Studies Directed Towards the Total Synthesis of (+)-Sieboldine A

by

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B.S. Chemistry
University of California, Berkeley, 2003

Submitted to the Department of Chemistry
in Partial Fulfillment of the Requirements
for the Degree of

DOCTOR OF PHILOSOPHY
IN ORGANIC CHEMISTRY

at the

Massachusetts Institute of Technology

May 2008

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To Eleanor and my family
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Abstract

Progress towards the total synthesis of sieboldine A is described. This synthetic approach uses a nickel-catalyzed alkyne-ketone reductive cyclization to form the hydrindane core of the natural product in good yield and with excellent diastereoselectivity about the newly formed tertiary allylic alcohol.

The hydrindane product from this reductive cyclization can be transformed into the tetracyclic N,O-acetal which is two steps removed from the natural product 1. Efforts directed towards completion of the synthesis of 1 via a direct late-stage amine oxidation are presented.

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Abbreviations

Ac  acetyl
Alloc allyl carbamate
Boc tert-butyl carbamate
BSA bis-(trimethylsilyl)acetamide
°C degree celcius
cod cyclooctadiene
DDQ 2,3-dichloro-5,6-dicyanoquinone
DEAD diethyl azodicarboxamide
DMF N,N’-dimethylformamide
DMDO dimethyldioxirane
DMSO dimethylsulfoxide
Et ethyl
g gram
gCOSY gradient correlation spectroscopy
HMBC heteronuclear multiple bond correlation spectroscopy
HRMS high resolution mass spectrometry
HSQC heteronuclear single quantum coherence spectroscopy
Hz hertz
IR infrared
KAPA potassium aminoproprylamide
KHMDS potassium hexamethyldisilazane
L liter
LDA lithium disopropylamide
m milli
mol mole
µ micro
M molar
Me methyl
MHz megahertz
Ms methanesulfonyl
NMO N-methyl morpholine N-oxide
Ph phenyl
PMB para-methoxy benzyl
PPTS pyridinium-para-toluenesulfonate
Py pyridine
TBAF tetrabutylammonium fluoride
TBS tert-butyl dimethyl silyl
THF tetrahydrofuran
TMS trimethylsilyl
Introduction

The Lycopodium alkaloids are a large group of natural products characterized by their compact polycyclic frameworks. These alkaloids derive their name from the *Lycopodium* species of plants from which they were originally isolated. This group of natural products is divided into four distinct structural classes (Figure 1). Hydrindane containing natural products, such as sieboldine A (1), alopecuridine (2a), and fawcettimine (2b), are classified in the fawcettimine group of the Lycopodium alkaloids, whereas natural products that contain a pyridine or pyridone ring, such as huperzine A (3), are classified in the lycodine group. Furthermore, alkaloids that contain four interconnected 6-membered rings, such as lycopodine (4), are members of the lycopodine group. Finally, the natural products that are devoid of one of the aforementioned structural features are members of the miscellaneous class of Lycopodium alkaloids, such as phlegmarine (5).  

Figure 1. Representative Lycopodium Alkaloids.

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Along with their complex structures, the Lycopodium alkaloids often have interesting biological activities, and plants or plant extracts containing these alkaloids have been used in traditional Chinese medicine. Recently, these alkaloids have received increased attention from practitioners of Western medicine as treatments for a variety of human diseases. 

In particular, huperzine A (3) has been the subject of many studies because of its acetylcholinesterase inhibition activity. This activity has current relevance because acetylcholinesterase inhibitors are used in the treatment of Alzheimer’s disease, myasthenia gravis, and some dementias. In general these diseases are associated with low levels of acetylcholine in the central nervous system and/or in the peripheral nervous system.

Figure 2. Acetylcholinesterase Inhibitors.

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Acetylcholinesterase inhibitors help treat these conditions by increasing the lifetime of acetylcholine through inhibition of the enzyme responsible for its breakdown. Huperzine A compares favorably with the currently prescribed drugs tacrine,\(^4\) donepezil,\(^5\) rivastigmine,\(^6\) and galantamine\(^7\) in terms of activity, bioavailability, half-life, and selectivity towards acetylcholinesterase. In clinical trials it has been shown to have beneficial effects on cognitive function and memory in patients with Alzheimer’s disease. In fact, huperzine A has been approved for treatment of Alzheimer’s disease in China and is currently in phase II clinical trials in the US.\(^8\)

These findings have spurred increased attention from both the synthetic organic chemistry community and the natural products community, culminating in several recent total syntheses\(^9\) and renewed interest in the isolation and characterization of novel Lycopodium alkaloid structures.\(^10\)

\(^4\) Marketed by Sciele Pharmaceuticals.
\(^5\) Marketed by Eisai Pharmaceuticals.
\(^6\) Marketed by Novartis Pharmaceuticals.
\(^7\) Marketed by Janssen Pharmaceuticals.
\(^8\) For details, see: http://www.alzforum.org/drg/drc/detail.asp?id=53.
In 2003, Kobayashi and coworkers reported the isolation of a novel alkaloid from the club moss *Lycopodium sieboldii* that was subsequently named sieboldine A (1) (Figure 3). NMR and X-ray studies established that 1 has a unique tetracyclic structure containing a cyclohexanone, a cyclopentanone, a tetrahydrofuran, and an aza-cyclononane ring. In addition, sieboldine A (1) has modest biological activity that includes cytotoxicity to murine lymphoma L1210 cells and inhibitory activity against acetylcholinesterase (AchE).

As one of its structural components, 1 contains an α-hydroxy ketone that features a tertiary alcohol vicinal to an all-carbon quaternary stereocenter. This substructure is a challenging motif, and one that might be well suited for assembly using nickel-catalyzed reductive coupling chemistry developed in our laboratories.

Transition metal-catalyzed carbon–carbon bond-forming reactions have become very powerful methods in synthetic organic chemistry because of their high efficiency and functional group tolerance. To this end the Jamison group and several others have investigated the nickel-catalyzed reactions of alkynes with a variety of electrophiles. These reactions provide access to synthetically useful functional groups such as allylic

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alcohols,\textsuperscript{13} allylic amines,\textsuperscript{14} and homoallylic alcohols.\textsuperscript{15} The versatility and functional group tolerance of these reductive coupling reactions have been featured as key steps in the synthesis of several complex natural products such as amphidinolide T\textsubscript{1},\textsuperscript{16} amphidinolide T\textsubscript{4},\textsuperscript{17} and (−)-gloeosporone.\textsuperscript{18}

Figure 4.

At the outset of this project the sole example of a nickel-catalyzed alkyne-ketone reductive cyclization reaction was observed in the course of the total synthesis of (−)-terpestacin (Figure 4).\textsuperscript{19} In this example, reaction between the cyclopentanone and the alkyne was observed in the presence of a pendant aldehyde. This reactivity was unexpected, as ketones had not previously been observed to react under nickel-catalyzed reductive cyclization conditions even when present in large excess.\textsuperscript{20} The increased reactivity of the ketone observed in this substrate may be the result of the proximity of the alkyne and ketone functional groups. This example served as a starting point for the total synthesis of 1.

\textsuperscript{20} Coupling reactions run in acetone show no trace of acetone coupling products.
Retrosynthetic Analysis and Structural Considerations

Figure 5. Structural Considerations.

The total synthesis of sieboldine A was initiated with the purpose of investigating a novel nickel-catalyzed alkyne-ketone reductive cyclization for assembly of the hydrindane core of 1. Besides the construction of the hydrindane core, the unique molecular framework of 1 presented three significant synthetic challenges (Figure 5). These challenges included: (i) construction of an all-carbon quaternary stereogenic center, (ii) formation of an \( \alpha \)-hydroxy ketone (containing a tertiary alcohol vicinal to the all-carbon quaternary stereocenter), and (iii) assembly of a hydroxylamine-containing \( N,O \)-acetal, which closes the polycyclic framework of 1.

Figure 6. Retrosynthetic Analysis.

Our retrosynthetic analysis starts from sieboldine A (1) via opening of the \( N,O \)-acetal to afford hydroxylamine 13 (Figure 6). This retrosynthetic hydrolysis reveals the alcohol, aldehyde, and hydroxylamine components that make up the \( N,O \)-acetal and provides inspiration for a condensation strategy to assemble the 9-membered ring in 1.
Further simplification of 13 via standard functional group manipulations and oxidation state adjustments affords cyclohexanone 14, where the α-hydroxy ketone is masked as an allylic alcohol.

**Figure 7. Disconnection of the Hydrindane Core.**

Application of the nickel-catalyzed alkyne-ketone reductive cyclization disconnection to hydrindane 14 opens the bicyclic system to afford diketone 15 (Figure 7). This transformation reveals the alkyne and ketone functional groups that are required for the reductive cyclization and identifies cyclohexanone 15 as an important intermediate towards the total synthesis of sieboldine A (1).

**Figure 8. Retrosynthetic Analysis.**

Simplification of alkyne 15 can be accomplished by disconnection of the allyl group at the all-carbon quaternary center to afford 1,3-diketone 16. The 1,3-diketone 16 can be simplified into enone 17 by application of a conjugate addition/aldol/oxidation strategy to afford 5-methyl-cyclopent-2-en-1-one (17) as the starting material.
This synthetic approach hinges upon a successful intramolecular alkyne-ketone reductive coupling of diketone 15 to form hydrindane 14. The cyclization must differentiate the two carbonyl groups in 15, as only reaction at the exocyclic carbonyl will afford the hydrindane 14. In addition to differentiating the two reaction sites, this reaction must differentiate between the two faces, *Re* and *Si*, of the carbonyl as only reaction on the *Si* face will afford the desired diastereomer about the allylic alcohol.

It was initially proposed that the site selectivity of the nickel-catalyzed alkyne-ketone reductive cyclization reaction would be controlled by the conformation of diketone 15 (Figure 10).

**Figure 9. Proposed Synthesis of the Hydrindane Core.**

![Diagram of Proposed Synthesis of the Hydrindane Core](image)

**Figure 10. Chair Conformations of Diketone 15.**

![Diagram of Chair Conformations of Diketone 15](image)

Diketone 15 is expected to have two major conformers in solution, conformer 15a and conformer 15b. In conformer 15a the propargyl group and the allyl group are in axial positions and the methyl group and the exocyclic carbonyl group are in equatorial positions. If the nickel-catalyzed reductive cyclization reaction were to take place from
conformer 15a this conformation would allow the propargyl group to interact with either of the carbonyl groups present in 15 and a mixture of cyclization products could be expected.\textsuperscript{21}

The situation is different in conformer 15b as in this conformation the methyl group and the exocyclic carbonyl group take up axial positions and the propargyl group and the allyl group take up equatorial positions. With the propargyl group in the equatorial position it can only interact with the exocyclic carbonyl group and this would lead to a site selective reaction.\textsuperscript{22} Based upon published $A$ values for the different substituents on the cyclohexyl ring, 15b is expected to be the dominant conformer in solution and should be favored by 0.6 to 1.6 kcal/mol.\textsuperscript{23,24} If reaction occurs through these conformers with similar rates selectivity for reaction with the exocyclic carbonyl would be predicted.

Modeling the diastereoselectivity of this reaction is another challenge as this is dependent upon which face of the carbonyl group, $Re$ or $Si$, reacts under these conditions. However, some insight can be gained by analysis of the catalytic cycle of the alkyne-ketone reductive cyclization (Figure 11).

\textsuperscript{21} This analysis assumes that the reaction proceeds through a low energy chair conformation and not another conformation.
\textsuperscript{22} If reaction of one conformer is much more rapid than the other a Curtin-Hammett situation could be imagined and high selectivity for reaction from the higher energy conformer 15a could be observed.
\textsuperscript{24} For this calculation the reported $A$ values for the methyl and allyl groups were used and approximate values were used for the exocyclic carbonyl (approximated as CH$_3$CO) and the propargyl group (approximated as CH$_2$CN).
Initially the nickel(0) catalyst binds the alkyne and the ketone. This complexation is followed by a reductive coupling to afford oxametallocyclopentene intermediate A.\(^{25}\) Formation of intermediate A is followed by transmetallation with Et\(_3\)B to afford ethyl-nickel complex B. Intermediate B then undergoes a \(\beta\)-hydride elimination to release ethylene and form nickel-hydride C. From this nickel-hydride species a reductive elimination releases the product D, as a borinate ester, and regenerates the nickel(0) catalyst.

Inspection of this catalytic cycle reveals that formation of the oxametallacyclopentene intermediate determines the diastereoselectivity about the

tertiary allylic alcohol. In the formation of this intermediate it is possible to predict the selectivity for the reaction considering two limiting cases, reaction through an early, reagent-like transition state and reaction through a late, product-like transition state.

To predict the facial selectivity for an early, reagent-like transition state it is useful to analyze the interactions that are important in the starting material, because these interactions will be present in the transition state. This analysis considers only steric interactions and electronic factors such as dipole-dipole interactions are omitted. Analysis for reaction from both 15a and 15b is presented.

Figure 12. Early Transition States From 15a.

For conformer 15a two transition states, 15a-e-Re and 15a-e-Si, can be proposed.

In these two transition states the exocyclic carbonyl is positioned to allow approach of the
alkyne-nickel complex along the Bürgi-Dunitz trajectory. As a consequence of this required trajectory, in 15a-e-Re the exocyclic carbonyl aligns with the cyclic carbonyl. In 15a-e-Si the exocyclic carbonyl aligns anti to the ring carbonyl. This forces the alkyl group of the exocyclic carbonyl to eclipse the ring carbonyl. On the basis of these interactions, 15a-e-Re should be the more accessible transition state. This would result in reductive cyclization onto the Re face of the exocyclic carbonyl group and formation of the undesired diastereomer about the tertiary allylic alcohol.

**Figure 13. Early Transition States from 15b.**

From conformer 15b two reagent-like transition states can be proposed, 15b-e-Re and 15b-e-Si. These transition states allow approach of the nickel-alkyne complex along the Bürgi-Dunitz angle just as in 15a. In 15b-e-Re the exocyclic carbonyl is rotated so that the C–O bond is placed over the ring. This forces the alkyl group to eclipse the allyl
group. In 15b-e-Si the carbonyl is rotated so that the alkyl group is placed over the ring and the carbonyl group eclipses the allyl group. With the eclipsed alkyl groups in 15b-e-Re it would be more difficult to access this transition state than 15-e-Si. Thus, if the reaction occurs through conformer 15b reaction on the Si face of the exocyclic carbonyl is predicted and would afford the desired diastereomer about the tertiary allylic alcohol.

In contrast, if the reaction occurs via a late transition state we should consider transition states similar to the oxametallacycle intermediate. Examining the important interactions in the oxametallacycle intermediates can then be used to predict the diastereoselectivity of the reductive cyclization.

Figure 14. Late Transition States from 15a.

In a late transition state 15a would afford two oxametallocyclopentene transition states arising from attack at the Re and the Si face of the exocyclic carbonyl to generate
**15a-l-Re** and **15a-l-Si** (Figure 15). In **15a-l-Re** the alkyl chain of the carbonyl eclipses the allyl group and engenders a severe steric interaction that should be significant in the transition state. In **15a-l-Si** the oxygen in the oxametalocyclopentene is placed near the allyl group. Since **15a-l-Si** is devoid of significant steric interactions, it should be a more accessible transition state than **15a-l-Re**. As a consequence of the accessibility of **15a-l-Re** if the reaction were to occur from conformer **15a** through a late transition state, reaction at the **Si** face of the carbonyl would be predicted. This would afford the desired diastereomer about the tertiary allylic alcohol.

**Figure 15. Late Transition States from 15b.**

Reaction through **15b** would afford two oxametalocyclopentene transition states, from attack at the **Re** and the **Si** face of the acyclic carbonyl to generate intermediates **15b-l-Re** and **15b-l-Si** (Figure 15). In **15b-l-Re** the alkyl chain of the acyclic carbonyl is very nearly eclipsed with the allyl group and engenders a severe steric interaction that
should be significant in the transition state. In 15b-1-Si, the oxygen in the oxametallacyclopentene is placed near the allyl group. This forces the alkyl group out over the cyclohexyl ring and would encounter significant steric interactions. While not as clearly differentiated, in this analysis the most accessible transition state for 15b would be reaction through 15-1-Si. Therefore regardless of chair conformation, 15a or 15b, a late transition state would predict formation of the desired diastereomer about the allylic alcohol.

To summarize, if the nickel-catalyzed alkyne-ketone reductive coupling occurs through an early transition state the undesired diastereomer about the allylic alcohol would be expected to be the major product. In contrast, if the reaction involves a late transition state, the desired diastereomer about the tertiary alcohol should be formed and could be elaborated towards the total synthesis of 1. To answer some of these questions and test these predictions the synthesis of diketone 15 was initiated.
Results and Discussion

Scheme 1.

Our studies directed towards the total synthesis of sieboldine A (1) began from (±)-5-methyl-cyclohex-2-en-1-one (17), which was readily obtained from ethyl crotonate (18) and ethyl acetoacetate (19) following literature procedures.  With a reliable and scalable synthesis of enone 17 in hand a tandem conjugate propargylation-aldol reaction was investigated.

