Development of Enantioselective Synthetic Routes to (−)-Myrcin G and (−)-Euonyminol.

Martin Tomanik

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Abstract

Development of Enantioselective Synthetic Routes to (−)-Myrocin G and (−)-Euonyminol.

Martin Tomanik

2021

In the first chapter, I describe the development of a synthetic strategy towards (−)-myrocin G (8), the putative active form of the antiproliferative fungal metabolite (+)-myrocin C (4). Myrocin C (4) has been proposed to cross-link DNA by two-fold nucleotide addition; however, this proposed bioalkylation hypothesis has not been tested with native DNA. Our synthetic efforts provided a highly convergent total synthesis of myrocin G (8) in 15 steps from simple starting materials. A key steps in the sequence involved a carefully designed fragment coupling–cyclization cascade (see $85 + 89 \rightarrow 90$). This transformation effectively unites the iodocyclopropane 85 with the enoxysilane 89 to provide in a single step and in 38% yield the protected form of the target. Next, I present our preliminary biological activity studies of the diosphenol (−)-myrocin G (8) including DNA cleavage and DNA cross-linking studies. The data collected from these studies indicates that myrocins do not cross-link or cleave DNA and rather suggests an alternative mode of action potentially involving a protein target.

In the second chapter, I present the development of an enantioselective synthesis of the heavily oxidized sesquiterpenoid (−)-euonyminol (99). Euonyminol (99) is the
dihydro-β-agarofuran nucleus of the macrocyclic terpenoid alkaloids known as the cathedulins. This natural product is characterized by a tricyclic framework comprising of a trans-decalin fused to a tetrahydrofuran ring and by possessing nine free hydroxyl groups. Our synthetic route to access euonyminol features several highly diastereoselective transformations that were specifically designed to overcome problems encountered. For example, we developed a metal catalyzed [3+2] dipolar cycloaddition reaction provided the vinylogous carbonate 147 and simultaneously established the C9 oxidation and the C10 quaternary stereocenter, a tandem lactonization–epoxide opening to form the trans-C2–C3 vicinal diol residue, and a late-stage diastereoselective α-ketol rearrangement necessary for the syn-C8–C9 oxidation pattern. The body of work presented in this chapter may set the stage for synthesizing the macrocyclic cathedulin alkaloids, such as cathedulin E-4 (104).
Development of Enantioselective Synthetic Routes to (−)-Myrocin G and
(−)-Euonyminol.

A Dissertation
Presented to the Faculty of the Graduate School
Of
Yale University
In Candidacy for the Degree of
Doctor of Philosophy

by
Martin Tomanik

Dissertation Director: Professor Seth B. Herzon

December 2021
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Next, I would like to thank Christos Economou for a great friendship and for inviting me to work with him on the myrocin project. I learned a tremendous amount from working with you. I am thankful for our never ending conversations, arguments, and laughs while sharing the same fume-hood together.

A special thank you goes to Olivia Goethe for her unwavering support and kindness. I can’t thank you enough for your reassuring presence during the exciting “highs” but also the stressful “lows” while at Yale. I am truly lucky to have met you and I am looking forward to dragging you across the country.

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home for me. I look forward to seeing what you all accomplish in the lab and in your independent careers. I hope to keep in touch.

Lastly, I would like to thank my family, the Ceplikas family, and all my college friends for their constant support and for always being there for me. I cannot put it into words how much you all mean to me and I definitely could not have achieved any of this without your encouragement.
List of Abbreviations

A                        alpha, specific rotation
[α]                      optical rotation
Ac                       acetyl
Ac$_2$O                   acetic anhydride
AcOH                     acetic acid
Ag$_2$O                   silver(I)oxide
Al(CH$_3$)$_3$            trimethylaluminum
Alloc                    allyloxycarbonyl
AllocCl                  allyl chloroformate
β                         beta
Br                       bromide
Bn                       benzyl
BnBr                     benzyl bromide
Boc                      tert-butoxycarbonyl
°C                        degree celsius
CAM                      cerium ammonium molybdate
CAN                      ammonium cerium(IV) nitrate
CH$_3$                    methyl
CH$_3$CN                  acetonitrile
CH$_3$I                   iodomethane
CH$_3$Li•LiBr             methyl lithium-lithium bromide complex
<table>
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<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>CH₂N₂</td>
<td>diazomethane</td>
</tr>
<tr>
<td>CH₃OH</td>
<td>methanol</td>
</tr>
<tr>
<td>CH₃OTf</td>
<td>methyl trifluoromethanesulfonate</td>
</tr>
<tr>
<td>(CH₃)₃SOI</td>
<td>trimethylsulfoxonium iodide</td>
</tr>
<tr>
<td>Cis</td>
<td>on the same side</td>
</tr>
<tr>
<td>Cl</td>
<td>chloride</td>
</tr>
<tr>
<td>Cs₂CO₃</td>
<td>cesium carbonate</td>
</tr>
<tr>
<td>CsF</td>
<td>cesium fluoride</td>
</tr>
<tr>
<td>Cu[TBS]</td>
<td>bis(N-(tert-butyl)salicylaldiminato)copper(II)</td>
</tr>
<tr>
<td>D</td>
<td>doublet</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N’-dicyclohexylidimide</td>
</tr>
<tr>
<td>DIBAL</td>
<td>di-iso-butylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMDO</td>
<td>dimethyldioxirane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N’-dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric excess</td>
</tr>
<tr>
<td>E</td>
<td>entegen, across</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>et al.</td>
<td>et alii (“and others”)</td>
</tr>
</tbody>
</table>
ent enantiomer
Et₃N triethylamine
EtOAc ethyl acetate
EtOH ethanol
gem geminal
HATU 1-[bis(dimethylamino)0methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluoro-phosphate
HCl hydrochloric acid
HF•Et₃N hydrogen fluoride triethylamine complex
Hg(OTf)₂ mercury triflate
HMBC heteronuclear multiple bond correlation
HPLC high-performance liquid chromatography
HRMS high resolution mass spectrometry
HSQC heteronuclear single quantum coherence
Hz Hertz
i-Pr iso-propyl
i-Pr₂NEt di-iso-propylethyl amine
i-PrMgCl iso-propylmagnesium chloride
J coupling constant
kcal kilocalorie
K₂CO₃ potassium carbonate
K₂OsO₄ potassium osmate(IV)
LaCl₃•2LiCl lanthanum chloride lithium chloride complex
LiAlH₄  lithium aluminum hydride
LiBH₄  lithium borohydride
LiCl  lithium chloride
LDA  lithium di-iso-propylamide
LC/MS  liquid chromatography/mass spectrometry
M  multiplet
M  molar concentration
μM  micro molar concentration
m-CPBA  3-chloroperoxybenzoic acid
mg  milligram
MIC  minimum inhibitory concentration
mL  milliliter
μL  microliter
mmol  millimole
μmol  micromole
MMPP  magnesium monoperoxyphthalate
MOM  methoxymethyl
MOMCl  methoxymethyl chloride
MsCl  methanesulfonyl chloride
N  normal
n-BuLi  n-butyllithium
NaBH₄  sodium borohydride
NaH  sodium hydride
<table>
<thead>
<tr>
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<th>Description</th>
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<tr>
<td>NaOCH₃</td>
<td>sodium methoxide</td>
</tr>
<tr>
<td>NH₄Cl</td>
<td>ammonium chloride</td>
</tr>
<tr>
<td>NMO</td>
<td>N-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>NaOEt</td>
<td>sodium ethoxide</td>
</tr>
<tr>
<td>NaOt-Bu</td>
<td>sodium tert-butoxide</td>
</tr>
<tr>
<td>OTf</td>
<td>trifluoromethanesulfonate</td>
</tr>
<tr>
<td>O₃</td>
<td>ozone</td>
</tr>
<tr>
<td>PAA</td>
<td>para-anisaldehyde</td>
</tr>
<tr>
<td>Pb(OAc)₄</td>
<td>lead tetraacetate</td>
</tr>
<tr>
<td>Pd/BaSO₄</td>
<td>palladium on barium sulfate</td>
</tr>
<tr>
<td>Pd(OAc)₂</td>
<td>palladium(II) acetate</td>
</tr>
<tr>
<td>Pd(PPh₃)₃</td>
<td>palladium(0) tetrakis(triphenylphosphine)</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
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<td>toluene</td>
</tr>
<tr>
<td>PhSH</td>
<td>thiophenol</td>
</tr>
<tr>
<td>PPTS</td>
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</tr>
<tr>
<td>PTSA</td>
<td>para-toluenesulfonic acid</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>R</td>
<td>general alkyl substituent</td>
</tr>
<tr>
<td>Rf</td>
<td>retention factor</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
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</table>
SeO$_2$  selenium dioxide
Si(OTf)$_2$($t$-Bu)$_2$  di-$t$-butylsilyl ditrifluormethanesulfonate
T  temperature
$t$-BuOH  $t$-butanol
TBAF  tetra-$n$-butylammonium fluoride
TBS  $t$-butylsilyl
TBSCl  tert-butyl chloride
TBSOTf  tert-butyldimethylsilyl trifluoromethanesulfonate
TMU  tetramethylurea
TMSOTf  trimethylsilyl trifluoromethanesulfonate
TFA  trifluoroacetic acid
Tf$_2$O  trifluoromethanesulfonic anhydride
THF  tetrahydrofuran
TLC  thin-layer chromatography
TMS  trimethylsilyl
TMSCl  trimethylsilyl chloride
TMSE  2-trimethylsilylethyl
$trans$  across
UV  ultraviolet
v/v  volume/volume
Z  zusammen, on the same side
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Chapter 1.

Development of a convergent and enantioselective synthesis of (−)-myrocin G.
1.1 Introduction.

The myrocins (2–8) are a small family of bioactive secondary metabolites originally isolated from the soil fungus *Myrothecium verrucaria* in 1989 (Figure 1). At the time of their isolation, the myrocins were shown to possess moderate antibiotic activity against various Gram-positive bacteria, yeast, and fungi (MICs ~ 10–100 μg/mL). They were also shown to prolong life in mouse models of Ehrlich ascites carcinoma. Preliminary chemical reactivity studies conducted with a synthetic sample of (±)-myrocin C (4), by Chu-Moyer and Danishefsky lead to a hypothesis that the bioactivity of these natural products derives from cross-linking of DNA. In the sections that follow, I will first review the structural features of these isolates, their biological activities, and prior synthetic studies that guided our approach. I will then provide a detailed development of our convergent and enantioselective strategy towards this family of compounds that ultimately provided (−)-myrocin G (8), the putative biologically-active form of (+)-myrocin C (4). Finally, I will present our preliminary cytotoxicity and DNA cross-linking studies of 8 and various other related compounds.

![Structure of isopimaric acid (1) and the structures of myrocin A–G (2–8).](image-url)

**Figure 1.** Structure of isopimaric acid (1) and the structures of myrocin A–G (2–8).
1.2 **Structural features and biological activity of the myrocins.**

The myrocins belong to the pimarane family of diterpene natural products and are derived biosynthetically from isopimaric acid precursor (1, Figure 1). A common feature of the myrocins is an activated cyclopropane moiety. This distinguishing feature arises from a biosynthetic conversion of the angular C20 methyl group to the residing C1–C10–C20 electrophilic cyclopropane. Additionally, myrocins also possess a highly oxygenated central ring, three all-carbon quaternary stereocenters, and a range of oxidation levels at the C11 position. Collectively, all of the above mentioned structural features define the myrocins as challenging targets for total synthesis.

At the time of their isolation in 1989, Nakayama and co-workers found that (−)-myrocin B (2) and (+)-myrocin C (4) exhibited a moderate antibiotic activity against several Gram-positive bacteria, yeast, and fungi (examples of tested organisms included: *Bacillus subtilis, Bacillus brevis, Staphylococcus aureus, Penicillium chrysogenum, or Candida albicans*) with MICs ~ 10–100 μg/mL. Additionally, 2 and 4 showed a promising *in vivo* antitumor activity in mouse model of Ehrlich ascites carcinoma (prolongation rate, test/control: 130% for 2 at 1.6 mg/kg, 169% for 4 at 2.4 mg/kg). Although this therapeutic effect can be characterized as moderate, a detailed understating of the biological target, mechanism of action, and structure–activity relationship of the myrocins could lead to the identification of new compounds and targets for the treatment of cancer and bacterial infections. To the best of our knowledge, however, no further biological evaluation of these compounds have since been conducted.
1.3 Prior synthetic art of the myrocins.

1.3.1 Total Synthesis of (±)-myrocin C by Chu-Moyer and Danishefsky.

In 1993, Chu-Moyer and Danishefsky reported the first total synthesis of (±)-myrocin C (4).\textsuperscript{7,8} Their approach started with a Diels–Alder reaction between a 2-[(tert-butyldimethylsilyl)oxy]-1-methylcyclohexa-1,3-diene and \textit{p}-benzoquinone provided the cycloadduct 9 (94%, Scheme 1). This intermediate was then advanced to the mesylate 10 for a key cyclopropane forming reaction. In a key step, treatment of 10 with trimethylstannyl lithium provided the dienyl alcohol 12 (66%).

![Scheme 1](image)

Scheme 1. Total synthesis of (±)-myrocin C (4) by Chu-Moyer and Danishefsky.

This transformation is believed to occur via addition of the stannylolithium reagent to the terminal position of the 1,3-diene. Subsequent, displacement of the mesylate
substituent (3-\textit{exo}-tet cyclization) would provide the allyl stannane intermediate \textbf{11}. Subsequent elimination of the stannyl substituent with concomitant epoxide opening would then provide the product \textbf{12}. To construct the right most ring of the natural product, \textbf{12} was first condensed with (\textit{E})-3-methyl-4-oxo-2-butenoic acid (DCC, DMAP) to provide ester \textbf{13}. Subsequent intramolecular Diels–Alder reaction (toluene, 80 °C) then generated the endo-bis(lactone) \textbf{14} (79\%, two steps).

The intermediate 14 contains all of the carbon atoms of the target. The remaining steps of the synthesis focused on adjusting the oxidation state of central B-ring. To this end, bis(lactone) \textbf{14} was advanced to the epoxide \textbf{15} by a seven-step sequence. Treatment of the epoxide \textbf{15} with the aluminum thiolate of 4-methoxythiophenol resulted in the formation of the sulfide \textbf{16} via a site selective opening of the C8–C9 epoxide. Subsequent selective oxidation of the thioether moiety with DMDO initially formed the sulfoxide that under the reaction conditions underwent [2,3]-elimination to generate the (±)-desoxymyrcin C (\textbf{17}, 55\% from \textbf{15}). Finally, (±)-desoxymyrcin C (\textbf{17}) was converted to (±)-myrcin C via a diastereoselective α-hydroxylation–reduction reaction (KO\textsubscript{t}-Bu, O\textsubscript{2}, then triethyl phosphite; 68\%).

\textbf{1.3.2 Synthetic studies towards (±)-myrcin C by Aso and co-workers.}

In 1998, the Aso group reported a synthetic approach towards (±)-myrcin C (\textbf{4}). In their approach, the central B-ring of the target was prepared by a diastereoselective intramolecular Diels–Alder reaction.\textsuperscript{9} Their approach started with a known thioketal \textbf{18} that was advanced to the propionate ester \textbf{19} in seven steps and in 33\% overall yield
After some experimentation, the authors found that desired cycloaddition could be effected by heating 19 to 70 °C in tetrahydrofuran. Under these conditions, the intramolecular [4+2] cycloadduct 20 was obtained in 65% yield. The lactone 20 was elaborated to the allylic alcohol 21 in additional four steps and in 66% yield. Treatment of the allylic alcohol 21 with diethyl zinc and chloriodomethane resulted in exclusive formation of the cyclopropyl intermediate 22 in 74% yield possessing the wrong stereochemistry at C1–C10 junction. Unable to correct the stereochemical outcome, further studies towards the (+)-myrocin C (4) were suspended.

**Scheme 2.** Synthesis of the cyclopropane 22 by Aso and co-workers.

### 1.4 On the mechanism of action of the myrocins.

Following the synthesis of (±)-myrocin C (4), Chu-Moyer and Danishefsky treated synthetic 4 with thiophenol in the presence of triethylamine and observed the formation of the bis(sulfide) 25 (63%, Scheme 3A). The authors suggested that the bis(sulfide) 25 is formed via a 1,4-conjugate addition of the thiolate, followed by a E1cb elimination of the C9 hydroxyl substituent. A ring-opening isomerization of the 5-hydroxy-γ-lactone moiety to the corresponding diosphenol 24, followed by addition of a second equivalent of thiolate to the cyclopropane, would then provide the observed product. Not surprisingly, treatment
of the synthetic (±)-desoxymyrocin C (17) with identical reaction conditions provided the sulfide 26 in 63% as the sole product (Schem 3B).\textsuperscript{10} This result indicates the ring-opening to the diosphenol is necessary to active the cyclopropane for a second nucleophilic addition. Based on the observed reactivity, Chu-Moyer and Danishefsky postulated that myrocins might be capable of forming DNA cross-links via a sequential nucleotide addition.\textsuperscript{11,12}

Scheme 3. A. The mechanism proposed for the formation of the bis(sulfide) 25 by Chu-Moyer and Danishefsky. B. Formation of sulfide 26 from (±)-desoxymyrocin C (17).

Hoffmann and co-workers investigated the stability of the sensitive 5-hydroxy-γ-lactone substructure of the myrocins. The authors showed that the model system 27 underwent a ring-opening transformation to the corresponding disophenol 28 under mildly
acidic or basic conditions (Scheme 4A). This result, coupled with the isolation of (−)-myrocin A (2, Figure 1), the product of the ring-opening of (−)-myrocin B (3), lead us to hypothesize that the diosphenol (−)-myrocin G (8) is likely the biologically-active form of (+)-myrocin C (4), even though 8 has not been isolated from natural sources (Scheme 4B). Taken together, we reasoned that the order of bond forming events in the proposed bioalkylation mechanism might be reversed relative to that proposed by Chu-Moyer and Danishefsky. Specifically, an initial ring-opening isomerization of the 5-hydroxy-γ-lactone to the diosphenol is suggested to precedes the first thiol addition as is shown in Scheme 4B.

A. Studies on model system 27 by Hoffmann and co-workers show the sensitive nature of the 5-hydroxy-γ-lactone moiety.

B. Newly proposed bioalkylation mechanisms for the formation of the bis(sulfide) 25.
1.5 Development of a convergent and enantioselective synthetic route to (–)-myrocin G.

1.5.1 General synthetic strategy and retrosynthetic analysis of (–)-myrocin G.

Interested in the proposed DNA damaging activity of myrocins coupled with our own analysis of the potential bioalkylation mechanism, we initiated a research program to develop synthetic strategy capable of providing access to the diosphenol (–)-myrocin G (8) and other myrocin derivatives. Seeking to study the bioactivity of these molecules in detail after the synthesis, we desired to formulate a highly convergent and scalable synthesis capable of producing substantial quantities of the natural products.

Scheme 5. Retrosynthetic analyses to the diosphenol (–)-myrocin G (8).

Our retrosynthetic analysis of 8 is shown in Scheme 5. We envisioned accessing the target from the α-hydroxyketone 30 via an intramolecular aldol–dehydration reaction. The α-hydroxyketone 30 residue was anticipated to be accessible by homologation of the vinyl halide 31, followed by functionalization. Further simplification of 31 via a cleavage of the C1–C9 bond provides the cyclopropyl fragment 32 and the unsaturated ketone 33 as two precursors of similar complexity. Strategically, this disconnection allows for independent preparation of the two distal all-carbon quaternary stereocenters at C4 and C13, which would have been more challenging to do otherwise.
1.5.2 Synthesis of the myrocin G model system.

To expedite the development of the synthesis, we initiated our work with the model fragments (±)-37 and the achiral α-iodoenone 39 (Scheme 6). The preparation of the A-ring cyclopropyl fragment 37 began with a kinetic deprotonation of cyclohex-2-ene-1-one (34) with excess LiHMDS followed by a C-selective carboxylation with *N*-tert-butoxycarbonylimidazole and a subsequent second alkylation with iodomethane to provide the α-methyl-β-ketoester 35 (54%, Scheme 6A). Dehydroiodination under Johnson conditions (iodine, pyridine, 77%)\(^\text{16}\) and a Corey–Chaykovsky cyclopropanation\(^\text{17}\) then provided the corresponding iodocyclopropane 37 in 47% yield. The cyclopropanation proceeded with 2.4:1 diastereoselectivity and the relative stereochemistry of 37 was established by X-ray analysis. The model C-ring fragment was prepared in a single transformation from a commercially available 4,4-dimethylcyclohex-2-en-1-one (38) via a dehydroiodination to furnish 39 (iodine, pyridine, 88%, Scheme 6B).
Scheme 6. **A.** Synthesis of the racemic cyclopropyl iodide fragment 37. **B.** Synthesis of the model α-iodoenone 39.

We found that exposure of 37 to iso-propylmagnesium chloride–lithium chloride complex in toluene at cryogenic temperatures (−78 ºC), followed by addition of the α-iodoenone 39 and subsequent warming of the reaction mixture to 23 ºC generated the fragment coupled adduct 41 (87%, 7:1 dr, Scheme 7A). The complete relative stereochemistry of coupling adduct 41 was determined by X-ray crystallographic analysis (Scheme 7B). The same stereochemical preference was observed when the alkynyl electrophile 42 was employed, to provide (after desilylation with potassium carbonate in methanol) the enyne fragment coupling product 43 (81%, 7:1 dr two steps).
Scheme 7. A. Fragment coupling reaction to form 41 and 43. B. X-ray analysis of the vinyl iodide 41. C. Stereochemical model for highly diastereoselective fragment coupling transformation.

We rationalized the high degrees of stereochemical control in this fragment coupling with the model shown in Scheme 7C. If approach of the nucleophile occurs along the Bürgi–Dunitz trajectory, the relative exo-type orientation between the nucleophile 40 and the electrophile 39 shown would minimize the non-bonded interactions between the C4 quaternary stereocenter in the nucleophile 40 and the bulky C8 halogen in the electrophile 39, leading to the observed diastereomer. The alternative endo-type approach (not shown) is disfavored due to superposition of the steric bulk of the incoming nucleophile over the plane of the electrophile.

Having discovered a robust access to the fragment coupling adduct 41, the next steps of the synthesis of (−)-myrocin G (8) focused on introducing the appropriate two carbon synthon to the vinyl iodide handle to arrive at the retrosynthetically desired α-hydroxyketone 30 shown in Scheme 5. The tertiary hydroxyl in 41 was first protected as the corresponding trimethylsilyl ether (TMSCl, imidazole, 98%). However, subsequent lithiation of the vinyl iodide (n-butyllithium, −78 °C) followed by addition of the Weinreb amide 46 did not introduce the desired glycolic-acid synthon, but rather we obtained the vinyl silane 48 in 52% yield. Compound 48 arise from an unproductive retro–Brook rearrangement of the vinyl lithium intermediate 47 with the C9 trimethylsilyl group as is shown in Scheme 8. To circumvent this, the fragment coupling product 41 was converted to the methoxymethyl ether 49 (sodium iodide, chloromethyl methyl ether, N,N-diisopropylethylamine, 85%). However, lithium–halogen exchange (n-butyllithium)
followed by addition of the identical Weinreb amide 46 provided the cyclobutanol 51 (48%). These two results indicated to us that strategies relying on metalation and subsequent trapping will not be capable of introducing the desired two carbon synthon in place of the vinyl iodide handle.

**Scheme 8.** Synthesis of the vinyl silane 48 and cyclobutanol 51 from the fragment coupling adduct 41.

The next strategy pursued to arrive at the desired α-hydroxyketone moiety employed the alkyne intermediate 43. We envisioned the direct conversion of 43 to the α-hydroxyketone 30 via an oxidative hydration of the alkyne residue, as described by Kita and co-workers.²⁰ However, only the ketofuran 53 was obtained (38%) when the enyne 43 was subjected to the oxidative hydration conditions (bis(trifluoroacetoxy)iodobenzene, water). The ketofuran 53 may form by intramolecular displacement of the activated alkyne by the C9 hydroxyl, as shown is in Scheme 9. Attempted oxidative functionalization of the alkyne moiety with the C9 hydroxyl group protected did not provide the desired α-hydroxyketone group. Nevertheless, ketofuran 53 provided us with an opportunity to
attempt an annulation reaction to access the ring-closed scaffold. We found that treatment of 53 with sodium hydroxide in ethanol produced the aldol product 54 in 66% yield as a single detectable diastereomer (1H NMR analysis). The relative stereochemistry of 54 was established by nuclear Overhauser effect analysis, which showed a strong correlation between the C5 hydroxyl proton and the C20 cyclopropane proton (Scheme 9).

Scheme 9. Synthesis of the pentacycle 54 via the ketofuran 53.

A successful strategy to access the desired α-hydroxyketone was eventually realized via the following two step protocol (Scheme 20). First, a Stille cross-coupling between the fragment coupling product 41 and tributyl(1-ethoxyvinyl)tin [copper(I) iodide, tetrakis(triphenylphosphine)palladium(0), cesium fluoride] provided the ethyl vinyl ether intermediate 55 in 94% yield. This was followed by a dihydroxylation of the vinyl ether residue [potassium osmate(VI) dihydrate, 4-methylmorpholine N-oxide] to provide the sought-after α-hydroxyketone 56 in moderate yield of 41%. However, in contrast to our experience with the ketofuran 53, attempted ring-closures of 56 by aldol addition under numerous basic and acidic reaction conditions resulted only in decomposition without any of the desired aldol product detected (1H NMR analysis). We reasoned that the acidic protons in 56 were impeding the desired addition.
To address this, the α-hydroxyketone 56 was first subjected to a two-fold silylation with excess chlorotrimethylsilane and imidazole, followed by a selective hydrolysis of the unstable primary trimethylsilyl ether group (aqueous hydrochloric acid) to provide a C9 trimethylsilyl protected intermediate (not shown, Scheme 10). Ensuing exposure of the silyl ether to silver(I) oxide and iodomethane furnished the fully protected methyl ether intermediate 58 (85%, two steps). After much experimentation, we found that aldol addition product 60 was obtained in 74% yield by the treatment of the methyl ether 58 with sodium tert-butoxide in a mixture of tetrahydrofuran and tert-butanol. However, to our surprise this aldol addition reaction was accompanied by a transfer of the trimethylsilyl group from the C9 hydroxyl to the newly formed C5 alkoxide as is shown in Scheme 10. This unexpected result was rigorously confirmed using NMR spectroscopy, which revealed a strong nuclear Overhauser effect correlations between the C5 silyl ether
residue and the C18 methyl group as well as the C6 methine proton that is consistent with the stereochemical assignment shown in Scheme 10.

Intrigued by the trimethylsilyl group migration, we envisioned using this migration strategically to activate the C5 hydroxyl group towards an elimination, to generate the corresponding cyclodehydration product. To realize this approach, 60 was first treated with potassium bis(trimethylsilyl)amide and methyl chloroformate to arrive at the carbonate 61 (58%, Scheme 11). Subsequent removal of the trimethylsilyl substituent with tetrabutylammonium fluoride provided the free alcohol intermediate 62. Finally, exposure of 62 to excess 1,8-diazabicyclo[5.4.0]undec-7-ene at elevated temperatures of 100 ºC generated the cyclodehydration product 64 (71% from 61). We believe that this transformation occurs via a transient formation of the shown cyclic carbonate intermediate 63, which is poised to undergo a facile by β-elimination.

**Scheme 11.** Synthesis of cyclodehydrated product 64 from the aldol product 60.

Unfortunately, our extensive efforts to remove the methyl enol ether and the tert-butyl ester substituents of 64 under various strongly acidic or Lewis acidic condition were
uniformly unsuccessful. Consequently, at this point we decided to look for alternative protecting groups for the carboxylic acid and the diosphenol functional groups.

After a period of experimentation, we speculated if we could employ 2-(trimethylsilyl)ethyl as an alternative protecting group for the carboxylic acid moiety. Accordingly, the tert-butyl ester of 37 was cleanly cleaved by a treatment with trifluoracetic acid (Scheme 12). Subsequent esterification of the resulting carboxylate with 2-(trimethylsilyl)ethyl alcohol) using $N,N'$-dicyclohexylcarbodiimide and DMAP as promoters provided the new A-ring fragment 66 (99%, two steps). The fragment coupling of 66 with the iodoenone 39 proceeded as expected to furnish the 1,2-addition adduct 67 (80%, 8:1 dr).

![Scheme 12. Synthesis of the 1,2-addition product 67 possessing a 2-(trimethylsilyl)ethyl (TMSE) protecting group.](image)

We modified the preceding $\alpha$-hydroxyketone synthesis to improve material throughput. The Stille cross-coupling product was hydrolyzed by direct addition of aqueous hydrochloric acid to the unpurified product, to generate the methyl ketone 68 (70%). Ensuing treatment of the methyl ketone 68 with excess trimethylsilyl trifluoromethanesulfonate and triethylamine resulted in silylation of the ketone and C9 hydroxyl group (not shown). Rubottom oxidation$^{21}$ ($meta$-chloroperoxybenzoic acid) provided the trimethylsilyl protected $\alpha$-hydroxyketone 69 (70%, two steps).
Next, we substituted the previously discussed C6 methyl ether for an allyl carbonate (Alloc) group (allyl chloroformate, pyridine, 96%). We found that treatment of this compound with our previously described aldol conditions (sodium tert-butoxide) resulted in formation of the expected silane transfer product 73 as only the minor product (15%, Scheme 13, path A). Instead, the major product of this transformation was the diosphenol 75 (58%). We speculated that formation of the diosphenol 75 arises from the preferential migration of the Alloc group from the C6 primary alcohol to the newly-formed C5 alkoxide (Scheme 13, path B), to provide the carbonate 74. Formal 1,2-proton transfer and β-elimination would then generate the observed product 75.

**Scheme 13.** Synthesis of diosphenol 75 via an Alloc group transfer and β-elimination.
The mechanistic insight gained from the synthesis of the diosphenol 75 lead to us consider an alternative C-ring fragment that contains a masked enolate equivalent. We hypothesized that such fragment could allow us to conduct the fragment coupling and annulation steps into a single operation by strategic use of the migration events we had discovered. This type of thinking lead us to rationally design the enoxysilane fragment 78 (Scheme 14A). Preparation of this model fragment was accomplished in six transformations from 39. Ketalization of the ketone group (triethylorthoformate, ethylene glycol, para-toluenesulfonic acid), followed by lithium–halogen exchange (n-butyl lithium) and trapping with the Weinreb amide 46 provided the ketone 76 in 57% yield. Next, desilylation (TBAF), followed by installation of the allyl carbonate group (allyl chloroformate, pyridine), and ketal hydrolysis (aqueous hydrochloric acid) provided the diketone 77 (64%, three steps). Finally, to mask the acidic α-protons we employed a site-selective enoxysilane formation via a kinetic deprotonation of 77 with LiHMDS and trapping with TMSCl to arrive at the model fragment 78 exclusively as the Z-isomer (65%, $^1$H NMR analysis).
Scheme 14. A. Synthesis of the newly-designed C-ring fragment 78. B. Synthesis of 
(±)-myrocin G model (65) via a fragment coupling–cyclization cascade.

After some experimentation, it was found that exposure of the 66 to \( n \)-butyllithium at cryogenic temperatures (\( \sim -78 \) °C) followed by addition of the model enoxysilane fragment 78 and warming the reaction mixture to 0 °C over 3 h provided the annulation product 75 in 36% yield (Scheme 14B). The mechanism we proposed for this one step fragment coupling–cyclization cascade begins with a diastereoselective 1,2-addition of 79 to 78 to generate the alkoxide intermediate 80. Migration of the trimethylsilyl group from the C7
enoxysilane to the C9 alkoxide would reveal the masked enolate 81. This enolate is poised to undergo an intramolecular ring-closing aldol addition to the C5 ketone. Subsequent Alloc group transfer from the C6 to the C5 alcohol followed by β-elimination would generate the desired diosphenol product 75. This transformation is noteworthy as it accomplishes five discrete transformation in one flask and provides the fully annulated protected from of myrocin G in a single operation. Finally, the conversion of 75 to the myrocin G model 65 was accomplished via a global deprotection by treatment with excess TBAF in DMF (64%).

1.5.3 Synthesis of (−)-myrocin G (8).

With a route to the myrocin G model 65 established, we shifted our focus to synthesis of (−)-myrocin G (8) via the developed sequence. The A-ring fragment was prepared in an enantioenriched form from the known β-ketoester 82. Asymmetric Robinson annulation using acrolein diethyl acetal provide the unsaturated ketone 83 in 32% and in 92% ee. Subsequent Johnson dehydroiodination (iodine, pyridine) and Corey–Chaykovsky cyclopropanation gave the iodocyclopropane A-ring fragment 85 (62%, two steps). The electrophile C-ring fragment 89 was prepared in nine steps from the know Diels–Alder adduct 86. Wittig homologation of 86 (KHMDS, methyl triphenylphosphonium bromide) provided the olefin 89. A tandem hydrolysis of the enoxysilane and β-carbamate elimination (aqueous hydrochloric acid) revealed the α,β-unsaturated ketone moiety (not shown). Johnson dehydroiodination (iodine, pyridine) generated α-iodo ketone 88 (22%, three steps). The corresponding enoxysilane ether C-
ring fragment 89 was then prepared from 88 in additional six steps and in 19% yield as shown for the model system 78 in Scheme 15.

Scheme 15. A. Synthesis of the cyclopropyl A-ring fragment 85. B. Synthesis of the enoxysilane C-ring fragment 89.

The fragment coupling–cyclization cascade employing 85 and 89 proceeded as expected, to provide the diosphenol 90 (38%). Global deprotection (TBAF, DMF) then generated (−)-myrocin G (8) (64%).26,27 To test the mechanistic hypothesis discussed in the introduction section 1.4, we treated (−)-myrocin G (8) with thiophenol and triethylamine at 23 °C, as described by Chu-Moyer and Danishefsky for (±)-myrocin C (3). Under these conditions the bis(sulfide) 25 was obtained in 74% yield. The spectroscopic data precisely matched the bis(sulfide) 25 reported by Chu-Moyer and Danishefsky (see Table S1).10 It is important to note that based solely on this result, we cannot rule out the pathway originally proposed, however, the successful formation of 25 from 8 indicates that the alternate order of events as we proposed is viable.
1.5.4 Explored strategies for the conversion of (−)-myrocin G to (+)-myrocin C.

Even though our synthetic target from the onset of our work was the diosphenol (−)-myrocin G (8), we were highly interested in attempting to convert the (−)-myrocin G (8) to (+)-myrocin C (4) in order to gain synthetic access to both of the compounds. Extensive experimentation was initially spent trying to convert the model system 65 to 91 via exposure of 65 to various polar solvents, reaction temperatures, or mildly acidic conditions. Unfortunately, all of these attempts were met with failure and resulted only in isolation of various unidentified decomposition products (Scheme 17).22

As an alternative, we envisioned that we might be able to access the γ-hydroxylactone moiety by temporarily disrupting the intramolecular hydrogen bond formed between the C7 ketone and the enol as is shown in Scheme 17. To this end, 65 was first subjected to esterification with allyl alcohol (HATU, triethylamine). This was followed by conversion of the diosphenol hydroxyl group to a para-methoxybenzyl group ether (para-methoxybenzyl chloride, tetrabutylammonium iodide, and cesium carbonate) to provide the allyl ester 92 (59%, two steps). Next, a palladium(II) acetate mediated cleavage of the allyl ester liberated the free carboxylic acid 93 (68%). Unfortunately, another extensive screen of reaction conditions attempted to convert 93 to the γ-
hydroxylactone 94 were uniformly unsuccessful. In many cases, we observed an unproductive decarboxylation reaction via the diosphenol moiety 95 leading to a mixture of undesired products.

Scheme 17. Attempted conversion of the myrocin G model 65 to the myrocin C model 91 via synthesis of the free acid 93.

1.6 Biological evaluation of (−)-myrocin G and related analogues.

Our synthetic route to (−)-myrocin G (8) and related structures, such as the protected geminal dimethyl model system 75, enabled us to probe the mechanism of action of these compounds. We were specifically interested in evaluating the DNA cross-linking hypothesis advanced by Chu-Moyer and Danishefsky.10 The protected model system 75 was prepared as a racemate. We were able to obtain enantiopure (>99% ee) (+)-75 and (−)-75 by chiral stationary phase supercritical fluid chromatography, which was carried out by our collaborators at Merck Research Laboratories (Scheme 18A). Both of the
enantiomers were treated with excess TBAF in DMF to remove the protecting groups. The absolute stereochemistry of (−)-65 was determined by X-ray analysis. The resolved enantiomer (−)-65 was then advanced to the azide (−)-96 (Scheme 18B) and the corresponding alkyne (−)-97 (Scheme 18C). The same set of transformations was performed on (+)-90, to afford the azide (+)-96 and the alkyne (+)-97 (for the purposes of clarity, these transformation are not shown in Scheme 18).

Scheme 18. A. Separation of (±)-75 by chiral stationary phase supercritical chromatography to provide the (+)-75 and (−)-75. B. Synthesis of the enantiopure azide (−)-96. C. Synthesis of the enantiopure alkyne (−)-97.

We evaluated the cytotoxicities of our compounds against cervical (HeLa), colorectal (HCT116), leukemia (K562) and prostate (LNCaP) cancer cell lines using a CellTiter-Glo assay, which utilizes ATP production as an indicator of cell viability. The results are shown in Table 1.22 (−)-Myrocin G (8) showed low micromolar activity against the HeLa and K562 cell lines, but was less active against LNCaP and HCT116 cell lines.
To our surprise, we observed no significant differences between the potencies of the two separated enantiomers, suggesting their toxicity may derive from non-specific binding to protein and/or DNA. Both the amides bearing an alkyne or azide showed stronger activity compared to the corresponding carboxylic acid. We speculate that this could be due to decreased cellular uptake of the carboxylic acid, although additional studies are required to fully establish this.

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Table 1. IC₅₀ Values (in μM) of (−)-myrocin G (8), the geminal dimethyl analogs (−)-65 and (+)-65, the azido probes (−)-96 and (+)-96, and the alkynyl probes (−)-97 and (+)-97. Cell were treated with compounds for 72h. Tamoxifen (60 μM) was used as a positive control.

We then examined reactivity of our synthetic (−)-myrocin G (8) toward DNA. Circular pBR322 plasmid DNA was incubated with varying concentration of 8 for 16 h at 37 °C. The DNA was then analyzed by native gel electrophoresis and the results are shown in Figure 2. Disappointingly, we did not observe detectable levels of DNA nicking or cleavage with concentration of 8 up to 500 μM.
Figure 2. DNA plasmid cleavage assay employing circular pBR322 plasmid DNA and
(−)-myrocin G (8). 5% DMSO was used as vehicle (negative control), and linearized
pBR322 DNA was used as positive control. DNA ladder (Lane #1); 5% DMSO, pH 8.0
(Lane #2); 500 µM 8, pH 8.0 (Lane #3); 100 µM 8, pH 8.0 (Lane #4); 50 µM 8, pH 8.0
(Lane #5); 10 µM 8, pH 8.0 (Lane #6); 5 µM 8, pH 8.0 (Lane #7); 1 µM 8, pH 8.0 (Lane
#8); linearized pBR322 DNA (Lane #9). Conditions (Lane #2): circular pBR322 DNA
(15.2 µM in base pairs), 5% DMSO (vehicle), TE buffer (10 mM Tris, 1 mM EDTA, pH
8.0), 16 h, 37 ºC. Conditions (Lanes #3 – #8): circular pBR322 DNA (15.2 µM in base
pairs), 8 (500 µM–1 µM), 5% DMSO, TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0), 16
h, 37 ºC. The DNA was analyzed by native gel electrophoresis (90 V, 1.5 h).

Next, we evaluated the cross-linking capability of the pair of enantiomeric geminal
dimethyl derivatives (−)-65 and (+)-65 (Figure 3). We incubated the linearized pUC19
DNA with (−)-65 or (+)-65 (1–100 µM) for 16 h at 37 ºC and then analyzed the treated
DNA by denaturing gel electrophoresis. Under these conditions, we did not detect any
DNA cross-links using either (−)-65 or (+)-65. These studies suggest to us that DNA is
unlikely to be the primary biological target of myrocins and that an alternative mode of
action, potentially involving a protein target, could explain their antiproliferative activities. To date, we are actively investigating the biological target by collaborating with the Adibekian lab at Scripps Florida.

Figure 3. DNA cross-linking assay employing linear pUC19 DNA and myrocin analogs (−)-65 and (+)-65. 5% DMSO was used as a negative control. Cisplatin (100 μM) and methyl methanesulfonate (MMS, 500 μM) were used as positive controls for cross-linking and monoalkylation, respectively. DNA ladder (Lane #1); 5% DMSO (Lane #2); 100 μM cisplatin (Lane #3); 500 μM MMS (Lane #4), 100 μM (−)-65 (Lane #5); 10 μM (−)-65 (Lane #6); 1 μM (−)-65 (Lane #7); 100 μM (+)-65 (Lane #8); 10 μM (+)-65 (Lane #9); 1 μM (+)-65 (Lane #10). Conditions (Lane #2): linearized pUC19 DNA (15.4 μM in base pairs), 5% DMSO (vehicle), TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0), 16 h, 37 °C. Conditions (Lane #4): linearized pUC19 DNA (15.4 μM in base pairs), 5% DMSO (vehicle), 100 μM cisplatin, TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0), 16 h, 37 °C. Conditions (Lane #5): linearized pUC19 DNA (15.4 μM in base pairs), 5% DMSO (vehicle), 500 μM MMS, TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0), 16 h, 37 °C. Conditions (Lanes #5–#7): linearized pUC19 DNA (15.4 μM in base pairs), 5% DMSO (vehicle), 100 μM cisplatin, 100 μM MMS, 10 μM cisplatin, 100 μM MMS, TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0), 16 h, 37 °C. Conditions (Lanes #7–#10): linearized pUC19 DNA (15.4 μM in base pairs), 5% DMSO (vehicle), 100 μM cisplatin, 100 μM cisplatin, 500 μM MMS, TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0), 16 h, 37 °C.
base pairs), 5% DMSO (vehicle), (-)-65 (100 µM–1 µM), TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0), 16 h, 37 °C. Conditions (Lanes #8–#10): linearized pUC19 DNA (15.4 µM in base pairs), 5% DMSO (vehicle), (+)-65. (100 µM–1 µM), TE buffer (10 mM Tris, 1 mM EDTA, pH 8.0), 16 h, 37 °C. The DNA was analyzed by 0.4% NaOH denature agarose gel electrophoresis (90 V, 1.5 h).

1.7 Conclusion.

In summary, I have presented our work towards (−)-myrocin G (8), the putative active form of antitumor antibiotic (+)-myrocin C (4). I described the development of our synthetic strategy, which was guided by several failed approaches and attempts. This work ultimately resulted in the discovery of a complex stereoselective fragment coupling–cyclization cascade employing the iodocyclopropane 85 and the enoxysilane 89 as two precursors of similar complexity. This powerful reaction allowed us to synthesize the fully annulated protected form of (−)-myrocin G (8) in a single operation. I then described our synthetic efforts to convert the diosphenol moiety of (−)-myrocin G (8) to the γ-hydroxylactone present in (+)-myrocin C (4). Lastly, I detailed our preliminary biological activity studies, which suggest that DNA is not the primary biological target of myrocins. Efforts to identify their biological target are currently ongoing in collaboration with the Adibekian lab at Scripps Florida.
1.8 Experimental section.

1.8.1 General information.

**General experimental procedures.** All reactions were performed in single-neck, flame-dried, round-bottomed flasks fitted with rubber septa under a positive pressure of argon unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula, or were handled in a nitrogen-filled drybox (working oxygen level <10 ppm). Organic solutions were concentrated by rotary evaporation at 28–32 °C. Flash-column chromatography was performed as described by Still et al.,\textsuperscript{28} employing silica gel (SiliaFlash® P60, 60 Å, 40–63 μm particle size) purchased from SiliCycle (Québec, Canada). Analytical thin-layered chromatography (TLC) was performed using glass plates pre-coated with silica gel (250 μm, 60 Å pore size) impregnated with a fluorescent indicator (254 nm). Preparative thin-layered chromatography (PTLC) was performed using glass plates precoated with silica gel (250 μm, 60 Å pore size) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and/or submersion in aqueous ceric ammonium molybdate solution (CAM), para-anisaldehyde (PAA), or aqueous potassium permanganate solution (KMnO₄), followed by brief heating on a hot plate (120 °C, 10–15 s).

**Materials.** Commercial solvents and reagents were used as received with the following exceptions. Dichloromethane, diethyl ether (ether), N,N-dimethylformamide, tetrahydrofuran, and toluene were purified according to the method of Pangborn et al.\textsuperscript{29} Pyridine was distilled from calcium hydride under an atmosphere of nitrogen immediately prior to use. Triethylamine was distilled from calcium hydride under an atmosphere of
nitrogen immediately prior to use. \( N,N\)-Di-iso-propylethylamine was distilled from calcium hydride and stored under argon. Sodium tert- butoxide, sodium hydride, lithium bis(trimethylsilyl)amide, and potassium bis(trimethylsilyl)amide were stored and handled in a nitrogen-filled drybox. The molarities of \( n \)-butyllithium and iso-propylmagnesium chloride–lithium chloride complex solutions were determined using the method of Love et al.\(^{30}\) Trimethylsilyl trifluoromethanesulfonate was purified by vacuum transfer distillation and stored under argon at \(-20 \, ^\circ\text{C}\). Trimethylsulfoxonium iodide was recrystallized from water, rinsed with acetone, dried under vacuum in the presence of calcium sulfate, and stored in a desiccator with protection from light. 3-Chloroperoxybenzoic acid (mCPBA) was recrystallized from dichloromethane and stored at \(-20 \, ^\circ\text{C}\). Chlorotrimethylsilane was distilled from calcium hydride and stored under argon. Compounds iodoenone \( 39^{31} \), the Weinreb amide \( 46^{19} \), the amine catalyst \( \text{S9}^{24} \), \( \beta \)-ketoester \( 82^{23} \), Diels–Alder adduct \( 86^{25} \) were prepared according to published procedures.

**Instrumentation.** Proton nuclear magnetic resonance (\(^1\)H NMR) spectra were recorded at 400, 500, or 600 megahertz (MHz) at 23 \( ^{\circ} \text{C} \), unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, \( \delta \) scale) downfield from tetramethylsilane and are referenced to residual proton in the NMR solvent (CHCl\(_3\), \( \delta \) 7.26; C\(_6\)HD\(_5\), \( \delta \) 7.16; CHD\(_2\)OD, \( \delta \) 3.31; (CD\(_2\)H)SO(CD\(_3\)), \( \delta \) 2.50). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, b = broad, app = apparent), coupling constant in Hertz (Hz), integration, and assignment. Proton-decoupled carbon nuclear magnetic resonance spectra (\(^{13}\)C NMR) were recorded at 100, 125, or 150 MHz at 23 \( ^{\circ} \text{C} \), unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, \( \delta \) scale) downfield from tetramethylsilane and are
referenced to the carbon resonances of the solvent (CDCl$_3$, δ 77.0; C$_6$D$_6$, δ 128.1; CD$_3$OD, δ 49.0; DMSO-$d_6$, δ 39.5). Distortionless enhancement by polarization transfer [DEPT (135)] spectra were recorded at 125 or 150 MHz at 23 °C, unless otherwise noted. Heteronuclear single quantum coherence (HSQC), and heteronuclear multiple bond correlation (HMBC) spectra were recorded at 125 or 150 MHz at 23 °C, unless otherwise noted. $^{13}$C NMR and DEPT (135)/HSQC data are combined and represented as follows: chemical shift, carbon type [obtained from DEPT (135) or HSQC experiments]. Two-dimensional nuclear Overhauser effect spectroscopy (2D NOESY) and two-dimensional rotating-frame nuclear Overhauser effect spectroscopy (2D ROESY) experiments were performed at 500 MHz at 23 °C, unless otherwise noted. Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra were obtained using a Thermo Electron Corporation Nicolet 6700 FTIR spectrometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm$^{-1}$), intensity of absorption (s = strong, m = medium, w = weak, br = broad). Analytical ultra-high-performance liquid chromatography/mass spectrometry (UPLC/MS) was performed on a Waters UPLC/MS instrument equipped with a reverse-phase C$_{18}$ column (1.7 μm particle size, 2.1 × 50 mm), dual atmospheric pressure chemical ionization (API)/electrospray (ESI) mass spectrometry detector, and photodiode array detector. Samples were eluted with a linear gradient of 5% acetonitrile– water containing 0.1% formic acid→100% acetonitrile containing 0.1% formic acid over 0.75 min, followed by 100% acetonitrile containing 0.1% formic acid for 0.75 min, at a flow rate of 800 μL/min. High-resolution mass spectrometry (HRMS) were obtained on a Waters UPLC/HRMS instrument equipped with a dual API/ESI high-resolution mass spectrometry detector and photodiode array detector. Unless otherwise
noted, samples were eluted over a reverse-phase C18 column (1.7 μm particle size, 2.1 × 50 mm) with a linear gradient of 5% acetonitrile–water containing 0.1% formic acid→95% acetonitrile–water containing 0.1% formic acid for 1 min, at a flow rate of 600 μL/min. Optical rotations were measured on a Rudolph Research Analytical Autopol IV polarimeter equipped with a sodium (589 nm, D) lamp. Optical rotation data are represented as follows: specific rotation ([α]_D^T, concentration (mg/mL), and solvent.
1.8.2 Synthetic procedures.

*Synthesis of the unsaturated ketone 35:*

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\text{Cyclohex-2-ene-1-one (34) (4.84 mL, 50.0 mmol, 1 equiv) was added to a solution of lithium bis(trimethylsilyl)amide (19.2 g, 115 mmol, 2.30 equiv) in tetrahydrofuran (50 mL) at –78 °C. The reaction mixture was stirred for 1 h at –78 °C. A solution of the 1-(tert-butoxycarbonylimidazole (12.6 g, 75.0 mmol, 1.50 equiv) in tetrahydrofuran (35 mL) was then added dropwise via syringe pump over 20 min at –78 °C. The reaction vessel was immediately removed from the cooling bath and the reaction mixture was allowed to warm over 1.5 h to 23 °C. Upon warming, a turbid, dark-red mixture formed. Iodomethane (9.34 mL, 150 mmol, 3.00 equiv) was then added at 23 °C. The reaction mixture was stirred for 18 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (50 mL) and water (50 mL). The resulting mixture was poured into a solution of 75% ether–pentane (v/v, 300 mL). The biphasic mixture was stirred for 10 min at 23 °C. The stirred mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ether (100 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 14% ether–hexanes) to provide the unsaturated ketone 35 as a pale yellow oil (5.66 g, 54%).} \]
Rf = 0.26 (20% ether–hexanes; UV, PAA). 1H NMR (500 MHz, CDCl₃): δ 6.90–6.86 (m, 1H, H1), 6.03 (ddd, J = 10.1, 2.6, 1.5 Hz, 1H, H6), 2.51–2.40 (m, 2H, H2a,3a), 2.35–2.27 (m, 1H, H2b), 1.90–1.81 (m, 1H, H3b), 1.42 (s, 9H, H5), 1.34 (s, 3H, H4). 13C NMR (125 MHz, CDCl₃): δ 197.3 (C), 171.8 (C), 148.8 (CH), 129.1 (CH), 81.7 (C), 53.9 (C), 33.6 (CH2), 27.8 (3 × CH3), 23.8 (CH2), 20.3 (CH3). IR (ATR-FTIR), cm⁻¹: 3005 (m), 2998 (m), 1655 (m). HRMS-CI (m/z): [M + H]⁺ calcd for C₁₂H₁₉O₃, 211.1334 found, 211.1334.
**Synthesis of the α-iodoenone 36:**

Iodine (6.27 g, 24.8 mmol, 1.80 equiv) was added to a solution of the enone 35 (2.61 g, 12.4 mmol, 1 equiv) in 50% pyridine–dichloromethane (v/v, 30 mL) at 23 °C. The reaction mixture was stirred for 24 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous sodium thiosulfate solution (30 mL), water (10 mL), ether (100 mL) and ethyl acetate (100 mL). The resulting biphasic mixture was stirred for 20 min at 23 °C. The stirred mixture was transferred to a separatory funnel and the layers were separated. The organic layer was washed sequentially with aqueous hydrochloric acid solution (1 N, 5 × 20 mL) and saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over magnesium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by elution over a short plug of silica gel (3.0’ × 5.0 cm, eluting with 20% ether–hexanes). The filtrate was collected and concentrated. The residue obtained was triturated with pentane (5 × 10 mL) to furnish the α-iodoenone 36 as a colorless solid (3.20 g, 77%).

