Efforts Toward a Total Synthesis of Acutumine

Robert Joseph Moreau

A dissertation presented to the faculty of
Princeton University
in candidacy for the degree of
Doctor of Philosophy

Recommended for acceptance by
the Department of Chemistry
Advisor: Erik J. Sorensen

April 2012
©2012 by Robert Joseph Moreau
All rights reserved.
Abstract

The evolution of our synthetic strategy toward a total synthesis of acutumine is described in this thesis. The first chapter provides background information on several topics: (1) the isolation, structure determination, and biological activity of acutumine; (2) Barton’s biosynthetic proposal and the synthetic work carried out by the Matoba and Wipf research groups in an attempt to experimentally validate aspects of this proposal; (3) biochemical studies on the biosynthesis of acutumine; (4) biohalogenation; and (5) the synthetic work carried out by the Castle research group during their successful total synthesis of acutumine. A synthetic strategy that utilized the oxygenated six-membered ring as its foundation to advance aromatic and quinone intermediates into highly functionalized [4.3.0] bicyclic systems that provided critical information about the acutumine system is described in the second chapter. The third chapter presents our evolved strategy to address the acutumine architecture from the vantage of the heterocycle, and how this new strategy led to a synthesis of the propellane-like [4.3.3.0] fused tricyclic core of acutumine in only seven transformations from a known and readily available pyrrolidine derivative. The final chapter describes our further efforts toward a total synthesis of acutumine, including the proposal to utilize a chloronium ion-induced semipinacol rearrangement to introduce both the spirocycle and the chlorine atom in short order from intermediates described during our synthesis of the tricyclic core of acutumine.
Dedicated to my wife and family
Acknowledgments

I owe a great debt of gratitude to my advisor, Professor Erik Sorensen. His love of teaching, his creativity, and his enthusiasm for scientific research have helped shape the scientist and person that I have become. He provided me with enough scientific freedom to learn how to solve on my own many of the chemical problems that I encountered, but he was always there to provide his support and unique insight during the tough times (and there were many). Beyond that, he saw something in me that allowed him to trust me to organize the move from Scripps to Princeton, as well as run the day-to-day operations of the group as lab manager for five years. The varied training that I received in his lab has proven invaluable.

I gratefully acknowledge my thesis committee members, past and present: Professors Abigail Doyle, Chulbom Lee, Robert Pascal, Jeffrey Schwartz, and Martin Semmelhack. I am indebted to them for making the time and effort to be involved in my graduate education. Their mentorship during my time at Princeton will always mean a great deal to me. Professor Semmelhack deserves special recognition and thanks for his careful reading of my thesis. Finally, I am grateful to Professor Edward Taylor for taking the time to involve me in some very inspirational chemical discussions.

With such limited space, it’s impossible to properly thank all of the people who made my experience in graduate school a rewarding and educational one. Special thanks go to Günther Scheid, my acutumine teammate for over two years, and Alexandre Côté, who joined me on the acutumine project during my last year in the lab and took over after my departure. Günther and I were paired together soon after I joined the Sorensen lab, and he was the driving force behind much of the early work toward acutumine that is
described in Chapter 2. He greatly aided my scientific advancement during my first
couple of years in graduate school, and he taught me much of what I know about hands-
on lab techniques. Alex joined the project during one of the most critical and challenging
times. He proved to be the kind of teammate that made me wish that I hadn’t gone solo
after Günther left. Both Günther and Alex were good friends during our time together.

Ed Anderson, Jason Rohde, Bill Shipe, and Chris Vanderwal represented the solid
core of the group when I arrived in La Jolla, and they were largely responsible for the
scholarly, yet easygoing atmosphere in our lab. Hirofumi Seike provided a unique
perspective and constant entertainment. Erik Alexanian, Klaus Pekari, and Günther
joined me when our group expanded to the lab next door, and they became close
colleagues that provided an enjoyable work atmosphere. Casey Mathison and Mark
Tichenor entered Scripps with me in 2002, and I thank them for all of the lunches and
study sessions, as well as for their friendship.

Erik, Jason, and Bill moved with the lab to Princeton, and Jeff Celaje, Steve
Miller, and Christoph Zapf joined us soon after. I thank them for the good times we had
discussing chemistry and playing poker and wiffleball. In addition to the aforementioned
people, my experience in the Sorensen lab over the years would not have been the same
without all of my fellow graduate students, but I thank Jess Frie and her “special friend
Mitch” for their friendship and many good times at Truman and in NYC. My thanks and
apologies to Doug McLeod for taking over as lab manager toward the end of my time at
Princeton. Our lab consistently benefited from high quality post-docs, and I thank B. J.
Chain, Adam Charnley, Eric Flamme, Brian Goess, Chris Jeffrey, Rachel MacCoss, John
Malona, Jason Roland, Glenn Sammis, and Jay Schneekloth for their friendship and for
helping to create a dynamic lab environment that made my tenure at Princeton very memorable.

Some of the students and post-docs at Princeton outside of the Sorensen lab deserve special thanks for their friendship: Phil Albiniak, Bill Brow, Jung Min Joo, Hahn Kim, Rob Matunas, Justin Roberts, and Sean Wiedemann. I thank the members of all the basketball, flag football, and softball teams I played on while at Princeton for the good times we had together, especially Seth Bell, Ryan Buzdygon, Valerie Cubon, Garret Lau, Mike Lowry, Karl Oyler, Angie Sauers, and Chris Traina. Thanks to the many members of the MacMillan lab that I had the pleasure of interacting with toward the end of my time at Princeton.

I owe a debt of gratitude to Laurie Colum (Scripps) and Lynn Mendenko (Princeton) for making our lives easier and always helping to keep the group running smoothly. As lab manager, I had the opportunity to work together with much of the administrative and support staff in the chemistry department at Princeton, so I thank all of them for their assistance and hard work throughout the years.

Technical assistance by the following people was greatly appreciated during the course of my research: Dr. Dee-Hua Huang and Dr. Laura Pasternack (NMR, Scripps), Dr. Carlos Pacheco and Dr. István Pelczer (NMR, Princeton), Dr. Gary Siuzdak (Mass Spectrometry, Scripps), Dr. John Eng and Dr. Dorothy Little (Mass Spectrometry, Princeton), and Dr. Douglas Ho (X-ray, Princeton).

Funding from the Scripps Research Institute Graduate Program, Bristol-Myers Squibb, and Princeton University helped defray the cost of my education, and I thank these agencies for their support.
Beyond Princeton, several people have had a profound impact on my education and my career. Professor Edward Calabrese at UMass-Amherst provided me with the great opportunity to work with him during many of my college break periods, and he has maintained an interest in my career development over the years. Professors Timothy Curran and Ronald Jarret at Holy Cross inspired me in the classroom and supported my desire to pursue a graduate degree in organic chemistry. Professor Curran gave me my first taste of laboratory research, and he is also responsible for providing me with the unique opportunity to work with Professor Daniel Kemp at MIT. The research that I carried out in the Kemp lab became the subject of my undergraduate thesis. I thank Professor Kemp for the attention and guidance that he provided to me, and also for his incredible generosity and amazing tangents. He urged me to apply to, and later attend, Scripps while I was looking at graduate schools, and also to work with Erik once I decided to move to La Jolla. My experience in the Kemp lab was made more memorable thanks to Robert Kennedy.

I know I don’t say it to them nearly enough, but I thank my parents for raising me right, and for their love and support in everything that I’ve ever done. It’s tough to find a greeting card that expresses my true feelings for them, so I hope that by acknowledging them here they realize how appreciative I am for everything. In addition, they have given me two of the greatest gifts I will ever receive – my brothers, Greg and Patrick (Stu). The three of us have an amazing relationship, and I wouldn’t be half the person that I am today without their love and friendship. At the times that I have been stationary on a small sailboat in a vast body of water, they have been the breezes that have helped to move me forward.
Without a doubt, one of the most influential people in my life has been my
grandfather, Bumpa (Albert). It is largely the result of the tragic loss of his wife, Eleanor
(Nana), when I was very young that my brothers and I have had the opportunity to spend
so much time with him and to grow as close to him as we have over the years. He is a
distinguished graduate of the School of Hard Knocks that went on to fight in WWII, work
for the railroad, grow a family business, and create a large and loving family. He is an
amazing man, and he is truly one of the greatest men from The Greatest Generation. I
thank him for everything he has done for my family and me. If I can live my life to enjoy
a fraction of the love, laughter, respect, and success that he has found in his life, I will
consider myself extremely fortunate.

Finally, I thank my wife, Meghan, for her patience, love, and support. She, more
than anyone, has helped share the burden of my chosen career path. With me, she
endured the long hours, the challenging and frustrating nature of the work, multiple
cross-country moves, and nearly annual in-town moves. I apologize for all of that, and
for asking her to read a draft of this document, but I thank her for doing it all so willingly.
I look forward to sharing with her what life has to offer. I also thank Meg’s parents, Fred
and Diane, for raising a wonderful young woman, and for welcoming me into their family
with open arms. I am grateful for their love and support.
Chapter 1. Introduction

1.1 Isolation and Structure Determination of Acutumine ......................... 2
1.2 Barton’s Proposal on the Biosynthesis of Acutumine......................... 4
1.3 Efforts to Experimentally Validate Barton’s Biosynthetic Proposal
   1.3.1 Matoba .......................................................... 7
   1.3.2 Wipf .............................................................. 8
1.4 Biochemical Studies on the Biosynthesis of Acutumine ....................... 10
1.5 Organohalogenens and Biohalogenation . . . . . . . . . . . . . . . . . . . . . . 12
1.5.1 Biohalogenation of Acutumine Alkaloids.......................... 13
1.5.2 Nucleophilic Biohalogenation via Halide Ion Addition ..... 14
1.5.3 Biohalogenation via Electrophilic or Radical Halogenation 16
1.6 Biological Activity of Acutumine............................................. 20
Chapter 2. Efforts Toward a Synthesis of the Acutumine Architecture

2.1 Synthetic Strategy ................................................................. 37
2.2 Phenol Oxidation Approach ...................................................... 38
2.3 The Trimethoxybenzaldehyde Route ......................................... 39
2.4 The Benzoquinone Route .......................................................... 41
  2.4.1 A Michael Addition/Curtius Sequence to Install the Amino-ethane
        Group ................................................................................. 43
  2.4.2 Exploiting the Reactivity of Triphenylarsine Oxide................. 45
  2.4.3 Elaboration of the Cyclic Imine ............................................. 51
  2.4.4 Studies Toward the Acutumine Architecture ......................... 54
2.5 References .................................................................................. 58

Chapter 3. A Synthesis of the Acutumine Core Structure

3.1 A New Synthesis Plan ................................................................. 62
3.2 Ketoprolpine Synthesis ............................................................... 63
3.3 Enone Studies ............................................................................. 67
3.4 1,3-Dicarbonyl Studies ................................................................. 70
3.5 Further Evolution of the Michael Addition Strategy ..................... 71
3.6 A Synthesis of the Vinylogous Carbonate Intermediate ............... 73
3.7 A Synthesis of the Acutumine Core Structure ........................................ 76
3.8 Efforts Toward an Asymmetric Synthesis of the Core Structure .... 80
3.9 Conclusions ........................................................................................................ 82
3.10 References ......................................................................................................... 83

Chapter 4. Efforts Toward the Completion of a Total Synthesis of Acutumine

4.1 Early Attempts Directed at the Installation of the Spirocyle ........ 88
4.2 A New Strategy for the Introduction of the Spirocyle ..................... 93
4.3 Early Attempts at a Vinyl Bromide Synthesis ............................ 97
4.4 A Successful Vinyl Bromide Synthesis ........................................ 99
4.5 Advancement of the Vinyl Bromide .................................................. 104
4.6 References ......................................................................................................... 110

Experimental Section

E.0 General Experimental Details ................................................................. 115
E.1 Instrumentation ........................................................................................... 115
E.2 Experimental for Chapter 2 ................................................................. 116
E.3 Experimental for Chapter 3 ................................................................. 131
E.4 Experimental for Chapter 4 ................................................................. 154
E.5 NMR spectra ............................................................................................. 181
List of Figures

Chapter 1

**Figure 1.1.** The evolution of the structure of acutumine

**Figure 1.2.** Acutumine and related alkaloids

**Figure 1.3.** The sporolide natural products

**Figure 1.4.** The cyanospolaside natural products

Chapter 2

**Figure 2.1.** The reactivity of triphenylarsine oxide investigated by Frøyen
# List of Schemes

## Chapter 1

<table>
<thead>
<tr>
<th>Scheme 1.1.</th>
<th>Barton's proposed biosynthesis of acutumine</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheme 1.2.</td>
<td>Matoba lab studies directed at Barton's proposed biosynthesis of the acutumine spirocycle</td>
<td>8</td>
</tr>
<tr>
<td>Scheme 1.3.</td>
<td>Wipf lab studies and alternative proposal for the biosynthesis of the acutumine spirocycle</td>
<td>10</td>
</tr>
<tr>
<td>Scheme 1.4.</td>
<td>Biosynthetic interrelationship of chlorinated <em>Menispermum</em> alkaloids</td>
<td>12</td>
</tr>
<tr>
<td>Scheme 1.5.</td>
<td>Nucleophilic biohalogenation via halide ion addition</td>
<td>16</td>
</tr>
<tr>
<td>Scheme 1.6.</td>
<td>Biohalogenation via haloperoxidase enzyme co-factors</td>
<td>17</td>
</tr>
<tr>
<td>Scheme 1.7.</td>
<td>Biohalogenation via halogenase enzyme co-factors</td>
<td>19</td>
</tr>
<tr>
<td>Scheme 1.8.</td>
<td>The Castle lab's synthesis of the core structure of acutumine</td>
<td>22</td>
</tr>
<tr>
<td>Scheme 1.9.</td>
<td>Castle lab's undesired 6-<em>endo-trig</em> radical cyclization</td>
<td>23</td>
</tr>
<tr>
<td>Scheme 1.10.</td>
<td>Castle lab's synthesis of the acutumine spirocycle by a radical-polar crossover reaction</td>
<td>26</td>
</tr>
<tr>
<td>Scheme 1.11.</td>
<td>The Castle lab's synthesis of acutumine</td>
<td>29</td>
</tr>
</tbody>
</table>

## Chapter 2

| Scheme 2.1. | A synthetic strategy based on tandem Michael-type additions | 38 |
| Scheme 2.2. | An early idea to address the complex architecture of acutumine | 39 |
| Scheme 2.3. | An approach toward acutumine derived from a quinone imine | 40 |
| Scheme 2.4. | An approach toward acutumine derived from 1,4-benzoquinone | 41 |
| Scheme 2.5. | The advancement of 1,4-benzoquinone | 42 |
Scheme 2.6. Acrylate addition and Curtius rearrangement to install the 
aminoethane group ................................................................. 45

Scheme 2.7. A successful imine formation ................................................................. 48

Scheme 2.8. A triphenylarsine oxide-mediated cyclic imine formation ........ 49

Scheme 2.9. Elaboration of the cyclic imine ......................................................... 52

Scheme 2.10. A serendipitous discovery provides material suitable for X-ray 
crystallographic analysis ....................................................................... 54

Scheme 2.11. Unsuccessful attempts toward the acutumine architecture .... 56

Scheme 2.12. Studies to address the enone and epoxide ......................... 57

Scheme 2.13. A route based on 2,3,4-trimethoxybenzaldehyde ............... 58

Chapter 3

Scheme 3.1. A new approach toward acutumine ........................................ 63

Scheme 3.2. Rapoport's ketoproline synthesis ............................................... 64

Scheme 3.3. Streamlined ketoproline synthesis ............................................. 66

Scheme 3.4. A successful intramolecular Horner-Wadsworth-Emmons 
reaction .......................................................................................... 68

Scheme 3.5. Propargylic and allylic transposition studies ....................... 70

Scheme 3.6. Examples of masked 1,3-dicarbonyl moieties that failed 
during enone synthesis ........................................................................ 71

Scheme 3.7. Why perform the enone? ............................................................... 73

Scheme 3.8. Synthesis of vinylogous carbonate intermediate 3.25 ........... 76

Scheme 3.9. Proposed cascade carbonyl reactivity ....................................... 77

Scheme 3.10. Cascade carbonyl reactivity affords the tricyclic core of
Scheme 3.11. Catalytic asymmetric phase transfer propargylation of a ketoproline .......................................................... 82

Scheme 3.12. Another ketoproline synthesis .......................................................... 84

Chapter 4

Scheme 4.1. Early unsuccessful efforts directed at addressing the spirocycle 90

Scheme 4.2. An unsuccessful effort directed at addressing the spirocycle by an intramolecular aldol cyclization. .................................................. 93

Scheme 4.3. A different fate for Barton's proposed aziridinium?................. 95

Scheme 4.4. A chloronium ion-induced semipinacol idea.............................. 97

Scheme 4.5. Early unsuccessful efforts directed at addressing the vinyl bromide .................................................................................. 99

Scheme 4.6. A rapid and efficient deoxygenation .......................................... 100

Scheme 4.7. Acrylate saponification and methyl ketone protection............. 103

Scheme 4.8. A successful vinyl bromide synthesis ....................................... 104

Scheme 4.9. Lithium-halogen exchange and cyclobutanone addition to give the desired vinyl cyclobutanol ........................................... 105

Scheme 4.10. An oxidative semipinacol rearrangement .............................. 107

Scheme 4.11. Lithium-halogen exchange, squarate addition, and a chlorinative semipinacol rearrangement .............................................. 109

Scheme 4.12. Synthesis of propargyl bromide 4.7 ..................................... 111

Scheme 4.13. Radical dechlorination of dauricumine .................................. 111
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>2,4-pentanedione</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2′-azobis(2-methylpropionitrile)</td>
</tr>
<tr>
<td>Alloc</td>
<td>allyloxycarbonyl</td>
</tr>
<tr>
<td>[α]_{D}^{23}</td>
<td>specific rotation at 23 °C and wavelength of sodium D line</td>
</tr>
<tr>
<td>Å</td>
<td>Angstrom</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2′-bis(diphenylphosphino)-1,1′-binaphthalene</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyloxycarbonyl</td>
</tr>
<tr>
<td>br s</td>
<td>broad singlet</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>c</td>
<td>concentration</td>
</tr>
<tr>
<td>C</td>
<td>Celsius</td>
</tr>
<tr>
<td>Cbz</td>
<td>benzyloxycarbonyl</td>
</tr>
<tr>
<td>CDI</td>
<td>1,1′-carbonyldiimidazole</td>
</tr>
<tr>
<td>cm</td>
<td>centimeter</td>
</tr>
<tr>
<td>CSA</td>
<td>10-camphorsulfonic acid</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
</tbody>
</table>
δ  chemical shift
DACH  1,2-diaminocyclohexane
dba  dibenzylideneacetone
DBN  1,5-diazabicyclo[4.3.0]non-5-ene
DBU  1,8-diazabicyclo[5.4.0]undec-7-ene
dd  doublet of doublets
DMAP  4-dimethylaminopyridine
DMF  \(N,N'\)-dimethylformamide
DMSO  dimethylsulfoxide
DPPA  diphenyl phosphoryl azide
dt  doublet of triplets
EDC  1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
equiv.  equivalents
ESI  electrospray ionization
Et  ethyl
Et₂O  diethyl ether
EtOAc  ethyl acetate
FT-IR  Fourier transform infrared spectroscopy
g  gram
h  hour
HPLC  high-performance liquid chromatography
HRMS  high-resolution mass spectrometry
Hz     Hertz
IBX    o-iodoxybenzoic acid
IC₅₀   half maximal inhibitory concentration
imid   imidazole
IR     infrared
J      coupling constant
KHmDS  potassium bis(trimethylsilyl)amide
L      liter
LAH    lithium aluminum hydride
LDA    lithium diisopropylamide
L-Selectride® lithium tri-sec-butylborohydride
M      molar
m      multiplet
m-CPBA 3-chloroperoxybenzoic acid
Me     methyl
mg     milligram
min    minute
mL     milliliter
µL  microliter
mm  millimeter
µM  micromolar
mmol millimole
mol mole
MS molecular sieves
Ms methanesulfonyl
m/z mass-to-charge ratio
NaHMDS sodium bis(trimethylsilyl)amide
NCS N-chlorosuccinimide
NMO 4-methylmorpholine N-oxide
NMR nuclear magnetic resonance
NOESY Nuclear Overhauser Effect Spectroscopy
Nu generic nucleophile
P generic protecting group
PCC pyridinium chlorochromate
Ph phenyl
pH negative log of hydrogen ion concentration
Ph₂O diphenyl ether
ppm parts per million
ppt  parts per trillion
PPTS  pyridinium 4-toluenesulfonic acid
Pr  propyl
$p$-TsOH  $para$-toluenesulfonic acid
R  generic organic group
$R_i$  retention factor
s  singlet
t  triplet
TBAF  tetra-$n$-butylammonium fluoride
TBAI  tetra-$n$-butylammonium iodide
TBS  $tert$-butyldimethylsilyl
TES  triethylsilyl
 Tf  trifluoromethanesulfonyl
THF  tetrahydrofuran
TLC  thin-layer chromatography
TMS  trimethylsilyl
TPAP  tetra-$n$-propylammonium perruthenate
UV  ultraviolet
wt.  weight
Chapter 1

Introduction
1.1 Isolation and Structure Determination of Acutumine

Acutumine was first isolated in a pure state in 1929 from the root of *Sinomenium acutum* Rehd. et Wills. by Kakuji Goto and Hideo Sudzuki from the Kitasato Institute in Tokyo, Japan.\(^1\) Crystallization of acutumine from chloroform solution was accelerated by the addition of methanol, providing pure material as pale yellow needles that melted at 240 °C. At this time, only the optical rotation of the hydrochloride salt of acutumine was reported, and it was measured to be \([\alpha]_D^{+} 60.20^\circ\) (no temperature, solvent or concentration given). Functional group analyses performed on the small amount of isolated material revealed that acutumine contained a ketone, an \(\text{N}-\text{methyl}\) and three methoxy groups (Figure 1.1, 1929). The presence of a carboxyl group was also suspected due to the very weakly basic nature of acutumine,\(^2\) though there was no definite proof to support this assumption. From their studies, Goto and Sudzuki proposed that acutumine had the molecular formula \(\text{C}_{20}\text{H}_{27}\text{NO}_8\) or \(\text{C}_{21}\text{H}_{27}\text{NO}_8\).

