivatizing Agents (CDAs).

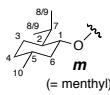


4005; MPA = α-methoxyphenylacetyl
4006; MPP = α-methoxyphenylpropionyl
4007; MTPA = α-methoxy-α-trifluoromethylphenylacetyl
4008; $MN_{(1)}A$ = α-methoxy-1-naphthylacetyl
4009; $MN_{(1)}P$ = α-methoxy-1-naphthylpropionyl
4010; $MTN_{(1)}A$ = α-methoxy-α-trifluoromethyl-1-naphthylacetyl
4011; $MN_{(2)}A$ = α-methoxy-2-naphthylacetyl
4012; $MN_{(2)}P$ = α-methoxy-2-naphthylpropionyl
4013; $MA_{(9)}A$ = α-methoxy-9-anthracenylacetyl
4014; $MA_{(2)}A$ = α-methoxy-2-anthracenylacetyl
4015; $MPhen_{(9)}P$ = α-methoxy-9-phenanthrenylpropionyl

Our work presented here provides additional insight for some of the aspects, for example, the relative effectiveness of various CDAs (from among **4005-4015**, Figure IV-1) to discriminate proton resonances distal to the point of attachment. We believe a more useful CDA leads to a greater anisotropic reach.[108] Perspective on the choice of CDA (more specifically, on its ability to discriminate analogous protons in a pair of diastereomeric derivatives of an analyte) is gained from consideration of the Δδ data for the (–)-menthol derivatives summarized in Table IV-1.

108. Seco, J. M.; Latypov, Sh.; Quiñoá, E.; Riguera, R. *Tetrahedron Lett.* **1994**, *35*, 2921–2924.

Table IV-1. Δδ Values of Menthyl Esters **4005m–4015m** Derived from CDAs **4005–4015**.

 (= menthyl)	MPA[109]	MPP[110]	MTPA[111]	$MN_{(1)}A$[112]	$MN_{(1)}P$[109]	$MTN_{(1)}A$	$MN_{(2)}A$[109]	$MN_{(2)}P$[110]	$MA_{(9)}A$[112,113]	$MA_{(2)}A$[113]	$MPhen_{(9)}P$[110,114]
	4005m	***4006m***	***4007m***	***4008m***	***4009m***	***4010m***	***4011m***	***4012m***	***4013m***	***4014m***	***4015m***
proton #	$\Delta\delta^{SR}$ (= $\delta_S - \delta_R$)										
1	+0.09	+0.05	+0.02	+0.15	+0.16	-0.19	+0.16	+0.06	+0.21	+0.08	+0.14
2	+0.11	+0.06	-0.03	–	+0.26	-0.30	+0.14	+0.06	+0.42	+0.14	+0.28
3eq	+0.07	+0.01	-0.02	–	+0.14	-0.20	+0.10	+0.01	+0.23/+0.26	+0.10/+0.13	+0.16
3ax	+0.07	+0.02	-0.02	–	+0.12	-0.14	+0.10	+0.02	+0.23/+0.26	+0.10/+0.13	+0.13
4eq	0.00	+0.01	0.00	–	+0.14	+0.02	0.00/-0.01	0.00	0.00/-0.10	0.00/-0.02	0.00
4ax	+0.01	-0.03	+0.01	–	0.00	0.00	0.00/-0.01	-0.01	0.00/-0.10	0.00/-0.02	-0.03
5	-0.04	-0.01	+0.02	–	-0.03	+0.03	-0.03	0.00	-0.04	-0.05	-0.04
6eq	-0.22	+0.01	+0.05	–	-0.28	+0.28	-0.15/-0.23	+0.02	-0.50/-0.51	-0.18/-0.23	-0.30
6ax	-0.14	+0.05	+0.14	–	-0.31	+0.34	-0.15/-023	-0.04	-0.50/-0.51	-0.18/-0.23	-0.37
7	+0.56	+0.07	-0.32	+0.93	+1.21	-1.48	+0.64	+0.09	+1.8	+0.58	+1.20
8/9	+0.26	+0.02	-0.10	+0.51	+0.55	-0.50	+0.35	+0.04	+0.79	+0.36	+0.52
9/8	+0.22	-0.02	-0.13	+0.46	+0.46	-0.67	+0.36	+0.05	+0.85	+0.35	+0.57
10	-0.06	-0.01	+0.03	-0.06	-0.10	+0.18	-0.08	0.00	-0.19	-0.10	-0.12
mean |Δδ|	**0.14**	**0.03**	**0.07**	**0.42**	**0.29**	**0.33**	**0.16**	**0.03**	**0.39**	**0.16**	**0.30**

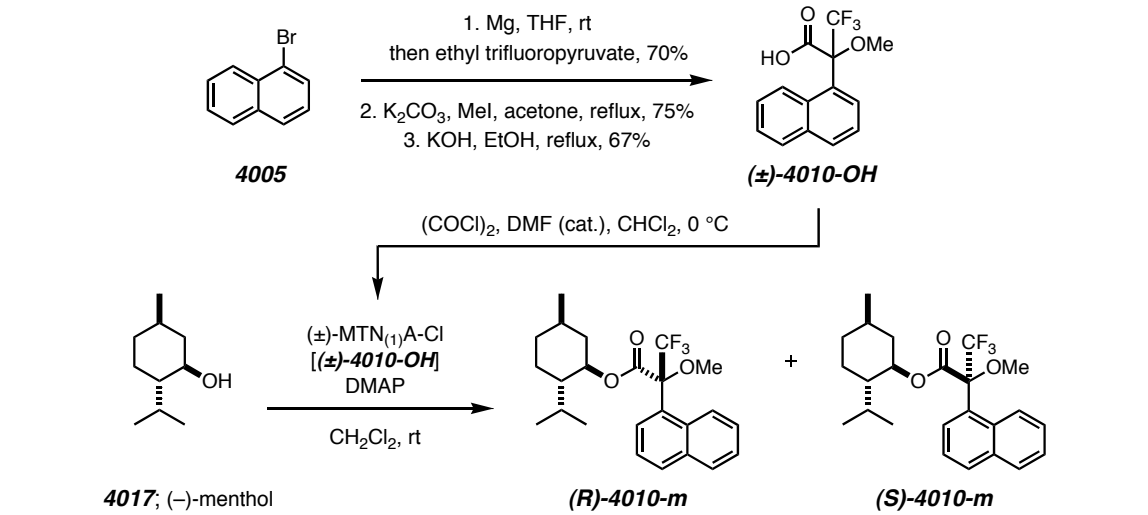
First, the magnitude of the Δδs is enhanced by the replacement of the phenyl with a

