Progress Toward the Total Synthesis of the Lomaiviticins and a Biomimetic Unified Strategy for the Synthesis of 7-Membered Ring-Containing Lycopodium Alkaloids

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Progress Toward the Total Synthesis of the Lomaiviticins and a Biomimetic Unified Strategy for the Synthesis of 7-Membered Ring-Containing *Lycopodium* Alkaloids

A dissertation presented
by
Amy S. Lee
to
The Department of Chemistry and Chemical Biology
in partial fulfillment of the requirements
for the degree of
Doctor of Philosophy
in the subject of
Chemistry

Harvard University
Cambridge, Massachusetts
July, 2014
Progress Toward the Total Synthesis of the Lomaiviticins and a Biomimetic Unified Strategy
for the Synthesis of 7-Membered Ring-Containing Lycopodium Alkaloids

Abstract

Lomaivitin A (1) and B (2) are natural products with remarkably complex C$_2$-symmetric structures and potent antiproliferative properties. Achieving total syntheses of 1 and 2 has been a long-standing project in the Shair group and part one of this thesis describes our first successful synthesis of the C4-epi-lomaivitin A and B core structures. A key stereoselective oxidative enolate dimerization of an oxanorbornanone system was employed to establish the highly hindered C2–C2' bond. Crucial to our completion of the lomaivitin core structures was the discovery of subtle yet far-reaching stereoelectronic effects imparted by the C4/C4'-stereocenters.

The Lycopodium alkaloids are a family of complex polycyclic alkaloid natural products that have long served as popular targets for developing synthetic chemistry. More recently, select members have been reported to exhibit neurological effects. Part two of this thesis presents the development of a biomimetic, unified strategy for the synthesis of 7-membered ring-containing Lycopodium alkaloids and its successful application toward the first total syntheses of the proposed structure of (−)-himeradine A (38), (−)-lycopecurine (39), and (−)-dehydrolycopecurine (199), and the syntheses of (+)-lyconadin A (31) and (−)-lyconadin B (32). A biosynthetically inspired one-pot cascade reaction sequence was developed to construct the strained polycyclic core structure shared amongst these alkaloids. Additionally, the syntheses of 38, 39, and 199 featured a biomimetic intramolecular Mannich reaction to furnish the tetracyclic ring system. The successful application of our unifying strategy toward the synthesis of a diverse set of alkaloids lends support to our biosynthetic hypothesis that 7-membered ring-containing Lycopodium alkaloids arise from a
common precursor. Our synthetic approach can potentially provide access to all such natural products.
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# List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Å</td>
<td>ångström</td>
</tr>
<tr>
<td>A(1,3)</td>
<td>1,3-allylic strain</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyloxycarbonyl</td>
</tr>
<tr>
<td>BOM</td>
<td>benzyloxymethyl</td>
</tr>
<tr>
<td>brsm</td>
<td>based on recovered starting material</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>c</td>
<td>concentration (g/100 mL)</td>
</tr>
<tr>
<td>°C</td>
<td>degree celsius</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic</td>
</tr>
<tr>
<td>Cbz</td>
<td>carbobenzyloxy</td>
</tr>
<tr>
<td>cis</td>
<td>L., on the same side</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>Cp</td>
<td>cyclopentadienyl</td>
</tr>
<tr>
<td>CSA</td>
<td>camphorsulfonic acid</td>
</tr>
<tr>
<td>D</td>
<td>dimensional</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
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<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-p-benzoquinone</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminum hydride</td>
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<tr>
<td>δ</td>
<td>chemical shift</td>
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<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
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<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
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</table>
$E$  
*Ger.*, entgegen

$ee$  
enantiomeric excess

$endo$  
*Gr.*, within

$ent$  
enantiomer

$Eq.$  
equation

$equiv$  
equivalent

$ESI$  
electrospray ionization

$Et$  
etyl

$exo$  
*Gk.*, external

$FABMS$  
fast atom bombardment mass spectrometry

$FTIR$  
Fourier transform infrared

$g$  
gram

$Grubbs II$  
Grubbs second-generation catalyst

$h$  
hour

$HMBC$  
heteronuclear multiple bond correlation

$HMDS$  
hexamethyldisilazane

$HMPA$  
hexamethylphosphoramidine

$HMOC$  
heteronuclear multiple quantum coherence

$HPLC$  
High-performance liquid chromatography

$HRMS$  
high-resolution mass spectrometry

$HSQC$  
heteronuclear single quantum coherence

$Hz$  
hertz

$Imid$  
imidazole

$IR$  
infrared

$J$  
coupling constant (in Hz)

$KHMDS$  
potassium hexamethyldisilazide

$LDA$  
lithium disopropylamide

$LiHMDS$  
lithium hexamethyldisilazide
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<td>lithium 2,2,6,6-tetramethylpiperidide</td>
</tr>
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<td>2,6-lut</td>
<td>2,6-lutidine</td>
</tr>
<tr>
<td>M</td>
<td>molar (mols/liter)</td>
</tr>
<tr>
<td>µ</td>
<td>micro</td>
</tr>
<tr>
<td>µm</td>
<td>micron</td>
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<td>m-CPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
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<td>MOM</td>
<td>methoxymethylether</td>
</tr>
<tr>
<td>MS</td>
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</tr>
<tr>
<td>MsCl</td>
<td>methanesulfonyl chloride</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NIS</td>
<td>N-iodosuccinimide</td>
</tr>
<tr>
<td>NMO</td>
<td>4-methylmorpholine N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>NOESY</td>
<td>nuclear Overhauser effect spectroscopy</td>
</tr>
<tr>
<td>Ns</td>
<td>2-nitrobenzenesulfonyl</td>
</tr>
<tr>
<td>NsCl</td>
<td>2-nitrobenzenesulfonyl chloride</td>
</tr>
<tr>
<td>Ox.</td>
<td>oxidation</td>
</tr>
<tr>
<td>OTf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>P</td>
<td>protecting group</td>
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pent  pentane
pH    hydrogen ion concentration
Ph    phenyl
Pht   phthalimide
PIFA  [bis(trifluoroacetoxy)iodo]benzene
Piv   pivaloyl
pKa   acid dissociation constant
ppm   parts per million
PPTS  pyridinium p-toluenesulfonic acid
"Pr   n-propyl
PS    polymer supported
PTLC  preparatory thin-layer chromatography
Py    pyridine
R     general substituent
R    rectus (Cahn–Ingold–Prelog system)
Rf    retention factor
ROESY rotating frame nuclear Overhauser effect spectroscopy
RT    room temperature
RXN   reaction
S     sinister (Cahn–Ingold–Prelog system)
sec   seconds
taut. tautomerization
TASF(Et) tris(diethylamino)sulfonyl trimethylsilylfluorosilicate
TBAF  tetrabutylammonium fluoride
TBHP  tert-butyl hydroperoxide
TBS   tert-butyl(dimethyl)silyl
TES   triethylsilyl
Tf    trifluoromethanesulfonyl
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<tr>
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<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TFE</td>
<td>2,2,2-trifluoroethanol</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin-layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N',N'-tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMP</td>
<td>2,2,6,6-tetramethylpiperidine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TMSE</td>
<td>2-trimethylsilylethyl</td>
</tr>
<tr>
<td>TOCSY</td>
<td>total correlation spectroscopy</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>trans</td>
<td>L., across</td>
</tr>
<tr>
<td>trig</td>
<td>trigonal</td>
</tr>
<tr>
<td>TsCl</td>
<td>p-toluenesulfonyl chloride</td>
</tr>
<tr>
<td>TsOH</td>
<td>p-toluenesulfonic acid</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>vis</td>
<td>visible</td>
</tr>
<tr>
<td>X</td>
<td>general substituent</td>
</tr>
<tr>
<td>Z</td>
<td>Ger., zusammen</td>
</tr>
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I. Progress Toward the Total Synthesis of Lomaiviticin A and B

Chapter 1

Introduction to Lomaiviticin A and B
Introduction

The lomaiviticins comprise a family of type-II polyketide natural products with remarkable $C_2$-symmetric structures (1 and 2, Figure 1.1). The lomaiviticins were first isolated by He and coworkers in 2001 \(^1\) from a strain of actinomycetes originally classified as *Micromonospora lomaivitiensis* (reclassified as *Salinispora pacifica*), \(^2\) and exhibit an array of biological activity. Lomaiviticin A (1) is potently cytotoxic toward 24 human cancer cell lines with IC\(_{50}\) values ranging from 0.007 to 72 nM. Furthermore, both 1 and lomaiviticin B (2) are antibiotics against Gram-positive bacteria, including *Staphylococcus aureus* and *Enterococcus faecium*.

![Lomaiviticin A (1) and B (2)](image)

**Figure 1.1.** Lomaiviticin A (1) and B (2).

Elucidating the biological mechanism of action of the lomaiviticins (1 and 2) has been an area of active research. In the original isolation report, He and coworkers discovered that lomaiviticin A (1) cleaves double-stranded DNA (dsDNA) in vitro under reductive conditions; the details of these experiments have not been published. The biological activity of the lomaiviticins is postulated to arise from the diazobenzofluorene system, in analogy to the kinamycins \(^2\) (Figure 1.2), which are

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closely related monomeric natural products. The kinamycins also display anticancer properties; (−)-kinamycin C is cytotoxic against the NCI-60 cell line panel\textsuperscript{3} with an average GI\textsubscript{50} = 340 nM.

Melander and coworkers have demonstrated that the kinamycins cleave dsDNA in the presence of a reducing cofactor, such as glutathione (GSH),\textsuperscript{4} at relevant intracellular concentrations. Two possible mechanisms for kinamycin-mediated dsDNA cleavage are proposed (Figure 1.3). First, an initial 2e\textsuperscript{−} reduction of kinamycin leads to the corresponding hydroquinone, such as 3 or 4. In the first proposed mechanism, subsequent expulsion of nitrogen may then afford the reactive ortho-quinone methide 5, which can alkylate DNA and induce subsequent DNA cleavage. Alternatively, an exogenous nucleophile could add to the terminal nitrogen of the electrophilic diazo group of 3, forming adduct 6, which could then undergo C–N bond homolysis to form sp\textsuperscript{2}-radical 7, leading to DNA damage. The lack of sequence specificity in the observed dsDNA cleavage products supports the latter radical-based mechanism.

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More recently,\(^5\) Herzon and coworkers have demonstrated that lomaiviticin A (1) induces dsDNA breaks in the presence of dithiothreitol (DTT) in a plasmid cleavage assay. Labelling studies seemed to suggest that DNA cleavage occurred via a radical pathway, supporting the formation of carbon-centered radical species 7. The anti-proliferative properties of the lomaiviticins are believed to be due to an analogous biological mechanism of action involving the diazobenzofluorene system (Figure 1.4). Vinyl radical species 9 could lead to DNA damage and the formation of ortho-quinone methide 10. Next, expulsion of the aminosugar residues at C4/C4’ would generate the corresponding vinylogous ortho-quinone methide intermediate, whereupon DNA could act as a nucleophile and add to the C4/C4’-positions to afford alkylated species 11. However, despite structural similarities with the kinamycins, the lomaiviticins exhibit enhanced cytotoxicity, which can likely be attributed to other structural elements. This includes the C\(_2\)-symmetric structure and the sugar residues, which may potentially serve as recognition elements for bringing the lomaiviticins to their biological target. In order to elucidate the biological mechanism of action, a synthesis of the lomaiviticins is necessary due to the low abundance of natural sources.

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Figure 1.4. Proposed biological mechanism of action for the lomaiviticins.

The biosynthesis of the kinamycins has been extensively studied and the kinamycin carbon skeleton has been demonstrated to be entirely polyketide-derived (10 equivalents of acetylcoenzyme A). Due to structural similarities with the kinamycins, the biosynthesis of the lomaiviticins is proposed to occur via a similar pathway, with key additional steps including two phenolic oxidations (Figure 1.5). An oxidation of the A-ring phenol in the kinamycins to the corresponding hydroquinone is required. Furthermore, a phenolic oxidative coupling is likely involved in the key dimerization.

---

reaction. Subsequently, the lomaiviticin biosynthetic pathway could then follow the biosynthesis of the kinamycins, concluding with glycosylations of the C4/C4'- and C3/C3'-hydroxyl groups.

![Proposed phenolic oxidative dimerization during the biosynthesis of the lomaiviticins.](image)

**Figure 1.5.** Proposed phenolic oxidative dimerization during the biosynthesis of the lomaiviticins.

---


8 Prekinamycin 12 is an intermediate identified in the biosynthetic pathway of the kinamycins.
First Total Synthesis and Selected Synthetic Studies of the Lomaiviticin Aglycon

The lomaiviticin family of natural products have long attracted synthetic interest due to their remarkable $C_2$-symmetric structures and complex architecture. The structural complexity of 1 and 2 poses several synthetic challenges (Figure 1.1). The highly oxidized carbon skeleton includes up to four 2-deoxyglycosides, and the central C2–C2' bond links two densely functionalized halves to generate up to eight contiguous stereocenters. Each monomeric half possesses an unusual diazofluorene system, a naphthazarin, and a $\beta$-alkoxyenone subunit.

Arguably, the stereoselective construction of the key C2–C2' bond presents the most formidable obstacle in achieving a synthesis of the lomaiviticins (Figure 1.6). Constructing the C2–C2' bond via a dimerization strategy is complicated by two critical challenges: (1) a high potential for $\beta$-elimination of the C3-alkoxy group by a C1–C2 enolate and (2) difficulty in achieving stereoselective formation of the C2/C2'-stereocenters.

Figure 1.6. Potential problems for an oxidative dimerization strategy.

Altogether, these features render the lomaiviticins challenging synthetic targets. Indeed, despite efforts by various groups, only one synthesis of the aglycon 35 has been accomplished to

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date\textsuperscript{10} and a total synthesis of the natural product has yet to be achieved. Selected synthetic studies toward the lomaiviticin aglycon, including the first synthesis, will be discussed.

The first approach to the core structures of lomaiviticin A (1) and B (2) utilizing a bridged tricyclic scaffold to control the stereochemistry of the model system by Nicolaou and coworkers will be discussed (Scheme 1.1).\textsuperscript{9} It was envisioned that core structures 16 or 17 could arise from tricycle 18, where X would serve as a tethering group to provide a conformationally locked system that could subsequently be converted to the corresponding 1,4-dicarbonyl function (17). Due to the locked framework in 1,4-dicarbonyl 19, organometallic double addition to the carbonyl groups should occur stereoselectively. 19 could arise from bis(cyclohexenone) 20.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme1}
\caption{Nicolaou’s retrosynthetic analysis of the lomaiviticin core structure featuring a bridged tricyclic scaffold to control the stereoselective synthesis of the model system (16).}
\end{figure}

The synthesis commenced with the conjugate addition of dimethyl malonate to bisenone 20, affording the double Michael-addition product 21 as a single diastereomer (Scheme 1.2). Exposure of 21 to ethyl cerium reagent generated in situ provided adduct 23 via proposed intermediate lactone 22. 23 was converted to ketone 24 in 7 steps in 68\% overall yield. Double $\alpha$-oxygenation of 24 upon treatment with KHMDS and P(OEt)$_3$ yielded $C_2$-symmetric ketone 25 as a single diastereomer. Reduction of the ketone in 25 with LiAlH$_4$ afforded triol 26. Finally, hydrogenolysis of the BOM ethers furnished pentaol 27.

Exposure of triol 26 to Pb(OAc)$_4$ resulted in the formation of tetracyclic acetal 28, which underwent reduction upon treatment with LiBH$_4$ and subsequent oxidative cleavage with Pb(OAc)$_4$ to afford hemiketal 29 as a 3:1 mixture of diastereomers (Scheme 1.3). Oxidation of the major diastereomer with TPAP and NMO then yielded the model core system of lomaiviticin A (30).

The synthesis of the lomaiviticin B core model system (Scheme 1.4) was accomplished from intermediate 27 by initial exposure of 27 to Pb(OAc)$_4$ to furnish formate 33 via: (1) cleavage of the cis-1,2-diol to afford keto-aldehyde 31 and (2) oxidative cleavage of intermediate hemiacetal 32. Finally, cleavage of the formate ester in 33 in the presence of methanolic ammonia provided the desired lomaiviticin B core 34. In conclusion, Nicolaou and coworkers achieved the first stereoselective synthesis of the lomaiviticin A and B core systems using a bridged tricyclic scaffold strategy.
Scheme 1.4. Synthesis of the model core system 34 of lomaivitcin B (2).

In 2011, Herzon and coworkers accomplished the first synthesis of the lomaivitcin aglycon (35, Scheme 1.5). Remarkably, an efficient enantioselective synthesis was realized in 13 steps from commercial starting material. Despite potential challenges associated with a synthetic strategy relying on late-stage dimerization of a monomer resembling kinamycin, including β-elimination of the C3-hydroxy or alkoxy group and uncertainty regarding the stereochemical outcome, a late-stage oxidative coupling was pursued.

Scheme 1.5. Herzon’s retrosynthesis of the lomaivitcin aglycon 35 featuring a late-stage oxidative dimerization to establish the key C2–C2’ bond.

A 1:1 diastereomeric mixture of mesitylaldehyde acetals 37 was synthesized in five steps from 3-ethylphenol (Scheme 1.6). 1,4-Conjugate addition of trimethylsilylmethylmagnesium chloride to enone 37 in the presence of Cul, followed by enolate trapping with TMSCl and subsequent Saegusa oxidation, afforded enone 38. 38 and naphthoquinone 39 were efficiently coupled together upon treatment with TASF(Et) to furnish tricycle 40. Heck cyclization mediated by Pd(OAc)₂ in the presence of polymer-supported (PS) PPh₃ provided cyclized product 41. Diazo transfer with TfN₃ then afforded diazofluorenes 42 and 43, which were readily separable at this stage. Finally, formation of silyl enol ether 44 from ketone 43 occurred readily, yielding the dimerization substrate.
An extensive screen of oxidants was next conducted to effect the oxidative dimerization of either 43 or 44 (Scheme 1.7). It was eventually discovered that Mn(hfacac)$_3$ was capable of accomplishing the oxidative coupling of silyl enol ether 44, albeit in low yield (26% desired diastereomer) and diastereoselectivity (~2:1 dr).

**Scheme 1.6.** Synthesis of diazofluorene dimerization substrate 44.

Finally, deprotection of 45 occurred upon exposure to TFA and TBHP to afford the desired lomaiviticin B aglycon 47 after purification. Prior to silica gel preparative thin-layer chromatography, the initial product isolated from the deprotection reaction exists in the form of the open-chain ketone isomer lomaiviticin A (see 35) aglycon, which could also be readily converted to 47 upon standing in MeOH. In conclusion, Herzon and coworkes have accomplished the first synthesis of the lomaiviticin aglycon by utilizing a late-stage oxidative silyl enol ether dimerization strategy.
Scheme 1.7. Completed synthesis of the lomaiviticin aglycon 47.

To summarize this chapter, a brief introduction and background for the lomaiviticin family of natural products was presented. Two selected key syntheses, Nicolaou’s synthesis of the model core systems of lomaiviticin A and B and Herzon’s enantioselective synthesis of the lomaiviticin aglycon, were discussed.
I. Progress Toward the Total Synthesis of Lomaiviticin A and B

Chapter 2

Progress Toward the Total Synthesis of Lomaiviticin A and B
Introduction

Achieving a synthesis of lomaiviticin A (1) and B (2) has been a long-standing project in the Shair group.\(^{11}\) We were first attracted to the lomaiviticins not only because of their interesting biological activity, but also because of their fascinating and complex architecture. The structural composition and relative stereochemistry of the aglycon and carbohydrate residues were elucidated by extensive \(^1\)H, \(^{13}\)C, COSY, TOCSY, HMQC, HMBC, and ROESY NMR experiments, as well as IR and FTICR mass spectrometry. At the outset of the project, the absolute stereochemistry of the aglycon and the carbohydrate residues was ambiguous; however, this was subsequently determined by Herzon and coworkers in 2012.\(^2\)

Selected routes pursued by the Shair group toward the synthesis of the lomaiviticin aglycon 47 will be discussed in detail.\(^{11}\) We envisioned constructing the central C2–C2' bond in 1 and 2 via a late-stage oxidative enolate dimerization reaction\(^{12}\) in order to minimize double processing (e.g., Scheme 1.5). A variety of oxidants\(^{13}\) reported in the literature are capable of performing such an oxidative enolate dimerization to afford the corresponding 1,4-diketone product. Examples of such oxidants include CuCl\(_2\), Cu(OTf)\(_2\), Cu(2-ethylhexanoate)\(_2\), FeCl\(_3\), Fe(acac)\(_3\), ferrocenium salts, I\(_2\), hypervalent iodine, and TiCl\(_4\).

\(^{11}\) (a) More than 10 different generations of routes have been pursued. Only the most relevant routes will be discussed. (b) Krygowski, E. S. Ph.D. Thesis, Harvard University, 2008. (c) Lee, H. G. Ph.D. Thesis, Harvard University, 2012.


While the exact mechanism for oxidative enolate dimerization is not completely understood, it is generally accepted that single electron transfers are involved. Three plausible mechanisms are shown in Scheme 2.1. In the first mechanism (Eq. 1), two equivalents of enoxy radical 50, generated by single electron oxidation of the enolate 49, can combine together to form 1,4-diketone 51. In the second mechanism (Eq. 2), the electrophilic enoxy radical 50 undergoes nucleophilic attack by one enolate equivalent 49, forming ketyl radical anion 52. A subsequent single electron oxidation of 52 then affords 51. Thirdly (Eq. 3), another possibility is the involvement of a metal chelated intermediate (53). Depending on the oxidant and conditions utilized, these mechanisms may be differentially operative in individual contexts.

Scheme 2.1. Possible mechanisms for oxidative enolate dimerizations.

While there was precedence supporting our proposed oxidative enolate dimerization reaction, several critical challenges existed. Not only does the central C2–C2′ bond link two densely functionalized and sterically hindered halves, but two key concerns needed to be addressed: (1) controlling the stereoselective formation of the C2–C2′ bond and (2) preventing β-elimination of the C3- and C3′-alkoxy groups.


15 At the outset of this project, a strategy utilizing an oxidative enolate dimerization for constructing the key C2–C2′ bond in the lomaivitcins had not been reported in the literature.
A solution to both of these problems was discovered in the form of the oxanorbornanone system, or specifically, an oxygen bridge between C3 and C6 (Figure 2.1). Stereoselective formation of the C2- and C2'-stereocenters is controlled by dimerization of the endocyclic enolate 54 from the less hindered convex exo face of the oxanorbornanone. Furthermore, in oxanorbornanone system 54, β-elimination is prevented due to the nearly orthogonal orientation of the endocyclic C1–C2 enolate π-system with the antibonding σ*-orbital of the bridging C–O bond. An exocyclic enolate (C5–C4a, see 55), however, would have greater conformational flexibility and can thus achieve requisite orbital overlap for β-elimination. We planned to exploit this stereoelectronic dichotomy of the oxanorbornannone system to achieve stereoselective oxidative endocyclic enolate dimerization without β-elimination, and at a subsequent stage, conduct regioselective fragmentation of the oxygen bridge via an exocyclic enolate.

Due to the fascinating structural complexity of lomaiviticin A (1) and B (2) and their interesting biological activity, we embarked on a total synthesis of these two natural products. Specifically, we wished to address whether an oxidative oxanorbornanone enolate dimerization reaction to construct the key C2–C2′ bond could be accomplished stereoselectively and without β-elimination of the C3-alkoxy group. At the outset of our project, a synthesis of the lomaiviticin aglycon had not yet been published.

**Figure 2.1.** Reactivity of endocyclic vs. exocyclic oxanorbornanone enolates.
Previous Approaches in the Shair Group

A simple model system was devised by Dr. Evan S. Krygowski and Dr. Kerry Murphy-Benenato in order to test the feasibility of an oxidative dimerization of an oxanorbornanone enolate or silyl enol ether (Scheme 2.2).20 Gratifyingly, they discovered that treatment of silyl enol ether 57 with Ag₂O in DMSO at 100 °C afforded the desired dimerization product as a 7:1 mixture of C₂-symmetric 58 and meso 59 diastereomers.21 Both products arise from exclusive exo-exo dimerization of 57 and no β-elimination products were observed.

Scheme 2.2. Stereoselective dimerization of an oxanorbornanone model system.

A second model system was synthesized in order to study the β-elimination of the oxygen bridge via an exocyclic enolate (Scheme 2.3). Surprisingly, exposure of oxanorbornanone 60 to K₂CO₃ in MeOH at 0 °C not only resulted in β-elimination of the oxygen bridge, but also displacement of the phenylsulfone group with methoxide (vide infra).22

Scheme 2.3. Successful β-elimination of the oxygen bridge and displacement of the phenylsulfone.

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21 A diastereomeric mixture of products was obtained because 57 was not a single enantiomer.

22 We originally hypothesized that 61 resulted from initial β-elimination of the phenylsulfone group, followed by 1,4-conjugate addition of methoxide and generation of the corresponding exocyclic enolate. β-Elimination of the oxygen bridge from this enolate intermediate would then furnish 61. This mechanism was subsequently revised.
In summary, we demonstrated that (1) an oxanorbornanone system can be dimerized stereoselectively and (2) subsequent β-elimination of the oxygen bridge via an exocyclic enolate can be achieved with displacement of the phenylsulfone group by a suitable nucleophile. With the success of these two model systems in hand, we embarked on a synthesis of the lomaiviticin aglycon. Initial efforts were focused on synthesizing the central CD/C'D'-ring system, which we believed would allow us to study our key strategy in detail and could potentially be elaborated to the full carbon skeleton. However, our ultimate goal was to perform a late-stage oxidative enolate dimerization of a tetracyclic precursor in order to minimize double processing.

To this end, oxanorbornanone tricycle 62 was synthesized\(^\text{20}\) and our key oxidative enolate dimerization reaction was investigated (Scheme 2.4). Unfortunately, the conditions utilized in our model system (Ag\(_2\)O, DMSO, 100 °C) did not translate to the trimethylsilyl enol ether derived from 62.\(^\text{23}\) Other oxidants, including Cu(OTf)\(_2\) and CAN did not afford any desired dimerization product. We next turned our attention to the oxidative dimerization of the enolate generated from 62.

Scheme 2.4. Synthesis of the lomaiviticin core in the form of a stable cyclic hydrate.

\(^{23}\) In all cases the TMS group was compromised and starting ketone 62 was recovered.
A screen\textsuperscript{11b} of oxidants (CuCl\textsubscript{2}, Cu(OTf)\textsubscript{2}, Cu(2-ethylhexanoate)\textsubscript{2}, FeCl\textsubscript{3}, Fe(acac)\textsubscript{3}, AgCl, PhI(OAc)\textsubscript{2}, and I\textsubscript{2}) for the dimerization of the enolate derived from 62 was next conducted. In all cases, no desired dimer 63 was obtained. One common problem of the aforementioned oxidants is that they all require temperatures of 0 °C or higher for enolate oxidation to occur. Unfortunately, however, the enolate generated from 62 was not stable above –20 °C and would undergo undesired β-elimination of the oxygen bridge. We rationalized that an oxidant capable of conducting single electron transfer at temperatures below –20 °C was necessary in order to achieve successful dimerization.

We next turned our attention to [Cp\textsubscript{2}Fe]PF\textsubscript{6}, a powerful outer-sphere, single-electron oxidant. There was precedence\textsuperscript{24} in the literature that [Cp\textsubscript{2}Fe]PF\textsubscript{6} was capable of oxidizing enolates at –78 °C. Gratifyingly, exposure of the lithium enolate of 62, generated from deprotonation by LiHMDS, to [Cp\textsubscript{2}Fe]PF\textsubscript{6} in the presence of HMPA at –78 °C, followed by subsequent warming to –20 °C and stirring for an additional 20 h, yielded the desired dimerization product 63 as a single diastereomer in 45–51% yield. Unfortunately, dimer 63 was only moderately stable to silica gel chromatography,\textsuperscript{25} which likely accounted for the diminished yield of 63.

With dimer 63 in hand, we next focused our attention on β-elimination of the oxygen bridge. To this end, global silyl deprotection, followed by DMP oxidation of the corresponding secondary carbinols, afforded cyclic hydrate 64, where a single molecule of H\textsubscript{2}O had added to the C1- and C1'-ketones. We hypothesized that a possible explanation for cyclic hydrate formation is the relief of ring strain introduced into the system by the newly formed sp\textsuperscript{2} carbon after DMP oxidation. Another possible rationale is that the C5- and C5'-ketones may inductively make the C1- and C1'-ketones


\textsuperscript{25} Re-exposure of pure isolated dimer product 63 to a silica gel column resulted in loss of one-third of the material.
more electron deficient, thus promoting cyclic hydrate formation. Exposure of 64 to K$_2$CO$_3$ in MeOH at 0 °C furnished bisenone 65 in good yield (85%). Re-exposure of 65 to K$_2$CO$_3$ in MeOH at room temperature resulted in displacement of the allylic phenylsulfone groups with methoxide with inversion of configuration, albeit in low yield (17%), to provide bisenone 66. Both transformations could be combined into a single one-pot operation (K$_2$CO$_3$, MeOH, 0 °C → RT) to afford 66 in 14% yield. Attempts to dehydrate 66 to the lomaiviticin B core system under acidic conditions proved unsuccessful and either resulted in recovery or decomposition of starting material.

In summary, we have demonstrated that the key C2−C2′ bond could be stereoselectively constructed via an oxidative enolate dimerization of an oxanorbornanone system without undesired β-elimination of the oxygen bridge. Specifically, we discovered that [Cp$_2$Fe]PF$_6$ promoted oxidative dimerization at sufficiently low temperatures at which oxygen bridge fragmentation did not occur. Furthermore, we were able to subsequently β-eliminate the oxygen bridge via an exocyclic enolate to reveal the lomaiviticin core system in the form of a cyclic hydrate. With the success of these discoveries in hand, we next embarked on a synthesis of the full carbon skeleton of the lomaiviticin aglycon.

In order to minimize double-processing, the optimal strategy was to utilize a late-stage oxidative dimerization of a tetracyclic enolate intermediate such as 69 (Scheme 2.5). Tetracycle 70 could be prepared from enone 71 and a phthalide derivative, such as 72 or 73, via an anionic annulation reaction. Enone 71 could be synthesized from a common intermediate utilized in our original model studies.

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In work by Dr. Hong Geun Lee, enone 71\textsuperscript{28} and cyanophthalide 74 underwent efficient Kraus annulation\textsuperscript{29} to afford hydroquinone 75 in 85% yield. Ketal-protection of the C5-ketone using Noyori\textsuperscript{30} conditions, followed by allyl-protection of the hydroquinone phenols, furnished allylated product 77. Finally, cleavage of the pivaloyl group and subsequent Ley oxidation of the resulting secondary carbinol yielded dimerization precursor 78. 78 was subjected to our optimized oxidative dimerization conditions.\textsuperscript{31} Quite surprisingly, the enolate of 78 did not undergo oxidative dimerization to provide the lomaiviticin full carbon skeleton 79. Indeed, only starting material was recovered (>80%). Other permutations of oxidants and solvents were investigated but yielded no desired product.

\textsuperscript{28} The synthesis of enone 71 will not be discussed here for brevity. Please see ref. 26 for details.


\textsuperscript{31} The enolate of 78 was not stable above –60 °C and would undergo undesired oxygen bridge fragmentation.
Scheme 2.6. Attempted oxidative dimerization of tetracycle 78.

We speculated that non-bonding interactions could be disfavoring dimerization by preventing favorable approach of the two reacting partners in the transition state (Figure 2.2). In model 80, we postulated that non-bonding interactions between the C3 and C11', and C3' and C11, ethyl and allyloxy groups, respectively, may be disfavoring dimerization. In the approach depicted in 81, severe steric interactions between the C3- and C3'-ethyl groups and the C11- and C11'-allyloxy groups exist. Thus, we rationalized that a smaller C11/C11'-alkoxy group may remedy this problem. Instead of protecting the hydroquinone phenols in 76 as the allyl ethers, the corresponding methyl ether derivative was synthesized. Unfortunately, however, only trace quantities of the desired dimerization product were isolated. Predicated on these results, we believed that replacing the C11/C11'-alkoxy groups with the smallest substituent possible—a hydrogen atom—may circumvent these problems and facilitate dimerization.
Figure 2.2. Postulated steric interactions during the dimerization event.

To this end, a modified Hauser annulation\textsuperscript{32} using a sulfoxide donor (82) was employed in order to access tetracycle 83 (Scheme 2.7). Deprotonation of sulfoxide donor 82 with LiHMDS, followed by addition of enone 71, furnished tetracycle 83 in 79\% yield via: (1) initial 1,4-conjugate addition of the sulfoxide anion to the enone, (2) subsequent Claisen condensation, (3) sulfoxide syn elimination, and (4) tautomerization to the corresponding phenol. Utilizing the same sequence for the synthesis of 78, tetracycle 83 was converted to our targeted dimerization substrate 86 in four straightforward steps.

Scheme 2.7. Successful oxidative dimerization of tetracycle 86.

Gratifyingly, tetracycle 86 underwent successful dimerization utilizing our optimal oxidative enolate coupling protocol to afford dimerization product 87 in 80\% yield as a single diastereomer.

Single crystal X-ray diffraction analysis of derivative 88 (Figure 2.3), obtained from cleavage of the allyl ethers in 87, unequivocally established the structure of 88. Interestingly, the C1–C2–C2′–C1′ dihedral angle in crystal 88 is 29° and the C11-hydrogen atom and C1'-ketone oxygen (and analogously, C11'-hydrogen atom and C1-ketone oxygen) were in very close proximity, which could potentially disfavor the dimerization reaction if the C11/C11'-substituent was larger than a hydrogen atom.

![Figure 2.3](image)

**Figure 2.3.** Single crystal X-ray diffraction analysis confirmed the structure of 88.

Finally, with the desired dimerization product 87 in hand, we were ready to test the next crucial step in our strategy—fragmentation of the oxygen bridge. As expected, treatment of 87 with TfOH (Scheme 2.8) provided diketone dimer 89 in the form of a cyclic hydrate. Unfortunately, despite a wide screen of conditions by Dr. Hong Geun Lee, 89 did not undergo oxygen bridge fragmentation. Investigation of a variety of bases in protic solvents, including MeOH, EtOH, t-BuOH, and H2O, only resulted in decomposition of starting material 89. Similar results were obtained when stronger bases such as LDA, LiHMDS, and t-BuOK were used. At the time, it was believed that one possible explanation for unsuccessful oxygen bridge fragmentation of 89 was due to the base-sensitivity of the cyclic hydrate.
Protection of the cyclic hydrate hydroxyl groups as the corresponding methyl ethers afforded cyclic hydrate 91 (Scheme 2.9). Exposure of 91 to KOH in THF/H₂O did not provide the desired oxygen bridge fragmentation product, but instead diol 92, which was formed by initial β-elimination of the C4/C4'-phenylsulfone groups followed by addition of hydroxide to the resultant enone, was isolated. Resubjection of 92 to a variety of basic conditions did not result in oxygen bridge β-elimination but only in recovered starting material or decomposition under more forcing conditions. Even 1,3-diketone dimer 93, synthesized from 92 via a Swern oxidation, did not undergo oxygen bridge fragmentation.

We next turned our attention towards a reductive approach for oxygen bridge fragmentation via α-elimination from the C1/C1'-ketones (Scheme 2.10). However, instead of the desired
diketone product 94, only cyclobutanediol 96,\textsuperscript{34} the result of an intramolecular pinacol coupling between the proximal C1 and C1' ketones, was isolated. This was not surprising, since the crystal structure of 88 suggested that the dimer preferentially adopts a conformation that places the C1/C1'-ketones in close proximity to each other.

\textbf{Scheme 2.10.} Attempted reductive oxygen bridge fragmentation.

We next decided to pursue a strategy that would utilize the electron-rich nature of the AB/A'B'-naphthalene systems to facilitate oxygen bridge fragmentation (Scheme 2.11). This strategy would first involve oxidation of the B/B'-rings in 87 to the corresponding hydroquinones in 97. Electron donation from the electron-rich AB/A'B'-naphthalene systems (specifically, the C11- and C11'-phenol groups), should assist in oxygen bridge fragmentation to provide intermediate 98, which can undergo tautomerization to afford the desired product 99.

\textsuperscript{34} The pinacol product was also isolated in an analogous reaction on the model system by Dr. Evan S. Krygowski. See ref. 11b.
Scheme 2.11. Proposed oxygen bridge fragmentation via the electron-rich AB/A'B'-naphthalene systems.

Oxidation of the B/B'-rings proved to be challenging. After extensive experimentation, it was eventually discovered that substrate 101, where the C5- and C5'-carbonyl groups have been removed, could be oxidized to quinone dimer 106 (Scheme 2.12). Diketone 102 was synthesized from diol 92 via: (1) LiEt₃BH reduction of the C5- and C5'-carbonyl groups, (2) acetylation of the resulting tetraol to provide the corresponding tetra-acetate, (3) ionic reduction in the presence of Et₃SiH and TfOH, (4) cleavage of the C4- and C4'-acetate groups, and (5) Ley oxidation of the C4- and C4'-secondary carbinol groups to the corresponding ketones. Diastereoselective reduction of the C4- and C4'-ketones in 102 afforded diol 103 with the correct stereochemistry found in the natural product. As expected, hydride delivery occurred from the convex face of the molecule, *anti* to the oxygen bridge.

35 In compounds where C5 existed as a ketone, ketal, or hydrazone, the B- and B'-rings could not be oxidized to the corresponding quinone. An electron-withdrawing group at C5 and C5' is likely responsible for suppressing oxidation of the B- and B'-rings. See ref. 11c.

36 Attempted oxygen bridge fragmentation via the C4- and C4'-ketones under basic or acidic conditions proved unsuccessful.

Cleavage of the allyl ethers in 103 occurred smoothly to provide naphthol dimer 104. Surprisingly, treatment of 104 with PhI(OCOCF₃)₂, afforded the unaromatized hydroquinone tautomer 105.⁴³ Exposure of 105 to a second oxidant, DDQ, then afforded the desired quinone dimer 106. In order to test our proposed strategy for fragmentation of the oxygen bridge via the electron-rich naphthalene systems, the quinone functions in 106 must be reduced to the corresponding

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⁴³ For an example where the unaromatized hydroquinone tautomer was isolated, see: Chikashita, H.; Porco, J. A.; Stout, T. J.; Clardy, J.; Schreiber, S. L. J. Org. Chem. 1991, 56, 1692–1694.
hydroquinone. Unfortunately, quinone reduction proved to be challenging and we were never able to isolate hydroquinone 107.

At this point, Dr. Hong Geun Lee decided to no longer pursue this route due to our inability to β-eliminate the oxygen bridge. Both the model systems investigated by Dr. Evan S. Krygowski and Dr. Kerry-Murphy Benenato and the full carbon skeleton of the aglycon studied by Dr. Hong Geun Lee have provided valuable insight into designing a new route to circumvent the previously observed challenges. A summary of our previous discussion is provided below (Scheme 2.13).

Scheme 2.13. Summary of previous work in the Shair group.

To summarize, in model system 64, we demonstrated that stereoselective oxidative enolate dimerization of an oxanorbornanone system could be achieved without undesired β-elimination. Furthermore, we were able to subsequently fragment the oxygen bridge in 64 at the appropriate time. However, displacement of the C4-phenylsulfone with various oxygen nucleophiles was extremely low-yielding and the resulting product could not be converted to the lomaiviticin core from the cyclic hydrate. Unexpectedly, in our most advanced system containing the full aglycon carbon skeleton, we were unable to fragment the oxygen bridge. I attributed the unsuccessful fragmentation to the additional strain and rigidity that the AB/A'B'-naphthalenes introduce to the system. In 64, C5a and C11a are both sp³-hybridized, whereas in the case of 108 they are sp²-hybridized. The sp²-hybridization introduces more strain into an already strained and rigid system and may thus prevent attainment of the requisite orbital overlap for β-elimination of the oxygen bridge.

Predicated on the aforementioned observations, I embarked on a new route to synthesize a substrate with the correct C4- and C4'-stereochemistry in order to obviate the need for a late-stage
allylic phenylsulfone displacement. Additionally, I planned to introduce the AB/A'B'-naphthalene systems after β-elimination of the oxygen bridge because of the aforementioned discussion.
Development of a New Route to the Core of Lomaiviticin A and B

Based on the observations and results discussed in the previous section by my predecessors, I embarked on a new route to the lomaiviticin core system. My first-generation retrosynthesis of the lomaiviticin aglycon (47) is outlined in Scheme 2.14. We envisioned that the AB/A'B'-naphthalenes of 109 could be constructed from lomaiviticin B core 110 via a late-stage double annulation reaction, such as a cyclopentadienyl anion bisannulation. 110 could arise from oxanorbornanone dimer 111, where the key C2–C2' bond would be established by a stereoselective oxidative enolate dimerization of monomer 112. The oxanorbornanone system could be constructed from an intramolecular exo-selective furan Diels–Alder reaction of a suitable precursor such as furanone 114 or related derivative. 114 can be readily assembled from commercially available (S)-malic acid and furan 115.

Scheme 2.14. First-generation retrosynthesis of the lomaiviticin aglycon.

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40 For a synthesis of furan 115, see ref. 11b.
Two key differences between the new proposed route and the previous systems investigated by Dr. Evan S. Krygowski and Dr. Hong Geun Lee are: (1) a substrate with the correct C4 and C4'-stereochemistry and oxygenation (111) would be utilized, obviating the need for displacement of a C4- and C4'-phenylsulfone group and (2) the AB/A'B'-naphthalene systems would be introduced after β-elimination of the oxygen bridge due to the aforementioned challenges faced by Dr. Hong Geun Lee in his studies when C5a and C11a were sp²-hybridized.

The synthesis commenced with the formation of the dimethyl ester of commercially available (S)-malic acid (Scheme 2.15). Selective monoreduction with BH₃•SMe₂ in the presence of catalytic NaBH₄,⁴¹ followed by protection of the resultant 1,2-diol afforded acetal 116. Reduction of the methyl ester in 116 with LiBH₄, followed by formation of the corresponding iodide, occurred smoothly to yield alkyl iodide 117. Lithiation of furan 115, followed by alkylation with 117, afforded coupled product 118. DIBAL-H regioselective opening of the acetal afforded primary alcohol 119 in 46% yield (66% brsm). Attempts to oxidize primary alcohol 119 were met with surprising difficulty. Standard DMP, Swern, and Ley oxidation conditions resulted in decomposition. In all cases, the siloxy furan was most likely compromised, possibly via an intramolecular or intermolecular aldol reaction with the putative aldehyde intermediate.

**Scheme 2.15.** Synthesis of furan Diels–Alder substrate 121.

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To circumvent this problem, the TIPS ether was cleaved upon treatment with TBAF to provide the corresponding furanone alcohol, which underwent subsequent Swern oxidation to provide furanone aldehyde 120. Aldehyde 120 was then converted to (Z)-enoate 121 (19:1 Z/E), the desired Diels–Alder substrate, via the Ando variant of the Still modification of the Horner-Wadsworth-Emmons olefination with Masamune and Roush’s adapted mild conditions. With 121 in hand, we were ready to test our key intramolecular exo-selective furan Diels–Alder reaction.

We anticipated that the stereoselectivity of the exo-selective intramolecular furan Diels–Alder reaction would be controlled by the single C5-stereocenter, which enforced a conformation where 1,3-allylic strain was minimized (Scheme 2.16). The exo transition state (122), which results in cis-5,5-fusion product 123, should be favored over the endo transition state (124), which would result in highly strained trans-5,5-fusion product 125.

Scheme 2.16. Rationale for the stereoselectivity of the intramolecular furan Diels–Alder reaction.

Initial attempts to promote the Diels–Alder reaction by conventional thermal (PhMe, 50 →

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100 °C) and Lewis acidic conditions (e.g., MeAlCl$_2$) failed to provide the desired cycloadduct in synthetically useful yields (<25%). We rationalized that tautomerization of the furanone to the requisite furan may be slow and that basic conditions may therefore promote the desired transformation. Addition of DBU to promote enolization resulted in complete conversion of 121 to two new compounds (Scheme 2.17), determined to be the desired product 126 and Michael adduct 127, in a 1.2:1 ratio, respectively. Both products were each isolated as single diastereomers.

![Scheme 2.17. Formal intramolecular furan Diels–Alder reaction.](image)

These results suggested a stepwise Diels–Alder mechanism, i.e., a Michael–Michael sequence (Scheme 2.18). A stepwise “exo” mechanism (128 and 129) would lead to formation of the desired Diels–Alder product 126. A stepwise “endo” mechanism should result in initial Michael adduct intermediate 130, which cannot undergo a second Michael reaction to provide the highly strained, trans-5,5-fused endo product 125 due to poor orbital overlap, thus resulting in isolation of Michael adduct 127. Separate resubjection of pure 126 and 127 to the reaction conditions resulted in complete recovery of starting material 126 or 127, respectively, suggesting that formation of Diels–Alder product 126 and Michael adduct 127 is irreversible under the given reaction conditions. In order to drive the reaction to Diels–Alder product 126 formation and prevent isolation of Michael adduct 127, conditions under which formation of 127 was reversible were required. We hypothesized

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44 See ref. 20.

45 The stereochemistry of 127, postulated as depicted, was not verified.
that a stronger base such that the ester enolate of 127 could be regenerated may provide such a solution.

Scheme 2.18. Rationale for formation of Diels–Alder product 126 and Michael adduct 127.