![Figure 1.1. The evolution of the structure of acutumine.](image)

For almost forty years, no reports were published on acutumine, leaving its structure at a rather simplistic level; however, in 1966, the Goto group detailed further efforts toward the structural elucidation of acutumine.\(^2\) With the aid of both mass spectrometric and combustion analysis, the presence of a chlorine atom in acutumine was established, and this allowed for the revision of the molecular formula to \(\text{C}_{19}\text{H}_{25}\text{NO}_6\text{Cl}\).
Interestingly, the chlorine atom was noted to be stable toward Ag₂O, LAH, and catalytic hydrogenolysis. Further characterization data of acutumine were also reported that included NMR and IR spectrometric data, as well as the optical rotation, which was measured to be $[\alpha]_D^{15} -206^\circ$ (c = 0.69, pyridine). Based on experimental evidence gained from spectrometric and spectroscopic data, as well as chemical degradation studies, the presence of three partial structures in acutumine was proposed: a dienyl secondary allylic alcohol, a chlorine- or oxygen-substituted ethane group (i.e., $X = \text{Cl or OR}$), and an enone substituted by one or two methoxyl groups at the $\alpha$- and $\beta$-positions (Figure 1.1, 1966). Further analysis led to publications in the following year that detailed slight modifications to these partial structures.³ These refinements led the Goto group to propose that the aforementioned partial structures were actually a $\gamma$-hydroxy-$\beta$-methoxycyclopentenone, a chloroethane group, and an $\alpha,\beta$-dimethoxyenone, respectively (Figure 1.1, 1967). However, it was not until X-ray crystallographic analysis of acutumine and its acetate was performed in 1967 and 1968 that the full constitution and absolute stereochemistry of acutumine (1.1) was revealed (Figure 1.1, 1967/8).³⁴ The remarkable structure of acutumine, with its complex cyclic connectivity and conspicuous chlorine atom, consists of a propellane-like [4.3.3.0] fused tricycle with appended spirocycle core and five contiguous stereogenic centers, of which three are fully substituted.

In recent years, many additional members of the acutumine family have been isolated and characterized, and they all have in common the propellane-like [4.3.3.0] fused tricycle with appended spirocycle core (Figure 1.2).³⁵¹¹ The key diversity element is the spirocycle, where both methylated 1,2- and 1,3-diketones have been isolated, as
well as compounds epimeric at the hydroxyl-bearing stereogenic center, or lacking the hydroxyl group altogether. Recently, hypserpanine (1.5) was isolated from *Hypserpa nitida*, and this close relative of dauricumine has a vinylogous N,N-diethylamide in place of the typical vinylogous methyl ester.¹¹ One particularly interesting relative, acutudaurin (1.11), even has a six-membered spirocycle (stereochemistry undetermined).⁸ In addition to the range of chlorinated alkaloids, the corresponding dechlorinated relative has been isolated for almost every member of the family. Nearly the same can be said for the extent of N-methylation.

![Figure 1.2. Acutumine and related alkaloids.](image)

### 1.2 Barton’s Proposal on the Biosynthesis of Acutumine

Shortly after the full structure of acutumine was revealed, Barton and co-workers described both their interest in and studies on the biosynthetic origin of acutumine.¹² They showed that many of the related alkaloids that were often isolated from natural
sources along with acutumine are not biosynthetic precursors of acutumine, leading them to suggest that acutumine derives biosynthetically via a unique pathway. Specifically, they proposed that acutumine may originate biosynthetically via phenolic coupling and further degradation of a simple benzylisoquinoline alkaloid (Scheme 1.1).\textsuperscript{12b} They postulated that if methoxylation patterns govern the positions of phenolic coupling in biosynthesis, then a suitable precursor for acutumine would be benzylisoquinoline 1.13, which after a \textit{para-para} oxidative coupling of two phenol radicals would give spirodienone 1.14. Bisepoxidation of 1.14 followed by a Favorskii- or benzilic acid-type rearrangement would give the ring-contracted carboxylic acid 1.16. A decarboxylative epoxide opening to provide diol 1.17 would then be followed by a selective oxidation to provide vinylogous ester 1.18, a compound bearing the spirocycle as found in acutumine. Ring contraction of piperidine 1.18 would be initiated by intramolecular conjugate addition of the tertiary amine onto the pendant enone to provide aziridinium 1.19, which after a [1,2]-hydride shift could allow for incorporation of chloride via the resulting intermediate secondary carbocation 1.20, thus providing the full acutumine architecture. The lone pair of the proximate nitrogen could perhaps stabilize this proposed intermediate carbocation as the distance between these two atoms was found to be only 3.2 Å in the crystal structure of acutumine. Reorganization of the cyclohexenone methoxylation pattern would complete the biosynthesis of acutumine.
Scheme 1.1. Barton's proposed biosynthesis of acutumine.
1.3 Efforts to Experimentally Validate Barton’s Biosynthetic Proposal

It speaks to the creativity and high level of interest in the ideas put forth by Barton and co-workers in their proposal that two independent laboratory investigations into the feasibility of the bisepoxidation/Favorskii/decarboxylation sequence for the biosynthetic installation of the acutumine spirocycle have been published.\textsuperscript{13,14} The experimental observations published by the Matoba and Wipf labs will be briefly reviewed herein.

1.3.1 Matoba

Studies by Matoba and co-workers in the early 1980s showed that six-membered diosphenol ether 1.22 could be oxidized with three equivalents of \textit{m}-CPBA in 1,1,1-trichloroethane at reflux to give a compound proposed to be bisoxidation product 1.23, likely via the intermediacy of epoxy ether 1.25 (Scheme 1.2).\textsuperscript{13} For the purposes of structural confirmation, oxidation product 1.23 was then treated with BF\textsubscript{3}•OEt\textsubscript{2} in methanol at reflux to yield adipate 1.24, suggesting that the overoxidation product was compound 1.23 (or an isomeric structure, \textit{vide infra}). While no ring contraction was observed under these conditions, oxidation of 1.22 with \textit{m}-CPBA under milder conditions permitted isolation of epoxy ether 1.25, a compound that was believed would allow for a more focused investigation of Barton’s proposal. When this compound was treated with BF\textsubscript{3}•OEt\textsubscript{2} in methanol at room temperature, a new compound was obtained, for which the spectroscopic and spectrometric data suggested a structure consistent with ring-contraction product 1.26. However, the published NMR data, specifically the methoxyl resonances at 3.29 and 3.41 ppm, perhaps suggest that this reaction gave not ring-contraction product 1.26, but rather the isomeric acetal product 1.27 from straightforward
solvolysis of the epoxy ether function. All other efforts to prepare the diepoxide substrate analogous to that proposed by Barton returned only products arising from overoxidation of the epoxy ether functionality (1.29, 1.31 and 1.32), thus a true test of Barton’s hypothesis could not be performed.

![Scheme 1.2](image-url)

**Scheme 1.2.** Matoba lab studies directed at Barton's proposed biosynthesis of the acutumine spirocycle.

### 1.3.2 Wipf

Almost 25 years after the report from Matoba and co-workers, the Wipf laboratory chose to revisit Barton’s biosynthetic proposal as an extension of their interest in spiroketal natural products. Like the Matoba lab, Wipf and co-workers studied model dienone 1.33 and found that its treatment with basic hydrogen peroxide gave
monoepoxide 1.28 (Scheme 1.3). However, when this material was oxidized with three equivalents of \textit{m}-CPBA at room temperature in the presence of dibasic phosphate, the only product isolated was a single diastereomer of epoxylactone 1.34, the structure of which was confirmed by X-ray crystallographic analysis. This product is similar to lactone acid 1.32 synthesized by the Matoba lab, and is also isomeric to their proposed overoxidation product 1.29 obtained from the same model system, though under more vigorous reaction conditions. This perhaps suggests that the Matoba lab had actually isolated similar lactone esters, rather than their proposed, and seemingly high-energy, lactone epoxy ethers 1.23, 1.29 and 1.31, an observation that Wipf and co-workers share in a footnote. Regardless, neither lab was able to provide any experimental support for Barton’s proposed spirocyclic ring contraction under a variety of experimental conditions. These results led Wipf and co-workers to the conclusion that

While an enzymatic pathway could easily take a different course, it appears that, chemically, \(\alpha\)-epoxy ethers of type [1.4] prefer alternative rearrangements to a migratory ring contraction. In fact, the recent isolation of acutudaurin [1.11], a possible precursor of acutumine-type natural products, supports a modified biosynthetic pathway.

In their modified biosynthetic proposal, Wipf and co-workers suggested that spirocyclic tyrosine dimer 1.35 could undergo an alternative oxidative rearrangement from that proposed by Barton to provide ring-contracted carboxylic acid 1.36, which could undergo decarboxylation to directly give vinylogous ester 1.37, a compound bearing the spirocycle found in acutumine and related alkaloids (Scheme 1.3).
1.4 Biochemical Studies on the Biosynthesis of Acutumine

In addition to the aforementioned experimental investigations on the feasibility of the oxidative rearrangement proposed by Barton and his co-workers, a number of plant feeding studies have led to a greater understanding of the early steps involved in the biosynthesis of acutumine. Support for Barton’s proposal that acutumine is derived biosynthetically from a benzylisoquinoline alkaloid was provided by separate $^{14}$C- and $^{13}$C-labeled tyrosine feeding experiments with *Menispermum dauricum* that revealed that acutumine derives biosynthetically from two molecules of tyrosine.$^{15}$ The biosynthetic formation of the benzylisoquinoline skeleton from two molecules of tyrosine has been well established.$^{16}$ With regard to Barton’s proposed oxidative fate of such a benzylisoquinoline alkaloid intermediate, it has been demonstrated that cytochrome P450 enzymes (CYP) are involved in both inter- and intramolecular oxidative phenolic couplings during the biosynthesis of related alkaloids,$^{17}$ so the involvement of related
processes in the biosynthesis of acutumine was evaluated. When *Menispermum dauricum* roots were treated with ketoconazole, a potent CYP inhibitor, and the resulting alkaloid content was analyzed, a buildup of tyramine, an early precursor of benzylisoquinoline alkaloids, was accompanied by a reduction in the amount of acutumine produced, thus providing circumstantial evidence that a CYP-mediated oxidative coupling is involved in the early steps of benzylisoquinoline biosynthesis, and that such a process is involved in the biosynthesis of acutumine.

A number of reports have also examined the later stages of the biosynthetic pathway in an attempt to gain some insight on the interrelationship between the members of the acutumine family. In 2001, *Menispermum dauricum* feeding experiments using medium containing radioactive $^{36}$Cl showed that four chlorinated alkaloids were produced: acutumine (1.1), acutumidine (1.2), dauricumine (1.3), and dauricumdine (1.4) (Scheme 1.4). These $^{36}$Cl-labeled alkaloids were then independently fed to *Menispermum dauricum* root cultures in chloride-deficient medium to study their biosynthesis, and it was found that the exogenous precursors were taken up very efficiently and metabolized in vivo to other chlorinated alkaloids as follows:

1. Acutumidine was converted to acutumine, and dauricumdine to dauricumine.
2. Conversion of acutumidine to dauricumdine was not observed, nor vice versa.
3. Dauricumine and acutumine were N-demethylated to dauricumdine and acutumidine, respectively.
4. Dauricumine was epimerized to acutumine, which was then N-demethylated to acutumidine; however, acutumine was not epimerized to dauricumine.
These findings, along with the higher levels of radioactivity that were detected in dauricumidine than those in acutumine and acutumidine, suggest that less epimerization occurs than N-demethylation and, further, that since all alkaloids are derived from dauricumine, that dauricumine is the first chlorine-containing alkaloid formed in the roots.

\[ \text{Epimerization} \]

1.3: dauricumine
1.4: dauricumidine

\[ \text{N-Demethylation} \quad \text{N-Methylation} \]

1.1: acutumine
1.2: acutumidine

\[ \text{Scheme 1.4. Biosynthetic interrelationship of chlorinated Menispermum alkaloids.} \]

1.5 Organohalogen and Biohalogenation

Of the over 2300 organochlorine natural products that have been discovered, approximately 300 have been isolated from terrestrial fungi and plants.\(^{18}\) While organochlorine natural products represent over half of the known halogenated natural products, approximately 2100 organobromines, 120 organoiodines and 30 organofluorines have also been isolated,\(^{18a}\) with the greater number of organochlorine and organobromine natural products coming presumably as a result of the greater abundance.
of chloride and bromide ions in the microenvironments of the producer organisms. Given the number and diversity of organohalogen compounds that have been isolated, both the biosynthetic processes of halogen incorporation and how these alterations in the physical and chemical properties are manifested in the biological function of these halogenated compounds have received much study.\textsuperscript{19}

### 1.5.1 Biohalogenation of Acutumine Alkaloids

Since its initial isolation from \textit{Sinomenium acutum}, acutumine has been isolated from various plant sources found around the world, often along with one or more of its relatives (for relatives, see Figure 1.2).\textsuperscript{20} As chlorine is generally a minor element in higher plants (2-20 mg/g dry matter)\textsuperscript{21} and terrestrial plants are relatively poor in halogenated metabolites,\textsuperscript{22} the presence of a chlorine atom in a terrestrial plant alkaloid was initially thought to be unusual. The possibility that this element had been introduced into the molecule during its isolation received consideration; however, numerous isolation studies have proven that the chlorine atom present in acutumine is not an artifact of its isolation, but is indeed introduced by a process of biosynthesis.\textsuperscript{3,12,15,23} As feeding studies proved that both acutumine and dechloroacutumine are derived from the same biosynthetic pathway,\textsuperscript{15b} it was suggested that dechloroacutumine is a biosynthetic precursor to acutumine. Hence, a study was performed in which \textit{Menispermum dauricum} roots were fed \textsuperscript{3}H-labeled dechloroacutumine and cultured in a chloride-enriched medium, and it was observed that acutumine was the only alkaloid metabolite formed.\textsuperscript{15b} While the roots took up 28\% of the initially administered \textsuperscript{3}H-labeled dechloroacutumine, only 5\% of this material was converted into acutumine. A few explanations for this low
conversion rate have been proposed. One suggests that dechloroacutumine may not be the immediate precursor to acutumine, and that other biosynthetic pathways could be involved. Based on a report that highly specific and unique compartments regulate and make possible the flow of precursors into natural products, it has also been suggested that the incomplete conversion of dechloroacutumine into acutumine might be due either to accumulation of dechloroacutumine in cell organelles, or to compartmentalization of the enzymes involved in the biosynthesis of acutumine. Given both the proven biosynthetic interrelationship of the acutumine alkaloids and the hypothesis that dauricumine is the first chlorinated alkaloid formed in the roots (vide supra), it was later proposed that dechlorodauricumine is the substrate for biochlorination; however, feeding studies with labeled dechlorodauricumine have not been performed to date. The exact precursor and specific mechanism of chlorination remain unknown.

1.5.2 Nucleophilic Biohalogenation via Halide Ion Addition

Since halogen uptake and accumulation by organisms occur predominantly in the form of halide ions, there is reason to believe that at least some organohalogens may arise by nucleophilic halogenation. This is the exclusive mode of reactivity involved in the formation of organofluorine natural products, and the structure and mechanism of a fluorinating enzyme isolated from the thienamycin-producing soil bacterium *Streptomyces cattleya* have recently been disclosed. This enzyme catalyzes the formation of 5'-fluoro-5'-deoxyadenosine (1.39, X = F) via nucleophilic displacement of L-methionine from S-adenosyl-L-methionine (SAM, 1.38) by fluoride ion, as well as the reverse reaction (Scheme 1.5). While this enzyme also has the capability to utilize
chloride ion to catalyze a reversible nucleophilic chlorination, the equilibrium of this reaction lies significantly in favor of the substrates.\textsuperscript{28} However, another SAM-dependent halogenase, SalL, was isolated from the marine bacterium \textit{Salinospora tropica} and has been found to more efficiently catalyze this nucleophilic chlorination to give 5′-chloro-5′-deoxyadenosine (\textbf{1.39}, \(X = \text{Cl}\)), which is a precursor to chloroethylmalonyl-CoA, itself an intermediate involved in the synthesis of salinosporamide A.\textsuperscript{29} Unlike the \textit{Streptomyces} halogenase, SalL will not accept fluoride ion, but will accept bromide and iodide ions. In a related process, SAM-dependent halogenases also catalyze the formation of methyl halides (\textbf{1.40}) via nucleophilic demethylation of S-adenosyl-L-methionine by halide ions.\textsuperscript{30} This process has been proposed to serve as a way in which organisms may eliminate halide ions found to be either toxic or in excess, and is largely responsible for the natural methyl halide release into the environment. Methyl chloride is the most abundant organohalogen in the atmosphere at approximately 550 ppt,\textsuperscript{31} with approximately 99.5\% coming from natural sources.\textsuperscript{32}

The recent isolation of the natural products sporolide\textsuperscript{33} and cyanosporaside,\textsuperscript{34} where the halogenated arene exists as either monohalogenated isomer but never the dihalogenated arene, has suggested that a new, nonenzymatic mechanism may also be responsible for halide incorporated into natural products. It has been proposed that the haloarenes present in these natural products arise from Bergman cyclization of a nine-membered enediyne precursor (\textbf{1.41}), and that halide incorporation occurs during the aromatization of the enediyne unit.\textsuperscript{34,35} Specifically, it has been proposed that halide incorporation occurs after the Bergman cyclization by addition to the \(p\)-benzyne intermediate (\textbf{1.42}) to give haloarene \textbf{1.44} after protonation of the resulting electron pair.
Experimental evidence has been disclosed that supports both the intermediacy of a nine-membered enediyne in the biosynthesis of these natural products, as well as the feasibility of the proposed mechanism for halide incorporation.