109. Harada, N,; Watanabe, M.; Kuwahara, S.; Kasai, Y.; Ichikawa, A. *Tetrahedron: Asymmetry* **2000**, *11*, 1249–1253.
110. Kasai, Y.; Sugio, A.; Kuwahara, S.; Matsumoto, T.; Watanabe, M.; Ichikawa, A.; Harada, N. *Eur. J. Org. Chem*. **2007**, *11*, 1811–1826.
111. Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nature Protocols* **2007**, *2*, 2451–2458
112. Latypov, Sh.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem*. **1995**, *60*, 504–515.
113. Kouda, K.; Kusumi, T; Ping, X.; Kan, Y; Hashimoto, T.; Asakawa, Y. *Tetrahedron Lett.* **1996**, *37*, 4541–4544
114. Ichikawa, A.; Ono. H.; Harada, N. *Tetrahedron: Asymmetry* **2003**, *14*, 1593–1597

naphthyl or anthracenyl moeity in the CDA. This is easily seen, for example, in the relative magnitude of the "mean |Δδ|" values in the bottom line of Table IV-1. Within each of the sets MPA vs. either $MN_{(1)}A$ or $MA_{(9)}A$, MPP vs. $MN_{(1)}P$, and MTPA vs. $MTN_{(1)}A$ the discriminating power of naphthyl or anthracenyl based CDA is greater [by factors of approximately three (*cf.* **4005m** vs. either **4008m** or **4013m**), ten (*cf.* **4006m** vs. **4009m**), and five (*cf.* **4007m** vs. **4010m**), respectively]. Second, whereas MPA shows greater discrimination than MTPA across the mean |Δδ| values for the same set of menthyl protons (*cf.* **4005m** vs. **4007m**) the opposite is true for the $MN_{(1)}A$ vs. $MTN_{(1)}A$ pairs (*cf.* **4008m** vs. **4010m**). Third, the difference in the position of substitution on the CDA aromatic moiety (i.e., C1 vs. C2 positions for naphthyl and C9 *vs*. C2 positions for anthracenyl groups) also affects the discriminating power of $MN_{(1)}A/MN_{(2)}A$, $MN_{(1)}P/MN_{(2)}P$, and $MA_{(9)}A/MA_{(2)}A$. Specifically, mean |Δδ| values are lower for the "C2" substituted positional isomers [by factors of approximately three (*cf.* **2008m** vs. **4011m**), ten (*cf.* **4009m** vs. **4012m**), and two (*cf.* **4013m** vs. **4014m**), respectively.

The desired racemic CDA acid **(±)-4010-OH** was prepared in three steps form the commercially available bromonaphthyl **4016** (Scheme IV-1).

Scheme IV-1. Synthesis of the Racemic $MTN_{(1)}A$-OH [**(±)-4010-OH**] and Its Use in Derivatizing (–)-Menthol (**4017**).



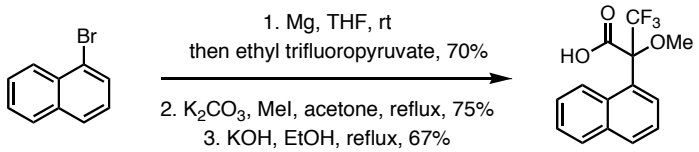
IV-C. Conclusion

In conclusion, we synthesized a powerful chiral derivatizing agent CDA, namely α-methoxy-α-trifluoromethyl-1-naphthylacetic acid [$MTN_{(1)}A$, **4010-OH**], for the ^{1}H-NMR analysis of Mosher-like esters. We compared the trends in the relative discriminating power of the menthyl ester of **4010** to a wide variety of Mosher-like esters (Table IV-1).

IV-D. Experimental Section

All reactions were performed under a dry nitrogen atmosphere or argon atmosphere, unless otherwise noted. All glassware was flame- and/or oven-dried before use. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were dried through Al_2O_3 columns; hexanes (Hex) and ethyl acetate (EtOAc) were used as received (reagent grade). Isopropyl alcohol was distilled prior to use. All other reagents and solvents were used as received. Thin layer chromatography (TLC) was performed using TLC plastic sheets with F254 indicator and visualization via UV-light or staining with either potassium permanganate or phosphomolybdic acid. Flash column purifications were performed using 40-63 mm silica gel. Medium pressure liquid chromatography (MPLC) purifications were performed using Michel-Miller columns, dry packed with ca. 25-35 mm silica gel. All NMR spectra were determined in $CDCl_3$. 1H NMR spectra were acquired on a Varian VI-500 (500 MHz 1H) and 19F NMR spectra were acquired on a Varian VXR-300 (282 MHz 19F) using $CDCl_3$ solvent. Chemical shifts (δ) for 1H NMR spectra are referenced to TMS at δ = 0.00 ppm, 13C NMR spectra are referenced to $CDCl_3$ at δ = 77.0 ppm, and 19F spectra are referenced to $CFCl_3$ at δ = 0.00 ppm. The following abbreviations are used to describe NMR signals: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), br (broad), and nfom (non-first order multiplet). Coupling constants (*J*) are reported in Hz. High-resolution mass spectra were recorded on a Bruker BioTOF II (ESI-TOF) instrument using PEG as an internal standard.