Gratifyingly, we discovered that treatment of 121 with LDA

(Scheme 2.19) provided the Diels–Alder product 126 as a 10:1 mixture of separable diastereomers, favoring the expected cis-5,5-fusion product (64% isolated yield). This process presumably occurs via a stepwise Michael–Michael reaction sequence. No Michael adduct 127 was observed under these conditions.

Scheme 2.19. Successful formal intramolecular exo-selective furan Diels–Alder reaction.

For reasons that will not be discussed in detail here, we revised our protecting group strategy due to challenges associated with removal of the PMB protecting group in 126 and cleavage of the ethyl ester to the corresponding carboxylic acid (Scheme 2.20). Instead of protecting the 1,2-diol as

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the corresponding PMP acetal, the two hydroxyl groups were differentially protected. Selective TBS-protection of the primary hydroxyl, followed by benzyl protection of the secondary hydroxyl group, reduction of the methyl ester in 133, and formation of the corresponding iodide occurred smoothly to yield alkyl iodide 134. Following the same sequence of operations utilized previously, lithiation of furan 115, followed by alkylation with 134, afforded coupled product 135. Global silyl deprotection with TBAF provided the corresponding furanone alcohol, which upon Swern oxidation\(^4\) cleanly delivered aldehyde 136. A (Z)-selective modified Horner-Emmons reaction then delivered (Z)-enoate 137. Treatment of 137 with LDA provided the Diels–Alder product 138 as a 10:1 mixture of diastereomers, once again favoring the desired cis,5,5-fusion product (64% isolated yield of 138). We were able to prepare over 10 g of 138 using this protocol. It was imperative to conduct this reaction under extremely dilute conditions (0.02 M) in order to suppress undesired intermolecular pathways.

\(^4\) It was imperative to remove all i-Pr\(_2\)NEt during workup of the reaction. Residual i-Pr\(_2\)NEt promoted 136 to undergo undesired intra-and intermolecular pathways via addition of the furanone moiety to the newly formed aldehyde.

Scheme 2.20. Revised protecting group scheme and synthesis of oxanorbornanone 138.

With oxanorbornanone 138 in hand, an oxidative “carboxy-inversion” sequence for converting the C4-ester to a hydroxyl group with retention of configuration was required (Scheme
First, the allyl ester of Diels–Alder product 138 was deprotected to carboxylic acid 139.
Next, m-chloroperbenzoic acid (m-CPBA) was coupled to carboxylic acid 139 via the acid chloride intermediate to afford diacyl peroxide 140, which underwent ionic rearrangement (“carboxy-inversion”) upon heating in benzene to afford the corresponding acyl carbonate species 141.
Methanolysis of this crude intermediate provided the desired secondary carbinol 142 as a single diastereomer. Attempted optimization of the carboxy-inversion sequence proved to be extremely challenging and the optimal yield obtained (33%, 4 steps) was irreproducible, especially on larger scale. Lewis acids (e.g., ZnCl₂, Sc(OTf)₃, MgBr₂), Brönsted acids (e.g., trichloroacetic acid), and more polar solvents (e.g., CCl₄, PhCF₃), all factors which are known to accelerate this ionic process, did not improve the yield. Indeed, in most cases, lower yields were observed.

Eventually, it was discovered that heating p-nitrobenzoyl peroxide 143 (Scheme 2.22),

Scheme 2.21. Carboxy-inversion reaction to install the C4-oxygenation with retention of stereochemistry.

Numerous minor byproducts resulted from the carboxy-inversion reaction, although none were present in significant quantities for characterization.


49 Numerous minor byproducts resulted from the carboxy-inversion reaction, although none were present in significant quantities for characterization.
synthesized via coupling of \( p \)-nitroperbenzoic acid (\( p \)-NPBA)\(^{50} \) with carboxylic acid 139, afforded desired alcohol 142 in 38% yield (4 steps). While this reaction did not significantly improve the yield, it was reproducible on scale. Furthermore, while \( m \)-chlorobenzoyl peroxide 140 required silica gel column chromatography, \( p \)-nitrobenzoyl peroxide 143 did not, obviating the need for an additional purification step. Protection of the hydroxyl group in 142 as a TBS ether yielded the dimerization precursor, oxanorbornanone 144.

**Scheme 2.22.** Use of \( p \)-nitrobenzoyl peroxide 143 in the carboxy-inversion reaction.

Utilizing the optimal oxidative enolate dimerization conditions developed in our group (Scheme 2.23), ketone 144 was added to LiHMDS and HMPA in THF at \(-78^\circ C\) to generate the corresponding lithium enolate, which was then exposed to \([\text{Cp}_2\text{Fe}]\text{PF}_6\) and allowed to stir at \(-55^\circ C\) for 4 days. Contrary to our prior studies where only \( \text{exo-exo} \) dimerization was observed, unsymmetrical \( \text{exo-endo} \) dimer 145 was obtained exclusively (44%). The structure of 145 was further confirmed by the nOe’s depicted in Scheme 2.23.

**Scheme 2.23.** Stereoselective oxidative enolate dimerization affords the \( \text{exo-end} \) dimer exclusively.

It appeared that although dimerization occurred with complete *exo* facial selectivity in the absence of any substitution on the oxanorbornanone carbon framework (Eq. 2, Scheme 2.24), the C4-substituent (pseudoaxial phenylsulfone) played a crucial role in reinforcing *exo-exo* selectivity (Eq. 3 and Eq. 4) in our prior more complex polycyclic systems.

**Scheme 2.24.** Effect of the relative stereochemistry at C4 on the stereoselectivity of the oxidative dimerization reaction. *The opposite enantiomer to that which is shown was synthesized, but is drawn as such for ease of comparison.

In the current system (Eq. 1), the C4-substituent was a sterically large pseudoequatorial TBS ether group, which likely disfavors *exo-exo* dimerization due to steric interactions, which may cause the ethyl groups to gear towards each other in the transition state. Use of a sterically smaller MOM protecting group on the C4-hydroxyl resulted in a 1:1 *exo-endo:*exo-exo mixture of diastereomers, suggesting that not only does the relative stereochemistry at C4 play an important role in the trajectory of the dimerization, but also the size of the substituent.
Attempts to improve the yield of dimerization product 145 above 44% proved to be challenging. Typically 10-15% of starting ketone 144 was recovered from the dimerization reactions. Increasing the reaction temperature (up to −40 °C), varying the concentration (0.05 M–0.20 M), varying the amount of LiHMDS used (1.2–2.2 equiv) or the use of LDA, and allowing the reaction to proceed longer (up to 5 days) did not result in increased yields. Byproducts were not present in sufficient quantities for characterization.

Fortunately, exo-endo dimer 145 could be selectively epimerized to the desired and thermodynamically favored exo-exo dimer 146 by treatment with 2-t-butyl-1,1,3,3-tetramethylguanidine (Barton’s base) (Scheme 2.25). With exo-exo dimer 146 in hand, the benzyl ethers were cleaved and the corresponding diol 147 was oxidized to 1,4-diketone dimer 148. Surprisingly, and quite fortuitously, 148 did not exist as a cyclic hydrate if silica gel column chromatography was avoided; this is in contrast to our previously discussed systems where the analogous C5-ketone substrates (Scheme 2.13) existed exclusively as the cyclic hydrates. One possible explanation was that the sterically large pseudoequatorial C4- and C4’-TBS ethers may cause the ethyl groups to orient towards each other such that the cyclic hydrate, where the ethyl groups are in close proximity, would be disfavored. Regardless, the C4-stereochemistry has subtle yet far-reaching stereoelectronic consequences on the system.

Scheme 2.25. Selective epimerization of exo-endo dimer 145 to the desired exo-exo dimer 146.

With a successful synthesis of 1,4-diketone dimer 148 completed, the key oxygen bridge fragmentation was next investigated (Scheme 2.26). Quite surprisingly, all attempts to fragment the oxygen bridge of 148 or the cyclic hydrate form of 148 were unsuccessful. Exposure of 148 to acidic
(e.g., PPTS, BF₃•OEt₂, BCl₃) and basic (e.g., K₂CO₃/MeOH, DBU, Barton’s base, KHMDS, KOH/THF/H₂O) conditions either resulted in nonspecific decomposition or no reaction. These results were especially surprising when compared to the model system studied by Dr. Evan S. Krygowski (Scheme 2.4). The only difference, aside from the absolute stereochemistry, between the current system and the previous model system is the stereochemistry and substituent at C4 (pseudoaxial phenylsulfone vs. pseudoequatorial TBS ether). Interestingly, deuterium incorporation studies (KOD in THF) revealed 100% deuterium incorporation at C4a/C4a' of 150 and 151.

Scheme 2.26. Attempted oxygen bridge fragmentation.

Unlike the original successful model studies where the dimer contained a pseudoaxial C4-phenylsulfone (Scheme 2.4), we rationalized that fragmentation is disfavored due to a 1,3-allylic interaction (Scheme 2.27) between the enolate (C5–C4a) oxygen of 152 and the pseudoequatorial C4-TBS-ether that must occur during the transition state in order to achieve proper orbital overlap for fragmentation to occur. Unfortunately, moving to a sterically smaller protecting group (MOM) or even the free hydroxyl did not remedy this problem. In line with our hypothesis, we predicted that the C4-epimer of 148 would not suffer from an unfavorable 1,3-allylic-type interaction during oxygen bridge fragmentation. However, before we discuss a synthesis of the C4-epimer of 148, other strategies we explored for β-eliminating the oxygen bridge in 148 will first be presented.
Scheme 2.27. Rationale for unsuccessful oxygen bridge fragmentation.

One strategy we considered was utilizing the electron-rich naphthalene system to facilitate oxygen bridge fragmentation (Scheme 2.28). This strategy was conceived prior to Dr. Hong Geun Lee’s discovery that reduction of the B-ring quinone to the corresponding hydroquinone was extremely challenging (Scheme 2.12).

Scheme 2.28. Proposed oxygen bridge fragmentation via the electron-rich AB/A’B’-naphthalene systems.

To this end, 1,4-diketone dimer 148 was converted to bisenone 156 via formation of the bis-trimethylsilyl enol ether followed by Saegusa oxidation (Scheme 2.29). A double Hauser or Kraus annulation should then deliver hydroquinone dimer 158. Several annulation donors were synthesized, including the cyanophthalide (157, X = CN), phenylsulfonylphthalide (157, X = SO₂Ph) and phenylsulfenylphthalide (157, X = SPh). Unfortunately, however, treatment of these annulation donors with base (e.g., t-BuOLi, LiHMDS), followed by addition of enone 156 under a variety of conditions, including the use of additives (e.g., ZnCl₂, HMPA), were unsuccessful. We hypothesized that the C1- and C1'-ketones and the C2- and C2'-protons may not be compatible with

51 We also attempted to stop the reaction at just the initial Michael addition, but this unfortunately also yielded complex product mixtures.
the basic reaction conditions and that the use of “neutral” annulation conditions may potentially circumvent this problem. We generated the corresponding siloxyisobenzofuran\textsuperscript{52} intermediate in situ from 157 by treating 157 with base, followed by trapping with TMSCl. Unfortunately, addition of enone 156 to this intermediate also afforded a complex product mixture. We did not attempt bisannulation of the cyclic hydrate form of 156 because this would result in a product that is highly similar to the system extensively studied by Dr. Hong Geun Lee (89, Scheme 2.8), which did not undergo oxygen bridge fragmentation.

![Scheme 2.29. Attempted bisannulation reactions to construct the naphthalene system.](image)

We next turned our attention to reductively fragmenting the oxygen bridge from bisenone 156 and 159 (Scheme 2.30). Treatment of enone 156 or 159 with Sml\textsubscript{2} resulted in complete decomposition. No reaction was observed when 156 was treated with freshly activated Zn in AcOH,\textsuperscript{53} even at high temperatures. Exposure of a derivative of cyclic hydrate 159, where the hydroxyl groups were protected as the corresponding TMS ethers, to Birch reduction conditions (Li(0) or Na(0) in NH\textsubscript{3}, THF, −78 °C) also resulted in decomposition.


Scheme 2.30. Attempted reductive fragmentation of the oxygen bridge in bisenone 156 and 159.

At this juncture, we decided to no longer pursue strategies for β-eliminating the oxygen bridge of 148, 156, and derivatives thereof. In summary, a highly efficient and scaleable route, featuring a “carboxy-inversion” sequence for installing the C4-oxygenation and an intramolecular exo-selective furan Diels–Alder reaction, to oxanorbornanone 144 was developed. Furthermore, a stereoselective oxidative dimerization of the enolate derived from 144 was achieved. Unfortunately, attempts to fragment the oxygen bridge to reveal the lomaiviticin core were unsuccessful.

The main obstacle preventing us from achieving a synthesis of the lomaiviticin core was β-elimination of the oxygen bridge. As discussed previously, we postulated that the C4-epimer of 148 would not suffer from the 1,3-allylic-type interaction during oxygen bridge fragmentation depicted in Scheme 2.27. Hence, we next turned our focus toward the development of a synthesis of the C4-epimer of 148.
Synthesis of the C4-Epi-Lomaiviticin A and B Cores and Studies Toward the Aglycon

Due to our unsuccessful attempts to achieve β-elimination of the oxygen bridge in 148, we decided to embark on a synthesis of the C4-epimer of 148. Based on our previous observation that reagents approach from the convex face of the cis-5,5-fused system (Scheme 2.9, 92), anti to the oxygen bridge, we believed that a Barton radical decarboxylation–oxidation reaction may afford the C4-epimer of 148. To this end, the Barton ester was formed from carboxylic acid 139 by using S-(1-oxido-2-pyridinyl) 1,1,3,3-tetramethylthiouronium hexafluorophosphate (HOTT) (Scheme 2.31). Upon complete formation of the Barton ester, the reaction was saturated with O2 and Sb(SPh)3 was added. This one-pot protocol afforded alcohol 162 as a 2:1 mixture of diastereomers, favoring the desired epimer in 46% isolated yield. The HOTT reagent was very effective in facilitating the formation of hindered carboxylic acids, as was the case in 139. Use of the more conventional Barton radical decarboxylation–oxidation conditions (Barton ester formation, followed by exposure to O2, t-BuSH, and a sunlamp, then reduction with PPh3) afforded the alcohol product in higher diastereoselectivity (4:1 dr) but in lower isolated yields of the desired diastereomer (37–40%). While the use of O2 and Sb(SPh)3 did not significantly improve the yield (46%), it permitted easier purification of the desired alcohol 162.

Alcohol 162 was protected as the corresponding TBS-ether, affording oxanorbornanone 163, the dimerization substrate. 163 underwent successful oxidative enolate dimerization to provide exo-exo dimer 164 exclusively. Benzyl ether cleavage and subsequent Parikh-Doering oxidation afforded


56 We experienced difficulty in driving the Barton ester formation to completion via addition of the sodium salt of 2-mercaptopyridine N-oxide to the acid chloride derived from carboxylic acid 139.

cyclic hydrate 166 in 47–57% yield over 3 steps. Due to the instability of dimeric intermediates 164 and 165 to silica gel column chromatography, purification could only be conducted on cyclic hydrate 166 after the 3-step sequence.\(^{58}\) Optimization efforts to improve the yield beyond 57% were unsuccessful. Varying the concentration (0.07–0.16 M), varying the amount of HMPA used (0–5.0 equiv), purifying the \([\text{Cp}_2\text{Fe}]\text{PF}_6\), and carefully deoxygenating the THF solvent, were all investigated. The diminished yield likely reflected the instability of dimeric products 164 and 165. With a successful synthesis of cyclic hydrate 166 completed, the key oxygen bridge fragmentation reaction was next investigated. Gratifyingly, a screen of basic conditions revealed that cyclic hydrate 166 underwent successful oxygen bridge fragmentation upon treatment with KOH in THF/H\(_2\)O at 0 °C, confirming our suspicion that the C4-stereocenter has far-reaching stereoelectronic effects.

Scheme 2.31. Successful oxygen bridge fragmentation and conversion to 4-epi-lomaivitcin A (168) and B (169) cores.

\(^{58}\) A very quick silica gel plug after the dimerization reaction to remove as much \([\text{Cp}_2\text{Fe}]\text{PF}_6\) and ferrocene byproduct as possible was conducted.
Bisenone product 167 was then converted to C4-epi-lomaiviticin B core 169 in two steps, involving (1) dehydration of cyclic hydrate 167 in the presence of MgSO₄⁵⁹ to yield C4-epi-lomaiviticin A core 168 and (2) stirring 168 with catalytic p-TsOH to provide C4-epi-lomaiviticin B core 169 (62%, 3 steps). The latter step required extensive optimization and use of various acidic (e.g., PPTS, CSA, Sc(OTf)₃, HCl, MgBr₂•OEt₂) and basic (e.g., K₂CO₃/MeOH, Et₃N, Barton’s base) conditions resulted in either low conversion or decomposition. Some byproducts isolated appeared to be the result of D-ring aromatization. With a successful synthesis of lomaiviticin B core 169, the stage was set for testing our key bisannulation strategy to install the AB/A′B′-naphthalene systems.

Despite the challenging aspects of double processing, our initial strategy was to pursue a cyclopentadienyl anion bisannulation (Scheme 2.32). We envisioned that a cyclopentadiene derivative (170) could be synthesized from 169. Exposure of cyclopentadiene 170 to excess base should result in formation of the cyclopentadienyl anion dimer 172, which upon treatment with two equivalents of an electrophilic phthalate derivative 171 should result in double addition to afford adduct 173 or 174. A second nucleophilic addition of the anion to the remaining ester of the electrophile should then afford the desired hydroquinone dimer 175. The closest literature precedence in support for such a transformation was a methodology developed by Birman and coworkers for the synthesis of benzofluorenes via an indanone dianion annulation,⁵⁹ which was applied to a synthesis of prekinamycin.

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⁵⁹ In addition to serving as a dehydrating agent, MgSO₄ likely also facilitated the reaction by acting as a mild Lewis acid. Furthermore, Dr. Evan S. Krygowski attempted a very similar set of reaction conditions to dehydrate his model system 66 (MgSO₄, DCE, Scheme 2.4), but did not observe any desired product.
In preparation for our key annulation, lomaiviticin B core 169 was treated with TMSOTf and Et$_3$N (Scheme 2.33), which resulted in both silyl enol ether formation and protection of the bis-hemiketal core to furnish cyclopentadiene dimer 176. In the event that 176 did not undergo cyclopentadienyl anion bisannulation, protected lomaiviticin B core 177 was synthesized from 169 by heating in neat TMSCN.

A variety of phthalate derivatives were synthesized (Figure 2.4) as potential annulation electrophiles. We originally anticipated that 2,2,2-trifluoroethanol (TFE) diester 179 would be the optimal electrophile for the bisannulation reaction, since it was most similar to the diester electrophile utilized in the indanone dianion annulation developed by Birman and coworkers. A control experiment where 179 was utilized as the electrophile in the presence of the dianion generated from indanone was performed and complete conversion to the hydroquinone product was observed. In the event that 179 was not a sufficiently reactive electrophile due to electronic
deactivation of the esters by the electron-donating MOM-protected phenols on the aryl ring, we attempted to synthesize phthalate derivatives dialdehyde 184, diacyl chloride 185, and diacyl fluoride 186. Unfortunately, however, dialdehyde 184 was prone to rapid polymerization and a synthesis of 185 and 186 was not realized due to insolubility problems encountered with the corresponding dicarboxylic acid precursor. Regardless, we believed TFE diester 179 was a promising electrophile with which to commence our cyclopentadienyl anion bisannulation studies.

![Chemical structures]

Figure 2.4. Successful (highlighted in blue) and attempted (in black) syntheses of annihilation electrophiles.

The typical procedure employed involved premixing cyclopentadiene 176 and electrophile 179 (Scheme 2.34), followed by addition of base (e.g., KHMD, LDA) and slow warming of the reaction to room temperature or higher (up to 50 °C). However, only unreacted starting material was recovered. Exposure of 177 to the described procedures also resulted in complete recovery of starting material. These results were not altogether surprising, as nucleophile 176 and 177 were extremely hindered and diester 179 was not very electrophilic. We rationalized that phthalate 178 (Figure 2.4), in which the phenol groups of the aryl ring are Boc-protected, would be a more reactive electrophile than 179. Another electrophile we considered was 180, where we believed initial cyclopentadienyl anion addition would occur on the aldehyde. Unfortunately, however, use of either electrophile 178 or 180 in the indanone annihilation control system failed to produce any hydroquinone product.
Scheme 2.34. Attempted cyclopentadienyl anion annulation to synthesize hydroquinone 190.

Eventually, we discovered that deprotonation of cyclopentadiene 176, followed by addition of aldehyde 183 (Scheme 2.35), afforded a mixture of monoaddition products, the regiochemistry of which were unverified, in low conversion. Efforts to obtain the double addition product and improve the conversion of the reaction proved unsuccessful. We suspected that the low conversion was due to incomplete deprotonation of 176. However, warming of 176 with base (e.g., LiHMDS, LDA, LiTMP, n-BuLi) to higher temperatures resulted in decomposition of starting material.

Scheme 2.35. Attempted cyclopentadienyl anion addition to aldehyde 183.

We discovered that we could perform a double aldol reaction (Scheme 2.36) with the enolate dimer generated from 177 and either aldehyde 183 or 181, furnishing the full carbon skeleton of the lomaiviticin aglycon (193 and 194). Next, we attempted to oxidize the newly generated β-hydroxy groups in 193 and 194 to afford the corresponding 1,3-dicarbonyl function. Unfortunately, however, use of conventional oxidation conditions (e.g., Swern, DMP, Parikh-Doering) resulted in either decomposition or recovery of starting material. While we were excited at having finally obtained the

60 The β-hydroxy groups were prone to β-elimination, especially under basic conditions.
full lomaiviticin aglycon carbon skeleton, it was difficult to envision a straightforward strategy for converting 193 or 194 to the desired hydroquinone 175. Hence, we decided to embark on a new strategy where instead of utilizing 177 as the nucleophile, it would instead serve as the electrophilic component.

Scheme 2.36. Successful double aldol reaction to yield the full lomaiviticin aglycon carbon skeleton.

Due to their anti-aromatic nature, cyclopentadienones are highly reactive and tend to self-dimerize rapidly in a [4+2] pathway. ⁶¹, ⁶² Although unprecedented, we hoped to exploit the reactivity of cyclopentadienones ⁶³ to our advantage (197) by generating cyclopentadienone intermediate 197 in situ (Scheme 2.37) in the presence of a suitable nucleophile such as cyanophthalide anion 196 to immediately trap this reactive species, affording double Michael adduct 198. A Claisen condensation, followed by elimination of cyanide and tautomerization, could then furnish desired hydroquinone dimer 200. Furthermore, we hypothesized that since 197 was relatively hindered, it may be less prone to self-dimerization.

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⁶³ For examples of 1,4-conjugate additions of Grignard reagents to cyclopentadienones, see: Pearson, A. J.; Kim, J. B. Org. Lett. 2003, 5, 2457–2459.
Scheme 2.37. Proposed cyclopentadienone bisannulation strategy.

To this end, several potential cyclopentadienone precursors were synthesized (Scheme 2.38). Treatment of cyclopentadiene \( \text{201} \) with NBS afforded \( \alpha \)-bromide dimer \( \text{202} \) (Eq.1).\(^ {64} \) However, exposure of \( \text{202} \) to basic conditions resulted in only \( \alpha \)-epimerization and no cyclopentadienone was observed. Next, we attempted to synthesize tetrabromide \( \text{204} \) from \( \text{177} \) by treatment with LiHMDS, followed by addition of NBS (Eq.2). Tetrabromide \( \text{204} \) was obtained only in minor quantities, with dibromide \( \text{203} \) being the major product. For reasons not entirely clear, efforts to drive the bromination reaction to completion were unsuccessful. Lastly, \( \beta \)-bromide dimer \( \text{205} \) was synthesized from \( \text{177} \) via a modified Wohl–Ziegler radical bromination with 1,3-dibromo-5,5-dimethylhydantoin (Eq.3). The major diastereomer obtained was unsymmetrical, an observation which will become important later (vide infra).

\(^ {64} \) Reaction was conducted on small-scale and yield was not determined.
Scheme 2.38. Synthesis of several cyclopentadienone precursors.

For ease of analysis, a $^1$H NMR experiment with dibromide 203 was conducted in order to determine whether a cyclopentadienone intermediate could be accessed from such a precursor (Scheme 2.39). Addition of DBU to dibromide 203 in CD$_2$Cl$_2$ resulted in formation of putative cyclopentadienone intermediate 206, with the diagnostic cyclopentadienone proton at $\delta = 7.00$ ppm.

Scheme 2.39. Observation of cyclopentadienone intermediate in $^1$H NMR experiment.

Encouraged by this result, but with only very limited quantities of tetrabromide 204 in hand, we decided to explore a Diels–Alder reaction of a suitable diene with the cyclopentadienone intermediate generated from 204 (Scheme 2.40), since cyclopentadienones are often utilized in the
literature\textsuperscript{65} in Diels–Alder reactions. Although unprecedented, we decided to add tetrabromide 204 to the siloxyisobenzofuran generated from phthalide 207\textsuperscript{66} in the presence of DBU. All starting material was consumed and a new compound, where no nucleophile had been incorporated, was isolated. Unfortunately, we were unable to determine the structure of this new compound,\textsuperscript{67} which was no longer $C_2$-symmetric and appeared to have undergone a skeletal rearrangement. The decision was made that pursuing this strategy was ultimately impractical due to the low yield and lack of scaleability in the synthesis of tetrabromide 204.

![Scheme 2.40. Attempted cyclopentadienone annulation to access double Diels–Alder adduct 208.](image)

Next, we investigated generation of cyclopentadienone from $\beta$-bromide dimer 205 (Scheme 2.41). Cyanophthalide anion was preformed by stirring 15.0 equivalents of cyanophthalide 209 with 17.0 equivalents of LiHMDS (note two equivalents excess base). $\beta$-bromide dimer 205 was subsequently added, under the hypothesis that the two extra equivalents of LiHMDS would generate the corresponding cyclopentadienone intermediate in situ. Unfortunately, a new compound, no longer $C_2$-symmetric, was isolated. No nucleophile was incorporated and once again, the molecule appeared to have undergone a skeletal rearrangement. It became apparent that a common observation


\textsuperscript{67} This new compound was not the result of self-dimerization.
was that when excess base was used in an attempt to generate the cyclopentadienone intermediate, the molecule would undergo a skeletal rearrangement without incorporation of nucleophile (see also Scheme 2.40). In consideration of this observation, another experiment in which cyanophthalide anion was preformed by stirring 12.0 equivalents of 209 with 11.8 equivalents of LiHMDS was conducted. Gratifyingly, monoadduct 230 was isolated in 45% yield and no rearranged byproducts were observed.

Scheme 2.41. Attempted cyclopentadienone bisannulation with cyanophthalide 209.

Efforts to obtain the corresponding double addition product by resubjecting monoadduct 230 to the reaction conditions and using more polar solvents (e.g., DMF) and various additives (e.g., TBAI) were unsuccessful. When DBU was used as an additive to discretely generate the cyclopentadienone from monoadduct 230, a new compound was isolated in which a second equivalent of nucleophile was not incorporated and the molecule appeared to have undergone a skeletal rearrangement, in line with our previous observations when excess base was used. We hypothesized that under the given reaction conditions, it was unlikely that the cyclopentadienone intermediate was generated, since the cyanophthalide anion is not very basic (pKₐ ~14). Rather, we believed that monoadduct 230 was the result of S₈2 displacement of the allylic bromide in 205 by the cyanophthalide anion. This notion appeared to be supported by two observations: (1) when DBU was used to discretely generate the cyclopentadienone intermediate, no nucleophile was incorporated

68 Cyanophthalide anion was not stable under these conditions and rapidly decomposed.
and (2) only the monoaddition product was obtained. Recall the aforementioned observation that the major diastereomer of 205 was unsymmetrical. The shape of the lomaivitcin core exists in the form of a deep bowl, indicating that in the unsymmetrical β-bromide dimer 205, one bromide is on the convex face and one bromide is on the concave face. If the formation of 230 occurs via an SN2 mechanism, only the concave bromide could be displaced via convex approach of the cyanophthalide anion. Displacement of the convex bromide would require concave approach by the nucleophile, which is highly disfavored, resulting in the isolation of only monoadduct 230. Predicated on the aforementioned hypothesis, we attempted to displace the allylic bromide in 230 with NaI and KI but without success. At this point, we decided to revise our strategy for introducing the AB/A'B'-naphthalene systems.

One of the main challenges involved in constructing the naphthalene system is the presence of the C5−C6 and C5'−C6' internal double bonds in 177 (Scheme 2.42, highlighted in red), which prevented us from employing conventional Hauser, Kraus, and related annulations. We therefore next planned on reductively removing the C5−C6 and C5'−C6' double bonds in 177 and subsequently oxidizing the resultant ketone 231 to enone 232, the desired annulation substrate. Unfortunately, 177 was completely inert to the hydrogenation conditions we screened (H2, from 1 to 20 atm, and Pd/C, PtO2, Rh/C, and Crabtree’s catalyst). These results were not surprising, as the internal double bonds in 177 are extremely hindered.

Scheme 2.42. Attempted reductive removal of the C5−C6 and C5'−C6' internal double bonds in 177.

Interestingly, exposure of 177 to Birch reduction conditions cleanly afforded ketone 235 (Scheme 2.43), the result of C5−C6 (or C5'−C6') enone reduction followed by intramolecular 1,4-
conjugate addition of the resultant anion at the C6 (or C6') position to the C5'–C6' (or C5–C6) enone on the other half of the molecule. Closer examination of a 3D hand-held molecular model of 177 revealed that C6 and C6' are in very close proximity due to the bowl-shaped structure of the lomaiviticin B core 177. While disappointing, this result further highlighted the unique reactivity of the lomaiviticin system.

Scheme 2.43. Birch reduction of 177.

Due to our unsuccessful attempts to reductively remove the C5–C6 and C5'–C6' double bonds, we next focused our attention on introducing nucleophiles to the C6 and C6' positions of 177 or 169 via 1,4-conjugate addition to the enone. However, our endeavors to add nucleophiles such as Et₂AlCN, Stryker's reagent, TBHP, PhSH, and EtSH under a variety of conditions resulted in no reaction. Eventually, we discovered that 169 underwent double nucleophilic epoxidation when treated with H₂O₂ and NaOH, providing bisepoxide 237 (Scheme 2.44). The bis-hemiketal core was protected as the TMS ethers, providing diketone substrate 238. For reasons not entirely clear, attempts to oxidize bisepoxide 238, including Saegusa oxidation of the corresponding TMS enol ether of 238 and α-selenation-elimination of the ketone in 238, to enone dimer 239 were unsuccessful.

Scheme 2.44. Synthesis of bisepoxide 237 via a double nucleophilic epoxidation.
At this point, a reevaluation of our strategy was necessary. Based on our unsuccessful bisannulation studies, it was evident that a new approach to installing the AB/A'B'-naphthalene systems was required. From our investigation, it was apparent that the main challenge was forming the C11a–C11 and C11a'–C11' bonds after β-elimination of the oxygen bridge. Thus, in our revised strategy we envisioned preforming the C11a–C11 and C11a'–C11' bonds prior to the dimerization event (Scheme 2.45). Not only does this minimize double processing, but also provides a handle for introduction of the naphthalene system after oxygen bridge fragmentation.

Scheme 2.45. Revised strategy involving preforming the C11a–C11 and C11a'–C11' bonds prior to the dimerization event.

In order to address the pressing question of whether a system such as oxanorbornanone 240 can undergo oxygen bridge fragmentation with a pendant substituent at C11a, enone 246 was synthesized from oxanorbornanone 163 in a few straightforward steps (Scheme 2.46). Reduction of ketone 163 with NaBH₄, followed by pivaloyl protection of the resultant secondary hydroxyl group, afforded pivaloyl ester 244. Hydrogenolysis of the benzyl ether group and subsequent Parikh-Doering oxidation of the secondary carbinol provided ketone 245. Saegusa oxidation of the TMS enol ether of 245 afforded enone 246. Transmetallation of the (α-benzyloxy)methyl)stannane 247 upon treatment with n-butyllithium, followed by addition of CuBr•SMe₂, resulted in formation of the corresponding (benzyloxy)methyl)copper reagent. ⁶⁹ Exposure of enone 246 to this

((benzyloxy)methyl)copper reagent, followed by addition of BF$_3$•OEt$_2$, resulted in successful 1,4-conjugate addition to afford adduct 248 as a single diastereomer.

Scheme 2.46. Synthesis of oxygen bridge fragmentation substrate 252.

Formation of the TIPS enol ether of 248, reductive cleavage of the pivaloyl ester with LiAlH$_4$, and oxidation of the resultant secondary carbinol with TPAP and NMO yielded the desired dimerization substrate 250. Exposure of monomer 250 to the optimal oxidative enolate dimerization conditions developed in our lab yielded dimer 251. Disappointingly, this result further highlighted the idiosyncratic nature of the oxanorbornanone system and the highly case-dependent success of β-elimination of the oxygen bridge.

The key oxygen bridge fragmentation reaction was next tested (Scheme 2.47). Quite surprisingly, exposure of cyclic hydrate 252 to the optimal β-elimination conditions (KOH, THF/H$_2$O) discovered earlier for a highly similar substrate (166), resulted in nonspecific decomposition. The only difference between 252 and 166, which underwent successful oxygen bridge fragmentation, was the presence of a substituent at C11a and C11a'. Disappointingly, this result further highlighted the idiosyncratic nature of the oxanorbornanone system and the highly case-dependent success of β-elimination of the oxygen bridge.

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70 Due to the small-scale nature of the dimerization reaction, an accurate yield was not determined.
At this point, one last strategy involving an intermediate synthesized by Jae Young Ahn from the original model system was investigated (Scheme 2.48). Due to readily accessible material and the highly successful oxygen bridge fragmentation of 64 in Dr. Evan S. Krygowski’s model system, we decided to explore the possibility of whether 257, in which the C11–C11a bond was preformed, could undergo β-elimination of the oxygen bridge. Although downstream manipulations would be necessary in order to construct the B- and B'-ring systems in the correct oxidation state, we believed this strategy was superior to that illustrated in Scheme 2.45 because the aryl ring has already been introduced, obviating the need to install the naphthalene system de novo via late-stage double-processing.

**Scheme 2.47.** Unsuccessful oxygen bridge fragmentation of cyclic hydrate 252.

**Scheme 2.48.** Unsuccessful oxygen bridge fragmentation of cyclic hydrate 257.
Reductive cleavage of the pivaloyl ester of \( \text{254}^{71} \) and subsequent Ley oxidation of the resultant secondary carbinol afforded ketone \( \text{255} \), the dimerization precursor. Oxanorbornanone \( \text{255} \) underwent successful oxidative enolate dimerization to furnish dimer \( \text{256} \), which contained the full carbon skeleton of the lomaivitcin aglycon, in 80% yield. Ketal cleavage occurred smoothly upon exposure of \( \text{256} \) to TfOH in acetone/H\(_2\)O to provide cyclic hydrate \( \text{257} \). Treatment of \( \text{257} \) with a variety of basic conditions (KOH/THF/H\(_2\)O, DBU/THF, K\(_2\)CO\(_3\)/MeOH) in an attempt to fragment the oxygen bridge resulted in nonspecific decomposition of \( \text{257} \). These results were quite unexpected, given the highly successful oxygen bridge \( \beta \)-elimination (85%) of \( \text{64} \) to \( \text{65} \) (Scheme 2.4) in Dr. Evan Krygowski’s original model system.

Due to the highly unpredictable and extremely case-dependent nature of \( \beta \)-elimination of the oxygen bridge, coupled with the lack of success in introducing the AB/A'\(^{\prime}\)/B'-naphthalene systems, the difficult decision was made to cease pursuing a synthesis of the lomaivitcin aglycon. Although we successfully achieved a synthesis of the lomaivitcin core, which necessitated oxygen bridge fragmentation prior to installation of the naphthalene system, we were forced to utilize exotic and unprecedented bisannulation strategies, which not only involved challenging double-processing but were ultimately unsuccessful. Furthermore, installation of functionality at C11a and C11a' predimerization, which would help enable subsequent introduction of the naphthalene ring systems after \( \beta \)-elimination of the oxygen bridge, again prevented oxygen bridge fragmentation. In fact, \( \beta \)-elimination could only be achieved in substrates containing the unnatural C4/C4'-stereochemistry and which lacked the C11a/C11a' substitution. Two important take-home lessons were realized from working on the lomaivitcin project: (1) the success of model systems rarely translate to the real system in a complex molecule setting and (2) double-processing is extremely challenging and when possible, should be avoided.

\(^{71}\) Courtesy of Jae Young Ahn. \( \text{254} \) was synthesized from intermediate \( \text{71} \).
Concluding Remarks

In conclusion, a synthesis of the C4-epi-lomaiviticin A and B cores was accomplished. A first-generation synthetic route featuring an intramolecular exo-selective furan Diels–Alder reaction to construct the oxanorbornanone system, a “carboxy-inversion” sequence for installing the correct C4-stereochemistry, and a stereoselective oxidative enolate dimerization reaction to establish the key C2–C2’ bond, allowed us to access an oxygen bridge fragmentation precursor substrate. However, the discovery of subtle stereoelectronic effects imparted by the C4/C4’-stereocenters necessitated a second-generation synthesis of a substrate with the opposite C4-stereochemistry to that found in the natural product, which ultimately resulted in successful β-elimination of the oxygen bridge, an accomplishment which had eluded our lab for more than four years. This constituted the first time a synthesis of the lomaiviticin A and B cores had been achieved in our lab since we first began pursuing a total synthesis of the lomaiviticin aglycon more than ten years ago.

Unfortunately, efforts to elaborate the lomaiviticin B core to the full carbon skeleton of the lomaiviticin aglycon proved extremely challenging and were ultimately unsuccessful. Because the success of oxygen bridge β-elimination hinged on fragmenting the oxygen bridge prior to installation of the naphthalenes, we were forced to explore unprecedented bisannulation strategies. A variety of approaches for introducing the naphthalene ring systems were pursued, including a cyclopentadienyl anion bisannulation, double aldol reaction, and cyclopentadienone bisannulation. Introduction of a handle in order to simplify installation of the naphthalene system after oxygen bridge fragmentation was also investigated. All of the strategies investigated, which involved challenging late-stage double-processing, ultimately did not provide the desired hydroquinone dimer product.

At this stage in the lomaiviticin project, the difficult decision was made to no longer pursue a total synthesis of the lomaiviticin aglycon due to the highly unpredictable and idiosyncratic oxygen bridge fragmentation and inability to introduce the AB/A'B'-naphthalene ring systems. In retrospect,
the oxanorbornanone system was an elegant strategy for stereoselectively establishing the key C2–C2′ central bond without undesired β-elimination of the oxygen bridge during the dimerization event. However, unexpected downstream complications were encountered when attempting to fragment the oxygen bridge at the appropriate time. In most systems investigated by our lab during the course of the past four years, we were unable to β-eliminate the oxygen bridge.

However, we are still optimistic that a successful synthesis of the aglycon can be achieved with our oxanorbornanone dimerization strategy from the knowledge we have obtained from our combined synthetic effort during the past ten years. We believe that the challenges associated with β-elimination of the oxygen bridge arise from the 5-membered C-ring (see 1, Figure 1.1), which significantly restricts the conformational flexibility of the oxanorbornanone system. We speculate, however, that if the C5a–C11a bond was not preformed prior to β-elimination of the oxygen bridge, we could potentially overcome the challenges we encountered and achieve a synthesis of the aglycon.
Experimental Section

**General Procedures.** All reactions were performed in flame-dried glassware under a positive pressure of argon unless otherwise noted. Flash column chromatography was performed as described by Still et al. employing silica gel 60 (40-63 μm, Whatman). Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel 60 F_{254} plates purchased from EMD Chemicals. Where necessary (so noted), silica gel was neutralized by treatment of the silica gel prior to chromatography with the eluent containing triethylamine (Et₃N) or 30% (w/v) ammonium hydroxide (NH₄OH). TLC plates were visualized by exposure to ultraviolet light (UV) and/or exposure to an acidic solution of *p*-anisaldehyde (Anis) or an aqueous solution of potassium permanganate (KMnO₄), followed by heating on a hot plate.

**Materials.** Commercial reagents and solvents were used as received with the following exceptions: tetrahydrofuran (THF), diethyl ether (Et₂O), dichloromethane (CH₂Cl₂), acetonitrile (MeCN), hexamethyldisilazane (HMDS), toluene (PhMe), benzene (PhH), and *N,N*-dimethylformamide (DMF) were degassed with argon and passed through a solvent purification system (designed by J. C. Meyer of Glass Contour) utilizing alumina columns as described by Grubbs et al. Triethylamine, diisopropylethylamine, pyridine, and hexamethylphosphoramid were distilled over calcium hydride before use. TMSOTf was also distilled prior to use. The celite used was Celite® 545, purchased from J.T. Baker. The molarities of *n*-butyllithium solutions were determined by titration using 1,10-phenanthroline as an indicator (average of three determinations).

**Instrumentation.** ¹H NMR spectra were recorded with a Varian INOVA-600 or Varian

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INOVA-500 spectrometer. Proton chemical shifts are reported in parts per million ($\delta$ scale) and are calibrated using residual undeuterated solvent as an internal reference (CDCl$_3$: $\delta$ 7.26 (CHCl$_3$), C$_6$D$_6$: $\delta$ 7.15 (C$_6$D$_5$H)). Data for $^1$H NMR spectra are reported as follows: chemical shift ($\delta$ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent, or combinations thereof. $^{13}$C NMR spectra were recorded with a Varian INOVA-500 spectrometer. Carbon chemical shifts are reported in parts per million ($\delta$ scale) and are referenced from the carbon resonances of the solvent (CDCl$_3$: $\delta$ 77.00, C$_6$D$_6$: $\delta$ 128.39). Infrared (FTIR) spectra were recorded on a Bruker Alpha FT-IR spectrophotometer referenced to a polystyrene standard. FTIR data is reported in frequency of absorption (cm$^{-1}$). High-resolution mass spectra (HRMS) were obtained from the Harvard University Mass Spectrometry Laboratory where electrospray ionization (ESI) mass spectroscopy (MS) experiments were performed on an Agilent 6210 TOF LC/MS instrument. Optical rotations were measured on a Jasco P-2000 digital polarimeter with a sodium lamp. Reported readings are the average of three measurements for each sample.

*(For clarity, intermediates that have not been assigned numbers in the text are numbered sequentially in the experimental section beginning with S1).*
(S)-Methyl 3-benzyloxy-4-(tert-butyl)dimethylsilyloxybutanoate (S2):

To a round-bottom flask was added (S)-Methyl 4-[(tert-butyl)dimethylsilyloxy]-3-hydroxybutanoate (S1)\(^\text{74}\) (1.00 g, 4.03 mmol, 1.00 equiv) and Et\(_2\)O (40 mL). Benzyl 2,2,2-trichloroacetimidate (1.12 mL, 6.04 mmol, 1.50 equiv) was then added via syringe and the solution was cooled to 0 °C. Catalytic trifluoromethanesulfonic acid (18.0 \(\mu\)L, 0.201 mmol, 0.05 equiv) was then added dropwise via syringe to the reaction mixture. Vigorous bubbling was observed. After 30 min, the reaction was allowed to warm to room temperature. After an additional 20 h, saturated aqueous NaHCO\(_3\) solution (30 mL) and Et\(_2\)O (30 mL) were added to the stirred reaction mixture. The layers were separated and the organic layer was washed with brine. The aqueous layers were combined and further extracted with Et\(_2\)O (3 × 30 mL). The organic layers were combined, dried over anhydrous MgSO\(_4\), and concentrated under reduced pressure. The resulting oil was then purified by flash column chromatography (silica gel, eluent: gradient, 12:1 → 7:1 hexanes:EtOAc) to afford (S)-methyl 3-benzyloxy-4-(tert-butyl)dimethylsilyloxybutanoate S2 (1.10 g, 81%) as a colorless oil.

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\): 7.35–7.30 (m, 4H), 7.29–7.27 (m, 1H), 4.66 (d, \(J = 11.7\) Hz, 1H), 4.61 (d, \(J = 11.7\) Hz, 1H), 4.01–3.93 (m, 1H), 3.72 (dd, \(J = 5.4, 10.3\) Hz, 1H), 3.67 (s, 3H), 3.59 (dd, \(J = 6.0, 10.4\) Hz, 1H), 2.64 (dd, \(J = 5.1, 15.9\) Hz, 1H), 2.53 (dd, \(J = 8.3, 15.6\) Hz, 1H), 0.89 (s, 9H), 0.05 (s, 6 H). \(^{13}\text{C NMR}\) (126 MHz, CDCl\(_3\)) \(\delta\): 172.1, 138.5, 128.3, 127.8, 127.6, 76.7, 72.6, 64.7, 51.6, 37.3, 25.9, 18.3, –5.4, –5.5. \(^\text{FTIR}\) (thin film) cm\(^{-1}\): 2953, 2928, 2857, 1741, 1437, 1254, 1113, 1086, 836, 778. \(^\text{HRMS}\) (ESI) \((m/z)\) calc’d for C\(_{19}\)H\(_{30}\)NaO\(_4\)Si \([M+Na]^+\): 361.1806, found 361.1815. \(^\text{TLC}\) (4:1 hexanes:EtOAc), \(R_f\): 0.63 (UV, KMnO\(_4\)).