A. Tandem Approach to β-Hydroxy Ketone

Tandem reactions are powerful methods in synthetic organic chemistry due to the rapid increase in molecular complexity that can be achieved by coupling two or more discrete bond-forming reactions. Of these methods the tandem conjugate addition-aldol reaction is particularly useful as it allows for the formation of two new carbon-carbon bonds and up to three new stereogenic centers. A wide variety of substrates participate in this process, providing valuable products that have been used in a number of total syntheses. The most widely encountered form of this reaction employs alkyl or alkenyl

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copper species for the conjugate addition and generation of the enolate used in the subsequent aldol addition.  

**Scheme 2.**

Application of this approach to the synthesis of β-hydroxy ketone 21 requires that the propargyl copper reagent undergo a selective propargyl addition to enone 17. Use of propargyl copper reagents for conjugate addition reactions are difficult and have encountered two main problems, i) low reactivity of the propargyl copper species and ii) low selectivity for propargyl versus allenyl addition products.

To overcome these problems several strategies have been taken, including attempts to bias the propargyl copper species for a selective addition and/or the use of alternative propargyl metal species. Despite the concerns over the tandem conjugate addition-aldol reaction investigation into this reaction sequence was explored, as this reaction to would provide rapid access to β-hydroxy ketone 21.

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Investigation into the tandem conjugate propargylation-aldol reaction began with the conditions listed in Table 1. A propargyl copper species (Table 1, entry 1) provided complex mixtures of products after reaction with enone 17 potentially due to competing propargyl and allenyl conjugate addition products.\(^{30}\) Alternative propargyl metal reagents, including a propargyl lithium species\(^ {31}\) (Table 1, entry 2) and a propargyl indium species\(^ {32}\) (Table 1, entry 3) were also ineffective for this transformation.

An alternative to nucleophilic propargyl metal species are allenyl metal reagents that undergo a $S_c^2$ reaction to afford propargylated products. In the presence of a Lewis acid promoter, allenylstannanes are reported to undergo a conjugate propargylation reaction with a variety of cyclohexenone substrates to provide β-propargylated cyclohexanones (Scheme 3).\(^ {33}\)

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\(^{30}\) For an example of competing propargyl and allenyl conjugate addition of propargyl copper species, see: Ganem, B. Tetrahedron Lett. 1974, 51/52, 4467-4470.


Scheme 3.

Presumably this reaction generates an intermediate titanium enolate, such as 24, that should be a competent nucleophile for aldol addition. While no tandem conjugate addition-aldol reactions have been reported for allenylstannanes, similar tandem processes with ally and allenylsilanes are known (Scheme 4).

Scheme 4. Tandem Reactions of Silanes.

With allylsilanes the initial conjugate addition affords an enolate species and this enolate has been added to a variety of electrophiles including aldehydes, acetals, and alkyl halides to afford α-functionalized products (Scheme 4, equation 1).\(^\text{34}\) Allenylsilanes also perform a similar conjugate addition reaction to afford an enolate, however in this instance intramolecular reaction with a vinyl cation that results from a 1,2-silyl migration affords trimethylsilylcyclopentenes (Scheme 4, eq. 2).\(^\text{35}\)

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tandem transformations are known with other S_{E2}' nucleophiles investigation into the tandem reaction of allenylstannanes began.

Table 2. Allenylstannane Propargylation Reactions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allenylstannane</th>
<th>Temperature (°C)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>tributylallenylstannane</td>
<td>-40</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>triphenylallenylstannane</td>
<td>-78 → -40</td>
<td>22, 15% yield^a</td>
</tr>
<tr>
<td>3</td>
<td>triphenylallenylstannane</td>
<td>-78 → -20</td>
<td>22, ~30% yield^a</td>
</tr>
</tbody>
</table>

^a Product contaminated with tin byproducts.

Initial propargylation reactions with tributylallenylstannane (Table 2, entry 1) resulted in a variety of decomposition products derived from enone 17. The analogous triphenylallenylstannane reagent (Table 2, entries 2 and 3) afforded small amounts of the desired product. Attempts to improve the reaction efficiency by varying temperature, stoichiometry, and reaction time proved ineffective, as only minor improvements in yield were observed. It was unclear whether an inefficient S_{E2}' reaction or the subsequent aldol reaction was leading to the poor yield in these reaction attempts.

Several factors may contribute to the poor efficiency of this tandem conjugate propargylation-aldol reaction with allenylstannanes. The initial conjugate addition reaction generates a titanium enolate and also generates triphenyltin chloride as a byproduct. The tin chloride may react with the enolate species to afford the corresponding tin enolate. Tin enolates have different reactivity profiles than the
corresponding titanium enolates and generally require an added promoter to afford efficient aldol reactions.\textsuperscript{36} The prevalence of both titanium and tin enolates in the reaction mixture could lead to poor reactivity in the aldol addition. Ultimately, the tandem conjugate propargylation-aldol reaction was abandoned due to its poor efficiency in producing the desired β-hydroxy ketone.

**B. Conjugate Propynylation**

Scheme 5.

Without direct access to β-hydroxy ketone 21, alternative means of installing the propargyl group were investigated. The most direct approach used a conjugate propynylation followed by an alkyne isomerization to install the propargyl group. This approach would require three additional transformations to access diketone 16 when compared to the tandem reaction approach but would rely upon well-established synthetic methods.

To begin, the conjugate propynylation of enone 17 was pursued. Standard organocuprate chemistry cannot be used to install the propynyl group due to the strength

of the copper-alkyne bond.\textsuperscript{37} Methods that rely upon the use of alkynyl aluminum\textsuperscript{38} or alkynyl zinc\textsuperscript{39} species with Lewis acid promoters are effective for this transformation and allow access to β-alkynylated cyclohexanones. In addition, with the appropriate choice of Lewis acid promoter the resultant enolate may be trapped as an enol ether providing the means to perform a regiospecific functionalization via the aldol reaction.

\textbf{Scheme 6.}

Treatment of enone 17 with propynyl zinc bromide and trimethylsilyl trifluoromethanesulfonate resulted in conjugate propynylation to afford silyl enol ether 31 in good yield. With access to silyl enol ether 31, investigation into its reactivity in the Mukaiyama aldol reaction was pursued.\textsuperscript{40} Treating silyl enol ether 31 with variety of promoters resulted in low isolated yields of β-hydroxy ketone 32 and instead led to hydrolysis of the silyl enol ether. The difficulty associated with the Mukaiyama aldol reaction led to the investigation of alternative methods for generation of β-hydroxy ketone 32.

\textsuperscript{38} Kim, S.; Park, J. H. \textit{Synlett} \textbf{1995}, \textit{163-164}.  

Generation of enolates from silyl enol ethers can be accomplished by nucleophilic cleavage of the silyl enol ether with a potassium alkoxide\textsuperscript{41} or an alkyl lithium reagent\textsuperscript{42}. Cleavage of silyl enol ethers with these reagents provide the corresponding potassium or lithium enolates which can be used in a variety of subsequent transformations, including aldol reactions\textsuperscript{43}.

**Scheme 7.**

![Scheme 7](image)

Treatment of silyl enol ether 31 with \textit{n}-butyllithium cleaved the silyl enol ether to generate the corresponding lithium enolate. Transmetallation of the lithium enolate to the zinc enolate\textsuperscript{44} followed by addition of aldehyde 20 resulted in an aldol reaction to provide \(\beta\)-hydroxy ketone 32 in good yield as a mixture of diastereomers. With access to \(\beta\)-hydroxy ketone 32, attention turned to base-mediated isomerization of the internal alkyne to the terminal position.

**Scheme 8.**

![Scheme 8](image)


Before exploration of the alkyne isomerization reaction, reduction of β-hydroxy ketone 32 with LiAlH₄ was performed to afford diol 30 as a mixture of diastereomers. This reduction was performed to prevent base-mediated decomposition of 32 as the majority of alkyne isomerization methods rely upon strongly basic conditions to promote the reaction.

The most commonly employed reagent for isomerization reactions of internal alkynes to terminal alkynes is potassium aminopropylamide (KAPA). The mechanism of this transformation involves initial propargylic deprotonation followed by a reprotonation step to afford an allenyl intermediate. The allenyl intermediate undergoes a similar deprotonation/reprotonation step to afford the terminal alkyne, which gets irreversibly deprotonated to afford the potassium acetylide.

**Scheme 9.**

One concern with the isomerization step is the competition between deprotonation at the propargylic methyl group, to afford allene 34, and deprotonation at the ring junction to afford allene 33 (Scheme 9). Formation of allene 33 has the potential to epimerize the stereocenter at the ring junction. Deprotonation at the propargylic methyl group should be favored because of its larger number of propargylic hydrogen atoms.

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vs 1), its increased acidity relative to the ring junction hydrogen atom, and its relative accessibility compared to the ring junction.

**Scheme 10.**

While formation of allene 33 is a concern, studies on isomerization reactions with exocyclic allenes\(^{46}\) suggest that there will be low selectivity for formation of the equatorial versus the axial alkyne product (Scheme 10, 36 vs. 37). If a small amount of allene 33 is formed, half will be epimerized and the remainder will return to 30. Considering this it was reasoned that little epimerization would occur in the isomerization reaction.

**Scheme 11.**

With these concerns in mind, isomerization of diol 30 was pursued. Initially isomerization of diol 30 was a difficult transformation plagued with inconsistent conversion of the starting material and often required multiple reaction attempts for complete isomerization. Full conversion could be obtained by increasing the amount of KAPA used in the isomerization reaction. Under these conditions the isomerization

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afforded good yields of diol 38. Unfortunately, at this time it was difficult to determine whether any epimerization at the ring junction had occurred.

Scheme 12.

Subsequent Swern oxidation of diol 38 followed by alkylation of the resulting 1,3-diketone assembled cyclohexanone 39 in good yield and with excellent diastereoselectivity. Notable, is that only two reaction products could be isolated from the alkylation, the desired product 39 and an O-alkylation product.\(^{47}\)

Figure 16. Rationale for observed diastereoselectivity.

The diastereoselectivity of the alkylation reaction can be rationalized by examining the two enolate conformations A and B (Figure 16). In conformer B there is \(A^{1,2}\) strain between the exocyclic carbonyl and the propargyl group which occupies a pseudo equatorial position. Conformer A is free of this allylic strain and is the dominant conformer in solution. Reaction occurs through conformer A where the propargyl group occupies a pseudo axial position and sterically hinders the top face of the enolate. Due to this steric shielding by the propargyl group, the allyl electrophile approaches from the

\(^{47}\) O-alkylation and C-alkylation account for \(~80-85\%) of the mass. No other alkylation products are observed in the crude reaction mixture.
bottom face of the enolate and sets the desired syn relationship between the propargyl
group and the exocyclic carbonyl.\textsuperscript{48} In addition to a direct alkylation, there is an
alternative reaction pathway available for formation of diketone 39; O-alkylation
followed by a Claisen rearrangement.

\textbf{Scheme 13.}

\begin{center}
\includegraphics[width=\textwidth]{scheme13.png}
\end{center}

Isolation of the O-alkylation product 40 and subsequent Claisen rearrangement
required much higher temperatures than those reached in the alkylation reaction. The
diastereoselectivity of the Claisen rearrangement was much lower, \(\sim 3:1\), than that
observed in the alkylation. Due to these observations it seems reasonable to assume that
the major reaction pathway for formation of 39 is by a direct alkylation.

\textbf{Scheme 14.}

\begin{center}
\includegraphics[width=\textwidth]{scheme14.png}
\end{center}

Sonogashira reaction of terminal alkyne 39 with iodobenzene afforded reductive
cyclization substrate 15 in good yield (Scheme 14).

C. Initial Reductive Cyclization

Figure 17. Reductive Cyclization Site Selectivity.

With an efficient route to diketone 15 (7 steps, 18% overall yield), investigation of the reductive cyclization reaction could begin. These studies were directed towards exploration of the site-selectivity (Figure 17, path A vs. path B) and the diastereoselectivity of the nickel-catalyzed alkyne-ketone reductive cyclization of diketone 15.

Scheme 15.

To answer these questions diketone 15 was treated with the nickel-catalyzed reductive cyclization conditions shown (Scheme 15). Purification of the reaction mixture afforded a single reductive coupling product. However, conclusive identification of the product as compound 14 or compound 41 could not be accomplished with simple ($^1$H, $^{13}$C, IR) spectroscopic techniques.

---

49 As determined by $^1$H, $^{13}$C, IR, HRMS.
Differentiation of the two possible reductive coupling products, 14 and 41, was accomplished with the use of gCOSY and HMBC spectra. The HMBC spectrum of the reductive coupling product showed a signal from a carbonyl carbon to hydrogen atoms that were located on the alkyl sidechain of the exocyclic carbonyl in diketone 15. This observation is consistent only with the structure of bicycle 41.

Formation of bicycle 41 from reaction with the ring carbonyl group suggested that the reaction was occurring through conformer 15a, where the propargyl group occupies an axial position (Figure 10). Since it was expected that reaction at either carbonyl could be obtained through conformer 15a, studies aimed at altering the site selectivity of the reductive cyclization were performed. However, in all cases the sole reductive coupling product was bicycle 41 resulting from reaction at the ring carbonyl. The consistent, and apparently exclusive, reactivity of this carbonyl group under the reductive cyclization conditions led to the investigation of strategies aimed at differentiating the two carbonyl functional groups in 15.

**D. Carbonyl Differentiation**

Most carbonyl differentiation methods, such as ketal formation, reduction, and cyanohydrin formation, rely upon large electronic or steric differences to provide the
basis for selectivity. In diketone 15, both carbonyl functional groups have similar steric and electronic characteristics, and it follows that differentiation of the two carbonyl groups could pose a significant challenge.

Ideally, the differentiation reaction would occur with complete selectivity for the cyclic carbonyl to afford compounds of general structure 42. These compounds could be directly screened in the reductive cyclization without the need for further transformations (Scheme 16). Less desirable is a selective reaction with the acyclic carbonyl to afford compounds such as 43. While still useful these compounds would require subsequent transformations before they could be screened in the reductive cyclization reaction.

**Scheme 16.**

Initially, a variety of nucleophilic differentiation methods were investigated, such as ketal formation, reduction, and cyanohydrin formation. These methods were unable to differentiate the two carbonyl groups of 15 and led to either intractable reaction mixtures or recovery of unreacted starting material. An alternative strategy to these intermolecular differentiation methods is an intramolecular approach.

---

Investigation into the intramolecular differentiation strategy began with oxidative deprotection of the PMB ether to afford diol 44 (Scheme 17). It was envisioned that upon treatment of diol 44 with Lewis or Brønsted acidic conditions that an intramolecular ketal formation would occur. Selectivity would be based upon the formation of the 5-membered ring versus a 7-membered ring and should allow access to ketal 45.

Scheme 17

While intramolecular ketal formation may allow differentiation of the two carbonyl groups in 39 it does have some limitations. The first is that the ketal product 45 may be formed as a mixture of diastereomers. While the diastereomers would not be a problem in the long term, due to eventual deprotection of the ketal, they will make analysis of the crude reaction mixture more difficult. Another problem is that the ketal product would require at least three further transformations before it could be investigated in the reductive cyclization reaction. Despite these limitations the intramolecular ketal formation was pursued, as it appeared to allow for differentiation of the two carbonyl groups.
### Table 3: Intramolecular Ketal Formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HCl, MeOH, 65 °C</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>PPTS, MeOH, C_6H_6, 80 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>BF_3·OEt_2, MeOSiMe_3, -78 °C</td>
<td>*</td>
</tr>
<tr>
<td>4</td>
<td>TsOH, C_6H_6, 80 °C</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5</td>
<td>BF_3·OEt_2, -78 °C</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

Treatment of diol 44 under a variety of reaction conditions did not lead to isolation of the desired methyl ketal 45. Several reaction conditions using strong acids and heating (Table 3, entries 1 and 3) resulted in decomposition of the starting material. Milder acids resulted in no reaction. Attempts at hemiacetal formation (Table 3, entries 4 and 5) were also unsuccessful. Since both intramolecular and intermolecular methods were ineffective for the differentiation of the two carbonyl groups in diketone 15, more unconventional methods were investigated. In particular a selective enolization strategy appeared attractive.

For enolate formation to occur an α-hydrogen atom must be aligned with the π-system of the carbonyl. This orientation increases the acidity of that hydrogen atom and allows formation of the enolate. For deprotonation of the hydrogen atoms α to the exocyclic carbonyl group, the ground state, with the alkyl chain eclipsed with the carbonyl group, must rotate to align the hydrogen atom with the π system of the carbonyl (Figure 19).
If the alkyl chain rotates to allow formation of the E-enolate the alkyl chain encounters a steric interaction with the substituents at the quaternary center. If the alkyl chain rotates towards to allow formation of the Z-enolate a hydrogen atom encounters a steric interaction with the quaternary stereocenter. These interactions destabilize the transition states for formation of an enolate from the exocyclic carbonyl.

In the ground state of the cyclic carbonyl the axial hydrogen is aligned with \( \pi \) system of the ring carbonyl as is required for enolate formation. \(^{51}\) Since the hydrogen atoms \( \alpha \) to the exocyclic carbonyl are destabilized in the orientations required for enolate formation and the axial hydrogen atom \( \alpha \) to the cyclic carbonyl does not encounter these interactions, a selective enolization reaction may be possible. \(^{52,53}\)

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\(^{53}\) This analysis assumes a kinetically controlled deprotonation.
Investigation into the selective enolization strategy began by treatment of 15 with LDA and Ac₂O, in an attempt to form an enol acetate, and resulted in isolation of starting material from the reaction mixture (Table 4, entry 1). Use of KH and TBSCI was also ineffective leading to a very low conversion at room temperature. However, use of KHMDS and TBSCI resulted in isolation of the desired silyl enol ether 46, albeit in low yield. Switching to soft enolization conditions (Table 4, entry 4) afforded silyl enol ether 46 in good yield and provided a high yielding method for differentiation of the two carbonyl groups in diketone 15.