1.5.3 Biohalogenation via Electrophilic or Radical Halogenation

Despite these examples of nucleophilic biohalogenation, the position of halogenation, in most cases, is more suggestive of electrophilic or radical halogenation. Greater than 40 years of research on a variety of halogenating enzymes has led to the discovery that these enzymes require one of four co-factors for biohalogenation: heme iron, vanadium, reduced flavin adenine dinucleotide (FADH$_2$), or nonheme iron (Schemes 1.6 and 1.7). Depending on the requirement of their co-factor for either hydrogen peroxide or dioxygen ($O_2$), these halogenating enzymes have been termed haloperoxidases or $O_2$-dependent halogenases, respectively.

The heme- and vanadium-dependent enzymes are haloperoxidases that utilize hydrogen peroxide as a co-substrate to generate hypohalite intermediates as the electrophilic halogenating agents that halogenate electron-rich substrates (Scheme 1.6).
In the absence of a suitable organic substrate, these intermediates will react with a second equivalent of hydrogen peroxide to produce dioxygen (in the singlet excited state) and halide ion.\textsuperscript{42} While the overall reaction profiles of these haloperoxidases are identical (i.e., $X^- + H_2O_2 + R-H + H^+ \rightarrow R-X + 2H_2O$), there are subtle differences in how they catalyze halogenation. The heme co-factor functions as a redox catalyst, and is generally anchored in the enzyme active site by a cysteine thiolate, though a histidine imidazole may also serve as the anchoring ligand. The catalyst resting state is water-ligated Fe(III)-heme \textsuperscript{1.45} that undergoes oxidation by hydrogen peroxide to Fe(IV)-oxo $\pi$-cation radical species \textsuperscript{1.46} via a short-lived Fe(III)-peroxo complex (not shown). It has been proposed that a nearby glutamic acid residue assists this process by specific acid activation of the distal oxygen of the peroxo species.\textsuperscript{43} It is the Fe(IV)-oxo species that performs the two-electron oxidation of halide ion to afford the hypohalite; the Fe(III) catalyst is regenerated as a result of this process.

![Scheme 1.6. Biohalogenation via haloperoxidase enzyme co-factors.](image)

In contrast to the heme redox catalyst, the vanadium co-factor maintains a V(V) oxidation state throughout the catalytic cycle and functions as a Lewis acid catalyst. The trigonal bipyramidal metal center is coordinated to the enzyme by an axial histidine imidazole, and the electron density of the three equatorial oxygens is diffused through a
network of hydrogen bonds to nearby arginine, lysine, serine, and glycine residues. Catalysis is initiated by coordination of hydrogen peroxide to the vanadium center to give V(V)-peroxo species 1.49, which is activated for halide oxidation by a lysine ammonium ion that is hydrogen-bonded to the coordinated peroxide (not shown). For both classes of haloperoxidases, experimental evidence suggests that halogenation occurs in the enzyme active site, but it is currently unclear whether the hypohalite generated by these catalysts is metal-bound as shown, or simply trapped within the enzyme substrate pocket but not coordinated to the metal.45

Unlike the heme- and vanadium-dependent haloperoxidases, the flavin- and nonheme iron-dependent enzymes are O₂-dependent halogenases that utilize dioxygen as a co-substrate to generate halogenating agents (Scheme 1.7). These enzymes will not function with hydrogen peroxide. The halogenations of organic substrates by these O₂-dependent halogenases proceed by mechanistically distinct pathways, a key point that is reflected in the substrates that undergo halogenation by each enzyme subclass.

The flavin-dependent halogenase enzymes employ a bound redox co-factor, FAD, and occupy a mechanistic middle ground between the haloperoxidases and the nonheme iron-dependent halogenases. The halogenation process is initiated by reduction of FAD by NAD(P)H to the dioxygen-reactive FADH₂ (1.51), which undergoes single electron transfer to dioxygen to give flavin semiquinone and dioxygen radical-anion, followed by radical recombination and proton transfer to give FAD hydroperoxide 1.52. This intermediate then reacts with halide ion to form the hypohalite that carries out the halogenation of electron-rich substrates in the enzyme active site. Depending upon at which oxygen of the hydroperoxide the halide reacts, it is possible that either diffusible or
FAD-bound hypohalite could be formed; there is some evidence that diffusible hypohalite is the species responsible for halogenation.\textsuperscript{46}

By contrast, the nonheme iron-dependent halogenases are powerful oxidants that utilize dioxygen and α-ketoglutarate as co-substrates to effect the halogenation of relatively unreactive substrates via a radical mechanism. These halogenations typically occur at positions of low chemical reactivity, such as aliphatic carbons. Association of the organic substrate (RH) in the enzyme active site initiates catalysis by triggering a conformational change that allows for coordination of dioxygen to the Fe(II) center of compound 1.54. This results in oxidative decarboxylation of complex 1.55 to give Fe(IV)-oxo species 1.56 that abstracts a hydrogen atom from the organic substrate. The resulting carbon radical (R•) then abstracts the iron-bound halogen atom, thus forming
the halogenated organic substrate (RCl) and regenerating Fe(II) catalyst 1.54 after halide association and succinate/α-ketoglutarate exchange.

1.6 Biological Activity of Acutumine

While the primary motivation for a synthesis of acutumine issues from its unique structure, several reports have detailed that acutumine and its relatives possess interesting bioactivity. The dry rhizome of Menispermum dauricum (Rhizoma Menispermi) is part of traditional Chinese medicine and is also officially included in the Chinese Pharmacopoeia as an analgesic and antipyretic (fever reducing agent). In 2002, Cheng, Qin and co-workers reported that among related alkaloids, acutumine was found to selectively inhibit human T-cell growth with moderate potency (IC$_{50}$ = 13.2 µM).$^{47}$ In 2004, a patent$^{48}$ described the dose-dependent mnemocognition-facilitating properties of acutumine as evaluated in three separate experimental animal models: (1) the Morris water maze test in mice,$^{49}$ (2) a social recognition test in rats,$^{50}$ and (3) an object recognition test in rats.$^{51}$ The positive results seen in these models led the authors to suggest that acutumine and related compounds could be useful for the treatment of deficiencies of memory associated with cerebral ageing and neurodegenerative disease. These interesting properties, coupled with the limited supplies available for testing, perhaps provide further impetus for synthesis.

1.7 Other Synthetic Efforts Toward Acutumine

While the intriguing structure of acutumine has almost certainly attracted the attention of numerous research groups since its full disclosure in the late 1960s, at the
time of this writing, only five publications directed at a synthesis of acutumine have appeared in the literature, none of them prior to 2005. In addition to our own work, only the Castle group at Brigham Young University has published progress toward a synthesis of acutumine, and their efforts culminated in the first total synthesis of acutumine in 2009. Their published work will be reviewed briefly herein.

1.7.1 Castle

In 2005, the Castle group disclosed a synthesis of the tricyclic core of acutumine. Their approach focused on the six-membered ring found in acutumine and was based upon the functionalization and advancement of aromatic compounds in such a way as to sequentially annulate the remaining five-membered rings. Accordingly, their synthesis began with 3,4,5-trimethoxycinnamic acid (1.58), from which an eight-step sequence capped by a Kita-type, hypervalent-iodine-induced Wessely oxidation of a phenolic indane gave masked o-benzoquinone 1.59 (Scheme 1.8). The [1,2]-addition of allylmagnesium chloride to 1.59 was followed by an anionic oxy-Cope [3,3]-sigmatropic rearrangement to return ketone 1.61, thus installing the vicinal, all-carbon quaternary centers found in acutumine. After oxidative processing of the terminal olefin to the aldehyde, reductive amination with methylamine gave 1.62. A TMSOTf-mediated, Michael-type addition of the secondary amine onto the pendant (now activated) olefin formed the pyrrolidine and completed their synthesis of the tricyclic core (1.63).
Two years later, the Castle lab revealed progress toward the synthesis and introduction of the acutumine spirocycle.\textsuperscript{53b} Their design for adapting their synthesis of the acutumine core structure to a total synthesis of acutumine focused on the replacement of the geminal dimethyl surrogate for the spirocycle with an oxygenated cyclopentane early in their design. With that ring in place from the outset, they planned to rely on the key elements of their synthesis of the core structure, namely the phenolic oxidation/oxy-Cope/Michael-type addition sequence, to complete a total synthesis. Since the early introduction of an oxygenated cyclopentane would likely preclude the use of a Friedel-Crafts alkylation to close the fused cyclopentane as had been done during their synthesis of the core, the Castle lab proposed a modified disconnection to forge the same bond via a radical cyclization.

The execution of their plan began with the union of vinyl iodide 1.64\textsuperscript{58} and Weinreb amide 1.66\textsuperscript{59} to give enone 1.67 (Scheme 1.9). The metalation conditions developed by the Knochel lab\textsuperscript{60} proved uniquely successful for the generation and further
reactivity of the desired Grignard reagent 1.65 used in this transformation. The enone was then subjected to a diastereoselective Corey-Bakshi-Shibata (CBS) reduction\(^{61}\) to give a 6.7:1 mixture of diastereomers favoring the desired S alcohol. S\(_\text{N}2\) chlorination of the allylic alcohol in the presence of \(N\)-chlorosuccinimide and methyl sulfide\(^{62}\) then gave the desired radical cyclization precursor 1.69. When this substrate was exposed to triethylborane, air, and tri-\(n\)-butyltin hydride, the only product obtained was fused tricycle 1.70, the product of a 6-\(\text{endo-trig}\) radical cyclization, rather than the desired 5-\(\text{exo-trig}\) process. However, the allylic chloride did emerge unscathed, suggesting that a radical-based approach to the formation of the acutumine spirocycle would be compatible with substrates containing this functionality.

![Scheme 1.9](image)

Scheme 1.9. Castle lab’s undesired 6-\(\text{endo-trig}\) radical cyclization.

(a) \(i\)-PrMgCl-LiCl, 15-crown-5, THF, -20 °C; 1.66, -20 to 0 °C, 59%. (b) (R)-CBS, BH\(_3\)•THF, THF, 0 °C, 83%, 6.7:1 dr. (c) NCS, Me\(_2\)S, CH\(_2\)Cl\(_2\), 43%. (d) Bu\(_3\)SnH, air, Et\(_2\)B, toluene, -30 °C, 53%.

In order to overcome the steric hindrance associated with the desired 5-\(\text{exo-trig}\) radical cyclization, the Castle lab reasoned that alkene polarization induced by oxidation of the cyclopentene to a cyclopentenone might allow them to achieve the desired bond
formation via attack of the electron-rich aryl radical onto the electron-deficient β-carbon of the cyclopentenone. To test this hypothesis, their synthesis began with the union of hydroxyl-differentiated vinyl iodide 1.71\textsuperscript{63} and Weinreb amide 1.66\textsuperscript{59} to give enone 1.73 (Scheme 1.10). As before, the metalation conditions developed by the Knochel lab proved uniquely successful.\textsuperscript{60} After some optimization, the diastereoselective Corey-Bakshi-Shibata reduction of 1.73 gave a 9:1 mixture of diastereomers favoring the desired S alcohol. While the Corey-Kim chlorination\textsuperscript{62} of 1.74 gave low and variable yields in this setting, S\textsubscript{N}2 chlorination of the allylic alcohol was found to proceed well under the influence of methanesulfonyl chloride and triethylamine in the cold. Selective triethylsilyl ether deprotection with HF•pyridine was followed by oxidation to enone 1.75 with pyridinium chlorochromate. To briefly revisit the desired transformation, it was hypothesized by the Castle lab that an aryl radical generated from a substrate such as 1.75 would undergo a 5-exo-trig radical cyclization onto the pendant enone, with the regiochemistry of this cyclization being governed by the polarity of the enone acceptor. With regard to matters of stereochemistry, it was proposed that the aryl radical would be directed to the face of the alkene opposite the bulky \(t\)-butyldimethylsilyl ether. It is also possible that the desired facial selectivity would be reinforced to some measure by organization of the substrate such as to minimize allylic 1,3-strain.\textsuperscript{64} This transformation alone would be an achievement; however, the Castle lab recognized that this radical cyclization would leave in its wake an α-keto radical, which, if exposed to an organometallic reagent capable of undergoing homolytic cleavage, would generate a metal-bound enolate that could participate further in a polar reaction process (hence, a radical-polar crossover reaction).\textsuperscript{65} If a suitable oxidant were present in the mixture, this
enolate could then be hydroxylated to provide a spirocyclic α-hydroxy ketone that would be one oxidation state away from the acutumine spirocycle. While stereochemical control of the hydroxylation step would not be critical as the natural products acutumine and dauricumine are epimeric at this position, it was hypothesized that the aryl hydrogen would shield the re face of the enolate and that a single diastereomer would result. Thus, in a single step they envisioned installing a ring, a hydroxyl group, and two stereogenic centers, including one all-carbon quaternary center. In the event, the Castle lab was able to effect the desired 5-exo-trig radical cyclization when compound 1.75 was irradiated with a sunlamp in the presence of hexabutylditin. After extensive optimization of the organometallic promoter of the proposed radical-polar crossover step, as well as the hydroxylating reagent and other reaction parameters, the Castle lab was able to isolate the desired α-hydroxy ketone 1.76 as a single isomer in 59% yield on >100 mg scale. The only other reaction products detected were the α-iodo ketone and the corresponding reduced compound (not shown), both of which were isolated as single isomers arising from the desired 5-exo-trig radical cyclization onto the desired diastereoface of the enone.
In 2009, the Castle lab disclosed the natural evolution of their earlier studies toward a total synthesis of acutumine. Their synthesis began in much the same way as did their radical-polar crossover studies, with a six-step sequence to advance vinyl iodide 1.71 to spirocyclic α-hydroxy ketone 1.76 (Scheme 1.11). As the carbonyl functionality of the cyclopentanone would be incompatible with the downstream nucleophilic allylation that was to precede the proposed anionic oxy-Cope rearrangement, the ketone was reduced with L-Selectride® and protected as its tert-butyldimethylsilyl ether. With the carbonyl now masked, phenol 1.78 was unveiled after hydrogenolysis of the phenolic benzyl ether in the presence of palladium on carbon. As in the model synthesis of the acutumine core, this phenol was the substrate for a Kita-type, hypervalent iodine-induced Wessely oxidation to give, after benzyl protection of the secondary neopentyl alcohol, masked α-benzoquinone 1.79. This compound was the subject of study for the necessary ketone allylation. Inspection of molecular models led the Castle lab to hypothesize that
the \textit{re} face of the ketone was slightly more accessible than the \textit{si} face, and this was confirmed experimentally when ketone \textbf{1.79} was treated with allylmagnesium bromide in the cold and a 7:3 mixture of diastereomers was obtained, in favor of the desired diastereomer \textbf{1.82}. While this is impressive substrate-directed stereocontrol for what appears to be a highly symmetrical compound with somewhat remote stereogenic centers, the Castle lab desired higher levels of stereocontrol in this allylation reaction. In their earlier studies on the isohasubanan alkaloids,\textsuperscript{66} a variety of reagents directed at the enantioselective allylation of ketones similar to \textbf{1.79} revealed that Nakamura’s chiral allylzinc reagent \textbf{1.80} was uniquely effective at achieving high levels of stereocontrol.\textsuperscript{67} When applied to ketone \textbf{1.79}, allylation with (\textit{S},\textit{S})-\textbf{1.80} gave homoallylic alcohol \textbf{1.82} in 79\% yield and 93:7 dr, presumably via transition state structure \textbf{1.81}. Interestingly, mismatched allylation with (\textit{R},\textit{R})-\textbf{1.80} also proceeded well to give the epimeric homoallylic alcohol in 70\% yield and 87:13 dr. With the desired homoallylic alcohol \textbf{1.82} in hand, an anionic oxy-Cope [3,3]-sigmatropic rearrangement returned ketone \textbf{1.83} in excellent yield, thus installing the vicinal, all-carbon quaternary centers found in acutumine. Careful optimization then allowed for a one-pot procedure for the oxidative processing of the terminal olefin and the reductive amination of the resultant aldehyde with methylamine to give secondary amine \textbf{1.84} in 54\% yield. When the conditions developed on the model system for the TMSOTf-mediated Michael-type addition of the secondary amine onto the pendant olefin to form the pyrrolidine were applied to the more elaborate substrate \textbf{1.84}, only trace amounts of the desired tetracycle \textbf{1.85} could be isolated. This prompted the Castle lab to revisit this transformation and, given that amine \textbf{1.84} was precious and in short supply, the further optimization of this cyclization was
performed on the more readily available model compound 1.62. A survey of conditions revealed that a variety of Brønsted and Lewis acids could induce this cyclization, though the yields were consistently modest, reaching a maximum of only 41% yield for reactions conducted in the presence of either trifluoroacetic acid or boron trichloride. Thus, these reagents emerged from this study as the reagents of choice for this cyclization despite the low isolated yields. In the event, boron trichloride proved superior: in the presence of 1.5 equivalents of boron trichloride in dichloromethane at -40 °C, pure tetracycle 1.85 could be isolated in 45% yield. To complete the synthesis, the silyl ethers were cleaved with tetra-n-butylammonium fluoride, and the unstable resultant diol was immediately oxidized with tetra-n-propylammonium perruthenate and 4-methylmorpholine N-oxide. Hydrogenolysis of the benzyl ether in the presence of palladium on carbon proceeded without event to give penultimate intermediate 1.86. Several methods were investigated for the selective methylation of the spirocyclic 1,3-dione. Of these, methylation with diazomethane proceeded well to return a 75% yield of methylation products, though as a near 1:1 isomeric mixture. However, switching to titanium tetrachloride in methanol gave a more favorable 3.7:1 ratio of isomers to provide pure acutumine in 52% isolated yield, thus completing the first total synthesis of acutumine in 28 steps.
Scheme 1.11. The Castle lab's synthesis of acutamine.

(a) i-PrMgCl-LiCl, 15-crown-5, THF, -20 °C; 1.66, -20 to 0 °C, 62%. (b) (R)-CBS, BH₃·THF, THF, -10 °C, 89%, 9:1 dr. (c) MsCl, Et₃N, CH₂Cl₂, -25 to 0 °C, 65%. (d) HF-pyr, THF, 69%. (e) PCC, CH₂Cl₂, 86%. (f) (Bu₃Sn)₂, hv, Et₂Al, THF, 0 °C; 1.77, 0 °C to rt, 62%. (g) L-Selectride®, THF, 0 °C, 88%, 9:1 dr. (h) TBSCI, imid, CH₂Cl₂, 87%. (i) H₂, Pd/C, MeOH, 96%. (j) Phl(OAc)₃, KHCO₃, MeOH, -10 °C, 67%. (k) NaH, BnBr, TBAI, DMF, 60 °C, 88%. (l) (S,S)-1.80, THF, -78 °C, 79%, 93:7 dr. (m) KOt-Bu, 18-crown-6, THF, 0 °C, 92%. (n) O₂, pyr, Et₃N, EtOAc; H₂NCH₃, NaBH₄-CN, 4 Å MS, MeOH, 54%. (o) BCl₃, CH₂Cl₂, -40 °C, 45%. (p) TBAF, THF. (q) TPAP, NMO, acetone, 57%, 2 steps. (r) H₂, Pd/C, MeOH, 99%. (s) TiCl₄, MeOH, 52%. 1.1: (−)-acutamine.
1.8 References


10. (a) Dechloroacutumidine and 1-epidechloracutumine (dechlorodauricumine): Yu, B-W.; Chen, J-Y.; Wang, Y-P.; Cheng, K-F.; Li, X-Y.; Qin, G-W. Phytochemistry 2002, 61, 439-442. (b) Dechlorodauricumine: Sugimoto Y.; Matsui, M.; Takikawa, H.; Sasaki, M.; Kato, M. Phytochemistry 2005, 66, 2627-2631. The authors of this article point out that “Isolation of 1-epidechloracutumine, the same compound as [dechlorodauricumine], had been reported by Yu et al. (2002). However, the physicochemical parameters reported for the compound were inconsistent with those obtained for dechlorodauricumine.” This suggests that Yu et al. isolated and characterized something other than dechlorodauricumine.