(S)-3-Benzxyloxy-4-(tert-butyl)dimethylsilyloxybutan-1-ol (S3):

A suspension of LiAlH₄ (2.36 g, 59.0 mmol, 1.10 equiv) in THF (170 mL) was cooled to −40 °C. A solution of (S)-methyl 3-benzyloxy-4-(tert-butyl)dimethylsilyloxybutanoate S2 (18.2 g, 53.6 mmol, 1.00 equiv) in THF (240 mL) was then added dropwise via syringe to the stirred suspension. After 40 min, a saturated aqueous NH₄Cl solution (250 mL) and EtOAc (200 mL) were added to the reaction mixture. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 150 mL). The organic layers were combined, washed with brine (200 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure. The resulting oil was then purified by flash column chromatography (silica gel plug, eluent: 2:1 hexanes:EtOAc) to afford alcohol S3 (15.6 g, 94%) as a colorless oil.

¹H NMR (500 MHz, CDCl₃) δ: 7.39–7.32 (m, 4H), 7.32–7.27 (m, 1H), 4.73 (d, J = 11.7 Hz, 1H), 4.59 (d, J = 11.7 Hz, 1H), 3.81–3.71 (m, 3H), 3.71–3.63 (m, 2H), 2.46 (t, J = 5.6 Hz, 1H), 1.92–1.71 (m, 2H), 0.91 (s, 9H), 0.07 (s, 6H). ¹³C NMR (126 MHz, CDCl₃) δ: 138.4, 128.4, 127.8, 127.7, 78.9, 72.2, 65.4, 60.3, 34.4, 25.9, 18.2, -5.4, -5.5. FTIR (thin film) cm⁻¹: 3403, 2954, 2928, 2857, 1472, 1255, 1091, 836, 776, 697. HRMS (ESI) (m/z) calc’d for C₁₇H₃₀NaO₃Si [M+Na]⁺: 333.1856, found 333.1858. TLC (2:1 hexanes:EtOAc), Rf: 0.57 (KMnO₄).
Iodide 134:

Triphenylphosphine (4.69 g, 17.7 mmol, 1.10 equiv) and iodine (5.32 g, 20.9 mmol, 1.30 equiv) were added sequentially in single portions to a stirred solution of imidazole (1.66 g, 24.2 mmol, 1.50 equiv) in CH₂Cl₂ (35 mL). After 20 min, a solution of alcohol S₃ (5.00 g, 16.1 mmol, 1.00 equiv) in CH₂Cl₂ (35 mL) was added dropwise via cannula to the reaction mixture. After 1 h, saturated aqueous Na₂SO₃ solution (50 mL) and EtOAc (20 mL) were sequentially added to the reaction. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was dissolved in Et₂O and triphenylphosphine oxide precipitated upon standing. The suspension was then filtered through a thin pad of silica gel and all volatiles were removed in vacuo. The resulting oil was then purified by flash column chromatography (silica gel, eluent: gradient, 20:1 → 15:1 hexanes:EtOAc) to afford iodide 134 (5.93 g, 88%) as a colorless oil.

¹H NMR (600 MHz, CDCl₃) δ: 7.40–7.32 (m, 4H), 7.32–7.27 (m, 1H), 4.74 (d, J = 11.4 Hz, 1H), 4.58 (d, J = 11.4 Hz, 1H), 3.72 (q, J = 5.3 Hz, 1H), 3.64–3.56 (m, 2H), 3.34–3.25 (m, 2H), 2.14–1.94 (m, 2H), 0.91 (s, 9H), 0.06 (s, 6H). ¹³C NMR (126 MHz, CDCl₃) δ: 138.6, 128.4, 127.9, 127.7, 79.5, 72.7, 64.9, 36.1, 25.9, 18.3, 3.1, −5.37, −5.40. FTIR (thin film) cm⁻¹: 2953, 2928, 2856, 1471, 1256, 1116, 837, 777, 734, 697. HRMS (ESI) (m/z) calc’d for C₁₇H₂₃INaO₂Si [M+Na]⁺: 443.0874, found 443.0830. TLC (7:1 hexanes:EtOAc), Rₓ: 0.71 (UV, Anis).
TIPS furan 115:

A solution of furanone S\textsuperscript{45} (309 mg, 2.76 mmol, 1.00 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (5.5 mL) was cooled to 0 °C. i-Pr\textsubscript{2}NEt (1.06 mL, 6.06 mmol, 2.20 equiv) and TIPSOTf (815 μL, 3.03 mmol, 1.10 equiv) were then added dropwise sequentially via syringe to the stirred reaction mixture, which was subsequently allowed to warm slowly to room temperature. After 2 h, saturated aqueous NH\textsubscript{4}Cl solution (5 mL) and CH\textsubscript{2}Cl\textsubscript{2} (5 mL) were added sequentially to the reaction. The layers were separated and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 3 mL). The organic layers were combined, washed with brine (5 mL), dried over anhydrous MgSO\textsubscript{4}, and concentrated under reduced pressure. The resulting oil was then purified by flash column chromatography (silica gel, eluent: hexanes, 1% Et\textsubscript{3}N) to afford TIPS furan 115 (455 mg, 61%) as a yellow oil.

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ: 7.08–6.86 (m, 1H), 5.78 (q, J = 1.0 Hz, 1H), 2.53 (dq, J = 1.0, 7.6 Hz, 2H), 1.24–1.15 (m, 6H), 1.09 (d, J = 6.8 Hz, 18H). \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ: 156.3, 144.4, 126.1, 101.8, 21.8, 17.8, 12.3, 11.9. FTIR (thin film) cm\textsuperscript{-1}: 2944, 2867, 1617, 1463, 1384, 1149, 999, 882, 859, 683. HRMS (ESI) (m/z) calc’d for C\textsubscript{15}H\textsubscript{29}O\textsubscript{2}Si [M+H]\textsuperscript{+}: 269.1931, found 269.1934. TLC (2:1 hexanes:EtOAc), R\textsubscript{f}: 0.95 (UV, Anis).

Alkylated furan 135:

A solution of TIPS furan 115 (5.40 g, 20.1 mmol, 1.30 equiv), which was azeotropically dried with benzene (3 × 10 mL), in THF (26 mL) was cooled to −78 °C. A solution of n-butyllithium in hexanes (2.62 M, 7.08 mL, 18.6 mmol, 1.20 equiv) was then added dropwise. After 10 min, the reaction mixture was allowed to warm to 0 °C. After an additional 75 min, the reaction was cooled to −78 °C and a solution of alkyl iodide 134 (6.50 g, 15.5 mmol, 1.00 equiv) in THF (26 mL) was added dropwise via syringe over 10 min. The reaction mixture was then allowed to warm slowly to 0 °C over 4 h, at which point brine (50 mL) and Et₂O (30 mL) were sequentially added. The organic and aqueous layers were separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure. The resulting oil was then purified by flash column chromatography (silica gel, eluent: 80:1 → 50:1 → 20:1 hexanes:EtOAc, 1% Et₃N) to afford alkylated furan 135 (8.84 g) as a yellow oil. Due to difficulties in removing trace TIPS furan from product 135, an accurate yield was determined after the next step.

**¹H NMR** (600 MHz, CDCl₃) δ: 7.36 (d, J = 6.7 Hz, 2H), 7.31 (t, J = 7.3 Hz, 2H), 7.26–7.23 (m, 1H), 5.67 (s, 1H), 4.69 (d, J = 11.7 Hz, 1H), 4.60 (d, J = 11.4 Hz, 1H), 3.71 (dd, J = 6.2, 10.5 Hz, 1H), 3.61 (dd, J = 5.0, 10.5 Hz, 1H), 3.52–3.46 (m, 1H), 2.74–2.67 (m, 1H), 2.61 (ddd, J = 6.6, 8.9, 15.2 Hz, 1H), 2.49 (q, J = 7.6 Hz, 2H), 1.91–1.81 (m, 1H), 1.81–1.70 (m, 1H), 1.22–1.13 (m, 6H), 1.08 (d, J = 7.3 Hz, 18H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ: 153.1, 139.2, 138.1, 138.0, 128.2, 127.7, 127.3, 101.2, 79.5, 72.3, 65.9, 30.0, 25.9, 21.8, 21.0, 18.3, 17.9, 12.5, 12.1, −5.35, −5.41. **FTIR** (thin film) cm⁻¹: 2944, 2866, 1641, 1463, 1409, 1251, 1072, 997, 883,
836, 776, 684. **HRMS** (ESI) (m/z) calc’d for C$_{32}$H$_{56}$NaO$_4$Si$_2$ [M+Na]$^+$: 583.3609, found 583.3611.

**TLC** (12:1 hexanes:EtOAc), $R_f$: 0.57 (UV, Anis).
Furanone alcohol S5:

A solution of furan 135 (8.84 g, 15.8 mmol, 1.00 equiv) in THF (79 mL) was cooled to 0 °C. A solution of TBAF in THF (1.00 M, 39.4 mL, 39.4 mmol, 2.50 equiv) was then added dropwise via syringe to the solution. After 2 h, the reaction mixture was allowed to warm to room temperature. After an additional 10 min, brine (50 mL) and Et₂O (50 mL) were added sequentially to the reaction. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 40 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure. The resulting oil was then purified by flash column chromatography (silica gel, eluent: gradient, 1:1 → 2:1 → 4:1 → 8:1 → 1:0 EtOAc:hexanes) to afford an inseparable 1:1 mixture of C₆-diastereomers of furanone alcohol S5 (4.16 g, 93% over 2 steps) as a yellow oil.

1H NMR (600 MHz, CDCl₃) δ: 7.38–7.28 (m, 10H), 5.44 (s, 2H), 4.61 (d, J = 11.4 Hz, 2H), 4.56 (m, 2H), 4.47–4.39 (m, 2H), 3.76–3.68 (m, 2H), 3.60–3.51 (m, 4H), 2.52 (m, 4H), 2.12–2.04 (m, 1H), 2.03–1.94 (m, 1H), 1.88–1.61 (m, 6H), 1.24 (t, J = 7.5 Hz, 3H), 1.23 (t, J = 7.5 Hz, 3H). 13C NMR (126 MHz, CDCl₃) δ: 204.75, 204.72, 195.4, 195.3, 138.1, 128.5, 128.3, 127.83, 127.80, 126.9, 102.78, 102.76, 85.9, 85.8, 79.0, 78.8, 71.63, 71.60, 63.9, 63.8, 27.0, 26.9, 25.8, 25.7, 24.2, 10.2. FTIR (thin film) cm⁻¹: 3435, 2939, 2878, 1693, 1590, 1390, 1108, 1059, 740, 699. HRMS (ESI) (m/z) calc’d for C₁₇H₂₂NaO₄ [M+Na]⁺: 313.1410, found 313.1418. TLC (2:1 EtOAc:hexanes), Rf: 0.25 (UV, Anis).
Furanone (Z)-enoate 137:

A solution of oxalyl chloride (6.86 mL, 79.5 mmol, 2.00 equiv) in CH$_2$Cl$_2$ (397 mL) was cooled to −78 °C. DMSO (11.3 mL, 159 mmol, 4.00 equiv) was then added dropwise. After 1.5 h, a solution of furanone alcohol S5 (11.5 g, 39.8 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (173 mL) at −78 °C was added dropwise via a dry-ice wrapped cannula to the stirred reaction. After 1 h, i-Pr$_2$NEt (41.5 mL, 239 mmol, 6.00 equiv) was added dropwise via syringe to the reaction mixture. After 15 min, the reaction was allowed to warm slowly to −20 °C over 30 min. After an additional 40 min, saturated aqueous NH$_4$Cl solution (500 mL) was added to the reaction, and the resultant mixture was allowed to warm to room temperature. EtOAc (1 L) was then added and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 300 mL). The organic layers were combined, washed with saturated aqueous NH$_4$Cl solution (8 × 700 mL), then brine (500 mL), and dried over anhydrous MgSO$_4$ and concentrated under reduced pressure. The crude aldehyde 136 was carried forward to the next step without further purification.

A solution of allyl diphenylphosphonoacetate$^{76}$ (14.5 g, 43.7 mmol, 1.10 equiv) in THF (300 mL) was cooled to 0 °C. NaI (7.29 g, 47.7 mmol, 1.20 equiv) and DBU (6.54 mL, 43.7 mmol, 1.10 equiv) were then added sequentially to the solution. After 20 min, the reaction was cooled to −78 °C before a solution of crude aldehyde 136 in THF (100 mL) was added dropwise via cannula. After 2.5 h, saturated aqueous NH$_4$Cl solution (300 mL) was added to the stirred reaction mixture, which was then allowed to warm to room temperature. The mixture was diluted with EtOAc (600 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 300 mL) and the organic

$^{76}$ Ando, K. J. Org. Chem. 1999, 64, 8406-8408.
layers were combined, washed with saturated aqueous NH$_4$Cl solution (5 × 300 mL), then brine (300 mL), and dried over anhydrous MgSO$_4$ and concentrated. The resulting oil was then purified by flash column chromatography twice using different eluent conditions (silica gel, eluent: (a) gradient, 20:1 → 15:1 → 10:1 → 7:1 → 5:1 → 2:1 CH$_2$Cl$_2$:EtOAc (removes unreacted allyl diphenylphosphonoacetate), (b) gradient, 6:1 → 4:1 → 2:1 hexanes:EtOAc) to afford an inseparable 1:1 mixture of C6-diastereomers of furanone (Z)-enoate 137 (11.0 g, 74% over 2 steps) as a pale yellow oil.

$^1$H NMR (600 MHz, CDCl$_3$) δ: 7.36–7.24 (m, 10H), 6.21 (dd, $J$ = 2.3, 8.5 Hz, 1H), 6.19 (dd, $J$ = 2.3, 8.5 Hz, 1H), 5.98–5.88 (m, 4H), 5.41 (m, 2H), 5.33 (m, 2H), 5.26 (m, 2H), 5.11–5.05 (m, 2H), 4.64–4.57 (m, 4H), 4.52 (m, 2H), 4.46 (dd, $J$ = 4.1, 7.9 Hz, 1H), 4.44–4.39 (m, 3H), 2.50 (q, $J$ = 7.6 Hz, 4H), 2.20–2.09 (m, 1H), 2.06–1.96 (m, 1H), 1.92–1.78 (m, 3H), 1.78–1.64 (m, 3H), 1.22 (t, $J$ = 7.6 Hz, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 204.68, 204.65, 195.13, 195.09, 165.29, 165.26, 150.81, 150.79, 138.23, 138.19, 132.0, 128.3, 127.8, 127.7, 127.62, 127.60, 121.5, 121.4, 118.5, 102.6, 86.0, 85.8, 74.5, 74.3, 71.4, 71.3, 65.1, 65.0, 30.0, 29.9, 27.1, 27.0, 24.1, 10.2. FTIR (thin film) cm$^{-1}$: 2981, 2942, 1718, 1698, 1595, 1389, 1181, 1071, 986, 824, 698. HRMS (ESI) (m/z) calc’d for C$_{22}$H$_{26}$NaO$_5$ [M+Na]$^+$: 393.1673, found 393.1676. TLC (1:1 hexanes:EtOAc), $R_f$: 0.41 (UV, Anis).
Oxanorbornanone allyl ester 138:

A solution of diisopropylamine (1.85 mL, 13.2 mmol, 1.40 equiv) in THF (140 mL) was cooled to −78 °C. A solution of n-butyllithium in hexanes (2.56 M, 4.78 mL, 12.3 mmol, 1.30 equiv) was then added dropwise via syringe to the solution. After 15 min, the reaction was allowed to warm to 0 °C for 20 min before recooling to −78 °C. Additional THF (210 mL) was added to the reaction at −78 °C. A solution of furanone (Z)-enoate 137 (3.49 g, 9.42 mmol, 1.00 equiv) in THF (120 mL) at −78 °C was added dropwise via a dry-ice wrapped cannula to the solution of LDA. After an additional 8.5 h, a solution of AcOH (3.5 mL) in THF (70 mL) was added via cannula to the stirred reaction. After an additional 15 min, saturated aqueous NH₄Cl solution (400 mL) was added to the mixture, which was then allowed to warm to room temperature. The resultant mixture was diluted with EtOAc (400 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 300 mL) and the organic layers were combined, washed with saturated aqueous NaHCO₃ solution (3 × 200 mL) and brine (300 mL). The organic layers were then dried over anhydrous MgSO₄ and concentrated under reduced pressure. The resulting oil was then purified by flash column chromatography (silica gel, eluent: gradient, 9:1 → 8:1 → 7:1 → 5:1 hexanes:EtOAc) to afford oxanorbornanone allyl ester 138 (2.24 g, 64%) as a colorless oil.

**1H NMR** (600 MHz, CDCl₃) δ: 7.33–7.24 (m, 5H), 5.90–5.82 (m, 1H), 5.30 (qd, J = 1.5, 17.0 Hz, 1H), 5.21 (qd, J = 1.1, 10.4 Hz, 1H), 4.61 (tdd, J = 1.3, 6.0, 13.0 Hz, 1H), 4.46 (tdd, J = 1.3, 6.0, 13.0 Hz, 1H), 4.42 (d, J = 11.4 Hz, 1H), 4.37 (d, J = 11.1 Hz, 1H), 4.28 (dd, J = 7.3, 13.5 Hz, 1H), 3.13 (d, J = 9.1 Hz, 1H), 2.62 (dd, J = 7.2, 9.2 Hz, 1H), 2.41–2.25 (m, 4H), 2.12–2.00 (m, 1H), 1.94–1.80 (m, 3H), 0.97 (t, J = 7.6 Hz, 3H). **13C NMR** (126 MHz, CDCl₃) δ: 208.1, 170.1, 138.2, 131.7, 128.3,
127.6, 127.5, 119.0, 95.6, 89.2, 80.2, 71.9, 65.4, 55.3, 51.6, 47.5, 32.5, 25.6, 21.2, 8.8. **FTIR** (thin film) cm$^{-1}$: 2938, 1761, 1733, 1455, 1354, 1184, 1152, 698. **HRMS** (ESI) ($m/z$) calc’d for C$_{22}$H$_{26}$NaO$_5$ [M+Na]$^+$: 393.1673, found 393.1657. **TLC** (2:1 hexanes:EtOAc), $R_f$: 0.66 (Anis).

**1D NOESY** (600 MHz, CDCl$_3$):
Carboxylic acid 139:

Pd(PPh₃)₄ (2.67 g, 2.28 mmol, 0.10 equiv) in THF (85 mL) was added via cannula to a stirred solution of oxanorbornanone allyl ester 138 (8.43 g, 22.8 mmol, 1.00 equiv) in THF (191 mL). Morpholine (19.9 mL, 228 mmol, 10.0 equiv) was then added via syringe to the reaction mixture. After 4 h, the reaction was concentrated under reduced pressure. The resultant residue was then dissolved in CH₂Cl₂ (100 mL) and washed with saturated aqueous NaHCO₃ solution (5 × 75 mL). The aqueous layers were combined and acidified by careful dropwise addition of 10% aqueous HCl until the pH reached 2. The aqueous layers were then extracted with CH₂Cl₂ (5 × 120 mL). The organic layers were combined, dried over anhydrous MgSO₄, and concentrated under reduced pressure to afford crude carboxylic acid 139 as a white solid (6.44 g, 86% mass recovery). The crude product was carried forward to the next step without further purification.

¹H NMR (500 MHz, CDCl₃) δ: 7.35–7.27 (m, 5H), 4.43 (d, J = 11.5 Hz, 1H), 4.38 (d, J = 11.2 Hz, 1H), 4.24 (q, J = 6.8 Hz, 1H), 3.17 (d, J = 9.0 Hz, 1H), 2.67 (dd, J = 6.8, 9.0 Hz, 1H), 2.43–2.27 (m, 4H), 2.17–2.06 (m, 1H), 2.00–1.83 (m, 3H), 1.00 (t, J = 7.7 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ: 207.4, 173.9, 138.0, 128.4, 127.74, 127.68, 95.8, 89.3, 80.3, 71.8, 55.4, 51.7, 47.2, 32.6, 25.7, 21.3, 8.9. FTIR (thin film) cm⁻¹: 2972, 2942, 1762, 1706, 1358, 1160, 1119, 1099, 965, 740, 699. HRMS (ESI) (m/z) calc’d for C₁₉H₂₂NaO₅ [M+Na]+: 353.1359, found 353.1363. TLC (1:1 hexanes:EtOAc and 1 drop of AcOH), Rf: 0.36 (Anis).
**Alcohol 142:**

A solution of carboxylic acid 139 (50.0 mg, 0.151 mmol, 1.00 equiv), which was azeotropically dried with benzene (3 × 0.5 mL) in CH$_2$Cl$_2$ (1.5 mL) was cooled to 0 °C. Oxalyl chloride (16.0 µL, 0.189 mmol, 1.25 equiv) and a single drop of DMF were then sequentially added via syringe to the stirred solution, which was subsequently allowed to warm to room temperature after 10 min. After 3 h, the reaction mixture was recooled to 0 °C.  $p$-Nitroperbenzoic acid$^{77}$ (37.0 mg, 0.197 mmol, 1.30 equiv), pyridine (28.0 µL, 0.348 mmol, 2.30 equiv), and a single crystal of 4-DMAP were then added sequentially to the stirred reaction mixture. After 1 h, CH$_2$Cl$_2$ (1 mL) and 10% aqueous HCl (1 mL) were sequentially added to the reaction. The mixture was further diluted with CH$_2$Cl$_2$ (1 mL) and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 1 mL). The organic layers were combined, washed with a saturated aqueous NaHCO$_3$ solution (3 × 1 mL), then dried over anhydrous MgSO$_4$ and concentrated under reduced pressure to afford crude diacyl peroxide 143, which was carried forward immediately to the next step without further purification.

A pressure tube was charged with crude 143 and benzene (5 mL), sealed, and heated to 80 °C. After 5.5 h, the reaction was allowed to cool to room temperature and was subsequently concentrated under reduced pressure. The crude residue was then suspended in methanol (3 mL) and the resultant mixture was cooled to 0 °C. K$_2$CO$_3$ (22.0 mg, 0.159 mmol, 1.05 equiv) was then added in a single portion. After 1 h, the reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in EtOAc (3 mL) and washed with a saturated aqueous NaHCO$_3$.

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solution (2 mL) and brine (2 mL), dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. The resulting crude residue was then purified by flash column chromatography (silica gel, eluent: gradient, 8:1 → 6:1 → 4:1 → 3:1 → 2:1 hexanes:EtOAc) to afford alcohol 142 (19.6 mg, 43% over 3 steps) as a pale yellow solid.

$^1$H NMR (500 MHz, CDCl$_3$) δ: 7.38–7.27 (m, 5H), 4.56 (d, $J = 12.0$ Hz, 1H), 4.48 (d, $J = 11.7$ Hz, 1H), 4.29 (dd, $J = 6.8$, 13.2 Hz, 1H), 4.20 (d, $J = 6.8$ Hz, 1H), 2.42 (t, $J = 7.0$ Hz, 1H), 2.37–2.30 (m, 2H), 2.27 (d, $J = 17.8$ Hz, 1H), 2.17 (d, $J = 18.1$ Hz, 1H), 2.08–1.92 (m, 2H), 1.89–1.75 (m, 2H), 1.01 (t, $J = 7.6$ Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 207.9, 138.3, 128.5, 127.8, 127.7, 95.7, 90.1, 77.8, 74.5, 71.7, 56.7, 42.9, 33.2, 23.7, 21.4, 8.5. FTIR (thin film) cm$^{-1}$: 3482, 2970, 2938, 1760, 1454, 1358, 1115, 1065, 739, 698. HRMS (ESI) ($m/z$) calc’d for C$_{18}$H$_{22}$NaO$_4$ [M+Na]$^+$: 325.1410, found 325.1405. TLC (2:1 hexanes:EtOAc), $R_f$: 0.36 (Anis). $[\alpha]_D^{25}$: $–4.1$ ($c = 1.41$, CH$_2$Cl$_2$).

1D NOESY (600 MHz, CDCl$_3$):
Oxanorbornanone dimerization precursor 144:

A solution of alcohol 142 (517 mg, 1.71 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 2 mL) in CH₂Cl₂ (19 mL) was cooled to 0 °C. i-Pr₂NEt (1.19 mL, 6.85 mmol, 4.00 equiv) and TBSOTf (590 µL, 2.56 mmol, 1.50 equiv) were then added dropwise sequentially via syringe to the stirred reaction, which was subsequently allowed to warm slowly to room temperature. After 11 h, additional i-Pr₂NEt (306 µL, 1.71 mmol, 1.00 equiv) and TBSOTf (152 µL, 0.684 mmol, 0.40 equiv) were added dropwise sequentially via syringe to the reaction. After an additional 16 h, saturated aqueous NH₄Cl solution (10 mL) was added and the resultant mixture was diluted with EtOAc (25 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The organic layers were combined, washed with brine (15 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure. The resulting crude residue was then purified by flash column chromatography (silica gel, eluent: gradient, 20:1 → 17:1 → 15:1 → 12:1 → 9:1 → 7:1 hexanes:EtOAc) to afford oxanorbornanone dimerization precursor 144 (570 mg, 80%) as a clear oil.

¹H NMR (500 MHz, CDCl₃) δ: 7.36–7.24 (m, 5H), 4.47 (d, J = 11.2 Hz, 1H), 4.39 (d, J = 11.2 Hz, 1H), 4.32 (td, J = 4.2, 6.0 Hz, 1H), 4.15 (d, J = 7.1 Hz, 1H), 2.47 (dd, J = 5.4, 17.8 Hz, 1H), 2.36 (d, J = 17.8 Hz, 1H), 2.33–2.19 (m, 1H), 2.10–1.94 (m, 2H), 1.92–1.84 (m, 1H), 1.76 (qd, J = 7.4, 14.4 Hz, 1H), 0.99 (t, J = 7.6 Hz, 3H), 0.94 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ: 209.0, 138.5, 128.32, 128.30, 127.4, 96.3, 89.8, 78.6, 76.4, 71.1, 58.0, 42.2, 32.1, 25.9, 25.8, 22.6, 18.3, 8.4, –4.6, –4.7. FTIR (thin film) cm⁻¹: 2956, 2929, 2856, 1763, 1463, 1254, 1122, 837, 776. HRMS (ESI) (m/z) calc’d for C₂₄H₃₇O₄Si [M+Na]⁺: 417.2456, found 417.2454. TLC (2:1 hexanes:EtOAc), Rf: 0.77 (Anis).
**Exo-end**o dimer 145:

A two-neck flask was equipped with a solid addition adaptor containing ferrocenium hexafluorophosphate \([\text{Cp}_2\text{Fe}]\text{PF}_6\) (661 mg, 2.00 mmol, 5.00 equiv). HMDS (150 µL, 0.719 mmol, 1.80 equiv) and THF (1.35 mL) were then added sequentially to the two-neck flask and the resultant solution was cooled to −78 °C. A solution of \(n\)-butyllithium in hexanes (2.56 M, 265 µL, 0.679 mmol, 1.70 equiv) was then added dropwise via syringe to the stirred solution. After 1 h, HMPA (140 µL, 0.799 mmol, 2.00 equiv) was added dropwise via syringe to the solution of LiHMDS. After an additional 1 h, a solution of oxanorbornanone monomer 144 (166 mg, 0.399 mmol, 1.00 equiv) in THF (1.35 mL) was slowly added down the vessel wall via syringe to the reaction mixture. After an additional 2 h, \([\text{Cp}_2\text{Fe}]\text{PF}_6\) was added to the reaction via the solid addition adaptor, yielding a deep blue suspension that turned green in color within 30 min. The reaction mixture was allowed to warm to −55 °C. After 4 d, a saturated aqueous NH\(_4\)Cl solution (2 mL) was added to the reaction, which was then allowed to warm to room temperature. The mixture was diluted with Et\(_2\)O (2 mL), EtOAc (2 mL), and water (2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 2 mL). The organic layers were combined, dried over anhydrous MgSO\(_4\), and concentrated under reduced pressure. The crude product was then purified by flash column chromatography (silica gel, eluent: gradient, 20:1 → 9:1 hexanes:EtOAc) to afford exo-end**o dimer 145 (72.6 mg, 44%) as a white flocculent solid.

**\(^1\)H NMR** (600 MHz, CDCl\(_3\)) \(\delta\): 7.35–7.28 (m, 10H), 4.61 (d, \(J = 7.6\) Hz, 1H), 4.48–4.43 (m, 2H), 4.41–4.36 (m, 2H), 4.36–4.30 (m, 2H), 4.22 (d, \(J = 7.6\) Hz, 1H), 2.91 (d, \(J = 7.6\) Hz, 1H), 2.39 (dt, \(J = 4.8, 7.5\) Hz, 2H), 2.36–2.27 (m, 3H), 2.26–2.18 (m, 2H), 2.14–2.00 (m, 4H), 1.99–1.83 (m, 3H),
1.40 (dd, $J = 7.8, 15.1$ Hz, 1H), 1.05 (t, $J = 7.6$ Hz, 3H), 0.98 (t, $J = 7.5$ Hz, 3H), 0.94 (s, 9H), 0.91 (s, 9H), 0.17 (s, 3H), 0.13 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 211.9, 211.7, 138.6, 138.5, 128.30, 128.25, 128.1, 127.39, 127.35, 127.3, 96.5, 96.3, 94.3, 92.8, 78.9, 78.83, 78.76, 74.1, 71.3, 70.8, 59.7, 58.3, 52.0, 51.0, 32.4, 31.7, 26.1, 25.9, 23.9, 23.7, 22.1, 21.1, 18.2, 18.2, 8.8, 8.1, –4.5, –4.6, –4.8, –4.9. FTIR (thin film) cm$^{-1}$: 2929, 2856, 1753, 1462, 1359, 1253, 1109, 836, 776, 733, 696. HRMS (ESI) (m/z) calc’d for $C_{48}H_{70}NaO_8Si_2$ [M+Na]$^+$: 853.4501, found 853.4508. TLC (4:1 hexanes:EtOAc), $R_f$: 0.62 (UV, Anis).

1D NOESY (500 MHz, CDCl$_3$):
**Exo-exo dimer 146:**

A solution of *exo-endo* dimer 145 (102 mg, 0.123 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 1 mL), in MeCN (7.2 mL) was cooled to −5 °C. Two drops of 2-tert-butyl-1,1,3,3-tetramethylguanidine (Barton’s base) was then added via syringe to the solution. After 24 h, saturated aqueous NH₄Cl solution (5 mL) was added to the reaction, which was then allowed to warm to room temperature. The resultant mixture was diluted with CH₂Cl₂ (15 mL) and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL) and the organic layers were combined, washed with saturated aqueous NH₄Cl solution (3 × 5 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure. The resulting crude *exo-exo* dimer 146 was then carried forward to the next step without further purification.

**1H NMR** (500 MHz, CDCl₃) δ: 7.35–7.29 (m, 8H), 7.26–7.22 (m, 2H), 4.46 (d, J = 11.5 Hz, 2H), 4.43 (d, J = 11.5 Hz, 2H), 4.41–4.36 (m, 4H), 2.97 (dd, J = 5.7, 7.4 Hz, 2H), 2.38–2.26 (m, 6H), 2.24 (s, 2H), 2.02–1.93 (m, 2H), 1.92–1.83 (m, 2H), 1.43 (qd, J = 7.4, 15.1 Hz, 2H), 1.03 (t, J = 7.4 Hz, 6H), 0.91 (s, 18H), 0.05 (s, 6H), 0.04 (s, 6H). **13C NMR** (126 MHz, CDCl₃) δ: 209.1, 138.7, 128.1, 127.3, 127.2, 97.8, 92.1, 78.8, 74.4, 71.1, 58.2, 47.8, 31.8, 25.9, 23.4, 20.9, 18.3, 7.9, −4.8, −5.0. **FTIR** (thin film) cm⁻¹: 2954, 2929, 2857, 1757, 1462, 1357, 1252, 1123, 963, 837, 776, 697. **HRMS (ESI) (m/z) calc’d for C₄₈H₇₀NaO₈Si₂ [M+Na]⁺: 853.4501, found 853.4516. **TLC** (4:1 hexanes:EtOAc), R_f: 0.60 (UV, Anis). [α]_D<sup>25</sup>: −48.3 (c = 0.43, CH₂Cl₂).
**Diol dimer 147:**

Pd(OH)$_2$ on carbon (20 wt%, 79.4 mg, 0.113 mmol, 1.00 equiv) was added in a single portion to a stirred solution of *exo-exo* dimer 146 (94.0 mg, 0.113 mmol, 1.00 equiv) in THF (5.65 mL). The reaction vessel was purged with H$_2$ and placed under an atmosphere of H$_2$. After 4 h, celite was poured into the stirred reaction mixture and the resultant slurry was filtered through a pad of celite. The solution was concentrated under reduced pressure and the residue was then purified by flash column chromatography (silica gel, eluent: gradient, 3:1 → 2:1 hexanes:EtOAc) to afford diol dimer 147 (73.6 mg, quant. over 2 steps) as a white crystalline solid.

$^1$H NMR (600 MHz, C$_6$D$_6$) δ: 4.69 (d, $J = 7.3$ Hz, 2H), 4.65 (app. t, $J = 7.0$ Hz, 2H), 2.90 (t, $J = 7.5$ Hz, 2H), 2.54–2.45 (m, 4H), 2.30 (ddd, $J = 4.4$, 10.8, 15.3 Hz, 2H), 2.07–2.00 (m, 2H), 1.78–1.68 (m, 2H), 1.58–1.48 (m, 2H), 1.43–1.33 (m, 2H), 1.09 (t, $J = 7.5$ Hz, 6H), 0.98 (s, 18H), 0.68 (d, $J = 7.0$ Hz, 2H), 0.19 (s, 6H), 0.04 (s, 6H). $^{13}$C NMR (126 MHz, C$_6$D$_6$) δ: 209.8, 98.5, 92.7, 75.0, 72.5, 60.1, 48.8, 36.1, 26.4, 22.7, 21.9, 18.8, 8.4, −4.3, −4.6. FTIR (thin film) cm$^{-1}$: 2951, 2930, 2858, 1757, 1462, 1254, 1126, 1065, 840, 776. HRMS (ESI) ($m/z$) calc’d for C$_{34}$H$_{58}$NaO$_8$Si$_2$ [M+Na]$^+$: 673.3562, found 673.3550. TLC (4:1 hexanes:EtOAc), $R_f$: 0.15 (Anis).
Tetracarbonyl oxanorbornanone dimer 148:

A solution of diol dimer 147 (73.2 mg, 0.112 mmol, 1.00 equiv), which was azeotropically dried with benzene (3 × 0.5 mL) in CH$_2$Cl$_2$ (2.8 mL) was cooled to −10 °C. DMSO (160 µL, 2.25 mmol, 20.0 equiv), i-Pr$_2$NEt (196 µL, 1.12 mmol, 10.0 equiv), and SO$_3$·Py (107 mg, 0.675 mmol, 6.00 equiv) were then added sequentially to the solution, which was then allowed to warm slowly to room temperature after stirring at 0 °C for 30 min. After an additional 90 min, water (3 mL), Et$_2$O (2 mL), and EtOAc (2 mL) were added sequentially to the reaction. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 2 mL). The organic layers were combined and washed with 10% aqueous HCl solution (3 × 5 mL), saturated aqueous NaHCO$_3$ solution (5 mL), and brine (5 mL). The organic layers were dried over anhydrous MgSO$_4$ and concentrated under reduced pressure to afford crude tetracarbonyl oxanorbornanone dimer 148 as a flocculent white solid (68.4 mg, crude mass).

$^1$H NMR (500 MHz, C$_6$D$_6$) δ: 4.77 (d, J = 7.6 Hz, 2H), 3.14 (d, J = 7.6 Hz, 2H), 2.62–2.47 (m, 4H), 2.40–2.26 (m, 2H), 1.90–1.80 (m, 4H), 1.74 (dd, J = 9.5, 12.7 Hz, 2H), 1.53 (qd, J = 7.4, 15.2 Hz, 2H), 1.06 (t, J = 7.4 Hz, 6H), 1.00 (s, 18H), 0.41 (s, 6H), 0.16 (s, 6H). $^{13}$C NMR (126 MHz, C$_6$D$_6$) δ: 208.9, 207.5, 96.3, 93.2, 77.5, 58.6, 48.6, 39.0, 26.5, 21.8, 20.8, 19.0, 8.4, −4.3, −5.0. FTIR (thin film) cm$^{-1}$: 2951, 2928, 2856, 1749, 1472, 1257, 1119, 886, 837. HRMS (ESI) (m/z) calc’d for C$_{34}$H$_{55}$O$_8$Si$_2$ [M+H]$^+$: 647.3430, found 647.3434. TLC (2:1 hexanes:EtOAc), R$_f$: 0.69 (Anis).
Alcohol 162:

Carboxylic acid 139 (300 mg, 0.908 mmol, 1.00 equiv) was azeotropically dried with CHCl₃ (4 × 2 mL) and benzene (5 × 2 mL) before THF (11.2 mL) was added. Et₃N (507 µL, 3.63 mmol, 4.00 equiv) was then added to the solution. The resultant solution of 139 and Et₃N in THF was added dropwise via cannula to a stirred solution of S-(1-oxido-2-pyridinyl) 1,1,3,3-tetramethylthiouronium hexafluorophosphate (HOTT)⁴⁴ (674 mg, 1.82 mmol, 2.00 equiv) and 4-DMAP (11.1 mg, 0.0910 mmol, 0.10 equiv) in THF (7.1 mL) at room temperature. After 5 h, additional THF (27.6 mL) was added to the reaction mixture. The reaction was then saturated with O₂ before Sb(SPh)₃⁵⁵ (1.22 g, 2.72 mmol, 3.00 equiv) was added in a single portion. The reaction flask was protected from light with aluminum foil. After 2 h, water (0.25 mL) was added to the reaction. After an additional 45 min, the mixture was filtered through celite and concentrated under reduced pressure. The resulting crude product was then purified by flash column chromatography (silica gel, eluent: gradient, 4:1 → 3:1 → 2:1 hexanes:EtOAc) to afford alcohol 162 (131.8 mg, 48%) as a yellow oil.

¹H NMR (500 MHz, CDCl₃) δ: 7.39–7.33 (m, 4H), 7.33–7.29 (m, 1H), 4.62 (d, J = 12.0 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 3.97 (app. q, J = 6.8 Hz, 1H), 3.94 (app. t, J = 2.9 Hz, 1H), 2.74 (d, J = 17.8 Hz, 1H), 2.36–2.25 (m, 2H), 2.14 (dd, J = 1.0, 17.8 Hz, 1H), 1.99 (dd, J = 2.7, 6.8 Hz, 1H), 1.93–1.85 (m, 1H), 1.83 (dq, J = 1.6, 7.5 Hz, 2H), 1.78 (d, J = 3.7 Hz, 1H), 1.76–1.68 (m, 1H), 1.00 (t, J = 7.6 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ: 208.8, 138.4, 128.6, 127.9, 127.7, 97.0, 88.4, 84.7, 80.1, 72.1, 62.0, 40.5, 32.3, 26.4, 21.9, 8.0. FTIR (thin film) cm⁻¹: 3441, 2969, 2933, 1758, 1574, 1453, 1418, 1097, 1060, 738, 699. HRMS (ESI) (m/z) calc’d for C₁₈H₂₂NaO₄ [M+Na]⁺: 325.1410, found 325.1407. TLC (2:1 hexanes:EtOAc and 1 drop of AcOH), Rf: 0.24 (Anis).

¹D NOESY (500 MHz, CD₃OD):
Oxanorbornanone dimerization precursor 163:

A solution of alcohol 162 (150 mg, 0.496 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 0.5 mL), in CH₂Cl₂ (5.5 mL) was cooled to 0 °C. i-Pr₂NEt (475 µL, 2.73 mmol, 5.50 equiv) and TBSOTf (233 µL, 0.992 mmol, 2.00 equiv) were then added dropwise sequentially via syringe to the stirred solution, which was subsequently allowed to warm slowly to room temperature. After 1.5 h, saturated aqueous NH₄Cl solution (5 mL) was added to the reaction. The resultant mixture was diluted with EtOAc (5 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 3 mL). The organic layers were combined, washed with brine (5 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude residue was then purified by flash column chromatography (silica gel, eluent: 16:1 hexanes:EtOAc) to afford oxanorbornanone dimerization precursor 163 (185 mg, 89%) as a pale yellow solid.

^1H NMR (500 MHz, C₆D₆) δ: 7.24 (d, J = 7.8 Hz, 2H), 7.19 (t, J = 7.6 Hz, 2H), 7.10 (t, J = 7.3 Hz, 1H), 4.27 (d, J = 11.7 Hz, 1H), 4.13 (d, J = 11.7 Hz, 1H), 3.95 (d, J = 2.0 Hz, 1H), 3.79 (app. q, J = 6.5 Hz, 1H), 2.78 (d, J = 17.6 Hz, 1H), 2.40 (ddd, J = 6.1, 10.0, 14.6 Hz, 1H), 2.18 (dd, J = 2.7, 6.6 Hz, 1H), 2.00 (dd, J = 1.0, 17.6 Hz, 1H), 1.91 (tdd, J = 6.3, 8.2, 12.8 Hz, 1H), 1.71 (dd, J = 6.2, 8.2, 14.6 Hz, 1H), 1.64 (q, J = 7.4 Hz, 2H), 1.61–1.52 (m, 1H), 0.89 (t, J = 7.4 Hz, 3H), 0.84 (s, 9H), 0.06 (s, 3H), 0.00 (s, 3H). ^13C NMR (126 MHz, CDCl₃) δ: 209.5, 137.9, 128.3, 127.8, 127.6, 96.8, 88.6, 84.3, 80.3, 71.8, 62.1, 40.8, 31.3, 25.9, 25.7, 22.4, 17.8, 7.9, –4.6, –5.2. FTIR (thin film) cm⁻¹: 2955, 2929, 2857, 1764, 1252, 1117, 1062, 863, 838, 778. HRMS (ESI) (m/z) calc’d for C₂₄H₃₂NaO₄Si [M+Na]^+: 439.2275, found 439.2291. TLC (4:1 hexanes:EtOAc), Rf: 0.63 (Anis). [α]D²⁵: +28.3 (c = 0.12, CH₂Cl₂).
Cyclic hydrate 166:

A two-neck flask was equipped with a solid addition adaptor containing ferrocenium hexafluorophosphate \([\text{Cp}_2\text{Fe}]\text{PF}_6\) (199 mg, 0.600 mmol, 5.00 equiv). HMDS (48.0 \(\mu\)L, 0.228 mmol, 1.90 equiv) and THF (477 \(\mu\)L) were added to the two-neck flask and the resultant stirred solution was cooled to \(-78 \, ^\circ\text{C}\). A solution of \(n\)-butyllithium in hexanes (2.56 M, 80.0 \(\mu\)L, 0.204 mmol, 1.70 equiv) was then added dropwise via syringe to the solution. After 30 min, HMPA (105 \(\mu\)L, 0.600 mmol, 5.00 equiv) was added dropwise via syringe to the solution of LiHMDS. After an additional 1 h, a solution of oxanorbornanone monomer 163 (50.0 mg, 0.120 mmol, 1.00 equiv) in THF (293 \(\mu\)L) was then slowly added down the vessel wall to the reaction. After another 2 h, \([\text{Cp}_2\text{Fe}]\text{PF}_6\) was added from the solid addition adaptor. The initially deep blue suspension turned green within 30 min and was allowed to stir at \(-60 \, ^\circ\text{C}\). After 5 d, saturated aqueous NH_4Cl solution (1 mL) was added to the stirred reaction mixture, which was allowed to warm to room temperature. The mixture was diluted with Et_2O (1 mL), EtOAc (1 mL), and water (0.5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 \(\times\) 1 mL). The organic layers were combined, dried over anhydrous MgSO_4, and concentrated under reduced pressure. Due to the high instability of crude dimer 164 to silica gel column chromatography, the crude product was quickly plugged through silica gel using 20:1 hexanes:EtOAc (removes ferrocene) and 2:1 hexanes:EtOAc (elutes product) within 10 min to afford crude dimer 164, which was carried forward without further purification.

Pd(OH)_2 on carbon (20 wt.%, 253 mg, 0.360 mmol, 3.00 equiv) was added in a single portion to a stirred solution of crude dimer 164 in THF (4 mL). The reaction vessel was purged with H_2 and placed under an atmosphere of H_2. After 4 h, celite (100 mg) was poured into the reaction,
and the resultant slurry was filtered through a pad of celite and concentrated under reduced pressure to afford crude diol 165, which was carried forward without further purification.

A solution of crude diol 165, which was azeotropically dried with benzene (5 × 0.5 mL), in CH₂Cl₂ (3 mL) was cooled to 0 °C. DMSO (228 µL, 3.20 mmol, 26.7 equiv), i-Pr₂NEt (278 µL, 1.60 mmol, 13.3 equiv), and SO₃•Py (153 mg, 0.960 mmol, 8.00 equiv) were then added sequentially to the reaction, which was allowed to warm slowly to room temperature after 30 min. After an additional 90 min, water (3 mL), Et₂O (2 mL), and EtOAc (2 mL) were added sequentially to the reaction mixture. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 2 mL). The organic layers were combined and washed with 10% aqueous HCl solution (3 × 5 mL), saturated aqueous NaHCO₃ solution (5 mL), and brine (5 mL). The organic layers were dried over anhydrous MgSO₄ and concentrated under reduced pressure. The resulting crude product was then purified by flash column chromatography (silica gel, eluent: gradient, 4:1 → 3:1 → 2:1 hexanes:EtOAc) to afford cyclic hydrate 166 (22.7 mg, 57% over 3 steps) as a white solid.

