Title
Gallium(III)-Catalyzed Cycloisomerization Approach Toward C20-Diterpenoid Alkaloids

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Gallium(III)-Catalyzed Cycloisomerization Approach Toward C\textsubscript{20}-Diterpenoid Alkaloids

By

Amy Michelle Hamlin

A dissertation submitted in partial satisfaction of the requirements for the degree of

Doctor of Philosophy

in

Chemistry

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, BERKELEY

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Abstract

Gallium(III)-Catalyzed Cycloisomerization Approach Toward C_{20}-Diterpenoid Alkaloids

By

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Doctor of Philosophy in Chemistry
University of California, Berkeley
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This dissertation discusses our gallium(III)-catalyzed cycloisomerization approach toward the hetidine and hetisine-type diterpenoid alkaloids. The first chapter presents the background of the gallium(III)-catalyzed cycloisomerization reaction. The initial reports for the skeletal rearrangements of 1,6-enyned will be presented and the expansion of the substrate scope to include indenyl alkynes to provide cycloheptadiene products will be discussed. The chapter will conclude with the application of the indenyl alkyne cycloisomerization reaction to the synthesis of several icetexane diterpenoids.

The second chapter focuses on the structure and classification of the C_{20}-diterpenoid alkaloids. The biological activity of selected alkaloids will be discussed. Several approaches toward the hetidine and hetisine cores will also be presented along with the two completed total syntheses of the hetisine-type diterpenoid alkaloid nominine.

Chapter three presents our approach toward the hetidine core using the gallium(III)-catalyzed cycloisomerization strategy. Our retrosynthetic analysis of a key-intermediate resembling the hetidine core, that we proposed could be used to access both hetidine and hetisine-type natural products, will be discussed. Synthesis of the cycloisomerization substrate will be presented along with the elaboration of the resulting cycloheptadiene to an intermediate similar to that used by Gin and Peese in their synthesis of nominine. Finally, an oxidative dearomatization approach toward the [2.2.2] bicycle and completion of the hetidine core will be presented.

The final chapter discusses the elaboration of the hetidine core to dihydronavirine A in an attempt to access the hetidine-type natural product navirine A. An interesting C-C bond cleaving reaction, which provides the atisine core from the hetidine core, was also explored.
# Table of Contents

Acknowledgements

<table>
<thead>
<tr>
<th>Chapter One: Gallium(III)-Catalyzed Cycloisomerization of Enynes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Introduction</td>
</tr>
<tr>
<td>1.2 Initial Reports</td>
</tr>
<tr>
<td>1.3 Cycloisomerization of Indenyl Alkynes</td>
</tr>
<tr>
<td>1.4 Proposed Cycloisomerization Mechanism</td>
</tr>
<tr>
<td>1.5 Synthesis of Icetexane Diterpenoids</td>
</tr>
<tr>
<td>1.6 Conclusion</td>
</tr>
<tr>
<td>1.7 References and Notes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter Two: Hetidine and Hetisine-Type C₂₀-Diterpenoid Alkaloids</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1 Introduction</td>
</tr>
<tr>
<td>2.2 Structure, Isolation, and Biological Activity</td>
</tr>
<tr>
<td>2.3 Proposed Biosynthesis and Degradation Studies of the C₂₀-Diterpenoid Alkaloids</td>
</tr>
<tr>
<td>2.4 Previous Synthetic Approaches</td>
</tr>
<tr>
<td>2.5 Total Syntheses of Nominine</td>
</tr>
<tr>
<td>2.6 Conclusion</td>
</tr>
<tr>
<td>2.7 References and Notes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chapter Three: Synthesis of the Hetidine Core</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1 Introduction</td>
</tr>
<tr>
<td>3.2 Retrosynthesis</td>
</tr>
<tr>
<td>3.3 Gallium(III)-Catalyzed Cycloisomerization</td>
</tr>
<tr>
<td>3.4 Installation of the Vinyl Group</td>
</tr>
<tr>
<td>3.5 Installation of the Allyl Group and C-N Bond Formation</td>
</tr>
<tr>
<td>3.6 Conversion of the Allyl Group to the Vinyl Group</td>
</tr>
<tr>
<td>3.7 Reductive Dearomatization</td>
</tr>
<tr>
<td>3.8 Oxidative Dearomatization and Completion of the Hetidine Core</td>
</tr>
<tr>
<td>3.9 Conclusion</td>
</tr>
<tr>
<td>3.10 Experimental Contributors</td>
</tr>
<tr>
<td>3.11 Experimental Methods</td>
</tr>
<tr>
<td>3.12 References and Notes</td>
</tr>
</tbody>
</table>

*Appendix One: Spectra Relevant to Chapter Three*  
95

<table>
<thead>
<tr>
<th>Chapter Four: Approach Toward the Navirines and Synthesis of the Atisine Core</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1 Introduction</td>
</tr>
<tr>
<td>4.2 The Navirines: Structure, Isolation, and Biological Activity</td>
</tr>
<tr>
<td>4.3 Synthetic Approaches Toward Navirine A</td>
</tr>
<tr>
<td>4.4 Synthesis of the Atisine Core</td>
</tr>
<tr>
<td>4.5 Conclusion</td>
</tr>
<tr>
<td>4.6 Experimental Contributors</td>
</tr>
<tr>
<td>4.7 Experimental Methods</td>
</tr>
<tr>
<td>4.8 References and Notes</td>
</tr>
</tbody>
</table>

*Appendix Two: Spectra Relevant to Chapter Four*  
149
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Steve Heller was also a great mentor in the lab. He is a great example of how to be an independent thinker and always encouraged me to think deeper about my projects and to ask as many questions as possible. He is also a constant source of knowledge. I am definitely a better chemist because of his example.

I am very grateful to the people who have worked on my project along with me. Jesse Cortez began the synthesis of nomine and worked alongside of me until he graduated. I then had the pleasure of working with Dr. David Lapointe who developed the enantioselective synthesis and helped to scale up the synthesis. We had a lot of fun setting up a new lab room together, quizzing each other about chemistry, and constantly bouncing ideas off of one another.

My classmates-Gary Gallego, Jessica Kisunzu, Rebecca Murphy, and Erica Schultz-have been a constant source of support and friendship during graduate school. I could not think of a better set of classmates to experience graduate school along with. My many other friends and labmates also helps to make the lab a great place to come to work everyday. Everyone in the group was always willing to answer questions and to share ideas.

Finally, I am grateful to my family and my friends both here in the Bay Area and back in Detroit. I know that it wasn’t easily on my parents for me to move so far away but I am glad they encouraged me to pursue my dreams. I am also especially grateful for my friend Lindsey Cullen for always being there.
Chapter One:
*Gallium(III)-Catalyzed Cycloisomerization of Enynes*

1.1 Introduction

Cycloisomerization reactions are an example of efficient transformations that increase molecular complexity from readily accessible starting materials. The gallium(III)-catalyzed cycloisomerization of 1,6-enynes to afford conjugated dienes was first reported by the group of Chatani and Murai. Our group later expanded on the scope of this methodology to include the cycloisomerization of indenyl alkynes, giving access to [6-7-6] carbocycles. This chapter will briefly discuss background pertaining to the gallium(III)-catalyzed cycloisomerization of enynes, the use of indenyl alkynes as substrates, a mechanistic proposal for this transformation, and the application of the indenyl alkyne cycloisomerization to the synthesis of several icetexane-type diterpenoids.

1.2 Initial Reports

Skeletal rearrangements of 1,6-enynes in the presence of metal salts or complexes to give vinylcycloalkenes can provide two different skeletal rearrangement products, which can be obtained selectively depending on the catalyst and the substrate used (A and B, Figure 1-1). Trost reported the first cycloisomerization of 1,6 enynes in 1988 using tetracarbomethoxy-palladacyclopentadiene (TCPC) as the catalyst. With the original Trost conditions, enynes with an ester group at the acetylenic position provided exclusively type A products whereas enynes containing a terminal alkyne gave a mixture of both type A and B products. Since the initial Trost report, other late transition metal complexes such as [RuCl₂(CO)₃]₂, PtCl₂, and [IrCl(CO)₃]₅ have also been employed for this purpose. These catalysts can be used to access type A products exclusively for substrates bearing a terminal alkyne. With internal alkynes bearing aliphatic substituents or ester groups at the acetylenic position, type B products are obtained as the major product.

![Figure 1-1. Skeletal rearrangement of 1,6-enynes to vinylcycloalkenes.](image)

In 2002, Chatani, Murai, and coworkers reported a skeletal rearrangement of 1,6-enynes (1.1) to afford vinylcycloalkenes (1.2) in the presence of GaCl₃ (Scheme 1.1). Gallium halides have been shown to activate alkynes and thus can be used as efficient catalysts for cycloisomerization reactions involving alkynes. The skeletal rearrangement of 1,6-enynes bearing a terminal alkyne in the presence of GaCl₃ leads exclusively to type A products in a stereospecific manner. The use of late transition metal salts and complexes, such as those based on Ru(II) or Pt(II), for the cycloisomerization of 1,6-enynes...
Enynes bearing a substituent at the terminal olefinic carbon leads to the trans product regardless of the stereochemistry of the starting substrate. The GaCl₃-catalyzed cycloisomerization also allows for the rearrangement of 1,6-enynes bearing two substituents at the terminal olefinic carbon, whereas these substrates are typically challenging with catalysts derived from late transition metals. Indium halides have also been shown to activate alkynes. For example, Chatani has shown InCl₃ to be an effective catalyst for the skeletal rearrangement of 1,6-enynes bearing a terminal alkyne leading to the same type A products.⁸

![Scheme 1-1. Gallium(III)-catalyzed cycloisomerization of 1,6-enynes.](image)

### 1.3 Cycloisomerization of Indenyl Alkynes

In 2004, the Sarpong group proposed to expand the scope of the enyne cycloisomerization reaction, to be able to include an indene in place of the olefin component. This would provide access to cycloheptadiene products (Figure 1-2). The cycloisomerization of tethered indenyl alkynes would provide an interesting tricyclic carbocycle that could be mapped onto the skeleton of various seven-membered ring containing natural products.

![Figure 1-2. Proposed enyne cycloisomerization of indenyl alkynes.](image)

The initial studies toward accessing cycloheptadiene products from indenyl alkynes were first explored by Dr. Eric Simmons in the Sarpong group using model substrate 1.3.⁹ Indenyl alkyne 1.3 was subjected to a variety of known enyne cycloisomerization conditions including PtCl₂, PtCl₄, [Ru(CO)₂Cl₂]₂ and [Rh(CO)₂Cl₂]₂/AgBF₄ (Table 1-1, entries 1-5). These selected transition metal complexes catalyzed the desired cycloisomerization to give the expected cycloheptadiene product (1.4) but as an inseparable mixture with undesired isomer 1.5. When GaCl₃ was used to catalyze the skeletal rearrangement of indenyl alkyne 1.3, cycloheptadiene 1.4 was obtained as the sole product (entry 6). The cycloisomerization reaction catalyzed by GaCl₃ was tolerant of substitution adjacent to the alkyne as well as varying levels of electron density around the aromatic ring. Notably, other gallium halides, such as GaI₃, were also found to be effective at catalyzing the desired cycloisomerization.¹⁰
Table 1-1. Initial optimization of indenyl alkyne cycloisomerization conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Temp (°C)</th>
<th>Ratio (1.4/1.5)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PtCl(_2)</td>
<td>50</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>PtCl(_2)</td>
<td>80</td>
<td>1.1:1</td>
</tr>
<tr>
<td>3</td>
<td>PtCl(_4)</td>
<td>50</td>
<td>0.6:1</td>
</tr>
<tr>
<td>4</td>
<td>[Ru(CO)(_2)Cl(_2)](_2)</td>
<td>80</td>
<td>2.5:1</td>
</tr>
<tr>
<td>5</td>
<td>[Rh(CO)(_2)Cl(_2)](_2)/AgBF(_4)</td>
<td>23</td>
<td>3:1</td>
</tr>
<tr>
<td>6</td>
<td>GaCl(_3)</td>
<td>23</td>
<td>1:0(^b)</td>
</tr>
</tbody>
</table>

\(^a\)Ratios based on integration of \(^1\)H NMR signals.

\(^b\)Reaction was complete after 1 h.

1.4 Proposed Cycloisomerization Mechanism

To explain the difference in selectivity observed for the late transition metal catalyzed reactions versus the GaCl\(_3\) catalyzed reaction two different mechanistic pathways have been proposed to obtain 1.4 versus 1.5.\(^{11}\) Both pathways involve the initial formation of nonclassical zwitterionic intermediate 1.7, which arises from the reversible coordination of the alkyne to the electrophilic metal center (1.6) (Scheme 1-2). Attack of the metal center by the alkyne leads to zwitterionic intermediate 1.7 and the double bond of the indene then attacks the resulting carbocation leading to nonclassical zwitterionic intermediate 1.8. Resonance structure 1.9 rationalizes the positive charge at the benzylic position, which undergoes attack by the metallated vinyl moiety to provide cyclobutane intermediate 1.10. Stepwise fragmentation of metallocyclobutane and dissociation of the metal gives the desired cycloheptadiene product. Formation of a free cyclobutene intermediate from 1.10 followed by a 4\(\pi\) electrocyclic ring opening to give rise to cycloheptadiene 1.4 is unlikely as the thermal 4\(\pi\) electrocyclic ring opening would proceed with conrotation, leading to a strained trans-double bond.
Scheme 1-2. Proposed mechanism for the formation of cycloheptadiene 1.4.

This mechanistic proposal for the formation of cycloheptadiene product 1.4 is supported by the isolation of a cyclobutene intermediates from the GaCl₃-catalyzed enyne cycloisomerization reactions reported by Chatani and Murai.¹² Dr. Eric Simmons also demonstrated a rate increase for the formation of the cycloheptadiene products using substrates possessing more electron rich aromatic cores. This result suggests that the benzylic carbocation (1.9) is more stabilized with electron-rich aromatic rings relative to other possible isomers. This observation lends further support to a benzylic carbocation intermediate and for the proposed mechanism.¹³

Formation of benzofulvene isomer 1.5, which is observed with the use of transition metal salts and complexes as catalysts results from the same nonclassical carbocation intermediate (1.8). Attack of the double bond of the indene can also give rise to tertiary carbocation 1.11 (Scheme 1-3) in addition to the previously suggested benzylic carbocation 1.9. Tertiary carbocation 1.11 can be stabilized through π-backbonding from the metal center as represented by metallocarbenoid 1.12. A proton transfer and isomerization of 1.12 then leads to benzofulvene 1.5. Fragmentation of the cyclopropane in 1.12 could also lead to benzylic carbocation 1.9 resulting in the formation of cycloheptadiene product 1.4.

Scheme 1-3. Mechanistic proposal for the formation of benzofulvene 1.5.
With late transition metal catalysts where the metal center possess accessible \( d \)-electrons for backbonding, such as \( \text{PtCl}_2 \), it is believed that both mechanistic pathways are operative, leading to the mixture of isomeric products observed for the skeletal rearrangement of indenyl alkynes under these conditions. Gallium, a main group element, does not contain accessible \( d \)-electrons, therefore, formation of a metal-carbenoid intermediate is not favored and cycloheptadiene 1.4 is obtained as the sole product.

1.5 Synthesis of Icetexane Diterpenoids

With a method to selectively access 6-7-6 carbocyclic skeletons in hand, Dr. Eric Simmons then turned to the preparation of more complex and synthetically useful cycloheptadienes that could be used to synthesize icetexane diterpenoids. The initial target was salviasperanol, an icetexane diterpenoid isolated from the root of the \textit{Salvia apera} plant (1.13 Figure 1-3).

![Figure 1-3](image)

**Figure 1-3.** Selected icetexane diterpenoid alkaloids.

Synthetic efforts toward salviasperanol began with the synthesis of indanone 1.18 in 5 steps from isopropyl veratrole (1.17, Scheme 1-4). A Claisen condensation with Mander’s reagent followed by alkylation with alkyl iodide 1.19 provided \( \beta \)-ketoester 1.20. Direct alkylation of indanone 1.18 resulted in over alkylation of the indanone. As a result, a carbomethoxy group was installed prior to the alkylation with 1.19 to prevent the second alkylation. A saponification and decarboxylation of the methylester provided the alkylated indanone (not shown). The resulting indanone was reduced to the indanol with DiBAl-H (not shown) and subsequently dehydrated (\( \text{Ms}_2\text{O} \) and \( \text{Et}_3\text{N} \)) to provide cycloisomerization substrate 1.21 as a single regioisomer. The cycloisomerization of indenyl alkyne 1.21 in the presence of \( \text{GaCl}_3 \) proceeded sluggishly compared to model substrate 1.3 presumably because of the sterics of the \textit{gem}-dimethyl group adjacent to the alkyne. However, it was found that by increasing the reaction temperature to 40 °C and adding powdered 4Å molecular sieves, cycloheptadiene 1.22 could be obtained in 90% yield.
Scheme 1-4. Synthesis of cycloheptadiene 1.22.

To complete the synthesis of salviasperanol, oxidation of cycloheptadiene 1.22 to the dihydrofuran was achieved through selective epoxidation of the tetrasubstituted double bond followed by a trifluoroacetic acid-catalyzed rearrangement to provide salviasperanol dimethyl ether (1.23, Scheme 1-5). Finally, methyl ether cleavage using sodium ethanethiolate provided salviasperanol (1.13).

Scheme 1-5. Completion of salviasperanol from cycloheptadiene 1.22.

Salviasperanol dimethyl ether (1.23) is a versatile intermediate that can be used to access other icetexane diterpenoids including 5,6-dihydro-6α-hydroxy-salviasperanol (1.26), brussonol (1.28), and abrotanone (1.14) (Schemes 1-6 and 1-7). To this end, hydroboration followed by a two-stage oxidation of salviasperanol dimethyl ether (1.23) provided ketone 1.24 (Scheme 1-6). Epimerization of 1.24 in the presence sodium methoxide led to complete isomerization to the trans-fused 6,7-bicycle (not shown). Finally, reduction of the resulting ketone to alcohol 1.25 followed by cleavage of the methyl ethers yielded 5,6-dihydro-6α-hydroxy-salviasperanol (1.26).
Scheme 1-6. Completion of 5,6-dihydro-6α-hydroxy-salviasperanol.

Alternatively, a Barton-McCombie deoxygenation of alcohol 1.25 to yield 1.27 followed by cleavage of the methyl ethers leads to brussonol (1.28, Scheme 1-7), a diterpenoid isolated from the roots of the Salvia broussonetii plant and shown to have moderate cytotoxic activity against insect and mammalian cell lines. Brussonol can be further elaborated to the diterpenoid abrotanone (1.14) through a net four-electron oxidation. This oxidation is mediated by Cu(NO$_3$)$_2$•3H$_2$O$^{17}$ and morpholine in methanol to form a hemiaminal (not shown). Treatment of the hemiaminal with sodium methoxide provides abrotanone.$^{18}$

Scheme 1-7. Synthesis of brussonol and abrotanone.

With the gallium(III)-catalyzed cycloisomerization proving to be a successful to access several icetexane diterpenoids containing a gem-dimethyl group, Dr. Eric Simmons and Dr. Felipe de Cortez next turned to the synthesis of icetexane diterpenoids containing a bridged lactone ring in place of the gem-dimethyl group.
Specifically, icetexone and epi-icetexone (1.15 and 1.16, see Figure 1-3) were targeted. Icetexone has been isolated from plants in the salvia genus and has been shown to possess activity against Trypanosoma cruzi, the parasite that causes Chagas’ disease.

Initial studies began with cycloheptadiene substrates similar to 1.22, which contained a gem-dimethyl group, but late-stage remote functionalization of the one of the geminal methyl groups was unsuccessful. As a result, it was necessary to install the necessary functionalization on the gem-dimethyl group prior to the cycloisomerization. To this end, alkyl iodide 1.34, which contains a methyl and cyano group adjacent to the terminal alkyne, was synthesized in nine steps from commercially available 3-bromo-1-propanol (1.29, Scheme 1-8). Silyl protection of 1.29 followed by alkylation of methyl cyanoacetate (1.30) with the resulting bromide as the electrophile provided 1.31. Methylation with iodomethane and chemoselective reduction of the ester group in the presence of NaBH₄ in THF/H₂O provided primary alcohol 1.32. Swern oxidation to the corresponding aldehyde followed by an Ohira-Bestmann homologation permitted installation of the terminal alkyne group (1.33). Finally, cleavage of the silyl protecting group, mesylation of the resulting primary alcohol, and displacement of the mesylate with sodium iodide provided alkyl iodide 1.34.

\[ \text{Scheme 1-8. Synthesis of alkyl iodide 1.34.} \]

A sequence similar to that employed for the synthesis of indenyl alkyne 1.21 was then used to access the variant containing the methyl and cyano group adjacent to the alkyne as well as an additional methoxy group on the aromatic ring (1.38, Scheme 1-9). Indanone 1.36 could be accessed in five steps from known benzyl alcohol 1.35. A Claisen condensation of indanone 1.36 with dimethyl carbonate provided a β-ketoester (not shown) that was then alkylated with alkyl iodide 1.34 to provide β-ketoester 1.37. Saponification and decarboxylation of the methyl ester group and selective reduction of the resulting indanone provided the indanol as a mixture of diastereomers (not shown). Dehydration of the indanol in the presence of KHSO₄ provided cycloisomerization substrate 1.38 as a single regioisomer. The cycloisomerization of 1.38 proceeded in the
presence of GaCl₃ (25 mol%) at 100 °C over 48 hours to give 91% yield of cycloheptadiene 1.39. A higher reaction temperature and longer reaction time was required for the cycloisomerization of 1.38 compared to 1.21 presumably because of the presence of the electron-withdrawing cyano group adjacent to the terminal alkyne reducing the nucleophilicity of the alkyne.


With the 6-7-6 carbocycle of icetexone in place, the next step was to install the lactone. Hydrolysis of the cyano group in 1.39 using the Ghaffar and Parkin's platinum complex 23 (1.40) as a catalyst provided access to primary amide 1.41 (Scheme 1-10). An iodolactonization of 1.41 in an attempt to install the bridging lactone ring was unsuccessful and instead led to lactonization of the cis-disubstituted double bond (not shown). Alternatively, it was found that the desired bridging lactone could be installed through a diastereoselective epoxidation of the tetrasubstituted double bond to give epoxide 1.42 followed by a reductive condensation in the presence of camphor sulfonic acid and tosylhydrazide to give the desired lactone albeit, as a mixture of epimers 1.43 and 1.44 in a combined 42% yield.24 Both epimers (1.43 and 1.44) could then be advanced to the natural products icetexone (1.15) and epi-icetexone (1.16) using procedures reported previously by Majetich.25
Scheme 1-10. Formal synthesis of icetexone and epi-icetexone.

With the installation of a single stereocenter that then directed the stereoselectivity of the remainder of the synthesis of icetexone and epi-icetexone, the opportunity presented itself to render the route enantioselective.\textsuperscript{26} By accessing the stereocenter bearing the methyl and cyano group enantioselectively, an enantioselective synthesis of icetexone and epi-icetexone could be achieved. Using a protocol originally reported by Sawamura et al.\textsuperscript{27} for the enantioselective conjugate addition of cyanopropionates into acrolein, Dr. David Lapointe was able to react cyanoester 1.45 with acrolein (1.46) in the presence of Rh(I)-2,2'-bis[1-(diarylphosphino)ethyl]-1,1'-bisferrocene complex and then immediately reduce and protect the resulting aldehyde to provide silyl protected alcohol 1.48 with 89% ee (Scheme 1-11). Selective reduction of the tert-butyl ester group to a primary alcohol provided enantioenriched 1.32. Enantioenriched cycloheptadiene 1.39 could then be accessed from alcohol 1.48 using the same procedures as before. The absolute stereochemistry of cycloheptadiene 1.39 (determined by X-ray analysis of p-bromobenzamide derivative 1.49, see ORTEP in Scheme 1-11) was found to correspond to the stereochemistry of naturally occurring icetexone and epi-icetexone.
1.1. Enantioselective synthesis of cycloheptadiene 1.39.

1.6 Conclusion

In conclusion, the gallium(III)-catalyzed cycloisomerization reaction methodology provides an expedient way to access carbocyclic [6-7-6] ring systems from easily accessible indenyl alkyne substrates. This methodology has been used to access several icetexane diterpenoids with varying levels of oxygenation. We wish to further expand the use of this methodology to the synthesis of more complex natural products containing a hidden [6-7-6] ring system, specifically the C$_{20}$ diterpenoid alkaloids.

1.7 References and Notes


7 For review on gallium halides see: Gupta, M. K.; O'Sullivan, T. P. *RSC Adv.*, **2013**, *3*, 25498.


11 See ref 9.

12 For example, cycloisomerization of 1.i yielded cyclobutene 1.ii. See ref 6.

13 Indenyl alkyne 1.iii displayed an accelerated rate compared to substrate 1.iv. See ref 9.


18 The synthesis of abrotanone from synthetic brussonol (also known as abrotandiol) led to the structural revision of abrotanone.


The initial approach toward icetexone involved the formation of oxime 1.vi from alcohol 1.v using a Barton nitrite ester reaction.


The proposed mechanism for the formation of bridged lactone 1.43 and 1.44 from primary amide 1.42 involves first protonation of the epoxide group in 1.42 to afford allylic cation 1.vii. Trapping of cation 1.vii with tosylhydrazide gives 1.viii which cyclizes forming the bridged lactone and undergoes a diazene rearrangement leading to 1.43 and 1.44.


see ref 19b.

Chapter Two:  
*Hetidine and Hetisine-Type C20-Diterpenoid Alkaloids*

2.1 Introduction

The hetidine and hetisine-type C20-diterpenoid alkaloids are highly caged natural products that are a subset within the atisane class of diterpenoid alkaloids. The hetidines and hetisines are of interest to synthetic chemists because of their structural complexity and diverse range of biological activities. This chapter will present the general structure and classification of the C20-diterpenoid alkaloids, the biological activities of select C20-diterpenoid alkaloids, and a proposed biosynthesis of the hetidine and hetisine cores. The synthetic approaches reported toward the azabicyclic core of the hetidines and hetisines, and the two existing total syntheses of the hetisine-type diterpenoid alkaloid nominine will also be presented.

2.2 Structure, Isolation, and Biological Activity

The diterpenoid alkaloids, as defined by Pelletier, are amine bases derived from tetracyclic or pentacyclic diterpenes with the nitrogen atom incorporated either from methylamine, ethylamine, or β-aminoethanol. They are classified as C18, C19- or C20-diterpenoid alkaloids based on the number of carbons present in the core structure. Alkaloids from all three categories are of interest to synthetic chemists because of their structural complexity as well as to biologists because of their potent and varied biological activities. Their medicinal properties have been the subject of a number of recent reviews by F.-P. Wang and coworkers. The C20-diterpenoid alkaloids are the focus of this chapter and are identified by the presence of the nitrogen atom attached to C19 and C20 to form a piperidine ring (see 2-1 for numbering).

![Numbering scheme for C20-diterpenoid alkaloids.](image)

Figure 2-1. Numbering scheme for C20-diterpenoid alkaloids.

To date, over 370 C20-diterpenoid alkaloids have been isolated from eight genera of plants within the Ranunculaceae family including *Aconitum*, *Dephinium*, and *Spiraea*. Extracts from these plants have long been used in traditional herbal medicine to treat a variety of ailments including sepsis, rheumatoid arthritis, and migraines. Further studies have revealed that diterpenoid alkaloids are the principle components of these plants that are responsible for their diverse biological activities.

Wang and Liang have divided the C20-diterpenoid alkaloids into four different structural classes based on the carbon skeletons (Figure 2-2). The atisane class (A) is
characterized by the presence of a [2.2.2] bicycle bearing an exomethylene group whereas, the kaurane class (B) contains a [3.2.1] bicycle bearing the exomethylene group. The rearranged class (C) results from the skeletal rearrangement of the right hand portion of the atisane and kaurane cores to give unique bicycles containing the exomethylene group and the bis-diterpenoid class (D) arises from the condensation of two C\textsubscript{20}-diterpenoid alkaloids from any of the previous three classes or from the condensation of one C\textsubscript{20}- and one C\textsubscript{19}-diterpenoid alkaloid to give carbon skeletons containing either 40 or 39 carbons.

![Diagram of four classes of C\textsubscript{20}-diterpenoid alkaloids]

**Figure 2-2.** Four classes of C\textsubscript{20}-diterpenoid alkaloids.

Each of the four classes is further divided into types. The atisane class is divided into eight different types based on the presence or absence of specific bonds relative to the basic atisine core (A I, Figure 2-3). We are specifically interested in the hetidine-type (A IV), which contains an additional C14-C20 bond, and the hetisine-type (A VII), which contains an additional C14-C20 bond and a N-C6 bond relative to the atisine core.
As of 2010, 53 hetidine-type and 126 hetisine-type diterpenoid alkaloids have been isolated. Nomineine (2.1, Figure 2-4), the simplest of the hetisines that has been isolated to date, containing only one additional hydroxyl group relative to the hetisine core, and was isolated in 1956 from the *Aconitium sanyoense* plant. The structure and absolute configuration of nomineine was not fully determined until 1982 through the chemical conversion of kobusine (2.2) to nomineine. Kobusine was isolated in 1940 and was one of the first C_{20}-diterpenoids to be analyzed using x-ray crystallography.

The hetidines and hetisines have shown a diverse range of biological activity, although most of these natural products isolated have not been thoroughly tested. Nomineine has been shown to have local anesthetic, anti-inflammatory, and anti-arrhythmic activity whereas the addition of one extra hydroxyl group, as in kobusine, results in vasodilatory activity. This activity is proposed to arise from the interaction of the diterpenoid alkaloids with voltage-dependent Na^{+}, K^{+}, or Ca^{2+} ion channels, which are critical to the function of nerve cells. Modification of voltage-gated ion channels has been shown to affect the activity of the central nervous system. The bioactivity of guan-fu base A (2.3, Figure 2-5), a hetisine-type alkaloid, has been extensively explored.
and the hydrochloride salt of guan-fu base A is approved for use in China for the treatment of paroxysmal supraventricular tachycardia in 2005 under the name acehytisine hydrochloride.\textsuperscript{10}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{structures.png}
\caption{Structures of guan-fu base A and coryphine.}
\end{figure}

Other C\textsubscript{20}-diterpenoid alkaloids, such as coryphine (2.4, Figure 2-5), a hetidine-type alkaloid isolated from \textit{Aconitum coreanum}\textsuperscript{11}, still have an effect on nerve function but do not change the cell potential suggesting that these alkaloids do not interact with voltage-dependent ion channels. Instead, it was found that alkaloids such as coryphine reversibly block the acetylcholine receptors of the postsynaptic membrane.\textsuperscript{12} Coryphine has been shown to have no effect on the cardiovascular system but, specifically interacts with the acetylcholine receptors of skeletal muscles resulting in myorelaxant (muscle relaxant) activity and like other diterpenoid alkaloids can be toxic at high doses.

The synthesis of the hetidine and hetisine natural products and of unnatural derivatives could be used to further understand how these small molecules interact with ion channels as well as to study diseases that affect voltage-gated ion channels including neurodegenerative diseases, such as Alzheimer’s disease. The remainder of this chapter presents an analysis of how nature synthesizes these molecules as well as how others have thought about assembling the hetidine and hetisine alkaloids.

\section*{2.3 Proposed Biosynthesis and Degradation Studies of C\textsubscript{20}-Diterpenoid Alkaloids}

The proposed biosynthesis of the C\textsubscript{20}-diterpenoid alkaloids as well as their associated degradation studies reveals many potential opportunities for inter-conversion between the structural types and may serve as inspiration as to how these molecules may be accessed synthetically. It is proposed from biosynthetic studies that the diterpenoid alkaloids arise from geranylgeranyl diphosphate (GGPP) (2.5, Scheme 2-1).\textsuperscript{13} Cyclization of GGPP leads to \textit{ent}-copalyl diphosphate (2.6), which can be further cyclized to give \textit{ent}-atisir-16-ene (2.11), the tetracyclic precursor to the atisane skeleton through the intermediacy of a nonclassical carbocation (2.9) followed by a C-C bond shift and a hydride shift to form the [2.2.2] bicycle.
Scheme 2-1. Proposed biosynthesis of the cyclic diterpene leading to the atisanes.