(±)-3,3,3-Trifluoromethyl-2-methoxy-2-(1-naphthyl)propanoic acid [(±)-6-OH]:



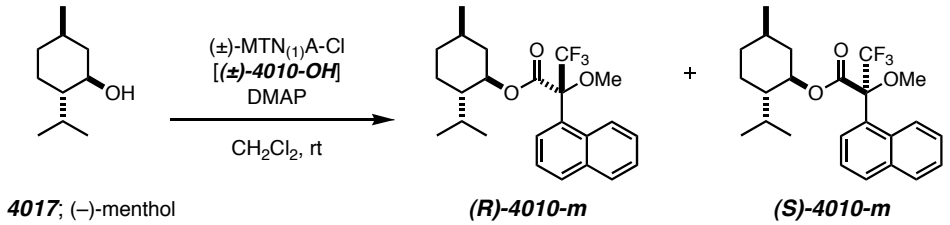
4005 ***(±)-4010-OH***

Racemic $MTN_{(1)}A$-acid **(±)-4010-OH** was prepared in 35% overall yield following literature procedures.[115]

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.08 (nfom, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.90 (nfom, 1H), 7.80 (ddq, *J* = 7.4, 1.5, 2.0 Hz, 1H), 7.53–7.50 (m, 3H), 3.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.6, 134.2, 131.5, 131.0, 129.5, 128.5 (q, *J* = 4 Hz), 127.8, 126.3, 125.3, 124.7, 123.8 (q, *J* = 291 Hz), 123.3, 85.1 (q, *J* = 27 Hz), and 54.9. ^{19}F NMR ($CDCl_3$, 282 MHz) δ -69.5. mp: 126–129.

115. du Boullay, O., T.; Alba, A.; Oukhatar, F.; Martin–Vaca, B.; Bourissou, D. *Org. Lett.* **2008**, *10*, 4669–4672.

Menthyl-(*R*)-MTN$_{(1)}$A ester (*R*)-4010m and menthyl-(*S*)-MTN$_{(1)}$A ester (*S*)-4010m:



4017; (–)-menthol ***(R)-4010-m*** ***(S)-4010-m***

The carboxylic acid **(±)-4010-OH** (100 mg, 0.35 mmol, 1.0 equiv) was dissolved in 4.0 mL of CH_2Cl_2 and hexane (1:1) in a 15 mL flask. The solution was cooled to 0 °C and treated with oxalyl chloride (270 mg, 2.11 mmol, 6.0 equiv) and ca. 10 μL of dimethylformamide. After being stirred for 15 minutes at room temperature, the mixture was diluted with hexanes, filtered through a plug of Celite, and concentrated to a faint yellow liquid (±)-MTN$_{(1)}$A-Cl **(±)-4010-Cl** (96 mg), which was used directly in the next step. The acid chloride (90 mg, 0.30 mmol) was dissolved in dichloromethane (2.0 mL). To this solution were sequentially added a solution of (–)-menthol (55 mg, 0.35 mmol, 1.2 equiv) in CH_2Cl_2 (1.5 mL), triethylamine (32 mg, 0.32 mmol, 1.1 equiv), and 4-dimethylaminopyridine (40 mg, 0.32 mmol, 1.1 equiv). The reaction mixture was stirred at room temperature for 24 hours and quenched by the addition of saturated aqueous NH_4Cl (3 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 10 mL), and the combined organic portions were dried over Na_2SO_4 and concentrated under vacuum to give a 1:1 mixture of diastereomers of **4010-m** as an oil (126 mg, 85% over two steps). A portion of this oil was purified by MPLC (98:2 Hex:EtOAc) to give, in order of elution, esters **(*R*)-4010-m** as a colorless crystalline solid and **(*S*)-4010-m** as a colorless oil.

Spectral data of (*R*)-4010-m:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.27 (br d, 1H, *J* = 9.3 Hz), 7.92 (br d, 1H, *J* = 8.0 Hz), 7.88 (nfom, 1H), 7.68 (br d, 1H, *J* = 7.5 Hz), 7.48–7.52 (m, 3H), 4.77 [ddd, 1H, *J* = 4.5, 11.0, and 11.0 Hz, H(1)], 3.35 (br s, 3H, OMe), 1.78 [m, 1H, H(C*H*Me_2)], 1.74 [m, 1H, H(6eq)], 1.62 [m, 1H, H(3eq)], 1.56 [m, 1H, H(4eq)], 1.38 [m, 1H, H(5)], 1.27 [dddd, 1H, *J* = 3.5, 3.5, 11.0, and 12.5, H(2)], 0.96, [dddd, 1H, *J* = 3, 12.5, 12, and 12 Hz, H(3ax)], 0.78 [d, 3H, *J* = 7.0 H(CH*Me*)], 0.77 (d, 3H, *J* = 6.5 Hz, H(CH*Me*)], 0.71 [dddd, 1H, *J* = 3.5, 12, 12, and 12 Hz, H(4ax)], 0.68 [d, 3H, *J* = 7.0 Hz, C(5)Me], and 0.54 [ddd, 1H, *J* = 12.0, 12.0, and 12.0 Hz, H(6ax)].

^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.7, 134.1, 131.2, 130.7, 129.1, 127.8 (q, *J* = 3 Hz), 127.4, 127.1, 126.0, 124.6, 124.4, 124.2 (q, *J* = 292), 85.6 (q, *J* = 26), 77.5, 54.7, 46.4, 39.6, 33.9, 31.2, 25.3, 22.7, 21.8, 20.8, and 15.5.

^{19}F NMR ($CDCl_3$, 282 MHz) δ -69.5. LR-EIMS [70 eV, *m*/*z* (rel. int.)] 422 (5), 239 (12), 155 (10), 139 (14), and 83 (100).