R<sub>f</sub> = 0.35 (20% ether–hexanes; UV, PAA). ¹H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.59–7.56 (m, 1H, H<sub>1</sub>), 2.59–2.51 (m, 1H, H<sub>2a</sub>), 2.49–2.43 (m, 1H, H<sub>3a</sub>), 2.37–2.30 (m, 1H, H<sub>2b</sub>), 1.96–1.89 (m, 1H, H<sub>3b</sub>), 1.41 (s, 9H, H<sub>5</sub>), 1.38 (s, 3H, H<sub>4</sub>). ¹³C NMR (125 MHz, CDCl<sub>3</sub>): δ 190.8 (C), 171.0 (C), 156.8 (CH), 102.2 (C), 82.4 (C), 54.0 (C), 33.4 (CH₂), 27.9 (CH₂), 27.8 (3
× CH₃), 21.0 (CH₃). IR (ATR-FTIR), cm⁻¹: 2973 (m), 2933 (m), 1720 (m), 1685 (m).
HRMS-CI (m/z): [M + H]⁺ calcd for C₁₂H₁₈IO₃, 337.0301; found 337.0301.
Synthesis of the cyclopropane 37:

Trimethylsulfoxonium iodide (3.54 g, 16.1 mmol, 1.40 equiv) was added in one portion to a suspension of sodium hydride (95%, 385 mg, 15.2 mmol, 1.33 equiv) in N,N-dimethylformamide (230 mL) at 23 °C. The resulting suspension was stirred for 40 min at 23 °C. The reaction mixture was cooled to −45 °C and stirred for 2 h at −45 °C. A solution of the α-iodoenone 36 (3.85 g, 11.4 mmol, 1 equiv) in N,N-dimethylformamide (25 mL) was then added dropwise via syringe pump over 1 h at −45 °C. The reaction mixture was placed in an ice bath and stirred for 18 h at 0 °C. The cold product mixture was then diluted sequentially with saturated aqueous ammonium chloride solution (25 mL), water (25 mL), and 50% ethyl acetate–hexanes (v/v, 200 mL). The resulting biphasic mixture was transferred to a separatory funnel the layers that formed were separated. The aqueous layer was extracted with 50% ethyl acetate–hexanes (v/v, 3 × 30.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (3 × 20 mL) and saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. 1H NMR analysis of the unpurified product mixture indicated the presence of a 2.4:1 mixture of diastereomers. The residue obtained was recrystallized (see Appendix A) from 5% ether–hexanes to furnish the cyclopropane 37 as an off-white solid (1.88 g, 47%).
$R_f = 0.36$ (20% ether–hexanes; faintly UV, PAA). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 2.25–2.17 (m, 2H, $H_{1,2a}$), 2.09 (td, $J = 13.7$, 4.6 Hz, 1H, $H_{3a}$), 1.97 (app t, $J = 6.6$ Hz, 1H, $H_{6a}$), 1.93–1.87 (m, 1H, $H_{3b}$), 1.67–1.61 (m, 1H, $H_{2b}$), 1.54 (dd, $J = 8.7$, 6.8 Hz, 1H, $H_{6b}$), 1.42 (s, 9H, $H_5$), 1.29 (s, 3H, $H_4$). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 200.4 (C), 171.7 (C), 81.8 (C), 53.7 (C), 30.7 (CH), 28.7 (CH$_2$), 27.8 (3 × CH$_3$), 21.9 (CH$_2$), 21.3 (CH$_2$), 18.1 (CH$_2$), 7.8 (C). IR (ATR-FTIR), cm$^{-1}$: 2976 (m), 2867 (m), 1730 (m), 1701 (m). HRMS-CI (m/z): [M + H]$^+$ calcd for C$_{13}$H$_{19}$INaO$_3$, 373.0277; found 373.0277.
**Synthesis of the fragment coupling product 41:**

A solution of *iso*-propylmagnesium chloride–lithium chloride complex in tetrahydrofuran (1.21 M, 530 μL, 641 μmol, 1.11 equiv) was added dropwise to a solution of the iodo cyclopropane 37 (225 mg, 642 μmol, 1.11 equiv) in toluene (2.6 mL) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C. A solution of the iodo enone 39 (145 mg, 580 μmol, 1 equiv) in toluene (500 μL) was then added to the reaction mixture at −78 °C. The reaction vessel was removed from its cooling bath and the reaction mixture was then warmed over 3 h to 23 °C. The product mixture was diluted with saturated aqueous ammonium chloride solution (500 μL), water (3.0 mL), and 25% hexanes–ether (v/v, 20.0 mL) at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with water (3.0 mL) and saturated aqueous sodium chloride solution (3.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 14% ether–hexanes). The fractions containing product (TLC) were combined and the combined fractions were concentrated. The residue obtained was recrystallized (see Appendix A) from 5% ether–pentane to provide the adduct 41 as a white solid (240 mg, 87%).
$R_f = 0.43$ (20% ether–hexanes; faintly UV, PAA). $^{1}H$ NMR (600 MHz, CDCl$_3$): $\delta$ 6.32 (s, 1H, H$_8$), 2.73 (bs, 1H, H$_7$), 2.21 (t, $J = 13.7$ Hz, 1H, H$_{11a}$), 2.13–1.99 (m, 3H, H$_{4a,10}$), 1.74–1.58 (m, 4H, H$_{3,4b,9b}$), 1.54–1.49 (m, 1H, H$_{8b}$), 1.42 (s, 9H, H$_6$), 1.36 (s, 3H, H$_3$), 1.21 (s, 3H, H$_{9a}$), 1.03 (s, 3H, H$_{9b}$). $^{13}C$ NMR (150 MHz, CDCl$_3$): $\delta$ 205.7 (C), 172.8 (C), 152.0 (CH), 106.2 (C), 81.1 (C), 72.4 (C), 54.9 (C), 41.7 (C), 38.0 (C), 32.9 (CH$_2$), 31.3 (C), 30.4 (CH$_3$), 29.9 (CH$_2$), 27.8 (3 × CH$_3$), 25.4 (CH$_3$), 23.7 (CH), 22.8 (CH$_3$), 17.5 (CH$_2$), 11.5 (CH$_2$). IR (ATR-FTIR), cm$^{-1}$: 2973 (m), 2931 (m), 2863 (m), 1737 (m), 1680 (m). HRMS-Cl (m/z): [M + H]$^+$ calcd for C$_{21}$H$_{32}$IO$_4$, 475.1345; found 475.1345.
Synthesis of the alkyne 42:

A round-bottom flask was charged with bis(triphenylphosphine)palladium(II) dichloride (206 mg, 293 μmol, 0.05 equiv), copper(I) iodide (33.6 mg, 176 μmol, 0.03 equiv), and the iodoenone 39 (1.47 g, 5.88 mmol, 1 equiv). The reaction vessel was sealed with a rubber septum. Tetrahydrofuran (30 mL) and triethylamine (2.90 mL, 20.8 mmol, 3.54 equiv) were then added in succession to the reaction vessel. The resulting suspension was deoxygenated by brief exposure to vacuum (~30 s) and subsequent backfilling with argon (1 atm). This process was repeated three times. Trimethylsilylacetylene (1.50 mL, 10.9 mmol, 1.87 equiv) was then added to the reaction mixture under argon at 23 °C. The reaction mixture was stirred for 7 h at 23 °C. The product mixture was diluted with 25% pentane–ether (v/v, 60 mL), saturated aqueous ammonium chloride solution (5.0 mL), and water (15 mL). The resulting biphasic mixture was stirred for 5 min at 23 °C. The mixture was then transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ether–hexanes) to provide the ethynylenone 42 as a yellow solid (799 mg, 62%).
$R_f = 0.35$ (20% ether–hexanes; UV, PAA). 1H NMR (500 MHz, CDCl$_3$): $\delta$ 7.01 (s, 1H, H4), 2.50 (dd, $J = 7.4$, 6.2 Hz, 2H, H2), 1.88–1.83 (m, 2H, H1), 1.18 (s, 6H, H5), 0.21 (s, 9H, H3). 13C NMR (125 MHz, CDCl$_3$): $\delta$ 195.1 (C), 163.9 (CH), 122.5 (C), 99.1 (C), 97.2 (C), 35.5 (CH$_2$), 34.3 (CH$_2$), 33.6 (C), 27.5 (2 x CH$_3$), $-0.11$ (3 x CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 2965 (m), 2865 (m), 1730 (m), 1737 (m), 1692 (m). HRMS–CI (m/z): [M + H]$^+$ calcd for C$_{13}$H$_{20}$NaOSi, 243.1181; found 243.1180.
Synthesis of the alkyne adduct 43:

Part 1: Fragment coupling of 37 and 42:

A solution of *iso*-propylmagnesium chloride–lithium chloride complex in tetrahydrofuran (1.21 M, 50.0 μL, 60.0 μmol, 1.20 equiv) was added dropwise to a solution of the iodocyclopropane 37 (21.0 mg, 60.0 μmol, 1.20 equiv) in toluene (500 μL) at –78 °C. The reaction mixture was stirred for 30 min at –78 °C. A solution of the alkyne 42 (11.0 mg, 50.0 μmol, 1 equiv) in toluene (100 μL) was then added to the reaction mixture at –78 °C. The reaction vessel was removed from its cooling bath and the reaction mixture was then warmed over 3 h to 23 °C. The product mixture was then diluted with saturated aqueous ammonium chloride solution (200 μL), water (1.0 mL), and 25% hexanes–ether (v/v, 5.0 mL) at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed sequentially with water (1.0 mL) and saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the next step.
Part 2: Removal of the trimethylsilyl group to provide 43:

Potassium carbonate (8.3 mg, 60.0 μmol, 1.20 equiv) was added to a solution of the unpurified fragment coupling product S1 obtained in the preceding step (nominally 50.0 μmol, 1 equiv) in methanol (250 μL) at 23 °C. The reaction mixture was stirred for 3 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (200 μL), water (1.0 mL), and 25% hexanes–ether (v/v, 5.0 mL) at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with water (1.0 mL) and saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 20% ether–hexanes) to provide the alkyne 43 as a white solid (15.0 mg, 81% over two steps).

R_f = 0.20 (25% ether–hexanes; faintly UV, PAA). ¹H NMR (600 MHz, CDCl₃): δ 6.07 (s, 1H, H₈), 2.89 (s, 1H, H₇), 2.36 (bs, 1H, H₁₂), 2.11 (td, J = 13.0, 5.9 Hz, 1H, H₁₁a), 2.05–1.88 (m, 4H, H₃a,₄a,₁₀), 1.68–1.45 (m, 7H, H₁,₃b,₄b,₈a,₁₁), 1.44–1.40 (m, 10H, H₈b,₆), 1.12 (s, 3H, H₀₉), 1.03 (s, 3H, H₀₆). ¹³C NMR (125 MHz, CDCl₃): δ 208.1 (C), 172.5 (C), 150.9 (CH), 121.1 (C), 83.0 (C), 81.2 (CH), 71.7 (C), 55.0 (C), 37.9 (C), 33.2 (CH₂), 33.1 (CH₂), 32.0 (C), 29.3 (CH₃), 29.0 (CH₃), 27.8 (3 × CH₃), 27.5 (CH₂), 22.3 (CH), 21.4 (CH₃), 17.4
(CH₂), 10.2 (CH₂). * IR (ATR-FTIR), cm⁻¹: 2935 (m), 2830 (m), 1739 (m), 1683 (m), 1446 (m). HRMS-Cl (m/z): [M + H]+ calcd for C₂₃H₃₃O₄, 373.2379; found 373.2379. *The quaternary tert-butyl carbon was not observed due to coincidence with the residual solvent peak.
Synthesis of the vinyl silane 48:

Part 1: Synthesis of the silyl ether S2:

imidazole (20.0 mg, 294 μmol, 2.96 equiv) was added in one portion to a solution of the adduct 41 (47 mg, 99.1 μmol, 1 equiv) and chlorotrimethylsilane (20.0 μL, 158 μmol, 1.59 equiv) in dichloromethane (500 μL) at 23 °C. The reaction mixture was stirred for 2 d at 23 °C. The product mixture was diluted with water (1.0 mL) and 50% ether–pentane (v/v, 5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered through a plug of silica gel (0.5 cm × 1.0 cm) and the filter cake was rinsed with ether (3 × 3.0 mL). The filtrates were combined and the combined filtrates were concentrated to provide the silyl ether S2 as a colorless oil. The unpurified silyl ether was used directly in the following step.
Part 2: Synthesis of the vinyl silane 48:

A solution of n-butyllithium in hexanes (2.4 M, 60.0 μL, 0.143 mmol, 1.44 equiv) was added to a solution of the unpurified silyl ether S2 obtained in the preceding step (nominally, 99.1 μmol, 1 equiv) in tetrahydrofuran (500 μL) at −78 °C. The reaction mixture was stirred for 20 min at −78 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (500 μL), water (1.0 mL) and ethyl acetate (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 5% ether–hexanes) to provide the vinyl silane 48 as a colorless oil (21.6 mg, 52%, two steps).

Rf = 0.41 (10% ether–hexanes; faintly UV, PAA). 1H NMR (600 MHz, CDCl3): δ 5.72 (s, 1H, H8), 5.23 (s, 1H, H12), 2.15–2.06 (m, 1H, H4a), 2.02–1.91 (m, 3H, H3,11a), 1.76–1.68 (m, 1H, H11b), 2.01–1.94 (m, 1H, H3b), 1.58–1.46 (m, 4H, H2,4b,10), 1.42 (s, 9H, H6), 1.34–1.23 (s, 4H, H1a,5), 1.11 (, J = 8.3, 5.7 Hz, 1H, H1b) 1.01 (s, 3H, H9a), 0.95 (s, 3H, H9b), 0.14 (s, 9H, H7). 13C NMR (125 MHz, CDCl3): δ 212.1 (C), 172.3 (C), 151.3 (CH), 139.2 (C),
81.4 (C), 77.5 (C), 55.4 (C), 36.2 (C), 34.9 (CH\textsubscript{2}), 33.7 (CH\textsubscript{2}), 33.3 (C), 29.7 (CH\textsubscript{3}), 29.3 (CH\textsubscript{3}), 28.3 (CH\textsubscript{2}), 27.8 (3 \times \text{CH}_3), 21.1 (CH\textsubscript{2}), 20.3 (CH), 16.7 (CH\textsubscript{2}), 9.9 (CH\textsubscript{2}), 1.6 (3 \times \text{CH}_3).
Synthesis of the methoxymethyl ether 49:

Chloromethyl methyl ether (40.0 μL, 527 μmol, 5.27 equiv) was added to a solution of sodium iodide (57.0 mg, 381 μmol, 3.81 equiv) in tetrahydrofuran (400 μL) at 23 °C. The reaction mixture was stirred for 5 min at 23 °C. A solution of the adduct 41 (47 mg, 99.1 μmol, 1 equiv) and di-iso-propylethylamine (10.0 μL, 574 μmol, 5.74 equiv) in tetrahydrofuran (200 μL) was added at 23 °C. The reaction vessel was sealed and the sealed vessel was placed in a heating block that had been preheated to 75 °C. The reaction mixture was stirred for 21 h at 75 °C. The product mixture was then cooled over 30 min to 23 °C. The cooled product mixture was diluted with saturated aqueous sodium bicarbonate solution (1.0 mL), water (1.0 mL), and ethyl acetate (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 5% ether–hexanes) to provide the methoxymethyl ether 49 as a colorless oil (44.0 mg, 85%).

Rf = 0.46 (10% ether–hexanes; faintly UV, PAA). 1H NMR (600 MHz, CDCl3): δ 6.57 (s, 1H, H8), 4.81 (d, J = 6.8 Hz, 1H, H7a), 4.51 (d, J = 6.8 Hz, 1H, H7b), 3.36 (s, 1H, H12), 2.80
(td, $J = 13.9, 4.5$ Hz, 1H, H$_{11a}$), 2.31–2.20 (m, 2H, H$_{2,4a}$), 2.08 (td, $J = 13.7, 4.5$ Hz, 1H, H$_{3a}$), 2.01–1.96 (m, 1H, H$_{4b}$), 1.80–1.70 (m, 3H, H$_{1a,10a,11b}$), 1.60–1.58 (m, 1H, H$_{3b}$), 1.51–1.46 (m, 1H, H$_{10b}$), 1.42 (s, 9H, H$_6$), 1.36 (s, 3H, H$_5$), 1.32–1.25 (m, 4H, H$_{1b,9a}$), 1.03 (s, 3H, H$_{9b}$). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 204.9 (C), 173.1 (C), 155.5 (CH), 101.7 (C), 91.5 (CH$_2$), 81.0 (C), 76.8 (C), 55.9 (CH$_3$), 55.1 (C), 43.0 (C), 37.5 (C), 32.7 (CH$_2$), 31.3 (CH$_2$), 30.9 (CH$_3$), 30.0 (CH$_3$), 27.8 (3 × CH$_3$), 25.5 (CH$_3$), 24.0 (CH), 23.1 (CH$_3$), 17.8 (CH$_2$), 11.9 (CH$_2$). IR (ATR-FTIR), cm$^{-1}$: 2975 (m), 2933 (m), 2868 (m), 1732 (m), 1682 (m). HRMS-Cl (m/z): [M + H]$^+$ calcd for C$_{23}$H$_{35}$INaO$_5$, 541.1427; found 541.1448.
**Synthesis of the cyclobutanol 51:**

A solution \( n \)-butyllithium in hexanes (2.4 M, 40.0 \( \mu \)L, 94.9 \( \mu \)mol, 1.20 equiv) was added to a solution of the methoxymethyl ether 49 (41.0 mg, 79.1 \( \mu \)mol, 1 equiv) in tetrahydrofuran (400 \( \mu \)L) at \(-78 ^\circ\)C. The reaction mixture was stirred for 30 min at \(-78 ^\circ\)C. The reaction mixture was then warmed over 1 h to 23 \(^\circ\)C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (500 \( \mu \)L), water (1.0 mL) and ethyl acetate (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 25% ether–hexanes) to provide the cyclobutanol 51 as a white solid (15.0 mg, 48%). The relative stereochemistry of cyclobutanol 51 was established by X-ray analysis (see Appendix A).

\[ R_f = 0.20 \text{ (25\% ether–hexanes; faintly UV, PAA).} \]

\( ^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta \) 5.74 (\( s \), 1H, H\(_8\)), 4.61 (d, \( J = 6.7 \text{ Hz} \), 1H, H\(_{7a}\)), 4.51 (d, \( J = 6.7 \text{ Hz} \), 1H, H\(_{7b}\)), 3.38 (\( s \), 1H, H\(_{12}\)), 1.99–1.92 (\( m \), 1H, H\(_{3a}\)), 1.90–1.82 (\( m \), 2H, H\(_{10a,11a}\)), 1.78–1.72 (\( m \), 1H, H\(_{3b}\)), 1.47 (\( s \), 3H, H\(_6\)), 1.46–1.40 (\( m \), 3H, H\(_{4,11b}\)), 1.35 (\( s \), 3H, H\(_5\)), 1.31–1.27 (\( m \), 1H, H\(_2\)), 1.13 (\( m \), 3H, H\(_{9a}\)).
1.00 (s, 3H, H$_{9b}$), 0.74 (d, $J = 9.5$, 5.1 Hz, 1H, H$_{1a}$), 0.55 (d, $J = 6.4$, 5.2 Hz, 1H, H$_{1b}$). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 176.5 (C), 146.0 (C), 135.1 (CH), 93.2 (CH$_2$), 82.1 (C), 82.0 (C), 80.0 (C), 55.8 (CH$_3$), 46.4 (C), 40.1 (C), 33.8 (C), 32.9 (CH$_2$), 30.4 (CH$_3$), 29.3 (CH$_2$), 29.3 (CH$_3$), 28.1 (3 × CH$_3$), 22.1 (CH$_2$), 19.2 (CH$_2$), 19.1 (CH$_3$), 13.8 (CH), 9.0 (CH$_2$).
Synthesis of the ketofuran 53:

A 10-mL round bottom flask fused to a Teflon-coated valve was charged with [bis(trifluoroacetoxy)iodo]benzene (94.6 mg, 220 μmol, 2.20 equiv), the adduct 43 (37.2 mg, 100 μmol, 1 equiv), and 1% water–acetonitrile (v/v, 2.0 mL). The reaction chamber was sealed and the reaction vessel was immersed in an oil bath that had been preheated to 80 °C. The reaction mixture was stirred for 1.5 h at 80 °C. The product mixture was cooled over 30 min to 23 °C. The cooled product mixture was diluted sequentially with saturated aqueous sodium bicarbonate solution (2.0 mL) and 50% ether–ethyl acetate (v/v, 10.0 mL) at 23 °C. The resulting biphasic mixture was then transferred to a separatory funnel and the layers that formed were separated. The organic layers were combined and the combined layers were washed sequentially with water (3 × 2.0 mL) and saturated aqueous sodium chloride solution (3.0 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used purified by preparative thin-layered chromatography (eluting with 50% ether–hexanes) to provide the ketofuran 53 as an amorphous solid (14.7 mg, 38%).

R<sub>f</sub> = 0.26 (50% ether–hexanes; UV, PAA). ¹H NMR (600 MHz, CDCl₃): δ 6.51 (s, 1H, H<sub>1</sub>), 4.29 (dd, J = 17.4, 1.0 Hz, 1H, H<sub>7a</sub>), 4.06 (dd, J = 17.4, 1.0 Hz, 1H, H<sub>7b</sub>), 2.38 (dt, J = 13.2, 3.4 Hz, 1H, H<sub>10a</sub>), 2.13–2.08 (m, 1H, H<sub>4a</sub>), 1.99–1.95 (m, 2H, H<sub>3</sub>), 1.71–1.65 (m, 1H, H<sub>10b</sub>), 1.63–1.51 (m, 3H, H<sub>4b,11</sub>), 1.46–1.41 (m, 10H, H<sub>1a,b</sub>), 1.27–1.23 (m, 4H, H<sub>2,5</sub>), 1.17
(s, 3H, H\textsubscript{9a}), 1.08 (s, 3H, H\textsubscript{9b}), 0.75 (dd, J = 8.3, 6.6 Hz, 1H, H\textsubscript{1b}). \textsuperscript{13}C NMR (150 MHz, CDCl\textsubscript{3}): \(\delta\) 204.2 (C), 203.7 (C), 172.4 (C), 146.3 (CH), 134.2 (C), 83.3 (C), 81.4 (C), 70.7 (CH\textsubscript{2}), 55.3 (C), 34.2 (C), 33.9 (C), 33.6 (CH\textsubscript{2}), 31.4 (CH\textsubscript{2}), 28.7 (CH\textsubscript{2}), 28.4 (2 \times CH\textsubscript{3}), 27.8 (3 \times CH\textsubscript{3}), 21.0 (CH), 20.7 (CH\textsubscript{3}), 16.7 (CH\textsubscript{2}), 8.9 (CH\textsubscript{2}). IR (ATR-FTIR), cm\textsuperscript{-1}: 2961 (m), 2955 (m), 2870 (m), 1732 (s), 1691 (m), 1654 (m). HRMS-Cl (m/z): [M + Na]\textsuperscript{+} calcd for C\textsubscript{23}H\textsubscript{33}O\textsubscript{5}, 389.2328; found, 389.2338.
Synthesis of the aldol product 54:

Powdered sodium hydroxide (1.0 mg, 25.0 μmol, 2.03 equiv) was added to a solution of the ketofuran 53 (5.0 mg, 12.3 μmol, 1 equiv) in ethanol (240 μL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (200 μL), water (1.0 mL), and ethyl acetate (5.0 mL) at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3.0 mL). The organic layers were combined and the combined organic layers were washed with water (2.0 mL) and saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 50% ether–hexanes) to provide the aldol product 54 as a white solid (3.2 mg, 66%).
The relative stereochemistry of the newly generated alcohol was determined by NOE analysis. Correlations between the cyclopropane hydrogen H1 and the hydroxyl proton H12 support the relative assignment shown.

R_f = 0.58 (33% ether–hexanes; faintly UV, PAA). 1H NMR (600 MHz, dimethylsulfoxide-d6): δ 6.20 (s, 1H, H8), 4.89 (s, 1H, H12), 4.74 (s, 1H, H9), 1.80–1.64 (m, 4H, H3,13), 1.52–1.41 (m, 3H, H2,4a,14a), 1.41 (s, 9H, H6), 1.22–1.18 (m, 1H, H4b), 1.16–1.10 (m, 1H, H14b), 1.10 (s, 3H, H9a), 1.03 (s, 3H, H9b), 0.99 (s, 3H, H5), 0.69 (t, J = 6.2 Hz, 1H, H1a), 0.35 (dd, J = 9.4, 6.0 Hz, 1H, H1b). 13C NMR (150 MHz, dimethylsulfoxide-d6): δ 198.2 (C), 174.2 (C), 137.2 (C), 1364 (CH), 84.4 (CH), 83.0 (C), 79.7 (C), 78.3 (C), 47.1 (C), 36.3 (C), 33.3 (CH2), 32.7 (C), 29.2 (CH3), 27.7 (3 × CH3), 27.3 (CH3), 22.6 (CH2), 21.2 (CH2), 18.3 (CH2), 17.6 (CH3), 12.7 (CH), 8.9 (CH2). IR (ATR-FTIR), cm⁻¹: 2930 (m), 1752 (m), 1726 (m), 1555 (m). HRMS-Cl (m/z): [M + Na]^+ calcd for C23H32NaO5, 411.2147; found, 411.2154.
Synthesis of the vinyl ether 55:

A screw-capped pressure vessel was charged with copper(I) iodide (24.0 mg, 124 μmol, 0.10 equiv), cesium fluoride (414 mg, 2.73 mmol, 2.20 equiv), tetrakis(triphenylphosphine)-palladium(0) (72.0 mg, 62.0 μmol, 0.05 equiv), the adduct 41 (590 mg, 1.24 mmol, 1 equiv), and acetonitrile (6.2 mL). The reaction vessel was fitted with a rubber septum and the headspace in the vessel was evacuated. The headspace was back-filled with argon. Tributyl(1-ethoxyvinyl) tin (460 μL, 1.36 mmol, 1.10 equiv) was added to the suspension under argon at 23 °C. The reaction chamber was then sealed and the reaction vessel was immediately placed into a bath that had been preheated to 60 °C. The reaction mixture was stirred for 6 h at 65 °C. The product mixture was then cooled over 30 min to 23 °C. The cooled product mixture was diluted with ether (30 mL). The diluted mixture was filtered through a pad of celite (2.5 × 4.0 cm) and the filter cake was rinsed with ether (3 × 10 mL). The filtrates were combined and the combined filtrates were transferred to a separatory funnel that had been charged with pentane (20 mL). The diluted filtrates were washed sequentially with saturated aqueous sodium bicarbonate solution (15 mL), saturated aqueous ammonium chloride solution (15 mL), and saturated aqueous sodium chloride solution (25 mL). The washed organic layer was dried over sodium sulfate. The solution was filtered and the filtrate was concentrated. The residue obtained
was purified by flash-column chromatography (eluting with 16% ether–hexanes) to provide the vinyl ether 55 as a yellow oil (490 mg, 94%).

R_f = 0.58 (33% ether–hexanes; faintly UV, PAA). 1H NMR (600 MHz, C_6D_6): δ 5.92 (s, 1H, H_10), 4.04 (s, 1H, H_11a), 3.67 (s, 1H, H_11b), 3.17 (q, J = 7.0 Hz, 2H, H_12), 2.96 (s, 1H, H_14), 2.84 (t, J = 15.4 Hz, 1H, H_7a), 2.14 – 2.05 (m, 1H, H_8a), 2.04 – 1.93 (m, 2H, H_1,2a), 1.69 (d, J = 10.2 Hz, 1H, H_7b), 1.66 – 1.60 (m, 2H, H_6a,3a), 1.56 – 1.47 (m, 1H, H_3b), 1.41 – 1.37 (m, 2H, H_6b,8b), 1.36 (s, 3H, H_4), 1.32 (s, 3H, H_9), 1.28 (s, 9H, H_5), 0.98 (s, 3H, H_9), 0.79 (t, J = 7.0 Hz, 3H, H_13). 13C NMR (150 MHz, C_6D_6): δ 205.4 (C), 172.9 (C), 142.7 (CH), 136.1 (C), 84.7. (CH_2), 80.4 (C), 70.1 (C), 63.1 (CH_2), 55.2 (C), 39.9 (CH2), 33.8 (C), 32.9 (CH_2), 31.8 (CH_2), 31.3 (CH_3), 30.5 (CH_2), 27.8 (3 × CH_3), 25.7 (CH_3), 23.5 (CH_3), 22.5 (CH), 18.9 (CH_2), 14.3 (CH_3), 10.9 (CH_2). IR (ATR-FTIR), cm⁻¹: 2990 (m), 1851 (m), 1776 (m), 1501 (m). HRMS-CI (m/z): [M + Na]^+ calcd for C_{25}H_{39}O_5, 419.2797; found, 419.2777.
Potassium osmate(VI) dihydrate (15.7 mg, 42.5 μmol, 5.0 mol%) was added to a mixture of the vinyl ether 55 (355 mg, 850 μmol, 1 equiv) and N-methyl-morpholine N-oxide (498 mg, 4.25 mmol, 5.00 equiv) in 66% acetone–water (v/v, 3.0 mL) at 23 °C. The reaction mixture was stirred for 18 h at 23 °C. The product mixture was poured into a stirring mixture of ethyl acetate (15 mL) and saturated aqueous sodium thiosulfate solution (10 mL). The diluted product mixture was stirred for 10 min at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the diol 56 as a white solid (143 mg, 41%).

\[ R_f = 0.10 \text{ (33\% ethyl acetate–hexanes; faintly UV, PAA).} \]

\[ ^1H \text{ NMR (600 MHz, CDCl}_3): \delta \]

6.39 (s, 1H, H\text{10}), 4.67 (dd, J = 18.6, 4.4 Hz, 1H, H\text{11a}), 4.14 (dd, J = 18.6, 4.5 Hz, 1H, H\text{11b}), 3.15 (t, J = 4.7 Hz, 1H, H\text{12}), 2.76 (s, 1H, H\text{13}), 2.36 (tt, J = 14.1, 2.8 Hz, 1H, H\text{7a}), 2.23–2.10 (m, 1H, H\text{1}), 2.07 (td, J = 13.7, 4.7 Hz, 1H, H\text{3a}), 2.01–1.89 (m, 2H, H\text{2}), 1.71 (td, J =
13.8, 3.4 Hz, 1H, H₈₉), 1.61–1.52 (m, 2H, H₆₉₇₇b), 1.51–1.44 (m, 2H, H₃₈₈₈₉b), 1.40 (s, 9H, H₅), 1.27 (s, 3H, H₉₉), 1.23 (dd, J = 8.5, 5.1 Hz, 1H, H₆₉), 1.11 (s, 3H, H₉₉), 1.04 (s, 3H, H₄). ¹³C NMR (150 MHz, CDCl₃): δ 207.3 (C), 203.5 (C), 172.7 (C), 151.4 (CH), 137.7 (C), 81.1 (C), 69.7 (C), 64.5 (CH₂), 55.0 (C), 39.8 (C), 33.4 (C), 32.5 (CH₂), 31.8 (CH₂), 30.3 (CH₃), 29.1 (CH₃), 27.8 (3 × CH₃), 25.2 (CH₃), 23.8 (CH), 21.5 (CH₃), 17.7 (CH₂), 11.7 (CH₂). IR (ATR-FTIR), cm⁻¹: 2905 (m), 1745 (m), 1733 (m), 1616 (m). HRMS-CI (m/z): [M + Na]⁺ calcd for C₂₃H₃₄NaO₆, 429.2253; found, 429.2205.
Synthesis of the silyl methyl ether 58:

Step 1: Synthesis of the silyl ether S3:

Chlorotrimethylsilane (102 μL, 812 μmol, 2.21 equiv) was added to a solution of the hydroxyketone 56 (150 mg, 369 μmol, 1 equiv), 4-dimethylaminopyridine (9.0 mg, 73.9 μmol, 20.0 mol%), and imidazole (121 mg, 1.77 mmol, 4.80 equiv) in dichloromethane (3.7 mL) at 23 °C. The reaction mixture was stirred for 22 h at 23 °C. The product mixture was diluted sequentially with 1 N aqueous hydrochloric acid solution (1.0 mL) and ethyl acetate (5.0 mL). The diluted product mixture was stirred for 30 min at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel that had been charged with ethyl acetate (10 mL) and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The silyl ether S3 obtained in this way was used directly in the following step.
Part 2: Synthesis of the silyl methyl ether 58:

Silver(I) oxide (427 mg, 1.85 mmol, 5.01 equiv) was added in one portion to a solution of the unpurified silyl ether S3 obtained in the preceding step (nominally, 369 μmol, 1 equiv) in 50% iodomethane–acetonitrile (v/v, 7.5 mL) at 23 °C. The reaction mixture was stirred vigorously for 18 h at 23 °C. The product mixture was filtered through a plug of celite (2.0 cm × 3.0 cm). The filter cake was rinsed with dichloromethane (3 × 5.0 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes) to provide the methyl ether 58 as a colorless oil (154.3 mg, 85% two steps).

Rf = 0.20 (15% ethyl acetate–hexanes; faintly UV, PAA). ¹H NMR (500 MHz, CDCl3): d 6.38 (s, 1H, H₁₀), 4.40 (d, J = 16.5 Hz, 1H, H₁₁a), 4.14 (d, J = 16.4 Hz, 1H, H₁₁b), 3.38 (s, 3H, H₁₂) 2.45–2.38 (m, 1H, H₇a), 2.34–2.27 (m, 1H, H₁), 2.24–2.16 (m, 1H, H₂a), 2.09–2.02 (m, 1H, H₃a), 1.93–1.88 (m, 1H, H₂b), 1.70–1.59 (m, 2H, H₆a,₈a), 1.52–1.52 (m, 3H, H₃b,₇b,₈b), 1.39 (s, 9H, H₅), 1.24 (s, 3H, H₉a), 1.17–1.12 (m, 4H, H₄,₆b), 1.11 (s, 3H, H₉b), 0.02 (s, 2H, H₁₃).
Synthesis of the silyl migration product 60:

A dispersion of sodium hydride in mineral oil (60% wt., 16.0 mg, 443 μmol, 1.20 equiv) was added in one portion to a solution of the methyl ether 58 (181.6 mg, 369 μmol, 1 equiv) in 5% tert-butanol–tetrahydrofuran (v/v, 4.9 mL) at 0 °C. The reaction mixture was stirred for 2 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (2.0 mL), water (2.0 mL), and ethyl acetate (15 mL). The resulting biphasic mixture was transferred to a separatory funnel that had been charged with ethyl acetate (10 mL) and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (5.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ether–hexanes) to provide the silyl migration product 60 as a colorless oil (134.3 mg, 74%).
The relative stereochemistry of the silyl migration product 60 was assigned via conclusive NOE correlations between the C6 methine and the C7 trimethylsilyl group as well as the correlation between C4 methyl group and the C7 trimethylsilyl group supporting the relative stereochemistry depicted.

Rf = 0.25 (25% ether–hexanes; PAA). 1H NMR (600 MHz, CDCl3): δ 6.83 (s, 1H, H11), 4.92 (s, 1H, H6), 3.52 (s, 3H, H13), 1.97–1.89 (m, 1H, H2a), 1.81–1.75 (m, 2H, H2b,9a), 1.59–1.53 (m, 3H, H3,10a), 1.45 (s, 9H, H5), 1.43–1.40 (m, 1H, H10b), 1.39–1.30 (m, 1H, H1), 1.25 (s, 3H, H4), 1.15–1.08 (m, 6H, H8a,3b,12a), 1.01 (s, 3H, H12b), 0.67 (dd, J = 9.8, 6.3 Hz, 1H, H8b), 0.13 (s, 9H, H7). 13C NMR (150 MHz, CDCl3): δ 197.3 (C), 176.5 (C), 145.6 (CH), 134.1 (C), 85.3 (CH), 80.1 (C), 76.2 (C), 74.6 (C), 59.2 (CH3), 35.4 (C), 33.8 (CH3), 32.1 (C), 28.3 (CH3), 29.7 (3 × CH3), 27.5 (CH3), 27.3 (CH2), 26.2 (CH2), 18.9 (CH2), 18.9 (CH3), 15.4 (CH), 12.1 (CH2), 2.6 (3 × CH3). IR (ATR-FTIR), cm⁻¹: 2999 (m), 2750 (m), 1645 (m), 1605 (m). HRMS-Cl (m/z): [M + Na]⁺ calcd for C27H44NaO6Si, 515.2805; found, 515.2801.
Synthesis of the methyl carbonate 61:

A solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M, 250 μL, 250 μmol, 1.50 equiv) was added dropwise via syringe pump over 5 min to a solution of the silyl migration product 60 (82.0 mg, 167 μmol, 1 equiv) in tetrahydrofuran (1.7 mL) at –78 °C. The reaction mixture was stirred for 5 min at –78 °C. Methyl chloroformate (128 μL, 1.67 mmol, 10.0 equiv) was then added at –78 °C. The reaction mixture was stirred for 5 h at –78 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (500 μL), water (1.0 mL), and ethyl acetate (10 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 16% ether–hexanes) to provide the methyl carbonate 61 as a colorless oil (149 mg, 58%).

Rf = 0.40 (20% ether–hexanes; UV, PAA). 1H NMR (500 MHz, CDCl3): δ 6.75 (s, 1H, H11), 4.41 (s, 1H, H6), 3.61 (s, 3H, H14), 3.56 (s, 3H, H13), 2.06 (td, J = 13.9, 5.8 Hz, 1H, H3a), 1.95–1.86 (m 1H, H2a), 1.84–1.80 (m, 1H, H2b), 1.63–1.53 (m, 3H, H9,10a), 1.41 (s, 9H, H5), 1.37 (s, 3H, H4), 1.22–1.14 (m, 2H, H1,3b,10b), 1.12 (s, 3H, H12a), 1.01 (s, 3H, H12b)
0.84–0.80 (m, 1H, H₈a), 0.67 (t, J = 7.0 Hz, 1H, H₈b), 0.12 (s, 9H, H₇). ¹³C NMR (125 MHz, CDCl₃): δ 194.9 (C), 173.9 (C), 153.3 (C), 143.6 (CH), 135.0 (C), 85.7 (C), 80.4 (CH), 79.7 (C), 74.6 (C), 60.58 (CH₃), 54.2 (CH₃), 48.1 (C), 33.9 (C), 33.8 (CH₂), 31.8 (C), 28.1 (CH₃), 27.8 (3 × CH₃), 27.7 (CH₃), 27.5 (CH₂), 25.2 (CH₂), 19.1 (CH₃), 18.6 (CH₂), 14.8 (CH₃), 13.8 (CH₂), 2.7 (3 × CH₃).
Synthesis of the methyl vinyl ether 64:

Part 1: Synthesis of methyl carbonate 62:

A solution of tetrabutylammonium fluoride in tetrahydrofuran (1.0 M, 130 μL, 130 μmol, 1.24 equiv) was added to a solution of the methyl carbonate 61 (53.5 mg, 97.2 μmol, 1 equiv) in tetrahydrofuran (1.0 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (500 μL), water (500 μL), and ethyl acetate (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The methyl carbonate 62 obtained in this way was used in the next step without further purification.
Part 2: Synthesis of the methyl vinyl ether 64:

1,8-Diazabicyclo[4.5.0]undec-7-ene (259 μL, 1.67 mmol, 17.2 equiv) was added to a solution of the unpurified methyl carbonate 62 obtained in the preceding step (nominally, 97.2 μmol, 1 equiv) dissolved in N,N-dimethylformamide (1.7 mL) at 23 °C. The reaction vessel was placed in a heating block that had been preheated to 100 °C. The reaction mixture was stirred and heated for 2 h at 100 °C. The product mixture was cooled over 30 min to 23 °C. The cooled product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (500 μL), water (3.0 mL), and ethyl acetate (10.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 3.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (1.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 33% ether–hexanes) to furnish the methyl vinyl ether 64 as colorless oil (23.0 mg, 71% over two steps).

R<sub>f</sub> = 0.20 (33% ether–hexanes; UV, PAA).<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 6.87 (s, 1H, H<sub>11</sub>), 3.67 (s, 3H, H<sub>22</sub>), 2.01–1.86 (m, 3H, H<sub>3</sub>), 1.77 (td, J = 13.9, 4.8 Hz, 1H, H<sub>9a</sub>), 1.71–
1.63 (m, 2H, H_{1,3a}), 1.51–1.43 (m, 2H, H_{3b,10}), 1.40–1.37 (m, 10H, H_{5,9}), 1.29 (s, 3H, H_{4}), 1.12 (m, 3H, H_{12a}), 1.00 (s, 3H, H_{12b}), 0.96 (dd, J = 8.9, 5.9 Hz, 1H, H_{8a}), 0.86 (t, J = 6.2 Hz, 1H, H_{8b}). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 181.4 (C), 174.7 (C), 148.8 (CH), 148.2 (C), 146.0 (C), 134.8 (C), 80.1 (CH), 70.7 (C), 58.7 (CH$_3$), 44.7 (C), 32.8 (C), 31.4 (CH$_2$), 29.6 (CH$_3$), 29.7 (CH$_3$), 28.8 (CH$_2$), 27.8 (3 × CH$_3$), 26.2 (CH$_3$), 26.1 (CH$_2$), 21.4 (CH$_3$), 17.4 (CH$_2$), 14.9 (CH), 12.7 (CH$_2$). IR (ATR-FTIR), cm$^{-1}$: 2980 (m), 2900 (m), 2350 (w), 1735 (s),1680 (m). HRMS-Cl (m/z): [M + Na]$^+$ calcd for C$_{24}$H$_{34}$NaO$_5$, 425.2304; found, 425.2302.
Synthesis of the iodocyclopropane 66:

Part 1: Synthesis of the carboxylic aid S4:

\[
\text{37} \quad \xrightarrow{TFA, CH}_2Cl_2, 0 \degree C \quad \text{S4}
\]

Trifluoroacetic acid (110 \( \mu \)L, 1.43 mmol, 10.0 equiv) was added to a solution of the cyclopropane 37 (50.0 mg, 143 \( \mu \)mol, 1 equiv) in dichloromethane (800 \( \mu \)L) at 0 \( \degree \)C. The reaction mixture was stirred for 2 h at 0 \( \degree \)C. The product mixture was concentrated. The residue obtained was re-concentrated twice from 50% ether–pentane (v/v, 4.0 mL). The carboxylic acid S4 was obtained as an off-white solid and was used in the next step without purification.
Part 2: Synthesis of the iodocyclopropane 66:

\[
\begin{align*}
N,N'\text{-Cyclohexylcarbodiimide} & (30.0 \text{ mg, 145} \ \mu\text{mol, 1.01 equiv)}, \ 4\text{-dimethylamino pyridine} \\
& (2.0 \text{ mg, 16.3} \ \mu\text{mol, 0.10 equiv}), \text{ and 2-trimethylsilylethanol} \\
& (68.5 \ \mu\text{L, 429} \ \mu\text{mol, 3.00 equiv}) \text{ were added in sequence to a solution of the unpurified carboxylic acid S4 obtained} \\
& \text{in the preceding step (nominally, 143} \ \mu\text{mol, 1 equiv) in dichloromethane} (800 \ \mu\text{L}) \text{ at 23} \ ^\circ\text{C. The reaction mixture was stirred for 3 h at 23} \ ^\circ\text{C. The product mixture was diluted} \\
& \text{sequentially with saturated aqueous ammonium chloride solution} (200 \ \mu\text{L}), \text{ water} (1.0 \ \text{mL}), \\
& \text{and ethyl acetate} (5.0 \ \text{mL}). \text{ The resulting biphasic mixture was transferred to a separatory} \\
& \text{funnel and the layers that formed were separated. The organic layer was washed} \\
& \text{sequentially with water} (1.0 \ \text{mL}) \text{ and saturated aqueous sodium chloride solution} (2.0 \ \text{mL}). \\
& \text{The washed organic layer was dried over sodium sulfate. The dried solution was filtered} \\
& \text{and the filtrate was concentrated. The residue obtained was partitioned into two portions} \\
& \text{and each portion was purified by flash-column chromatography (eluting with 25% ether–} \\
& \text{hexanes) to furnish the cyclopropane 66 as a white solid} (55.7 \ \text{mg, 99% over two steps}). \\
\end{align*}
\]

\[R_f = 0.36 \ (20\% \ \text{ether–hexanes; faintly UV, PAA}).\]

\(^1\text{H NMR} (600 \ \text{MHz, CDCl}_3): \ \delta 4.17\ (\text{ddt, } J = 10.3, 7.1, 3.7 \ \text{Hz}, 2\text{H, H}_5), \ 2.27\text{–}2.19 \ (\text{m, 2H, H}_1, \text{H}_2a), \ 2.13 \ (\text{td, } J = 13.6, 4.4 \ \text{Hz}, \ 1\text{H, H}_3a), \ 2.01 \ (\text{t, } J = 6.8 \ \text{Hz}, 1\text{H, H}_8a), \ 1.92 \ (\text{dq, } J = 12.0, 2.9, 2.5 \ \text{Hz}, 1\text{H, H}_2b), \ 1.65 \ (\text{dt, } J = 14.3, 3.9 \ \text{Hz}, 1\text{H, H}_3b), \ 1.56 \ (\text{dd, } J = 8.8, 7.0 \ \text{Hz}, 1\text{H, H}_8b), \ 1.35 \ (\text{s, 3H, H}_4) \ 1.04\text{–}0.93 \ (\text{m, 2H, H}_6), \ 0.03 \ (\text{s, 9H, H}_7). \ \ ^{13}\text{C NMR} (150 \ \text{MHz, CDCl}_3): \ \delta 200.2 \ (\text{C}), \ 172.8 \ (\text{C}), \ 64.0\]
(CH$_2$), 53.1 (C), 30.7 (CH), 28.6 (CH$_2$), 22.1 (CH$_3$), 21.5 (CH$_2$), 18.1 (CH$_2$), 17.3 (CH$_2$),
7.5 (C), −1.6 (3 × CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 2953 (w), 1737 (s), 1692 (s). HRMS-Cl
(m/z): [M + Na]$^+$ calcd for C$_{14}$H$_{23}$INaO$_3$Si, 417.0353; found, 417.0396.
Synthesis of the adduct 67:

A solution of iso-propylmagnesium chloride–lithium chloride complex in tetrahydrofuran (1.25 M, 8.40 mL, 10.5 mmol, 1.05 equiv) was added dropwise to a solution of the iodo cyclopropane 66 (4.14 g, 10.5 mmol, 1.1 equiv) in toluene (50 mL) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C. A solution of the iodo enone 39 (2.5 g, 10.0 mmol, 1 equiv) in toluene (5.0 mL) was then added to the reaction mixture over 30 min at −78 °C. The reaction mixture was then removed from the cooling bath and warmed over 1 h to 23 °C. The warmed mixture was stirred for 19 h at 23 °C. The product mixture was diluted with saturated aqueous ammonium chloride solution (15 mL), water (50 mL), and 66% ether–pentane (v/v, 150 mL) at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed sequentially with water (25 mL) and saturated aqueous sodium chloride solution (25 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 14% ether–hexanes) to provide the adduct 67 as a pale yellow oil (4.35 g, 80%).

¹H NMR analysis of the unpurified product mixture indicated the presence of a 8:1 mixture of diastereomers.
R_f = 0.25 (20% ether–hexanes; PAA). \(^{1}\)H NMR (600 MHz, CDCl\(_3\)): \(\delta 6.33\) (s, 1H, H\(_{11}\)), 4.21–4.11 (m, 2H, H\(_5\)), 2.78 (bs, 1H, H\(_{13}\)), 2.28–1.98 (m, 4H, H\(_{3a,9a,10}\)), 1.72–1.49 (m, 7H, H\(_{1,2,3b,8,9b}\)), 1.43 (s, 3H, H\(_4\)), 1.21 (s, 3H, H\(_{9a}\)), 1.04 (s, 3H, H\(_{9b}\)), 1.01–0.93 (m, 2H, H\(_6\)), 0.04 (s, 9H, H\(_7\)). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 205.3\) (C), 173.9 (C), 152.2 (CH), 149.9 (C), 106.7 (C), 72.4 (CH\(_2\)), 63.5(C), 54.4 (C), 38.0 (C), 32.9 (CH\(_2\)), 31.5 (C), 30.4 (CH\(_3\)), 29.9 (CH\(_2\)), 25.4 (CH\(_3\)), 23.5 (CH), 23.1 (CH\(_3\)), 17.4 (CH\(_2\)), 17.1 (CH\(_2\)), 11.5 (CH\(_2\)), -1.5 (3 \times CH\(_3\)). IR (ATR-FTIR), cm\(^{-1}\): 3515 (m), 2953 (m), 2930 (m), 1738 (m), 1681 (m), 1446 (w). HRMS-CI (m/z): [M + Na]\(^+\) calcd for C\(_{22}\)H\(_{35}\)NaO\(_4\)Si\(_1\), 541.1247; found, 541.1266.
Synthesis of the methyl ketone 68:

A screw-capped pressure vessel was charged with copper(I) iodide (22.0 mg, 120 μmol, 0.20 equiv), cesium fluoride (973 mg, 6.41 mmol, 1.10 equiv), tetrakis(triphenylphosphine)-palladium(0) (336 mg, 290 μmol, 0.05 equiv), the adduct 67 (3.02 g, 5.82 mmol, 1 equiv), and acetonitrile (30 mL). The reaction vessel was fitted with a rubber septum and the headspace in the vessel was evacuated. The headspace was back-filled with argon. Tributyl(1-ethoxyvinyl) tin (2.20 mL, 6.48 mmol, 1.11 equiv) was added to the suspension under argon at 23 °C. The reaction chamber was then sealed and the reaction vessel was immediately placed into an oil bath that had been preheated to 65 °C. The reaction mixture was stirred and heated for 9 h at 65 °C. The product mixture was cooled over 30 min to 23 °C. The cooled product mixture was diluted with ethyl acetate (30 mL). The diluted mixture was filtered through a pad of celite (2.5 × 4.0 cm) and rinsed with ethyl acetate (3 × 15 mL). The filtrates were combined and the combined filtrates were transferred to a separatory funnel. The filtrates were washed sequentially with 30% aqueous ammonium hydroxide solution (w/v, 3 × 10 mL), saturated aqueous sodium bicarbonate solution (25 mL), and saturated aqueous sodium chloride solution (25 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and concentrated. The residue obtained was dissolved in tetrahydrofuran (30 mL). 1 N
aqueous hydrochloric acid solution (7.00 mL, 7.00 mmol, 1.20 equiv) was added at 23 °C. The reaction mixture was stirred for 1.5 h at 23 °C. The product mixture was then diluted sequentially with saturated aqueous sodium bicarbonate (30 mL, CAUTION: gas evolution!), water (15 mL), and ethyl acetate (60 mL) at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 15 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ether–hexanes) to provide the methyl ketone 68 as a white solid (1.77 g, 70%).

Rf = 0.20 (33% ether–hexanes; UV, PAA). 1H NMR (500 MHz, CDCl3): δ 6.49 (d, J = 1.3 Hz, 1H, H11), 4.24–4.03 (m, 2H, H3), 3.16 (s, 1H, H14), 2.41 (t, J = 14.2 Hz, 1H, H9a), 2.22 (s, 3H, H13), 2.21–2.17 (m, 1H, H1), 2.09 (dt, J = 13.5, 9.1 Hz, 1H, H3a), 2.02–1.96 (m, 2H, H2), 1.66 (td, J = 13.8, 3.3 Hz, 1H, H10a), 1.54–1.39 (m, 4H, H3b,8a,9b,10b), 1.29 (s, 3H, H12a), 1.21 (dd, J = 8.5, 5.0 Hz, 1H, H8b), 1.12 (s, 3H, H14), 1.10 (s, 3H, H12b), 0.95 (ddd, J = 8.8, 7.4, 4.3 Hz, 1H, H6), 0.02 (s, 9H, H7). 13C NMR (125 MHz, CDCl3): δ 206.5 (C), 204.4 (C), 173.9 (C), 151.8 (CH), 140.3 (C), 69.9 (C), 63.5 (CH2), 54.7 (C), 39.6 (C), 33.3 (C), 32.8 (CH2), 32.1 (CH2), 30.6 (CH3), 28.7 (CH2), 26.6 (CH3), 25.2 (CH3), 22.8 (CH), 21.4 (CH3), 17.4 (CH2), 17.1 (CH2), 11.3 (CH2), –1.5 (3 × CH3). IR (ATR-FTIR), cm⁻¹: 2953 (w), 1737 (s), 1692 (s). HRMS-CI (m/z): 9530 (w), 1730 (s), 1671 (s), 1370 (s); [M + Na]+ calcd for C24H38NaO5Si, 457.2386; found, 457.2394.
Synthesis of the hydroxyketone 69:

Part 1: Synthesis of the enoxysilane S5:

Trimethylsilyl trifluoromethanesulfonate (1.86 mL, 10.3 mmol, 8.00 equiv) was added to a solution of triethylamine (2.17 ml, 15.4 mmol, 12.0 equiv) and the methyl ketone 68 (650.0 mg, 1.28 mmol, 1 equiv) in dichloromethane (6.5 mL) at 0 ºC. The reaction mixture was stirred for 1 h at 0 ºC. The cold product mixture was then diluted sequentially with saturated aqueous sodium bicarbonate solution (5.0 mL), water (5.0 mL) and dichloromethane (15 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (15 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The enoxysilane ether residue S5 was found to readily hydrolyze to the corresponding methyl ketone and was consequently used directly in the next step without purification.
Part 2: Synthesis of the hydroxyketone 69:

3-Chloroperoxybenzoic acid (332.1 mg, 1.92 mmol, 1.5 equiv) was added in one portion to a solution of the unpurified enoxysilane S5 obtained in the preceding step (nominally, 1.28 mmol, 1 equiv) in dichloromethane (6.5 mL) at 0 °C. The reaction mixture was immediately removed from the cooling bath and allowed to warm over 30 min to 23 °C. The reaction mixture was stirred for 2 h at 23 °C. The product mixture was diluted sequentially with 10% aqueous sodium thiosulfate solution (w/v, 6 mL), water (5.0 mL), and ethyl acetate (15 mL) at 23 °C. The resulting biphasic mixture was stirred for 1 h at 23 °C. The mixture was then transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed sequentially with 10% aqueous potassium carbonate solution (w/v, 2 × 6 mL) and saturated aqueous sodium chloride solution (15 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes) to provide the hydroxyketone 69 as a white solid (468 mg, 70% over two steps).

Rf = 0.20 (33% ethyl acetate–hexanes; UV, PAA). 1H NMR (600 MHz, CDCl3): δ 6.45 (s, 1H, H11), 4.49 (dd, J = 17.6, 4.4 Hz, 1H, H13a), 4.25 (dd, J = 17.6, 4.3 Hz, 1H, H13b), 4.15 – 4.08 (m, 2H, H5), 3.41 (t, J = 4.5 Hz, 1H, H15), 2.49 (td, J = 14.3, 3.3 Hz, 1H, H9a), 2.30 (ddt, J = 8.9, 6.3, 3.3 Hz, 1H, H1), 2.24–2.03 (m, 2H, H2a, H3a), 1.96 (dq, J = 13.4, 3.4 Hz,
1H, H_{2b}), 1.66 (td, J = 14.0, 3.1 Hz, 1H, H_{10}), 1.60–1.57 (m, 1H, H_{8a}), 1.53–1.45 (m, 2H, H_{3b}, H_{9b}, H_{10b}), 1.25 (s, 3H, H_{12a}), 1.16 (dd, J = 8.5, 5.0 Hz, 1H, H_{8b}), 1.14 (s, 3H, H_{12b}), 1.08 (s, 3H, H_{4}), 0.94 (ddd, J = 10.6, 6.8, 2.3 Hz, 2H, H_{6}), 0.02 (s, 9H, H_{14}), 0.00 (s, 9H, H_{7}). ¹³C NMR (125 MHz, CDCl₃): δ 207.1 (C), 199.0 (C), 174.2 (C), 153.1 (CH), 136.6 (C), 72.0 (C), 64.5 (CH₂), 63.4 (CH₂), 54.5 (C), 40.8 (C), 34.1 (CH₂), 33.5 (C), 32.2 (CH₂), 29.7 (CH₃), 29.5 (CH₂), 25.5 (CH₃), 24.3 (CH), 21.9 (CH₃), 17.8 (CH₂), 17.1 (CH₂), 12.2 (CH₂), 2.2 (3 × CH₃), −1.5 (3 × CH₃). IR (ATR-FTIR), cm⁻¹: 2954 (m), 2930 (m), 2361 (m), 2339 (m), 1398 (w). HRMS-CI (m/z): [M + Na]⁺ calcd for C_{27}H_{46}NaO_{6}Si_{2}, 545.2730; found, 545.2794.
Synthesis of the allyl carbonate 70:

Allyl chloroformate (935 μL, 8.80 mmol, 5.00 equiv) was added dropwise via syringe to a solution of the hydroxyketone 69 (920.0 mg, 1.76 mmol, 1 equiv) in 5% pyridine–dichloromethane (v/v, 6.0 mL) at 0 °C. The reaction mixture was allowed to warm with its bath over ~1 h to 23 °C. The reaction mixture was stirred for an additional 1 h at 23 °C. The product mixture was diluted sequentially with ethyl acetate (20 mL) and water (20 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed sequentially with 1 N aqueous hydrogen chloride solution (3 × 7 mL), saturated aqueous sodium bicarbonate solution (15 mL), and saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ether–hexanes) to provide the allyl carbonate 70 as a colorless oil (1.05 g, 96%).