Carbocation intermediate 2.8 has also been proposed to be an intermediate in the synthesis of ent-kaur-16-ene (2.13, Scheme 2-2), the tetracyclic diterpene leading to the kaurane group of diterpenoid alkaloids, which contains a [3.2.1] bicycle.

Scheme 2-2. Proposed biosynthesis for the cyclic diterpene leading to the kauranes.

It is proposed that after the construction of the cyclic diterpene (e.g., 2.11 and 2.13), the nitrogen atom is incorporated from β-aminoethanol (2.15), a compound commonly found in plants, through a double Mannich-type condensation with dialdehyde 2.14. This transformation gives rise to the atisine skeleton (2.16, Scheme 2-3). The C14-C20 bond is proposed to arise from opening of the oxazolidine ring to form an imine and subsequent attack of the imine carbon resulting in the hetidine skeleton (2.18). Finally, nucleophilic attack of the amine at the oxygenated C6 position forms the N-C6 bond giving rise to the hetisine skeleton (2.19).
There also exists several interesting hetidines and hetisines, such as coryphine (2.4), that incorporate a rearranged hordenine side chain attached to the C17 carbon. It is proposed that this side chain arises from the coupling of hordenine (2.21), a phenol natural product isolated along with the diterpenoid alkaloids, with the C17 carbon of the exomethylene (Scheme 2-4). Demethylation of the dimethylamine (2.22) followed by a Claisen rearrangement then a Cope rearrangement provides 2.24. Finally a 1,4-conjugate addition of the secondary amine into the resulting dienone results in the unique hexahydro-N-methylindol-6-one side chain (2.25). It is also possible that the demethylation occurs after the rearrangement and 1,4-conjugate addition. There have also been several natural products isolated, such as the navirines,\textsuperscript{16} which contain the hordenine side chain as seen in 2.22.

A careful study of the structure and biosynthesis of the diterpenoid alkaloids has revealed a biogenetic relationship among the different carbon skeletons arising from the
This relationship is also supported by degradation studies where one carbon skeleton can be converted to another through a series of chemical transformations. This is exemplified by the degradation studies of kobusine, which was reported by Okamoto and coworkers. Starting from kobusine (2.2, Scheme 2-5), a hetisine-type alkaloid, they investigated the cleavage and reformation of the C14–C20 and N–C6 bonds, as these are key bonds that establish the relationship between the hetidine, hetisine, and atisine cores.

Scheme 2-5. Degradation studies of kobusine.

Subjection of kobusine to reducing conditions (sodium in n-propanol) followed by acylation gave acetate 2.26. Treatment of 2.26 with phenyl chloroformate in o-dichlorobenzene at reflux delivered carbamate 2.27 in 90% yield, where the N–C6 bond had been cleaved. Interestingly, it was observed that hydrolysis of the carbamoyl group resulted in reformation of the N–C6 bond (to yield 2.26) when the C6–C7 double bond was in place as in 2.27. Therefore, reduction of the C6–C7 double bond was necessary in order to achieve further manipulation. This observation is of note because forming the strained azabicycle of the hetisines from the hetidines is a significant challenge. Synthetic planning could therefore benefit from mimicking this type of innate reactivity.

From carbamate 2.27, sequential reductions of the tri- and di-substituted double bonds resulted in a fully saturated framework (not shown). Removal of the acetyl group proceeded without complication, and cleavage of the carbamate was accomplished in two steps to arrive at amine 2.28. In order to cleave the C14–C20 bond (see 2.28 for numbering) to arrive at the atisine-type core, polycycle 2.28 was first converted to the chloramine (not shown), then treated with sodium methoxide in methanol at reflux to deliver chloroimine 2.30 in 38% yield. Among the compounds isolated from the crude mixture was 2.29 in which the N–C6 bond was reformed, presumably via a Hoffman-Löffler-Freytag-type mechanism. This transformation again provides insight into the importance of proximity and potential reactivity of key atoms that could be exploited in the synthesis of hetisine-type natural products. Imine 2.30 could be reduced to the secondary amine (not shown) or treated with activated magnesium to reform the C14–C20 bond and regenerate 2.28. Through these chemical conversion studies, Okamoto and coworkers were able to demonstrate the intrinsic reactivity of kobusine-derived
caged structures that may be applied to the synthesis of related hetidine and hetisine-type diterpenoid alkaloids.

**2.4 Previous Synthetic Approaches**

To date, several synthetic approaches toward the hetidine and hetisine-type diterpenoids have been reported. Many of these approaches focus only on the construction of part of the skeleton whereas others are attempts toward a specific natural product. However, all of the approaches provide useful insights into how the C$_{20}$-diterpenoid alkaloids can be deconstructed retrosynthetically and how key bonds within the cores can be accessed.

Retrosynthetic analysis of the C$_{20}$-diterpenoid alkaloid core often focuses on the deconstruction of two structural units: the nitrogen-containing rings and the all-carbon [2.2.2] bicycle containing an exomethylene (Figure 2-6, red bonds). Most of the existing studies toward the hetidines and hetisines focuses on the construction of the azabicycle followed by the formation of the [2.2.2] bicycle at a later stage. A review of the synthetic work toward these natural products therefore begins with a discussion of the strategies employed to form the piperidine ring of the azabicycle, followed by C–C bond formation to construct the [2.2.2] bicycle, and completion of the core.

![Figure 2-6. Structural units of the hetidines and hetisines.](image)

The general tetracyclic structure **2.31** was identified by Pelletier as a versatile intermediate that was used in various early synthetic studies toward diterpenoid alkaloids in the atisane or kaurane class. While this seminal work was not directed specifically at the hetidine or hetisine frameworks, much of the work that followed from other investigators adopted similar intermediates (e.g., **2.32**) as targets (vide infra).

![Figure 2-7. Key tricyclic intermediates identified by Pelletier.](image)

Van der Baan and Bickelhaupt reported one of the earliest model studies toward the hetisine-type diterpenoid alkaloids in 1975. While studying the reactivity of cyanopyridinediols such as **2.35** (Scheme 2-6), which could easily be prepared from
ethyl cyclohexanone-2-carboxylate (2.33) and malononitrile or cyanoacetamide (2.34), they observed that alkylation of these diols (e.g., with allyl bromide) occurred exclusively at the carbon atom bearing the cyano group to give compounds such as 2.36. Protection of the imide nitrogen followed by Cope rearrangement delivered imide 2.37 in which the quaternary center at C10 was now in place. Bromohydroxylation of the terminal olefin group and subsequent protection of the secondary hydroxyl as a tetrahydropyran ether gave 2.38, which was now poised for cyclization. Treatment of 2.38 with NaH in DMF gave the cyclized product (2.39) via initial deprotonation of the vinyl nitrile. Imide 2.40, bearing an additional carbonyl group, was accessed through THP-cleavage and subsequent oxidation of the secondary hydroxyl group. This compound maps closely onto 2.32 (Figure 2-7), and contains the 2 C–N bonds present in the hetidine core, as well as a functional handle at C6, should the hetisine-type alkaloids be of interest.

Scheme 2-6. Bickelhaupt’s tricycle formation from cyanopyridinediol 2.35.

In 2001, the Winkler group reported a methodology that they posited could be used to access a different portion of the hetisine azabicycle. To demonstrate their strategy, Winkler and Kwak began with α,β unsaturated amide 2.41, which was used to access 1,5-diene 2.42 in three steps (Scheme 2-7). Irradiation of vinylogous amide 2.42 gave “crossed” photoadduct 2.43 in good yield. Heating 2.43 in ethanol followed by the addition of catalytic pyridinium p-toluenesulfonate delivered tricycle 2.45 via sequential retro-Mannich/Mannich reactions. This azabicyclic[3.2.1]octanone has the same decalin system as the Bickelhaupt model system (i.e., 2.40), but with the pyrrolidine ring in place rather than the piperidine (compare 2.45 to 2.40). Superimposed onto the hetidine core, the C–N bonds resident in 2.45 correspond to the N–C6 and N–C20 bonds of the hetisines.
Mander, Williams, and coworkers have investigated several model systems of the hetidine and hetisine structural cores. Two are discussed here—one that contains the desired N–C20 bond (forming a piperidine ring) and one that has the N–C6 bond forged (to access the requisite pyrrolidine ring).\(^{25}\) The first of these sequences was published in 2003 by Williams and Mander\(^ {26}\) and utilized a silver(I)-promoted bridgehead arylation. Starting from azabicycle 2.46, which was accessed via a double Mannich reaction, they were able install the piperidine ring at the onset (Scheme 2-8). The addition of aryl acetylide 2.47 to 2.46 provided access to the desired diastereomer of adduct 2.48 in 64% yield. From this adduct, they were able to access cyclization precursor 2.49 in three steps. At this point, numerous silver(I) salts and solvents were screened to effect bridgehead arylation. Ultimately, silver 2,4,6-trinitrobenzenesulfonate (2.50) in nitromethane emerged as the optimal combination for delivering arylated product 2.51. This substrate contains the 6-6-6 tricycle present in the natural product core and is analogous to the tetracyclic intermediate utilized by Pelletier (for example see 2.31, Figure 2-7).
Several years later, Mander and Hutt reported another approach to the hetisine structural core, this time focusing on the installation of the pyrrolidine ring containing the N–C6 bond.\textsuperscript{27} Key to this sequence was a reductive acylation as well as a Lewis acid-catalyzed 1,6-addition of a carbamate to form the N–C6 bond. Enone 2.52 was accessed in eight steps from commercial starting materials using known procedures (Scheme 2-9). At this juncture, reducing metal conditions were employed to reduce the enone, followed by quenching the resulting enolate with methyl cyanoformate, to afford a β-ketoester (not shown). Subsequent protection of the β-ketoester gave MOM enol ether 2.53. Vinylogous carbonate 2.53 was reduced to methylene alcohol 2.54 using lithium and NH\textsubscript{3} with complete diastereoselectivity. From this point, Mander and Hutt were able to install the requisite nitrogen atom in three steps through oxime formation and subsequent dehydration to the nitrile (2.55). Enone 2.56 was accessed in a six-step sequence, which left the investigators poised to test a 1,6-conjugate addition to form the C–N bond. While basic and strongly acidic conditions resulted in no reaction or decomposition of 2.56, it was found that milder Lewis acidic conditions—namely, FeCl\textsubscript{3} and TMSCl—delivered the desired pyrrolidine (2.57), albeit in 21% yield. In this way, Hutt and Mander were able to demonstrate the utility of a 1,6-conjugate addition strategy, as well as highlight the use of methyl cyanoformate in the context of a reductive acylation that provided a critical substituent for the natural product scaffold.

Scheme 2-8. Mander’s first approach toward the hetidines and hetisines.
Scheme 2-9. Mander’s second approach toward the hetisines.

In 1985, Shibanuma and Okamoto reported an approach to the hetisine core with kobusine (2.2) as the intended target. \(^{28}\) Starting from tetrahydrophenanthol (2.58, Scheme 2-10), they were able to access amine 2.59 in seven steps, which was then used to access the azabicycle. The first key step in their approach was the formation of the N–C6 bond. This was accomplished by treatment of amine 2.59 with lead tetraacetate, which resulted in aziridine 2.60. Crude aziridine 2.60 was then treated with benzyl chloroformate to effect a regioselective ring opening to provide benzyl carbamate 2.61. Reduction of chlorocarbamate 2.61 with Raney Nickel gave secondary amine 2.62. At this stage, Okamoto envisioned forming the N–C19 bond (see 2.62) using a Hofmann–Löffler–Freytag (HLF) reaction. The HLF transformation is often used to form 5-membered azacycles via an N-halo intermediate. Treatment of amine 2.62 with N-chlorosuccinimide provided the requisite N-chloro compound (not shown) that was then submitted to photoirradiation under acidic conditions (400 W high-pressure Hg lamp, trifluoroacetic acid) to provide 2.64 via alkyl chloride intermediate 2.63.
In conclusion, structural classifications of the diterpenoid alkaloids are partially guided by the presence or absence of specific C–N bonds. Therefore, structural analyses and methodologies that address the formation of the azabicycle in different ways provide insight into the reactivity and conformations of these compounds. Although the strategies and model studies presented thus far have not led the synthesis of a hetidine or hetisine-type diterpenoid alkaloid, they highlight several strategies that can be employed for formation of the C–N bonds present in these natural products.

2.5 Total Syntheses of Nominine

To date, only one hetidine-type C20-diterpenoid alkaloid, nominine (2.1), has been accessed by total synthesis by two different research groups. The first total synthesis of nominine was completed by the group of Muratake and Natsume and the second by Gin and Peese. Both groups have published full papers reporting their synthetic efforts, which include their retrosynthetic analyses and a discussion of routes that were not fruitful toward the total synthesis of nominine. An analysis of these accounts toward nominine provides a great starting point for the synthesis of other diterpenoid alkaloids. The remainder of the chapter will discuss both of the completed syntheses of nominine.

Muratake and Natsume

Muratake and Natsume reported an initial approach toward nominine (2.11) in 2002. In this first approach, they sought to use a strategy similar to a previous approach reported by Shibanuma and Okamoto where the azabicycle is constructed early in the synthesis. They envisioned accessing the [2.2.2] bicycle at a late stage from functional handles present on hexacyclic compound 2.65 (Scheme 2-11) where all three bonds to the basic amine are already installed. Azabicycle 2.65 could arise from functionalization of tricycle 2.66, where the tertiary amine is installed over a series of steps. Tricycle 2.66 could be obtained from a palladium-catalyzed intramolecular arylation, a method previously developed by the Natsume group. Using this initial
approach, Muratake and Natsume were able to access azabicycle 2.65 (where R = CH₂CH₂OBz), but were unsuccessful in their use of this intermediate to access the [2.2.2] bicycle of the hetisine core.

![Diagram of compounds](image)

**Scheme 2-11.** Muratake and Natsume’s first generation retrosynthesis.

The synthesis of azabicycle 2.65 (where R = CH₂CH₂OBz) began with the palladium-catalyzed α-arylation of aldehyde 2.67 (Scheme 2-12) to arrive at tricycle 2.66. The tricycle was elaborated through a sequence of six steps to provide 2.68. Treatment of 2.68 with boron trifluoride effected an acetyl-ene cyclization to forge a key C–C bond between C14 and C20. Transposition of the ketone in 2.69 followed by installation of the methyl group at C4 gave 2.70 over four steps. A Nagata reaction with Et₂AlCN was used to install a cyano group (see 2.71), which provided the nitrogen atom that would be used to construct the azabicycle. The MOM and 2-hydroxyethyl protecting groups at C20 were then removed over a three-step sequence to reveal a hydroxyl group that would be used to form the third and final C–N bond. To access the N–C6 bond and form the pyrrolidine ring, the carbonyl was first protected as a silyl enol ether and the nitrile group was reduced to a primary amine. The primary amine immediately condensed with the incipient ketone generated upon cleavage of the silyl group. Protection of the resulting imine with Boc anhydride gave 2.73. Reduction of the enamine and selective protection of the primary alcohol provided 2.74, which on exposure to trifluoroacetic acid revealed a secondary amine. Treatment of the secondary amine with thionyl chloride led to cyclization by displacement of the secondary hydroxyl group at C20 (see 2.65) to complete the azabicycle.
Hexacyclic compound 2.65 is composed of almost the entire skeleton of the hetisines, except for the 6-membered ring bearing the exomethylene group. Unfortunately, because of the basicity of the tertiary amine, Muratake and Natsume were unable to advance this intermediate any further toward the hetisine core.

In 2004, Muratake and Natsume reported a revised approach to the hetisine core that involved formation of the N–C20 bond last, thus avoiding the need to carry a basic amine through several steps in the synthesis. In this approach, the [2.2.2] bicycle would be constructed before completion of the azabicycle to enable the basic amine to be carried through the majority of the synthesis protected as an amide (see 2.75, Scheme 2-13). Herein, the key insights that led to the first total synthesis of nominine are analyzed. The initial report was published 2004 and was followed by a series of full papers, which were published in 2006.
Scheme 2-13. Muratake and Natsume’s second generation retrosynthesis.

In the revised approach to the hetisine core, Muratake and Natsume first explored ways to access the [2.2.2] bicycle directly following the acetyl-ene reaction (Scheme 2-14). Allylic oxidation of acetyl-ene product 2.77 with chromium trioxide provided a mixture of enones (2.78 and 2.79). Each enone was used as a model substrate to study how the [2.2.2] bicycle could be installed.


Enone 2.78 was advanced to keto-aldehyde 2.80 over a three-step sequence (not shown). Homologation of aldehyde 2.80 with the Ohira-Bestmann reagent (2.81) provided the desired alkyne (2.82) along with a small amount of aldol product 2.83 where the [2.2.2] bicycle had been formed, but in a low 7% yield (Scheme 2-15). Treatment of keto-alkyne 2.82 with LDA and TMSCl followed by carbomercuration with mercuric triflate-N,N,N',N'-tetramethylurea complex [Hg(OTf)_2(TMU)_2] led to an aldol reaction upon acidic workup. This sequence provided access to 2.85 where the [2.2.2] bicycle was in place as well as the exomethylene group at C16.
Scheme 2-15. Functionalization of keto-aldehyde 2.80.

Enone 2.79 was converted to keto-aldehyde 2.86 through the same three-step sequence used to prepare 2.82 (not shown). Exposure of aldehyde 2.86 to K₂CO₃ in refluxing methanol effected an aldol cyclization to give 2.87 as a mixture of epimers at the hydroxyl-bearing C16 position (Scheme 2-16). Aldehyde 2.86 could also be converted to alkyne 2.88 through an Ohira-Bestmann homologation. Carbomercuration of alkyne 2.88 with [Hg(OTf)₂(TMU)₂] followed by an aldol cyclization of the resulting ketone (2.89) in the presence of LDA provided access to a [2.2.2] bicycle as a single diastereomer (2.90, stereochemistry was not determined).
Scheme 2-16. Functionalization of keto-aldehyde 2.86.

With several strategies to access the [2.2.2] bicycle in hand, Muratake and Natsume next explored ways to install the amine prior to the formation of the [2.2.2] bicycle. The pyrrolidine was installed using a strategy similar to their first reported approach beginning with intermediate 2.71. In this new approach, the hydroxyl group at C20 remained protected with the MOM group and 2-hydroxyethyl protecting groups until the final stages of the synthesis.

The N–C6 bond was forged using the same sequence previously described to access 2.73 and the resulting enamine was protected with either a Boc group or a Cbz group to provide 2.91 and 2.92, respectively (Scheme 2-17). Reduction of the enamine and protection of the primary hydroxyl group as a benzoate provided 2.93 and 2.94 over two steps. Allylic oxidation of the Boc-protected amine substrate (2.93) in the presence of chromium trioxide, as before, gave a mixture of enones 2.95 and 2.97 in 45% and 28% yield, respectively. Using the Cbz protected substrate (2.94), the yields for the chromium trioxide oxidation were even lower with only 12% of 2.96 and 6% of 2.98 obtained with a 50% recovery of 2.94. Because of the low yields associated with the oxidation of Cbz-protected amine substrate 2.94, only enone 2.95 was carried forward.
Scheme 2-17. Formation of pyrrolidine ring and allylic oxidation.

Enone 2.95 was converted to keto-aldehyde 2.99 using a three-step sequence (not shown) and treatment of keto-aldehyde 2.99 with Ohira-Bestmann homologation conditions gave 34% yield of the desired alkyne (2.100) as well as 55% of aldol product 2.101 as a mixture of diastereomers at C16 (Scheme 2-18). Oxidation of the C16 hydroxyl group of 2.101 proceeded in the presence of PCC-Al₂O₃ to yield diketone 2.102 but unfortunately, attempts at a Wittig reaction to install the exomethylene group at C16 only returned starting material.
Scheme 2-18. [2.2.2] Bicycle formation via an Aldol reaction.

Because the aldol reaction approach to form the [2.2.2] bicycle was low yielding, the use of a radical-mediated methodology to form a similar [2.2.2] bicycle was explored. It was proposed that a radical intermediate obtained from a xanthate-containing compound in the presence of a tethered alkyne (see 2.103) could be used to access the desired [2.2.2] bicycle containing the exomethylene group. Xanthate 2.103 was obtained from 2.91 through a five-step sequence (Scheme 2-19). Treatment of xanthate 2.103 with tributyltin hydride in the presence of catalytic AIBN generated a radical intermediate that cyclized with the alkyne group to provide 2.104 in 85% yield.

Scheme 2-19. Radical cyclization of xanthate 2.103.

Generation of a radical intermediate to access the [2.2.2] bicycle proved to be an effective strategy. Unfortunately, following the cyclization, the MOM and Boc protecting
groups could not be removed because of the unexpected instability of the methylene- [2.2.2] bicycle moiety toward acidic conditions. The synthesis of the xanthate (not shown) from olefin 2.91 was also low yielding. With these challenges in mind, Muratake and Natsume next explored an enyne radical cyclization from enyne 2.105 where the secondary amine was protected with a Cbz group and the MOM group was removed before the cyclization. This final approach would not require the use of a xanthate to generate the radical intermediate and would avoid the acidic conditions required to cleave the protecting groups. Enyne radical cyclization substrate 2.105 was obtained from 2.92 over a four-step sequence (Scheme 2-20). Treatment of enyne 2.105 with tributyltin hydride and catalytic AIBN in refluxing toluene provided the [2.2.2] bicycle bearing the exomethylene (2.106) in 50% yield. With the [2.2.2] bicycle in place, oxygenation at C15 was introduced and the 2-hydroxyethyl protecting group was removed over a six-step sequence to give 2.75 (where PG = Cbz). The Cbz group was removed with triethylsilane in the presence of a catalytic amount of palladium(II) acetate and the resulting amino alcohol was treated with thionyl chloride to form the final C–N bond. Cleavage of the acetyl protecting group provided nominine (2.1) in a total of 40 steps from commercially available starting materials.

Scheme 2-20. Completion of the first total synthesis of nominine.

Muratake and Natsume completed the first total synthesis of nominine using several key steps including a palladium-catalyzed α-arylation to access a 6-6-6 ring system, an acetyl-ene reaction to form the bonds between C14 and C20 and a radical cyclization to access the [2.2.2] bicycle bearing the exomethylene group.
Gin and Peese

The Peese and Gin total synthesis of nominine, first reported in 2006, used a convergent, dual-cycloaddition approach to access the hetisine core. They envisioned accessing the bridged pyrrolidine ring of nominine using a 1,3-dipolar cycloaddition from an aza-dipole and dipolarophile to form bonds between C5-C6 and C10-C20 simultaneously (Scheme 2-21). The [2.2.2] bicycle could then be assembled using a Diels–Alder reaction between an appropriately placed diene and dienophile to form the final two C–C bonds. Because functional group incompatibility would most likely thwart a tandem cycloaddition, the 1,3-dipolar cycloaddition was explored first, and was then followed by the Diels–Alder reaction from a latent diene and dienophile pair.

Scheme 2-21. Peese and Gin’s cycloaddition approach toward nominine.

Peese and Gin first explored the feasibility of using a 1,3-dipolar cycloaddition to access the azabicycle found in the hetisine core. They ultimately decided to use a 3-oxidopyridinium betaine as the aza-dipole because it is significantly more stable than other aza-dipoles such as azomethine ylides but still moderately reactive in cycloadditions. Initial investigations began with a 3-oxidopyridinium betaine tethered to a 2-enenitrile dipolarophile (2.109, Scheme 2-22). Betaine 2.109 was accessed from furan 2.108 through an aza-Achmatowicz reaction in the presence of bromine. However, heating oxidopyridinium 2.109 to affect the dipolar cycloaddition was unsuccessful. Instead, an intramolecular conjugate addition of the oxidopyridinium followed by rearomatization occurred to provide 2.110 in 73% yield.
Scheme 2-22. Initial cycloaddition investigation.

In order to suppress the 1,4-conjugate addition pathway, Gin and Peese envisioned a cycloaddition substrate bearing a removable electron deficient group (Z) at C5 rather than at C10 of the dipolarophile (see Figure 2-8). Conjugate addition would then occur at the C10 position leading to a strained bridged [3.3.1] bicycle. It was anticipated that the high barrier associated with the generation of a strained bicycle would possibly suppress the 1,4-conjugate addition pathway and instead favor the 1,3-dipolar cycloaddition pathway.

Figure 2-8. [3+2] cycloaddition versus conjugate addition pathway.

Cycloaddition precursor 2.112 (bearing a phenyl sulfone at C5) was obtained in racemic form in five steps from 2-cyano-2-methylcyclohexanone (2.11, Scheme 2-23). An enantioselective synthesis of 2.112 was also reported starting from 2-oxocyclohexanecarboxylic acid ethyl ester (2.114). An asymmetric α-methylation of the (S)-t-butylvaline enamine derivative of 2.114 provided cyclohexanone 2.115 (98:2 er). Enantioenriched 2.112 could then be obtained from 2.115 in six additional steps. Heating cycloaddition precursor 2.112 in toluene at reflux provided cycloadduct 2.113 in 70% yield with no trace of a 1,4-conjugate addition product. With the cycloaddition successfully accomplished, the sulfone group could then be removed by reduction of enone 2.113 to olefin 2.116 over two steps followed by desulfurization with sodium/mercury amalgam to provide 2.117.
The 1,3-dipolar cycloaddition strategy proved to be an effective strategy to generate the azabicycle found in the hetisine-type natural products and Gin and Peese ultimately provided the first example of accessing the azabicyclo moiety enantioselectively. From azabicycle 2.117, installation of the diene group could be envisioned through various annulation strategies at C8–C14 but unfortunately, accessing the dienophile at C10 remained a challenge.

Given the challenge of installing the dienophile after the cycloaddition, Gin and Peese next explored the use of an appropriate functional group handle at C10, which would be installed before the cycloaddition. For this purpose, they chose to introduce a nitro group at C10 (2.118, Scheme 2-24). Heating the nitro containing oxidopyridinium betaine in the microwave gave only one regioisomer of cycloadduct 2.119 with no trace of the conjugate addition product. However, the reaction did not proceed past 14% conversion. Furthermore, resubmission of cycloadduct 2.119 to the microwave reaction conditions provided a ~6:1 ratio of betaine 2.118 to cycloadduct 2.119 suggesting that the dipolar cycloaddition reaction is under thermodynamic control.
Scheme 2-24. Nitro-containing cycloaddition substrate.

To address the unfavorable equilibrium observed in the dipolar cycloaddition of 3-oxidopyridinium substrate 2.118 to give pyrrolidine adduct 2.119, Gin and Peese once again decided to redesign the cycloaddition substrate. The use of a 4-oxidoisoquinolinium betaine as the dipole was explored. It was proposed that lowering the energetic cost of breaking aromaticity of the dipole during the cycloaddition would allow for a more thermodynamically favored dipolar cycloaddition. The 4-oxidoisoquinolinium betaine (2.122) was accessed using a Staudinger-aza-Wittig reaction between dipole precursor 2.120 and dipolarophile 2.121 followed by a trifluoroacetic acid-promoted extrusion of methanol (Scheme 2-25).

Scheme 2-25. Synthesis of oxidoisoquinolinium betaine 2.122.

Heating betaine 2.122 in toluene at 90 °C in the microwave for 30 min provided a mixture of three isomeric products: cycloaddition products 2.123 and 2.124 and intramolecular conjugate addition product 2.125, in a 4:2:3 ratio (Scheme 2-26). Unfortunately, longer reaction times lead to exclusive formation of 2.125. Because of the reversibility of the cycloaddition reaction, the reversion of cycloaddition products 2.123 and 2.124 to betaine 2.122 enabled eventual funneling of all the material to the conjugate addition product 2.125, which is the thermodynamic sink of the reaction.
Scheme 2-26. Cyclization results with nitro-containing oxidoisoquinolinium betaine 2.122.

In order to suppress the competing irreversible conjugate addition of 2.122, one last modification of the dipolarophile component was made. The use of a less activated ene-nitrile as the dipolarophile was re-investigated using the 4-oxidoisoquinolinium as the dipole component. Dipolarophile precursor 2.126 was accessed from cyclohexenone in three steps (not shown). The Staudinger-aza-Wittig reaction followed by subsequent extrusion of methanol was used to couple aldehyde 2.126 to azide 2.121 giving access to betaine 2.127 (Scheme 2-27).

Scheme 2-27. Final cycloaddition substrate bearing a cyano group.

Heating cycloaddition precursor 2.127 to 180 °C provided two cycloadducts (2.128 and 2.129) as the only products with the undesired regioisomer (2.129) being the major
product in a ratio of 1:3.6 (desired: undesired). This ratio remained unchanged over extended reaction times and no conjugate addition products were detected. The observations indicate that the cycloaddition reaction was exothermic and the undesired conjugate addition pathway had been completely suppressed. Because the cycloaddition was under thermodynamic control, the undesired diastereomer (2.129) could be isolated and re-equilibrated using the same reaction conditions to give the same ratio of the desired to undesired diastereomer, which allowed for accumulation of ~20% of 2.128 per re-equilibration of 2.129 with little loss of material.

To complete the synthesis of nominine from cycloadduct 2.128, the benzylic ketone group was removed and the cyano group was converted to the vinyl group that would serve as the dienophile in the [4+2] cycloaddition reaction (Scheme 2-28). To access the diene, a reductive dearomatization using standard Birch reduction conditions was performed on the methoxy arene followed by hydrolysis of the resulting methyl enol ether. It was expected that isomerization of the tetrasubstituted double bond of 2.131 into conjugation with the ketone would subsequently lead to formation of the requisite diene. All attempts to isomerize 2.131 to a conjugated enone under both acidic and basic conditions led only to returned starting material or decomposition suggesting that 2.131 is the thermodynamically favored isomer. In an attempt to form the diene using iminium/enamine intermediates, it was found that by treating 2.131 with pyrrolidine in refluxing methanol, the [4+2] cycloaddition product (2.134) could be obtained as the sole product. Although several dienamine species are possible, diene 2.132 is the only one poised for the intramolecular Diels–Alder cycloaddition. Thus, the equilibrating intermediates could be funneled to the irreversible cycloaddition adduct (2.133). Ketone 2.134 could then be obtained from 2.133 following enamine hydrolysis. Finally, Wittig olefination of ketone 2.134 followed by allylic oxidation of the resulting alkene (2.135) with selenium dioxide provided nominine in a total of 15 steps from commercially available materials.

Gin and Peese also completed the first asymmetric synthesis of nominine by setting the stereocenter at C4 of \( \text{2.136} \) using an enantioselective 1,4-conjugate addition of a dialkylzinc reagent into enone \( \text{2.136} \) in the presence copper(I) triflate and chiral N-heterocyclic carbene ligand complex \( \text{2.137} \) (Scheme 2-29). The resulting zinc enolate was then trapped as vinyl triflate \( \text{2.138} \). A two-step sequence from vinyl triflate \( \text{2.138} \) provided enantioenriched dipolarophile \( \text{2.126} \), which was then used to access dipolar cycloaddition product \( \text{2.128} \) in enantioenriched form. Recrystallization of \( \text{2.128} \) further enhanced the enantiopurity to provide material, which was used to complete the first enantioselective synthesis of nominine (2.1).

Scheme 2-29. First enantioselective synthesis of nominine.

Gin and Peese reported a very elegant synthesis of nominine, which stands as the shortest and most efficient approach to these molecules to date. By using a convergent dual cycloaddition strategy, they were able to rapidly and efficiently access the hetisine core and thereby set the standard for future syntheses of the hetisines and related frameworks.