**E. Reductive Cyclization**

With an effective way of differentiating the two carbonyl groups in 15, attention turned to exploration of the reactivity and diastereoselectivity of silyl enol ether 46 under nickel-catalyzed reductive cyclization conditions.
Treatment of 46 with Ni(cod)$_2$, PBU$_3$, and Et$_3$B at room temperature led to complete recovery of starting material. Interestingly the alkyne in 46 did not undergo commonly observed side reactions, including cyclotrimerization, oligomerization, or reduction.\textsuperscript{54} This pointed to a congested steric environment about the alkyne. In an effort to overcome the steric hindrance heating of the reaction mixture was investigated. At elevated temperatures silyl enol ether 46 underwent a smooth reductive cyclization reaction to afford bicycle 47 in good yield and with excellent diastereoselectivity.\textsuperscript{55,56}

Figure 20. Rationale for Observed Diastereoselectivity.

The high diastereoselectivity for formation of the allylic alcohol can be rationalized by assuming a late transition state structure and examining two diastereomeric oxametallacycles, \textit{Re} and \textit{Si} (Figure 20).\textsuperscript{57} Reaction with the \textit{Re} face of the carbonyl affords oxametallacyle \textit{Re} and results in a severe steric interaction between

\textsuperscript{54} Many nickel-mediated side reactions of alkynes require the binding of two alkynes at the same time.
\textsuperscript{55} Diastereoselectivity confirmed by NOESY.
\textsuperscript{56} Lower catalyst loadings may be used but lead to slightly lower yields of 47.
\textsuperscript{57} This analysis assumes the reaction is kinetically controlled, i.e. formation of \textit{Re} and \textit{Si} is irreversible, and that this occurs through a late transition state.
the allyl group and the alkyl side chain of the carbonyl. Reaction with the Si face of the carbonyl affords oxanickelacycle $Si$ and results in the placement of the oxygen atom $syn$ to the allyl group. Reaction occurs through the more accessible transition state to afford bicycle 47 with the observed diastereoselectivity.

**Scheme 19.**

With use of the alkyne-ketone reductive cyclization, bicycle 47 has been constructed over 9 steps in 14% overall yield (Scheme 20). The synthesis of 47 has installed several of the notable features of sieboldine A (1), including the all-carbon quaternary stereocenter, the tertiary alcohol, and the hydrindane ring system. With many of the key features already installed the focus turned to assembly of the final two rings in sieboldine A (1).
**F. Deprotection of 47 and Instability of β-Hydroxy Ketone 14.**

Scheme 20.

![Scheme 20](image)

From the reductive coupling product 47 deprotection of the silyl enol ether allowed access to β-hydroxy ketone 14. However, β-hydroxy ketone 14 was prone to decomposition reactions under acidic and basic conditions.

Scheme 21.

![Scheme 21](image)

The major decomposition pathway of β-hydroxy ketone 14 is likely a retro-aldol reaction to form an enone such as 48. This decomposition reaction readily occurred upon treatment with tertiary amine bases or upon exposure to silica gel. The instability of β-hydroxy ketone 14 made subsequent functionalization difficult and investigation into more robust synthetic intermediates was pursued.

To increase the stability of β-hydroxy ketone 14 attempts to protect the tertiary alcohol were pursued. Due to its sensitivity to both acidic and basic conditions the protection conditions were limited to those occurring under neutral conditions.
Table 5. Protection of β-Hydroxy Ketone 14

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ac₂O, DMAP, NEt₃</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>Ac₂O, DMSO</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>TMSCN, DCE, 40 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>TMSCN (neat), 100 °C</td>
<td>50% 49, R = SiMe₃</td>
</tr>
</tbody>
</table>

β-Hydroxy ketone 14 was treated with the conditions indicated in table 5. Exposure of 14 to tertiary amine bases resulted in decomposition of the starting material, likely via the retro aldol reaction. Less basic conditions resulted in recovery of starting ketone 14 unchanged (Table 5, entries 2 and 3). Forcing conditions with TMSCN lead to successful protection as the silyl ether (table 5, entry 4). For use of TMSCN in the protection of a base sensitive compound, see: Corey, E. J.; Wu, Y. -J. J. Am. Chem. Soc. 1993, 115, 8871-8872.

Scheme 22.
While the sensitivity of β-hydroxy ketone 14 was an unexpected problem it may explain the site selectivity observed in the reductive cyclization of diketone 15 (Scheme 23). Reaction at the cyclic carbonyl of 15 affords the bicyclic compound 41, which was isolated and characterized (Scheme 15). In contrast, reaction at the exocyclic carbonyl would afford the sensitive β-hydroxy ketone 14 which may decompose under the reaction conditions or upon workup and isolation. Thus the apparent site-selectivity may be a consequence of the sensitivity of β-hydroxy ketone 14 and its selective destruction under the reaction conditions.59

**G. Tertiary Alcohol Protection**

In order to circumvent the decomposition reactions of β-hydroxy ketone 14, a strategy involving protection of the tertiary alcohol of 47, followed by subsequent functional group transformations was pursued.

![Chemical structure](image)

In model reactions with a substrate containing a 1,3-enzyme component the crude reaction mixture displayed two peaks corresponding to reductive coupling products. Additionally, GC/MS trace also showed the presence of two reductive coupling products. However, only one product could be isolated from the reaction mixture and it corresponded to reaction at the ring carbonyl.
Table 6. Protection of Allylic Alcohol 47.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ac₂O, DMAP, NEt₃, C₆H₆, 80 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>TBSOTf, NEt₃</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>TMSOTf, NEt₃</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>PMBCI, NaH, TBAI</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5</td>
<td>BSA, DMF, 70 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>KOH, DMSO, Me</td>
<td>62 % 50, R = Me</td>
</tr>
</tbody>
</table>

The tertiary allylic alcohol of 47 could not be protected under a variety of intermolecular reaction conditions (Table 4, entries 1-5). This is likely the result of the severely congested environment about the allylic alcohol of 47. The only successful protection of 47 was accomplished upon treatment with iodomethane in DMSO to form methyl ether 50 (Table 4, entry 6). While this product was potentially useful for spectroscopic studies, it was not synthetically useful due to the harsh reaction conditions required to remove this protecting group.⁶⁰

In an attempt to circumvent some of the difficulties encountered with the intermolecular protection of 47 an intramolecular protection strategy was pursued. It was reasoned that an intramolecular protection would be less sensitive to the steric environment about the alcohol and would allow for protection of the tertiary alcohol 47.

⁶⁰ Methyl ether 50 was formed for subsequent NOESY studies.
Pursuit of the intramolecular protection strategy began with an oxidative deprotection of the PMB ether of 47 to afford diol 51 in good yield. Subsequent Swern oxidation of diol 51 afforded hemiacetal 52. Fortuitously, hemiacetal 52 was a crystalline solid and an X-ray crystal structure confirmed the relative stereochemistry shown (Figure 21).
Figure 21. Confirmation of Relative Stereochemistry.

Scheme 24.

Treatment of hemiacetal 52 with MeOH and PPTS afforded a methyl acetal, which was subsequently treated with buffered TBAF to afford the cyclohexanone 53 (Scheme 25). This four-step process accomplished protection of the hindered tertiary
alcohol of 47, formation of the THF ring in 1, and afforded the cyclohexanone substrate used in subsequent transformations.

**H. Synthesis of Diketone 55**

Scheme 25.

Functionalization of the terminal olefin of 53 via a hydroboration/oxidation sequence afforded a primary alcohol, which was treated with the commercially available Boc protected hydroxylamine reagent under Mitsunobu conditions. This afforded the desired hydroxylamine compound 54, which was treated with ozone to oxidatively cleave the aryl-substituted olefin and form diketone 55 in good yield.

---

Diketone 55 possesses all of the necessary functional groups to form 1. It was envisioned that treatment of 55 with Lewis or Brønsted acids would remove the Boc groups from the hydroxylamine, thereby freeing the hydroxylamine to react with oxocarbenium ion 56 generated from the methyl acetal under acidic reaction conditions (Figure 22). If successful, this reaction would assemble a 9-membered ring and complete the total synthesis of 1.

**Table 7. Condensation Attempts.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcCl, MeOH</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>TFA, CH₂Cl₂</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>TMSI, CH₂Cl₂</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CAN, MeCN</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>ZnBr₂, CH₂Cl₂</td>
<td>16% 57</td>
</tr>
</tbody>
</table>
Treatment of diketone 55 with a variety of Brønsted and Lewis acids resulted in complete destruction of the starting material (Table 4, entries 1-4). In only one case was successful Boc deprotection observed (Table 4, entry 5). Unfortunately, under these conditions the freed hydroxylamine cyclized onto the cyclohexanone to form nitrone 57.

Scheme 26.

In retrospect nitrone formation should have been a larger concern as formation of a 6-membered ring should be much more facile than formation of a 9-membered ring. Isolation and characterization of nitrone 57 conclusively demonstrated that an alternative ring-closing strategy was required to complete the total synthesis of sieboldine A (1).

I. Synthesis of Alloc Derivatives

From the cyclization studies with diketone 55 three main problems were identified, they are i) condensation of the hydroxylamine with the cyclohexanone, ii) low reactivity of the methyl acetal, and iii) difficulty in removing the Boc groups from the hydroxylamine.
These problems were addressed by targeting hydroxylamine 59 as the ring-forming substrate. With the cyclohexanone protected as a silyl enol ether, nitrone formation cannot occur. Additionally, with the silyl enol ether in place a hemiacetal can be used as the electrophile in ring-closing reactions and should be much more reactive than the methyl acetal. Finally, replacing the Boc protecting groups with readily removable and differentiable protecting groups should allow for facile access to a variety of ring-closing substrates.

The one complication of targeting hydroxylamine 59 is that oxidative cleavage of the aryl-substituted olefin becomes more challenging. Due to the Alloc protecting group, the
olefin must be cleaved before introduction of the protected hydroxylamine. This would require a selective oxidation of the aryl-substituted olefin in the presence of the silyl enol ether (Figure 24). This reaction was expected to be difficult due to the presence of an electron rich silyl enol ether which should react more readily than the aryl-substituted olefin under the oxidative cleavage conditions.

**Figure 25. Selective Oxidative Cleavage of Alkene 58.**

If the oxidative cleavage of 60 to 61 is difficult, the aryl-substituted olefin could be cleaved after formation of the nine-membered ring (Figure 25). This would also be a challenging transformation as oxidative cleavage after ring formation must be selective for reaction with the aryl-substituted olefin in the presence of a secondary hydroxylamine. In an effort to determine whether the aryl-substituted olefin could be cleaved in the presence of a silyl enol ether studies on this oxidative cleavage were performed.

**Scheme 27.**

These studies began from the reductive cyclization product 47. From 47 a chemoselective hydroboration afforded primary alcohol 60 after oxidative workup. The
selectivity of this hydroboration was surprising given that it reacted preferentially with the terminal olefin, which is less electron-rich than the silyl enol ether. Presumably, this is a result of the steric hindrance about the silyl enol ether.

**Table 8. Oxidative Cleavage.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ac</td>
<td>1% Pyridine, O₃, PPh₃</td>
<td>No enol ether present</td>
</tr>
<tr>
<td>2</td>
<td>PMB</td>
<td>(C₁₅H₃₃)NMe₃MnO₄, CH₂Cl₂</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>PMB</td>
<td>OsO₄, Pyridine, NMO, tBuOH, H₂O, THF</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>Ac</td>
<td>RuCl₂·H₂O, NaIO₄</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>PMB</td>
<td>KMnO₄, THF, H₂O</td>
<td>Trace 64</td>
</tr>
</tbody>
</table>

Primary alcohol 63 was subjected to the oxidative cleavage conditions indicated. Ozone, in the presence of pyridine, reacted preferentially with the silyl enol ether.⁶² OsO₄-mediated dihydroxylation conditions were unsuccessful as both the aryl substituted olefin and the silyl enol ether proved unreactive under catalytic or stochiometric metal loading. Even RuO₄, a very reactive oxidant, failed to react with either olefin in 63 and resulted in isolation of starting material.

Permanganate reactions were probed next. Cetyltrimethylammonium permanganate is reported to be selective for the oxidative cleavage of aryl-substituted olefins in the presence of alcohols and non-conjugated olefins,⁶³ but this reagent did not

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react with alcohol 63. Finally, alcohol 63 was treated with KMnO₄ and a trace amount of diketone 64 was isolated. This product results from cleavage of the aryl-substituted olefin and transfer of the aryl group to the tertiary alcohol as a benzoate. Unfortunately, optimization of this oxidative cleavage reaction could not be achieved.

The steric environment about the aryl-substituted olefin likely contributes to its low reactivity with these oxidants. One other possible explanation for the difficulty encountered in the oxidative cleavage of the aryl-substituted olefin of 63 is that the primary alcohol participates in undesired oxidation reactions and/or sequesters the oxidant in some way. To test this hypothesis studies upon compounds without the free primary alcohol were pursued.

**Table 9. Oxidative Cleavage**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OAc</td>
<td>KMnO₄, THF, H₂O</td>
<td>No Reaction</td>
</tr>
<tr>
<td>2</td>
<td>N₃</td>
<td>RuCl₃·H₂O, Ozone, NaHCO₃, CH₂CN, H₂O</td>
<td>No Reaction</td>
</tr>
<tr>
<td>3</td>
<td>N₃</td>
<td>RuCl₃·H₂O, NaIO₄, CH₂CN, H₂O</td>
<td>No Reaction</td>
</tr>
<tr>
<td>4</td>
<td>N₃</td>
<td>RuCl₃·H₂O, NaIO₄, CH₂CN, H₂O, 50 °C</td>
<td>20% 66</td>
</tr>
</tbody>
</table>

Treatment of 65 with KMnO₄ resulted in recovery of starting material. RuO₄-catalyzed oxidative cleavage conditions at room temperature showed low reactivity to both the aryl-substituted olefin and the silyl enol ether. Under forcing conditions RuO₄
did oxidize the aryl-substituted olefin, however instead of cleaving the olefin to provide 67 it afforded a product tentatively assigned as epoxide 66.\textsuperscript{64} After these extensive screens, efficient and selective oxidative cleavage of the aryl-substituted olefin remained elusive. Despite concerns about when and how the oxidative cleavage of the aryl-substituted olefin could be accomplished investigation into the Alloc protecting group strategy continued.

**Scheme 28.**

```
\begin{align*}
\text{HN(OCOOME)Alloc} & \quad \text{PPh}_3, \text{ DEAD} \\
\text{Ph} & \quad \text{Me} \quad \text{HN(OCOOME)Alloc} \\
\text{OH} & \quad \text{Me} \quad \text{OH} \\
\text{Ph} & \quad \text{Me} \quad \text{OH} \\
\text{TBSO} & \quad \text{TBSO} \\
\text{OPMB} & \quad \text{OPMB} \\
\end{align*}
```

From primary alcohol 60 a Mitsunobu reaction installed the protected hydroxylamine derivative to afford compound 68. Subsequent oxidative deprotection of the PMB ether afforded diol 69, which was oxidized to afford hemiacetal 59.

\textsuperscript{64} RuO\textsubscript{4} is reported to epoxidize sterically hindered olefins. For an example, see: Kametani, T.; Katoh, T.; Tsubuki, M.; Honda, T. *Chem. Lett.* 1985, 485-488.
At this point removal of the Alloc group was required so that formation of the 9-membered ring could be investigated. Treatment of hemiacetal 59 with standard Alloc deprotection conditions resulted in isolation of only trace amounts of the deprotected product 70. The difficulty in removing the Alloc group was ascribed to the formation of an alternative π-allyl species between the hemiacetal and the aryl-substituted olefin. Formation of this alternative π-allyl species destroys the tertiary allylic alcohol that had been installed in the reductive cyclization. Without access to hydroxylamine 70, investigation into formation of the 9-membered ring could not be pursued, and our attention turned to alternative synthetic strategies.

**J. Staudinger aza-Wittig Approach**

The problems with deprotecting the Alloc group of 59 resulted in a significant redesign of the synthesis. While the silyl enol ether and hemiacetal functional groups of

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65 This assertion is supported by the observation that diol 69, without the hemiacetal present, undergoes facile Alloc deprotection.
the new target were kept intact, the hydroxylamine portion of the molecule was replaced with an azide (Figure 26). Substitution of the hydroxylamine moiety with an azide reduces the number of protecting group manipulations and allows the use of an alternative ring-closing strategy, the Staudinger aza-Wittig reaction.66

Figure 26. Staudinger aza-Wittig Approach

While the azide simplifies the synthesis in some aspects, the main complication of pursuing a Staudinger aza-Wittig approach is that the nitrogen atom is no longer in the same oxidation state in N,O-acetal 71 as it is in sieboldine A (1). Substituting an azide for the hydroxylamine would require the use of a selective, late-stage oxidation of N,O-acetal 71 to a hydroxylamine containing N,O-acetal for completion of the total synthesis of sieboldine A (1).