R_f = 0.33 (20% ether–hexanes; UV, PAA). ^1H NMR (500 MHz, CDCl₃): δ 6.41 (s, 1H, H₁₁), 6.02–5.87 (m, 1H, H₁₆), 5.46–5.34 (m, 1H, H₁₇ₐ), 5.33–5.23 (m, 1H, H₁₇ₖ), 5.14 (d, J = 16.1 Hz, 1H, H₁₃ₐ), 4.68 (d, J = 16.3 Hz, 1H, H₁₃ₖ), 4.66–4.64 (m, 2H, H₁₅), 4.18–4.06 (m, 2H, H₃), 2.47 (td, J = 15.4, 14.6, 4.0 Hz, 1H, H₀₆), 2.29 (td, J = 7.0, 6.4, 3.2 Hz, 1H, H₁), 2.15 (tt, J = 13.5, 3.6 Hz, 1H, H₂₆), 2.06 (td, J = 13.5, 4.1 Hz, 1H, H₃ₐ), 1.90 (dq, J =
13.2, 3.4 Hz, 1H, H_{2b}), 1.71–1.63 (m, 1H, H_{10a}), 1.56 (app t, \( J = 6.0 \) Hz, 1H, H_{8a}), 1.54–1.44 (m, 3H, H_{3b,9b,10b}), 1.25 (s, 3H, H_{12a}), 1.16–1.12 (m, 7H, H_{4,8b,12b}), 0.93 (ddd, \( J = 9.8, 6.6, 1.3 \) Hz, 2H, H_{6}), 0.02 (s, 9H, H_{14}), 0.01 (s, 9H, H_{7}). 13C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 207.2 (C), 192.1 (C), 174.3 (C). 154.6 (C), 151.9 (CH), 137.1 (C), 131.4 (CH), 118.7 (CH\(_2\)), 72.0 (C), 68.7 (CH\(_2\)), 68.2 (CH\(_2\)), 63.4 (CH\(_2\)), 54.6 (C), 40.8 (C), 34.0 (CH\(_2\)), 33.5 (C), 32.2 (CH\(_2\)), 29.8 (CH\(_3\)), 29.7 (CH\(_2\)), 25.7 (CH\(_3\)), 24.5 (CH), 22.1 (CH\(_3\)), 17.8 (CH\(_2\)), 17.1 (CH\(_2\)), 12.4 (CH\(_2\)), 2.2 (3 \times CH\(_3\)), −1.5 (3 \times CH\(_3\)). IR (ATR-FTIR), cm\(^{-1}\): 2953 (m), 2901 (w), 1754 (s), 1695 (s), 1624 (w). HRMS-CI (m/z): [M + Na]\(^+\) calcd for C\(_{31}\)H\(_{50}\)NaO\(_8\)Si\(_2\), 629.2942; found, 629.2994.
Synthesis of the diosphenol 75 and the silyl transfer product 73:

A solution of the carbonate 70 (509 mg, 840 μmol, 1 equiv) in tetrahydrofuran (1.6 mL) was added via syringe pump over 20 min to a solution of sodium tert-butoxide (173 mg, 1.80 mmol, 2.14 equiv) in tetrahydrofuran (4.4 mL) at −78 °C. The reaction mixture was stirred for 2 h at −78 °C. The reaction mixture was then transferred to an ice bath at 0 °C. The reaction mixture was stirred for additional 20 min at 0 °C. The product mixture was diluted with saturated aqueous ammonium chloride solution (4.0 mL), water (3.0 mL) and ethyl acetate (20 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting initially with 14% ether–hexanes, grading to 33% ether–hexanes, one step) to provide separately the diosphenol 75 as a yellow oil (246 mg, 58%) and the silane transfer product 73 (79 mg, 15%).
Separation of the enantiomers of 75 was achieved by preparative chiral stationary phase supercritical fluid chromatography (elueting with 15% methanol–supercritical carbon dioxide) to furnish separately (+)-75 ([α]D20 = +23.4 (c= 0.4, chloroform)) and (−)-75 ([α]D20 = −28.1 (c= 0.4, chloroform)).

Diosphenol 75: Rf = 0.37 (50% ether–hexanes; UV, PAA). 1H NMR (600 MHz, CDCl3): δ 6.78 (d, J = 1.3 Hz 1H, H11), 6.21 (s, 1H, H13), 4.19 (td, J = 10.8, 6.1 Hz, 1H, H5a), 4.11 (td, J = 10.8, 6.4 Hz, 1H, H5b), 3.57 (d, J = 5.6 Hz, 1H, H13), 1.97 (ddd, J = 17.7, 10.7, 3.9 Hz, 1H, H9a), 1.91–1.85 (m, 1H, H9b), 1.78 (td, J = 12.6, 5.0 Hz, 1H, H3b), 1.65 (td, J = 12.6, 5.0 Hz, 2H, H3a,10b), 1.38 (s, 3H, H4), 1.14 (s, 3H, H12), 1.00 (s, 3H, H12), 0.98–0.86 (m, 4H, H6,8), 0.00 (s, 9H, H7), −0.02 (s, 9H, H14). 13C NMR (150 MHz, CDCl3): δ 183.2 (C), 177.0 (C), 149.0 (CH), 143.3 (C), 134.4 (C), 133.8 (C), 75.1 (C), 63.2 (CH2), 44.0 (C), 32.8 (C), 31.6 (CH2), 29.7 (C), 29.2 (CH2), 29.1 (CH3), 27.4 (CH2), 26.8 (CH3), 19.8 (CH3), 17.7 (CH2), 17.3 (CH2), 15.7 (CH2), 13.2 (CH2), 2.85 (3 × CH3), −1.35 (3 × CH3). IR (ATR-FTIR), cm⁻¹: 2954 (m), 2901 (m), 1734 (s), 1718 (m), 1636 (w). HRMS-Cl (m/z): [M + H]+ calcd for C28H49O6Si2, 505.2805; found, 505.2877.

Silyl transfer product 73: Rf = 0.29 (50% ether–hexanes; UV, PAA). 1H NMR (600 MHz, CDCl3): δ 6.89 (s, 1H, H11), 5.59 (s, 1H, H16), 5.29 (d, J = 5.6 Hz, 1H, H13), 4.32–4.06 (m, 2H, H5), 3.57 (d, J = 5.6 Hz, 1H, H13), 1.98–1.91 (m, 1H, H2a), 1.83–1.77 (m, 2H, H2b,3a), 1.63–1.54 (m, 3H, H9,10a), 1.45–1.41 (m, 1H, H10b), 1.40–1.36 (m, 4H, H1,4), 1.18–1.13 (m, 2H, H3b,8a), 1.11 (s, 3H, H12a), 1.07–0.97 (m, 5H, H6,12b), 0.69 (dd, J = 9.4, 6.6 Hz, 1H, H8b), 0.11 (s, 9H, H14), 0.04 (s, 9H, H7). 13C NMR (150 MHz, CDCl3): δ 198.5 (C), 179.6
(C), 147.2 (CH), 133.1 (C), 76.2 (C), 75.9 (CH), 74.4 (C), 63.7 (CH₂), 44.8 (C), 35.0 (C), 33.7 (CH₂), 32.3 (C), 28.3 (CH₃), 27.5 (CH₃), 27.2 (CH₂), 26.2 (CH₂), 18.7 (CH₂), 18.3 (CH₃), 17.0 (CH₂), 15.2 (CH₂), 12.5 (CH₂), 2.6 (3 × CH₃), –1.5 (3 × CH₃). IR (ATR-FTIR), cm⁻¹: 2903 (m), 2901 (m), 1705 (s), 1632 (m). [M + Na]⁺ calcd for C₂₇H₄₆NaO₆Si₂, 545.2731; found, 545.2744.
Synthesis of the ketone 76:

Part 1: Synthesis of the ketal S6:

\[ \text{HO-C(OH)(CH}_2\text{CH}_3\text{)} + \text{(EtO)}_3\text{CH} + \text{p-TsOH} \cdot \text{H}_2\text{O} \rightarrow \text{Et}_2\text{O, 40 ºC} \]

87%

Triethyl orthoformate (3.00 mL, 27.4 mmol, 5.04 equiv) was added to a solution of ethylene glycol (1.20 mL, 21.5 mmol, 3.95 equiv), para-toluenesulfonic acid monohydrate (52.0 mg, 273 μmol, 0.05 equiv) and the iodoenone 39 (1.36 g, 5.44 mmol, 1 equiv) in ether (7.0 mL) under argon in a screw-capped pressure vessel at 23 °C. The reaction vessel was sealed under argon and the sealed vial was placed in an oil bath that had been preheated to 40 °C. The reaction mixture was stirred and heated for 2 d at 40 °C. The product mixture was cooled over 30 min to ~23 °C. The cooled product mixture was diluted with ethyl acetate (20 mL). The diluted mixture was transferred to a separatory funnel and washed sequentially with saturated aqueous sodium bicarbonate solution (10 mL) and saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ether–hexanes) to provide the known ketal S6 as a yellow oil (1.39 g, 87%).

\(^1\)H NMR spectroscopic data for S6 obtained in this way were in agreement with those reported by Takahashi et al.
Part 2: Synthesis of the ketone 76:

A solution of \( n \)-butyllithium in hexanes (2.33 M, 3.00 mL, 6.99 mmol, 1.07 equiv) was added dropwise via syringe to a solution of the ketal S6 (2.00 g, 6.53 mmol, 1 equiv) in tetrahydrofuran (30 mL) at \(-78 \, ^\circ\text{C}\). The reaction mixture was stirred at \(-78 \, ^\circ\text{C}\) for 2 min. A solution of the amide 46 (1.82 g, 7.79 mmol, 1.19 equiv) in tetrahydrofuran (8.0 mL) was then added to the reaction mixture slowly at \(-78 \, ^\circ\text{C}\). The reaction mixture was stirred for 2 h at \(-78 \, ^\circ\text{C}\) and warmed gradually with its cooling bath over 21 h to 23 \, ^\circ\text{C}\). The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (5.0 mL), water (10 mL), and ethyl acetate (75 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted ethyl acetate (2 \times 15\, mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting initially with 10\% ether–hexanes initially, grading to 14\% ether–hexanes, 1 step) to provide the ketone 76 as a colorless oil (1.45 g, 65\%).

\( R_f = 0.39 \) (20\% ether–hexanes; UV, PAA). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 6.47 (s, 1H, \( H_5 \)), 4.48 (s, 1H, \( H_6 \)), 4.17–4.08 (m, 2H, \( H_{4a} \)), 4.03–3.96 (m, 2H, \( H_{4b} \)), 1.81–1.73 (m, 2H,
$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 198.8 (C), 151.6 (CH), 134.2 (C), 106.2 (C), 68.5 (CH$_2$), 64.6 (2 × CH$_2$), 33.6 (CH$_2$), 32.7 (C), 30.6 (CH$_2$), 28.0 (2 × CH$_3$), 25.8 (3 × CH$_3$), 18.5 (C), −5.4 (2 × CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 2956 (m), 2857 (m), 1705 (m), 1627 (w). HRMS-Cl (m/z): [M + H]$^+$ calcd for C$_{18}$H$_{33}$O$_4$Si, 341.2143; found, 341.2144.
Synthesis of the diketone 77:

Part 1: Synthesis of the ketone S7:

A solution of tetrabutylammonium fluoride in tetrahydrofuran (1 M, 5.30 ml, 5.30 mmol, 1.11 equiv) was added to a solution of the ketone 76 (1.69 g, 4.79 mmol, 1 equiv) in tetrahydrofuran (24 mL) at 0 ºC. The reaction mixture was stirred for 30 min at 0 ºC. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (15 mL), water (15 mL), and ethyl acetate (50 mL) at 0 ºC. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The ketone product S7 obtained in this way was used directly in the following step.
**Part 2: Synthesis of the allyl carbonate S8:**

Allyl chloroformate (2.60 mL, 24.5 mmol, 5.11 equiv) was added dropwise via syringe to a solution of the unpurified ketone S7 obtained in the preceding step (nominally 4.79 mmol, 1 equiv) in 5% pyridine–dichloromethane (w/v, 15 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and warmed gradually with its cooling bath over 14 h to 23 °C. Additional allyl chloroformate (1.00 mL, 9.41 mmol, 1.96 equiv) was added carefully to the reaction mixture at 23 °C. The reaction mixture was stirred for 3 h at 23 °C. The product mixture was diluted sequentially with ethyl acetate (75 mL) and 1 N aqueous hydrogen chloride solution (30 mL), with stirring. The resulting biphasic mixture was stirred for 30 min at 23 °C and then transferred to a separatory funnel. The layers that formed were separated. The organic layer was washed sequentially with 1 N aqueous hydrogen chloride solution (3 × 20 mL), saturated aqueous sodium bicarbonate solution (20 mL), and saturated aqueous sodium chloride solution (20 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The carbonate S8 obtained in this way was used without further purification.
Part 3: Synthesis of the diketone 77:

Aqueous hydrogen chloride solution (1 N, 24.0 mL, 24.0 mmol, 5.01 equiv) was added to a solution of the unpurified carbonate S8 obtained in the preceding step (nominally 4.79 mmol, 1 equiv) in tetrahydrofuran (50 mL) at 23 °C. The reaction mixture was stirred for 5 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous sodium bicarbonate solution (50 mL), water (30 mL), and ethyl acetate (150 mL), with stirring. The resulting biphasic mixture was stirred for 30 min at 23 °C. The mixture was then transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 30 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used purified by flash-column chromatography (eluting with 50% ether–hexanes) to furnish the diketone 77 as a colorless oil (422 mg, 64% over three steps).

Rf = 0.47 (50% ether–hexanes; UV, PAA). 1H NMR (500 MHz, CDCl3): δ 7.64 (s, 1H, H4), 6.00–5.89 (m, 1H, H7), 5.44–5.34 (m, 1H, H8a), 5.31–5.24 (m, 1H, H8b), 5.16 (s, 2H, H5), 4.66 (d, J = 5.3 Hz, 2H, H6), 2.54 (t, J = 7.0 Hz, 2H, H3), 1.89 (t, J = 6.8 Hz, 2H, H2), 1.23 (s, 6H, H1). 13C NMR (125 MHz, CDCl3): δ 196.9 (C), 191.7 (C), 168.5 (CH), 154.7 (C), 133.2 (C), 131.4 (CH), 118.8 (CH2), 71.9 (CH2), 68.8 (CH2), 35.2 (CH2), 35.1 (CH2),
34.60 (C), 27.2 (2 × CH₃). IR (ATR-FTIR), cm⁻¹: 2962 (w), 1750 (s), 1704 (s), 1679 (s), 1598 (m). HRMS-CI (m/z): [M + H]⁺ calcd for C₁₄H₁₉O₅, 289.1046; found, 289.1049.
Synthesis of the enoxysilane ether 78:

A solution of lithium bis(trimethylsilyl)amide (95%, 74.0 mg, 420 μmol, 1.40 equiv) in tetrahydrofuran (800 μL) at 23 °C was transferred via cannula to a solution of chlorotrimethylsilane (50.0 μL, 394 μmol, 1.31 equiv) and the diketone 77 (80.0 mg, 300 μmol, 1 equiv) in tetrahydrofuran (1.2 mL) at −78 °C. The reaction mixture was stirred for 1 h at −78 °C. The product mixture was diluted sequentially with triethylamine (600 μL) and ethyl acetate (10 mL) at −78 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed sequentially with saturated aqueous sodium bicarbonate solution (3.0 mL) and saturated aqueous sodium chloride solution (3.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ether–hexanes) to provide the enoxysilane 78 as a colorless oil (66.0 mg, 65%).

Rf = 0.31 (25% ether–hexanes; UV, PAA). ¹H NMR (600 MHz, C₆D₆): δ 8.46 (s, 1H, H₅), 6.79 (s, 1H, H₄), 5.59–5.55 (m, 1H, H₇), 5.05 (d, J = 17.8 Hz, 1H, H₈a), 4.89 (d, J = 10.5 Hz, 1H, H₈b), 4.31 (d, J = 5.3 Hz, 2H, H₆), 2.18 (t, J = 5.5 Hz, 2H, H₃), 1.26 (t, J = 6.8 Hz, 2H, H₂), 0.75 (s, 6H, H₁), 0.35 (s, 9H, H₉). ¹³C NMR (150 MHz, C₆D₆): δ 195.4 (C), 154.8 (CH), 152.6 (C), 134.9 (C), 131.6 (CH), 131.1 (C), 126.9 (CH), 118.4 (CH₂), 68.8 (CH₂), 36.0 (CH₂), 35.5 (CH₂), 32.9 (C), 27.7 (2 × CH₃), 0.5 (3 × CH₃). IR (ATR-FTIR), cm⁻¹:
2962 (m), 1752 (s), 1705 (s), 1681 (s), 1603 (m). HRMS-CI (m/z): [M + H]^+ calcd for C_{17}H_{26}NaO_{5}Si, 361.1447; found, 361.1446.
Synthesis of the diosphenol 75 by the fragment coupling–cyclization cascade:

A solution of \( n \)-butyllithium in hexanes (2.20 M, 50.0 μL, 110 μmol, 2.20 equiv) was added to a solution of the iodocephosphate 66 (43.0 mg, 110 μmol, 2.20 equiv) in tetrahydrofuran (500 μL) at −78 °C. A solution of the enoxysilane 78 (17.0 mg, 50.0 μmol, 1 equiv) in tetrahydrofuran (150 μL) was added then immediately added dropwise down the inside wall of the flask. The reaction mixture was stirred for 2 h at −78 °C. The reaction mixture was then immersed in a cooling bath at 0 °C. The reaction mixture was stirred for 3 h at 0 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (150 μL), water (500 μL), and ethyl acetate (8.0 mL). The resulting biphasic solution was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparatory thin-layered chromatography (eluting with 16% ether–hexanes) to furnish the diosphenol 75 as light-yellow oil (9.0 mg, 36%).

\(^1\)H NMR and \(^{13}\)C NMR spectroscopic data for 75 obtained in this way agreed with those obtained by the cyclodehydration sequence 70 → 75.
Synthesis of the geminal dimethyl myrocin G analog 65:

A solution of tetrabutylammonium fluoride in tetrahydrofuran (1.0 M, 0.168 ml, 0.168 mmol, 2.10 equiv) was added to a solution of the diosphenol 75 (38.0 mg, 0.0753 mmol, 1 equiv) in N,N-dimethylformamide (350 μL) at 23 °C. The reaction mixture was stirred for 6 h at 23 °C. The reaction vessel was placed in an oil bath that had been preheated to 35 °C. The reaction mixture was stirred and heated for 2 h at 35 °C. The reaction vessel was removed from the oil bath and allowed to cool over 5 min to ~23 °C. The cooled product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (3.0 mL), water (3.0 mL), and ethyl acetate (15 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 4.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (3 × 3.0 mL) and saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 1% acetic acid–50% acetone–hexanes). The fractions containing product (TLC analysis) were combined and the combined fractions were diluted with 60 mL of toluene and then concentrated to provide the geminal dimethyl myrocin G analog 65 as an off-white solid.
(15.9 mg, 64%). The structure of the methyl analog product 65 was confirmed by X-ray analysis (see Appendix A). Deprotection of the enantiomers of (+)-75 and (−)-75 under the above described conditions furnished (+)-65 ([α]_{D}^{20} = +68.8 (c= 0.12, methanol)) and (−)-65 ([α]_{D}^{20} = −82.8 (c= 0.10, methanol)).

R_{f} = 0.20 (1% acetic acid–50% acetone–hexanes; UV, PAA). \textsuperscript{1}H NMR (600 MHz, methanol-\textit{d}_{4}): δ 6.81 (d, J = 5.6 Hz, 1H, H\textsubscript{11}), 2.06 (ddd, J = 18.5, 9.5 Hz, 1H, H\textsubscript{2a}), 1.91–1.83 (m, 2H, H\textsubscript{2b,3a}), 1.79–1.71 (m, 1H, H\textsubscript{10a}), 1.68 (dd, J = 10.4, 5.0 Hz, 1H, H\textsubscript{1}), 1.57 (td, J = 13.9, 12.8 Hz, 1H, H\textsubscript{9a}), 1.51–1.39 (m, 2H, H\textsubscript{10b,9b}), 1.37 (s, 3H, H\textsubscript{4}), 1.31–1.27 (m, 1H, H\textsubscript{3b}), 1.12 (s, 3H, H\textsubscript{12}), 1.06 (dd, J = 8.9, 5.7 Hz, 1H, H\textsubscript{8a}), 1.04 (s, 3H, H\textsubscript{12}), 0.93 (t, J = 6.2 Hz, 1H, H\textsubscript{8b}). \textsuperscript{13}C NMR (150 MHz, methanol-\textit{d}_{4}): δ 183.7 (C), 180.9 (C), 150.2 (CH), 145.5 (C), 135.3 (C), 135.2 (C), 72.3 (C), 45.1 (C), 45.1 (C), 33.8 (C), 32.3 (CH\textsubscript{2}), 30.6 (CH\textsubscript{2}), 29.9 (CH\textsubscript{3}), 29.4 (C), 27.7 (CH\textsubscript{2}), 26.5 (CH\textsubscript{3}), 20.1 (CH\textsubscript{3}), 18.5 (CH\textsubscript{2}), 16.6 (CH), 13.4 (CH\textsubscript{2}). IR (ATR-FTIR), cm\textsuperscript{−1}: 2945 (m), 2933 (m), 1712 (s), 1658 (s), 1604 (s). HRMS- CI (m/z): [M + H]\textsuperscript{+} calcd for C\textsubscript{19}H\textsubscript{25}O\textsubscript{5}, 333.1702; found, 333.1728.
Synthesis of the unsaturated ketone 83:

A solution of acrolein diethyl acetal (4.16 mL, 27.3 mmol, 1 equiv) in acetonitrile (35.0 mL) was added dropwise via syringe pump over 24 h to a solution of the β-ketoester 82 (10.3 g, 47.8 mmol, 1.75 equiv), the amine catalyst S9 (2.14 g, 6.64 mmol, 24.3 mol %), and 3-nitrobenzoic acid (913 mg, 5.46 mmol, 20.0 mol %) in acetonitrile (60.0 mL) with exclusion of light at 23 ºC. The reaction mixture was stirred for 3 days at 23 ºC. The product mixture was transferred to a separatory funnel that had been charged with ethyl acetate (400 mL). The diluted mixture was washed sequentially with water (100 mL) and 2 M aqueous sodium hydroxide solution (3 × 30 mL). The aqueous layers were combined and the combined aqueous layers were extracted with ethyl acetate (2 × 50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting initially with 14% ether–hexanes, grading to 25% ether–hexanes, one step) to provide the unsaturated ketone 83 as a yellow oil (2.23 g, 32%).
The enantiomeric excess (ee) of 83 obtained in this way was determined to be 92% by chiral stationary phase HPLC analysis (Chiralpak® IG column, eluting with 5% ethanol–hexanes, flow rate of 500 µL/min, 30 min).

R_f = 0.33 (20% ether–hexanes; UV, PAA). ^1H NMR (600 MHz, CDCl_3): δ 6.92–6.89 (m, 1H, H_1), 6.04 (d, J = 10.0 Hz, 1H, H_8), 4.21–4.17 (m, 2H, H_5), 2.52–2.48 (m, 2H, H_{2a}, H_{3a}), 2.37–2.30 (m, 1H, H_{2b}), 1.91–1.86 (m, 1H, H_{3b}), 1.38 (s, 3H, H_4), 1.02–0.93 (m, 2H, H_6), 0.02 (s, 9H, H_7). ^13C NMR (150 MHz, CDCl_3): δ 197.0 (C), 172.8 (C), 149.3 (CH), 128.9 (CH), 63.7 (CH_2), 53.3 (C), 33.3 (CH_2), 23.7 (CH_2), 20.3 (CH_3), 17.3 (CH_2), −1.6 (3 × CH_3). IR (ATR-FTIR), cm⁻¹: 2956 (m), 1728 (s), 1684 (s). HRMS-CI (m/z): [M + Na]^+ calcd for C_{13}H_{22}NaO_3Si, 277.1230; found, 277.1249. \([\alpha]_D^{20} = +25.1 \ (c = 1.33, \text{CDCl}_3)\).
Synthesis of the α-iodoenone 84:

Iodine (420 mg, 1.65 mmol, 2.00 equiv) was added to a solution of the unsaturated ketone 83 (210 mg, 830 μmol, 1 equiv) in 5% pyridine–dichloromethane (v/v, 2.8 mL) at 23 ºC. The reaction mixture was stirred for 15 h at 23 ºC. The product mixture was diluted sequentially with saturated aqueous sodium thiosulfate solution (5.0 mL), water (5.0 mL), and ethyl acetate (15 mL). The resulting biphasic mixture was stirred for 20 min at 23 ºC. The stirred mixture was transferred to a separatory funnel and the layers were separated. The organic layer was washed with saturated aqueous sodium chloride solution (5.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ether–hexanes) to furnish the α-iodoenone 84 as a pale-yellow oil (307 mg, 97%).

R_f = 0.35 (20% ether–hexanes; UV, PAA). ¹H NMR (500 MHz, CDCl₃): δ 7.64–7.61 (m, 1H, H₁), 4.24–4.12 (m, 2H, H₃), 2.65–2.47 (m, 2H, H₂ₐ,3ₐ), 2.44–2.26 (m, 2H, H₂₈), 1.99–1.92 (m, 1H, H₃₈), 1.42 (s, 3H, H₄), 0.96 (ddd, J = 11.1, 6.4, 3.3 Hz, 2H, H₆), 0.03 (s, 9H, H₇). ¹³C NMR (125 MHz, CDCl₃): δ 190.4 (C), 171.9 (C), 157.7 (CH), 102.0 (C), 64.1 (CH₂), 53.4 (C), 33.2 (CH₂), 27.8 (CH₂), 21.1 (CH₃), 17.3 (CH₂), -1.56 (3 × CH₃). IR
(ATR-FTIR), cm$^{-1}$: 2953 (m), 1727 (s), 1695 (s), 1596 (w). HRMS-CI (m/z): [M + Na]$^+$ calcd for C$_{13}$H$_{21}$INaO$_3$Si, 403.0197; found, 403.0209. $[\alpha]_D^{20} = +68.1$ (c = 0.93, CHCl$_3$).
Synthesis of the iodocyclopropane 85:

Trimethylsulfoxonium iodide (2.99 g, 13.6 mmol, 1.20 equiv) was added in one portion to a suspension of sodium hydride (95%, 313 mg, 12.4 mmol, 1.10 equiv) in N,N-dimethylformamide (90 mL) at 23 °C. The resulting white suspension was stirred for 1 h at 23 °C. The resulting mixture was then cooled over 30 min to 0 °C. A solution of the α-iodoenone 84 (4.29 g, 11.3 mmol, 1 equiv) in N,N-dimethylformamide (22 mL) was then added dropwise via syringe pump over 1 h at 0 °C. Upon completion of the addition, the reaction mixture was stirred for 1.5 h at 0 °C. The cold product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (25 mL), water (25 mL), and ethyl acetate (200 mL). The resulting biphasic mixture was transferred to a separatory funnel and diluted with hexanes (50 mL). The layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (3 × 20 mL) and saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 14% ether–hexanes) to provided α-iodocyclopropane 85 as an off-white solid (2.84 g, 64%).
\(^1\)H NMR analysis of the unpurified product mixture indicated the presence of a 2.3:1 mixture of diastereomers (500 MHz).

R\(_f\) = 0.36 (20\% ether–hexanes; faintly UV, PAA). \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 4.17 (ddt, \(J = 10.3, 7.1, 3.7\) Hz, 2H, H\(_5\)), 2.27–2.19 (m, 2H, H1, H\(_{2a}\)), 2.13 (td, \(J = 13.6, 4.4\) Hz, 1H, H\(_{3a}\)), 2.01 (t, \(J = 6.8\) Hz, 1H, H\(_{8a}\)), 1.92 (dq, \(J = 12.0, 2.9, 2.5\) Hz, 1H, H\(_{2b}\)), 1.65 (dt, \(J = 14.3, 3.9\) Hz, 1H, H\(_{3b}\)), 1.56 (dd, \(J = 8.8, 7.0\) Hz, 1H, H\(_{8b}\)), 1.35 (s, 3H, H\(_4\)) 1.04–0.93 (m, 2H, H\(_6\)), 0.03 (s, 9H, H\(_7\)). \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 200.2 (C), 172.8 (C), 64.0 (CH\(_2\)), 53.1 (C), 30.7 (CH), 28.6 (CH\(_2\)), 22.1 (CH\(_3\)), 21.5 (CH\(_2\)), 18.1 (CH\(_2\)), 17.3 (CH\(_2\)), 7.5 (C), −1.6 (3 \times CH\(_3\)). IR (ATR-FTIR), cm\(^{-1}\): 2953 (w), 1737 (s), 1692 (s). HRMS-Cl (m/z): [M + Na]\(^+\) calcd for C\(_{14}\)H\(_{23}\)INaO\(_3\)Si, 417.0353; found, 417.0396.
**Synthesis of the olefin 87:**

A solution of potassium bis(trimethylsilyl)amide (6.36 g, 31.9 mmol, 1.20 equiv) in tetrahydrofuran (90 mL) was transferred via cannula to a solution of methyltriphenylphosphonium bromide (11.5 g, 31.9 mmol, 1.20 equiv) in tetrahydrofuran (130 mL) at 0 ºC. The reaction mixture was stirred for 30 min at 0 ºC. A solution of the aldehyde 86 (11.1 g, 26.6 mmol, 1 equiv) in tetrahydrofuran (18 mL) was then added dropwise. The reaction mixture was stirred for 45 min at 0 ºC. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (200 mL), water (100 mL), and ethyl acetate (200 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ether–hexanes) to furnish the olefin 87 as a yellow oil (12.2 g, 93%).

\[ R_f = 0.30 \text{ (33\% ethyl acetate–hexanes; PAA).} \]

\[ ^1H \text{ NMR (500 MHz, (CD}_3)_2\text{SO, 120 ºC) } \delta 7.26 (t, J = 7.6 \text{ Hz, 2H, H}_{10}), 7.15 (dd, J = 20.8, 7.4 \text{ Hz 3H, H}_{9,11}), 6.01 (dd, J = 17.6, 11.0 \text{ Hz, 1H, H}_2), 5.06–4.96 \ (m, 2H, H_1), 4.68 \ (s, 1H, H_7 \text{ or } 6), 4.64 \ (d, J = 4.4 \text{ Hz, 1H, H}_6 \text{ or } 7), \]

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4.41 (d, $J = 16.3$ Hz, 1H, H$_{8a}$), 4.29 (d, $J = 16.3$ Hz, 1H, H$_{8b}$), 3.53 (s, 3H, H$_{12}$), 2.08 (h, $J = 9.9$, 9.3 Hz, 2H, H$_5$), 1.80 (dt, $J = 14.9$, 7.6 Hz 1H, H$_{4a}$), 1.57–1.45 (m, 1H, H$_{4b}$), 1.07 (s, 3H, H$_3$), 0.84 (s, 9H, H$_{13}$), −0.02 (d, 1H, $J = 9.4$ Hz, H$_{14}$). IR (ATR-FTIR), cm$^{-1}$: 2954 (m), 2930 (m), 2857 (m), 1721 (s), 1694 (s), 1665 (s) 1450 (m). $[\alpha]_D^{20} = -92.7$ (c= 0.42, CHCl$_3$).
**Synthesis of the α-iodoenone 88:**

**Part 1: Synthesis of the unsaturated ketone S10:**

A 500-mL flask fused to a Teflon-coated valve was charged with the olefin 87 (6.60 g, 15.9 mmol, 1 equiv) and tetrahydrofuran (160 mL). Aqueous hydrochloric acid solution (1 N, 33.0 mL, 33.0 mmol, 2.08 equiv) was then added at 23 ºC. The reaction vessel was sealed and the sealed reaction vessel was placed in an oil bath that had been preheated to 70 ºC. The reaction mixture was stirred for 3 days at 70 ºC. The product mixture was then cooled over 45 min to ~23 ºC. The cooled product mixture was diluted slowly and sequentially with saturated aqueous sodium bicarbonate solution (100 mL, CAUTION: Gas evolution!), water (50 mL), and ethyl acetate (150 mL), with stirring. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (150 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.
**Part 2: Synthesis of the α-iodoenone 88:**

Iodine (12.0 g, 47.6 mmol, 3.00 equiv) was added to a solution of the unsaturated ketone S10 (nominally 15.9 mmol, 1 equiv) in 5% pyridine–dichloromethane (v/v, 80 mL) at 23 °C. The reaction mixture was stirred for 5 days at 23 °C. The product mixture was diluted sequentially with saturated aqueous sodium thiosulfate solution (50 mL), water (50 mL), and ethyl acetate (100 mL). The resulting biphasic mixture was stirred for 20 min at 23 °C. The stirred mixture was transferred to a separatory funnel and the layers were separated. The organic layer was washed sequentially with 1 N aqueous hydrochloric acid solution (2 × 40 mL) and saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 14% ether–hexanes) to furnish the α-iodoenone 88 as a pale-yellow oil (2.65 g, 64% two steps).

\[ R_f = 0.35 \text{ (20\% ether–hexanes; UV, PAA)}. \]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.43 (s, 1H, H$_6$), 5.76 (dd, $J = 17.3$, 10.5 Hz 1H, H$_2$), 5.16 (d, $J = 17.4$ Hz, 1H, H$_{1a}$), 5.06 (d, $J = 17.4$ Hz, 1H, H$_{1b}$), 2.64 (t, $J = 6.4$ Hz, 2H, H$_5$), 2.00 (t, $J = 6.6$ Hz, 2H, H$_4$), 1.27 (s, 3H, H$_3$).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 192.3 (C), 164.5 (CH), 141.7 (CH), 115.3 (CH$_2$), 103.4 (C), 44.5 (C), 34.9 (CH$_2$), 33.6 (CH$_2$), 26.7 (CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 2962 (m), 2933
(m), 1686 (s), 1583 (m). HRMS-Cl (m/z): [M + H]^+ calcd for C₉H₁₂IO, 262.9932; found, 262.9975. \([\alpha]_D^{20} = -55.7 \) (c= 0.75, CHCl₃).
Synthesis of the ketal S11:

Triethyl orthoformate (8.50 mL, 51.1 mmol, 7.09 equiv) was added to a solution of ethylene glycol (2.00 mL, 35.8 mmol, 4.97 equiv), para-toluenesulfonic acid monohydrate (68.9 mg, 360 μmol, 5.0 mol %), and the iodoenone 88 (1.89 g, 7.21 mmol, 1 equiv) in ether (14 mL) at 23 ºC. The reaction vessel was sealed and the sealed reaction vessel was placed in an oil bath that had been preheated to 50 ºC. The reaction mixture was stirred for 29 h at 50 ºC. The product mixture was cooled to 23 ºC over 30 min. The cooled product mixture was diluted with ethyl acetate (25 mL). The diluted mixture was transferred to a separatory funnel and washed sequentially with saturated aqueous sodium bicarbonate solution (15 mL) and saturated aqueous sodium chloride solution (15 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ether–hexanes) to provide the ketal S11 as a colorless oil (2.10 g, 95%).

R<sub>f</sub> = 0.50 (10% ether–hexanes; UV, PAA). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 6.38 (s, 1H, H<sub>7</sub>), 5.66 (dd, J = 17.4, 10.5 Hz, 1H, H<sub>2</sub>), 5.14–4.90 (m, 2H, H<sub>1</sub>), 4.30–4.14 (m, 2H, H<sub>6a</sub>), 4.08–3.88 (m, 2H, H<sub>6b</sub>), 2.03–1.83 (m, 2H, H<sub>3</sub>), 1.83–1.67 (m, 2H, H<sub>4</sub>), 1.12 (s, 3H, H<sub>3</sub>). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 150.3 (CH), 143.4 (CH), 113.6 (CH<sub>2</sub>), 105.9 (C), 103.4
(C), 65.8 (CH₂), 65.4 (CH₂), 43.5 (C), 32.7 (CH₂), 30.6 (CH₂), 26.7 (CH₃). IR (ATR-FTIR), cm⁻¹: 2957 (m), 2926 (m), 2888 (m), 1636 (w), 1344 (m). HRMS-Cl (m/z): [M + H]⁺ calcd for C₁₁H₁₆IO₂, 307.0189; found, 307.0177. [α]D²⁰ = −40.4 (c = 4.55, CHCl₃).
**Synthesis of the ketone S12:**

A solution of \( n \)-butyllithium in hexanes (2.33 M, 3.00 mL, 6.99 mmol, 1.07 equiv) was added dropwise via syringe to a solution of the ketal S11 (2.00 g, 6.53 mmol, 1 equiv) in tetrahydrofuran (30 mL) at \(-78 \) °C. The reaction mixture was stirred for 2 min at \(-78 \) °C. A solution of the Weinreb amide 46 (1.82 g, 7.79 mmol, 1.19 equiv) in tetrahydrofuran (8.0 mL) was then added dropwise via syringe pump over 20 min at \(-78 \) °C. The reaction mixture was stirred for 2 h at \(-78 \) °C. The reaction mixture was then allowed to warm to 23 °C over 21 h. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (5.0 mL), water (10 mL), and ethyl acetate (75 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted ethyl acetate (2 × 15 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting initially with 10% ether–hexanes, grading to 14% ether–hexanes, one step) to provide the ketone S12 as a colorless oil (1.70 g, 74%).
$R_f = 0.39$ (20% ether–hexanes; UV, PAA). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.47 (s, 1H, H$_7$), 5.72 (dd, $J = 17.5$, 10.5 Hz, 1H, H$_2$), 5.04 (dd, $J = 10.5$, 1.0 Hz, 1H, H$_{1a}$), 4.95 (dd, $J = 17.5$, 1.0 Hz, 1H, H$_{1b}$) 4.51 (dd, $J = 18.0$, 9.5 Hz, 2H, H$_8$), 4.18–4.09 (m, 2H, H$_{6a}$), 4.05–3.90 (m, 2H, H$_{6b}$), 1.76–1.66 (m, 4H, H$_{4,5}$), 1.16 (s, 3H, H$_3$), 0.91 (s, 9H, H$_9$), 0.86 (s, 6H, H$_{10}$). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 198.7 (C), 148.1 (CH), 143.4 (CH), 136.0 (C), 113.8 (CH$_2$), 106.1 (C), 68.6 (CH$_2$), 64.9 (CH$_2$), 64.5 (CH$_2$), 39.1 (C), 32.2 (CH$_2$), 30.1 (CH$_2$), 26.7 (CH$_3$), 25.9 (3 × CH$_3$), 18.6 (C), −5.35 (CH$_3$), −5.36 (CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 2957 (m), 2928 (m), 2858 (w), 1706 (m). HRMS-Cl (m/z): [M + H]$^+$ calcd for C$_{19}$H$_{33}$O$_4$Si 353.2143; found, 353.2192. $[^2]\alpha_{D}^0 = -97.0$ (c = 0.33, CHCl$_3$).
Synthesis of the allyl carbonate S14:

Part 1: Synthesis of the ketone S13:

A solution of tetrabutylammonium fluoride in tetrahydrofuran (1 M, 5.30 mL, 5.30 mmol, 1.11 equiv) was added to a solution of the ketone S12 (1.69 g, 4.79 mmol, 1 equiv) in tetrahydrofuran (24 mL) at 0 ºC. The reaction mixture was stirred for 30 min at 0 ºC. The cold product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (15 mL), water (15 mL), and ethyl acetate (50 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the next step without further purification.
Part 2: Synthesis of the allyl carbonate S14:

Allyl chloroformate (2.60 mL, 24.5 mmol, 5.11 equiv) was added dropwise via syringe to the ketone S13 residue obtained in the previous step (nominally, 4.79 mmol, 1 equiv) dissolved in 5% pyridine–dichloromethane (v/v, 15 mL) and the resulting solution was cooled to 0 °C. The resulting mixture was stirred for 1 h at 0 °C. The reaction mixture was then allowed to warm to 23 °C over 14 h. An additional portion of allyl chloroformate (1.00 mL, 9.41 mmol, 1.96 equiv) was then added. The reaction mixture was stirred for 3 h at 23 °C. The product mixture was diluted sequentially with ethyl acetate (75 mL) and 1 N aqueous hydrochloric acid solution (30 mL). The resulting biphasic mixture was stirred for 30 min at 23 °C. The stirred biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The organic layer was washed sequentially with 1 N aqueous hydrochloric acid solution (3 × 20 mL), saturated aqueous sodium bicarbonate solution (20 mL), and saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting initially with 20% ether–hexanes, grading to 50% ether hexanes, one step) to provide the allyl carbonate S14 as a colorless oil (829 mg, 54% two steps).
$R_f = 0.72$ (33% ethyl acetate–hexanes; UV, PAA). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.64 (s, 1H, H$_7$), 5.97–5.87 (m, 1H, H$_{10}$), 5.70 (dd, $J = 17.5, 10.6$ Hz, 1H, H$_2$), 5.37 (dt, $J = 17.2, 1.4$ Hz, 1H, H$_{11a}$), 5.25 (dt, $J = 10.5, 1.2$ Hz, 1H, H$_{11b}$), 5.05–4.85 (m, 4H, H$_{1,8}$), 4.64 (dq, $J = 5.7, 1.3$ Hz, 2H, H$_9$), 4.19–3.99 (m, 4H, H$_6$), 1.82–1.62 (m, 4H, H$_{4,5}$), 1.16 (s, 3H, H$_3$).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 192.6 (C), 154.6 (C), 150.1 (CH), 143.0 (CH), 134.9 (C), 131.3 (CH), 118.7 (CH$_2$), 114.0 (CH$_2$), 105.8 (C), 69.8 (CH$_2$), 68.7 (CH$_2$), 64.4 (CH$_2$), 64.1 (CH$_2$), 39.2 (C), 32.0 (CH$_2$), 29.5 (CH$_2$), 26.6 (CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 2961 (m), 2902 (w), 1754 (s), 1704 (m), 1625 (w), 1418 (w). HRMS-CI (m/z): [M + H]$^+$ calcd for C$_{17}$H$_{23}$O$_6$, 323.1489; found, 323.1481. $[\alpha]_D^{20} = -74.2$ (c = 0.50, CHCl$_3$).
Synthesis of the diketone S15:

1 N aqueous hydrochloric acid solution (12.4 mL, 12.4 mmol, 5.00 equiv) was added to a solution of the ketone S14 (800 mg, 2.48 mmol, 1 equiv) in tetrahydrofuran (25 mL) at 23 ºC. The reaction mixture was stirred for 14 h at 23 ºC. The product mixture was diluted sequentially with saturated aqueous sodium bicarbonate (30 mL), water (10 mL), and ethyl acetate (50 mL). The resulting biphasic mixture was stirred for 30 min at 23 ºC. The stirred mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 30 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 50% ether–hexanes) to furnish the diketone S15 as a colorless oil (588 mg, 85%).

R_f = 0.47 (50% ether–hexanes; UV, PAA). ^1H NMR (500 MHz, CDCl_3): δ 7.58 (s, 1H, H_7), 5.97–5.87 (m, 1H, H_{10}), 5.77 (dd, J = 17.6, 10.6 Hz, 1H, H_2), 5.36 (dq, J = 17.2, 1.5 Hz, 1H, H_6a), 5.25 (dq, J = 10.5, 1.4 Hz, 1H, H_{6b}), 5.17–5.12 (m, 3H, H_{1a,b}), 4.97 (d, J = 17.5 Hz, 1H, H_{1b}), 4.63 (dt, J = 5.7, 1.5 Hz, 2H, H_9), 2.57–2.43 (m, 2H, H_3), 2.01–1.88 (m, 2H, H_4), 1.29 (s, 3H, H_3). ^13C NMR (125 MHz, CDCl_3): δ 196.8 (C), 191.5 (C), 164.6 (CH), 154.6 (C), 141.0 (CH), 134.6 (C), 131.3 (CH), 118.7 (CH_2), 115.4 (CH_2), 71.7 (CH_2),
68.7 (CH\(_2\)), 40.1 (C), 34.9 (CH\(_2\)), 33.6 (CH\(_2\)), 26.4 (CH\(_3\)). IR (ATR-FTIR), cm\(^{-1}\): 2959 (w), 1753 (s), 1706 (s), 1684 (s), 1598 (w). HRMS-CI (m/z): [M + H]\(^+\) calcd for C\(_{15}\)H\(_{19}\)O\(_5\), 279.1227; found, 279.1201. \([\alpha]^{20}_D = -87.9 \ (c = 0.33, \text{CHCl}_3)\).
Synthesis of the enoxysilane ether 89:

A solution of lithium bis(trimethylsilyl)amide (108 mg, 611 μmol, 1.22 equiv) in tetrahydrofuran (1.20 mL) was added dropwise via cannula to a solution of chlorotrimethylsilane (90.0 μL, 709 μmol, 1.42 equiv) and the diketone S15 (140 mg, 503 μmol, 1 equiv) in tetrahydrofuran (2.5 mL) at –78 °C. The resulting mixture was stirred for 1 h at –78 °C. The cold product mixture was diluted with saturated aqueous sodium bicarbonate solution (500 μL), water (2.0 mL), and ethyl acetate (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted ethyl acetate (10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (3.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 14% ether–hexanes) to provide the enoxysilane 89 as a colorless oil (103.0 mg, 59%).

The enoxysilane 89 was isolated as a single olefin isomer. The orientation of this isomer was assigned via conclusive NOE correlations between the C11 trimethylsilyl group and the C8 allyl carbonate substituent supporting the relative orientation depicted.
$R_f = 0.32$ (25% ether–hexanes; UV, PAA). $^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 8.53 (s, 1H, H$_8$), 6.85 (s, 1H, H$_7$), 5.62–5.52 (m, 1H, H$_{10}$), 5.40 (dd, $J = 17.4$, 10.5 Hz, 1H, H$_2$), 5.05 (d, $J = 17.2$ Hz, 1H, H$_{6a}$), 4.89 (d, $J = 10.5$ Hz, 1H, H$_{6b}$), 4.86–4.77 (m, 2H, H$_1$), 4.32–4.29 (m, 2H, H$_5$), 2.30–2.21 (m, 2H, H$_3$), 1.39–1.29 (m, 2H, H$_4$), 0.86 (s, 3H, H$_3$), 0.86 (s, 9H, H$_{11}$). $^{13}$C NMR (125 MHz, C$_6$D$_6$): $\delta$ 195.5 (C), 152.6 (C), 151.1 (CH), 143.2 (CH), 134.8 (C), 132.6 (C), 131.7 (CH), 127.2 (CH), 118.5 (CH$_2$), 113.9 (CH$_2$), 68.8 (CH$_2$), 39.7 (C), 35.9 (CH$_2$), 34.1 (CH$_2$), 27.1 (CH$_3$), 0.6 (3 × CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 2960 (w), 1761 (s), 1686 (s). [$\alpha$]$_D^{20} = -83.5$ (c = 0.60, CHCl$_3$).
Synthesis of the diosphenol 90 by the fragment coupling–cyclization cascade:

A solution of \( n\)-butyllithium in hexanes (2.20 M, 50.0 \( \mu \)L, 110 \( \mu \)mol, 2.20 equiv) was added to a solution of the iodoncyclopropane 85 (43.0 mg, 110 \( \mu \)mol, 2.20 equiv) in tetrahydrofuran (500 \( \mu \)L) at \(-78^\circ\)C. A solution of the enoxysilane 89 (17.5 mg, 50.0 \( \mu \)mol, 1 equiv) in tetrahydrofuran (150 \( \mu \)L) was added then immediately added dropwise down the inside wall of the flask. The reaction mixture was stirred for 2 h at \(-78^\circ\)C. The reaction mixture was then immersed in a cooling bath at 0 \( ^\circ\)C. The reaction mixture was stirred for 3 h at 0 \( ^\circ\)C. The product mixture was then diluted sequentially with saturated aqueous ammonium chloride solution (150 \( \mu \)L), water (500 \( \mu \)L), and ethyl acetate (8.0 mL). The resulting biphasic solution was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by preparative thin-layered chromatography (eluting with 16% ether–hexanes) to furnish the diosphenol 90 as light yellow oil (9.5 mg, 38%).

\[ R_f = 0.50 \text{ (33\% ether–hexanes; UV, PAA).} \]
\[ ^1\text{H NMR (600 MHz, CDCl}_3\text{): } \delta \text{ 6.86 (s, 1H, H}_{14}\text{), 6.21 (d, } J = 17.5 \text{ Hz, 1H, H}_{16}\text{), 5.86 (dd, } J = 17.5, 10.7 \text{ Hz, 1H, H}_{12}\text{), 5.12–5.06 (m,} \]

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2H, H_{13}), 4.24–4.14 (m, 1H, H_{5a}), 4.16–4.07 (m, 1H, H_{5b}), 1.97 (ddd, \( J = 17.5, 8.7, 3.7 \) Hz, 1H, H_{9a}), 1.91–1.86 (m, 1H, H_{2a}), 1.85–1.75 (m, 2H, H_{3a,9b}), 1.68–1.62 (m, 1H, H_{1}), 1.56 (dd, \( J = 9.9, 4.4 \) Hz, 2H, H_{10}), 1.54–1.49 (m, 1H, H_{2b}), 1.43 (dt, \( J = 13.6, 2.9 \) Hz, 1H, H_{3b}), 1.39 (s, 3H, H_{3}), 1.10 (s, 3H, H_{11}), 1.01–0.88 (m, 4H, H_{6,8}), 0.01 (s, 9H, H_{7}), −0.03 (s, 9H, H_{15}). \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \( \delta \) 182.9 (C), 179.9 (C), 145.8 (CH), 144.8 (CH), 143.3 (C), 135.1 (C), 134.0 (C), 112.9 (CH\(_2\)), 75.1 (C), 63.2 (CH\(_2\)), 44.1 (C), 38.8 (C), 29.7 (CH\(_2\)), 29.6 (CH\(_2\)), 29.2 (CH\(_2\)), 27.1 (CH\(_3\)), 25.1 (CH\(_3\)), 19.8 (CH\(_3\)), 17.8 (CH\(_2\)), 17.3 (CH\(_2\)), 15.8 (CH), 13.2 (CH\(_2\)), 2.8 (3 × CH\(_3\)), 1.4 (3 × CH\(_3\)). IR (ATR-FTIR), cm\(^{-1}\): 2952 (m), 1731 (s), 1655 (s), 1609 (s). HRMS-CI (m/z): [M + H]\(^{+}\) calcd for C\(_{28}\)H\(_{45}\)O\(_5\)Si\(_2\), 517.2805; found, 517.2855. \([\alpha]_{D}^{20} = −13.3 \) (c = 0.50, CHCl\(_3\)).
Synthesis of $(-)$-myrocin G (8):

A solution of tetrabutylammonium fluoride in tetrahydrofuran (1 M, 49.0 μL, 49.0 μmol, 2.10 equiv) was added to a solution of the diosphenol 90 (12.0 mg, 23.2 μmol, 1 equiv) in N,N-dimethylformamide (200 μL) at 23 ºC. The reaction mixture was stirred for 5 h at 23 ºC. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (500 μL), water (1.0 mL), and ethyl acetate (7.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 4.0 mL). The organic layers were combined and the combined organic layers were washed sequentially with water (3 × 2.0 mL) and saturated aqueous sodium chloride solution (3.0 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 1% acetic acid–50% acetone–hexanes). The fractions containing product (TLC analysis) were combined. The combined fractions were dissolved in toluene (5.0 mL) and the resulting solution was concentrated to provide $(-)$-myrocin G (8) as a white solid (5.0 mg, 64%).

$R_f = 0.20$ (1% acetic acid–50% acetone–hexanes; UV, PAA). $^1$H NMR (400 MHz, CD$_3$OD): $\delta$ 6.84 (d, $J = 1.3$ Hz, 1H, H$_{11}$), 5.89 (dd, $J = 17.5$, 10.7 Hz, 1H, H$_9$), 5.16–5.14
(m, 2H, H_{10}), 2.10–2.03 (m, 1H, H_{2a}), 1.93–1.83 (m, 3H, H_{2b,3}), 1.72–1.67 (m, 1H, H_{1}), 1.63 (td, J = 13.7, 12.6, 3.6 Hz, 1H, H_{6a}), 1.56–1.48 (m, 2H, H_{6b,7a}), 1.48–1.41 (m, 1H, H_{7b}), 1.37 (s, 3H, H_{4}), 1.09 (s, 3H, H_{8}), 1.09 (dd, J = 8.9, 5.8 Hz 1H, H_{12a}), 0.94 (t, J = 6.1Hz, 1H, H_{12b}). ^{13}C NMR (100 MHz, CD_{3}OD): δ 183.6 (C, C_{19}), 180.9 (C, C_{15}), 147.1 (CH, C_{11}), 146.9 (CH, C_{9}), 145.5 (C, C_{18}), 136.0 (C, C_{20}), 135.4 (C, C_{17}), 112.9 (CH_{2}, C_{10}), 72.2 (C, C_{21}), 45.1 (C, C_{16}), 39.9 (C, C_{23}), 30.7 (CH_{2}, C_{3}), 30.6 (CH_{2}, C_{7}), 29.4 (C, C_{22}), 27.3 (CH_{2}, C_{6}), 24.4 (CH_{3}, C_{8}), 20.1 (CH_{3}, C_{4}), 18.5 (CH_{2}, C_{2}), 16.6 (CH, C_{1}), 13.4 (CH_{2}, C_{12}). IR (ATR-FTIR), cm\(^{-1}\): 3393 (m), 2922 (m), 2868 (w), 1701 (s), 1653 (s), 1635 (m), 1601 (m). HRMS-Cl (m/z): [M + H]\(^{+}\) calcd for C_{20}H_{25}O_{3} 345.1702, found 345.1723. [\alpha]_D^{20} = −78.7 (c = 0.20, CHCl_{3}).
**Synthesis of the bis(sulfide) 25:**

Thiophenol (9.0 μL, 87.0 μmol, 10.0 equiv) and triethylamine (12.0 μL, 87.0 μmol, 10.0 equiv) were added in sequence to a solution of (–)-myrocin G (8, 3.0 mg, 8.7 μmol, 1 equiv) in tetrahydrofuran (200 μL) at 23 ºC. The headspace in the reaction vessel was evacuated and the evacuated vessel was filled with argon. This process was repeated twice. The reaction mixture was stirred for 15 h at 23 ºC. The product mixture was diluted sequentially with 1 N aqueous hydrochloric acid solution (100 μL), water (500 μL) and dichloromethane (1.5 mL). The resulting biphasic mixture was transferred to a separatory funnel that had been charged with dichloromethane (5.0 mL). The layers that formed were separated, and the aqueous layer was extracted with dichloromethane (3 × 3.0 mL). The organic layers were combined and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 1% acetic acid–33% acetone–hexanes) to provide the bis(sulfide) 25 as a white solid (3.5 mg, 74%).

R\(_f\) = 0.14 (1% acetic acid–33% acetone–hexanes; UV, PAA). \(^1\)H NMR (600 MHz, CDCl\(_3\)): δ 7.41 (d, \(J = 7.4\), 2H, H\(_9\)), 7.36–7.32 (m, 2H, H\(_{14}\)), 7.29 (t, \(J = 7.6\), 2H, H\(_{10}\)), 7.24–7.17 (m, 4H, H\(_{11,15,16}\)), 5.85 (dd, \(J = 17.5\), 10.8 Hz, 1H, H\(_{12}\)), 5.01 (d, \(J = 17.5\) Hz, 1H, H\(_{13a}\)), 4.86 (d, \(J = 10.8\) Hz, 1H, H\(_{13b}\)), 4.23 (s, 1H, H\(_5\)), 3.04–2.87 (m, 3H, H\(_{1,8}\)), 2.46 (dd, \(J =
17.3, 6.0 Hz, 1H, H$_{6a}$), 2.37–2.23 (m, 3H, H$_{2a,3a,6b}$), 2.01–1.95 (m, 1H, H$_{7a}$), 1.81 (app t, $J$

= 14.3 Hz, 1H, H$_{2b}$), 1.74 (app d $J$ = 13.5 Hz, 1H, H$_{3b}$), 1.53–1.45 (m, 4H, H$_{4,7b}$), 0.98 (s, 3H, H$_{17}$). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 183.2 (C, C$_{28}$), 146.1 (CH, C$_{12}$), 141.6 (C, C$_{20}$), 139.7 (C, C$_{21}$), 136.1 (C, C$_{26}$), 135.5 (C, C$_{27}$), 131.7 (CH, C$_{9}$), 130.9 (CH, C$_{14}$), 130.1 (C, C$_{24}$), 128.9 (CH, C$_{10}$), 128.8 (CH, C$_{15}$), 127.3 (CH, C$_{11}$), 126.6 (CH, C$_{16}$), 126.2 (C, C$_{19}$), 125.2 (C, C$_{23}$), 123.1 (C, C$_{22}$), 112.0 (CH$_2$, C$_{13}$), 53.8 (CH, C$_{5}$), 44.7 (C, C$_{18}$), 39.7 (C, C$_{25}$), 37.4 (CH$_2$, C$_{8}$), 33.3 (CH, C$_{1}$), 29.9 (CH$_2$, C$_{3}$), 27.1 (CH$_2$, C$_{7}$), 23.3 (CH$_3$, C$_{4}$), 22.9 (CH$_3$, C$_{17}$), 21.6 (CH$_2$, C$_6$), 20.8 (CH$_2$, C$_2$). IR (ATR-FTIR), cm$^{-1}$: 2931 (s), 1701 (s), 1439 (m). HRMS-CI (m/z): [M + Na]$^+$ calcd for C$_{32}$H$_{34}$NaO$_4$O$_2$ 569.1798, found 569.1805. $[\alpha]_{D}^{20}$ = $-$29.2 ($c$ = 0.10, CHCl$_3$).
Synthesis of the allyl ester 92:

Part 1: Synthesis of diosphenol allyl ester S16:

Allyl alcohol (30.0 μL, 441 μmol, 16.3 equiv) was added to a solution of the analogue 65 (9.0 mg, 27.1 μmol, 1 equiv) and 1-[bis(dimethylamino)-methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium-3-oxide hexafluorophosphate (HATU) (22.0 mg, 136 μmol, 5.00 equiv) in tetrahydrofuran (300 μL) at 23 ºC. The reaction mixture was stirred for 5 d at 23 ºC. The product mixture was diluted with saturated aqueous ammonium chloride solution (2.0 mL), water (1.0 mL), and ethyl acetate (5.0 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 2.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (1.0 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was eluted over a short plug of silica gel (1.0 cm × 3.0 cm, eluting with 50% ether–hexanes). The filtrate was collected and concentrated. The diosphenol allyl ester S16 obtained in this way was used in the following step without further purification.
Part 2: Synthesis of the allyl ester 92:

Tetrabutylammonium iodide (1.2 mg, 3.40 μmol, 0.20 equiv), cesium carbonate (6.6 mg, 20.0 μmol, 1.20 equiv) and para-methoxybenzoyl chloride (2.70 μL, 20.0 μmol, 1.20 equiv) were added in sequence to a solution of the unpurified allyl ester diosphenol S16 obtained in the preceding step (nominally, 17.0 μmol, 1 equiv) in 33% tetrahydrofuran–acetonitrile (v/v, 300 μL) at 23 °C. The reaction mixture was stirred for 16 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (1.0 mL), water (1.0 mL) and ethyl acetate (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 3.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 25% ethyl acetate–hexanes initially, grading to 50% ethyl acetate–hexanes, 1 step) to provide the allyl ester 92 as a colorless oil (7.5 mg, 59% two steps).

R<sub>f</sub> = 0.40 (50% ethyl acetate–hexanes; UV, PAA). <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ 7.33 (d, <i>J</i> = 8.6 Hz, 2H, H<sub>11</sub>), 6.92 (s, 1H, H<sub>8</sub>), 6.86 (d, <i>J</i> = 8.6 Hz, 2H, H<sub>12</sub>), 5.81–5.74 (m, 1H,
H15), 5.16 (d, J = 17.2 Hz, 1H, H16a), 5.09 (d, J = 10.5 Hz, 1H, H16b), 4.92 (d, J = 10.6 Hz, 1H, H10a), 4.82 (d, J = 10.6 Hz, 1H, H10b), 4.43–4.38 (m, 1H, H14a), 4.35–4.31 (m, 1H, H14b), 3.79 (s, 3H, H13), 1.98–1.84 (m, 2H, H6), 1.80 (td, J = 13.9, 4.7 Hz, 1H, H3a), 1.72–1.62 (m, 2H, H2a,6b), 1.51–1.36 (m, 5H, H1,2b,3b,7), 1.22 (s, 3H, H4), 1.15 (s, 3H, H9a), 1.01 (s, 3H, H9b), 0.95 (dd, J = 8.9, 5.9 Hz, 1H, H5a), 0.84 (t, J = 6.2 Hz, 1H, H5b). 13C NMR (150 MHz, CDCl3): δ 181.6 (C), 175.3 (C), 159.5 (C), 149.1 (CH), 146.6 (C), 145.2 (C), 134.9 (C), 132.7 (C), 130.7 (CH), 129.2 (C), 117.3 (CH), 113.6 (CH2), 71.9 (C), 70.6 (CH2), 65.4 (CH2), 55.2 (CH3), 43.8 (C), 32.9 (C), 31.3 (CH2), 28.4 (CH3), 28.0 (CH2), 26.1 (CH3), 26.0 (CH2), 21.0 (CH3), 17.2 (CH2), 14.5 (CH2), 12.7 (CH2).
Synthesis of the free acid 93:

A one-dram vial was sequentially charged with 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (1.9 mg, 4.0 μmol, 0.40 equiv), the allyl ester 92 (4.0 mg, 10.0 μmol, 1 equiv), palladium(II) acetate (1.0 mg, 4.0 μmol, 0.40 equiv), 1,3-dimethylbarbituric acid (7.8 mg, 50.0 μmol, 5.00 equiv), and tetrahydrofuran (200 μL). The reaction vessel was sealed and the sealed vessel was placed on a heating block that had been preheated to 40 °C. The reaction mixture was stirred and heated for 1 h at 40 °C. The reaction mixture was then warmed to 50 °C. The reaction mixture was stirred and heated for 2.5 h at 50 °C. The reaction mixture was then warmed to 70 °C. The reaction mixture was stirred and heated for 2.5 h at 70 °C. The product mixture was cooled over 30 min to 23 °C. The cooled product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (1.0 mL), water (1.0 mL) and ethyl acetate (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (2 × 3.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The
residue obtained was purified by preparative thin-layered chromatography (eluting with 50% ethyl acetate–hexanes) to provide the free acid 93 as a white solid (2.5 mg, 68%).

R$_f$ = 0.10 (50% ethyl acetate–hexanes; UV, PAA). $^1$H NMR (600 MHz, CDCl$_3$): δ 7.33 (d, $J$ = 8.6 Hz, 2H, H$_{11}$), 6.92 (s, 1H, H$_8$), 6.85 (d, $J$ = 8.6 Hz, 2H, H$_{12}$), 4.94–4.90 (m, 2H, H$_{10}$), 3.78 (s, 3H, H$_{13}$), 1.99–1.87 (m, 2H, H$_6$), 1.80 (td, $J$ = 13.9, 4.8 Hz, 1H, H$_{3a}$), 1.72–1.64 (m, 2H, H$_{2a,6b}$), 1.51–1.37 (m, 5H, H$_{1,2b,3b,7}$), 1.21 (s, 3H, H$_4$), 1.15 (s, 3H, H$_{9a}$), 1.01 (s, 3H, H$_{9b}$), 0.97 (dd, $J$ = 8.8, 6.0 Hz, 1H, H$_{5a}$), 0.86 (t, $J$ = 5.9 Hz, 1H, H$_{5b}$). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 181.7 (C), 178.7 (C), 159.5 (C), 149.2 (CH), 146.7 (C), 144.7 (C), 134.9 (C), 130.7 (C), 129.1 (CH), 113.6 (CH), 72.1 (C), 70.7 (CH$_2$), 55.2 (CH$_3$), 43.4 (C), 32.9 (C), 31.9 (CH$_2$), 31.3 (CH$_3$), 28.4 (CH$_3$), 28.0 (CH$_2$), 26.1 (CH$_3$), 26.0 (CH$_2$), 14.5 (CH$_2$), 20.7 (CH$_3$), 17.2 (CH$_2$), 14.5 (CH$_2$), 12.7 (CH$_2$).
Synthesis of the azide probe (−)-96:

3-Azido-1-propanamine (3.1 μL, 0.0301 mmol, 2.0 equiv) was added to a solution of the analogue (−)-65 (5.0 mg, 15.0 μmol, 1 equiv), 1-[bis(dimethylamino)-methylene]-1H-1,2,3-triazolo[4,5- b]pyridinium-3-oxide hexafluorophosphate (HATU) (1.5 mg, 23.0 μmol, 1.50 equiv), and N,N-diisopropylethylamine (13.0 μL, 75.0 μmol, 5.00 equiv) in N,N-dimethylformamide (300 μL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then was warmed to 23 °C. The reaction mixture was stirred for 30 min at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (2.0 mL), water (1.0 mL), and ethyl acetate (5.0 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 2.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2.0 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 50% ethyl acetate–hexanes) to provide the azido ester (−)-96 as a colorless oil (5.9 mg, 95%).
Azido ester (+)-96 was prepared in an analogous fashion. $^1$H NMR and $^{13}$C NMR data for (+)-96 obtained matched that of the (−)-96.

$R_f=0.30$ (50% ethyl acetate–hexanes, UV, PAA). $^1$H NMR (500 MHz, CD$_3$OD): $\delta$ 7.30 (t, $J = 5.5 \text{ Hz}$, 1H, H$_{11}$), 6.81 (s, 1H, H$_8$), 3.37 – 3.31 (m, 2H, H$_{12}$), 3.22 (q, $J = 6.4 \text{ Hz}$, 2H, H$_{14}$), 2.04 (tt, $J = 14.2$, 4.2 Hz, 1H, H$_{7a}$), 1.85 (ddt, $J = 13.7$, 4.8, 2.5 Hz, 1H, H$_{7b}$), 1.79–1.69 (m, 3H, H$_{13,3a}$), 1.75–1.68 (m, 1H, H$_1$), 1.67 (tt, $J = 6.0$, 3.1 Hz, 1H, H$_{3b}$), 1.58 (td, $J = 13.6$, 12.6, 3.4 Hz, 1H, H$_{2a}$), 1.51–1.36 (m, 2H, H$_{2b,15}$), 1.39–1.37 (m, 5H, H$_{4,6}$), 1.29 (s, 3H, H$_9$), 1.12–1.07 (m, 1H, H$_{5a}$), 1.03–0.983 (m, 4H, H$_{9,5b}$). $^{13}$C NMR (150 MHz, CD$_3$OD): $\delta$ 182.5 (C), 178.9 (C), 178.8 (C), 148.9 (CH), 133.8 (C), 133.0 (C), 70.8 (C), 49.06 (CH$_2$), 44.7(C), 44.7 (C), 36.9 (CH$_2$), 32.3(C), 30.9 (CH$_2$), 30.3 (CH$_2$), 28.4 (CH$_3$), 28.1(CH$_2$), 26.3(CH$_2$), 25.0 (CH$_3$), 18.2 (CH$_3$), 17.2 (CH$_2$), 15.14 (CH$_3$), 12.1 (CH$_2$). IR (ATR-FTIR), cm$^{-1}$: 3404 (m), 2957 (m), 2926 (m), 1652 (s), 1605 (s). HRMS- CI (m/z): [M + Na]$^+$ calcd for C$_{22}$H$_{30}$N$_4$NaO$_4$, 437.2165; found, 437.2179.
1-Amino-3-butyne (2.50 μL, 30.1 μmol, 2.00 equiv) was added to a solution of the analogue (−)-65 (5.0 mg, 15.0 μmol, 1 equiv), 1-[bis(dimethylamino)-methylene]-1H-1,2,3-triazolo[4,5- b]pyridinium-3-oxide hexafluorophosphate (HATU) (1.5 mg, 26.0 μmol, 1.50 equiv), and N,N-diisopropylethylamine (13.0 μL, 75.0 μmol, 5.00 equiv) in N,N-dimethylformamide (300 μL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and was then warmed to 23 °C. The reaction mixture was stirred for 30 min at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (2.0 mL), water (1.0 mL), and ethyl acetate (5.0 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 2.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (1.0 mL). The organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layered chromatography (eluting with 30% hexanes–ethyl acetate) to provide the alkynyl ester (−)-97 as a yellow oil (5.8 mg, 94%).
Alkynyl ester (+)-97 was prepared in an analogous fashion. $^1$H NMR and $^{13}$C NMR data for (+)-97 obtained matched that of the (−)-97.

$R_f = 0.35$ (50% ethyl acetate–hexanes, UV, PAA).$^1$H NMR (500 MHz, CD$_3$OD): $\delta$ 7.32 (t, $J = 5.9$ Hz, 1H, H$_{11}$), 6.81 (d, $J = 1.5$ Hz, 1H, H$_8$), 3.25–3.23 (m, 2H, H$_{12}$), 2.81 (s, 1H, H$_{15}$), 2.37 (ddt, $J = 9.0$, 6.7, 2.4 Hz, 2H, H$_{13}$), 2.23 (t, $J = 2.7$ Hz, 1H, H$_{14}$), 2.05 (tt, $J = 13.9$, 4.1 Hz, 1H, H$_{6a}$), 1.87–1.82 (m, 1H, H$_{6b}$), 1.79–1.70 (m, 2H, H$_{7a,2a}$), 1.67 (tt, $J = 6.1$, 3.1 Hz, 1H, H$_1$), 1.59 (td, $J = 13.6$, 12.6, 3.5 Hz, 1H, H$_{3a}$), 1.49–1.4 (m, 3H, H$_{7b,2a,3b}$), 1.39 (s, 3H, H$_4$), 1.13–1.08 (m, 4H, H$_{9,5a}$), 1.03–0.983 (m, 4H, H$_{9,5a}$).$^{13}$C NMR (150 MHz, CD$_3$OD): $\delta$ 183.9 (C), 180.2 (C), 150.4 (CH), 145.6 (C), 135.2 (C), 134.3 (C), 82.6 (C), 72.3 (C), 70.4 (CH), 46.0 (C), 39.9 (CH$_2$), 33.7 (C), 32.3 (CH$_2$), 31.6 (CH$_2$), 29.8 (CH$_3$), 29.5 (C), 27.7 (CH$_2$), 26.4 (CH$_3$), 19.6 (CH$_3$), 19.4 (CH$_2$), 18.6 (CH$_2$), 16.5 (CH), 13.6 (CH$_2$). IR (ATR-FTIR), cm$^{-1}$: 2924 (m), 22805 (m), 1738 (m), 1655 (s), 1605 (s). HRMS-Cl (m/z): [M + Na]$^+$ calcd for C$_{23}$H$_{30}$NO$_4$, 384.2175; found, 384.2176.
Table S1. Comparison of $^1$H NMR data for the bis(sulfide) 25:

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$^a$13C NMR data for (±)-25 were not reported.
1.9 Bibliography.


Chapter 2.

Development of an enantioselective synthesis of (−)-euonyminol.
2.1 Introduction.

Dihydro-β-agarofurans (e.g., 98–102) are a diverse family of secondary metabolites isolated from the *Celastraceae* plant family, which is native to the sub-tropical regions of the world (Figure 4). These isolates are characterized by a highly-oxidized tricyclic carbogenic skeleton. The related isolates known as the cathedulins (e.g., 103–105) are macrocyclic terpenoid alkaloids possessing the common dihydro-β-agarofurans nucleus known as euonyminol (99). In the sections that follow, I will review the interesting biological properties of these natural products, their characteristic structural features, and the prior related synthetic work. I will then describe in detail the development of the first enantioselective synthetic route to (−)-euonyminol (99) and discuss the potential adaptation of this route towards the synthesis of the macrocyclic cathedulins.

**Figure 4.** A. Structures of the dihydro-β-agarofuran skeleton (98), (−)-euonyminol (99), and additional representative isolates (100–102). B. Structures of several representative cathedulin terpenoid alkaloids (103–105). C. Structure of evonine (106).
2.2 Biological properties and structural features of the dihydro-β-agarofuran natural products.

2.2.1 Biological properties of the dihydro-β-agarofuran and of the cathedulins.

The Celastraceae plant family, the source of the dihydro-β-agarofurans, has been extensively used in traditional farming methods.9-11 For example, the crude extracts of the plant Celastrus angulatus were employed as insecticides in Chinese agriculture.12 Detailed analysis of these extracts revealed the dihydro-β-agarofuran celangulin (100) as the metabolite responsible for the potent insecticidal property.13,2 Further screening experiments in 1990 revealed that 100 exhibits pesticidal activity against the fall armyworm Mythimma separata at 5 parts per million (ppm), the cabbage leaf worm Pieris rapae at 222 ppm, and against the Asian corn borer Ostrinia furnacalis at 222 ppm.13 These activities were not unique to celangulin (100) as subsequent studies identified additional dihydro-β-agarofurans possessing insect antifeedant properties similar to the known commercial pesticide azadirachtin.14

Celastraceae extracts have also been used in traditional medicine owing to their anti-inflammatory, anti-bacterial, and digestive healing properties.2-3,11 Additionally, the widespread search for cancer treatments lead to the identification of various dihydro-β-agarofurans as promising anti-tumor agents.15-16 For example, celaglaumin (101) exhibited modest activity against murine leukemia cell line L1210 (IC50 = 2.11 µg/mL) and against lymphatic leukemia cell line P-388 (IC50 = 4.12 µg/mL).17 Related studies done by Takaishi and co-workers established that the dihydro-β-agarofuran triptogelin A-1 (102) reduced both the incidence and the frequency of skin cancer in mice without excessive
Collectively, these studies suggest that these natural products may constitute for the development of additional anti-cancer therapeutics.\textsuperscript{15,18}

The cathedulin terpenoid alkaloids are complex macrocyclic natural products isolated from the small shrub \textit{Catha edulis}.\textsuperscript{4} Extracts from freshly cut leaves of this shrub are known to produce a substance that is commonly referred to as Khat. Simple chewing of Khat is widely popular in East Africa and in several parts of the Middle East as it leads to a mental stimulation and produces feelings of euphoria.\textsuperscript{4} Pharmacological studies of Khat have identified that the stimulatory effects are primarily caused by norpseudioehedrine (cathine) but these studies have also implicated cathedulins as possibly responsible for some of the observed physiological effects associated with Khat digestion.\textsuperscript{5,19} To date, over twenty macrocyclic cathedulins have been identified from natural sources possessing either one or two macrocycles in studies carried out by Crombie and co-workers.\textsuperscript{6-8} The former structures are exemplified by cathedulin K-2 (103)\textsuperscript{6} wherein the macrocycle bridges the C13 and C3 hydroxyl groups. The more complex bis(macroyclic structures) structures possess an additional bridge between C8 and C15 hydroxyl groups, as exemplified by cathedulins E-4 (104)\textsuperscript{8} and K-19 (105)\textsuperscript{8}. A unifying structural feature across this family is the presence of a common tricyclic nucleus identified as the sesquiterpenoid euonyminol (99, Figure 4), which will be discussed in the subsequent section.
2.2.2 Structural features of the dihydro-β-agarofurans and introduction to euonyminol.

Structurally, the dihydro-β-agarofurans are characterized by the tricyclic scaffold shown in Figure 4. This skeleton is comprised of a trans-decalin (A- and B- rings) that is further appended by a tetrahydrofuran (C-ring). As is seen in structures 99–102, these natural products possess an unusually high degree of oxygenation around the tricyclic scaffold, leading to a large structure diversity among the family, as evidenced by the isolation of over four hundred distinct metabolites. Euonyminol (99) is the most heavily-oxygenated family member with a total of ten oxygen atoms, nine of which are free hydroxyl groups. To the best of our knowledge, this natural product was first described in the literature by Beroza and co-workers 1952. These researches concluded that euonyminol (99) is a polyhydroxy substance without a definite melting point and having a molecular formula C_{15}H_{26}O_{10}. In 1971, Hirata first advanced a structure for euonyminol based on degradation and NMR spectroscopy studies. The structure was unambiguously confirmed by the same group in 1972 via X-ray crystallographic analysis of the related alkaloid evonine (106), which was isolated from a different Celastraceae plant species. Though evonine (106) possess a ketone oxidation state at the C8 position, a direct link between these two natural products was found when evonine (106) was treated with lithium aluminum hydride (LiAlH₄) resulting in formation of euonyminol (99) (30%) as the major product along with the C8 epi-euonyminol as the minor byproduct (15%).
2.3 Prior synthetic art towards the dihydro-β-agarofurans.

2.3.1 Total synthesis of (±)-euonyminol by White and co-workers.

In 1995, White and co-workers reported the first synthesis of (±)-euonyminol (99).\textsuperscript{24,25} Their synthesis began with a silver-mediated Diels–Alder reaction between methyl 2,5-dihydroxybenzoate (107) and the diene 108, to generate the adduct 109 (94%, Scheme 19). This adduct was then advanced to the bis(epoxide) 110 which served as a substrate for a key transformation. Exposure of 110 to trifluoracetic acid resulted in a two-fold epoxide opening ring-forming cascade with trapping of the final allylic cation by trifluoroacetate, to provide the tricyclic diol 111. A two-step sequence comprising of a cleavage of the trifluoroacetate ester (aqueous tetrahydrofuran and pyridine) followed by imidazole-promoted lactonization then provided the lactone diol 112 (75% form 110).

Scheme 19. Synthesis of (±)-euonyminol (99) by White and co-workers.
The diol residue was then protected as a benzylidene acetal (benzaldehyde dimethyl acetal, pyridinium para-toluenesulfonate). After some experimentation, the authors found that the stereochemistry at C1 could be corrected via a retro-Aldol–Aldol addition initiated by exposing the acetal intermediate to tetrabutylammonium fluoride, to provide the ketone 113 (80%, two steps). The ketone 113 possesses all of the carbons of the target, however, the oxidation state of 113 needed to be significantly increased in subsequent manipulations.

To this end, 113 was advanced to the heptaacetate intermediate 114 in six steps (28% overall). The authors then pursued dihydroxylation of the C3–C4 olefin as a means to install the final missing 1,2-diol residue. In the event, treatment of 114 with osmium tetraoxide in the presence of pyridine, followed by acetylation with acetic anhydride and DMAP provided euonyminol octaacetate (116) and its stereoisomer 115 in 76% combined yield and 1:8 ratio favoring the undesired diastereomer 115. As the authors were unable to improve the stereoselectivity of the osmylation or perform this transformation at an earlier point of the synthesis, they elected to carry on with this result and complete the synthesis. Consequently, the minor isomer 116 was treated with sodium methoxide in methanol to deliver (±)-euonyminol (99) in 99% yield.

2.3.2 Synthetic studies towards (−)-euonyminol by Spivey and co-workers.

In 2013, the Spivey laboratory reported an enantioselective synthesis of the tricycle 123 possessing the fully functionalized lower region of euonyminol (99).26 Their synthesis commenced with the epoxide 117, which was advanced to the meso diallylic alcohol 118 in five transformations (52% overall, Scheme 20). The authors desymmetrized 118 by an asymmetric epoxidation employing zirconium(IV) isopropoxide, (+)-diisopropyl L-tartarte
and tert-butyl hydroperoxide, to generate the monoepoxide 119 in 90% yield and in 92% ee. The intermediate 119 was then converted to the ester 120 for a pivotal transformation. A silylketene acetal (not shown) was generated by treatment of the ester 118 with LiHMDS and TMSCl; subsequent Ireland ester Claisen rearrangement afforded the allylic epoxide intermediate 121 which underwent lactonization via SN’ epoxide opening to the tricycle 122 (38%). This transformation is notable as it simultaneously established the C6 and C7 stereocenters while also introducing an allylic alcohol for further manipulations. Subsequent manipulations provided the tricycle 123, which possess the fully functionalized lower region of euonyminol (99).

Scheme 20. Synthesis of the tricycle 123 by Spivey and co-workers.

2.3.3 Total synthesis of (−)-4-hydroxyzinowol by Inoue and co-workers.

In 2014, Inoue and co-workers reported a total synthesis of the polyoxygenated dihydro-β-agarofuran (−)-4-hydroxyzinowol (134). Their synthesis began with the naphthalene derivative 124, which was advanced to the epoxide 125 in thirteen steps (Scheme 21). Heating of the epoxide to 80 °C in the presence of ethynyl para-tolyl sulfone provided the Diels–Alder adduct 126 as a single isomer in 70% yield. Cleavage of the
acetonide (trifluoracetic acid), followed by regioselective epoxide opening with cesium benzoate as nucleophile, provided the triol 127. An intramolecular substitution was achieved by exposure of the triol 127 to PTSA, resulting in production of the tricycle 128 (59%, two steps).

Scheme 21. Total synthesis of (−)-4-hydroxyzinowol (134) by Inoue and co-workers.

Silylation of the C8–C9 diol (tert-butyldimethylsilyl trifluoromethanesulfonate), followed by cleavage of the C6 benzoate ester (sodium methoxide) provided the secondary alcohol 129. The remaining carbon of the natural product was introduced via a diastereoselective addition of methyl magnesium bromide to the C4 ketone. This reaction presumably occurred via formation of a magnesium chelate between the C6 alcohol and the ketone, which would then direct approach of the nucleophile to the β-face, forming the tertiary alcohol 130 (79% from 128). With all of the carbon atoms present in 128, several
additional reactions highlighted in Scheme 21 were required to adjust the oxidation state of 128 and to complete the synthesis of (−)-4-hydroxyzinowol (134).

2.4 Development of an enantioselective synthetic route to (−)-euonyminol.

2.4.1 Synthesis of the exocyclic olefin 179 via a novel oxyalkylation reaction of an allylic alcohol.

Our interest in (−)-euonyminol (99) was motivated by the synthetic challenge associated with construction of the heavily oxygenated dihydro-β-agarofuran skeleton, which resembles a carbosaccharide. The goal from the start of this research project was to develop a robust strategy that would not only provide access to (−)-euonyminol (99) but would also be easily adaptable for the synthesis of the cathedulin alkaloids. With this goal in mind, we devised an initial approach as summarized in Scheme 22.

![Scheme 22. First retrosynthetic analysis of (−)-euonyminol (99).](image)

We envisioned accessing the target from the exocyclic olefin 135 via a late-stage oxidation at the C8 position, followed by a Mukaiyama hydration of the olefin to establish
the C4 stereocenter. This intermediate, in turn, could be derived from the alkyne 136 via a ring closing nickel-catalyzed alkyne–aldehyde reductive cyclization. The intermediate 136 could be traced back to the neopentyl aldehyde 137. The C10 quaternary stereocenter of 137 was anticipated to be accessible by a Lewis-acid mediated semipinacol rearrangement of the epoxide 138, which in turn could be simplified to the known carvone derivative 139 as the starting point for our synthesis.

We began by evaluating the diastereoselective epoxidation of the C11–C12 alkene within 139 (Scheme 23). Epoxidation with the levorotary enantiomer of the Shi ketone provided the epoxide 140 as well as its diastereomer (not shown) in a 2.4:1 ratio. Following chromatographic separation the epoxide 140 was obtained in 70% yield on a multigram scale. The addition of lithium trimethylsilyl acetylide to the ketone 140 proceeded with 13:1 diastereoselectivity to provide a C5 alcohol intermediate (not shown). Exposure of the unpurified alcohol to pyridinium para-toluenesulfonate then promoted the formation of the C-ring via a regioselective ring-opening of the C11–C12 epoxide, to yield the cyclic ether 141 (87% overall). The relative stereochemistry of 141 was confirmed by X-ray analysis. Protection of the primary alcohol group as the methoxymethyl ether (methoxymethyl chloride, Hünig’s base, 93%) was followed by an allylic oxidation (selenium dioxide) and a reduction of the unsaturated aldehyde under Luche conditions (sodium borohydride, cerium chloride) to generate the allylic alcohol intermediate 143 (80%, two steps). A two-step sequence comprising stereoselective epoxidation (mCBPA) and oxidation (Dess–Martin periodinane, pyridine) generated the aldehyde 144 (68% overall). The addition of vinylmagnesium bromide to 144 followed by silylation of the resulting allylic alcohol (TMSCl, imidazole) formed 145, the key precursor for the
semipinacol rearrangement (77%, 3.4:1 dr at C1). The relative stereochemistry of the major diastereomer was not assigned.

Scheme 23. Synthesis of the epoxide 146.

Unfortunately, all of our attempts to promote the desired semipinacol transformation to establish the C10 quaternary stereocenter were unsuccessful.\(^1\) A variety of Lewis acids commonly employed in this transformation (see inset, Scheme 23) resulted in decomposition of substrate 145 via ring-opening of the tetrahydrofuran C-ring. We hypothesize that the two methoxymethyl ether substituents create a binding pocket capable of chelating the Lewis acids in the vicinity of the tetrahydrofuran ring, thereby promoting its ring-opening. Attempts to simply exchange the protecting groups were unsuccessful.
This result motivated us to formulate a different approach to construct the C10 quaternary stereocenter.

Based on our difficulties in the semipinacol approach, an alternative strategy based on a cyclopropanation of the C9–C10 olefin was devised. We envisioned elaborating the possible cyclopropane intermediate via a decarboxylation and a subsequent cyclopropane ring-opening to liberate the C10 stereocenter, which would also introduce a C8–C9 olefin handle for future oxidation (Scheme 24).

\[ \text{Scheme 24. Synthesis of the vinylogous carbonate 147.} \]

Accordingly, the \( \alpha \)-diazo-\( \beta \)-ketoester 144 was prepared by treatment of the allylic alcohol 143 with diketene in the presence of DMAP, followed by a diazo transfer ((4-acetamido)benzensulfonyl azide, triethylamine; 93% over two steps). Thermolysis of the \( \alpha \)-diazo-\( \beta \)-ketoester 144 in the presence of bis(N-(tert-butyl)salicylaldiminato)copper did not, however, provide the expected product. Instead we isolated the vinylogous carbonate 147, which arises from formal [3+2] addition of a carbenoid to the alkene (40%, Scheme 24).
The structure of the vinylogous carbonate intermediate 147, including complete relative stereochemistry, was unambiguously confirmed by X-ray analysis. While not the anticipated product, we recognized that this transformation served to simultaneously introduce the C10 quaternary stereocenter and the C9 oxidation of the target in a single step. Accordingly, we conducted a thorough optimization of reaction conditions to improve the yield of this transformation, as summarized in Table 2.

![Image](image.png)

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>T</th>
<th>Yield of 147 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
<td>1</td>
<td>Cu(OTf)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>DCE</td>
<td>50 °C</td>
<td>nd&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Rh&lt;sub&gt;2&lt;/sub&gt;(OAc)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>23 °C</td>
<td>nd</td>
</tr>
<tr>
<td>3</td>
<td>Rh&lt;sub&gt;2&lt;/sub&gt;(esp)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>23 °C</td>
<td>nd</td>
</tr>
<tr>
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<td>PhCH&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>40%</td>
</tr>
<tr>
<td>5</td>
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<td>PhCH&lt;sub&gt;3&lt;/sub&gt;&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
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<td>PhCH&lt;sub&gt;3&lt;/sub&gt;&lt;sup&gt;d,e&lt;/sup&gt;</td>
<td>100 °C</td>
<td>83%</td>
</tr>
<tr>
<td>7</td>
<td>Cu(TBS)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>PhCH&lt;sub&gt;3&lt;/sub&gt;&lt;sup&gt;d,e,f&lt;/sup&gt;</td>
<td>100 °C</td>
<td>78%</td>
</tr>
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<sup>a</sup>Conditions: (30 mol%) catalyst loading, [144] = 0.10 M. <sup>b</sup>Isolated yields following purification by flash-column chromatography. <sup>c</sup>None detected. <sup>d</sup>Reaction concentration lowered: [144] = 0.02M.<sup>e</sup>Solvent was deoxygenated by sparging with argon for 1h. <sup>f</sup>Reaction done on a 3.0g scale.
We observed no product formation when we treated the α-diazo-β-ketoester 144 with dirhodium tetraacetate, copper triflate, or Rh$_2$(esp)$_2$ as the catalysts (entries 1–3). Only the product of hydrodediazotization was observed. The yield of product 147 increased to 67% when the reaction concentration was decreased from 0.10 M to 0.02 M and the reaction temperature was lowered to 100 °C (entry 5). Deoxygenation of the solvent (toluene) by sparging with argon increased the yield to 83% (entry 6). Comparable yields were obtained when the reaction was conducted on an 3.0g scale (78%, entry 7).

To the best of our knowledge, related [3+2] cycloadditions have only been observed when heteroatom-substituted alkenes, such as alkyl enol ether or furans, are employed.\textsuperscript{32,32a} Accordingly, we sought to probe the scope of this transformation (Table 3). Several derivatives of 147 transformed smoothly to [3+2] cycloaddition products in comparable yield (entries 1–5, 63–86%). The terminal acetylene 160 did not convert to product, presumably due to competitive interaction of the alkyne with the copper catalyst (entry 6). The perillaldehyde derivative 162, which lacks the bicyclic structure the dihydro-β-agarofuran scaffold, transformed to a complex mixture of products (entry 7). The pinene derivative 164 provided the expected cycloaddition product 165 (23%) as well as the corresponding cyclopropane 165a (54%, entry 8).
Table 3. Scope of the [3+2] cycloaddition reaction of allylic alcohols. \( ^{a} \)Conditions: (30 mol%), toluene solvent was deoxygenated by sparging with argon for 1h, 100 °C.  
\( ^{b} \)Isolated yields following purification by flash-column chromatography.  
\( ^{c} \)None detected.  
\( ^{d} \)Yield determined by \(^1\)H NMR analysis of the unpurified reaction mixture.  
\( ^{e} \)The corresponding cyclopropane 165a was obtained in 54%.

We hypothesized that this reaction may proceed by rearrangement of a cyclopropanation product. However, the pinene-derived cyclopropane 165a did not convert to the [3+2] cycloaddition product when resubjected to the reaction conditions.
(Scheme 25A). Based on these results as well as the existing literature, we reasoned that the [3+2] cycloaddition product may arise from a pathway that involves participation of the tetrahydofuranyl oxygen (Scheme 25B). Specifically, we suggest that the product is generated by formation of an electrophilic carbenoid 166, followed by addition of the alkene with participation of the tetrahydofuranyl oxygen, to form the oxonium ion 167 (Scheme 25B). Next, a 1,2-alkyl shift is accompanied by trapping with the carbonyl oxygen and elimination of the copper catalyst to generate the cyclization product. In the case of the pinene-derived substrate 164, we suggest that a non–classical cation 33 is formed (instead of an oxonium ion) leading to a parallel mechanistic pathway (Scheme 25C). The reduced electron-donating ability of the carbon–carbon bond in 164 vs. the oxygen lone pair in the more complex substrates would explain why some of the cyclopropane was observed in the transformation of 164.

Scheme 25. A. Attempted conversion of the cyclopropane 165a to the cycloaddition product 165. B. Proposed mechanism for the formation of the vinylogous carbonate 147.
C. Proposed mechanism for the formation of the vinylogous carbonate 165 from the pinene derivative 164.

The vinylogous carbonate 147 was advanced by the pathway shown in Scheme 26. Oxidative cleavage of 147 (ozone) provided the α-ketolactone 169 (85%). Baeyer–Villiger oxidation of 169 using magnesium monoperoxyphthalate (MMPP) followed by hydrolytic ring-opening proceeded smoothly to generate a corresponding carboxylic acid intermediate (not shown) that was esterified with diazomethane to generate the methyl ester 170 (78%). Next, removal of alkynyl silane (hydrogen fluoride–triethylamine complex) and oxidation of the primary alcohol (DMP, pyridine) generated the aldehyde 171 (70%, two steps).

![Scheme 26. Synthesis of the tetracyclic acetonide 174 from 147.](image)

The addition of vinylmagnesium bromide to the aldehyde 171 in the presence of lanthanum chloride–lithium chloride\textsuperscript{34} provided, after cleavage of the acetate ester, the allylic alcohol 173 in 68% yield (3.1:1 dr, $^1$H NMR analysis). Protection of the 1,3-diol
(PTSA, 2,2-dimethoxypropane, 90%) gave the tetracyclic acetonide 174. An NOE analysis established that the C1 center possessed the desired (S)-configuration (see orange arrows, Scheme 26). We speculate that the addition proceeds via formation of the chelate 172, which guides the nucleophile to the less-hindered α-face of the molecule, to yield the desired C1 stereochemistry.

To synthesis of the cyclization precursor 136 was completed by the pathway shown in Scheme 27. Dihydroxylation of the acetonide 174 (osmium tetroxide, N-methylmorpholine N-oxide) provided the vicinal diol as a single detectable diastereomer (1H NMR analysis) that upon exposure to potassium carbonate in methanol underwent a selective lactonization reaction to produce the lactone 175 (95%, two steps). The relative stereochemistry of 175 was determined by NOE correlations between the C2 methine proton and the C15 methyl substituent supporting the stereochemical assignment shown.

Scheme 27. Synthesis of the exocyclic olefin 179.
Oxidation of the primary alcohol (TEMPO, sodium hypochlorite, potassium bromide, tetrabutylammonium chloride) generated the aldehyde 176. Because the aldehyde was unstable toward all purification conditions examined (flash-column chromatography, PTLC) and was also found to undergo appreciable decomposition at room temperature within 2 h in various solvents, it was used without purification in the ensuing reductive cyclization. Reductive cyclization of 176 under conditions developed by Montgomery and co-workers (nickel bis(1,4-cyclooctadiene), 1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene, and triethylsilane) provided the desired exocyclic olefin 179 in 9% along with a large number of unidentified decomposition products (as determined by 1H NMR analysis of the unpurified product mixture). The instability of the aldehyde 176 prevented us from characterizing these products in detail. However, we speculate that the decomposition derives from the lactone-opening pathway highlighted in red arrows in Scheme 2. Moreover, a comprehensive search of the literature did not reveal any α-oxygen-substituted aldehyde as substrates in related cyclization reactions. Even though the olefin 179 closely resembles the natural product, we were unable to improve the yield of this intermediate and were forced to adjust our synthetic strategy accordingly.

2.4.2 Synthesis of the lactone 197 by an aldol–dehydration strategy.

Our second retrosynthetic analysis is summarized in Scheme 28. In this approach, we envisioned accessing the target from the lactone 180 via late-stage oxidation at C8, as discussed above. We then anticipated accessing the lactone 180 from the epoxide 181 by cleavage of the methyl ester and a subsequent lactonization via epoxide-opening. The
intermediate 181 was simplified retrosynthetically to the unsaturated ketone 182, via a diastereoselective 1,2-addition of metyllithium, followed by epoxidation. Further simplification of 182 via an aldol–dehydration revealed the ketoaldehyde 183, which in turn could prepared by hydration of the acetonide 174, followed by oxidative cleavage.

Scheme 28. Alternative retrosynthetic analysis of (−)-euonyminol (99)

Hydration of the alkyne within 174 proved challenging (Scheme 28A). A survey of conditions employing mercury or gold catalysts failed to yield any of the desired methyl ketone (1H NMR and LC/MS analysis).36a In most instances, the need for strongly acid conditions resulted in decomposition of the starting material or in a deprotection of the acid-labile methoxymethyl ether protecting groups. Fortunately, we found that the primary alcohol (185, derived from the methyl ester 170) underwent smooth hydration using mercury triflate and tetramethylurea as promoters, to provide the Markovnikov-selective hydration product 187 (83%).37 We speculate that this successful hydration proceeds via an intramolecular attack of the primary alcohol on the activated alkyne, to form the vinyl
ether 186, which under the reaction conditions further hydrolyzes to the methyl ketone product.

Scheme 29. A. Unsuccessful alkyne hydration of 174. B. Synthesis of the propargylic alcohol 190 via alkyne hydration of the primary alcohol 185.

Oxidation of the alcohol (DMP, pyridine) then gave the aldehyde 188 (90%). Nucleophilic additions to the hindered aldehyde 188 also proved challenging. It was discovered that the addition proceeded only with ethynylmagnesium bromide in the presence of lanthanum chloride–lithium chloride\textsuperscript{34} additive, to give the propargylic alcohol 190 in 94% yield as a single detectable diastereomer (\textsuperscript{1}H NMR analysis of unpurified reaction mixture). The C1 configuration of the addition product 190 was determined by
conversion of the propargylic alcohol 190 to the rigidified cyclic carbonate 190b in two steps. Conclusive NOE correlations of 190b shown in Scheme 29 supported the relative configuration shown. We hypothesize that the stereoselectivity arises from addition of the acetylide to the α-face of the chelated structure 189. Extensive efforts to alter the stereoselectivity, for example, by employing alternative nucleophiles such as vinyl lithium, vinlylmagnesium bromide, or dithiane, were all uniformly unsuccessful and did not result in productive addition to the sterically encumbered neopentyl aldehyde. When trimethylsilylcyanide was used as the nucleophile, we observed formation of 3:1 mixture of addition diastereomers in 64% combined yield. However, all of our attempts to advance or determine the stereochemistry of this addition product suffered from a facile retro–Aldol elimination of the cyanide.

We found that the C1 configuration could be inverted by treatment of 190 with trifluoromethanesulfonic anhydride and DMAP, which provided the vinyl ether 191 in 50% (63% yield based on recovered starting material; Scheme 30) This transformation likely proceeds via an intramolecular displacement of a transient C1 triflate with the oxygen of the methyl ketone moiety. Despite this moderate yield, this inversion strategy was singularly successful among a large range of conditions surveyed, such as oxidation/reduction or Mitsunobu inversion.
Scheme 30. Synthesis of the lactone 197 via aldol–dehydration reaction of the ketoaldehyde 193.

The vinyl ether 191 was elaborated to the tricycle 192 via a three-step sequence comprising hydrolytic opening of the vinyl ether (hydrochloric acid), removal of the acetate ester (potassium carbonate, methanol), and silylene ether formation (di-tert-butyldimethyl ditrifluoromethanesulfonate; 60%, three steps; Scheme 29). Partial hydrogenation of the alkyne (palladium–barium sulfonate, dihydrogen) and ozonolysis of the resulting alkene then formed the ketoaldehyde 193 (85%, two steps). We found that exposure of the ketoaldehyde 193 to a freshly prepared sodium ethoxide in ethanol gave the expected aldol addition product (not shown); activation of the alcohol with methanesulfonyl chloride and
triethylamine provided the unsaturated ketone 194 (74%, two steps). The addition of methyllithium to the C4 ketone within 194 proceeded with 9:1 diastereoselectivity (\(^1\)H NMR analysis) to provide the tertiary alcohol 195 (90%) as well as it separable C4 diastereomer. Oxidation of the allylic alcohol 195 (dimethyldioxirane) proceeded smoothly to afford the epoxide 196 as a single detectable diastereomer (\(^1\)H NMR analysis). The relative stereochemistry of 196 was determined by X-ray analysis (vide infra). Heating of this epoxide 196 with lithium chloride in DMF at 130 °C effected dealkylation of the ester with concomitant epoxide opening–lactonization, to provide a C3–C4 vicinal diol (not shown). Protection of the C3–C4 diol (PTSA, 2,2-dimethoxypropane) generated the crystalline lactone 197 (68%, two steps).

2.4.3 Completion of the synthesis of (−)-euonyminol.

The lactone 197 contains all of the carbon atoms of (−)-euonyminol (99) and only lacks a single oxidation at the C8 position on the A-ring. We envisioned installing this hydroxyl equivalent via an intermolecular or a directed C–H oxidation.\textsuperscript{38-43} Our attempts to achieve this oxidation are shown in Table 4. Unfortunately, all of these conditions were unsuccessful. Many of the attempted transformations only returned the unreacted starting material (entries 4–6) or provided products of oxidative cleavage of the primary methoxymethyl ether group, without detectable (\(^1\)H NMR and LC/MS analysis) oxidation at C8 (entries 1–2). We anticipated that we would be able to reduce the lactone to reveal a primary hydroxyl group, which could be used in a directed oxidation.\textsuperscript{44} Unfortunately, efforts to reduce this lactone were not successful, likely due to the substantial steric crowding arising from the neighboring silylene acetal.
entry | conditions | results
---|---|---
1. | Fe(S,S-PDP), H$_2$O$_2$ | oxidation of the MOM residues, then decomposition
2. | Fe(R,R-PDP), H$_2$O$_2$ | oxidation of the primary MOM residue to the corresponding formate, then decomposition
3. | TFDO | complex mixture
4. | DMDO | no reaction
5. | , blue LED | no reaction
6. | , visible light | no reaction

Table 4. Conditions evaluated for the late-stage C8 oxidation of the lactone 197.

In light of these difficulties, we devised an alternative strategy to introduce the remaining oxygen (Scheme 31). Removal of the silylene ether protecting group (TBAF, 95%), followed by site-selective oxidation of the C9 hydroxyl group (DMP, pyridine), and silylation of the remaining C1 hydroxyl group at C1 (TBSOTf, triethylamine) provided the ketone 200 (71%, two steps). α-Acetoxylation of 200 (lead tetraacetate) provided an α-actoxyketone (not shown) as a single detectable diastereomer (¹H NMR analysis). Cleavage of the acetate ester (potassium carbonate, methanol) provided the α-hydroxyketone 201 (88%, two steps). Reduction of the C9 ketone within 201 delivered
exclusively the undesired C8–C9 trans-diol, under a large range of conditions. For example, treatment of 201 with sodium borohydride in methanol provided the unproductive anti-vicinal diol 202 in 99% yield. The stereochemistry of the reduction product was readily determined by analysis of the $^3J_{H8-H9}$ coupling constant (0 Hz). Identical results were obtained with additional reductants such as di-iso-butyraluminum hydride, lithium aluminum hydride, or Superhydride.

Scheme 31. Synthesis of the bis(acetonide) 203 from the lactone 197.

Due to the problematic C9 reduction, we implemented an $\alpha$-ketol rearrangement, as first reported by White and co-workers$^{24}$ on a similar substrate. Treatment of the $\alpha$-
hydroxyketone 201 with trimethylaluminum provided the isomeric \( \alpha \)-hydroxyketone 203 (90%) as a single detectable diastereomer (\(^1\)H NMR analysis). The stereochemical configuration of the C9 hydroxyl group was determined by NOE correlations between the C13 methyl substituent and the C8 methine proton. Reduction of the transposed intermediate 203 with sodium borohydride in methanol gave the anti-vicinal diol 204 in 80% yield and 8:1 dr (\(^1\)H NMR analysis). The stereochemistry of this reduction product was readily determined by analysis of the \( ^3J_{\text{H}8-H9} \) (9.1 Hz) which is consistent with the anti-stereochemical assignment shown. Fortunately, we found that the addition of cerium chloride heptahydrate\(^{45}\) to this sodium borohydride reduction led to a reversal of the diastereoselectivity and preferential formation of the syn-C8–C9 diol stereochemistry (4.1:1 dr, \(^1\)H NMR analysis). We found that the diol intermediate (not shown) rapidly underwent translactonization upon exposure to acidic or basic conditions. Consequently we treated the unpurified diol with PTSA and 2,2-dimethoxypropane to generate the bis(acetonide) 206, which was stable toward purification (61%, two steps).

The synthesis of (−)-euonyminol (99) was completed by the pathway shown in Scheme 32. Our attempts to reduce the lactone in the presence of the C1 silyl ether group were met with failure, again likely due to the steric congestion introduced by the acetonide and the silyl ether groups. Therefore, we first treated 206 with TBAF, to generate the lactone 208. Treatment of 208 with excess of lithium aluminum hydride afforded the fully reduced triol intermediate 209 (66% yield, two steps). Finally, removal of all of the acid-labile protecting groups was accomplished by heating the triol 209 to 80 °C in aqueous acetic acid. Because of the very high polarity of (−)-euonyminol (99), we subjected the
unpurified product to exhaustive acylation (acetic anhydride), to generate the euonyminol octaacetate (116), which could be purified using normal phase chromatography. The sample obtained in this way was analytically pure and its spectroscopic data precisely matched natural euonyminol octaacetate (116) reported in the literature by Hirata and co-workers (see Table S2 and Table S3). Removal of the eight acetate residues (sodium methoxide, methanol) then provided (−)-euonyminol (99), estimated to be >95% pure by \(^1\)H NMR analysis (99%).

**Scheme 32.** Completion of the synthesis of (−)-euonyminol (99).
To the best of our knowledge, spectroscopic data for natural (–)-euonyminol (99) were not disclosed by the isolation chemists or published in the literature. White and co-workers provided $^1$H NMR chemical shifts for synthetic (±)-euonyminol in deuterium oxide. $^1$H NMR spectroscopic data for our synthetic (–)-euonyminol (99) in the same solvent did not perfectly match the data reported by White and co-workers (see Table S4). The basis for this discrepancy is not known; however, White and co-workers failed to produce graphical representation of their $^1$H NMR spectrum and they also did not disclose $^{13}$C chemical shifts for their synthetic compound. They also acquired their data on <1 mg of material, which may render the NMR shifts sensitive to impurities.

To rigorously confirm we had indeed synthesized (–)-euonyminol (99), the synthetic material was reacetylated (89%). The octaacetate 116 obtained in this way provided spectroscopic data that was indistinguishable from our earlier sample or from the data in the literature. This result indicates that no unexpected transformations or rearrangements had occurred in the original deacetylation step. We obtained complete NMR spectroscopic data for (–)-euonyminol (99) in deuterium oxide and methanol-$d_4$, which we believe will be of use to future synthetic research in this area.

2.4.4 Improved synthesis of the unsaturated ketone 216 via a 6-endo-trig radical cyclization.

The synthesis of (–)-euonyminol (99) that we developed suffers from some limitations that make its adaptation to the cathedulins challenging. Specifically, the most significant bottleneck of our synthesis corresponds to the inversion of stereochemistry at
the C1 (see 190→191, Scheme 30). This reaction proceeds in 50% yield. As discussed in section 2.4.2, we were unable to overcome the preferential sense of the nucleophilic addition to the aldehyde 188 with various nucleophiles and were forced to proceed with this inversion strategy.

Scheme 33. A. Synthesis of 211 via 5-exo-trig cyclization. B. Improved synthesis of the unsaturated ketone 194 from the acetonide 174 via a 6-endo-trig radical cyclization.

To identify an alternative approach, we revisited the enyne intermediate 173, which possesses the correct stereochemistry at C1. Previously, we were forced to abandon this intermediate because we were unable to hydrolyze the hindered neopentyl alkyne to the methyl ketone needed for the ring-closing aldol–dehydration sequence. We evaluated this
compound in an alternative ring-closing free-radical cyclization (Scheme 33). To this end, the 1,3-diol of 173 was protected as the silylene ether (di-tert-butylsilyl difluoromethanesulfonate) to generate 210 (79%). Heating of 210 with tri-n-butyltin hydride and AIBN provided exclusively the 5-exo-trig-cyclization product 211 (90%, Scheme 33A). We believed that we could change the outcome of this radical cyclization to favor the desired 6-membered ring formation by varying the 1,3-diol protecting group. We found that the acetonide 174 underwent 6-endo-trig cyclization prefentially, to provide 212, under identical conditions (tri-n-butyltin hydride, AIBN; 71%, Scheme 33B). Computational studies aiming to elucidate the exact reasoning behind the shift from 5-exo-trig to 6-endo-trig are currently ongoing by the Batista research group. We speculate that the differences in bond lengths between carbon–oxygen and carbon–silicon bonds influence the selectivity in the ring closure, but further studies are required to fully understand the different reaction outcomes.

Protodestannylation of the vinyl stannane 212 with accompanying removal of the acetonide protecting group (camphorsulfonic acid) provided the exocyclic olefin 213 (99%). Ozonolysis and silylene ether formation proceeded uneventfully to generate the ketone 214 (80%, two steps). A two-step sequence comprising enoxysilane formation (LiHMDS, TMSI, 93%) and oxidation47 (2-iodobenzoic acid, 91%) then provided the unsaturated ketone 194, that can be advanced to the natural product. This alternative synthesis of the unsaturated ketone 194 avoids the low-yielding stereochemical inversion at C1 and also nearly doubles the overall yield from the primary alcohol 170 to 194 (21.7% vs 12.7%), thereby expediting the material throughput and shortening the synthetic step count.
2.4.5 Application of the synthetic strategy towards the macrocyclic cathedulin alkaloids.

As stated above, it is our desire to apply the developed synthetic strategy towards the synthesis of the cathedulin alkaloids. Our current synthetic plan towards the cathedulin K-19 (105) is shown in Scheme 34. Beginning with the lactone 197, removal of the silylene ether group (TBAF) followed by a reduction of the lactone (lithium aluminum hydride) will provide the tetraol 216. Selective esterification of the C15 primary hydroxyl group with the evioninic acid derivative 217 and protection of the syn-1,2 diol as an acetonide would provide the bis(acetonide) 218. Similar to the euonyminol sequence, we propose to install the C8 hydroxyl group via an $\alpha$-oxidation reaction followed by a trimethyl aluminum mediated rearrangement and reduction, to obtain the ketone 219. Installation of the methyl 2-acetoxypropanoate and a cerium chloride mediated sodium borohydride reduction will then give 220.

We plan to access the top macrocycle via a base mediated lactonization to arrive at 221. Next, we propose to selectively remove the primary methoxy methyl ether group (trimethylsilyl iodide) and esterify the C13 primary hydroxyl with the cathic acid derivative 222, to generate 223. Deprotection of all of the acid labile protecting groups with aqueous acetic acid is expected to then generate the shown pentaol 224. Finally, a second base-mediated lactonization reaction between the C3 axial hydroxyl and the cathic acid would complete the lower-rim macrocycle and subsequent exposure of this intermediate to excess acetic anhydride will provide the cathedulin K-19 (105).
Scheme 34. Application of the synthetic strategy towards the synthesis of the macrocyclic cathedulin K-19 (105).

2.5 Conclusion.

In this chapter, I described the development of our enantioselective total synthesis of the nonahydroxylated natural product (–)-euonyminol (99). Our strategy began with the readily-available carvone derivative 139 and featured several transformations that were
specifically developed to overcome challenges met in the synthesis. These include a novel oxyalkylation reaction of an allylic alcohol that established the C10 quaternary stereocenter along with the oxidation state of the neighboring carbon. We also developed a tandem lactonization–epoxide opening reaction to form the trans-C2–C3 vicinal diol residue as well as a highly diastereoselective late-stage α-ketol rearrangement, which was essential to establish the correct stereochemistry at the C8 position. I presented an unpublished radical cyclization approach that provides the tricyclic framework of the target from the enyne 174. Successful implementation of this reaction nearly doubled the overall yield through the middle steps of the synthesis and avoided the problematic stereochemical inversion of the C1 alcohol. Finally, I described the application of this synthetic strategy toward the macrocyclic cathedulin alkaloids.
2.6 Experimental section.

2.6.1 General information.

General experimental procedures. All reactions were performed in single-neck, flame-dried, round-bottomed flasks fitted with rubber septa under a positive pressure of argon unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula, or were handled in a nitrogen-filled drybox (working oxygen level <10 ppm). Organic solutions were concentrated by rotary evaporation at 28–32 °C. Flash-column chromatography was performed as described by Still et al.,\textsuperscript{48} employing silica gel (‘SiliaFlash® P60’, 60 Å, 40–63 μm particle size) purchased from SiliCycle (Québec, Canada). Analytical thin-layered chromatography (TLC) was performed using glass plates pre-coated with silica gel (250 μm, 60 Å pore size) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and/or submersion in aqueous ceric ammonium molybdate solution (CAM), para-anisaldehyde (PAA), or aqueous potassium permanganate solution (KMnO₄), followed by brief heating on a hot plate (120 °C, 10–15 s).

Materials. Commercial solvents and reagents were used as received with the following exceptions. Dichloromethane, diethyl ether (ether), \textit{N,N}-dimethylformamide, tetrahydrofuran, and toluene were purified according to the method of Pangborn et al.\textsuperscript{49} Pyridine was distilled from calcium hydride under an atmosphere of nitrogen immediately prior to use. Triethylamine was distilled from calcium hydride immediately prior to use. Di-\textit{iso}-propylethylamine was distilled from calcium hydride and stored in a round-bottomed flask fused to a Teflon-coated valve under an atmosphere of argon. The
molarities of n-butyllithium, ethynylmagnesium bromide, and methyllithium lithium bromide solutions were determined by titration against a standard solution of menthol and 1,10-phenanthroline in tetrahydrofuran (average of three determinations).\textsuperscript{50} Bis (N-tert-butylsalicylaldiminato) copper (II) was prepared according to the method of Beenakker et al.\textsuperscript{51} Diazomethane was prepared according to the procedure of Arndt.\textsuperscript{52} Dimethyldioxirane was prepared according to the procedure of Taber et al.\textsuperscript{53} Trifluoromethanesulfonic anhydride and tert-butyldimethylsilyl trifluoromethanesulfonate were purified by vacuum transfer distillation and stored in a round-bottomed flask fused to a Teflon-coated valve under an atmosphere of argon at –20 °C. Compounds methoxymethyl ether \textsuperscript{139} and the Shi ketone (S\textsuperscript{17})\textsuperscript{54} were prepared according to published procedures.

**Instrumentation.** Proton nuclear magnetic resonance spectra (\textsuperscript{1}H NMR) were recorded at 400, 500, or 600 megahertz (MHz) at 23 °C, unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, \( \delta \) scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (CHCl\textsubscript{3}, \( \delta \) 7.26; C\textsubscript{6}D\textsubscript{5}H, \( \delta \) 7.16; CD\textsubscript{3}HOD, \( \delta \) 3.31; DHO, \( \delta \) 4.79). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, b = broad, app = apparent), coupling constant in Hertz (Hz), integration, and assignment. Proton-decoupled carbon nuclear magnetic resonance spectra (\textsuperscript{13}C NMR) were recorded at 100, 125, or 150 MHz at 23 °C, unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, \( \delta \) scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl\textsubscript{3}, \( \delta \) 77.0; C\textsubscript{6}D\textsubscript{6}, \( \delta \) 128.1; CD\textsubscript{3}OD, \( \delta \) 49.0). Distortionless enhancement by polarization transfer [DEPT (135)], heteronuclear
single quantum coherence (HSQC), and heteronuclear multiple bond correlation (HMBC) spectra were recorded at 125 or 150 MHz at 23 °C, unless otherwise noted. $^{13}C$ NMR and DEPT (135)/HSQC data are combined and represented as follows: chemical shift, carbon type [obtained from DEPT (135) or HSQC experiments]. Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra were obtained using a Thermo Electron Corporation Nicolet 6700 FTIR spectrometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm$^{-1}$), intensity of absorption (s = strong, m = medium, w = weak, br = broad). Analytical ultra high-performance liquid chromatography/mass spectrometry (UPLC/MS) was performed on a Waters UPLC/MS instrument equipped with a reverse-phase C$_{18}$ column (1.7 µm particle size, 2.1 × 50 mm), dual atmospheric pressure chemical ionization (API)/electrospray (ESI) mass spectrometry detector, and photodiode array detector. Samples were eluted with a linear gradient of 5% acetonitrile–water containing 0.1% formic acid→100% acetonitrile containing 0.1% formic acid over 0.75 min, followed by 100% acetonitrile containing 0.1% formic acid for 0.75 min, at a flow rate of 800 µL/min. High-resolution mass spectrometry (HRMS) were obtained on a Waters UPLC/HRMS instrument equipped with a dual API/ESI high-resolution mass spectrometry detector and photodiode array detector. Unless otherwise noted, samples were eluted over a reverse-phase C$_{18}$ column (1.7 µm particle size, 2.1 × 50 mm) with a linear gradient of 5% acetonitrile–water containing 0.1% formic acid→95% acetonitrile–water containing 0.1% formic acid for 1 min, at a flow rate of 600 µL/min. Optical rotations were measured on a Rudolph Research Analytical Autopol IV polarimeter equipped with a sodium (589 nm, D) lamp. Optical rotation data are represented as follows: specific rotation ([α]$_{T}^T$), concentration (g/mL), and solvent.
2.6.2 Synthetic procedures.

Synthesis of the epoxide 140:

The (−)-Shi ketone (S17, 12.3 g, 47.6 mmol, 1.00 equiv), a solution of sodium tetraborate decahydrate and ethylenediamine tetraacetic acid disodium salt dihydrate (EDTA–Na₂) in water (50 mM in sodium tetraborate decahydrate, 400 μM in EDTA–Na₂, 1.24 L) and tetrabutylammonium hydrogensulfate (3.23 g, 9.51 mmol, 0.200 equiv) were added in sequence to a solution of the unsaturated ketone 139 (10.0 g, 47.6 mmol, 1 equiv) in acetonitrile–dimethoxymethane (1:2 v/v, 950 mL) at 23 °C. The reaction mixture was then cooled to 0 °C. A solution of oxone and EDTA–Na₂ in water (212 mM in oxone, 400 μM in EDTA–Na₂, 448 mL, 95.1 mmol, 2.00 equiv oxone) and aqueous potassium carbonate (890 mM, 428 mL, 380 mmol, 8.00 equiv) were then added dropwise simultaneously using two addition funnels over 1 h. Upon completion of the addition, the reaction mixture was stirred for 1 h at 0 °C. The product mixture was warmed to 23 °C over 1 h. The warmed product mixture was diluted sequentially with water (1.0 L) and ethyl acetate (1.0 L). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 1.0 L). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (500 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The
residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes) to provide the epoxide 140 as a yellow oil (7.50 g, 70%).

$^1$H NMR analysis of the unpurified product mixture indicated the presence of a 2.4:1 mixture of diastereomers. The relative stereochemistry of 140 was established by X-ray analysis of the ether 141.

Rf = 0.40 (25% ethyl acetate–hexanes; UV, PAA). 1H NMR (600 MHz, CDCl3): $\delta$ 6.70 (td, $J=3.4$ Hz, H$_4$, 1H), 4.75 (d, $J=6.7$ Hz, H$_{6a}$, 1H), 4.68 (d, $J=6.7$ Hz, H$_{6b}$, 1H), 4.20 (d, $J=3.7$ Hz, H$_1$, 1H), 3.36 (s, H$_7$, 3H), 2.75 (d, $J=4.8$ Hz, H$_{9a}$, 1H), 2.73–2.65 (m, H$_{3a}$, 1H), 2.62 (d, $J=4.7$ Hz, H$_{9b}$, 1H), 2.49–2.40 (m, H$_{3b}$, 1H), 2.11 (ddd, $J=7.4$, 5.5, 3.7 Hz, H$_2$, 1H), 1.80 (q, $J=1.9$ Hz, H$_5$, 3H), 1.33 (s, H$_8$, 3H). 13C NMR (150 MHz, CDCl3): $\delta$ 197.2 (C), 143.6 (CH), 134.1 (C), 95.8 (CH$_2$), 77.0 (CH), 57.4 (C), 56.2 (CH$_3$), 53.9 (CH$_2$), 46.2 (CH), 25.6 (CH$_2$), 20.2 (CH$_3$), 15.9 (CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 3733 (s), 3710 (m), 3628 (m), 2984 (m), 1683 (m). HRMS-Cl (m/z): [M + Na]$^+$ calcd for C$_{12}$H$_{18}$NaO$_4$, 249.1103; found, 249.1110. $\left[\alpha\right]^B_D = 18.6 \ (c = 0.06, \text{CHCl}_3)$. 
Synthesis of the cyclic ether 141:

**Part 1: Synthesis of the tertiary alcohol S18:**

A solution of \(n\)-butyllithium in hexanes (2.50 M, 42.4 mL, 106 mmol, 1.20 equiv) was added dropwise via a syringe over 30 min to a solution of trimethylsilylacetylene (14.5 mL, 101 mol, 1.15 equiv) in tetrahydrofuran (380 mL) at \(-78^\circ\mathrm{C}\). The resulting solution was stirred for 1 h at \(-78^\circ\mathrm{C}\). The reaction vessel was then placed in an ice bath. The mixture was stirred for 30 min at 0 °C and then was cooled to \(-78^\circ\mathrm{C}\) over 30 min. A solution of the epoxide 140 (20.0 g, 88.4 mmol, 1 equiv) in tetrahydrofuran (65 mL) was added dropwise over 30 min. The reaction mixture was stirred for 1 h at \(-78^\circ\mathrm{C}\). The reaction vessel was then placed in an ice bath and the product mixture was allowed to warm to 0 °C over 30 min. The warmed product mixture was diluted sequentially with saturated ammonium chloride (200 mL) and ethyl acetate (200 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 300 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the next step without further purification.
Part 2: Synthesis of the cyclic ether 141:

Pyridinium p-toluenesulphonate (PPTS, 4.40 g, 18.0 mmol, 0.200 equiv) was added in one portion to a solution of the residue obtained in the preceding step (nominally 62.4 mmol, 1 equiv) in dichloromethane (440 mL) at 23 °C. The resulting solution was stirred for 2 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous sodium bicarbonate solution (200 mL) and dichloromethane (200 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 200 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes initially, grading to 20% ethyl acetate–hexanes, one step) to provide the cyclic ether 141 as a yellow oil (25.0 g, 87% over two steps). The relative stereochemistry of cyclic ether 141 was established by X-ray analysis (see Appendix A).

Rf = 0.30 (50% ethyl acetate–hexanes; PAA). 1H NMR (600 MHz, CDCl3): δ 5.40 (s, H4, 1H), 4.90 (d, J = 8.7 Hz, H6a, 1H), 4.77 (d, J = 8.7 Hz, H6b, 1H), 4.27 (s, H1, 1H), 3.81 (s, H9a, 1H), 3.46 (d, J= 10.9 Hz, H9b, 1H), 3.44 (s, H7, 1H), 2.55 (s, H10, 1H),
2.43 (d, \( J = 17.9 \text{ Hz}, H_{3a}, 1\text{H} \)), 2.35 (s, H2, 1H), 2.29 (d, \( J = 23.7 \text{ Hz}, H_{3b}, 1\text{H} \)), 1.86 (s, H5, 3H), 1.32 (s, H8, 3H), 0.16 (s, H11, 9H). 13C NMR (150 MHz, CDCl3): \( \delta \) 137.5 (C), 122.3 (CH), 101.3 (C), 95.2 (CH₂), 93.1 (C), 86.2 (C), 84.2 (CH), 80.0 (C), 69.6 (CH₂), 55.6 (CH₃), 43.6 (CH), 30.5 (CH₂), 21.0 (CH₃), 20.0 (CH₃), –0.3 (3 ×CH₃). IR (ATR-FTIR), cm⁻¹: 3726 (m), 3212 (m), 3011 (m). HRMS-Cl (m/z): [M + Na]⁺ calcd for C17H28NaO4Si, 347.1655; found, 347.1673. \([\alpha]_D^{20} = 17.6 \ (c = 0.20, \text{CHCl}_3)\).
**Synthesis of the methoxymethyl ether 142:**

4-Dimethylaminopyridine (565 mg, 4.62 mmol, 0.03 equiv) and diisopropylethylamine (134 mL, 770 mmol, 5.00 equiv) were added in sequence to a solution of the ether 141 (50.0 g, 154 mmol, 1 equiv) in dichloromethane (500 mL) at 23 °C. The reaction vessel was then placed in an ice bath and allowed to cool to 0 °C over 20 min. Chloromethyl methyl ether (15.2 mL, 200 mmol, 1.30 equiv) was added dropwise via a syringe pump over 30 min. Upon completion of the addition, the ice bath was removed and the reaction mixture was allowed to warm to 23 °C over 30 min. The warmed reaction vessel was then immersed in an oil bath that had been preheated to 45 °C. The reaction mixture was stirred and heated for 3 d at 45 °C. The product mixture was cooled to 23 °C over 30 min. The cooled product mixture was diluted sequentially with dichloromethane (200 mL) and saturated aqueous ammonium chloride solution (100 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 300 mL). The organic layers were combined and the combined organic layers were washed sequentially with 1 N aqueous hydrochloric acid solution (200 mL) and saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by a flash-
column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the cyclic ether 142 as a yellow oil (52.7 g, 93%).

Rf = 0.70 (50% ethyl acetate–hexanes; PAA). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.37 (ddt, $J$ = 4.2, 2.6, 1.4 Hz, H$_4$, 1H), 4.90 (d, $J$ = 6.8 Hz, H$_{6a}$, 1H), 4.78 (d, $J$ = 6.8 Hz, H$_{6b}$, 1H), 4.62 (q, $J$ = 6.3 Hz, H$_{11}$, 2H), 4.27 (s, H$_1$, 1H), 3.86 (d, H$_{9a}$, $J$ = 8.9 Hz, 1H), 3.48 (d, H$_{9b}$, $J$ = 8.9 Hz, 1H), 3.44 (s, H$_{12}$, 3H), 3.34 (s, H$_7$, 3H), 2.59 – 2.46 (m, H$_2$, 1H), 2.44 – 2.37 (m, H$_{3a}$,1H), 2.30 – 2.23 (m, H$_{3b}$,1H), 1.86 (s, H$_5$, 1H), 1.34 (s, H$_8$, 3H), 0.15 (s, H$_{10}$, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 138.4 (C), 122.0 (CH), 101.8 (C), 96.8 (CH$_2$), 95.3 (CH$_2$), 92.9 (C), 85.2 (C), 84.4 (CH), 80.1 (C), 74.6 (CH$_2$), 55.5 (CH$_3$), 55.3 (CH$_3$), 43.4 (CH), 30.8 (CH$_3$), 22.3 (CH$_3$), 20.1 (CH$_3$), – 0.1 (3 ×CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 3734 (s), 3685 (m), 2956 (s), 2901 (s). HRMS-CI (m/z): [M + Na]$^+$ calcd for C19H32NaO5Si, 391.1917; found, 391.1935. $[\alpha]_D^{20} = 21.8$ (c = 0.25, CHCl$_3$).
Synthesis of the allylic alcohol 143:

Part 1: Synthesis of the unsaturated aldehyde S19:

Pyridine N-oxide (23.7 g, 250 mmol, 4.00 equiv) and selenium dioxide (13.9 g, 125 mmol, 2.00 equiv) were added in sequence to a solution of the cyclic ether 142 (23.0 g, 62.4 mmol, 1 equiv) in 1,4-dioxane (520 mL) at 23 °C. The reaction vessel was fitted with a reflux condenser and then immersed in an oil bath that had been preheated to 95 °C. The reaction mixture was stirred and heated for 12 h at 95 °C. The product mixture was cooled to 23 °C over 30 min. The cooled product mixture was diluted sequentially with ethyl acetate (200 mL), water (100 mL), and saturated aqueous sodium bicarbonate solution (100 mL). The diluted mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 300 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.
Part 2: synthesis of the allylic alcohol \textbf{143}:

Cerium (III) chloride heptahydrate (23.2 g, 62.4 mmol, 1.00 equiv) was added in one portion to a solution of the residue obtained in the preceding step (nominally 62.4 mmol, 1 equiv) in methanol (310 mL) at 0 °C. The resulting solution was allowed to stir for 30 min at 0 °C. Sodium borohydride (472 mg, 12.5 mmol, 0.20 equiv) was then added portionwise at 5 min intervals, until a total of 2.36 g (62.4 mmol, 1.00 equiv) had been introduced. Upon completion of the addition, the reaction mixture was stirred for 1 h at 0 °C. The cold product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (100 mL), water (100 mL), and ethyl acetate (200 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 200 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes) to provide the allylic alcohol \textbf{143} as a yellow oil (19.2 g, 80% over two steps).
Rf = 0.45 (50% ethyl acetate–hexanes; PAA). \(^1\)H NMR (500 MHz, CDCl\(_3\)):
\[ \delta 5.69 \text{ (s, H}_4\text{, 1H)}, \ 4.89 \text{ (d, } J = 6.8 \text{ Hz, } H_{6a}\text{, 1H}), \ 4.78 \text{ (d, } J = 6.8 \text{ Hz, } H_{6b}\text{, 1H}), \ 4.62 \text{ (q, } J = 6.3 \text{ Hz, } H_{11}\text{, 2H}), \ 4.30 \text{ (s, H}_1\text{, 1H)}, \ 4.25 \text{ (s, H}_5\text{, 2H)} \]
\[ 3.85 \text{ (d, } J = 8.9 \text{ Hz, } H_{9a}\text{, 1H}), \ 3.50 \text{ (d, } J = 8.9 \text{ Hz, } H_{9b}\text{, 1H}), \ 3.43 \text{ (s, H}_12\text{, 3H)}, \ 3.34 \text{ (s, H}_7\text{, 3H)}, \ 2.55 - 2.30 \text{ (m, H}_{2,3}\text{, 3H)}, \ 1.35 \text{ (s, H}_8\text{, 3H)}, \ 0.17 \text{ (s, H}_10\text{, 9H}). \]

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)):
\[ \delta 141.6 \text{ (C), 124.2 (CH), 101.0 (C), 96.6 (CH}_2\text{), 95.2 (CH}_2\text{), 93.2 (C), 85.4 (C), 84.3 (CH), 78.0 (C), 74.3 (CH}_2\text{), 63.9 (CH}_2\text{), 55.4 (CH}_3\text{), 55.2 (CH}_3\text{), 43.4 (CH), 30.5 (CH}_2\text{), 22.2 (CH}_3\text{), } - 0.4 \text{ (3 × CH}_3\text{).} \]

IR (ATR-FTIR), cm\(^{-1}\):
\[ 3733 \text{ (s), 3710 (m), 3628 (m), 2953 (s).} \]

HRMS-Cl (m/z): [M + Na]\(^{+}\) calculated for C\(_{19}\)H\(_{32}\)NaO\(_6\)Si, 407.1866; found, 407.1883. \([\alpha]_D^{20} = 19.0 \text{ (c = 0.35, CHCl}_3\text{).} \]
Synthesis of the epoxide $S_{20}$:

$\text{meta-Chloroperoxybenzoic acid (923 mg, 3.75 mmol, 1.80 equiv) was added in one portion to a solution of the allylic alcohol 143 (800 mg, 3.75 mmol, 1 equiv) in dichloromethane (10.5 mL) at 0 °C. The resulting solution was allowed to stir for 30 min at 0 °C. The cooling bath was then removed and the reaction mixture was allowed to warm to 23 °C over 30 min. The reaction mixture was stirred for 10 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (50 mL), water (50 mL), and dichloromethane (100 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ethyl acetate–hexanes) to provide the epoxide $S_{20}$ as a yellow oil (750 mg, 90%).}
Within the limits of detection, the epoxide S20 was formed as a single diastereomers (1H NMR analysis, 400 MHz). The relative stereochemistry at the C5 position of the epoxide S20 was established via conversion to the aldehyde 144.

Rf = 0.40 (50% ethyl acetate–hexanes; PAA). 1H NMR (500 MHz, CDCl3): δ 4.80 (d, J = 6.8 Hz, H7a, 1H), 4.69 (d, J = 6.8 Hz, H7b, 1H), 4.66 – 4.59 (m, H11, 2H), 4.26 (s, H2, 1H), 4.10 (d, J = 2.7 Hz, H1, 2H), 3.80 (d, J = 9.0 Hz, H10a, 1H), 3.55 (d, J = 9.0 Hz, H10b, 1H), 3.39 (s, H8, 3H), 3.34 (s, H5, H12, 4H), 2.33 (d, J = 1.7 Hz, H3, 1H), 2.12 (t, J = 3.3 Hz, H4, 2H), 1.33 (s, H9, 3H), 0.17 (s, H6, 9H). 13C NMR (125 MHz, CDCl3): δ 99.3 (C), 96.8 (CH2), 95.8 (CH2), 94.4 (C), 85.1 (C), 82.1 (CH), 81.0 (C), 74.0 (CH2), 66.0 (C), 59.9 (CH2), 55.6 (CH3), 55.4 (CH3), 54.8 (CH), 44.2 (CH), 27.3 (CH2), 22.6 (CH3), -0.2 (3×CH3). IR (ATR-FTIR), cm−1: 3015 (m), 2975 (s), 1412 (s). HRMS-Cl (m/z): calcd for C19H32NaO7Si, 423.1815; found: 423.1810. [α]D 20 = 5.77 (c = 0.17, CHCl3).
Synthesis of the aldehyde 144:

The Dess–Martin periodinane (826 mg, 1.95 mmol, 1.50 equiv) was added in five equal portions over 1 h to a solution of the epoxide S20 (520 mg, 1.30 mmol, 1 equiv) and pyridine (731 μL, 9.09 mmol, 7.0 equiv) in dichloromethane (13 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was warmed to 23 °C over 30 min. The warmed mixture was stirred for 2 h at 23 °C. The product mixture was then diluted sequentially with dichloromethane (50 mL), saturated aqueous sodium bicarbonate solution (20 mL), and saturated aqueous sodium thiosulfate solution (20 mL). The diluted product mixture was stirred for 30 min at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the aldehyde 144 as a colorless oil (750 mg, 76%).
NOE correlations between the C5 hydrogen atom and the C9 methyl substituent support the relative configuration depicted.

\[
\text{R}_{f} = 0.30 \text{ (25\% ethyl acetate–hexanes; PAA).} \quad \text{^1H NMR (400 MHz, CDCl}_3): \quad \delta 9.98 \text{ (s, H}_1, 1\text{H}), 4.83 \text{ (d, H}_7\text{a, } J = 6.8 \text{ Hz, 1H}), 4.71 \text{ (d, H}_7\text{b, } J = 6.8 \text{ Hz, 1H}), 4.67 - 4.58 \text{ (m, H}_{11}, 2\text{H}), 4.25 \text{ (s, H}_2, 1\text{H}), 3.85 \text{ (d, H}_{10\text{a}}, J = 9.1 \text{ Hz, 1H}), 3.59 \text{ (d, H}_{10\text{b}}, J = 9.0 \text{ Hz, 1H}), 3.40 \text{ (s, H}_{12}, 3\text{H}), 3.35 \text{ (s, H}_8, 3\text{H}), 3.32 \text{ (s, H}_5, 1\text{H}), 2.39 \text{ (s, H}_3, 1\text{H}), 2.18 \text{ (t, } J = 3.0 \text{ Hz, H}_4, 2\text{H}), 1.32 \text{ (s, H}_9, 3\text{H}), 0.15 \text{ (s, H}_6, 9\text{H).} \quad \text{^13C NMR (100 MHz, CDCl}_3): \quad \delta 196.4 \text{ (CH), 98.8 \text{ (C), 96.7 (CH}_2), 95.7 \text{ (CH}_2), 95.0 \text{ (C), 85.6 \text{ (C), 81.5 (CH), 78.5 \text{ (C), 73.6 (CH}_2), 66.6 \text{ (C), 58.4 (CH), 55.6 (CH}_3), 55.3 (CH}_3), 44.1 (CH), 27.5 (CH}_2), 22.7 (CH}_3), -0.4 (3\times\text{CH}_3).} \quad \text{IR (ATR-FTIR), cm}^{-1}: \quad 3734 \text{ (s), 3628 (m), 2932 (s), 1733 (s).} \quad \text{HRMS-Cl (m/z): calcd for C}_{19}\text{H}_{30}\text{NaO}_{7}\text{Si, 421.1658; found: 421.1653.} \quad [\alpha]_D^{20} = 21.1 \text{ (c = 0.30, CHCl}_3).}
Part 1: Synthesis of the allylic alcohol \textit{S21}:

A solution of vinylmagnesium bromide in tetrahydrofuran (700 mM, 2.84 mL, 1.98 mmol, 2.00 equiv) was added dropwise via a syringe over 30 min to a solution of aldehyde 144 (395 mg, 991 μmol, 1 equiv) in tetrahydrofuran (8 mL) at –78 °C. The reaction mixture was stirred for 2 h at –78 °C. The product mixture was then warmed to 0 °C over 30 min, where it was diluted sequentially with saturated aqueous ammonium chloride solution (20 mL), water (20 mL), and ethyl acetate (50 mL). The resulting mixture was warmed up 23 °C over 30 min. The warmed product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

Within the limits of detection, the product \textit{S21} was formed as 3.4:1 inconsequential mixture of diastereomers (\textit{^1}H NMR analysis, 400 MHz).
Trimethylsilyl chloride (252 μL, 1.98 mmol, 2.00 equiv) was added dropwise via syringe to a solution of the residue obtained in the preceding step (nominally, 991 μmol, 1 equiv) and imidazole (270 mg, 3.96 mmol, 4.00 equiv) in dichloromethane (6 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then the cooling bath was removed. The reaction mixture was allowed to warm to 23 °C and stirred for 8 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (15 mL), water (15 mL), and dichloromethane (50 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes) to provide the silyl ether 145 as a colorless oil (370 mg, 77% over two steps).

\[ R_f = 0.50 \text{ (40\% ethyl acetate–hexanes; PAA).} \]  
*Denotes second diastereomer.  
\[^1\text{H NMR (400 MHz, CDCl}_3\text{)}: \delta 6.30 \text{ (ddd, } H_6, J = 16.8, 10.4, 4.6 \text{ Hz, } 1\text{H}), 6.13–5.97 \text{ (m, } H_6^*, 1\text{H),} \]
5.34 – 5.22 (m, H_{7a,7a*}, 2H), 5.20 – 5.08 (m, H_{7b,7b*}, 2H), 4.98 (d, H_{5*}, J = 5.0 Hz, 1H), 4.85 (d, H_{5}, J = 4.7 Hz, 1H), 4.80 (dd, H_{12a,12a*}, J = 14.6, 6.7 Hz, 2H), 4.68 (d, H_{12b,12b*}, J = 6.8 Hz, 2H), 4.63 – 4.55 (m, H_{14,14*}, 4H), 4.34 (s, H_{1}, 1H), 4.22 (s, H_{1*}, 1H), 3.84 (t, H_{11a,11a*}, J = 9.5 Hz, 2H), 3.51 (d, H_{12b*}, J = 8.9 Hz, 1H), 3.46 (d, H_{11b}, J = 8.9 Hz, 1H), 3.38 (s, H_{13}, 3H), 3.37 (s, H_{13*}, 3H), 3.34 (s, H_{15*}, 3H), 3.32 (s, H_{15}, 3H), 3.29 – 3.24 (m, H_{4,4*}, 2H), 2.31 (s, H_{2,2*}, 2H), 2.13 – 1.89 (m, H_{3,3*}, 4H), 1.33 (s, H_{10}, 3H), 1.22 (s, H_{10*}, 3H), 0.18 (s, H_{9}, 9H), 0.17 (s, H_{9*}, 9H), 0.13 (s, H_{8*}, 9H), 0.10 (s, H_{8}, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 138.0 (CH), 136.9 (CH)*, 115.6 (CH$_2$)*, 113.8 (CH$_2$), 100.5 (C)*, 99.9 (C), 96.69 (CH$_2$)*, 96.67 (CH$_2$), 95.76 (CH$_2$), 95.76 (CH$_2$)*, 93.9 (C)*, 93.6 (C), 84.9 (C)*, 84.7 (C), 82.9 (CH), 82.6 (CH)*, 81.8 (C)*, 80.9 (C), 74.2. (CH$_2$), 74.2 (CH$_2$)*, 70.4 (CH)*, 69.6 (CH), 68.7 (C)*, 66.9 (C), 55.42 (CH$_3$), 55.39 (CH$_3$)*, 55.2 (CH$_3$), 54.8 (CH$_3$)*, 52.5 (CH), 52.5 (CH)*, 43.9 (CH), 43.7 (CH)*, 27.2 (CH$_2$)*, 26.8 (CH$_2$), 22.6 (CH$_3$)*, 22.4 (CH$_3$), 0.45 (3×CH$_3$)*, 0.041 (3×CH$_3$), 0.3 (3×CH$_3$), –0.4 (3×CH$_3$)*. IR (ATR-FTIR), cm$^{-1}$: 3734 (m), 3646 (m), 2956 (m), 1683 (m). HRMS-Cl (m/z): calcd for C$_{24}$H$_{42}$NaO$_7$Si$_2$, 521.2367; found: 521.2376. $[\alpha]_D^{20} = 25.2$ (c = 0.08, CHCl$_3$).
Synthesis of the diazoester 144:

Part 1: Synthesis of the β-keto ester S22:

Diketene (11.4 mL, 148 mmol, 3.00 equiv) was added dropwise via a syringe over 30 min to a solution of the allylic alcohol 143 (19.0 g, 49.4 mmol, 1 equiv) and (4-dimethylamino)pyridine (DMAP, 302 mg, 2.47 mmol, 0.05 equiv) in ether (250 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to 23 °C over 30 min. The reaction mixture was stirred for 2 h at 23 °C. The product mixture was diluted sequentially with water (200 mL) and ethyl acetate (200 mL). The diluted mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 200 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.
Part 2: Synthesis of diazoester 144:

Triethylamine (20.6 mL, 148 mmol, 3.00 equiv) was added dropwise via syringe over 1 h to a solution of (4-acetamido)benzenesulfonyl azide (p-ABSA, 14.2 g, 59.3 mmol, 1.20 equiv) and the residue obtained in the preceding step (nominally 49.4 mmol, 1 equiv) in acetonitrile (490 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to 23 °C. The reaction mixture was stirred for 6 h at 23 °C. The product mixture was diluted sequentially with water (100 mL) and ethyl acetate (200 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 200 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes) to provide the diazoester 144 as a yellow oil (22.8 g, 93% over two steps).

Rf = 0.20 (50% ethyl acetate–hexanes; UV, PAA). 1H NMR (500 MHz, CDCl3): δ 5.77 (ddd, J = 4.0, 2.6, 1.3 Hz, H4, 1H), 4.93 (d, J = 12.7 Hz, H6a, 1H), 4.90 (d, J = 6.9 Hz, H5a,
1H), 4.77 (d, \( J = 6.9 \, \text{Hz}, \, H_{5b}, \, 1\H), 4.76 (d, \( J = 12.7 \, \text{Hz}, \, H_{6b}, \, 1\H), 4.63 – 4.59 (m, \, H_{11}, \, 2\H), 4.27 (s, \, H_1, \, 1\H), 3.87 (d, \( J = 8.9 \, \text{Hz}, \, H_{9a}, \, 1\H), 3.44 (d, \( J = 8.9 \, \text{Hz}, \, H_{9b}, \, 1\H), 3.43 (s, \, H_7, \, 3\H), 3.34 (s, \, H_{12}, \, 3\H), 2.56 (s, \, H_3, \, 1\H), 2.52 – 2.48 (m, \, H_{2a}, \, 1\H), 2.48 (s, \, H_{13}, \, 3\H), 2.44 – 2.35 (m, \, H_{2b}, \, 1\H), 1.30 (s, \, H_8, \, 3\H), 0.15 (s, \, H_{10}, \, 9\H).  

\[ \begin{align*}
13C\, \text{NMR} & \quad (125 \, \text{MHz, CDCl}_3): \delta \\
190.3 & \quad (C), \quad 161.3 & \quad (C), \quad 136.6 & \quad (C), \quad 128.5 & \quad (CH), \quad 100.4 & \quad (C), \quad 96.8 & \quad (CH_2), \quad 95.3 & \quad (CH_2), \quad 93.3 & \quad (C), \quad 85.5 & \quad (C), \quad 84.3 & \quad (CH), \quad 78.3 & \quad (C), \quad 77.4 & \quad (C), \quad 74.5 & \quad (CH_2), \quad 65.9 & \quad (CH_2), \quad 55.6 & \quad (CH_3), \quad 55.4 & \quad (CH_3), \quad 43.4 & \quad (CH), \quad 30.9 & \quad (CH_2), \quad 28.5 & \quad (CH_3), \quad 22.4 & \quad (CH_3), \quad -0.2 & \quad (3 \times \, CH_3). \end{align*} \]

IR (ATR-FTIR), cm\(^{-1}\): \( 2953 \) (m), \( 2889 \) (m), \( 2141 \) (s), \( 1717 \) (s), \( 1655 \) (s).  

HRMS-Cl (m/z): [M + Na]\(^+\) calculated for \( C_{23}H_{34}N_2NaO_8Si \), 517.1982; found, 517.1975.  

\[ [\alpha]_D^{20} = 17.5 \, (c = 0.28, \, \text{CHCl}_3). \]
Synthesis of the vinylogous carbonate 147:

Bis (N-tert-butylsalicylaldiminato) copper (II) (522 mg, 1.25 mmol, 0.300 equiv), the diazo ester 144 (2.07 g, 4.18 mmol, 1 equiv), and toluene (220 mL) were combined in a 500-mL screw-capped pressure vessel in a nitrogen-filled glovebox. The reaction vessel was sealed and the sealed vessel was removed from the glovebox. The reaction vessel was placed in an oil bath that had been preheated to 100 °C. The reaction mixture was stirred and heated for 1 h at 100 °C. CAUTION: gas evolution will occur! The product mixture was cooled to 23 °C over 30 min. The cooled product mixture was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes initially, grading to 20% ethyl acetate–hexanes, one step) to provide the vinylogous carbonate 147 as a colorless solid (1.62 g, 83%). The relative stereochemistry of the vinylogous carbonate 147 was established by X-ray analysis (see Appendix A).

Rf = 0.20 (33% ethyl acetate–hexanes; UV, KMnO4). 1H NMR (600 MHz, CDCl3): δ 4.99 (dd, J = 9.4, 1.2 Hz, Hs5a, 1H), 4.91 – 4.82 (m, H6a, 2H), 4.72 (dd, J = 6.9, 1.0 Hz, Hs6b, 1H), 4.63 (qd, J = 6.4, 1.0 Hz, H11, 2H), 4.26 (s, H1, 1H), 3.94 (d, J = 9.4 Hz, H5b, 1H), 3.87 (d, J = 9.0 Hz, H9a, 1H), 3.60 (d, J = 9.0 Hz, H9b, 1H), 3.41 (s, H7, 3H), 3.36 (s, H12, 3H), 2.52 (d, J = 6.4 Hz, H2, 1H), 2.45 – 2.32 (m, H3, 2H), 2.13 (s, H13, 3H), 1.13 (s, Hs,
$3\text{H}$, 0.15 (s, H$_{10}$, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 165.6 (C), 164.7 (C), 108.6 (C), 99.1 (C), 96.8 (CH$_2$), 95.7 (CH$_2$), 93.9 (C), 89.2 (CH), 84.3 (C), 83.6 (C), 80.9 (CH), 73.91 (CH$_2$), 73.90 (CH$_2$), 63.7 (C), 55.7 (CH$_3$), 55.4 (CH$_3$), 42.4 (CH), 30.0 (CH$_2$), 22.9 (CH$_3$), 13.3 (CH$_3$), -0.4 (3 × CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 2855 (m), 2769 (m), 1759 (s), 1678 (s). HRMS-CI (m/z): [M + Na]$^+$ calculated for C$_{23}$H$_{34}$NaO$_8$Si, 489.1921; found 489.1942. $[\alpha]_D^{20} = -9.91$ (c = 0.38, CHCl$_3$).
Synthesis of the diketone 169:

Ozone was passed through a solution of the vinylogous carbonate 147 (5.60 g, 12.0 mmol, 1 equiv) in dichloromethane (350 mL) and methanol (80 mL) at −78 °C. The addition of ozone was continued until a blue color persisted. Dioxygen was then passed through the solution to remove any dissolved ozone, resulting in a colorless solution. Triphenylphosphine (6.30 g, 24.0 mmol, 2.00 equiv) was then added to the cold mixture. Upon completion of the addition, the cooling bath was removed and the product mixture was allowed to warm to 23 °C over 1 h. The warmed product mixture was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes) to provide the diketone 169 as a white solid (5.09 g, 85%). The relative stereochemistry of the diketone 169 was established by X-ray analysis (see Appendix A).

Rf = 0.55 (50% ethyl acetate–hexanes; UV, PAA). $^1$H NMR (500 MHz, CDCl$_3$): δ 5.23 (d, J = 10.4 Hz, H$_{5a}$, 1H), 5.12 (dd, J = 10.7, 7.1 Hz, H$_4$, 1H), 4.89 (s, H$_1$, 1H), 4.69 (s, H$_6$, 2H), 4.62 (s, H$_{11}$, 2H), 4.40 (d, J = 10.4 Hz, H$_{5b}$, 1H), 3.94 (d, J = 9.2 Hz, H$_{9a}$, 1H), 3.60 (d, J = 9.2 Hz, H$_{9b}$, 1H), 3.38 (s, H$_7$, 3H), 3.36 (s, H$_{12}$, 3H), 2.58 (t, J = 3.4 Hz, H$_2$, 1H), 2.39 (ddd, J = 13.8, 7.2, 4.1 Hz, H$_{3a}$, 1H), 2.01 (s, H$_{13}$, 3H), 1.99 – 1.95 (m, H$_{3b}$, 1H), 1.49
(s, H₈, 3H), 0.13 (s, H₁₀, 9H). ¹³C NMR (125 MHz, CDCl₃): δ 192.5 (C), 170.2 (C), 159.4 (C), 98.2 (C), 97.0 (C), 96.8 (CH₂), 95.7 (CH₂), 87.5 (C), 83.1(C), 80.4 (CH), 73.6 (CH₂), 72.6 (CH₂), 72.0 (CH), 57.7 (C), 55.8 (CH₃), 55.4 (CH₃), 42.4 (CH), 30.6 (CH₂), 20.9 (CH₃), 20.2 (CH₃), -0.6 (3 × CH₃). IR (ATR-FTIR), cm⁻¹: 2956 (s), 2362 (m), 2338 (m), 1794 (s), 1768 (m), 1749 (s). HRMS-CI (m/z): [M + Na]+ calculated for C₂₃H₃₄NaO₁₀Si, 521.1819; found 521.1816. [α]²⁰D = −57.4 (c = 0.14, CHCl₃).
Synthesis of the methyl ester 170:

Magnesium monoperoxyphthalate (MMPP, 37.2 g, 75.2 mmol, 5.00 equiv) was added to a mixture of water (4.07 mL, 225 mmol, 15.0 equiv), sodium bicarbonate (15.8 g, 150.0 mmol, 10.0 equiv), and the diketone 169 (7.50 g, 15.0 mmol, 1 equiv) in tetrahydrofuran (190 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The cooling bath was removed and the reaction mixture was allowed to warm to 23 °C over 30 min. The warmed mixture was stirred for 3 h at 23 °C. Aqueous hydrochloric acid solution (1 N, 22.6 mL, 22.6 mmol, 1.50 equiv) was then added. Upon completion of the addition, the reaction vessel was placed in an oil bath that had been preheated to 50 °C. CAUTION: gas evolution will occur! The reaction mixture was stirred and heated for 3 h at 50 °C. The product mixture was cooled to 0 °C over 1 h. The cooled mixture was diluted with a solution of diazomethane in ether (~0.66 M, 113.6 mL, 75.0 mmol, 5.00 equiv). CAUTION: gas evolution will occur! Upon completion of the addition, the reaction mixture was stirred for 2 h at 0 °C. The product mixture was warmed to 23 °C over 30 min. The warmed product mixture was diluted sequentially with ethyl acetate (100 mL) and water (100 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The organic layers were combined and the combined organic layers
were washed with saturated aqueous sodium chloride solution (100 mL). The washed
organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate
was concentrated. The residue obtained was purified by flash-column chromatography
(eluting with 20% ethyl acetate–hexanes) to provide the methyl ester 170 as a yellow oil
(5.87 g, 78%).

\[ R_f = 0.55 \] (50% ethyl acetate–hexanes; PAA). \(^1\)H NMR (600 MHz, CDCl\(_3\)): \( \delta 5.63 \) (dd, \( J = 10.5, 7.6 \) Hz, \( H_4 \), 1H), 5.22 (s, \( H_1 \), 1H), 4.79 (d, \( J = 6.7 \) Hz, \( H_{6a} \), 1H), 4.68 (d, \( J = 6.7 \) Hz, \( H_{6b} \), 1H), 4.62 (s, \( H_{11} \), 2H), 4.29 (d, \( J = 12.1 \) Hz, \( H_{5a} \), 1H), 4.03 (d, \( J = 12.1 \) Hz, \( H_{5b} \), 1H),
3.98 (d, \( J = 9.2 \) Hz, \( H_{9a} \), 1H), 3.76 (s, \( H_{14} \), 3H), 3.54 (d, \( J = 9.2 \) Hz, \( H_{9b} \), 1H), 3.39 (s, \( H_7 \),
3H), 3.35 (s, \( H_{12} \), 3H), 2.50 (d, \( J = 3.1 \) Hz, \( H_2 \), 1H), 2.48 – 2.39 (m, \( H_{3a} \), 1H), 2.03 – 1.94
(m, \( H_{3b,13} \), 4H), 1.53 (s, \( H_8 \), 3H), 0.15 (s, \( H_{10} \), 9H). \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \( \delta 170.1 \)
(C), 169.9 (C), 99.3 (C), 96.7 (CH\(_2\)), 95.5 (CH\(_2\)), 94.7 (C), 86.5 (C), 85.1 (C), 82.2 (CH),
73.7 (CH\(_2\)), 68.5 (CH), 64.5 (CH\(_2\)), 60.8 (C), 55.4 (CH\(_3\)), 55.2 (CH\(_3\)), 52.2 (CH\(_3\)), 42.7
(CH), 31.5 (CH\(_2\)), 21.0 (CH\(_3\)), 20.0 (CH\(_3\)), \( -0.4 \) (3 \( \times \) CH\(_3\)). IR (ATR-FTIR), cm\(^{-1}\): 2954
(m), 2892 (m), 1733 (s). HRMS-Cl (m/z): [M + Na]+ calculated for C\(_{23}\)H\(_{38}\)NaO\(_{10}\)Si,
525.2132; found 525.2134. \([\alpha]\)_D\(^{20}\) = \(-5.00\) (c = 0.14, CHCl\(_3\)).
Synthesis of the alkyne 185:

Triethylamine trihydrofluoride (2.90 mL, 23.4 mmol, 2.00 equiv) was added dropwise via syringe to a solution of the methyl ester 170 (5.87 g, 11.7 mmol, 1 equiv) and water (300 μL) in tetrahydrofuran (58 mL) at 23 °C. The resulting mixture was stirred for 60 h at 23 °C. The product mixture was then cooled to 0 °C over 30 min. The cooled product mixture was diluted sequentially with ethyl acetate (50 mL) and saturated aqueous sodium bicarbonate solution (20 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes) to provide the alkyne 185 as a white solid (4.80 g, 95%).

Rf = 0.35 (50% ethyl acetate–hexanes; PAA). ¹H NMR (500 MHz, CDCl₃): δ 5.63 (dd, J = 10.6, 7.5 Hz, H₄, 1H), 5.21 (s, H₅, 1H), 4.78 (d, J = 6.8 Hz, H₆a, 1H), 4.72 (d, J = 6.8 Hz, H₆b, 1H), 4.61 (s, H₇, 2H), 4.29 (dd, J = 12.1, 5.5 Hz, H₅b, 1H), 4.06 (dd, J = 12.1, 8.3 Hz,
H$_{5b}$, 1H), 3.96 (d, J = 9.2 Hz, H$_{9a}$, 1H), 3.79 (s, H$_{14}$, 3H), 3.56 (d, J = 9.2 Hz, H$_{9b}$, 1H), 3.40 (s, H$_{7}$, 3H), 3.35 (s, H$_{12}$, 3H), 2.73 (dd, J = 8.3, 5.6 Hz, H$_{15}$, 1H), 2.65 (s, H$_{10}$, 1H), 2.53 (d, J = 3.5 Hz, H$_{2}$, 1H), 2.45 (ddd, J = 13.7, 7.6, 4.0 Hz, H$_{3a}$, 1H), 1.99 (s, H$_{13}$, 3H), 1.98 (d, J = 4.2 Hz, H$_{3b}$, 1H), 1.60 (s, H$_{8}$, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 170.2 (C), 170.0 (C), 96.9 (CH$_2$), 95.9 (CH$_2$), 86.8 (C), 84.8 (C), 82.6 (CH), 78.2 (C), 77.8 (CH), 73.8 (CH$_2$), 68.6 (CH), 64.7 (CH$_2$), 60.7 (C), 55.7 (CH$_3$), 55.4 (CH$_3$), 52.5 (CH$_3$), 42.8 (CH), 31.6 (CH$_2$), 21.1 (CH$_3$), 20.1 (CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 3734 (m), 3628 (m), 2953 (m), 1733 (s). HRMS-Cl (m/z): [M + Na]$^+$ calculated for C$_{20}$H$_{30}$NaO$_{10}$, 453.1737; found 453.1728. $[\alpha]_D^{20} = -17.8$ (c = 0.14, CHCl$_3$).
**Synthesis of the aldehyde 171:**

![Chemical structures](image)

The Dess–Martin periodinane (3.70 g, 8.71 mmol, 1.50 equiv) was added in five equal portions over 1 h to a solution of the alcohol 185 (2.50 g, 5.81 mmol, 1 equiv) and pyridine (3.30 mL, 40.7 mmol, 7.0 equiv) in dichloromethane (40 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The product mixture was then diluted sequentially with dichloromethane (100 mL), saturated aqueous sodium bicarbonate solution (40 mL), and saturated aqueous sodium thiosulfate solution (40 mL). The diluted product mixture was stirred for 30 min at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ethyl acetate–hexanes) to provide the aldehyde 171 as a colorless oil (1.85 g, 74%).

R_f = 0.50 (50% ethyl acetate–hexanes; PAA). ^1H NMR (400 MHz, CDCl_3): ð 9.99 (s, H_5, 1H), 5.78 (dd, J = 10.6, 7.1 Hz, H_4, 1H), 5.28 (s, H_1, 1H), 4.84 (d, J = 6.7 Hz, H_{12a}, 1H),
4.76 (d, J = 6.7 Hz, H_{12b}, 1H), 4.60 (s, H_{10}, 2H), 3.92 (d, J = 9.2 Hz, H_{9a}, 1H), 3.82 (s, H_{6}, 3H), 3.52 (d, J = 9.1 Hz, H_{9b}, 1H), 3.42 (s, H_{11}, 3H), 3.34 (s, H_{13}, 3H), 2.81 (s, H_{14}, 1H), 2.54 – 2.52 (m, H_{3a}, 1H), 2.53 (s, H_{2}, 1H), 1.97 (s, H_{7}, 3H), 1.89 – 1.87 (m, H_{3b}, 1H), 1.46 (s, H_{8}, 3H). \[^{13}\text{C NMR}\] (100 MHz, CDCl\textsubscript{3}): δ 193.8 (C), 169.3 (C), 167.1 (C), 96.7 (CH\textsubscript{2}), 96.0 (CH\textsubscript{2}), 87.1 (C), 82.3 (CH), 81.7 (C), 79.2 (CH), 77.4 (C), 73.5 (CH\textsubscript{2}), 68.6 (C), 65.9 (CH), 55.7 (CH\textsubscript{3}), 55.3 (CH\textsubscript{3}), 52.8 (CH\textsubscript{3}), 42.5 (CH), 31.2 (CH\textsubscript{2}), 20.8 (CH\textsubscript{3}), 20.0 (CH\textsubscript{3}).

IR (ATR-FTIR), cm\(^{-1}\): 3734 (s), 2953 (s), 2119 (m), 1748 (s), 1728 (s). HRMS-CI (m/z): calcd for C\textsubscript{20}H\textsubscript{28}NaO\textsubscript{10}, 451.1580; found: 451.1574. \[^{[a]}\text{D} = 36.3 (c = 0.17, CHCl\textsubscript{3}).\]
Synthesis of the diol 173:

Part 1: Synthesis of the allylic alcohol S23:

A solution of lanthanum(III) chloride bis(lithium chloride) complex in tetrahydrofuran (600 mM, 14.0 mL, 8.40 mmol, 3.00 equiv) was added to a solution of the aldehyde 171 (1.20 g, 2.80 mmol, 1 equiv) in tetrahydrofuran (20 mL) at 23 °C. The resulting solution was stirred for 1 h at 23 °C and then cooled to 0 °C. A solution of vinylmagnesium bromide in tetrahydrofuran (700 mM, 12.0 mL, 8.40 mmol, 3.00 equiv) was then added dropwise via syringe over 30 min at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. The product mixture was diluted sequentially with saturated aqueous potassium sodium tartrate solution (50 mL), saturated aqueous sodium chloride solution (50 mL), and ethyl acetate (100 mL). The resulting mixture was warmed up 23 °C over 30 min, and then stirred vigorously for 45 min at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.
Within the limits of detection, the product $\textbf{S23}$ was formed as a 3.6:1 mixture of diastereomers ($^1$H NMR analysis, 400 MHz). The relative stereochemistry at the C5 position of the allylic alcohol $\textbf{S23}$ was established via conversion to the acetonide $\textbf{174}$. 
Part 2: Synthesis of the diol 173:

Potassium carbonate (774 mg, 5.60 mmol, 2.00 equiv) was added in one portion to a solution of the residue obtained in the preceding step (nominally, 2.80 mmol, 1 equiv) in methanol (20 mL) at 0 °C. The reaction mixture stirred for 1 h at 0 °C. The cold product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (10 mL), water (10 mL), and ethyl acetate (30 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% ethyl acetate–hexanes) to provide the diol 173 as a yellow oil (788 mg, 68% over two steps).

Rf = 0.20 (40% ethyl acetate–hexanes; PAA). $^1$H NMR (400 MHz, CDCl$_3$): δ 6.16 (ddd, $J$ = 17.4, 10.4, 7.2 Hz, H$_6$, 1H), 5.27 (d, $J$ = 17.1 Hz, H$_{7a}$, 1H), 5.21 (d, $J$ = 7.2 Hz, H$_5$, 1H), 5.12 (d, $J$ = 9.5 Hz, H$_{7b}$, 1H), 4.72 (d, $J$ = 6.8 Hz, H$_{13a}$, 1H), 4.69 (d, $J$ = 6.8 Hz, H$_{13b}$, 1H), 4.67 – 4.65 (m, H$_4$, 1H), 4.61 (s, H$_{11}$, 2H), 4.17 (s, H$_1$, 1H), 3.97 (d, $J$ = 9.3 Hz, H$_{10a}$, 1H),
3.74 (s, H₈, 3H), 3.54 (d, J = 9.2 Hz, H₉b, 1H), 3.37 (s, H₁₂, 3H), 3.35 (s, H₁₄, 3H), 2.77 (s, H₁₅, 1H), 2.49 – 2.47 (m, H₂, 1H), 2.33 (ddd, J = 13.9, 7.0, 3.7 Hz, H₃a, 1H), 1.92 (ddd, J = 14.1, 11.2, 3.0 Hz, H₃b, 1H), 1.47 (s, H₉, 3H). 

¹³C NMR (100 MHz, CDCl₃): δ 172.2 (C), 137.5 (CH), 116.4 (CH₂), 96.6 (CH₂), 95.3 (CH₂), 87.8 (C), 86.2 (C), 83.3 (CH), 78.6 (CH), 77.2 (C), 75.9 (CH), 73.3 (CH₂), 64.7 (CH), 63.2 (C), 55.5 (CH₃), 55.3 (CH₃), 52.2 (CH₃), 43.2 (CH), 35.1 (CH₂), 19.2 (CH₃). IR (ATR-FTIR), cm⁻¹: 3735 (s), 3628 (s), 2950 (m), 1717 (s). HRMS-Cl (m/z): calcd for C₂₀H₃₀NaO₉, 437.1788; found: 437.1783. [α]²⁰_D = −6.27 (c = 0.17, CHCl₃).
**Synthesis of the acetonide 174:**

Para-Toluenesulfonic acid monohydrate (46.6 mg, 241 μmol, 0.20 equiv) was added in one portion to a solution of the diol 173 (500 mg, 121 mmol, 1 equiv) in acetone (4.0 mL) and 2,2-dimethoxypropane (4.0 mL) at 23 °C. The reaction mixture was stirred for 15 h at 23 °C. The product mixture was then diluted sequentially with ethyl acetate (40 mL), water (10 mL), and saturated aqueous sodium bicarbonate solution (10 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the acetonide 174 as a colorless oil (490 mg, 90%).

NOE correlations between the C4 hydrogen atom and the C17 methyl substituent, as well the C5 hydrogen and the C17 methyl substituent, and also C4 hydrogen atom and the C5 hydrogen support the relative configuration depicted.
$R_f = 0.50$ (33% ethyl acetate–hexanes; PAA). $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 6.59 (ddd, $J = 16.9, 10.5, 6.2$ Hz, H$_6$, 1H), 5.36 (d, $J = 17.0$ Hz, H$_7a$, 1H), 5.21 (d, $J = 10.5$ Hz, H$_7b$, 1H), 4.74 (d, $J = 6.8$ Hz, H$_{13a}$, 1H), 4.67 (d, $J = 7.0$ Hz, H$_{13b}$, 2H), 4.62 (s, H$_{11}$, 2H), 4.46 (dd, $J = 12.1, 5.9$ Hz, H$_4$, 1H), 4.12 (s, H$_1$, 1H), 4.02 (d, $J = 9.2$ Hz, H$_{10a}$, 1H), 3.77 (s, H$_8$, 3H), 3.60 (d, $J = 9.2$ Hz, H$_{10b}$, 1H), 3.36 (s, H$_{12}$, 3H), 3.35 (s, H$_{14}$, 3H), 2.64 (s, H$_{15}$, 1H), 2.54 (t, $J = 3.4$ Hz, H$_2$, 1H), 2.13 (td, $J = 12.5, 2.8$ Hz, H$_{3a}$, 1H), 1.99 (ddd, $J = 13.3, 5.9, 3.9$ Hz, H$_{3b}$, 1H), 1.53 (s, H$_{16}$, 3H), 1.51 (s, H$_9$, 3H), 1.43 (s, H$_{17}$, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 169.6 (C), 135.0 (CH), 118.1 (CH$_2$), 100.2 (C), 96.7 (CH$_2$), 95.3 (CH$_2$), 87.6 (C), 84.5 (CH), 82.6 (C), 79.8 (C), 78.5 (CH), 76.3 (CH), 73.8 (CH$_2$), 69.8 (CH), 59.0 (C), 55.5 (CH$_3$), 55.3 (CH$_3$), 51.5 (CH$_3$), 43.1 (CH), 30.6 (CH$_2$), 29.5 (CH$_3$), 19.7 (CH$_3$), 19.1 (CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 3735 (s), 3648 (m), 2948 (m), 1735 (s). HRMS-Cl (m/z): calcd for C$_{23}$H$_{34}$NaO$_9$, 477.2101; found: 477.2100. $[^{[\alpha]}_D^{20} = 8.00$ (c = 0.15, CHCl$_3$).
Synthesis of the diol S24:

Potassium osmate(VI) dihydrate (12.2 mg, 33.0 μmol, 10.0 mol %) was added to a solution of the acetonide 174 (150 mg, 330 μmol, 1 equiv) and N-methyl-morpholine N-oxide (116 mg, 990 μmol, 3.00 equiv) in 66% acetone–water (v/v, 3.0 mL) at 23 °C. The reaction mixture was stirred for 18 h at 23 °C. The product mixture was then poured into a stirring mixture of ethyl acetate (15 mL) and saturated aqueous sodium thiosulfate solution (10 mL). The diluted product mixture was stirred for 10 min at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue obtained was purified by flash column chromatography (eluting with 50% ethyl acetate–hexanes) to provide the diol S24 as a colorless oil (159 mg, 99%).
Within the limits of detection, the diol **S24** was formed as a >20:1 mixture of diastereomers (\(^1\)H NMR analysis, 400 MHz). The relative stereochemistry at the C6 position of the diol **S24** was established via conversion to the lactone **175**.

\[ \text{R}_f = 0.10 \text{ (50\% ethyl acetate–hexanes; PAA). } \]

\(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)): \( \delta \) 5.35 (t, \( J = 5.2 \text{ Hz}, H_4, 1\text{H} \)), 4.62 (d, \( J = 6.8 \text{ Hz}, H_{13a}, 1\text{H} \)), 4.56 – 4.40 (m, H\(_1\), H\(_5\), H\(_6\), H\(_{11}\), H\(_{13b}\), 6H), 4.22 (d, \( J = 9.3 \text{ Hz}, H_{10a}, 1\text{H} \)), 4.08 – 4.01 (m, H\(_7a\), 1H), 3.97 – 3.90 (m, H\(_7b\), 1H), 3.70 (d, \( J = 5.1 \text{ Hz}, H_{18}, 1\text{H} \)), 3.62 (d, \( J = 9.3 \text{ Hz}, H_{10b}, 1\text{H} \)), 3.43 (s, H\(_8\), 3H), 3.16 (s, H\(_{12}\), 3H), 3.12 (s, H\(_{14}\), 3H), 2.48 (s, H\(_{19}\), 1H), 2.38 (t, \( J = 3.4 \text{ Hz}, H_2, 1\text{H} \)), 2.30 (td, \( J = 12.6, 2.8 \text{ Hz}, H_{3a}, 1\text{H} \)), 2.14 (s, H\(_{15}\), 1H), 1.93 – 1.80 (m, H\(_{3b}\), 1H), 1.44 (s, H\(_9\), 3H), 1.32 (s, H\(_{16}\), 3H), 1.28 (s, H\(_{17}\), 3H). \(^{13}\)C NMR (100 MHz, C\(_6\)D\(_6\)): \( \delta \) 170.3 (C), 136.4 (C), 100.5 (CH\(_2\)), 96.9 (CH\(_2\)), 95.6 (C), 88.1 (CH), 84.7 (C), 82.5 (CH), 81.8 (C), 81.1 (CH), 78.2 (CH\(_2\)), 74.2 (CH\(_2\)), 71.8 (CH), 70.2 (CH), 64.1 (CH\(_2\)), 59.9 (C), 55.4 (CH\(_3\)), 55.0 (CH\(_3\)), 51.2 (CH\(_2\)), 43.3(CH), 31.3 (CH\(_3\)), 29.5 (CH\(_3\)), 19.4 (CH\(_3\)), 19.3 (CH\(_3\)). IR (ATR-FTIR), cm\(^{-1}\): 3733 (s), 3260 (s), 2990 (s), 2950 (m), 1733 (s). HRMS-CI (m/z): calcd for C\(_{23}\)H\(_{36}\)NaO\(_{11}\), 511.2155; found: 511.2146. \([ \alpha ]_D^{20} = 1.35 \text{ (c = 0.27, CHCl3).} \)
Synthesis of the lactone 175:

Potassium carbonate (56.6 mg, 409 µmol, 2.00 equiv) was added in one portion to a solution of the diol S24 (100 mg, 205 µmol, 1 equiv) in methanol (2.0 mL) at 0 °C. The reaction mixture stirred for 1 h at 0 °C. The cold product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (5.0 mL), water (5.0 mL), and ethyl acetate (20 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ethyl acetate–hexanes) to provide the lactone 175 as a yellow oil (90 mg, 96%).

NOE correlations between the C6 hydrogen atom and the C16 methyl substituent support the relative configuration depicted.
R_f = 0.40 (50% ethyl acetate–hexanes; PAA). ^1^H NMR (400 MHz, C_6D_6): δ 5.96 (s, H_1, 1H), 4.84 (d, J = 1.5 Hz, H_5, 1H), 4.72 (d, J = 6.5 Hz, H_{13a}, 1H), 4.69 – 4.62 (m, H_{4,6}, 2H), 4.60 (d, J = 6.5 Hz, H_{13b}, 1H), 4.56 – 4.47 (m, H_{11}, 2H), 4.26 (d, J = 9.3 Hz, H_{10a}, 1H), 3.83 (ddd, J = 11.8, 8.0, 3.7 Hz, H_{2a}, 1H), 3.67 (d, J = 9.3 Hz, H_{10b}, 1H), 3.60 (dt, J = 12.3, 6.8 Hz, H_7, 1H), 3.22 (s, H_{12}, 3H), 3.17 (s, H_{14}, 3H), 2.49 (t, J = 3.4 Hz, H_2, 1H), 2.41 (td, J = 13.0, 2.5 Hz, H_{3a}, 1H), 1.92 (s, H_{19}, 1H), 1.79 (ddd, J = 13.2, 6.1, 4.2 Hz, H_{3b}, 1H), 1.48 (s, H_9, 3H), 1.32 (s, H_{16}, 3H), 1.26 (s, H_{17}, 3H). ^1^3^C NMR (100 MHz, C_6D_6): δ 174.3 (C), 104.1 (C), 96.8 (CH_2), 96.3 (CH_2), 87.7 (C), 84.6 (CH), 82.6 (C), 82.0 (CH), 80.2 (C), 78.5 (CH), 77.3 (CH), 74.4 (CH_2), 66.0 (CH), 63.4 (CH_2), 59.1 (C), 55.5 (CH_3), 55.0 (CH_3), 43.1 (CH), 28.4 (CH_3), 28.1 (CH_2), 27.7 (CH_3), 19.6 (CH_3). IR (ATR-FTIR), cm^{-1}: 3736 (s), 3260 (s), 2949 (s), 2159 (m), 1762 (s). HRMS-Cl (m/z): calcd for C_{23}H_{32}NaO_{10}, 479.1893; found: 479.1891. [alpha]_D^{20} = 17.2 (c = 0.33, CHCl_3).
Synthesis of the olefin 179:

Part 1: Synthesis of the aldehyde 176:

A stock solution of potassium bromide (29.0 mg, 0.244 mmol) and tetrabutylammonium chloride (30.0 mg, 0.108 mmol) in saturated aqueous sodium bicarbonate solution (4.0 mL) was prepared. A second stock solution of aqueous sodium hypochlorite (10-15 % chlorine, 2.75 mL), saturated aqueous sodium bicarbonate solution (4.0 mL) and saturated aqueous sodium chloride solution (11.0 mL) was also prepared. 274 μL of the potassium bromide solution and 183 μL of the aqueous sodium hypochlorite solution were sequentially added to a stirring solution of the lactone 175 (25 mg, 55.0 μmol, 1 equiv) and TEMPO (1.0 mg, 6.0 μmol, 0.10 eq) in dichloromethane (200 μL) at 0 °C. The biphasic reaction mixture was stirred vigorously for 90 min at 0 °C. The product mixture was then diluted sequentially with dichloromethane (5.0 mL), saturated aqueous sodium bicarbonate solution (5.0 mL), and saturated aqueous sodium thiosulfate solution (5.0 mL). The dilute product mixture was stirred for 30 min at 0 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 5 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10
mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The aldehyde residue obtained was used directly in the following step.

The lactone product 176 proved unstable towards silica gel purification and was also found to decompose appreciably within 2h at 23 °C.

\( R_f = 0.50 \) (33% ethyl acetate–hexanes; PAA). \(^1\)H NMR (600 MHz, CD\(_6\)D\(_6\)) \( \delta \) 9.29 (s, H\(_7\), 1H), 5.70 (s, H\(_1\), 1H), 5.25 (s, H\(_6\), 1H), 4.62 (d, \( J = 6.6 \) Hz, H\(_{13a}\), 1H), 4.54 (dd, \( J = 12.5, 6.3 \) Hz, H\(_4\), 1H), 4.51 – 4.47 (m, H\(_{11a,13b}\), 2H), 4.45 (d, \( J = 6.3 \) Hz, H\(_{11b}\), 1H), 4.38 (d, \( J = 1.1 \) Hz, H\(_5\), 1H), 4.18 (d, \( J = 9.3 \) Hz, H\(_{10a}\), 1H), 3.58 (d, \( J = 9.3 \) Hz, H\(_{10b}\), 1H), 3.16 (s, H\(_{12}\), 3H), 3.14 (s, H\(_{14}\), 3H), 2.44 (t, \( J = 3.3 \) Hz, H\(_2\), 1H), 2.36 (td, \( J = 13.0, 2.5 \) Hz, H\(_{3a}\), 1H), 1.83 – 1.72 (m, H\(_{3b,15}\), 2H), 1.40 (s, H\(_9\), 3H), 1.21 (s, H\(_{16}\), 4H), 1.17 (s, H\(_{17}\), 3H).
Part 2: Synthesis of the olefin 179:

A stock solution of the catalyst was prepared in a nitrogen-filled glovebox by stirring a solution of bis(1,5-cyclooctadiene)nickel(0) (46.0 mg, 167 μmol, 1.00 equiv) and 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr, 65.4 mg, 167 μmol, 1.00 equiv) in tetrahydrofuran (1.0 mL) at 20 °C for 30 min. A portion of the catalyst stock solution (100 μL, 30 mol%) was added to a 25-mL screw-capped pressure vessel containing a stirring solution of the aldehyde residue obtained in the preceding step (nominally 55.0 μmol, 1 equiv) and triethylsilane (26.0 μL, 165 μmol, 3.00 equiv) in tetrahydrofuran (1.8 mL) at 20 °C. The reaction vessel was subsequently sealed and the sealed vessel was removed from the glovebox. The reaction vessel was placed in an oil bath that had been preheated to 60 °C. The resulting solution was stirred for 2 h at 60 °C. The product mixture was then cooled to 23 °C over 30 min. The cooled product mixture was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes) to provide the olefin 179 as a colorless oil (2.90 mg, 9% over two steps).

NOE correlations between the C5 hydrogen atom and the C18 methyl substituent of the triethylsilyl group support the relative configuration depicted.
R_f = 0.50 (33% ethyl acetate–hexanes; PAA). \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 6.18 (s, H\(_{8a}\), 1H), 5.70 (s, H\(_{8b}\), 1H), 4.78 (s, H\(_5\), 1H), 4.66 (s, H\(_1\), 1H), 4.65 – 4.58 (m, H\(_4, 11a, 11b, 13a\), 4H), 4.50 (d, J = 7.7 Hz, H\(_7, 13b\), 2H), 4.25 (d, J = 3.6 Hz, H\(_6\), 1H), 4.02 (d, J = 9.2 Hz, H\(_{10a}\), 1H), 3.62 (d, J = 9.2 Hz, H\(_{10b}\), 1H), 3.36 (s, H\(_{12}\), 3H), 3.32 (s, H\(_{14}\), 3H), 2.64 (s, H\(_2\), 1H), 2.48 (t, J = 12.7 Hz, H\(_{3a}\), 1H), 2.05 – 1.96 (m, H\(_{3b}\), 1H), 1.56 (s, H\(_{16}\), 3H), 1.51 (s, H\(_9\), 3H), 1.43 (s, H\(_{17}\), 3H), 0.97 (t, J = 7.9 Hz, H\(_{18}\), 9H), 0.66 (q, J = 8.0 Hz, H\(_{15}\), 6H). \(^1\)C NMR (125 MHz, CDCl\(_3\)): δ 174.2 (C), 140.8 (C), 129.9 (CH\(_2\)), 101.2 (C), 96.7 (CH\(_2\)), 96.4 (CH\(_2\)), 85.6 (C), 84.0 (CH), 82.9 (C), 79.8 (CH), 74.1 (CH\(_2\)), 71.4 (CH), 71.4 (CH), 64.8 (CH), 55.9 (CH\(_3\)), 55.3 (CH\(_3\)), 54.0 (C), 44.5 (CH), 29.5 (CH\(_3\)), 28.7 (CH\(_2\)), 20.5 (CH\(_3\)), 19.3 (CH\(_3\)), 6.8 (3 × CH\(_3\)), 4.9 (3 × CH\(_2\)). IR (ATR-FTIR), cm\(^{-1}\): 3734 (s), 3628 (s), 2975 (m), 1717 (m). HRMS-Cl (m/z): calcd for C\(_{28}\)H\(_{46}\)NaO\(_{10}\)Si, 593.2758; found: 593.2752. [\(\alpha\)]\(_D\) = -6.81 (c = 0.07, CHCl\(_3\)).
Synthesis of the methyl ketone 187:

Water (502 μL, 27.9 mmol, 2.50 equiv), \( N,N,N',N' \)-tetramethylurea (268 μL, 2.23 mmol, 0.200 equiv), and mercury (II) trifluoromethanesulfonate (556 mg, 1.11 mmol, 0.100 equiv) were added in sequence to a solution of the alkyne 185 (4.80 g, 11.2 mmol, 1 equiv) in acetonitrile (56 mL) and dichloromethane (2.8 mL) at 23 °C. The reaction mixture was stirred for 2 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous sodium bicarbonate solution (100 mL) and ethyl acetate (100 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 200 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes) to provide the methyl ketone 187 as a colorless solid (4.15 g, 83%).

Rf = 0.30 (50% ethyl acetate–hexanes; PAA). \(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 5.40 (s, H₁, 1H), 4.92 (dd, \( J = 10.6, 7.4 \) Hz, H₄, 1H), 4.64 (s, H₁₁, 2H), 4.56 (d, \( J = 6.7 \) Hz, H₆a, 1H), 4.48 (d, \( J = 6.7 \) Hz, H₆b, 1H), 4.03 (d, \( J = 9.0 \) Hz, H₉a, 1H), 3.87 (s, H₁₄, 3H), 3.66 (d, \( J = \)
9.0 Hz, H$_{9b}$, 1H), 3.37 (s, H$_{12}$, 3H), 3.29 (s, H$_{7}$, 3H), 2.61 (bs, H$_{15}$, 1H), 2.53 (s, H$_{2}$, 1H), 2.33 (ddd, J = 13.6, 7.4, 4.0 Hz, H$_{3a}$, 1H), 2.24 (s, H$_{10}$, 3H), 1.98 (s, H$_{13}$, 3H), 1.94 (ddd, J = 13.5, 10.6, 2.8 Hz, H$_{3b}$, 1H), 1.57 (s, H$_{8}$, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 210.1 (C), 171.5 (C), 170.2 (C), 96.9 (CH$_2$), 96.0 (CH$_2$), 92.9 (C), 87.3 (C), 84.0 (CH), 73.9 (CH$_2$), 70.5 (CH), 64.1 (CH$_2$), 61.4 (C), 55.8 (CH$_3$), 55.5 (CH$_3$), 52.5 (CH$_3$), 42.3 (CH), 31.3 (CH$_2$), 28.9 (CH$_3$), 21.1 (CH$_3$), 20.5 (CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 3734 (s), 3628 (m), 2953 (m), 1733 (s). HRMS-Cl (m/z): [M + Na]$^+$ calculated for C$_{20}$H$_{32}$NaO$_{11}$, 471.1842; found 471.1830. $[\alpha]_D^{20} = -112.8$ (c = 0.08, CHCl$_3$).
Synthesis of the aldehyde 188:

The Dess–Martin periodinane (7.57 g, 17.9 mmol, 2.00 equiv) was added in five equal portions over 1 h to a solution of the methyl ketone 187 (4.00 g, 8.92 mmol, 1 equiv) and pyridine (7.06 mL, 89.2 mmol, 10.0 equiv) in dichloromethane (45 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was warmed to 23 °C over 30 min. The warmed mixture was stirred for 12 h at 23 °C. The product mixture was diluted sequentially with dichloromethane (50 mL), saturated aqueous sodium bicarbonate solution (100 mL), and saturated aqueous sodium thiosulfate solution (100 mL). The diluted product mixture was stirred for 1 h at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 200 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes) to provide the aldehyde 188 as a colorless oil (3.60 g, 90%).
Rf = 0.50 (50% ethyl acetate–hexanes; PAA). \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 9.31 (s, H\(_5\), 1H), 5.61 – 5.50 (m, H\(_{4,1}\), 2H), 4.62 (s, H\(_{11}\), 2H), 4.59 (d, \(J = 6.6\) Hz, H\(_{6a}\), 1H), 4.52 (d, \(J = 6.6\) Hz, H\(_{6b}\), 1H), 4.05 (d, \(J = 9.0\) Hz, H\(_{9a}\), 1H), 3.83 (s, H\(_{14}\), 3H), 3.62 (d, \(J = 9.0\) Hz, H\(_{9b}\), 1H), 3.36 (s, H\(_{12}\), 3H), 3.29 (s, H\(_7\), 3H), 2.59 (t, \(J = 3.5\) Hz, H\(_2\), 1H), 2.44 (ddd, \(J = 13.6, 7.2, 4.0\) Hz, H\(_{3a}\), 1H), 2.33 (s, H\(_{10}\), 3H), 2.03 (s, H\(_{13}\), 3H), 2.00 (ddd, \(J = 13.6, 10.8, 2.8\) Hz, H\(_{3b}\), 1H), 1.54 (s, H\(_8\), 3H). \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 209.6 (C), 192.2 (CH), 170.0 (C), 167.4 (C), 96.9 (CH\(_2\)), 96.1 (CH\(_2\)), 92.5 (C), 87.9 (C), 83.3 (CH), 73.5 (CH\(_2\)), 69.0 (C), 68.0 (CH), 55.9 (CH\(_3\)), 55.6 (CH\(_3\)), 52.9 (CH\(_3\)), 42.5 (CH), 30.3 (CH\(_2\)), 28.7 (CH\(_3\)), 21.0 (CH\(_3\)), 20.3 (CH\(_3\)). IR (ATR-FTIR), cm\(^{-1}\): 2952 (m), 1747 (s), 1727 (s). HRMS-CI (m/z): [M + Na\(^+\)] calculated for C\(_{20}\)H\(_{30}\)NaO\(_{11}\), 469.1686; found 469.1687. \([\alpha]\)\(^D\) = –107.6 (c = 0.36, CHCl\(_3\)).
Synthesis of the propargylic alcohol 190:

A solution of lanthanum(III) chloride bis(lithium chloride) complex in tetrahydrofuran (600 mM, 40.3 mL, 24.2 mmol, 3.00 equiv) was added to a solution of the aldehyde 188 (3.60 g, 8.06 mmol, 1 equiv) in tetrahydrofuran (40 mL) at 23 °C. The resulting solution was stirred for 1 h at 23 °C and then cooled to 0 °C. A solution of ethynylmagnesium bromide in tetrahydrofuran (500 mM, 74.2 mL, 37.1 mmol, 4.60 equiv) was then added dropwise via syringe over 30 min. The reaction mixture was stirred for 2 h at 0 °C. The product mixture was diluted sequentially with saturated aqueous potassium sodium tartrate solution (250 mL), saturated aqueous sodium chloride solution (500 mL), and ethyl acetate (500 mL). The resulting mixture was warmed up 23 °C over 30 min, and then stirred vigorously for 45 min at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 250 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (300 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the propargylic alcohol 190 as a colorless oil (3.56 g, 94%).
Within the limits of detection, the product 190 was formed as a single diastereomer (\textsuperscript{1}H NMR analysis, 500 MHz).

R\textsubscript{f} = 0.45 (50\% ethyl acetate–hexanes; PAA). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \( \delta \) 5.24 (s, H\textsubscript{1}, 1H), 4.93 (dd, J = 10.1, 7.8 Hz, H\textsubscript{4}, 1H), 4.81 – 4.75 (m, H\textsubscript{5}, 1H), 4.63 (s, H\textsubscript{11}, 2H), 4.55 (d, J = 6.7 Hz, H\textsubscript{6a}, 1H), 4.46 (d, J = 6.7 Hz, H\textsubscript{6b}, 1H), 4.01 (d, J = 9.0 Hz, H\textsubscript{9a}, 1H), 3.92 (s, H\textsubscript{14}, 3H), 3.65 (d, J = 9.0 Hz, H\textsubscript{9b}, 1H), 3.37 (s, H\textsubscript{12}, 3H), 3.29 (s, H\textsubscript{7}, 3H), 2.52 (t, J = 3.1 Hz, H\textsubscript{2}, 1H), 2.46 – 2.37 (m, H\textsubscript{3a}, 1H), 2.32 (d, J = 2.3 Hz, H\textsubscript{15}, 1H), 2.21 (s, H\textsubscript{10}, 3H), 1.97 (s, H\textsubscript{13}, 3H), 1.90 (t, J = 12.0 Hz, H\textsubscript{3b}, 1H), 1.58 (s, H\textsubscript{8}, 3H). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \( \delta \) 209.1 (C), 170.1 (C), 169.7 (C), 96.8 (CH\textsubscript{2}), 95.8 (CH\textsubscript{2}), 92.6 (C), 87.6 (C), 84.1 (CH), 82.1 (CH), 73.6 (CH\textsubscript{2}), 72.8 (C), 70.0 (CH), 64.7 (CH), 64.1 (C), 55.7 (CH\textsubscript{3}), 55.4 (CH\textsubscript{3}), 52.3 (CH\textsubscript{3}), 41.9 (CH), 31.8 (CH\textsubscript{2}), 28.7 (CH\textsubscript{3}), 21.2 (CH\textsubscript{3}), 20.5 (CH\textsubscript{3}). IR (ATR-FTIR), cm\textsuperscript{–1}: 3726 (m), 3628 (m), 3274 (m), 2952 (m), 1717 (s). HRMS-CI (m/z): [M + Na]\textsuperscript{+} calculated for C\textsubscript{22}H\textsubscript{32}NaO\textsubscript{11}, 495.1842; found 495.1838. [\textgreek{a}]\textsubscript{D}\textsuperscript{20} = −69.2 (c = 0.16, CHCl\textsubscript{3}).
Synthesis of the vinyl ether 191:

(4-Dimethylamino)pyridine (DMAP, 10.0 mg, 9.1 μmol, 0.05 equiv), pyridine (1.20 mL, 14.6 mmol, 8.00 equiv), and triflic anhydride (490 μL, 2.91 mmol, 1.60 equiv) were added in sequence to a solution of the propargylic alcohol 190 (860 mg, 1.82 mmol, 1 equiv) in dichloromethane (13 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The cooling bath was then removed, and the reaction mixture was allowed to warm to 23 °C over 30 min. The reaction mixture was stirred for 2 h at 23 °C. The product mixture was diluted sequentially with dichloromethane (20 mL) and water (20 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (500 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes initially, grading to 50% ethyl acetate–hexanes, 2 steps) to provide separately the vinyl ether 191 (colorless oil, 413 mg, 50%) and the propargylic alcohol 190 (colorless oil, 177 mg, 21%).
$R_f = 0.40$ (50% ethyl acetate–hexanes; PAA). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.85 (dd, $J = 10.6, 6.4$ Hz, H$_4$, 1H), 5.51 (s, H$_5$, 1H), 4.90 (s, H$_1$, 1H), 4.74 (d, $J = 6.7$ Hz, H$_{6a}$, 1H), 4.65 (s, H$_{10a}$, 1H), 4.63 (d, $J = 6.7$ Hz, H$_{6b}$, 1H), 4.59 (s, H$_{11}$, 2H), 4.51 (s, H$_{10b}$, 1H), 4.12 (d, $J = 9.1$ Hz, H$_{9a}$, 1H), 3.80 (s, H$_{14}$, 3H), 3.46 (d, $J = 9.1$ Hz, H$_{9b}$, 1H), 3.37 (s, H$_{12}$, 3H), 3.34 (s, H$_7$, 3H), 2.74 (s, H$_{15}$, 1H), 2.72 (s, H$_2$, 1H) 2.42 (d, $J = 13.0$ Hz, H$_{3a}$, 1H), 2.25 (t, $J = 12.3$ Hz, H$_{3b}$, 1H), 2.03 (s, H$_{13}$, 3H), 1.60 (s, H$_8$, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 170.3 (C), 169.7 (C), 156.5 (C), 97.0 (CH$_2$), 95.4 (CH$_2$), 88.5 (C), 86.8 (CH$_2$), 84.9 (C), 80.4 (CH), 78.83 (CH), 78.76 (C), 74.4 (CH$_2$), 73.1 (CH), 71.4 (CH), 65.2 (C), 56.0 (CH$_3$), 55.5 (CH$_3$), 53.1 (CH$_3$), 44.0 (CH), 30.8 (CH$_2$), 21.1 (CH$_3$), 19.5 (CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 3734 (m), 3627 (m), 3271 (m), 2953 (s), 1732 (s). HRMS-Cl (m/z): [M + Na]$^+$ calculated for C$_{22}$H$_{36}$NaO$_{10}$, 477.1737; found 477.1723. $[\alpha]^2_D = -60.2$ (c = 0.18, CHCl$_3$).
Aqueous hydrochloric acid solution (1 N, 24.2 mL, 24.2 mmol, 5.00 equiv) was added to a solution of the vinyl ether 191 (2.20 g, 4.84 mmol, 1 equiv) in tetrahydrofuran (73 mL) at 23 °C. The reaction vessel was then placed in an oil bath that had been preheated to 50 °C. The reaction mixture was stirred and heated for 2 h at 50 °C. The product mixture was then cooled to 0 °C over 15 min. The cooled product mixture was diluted sequentially with ethyl acetate (100 mL), water (100 mL), and saturated aqueous sodium bicarbonate solution (100 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (5 × 100 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.
Part 2: Synthesis of the alcohol S26:

Potassium carbonate (1.34 g, 9.68 mmol, 2.50 equiv) was added in one portion to a solution of the residue obtained in the preceding step (nominally 4.84 mmol, 1 equiv) in methanol (48 mL) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C. The cold product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (50 mL), water (100 mL), and ethyl acetate (100 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (5 × 100 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.
Part 3: Synthesis of the silylene ether 192:

Di-tert-butyldisilyl bis(trifluoromethanesulfonate) (2.40 mL, 7.26 mmol, 1.50 equiv) was added dropwise via syringe to a solution of the residue obtained in the preceding step (nominally 4.84 mmol, 1 equiv) and pyridine (1.90 mL, 24.2 mmol, 5.00 equiv) in dichloromethane (48 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then the cooling bath was removed. The reaction mixture was allowed to warm to 23 °C and then stirred for 7 d at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (50 mL), water (50 mL), and ethyl acetate (100 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the silylene ether 192 as a colorless oil (1.66 g, 60% over three steps).
$R_f = 0.50 \text{ (33\% ethyl acetate–hexanes; PAA)}$. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.25 (s, H$_{1,5}$, 2H), 4.63 (s, H$_{11}$, 2H), 4.57 (dd, $J = 11.4$, 6.4 Hz, H$_4$, 1H), 4.49 (d, $J = 6.5$ Hz, H$_{6a}$, 1H), 4.42 (d, $J = 6.5$ Hz, H$_{6b}$, 1H), 3.95 (d, $J = 9.1$ Hz, H$_{9a}$, 1H), 3.77 (s, H$_{13}$, 3H), 3.72 (d, $J = 9.1$ Hz, H$_{9b}$, 1H), 3.36 (s, H$_{12}$, 3H), 3.27 (s, H$_7$, 3H), 2.57 (d, $J = 2.2$ Hz, H$_{15}$, 1H), 2.50 (d, $J = 3.3$ Hz, H$_2$, 1H), 2.41 (ddd, $J = 13.4$, 6.3, 3.9 Hz, H$_{3a}$, 1H), 2.24 (s, H$_{10}$, 3H), 2.08 (ddd, $J = 13.4$, 6.3, 3.9 Hz, H$_{3b}$, 1H), 1.55 (s, H$_8$, 3H), 1.11 (s, H$_{14}$, 9H), 0.95 (s, H$_{15}$, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 207.8 (C), 169.3 (C), 96.9 (CH$_2$), 96.5 (CH$_2$), 94.0 (C), 88.9 (C), 84.6 (CH), 82.4 (C), 76.2 (CH), 74.2 (CH), 74.0 (CH$_2$), 69.6 (CH), 63.3 (C), 55.9 (CH$_3$), 55.6 (CH$_3$), 52.0 (CH$_3$), 42.5 (CH), 32.9 (CH$_2$), 30.5 (CH$_3$), 29.1 (3 × CH$_3$), 27.0 (3 × CH$_3$), 22.9 (C), 19.9 (C). IR (ATR-FTIR), cm$^{-1}$: 3726 (m), 3628 (m), 2937 (s), 2859 (m), 1721 (s). HRMS-Cl (m/z): [M + Na]$^+$ calculated for C$_{28}$H$_{46}$NaO$_{10}$Si, 593.2758; found 593.2745. $[\alpha]_D^{20} = -34.4 \text{ (c = 0.80, CHCl}_3)$. 

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Synthesis of the aldehyde 193:

Part 1: Synthesis of the olefin S27:

Palladium on barium sulfate (10% w/w, 143 mg) was added to a solution of the silylene ether 192 (1.43 g, 2.51 mmol, 1 equiv) in methanol (28 mL) and pyridine (2.8 mL) at 23 °C. The reaction vessel was then transferred to a stainless steel hydrogenation apparatus. The apparatus was purged with dihydrogen by pressurizing to 5 atm and venting. This process was repeated three times. The vessel was then pressurized to 5 atm dihydrogen and sealed. The reaction mixture was stirred for 1 h at 23 °C. The apparatus was then slowly vented. The product mixture was diluted with ethyl acetate (20 mL) and the diluted solution was filtered through a pad of Celite. The filtrate was concentrated and the residue obtained was used directly in the following step.
Part 2: Synthesis of the aldehyde 193:

Ozone was passed through a solution of the residue obtained in the preceding step (nominally 2.51 mmol, 1 equiv) in dichloromethane (50 mL) and methanol (8.0 mL) at –78 °C until a dark blue color persisted. Dioxygen was then passed through the solution to remove any unreacted ozone, resulting in a colorless solution. Triphenylphosphine (1.32 g, 5.03 mmol, 2.00 equiv) was then added in one portion. The cooling bath was removed, and the mixture was allowed to warm to 23 °C over 1 h. The warmed product mixture was concentrated and the residue obtained was purified by flash-column chromatography (eluting with 25% ethyl acetate–hexanes) to provide the aldehyde 193 as a colorless solid (1.23 g, 85%, two steps).

Rf = 0.40 (33% ethyl acetate–hexanes; PAA). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 9.48 (s, H$_{15}$, 1H), 5.17 (s, H$_{1}$, 1H), 4.63 (s, H$_{11}$, 2H), 4.62 – 4.58 (m, H$_{4}$, 1H), 4.56 (d, J = 1.4 Hz, H$_{5}$, 1H), 4.49 (d, J = 6.6 Hz, H$_{6a}$, 1H), 4.37 (d, J = 6.6 Hz, H$_{6b}$, 1H), 3.99 (d, J = 9.0 Hz, H$_{9a}$, 1H), 3.76 (s, H$_{14}$, 3H), 3.71 (d, J = 9.0 Hz, H$_{9b}$, 1H), 3.36 (s, H$_{12}$, 3H), 3.25 (s, H$_{7}$, 3H), 2.49 (s, H$_{2}$, 1H), 2.40 – 2.31 (m, H$_{3a}$, 1H), 2.27 (s, H$_{10}$, 3H), 2.17 – 2.06 (m, H$_{3b}$, 1H), 1.56 (s, H$_{8}$, 3H), 1.10 (s, H$_{13}$, 9H), 0.97 (s, H$_{16}$, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 207.5 (C),
201.8 (CH), 169.4 (C), 96.8 (CH₂), 96.2 (CH₂), 93.3 (C), 89.0 (C), 84.7 (CH), 81.3 (CH), 73.7 (CH₂), 72.9 (CH), 55.7 (CH₃), 55.4 (CH₃), 52.5 (C), 41.9 (CH), 32.8 (CH₂), 29.6 (CH₃), 28.7 (3 × CH₃), 26.9 (3 × CH₃) 22.5 (C), 19.82 (CH₃), 19.77 (C). IR (ATR-FTIR), cm⁻¹: 3734 (s), 3628 (m), 2937 (s), 2859 (m), 1734 (s). HRMS-CI (m/z): [M + Na]⁺ calculated for C₂₇H₄₆NaO₇Si, 597.2707; found 597.2686. [α]ᵢD = –63.6 (c = 0.22, CHCl₃).
Synthesis of the unsaturated ketone 194:

Part 1: Synthesis of the β-hydroxyketone S28:

A solution of sodium ethoxide in ethanol (500 mM, 4.40 mL, 2.18 mmol, 2.00 equiv) was added dropwise via syringe over 10 min to a solution of the aldehyde 193 (628 mg, 1.09 mmol, 1 equiv) in ethanol (13.5 mL) at 0 °C. The resulting mixture was stirred for 45 min at 0 °C. The product mixture was diluted sequentially with water (25 mL) and ethyl acetate (50 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (5 × 50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.
Part 2: Synthesis of the unsaturated ketone 194:

![Diagram of molecules S28 and 194]

Triethylamine (456 µL, 3.28 mmol, 3.00 equiv) and methanesulfonyl chloride (135 µL, 1.75 mmol, 1.60 equiv) were added in sequence to a solution of the residue obtained in the preceding step (nominally 1.09 mmol, 1 equiv) in dichloromethane (18 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The cold product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (20 mL), water (20 mL), and dichloromethane (50 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 500 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the unsaturated ketone 194 as a colorless oil (450 mg, 74% over two steps).

Rf = 0.40 (33% ethyl acetate–hexanes; UV, CAM). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 6.91 (dd, J = 10.6, 1.9 Hz, H\(_2\), 1H), 5.93 (dd, J = 10.6, 3.0 Hz, H\(_3\), 1H), 5.43 (d, J = 2.5 Hz, H\(_1\),
1H), 4.92 (dd, J = 11.7, 6.4 Hz, H9, 1H), 4.66 – 4.57 (m, H16,18a, 3H), 4.55 (s, H6, 1H), 4.43 (d, J = 7.0 Hz, H18b, 1H), 3.99 (d, J = 9.4 Hz, H12a, 1H), 3.67 (s, H20, 3H), 3.64 (d, J = 9.4 Hz, H12b, 1H), 3.34 (s, H17, 3H), 3.31 (s, H19, 3H), 2.52 (d, J = 3.4 Hz, H7, 1H), 2.48 (ddd, J = 14.5, 11.8, 2.9 Hz, H8a, 1H), 2.17 (ddd, J = 13.3, 6.4, 3.8 Hz, H8b, 1H), 1.52 (s, H13, 3H), 1.15 (s, H21, 9H), 0.96 (s, H22, 9H). 13C NMR (125 MHz, CDCl3): δ 190.9 (C), 170.1 (C), 149.8 (CH), 128.0 (CH), 96.8 (CH2), 96.2 (CH2), 87.8 (C), 82.6 (CH), 82.5 (CH), 75.4 (CH), 74.8 (CH), 74.0 (CH2), 64.5 (C), 55.6 (CH3), 55.4 (CH3), 52.2 (C), 45.3 (CH), 32.7 (CH2), 29.2 (3 × CH3), 27.2 (3 × CH3), 23.3 (C), 19.8 (C), 19.1 (CH3). IR (ATR-FTIR), cm⁻¹: 3734 (m), 3690 (m), 3648 (m), 2940 (s), 2160 (m), 2009 (m). HRMS-Cl (m/z): [M + Na]+ calculated for C27H44NaO10Si, 579.2601; found 579.2591. [α]D^20 = 127.5 (c = 0.04, CHCl3).
Synthesis of the tertiary alcohol 195:

A solution of methyllithium–lithium bromide complex in diethyl ether (1.50 M, 6.00 mL, 8.98 mmol, 5.00 equiv) was added dropwise via syringe over 10 min to a solution of the enone 194 (1.00 g, 1.80 mmol, 1 equiv) in tetrahydrofuran (36 mL) at –78 °C. The reaction mixture was stirred for 30 min at –78 °C. The cold product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (50 mL), saturated aqueous sodium chloride solution (50 mL), and ethyl acetate (50 mL). The diluted product mixture was then allowed to warm to 23 °C over 20 min. The warmed biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the tertiary alcohol 195 as a colorless oil (925 mg, 90%, minor diastereomer not isolated).
H NMR analysis of the unpurified product mixture indicated the presence of a 9:1 mixture of diastereomers. NOE correlations between the C14 methyl substituent and the ester substituent (C20) support the relative configuration depicted.

Rf = 0.40 (50% ethyl acetate–hexanes; CAM). \(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 5.80 (dd, J = 10.7, 1.7 Hz, H\(_2\), 1H), 5.33 (dd, J = 10.6, 3.0 Hz, H\(_3\), 1H), 5.19 (dd, J = 3.0, 1.8 Hz, H\(_1\), 1H), 4.88 (d, J = 0.9 Hz, H\(_6\), 1H), 4.79 (dd, J = 12.0, 6.4 Hz, H\(_9\), 1H), 4.75 (d, J = 6.7 Hz, H\(_{18a}\), 1H), 4.70 – 4.59 (m, H\(_{18b,16}\), 3H), 3.95 (d, J = 9.2 Hz, H\(_{12a}\), 1H), 3.83 (d, J = 9.2 Hz, H\(_{12b}\), 1H), 3.67 (s, H\(_{20}\), 3H), 3.40 (s, H\(_{17}\), 3H), 3.36 (s, H\(_{19}\), 3H), 3.29 (d, J = 0.9 Hz, H\(_{23}\), 1H), 2.57 (dd, J = 4.0, 2.7 Hz, H\(_7\), 1H), 2.53 – 2.44 (m, H\(_{8a}\), 1H), 2.12 (ddd, J = 13.3, 6.4, 4.1 Hz, H\(_{8b}\), 1H), 1.56 (s, H\(_{13}\), 3H), 1.28 (s, H\(_{14}\), 3H), 1.12 (s, H\(_{21}\), 9H), 0.94 (s, H\(_{22}\), 9H).

\(^1\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 170.5 (C), 132.6 (CH), 128.1 (CH), 97.1(CH\(_2\)), 96.8 (CH\(_2\)), 90.0 (C), 86.5 (C), 84.13 (CH), 77.2 (CH), 75.7 (CH), 74.2 (CH\(_2\)), 70.0 (C), 62.9 (C), 56.8 (CH\(_3\)), 55.5 (CH\(_3\)), 51.7 (C), 43.3 (CH), 32.3 (CH\(_2\)), 29.3 (3 × CH\(_3\)), 27.0 (3 × CH\(_3\)), 24.5 (CH\(_3\)), 22.9 (C), 19.6 (CH\(_3\)), 19.2 (C). IR (ATR-FTIR), cm\(^{-1}\): 3726 (m), 3710 (m), 3628 (m), 2933 (s), 2858 (m), 1718 (s). HRMS-Cl (m/z): [M + Na]\(^+\) calculated for C\(_{28}\)H\(_{48}\)NaO\(_{10}\)Si, 595.2914; found 595.2908. \([\alpha]_D^{20}\) = 6.37 (c = 0.11, CHCl\(_3\)).
Synthesis of the epoxide 196:

A solution of dimethyldioxirane in acetone (~60 mM, 102 mL, 6.11 mmol, 5.00 equiv) was added to a solution of the allylic alcohol 195 (700 mg, 1.23 mmol, 1 equiv) in acetone (19 mL) at 0 °C. The reaction mixture was stirred for 14 h at 0 °C. The product mixture was then warmed to 23 °C. The warmed product mixture was concentrated to provide the epoxide 196 as a pale yellow oil (709 mg, 99%).

Within the limits of detection, the epoxide 196 was formed as a single diastereomer (1H NMR analysis, 500 MHz). The relative stereochemistry of the epoxide 196 was established via X-ray analysis (see Appendix A).

Rf = 0.20 (50% ethyl acetate–hexanes; CAM). 1H NMR (500 MHz, benzene-d6): δ 5.03 (s, H1, 1H), 4.91 (s, H6, 1H), 4.84 (dd, J = 12.0, 6.4 Hz, H9, 1H), 4.46 (d, J = 6.5 Hz, H16a, 1H), 4.42 – 4.35 (m, H18,16b, 3H), 3.96 (s, H23, 1H), 3.89 (d, J = 9.6 Hz, H12a, 1H), 3.81 (d, J = 9.6 Hz, H12b, 1H), 3.73 (s, H5, 1H), 3.33 (s, H20, 3H), 3.21 (s, H17, 3H), 3.16 (s, H2, 1H), 3.10 (s, H19, 3H), 3.58 (s, H8a, 1H), 2.27 (s, H7, 1H), 2.26 (ddd, J = 13.2, 6.4, 4.1 Hz, H8b, 1H), 1.47 (s, H13, H14, 6H), 1.17 (s, H22, 9H), 1.08 (s, H21, 9H). 13C NMR (125 MHz,
benzene-\(d_6\): \(\delta\) 170.9 (C), 97.1 (CH\(_2\)), 96.9 (CH\(_2\)), 90.3 (C), 87.2 (C), 85.1 (CH), 78.3 (CH), 76.3 (CH), 75.1 (CH\(_2\)), 70.0 (C), 63.0 (CH), 62.0 (C), 60.2 (CH), 56.5 (CH\(_3\)), 55.2 (CH\(_3\)), 51.4 (CH\(_3\)), 42.9 (CH), 32.9 (CH\(_2\)), 29.3 (3 \times CH\(_3\)), 27.3 (3 \times CH\(_3\)), 23.1 (C), 23.0 (CH\(_3\)), 19.9 (C), 19.0 (CH\(_3\)). IR (ATR-FTIR), cm\(^{-1}\): 3734 (s), 3628 (m), 2925 (s), 2655 (m), 1724 (s). HRMS-Cl (m/z): [M + Na\(^+\) calculated for \(C_{28}H_{48}NaO_{11}Si\), 611.2864; found 611.2846. \([\alpha]_{D}^{20} = -10.6\ (c = 0.10, \text{CHCl}_3)\).
Synthesis of the lactone 197:

Part 1: Synthesis of the diol S29:

Lithium chloride (306 mg, 7.23 mmol, 6.00 equiv) was added to a solution of the epoxide 196 (709 mg, 1.24 mmol, 1 equiv) in N,N-dimethylformamide (28 mL) at 23 °C. The reaction vessel was sealed and the sealed vessel was placed in an oil bath that had been preheated to 130 °C. The reaction mixture was stirred and heated for 14 h at 130 °C. The product mixture cooled to 23 °C over 30 min. The cooled product mixture was diluted sequentially with ethyl acetate (50 mL), water (20 mL), and saturated aqueous sodium chloride solution (20 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.
Part 2: Synthesis of the lactone 197:

\[
\text{para-Toluenesulfonic acid (35.4 mg, 186 µmol, 0.15 equiv) was added to a solution of the residue obtained in the preceding step (nominally 1.24 mmol, 1 equiv) in 2,2-dimethoxypropane (2,2-DMP, 8.3 mL) at 23 °C. The reaction mixture was stirred for 24 h at 23 °C. The product mixture was diluted sequentially with ethyl acetate (30 mL), water (20 mL), and saturated aqueous sodium bicarbonate solution (20 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes) to provide the lactone 197 as a colorless oil (521 mg, 68% over two steps). The relative stereochemistry of the lactone 197 was established via X-ray analysis (see Appendix A).}
\]

\[
\text{Rf} = 0.30 \text{ (33% ethyl acetate–hexanes; CAM).} 
\]

\[
\text{\textsuperscript{1}H NMR (500 MHz, CDCl}\textsubscript{3}): \delta 5.07 \text{ (s, H}_1, 1\text{H}), 4.84–4.73 \text{ (m, H}_9,2,16\text{a, 3H), 4.64 (d, J = 6.7 Hz, H}_{16\text{b}}, 1\text{H), 4.61 (d, J = 6.3 Hz, H}_{18\text{a}},}
\]

\[
\text{H}_{18\text{b}}\text{, H}_{19,20,22,23}) \text{, 2.40 (dd, J = 13.5, 7.0 Hz, H}_2,3\text{H), 2.34 (dd, J = 13.5, 7.0 Hz, H}_3,2\text{H), 2.18 (ddd, J}
\]

\[
\text{= 13.5, 10.0, 7.0 Hz, H}_5\text{, 2H), 2.06 (d, J = 6.7 Hz, H}_{16\text{a}}, 1\text{H), 2.02 (d, J = 6.3 Hz, H}_{18\text{a}}, 1\text{H), 1.20 (s, H}_3,5\text{c, 9H),}
\]

\[
\text{1.19 (s, H}_1,23\text{, 9H), 1.02 (s, H}_1,23\text{, 9H), 1.00 (s, H}_1,23\text{, 9H), 0.99 (s, H}_1,23\text{, 9H), 0.97 (s, H}_1,23\text{, 9H).}
\]
1H), 4.56 (d, J = 6.3 Hz, H_{18b}, 1H), 4.43 (s, H_6, 1H), 4.25 (d, J = 5.0 Hz, H_3, 1H), 4.11 (d, J = 8.6 Hz, H_{12a}, 1H), 3.43 (d, J = 9.9 Hz, H_{12b}, 1H), 3.39 (s, H_{17}, 3H), 3.34 (s, H_{19}, 3H), 2.65 (d, J = 3.4 Hz, H_7, 1H), 2.13 (dd, J = 8.0, 3.3 Hz, H_8, 2H), 1.62 (s, H_{14}, 3H), 1.56 (s, H_{23}, 3H), 1.49 (s, H_{13}, 3H), 1.40 (s, H_{22}, 3H), 1.11 (s, H_{20}, 9H), 0.98 (s, H_{21}, 9H). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \delta 173.6 (C), 112.5 (C), 96.9 (CH\textsubscript{2}), 96.7 (CH\textsubscript{2}), 88.6 (C), 86.7 (C), 85.0 (CH), 82.7 (CH), 80.9 (C), 79.8 (CH), 77.3 (CH), 74.0 (CH\textsubscript{2}), 67.5 (CH), 60.7 (C), 56.9 (CH\textsubscript{3}), 55.5 (CH\textsubscript{3}), 41.2 (CH), 32.2 (CH\textsubscript{2}), 28.5 (3 \times CH\textsubscript{3}), 27.04 (CH\textsubscript{3}), 27.02 (CH\textsubscript{3}), 26.97 (3 \times CH\textsubscript{3}), 25.9 (CH\textsubscript{3}), 22.5 (C), 20.5 (CH\textsubscript{3}), 20.1 (C). IR (ATR-FTIR), cm\textsuperscript{-1}: 3734 (s), 3649 (m), 3628 (m), 2938 (s), 2889 (m), 2860 (m), 1786 (s). HRMS-Cl (m/z): [M + Na]+ calculated for C\textsubscript{30}H\textsubscript{50}NaO\textsubscript{11}Si, 637.3020; found 637.3015. [\alpha\textsubscript{D}\textsuperscript{20}] = –4.75 (c = 0.08, CHCl\textsubscript{3}).
Synthesis of the 1,3-diol 199:

A solution of tetra-n-butylammonium fluoride in tetrahydrofuran (1.00 M, 1.70 mL, 1.71 mmol, 2.50 equiv) was added dropwise via syringe to a solution of the acetonide 197 (350 mg, 569 μmol, 1 equiv) in tetrahydrofuran (5.7 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C. The cooling bath was removed, and the reaction mixture was allowed to warm to 23 °C over 20 min. The warmed reaction mixture was stirred for 2 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (10 mL), saturated aqueous sodium chloride solution (10 mL), and ethyl acetate (10 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 100 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes) to provide the 1,3-diol 199 as a colorless oil (256 mg, 95%).

Rf = 0.30 (75% ethyl acetate–hexanes; CAM). 1H NMR (500 MHz, CDCl₃): δ 4.93 (d, J = 5.4 Hz, H₁, 1H), 4.82 (d, J = 4.8 Hz, H₂, 1H), 4.79 (d, J = 6.8 Hz, H₁₈a, 1H), 4.67 (d, J =
6.9 Hz, H$_{18b}$, 1H), 4.60 (d, J = 6.3 Hz, H$_{16a}$, 1H), 4.56 (d, J = 6.3 Hz, H$_{16b}$, 1H), 4.45 (td, J = 10.8, 8.0 Hz, H$_9$, 1H), 4.25 (d, J = 4.9 Hz, H$_3$, 1H), 4.22 (s, H$_6$, 1H), 4.07 (dd, J = 8.9, 1.0 Hz, H$_{12a}$, 1H), 3.43 (d, J = 8.9 Hz, H$_{12b}$, 1H), 3.40 (s, H$_{19}$, 3H), 3.34 (s, H$_{17}$, 3H), 3.15 (d, J = 5.4 Hz, H$_{23}$, 1H), 2.65 (t, J = 3.5 Hz, H$_7$, 1H), 2.51 (d, J = 10.6 Hz, H$_{22}$, 1H), 2.45 (ddd, J = 14.0, 8.0, 3.9 Hz, H$_{8a}$, 1H), 1.88 (ddd, J = 14.1, 11.0, 3.2 Hz, H$_{8b}$, 1H), 1.61 (s, H$_{14}$, 3H), 1.55 (s, H$_{20}$, 3H), 1.48 (s, H$_{13}$, 3H), 1.40 (s, H$_{21}$, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): δ 175.2 (C), 112.7 (C), 96.9 (CH$_2$), 96.8 (CH$_2$), 89.2 (C), 86.1 (C), 85.2 (CH), 82.5 (CH), 81.2 (CH), 80.9 (C), 74.6 (CH), 73.9 (CH$_2$), 66.4 (CH), 62.5 (C), 57.0 (CH$_3$), 55.6 (CH$_3$), 41.2 (CH), 35.7 (CH$_2$), 27.1 (CH$_3$), 26.6 (CH$_3$), 26.0 (CH$_3$), 21.3 (CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 3734 (s), 3628 (m), 2929 (s), 2859 (m), 1772 (s). HRMS-Cl (m/z): [M + Na]$^+$ calculated for C$_{22}$H$_{34}$NaO$_{11}$, 497.1999; found 497.1998. $[\alpha]_D^{20} = -3.25$ (c = 0.13, CHCl$_3$).
Synthesis of the ketone S30:

The Dess–Martin periodinane (217 mg, 285 μmol, 1.00 equiv) was added in five equal portions over 1 h to a solution of the 1,3-diol 199 (135 mg, 285 μmol, 1 equiv) and pyridine (137 μL, 1.71 mmol, 6.00 equiv) in dichloromethane (2.8 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to 23 °C over 20 min. The warmed reaction mixture was stirred for 2 h at 23 °C. The product mixture was diluted sequentially with dichloromethane (10 mL), saturated aqueous sodium bicarbonate solution (20 mL), and saturated aqueous sodium thiosulfate solution (20 mL). The diluted product mixture was vigorously stirred for 1 h at 23 °C. The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 40% ethyl acetate–hexanes) to provide the ketone S30 as a colorless oil (104 mg, 77%).

Rf = 0.30 (50% ethyl acetate–hexanes; CAM). 1H NMR (600 MHz, CDCl3): δ 5.19 (s, H1, 1H), 5.05 (s, H22, 1H), 4.88 (d, J = 6.9 Hz, H18α, 1H), 4.83 (d, J = 4.6 Hz, H2, 1H), 4.77 (d,
\[ J = 6.9 \text{ Hz, } H_{18b}, 1H \), 4.59 (q, \( J = 6.4 \text{ Hz, } H_{16}, 2H \), 4.45 (s, \( H_6, 1H \), 4.25 (d, \( J = 4.6 \text{ Hz, } H_3, 1H \), 4.04 (d, \( J = 9.0 \text{ Hz, } H_{12a}, 1H \), 3.51 (d, \( J = 9.0 \text{ Hz, } H_{12b}, 1H \), 3.44 (s, \( H_{17}, 3H \), 3.34 (s, \( H_9, 3H \), 2.90 (s, \( H_7, 1H \), 2.90 – 2.80 (m, \( H_8, 2H \), 1.63 (s, \( H_{14}, 3H \), 1.56 (s, \( H_{21}, 3H \), 1.41 (s, \( H_20, 3H \), 1.31 (s, \( H_{13}, 3H \). \(^{13}\text{C NMR (150 MHz, CDCl}_3): \delta 210.1 (C), 171.6 (C), 112.4 (C), 96.9 (CH_2), 96.7 (CH_2), 88.7 (C), 86.1 (C), 84.8 (CH), 81.6 (CH), 81.3 (CH), 80.3 (C), 74.0 (CH), 73.3 (CH_2), 67.5 (C), 56.9 (CH_3), 55.5 (CH_3), 45.1 (CH_2), 40.3 (CH), 26.7 (CH_3), 25.7 (CH_3), 25.6 (CH_3), 23.3 (CH_3). \text{IR (ATR-FTIR), cm}^{-1}: 3734 (m), 3629 (m), 2955 (s), 1772 (s). \text{HRMS-CI (m/z): } [M + Na]^+ \text{ calculated for C}_{22}\text{H}_{32}\text{NaO}_{11}, 495.1842; \text{found 495.1843.} \ [\alpha]_D^{20} = 10.9 (c = 0.07, \text{CHCl}_3).
Synthesis of the silyl ether 200:

Triethylamine (113 μL, 813 μmol, 6.00 equiv) and tert-butyldimethylsilyl trifluoromethanesulfonate (54.0 μL, 230 μmol, 1.70 equiv) were added in sequence to a solution of the ketone S30 (64.0 mg, 135 μmol, 1 equiv) in dichloromethane (1.4 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The cold product mixture was diluted sequentially with dichloromethane (10 mL) and water (20 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes) to provide silyl ether 200 as a yellow oil (73.0 mg, 92%).

Rf = 0.60 (50% ethyl acetate–hexanes; CAM). 1H NMR (500 MHz, CDCl3): δ 5.30 (s, H1, 1H), 4.86 (d, J = 6.9 Hz, H16a, 1H), 4.75 (d, J = 6.9 Hz, H16b, 1H), 4.64 (d, J = 4.5 Hz, H2, 1H), 4.62 – 4.57 (m, H18, 2H), 4.35 (s, H6, 1H), 4.20 (d, J = 4.5 Hz, H3, 1H), 4.03 (d, J = 8.9 Hz, H12a, 1H), 3.55 (d, J = 8.9 Hz, H12b, 1H), 3.42 (s, H17, 3H), 3.34 (s, H19, 3H), 2.85
2.67 (m, H\textsubscript{7,6}, 3H), 1.60 (s, H\textsubscript{14}, 3H), 1.58 (s, H\textsubscript{20}, 3H), 1.41 (s, H\textsubscript{21}, 3H), 1.34 (s, H\textsubscript{13}, 3H), 0.92 (s, H\textsubscript{24}, 9H), 0.07 (d, J = 3.1 Hz, H\textsubscript{22,23}, 6H). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): δ 199.8 (C), 173.1 (C), 112.3 (C), 96.9 (CH\textsubscript{2}), 96.8 (CH\textsubscript{2}), 89.1 (C), 85.6 (C), 85.2 (CH), 82.5 (CH), 82.2 (CH), 80.3 (C), 75.2 (CH), 73.5 (CH\textsubscript{2}), 69.8 (C), 57.0 (CH\textsubscript{3}), 55.6 (CH\textsubscript{3}), 44.3 (CH\textsubscript{2}), 40.2 (CH), 26.9 (CH\textsubscript{3}), 25.9 (CH\textsubscript{3}), 25.8 (3 × CH\textsubscript{3}), 25.44 (CH\textsubscript{3}), 23.7 (CH\textsubscript{3}), 18.1 (C), -4.5 (CH\textsubscript{3}), -4.6 (CH\textsubscript{3}). IR (ATR-FTIR), cm\textsuperscript{-1}: 3726 (m), 3627 (m), 2929 (s), 2859 (m), 1784 (s), 1716 (s). HRMS-CI (m/z): [M + Na]\textsuperscript{+} calculated for C\textsubscript{28}H\textsubscript{46}NaO\textsubscript{11}Si, 609.2707; found 609.2703. [\alpha]_{D}^{20} = 13.6 (c = 0.32, CHCl\textsubscript{3}).
Synthesis of the acetate S31:

Lead tetraacetate (291 mg, 654 µmol, 3.00 equiv) was added in a single portion to a screw-capped vessel containing a solution of the ketone 200 (128 mg, 218 µmol, 1 equiv) in benzene (4.4 mL) at 23 °C. The reaction vessel sealed and the sealed reaction vessel was placed in an oil bath that had been preheated to 82 °C. The reaction mixture was stirred for 14 h at 82 °C. The product mixture was cooled to 23 °C over 30 min. The cooled product mixture was filtered through a short pad of Celite (1.5 × 2.0 cm). The filter cake was rinsed with ethyl acetate (3 × 10 mL). The filtrates were combined and the combined filtrates were diluted sequentially with water (20 mL) and saturated aqueous sodium bicarbonate solution (20 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes) to provide the acetate S31 as a yellow oil (124 mg, 88%).
Within the limits of detection, the acetate S31 was formed as a single diastereomer (1H NMR analysis, 500 MHz). NOE correlations between the C8 equatorial hydrogen and the C13 methyl substituent support the relative configuration depicted.

Rf = 0.40 (50% ethyl acetate–hexanes; CAM). 1H NMR (500 MHz, CDCl3): δ 5.35 (d, J = 2.4 Hz, H8, 1H), 5.30 (s, H1, 1H), 4.78 (d, J = 6.8 Hz, H18a, 1H), 4.74 (d, J = 6.8 Hz, H18b, 1H), 4.66 (d, J = 4.4 Hz, H2, 1H), 4.60 (s, H16a, 1H), 4.60 (s, H16b, 1H), 4.57 (s, H6, 1H), 4.22 (d, J = 4.4 Hz, H3, 1H), 4.00 (d, J = 9.0 Hz, H12a, 1H), 3.56 (d, J = 9.0 Hz, H12b, 1H), 3.38 (s, H17, 3H), 3.34 (s, H19, 3H), 2.90 (d, J = 2.6 Hz, H7, 1H), 2.15 (s, H24, 3H), 1.61 (s, H14, 3H), 1.59 (s, H20, 3H), 1.43 (s, H21, 3H), 1.41 (s, H13, 3H), 0.90 (s, H25, 9H), 0.07 (s, H22, 3H), 0.04 (s, H23, 3H). 13C NMR (125 MHz, CDCl3): δ 196.7 (C), 172.2 (C), 169.8 (C), 112.4 (C), 97.2 (CH2), 96.8 (CH2), 89.0 (C), 84.1 (C), 82.2 (CH), 82.1 (2 × CH), 80.1 (C), 75.2 (CH), 74.1 (CH), 73.8 (CH2), 70.4 (C), 57.0 (CH3), 55.6 (CH3), 46.1 (CH), 26.8 (CH3), 25.9 (CH3), 25.7 (3 × CH3), 25.1 (CH3), 23.3 (CH3), 21.0 (CH3), -4.52 (CH3), -4.54 (CH3). IR (ATR-FTIR), cm–1: 3734 (s), 3710 (m), 1717(s). HRMS-CI (m/z): [M + Na]+ calculated for C30H48NaO13Si, 667.2762; found 667.2766. [α]D20 = 40.7 (c = 0.08, CHCl3).
Synthesis of the α-hydroxy ketone 201:

Potassium carbonate (39.9 mg, 288 µmol, 1.50 equiv) was added in a single portion to a solution of the acetate S31 (124 mg, 192 µmol, 1 equiv) in methanol (3.7 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. The product mixture was diluted sequentially with ethyl acetate (20 mL), water (10 mL), and saturated aqueous ammonium chloride solution (10 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (15 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 50% ethyl acetate–hexanes) to provide the α-hydroxy ketone 201 as a colorless oil (115 mg, 99%).

Rf = 0.55 (33% ethyl acetate–hexanes; CAM). ¹H NMR (500 MHz, CDCl₃): δ 5.30 (s, H₁, 1H), 4.84 (d, J = 6.7 Hz, H₁₈a, 1H), 4.76 (d, H₁₈b, J = 6.7 Hz, 1H), 4.65 – 4.57 (m, H₂,1₆,6, 4H), 4.22 (d, J = 4.4 Hz, H₃, 1H), 4.16 (t, J = 2.0 Hz, H₈, 1H), 4.06 (d, J = 8.9 Hz, H₁₂a, 1H), 3.54 (d, J = 8.9 Hz, H₁₂b, 1H), 3.43 (s, H₁₉, 3H), 3.35 (s, H₁₇, 3H), 2.97 (d, J = 2.2 Hz,
H_7, 1H), 2.76k (d, J = 1.7 Hz, H_{25}, 1H), 1.63 (s, H_{14}, 3H), 1.59 (s, H_{20}, 3H), 1.41 (s, H_{21},
3H), 1.35 (s, H_{13}, 3H), 0.90 (s, H_{24}, 9H), 0.08 (s, H_{22}, 3H), 0.03 (s, H_{23}, 3H). ^{13} C NMR
(125 MHz, CDCl_3): δ 203.4 (C), 172.4 (C), 112.3 (C), 96.86 (CH_2), 96.86 (CH_2), 89.0 (C),
83.9 (C), 82.3 (CH), 82.0 (CH), 81.8 (CH), 80.2 (C), 75.1 (CH), 74.1 (CH), 73.9 (CH_2),
70.7 (C), 57.3 (CH_3), 55.6 (CH_3), 46.6 (CH), 26.8 (CH_3), 26.0 (CH_3), 25.7 (3 × CH_3), 25.1
(CH_3), 23.6 (CH_3), 18.0 (C), -4.5 (CH_3), -4.6 (CH_3). IR (ATR-FTIR), cm⁻¹: 3734 (s), 3628
(m), 2917 (s), 1792 (m). HRMS-CI (m/z): [M + Na]^+ calculated for C_{28}H_{46}NaO_{12}Si,
625.2656; found 625.2634. \ [\alpha]_D^{20} = 23.8 (c = 0.02, CHCl_3).
Synthesis of the vicinal diol 202:

Sodium borohydride (2.0 mg, 50.0 μmol, 10.0 equiv) was added in one portion to a solution of the ketone 201 (3.0 mg, 5.00 μmol, 1 equiv) in methanol (500 μL) at 0 °C. The resulting mixture was stirred for 20 min at 0 °C. The cold product mixture was subsequently diluted sequentially with ethyl acetate (10 mL), water (5.0 mL), and saturated aqueous sodium chloride solution (5.0 mL). The resulting mixture was allowed to warm to 23 °C over 30 min. The warmed biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (5.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layer chromatography (eluting with 50% ethyl acetate–hexanes) to provide the diol 202 as a colorless oil (3.0 mg, 99%).

Within the limits of detection, the diol 202 was formed as a single diastereomer (1H NMR analysis, 600 MHz). The relative stereochemistry of the C4 hydroxyl substituent was established by the indicative J_{H4–H3} = 0 Hz supporting the diequatorial configuration depicted.
R_f = 0.30 (33% ethyl acetate–hexanes; PAA). ¹H NMR (600 MHz, CDCl₃): δ 5.22 (s, H₅, 1H), 4.77 (d, J = 6.8 Hz, H₁₂a, 1H), 4.74 (d, J = 4.8 Hz, H₆, 1H), 4.69 (d, J = 6.7 Hz, H₁₂b, 1H), 4.61 (d, J = 6.3 Hz, H₁₄a, 1H), 4.58 (d, J = 6.3 Hz, H₁₄b, 1H), 4.47 (d, J = 1.6 Hz, H₁₇, 1H), 4.35 (s, H₄, 1H), 4.34 (s, H₁, 1H), 4.32 (d, J = 2.9 Hz, H₃, 1H), 4.22 (d, J = 4.8 Hz, H₇, 1H), 4.08 (d, J = 8.8 Hz, H₁₁a, 1H), 3.44 (d, J = 8.7 Hz, H₁₁b, 1H), 3.41 (s, H₁₃, 3H), 3.35 (s, H₁₅, 3H), 2.74 (d, J = 2.9 Hz, H₂, 1H), 1.64 (s, H₁₆, 3H), 1.59 (s, H₈, 3H), 1.58 (s, H₉, 3H), 1.40 (s, H₁₀, 3H), 0.91 (s, H₂₀, 9H), 0.21 (s, H₁₈, 3H), 0.20 (s, H₁₉, 3H). ¹³C NMR (150 MHz, CDCl₃): δ 176.6 (C), 112.3 (C), 96.7 (CH₂), 96.6 (CH₂), 89.2 (C), 85.2 (C), 81.9 (CH), 80.7 (CH), 80.6 (C), 80.3 (CH), 76.5 (CH), 75.3 (CH), 75.0 (CH), 74.4 (CH₂), 63.1 (C), 57.0 (CH₃), 55.4 (CH₃), 49.1 (CH), 26.8 (CH₃), 25.8 (CH₃), 25.8 (3 × CH₃), 25.4 (CH₃), 21.9 (CH₃), 17.8 (C), −4.1 (CH₃), −5.0 (CH₃). IR (ATR-FTIR), cm⁻¹: 3015 (s), 2975 (s), 2361 (s), 1784 (m), 1412 (s). HRMS–CI (m/z): [M + Na]⁺ calculated for C₂₈H₄₈NaO₁₂Si, 627.2813; found, 627.2820. [α]D²⁰ = 5.33 (c = 0.03, CHCl₃).
Synthesis of the transposed $\alpha$-hydroxy ketone 203:

A solution of trimethylaluminum in toluene (2.00 M, 471 $\mu$L, 942 $\mu$mol, 6.00 equiv) was added dropwise via syringe to a solution of the $\alpha$-hydroxy ketone 201 (94.6 mg, 157 $\mu$mol, 1 equiv) in tetrahydrofuran (2.2 mL) at 0 °C. Upon completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to 23 °C over 20 min. The warmed product mixture was stirred for 6 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous potassium sodium tartrate solution (10 mL), saturated aqueous sodium chloride solution (50 mL), and ethyl acetate (50 mL). The diluted product mixture was vigorously stirred for 45 min at 23 °C. The resulting clear, biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 25 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to provide the transposed $\alpha$-hydroxy ketone 203 as a white solid (85.0 mg, 90%).
Within the limits of detection, the transposed α-hydroxyketone 203 was formed as a single diastereomer (¹H NMR analysis, 500 MHz). NOE correlations between the C9 hydrogen and the C13 methyl substituent, as well the C9 and C1 hydrogen atoms support the relative configuration depicted.

\[ R_f = 0.50 \ (33\% \ \text{ethyl acetate–hexanes; CAM}) \]

¹H NMR (500 MHz, CDCl₃): δ 5.12 (s, H₁, 1H), 4.75 (d, J = 2.2 Hz, H₁₆a, 1H), 4.74 (s, H₂, 1H), 4.65 (d, J = 6.7 Hz, H₁₆b, 1H), 4.61 (d, J = 6.4 Hz, H₁₈a, 1H), 4.57 (d, J = 6.4 Hz, H₁₈b, 1H), 4.38 (d, J = 5.3 Hz, H₉, 1H), 4.32 (s, H₆, 1H), 4.27 (d, J = 4.7 Hz, H₃, 1H), 4.10 (d, J = 9.1 Hz, H₁₂a, 1H), 3.54 (s, H₇, 1H), 3.51 (d, J = 9.0 Hz, H₁₂b, 1H), 3.39 (s, H₁₇, 3H), 3.34 (s, H₁₉, 3H), 1.62 (s, H₁₄, 3H), 1.58 (s, H₂₀, 3H), 1.42 (s, H₂₁, 3H), 1.40 (s, H₁₃, 3H), 0.93 (s, H₂₄, 9H), 0.16 (s, H₂₂, 3H), 0.15 (s, H₂₃, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 204.0 (C), 172.7 (C), 112.8 (C), 97.3 (CH₂), 96.8 (CH₂), 91.0 (C), 85.6 (C), 82.8 (CH), 82.1 (C), 80.8 (C), 80.5 (CH), 74.5 (CH), 73.4 (CH₂), 72.4 (CH), 62.9 (C), 59.4 (CH), 57.2 (CH₃), 55.7 (CH₃), 26.4 (CH₃), 26.0 (CH₃), 25.7 (3 × CH₃), 22.1 (CH₃), 18.1 (C), -4.4 (CH₃), -4.7 (CH₃). IR (ATR-FTIR), cm⁻¹: 3734 (s), 3628 (m), 2930 (s), 1784 (s), 1733 (s). HRMS-CI (m/z): [M + Na]+ calculated for C₂₈H₄₆NaO₁₂Si, 625.2656; found 625.2634. \([\alpha]_D^{20} = 27.6 \ (c = 0.10, \text{CHCl}_3)\)
**Synthesis of the vicinal diol 204:**

Sodium borohydride (1.5 mg, 40.0 μmol, 6.0 equiv) was added in one portion to a solution of the ketone 203 (4.0 mg, 7.00 μmol, 1 equiv) in methanol (500 μL) at 0 °C. The resulting mixture was stirred for 40 min at 0 °C. The cold product mixture was subsequently diluted sequentially with ethyl acetate (10 mL), water (5.0 mL), and saturated aqueous sodium chloride solution (5.0 mL). The resulting mixture was allowed to warm to 23 °C over 30 min. The warmed biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (5.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-layer chromatography (eluting with 50% ethyl acetate–hexanes) to provide the diol 204 as a colorless oil (3.2 mg, 80%).

Within the limits of detection, the diol 204 was formed as a 8:1 mixture of diastereomers (1H NMR analysis, 500 MHz). The relative stereochemistry of the C3 hydroxyl substituent was established by the J\textsubscript{H4–H3} = 9.1 Hz supporting the diaxial configuration depicted.
Rf = 0.20 (33% ethyl acetate–hexanes; PAA). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.06 (s, H$_5$, 1H), 4.79 (d, $J = 6.8$ Hz, H$_{14a}$, 1H), 4.67 (m, H$_{6,14b}$, 2H), 4.62–4.56 (m, H$_{12}$, 2H), 4.31 (d, $J = 9.1$ Hz, H$_4$, 1H), 4.20 (d, $J = 4.7$ Hz, H$_3$, 7, 2H), 4.15 (s, H$_1$, 1H), 4.09 (d, $J = 9.0$ Hz, H$_{11a}$, 1H), 3.40 (s, H$_{11b,13}$, 4H), 3.34 (s, H$_{15}$, 3H), 2.86 (d, $J = 3.4$ Hz, H$_2$, 1H), 1.62 (s, H$_{16}$, 3H), 1.59 (s, H$_8$, 3H), 1.56 (s, H$_{10}$, 3H), 1.39 (s, H$_9$, 3H), 0.95 (s, H$_{20}$, 9H), 0.21 (s, H$_{18}$, 3H), 0.19 (s, H$_{19}$, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 173.2 (C), 112.5 (C), 96.8 (CH$_2$), 96.6 (CH$_2$), 89.9 (C), 86.1 (C), 82.9 (CH), 82.7 (CH), 80.7 (C), 80.0 (CH), 75.9 (CH), 74.3 (CH$_2$), 74.3 (CH), 71.9 (CH), 61.7 (C), 56.9 (CH$_3$), 55.4 (CH$_3$), 46.4 (CH), 26.9 (CH$_3$), 26.3 (CH$_3$), 25.8 (3 × CH$_3$), 25.7 (CH$_3$), 22.0 (C), 17.9 (C), −4.6 (CH$_3$), −4.8 (CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 3015 (s), 2995 (m), 2975 (s), 2956 (m), 2360 (s), 1785 (m), 1721 (m), 1412 (s). HRMS-Cl (m/z): [M + Na]$^+$ calculated for C$_{28}$H$_{48}$NaO$_{12}$Si, 627.2813; found, 627.2822. [$\alpha$]$_D^{20}$ = −0.20 (c = 0.10, CHCl$_3$).
Synthesis of the bis(acetonide) \( \text{206} \):

Part 1: Synthesis of the diol \( \text{S32} \):

Cerium (III) chloride heptahydrate (131 mg, 353 μmol, 2.50 equiv) was added in one portion to a solution of the α-hydroxy ketone \( \text{203} \) (85.0 mg, 141 μmol, 1 equiv) in methanol (2.8 mL) at 23 °C. The resulting solution was cooled to −78 °C. Sodium borohydride (26.7 mg, 705 μmol, 5.00 equiv) was added in one portion and the resulting mixture was stirred for 35 min at −78 °C. The cold product mixture was diluted sequentially with ethyl acetate (10 mL), water (5.0 mL), and saturated aqueous sodium chloride solution (50 mL). The resulting mixture was allowed to warm to 23 °C over 20 min. The warmed biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was used directly in the following step.

\(^1\)H NMR analysis of the unpurified product mixture indicated the presence of 4.1:1 mixture of diastereomers. The relative stereochemistry of the C8 hydroxyl substituent was established by conversion of diol \( \text{S32} \) to the bis(acetonide) \( \text{206} \).
Part 2: Synthesis of the bis(acetonide) 206:

Pyridinium para-toluenesulfonate (10.6 mg, 42.3 μmol, 0.30 equiv) was added in one portion to a screw-capped vessel containing a solution of the unpurified diol S32 obtained in the preceding step (nominally 141 μmol, 1 equiv) in toluene (2.3 mL) and 2,2-dimethoxypropane (2.3 mL) at 23 °C. The reaction vessel was sealed and the sealed vessel was placed in an oil bath that had been preheated to 80 °C. The reaction mixture was stirred and heated for 24 h at 80 °C. The product mixture was cooled to 23 °C over 30 min. The cooled product mixture was diluted sequentially with ethyl acetate (10 mL), water (10 mL), and saturated aqueous sodium bicarbonate solution (10 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33% ethyl acetate–hexanes) to provide the bis(acetonide) 206 as a colorless oil (55.1 mg, 61% over two steps).
NOE correlations between the C8 hydrogen atom and the C13 methyl substituent, as well as the C9 hydrogen and the C13 methyl substituent, support the relative configuration depicted.

\[ R_f = 0.20 \text{ (33\% ethyl acetate–hexanes; CAM).} \]

\[ ^1H \text{ NMR (500 MHz, CDCl}_3\) : } \delta 4.82 \text{ (s, H}_1, \text{ 1H)}, 4.77 \text{ (d, J = 6.7 Hz, H}_16a, \text{ 1H)}, 4.70 \text{ (d, J = 6.7 Hz, H}_16b, \text{ 1H)}, 4.63 \text{ (s, H}_6, \text{ 1H)}, 4.62 – 4.55 \text{ (m, H}_2,8,18, \text{ 4H)}, 4.37 \text{ (d, J = 7.1 Hz, H}_9, \text{ 1H)}, 4.18 \text{ (d, J = 4.7 Hz, H}_3, \text{ 1H)}, 4.11 \text{ (d, J = 8.9 Hz, H}_12a, \text{ 1H)}, 3.47 – 3.41 \text{ (m, H}_12a,17, \text{ 3H)}, 3.35 \text{ (s, H}_19, \text{ 3H)}, 2.99 \text{ (d, J = 3.1 Hz, H}_7, \text{ 1H)}, 1.69 \text{ (s, H}_25, \text{ 3H)}, 1.61 \text{ (s, H}_14, \text{ 3H)}, 1.54 \text{ (s, H}_20, \text{ 3H)}, 1.41 \text{ (s, H}_13, \text{ 3H)}, 1.38 \text{ (s, H}_21, \text{ 3H)}, 1.29 \text{ (s, H}_26, \text{ 3H)}, 0.92 \text{ (s, H}_24, \text{ 9H)}, 0.13 \text{ (d, J = 5.1 Hz, H}_22,23, \text{ 6H)}. \]

\[ ^{13}C \text{ NMR (125 MHz, CDCl}_3\) : } \delta 171.7 \text{ (C)}, 112.0 \text{ (C)}, 110.7 \text{ (C)}, 97.2 \text{ (CH}_2\), 96.7 \text{ (CH}_2\), 89.6 \text{ (C)}, 84.4 \text{ (C)}, 82.7 \text{ (CH)}, 80.9 \text{ (C)}, 80.2 \text{ (CH)}, 78.8 \text{ (CH)}, 76.1 \text{ (CH)}, 73.7 \text{ (CH}_2\), 73.4 \text{ (CH)}, 71.2 \text{ (CH)}, 62.6 \text{ (C)}, 57.1 \text{ (CH}_3\), 55.4 \text{ (CH}_3\), 45.0 \text{ (CH)}, 26.8 \text{ (CH}_3\), 26.0 \text{ (CH}_3\), 25.9 \text{ (CH}_3\), 25.5 \text{ (3 × CH}_3\), 25.1 \text{ (CH}_3\), 24.6 \text{ (CH}_3\), 22.0 \text{ (CH}_3\), 18.0 \text{ (C)}, –4.3 \text{ (CH}_3\), –5.1 \text{ (CH}_3\). \]

IR (ATR-FTIR), cm\(^{-1}\): 3735 (s), 3649 (m), 2929 (s), 1792 (s). HRMS-Cl (m/z): [M + Na]\(^+\) calculated for C\(_{31}\)H\(_{52}\)NaO\(_{12}\)Si, 667.3126; found 667.3105. \([\alpha]_D^{20} = 2.56 \text{ (c = 0.05, CHCl}_3\).}
Synthesis of the alcohol 208:

A solution of tetra-\(n\)-butylammonium fluoride in tetrahydrofuran (1.00 M, 140 \(\mu\)L, 140 \(\mu\)mol, 2.00 equiv) was added dropwise via syringe to a solution of the bis(acetonide) 206 (45.0 mg, 70.0 \(\mu\)mol, 1 equiv) in tetrahydrofuran (690 \(\mu\)L) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The cold product mixture was diluted sequentially with ethyl acetate (10 mL), saturated aqueous ammonium chloride solution (5.0 mL), and water (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 \(\times\) 5 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 33\% ethyl acetate–hexanes) to provide the alcohol 208 as a colorless oil (31.0 mg, 83\%).

\(R_f = 0.50\) (50\% ethyl acetate–hexanes; CAM). \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 4.82 (s, \(H_1\), 1H), 4.78 (d, \(J = 6.7\) Hz, \(H_{18a}\), 1H), 4.75 (d, \(J = 4.7\) Hz, \(H_2\), 1H), 4.71 (d, \(J = 6.7\) Hz, \(H_{18b}\), 1H), 4.68 (s, \(H_6\), 1H), 4.64 – 4.56 (m, \(H_{8,9,16}\), 4H), 4.21 (d, \(J = 4.7\) Hz, \(H_3\), 1H), 4.12 (d, \(J = 8.9\) Hz, \(H_{12a}\), 1H), 3.44 (d, \(J = 8.9\) Hz, \(H_{12b}\), 1H), 3.43 (s, \(H_{19}\), 3H), 3.35 (s, \(H_{17}\), 3H), 3.03 (d, \(J = 3.1\) Hz, \(H_7\), 1H), 1.72 (s, \(H_{23}\), 3H), 1.63 (s, \(H_{14}\), 3H), 1.55 (s, \(H_{20}\), 3H), 1.44 (s, \(H_{13}\),
3H), 1.39 (s, H$_{22}$, 3H), 1.36 (s, H$_{21}$, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): δ 171.5 (C), 112.4 (C), 111.8 (C), 97.5 (CH$_2$), 96.9 (CH$_2$), 89.8 (C), 85.1 (C), 82.8 (CH), 81.1 (C), 80.3 (CH), 79.2 (CH), 76.5 (CH), 74.0 (CH$_2$), 73.2 (CH), 71.6 (CH), 62.8 (C), 57.3 (CH$_3$), 55.7 (CH$_3$), 45.1 (CH), 27.1 (CH$_3$), 26.2 (CH$_3$), 26.1 (CH$_3$), 25.4 (CH$_3$), 25.3 (CH$_3$), 22.3 (CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 3452 (m), 2983 (m), 2930 (s), 1787 (s). HRMS-CI (m/z): [M + Na]$^+$ calculated for C$_{25}$H$_{38}$NaO$_{12}$, 553.2261; found 553.2252. $[^{\alpha}]_D^{20} = -9.14$ (c = 0.27, CHCl$_3$).
Synthesis of the triol 209:

A solution of lithium aluminum hydride in tetrahydrofuran (1.00 M, 132 μL, 132 μmol, 5.00 equiv) was added dropwise via syringe to a solution of the alcohol 208 (14.0 mg, 26.0 μmol, 1 equiv) in tetrahydrofuran (1.0 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. Five drops of water were then added to the cold product mixture, and the resulting solution was stirred for 30 min at 0 °C. The product mixture was diluted sequentially with ethyl acetate (10 mL) and saturated aqueous potassium sodium tartrate solution (5.0 mL). The diluted product mixture was warmed to 23 °C over 30 min. The warmed biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (5 × 8 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 70% ethyl acetate–hexanes) to provide the triol 209 as a colorless oil (11.5 mg, 80%).

Rf = 0.30 (70% ethyl acetate–hexanes; CAM). 1H NMR (500 MHz, CDCl3): δ 4.78 (d, J = 6.9 Hz, H18a, 1H), 4.68 (d, J = 6.9 Hz, H18b, 1H), 4.63 (dd, J = 6.6, 3.2 Hz, H8, 1H), 4.61 – 4.53 (m, H9,10a,16, 4H), 4.40 – 4.33 (m, H1,2,3, 3H), 3.93 (d, J = 11.5 Hz, H10a, 1H), 3.44 (s,
H₁₇, 3H), 3.39 (d, J = 8.7 Hz, H₁₂b, 1H), 3.34 (s, H₁₉, 3H), 3.05 (d, J = 3.2 Hz, H₇, 1H), 1.67 (s, H₁₄, 3H), 1.63 (s, H₂₂, 3H), 1.46 (s, H₂₀, 3H), 1.43 (s, H₂₃, 3H), 1.41 (s, H₁₃, 3H), 1.39 (s, H₂₁, 3H). ¹³C NMR (125 MHz, CDCl₃): δ 109.4 (C), 108.1 (C), 96.7 (CH₂), 96.3 (CH₂), 91.3 (C), 86.1 (CH), 83.3 (C), 80.8 (CH), 79.4 (CH), 78.4 (C), 77.3 (CH), 74.1 (CH₂), 73.9 (CH), 70.6 (CH), 67.5 (CH₂), 56.9 (CH), 55.5 (CH), 52.7 (C), 44.9 (CH), 27.6 (CH₃), 26.4 (CH₃), 26.2 (CH₃), 25.9 (CH₃), 24.7 (CH₃), 22.4 (CH₃). IR (ATR-FTIR), cm⁻¹: 3734 (CH₃) (m), 3628 (m), 3446 (m), 2936 (m). HRMS-Cl (m/z): [M + Na]⁺ calculated for C₂₅H₄₂NaO₁₂, 557.2574; found 557.2574. [α]₀²⁰ = −25.3 (c = 0.12, CHCl₃).
**Synthesis of the euonyminol octaacetate (116):**

**Part 1: Synthesis of euonyminol (99):**

Glacial acetic acid (900 μL) was added in one portion to a screw-capped vessel containing a solution of the triol 209 (11.0 mg, 20.6 μmol, 1 equiv) in tetrahydrofuran–water (1:1 v/v, 600 μL) at 23 °C. The reaction vessel was sealed and the sealed vessel was placed in an oil bath that had been preheated to 85 °C. The reaction mixture was stirred and heated for 42 h at 85 °C. The product mixture was cooled to 23 °C over 30 min. The cooled product mixture was concentrated and the residue obtained was used directly in the following step.

The product 99 was converted to the known euonyminol octaacetate (116) to facilitate purification and characterization.
Part 2: Synthesis of the euonyminol octaacetate (116):

Triethylamine (1.15 mL, 8.24 mmol, 400 equiv) and acetic anhydride (583 μL, 6.18 mmol, 300 equiv) were added in sequence to a solution of the residue obtained in the preceding step (nominally 20.6 μmol, 1 equiv) in tetrahydrofuran–dichloromethane (1:1 v/v, 440 μL) in a screw-capped vial at 23 °C. The reaction vessel was sealed and the sealed reaction vessel was placed in an oil bath that had been preheated to 60 °C. The reaction mixture was stirred for 1 h at 60 °C. The product mixture was cooled to 23 °C over 15 min and the cooled reaction mixture was then sonicated for 5 min at 23 °C. The reaction vessel was then placed in an oil bath that had been preheated to 60 °C and heated for an additional hour. This heating–cooling–sonicating procedure was repeated a total of six times as described above. After the sixth cycle, the product mixture was diluted sequentially with ethyl acetate (10 mL), water (5.0 mL), and saturated aqueous sodium bicarbonate solution (5.0 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (5.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 50%
ethyl acetate–hexanes) to provide euonyminol octaacetate (116) as a colorless oil (8.7 mg, 60% over two steps).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.77 (s, H$_6$, 1H), 5.58 (d, J = 3.7 Hz, H$_1$, 1H), 5.48 (dd, J = 5.8, 3.9 Hz, H$_8$, 1H), 5.34 (d, J = 6.0 Hz, H$_9$, 1H), 5.29 – 5.25 (m, H$_2$, 1H), 5.21 (d, J = 13.3 Hz, H$_{15a}$, 1H), 4.89 (d, J = 11.6 Hz, H$_{12a}$, 1H), 4.82 (d, J = 2.5 Hz, H$_3$, 1H), 4.42 (d, J = 13.3 Hz, H$_{15b}$, 1H), 4.16 (s, H$_{OH-4}$, 1H), 3.95 (d, J = 11.6 Hz, H$_{12b}$, 1H), 2.32 (d, J = 3.9 Hz, H$_7$, 1H), 2.25 (s, H$_{Ac-15}$, 3H), 2.17 (s, H$_{Ac-8}$, 3H), 2.16 (s, H$_{Ac-3}$, 3H), 2.13 (s, H$_{Ac-6}$, 3H), 2.12 (s, H$_{Ac-2}$, 3H), 2.11 (s, H$_{Ac-12}$, 3H), 1.98 (s, H$_{Ac-9}$, 3H), 1.88 (s, H$_{Ac-1}$, 3H), 1.57 (s, H$_{13}$, 3H), 1.48 (s, H$_{14}$, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 170.7 (C), 170.13 (C), 170.07 (C), 169.8 (C), 169.5 (C), 169.3 (C), 168.9 (C), 168.7 (C), 93.0 (C), 84.1 (C), 75.8 (CH), 73.9 (CH), 73.2 (CH), 71.0 (CH), 69.5 (CH$_2$), 69.3 (C), 69.03 (CH), 68.98 (CH), 60.3 (CH$_2$), 51.9 (C), 50.7 (CH), 23.3 (CH$_3$), 21.5 (CH$_3$), 21.3 (CH$_3$), 21.0 (CH$_3$), 20.9 (CH$_3$), 20.8 (CH$_3$), 20.54 (CH$_3$), 20.50 (CH$_3$), 18.3 (CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 3468 (m), 3456 (m), 2957 (m), 2919 (m), 2850 (m), 1743 (s). HRMS-Cl (m/z): [M + Na]$^+$ calculated for C$_{31}$H$_{42}$NaO$_{18}$, 725.2269; found 725.2247. $\left[\alpha\right]_{D}^{20} = -5.96$ (c = 0.20, CHCl$_3$).
Synthesis of euonyminol (99):

A solution of a freshly prepared sodium methoxide in methanol (0.10 M, 7.0 μL, 0.70 μmol, 0.20 equiv) was added dropwise via syringe to a solution of euonimynol octaacetate (116, 2.50 mg, 3.60 μmol, 1 equiv) in methanol (300 μL) at 23 °C. The reaction mixture was stirred for 36 h at 23 °C. The product mixture was concentrated to provide analytically pure euonyminol (99) as an off-white solid (1.30 mg, >99%).

\(^1\)H NMR (500 MHz, CD\(_3\)OD): \(\delta\) 5.37 (s, H\(_6\), 1H), 4.44 (d, J = 12.9 Hz, H\(_{15a}\), 1H), 4.30 – 4.27 (m, H\(_{1,9}\), 2H), 4.16 – 4.05 (m, H\(_{8,15b}\), 2H), 3.97 – 3.87 (m, H\(_{12a,2}\), 2H), 3.64 (d, J = 11.1 Hz, H\(_{12b}\), 1H), 3.57 (d, J = 3.0 Hz, H\(_3\), 1H), 2.28 (dd, J = 4.2, 1.1 Hz, H\(_7\), 1H), 1.77 (s, H\(_{14}\), 3H), 1.43 (s, H\(_{13}\), 3H). \(^{13}\)C NMR (125 MHz, CD\(_3\)OD): \(\delta\) 94.5 (C), 85.9 (C), 79.3 (CH), 76.9 (CH), 75.8 (CH), 74.97 (CH), 74.97 (CH), 73.4 (C), 71.0 (CH), 68.9 (CH\(_2\)), 59.6 (CH\(_2\)), 55.0 (C), 53.9 (CH), 25.9 (CH\(_3\)), 18.9 (CH\(_3\)). IR (ATR-FTIR), cm\(^{-1}\): 3354 (s), 2920 (m), 2852 (m), 1653 (m), 1053 (m). HRMS-Cl (m/z): [M + Na]\(^{+}\) calculated for C\(_{15}\)H\(_{26}\)NaO\(_{10}\), 389.1424; found 389.1418. \([\alpha]_{D}^{20} = -4.70\) (c = 0.08, CD\(_3\)OD).

\(^1\)H NMR (500 MHz, D\(_2\)O): \(\delta\) 5.22 (s, H\(_6\), 1H), 4.43 (d, J = 13.1 Hz, H\(_{15a}\), 1H), 4.37 (d, J = 5.4 Hz, H\(_9\), 1H), 4.33 (d, J = 3.5 Hz, H\(_1\), 1H), 4.21 (dd, J = 5.3, 4.1 Hz, H\(_8\), 1H), 4.09 (d, J = 13.1 Hz, H\(_{15b}\), 1H), 4.03 (t, J = 3.2 Hz, H\(_2\), 1H), 3.92 (d, J = 11.4 Hz, H\(_{12a}\), 1H), 3.73 (d, J = 13.1 Hz, H\(_{15a}\), 1H), 3.71 (t, J = 3.2 Hz, H\(_2\), 1H), 3.67 (d, J = 11.4 Hz, H\(_{12a}\), 1H), 3.65 (s, H\(_3\), 1H), 3.54 (s, H\(_4\), 1H), 3.46 (s, H\(_5\), 1H), 3.37 (s, H\(_6\), 1H), 3.30 (s, H\(_7\), 1H), 3.27 (s, H\(_8\), 1H), 3.23 (s, H\(_9\), 1H), 3.17 (s, H\(_{10}\), 1H), 3.14 (s, H\(_{11}\), 1H), 3.12 (s, H\(_{12}\), 1H), 2.84 (s, H\(_{13}\), 1H), 2.73 (s, H\(_{14}\), 3H), 2.65 (s, H\(_{15}\), 3H).
11.4 Hz, H_{12b}, 1H), 3.66 (d, J = 2.9 Hz, H_{3}, 1H), 2.39 (d, J = 4.0 Hz, H_{7}, 1H), 1.74 (s, H_{14}, 3H), 1.44 (s, H_{13}, 3H). ^{13}\text{C} \text{ NMR (125 MHz, D}_2\text{O)}: \delta 92.7 (C), 84.4 (C), 77.1 (CH), 74.8 (CH), 74.0 (CH), 73.0 (CH), 72.8 (CH), 71.7 (C), 69.4 (CH), 67.2 (CH_{2}), 58.2 (CH_{2}), 53.5 (C), 61.9 (CH), 24.0 (CH_{3}), 17.8 (CH_{3}).
Re-acylation of synthetic euonyminol (99) to provide euonyminol octaacetate (116):

Triethylamine (197 μL, 1.42 mmol, 400 equiv) and acetic anhydride (100 μL, 1.06 mmol, 300 equiv) were added in sequence to a solution of synthetic euonyminol (99) obtained in the preceding experiment (1.30 mg, 3.50 μmol, 1 equiv) in tetrahydrofuran–dichloromethane (1:1 v/v, 300 μL) in a screw-capped vial at 23 °C. The reaction vessel was sealed and the sealed reaction vessel was placed in an oil bath that had been preheated to 60 °C. The reaction mixture was stirred for 9 h at 60 °C. The product mixture was cooled to 23 °C over 15 min. The cooled product mixture was diluted sequentially with ethyl acetate (8.0 mL), water (3.0 mL), and saturated aqueous sodium bicarbonate solution (3.0 mL). The diluted product mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (5.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by preparative thin-column chromatography (eluting with 50% ethyl acetate–hexanes) to provide euonyminol octaacetate (116) as a colorless oil (2.2 mg, 89%).
$^1$H NMR analysis of the re-acylated euonyminol octaacetate (116) was in complete agreement with the $^1$H NMR of synthetic 116.
Synthesis of the silylene ether 210:

Di-tert-butylsilyl bis(trifluoromethanesulfonate) (118 μL, 362 μmol, 1.50 equiv) was added dropwise via syringe to a solution of the diol 173 (100 mg, 241 μmol, 1 equiv) and pyridine (97.0 μL, 1.21 mmol, 5.00 equiv) in dichloromethane (1.5 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then the cooling bath was removed. The reaction mixture was allowed to warm to 23 °C and then stirred for 12 h at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (5.0 mL), water (5.0 mL), and dichloromethane (15 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 10.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ethyl acetate–hexanes) to provide the silylene ether 210 as a yellow oil (106 mg, 79%).

Rf = 0.30 (33% ethyl acetate–hexanes; PAA). \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ 6.95 (ddd, H\(_6\), J = 16.9, 10.4, 5.1 Hz, 1H), 5.37 (d, H\(_{7a}\), J = 18.6 Hz, 1H), 5.11 (d, H\(_{7b}\), J = 10.4 Hz, 1H), 5.01 (d, H\(_5\), J = 5.1 Hz, 1H), 4.72 – 4.57 (m, H\(_{5,11,13}\), 5H), 4.41 (s, H\(_1\), 195H), 3.98 (d,
H_{10a}, J = 9.2 \text{ Hz}, 1H), 3.69 (s, H_{15}, 3H), 3.57 (d, H_{10b}, J = 9.2 \text{ Hz}, 1H), 3.35 (s, H_{12,14}, 6H), 2.67 (s, H_8, 1H), 2.50 (t, H_2, J = 2.9 \text{ Hz}, 1H), 2.37 – 2.26 (m, H_{3a}, 1H), 2.19 – 2.08 (m, H_{3b}, 1H), 1.47 (s, H_9, 3H), 1.11 (s, H_{16}, 9H), 0.96 (s, H_{17}, 9H). ^{13}C \text{ NMR (125 MHz, CDCl}_3): \delta 169.7 (C), 138.6 (CH), 114.5 (CH_2), 96.7 (CH_2), 95.5 (CH_2), 87.6 (C), 83.4 (CH), 83.3 (C), 80.6 (CH), 79.9 (C), 79.2 (C), 73.8 (CH_2), 72.9 (CH), 63.9 (C), 55.5 (CH_3), 55.2 (CH_3), 51.4 (CH_3), 42.8 (CH), 33.3 (CH_2), 28.7 (3 \times CH_3), 27.2 (3 \times CH_3), 22.7 (C), 19.8 (C), 19.2 (CH_3). \text{ IR (ATR-FTIR), cm}^{-1}: 3015 (s), 2996 (m), 2975 (s), 2360 (m), 2003 (m), 1400 (s). \text{ HRMS-Cl (m/z): [M + Na]+ calculated for C}_{28}H_{46}NaO_9Si, 577.2809; found, 577.2819. [\alpha]^D_{D} = 2.48 (c = 0.10, CHCl_3).
Synthesis of the vinyl stannane 211:

A solution of azobisisobutyronitrile (1.0 mg, 5.0 μmol, 0.10 equiv) in degassed toluene (1.00 mL) and a solution of tributyltin hydride (29.0 μL, 108 μmol, 2.00 equiv) in degassed toluene (1.00 mL) were added simultaneously via two syringe pumps over 2 h to a solution of the silylene ether 210 (25.0 mg, 54.0 μmol, 1 equiv) in a degassed toluene (2.70 mL) at 80 °C. Upon completion of the addition, the reaction mixture was stirred for an additional 1 h at 80 °C. The product mixture was then cooled to 23 °C over 1 h. The cooled product mixture was concentrated and the residue obtained was directly purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes) to provide the vinyl stannane 211 as a yellow oil (41.0 mg, 90%).

NOE correlations between the C6 hydrogen and the C9 methyl substituent and C8 vinyl hydrogen and the C1 hydrogen substituent support the shown stereochemical configuration.
$R_f = 0.50$ (25% ethyl acetate–hexanes; PAA). $^1$H NMR (500 MHz, $C_6D_6$): δ 7.02 (d, $H_8$, $J$ = 2.4 Hz, 1H), 5.11 (dd, $H_4$, $J$ = 11.8, 6.0 Hz, 1H), 4.74 (d, $H_5$, $J$ = 9.2 Hz, 1H), 4.64 – 4.58 (m, $H_{1,13a}$, 2H), 4.56 (d, $H_{13b}$, $J$ = 6.5 Hz, 1H), 4.51 – 4.42 (m, $H_{11}$, 2H), 4.27 (d, $H_{10a}$, $J$ = 9.2 Hz, 1H), 3.78 (ddd, $H_6$, $J$ = 9.3, 6.7, 2.5 Hz, 1H), 3.62 (d, $H_{10b}$, $J$ = 9.1 Hz, 1H), 3.50 (s, $H_{15}$, 3H), 3.23 (s, $H_{12}$, 3H), 3.12 (s, $H_{14}$, 3H), 3.00 – 2.90 (m, $H_{3a}$, 1H), 2.54 (t, $H_2$, $J$ = 3.3 Hz, 1H), 2.15 (ddd, $H_{3b}$, $J$ = 13.1, 5.9, 3.6 Hz, 1H), 1.62 (dtd, $H_{18}$, $J$ = 14.3, 7.6, 7.2, 3.2 Hz, 6H), 1.55 (d, $H_{9,7}$, $J$ = 6.3 Hz, 6H), 1.36 (q, $H_{20}$, $J$ = 7.4 Hz, 6H), 1.31 (s, $H_{16}$, 9H), 1.15 (s, $H_{17}$, 9H), 1.07 (td, $H_{19}$, $J$ = 7.4, 3.1 Hz, 6H), 0.93 (t, $H_{21}$, $J$ = 7.3 Hz, 9H). $^{13}$C NMR (125 MHz, $C_6D_6$): δ 171.2 (C), 162.1 (C), 127.8 (CH), 96.8 (CH$_2$), 94.9 (CH$_2$), 88.4 (C), 87.8 (CH), 83.9 (C), 83.5 (CH), 75.9 (CH), 75.1 (CH$_2$), 66.5 (C), 55.3 (CH$_3$), 54.9 (CH$_3$), 51.4 (CH$_3$), 45.6 (CH), 44.5 (CH), 32.4 (CH$_2$), 29.6 (3 $\times$ CH$_3$), 29.5 (3 $\times$ CH$_2$), 27.7 (3 $\times$ CH$_2$), 27.5 (3 $\times$ CH$_3$), 23.4 (C), 21.1 (CH$_3$), 20.1 (C), 19.8 (CH$_3$), 13.9 (3 $\times$ CH$_3$), 10.7 (3 $\times$ CH$_2$). IR (ATR-FTIR), cm$^{-1}$: 3015 (s), 2996 (m), 2975 (s), 1400 (s). HRMS-Cl (m/z): [M + Na]$^+$ calculated for C$_{40}$H$_{74}$NaO$_9$SiSn, 864.4022; found, 573.1631. $[\alpha]_D^{20} = -1.44$ (c = 0.13, CHCl$_3$).
**Synthesis of the olefin 213:**

**Part 1: Synthesis of the vinyl stannane 212:**

A solution of azobisisobutyronitrile (2.0 mg, 11.0 μmol, 0.10 equiv) in degassed toluene (1.50 mL) and a solution of tributyltin hydride (36.0 μL, 132 μmol, 1.20 equiv) in degassed toluene (1.50 mL) were added simultaneously via two syringe pumps over 2 h to a solution of the acetonide 174 (50.0 mg, 110 μmol, 1 equiv) in a degassed toluene (5.50 mL) at 80 °C. Upon completion of the addition, the reaction mixture was stirred for an additional 1 h at 80 °C. The product mixture was then cooled to 23 °C over 1 h. The cooled product mixture was directly concentrated and the residue obtained was used directly in the following step.

An analytically pure sample of the vinyl stannane 212 was obtained by a preparative thin-layered chromatography (eluting with 25% ethyl acetate–hexanes). NOE correlations between the C17 hydrogen and the C1 hydrogen support the configuration depicted.
$R_f = 0.50$ (25% ethyl acetate–hexanes; PAA). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.11 (s, H$_{17}$, 1H), 4.70 (d, H$_{13a}$, J = 6.7 Hz, 1H), 4.63 – 4.56 (m, H$_{13b,11}$, 3H), 4.53 (s, H$_1$, 1H), 4.48 (dd, H$_4$, J = 12.3, 6.1 Hz, 1H), 4.34 (dd, H$_5$, J = 12.0, 5.3 Hz, 1H), 3.90 (d, H$_{10a}$, J = 9.0 Hz, 1H), 3.67 (d, H$_8$, J = 1.6 Hz, 3H), 3.60 (d, H$_{10b}$, J = 9.1 Hz, 1H), 3.38 (s, H$_{12}$, 3H), 3.34 (s, H$_{14}$, 3H), 2.73 – 2.56 (m, H$_{7a,2}$, 2H), 2.55 – 2.38 (m, H$_{3a,6a}$, 2H), 2.13 – 2.03 (m, H$_{7b}$, 1H), 1.99 (dd, H$_{3b}$, J = 11.6, 6.1 Hz, 1H), 1.80 – 1.72 (m, H$_{6b}$, 1H), 1.58 – 1.44 (m, H$_{18,15,9}$, 12H), 1.41 – 1.20 (m, H$_{16,20}$, 9H), 0.98 – 0.82 (m, H$_{19,21}$, 15H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 171.1 (C), 149.8 (C), 127.1 (CH), 101.7 (C), 96.7 (CH$_2$), 95.9 (CH$_2$), 87.3 (C), 84.4 (C), 83.2 (CH), 75.5 (CH), 74.9 (CH$_2$), 72.9 (CH), 60.1 (C), 56.5 (CH$_3$), 55.3 (CH$_3$), 51.1 (CH$_3$), 43.4 (CH), 34.5 (CH$_2$), 30.1 (CH$_2$), 29.8 (CH$_2$), 29.7 (CH$_3$), 29.2 (3 × CH$_2$), 27.3 (3 × CH$_2$), 20.3 (CH$_3$), 19.8 (CH$_3$), 13.7 (3 × CH$_3$), 10.2 (3 × CH$_2$). IR (ATR-FTIR), cm$^{-1}$: 3015 (s), 2996 (m), 2975 (s), 1401 (s). HRMS-CI (m/z): [M + Na]$^+$ calculated for C$_{35}$H$_{62}$NaO$_6$Sn, 769.3313; found, 769.3335. $[\alpha]_D^{20} = -63.3$ (c = 0.17, CHCl$_3$).
Camphorsulfonic acid (43.4 mg, 187 μmol, 1.70 equiv) was added in a single portion to a solution of the residue obtained in the preceding step (nominally, 110 μmol, 1 equiv) in dichloromethane (1.5 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The cold product mixture was diluted sequentially with dichloromethane (10 mL), saturated aqueous sodium bicarbonate solution (5.0 mL), and water (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 50% ethyl acetate–hexanes) to provide the olefin *213* as a colorless oil (32.5 mg, 71% two steps).