2.6 Conclusion

The hetidine and hetisine-type diterpenoid alkaloids are structurally complex alkaloids that are of interest because of their highly caged structures and interesting biological activities. However, accessing many of these natural products through total synthesis still remains a challenge for synthetic chemists. An analysis of the proposed biosynthesis and the degradation studies performed by Okamoto and coworkers presents several opportunities for inter-conversion between the atisine, hetidine, and hetisine cores and provides inspiration for how these molecules could be accessed through synthetic efforts. The reported approaches toward the hetidines and hetisines and the two completed total syntheses of nominine provide useful insight as to how others have thought about building these caged molecules and have set the stage for further synthetic exploration of these natural products.
2.7 References and Notes


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Chapter Three:
*Synthesis of the Hetidine Core*

3.1 Introduction

The hetidine and hetisine-type diterpenoid alkaloids are highly caged natural products characterized by the presence of both a piperidine ring and a [2.2.2] bicycle. There has been increasing interest in the synthesis of several different types of C\textsubscript{20}-diterpenoid alkaloids, including the hetidines and hetisines, because of their complex structures and interesting biological activity (see Chapter 2). To date, only the hetisine-type diterpenoid alkaloid nominine has been accessed by synthetic efforts. This chapter will present several different approaches toward the hetidine core from a [6-7-6] carbocyclic precursor. A possible chemical conversion from the hetidine core to the hetisine core will be discussed. Our original retrosynthetic analysis, inspired by the work of Gin and Peese in their synthesis of nominine, will be presented and the attempts to form the piperidine ring and the [2.2.2] bicycle of the hetidine core will be discussed. Challenges encountered throughout the synthesis will also be highlighted. Finally, a route providing access to the hetidine core will be presented.

3.2 Retrosynthesis

The hetidine-type C\textsubscript{20}-diterpenoid alkaloids are highly caged alkaloids characterized by the presence of a basic amine within a piperidine ring and a [2.2.2] bicycle. The hetidine skeleton contains three all-carbon quaternary centers and eight stereocenters, seven of which are contiguous. Further analysis of the hetidine skeleton reveals a fused [6-7-6] carbocycle motif hidden in the core (see bonds highlighted in red, 3.1, Scheme 3-1). We proposed that an appropriately functionalized [6-7-6] fused system, such as cycloheptadiene 3.3, could be used as a synthetic precursor to the highly caged hetidine framework. Access to [6-7-6] cycloheptadienes similar to 3.3 have been accessed from indenyl alkynes, such as 3.4, using a gallium(III)-catalyzed cycloisomerization methodology, which was previously developed in the Sarpong group.\textsuperscript{1}

Scheme 3-1. General strategy to access the hetidines and hetisines
The hetisine core (3.2) is structurally related to the hetidine core (3.1), but contains an additional N-C6 bond. Degradation studies performed by Okamoto et al. suggest that the hetisine framework could arise from the hetidine core through a formal dehydrogenative C-N bond forming reaction, such as a Hoffman-Löffler-Freytag (HLF) reaction. Okamoto was able to achieve this transformation from the corresponding N-chloro compound in the presence of silver salts, albeit in low yields. We envisioned using a similar strategy to access the hetisine core from the hetidine core, thus providing access to both the hetidines and the hetisines from a common late-stage intermediate containing a [6-7-6] carbocycle motif.

With the goal of accessing both the hetidine and hetisine cores in mind, we chose 3.5 (Scheme 3-2) as our initial synthetic target. This late stage intermediate resembles the hetidine core and is similar to a late stage intermediate used by Peese and Gin in their synthesis of nominine, a hetisine-type alkaloid. In our case though, we lack the C-N bond between N and C6 (see 3.5 for numbering), which provides an opportunity to access both hetidine, and hetisine natural products from 3.5 provided the N-C6 bond can be forged at a late-stage.

Scheme 3-2. Retrosynthetic analysis of key intermediate 3.5.

Inspired by the very elegant work of Gin and Peese in their synthesis of nominine, we envisioned using a similar end game strategy to construct the [2.2.2] bicycle. This entails a reductive dearomatization of a methoxy arene followed by a [4+2] cycloaddition to form bonds between the carbons indicated in red (see 3.6, Scheme 3-2). The piperidine ring in 3.6 can be accessed from the dehydration of amino alcohol 3.7. Amino alcohol 3.7, in turn, could arise from the functionalization of cycloheptadiene 3.3 where the vinyl group, the benzylic hydroxy group and the amine would be installed in the forward sense. Cycloheptadiene 3.3 can be accessed from indenyl alkyne 3.4 through a gallium(III)-catalyzed cycloisomerization reaction.
3.3 Gallium(III)- Catalyzed Cycloisomerization

The synthesis of the gallium(III)-catalyzed cycloisomerization substrate began with the alkylation of commercially available β-ketoester 3.8 with known alkyl iodide 3.9, which can be accessed from 3-bromo-1-propanol in nine steps to provide β-ketoester 3.10 (Scheme 3-3). Saponification and decarboxylation of 3.10 under basic conditions (LiOH•H$_2$O) provided indanone 3.11 in quantitative yield. A selective reduction of the indanone (3.11) in the presence of the nitrile group with sodium borohydride and elimination of the resulting hydroxyl group under acidic conditions using pyridinium $p$-toluenesulfonate (PPTS) provided indene 3.4 in 71% yield over two steps.


Subjecting indenyl alkyne 3.4 to catalytic GaI$_3$ (25 mol%) in the presence of 4 Å powdered molecular sieves in toluene at 100 °C for 48 h provided cycloheptadiene 3.3 in 89% yield (Scheme 3-4). The higher temperature and longer reaction time were needed compared to previous indenyl alkyne cycloisomerization reactions because of the presence of the cyano group, which may interact with the catalyst and decrease the inherent nucleophilicity of the alkyne group, and the use of a less electron-rich arene compared to previously employed indenyl alkyne substrates. The use of the more active GaI$_3$ catalyst at 25 mol% loading was also necessary in order for the reaction to reach full conversion. Other Lewis acidic catalysts previously used for indenyl alkyne cycloisomerizations were explored, including GaCl$_3$ and InCl$_3$, but these Lewis acids led to incomplete conversion and/or low yields of the desired cycloheptadiene. In order to obtain consistent yields for the cycloisomerization reaction, the indenyl alkyne substrate (3.4) must be dried via azeotrope with benzene or toluene and the reaction must be run under rigorously dry conditions. It is proposed that the presence of trace water in the reaction lead to the formation of inactive gallium(III) hydroxide and HI, which decomposes the material at higher temperatures.
Selective reduction of the disubstituted double bond of cycloheptadiene 3.3 with diimide provided 3.12 in 82% yield. Next, oxidation of the benzylic-allylic position of 3.12 with ceric ammonium nitrate (CAN) absorbed onto silica provided enone 3.13 in modest yield. After extensive optimization, 52% yield on a 200 mg (0.75 mmol) scale (entry 9) was the best yield that could be obtained for this step. A summary of the various conditions screened for this oxygenation is presented in Table 3-1. Oxidation with CAN provided the highest yield on small scale (0.04 mmol, entry 8) but upon scaling the reaction, the yield dropped significantly. With the use of CAN supported on silica, the drop in yield upon scaling was not as drastic and the oxidation could be scaled to 0.75 mmol (entry 9) without much decrease in yield.
Table 3-1. Oxidation of 3.12 to enone 3.13 optimization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Solvent</th>
<th>Scale</th>
<th>Temp (°C)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CrO$_2$</td>
<td>DCM</td>
<td>0.02 mmol</td>
<td>50</td>
<td>no rxn</td>
</tr>
<tr>
<td>2</td>
<td>CrO$_3$, Ac$_2$O, AcOH</td>
<td>Benzene</td>
<td>0.02 mmol</td>
<td>0</td>
<td>22%</td>
</tr>
<tr>
<td>3</td>
<td>DDQ</td>
<td>20:1 THF/H$_2$O</td>
<td>0.08 mmol</td>
<td>rt</td>
<td>8%</td>
</tr>
<tr>
<td>4</td>
<td>Ba(MnO$_4$)$_2$</td>
<td>DCM</td>
<td>0.02 mmol</td>
<td>50</td>
<td>no rxn</td>
</tr>
<tr>
<td>5</td>
<td>KMnO$_4$</td>
<td>1,2 DCE</td>
<td>0.02 mmol</td>
<td>0</td>
<td>decomp</td>
</tr>
<tr>
<td>6</td>
<td>CAN</td>
<td>4:1 MeCN/H$_2$O</td>
<td>0.04 mmol</td>
<td>0 to rt</td>
<td>47%</td>
</tr>
<tr>
<td>7</td>
<td>CAN</td>
<td>4:1 MeCN/H$_2$O</td>
<td>0.75 mmol</td>
<td>0</td>
<td>21%</td>
</tr>
<tr>
<td>8</td>
<td>CAN on SiO$_2$</td>
<td>4:1 CH$_2$Cl$_2$/H$_2$O</td>
<td>0.04 mmol</td>
<td>0</td>
<td>56%</td>
</tr>
<tr>
<td>9</td>
<td>CAN on SiO$_2$</td>
<td>4:1 CH$_2$Cl$_2$/H$_2$O</td>
<td>0.75 mmol</td>
<td>0</td>
<td>52%</td>
</tr>
<tr>
<td>10</td>
<td>CAN on SiO$_2$</td>
<td>4:1 CH$_2$Cl$_2$/H$_2$O</td>
<td>1.9 mmol</td>
<td>0</td>
<td>44%</td>
</tr>
</tbody>
</table>

The double bond of enone 3.13 could be reduced in the presence of hydrogen and palladium on carbon to give a single diastereomer of ketone 3.14 (Scheme 3-5). X-ray analysis confirmed that the desired diastereomer of ketone 3.14 was obtained as the sole product.


We propose that the diastereoselectivity observed in the hydrogenation of enone 3.13 is a result of the difference in A-values between the methyl group (1.7 kcal/mol) and the cyano group (0.17 kcal/mol) around the cyclohexane ring thus placing the cyano group in the axial position.$^6$ With the cyano group in the axial position, the opposite face
is less sterically hindered allowing for hydrogenation to occur on the same side of the methyl group. An electronic argument could also be proposed to explain the observed diastereoselectivity. When the cyano group is in the more favored axial position, the electron-deficient π orbitals of the cyano group could favorably interact with the π* orbitals of the enone double bond deactivating the bottom face of the enone. Thus, when the cyano group is in the axial position, the olefin is more electron-depleted allowing the enone to be more susceptible to reduction on the same side as the methyl substituent.7

3.4 Installation of the Vinyl Group

With ketone 3.14 in hand, the next key transformation was to install the vinyl group needed for the [4+2] cycloaddition. Deprotonation at the α-position of ketone 3.14 with sodium hydride followed by quenching of the enolate with phenyl vinyl sulfoxide to gave sulfoxide 3.15 in 87% yield (Scheme 3-6). Heating sulfoxide 3.15 to 160 °C in the microwave promoted a sulfoxide extrusion and provided exclusively the desired diastereomer of 3.16 as confirmed by X-ray analysis.

![Scheme 3-6. Installation of the vinyl group from ketone 3.14.](image)

Global reduction of the ketone and the cyano group of 3.16 with lithium aluminum hydride followed by immediate protection of the primary amine provided Boc-protected amino alcohol 3.7 (where R = Boc) as a mixture of diastereomers (Scheme 3-7). We envisioned that treatment of 3.7 with an activating agent to promote ionization of the hydroxyl group at the benzylic position would allow for cyclization to form the piperidine ring. We further proposed that ionization of the hydroxyl group could be assisted by the methoxy substituent on the arene to form an extended oxocarbenium ion, thus making the mixture of diastereomers of the hydroxyl group inconsequential. Unfortunately, treatment of amino alcohol 3.7 (where R = Boc) with a variety of activating agents, including thionyl chloride and oxalyl chloride, only led to a complex mixture of products in which the vinyl group appears to also engaged the extended oxocarbenium ion.
Scheme 3-7. Attempted C-N bond formation from 3.16.

Other routes to access an amino alcohol related to 3.7 as a single diastereomer from ketone 3.16 were also explored. Selective reduction of the ketone group in the presence of the cyano group with sodium borohydride only returned starting material and the stronger reducing agent Red-Al™ provided a 0.9:1 mixture of diastereomers of alcohol 3.18 (Scheme 3-8). Alternatively, reduction of 3.16 with DIBAL-H provided only one diastereomer of the hydroxyl group and also reduced the cyano group to an aldehyde to provide 3.19.8

Scheme 3-8. Reduction of 3.16.

Attempts to install a primary amine from aldehyde 3.19 provided an inseparable mixture of 3.7 (where R = H) along with a secondary amine resulting from the reductive amination between aldehyde 3.19 and the newly formed primary amine (Scheme 3-9). Installation of a secondary amine from aldehyde 3.19 was successful using a reductive...
amination with p-methoxybenzyl amine to provide 3.7 (where R = PMB) in excellent yield. Unfortunately, activation of the benzylic alcohol of 3.7 led to the same complex mixture of products observed previously in which the vinyl group appears to have engaged the extended oxocarbenium ion. An intramolecular displacement of the hydroxyl group (following its activation) by the p-methoxybenzyl-protected amine also led to a mixture of products.


### 3.5 Installation of the Allyl Group and C-N Bond Formation

Unable to form the C-N bond from compounds with the vinyl group already in place (e.g., 3.7 where R = Boc or PMB), we next envisioned installation of an allyl group that could later be converted to a vinyl group following C-N bond formation to forge the piperidine ring. Deprotonation of ketone 3.14 with sodium hydride in the presence of allyl bromide provided a mixture of O-allylated and C-allylated products (Scheme 3-10). The mixture of products converged to the C-allylated product (3.20) upon heating in the microwave (160 °C) through a Claisen rearrangement. Global reduction of the ketone and cyano group of 3.20 with lithium aluminum hydride followed by immediate Boc-protection of the resulting primary amine provided 3.21 as a single diastereomer. Treatment of carbamate alcohol 3.21 with thionyl chloride effected a cyclization to form the piperidine ring (3.22).
Scheme 3-10. Installation of an allyl group and C-N bond formation.

The stereochemistry of 3.22 was unambiguously confirmed through X-ray analysis of the \( p \)-nitrobenzamide derivative (3.25). Deprotection of Boc-protected amine 3.22 with trifluoroacetic acid followed by treatment of the resulting secondary amine with \( p \)-nitrobenzoylchloride (3.24) provided 3.25.

Scheme 3-11. Confirming stereochemistry of 3.25.

With the piperidine ring in place, formation of the N-C6 bond found in the hetisines through a Hoffman-Löffler-Freytag (HLF) type reaction\(^\text{11}\) was explored (Scheme 3-12).
Treatment of amine 3.23 with N-chlorosuccinimide provided N-chloramine 3.26 in 83% yield. Exposure of 3.26 to strong acids typically used for the HLF reaction (H₂SO₄, HCl, AcOH or TFA) led to immediate decomposition even in the absence of light or heat. Acid-free HLF conditions¹² (Et₂O, Hg lamp) provided disproportion product 3.28 suggesting that an N-centered radical was formed but was not in close enough proximity to C6 to abstract a hydrogen atom from the C6 position. Alternatively, 3.28 may have arisen from the loss of HCl from 3.26 through a polar mechanism. Although formation of the N-C6 bond was not possible from N-chloramine 3.26 using an HLF reaction, this transformation may still be possible late-stage after installation of the [2.2.2] bicycle given the precedent of Okamoto and coworkers.¹³

![Scheme 3-12. Attempted N-C6 bond formation from N-chloramine 3.26.](image)

### 3.6 Conversion of the Allyl Group to the Vinyl Group

After formation of the piperidine ring, several strategies were used in an attempt to convert the allyl group of 3.22 to a vinyl group. A dihydroxylation followed by a periodate cleavage provided aldehyde 3.29 in 88% yield (Scheme 3-13). From aldehyde 3.29, a Bamford-Stevens reaction was attempted. Condensation of aldehyde 3.29 with tosyl hydrazine provided hydrazone 3.30 in 95% yield. Deprotonation of 3.30 with sodium hydride presumably generated a diazo intermediate that decomposed to give a short-lived carbene. Instead of getting the desired 1,2 hydride shift however, only C-H insertion products, such as 3.31, were detected by mass spectroscopic analysis. The use of a polar solvent with sodium hydride to form a carbenium ion instead of the carbene and as well as the use of a lithium base (Shapiro reaction) were also attempted but only led to the return of starting material.
Scheme 3-13. Attempted Bamford-Stevens reaction.

Alternatively, reduction of aldehyde 3.29 to primary alcohol 3.32 (Scheme 3-14) provided several more opportunities for installation of the vinyl group through a formal dehydration. Unfortunately, a one-step dehydration of alcohol 3.32 with strong dehydrating agents such as Martin sulfurane and Burgess reagent only returned starting material.

Scheme 3-14. Reduction of aldehyde 3.29.

Several other elimination reactions such as the Chugaev elimination and the Greico elimination from alcohol 3.32 were also attempted. Xanthate 3.33 could be accessed from alcohol 3.32 using standard conditions (NaH, CS₂, MeI) (Scheme 3-15). Unfortunately, heating xanthate 3.33 in the microwave (up to 200 °C) to effect the Chugaev elimination only returned starting material. The Greico elimination was also unsuccessful as attempts to form o-nitrophenyl selenide 3.34 from alcohol 3.32 using Mitsunobu-type conditions only returned starting material.
Scheme 3-15. Attempted Chugaev and Greico eliminations.

Ultimately, a sulfoxide extrusion was successful in generating the vinyl group from alcohol 3.32 (Scheme 3-16). Phenyl sulfoxide 3.35 was accessed from 3.32 over a two-step sequence involving a Mitsunobu-type displacement with diphenyl disulfide and tributylphosphine followed by oxidation of the resulting sulfide (not shown) with hydrogen peroxide and catalytic scandium(III) triflate. Heating 3.35 in the microwave to 180 °C effected a sulfoxide extrusion to provide vinyl compound 3.6 (where R = Boc) in 80% yield.

Scheme 3-16. Sulfoxide extrusion reaction to install the vinyl group.

3.7 Reductive Dearomatization

With vinyl compound 3.6 (where R = Boc) in hand, an endgame strategy similar to that employed by Gin and Peese, which involves a Birch reduction followed by a [4+2] cycloaddition, could be used to form the [2.2.2] bicycle. Subjecting methoxy arene 3.36 to Birch reduction conditions (Scheme 3-17) provided 1,4-cyclohexadiene 3.36 based on crude NMR analysis. However, hydrolysis of the methyl enol ether using the Gin procedure (3 N HCl) led to an inseparable mixture of conjugated (not shown) and unconjugated (3.37) enones. Gin and Peese never observed isomerization to the conjugated enone under hydrolysis conditions and were unable to isomerize the double bond into conjugation with the ketone using a variety of both acidic and basic conditions.
By switching to citric acid, the unconjugated enone (3.37) could be obtained as the sole product based on crude NMR but decomposed upon further attempts at purification. Subjection of crude 3.37 to pyrrolidine in methanol to promote the [4+2] cycloaddition through the intermediacy of aminodiene 3.38 also led to immediate decomposition.

Scheme 3-17. Birch reduction of Boc-protected methoxy arene 3.6.

The Birch reduction followed by methyl enol ether hydrolysis and pyrrolidine promoted [4+2] cycloaddition sequence was attempted on the free amine (3.6 where R = H, Scheme 3-18). The Boc protecting group could be removed prior to the Birch reduction by treating 3.6 (where R = Boc) with trifluoroacetic acid. The free amine was then subjected to dissolving metal reduction conditions to yield 3.39 (based on crude NMR analysis). Stirring 3.39 with oxalic acid supported on silica provided exclusively 3.40 in low yields. Once again, subjecting non-conjugated enone 3.40 to pyrrolidine led to immediate decomposition. Alternately, secondary amine 3.39 could also be benzyl protected and then treated with KHSO₄ to provided one diastereomer of conjugated enone 3.41 in low yield. Treatment of conjugated enone 3.41 with pyrrolidine also led to immediate decomposition.
Scheme 3-18. Birch reduction of methoxy arene 3.6 (where R = H).

Unable to achieve the desired [4+2] cycloaddition through the intermediacy of enamine 3.38 (Scheme 3-19) as Gin had done in his synthesis of nominine, a new approach to the [2.2.2] bicycle was developed. The same bonds could be formed through a Michael addition followed by an aldol reaction from an enone-aldehyde such as 3.42. This approach would also install a hydroxyl group at C11 (see 3.43 for numbering), which is found in several natural products, such as kobusine.

Scheme 3-19. Approaches toward the [2.2.2] bicycle of the hetidine skeleton.
A Birch reduction of allyl containing methoxy arene \textbf{3.22} followed by hydrolysis of the resulting methyl enol ether (\textbf{3.44}) with 3 N HCl provided a single diastereomer of enone \textbf{3.45} in low yields (Scheme 3-20). Subjection of crude \textbf{3.45} to a two-step dihydroxylation and periodate cleavage sequence provided enone-aldehyde \textbf{3.42} (where \(R = \text{Boc}\)) in 60% yield. Unfortunately, attempts to promote a tandem Michael addition-aldol reaction of \textbf{3.42} with pyrrolidine led to immediate decomposition.

\begin{align*}
\text{Na, IPA} & \quad \text{NH}_3, \text{THF, -78 °C} \\
\text{then 1 N HCl} & \quad 3 \text{N HCl} \\
\text{15-30\% (2 steps)} & \quad \text{decomp}
\end{align*}

\textbf{Scheme 3-20}. Birch reduction of allyl containing compound \textbf{3.22}.

Several challenges were encountered with the reductive dearomatization approach toward the [2.2.2] bicycle of the hetidine core. The first was that the yields of the Birch reduction and hydrolysis sequence were low and irreproducible and the resulting enones quickly decomposed upon purification. Second, in the absence of the N-C6 bond, isomerization to the conjugated enone could also be leading to the wrong diastereomer with respect to the stereocenter at C14 (see \textbf{3.42}, Scheme 3-20) preventing the [4+2] cycloaddition or the tandem Michael addition-aldol reaction from occurring. With these challenges in mind, another approach toward the [2.2.2] bicycle involving an oxidative dearomatization instead of a reductive dearomatization was explored.

\textbf{3.8 Oxidative Dearomatization and Completion of the Hetidine Core}

Oxidative dearomatization of methoxy arene \textbf{3.6} or \textbf{3.22} (see Schemes 3-16 and 3-10 respectively) could provide access to enones containing oxygenation at C14 (see \textbf{3.46}, Scheme 3-21). A [4+2] cycloaddition (from \textbf{3.6}) or a tandem Michael addition-aldol reaction (from \textbf{3.22}) could then be envisioned to access the [2.2.2] bicycle. Controlling the diastereoselectivity at C14 still remained a challenge, but the caged nature of the oxidative dearomatization precursor may allow for some substrate control for the nucleophilic addition of water. Alternatively, a nucleophile may be tethered to the nitrogen atom allowing for an intramolecular nucleophilic addition at C14.

Demethylation of 3.6 (where R = Boc) with ethanethiolate at elevated temperatures (microwave, 180 °C) provided phenol 3.47 in 85% yield (Scheme 3-22). Subjecting phenol 3.47 to oxidative dearomatization conditions with PIDA ((diacetoxyiodo)benzene) in 1:1 water/MeCN provided cyclic carbamate 3.49 as the sole product in 15% yield. Oxazolidinone 3.49 likely forms through nucleophilic addition of the Boc-carbamate through the presumed intermediacy of 3.48, which correctly set the stereocenter at C14. Switching the oxidant to PIFA ([bis(trifluoroacetoxy)iodo]benzene), buffering the reaction with NaHCO₃, and using trifluoroethanol in place of water as the co-solvent provided 3.49 in 82% yield from phenol 3.47. To the best of our knowledge, this is the first example of a Boc carbamate participating as a nucleophile in an oxidative dearomatization reaction. With quinol 3.49 in hand, a selective reduction of the disubstituted bond was attempted with Stryker’s reagent ((triphenylphosphine)copper hydride hexamer), but only a mixture of over-reduction products was obtained.

Scheme 3-22. Oxidative dearomatization of vinyl containing phenol 3.47.

Our most successful approach toward the hetidine core involved a Michael addition followed by an aldol reaction to form the [2.2.2] bicycle starting with allyl containing compound 3.22 (Scheme 3-23). Demethylation of methoxy arene 3.22 followed by oxidative dearomatization of the resulting phenol (3.50) using the previously optimized reaction conditions with PIFA provided oxazolidinone 3.51 in 54% yield. Two equivalents of iodosobenzene can also be used in place of one equivalent of PIFA in the oxidative dearomatization reaction to provide the product in similar yields.
Scheme 3-23. Oxidative dearomatization of phenol 3.50 and completion of hetidine core.

From quinol 3.51, a dihydroxylation and periodate cleavage sequence provided aldehyde 3.52. Stirring 3.52 in silica gel promoted a Michael addition to give 3.53 where the first C-C bond of the [2.2.2] bicycle is formed. Finally, selective reduction of enone 3.53 to ketone 3.54 with hydrogen and rhodium on alumina followed by an aldol reaction provided the hetidine core (3.55).

3.9 Conclusion

The hetidine core (3.55) was accessed in 20-steps from known starting materials. The key steps in the synthesis of the hetidine core include a gallium(III)-catalyzed cycloisomerization to access a [6-7-6] carbocycle, an oxidative dearomatization, and finally a Michael addition and an aldol reaction to complete the [2.2.2] bicycle. Elaboration of the hetidine core will be discussed in the next chapter.
3.10 Experimental Contributors

Dr. Felipe de Jesus Cortez made significant contributions to the synthesis of alkyl iodide 3.9 and the synthesis of cycloheptadiene 3.3. Dr. David Lapointe developed an enantioselective route to alkyl iodide 3.9, optimized the scale up of the synthesis, and assisted in bringing up material. Kyle Owens and Christopher Marth also assisted in scaling up reactions. Amy M. Hamlin performed all initial investigations starting from cycloheptadiene 3.3.

3.11 Experimental Methods

General Methods and Procedures

**General.** All reagents were obtained from commercial chemical suppliers and used without further purification unless otherwise noted. All reactions were performed in round-bottomed flasks or microwave vials sealed with rubber septa, under an atmosphere of nitrogen, and stirred with a Teflon™-coated magnetic stir bar unless otherwise noted. Temperatures above 23 °C were controlled by an IKA® temperature modulator. Microwave reactions were performed in a Biotage® Initiator Microwave Reactor. Pre-dried tetrahydrofuran (THF), benzene, toluene, acetonitrile (MeCN), methanol (MeOH), and triethylamine (Et₃N), were degassed with argon for 60 min and passed through activated alumina columns. Dichloromethane (CH₂Cl₂) was distilled over calcium hydride before use. Reactions were monitored by thin layer chromatography (TLC) using Silicycle Siliaplate™ glass backed TLC plates (250 μm thickness, 60 Å porosity, F- 254 indicator) and visualized using UV (254 nm) and p-anisaldehyde stain or KMnO₄ stain. Volatile solvents were removed using a rotary evaporator under reduced pressure. Silica gel chromatography was performed using Sorbent Technologies 60 Å, 230 x 400 mesh silica gel (40-63 μm). ¹H NMR and ¹³C NMR were obtained in CDCl₃ on Bruker 400, 500, or 600 MHz spectrometers with ¹³C operating frequencies of 100, 126, or 151 MHz, respectively. Chemical shifts are reported in parts per million (δ) relative to residual chloroform (7.26 ppm for ¹H and 77.16 ppm for ¹³C). Data for ¹H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens). Multiplicity is designated as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), or m (multiplet). IR spectra were obtained using a Nicolet MAGNA-IR 850 spectrometer as thin films on NaCl plates and reported in frequency of absorption (cm⁻¹). High-resolution mass spectral (HRMS) data was obtained from the Mass Spectral facility at the University of California, Berkeley.

**Synthetic Procedure and Physical Characterization Data.**
(3-Bromopropoxy)triisopropylsilane (3.ii): To a solution of 3-bromo-1-propanol (3.i, 20.0 mL, 230 mmol, 1 equiv) in CH₂Cl₂ (575 mL, 0.4 M) was added imidazole (39.0 g, 575 mmol, 2.5 equiv) and triisopropylsilyl chloride (59 mL, 280 mmol, 1.2 equiv). The cloudy reaction mixture was stirred at room temperature for 12 h. The solution was poured into water (500 mL) and extracted with CH₂Cl₂ (2 × 500 mL). The combined organic layers were washed with brine (300 mL), dried over MgSO₄, and concentrated to give 68 g (230 mmol, 100% yield) of 3.ii as a clear oil that was used without further purification. Rf 0.84 (2:1 hexanes: EtOAc, KMnO₄); ¹H NMR (600 MHz, CDCl₃) δ 3.82 (t, J = 5.7 Hz, 2H), 3.56 (t, J = 6.5 Hz, 2H), 2.06 (p, J = 6.2 Hz, 2H), 1.08 – 1.03 (m, 21H); ¹³C NMR (151 MHz, CDCl₃) δ 60.8, 36.0, 30.8, 18.1, 12.1; the spectroscopic data were consistent with reported literature values.¹⁵

Methyl 2-cyano-5-(triisopropylsilyloxy)pentanoate (3.iii): To a solution of 3.ii (68 g, 230 mmol, 1 equiv) in DMF (460 mL, 0.5 M) was added K₂CO₃ (95 g, 690 mmol, 3 equiv) and methyl cyanoacetate (40 mL, 350 mmol, 1.5 equiv) at room temperature. The flask was fitted with a reflux condenser, and heated to 65 °C for 1 h. After cooling to room temperature, the mixture was diluted with water (500 mL) and extracted with Et₂O (3 × 100 mL). The combined organic layers were washed with brine (1.5 L), dried over MgSO₄, and concentrated. Flash chromatography (9:1 hexanes: EtOAc) provided 65 g (210 mmol, 91% yield) of 3.iii as a clear oil. Rf 0.68 (2:1 hexanes: EtOAc, KMnO₄); ¹H NMR (500 MHz, CDCl₃) δ 3.82 (s, 3H), 3.76 (td, J = 5.9, 3.3 Hz, 2H), 3.67 (dd, J = 8.4, 5.8 Hz, 1H), 2.18 – 2.00 (m, 2H), 1.78 – 1.68 (m, 2H), 1.11 – 1.01 (m, 21H); ¹³C NMR (126 MHz, CDCl₃) δ 166.8, 116.6, 62.3, 37.3, 29.8, 18.1, 17.8, 12.4, 12.0; IR (NaCl, thin film) νmax 2943, 2867, 1754, 1463, 1250, 1110, 1013 cm⁻¹; HRMS (ESI) calc’d for C₁₆H₃₂NO₃Si ([M+H]⁺): m/z 314.2146, found 314.2143.

Methyl 2-cyano-2-methyl-5-((triisopropylsilyl)oxy)pentanoate (3.iv): To a solution of 3.iii (65 g, 210 mmol, 1 equiv) in DMF (400 mL, 0.5 M) was added NaH (60 wt% in mineral oil, 9.9 g, 250 mmol, 1.2 equiv) portion-wise, followed by methyl iodide (26 mL, 420 mmol, 2 equiv) at room temperature. The reaction mixture was stirred for 1 h, after which the reaction was quenched with water (500 mL) then extracted with Et₂O
The combined organic layers were washed with water (500 mL) and brine (300 mL), dried over MgSO₄, and concentrated to give 69 g (210 mmol, 100% yield) of 3.iv as a clear oil, which was used without further purification. Rₚ 0.54 (4:1 hexanes: EtOAc, KMnO₄); ¹H NMR (500 MHz, CDCl₃) δ 3.81 (s, 3H), 3.71 (t, J = 5.9 Hz, 2H), 2.08 – 2.00 (m, 1H), 1.93 – 1.85 (m, 1H), 1.75 (td, J = 6.5, 1.7 Hz, 1H), 1.60 (s, 3H), 1.62 – 1.54 (m, 1H), 1.11 – 1.04 (m, 21H); ¹³C NMR (126 MHz, CDCl₃) δ 170.1, 120.1, 62.4, 53.6, 43.8, 35.2, 29.0, 23.5, 18.1, 12.0. IR (NaCl, thin film) νmax 2943, 2866, 1750, 1462, 1383, 1252, 1105 cm⁻¹; HRMS (ESI) calc’d for C₁₇H₃₃NO₃SiNa ([M+Na]+): m/z 350.2122, found 350.2121.