While a variety of oxidation methods are reported to allow formation of hydroxylamines from secondary amines, including oxidation with DMDO,\textsuperscript{67} Davis' reagent,\textsuperscript{68} Oxone/silica,\textsuperscript{69} and benzoyl peroxide,\textsuperscript{70} these methods generally rely upon strict control of the oxidant stoichiometry to prevent over-oxidation of the amine. Additionally, these methods are reported for oxidations of dialkyl amines, and it is unclear how an \textit{N,O}-acetal will behave under the same oxidation conditions. Despite concerns about the final oxidation step, this strategy was pursued because it appeared to allow the most straightforward access to the natural product 1.

Starting from primary alcohol 60, mesylation followed by sodium azide displacement, and oxidative deprotection of the PMB ether affords diol 73 in good yield.

\textsuperscript{70} Biloski, A. J.; Ganem, B. \textit{Synthesis} 1983, 537-538.
over three steps. Oxidation of diol 73 under Parikh-Doering conditions resulted in clean conversion of the diol into hemiacetal 72.\textsuperscript{71}

Investigation into the intramolecular Staudinger \textit{aza}-Wittig reaction began by treatment of azide 72 with triphenylphosphine. At room temperature no reaction was observed between the azide and triphenylphosphine, but upon heating slow disappearance of the starting material was observed. Presumably, the phosphine was reducing the azide to form an iminophosphorane. However, upon prolonged heating the iminophosphorane generated from triphenylphosphine and azide 72 slowly decomposed without any observed \textit{aza}-Wittig reaction.

\textbf{Scheme 31.}

Other phosphines are capable of participating in the Staudinger \textit{aza}-Wittig reaction, and a report comparing the reactivity of different phosphines\textsuperscript{72} suggested that small electron rich phosphines would be more reactive in both initial formation of the iminophosphorane and in the subsequent \textit{aza}-Wittig reaction. To this end, azide 72 was

\begin{footnotesize}
\begin{thebibliography}{99}
\end{thebibliography}
\end{footnotesize}
treated with trimethylphosphine in refluxing toluene and afforded the tetracyclic N,O-acetal 77 in modest yield (Scheme 31).

Figure 28. Aminophosphonium Salts

In an attempt to gain further understanding of the aza-Wittig reaction of 72 simple $^{31}$P NMR experiments were conducted. These experiments showed that initial reduction of the azide with PMe$_3$ required heating to approximately 50 °C. Interestingly, a $^{31}$P NMR signal was not observed for the intermediate iminophosphorane (-10 to 0 ppm)$^{73}$ or oxazaphosphetane (-55 to -35 ppm).$^{74}$ Instead, signals were observed between 30 and 40 ppm and most closely correspond to the chemical shifts of aminophosphonium salts (30 to 45pppm).$^{70}$ Aminophosphonium salts, such as 78 or 79, result from protonation of the iminophosphorane (Figure 28). Attempts to regenerate the iminophosphorane from the presumed aminophosphonium salt were pursued by addition of an external base. However these attempts directed towards regeneration of the iminophosphorane intermediate did not provide better results.

Assuming that the proton source for formation of the aminophosphonium intermediate was derived from the hemiacetal, treatment of hemiacetal 72 with strong base before addition of trimethylphosphine was explored. This reaction did not lead to an

improvement of the yield of the Staudinger aza-Wittig reaction and additional attempts to improve the chemical yield of this ring-forming step were unsuccessful. Eventually, it was decided that the modest yield of this reaction was acceptable in light of the challenges involved in construction of medium-sized rings and the complexity of the system.

**Scheme 32.**

To continue protection of \(N,O\)-acetal was necessary. Initially Cbz protection of \(N,O\)-acetal 77 as was pursued. However, with several reagents and reaction conditions the Cbz protected \(N,O\)-acetal 80 was not isolated. The low reactivity of \(N,O\)-acetal 77 with the Cbz donors was unexpected and suggested that the nitrogen of the \(N,O\)-acetal was a poor nucleophile. This may be attributed to its steric hindrance and the donation of electron density into the \(N,O\)-acetal. Due to the reduced nucleophilicity of 77 more electrophilic acylating reagents were explored.

**Scheme 33.**
Protection of the tetracyclic $N,O$-acetal could be accomplished with trifluoroacetic acid anhydride and triethylamine to afford a trifluoroacetamide product. Subsequent deprotection of the silyl enol ether afforded cyclohexanone $81$.

**Scheme 34.**

![Scheme 34](image)

Oxidative cleavage of the aryl-substituted olefin of $81$ proceeded smoothly to afford diketone $82$. This diketone is a deprotection step and an amine oxidation step removed from sieboldine A (1).

**K. Amine Oxidation Studies**

**Table 10**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ba(OH)$_2$</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>NaBH$_4$</td>
<td>&quot;</td>
</tr>
<tr>
<td>3</td>
<td>K$_2$CO$_3$, MeOH, THF</td>
<td>&quot;</td>
</tr>
<tr>
<td>4</td>
<td>K$_2$CO$_3$, MeOH, THF, H$_2$O</td>
<td>slow, inconsistent conversion</td>
</tr>
<tr>
<td>5</td>
<td>K$_2$CO$_3$, MeOH, THF, H$_2$O</td>
<td>consistent formation of $71$ over 1 h</td>
</tr>
</tbody>
</table>

Deprotection of the trifluoroacetamide was much more difficult than initially anticipated. Treatment of trifluoroacetamide $82$ with several conditions resulted in decomposition of the substrate. After several attempts, deprotection of
trifluoroacetamide 82 could be consistently achieved by treatment with K₂CO₃ in THF/MeOH/H₂O (2:2:1) (Table 10). Free N,O-acetal 71 was used in the subsequent oxidation studies without purification due to concerns about its stability.⁷⁵

Table 11. Amine Oxidation Studies.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMDO</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>Davis's Reagent</td>
<td>&quot;</td>
</tr>
<tr>
<td>3</td>
<td>Oxone, SiO₂</td>
<td>&quot;</td>
</tr>
<tr>
<td>4</td>
<td>mCPBA</td>
<td>&quot;</td>
</tr>
<tr>
<td>5</td>
<td>MTO, UHP</td>
<td>&quot;</td>
</tr>
<tr>
<td>6</td>
<td>Benzoyl Peroxide</td>
<td>No Reaction</td>
</tr>
</tbody>
</table>

Treatment of the unpurified N,O-acetal 71 with several different oxidants afforded a variety of unidentifiable oxidation products (Table 7, entries, 1, 2-7). Attempts at the direct oxidation with DMDO, Davis’ reagent, methyltrioxorhenium/urea hydrogen peroxide, and Oxone/silica resulted in destruction of the starting N,O-acetal. Treatment of N,O-acetal with mCPBA, in an attempt to oxidize directly to the nitrone, also resulted in destruction of the starting material.

An attempt at a one-step deprotection/oxidation with LiOOH was also pursued. This attempt relied upon the in situ generation of trifluoroperacetic acid (TFPAA) for oxidation of the N,O-acetal. This was an attractive approach because exactly one

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⁷⁵ Studies with model N,O-acetals showed them to be very sensitive to purification on silica gel and alumina resulting in hydrolysis of the N,O-acetal
equivalent of TFPAA would be generated from the deprotection of trifluoroacetamide 82.

It was reasoned that with an exactly stoichiometric amount of TFPAA, a selective oxidation would occur to afford sieboldine A (1).

Scheme 35.

Unfortunately, this reaction did not result in isolation of the natural product 1. Instead, treatment of 82 with LiOOH afforded an unidentifiable mixture of oxidation products. While exactly 1 equivalent of TFPAA would be formed in this reaction an excess of hydrogen peroxide was present. Hydrogen peroxide may have led to additional oxidation events as this reagent is known to oxidize amines.

Figure 29.

The destruction of N,O-acetal 71 under these conditions may be due to over-oxidation to form nitrone 83. If nitrone 83 were formed a variety of different reactions could occur. In particular, a hydrolysis reaction either upon workup or under the reaction conditions would afford the oxime 84. Other nucleophiles could also react with nitrone 83 such as N,O-acetal 71 thereby providing an oxidative dimer. Unfortunately, none of
the oxidation products could be isolated and characterized and the reactivity of \(N,O\)-acetal 71 under these oxidation conditions is still unknown. Due to the difficulty with the direct oxidation of \(N,O\)-acetal 71 to sieboldine A (1) investigation into alternative amine oxidation strategies were pursued.

One possible strategy towards the total synthesis of 1 could rely upon formation of the hydroxylamine by a Cope elimination.\(^{76}\) In this reaction an amine \(N\)-oxide undergoes a thermal elimination to afford a secondary hydroxylamine and an olefin. The elimination occurs intramolecularly with the amine \(N\)-oxide acting as base and proceeds through a 5-membered ring transition state. In the classic reaction, selectivity between elimination of different substituents is determined by the number of \(\beta\)-hydrogen atoms.

**Figure 30.**

![Figure 30](image)

More recent studies have focused upon the use of \(\beta\)-electron withdrawing groups. This allows the elimination to occur at lower temperatures and provides selectivity for elimination of the substituent substituted with the \(\beta\)-electron withdrawing group (Figure 24).\(^{77}\) The Cope strategy is an attractive approach because it avoids the difficult problem of a selective amine oxidation reaction. The oxidation required for the Cope elimination is from tertiary amine to amine \(N\)-oxide, a process that is not plagued by the same over-oxidation concerns as the direct oxidation approach.

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The Cope elimination requires a tertiary amine substrate and the first attempts to access tertiary amine substrates began with \(N,O\)-acetal 77 (Scheme 36). It was envisioned that an *aza*-Michael reaction of \(N,O\)-acetal 77 and acrylonitrile would afford tertiary amine 88. Subsequent oxidation would afford the the \(N\)-oxide for the Cope elimination.

**Scheme 36.**

Unfortunately, \(N,O\)-acetal 77 failed to react with acrylonitrile under the reaction conditions. The poor reactivity of this system is likely due to the reduced nucleophilicity of the nitrogen atom due to donation of electron density into the C–O \(\sigma^*\) orbital and the steric environment about the \(N,O\)-acetal.

**Scheme 37.**

Another attempt at formation of the tertiary amine entailed treatment of 82 with the deprotection conditions in the presence of acrylonitrile. Unfortunately, this did not

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\(^7^8\)An initial screen of conditions used this compound as a model for 77:
result in the formation of the desired tertiary amine 89 and instead resulted in decomposition of the \( N,O \)-acetal. With the aza-Michael ineffective alternative methods for tertiary amine synthesis were investigated.

The next strategy investigated for tertiary amine synthesis was reductive amination. While this method could not allow access to the \( \beta \)-cyano amines, it should allow access to a variety of tertiary amine substrates.

**Scheme 38.**

![Scheme 38](image)

Treatment of 71 with acetaldehyde and sodium triacetoxyborohydride afforded tertiary amine 90. Tentatively characterized by \(^1\)H NMR.

From tertiary amine 90 oxidation of the amine to the \( N \)-oxide was attempted with \( m \)CPBA. While consumption of starting material was observed it was not possible to determine whether formation of the amine \( N \)-oxide had occurred. The difficulty encountered in the amine oxidation of \( N,O \)-acetal 71 led to exploration of alternative targets that could be constructed with a nickel-catalyzed alkyne ketone reductive cyclization.

**Figure 31. Alopecuridine.**

\(^{79}\) Tentatively characterized by \(^1\)H NMR.
Among the Lycopodium alkaloids, alopecuridine (2a) is an attractive target displaying similar structural characteristics to sieboldine A (1), including the hydrindane core, the all-carbon quaternary center, and the $\alpha$-hydroxy ketone motif, but without the hydroxylamine containing $N,O$-acetal (Figure 31).

**Figure 32. Keto-amine and Carbinolamine Forms of Alopecuridine.**

Alopecuridine was first isolated in 1967 by Ayer and coworkers from Lycopodium alopecuroides.\textsuperscript{80} Initially only a basic outline of the structural features of 2a were reported due to some unusual characteristics noted in its IR spectra. A subsequent X-ray structure confirmed the structure shown in Figure 32.\textsuperscript{81} The IR characteristics of this compound were explained by the formation of an equilibrium mixture of the keto-amine (2a) and carbinolamine (2a') forms of alopecuridine wherein the secondary amine adds to the cyclohexanone (Figure 32). Two retrosynthetic analyses were considered for 2a, both intercepting intermediates formed in the studies directed towards the total synthesis of 1.

\textsuperscript{81} Ayer, W. A.; Altenkirk, B.; Fukuzawa, Y. Tetrahedron, 1974, 30, 4213-4214.
The first retrosynthetic analysis led to the notion of preparing alopecuridine (2a) via oxidation state adjustments and functional group manipulations of tricyclic amine 91. Amine 91 could be accessed from tetracycle 77 via reduction of the N,O-acetal. This approach is attractive as it intercepts an advanced intermediate already prepared (77).

An alternative retrosynthesis of 2a is shown in figure 34. Starting from 2a, oxidation state adjustments and functional group manipulations would suggest tricycle 92 as a logical precursor. The hydrindane core of 92 could in turn be constructed from precursor 93, a novel substrate for the nickel-catalyzed alkyne-ketone reductive cyclization.
Ketone 93 could be prepared from 16 by way of a cyclization reaction and other functional group manipulations reminiscent of those already performed on closely related compounds.

This second approach is interesting as it relies upon formation of the aza-cyclononane before the nickel-catalyzed alkyne-ketone reductive cyclization. Investigation into the synthesis of alopecuridine (2a) is currently ongoing and will be reported in due course.
A nickel-catalyzed alkyne-ketone reductive cyclization was employed to assemble the hydridane core of 1. Treatment of ketone 46 with reductive cyclization conditions resulted in formation of bicycle 47 with high yield and high diastereoselectivity. This reaction assembles the vicinal quaternary stereogenic centers of 1.

Subsequent elaboration of 47 allows access to hemiacetal 72. Treatment of hemiacetal 72 with trimethylphosphine results in an intramolecular Staudinger aza-Wittig reaction to afford the tetracyclic $N,O$-acetal shown. This $N,O$-acetal was then protected and the silyl enol ether removed to afford tetracyclic cyclohexanone 81.

These two steps allow access to the tetracyclic diketone 82. This intermediate contains the tetracyclic structure of the natural product and is a trifluoroacetamide deprotection and an amine oxidation removed from sieboldine A (1). Overall, tetracyclic diketone 82 is assembled over 18 steps and in 1% yield from enone 17.
Studies directed towards the application of a nickel-catalyzed alkyne-ketone reductive cyclization towards the synthesis of alopecuridine are currently under investigation.
Experimental Section:

General Information. Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of inert gas (Ar, N₂) with rigid exclusion of moisture from reagents and glassware. Dichloromethane and toluene were distilled from calcium hydride. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were distilled from a blue solution of benzophenone ketyl. Diisopropylamine (iPr₂NH) and 1,3-diaminopropylamine (APA) were distilled from calcium hydride and stored over potassium hydroxide. Trifluoroacetic anhydride ((CF₃CO)₂O) was distilled from phosphorous pentoxide. All other reagents were used as received from commercial supplier. Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F254 plates. The developed chromatogram was visualized by UV lamp (254 nm), ethanolic phosphomolybdic acid (PMA) or cerium molybdate (CAM). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230-400 mesh). ¹H, ¹⁹F, and ¹³C NMR spectra were recorded in CDCl₃, unless otherwise noted, on a Varian Mercury 300 MHz spectrometer, Bruker Avance 400 MHz spectrometer, a Varian Inova 500 MHz spectrometer, or a Bruker Avance 600 MHz spectrometer. Chemical shifts in ¹H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm) or benzene (7.16 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d= doublet, t = triplet, q = quartet, p = pentet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, m = multiplet), coupling constant in hertz (Hz), and integration. Chemical shifts of ¹⁹F NMR
spectra are reported in ppm from an external standard of trifluoroacetic acid (-76.55 ppm). Chemical shifts of $^{13}$C NMR spectra are reported in ppm from the central peak of CDCl$_3$ (77.23 ppm) or $C_6D_6$ (128.4 ppm). Infrared (IR) spectra were recorded on a Perkin-Elmer 2000 FT-IR. High resolution mass spectra (HR-MS) were obtained on a Bruker Daltronics ApexIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer by Dr. Li Li of the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Melting points were recorded on a Mel-Temp II melting point apparatus.