This is due in large part to the prohibitively high redox potential of fluoride ion, making it incompatible with Nature’s oxidative machinery. However, other challenges exist that may account for the relatively small number of fluorinated natural products, most importantly the high energy penalty associated with the desolvation of fluoride ion that is required to make it sufficiently nucleophilic in an aqueous environment: Yang, Z.-Z.; Li, X. J. Phys. Chem. A 2005, 109, 3517-3520.


![Figure 1.3. The sporolide natural products.](image-url)

![Cyanosporaside A (X1=H, X2=Cl) Cyanosporaside B (X1=Cl, X2=H)](image)

Figure 1.4. The cyanosporaside natural products.


58. Vinyl iodide 1.64 was synthesized in eight steps from cis-3,5-diacetoxy-1-cyclopentene. See Ref 54.
59. Weinreb amide 1,66 was synthesized in nine steps from 2,3-dimethoxphenol. See Ref 54.


63. Vinyl iodide 1,71 was synthesized in nine steps from cis-3,5-diacetoxy-1-cyclopentene. See Ref 54.

64. For a comprehensive review of allylic 1,3-strain as a controlling factor in stereoselective transformations, see: Hoffmann, R. W. Chem. Rev. 1989, 89, 1841-1860.


Chapter 2

Efforts Toward a Synthesis of the Acutumine Architecture
2.1 Synthetic Strategy

At the outset of this project, we carefully considered a synthetic design based on the biosynthetic proposal put forth by Barton and co-workers (see Section 1.2). At the time, the synthetic work from the Matoba lab was the only published attempt to validate Barton’s proposal (see Section 1.3.1) and there was no published work toward a synthesis of acutumine. While we found Barton’s proposal highly intriguing, we felt that it would be challenging to realize such a design in the laboratory. Instead, we chose to focus on a strategy that would build the acutumine architecture from the core six-membered ring and leave the introduction of the oxygenated spirocycle until the later stages of the synthesis.

Given the anticipated challenges of installing the three contiguous, fully-substituted stereogenic centers, we identified the crowded C11-C12 bond as a strategic bond.\textsuperscript{1} We proposed that we could synthesize the [4.3.0] bicyclic framework with the nitrogen-bearing, fully-substituted stereogenic center at C13 already in place and decorated with an appropriately functionalized ethyl group that would allow us to append a moiety that would represent the acutumine spirocycle (Scheme 2.1). This would allow us to encourage a union about the C11-C12 bond by making the bond-forming event an intramolecular process, perhaps by a Michael-type addition of the spirocyclic precursor onto a pendant activated olefin. Since a β-elimination process initiated by an anion derived from a cyclopentanone spirocyclic precursor would almost certainly preclude having any useful functionality on the ethyl bridge that would later allow us to install the chlorine atom, we wondered if this undesired β-elimination process could be used to our advantage. If we could instead increase the oxidation state of the cyclopentane and utilize a cyclopentanedione-derived spirocyclic precursor it would allow us to unveil a
doubly-activated Michael acceptor in the presence of a suitable nucleophile, and perhaps the equilibrium of the nucleophilic addition/β-elimination process could be shifted in our favor to trigger a tandem Michael-type addition sequence that could be used to forge the C11-C12 bond and introduce functionality that would later become the secondary chloride.

![Scheme 2.1. A synthetic strategy based on tandem Michael-type additions.](image)

### 2.2 Phenol Oxidation Approach

One of our early ideas to address the acutumine architecture involved a phenol oxidation of benzazepine 2.3 to transiently generate an intermediate that might allow us to study the tandem Michael-type addition sequence (Scheme 2.2). Our laboratory’s synthesis\(^2\) of FR901483 supported the idea that an electron-deficient intermediate arising from a phenol oxidation of 2.3 could engage the unshared electrons of the proximal nitrogen atom and lead to the formation of a new azacycle. In the context of the putative intermediate 2.4, this process could conceivably produce azetidinium ion 2.5, which would be expected to suffer a facile β-elimination due to the acidity of the doubly-activated methine and the ring strain of the azetidine. Finally, a conjugate addition to the highly electron-deficient alkene of 2.6 by an appropriate nucleophile would trigger an intramolecular Michael addition to afford the complex architecture of acutumine. With
some effort, we were eventually able to synthesize the synthetic precursor to 2.3, but this route was abandoned due to the need to focus on a related route that, at the time, was showing more promise. That route will be the subject of the rest of this chapter.

![Scheme 2.2. An early idea to address the complex architecture of acutumine.]

2.3 The Trimethoxybenzaldehyde Route

An approach to address the acutumine architecture complimentary to that shown above focused on the advancement of a simple aromatic building block, in this case 2,3,4-trimethoxybenzaldehyde, to a quinone imine, which would then be elaborated to include a model spirocycle that would allow us to study the tandem Michael-type addition strategy (Scheme 2.3).
While quinone imine 2.9 was readily accessible from 2,3,4-trimethoxybenzaldehyde, fruitful additions to the imine function of this and related structures were thwarted, in most cases, by the presence of the dimethoxy olefin, which either led to nonselective addition products or caused sensitivity to reagents used in subsequent steps. As a result, we proposed that masking this functionality in the form of an epoxide would not only avoid these issues, but also may allow us the opportunity to design an asymmetric synthesis from a bulk chemical such as 1,4-benzoquinone (Scheme 2.4).
2.4 The Benzoquinone Route

One advantage of our 2,3,4-trimethoxybenzaldehyde-derived effort\(^3\) was that it allowed us to quickly elaborate the aldehyde function into the necessary aminoethane group while maintaining the core six-membered ring in a reduced state, thus obviating the need to protect or otherwise modify a quinone in order to discourage undesired reactivity with any of its six electrophilic carbons. However, if our new design was to begin with 1,4-benzoquinone, then we believed it would be necessary to find a way to protect one half of the molecule such that we could selectively introduce both the epoxide and the aminoethane group. When the system allows it, a cyclopentadiene Diels-Alder [4+2] cycloadduct functions as an excellent olefin protecting group,\(^4\) and this is often the protecting group of choice when working the quinone arena. As such, our efforts began
with the smooth union of freshly cracked and redistilled cyclopentadiene with 1,4-benzoquinone in methanol (Scheme 2.5). This Diels-Alder cycloadduct not only selectively masks the reactivity of one quinone olefin, but also serves to shield an entire face of the once planar molecule such that only the exo epoxide is produced when the cycloadduct is epoxidized with hydrogen peroxide under basic conditions at ice bath temperature, thus providing meso epoxydione 2.17. This efficient two-step sequence did not require chromatography and could easily be performed on large scale.

![Scheme 2.5. The advancement of 1,4-benzoquinone.](image)

Though our initial studies on the reactivity of dione 2.17 focused on straightforward monoreductions to provide alcohol 2.18 in racemic form, the possibility that we might be able to employ a Noyori transfer hydrogenation to desymmetrize meso epoxydione 2.19 was encouraged by the success of a related reduction as disclosed by scientists at Hoffman-La Roche. In the event, the S alcohol was produced in 90% yield and approximately 73% ee when (1S,2S)-pseudoephedrine (2.21) was employed as the
chiral ligand for the ruthenium catalyst (Scheme 2.5). This result was deemed to be acceptable, and we moved forward with the idea that this reduction would be revisited if our downstream efforts were successful. While the hindered secondary alcohol could be masked with a variety of protecting groups, we initially focused on the TES ether, but we quickly found it to be too labile and so the TBS ether was used to study further reactions. Regardless of the protecting group on the alcohol, we encountered our first challenge on this route when attempting to introduce the aminoethane group at the α-position of ketone 2.19. Encouraged by the success of the aza-Wittig reaction used to close the cyclic imine in our 2,3,4-trimethoxybenzaldehyde-derived effort,³ we focused on the installation of an ethane moiety that was terminated by a primary amine or an azide so that we could again exploit the aza-Wittig reaction. Unfortunately, all reactions of ketone 2.19 with 1,2-disubstituted ethane electrophiles under a variety of conditions returned only unchanged ketone 2.19 (Scheme 2.5).

2.4.1 A Michael Addition/Curtius Sequence to Install the Aminoethane Group

After struggling to introduce an appropriately functionalized ethane group, we decided to evaluate the reactivity of the activated bridgehead methine of 2.19 with more potent electrophiles, such as formaldehyde and allyl bromide. In both cases, the desired addition product was readily produced under basic conditions similar to those employed in reactions with the 1,2-disubstituted ethane electrophiles, thus validating the nucleophilicity of the enolate derived from ketone 2.19. This suggested that the difficulties we had encountered were related to our choice of electrophile. We attempted to make use of the allylation product to access the aminoethane group by an oxidative
olefin cleavage/reductive amination strategy, but we were undermined by the reactivity of the strained cyclopentene olefin. Removal of this problematic functionality by a retro Diels-Alder reaction did not lead to any improvement. As such, we needed to find another potent electrophile with functionality that could be viewed as a latent amine. We hypothesized that an acrylate would serve nicely to meet our needs as the initial union with ketone 2.19 via a Michael addition could be followed by ester saponification and a Curtius rearrangement to install the desired primary amine.

During our studies on the Michael addition of ketone 2.19 to methyl acrylate, we found that the desired transformation could be cleanly effected by employing a slight excess of sodium hydride in a nonpolar solvent such as benzene or toluene at room temperature (Scheme 2.6). On small scale, reproducible reactivity was seen when the hydroxyl of compound 2.19 was protected as a silyl ether; however, on scale-up we found that cleaner, higher yielding, and more reproducible reactivity could be achieved when the hydroxyl was instead protected in the form of an ethoxyethyl ether. After the Michael addition, we could effect a high-yielding protecting group exchange to the TBS ether, which we later found to be more compatible when used to explore further reactions on small scale. Following straightforward ester saponification with lithium hydroxide in aqueous THF, we carried out the Curtius rearrangement in the presence of DPPA,

and then hydrolyzed the intermediate isocyanate to give primary amine 2.24. While we found that this sequence could nicely install the aminoethane group, our efforts to form the cyclic imine by condensation with the pendant ketone were generally unsuccessful.
2.4.2 Exploiting the Reactivity of Triphenylarsine Oxide

Despite the excellent reactivity we had seen up to this point, the failure of the
cyclocondensation under classical conditions left us at a crossroads. While we could
have transformed primary amine 2.24 into the terminal azide and again used an aza-
Wittig reaction to close the cyclic imine as we had done in our 2,3,4-
trimethoxybenzaldehyde-derived effort,3 we wondered if we could avoid this multi-step
imine formation and exploit the utility of the Curtius rearrangement in a different way.
After surveying the literature, we found an interesting set of papers from Paul Frøyen that
explored the reactivity of isocyanates and arsine compounds.9 Based on an earlier
report10 that demonstrated the synthesis of carbodiimides from isocyanates in the
presence of triphenylarsine oxide (Figure 2.1, Equation 1), presumably through the
intermediacy of a triphenylarsine imine, Frøyen began to study the synthesis and
reactivity of arsine imines. He quickly discovered that the stoichiometric reaction of triphenylarsine oxide with electron-poor isocyanates\textsuperscript{9a} or \(N\)-sulfinyl compounds\textsuperscript{9b} was able to provide the corresponding triphenylarsine imines (Figure 2.1, Equation 2). These electronically-stabilized arsine imines were found to be stable on exposure to the atmosphere and to water, and, as a consequence, they could generally be isolated in high yield. Frøyen was able to extend this method to aryl and vinyl isocyanates,\textsuperscript{9d} where he found that the conversion to carbodiimides could be arrested at the stage of the intermediate arsine imine, provided that the temperature of the reaction was maintained at room temperature or below (Figure 2.1, Equation 3). The further conversion to the carbodiimide could be achieved by brief heating of the reaction mixture to 60-80 °C (Figure 2.1, Equation 4). Interestingly, this controlled reactivity was limited to the aforementioned classes of isocyanate; in no instance were arsine imines obtained from alkyl isocyanates. Beyond their reactivity with isocyanates to provide carbodiimides, arsine imines were also found to react smoothly with aldehydes and ketones to form imines (Figure 2.1, Equation 5). This method was extended to a procedure in which an equimolar mixture of carbonyl compound and isocyanate was stirred at room temperature in the presence of a catalytic amount of triphenylarsine oxide to directly provide the desired imine in high yield.\textsuperscript{9d} This is a powerful method that proved to be successful even with challenging substrates, such as quinones and 1,2-dicarbonyls. In both of these cases, either the mono- or diimines could be obtained by simply employing the proper amount of isocyanate.
While Frøyen was not able to isolate arsine imines from alkyl isocyanates in the course of his work, we wondered if we could exploit this reactivity in our intramolecular setting to directly convert keto acid 2.23 into the desired cyclic imine through the intermediacy of alkyl isocyanate 2.35, which would be generated by the Curtius rearrangement. We began with a stepwise approach to study this transformation. We first treated acid 2.23 with DPPA in hot benzene to effect the Curtius rearrangement in the absence of any trapping reagent so that we could isolate isocyanate 2.35 and study its pure reactivity (Scheme 2.7). Upon treatment of isocyanate 2.35 with a substoichiometric amount of triphenylarsine oxide in hot benzene, we were delighted to isolate the desired cyclic imine in 32% yield over the two-step sequence.
With the desired reactivity validated in our stepwise approach, we began to study the one-pot advancement of keto acid \textbf{2.23} to cyclic imine \textbf{2.25}. Given that the solvent and temperature used in both steps were identical, we hoped that we could simply add the triphenylarsine oxide along with the reagents required to effect the Curtius rearrangement and isolate the imine after a period of heating. This turned out to be possible, but our initial studies only returned the imine in low yield, similar to the stepwise approach. After some experimentation, we discovered that the inclusion of powdered 4 Å molecular sieves was critical to the success of this transformation. This additive presumably functions to preserve the integrity of the isocyanate and arsine imine, both of which are water-sensitive intermediates. Under optimized conditions, we found that when a mixture of acid \textbf{2.23}, 10 mol % triphenylarsine oxide, and powdered 4 Å molecular sieves in dry benzene at room temperature is treated with freshly distilled triethylamine and DPPA, and then warmed to 70 °C for slightly more than one hour, the desired cyclic imine \textbf{2.25} could be isolated in 69-91% yield, with the yield being inversely scale-dependent for reactions run with between 1 g and 10 g of keto acid \textbf{2.23} (Scheme 2.8). Mechanistically, this reaction likely proceeds by an initial DPPA-mediated Curtius rearrangement to provide the intermediate alkyl isocyanate \textbf{2.35}, which then undergoes a formal [2+2] cycloaddition with triphenylarsine oxide to provide cyclic arsine carbamate \textbf{2.36}. This intermediate then suffers concerted elimination of carbon dioxide to generate...
arsine imine 2.37, which undergoes an aza-Wittig reaction with the pendant ketone to provide the desired cyclic imine and regenerate the triphenylarsine oxide to complete the catalytic cycle.

Under the optimized conditions, we also evaluated the competency of phosphine oxides in this reaction, and we found that the yields of imine 2.25 were much lower than what could be achieved in the presence of triphenylarsine oxide due to the undesired formation of carbodiimide and urea dimerization products, as well as other unidentified reaction products. The fact that triphenylarsine oxide is uniquely successful in this reaction can be attributed to a number of factors, many of which are a direct result of the larger atomic radius of arsenic relative to phosphorus. The larger 4d orbitals of arsenic result in poorer $\pi$-$d\pi$ orbital overlap with the period 2 elements and lead to arsenic being less capable of stabilizing adjacent negative charge in the form of a “double bond”, thus there exists a greater contribution of the more reactive dipolar canonical form versus the
covalent canonical form.\textsuperscript{11} This is manifested in the greater dipole moment\textsuperscript{12} of triphenylarsine oxide compared to that of triphenylphosphine oxide, as well as the longer\textsuperscript{13} and weaker\textsuperscript{14} arsine oxide bond. Taken together, these data support the greater observed reactivity of triphenylarsine oxide with isocyanates compared to that of triphenylphosphine oxide. These trends in physical properties also hold true for the corresponding metalloid imine species, and experimental evidence clearly demonstrates that triphenylarsine phenylimine is far more reactive toward carbonyl compounds than is triphenylphosphine phenylimine.\textsuperscript{9c,15} As many studies show that the first step of the Wittig, which is slow and reversible, is the rate-determining step,\textsuperscript{16} the heightened reactivity of arsine imines is likely due to their more dipolar nature, as well as their greater bond lengths, which would lead to less steric hindrance in the formation of the four-membered ring transition state. While the arsine compounds show greater reactivity along the desired reaction pathway shown in Scheme 2.8 than do their phosphorus analogs, it has been shown experimentally that triphenylphosphine phenylimine is far more reactive toward phenyl isocyanate than is triphenylarsine phenylimine,\textsuperscript{9c} and it was also found that triphenylphosphine phenylimine reacts $10^6$-$10^7$ times faster with phenyl isocyanate than does triphenylphosphine oxide.\textsuperscript{17} Despite the fact that arsine imines are generally far better nucleophiles than their phosphine counterparts, the reversible formation of the four-membered intermediate in their reactions with isocyanates may be less important than the decomposition of this intermediate to the corresponding oxide and the Schiff base. Here, the heightened reactivity of phosphorus relative to arsenic presumably comes as a result of the greater thermodynamic driving force due to the formation of the much stronger phosphine oxide bond. When all of this information is
viewed in the context of the reaction process in question, the poor performance of catalytic amounts of phosphine oxides in the cyclic imine formation is presumably due to the higher phosphine oxide bond strength, which discourages its reaction with isocyanate and leads to a buildup of this intermediate in the presence of the small amount of the phosphine imine that is generated and persists due to its lower reactivity toward the ketone carbonyl. This results in the formation of greater amounts of carbodiimide and urea dimerization products, thus lowering the yield of the desired cyclic imine. The unique reactivity of arsenic relative phosphorous has also been exploited in the traditional Wittig olefin synthesis, as well as in transition metal-mediated processes such as the Stille reaction.

2.4.3 Elaboration of the Cyclic Imine

With an efficient synthesis of imine 2.25 in place, we began to explore ways to introduce functionality that we hoped would eventually allow us to study the tandem Michael-type addition sequence. While the cyclopentadiene Diels-Alder cycloadduct had functioned admirably to this point as an olefin protecting group, its presence was now preventing nucleophilic additions to the necessary si face of the imine, and it was time to dispense with the cyclopentadiene moiety. The retro Diels-Alder reaction was found to proceed well in either diphenyl ether or triglyme at 200 °C to give α,β-unsaturated imine 2.38 (Scheme 2.9). Incidentally, while the retro Diels-Alder reaction could also be performed at the stage of ester 2.22 or acid 2.23, the subsequent triphenylarsine oxide-catalyzed imine formation was only found to be successful in the context of acid 2.23 due to complications encountered during ester saponification in the presence of the α,β-
unsaturated imine. With α,β-unsaturated imine 2.38 in hand, the stage was set for an examination of one of the key questions in the synthesis: Will the addition of nucleophiles such as allyl Grignard have any selectivity for 1,2-addition to the imine in the presence of three other electrophilic sites and, if so, would there be any measure of facial selectivity? In the event, treatment of imine 2.38 with allylmagnesium chloride at low temperature resulted in a diastereoselective 1,2-addition to give allylated pyrrolidine 2.39, which was directly treated with Boc anhydride and triethylamine in dichloromethane to provide N-Boc amine 2.40 in 55% yield over two steps. This sequence was followed by the straightforward stepwise oxidative cleavage of the terminal olefin to aldehyde 2.41, an intermediate that we believed would be critical to our further studies.