2-(Hydroxymethyl)-2-methyl-5-(triisopropylsiloxy)pentanenitrile (3.v): To a solution of the ester 3.iv (69 g, 210 mmol, equiv) in 14:1 THF/water (690 mL, 0.3 M) was added NaBH₄ (39 g, 1.0 mol, 5 equiv) at room temperature. After stirring for 3 h, the reaction mixture was extracted with Et₂O (3 × 500 mL) and the combined organic layers were washed with saturated aq. NaHCO₃ (1 × 300 mL), and brine (1 × 300 mL), dried over MgSO₄, and concentrated to give 62 g (210 mmol, 100% yield) of 3.v as a clear oil which was used immediately without further purification. Rₚ 0.47 (2:1 hexanes: EtOAc, KMnO₄); ¹H NMR (500 MHz, CDCl₃) δ 3.74 (t, J = 5.8 Hz, 2H), 3.70 – 3.58 (m, 2H), 2.02 (t, J = 6.7 Hz, 1H), 1.86 – 1.69 (m, 1H), 1.64 – 1.56 (m, 3H), 1.35 (s, 3H), 1.16 – 1.01 (m, 21H); ¹³C NMR (151 MHz, CDCl₃) δ 123.3, 68.2, 63.0, 39.6, 32.2, 28.2, 21.2, 18.2, 12.1; IR (NaCl, thin film) νmax 3454, 2943, 2866, 1463, 1383, 1106, 1069 cm⁻¹; HRMS (ESI) calc’d for C₁₃H₂₆NO₂Si ([M-C₃H₇]+): m/z 256.1733, found 256.1737.

2-Ethynyl-2-methyl-5-(triisopropylsiloxy)pentanenitrile (3.vi): To a solution of anhydrous DMSO (31 mL, 440 mmol, 4 equiv) in CH₂Cl₂ (500 mL, 0.2 M) was added oxalyl chloride (18 mL, 220 mmol, 2 equiv) under N₂ at -78 °C. After stirring for 2 h, a solution of alcohol 3.v (33 g, 110 mmol, 1 equiv) in CH₂Cl₂ (100 mL, 1.1 M) was added at -78 °C via cannula. After an additional 4 h at -78 °C, Et₃N (120 mL, 870 mmol, 8
equiv) was added at -78 °C. The resulting mixture was allowed to warm to room
temperature and stirred for 12 h and then poured into a mixture of saturated aq. NH₄Cl
(300 mL) and water (300 mL). The layers were separated and the aqueous layer was
extracted with CH₂Cl₂ (3 × 500 mL). The combined organic layers were washed with
brine (1 × 300 mL), dried over MgSO₄, and concentrated to give the aldehyde as a
yellow oil, which was taken on immediately without further purification. Rf 0.50 (2:1
hexanes: EtOAc, KMnO₄).

To a solution of the crude aldehyde (32 g, 110 mmol, 1 equiv) in MeOH (600 mL,
0.18 M) was added K₂CO₃ (30 g, 220 mmol, 2 equiv) and Ohira-Bestmann reagent (23
g, 120 mmol, 1.1 equiv) at 0 °C. After stirring for 2 h, the reaction mixture was poured
into a mixture of saturated aq. NaHCO₃ (150 mL) and water (150 mL), and extracted
with Et₂O (3 × 500 mL). The combined organic layers were washed with brine (1 × 300
mL), dried over MgSO₄, and concentrated. Flash chromatography (9:1 hexanes: EtOAc)
gave 27 g (93 mmol, 85% yield over two steps) of alkyne 3.vi as a light yellow oil. Rf
0.67 (2:1 hexanes: EtOAc, KMnO₄); ¹H NMR (500 MHz, CDCl₃) δ 3.76 (t, J = 5.6 Hz,
2H), 2.38 (s, 1H), 2.01 – 1.76 (m, 4H), 1.66 (s, 3H), 1.13 – 0.99 (m, 21H); ¹³C NMR
(126 MHz, CDCl₃) δ 120.5, 81.1, 72.1, 62.5, 37.9, 31.2, 29.2, 27.3, 18.1, 12.1; IR (NaCl,
thin film) νmax 3312, 2943, 2866, 1463, 1382, 1367, 1240, 1107, 1070, 1014 cm⁻¹; HRMS
(ESI) calc’d for C₁₇H₃₁NOSi ([M+H]⁺): m/z 294.2248, found 294.2259.

2-Ethynyl-5-hydroxy-2-methylpentanenitrile (3.vii): To a solution of TIPS
protected alcohol 3.vi (27 g, 93 mmol, 1 equiv) in THF (370 mL, 0.25 M) was added tert-
butylammonium fluoride (1.0 M in THF, 110 mL, 110 mmol, 1.2 equiv) at room
temperature. After stirring for 12 h, the reaction mixture was poured into saturated aq.
NaHCO₃ (300 mL) and extracted with Et₂O (3 × 300 mL), the combined organic layers
were washed with brine (1 × 200 mL), dried over MgSO₄, and concentrated. Flash
chromatography (2:1 hexanes: EtOAc) gave 9.8 g (71 mmol, 76% yield) of the alcohol
3.vii as a clear oil. Rf 0.13 (2:1 hexanes: EtOAc, KMnO₄); ¹H NMR (600 MHz, CDCl₃) δ
3.65 (t, J = 5.4 Hz, 2H), 2.54 (s, 1H), 2.40 (s, 1H), 1.93 – 1.72 (m, 4H), 1.62 (s, 3H); ¹³C
NMR (151 MHz, CDCl₃) δ 120.4, 80.7, 72.4, 61.5, 37.5, 31.1, 28.7, 27.1; IR (NaCl, thin
film) νmax 3296, 2992, 2941, 2878, 2243, 1453, 1382, 1302, 1253, 1222, 1059 cm⁻¹;
HRMS (EI⁺) calc’d for C₈H₁₁NO ([M⁺]: m/z 137.0841, found 137.0845.
2-Ethynyl-5-iodo-2-methylpentanenitrile (3.9): To a solution of alcohol 3.vii (9.8 g, 71 mmol, 1 equiv) in CH$_2$Cl$_2$ (280 mL, 0.25 M) at 0 ºC was added methanesulfonyl chloride (6.0 mL, 78 mmol, 1.1 equiv) and Et$_3$N (15 mL, 110 mmol, 1.5 equiv). The resulting mixture was allowed to warm to room temperature. After stirring for 2 h, the reaction mixture was washed with 1 N HCl (150 mL), saturated aq. NaHCO$_3$ (150 mL), and brine (150 mL), dried over MgSO$_4$, and concentrated to give the mesylate as a light yellow oil that was immediately used without further purification. R$_f$ 0.63 (EtOAc, KMnO$_4$); $^1$H NMR (600 MHz, CDCl$_3$) δ 4.33 – 4.25 (m, 2H), 3.02 (s, 3H), 2.44 (s, 1H), 2.16 – 2.00 (m, 2H), 1.97 – 1.91 (m, 1H), 1.91 – 1.84 (m, 1H) 1.67 (s, 3H).

The resulting mesylate (15 g, 71 mmol) was added to a Schlenk flask with acetone (280 mL, 0.25 M). NaI (16.0 g, 107 mmol) was added and the flask was sealed and placed in an oil bath preheated to 65 ºC. After stirring at 65 ºC for 15 h, the mixture was allowed to cool to room temperature and quenched with water (280 mL). The reaction mixture was extracted with pentane (3 × 300 mL) and the combined organic layers were washed with brine (200 mL), dried over MgSO$_4$, and concentrated to give 14 g (57 mmol, 80% yield over 2 steps) of 3.9 as a light yellow oil that was used without further purification. R$_f$ 0.62 (2:1 hexanes: EtOAc, KMnO$_4$); $^1$H NMR (500 MHz, CDCl$_3$) δ 3.30 – 3.18 (m, 2H), 2.42 (s, 1H), 2.24 – 2.08 (m, 2H), 1.97 – 1.83 (m, 2H), 1.68 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 120.0, 80.5, 72.7, 41.8, 30.6, 29.4, 27.3, 4.7; IR (NaCl, thin film) $\nu_{max}$ 3290, 2939, 1451, 1382, 1294, 1253, 1185, 1148 cm$^{-1}$; HRMS (EI) calc’d for C$_8$H$_{18}$NI ([M]$^+$): m/z 246.9858, found 246.9858.

(E)-3-(4-Methoxyphenyl)acrylic acid (3.ix). p-Anisaldehyde (3.vii, 30 mL, 250 mmol, 1 equiv) was added to a solution of malonic acid (51 g, 490 mmol, 2 equiv) in pyridine (250 mL, 1.0 M) and the heterogeneous mixture was stirred and heated to 50 ºC until malonic acid completely dissolved (~20 min). Piperidine (4.1 mL, 42 mmol, 0.17 equiv) was added and the solution was then slowly heated to 80 ºC over the next hour at a rate of 5 ºC every 10 min. The reaction mixture was stirred at 80 ºC for 2 h at which time the temperature was further increased to 110 ºC for an additional 2 h. The reaction mixture was cooled to room temperature and acidified with 4.8 M HCl (200 mL). The white precipitate was isolated by vacuum filtration, washed with 1 N HCl (50 mL) and water (50 mL), and dried under vacuum to give 40 g (220 mmol, 88% yield) of 3.ix as a white solid. R$_f$ 0.27 (2:1 hexanes: EtOAc, UV); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.74 (d, J = 15.9 Hz, 1H), 7.51 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.32 (d, J = 15.9 Hz, 1H), 3.85 (s, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 172.3, 161.9, 146.9, 130.3, 127.0, 114.8, 114.6, 55.6; The spectroscopic data were consistent with reported literature values. 16
3-(4-Methoxyphenyl)propanoic acid (3.x). Palladium on carbon (10%, 1.0 g, 2.5 wt% relative to 3.ix) was added to a suspension of cinnamic acid 3.ix (40 g, 220 mmol) in EtOAc (450 mL, 0.5 M). The flask was evacuated and backfilled with H₂ (3x) and stirred under a balloon of H₂ for 24 h. The light grey solution turned black as the reaction progressed and the acid became soluble upon hydrogenation. The reaction mixture was filtered through a pad of Celite™, washed with EtOAc (100 mL), and concentrated to give 40 g (220 mmol, 100% yield) of acid 3.x as a white solid. \( R_f \) 0.27 (2:1 hexanes: EtOAc, UV) \(^1\)H NMR (600 MHz, CDCl₃) \( \delta \) 7.13 (d, \( J = 8.6 \) Hz, 2H), 6.84 (d, \( J = 8.6 \) Hz, 2H), 3.79 (s, 3H), 2.91 (t, \( J = 7.8 \) Hz, 2H), 2.65 (t, \( J = 7.8 \) Hz, 2H); \(^{13}\)C NMR (126 MHz, CDCl₃) \( \delta \) 179.5, 158.2, 132.3, 129.4, 114.1, 55.4, 36.1, 29.9; The spectroscopic data were consistent with reported literature values.\\n\\n6-Methoxy-2,3-dihydro-1H-inden-1-one (3.xi). Oxalyl chloride (2.6 mL, 31 mmol, 1.1 equiv) was added to a solution of acid 3.x (5.0 g, 28 mmol, 1 equiv) in CH₂Cl₂ (70 mL, 0.4 M) at 0 °C followed by catalytic DMF (0.05 mL). The reaction mixture was warmed to room temperature and stirred until gas evolution ceased (~1 h). When formation of the acid chloride was complete, the solution was concentrated to 20 mL on a rotary evaporator and then transferred to a syringe. To a round bottom flask at 0 °C, which contained CH₂Cl₂ (140 mL, 0.2 M), was added portion wise additions of AlCl₃ (5.6 g, 1.1 mmol) and the acid chloride solution every hour for 4 h. After the fourth addition, the reaction mixture was warmed to room temperature and stirred for 12 h. The reaction was quenched by slow, sequential addition of water (1.0 mL), 15% NaOH in H₂O (1.0 mL), and water (3.0 mL) and then stirred vigorously until the solution turned transparent and the white precipitates settled (~1 h). The precipitate was removed by filtration through a pad of Celite™ and the solution was concentrated in vacuo to give a pale yellow solid. Recrystallization from 4:1 hexanes: EtOAc (75 mL) provided 2.3 g (14 mmol, 50% yield) of indanone 3.xi as a white solid. \( R_f \) 0.43 (2:1 hexanes: EtOAc, UV); \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 7.37 – 7.30 (m, 1H), 7.21 – 7.10 (m, 2H), 3.81 (s, 3H), 3.04 (t, \( J = 5.7 \) Hz, 2H), 2.69 (t, \( J = 5.7 \) Hz, 2H); \(^{13}\)C NMR (126 MHz, CDCl₃) \( \delta \) 207.1, 159.4, 148.1, 138.3, 127.4, 124.1, 104.9, 55.7, 37.1, 25.2; The spectroscopic data were consistent with reported literature values.
Methyl 6-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (3.8). Sodium hydride (60 wt% dispersion in mineral oil, 1.9 g, 48 mmol, 2.5 equiv) was added to a round bottom flask and washed with hexanes (2 x 10 mL). Dimethyl carbonate (38 mL, 0.5 M) was added and the flask was placed in an oil bath at room temperature. Indanone 3.xi (3.1 g, 19 mmol, 1 equiv) was added in one portion and the flask was heated to 100 °C under a reflux condenser and stirred. Upon completion of the reaction, the solution turned solid and dark green/black (~2 h). The reaction mixture was cooled to rt and quenched slowly with 1 N HCl (50 mL) and extracted with EtOAc (3 x 75 mL), dried over MgSO₄, and concentrated to give a reddish orange solid. Recrystallization from hexanes (50 mL) provided 1.9 g (8.7 mmol, 46% yield) of β-ketoester 3.8 as a white solid. Rf 0.47 (2:1 hexanes: EtOAc, UV and p-anisaldehyde stain); ¹H NMR (500 MHz, CDCl₃) δ 7.39 (dd, J = 8.3, 0.8 Hz, 1H), 7.22 (dd, J = 8.3, 2.5 Hz, 1H), 7.20 (d, J = 2.5 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.76 (dd, J = 8.1, 3.8 Hz, 1H), 3.47 (ddd, J = 16.9, 3.8, 1.0 Hz, 1H), 3.31 (dd, J = 16.9, 8.1 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 199.6, 169.7, 159.9, 146.7, 136.5, 127.3, 125.2, 105.8, 55.8, 54.0, 52.9, 29.8; The spectroscopic data were consistent with reported literature values.

Methyl 2-(4-cyano-4-methylhex-5-yn-1-yl)-6-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (3.10). Alkyl iodide 3.9 (3.3 g, 13 mmol, 1 equiv) and K₂CO₃ (5.6 g, 40 mmol, 3 equiv) were added to a round-bottomed flask containing β-ketoester 3.8 (3.0 g, 13 mmol, 1 equiv) in acetone (67 mL, 0.2 M). The reaction vessel was fitted with a reflux condenser and the reaction mixture was heated to 65 °C and stirred. After 18 h, the mixture was cooled to room temperature, diluted with water (75 mL), and extracted with EtOAc (3 x 75 mL). The combined organics were washed with brine (1 x 50 mL), dried over MgSO₄, and concentrated. The resulting solid was purified by flash chromatography (9:1 hexanes: EtOAc to 4:1 hexanes: EtOAc) to obtain 3.5 g (10 mmol, 77% yield) of β-ketoester 3.10 as a pale orange solid (1:1 mixture of diastereomers). MP 99 – 102 °C; Rf 0.48 (2:1 hexanes: EtOAc, UV and p-anisaldehyde stain); ¹H NMR (500 MHz, CDCl₃) δ 7.38 (d, J = 8.3 Hz, 1H), 7.22 (dd, J = 8.4, 2.6 Hz, 1H), 7.18 (d, J = 2.6 Hz, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 3.63 (dd, J = 17.0, 3.9 Hz, 1H), 3.03 (d, J = 17.0 Hz, 1H), 2.35 (d, J = 20.2 Hz, 1H), 2.23 – 2.12 (m, 1H), 1.94 – 1.65 (m, 4H), 1.60 (d, J = 3.0 Hz, 3H) 1.58 – 1.48 (m, 1H); ¹³C NMR (151 MHz, CDCl₃) δ 202.2, 202.2, 171.4, 171.4,
2-Ethynyl-5-(6-methoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)-2-methylpentanenitrile (3.11). Lithium hydroxide monohydrate (1.1 g, 26 mmol, 2.5 equiv) was added to a stirred solution of \( \beta \)-ketoester 3.10 (3.5 g, 10 mmol, 1 equiv) in a 4:1 mixture of THF: H\(_2\)O (52 mL, 0.2 M). The heterogeneous mixture was heated to 65 \(^\circ\)C in the reaction vessel fitted with a reflux condenser. After 12 hours, the reaction mixture was cooled to room temperature, acidified with 1 N HCl (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine (1 x 25 mL), dried over MgSO\(_4\), and concentrated to yield 2.9 g (10 mmol, 100% yield) of indanone 3.11 as a yellow oil that was used without further purification (1:1 mixture of diastereomers based on \(^1\)H NMR). \( R_t \) 0.61 (2:1 hexanes: EtOAc, UV and \( p \)-anisaldehyde stain); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta 7.37 – 7.33 \) (m, 1H), 7.21 – 7.17 (m, 2H), 3.83 (s, 3H), 3.30 (dd, \( J = 16.6, 7.6 \) Hz, 1H), 2.76 (ddt, \( J = 16.9, 3.1, 1.6 \) Hz, 1H), 2.73 – 2.67 (m, 1H), 2.40 (d, \( J = 9.5 \) Hz, 1H), 2.06 – 1.96 (m, 1H), 1.89 – 1.73 (m, 4H), 1.64 (s, 3H), 1.58 – 1.46 (m, 1H); \(^13\)C NMR (126 MHz, CDCl\(_3\)) \( \delta 208.5, 159.6, 146.5, 137.9, 137.8, 127.4, 124.4, 124.4, 120.4, 105.2, 81.0, 72.4, 72.3, 55.7, 48.2, 48.0, 41.0, 41.0, 32.3, 32.2, 31.4, 31.4, 31.1, 30.9, 27.3, 27.3, 24.0, 23.7; IR (NaCl, thin film) \( \nu_{\text{max}} \) 3285, 2838, 1705, 1614 cm\(^{-1}\); HRMS (ESI) calc’d for [C\(_{18}\)H\(_{20}\)NO\(_2\)] ([M+H]\(^+\)): m/z 282.1489, found 282.1489.

2-Ethynyl-5-(5-methoxy-1H-inden-2-yl)-2-methylpentanenitrile (3.4). Sodium borohydride (0.39 g, 10 mmol, 1 equiv) was added to a stirred solution of indanone 3.11 (2.9 g, 10 mmol, 1 equiv) in EtOH (95%, 51 mL, 0.2 M) at 0 \({}^\circ\)C. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched by the slow addition of sat. aqueous NH\(_4\)Cl (25 mL). Ethanol was removed using a rotary evaporator and the resulting concentrate was extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine (1 x 25 mL), dried over MgSO\(_4\), and concentrated to give 2.9 g (10 mmol, 100% yield) of the desired indanol as a yellow oil that was used without further purification. \(^1\)H NMR analysis showed a 3:2 dr
(major diastereomer not determined). \( R_f \) 0.36 (2:1 hexanes: EtOAc, UV and \( p \)-anisaldehyde stain); **Major Diastereomer:** \(^1\)H NMR (600 MHz, \( \text{CDCl}_3 \)) \( \delta \) 7.10 (d, \( J = 8.2 \) Hz, 1H), 6.92 (d, \( J = 2.4 \) Hz, 1H), 6.80 (dd, \( J = 8.2, 2.5 \) Hz, 1H), 4.79 (d, \( J = 7.2 \) Hz, 1H), 3.80 (s, 3H), 3.07 (dd, \( J = 15.2, 7.9 \) Hz, 1H), 2.42 (d, \( J = 8.5 \) Hz, 1H), 2.40 (s, 1H), 2.24 – 2.15 (m, 2H), 1.92 – 1.71 (m, 4H), 1.65 (m, 3H) 1.61 – 1.52 (m, 1H). **Minor Diastereomer:** \(^1\)H NMR (600 MHz, \( \text{CDCl}_3 \)) \( \delta \) 7.14 (d, \( J = 8.3 \) Hz, 1H), 6.96 (d, \( J = 2.4 \) Hz, 1H), 6.83 (dd, \( J = 8.3, 2.5 \) Hz, 1H), 4.99 (d, \( J = 5.7 \) Hz, 1H), 3.80 (s, 3H), 2.90 (dd, \( J = 15.3, 7.5 \) Hz, 1H), 2.68 (dd, \( J = 15.3, 8.7 \) Hz, 1H), 2.45 (d, \( J = 8.7 \) Hz, 1H), 2.24 – 2.15 (m, 2H), 1.92 – 1.71 (m, 4H), 1.65 (m, 3H), 1.61 – 1.52 (m, 1H); \(^{13}\)C NMR (151 MHz, \( \text{CDCl}_3 \)) \( \delta \) 159.3, 159.1, 146.3, 146.2, 135.3, 133.4, 125.8, 125.8, 125.6, 120.6, 120.5, 115.3, 114.9, 114.9, 109.8, 109.8, 108.7, 81.8, 81.8, 81.2, 81.1, 72.3, 72.2, 72.2, 55.6, 51.4, 51.3, 45.6, 45.6, 41.4, 41.3, 41.2, 41.2, 35.4, 35.4, 35.3, 35.3, 33.0, 33.0, 31.5, 31.5, 31.5, 28.5, 28.5, 27.4, 27.3, 24.5, 24.4, 24.3; IR (NaCl, thin film) \( \nu_{\text{max}} \) 3281, 2992, 2938, 2242, 1613 cm\(^{-1}\); HRMS (ESI) calc’\(d\) for \([\text{C}_{18}\text{H}_{21}\text{NO}_2\text{Na}] \) ([M+Na])\(^+\): m/z 306.1465, found 306.1462.

Pyridinium \( p \)-toluenesulfonate (PPTS) (3.1 g, 12 mmol, 1.2 equiv) was added to a stirred solution of the crude indanol (2.9 g, 10 mmol, 1 equiv) in benzene (68 mL, 0.15 M) and the mixture was heated to 80 °C in a flask fitted with a reflux condenser for 24 h. The reaction mixture was cooled to room temperature, filtered through a pad of Celite\(^\text{TM}\), washed with EtOAc (200 mL), and concentrated. The crude yellow oil was purified by flash chromatography (9:1 hexanes: EtOAc) to yield 1.9 g (7.1 mmol, 71% yield) of indene 3.4 as a white solid. MP 59 – 60 °C; \( R_f \) 0.62 (2:1 hexanes: EtOAc, UV and \( p \)-anisaldehyde stain); \(^1\)H NMR (500 MHz, \( \text{CDCl}_3 \)) \( \delta \) 7.26 (d, \( J = 8.1 \) Hz, 1H), 6.85 (d, \( J = 2.4 \) Hz, 1H), 6.68 (dd, \( J = 8.1, 2.4 \) Hz, 1H), 6.51 (t, \( J = 1.7 \) Hz, 1H), 3.82 (s, 3H), 3.29 – 3.24 (m, 2H), 2.57 (t, \( J = 7.3 \) Hz, 2H), 2.40 (s, 1H), 2.03 – 1.88 (m, 2H), 1.87 – 1.74 (m, 2H), 1.65 (s, 3H); \(^{13}\)C NMR (151 MHz, \( \text{CDCl}_3 \)) \( \delta \) 159.1, 150.6, 146.8, 135.2, 127.2, 123.9, 120.4, 109.8, 106.1, 81.0, 72.3, 55.6, 40.6, 40.3, 31.4, 30.7, 27.3, 24.9; IR (NaCl, thin film) \( \nu_{\text{max}} \) 3283, 2929, 2241, 1615, 1578 cm\(^{-1}\); HRMS (ESI) calc’d for \([\text{C}_{18}\text{H}_{20}\text{NO}] \) ([M+H])\(^+\): m/z 266.1539, found 266.1539.

![Chemical structure of 3.4 and 3.3](image)

8-Methoxy-1-methyl-2,3,4,5-tetrahydro-1\( H \)-dibenzo[\( a,d \)][7]annulene-1-carbonitrile (3.3). Indene 3.4 was dried by azetotrope with benzene (3 x 5 mL) and dried under vacuum for 12 hours before use. Gallium(III) iodide (0.80 g, 1.8 mmol, 0.25 equiv) and 4 Å activated powdered molecular sieves (1.6 g, 2.0 g per gram of GaI\(_3\)) were added to a Schlenk flask in a \( \text{N}_2 \) dry box. The Schlenk flask was removed from the dry box and a solution of indene 3.4 (1.9 g, 7.1 mmol, 1 equiv) in freshly distilled toluene (36 mL, 0.2 M) was added to the flask via cannula. The Schlenk flask was sealed and the pale yellow mixture was heated to 100 °C and stirred vigorously for 48 h. The reaction mixture was cooled to room temperature, filtered through a pad of Celite\(^\text{TM}\),
washed with EtOAc (200 mL), and concentrated. The crude product was immediately purified by flash chromatography (9:1 hexanes: EtOAc) to yield 1.7 g (6.3 mmol, 89% yield) of cycloheptadiene 3.3 as a clear oil. Rf 0.62 (2:1 hexanes: EtOAc, UV and p-anisaldehyde stain); 1H NMR (600 MHz, CDCl₃) δ 7.05 (d, J = 6.8 Hz, 1H), 7.03 (d, J = 3.6 Hz, 1H), 6.89 (dd, J = 8.3, 2.6 Hz, 1H), 6.83 (d, J = 2.5 Hz, 1H), 6.63 (d, J = 11.7 Hz, 1H), 3.80 (s, 3H), 2.98 – 2.88 (m, 2H), 2.39 (qt, J = 12.3, 9.1, 2.6 Hz, 1H), 1.77 (ddt, J = 14.7, 5.8, 2.4 Hz, 1H), 1.72 (ddt, J = 13.2, 8.8, 2.4 Hz, 1H), 1.69 – 1.61 (m, 1H), 1.41 (s, 3H); 13C NMR (126 MHz, CDCl₃) δ 157.9, 137.3, 136.5, 133.1, 129.6, 128.7, 128.1, 126.9, 124.8, 115.2, 112.1, 55.5, 40.2, 35.5, 35.5, 31.3, 26.7, 19.0; IR (NaCl, thin film) νmax 3441, 2940, 2229, 1606 cm⁻¹; HRMS (ESI) calc’d for [C₁₈H₁₉NONa] ([M+Na]+): m/z 288.1359, found 288.1357.

8-Methoxy-1-methyl-2,3,4,5,10,11-hexahydro-1H-dibenzo[a,d][7] annulene-1-carbonitrile (3.12). p-Toluenesulfonyl hydrazide (11 g, 61 mmol, 8 equiv) and Et₃N (17 mL, 120 mmol, 16 equiv) was added to a solution of cycloheptadiene 3.3 (2.0 g, 7.7 mmol, 1 equiv) in 1,2-dichloroethane (31 mL, 0.25 M). The reaction mixture was heated to 65 °C and stirred. After 24 h, the reaction was observed to have stalled. The mixture was filtered through a pad of Celite™, washed with EtOAc (50 mL), and concentrated. The unreacted cycloheptadiene (3.3) and the product (3.12) were isolated together by column chromatography (100% hexanes to 4:1 hexanes: EtOAc) and resubmitted to the reaction conditions for another 24 h. The final product was isolated by flash chromatography (100% hexanes to 9:1 hexanes: EtOAc) to give 1.7 g (6.3 mmol, 82% yield) of cycloheptene 3.12 as a white solid. MP 63 – 68 °C; Rf 0.62 (2:1 hexanes: EtOAc, UV and p-anisaldehyde stain); 1H NMR (600 MHz, CDCl₃) δ 6.97 (d, J = 8.2 Hz, 1H), 6.71 (d, J = 2.7 Hz, 1H), 6.65 (dd, J = 8.2, 2.7 Hz, 1H), 3.79 (s, 3H), 3.59 (d, J = 16.5 Hz, 1H), 3.16 (ddd, J = 14.3, 10.9, 3.3 Hz, 1H), 3.08 (d, J = 16.6 Hz, 1H), 2.84 (ddd, J = 14.5, 7.5, 3.5 Hz, 1H), 2.61 (ddt, J = 17.1, 7.4, 2.5 Hz, 1H), 2.48 – 2.39 (m, 1H), 2.15 (tt, J = 5.8, 2.6 Hz, 2H), 2.06 (ddt, J = 11.7, 6.8, 3.0 Hz, 1H), 1.82 – 1.70 (m, 2H), 1.59 (dd, J = 23.9, 3.1 Hz, 1H), 1.39 (s, 3H); 13C NMR (151 MHz, CDCl₃) δ 158.5, 142.3, 134.6, 131.1, 129.3, 128.2, 124.9, 114.2, 110.7, 55.3, 39.6, 37.7, 36.1, 33.0, 32.2, 29.6, 25.3, 19.6; IR (NaCl, thin film) νmax 2936, 2227, 1609, 1503 cm⁻¹; HRMS (EI) calc’d for [C₁₈H₂₁NO] ([M]+): m/z 267.1623, found 267.1629.
8-Methoxy-1-methyl-5-oxo-2,3,4,5,10,11-hexahydro-1H-dibenzo[a,d][7]annulene-1-carbonitrile (3.13). Ceric ammonium nitrate (CAN) (3.6 g, 3.4 mmol, 5 equiv), silica (5.3 g, 2.0 g per gram of CAN) and water (2.6 mL, 0.5 M) were added to a 50 mL beaker and stirred with a spatula until a uniform yellow powder formed. The beaker was cooled to 0 °C and a solution of cycloheptene 3.12 (350 mg, 1.3 mmol, 1 equiv) in CH₂Cl₂ (10 mL, 0.125 M) was added slowly and the resulting orange slurry was vigorously stirred for 5 minutes with a spatula. The mixture was filtered through a pad of Celite™, washed with CH₂Cl₂ (100 mL), and concentrated. The crude orange oil was purified by flash chromatography (9:1 hexanes: EtOAc) to give 190 mg (0.68 mmol, 52% yield) of enone 3.13 as a yellow solid. MP 105 – 106 °C; Rf 0.36 (2:1 hexanes: EtOAc, UV and p-anisaldehyde stain); ¹H NMR (600 MHz, CDCl₃) δ 7.82 (d, J = 8.7 Hz, 1H), 6.76 (dd, J = 8.7, 2.6 Hz, 1H), 6.62 (d, J = 2.6 Hz, 1H), 3.79 (s, 3H), 3.13 (dd, J = 15.7, 11.2 Hz, 1H), 2.92 (dd, J = 15.8, 8.3 Hz, 1H), 2.75 – 2.66 (m, 1H), 2.61 (ddd, J = 17.0, 11.0, 2.5 Hz, 1H), 2.47 (dd, J = 18.3, 6.0 Hz, 1H), 2.38 – 2.28 (m, 1H), 2.16 – 2.07 (m, 1H), 1.79 – 1.64 (m, 3H), 1.50 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 194.0, 162.6, 143.9, 143.9, 138.6, 133.0, 130.6, 123.5, 113.5, 112.2, 55.3, 38.3, 35.6, 34.5, 30.7, 26.5, 24.8, 18.6; IR (NaCl, thin film) vₘₐₓ 2942, 2230, 1626, 1596 cm⁻¹; HRMS (ESI) calc’d for [C₁₈H₂₀NO₂] [M+H⁺]: m/z 282.1489, found 282.1496.

(1R,4aS,11aS)-8-Methoxy-1-methyl-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1H-dibenzo[a,d][7]annulene-1-carbonitrile (3.14). Palladium on carbon (5 wt%, 200 mg) was added to a stirred solution of enone 3.13 (720 mg, 2.6 mmol, 1 equiv) in EtOAc (26 mL, 0.1 M). The flask was evacuated under vacuum and backfilled with H₂ (3x) and stirred under a balloon of H₂ for 48 h. The reaction mixture was filtered through a pad of Celite™, washed with EtOAc (50 mL), and concentrated to give 720 mg of ketone 3.14 (2.6 mmol, 100% yield) as a white solid that was used without further purification. A single diastereomer (determined by ¹H NMR) was isolated. Slow diffusion crystallization from benzene and hexanes provided x-ray quality crystals. MP 154 – 156 °C; Rf 0.25 (2:1 hexanes: EtOAc, UV); ¹H NMR (400 MHz, CDCl₃) δ 8.03 (d, J = 8.7 Hz, 1H), 6.78 (dd, J = 8.9, 2.6 Hz, 1H), 6.70 (d, J = 2.7 Hz, 1H), 3.82 (s, 3H), 3.20 – 3.12 (m, 1H), 3.02 (ddd, J = 41.6, 16.2, 9.1 Hz, 2H), 2.51 (dt, J = 14.6, 7.4 Hz, 1H), 2.40 (ddd, J = 16.8, 10.0, 3.4 Hz, 1H), 2.31 – 2.17 (m, 1H), 2.05 (dt, J = 13.4, 3.9 Hz, 1H), 1.95 (dt, J = 11.7, 7.1 Hz, 1H), 1.77 – 1.62 (m, 2H), 1.47 – 1.36 (m, 2H), 1.35 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 199.8, 162.3, 146.4, 132.1, 131.1, 122.5, 115.2, 111.9, 55.4, 46.2, 44.3, 38.1, 37.8, 32.9, 29.7, 27.0, 26.5, 20.6; IR (NaCl, thin film) vₘₐₓ 2941, 2232, 1670, 1600 cm⁻¹; HRMS (ESI) calc’d for [C₁₈H₂₁NO₂Na] [M+Na⁺]: m/z 306.1465, found 306.1470.
(1R,4aR,11aR)-8-methoxy-1-methyl-5-oxo-4a-vinyl-2,3,4,4a,5,10,11,11a-octahydro-1H-dibenzo[a,d][7]annulene-1-carbonitrile (3.16). Sodium hydride (60 wt% dispersion in mineral oil, 120 mg, 3.1 mmol, 5 equiv) was added to a Schlenk flask followed by a solution of ketone 3.14 (170 mg, 0.61 mmol, 1 equiv) and phenyl vinylsulfoxide (80 μL, 0.61 mmol, 1 equiv) in dry DMF (6.0 mL, 0.1 M). The Schlenk flask was sealed and heated to 50 °C for 20 min. The reaction mixture was cooled to room temperature and quenched by dropwise addition of water until gas evolution ceased (~0.5 mL). The reaction mixture was diluted with EtOAc (50 mL), washed with water (3 × 25 mL), and brine (1 × 25 mL), dried over MgSO₄, and concentrated. The crude yellow oil was purified by flash chromatography (4:1 hexanes: EtOAc to 100% EtOAc) to give 230 mg (0.53 mmol, 87% yield) of sulfoxide 3.15 as a clear oil that was immediately carried on to the sulfoxide extrusion. Rf 0.07 (2:1 hexanes: EtOAc, UV and p-anisaldehyde stain).

Sulfoxide 3.15 (230 mg, 0.53 mmol, 1 equiv) was dried by azeotrope with benzene (1 × 10 mL) and transferred to a microwave vial with freshly distilled toluene (11 mL, 0.05 M). The solution was sparged with argon for 1 h and then the reaction mixture was heated in the microwave to 160 °C for 2 h. The reaction mixture was diluted with EtOAc (75 mL), washed with water (3 × 50 mL), and brine (1 × 25 mL), dried over MgSO₄, and concentrated. The crude yellow oil was purified by flash chromatography (4:1 hexanes: EtOAc to 100% EtOAc) to give 115 mg (0.37 mmol, 70% yield) of ketone 3.16 as a white solid. Slow diffusion crystallization from benzene and hexanes provided X-ray quality crystals. MP 127 – 128 °C; Rf 0.47 (2:1 hexanes: EtOAc, UV and p-anisaldehyde stain); ¹H NMR (500 MHz, CDCl₃) δ 7.80 (d, J = 8.7 Hz, 1H), 6.80 (dd, J = 8.8, 2.6 Hz, 1H), 6.63 (d, J = 2.6 Hz, 1H), 5.88 (dd, J = 17.6, 10.7 Hz, 1H), 4.93 (d, J = 10.8 Hz, 1H), 4.77 (d, J = 17.6 Hz, 1H), 3.82 (s, 3H), 3.31 – 3.20 (m, 1H), 3.07 (ddd, J = 16.7, 6.8, 2.3 Hz, 1H), 2.50 (tdd, J = 9.4, 8.2, 5.1 Hz, 1H), 2.21 – 2.09 (m, 2H), 2.02 – 1.94 (m, 3H), 1.67 (ddd, J = 13.9, 9.7, 6.0, 2.5 Hz, 1H), 1.56 (t, J = 13.4 Hz, 1H), 1.52 – 1.45 (m, 1H), 1.42 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 201.8, 162.0, 146.3, 143.1, 133.5, 131.5, 123.6, 114.9, 114.8, 112.2, 58.0, 55.4, 48.6, 38.8, 37.0, 33.6, 29.2, 26.5, 19.8; IR (NaCl, thin film) νmax 2938, 1662, 1599 cm⁻¹; HRMS (ESI) calc’d for [C₂₀H₂₃NO₂Na] [(M+Na)⁺]: m/z 332.1621, found 332.1623.
\((1R,4aR,11aR)-4a\text{-Allyl-8-methoxy-1-methyl-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1H-dibenzo[a,d][7]annulene-1-carbonitrile} \ (3.20)\). Sodium hydride (60 wt% dispersion in mineral oil, 0.51 g, 13 mmol, 5 equiv) was added to a Schlenk flask followed by a solution of ketone \(3.14\) (720 mg, 2.6 mmol, 1 equiv) and allyl bromide (0.22 mL, 2.6 mmol, 1 equiv) in dry DMF (25 mL, 0.1 M). The flask was sealed and heated to 50 °C for 45 min. The reaction mixture was cooled to room temperature and quenched by dropwise addition of water until bubbling ceased (~0.5 mL). The reaction mixture was diluted with EtOAc (100 mL), washed with water (3 × 50 mL), and brine (1 × 25 mL), dried over MgSO\(_4\), and concentrated to give a 96:4 mixture of O-allylated product to C-allylated product \(3.20\) (based on \(^1H\) NMR) as a clear oil that was carried on crude.

The crude mixture of products was dried by azeotrope with benzene (1 x 10 mL) and transferred to a microwave vial with DMF (25 mL, 0.1 M). The reaction mixture was heated in the microwave to 160 °C for 45 min. The reaction mixture was diluted with EtOAc (100 mL), washed with water (3 x 50 mL), and brine (1 x 25 mL), dried over MgSO\(_4\), and concentrated. The crude yellow oil was purified by flash chromatography (4:1 hexanes: EtOAc) to give 570 mg (1.8 mmol, 69% over 2 steps) of C-allylated ketone \(3.20\) as a clear oil.

**\(^{1}H\) NMR** (600 MHz, CDCl\(_3\)) \(\delta\) 7.55 (d, \(J = 8.7\) Hz, 1H), 6.76 (dd, \(J = 8.7\), 2.5 Hz, 1H), 6.64 (d, \(J = 2.5\) Hz, 1H), 5.51 (dddd, \(J = 16.4\), 9.4, 8.1, 6.7 Hz, 1H), 5.01 (dd, \(J = 10.0\), 1.8 Hz, 1H), 4.85 (dd, \(J = 17.0\), 2.0 Hz, 1H), 3.82 (s, 3H), 3.76 (dddd, \(J = 16.4\), 13.8, 2.6 Hz, 1H), 2.78 (ddd, \(J = 16.4\), 6.2, 2.5 Hz, 1H), 2.47 (ddt, \(J = 16.5\), 13.6, 3.1 Hz, 1H), 2.43 – 2.29 (m, 3H), 2.29 – 2.21 (m, 1H), 2.09 (dd, \(J = 13.9\), 8.0 Hz, 1H), 2.04 (dq, \(J = 12.9\), 2.7 Hz, 1H), 1.72 (dt, \(J = 14.8\), 4.1 Hz, 1H), 1.68 – 1.66 (m, 1H), 1.46 (s, 3H), 1.46 – 1.41 (m, 1H), 1.12 (td, \(J = 14.0\), 13.5, 4.3 Hz, 1H); \(^{13}C\) NMR (151 MHz, CDCl\(_3\)) \(\delta\) 206.1, 161.8, 139.8, 133.7, 133.6, 132.1, 124.3, 119.2, 115.5, 111.8, 55.4, 54.7, 50.0, 45.1, 40.7, 36.0, 33.7, 32.4, 26.7, 24.1, 20.5; IR (NaCl, thin film) \(\nu_{\text{max}}\) 2946, 2227, 1666, 1601 cm\(^{-1}\); HRMS (ESI) calc’d for \([\text{C}_{21}\text{H}_{26}\text{NO}_2]\) ([M+H]+): m/z 324.1958, found 324.1967.
(1R,4aR,11aR)-4a-Allyl-8-methoxy-1-methyl-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1H-dibenzo[a,d][7]annulene-1-carbonitrile (3.21). LiAlH₄ (330 mg, 8.8 mmol, 5 equiv, from Aldrich) was added to a flame dried Schlenk flask followed by a solution of ketone 3.20 (570 mg, 1.8 mmol, 1 equiv) in THF (35 mL, 0.05 M) and heated to 65 °C for 4 h. The reaction mixture was cooled to room temperature and slowly quenched with powdered Na₂SO₄•10H₂O (1.8 g, 0.2 g per mmol LiAlH₄) and stirred until the gray color disappeared and the white precipitate clumped to bottom of flask (~ 12 h). The clear solution was filtered through a pad of Celite™, washed with Et₂O (75 mL), and concentrated to give an amino alcohol that was immediately subjected to the Boc-protection conditions. 

Di-tert-butyl dicarbonate (Boc₂O) (580 mg, 2.6 mmol, 1.5 equiv) and Et₃N (0.32 mL, 2.3 mmol, 1.3 equiv) were added to a solution of the crude amino alcohol (580 mg, 1.8 mmol, 1 equiv) in CH₂Cl₂ (44 mL, 0.04 M). After 45 min the solution was concentrated and the crude clear oil was purified by flash chromatography (4:1 hexanes: EtOAc) to give 700 mg (1.6 mmol, 93% yield over 2 steps) of Boc-protected amino alcohol 3.21 as a clear oil. Rf 0.02 (100% EtOAc, UV and p-anisaldehyde stain); ¹H NMR (600 MHz, CDCl₃) δ 7.01 (d, J = 8.0 Hz, 1H), 6.66 – 6.53 (m, 2H), 5.74 (dt, J = 17.1, 8.0 Hz, 1H), 5.00 (dd, J = 9.9, 2.6 Hz, 1H), 4.87 (d, J = 16.9 Hz, 1H), 4.72 (t, J = 6.4 Hz, 1H), 4.38 (s, 1H), 3.76 (s, 4H), 3.63 (d, J = 13.3 Hz, 1H), 3.35 – 3.18 (m, 2H), 2.68 – 2.55 (m, 1H), 2.36 – 1.96 (m, 4H), 1.93 – 1.69 (m, 5H), 1.43 (s, 9H), 1.10 – 0.91 (m, 5H); ¹³C NMR (151 MHz, CDCl₃) δ 159.0, 156.4, 142.9, 135.3, 132.9, 131.9, 117.8, 115.5, 110.3, 78.8, 55.2, 55.2, 50.5, 44.4, 44.0, 38.8, 34.3, 34.1, 31.7, 28.9, 28.6, 28.5, 22.8, 22.7, 18.8, 14.2; IR (NaCl, thin film) v_{max} 3459, 2930, 2248, 1701, 1608 cm⁻¹; HRMS (ESI) calc'd for [C₂₆H₃₉NO₄Na] ([M+Na]⁺): m/z 452.2771, found 452.2780.

(1R,4aR,11aR)-tert-Butyl 4a-allyl-8-methoxy-1-methyl-2,3,4,4a,5,10,11, 11a-octahydro-1H-5,1-(epiminomethano)dibenzo[a,d][7]annulene-12-carboxylate (3.22). Boc-protected amino alcohol 3.21 was dried by azeotrope with benzene (1 × 10
A solution of Boc-protected amino alcohol 3.21 (430 mg, 1.0 mmol, 1 equiv) in CH₂Cl₂ (13 mL, 0.08 M) was added dropwise over 20 minutes to a stirred solution of SOCl₂ (0.22 mL, 3.0 mmol, 3 equiv) in CH₂Cl₂ (13 mL, 0.08 M) and stirred at room temperature. After 1 h, water (10 mL) was added and stirring was continued for an additional 15 min. The mixture was poured into water (40 mL) and extracted with CH₂Cl₂ (3 × 40 mL). The combined organics were washed with brine (1 × 20 mL), dried over MgSO₄, and concentrated. The crude oil was purified by flash chromatography (9:1 hexanes: EtOAc) to give 300 mg (0.72 mmol, 72% yield) of 3.22 as a clear oil. Rₜ 0.62 (2:1 hexanes: EtOAc, UV and p-anisaldehyde stain); ¹H NMR (600 MHz, CDCl₃, mixture of 2 rotamers) δ 7.31 - 7.27 (m), 7.08 (d, J = 8.1 Hz), 6.66 - 6.54 (m), 5.73 (dt, J = 17.2, 7.2, 3.6 Hz), 5.02 - 4.94 (m), 4.89 - 4.81 (m), 4.86 (s) 4.60 (s), 3.76 (s), 3.75 (s), 3.72 (s), 3.65 (d, J = 13.9 Hz), 3.39 - 3.28 (m), 2.55 (tt, J = 16.6, 4.0 Hz, 1H), 2.08 - 2.00 (m, 2H), 1.91 - 1.80 (m, 3H), 1.80 - 1.68 (m, 2H), 1.64 (dd, J = 12.9, 5.5 Hz, 1H), 1.62 - 1.47 (m, 3H), 1.43 (s, 3H), 1.04 (s), 1.02 (s), (1.74:1 ratio of major to minor rotamer); Major Rotamer: ¹H NMR (600 MHz, CDCl₃) δ 7.08 (d, J = 8.1 Hz, 1H), 6.66 - 6.54 (m, 2H), 5.73 (dt, J = 17.2, 7.2, 3.6 Hz, 1H), 5.02 - 4.94 (m, 1H), 4.89 - 4.81 (m, 1H), 4.60 (s, 1H), 3.76 (s, 3H), 3.75 - 3.72 (m, 1H), 3.39 - 3.28 (m, 2H), 2.55 (tt, J = 16.6, 4.0 Hz, 1H), 2.08 - 2.00 (m, 2H), 1.91 - 1.80 (m, 3H), 1.80 - 1.68 (m, 2H), 1.64 (dd, J = 12.9, 5.5 Hz, 1H), 1.62 - 1.47 (m, 3H), 1.43 (s, 9H), 1.04 (s, 3H); Minor Rotamer: ¹H NMR (600 MHz, CDCl₃) δ 7.31 - 7.27 (m, 1H), 6.66 - 6.54 (m, 2H), 5.73 (dt, J = 17.2, 7.2, 3.6 Hz, 1H), 5.02 - 4.94 (m, 1H), 4.89 - 4.81 (m, 1H), 4.86 (s, 1H), 3.75 (s, 3H), 3.65 (d, J = 13.9 Hz, 1H), 3.39 - 3.28 (m, 2H), 2.55 (tt, J = 16.6, 4.0 Hz, 1H), 2.08 - 2.00 (m, 2H), 1.91 - 1.80 (m, 3H), 1.80 - 1.68 (m, 2H), 1.64 (dd, J = 12.9, 5.5 Hz, 1H), 1.62 - 1.47 (m, 3H), 1.41 (s, 9H), 1.02 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 158.5, 155.1, 141.5, 141.1, 134.8, 134.2, 134.0, 134.0, 133.2, 133.1, 117.9, 117.9, 117.9, 117.0, 116.7, 109.9, 109.8, 79.8, 79.4, 65.5, 64.0, 55.12 55.14 53.0, 52.6, 45.8, 45.5, 45.1, 44.8, 43.9, 43.9, 39.7, 39.3, 38.5, 38.4, 34.6, 34.5, 33.7, 33.5, 28.8, 26.6, 26.5, 23.5, 21.3, 21.2; IR (NaCl, thin film) νmax 2931, 1684 cm⁻¹; HRMS (ESI) calc’d for [C₂₆H₃₈NO₃] ([M+H]⁺): m/z 412.2846, found 412.2862.  

(1R,4aR,11aR)-4a-allyl-8-methoxy-1-methyl-2,3,4,4a,5,10,11,11a-octahydro-1H-5,1-(epiminomethano)dibenzo[a,d][7]annulene (3.23). Trifluoroacetic acid (1.3 mL, 0.2 M) was added to a stirred solution of Boc-protected amine 3.22 (110 mg, 0.26 mmol, 1 equiv) in CH₂Cl₂ (1.3 mL, 0.2 M) at room temperature. After 30 minutes, 1 N NaOH was slowly added (10 mL) and the mixture was extracted with CH₂Cl₂ (3 × 15 mL). The combined organics were washed with brine (1 × 20 mL), dried over MgSO₄ and concentrated. The crude amine was purified by flash chromatography (9:1 CH₂Cl₂:MeOH, 1% NH₄OH) to provide 64 mg (0.21 mmol, 81% yield) of the free amine (3.23) as a clear oil. Rₜ 0.50 (9:1 CH₂Cl₂:MeOH 1% NH₄OH, UV and p-anisaldehyde
stain); $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 6.96 (d, $J = 8.2$ Hz, 1H), 6.68 – 6.64 (m, 1H), 6.61 (dd, $J = 8.2$, 2.8 Hz, 1H), 5.74 (ddt, $J = 17.2$, 10.0, 7.3 Hz, 1H), 4.99 – 4.95 (m, 1H), 4.83 (ddt, $J = 16.9$, 2.4, 1.3 Hz, 1H), 3.79 (s, 1H), 3.77 (s, 3H), 3.48 (td, $J = 15.9$, 14.2, 4.0 Hz, 1H), 3.32 (dd, $J = 12.4$, 2.9 Hz, 1H), 2.72 (d, $J = 12.5$ Hz, 1H), 2.62 (dt, $J = 16.6$, 4.1 Hz, 1H), 2.54 (dq, $J = 19.5$, 7.2 Hz, 1H), 2.24 (s, 1H), 2.12 (tt, $J = 14.9$, 3.7 Hz, 1H), 2.07 – 1.99 (m, 1H), 1.85 (d, $J = 7.3$ Hz, 2H), 1.72 (dd, $J = 13.7$, 5.9 Hz, 1H), 1.67 – 1.53 (m, 2H), 1.47 – 1.44 (m, 1H), 1.43 – 1.39 (m, 1H), 0.95 (s, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 158.5, 141.4, 137.0, 134.4, 132.9, 117.6, 117.6, 110.7, 67.9, 55.3, 53.2, 46.0, 44.6, 44.5, 39.5, 38.5, 35.6, 34.1, 27.0, 23.5, 22.9; IR (NaCl, thin film) $\nu_{max}$ 3353, 2919, 1606 cm$^{-1}$; HRMS (ESI) calc’d for [C$_{21}$H$_{30}$NO] ([M+H]$^+$): m/z 312.2322, found 312.2332.

(1$R$,4a$R$,11a$R$)-4-Nitrophenyl 4a-allyl-8-methoxy-1-methyl-2,3,4,4a,5,10,11,11a-octahydro-1H,5,1-(epiminomethano)dibenzo[a,d][7]annulene-12-carboxylate (3.25). Triethylamine (5.0 µL, 0.035 mmol, 1.5 equiv) and 4-nitrobenzoylchloride (3.24, 4.7 mg, 0.025 mmol, 1.1 equiv) were added to a stirred solution of free amine 3.23 (7.2 mg, 0.023 mmol, 1 equiv) in CH$_2$Cl$_2$ (0.46 mL, 0.05 M) at room temperature. After 1 h, the solution was diluted with CH$_2$Cl$_2$ (5 mL) and washed with 1 N HCl (1 × 1 mL), saturated NaHCO$_3$ (1 × 1 mL), and brine (1 × 1 mL), dried over MgSO$_4$, and concentrated. The resulting white solid was purified by flash chromatography (4:1 hexanes: EtOAc) and slow evaporation of the column eluent provided X-ray quality crystals of 3.25. MP 88 – 89 ºC; R$_f$ 0.47 (2:1 hexanes: EtOAc, UV and p-anisaldehyde stain); $^1$H NMR (600 MHz, CDCl$_3$, mixture of 2 rotamers) $\delta$ 8.30 (dd, $J = 7.3$, 1.6 Hz), 8.23 (dd, $J = 7.3$, 1.5 Hz), 7.44 (d, $J = 8.1$ Hz), 7.41 (dd, $J = 6.9$, 1.8 Hz), 7.37 (d, $J = 7.8$ Hz), 6.70 – 6.67 (m), 6.67 (d, $J = 2.7$ Hz), 6.61 (d, $J = 2.7$ Hz), 6.28 (dd, $J = 8.4$, 2.7 Hz), 5.76 (ddt, $J = 17.3$, 10.1, 7.3 Hz), 5.61 – 5.57 (m), 5.55 (s), 5.53 (d, $J = 8.4$ Hz), 5.04 (dd, $J = 10.2$, 2.2 Hz), 4.97 (dd, $J = 10.2$, 2.1 Hz), 4.90 (dq, $J = 16.7$, 1.5 Hz), 4.81 (dq, $J = 16.9$, 1.6 Hz), 4.46 (s), 4.17 (d, $J = 14.9$ Hz), 3.79 (s), 3.73 (s), 3.67 (dd, $J = 13.5$, 2.4 Hz), 1.55 – 1.51 (m), 1.53 (dd, $J = 14.9$, 2.6 Hz), 3.46 – 3.33 (m), 3.14 (d, $J = 13.5$ Hz), 2.72 (dt, $J = 16.7$, 3.9 Hz), 2.59 (dt, $J = 16.4$, 4.0 Hz), 2.18 (tt, $J = 15.1$, 3.8 Hz), 2.13 – 1.99 (m), 1.94 (d, $J = 7.4$ Hz), 1.92 – 1.88 (m), 1.87 – 1.82 (m), 1.77 (p, $J = 7.6$ Hz), 1.75 – 1.68 (m), 1.67 – 1.58 (m), 1.57 – 1.55 (m), 1.51 – 1.43 (m), 1.43 – 1.36 (m), 1.31 – 1.27 (m), 1.26 – 1.23 (m), 1.16 (s), 0.95 (s), 0.88 (t, $J = 7.3$ Hz). (1.6:1 ratio of major to minor rotamer); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 169.8, 168.0, 159.1, 158.8, 148.1, 148.1, 144.1, 144.0, 141.8, 140.9, 135.3, 133.5, 133.0, 133.0, 131.9, 131.5, 127.4, 124.0,
123.8, 118.8, 118.5, 117.8, 117.6, 110.5, 109.9, 68.9, 62.7, 56.9, 55.3, 52.2, 45.9, 45.7, 44.6, 43.8, 43.6, 39.2, 39.1, 38.4, 36.8, 35.0, 34.7, 34.4, 33.3, 33.6, 26.5, 26.2, 23.4, 23.2, 22.5, 21.6, 21.5, 14.2; IR (NaCl, thin film) \( \nu_{\text{max}} \): 2919, 1606, 1500 cm\(^{-1}\); HRMS (ESI) calc'd for \([C_{28}H_{33}N_2O_4]\) ([M+H]\(^+\)): m/z 461.2435, found 461.2441.

(1R,4aR,11aR)-4a-allyl-12-chloro-8-methoxy-1-methyl-2,3,4,4a,5,10,11,11a-octahydro-1H-5,1-(epiminomethano)dibenzo[a,d][7]annulene (3.26). N-chlorosuccinimide (48 mg, 0.36 mmol, 2 equiv) was added to a stirred solution of amine 3.23 (55 mg, 0.18 mmol, 1 equiv) in CH\(_2\)Cl\(_2\) (3.5 mL, 0.05 M) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h, then diluted with CH\(_2\)Cl\(_2\) (3 mL), washed with saturated aq. Na\(_2\)CO\(_3\) (1 \times 3 mL), and water (1 \times 3 mL), dried over MgSO\(_4\), and concentrated. Flash chromatography (4:1 hexanes: EtOAc) provided 51 mg (0.15 mmol, 83% yield) of N-chloro amine 3.26 as a clear oil \( R_f = 0.50 \) (2:1 hexanes: EtOAc, UV and \( p \)-anisaldehyde stain); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 7.04 (d, \( J = 8.2 \) Hz, 1H), 6.69 (d, \( J = 2.7 \) Hz, 1H), 6.67 (dd, \( J = 8.3, 2.6 \) Hz, 1H), 5.70 (ddt, \( J = 17.3, 10.2, 7.4 \) Hz, 1H), 4.98 (ddt, \( J = 10.1, 2.1, 1.0 \) Hz, 1H), 4.81 (ddt, \( J = 17.0, 2.5, 1.4 \) Hz, 1H), 3.95 (s, 1H), 3.80 (s, 3H), 3.54 – 3.43 (m, 2H), 3.09 (d, \( J = 10.9 \) Hz, 1H), 2.72 – 2.61 (m, 2H), 2.15 (tt, \( J = 14.8, 3.8 \) Hz, 1H), 2.05 – 1.88 (m, 3H), 1.78 (dd, \( J = 13.2, 6.4 \) Hz, 1H), 1.65 (dd, \( J = 13.1, 6.2 \) Hz, 1H), 1.62 – 1.50 (m, 2H), 1.46 – 1.41 (m, 1H), 1.39 (t, \( J = 3.5 \) Hz, 1H), 1.02 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \): 158.9, 141.9, 137.3, 133.9, 130.7, 118.1, 117.4, 109.8, 80.5, 68.6, 55.2, 45.3, 44.8, 44.0, 43.1, 39.0, 38.8, 35.8, 26.2, 23.3, 22.9; IR (NaCl, thin film) \( \nu_{\text{max}} \): 2922, 2858, 1606, 1263 cm\(^{-1}\); HRMS (ESI) calc'd for \([C_{21}H_{29}NOCl]\) ([M+H]\(^+\)): m/z 346.1932, found 346.1939.

(1R,4aR,11aR)-tert-butyl 8-methoxy-1-methyl-4a-(2-oxoethyl)-2,3,4,4a,5,10,11,11a-octahydro-1H-5,1-(epiminomethano)dibenzo[a,d][7]annulene-12-carboxylate (3.29). Osmium(IV) tetroxide (2.5 wt% in t-butanol, 0.10 mL, 0.008 mmol, 0.01 equiv) was added to a stirred solution of 3.22 (340 mg, 0.84 mmol, 1 equiv) in 2:1 acetone:H\(_2\)O (21 mL, 0.04 M). After 5 min, 4-methylmorpholine N-oxide (NMO, 200 mg, 1.7 mmol, equiv) was added. The reaction mixture was stirred at room temperature for 18 h, then diluted with EtOAc (100 mL), washed with water (1 \times 50 mL) and brine (1 \times 50 mL), dried over MgSO\(_4\), and concentrated. Silica plug (10% MeOH in CH\(_2\)Cl\(_2\)) provided 350 mg (0.79 mmol, 94% yield) of the diol that was immediate carried
onto the oxidative cleavage. R_t 0.13 (2:1 hexanes: EtOAc, UV and p-anisaldehyde stain).

NaO_4 on silica\textsuperscript{20} (1.6 g, 2 g/mmol diol) was added to a stirred solution of the diol (350 mg, 0.79 mmol, 1 equiv) in CH$_2$Cl$_2$ (8 mL, 0.1 M). After 1 h the mixture was filtered through a pad of Celite\textsuperscript{TM}, washed with CH$_2$Cl$_2$ (30 mL), and concentrated to give 320 mg (0.77 mmol, 97% yield) of aldehyde \textbf{3.29} as a clear oil that was used without further purification. R_t 0.43 (2:1 hexanes: EtOAc, UV and p-anisaldehyde stain); \textsuperscript{1}H NMR (600 MHz, CDCl$_3$) $\delta$ 9.72 (dd, $J = 3.4$, 1.9 Hz), 9.68 (dd, $J = 2.8$, 1.9 Hz), 7.27 – 7.24 (m), 7.04 (d, $J = 8.3$ Hz), 6.61 – 6.55 (m), 5.05 (s), 4.86 (s), 3.73 (s), 3.73 – 3.71 (m), 3.65 (d, $J = 14.0$ Hz), 3.38 – 3.29 (m), 2.54 (tt, $J = 16.1$, 4.0 Hz), 2.24 – 2.17 (m), 2.14 – 2.04 (m), 2.03 – 1.83 (m), 1.66 – 1.57 (m), 1.57 – 1.50 (m), 1.40 (s), 1.03 (s). Major Rotamer \textsuperscript{1}H NMR (600 MHz, CDCl$_3$) $\delta$ 9.68 (dd, $J = 2.8$, 1.9 Hz, 1H), 7.04 (d, $J = 8.3$ Hz, 1H), 6.61 – 6.55 (m, 2H), 4.86 (s, 1H), 3.75 – 3.71 (m, 1H), 3.73 (s, 3H), 3.38 – 3.29 (m, 2H), 2.54 (tt, $J = 16.1$, 4.0 Hz, 1H), 2.24 – 2.17 (m, 1H), 2.14 – 2.04 (m, 2H), 2.03 – 1.83 (m, 2H), 1.66 – 1.57 (m, 3H), 1.57 – 1.50 (m, 3H), 1.40 (s, 3H), 1.03 (s, 3H); Minor Rotamer \textsuperscript{1}H NMR (600 MHz, CDCl$_3$) $\delta$ 9.72 (dd, $J = 3.4$, 1.9 Hz, 1H), 7.27 – 7.24 (m, 1H), 6.61 – 6.55 (m, 2H), 5.05 (s, 1H), 3.72 (s, 3H), 3.65 (d, $J = 14.0$ Hz, 1H), 3.38 – 3.29 (m, 2H), 2.54 (tt, $J = 16.1$, 4.0 Hz, 1H), 2.24 – 2.17 (m, 1H), 2.14 – 2.04 (m, 2H), 2.03 – 1.83 (m, 2H), 1.66 – 1.57 (m, 3H), 1.57 – 1.50 (m, 3H), 1.39 (s, 9H), 1.02 (s, 3H);

\textsuperscript{13}C NMR (151 MHz, CDCl$_3$) $\delta$ 202.5, 202.1, 158.7, 158.6, 155.0, 154.5, 141.1, 140.8, 134.5, 134.0, 132.7, 132.5, 117.3, 117.0, 110.2, 110.0, 80.2, 79.7, 64.3, 63.3, 55.1, 55.1, 52.9, 52.9, 52.7, 52.5, 46.0, 45.9, 44.7, 44.5, 40.2, 40.1, 39.3, 39.3, 34.3, 34.3, 33.5, 33.3, 28.7, 26.6, 26.5, 23.8, 23.8, 21.0, 21.0; IR (NaCl, thin film) $\nu_{\text{max}}$ 2931, 1719, 1683, 1607 cm\textsuperscript{-1}; HRMS (ESI) calc’d for [C$_{25}$H$_{36}$O$_{4}$] ([M+H]$^+$): m/z 414.2639, found 414.2648.

\begin{align*}
\textbf{3.29} \xrightarrow{\text{MeOH}} \textbf{3.32} \xrightarrow{\text{MeCN}} \textbf{3.xii}
\end{align*}

(1R,4aR,11aR)-tert-butyldiphenyl disulfide (0.79 g, 3.6 mmol, 5 equiv) was added to the flask and the
headspace was evacuated and backfilled with N\textsubscript{2} (3x). Acetonitrile (15 mL, 0.05 M) was then added followed by a dropwise addition of tributylphosphine (0.9 mL, 3.6 mmol, 5 equiv). The reaction mixture was allowed to stir at room temperature for 18 h then 1 N NaOH (10 mL) was added and stirred for 30 min. The mixture was then poured into 1 N NaOH (100 mL) and extracted with EtOAc (3 \times 75 mL). The combined organics were washed with 1 N NaOH (1 \times 75 mL) and brine (1 \times 75 mL), dried over MgSO\textsubscript{4}, and concentrated. The crude sulfide was purified by flash chromatography (9:1 hexanes: EtOAc) to give 370 mg (0.72 mmol, 100% yield) of sulfide 3.xii as a clear oil. R\textsubscript{f} 0.57 (2:1 hexanes: EtOAc, UV and \textit{p}-anisaldehyde stain); ¹H NMR (600 MHz, CDCl\textsubscript{3}) \(\delta 7.35 \text{–} 7.31 \text{ (m)}, 7.17 \text{–} 7.06 \text{ (m)}, 7.01 \text{–} 6.97 \text{ (m)}, 6.96 \text{–} 6.92 \text{ (m)}, 6.64 \text{ (dd, } J = 8.3, 2.8 \text{ Hz), } 6.61 \text{ –} 6.55 \text{ (m), } 4.94 \text{ (s), } 4.65 \text{ (s), } 3.80 \text{ (s), } 3.79 \text{ (s), } 3.74 \text{ (d, } J = 14.1 \text{ Hz), } 3.65 \text{ (d, } J = 13.9 \text{ Hz), } 3.35 \text{–} 3.24 \text{ (m), } 2.86 \text{–} 2.77 \text{ (m), } 2.55 \text{–} 2.44 \text{ (m), } 2.01 \text{–} 1.93 \text{ (m), } 1.93 \text{–} 1.81 \text{ (m), } 1.76 \text{–} 1.66 \text{ (m), } 1.64 \text{–} 1.48 \text{ (m), } 1.44 \text{ (s), } 1.41 \text{ (s), } 1.02 \text{ (s), } 1.01 \text{ (s), (1.75:1 ratio of major to minor rotamer); Major Rotamer} ¹H NMR (600 MHz, CDCl\textsubscript{3}) \(\delta 7.35 \text{–} 7.31 \text{ (m, } 1\text{H), } 7.17 \text{–} 7.06 \text{ (m, } 3\text{H), } 7.01 \text{–} 6.97 \text{ (m, } 2\text{H), } 6.64 \text{ (dd, } J = 8.3, 2.8 \text{ Hz, } 1\text{H), } 6.61 \text{–} 6.55 \text{ (m, } 1\text{H), } 4.65 \text{ (s, } 1\text{H), } 3.80 \text{ (s, } 3\text{H), } 3.74 \text{ (d, } J = 14.1 \text{ Hz, } 1\text{H), } 3.35 \text{–} 3.24 \text{ (m, } 2\text{H), } 2.86 \text{–} 2.77 \text{ (m, } 2\text{H), } 2.55 \text{–} 2.44 \text{ (m, } 1\text{H), } 2.01 \text{–} 1.93 \text{ (m, } 2\text{H), } 1.93 \text{–} 1.81 \text{ (m, } 3\text{H), } 1.76 \text{–} 1.66 \text{ (m, } 1\text{H), } 1.64 \text{–} 1.48 \text{ (m, } 5\text{H), } 1.44 \text{ (s, } 9\text{H), } 1.02 \text{ (s, } 3\text{H}); Minor Rotamer} ¹H NMR (600 MHz, CDCl\textsubscript{3}) \(\delta 7.17 \text{–} 7.06 \text{ (m, } 4\text{H), } 6.96 \text{–} 6.92 \text{ (m, } 2\text{H), } 6.61 \text{–} 6.55 \text{ (m, } 2\text{H), } 4.94 \text{ (s, } 1\text{H), } 3.79 \text{ (s, } 3\text{H), } 3.65 \text{ (d, } J = 13.9 \text{ Hz, } 1\text{H), } 3.35 \text{–} 3.24 \text{ (m, } 2\text{H), } 2.86 \text{–} 2.77 \text{ (m, } 2\text{H), } 2.01 \text{–} 1.93 \text{ (m, } 2\text{H), } 1.93 \text{–} 1.81 \text{ (m, } 3\text{H), } 1.76 \text{–} 1.66 \text{ (m, } 1\text{H), } 1.64 \text{–} 1.48 \text{ (m, } 5\text{H), } 2.55 \text{–} 2.44 \text{ (m, } 1\text{H), } 1.41 \text{ (s, } 9\text{H), } 1.01 \text{ (s, } 3\text{H); } ¹³C NMR (151 MHz, CDCl\textsubscript{3}) \(\delta 158.6, 158.5, 155.0, 154.7, 141.5, 136.4, 134.5, 134.0, 132.7, 132.6, 129.0, 128.9, 128.8, 128.7, 125.8, 125.6, 117.3, 117.0, 110.2, 110.1, 80.0, 79.6, 64.8, 63.1, 55.2, 55.2, 52.9, 52.5, 46.7, 46.1, 44.9, 44.7, 39.6, 39.5, 39.3, 38.9, 38.7, 38.6, 34.6, 34.4, 33.6, 33.4, 28.8, 28.8, 27.5, 26.6, 26.5, 23.3, 23.2, 21.2, 21.2; IR (NaCl, thin film) \(\nu_{\text{max}}\) 2930, 2871, 1738, 1684, 1606 cm\textsuperscript{-1}; HRMS (ESI) calc'd for [C\textsubscript{31}H\textsubscript{42}NO\textsubscript{3}S] ([M+H]\textsuperscript{+}): m/z 508.2880, found 508.2899.

(1R,4aR,11aR)-tert-butyl 8-methoxy-1-methyl-4a-vinyl-2,3,4,4a,5,10,11,11a-octahydro-1H-5,1-(epiminomethano)dibenzo[a,d][7]annulene-12-carboxylate (3.6 where \(R = \text{Boc}\)). Scandium(III) triflate (71 mg, 0.14 mmol, 0.2 equiv) was added to a stirred solution of hydrogen peroxide (30 wt%, 0.82 mL, 7.2 mmol, 10 equiv) in 9:1 CH\textsubscript{2}Cl\textsubscript{2}:MeOH (35 mL, 0.02 M). After stirring the mixture at room temperature for 5 min,
sulfide 3.xii (370 mg, 0.72 mmol, 1 equiv) in 9:1 CH₂Cl₂:MeOH (35 mL, 0.02 M) was added. After 18 h, the reaction mixture was poured into water (100 mL) and extracted with CH₂Cl₂ (3 × 100 mL). The combined organics were washed with brine (1 × 100 mL), dried over MgSO₄ and concentrated to give sulfoxide 3.35 that was immediately used without further purification. R₁ 0.07 (2:1 hexanes: EtOAc, UV and p-anisaldehyde stain).

Crude sulfoxide 3.35 was dried by azeotrope with benzene (1 × 20 mL) and transferred to two separate microwave vials with freshly distilled toluene (29 mL, 0.025 M). The solutions were sparged with argon for 2 h and then heated in the microwave to 180 °C for 2 h. The reaction mixtures were recombined and concentrated. Flash chromatography (9:1 hexanes: EtOAc) provided 190 mg (0.47 mmol, 65% yield over 2 steps) of vinyl compound 3.6 (where R = Boc) as a clear oil. R₁ 0.62 (2:1 hexanes: EtOAc, UV and p-anisaldehyde stain); ¹H NMR (500 MHz, CDCl₃) δ 7.31 (d, J = 8.3 Hz), 7.10 (d, J = 8.1 Hz), 6.62 (dd, J = 8.3, 2.7 Hz), 6.61 – 6.55 (m), 5.67 – 5.56 (m), 5.03 (s), 4.94 – 4.83 (m), 4.74 (s), 3.78 (s), 3.76 (s), 3.75 (s), 3.74 (s), 3.66 (d, J = 13.8 Hz), 3.40 – 3.27 (m), 2.58 – 2.46 (m), 2.17 (tt, J = 14.8, 3.5 Hz), 2.07 – 1.97 (m), 1.96 – 1.80 (m), 1.68 – 1.52 (m), 1.43 (s), 1.42 (s), 1.07 (s), 1.05 (s), (1.88:1 ratio of major to minor rotamer); Major Rotamer ¹H NMR (500 MHz, CDCl₃) δ 7.10 (d, J = 8.1 Hz, 1H), 6.61 – 6.55 (m, 2H), (dd, J = 17.8, 11.3 Hz, 1H), 4.94 – 4.85 (m, 2H), 4.74 (s, 1H), 3.76 (d, J = 19.7 Hz, 1H), 3.76 (s, 3H), 3.40 – 3.27 (m, 2H), 2.58 – 2.46 (m, 1H), 2.17 (tt, J = 14.8, 3.5 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.96 – 1.80 (m, 2H), 1.68 – 1.52 (m, 5H), 1.43 (s, 9H), 1.07 (s, 3H); Minor Rotamer ¹H NMR (500 MHz, CDCl₃) δ 7.31 (d, J = 8.3 Hz, 1H), 6.62 (dd, J = 8.3, 2.7 Hz, 1H), 6.61 – 6.55 (m, 1H), 5.63 (dd, J = 17.9, 11.3 Hz, 1H), 5.03 (s, 1H), 4.91 – 4.85 (m, 2H), 3.75 (s, 3H), 3.66 (d, J = 13.8 Hz, 1H), 3.40 – 3.27 (m, 2H), 2.58 – 2.46 (m, 1H), 2.17 (tt, J = 14.8, 3.5 Hz, 1H), 2.07 – 1.97 (m, 1H), 1.96 – 1.80 (m, 2H), 1.68 – 1.52 (m, 5H), 1.42 (s, 9H), 1.05 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 158.4, 158.2, 155.0, 154.5, 145.5, 145.4, 141.4, 141.1, 134.9, 134.3, 133.7, 133.6, 116.8, 116.6, 112.9, 112.7, 110.0, 109.9, 79.9, 79.5, 64.8, 63.4, 55.1, 55.1, 52.7, 52.3, 46.5, 46.4, 44.9, 44.7, 42.1, 42.1, 42.0, 42.0, 34.5, 34.4, 33.7, 33.5, 28.7, 26.6, 26.4, 24.2, 24.1, 21.4, 21.4; IR (NaCl, thin film) νmax 2931, 1684, 1607 cm⁻¹; HRMS (ESI) calc’d for [C₂₅H₃₆NO₃] ([M+H]⁺): m/z 398.2690, found 398.2705.

(1R,4aR,11aR)-8-methoxy-1-methyl-4a-vinyl-2,3,4,4a,5,10,11,11a-octahydro-1H-5,1-(epiminomethano) dibenzo[a,d][7]annulene (3.6 where R = H). Trifluoroacetic acid (0.65 mL, 0.2 M) was added to a stirred solution of Boc-protected amine 3.6 (where R = Boc, 60 mg, 0.13 mmol, 1 equiv) in CH₂Cl₂ (0.65 mL, 0.2 M) at room temperature. After 30 minutes, 1 N NaOH was slowly added (5 mL) and the mixture was extracted with CH₂Cl₂ (3 × 5 mL). The combined organics were washed with brine (1 × 5 mL), dried over MgSO₄ and concentrated. The crude amine was purified by flash chromatography (9:1 CH₂Cl₂:MeOH, 1% NH₄OH) to provide 40 mg (0.13 mmol, 100%
yield) of the free amine (3.6 where R = H) as a clear oil. Rf 0.07 (9:1 CH2Cl2:MeOH 1% NH4OH, UV and p-anisaldehyde stain); 1H NMR (500 MHz, CDCl3) δ 6.99 – 6.95 (m, 1H), 6.65 – 6.60 (m, 2H), 5.68 (dd, J = 17.8, 11.3 Hz, 1H), 4.85 (dd, J = 8.4, 1.3 Hz, 1H), 4.82 (dd, J = 14.9, 1.3 Hz, 1H), 3.93 (d, J = 1.1 Hz, 1H), 3.76 (s, 3H), 3.49 (dd, J = 17.4, 14.8, 3.8 Hz, 1H), 3.37 (dd, J = 12.2, 2.9 Hz, 1H), 2.73 (d, J = 12.3 Hz, 1H), 2.70 – 2.57 (m, 2H), 2.23 (tt, J = 14.7, 3.7 Hz, 1H), 2.02 (dq, J = 14.9, 4.3 Hz, 1H), 1.87 – 1.79 (m, 1H), 1.79 – 1.59 (m, 5H), 1.55 – 1.46 (m, 1H), 0.97 (s, 3H); 13C NMR (151 MHz, CDCl3) δ 158.3, 147.1, 141.4, 132.9, 117.4, 112.5, 110.9, 67.5, 55.2, 53.0, 47.1, 44.6, 42.4, 42.1, 35.6, 34.1, 26.9, 24.7, 23.3; IR (NaCl, thin film) νmax 3364, 2930, 1607, 1505 cm⁻¹; HRMS (ESI) calc’d for [C20H28NO] ([M+H]+): m/z 298.2165, found 298.2163.

General Conditions for Birch Reduction. Anhydrous NH3 (0.05 M) was condensed in a Schlenk tube at -78 °C. The methoxy arene (1 equiv) in a 1:1 mixture of iPrOH:THF (0.085 M) was added to the tube and the mixture was stirred for 15 min. Sodium metal (35 equiv) was then added and the solution turned dark blue. After 4 h, the reaction was quenched with solid NH4Cl (10 mg per mg of sodium) and then warmed to room temperature and poured into saturated aq. NaHCO3. The aqueous phase was extracted with CH2Cl2 (3×), dried over MgSO4, and concentrated. The crude enol ether was then immediately carried onto the acid hydrolysis which lead to a mixture of conjugated and nonconjugated enone products (based on crude 1H NMR) and as well as decomposition. Instability of the products prevented further isolation/purification and characterization.

(1R,4aR,11aR)-tert-butyl 8-hydroxy-1-methyl-4a-vinyl-2,3,4,4a,5,10,11,11a-octahydro-1H-5,1-(epiminomethano)dibenzo[a,d][7]annulene-12-carboxylate (3.47). Sodium hydride (60 wt% dispersion in mineral oil, 88 mg, 2.2 mmol, 10 equiv) was added to a microwave vial, washed with hexanes (1 × 1 mL) and dried under vacuum. Dry DMF (5.5 mL, 0.04 M) was added and the vial was cooled to 0 °C. Ethanethiol (0.16 mL, 2.2 mmol, 10 equiv) was added drop wise and the solution was warmed to room temperature and stirred until the solution turned clear (~5 min) at which time, 3.6 (where R = Boc, 88 mg, 0.22 mmol, 1 equiv) in dry DMF (5.5 mL, 0.04 M) was added. The reaction mixture was heated in the microwave to 180 °C for 15 min. The mixture was diluted with EtOAc (50 mL), washed with water (3 × 15 mL) and brine (1 × 10 mL), dried over MgSO4, and concentrated. The crude oil was purified by flash
chromatography (4:1 hexanes: EtOAc) to give 65 mg (0.17 mmol, 77% yield) of 3.47 as a clear oil. Rf 0.47 (2:1 hexanes: EtOAc, UV and p-anisaldehyde stain); 1H NMR (600 MHz, CDCl3) δ 7.04 (t, J = 8.3 Hz), 6.56 (dd, J = 8.2, 2.5 Hz), 6.53 (d, J = 2.6 Hz), 6.20 (dd, J = 8.3, 2.6 Hz), 6.25 – 5.94 (m), 5.62 (dd, J = 23.1, 17.8, 11.3 Hz), 4.98 (s), 4.91 (d, J = 17.8 Hz), 4.89 – 4.82 (m), 4.73 (s), 3.72 (d, J = 13.8 Hz), 3.67 (d, J = 13.9 Hz), 3.37 (dd, J = 13.9, 2.6 Hz), 3.34 (dd, J = 13.8, 2.6 Hz), 3.32 – 3.22 (m), 2.49 (dt, J = 16.3, 4.0 Hz), 2.41 (dt, J = 16.3, 4.0 Hz), 2.22 – 2.10 (m), 2.02 – 1.94 (m), 1.94 – 1.79 (m), 1.68 – 1.52 (m), 1.52 – 1.46 (m), 1.43 (d, J = 3.2 Hz), 1.04 (d, J = 2.2 Hz), (1.88:1 ratio of major to minor rotamer); Major Rotamer 1H NMR (600 MHz, CDCl3) δ 7.04 (t, J = 8.3 Hz, 1H), 6.56 (dd, J = 8.2, 2.5 Hz, 1H), 6.53 (d, J = 2.6 Hz, 1H), 6.28 – 5.96 (bs, 1H), 5.65 (dd, J = 17.8, 11.3 Hz, 1H), 4.91 (d, J = 17.8 Hz, 1H), 4.87 (d, J = 11.3 Hz, 1H), 4.73 (s, 1H), 3.72 (d, J = 13.8 Hz, 1H), 3.34 (dd, J = 13.8, 2.6 Hz, 1H), δ 3.32 – 3.22 (m, 1H), 2.41 (dt, J = 16.3, 4.0 Hz, 1H), 2.22 – 2.09 (m, 1H), 2.03 – 1.95 (m, 1H), 1.93 – 1.79 (m, 2H), 1.67 – 1.52 (m, 5H), 1.43 (s, J = 3.2 Hz, 9H), 1.04 (d, J = 2.2 Hz, 3H); Minor Rotamer 1H NMR (600 MHz, CDCl3) δ 7.04 (t, J = 8.3 Hz, 1H), 6.53 (d, J = 2.6 Hz, 1H), 6.28 – 5.96 (bs, 1H), 6.20 (dd, J = 8.3, 2.6 Hz, 1H), 5.61 (dd, J = 17.8, 11.3 Hz, 1H), 4.98 (s, 1H), 4.86 (d, J = 17.8 Hz, 1H), 4.84 (d, J = 11.3 Hz, 1H), 3.67 (d, J = 13.9 Hz, 1H), 3.37 (dd, J = 13.9, 2.6 Hz, 1H), 3.32 – 3.22 (m, 1H), 2.49 (dt, J = 16.3, 4.0 Hz, 1H), 2.22 – 2.09 (m, 1H), 2.03 – 1.95 (m, 1H), 1.93 – 1.79 (m, 2H), 1.67 – 1.52 (m, 4H), 1.51 – 1.46 (m, 1H), 1.44 (s, J = 3.2 Hz, 9H), 1.04 (d, J = 2.2 Hz, 3H); 13C NMR (151 MHz, CDCl3) δ 155.4, 154.9, 154.9, 154.7, 145.5, 145.5, 141.6, 141.2, 135.1, 134.5, 133.3, 118.2, 117.8, 112.9, 112.7, 112.4, 112.0, 80.4, 79.9, 65.0, 63.6, 52.7, 52.4, 46.6, 46.4, 44.9, 44.8, 42.1, 42.1, 42.0, 41.9, 34.4, 34.2, 33.7, 33.5, 28.9, 28.8, 26.6, 26.4, 24.2, 24.0, 21.5, 21.4; IR (NaCl, thin film) vmax 3338, 2931, 2871, 1655, 1607 cm⁻¹; HRMS (ESI) calc'd for [C24H34NO3] ([M+H]+): m/z 384.2533, found 384.2543.

(4R,4aR,10aR,13bR)-4-methyl-13-b-vinyl-2,3,4,4a,5,6-hexahydro-1H-4,13-methanodibenzo[2,3:6,7]cyclohepta[1,2-d]oxazole-8,12(13aH,13bH)-dione (3.49). A solution of phenol 3.47 (65 mg, 0.17 mmol, 1 equiv) in a 1:1 mixture of acetonitrile:2,2,2-trifluoroethanol (2.8 mL, 0.06 M) was added drop wise over 20 minutes to a stirred solution of bis(trifluoroacetoxy)iodobenzene (PIFA) (110 mg, 0.26 mmol, 1.5 equiv) and NaHCO3 (140 mg, 1.7 mmol, 10 equiv) in acetonitrile:2,2,2-trifluoroethanol (2.8 mL, 0.06 M) at 0 °C and stirred for an additional 1 h. The reaction mixture was poured into brine (10 mL), extracted with EtOAc (3 x 20 mL), dried over MgSO4, and concentrated. The crude product was purified by flash chromatography (4:1 hexanes: EtOAc to 1:1 hexanes: EtOAc) to give 65 mg (0.17 mmol, 82% yield) of quinol 3.49 as a clear oil. Rf 0.20 (2:1 hexanes: EtOAc, UV and p-anisaldehyde stain); 1H NMR (500 MHz, CDCl3) δ 6.84 (d, J = 10.0 Hz, 1H), 6.32 (dd, J = 10.0, 1.9 Hz, 1H), 6.06 – 6.02 (m, 1H), 5.86 (dd, J = 17.6, 11.1 Hz, 1H), 5.04 (d, J = 17.5 Hz, 1H), 4.94 (d, J = 11.1 Hz, 1H), 3.98 (s, 1H),
3.23 (s, 2H), 2.44 (dt, $J = 13.7, 3.9$ Hz, 1H), 2.21 – 2.11 (m, 2H), 2.12 – 2.01 (m, 1H), 1.79 (dt, $J = 13.4, 2.8$ Hz, 1H), 1.71 (dd, $J = 5.5, 2.0$ Hz, 1H), 1.68 – 1.55 (m, 2H), 1.54 – 1.46 (m, 1H), 1.34 (ddt, $J = 25.5, 13.0, 5.4$ Hz, 2H), 1.12 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 185.3, 158.6, 156.3, 145.4, 137.8, 131.7, 129.9, 116.0, 80.1, 65.3, 51.1, 45.1, 44.5, 44.0, 41.5, 33.7, 31.9, 28.5, 25.0, 19.6; IR (NaCl, thin film) $\nu_{\text{max}}$ 2928, 2871, 1756, 1672, 1636 cm$^{-1}$; HRMS (ESI) calc’d for [C$_{20}$H$_{24}$NO$_3$] ([M+H]$^+$): m/z 36.1751, found 326.1758.

(4R,4aR,10aR,13bR)-13b-Allyl-4-methyl-2,3,4,4a,5,6-hexahydro-1H-4,13-methanodibenzo[2,3,6:7]cyclohepta[1,2-d]oxazole-8,12(13aH,13bH)-dione (3.50). Sodium hydride (60 wt% dispersion in mineral oil, 52 mg, 1.3 mmol, 10 equiv) was added to a microwave vial, washed with hexanes (1 × 1 mL) and dried under vacuum. Dry DMF (2.5 mL, 0.05 M) was added and the vial was cooled to 0 °C. Ethanethiol (0.10 mL, 1.3 mmol, 10 equiv) was added dropwise and the solution was warmed to room temperature and stirred until the solution turned clear (~5 min) at which time, 3.22 (54 mg, 0.13 mmol, 1 equiv) in dry DMF (2.5 mL, 0.05 mmol) was added. The reaction mixture was heated in the microwave to 180 °C for 15 min. The mixture was diluted with EtOAc (50 mL), washed with water (3 × 15 mL) and brine (1 × 10 mL), dried over MgSO$_4$, and concentrated. The crude oil was purified by flash chromatography (4:1 hexanes: EtOAc) to give 42 mg (0.11 mmol, 85% yield) of 3.50 as a clear oil. R$_f$ 0.47 (2:1 hexanes: EtOAc, p-anisaldehyde stain); $^1$H NMR (500 MHz, CDCl$_3$, mixture of 2 rotamers) δ 7.00 (dd, $J = 10.3, 7.9$ Hz, 6.92 (s), 6.70 (s), 6.59 (d, $J = 2.4$ Hz), 6.57 (s), 6.15 (dd, $J = 8.2, 2.6$ Hz), 5.71 (dp, $J = 16.5, 8.9, 8.2$ Hz), 5.00 (dd, $J = 10.3, 2.4$ Hz), 4.95 (dd, $J = 9.9, 2.5$ Hz), 4.87 (d, $J = 16.9$ Hz), 4.83 – 4.77 (m), 4.58 (s), 3.70 (d, $J = 13.9$ Hz), 3.66 (d, $J = 13.9$ Hz), 3.35 (ddd, $J = 19.3, 13.8, 2.6$ Hz), 3.30 – 3.19 (m), 2.51 (dt, $J = 16.1, 4.0$ Hz), 2.41 (dt, $J = 16.3, 3.9$ Hz), 2.00 (dt, $J = 11.4, 3.8$ Hz), 1.82 (ddt, $J = 30.2, 13.9, 7.4$ Hz), 1.72 – 1.60 (m), 1.59 – 1.47 (m), 1.43 (d, $J = 2.7$ Hz), 1.37 – 1.28 (m), 1.26 (q, $J = 5.3, 3.6$ Hz), 1.02 (s), 1.00 (s). Major Rotamer $^1$H NMR (500 MHz, CDCl$_3$) δ 7.00 (d, $J = 10.3$ Hz, 1H), 6.70 (s, 1H), 6.57 (s, 2H) 5.71 (dp, $J = 16.5, 8.9, 8.2$ Hz, 1H), 5.00 (dd, $J = 10.3, 2.4$ Hz, 1H), 4.87 (d, $J = 16.9$ Hz, 1H), 4.58 (s, 1H), 3.70 (d, $J = 13.9$ Hz, 1H), 3.35 (ddd, $J = 19.3, 13.8, 2.6$ Hz, 1H), 3.30 – 3.19 (m, 1H), 2.41 (dt, $J = 16.3, 3.9$ Hz, 1H), 2.00 (dt, $J = 11.4, 3.8$ Hz, 2H), 1.82 (ddt, $J = 30.2, 13.9, 7.4$ Hz, 4H), 1.72 – 1.60 (m, 1H), 1.59 – 1.47 (m, 3H), 1.43 (s, 9H), 1.37 – 1.28 (m, 1H), 1.00 (s, 3H); Minor Rotamer $^1$H NMR (500 MHz, CDCl$_3$) δ 7.00 (d, $J = 7.9$ Hz, 1H), 6.92 (s, 1H), 6.59 (d, $J = 2.4$ Hz, 1H), 6.15 (dd, $J = 8.2, 2.6$ Hz, 1H), 5.71 (dp, $J = 16.5, 8.9, 8.2$ Hz, 1H), 4.95 (dd, $J = 9.9, 2.5$ Hz, 1H), 4.83 – 4.77 (m, 2H), 3.66 (d, $J = 13.9$ Hz, 1H), 3.35 (ddd, $J = 19.3, 13.8, 2.6$ Hz, 1H), 3.30 – 3.19 (m, 1H), 2.51 (dt, $J = 16.1, 4.0$ Hz, 1H), 2.00 (dt, $J = 11.4, 3.8$ Hz, 2H), 1.82 (ddt, $J = 30.2, 13.9, 7.4$ Hz, 3H), 1.72 – 1.60 (m, 2H), 1.59 – 1.47 (m, 3H), 1.43 (s, 9H), 1.26 (q, $J = 5.3, 3.6$ Hz, 1H), 1.02 (s, 3H); $^{13}$C
NMR (126 MHz, CDCl$_3$) $\delta$ 155.7, 155.2, 155.1, 154.8, 141.4, 141.2, 135.9, 134.3, 134.0, 132.5, 131.9, 118.3, 118.0, 117.9, 112.4, 112.0, 80.5, 78.0, 65.6, 64.3, 53.0, 52.8, 45.6, 45.3, 43.8, 43.8, 39.7, 39.2, 38.5, 38.4, 34.3, 33.7, 33.5, 28.8, 26.6, 26.4, 23.4, 21.3, 21.2; IR (NaCl, thin film) $\nu_{\text{max}}$ 3339, 2928, 1651, 1583 cm$^{-1}$; HRMS (ESI) calc’d for [C$_{25}$H$_{35}$NO$_3$Na] ([M+Na]$^+$): m/z 420.2509, found 420.2519.

(4R,4aR,10aR,13bR)-13b-allyl-4-methyl-2,3,4,4a,5,6-hexahydro-1H-4,13-methanodibenzo[2,3,6,7]cyclohepta[1,2-d]oxazole-8,12(13aH,13bH)-dione (3.51). A solution of phenol 3.51 (20 mg, 0.050 mmol, 1 equiv) in a 1:1 mixture of acetonitrile:2,2,2-trifluoroethanol (2.5 mL, 0.02 M) was added dropwise over 20 minutes to a stirred solution of bis(trifluoroacetoxy)iodobenzene (PIFA) (32 mg, 0.075 mmol, 1.5 equiv) and NaHCO$_3$ (21 mg, 0.25 mmol, 5 equiv) in acetonitrile:2,2,2-trifluoroethanol (2.5 mL, 0.02 M) at 0°C and stirred for an additional 1 h. The reaction mixture was poured into brine (10 mL), extracted with EtOAc (3 x 20 mL), dried over MgSO$_4$, and concentrated. The crude product was purified by flash chromatography (4:1 hexanes:EtOAc) to give 9.1 mg (0.027 mmol, 54% yield) of quinol 3.51 as a clear oil. R$_f$ 0.20 (2:1 hexanes:EtOAc, UV and KMnO$_4$ stain); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.85 (d, $J = 10.0$ Hz, 1H), 6.36 (dd, $J = 10.0$, 1.9 Hz, 1H), 6.11 (s, 1H), 5.62 (ddt, $J = 17.1$, 10.1, 7.2 Hz, 1H), 5.08 (dd, $J = 10.1$, 1.9 Hz, 1H), 4.97 (dd, $J = 16.9$, 2.1 Hz, 1H), 3.92 (s, 1H), 3.27 – 3.14 (m, 2H), 2.50 (dt, $J = 14.5$, 4.5 Hz, 1H), 2.42 (dd, $J = 13.8$, 6.9 Hz, 1H), 2.28 – 2.15 (m, 2H), 1.84 (dd, $J = 13.9$, 7.6 Hz, 1H), 1.76 (tt, $J = 14.4$, 3.9 Hz, 1H), 1.68 – 1.55 (m, 1H), 1.46 (dq, $J = 9.6$, 2.9, 2.5 Hz, 3H), 1.40 – 1.32 (m, 1H), 1.27 – 1.15 (m, 2H), 1.07 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 185.2, 158.7, 157.8, 144.8, 132.1, 131.9, 129.1, 119.7, 80.1, 66.9, 51.4, 44.5, 44.0, 40.6, 38.6, 38.4, 33.5, 32.5, 28.2, 25.8, 19.4; IR (NaCl, thin film) $\nu_{\text{max}}$ 2926, 1756, 1671 cm$^{-1}$; HRMS (ESI) calc’d for [C$_{21}$H$_{26}$NO$_3$] ([M+H]$^+$): m/z 340.1907, found 340.1914. Alternative procedure: A solution of phenol 3.50 (160 mg, 0.40 mmol, 1 equiv) in a 1:1 mixture of acetonitrile:2,2,2-trifluoroethanol (8 mL, 0.05 M) was added dropwise over 5 minutes to a stirred solution of iodosobenzene (200 mg, 0.88 mmol, 2.2 equiv) in acetonitrile:2,2,2-trifluoroethanol (8 mL, 0.05 M) at room temperature and stirred for an additional 30 min. The cloudy mixture was filtered through a pad of Celite$^\text{TM}$, washed with EtOAc (20 mL), and concentrated. Flash chromatography (4:1 hexanes:EtOAc) gave 73 mg (0.22 mmol, 55% yield) of quinol 3.51 as a clear oil.
2-((4R,4aR,10aR,13bR)-4-Methyl-8,12-dioxo-2,3,4,4a,5,6,8,12,13a,13b-decahydro-1H-4,13-methanodibenzo[2,3:6,7]cyclohepta[1,2-d]oxazol-13-yl)acetaldehyde (3.52). 4-Methylmorpholine N-oxide (28 mg, 0.24 mmol, 2 equiv) and OsO\(_4\) (2.5 wt% in t-butanol, 15 \(\mu\)L, 0.0012 mmol, 0.01 equiv) was added to a stirred solution of 3.51 (41 mg, 0.12 mmol, 1 equiv) in a 2:1 mixture of THF:H\(_2\)O (4 mL, 0.03 M). The mixture was stirred at room temperature for 24 h at which time the reaction mixture was diluted with EtOAc (20 mL), washed with water (1 \(\times\) 10 mL) and brine (1 \(\times\) 5 mL), dried over MgSO\(_4\), and concentrated. The resulting diol was filtered through a pad of silica with 9:1 CH\(_2\)Cl\(_2\):MeOH (10 mL), concentrated, and used without any further purification. \(R_f\) 0.05 (100% EtOAc, UV and KMnO\(_4\) stain).

\(\text{NaIO}_4\) on silica (240 mg, 2.0 g/mmol diol) was added to a stirred solution of the diol (45 mg, 0.12 mmol, 1 equiv) in CH\(_2\)Cl\(_2\) (1.2 mL, 0.1 M). After 30 min the mixture was filtered through a pad of Celite\textsuperscript{TM}, washed with CH\(_2\)Cl\(_2\) (10 mL), and concentrated. The crude aldehyde was purified by flash chromatography (1:1 hexanes: EtOAc) to give 25 mg (0.070 mmol, 58% yield over 2 steps) of aldehyde 3.52 as a clear oil. \(R_f\) 0.14 (1:1 hexanes: EtOAc, UV and KMnO\(_4\) stain); \(\text{^1H NMR} (500 MHz, CDCl}_3) \delta 9.63 (t, \(J = 1.5\) Hz, 1H), 6.81 (d, \(J = 10.0\) Hz, 1H), 6.33 (dd, \(J = 10.1, 1.8\) Hz, 1H), 6.14 (d, \(J = 2.0\) Hz, 1H), 4.20 (s, 1H), 3.29 – 3.18 (m, 2H), 2.67 – 2.55 (m, 2H), 2.55 – 2.48 (m, 1H), 2.34 – 2.19 (m, 2H), 1.99 (dq, \(J = 13.1, 2.7\) Hz, 1H), 1.78 (ddt, \(J = 14.4, 12.6, 3.7\) Hz, 1H), 1.72 – 1.57 (m, 4H), 1.56 – 1.42 (m, 2H), 1.35 – 1.22 (m, 2H), 1.11 (s, 3H); \(\text{^13C NMR} (151 MHz, CDCl}_3) \delta 199.7, 184.8, 158.3, 156.9, 145.4, 131.8, 129.7, 79.8, 65.3, 51.2, 48.9, 46.3, 43.9, 40.7, 38.6, 33.5, 32.3, 28.4, 26.1, 19.4; \text{IR (NaCl, thin film)} \nu_{\text{max}} 2929, 2873, 1755, 1719, 1671, 1636 cm\(^{-1}\); \text{HRMS (ESI)} calc’d for [C\(_{20}\)H\(_{24}\)NO\(_4\)] \([\text{M+H}^+]\): m/z 342.1700, found 342.1708.

\((4R,4aR,6aS,10aR,13bS,14S)-4-Methyl-8,12-dioxo-2,3,4,4a,5,6,7,8,12,13a-decahydro-1H-4,13:6a,13b-dimethanodibenzo[2,3:6,7]cyclohepta[1,2-d]oxazole-14-carbaldehyde (3.53). \text{Silica (86 mg, 10 mg per 1 mg 3.52) was added to a stirred solution of aldehyde 3.52 (8.6 mg, 0.025 mmol, 1 equiv) in CH\(_2\)Cl\(_2\) (0.5 mL, 0.05 M). After 36 h, the mixture was filtered through a pad of Celite\textsuperscript{TM}, washed with EtOAc (20 mL), and concentrated to give 6.9 mg (0.020 mmol, 80% yield) of 3.53 as 2.5:1 mixture
of epimers alpha to the aldehyde (based in \(^1\)H NMR) as a clear oil that was used without further purification. \(R_t\) 0.16 (major), 0.15 (minor) (1:1 hexanes: EtOAc, UV and KMnO\(_4\) stain); **Major Epimer:** \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 9.88 (d, \(J = 1.7\) Hz, 1H), 6.59 (d, \(J = 10.1\) Hz, 1H), 6.19 (d, \(J = 10.0\) Hz, 1H), 3.66 (d, \(J = 14.2\) Hz, 1H), 3.63 (s, 1H), 3.00 (d, \(J = 14.1\) Hz, 1H), 2.60 (d, \(J = 16.8\) Hz, 1H), 2.58 (d, \(J = 16.8\) Hz, 1H), 2.27 (t, \(J = 2.1\) Hz, 1H), 2.10 – 2.03 (m, 1H), 1.89 – 1.81 (m, 3H), 1.81 – 1.77 (m, 1H), 1.74 (ddddd, \(J = 14.7, 12.3, 6.3, 3.2\) Hz, 2H), 1.68 (dq, \(J = 13.8, 4.6\) Hz, 1H), 1.48 – 1.39 (m, 3H), 1.03 (s, 3H). **Minor Epimer:** \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\) 9.62 (d, \(J = 5.3\) Hz, 1H), 6.73 (d, \(J = 10.1\) Hz, 1H), 6.21 (d, \(J = 10.1\) Hz, 1H), 4.10 (s, 1H), 3.72 (d, \(J = 14.3\) Hz, 1H), 3.01 (d, \(J = 14.1\) Hz, 1H), 2.43 (d, \(J = 18.0\) Hz, 1H), 2.28 (d, \(J = 5.4\) Hz, 1H), 2.20 (dd, \(J = 14.3, 9.3\) Hz, 1H), 2.10 – 2.03 (m, 1H), 1.89 – 1.81 (m, 3H), 1.81 – 1.77 (m, 1H), 1.74 (ddddd, \(J = 14.7, 12.3, 6.3, 3.2\) Hz, 1H), 1.68 (dq, \(J = 13.8, 4.6\) Hz, 2H), 1.48 – 1.39 (m, 3H), 1.05 (s, 3H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 200.6, 196.2, 158.7, 144.9, 130.6, 81.8, 67.1, 60.4, 49.1, 47.8, 45.6, 43.4, 41.3, 40.5, 36.4, 35.6, 28.6, 27.6, 20.1, 19.9. **Minor Epimer:** \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 200.8, 195.1, 158.8, 144.4, 132.5, 82.4, 70.5, 67.9, 48.8, 46.1, 44.8, 42.7, 41.1, 36.1, 35.9, 33.2, 29.9, 27.8, 20.5, 19.8; IR (NaCl, thin film) \(\nu_{\text{max}}\) 2924, 1755, 1714 cm\(^{-1}\); HRMS (ESI) calc’d for [C\(_{20}\)H\(_{24}\)NO\(_4\)] ([M+H]+): m/z 342.1700, found 342.1710.

\[(4R,4aR,6aS,10aR,13bS,14S)-4\text{-Methyl}-8,12\text{-dioxododecahydro-1H-4,13:6a,13b-dimethanodibenzo[2,3\text{-d}]cyclohepta[1,2\text{-d}]oxazole-14-carbaldehyde} \quad (3.54)\]

Rhodium on alumina (5 wt%, 9.5 mg) was added to a solution of enone 3.53 (19 mg, 0.055 mmol, 1 equiv) in benzene (1.8 mL, 0.03 M). The flask was evacuated under vacuum and backfilled with hydrogen (3 x) and stirred vigorously under a balloon of hydrogen for 24 h. The reaction mixture was filtered through a pad of Celite\textsuperscript{TM}, washed with EtOAc (25 mL), and concentrated. The crude ketone was purified by flash chromatography (1:1 hexanes: EtOAc) to obtain 10 mg (0.030 mmol, 55% yield) of ketone 3.54 as a clear oil. \(R_t\) 0.38 (100% EtOAc, KMnO\(_4\) stain); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.92 (d, \(J = 2.1\) Hz, 1H), 3.65 (d, \(J = 14.2\) Hz, 1H), 3.43 (s, 1H), 2.96 (d, \(J = 14.2\) Hz, 1H), 2.77 – 2.68 (m, 1H), 2.57 (d, \(J = 15.6\) Hz, 1H), 2.38 – 2.29 (m, 3H), 2.27 (t, \(J = 2.2\) Hz, 1H), 2.17 – 2.07 (m, 2H), 1.87 – 1.65 (m, 5H), 1.44 (ddd, \(J = 13.2, 4.1, 2.3\) Hz, 2H), 1.28 (ddddd, \(J = 26.8, 13.7, 11.7, 6.6\) Hz, 3H), 1.02 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 208.3, 201.5, 159.0, 84.4, 66.8, 62.8, 51.2, 48.8, 47.9, 46.1, 41.3, 40.3, 36.7, 35.7, 35.6, 34.4, 29.8, 27.7, 20.2, 20.0; IR (NaCl, thin film) \(\nu_{\text{max}}\) 2924, 1747 cm\(^{-1}\); HRMS (ESI) calc’d for [C\(_{20}\)H\(_{26}\)NO\(_4\)] ([M+H]+): m/z 344.1856, found 344.1861.
(4R,4aR,6aS,10aR,13bS,14S)-15-hydroxy-4-methyloctahydro-1H-6a,13b,9-(epiethane[1,1,2]triyl)-4,13-methanodibenzo[2,3:6,7]cyclohepta[1,2-d]oxazole-8,12(7H,13aH)-dione (3.55). Potassium carbonate (30 mg, 0.23 mmol, 10 equiv) was added to a stirred solution of keto-aldehyde 3.54 (8.0 mg, 0.023 mmol, 1 equiv) in 9:1 MeOH:CH₂Cl₂ (2.3 mL, 0.01 M). After 4 h at room temperature, the mixture was poured into water (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL), dried over MgSO₄, and concentrated. The crude product was purified by flash chromatography (100% EtOAc) to give 6.3 mg (0.018 mmol, 78% yield) of hetidine core 3.55 as a white solid. Slow diffusion crystallization from benzene and hexanes provided x-ray quality crystals. MP 160 °C (decomp.); Rf 0.42 (100% EtOAc, KMnO₄ stain); ¹H NMR (600 MHz, CDCl₃) δ 4.43 (d, J = 4.1 Hz, 1H), 3.56 (d, J = 14.1 Hz, 1H), 3.40 (s, 1H), 2.88 (d, J = 14.1 Hz, 1H), 2.61 – 2.54 (m, 2H), 2.46 (s, 1H), 2.23 (d, J = 14.4, 1H), 2.15 (d, J = 19.8 Hz, 1H), 2.09 (dd, J = 14.5, 5.1 Hz, 1H), 2.03 – 1.98 (m, 1H), 1.95 (dd, J = 14.7, 9.3 Hz, 1H), 1.81 – 1.71 (m, 2H), 1.66 – 1.60 (m, 2H), 1.55 (t, J = 2.2 Hz, 1H), 1.52 (s, 1H), 1.48 – 1.40 (m, 2H), 1.32 (td, J = 13.4, 4.5 Hz, 1H), 1.16 – 1.07 (m, 1H), 1.04 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 210.7, 158.6, 85.5, 70.5, 69.7, 58.0, 51.3, 48.6, 45.5, 44.9, 42.6, 41.8, 41.4, 36.5, 34.9, 31.9, 30.0, 28.1, 20.5, 20.3; IR (NaCl, thin film) νmax 3399, 2923, 1735 cm⁻¹; HRMS (ESI) calc’d for [C₂₀H₂₆NO₄] ([M+H]⁺): m/z 344.1856, found 344.1867.
11<=k<=11, -13<=l<=13.  2583 reflections were found to be symmetry independent, with an R_{int} of 0.0144. Indexing and unit cell refinement indicated a primitive, triclinic lattice. The space group was found to be P-1 (No. 2). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SIR-2008) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97.

Empirical formula C18 H21 N O2
Formula weight 283.36
Temperature 100(2) K
Wavelength 1.54178 Å
Crystal system Triclinic
Space group P-1
Unit cell dimensions
\[ a = 6.8510(4) \, \text{Å} \quad a = 72.935(2)^\circ.\]
\[ b = 9.9785(6) \, \text{Å} \quad b = 85.192(2)^\circ.\]
\[ c = 11.1538(7) \, \text{Å} \quad g = 86.501(2)^\circ.\]
Volume 725.84(8) Å³
Z 2
Density (calculated) 1.297 Mg/m³
Absorption coefficient 0.665 mm⁻¹
F(000) 304
Crystal size 0.10 x 0.10 x 0.10 mm³
Crystal color/habit colorless prism
Theta range for data collection 4.16 to 68.26°.
Index ranges -7<=h<=8, -11<=k<=11, -13<=l<=13
Reflections collected 12152
Independent reflections 2583 \[ R(int) = 0.0144 \]
Completeness to theta = 67.00° 98.3 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 0.9365 and 0.9365
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 2583 / 0 / 192
Goodness-of-fit on F² 1.062
Final R indices [I>2sigma(I)] R1 = 0.0349, wR2 = 0.0914
R indices (all data) R1 = 0.0361, wR2 = 0.0929
Largest diff. peak and hole 0.249 and -0.210 e.Å⁻³
X-Ray Crystallography Data for 3.16

A colorless prism 0.150 x 0.100 x 0.100 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of 2.0°. Data collection was 98.3% complete to 67.000° in q. A total of 21234 reflections were collected covering the indices, -10<=h<=10, -20<=k<=20, -13<=l<=10. 2613 reflections were found to be symmetry independent, with an R_int of 0.0242. Indexing and unit cell refinement indicated a C-centered, monoclinic lattice. The space group was found to be Cc (No. 9). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

**Empirical formula**  
C20 H23 N O2

**Formula weight**  
309.39

**Temperature**  
100(2) K

**Wavelength**  
1.54178 Å

**Crystal system**  
Monoclinic

**Space group**  
Cc

**Unit cell dimensions**  

\[
\begin{align*}
& a = 8.9580(4) \text{ Å} \\
& b = 17.1507(9) \text{ Å} \\
& c = 11.2099(5) \text{ Å}
\end{align*}
\]

\[ a=90°, b=107.6180(10)°, g=90°. \]

**Volume**  
1641.46(14) Å³

**Z**  
4

**Density (calculated)**  
1.252 Mg/m³

**Absorption coefficient**  
0.632 mm⁻¹
X-Ray Crystallography Data for 3.25

A colorless block 0.08 x 0.05 x 0.04 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 5 seconds per frame using a scan width of 1.0°. Data collection was 97.2% complete to 67.00° in q. A total of 35747 reflections were collected covering the indices, -12<=h<=12, -17<=k<=18, -19<=l<=19. 8318 reflections were found to be symmetry independent, with an \(R_{\text{int}} \) of 0.0241. Indexing and unit cell refinement indicated a
primitive, triclinic lattice. The space group was found to be P-1 (No. 2). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SIR-2008) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97.

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<td>Wavelength</td>
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<td>Space group</td>
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<tr>
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<td>Independent reflections</td>
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<tr>
<td>Completeness to theta = 67.00°</td>
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<td>Largest diff. peak and hole</td>
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X-Ray Crystallography Data for 3.55 (hetidine core)

X-Ray Data and Crystal Refinement for 3.55

A colorless plate 0.10 x 0.04 x 0.01 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 10 seconds per frame using a scan width of 1.0°. Data collection was 99.9% complete to 67.00° in θ. A total of 24698 reflections were collected covering the indices, -14<=h<=14, -24<=k<=23, -10<=l<=10. 3714 reflections were found to be symmetry independent, with an Rint of 0.0633. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P2(1)/c (No. 14). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SIR-2011) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97.

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<td>Wavelength</td>
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<td>Crystal system</td>
<td>Monoclinic</td>
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<tr>
<td>Space group</td>
<td>P2(1)/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
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<tr>
<td></td>
<td>b = 20.2575(5) Å, b = 105.083(2)°.</td>
</tr>
<tr>
<td></td>
<td>c = 8.7950(2) Å, g = 90°.</td>
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<tr>
<td>Z</td>
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<td>Crystal color/habit</td>
<td>colorless plate</td>
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</tbody>
</table>
Theta range for data collection 3.83 to 68.15°.
Index ranges -14 <= h <= 14, -24 <= k <= 23, -10 <= l <= 10
Reflections collected 24698
Independent reflections 3714 [R(int) = 0.0633]
Completeness to theta = 67.00° 99.9 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 0.9928 and 0.9308
Refinement method Full-matrix least-squares on F2
Data / restraints / parameters 3714 / 0 / 282
Goodness-of-fit on F2 1.008
Final R indices [I>2sigma(I)] R1 = 0.0439, wR2 = 0.0861
R indices (all data) R1 = 0.0764, wR2 = 0.0975
Largest diff. peak and hole 0.216 and -0.185 e.Å⁻³

3.12 References and Notes

1 (a) Simmons, E. M.; Sarpong, R. Org. Lett. 2006, 8, 2883.
8 A major diastereomer was obtained. However, it was not unambiguously characterized.
9 A major diastereomer was obtained. However, it was not unambiguously characterized.
13 See ref. 2.


Appendix One:
Spectra Relevant to Chapter Three

Figure A1-1. $^1$H NMR for 3.ii.

Figure A1-2. $^{13}$C NMR for 3.ii.
Figure A1-3. $^1$H NMR for 3.iii.

Figure A1-4. $^{13}$C NMR for 3.iii.
Figure A1-5. $^1$H NMR for 3.iv.

Figure A1-6. $^{13}$C NMR for 3.iv.
Figure A1-7. $^1$H NMR for 3.v.

Figure A1-8. $^{13}$C NMR for 3.v.
Figure A1-9. $^1$H NMR for 3.vi.

Figure A1-10. $^{13}$C NMR for 3.vi.
Figure A1-11. $^1$H NMR for 3.vii.

Figure A1-12. $^{13}$C NMR for 3.vii.
Figure A1-13. $^1$H NMR for mesylate.
Figure A1-14. $^1$H NMR for 3.9.

Figure A1-15. $^{13}$C NMR for 3.9.
Figure A1-16. $^1$H NMR for 3.ix.

Figure A1-17. $^{13}$C NMR for 3.ix.
Figure A1-18. $^1$H NMR for 3.x.

Figure A1-19. $^{13}$C NMR for 3.x.
Figure A1-20. $^1$H NMR for 3.xi.

Figure A1-21. $^{13}$C NMR for 3.xi.
Figure A1-22. $^1$H NMR for 3.8.

Figure A1-23. $^{13}$C NMR for 3.8.
Figure A1-24. $^1$H NMR for 3.10.

Figure A1-25. $^{13}$C NMR for 3.10.
Figure A1-26. $^1$H NMR for 3.11.

Figure A1-27. $^{13}$C NMR for 3.11.
Figure A1-28. $^1$H NMR for the indanol.

Figure A1-29. $^{13}$C NMR for the indanol.
Figure A1-30. $^1$H NMR for 3.4.

Figure A1-31. $^{13}$C NMR for 3.4.
Figure A1-32. $^1$H NMR for 3.3.

Figure A1-33. $^{13}$C NMR for 3.3.
Figure A1-34. $^1$H NMR for 3.12.

Figure A1-35. $^{13}$C NMR for 3.12.
Figure A1-36. $^1$H NMR for 3.13.

Figure A1-37. $^{13}$C NMR for 3.13.
Figure A1-38. $^1$H NMR for 3.14.

Figure A1-39. $^{13}$C NMR for 3.14.
Figure A1-40. $^1$H NMR for 3.16.

Figure A1-41. $^{13}$C NMR for 3.16.
Figure A1-42. $^1$H NMR for O-allylated product.
Figure A1-43. $^1$H NMR for 3.20.

Figure A1-44. $^{13}$C NMR for 3.20.
Figure A1-45. $^1$H NMR for 3.21.

Figure A1-46. $^{13}$C NMR for 3.21.
**Figure A1-47.** $^1$H NMR for 3.22.

**Figure A1-48.** $^{13}$C NMR for 3.22.
Figure A1-49. $^1$H NMR for 3.23.

Figure A1-50. $^{13}$C NMR for 3.23.
Figure A1-51. $^1$H NMR for 3.25.

Figure A1-52. $^{13}$C NMR for 3.25.
Figure A1-53. $^1$H NMR for 3.26.

Figure A1-54. $^{13}$C NMR for 3.26.
Figure A1-55. $^1$H NMR for 3.29.

Figure A1-56. $^{13}$C NMR for 3.29.
Figure A1-57. $^1$H NMR for 3.xii.

Figure A1-58. $^{13}$C NMR for 3.xii.
Figure A1-59. $^1$H NMR for 3.6 (where R = Boc).

Figure A1-60. $^{13}$C NMR for 3.6 (where R = Boc).
Figure A1-61. $^1$H NMR for 3.6 (where R = H).

Figure A1-62. $^{13}$C NMR for 3.6 (where R = H).
Figure A1-63. $^1$H NMR for 3.47.

Figure A1-64. $^{13}$C NMR for 3.47.
Figure A1-65. $^1$H NMR for 3.49.

Figure A1-66. $^{13}$C NMR for 3.49.
Figure A1-67. $^1$H NMR for 3.50.

Figure A1-68. $^{13}$C NMR for 3.50.
Figure A1-69. $^1$H NMR for 3.51.

Figure A1-70. $^{13}$C NMR for 3.51.
Figure A1-71. $^1$H NMR for 3.52.

Figure A1-72. $^{13}$C NMR for 3.52.
Figure A1-73. $^1$H NMR for 3.53.

Figure A1-74. $^{13}$C NMR for 3.53.
Figure A1-75. $^1$H NMR for 3.54.

Figure A1-76. $^{13}$C NMR for 3.54.
Figure A1-77. $^1$H NMR for 3.55.

Figure A1-78. $^{13}$C NMR for 3.55.
Chapter Four:  
Approach Toward the Navirines and Synthesis of the Atisine Core

4.1 Introduction

The navirines are hetidine-type C_{20}-diterpenoid alkaloids containing a hordenine side chain at C17. Very little is known about the biological properties of the navirines and to date, none of the navirines have been accessed through total synthesis efforts. This chapter will present our synthetic route toward navirine A, which resulted in the synthesis of dihydronavirine A. An interesting oxidative C-C bond cleaving reaction, which leads to the atisine core, discovered in an attempt to form the imine that is present in navirine A will also be discussed.

4.2 The Navirines: Structure, Isolation, and Biological Activity

The navirines are hetidine-type C_{20}-diterpenoid alkaloids isolated from Aconitium naviculare, a perennial herb found in the Himalayas of Nepal and Tibet. The plant has been used in Nepalese and Tibetan folk medicine as a sedative, an analgesic and a febrifuge (fever reducer). The navirines are characterized by the presence of a hordenine side chain attached to C17 (see 4.1, Figure 4-1). Navirine A (4.1) was first isolated, along with hordenine (4.4), by the Yang group in 2004. The isolation of navirines B (4.2) and C (4.3) where reported later in 2008 by Dall’Acqua and coworkers.

![Figure 4-1. Structure of the navirines.](image)

The antiproliferative activity of navirines B and C have been studied against ovarian adenocarcinoma (2008 cells) and colon adenocarcinoma (LoVo cells). Navirine B has an IC_{50} of 33 μM against the LoVo cells and an IC_{50} of 22 μM against the 2008 cells. Navirine C showed no antiproliferative activity against either of the cell lines tested.

4.3 Synthetic Approach Toward Navirine A

We propose accessing navirine A, which contains a hydroxyl group at C14, from hetidine core intermediate 4.5 (see Scheme 4-1) where the oxygenation at C14 has already been installed. This necessitated the removal of the hydroxyl group at C11, which was accomplished using a Barton-McCombie deoxygenation. From 4.6, navirine
A could be accessed through installation of the side chain and cleavage of the oxazolidinone followed by oxidation of the secondary amine to an imine.

The first step toward navirine A from 4.5 was removal of the hydroxyl group using a Barton-McCombie deoxygenation to provide 4.6 in 65% yield over two-steps (Scheme 4-1). Deprotonation of the α-position of ketone 4.6 with LiHMDS followed by treatment with Comins’ reagent (4.7) provided access to vinyl triflate 4.8. The C17 methylene could then be installed from vinyl triflate 4.8 using a Stille cross-coupling reaction with (tributylstannyl)methanol (4.9) to afford allylic alcohol 4.10.

Scheme 4-1. Functionalization of hetidine core (4.5).

With allylic alcohol 4.10 in hand, the hordenine portion could be installed using a two-step sequence involving mesylation of the hydroxyl group followed by displacement of the allylic mesylate with the sodium salt of hordenine (4.4) (Scheme 4-2). A one-step Mitsunobu displacement of the allylic hydroxyl group with hordenine was also attempted but only returned starting material. After an extensive survey of reaction conditions, the oxazolidinone of 4.11 could be cleaved with barium hydroxide at 160 °C (microwave) to provide dihydronavirine A (4.12).
Scheme 4-2. Synthesis of dihydronavirine A.

The last transformation needed to access navirine A (4.1) from dihydronavirine A (4.12) is oxidation of the secondary amine to the corresponding imine. Treatment of 4.12 with iodosobenzene, in an attempt to effect the final oxidation led exclusively to ketone-imine 4.13 where the C14-C20 bond was cleaved instead (Scheme 4-3). Attempted dehydrogenation of 4.12 to the corresponding imine with other oxidants, such as chromium trioxide and manganese dioxide, also led to keto-imine 4.13 with no trace of the desired natural product (i.e. navirine A). Treatment of 4.13 with N-iodosuccinimide in an attempt to form an N-iodo compound that could be subjected to elimination to provide the desired imine also resulted only in 4.13.

Scheme 4-3. Oxidative fragmentation of dihydronavirine A.

4.4 Synthesis of the Atisine Core

Although oxidation of dihydronavirine A did not lead to navirine A, cleavage of the C14-C20 provided access to an unnatural alkaloid containing the atisane core. Intrigued by this reactivity, we decided to explore this fragmentation further to see if the key intermediate containing the hetidine core (4.5) could also be used to access the atisine core and thus atisine-type natural products. Treatment of cyclic carbamate 4.5
with barium hydroxide cleaves the oxazolidinone ring to give amino diol \textbf{4.14} (Scheme 4-4). Subjecting \textbf{4.14} to oxidation conditions with iodosobenzene led to C14-C19 bond cleaved product \textbf{4.15} providing access to the atisine core from the hetidine core. The structure of keto-imine was unambiguously confirmed by X-ray analysis.

\begin{equation}
\textbf{4.14} \xrightarrow{\text{Ba(OH)}_2 \cdot 8\text{H}_2\text{O}} \text{EtOH:}\text{H}_2\text{O} \xrightarrow{2:1 \text{ microwave}} \text{160}^\circ\text{C, 30 min} \xrightarrow{58\%} \textbf{4.15}
\end{equation}

\begin{equation}
\textbf{4.5} \xrightarrow{\text{PhI}} \textbf{4.15} \xrightarrow{\text{NaHCO}_3} \text{CH}_2\text{Cl}_2 \xrightarrow{75\% \text{ yield}}
\end{equation}

\textbf{Scheme 4-4.} Synthesis of atisine core.

Two different reaction mechanisms can be proposed for the formation of keto-imine \textbf{4.15} from \textbf{4.14} (Scheme 4-5). The first proposed mechanism is activation of the hydroxyl group with iodosobenzene leading to \textbf{4.16}. Deprotonation of the amine followed by C-C bond cleavage and the loss of phenyl iodide would provide \textbf{4.15}. Fragmentation followed by amine deprotonation could also be considered. The other possible mechanism involves activation of the more nucleophilic amine to provide intermediate \textbf{4.17}. Deprotonation of the hydroxyl group followed by formation of the ketone group and C-C bond cleavage would also yield \textbf{4.15}.
Scheme 4-5. Proposed mechanism for C-C bond cleavage.

4.5 Conclusion

In conclusion, key intermediate 4.5 could be elaborated to dihydronavirine A (4.12) in 7 steps. Oxidation of dihydronavirine A to navirine A (4.1) was unsuccessful and instead led to C-C bond cleaved product 4.13. Further exploration of the oxidative C-C bond cleavage reaction reveals that the atisine core may be accessed from the hetidine core providing possible access to both hetidine and atisine-type diterpenoid alkaloids from 4.5.

4.6 Experimental Contributors

Amy M. Hamlin performed all experiments reported in this chapter.

4.7 Experimental Methods

General Methods and Procedures

General. All reagents were obtained from commercial chemical suppliers and used without further purification unless otherwise noted. All reactions were performed in round-bottomed flasks or microwave vials sealed with rubber septa, under an atmosphere of nitrogen, and stirred with a Teflon™-coated magnetic stir bar unless otherwise noted. Temperatures above 23 °C were controlled by an IKA® temperature modulator. Microwave reactions were performed in a Biotage® Initiator Microwave Reactor. Pre-dried tetrahydrofuran (THF), benzene, toluene, acetonitrile (MeCN), methanol (MeOH), and triethylamine (Et₃N), were degassed with argon for 60 min and passed through activated alumina columns. Dichloromethane (CH₂Cl₂) was distilled over calcium hydride before use. Reactions were monitored by thin layer
chromatography (TLC) using Silicycle Siliaplate™ glass backed TLC plates (250 μm thickness, 60 Å porosity, F-254 indicator) and visualized using UV (254 nm) and p-anisaldehyde stain or KMnO₄ stain. Volatile solvents were removed using a rotary evaporator under reduced pressure. Silica gel chromatography was performed using Sorbent Technologies 60 Å, 230 x 400 mesh silica gel (40-63 μm). ¹H NMR and ¹³C NMR were obtained in CDCl₃ on Bruker 400, 500, or 600 MHz spectrometers with ¹³C operating frequencies of 100, 126, or 151 MHz, respectively. Chemical shifts are reported in parts per million (δ) relative to residual chloroform (7.26 ppm for ¹H and 77.16 ppm for ¹³C). Data for ¹H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens). Multiplicity is designated as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), or m (multiplet). IR spectra were obtained using a Nicolet MAGNA-IR 850 spectrometer as thin films on NaCl plates and reported in frequency of absorption (cm⁻¹). High-resolution mass spectral (HRMS) data was obtained from the Mass Spectral facility at the University of California, Berkeley.

Synthetic Procedure and Physical Characterization Data.