(±)-Trimethyl((3R, 5R)-5-methyl-3-(prop-1-ynyl)cyclohex-1-enyloxy)silane (31): To a round-bottomed flask at −42 °C was condensed propyne (2.5 mL, 46 mmol) followed by slow addition of Et$_2$O (91 mL) down the sides of the flask. To this solution was added nBuLi (18 mL, 2.5 M, 46 mmol) and a solution of anhydrous ZnBr$_2$ (10 g, 46 mmol) in THF (46 mL). The alkynyl zinc solution was warmed to room temperature and stirred 10 min before being cooled to −42 °C and addition of 17 (4.0 g, 36 mmol) and TMSOTf (8.2 mL, 46 mmol). The solution was stirred at −42 °C for 15 min before quenching with a saturated aqueous solution of NaHCO$_3$. The layers were separated and the aqueous was extracted with hexane. The organic layers were combined, washed with water, brine, dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure. The crude residue was distilled at reduced pressure (2 torr, 90 °C) to yield 4.9 g (62%) of 31.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.85 (dd, $J = 4.9$, 1.8 Hz, 1H), 3.12 (m, 1H), 2.12-2.01 (m, 2H), 1.77 (d, $J = 2.4$ Hz, 3H), 1.69-1.58 (m, 2H), 1.31 (ddd, $J = 12.7$, 10.6, 5.6 Hz, 1H), 0.97 (d, $J = 6.5$ Hz, 3H), 0.18 (s, 9H)

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 150.9, 104.8, 82.8, 75.3, 38.3, 36.9, 26.1, 26.1, 21.3, 3.8, 0.5

IR (thin film NaCl): 2957, 1667, 1457, 1370, 1304, 1253, 1197, 899, 845, 755, 684 cm$^{-1}$

HRMS ESI (m/z): [M+Na]$^+$ calcd for C$_{13}$H$_{22}$OSiNa, 245.1332; found 245.1339.

$(\pm)$-(3R,5R)-2-(1-Hydroxy-4-(4-methoxybenzoyloxy)butyl)-5-methyl-3-(prop-1-ynyl)cyclohexanone (32): To a round-bottomed flask equipped was added 31 (4.9 g, 22 mmol) and THF (90 mL) before cooling to $-42$ °C and addition of nBuLi (9.2 mL, 2.5 M, 23 mmol). This solution was stirred at $-42$ °C for 4 h before cooling to $-78$ °C and addition of a solution ZnBr$_2$ (2.5 g, 11 mmol) in THF (20 mL). This solution was stirred for 1 hour at $-78$ °C before addition of 20 and stirred for 1 hour at $-78$ °C before quenching with saturated aqueous NH$_4$Cl. The layers were separated and extracted with EtOAc. The organic layers were combined, washed with water, brine, dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure. The crude residue
was purified by silica gel chromatography (15% EtOAc/hex - 50% EtOAc/hex) to yield 6.0 g (76%) of 32 as a mixture of diastereomers.

\(^1\)H NMR (500MHz, CDCl\(_3\), major diastereomer) \(\delta\) 7.24 (d, \(J = 8.6\) Hz, 2H), 6.86 (d, \(J = 8.6\) Hz, 2H), 4.44 (d, \(J = 11.5\) Hz, 1H), 4.41 (d, \(J = 11.5\) Hz, 1H), 3.90-3.84 (m, 1H), 3.78 (s, 3H), 3.49-3.43 (m, 2H), 3.05 (d, \(J = 8.7\) Hz, 1H), 3.02-2.96 (m, 1H), 2.44 (dd, \(J = 13.2, 5.2\) Hz, 1H), 2.38-2.31 (m, 2H), 2.13 (dd, \(J = 13.1, 7.4\) Hz, 1H), 1.89-1.6 (m, 6H), 1.75 (d, \(J = 2.3\) Hz, 3H), 0.96 (d, \(J = 6.9\) Hz, 3H)

\(^{13}\)C NMR (125 MHz, CDCl\(_3\), major diastereomer) \(\delta\) 212.5, 159.3, 130.4, 129.5, 113.9, 80.3, 78.7, 72.8, 71.4, 70.1, 60.0, 55.4, 49.0, 36.7, 33.4, 30.7, 30.4, 26.6, 20.3, 3.7

IR (thin film NaCl): 3419, 2952, 2868, 1709, 1612, 1513, 1456, 1363, 1302, 1248, 1174, 1095, 1035, 820 cm\(^{-1}\)

HRMS ESI (m/z): [M+Na]\(^+\) calcd for C\(_{22}\)H\(_{30}\)O\(_4\)Na, 381.2036; found 381.2030.
(±)-(3R,5R)-2-(1-Hydroxy-4-(4-methoxybenzyl)oxy)butyl)-5-methyl-3-(prop-1-ynyl) cyclohexanol (30): To a round-bottomed flask was added LiAlH₄ (513 mg, 14 mmol) and THF (50 mL). This suspension was cooled to 0 °C and a THF (20 mL) solution of 32 (2.4 g, 6.7 mmol) was added dropwise and stirred with warming to room temperature overnight. After stirring overnight the reaction was cooled to 0 °C and carefully quenched with 0.51 mL H₂O, followed by 0.51 mL 15% (w/w) NaOH solution, and an additional 1.0 mL H₂O. The resulting precipitate was removed by filtration and the filtrate concentrated. The crude residue was purified by silica gel chromatography (40%) to yield 2.1 g (88%) 30 as a mixture of diastereomers.

¹H NMR (500 MHz, CDCl₃, major diastereomer) δ 7.25 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.47 (d, J = 11.6 Hz, 1H), 4.44 (d, J = 11.6 Hz, 1H), 4.39-4.28 (m, 2H), 4.28-4.24 (m, 1H), 4.12-4.05 (m, 1H), 3.81 (s, 3H), 3.50 (t, J = 5.6 Hz, 2H), 2.87-2.81 (m, 1H), 1.99-1.91 (m, 1H), 1.82-1.65 (m, 5H), 1.78 (d, J = 2.4 Hz, 3H), 1.60-1.40 (m, 3H), 1.32-1.21 (m, 1H), 1.02 (d, J = 6.8 Hz, 3H)

¹³C NMR (125 MHz, CDCl₃, major diastereomer) δ 159.4, 130.0, 129.6, 129.6, 114.0, 113.9, 82.0, 77.4, 77.2, 73.0, 70.4, 55.4, 48.0, 39.2, 33.0, 27.5, 26.0, 21.9, 21.8, 3.7
IR (thin film NaCl): 3334, 2921, 2857, 1612, 1586, 1513, 1456, 1362, 1302, 1248, 1173, 1096, 1036, 820 cm\(^{-1}\)

HRMS ESI (\(m/z\)): [M+Na]\(^+\) calcd for C\(_{22}\)H\(_{32}\)O\(_4\)Na, 383.2193; found 383.2183.

(±)-(3S,5R)-2-(1-Hydroxy-4-(4-methoxybenzyloxy)butyl)-5-methyl-3-(prop-2-ynyl) cyclohexanol (38): To a round-bottomed flask at 0 °C charged with KAPA\(^1\) solution (71 mL, 1.3 M, 92 mmol) was added 30 (2.1 g, 5.9 mmol) as a solution in THF (10 mL). The reaction was stirred for 2 h while warming from 0 °C to room temperature. After 2 h, the solution was cooled to 0 °C and quenched with H\(_2\)O. The aqueous layer was extracted with EtOAc and the combined organics were washed with 1 M HCl, H\(_2\)O, and brine before being dried over anhydrous Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 20% EtOAc/hec -60% EtOAc/hex) to yield 1.8 g (84%) of 38.

\(^1\)H NMR (500 MHz, CDCl\(_3\), major diastereomer) \(\delta\) 7.25 (d, \(J = 8.6\) Hz, 2H), 6.88 (d, \(J = 8.6\) Hz, 2H), 4.47 (d, \(J = 11.6\) Hz, 1H), 4.45 (d, \(J = 11.6\) Hz, 1H), 4.40-4.24 (m, 2H), 4.13-4.07 (m, 1H), 4.04-3.99 (m, 1H), 3.80 (s, 3H), 3.55-3.47 (m, 2H), 2.34 (ddd, \(J =

16.9, 7.1, 2.6 Hz, 1H), 2.25 (ddd, J = 16.9, 6.2, 2.6 Hz, 1H), 2.19-2.12 (m, 1H), 1.98 (t, J = 2.6 Hz, 1H), 1.83-1.67 (m, 6H), 1.64-1.46 (m, 3H), 1.30-1.23 (m, 1H), 1.05 (d, J = 6.8 Hz, 3H)

^13^C NMR (125 MHz, CDCl₃, major diastereomer) δ 159.4, 130.0, 129.7, 114.0, 114.0, 83.1, 73.0, 71.5, 70.5, 70.0, 69.5, 55.4, 46.3, 39.4, 35.3, 33.2, 26.9, 26.3, 22.8, 22.1

IR (thin film NaCl): 3340, 3296, 2927, 2869, 2115, 1613, 1586, 1513, 1457, 1362, 1302, 1248, 1174, 1096, 1034, 820, 637 cm⁻¹

HRMS ESI (m/z): [M+Na]⁺ calcd for C₂₂H₃₂O₄Na, 383.2193; found 383.2203.

(±)-(2S, 3S, 5R)-2-Allyl-(4-(4-methoxybenzyl)oxy)butanoyl)-5-methyl-3-(prop-2-ynyl) cyclohexanone (39): To a round-bottomed flask was added oxalyl chloride (6.0 mL, 70 mmol) and CH₂Cl₂ (120 mL) before cooling to -78 °C. To this solution was added DMSO (9.9 mL, 140 mmol) dropwise over 5 min and the solution stirred for 15 min before dropwise addition of 38 (5.0 g, 14 mmol) as a solution CH₂Cl₂ (20 mL). The resulting solution was stirred for 15 min at -78 °C before addition of triethylamine (39 mL, 280 mmol) and removal of the cold bath. After warming to room temperature the
solution was poured into water and extracted with ether. The combined organics were washed with water and brine before being dried over Na₂SO₄, filtered, and concentrated. The crude residue was purified by silica gel chromatography (gradient, 10% EtOAc/hex to 20% EtOAc/hex) to afford 4.4 g (89%) of the 1,3-diketone as a mixture of tautomers.

To a round-bottomed flask was added potassium carbonate (6.8 g, 50 mmol), acetone (125 mL), and the 1,3-diketone (4.4 g, 12 mmol). The reaction flask was fitted with a reflux condenser before heating to reflux. After reaching reflux, allyl iodide (1.4 mL, 16 mmol) was added and the reaction was stirred overnight before being cooled to room temperature, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 3% EtOAc/hex to 8% EtOAc/hex) to yield 3.0 g (62%) of 39.

$^1$H NMR (600 MHz, CDCl₃) δ 7.24 (d, $J = 8.8$ Hz, 2H), 6.88 (d, $J = 8.7$ Hz, 2H), 5.69-5.57 (m, 1H), 5.16 (d, $J = 7.2$ Hz, 1H), 5.13 (s, 1H), 4.39 (s, 2H), 3.81 (s, 3H), 3.39 (t, $J = 6.1$ Hz, 2H), 3.15 (ddt, $J = 14.0, 5.5, 1.6$ Hz, 1H), 2.59-2.17 (m, 10H), 1.97 (t, $J = 2.7$ Hz, 1H), 1.92-1.79 (m, 3H), 0.98 (d, $J = 6.7$ Hz, 3H)

$^{13}$C NMR (125 MHz, CDCl₃) δ 208.9, 208.2, 159.3, 132.8, 130.6, 129.5, 119.6, 113.9, 83.3, 72.7, 69.8, 69.6, 68.9, 55.5, 47.2, 38.0, 37.3, 36.6, 32.8, 28.9, 23.8, 20.5, 19.8

IR (thin film NaCl): 3289, 2925, 2852, 2117, 1694, 1611, 1585, 1511, 1245

HRMS ESI (m/z): [M+Na]$^+$ Calcd for C₂₅H₃₂O₄Na, 419.2193; found 419.2192.
(±)-(2S,3S,5R)-2-Allyl-2-(4-(4-methoxybenzyloxy)butanoyl)-5-methyl-3-(3-phenylprop-2-ynyl)cyclohexanone (15): To a round-bottomed flask was added Pd(PPh₃)₄ (0.45 g, 0.39 mmol), CuI (150 mg, 0.77 mmol), and iPr₂NH (38 mL). The solution was cooled to 0 °C before addition of iodobenzene (1.3 mL, 12 mmol) and stirred 5 min before dropwise addition of a solution of 39 (3.0 g, 7.7 mmol) in THF (15 mL). Reaction stirred with warming from 0 °C to room temperature overnight before being diluted with ether and addition of saturated aqueous NH₄Cl. The layers were separated and the aqueous extracted with Et₂O. The combined organics were washed with NH₄Cl, H₂O, and brine before being dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 5% EtOAc/hex to 10% EtOAc/hex) to yield 3.4 g (94%) of 15.

¹H NMR (600 MHz, CDCl₃) δ 7.40-7.37 (m, 2H), 7.30-7.27 (m, 3H), 7.24 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.70-5.62 (m, 1H), 5.18 (d, J = 17.7 Hz, 1H) 5.15 (d, J = 11.4, 1H), 4.39 (s, 2H), 3.81 (s, 3H), 3.41 (t, J = 6.1 Hz, 2H), 3.16 (dd, J = 13.9, 5.6 Hz, 1H), 2.63-2.45 (m, 6H), 2.44-2.38 (m, 1H), 2.36-2.23 (m, 3H), 1.92 (dt, J = 13.4, 5.3 Hz, 1H), 1.86-1.78 (m, 2H), 1.01 (d, J = 6.8 Hz, 3H)
$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 209.0, 208.5, 159.3, 132.8, 131.7, 130.6, 129.5, 128.4, 127.9, 123.9, 119.6, 114.0, 88.9, 82.0, 72.7, 69.7, 68.9, 55.5, 47.3, 38.4, 37.7, 36.9, 33.2, 28.9, 23.8, 21.0, 20.7

IR (thin film NaCl): 2955, 2927, 2857, 1685, 1612, 1512, 1247, 1098, 1034 cm$^{-1}$

HRMS ESI (m/z): [M+ Na]$^+$ calcd for C$_{31}$H$_{36}$O$_4$Na, 495.25058; found 495.24512.

(±)-1-((1S,3R,5S,8R,E)-8-Allyl-7-benzylidene-1-hydroxy-3-methylbicyclo[3.2.1]octan-8-yl)-4-(4-methoxybenzyl oxy)butan-1-one (41): To a round-bottomed flask in a glovebox was added Ni(cod)$_2$ (11 mg, 0.040 mmol) and PBu$_3$ (21 µL, 0.084 mmol). This flask was removed from the glovebox before addition of BEt$_3$ (65 µL, 0.45 mmol) and toluene (3 mL). To this yellow catalyst solution was added a solution of 15 in toluene (2 mL) over 5 min. The reaction was stirred overnight before opening to air and stirring for 45 min. The reaction was filtered and concentrated under reduced pressure and the crude residue was purified by silica gel chromatography (gradient, 5% EtOAc/hex to 10% EtOAc/hex) to afford 70 mg (67%) of 41.
1H NMR (600 MHz, CDCl₃) δ 7.36-7.30 (m, 4H), 7.23 (d, J = 8.6 Hz, 2H), 7.19 (t, J = 7.0 Hz, 1H), 6.89 (d, J = 8.6 Hz, 2H), 6.51 (s, 1H), 6.04-5.97 (m, 1H), 5.05 (d, J = 17.0 Hz, 1H), 5.03 (d, J = 9.5 Hz, 1H), 4.85 (s, 1H), 4.38 (d, J = 11.6 Hz, 1H), 4.35 (d, J = 11.5 Hz, 1H), 3.81 (s, 3H), 3.38 (t, J = 6.0 Hz, 2H), 2.79 (dd, J = 14.8, 6.1 Hz, 1H), 2.63 (dt, J = 7.1, 2.8 Hz, 2H), 2.60-2.53 (m, 3H), 2.49 (dd, J = 14.9, 8.8 Hz, 1H), 1.85-1.70 (m, 4H), 1.59-1.49 (m, 3H), 0.94 (d, J = 6.0 Hz, 3H)

13C NMR (125 MHz, CDCl₃) δ 218.4, 159.3, 147.4, 138.0, 134.2, 130.6, 129.4, 128.5, 128.5, 126.4, 120.2, 117.4, 113.9, 82.9, 72.6, 69.0, 62.6, 55.5, 44.1, 37.6, 34.9, 34.4, 34.3, 34.2, 25.4, 23.5, 21.5

IR (thin film NaCl): 3468, 2928, 2863, 1688, 1613, 1446, 1360, 1301, 1248, 1174, 1096, 1035, 916, 820, 755, 695 cm⁻¹

HRMS ESI (m/z): [M+ Na]** calcd for C₃₁H₃₆O₄Na, 497.2657; found 497.2662.

(±)-(2S,3S,5R)-2-Allyl-2-(4-hydroxybutanoyl)-5-methyl-3-(prop-2-ynyl)cyclohexanone (44): To a round-bottomed flask was added 39 (59 mg, 0.15 mmol), CH₂Cl₂ (5 mL), and pH 7.0 buffer (0.5 mL), before cooling to 0 °C. To the
solution was added DDQ (43 mg, 0.19 mmol) and the reaction stirred at 0 °C for 1.25 h before addition of a saturated aqueous solution of NaHCO₃. The reaction mixture was then extracted with EtOAc, washed with water, brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 10% EtOAc/hex to 20% EtOAc/hex) to afford 30 mg of 44 (72%).