¹H NMR (600 MHz, C₆D₆) δ: 4.32 (d, J = 2.6 Hz, 2H), 3.21 (s, 2H), 3.18 (s, 2H), 2.71 (d, J = 2.6 Hz, 2H), 2.20–2.12 (m, 2H), 2.11–1.98 (m, 4H), 1.95–1.88 (m, 2H), 1.85–1.79 (m, 2H), 1.79–1.70 (m, 2H), 0.96 (t, J = 7.6 Hz, 6H), 0.94 (s, 18H), 0.33 (s, 6H), 0.19 (s, 6H). ¹³C NMR (126 MHz, C₆D₆) δ: 215.0, 115.6, 94.4, 90.5, 79.5, 61.0, 49.9, 36.9, 26.2, 24.8, 21.4, 18.2, 8.6, –4.3, –4.9. FTIR (thin film) cm⁻¹: 3397, 2928, 2856, 1743, 1463, 1251, 1109, 1060, 839, 778. HRMS (ESI) (m/z) calc’d for C₃₄H₅₆NaO₉Si₂ [M+Na⁺]: 687.3355, found 687.3399. TLC (2:1 hexanes:EtOAc), Rf: 0.28 (Anis). [α]₀°D: +61.4 (c = 0.14, CH₂Cl₂).
**Epi-lomaiviticin B core 169:**

A 1 M solution of KOH in water (339 µL, 0.339 mmol, 7.00 equiv) was added dropwise via syringe to a solution of cyclic hydrate 166 (32.2 mg, 0.0480 mmol, 1.00 equiv) in 3:1 THF/water (4.85 mL) at 0 °C. After 24 h, saturated aqueous NH₄Cl solution (1 mL) was added to the stirred reaction mixture, which was then allowed to warm to room temperature. The resultant mixture was diluted with EtOAc (3 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 3 mL). The organic layers were combined and washed with brine (5 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure to afford crude bisenone cyclic hydrate product 167, which was carried forward to the next step without further purification.

MgSO₄ (70.0 mg, 0.581 mmol, 12.0 equiv) was added in a single portion to a stirred solution of crude 167 in benzene (6.9 mL), and the resultant slurry was heated to 80 °C. After 24 h, the slurry was filtered and concentrated under reduced pressure to afford crude *epi*-lomaiviticin A core 168, which was carried forward to the next step without further purification.

*p-TsOH·H₂O* (1.9 mg, 0.010 mmol, 0.20 equiv) was added in a single portion to a stirred solution of crude 168 in benzene (6.9 mL). After 24 h, saturated aqueous NaHCO₃ solution was added to the stirred reaction mixture. The resultant mixture was diluted with EtOAc (4 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 4 mL) and the organic layers were combined, washed with brine (6 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude residue was then purified by flash column chromatography (silica gel, eluent: gradient, 4:1 → 3:1 → 2:1 hexanes:EtOAc) to afford *epi*-lomaiviticin B core 169 (19.4 mg, 62% over 3 steps) as a white solid.
$^1$H NMR (600 MHz, C$_6$D$_6$) $\delta$: 4.73 (s, 2H), 3.18 (s, 2H), 2.17–2.07 (m, 2H), 2.00–1.91 (m, 4H), 1.90–1.78 (m, 6H), 1.08 (t, $J = 7.3$ Hz, 6H), 0.93 (s, 18H), 0.26 (s, 6H), 0.08 (s, 6H). $^{13}$C NMR (126 MHz, C$_6$D$_6$) $\delta$: 206.4, 170.2, 139.8, 102.9, 90.3, 61.6, 60.6, 35.5, 30.4, 26.3, 23.1, 18.6, 7.7, −4.0, −4.9. FTIR (thin film) cm$^{-1}$: 3400, 2956, 2929, 2856, 1690, 1658, 1253, 1097, 1041, 838, 777. HRMS (ESI) (m/z) calc’d for C$_{34}$H$_{54}$NaO$_8$Si$_2$ [M+Na]$^+$: 669.3249, found 669.3262. TLC (2:1 hexanes:EtOAc), $R_f$: 0.27 (UV, Anis). $[\alpha]_D^{25}$: +35.0 ($c = 0.53$, CH$_2$Cl$_2$).
II. A Biomimetic Unified Strategy for the Synthesis of 7-Membered Ring-Containing *Lycopodium* Alkaloids

Chapter 3

Introduction to the *Lycopodium* Alkaloids
Introduction

The *Lycopodium* alkaloids, isolated from the *Lycopodium* club mosses, are a diverse family of complex polycyclic natural products that have long attracted interest in synthetic chemistry due to their fascinating structures and interesting biological activity.\(^7\) Since the isolation of the first *Lycopodium* alkaloid, lycopodine\(^7\) (1, Figure 3.1), by Bödeker from *Lycopodium complanatum* in 1881, over 250 *Lycopodium* alkaloids have been isolated and characterized to date.\(^7\) Not only have the *Lycopodium* alkaloids served as challenging targets for total synthesis, but their complex structures have also provided ample opportunities for new synthetic methodology development.

**Figure 3.1.** Representative members of the four *Lycopodium* alkaloid structural classes.\(^8\)

The *Lycopodium* alkaloids have been categorized into four general structural classes, comprising the lycopodine, lycodine, fawcettimine, and the miscellaneous classes,\(^7\) representative members of which are shown in Figure 3.1 The lycopodine structural class (1) is characterized by four fused six-membered rings, two of which (A- and C-rings) form a quinolizidine. In the lycodine class (2), members characteristically contain four rings, with the B-, C-, and D-rings being the same as in the lycopodine class. However, the A-ring is rearranged (no Nβ–C1 connectivity) and typically

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\(^9\) The positional numbering system is represented in accordance with Conroy’s original proposed biosynthesis. Please see: Conroy, H. *Tetrahedron Lett.* 1960, 1, 34–37.
exists as a pyridine or pyridone ring. Thus far, all of the *Lycopodium* alkaloids, notably huperzine A, with biological activity associated with acetylcholinesterase inhibition belong to the lycopodine class. The fawcettimine class (3) can be derived from the lycopodine class via C4–C13 to C4–C12 bond migration. Lastly, the miscellaneous class (4) encompasses all of the *Lycopodium* alkaloids that do not fall into the category of the three aforementioned classes. In particular, members of the miscellaneous class do not contain either C4–C13 or C4–C12 connectivity.

Since Conroy’s original biosynthetic hypothesis, a revised biosynthesis of the *Lycopodium* alkaloids based on $^{14}$C- and $^{13}$C-feeding studies has been proposed. Lysine could initially undergo decarboxylation and subsequent oxidative cyclization to afford $\Delta^1$-piperideine (7, Figure 3.2). Next, a Mannich reaction between 7 and 3-oxoglutaric acid, followed by decarboxylation, could provide pelleterine (9). 9 may then undergo dimerization via an intermolecular aldol reaction to furnish dimer 10. Phlegmarine carbon skeleton 12 could then arise from 10 via oxidation and a subsequent intramolecular aldol reaction to form the C7–C12 bond. An intramolecular Mannich reaction could then establish the C4–C13 bond, resulting in tetracycle 13, from which the lycodine structural class may arise. Alternatively, the lycopodine class (1) could be derived from 13 via: (1) hydrolysis of the Nα–C5 imine, (2) deamination, and (3) formation of the Nβ–C1 bond. Subsequent oxidation of 1 at C12 could then result in the formation of lycodoline (14). The fawcettimine class may be accessed from 14 via migration of C4 from C13 to C12. Further rearrangement and oxidation of members of each structural class could then engender the vast and diverse *Lycopodium* alkaloid natural products.

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Figure 3.2. Proposal for the biosynthesis of the *Lycopodium* alkaloids.
Selected Total Syntheses of the Lycopodium Alkaloids

The structurally diverse Lycopodium alkaloids have had an established history in the field of organic synthesis ever since the foundational syntheses of lycopodine (1) by Stork and Ayer in 1968; they continue to attract widespread interest due to their fascinating and complex polycyclic structures and promising bioactivity. A survey of relevant total syntheses of various Lycopodium alkaloids will be presented.

Highlights from the inaugural synthesis of (+)-lycopodine (1) by Stork and coworkers will first be discussed. The synthesis commenced with the diastereoselective 1,4-conjugate addition of methylocuprate, generated from MeMgI and CuCl, to cyclohexenone 15, furnishing cyclohexanone 16 (Scheme 3.1). The diastereoselectivity of this reaction was controlled through stereoelectronically favored axial attack by the methylocuprate anti to the pseudo-equatorial C7-substituent. Condensation of 16 with pyrrolidine in the presence of p-TsOH resulted in formation of the corresponding pyrrolidinamine. Treatment with acrylamide then yielded two separable regioisomeric quinolones. Upon exposure to H$_3$PO$_4$/HCO$_2$H, desired quinolone 17 underwent an intramolecular Friedel–Crafts alkylation to afford tetracycle 20 as a single diastereomer. This transformation occurred via initial formation of N-acyliminium ions 18 and 19, which could then undergo an intramolecular Friedel–Crafts reaction to establish the C4–C13 bond by trapping with the pendant p-methoxybenzyl group, leading to two possible epimeric products at C12, 21 and 20, respectively. Stork and coworkers postulated that a Curtin-Hammett situation could be operative and if initial protonation of enamide 17 was reversible and faster than the ensuing intramolecular Friedel–Crafts reaction, then only the desired C12-epimer 20 would be obtained from N-acyliminium 19, since the reactive conformation of 18 is unfavorable. A total synthesis of lycopodine (1) was then accomplished from 20.

Scheme 3.1. Stork’s total synthesis of (±)-lycopodine (1).

In 1978, Heathcock and coworkers also achieved a synthesis of (±)-lycopodine (1). The synthesis commenced with stereoelectronically favored 1,4-conjugate addition of the lithium anion of $N,N$-dimethylhydrazone 23 to cyclohexenone 22 anti to the C16-methyl group, furnishing cyclohexanone 24 upon hydrolysis of the hydrazone (Scheme 3.2). A ~1:1 mixture of inconsequential C12-epimers (vide infra) was obtained as a result of unselective protonation of the copper enolate intermediate. Ketal-protection of the carbonyl groups followed by nitrile reduction afforded primary amine 25. Heating 25 in the presence of HCl then furnished tricycle 26 as a single diastereomer via a cascade set of reactions. This cascade occurred via: (1) cleavage of the ketal groups, (2) condensation of the primary amine with the C13-ketone to form the corresponding iminium ion intermediate, and (3) an intramolecular Mannich reaction to establish the C4–C13 bond. Although 25 existed as a ~1:1 mixture of C12-epimers, Heathcock postulated that rapid interconversion of the C12-epimers of the C13-iminium ion intermediate could occur via the Nβ–

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C13–C12 enamine tautomer. However, only one C12-epimer of the C13-iminium ion could undergo a favorable intramolecular Mannich cyclization reaction. Tricycle 26 was then converted to (±)-lycopodine (1) in two steps.

Scheme 3.2. Heathcock’s total synthesis of (±)-lycopodine (1).

More recently, Smith and Beshore achieved the total syntheses of (+)-lyconadin A (31) and (−)-lyconadin B (32), members of the miscellaneous class (Scheme 3.3). The lyconadins contain an additional C4–C10 linkage, resulting in a 7-membered ring. The key transformation involved exposure of ketoaldehyde 27 to HCl to afford tricycle 30 as a single diastereomer (84% yield) via: (1) a Robinson annulation to construct cyclohexenone intermediate 28, (2) intramolecular 7-endo-trig 1,4-conjugate addition to form the C6–C7 bond via stereoelectronically favored axial attack anti to the C16-methyl group, and (3) protonation of the resultant enol intermediate 29 to provide the incorrect C12-stereocenter. Unfortunately, the C12-stereocenter could not be directly epimerized, and several synthetic operations were required to invert the configuration of this stereocenter.


89 Pseudoequatorial attack of cyclohexenone intermediate 28 is disfavored due to a developing 1,2-allylic strain between the C7- and C12-substituents in the transition state. This rationale likely accounts for the stereoselectivity of the conjugate addition in the key step of Heathcock’s synthesis of lycopodine (22 to 24).
Scheme 3.3. Key step from Smith’s syntheses of (+)-lyconadin A (31) and (−)-lyconadin B (32).

In 2009, Sarpong and coworkers also completed a total synthesis of (+)-lyconadin A (31) (Scheme 3.4).

Hydrogenolysis of advanced intermediate 33, followed by addition of NaBH₄, delivered secondary amine 34 via: (1) cleavage of the Cbz group, (2) condensation of the resultant amine with the ketone to form the corresponding imine, and (3) reduction of the imine intermediate. Treatment of 34 with n-BuLi resulted in deprotonation of the amine and the pseudobenzyllic position to form the corresponding dianion, which upon addition of I₂, furnished desired pentacycle 36. Alternatively, 36 could also be accessed via a two-step protocol involving: (1) addition of NIS to the dianion generated from n-BuLi at −78 °C to afford iodide 35, and (2) heating 35 with t-BuOK to yield the tertiary amine with the desired C6–N connectivity. Finally, cleavage of the methyl ether in 36 with NaSeEt delivered (+)-lyconadin A (31).

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Scheme 3.4. Key transformations from Sarpong’s synthesis of (+)-lyconadin A (31).

To summarize this chapter, a brief introduction and background for the *Lycopodium* alkaloid family of natural products was presented. Selected relevant syntheses, including Stork and Heathcock’s respective total syntheses of (+)-lycopodine (1) and Smith and Sarpong’s respective syntheses of lyconadins A and B (31 and 32, respectively), were reviewed. Key lessons learned from the syntheses presented, which are relevant to our own syntheses of himeradine A (38), lycopecurine (39), and lyconadins A (31) and B (32), include: (1) introduction of the C6–C7 bond *anti* to the C16-methyl group could be accomplished stereoselectively, (2) the C4–C13 bond could be established via a biomimetic Mannich reaction, and (3) the C6–N bond of the lyconadins could be introduced at a late-stage through an oxidative amination reaction.
II. A Biomimetic Unified Strategy for the Synthesis of 7-Membered Ring-Containing Lycopodium Alkaloids

Chapter 4

Total Synthesis of the Proposed Structure of (−)-Himeradine A
Introduction

A unique subset of the lycodine structural class, including (+)-fastigiatine (37)\textsuperscript{91} and (–)-himeradine A (38),\textsuperscript{92} contains an unprecedented pentacyclic core with a C4–C10 or C14–C3 bond, respectively, in contrast to lycodine (2) (Figure 4.1). The C4–C10 or C14–C3 linkage introduces significant strain and complexity to these structures, resulting in five contiguous stereocenters and a densely functionalized pyrrolidine ring. From a synthetic perspective, (–)-himeradine A (38) is arguably the most challenging Lycopodium alkaloid and contains seven rings, three potentially basic nitrogens, ten stereocenters, and a quinolizidine subunit appended to the pentacyclic core via a methylene linker.

![Diagram of Lycodine Alkaloids](image)

Figure 4.1. Examples of Lycopodium alkaloids containing an unprecedented pentacyclic core.

Although the relative stereochemistry of fastigiatine (37) was unambiguously established by single crystal X-ray diffraction analysis,\textsuperscript{91} the structure and relative stereochemistry of each individual subunit of himeradine A (38), the pentacyclic core and the quinolizidine, were elucidated by \textsuperscript{1}H, \textsuperscript{13}C, COSY, HMQC, HMBC, and NOESY NMR experiments in addition to IR and FABMS/MS data.\textsuperscript{92} However, the relative stereochemistry between the pentacyclic core and the quinolizidine remains ambiguous due to their relative isolation from one another. The large vicinal coupling constants observed between H11'b/H17 and H11'b/H10' suggest that the relative conformation between the two individual subunits is rigidly locked through H11'. Furthermore, a


Monte Carlo simulation followed by minimization was consistent with the observed NOESY data and proton vicinal coupling constants. Thus, the relative stereochemistry of himeradine A (38) was assigned as illustrated in Figure 4.1.

MacLean and coworkers originally proposed a biosynthesis of the pentacyclic core of fastigiatine (37) and himeradine A (38)\(^{91a}\) (Figure 4.2). Iminium ion intermediate 41 was postulated to undergo an intramolecular Mannich reaction,\(^{82,83}\) forming the C4–C13 bond to afford lycodane skeleton 42. 42 could then undergo oxidative functionalization at C10 to yield tetracycle 43. Next, it was proposed that an enamine S\(_{N2}\) cyclization to form the key C4–C10 bond occurs, furnishing the desired pentacyclic core 44. We speculated, however, that this proposed S\(_{N2}\) alkylation requires accessing an unfavorable, strained boat-like conformation in order to achieve requisite orbital overlap. Furthermore, 43 is not a particularly reactive electrophile.

**Figure 4.2.** MacLean’s proposal for the biosynthesis of the pentacyclic core of fastigiatine (37) and himeradine A (38) and our revised biosynthesis.

Hence, we proposed an alternative biosynthetic pathway for accessing the strained pentacyclic core of 37 and 38. We speculated that the C4–C10 bond of 41 is installed prior to the formation of the C4–C13 bond, potentially via an intramolecular enamine S\(_{N2}\) reaction of an
oxidatively functionalized derivative of 41 at C10. The proposed reactive conformation for this intramolecular S_N2 reaction to occur is less strained than that required for 43. Drawing analogy to MacLean’s proposed biosynthesis, tetracycle 45 (redrawn in 3D as 46) could now undergo a key intramolecular transannular Mannich reaction to construct the pentacyclic core of fastigiatine (37) and himeradine A (38). Other Lycopodium alkaloids could also be accessed from intermediate 45, including lyconadin A (31), lucidine B (47), and nankakurine A (48) via reduction of the C13-iminium ion. Our proposed biosynthetic hypothesis straightforwardly illuminates both the common origin and divergence of 7-membered ring-containing Lycopodium alkaloids. MacLean’s biosynthetic proposal, however, would require 44 to undergo a retro-Mannich reaction to 46, which although plausible, seems circuitous.

We were attracted to a synthesis of fastigiatine (37) and himeradine A (38) not only because of their structural complexity and unprecedented pentacyclic cores, but we also wanted to address our proposed biosynthetic hypothesis and whether a transannular Mannich reaction could be employed. Furthermore, due to their low abundance from natural sources, extensive biological testing of 37 and 38 has not been conducted. Himeradine A (38) has been demonstrated to exhibit cytotoxicity against murine lymphoma L1210 cells in vitro with IC_{50} = 10 \mu g/mL,92 and related members have shown promising neurological bioactivity. At the outset of this project, a synthesis of fastigiatine (37) and himeradine A (38) had not yet been achieved in the literature. In 2010, Dr. Brian B. Liau93 in the Shair group accomplished the first total synthesis of (+)-fastigiatine, which will be discussed in the next section.

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93 Liau, B. B.; Shair, M. D. J. Am. Chem. Soc. 2010, 132, 9594–9595
**Total Synthesis of (+)-Fastigiatine**

Dr. Brian B. Liau’s proposed cascade sequence\(^\text{94}\) for the synthesis of (+)-fastigiatine (37) is illustrated in Scheme 4.1. As discussed previously, we envisioned installing the C4–C13 bond in tetracycle 57 via a biomimetic transannular Mannich reaction to afford the strained pentacyclic core 58. Tetracycle 57 could be accessed from enone 49 via initial condensation of Nα with the C5-ketone to form imine 50, followed by tautomerization to the exocyclic Nα–C5–C6 enamine,\(^\text{95,96}\) which is now poised to undergo a 7-endo-trig intramolecular cyclization\(^\text{88}\) to form the C6–C7 bond. Two possible reactive conformations exist, 51 and 52, which result from either stereoelectronically favored pseudoaxial\(^\text{97}\) 1,4-conjugate addition syn or anti to the C16-methyl group, respectively. Based on a steric argument, addition anti to the C16-methyl group should be favored.\(^\text{88}\) Next, stereoelectronically favored axial protonation of the resultant enol 53 (redrawn as 54) at C12 could then afford tricycle 55. At this stage of synthetic planning, the exact order of bond-forming events was considered flexible and hence, numerous strategies could be possible depending on a judicious selection of nitrogen protecting groups.

Tricycle 55 could either exist as the keto-enamine form or undergo a subsequent transannular aldol reaction to afford tetracycle 56. However, if the C13-ketone is kinetically accessible from 56, then condensation of Nβ with the C13-ketone could occur to provide iminium ion intermediate 57, which could then undergo the key biomimetic transannular Mannich reaction to furnish the desired pentacyclic core 58. This cascade sequence, which constitutes a formal [3+3]-

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\(^{95}\) Although the endocyclic enamine tautomer is thermodynamically favored over the exocyclic tautomer in related systems, the exocyclic enamine tautomer can be accessed. Please see: Movassaghi, M.; Chen, B. *Angew. Chem. Int. Ed.* **2007**, *46*, 565–568.

\(^{96}\) This would render the C4-stereocenter inconsequential to the cascade reaction.

\(^{97}\) Pseudo-equatorial attack would result in an intermediate that suffers 1,2-allylic strain.
Our retrosynthetic analysis of the cascade precursor 59 is shown in Scheme 4.2. Diamine 59 could be accessed from a pyrrolidinone precursor such as 60, which could be assembled in a highly convergent fashion from three building blocks via nucleophilic opening of cyclopropane by organometallic 61 to form the C12–C11 bond, followed by alkylation of the resultant dicarbonyl anion intermediate with electrophile 63.

Scheme 4.1. Proposed cascade sequence for the total synthesis of (+)-fastigiatine (37).

cycloaddition, could potentially occur in a one-pot operation to generate up to two σ C–C bonds, two σ C–N bonds, and one σ C–H bond. (+)-Fastigiatine (37) could then be synthesized from pentacycle 58 in a few straightforward steps.
Scheme 4.2. Retrosynthetic analysis of cascade precursor 59.

In beautiful work by Dr. Brian B. Liau, the synthesis commenced with the nucleophilic opening of cyclopropane 64, which was prepared in six steps from (S)-epichlorohydrin, by organometallic 65 (Scheme 4.3).\(^\text{93,100}\) Upon treatment with mixed dioorganocuprate 65, cyclopropane 64 underwent regioselective opening at C11 to afford carboxyimide 66 in excellent yield (93%). This convergent coupling could be conducted on greater than 5-g scale. Carboxyimide 66 underwent efficient alkylation with 1-chloro-3-iodopropane and the resultant primary chloride was then displaced with NaN\(_3\) to yield azide 67. Exposure of 67 to TBAF in the presence of DBU resulted in cleavage of the 2-(trimethylsilyl)ethyl (TMSE) ester with concomitant decarboxylation,\(^\text{101}\) followed by in situ base-catalyzed epimerization at C4. Next, the C6-carbon was introduced by addition of MeMgBr to the C5-carbonyl, affording hemiaminal 69 as a mixture of diastereomers. Dehydration and ketal deprotection of 69 with CSA occurred smoothly to furnish the corresponding dihydropyrrole. Staudinger reduction of the azide then yielded primary amine 70.


\(^{101}\) Knobloch, E.; Brückner, R. *Synlett* 2008, 12, 1865–1869.
Scheme 4.3. Synthesis of cascade precursor dihydropyrrole 70.

Although the C–N bond connectivity was incorrect, 70 could still potentially serve as a cascade substrate since the more nucleophilic Nα-amine could theoretically exchange with the Nβ-carbamate to provide imine 74 (Scheme 4.4). At the time, we assumed that 70 could not undergo 5-endo-trig cyclization to form the undesired C4–C7 bond since this would be in violation of Baldwin’s rules. Imine 74 could then undergo 7-endo-trig cyclization to afford tricycle 75, which, after a subsequent transannular aldol reaction, should result in the formation of tetracycle 71 or 72. Heating 70 with PPTS in EtOH resulted in the formation of a single new product. However, instead of obtaining desired tetracycle 71 or 72, constitutional isomer 73 was isolated instead.

\[\text{Scheme 4.3. Synthesis of cascade precursor dihydropyrrole 70.}\]

Our proposed mechanism for the formation of 73 is illustrated in Scheme 4.5. Formation of the corresponding oxocarbenium from dihydropyrrrole 70 resulted in a 5-endo-trig cyclization to establish the undesired C4–C7 bond anti to the C16-methyl group in the cis-5,5-bicyclic iminium ion intermediate 76. The highly charged oxocarbenium intermediate most likely allowed an exception to Baldwin’s rules, which generally disfavors 5-endo-trig cyclizations. Nα and Nβ could then undergo transamination to provide imine 77, which upon tautomerization to the corresponding exocyclic enamine, could undergo cyclization via a transannular aldol reaction to yield 73. Two important lessons were learned from such a disappointing result: (1) the correct C–N bond connectivity was required for the cascade reaction because (2) the 5-endo-trig cyclization was facile.

To this end, we next focused our attention on installing the correct C–N bond connectivity (Scheme 4.6). Unfortunately, however, efforts to form the 6-membered imine 78 with the correct
C5–Nα bond connectivity from 69 proved unsuccessful (Eq. 1). We speculate that these results were suggestive of a strong thermodynamic preference for the 5-membered ring system containing the incorrect C5–Nβ bond.\textsuperscript{103} Hydrolysis of the C5–Nβ bond or formation of the corresponding Weinreb amide from 68 (Eq. 2) were also explored. Unsurprisingly, recyclyzation back to 68 was a recurring problem. Eventually we discovered that Staudinger reduction of the azide in 68 resulted in formation of valerolactam 79, which possessed the desired C5–Nα bond connectivity.

\textbf{Scheme 4.6.} Efforts to install the correct C5–Nα bond connectivity.

Attempted introduction of the C6-carbon unit proved challenging (Scheme 4.7). We initially planned to synthesize the corresponding thioamide of 79, followed by a subsequent Eschenmoser coupling reaction. However, thioamide formation proved unsuccessful. Efforts to synthesize the exocyclic enamide\textsuperscript{104} of Boc-protected lactam 80 with Petasis reagent\textsuperscript{105} resulted in translactamization to 81.

\textsuperscript{103} A very similar thermodynamic preference to form the 5-membered ring system was also observed with the butyrolactone series. See ref. 94.


Scheme 4.7. Attempted incorporation of the C6-carbon unit.

At this point, it became apparent that a revised protecting group strategy was necessary in order to reduce the propensity of our system to form the cyclic 5-membered ring with the incorrect C5–Nβ bond connectivity. We postulated that such a solution could be realized by replacing the Nβ-Boc group with a 2-nitrobenzenesulfonyl (Ns) group, which should inductively deactivate the nitrogen atom. To this end, chemoselective cleavage of the N-Boc group of 68 with Mg(ClO₄)₂ in the presence of the C13-ketal occurred smoothly (Scheme 4.8). Protection of the resultant pyrrolidinone with a Ns group afforded N-Ns-2-pyrrolidinone 82. Gratifyingly, addition of the lithium enolate of t-butyacetate to the C5-carbonyl occurred smoothly to furnish β-keto ester 83, with Nβ completely disengaged from C5. Heating 83 with PPh₃ resulted in a Staudinger reaction to provide vinylogous urethane 84 as an inconsequential ~3:2 mixture of C4-epimers. The C6-t-butyloxycarbonyl serves two crucial functions, one of which was to induce preferential formation of the exocyclic Nα–C5–C6 enamine in order to suppress undesired 5-endo-trig cyclization. Secondly, vinylogous urethanes are easier to handle in comparison to their enamine counterparts because they are stable, non-basic, and can be readily purified.

All that remained in order to test the key cascade sequence included: (1) deprotection of the Nβ-Ns group, (2) cleavage of the C13-ketal, and (3) condensation of Nβ with the C13-carbonyl to

form the corresponding iminium ion intermediate. Attempted cleavage of the Νβ-Ns group, however, resulted in the formation of 5-membered vinylogous urethane 85, the product of a facile transamination reaction. Hence, it was clear from these results that the Νβ-Ns group would have to be removed at a later stage.

Scheme 4.8. Installation of the correct C5–Nα connectivity via inductive deactivation of Nβ.

Instead, vinylogous urethane 84 was directly exposed to aqueous HCl (Scheme 4.9), which furnished tetracycle 92 as a single diastereomer in 92% yield via: (1) initial C13-dioxolane cleavage, (2) 7-endo-trig intramolecular 1,4-conjugate addition\(^{88}\) to form the C6–C7 bond via stereoelectronically favored axial attack anti to the C16-methyl group, (3) tautomerization to secure the C12-stereocenter via stereoelectronically favored axial protonation, and (4) a transannular aldol reaction to form the C4–C13 bond. This transformation constitutes a formal [3+3]-cycloaddition.\(^{109}\)

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Scheme 4.9. A formal [3+3]-cycloaddition reaction to construct tetracycle 92.

All that remained in order to complete a synthesis of the pentacyclic core of fastigiatine (37) was to formally exchange the C13-hydroxyl with Nβ (Scheme 4.10). This was accomplished via initial alkylation of 92 with MeI in the presence of K2CO3, followed by addition of PhSH, to yield N-methylamine 93. Heating 93 in 2,2,2-trifluoroethanol (TFEOH) cleanly delivered pentacycle 96 in 85% yield via: (1) an initial retro-aldol reaction, (2) condensation of Nβ with the C13-ketone to form the corresponding iminium ion, and (3) the pivotal biomimetic transannular Mannich reaction. Use of TFEOH, a strong hydrogen-bond donor but not a strong acid, as solvent was crucial to the success of this reaction. We speculated that under acidic conditions, protonation of Nβ would occur, thus disfavoring the formation of the positively charged intermediates involved in the retro-aldol reaction. Next, heating 96 in the presence of p-TsOH induced t-butyloxycarbonyl removal to afford the corresponding imine. Finally, exposure of the resultant imine to Ac2O in the presence of Et3N cleanly delivered (+)-fastigiatine (37). The structure of 37 was unambiguously confirmed by single crystal X-ray diffraction analysis.
Scheme 4.10. Completed total synthesis of (+)-fastigiatine (37).

Key lessons learned from Dr. Brian B. Liau’s synthesis of fastigiatine (37), which would subsequently be applied to a successful synthesis of the proposed structure of (−)-himeradine A (38), include a highly convergent fragment coupling via a nucleophilic cyclopropane opening, a diastereoselective formal [3+3]-cycloaddition reaction, and a transannular Mannich reaction to construct the pentacyclic core common to both 37 and 38. However, the ultimate goal we hoped to achieve in a total synthesis of himeradine A (38), which was not realized in our synthesis of fastigiatine (37), was a one-pot cascade reaction to construct the strained core system that would obviate the need to formally exchange the C13-hydroxyl with Nβ. Furthermore, we envisioned we could program the new cascade sequence order such that we could potentially access all 7-membered ring-containing Lycopodium alkaloids via a unified, biomimetic, convergent strategy.
Total Synthesis of the Proposed Structure of (–)-Himeradine A

(–)-Himeradine A (38) is arguably the most synthetically challenging Lycopodium alkaloid and contains, in addition to the aforementioned unprecedented pentacyclic core with a C3–C14 linkage, seven rings, three potentially basic nitrogens, ten stereocenters, and a quinolizidine subunit appended to the core via a methylene linker. A synthesis of himeradine A (38) has not yet been reported in the literature. Our retrosynthetic analysis of 38 is outlined in Scheme 4.11. Analogous to our synthesis of fastigiatine (37), we envisioned constructing the C6–C14 bond in 38 from hexacyclic intermediate 97 via a biomimetic transannular Mannich reaction to afford the strained core skeleton. Intermediate 97 (redrawn in 2D as 98) could arise from a 7-endo-trig intramolecular 1,4-conjugate addition of the β-keto ester to the cyclohexenone in 99, and condensation of Nα and Nβ with the C13- and C6-carbonyls, respectively. As discussed previously, the ultimate objective was to accomplish a one-pot cascade reaction to construct the strained core in 38 from β-keto ester 99 in a single operation, a goal not realized in our synthesis of fastigiatine (37). 99 could be synthesized in a highly convergent fashion from three building blocks via alkylation of β-carboxyimide 100 with quinolizidine iodide 101 or related derivatives, followed by subsequent addition of the lithium enolate of t-butylacetate 102 to the C13-carbonyl.

Scheme 4.11. Retrosynthetic analysis of (–)-himeradine A (38).
Our first-generation retrosynthesis of the quinolizidine subunit is outlined in Scheme 4.12. The desired carboxyimide alkylation electrophile 101 could potentially be synthesized from quinolizidine 103 via a few straightforward manipulations, including a Mitsunobu displacement of the C17-hydroxyl group by azide. Quinolizidine 103 could be constructed from allyl N-Boc-piperidine 104. The C6'-stereocenter in 104 could be installed via a diastereotopic deprotonation at C6' in N-Boc piperidine 105, followed by alkylation. Furthermore, we envisioned installing the C10'- and C17-stereocenters by relaying the stereochemical information of the single C8'-stereocenter in N,O-methoxyacetal 106 to first introduce the C10'- followed by the C17-stereocenter.

Scheme 4.12. First-generation retrosynthesis of the quinolizidine subunit.

The synthesis commenced with the lipase-mediated desymmetrization of 3-methylglutaric anhydride with n-PrOH to afford carboxylic acid 107 (93% ee) (Scheme 4.13).\textsuperscript{110} Chemoselective reduction of the carboxylic acid with BH\textsubscript{3}•SMe\textsubscript{2} occurred smoothly to provide the corresponding carbinol, which underwent Parikh-Doering oxidation to yield aldehyde 108. Heating 108 in NH\textsubscript{3}/MeOH afforded a mixture of N,O-hydroxy- and N,O-methoxyacetals. Exposure of this crude product mixture to p-TsOH in MeOH\textsuperscript{111} at 50 °C resulted in complete conversion to the desired N,O-methoxyacetal 106 as a mixture of diastereomers.


Exposure of N,O-methoxyacetal 106 to BF$_3$•OEt$_2$ in the presence of silyl enol ether 109 afforded lactam 110 as a single diastereomer via an N-acyliminium ion Mannich reaction (Scheme 4.14).$^{112}$ The diastereoselectivity of this reaction was controlled through stereoelectronically favored axial attack by silyl enol ether 109 at C10 of the intermediate N-acyliminium ion anti to the C12$^\prime$-methyl group. Chelate-controlled 1,3-syn reduction$^{113}$ of the ketone in 110 with DIBAL-H afforded alcohol 111 as a single diastereomer. TBS-protection of the C17-hydroxyl, followed by N-Boc protection of the lactam, provided imide 112. Next, reduction of the carbonyl in 112 with DIBAL-H and subsequent exposure to BF$_3$•OEt$_2$ in the presence of Et$_3$SiH,$^{114}$ delivered N-Boc-piperidine 114. With 114 in hand, we could next investigate the introduction of the C6$^\prime$-stereocenter.

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We envisioned installing the C6'-stereocenter via a diastereotopic deprotonation at C6', followed by addition of a suitable electrophile. A diastereotopic deprotonation of 114 at C6' was performed with sec-BuLi in the presence of TMEDA (Scheme 4.15). The conformation of lithiated N-Boc piperidine 115 is rigidly locked due to 1,3-allylic strain minimization between the N-Boc group and the C10'-stereocenter, which is further reinforced by equatorial positioning of the C12'-methyl group. Equatorial organolithium 115 was favored due to chelation with the N-Boc group. Transmetallation with Cu(I), followed by alkylation with allyl bromide, furnished the desired allylated piperidine 116 (redrawn as 117) as a single diastereomer in 50% yield (97% brsm).

Scheme 4.15. Successful introduction of the C6'-stereocenter.

Attempts to improve the yield of the allylated product 116 beyond 50% proved challenging. Transmetallation with Cu(I) was essential or else only trace quantities of 116 were obtained. Varying

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the temperature, concentration, and time allotted for deprotonation, as well as the amount of sec-BuLi (from 1.3 to 3.0 equiv), TMEDA (from 1.3 to 3.0 equiv), CuCN•2LiCl (from 0.6 to 1.8 equiv), and AllylBr (from 1.5 to 3.6 equiv) used all resulted in similar or diminished yields. We suspected that complete deprotonation of sterically encumbered C6’ was challenging. However, warming of the deprotonation with sec-BuLi (up to 0 °C) resulted in partial cleavage of the N-Boc protecting group. Alkylation with various electrophiles, which could potentially result in fewer downstream step manipulations, was also explored (Figure 4.3). However, in all cases, either trace quantities of the corresponding product or complete recovery of starting material 114 was observed.

![Figure 4.3](image)

**Figure 4.3.** Attempted introduction of other electrophiles to the C6’ position.

Next, allyl N-Boc-piperidine 117 was converted to the desired quinolizidine 127 (Scheme 4.16). Exposure of 117 to TMSOTf in the presence of 2,6-lutidine afforded the corresponding Boc-cleaved piperidine, which underwent subsequent alkylation with AllylBr and K₂CO₃ to provide tertiary amine 123. A Grubbs II-catalyzed ring-closing metathesis with p-TsOH protonation of the tertiary amine cleanly delivered cyclized product 124. Hydrogenation of the alkene in 124 in the presence of AcOH furnished quinolizidine 125. Global silyl deprotection upon heating with HCl in MeOH, followed by selective monosilylation of the primary hydroxyl group, afforded TBS-ether 126. Finally, Mitsunobu displacement of the secondary hydroxyl group in 126 with azide, followed by cleavage of the primary TBS ether, occurred smoothly to yield alcohol 127.

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Unfortunately, efforts to synthesize a suitable alkylation electrophile for carboxyimide 66 from alcohol 127 were unsuccessful. Attempted synthesis of the corresponding mesylate, tosylate, and iodide from 127 resulted in decomposition in all cases. We speculate that the observed decomposition could be attributed to facile intra- and intermolecular alkylation of the desired product by the tertiary amine. Nonetheless, we demonstrated, as a proof-of-principle, that successful construction of the quinolizidine subunit from N-Boc-piperidine 117 was possible. In the global scheme, the quinolizidine would either have to be constructed after alkylation with imide 66 or introduced in a protected form.

To this end, we decided to synthesize the quinolizidone, a protected form of the quinolizidine (Scheme 4.17). Cleavage of the N-Boc protecting group, followed by condensation of the resultant secondary amine with acryloyl chloride, yielded amide 129. A Grubbs II-catalyzed ring-closing metathesis cleanly provided cyclized amide 130. Hydrogenation of the alkene in 130 yielded quinolizidone 131, which was converted in six steps to the desired alkylation electrophile, iodide 132.

Imide 66 underwent efficient alkylation with iodide 132 to furnish the desired alkylated product 133 in excellent yield (Scheme 4.18). 133 was converted to vinylogous urethane 134 in five steps, analogous to the sequence used in our synthesis of fastigiatine (37). At the outset, as a proof-of-concept, we decided to replicate the cascade utilized in our synthesis of fastigiatine (37) to construct the strained pentacyclic core of himeradine A (38). To this end, exposure of 134 to aqueous HCl resulted in a formal [3+3]-cycloaddition to afford hexacycle 136 as a single diastereomer. Next, in order to conduct a formal exchange between the C6-hydroxyl group with Nβ, the N-Ns protecting group must be cleaved. Surprisingly, attempted cleavage of the Ns group of 136, or alkylated derivatives 137 and 138, by treatment with PhSH in the presence of K₂CO₃ resulted in decomposition. We rationalized that milder deprotection conditions could be employed if a more readily cleaved Nβ-protecting group was utilized. Instead of a 2-nitrobenzenesulfonyl group, we were able to protect Nβ with a 2,4-dinitrobenzenesulfonyl group, which, unfortunately, was immediately cleaved upon addition of lithiated t-butylacetate during attempted formation of the desired β-ketoester analogue precursor to 134.
Scheme 4.18. Successful formal [3+3]-cycloaddition to afford hexacycle 136.

A new cascade order was subsequently developed in order to circumvent the need for the C6-hydroxyl and Nβ exchange as well as to potentially permit the one-pot construction of the strained core structure in a single operation, which was not realized in our synthesis of fastigiatine (37) (Scheme 4.19). To this end, our strategy was revised and instead of forming vinylogous urethane 134, 140 was directly exposed to aqueous HCl, which resulted in facile cleavage of the C6-dioxolane, affording enone 141. Treatment of 141 with Barton’s base cleanly delivered ketone 143 via: (1) a 7-endo-trig intramolecular 1,4-conjugate addition to form the C10–C11 bond via stereoelectronically favored axial attack anti to the C12-methyl group, and (2) tautomerization of the ensuing C5–C6 enol to secure the C5-stereocenter through stereoelectronically favored axial protonation. Next, cleavage of the N-Ns protecting group by treatment with PhSH in the presence of K₂CO₃ cleanly provided the tricyclic core of imine 144. By forming the C10–C11 bond in 143 prior to Ns deprotection, we avoided problems associated with C13–Nβ bond formation and 5-endo-trig cyclizations that plagued our first-generation synthesis of fastigiatine (37). Furthermore, we believed that under the appropriate conditions, we could perform all of the aforementioned events in a single one-pot operation (141 → 144).
While developing this novel, revised cascade sequence, we also concurrently investigated conversion of the quinolizidone moiety to the corresponding quinolizidine on a model system. Due to sensitive functionalities present in the molecule, only limited methods for converting the quinolizidone to the desired quinolizidine subunit were available. These methods include treatment of the amide with Meerwein’s salt (Me₃OBF₄) and subsequent reduction (NaBH₄), triflation of the tertiary amide followed by reduction, and formation of the corresponding thioamide and subsequent reduction. Unfortunately, however, all of these methods failed to provide any desired product on our simpler model systems. Hence, another revision in our strategy was necessary.

Instead of preforming the quinolizidine or quinolizidone from 116, we decided to carry the N-Boc allyl piperidine 116 forward and construct the quinolizidine bicyclic structure at a later stage (Scheme 4.20). Global silyl deprotection of N-Boc-piperidine 116, followed by selective protection of the resultant primary hydroxyl, afforded TBS ether 145. Following the same reaction sequence

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utilized previously, Mitsunobu displacement of the secondary hydroxyl group in 145 with azide, followed by cleavage of the TBS ether, and formation of the corresponding iodide, occurred smoothly to yield the desired alkylation partner, iodide 147.


Imide 66 underwent efficient alkylation with iodide 147 to provide the desired alkylated product 148 in excellent yield (94%) (Scheme 4.21). Cleavage of the TMSE ester with concomitant decarboxylation upon treatment with TBAF, followed by chemoselective cleavage of the N-Boc group of 149 with Mg(ClO₄)₂, occurred smoothly to afford pyrrolidinone 150. Protection of 150 with a Ns group then delivered N-Ns-2-pyrrolidinone 151.¹¹⁹ Next, addition of the lithium enolate of t-butylacetate to the C13-carbonyl of 151 furnished β-ketoester 152.

¹¹⁹ Unfortunately, performing an exchange of protecting groups from Boc to Ns was necessary because attempted nucleophilic cyclopropane opening of the corresponding Ns-protected derivative of cycopropane 64 did not yield any desired product. The Ns group appeared to have been compromised.
Scheme 4.21. Successful imide alkylation and synthesis of β-ketoester 152.

Next, the C6-dioxolane of 152 was directly cleaved upon treatment with p-TsOH to provide enone 153 (Scheme 4.22). Next, we discovered that in a one-pot sequence involving initial exposure of 153 to Barton’s base in MeCN, followed by subsequent addition of PhSH in the presence of K₂CO₃, 153 was converted to imine 156 (84%, 3 steps) via: (1) 7-endo-trig intramolecular conjugate addition to form the C10–C11 bond, (2) tautomerization of the ensuing C5–C6 enol to secure the C5 stereocenter, (3) cleavage of the N-Ns protecting group upon addition of PhSH in the presence of K₂CO₃, and (4) in situ condensation of Nβ with the C6-ketone to form the corresponding imine.

Isolation of imine 156 was exciting; we believe 156 lends credence to our biosynthetic hypothesis (Figure 4.2), and this type of intermediate could potentially allow us to access other 7-membered ring-containing Lycopodium alkaloids, including lyconadins A-C, nankakurines A-B,¹²⁰ and lucidines A-B,¹²¹ via reduction of the imine. Alternatively, if imine 156 undergoes the key

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biomimetic transannular Mannich reaction, not only could himeradine A (38) be accessed, but also lycopecurine (39) and inundatine (40). In accord with our proposed biosynthetic hypothesis, a diverse set of *Lycopodium* alkaloids could arise from a common precursor derivative such as 156.

**Scheme 4.22.** Successful one-pot sequence to construct imine 156, containing the strained core of himeradine A (38).

Next, exposure of azide 156 to PPh₃ in the presence of water afforded hexacyclic vinylogous urethane 157 in 75% yield via: (1) Staudinger reduction of the azide to the corresponding amine, (2) condensation of the resultant amine with the neighboring β-ketoester to form the vinylogous urethane, and (3) the key pivotal transannular Mannich reaction to construct the C6–C14 bond. Acetylation of the secondary amine in 157 with Ac₂O and Et₃N provided hexacycle 158 in 83% yield.

With 158 in hand, all that remained in order to complete a total synthesis of himeradine A (38) was to convert the N-Boc allyl piperidine moiety in 158 to the corresponding quinolizidine and cleave the t-buty1 ester. As described previously (Scheme 4.16), a reaction sequence had already been developed for the construction of the quinolizidine subunit. To this end, formation of the corresponding silyloxy carbamate from N-Boc piperidine 158 occurred smoothly upon exposure to TBSOTf and 2,6-lutidine (Scheme 4.23). Treatment with TBAF resulted in cleavage of the silyloxy
carbamate with concomitant decarboxylation, furnishing piperidine 159. Alkylation of 159 with AllylBr in the presence of K₂CO₃ afforded allylated product 160. However, increasing the scale of this alkylation reaction resulted in a complex product mixture, including byproducts in which the vinylogous urethane nitrogen was allylated. A new strategy for installing the quinolizidine subunit was necessary.