(4R,4aR,6aS,10aR,13bS,14S)-4-methyloctahydro-1H-6a,13b,9-(epiethane[1,1,2]triyl)-4,13-methanodibenzo[2,3:6,7]cyclohepta[1,2-d]oxazole-8,12(7H,13aH)-dione (4.6). Alcohol 4.5 (66 mg, 0.19 mmol, 1 equiv) was added to a flame dried round bottom flask with THF (19 mL, 0.01 M). The flask was cooled to 0 °C and NaH (60 wt%, 76 mg, 1.9 mmol, 10 equiv) was added in one portion. The suspension was stirred at 0 °C for 1 h then CS₂ (0.75 mL, 13 mmol, 66 equiv) was added drop wise. The mixture was stirred at 0 °C for 1 h then MeI (0.38 mL, 6.1 mmol, 32 equiv) was added drop wise. The mixture was stirred at 0 °C for 1 h then quenched drop wise with water (1.0 mL) and then warmed to room temperature. The mixture was diluted with brine (30 mL) and extracted with ethyl acetate (3 x 30 mL), dried over MgSO₄, and concentrated. The resulting xanthate was purified by flash chromatography (2:1 hexanes: EtOAc) to give 59 mg (0.14 mmol, 74 % yield) of the xanthate as a white solid. MP 123 – 124°C; Rf 0.30 (1:1 hexanes: EtOAc, KMnO₄ stain); ¹H NMR (600 MHz, CDCl₃) δ 6.28 (dd, J = 4.1, 1.4 Hz, 1H), 3.56 (d, J = 14.1 Hz, 1H), 3.49 (s, 1H), 2.93 – 2.90 (m, 1H), 2.89 (d, J = 14.2 Hz, 1H), 2.64 (d, J = 20.0 Hz, 1H), 2.50 (s, 3H), 2.27 (dd, J = 14.6, 1.2 Hz, 1H), 2.22 (d, J = 19.9 Hz, 1H), 2.19 (dd, J = 14.7, 5.2 Hz, 1H), 2.05 – 2.02 (m, 1H), 1.99 (dd, J = 14.8, 9.5 Hz, 1H), 1.81 – 1.72 (m, 3H), 1.63 – 1.56 (m, 2H), 1.45 (ddt, J = 13.6, 4.2, 2.1 Hz, 1H), 1.38 (td, J = 13.5, 4.1 Hz, 1H), 1.28 (td, J = 13.5, 4.5 Hz, 1H), 1.25 – 1.23 (m, 1H), 1.14 (ddt, J = 15.5, 11.5, 9.7 Hz, 1H), 1.03 (s, 3H); ¹³C NMR (151 MHz, CDCl₃) δ 214.4, 207.5, 158.3, 85.2, 79.7, 69.5, 55.6, 48.5, 46.9 45.9, 44.9, 43.0, 41.8, 41.3, 36.5, 34.7, 32.6, 29.8, 28.0, 20.3,
The xanthate (59 mg, 0.14 mmol, 1 equiv) was added to a round bottom flask and dried via azeotrope with benzene (1 × 1 mL). AIBN (5.7 mg, 0.035 mmol, 0.25 equiv) was added followed by toluene (5.6 mL, 0.025 M). The flask was evacuated and backfilled with nitrogen (3x) and nBu3SnH (1.0 M in cyclohexane, 0.25 mL, 0.25 mmol, 1.8 equiv) was added. The mixture was heated to 95 °C under nitrogen. After 1 h, the reaction mixture was cooled to room temperature and concentrated. The crude product was purified by flash chromatography (100% hexanes then 2:1 hexanes: EtOAc to give 40 mg (0.12 mmol, 86% yield) of vinyl triflate 4.6 as a clear oil. Rf 0.59 (100% EtOAc, KMnO4 stain); 1H NMR (500 MHz, CDCl3) δ 3.56 (d, J = 14.4 Hz, 1H) 3.55 (s, 1H), 2.87 (d, J = 14.0 Hz, 1H), 2.56 (d, J = 19.7 Hz, 1H), 2.34 – 2.27 (m, 1H), 2.21 (dd, J = 14.2, 5.2 Hz, 1H), 2.08 (dt, J = 15.4, 3.3 1H), 2.05 (d, J = 19.8 Hz, 1H), 1.99 – 1.84 (m, 3H), 1.74 (dt, J = 14.8, 6.3, 5.2, 3.8 Hz, 2H), 1.63 – 1.56 (m, 1H), 1.51 – 1.40 (m, 3H), 1.25 (ddt, J = 20.5, 13.5, 4.4 Hz, 3H), 1.11 (ddt, J = 15.4, 11.5, 9.7 Hz, 1H), 1.02 (s, 3H); 13C NMR (126 MHz, CDCl3) δ 212.9, 158.7, 85.9, 69.5, 48.5, 47.6, 46.4, 44.7, 43.1, 42.6, 42.2, 41.4, 38.3, 36.5, 32.3, 30.1, 28.0, 25.6, 20.6, 20.3.; FTIR (NaCl, thin film) v<sub>max</sub> 2924, 1744 cm<sup>-1</sup>; HRMS (ESI) calc’d for [C<sub>20</sub>H<sub>26</sub>O<sub>3</sub>N] [(M+H)<sup>+</sup>]: m/z 328.1907, found 328.1911.

\[
\begin{align*}
\text{LiHMDS} & \quad \text{THF, -78 °C, 1 h} \\
\text{then Comins’ reagent (4.7)} & \quad \text{-78 °C, 3 h} \\
\text{83%} & \quad \text{yield}
\end{align*}
\]

\[
\begin{align*}
4.6 & \quad \text{LiHMDS} \\
& \quad \text{THF, -78 °C, 1 h} \\
& \quad \text{then Comins’ reagent (4.7)} \\
\text{83%} & \quad \text{yield}
\end{align*}
\]

\[
\begin{align*}
\text{4.8} & \quad \text{Comins’ Reagent (4.7)}
\end{align*}
\]

(4R,4aR,6aR,10aR,13bS,14S)-4-methyl-12-oxo-2,3,4,4a,5,6,9,10,12,13a-decahydro-1H-6a,13b,9-(epiethane[1,1,2]triyl)-4,13-methanodibenzo
[2,3:6,7]cyclohepta[1,2-d]oxazol-8-yl trifluoromethanesulfonate (4.8). Ketone 4.6
(40 mg, 0.12 mmol, 1 equiv) was added to a round bottom flask and dried via azeotrope with benzene (1 × 1 mL). THF (3.0 mL, 0.04 M) was added and the flask was cooled to -78 °C and LiHMDS (1.0 M in THF, 0.25 mL, 0.25 mmol, 2 equiv) was added. After 1 h, N-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide (4.7, 94 mg, 0.12 mmol, 2 equiv)
in THF (3.0 mL, 0.04 M) was added and the reaction mixture was stirred at -78 °C for an additional 3 h. The reaction mixture was quenched with saturated aq. NaHCO3 (3 mL) at -78 °C and warmed to room temperature. The mixture was diluted with water (20 mL) and extracted with CH2Cl2 (3 x 20 mL). The combined organics were washed with 10% aq. NaOH (1 x 20 mL) and brine (1 x 20 mL), dried over MgSO4, and concentrated. The crude vinyl triflate was purified by flash chromatography (4:1 hexanes: EtOAc) to give 46 mg (0.10 mmol, 83% yield) of vinyl triflate 4.8 as a white solid. MP 192 – 193°C; Rf 0.50 (1:1 hexanes: EtOAc, KMnO4 stain); 1H NMR (500 MHz, CDCl3) δ 5.45 (d, J = 2.8 Hz, 1H), 3.56 (d, J = 14.1 Hz, 1H), 3.51 (d, J = 1.2 Hz, 1H), 2.86 (d, J = 14.1 Hz, 1H), 2.67 (tt, J = 2.9, 1.6 Hz, 1H), 2.29 (dd, J = 14.5, 9.5 Hz, 1H), 2.13 – 2.09 (m, 1H), 2.08 – 2.03 (m, 1H), 1.92 – 1.84 (m, 1H), 1.84 – 1.76 (m, 4H), 1.74 – 1.69 (m, 1H), 1.60 (dd, J
= 9.1, 4.8 Hz, 2H), 1.42 (dt, J = 4.2, 2.5 Hz, 1H), 1.33 – 1.23 (m, 3H), 1.15 (ddt, J = 15.4, 11.2, 9.5 Hz, 1H), 1.03 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 158.7, 154.3, 119.8, 118.7 (q, J = 321, CF$_3$) 87.0, 69.4, 50.2, 50.0, 48.5, 46.5, 44.8, 41.5, 41.4, 36.5, 34.4, 34.0, 29.0, 28.3, 28.1, 20.7, 20.2; FTIR (NaCl, thin film) $\nu_{\text{max}}$ 2924, 1748, 1673 cm$^{-1}$; HRMS (ESI) calc’d for [C$_{21}$H$_{25}$O$_5$NF$_3$S] ([M+H]$^+$): m/z 460.1400, found 460.1409.

(tributylstannyl)methanol (4.9). n-BuLi (1.5 M in hexanes, 2.7 mL, 4.1 mmol, 1.1 equiv) was added dropwise to solution of diisoproplyamine (0.6 mL, 4.3 mmol, 1.15 equiv) in THF (7.4 mL, 0.5 M) at 0 °C and stirred for 1 h. Tributyltin hydride (4.1, stabilized with 0.05% BHT, 1.0 mL, 3.7 mmol, 1 equiv) was added dropwise and the yellow solution was stirred for 50 min. Paraformaldehyde (180 mg, 6.0 mmol, 1.4 equiv) was added in one portion and the slurry was warmed to room temperature and stirred until the solution turned clear and homogenous (~ 3 h). The reaction mixture was diluted with hexanes (50 mL), washed with water (1 × 50 mL) and brine (1 × 50 mL), dried over MgSO$_4$, and concentrated. Flash chromatography (19:1 hexanes:EtOAc) provided 1.0 g (3.1 mmol, 72% yield) of 4.9 as a clear liquid. The (tributylstannyl)methanol was stored under N$_2$ at 0 °C and was further purified by filtration through a pad of basic alumina immediately before use. $^1$H NMR (500 MHz, CDCl$_3$) δ 4.02 (s, 2H), 1.59 – 1.44 (m, 6H), 1.31 (h, J = 7.3 Hz, 6H), 0.94 – 0.85 (m, 15H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 53.8, 29.3, 27.5, 13.9, 8.7; The spectroscopic data were consistent with reported literature values.

(4R,4aR,6aS,10aR,13bS,14S)-8-(hydroxymethyl)-4-methyl-2,3,4,4a,5,6,9,10-octahydro-1H-6a,13b,9-(epiethane[1,1,2]triyl)-4,13-methanodibenzo[2,3:6,7]cyclohepta[1,2-d]oxazol-12(13aH)-one (4.10). Triflate 4.8 (13 mg, 0.028 mmol, 1 equiv) was added to a 4 mL vial and dried via azeotrope with benzene (1 × 0.5 mL). Flame dried lithium chloride (3.6 mg, 0.084 mmol, 3 equiv) and Pd(PPh$_3$)$_4$ (3.3 mg, 0.0028 mmol, 0.1 equiv) was added to the vial followed by a solution of (tributylstannyl)methanol (4.9, 27 mg, 0.086 mmol, 3 equiv) in THF (0.6 mL, 0.05 M). The vial was sealed with a Teflon cap and heated to 70 °C for 1 h. The reaction mixture was concentrated and the crude allylic alcohol was purified by flash chromatography (2:1 hexanes:EtOAc) to give 9.2 mg (0.027 mmol, 96% yield) of allylic alcohol 4.10 as a white solid. MP 204 – 207 °C; R$_f$ 0.13 (1:1 hexanes:EtOAc, KMnO$_4$ stain); $^1$H NMR (500 MHz, CDCl$_3$) δ 5.47 (q, J = 1.7 Hz, 1H), 4.25 – 4.20 (m, 2H), 3.56 (d, J = 14.0 Hz, 1H), 3.49 (s, 1H), 2.85 (d, J = 14.0 Hz, 1H), 2.49 (dd, J = 4.4, 2.4 Hz, 1H), 2.24 (dd, J = 14.0 Hz, 1H), 2.03 – 1.98 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 158.7, 154.3, 119.8, 118.7 (q, J = 321, CF$_3$) 87.0, 69.4, 50.2, 50.0, 48.5, 46.5, 44.8, 41.5, 41.4, 36.5, 34.4, 34.0, 29.0, 28.3, 28.1, 20.7, 20.2; FTIR (NaCl, thin film) $\nu_{\text{max}}$ 2924, 1748, 1673 cm$^{-1}$; HRMS (ESI) calc’d for [C$_{21}$H$_{25}$O$_5$NF$_3$S] ([M+H]$^+$): m/z 460.1400, found 460.1409.
14.0, 9.4 Hz, 1H), 1.96 (dd, J = 12.4, 4.4 Hz, 1H), 1.88 – 1.83 (m, 1H), 1.82 – 1.76 (m, 1H), 1.76 – 1.73 (m, 1H), 1.71 (q, J = 2.4 Hz, 1H), 1.69 (dd, J = 5.0, 2.5 Hz, 1H), 1.62 (ddd, J = 17.9, 8.8, 4.1 Hz, 1H), 1.45 – 1.35 (m, 4H), 1.35 – 1.31 (m, 1H), 1.29 – 1.21 (m, 3H), 1.19 – 1.09 (m, 1H), 1.03 (s, 3H); \textsuperscript{13}C\text{ NMR} (151 MHz, CDCl\textsubscript{3}) \delta 159.2, 149.3, 126.9, 87.9, 69.9, 63.2, 51.0, 48.6, 47.7, 46.1, 45.2, 41.7, 41.5, 36.6, 33.9, 31.8, 28.9, 28.2, 27.4, 20.8, 20.4; \textsuperscript{FTIR} (NaCl, thin film) \nu\text{max} 3427, 2924, 1731 cm\textsuperscript{-1}; \textsuperscript{HRMS} (ESI) calc'd for [C\textsubscript{21}H\textsubscript{28}O\textsubscript{3}N] ([M+H]+): m/z 342.2064, found 342.2069.

\textbf{Hordenine (4.4).} 4-(2-bromoethyl)phenol (4.ii, 500 mg, 2.5 mmol, 1 equiv) was added to a solution of dimethylamine (40% in water, 15 mL, 0.17 M). The mixture was stirred at room temperature for 12 h then extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 x 30 mL), dried over MgSO\textsubscript{4}, and concentrated. Flash chromatography (9:1 CH\textsubscript{2}Cl\textsubscript{2}: MeOH, 1% NH\textsubscript{4}OH) provided 220 mg (1.3 mmol, 52% yield) of hordenine as a white solid. \textit{R}\textsubscript{f} 0.01 (9:1 CH\textsubscript{2}Cl\textsubscript{2}: MeOH, 1% aq. NH\textsubscript{4}OH, p-anisaldehyde stain); \textit{1H NMR} (500 MHz, CDCl\textsubscript{3}) \delta 6.99 (d, J = 7.9 Hz, 2H), 6.63 (dd, J = 6.5, 1.9 Hz, 2H), 2.73 (dd, J = 9.5, 6.2 Hz, 2H), 2.60 (dd, J = 9.7, 6.3 Hz, 2H), 2.34 (s, 6H); \textit{13C NMR} (126 MHz, CDCl\textsubscript{3}) \delta 155.3, 130.6, 129.7, 115.8, 61.6, 45.1, 32.9. The spectroscopic data were consistent with reported literature values.

(4R,4aR,6aS,10aR,13bS,14S)-8-((4-(2-(dimethylamino)ethyl)phenoxy) methyl)-4-methyl-2,3,4,4a,5,6,9,10-octahydro-1H-6a,13b,9-(epiethane[1,1,2] triyl)-4,13-methanodibenzo[2,3:6,7]cyclohepta[1,2-d]oxazol-12(13aH)-one (4.11). Triethylamine (28 \muL, 0.20 mmol, 2 equiv) was added to a stirred solution of allylic alcohol 4.10 (35 mg, 0.10 mmol, 1 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (3.0 mL, 0.03 M) followed by methanesulfonyl chloride (12 \muL, 0.15 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 15 min then filtered through a pad of Celite\textsuperscript{TM} and washed with 10 mL (1:1 hexanes: EtOAc) while still cold. The resulting mesylate was concentrated and immediately carried onto the next reaction. If the reaction was allowed to warm above 0 °C before filtration through silica the allylic chloride was obtained as the major product. Allylic mesylate \textit{R}\textsubscript{f} 0.15 (9:1 CH\textsubscript{2}Cl\textsubscript{2}: MeOH, 1% aq. NH\textsubscript{4}OH, p-anisaldehyde stain); Allylic chloride \textit{R}\textsubscript{f} 0.50 (9:1 CH\textsubscript{2}Cl\textsubscript{2}: MeOH, 1% aq. NH\textsubscript{4}OH, p-anisaldehyde stain);
Sodium hydride (60 wt% dispersion in mineral oil, 4.0 mg, 0.10 mmol, 1 equiv) was added to a stirred solution of the mesylate (41 mg, 0.10 mmol, 1 equiv) and hordenine (4.4, 16 mg, 0.10 mmol, 1 equiv) in THF (4.0 mL, 0.025 M). After 1 h at room temperature, wet CH₂Cl₂ (1 mL) was added and the reaction mixture was concentrated. Flash chromatography (19:1 CH₂Cl₂: MeOH, 1% NH₄OH) provided 24 mg (0.050 mmol, 50% yield) of 4.11 as a white solid. The product 4.11 can also be obtained from the allylic chloride in diminished yields using the same conditions reported above except the reaction must be heated to 70 °C for 1 h. MP 132 – 137 °C; Rf 0.13 (9:1 CH₂Cl₂: MeOH, 1% aq. NH₄OH, p-anisaldehyde stain); ¹H NMR (500 MHz, CDCl₃) δ 7.10 (dd, J = 6.7, 1.9 Hz, 2H), 6.82 (dd, J = 6.5, 2.0 Hz, 2H), 5.59 (d, J = 2.0 Hz, 1H), 4.56 (t, J = 1.9 Hz, 2H), 3.56 (d, J = 14.0 Hz, 1H), 3.49 (s, 1H), 2.85 (d, J = 13.9 Hz, 1H), 2.76 – 2.70 (m, 2H), 2.61 – 2.57 (m, 1H), 2.57 – 2.50 (m, 2H), 2.32 (s, 6H), 2.24 (dd, J = 14.1, 9.4 Hz, 1H), 1.94 (dd, J = 12.5, 4.3 Hz, 1H), 1.88 – 1.81 (m, 2H), 1.80 – 1.66 (m, 3H), 1.60 (tdd, J = 13.8, 9.4, 4.0 Hz, 1H), 1.45 – 1.39 (m, 3H), 1.36 (td, J = 10.6, 2.4 Hz, 1H), 1.25 (tdd, J = 13.4, 9.2, 4.4 Hz, 3H), 1.19 – 1.08 (m, 1H), 1.02 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 159.2, 157.3, 145.5, 132.5, 129.7, 129.5, 114.8, 87.9, 69.9, 68.1, 61.7, 50.8, 48.6, 47.8, 45.8, 45.4, 45.1, 41.6, 41.5, 36.5, 33.8, 33.3, 31.7, 28.8, 28.2, 27.3, 20.8, 20.4; FTIR (NaCl, thin film) νmax. 2925, 1748 cm⁻¹; HRMS (ESI) calc’d for [C₃₁H₄₁O₃N₂] ([M+H]⁺): m/z 489.3116, found 489.3112.

(1R,4aS,5aR,9aS,11aR,12S)-8-((4-(2-(dimethylamino)ethyl) phenoxy)methyl)-1-methyl-2,3,4,5,5a,6,7,10,11,11a-decahydro-1H-4a,9a,7-(epiethane[1,1,2]triyl)-5,1-(epiminomethano)dibenzo[a,d][7]annulen-5a-ol (4.12). Barium hydroxide octahydrate (28 mg, 0.09 mmol, 10 equiv) and cyclic carbamate 4.11 (4.4 mg, 0.009 mmol, 1 equiv) were added to a microwave vial. The vial was sealed and EtOH (95%, 0.6 mL, 0.015 M) was added followed by water (0.3 mL, 0.03 M). The headspace was evacuated and backfilled with N₂ (3x) and then the reaction mixture was heated in the microwave to 160 °C for 90 min. The reaction mixture was concentrated and the crude amino alcohol was purified by flash chromatography (19:1 CH₂Cl₂: MeOH, 1% NH₄OH) to provide 3.7 mg (0.008 mmol, 89% yield) of amino alcohol 4.12 as a clear oil. Rf 0.03 (9:1 CH₂Cl₂:MeOH, 1% aq. NH₄OH, p-anisaldehyde stain); ¹H NMR (500 MHz, CDCl₃) δ 7.09 (dd, J = 6.3, 2.1 Hz, 2H), 6.84 (dd, J = 6.6, 2.0 Hz, 2H), 5.66 (d, J = 2.0 Hz, 1H), 4.57 – 4.49 (m, 2H), 2.99 (d, J = 12.1 Hz, 1H), 2.82 (s, 1H), 2.79 (d, J = 12.1 Hz, 1H), 2.73 (dd, J = 10.0, 6.3 Hz, 2H), 2.53 (dd, J = 10.2, 6.1 Hz, 2H), 2.45 (s, 1H), 2.32 (s, 6H), 2.13 (dd, J = 12.9, 7.4 Hz, 1H), 1.88 (d, J = 13.4 Hz, 1H), 1.66 (ddt, J = 28.8, 17.3, 4.6 Hz, 4H), 1.49 – 1.38 (m, 3H), 1.34 – 1.17 (m, 9H), 0.87 (s, 3H); ¹³C NMR (151 MHz,
CDCl$_3$ δ 157.6, 145.1, 132.4, 131.6, 129.6, 82.8, 68.8, 67.4, 61.9, 51.0, 50.5, 50.4, 46.6, 46.5, 42.5, 40.0, 35.5, 33.9, 33.6, 32.2, 30.3, 28.1, 27.7, 21.8, 21.2; FTIR (NaCl, thin film) $\nu$$_\text{max}$ 3329, 2925, 2853, 1511 cm$^{-1}$; HRMS (ESI) calc’d for [C$_{30}$H$_{43}$N$_2$O$_2$] ([M+H]$^+$): m/z 463.3319, found 463.3313.

(4bS,8R,8aR)-2-((4-(2-(dimethylamino)ethyl)phenoxy)methyl)-8-methyl-3,4,4a,5,6,7,8,8a,9,10-decahydro-3,10a-ethano-8,4b-(methanoazenumetheno)phenanthren-11-one (4.13). Iodosobenzene (3.3 mg, 0.015 mmol, 1.5 equiv) was added to a stirred suspension of amino alcohol 4.12 (4.6 mg, 0.010 mmol, 1 equiv) and NaHCO$_3$ (2.5 mg, 0.03 mmol, 3 equiv) in CH$_2$Cl$_2$ (1.0 mL, 0.01 M) at room temperature. After 1 h, the reaction mixture as filtered through a pad of Celite$^{\text{TM}}$, washed with CH$_2$Cl$_2$ (5 mL) and concentrated. Flash chromatography (19:1 CH$_2$Cl$_2$: MeOH, 1% NH$_4$OH) provided 3.4 mg (0.0075 mmol, 75% yield) of 4.13 as a clear oil. R$_f$ 0.07 (9:1 CH$_2$Cl$_2$: MeOH, 1%aq. NH$_4$OH, p-anisaldehyde stain); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.56 (d, $J$ = 2.8 Hz, 1H), 7.11 (d, $J$ = 8.1 Hz, 2H), 6.82 (d, $J$ = 8.5 Hz, 2H), 5.81 (d, $J$ = 2.0 Hz, 1H), 4.55 (d, $J$ = 1.6 Hz, 2H), 3.46 – 3.35 (m, 2H), 3.04 (q, $J$ = 2.8 Hz, 1H), 2.81 – 2.75 (m, 2H), 2.65 – 2.55 (m, 2H), 2.42 (dd, $J$ = 9.5, 3.0 Hz, 2H), 2.37 (s, 6H), 2.18 (d, $J$ = 2.7 Hz, 2H), 1.94 (dd, $J$ = 8.1, 2.7 Hz, 2H), 1.73 – 1.59 (m, 3H), 1.52 – 1.41 (m, 2H), 1.34 – 1.17 (m, 3H), 1.06 (ddd, $J$ = 19.8, 11.9, 6.1 Hz, 2H), 0.83 (s, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 211.2, 162.5, 157.1, 145.6, 131.5, 129.7, 114.9, 68.4, 61.7, 60.9, 52.7, 48.2, 47.4, 45.5, 42.3, 42.1, 35.3, 33.7, 33.4, 33.3, 29.9, 28.7, 27.0, 26.0, 20.7, 20.3; FTIR (NaCl, thin film) $\nu$$_\text{max}$ 3399, 2927, 1715, 1652, 1512 cm$^{-1}$; HRMS (ESI) calc’d for [C$_{30}$H$_{41}$N$_2$O$_2$] ([M+H]$^+$): m/z 461.3163, found 461.3166.

(1R,4aS,5aR,9aS,11aR,12S)-5a,13-dihydroxy-1-methyldecahydro-1H-4a,9a,7-(epiethane[1,1,2]triyl)-5,1-(epiminomethano) dibenzo[a,d][7]annulen-8(2H)-one (4.14). Barium hydroxide octahydrate (85 mg, 0.27 mmol, 5 equiv) and cyclic carbamate 4.5 (18 mg, 0.053 mmol, 1 equiv) were added to a microwave vial. The vial was sealed and EtOH (95%, 6.6 mL, 0.008 M) was added followed by water (3.3 mL, 0.016 M). The headspace was evacuated and backfilled with N$_2$ (3×) and then the reaction mixture was heated in the microwave to 160 °C for 30 min. The reaction mixture was concentrated
and the crude amino alcohol was purified by flash chromatography (9:1 CH$_2$Cl$_2$: MeOH, 1% NH$_4$OH) to provide 9.7 mg (0.031 mmol, 58% yield) of amino diol 4.14 as a white solid. MP 226 – 229 °C; R$_f$ 0.03 (9:1 CH$_2$Cl$_2$: MeOH, 1% aq. NH$_4$OH, p-anisaldehyde stain); $^1$H NMR (500 MHz, CDCl$_3$) δ 4.38 (d, J = 4.2 Hz, 1H), 2.99 (d, J = 12.1 Hz, 1H), 2.78 (d, J = 12.1 Hz, 1H), 2.67 (s, 1H), 2.52 (d, J = 19.8 Hz, 1H), 2.46 (t, J = 4.6 Hz, 1H), 2.07 (d, J = 19.8 Hz, 1H), 2.07 – 2.02 (m, 1H), 1.89 (d, J = 14.3 Hz, 1H), 1.80 – 1.74 (m, 1H), 1.74 – 1.61 (m, 3H), 1.36 (s, 1H), 1.33 – 1.23 (m, 4H), 0.86 (s, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 213.7, 75.6, 70.7, 67.2, 57.8, 52.0, 45.0, 44.6, 43.6, 42.4, 42.2, 40.8, 40.4, 33.7, 33.4, 31.3, 28.0, 21.4, 21.0; FTIR (NaCl, thin film) $\nu_{max}$ 3350, 2913, 1712 cm$^{-1}$; HRMS (ESI) calc'd for [C$_{19}$H$_{28}$NO$_3$] ([M+H]$^+$): m/z 318.2064, found 318.2061.

Iodosobenzene (4.0 mg, 0.018 mmol, 1.5 equiv) was added to a stirred suspension of amino alcohol 4.14 (3.7 mg, 0.012 mmol, 1 equiv) and NaHCO$_3$ (3.0 mg, 0.036 mmol, 3 equiv) in CH$_2$Cl$_2$ (1.2 mL, 0.01 M) at room temperature. After 30 min, the reaction mixture as filtered through a pad of Celite$^\text{TM}$, washed with CH$_2$Cl$_2$ (5 mL) and concentrated. Flash chromatography (19:1 CH$_2$Cl$_2$: MeOH, 1% aq. NH$_4$OH, p-anisaldehyde stain) provided 3.0 mg (0.009 mmol, 75% yield) of 4.15 as a white solid. Slow diffusion of isopropyl ether into 3:1 ethanol: acetonitrile provided X-ray quality crystals. MP 245 – 246 °C; R$_f$ 0.33 (9:1 CH$_2$Cl$_2$: MeOH, 1% NH$_4$OH, p-anisaldehyde stain); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.59 (s, 1H), 4.68 (t, J = 3.8 Hz, 1H), 3.47 – 3.34 (m, 2H), 2.92 (q, J = 3.1 Hz, 1H), 2.63 (dd, J = 19.9, 2.8 Hz, 1H), 2.48 (dd, J = 20.0, 3.2 Hz, 1H), 2.38 – 2.27 (m, 2H), 2.18 (dt, J = 13.4, 3.0 Hz, 1H), 1.99 – 1.90 (m, 1H), 1.78 (d, J = 3.9 Hz, 1H), 1.67 – 1.61 (m, 1H), 1.61 – 1.56 (m, 1H), 1.48 (t, J = 12.7 Hz, 1H), 1.36 – 1.23 (m, 3H), 1.20 (dd, J = 12.8, 3.5 Hz, 1H), 1.16 (s, 1H), 1.05 (td, J = 13.3, 4.1 Hz, 1H), 0.86 (s, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ 209.8, 209.2, 164.0, 68.4, 60.0, 55.7, 54.0, 49.2, 48.6, 46.7, 43.7, 42.1, 37.1, 34.3, 33.1, 29.8, 25.8, 20.4 20.0.; FTIR (NaCl, thin film) $\nu_{max}$ 3400, 2926, 1726 cm$^{-1}$; HRMS (ESI) calc'd for [C$_{19}$H$_{26}$NO$_3$] ([M+H]$^+$): m/z 316.1907, found 316.1894.
X-Ray Crystallography Data for Imine-Ketone 4.15

A colorless needle 0.050 x 0.020 x 0.010 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 10 seconds per frame using a scan width of 2.0°. Data collection was 100.0% complete to 67.000° in θ. A total of 22824 reflections were collected covering the indices, -13<=h<=13, -8<=k<=8, -13<=l<=13. 3360 reflections were found to be symmetry independent, with an R_int of 0.0744. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21 (No. 4). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Absolute stereochemistry was unambiguously determined to be R at C1 and C7, and S at C2, C3, C8, C11, and C14, respectively.

Empirical formula: C21 H31 N O4
Formula weight: 361.47
Temperature: 100(2) K
Wavelength: 1.54178 Å
Crystal system: Monoclinic
Space group: P 21
Unit cell dimensions:
\[ a = 10.9297(3) \, \text{Å} \]
\[ b = 7.3691(2) \, \text{Å} \]
\[ c = 11.4432(4) \, \text{Å} \]
Volume: 919.17(5) \, \text{Å}^3
Z: 2
Density (calculated)  
Absorption coefficient  
F(000)  
Crystal size  
Theta range for data collection  
Index ranges  
Reflections collected  
Independent reflections  
Completeness to theta = 67.000°  
Absorption correction  
Max. and min. transmission  
Refinement method  
Data / restraints / parameters  
Goodness-of-fit on F^2  
Final R indices [I&g;2sigma(I)]  
R indices (all data)  
Absolute structure parameter  
Extinction coefficient  
Largest diff. peak and hole  

4.7 References and Notes

Appendix Two:
Spectra Relevant to Chapter Four

Figure A2-1. $^1$H NMR for 4.i.

Figure A2-2. $^{13}$C NMR for 4.i.
**Figure A2-3.** $^1$H NMR for 4.6.

**Figure A2-4.** $^{13}$C NMR for 4.6.
Figure A2-5. $^1$H NMR for 4.8.

Figure A2-6. $^{13}$C NMR for 4.8.
**Figure A2-7.** $^1$H NMR for 4.9.

**Figure A2-8.** $^{13}$C NMR for 4.9.
Figure A2-9. $^1$H NMR for 4.10.

Figure A2-10. $^{13}$C NMR for 4.10.
Figure A2-11. $^1$H NMR for 4.4.

Figure A2-12. $^{13}$C NMR for 4.4.
Figure A2-13. $^1$H NMR for 4.44.

Figure A2-14. $^{13}$C NMR for 4.11.
Figure A2-15. $^1$H NMR for 4.12.

Figure A2-16. $^{13}$C NMR for 4.12.
Figure A2-17. $^1$H NMR for 4.13.

Figure A2-18. $^{13}$C NMR for 4.13.
Figure A2-19. $^1$H NMR for 4.14.

Figure A2-20. $^{13}$C NMR for 4.14.
Figure A2-21. $^1$H NMR for 4.15.

Figure A2-22. $^{13}$C NMR for 4.15.