¹H NMR (400 MHz, CDCl₃) δ 5.62 (m, 1H), 5.17 (d, J = 9.0 Hz, 1H), 5.14 (s, 1H), 3.61 (m, 2H), 3.15 (dd, J = 14.0, 5.7 Hz, 1H), 2.56-2.18 (m, 10H), 2.0-1.97 (m, 1H), 1.92-1.84 (m, 1H), 1.78 (p, J = 6.8 Hz, 2H), 1.67-1.62 (m, 1H), 1.00 (d, J = 6.6 Hz, 3H)

¹³C NMR (125 MHz, CDCl₃) δ 209.3, 209.0, 132.5, 119.8, 83.2, 69.8, 69.7, 62.1, 47.3, 38.2, 37.5, 37.0, 32.8, 28.9, 26.6, 20.7, 19.8

IR (thin film NaCl): 3400, 3291, 2956, 2928, 2874, 2117, 1694, 1437, 1383, 1221, 1056, 1018, 921 cm⁻¹

HRMS ESI (m/z): [M+ Na]⁺ calcd for C₁₇H₂₄O₃Na, 299.16177; found 299.16120.
(±)-1-((1R, 4R, 6S)-1-allyl-2-(tert-butyldimethylsilyloxy)-4-methyl-6-(3-phenylprop-2-ynyl)cyclohex-2-enyl)-4-(4-methoxybenzoyloxy)butan-1-one (46): To a round-bottomed flask was added 15 (3.4 g, 7.2 mmol), dichloromethane (36 mL), and triethylamine (6.0 mL, 43 mmol) before cooling to 0 °C. To this solution was added TBSOTf (8.3 mL, 36 mmol) and the reaction stirred at 0 °C for 3 h before being quenched by addition of a saturated aqueous solution of NaHCO₃. The aqueous was extracted with dichloromethane and the combined organics were washed with water, brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (10% Et₂O/pentanes) to yield 3.8 g (90%) of 46.

¹H NMR (600 MHz, CDCl₃) δ 7.39-7.37 (m, 2H), 7.29-7.26 (m, 3H), 7.24 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.60 (m, 1H), 5.15 (d, J = 23.3 Hz, 1H), 5.14 (s, 1H), 5.06 (d, J = 5.7 Hz, 1H), 4.40 (s, 2H), 3.81 (s, 3H), 3.43 (t, J = 6.2 Hz, 2H), 2.75 (ddd, J = 18.7, 8.3, 5.8 Hz, 1H), 2.70-2.62 (m, 2H), 2.57 (dd, J = 16.8, 3.9 Hz, 1H), 2.56-2.48 (m, 2H), 2.24-2.18 (m, 1H), 1.97 (dd, J = 16.8, 10.2 Hz, 1H), 1.91-1.76 (m, 4H), 1.06 (d, J = 7.0 Hz, 3H), 0.87 (s, 9H), 0.21 (s, 3H), 0.19 (s, 3H)
\(^\text{\textsuperscript{13}}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 212.1, 159.3, 149.3, 135.0, 131.7, 130.8, 129.5, 128.4, 127.8, 124.1, 118.7, 113.9, 111.3, 89.2, 81.9, 72.6, 69.3, 59.2, 55.5, 38.7, 36.0, 34.2, 31.6, 27.7, 25.7, 23.9, 22.0, 21.6, 18.2, -4.6, -4.9

IR (thin film NaCl): 2930, 1703, 1660, 1613, 1513, 1490, 1250, 1196, 1100, 1038, 839 cm\(^{-1}\)

HRMS ESI (\(m/z\)): [M+ Na]\(^+\) calcd for C\(_{37}\)H\(_{50}\)O\(_4\)SiNa, 609.3371; found 609.3372.

(±)-(1\(S\),3\(a\)S,5\(R\),7\(a\)S,E)-7a-Allyl-2-benzylidene-7-(tert-butyldimethylsilyloxy)-1-(3-(4-methoxybenzyloxy)propyl)-5-methyl-2,3,3\(a\),4,5,7\(a\)-hexahydro-1\(H\)-inden-1-ol (47): To a round-bottomed flask in a glovebox was added Ni(cod)\(_2\) (116 mg, 0.422 mmol) and PBu\(_3\) (210 \(\mu\)L, 0.842 mmol). The flask was removed from the glovebox before addition of triethylborane (610 \(\mu\)L, 4.20 mmol) and toluene (21 mL). The solution was heated to 50 °C in an oil bath before dropwise addition of 46 (1.23 g, 2.10 mmol) as a solution in toluene (21 mL). The reaction was stirred at 50 °C for 6 h before cooling to room temperature and opening to air. Reaction stirred open to air 45 min before being filtered through celite and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (3% EtOAc/hex) to afford 1.03 g (84%) of 47.
$^1$H NMR (600 MHz, CDCl$_3$) δ 7.36-7.31 (m, 4H), 7.24 (d, $J = 8.5$ Hz, 2H), 7.23-7.19 (m, 1H), 6.86 (d, $J = 8.6$ Hz, 2H), 6.44 (s, 1H), 5.68-5.60 (m, 1H), 5.01 (d, $J = 10.4$ Hz, 1H), 4.99 (d, $J = 6.2$ Hz, 1H), 4.94 (d, $J = 16.9$ Hz, 1H), 4.41 (s, 2H), 3.81 (s, 3H), 3.46-3.41 (m, 2H), 2.96 (dd, $J = 18.8$, 9.8 Hz, 1H), 2.80 (dd, $J = 13.9$, 4.9 Hz, 1H), 2.39-2.33 (m, 1H), 2.33-2.26 (m, 1H), 2.23 (s, 1H), 2.14 (dt, $J = 17.6$, 3.6 Hz, 1H), 1.88-1.80 (m, 1H), 1.77-1.63 (m, 5H), 1.55 (dd, $J = 13.3$, 6.4 Hz, 1H), 0.98 (d, $J = 7.1$ Hz, 3H), 0.96 (s, 9H), 0.25 (s, 3H), 0.22 (s, 3H)

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 159.2, 150.8, 145.0, 137.9, 136.5, 131.0, 129.4, 129.1, 128.3, 126.3, 121.9, 117.5, 113.9, 110.3, 84.0, 72.4, 70.7, 55.5, 52.3, 37.9, 36.5, 35.6, 33.4, 32.7, 29.0, 26.1, 23.8, 21.9, 18.2, -4.0, -4.6

IR (thin film NaCl): 3578, 2929, 2857, 1654, 1612, 1512, 1463, 1362, 1248, 1177, 1036, 827 cm$^{-1}$

HRMS ESI (m/z): [M+ Na]$^+$ calcd for C$_{37}$H$_{52}$O$_4$SiNa, 611.3527; found 611.3525.
(±)-(3S,3aS,6R,7aS,E)-3a-Allyl-2-benzylidene-3-hydroxy-3-(3-(4-methoxybenzyloxy)propyl)-6-methylhexahydro-1H-inden-4(2H)-one (14): To a round-bottomed flask was added 47 (23 mg, 0.039 mmol) and THF (0.78 mL) before cooling to 0 °C. To this solution was added a pre-mixed solution of AcOH and TBAF (85 μL of a solution consisting of 180 μL AcOH and 2.0 mL of a 1.0 M TBAF solution in THF). The reaction was stirred at 0 °C for 15 min before addition of H₂O. The reaction was extracted with Et₂O, washed with H₂O, brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford 18 mg (98%) of 14.

¹H NMR (600 MHz, CDCl₃) δ 7.37-7.33 (m, 2H), 7.31-7.29 (m, 2H), 7.25-7.22 (m, 1H), 7.24 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 6.49 (s, 1H), 5.64-5.57 (m, 1H), 5.03-4.97 (m, 2H), 4.41 (d, J = 11.8 Hz, 1H), 4.39 (d, J = 11.8 Hz, 1H), 3.81 (s, 3H), 3.40 (t, J = 6.0 Hz, 2H), 2.97-2.90 (m, 2H), 2.55 (s, 1H), 2.50-2.42 (m, 2H), 2.24 (dd, J = 7.2, 2.9 Hz, 1H), 2.22-2.17 (m, 1H), 2.06 (dd, J = 17.9, 6.9 Hz, 1H), 1.85 (dd, J = 13.3, 8.8 Hz, 1H), 1.81-1.73 (m, 3H), 1.72-1.57 (m, 2H), 1.49-1.44 (m, 1H), 1.02 (d, J = 6.9 Hz, 3H)

¹³C NMR (125 MHz, CDCl₃) δ 217.3, 159.3, 143.6, 137.5, 134.9, 130.6, 129.5, 129.1, 128.4, 126.7, 122.8, 118.9, 113.9, 84.7, 72.6, 70.0, 60.1, 55.5, 49.8, 41.9, 37.6, 35.7, 33.3, 27.3, 23.7, 21.3
IR (thin film NaCl): 3451, 2925, 1683, 1611, 1512, 1247 cm⁻¹

HRMS ESI (m/z): [M+ Na]⁺ calcd for C₃₁H₃₈O₄Na, 497.2662; found 497.2648.

(±)-(1S, 3aS, 5R, 7aS, E)-7a-Allyl-2-benzylidene-7-(tert-butyldimethylsilyloxy)-1-(3-hydroxypropyl)-5-methyl-2,3,3a,4,5,7a-hexahydro-1H-inden-1-ol (51): To a round-bottomed flask was added 47 (218 mg, 0.370 mmol), CH₂Cl₂ (7.9 mL), and H₂O (0.79 mL) before the reaction was cooled to 0 °C. and addition of DDQ (223 mg, 0.982 mmol). The reaction was stirred at 0 °C for 1 hour before addition of saturated aqueous NaHCO₃. The reaction was extracted with CH₂Cl₂ and the organics were washed with saturated aqueous NaHCO₃, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 5% EtOAc/hex to 10% EtOAc/hex) to yield 136 mg (78%) of 51.

¹H NMR (600 MHz, CDCl₃) δ 7.37-7.34 (m, 4H), 7.25-7.20 (m, 1H), 6.45 (s, 1H), 5.69-5.61 (m, 1H), 5.02 (d, J = 12.7 Hz, 1H), 5.01 (d, J = 6.4 Hz, 1H), 4.95 (d, J = 17.0 Hz, 1H), 3.64 (t, J = 6.0 Hz, 2H), 2.99 (dd, J = 17.5, 9.8 Hz, 1H), 2.79 (dd, J = 13.9, 4.9 Hz, 2H), 1H), 1.62 (s, 9H).
1H), 2.39-2.28 (m, 2H), 2.33 (s, 1H), 2.17 (dt, J = 17.6, 3.8 Hz, 1H), 1.85-1.59 (m, 7H), 1.57 (dd, J = 12.9, 6.2 Hz, 1H), 1.00-0.96 (m, 12H), 0.28 (s, 3H), 0.24 (s, 3H)

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 150.7, 144.9, 137.8, 136.4, 129.1, 128.4, 126.4, 122.2, 117.6, 110.4, 84.0, 63.8, 52.2, 37.9, 36.4, 35.6, 33.4, 32.6, 29.0, 27.0, 26.1, 21.9, 18.2, -4.0, -4.6

IR (thin film NaCl): 3579, 3357, 2953, 2929, 2859, 1658, 1462, 1471, 1257, 1180, 838 cm$^{-1}$

HRMS ESI (m/z): [M+ Na]$^+$ calcd for C$_{29}$H$_{44}$O$_3$Na, 491.2952; found 491.2966.

(±)-(1'S,3a'S,5'R,7a'S,E)-7a'-Allyl-2'-benzylidene-7'-tert-butyldimethylsilyloxy)-5'-methyl-2',3',3a',4',5',5',7a'-octahydro-3H-spiro[furan-2,1'-inden]-5-ol (52): To a round-bottomed flask was added CH$_2$Cl$_2$ (10 mL) and oxalyl chloride (26 µL, 0.30 mmol) before being cooled to −78 °C. To this solution was added DMSO (34 µL, 0.48 mmol) and the solution stirred for 15 min before addition of 51 (113 mg, 0.24 mmol) as a solution in CH$_2$Cl$_2$ (2 mL). The solution was stirred an additional 15 min at −78 °C before addition of NEt$_3$ (100 µL, 0.72 mmol), removal of the cold bath, and warming to
room temperature. The reaction was poured into H₂O, extracted with Et₂O, washed with water, brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (2% EtOAc/hex to 5% EtOAc/hex) to afford 92 mg (82%) 52.

¹H NMR (500 MHz, CDCl₃, * denotes minor diastereomer) δ 7.40-7.32 (m, 4H), 7.20 (t, J = 7.1 Hz, 1H), 6.79 (s, 1H), 6.28* (s, 1H), 5.69-5.56 (m, 2H), 5.15* (d, J = 5.5 Hz, 1H), 5.50-4.98 (m, 2H), 4.97-4.94 (m, 1H), 3.65* (d, J = 7.7 Hz, 1H), 3.01 (d, J = 4.5 Hz, 1H), 3.00-2.87 (m, 2H), 2.50-2.43 (m, 1H), 2.38-2.27 (m, 2H), 2.27-2.16 (m, 2H), 2.01 (s, 1H), 1.97 (dd, J = 12.3, 7.4 Hz, 1H), 1.93-1.86 (m, 1H), 1.77 (dd, J = 14.1, 10.0 Hz, 1H), 1.70-1.61 (m, 1H), 1.50-1.44* (m, 1H), 1.39 (dd, J = 13.3, 3.4 Hz, 1H), 1.02* (d, J = 7.0 Hz, 1H), 0.98 (d, J = 7.3 Hz, 3H), 0.95 (s, 9H), 0.27* (s, 3H), 0.26* (s, 3H), 0.22 (s, 3H), 0.21 (s, 3H)

¹³C NMR (125 MHz, CDCl₃) δ 150.4, 150.3, 149.3, 147.0, 138.2, 137.7, 136.5, 136.0, 129.0, 129.0, 128.4, 128.4, 126.5, 126.4, 122.6, 121.1, 117.5, 117.0, 115.0, 111.5, 99.1, 99.1, 96.0, 95.2, 52.2, 52.1, 36.9, 36.5, 35.8, 35.2, 34.9, 34.0, 33.8, 33.1, 33.1, 33.0, 32.5, 32.4, 28.6, 28.5, 26.6, 26.1, 22.5, 22.0, 18.9, 18.5, -3.8, -3.9, -4.0, -4.8

IR (thin film NaCl): 3387, 2955, 2930, 2860, 1648, 1470, 1352, 1257, 1183, 1166, 1133, 907, 731 cm⁻¹

HRMS ESI (m/z): [M+ Na]⁺ calcd for C₂₉H₄₂O₃SiNa, 489.2795; found 489.2800.
(±)-(1'S, 3a'S, 5'R, 7a'S, E)-7a'-Allyl-2'-benzylidene-5-methoxy-5'-methyl-octahydro-3H-spiro[furan-2,1'-inden]-7'(7a'H)-one (53): To a round-bottomed flask were added 52 (53 mg, 0.11 mmol), benzene (2.3 mL), and anhydrous methanol (0.46 mL) before addition of PPTS (2.8 mg, 0.011 mmol). The solution was stirred overnight at room temperature before addition of a saturated aqueous solution of NaHCO₃. The layers were separated and the aqueous extracted with EtO. The combined organics were washed with water and brine before being dried over anhydrous Na₂SO₄. The solution was filtered and concentrated under reduced pressure to yield the crude residue which was purified by silica gel chromatography (hexanes to 10% EtOAc/hexanes) to afford 50 mg (91%) of the methyl acetal as a mixture of diastereomers about the acetal carbon ~3:1.