Scheme 4.23. Attempted construction of the quinolizidine subunit.

To this end, cross-metathesis¹²² of the allyl group in 158 with acrolein was accomplished with Hoveyda–Grubbs catalyst II, which furnished enal 161 (Scheme 4.24). Hydrogenation of 161, followed by reduction of the resultant aldehyde and tosylation of the corresponding hydroxyl group, afforded tosylate 162 (70%, 3 steps). Exposure of 162 to TBSOTf resulted in formation of the silyloxy carbamate, which was cleaved upon treatment with TBAF. In situ cyclization via S₉₂ displacement of the tosylate group with the resultant secondary amine delivered heptacyle 163 (48%, 2 steps), which now contains the quinolizidine subunit.


Finally, treatment of 163 with TFA resulted in facile removal of the $\tau$-butoxycarbonyl group to yield the proposed structure of (−)-himeradine A (38) as the double TFA salt (quant., $[\alpha]_D^{24} = -19$ (c 0.3, MeOH)). Except for the chemical shift of H10', which is shifted upfield by $\Delta \delta = 0.14$ ppm (Figure 4.4), the $^1$H NMR, $^{13}$C NMR, COSY, NOESY, HSQC, and HMBC spectra for synthetic (−)-himeradine A (38) are in good agreement with the values reported for the natural product ($[\alpha]_D^{25} = -23$ (c 0.3, MeOH)).
Figure 4.4. Comparison of $^1$H NMR spectra of synthetic (38) and natural (−)-himeradine A as the double TFA salt in CD$_3$OD.
Because the protonation state of basic nitrogen atoms can have a significant impact on proton chemical shifts, we carefully titrated the double TFA salt of himeradine A (38) with a solution of NaOCD$_3$ in CD$_3$OD until the free base was obtained, and then incrementally titrated known aliquots of TFA in CD$_3$OD until the double TFA salt was reisolated. At no point during the titration experiments were we able to identically replicate the $^1$H NMR spectrum of natural himeradine A (38). Variable concentration and temperature effects were also investigated and found not to have an effect on H10' proton chemical shift.

We were able to obtain the $^1$H NMR spectrum of the free base of natural himeradine A in CD$_3$OD via private communication with Professor Hiroshi Morita (Figure 4.5). While the $^1$H NMR spectra of the free base of natural and synthetic himeradine A (38) appeared to correspond, we suspected that a structural misassignment of natural himeradine A in the original isolation report may have occurred. Several misassignment possibilities existed (Figure 4.6), including (1) the C10'-stereocenter, (2) the C6'-stereocenter, (3) the C17-stereocenter, (4) the absolute stereochemistry of the quinolizidine subunit, and (5) permutations thereof.

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Figure 4.5. Comparison of $^1$H NMR spectra of synthetic (38) and natural (−)-himeradine A as the free base in CD$_2$OD.
Synthesis of Quinolizidine Models for the Structural Reassignment of Himeradine A

Figure 4.6. Possible candidates for the structural misassignment of himeradine A (38).

Since other related Lycopodium alkaloids\(^{124}\) containing a quinolizidine subunit all possess the same absolute stereochemistry at the C12'-methyl group position, we believed it was unlikely that the absolute stereochemistry of the quinolizidine was misassigned (Figure 4.7). Additionally, we hypothesized that the stereochemical assignment of the C17-stereocenter was correct since the chemical shift of H17 for synthetic (38) and natural himeradine A are in good agreement. Furthermore, we believed at the time that if H17 was equatorial instead of axial, there would be a significant perturbation to the chemical shift, especially due to the adjacent imine \(\pi\)-system.

Figure 4.7. Examples of Lycopodium alkaloids possessing a quinolizidine subunit with the same absolute stereochemistry (denoted by *) as the C12'-methyl group in himeradine A (38).

Due to the aforementioned discussion, we suspected that a stereochemical misassignment of the quinolizidine subunit (C10' or C6') may have occurred, resulting in four possible stereoisomers. In the original isolation report by Kobayashi and coworkers, the stereochemical assignment of the quinolizidine subunit was made based on the putative observation of several key NOESY

correlations (Figure 4.8). However, in the 2D NOESY spectrum provided in the isolation report, NOESY correlations between H6' and H8', and H6' and H2' are not readily apparent. Furthermore, we were skeptical of the assignment of H8' to δ = 1.92 ppm in CD3OD, since in the published 1H NMR spectrum, this region encompassed one broad nondescript and undefined cluster of twelve protons.

![Figure 4.8](image-url)  
**Figure 4.8.** Putative NOESY correlations observed in the original isolation report of himeradine A (38).

Based on 1H NMR spectra comparisons between the TFA salts of natural himeradine A (38) and cermizine D,\(^{125}\) a *Lycopodium* alkaloid in which both C10' and C6' have the opposite configuration to the proposed structure (see Figure 4.7), we ruled out the possibility that both C10' and C6' in the proposed structure of himeradine A were misassigned. Hence, we embarked on a new synthetic effort to independently invert the C10'- and C6'-stereocenters.

Since the quinolizidine is relatively remote from the pentacyclic core of himeradine A (38), we believed that we could synthesize only the quinolizidine subunit with either C10' or C6' inverted as a model to predict the 1H NMR chemical shifts of the final natural product. As a control, we synthesized the TFA salt of only the quinolizidine subunit of the proposed structure of himeradine A (38) and were pleased to discover that the 1H NMR chemical shifts of H10', H6', and H2' were in excellent agreement with synthetic himeradine A (38) (Figure 4.9).

We decided to first embark on a synthesis of a quinolizidine subunit model in which the C6'-stereocenter is inverted relative to the proposed structure of himeradine A (38). This can be readily accomplished with the synthetic route we have previously developed and discussed, with minor modifications (Scheme 4.25). The C6'-stereocenter was introduced via exposure of intermediate 113 to AllylSnBu₃ in the presence of BF₃•OEt₂, delivering allyl N-Boc piperidine 165 as a single diastereomer. The diastereoselectivity of this reaction is controlled through stereoelectronically favored axial attack of the corresponding N-acyliminium ion intermediate by AllylSnBu₃ antī to the C12'-methyl group. Cleavage of the N-Boc protecting group in 165, followed by allylation of the resultant piperidine, occurred smoothly to afford tertiary amine 166. 166 was transformed to quinolizidine 168 in four steps via: (1) ring-closing metathesis to provide alkene 167, (2)
hydrogenation of the resultant alkene, (3) global silyl deprotection, and (4) selective protection of the resultant primary hydroxyl group. Finally, Mitsunobu displacement of the secondary hydroxyl group in \(168\) with azide, followed by cleavage of the primary TBS ether, yielded quinolizidine \(169\), our desired model substrate.

**Scheme 4.25.** Synthesis of a model of the quinolizidine subunit \(169\) in which the \(C6\)-stereocenter is inverted relative to the proposed structure of himeradine A (38).

Treatment of \(169\) with TFA cleanly provided the corresponding TFA salt, the \(^1\)H NMR spectrum of which was directly compared with that of natural himeradine A (Figure 4.10). As is readily apparent, the \(^1\)H NMR spectrum of the TFA salt of \(169\) is noticeably different from natural himeradine A. We were originally concerned about the accuracy of our quinolizidine model system in which \(C17\) is connected to an azide (169), versus an imine functionality in himeradine A, in predicting the chemical shift of the \(H10\)-proton. However, it is evident that the chemical shifts of the \(H2\)-protons in \(169\) (\(\delta = 3.82\) and 2.89 ppm (the latter is not shown in Figure 4.10)) were remarkably different from that in natural himeradine A (\(\delta = 3.33\) and 3.19 ppm). Hence, we concluded that it was unlikely that the \(C6\)-stereocenter in the proposed structure of himeradine A (38) was misassigned.
Figure 4.10. Comparison of $^1$H NMR spectra of quinolizidine subunit model 169, in which the C6'-stereocenter has been inverted, and natural himeradine A as the TFA salts in CD$_3$OD.

Next, we turned our focus to inverting the C10'-stereocenter, which unfortunately could not be accomplished with the previously developed synthetic route. A new strategy was devised (Scheme 4.26). Utilizing the enantioselective transfer aminoallylation reaction developed by Kobayashi et al.,$^{126}$ aldehyde 108 and $\alpha$-aminoketone 170, derived from (1R)-(−)-camphorquinone, were stirred together in the presence of catalytic CSA, furnishing lactam 171 as a single diastereomer via: (1) condensation of aldehyde 108 with the amine in 170, (2) a 2-aza-Cope rearrangement of the resultant imine, (3) cleavage of the newly formed imine under acidic conditions with the use of HONH$_2$•AcOH to reveal the homoallylamine product, and (4) in situ lactam formation.

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Scheme 4.26. Synthesis of a model of the quinolizidine subunit 176 in which the C10'-stereocenter is inverted relative to the proposed structure of himeradine A (38).

Protection of lactam 171 as the corresponding Boc-imide, followed by exposure to OsO₄ and NaIO₄ in the presence of 2,6-lutidine,¹²⁷ yielded aldehyde 172 via oxidative cleavage of the terminal olefin. An asymmetric allylboration of 172 with Brown’s chiral (+)-Ipc₂B(allyl) allylborane reagent¹²⁸ provided alcohol 173 as a single diastereomer. Mitsunobu displacement of the secondary hydroxyl group in 173 with azide occurred smoothly to afford azide 174. 174 was converted to amine 175 as a single diastereomer via a three-step protocol involving: (1) addition of Grignard reagent TIPSO(CH₂)₄Mgl to the imide functionality, (2) subsequent exposure to TFA to cleave the N-Boc group and form the corresponding imine with concomitant cleavage of the TIPS ether group, and (3) reductive amination with NaBH(OAc)₃ in the presence of AcOH. Finally, 175 underwent an Appel reaction with CBr₄ and PPh₃ in the presence of Et₃N, resulting in the formation of the corresponding bromide and in situ intramolecular S_N₂ cyclization to deliver quinolizidine 176, the desired model.

Treatment of 176 with TFA cleanly provided the corresponding TFA salt, the ¹H NMR


spectrum of which was directly compared with that of natural himeradine A (Figure 4.11). Once again, the $^1$H NMR spectrum of the TFA salt of 176 was distinctively different from natural himeradine A. Not only was the chemical shift of H10' considerably different ($\delta = 3.22$ ppm versus 3.77 ppm in natural himeradine A), but also the chemical shifts of the H2'-protons in 176 ($\delta = 3.86$ and 2.75 ppm (the latter is not shown in Figure 4.11) versus 3.33 and 3.19 ppm in natural himeradine A). Hence, we concluded that it was unlikely that the C10'-stereocenter in the proposed structure of himeradine A (38) was misassigned.

Figure 4.11. Comparison of $^1$H NMR spectra of quinolizidine subunit model 176, in which the C10'-stereocenter has been inverted, and natural himeradine A as the TFA salts in CD$_3$OD.
Figure 4.12. Selected NOESY correlations observed for the proposed structure of himeradine A (38).

Although these results were discouraging, we turned our attention to the most probable remaining candidate for stereochemical misassignment—the C17-stereocenter. In the original isolation report by Kobayashi and coworkers, the stereochemical assignment of H17 as the axial configuration was based on observed NOESY correlations (Figure 4.12) between H17 and H10', 11'a and H8', H11'a and H6', and H11'b and H2'. However, both the axial and equatorial configurations of H17 would result in these observed NOESY correlations. Hence, we believed the proposed C17 stereochemical assignment was ambiguous. Furthermore, both epimers of C17 exist in related Lycopodium alkaloids, lucidines A and B, suggesting that the opposite C17 configuration to the proposed structure of himeradine A (38) was plausible (Figure 4.13).

Figure 4.13. Lucidine A and B are epimeric at the C17-stereocenter.
Candidate for the Structural Reassignment of (−)-Himeradine A

As discussed in the previous section, we next embarked on a synthesis of the C17-epimer of the proposed structure of himeradine A (38). This could readily be accomplished with the synthetic route we originally developed with minor modifications (Scheme 4.27). In order to introduce the C17-stereocenter, a double inversion of the secondary hydroxyl group in intermediate 145 is required. Mitsunobu displacement of the C17-hydroxyl with p-nitrobenzoic acid,129 followed by cleavage of the resultant ester, afforded inverted alcohol 177. A second Mitsunobu displacement with azide then yielded azide 178. Cleavage of the TBS-ether, followed by iodide formation, furnished alkyl iodide 179, the desired alkylation electrophile. β-carboxyimide 66 underwent efficient alkylation with 179 in the presence of Cs₂CO₃ to provide alkylated product 180 in 77% yield.

Scheme 4.27. Double inversion of the C17-stereocenter.

Following the same reaction sequence utilized in the synthesis of the proposed structure of himeradine A (38), 180 was converted to N-Ns-2-pyrrolidinone 181 in three steps via: (1) cleavage of the TMSE ester with concomitant decarboxylation, (2) cleavage of the N-Boc group with

Mg(ClO₄)₂, and (3) protection of the resultant pyrrolidinone with a Ns group (Scheme 4.28). Addition of the lithium enolate of t-butylacetate to C13 of 181 and subsequent cleavage of the C6-dioxolane yielded enone 182. Utilizing our optimized one-pot protocol, exposure of 182 to Barton’s base, followed by addition of PhSH in the presence of K₂CO₃, furnished imine 183. Next, a Staudinger reduction of the azide in 183 and condensation of the resultant amine with the neighboring β-ketoester, provided the corresponding vinylogous urethane product, which underwent subsequent acetylation to afford amide 184 (50%, 2 steps). Next, a cross-metathesis of the allyl group in 184 with acrolein in the presence of Hoveyda–Grubbs II catalyst occurred smoothly to yield enal 185 (88%).

Scheme 4.28. Successful application of our one-pot sequence protocol toward the synthesis of himeradine A candidate structure 188.

Hydrogenation of 185, reduction of the corresponding aldehyde with NaBH₄, and tosylation of the resultant hydroxyl group provided tosylate 186 (73%, 3 steps) (Scheme 4.29). 186 was converted to quinolizidine 187 (59%, 2 steps) via: (1) initial formation of the silyloxy carbamate by exposure to TBSOTf and 2,6-lutidine, (2) subsequent cleavage of the carbamate with concomitant decarboxylation upon treatment with TBAF, and (3) in situ cyclization via S₂N₂ displacement of the tosylate group with the resultant secondary amine. Exposure of 187 to TFA then yielded our
candidate structure for (-)-himeradine A (188) as the double TFA salt ([α]D22 = −56 (c 0.3, MeOH)).

Scheme 4.29. Synthesis of our candidate structure for himeradine A (188).

We were excited to discover that the chemical shift of H10' (δ = 3.79–3.74 ppm) in our candidate structure for himeradine A (188) was in excellent agreement with that for natural himeradine A (δ = 3.77 ppm) (Figure 4.14). In fact, the chemical shifts of the key protons of the quinolizidine subunit (H6', H10', and H2') are all in good agreement with the values reported for natural himeradine A. Unfortunately, however, several protons corresponding to the pentacyclic core of 188 (boxed in red) no longer match the reported values. Additionally, as expected, H17 is shifted upfield relative to the chemical shift in natural himeradine A.

Based on the combined results of our quinolizidine model systems (169 and 176) and our candidate structure for himeradine A (188), we speculated that it could indeed be the absolute stereochemistry of the quinolizidine subunit, and not the relative configuration of the C17-, C6'-, or C10'-stereocenters, of himeradine A (38) that may have been misassigned. The synthesis of the opposite absolute stereochemistry of the quinolizidine subunit of 38 should be readily feasible with our developed route due to the latent C2-symmetry of starting material 107. However, embarking on a new route without further information—in particular, an authentic sample of himeradine A—would
be impractical. Despite our educated hypothesis based on our model studies, there are still theoretically a total of sixteen possible stereoisomers. Furthermore, we cannot definitively rule out the possibility that we have successfully synthesized the correct structure of himeradine A (38) without an authentic sample of the natural product. Nonetheless, we have demonstrated that all sixteen possible stereoisomers could theoretically be accessed from the chemistry that we have developed.
Figure 4.14. Comparison of $^1$H NMR spectra of candidate (188) and natural (−)-himeradine A as the double TFA salt in CD$_3$OD.

In summary, this constitutes the first reported total synthesis of the proposed structure of (−)-himeradine A (38). Noteworthy transformations include a biosynthetically inspired, diastereoselective, one-pot sequence for constructing the strained core common to himeradine A (38)
and other *Lycopodium* alkaloids, and a key biomimetic transannular Mannich reaction. This highly convergent and unifying strategy can now be applied towards the streamlined synthesis of other 7-membered ring-containing *Lycopodium* alkaloids, which will be the subject of the next chapter.
II. A Biomimetic Unified Strategy for the Synthesis of 7-Membered Ring-Containing 

*Lycopodium* Alkaloids

Chapter 5

Total Syntheses of 7-Membered Ring-Containing *Lycopodium* Alkaloids
Introduction

In the previous chapter, we presented the development of a biosynthetically inspired one-pot cascade sequence for the construction of the strained core system common to a variety of 7-membered ring-containing *Lycopodium* alkaloids, including himeradine A (38) and fastigiatine (37). This unifying and highly convergent strategy supports our biosynthetic hypothesis (Figure 4.2) and can be applied towards the synthesis of a diverse set of *Lycopodium* alkaloids (Scheme 5.1).

![Scheme 5.1](image)

**Scheme 5.1.** A biomimetic and unified strategy for the total syntheses of structurally diverse *Lycopodium* alkaloids.

As illustrated in Scheme 5.2, a variety of structurally diverse *Lycopodium* alkaloids can be accessed with our strategy by varying the alkylation electrophile partner of carboxyimide 66. Examples of such alkaloids include not only himeradine A (38) and fastigiatine (37), but also lycopecurine (39), lyconadins A (31), B (32), and C (189), and nankakurine (48). General precursor imine 190 can be accessed from the one-pot reaction sequence that we have developed. A subsequent
biomimetic transannular Mannich reaction would deliver himeradine A (38), fastigiatine (37), and lycopecurine (39). Alternatively, reduction of 190 by hydride could give rise to the lyconadin group of alkaloids, such as lyconadin B (32) and lyconadin C (189), or nankakurine A (48), which has undergone a subsequent rearrangement.

Scheme 5.2. Proposed unified strategy for the synthesis of a variety of Lycopodium alkaloids. Highlighted in red is the common 7-membered ring structural motif. Highlighted in gray is the variable alkyl chain.

A structurally diverse set of Lycopodium alkaloids could potentially be accessed from our biosynthetically inspired unifying strategy. The successful application of our unifying approach to the total syntheses of other Lycopodium alkaloids would lend credence to our biosynthetic hypothesis and showcase the utility of the one-pot reaction sequence that we have developed.
Total Synthesis of Dehydrolycopecurine and Lycopecurine

Lycopecurine (39), isolated in 1969 from Lycopodium alopecuroides,\(^{130}\) contains the strained tetracyclic core common to himeradine A (38) and fastigiatine (37). Although no NMR spectra were provided, the structure was unambiguously determined by single crystal X-ray crystallography of the hydrobromide salt of lycopecurine (39). To date, a synthesis of lycopecurine has not yet been achieved. We envisioned that we could achieve the first total synthesis of lycopecurine with our biosynthetically inspired, unifying strategy to construct the strained core system.

To this end, alkylation of β-carboxyimide 66 with benzyl 3-bromopropylether occurred smoothly to provide alkylated product 191 (Scheme 5.3). Employing the same reaction sequence used in the synthesis of himeradine A (38), 191 was converted in five steps to enone 194. In a one-pot reaction sequence involving initial exposure to \(\text{K}_2\text{CO}_3\) and subsequent addition of PhSH, 194 underwent a cascade reaction to afford imine 195 (84%, 3 steps) via: (1) 7-endo-trig intramolecular conjugate addition and (2) in situ condensation of N\(\beta\) with the C13-ketone.

Scheme 5.3. Synthesis of imine 195.

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Next, treatment of 195 with TFA resulted in loss of the \( t \)-butyloxy carbonyl group to afford the corresponding ketone, which then underwent the key biomimetic transannular Mannich reaction upon heating with HCl in MeOH\(^{87} \) to construct the C4–C13 bond in tetracycle 197 (95%, 2 steps) (Scheme 5.4). Hydrogenolysis of the benzyl group in 197, followed by exposure of the resultant alcohol 198 to 25% HBr in glacial AcOH\(^{87} \) resulted in bromination of the hydroxyl group and formation of the ammonium bromide salt. Upon treatment with K\(_2\)CO\(_3\), this intermediate underwent cyclization to yield dehydrolycopecurine\(^{131} \) (199) in 59% yield over 2 steps ([\( \alpha \)\( ]_D^{22} = -69 \) (c 0.34, MeOH)). Finally, reduction of the ketone with LiEt\(_3\)BH delivered lycopuerine (39) in 66% yield ([\( \alpha \)\( ]_D^{22} = -19 \) (c 0.14, MeOH)), constituting the first total syntheses of Lycopodium alkaloids 39 and 199. The structure of 39 was unambiguously established via single crystal X-ray diffraction analysis of the hydrobromide salt of 39.

Scheme 5.4. Total synthesis of dehydrolycopecurine (199) and lycopuerine (39).

By varying the alkylation electrophile partner with carboxyimide 66, we were able to accomplish the first total syntheses of dehydrolycopecurine (199) and lycopuerine (39) using our biosynthetically inspired, unifying strategy. Our one-pot cascade sequence was employed in the construction of the tricyclic core of 199 and 39. A key biomimetic transannular Mannich reaction

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then established the C4–C13 bond, furnishing the tetracyclic core common to himeradine A (38) and fastigiatine (37).
**Total Synthesis of (+)-Lyconadin A and (−)-Lyconadin B**

In 2001, Kobayashi and coworkers isolated (+)-lyconadin A (31) from the club moss *Lycopodium complanatum*. The structure of lyconadin A (31) was revealed to contain a pentacyclic core, including a 2-pyridone ring, six stereocenters, and a tertiary amine. 31 exhibits modest cytotoxicity against murine lymphoma L1210 cells (IC$_{50}$ = 0.46 µg/mL) and human epidermoid carcinoma KB cells (IC$_{50}$ = 1.7 µg/mL). Four syntheses of 31 have been accomplished to date. (−)-Lyconadin B (32), which differs from 31 in that it contains a dihydropyridone instead of a pyridone moiety, was isolated in 2006. To date, two total syntheses of lyconadin B (32) have been achieved. Both 31 and 32 demonstrate enhanced mRNA expression for nerve growth factor in 1321N1 human astrocytoma cells. We envisioned that a synthesis of lyconadin A (31) and B (32) could be realized by utilizing our unifying strategy to construct the core system via our one-pot reaction sequence.

To this end, alkylation of β-carboxyimide 66 with acrylonitrile proceeded smoothly to afford alkylated product 200 (Scheme 5.5). Utilizing the same reaction sequence employed in the synthesis of himeradine A (38) and lycopercurine (39), 200 was converted to enone 203 in five steps. A one-pot reaction sequence involving initial exposure to K$_2$CO$_3$ followed by addition of PhSH then delivered tricyclic imine 204 (63%, 3 steps).

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Scheme 5.5. Synthesis of imine 204.

Unlike himeradine A (38) and lycopecurine (39), which underwent a subsequent transannular Mannich reaction, a synthesis of the lyconadins would require reduction of the imine functionality (Scheme 5.6). Treatment of 204 (redrawn as 205) with NaBH(OAc)$_3$ and AcOH resulted in chemoselective reduction of the imine to furnish amine 206. Next, treatment of 206 with TFA resulted in removal of the t-butyloxy carbonyl group to afford ketone 207 (59%, 2 steps).

Scheme 5.6. Total synthesis of (+)-lyconadin A (31) and (−)-lyconadin B (32).

Deprotonation of 207 with LiHMDS, followed by trapping with I$_2$, directly delivered amine 208 (73%); this presumably occurred via one of two possible mechanisms, including: (1) initial α-iodination of the ketone from the convex face, followed by intramolecular S$_{N}$2 displacement of the iodide by the secondary amine, or (2) oxidative enolate amination via a radical pathway.
Finally, heating nitrile 208 in a 7.0 M NH$_3$/MeOH\textsuperscript{135} solution in a sealed vessel at 120 °C furnished (--)-lyconadin B (32) in 57% yield ([α]$_D^{21} = -102$ (c 0.5, MeOH)). The $^1$H NMR (Figure 5.1) and $^{13}$C NMR spectra for synthetic (--)-lyconadin B (32) are in good agreement with the spectra reported for the natural product. During our studies to convert 208 to lyconadin B (32), we discovered a trace byproduct in the crude $^1$H NMR corresponding to lyconadin A (31) after heating the reaction in NH$_3$/MeOH for two days.\textsuperscript{136} Lyconadin A (31) presumably formed by autoxidation in the presence of trace oxygen. Gratifyingly, heating lyconadin B (32) neat at 160 °C under an atmosphere of air afforded lyconadin A (31) in 57% yield ([α]$_D^{22} = +37$ (c 0.12, MeOH)). The $^1$H NMR and $^{13}$C NMR spectra for synthetic and natural (+)-lyconadin A (31) are in good agreement (Figure 5.2)


\textsuperscript{136} A similar observation was made by Fukuyama and coworkers: See ref. 134.
Figure 5.1. Comparison of $^1$H NMR spectra of natural and synthetic (−)-lyconadin B (32) in CD$_3$OD.
Figure 5.2. Comparison of $^1$H NMR spectra of natural and synthetic (+)-lyconadin A (31) in CD$_3$OD.

The successful total syntheses of lyconadin A (31) and lyonadin B (32) further lend support to our biosynthetic hypothesis that 7-membered ring-containing Lycopodium alkaloids arise from a common imine precursor, which can then undergo either a transannular Mannich reaction or imine reduction to generate a large diverse group of alkaloid natural products. Our biomimetic and unifying strategy has allowed us to readily and efficiently access a variety of structurally diverse Lycopodium alkaloids by simply varying the carboxymide alkylation electrophile partner. The application of our
strategy enabled the successful total syntheses of himeradine A (38), lycopercine (39),
dehydrolycopecurine (199), lyconadin A (31), and lyconadin B (32), and can potentially be used to
synthesize all other 7-membered ring-containing *Lycopodium* alkaloids.
Concluding Remarks

In conclusion, the first total synthesis of the proposed structure of himeradine A (38), arguably the most complex and synthetically challenging \textit{Lycopodium} alkaloid, was achieved. A biosynthetically inspired, diastereoselective, one-pot reaction sequence for constructing the strained core common to 7-membered ring-containing \textit{Lycopodium} alkaloids was developed. A key biomimetic transannular Mannich reaction was successfully executed in the synthesis of the pentacyclic core of 38.

This biosynthetically inspired reaction sequence was further applied towards the first total syntheses of lycopecurine (39) and dehydrolycopecurine (199), which also featured a key biomimetic intramolecular Mannich reaction. Our one-pot cascade sequence was also successfully utilized in a concise and streamlined synthesis of (+)-lyconadin A (31) and (−)-lyconadin B (32), which involved reduction of an imine intermediate instead of a transannular Mannich reaction to construct the core system. Our results constitute a unified strategy towards the synthesis of a structurally diverse set of 7-membered ring-containing \textit{Lycopodium} alkaloids, lending support to our proposed revised biosynthetic hypothesis of these natural products.

\textbf{Scheme 5.7}. Successful synthesis of a diverse set of 7-membered ring-containing \textit{Lycopodium} alkaloids by employing our biomimetic unifying strategy.
Experimental Section

**General Procedures.** All reactions were performed in flame-dried glassware under a positive pressure of argon unless otherwise noted. Flash column chromatography was performed as described by Still et al. employing silica gel 60 (40-63 µm, Whatman). Where necessary (so specified), silica gel was neutralized by treatment of the silica gel prior to chromatography with the eluent containing triethylamine or 5 M aqueous NH₄OH. Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel 60 F₂₅₄ plates purchased from EMD Chemicals. TLC plates were visualized by exposure to ultraviolet light (UV) and/or exposure to an acidic solution of p-anisaldehyde (Anis) or an aqueous solution of potassium permanganate (KMnO₄), followed by heating on a hot plate.

**Materials.** Commercial reagents and solvents were used as received with the following exceptions: tetrahydrofuran (THF), diethyl ether (Et₂O), dichloromethane (CH₂Cl₂), acetonitrile (MeCN), hexamethyldisilazane (HMDS), benzene (PhH), and N,N-dimethylformamide (DMF) were degassed with argon and passed through a solvent purification system (designed by J. C. Meyer of Glass Contour) utilizing alumina columns as described by Grubbs et al. Triethylamine, diisopropylamine, and pyridine were distilled over calcium hydride before use. TMSOTf was distilled before use. N,N,N′N′-Tetramethylethylenediamine was distilled over potassium hydroxide immediately before use. The celite used was Celite®, purchased from J.T. Baker. The molarities of n-butyllithium and sec-butyllithium solutions were determined by titration using 1,10-phenanthroline as an indicator (average of three determinations).

**Instrumentation.** ¹H NMR spectra were recorded with a Varian INOVA-600 or Varian INOVA-500 spectrometer. Proton chemical shifts are reported in parts per million (δ scale) and are calibrated using residual undeuterated solvent as an internal reference (CDCl₃: δ 7.26 (CHCl₃)),
CD$_3$OD: δ 3.31 (CD$_2$OD), C$_6$D$_6$: δ 7.15 (C$_6$D$_5$H). Data for $^1$H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent, or combinations thereof. $^{13}$C NMR spectra were recorded with a Varian INOVA-500 spectrometer. Carbon chemical shifts are reported in parts per million (δ scale) and are referenced from the carbon resonances of the solvent (CDCl$_3$: δ 77.00, CD$_3$OD: δ 49.00, C$_6$D$_6$: δ 128.39). Infrared (FTIR) spectra were recorded on a Bruker Alpha FT-IR spectrophotometer referenced to a polystyrene standard. FTIR data is reported in frequency of absorption (cm$^{-1}$). High-resolution mass spectra (HRMS) were obtained from the Harvard University Mass Spectrometry Laboratory where electrospray ionization (ESI) mass spectroscopy (MS) experiments were performed on an Agilent 6210 TOF LC/MS instrument. Optical rotations were measured on a Jasco P-2000 digital polarimeter with a sodium lamp. Reported readings are the average of five measurements for each sample. The structure of (–)-lycopecurine (39) was obtained with the assistance of Dr. Shao-Liang Zheng at the X-ray diffraction facility of the Department of Chemistry and Chemical Biology, Harvard University.

(For clarity, intermediates that have not been assigned numbers in the text are numbered sequentially in the experimental section beginning with SI).
(R)-Propyl 3-methyl-5-oxopentanoate (108):

Borane dimethyl sulfide complex (4.54 mL, 46.3 mmol, 1.20 equiv) was added dropwise via syringe to a stirred solution of (R)-3-methyl-5-oxo-5-propoxypentanoic acid (107)\textsuperscript{110,137} (7.26 g, 38.6 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 10 mL), in THF (103 mL) at 0 °C, which was subsequently allowed to warm naturally to room temperature. After stirring for an additional 21 h, the reaction mixture was recooled to 0 °C and water (40 mL) was added. The resultant mixture was stirred vigorously and allowed to warm to room temperature. All volatiles were subsequently removed \textit{in vacuo} and the resultant solution was partitioned between Et\textsubscript{2}O (150 mL) and water (60 mL). The layers were separated and the aqueous layers were further extracted with Et\textsubscript{2}O (3 × 50 mL). The organic layers were combined, washed with saturated aqueous NaHCO\textsubscript{3} solution (100 mL) and brine (100 mL), then dried over anhydrous MgSO\textsubscript{4}, filtered, and concentrated under reduced pressure to afford the corresponding alcohol S\textsubscript{1} as a colorless oil, which was carried forward to the next step without further purification.

A solution of alcohol S\textsubscript{1}, which was azeotropically dried with benzene (5 × 50 mL), in CH\textsubscript{2}Cl\textsubscript{2} (193 mL) was cooled to 0 °C. DMSO (27.4 mL, 386 mmol, 10.0 equiv), i-Pr\textsubscript{2}NEt (33.6 mL, 193 mmol, 5.00 equiv), and SO\textsubscript{3}•Py (18.4 g, 116 mmol, 3.00 equiv) were then added sequentially to the solution, which was then allowed to warm to room temperature. After stirring for 1 h, water (200 mL) and Et\textsubscript{2}O (400 mL) were added to the reaction mixture. The layers were separated and the aqueous layer was extracted with Et\textsubscript{2}O (3 × 150 mL). The organic layers were combined and washed with 10% aqueous HCl solution (3 × 150 mL), saturated aqueous NaHCO\textsubscript{3} solution (200 mL), and

\textsuperscript{137} Synthesized in one step from 3-methylglutaric anhydride. The enantiopurity of 107 was determined to be 93% ee by chiral HPLC using authentic (±)-107.
brine (200 mL). The organic layers were dried over anhydrous MgSO₄ and concentrated under reduced pressure to afford crude (R)-propyl 3-methyl-5-oxopentanoate **108** as a pale yellow oil, which was carried forward to the next step without further purification.

**¹H NMR** (500 MHz, CDCl₃) δ: 9.76 (t, J = 2.2 Hz, 1H), 4.04 (t, J = 6.7 Hz, 2H), 2.64–2.48 (m, 2H), 2.39–2.32 (m, 2H), 2.28 (dd, J = 7.1, 15.1 Hz, 1H), 1.65 (sxt, J = 7.1 Hz, 2H), 1.04 (d, J = 6.6 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ: 201.5, 172.3, 66.0, 50.1, 40.9, 25.2, 21.9, 20.1, 10.4. **FTIR** (thin film) cm⁻¹: 2966, 2880, 1724, 1460, 1263, 1213, 1170, 1088. **HRMS** (ESI) (m/z) calc’d for C₉H₁₆NaO₃ [M+Na]⁺: 195.0992, found 195.0995. **TLC** (1:1 hexanes:EtOAc), Rₛ : 0.84 (KMnO₄).
4-((Triisopropylsilyl)oxy)butan-2-one (S3):

Imidazole (39.5 g, 581 mmol, 2.50 equiv) and TIPSCI (55.0 mL, 279 mmol, 1.10 equiv) were added successively to a solution of 4-hydroxy-2-butanone (S2) (20.0 mL, 232 mmol, 1.00 equiv) in DMF (42 mL) at room temperature. The resultant solution was allowed to stir for 19.5 h, at which point water (150 mL), Et₂O (100 mL), and EtOAc (100 mL) were added. The layers were separated and the aqueous layer was extracted with Et₂O (3 × 200 mL). The organic layers were combined, washed with brine (300 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting oil was then purified by flash column chromatography (silica gel, eluent: 12:1 hexanes:EtOAc) to afford 4-(triisopropylsilyl)oxy)butan-2-one (S3) (56.8 g, quant.) as a clear colorless oil.

^1H NMR (500 MHz, CDCl₃) δ: 3.98 (t, J = 6.3 Hz, 2H), 2.64 (t, J = 6.3 Hz, 2H), 2.20 (s, 3H), 1.12–1.02 (m, 21 H). ^13C NMR (126 MHz, CDCl₃) δ: 208.3, 59.3, 46.7, 30.9, 17.9, 11.9. FTIR (thin film) cm⁻¹: 2942, 2866, 1716, 1463, 1356, 1105, 882, 680. HRMS (ESI) (m/z) calc’d for C₁₃H₂₈NaO₂Si [M+Na]⁺: 267.1751, found 267.1755. TLC (4:1 hexanes:EtOAc), Rf: 0.62 (KMnO₄).
Silyl enol ether 109:

To a solution of diisopropylamine (21.5 mL, 153 mmol, 1.50 equiv) in THF (255 mL) at 0 °C was added dropwise a solution of n-butyllithium in hexanes (2.60 M, 57.0 mL, 148 mmol, 1.45 equiv). After 10 min, the reaction was recooled to −78 °C and TMSCl (65.0 mL, 511 mmol, 5.00 equiv) was added dropwise via syringe. After stirring the resultant mixture for 20 min, a solution of 4-(triisopropylsilyl)oxy)butan-2-one (S3) (25.0 g, 102 mmol, 1.00 equiv) in THF (255 mL), which was azeotropically dried with benzene (5 × 50 mL), was added dropwise via cannula to the stirred reaction at −78 °C. After 15 min, Et₃N (47.0 mL, 338 mmol, 3.30 equiv) was added dropwise via syringe to the reaction. The reaction was stirred for an additional 1.5 h at −78 °C, at which point a saturated aqueous NaHCO₃ solution (400 mL) was added. The resultant mixture was allowed to warm to room temperature and Et₂O (200 mL), EtOAc (200 mL), and water (100 mL) were subsequently added. The layers were separated and the aqueous layer was extracted with Et₂O (3 × 300 mL). The organic layers were combined, washed with brine (300 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to afford crude silyl enol ether 109 as a pale yellow oil and as a 2:1 mixture of regioisomers, favoring the indicated 109. The crude silyl enol ether was carried forward to the next step without further purification.
Lactam 110:

Aldehyde 108 (800 mg, 4.65 mmol, 1.00 equiv), which was azeotropically dried with benzene (3 × 5 mL), was dissolved in a solution of NH₃ in MeOH (2.00 M, 24.0 mL) and heated at 50 °C for 8 h. The reaction mixture was subsequently concentrated under reduced pressure to afford a mixture of N,O-hydroxy- and N,O-methoxyacetals, and uncyclized (3R)-propyl 5-amino-5-hydroxy-3-methylpentanoate. The crude product mixture was carried forward to the next step without further purification.

p-TsOH•H₂O (177 mg, 0.930 mmol, 0.20 equiv) was added as a single portion to a stirred solution of the crude product mixture in MeOH (46.5 mL), which was subsequently heated at 50 °C for 2 days, during which additional p-TsOH•H₂O (40.0 mg, 0.210 mmol, 0.05 equiv) was added. The reaction was then allowed to cool to room temperature and a saturated aqueous NaHCO₃ solution (50 mL) was added. The mixture was subsequently concentrated under reduced pressure to remove all volatiles. The resultant aqueous layer was diluted with CHCl₃ (100 mL), water (50 mL), and brine (50 mL), and the layers were separated. The aqueous layer was further extracted with CHCl₃ (5 × 50 mL) and the organic layers were combined, washed with brine (100 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure to afford a diastereomeric mixture of N,O-methoxyacetals 106 as a crude white solid, which was carried forward to the next step without further purification.

BF₃•OEt₂ (922 µL, 7.47 mmol, 2.00 equiv) was added dropwise to a solution of crude 106 and silyl enol ether 109 (7.10 g, 22.4 mmol, 6.00 equiv), which were azeotropically dried with benzene (5 × 15 mL), in MeCN (37.5 mL) at −40 °C. The reaction was allowed to warm gradually to room temperature. After 2.5 h, water (100 mL), Et₂O (50 mL), and EtOAc (50 mL) were added to
the reaction mixture. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with brine (200 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure. The resulting oil was then purified by flash column chromatography (silica gel, eluent: gradient: EtOAc → 15:1 EtOAc:MeOH) to afford lactam 110 (709 mg, 43% over 3 steps) as a single diastereomer and as a pale yellow oil.

¹H NMR (500 MHz, CDCl₃) δ: 6.26 (s, 1H), 4.06–3.89 (m, 3H), 2.78 (dd, J = 9.5, 18.3 Hz, 1H), 2.69 (dd, J = 3.2, 18.3 Hz, 1H), 2.66–2.51 (m, 2H), 2.41 (dd, J = 4.2, 17.8 Hz, 1H), 1.98 (dd, J = 8.3, 16.8 Hz, 1H), 1.68–1.60 (m, 1H), 1.15–0.97 (m, 23H). ¹³C NMR (126 MHz, CDCl₃) δ: 208.9, 171.3, 59.3, 50.8, 46.1, 45.8, 39.3, 34.8, 24.3, 20.4, 17.9, 11.8. FTIR (thin film) cm⁻¹: 2942, 2866, 1712, 1662, 1462, 1364, 1101, 882, 681. HRMS (ESI) (m/z) calc’d for C₁₉H₃₇NNaO₃Si [M+Na]⁺: 378.2435, found 378.2448. [α]D²²: −52 (c = 0.94, CH₂Cl₂). TLC (9:1 EtOAc:MeOH), Rf: 0.50 (KMnO₄, UV).

1D NOESY (500 MHz, CDCl₃):
**Alcohol 111:**

Diisobutylaluminum hydride (3.80 mL, 21.3 mmol, 8.00 equiv) was added to a stirred solution of lactam 110 (945 mg, 2.66 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 5 mL), in THF (53 mL) at −78 °C. After stirring the resultant reaction for 4 h at −78 °C, a saturated aqueous solution of Rochelle’s salt (200 mL) was carefully added at a slow rate. The resultant mixture was allowed to warm to room temperature and was subsequently diluted with Et₂O (150 mL) and EtOAc (150 mL), and stirred vigorously for 12 h. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 150 mL). The organic layers were combined, washed with brine (200 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure to afford crude alcohol 111 as a single diastereomer and as a pale yellow oil, which was carried forward to the next step without further purification.

**¹H NMR** (600 MHz, CDCl₃) δ: 76.83 (br. s, 1H), 4.10–3.97 (m, 3H), 3.93 (dt, J = 2.7, 10.3 Hz, 1H), 3.77–3.68 (m, 1H), 2.43 (dd, J = 5.5, 17.2 Hz, 1H), 2.18–2.09 (m, 1H), 2.04 (dd, J = 5.5, 17.2 Hz, 1H), 1.81–1.71 (m, 1H), 1.71–1.57 (m, 4H), 1.49 (d, J = 13.7 Hz, 1H), 1.17–1.01 (m, 24H).

**¹³C NMR** (126 MHz, CDCl₃) δ: 171.2, 73.0, 63.6, 49.2, 44.0, 38.7, 38.6, 35.4, 24.6, 19.8, 17.9, 11.7.

**FTIR** (thin film) cm⁻¹: 2941, 2865, 1650, 1462, 1316, 1095, 882, 679. **HRMS** (ESI) (m/z) calc’d for C₁₉H₃₅NNaO₃Si [M+Na]⁺: 380.2591, found 380.2588. **TLC** (9:1 EtOAc:MeOH), Rₛ: 0.42 (KMnO₄).
**Cyclic imide S5:**

A solution of \textit{n}-butyllithium in hexanes (2.56 M, 15.5 µL, 0.0396 mmol, 2.50 equiv) was added to a stirred solution of alcohol \textit{S4}\textsuperscript{138} (5.0 mg, 0.016 mmol, 1.0 equiv), which was azeotropically dried with benzene (5 × 1 mL), in THF (200 µL) at −78 °C. After 20 min, the reaction was allowed to warm to 0 °C and stirred for an additional 10 min, at which point the solution was recooled to −78 °C. A solution of 1,1'-carbonyldiimidazole (9.0 mg, 0.055 mmol, 3.5 equiv) in THF (200 µL) was added to the stirred reaction mixture, which was subsequently allowed to warm gradually to room temperature over 30 min. A solution of saturated aqueous NH\textsubscript{4}Cl (1 mL) and EtOAc (1 mL) were added sequentially to the reaction mixture. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 1 mL). The organic layers were combined, washed with brine (2 mL), dried over anhydrous MgSO\textsubscript{4}, and concentrated under reduced pressure. The resultant residue was purified by flash column chromatography (silica gel, eluent: 2:1 EtOAc:hexanes) to afford cyclic imide \textit{S5} as a white solid.

\textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}) δ: 4.54–4.47 (m, 1H), 3.99 (tt, \textit{J} = 4.4, 11.4 Hz, 1H), 3.85–3.78 (m, 1H), 3.73 (td, \textit{J} = 5.2, 10.3 Hz, 1H), 2.64 (dd, \textit{J} = 5.1, 15.4 Hz, 1H), 2.34–2.26 (m, 1H), 2.19 (ddd, \textit{J} = 2.0, 4.8, 14.0 Hz, 1H), 1.94–1.84 (m, 2H), 1.82–1.63 (m, 4H), 1.10 (d, \textit{J} = 6.6 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H). \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ: 171.9, 148.1, 74.1, 58.2, 52.7, 42.1, 37.9, 37.3, 35.1, 25.9, 24.3, 21.6, 18.2, −5.4, −5.4. FTIR (thin film) cm\textsuperscript{−1}: 2957, 2927, 2855, 1762, 1313, 1101, 837, 773. HRMS (ESI) (m/z) calc’d for C\textsubscript{17}H\textsubscript{31}NNaO\textsubscript{4}Si [M+Na]\textsuperscript{+}: 364.1915, found 364.1931. TLC (9:1 EtOAc:MeOH), \textit{Rf}: 0.68 (KMnO\textsubscript{4}, UV).

\textsuperscript{138} \textit{S4} was synthesized according to the sequence utilized in the synthesis of \textit{111}.
1D NOESY (500 MHz, CDCl₃):
Silyl ether S6:

Imidazole (905 mg, 13.3 mmol, 5.00 equiv) and TBSCl (962 mg, 6.38 mmol, 2.40 equiv) were added successively to a stirred solution of crude alcohol 111, which was azeotropically dried with benzene (3 × 3 mL), in DMF (26 mL) at room temperature. After 15.5 h, water (50 mL), Et₂O (30 mL), and EtOAc (30 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with brine (100 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure. The resulting oil was then purified by flash column chromatography (silica gel, eluent: EtOAc) to afford silyl ether S6 (1.23 g, 98%) as a clear colorless oil.