![Scheme 2.9. Elaboration of the cyclic imine.](image)

Given the perceived importance of aldehyde 2.41, we briefly attempted to increase the yield of the allylation/protection sequence before moving forward with the
synthesis (Scheme 2.10). While the allylation was found to proceed equally well regardless of changes in the reaction conditions, when we attempted a Boc protection with Boc anhydride and DMAP in acetonitrile, we believed that we had been able to raise the two-step yield of **2.40** from 55% to 79%. When this material was carried forward and treated under the same conditions as used previously for the oxidative cleavage of the terminal olefin, the product aldehyde was isolated in high yield. This material turned out to be highly crystalline, and we were able to obtain material suitable for single crystal X-ray analysis.\textsuperscript{20} To our delight, the crystal structure confirmed that the allyl group had been delivered to the face of the imine opposite the epoxide, thus the stereogenic center formed during the allylation event was of the desired configuration relative to the hydroxyl-bearing stereogenic center that had been set by the Noyori transfer hydrogenation. However, the crystal structure also indicated that we did not have in place the desired Boc protecting group, but rather a tert-butyl mixed carbonic-carbamic anhydride.\textsuperscript{21} These mixed anhydrides are usually either fleeting intermediates during the course of the Boc protection reaction or unstable if isolated, though they may persist if the parent amine is sufficiently hindered, as may be the case with our unusually stable compound. To the best of our knowledge at the time, this was the first crystal structure of such a mixed carbonic-carbamic anhydride. In the end, no significant improvements could be made to the four-step sequence leading up to aldehyde **2.41**, so we carried on with the route as outlined in Scheme 2.9.
2.4.4 Studies Toward the Acutumine Architecture

With aldehyde 2.41 in hand, we began to study conditions to transform the TBS protected secondary allylic alcohol into the desired enone. We found that treatment of aldehyde 2.41 with either TBAF in cold THF or p-TsOH•H₂O in wet DMSO at room temperature cleanly removed the silyl ether, and that oxidation of the secondary alcohol could be effected with Dess-Martin periodinane²² or under Ley’s conditions²³ to provide enone 2.44, though in modest yield (unoptimized). From here, we immediately began to investigate unions between enone 2.44 and 1,3-cyclopentanedione, which was to serve as our model spirocycle (Scheme 2.11). We screened numerous conditions in the presence of a variety of nucleophiles hoping, at the very least, to observe products arising from
successful trapping of the Knovenagel condensation product. In each case, a number of products were produced, though none could be identified as the desired nucleophile-trapped product of the Knovenagel condensation or as the product of further cyclization.

It has been pointed out in the literature that Knovenagel condensations with 1,3-cyclopentanedione can be somewhat problematic due to the rapid trapping of the doubly-activated olefin with another molecule of 1,3-cyclopentanedione to provide the dimerization product.\textsuperscript{24} As a result, we wondered if we could avoid the condensation event and again utilize cyclopentadiene in our synthesis to install a fulvene, which would treat cyclopentadiene as our model spirocycle and already have in place an activated olefin. Nucleophilic additions to the fulvene would produce the stabilized aromatic cyclopentadiene anion, which we hoped we could then coerce to cyclize onto the pendant enone under some conditions. While we were able to synthesize fulvene \textbf{2.46}, albeit by a low yielding sequence, its further reactivity proved to be just as problematic as with 1,3-cyclopentanedione.\textsuperscript{25} Recognizing that the fulvene idea was somewhat risky, we retreated to the idea that we would study the desired reactivity on simple bisenone \textbf{2.48}. Unfortunately, this brought no improvement; while we could observe the disappearance of the acyclic enone olefin after treatment with good nucleophiles such as thiophenol, products arising from cyclization onto the pendant cyclohexenone could not be isolated.
Given the complexity of the desired transformation, we decided to study the reactivity of both the aldehyde and the enone in isolation to obtain more information on how we might optimize the individual processes before attempting to merge the reactivity. While our first few experiments with aldehyde 2.41 revealed complex reaction profiles similar to the more advanced aldehyde-enone system, our studies on the reactivity of enone 2.51 quickly revealed that under many basic conditions similar to those being used to study the tandem Michael-type addition sequence, rapid and clean deconjugation of the olefin into the pyrrolidine was observed to give compound 2.52 (Scheme 2.12). The facility of this deconjugation event is perhaps a result of the relief of strain in the six-membered ring when one of the five non-sp³ carbons becomes sp³-hybridized. This outcome suggested that our tandem Michael-type addition strategy
would need to be studied in a different context. We hypothesized that opening of the epoxide, something that we were obliged to do anyway to address the dimethoxy olefin, might help relieve ring strain and prevent this unproductive olefin deconjugation.\textsuperscript{26} We studied a variety of ways to transform the epoxide at the stage of both the allylic alcohol and the enone, and we found that we could effect a high pressure carboxylation and a Wharton deoxygenation to transform the epoxide into cyclic carbonate 2.53 and diene 2.54, respectively; however, productive advancement of these compounds proved extremely difficult. Other studies were performed in an attempt to rescue this route, including transition metal-catalyzed transformations of the secondary allylic alcohol; however, after a long struggle without being able to effect any C11-C12 bond formation, it was decided that a change in strategy would be the most beneficial way to move this project forward. This new strategy will be described in the following chapter.

![Scheme 2.12. Studies to address the enone and epoxide.](image-url)
2.5 References


3. Scheme 2.13 details our route to compound 2.9 from 2,3,4-trimethoxybenzaldehyde. Much of the experimentation was performed on compound 2.60. We also developed a short route (not shown) that began with dimethyl squarate and relied on a Danheiser-type benzannulation to directly provide a quinone relative of compound 2.9.

### Scheme 2.13

- **2.8** → **2.55** via AlCl₃, benzene (83%)
- **2.55** → **2.56** via CH₃NO₂, NH₄OAc, AcOH, 110 °C (74%)
- **2.56** → **2.57** via LAH, THF, 55 °C (82%)
- **2.57** → **2.58** via DMSO-MeCN, DMF (57%)
- **2.58** → **2.59** via salcomine, O₂ (57%)
- **2.59** → **2.60** via PPh₃, THF (87%)
- **2.60** → **2.9** via Ph₂O, 200 °C (40%)


58
7. The % ee was determined by comparing the optical rotation of TBS ether 2.19 to the value reported in the literature. TBS ether 2.19 was found to be a colorless solid, mp 65–67 °C, [α]D25 +41.1° (c 1.19, CHCl3). Lit. mp 66–67 °C, [α]D28 +56.22° (c 1.19, CHCl3). See: Kamikubo, T.; Ogasawara, K. Tetrahedron Lett. 1995, 36, 1685-1688.


12. Dipole moments for triphenylarsine oxide (5.50 D) and triphenylphosphine oxide (4.31 D) were reported in ref 9b.


59
20. Between the departure of our crystallographer, Douglas M. Ho, Ph.D., and computer turnover in our group, the original coordinates for structure 2.43 have been lost. All that remains is the image file, which is shown in Scheme 2.10 and in the Experimental Section.


23. See Chapter 1, ref 68.


25. Other cyclopentadiene-related studies can be found in: Khov, N. Studies toward acutumine’s core architecture. B.A. Thesis, Princeton University, April 2007.

26. The reversibility of this olefin isomerization was not studied in great detail, so the possibility exists that isomerization under some conditions could have allowed us to achieve the desired bond formation.
Chapter 3

A Synthesis of the Acutumine Core Structure
3.1 A New Synthesis Plan

While our aforementioned approach toward a synthesis of acutumine advanced the simple building block 1,4-benzoquinone in a highly stereocontrolled manner to structures such as compound 2.53, which contained the heterocycle and what we believed would be sufficient functionality to access the [4.3.3.0] tricyclic core of acutumine, all of our efforts were thwarted by our inability to forge the key C11-C12 bond and we were forced to reevaluate our synthetic strategy (Scheme 3.1). Rather than utilize the oxygenated six-membered ring as our foundation, we reasoned that we could rapidly and effectively address the acutumine architecture from the vantage of the heterocycle and delay the formation of the six-membered ring until after the formation of the C11-C12 bond. In addition, we sought a design that would allow us to address both the oxygenated spirocycle and the chlorine-bearing stereogenic center such that we could further elaborate our synthesis of the acutumine architecture into a total synthesis of acutumine and several of its relatives from a common intermediate. Such a design would require significant functionalization of a pyrrolidine ring structure, namely the stereocontrolled generation of suitably functionalized vicinal, fully-substituted carbon atoms, a challenge that we believed could be aptly addressed from a 3-ketoproline building block (3.1) through a series of reactions rooted in the strong foundation provided by classical carbonyl chemistry. Along with this change in core strategy, we also reevaluated how we could address the spirocycle. Specifically, we hypothesized that the entire northern portion of the acutumine architecture could be accessed from a simple β-keto ester, thus simplifying our synthetic target to a structure such as compound 3.2. The rest of this chapter will be devoted to our efforts toward this substructural goal.
### 3.2 Ketoproline Synthesis

As the heterocycle would serve as the key building block in our new design, we needed a way to procure large amounts of an appropriately functionalized 3-ketoproline (i.e. – simple ester, good nitrogen protecting group) to make our synthetic plan viable. A survey of the literature revealed that many 3-ketoproline derivatives are known and, while they can be synthesized via Dieckmann condensations of glycine/acrylate hetero-Michael adducts, the yields are often low due to the poor selectivity in the Dieckmann condensation and the tedious separation of the isomeric byproduct. However, in the mid-1980s, Rapoport and co-workers carried out an excellent study of intramolecular Rh$_2$(OAc)$_4$-catalyzed N-H, O-H, and S-H insertions of α-diazo β-keto esters that included
an efficient synthesis of 3-ketoprolines that does not suffer from the drawbacks of the Dieckmann approach (Scheme 3.2). The Rapoport synthesis began with a two-pot Masamune-Claisen condensation of the magnesium dianion of hydrogen methyl malonate with the N-acyl imidazole generated from N-Cbz-β-alanine and CDI, followed by a diazo transfer reaction with (p-carboxyphenyl)sulfonyl azide to give the requisite α-diazo β-keto ester 3.5, which was decomposed with Rh2(OAc)4 in hot benzene under dilute conditions to effect the N-H insertion and provide N-Cbz-3-ketoproline 3.6.

With the Rapoport synthesis, it seemed we would be able to quickly synthesize the desired ketoproline; however, anticipating the need for large amounts of material, we sought to improve upon this already efficient series of transformations. Specifically, we had a goal to improve each step of the process to meet our needs:

1. Design a one-pot malonate acylation.
2. Find a more cost-effective alternative to (p-carboxyphenyl)sulfonyl azide.
3. Avoid the use of large volumes of benzene for the N-H insertion.
With these goals in mind, we set out to first make the malonate acylation more operationally straightforward such that it would be more amenable to scale up. While our initial efforts were met with limited success, the solution came in a paper from the Smith lab at Williams College in which they were able to convert $N$-acyl thiazolidinethiones to $\beta$-keto esters by treatment with imidazole, magnesium chloride and methyl potassium malonate in a reaction that was presumed to proceed through the intermediacy of an $N$-acyl imidazole. This reaction is formally an extension and one-pot variant of the mild acylation of methyl magnesium malonate with $N$-acyl imidazoles pioneered by Masamune and co-workers in 1979 and used by the Rapoport lab in their studies. When applied to our situation, treatment of the $N$-acyl imidazole generated from $N$-Boc-$\beta$-alanine and $N,N'$-carbonyldiimidazole in THF with magnesium chloride and methyl potassium malonate provided the desired $\beta$-keto ester in quantitative yield after only an aqueous workup (Scheme 3.3). Despite being a heterogeneous reaction, this one-pot "dump and stir" method proved to be extremely robust, allowing repeated runs on a 128.5 mmol scale without incident. This was the largest scale attempted in a single run, as we believed it would allow us to use reasonably-sized glassware (<2 L) throughout the process. To make the diazo transfer reaction more cost-effective, we made the simple change to ($m$-carboxyphenyl)sulfonyl azide, which was 30% of the cost of ($p$-carboxyphenyl)sulfonyl azide at the time of our work. With the ($m$-carboxyphenyl)sulfonyl azide, the diazo transfer reaction proceeded well to give the desired $\alpha$-diazo $\beta$-keto ester 3.9 in quantitative yield after a mild aqueous workup to remove both the sulfonamide byproduct and the slight excess of sulfonyl azide. It is often the case with other reagents used for this transformation that, even after careful
trituration or a strongly basic aqueous workup, traces of the sulfonamide byproduct or excess sulfonyl azide can remain and necessitate purification by column chromatography, so we were pleased that a simple aqueous workup was sufficient to provide analytically pure α-diazo β-keto ester 3.9. With the first two steps satisfactorily modified, we turned our attention to the Rh$_2$(OAc)$_4$-catalyzed N-H insertion reaction. We surveyed various conditions in an attempt to improve this reaction and found that simply changing the solvent from benzene to toluene and increasing the reaction concentration from 0.05 M to 0.1 M provided the most satisfactory results. Even when the modified three-step sequence was run on our maximal scale of 128.5 mmol, the desired N-Boc-3-ketoproline methyl ester (3.10) was obtained in 93% overall yield with the only nonaqueous purification method coming in the form of a filtration through Celite® to remove the Rh$_2$(OAc)$_4$ from the final product.

Scheme 3.3. Streamlined ketoproline synthesis.
3.3 Enone Studies

With multi-gram quantities of the desired \(N\)-Boc-3-ketoproline methyl ester building block in hand, we set out to evaluate if we could install a suitable 1,3-dicarbonyl system at the 2-position of the pyrrolidine and an acyclic enone at the 3-position, then coerce them to join via a Michael addition to forge the C11-C12 bond that had eluded us during our quinone-based efforts. Since we assumed we would be able to introduce almost any 1,3-dicarbonyl moiety at the 2-position, our early efforts focused on the introduction of the enone. Using \(N\)-Boc-2-allyl-3-ketoproline methyl ester (3.11)\(^8\) as a model substrate, we studied a variety of standard intermolecular condensations in an attempt to install a Michael acceptor at the 3-position; however, the sterically hindered ketone often failed to react and, when it did react, ring opening by a retro-Dieckmann process was frequently observed. To prove to ourselves that this poor reactivity was only due to the intermolecular nature of this process and was not a result of some unique deficiency in the reactivity of this ketone, we decided to evaluate the reactivity in the context of an intramolecular Horner-Wadsworth-Emmons reaction.\(^9\) The substrate necessary to study this transformation was quickly synthesized from 2-allyl-3-ketoproline 3.11 by a sequence of chemoselective ester reduction with LAH in the presence of the more electrophilic ketone by in situ protection of the ketone as its lithium enolate,\(^10\) followed by EDC coupling with diethylphosphonoacetic acid (Scheme 3.4). In the event, the intramolecular Horner-Wadsworth-Emmons reaction of phosphonoacetate 3.14 could be effected under the mild, Hünig’s base-mediated Masamune-Roush conditions,\(^11\) thus completing a high-yielding synthesis of lactone 3.15 and rather quickly getting us to a substrate that closely resembled intermediates from the quinone route. Given this strong
resemblance and the difficulties encountered in the related series, we chose to use this synthesis only as a proof of concept and we did not pursue any further chemistry on this substrate.

![Scheme 3.4. A successful intramolecular Horner-Wadsworth-Emmons reaction. $R = -\text{CH}_2\text{CHCH}_2$](image)

Since the aforementioned results suggested that a standard intermolecular condensation on ketone 3.11 was perhaps not the best way to introduce the enone function, we began to explore other methods to synthesize the desired acyclic enone. One possibility that seemed particularly attractive was the union of an alkene or alkyne moiety with ketone 3.11 to give an allylic or propargylic alcohol, respectively, followed by a [1,3]-oxygen transposition to afford the enone.\(^{12-15}\) The case of the propargylic alcohol seemed most attractive as it would maintain the desired oxidation state and provide the enone directly; however, the Dauben, PCC-mediated oxidative transposition\(^{13}\) of a tertiary allylic alcohol was also an option. Regardless, both substrates could be conveniently accessed from ketone 3.11 and were worthy of study. Our efforts commenced by treating ketone 3.11 with the sodium acetylide generated from TBS...
propargyl ether and NaHMDS in the cold to give propargyl alcohol 3.16, which was then exposed to various vanadium\textsuperscript{14} and rhenium\textsuperscript{15a} catalysts known to effect [1,3]-oxygen transposition in propargylic systems (Scheme 3.5). Despite having verified the activity of the catalysts in a model system, each attempt to effect the transposition with propargyl alcohol 3.16 returned only starting material. This suggested that our tertiary neopentyl alcohol was too hindered to engage the somewhat bulky catalysts, and so we reasoned that if we could perform a Lindlar reduction\textsuperscript{16} of the alkyne function of compound 3.16, a smaller and more reactive reagent such as PCC might be able to engage the resulting tertiary allylic alcohol and effect the desired oxidative [1,3]-transposition. In the event, the Lindlar reduction was found to be uniquely successful in ethyl acetate and gave cis-allylic alcohol 3.17 in quantitative yield. This reduction was followed by treatment with PCC in the presence of 4Å molecular sieves\textsuperscript{17} to give the desired acyclic enone 3.18, though in modest yield. While we were pleased to have isolated the desired enone, we chose to delay the optimization of this sequence until we had a more suitable substrate since all of these operations had been performed in a model system with an allyl group at the 2-position of the ketoproline.
3.4 1,3-Dicarbonyl Studies

Having developed a short sequence to access the desired acyclic enone in a model system, we turned our attention to the matter of introducing a suitable 1,3-dicarbonyl system at the 2-position of the ketoproline. While we were able to quickly evaluate a number of different masked 1,3-dicarbonyl moieties in the context of the desired sequence, unfortunately, all met with failure when attempting to introduce the acyclic enone and we were unable to synthesize a substrate suitable for the study of the intramolecular Michael addition (Scheme 3.6).
3.5 Further Evolution of the Michael Addition Strategy

At this stage of the project, we began to worry that our revised strategy would only be met with the same limited success that we had experienced on the quinone route. Despite these reservations, we took a more critical look at the desired transformation before we moved away from this new strategy. In a broad sense, we were attempting to create a molecule such as 3.24 that contained discrete 1,3-dicarbonyl and enone moieties in proximity such that they might then be coerced to join under basic conditions via a Michael addition to forge the C11-C12 bond (Scheme 3.7). While this process seemed perfectly reasonable to us, we expanded our analysis to include even nonproductive pathways that might occur. Under the basic conditions of the reaction, we reasoned that vinylogous carbonate 3.25 would likely be a kinetically competent intermediate that
could arise from reversible C-O bond formation from enone 3.24. Due to this reversibility, the intermediacy of vinylogous carbonate 3.25 would not preclude the desired C-C bond formation, and the overall reaction process would almost certainly lead to the thermodynamically preferred cyclized product 3.27 under basic conditions, driven by enolization of the resultant cyclic β-keto ester. With this in mind, and given the difficulties we were having synthesizing substrates similar to 3.24 that contained discrete 1,3-dicarbonyl and enone moieties, we set vinylogous carbonate 3.25 as our new synthetic target. This substrate would not only allow us to study the key Michael addition during the course of a crowded C-O to C-C bond isomerization, but it would also have the advantage of containing both the 1,3-dicarbonyl and the enone moieties protected in the form of a vinylogous carbonate. We also felt that this substrate would benefit from a more straightforward synthesis, with a Semmelhack palladium(II)-catalyzed oxycarbonylation18 able to provide vinylogous carbonate from syn hydroxyl alkyne 3.28, itself the addition product of acetone and 2-propargyl-3-ketoproline 3.29.
3.6 A Synthesis of the Vinylogous Carbonate Intermediate

The route to access our new target (3.25) began with straightforward alkylation of the stabilized sodium enolate derived from N-Boc-3-ketoproline methyl ester (3.10) with propargyl bromide in a mixed solvent system of THF and DMF (Scheme 3.8). In our search for an appropriate acetone nucleophile equivalent, we found that we could add a variety of nucleophiles to the resulting neopentyl ketone, but commercially available 2-methylallylmagnesium chloride quickly became our reagent of choice. Thus, homoallylic alcohol 3.31 was produced by a chemoselective addition of 2-methylallylmagnesium chloride to the ketone carbonyl of 3.29. This reaction was efficient and highly diastereoselective; nucleophilic addition occurred to the face away from the propargyl chain,\(^9\) thus directly establishing the necessary syn relationship between the hydroxyl
and the alkyne. We immediately treated this compound under the conditions developed by the Marshall lab\textsuperscript{20} for the Semmelhack palladium(II)-catalyzed oxycarbonylation but we were disappointed to find a rather complex reaction mixture, which led us to assume that the presence of the nucleophilic alkene was complicating what is otherwise known to be a clean reaction. Since we were already committed to an eventual oxidative cleavage of the alkene to study the intramolecular Michael addition, we began to focus on this transformation at this stage. Not surprisingly given the presence of the alkyne, ozone-, osmium-, and ruthenium-based oxidative cleavage methods to directly provide the methyl ketone proved to be too aggressive, so we retreated to a two-step epoxidation/oxidative cleavage sequence. Treatment of alkene 3.31 with \textit{m}-CPBA did afford the desired epoxide 3.32 in 60-76\% yield; however, when this substrate was oxidatively degraded to the methyl ketone with periodic acid, we also observed cyclization of the hydroxyl onto the pendant alkyne to give the cyclic enol ether under the acidic conditions of the reaction. Given this result, we chose to attempt the Marshall-Semmelhack oxycarbonylation at the stage of the epoxide. With the alkene now protected in the form of an epoxide, and with hydroxyl and alkyne groupings in neighboring regions of space, compound 3.32 was an excellent substrate for the desired palladium(II)-catalyzed, carbylnative cyclization to vinylogous carbonate 3.33. This intermediate proved to be somewhat sensitive to chromatographic purification, but the high efficiency of this reaction allowed compound 3.33 to be taken on to the next step without further purification. With the desired vinylogous carbonate in place, we only needed to oxidatively degrade the disubstituted epoxide to the methyl ketone to begin to study the Michael addition in the context of the C-O to C-C bond isomerization. Initial treatment
of epoxide \textbf{3.33} with periodic acid in THF-Et\textsubscript{2}O solution at room temperature gave the desired ketone along with some degradation products, which we believed might be formed as a result of the somewhat acidic reaction conditions. When the reaction was simply buffered with sodium periodate in aqueous THF\textsuperscript{21} epoxide \textbf{3.33} was smoothly converted to the desired methyl ketone, compound \textbf{3.25}. In the process of scaling up this sequence, a Sharpless, vanadium-based epoxidation\textsuperscript{22} of the disubstituted alkene function in \textbf{3.31} proved superior to epoxidation with \textit{m}-CPBA.\textsuperscript{23} This Sharpless oxidation, which was presumably hydroxyl-directed,\textsuperscript{24} gave rise to essentially only one diastereomer, although we did not establish the configuration of the newly formed stereogenic center. This stereochemical matter was ultimately inconsequential as the epoxide was only serving to mask the reactivity of the disubstituted alkene and was a direct precursor to the trigonal keto group.
3.7 A Synthesis of the Acutumine Core Structure

To briefly revisit the desired transformation, our intention was to achieve a spontaneous conversion of bicyclic vinylogous carbonate 3.25 to the tricyclic core of acutumine (3.34) in the presence of a suitable base (Scheme 3.8). While such a transformation could well be mechanistically degenerate, we envisioned that it might occur by a sequence of carbonyl-dependent reactions starting with a base-mediated β-elimination (Scheme 3.9). This event would leave in its wake a delocalized enolate ion.
and an electrophilic enone, thus enabling an intramolecular Michael reaction to give compound 3.27. An analogous rearrangement carried out by Vorbrüggen and co-workers in the course of a synthesis of prostacyclin analogs bolstered our confidence in this type of crowded C-O to C-C bond isomerization. In base, enolization of the newly formed β-keto ester would render this grouping unreactive toward nucleophiles. A subsequent kinetic enolization of the methyl ketone in 3.27 would then trigger a final Dieckmann-like cyclization to tricyclo[4.3.3.0]dodecane 3.34, a compound having key elements of acutumine.

By the synthetic route shown in Scheme 3.8, we were able to advance multi-gram quantities of N-Boc-3-ketoproline methyl ester (3.10) to the stage of methyl ketone 3.25 in preparation for a focused study of the desired cascade carbonyl reactivity. It was possible to directly convert bicyclic vinylogous carbonate 3.25 to tricycle 3.34 with strong, non-nucleophilic bases, although these reactions were inefficient and produced
several byproducts. Given these difficulties, it became necessary to study the \( \beta \)-elimination/Michael addition process and the Dieckmann-like condensation separately. We began with the \( \beta \)-elimination/Michael addition sequence as we felt it could be conducted under more mildly basic conditions that would not be complicated by the Dieckmann-like condensation or other undesired reaction pathways. Based on the Vorbrüggen precedent of using DBN for a \( \beta \)-elimination/Michael addition process similar to the one we were hoping to effect, we screened a variety of amine bases under the conditions used by Vorbrüggen and co-workers but did not see any reactivity unless we added a mild Lewis acid such as lithium chloride. With our system being more hindered than that studied by Vorbrüggen and co-workers, we wondered if an internal, relay deprotonation could be effected by saponification of the nearby ester. To this end, we treated compound 3.25 with one equivalent of lithium hydroxide at room temperature and we isolated a new product whose \(^1\)H NMR spectrum no longer contained a vinyl proton resonance, but it did contain a downfield enol/acidic proton resonance, as well as both esters. All of the data indicated that we had been able to cleanly form \( \beta \)-keto ester 3.27 by an external deprotonation, rather than by an internal, relay deprotonation, which is perhaps not surprising given the hindered nature of the bridgehead methyl ester, something that would play a critical role in the next step and in our future efforts. We later found that mild bases such as cesium carbonate and tetra-\( n \)-butylammonium acetate or fluoride are capable of cleanly transforming vinylogous carbonate 3.25 to the isomeric bicycle 3.27 (Scheme 3.10). These reagents were equally effective; we could typically isolate bicycle 3.27 in 64% yield over two steps from epoxide 3.33. After scaling up \( \beta \)-keto ester 3.27, we performed a systematic study of conditions to effect the desired
Dieckmann-like condensation. We quickly found that when a cold solution of 3.27 in THF was first treated with excess NaHMDS and then allowed to warm to room temperature, the desired Dieckmann-like cyclization occurred and generated compound 3.34. The $^1$H NMR spectrum of 3.34 at room temperature in CDCl$_3$ is consistent with the structure and enolic form as drawn. Sharp singlets for the signals corresponding to both the 1,3-dicarbonyl enol hydrogen and the Boc tert-buty1 hydrogens suggest an intramolecular hydrogen bond between this enol hydrogen and the carbonyl of the Boc group. This results in an overall simplification of the $^1$H and $^{13}$C NMR spectra consistent with a single N-Boc rotamer.
3.8 Efforts Toward an Asymmetric Synthesis of the Core Structure

With a successful synthesis of the acutumine core structure in hand, we began to explore the development of an asymmetric synthesis. Inspection of our aforementioned route suggested that all that would be required for an asymmetric synthesis of the tricyclic core of acutumine was the direct asymmetric propargylation of our ketoproline building block. Control of the configuration at the fully-substituted α-carbon of the ketoproline would enable the neighboring quaternary stereogenic center to be set by
substrate control\textsuperscript{24,29} during the base-mediated isomerization of the corresponding vinylogous carbonate intermediate. Many methods for the asymmetric alkylation of β-keto esters are known,\textsuperscript{1} and a survey of the literature revealed that the asymmetric phase transfer alkylation\textsuperscript{30} of the tert-butyl ester derivative of ketoproline \textbf{3.10} had been achieved by the Maruoka lab.\textsuperscript{31} Despite not having direct precedent for our desired transformation, we were encouraged by the report from the Maruoka lab and we synthesized \textit{N}-Boc-3-ketoproline tert-butyl ester (\textbf{3.35})\textsuperscript{32} and (\textit{R},\textit{R})-\textbf{3.36}, the antipode of the asymmetric phase transfer catalyst that was reported in their article. When the reaction between \textbf{3.35} and propargyl bromide was carried out according to their procedure at 0 °C in the presence of catalyst (\textit{R},\textit{R})-\textbf{3.36}, the desired propargylated compound \textbf{3.37} was obtained in excellent yield; however, when we examined compound \textbf{3.37} by chiral HPLC, we discovered that material of only 48% ee was obtained (Scheme 3.11).\textsuperscript{33} Given that this transformation had proceeded well at 0 °C in the prescribed biphasic reaction mixture, we performed a few test reactions with tetra-\textit{n}-butylammonium bromide to explore how much we could decrease the temperature and still achieve a reasonable rate of conversion. From these studies, we determined that this transformation could be run at temperatures as low as -15 °C; however, repeating the experiment with catalyst (\textit{R},\textit{R})-\textbf{3.36} at this temperature only resulted in slight enrichment of the enantiomeric excess of \textbf{3.37} to 54% ee. We wondered if an uncatalyzed background reaction could be responsible for the observed moderate enantiomeric excess, so we also examined the reaction between \textbf{3.35} and propargyl bromide in the absence of any phase transfer catalyst. In the event, we observed no conversion at 0 °C in the timeframe necessary to see complete conversion in the catalyzed reaction, and only very
low conversion at room temperature after 24 hours. These results suggested that the moderate enantiomeric excess of 3.37 obtained by this method was not a result of any significant background reaction, but that catalyst $(R,R)$-3.36 was not particularly well suited to control the asymmetric alkylation of 3.35 with an electrophile as compact as propargyl bromide in the course of this transformation. Regardless, we deemed this a very promising result, but we chose to delay further optimization of this reaction, as well as the investigation of other methods, until after we had more sufficiently addressed the full architecture of acutumine.

![Scheme 3.11. Catalytic asymmetric phase transfer propargylation of a ketoproline.](image)

3.9 Conclusions

With the success of the Dieckmann-like cyclization, we had produced the propellane-like [4.3.3.0] fused tricyclic core of acutumine in only seven transformations from a known and readily available pyrrolidine derivative. Four of these transformations were enabled by the properties and reactivity of the carbonyl group. The concise
construction of this rigid, acutumine-like substructural element provided a basis for addressing the larger goal of achieving a stereocontrolled synthesis of the highly challenging full structure of acutumine, as well as many other acutumine-like compounds. The efforts made in this vein will be the subject of the following chapter.

3.10 References


7. In 2006, the prices for 25 g of (m-carboxyphenyl)sulfonyl chloride and (p-carboxyphenyl)sulfonyl chloride from Aldrich were $71.70 and $237.50, respectively.

8. N-Boc-2-allyl-3-ketoproline methyl ester (3.11) was readily synthesized from N-Boc-3-ketoproline methyl ester (3.10) by traditional alkylation with allyl bromide. Alternatively, the allyl group could be introduced with allyl acetate in the presence of low valent palladium and a variety of ligands and bases. Interestingly, N-allyl-2-allyl-3-ketoproline ethyl ester (3.41) could be synthesized from Nazarov’s reagent (3.39) by an efficient rhodium-catalyzed Stevens rearrangement (Scheme 3.12). For Nazarov’s reagent, see: (a) Nazarov, I. N.; Zavyalov, S. I. Zh. Obshch. Khim. 1953, 23, 1703-1705; Eng. Transl. 1953, 23, 1793-1794. (b) Zibuck, R.; Streiber, J. Org. Synth. 1993, 71, 236-239. For the Stevens rearrangement, see: (c) Stevens, T. S.; Creighton, E. M.; Gordon, A. B.;
Scheme 3.12. Another ketoproline synthesis.


12. In the case of the propargylic system, this reaction is formally a Meyer-Schuster reaction. See: Meyer, K. H.; Schuster, K. *Berichte* 1922, 55, 819-823.


15. (a) Bellemin-Laponnaz, S.; Gisie, H.; Le Ny, J. P.; Osborn, J. A. *Angew. Chem. Int. Ed. Engl.* 1997, 36, 976-978. These transformations are also catalyzed by...


23. The Sharpless, vanadium-based epoxidation returned epoxide 3.32 in 80% yield on a 5 g scale versus 60% yield on a 2.25 g scale for epoxidation with m-CPBA.


32. $N$-Boc-3-ketoproline tert-butyl ester (3.35) was prepared as reported for $N$-Boc-3-ketoproline methyl ester (3.10), except mono-tert-butyl malonate was used in place of methyl potassium malonate. See Experimental Section.

33. The enantioselectivity of $N$-Boc-2-propargyl-3-ketoproline tert-butyl ester (3.37) was determined by chiral HPLC analysis with a Chiralpak AD-H column, hexanes/i-PrOH = 100:1, flow rate = 0.5 mL/min. This analysis was performed by Christina Kraml of Lotus Separations, LLC.
Chapter 4

Efforts Toward the Completion of a Total Synthesis of

Acutumine
4.1 Early Attempts Directed at the Installation of the Spirocycle

With a concise and efficient synthesis of the propellane-like [4.3.3.0] fused tricyclic core of acutumine in hand (see Chapter 3), we began to address how we might advance this rigid, acutumine-like substructural element toward the larger goal of achieving a stereocontrolled synthesis of acutumine. Having already relied heavily on the utility of the carbonyl group in our synthesis of the core, we first evaluated whether or not we could again exploit carbonyl reactivity to install the spirocycle via a union of β-keto ester 3.27 with an acetone electrophile equivalent, followed by a Dieckmann-type cyclization (Scheme 4.1). Further, we envisioned that perhaps we could close both of the remaining rings in the course of a double Dieckmann-type cyclization to give the full acutumine architecture (represented by compound 4.2) in short measure. Retrosynthetically, we hypothesized that the methyl ketone would be the product of a Wacker oxidation of a simple allyl grouping, which we believed would lend itself nicely to straightforward introduction onto β-keto ester 3.27. In the event, when β-keto ester 3.27 was treated with allyl bromide and potassium carbonate in acetone at reflux, exclusive O-allylation was observed to give compound 4.3. Clearly, as we were attempting to forge the third contiguous, fully-substituted carbon center in the course of this alkylation reaction, the hindered nature of the α-position encouraged allylation of the much more accessible oxygen atom of the β-keto ester moiety. While it was disappointing that no C-allylation was observed, we recognized that compound 4.3 could potentially be isomerized to the thermodynamically preferred, and more synthetically desirable, C-allylated product in the course of a Claisen-type [3,3]-sigmatropic rearrangement, either under thermal conditions or transition metal catalysis. In fact,
the thermal isomerization of an O-allyl acetoacetic ester to a 2-allyl acetoacetic ester was one of the first [3,3]-sigmatropic rearrangements reported by Claisen in 1913.\textsuperscript{3a}

Gratifyingly, when compound 4.3 was either thermalized in diphenyl ether at 200 °C or treated with low-valent palladium in the presence of (S)-BINAP (\textit{vide infra}) at 60 °C in toluene, the desired crowded C-C bond-forming event could be effected, thus providing C-allylated product 4.4, along with the compound epimeric at C11 (not shown). While we observed the formation of a near equal mixture of products epimeric at the newly formed stereogenic center, these products were easily separable by silica gel column chromatography. With the aid of NOESY analysis, we were able to determine which of these two products had the desired configuration at C11,\textsuperscript{4} and we set out to optimize the conditions for its formation. We quickly found it to be more desirable to either introduce the allyl group onto β-keto ester 3.27 as the more activated Alloc group (see compound 4.5), or perform a direct, palladium-catalyzed allylation\textsuperscript{5} of β-keto ester 3.27; in both cases, the temperature required to effect the desired C-allylation reaction could be lowered to room temperature or below. When these later palladium-catalyzed allylation studies of 3.27 and 4.5 were conducted at room temperature in the presence of Trost’s DACH-phenyl ligand (4.6),\textsuperscript{5f} the ratio of diastereomers formed in each case shifted to approximately 2:1 in favor of the desired epimer, regardless of which antipode of the chiral ligand was employed; no studies with achiral phosphines were performed and further optimization was delayed pending the outcome of our investigation of the downstream chemical transformations.
This reaction was found to perform well in aqueous DMF with palladium(II) chloride and...
either copper(I) chloride/dioxygen or benzoquinone as reoxidant, thus permitting the isolation of pure triketone 4.1 (Scheme 4.1). Despite the anticipated difficulties that would be caused by the reactive potential of the cyclopentanone carbonyl of the quaternized β-keto ester system, we decided to attempt the double Dieckmann-type cyclization with the small amount of triketone 4.1 that we had in hand. Thus, triketone 4.1 was subjected to the conditions that were first used to effect our earlier Dieckmann-like cyclization, namely excess KHMDS in THF at -78 °C, followed by warming to room temperature. Predictably, this resulted in a complex mixture of products by crude 1H NMR and we could not discern whether even a small amount of the desired reaction product was formed. Having validated that we could install the desired methyl ketone at the α-position of β-keto ester 3.27, we focused on selectively masking the cyclopentanone carbonyl of C-allylated product 4.4. Unfortunately, all efforts at selective operation on the cyclopentanone carbonyl were met with failure. In hindsight, perhaps we should have spent more time attempting to advance compounds along this series. For example, one idea that was never attempted was the Noyori hydrogenation of β-keto ester 3.27 to give the corresponding β-hydroxy ester, followed by a Fráter-Seebach alkylation to provide the selectively alkylated and reduced compound that we were seeking. While we also never investigated the protection of the methyl ketone prior to operation on the β-keto ester function, we did briefly explore the Alloc sequence in a system where the methyl ketone had been replaced by a methyl ester early in the synthesis. Unfortunately, this route was also met with limited success.

Another strategy that we evaluated sought to close the spirocycle by a different intramolecular cyclization. Specifically, we would install, at an early stage, an advanced
propargyl moiety that would include all of the carbon atoms necessary to allow us to study the introduction of the spirocycle, this time closing the spirocycle under the milder conditions of an intramolecular aldol reaction\textsuperscript{9} at C11. Synthesis of the requisite propargyl bromide 4.7 was accomplished through a straightforward sequence,\textsuperscript{10} and the alkylation of ketoproline 3.10 proceeded without event to provide compound 4.8 (Scheme 4.2). When it came to the introduction of the acetone nucleophile equivalent onto the ketone carbonyl of compound 4.8, 2-methylallylmagnesium chloride was again found to add smoothly and in a highly diastereoselective manner. When the resulting compound was subjected to the conditions of the Sharpless, vanadium-catalyzed epoxidation, the acid sensitivity of the ketal was exposed and only vinylogous carbonate formation was observed. Attempts to oxidize the alkene with \textit{m}-CPBA or osmium tetroxide led to complex mixtures, as before (see Chapter 3). Fortunately, addition of allylmagnesium chloride, followed by cyclization of the resultant tertiary alcohol onto the pendant alkyne under mildly acidic conditions, allowed us to then access the desired methyl ketone via a Wacker oxidation, thus giving vinylogous ester 4.10. As demonstrated in Chapter 3, treatment of vinylogous ester 4.10 under mildly basic conditions was found to effect the desired rearrangement to diketone 4.11; however, from here, all attempts to oxidatively close the spirocycle led to complex mixtures and this route was abandoned.
4.2 A New Strategy for the Introduction of the Spirocycle

After considerable effort was expended on the aforementioned approaches to install the spirocycle, as well as other much less successful approaches, we decided that a change in strategy was in order. Our failed attempts to wield polycarbonyl systems of the type shown above with any measure of selectivity led us to a new plan that would circumvent what we believed at the time was the most problematic functionality, the cyclopentanone carbonyl. Our plan all along for this functionality was its late-stage reduction and conversion to the conspicuous chlorine atom found in acutumine and many relatives – a pedestrian strategy, at best, to introduce the halogen. Inspired somewhat by Nature, and also by necessity, we wondered if an electrophilic chlorination could be...
employed to install the chlorine atom (see Chapter 1). From the very beginning of our studies toward a synthesis of acutumine, we had been intrigued by the biosynthetic proposal put forth by Barton and co-workers, as well as the biosynthetic conversion of dechloroacutumine to acutumine, especially since their respective suggestion of the biosynthetic introduction of the chlorine atom seemed at odds. As covered in Chapter 1, the low incidence of nucleophilic halogenations in Nature calls into question the fate of Barton’s proposed aziridinium ion 1.19. Many possibilities certainly exist, but one wonders whether Barton’s proposed [1,2]-hydride shift would be followed instead by reduction with a hydride source (or perhaps even direct reduction of the aziridinium) to directly provide an intermediate such as compound 4.13 that features the undecorated ethano bridge found in the dechloroacutumine-type alkaloids (Scheme 4.3). From here, a downstream, radical-mediated chlorination11 could account for the isolation of both the chlorinated and dechlorinated alkaloids, as well as the observation that dechloroacutumine is biosynthetically converted to acutumine. Alternatively, perhaps E2 elimination could occur in preference to the proposed [1,2]-hydride shift, thus resulting in the formation of cyclopentene 4.14, which could either undergo reduction to provide the dechlorinated alkaloids or engage one of Nature’s electrophilic halogenation reagents. The resultant chloronium ion 4.15 could then engage the nearby nitrogen atom, reforming an aziridinium ion that could then be reduced by a hydride source. This accounts for both the observed position and stereochemistry of chlorination seen in the acutumine family of natural products. Perhaps genetic analysis of the biosynthetic machinery employed by Nature to synthesize acutumine could shed some light on the nature and timing of the halogenation event.
Regardless of what actually occurs biosynthetically, if we inspect the northern portion of acutumine (represented as compound 4.17 in Scheme 4.4), we could consider an alternative chloronium ion intermediate from that proposed above, one in which a lone
pair of electrons from the chlorine atom would help to stabilize a buildup of positive charge at C11 rather than at C9 (Scheme 4.4). Retrosynthetically, such a buildup of positive charge could be generated by the migration of the C1-C11 bond from the quaternary center at C11 into the adjacent carbonyl at C4, thus transforming spirocyclopentanone 4.17 into cyclobutanol 4.18. If we imagine that the chloronium ion of intermediate 4.18 arises from allylic alcohol 4.19, then we can consider the transdifunctionalization required to advance allylic alcohol 4.19 to chlorinated spirocycle 4.17 could be achieved in the process of a chloronium ion-induced semipinacol rearrangement, thus transforming a vinyl cyclobutanol intermediate into a compound displaying all of the functionality found in the northern portion of acutumine. Crucial to the success of this transformation is the ability to control which face of the trisubstituted alkene present in compound 4.19 engages the source of electrophilic chlorine, as this facial selectivity is ultimately responsible for setting the configuration of the stereogenic centers at both C10 and C11. Considering that compound 4.19 is a highly advanced [3.3.0] fused bicycle, we hypothesized that we could exploit the natural tendency for functionalization of related systems to occur on the more accessible convex face of the bicycle, thus substrate control would be relied upon to control which face of the alkene would engage a chlorinating reagent and, as a result, this event would control the configuration of the stereogenic centers at both C10 and C11. To access vinyl cyclobutanol 4.19, we propose that a vinyl metal species derived from vinyl bromide 4.20 could join with an appropriately substituted cyclobutanone, here depicted as compound 4.21 to account for all of the functionality that would be required for a direct synthesis of the acutumine spirocycle, though other less complex cyclobutanones would initially be
studied. If the transformation of vinyl bromide 4.20 into spirocyclic compound 4.17 could be achieved as proposed, a remarkable advancement in architectural complexity would be achieved in only two steps.

![Scheme 4.4. A chloronium ion-induced semipinacol idea.](image)

### 4.3 Early Attempts at a Vinyl Bromide Synthesis

With the proposed chloronium ion-induced semipinacol approach set as our new course, we focused our efforts on a synthesis of a vinyl bromide related to compound 4.20. Hoping to reduce the step count required to access such a compound, we returned to ketoproline 3.10 and we were quickly able to synthesize allylic alcohol 4.24 by a straightforward sequence (Scheme 4.5). It was our hope to use this compound to effect a [3,3]-sigmatropic rearrangement that would both forge the quaternary center at C12 and install the vinyl bromide directly. Unfortunately, all variants of the Claisen-type [3,3]-
sigmatropic rearrangement failed to give more than a trace of the desired compound. This likely due to the steric hindrance associated with the formation of vicinal, fully-substituted stereogenic centers, as well as the fact the desired rearrangement would most likely be forced to go through a boat-like transition state so as to minimize steric clashing between the methyl ester and the substituent on the vinyl group appended to the allylic alcohol during the rearrangement; however, a boat-like transition state would then introduce steric clashing between the vinyl substituent and the proximal bromine atom. In an attempt to avoid such a congested transition state for the desired rearrangement, we decided to study exocyclic rather than endocyclic [3,3]-sigmatropic rearrangements. To do so, we synthesized allylic alcohol 4.27 and attempted to effect the desired bond formation at C12 by an anionic oxy-Cope [3,3]-sigmatropic rearrangement, but we were disappointed to find that only clean nucleophilic demethylation of the ester had occurred. Conditions other than those shown in Scheme 4.5 proved equally unsuccessful at effecting the desired rearrangement. We also synthesized substrates such as allylic acetate 4.29 to evaluate Claisen-type [3,3]-sigmatropic rearrangements, but these were met with the same limited success. Given the aforementioned results, it became clear to us that this type of strategy should be abandoned.
4.4 A Successful Vinyl Bromide Synthesis

After our brief, unsuccessful foray into vinyl bromide synthesis by a [3,3]-
sigmatropic rearrangement strategy, we returned to intermediates from our route to the
tricyclic core, specifically β-keto ester 3.27 (see Scheme 4.1). In theory, this compound
would be only two steps away from a vinyl bromide related to compound 4.20 – a deoxygenation, followed by a decarboxylative bromination. We first attempted the direct, Zr-mediated deoxygenation of β-keto ester 3.27 under the conditions of Ganem, but a complex mixture resulted. This prompted us to attempt a triflation/reduction sequence. While vinyl triflate 4.33 could be synthesized from β-keto ester 3.27 with Comins’ reagent (4.32) in the presence of a variety of bases, we found that we could save one synthetic step and perform the triflation as part of a one-pot rearrangement/triflation sequence from vinylogous carbonate 3.25 in the presence of cesium carbonate (Scheme 4.6). From here, the palladium-catalyzed reduction proceeded well in hot THF in the presence of triethylammonium formate to provide acrylate 4.34 in excellent overall yield.

With a successful deoxygenation protocol in place, we turned our attention to transforming acrylate 4.34 into the desired vinyl bromide. We envisioned that this transformation would proceed by a radical decarboxylation of a Barton ester in the
presence of a suitable brominating reagent. Thus, we would need to selectively saponify the methyl ester of the acrylate function in the presence of the methyl ester adjacent to the pyrrolidine nitrogen, and then couple the resulting carboxylic acid with 2-mercaptopyridine N-oxide to form the Barton ester. Given both the hindered nature of the methyl ester adjacent to the pyrrolidine nitrogen and how robust it had proven to be up to this point, we believed that a selective saponification of the acrylate would proceed without event. When we subjected compound 4.34 to the conditions we had come to favor for ester saponifications, namely lithium hydroxide in equal volumes of THF, methanol, and water at room temperature, we were surprised to find that a rather non-selective saponification had taken place to give a mixture of carboxylic acids 4.35 and 4.36 (Scheme 4.7). We hypothesized that the undesired saponification of the sterically hindered pyrrolidine ester did not proceed by an intermolecular attack of hydroxide, but rather by a unique mechanism that involved initial attack of hydroxide on the more electrophilic ketone, followed by intramolecular attack of the resulting lithiated ketal 4.37 on the pendant ester. Intermediate lithiated ketal 4.37 could, in theory, attack either ester with facility and be the species directly responsible for the formation of both 4.35 and 4.36, or perhaps saponification of the pyrrolidine ester by this mechanism makes the rate of hydrolysis at this site competitive with the rate of intermolecular saponification of the acrylate. Regardless, we recognized that the ketone function would need to be protected at some point during our synthesis of the desired vinyl bromide, and we believed that performing this task at the stage of compound 4.34 would allow us to mitigate the formation of undesired acid 4.35. In the event, protection of the ketone with ethylene glycol in hot dichloromethane in the presence of CSA, 2-ethyl-2-methyl-1,3-dioxolane,
and trimethylorthoformate proceeded well to give dioxolane 4.38, which was of sufficient purity after an aqueous workup to be taken on to the next step without further purification. When dioxolane 4.38 was treated under the same conditions as used for the saponification of compound 4.34, no reaction was seen at room temperature. Upon warming the reaction to at least 45 °C, a clean and highly selective saponification of the acrylate ester could be achieved to provide acid 4.39 in excellent yield over the two-step sequence. It is tempting to suggest that this result, namely that heating was now required for any saponification of compound 4.38 to proceed at a synthetically useful rate, provides some support for our hypothesis of an intramolecular saponification mechanism in the case of compound 4.34; however, the increase in steric bulk in proximity to both ester functions as a consequence of the installation of the dioxolane could also play an important role in this reaction. Further studies would be necessary to lend additional support to either reaction mechanism.
Having executed both protection of the ketone carbonyl and hydrolysis of the acrylate ester, we were now prepared to focus on the synthesis of the Barton ester and its subsequent decomposition to provide the desired vinyl bromide. The coupling of acid 4.39 and 2-mercaptopyridine N-oxide proceeded without event in the presence of EDC and catalytic DMAP in dichloromethane at room temperature to provide compound 4.40 (Scheme 4.8). With the desired Barton ester in hand, we quickly found that it could be decomposed to vinyl bromide 4.41 by the instigation of AIBN in hot bromotrichloromethane, though this reaction proceeded in only modest yield. Attempts at further optimization of this reaction failed to significantly improve the yield beyond approximately 50% over the two-step sequence. Regardless, we were now poised to
investigate whether or not we could use this vinyl bromide in our desired metalation/carbonyl addition/chlorination sequence that would hopefully allow us to rapidly generate the complexity found within the northern portion of the acutumine structure in the form of the spirocycle and chlorinated cyclopentane.

4.5 Advancement of the Vinyl Bromide

Our initial studies with vinyl bromide 4.41 focused on finding appropriate metalation conditions that would allow us to generate and trap the vinyl metal species at low temperature. For these early studies, we chose to use commercially available cyclobutanone as our model electrophile. In our first attempt, we found that lithium-halogen exchange\textsuperscript{17} was complete nearly instantaneously upon treatment of vinyl bromide 4.41 with slightly more than two equivalents of \( t \)-BuLi in THF at -78 °C. The resulting vinyl lithium species was found to smoothly add to cyclobutanone to provide the desired products.
allylic alcohol 4.43 in 46% yield, though this product was accompanied by the formation of the proton-quenched cyclopentene 4.44 in 49% yield (Scheme 4.9). Not unexpectedly, these products were easily separable by silica gel column chromatography. Given the hygroscopicity of cyclobutanone, we repeated this experiment with a new bottle of cyclobutanone that was stored over drying agent. As this only slightly increased the yield of allylic alcohol 4.43, we realized that we would need to screen further conditions and perhaps alter the basicity of the vinyl metal species to prevent quenching by what was presumably a deprotonation of cyclobutanone. One interesting point of note with regard to allylic alcohol 4.43 is its somewhat unique $^1$H NMR spectrum in CDCl$_3$ that reveals hydrogen bonding between the hydroxyl and dioxolane moieties. This is manifested in two doublets at 4.60 and 4.63 ppm corresponding to the hydroxyl proton (rotamers), as well as the downfield shift and greater resolution of the protons on the ethane bridge of the dioxolane. This suggests a preorganization of the allylic alcohol function in nonpolar solvents that could favor reactivity at the desired convex face of the cyclopentene, especially for hydroxyl-directed transformations.

In addition to $t$-BuLi, $n$-BuLi was also found to be capable of rapidly and cleanly generating the vinyl metal species; however, the solvent for these reactions proved critical, with the lithium-halogen exchange being orders of magnitude faster in THF than
in Et₂O at -78 °C. We initially attempted to reduce the basicity of the vinyl metal species generated in THF by adding freshly dried CeCl₃, but the overall reactivity was suppressed and no significant improvement in the ratio of allylic alcohol to cyclopentene was observed. We then investigated the competency of magnesium reagents derived from i-PrMgCl in the metal-halogen exchange reaction. Surprisingly, no metal-halogen exchange was observed with i-PrMgCl•LiCl in THF, even at room temperature; however, exchange with the in situ-generated, higher order magnesium reagent i-PrBu₂MgLi was complete in less than 30 minutes at 0 °C in THF. The vinyl metal species that resulted from this exchange was also found to smoothly add to cyclobutanone to provide desired allylic alcohol 4.43, though the ratio of allylic alcohol to cyclopentene did not significantly improve. Despite being unable to improve this ratio during these brief studies, we were able to generate enough of allylic alcohol 4.43 that we could begin to investigate the competency of this material in the desired semipinacol rearrangement. We first used a Sharpless, vanadium-based epoxidation to gauge the propensity of allylic alcohol 4.43 to undergo the desired ring expansion by a semipinacol rearrangement (Scheme 4.10). When a solution of allylic alcohol 4.43 in CDCl₃ was treated with VO(acac)₂ and anhydrous t-BuOOH and the reaction was monitored by ¹H NMR at room temperature, washing out of the hydroxyl proton was observed; however, no reaction of the olefin was seen. After brief heating of the reaction solution at 50 °C, the peaks at 5.56 and 5.60 ppm corresponding to the vinyl proton were replaced by a new peak at 4.59 ppm. Following purification of the reaction mixture by silica gel column chromatography, we isolated in low yield a product whose ¹H NMR spectrum contained this new, more shielded proton, but the rest of the spectrum was very complex, especially
in the aliphatic region. From what we could glean, oxidative functionalization of the olefin had taken place, though the complex spectra suggested that we isolated a mixture of compound 4.46 along with its methyl ketone analog. The fact the products from this reaction were isolated as an inseparable mixture prohibited absolute structural confirmation.

![Diagram of oxidative semipinacol rearrangement](image_url)

**Scheme 4.10.** An oxidative semipinacol rearrangement.

In an attempt to avoid the spectral complexities caused by the introduction of the cyclobutanol/cyclopentanone moiety in the aforementioned model system, we decided to study the introduction of more oxygenated cyclobutanones that would give symmetrical spirocycles with fewer aliphatic $^1$H NMR resonances after rearrangement. This symmetry was especially important, as it would obviate spectral complexities that would arise from the formation of diastereomers if facial selectivity of the olefin proved poor. Our first choice for a new model spirocycle precursor was a squaric acid ester derivative. Not only are these compounds either commercially available or readily synthesized, but they are also highly reactive toward nucleophilic addition, and they lack acidic protons, a feature that we hypothesized would help to increase the yield of the addition reaction (vide supra). Beyond these advantages, the ring expansion behavior of squarate addition products has been well studied. In the event, a smooth union between dimethyl squarate and the vinyl lithium species generated from vinyl bromide 4.41 with $n$-BuLi in THF at -78 °C gave the desired addition product in high yield (Scheme 4.11).
The clean reactivity that was observed, as well as the reported acid sensitivity\textsuperscript{27} of addition products such as compound \textbf{4.47}, caused us to take the crude reaction mixture forward without purification, but did not preclude us from evaluating the performance of compound \textbf{4.47} in the Sharpless, vanadium-based epoxidation. As one may have expected, the somewhat acidic conditions of this reaction caused the formation of the extended conjugation product \textbf{4.48} within a few hours at room temperature. Since our ultimate goal was to achieve a chloronium ion-induced semipinacol rearrangement, we began to focus on this type of transformation with the squarate addition products. An earlier screen of chlorinating reagents with allylic alcohol \textbf{4.43} revealed that strong chlorinating agents such as \textit{t}-BuOCl\textsuperscript{28} and gentle warming were required to effect any conversion of the starting material. When a solution of \textit{t}-BuOCl and squarate addition product \textbf{4.49} in CDCl\textsubscript{3} was allowed to heat at 55 °C for a few hours, the crude \textsuperscript{1}H NMR showed that not only were the peaks at 5.57 and 5.62 ppm corresponding to the vinyl proton replaced by a new peak at 5.58 ppm, but the resolved squarate methoxyl resonances at 3.94 and 4.13 ppm observed for compound \textbf{4.49} converged and shifted upfield into the same region of the spectrum as the methyl ester (ca. 3.7 ppm). Following purification of the reaction mixture by silica gel column chromatography, we isolated in low yield a product whose \textsuperscript{1}H NMR spectrum contained the new, more shielded proton at 5.58 ppm, as well as three methoxyl resonances centered closely around 3.7 ppm. Furthermore, the \textsuperscript{1}H and \textsuperscript{13}C chemical shifts of the chlorinated cyclopentane methine are consistent with those found in acutumine and related structures (e.g. – 5.16 ppm and 57.9 ppm for acutumine in pyridine-d\textsubscript{5}). The remaining features of the molecule are also represented by the NMR spectral data; however, mass spectrometric analysis indicated
that not one, but two chlorine atoms had been incorporated. At the time of this writing, it remains unclear where the other halogen was incorporated. This result was, of course, highly encouraging, and we spent a good deal of time attempting to unambiguously assign the structure of this product as we continued to explore the chemistry surrounding this chloronium ion-induced semipinacol strategy; however, as of my departure from the Sorensen lab, absolute structural proof could not be obtained. The further work of my colleagues Dr. Alexandre Côté and Amy Bittner (and perhaps others) toward the ultimate goal of a total synthesis of acutumine will be reported in due course.

Scheme 4.11. Lithium-halogen exchange, squarate addition, and a chlorinative semipinacol rearrangement.
4.6 References


4. NOESY cross peaks were observed between the allylic methylene and the pyrrolidine $3\beta$-H.


10. Advanced propargyl bromide 4.7 was synthesized as shown below in Scheme 4.12. See Experimental Section for further details.

![Scheme 4.12. Synthesis of propargyl bromide 4.7.](image)

11. While many of Nature’s observed radical chlorinations occur on terminal carbon atoms, it is conceivable that a unique enzyme could achieve chlorination at C10 to afford the acutumine alkaloids. In the laboratory, a carbon-centered radical generated at C10 is able to engage the spirocycle carbonyl of dauricumine to form the ring-fused by-product dechlorodauricumine (1.10). Interestingly, when acutumine is treated under the same conditions, only dechloroacutumine is obtained. See: Sugimoto, Y.; Matsui, M.; Takikawa, H.; Sasaki, M.; Kato, M. Phytochemistry 2005, 66, 2627-2631.

![Scheme 4.13. Radical dechlorination of dauricumine.](image)

16. It is likely that the formation of Barton esters proceeds by initial acylation of the thiol, followed by an intramolecular S→O acyl transfer, similar to native chemical ligation.
22. Under otherwise identical conditions, incomplete metal-halogen exchange was observed with this reagent at -78 °C after 30 minutes.