To a round-bottomed flask was added the methyl acetal (50 mg, 0.10 mmol), THF (5.0 mL) and the solution cooled to 0 °C. To this flask was added pre-mixed solution of TBAF and AcOH (210 μL of solution composed of 180 μL AcOH and 2.0 mL of a 1.0 M TBAF solution in THF). The reaction was stirred at room temperature for 45 min before quenching with saturated aqueous NaHCO₃. The reaction was extracted with Et₂O, washed with H₂O, brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford 35 mg (93%) of 53.
$^1$H NMR (600 MHz, CDCl$_3$, * denotes minor diastereomer) δ 7.35-7.30 (m, 4H), 7.23-7.18 (m, 1H), 6.57 (t, $J = 2.5$ Hz, 1H), 6.31* (t, $J = 2.5$ Hz, 1H), 5.80-5.72* (m, 1H), 5.71-5.64 (m, 1H), 5.09 (dd, $J = 16.9$, 1.8 Hz, 1H), 5.06 (dd, $J = 5.0$, 1.8 Hz, 1H), 5.04-5.00 (m, 1H), 3.43* (s, 3H), 3.29 (s, 3H), 2.96-2.90* (m, 1H), 2.88 (ddd, $J = 17.4$, 9.3, 2.4 Hz, 1H), 2.81 (dd, $J = 14.8$, 7.3 Hz, 1H), 2.74-2.66 (m, 1H), 2.52 (dt, $J = 14.2$, 8.9 Hz, 1H), 2.42-2.10 (m, 9H), 2.06-1.94 (m, 3H), 1.80 (dt, $J = 14.2$, 4.2 Hz, 1H), 1.74-1.65 (m, 1H), 1.01 (d, $J = 6.4$ Hz, 3H), 0.99* (d, $J = 6.6$ Hz, 3H)

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 213.8, 212.7, 145.4, 144.9, 138.3, 137.5, 135.1, 134.9, 129.1, 129.0, 128.4, 128.3, 126.8, 126.5, 122.5, 120.9, 118.1, 117.9, 105.0, 104.3, 96.8, 95.4, 62.5, 61.8, 55.1, 54.6, 49.6, 49.1, 41.5, 41.2, 36.9, 36.5, 34.6, 33.8, 33.6, 33.1, 32.7, 31.8, 29.9, 29.7, 29.6, 29.1, 29.0, 22.2, 22.0

IR (thin film NaCl): 2952, 2922, 1705, 1560, 1492, 1447, 1367, 1212, 1102, 1036, 985, 955, 917, 752, 695 cm$^{-1}$

HRMS ESI (m/z): [M+ Na]$^+$ calcd for C$_{24}$H$_{30}$O$_3$Na, 389.2087; found 389.2087.
(±)-tert-Butyl-3-((1'S,3a'S,5'R,7a'S,E)-2'-benzylidene-5-methoxy-5'-methyl-7'-oxodecahydro-3H-spiro[furan-2,1'-indene]-7a'-yl)propyl(tert-butoxycarbonyloxy) carbamate (54): To a round-bottomed flask was added 53 (35 mg, 0.074 mmol), THF (0.73 mL) before addition of BH₃*SMe₂ (37 μL of a 2.0 M THF solution, 0.074 mmol). Reaction stirred at room temperature for 4.25 h before addition of NaBO₃*4H₂O (31 mg, 0.20 mmol) and H₂O (0.73 mL). The solution was stirred at room temperature overnight before extracting with EtOAc. The combined organics were washed with H₂O, brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to afford the crude residue. The crude residue was purified by silica gel chromatography (40% EtOAc/hex to 50% EtOAc/hex) to afford 15 mg (53%) of the primary alcohol and 7.0 mg (27%) of recovered 32. To a round-bottomed flask was added the hydroboration product (15 mg, 0.039 mmol), PPh₃ (39 mg, 0.15 mmol), HN(OBoc)Boc (37 mg, 0.16 mmol) and toluene (3.9 mL) before addition of DEAD (28 μL, 0.18 mmol). The reaction was heated to 80 °C for 3 h. After 3 h the reaction was cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 2% EtOAc/hex to 20% EtOAc/hex) to afford 16 mg (69%) of 54.
\(^1\)H NMR (600 MHz, CDCl\(_3\), * denotes minor diastereomer) \(\delta\) 7.34-7.28 (m, 4H), 7.22-7.17 (m, 1H), 6.55 (s, 1H), 6.32* (s, 1H), 5.06 (d, \(J = 4.9\) Hz, 1H), 4.99* (d, \(J = 5.0\) Hz, 1H), 3.64-3.48 (m, 2H), 3.41* (s, 3H), 3.26 (s, 3H), 2.90* (dd, \(J = 17.6, 9.7\) Hz, 1H), 2.85 (dd, \(J = 17.4, 9.3\), 1H), 2.71-2.62 (m, 1H), 2.60-2.48 (m, 1H), 2.43-1.94 (m, 10H), 1.83-1.60 (m, 5H), 1.53 (s, 9H), 1.49 (s, 9H), 1.01 (d, \(J = 6.3\) Hz, 3H), 1.00-0.98* (m, 3H)

\(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 214.2, 213.4, 155.2, 155.1, 152.4, 145.4, 145.3, 138.3, 137.6, 129.1, 128.9, 128.3, 128.3, 126.7, 126.5, 122.3, 121.0, 104.8, 104.5, 96.7, 95.3, 94.9, 85.0, 84.8, 82.5, 82.4, 62.3, 62.0, 55.3, 54.5, 51.0, 49.0, 49.0, 43.1, 42.4, 37.7, 36.8, 33.9, 33.8, 33.5, 33.0, 32.8, 29.7, 29.3, 29.3, 28.7, 28.3, 27.8, 23.4, 22.3, 22.1

IR (thin film NaCl): 2954, 2980, 2929, 1783, 1706, 1599, 1576, 1457, 1395, 1370, 1275, 1255, 1149, 1133, 1035, 985, 955, 916, 835, 753, 733, 696, 648 cm\(^{-1}\)

HRMS ESI (m/z): [M+ Na]\(^+\) calcd for C\(_{34}\)H\(_{49}\)NO\(_8\)Na, 622.3350; found 622.3335.

(±)-tert-Butyl tert-butoxycarbonyloxy(3-((1'R,3a'S,5'R,7a'S)-5-methoxy-5'-methyl-2',7'-dioxodecahydro-3H-spiro[furan-2,1'-indene]-7a'-yl)propyl)carbamate (55): To a round-bottomed flask was added 33 (25 mg, 0.041 mmol), CH\(_2\)Cl\(_2\) (4.1 mL), and
cooled to –78 °C before passing a stream of ozone through solution until the blue color remains. Argon was bubbled through the blue solution to remove any dissolved ozone before addition of PPh₃ (22 mg, 0.082 mmol) and removal of the cold bath. The reaction was warmed to room temperature over 2 h and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 10% EtOAc/hex to 20% EtOAc/hex) to yield 19 mg of 55 (87%)

H NMR (600 MHz, CDCl₃) δ 5.01 (d, J = 4.9 Hz, 1H), 3.65-3.54 (m, 2H), 3.17 (s, 3H), 2.88-2.83 (m, 1H), 2.50 (dd, J = 19.5, 9.3 Hz, 1H), 2.41 (t, J = 12.4 Hz, 1H), 2.17 (dd, J = 11.9, 2.6 Hz, 1H), 2.13-2.00 (m, 1H), 1.94 (dd, J = 19.5, 11.1 Hz, 1H), 1.91-1.86 (m, 1H), 1.85-1.78 (m, 1H), 1.74-1.69 (m, 1H), 1.65-1.54 (m, 2H), 1.53 (s, 9H), 1.49 (s, 1H), 1.46-1.36 (m, 2H), 1.08 (d, J = 6.4 Hz, 3H)

C NMR (125 MHz, CDCl₃) δ 214.2, 210.1, 155.3, 152.4, 105.1, 90.5, 85.2, 82.8, 62.1, 54.7, 50.8, 47.9, 41.5, 36.6, 33.7, 32.1, 31.6, 28.3, 27.8, 26.6, 24.3, 23.4, 22.4

IR (thin film NaCl): 2930, 1783, 1760, 1702, 1458, 1395, 1369, 1245, 1148, 1106, 1035, 977, 949, 852, 761 cm⁻¹

HRMS ESI (m/z): [M+ Na]⁺ calcd for C_{27}H_{43}NO_9Na, 548.2830; found 548.2835.
(±)-(2'R,4'R,7aS,9R)-5'-Methoxy-9-methyl-6-oxo-3,4,4',5',6,7,7a,8,9,10-decahydro-2H,3'H-spiro[cyclopenta[e]quinoline-5,2'-furan]-1-oxide (57): To a round-bottomed flask was added 55 (6.5 mg, 0.012 mmol), CH₂Cl₂ (1.2 mL), and anhydrous ZnBr₂ (11 mg, 0.049 mmol). Reaction stirred at room temperature for 5 h before addition of saturated aqueous solution of NaHCO₃. The reaction was extracted with EtOAc, washed with H₂O, brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 60% EtOAc/hex to 5% MeOH/CHCl₃) to afford 0.6 mg (16%) 57.

¹H NMR (600 MHz, CDCl₃) δ 5.07 (dd, J = 5.2, 2.5 Hz, 1H), 3.93 (m, 2H), 3.34 (s, 3H), 3.16 (dd, J = 18.7, 6.5 Hz, 1H), 2.96 (dd, J = 17.9, 10.8 Hz, 1H), 2.47 (dt, J = 13.4, 4.7 Hz, 1H), 2.38 (dt, J = 10.8, 2.3 Hz, 1H), 2.27-2.21 (m, 2H), 2.14 (dd, J = 17.9, 2.3 Hz, 1H), 2.12-1.88 (m, 5H), 1.78 (ddd, J = 13.1, 9.1, 5.3 Hz, 1H), 1.63-1.53 (m, 2H), 1.41 (ddd, J = 13.9, 9.3, 5.7 Hz, 1H), 1.01 (d, J = 6.7 Hz, 3H)

¹³C NMR (125 MHz, CDCl₃) δ 213.5, 149.3, 106.4, 91.7, 57.9, 55.6, 48.1, 40.3, 38.6, 36.7, 33.6, 32.7, 30.1, 29.2, 25.5, 22.0, 20.5

IR (thin film NaCl): 3387, 2953, 1750, 1457, 1214, 1104, 1034, 949 cm⁻¹
HRMS ESI (m/z): [M+ H]+ calcd for C_{17}H_{26}NO_{3}, 308.1856; found 308.1955.

(±)-(1S,3aS,5R,7aS,E)-2-Benzylidene-7-(tert-butyldimethylsilyloxy)-7a-(3-hydroxypropyl)-1-(3-(4-methoxybenzyloxy)propyl)-5-methyl-2,3,3a,4,5,7a-hexahydro-1H-inden-1-ol (60): To a round-bottomed flask were added 47 (1.7 g, 2.9 mmol), THF (58 mL), and BH_3·DMS (2.9 mL of a 2.0 M solution in THF, 5.8 mmol). This solution was stirred at room temperature for 30 min before addition of NaBO_3·4H_2O (2.7 g, 17 mmol) and H_2O (58 mL). The reaction was stirred overnight before separating the layers and extracting with EtOAc. The combined organic layers were washed with H_2O, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (gradient, 10% EtOAc/hex to 20% EtOAc/hex) to yield 1.2 g (67%) of 60.

^1H NMR (500 MHz, CDCl_3) δ 7.36-7.29 (m, 4H), 7.26-7.18 (m, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.43 (s, 1H), 4.99 (d, J = 6.0 Hz, 1H), 4.41 (s, 2H), 3.81 (s, 3H), 3.63-3.53 (m, 2H), 3.43 (t, J = 5.9 Hz, 2H), 2.97 (dd, J = 17.3, 9.7 Hz, 1H), 2.42-2.35 (m, 1H), 2.29-2.23 (m, 1H), 2.22 (s, 1H), 2.15 (dt, J = 17.6, 3.7 Hz, 1H), 1.99 (dt, J = 13.0, 3.7 Hz, 1H), 1.88-1.63 (m, 5H), 1.58 (dd, J = 13.2, 6.2 Hz, 1H), 1.54-1.45 (m, 1H), 1.41-1.32 (m,
1H), 1.30-1.25 (m, 1H), 1.06 (dt, J = 12.9, 4.6 Hz, 1H), 1.02 (d, J = 7.1 Hz, 3H), 0.95 (s, 9H), 0.24 (s, 3H), 0.22 (s, 3H)

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 159.2, 151.0, 144.9, 137.8, 131.0, 129.4, 129.1, 128.3, 126.4, 121.9, 113.9, 110.2, 84.0, 72.4, 70.7, 63.9, 55.5, 52.2, 36.6, 35.7, 33.6, 33.5, 28.8, 28.8, 28.3, 26.0, 23.8, 22.1, 18.2, -4.1, -4.6

IR (thin film NaCl): 3583, 3399, 2929, 2857, 1656, 1612, 1463, 1363, 1248, 1172, 1099, 1036, 837 cm$^{-1}$

HRMS ESI (m/z): [M+ Na]$^+$ calcd for C$_{37}$H$_{54}$O$_5$SiNa, 629.3633; found 629.3645.

(±)-Allyl 3-((3S,3aS,6R,7aS,E)-2-benzylidene-4-(tert-butyldimethylsilyloxy)-3-hydroxy-3-(3-(4-methoxybenzyloxy)propyl)-6-methyl-2,3,3a,6,7,7a-hexahydro-1H-inden-3a-yl)propyl(methoxycarbonyloxy)carbamate (68): To a round-bottomed flask was added 60 (45 mg, 0.075 mmol), PPh$_3$ (34 mg, 0.13 mmol), HN(OCOOMe)Alloc (26 mg, 0.15 mmol), and toluene (1.5 mL). To this solution was added DEAD (24 μL, 0.15 mmol) and the reaction stirred for 1 hour at room temperature. The reaction mixture was
loaded directly onto silica gel and purified by silica gel chromatography (10% EtOAc/hex) to yield 40 mg (70%) of 68.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.36-7.28 (m, 4H), 7.26-7.18 (m, 3H), 6.86 (d, $J = 8.6$ Hz, 2H), 6.42 (s, 1H), 5.88 (m, 1H), 5.28 (d, $J = 17.2$ Hz, 1H), 5.20 (d, $J = 10.4$ Hz, 1H), 4.98 (d, $J = 6.0$ Hz, 1H), 4.62 (m, 2H), 4.40 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.55 (m, 2H), 3.43 (t, $J = 6.0$ Hz, 2H), 2.96 (dd, $J = 17.4$, 9.6 Hz, 1H), 2.37 (m, 1H), 2.25-2.18 (m, 1H), 2.19 (s, 1H), 2.14 (dt, $J = 17.7$, 3.7 Hz, 1H), 1.95 (dt, $J = 13.1$, 3.7 Hz, 1H), 1.87-1.78 (m, 1H), 1.76-1.70 (m, 1H), 1.69-1.62 (m, 2H), 1.60-1.53 (m, 2H), 1.47-1.31 (m, 1H), 1.01 (dt, $J = 13.2$, 4.6 Hz, 1H), 1.00 (d, $J = 7.1$ Hz, 3H), 0.94 (s, 9H), 0.23 (s, 3H), 0.20 (s, 3H)

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 159.2, 155.4, 155.0, 150.8, 144.7, 137.8, 132.0, 130.9, 129.4, 129.1, 128.3, 126.4, 122.0, 118.5, 113.9, 110.4, 83.9, 72.4, 70.7, 67.3, 56.2, 55.5, 52.3, 51.5, 36.6, 35.7, 33.6, 33.5, 29.5, 28.8, 26.0, 23.8, 22.5, 22.0, 18.2, -4.1, -4.9

IR (thin film NaCl): 3583, 2928, 1793, 1734, 1653, 1457, 1247, 1202, 839 cm$^{-1}$

HRMS ESI (m/z): [M+ Na]$^+$ calcd for C$_{43}$H$_{61}$NO$_9$SiNa, 786.4008; found 786.4025.
(±)-Allyl-3-((3S,3aS,6R,7aS,E)-2-benzylidene-4-(tert-butyldimethylsilyloxy)-3-hydroxy-3-(3-hydroxypropyl)-6-methyl-2,3,3a,6,7,7a-hexahydro-1H-inden-3a-yl)propyl(methoxycarbonyloxy)carbamate (69): To a round-bottomed flask was added 68 (40 mg, 0.052 mmol), CH₂Cl₂ (1.0 mL), and H₂O (52 μL), before cooling to 0 °C. To the solution was added DDQ (15 mg, 0.065 mmol) and the reaction stirred at 0 °C for 2 h before addition of a saturated aqueous solution of NaHCO₃. The reaction mixture was then extracted with CH₂Cl₂, washed brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 10% EtOAc/hex to 15% EtOAc/hex) to afford 25 mg (73%) of 69.

¹H NMR (500 MHz, CDCl₃) δ 7.36-7.31 (m, 4H), 7.23-7.19 (m, 1H), 6.43 (s, 1H), 5.87 (m, 1H), 5.28 (d, J = 17.2 Hz, 1H), 5.20 (d, J = 10.5 Hz, 1H), 5.00 (d, J = 6.1 Hz, 1H), 4.62 (m, 2H), 3.83 (s, 3H), 3.63 (t, J = 5.8 Hz, 2H), 3.60-3.53 (m, 2H), 2.99 (dd, J = 17.3, 9.4 Hz, 1H), 2.37 (m, 1H), 2.28-2.13 (m, 3H), 1.94 (dt, J = 13.1, 3.7 Hz, 1H), 1.83-1.64 (m, 4H), 1.64-1.52 (m, 3H), 1.48-1.38 (m, 1H), 1.03 (dt, J = 13.1, 4.6 Hz, 1H), 1.00 (d, J = 7.1 Hz, 3H), 0.96 (s, 9H), 0.26 (s, 3H), 0.22 (s, 3H)

¹³C NMR (125 MHz, CDCl₃) δ 155.4, 155.0, 150.6, 144.6, 137.6, 132.0, 129.1, 128.4, 126.5, 122.2, 118.5, 110.5, 83.9, 67.3, 63.8, 56.2, 52.3, 51.5, 36.5, 35.7, 33.5, 33.5, 29.5, 28.8, 26.9, 26.0, 22.5, 22.0, 18.2, -4.1, -4.9
IR (thin film NaCl): 3584, 2928, 2857, 1795, 1725, 1653, 1441, 1376, 1240, 1202, 1141, 931, 839 cm\(^{-1}\)

HRMS ESI (m/z): [M+ Na]\(^+\) calcd for C\(_{35}\)H\(_{53}\)NO\(_8\)SiNa, 666.3433; found 666.3409.