HRMS (ESI) calculated 445.1961 ($C_{24}H_{29}F_3O_3Na^+$), observed 445.1996.

mp: 105–106 °C.

Spectral data of (*S*)-4010-m:

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.30 (nfom, 1H), 7.90 (br d, 1H, *J* = 8.5 Hz), 7.78 (nfom, 1H), 7.75 (br d, 1H, *J* = 7.5 Hz), 7.48–7.52 (m, 3H), 4.58 [ddd, 1H, *J* = 4.5, 11.0, and 11.0 Hz, H(1)], 3.31 (q, 3H, *J* = 1.5 Hz, OMe), 2.02 [dddd, 1H, *J* = 2.0, 4.0, 4.0, 12.0, H(6eq)], 1.58 [m, 1H, H(4 eq)], 1.42 [dddd, 1H, *J* = 4.0, 4.0, 4.0, and 13.5 Hz, H(3 eq)], 1.41 [m, 1H, H(5)], 0.97 [dddd, 1H, *J* = 2.5, 3.5, 11.0, and 12.5 Hz, H(2)], 0.88 [ddd, 1H, *J* = 12.0, 12.0, and 12.0 Hz, H(6ax)], 0.86 [d, 3H, *J* = 6.5 Hz, C(5)Me], 0.82 [dddd, 1H, *J* = 3.0, 13.0, 13.0, and 13.0 Hz, H(3ax)], 0.71 [dddd, 1H, *J* = 3.5, 12.5, 12.5, and 12.5 Hz, H(4ax)], 0.30 [m, 1H, H(C*H*Me_2)], 0.28 [d, 3H, *J* = 6 Hz, H(CH*Me*)], and 0.10

[d, 3H, *J* = 6.0 Hz, H(CH*Me*)].

^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.4, 134.0, 131.4, 130.4, 129.0, 127.6 (q, *J* = 3 Hz), 127.5, 127.0, 126.1, 124.6, 124.3, 124.2 (q, *J* = 292), 85.5 (q, *J* = 26), 77.2, 54.4, 46.4, 39.7, 34.0, 31.3, 24.9, 22.7, 21.9, 20.2 and 15.1.

^{19}F NMR ($CDCl_3$, 282 MHz) δ -68.9.

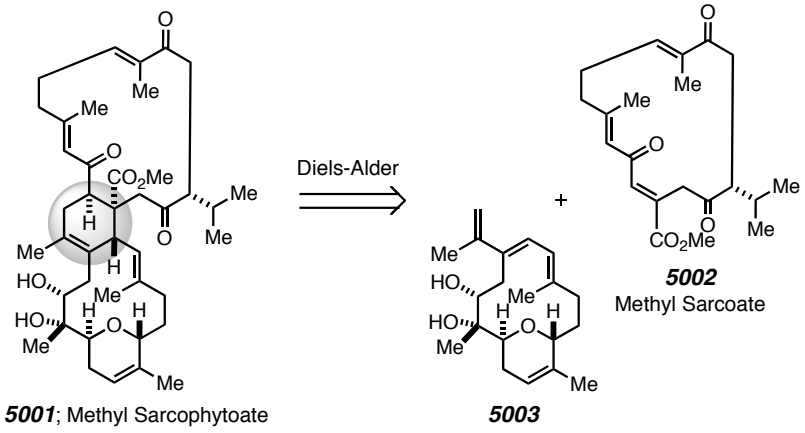
HRMS (ESI) calculated 445.1961 ($C_{24}H_{29}F_3O_3Na^+$), observed 445.1995.

Chapter – V: Exploring the Non-enzymatic Formation of the Methyl Sarcophytoate Core

V-A. Introduction and Background

Methyl sarcophytoate (**5001**, Scheme V-1) has been isolated from the Okinawan soft coral *Sarcophyton glaucum* and exhibits cytotoxic activities against KB cells.[116] Biogenetically, **5001** is considered to be formed by an intermolecular Diels-Alder reaction of two subunits: methyl sarcoate (**5002**), another natural terpenoid isolated from the same coral, and the diene unit **5003**.[117]

Scheme V-1. Proposed Biosynthesis of Methyl Sarcophytoate (**5001**).



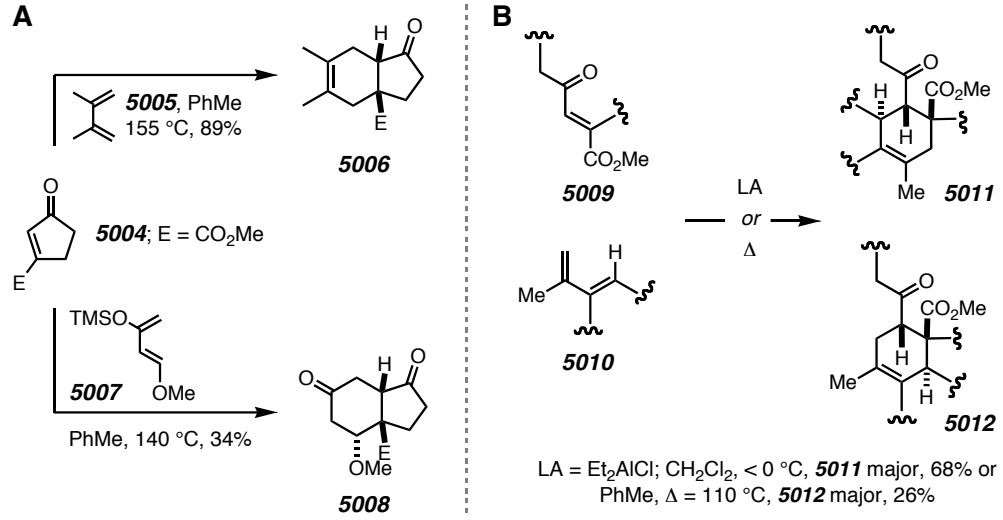
The Diels-Alder reaction is one of the most versatile C-C bond forming reactions. An organism can utilize either inter- or intramolecular versions of a Diels-Alder reaction in order to produce complex molecules. However, to our practical thinking, it is unlikely that an organism would have evolved an enzyme to connect two very complex

116. Kusumi, T.; Igari, M.; Ishitsuka, M, O.; Ichikawa, A.; Itezono, Y.; Makayama, N.; Kakisawa, H. *J. Org. Chem*. **1990**, *55*, 6286–6291.
117. Leone, P. A.; Bowden, B. F.; Carroll, A, R.; Coll, J. C.; Meehan, G. V. *J. Nat. Prod*. **1993**, *56*, 521–526.

compounds like **5002** and **5003**.