**¹H NMR** (500 MHz, CDCl₃) δ: 5.94 (br. s., 1H), 4.04–3.97 (m, 1H), 3.76–3.70 (m, 2H), 3.67–3.61 (m, 1H), 2.42 (dd, J = 5.5, 17.2 Hz, 1H), 2.15–2.05 (m, 1H), 2.00 (dd, J = 7.1, 17.3 Hz, 1H), 1.86–1.78 (m, 1H), 1.77–1.71 (m, 1H), 1.68–1.57 (m, 4H), 1.13–1.01 (m, 24H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H). **¹³C NMR** (126 MHz, C₆D₆) δ: 171.3, 68.4, 60.8, 47.8, 44.9, 41.6, 39.9, 35.5, 26.5, 24.9, 20.6, 18.7, 18.6, 12.7, −3.7, −3.9. **FTIR** (thin film) cm⁻¹: 3202, 3090, 2941, 2928, 2864, 1663, 1462, 1252, 1100, 1070, 835, 774. **HRMS** (ESI) (m/z) calc’d for C₂₅H₅₃NNaO₃Si₂ [M+Na]⁺: 494.3456, found 494.3465. [α]D²²: −4.2 (c = 1.4, CH₂Cl₂). **TLC** (EtOAc), Rf: 0.45 (KMnO₄).
Imide 112:

Boc₂O (5.82 g, 25.9 mmol, 2.00 equiv) and 4-DMAP (1.90 g, 15.5 mmol, 1.20 equiv) were added successively to a solution of silyl ether S6 (6.10 g, 12.9 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 10 mL), in MeCN (120 mL) at room temperature. The resultant solution was stirred for 96 h, during which additional Boc₂O (23.3 g, 103 mmol, 8.00 equiv) and 4-DMAP (7.60 g, 62.0 mmol, 4.80 equiv) were added in four portions. Water (100 mL), Et₂O (150 mL), and EtOAc (100 mL) were added to the reaction mixture. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The organic layers were combined, washed with brine (200 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure. The resulting oil was then purified by flash column chromatography (silica gel, eluent: gradient: 12:1 → 7:1 hexanes:EtOAc) to afford imide 112 (6.24 g, 84%) as a pale yellow oil.

¹H NMR (600 MHz, CDCl₃) δ: 4.44–4.37 (m, 1H), 4.04–3.95 (m, 1H), 3.80–3.68 (m, 2H), 2.59 (dd, J = 3.9, 17.3 Hz, 1H), 2.17–2.09 (m, 1H), 2.08–1.97 (m, 2H), 1.87–1.72 (m, 3H), 1.64 (dt, J = 5.7, 13.0 Hz, 1H), 1.53–1.49 (m, 10H), 1.14–1.01 (m, 21H), 0.98 (d, J = 6.3 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). ¹³C NMR (126 MHz, C₆D₆) δ: 170.9, 154.9, 82.3, 67.9, 60.8, 52.9, 43.5, 41.3, 41.1, 34.7, 28.5, 26.5, 24.6, 21.9, 18.7, 12.7, −3.8, −3.9. FTIR (thin film) cm⁻¹: 2941, 2929, 2865, 1715, 1367, 1291, 1249, 1158, 1100, 836, 775. HRMS (ESI) (m/z) calc’d for C₃₀H₆₁NNaO₅Si₂ [M+Na]^+: 594.3971, found 594.3980. TLC (12:1 hexanes:EtOAc), Rₜ: 0.58 (KMnO₄).
**N-Boc piperidine 114:**

Diisobutylaluminum hydride (887 µL, 4.97 mmol, 4.00 equiv) was added to a stirred solution of imide 112 (711 mg, 1.24 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 5 mL), in THF (12.4 mL) at −78 °C. The reaction was allowed to warm gradually to room temperature over 2 h, at which point a saturated aqueous solution of Rochelle’s salt (50 mL) was carefully added at a slow rate. The resultant mixture was subsequently diluted with Et₂O (50 mL) and EtOAc (50 mL), and stirred vigorously for 5 h. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with brine (100 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure to afford crude N,O-hemiaminal 113 as a pale yellow flocculent solid and as a 1:1 mixture of diastereomers, which was carried forward to the next step without further purification.

BF₃•OEt₂ (1.53 mL, 12.4 mmol, 10.0 equiv) was added dropwise to a solution of crude 113, which was azeotropically dried with benzene (5 × 5 mL), and Et₃SiH (1.99 mL, 12.4 mmol, 10.0 equiv) in CH₂Cl₂ (62 mL) at −78 °C. After 2 h, saturated aqueous NaHCO₃ solution (50 mL), Et₂O (50 mL), and EtOAc (50 mL) were added successively to the reaction. The resultant mixture was allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with brine (100 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure. The resulting oil was then purified by flash column chromatography (silica gel, eluent: gradient: 20:1 → 7:1 hexanes:EtOAc) to afford N-Boc piperidine 114 (522 mg, 75% over 2 steps) as a clear colorless oil.

**1H NMR** (600 MHz, CDCl₃, 50 °C) δ: 4.45–4.31 (m, 1H), 4.17–3.93 (m, 1H), 3.86–3.78 (m, 2H), 3.77–3.70 (m, 1H), 2.78 (t, J = 13.6 Hz, 1H), 1.85–1.76 (m, 3H), 1.76–1.65 (m, 3H), 1.63–1.54 (m,
2H), 1.46 (s, 9H), 1.24–1.16 (m, 1H), 1.12–1.02 (m, 24H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

$^{13}$C NMR (126 MHz, C$_6$D$_6$, 70 °C) δ: 155.1, 79.3, 68.8, 61.5, 48.4, 41.0, 40.1, 39.1, 38.4, 35.0, 29.1, 26.6, 26.2, 22.7, 18.7, 13.0, −3.7, −3.9. FTIR (thin film) cm$^{-1}$: 2946, 2927, 2865, 1693, 1413, 1364, 1251, 1164, 1095, 1070, 836, 773. HRMS (ESI) (m/z) calc’d for C$_{30}$H$_{63}$NNaO$_4$Si$_2$ [M+Na]$^+$: 580.4188, found 580.4165. \([\alpha]_D^{22}\): $–5.6$ ($c = 0.67$, CH$_2$Cl$_2$). TLC (6:1 hexanes:EtOAc), R$_f$: 0.45 (KMnO$_4$).
Allyl N-Boc piperidine 116:

A solution of sec-butyllithium in cyclohexane (1.45 M, 968 µL, 1.40 mmol, 1.50 equiv) was added to a stirred solution of N-Boc piperidine 114 (522 mg, 0.935 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 5 mL), and TMEDA (210 µL, 1.40 mmol 1.50 equiv) in Et₂O (11 mL) at −78 °C. The reaction was stirred for 7 h at −78 °C.

During this period, a separate 0.10 M stock solution of CuCN•2LiCl in THF was prepared according to the following protocol: CuCN (100 mg, 1.12 mmol, 1.00 equiv) and LiCl (94.6 mg, 2.24 mmol, 2.00 equiv) in THF (11.1 mL) were stirred vigorously for 20 min at room temperature prior to use.

After the 7 h deprotonation period of 114, a solution of CuCN•2LiCl in THF (0.10 M, 5.60 mL, 0.60 equiv) was added slowly via syringe down the walls of the reaction vessel. The resultant reaction was stirred vigorously for 1 h, at which point allyl bromide (151 µL, 1.68 mmol, 1.80 equiv) was added dropwise via syringe to the reaction mixture, which immediately turned bright yellow. After stirring for 1 h at −78 °C, the reaction was gradually allowed to warm to room temperature over 3 h. After stirring for an additional 1 h at room temperature, the reaction was cooled to 0 °C and an aqueous solution of 5 M NH₄OH (3 mL) was added. The resultant mixture was allowed to warm to room temperature and was stirred vigorously for 30 min, at which point the mixture was filtered through Celite. The Celite filter cake was washed with Et₂O (50 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 × 50 mL). The organic layers were combined, washed with water (100 mL), then brine (100 mL), and dried over anhydrous MgSO₄ and concentrated under reduced pressure. The resulting oil was then purified by flash column
chromatography (silica gel, eluent: gradient: 30:1 → 7:1 → 4:1 hexanes:EtOAc) to afford allyl N-Boc piperidine 116 (277 mg, 50%, 97% brsm) as a single diastereomer as a clear colorless oil.

$^1$H NMR (600 MHz, C$_6$D$_6$) δ: 6.00–5.91 (m, 1H), 5.17 (d, $J = 17.1$ Hz, 1H), 5.09 (d, $J = 10.3$ Hz, 1H), 4.51–4.42 (m, 1H), 4.08–4.02 (m, 1H), 3.98–3.92 (m, 1H), 3.87 (td, $J = 6.5$, 9.6 Hz, 1H), 3.43–3.31 (m, 1H), 3.09–2.96 (m, 1H), 2.53–2.39 (m, 1H), 2.13 (ddd, $J = 5.4$, 8.3, 13.9 Hz, 1H), 2.04–1.88 (m, 2H), 1.75–1.63 (m, 2H), 1.61–1.52 (m, 1H), 1.49 (s, 9H), 1.31–1.22 (m, 2H), 1.19 (d, $J = 13.2$ Hz, 1H), 1.17–1.09 (m, 21H), 1.04 (s, 9H), 0.79 (d, $J = 6.6$ Hz, 3H), 0.18 (s, 3H), 0.18 (s, 3H). $^{13}$C NMR (126 MHz, C$_6$D$_6$) δ: 156.1, 137.6, 116.86, 79.3, 68.1, 61.2, 54.3, 51.0, 40.5, 40.3, 39.5, 37.1, 36.9, 28.9, 26.6, 26.5, 23.0, 18.7, 18.6, 12.7, −3.6, −4.0. FTIR (thin film) cm$^{-1}$: 2927, 2865, 1702, 1365, 1251, 1171, 1097, 836, 774. HRMS (ESI) (m/z) calc’d for C$_{33}$H$_{67}$NNaO$_4$Si$_2$ [M+Na]$^+$: 620.4501, found 620.4526. TLC (6:1 hexanes:EtOAc), $R_f$: 0.71 (KMnO$_4$).

$^1$D NOESY (500 MHz, C$_6$D$_6$):
**Dion S7:**

A solution of TBAF in THF (1.00 M, 8.10 mL, 8.06 mmol, 6.00 equiv) was added to a solution of allyl N-Boc piperidine 116 (803 mg, 1.34 mmol, 1.00 equiv) in THF (13.4 mL) at 0 °C. After 5 min, the reaction was allowed to warm to room temperature and was stirred for an additional 3.5 h, at which point saturated aqueous NH₄Cl solution (25 mL), water (10 mL), Et₂O (20 mL), and EtOAc (20 mL) were added successively. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The organic layers were combined, washed with brine (50 mL), then dried over anhydrous MgSO₄ and concentrated under reduced pressure. The resultant oil was purified by flash column chromatography (silica gel, eluent: gradient: 2:1 EtOAc:hexanes → EtOAc) to afford diol S7 (439 mg, quant.) as a pale yellow oil.

**¹H NMR** (500 MHz, CDCl₃) δ: 5.80–5.70 (m, 1H), 5.12–5.02 (m, 2H), 4.16–4.09 (m, 1H), 4.07 (br. s., 1H), 3.92 (tt, J = 3.8, 8.2 Hz, 2H), 3.83 (t, J = 5.5 Hz, 2H), 3.56 (dt, J = 5.9, 9.9 Hz, 1H), 3.00 (br. s., 1H), 2.59 (td, J = 6.0, 13.5 Hz, 1H), 2.30 (td, J = 8.5, 13.7 Hz, 1H), 1.90 (td, J = 6.4, 12.4 Hz, 1H), 1.87–1.77 (m, 2H), 1.73–1.63 (m, 4H), 1.51–1.43 (m, 10H), 1.33 (td, J = 6.1, 13.9 Hz, 1H), 1.01 (d, J = 6.8 Hz, 3H). **¹³C NMR** (126 MHz, CDCl₃) δ: 156.3, 135.8, 117.1, 110.7, 80.2, 71.4, 61.8, 52.8, 51.2, 41.9, 40.2, 38.7, 35.8, 33.0, 28.5, 23.2. **FTIR** (thin film) cm⁻¹: 3401, 2950, 2928, 2871, 1661, 1399, 1365, 1168, 1115, 1069. **HRMS** (ESI) (m/z) calc’d for C₁₈H₃₃KNO₄ [M+K]⁺: 366.2041, found 366.2056. [α]D²²: –4.4 (c = 0.50, CH₂Cl₂). **TLC** (2:1 EtOAc:hexanes), Rₜ: 0.14 (KMnO₄).
Silyl ether 145:

Et₃N (220 μL, 1.57 mmol, 1.20 equiv), TBSCl (217 mg, 1.44 mmol, 1.10 equiv), and 4-DMAP (16.0 mg, 0.131 mmol, 0.10 equiv) were added sequentially to a stirred solution of diol S7 (428 mg, 1.31 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 1.5 mL), in CH₂Cl₂ (13 mL) at room temperature. After 17 h, saturated aqueous NH₄Cl solution (15 mL) was added and the resultant mixture was diluted with EtOAc (15 mL), Et₂O (20 mL), and water (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 20 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure. The resulting crude residue was then purified by flash column chromatography (silica gel, eluent: gradient: 12:1 → 6:1 hexanes:EtOAc) to afford silyl ether 145 (560 mg, 97%) as a clear colorless oil.

¹H NMR (500 MHz, CDCl₃) δ: 5.82–5.71 (m, 1H), 5.07 (d, J = 16.8 Hz, 1H), 5.02 (d, J = 10.0 Hz, 1H), 4.23–4.16 (m, 1H), 3.91–3.75 (m, 3H), 3.64 (br. s., 1H), 3.50–3.42 (m, 1H), 2.70–2.60 (m, 1H), 2.37–2.27 (m, 1H), 1.95–1.88 (m, 1H), 1.88–1.81 (m, 1H), 1.78–1.55 (m, 5H), 1.49–1.41 (m, 9H), 1.39–1.31 (m, 1H), 1.24 (td, J = 7.7, 13.9 Hz, 1H), 0.96 (d, J = 6.6 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 1H). ¹³C NMR (126 MHz, CDCl₃) δ: 155.9, 136.3, 116.7, 79.5, 69.4, 62.1, 52.9, 50.6, 39.9, 39.9, 38.5, 35.9, 34.5, 28.5, 25.9, 24.5, 22.9, 18.2, −5.5, −5.5. FTIR (thin film) cm⁻¹: 3419, 2952, 2928, 2857, 1686, 1662, 1392, 1365, 1251, 1171, 1090, 836, 775. HRMS (ESI) (m/z) calc’d for C₂₄H₄₇NaO₅Si [M+Na]⁺: 464.3167, found 464.3195. [α]ᵦ°: −2.2 (c = 0.72, CH₂Cl₂). TLC (2:1 EtOAc: hexanes), R_f: 0.82 (KMnO₄).
Azide 146:

Triphenylphosphine (1.32 g, 5.02 mmol, 4.00 equiv), diethyl azodicarboxylate (806 µL, 5.02 mmol, 4.00 equiv), and diphenyl phosphoryl azide (1.11 mL, 5.02 mmol, 4.00 equiv) were added sequentially to a stirred solution of silyl ether 145 (554 mg, 1.25 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 1 mL), in THF (20 mL) at room temperature. After 1 h, the reaction was concentrated under reduced pressure. The resultant residue was then purified by flash column chromatography (silica gel, eluent: 16:1 hexane:EtOAc) to afford alkyl azide 146 (479 mg, 82%) as a pale yellow oil.

\[ \text{Azide 146} \]

1H NMR (500 MHz, CDCl3) δ: 5.82–5.72 (m, 1H), 5.08 (qd, \( J = 1.6, 17.1 \) Hz, 1H), 5.02 (td, \( J = 1.0, 10.2 \) Hz, 1H), 4.26–4.15 (m, 1H), 3.79–3.69 (m, 2H), 3.59–3.51 (m, 1H), 3.38–3.31 (m, 1H), 2.71 (td, \( J = 6.6, 13.5 \) Hz, 1H), 2.39–2.29 (m, 1H), 2.03 (ddd, \( J = 3.8, 9.8, 14.0 \) Hz, 1H), 1.82–1.73 (m, 2H), 1.72–1.61 (m, 3H), 1.52–1.43 (m, 10H), 1.34–1.15 (m, 2H), 0.94 (d, \( J = 6.6 \) Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H). 13C NMR (126 MHz, CDCl3) δ: 155.9, 136.4, 116.5, 79.5, 59.5, 57.7, 53.5, 50.8, 39.4, 38.2, 36.8, 36.2, 35.7, 28.5, 25.9, 25.8, 22.5, 18.3, −5.4, −5.5. FTIR (thin film) cm\(^{-1}\): 2953, 2928, 2857, 2104, 1694, 1365, 1322, 1252, 1167, 1109, 835, 776. HRMS (ESI) (\( m/z \)) calc’d for \( \text{C}_{23}\text{H}_{47}\text{N}_{4}\text{O}_{3}\text{Si} [\text{M+H}]^+ \): 467.3412, found 467.3417. \([\text{a}]_D^{23}\) : −13 (c = 0.39, CH\(_2\)Cl\(_2\)). TLC (12:1 hexanes:EtOAc), \( R_f \): 0.69 (KMnO\(_4\)).
Alcohol S8:

A solution of TBAF in THF (1.00 M, 2.00 mL, 2.02 mmol, 2.00 equiv) was added to a solution of alkyl azide 146 (472 mg, 1.01 mmol, 1.00 equiv) in THF (20 mL) at 0 °C. After 5 min, the reaction was allowed to warm to room temperature and was stirred for an additional 1 h, at which point saturated aqueous NH₄Cl solution (10 mL), water (10 mL), Et₂O (15 mL), and EtOAc (15 mL) were added successively. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The organic layers were combined, washed with brine (30 mL), then dried over anhydrous MgSO₄ and concentrated under reduced pressure. The resultant oil was purified by flash column chromatography (silica gel, eluent: gradient: 4:1 → 2:1 hexanes:EtOAc) to afford alcohol S8 (340 mg, 96%) as a pale yellow oil.

**1H NMR** (500 MHz, CDCl₃) δ: 5.79 (tdd, J = 7.1, 10.1, 17.2 Hz, 1H), 5.08 (dd, J = 1.3, 17.2 Hz, 1H), 5.03 (td, J = 1.0, 10.3 Hz, 1H), 3.97 (dd, J = 4.9, 8.8 Hz, 1H), 3.84–3.73 (m, 2H), 3.62–3.50 (m, 2H), 2.61 (td, J = 6.8, 13.5 Hz, 1H), 2.32–2.22 (m, 2H), 1.93–1.84 (m, 1H), 1.79–1.66 (m, 4H), 1.48–1.39 (m, 10H), 1.31–1.22 (m, 1H), 1.19 (td, J = 9.4, 13.2 Hz, 1H), 0.95 (d, J = 6.1 Hz, 3H). **13C NMR** (126 MHz, CDCl₃) δ: 156.1, 136.2, 116.6, 79.7, 59.4, 57.8, 54.1, 50.0, 39.3, 37.1, 36.5, 36.1, 35.5, 28.5, 25.7, 22.3. **FTIR** (thin film) cm⁻¹: 3432, 2951, 2929, 2873, 2102, 1685, 1366, 1323, 1253, 1166, 1117. **HRMS** (ESI) (m/z) calc’d for C₁₈H₃₃N₄O₃ [M+H⁺]: 353.2547, found 353.2549. [α]D²³: −2.0 (c = 0.59, CH₂Cl₂). **TLC** (2:1 hexanes:EtOAc), Rf: 0.22 (KMnO₄).
Alkyl iodide 147:

Triphenylphosphine (671 mg, 2.56 mmol, 2.70 equiv) and iodine (722 mg, 2.84 mmol, 3.00 equiv) were added sequentially as single portions to a stirred solution of imidazole (387 mg, 5.69 mmol, 6.00 equiv) in CH₂Cl₂ (9.5 mL). After 20 min, a solution of alcohol S8 (334 mg, 0.948 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 1 mL), in CH₂Cl₂ (9.5 mL) was added dropwise via syringe to the reaction mixture. After 30 min, saturated aqueous Na₂S₂O₃ solution (20 mL), EtOAc (15 mL), and Et₂O (15 mL) were added sequentially to the reaction. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure. The resulting residue was then purified by flash column chromatography (silica gel, eluent: 12:1 hexanes:EtOAc) to afford alkyl iodide 147 (419 mg, 96%) as a pale yellow oil.

¹H NMR (500 MHz, CDCl₃) δ: 5.81 (dddd, J = 6.2, 8.0, 10.3, 16.9 Hz, 1H), 5.10 (qd, J = 1.5, 17.2 Hz, 1H), 5.05 (td, J = 1.1, 10.1 Hz, 1H), 4.24–4.16 (m, 1H), 3.51 (tt, J = 4.2, 9.1 Hz, 1H), 3.38–3.32 (m, 1H), 3.32–3.19 (m, 2H), 2.74 (td, J = 6.5, 13.6 Hz, 1H), 2.37–2.26 (m, 1H), 2.09–1.92 (m, 3H), 1.82–1.73 (m, 1H), 1.72–1.67 (m, 1H), 1.63 (td, J = 4.5, 13.6 Hz, 1H), 1.55–1.49 (m, 1H), 1.47 (s, 9H), 1.31 (ddd, J = 5.5, 11.7, 13.6 Hz, 1H), 1.26–1.17 (m, 1H), 0.95 (d, J = 6.6 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ: 155.9, 136.4, 116.8, 79.7, 60.8, 53.7, 50.5, 39.4, 39.0, 36.2, 36.0, 35.7, 28.5, 25.8, 22.5, 1.7. FTIR (thin film) cm⁻¹: 2952, 2927, 2118, 2100, 1690, 1365, 1322, 1252, 1167, 1111. HRMS (ESI) (m/z) calc’d for C₁₈H₃₁IN₄NaO₂ [M+Na]⁺: 485.1384, found 485.1388. TLC (1:1 hexanes:EtOAc), Rf: 0.68 (KMnO₄, UV).
Alkylated imide 148:

A solution of alkyl iodide 147 (419 mg, 0.906 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 1 mL), in DMF (5 mL) was added dropwise to a stirred solution of β-carboxyimide 66\(^\text{93}\) (584 mg, 1.18 mmol, 1.30 equiv) and Cs\(_2\)CO\(_3\) (886 mg, 2.72 mmol, 3.00 equiv) in DMF (4 mL). After 12.5 h, Et\(_2\)O (20 mL) and saturated aqueous NH\(_4\)Cl solution (15 mL) were added sequentially to the reaction mixture. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined and washed with brine (20 mL), dried over anhydrous MgSO\(_4\), and concentrated under reduced pressure. The resultant residue was purified by flash column chromatography (silica gel, eluent: gradient: 9:1 → 7:1 → 4:1 hexanes:EtOAc, 1% Et\(_3\)N) to afford alkylated imide 148 (708 mg, 94%) as a white flocculent solid.

\(\text{1H NMR (500 MHz, C}_6\text{D}_6\) \(\delta: 6.05–5.93 (m, 1H), 5.60 (d, J = 3.9 Hz, 1H), 5.23 (d, J = 18.3 Hz, 1H), 5.14 (d, J = 10.3 Hz, 1H), 4.44–4.36 (m, 1H), 4.28–4.19 (m, 1H), 4.18–4.09 (m, 1H), 4.09–4.01 (m, 1H), 3.84–3.74 (m, 3H), 3.73–3.68 (m, 1H), 3.57–3.48 (m, 2H), 3.06 (br. s., 2H), 2.89–2.76 (m, 2H), 2.51–2.41 (m, 1H), 2.32 (dt, J = 4.4, 13.2 Hz, 1H), 2.26–2.18 (m, 1H), 2.06–1.88 (m, 4H), 1.84–1.72 (m, 3H), 1.49 (s, 9H), 1.44 (s, 9H), 1.40–1.25 (m, 5H), 1.24–1.04 (m, 3H), 0.89–0.84 (m, 2H), 0.80 (d, J = 6.6 Hz, 3H), 0.71 (d, J = 6.3 Hz, 3H), –0.17 (s, 9H). \(\text{13C NMR (126 MHz, C}_6\text{D}_6\) \(\delta: 171.4, 170.5, 156.3, 151.6, 137.7, 134.9, 132.3, 117.1, 108.8, 83.1, 79.5, 65.8, 64.5, 64.2, 62.2, 61.4, 54.5, 51.6, 50.6, 42.5, 39.8, 38.4, 37.3, 37.1, 36.6, 34.6, 31.2, 30.8, 29.8, 28.9, 28.4, 28.1, 26.8, 22.8, 21.9, 18.1, 1.4. FTIR (thin film) cm\(^{-1}\): 2952, 2106, 1719, 1701, 1367, 1314, 1251, 1171, 839. HRMS (ESI) \((m/z)\) calc’d for C\(_{43}\)H\(_{71}\)N\(_3\)NaO\(_9\)Si \([\text{M+Na}^+]\): 852.4918, found 852.4913. TLC (4:1 hexanes:EtOAc), \(R_f\): 0.65 (Anis, KMnO\(_4\), UV).
**N-Boc-2-pyrrolidinone 149:**

A solution of TBAF in THF (1.00 M, 843 µL, 0.843 mmol, 1.00 equiv) was added to a solution of alkylated imide 148 (700 mg, 0.843 mmol, 1.00 equiv) and DBU (32.0 µL, 0.211 mmol, 0.25 equiv) in THF (17 mL) at room temperature. After 5 min, the reaction was heated to 50 °C and was stirred for 16 h, at which point water (20 mL), Et₂O (15 mL), and EtOAc (15 mL) were added successively. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The organic layers were combined, washed with brine (30 mL), then dried over anhydrous MgSO₄ and concentrated under reduced pressure. The resultant residue was purified by flash column chromatography (silica gel, eluent: gradient: 8:1 → 6:1 → 4:1 → 2:1 hexanes:EtOAc, 1% Et₃N) to afford N-Boc-2-pyrrolidinone 149 (562 mg, 97%) as a white flocculent solid.

**¹H NMR** (500 MHz, C₆D₆) δ: 6.05–5.88 (m, 1H), 5.44 (d, J = 3.4 Hz, 1H), 5.20 (d, J = 17.1 Hz, 1H), 5.12 (dd, J = 2.0, 10.3 Hz, 1H), 4.42–4.36 (m, J = 4.6 Hz, 1H), 3.97–3.88 (m, 1H), 3.68–3.53 (m, 3H), 3.51–3.39 (m, 3H), 3.05 (dd, J = 8.8, 10.7 Hz, 3H), 2.36 (dd, J = 4.5, 13.8 Hz, 1H), 2.29–2.22 (m, 1H), 2.20–2.12 (m, 1H), 1.98–1.89 (m, 2H), 1.88–1.81 (m, 1H), 1.81–1.68 (m, 5H), 1.49 (s, 9H), 1.47 (s, 9H), 1.45–1.27 (m, 5H), 1.27–1.04 (m, 3H), 0.82 (d, J = 6.6 Hz, 3H), 0.73 (d, J = 6.3 Hz, 3H). **¹³C NMR** (126 MHz, C₆D₆) δ: 174.2, 156.3, 151.6, 137.8, 135.7, 131.3, 117.0, 108.7, 82.4, 79.5, 65.8, 64.4, 61.5, 54.4, 51.6, 50.7, 49.5, 42.6, 39.9, 37.2, 37.2, 36.6, 35.8, 35.0, 34.6, 32.6, 28.9, 28.5, 28.1, 26.8, 26.1, 22.8, 22.0. **FTIR** (thin film) cm⁻¹: 2950, 2925, 2074, 1784, 1712, 1367, 1316, 1160. **HRMS** (ESI) (m/z) calc’d for C₃₇H₅₉N₅NaO₇ [M+Na]⁺: 708.4307, found 708.4306. **TLC** (1:1 hexanes:EtOAc), Rf: 0.61 (Anis, KMnO₄, UV).
**N-2-Nitrobenzenesulfonyl-2-pyrrolidinone 151:**

Mg(ClO₄)₂ (36.5 mg, 0.164 mmol, 0.20 equiv) was added as a single portion to a stirred solution of N-Boc-2-pyrrolidinone 149 (561 mg, 0.818 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 1 mL), in MeCN (13.6 mL) at room temperature. The resultant mixture was heated to 60 °C and stirred for 2 h, at which point it was cooled to room temperature and Et₂O (25 mL) and saturated aqueous NH₄Cl solution (15 mL) were added sequentially. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The organic layers were combined, washed with brine (30 mL), then dried over anhydrous MgSO₄ and concentrated under reduced pressure to afford crude 2-pyrrolidinone 150 as a white flocculent solid, which was carried forward to the next step without further purification.

A freshly prepared solution of LiHMDS in THF (1.00 M, 982 µL, 0.982 mmol, 1.20 equiv) was added dropwise to a solution of 150, which was azeotropically dried with benzene (5 × 1 mL), in THF (4.25 mL) at room temperature. After 1 h, the reaction was cooled to 0 °C and a solution of NsCl in THF (1.00 M, 1.06 mL, 1.06 mmol, 1.30 equiv) was added. After 5 min, the reaction was warmed to room temperature and stirred for 1 h. Saturated aqueous NH₄Cl solution (10 mL), and then Et₂O (10 mL), were added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (20 mL), dried over anhydrous MgSO₄, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, eluent: gradient: 7:1 → 4:1 → 2:1 hexanes:EtOAc, 1% Et₃N) to afford N-2-nitrobenzenesulfonyl-2-pyrrolidinone 151 (566 mg, 90% over 2 steps) as a white flocculent solid.
$^1$H NMR (500 MHz, C$_6$D$_6$) $\delta$: 8.45 (dd, $J = 1.3, 7.9$ Hz, 1H), 6.76–6.71 (m, 1H), 6.66–6.60 (m, 1H), 6.49–6.41 (m, 1H), 5.99–5.84 (m, 1H), 5.52 (d, $J = 3.7$ Hz, 1H), 5.14 (d, $J = 17.1$ Hz, 1H), 5.07 (dd, $J = 2.0, 10.0$ Hz, 1H), 4.33–4.23 (m, 2H), 3.69 (dd, $J = 4.5, 7.4$ Hz, 1H), 3.66 (d, $J = 6.8$ Hz, 2H), 3.56–3.46 (m, 2H), 3.40–3.31 (m, 1H), 3.07–2.96 (m, 1H), 2.55–2.43 (m, 1H), 2.36 (dd, $J = 5.7, 14.0$ Hz, 1H), 2.25–2.14 (m, 1H), 1.98–1.79 (m, 4H), 1.78–1.63 (m, 3H), 1.60–1.50 (m, 1H), 1.47–1.42 (m, 11H), 1.40–1.23 (m, 6H), 1.18–1.02 (m, 3H), 0.82 (d, $J = 6.6$ Hz, 3H), 0.71 (d, $J = 6.3$ Hz, 3H).

$^{13}$C NMR (126 MHz, C$_6$D$_6$) $\delta$: 175.6, 156.3, 148.7, 137.7, 135.2, 135.0, 134.6, 132.5, 132.1, 131.7, 124.1, 116.9, 108.7, 79.6, 65.7, 64.5, 61.2, 54.4, 51.6, 51.5, 48.9, 42.5, 39.9, 37.8, 37.1, 36.5, 34.9, 34.5, 32.5, 29.0, 28.0, 26.7, 25.8, 22.7, 21.9. FTIR (thin film) cm$^{-1}$: 2952, 2926, 2102, 1737, 1691, 1545, 1366, 1174, 1128, 594. HRMS (ESI) ($m/z$) calc’d for C$_{38}$H$_{55}$N$_6$O$_9$S [M+H]$^+$: 771.3746, found 771.3738. TLC (2:1 hexanes:EtOAc), $R_f$: 0.39 (Anis, KMnO$_4$, UV).
Enone 153:

A solution of n-butyllithium in hexanes (2.53 M, 869 µL, 2.20 mmol, 3.00 equiv) was added dropwise to a stirred solution of diisopropylamine (339 µL, 2.42 mmol, 3.30 equiv) in THF (4.2 mL) at −78 °C. The reaction was stirred for 10 min, at which point it was warmed to 0 °C. After 10 min, the reaction was warmed to room temperature. The solution was recooled to −78 °C after 5 min. t-Butylacetate (295 µL, 2.20 mmol, 3.00 equiv) was then added dropwise to the reaction mixture. After 1 h, a solution of 151 (565 mg, 0.733 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 2 mL), in THF (9.3 mL) was added dropwise down the walls of the reaction vessel. After stirring at −78 °C for 1.5 h, saturated aqueous NH₄Cl solution (15 mL) was added to the deep red reaction mixture at −78 °C. The resultant mixture was then allowed to warm to room temperature. Et₂O (15 mL) and EtOAc (15 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (30 mL), then dried over anhydrous MgSO₄ and concentrated under reduced pressure to afford crude β-ketoester 152 as a white flocculent solid, which was carried forward to the next step without further purification.

p-TsOH•H₂O (70.0 mg, 0.366 mmol, 0.50 equiv) was added as a single portion to a stirred solution of crude 152 in THF (13 mL) and water (1.6 mL) at room temperature. After 3 h, a saturated aqueous NaHCO₃ solution (20 mL) was added, followed by Et₂O (10 mL), EtOAc (10 mL), and water (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (30 mL), then dried over anhydrous
MgSO$_4$ and concentrated under reduced pressure to afford crude enone 153 as a white flocculent solid, which was carried forward to the next step without further purification.
Imine 156:

2-\textit{t}-Butyl-1,1,3,3-tetramethylguanidine (591 µL, 2.90 mmol, 5.00 equiv) was added dropwise to a solution of crude enone 153, which was azeotropically dried with benzene (5 × 2 mL), in MeCN (29 mL) at 0 °C. After 15 min, the reaction mixture was warmed to room temperature and stirred for 18 h, at which point K₂CO₃ (401 mg, 2.90 mmol, 5.00 equiv) was added as a single portion. The suspension was then cooled to 0 °C and PhSH (298 µL, 2.90 mmol, 5.00 equiv) was added dropwise via syringe. After 10 min, the reaction was warmed to room temperature and stirred for an additional 4.5 h, at which point water (100 mL), Et₂O (100 mL), and EtOAc (100 mL) were added sequentially. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with brine (100 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude residue was then purified by flash column chromatography (silica gel, eluent: gradient: 2:1 → 1:1 → 0:1 hexanes:EtOAc, 1% Et₃N) to afford imine 156 (312 mg, 84% over 3 steps) as a pale yellow flocculent solid.

\textit{H} NMR (500 MHz, C₆D₆) δ: 6.06–5.89 (m, 1H), 5.17 (d, J = 16.6 Hz, 1H), 5.08 (d, J = 9.8 Hz, 1H), 4.37–4.25 (m, 1H), 4.03 (d, J = 18.3 Hz, 1H), 3.57–3.52 (m, J = 7.8 Hz, 1H), 3.49 (d, J = 3.2 Hz, 1H), 3.23 (d, J = 19.5 Hz, 1H), 3.20–3.14 (m, 1H), 3.09–2.97 (m, J = 5.9 Hz, 1H), 2.87 (br. s., 1H), 2.64–2.56 (m, 1H), 2.51 (d, J = 12.0 Hz, 1H), 2.34–2.20 (m, 2H), 2.05 (t, J = 11.8 Hz, 1H), 1.95 (br. s., 1H), 1.86 (br. s., 1H), 1.82–1.71 (m, 2H), 1.66 (br. s., 1H), 1.58–1.50 (m, 4H), 1.48 (s, 9H), 1.46–1.40 (m, J = 12.2 Hz, 2H), 1.37 (s, 9H), 1.36–1.32 (m, 3H), 1.19–1.02 (m, 3H), 0.73 (d, J = 6.1 Hz, 3H), 0.62 (d, J = 6.1 Hz, 3H). \textit{C} NMR (126 MHz, CDCl₃) δ: 205.1, 170.5, 169.0, 156.3, 137.7, 116.9, 82.2, 79.5, 66.2, 61.4, 55.3, 54.6, 51.5, 49.2, 48.4, 43.4, 39.9, 39.0, 38.3, 37.3, 37.1, 36.1,
34.4, 33.1, 30.2, 29.8, 28.9, 28.3, 26.9, 26.7, 22.7, 22.6. **FTIR** (thin film) cm$^{-1}$: 2951, 2926, 2101, 1699, 1455, 1366, 1253, 1154. **HRMS** (ESI) ($m/z$) calc’d for C$_{36}$H$_{58}$N$_5$O$_5$ [M+H]$^+$: 640.4432, found 640.4418. **TLC** (90:9:1 CHCl$_3$:MeOH:NH$_4$OH), $R_f$: 0.38 (KMnO$_4$, UV).
Vinylogous Urethane 157:

Triphenylphosphine (84.0 mg, 0.321 mmol, 1.50 equiv) was added as a single portion to a stirred solution of imine 156 (137 mg, 0.214 mmol, 1.00 equiv) in THF (6.2 mL) and water (780 µL) at room temperature. The reaction was heated to 70 °C and stirred for 23 h, at which point the reaction was cooled to room temperature and concentrated. The resultant residue was azeotropically dried with MeOH (5 × 3 mL), then benzene (3 × 3 mL), and stirred with silica gel (200 mg) in CH₂Cl₂ (5 mL) for 2 h. The slurry was subsequently filtered and washed with 90:9:1 CHCl₃:MeOH:NH₄OH (10 × 5 mL) and concentrated in vacuo. The crude residue was then purified by flash column chromatography (silica gel, eluent: gradient: 1:1 → 0:1 hexanes:EtOAc, 1% Et₃N → 90:9:1 CHCl₃:MeOH:NH₄OH) to afford vinylogous urethane 157 (95.4 mg, 75%) as a pale yellow flocculent solid.

¹H NMR (500 MHz, C₆D₆) δ: 9.73 (s, 1 H), 6.03–5.83 (m, 1H), 5.17 (d, J = 16.1 Hz, 1H), 5.07 (d, J = 12.5 Hz, 1H), 4.21–4.07 (m, 1H), 3.59–3.48 (m, 1H), 3.31–3.22 (m, J = 6.2, 11.8 Hz, 1H), 2.95 (d, J = 3.7 Hz, 1H), 2.90 (dd, J = 6.6, 12.5 Hz, 1H), 2.76 (d, J = 7.8 Hz, 1H), 2.48–2.36 (m, 1H), 2.17 (br. s., 1H), 2.08–2.01 (m, 2H), 2.01–1.90 (m, 1H), 1.88–1.81 (m, J = 6.1 Hz, 1H), 1.80–1.73 (m, 1H), 1.71–1.61 (m, J = 8.5 Hz, 2H), 1.57–1.52 (m, J = 6.3 Hz, 2H), 1.51 (s, 9H), 1.47 (s, 9H), 1.40–1.29 (m, 4H), 1.21 (t, J = 13.9 Hz, 1H), 1.16–1.07 (m, J = 10.3 Hz, 3H), 1.07–0.98 (m, 2H), 0.95 (d, J = 6.1 Hz, 3H), 0.79 (d, J = 5.9 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ: 170.9, 162.8, 156.2, 137.6, 116.7, 90.5, 79.3, 78.0, 63.9, 54.2, 51.7, 51.3, 50.4, 50.3, 47.6, 47.0, 41.4, 40.5, 40.5, 39.9, 38.1, 36.3, 35.7, 34.0, 29.2, 29.0, 27.9, 25.6, 25.5, 23.1, 23.1, 21.5. FTIR (thin film) cm⁻¹: 2948, 2926, 2868, 1686, 1635, 1594, 1453, 1364, 1249, 1155, 1114. HRMS (ESI) (m/z) calc’d for
C\textsubscript{36}H\textsubscript{58}N\textsubscript{3}O\textsubscript{4} [M+H]\textsuperscript{+}: 596.4422, found 596.4416. \([\alpha]_b^{23}: -69\ (c = 0.55, \text{CH}_2\text{Cl}_2)\). TLC (90:9:1 CHCl\textsubscript{3}:MeOH:NH\textsubscript{4}OH), \(R_f: 0.20\) (KMnO\textsubscript{4}, UV).
Amide 158:

Acetic anhydride (562 µL, 5.95 mmol, 20.0 equiv) was added dropwise to a stirred solution of vinylogous urethane 157 (177 mg, 0.297 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 3 mL), and Et₃N (830 µL, 5.95 mmol, 20.0 equiv) in CH₂Cl₂ (6 mL) at room temperature. After stirring for 30 h, the reaction was concentrated under reduced pressure. The resultant residue was then directly purified by flash column chromatography (silica gel, eluent: gradient: 2:1 → 1:1 → 0:1 hexanes:EtOAc) to afford amide 158 (158 mg, 83%) as a white flocculent solid.

¹H NMR (600 MHz, C₆D₆) δ: 9.58 (s, 1H), 5.97–5.86 (m, 1H), 5.17 (d, J = 17.0 Hz, 1H), 5.08 (d, J = 10.3 Hz, 1H), 4.21–4.09 (m, J = 5.0 Hz, 1H), 3.66 (t, J = 13.1 Hz, 1H), 3.60–3.49 (m, 1H), 3.28–3.16 (m, 1H), 3.00 (br. s., 1H), 2.93–2.81 (m, 2H), 2.70–2.59 (m, 1H), 2.46–2.32 (m, 2H), 2.08 (dd, J = 6.9, 13.1 Hz, 1H), 2.02 (br. s., 1H), 1.95 (d, J = 11.2 Hz, 1H), 1.80–1.73 (m, 2H), 1.73–1.71 (m, 1H), 1.70 (s, 3H), 1.67–1.60 (m, 1H), 1.59–1.51 (m, 2H), 1.50–1.45 (m, 18H), 1.42–1.25 (m, 5H), 1.18–1.09 (m, 2H), 1.08–1.05 (m, 1H), 1.03 (d, J = 6.2 Hz, 3H), 0.80 (d, J = 6.2 Hz, 3H).

¹³C NMR (126 MHz, C₆D₆) δ: 170.8, 170.7, 161.2, 156.1, 137.5, 116.8, 90.9, 79.4, 78.4, 70.5, 54.5, 54.1, 52.7, 51.8, 50.3, 43.3, 42.9, 41.2, 40.7, 40.0, 39.2, 36.1, 35.5, 34.5, 33.8, 29.1, 29.0, 27.5, 25.6, 25.3, 24.9, 23.1, 23.0, 22.1. FTIR (thin film) cm⁻¹: 2972, 2948, 2928, 2870, 1686, 1655, 1641, 1596, 1389, 1365, 1251, 1166, 1155. HRMS (ESI) (m/z) calc’d for C₃₈H₅₉N₅O₅ [M+Na]⁺: 660.4347, found 660.4374. [α]D²³: −156 (c = 0.23, CH₂Cl₂). TLC (90:9:1 CHCl₃:MeOH:NH₄OH), Rf: 0.79 (KMnO₄, UV).

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**Enal 161:**

Hoveyda-Grubbs 2nd generation catalyst (20.0 mg, 0.0322 mmol, 0.50 equiv) was added as a single portion to a solution of amide 158 (41.4 mg, 0.0644 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 1 mL), and acrolein (50.0 µL, 0.644 mmol, 10.0 equiv) in CH$_2$Cl$_2$ (1.8 mL) at room temperature. The reaction was stirred for 21 h, at which point additional acrolein (25.0 µL, 0.322 mmol, 5.00 equiv) and Hoveyda-Grubbs catalyst (10.0 mg, 0.0161 mmol, 0.25 equiv) were added. After stirring for a further 12 h, the reaction was concentrated under reduced pressure. The resultant residue was then directly purified by flash column chromatography (silica gel, eluent: gradient: 4:1 → 2:1 → 1:1 hexanes:EtOAc) to afford enal 161 (43.0 mg, quant.) as a yellow solid.

$^1$H NMR (500 MHz, C$_6$D$_6$) δ: 9.56 (s, 1H), 9.42 (d, $J = 7.8$ Hz, 1H), 6.53–6.44 (m, 1H), 6.14 (dd, $J = 7.7$, 15.7 Hz, 1H), 4.01 (br. s., 1H), 3.66 (t, $J = 13.5$ Hz, 1H), 3.43 (br. s., 1H), 3.25–3.12 (m, 1H), 3.03–2.85 (m, 3H), 2.64 (br. s., 1H), 2.43 (d, $J = 8.8$ Hz, 1H), 2.26 (td, $J = 7.0$, 14.6 Hz, 1H), 2.04 (br. s., 1H), 2.02–1.90 (m, 3H), 1.80 (d, $J = 12.4$ Hz, 1H), 1.75–1.68 (m, 4H), 1.65–1.59 (m, 1H), 1.53–1.48 (m, $J = 5.9$ Hz, 1H), 1.45 (s, 9H), 1.42 (s, 9H), 1.37–1.23 (m, 6H), 1.06 (d, $J = 6.3$ Hz, 4H), 1.04–0.97 (m, 1H), 0.97–0.93 (m, 1H), 0.89–0.86 (m, 1H), 0.73 (d, $J = 6.3$ Hz, 3H). $^{13}$C NMR (126 MHz, C$_6$D$_6$) δ: 193.3, 171.1, 161.2, 156.1, 155.3, 134.9, 128.9, 91.4, 79.9, 78.3, 70.3, 54.5, 53.5, 52.6, 51.7, 50.4, 43.4, 42.8, 41.1, 40.0, 39.2, 38.6, 36.8, 36.5, 34.5, 33.7, 29.1, 28.9, 27.7, 25.8, 25.5, 24.9, 23.0, 22.8, 22.1. FTIR (thin film) cm$^{-1}$: 2949, 2927, 2869, 1691, 1653, 1639, 1596, 1390, 1365, 1166, 1154. HRMS (ESI) (m/z) calc’d for C$_{39}$H$_{59}$N$_3$NaO$_6$ [M+Na]$^+$: 688.4296, found 688.4289. $[^{[a]}_D]$: $–86 \ (c = 0.35, \text{CH}_2\text{Cl}_2)$. TLC (EtOAc), $R_f$: 0.43 (KMnO$_4$, UV).
**Tosylate 162:**

Palladium on carbon (10 wt%, 14.0 mg, 0.0130 mmol, 0.20 equiv) was added as a single portion to a stirred solution of enal 161 (43.0 mg, 0.0650 mmol, 1.00 equiv) in EtOAc (3.2 mL). The reaction vessel was purged with H₂ and placed under an atmosphere of H₂. After 2 h, Celite was poured into the stirred reaction mixture and the resultant slurry was then filtered through a pad of Celite. The solution was concentrated under reduced pressure to afford the corresponding aldehyde, which was carried forward to the next step without further purification.

NaBH₄ (5.0 mg, 0.13 mmol, 2.0 equiv) was added as a single portion to a stirred solution of the crude aldehyde, which was azeotropically dried with benzene (5 × 1 mL), in EtOH (1.5 mL) at 0 °C. The reaction was stirred for 40 min, at which point saturated aqueous NH₄Cl solution (0.5 mL) was added and all volatiles were removed *in vacuo*. Water (2 mL), Et₂O (2 mL), and EtOAc (2 mL) were added sequentially to the crude residue. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 2 mL). The organic layers were combined, washed with brine (5 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure to provide alcohol S9, which was carried forward to the next step without further purification.

Next, Et₃N (75.0 µL, 0.520 mmol, 8.00 equiv), 4-DMAP (8.0 mg, 0.065 mmol, 1.0 equiv), and p-TsCl (50.0 mg, 0.260 mmol, 4.00 equiv) were added sequentially to a stirred solution of crude alcohol S9, which was azeotropically dried with benzene (5 × 1 mL), in CH₂Cl₂ (1.3 mL) at room temperature. After stirring for 12 h, a saturated aqueous NaHCO₃ solution (2 mL) and brine (2 mL) were added sequentially, followed by Et₂O (2 mL), and EtOAc (2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 2 mL). The organic layers were combined, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by
flash column chromatography (silica gel, eluent: gradient: 2:1 → 1:1 → 0:1 hexanes:EtOAc) to afford tosylate 162 (37.5 mg, 70% over 3 steps) as a yellow solid.

\(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)) \(\delta\): 9.57 (s, 1H), 7.77 (d, \(J = 7.8\) Hz, 2H), 6.73 (d, \(J = 8.1\) Hz, 2H), 4.13 (br. s., 1H), 3.97–3.84 (m, 2H), 3.66 (t, \(J = 12.9\) Hz, 1H), 3.27 (br. s., 1H), 3.25–3.19 (m, 1H), 2.98 (d, \(J = 2.9\) Hz, 1H), 2.93 (d, \(J = 8.1\) Hz, 1H), 2.64 (t, \(J = 5.4\) Hz, 1H), 2.44 (d, \(J = 8.5\) Hz, 1H), 2.07 (dd, \(J = 3.0, 4.3\) Hz, 1H), 2.05–2.00 (m, 2H), 1.93 (d, \(J = 11.5\) Hz, 2H), 1.84 (s, 3H), 1.82–1.76 (m, 2H), 1.73 (s, 3H), 1.68–1.62 (m, 1H), 1.58–1.51 (m, 3H), 1.48 (s, 9H), 1.46 (s, 9H), 1.41–1.32 (m, 7H), 1.31–1.24 (m, 3H), 1.18–1.05 (m, 3H), 1.01 (d, \(J = 5.6\) Hz, 3H), 0.79 (d, \(J = 6.1\) Hz, 3H). \(^{13}\)C NMR (126 MHz, C\(_6\)D\(_6\)) \(\delta\): 170.8, 170.7, 161.2, 156.3, 144.4, 135.0, 130.2, 128.0, 90.9, 79.5, 78.4, 70.7, 70.5, 54.5, 54.3, 52.7, 51.9, 50.6, 43.3, 42.9, 41.3, 40.0, 39.2, 36.9, 36.7, 35.0, 34.4, 33.8, 29.7, 29.1, 29.0, 27.7, 26.0, 25.6, 24.9, 23.7, 23.0, 23.0, 22.1, 21.5. FTIR (thin film) cm\(^{-1}\): 2946, 2928, 2851, 1685, 1654, 1638, 1595, 1389, 1364, 1175, 1166, 1154. HRMS (ESI) (m/z) calc’d for C\(_{46}\)H\(_{69}\)N\(_3\)NaO\(_8\)S [M+Na]\(^{+}\): 846.4698, found 846.4716. TLC (EtOAc), \(R_f\): 0.56 (KMnO\(_4\), UV).
Quinolizidine 163:

2,6-Lutidine (13.5 μL, 0.115 mmol, 10.0 equiv) was added dropwise to a stirred solution of tosylate 162 (9.5 mg, 0.012 mmol, 1.0 equiv), which was azeotropically dried with benzene (5 × 0.5 mL) in CH₂Cl₂ (1 mL) at 0 °C, followed by TBSOTf (21.0 μL, 0.0922 mmol, 8.00 equiv). After stirring for 5 min at 0 °C, the reaction mixture was allowed to warm to room temperature and was stirred for an additional 16.5 h, at which point a saturated aqueous NaHCO₃ solution (0.5 mL) was added, followed by Et₂O (1 mL) and EtOAc (1 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 1 mL). The organic layers were combined, washed with brine (2 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure to afford the corresponding silyloxy carbamate S10, which was carried forward to the next step without further purification.

A solution of TBAF in THF (1.00 M, 23.0 μL, 0.0230 mmol, 2.00 equiv) was added to a solution of crude silyloxy carbamate S10 in THF (1 mL) at 0 °C. After stirring for 0.5 h at 0 °C, 8 drops of AcOH were added and the reaction was concentrated under reduced pressure. The resultant residue was then directly purified by flash column chromatography (silica gel, eluent, gradient: 2:1 → 1:1 → 0:1 hexanes:EtOAc, 1% Et₃N → 9:1 CH₂Cl₂:MeOH, 1% Et₃N) to afford quinolizidine 163. 163 was further purified by preparatory thin-layer chromatography (PTLC) using 90:9:1 CHCl₃:MeOH: NH₄OH, furnishing quinolizidine 163 (4.2 mg, 66% over 2 steps) as a white solid.

¹H NMR (600 MHz, C₆D₆) δ: 9.57 (br. s., 1H), 3.67 (t, J = 13.2 Hz, 1H), 3.11 (dt, J = 5.4, 11.6 Hz, 1H), 3.01 (br. s., 1H), 2.92 (d, J = 5.1 Hz, 1H), 2.88 (d, J = 6.8 Hz, 1H), 2.70–2.63 (m, 1H), 2.58 (d, J = 10.8 Hz, 1H), 2.41 (d, J = 8.3 Hz, 2H), 2.15–2.06 (m, 1H), 2.05–1.92 (m, 3H), 1.80 (d, J = 13.4 Hz, 2H).
Hz, 1H), 1.72 (s, 3H), 1.70–1.62 (m, 3H), 1.61–1.50 (m, 6H), 1.46 (s, 9H), 1.38 (d, $J = 14.2$ Hz, 1H), 1.34–1.19 (m, 6H), 1.18–1.06 (m, 2H), 1.03 (d, $J = 6.1$ Hz, 3H), 1.00–0.94 (m, 1H), 0.93–0.87 (m, 1H), 0.84 (d, $J = 5.6$ Hz, 3H). $^{13}$C NMR (126 MHz, C$_6$D$_6$) δ: 170.7, 170.6, 161.1, 90.9, 78.4, 70.4, 57.3, 54.4, 53.2, 52.7, 52.3, 52.0, 43.3, 42.9, 42.0, 40.0, 39.2, 37.5, 34.8, 34.5, 33.8, 33.3, 29.1, 27.5, 27.4, 25.6, 25.6, 24.9, 24.7, 23.2, 23.1, 22.1. FTIR (thin film) cm$^{-1}$: 2926, 2866, 1655, 1641, 1596, 1388, 1154. HRMS (ESI) (m/z) calc’d for C$_{34}$H$_{54}$N$_3$O$_3$ [M+H]$^+$: 552.4160, found 552.4173. $[^\alpha]_D^{23}$: $-91$ (c = 0.22, CH$_2$Cl$_2$). TLC (90:9:1 CHCl$_3$:MeOH:NH$_4$OH), $R_f$: 0.16 (KMnO$_4$, UV).
Proposed structure of (−)-himeradine A (38):

Trifluoroacetic acid (500 µL) was added to a stirred solution of quinolizidine 163 (9.4 mg, 0.017 mmol, 1.0 equiv) in CH₂Cl₂ (500 µL) at room temperature. After stirring for 13 h, the reaction was concentrated in vacuo to afford (−)-himeradine A (38) as the double TFA salt (11.6 mg, quant.) and as a white solid.

¹H NMR (600 MHz, CD₃OD) δ: 4.08 (tt, J = 5.0, 9.9 Hz, 1H), 3.81 (d, J = 9.4 Hz, 1H), 3.63 (d, J = 11.7 Hz, 1H), 3.36 (d, J = 9.4 Hz, 1H), 3.28 (d, J = 11.2 Hz, 1H), 3.26–3.21 (m, 1H), 3.17 (dt, J = 2.3, 12.5 Hz, 1H), 3.03 (dd, J = 12.6, 14.1 Hz, 1H), 2.69 (dd, J = 2.9, 4.7 Hz, 1H), 2.62–2.56 (m, 1H), 2.53–2.46 (m, 1H), 2.38 (d, J = 4.4 Hz, 1H), 2.32–2.26 (m, 1H), 2.16–2.09 (m, 1H), 2.03 (s, 3H), 2.01–1.93 (m, 7H), 1.87–1.75 (m, 5H), 1.74–1.64 (m, 3H), 1.64–1.58 (m, 1H), 1.55 (t, J = 11.2 Hz, 2H), 1.37–1.26 (m, 3H), 1.22 (q, J = 12.3 Hz, 1H), 1.00 (d, J = 6.2 Hz, 3H), 0.98 (d, J = 5.9 Hz, 3H). ¹³C NMR (126 MHz, C₆D₆) δ: 196.5, 174.3, 75.9, 59.7, 58.7, 57.4, 57.1, 55.9, 53.1, 45.1, 43.0, 40.7, 40.6, 40.5, 35.4, 35.3, 35.0, 32.6, 31.5, 29.6, 27.7, 24.6, 24.6, 24.4, 24.1, 23.0, 22.8, 21.4, 20.3.

FTIR (thin film) cm⁻¹: 3430, 2955, 2931, 2875, 1667, 1400, 1199, 1132. HRMS (ESI) (m/z) calc’d for C₂₁H₄₆N₃O [M+H⁺]: 452.3635, found 452.3637. [α]D⁻¹⁹: −19 (c = 0.3, MeOH).¹³⁹ TLC (80:18:2 CHCl₃:MeOH:NH₄OH), Rf: 0.62 (KMnO₄).

¹³⁹ The reported specific rotation for (−)-himeradine A (38) is [α]D⁻²³: −23 (c = 0.3, MeOH).
**Table S1.** $^1$H NMR Data Comparison Between Natural and Synthetic Proposed Structure of (−)-Himeradine A (38) as the Double TFA Salt in CD$_3$OD.

<table>
<thead>
<tr>
<th>Isolation Report$^a$ (1H, 600 MHz, CD$_3$OD)</th>
<th>Synthetic (−)-Himeradine A (38) (1H, 600 MHz, CD$_3$OD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.96 (d, $J = 4.6$ Hz, 3H)</td>
<td>0.98 (d, $J = 5.9$ Hz, 3H)</td>
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<tr>
<td>0.98 (d, $J = 5.9$ Hz, 3H)</td>
<td>1.00 (d, $J = 6.2$ Hz, 3H)</td>
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<td>1.19 (br. q, $J = 13.2$ Hz, 1H)</td>
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<td>1.23–1.32 (m, 3H)</td>
<td>1.37–1.26 (m, 3H)</td>
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<td>1.54–1.58 (m, 3H)</td>
<td>1.55 (t, $J = 11.2$ Hz, 2H)</td>
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<td>1.64–1.66 (m, 3H)</td>
<td>1.74–1.64 (m, 3H)</td>
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<td>1.73–1.82 (m, 5H)</td>
<td>1.87–1.75 (m, 5H)</td>
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<td>1.90–1.95 (m, 7H)</td>
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<td>2.03 (s, 3H)</td>
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<td>2.10 (m, 1H)</td>
<td>2.16–2.09 (m, 1H)</td>
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<td>2.32–2.26 (m, 1H)</td>
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<td>2.69 (dd, $J = 2.9$, 4.7 Hz, 1H)</td>
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<td>3.19 (m, 1H)</td>
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<td>3.26–3.21 (m, 1H)</td>
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<td>3.34 (m, 1H)</td>
<td>3.36 (d, $J = 9.4$ Hz, 1H)</td>
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<td>3.77 (m, 1H)*</td>
<td>3.63 (d, $J = 11.7$ Hz, 1H)*</td>
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<td>3.80 (m, 1H)</td>
<td>3.81 (d, $J = 9.4$ Hz, 1H)</td>
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<td>4.09 (m, 1H)</td>
<td>4.08 (tt, $J = 5.0$, 9.9 Hz, 1H)</td>
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*The chemical shift of H10' in the synthetic proposed structure of himeradine A (38) was shifted upfield by $\Delta \delta = 0.14$ ppm relative to natural himeradine A.
Figure S1. Comparison of $^1$H NMR Spectra of Natural and Synthetic Proposed Structure of (−)-Himeradine A (38) as the Double TFA Salt in CD$_3$OD.
Figure S2. Comparison of $^1$H NMR Spectra of Natural and Synthetic Proposed Structure of (−)-Himeradine A (38) as the Free Base in CD$_3$OD.$^{140}$

$^{140}$ The free base $^1$H NMR spectrum of natural himeradine A (38) in CD$_3$OD was kindly provided by Professor Hiroshi Morita via private communication.
Table S2. $^{13}$C NMR Data Comparison Between Natural and Synthetic Proposed Structure of (−)-Himeradine A (38) as the Double TFA Salt in CD$_3$OD.

<table>
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<th>Isolation Report$^{19}$ ($^{13}$C, 150 MHz, CD$_3$OD)</th>
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$^{141}$ In pyridine-$d_5$.  

203
Figure S3. Comparison of $^{13}$C NMR Spectra of Synthetic Proposed Structure and Natural (−)-Himeradine A (38) as the Double TFA Salt in CD$_3$OD.
Candidate amide 184:

Triphenylphosphine (31.0 mg, 0.118 mmol, 1.50 equiv) was added as a single portion to a stirred solution of imine 183 (50.2 mg, 0.0785 mmol, 1.00 equiv) in THF (1.4 mL) and water (180 µL) at room temperature. The reaction was heated to 70 °C and stirred for 15.5 h, at which point the reaction was cooled to room temperature and concentrated. The resultant residue was azeotroped with MeOH (5 × 1 mL), followed by benzene (3 × 1 mL), then stirred with silica gel (100 mg) in CH₂Cl₂ (5 mL) for 4 h. The slurry was subsequently filtered and washed with a solution of 80:18:2 CHCl₃:MeOH:NH₄OH (10 × 1 mL) and concentrated in vacuo. The crude residue was then purified by flash column chromatography (silica gel, eluent: gradient: 1:1 → 0:1 hexanes:EtOAc, 1% Et₃N → 90:9:1 CHCl₃:MeOH:NH₄OH) to afford vinylogous urethane S11 as a pale white flocculent solid. S11 was contaminated with inseparable Ph₃PO byproduct and was carried forward to the next step without further purification.

Acetic anhydride (150 µL, 1.58 mmol, 20.0 equiv) was added dropwise to a stirred solution of vinylogous urethane S11, which was azeotropically dried with benzene (5 × 1 mL), and Et₃N (331 µL, 1.58 mmol, 20.0 equiv) in CH₂Cl₂ (1.6 mL) at room temperature. After stirring for 10 h, the reaction was concentrated under reduced pressure. The resultant residue was then directly purified by flash column chromatography (silica gel, eluent, gradient: 2:1 → 1:1 hexanes:EtOAc) to afford amide 184 (25.0 mg, 50% over 2 steps) as a white flocculent solid.

¹H NMR (500 MHz, C₆D₆) δ: 9.60 (s, 1H), 5.92–5.82 (m, 1H), 5.15 (dd, J = 1.7, 17.1 Hz, 1H), 5.06 (dd, J = 1.8, 10.1 Hz, 1H), 4.32 (br. s., 1H), 3.68 (t, J = 12.8 Hz, 1H), 3.39 (br. s., 1H), 3.13 (dd, J = 7.8, 17.3 Hz, 1H), 3.04–2.93 (m, 2H), 2.87 (d, J = 9.3 Hz, 1H), 2.65 (br. s., 1H), 2.41 (d, J = 8.5 Hz,
2.27–2.13 (m, 1H), 2.03–1.90 (m, 3H), 1.83 (dd, $J = 5.4$, $15.1$ Hz, 1H), 1.80–1.74 (m, 1H), 1.71 (s, 3H), 1.69–1.63 (m, 1H), 1.61–1.51 (m, 2H), 1.48 (s, 9H), 1.46 (s, 9H), 1.40–1.31 (m, 5H), 1.31–1.24 (m, 2H), 1.18 (dd, $J = 5.2$, $11.8$ Hz, 1H), 1.11–1.07 (m, 2H), 1.03 (d, $J = 6.6$ Hz, 3H), 0.74 (d, $J = 6.3$ Hz, 3H). $^{13}$C NMR (126 MHz, $C_6D_6$) $\delta$: 171.1, 170.6, 161.5, 156.4, 137.5, 116.8, 91.2, 79.6, 78.3, 70.8, 54.8, 54.0, 52.5, 50.9, 47.8, 43.2, 43.0, 39.9, 39.8, 39.5, 39.1, 37.1, 37.1, 34.5, 33.5, 29.2, 28.9, 26.4, 25.8, 24.9, 24.9, 23.1, 22.9, 19.2. FTIR (thin film) cm$^{-1}$: 2949, 2925, 2870, 1686, 1654, 1641, 1597, 1390, 1348, 1250, 1232, 1166, 1153. HRMS (ESI) ($m/z$) calc’d for C$_{38}$H$_{60}$N$_3$O$_5$ [M+H]$^+$: 638.4527, found 638.4548. TLC (90:9:1 CHCl$_3$:MeOH:NH$_4$OH), $R_f$: 0.68 (KMnO$_4$, UV).
Candidate enal 185:

Hoveyda-Grubbs 2nd generation catalyst (12.3 mg, 0.0200 mmol, 0.50 equiv) was added as a single portion to a solution of amide 184 (25.0 mg, 0.0390 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 1 mL), and acrolein (30.0 µL, 0.390 mmol, 10.0 equiv) in CH₂Cl₂ (800 µL) at room temperature. The reaction was stirred for 32.5 h, at which point the reaction was concentrated under reduced pressure. The resultant residue was then directly purified by flash column chromatography (silica gel, eluent: gradient: 4:1 → 2:1 → 1:1 → 1:2 hexanes:EtOAc) to afford enal 185 (22.8 mg, 88%) as a yellow flocculent solid.

¹H NMR (500 MHz, C₆D₆) δ: 9.57 (s, 1H), 9.41 (d, J = 7.6 Hz, 1H), 6.47–6.33 (m, 1H), 6.13 (dd, J = 7.7, 15.5 Hz, 1H), 4.21 (br. s., 1H), 3.67 (t, J = 13.2 Hz, 1H), 3.25–3.15 (m, 1H), 3.04–2.93 (m, 3H), 2.64 (t, J = 5.4 Hz, 1H), 2.51 (d, J = 8.8 Hz, 1H), 2.13–2.02 (m, 1H), 2.01–1.88 (m, 4H), 1.82 (d, J = 14.9 Hz, 1H), 1.79–1.74 (m, 1H), 1.73 (s, 3H), 1.68 (d, J = 14.4 Hz, 1H), 1.59 (td, J = 4.4, 13.7 Hz, 1H), 1.47 (s, 9H), 1.40 (s, 9H), 1.36–1.27 (m, 4H), 1.25–1.15 (m, 2H), 1.14–1.05 (m, 2H), 1.02 (d, J = 6.4 Hz, 3H), 0.99–0.82 (m, 3H), 0.69 (d, J = 6.4 Hz, 3H). ¹³C NMR (126 MHz, C₆D₆) δ: 192.9, 170.9, 170.7, 161.6, 156.2, 155.4, 135.0, 91.7, 80.0, 78.4, 70.8, 55.0, 52.9, 52.4, 51.1, 47.8, 43.6, 43.0, 39.8, 39.5, 38.9, 38.1, 37.7, 37.1, 34.5, 33.5, 29.1, 28.8, 26.4, 25.9, 25.5, 24.9, 23.1, 22.7, 19.8. FTIR (thin film) cm⁻¹: 2951, 2907, 2869, 1691, 1637, 1597, 1390, 1167, 1154. HRMS (ESI) (m/z) calc’d for C₃₉H₅₉N₄O₆ [M+Na]⁺: 688.4296, found 688.4314. TLC (EtOAc), Rₛ: 0.58 (KMnO₄, UV).
Candidate tosylate 186:

Palladium on carbon (10 wt%, 7.3 mg, 0.0069 mmol, 0.20 equiv) was added as a single portion to a stirred solution of enal 185 (22.8 mg, 0.0342 mmol, 1.00 equiv) in EtOAc (1.7 mL). The reaction vessel was purged with H$_2$ and placed under an atmosphere of H$_2$. After 1 h, Celite was poured into the stirred reaction mixture and the resultant slurry was then filtered through a pad of Celite. The solution was concentrated under reduced pressure to afford the corresponding aldehyde, which was carried forward to the next step without further purification.

NaBH$_4$ (2.6 mg, 0.069 mmol, 2.0 equiv) was added as a single portion to a stirred solution of the crude aldehyde, which was azeotropically dried with benzene (5 × 1 mL), in EtOH (850 µL) at 0 °C. The reaction was stirred for 50 min, at which point saturated aqueous NH$_4$Cl solution (0.5 mL) was added and all volatiles were removed in vacuo. Water (1 mL), Et$_2$O (1 mL), and EtOAc (1 mL) were added sequentially to the crude residue. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 1 mL). The organic layers were combined, washed with brine (4 mL), dried over anhydrous MgSO$_4$, and concentrated under reduced pressure to provide alcohol S12, which was carried forward to the next step without further purification.

Next, Et$_3$N (9.5 µL, 0.068 mmol, 2.0 equiv), Me$_3$N•HCl (3.3 mg, 0.034 mmol, 1.0 equiv), and p-TsCl (7.8 mg, 0.041 mmol, 1.2 equiv) were added sequentially to a stirred solution of crude alcohol S12, which was azeotropically dried with benzene (5 × 1 mL), in MeCN (1.1 mL) at room temperature. After stirring for 6.5 h, additional Et$_3$N (4.8 µL, 0.034 mmol, 1.0 equiv), Me$_3$N•HCl (1.7 mg, 0.017 mmol, 0.50 equiv), and p-TsCl (3.9 mg, 0.021 mmol, 0.60 equiv) were added successively. After stirring for an additional 2 h, water (1 mL), Et$_2$O (1 mL), and EtOAc (1 mL)
were added to the reaction mixture. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 1 mL). The organic layers were combined, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient: 2:1 → 1:1 → 1:2 → 0:1 hexanes:EtOAc) to afford tosylate 186 (20.6 mg, 73% over 3 steps) as a pale yellow flocculent solid.

**¹H NMR** (600 MHz, C₆D₆) δ: 9.61 (s, 1H), 7.79 (d, J = 8.2 Hz, 2H), 6.77 (d, J = 8.5 Hz, 2H), 4.26 (br. s., 1H), 3.94–3.85 (m, 2H), 3.69 (t, J = 13.5 Hz, 1H), 3.37 (dd, J = 4.7, 9.7 Hz, 1H), 3.04–2.97 (m, 2H), 2.88 (br. s., 1H), 2.66 (t, J = 5.9 Hz, 1H), 2.55 (d, J = 8.8 Hz, 1H), 2.10 (dd, J = 2.6, 4.4 Hz, 1H), 2.06 (d, J = 9.4 Hz, 1H), 2.03–1.94 (m, 3H), 1.86 (s, 3H), 1.85–1.82 (m, 1H), 1.75 (s, 3H), 1.73–1.69 (m, 1H), 1.63–1.55 (m, 2H), 1.47 (s, 9H), 1.46 (s, 9H), 1.45–1.40 (m, 2H), 1.40–1.29 (m, 5H), 1.29–1.19 (m, 3H), 1.19–1.07 (m, 4H), 1.03 (d, J = 6.2 Hz, 3H), 0.98 (q, J = 10.6 Hz, 1H), 0.73 (d, J = 6.5 Hz, 3H). **¹³C NMR** (126 MHz, C₆D₆) δ: 170.9, 170.8, 161.9, 156.5, 144.5, 135.0, 130.2, 128.0, 91.4, 79.6, 78.3, 70.7, 55.0, 53.9, 52.6, 50.7, 47.8, 43.4, 43.0, 39.9, 39.5, 38.8, 38.4, 37.5, 34.6, 34.5, 33.6, 29.7, 29.2, 29.1, 28.9, 27.0, 25.9, 24.9, 24.7, 23.8, 23.1, 22.8, 21.5, 19.3. **FTIR** (thin film) cm⁻¹: 2948, 2927, 2870, 1686, 1648, 1596, 1389, 1364, 1175, 1153. **HRMS** (ESI) (m/z) calc’d for C₄₆H₆₉N₃NaO₈S [M+Na]⁺: 846.4698, found 846.4698. **TLC** (EtOAc), Rₛ: 0.59 (KMnO₄, UV).
Candidate quinolizidine 187:

2,6-Lutidine (18.0 µL, 0.150 mmol, 10.0 equiv), followed by TBSOTf (28.0 µL, 0.120 mmol, 8.00 equiv), were added dropwise to a stirred solution of tosylate 186 (12.4 mg, 0.0150 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 0.5 mL), in CH₂Cl₂ (1.5 mL) at 0 °C. After stirring for 5 min at 0 °C, the reaction mixture was allowed to room temperature and was stirred for an additional 12 h, at which point a saturated aqueous NaHCO₃ solution (0.5 mL) was added, followed by Et₂O (1 mL), and EtOAc (1 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 1 mL). The organic layers were combined, washed with brine (2 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure to afford the corresponding silyloxy carbamate S13, which was carried forward to the next step without further purification.

A solution of TBAF in THF (1.00 M, 30.0 µL, 0.0301 mmol, 2.00 equiv) was added to a solution of crude silyloxy carbamate S13 in THF (1.5 mL) at 0 °C. After stirring for 45 min at 0 °C, AcOH (13.0 µL, 0.226 mmol, 15.0 equiv) was added and the reaction was concentrated under reduced pressure. The resultant residue was then directly purified by flash column chromatography (silica gel, eluent: gradient: 2:1 → 1:1 → 0:1 hexanes:EtOAc, 1% Et₃N → 9:1 CH₂Cl₂:MeOH, 1% Et₃N) to afford quinolizidine 187. 187 was further purified by preparatory thin-layer chromatography (PTLC) using 90:9:1 CHCl₃:MeOH:NH₄OH, furnishing quinolizidine 187 (4.9 mg, 59% over 2 steps) as a white solid.
$^{1}H$ NMR (600 MHz, C$_{6}$D$_{6}$) $\delta$ : 9.70 (br. s., 1H), 3.66 (t, $J$ = 13.5 Hz, 1H), 3.13 (br. s., 1H), 3.07 (d, $J$ = 5.3 Hz, 1H), 2.99 (br. s., 1H), 2.89 (d, $J$ = 7.9 Hz, 1H), 2.70 (d, $J$ = 10.9 Hz, 1H), 2.63 (t, $J$ = 5.6 Hz, 1H), 2.43 (d, $J$ = 8.8 Hz, 1H), 2.31 (dt, $J$ = 2.1, 11.0 Hz, 1H), 2.06 (t, $J$ = 10.3 Hz, 1H), 2.00–1.86 (m, 4H), 1.83 (d, $J$ = 11.4 Hz, 1H), 1.73 (s, 3H), 1.66 (td, $J$ = 2.6, 12.8 Hz, 1H), 1.63–1.59 (m, 2H), 1.58–1.48 (m, 4H), 1.45 (s, 9H), 1.36–1.29 (m, 3H), 1.28–1.21 (m, 3H), 1.21–1.14 (m, 2H), 1.12–1.05 (m, 2H), 1.01 (d, $J$ = 6.2 Hz, 3H), 0.96–0.88 (m, 2H), 0.83 (d, $J$ = 5.3 Hz, 3H). $^{13}C$ NMR (126 MHz, C$_{6}$D$_{6}$) $\delta$ : 170.7, 170.5, 161.2, 92.3, 78.4, 70.7, 57.6, 54.9, 53.5, 52.5, 52.1, 49.3, 43.3, 43.0, 42.6, 40.0, 39.4, 38.3, 35.0, 34.6, 33.6, 32.5, 29.1, 27.3, 27.1, 25.9, 25.8, 24.9, 24.9, 23.1, 22.9, 19.5. FTIR (thin film) cm$^{-1}$: 2929, 2896, 1643, 1595, 1388, 1232, 1167, 1152. HRMS (ESI) (m/z) calc’d for C$_{34}$H$_{54}$N$_{3}$O$_{3}$ [M+H]$^+$: 552.4160, found 552.4175. TLC (90:9:1 CHCl$_{3}$:MeOH:NH$_{4}$OH), $R_f$ : 0.69 (KMnO$_{4}$, UV).
Candidate (−)-himeradine A (188):

Trifluoroacetic acid (300 µL) was added to a stirred solution of quinolizidine 187 (4.9 mg, 0.0089 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (300 µL) at room temperature. After stirring for 14 h, the reaction was concentrated in vacuo to afford candidate (−)-himeradine A (188) as the double TFA salt (6.0 mg, quant.) and as a white solid.

$^1$H NMR (600 MHz, CD$_3$OD) δ: 4.04–3.94 (m, J = 5.0 Hz, 1H), 3.81 (d, J = 9.4 Hz, 1H), 3.79–3.74 (m, 1H), 3.37 (d, J = 9.4 Hz, 1H), 3.34–3.31 (m, 1H), 3.29–3.22 (m, 2H), 3.04 (t, J = 12.9 Hz, 1H), 2.79 (br. s., 1H), 2.62 (dd, J = 2.8, 4.8 Hz, 1H), 2.61–2.56 (m, 1H), 2.47 (td, J = 4.7, 10.3 Hz, 1H), 2.38 (d, J = 3.5 Hz, 1H), 2.23–2.11 (m, 2H), 2.04 (s, 3H), 2.02–1.89 (m, 7H), 1.89–1.74 (m, 5H), 1.72–1.62 (m, 3H), 1.61–1.50 (m, 2H), 1.36–1.28 (m, 2H), 1.26–1.16 (m, 2H), 1.00 (d, J = 6.2 Hz, 3H), 0.98 (d, J = 6.2 Hz, 3H). $^{13}$C NMR (126 MHz, CD$_3$OD) δ: 197.1, 174.3, 76.4, 60.2, 58.4, 57.7, 57.2, 54.9, 52.7, 46.2, 43.2, 40.6, 40.5, 37.1, 35.8, 34.8, 32.5, 31.6, 30.4, 28.3, 25.2, 24.6, 24.4, 24.2, 22.9, 22.7, 21.5, 19.1. FTIR (thin film) cm$^{-1}$: 3367, 2956, 2929, 2876, 1671, 1404, 1200, 1131, 720. HRMS (ESI) (m/z) calc’d for C$_{29}$H$_{46}$N$_3$O [M+H]$^+$: 452.3635, found 452.3633. [α]$_D^{22}$: −56 (c = 0.35, MeOH). TLC (80:18:2 CHCl$_3$;MeOH;NH$_4$OH), R$_f$: 0.50 (KMnO$_4$).
**Figure S4.** Comparison of $^1$H NMR Spectra of Natural and Candidate (−)-Himeradine A (188) as the Double TFA Salt in CD$_3$OD.
Figure S5. Comparison of $^{13}$C NMR Spectra of Natural and Candidate (−)-Himeradine A (188) as the Double TFA Salt in CD$_3$OD.
Alkylated imide 191:

Benzyl 3-bromopropyl ether (118 µL, 0.656 mmol, 1.30 equiv) was added dropwise to a stirred solution of β-carboxyimide 66 (250 mg, 0.504 mmol, 1.00 equiv) and Cs₂CO₃ (329 mg, 1.01 mmol, 2.00 equiv) in DMF (3.4 mL). After 17.5 h, Et₂O (5 mL) and saturated aqueous NH₄Cl solution (10 mL) were added sequentially to the reaction mixture. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined and washed with brine (20 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure. The resultant residue was purified by flash column chromatography (silica gel, eluent: 6:1 hexanes:EtOAc, 1% Et₃N) to afford alkylated imide 191 (325 mg, quant.) as a 9:1 mixture of diastereomers at C4 and as a clear colorless oil.

¹H NMR (500 MHz, C₆D₆, major C4-epimer reported) δ: 7.21 (d, J = 7.6 Hz, 2H), 7.12 (d, J = 7.8 Hz, 2H), 7.06 (t, J = 7.1 Hz, 1H), 5.53 (d, J = 3.7 Hz, 1H), 4.21 (s, 2H), 4.20–4.17 (m, 1H), 4.17–4.09 (m, 1H), 4.07–3.99 (m, 1H), 3.79 (t, J = 10.3 Hz, 1H), 3.68–3.58 (m, 2H), 3.57–3.49 (m, 1H), 3.46–3.37 (m, 1H), 3.36–3.22 (m, 2H), 2.81 (d, J = 9.8 Hz, 2H), 2.39 (td, J = 4.9, 12.5 Hz, 1H), 2.27 (td, J = 4.2, 13.2 Hz, 1H), 2.00 (t, J = 13.2 Hz, 1H), 1.96–1.86 (m, 2H), 1.83–1.73 (m, 2H), 1.71 (d, J = 12.9 Hz, 1H), 1.45 (s, 9H), 1.40–1.31 (m, 1H), 1.27 (t, J = 13.2 Hz, 1H), 0.89–0.82 (m, 2H), 0.77 (d, J = 6.8 Hz, 3H), –0.17 (s, 3H), –0.18 (s, 3H). ¹³C NMR (126 MHz, C₆D₆, major C4-epimer reported) δ: 171.6, 170.7, 151.7, 139.7, 135.1, 131.8, 128.8, 128.7, 127.9, 108.8, 82.9, 73.3, 71.1, 65.8, 64.3, 64.0, 61.4, 50.6, 42.6, 38.0, 34.6, 30.8, 29.8, 28.4, 28.1, 25.5, 21.9, 18.1, –1.4. FTIR (thin film) cm⁻¹: 2952, 2925, 2871, 1753, 1716, 1313, 1250, 1172, 1156, 839. HRMS (ESI) (m/z) calc’d
for C\textsubscript{35}H\textsubscript{53}NNaO\textsubscript{8}Si [M+Na]\textsuperscript{+}: 666.3433, found 666.3438. **TLC** (3:1 hexanes:EtOAc), \(R_f\) : 0.32 (Anis, UV).
**N-Boc-2-pyrrolidinone S14:**

A solution of TBAF in THF (1.00 M, 530 µL, 0.530 mmol, 1.00 equiv) was added to a solution of alkylated imide 191 (341 mg, 0.530 mmol, 1.00 equiv) and DBU (20.0 µL, 0.133 mmol, 0.25 equiv) in THF (10 mL) at room temperature. After 5 min, the reaction was heated to 50 °C and was stirred for 19 h, at which point water (15 mL), Et2O (10 mL), and EtOAc (10 mL) were added successively. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (25 mL), then dried over anhydrous MgSO4 and concentrated under reduced pressure. The resultant residue was purified by flash column chromatography (silica gel, eluent: 2:1 hexanes:EtOAc, 1% Et3N) to afford N-Boc-2-pyrrolidinone S14 (232 mg, 87%) as a >4:1 mixture of diastereomers at C4 and as a clear colorless oil.

**1H NMR** (500 MHz, C6D6, major C4-epimer reported) δ: 7.27 (d, J = 7.6 Hz, 2H), 7.18 (d, J = 1.7 Hz, 2H), 7.11–7.05 (m, 1H), 5.45–5.34 (m, 1H), 4.28 (s, 2H), 3.90 (dd, J = 7.8, 11.0 Hz, 1H), 3.57–3.45 (m, 3H), 3.43–3.35 (m, 1H), 3.32–3.27 (m, 2H), 3.09 (dd, J = 8.3, 10.7 Hz, 1H), 2.41 (dd, J = 3.4, 14.6 Hz, 1H), 2.18–2.06 (m, 1H), 1.96–1.85 (m, 2H), 1.84–1.60 (m, 6H), 1.48 (s, 9H), 1.42–1.33 (m, 2H), 1.31–1.23 (m, 1H), 0.78 (d, J = 6.6 Hz, 3H). **13C NMR** (126 MHz, C6D6, major C4-epimer reported) δ: 174.6, 151.8, 139.8, 135.8, 131.1, 128.9, 128.1, 127.9, 108.7, 82.2, 73.3, 70.8, 65.7, 64.3, 50.6, 49.9, 42.7, 36.0, 35.1, 34.5, 28.5, 28.0, 27.6, 26.7, 21.9. **FTIR** (thin film) cm⁻¹: 2949, 2925, 2869, 1783, 1747, 1712, 1367, 1314, 1157, 1124. **HRMS** (ESI) (m/z) calc’d for C29H42NO6 [M+H]+: 500.3007, found 500.3016. **TLC** (2:1 hexanes:EtOAc), Rf: 0.34 (Anis, UV).
N-2-Nitrobenzenesulfonyl-2-pyrrolidinone 193:

\[
\text{Mg(ClO}_4\text{)}_2 \ (21.0 \text{ mg, 0.0927 mmol, 0.20 equiv}) \text{ was added as a single portion to a stirred solution of N-Boc-2-pyrrolidinone S14 (232 mg, 0.464 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 \times 1 \text{ mL}), in MeCN (7.7 mL) at room temperature. The resultant mixture was heated to 60 °C and stirred for 5.5 h, at which point it was cooled to room temperature and Et}_2\text{O (10 mL) and saturated aqueous NH}_4\text{Cl solution (10 mL) were added sequentially. The layers were separated and the aqueous layer was extracted with EtOAc (3 \times 10 \text{ mL}). The organic layers were combined, washed with brine (20 mL), then dried over anhydrous MgSO}_4\text{ and concentrated under reduced pressure to afford crude 2-pyrrolidinone 192 as a white flocculent solid, which was carried forward to the next step without further purification.}
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A solution of freshly prepared LiHMDS in THF (1.00 M, 478 µL, 0.478 mmol, 1.20 equiv) was added to a solution of 192, which was azeotropically dried with benzene (5 \times 1 mL), in THF (4 mL) at room temperature. After 1 h, the reaction was cooled to 0 °C and a solution of NsCl in THF (1.00 M, 518 µL, 0.518 mmol, 1.30 equiv) was added dropwise. After 5 min, the reaction was allowed to warm to room temperature and stirred for 2 h, at which point saturated aqueous NH}_4\text{Cl solution (5 mL) and Et}_2\text{O (5 mL) were added sequentially. The layers were separated and the aqueous layer was extracted with EtOAc (3 \times 5 mL). The organic layers were combined, washed with brine (15 mL), then dried over anhydrous MgSO}_4\text{ and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient: 6:1 \rightarrow 4:1 \rightarrow 2:1 hexanes:EtOAc, 1% Et}_3\text{N) to afford N-2-nitrobenzenesulfonyl-2-pyrrolidinone 193 (585 mg, 95% over 2 steps) as a 5:1 mixture of diastereomers at C4 and as a white flocculent solid.}
\(^1\)H NMR (500 MHz, C\(_6\)D\(_6\), major C4-epimer reported) δ: 8.48 (dd, \(J = 1.3, 7.9\) Hz, 1H), 7.22–7.19 (m, 2H), 7.14–7.11 (m, 2H), 7.10–7.04 (m, 1H), 6.72 (dd, \(J = 1.2, 7.8\) Hz, 1H), 6.64 (dt, \(J = 1.2, 7.8\) Hz, 1H), 6.44 (dt, \(J = 1.3, 7.8\) Hz, 1H), 5.48 (d, \(J = 3.4\) Hz, 1H), 4.28 (dd, \(J = 7.7, 9.9\) Hz, 1H), 4.20 (s, 2H), 3.67–3.59 (m, 1H), 3.58–3.54 (m, 2H), 3.51 (dd, \(J = 8.1, 9.8\) Hz, 1H), 3.48–3.40 (m, 1H), 3.20–3.12 (m, 2H), 2.50–2.35 (m, 2H), 1.98–1.84 (m, 2H), 1.83–1.67 (m, 4H), 1.65–1.52 (m, 2H), 1.45–1.31 (m, 2H), 1.26 (t, \(J = 13.2\) Hz, 1H), 0.78 (d, \(J = 6.6\) Hz, 3H). \(^{13}\)C NMR (126 MHz, C\(_6\)D\(_6\), major C4-epimer reported) δ: 175.9, 148.6, 139.6, 135.2, 135.0, 134.5, 132.6, 132.3, 131.9, 131.6, 128.9, 128.1, 124.0, 108.7, 73.2, 70.4, 65.7, 64.3, 51.5, 49.1, 42.5, 37.9, 34.9, 34.5, 28.0, 27.4, 26.4, 21.9. FTIR (thin film) cm\(^{-1}\): 2951, 2923, 2854, 1735, 1543, 1366, 1173, 1126, 1096, 966, 738, 594.

HRMS (ESI) (m/z) calc’d for C\(_{30}\)H\(_{37}\)N\(_2\)O\(_8\)S [M+H]\(^+\): 585.2265, found 585.2272. TLC (1:1 hexanes:EtOAc), \(R_f\): 0.72 (Anis, UV).
Enone 194:

A solution of \( n \)-butyllithium in hexanes (2.55 M, 445 µL, 1.14 mmol, 3.00 equiv) was added dropwise to a stirred solution of diisopropylamine (175 µL, 1.25 mmol, 3.30 equiv) in THF (2.1 mL) at \(-78^\circ C\). The reaction was allowed to stir for 10 min, at which point it was warmed to 0 \(^\circ C\). After 10 min, the reaction was warmed to room temperature. The solution was recooled to \(-78^\circ C\) after 10 min. \( t \)-Butylacetate (152 µL, 1.14 mmol, 3.00 equiv) was then added dropwise to the reaction mixture. After 1.5 h, a solution of 193 (221 mg, 0.379 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 1 mL), in THF (4.7 mL) was added dropwise down the walls of the reaction vessel. After stirring at \(-78^\circ C\) for 2.5 h, saturated aqueous NH\(_4\)Cl solution (10 mL) was added to the deep red reaction mixture at \(-78^\circ C\). The resultant mixture was then allowed to warm to room temperature. Et\(_2\)O (10 mL) and EtOAc (10 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (30 mL), then dried over anhydrous MgSO\(_4\) and concentrated under reduced pressure to afford crude \( \beta \)-ketoester S15 as a pale yellow flocculent solid, which was carried forward to the next step without further purification.

10% aqueous HCl (680 µL) was added dropwise to a stirred solution of crude S15 in THF (5.5 mL) at room temperature. After 4 h, a saturated aqueous NaHCO\(_3\) solution (10 mL) was added, followed by Et\(_2\)O (10 mL), EtOAc (10 mL), and water (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (30 mL), then dried over anhydrous MgSO\(_4\) and concentrated under reduced pressure to afford crude enone 194 as a yellow flocculent solid, which was carried forward to the next step without further purification.
Imine 195:

K$_2$CO$_3$ (262 mg, 1.90 mmol, 5.00 equiv) was added in a single portion to a stirred solution of crude enone 194, which was azeotropically dried with benzene (5 × 1 mL), in DMF (5.4 mL) at room temperature. After 18.5 h, the suspension was cooled to 0 °C and PhSH (97.0 µL, 0.948 mmol, 2.50 equiv) was added dropwise via syringe. After 5 min, the reaction was warmed to room temperature and stirred for an additional 6.5 h, at which point water (10 mL), Et$_2$O (10 mL), and EtOAc (10 mL) were added sequentially. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (30 mL), dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. The crude residue was then purified by flash column chromatography (silica gel, eluent: gradient: 1:1 → 0:1 hexanes:EtOAc, 1% Et$_3$N → 90:9:1 CHCl$_3$:MeOH:NH$_4$OH) to afford imine 195 (145 mg, 84% over 3 steps) as a >4:1 mixture of diastereomers at C4 and as a pale yellow oil.