(±)-Allyl 3-((1’S,3a’S,5'R,7a'S,E)-2'-benzylidene-7'- (tert-butyldimethylsilyloxy)-5'-hydroxy-5'-methyl-2',3',4',5',5',7a'-octahydro-3H-spiro[furan-2,1'-indene]-7a'-yl)propyl(methoxycarbonyloxy)carbamate (59): To a round-bottomed flask was added CH\(_2\)Cl\(_2\) (0.5 mL) and oxalyl chloride (3 μL, 0.035 mmol) before being cooled to \(-78^\circ C\). To this solution was added DMSO (5 μL, 0.071 mmol) and the solution stirred for 15 min before addition of 69 (8.9 mg, 0.014 mmol) as a solution in CH\(_2\)Cl\(_2\) (0.5 mL). The solution was stirred an additional 15 min at \(-78^\circ C\) before addition of NEt\(_3\) (20 μL, 0.14 mmol), removal of the cold bath, and warming to room temperature and addition of H\(_2\)O. The reaction was extracted with Et\(_2\)O, washed with water, brine, dried over anhydrous Na\(_2\)SO\(_4\), and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (10% EtOAc/hex to 20% EtOAc/hex) to afford 5.7 mg (64%) of 59.
\^{1}H NMR (500 MHz, CDCl$_3$, * denotes minor diastereomer) \(\delta\) 7.37-7.30 (m, 4H), 7.24-7.18 (m, 1H), 6.74 (s, 1H), 6.25* (s, 1H), 5.92-5.84 (m, 1H), 5.62-5.58 (m, 1H), 5.29 (dd, \(J = 17.2, 1.4\) Hz, 1H), 5.21 (dd, \(J = 10.5, 1.2\) Hz, 1H), 5.10* (d, \(J = 5.2\) Hz, 1H), 4.94 (d, \(J = 5.2\) Hz, 1H), 4.67-4.58 (m, 3H), 3.84 (s, 3H), 3.61-3.52 (m, 2H), 3.46* (d, \(J = 7.5\) Hz, 1H), 2.97 (dd, \(J = 17.3, 9.3\) Hz, 1H), 2.92* (dd, \(J = 18.0, 9.6\) Hz, 1H), 2.74 (d, \(J = 4.8\) Hz, 1H), 2.45-2.38 (m, 1H), 2.36-2.13 (m, 4H), 2.11-1.98 (m, 2H), 1.96-1.84 (m, 2H), 1.79-1.63 (m, 2H), 1.48-1.38 (m, 2H), 1.21-1.14 (m, 1H), 1.02* (d, \(J = 7.0\) Hz, 3H), 0.99 (d, \(J = 7.1\) Hz, 3H), 0.98* (s, 9H), 0.94 (s, 9H), 0.25* (s, 3H), 0.23* (s, 3H), 0.21 (s, 3H), 0.20 (s, 3H)

\(^{13}\)C NMR (125 MHz, CDCl$_3$) \(\delta\) 155.4, 155.0, 155.0, 150.3, 150.3, 148.8, 146.5, 138.0, 137.5, 132.0, 132.0, 129.0, 129.0, 128.4, 128.4, 126.4, 126.4, 122.2, 120.9, 118.5, 118.5, 114.8, 111.6, 99.1, 99.0, 95.8, 95.4, 67.4, 67.3, 56.2, 56.2, 52.3, 52.3, 51.4, 51.4, 35.7, 35.4, 35.2, 33.9, 33.8, 33.7, 33.6, 33.1, 32.6, 32.1, 28.8, 28.3, 28.3, 28.1, 26.5, 26.3, 26.0, 22.6, 22.5, 22.4, 22.1, 18.9, 18.4, -3.9, -4.0, -4.3, -5.1

IR (thin film NaCl): 3460, 2956, 2859, 1796, 1726, 1650, 1600, 1441, 1405, 1362, 1239, 1193, 1140, 1046, 992, 931, 838, 778, 754, 696, 669 cm$^{-1}$

HRMS ESI (m/z): [M+ Na]$^+$ calcd for C$_{35}$H$_{51}$NO$_8$SiNa, 664.3276; found 664.3269.
(±)-(1S,3aS,5R,7aS,E)-7a-(3-Azidopropyl)-2-benzylidene-7-(tert-butyl(dimethyl)silyloxy)-1-(3-hydroxypropyl)-5-methyl-2,3,3a,4,5,7a-hexahydro-1H-inden-1-ol (73): To a round-bottomed flask was added 60 (697 mg, 1.15 mmol), CH₂Cl₂ (5.8 mL), and NEt₃ (320 µL, 2.30 mmol). This solution was cooled to 0 ºC before addition of MsCl (107 µL, 1.38 mmol) and stirred at 0 ºC for 20 min before addition of H₂O. The layers were separated before the aqueous was extracted with Et₂O and the combined organics washed with H₂O, brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude mesylate was added to a round-bottomed flask before addition of DMF (7.7 mL) and NaN₃ (224 mg, 3.45 mmol). The reaction was heated to 50 ºC overnight before cooling to room temperature. After cooling to room temperature the reaction was diluted with H₂O, extracted with Et₂O, washed with H₂O, brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the crude azide. To a round-bottomed flask was added the crude azide, CH₂Cl₂ (23 mL), and H₂O (1.2 mL), before cooling to 0 ºC. To the solution was added DDQ (654 mg, 2.08 mmol) and the reaction stirred at 0 ºC for 1 hour before addition of a saturated aqueous solution of NaHCO₃. The reaction mixture was then extracted with CH₂Cl₂, brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography.
(gradient, 5% EtOAc/hex to 10% EtOAc/hex) to afford 401 mg (68% yield over the three steps) of 73.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.37-7.31 (m, 4H), 7.24-7.20 (m, 1H), 6.44 (s, 1H), 5.01 (d, $J=6.1$ Hz, 1H), 3.63 (m, 2H), 3.21 (t, $J=7.2$ Hz, 2H), 3.00 (dd, $J=17.0$, 9.3 Hz, 1H), 2.43-2.35 (m, 1H), 2.28 (s, 1H), 2.26-2.15 (m, 2H), 2.01 (dt, $J=13.1$, 3.8 Hz, 1H), 1.82-1.33 (m, 9H), 1.07 (dt, $J=13.1$, 4.5 Hz, 1H), 1.02 (d, $J=7.1$ Hz, 3H), 0.97 (s, 9H), 0.28 (s, 3H), 0.24 (s, 3H)

$^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 150.7, 144.5, 137.6, 129.1, 128.4, 126.5, 122.2, 110.4, 84.0, 63.8, 52.3, 52.2, 36.6, 35.6, 33.6, 33.5, 30.0, 28.8, 26.9, 26.0, 24.6, 22.0, 18.2, -4.1, -4.6

IR (thin film NaCl): 3583, 3353, 2929, 2859, 2095, 1654, 1463, 1363, 1260, 1172, 837 cm$^{-1}$

HRMS ESI (m/z): [M+ Na]$^+$ calcd for C$_{29}$H$_{45}$N$_3$O$_3$SiNa, 534.3122; found 534.3115.
(±)-(1'S,3a'S,5'R,7a'S,E)-7a'-(3-Azidopropyl)-2'-benzyldiene-7'-(tert-butyldimethylsilyloxy)-5'-methyl-2',3',3a',4,4',5,5',7a'-octahydro-3H-spiro[furan-2,1'-inden]-5-ol (72): To a round-bottomed flask was added 73 (240 mg, 0.469 mmol), DMSO (9.4 mL), NEt₃ (390 µL, 2.82 mmol) before addition of solid SO₃·Py (224 mg, 1.41 mmol). The reaction was stirred at room temperature for 1 hour before addition of water and extracting with EtOAc. The combined organics were washed with water, brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 5% EtOAc/hex to 10% EtOAc/hex) to afford 188 mg (79%) of 72.

¹H NMR (500 MHz, CDCl₃, * denotes minor diastereomer) δ 7.37-7.30 (m, 4H), 7.24-7.19 (m, 1H), 6.76 (s, 1H), 6.26* (s, 1H), 5.63-5.59 (m, 1H), 5.12* (d, J = 5.3 Hz, 1H), 4.96 (d, J = 5.2 Hz, 1H), 3.42* (d, J = 7.5 Hz, 1H), 3.29-3.22 (m, 1H), 3.21-3.09 (m, 1H), 2.98 (ddd, J = 17.6, 8.9, 2.2 Hz, 1H), 2.93* (ddd, J = 17.6, 9.4, 2.0 Hz, 1H), 2.77 (d, J = 4.8 Hz, 1H), 2.45-2.02 (m, 6H), 1.98-1.85 (m, 2H), 1.79-1.64 (m, 2H), 1.60-1.36 (m, 4H), 1.22 (dt, J = 13.0, 4.5 Hz, 1H), 1.09* (dd, J = 13.0, 4.3 Hz, 1H), 1.04* (d, J = 7.0 Hz, 3H), 1.01 (d, J = 7.0 Hz, 3H), 0.99* (s, 9H), 0.95 (s, 9H), 0.27* (s, 3H), 0.26* (s, 3H), 0.23 (s, 3H), 0.22 (s, 3H)

¹³C NMR (125 MHz, CDCl₃) δ 150.4, 150.2, 148.7, 146.4, 138.0, 137.5, 129.0, 129.0, 128.4, 128.4, 126.6, 126.4, 122.3, 121.0, 114.8, 111.6, 99.1, 99.0, 95.8, 95.4, 52.3, 52.2, 52.1, 35.7, 35.5, 35.2, 34.0, 33.9, 33.8, 33.7, 33.1, 32.6, 32.2, 29.2, 28.5, 28.3, 26.6, 26.0, 24.7, 24.6, 22.5, 22.1, 18.9, 18.4, -3.8, -4.0, -4.1, -4.8
IR (thin film NaCl) 3584, 3424, 2955, 2930, 2850, 2095, 1650, 1600, 1464, 1363, 1260, 1177, 1109, 1046, 991, 932, 918, 837, 777, 754, 695 cm⁻¹

HRMS ESI (m/z): [M+ Na]⁺ calcd for C_{29}H_{43}N_{3}O_{3}SiNa, 532.2966; found 532.2962.

Tetracyclic diene (77): To a round-bottomed flask was added 72 (127 mg, 0.25 mmol), toluene (25 mL), and PMe₃ (0.74 mL of a 1.0 M solution in toluene, 0.74 mmol) before heating to reflux for 5 h. Reaction cooled to room temperature and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (wash silica with 1% NEt₃/3% EtOAC/hex, followed by purification by silica gel chromatography (3% EtOAC/Hex) to afford 61 mg (54%) of 77.

¹H NMR (500 MHz, CDCl₃) δ 7.33 (t, J = 7.5 Hz, 2H), 7.28 (d, J = 9.1 Hz, 2H), 7.20 (t, J = 7.4 Hz, 1H), 6.12 (s, 1H), 4.72 (d, J = 6.4 Hz, 1H), 4.56 (s, 1H), 3.05 (t, J = 10.6 Hz, 1H), 3.00-2.92 (m, 1H), 2.77-2.71 (m, 1H), 2.62-2.56 (m, 1H), 2.34-2.18 (m, 3H), 2.09 (dd, J = 12.8, 6.0 Hz, 1H), 2.05-1.98 (m, 1H), 1.93-1.84 (m, 1H), 1.77 (dd, J = 11.3, 6.3 Hz, 1H), 1.73-1.63 (m, 1H), 1.45-1.13 (m, 5H), 1.01 (s, 9H), 0.82 (d, J = 6.7 Hz, 3H), 0.21 (s, 3H), 0.19 (s, 3H)
$^{13}$C NMR (125 MHz, CDCl$_3$) δ 149.9, 147.3, 138.2, 129.1, 126.3, 118.0, 113.3, 96.9, 89.5, 51.1, 46.1, 41.3, 35.2, 33.9, 33.2, 29.0, 27.5, 26.7, 26.3, 25.1, 22.8, 18.7, -3.7, -4.7

IR (thin film NaCl): 2954, 2927, 2856, 1649, 1471, 1362, 1253, 1174, 1122, 1009, 990, 955, 914, 830, 778, 734, 695 cm$^{-1}$

HRMS ESI (m/z): [M+ H]$^+$ calcd for C$_{29}$H$_{44}$NO$_2$Si, 466.3136; found 466.3127.

Tetracyclic cyclohexanone (81): To a round-bottomed flask was added the 77 (77 mg, 0.17 mmol), CH$_2$Cl$_2$ (3.3 mL), and NEt$_3$ (46 µL, 0.33 mmol) before being cooled to 0 °C and addition of freshly distilled (CF$_3$CO)$_2$O (28 µL, 0.20 mmol). The reaction was stirred for 45 min at 0 °C before addition of saturated aqueous solution of NaHCO$_3$. The reaction solution was extracted with CH$_2$Cl$_2$, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (3% EtOAC/hex) to afford the trifluoroacetamide product. To a round bottom flask was added the trifluoroacetamide and THF before the reaction was cooled to 0 °C and addition of AcOH (21 µL, 0.38 mmol) and TBAF (0.25 mL of a 1.0 M solution in THF, 0.25 mmol). Stir at 0 °C for 1 hour before addition of a saturated aqueous solution of NaHCO$_3$. The reaction was extracted with EtOAc, washed with H$_2$O, brine,
dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (gradient, 15% EtOAc/hex to 20% EtOAc/hex) to afford 52 mg (71% over the two steps) of 81.

¹H NMR (500 MHz, CDCl₃, * denotes minor diastereomer) δ 7.38-7.28 (m, 4H), 7.25 (t, J = 7.3 Hz, 1H), 6.40* (s, 1H), 6.38 (s, 1H), 5.53 (t, J = 7.0 Hz, 1H), 3.54-3.44 (m, 2H), 2.85 (dd, J = 17.4, 9.4 Hz, 1H), 2.74-2.65 (m, 2H), 2.49-2.38 (m, 1H), 2.36-2.25 (m, 2H), 2.23-1.93 (m, 6H), 1.91-1.83 (m, 2H), 1.78 (d, J = 14.0 Hz, 1H), 1.73-1.65 (m, 2H), 1.08 (d, J = 5.8 Hz, 3H), 1.02 (d, J = 6.4 Hz, 3H)

¹³C NMR (100 MHz, CDCl₃) δ 212.9, 212.6, 143.9, 137.1, 129.2, 128.9, 128.5, 127.2, 122.3, 117.8, 115.0, 94.1, 93.3, 83.4, 62.1, 61.9, 60.6, 48.4, 43.2, 36.8, 33.1, 32.5, 30.6, 30.2, 29.9, 28.2, 27.8, 24.9, 23.8, 22.3, 21.8, 14.4

¹⁹F NMR (500 MHz, CDCl₃) δ -71.7, -72.6

IR (thin film NaCl): 2956, 2925, 1700, 1653, 1457, 1225, 1199, 1144, 1044, 1000, 913, 734, 694 cm⁻¹

HRMS ESI (m/z): [M+ H]⁺ calcd for C₂₅H₂₉F₃NO₃, 448.2094; found 448.2104.
Tetracyclic diketone (82): To a round-bottomed flask at -78 °C charged with 81 (44 mg, 0.098 mmol) and CH₂Cl₂ (9.8 mL) was bubbled a stream of O₃ until the solution turned blue. Argon was then bubbled through the solution to remove any remaining dissolved O₃ before addition of PPh₃ (51 mg, 0.19 mmol). The cold bath was removed and the solution was allowed to warm to room temperature over 2 h before the solution was concentrated under reduced pressure. The resulting crude residue was purified by silica gel chromatography (gradient, 15% EtOAc/hex to 25% EtOAc/hex) to afford 23 mg (63%) of 82.

$^1$H NMR (500 MHz, CDCl₃) δ 5.42 (dd, J = 9.3, 4.9 Hz, 1H), 3.65-3.56 (m, 1H), 3.34-3.26 (m, 1H), 2.81-2.74 (m, 1H), 2.74-2.65 (m, 1H), 2.47 (dd, J = 19.5, 8.5 Hz, 1H), 2.42 (t, J = 12.4 Hz, 1H), 2.31-2.21 (m, 4H), 2.16-2.06 (m, 1H), 2.05-1.94 (m, 2H), 1.87-1.66 (m, 4H), 1.47-1.39 (m, 1H), 1.11 (d, J = 1.4 Hz, 3H)

$^{13}$C NMR (100 MHz, CDCl₃, peaks due to trifluoroacetamide not observed) δ 213.1, 209.4, 87.3, 84.9, 61.7, 47.9, 42.7, 42.6, 36.3, 32.5, 31.3, 30.5, 26.9, 25.2, 23.9, 22.3

$^{19}$F NMR (300 MHz, CDCl₃) δ -71.5, -72.6

IR (thin film NaCl): 2959, 1752, 1701, 1653, 1559, 1457, 1196, 1147, 1033, 909, 735 cm⁻¹

HRMS ESI (m/z): [M+ H]$^+$ calcd for C₁₈H₂₃F₃NO₄, 374.1574; found 374.1561.
Curriculum Vitae

Education:

2003-2008  Ph.D. Candidate
Department of Chemistry
Massachusetts Institute of Technology, Cambridge, MA
Research Advisor: Professor Timothy F. Jamison
Studies directed towards the total synthesis of sieboldine A

1999-2003  B.S. Chemistry
College of Chemistry
University of California, Berkeley, Berkeley, CA

Research and Teaching Experience:

2003-2008  Graduate Research Assistant with Professor Timothy F. Jamison
Massachusetts Institute of Technology, Cambridge, MA

2003-2005  Teaching Assistant/Head Teaching Assistant

2002  Intern
Sunesis Pharmaceuticals, South San Francisco, CA

2001  Undergraduate Research Assistant with Professor John Ellman
University of California, Berkeley, Berkeley, CA

2000-2001  Undergraduate Research Assistant with Professor Sung-Ho Kim
University of California, Berkeley, Berkeley, CA

Honors and Awards:

2007  AstraZeneca Graduate Fellowship in Organic Chemistry
2007  Morse Travel Grant, Massachusetts Institute of Technology
2003  Graduated with Honors, University of California, Berkeley

Publications and Presentations:
