2009-12-11

Progress Toward the Total Synthesis of Lyconadin A

Yu Zhang
Brigham Young University - Provo

Follow this and additional works at: https://scholarsarchive.byu.edu/etd

Part of the Biochemistry Commons, and the Chemistry Commons

BYU ScholarsArchive Citation
https://scholarsarchive.byu.edu/etd/2345

This Dissertation is brought to you for free and open access by BYU ScholarsArchive. It has been accepted for inclusion in All Theses and Dissertations by an authorized administrator of BYU ScholarsArchive. For more information, please contact scholarsarchive@byu.edu, ellen_amatangelo@byu.edu.
Progress Towards Total Synthesis of Lyconadin A

Yu Zhang

A dissertation submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

Steven L. Castle, Chair
Merrit B. Andrus
Paul B. Savage
Young W. Ham
Allen R. Buskirk

Department of Chemistry and Biochemistry
Brigham Young University
April 2010

Copyright © 2010 Yu Zhang
All Rights Reserved
ABSTRACT

PROGRESS TOWARDS TOTAL SYNTHESIS OF LYCONADIN A

Yu Zhang

Department of Chemistry and Biochemistry
Doctor of Philosophy

Lyconadin A is a pentacyclic Lycopodium alkaloid isolated from the club moss Lycopodium complanatum with antitumor properties. We have developed a novel 7-exo/6-exo acyl radical cascade cyclization as a method of making the bicyclo[5.4.0]undecane ring system of lyconadin A. The model products are trans-fused ring systems, while a cis-fused ring system is needed in lyconadin A. We have discovered a method to convert the trans-fused model cascade cyclization product into the desired cis isomer. Based on Donohoe’s pyridone synthesis, we developed a method for the construction of 5-alkyl and 3,5-dialkyl-6-carbomethoxy-2-pyridones, the former of which is a subunit of lyconadin A. An intramolecular Reformatsky reaction is a key step in this process. We have proceeded with our total synthesis, in which we generated an epoxide by Shi asymmetric epoxidation and regioselectively opened epoxide rings. We have prepared carboxylic acid 197.

Keywords: radical cyclization, pyridone, lyconadin A
ACKNOWLEDGMENTS

I am very grateful for the support that I have received throughout this project from Dr. Castle. He has been a great advisor for suggestions on the project as well as advice on career paths.

I would like to thank all of my committee members, Dr. Paul B. Savage, Dr. Merritt B. Andrus., Dr. Young W. Ham, Dr. Allen R. Buskirk for their guidance and suggestions.

I also want to thank my associates in Dr. Castle’s group who have provided me with intellectual and emotional support.

I gratefully acknowledge the financial support of this work by the Brigham Young University Department of Chemistry and Biochemistry.

Most of all I want to express my appreciation to my husband, Zhaofan, and my parents, Rongbang and Zhilan, for their love. It is to them that I dedicate this dissertation.
# TABLE OF CONTENTS

**LIST OF FIGURES...........................................................................................................** xi  
**LIST OF SCHEMES.......................................................................................................** xii  
**LIST OF TABLES........................................................................................................** xv  

**Chapter 1. Introduction .................................................................................................** 1  
1.1 *Lycopodium* Alkaloids.............................................................................................. 1  
1.2 Lyconadin A .............................................................................................................. 3  
1.3 Total Synthesis .......................................................................................................... 3  
1.4 Seth Grant's work on Acyl Radical Cascade Cyclization ........................................ 10  
1.5 References .............................................................................................................. 12  

**Chapter 2. Model Studies Towards Acyl Radical Cascade Cyclization and Conversion to *cis*-Fusion........................................................................................................** 14  
2.1 Alkylation .................................................................................................................. 15  
2.2 Synthesis of the Phenyl Selenoester ......................................................................... 15  
2.3 Acyl Radical Cascade Cyclization .......................................................................... 17  
2.4 Epimerization ........................................................................................................... 18  
2.5 References .............................................................................................................. 23  

**Chapter 3. Model Pyridone Synthesis Studies ................................................................** 25  
3.1 Kozikowski Synthesis ............................................................................................. 25
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2</td>
<td>H–W–E Reaction for the RCM</td>
<td>32</td>
</tr>
<tr>
<td>3.3</td>
<td>Reformatsky Reaction for the RCM</td>
<td>36</td>
</tr>
<tr>
<td>3.4</td>
<td>Pyridone Synthesis</td>
<td>37</td>
</tr>
<tr>
<td>3.5</td>
<td>References</td>
<td>41</td>
</tr>
<tr>
<td>3.6</td>
<td>References</td>
<td></td>
</tr>
</tbody>
</table>

**Chapter 4. Attempted Synthetic Approaches to Lyconadin A**  
4.1 Enzymatic Approach                                         44  
4.2 One Carbon Short Chiral Auxiliary-Mediated Approach         52  
4.3 References                                                 55  

**Chapter 5. Progress Towards Total Synthesis of Lyconadin A**  
5.1 Retrosynthesis                                              56  
5.2 First Attempt to the Synthesis of the Precursor of Epoxidation 57  
5.3 Second Attempt to the Synthesis of the Precursor of Epoxidation 58  
5.4 Shi-Epoxidation                                             59  
5.5 Ring Opening Reaction                                      60  
5.6 Synthesis of Carboxylic Acid                               67  
5.7 References                                                 68  

**Chapter 6. Conclusion and Future Work**                       70  
6.1 Conclusion                                                 70  
6.2 Future Work                                                71  
6.3 References                                                 73  

**Chapter 7. Experimental Information**                         74
LIST OF FIGURES

Chapter 1. Introduction

Figure 1. Representative Compounds of the Four Major Classes of Lycopodium Alkaloids ................................................................. 2

Figure 2. Lyconadin A ........................................................................ 3

Chapter 2. Model Studies Towards Acyl Radical Cascade Cyclization and Conversion to cis-Fusion

Figure 1. Stereochemistry of Compound 51 ........................................ 18
LIST OF SCHEMES

Chapter 1. Introduction

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Smith’s Synthesis of Diketone 2</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>Synthesis of (+)-Lyconadin A</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>Retrosynthesis of Lyconadin A in Sarpong Group</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>Synthesis of Racemic 33</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>Synthesis of 33</td>
<td>9</td>
</tr>
<tr>
<td>6</td>
<td>Synthesis of (+)-Lyconadin A</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>Synthesis of 39</td>
<td>11</td>
</tr>
<tr>
<td>8</td>
<td>Proposed Stereochemistry of the Acyl Radical Cascade Cyclization</td>
<td>12</td>
</tr>
</tbody>
</table>

Chapter 2. Model Studies Towards Acyl Radical Cascade Cyclization and Conversion to cis-Fusion

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Synthesis of Ketone 36</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>Synthesis of Phenyl Selenoester 48</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>Tandem Cyclization of Alcohol 49</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>Tandem 7-exo-6-exo Cyclization of 48</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>Structure of Comparison</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>Proposed Kinetically Controlled Protonation</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>Planned Epimerization of 51</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>Attempted Epimerization of 39</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>Attempted Enone 58 Formation</td>
<td>21</td>
</tr>
<tr>
<td>10</td>
<td>Enone 60 Formation</td>
<td>21</td>
</tr>
<tr>
<td>11</td>
<td>Tried Epimerization of 39</td>
<td>22</td>
</tr>
<tr>
<td>12</td>
<td>Epimerization of 50</td>
<td>23</td>
</tr>
</tbody>
</table>

Chapter 3. Model Pyridone Synthesis Studies

xii
Scheme 1. Kozikowski Pyridone Synthesis................................................................. 25
Scheme 2. Attempted Kozikowski Pyridone Annulation........................................... 26
Scheme 3. Attempted Kozikowski Pyridone Annulation............................................ 26
Scheme 4. Proposed Mechanism of Pyridone Regioisomer Formation ....................... 27
Scheme 5. Benzyl Deprotection of 67 ....................................................................... 27
Scheme 6. Attempted Pyridone Annulation ................................................................ 30
Scheme 7. Attempted Pyridone Annulation ................................................................ 31
Scheme 8. Proposed Mechanism of Pyridone Annulation ........................................... 31
Scheme 9. Attempted Pyridone Annulation ................................................................ 32
Scheme 10. Donohoe Pyridone Annulation.................................................................. 33
Scheme 11. Synthesis of Tosylamine 85 ..................................................................... 34
Scheme 13. Intramolecular Reformatsky-type Condensation ....................................... 36
Scheme 14. Proposed Pathway to the Synthesis of 91 ................................................. 38
Scheme 15. Proposed Pathway to the Synthesis of 91 ................................................. 38
Scheme 16. Synthesis of Pyridone 94 ....................................................................... 39
Scheme 17. Synthesis of Isopropyl-substituted Pyridone 100 ...................................... 39
Scheme 18. Synthesis of Dialkyl-substituted Pyridone 113 ......................................... 40

Chapter 4. Attempted Synthetic Approaches to Lyconadin A

Scheme 1. Retrosynthesis of Lyconadin A................................................................. 45
Scheme 2. Synthesis of Diol 125 .............................................................................. 46
Scheme 3. Asymmetrization with Organic Catalyst 129 ........................................ 48
Scheme 4. Attempt to Determine the Conifiguration of Monoacetate 126 ............... 49
Scheme 5. Synthesis of Secondary Amine 141 ....................................................... 50
Scheme 6. Synthesis of Epoxide ............................... 51
Scheme 7. Ring Opening of Epoxide................................. 52
Scheme 8. Synthesis of Epoxide ............................... 54

Chapter 5. Progress Towards Total Synthesis of Lyconadin A

Scheme 1. Current Retrosynthesis of Lyconadin A .................. 57
Scheme 2. Failed Synthesis of DMB ether ............................ 58
Scheme 3. Synthesais of Compound ............................... 59
Scheme 4. Attempted Ring Opening of Epoxide and .................. 63
Scheme 5. Synthesis of Compound ............................... 64
Scheme 6. Attempted to Synthesize Compound .................. 66
Scheme 7. Synthesis of Compound ............................... 67
Scheme 8. Synthesis of Carboxylic Acid .................. 68

Chapter 6. Conclusion and Future work

Scheme 1. Future work ................................................. 72
LIST OF TABLES

Chapter 3. Model Pyridone Synthesis Studies

Table 1. PMB Deprotection of 68 ................................................................. 28
Table 2. 3,4-DMB Deprotection of 69 ............................................................... 28
Table 3. Modified Kozikowski Pyridone Annulation .......................................... 29
Table 4. Attempted Pyridone Annulation ............................................................ 30
Table 5. Attempted Synthesis of Horner–Wadsworth–Emmons Cyclization Substrate 35

Chapter 4. Attempted Synthetic Approaches to Lyconadin A

Table 1. Lipase Catalyzed Desymmetrization

Chapter 5. Progress Towards Total Synthesis of Lyconadin A

Table 1. Synthesis of Epoxide 172 ........................................................................ 60
Table 2. Attempted Ring Opening of Compound 172 ............................................. 61
Table 3. Attempted Epoxide 176 Formation .......................................................... 62
Table 4. Attempted NAP Protection of Compound 167 .......................................... 65
Chapter 1. Introduction

1.1 *Lycopodium* Alkaloids

The genus *Lycopodium* consists of low, evergreen, coarse moss–like plants, which are commonly known as club mosses. They are non–flowering plants and reproduce via spores rather than seeds. The name club mosses originates from the fact that the strobili look like club–shaped growths at the tips of the moss-like branches.\(^1\) *Lycopodium* species produce a lot of structurally diverse alkaloids with quinolizine, pyridine or α–pyridone type skeletons.

In 1881, Bödeker made the first investigations on *Lycopodium* alkaloids.\(^2\) He isolated lycopodine from *Lycopodium complanatum*. In 1938, Achmatowicz and Uzieblo gave the correct molecular formula for lycopodine.\(^3\) Since the 1940s, W. A. Ayer’s group has explored the isolation, structural determination, biogenesis, and chemical synthesis of *Lycopodium* alkaloids.\(^4\) During the period of 1986-1990, some *Lycopodium* alkaloids were found to possess potent acetylcholinesterase inhibition activity.\(^5,6\) Chinese scientists Liu and co-workers isolated huperzine A from the Chinese herb Qian Ceng Ta. Huperzine A has been shown to be the most potent, reversible inhibitor of acetylcholine esterase. It can increase efficiency for learning and memory and it shows promise in the treatment of Alzheimer’s disease and myasthenia gravis.
disease, which is a chronic disease characterised by fluctuating levels of muscle weakness.\textsuperscript{7,8,9} So far, over 200 \textit{Lycopodium} alkaloids have been characterized from 54 species of \textit{Lycopodium}.

\textit{Lycopodium} alkaloids can be separated into four classes according to their structures: The lycopodine class, alkaloids possessing the lycopodane skeleton; the lycodine class, the dinitrogenous alkaloids which contain a pyridine or pyridine ring; the fawcettimine class, those containing a five-membered B ring; and a miscellaneous class, alcoloids possessing unique frameworks distinct from the traditional structural class.\textsuperscript{10} Lycopodine, lycodine, fawcettimine and phlegmarine are representative compounds for these classes (Figure 1).\textsuperscript{4}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Representative Compounds of the Four Major Classes of Lycopodium Alkaloids}
\end{figure}

\textit{Lycopodium} alkaloids have wonderful bioactivities. Nevertheless, these plants are not abundant. They grow very slowly, and are only found in special places. They have not been cultivated successfully. Tissue culture also appears to be very difficult. Thus, very few biosynthetic studies have been performed with \textit{Lycopodium} alkaloids.\textsuperscript{11,12,13,14} However, total synthesis can provide material for investigation of the biological properties of \textit{Lycopodium} alkaloids. Moreover, the complex structures provide a significant challenge to synthetic chemists.
1.2 Lyconadin A

The alkaloid lyconadin A is a member of the *Lycopodium* alkaloid family which belongs to the miscellaneous class (Figure 2). It was isolated by Kobayashi and co-workers from the club moss *Lycopodium complanatum*.\(^\text{15}\) It possesses a unique molecular skeleton consisting of an \(\alpha\)-pyridone ring as well as one five-membered and three six-membered rings. It contains six stereocenters. In addition to its novel structure, lyconadin A exhibits modest in vitro cytotoxicity against murine lymphoma L 1210 cells (IC\(_{50}\) = 0.46 \(\mu\)g/mL) and human epidermoid carcinoma KB cells (IC\(_{50}\) = 1.70 \(\mu\)g/mL).\(^\text{15}\) This unprecedented framework and biological activity make it a challenging and attractive target for total synthesis.

![Figure 2. Lyconadin A](image)

1.3 Total Synthesis

Lyconadin A possesses an unprecedented pentacyclic ring system, with an \(\alpha\)-pyridone ring fused to a tetracyclic core. The tightly functionalized structure containing four adjacent stereocenters makes lyconadin A a challenging synthetic target. The first total synthesis of (+)-lyconadin A was reported by Smith in 2007.\(^\text{16}\) Sarpong finished a total synthesis of racemic lyconadin A in 2008\(^\text{17}\) and an enantioselective synthesis in 2009.\(^\text{18}\)

In Smith’s synthesis, the pentacyclic sketon of lyconadin A was constructed by the key intermediate enone 1 (Scheme 1), which was mainly installed by the coupling of iodide 9 with
hydrazone 13 and resultant intramolecular aldol condensation of 15. The iodide 9 was prepared from the commercially available enantiomerically pure lactone 4. Then, they introduced the L-Phe oxazolidinone chiral auxiliary to enable diastereoselective hydroxymethylation. Then, TBS protection, removal of chiral auxiliary, cyclization and iodination provided iodide 9. The enantiomerically pure secondary methyl substituent of 15 derived from the monoester 10. Lactone formation followed by opening of lactone with HCONHCH₂·HCl afforded, after protection, Weinreb amide 12. Alkylation of the derived hydrazone 13, after deprotection, led to 15. Under the acidic condition, the intramolecular aldol condensation and Michael addition gave the trans-fused bicyclic diketone 2.
Lyconadin A possesses a cis-fused ring system. So, it was necessary to epimerize 2 to the cis ring fusion 16 (Scheme 2). Smith and Beshore tried to dehydrate the tertiary alcohol of 16, but failed because of Bredt’s rule. Then, they cleaved the C-N bond by selective reduction followed by protection to deliver 17. Later, the C-N bond was reinstalled by exposure of 18 to NIS to lead
to 19. Michael addition followed by cyclocondensation to provide 3 (+)-lyconadin A. Smith and Beshore finished the total synthesis in 28 steps and 2.2% overall yield.

Scheme 2. Synthesis of (+)-Lyconadin A

The Sarpong group postulated that the majority of miscellaneous *Lycopodium* alkaloids could originate synthetically from a common precursor related to the tetracyclic core of 23 (Scheme 3). They sought to highlight a unified approach to the miscellaneous group of *Lycopodium* alkaloids by designing the synthesis of lyconadin A. A key result was that they developed a simple C-N bond formation reaction to make the pentacyclic core of lyconadins.
Scheme 3. Retrosynthesis of Lyconadin A in Sarpong Group

In the racemic total synthesis of lyconadin A published in 2008 by Sarpong group, they coupled enone 26 with bromopicoline derivative 27 in a Stork–Danheiser sequence. Unfortunately, after cross-metathesis, intramolecular Heck reaction, Luche reduction, and hydrogenation, they obtained a diastereomer of 23 with an axial methyl group. They turned to react a derivative of 26, without the methyl group, with 27, and at the late stage conjugate addition of a Gilman reagent to the enone provided the desired stereochemistry at C15 (Scheme 4). Hydrogenation provided racemic 33.
In their enatoselective total synthesis of lyconadin A, Sarpong and co-workers created a temporary stereocenter, and used this stereocenter to control further asymmetric chemistry (Scheme 5). The chiral secondary hydroxyl group in 29 was formed by CBS reduction in high yield and enantiomeric excess. This hydroxyl group directed hydrogenation of both double bonds to generate 30 with three required stereocenters in excellent diastereometric excess. Then, the hydroxyl group was oxidized back to ketone 31. After similar sequences, 31 was converted into enantioselective 33 in 99% ee.
The intermediate 33 is close to the target, but it lacks a key C-N bond. Apparently, it also lacks a functional group with which to build this bond. Sarpong and co-workers tried a lot of name reactions to install this group, and no good result was achieved. Later, they used excess base to form a chelated dianionic bridged intermediate (Scheme 6). The lyconadin A skeleton was completed by treatment with I₂. Demethylation of 34 provided enantiopure (+)-lyconadin A.
Sarpong and co-worker finished the total synthesis of racemic lyconadin A in 18 steps with 10% overall yield, and enantiopure (+)-lyconadin A in 17 steps with 6.5% overall yield.

1.4 Seth Grant's work on Acyl Radical Cascade Cyclization

Lyconadin A possesses a bicyclo[5.4.0]undecane ring system fused to a pyridone ring. An efficient approach to installing this framework involves building two rings in a single reaction. A radical reaction is suitable for this purpose. The radical reactions which lead to seven-membered rings are rare and only applied to special substrates. The rate of 7-exo radical cyclization is slow, so the short-lived alkyl radical is not very useful. However, Boger demonstrated that acyl radicals can participate in 7-exo-trig cyclizations as long as an aromatic ring is present in the tether between the radical and the acceptor. Evans, Bonjoch, and Ryu disclosed various 7-exo acyl radical reactions. Nevertheless, there are no examples of cascade reactions that involve a 7-exo acyl radical cyclization before the work of Seth Grant in our group.

To study the feasibility and stereoselectivity of an acyl radical cyclization which could be used in the total synthesis of lyconadin A, Seth first performed a tandem 7-exo-6-exo reaction with model substrate 38 (Scheme 7). He used a phenyl-tethered phenyl selenoester as his
cyclization substrate to mimic the 2-pyridone moiety of lyconadin A. He started his synthesis from 1-isochromanone 35, and got diester 36 via 7 steps. Reduction of 36 with NaBH$_4$ was modestly syn selective and provided 37 as a mixture of diastereomers. After 10 steps, the precursor of tandem 7-exo-6-exo cyclization, phenyl selenoester 38, was achieved. Treatment of 38 with Et$_3$B, air, and tris(trimethylsilyl)silane provided tricyclic 39 in excellent yield as a single diastereomer.

Scheme 7. Synthesis of 39

The trans ring fusion and relative configuration of 39 were determined by both 1D and 2D NMR experiments. The stereochemistry of the radical reaction is consistent with cyclization via chairlike or pseudochairlike transition states (Scheme 8).
Scheme 8. Proposed Stereochimistry of the Acyl Radical Cascade Cyclization

1.5 References

11. Freeberg, J. A.; Wetmore, R. H. *Phytomorphology* 1957, 7, 204.


Chapter 2. Model Studies Towards Acyl Radical Cascade

Cyclization and Conversion to cis-Fusion

In our group, Seth Grant demonstrated the first example of a 7-exo-6-exo acyl radical cascade reaction. In this reaction, two new C-C bonds and two stereocenters are formed in a highly regio- and stereoselective fashion. The relative configurations of the products are consistent with cyclization occurring via chairlike or pseudochairlike transition states. This acyl radical cascade cyclization should be useful in the preparation of the bicyclo[5.4.0]undecane ring system and could be employed in the total synthesis of lyconadin A. To determine if the bulky TBS group has some effect on the diastereoselectivity, we removed the TBS group from Seth’s substrate, and performed the cyclization with the free alcohol. We also studies the role of OTBS configuration by cyclization with the diastereomer of Seth’s substrate. In addition, we developed a method to epimerize the model products to cis –fused isomers, which is needed in lyconadin A.
2.1. Alkylation

The synthesis of the diester 36 was developed by Seth Grant, and is shown in Scheme 1. Commercially available isochroman was oxidized into lactone 35, which was hydrolyzed under basic conditions. Protection of both alcohol and carboxylic acid functionalities of the resulting hydroxy acid with PMB-Cl provided 40. Reduction of 40 with LAH followed by treatment of the resultant alcohol with TBS-Cl afforded differentially protected diol 41. The PMB group was then removed under oxidative conditions to afford alcohol 42, which was converted into a bromide in excellent yield. Alkylation of diethyl acetonedicarboxylate (DEADC) by this bromide delivered ketone 36.

![Scheme 1. Synthesis of Ketone 36](image)

2.2 Synthesis of the Phenyl Selenoester

Based on Seth Grant’s work, we were able to access phenyl selenoester 48, the diastereomer of 38, by simply changing the conditions for reduction of ketone 36. Reduction of 36 with
freshly prepared Zn(BH₄)₂ followed by TBS protection provided *anti* isomer 43 in 4:1 dr (Scheme 2). Conversion of both ester moieties into Weinreb amides provided 44. Due to significant differences in the reduction rates of the two amides, the reduction–Wittig olefination sequence was conducted twice. Treatment of 44 with Dibal-H followed by Wittig reaction afforded monoalkene 45, which was subjected to further Dibal-H reduction and Wittig reaction to produce 46. Selective cleavage of the primary benzylic silyl ether mediated by CSA delivered 47. Swern oxidation, further oxidation of the resultant aldehyde, and phenyl selenoesterification provided 48 in good yield.

Scheme 2. Synthesis of Phenyl Selenoester 48
2.3 Acyl Radical Cascade Cyclization

To probe the role of the OTBS group in the stereoselectivity of the radical cyclization, we generated free alcohol 49 from 38 via treatment with CSA (Scheme 3). Cyclization of 49 delivered alcohol 50 as a single diastereomer which has the same structure as that obtained from deprotection of 39. Accordingly, the bulky TBS group is not required to achieve stereoselectivity in this process.

![Scheme 3. Tandem Cyclization of Alcohol 49](image)

Treatment of 48 with Et3B, air, and tris(trimethylsilyl)silane provided tricycle 51 in good yield as a single diastereomer (Scheme 4).

![Scheme 4. Tandem 7-exo-6-exo Cyclization of 48](image)

To determine the relative configuration of all the stereocenters of 51, we performed NMR analysis \( (^1H, ^13C, COSY, NOE) \). From the 1H NMR of 51, the coupling constant between the
proton 10 and proton 15 is 9.0 Hz or 13.0 Hz, which indicates a *trans* ring configuration.

Furthermore, when the proton 13 was irradiated, the signal at proton 11 was enhanced. This suggests that the relative stereochemistry of the OTBS group and methyl group are *cis*.

Irradiation of the proton 10 did not lead to an enhancement in the signal at proton 11. This indicates that proton 10 and proton 11 are *trans* to each other. Based on these results, the stereochemistry of 51 is derived as shown in Figure 1. Thus, based the cyclizations of 38 and 48, it is clear that this 7-*exo*-6-*exo* cascade radical cyclization occurs with excellent diastereoselectivity regardless of the relative configuration of the OTBS group.

![Figure 1. Stereochemistry of Compound 51](image)

### 2.4 Epimerization

Comparing the structures of our obtained model compounds 39 and 51 with targeted lyconadin A, we could find that the cyclization installed the correct stereochemistry at C15 but not at C7 (Scheme 5).
In order to develop a method for building cis-fused lyconadin A, we explored the conversion of the trans-fused model cascade cyclization product into the desired cis isomer. Since C7 is adjacent to a carbonyl, it may be epimerized via a kinetically controlled protonation (Scheme 6). Thus, treatment of the enolate derived from 39 with BHT or other bulky hydrogen source should result in formation of cis-fused isomer 52. Because OTBS group is more bulky than methyl group, it will shield the top face of 39. So the enolate will be expected to attack the proton source, especially a bulky one, from the bottom face to obtain cis-fused isomer 52.

To generate the enolate, t-BuLi was chosen as a base for this reaction. We treated 39 with t-BuLi at −78 °C. After 10 seconds, we quenched the reaction with a solution of butylated hydroxytoluene (BHT) in THF. Unfortunately, we only recovered the starting material. Then, we tried to quench the reaction at −78 °C after 3 minutes, 10 minutes, 30 minutes and 1 hour respectively, but we still recovered starting material. To make sure that the enolate was formed after treating with t-BuLi, we quenched the reaction with D₂O. The ¹H NMR and mass spectrum
showed that the deuterated compound of 39 was obtained. Thus the enolate was formed in this reaction. Other hydrogen sources, t-BuOH and triphenylacetic acid, were tried to replace BHT respectively. However, only starting material was recovered. Then other bases, n-BuLi and LDA, were tried respectively. The resulting enolate was treated with BHT, t-BuOH, and triphenylacetic acid respectively. Unfortunately, we still recovered all the starting material.

Then, we turned to an alternative sequence (Scheme 7). Oxidation of of 51 according to the protocol of Nicolaou-Baran or Saegusa and resulting silyl ether deprotection should afford enone 53. With enone in hand, hydroxyl-directed hydrogenation would result in the desired cis-fused product 54.

Scheme 7. Planned Epimerization of 51

Due to the ready availability of 39, we tried to oxidize 39 with IBX in DMSO at 70 °C, but failed to get the enone 55, and only recovered starting material (Scheme 8). We changed to the mixed solvent system of DMSO and toluene, and still no reaction was observed. Then, a catalytic amount of p-TsOH was added, and the mixture was heated to 85 °C. Unfortunately, only TBS deprotected by-product was provided. Later, IBX-MPO as an oxidant was used in DMSO and CH₂Cl₂ at room temperature. However, only starting material was recovered.
Oxidation of a silyl enol ether is a mild condition for the synthesis of an enone (Scheme 9). Treatment of ketone 39 with LDA followed by adding TMS-Cl at $-78 \, ^\circ\text{C}$ provided silyl enol ether 57. Then, oxidation of 57 was attempted with both IBX-MPO and Pd(OAc)$_2$. Unfortunately, no enone formation was detected, and only silyl enol ether 57 was obtained.

Because phenyl selenide can be oxidized to enone by H$_2$O$_2$, we converted 39 to selenide 59 (Scheme 10). Fortunately, oxidation of 59 with H$_2$O$_2$ provided enone 60.

Based on this result, we believed that this procedure would work for substrate 51. Due to the ready availability of 39, we tried to epimerize the stereocenter of OTBS group in 39 by Mitsunobu reaction, then followed the procedure shown in Scheme 10. In the real total
synthesis of lyconadin A, we will not need to do this, because we would obtain a substrate with 51-type stereochemistry. Treatment of 39 with TBAF provided alcohol 50, which was exposed to Mitsunobu conditions to afford 61 (Scheme 11). Hydrolysis of 61 under basic conditions delivered alcohol 62. Unfortunately, TBS protection of 62 led to 63, rather than 51.

![Scheme 11. Tried Epimerization of 39](image)

Finally, we got the epimerized product via the following route (Scheme 12). Enone formation followed by hydrolysis afforded enone 65. With enone 65 in hand, we tried hydrogenation directed by cationic rhodium catalyst with 1000 Psi of H₂. Unfortunately, only starting material was recovered. Later, the Crabtree catalyst was applied, and stirred for 48 hours at room temperature. Fortunately, desired product 66 was obtained. We compared the mass spectrum and ¹H NMR of 66 with those of 62. We found they have the same mass spectrum, but
they have different $^1$H NMR spectrum. So, we successfully epimerized the proton adjacent to the carbonyl in the model compound 39.

Scheme 12. Epimerization of 50

Based on the successful protocol for epimerization of the model product, we could use our acyl radical tandem cyclization to make lyconadin A.

2.5 References


Chapter 3. Model Pyridone Synthesis Studies

Many biologically active natural products possess a 2-pyridone ring system.\(^1\) As a result, numerous annulation methods have been developed to install this ring.\(^2\) We are interested in synthesizing lyconadin A, which contains a 2-pyridone ring moiety. In our total synthesis, we plan to install the pyridone moiety at an early stage. Thus, it is necessary to develop a new protocol to prepare a pyridone system with an alkyl group at C-5 and a carboxy group at C-6.

3.1 Kozikowski Synthesis

In 1990, Kozikowski and co-workers developed a 2-pyridone synthesis by condensation of ketone, methyl propiolate and ammonia in one pot (Scheme 1).\(^3\) This method results in the formation of 5,6-disubstituted 2-pyridone. Unfortunately, it only can be used with symmetrical ketones and ketones which can only form a single enamine. As a member of the latter category, an \(\alpha\)-keto ester, if subjected to the Kozikowski pyridone annulation, would afford a 6-carboxy-substituted 2-pyridone.

![Scheme 1. Kozikowski Pyridone Synthesis](image)

In order to overcome the problem of regioselectivity in enamine formation, we selected methyl pyruvate as the ketone component in the Kozikowski pyridone synthesis (Scheme 2). This reaction was conducted in a sealed tube. Unfortunately, reaction with ammonia failed to give any pyridone product.
Then, we employed benzylamines to replace ammonia (Scheme 3). In these cases, we were able to obtain pyridones 67, 68, and 69. However, $^1$H NMR spectra revealed that the methyl ester group was located on C-5 rather than C-6.

The proposed mechanism for the formation of 67–69 is shown in Scheme 4. It involves Michael addition of the amine to methyl propiolate to form an allenolate. Then, a second Michael addition of the allenolate to another molecule of methyl propiolate occurred. Lactamization afforded 2-pyridone. Apparently, the $\alpha$-keto ester was not participating in this reaction. To confirm this hypothesis, the reaction was carried out with ethyl pyruvate in EtOH. A pyridone with a methyl ester was obtained, and none of the corresponding ethyl ester was detected.
Scheme 4. Proposed Mechanism of Pyridone Regioisomer Formation

Because there is no substituent on the N atom of lyconadin A, we would face the removal of the N atom substituent at some point in the total synthesis. With the regioisomeric pyridone in hand, we tried to deprotect the Bn, PMB, and 3,4-DMB groups (Table 1 and Table 2). Exposure of 67 to Pd(OH)$_2$ and H$_2$ under acidic conditions provided 70.$^4$

Scheme 5. Benzyl Deprotection of 67

Table 1 shows the conditions we examined for PMB deprotection of 68. When this compound was subjected to AlCl$_3$ in anisole, only starting material was recovered.$^5$ CAN made most of the starting material decompose.$^6$ Fortunately, treatment of 68 with DDQ delivered 70 in good yield.$^7$
Table 1. PMB Deprotection of 68

The conditions used to attempt 3,4-DMB deprotection of 69 are shown in Table 2. Under acidic conditions, 69 was untouched. DDQ did not work for this reaction. Fortunately, CAN in CH$_3$CN and H$_2$O resulted in the formation of 70 in 78% yield.

<table>
<thead>
<tr>
<th>Conditions:</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. AlCl$_3$, anisole, rt.</td>
<td>No Reaction</td>
</tr>
<tr>
<td>2. (NH$_4$)$_2$C$_6$(NO$_3$)$_6$,CH$_3$CN:H$_2$O = 2:1</td>
<td>SM. disappeared, small amount of product obtained</td>
</tr>
<tr>
<td>3. DDQ ,CH$_2$Cl$_2$, H$_2$O , rt.</td>
<td>78%</td>
</tr>
</tbody>
</table>

Table 2. 3,4-DMB Deprotection of 69

To improve the reactivity of the $\alpha$-keto ester, we formed the nucleophilic pyrrolidine enamine 72 and reacted it with propiolamide 71 (Table 3). After some experimentation, we found that annulation of enamine 72 and propioamide 71 proceeded in the presence of toluenesulfonic acid, providing 2-pyridone 73.
However, when we replaced the propiolamide \(71\) with benzyl propiolamide \(74\), we could only obtain a 20% yield of pyridone \(75\) (Table 4).
Then we replaced the ethyl pyruvate with a more hindered α-keto ester. We tried many solvents, such as DMF, CH$_3$CN, toluene, DMSO, triflorotoluene, dioxane, CCl$_4$, CHCl$_3$, and benzene in the presence of toluenesulfonic acid. However, the reaction did not occur (Scheme 6).

```
tried conditions: results
1. benzene, 1 eq p-TSOH, 80 °C, 48 h, 110°C, 12 h 20%
2. benzene, 0.1 eq p-TSOH, 80 °C, 48 h, 110°C, 12 h 14%
3. benzene, 1 eq PPTS, 80 °C, 48 h, 110°C, 12 h 17%
4. benzene, 0.1 eq PPTS, 80 °C, 48 h, 110°C, 12 h 10%
5. (i) benzene, 80 °C, 48 h (ii) 1 eq p-TSOH, 110°C, 12 h 6%
6. benzene, DBU, 80 °C, 48 h no product
```

Table 4. Attempted Pyridone Annulation.

Then we replaced the ethyl pyruvate with a more hindered α-keto ester. We tried many solvents, such as DMF, CH$_3$CN, toluene, DMSO, triflorotoluene, dioxane, CCl$_4$, CHCl$_3$, and benzene in the presence of toluenesulfonic acid. However, the reaction did not occur (Scheme 6).

Scheme 6. Attempted Pyridone Annulation.
Apparently, the increased steric hindrance of these substrates prevented the reaction.

Then, we tried to make the enolate of the $\alpha$-keto ester. Surprisingly, reaction of the enolate with propioamide provided undesired product 78 (Scheme 7).\textsuperscript{12,13}

Scheme 7. Attempted Pyridone Annulation.

The following is the proposed mechanism (Scheme 8). It involves Michael addition of the sodium ethoxide to the enolate of the $\alpha$-keto ester followed by a second Michael addition to form an $\alpha,\beta$-unsaturated amide. Then, the dihydropyridone formation followed by elimination provides 2-pyridone.

Scheme 8. Proposed Mechanism of Pyridone Annulation
We tried the reaction with Me₄NOAc, and got an unidentified compound in 81–93% yield (Scheme 9). Initially, we thought it was 79, since the unidentified compound has the same mass spectrum as that of the compound 79 and it possesses the following ¹H NMR peaks: δ 8.17 (d, J = 3 Hz, 1H), 7.58 (dd, J = 3 Hz, 9.8 Hz, 1H), 6.57 (d, J = 9.5 Hz, 1H), 5.64 (br s, 1H), 3.61 (s, 3H). However, we compared the ¹H NMR of this compound with the reported ¹H NMR data of 79.¹⁴ They do not match.

![Scheme 9. Attempted Pyridone Annulation.](attachment:scheme9.png)

Thus, the modified Kozikowski pyridone annulation was unsuitable for our case.

3.2 H–W–E Reaction for the RCM

In 2008, Donohoe and co-workers developed a novel pyridone synthesis strategy, which can provide a wide variety of substituted pyridones including 5-alkyl-6-carboxypyridones.¹⁵ This process is summarized in Scheme 10. They employ ring-closing metathesis to form a dihydropyridone. Then, elimination generates the pyridone. However, ring-closing metathesis could not be used in our case, because the substrate required for the total synthesis of lyconadin A would possess additional double bonds for use in the radical cascade cyclization. Thus, we tried to develop a pyridone annulation method based on the Donohoe strategy. We would employ a different reaction in the cyclization step.
We attempted to substitute an intramolecular Horner–Wadsworth–Emmons reaction for the ring-closing metathesis. The electron-deficient methyl ester group, which is needed in our total synthesis, was installed at C-6 to make the $\alpha$-proton more acidic and help the base-induced aromatization. We started our model study from dimethyl malonate. Ozonolysis of dimethyl malonate provided aldehyde $80$, which was converted into oxime $81$ by treatment with $\text{H}_2\text{NOBn}$ (Scheme 11). We tried a Mannich reaction of oxime $81$ with a silyl enol ether catalyzed by a Lewis acid, such as $\text{Cu(OTf)}_2$, $\text{Zn(OTf)}_2$, or $\text{Cu(OTf)}$, but only recovered starting material. The OBn group is an electron-donating group, which lowers the electrophilicity of oxime $81$. The protocol mediated by the Lewis base LiOAc provided Claisen adduct $82$ as the major product in modest yield, and $\beta$-lactam $83$ was a minor product of this reaction. In this reaction, the OBn group increases the nucleophilicity of $81$, and under the basic conditions, the by-product $83$ is generated. Then, we changed the OBn group into a Ts group, which is an electron-withdrawing group. Thermal [2+2] cycloaddition of $\rho$-toluenesulfonylisocyanate and methyl glyoxylate $80$ followed by loss of CO$_2$ afforded tosylimine $84$. The Lewis-base-catalyzed reaction between trimethylsilyl enol ether and tosyl imine $84$ led to Mannich adduct $85$ in good yield as a ca. 6:1 mixture of diastereomers. The Lewis acid Cu(OTf)$_2$ did not work in this reaction. The major
isomer was assumed to possess the \textit{anti} configuration according to the acyclic transition state proposed by Mukaiyama and co-workers for the Mannich reaction.\textsuperscript{17} Because both stereocenters would be destroyed later in the synthesis, the mixture was carried forward without separation.

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme11}
\caption{Synthesis of Tosylamine 85.}
\end{scheme}

To prepare the precursor 86 of Horner–Wadsworth–Emmons reaction, we tried acylation reactions between acyl chloride and tosylamine 85 in different conditions, however we were unable to obtain desired product (Table 5).
Table 5. Attempted Synthesis of Horner–Wadsworth–Emmons Cyclization Substrate

Then, we turned to reactions between carboxylic acid and tosylamine 85 (Scheme 12). We tried conditions of DCC and PPY, carbonyl diimidazole, and N-methyl-2-chloropyridine salt. Unfortunately, we only recovered starting material. Apparently, the tosylamine is not nucleophilic enough to react with inductively deactivated acid chlorides. In this case, Horner–Wadsworth–Emmons reaction is not feasible.

3.3 Reformatsky Reaction for the RCM

It seemed that a Reformatsky reaction might meet our needs. We hoped to perform the metal-induced intramolecular reaction of an \( \alpha \)-halocarbonyl with the thioester in our substrate. A bromide is commonly used in the Reformatsky reaction. We tried the reaction of tosylamine 85 with bromoacetyl chloride in pyridine, but only starting material was returned. The reaction of tosylamine 85, bromoacetyl chloride, and DMAP in CH\(_2\)Cl\(_2\)/DMF did not work either.\(^{20}\) Then, NaH in benzene was tried in this reaction. We only obtained a trace amount of product. Eventually, acylation of 85 with bromoacetyl chloride was successful when we treated 85 with \( n \)-BuLi in THF, affording bromide 88 in good yield (Scheme 13). With the bromide 88 in hand, we tried to selectively reduce the thioester moiety in 88 to aldehyde. Unfortunately, we were unable to obtain aldehyde, as exposure to Raney Ni\(^{22}\) or Lindlar catalyst/Et\(_3\)SiH\(^{23}\) resulted in debromination. Similar results were obtained with the chlorinated analogue of 88.

![Scheme 13. Intramolecular Reformatsky-type Condensation.](image)

Reformatsky reactions employing thioesters as electrophiles are unknown.\(^{24}\) However, we were encouraged by some examples of Reformatsky reactions with species such as \( N \)-acyloxazolidinones,\(^{25}\) \( N \)-acylpyrazoles,\(^{26}\) and lactones.\(^{27}\) We determined to directly attempt the cyclization of 88. SmI\(_2\) is typically used in intramolecular Reformatsky reactions.\(^{28}\) However, the
reaction of 88 under these conditions led to debromination. Then, we discovered the work of Hashimoto and co-workers. They combined PPh$_3$ and TiCl$_4$ to generate an enolate from an $\alpha$-bromothioester, which underwent both self-condensations and crossed-Claisen-type reactions to provide various types of $\beta$-ketothioester adducts. Bromo tosylamide 88 was subjected to Hashimoto protocol. Fortunately, the cyclized product was achieved. Interestingly, a vinylogous thiocarbamate was formed rather than the corresponding Dieckmann-type product. This reaction is very sensitive to moisture, which led to the formation of debrominated starting material.

### 3.4 Pyridone Synthesis

Elimination and desulfurization of 89 were needed to prepare the 2-pyridone. In principle, these two steps could be carried out in either order. However, we failed to remove the sulfide from 89. Among numerous desulfurizing reagents, nickel reagents occupy an important position. NiCl$_2$/NaBH$_4$ and Ra(Ni) led to over-reduction to the saturated derivative. NiCRA’s and NiCRA-bPy’s are effective desulfurization reagents for aromatic sulfoxides or vinyl thioethers. We tried these reactions with different ratios of reagents and different temperatures, but we only obtained elimination product, pyridone, rather than desulfurization product.

Hydrolysis of vinyl thioether catalyzed by acid/Lewis acid is a good method to prepare a ketone. If ketone 90 is achieved, then reduction followed by elimination would provide desired dihydropyridone 91 (Scheme 14). We tried to form ketone 90 by treatment of 89 with HgCl$_2$, HCl, TiCl$_4$, AgNO$_3$, but only recovered starting material.
Scheme 14. Proposed Pathway to the Synthesis of 91

Treatment of vinylogous thiocarbamate 89 with NaOMe should provide vinylogous carbamate 92. Then hydrolysis under acidic conditions followed by reduction and elimination will also achieve our desulfurization goal (Scheme 15). We tried to treat 89 with NaOMe, but we got carboxylic acid 93 rather than 92. Hydrolysis of the thioether did not happen. Under basic conditions, elimination occurred first, and generated aromatic pyridone thioether 93. It is too difficult to substitute SMe for OMe on an aromatic ring.

Scheme 15. Proposed Pathway to the Synthesis of 91

Due to the problems encountered in the desulfurization of 89, we decided to perform the elimination step first. Thus, treatment of 89 with DBU in DMF provided pyridone 95 in excellent yield (Scheme 16). Pyridone 95 was subjected to Lindlar catalyst and Et3SiH in acetone at room
temperature to afford 94 in 95% yield.\textsuperscript{38} The combination of Lindlar catalyst and \text{Et}_3\text{SiH} selectively cleaved the vinyl sulfide without reducing the pyridone.

![Synthesis of Pyridone 94](image)

**Scheme 16. Synthesis of Pyridone 94.**

We had developed a novel method to generate the 5-alkyl-6-carbomethoxy-2-pyridone nucleus. To explore the scope of the annulation method, we used a larger group at C-5 (Scheme 17). The Mannich reaction between silyl ketene thioacetal and tosylimine was less selective (1.6:1) than the corresponding reaction shown in Scheme 13. Acylation of the tosylamine 96 provided 97 in lower yield. Cyclization, elimination, and desulfurization proceeded smoothly, providing isopropyl-substituted pyridone 100 in good yield.

![Synthesis of Isopropyl-substituted Pyridone 100](image)

**Scheme 17. Synthesis of Isopropyl-substituted Pyridone 100.**
We also synthesized 3,5-dialkyl-substituted pyridone 113 via this protocol, as outlined in Scheme 18. Cyclization of 110 afforded a 1:2.4 mixture of vinyl sulfide 111 and ketone 112 in 80% overall yield. So, the substituent on the enolate intermediate has effect on the product distribution of the cyclization. In theory, we can convert compound 112 into 113 by means of a sequence of ketone reduction, mesylation (or halogenation) of the resulting alcohol, and elimination.


In conclusion, inspired by Donohoe’s pyridone synthesis, we developed a method for the construction of 5-alkyl and 3,5-dialkyl-6-carbomethoxy-2-pyridone, which is an important moiety of lyconadin A. We employed the Mannich reaction to make a tosylamine. Acylation of
the resulting tosylamine generated the cyclization substrate. We used intramolecular
Reformatsky-type reaction to construct the 6-membered ring. The typical cyclization products
were vinylogous thiocarbamates (i.e. 89, 98, and 111), but in one case the Dieckmann-type
product was also formed (112). Elimination and desulfurization delivered the desired pyridones.
We believe that this new method could be used in the synthesis of complex molecules such as
lyconadin A.

3.5 References


Chapter 4. Attempted Synthetic Approaches to Lyconadin A.

Our model studies towards the acyl radical cascade cyclization have given us confidence that a tandem 7-exo/6-exo cyclization can be used to install the central portion of lyconadin A. In addition, we were exploring the modified Kozikowski pyridone annulation, which involved the condensation of pyrrolidine enamine and propiolamide in the presence of toluenesulfonic acid, and we found that the desired 2-pyridone 73 was provided. Before we probed the scope of this pyridone annulation, we assumed that this strategy could be used in the total synthesis of lyconadin A. Based on these two model studies, we started our total synthesis of lyconadin A.

4.1 Enzymatic Approach

The retrosynthesis of lyconadin A is shown in Scheme 1. Cleavage of the C6–N and C13–N bonds and protection of the resulting primary amine will provide tricyclic compound 114. Then, disconnection of the C8–C15 and C6–C7 bonds in 114 will afford ene-yne 115, the precursor of a radical cascade cyclization. The compound 115 could be derived from α-keto ester 116 via condensation of pyrrolidine enamine of 116 and propiolamide. Removal of α-keto ester from 116 will form intermediate 117, which could be obtained by regioselective ring opening of epoxide 118. Scission of alkyne from 118 will result in epoxide 119, which can be generated from alkene 120 by means of the Shi asymmetric epoxidation.¹ The alkene 120 could be synthesized from alkene 121. The alkene 121 will be obtained by an enzymatic desymmetrization of a diol,² which can be prepared from 2-butyne-1,4-diol.
We started our total synthesis with 2-butyne-1,4-diol (Scheme 2). Tritylation of 2-butyne-1,4-diol with 1 equiv. of TrCl and 1.1 equiv. of Et$_3$N provided alkyne 122. Reduction of 122 with LiAlH$_4$ provided alkene 123. Bromination of 123 led to bromide 124. Alkylation of 124 with diethyl malonate followed by reduction with LAH afforded diol 125.

Scheme 1. Retrosynthesis of Lyconadin A
The preparation of chiral building blocks can be accomplished using chemical or enzymatic methodologies. In particular, the asymmetrization of 1,3-propanediols using lipases has been extensively studied.\(^2\) 1,3-Diol 125 was asymmetrized by enantioselective acetylation in organic solvent catalyzed by a lipase. We tried a series of reactions catalyzed by different lipases (Table 1). Treatment of 125 with PSPL or CAL B led to diacetate 127.\(^3,4\) The acetylation catalyzed by PCL led to higher ee in 1,4-dioxane/THF than in THF.\(^4\) A long stirring time was helpful to increase the ee value, but the highest we obtained is 70% ee with stirring for one week. PPL only delivered poor ee.\(^5\) For the reaction catalyzed by ANL, the ee value changed with time. It increased first and then decreased. The best result we obtained is 84% ee.
<table>
<thead>
<tr>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSPL, 4Å M.S., vinyl acetate, 35 °C or rt</td>
<td>obtained 127</td>
</tr>
<tr>
<td>PCL, vinyl acetate, 1,4–dioxane:THF=5:1, 0 °C</td>
<td>81%, 70% ee</td>
</tr>
<tr>
<td>PCL, vinyl acetate, THF, 0 °C</td>
<td>56%, 55% ee</td>
</tr>
<tr>
<td>PPL, vinyl acetate, 30°C</td>
<td>86%, 26% ee</td>
</tr>
<tr>
<td>PFL, vinyl acetate, 30°C</td>
<td>90%, 64% ee</td>
</tr>
<tr>
<td>ANL, vinyl acetate, 30°C</td>
<td>91%, 84% ee</td>
</tr>
<tr>
<td>CAL B, vinyl acetate, 4 Å M. S., rt</td>
<td>obtained 127</td>
</tr>
</tbody>
</table>

Table 1. Lipase Catalyzed Desymmetrization

In 2002, Oriyama and co-workers developed a promising catalyst for asymmetrization of symmetrical 1,3-diol. This is the first example of non-enzymatic catalytic asymmetrization of meso-1,3-propanediol. It involves the reaction of a 1,3-diol with benzoyl chloride or derivatives catalyzed by a chiral 1,2-diamine derived from (S)-proline to provide highly enantiomerically enriched 3-acyloxy alcohol. We tried this reaction with acetic anhydride as acylating agent catalyzed by 1,2-diamine 129 (Scheme 3). Unfortunately, it afforded the monoacetate 126 as a racemic mixture.
Scheme 3. Asymmetrization With Organic Catalyst 129

In order to determine the absolute configuration of monoacetate 126, we converted 126 to known compound 137. Protection of 126 as a PMB ether under basic conditions led to acetate hydrolysis. So, Dudley’s reagent 133, which forms PMB ethers under mild conditions, was employed. Treatment of alcohol 126 with 133 provided PMB ether 134 (Scheme 4).\(^7\) Ozonolysis followed by Wittig reaction of the resulting aldehyde 136 delievered alkene 137, which possesses identical rotation to that reported in the literature. The standard rotation is \(-13.8\) (c 1.2, CHCl\(_3\)), and we got \(-6.5\). So, we obtained the desired enantiomer in the desymmetrization step.
Scheme 4. Attempt to Determine the Configuration of Monoacetate 126

We converted monoacetate 126 to secondary amine 138 via a Mitsunobu reaction (Scheme 5). Then, treatment of 138 with K$_2$CO$_3$ afforded hydroxy amine 139. 3,4-DMB protection of 139 with 3,4-DMB-Br led to compound 140, which was further protected with 3,4-DMB group to provide secondary amine 141.
The Shi epoxidation is an asymmetric epoxidation of an olefin with oxone and a fructose-derived catalyst.\textsuperscript{10} This procedure generates epoxides with high ee from \textit{trans}-disubstituted alkenes and trisubstituted alkenes. In addition, the reagents are cheap. We are greatly attracted by this protocol and planned to employ this method in our synthesis by constructing epoxide 144. The chiral ketone 143 was prepared via protection of D-fructose with acetone followed by PCC oxidation of the resulting ketal 142 (Scheme 6). We tried the epoxidation with mCPBA first.\textsuperscript{11} We found that there is no diastereoselectivity, and we got a 1:1 ratio of diastereomers. We tried three Shi epoxidation conditions. The conditions shown in entries 1 and 2 only led to recovered starting material. For entry 3, if the reaction was carried out at 0 °C, we only obtained a very small amount of product, and recovered most of the starting material.\textsuperscript{12} When the reaction was performed at 4–5 °C (\textit{i. e.} ice water bath), desired product was achieved in 45 % yield with 43 % starting material recovered.
With epoxide 144 in hand, we hoped to open the epoxide ring by treatment with an alkynyllithium reagent (Scheme 7). In theory, because the trityl group is bulky, the alkynyl group will attack the epoxide from the less hindered position to provide product 145. Unfortunately, when we performed the reaction with lithium reagent catalyzed by BF₃·O(C₂H₅)₂, or BF₃·THF at
−78 °C, we only obtained a small amount of detritylation product 147, and recovered most of the starting material.\textsuperscript{13,14} If we allowed the reaction to warm to rt and stir at rt, we obtained a mixture of 144, 146 and 147. The trityl group is sensitive to Lewis acids, and it is removed before the alkynyl group attacks the epoxide. The HOCH\textsubscript{2} group is less hindered. Thus, the alkynyl group attacks from the less hindered side to afford undesired product 146. So this synthetic route is not feasible.

![Scheme 7. Ring Opening of Epoxide 144](image)

4.2. One Carbon Short Chiral Auxiliary-Mediated Approach

Based on the drawbacks of the previous route (ee value is difficult to control and Tr group is labile), we turned to another route to construct the building block. We introduced the chiral auxiliary pseudoephedrine to control diastereoselectivity and switched the Tr group to a TIPS group. We started our total synthesis with 2-butyne-1,4-diol (Scheme 8). Protection of 2-butyne-1,4-diol with a TIPS group provided alkyn 148. Reduction of 148 with LiAlH\textsubscript{4} provided alkene 149. Mesylation of crude 149 followed by iodination of the resulting meyslate 150 afforded iodide 151. Treatment of (1S, 2S)-(+)pseudoephedrine with methyl-3-hydroxy propanoate provided 152. Myers asymmetric alkylation followed by protection of primary alcohol 153 with
3,4-DMB group afforded 154. Removal of chiral auxiliary formed alcohol 155 with 76% ee.

Benzylation with BnBr resulted in 156. Shi epoxidation of 156 led to 157 in excellent yield with 96% de.
While we were working on this synthetic approach, we were also conducting the
model studies towards 2-pyridone synthesis. Based on the results of these studies, we recognized the benefit of having one more carbon on the chain of 152. So, we halted work on this route.

4.3 References


Chapter 5. Progress Towards Total Synthesis of Lyconadin A

When we explored the scope of the modified Kozikowski pyridone annulation, which involved the condensation of pyrrolidine enamine and propiolamide in the presence of toluenesulfonic acid, we found that the increased steric hindrance on pyrrolidine enamine prevents the reaction. Then, we successfully developed a method for the construction of 5-alkyl and 3,5-dialkyl-6-carbomethoxy-2-pyridones based on Donohoe’s pyridone synthesis. We plan to use this pyridone annulation protocol in our total synthesis of lyconadin A. The synthetic route shown in Scheme 9 of Chapter 4 was designed for the pyridone synthesis based on modified the Kozikowski protocol. We made a small change to that route to match our modified Donohoe’s pyridone synthesis by adding one more carbon on the chain of 152.

5.1. Retrosynthesis

Scheme 1 shows our current retrosynthetic strategy of lyconadin A. We will epimerize the stereocenter adjacent to the carbonyl group in compound 163 to generate cis-fused compound 162 via the directed hydrogenation method we tried in the model product. The tricyclic intermediate 163 would be derived from compound 164 by means of a tandem 7-exo/6-exo radical cyclization. The thioester 165 could be converted into pyridone 164 via the strategy developed by us. The thioester 165 could be prepared from 166 via a sequence of reactions. Compound 166 could be prepared from alkene 167 by epoxide formation, followed by ring opening. We introduced chiral auxiliary pseudoephedrine to control the stereochemistry of compound 167.
Scheme 1. Current Retrosynthesis of Lyconadin A

5.2. First Attempt to the Synthesis of the Precursor of Epoxidation

Treatment of (1S, 2S)-(+)-pseudoephedrine with methyl-4-hydroxy butanoate provided 158 (Scheme 2). Myers asymmetric alkylation followed by protection of the resulting primary alcohol 159 with a 3,4-dimethoxybenzyl (DMB) group afforded 160. Removal of the chiral auxiliary by treatment with borane–ammonia formed undesired diol 161. In this reaction, lithium coordinated with both oxygen of alcohol and ODMB to form a 7-membered ring. H– then attacked the CH2 of DMB group to provide diol 161 in 35% ee. In the alkylation step, the lithium
apparently coordinated with the free primary alcohol of 158 along with the secondary alcohol and the carbonyl. This lowers the diastereoselectivity of alkylation.

![Scheme 2. Failed Synthesis of DMB Ether](image)

**5.3. Second Attempt to the Synthesis of the Precursor of Epoxidation**

To avoid coordination, we protected primary alcohol 158 with a bulky TBDPS group before alkylation. To control the regioselectivity of ring-opening in a later step, we installed a Tr group in place of the TIPS group.

Treatment of pseudoephedrine with methyl 4-hydroxyl butanoate provided amide 158 (Scheme 3). Then, we protected the hydroxyl group with a bulky TBDPS group to prevent lithium coordination. Asymmetric alkylation of 168 provided 170. Removal of the chiral auxiliary in 170 generated alcohol 167 in 91% yield and 96% ee. Benzylation of 167 afforded 171 in excellent yield.
5.4. Shi-Epoxidation

The Shi epoxidation\(^3\) is highly pH dependent. Generally, higher pH results in more rapid autodecomposition of oxone, which leads to the decrease of epoxidation efficiency. However, at lower pH, the chiral ketone decomposed very rapidly. The epoxidation is typically carried out around pH 10.5. Our substrate 171 is sterically hindered. So, it reacted slowly under Shi epoxidation conditions. Therefore, we added chiral ketone and oxone–KOH once more after 4 hours of reaction time. Shi epoxidation of alkene 171 conducted in this way provided epoxide 172 in 63% yield with 96% de, and recovered starting material in 15% yield (Table 1, entry 3). The stereochemistry of epoxidation is based on the spiro transition state proposed by Shi and co-workers. We tried other Shi epoxidation conditions, but they did not work (entries 1 and 2).
5.5. Ring Opening Reaction

The regioselective ring-opening of epoxides by Grignard reagents has been restricted mostly to unhindered epoxides and those activated by an adjacent vinyl or aryl group. Disubstituted epoxides present regioselectivity problems and due to Lewis acid (magnesium halide salts), the formation of side products (rearrangement, elimination, reduction, etc.) may be observed. In our substrate 172, a bulky Tr group is installed to control the regiochemistry. In this epoxide ring-opening reaction, since Tr group is bulky, the vinyl group should attack the less hindered carbon. We tried a series of copper salts in different ratios of Et₂O/THF (Table 2). However, all the results were poor. We recovered starting material or got a trace of product along with major elimination and reduction side products.

**Table 1. Synthesis of Epoxide 172**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 30% H₂O₂, CH₃CN/dimethoxy methane, chiral ketone, 2M K₂CO₃, 4x10⁻⁴ M EDTA</td>
<td>trace of product</td>
</tr>
<tr>
<td>2. Na₂B₄O₇·10H₂O, Na₂EDTA, Bu₄NHSO₄, CH₃CN, chiral ketone, oxone, K₂CO₃</td>
<td>recovered SM</td>
</tr>
<tr>
<td>3. oxone/4x10⁻⁴ M Na₂EDTA, 1.47 M KOH, Bu₄NHSO₄, chiral ketone, K₂CO₃+CH₃COOH, DMM/CH₃CN, 4°C</td>
<td>63%, 96% de</td>
</tr>
<tr>
<td></td>
<td>recovered 15% SM</td>
</tr>
</tbody>
</table>
Table 2. Attempted Ring Opening of Compound 172

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MgBr, Cul, Me₂S, THF, ice-bath</td>
<td>trace of product</td>
</tr>
<tr>
<td>MgBr, CeCl₃, THF, -78°C to rt</td>
<td>recovered SM</td>
</tr>
<tr>
<td>MgBr, Cul, Et₂O, THF, -78 °C to rt</td>
<td>trace of product</td>
</tr>
<tr>
<td>MgBr, Cul, Et₂O/THF= 7/1, -20 °C to rt</td>
<td>trace of product</td>
</tr>
<tr>
<td>MgBr, Cul, Et₂O/THF= 7/1, 30°C</td>
<td>decomposed</td>
</tr>
<tr>
<td>(2-thienyl)Cu(CN)Li₂, THF/Et₂O=3/5</td>
<td>recovered SM</td>
</tr>
<tr>
<td>(2-thienyl)Cu(CN)Li₂, THF/Et₂O=3/5, BF₃Et₂O</td>
<td>recovered SM</td>
</tr>
<tr>
<td>Cu(CN)Li</td>
<td>recovered SM</td>
</tr>
<tr>
<td>Cu(CN)Li, BF₃Et₂O</td>
<td>decomposed</td>
</tr>
<tr>
<td>MgBr,CuBr, SMe₂, SMe₂, Et₂O/THF</td>
<td>trace of product</td>
</tr>
</tbody>
</table>

Prieto’s work⁴ manifests that the copper-catalyzed Grignard cleavage of hindered epoxide does tolerate a free hydroxyl group. In order to decrease the hindrance of epoxide, we planned to perform the ring-opening reaction with epoxide 176 with free hydroxyl group. Unfortunately, in the epoxidation step, we got cyclized compound 177, rather than epoxide 176 (Table 3).
Table 3. Attempted Epoxide Formation

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Na$_2$B$_4$O$_7$.10H$_2$O, Na$_2$EDTA, Bu$_4$NHSO$_4$, CH$_3$CN, chiral ketone, oxone, K$_2$CO$_3$</td>
<td>recovered SM</td>
</tr>
<tr>
<td>2. oxone/4x10$^{-4}$ M Na$_2$EDTA, 1.47 M KOH, Bu$_4$NHSO$_4$, chiral ketone, K$_2$CO$_3$+CH$_3$COOH, DMM/CH$_3$CN, 4°C</td>
<td>recovered SM</td>
</tr>
<tr>
<td>3. oxone/4x10$^{-4}$ M Na$_2$EDTA, 1.47 M KOH, Bu$_4$NHSO$_4$, chiral ketone, K$_2$CO$_3$+CH$_3$COOH, DMM/CH$_3$CN, rt</td>
<td>obtained mostly 177</td>
</tr>
</tbody>
</table>

Then, we protected the alcohol 167 with PMB and TBS respectively (Scheme 4). Shi epoxidation afforded desired epoxides 179 and 182 respectively. However, the ring-opening of epoxide 179 only resulted in decomposed compound 176, and ring-opening of epoxide 182 only afforded recovered starting material.
Scheme 4. Attempted Ring Opening of Epoxide 179 and 182

Then, we protected 167 with a 2-naphthylmethyl (NAP) group to form 184 (Scheme 5). Shi epoxidation of compound 184 afforded epoxide 185 with 97\% de. We tried the ring opening reaction by treating the epoxide 185 with Lewis acid CuI at first, and we obtained compound 186 in 35\% yield.\(^5\) We believe that we could improve the yield of ring opening reaction by optimization.
Scheme 5. Synthesis of Compound 186

The NAP protection was challenging, because the TBDPS group and the Tr group are sensitive to base and acid respectively. NaH and NAPBr delivered product 184 and di-NAP 187 by-product (Table 4). In the presence of imidazole, there was no di-NAP 187 by-product formed. However, the TBDPS group migration by-product was formed. Pyridine, BuLi, or Bu₂SnO at room temperature with NAPBr resulted in recovered starting material.⁶
Table 4. Attempted NAP Protection of Compound 167

We also tried some mild conditions (Scheme 6). 2-Benzylxyloxy-1-methylpyridinium triflate is a novel benzylation reagent for alcohols.7 No acidic or basic promoters are needed for benzyl transfer, which occurs upon warming in the presence of the alcohol substrate under mild conditions. However, in our case, triflated salt of compound 188 led to a mixture of product 184, di-NAP 187, TBDPS migration by-product, and other by-products. We also tried a TMSOTf-catalyzed benzyl ether synthesis from aldehyde and TMS ether 189 via triethylsilane-reduction.8 Unfortunately, it delivered decomposed by-products.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4 eq NaH, NAPBr, THF/DMF, rt</td>
<td>most of 187</td>
</tr>
<tr>
<td>1.4 eq NaH, NAPBr, Bu4NI, THF/DMF, 0°C</td>
<td>184:187 = 1:1</td>
</tr>
<tr>
<td>0.86 eq NaH, NAPBr, Bu4NI, THF/DMF, –5°C</td>
<td>184:187 = 1:1</td>
</tr>
<tr>
<td>0.86 eq NaH, NAPBr, Bu4NI, THF, –5°C</td>
<td>most of SM + 184:187 = 1:1</td>
</tr>
<tr>
<td>NAPBr, Ag2O, DMF</td>
<td>decomposed</td>
</tr>
<tr>
<td>NAPBr, Pyr. rt</td>
<td>recovered SM</td>
</tr>
<tr>
<td>NAPBr, BuLi, THF, –78 °C to 5°C</td>
<td>recovered SM</td>
</tr>
<tr>
<td>Bu4NHSO4, 50% KOH, NAPBr, benzene</td>
<td>most of diol+ 187</td>
</tr>
<tr>
<td>NAPBr, NaH, CuCl2, TBAI, THF</td>
<td>decomposed</td>
</tr>
<tr>
<td>Bu2SnO, NAPBr, TBAI, CSF, toluene, DMF, rt</td>
<td>recovered SM</td>
</tr>
<tr>
<td>Bu2SnO, NAPBr, TBAI, CSF, toluene, DMF, 95 °C</td>
<td>decomposed</td>
</tr>
<tr>
<td>NAPBr, NaH, imidazole, TBAI, THF/DMF = 4/1, 0 °C</td>
<td>41–62% 184+ TBDPS migration</td>
</tr>
</tbody>
</table>
Scheme 6. Attempts to Synthesize Compound 184

Based on all our attempted reactions, we realized that the TBDPS group in our substrate is very sensitive to base and easy to migrate. Because a TIPS group is more stable to base and less likely to migrate than a TBDPS group, the TBDPS group was switched to a TIPS group in the alkylation substrate (Scheme 7). We tried the ring opening of the derivative of epoxide 185 with TIPS group rather than TBDPS group. However, we only recovered starting material. Thus, after the NAP protection of alcohol 192, we cleaved the TIPS group, and reprotected with TBDPS group. The overall yield of these three steps was 77%. Then, we optimized the ring opening reaction. This reaction is very sensitive to moisture and air, and a more concentrated solution is also helpful to improve the yield. Because our substrate 185 is more hindered, stirring at room temperature after adding all the starting materials is necessary.
5.6. Synthesis of Carboxylic Acid

Compound 186 was subjected to CSA to lead to diol 193 (Scheme 8). This reaction could not be stirred for more than 4 hour, since the NAP group would be cleaved by CSA after a long time. Diol 193 was exposed to 1-(2,4,6-trisopropylbenzenesulfonyl) imidazole to form epoxide 194. Ring opening of epoxide 194 delivered alcohol 195. Initially, we protected the alcohol 195
with a TBS group. Unfortunately, in a later step, we were unable to selectively remove the TBDPS group without touching the TBS group. So, we protected the alcohol 195 with a Tr group to provide compound 196. Treatment of 196 with TBAF afforded primary alcohol 197, which was oxidized to carboxylic acid 198.

Scheme 8. Synthesis of Carboxylic Acid 198

5.7 References


Chapter 6. Conclusion and Future Work

6.1. Conclusion

In our group, Seth Grant developed a novel 7-exo/6-exo acyl radical cascade cyclization as a method of making the bicyclo[5.4.0]undecane ring system of lyconadin A, and he obtained trans-fused product in high yield as a single diastereomer. To explore the origin of stereochemistry, we performed the radical cascade cyclization with a free alcohol derived from Seth’s precursor of cyclization. An alcohol was obtained as a single diastereomer which has the same stereochemistry as Seth’s cyclization product. In addition, a cyclization of a diastereomeric substrate also afforded a single diastereomer. These experiments prove that the 7-exo/6-exo cascade radical cyclization happens with excellent diastereoselectivity. The stereochemistry is consistent with chairlike or pseudochairlike transition states. The model products are trans-fused ring systems, while a cis-fused ring system is needed in lyconadin A. We have discovered a method to convert trans-fused model cascade cyclization product into the desired cis isomer.

Based on Donohoe’s pyridone synthesis, we developed a method for the construction of 5-alkyl and 3,5-dialkyl-6-carboxmethoxy-2-pyridones, the former of which is an important moiety of lyconadin A. An intramolecular Reformatsky reaction is a key step in this process. We believe that this new method could be used in the total synthesis of lyconadin A.

We have proceeded with our total synthesis, in which we generated an epoxide by Shi asymmetric epoxidation and regioselectively opened epoxide rings. So far, we have prepared carboxylic acid 197.
6.2. Future Work

Our future work is shown in Scheme 1. The carboxylic acid 198 will be converted into thioester 199,\textsuperscript{1} which we will use to install pyridone 202 by means of the pyridone synthesis developed by us.\textsuperscript{2} Mannich reaction of thioester and tosylimine will provide tosylamine 200. Acylation of tosylamine 200 with bromoacetyl chloride will give tosylamide 201. Reformatsky reaction, elimination, and desulfurization will result in pyridone 202. Ester hydrolysis and phenyl selenoesterification will deliver phenyl selenoester 203, the precursor of tandem radical cyclization. We will perform tandem 7-exo/6-exo radical cyclization to convert 203 to tricyclic compound 204.\textsuperscript{3} Then, we will epimerize the stereocenter adjacent to the carbonyl group in compound 204 via the method employed in the model system. The phenyl selenide formation, oxidation, and the Tr deprotection will afford enone 205. Stereoselective reduction of ketone 205 followed by hydrogenation directed by hydroxyl group will lead to compound 206. The NAP deprotection, Mitsunobu reaction of the resulting alcohol,\textsuperscript{4} and mesylation will generate compound 207. According to our experience, K₂CO₃ can cleave a Phth group in methanol at rt. Treatment of 207 with K₂CO₃ in methanol will afford lyconadin A.
Scheme 1. Future Work
6.3. References


Chapter 7 Experimental Information

Benzene, dimethylformamide, methanol, methylene chloride, tetrahydrofuran, and toluene were dried by passage through a solvent drying system containing cylinders of activated alumina. Flash chromatography was carried out using 60–230 mesh silica gel. $^1$H NMR spectra were acquired on 300 or 500 MHz spectrometers with chloroform (7.27 ppm) or pyridine (8.74 ppm) as internal references. Signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), br s (broad singlet), m (multiplet). Coupling constants are reported in hertz (Hz). $^{13}$C NMR spectra were acquired on spectrometers operating at 75 or 125 MHz with chloroform (77.23 ppm) or pyridine (149.80) as internal references. Infrared spectra were obtained on an FT-IR spectrometer. Mass spectral data were obtained using ESI techniques.

![Chemical Structure Image]

*anti*-Diethyl 3-((tert-butyldimethylsilyloxy)-2-(2-((tert-butyldimethylsilyloxy)methyl)phenethyl)pentanedioate (43). Freshly prepared Zn(BH$_4$)$_2$ $^1$ (0.10 M in ether, 50 mL, 4.99 mmol) was added dropwise at 0 °C under Ar to a stirred solution of 36 (1.50 g, 3.33 mmol)

---

in anhydrous Et₂O (68 mL). The resulting solution was stirred for 10 min at 0 °C, and then treated with sat aq NH₄Cl (1 mL). The organic phase was collected, and the aqueous phase was extracted with CH₂Cl₂ (3 × 5 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo.

To a solution of the crude alcohol in anhydrous CH₂Cl₂ (16.6 mL) at 0 °C under Ar was added 2,6-lutidine (1.16 mL, 1.07 g, 9.98 mmol). The solution was stirred at 0 °C for 5 min, then treated dropwise with TBS-OTf (1.53 mL, 1.76 g, 6.66 mmol). The resultant mixture was stirred for 16 h, then treated with sat aq NaHCO₃ (18 mL). The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. Flash chromatography (SiO₂, 5% EtOAc in hexanes elution) afforded 43 (1.215 g, 2.14 mmol, 64%, ca. 4:1 mixture of diastereomers) as a yellow oil:

$^{1}$H NMR (CDCl₃, 500 MHz) δ 7.46–7.42 (m, 1H), 7.23–7.20 (m, 2H), 7.15–7.12 (m, 1H), 4.75 and 4.74 (2s, 2H), 4.44–4.36 (m, 1H), 4.22–4.08 (m, 4H), 2.69–2.61 (m, 2H), 2.59–2.44 (m, 3H), 1.98–1.71 (m, 2H), 1.31 (t, J = 7.0 Hz, 3H), 1.25 (t, J = 7.0 Hz, 3H), 0.95 (s, 9H), 0.85 (s, 9H), 0.11 and 0.10 (2s, 6H) 0.06 and 0.02 (2s, 3H), 0.04 (s, 3H); $^{13}$C NMR (CDCl₃, 125 Hz) δ 173.7 and 173.3, 171.9 and 171.7, 139.0 and 138.9, 138.6 and 138.6, 129.1 and 129.0, 127.3 and 127.2, 127.1, 126.4, 70.8 and 70.4, 63.0 and 62.8, 60.7 and 60.6, 52.2 and 51.8. 40.0 and 39.8, 30.6 and 30.5, 29.4, 27.9, 26.2 (3C), 25.9 (3C), 18.6, 18.2 and 18.1, 14.5, 14.4, –4.5, –4.7, –5.0 (2C); IR (film) νmax 2955, 2929, 2896, 2856, 1736, 1471, 1463, 1376, 1254, 1182, 1081, 836, 776 cm⁻¹; HRMS (ESI) m/z 567.3534 (MH⁺, C₃₀H₅₄O₆Si₂H requires, 567.3531).
anti-3-((tert-Butyldimethylsilyloxy)-2-((tert-butyldimethylsilyloxy)methyl)-phenethyl)-N^1,N^5-dimethoxy-N^1,N^5-dimethylpentanediameide (44). To a stirred suspension of MeNH(OMe)•HCl (106 mg, 1.09 mmol) in anhydrous THF (2.0 mL) at −10 °C (ice/acetone bath) under Ar was added i-PrMgCl (2.0 M in THF, 1.1 mL, 2.2 mmol) dropwise. The mixture was stirred for 10 min at −10 °C, then treated with a solution of diester 43 (244 mg, 0.43 mmol) in anhydrous THF (0.8 mL + 0.4 mL rinse). The resultant mixture was allowed to warm to rt and stir under Ar for 26 h, then treated with sat aq NH₄Cl (5 mL) and extracted with CH₂Cl₂ (4 × 5 mL). The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. Flash chromatography (SiO₂, 2.5 × 23 cm, 2% MeOH in CH₂Cl₂ elution) afforded bis-Weinreb amide 44 (172 mg, 0.287 mmol, 67%) as an orange oil: ^1H NMR (CDCl₃, 500 MHz) δ 7.44–7.42 (m, 1H), 7.21–7.15 (m, 3H), 4.74 (s, 2H), 4.53–4.49 (m, 1H), 3.67 (s, 3H), 3.63 (s, 3H), 3.20 (s, 3H), 3.16–3.13 (m, 1H), 3.15 (s, 3H), 2.77 (m, 1H), 2.66–2.52 (m, 3H), 2.05–1.99 (m, 1H), 1.88–1.83 (m, 1H), 0.94 (s, 9H), 0.86 (s, 9H), 0.10 (s, 6H), 0.05 (s, 3H), 0.02 (s, 3H); ^13C NMR (CDCl₃, 125 MHz) δ 175.0, 172.3, 139.1, 139.0, 128.9, 127.2, 127.0, 126.2, 126.0, 70.5, 62.9, 61.5, 61.3, 47.0, 38.1, 32.3 (2C), 30.2, 28.7, 26.2 (3C), 26.2 (3C), 18.6, 18.2, −4.5 (2C), −5.0 (2C); IR (film) νmax 2929, 2894, 2856, 1665, 1462, 1413, 1385, 1360, 1254, 939, 812 cm⁻¹; HRMS (ESI) m/z 619.3564 (MNa⁺, C₃₀H₅₆N₂O₆Si₂Na requires 619.3569).
anti-3-(tert-Butyldimethylsilyloxy)-2-(2-((tert-butyldimethylsilyloxy)methyl)phenethyl)-N-methoxy-N-methylhex-5-enamide (45). To a solution of bis-Weinreb amide 44 (184 mg, 0.31 mmol) in anhydrous THF (1.8 mL) at −78 °C under Ar was added DIBAL (1.0 M in THF, 1.23 mL, 1.23 mmol) dropwise, and the solution was stirred at −78 °C under Ar for 2.0 h, then treated with sat aq potassium sodium tartrate (5.0 mL). The mixture was allowed to warm to rt and stirred vigorously at rt for 1.0 h, then extracted with CH$_2$Cl$_2$ (4 × 4 mL). The combined extracts were washed with brine (5 mL), dried (Na$_2$SO$_4$), filtered, and concentrated in vacuo to give the crude monoaldehyde (192 mg).

To a suspension of methyltriphenylphosphonium bromide (359 mg, 1.01 mmol) in anhydrous THF (2.0 mL) under Ar was added $n$-BuLi (1.6 M in hexanes, 0.54 mL, 0.86 mmol) dropwise, and the yellow solution was stirred at rt for 10 min then cooled to −78 °C. A solution of the crude monoaldehyde (192 mg) in anhydrous THF (0.4 mL + 2 × 0.3 mL rinses) was then added dropwise, and the mixture was allowed to warm to rt and stir under Ar for 18.5 h. The reaction was quenched with sat aq NH$_4$Cl (3 mL), and the mixture was extracted with EtOAc (4 × 3 mL). The combined organic layers were washed with brine (7 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo. The residue was purified by flash chromatography (SiO$_2$, 2.5 × 22 cm, 0.5% MeOH in CH$_2$Cl$_2$ elution) to afford 45 (90 mg, 0.17 mmol, 54%) as a yellow oil: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.44 (t, $J$ = 5.0 Hz, 1H), 7.21–7.14 (m, 3H), 5.86–5.78 (m, 1H), 5.04–5.00 (m, 2H), 4.75 (d, $J$ = 13.0 Hz, 1H), 4.71 (d, $J$ = 13.5 Hz, 1H), 4.02 (dt, $J$ = 4.0, 6.5 Hz, 1H), 3.59 (s, 3H), 3.19 (s, 3H), 3.00 (br s, 1H), 2.63–2.49 (m, 2H), 2.37–2.23 (m, 2H), 2.00–1.94 (m, 2H), 0.95 (s, 9H), 0.89 (s, 9H), 0.10 (s, 6H), 0.06 (s, 3H), 0.04 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 175.6, 139.1 (2C), 135.0, 128.7, 127.1, 126.9, 126.1, 117.4, 73.0, 62.9, 61.3, 46.3, 40.8, 32.5, 29.9, 29.0, 26.2 (3C), 26.2 (3C), 18.6, 18.3, −3.9, −4.2, −5.0 (2C); IR
(film) $\nu_{\text{max}}$ 2928, 2856, 1663, 1471, 1384, 1254, 1078, 837, 775 cm$^{-1}$; HRMS (ESI) $m/z$ 558.3417 (M$\text{Na}^+$, C$_{20}$H$_{53}$NO$_4$Si$_2$Na requires 558.3405).

**anti-4-(tert-Butyldimethylsilyloxy)-3-(2-((tert-butyldimethylsilyloxy)methyl)phenethyl)-1,6-heptadiene (46).** To a solution of Weinreb amide 45 (131 mg, 0.24 mmol) in anhydrous THF (1.3 mL) at –78 °C under Ar was added DIBAL (1.0 M in THF, 1.22 mL, 1.22 mmol) dropwise, and the resulting solution was stirred at –78 °C under Ar for 6 h, then poured into a stirred solution of sat aq potassium sodium tartrate (5.0 mL). The quenched mixture was stirred vigorously at rt for 2.5 h, then diluted with H$_2$O (2.0 mL) and extracted with CH$_2$Cl$_2$ (4 × 4 mL). The combined extracts were dried (Na$_2$SO$_4$), filtered, and concentrated in vacuo to give the crude aldehyde, which was combined with another portion of the identical aldehyde (43 mg, 0.09 mmol).

To a suspension of methyltriphenylphosphonium bromide (523 mg, 1.55 mmol) in anhydrous THF (1.4 mL) under Ar was added $n$-BuLi (1.4 M in hexanes, 1.0 mL, 1.4 mmol) dropwise. The red solution was stirred at rt for 10 min, cooled to –78 °C, and then added dropwise via syringe to a solution of the aldehyde (149 mg) in anhydrous THF (1.0 mL) at –78 °C. The resulting solution was allowed to warm to rt and stir under Ar for 18 h, then poured into sat aq NH$_4$Cl (5 mL). The mixture was extracted with EtOAc (4 × 3 mL), and the combined extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo. The crude product was purified by flash chromatography (SiO$_2$, 2.5 × 20 cm, 2% Et$_2$O in hexanes elution) to afford diene 46 (91 mg, 0.19 mmol, 59%) as a colorless oil: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.45–7.43 (t, $J$ = 4.5 Hz, 78
To a solution of 46 (87 mg, 0.18 mmol) in CH₂Cl₂ (1.9 mL) at 0 °C under Ar was added a solution of (1S)-(+-)(10)-camphorsulfonic acid (9.3 mg, 0.04 mmol) in MeOH (1.9 mL). The mixture was stirred at 0 °C under Ar for 1 h and 40 min, then poured into sat aq NaHCO₃ (3 mL) and diluted with CH₂Cl₂ and H₂O (1 mL each). The organic phase was collected and the aqueous phase extracted with CH₂Cl₂ (3 × 3 mL). The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo, then purified by flash chromatography (SiO₂, 1.5 × 16.5 cm, 7% EtOAc in hexanes elution) to afford benzyl alcohol 47 (57 mg, 0.16 mmol, 87%) as a yellow oil: ¹H NMR (CDCl₃, 500 MHz) δ 7.39–7.37 (m, 1H), 7.27–7.19 (m, 3H), 5.85–5.69 (m, 2H), 5.16 (dd, J = 2.0, 10.0 Hz, 1H), 5.10–5.00 (m, 3H), 4.74–4.69 (m, 2H), 3.64 (q, J = 5.5 Hz, 1H), 2.77–2.71 (m, 1H), 2.53–2.47 (m, 1H), 2.29–2.18 (m, 3H), 1.92–1.85 (m, 1H), 1.53–1.45 (m, 2H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 141.0, 140.0, 138.5, 135.4, 129.6, 134.3, 133.7, 132.2, 130.8, 128.9, 128.4, 127.2, 126.9, 126.0, 117.1, 116.8, 75.3, 63.0, 49.6, 39.2, 30.5, 30.2, 26.2 (3C), 26.2 (3C), 18.7, 18.4, −3.9, −4.2, −5.0 (2C); IR (film) νmax 3072, 2954, 2928, 2856, 1471, 1462, 1434, 1254, 1072, 1004, 913, 836, 774 cm⁻¹; HRMS (ESI) m/z 492.3708 (MNH₄⁺, C₂₈H₅₀O₂Si₂NH₄ requires 492.3687).
128.4, 128.2, 126.4, 117.1, 116.9, 75.2, 63.3, 49.5, 39.3, 31.1, 30.4, 26.2 (3C), 18.4, –3.9, –4.2;
IR (film) \( \nu_{\text{max}} \) 3327 (br), 3074, 2954, 2928, 2856, 1639, 1471, 1462, 1255, 1065, 1004, 913, 836, 774 cm\(^{-1}\); HRMS (ESI) \( m/z \) 383.2357 (M\( \text{Na}^+ \), \( C_{22}H_{36}O_2SiNa \) requires 383.2376).

**Se-Phenyl \ 2-(anti-4-(tert-butyldimethylsilyloxy)-3-vinylhept-6-enyl)benzoselenoate** (48). To a solution of oxalyl chloride (51 \( \mu \)L, 74 mg, 0.58 mmol) in anhydrous \( CH_2Cl_2 \) (1.0 mL) at –78 °C under Ar was added a solution of DMSO (80 \( \mu \)L, 88 mg, 1.13 mmol) in anhydrous \( CH_2Cl_2 \) (0.6 mL) dropwise. The resultant solution was stirred at –78 °C under Ar for 15 min, then treated with a solution of benzyl alcohol 47 (66 mg, 0.18 mmol) in anhydrous \( CH_2Cl_2 \) (0.5 mL + 2 \( \times \) 0.5 mL rinses). The resulting solution stirred at –78 °C under Ar for 80 min. A solution of \( Et_3N \) (260 \( \mu \)L, 189 mg, 1.87 mmol) in anhydrous \( CH_2Cl_2 \) (0.6 mL) was then added, and stirring continued as the mixture warmed from –78 to 10 °C over 2.5 h. The reaction was then quenched with sat aq NaHCO\(_3\) (3 mL). The organic phase was collected and the aqueous phase extracted with \( CH_2Cl_2 \) (3 \( \times \) 3 mL). The combined organic layers were dried (\( Na_2SO_4 \)) and concentrated in vacuo to give the aldehyde (67 mg).

To a solution of the crude aldehyde in \( t-BuOH \) (2.0 mL) and \( H_2O \) (0.5 mL) was added successively 2-methyl-2-butene (0.24 mL, 156 mg, 2.23 mmol), \( NaH_2PO_4 \) (28 mg, 0.24 mmol), and \( NaOClO \) (102 mg, 1.13 mmol). The orange solution was stirred at rt under Ar for 13 h and 45 min, after which it had faded to a clear solution. It was then treated with sat aq NH\(_4\)Cl (3 mL)
and extracted with CH$_2$Cl$_2$ (4 × 3 mL). The combined extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo to give the benzoic acid (71 mg).

To a solution of the crude acid in anhydrous CH$_2$Cl$_2$ (1.8 mL) under Ar was added PhSeSePh (1.0 M solution in CH$_2$Cl$_2$, 0.28 mL, 0.28 mmol) and Bu$_3$P (0.11 mL, 86 mg, 0.43 mmol) dropwise. The orange solution was stirred at rt under Ar for 5 h and 40 min, after which TLC analysis indicated incomplete conversion. Additional PhSeSePh (1.0 M solution in CH$_2$Cl$_2$, 0.15 mL, 0.15 mmol) and Bu$_3$P (75 µL, 62 mg, 0.30 mmol) were added, and the solution was stirred at rt under Ar for an additional 2.5 h, then treated with sat aq NH$_4$Cl (3 mL). The layers were separated, and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 3 mL). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo. Flash chromatography (SiO$_2$, 2.5 × 28 cm, 1% Et$_2$O in hexanes elution) afforded phenyl selenoester 48 (74.4 mg, 0.147 mmol, 80%) as a yellow oil: $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.83 (dd, $J = 1.5, 8.0$ Hz, 1H), 7.61–7.59 (m, 2H), 7.46–7.43 (m, 4H), 7.32 (dt, $J = 1.0, 7.5$ Hz, 1H), 7.28–7.26 (m, 1H), 5.80–5.68 (m, 2H), 5.11 (dd, $J = 2.0, 10.0$ Hz, 1H), 5.06–4.96 (m, 3H), 3.61 (q, $J = 5.5$ Hz, 1H), 2.89–2.83 (m, 1H), 2.69–2.63 (m, 1H), 2.25–2.14 (m, 3H), 1.86–1.80 (m, 1H), 1.56–1.48 (m, 1H), 0.87 (s, 9H), 0.02 (s, 3H), −0.01 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 195.6, 141.0, 139.8, 139.0, 136.2 (2C), 135.7, 132.1, 131.2, 129.6 (2C), 129.1, 128.7, 127.5, 126.2, 117.0, 116.7, 75.4, 49.2, 39.0, 31.6, 31.2, 26.2 (3C), 18.4, −4.0, −4.2; IR (film) $\nu_{\text{max}}$ 3073, 2953, 2927, 2855, 1703, 1639, 1570, 1476, 1438, 1254, 1183, 1065, 912, 835, 736 cm$^{-1}$; HRMS (ESI) $m/z$ 532.2192 (MNH$_4^+$, C$_{28}$H$_{38}$O$_2$SeSiNH$_4$ requires 532.2144).
**Se-Phenyl 2-(sym-4-hydroxy-3-vinylhept-6-enyl)benzoselenoate (49).** A solution of 38 (10 mg, 0.019 mmol) in anhydrous CH₂Cl₂ (0.4 mL) at 0 °C under Ar was treated with a solution of (1S)-(+)-(10)-camphorsulfonic acid (9 mg, 0.039 mmol) in CH₃OH (0.4 mL). The resulting mixture was allowed to warm to rt and stir under Ar for 12 h. It was then poured into sat aq NaHCO₃ (0.3 mL), diluted with CH₂Cl₂ and H₂O (ca. 0.1 mL each), and extracted with CH₂Cl₂ (4 × 1 mL). The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. Flash chromatography (SiO₂, 7% EtOAc in hexanes elution) gave 49 (6.5 mg, 0.016 mmol, 84%) as a yellow oil: ¹H NMR (CDCl₃, 500 MHz) δ 7.86 (dd, J = 1.0, 8.0 Hz, 1H), 7.61–7.59 (m, 2H), 7.47–7.43 (m, 4H), 7.33 (dt, J = 1.0, 7.5 Hz, 1H), 7.28 (d, J = 7.0 Hz, 1H), 5.86–5.70 (m, 2H), 5.23 (dd, J = 2.0, 10.5 Hz, 1H), 5.15–5.08 (m, 3H), 3.60–3.57 (m, 1H), 2.85–2.72 (m, 2H), 2.31–2.26 (m, 1H), 2.19–2.09 (m, 2H), 1.86–1.79 (m, 1H), 1.68–1.60 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 196.0, 140.8, 138.9, 138.4, 136.3 (2C), 135.4, 132.3, 131.3, 129.7 (2C), 129.3, 128.9, 127.4, 126.4, 118.5, 117.9, 72.6, 49.8, 39.6, 33.2, 31.7; IR(film) νmax 3444, 2925, 1700, 1639, 1477, 1438, 1184, 885, 738 cm⁻¹; HRMS (ESI) m/z 401.1017 (MH⁺, C₂₂H₂₄O₂SeH requires 401.1014).

**Tricycle 50.** Phenyl selenoester 49 (7.5 mg, 0.019 mmol) was dried azeotropically with anhydrous benzene (2 × 2.0 mL) then dissolved in anhydrous benzene (6.4 mL) in a 3-necked round-bottom flask under an atmosphere of dry air. (TMS)₃SiH (18.2 µL, 0.0591 mmol) and Et₃B (1.0 M in hexane, 54 µL, 0.054 mmol) were added to the mixture, and additional Et₃B (1.0 M in hexane, 536 µL, 0.536 mmol) was then added slowly by syringe pump over 4 h while a
continuous flow of compressed air was passed over the reaction. TLC analysis indicated incomplete conversion, so additional (TMS)$_3$:SiH (54 µL, 0.0591 mmol) was added, and another portion of Et$_3$B (1.0 M in hexane, 536 µL, 0.536 mmol) was added by syringe pump over 40 min while a constant supply of air was still passed over the reaction. Following the addition the reaction was stirred for an additional 3 h, then concentrated in vacuo. Flash chromatography (SiO$_2$, 1.5% ether in hexanes elution) afforded 50 (3.8 mg, 0.016 mmol, 82%) as a yellow oil: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.33 (dt, $J = 1.0$, 7.0 Hz, 1H), 7.27–7.23 (m, 2H), 7.19–7.14 (m, 1H), 4.12 (br s, 1H), 2.84–2.74 (m, 3H), 2.54–2.45 (m, 2H), 2.10–2.04 (m, 1H), 1.94–1.89 (m, 1H), 1.76–1.63 (m, 3H), 1.45–1.39 (m, 1H), 1.26 (br s, 1H), 0.93 (d, $J = 7.0$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125MHz) $\delta$ 211.8, 142.8, 137.8, 130.0, 129.8, 126.4, 123.7, 75.8, 50.7, 48.7, 42.7, 40.8, 34.8, 32.6, 30.6, 15.9; IR (film) $\nu_{max}$ 3445 (br), 2924, 1693, 1456, 1286, 1266, 1101, 1023, 758 cm$^{-1}$; HRMS (ESI) $m/z$ 245.1538 (MH$^+$, C$_{16}$H$_{20}$O$_2$H requires 245.1536).

**Tricycle 51.** Phenyl selenoester 48 (5.0 mg, 0.0097 mmol) was dried azeotropically with anhydrous benzene (2 × 2.0 mL), then dissolved in anhydrous benzene (2.0 mL) in a 3-necked round-bottom flask under an atmosphere of dry air. (TMS)$_3$:SiH (6.0 µL, 0.0195 mmol) and Et$_3$B (1.0 M in hexane, 18 µL, 0.018 mmol) were added to the mixture, and additional Et$_3$B (1.0 M in hexane, 177 µL, 0.177 mmol) was then added slowly by syringe pump over 1.5 h while a continuous flow of compressed air was passed over the reaction. The mixture was stirred
vigorously throughout the addition time. TLC analysis indicated incomplete conversion, so additional \((\text{TMS})_3\text{SiH}\) (6.0 \(\mu\)L, 0.0195 mmol) was added, and another portion of \(\text{Et}_3\text{B}\) (1.0 M in hexane, 177 \(\mu\)L, 0.177 mmol) was added by syringe pump over 15 min while the reaction was still stirring vigorously under air. Following the addition, the reaction was stirred for an additional 3 h, then concentrated in vacuo. Flash chromatography (SiO\(_2\), 1.5% ether in hexanes elution) afforded \(51\) (2.8 mg, 0.0079 mmol, 81%) as a yellow oil: \(^1\text{H NMR (CDCl}_3, 500 \text{MHz})\) \(\delta\) 7.31 (dt, \(J = 1.5, 7.5 \text{ Hz, 1H}\)), 7.23 (dt, \(J = 1.0, 7.5 \text{ Hz, 1H}\)), 7.16 (d, \(J = 8.0 \text{ Hz, 1H}\)), 7.11 (d, \(J = 7.5 \text{ Hz, 1H}\)), 3.59 (dt, \(J = 6.0, 8.5 \text{ Hz, 1H}\)), 2.79–2.74 (m, 2H), 2.69 (ddd, \(J = 3.0, 9.5, 14.0 \text{ Hz, 1H}\)), 2.57 (dd, \(J = 12.0, 13.5 \text{ Hz, 1H}\)), 2.15 (tdd, \(J = 3.5, 9.0, 13.0 \text{ Hz, 1H}\)), 2.09–2.02 (m, 1H), 1.90–1.85 (m, 1H), 1.84–1.79 (m, 1H), 1.59–1.53 (m, 1H), 1.34–1.24 (m, 2H), 0.94 (d, \(J = 7.0 \text{ Hz, 3H}\)), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); \(^{13}\text{C NMR (CDCl}_3, 125 \text{ MHz})\) \(\delta\) 212.0, 142.6, 138.1, 129.9, 129.6, 126.3, 123.5, 70.2, 54.5, 49.0, 42.1, 40.6, 34.1, 33.6, 32.9, 26.1 \((3\text{C})\), 18.2, 16.1, –4.5, –4.2; IR (film) \(\nu_{\text{max}}\) 3348\,(br), 2954, 2926, 2855, 1700, 1598, 1471, 1360, 1287, 1125, 1090, 868, 775 cm\(^{-1}\); HRMS (ESI) \(m/z\) 381.2216 (MNa\(^+\), \(\text{C}_{22}\text{H}_{34}\text{O}_{2}\text{SiNa}\) requires 381.2220).

\(^{2}\text{D} \ ^{1}\text{H–}^{1}\text{H COSY NMR (CDCl}_3, 500 \text{ MHz})\) \(3.59/1.84–1.79\) (m, H-11/H-12), \(3.59/1.59–1.53\) (w, H-11/H-9), \(3.59/1.34–1.24\) (m, H-11/H-12), \(2.79–2.74/2.57\) (s, H-15/H-14\(_{\text{ax}}\)), \(2.79–2.74/2.15\) (s, H-15/H-10), \(2.79–2.74/1.90–1.85\) (w, H-15/H-14\(_{\text{eq}}\)), \(2.79–2.74/1.34–1.24\) (w, H-18/H-9), \(2.69/1.34–1.24\) (m, H-8/H-9), \(2.57/1.90–1.85\) (s, H-14\(_{\text{ax}}\)/H-14\(_{\text{eq}}\)), \(2.15/1.34–1.24\) (m, H-10/H-9), \(2.09–2.02/1.90–1.85\) (w, H-13/H-14\(_{\text{eq}}\)), \(2.09–2.02/1.84–1.79\) (w, H-13/H-12), \(2.09–2.02/1.34–1.24\) (m, H-13/H-12), \(2.09–2.02/0.94\) (s, H-13/H-16), \(1.84–1.79/1.34–1.24\) (s, H-12/H-12), \(1.59–1.53/1.34–1.24\) (m, H-9/H-9); \(^{1}\text{D nOe NMR (CDCl}_3, 500 \text{ MHz})\) Irradiation of the signal at 2.09–2.02 led to an enhancement in the signal at 3.59 (H-13/H-11).
(1S, 3S, 4aR, 11aS)-3-methyl-5-oxo-2,3,4,4a,5,10,11,11a-octahydro-1H-dibenzo[a,d][7]annulen-1-yl 4-nitrobenzoate (61) To a stirred solution of alcohol 50 (3.8 mg, 0.0156 mmol) in THF (0.35 mL) at 0°C under Ar was added PPh₃ (16.4 mg, 0.0625 mmol) followed by 4-nitrobenzoic acid (10.7 mg, 0.0640 mmol). Then, DEAD (10 µL, 0.0656 mmol) was added dropwise. The resultant mixture was stirred at –5 °C under Ar for 5 h. The reaction was quenched by the addition of 1 N HCl (0.17 mL). The mixture was extracted with Et₂O (3 × 1 mL), and the combined organic layers were washed with brine (0.3 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (SiO₂, 20% EtOAc in hexanes elution) afforded 61 (5.3 mg, 0.0135 mmol, 86%) as a white solid: ¹H NMR (CDCl₃, 300 MHz) δ 8.32 (d, J = 9 Hz, 2H), 8.19 (d, J = 9 Hz, 2H), 5.01 (q, J = 6 Hz, 1H), 2.95–2.67 (m, 4H), 2.33–2.16 (m, 4H), 2.11–2.04 (m, 2H), 1.62–1.53 (m, 1H), 1.07 (d, J = 7.2 Hz, 3H); HRMS (ESI) m/z 411.19134 (MNH₄⁺, C₂₃H₂₃NO₅NH₄⁺ requires 411.19145).

(1S,3R,11aS)-3-methyl-5-oxo-2,3,5,10,11,11a-hexahydro-1H-dibenzo[a,d][7]annulen-1-yl 4-nitrobenzoate (64) A solution of 61 (6 mg, 0.0153 mmol) in THF (0.2 mL) was added dropwise to freshly prepared solution of LDA (0.23 M, 0.82 mL, 0.189 mmol) at -78 °C under
Ar. The resultant mixture was stirred at –78 °C under Ar for 1 h. A precooled solution of PhSeSePh (9.5 mg, 0.0304 mmol) in dry THF (2 × 0.1 mL) was added. The resultant mixture was stirred at –78 °C under Ar for 1 h. Then, it was warmed to –20 °C and stirred for another 1 h till Starting material was all consumed. The reaction was quenched by the addition of saturated NH₄Cl (0.2 mL). The mixture was extracted with EtOAc (3 × 1.2 mL), and the combined organic layers were washed with brine (0.4 mL), dried (Na₂SO₄), and concentrated in vacuo. H₂O₂ (30%, 0.2 mL) was added to the crude product in THF (0.4 mL) at 0 °C. The resultant mixture was stirred at rt for 12 h. The reaction was quenched by the addition of brine (0.4 mL). The mixture was extracted with EtOAc (3 × 1 mL), and the combined organic layers were washed with brine (1 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (SiO₂, 10% EtOAc in hexanes elution) afforded 64 (3.7 mg, 0.00945 mmol, 63%) as a colorless oil: ¹H NMR (CDCl₃, 500 MHz) δ 8.24 (d, J = 7 Hz, 2H), 8.07 (d, J = 7 Hz, 2H), 7.65–7.06 (m, 4H), 5.26 (br s, 1H), 3.03–3.05 (m, 1H), 2.81 (t, J = 7.5 Hz, 2H), 2.55–2.50 (m, 1H), 2.20–2.16 (m, 1H), 1.76–1.47 (m, 2H), 1.38–1.26 (m, 2H), 1.21–1.19 (d, J = 8 Hz, 3H); HRMS (ESI) m/z 414.1295 (MNa⁺, C₂₃H₂₁NO₃Na⁺ requires 414.13119).

1S,3R,11aS)-1-hydroxy-3-methyl-2,3,11,11a-tetrahydro-1H-dibenz[a,d][7]annulen-5(10H)-one (65) A solution of 64 (5 mg, 0.0128 mmol) in MeOH (20 mL) at rt was treated with KCN (0.416 mg, 0.00639 mmol). The resultant mixture was stirred at rt for 5 h. The solvent was removed in vacuo. The crude mixture was washed with brine (0.5 mL), and extracted with
EtOAc (3 × 1 mL). The combined organic layers were washed with brine (0.5 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (SiO₂, 35% EtOAc in hexanes elution) afforded 65 (2.9 mg, 0.0118 mmol, 92%) as a colorless oil: ¹H NMR (CDCl₃, 500 MHz) δ 7.44–7.18 (m, 4H), 5.35 (br s, 1H), 2.98–2.97 (m, 1H), 2.83–2.81 (t, J = 7 Hz, 2H), 2.63–2.60 (m, 1H), 2.25–2.18 (m, 1H), 1.72–1.56 (m, 2H), 1.50–1.37 (m, 2H), 1.34 (d, J = 7 Hz, 3H); HRMS (ESI) m/z 243.13786 (MH⁺, C₁₆H₁₈O₂H⁺ requires 243.13796).

![Chemical Structure](image)

(1S,3S,4aS,11aS)-1-hydroxy-3-methyl-2,3,4,4a,11,11a-hexahydro-1H-dibenzo[a,d][7]annulen-5(10H)-one (66) A solution of alcohol 65 (1 mg, 0.00413 mmol) in anhydrous THF (1 mL) was added a trace amount of Crabtree catalyst. Then, put the reaction vial in a hydrogenator, which was pressure-flushed with hydrogen for three times and pressurized to 1000 Psi. The resultant mixture was stirred at rt for 2 days. The catalyst was removed by filtration. The residue was purified by flash chromatography (SiO₂, 35% EtOAc in hexanes elution) to afford 66 (0.96 mg, 0.00392 mmol, 95%) as a colorless oil: ¹H NMR (CDCl₃, 500 MHz) δ 7.61–7.15 (m, 4H), 3.27–3.29 (m, 1H), 3.14 (t, J = 7 Hz, 2H), 2.94–2.86 (m, 1H), 2.36–2.32 (m, 1H), 1.98–1.96 (m, 1H), 1.83–1.78 (m, 3H), 1.68–1.65 (m, 1H), 1.25–1.21 (m, 2H), 1.23 (d, J = 7.6 Hz, 3H); HRMS (ESI) m/z 245.15291 (MH⁺, C₁₆H₂₀O₂H⁺ requires 245.15361).
Methyl 1-benzyl-6-oxo-1,6-dihydropyridine-3-carboxylate (67) To a solution of methyl pyruvate (17.5 µL, 19.4 mg, 0.190 mmol) and methyl propiolate (32.0 µL, 32.2 mg, 0.383 mmol) in MeOH (0.6 mL) was added benzylamine (41.5 µL, 40.7 mg, 0.380 mmol). The reaction vessel was sealed, and the mixture was heated at 120 °C for 2 d. After cooling to rt, the mixture was concentrated in vacuo. Flash chromatography (SiO₂, 25% EtOAc in hexanes elution) afforded 67 (33.9 mg, 0.139 mmol, 73%) as a colorless oil: ¹H NMR (CDCl₃, 500 MHz) δ 8.19 (d, J = 3.0 Hz, 1H), 7.84 (dd, J = 9.2, 2.8 Hz, 1H), 7.38–7.32 (m, 5H), 6.58 (d, J = 9.5 Hz, 1H), 5.17 (s, 2H), 3.84 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 164.9, 162.7, 142.9, 138.7, 135.7, 129.3 (2C), 128.6, 128.4 (2C), 120.3, 110.2, 52.9, 52.3; IR (film) νmax 2951, 1719, 1666, 1612, 1542, 1496, 1446, 1300, 1151 cm⁻¹; HRMS (ESI) m/z 266.07975 (MNa⁺, C₁₄H₁₃NO₃Na⁺ requires 266.07876).

Methyl 1-(4-methoxybenzyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (68) To a solution of methyl pyruvate (17.5 µL, 19.4 mg, 0.190 mmol) and methyl propiolate (31.8 µL, 31.9 mg,
0.380 mmol) in MeOH (0.6 mL) was added p-methoxybenzylamine (49.3 µL, 52.1 mg, 0.380 mmol). The reaction vessel was sealed, and the mixture was heated at 120 °C for 2 d. After cooling to rt, the mixture was concentrated in vacuo. Flash chromatography (SiO₂, 25% EtOAc in hexanes elution) afforded 68 (38.0 mg, 0.139 mmol, 73%) as a colorless oil: ¹H NMR (CDCl₃, 500 MHz) δ 8.17 (d, J = 2.5 Hz, 1H), 7.81 (dd, J = 9.8, 2.8 Hz, 1H), 7.29 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 6.56 (d, J = 9.5 Hz, 1H), 5.09 (s, 2H), 3.83 (s, 3H), 3.80 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 164.9, 162.7, 159.9, 142.7, 138.6, 130.1 (2C), 127.8, 120.2, 114.6 (2C), 110.1, 55.5, 52.5, 52.3; IR (film) νmax 2953, 2838, 1716, 1612, 1544, 1515, 1396, 1297, 1114 cm⁻¹; HRMS (ESI) m/z 274.10674 (MH⁺, C₁₅H₁₅NO₄H⁺ requires 274.10738).

Methyl 1-(3,4-dimethoxybenzyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (69) To a solution of methyl pyruvate (17.5 µL, 19.4 mg, 0.190 mmol) and methyl propiolate (31.8 µL, 31.9 mg, 0.380 mmol) in MeOH (0.6 mL) was added 3,4-dimethoxybenzylamine (56.4 µL, 63.5 mg, 0.380 mmol). The reaction vessel was sealed, and the mixture was heated at 120 °C for 2 d. After cooling to rt, the mixture was concentrated in vacuo. Flash chromatography (SiO₂, 25% EtOAc in hexanes elution) afforded 69 (45.4 mg, 0.150 mmol, 79%) as a colorless oil: ¹H NMR (CDCl₃, 500 MHz) δ 8.17 (d, J = 2.5 Hz, 1H), 7.83 (dd, J = 10.0, 2.5 Hz, 1H), 6.91–6.89 (m, 2H), 6.84 (d, J = 7.5 Hz, 1H), 6.58 (d, J = 9.5 Hz, 1H), 5.10 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 164.9, 162.8, 159.9, 149.6, 149.5, 142.6, 138.7, 128.2, 121.2, 120.2, 111.9, 111.5, 110.2, 56.22, 56.16, 52.7, 52.3; IR (film) νmax 1718, 1667, 1517,
1446, 1301, 1263, 1239 cm\(^{-1}\); HRMS (ESI) \(m/z\) 304.11635 (MH\(^+\), C\(_{16}H_{17}NO_5H^+\) requires 304.11795).

Ethyl 6-oxo-1,6-dihydropyridine-2-carboxylate (73) A mixture of ethyl pyruvate (21 \(\mu\)L, 22 mg, 0.19 mmol), 4 Å MS (66.2 mg), pyrrolidine (19.5 \(\mu\)L, 16.9 mg, 0.238 mmol) and anhydrous benzene (2.0 mL) was refluxed at 80 °C for 5 h. The mixture was allowed to cool to rt and was then filtered under Ar. The solution of crude enamine was placed in a sealable tube and treated with propiolamide\(^{23}\) (33 mg, 0.48 mmol) followed by \(p\)-TsOH (36 mg, 0.21 mmol). The vessel was sealed, and the resulting mixture was stirred at 80 °C for 48 h, then at 110 °C for 12 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography (SiO\(_2\), 4% MeOH in EtOAc elution), affording 73 (22.5 mg, 0.135 mmol, 71%) as a white solid: \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 9.73 (br s, 1H), 7.46 (dd, \(J = 9.2, 6.8\) Hz, 1H), 6.98 (dd, \(J = 7.0, 1.0\) Hz, 1H), 6.81 (dd, \(J = 9.5, 1.0\) Hz, 1H), 4.42 (q, \(J = 7.0\) Hz, 2H), 1.41 (t, \(J = 7.0\) Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 162.3, 160.1, 140.0, 133.9, 127.3, 109.4, 63.1, 14.4; IR (film) \(\nu_{\text{max}}\) 2979, 1726, 1661, 1610, 1472, 1349, 1284, 1164, 1022 cm\(^{-1}\); HRMS (ESI) \(m/z\) 190.04838 (MNa\(^+\), C\(_8\)H\(_9\)NO\(_3\)Na\(^+\) requires 190.04746).
S-methyl 4-(benzyloxyimino)-2-ethyl-3-oxobutanethioate (82) n-BuLi (1.6 M in hexane, 567 µL, 0.907 mmol) was added to a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (198 µL, 153 mg, 0.950 mmol) in anhydrous THF (2.0 mL) at –5 °C under Ar. The resulting mixture was stirred at –5 °C for 30 min, cooled to –78 °C, and treated with a solution of S-methyl butanethioate (101 µL, 97.5 mg, 0.825 mmol) in anhydrous THF (590 µL). The mixture was then stirred at –78 °C for 30 min, treated with TMSCl (121 µL, 104 mg, 0.953 mmol), stirred at –78 °C for 1 h, allowed to warm to rt, and stirred at rt for 15 min. The solvent was removed in vacuo, the residue was suspended in hexane, and crude silyl ketene thioacetal was obtained by filtration. The crude silyl ketene thioacetal was then dissolved in anhydrous DMF (650 µL), and this solution was added to a stirred solution of LiOAc (3.9 mg, 0.059 mmol) in anhydrous DMF (880 µL) at rt under Ar. Next, a solution of methyl 2-(benzyloxyimino)acetate (81, 113.8 mg, 0.589 mmol) in anhydrous DMF (650 µL) was added to the mixture, and it was stirred at rt under Ar for 6 h. The reaction was quenched by the addition of sat. aq. NH₄Cl (0.2 mL), and the mixture was extracted with EtOAc (3 × 1 mL). The combined organic layers were washed with brine (0.3 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (SiO₂, 20% EtOAc in hexanes elution) afforded 82 (67.4 mg, 0.241 mmol, 41%) as a colorless oil: ¹H NMR (CDCl₃, 500 MHz) δ 7.54 (s, 1H), 7.40–7.36 (m, 5H), 5.31 (s, 2H), 4.47 (t, J = 7.2 Hz, 1H), 2.28 (s, 3H), 1.99–1.92 (m, 2H), 0.92 (t, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 195.5, 192.3, 147.6, 142.8, 136.2, 129.0 (2C), 128.8 (2C), 78.6, 63.0, 23.0, 19.5, 12.1; IR (film) νₘₚₓ 2968, 2932, 1748, 1705, 1678, 1583, 1367, 1340, 1269, 1181, 1009 cm⁻¹; HRMS (ESI) m/z 280.10158 (MH⁺, C₁₄H₁₇NO₃SH⁺ requires 280.10019). Additionally, an undetermined amount of β-lactam 83 (identified by HRMS) could be obtained contaminated with recovered 81.
Methyl 2-[(4-methylphenyl)sulfonamido]-3-(methylthiocarbonyl)pentanoate (85) $n$-BuLi (1.6 M in hexane, 690 µL, 1.1 mmol) was added to a stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (240 µL, 186 mg, 1.15 mmol) in anhydrous THF (4.3 mL) at $-5 \, ^\circ C$ under Ar. The resulting mixture was stirred at $-5 \, ^\circ C$ for 30 min, cooled to $-78 \, ^\circ C$, and treated with a solution of $S$-methyl butanethioate (120 µL, 118 mg, 0.998 mmol) in anhydrous THF (810 µL). The mixture was then stirred at $-78 \, ^\circ C$ for 30 min, treated with TMSCl (146 µL, 125 mg, 1.15 mmol), stirred at $-78 \, ^\circ C$ for 1 h, allowed to warm to rt, and stirred at rt for 15 min. The solvent was removed in vacuo, the residue was suspended in hexane, and crude silyl ketene thioacetal was obtained by filtration. The crude silyl ketene thioacetal was then dissolved in anhydrous DMF (1.0 mL), and this solution was added to a stirred solution of LiOAc (4.2 mg, 0.0643 mmol) in anhydrous DMF (0.84 mL) at rt under Ar. Next, a solution of methyl 2-(tosylimino)acetate (84, 156 mg, 0.647 mmol) in anhydrous DMF (1.0 mL) was added to the mixture, and the resulting mixture was stirred at rt under Ar for 6 h. The reaction was quenched by the addition of sat. aq. NH$_4$Cl (0.2 mL), and the mixture was extracted with EtOAc (3 × 1 mL). The combined organic layers were washed with brine (0.3 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo. Flash chromatography (SiO$_2$, 20% EtOAc in hexanes elution) afforded 11 (193 mg, 0.537 mmol, 83%) as a white solid that was a 6:1 mixture of diastereomers favoring the anti isomer (data for major isomer): $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.71 (d, $J = 8.5$ Hz, 2H), 7.28 (d, $J = 9.0$ Hz, 2H), 5.56 (d, $J = 11.0$ Hz, 1H), 4.15 (dd, $J = 10.2$, 4.8 Hz, 1H), 3.46 (s, 3H), 3.00–
2.96 (m, 1H), 2.41 (s, 3H), 2.25 (s, 3H), 1.89–1.80 (m, 1H), 1.72–1.63 (m, 1H), 0.98 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 201.2, 170.7, 143.8, 137.4, 129.7 (2C), 127.5 (2C), 56.8, 56.5, 52.8, 23.0, 21.8, 12.0, 11.8; IR (film) $\nu_{\text{max}}$ 3279, 2966, 1744, 1674, 1598, 1435, 1385, 1165 cm$^{-1}$; HRMS (ESI) $m/z$ 360.09427 (MH$^+$, C$_{15}$H$_{21}$NO$_5$S$_2$H$^+$ requires 360.09339).

Methyl 2-(2-bromo-N-tosylacetamido)-3-(methylthiocarbonyl)pentanoate (88) A solution of 85 (100 mg, 0.278 mmol) in anhydrous THF (3.0 mL) at $-78$ °C under Ar was treated with n-BuLi (1.6 M in hexane, 180 $\mu$L, 0.289 mmol), stirred at $-78$ °C for 10 min and at rt for 5 min, then recooled to $-78$ °C. Bromoacetyl chloride (25.5 $\mu$L, 48.8 mg, 0.310 mmol) was added, and the resulting mixture was stirred at $-78$ °C under Ar for 30 min, warmed to rt, and stirred for 12 h. The reaction was quenched by the addition of sat. aq. NH$_4$Cl (0.5 mL), and the mixture was extracted with EtOAc (3 x 2 mL). The combined organic layers were washed with brine (0.5 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo. Flash chromatography (SiO$_2$, 8% EtOAc in hexanes elution) afforded 88 (106 mg, 0.221 mmol, 79%) as a colorless oil that was a 6:1 mixture of diastereomers favoring the anti isomer (data for major isomer): $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.94 (d, $J = 8.5$ Hz, 2H), 7.42 (d, $J = 8.5$ Hz, 2H), 5.46 (d, $J = 10.0$ Hz, 1H), 4.56 (d, $J = 13.0$ Hz, 1H), 4.18 (d, $J = 13.5$ Hz, 1H), 3.56 (s, 3H), 3.54–3.51 (m, 1H), 2.49 (s, 3H), 2.39 (s, 3H), 1.60–1.54 (m, 2H), 0.99 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 201.9, 168.7, 166.5, 146.4, 135.2, 130.3 (2C), 128.8 (2C), 62.5, 53.7, 52.8, 29.2, 23.7, 22.0, 12.1, 11.8; IR
(film) $\nu_{\text{max}}$ 2958, 1747, 1682, 1596, 1436, 1369, 1023 cm$^{-1}$; HRMS (ESI) $m/z$ 501.99658 (MNa$^+$, C$_{17}$H$_{22}$NO$_6$Br$_2$Na$^+$ requires 501.99641).

Methyl 3-ethyl-4-(methylthio)-6-oxo-1-tosyl-1,2,3,6-tetrahydropyridine-2-carboxylate (89) A solution of 88 (28.1 mg, 0.0585 mmol) in anhydrous 1,2-dichloroethane (810 µL) at –20 °C under Ar was treated with TiCl$_4$ (1.0 M in CH$_2$Cl$_2$, 87 µL, 0.087 mmol) followed by a solution of PPh$_3$ (22 mg, 0.0839 mmol) in anhydrous CH$_2$Cl$_2$ (270 µL). The resultant mixture was stirred at –5 °C under Ar for 16 h. The reaction was quenched by the addition of H$_2$O (100 µL), and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 1 mL), and the combined organic layers were washed with brine (0.3 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo. Flash chromatography (SiO$_2$, 15% EtOAc in hexanes elution) afforded 89 (16.2 mg, 0.0422 mmol, 72%) as a colorless oil that was a 6:1 mixture of diastereomers favoring the anti isomer (data for major isomer): $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.94 (d, $J = 8.0$ Hz, 2H), 7.31 (d, $J = 8.0$ Hz, 2H), 5.46 (d, $J = 2.5$ Hz, 1H), 5.39 (d, $J = 5.0$ Hz, 1H), 3.59 (s, 3H), 3.17–3.13 (m, 1H), 2.43 (s, 3H), 2.24 (s, 3H), 2.14–2.09 (m, 1H), 1.69–1.63 (m, 1H), 1.22 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 168.6, 161.7, 161.0, 145.0, 135.8, 129.6 (2C), 129.3 (2C), 112.6, 58.5, 52.7, 45.2, 21.9, 21.1, 14.9, 12.4; IR (film) $\nu_{\text{max}}$ 2924, 2853, 1747, 1682, 1532, 1260, 1167, 1087 cm$^{-1}$; HRMS (ESI) $m/z$ 406.07600 (MNa$^+$, C$_{17}$H$_{21}$NO$_5$S$_2$Na$^+$ requires 406.07534).
**Methyl 3-ethyl-4-(methylthio)-6-oxo-1,6-dihydropyridine-2-carboxylate (95)** A solution of 89 (33 mg, 0.086 mmol) in DMF (3.0 mL) at rt was treated with DBU (193 µL, 197 mg, 1.29 mmol). The resulting mixture was stirred at rt for 6 h, treated with H₂O (0.5 mL) and sat. aq. NH₄Cl (0.5 mL), and extracted with EtOAc (3 × 1 mL). The combined organic layers were washed with brine (0.3 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (SiO₂, 3% MeOH in CH₂Cl₂ elution) afforded 95 (19 mg, 0.084 mmol, 97%) as a white solid: ¹H NMR (CDCl₃, 500 MHz) δ 9.50 (br s, 1H), 6.41 (s, 1H), 3.97 (s, 3H), 2.93 (q, J = 7.3 Hz, 2H), 2.43 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 161.8, 160.0, 157.9, 128.3, 126.3, 117.2, 53.5, 21.3, 15.0, 14.2; IR (film) νmax 2965, 2930, 1739, 1641, 1527, 1423, 1343, 1280, 1229, 1109, 1055, 927 cm⁻¹; HRMS (ESI) m/z 228.06996 (MH⁺, C₁₀H₁₃NO₃SH⁺ requires 228.06889).

**Methyl 3-ethyl-6-oxo-1,6-dihydropyridine-2-carboxylate (94)** To a vigorously stirred mixture of 95 (20.6 mg, 0.0906 mmol) and Lindlar catalyst (606.6 mg) in acetone (4.0 mL) at rt under Ar was added Et₃SiH (214.5 µL, 156 mg, 1.34 mmol) dropwise. The resulting mixture was stirred at rt for 4 h, filtered through a plug of Celite (washed with 7 × 3.5 mL acetone), and
concentrated in vacuo. Flash chromatography (SiO₂, 4% MeOH in CH₂Cl₂ elution) afforded 94 (15.6 mg, 0.0861 mmol, 95%) as a white solid: \(^1\)H NMR (CDCl₃, 500 MHz) \(\delta 9.51\) (br s, 1H), 7.34 (d, \(J = 9.0\) Hz, 1H), 6.76 (d, \(J = 9.5\) Hz, 1H), 3.97 (s, 3H), 2.84 (q, \(J = 7.5\) Hz, 2H), 1.18 (t, \(J = 7.5\) Hz, 3H); \(^{13}\)C NMR (CDCl₃, 125 MHz) \(\delta 161.9, 161.4, 144.6, 128.9, 128.1, 127.3, 53.4, 25.0, 15.2\); IR (film) \(\nu_{\text{max}}\) 2968, 1736, 1662, 1605, 1437, 1324, 1282, 1234, 1099 cm\(^{-1}\); HRMS (ESI) \(m/z\) 182.08252 (MH\(^+\), C₉H₁₁NO₃S\(^-\)H\(^+\) requires 182.08117).

Methyl 4-methyl 2-(4-methylphenylsulfonylamo)-3-(methylthiocarbonyl)pentanoate (96)
Following the procedure detailed for the synthesis of 85, but using \(n\)-BuLi (1.6 M in hexane, 3.40 mL, 5.5 mmol), 1,1,1,3,3,3-hexamethyldisilazane (1.20 mL, 930 mg, 5.75 mmol), anhydrous THF (12 mL), S-methyl 3-methylbutanethioate (661.2 mg, 5.00 mmol), anhydrous THF (3.5 mL), TMSCl (750 \(\mu\)L, 625 mg, 5.75 mmol), anhydrous DMF (4.5 mL), LiOAc (66.0 mg, 1.00 mmol), 84 (1.207 g, 5.00 mmol), and anhydrous DMF (3.5 mL) afforded 96 (1.382 g, 3.70 mmol mmol, 74%) as a white solid that was a 1.6:1 mixture of diastereomers favoring the \textit{anti} isomer. The isomers could be separated for characterization purposes. For \textit{anti}-96: \(^1\)H NMR (CDCl₃, 500 MHz) \(\delta 7.70\) (d, \(J = 8.5\) Hz, 2H), 7.28 (d, \(J = 8.5\) Hz, 2H), 5.42 (d, \(J = 9.0\) Hz, 1H), 4.16 (dd, \(J = 8.8, 5.8\) Hz, 1H), 3.48 (s, 3H), 2.71 (dd, \(J = 8.0, 6.0\) Hz, 1H), 2.40 (s, 3H), 2.25 (s, 3H), 2.24–2.18 (m, 1H), 1.03 (d, \(J = 7.0\) Hz, 3H), 0.90 (d, \(J = 7.0\) Hz, 3H); \(^{13}\)C NMR (CDCl₃, 125 MHz) \(\delta 199.5, 170.5, 144.1, 136.7, 129.9\) (2C), 127.6 (2C), 64.6, 55.5, 52.8, 28.0, 21.8, 21.1, 20.0, 12.2; IR (film) \(\nu_{\text{max}}\) 3279, 2957, 1741, 1674, 1455, 1432, 1339, 1312, 1200, 1164, 1093 cm\(^{-1}\); HRMS (ESI) \(m/z\) 374.10872 (MH\(^+\), C₁₆H₂₃NO₃S₂H\(^+\) requires 374.10904).
For syn-96: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.69 (d, $J =$ 8.0 Hz, 2H), 7.26 (d, $J =$ 7.5 Hz, 2H), 5.62 (d, $J =$ 10.5 Hz, 1H), 4.27 (dd, $J =$ 10.5, 4.0 Hz, 1H), 3.40 (s, 3H), 2.64 (dd, $J =$ 9.5, 4.0 Hz, 1H), 2.40 (s, 3H), 2.24 (s, 3H), 2.22–2.16 (m, 1H), 0.98 (d, $J =$ 7.0 Hz, 3H), 0.94 (d, $J =$ 7.0 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 201.1, 170.5, 143.7, 137.5, 129.7 (2C), 127.4 (2C), 61.6, 55.9, 52.6, 28.1, 21.7, 20.9, 19.9, 12.1; IR (film) $\nu_{\text{max}}$ 3342, 2965, 1745, 1670, 1342, 1168, 1143, 1093 cm$^{-1}$; HRMS (ESI) $m/z$ 374.10852 (MH$^+$, C$_{16}$H$_{23}$NO$_5$S$_2$H$^+$ requires 374.10904).

Methyl 2-(2-bromo-N-tosylacetamido)-4-methyl-3-(methylthiocarbonyl)pentanoate

(19) Following the procedure detailed for the synthesis of 88, but using 96 (448.2 mg, 1.20 mmol), anhydrous THF (3.0 mL), $n$-BuLi (1.6 M in hexane, 1.1 mL, 1.8 mmol), and bromoacetyl chloride (400 $\mu$L, 756 mg, 4.80 mmol) afforded 97 (304.8 mg, 0.616 mmol, 51%) as a colorless oil that was a 1.6:1 mixture of diastereomers: $^1$H NMR (CDCl$_3$, 500 MHz, data for major isomer) $\delta$ 7.97 (d, $J =$ 7.0 Hz, 2H), 7.39 (d, $J =$ 8.5 Hz, 2H), 5.34 (d, $J =$ 7.0 Hz, 1H), 4.53 (d, $J =$ 14.5 Hz, 1H), 4.06 (d, $J =$ 13.5 Hz, 1H), 3.59 (s, 3H), 3.56–3.51 (m, 1H), 2.47 (s, 3H), 2.36 (s, 3H), 2.28–2.17 (m, 1H), 1.05 (d, $J =$ 6.5 Hz, 3H), 0.92 (d, $J =$ 6.5 Hz, 3H); HRMS (ESI) $m/z$ 494.03259 (MH$^+$, C$_{18}$H$_{24}$BrNO$_6$S$_2$H$^+$ requires 494.03012).
Methyl 3-isopropyl-4-(methylthio)-6-oxo-1-tosyl-1,2,3,6-tetrahydropyridine-2-carboxylate (98) Following the procedure detailed for the synthesis of 89, but using 97 (19.7 mg, 0.0398 mmol), anhydrous 1,2-dichloroethane (540 µL), TiCl$_4$ (1.0 M in CH$_2$Cl$_2$, 61 µL, 0.061 mmol), PPh$_3$ (16 mg, 0.061 mmol), and anhydrous CH$_2$Cl$_2$ (180 µL) afforded 98 (13 mg, 0.033 mmol, 82%) as a colorless oil that was a ca. 3:1 mixture of diastereomers: $^1$H NMR (CDCl$_3$, 500 MHz, data for major isomer) δ 8.00 (d, $J$ = 8.5 Hz, 2H), 7.32 (d, $J$ = 9.0 Hz, 2H), 5.43 (s, 1H), 5.41 (d, $J$ = 2.0 Hz, 1H), 3.68 (s, 3H), 2.73 (dd, $J$ = 7.0, 2.0 Hz, 1H), 2.44 (s, 3H), 2.28 (s, 3H), 2.07–2.00 (m, 1H), 1.14 (d, $J$ = 7.0 Hz, 3H), 1.13 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz, data for major isomer) δ 170.6, 161.3, 160.2, 145.0, 132.4, 130.0 (2C), 129.1 (2C), 112.2, 58.8, 53.2, 49.7, 31.5, 21.9, 21.3, 20.3, 15.0; IR (film) ν$_{max}$ 2961, 1749, 1683, 1352, 1167 cm$^{-1}$; HRMS (ESI) m/z 398.10827 (MH$^+$, C$_{18}$H$_{23}$NO$_5$S$_2$H$^+$ requires 398.10904).

\[ \text{Methyl 3-isopropyl-4-(methylthio)-6-oxo-1,6-dihydropyridine-2-carboxylate (99)} \]

Following the procedure detailed for the synthesis of 95, but using 98 (26 mg, 0.065 mmol), DMF (2.2 mL), and DBU (147 µL, 149 mg, 0.981 mmol) afforded 99 (15.2 mg, 0.063 mmol, 96%) as a colorless film: $^1$H NMR (CDCl$_3$, 500 MHz) δ 9.80 (br s, 1H), 6.38 (s, 1H), 3.96 (s, 3H), 2.43 (s, 3H), 2.06–1.99 (m, 1H), 1.35 (d, $J$ = 7.0 Hz, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 177.7, 173.0, 159.8, 139.0, 130.2, 116.4, 53.5, 28.2, 20.6 (2C), 15.7; IR (film) ν$_{max}$ 2925, 1737, 1650, 1461 cm$^{-1}$; HRMS (ESI) m/z 242.08599 (MH$^+$, C$_{11}$H$_{15}$NO$_5$SH$^+$ requires 242.08454).
Methyl 3-isopropyl-4-(methylthio)-6-oxo-1,6-dihydropyridine-2-carboxylate (100)

Following the procedure detailed for the synthesis of 94, but using 99 (10 mg, 0.041 mmol), Lindlar catalyst (300 mg), acetone (2.0 mL), and Et₃SiH (98 µL, 71 mg, 0.61 mmol) afforded 100 (6.7 mg, 0.034 mmol, 83%) as a white solid: ¹H NMR (CDCl₃, 500 MHz) δ 9.28 (br s, 1H), 7.54 (d, J = 10.0 Hz, 1H), 6.80 (d, J = 9.5 Hz, 1H), 3.97 (s, 3H), 2.06–1.96 (m, 1H), 1.19 (d, J = 7.0 Hz, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 166.1, 159.4, 145.3, 131.2, 128.7, 127.2, 52.9, 27.2, 22.9 (2C); IR (film) νmax 2973, 1696, 1668, 1378 cm⁻¹; HRMS (ESI) m/z 196.09627 (MH⁺, C₁₀H₁₃NO₃H⁺ requires 196.09682).

Methyl 2-(2-bromo-N-tosylpropanamido)-3-(methylthiocarbonyl)pentanoate (110)

Following the procedure detailed for the synthesis of 88, but using 85 (584.5 mg, 1.63 mmol), anhydrous THF (8.0 mL), n-BuLi (1.6 M in hexane, 1.50 mL, 2.40 mmol), and 2-bromopropanoyl chloride (1.111 g, 6.50 mmol) afforded 110 (561 mg, 1.13 mmol, 70%) as a colorless oil that was a mixture of diastereomers at the bromo-bearing carbon: ¹H NMR (CDCl₃, 500 MHz) δ 7.68 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 5.77–5.72 (m, 1H), 4.14–4.10 (m, 1H), 3.58 (s, 3H), 2.77–2.72 (m, 1H), 2.40 (s, 3H), 2.08 (s, 3H), 1.63–1.54 (m, 1H), 1.48–1.40
(m, 1H), 1.27–1.19 (m, 3H), 0.88–0.81 (m, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 200.7, 175.7, 172.3, 143.3, 139.2, 129.6 (2C), 127.4 (2C), 60.6, 51.8, 50.4, 31.7, 23.7, 22.3, 21.7, 17.8, 14.0, 11.9; IR (film) $\nu_{\text{max}}$ 2960, 1738, 1435, 1336, 1161 cm$^{-1}$; HRMS (ESI) m/z 494.02870 (MH$^+$, C$_{18}$H$_{24}$BrNO$_6$S$_2$H$^+$ requires 494.03012).

Methyl 3-ethyl-5-methyl-4-(methylthio)-6-oxo-1-tosyl-1,2,3,6-tetrahydropyridine-2-carboxylate (111) Following the procedure detailed for the synthesis of 89, but using 110 (43 mg, 0.0870 mmol), anhydrous 1,2-dichloroethane (1.2 mL), TiCl$_4$ (1.0 M in CH$_2$Cl$_2$, 140 µL, 0.140 mmol), PPh$_3$ (34 mg, 0.13 mmol), and anhydrous CH$_2$Cl$_2$ (400 µL) afforded 111 (8.1 mg, 0.020 mmol, 24%) as a colorless film that was a ca. 1.1:1 mixture of diastereomers, and ketone 112 (18 mg, 0.049 mmol, 56%) as a colorless film. for 111: $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.77 and 7.74 (2d, $J = 8.5$ Hz, 2H), 7.31–7.27 (m, 2H), 6.00 and 5.57 (2d, $J = 9.0$ and 10.0 Hz, 1H), 3.65 and 3.66 (2s, 3H), 2.98–2.94 and 2.86–2.82 (2m, 1H), 2.43 and 2.42 (2s, 3H), 2.18 (s, 3H), 1.73–1.64 and 1.85–1.79 (2m, 1H), 1.57 (s, 3H), 1.53–1.46 and 1.43–1.38 (2m, 1H), 0.92 and 0.99 (2t, $J = 7.5$ Hz, 3H); HRMS (ESI) m/z 398.10839 (MH$^+$, C$_{18}$H$_{23}$NO$_5$S$_2$H$^+$ requires 398.10904).

For 112: $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.93 (d, $J = 8.5$ Hz, 2H), 7.33 (d, $J = 8.5$ Hz, 2H), 5.45 (s, 1H), 3.80 (s, 3H), 3.16 (q, $J = 7.5$ Hz, 1H), 2.73 (sextet, $J = 7.3$ Hz, 1H), 2.47–2.40 (m, 1H), 2.44 (s, 3H), 2.36 (sextet, $J = 7.2$ Hz, 1H), 1.38 (d, $J = 7.0$ Hz, 3H), 1.12 (t, $J = 7.2$ Hz, 3H); $^{13}$C
NMR (CDCl₃, 125 MHz) δ 170.9, 169.5, 145.4, 135.4, 129.7 (2C), 129.4 (2C), 61.3, 53.3, 42.0, 25.2, 21.9, 18.5, 14.6, 12.5; IR (film) vₘₐₓ 2931, 1749, 1708, 1359, 1171, 1087 cm⁻¹; HRMS (ESI) m/z 368.11745 (MH⁺, C₁₇H₂₁NO₆SH⁺ requires 368.11623).

Methyl 3-ethyl-5-methyl-6-oxo-1,6-dihydropyridine-2-carboxylate (113) Following the procedure detailed for the synthesis of 95, but using 111 (3.7 mg, 0.0093 mmol), DMF (1.1 mL), and DBU (71 µL, 72 mg, 0.47 mmol) afforded the vinyl sulfide intermediate, which was reduced according to the procedure detailed for the synthesis of 94, but using Lindlar catalyst (230 mg), acetone (1.5 mL), and Et₃SiH (75 µL, 55 mg, 0.47 mmol), affording 113 (1.4 mg, 0.0072 mmol, 77%) as a white film: ¹H NMR (CDCl₃, 500 MHz) δ 9.36 (br s, 1H), 7.20 (s, 1H), 3.95 (s, 3H), 2.82 (q, J = 7.5 Hz, 2H), 2.21 (s, 3H), 1.18 (t, J = 7.2 Hz, 3H); HRMS (ESI) m/z 218.06491 (MNa⁺, C₁₀H₁₃NO₃Na⁺ requires 218.07876).

4-hydroxy-N-((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-N-methylbutanamide (158) A solution of n-BuLi (1.6 M in hexane, 227 mL, 363.108 mmol) was added to an ice-cooled suspension of LiCl (17.9575 g, 423.626 mmol) and (1S, 2S)-(+) pseudoephedrine (20 g, 121.036 mmol) in THF (710 mL), and the suspension was stirred at 0 °C for 30 min. Then, methyl-4-hydroxy butanoate (crude, 121.036 mmol) was added to the suspension. The mixture was
warmed to rt and stirred at rt for overnight. The reaction was quenched by the addition of 0.5 N NaOH (460 mL). The solvent was removed in vacuo. The residue was extracted with 10% MeOH-CH₂Cl₂ (3 × 50 mL), and the combined organic layers were washed with brine (30 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (SiO₂, 10% MeOH in CH₂Cl₂ elution) afforded 158 (23.7 g, 94.408 mmol, 54%) as a brown oil: ¹H NMR (CDCl₃, 500 MHz) δ 7.12–6.99 (m, 5H), 4.79 (br s, 1H), 4.39 (br s, 1H), 4.29 (d, J = 8 Hz, 2H), 3.31–3.26 (m, 2H), 2.67 (q, J = 7 Hz, 1H), 2.61 and 2.59 (2s, 3H), 2.39–2.05 (m, 2H), 1.60–1.49 (m, 2H), 0.96 (t, J = 7.5 Hz, 2H), 0.71–0.69 (m, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 175.0 and 174.5, 142.4 and 142.2, 128.5 (2C) and 128.3 (2C), 128.0 and 127.6, 127.1 (2C) and 126.9 (2C), 75.4 and 74.9, 61.6 and 61.6, 58.4 and 46.4, 31.1 and 30.2, 28.1 and 27.8, 21.2 and 15.6, 14.37 and 9.6; IR (film) νmax 3376, 2937, 1614, 1482, 1453, 1407, 1049; HRMS (ESI) m/z 274.14082 (MNa⁺, C₁₄H₂₁NO₃Na⁺ requires 274.14136).

N-((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-N-methyl-4-((triisopropylsilyl)oxy)butanamide (190) A solution of 158 (9.5 g, 37.8 mmol) in anhydrous DMF (50 mL) at rt was treated with imidazole (6.4 g, 94.6 mmol). The resultant mixture was stirred at rt for 36 h. The reaction was quenched by the addition of brine (25 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 30 mL), and the combined organic layers were washed with brine (30 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (SiO₂, 5% MeOH in CH₂Cl₂ elution) afforded 190 (13.41 g, 32.87 mmol, 87%) as a yellow oil: ¹H NMR
(CDCl₃, 500 MHz) δ 7.27–7.15 (m, 5H), 4.47–4.45 (m, 2H), 3.63–3.61 (m, 2H), 2.80–2.79 (m, 1H), 2.75 and 2.74 (2s, 3H), 2.48–2.38 (m, 1H), 2.32–2.29 (m, 1H), 1.78–1.69 (m, 2H), 1.04–0.86 (m, 24H); ¹³C NMR (CDCl₃, 125 MHz) δ 174.4 and 174.0, 142.7 and 142.7, 128.3 (2C) and 128.1 (2C), 127.7(2C) and 127.3 (2C), 127.0 and 126.7, 75.6 and 75.1, 62.8 and 62.4, 58.3 and 56.2, 31.5 and 30.6, 30.2 and 30.0, 28.7 and 28.3, 18.1 (6C), 15.4 and 14.2, 12.0 (12C); IR (film) ν_max 3388, 2942, 2865, 1623, 1463, 1405, 1105, 1067; HRMS (ESI) m/z 430.27546 (MNa⁺, C₂₃H₄₁NO₃SiNa⁺ requires 430.27479).

(S,E)-N-((1S,2S)-1-hydroxy-1-phenylpropan-2-yl)-N-methyl-2-(2-((triisopropylsilyl)oxy)ethyl)-6-(trityloxy)hex-4-enamide (191) A solution of n-BuLi (1.6 M in hexane, 68 mL, 109.08 mmol) was added to a suspension of LiCl (flamed dried) (13.34 g, 314.64 mmol) and i-Pr₂NH (16.7 mL, 118 mmol) in THF (126 mL) at −78 °C under Ar. The suspension was stirred at −78 °C under Ar for 10 minutes. The resulting suspension was warmed to 0 °C briefly for 5 min and then it was cooled to −78 °C. An ice-cooled solution of 190 (21.35 g, 52.44 mmol) in THF (64 mL) was added. The mixture was stirred at −78 °C for 1 h, at 0 °C for 15 min, and at rt for 5 min. The mixture was cooled to 0 °C. The iodide (25.4 g, 57.69 mmol) was added to the reaction mixture. The resultant mixture was stirred at 0 °C under Ar for 18 h. The reaction was quenched by the addition of half-sat. NH₄Cl (35 mL) solution, extracted with
EtOAc (3 × 40 mL). Flash chromatography (SiO₂: 1% MeOH in CH₂Cl₂) provided 191 (18.36 g, 39.86 mmol, 76 %) as a white solid: ¹H NMR (CDCl₃, 500 MHz) δ 7.50–7.48 (m, 3H), 7.38–7.20 (m, 7H), 5.74–5.60 (m, 2H), 4.65–4.62 (m, 1H), 4.48 (br s, 1H), 3.81–3.77 (m, 2H), 3.69–3.65 (m, 1H), 3.60–3.52 (m, 2H), 3.13–3.09 (m, 1H), 2.97 and 2.95 (2s, 3H), 2.42–2.36 (m, 1H), 2.25–2.20 (m, 1H), 1.93–1.86 (m, 1H), 1.78–1.69 (m, 1H), 1.17–1.05 (m, 24H); ¹³C NMR (CDCl₃, 125 MHz) δ 178.0 and 176.9, 144.6 (3C) and 144.5 (3C), 142.9 and 142.0, 131.1 and 129.6, 129.0 (2C), 128.9 (2C) and 128.8 (2C), 128.6 (4C), 128.5 (12C), 128.0 (12C), 127.7 and 126.6, 127.2 (6C), 76.4 and 75.7, 65.2 and 64.9, 61.2 and 61.1, 61.0 and 60.8, 38.6 and 37.5, 36.1 and 35.5, 35.7 and 31.9, 27.7 and 27.3, 18.4 (2C), 16.2 and 14.9, 14.7 (3C) and 14.5 (3C), 12.5 (6C) and 12.2 (6C); IR (film) νmax 3388, 2942, 2865, 1623, 1463, 1405, 1366, 1105; HRMS (ESI) m/z 742.42604 (MNa⁺, C₄₆H₆₁NO₄SiNa⁺ requires 742.42621).

(S,E)-2-(2-((triisopropylsilyl)oxy)ethyl)-6-(trityloxy)hex-4-en-1-ol (192) To a flamed dried round bottom flask, THF (200 mL) was added under Ar. The flask was cooled to −78 °C. i-Pr₂NH (10.3 mL, 72.97 mmol) and n-BuLi (1.6 M in hexanes, 42 mL, 647.76 mmol) were added to the reaction flask respectively. The resultant reaction mixture was stirred at −78 °C for 10 min. Then, it was stirred at 0 °C for 5 min and cooled to −78 °C. Borane-ammonia complex (90%, 2.38 g, 69.50 mmol) was added to the reaction mixture in one portion. The reaction mixture was warmed to 0 °C, and stirred at 0 °C for 20 min. Then, it was warmed to rt, and stirred at rt for 20 min. The resultant reaction mixture was cooled to 0 °C. A solution of 191 (12.5 g, 17.37 mmol)
in THF (127 mL) was added to the reaction mixture dropwise. The reaction was stirred at rt for 50 min. Then it was cooled to 0 °C, and quenched with sat. NH₄Cl (50 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with brine (25 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (SiO₂, 20% EtOAc in hexanes elution) afforded 192 (8.83 g, 15.81 mmol, 93%) as a colorless oil:

\[ \text{H NMR (CDCl}_3\text{, }500 \text{ MHz)} \delta 7.55 (d, J = 7 \text{ Hz, } 6 \text{H}), 7.36 (t, J = 7.5 \text{ Hz, } 6 \text{H}), 7.28 (t, J = 7 \text{ Hz, } 3 \text{H}), 5.84–5.78 (m, 1H), 5.74–5.69 (m, 1H), 3.97–3.93 (m, 1H), 3.86–3.81 (m, 1H), 3.75–3.69 (m, 1H), 3.66 (d, J = 5.5 Hz, 2H), 3.60–3.56 (m, 1H), 3.49 (br s, 1H), 2.63–2.21 (m, 1H), 2.17–2.09 (m, 1H), 1.88–1.84 (m, 1H), 1.82–1.76 (m, 1H), 1.69–1.63 (m, 1H), 1.18–1.16 (m, 21H);

\[ ^{13}\text{C NMR (CDCl}_3\text{, }125 \text{ MHz)} \delta 144.6, 130.8, 129.0 (6\text{C}), 128.1 (6\text{C}), 127.2 (3\text{C}), 87.1, 66.2, 65.2, 62.5, 39.9, 35.6, 35.3, 18.4, 18.3 (6\text{C}), 12.2 (3\text{C}); \text{ IR (film)} \nu_{\text{max}} 3415, 2941, 2865, 1490, 1448, 1381, 1098, 1055; \text{ HRMS (ESI)} m/z 576.38523 (MNH₄⁺, C₃₆H₅₀O₃SiNa⁺ requires 576.38675).

(S,E)-tert-butyl((3-((naphthalen-2-ylmethoxy)methyl)-7-(trityloxy)hept-5-en-1-ylooxy)diphenylsilane (184) A solution of 192 (500 mg, 0.895 mmol) in anhydrous DMF/THF (1:1) (20 mL) at 0 °C under Ar was treated with NaH (60%, 72 mg, 1.79 mmol) followed by NAPBr (297 mg, 1.34 mmol). The resultant mixture was stirred at 0 °C under Ar for 12 h. The reaction was quenched by the addition of sat. NH₄Cl (6 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with brine (5 mL), dried
(Na$_2$SO$_4$), and concentrated in vacuo. Flash chromatography (SiO$_2$, 2% EtOAc in hexanes elution) afforded triether product (557 mg, 0.797 mmol, 89%) as a colorless oil.

A solution of the obtained triether (557 mg, 0.797 mmol) in anhydrous THF (15 mL) at 0 °C under Ar was treated with TBAF (1.0 M in THF, 1.8 mL, 1.79 mmol). The resultant mixture was warmed to rt and stirred at rt under Ar for 8 h. The reaction was quenched by the addition of sat. NH$_4$Cl (4 mL). The aqueous layer was extracted with EtOAc (3 × 8 mL), and the combined organic layers were washed with brine (5 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo. Flash chromatography (SiO$_2$, 35% EtOAc in hexanes elution) afforded alcohol (411 mg, 0.757 mmol, 95%) as a colorless oil.

A solution of the obtained alcohol (411 mg, 0.757 mmol) in anhydrous 1,2-dichloroethane (6 mL) at 0 °C under Ar was treated with Et$_3$N (0.15 mL, 0.109 g, 1.074 mmol, DMAP (22 mg, 0.179 mmol), and TBDPS-Cl (0.26 mL, 0.275 g, 0.984 mmol). The resultant mixture was stirred at rt under Ar for 24 h. The reaction was quenched by the addition of sat. NH$_4$Cl (3 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organic layers were washed with brine (4 mL), dried (Na$_2$SO$_4$), and concentrated in vacuo. Flash chromatography (SiO$_2$, 2% EtOAc in hexanes elution) afforded 184 (411.8 mg, 0.527 mmol, 92%) as a colorless oil: $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.85–7.76 (m, 4H), 7.67–7.65 (m, 4H), 7.48–7.21 (m, 24H), 5.71–5.66 (m, 1H), 5.64–5.59 (m, 1H), 4.64 (s, 2H), 3.76 (dt, $J$ = 1 Hz, 6.8 Hz, 2H), 3.54 (d, $J$ = 5 Hz, 2H), 3.45–3.38 (m, 2H), 2.27–2.23 (m, 1H), 2.18–2.14 (m, 1H), 2.02–1.98 (m, 1H), 1.71–1.63 (m, 2H), 1.07 (s, 9H); 144.5 (3C), 136.3, 135.7 (2C), 134.1, 133.4, 133.0, 130.6, 130.4, 129.7 (2C), 128.8 (4C), 128.7, 128.2, 128.2, 128.0, 127.9 (4C), 127.8, 127.7 (6C), 127.0 (6C), 126.3, 126.1, 125.8 (3C), 73.2, 73.0, 65.1, 62.2, 60.5, 35.5, 34.6, 34.1, 27.0 (3C), 19.3; IR (film)
ν\text{max} 3055, 2929, 2856, 1489, 1428, 1372, 1265, 1110; HRMS (ESI) \textit{m/z} 798.43376 (MNH}_4^+ , C_{54}H_{56}O_3SiNa^+ \text{ requires 798.43370).}

tert-butyl((R)-4-(naphthalen-2-ylmethoxy)-3-((2R,3R)-3-((trityloxy)methyl)oxiran-2-yl)methyl)butoxy)diphenylsilane (185) The alkene 184 (0.1286 g, 0.2006 mmol) was dissolved in DMM/CH\textsubscript{3}CN (2:1, 1.86 mL). Then, the K\textsubscript{2}CO\textsubscript{3}-CH\textsubscript{3}COOH (1.12 mL) buffer solution, Bu\textsubscript{4}NHSO\textsubscript{4} (1.5 mg, 0.0044 mmol), chiral ketone (52 mg, 0.2006 mmol) were added respectively. A solution of oxone (0.1612 g, 0.3009 mmol) in aqueous 4 \times 10^{-4} \text{Na}_2\text{EDTA} solution (0.62 mL) and 1.47 M KOH aqueous solution (0.62 mL) were added slowly at the same rate. The resulting suspension was stirred at rt for 5 hr. Added chiral ketone (52 mg, 0.2006 mmol) once more. Then A solution of oxone (0.1612 g, 0.3009 mmol) in aqueous 4 \times 10^{-4} \text{Na}_2\text{EDTA} solution (0.62 mL) and 1.47 M KOH aqueous solution (0.62 mL) were added slowly at the same rate again. The resultant suspension was stirred at rt for 4 h. The solution was extracted with EtOAc (3 \times 5 mL), and the combined organic layers were washed with brine (3 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), and concentrated in vacuo. Flash chromatography (SiO\textsubscript{2}, 1% EtOAc in hexanes elution) afforded 185 (115 mg, 0.144 mmol, 72%) as a colorless oil: \textit{^1H NMR (CDCl\textsubscript{3}, 500 MHz)} δ 7.83–7.71 (m, 4H), 7.65–7.62 (m, 4H), 7.48–7.44 (m, 8H), 7.41–7.21 (m, 16H), 4.60 (s, 2H), 3.72 (t, \textit{J} = 6.5 Hz, 2H), 3.45 (d, \textit{J} = 5.5 Hz, 2H), 3.23 (, dd, \textit{J} = 3.5 Hz, 10 Hz, 1H), 3.09 (dd, \textit{J} = 6 Hz, 11 Hz, 1H), 2.90–2.88 (m, 1H), 2.82–2.81 (m, 1H), 2.13–2.08 (m, 1H), 1.71–1.56 (m, 4H), 1.02 (s, 9H); \textit{^13C NMR (CDCl\textsubscript{3}, 125 MHz)} δ 143.9 (3C), 136.0, 135.5 (2C), 133.8,
133.2, 132.9, 129.6 (2C), 128.7 (4C), 128.1 (4C), 127.9, 127.8 (6C), 127.7, 127.6 (6C), 127.0 (3C), 126.2, 126.0, 125.7, 125.7, 73.1, 73.1, 64.7, 61.8, 57.2, 55.0, 34.2, 34.1, 33.8, 26.9 (3C), 19.2, –0.002; IR (film) νmax 2928, 1448, 1427, 1110, 744; HRMS (ESI) m/z 814.43165 (MNH₄⁺, C₅₄H₅₆O₄SiNH₄⁺ requires 814.42861).

2S,3R,5S)-7-((tert-butyldiphenylsilyl)oxy)-5-((naphthalen-2-ylmethoxy)methyl)-1-(trityloxy)-3-vinylheptan-2-ol (186) To a mixture of CuBr·Me₂S (23.2 mg, 0.1129 mmol) and Me₂S (51 µL) in Et₂O (0.51 mL) was added vinyl magnesium bromide (1 M in THF, 0.34 mL, 0.3387 mmol) at –15 °C. The resultant mixture was stirred at –15 °C for 30 min. Then, it was warmed to 0 °C, and stirred at 0 °C for 30 min. The epoxide 185 (45 mg, 0.05645 mmol) in Et₂O (0.2 mL) was added to the reaction mixture. The resultant mixture was warmed to rt and stirred at rt for 18 h. The reaction was quenched by the addition of brine (0.5 mL). The mixture was extracted with EtOAc (3 × 3 mL), and the combined organic layers were washed with brine (1 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (SiO₂, 5% EtOAc in hexanes elution) afforded 186 (37.8 mg, 0.04572 mmol, 81%) as a colorless oil: ¹H NMR (CDCl₃, 500 MHz) δ 7.84–7.65 (m, 8H), 7.50–7.43 (m, 9H), 7.41–7.23 (m, 15H), 5.77 (dt, J = 2 Hz, 8.8 Hz, 1H), 5.31 (dd, J = 1.5 Hz, 17.5 Hz, 1H), 5.18 (dq, J = 1.5 Hz, 7.3 Hz, 1H), 4.58 (s, 2H), 3.73–3.67 (m, 2H), 3.38–3.30 (m, 2H), 3.11–3.10 (m, 1H), 3.04 (t, J = 8 Hz, 1H), 2.36 (d, J = 5.5 Hz, 1H), 1.75–1.73 (m, 1H), 1.62–1.52 (m, 3H), 1.44–1.37 (m, 1H), 1.02 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 144.0 (3C), 142.0, 136.4, 135.8 (2C), 134.3, 133.5, 133.2, 129.7
(2S,3R,5S)-7-((tert-butyldiphenylsilyl)oxy)-5-((naphthalen-2-ylmethoxy)methyl)-3-vinylheptane-1,2-diol (193) 10-CSA (1.8 mg, 0.00728 mmol) was added to a solution of 186 (10 mg, 0.012129 mmol) in EtOH/CH$_2$Cl$_2$ (2:1, 1.6 mL) at rt. The reaction mixture was stirred for 4 h. The reaction was quenched by the addition of solid NaHCO$_3$, filtered and concentrated. Flash chromatography (SiO$_2$, 30% EtOAc in hexanes elution) provided 193 (5.02 mg, 0.00861 mmol, 71%) as a colorless oil: $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.86–7.75 (m, 4H), 7.7.68–7.66 (m, 4H), 7.50–7.48 (m, 2H), 7.45–7.41 (m, 3H), 7.39–7.37 (m, 4H), 5.73 (dd, $J$ = 11 Hz, 17 Hz, 1H), 5.33 (dd, $J$ = 5 Hz, 17 Hz, 1H), 5.24 (d, $J$ = 10.5 Hz, 1H), 4.61 (s, 2H), 3.74–3.70 (m, 2H), 3.45–3.40 (m, 4H), 3.37–3.34 (m, 1H), 1.87–1.85 (m, 1H), 1.64–1.54 (m, 3H), 1.47–1.42 (m, 2H), 1.06 (s, 9H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 140.7, 140.6, 135.6 (2C), 134.0, 133.3, 129.6 (4C), 128.1, 127.9, 127.9, 127.7 (4C), 127.6 (4C), 126.3, 126.1, 125.8, 125.8, 125.8, 115.3, 73.1, 68.9, 68.8, 62.0, 62.0, 35.4, 35.2, 34.5, 34.0 33.8, 26.9 (3C), 19.2; IR (film) $\nu_{\text{max}}$ 3418, 2930, 2857, 1471, 1427, 1389, 1110; HRMS (ESI) $m/z$ 605.30492 (MNa$^+$, C$_{37}$H$_{46}$O$_4$SiNa$^+$ requires 605.30576).
tert-butyld(3S,5R)-3-((naphthalen-2-ylmethoxy)methyl)-5-((S)-oxiran-2-yl)hept-6-en-1-yl)oxy)diphenylsilane (194) To a solution of 193 (4 mg, 0.00686 mmol) in THF (0.3 mL) at 0 °C was added NaH (0.8 mg, 0.0206 mmol). The resultant reaction mixture was warmed to rt and stirred at rt for 30 min. Then, it was cooled to 0 °C. N-(2,4,6-Triisopropylbenzenesulfonyl)imidazole (2.5 mg, 0.00755 mmol) was added in one portion. The reaction mixture was allowed to warm to rt and stirred at rt for 2 h. The reaction was quenched with sat. NH₄Cl (0.2 mL), extracted with EtOAc (3 × 0.5 mL). The combined organic layers were washed with brine (0.5 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (SiO₂, 6% EtOAc in hexanes elution) afforded 193 (2.7 mg, 70%) as a colorless oil: ¹H NMR (CDCl₃, 500 MHz) δ 7.86–7.75 (m, 3H), 7.68–7.66 (m, 4H), 7.49 (t, J = 4.5 Hz, 2H), 7.45–7.43 (m, 3H), 7.38 (t, J = 7 Hz, 4H), 5.77–5.71 (m, 1H), 5.33 (d, J = 17.5 Hz, 1H), 5.20 (d, J = 10.5 Hz, 1H), 4.62 (s, 2H), 3.75–3.71 (m, 3H), 3.44–3.35 (m, 3H), 2.77 (t, J = 5 Hz, 1H), 2.66–2.65 (m, 1H), 1.89–1.87 (m, 1H), 1.75–1.52 (m, 3H), 1.51–1.44 (m, 1H), 1.06 (s, 9H); 13C NMR (CDCl₃, 125 MHz) δ 170.6 (s), 153.8 (s), 134.0, 133.3, 132.9, 129.6 (4C), 128.1, 127.9, 127.7, 127.6 (4C), 126.2, 126.1, 125.8, 125.7 (2C), 116.5, 73.1, 73.0, 73.0, 62.0, 55.0, 54.9, 35.2, 35.1, 34.4, 26.9 (3C), 19.2; IR (film) νmax 2929, 2856, 2359, 1472, 1428, 1362, 1111; HRMS (ESI) m/z 582.34114 (MNH₄⁺, C₃₇H₄₄O₃SiNH₄ requires 582.33980).
(4R,5R,7S)-9-((tert-butyldiphenylsilyl)oxy)-7-((naphthalen-2-ylmethoxy)methyl)-5-vinylnon-1-en-4-ol (195) To a mixture of CuI (7.6 mg, 0.04 mmol) in Et₂O (1.2 mL) was added vinyl magnesium bromide (0.12 mL, 0.12 mmol) at −15 °C under Ar. The resultant mixture was stirred at at −15 °C for 30 min. Then, it was warmed to 0 °C, and stirred at 0 °C for 30 min. The epoxide 194 (11.3 mg, 0.02 mmol) in Et₂O (0.3 mL) was added to the reaction mixture. The resultant mixture was warmed to rt and stirred at rt for 18 h. The reaction was quenched by the addition of brine (1 mL). The mixture was extracted with EtOAc (3 × 3 mL), and the combined organic layers were washed with brine (1 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (SiO₂, 8% EtOAc in hexanes elution) provided 195 as a colorless oil: ¹H NMR (CDCl₃, 500 MHz) δ 7.83–7.71 (m, 4H), 7.66–7.64 (m, 4H), 7.47–7.33 (m, 9H), 5.80–5.72 (m, 1H), 5.41 (t, J = 15 Hz, 1H), 5.03–4.93 (m, 4H), 4.60 (s, 2H), 4.01 (d, J = 4.5 Hz, 1H), 3.73–3.69 (m, 1H), 3.4–3.41 (m, 1H), 3.37–3.34 (m, 1H), 2.75 (t, J = 7 Hz, 2H), 2.07 (t, J = 8.5 Hz, 1H), 1.68–1.59 (m, 2H), 1.52–1.39 (m, 1H), 1.03 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 140.4, 136.9, 136.1, 135.6 (2C), 134.0, 133.3, 132.9, 129.6 (4C), 128.1, 127.9, 127.7, 127.6 (4C), 126.3, 126.0, 125.8, 125.7 (2C), 123.7, 114.8, 73.2, 73.0, 67.1, 62.1, 35.3, 34.4, 31.8, 30.4 (3C), 26.9, 25.3, 19.2; IR (film) νmax 3069, 2929, 2856, 2359, 1636, 1589, 1471, 1427, 1110; HRMS (ESI) m/z 610.37184 (MNH₄⁺, C₃⁹H₄₈O₃SiNa⁺ requires 610.37110).
tert-butyl(((3S,5R,6R)-3-((naphthalen-2-ylmethoxy)methyl)-6-(trityloxy)-5-vinyl-8-en-1-yl)oxy)diphenylsilane (196) A solution of 195 (3 mg, 0.00516 mmol) in anhydrous 1,2-dichloroethane (0.4 mL) at 0 °C under Ar was treated with 2,6-lutidine (3 µL, 0.32 mg, 0.0253 mmol) followed by TrOTf (crude, 0.01265 mmol) in anhydrous CCl₄ (0.4 mL). The resultant mixture was warmed to rt and stirred at rt for 12 h. The reaction was quenched by the addition of sat. NH₄Cl (0.5 mL). The layers were separated. The aqueous layer was extracted with EtOAc (3 × 1 mL), and the combined organic layers were washed with brine (0.3 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (SiO₂, 8% EtOAc in hexanes elution) afforded 89 (3.13 mg, 0.00374 mmol, 74%) as a colorless oil: ¹H NMR (CDCl₃, 500 MHz) δ 7.82–7.64 (m, 5H), 7.47 (d, J = 7.5 Hz, 4H), 7.40–7.15 (m, 23H), 5.83–5.78 (m, 1H), 5.57–5.54 (m, 1H), 5.03 (dd, J = 2 Hz, 17 Hz, 2H), 4.68 (dd, J = 1.5 Hz, 10.5 Hz, 2H), 4.55 (s, 2H), 3.71–3.64 (m, 2H), 3.69–3.63 (m, 2H), 3.51 (br s, 1H), 3.56–3.29 (m, 2H), 2.80 (t, J = 6.5 Hz, 2H), 2.05 (t, J = 8.5 Hz, 1H), 1.78–1.73 (m, 1H), 1.67–1.56 (m, 2H), 1.48–1.30 (m, 2H), 1.03 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz) δ 144.3 (3C), 138.2, 135.6 (2C), 129.5 (2), 129.5, 129.3, 128.8, 128.7 (4C), 128.3 (2C), 128.0, 127.9, 127.7 (4C), 127.7, 127.6 (6C), 127.3, 126.9 (6C), 126.3, 126.2, 126.0, 125.7 (2C), 123.3 (3C), 114.6, 73.1, 73.1, 67.5, 62.2, 35.5, 34.5, 31.8, 30.6, 26.9, 26.9 (3C), 25.9, 19.2; IR (film) νmax 3478, 2929, 2856, 2360, 1698, 1597, 1490, 1446, 1332, 1157, 1088; HRMS (ESI) m/z 857.43633 (MNa⁺, C₅₈H₆₂O₃SiNa⁺ requires 857.43604).
A solution of 196 (8 mg, 0.0096 mmol) in anhydrous THF (1 mL) at 0 °C under Ar was treated with TBAF (1.0 M in THF, 0.11 mL, 0.11 mmol). The resultant mixture was warmed to rt and stirred at rt under Ar for 8 h. The reaction was quenched by the addition of sat. NH₄Cl (4 mL). The aqueous layer was extracted with EtOAc (3 × 1 mL), and the combined organic layers were washed with brine (0.5 mL), dried (Na₂SO₄), and concentrated in vacuo. Flash chromatography (SiO₂, 25% EtOAc in hexanes elution) afforded alcohol 197 (4.8 mg, 0.00806 mmol, 84%) as a colorless oil: ¹H NMR (CDCl₃, 500 MHz) δ 7.85–7.73 (m, 4H), 7.50–7.38 (m, 9H), 7.28–7.22 (m, 9H), 5.84–5.54 (m, 1H), 5.06 (t, J = 7 Hz, 1H), 5.02–4.94 (m, 4H), 3.68–3.63 (m, 1H), 3.59–3.55 (m, 1H), 3.52 (br s, 1H), 3.45 (dd, J = 3.5 Hz, 8.8 Hz, 1H), 3.36–3.32 (m, 1H), 2.80 (t, J = 6.5 Hz, 1H), 2.62–2.58 (m, 1H), 2.11–2.06 (m, 2H), 1.71–1.63 (m, 2H), 1.58–1.53 (m, 1H), 1.35–1.20 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 144.3 (3C), 137.8, 137.0, 135.3, 133.2, 133.0, 128.7 (6C), 128.3, 127.9, 127.7 (6C), 127.7, 126.9 (3C), 126.6, 126.1, 125.9, 125.8, 123.8, 114.7, 73.9, 73.5, 67.5, 61.1, 36.6, 36.2, 31.8, 30.6, 29.7, 25.9; IR (film) νₘₐₓ 3630, 3058, 2924, 2854, 2192, 1638, 1600, 1448, 1030; HRMS (ESI) m/z 619.31684 (MNa⁺, C₄₂H₄₄O₃Na⁺ requires 619.31827).

(3S,5R,6R)-3-((naphthalen-2-ylmethoxy)methyl)-6-(trityloxy)-5-vinynon-8-en-1-ol (198)

(3S,5R,6R)-3-((naphthalen-2-ylmethoxy)methyl)-6-(trityloxy)-5-vinynon-8-enoic acid (198) BAIB (3.6 mg, 0.01106 mmol), TEMPO (0.2 mg, 0.001 mmol), NaHCO₃ (0.4 mg, 0.005
mmol) and alcohol 197 (3 mg, 0.005 mmol) were combined in a vial at 0 °C, and to this mixture was added 0.4 mL of a 1:1 acetonitrile–water solution. The reaction mixture was stirred at 0 °C for 3 h. The reaction was filtered and triturated with diethyl ether to remove the catalytic amount of TEMPO and reaction byproducts. Then the crude product was used directly for the next step. HRMS (ESI) m/z 633.29427 (MNa\(^+\), C\(_{42}\)H\(_{42}\)O\(_4\)Na\(^+\) requires 633.29753).