Several research groups have studied intermolecular Diels-Alder reactions of intermediates that are structurally related to **5002** and **5003** using bench-chemicals.[118,119] In those studies, α,β-unsaturated keto-esters **5004** (Panel A in Scheme V-2) or **5009** (Panel B) are reported to react with substituted dienes **5005** and **5007**, or **5010**, respectively. In each system, coupling partners lead to the α-keto cyclohenes (cyclohexanone when **5007** was used) at elevated temperature or under Lewis acid conditions.

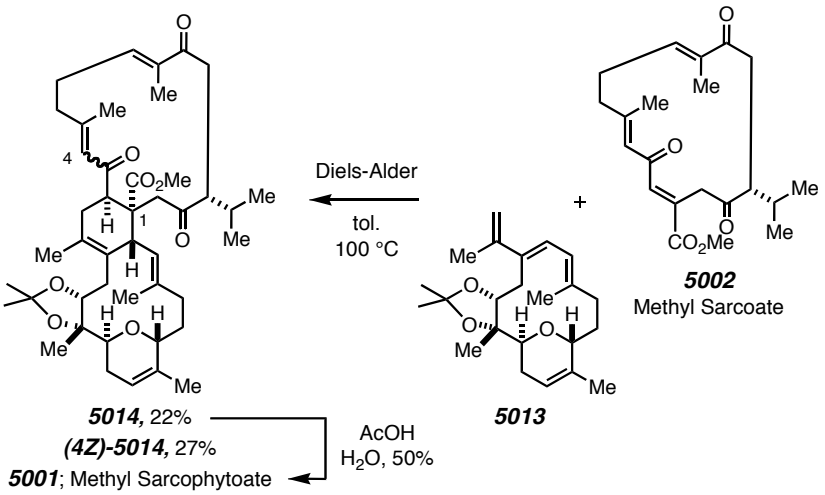
Scheme V-2. Reported Diels-Alder Reactions Involving α,β-Unsaturated Keto-Esters.



The Nakata laboratory, which has reported the transformations shown in Panel B (Scheme V-2), has been at the forefront with the synthesis of methyl sarcophytoate (**5001**). The group has achieved the total syntheses of both of the proposed biosynthetic coupling partners **5002** and diol-protected **5003** (**5013**, Scheme V-3).[120] Once these macromolecules were in hand, Nakata and co-workers studied the corresponding Diels-

118. Nantz, M. H.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 5298–5299.
119. (a) Nakata, M.; Yasuda, M.; Suzuki, S.; Ohba, S. *Synlett.* **1994**, 71–74.
120. Ichige, T.; Okano, Y.; Kanoh, N.; Nakata, M. *J. Am. Chem. Soc.* **2007**, *129*, 9862–9863.

Scheme V-3. Nakata's Synthesis of Methyl Sarcophytoate (**5001**).

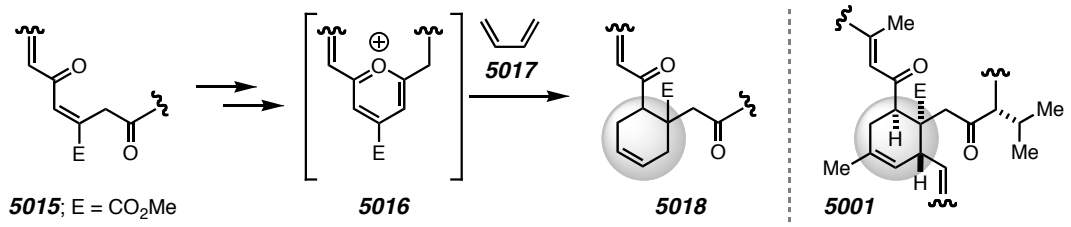


Alder reaction, and reported 22% isolated yield of **5014** in toluene at 100 °C. They also observed approximately the same amount of the C-4 alkene isomer of **5014**.

We have envisioned utilizing a specific set of functional groups (in particular for the diketone partner **5002**, or a simpler version), with which we will have the opportunity to perform a related Diels-Alder reaction in much milder conditions than reported ones. A satisfactory result will then help us better understand the biosynthesis of **5001** and its analogues. In addition, it will further motivate us to explore more transformations that can be performed without the need of an enzymatic action.