R<sub>f</sub> = 0.50 (25% ethyl acetate–hexanes; PAA). ¹H NMR (500 MHz, CDCl₃): δ 5.08 (s, Hₑ,1H), 5.01 (s, H₁₇a,1H), 4.97 (s, H₁₇b,1H), 4.77 (d, H₁₃a,J = 6.6 Hz, 1H), 4.67 (d, H₁₃b,J = 6.8 Hz, 1H), 4.57 (s, H₁₁, 2H), 4.48 (dt, H₄, J = 12.0, 6.4 Hz, 1H), 4.36 – 4.24 (m, H₅, 1H), 3.89 (d, H₁₀a, J = 9.0 Hz, 1H), 3.74 (s, H₈, 3H), 3.48 (d, H₁₀b, J = 9.1 Hz, 1H), 3.43 (s, H₁₂, 3H), 3.33 (s, H₁₄, 3H), 3.30 (d, H₁₆, J = 9.4 Hz, 1H), 3.04 (d, H₁₅, J = 5.7 Hz, 1H), 2.63 –
2.47 (m, H_{2,6a}, 2H), 2.29 (ddd, H_{3a}, J = 13.8, 7.0, 4.1 Hz, 1H), 2.13 (ddd, H_{6b}, J = 13.1, 5.3, 2.1 Hz, 1H), 2.07 – 1.87 (m, H_{3b,7}, 3H), 1.49 (s, H_{9}, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 172.2 (C), 143.6 (C), 111.9 (CH$_2$), 96.7 (CH$_2$), 96.1 (CH$_2$), 88.5 (C), 83.7 (C), 82.8 (CH), 77.5 (CH), 74.6 (CH$_2$), 73.8 (CH), 65.7 (C), 56.6 (CH$_3$), 55.4 (CH$_3$), 51.8 (CH$_3$), 42.1 (CH), 33.9 (CH$_2$), 33.1 (CH$_2$), 31.4 (CH$_2$), 20.4 (CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 3499 (m), 3015 (s), 2996 (m), 2975 (s), 2957 (m), 2691 (m), 2265 (m), 2069 (m), 2003 (m), 1710 (s), 1458 (s). HRMS-CI (m/z): [M + Na]$^+$ calculated for C$_{20}$H$_{32}$NaO$_9$, 439.1944; found, 439.1946. $\left[ \alpha \right]_{D}^{20} = -48.1 \ (c = 0.10, \text{CHCl}_3)$. 
Synthesis of the silylene ether 214:

Part 1: Synthesis of the ketone S33:

Ozone was passed through a solution of the olefin 213 (30.0 mg, 72.0 μmol, 1 equiv) in dichloromethane (1.30 mL) and methanol (500 μL) at –78 °C until a dark blue color persisted. Dioxygen was then passed through the solution to remove any unreacted ozone, resulting in a colorless solution. Triphenylphosphine (37.8 mg, 141 μmol, 2.00 equiv) was then added in one portion. The cooling bath was removed, and the mixture was allowed to warm to 23 °C over 1 h. The warmed product mixture was concentrated and the residue obtained was partially purified by elution over a short plug of silica gel (2.0 cm × 1.0 cm, eluting with 50% ethyl acetate – hexanes). The filtrate was collected and the residue obtained was used directly in the following step.
Part 2: Synthesis of the silylene ether 214:

Di-tert-butylsilyl bis(trifluoromethanesulfonate) (25.0 μL, 79.2 μmol, 1.10 equiv) was added dropwise via syringe to a solution of the residue obtained in the preceding step (nominally 72.0 μmol, 1 equiv) and pyridine (16.0 μL, 202 μmol, 2.80 equiv) in dichloromethane (500 μL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and then the cooling bath was removed. The reaction mixture was allowed to warm to 23 °C and then stirred for 1 d at 23 °C. The product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (3.0 mL), water (3.0 mL), and dichloromethane (10 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with dichloromethane (3 × 5.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (5.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 25% ethyl acetate–hexanes) to provide the silylene ether ketone 214 as a colorless oil (32.0 mg, 80% over two steps).

\[ R_f = 0.50 \text{ (33\% ethyl acetate–hexanes; PAA). } ^1H \text{ NMR (600 MHz, CDCl}_3\text{): } \delta 4.87 \text{ (dd, } H_4, J = 11.8, 6.4 \text{ Hz, } 1H), 4.85 - 4.79 \text{ (m, } H_5, 1H), 4.69 \text{ (d, } H_{12a}, J = 6.9 \text{ Hz, } 1H), 4.63 \text{ (d, } H_{12b}, \]
J = 7.0 Hz, 1H), 4.59 (d, H$_{10a}$, J = 7.2 Hz, 1H), 4.56 (d, H$_{10b}$, J = 7.1 Hz, 1H), 4.25 (s, H$_1$, 1H), 3.91 (d, H$_{9a}$, J = 9.3 Hz, 1H), 3.67 (s, H$_{14}$, 1H), 3.54 (d, H$_{9b}$, J = 9.2 Hz, 1H), 3.36 (s, H$_{11}$, 3H), 3.33 (s, H$_{13}$, 1H), 2.97 – 2.83 (m, H$_7$, 1H), 2.74 – 2.63 (m, H$_6$, 1H), 2.47 (s, H$_2$, 1H), 2.44 – 2.30 (m, H$_{3a,7b}$, 2H), 2.22 – 2.03 (m, H$_{3b,6b}$, 2H), 1.54 (s, H$_8$, 3H), 1.14 (s, H$_{16}$, 9H), 0.93 (s, H$_{15}$, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 202.9 (C), 170.2 (C), 97.1 (CH$_2$), 96.6 (CH$_2$), 87.5 (C), 86.6 (C), 81.4 (CH), 77.3 (CH), 74.8 (CH), 74.3 (CH$_2$), 63.7 (C), 55.5 (CH$_3$), 55.2 (CH$_3$), 51.7 (CH$_3$), 44.5 (CH), 37.7 (CH$_2$), 32.4 (CH$_2$), 31.6 (CH$_2$), 29.0 (3 × CH$_3$), 27.1 (3 × CH$_3$), 23.1 (C), 19.6 (C), 19.5 (CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 3014 (s), 2997 (m), 2975 (s), 2958 (m), 2808 (m), 2691 (m), 2262 (s), 2070 (m), 2004 (s), 1458 (s). HRMS-CI (m/z): [M + Na]$^+$ calculated for C$_{27}$H$_{46}$NaO$_{10}$Si, 581.2758; found, 581.2769. $[\alpha]_D^{20} = 12.2$ (c = 0.07, CHCl$_3$).
Synthesis of the enoxysilane ether 215:

A solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.00 M, 179 μL, 179 μmol, 5.00 equiv) was added dropwise via a syringe to a solution of ketone 214 (20.0 mg, 35.8 μmol, 1 equiv) in tetrahydrofuran (900 μL) at –78 °C. The resulting solution was stirred for 15 min at –78 °C. The reaction vessel was then placed in an ice bath. The mixture was stirred for 1 h at 0 °C. The reaction vessel was then cooled to –78 °C. Chlorotrimethylsilane (36.0 μL, 285 μmol, 8.00 equiv) was added dropwise via a syringe to the reaction mixture at –78 °C. The resulting solution was stirred for 15 min at –78 °C. The reaction vessel was then again placed in an ice bath and stirred at 0 °C for 30 min. The cold product mixture was diluted sequentially with ethyl acetate (10 mL), water (4.0 mL), and aqueous sodium bicarbonate solution (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 5.0 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (10.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% ethyl acetate–hexanes) to provide the enoxysilane 215 as a colorless oil (21.0 mg, 93%).
$R_f = 0.30$ (15% ethyl acetate–hexanes; PAA). $^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 5.13 – 5.00 (m, H$_{7,4}$, 2H), 4.92 – 4.84 (m, H$_5$, 1H), 4.72 (d, H$_{12a}$, $J = 6.8$ Hz, 1H), 4.66 (s, H$_2$, 1H), 4.63 (d, H$_{10a}$, $J = 6.2$ Hz, 1H), 4.59 (d, H$_{10b}$, $J = 6.2$ Hz, 1H), 4.42 (dd, H$_{12b,9a}$, $J = 15.3$, 8.0 Hz, 2H), 3.52 (d, H$_{9b,14}$, $J = 11.3$ Hz, 4H), 3.22 (s, H$_{11}$, 3H), 3.16 – 3.02 (m, H$_{13,6a}$, 4H), 2.82 – 2.70 (m, H$_{3a}$, 1H), 2.57 – 2.46 (m, H$_{2,6b}$, 2H), 2.28 – 2.14 (m, H$_{3b}$, 1H), 1.57 (s, H$_8$, 3H), 1.19 (s, H$_{16}$, 9H), 1.14 (s, H$_{15}$, 9H), 0.22 (s, H$_{17}$, 9H). $^{13}$C NMR (125 MHz, C$_6$D$_6$): $\delta$ 170.6 (C), 146.9 (C), 107.7 (CH), 96.8 (CH$_2$), 95.8 (CH$_2$), 85.5 (C), 85.0 (C), 82.6 (CH), 74.8 (CH), 74.6 (CH$_2$), 74.6 (CH), 60.7 (C), 55.0 (CH$_3$), 54.7 (CH$_3$), 51.2 (CH$_3$), 45.7 (CH), 33.2 (CH$_2$), 31.6 (CH$_2$), 29.2 (3 × CH$_3$), 27.6 (3 × CH$_3$), 23.2 (C), 19.9 (C), 19.5 (CH$_3$), 0.35 (3 × CH$_3$). IR (ATR-FTIR), cm$^{-1}$: 3015 (s), 2996 (m), 2975 (s), 2808 (m), 2691 (m), 2067 (m), 2005 (m), 1400 (s). $[\alpha]_{D}^{20} = -5.92$ (c = 0.10, CHCl$_3$).
2-Iodoxybenzoic acid (4.30 mg, 15.2 μmol, 1.20 equiv) was vigorously stirred for 30 min in dimethyl sulfoxide (150 μL) at 23 °C. After 30 min, enoxysilane 215 (8.00 mg, 12.7 μmol, 1 equiv) dissolved in dimethyl sulfoxide (150 μL) was added via a syringe to the homogeneous 2-iodoxybenzoic acid solution at 23 °C. The reaction vessel was then placed to an oil bath that had been preheated to 65 °C. The reaction mixture was stirred for 5 h at 65 °C. The product mixture was then cooled to 23 °C over 30 min. The cooled product mixture was subsequently diluted sequentially with ethyl acetate (8.0 mL), water (3.0 mL), and saturated aqueous sodium bicarbonate solution (3.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 × 8.0 mL). The organic layers were combined and the combined organic layers were washed with water (8.0 mL), and saturated aqueous sodium chloride solution (10.0 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes) to provide the unsaturated ketone 194 as a colorless oil (6.4 mg, 91%).
$^1$H and $^{13}$C NMR spectroscopic data for the unsaturated ketone 194 obtained in this way was in agreement with shown from the aldol–dehydration sequence.
Table S2. Comparison of $^1$H NMR data of natural and synthetic euonyminol octaacetate (116).

<table>
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<tr>
<th>position</th>
<th>natural (−)-116$^{23}$ [CDCl$_3$]</th>
<th>synthetic (−)-116 [500 MHz, CDCl$_3$]</th>
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</thead>
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<td>H-1</td>
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<td>5.58 (d, 3.7)</td>
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<td>H-2</td>
<td>5.26 (dd, 3.6, 2.8)</td>
<td>5.29 – 5.25 (m)</td>
</tr>
<tr>
<td>H-3</td>
<td>4.82 (d, 2.8)</td>
<td>4.82 (d, 2.5)</td>
</tr>
<tr>
<td>H-6</td>
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<td>6.77 (s)</td>
</tr>
<tr>
<td>H-7</td>
<td>2.32 (d, 3.6)</td>
<td>2.32 (d, 3.9)</td>
</tr>
<tr>
<td>H-8</td>
<td>5.48 (dd, 5.9, 3.6)</td>
<td>5.48 (dd, 5.8, 3.9)</td>
</tr>
<tr>
<td>H-9</td>
<td>5.34 (d, 5.9)</td>
<td>5.34 (d, 6.0)</td>
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<tr>
<td>H-12a</td>
<td>4.89 (d, 11.6)</td>
<td>4.89 (d, 11.6)</td>
</tr>
<tr>
<td>H-12b</td>
<td>3.94 (d, 11.6)</td>
<td>3.95 (d, 11.6)</td>
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<tr>
<td>H-13</td>
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</tr>
<tr>
<td>H-14</td>
<td>1.47 (s)</td>
<td>1.48 (s)</td>
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<tr>
<td>H-15a</td>
<td>5.25 (d, 13.3)</td>
<td>5.21 (d, 13.3)</td>
</tr>
<tr>
<td>H-15b</td>
<td>4.42 (d, 13.3)</td>
<td>4.42 (d, 13.3)</td>
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<tr>
<td>Ac-1</td>
<td>1.88 (s)</td>
<td>1.88 (s)</td>
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<td>Ac-2</td>
<td>2.12 (s)</td>
<td>2.12 (s)</td>
</tr>
<tr>
<td>Ac-3</td>
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<td>2.13 (s)</td>
</tr>
<tr>
<td>Ac-8</td>
<td>2.16 (s)</td>
<td>2.17 (s)</td>
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<tr>
<td>Ac-9</td>
<td>1.98 (s)</td>
<td>1.98 (s)</td>
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<td>Ac-14</td>
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<td>2.11 (s)</td>
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<tr>
<td>Ac-15</td>
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Table S3. Comparison of $^{13}$C NMR data of natural and synthetic euonyminol octaacetate (116).

![Euonyminol Octaacetate](image)

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<thead>
<tr>
<th>position</th>
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<th>synthetic (--) [500 MHz, CDCl$_3$]</th>
<th>position</th>
<th>natural$^{23}$ [CDCl$_3$]</th>
<th>synthetic (--) [500 MHz, CDCl$_3$]</th>
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</thead>
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<td>C-1</td>
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<td>Ac-1</td>
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<td>20.5</td>
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<td>C-2</td>
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<td>69.0</td>
<td>Ac-2</td>
<td>169.3</td>
<td>169.3</td>
</tr>
<tr>
<td>C-3</td>
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<td>75.8</td>
<td>Ac-3</td>
<td>20.8</td>
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<td>Ac-4</td>
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<td>92.9</td>
<td>Ac-5</td>
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<td>20.9</td>
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<td>C-6</td>
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<td>73.9</td>
<td>Ac-6</td>
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<td>169.5</td>
</tr>
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<td>50.7</td>
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<td>21.0</td>
</tr>
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<td>Ac-8</td>
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<td>70.9</td>
<td>Ac-9</td>
<td>20.9</td>
<td>21.0</td>
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<td>51.9</td>
<td>Ac-10</td>
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<td>170.1</td>
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<td>C-11</td>
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<td>84.1</td>
<td>Ac-11</td>
<td>20.5</td>
<td>20.5</td>
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<td>69.5</td>
<td>Ac-12</td>
<td>168.9</td>
<td>169.0</td>
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<td>Ac-13</td>
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<td>21.5</td>
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<td>23.3</td>
<td>Ac-14</td>
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<td>60.3</td>
<td>Ac-15</td>
<td>21.2</td>
<td>21.3</td>
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Table S4. Comparison of \(^1\)H NMR data of synthetic euonyminol (99).

<table>
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<tr>
<th>position</th>
<th>synthetic (±)-99(^{25}) (White and co-workers) [D(_2)O](^a)</th>
<th>synthetic (−)-99 [500 MHz, D(_2)O]</th>
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</thead>
<tbody>
<tr>
<td>H-1</td>
<td>4.30 (m)</td>
<td>4.33 (d, 3.5)</td>
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<tr>
<td>H-2</td>
<td>4.00 (m)</td>
<td>4.03 (t, 3.2)</td>
</tr>
<tr>
<td>H-3</td>
<td>3.65 (d, 4)</td>
<td>3.66 (d, 2.9)</td>
</tr>
<tr>
<td>H-6</td>
<td>5.10 (s)</td>
<td>5.22 (s)</td>
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<td>H-7</td>
<td>2.30 (s)</td>
<td>2.39 (d, 4.0)</td>
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<td>H-8</td>
<td>4.30 (m)</td>
<td>4.21 (dd, 5.3, 4.1)</td>
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<td>H-9</td>
<td>4.30 (m)</td>
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<td>H-12(_a)</td>
<td>3.95 (m)</td>
<td>3.92 (d, 11.4)</td>
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<td>H-12(_b)</td>
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<td>H-13</td>
<td>1.36 (s)</td>
<td>1.44 (s)</td>
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<td>H-14</td>
<td>1.58 (s)</td>
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<tr>
<td>H-15(_a)</td>
<td>4.30 (m)</td>
<td>4.43 (d, 13.1)</td>
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<tr>
<td>H-15(_b)</td>
<td>4.09 (d, 11)</td>
<td>4.09 (d, 13.1)</td>
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</table>

\(^a\)\(^{13}\)C NMR data for (±)-99 were not reported.
2.7 Bibliography.


Appendix A: Catalogue of Crystallographic Data.
Crystallographic data for the cyclopropyl iodide 37.

Single crystals of compound 37 suitable for the X-ray crystal structure analysis were obtained by the slow evaporation of a solution of compound 37 in n-pentane/diethyl ether (v/v = 10:1) at room temperature. Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structure of 007-15166. The diffraction images were processed and scaled using the Rigaku CrystalClear software (CrystalClear and CrystalStructure; Rigaku/MSC: The Woodlands, TX, 2005). The structure was solved with SHELXT and was refined against F^2 on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The full numbering scheme of compound 007-15166 can be found in the Supporting Information. Full details of the X-ray structure determination are in the CIF included as Supporting Information. CCDC number 1992798 (007-15166) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
Figure S1. The complete numbering scheme of cyclopropane 37 with 50% thermal ellipsoid probability levels. The hydrogen atoms have been omitted for clarity.

Table S5. X-ray crystal data and structure refinement for compound 37.

<table>
<thead>
<tr>
<th>Identification code</th>
<th>007-15166</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{13}H_{19}IO_{3}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>350.18</td>
</tr>
<tr>
<td>Temperature</td>
<td>93(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54178 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2_1/n</td>
</tr>
</tbody>
</table>
Unit cell dimensions

\[ a = 24.906(17) \, \text{Å} \quad \alpha = 90^\circ. \]
\[ b = 6.3095(4) \, \text{Å} \quad \beta = 110.855(2)^\circ. \]
\[ c = 28.910(2) \, \text{Å} \quad \gamma = 90^\circ. \]

Volume: 4244.5(5) Å\(^3\)

Z: 12

Density (calculated): 1.644 Mg/m\(^3\)

Absorption coefficient: 17.753 mm\(^{-1}\)

F(000): 2088

Crystal size: 0.200 x 0.080 x 0.020 mm\(^3\)

Crystal color and habit: Colorless Needel

Diffractometer: Rigaku Saturn 944+ CCD

Theta range for data collection: 3.272 to 66.592°.

Index ranges: -29\(\leq h \leq 28, \quad -7\leq k \leq 7, \quad -34\leq l \leq 34\)

Reflections collected: 131210

Independent reflections: 7415 [R(int) = 0.1267]

Observed reflections (I > 2σ(I)): 6646

Completeness to theta = 66.592°: 98.5 %

Absorption correction: Semi-empirical from equivalents

Max. and min. transmission: 0.718 and 0.384

Solution method: SHELXT-2014/5 (Sheldrick, 2014)

Refinement method: SHELXL-2014/7 (Sheldrick, 2014)

Data / restraints / parameters: 7415 / 0 / 472

Goodness-of-fit on F\(^2\): 1.019
Final R indices [$I>2\sigma(I)$]  
R1 = 0.0474, wR2 = 0.1220

R indices (all data)  
R1 = 0.0519, wR2 = 0.1262

Largest diff. peak and hole  
1.079 and -1.984 eÅ$^{-3}$
Crystallographic data for the vinyl iodide 41.

Single crystals of compound 41 suitable for the X-ray crystal structure analysis were obtained by the slow evaporation of a solution of compound 41 in n-pentane/diethyl ether (v/v = 20:1) at room temperature. Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structure of 007-17082. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against F² on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The only exceptions are H1 and H5, which were found and semi-freely refined with distance restraints of 0.83(2), as suggested by the difference map. The full numbering scheme of compound 007-17082 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 1992803 (007-17082) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
**Figure S2.** The complete numbering scheme of the vinyl iodine 41 with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity. Dashed lines highlight hydrogen bond interactions.

**Table S6.** X-ray crystal data and structure refinement for compound 41.

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<td>Wavelength</td>
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<td>Monoclinic</td>
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<td>Space group</td>
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<td>Property</td>
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<tr>
<td>----------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>b</td>
<td>11.1326(3) Å</td>
</tr>
<tr>
<td>β</td>
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<td>c</td>
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<td>γ</td>
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<td>4262.75(18) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>8</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.478 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>11.978 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>1936</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.100 x 0.100 x 0.020 mm³</td>
</tr>
<tr>
<td>Crystal color and habit</td>
<td>Colorless Plate</td>
</tr>
<tr>
<td>Diffractometer</td>
<td>Rigaku Saturn 944+ CCD</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>2.726 to 66.598°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-20&lt;=h&lt;=20, -13&lt;=k&lt;=12, -28&lt;=l&lt;=28</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>151643</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>7514 [R(int) = 0.0881]</td>
</tr>
<tr>
<td>Observed reflections (I &gt; 2sigma(I))</td>
<td>6222</td>
</tr>
<tr>
<td>Completeness to theta = 66.598°</td>
<td>99.8 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>1.00000 and 0.59010</td>
</tr>
<tr>
<td>Solution method</td>
<td>SHELXT-2014/5 (Sheldrick, 2014)</td>
</tr>
<tr>
<td>Refinement method</td>
<td>SHELXL-2014/7 (Sheldrick, 2014)</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>7514 / 2 / 489</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.057</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0381, wR2 = 0.0832</td>
</tr>
</tbody>
</table>
R indices (all data)  \[ R1 = 0.0514, \ wR2 = 0.0892 \]

Largest diff. peak and hole  \[ 0.831 \text{ and } -1.078 \text{ e.Å}^{-3} \]
Crystallographic data for the cyclobutanol 51.

Single crystals of compound 51 suitable for the X-ray crystal structure analysis were obtained by the slow evaporation of a solution of compound 51 in n-hexanes/diethyl ether (v/v = 4:1) at room temperature. Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structure of 007a-18078. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against F² on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The only exception are the hydrogen atoms associated with oxygen atoms. These sites were found in the difference map and freely refined (see Table 7). The full numbering scheme of compound 007a-18078 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 1992800 (007a-18078) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via [www.ccdc.cam.ac.uk/data_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
Figure S3. The complete numbering scheme of compound 51 with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

Table S7. X-ray crystal data and structure refinement for compound 51.

<table>
<thead>
<tr>
<th>Identification code</th>
<th>007a-18078</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C23 H36 O5</td>
</tr>
<tr>
<td>Formula weight</td>
<td>392.52</td>
</tr>
<tr>
<td>Temperature</td>
<td>93(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54184 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>Pca21</td>
</tr>
</tbody>
</table>
Unit cell dimensions  
\[ a = 19.7853(3) \, \text{Å} \quad \alpha = 90^\circ. \]
\[ b = 22.1644(4) \, \text{Å} \quad \beta = 90^\circ. \]
\[ c = 10.4000(2) \, \text{Å} \quad \gamma = 90^\circ. \]

Volume  
4560.70(14) Å³

\[ Z = 8 \]

Density (calculated)  
1.143 Mg/m³

Absorption coefficient  
0.633 mm⁻¹

\[ F(000) = 1712 \]

Crystal size  
0.100 x 0.100 x 0.070 mm³

Crystal color and habit  
Colorless Block

Diffractometer  
Rigaku Saturn 944+ CCD

Theta range for data collection  
1.993 to 66.599°.

Index ranges  
-23\leq h \leq 23, -26\leq k \leq 26, -12\leq l \leq 12

Reflections collected  
164334

Independent reflections  
8074 [R(int) = 0.0727]

Observed reflections (I > 2\sigma(I))  
7400

Completeness to theta = 66.599°  
100.0 %

Absorption correction  
Semi-empirical from equivalents

Max. and min. transmission  
1.00000 and 0.65736

Solution method  
SHELXT-2014/5 (Sheldrick, 2014)

Refinement method  
SHELXL-2014/7 (Sheldrick, 2014)

Data / restraints / parameters  
8074 / 1 / 527

Goodness-of-fit on F²  
1.035
<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final R indices [I&gt;2(\sigma(I))]</td>
<td>(R1 = 0.0318, wR2 = 0.0736)</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>(R1 = 0.0368, wR2 = 0.0761)</td>
</tr>
<tr>
<td>Absolute structure parameter</td>
<td>0.07(6)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.218 and -0.120 e.Å(^{-3})</td>
</tr>
</tbody>
</table>
Crystalllographic data for the geminal dimethyl analog (−)-65.

Crystals of compound (−)-65 for the X-ray crystal structure analysis were obtained by the slow evaporation of a solution of compound (−)-65 in ethyl acetate/methanol (v/v = 5:1) at room temperature. Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structure of 007b-20019. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against F² on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The only exceptions are H1, H3, and H5 which were found in the difference map and freely refined. The full numbering scheme of compound 007b-20019 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 1992801 (007b-20019) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
The crystal used for the diffraction experiment was small and only had light atoms present which made measuring any differences from anomalous dispersion in Bijvoet pairs difficult. The output from the analysis performed by SHELXL is copied below.

Flack x = -0.476(533) by classical fit to all intensities

-0.876(401) from 791 selected quotients (Parsons' method)

However, a Bayesian statistical analysis of the Bijvoet pairs suggest the model reported here, (–)-65 with stereocenters S,S,S,S, is the most likely model, with only an exceedingly small probability of a model with the opposite chirality or a racemic twin. This analysis was calculated with the PLATON software package (A.L.Spek, Acta Cryst. 2009, D65, 148-155.).

**S,S,S,S model**

*Space Group*  
$P2_1$

Wavelength 1.54184

Flack x .... -0.9(4)

Parsons z .. -0.5(2)

*Bijvoet Pairs* 1310

Coverage ... 98
DiffCalcMax. 9.24
Outlier Crit 18.48

**Student-T Prob. Plot**

Sample Size. 1300
Corr. Coeff. 0.999
Intercept .. 0.291
Slope ...... 1.222

**Bayesian Statistics**

Student_T Nu 39
Select Pairs 1310
Theta_Min .. 7.94
Theta_Max .. 66.55
P2(true).... 1.000
P3(true).... 0.990
P3(racemic-twin) 0.010
P3(false) .. 0.6E-05
G ........... 2.1385
G (su) ..... 0.5973
Hooft y .... -0.6(3)
**R.R.R.R model**

*Space Group*  \(P2_1\)

Wavelength  1.54184

Flack x ....  1.9(4)

Parsons z ..  1.5(2)

Bijvoet Pairs  1310

Coverage ...  98

DiffCalcMax.  9.25

Outlier Crit  18.50

*Student-T Prob. Plot*

Sample Size.  1300

Corr. Coeff.  0.999

Intercept ..  0.291

Slope ......  1.222

*Bayesian Statistics*
Select Pairs  1310

Theta_Min ..  7.94
Theta_Max ..  66.55
P2(true)....  0.7E-05
P3(true)....  0.7E-05
P3(racemic -twin)  0.010
P3(false) ..  0.990
G ............ -2.1426
G (su) .....  0.5989
Hooft y ....  1.6(3)

Figure S4. The complete numbering scheme of the geminal dimethyl analog (−)-65 with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.
<table>
<thead>
<tr>
<th><strong>Table S8.</strong> X-ray crystal data and structure refinement for compound (–)-65.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Identification code</strong></td>
</tr>
<tr>
<td><strong>Empirical formula</strong></td>
</tr>
<tr>
<td><strong>Formula weight</strong></td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
</tr>
<tr>
<td><strong>Wavelength</strong></td>
</tr>
<tr>
<td><strong>Crystal system</strong></td>
</tr>
<tr>
<td><strong>Space group</strong></td>
</tr>
<tr>
<td><strong>Unit cell dimensions</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Volume</strong></td>
</tr>
<tr>
<td><strong>Z</strong></td>
</tr>
<tr>
<td><strong>Density (calculated)</strong></td>
</tr>
<tr>
<td><strong>Absorption coefficient</strong></td>
</tr>
<tr>
<td><strong>F(000)</strong></td>
</tr>
<tr>
<td><strong>Crystal size</strong></td>
</tr>
<tr>
<td><strong>Crystal color and habit</strong></td>
</tr>
<tr>
<td><strong>Diffractometer</strong></td>
</tr>
<tr>
<td><strong>Theta range for data collection</strong></td>
</tr>
<tr>
<td><strong>Index ranges</strong></td>
</tr>
<tr>
<td><strong>Reflections collected</strong></td>
</tr>
</tbody>
</table>
Independent reflections 2906 [R(int) = 0.1509]
Observed reflections (I > 2sigma(I)) 2243
Completeness to theta = 66.548° 98.3 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 1.00000 and 0.32765
Solution method SHELXT-2014/5 (Sheldrick, 2014)
Refinement method SHELXL-2014/7 (Sheldrick, 2014)
Data / restraints / parameters 2906 / 1 / 232
Goodness-of-fit on F² 1.030
Final R indices [I>2sigma(I)] R1 = 0.0575, wR2 = 0.1260
R indices (all data) R1 = 0.0824, wR2 = 0.1414
Absolute structure parameter -0.9(4)
Largest diff. peak and hole 0.168 and -0.216 e.Å⁻³
Crystallographic data for the cyclic ether 141.

Single crystals of the cyclic ether 141 suitable for X-ray crystal analysis were obtained by the slow evaporation of a solution of 141 in n-pentane–ethyl acetate (6:1 v/v) at 23 °C. Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structure of 007c-20068. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against F^2 on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl and alcohol groups). The full numbering scheme of compound 007c-20068 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 2047849 (007b-20068) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
**Figure S5.** The complete numbering scheme of cyclic ether 141 with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

**Table S9.** Crystal data and structure refinement for the cyclic ether 141:

<table>
<thead>
<tr>
<th>Identification code</th>
<th>007b-20068</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C68 H112 O16 Si4</td>
</tr>
<tr>
<td>Formula weight</td>
<td>1297.93</td>
</tr>
<tr>
<td>Temperature</td>
<td>93(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54184 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2₁2₁2₁</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 6.05410(10) Å  (\alpha = 90^\circ).</td>
</tr>
</tbody>
</table>
b = 14.1336(3) Å  \quad \beta = 90^\circ.

c = 21.0131(3) Å  \quad \gamma = 90^\circ.

Volume 1798.01(5) Å\(^3\)

Z 1

Density (calculated) 1.199 Mg/m\(^3\)

Absorption coefficient 1.275 mm\(^{-1}\)

F(000) 704

Crystal size 0.100 x 0.080 x 0.060 mm\(^3\)

Crystal color and habit Colorless Block

Diffractometer Rigaku Saturn 944+ CCD

Theta range for data collection 3.769 to 66.590°.

Index ranges \(-7\leq h\leq 7, -16\leq k\leq 16, -25\leq l\leq 25\)

Reflections collected 62296

Independent reflections 3166 [R(int) = 0.0686]

Observed reflections (I > 2\sigma(I)) 2963

Completeness to theta = 66.590° 100.0 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 1.00000 and 0.51229

Solution method SHELXT-2014/5 (Sheldrick, 2014)

Refinement method SHELXL-2014/7 (Sheldrick, 2014)

Data / restraints / parameters 3166 / 0 / 206

Goodness-of-fit on F\(^2\) 1.040

Final R indices [I>2\sigma(I)] R1 = 0.0298, wR2 = 0.0694
<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>R indices (all data)</td>
<td>$R_1 = 0.0336, \text{wR}^2 = 0.0711$</td>
</tr>
<tr>
<td>Absolute structure parameter</td>
<td>$-0.023(12)$</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>$0.154$ and $-0.250$ eÅ$^{-3}$</td>
</tr>
</tbody>
</table>
Crystallographic data for the vinylogous carbonate 147.

Single crystals of the vinylogous carbonate compound 147 suitable for X-ray analysis were obtained by the slow evaporation of a solution of compound 147 in n-pentane–ethyl acetate (10:1 v/v) at 23 °C. Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structure of 007b-20073. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against F² on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The full numbering scheme of compound 007b-20073 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 2047844 (007b-20073) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
Figure S6. The complete numbering the vinylogous carbonate compound 147 with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

Table S10. Crystal data and structure refinement for the vinylogous carbonate 147:

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>007b-20073</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C23 H33 O8 Si</td>
</tr>
<tr>
<td>Formula weight</td>
<td>465.58</td>
</tr>
<tr>
<td>Temperature</td>
<td>93(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54184 Å</td>
</tr>
</tbody>
</table>
Crystal system
Monoclinic

Space group
P2₁

Unit cell dimensions
\( a = 9.19220(10) \text{ Å} \), \( \alpha = 90° \).
\( b = 11.22070(10) \text{ Å} \), \( \beta = 100.280(10)° \).
\( c = 11.73690(10) \text{ Å} \), \( \gamma = 90° \).

Volume
1191.15(2) Å³

Z
2

Density (calculated)
1.298 Mg/m³

Absorption coefficient
1.258 mm⁻¹

F(000)
498

Crystal size
0.200 x 0.200 x 0.200 mm³

Crystal color and habit
Colorless Block

Diffractometer
Rigaku Saturn 944+ CCD

Theta range for data collection
3.828 to 66.543°.

Index ranges
\(-10 \leq h \leq 10, -13 \leq k \leq 12, -13 \leq l \leq 13\)

Reflections collected
41790

Independent reflections
4112 [R(int) = 0.0318]

Observed reflections (I > 2σ(I))
4009

Completeness to theta = 66.543°
100.0 %

Absorption correction
Semi-empirical from equivalents

Max. and min. transmission
1.00000 and 0.80843

Solution method
SHELXT-2014/5 (Sheldrick, 2014)

Refinement method
SHELXL-2014/7 (Sheldrick, 2014)
<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data / restraints / parameters</td>
<td>4112 / 1 / 296</td>
</tr>
<tr>
<td>Goodness-of-fit on $F^2$</td>
<td>1.084</td>
</tr>
<tr>
<td>Final R indices [$I&gt;2\sigma(I)$]</td>
<td>$R_1 = 0.0294$, $wR_2 = 0.0810$</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>$R_1 = 0.0304$, $wR_2 = 0.0818$</td>
</tr>
<tr>
<td>Absolute structure parameter</td>
<td>0.000(7)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.502 and -0.458 eÅ$^{-3}$</td>
</tr>
</tbody>
</table>
Crystallographic data for the α-ketolactone 169.

Single crystals of the α-ketolactone 169 suitable for X-ray analysis were obtained by the slow evaporation of a solution of compound 169 in n-pentane–ethyl acetate (4:1 v/v) at 23 °C. Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structure of 007b-19082. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against F^2 on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The full numbering scheme of compound 007b-19082 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 2047847 (007b-19082) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
**Figure S7.** The complete numbering scheme of \(\alpha\)-ketolactone 169 with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

**Table S11.** Crystal data and structure refinement for the \(\alpha\)-ketolactone 169:

<table>
<thead>
<tr>
<th>Identification code</th>
<th>007b-19082</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C23 H33 O10 Si</td>
</tr>
<tr>
<td>Formula weight</td>
<td>497.58</td>
</tr>
<tr>
<td>Temperature</td>
<td>93(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54184 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>(P2_12_12_1)</td>
</tr>
<tr>
<td>Property</td>
<td>Value</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 10.13664(18) Å, α = 90°</td>
</tr>
<tr>
<td></td>
<td>b = 12.97562(19) Å, β = 90°</td>
</tr>
<tr>
<td></td>
<td>c = 19.3014(3) Å, γ = 90°</td>
</tr>
<tr>
<td>Volume</td>
<td>2538.69(7) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.302 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>1.276 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>1060</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.200 x 0.200 x 0.020 mm³</td>
</tr>
<tr>
<td>Crystal color and habit</td>
<td>colorless plate</td>
</tr>
<tr>
<td>Diffractometer</td>
<td>Rigaku Saturn 944+ CCD</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>4.105 to 66.753°.</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-12 ≤ h ≤ 12, -15 ≤ k ≤ 15, -22 ≤ l ≤ 22</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>89551</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>4500 [R(int) = 0.0886]</td>
</tr>
<tr>
<td>Observed reflections (I &gt; 2σ(I))</td>
<td>4410</td>
</tr>
<tr>
<td>Completeness to theta = 66.753°</td>
<td>99.9 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>1.0000 and 0.41076</td>
</tr>
<tr>
<td>Solution method</td>
<td>SHELXT-2014/5 (Sheldrick, 2014)</td>
</tr>
<tr>
<td>Refinement method</td>
<td>SHELXL-2014/7 (Sheldrick, 2014)</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>4500 / 0 / 314</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>1.037</td>
</tr>
</tbody>
</table>
Final R indices [I>2\sigma(I)] \hspace{1cm} R1 = 0.0278, wR2 = 0.0745
R indices (all data) \hspace{1cm} R1 = 0.0285, wR2 = 0.0751
Absolute structure parameter \hspace{1cm} 0.000(9)
Largest diff. peak and hole \hspace{1cm} 0.469 and -0.356 e Å⁻³
Crystallographic data for the epoxide 196.

Single crystals of the epoxide 196 suitable for the X-ray analysis were obtained by the slow evaporation of a solution of compound 196 in n-pentane–ethyl acetate (4:1 v/v) at 23 °C. Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structure of 007a-20027. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against F² on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The full numbering scheme of compound 007a-20027 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 2047848 (007a-20027) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
**Figure S8.** The complete numbering scheme of the epoxide 196 with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

**Table S12.** Crystal data and structure refinement for the epoxide 196:

<table>
<thead>
<tr>
<th>Identification code</th>
<th>007a-20027</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C28 H48 O11 Si</td>
</tr>
<tr>
<td>Formula weight</td>
<td>588.75</td>
</tr>
<tr>
<td>Temperature</td>
<td>93(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54184 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2₁</td>
</tr>
</tbody>
</table>
Unit cell dimensions
\[ a = 10.7097(3) \text{ Å} \quad \alpha = 90^\circ. \]
\[ b = 9.3455(3) \text{ Å} \quad \beta = 90.187(2)^\circ. \]
\[ c = 14.9090(4) \text{ Å} \quad \gamma = 90^\circ. \]

Volume \[ 1492.20(8) \text{ Å}^3 \]

\[ Z \]
2

Density (calculated) \[ 1.310 \text{ Mg/m}^3 \]

Absorption coefficient \[ 1.188 \text{ mm}^{-1} \]

\[ F(000) \]
636

Crystal size \[ 0.200 \times 0.020 \times 0.020 \text{ mm}^3 \]

Crystal color and habit Colorless Needle

Diffractometer Rigaku Saturn 944+ CCD

Theta range for data collection \[ 2.964 \text{ to } 66.595^\circ. \]

Index ranges \[-12 \leq h \leq 12, \quad -11 \leq k \leq 10, \quad -17 \leq l \leq 17 \]

Reflections collected \[ 53607 \]

Independent reflections \[ 5217 \quad [R(\text{int}) = 0.1009] \]

Observed reflections (I > 2\sigma(I)) \[ 4686 \]

Completeness to theta = 66.595° \[ 100.0 \% \]

Absorption correction Semi-empirical from equivalents

Max. and min. transmission \[ 1.00000 \text{ and } 0.75758 \]

Solution method SHELXT-2014/5 (Sheldrick, 2014)

Refinement method SHELXL-2014/7 (Sheldrick, 2014)

Data / restraints / parameters \[ 5217 / 1 / 373 \]

Goodness-of-fit on \( F^2 \) \[ 1.062 \]
<table>
<thead>
<tr>
<th>Description</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final R indices [I&gt;2\sigma(I)]</td>
<td>R1 = 0.0429, wR2 = 0.1067</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0493, wR2 = 0.1108</td>
</tr>
<tr>
<td>Absolute structure parameter</td>
<td>-0.03(2)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.165 and -0.356 e.Å⁻³</td>
</tr>
</tbody>
</table>
Crystallographic data for the lactone 197.

Single crystals of the lactone 197 suitable for X-ray analysis were obtained by the slow evaporation of a solution of compound 197 in n-pentane–ethyl acetate (3:1 v/v) at 23 °C. Low-temperature diffraction data (ω-scans) were collected on a Rigaku MicroMax-007HF diffractometer coupled to a Saturn994+ CCD detector with Cu Kα (λ = 1.54178 Å) for the structure of 007a-20025. The diffraction images were processed and scaled using Rigaku Oxford Diffraction software (CrysAlisPro; Rigaku OD: The Woodlands, TX, 2015). The structure was solved with SHELXT and was refined against F² on all data by full-matrix least squares with SHELXL (Sheldrick, G. M. Acta Cryst. 2008, A64, 112–122). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of all hydrogen atoms were fixed to 1.2 times the U value of the atoms to which they are linked (1.5 times for methyl groups). The full numbering scheme of compound 007a-20025 can be found in the full details of the X-ray structure determination (CIF), which is included as Supporting Information. CCDC number 2047845 (007a-20025) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
**Figure S9.** The complete numbering of one of the lactone 197 with 50% thermal ellipsoid probability levels. The hydrogen atoms are shown as circles for clarity.

**Table S13.** Crystal data and structure refinement for the lactone 197:

<table>
<thead>
<tr>
<th>Identification code</th>
<th>007a-20025</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C30 H50 O11 Si</td>
</tr>
<tr>
<td>Formula weight</td>
<td>614.79</td>
</tr>
<tr>
<td>Temperature</td>
<td>93(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54184 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2₁2₁2₁</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 11.95000(10) Å  ( \alpha = 90^\circ ).</td>
</tr>
</tbody>
</table>
b = 16.74580(10) Å  \quad \beta = 90^\circ.

c = 31.7086(2) Å  \quad \gamma = 90^\circ.

Volume 6345.28(8) Å\(^3\)

Z 8

Density (calculated) 1.287 Mg/m\(^3\)

Absorption coefficient 1.140 mm\(^-1\)

F(000) 2656

Crystal size 0.120 x 0.080 x 0.050 mm\(^3\)

Crystal color and habit Colorless Plate

Diffractometer Rigaku Saturn 944+ CCD

Theta range for data collection 2.787 to 66.593°.

Index ranges -14<=h<=14, -19<=k<=19, -37<=l<=37

Reflections collected 179290

Independent reflections 11215 [R(int) = 0.0886]

Observed reflections (I > 2sigma(I)) 10633

Completeness to theta = 66.593° 100.0 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 1.00000 and 0.60386

Solution method SHELXT-2014/5 (Sheldrick, 2014)

Refinement method SHELXL-2014/7 (Sheldrick, 2014)

Data / restraints / parameters 11215 / 0 / 781

Goodness-of-fit on F\(^2\) 1.014

Final R indices [I>2sigma(I)] R1 = 0.0329, wR2 = 0.0859
<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0355, wR2 = 0.0878</td>
</tr>
<tr>
<td>Absolute structure parameter</td>
<td>-0.002(8)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.302 and -0.184 e Å⁻³</td>
</tr>
</tbody>
</table>
Appendix B: Catalogue of Spectroscopic Data.
$^{1}$H NMR, CDCl$_3$, 500 MHz

35
$^{13}$C NMR, CDC$_3$, 125 MHz
$^1$H NMR, CDCl$_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz

CHCl$_3$
$^1$H NMR, CDCl$_3$, 600 MHz

CHCl$_3$
37
$^{1}H$ NMR, CDCl$_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz

$\text{CHCl}_3$
$^1$H NMR, CDCl$_3$, 500 MHz

H NMR, CDCl$_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz

1H NMR, DMSO-d$_6$, 400 MHz

$^1$H NMR, CDCl$_3$, 100 MHz

$^1$H NMR, CDCl$_3$, 500 MHz
$^1$H NMR, CDCl$_3$, 600 MHz

43
$^{1}H$ NMR, CDCl$_3$, 600 MHz
$^{13}$C NMR, CDCl$_3$, 150 MHz

CHCl$_3$
$^{13}$C NMR, CDCl$_3$, 150 MHz
$^1$H NMR, CDCl$_3$, 600 MHz

51

CHCl$_3$

$\text{A (d)}$
4.61

$\text{B (d)}$
4.51

$\text{C (dd)}$
0.74

$\text{D (dd)}$
0.55
$^{13}$C NMR, CDCl$_3$, 150 MHz

CHCl$_3$
$^1$H NMR, CDCl$_3$, 600 MHz
$^{13}$C NMR, CDCl$_3$, 150 MHz
$^1$H NMR, DMSO-$d_6$, 600 MHz
$^{13}$C NMR, DMSO-$d_6$, 150 MHz

![NMR spectrum](image)

DMSO-$d_6$
$^1$H NMR, CDCl$_3$, 600 MHz

CHCl$_3$

A (dd) 4.67  B (dd) 4.14  C (t) 3.15  D (td) 2.07  G (dd) 1.23
\[ ^{13}C \text{ NMR, CDCl}_3, 150 \text{ MHz} \]

Chemical shift values: 207.3, 203.5, 172.7, 161.4, 152.7, 81.5, 80.4, 89.7, 84.5, 85.0, 58.6, 22.6, 21.5, 20.7, 29.1, 27.1, 27.8, 22.6, 22.8, 21.5, 21.7, 11.7

Chemical: CHCl$_3$
$^{1}$H NMR, CDCl$_3$, 600 MHz

1H NMR, CDCl$_3$, 600 MHz
$^{13}$C NMR, CDCl$_3$, 150 MHz

[Chemical structure image]

CHCl$_3$
$^1$H NMR, CDCl$_3$, 500 MHz
$^1$H NMR, CDCl$_3$, 125 MHz

$^1$C NMR, CDCl$_3$, 125 MHz
$^1$H NMR, CDCl$_3$, 600 MHz
$^{13}$C NMR, CDCl$_3$, 150 MHz
$\text{H NMR, CDCl}_3, 600\text{ MHz}$
$^{13}$C NMR, CDCl$_3$, 150 MHz
$^{13}$C NMR, CDCl₃, 150 MHz

1H NMR, CDCl₃, 300 MHz

CHCl₃
$^1$H NMR, CDCl$_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz
$^1$H NMR, CDCl$_3$, 600 MHz

A (dd) 4.49
B (dd) 4.25
C (m) 4.12
D (t) 3.41
E (td) 2.49

$^3$CHCl$_3$
$^{13}$C NMR, CDCl$_3$, 150 MHz
$^{1}$H NMR, CDCl$_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz
$^1$H NMR, CDCl$_3$, 600 MHz

CHCl$_3$
$^{13}$C NMR, CDCl$_3$, 150 MHz

$\delta$ ppm

0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 210 220 230
\[ ^1H \text{ NMR, CDCl}_3, 600 \text{ MHz} \]

A (dd) 5.29
B (dd) 3.57

\[ \text{CHCl}_3 \]
$^1$H NMR, CDCl$_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz

CHCl$_3$

13C NMR, CDCl$_3$, 125 MHz

1H-19

1H-18

1H-17

1H-16

1H-15

1H-14

1H-13

1H-12

1H-11

1H-10

1H-9

1H-8

1H-7

1H-6

1H-5

1H-4

1H-3

1H-2

1H-1

1H-0

1H-0

1H-0

1H-0

1H-0

1H-0

1H-0

1H-0

1H-0

1H-0

1H-0

1H-0

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1H-0

1H-0

1H-0

1H-0

1H-0
\[ \text{H NMR, CDCl}_3, 500 \text{ MHz} \]
$^{13}$C NMR, CDCl$_3$, 125 MHz

77
$^1H$ NMR, CD$_2$OD, 600 MHz
$^{1}H$ NMR, CDCl$_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz
$^1$H NMR, DMSO-$d_6$, 400 MHz
$^{1}H$ NMR, CDCl$_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz
$^1$H NMR, CDCl$_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz
405
$^{13}$C NMR, CDCl$_3$, 125 MHz

[Chemical structure image with peaks labeled]
$^1$H NMR, C$_6$D$_6$, 500 MHz
^1H NMR, CDCl₃, 600 MHz
$^{13}$C NMR, CDCl$_3$, 150 MHz

-102.82
-176.82
145.74
144.67
134.92
127.78
71.90
74.15
63.10
43.95
38.84
34.90
31.90
30.90
19.97
17.02
15.60
13.11
2.67
-1.81

CHCl$_3$
\( \text{CH}_3 \)

\( \text{CH}_2 \text{OH} \)

\( \text{CH}_3 \text{OH} \)

\( \text{CH}_3 \text{COO}^{-} \)

\( \text{HO} \)

\( \text{H} \)

\( \text{N} \)

\( \text{M} \)

\( \text{H} \)

\( \text{NMR, CDCl}_3, 400 \text{ MHz} \)

\( (+)-\text{myrocin G (8)} \)
$^{13}$C NMR, CD$_2$OD, 100 MHz

\[ \text{(-)-myrocin G (8)} \]
$^{13}$C NMR, CDCl$_3$, 150 MHz
$^{13}$C NMR, CDCl$_3$, 150 MHz

CHCl$_3$
1H NMR, CDCl₃, 500 MHz
$^1$H NMR, CD$_2$OD, 500 MHz
$^13$C NMR, CD$_2$OD, 125 MHz
$^1$H NMR, CDCl$_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz

![Chemical structure image]

CHCl$_3$
1H NMR, CDCl₃, 600 MHz
$^{13}$C NMR, CDCl$_3$, 150 MHz
$^{1}H$ NMR, CDCl$_3$, 600 MHz
$^{13}$C NMR, CDCl$_3$, 150 MHz

CHCl$_3$
$\text{CHCl}_3$

$\text{OCH}_3$

$\text{TMS}$

$\text{OCH}_3$

$\text{OH}$

$\text{H NMR, CDCl}_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz
$^{1}H$ NMR, CDCl$_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz
$^1$H NMR, CDCl$_3$, 400 MHz
$\text{CHCl}_3$
$^{13}$C NMR, CDCl$_3$, 100 MHz

CHCl$_3$
$^{1}H$ NMR, CDCl$_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 150 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz
$\text{CHCl}_3$

$\text{C NMR, CDCl}_3, 125 \text{ MHz}$
$^{1}$H NMR, CDCl$_3$, 500 MHz
$\text{CHCl}_3$
$^{1} \text{H NMR, CDCl}_3$, 400 MHz

CHCl$_3$
$^{13}$C NMR, CDCl$_3$, 100 MHz
\textsuperscript{1}H NMR, CDCl$_3$, 400 MHz
$^{13}$C NMR, CDCl$_3$, 100 MHz
$^{13}$C NMR, CD$_3$OD, 100 MHz

$^{13}$C NMR, CD$_3$OD, 100 MHz

C$_9$H$_{12}$D
$^{1}H$ NMR, CDCl$_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz
$^1$H NMR, CDCl$_3$, 600 MHz
$^1\text{H NMR, CDCl}_3, 500 \text{ MHz}$
$^{13}$C NMR, CDCl$_3$, 125 MHz

CDCl$_3$
$^{1}H$ NMR, CDCl$_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz
$^1$H NMR, CDCl$_3$, 500 MHz
$\text{H NMR, CDCl}_3$, 500 MHz
$^{13}C$ NMR, CDCl$_3$, 125 MHz
$^{1}H$ NMR, CDCl$_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz

![NMR Spectrum Image]
$^{13}$C NMR, CDCl$_3$, 125 MHz
$\text{C NMR, CDCl}_3, 125 \text{ MHz}$
$^{1}H$ NMR, CDCl$_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz
\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{CH}_3 & \quad \text{O} \\
\text{CH}_3 & \quad \text{O} \\
\text{HO} & \quad \text{O} \\
\text{CH}_3 & \quad \text{O} \\
\text{CH}_3 & \quad \text{O} \\
\text{CH}_3 & \quad \text{O} \\
\end{align*}
\]

\[\text{CHCl}_3, 500 \text{ MHz}\]
$1^3$C NMR, CDCl$_3$, 100 MHz
$\text{CHCl}_3$
\( ^{13}C\) NMR, CDCl\(_3\), 150 MHz
$^{1}H$ NMR, CDCl$_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz
$^{1}H$ NMR, CDCl$_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz
$^{1}H$ NMR, CDCl$_3$, 500 MHz
$^{13}$C NMR, CDCl$_3$, 125 MHz
$^1$H NMR, CDCl$_3$, 600 MHz
$^{13}$C NMR, CDCl$_3$, 150 MHz
$^{1}H$ NMR, CDCl$_3$, 500 MHz

Diagram of a molecular structure with peaks and chemical shifts indicated in ppm.
$^{13}$C NMR, CDCl$_3$, 125 MHz
\[ \text{H NMR, CDCl}_3, 500 \text{ MHz} \]
$^{13}$C NMR, CDCl$_3$, 125 MHz

![NMR spectrum](image)
$^{1}H$ NMR, CDCl$_3$, 500 MHz
$^{13}C$ NMR, CDCl$_3$, 125 MHz
$\text{C}_9\text{H}_{20}\text{O}_4\text{Cl}_3$
$\text{C NMR, CDCl}_3, 125 \text{ MHz}$
euonyminol octaacetate (116)

$\text{H NMR, CDCl}_3, 500 \text{ MHz}$
Euonymol octaacetate (116)

$\text{Euonyminol octaacetate (116)}$

$^{13}$C NMR, CDCl$_3$, 125 MHz
\[ \text{euonyminol (99)} \]

$^1$H NMR, CD$_3$OD, 500 MHz
$^{13}$C NMR, CD$_3$OD, 125 MHz

Euonyminol (99)
$\text{DHO euonyminol (99)}$ 

$\text{CH}_3 \text{OH}$ 

$\text{HO}$ 

$\text{OH}$ 

$\text{CH}_3 \text{OH}$ 

$\text{HO}$ 

$\text{OH}$ 

$\text{OH}$ 

$\text{H NMR, D}_2\text{O, 500 MHz}$
$^1$H NMR, CDCl$_3$, 500 MHz

CHCl$_3$
$^1$H NMR, CDCl$_3$, 125 MHz

$^{13}$C NMR, CDCl$_3$, 125 MHz

210

CDCl$_3$
$^{13}$C NMR, C$_6$D$_6$, 125 MHz

$\text{C}_6\text{D}_6$
$^{1}H$ NMR, CDCl$_3$, 500 MHz

Structure:

212

CHCl$_3$
$^{13}$C NMR, CDCl$_3$, 125 MHz

\[
\begin{align*}
\text{CDCl}_3
\end{align*}
\]
$^{1}$H NMR, CDCl$_3$, 500 MHz

![NMR Spectrogram]

213
$\text{C NMR, CDCl}_3$, 150 MHz
\[ \text{H NMR, } C_6D_6, 500 \text{ MHz} \]

![Graph of H NMR spectrum for } C_6D_6 \text{ with peaks and chemical shifts.}