$^1$H NMR (500 MHz, C$_6$D$_6$, major C4-epimer reported) δ: 7.30 (d, $J = 7.6$ Hz, 2H), 7.18 (t, $J = 7.6$ Hz, 2H), 7.10 (t, $J = 7.1$ Hz, 1H), 4.31 (s, 2H), 3.98 (d, $J = 18.1$ Hz, 1H), 3.47 (d, $J = 3.4$ Hz, 1H), 3.32 (dd, $J = 6.1$, 8.8 Hz, 1H), 3.27 (td, $J = 2.9$, 9.3 Hz, 1H), 3.21 (d, $J = 15.6$ Hz, 1H), 2.92–2.86 (m, 1H), 2.61–2.53 (m, 2H), 2.19–2.07 (m, 1H), 2.01–1.92 (m, 1H), 1.89 (t, $J = 6.1$ Hz, 1H), 1.79–1.61 (m, 3H), 1.60–1.46 (m, 3H), 1.38–1.34 (m, 2H), 1.32 (s, 9H), 1.10 (td, $J = 3.7$, 12.9 Hz, 1H), 0.61 (d, $J = 6.6$ Hz, 3H). $^{13}$C NMR (126 MHz, C$_6$D$_6$, major C4-epimer reported) δ: 205.2, 170.5, 169.2, 139.8, 128.9, 128.1, 127.9, 82.1, 73.4, 71.0, 66.2, 55.2, 49.1, 48.2, 43.4, 38.8, 38.3, 32.9, 30.1, 29.8, 29.3, 28.3, 27.5, 22.6. FTIR (thin film) cm$^{-1}$: 2949, 2924, 2862, 1737, 1701, 1668, 1455, 1368, 1154, 1110, 734. HRMS (ESI) (m/z) calc’d for C$_{28}$H$_{30}$NNaO$_4$ [M+Na]$^+$: 476.2781, found 476.2771. TLC (90:9:1 CHCl$_3$:MeOH:NH$_4$OH), $R_f$: 0.40 (KMnO$_4$, UV).
Amine 197:

Trifluoroacetic acid (2.1 mL) was added to a stirred solution of imine 195 (43.4 mg, 0.0957 mmol, 1.00 equiv) in CH₂Cl₂ (2.1 mL) at room temperature. After stirring for 19 h, the reaction was concentrated in vacuo to afford ketone 196, which was carried forward to the next step without further purification.

A solution of HCl in Et₂O (2.00 M, 144 µL, 0.287 mmol, 3.00 equiv) was added to a stirred solution of crude ketone 196 in MeOH (1.9 mL). The resultant mixture was heated to 65 °C and stirred for 3 d, at which point it was cooled to room temperature and concentrated under reduced pressure. The crude residue was then purified by flash column chromatography (silica gel, eluent: 90:9:1 CHCl₃:MeOH:NH₄OH) to afford amine 197 (32.3 mg, 95% over 2 steps) as a pale yellow oil.

¹H NMR (500 MHz, C₆D₆) δ: 7.36–7.33 (m, 2H), 7.17 (t, J = 7.6 Hz, 2H), 7.08 (t, J = 7.3 Hz, 1H), 4.41 (s, 2H), 3.54 (td, J = 5.9, 9.0 Hz, 1H), 3.47 (ddd, J = 6.0, 7.5, 9.1 Hz, 1H), 2.84 (td, J = 2.6, 9.2 Hz, 1H), 2.36 (d, J = 8.8 Hz, 1H), 2.35–2.31 (m, 1H), 2.29 (dd, J = 8.5, 18.8 Hz, 1H), 1.99 (d, J = 19.1 Hz, 1H), 1.88 (t, J = 3.8 Hz, 1H), 1.75 (td, J = 4.1, 12.0 Hz, 1H), 1.71 (dd, J = 2.8, 7.5 Hz, 1H), 1.65 (q, J = 1.0 Hz, 2H), 1.45 (ddd, J = 1.6, 4.0, 13.4 Hz, 1H), 1.40–1.34 (m, 1H), 1.33 (dt, J = 2.3, 4.8 Hz, 1H), 1.30 (d, J = 7.9 Hz, 1H), 1.29–1.26 (m, 1H), 1.25–1.21 (m, 1H), 0.90 (t, J = 12.6 Hz, 1H), 0.81 (dt, J = 3.2, 12.6 Hz, 1H), 0.67 (d, J = 6.5 Hz, 3H). ¹³C NMR (126 MHz, C₆D₆) δ: 214.2, 140.0, 128.9, 128.7, 127.9, 73.3, 72.0, 69.5, 64.8, 53.2, 47.4, 44.8, 43.0, 41.5, 36.9, 33.8, 32.0, 27.4, 26.2, 23.7, 23.0. FTIR (thin film) cm⁻¹: 3340, 2949, 2909, 2869, 1685, 1453, 1099, 735, 698. HRMS (ESI) (m/z) calc’d for C₂₃H₃₁NNaO₂ [M+Na]⁺: 376.2247, found 376.2250. [α]_D²³: −41 (c = 0.56, CH₂Cl₂). TLC (80:18:2 CHCl₃:MeOH:NH₄OH), Rf: 0.58 (KMnO₄, UV).
Alcohol 198:

Palladium on carbon (10 wt%, 146 mg, 0.137 mmol, 1.50 equiv) was added as a single portion to a stirred solution of amine 197 (32.3 mg, 0.0914 mmol, 1.00 equiv) and aqueous HCl (3.00 M, 46.0 µL, 0.137 mmol, 1.50 equiv) in EtOH (3 mL). The reaction vessel was purged with H₂ and placed under an atmosphere of H₂. After 1.5 h, Celite was poured into the stirred reaction mixture and the resultant slurry was then filtered through a pad of Celite and washed with CHCl₃ (10 mL). The filtrate was concentrated under reduced pressure and the resultant crude residue was then purified by flash column chromatography (silica gel, eluent: gradient: 90:9:1 → 80:18:2 CHCl₃:MeOH:NH₄OH) to afford alcohol 198 (19.3 mg, 80%) as a pale yellow oil.

¹H NMR (500 MHz, CDCl₃) δ: 3.73–3.61 (m, 2H), 3.09 (td, J = 2.9, 9.4 Hz, 1H), 2.72 (d, J = 9.3 Hz, 1H), 2.64 (dd, J = 8.6, 19.1 Hz, 1H), 2.26 (t, J = 4.2 Hz, 1H), 2.20–2.11 (m, 3H), 2.07–2.02 (m, 1H), 1.95–1.85 (m, 1H), 1.79 (tdd, J = 2.4, 4.8, 13.5 Hz, 1H), 1.75–1.65 (m, 3H), 1.63–1.54 (m, 2H), 1.40–1.30 (m, 2H), 1.21–1.12 (m, 2H), 0.89 (d, J = 6.4 Hz, 3H). ¹³C NMR (126 MHz, CDCl₃) δ: 213.8, 71.4, 64.2, 63.0, 51.7, 44.0, 43.6, 42.1, 40.3, 35.2, 33.0, 30.8, 29.1, 25.6, 22.4, 22.2. FTIR (thin film) cm⁻¹: 3341, 2951, 2913, 1687, 1456, 1059, 731. HRMS (ESI) (m/z) calc’d for C₁₆H₂₆N₂O₂ [M+H]+: 264.1958, found 264.1972. TLC (80:18:2 CHCl₃:MeOH:NH₄OH), Rf: 0.18 (KMnO₄).
Dehydrolycopecurine (199):

An aqueous solution of HBr (48 wt%, 800 µL) was added to a stirred solution of alcohol 198 (19.3 mg, 0.0736 mmol, 1.00 equiv) in AcOH (2.4 mL). After 14 h, all volatiles were removed in vacuo and the resultant residue was azeotropically dried with MeOH (5 × 2 mL), then benzene (5 × 2 mL), and carried forward to the next step without further purification.

K₂CO₃ (152 mg, 1.10 mmol, 15.0 equiv) was added as a single portion to a stirred solution of the crude product, which was azeotropically dried with benzene (5 × 1 mL), in MeCN (3.6 mL). The reaction was heated to 60 °C and stirred for 18.5 h, at which point it was cooled to room temperature and diluted with Et₂O (1 mL). The resultant slurry was then filtered through a pad of Celite and washed with Et₂O (6 mL). The filtrate was concentrated under reduced pressure and the resultant crude residue was then purified by flash column chromatography (silica gel, eluent: gradient: 90:9:1 → 80:18:2 CHCl₃:MeOH:NH₄OH) to afford dehydrolycopecurine (199) (10.7 mg, 59% over 2 steps) as a white solid.

¹H NMR (600 MHz, CDCl₃) δ: 3.18 (td, J = 7.9, 14.4 Hz, 1H), 3.12 (td, J = 4.2, 10.9 Hz, 1H), 2.74 (d, J = 10.9 Hz, 1H), 2.65 (dd, J = 8.8, 19.7 Hz, 1H), 2.61–2.55 (m, 1H), 2.27 (t, J = 4.5 Hz, 1H), 2.25–2.22 (m, 1H), 2.17–2.14 (m, 1H), 2.12 (d, J = 20.0 Hz, 1H), 2.04 (br. s., 1H), 1.98–1.86 (m, 3H), 1.76–1.71 (m, 1H), 1.63–1.59 (m, 1H), 1.57 (dd, J = 8.4, 13.1 Hz, 1H), 1.53–1.46 (m, 1H), 1.42 (dd, J = 2.3, 6.2, 10.2 Hz, 1H), 1.30 (t, J = 13.2 Hz, 1H), 1.20 (dt, J = 2.9, 12.6 Hz, 1H), 0.95 (d, J = 6.5 Hz, 3H).

¹³C NMR (126 MHz, CDCl₃) δ: 215.2, 68.4, 59.7, 58.8, 47.8, 46.5, 43.7, 42.2, 40.8, 35.4, 34.9, 34.3, 25.4, 22.8, 19.2, 15.6. FTIR (thin film) cm⁻¹: 3382, 2950, 2912, 1687, 1455, 1216, 1124, 1099, 830. HRMS (ESI) (m/z) calc’d for C₁₆H₂₅NO [M+H]⁺: 246.1852, found 246.1863. [α]ᵢ₂₀²: −69 (c = 0.34, MeOH). TLC (80:18:2 CHCl₃:MeOH:NH₄OH), Rₜ: 0.33 (KMnO₄).
**Lycopecurine (39):**

A solution of LiEt$_3$BH in THF (1.00 M, 21.0 µL, 0.0210 mmol, 2.50 equiv) was added dropwise to a stirred solution of dehydrolycopecurine (199) (2.1 mg, 0.0086 mmol, 1.0 equiv) in THF (400 µL) at 0 °C. The reaction was allowed to warm naturally to room temperature and was stirred for 3 h, at which point saturated aqueous NH$_4$Cl solution (100 µL), followed by a 1 M NaOH aqueous solution (until pH > 10), were added. CHCl$_3$ (1 mL) was added and the layers were separated. The aqueous layer was further extracted with CHCl$_3$ (3 × 1 mL). The organic layers were combined, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. The resultant crude residue was then purified by flash column chromatography (silica gel, eluent: gradient: 90:9:1 → 80:18:2 CHCl$_3$:MeOH:NH$_4$OH) to afford lycopecurine (39) (1.4 mg, 66%) as a white crystalline solid. The structure of 39 was unambiguously established via single crystal X-ray diffraction analysis. Crystals suitable for X-ray diffraction were obtained by recrystallization of the hydrobromide salt of 39 from MeOH and acetone.

$^1$H NMR (600 MHz, CDCl$_3$) δ: 3.99 (dd, $J = 1.0, 8.8$ Hz, 1H), 3.47 (ddd, $J = 7.3, 9.8, 13.6$ Hz, 1H), 3.26 (td, $J = 4.1, 11.7$ Hz, 1H), 3.09 (d, $J = 10.9$ Hz, 1H), 2.92 (ddd, $J = 9.5, 13.1$ Hz, 1H), 2.55 (td, $J = 9.0, 16.4$ Hz, 1H), 2.49–2.39 (m, 2H), 2.31 (dq, $J = 5.4, 11.8$ Hz, 1H), 2.20 (t, $J = 4.3$ Hz, 1H), 2.17 (dd, $J = 4.4, 12.9$ Hz, 1H), 2.14–2.09 (m, 1H), 2.05–1.94 (m, 1H), 1.92–1.83 (m, 1H), 1.70–1.63 (m, 1H), 1.62–1.50 (m, 4H), 1.31 (d, $J = 16.1$ Hz, 1H), 1.20 (td, $J = 3.2, 13.2$ Hz, 1H), 0.99 (d, $J = 14.2$)

$^{142}$The hydrobromide salt of 39 was prepared from 39 via the following procedure: two drops of HBr (48 wt% in water) was added to a solution of 39 (1.4 mg) in CH$_2$Cl$_2$. The resulting suspension was concentrated in vacuo and the resultant solid was recrystallized from MeOH (single drop) and acetone (300 µL). This protocol provided crystals of the hydrobromide salt of 39 that were suitable for X-ray diffraction analysis.
6.7 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 67.8, 56.4, 52.0, 45.4, 45.4, 41.1, 39.9, 36.0, 35.8, 34.3, 33.2, 29.7, 24.6, 22.6, 19.9, 15.7. FTIR (thin film) cm$^{-1}$: 3349, 2951, 2924, 2581, 1579, 1456, 1399, 1062, 1052. HRMS (ESI) (m/z) calc’d for C$_{16}$H$_{26}$NO [M+H]$^+$: 248.2009, found 248.2021. $[\alpha]_D^{22}$: −19 (c = 0.14, MeOH). M.p.: 236–238 °C.$^{143}$ TLC (80:18:2 CHCl$_3$:MeOH:NH$_4$OH), R$_f$: 0.18 (KMnO$_4$).

$^{143}$ The reported melting point for lycopersic acid (39) is 239–241 °C.
**N-Boc-2-pyrrolidinone S16:**

Acrylonitrile (150 µL, 2.27 mmol, 3.00 equiv) and n-Bu₄NOH•30H₂O (61.0 mg, 0.0757 mmol, 0.10 equiv) were added sequentially to a stirred solution of β-carboxyimide 66 (375 mg, 0.757 mmol, 1.00 equiv) in MeCN (19 mL) at 0 ºC. After 5 min, the reaction was allowed to warm to room temperature and was stirred for 2 h, at which point water (10 mL), Et₂O (15 mL), and EtOAc (10 mL) were added sequentially. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous MgSO₄, and concentrated under reduced pressure to afford alkylated imide 200, which was carried forward to the next step without further purification.

A solution of TBAF in THF (1.00 M, 757 µL, 0.757 mmol, 1.00 equiv) was added to a solution of crude 200 and DBU (28.0 µL, 0.189 mmol, 0.25 equiv) in THF (15 mL) at room temperature. After 5 min, the reaction was heated to 50 ºC and was stirred for 15 h, at which point water (10 mL), Et₂O (15 mL), and EtOAc (10 mL) were added successively. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (30 mL), then dried over anhydrous MgSO₄ and concentrated under reduced pressure. The resultant residue was purified by flash column chromatography (silica gel, eluent: gradient: 2:1 → 1:1 hexanes:EtOAc, 1% Et₃N) to afford N-Boc-2-pyrrolidinone S16 (239 mg, 78% over 2 steps) as a >14:1 mixture of diastereomers at C4 and as a white flocculent solid.

**1H NMR** (600 MHz, C₆D₆, major C4-epimer reported) δ: 5.38 (d, J = 4.1 Hz, 1H), 3.74 (dd, J = 7.6, 10.9 Hz, 1H), 3.56–3.51 (m, 1 H), 3.49–3.45 (m, 1H), 3.44–3.37 (m, 2H), 2.85 (dd, J = 8.8, 10.9 Hz, 1H), 2.20 (td, J = 8.1, 16.7 Hz, 1H), 2.11 (dd, J = 4.7, 14.1 Hz, 1H), 1.97 (td, J = 6.4, 16.9 Hz, 1H), 1.92–1.86 (m, 1H), 1.82 (td, J = 5.3, 10.3 Hz, 1H), 1.78–1.63 (m, 4H), 1.47 (s, 9H), 1.46–1.40 (m,
1H), 1.39–1.29 (m, 2H), 1.25 (t, J = 12.9 Hz, 1H), 0.79 (d, J = 6.7 Hz, 3H). \(^{13}\text{C NMR}\) (126 MHz, C\(_6\)D\(_6\), major C4-epimer reported) δ: 173.7, 151.3, 135.3, 131.6, 119.7, 108.6, 82.5, 65.6, 64.4, 50.4, 48.0, 42.5, 36.2, 34.5, 34.4, 28.5, 28.0, 26.2, 21.9, 14.9. \(\text{FTIR}\) (thin film) cm\(^{-1}\): 2951, 2930, 1782, 1744, 1714, 1368, 1314, 1157, 1125, 967. \(\text{HRMS}\) (ESI) \((m/z)\) calc’d for C\(_{22}\)H\(_{32}\)N\(_2\)NaO\(_5\) [M+Na]\(^{+}\): 427.2203, found 427.2203. \(\text{TLC}\) (1:1 hexanes:EtOAc), \(R_f\): 0.48 (Anis).
**N-2-Nitrobenzenesulfonyl-2-pyrrolidinone 202:**

Mg(ClO₄)₂ (18.5 mg, 0.0830 mmol, 0.20 equiv) was added as a single portion to a stirred solution of N-Boc-2-pyrrolidinone S16 (168 mg, 0.415 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 1 mL), in MeCN (6.9 mL) at room temperature. The resultant mixture was heated to 60 °C and stirred for 4 h, at which point it was cooled to room temperature and Et₂O (10 mL) and saturated aqueous NH₄Cl solution (10 mL) were added sequentially. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (20 mL), then dried over anhydrous MgSO₄ and concentrated under reduced pressure to afford crude 2-pyrrolidinone 201 as a white flocculent solid, which was carried forward to the next step without further purification.

A solution of freshly prepared LiHMDS in THF (1.00 M, 610 µL, 0.610 mmol, 1.20 equiv) was added to a solution of 201, which was azeotropically dried with benzene (5 × 1 mL), in THF (5 mL) at room temperature. After 1 h, the reaction was cooled to 0 °C and a solution of NsCl in THF (1.00 M, 661 µL, 0.661 mmol, 1.30 equiv) was added dropwise. After 5 min, the reaction was allowed to warm to room temperature and stirred for 2 h, at which point saturated aqueous NH₄Cl solution (5 mL) and Et₂O (5 mL) were added sequentially. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The organic layers were combined, washed with brine (15 mL), then dried over anhydrous MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient: 4:1 → 2:1 → 1:1 hexanes:EtOAc, 1% Et₃N) to afford N-2-nitrobenzenesulfonyl-2-pyrrolidinone 202 (158 mg, 64% over 2 steps) as a white flocculent solid.
$^1$H NMR (600 MHz, C$_6$D$_6$) δ: 8.41 (dd, $J = 1.3$, 8.1 Hz, 1H), 6.72 (dd, $J = 1.2$, 7.9 Hz, 1H), 6.64 (dt, $J = 1.3$, 7.8 Hz, 1H), 6.44 (dt, $J = 1.3$, 7.7 Hz, 1H), 5.45 (d, $J = 3.2$ Hz, 1H), 4.16 (dd, $J = 7.9$, 10.0 Hz, 1H), 3.63–3.58 (m, 1H), 3.57–3.52 (m, 1H), 3.49–3.43 (m, 2H), 3.32 (dd, $J = 8.5$, 10.0 Hz, 1H), 2.20–2.13 (m, 1H), 2.12–2.05 (m, 1H), 1.94–1.87 (m, 2H), 1.85 (dd, $J = 5.6$, 7.9 Hz, 1H), 1.83–1.78 (m, 1H), 1.75 (dd, $J = 8.7$, 13.9 Hz, 1H), 1.73–1.68 (m, 2H), 1.46–1.39 (m, 1H), 1.33–1.26 (m, 1H), 1.23 (t, $J = 12.9$ Hz, 1H), 1.20–1.14 (m, 1H), 0.79 (d, $J = 6.7$ Hz, 3H). $^{13}$C NMR (126 MHz, C$_6$D$_6$) δ: 175.0, 134.9, 134.8, 134.7, 132.5, 131.8, 127.9, 127.7, 124.1, 119.2, 108.5, 65.6, 64.4, 51.4, 47.4, 42.4, 38.0, 34.5, 34.3, 28.0, 25.8, 21.9, 14.6. FTIR (thin film) cm$^{-1}$: 2952, 2910, 1733, 1543, 1367, 1174, 1128, 1046, 966, 594. HRMS (ESI) (m/z) calc’d for C$_{23}$H$_{27}$N$_3$NaO$_7$S [M+Na]$^+$: 512.1462, found 512.1463. TLC (1:1 hexanes:EtOAc), $R_f$: 0.38 (Anis).
A solution of $n$-butyllithium in hexanes (2.53 M, 414 µL, 1.05 mmol, 3.00 equiv) was added dropwise to a stirred solution of diisopropylamine (161 µL, 1.15 mmol, 3.30 equiv) in THF (2 mL) at −78 °C. The reaction was allowed to stir for 10 min, at which point it was warmed to 0 °C. After 10 min, the reaction was warmed to room temperature. The solution was recooled to −78 °C after 10 min. $t$-Butylacetate (140 µL, 1.05 mmol, 3.00 equiv) was then added dropwise to the reaction mixture. After 1 h, a solution of 202 (171 mg, 0.349 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 1 mL), in THF (4.3 mL) was added dropwise down the walls of the reaction vessel. After stirring at −78 °C for 3 h, saturated aqueous NH$_4$Cl solution (10 mL) was added to the deep red reaction mixture at −78 °C. The resultant mixture was then allowed to warm to room temperature. Et$_2$O (10 mL) and EtOAc (10 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (30 mL), then dried over anhydrous MgSO$_4$ and concentrated under reduced pressure to afford crude β-ketoester S17 as a pale yellow flocculent solid, which was carried forward to the next step without further purification.

10% aqueous HCl (775 µL) was added dropwise to a stirred solution of crude S17 in THF (6.2 mL) at room temperature. After 1 h, a saturated aqueous NaHCO$_3$ solution (10 mL) was added, followed by Et$_2$O (10 mL), EtOAc (10 mL), and water (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (30 mL), then dried over anhydrous MgSO$_4$ and concentrated under reduced pressure to afford crude enone 203 as a yellow flocculent solid, which was carried forward to the next step without further purification.
Imine 204:

K$_2$CO$_3$ (241 mg, 1.75 mmol, 5.00 equiv) was added as a single portion to a stirred solution of crude enone 203, which was azeotropically dried with benzene (5 × 1 mL), in DMF (5.8 mL) at room temperature and stirred for 13 h, at which point the suspension was then cooled to 0 °C and PhSH (90.0 µL, 0.873 mmol, 2.50 equiv) was added dropwise via syringe. After 5 min, the reaction was warmed to room temperature and stirred for an additional 10 h, at which point water (10 mL), Et$_2$O (10 mL), and EtOAc (10 mL) were added sequentially. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine (30 mL), dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. The crude residue was then purified by flash column chromatography (silica gel, eluent: gradient: 2:1 → 1:1 → 0:1 hexanes:EtOAc, 1% Et$_3$N → 90:9:1 CHCl$_3$:MeOH:NH$_4$OH) to afford imine 204 (79.5 mg, 63% over 3 steps) as a >3:1 mixture of diastereomers at C4 and as a pale yellow flocculent solid.

$^1$H NMR (600 MHz, C$_6$D$_6$, major C4-epimer reported) δ: 3.62 (dd, $J = 2.3$, 17.9 Hz, 1H), 3.40 (d, $J = 3.5$ Hz, 1H), 3.06–3.00 (m, 1H), 2.83 (td, $J = 3.8$, 8.0 Hz, 1H), 2.61 (td, $J = 4.7$, 9.2 Hz, 1H), 2.46 (ddd, $J = 2.2$, 4.0, 12.8 Hz, 1H), 2.02 (tdd, $J = 6.6$, 9.2, 13.7 Hz, 1H), 1.92–1.83 (m, 1H), 1.77 (ddd, $J = 2.1$, 5.2, 7.4 Hz, 1H), 1.68–1.63 (m, 2H), 1.61–1.57 (m, 1H), 1.52–1.46 (m, 2H), 1.36 (s, 9H), 1.35–1.32 (m, 1H), 1.25–1.21 (m, 1H), 1.13–1.04 (m, 2H), 0.60 (d, $J = 6.5$ Hz, 3H). $^{13}$C NMR (126 MHz, C$_6$D$_6$, major C4-epimer reported) δ: 204.7, 170.1, 169.5, 119.9, 83.0, 66.3, 53.2, 48.8, 48.2, 43.5, 39.0, 38.0, 32.7, 29.9, 29.7, 28.4, 28.2, 26.4, 22.5, 15.4. FTIR (thin film) cm$^{-1}$: 2947, 2927, 2869, 1735, 1670, 1368, 1249, 1152. HRMS (ESI) (m/z) calc’d for C$_{21}$H$_{30}$N$_2$NaO$_3$ [M+Na]$^+$: 381.2149, found 381.2150. TLC (90:9:1 CHCl$_3$:MeOH:NH$_4$OH), R$_f$: 0.45 (KMnO$_4$).
Amine 207:

NaBH(OAc)$_3$ (99.0 mg, 0.444 mmol, 2.00 equiv) was added as a single portion to a stirred solution of imine 204, which was azeotropically dried with benzene (5 × 0.5 mL), and AcOH (15.2 µL, 0.266 mmol, 1.20 equiv) in CH$_2$Cl$_2$ (4.4 mL) at 0 °C. After 5 min, the reaction was warmed to room temperature and stirred for 3.5 h. Additional NaBH(OAc)$_3$ (50.0 mg, 0.222 mmol, 1.00 equiv) and AcOH (7.6 µL, 0.13 mmol, 0.60 equiv) were added and the reaction was stirred for 5 h, at which point a 1 M NaOH aqueous solution (5 mL) and CHCl$_3$ (10 mL) were added sequentially. The layers were separated and the aqueous layer was extracted with CHCl$_3$ (3 × 5 mL). The organic layers were combined, dried over anhydrous MgSO$_4$, and concentrated under reduced pressure to afford crude amine 206, which was carried forward to the next step without further purification.

Trifluoroacetic acid (3.7 mL) was added to a stirred solution of crude amine 206 in CH$_2$Cl$_2$ (3.7 mL) at room temperature. After stirring for 17 h, the reaction was concentrated in vacuo. The crude residue was then purified by flash column chromatography (silica gel, eluent: 90:9:1 CHCl$_3$:MeOH:NH$_4$OH) to afford amine 207 (34.1 mg, 59% over 2 steps) as a pale yellow solid.

$^1$H NMR (500 MHz, C$_6$D$_6$) δ: 3.46 (dd, $J = 10.0$, 12.2 Hz, 1H), 2.47 (d, $J = 12.0$ Hz, 1H), 2.38–2.30 (m, 1H), 2.21 (td, $J = 5.3$, 10.7 Hz, 1H), 2.14 (dd, $J = 3.5$, 12.1 Hz, 1H), 2.10–2.03 (m, 1H), 1.80–1.69 (m, 3H), 1.69–1.63 (m, 2H), 1.51 (td, $J = 5.9$, 14.1 Hz, 1H), 1.40–1.31 (m, 2H), 1.24–1.18 (m, 1H), 1.18–1.12 (m, 2H), 1.11–1.02 (m, 1H), 0.91 (dtd, $J = 4.1$, 12.8, 16.4 Hz, 2H), 0.74 (d, $J = 6.6$ Hz, 3H).

$^{13}$C NMR (126 MHz, C$_6$D$_6$) δ: 211.1, 119.7, 57.6, 56.4, 49.4, 48.4, 48.3, 43.5, 42.7, 37.3, 35.6, 32.2, 26.5, 23.0, 21.7, 15.8. FTIR (thin film) cm$^{-1}$: 3335, 2946, 2912, 2870, 1691, 1454, 1445, 1430, 1085. HRMS (ESI) (m/z) calc’d for C$_{16}$H$_{25}$N$_2$O [M+H]$^+$: 261.1961, found 261.1963. TLC (80:18:2 CHCl$_3$:MeOH:NH$_4$OH), $R_f$: 0.70 (KMnO$_4$, UV).

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Tertiary amine 208:

A solution of freshly prepared LiHMDS in THF (1.00 M, 170 µL, 0.171 mmol, 3.00 equiv) was added to a solution of 207 (14.8 mg, 0.0568 mmol, 1.00 equiv), which was azeotropically dried with benzene (5 × 1 mL), in THF (1.5 mL) at −78 °C. After 2 h, a freshly prepared solution of iodine in THF (1.00 M, 170 µL, 0.171 mmol, 3.00 equiv) was added dropwise to the stirred reaction mixture. After stirring for 1 h at −78 °C, the reaction was allowed to warm to 0 °C and was stirred for an additional 2 h, at which point water (0.5 mL), a saturated aqueous NaHSO₃ solution (1 mL), a 1 M NaOH aqueous solution (until pH > 10), and CHCl₃ (2 mL) were added sequentially. The layers were separated and the aqueous layer was extracted with CHCl₃ (3 × 2 mL). The organic layers were combined, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluent: gradient: 2:1 → 1:1 → 0:1 hexanes:EtOAc, 1% Et₃N → 90:9:1 CHCl₃:MeOH:NH₄OH) to afford tertiary amine 208 (10.7 mg, 73%) as a > 9:1 mixture of diastereomers at C4 and as a pale yellow oil.

**¹H NMR** (500 MHz, C₆D₆, major C4-epimer reported) δ: 3.58 (s, 1H), 2.65 (d, J = 1.7 Hz, 1H), 2.56 (s, 1H), 1.99 (t, J = 6.7 Hz, 1H), 1.90 (d, J = 4.1 Hz, 1H), 1.85–1.79 (m, 1H), 1.79–1.76 (m, 1H), 1.77–1.72 (m, 1H), 1.66–1.59 (m, 3H), 1.59–1.52 (m, 2H), 1.34–1.29 (m, 1H), 1.28 (t, J = 3.0 Hz, 1H), 1.23 (d, J = 2.7 Hz, 1H), 1.21–1.18 (m, 1H), 0.96 (dd, J = 2.1, 4.0 Hz, 1H), 0.71 (d, J = 0.7 Hz, 1H), 0.68 (d, J = 6.6 Hz, 3H). **¹³C NMR** (126 MHz, C₆D₆, major C4-epimer reported) δ: 213.1, 119.5, 73.8, 70.8, 56.7, 51.2, 46.8, 46.0, 41.0, 39.9, 38.3, 33.3, 26.9, 25.2, 22.4, 15.5. **FTIR** (thin film) cm⁻¹: 2924, 2880, 2007, 1705, 1453. **HRMS** (ESI) (m/z) calc’d for C₁₆H₂₂N₂NaO [M+Na]⁺: 281.1624, found 281.1624. **TLC** (90:9:1 CHCl₃:MeOH:NH₄OH), Rᶠ: 0.22 (KMnO₄).
(−)-Lyconadin B (32):

A solution of NH₃ in MeOH (7.00 M, 2 mL) was added to tertiary amine 208 (10.7 mg, 0.0414 mmol, 1.00 equiv). The resultant solution was heated to 120 °C and stirred for 3 d, at which point it was cooled to room temperature and concentrated under reduced pressure. The crude residue was then purified by preparatory thin-layer chromatography (silica gel, eluent: 85:13.5:1.5 CHCl₃:MeOH:NH₄OH) to afford (−)-lyconadin B (32) (6.1 mg, 57%) as a white solid.

$^1$H NMR (600 MHz, CD₃OD) δ: 3.50 (s, 1H), 3.31 (s, 1H), 3.29 (dd, $J = 3.2$, 12.0 Hz, 1H), 2.86 (d, $J = 12.3$ Hz, 1H), 2.54–2.43 (m, 2H), 2.43–2.32 (m, 2H), 2.27 (d, $J = 5.0$ Hz, 1H), 2.15–2.11 (m, 1H), 2.00–1.94 (m, 2H), 1.93 (dd, $J = 3.7$, 5.7 Hz, 1H), 1.89–1.82 (m, 1H), 1.79–1.72 (m, 1H), 1.70 (d, $J = 13.5$ Hz, 1H), 1.07 (ddd, $J = 2.1$, 12.1, 13.7 Hz, 1H), 0.95 (t, $J = 13.2$ Hz, 1H), 0.90 (d, $J = 6.5$ Hz, 3H). $^{13}$C NMR (126 MHz, CD₃OD) δ: 173.2, 135.2, 120.7, 73.0, 63.9, 61.6, 49.5, 48.5, 40.6, 40.4, 34.3, 33.0, 31.4, 26.1, 24.9, 22.0. FTIR (thin film) cm⁻¹: 3403, 3205, 2946, 2923, 2849, 1672, 1372. HRMS (ESI) (m/z) calc’d for C₁₆H₂₃N₂O [M+H]$^+$: 259.1805, found 259.1810. $[^{[a]}]D^{21} = −102$ (c = 0.5, MeOH).$^{144}$ TLC (80:18:2 CHCl₃:MeOH:NH₄OH), $R_f$: 0.33 (KMnO₄, UV).

$^{144}$ The specific rotation reported for (−)-lyconadin B (32), which is contaminated with impurities, is $[^{[a]}]D^{23} = −66$ (c = 0.5, MeOH).
Table S3. $^1$H NMR Data Comparison Between Natural and Synthetic (−)-Lyconadin B (32) in CD$_3$OD.

<table>
<thead>
<tr>
<th>Isolation Report$^{[22b]}$ ($^1$H, 600 MHz, CD$_3$OD)</th>
<th>Synthetic (−)-Lyconadin B (32) ($^1$H, 600 MHz, CD$_3$OD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.89 (d, $J = 6.5$ Hz, 3H)</td>
<td>0.90 (d, $J = 6.5$ Hz, 3H)</td>
</tr>
<tr>
<td>0.94 (t, $J = 13.2$ Hz, 1H)</td>
<td>0.95 (t, $J = 13.2$ Hz, 1H)</td>
</tr>
<tr>
<td>1.04 (ddd, $J = 2.4$, 12.6, 12.6 Hz, 1H)</td>
<td>1.07 (ddd, $J = 2.1$, 12.1, 13.7 Hz, 1H)</td>
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<tr>
<td>1.68 (d, $J = 13.5$ Hz, 1H)</td>
<td>1.70 (d, $J = 13.5$ Hz, 1H)</td>
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<td>1.74 (m, 1H)</td>
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<tr>
<td>1.84 (m, 1H)</td>
<td>1.89–1.82 (m, 1H)</td>
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<tr>
<td>1.89 (s, 1H)</td>
<td>1.93 (dd, $J = 3.7$, 5.7 Hz, 1H)</td>
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<td>1.95 (m, 2H)</td>
<td>2.00–1.94 (m, 2H)</td>
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<tr>
<td>2.10 (m, 1H)</td>
<td>2.15–2.11 (m, 1H)</td>
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<td>2.25 (d, $J = 4.8$ Hz, 1H)</td>
<td>2.27 (d, $J = 5.0$ Hz, 1H)</td>
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<td>2.37 (m, 2H)</td>
<td>2.43–2.32 (m, 2H)</td>
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<tr>
<td>2.47 (m, 2H)</td>
<td>2.54–2.43 (m, 2H)</td>
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<tr>
<td>2.83 (d, $J = 12.0$ Hz, 1H)</td>
<td>2.86 (d, $J = 12.3$ Hz, 1H)</td>
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<td>3.25 (m, 1H)</td>
<td>3.29 (dd, $J = 3.2$, 12.0 Hz, 1H)</td>
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<tr>
<td>3.26 (d, $J = 3.1$ Hz, 1H)</td>
<td>3.31 (s, 1H)</td>
</tr>
<tr>
<td>3.45 (s, 1H)</td>
<td>3.50 (s, 1H)</td>
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Figure S6. Comparison of $^1$H NMR Spectra of Natural and Synthetic (−)-Lyconadin B (32) in CD$_3$OD.
Table S4. $^{13}$C NMR Data Comparison Between Natural and Synthetic (−)-Lyconadin B (32) in CD$_3$OD.

<table>
<thead>
<tr>
<th>Isolation Report$^{13}$C (13C, 126 MHz, CD$_3$OD)</th>
<th>Synthetic (−)-Lyconadin B (32) $^{13}$C (13C, 126 MHz, CD$_3$OD)</th>
</tr>
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<tbody>
<tr>
<td>22.1</td>
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<td>173.3</td>
<td>173.2</td>
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</tbody>
</table>
Figure S7. Comparison of $^{13}$C NMR Spectra of Natural and Synthetic (−)-Lyconadin B (32) in CD$_3$OD.
(+)-Lyconadin A (31):

Lyconadin B (32) was heated neat under an atmosphere of air at 160 °C for 25 h. The crude residue was then purified by flash column chromatography (silica gel, eluent: gradient: 90:9:1 → 80:18:2 CHCl₃:MeOH:NH₄OH) to afford (+)-lyconadin A (31) (1.8 mg, 57%) as a white solid.

1H NMR (600 MHz, CD₃OD) δ: 7.39 (d, J = 9.1 Hz, 1H), 6.32 (d, J = 8.8 Hz, 1H), 4.05 (s, 1H), 3.44 (dd, J = 2.9, 12.6 Hz, 1H), 3.38 (br. s., 1H), 2.79 (d, J = 12.3 Hz, 1H), 2.72 (br. s., 1H), 2.19 (d, J = 4.4 Hz, 1H), 2.12 (ddd, J = 3.5, 5.3, 13.5 Hz, 1H), 2.03–1.97 (m, 1H), 1.95 (br. s., 1H), 1.93–1.88 (m, 1H), 1.83 (dt, J = 6.0, 12.0 Hz, 1H), 1.69 (d, J = 14.1 Hz, 1H), 1.11 (t, J = 12.2 Hz, 1H), 1.01 (t, J = 12.5 Hz, 1H), 0.93 (d, J = 6.5 Hz, 3H). 13C NMR (126 MHz, CD₃OD) δ: 165.4, 149.3, 141.8, 126.3, 116.6, 72.6, 64.0, 61.7, 50.8, 48.1, 41.0, 40.5, 34.3, 33.8, 26.2, 22.0. FTIR (thin film) cm⁻¹: 3197, 2922, 2850, 1655, 1611, 1457, 947. HRMS (ESI) (m/z) calc’d for C₁₆H₂₁N₂O [M+H]+: 257.1648, found 257.1660. [a]D²²: +37 (c = 0.12, MeOH). TLC (80:18:2 CHCl₃:MeOH:NH₄OH), Rf : 0.33 (KMnO₄).
Table S5. $^1$H NMR Data Comparison Between Natural and Synthetic (+)-Lyconadin A (31) in CD$_3$OD.

<table>
<thead>
<tr>
<th>Isolation Report$^{12a}$ ($^1$H, 600 MHz, CD$_3$OD)</th>
<th>Synthetic (+)-Lyconadin A (31) ($^1$H, 600 MHz, CD$_3$OD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.95 (d, $J$ = 6.4 Hz, 3H)</td>
<td>0.93 (d, $J$ = 6.5 Hz, 3H)</td>
</tr>
<tr>
<td>1.05 (t, $J$ = 13.0 Hz, 1H)</td>
<td>1.01 (t, $J$ = 12.5 Hz, 1H)</td>
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<tr>
<td>1.18 (t, $J$ = 12.1 Hz, 1H)</td>
<td>1.11 (t, $J$ = 12.2 Hz, 1H)</td>
</tr>
<tr>
<td>1.74 (br. d., $J$ = 13.9 Hz, 1H)</td>
<td>1.69 (d, $J$ = 14.1 Hz, 1H)</td>
</tr>
<tr>
<td>1.86 (m, 1H)</td>
<td>1.83 (dt, $J$ = 6.0, 12.0 Hz, 1H)</td>
</tr>
<tr>
<td>1.94 (m, 1H)</td>
<td>1.93–1.88 (m, 1H)</td>
</tr>
<tr>
<td>2.04 (m, 1H)</td>
<td>1.95 (br. s., 1H)</td>
</tr>
<tr>
<td>2.07 (m, 1H)</td>
<td>2.03–1.97 (m, 1H)</td>
</tr>
<tr>
<td>2.14 (ddd, $J$ = 3.9, 5.6, 13.9 Hz, 1H)</td>
<td>2.12 (ddd, $J$ = 3.5, 5.3, 13.5 Hz, 1H)</td>
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<td>2.25 (br. d., $J$ = 4.4 Hz, 1H)</td>
<td>2.19 (d, $J$ = 4.4 Hz, 1H)</td>
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<td>2.81 (m, 1H)</td>
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<td>2.88 (d, $J$ = 13.7 Hz, 1H)</td>
<td>2.79 (d, $J$ = 12.3 Hz, 1H)</td>
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<td>3.54 (d, $J$ = 2.7 Hz, 1H)</td>
<td>3.38 (br. s., 1H)</td>
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<td>3.55 (dd, $J$ = 3.1, 13.7 Hz, 1H)</td>
<td>3.44 (dd, $J$ = 2.9, 12.6 Hz, 1H)</td>
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<tr>
<td>4.19 (br. s., 1H)</td>
<td>4.05 (s, 1H)</td>
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<td>7.39 (d, $J$ = 9.1 Hz, 1H)</td>
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Figure S8. Comparison of $^1$H NMR Spectra of Natural and Synthetic (+)-Lyconadin A (31) in CD$_3$OD.
Table S6. $^{13}$C NMR Data Comparison Between Natural and Synthetic (+)-Lyconadin A (31) in CD$_3$OD.

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<th>Isolation Report$^{12a}$ (13C, 126 MHz, CD$_3$OD)</th>
<th>Synthetic (+)-Lyconadin A (31) (13C, 126 MHz, CD$_3$OD)</th>
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<td>165.4</td>
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Figure S9. Comparison of $^{13}$C NMR Spectra of Natural and Synthetic (+)-Lycopadin A (31) in CD$_3$OD.
Appendix A

Chapter Two Catalog of $^1$H and $^{13}$C NMR Spectra
Chemical Shift (ppm)

BnO

OTBS

Et

163
epi-Lomaritichin B core

169
epi-lomaiviticin B core
Appendix B

Chapter Four Catalog of $^1$H and $^{13}$C NMR Spectra
Chemical Shift (ppm)

TIPSO

S3
Chemical Shift (ppm)

HN
O
Me
H
HO
TIPSO
Chemical Shift (ppm)
(-)-Himeradine A (38)
Chemical Shift (ppm)

Candidate

(-)-Himeradine A (188)
(-)-Himeradine A (188) Candidate
Appendix C

Chapter Five Supplementary Figures
Figure S10. X-Ray Crystal Structure of (−)-Lycopecurine (39).
X-Ray Crystallography: A crystal mounted on a diffractometer was collected data at 100 K. The intensities of the reflections were collected by means of a Bruker APEX II DUO CCD diffractometer (Cu$_\text{Kα}$ radiation, $\lambda=1.54178$ Å), and equipped with an Oxford Cryosystems nitrogen flow apparatus. The collection method involved 1.0° scans in $\omega$ at 30°, 55°, 80° and 115° in 2$\theta$. Data integration down to 0.84 Å resolution was carried out using SAINT V7.46 A (Bruker diffractometer, 2009) with reflection spot size optimisation. Absorption corrections were made with the program SADABS (Bruker diffractometer, 2009). The structure was solved by the direct methods procedure and refined by least-squares methods again $F^2$ using SHELXS-97 and SHELXL-97 (Sheldrick, 2008) with OLEX 2 interface (Dolomanov, et al., 2009). Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table 1, geometric parameters are shown in Table 2 and hydrogen-bond parameters are listed in Table 3. The Ortep plots produced with SHELXL-97 program, and the other drawings were produced with Accelrys DS Visualizer 2.0 (Accelrys, 2007).

Table S7. Experimental Details.

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\[
R_{\text{int}} \quad 0.039
\]
\[
\frac{\sin \theta}{\lambda}_{\text{max}} (\text{Å}^{-1}) \quad 0.595
\]

**Refinement**

\[ R(F^2 > 2\sigma(F^2)), wR(F^2), S \quad 0.016, 0.043, 1.09 \]

No. of reflections 2677

No. of parameters 181

H-atom treatment H atoms treated by a mixture of independent and constrained refinement

\[ \Delta \rho_{\text{max}}, \Delta \rho_{\text{min}} (\text{e Å}^{-3}) \quad 0.23, -0.30 \]


Absolute structure parameter -0.013 (12)

Computer programs: *APEX2* v2009.3.0 (Bruker-AXS, 2009), *SAINT* 7.46A (Bruker-AXS, 2009), *SHELXS97* (Sheldrick, 2008), *SHELXL97* (Sheldrick, 2008), Bruker *SHELXTL* (Sheldrick, 2008).

**Table S8.** Geometric parameters (Å, °).

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<td>C10—C11—C12—C13</td>
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<td>37.25 (15)</td>
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<td>N21—H21···Br1(^i)</td>
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Symmetry code(s):  (i) x, y+1, z.
Figure S11. Perspective views showing 50% probability displacement.
Figure S12. Three-dimensional supramolecular architecture viewed along the $a$-axis direction.
Appendix D

Chapter Five Catalog of $^1$H and $^{13}$C NMR Spectra
Lycopecurine (39)
Lyconadin B (32)
Lyconadin B (32)