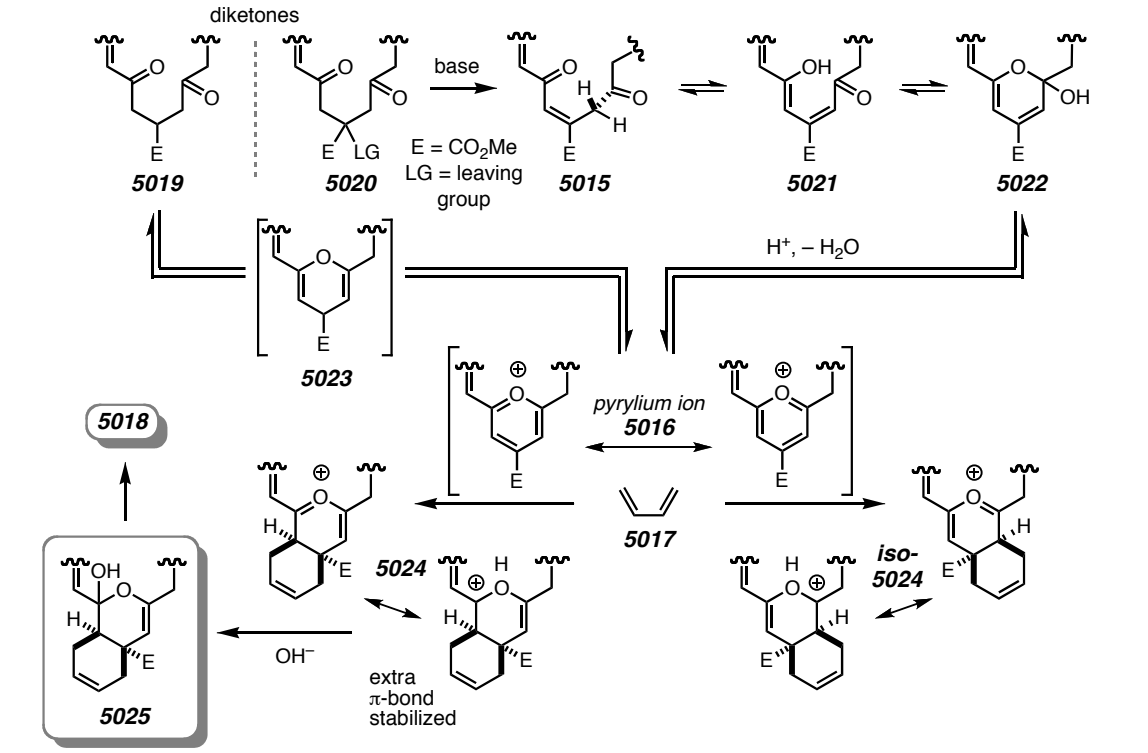
We have proposed that a diketoenoate like **5015** (Scheme V-4) may react spontaneously with a diene [e.g., *cis*-1,3-butadiene (**5017**) being the simplest model diene] at ambient temperature through a pyrylium ion intermediate **5016**. This will result in formation of the cyclohexene ring with the proper carbon connectivity and, due to the inherent electronic properties of the reactive intermediate **5018**, the desired regio-selectivity.

Scheme V-4. Overview of Our Proposed Diels-Alder Reaction Forming the Cyclohexene Core of **5001**.



We have planned to study whether the reaction presented in Scheme VI-4 can occur spontaneously, in a physiological environment (i.e. pH near neutrality, polar solvent, and ambient temperature), and without the aid of any specific enzyme, in this case a Diels-Alderase. Therefore, we focused on testing our hypothesis using the model compounds **5015** (mimicking the southern portion of **5002**) and proper dienes. More specifically, by taking advantage of the diketone functionality, we expect that **5020** will undergo a keto-enol tautomerization and subsequent protonation-dehydration processes to generate a reactive dienophilic pyrylium intermediate **5016** (Scheme V-5). This will eventually react with **5017** to give the cyclic methyl esters **5024** and its regioisomer, ***iso*-5024**. We expect that **5024** is a thermodynamically more favored Diels-Alder adduct than ***iso*-5013**, because the resonance contributor of the former has an extra stabilization through π-electron donation on oxo-carbinium carbon. Alternatively, the key pyrylium species can be generated from a diketone like **5019** via an oxidative dehydration process (Scheme V-5).

Scheme V-5. Mechanistic Rationale for the Formation of The Pyrylium Intermediate **5016**.

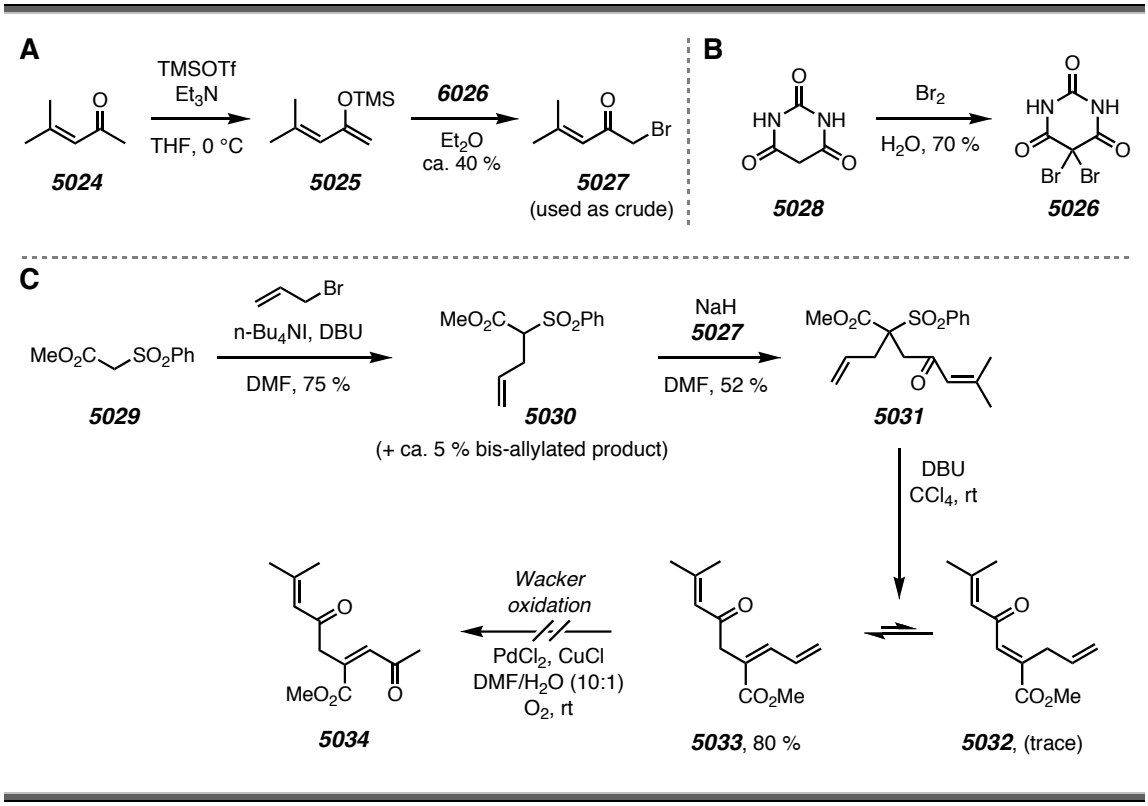


V-B. Results and Discussion

We explored the synthesis of a diketone like **5020** starting from commercially available mesityl oxide (**5024**, Panel A in Scheme V-6) and the sulfonyl acetate **5028** (Panel C). Isopropylene moiety existing in the diketone **5020** (cf. Scheme V-5) was envisioned to come from **5024**.

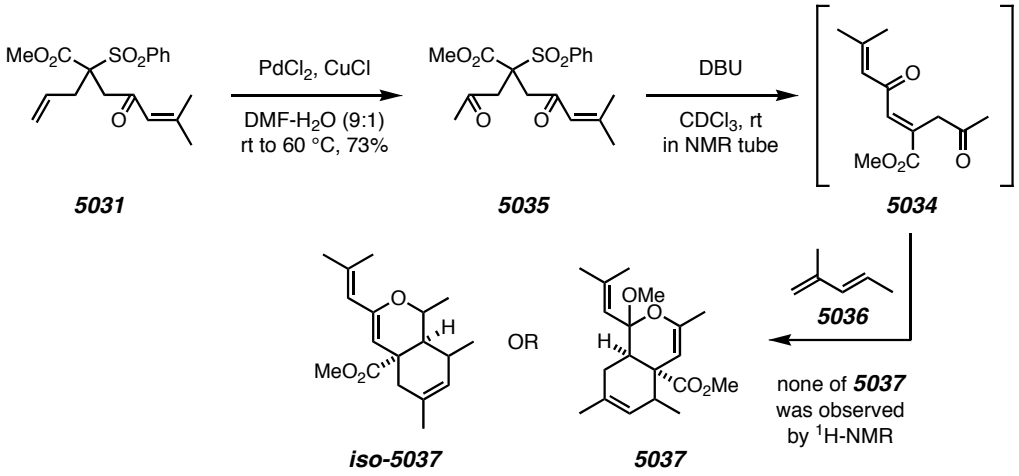
We envisioned converting mesityl oxide (**5024**) to its α-bromoketone analog **5027** to facilitate a soft carbanion displacement with the deprotonated sulfonyl acetate (**5030**). However, α-bromination on **5024** (using Br_2 or NBS) was difficult, in particular, non-selective. In many experiments, we observed the formation of poly-brominated products.

Scheme V-6. Synthesis of a Proposed Pyrylium Intermediate **5034**.



Gladly, bromination of the silyloxidiene **5025**, which was generated from **5024** with TMSOTf/Et_3N,[121] was isolated in good yield using a mild brominating agent, namely bromo barbituric acid (**5026**[122a], Panel B).[122b] We prepared this reagent from barbituric acid (**5028**) using liquid bromine in water. Wacker oxidation is the key feature to establish the required second ketone functionality (Scheme V-6). However, the oxidation caused the formation of an aldehyde by-product along with the decomposition of the starting triene. We could isolate the diketone **5035** was efficiently when we switched the order of oxidation-elimination steps (subjecting **5031** to the Wacker oxidation first, Scheme V-7. This molecule would serve as the pyrylium precursor after a proposed base promoted elimination.

Scheme V-7. An Alternative Strategy to Access a Pyrylium Precursor (**5035**).

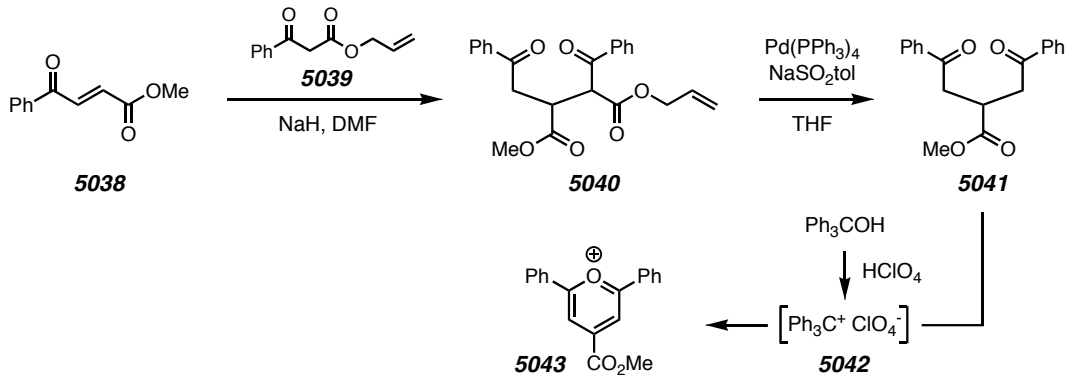


We succeeded in generating a pyrylium species when Dawen Niu (at the time, a third year graduate student in the Hoye group) came on board and explored different strategies. He synthesized the diketo-diester **5040** by a conjugate addition of the keto-allyl ester **5039** to the starting methyl ester **5038** under sodium hydride conditions

121. Jung, M. E.; Nishimura, N.; Novack, A. R. *J. Am. Chem. Soc.* **2005**, *127*, 11206–11207.
122. (a) Grundke, G.; Keese, W.; Rimpler, M. *Chem. Ber.* **1985**, *118*, 4288–4291. (b) Performing a reported procedure where Br_2 was used on **5025** led to the formation of complex reaction mixture.[122c] (c) Sibi, M. P.; Zhang, R.u; Manyem, S. *J. Am. Chem. Soc.* **2003**, *125*, 9306–9307

(Scheme V-6). A Pd(0) initiated one pot deallylation-decarboxylation step provided the pyrylium precursor **5041**. An oxidative dehydration reaction of **5041** using triphenyl methyl perchlorate (**5042**), which I prepared from triphenyl methane, provided the isolable chlorate salt of the pyrylium species **5041**.

Scheme V-6. Isolation of the Dihenyl Pyrylium **5043**.



V-C. Conclusion

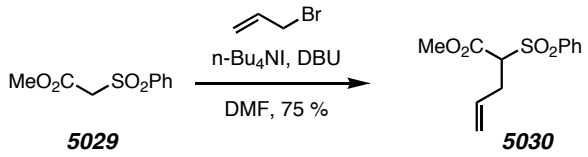
In conclusion, we studied the synthesis of diketone compounds **5019** and **5020** to test our hypothesis for a spontaneous DA reaction that accounts for the cyclohexene core of methyl sarcophytoate (**5001**). It is conceivable that a keto-enol tautomerization leading to a dienol like **5021** can dehydrate (under reduced pH), and undergo a DA reaction through a pyrylium dienophile. A potential hydroxylation (under elevated pH) can provide the **5018** carbon skeleton.

Our efforts to generate a pyrylium intermediate have reached to a promising level where we can now isolate a relatively stable diphenyl pyrylium species, **5043**. From here on, this project requires a careful search of dienes and test of reaction conditions to observe any significant amount of Diels-Alder adducts.

V-D. Experimental Section

All reactions were performed under a dry nitrogen atmosphere or argon atmosphere, unless otherwise noted. All glassware was flame- and/or oven-dried before use. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were dried through Al_2O_3 columns; hexanes (Hex) and ethyl acetate (EtOAc) were used as received (reagent grade). Flash column purifications were performed using 40-63 μm silica gel. All NMR spectra were determined in $CDCl_3$. ^1H NMR spectra were acquired on a Varian VI-500 (500 MHz ^1H). Chemical shifts (δ) for ^1H NMR spectra are referenced to TMS at δ = 0.00 ppm, ^{13}C NMR spectra are referenced to $CDCl_3$ at δ = 77.0 ppm. The following abbreviations are used to describe NMR signals: s (singlet), and d (doublet). Coupling constants (*J*) are reported in Hz.

Methyl 2-(phenylsulfonyl)pent-4-enoate (5030).



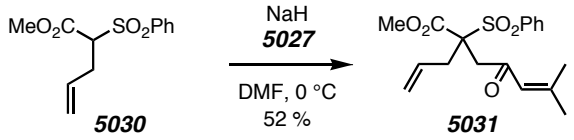
5029 ***5030***

To a DMF solution of **5029** (0.2 M, 1 equiv), DBU (1 equiv), and *n*-Bu_4NI (0.15 equiv) was slowly added allyl bromide via a syringe pump over 1 h at room temperature. The reaction mixture was stirred at the same temperature for 16 h, and quenched by addition of water. The organics were extracted by EtOAc, washed with brine, and dried over $NaSO_4$. The combined organic layers were concentrated under reduced pressure to give the desired ester **5030** as a mixture with ca. 5 % bis allylated ester by-product. The crude material was used in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.71 (ddd, *J* = 7.5, 1.5, 1.5 Hz, 1H), 7.60 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 2H), 5.66 (dddd, *J* = 17.0, 10.0, 7.0, 6.5 Hz, 1H), 5.13 (dddd, *J* = 17.0, 1.5, 1.5, 1.5 Hz, 1H), 5.11 (dddd, *J* = 10.5, 1.5, 1.5, 1.5 Hz, 1H), 4.04 (dd, *J* = 11.5, 4.0 Hz, 1H), 3.67 (s, 3H), 2.79 (ddddd, *J* = 14.0, 10.5, 4.0, 1.5, 1.5 Hz, 1H), and 2.69 (ddddd, *J* = 14.0, 11.5, 7.5, 1.5, 1.5 Hz, 1H).

.

Methyl 2-allyl-6-methyl-4-oxo-2-(phenylsulfonyl)hept-5-enoate (5031).



To a suspension of NaH in DMF (0.3 M) at 0 °C was added dropwise a DMF solution of **5030** (1.0 M). After being stirred for 30 min, the reaction mixture was transferred via slow addition by a syringe into another reaction flask containing a DMF solution of **5027** (1.0 M) at °C. The resulting mixture was stirred at the same temperature for 6 h and quenched with water. The organics were extracted by EtOAc, washed with brine, and dried over $NaSO_4$. The combined organic layers were concentrated under reduced pressure to give the crude material. A silica gel purification (2:1, Hex:EtOAc) provided the title compound **5031**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.69 (ddd, *J* = 7.5, 1.5, 1.5 Hz, 1H), 7.57 (ddd, *J* = 8.0, 7.5, 1.5 Hz, 2H), 6.02 (dd, *J* = 1.5, 1.5 Hz, 1H), 6.00 (dddd, *J* = 19.0, 9.0, 7.0, 6.0 Hz, 1H), 5.10 (dddd, *J* = 17.5, 1.5, 1.5, 1.5 Hz, 1H), 5.05 (dddd, *J* = 10.5, 1.5, 1.5, 1.5 Hz, 1H), 3.64 (s, 3H), 3.47 (dd, *J* = 17.0, 1.5 Hz, 1H), 3.19 (d, *J* = 17.0 Hz, 1H), 3.04 (dddd, *J* = 14.0, 7.5, 1.5, 1.5 Hz, 1H), 3.00 (dddd, *J* = 14.0, 4.0, 1.5, 1.5 Hz, 1H), 2.07 (s, 3H), and 1,89 (s, 3H).

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4. From here on, "ORIA" will be used to refer the molecules depicted in Figure I-1, even though the open-ring indole alkaloids encompass a significantly bigger group of compounds.
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