26. With comparable reactivity observed for both *t*-BuLi and *n*-BuLi in the lithium-halogen exchange, *n*-BuLi was frequently the reagent of choice during our studies due to its greater stability and ease of use.


Experimental Section
E.0 General Experimental Details

Unless otherwise noted, all reactions were carried out under an atmosphere of argon or nitrogen. Tetrahydrofuran (THF), toluene, Et₂O, methylene chloride (CH₂Cl₂), and N,N-dimethylformamide (DMF) were dried by passing through activated alumina columns. Commercial reagents of high purity were purchased and used without further purification unless otherwise noted. Organolithium reagents were titrated using sec-butanol in ether, with 1,10-phenanthroline as an indicator. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60 F₂₅₄) using UV light as a visualizing agent and aqueous ceric sulfate/phosphomolybdic acid or aqueous potassium permanganate solution and heat as developing agents. E. Merck silica gel 60 (230-400 mesh) was used for flash column chromatography.

E.1 Instrumentation

FT-IR spectra were obtained on a Perkin-Elmer Paragon 500 FT-IR. NMR spectra were obtained on Bruker DRX–600, DRX–500, AMX–400, and Varian Inova–500, Inova–400, and Mercury-Vx–300 instruments and calibrated to the residual solvent peak. NMR spectra were obtained on a Varian Inova-500 instrument and calibrated to the residual solvent peak. The multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app s = apparent singlet, app d = apparent doublet, app t = apparent triplet br = broad signal. All coupling constants are reported in Hz. Optical rotations were recorded on a Perkin-Elmer model 241 polarimeter using a 1 mL, 1 dm cell. Mass spectra were obtained on an Agilent ESI-TOF mass spectrometer.
E.2 Experimental for Chapter 2

Epoxy dione 2.17: A solution of benzoquinone (2.12) (28.8 g, 266 mmol, 1.0 equiv.) in 50 mL methanol was allowed to cool to 0 °C, then a solution of freshly cracked and redistilled cyclopentadiene (23 mL, 280 mmol, 1.05 equiv.) in 15 mL methanol was added over 5-10 minutes. A precipitate formed within several minutes. The cooling bath was removed and the suspension was allowed to stir at rt for 20 minutes before it was again allowed to cool to 0 °C. After the solid product was collected by vacuum filtration, the mother liquor was reduced in volume under reduced pressure and filtered to provide a second crop of product. In total, 41.71 g of cycloadduct 2.16 was obtained as yellow needles (90%). Cycloadduct 2.16 was then dissolved in 415 mL acetone and allowed to cool to 0 °C. To this cold solution was added 41 mL of 20% aqueous Na$_2$CO$_3$, followed by 82 mL of 30% aqueous H$_2$O$_2$. After allowing the reaction mixture to stir at 0 °C for 15 minutes, 623 mL water was added to precipitate the product, which was collected by vacuum filtration, rinsed with water and allowed to dry open to the atmosphere overnight to provide 40.39 g (89%) of epoxy dione 2.17 as white crystals, mp 120–123 °C. TLC: $R_f=0.35$ (SiO$_2$, 1:4 EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.03 (t, $J = 1.8$, 2H), 3.49 (s, 2H), 3.41 (dd, $J = 1.2$, 2.0, 2H), 3.30 (dt, $J = 1.5$, 3.3, 2H), 1.46 (dt, $J = 1.9$, 8.8, 1H), 1.30 – 1.22 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 204.43, 136.93, 58.09, 49.73, 46.59, 43.51.
Epoxy alcohol 2.18: To a 2 L round bottom flask containing a stirbar was added 1050 mL isopropanol. The isopropanol was degassed with five cycles of high vacuum/argon refill while maintaining efficient stirring. Approximately 50 mL of isopropanol was then transferred to a 100 mL round bottom flask under argon that contained a stirbar and NaOH NMR (200 mg, 5 mmol, 0.025 equiv.). This mixture was allowed to stir at rt until complete dissolution (approximately one hour). To the 2 L round bottom flask containing the remaining 1000 mL of isopropanol was added under a stream of argon benzeneruthenium(II) chloride dimer (1.00 g, 2 mmol, 0.01 equiv.) and (1S,2S)-pseudoephedrine (2.21) (1.32 g, 8 mmol, 0.04 equiv.). The resulting red-brown mixture was placed into a preheated oil bath and allowed to heat at 80 °C for one hour, then the red-brown solution was allowed to cool to rt before epoxy dione 2.17 (38.04 g, 200 mmol, 1.0 equiv.) was added under a stream of argon, followed by the NaOH/isopropanol solution. The resulting mixture was allowed to stir at rt for 90 minutes, during which time the mixture became a black solution. This solution was filtered through a pad of silica gel over Celite®, the cake rinsed with EtOAc and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (SiO₂, 1:2 EtOAc/hexanes) to give 34.09 g (89%) of epoxy alcohol 2.18 as a light yellow, powdery solid, mp 65–70 °C. This material was generally taken on to the next step, but could be recrystallized from Et₂O-pentane to give colorless, crystalline product. TLC: \( R_f = 0.37 \) (SiO₂, 1:1 EtOAc/hexanes); \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 6.21 (dd, \( J = 3.1, 5.5, 1 \)H),
6.17 (dd, J = 2.9, 5.5, 1H), 4.62 (ddd, J = 3.4, 5.7, 9.3, 1H), 3.54 (dd, J = 3.6, 4.2, 1H), 3.26 (d, J = 4.4, 1H), 3.13 (dd, J = 3.4, 11.2, 1H), 3.07 (s, 1H), 2.99 (s, 1H), 2.94 (ddd, J = 3.3, 5.8, 11.2, 1H), 1.41 (dt, J = 1.8, 8.4, 1H), 1.27 (d, J = 8.4, 1H), 1.15 (d, J = 9.6, 1H); ¹³C NMR (126 MHz, CDCl₃) δ 208.13, 136.08, 135.73, 67.54, 59.74, 54.90, 51.57, 49.83, 45.26, 45.01, 42.79; HRMS (ESI-TOF) C₁₁H₁₂O₅ m/z calcd for [M+H]⁺ 193.0865; found 193.0866.

TBS ether 2.19: To a solution of epoxy alcohol 2.18 (5.55 g, 28.9 mmol, 1.0 equiv.) in 48 mL DMF was added TBSCl (8.71 g, 57.8 mmol, 2.0 equiv.), followed by imidazole (7.87 g, 115.6 mmol, 4.0 equiv.). The resulting solution was allowed to stir at 35 °C overnight, then allowed to cool to rt before water and saturated aqueous NH₄Cl were added. The mixture was poured into a separatory funnel and extracted three times with Et₂O. The combined organic extracts were washed twice with water, once with brine, then dried over MgSO₄, filtered, and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (SiO₂, 10 → 15 → 20% EtOAc/hexanes) to give 7.61 g (86%) of TBS ether 2.19 as a colorless solid, mp 65–67 °C, [α]D 25 +41.1° (c 1.19, CHCl₃) [lit. mp 66–67 °C, [α]D 28 +56.22° (c 1.19, CHCl₃)]. TLC: Rf =0.57 (SiO₂, 1:4 EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 5.99 (qd, J = 2.7, 5.5, 2H), 4.64 (dd, J = 3.3, 5.4, 1H), 3.35 (dd, J = 3.4, 4.3, 1H), 3.21 (d, J = 4.4, 1H), 3.07 – 3.00 (m, 2H), 2.87 – 2.81 (m, 2H), 1.34 (dt, J = 1.8, 8.2, 1H), 1.20 (d, J = 8.2, 1H), 0.83 (s, 9H), 0.09 (s,
$^{13}$C NMR (126 MHz, CDCl$_3$) δ 207.40, 136.71, 132.45, 67.16, 59.77, 54.75, 50.88, 49.36, 45.35, 45.21, 42.76, 26.01, 18.22, -4.13, -4.79; HRMS (ESI-TOF) C$_{17}$H$_{26}$O$_5$Si m/z calcd for [M+H]$^+$ 307.1729; found 307.1731.

![Chemical structure](image)

Keto ester 2.22: TBS ether 2.19 (1 g, 3.26 mmol, 1.0 equiv.) was dissolved in 9 mL toluene, and then ethyl acrylate (588 µL, 6.53 mmol, 2.0 equiv.) was added, followed by NaH (60% in mineral oil, 196 mg, 4.89 mmol, 1.5 equiv.). The resulting suspension was allowed to stir at rt for 24 hours before the reaction was quenched by the slow addition of saturated aqueous NH$_4$Cl. The biphasic mixture was poured into a separatory funnel, the layers separated and the aqueous layer extracted with EtOAc. The combined organic extracts were dried with MgSO$_4$, filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO$_2$, 1:3 EtOAc/hexanes) to give 997 mg (78%) of keto ester 2.22 as a colorless oil. TLC: $R_f$=0.56 (SiO$_2$, 1:4 EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) δ 6.00 (dd, $J$ = 2.9, 5.5, 1H), 5.81 (dd, $J$ = 3.1, 5.5, 1H), 4.51 (dd, $J$ = 1.9, 7.8, 1H), 3.53 (s, 3H), 3.14 (dd, $J$ = 2.0, 3.8, 1H), 3.03 (d, $J$ = 3.8, 1H), 2.81 (s, 1H), 2.75 (s, 1H), 2.39 (dd, $J$ = 3.2, 7.8, 1H), 2.30 (ddd, $J$ = 5.5, 11.0, 13.5, 1H), 2.20 (ddd, $J$ = 4.8, 10.9, 15.9, 1H), 2.05 (ddd, $J$ = 5.5, 10.9, 16.2, 1H), 1.90 (ddd, $J$ = 4.9, 11.0, 13.6, 1H), 1.37 (d, $J$ = 8.9, 1H), 1.21 (d, $J$ = 8.9, 1H), 0.81 (s, 9H), 0.05 and 0.03 (2s, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 208.01, 173.41, 137.68,
Keto acid 2.23: To a solution of methyl ester 2.22 (3.50 g, 8.92 mmol, 1.0 equiv.) in 90 mL THF was added a solution of LiOH•H₂O (562 mg, 13.4 mmol, 1.5 equiv.) in 54 mL water. The initially cloudy, colorless solution was allowed to stir at rt for three hours, during which time the solution became clear and pale yellow. The reaction was quenched by the addition of 50 mL saturated aqueous NH₄Cl, poured into a separatory funnel and extracted three times with Et₂O. The combined organic extracts were dried with MgSO₄, filtered, and the solvent was removed under reduced pressure to give 3.2 g (95%) of acid 2.23 as a pale yellow foam, mp 106–109 °C. TLC: Rₚ=0.39 (SiO₂, 1:1 EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 11.51 (s, 1H), 6.03 (dd, J = 2.8, 5.4, 1H), 5.84 (dd, J = 3.0, 5.3, 1H), 4.54 (dd, J = 1.5, 7.7, 1H), 3.18 (dd, J = 1.9, 3.7, 1H), 3.07 (d, J = 3.8, 1H), 2.84 (s, 1H), 2.78 (s, 1H), 2.41 (dd, J = 3.1, 7.8, 1H), 2.38 – 2.22 (m, 2H), 2.18 – 2.06 (m, 1H), 1.97 – 1.88 (m, 1H), 1.39 (d, J = 8.8, 1H), 1.25 (d, J = 8.8, 1H), 0.83 (s, 9H), 0.08 and 0.06 (2s, 6H); ¹³C NMR (126 MHz, CDCl₃) δ 208.30, 179.30, 137.79, 133.61, 66.45, 60.39, 58.25, 54.63, 53.07, 49.26, 45.98, 45.42, 34.57, 30.70, 25.96, 18.20, -4.49, -4.99; HRMS (ESI-TOF) C₂₀H₃₈O₅Si m/z calcd for [M+Na]⁺ 401.1760; found 401.1753.
Cyclic imine 2.25: To a 100 mL round bottom flask was added a stirbar and 13 g of powdered 4Å molecular sieves. The flask was evacuated under high vacuum and heated first with a Bunsen burner for 5-10 minutes, then in an oil bath at 160 °C for three hours. The flask and its contents were allowed to cool to rt under vacuum, then the flask was refilled with inert gas. A solution of keto acid 2.23 (1.514 g, 4.00 mmol, 1.0 equiv.) and triphenylarsine oxide (258 mg, 0.800 mmol, 0.2 equiv.) in 20 mL benzene was added to the flask containing the powdered 4Å molecular sieves, followed by Et₃N (2.23 mL, 1.60 mmol, 4.0 equiv.) and DPPA (1.03 mL, 4.8 mmol, 1.2 equiv.). The flask was then placed into a rt oil bath and the oil was set to heat to 70 °C. Once this temperature was reached, the reaction mixture was allowed to stir at 70 °C for one hour before the flask was removed and the reaction mixture was allowed to cool to rt. The reaction mixture was diluted with 20 mL EtOAc and filtered through Celite®. The filter cake was rinsed well with EtOAc, the solvents were removed under reduced pressure and the residue was purified by flash chromatography (SiO₂, 1:2 → 1:1 → 2:1 EtOAc/hexanes) to give 1.22 g (91%) of cyclic imine 2.25 as a colorless, crystalline solid, mp 81–83 °C. TLC: \( R_f = 0.27 \) (SiO₂, 1:1 EtOAc/hexanes); \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 6.20 (dd, \( J = 2.9, 5.6, 1H \)), 5.94 (dd, \( J = 3.0, 5.6, 1H \)), 3.98 – 3.91 (m, 1H), 3.77 – 3.68 (m, 2H), 3.28 (dd, \( J = 1.3, 4.1, 1H \)), 3.12 (s, 1H), 2.83 (dd, \( J = 1.7, 4.2, 1H \)), 2.71 (s, 1H), 2.32 (dd, \( J = 3.6, 7.2, 1H \)), 2.05 – 1.93 (m, 2H), 1.58 (d, \( J = 8.6, 1H \)), 1.46 (d, \( J = 8.6, 1H \)), 0.92 (s, 9H), 0.09 and 0.07 (2s, 6H); \(^{13}\)C NMR (126 MHz, CDCl₃) \( \delta \) 176.05, 137.05, 133.80, 71.36, 59.59,
α,β-Unsaturated imine 2.38: A solution of cyclic imine 2.25 (100 mg, 3.00 mmol) in 1 mL of diphenyl ether was degassed with five cycles of high vacuum/argon refill while maintaining efficient stirring. The flask containing the reaction solution was placed into an oil bath preheated to 200 °C and allowed to heat there for 30 minutes. The flask was removed and the reaction solution was allowed to cool to rt before direct purification by flash chromatography (0 → 50% EtOAc/hexanes) to give 58 mg (72%) of α,β-unsaturated imine 2.38 as an oil. TLC: \( R_f = 0.41 \) (SiO₂, 1:1 EtOAc/hexanes); \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 5.60 (d, \( J = 1.8 \), 1H), 4.63 – 4.59 (m, 1H), 3.98 (ddd, \( J = 3.2, 8.1, 17.0, 1H \)), 3.89 (ddd, \( J = 5.9, 6.8, 17.1, 1H \)), 3.79 (d, \( J = 3.6, 1H \)), 3.49 – 3.43 (m, 1H), 2.59 – 2.42 (m, 2H), 0.87 (s, 9H), 0.11 and 0.09 (2s, 6H); \(^{13}\)C NMR (126 MHz, CDCl₃) \( \delta \) 167.17, 139.23, 121.61, 65.43, 59.38, 57.67, 49.55, 27.61, 25.93, 18.36, -4.35, -4.48; HRMS (ESI-TOF) C₁₄H₂₃NO₂Si \( m/z \) calcd for [M+H]⁺ 266.1576; found 266.1571.
N-Boc-2-allyl pyrrolidine **2.40**: A solution of α,β-unsaturated imine **2.38** (3.76 g, 14.2 mmol, 1.0 equiv.) in 14.2 mL THF was allowed to cool to -78 °C before allylmagnesium chloride (2.0 M in THF, 7.8 mL, 15.6 mmol, 1.1 equiv.) was added dropwise over several minutes. The resulting solution was allowed to stir at -78 °C for 20 minutes, then quenched with saturated aqueous NH₄Cl and allowed to warm to rt. Enough water was added to dissolve the solids, and then the biphasic solution was poured into a separatory funnel. The aqueous layer was extracted three times with Et₂O, and then the combined organic extracts were dried with MgSO₄, filtered and the solvents removed under reduced pressure to provide crude 2-allyl pyrrolidine **2.39**, which was taken on without further purification. Crude 2-allyl pyrrolidine **2.39** was dissolved in 71 mL CH₂Cl₂, and then Et₃N (4 mL, 28.4 mmol, 2.0 equiv.) was added, followed by Boc₂O (3.41g, 15.6 mmol, 1.1 equiv.). The resulting solution was allowed to stir at rt overnight before being quenched with saturated aqueous NH₄Cl. The biphasic mixture was poured into a separatory funnel, the organic layer was removed and the aqueous layer was extracted three times with CH₂Cl₂. The combined organic extracts were dried with MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 10 → 15% EtOAc/hexanes) to give 3.04 g (53%, two steps) of N-Boc-2-allyl pyrrolidine **2.40** as a faint brown oil. This material solidified after standing at −20 °C overnight. TLC: Rₜ=0.48 (SiO₂, 1:4 EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 5.71 (ddt, J = 6.7, 8.5, 10.4, 1H), 5.47 (dd, J = 0.7, 6.2, 1H), 5.09 – 4.98 (m, 2H), 4.52 – 4.46 (m, 1H), 4.17 (d, J = 4.0, 0.5H), 3.86 (d, J = 4.0, 0.5H), 3.59 (td, J = 1.4, 10.3, 0.5H), 3.48 (td, J = 1.6, 10.3, 0.5H), 3.22 – 3.12 (m, 2H), 2.99 (dd, J = 7.1, 13.4, 0.5H), 2.82 (dd, J = 6.7, 13.5, 0.5H), 2.59 – 2.49 (m, 1H), 2.46 (ddd, J = 2.6, 8.1, 13.5,
1H), 2.34 – 2.25 (m, 1H), 1.51 and 1.45 (2s, 9H), 0.88 (2s, 9H), 0.11 – 0.09 (4s, 6H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \(\delta\) 154.24, 153.72, 142.55, 141.86, 133.64, 133.33, 118.49, 118.37, 118.08, 118.00, 80.53, 79.52, 64.61, 64.53, 64.29, 64.04, 54.59, 54.01, 53.41, 53.31, 45.52, 45.34, 41.89, 40.49, 29.68, 29.19, 28.84, 28.73, 25.92, 18.17, -4.21, -4.64; HRMS (ESI-TOF) \(C_{22}H_{37}NO_4Si\) \(m/z\) calcd for [M+H]\(^+\) 408.2570; found 408.2564.

Aldehyde 2.41: A solution of \(N\)-Boc-2-allyl pyrrolidine 2.40 (315 mg, 0.773 mmol, 1.0 equiv.) in 4 mL acetonitrile was treated with NMO (50 wt.% in H\(_2\)O, 420 mL, 1.55 mmol, 2.0 equiv.) and OsO\(_4\) (4 wt.% solution in H\(_2\)O, 100 mL, 0.0155 mmol, 0.02 equiv.). The resulting light brown solution was allowed to stir at rt overnight before it was poured into a separatory funnel. The flask was rinsed with EtOAc and the organic layer was washed once with brine. The organic layer was dried with MgSO\(_4\), filtered and the solvents were removed under reduced pressure to give an orange oil. This oil was dissolved in 8 mL of CH\(_2\)Cl\(_2\) and NaIO\(_4\)/SiO\(_2\) (0.68 mmol/g, 1.55 g, 1.05 mmol, 1.36 equiv.) was added. The resulting mixture was allowed to stir at rt for three hours, and then the silica was removed by filtration through Celite\(^\circ\). The filter cake was rinsed well with CH\(_2\)Cl\(_2\), and then the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO\(_2\), 15% EtOAc/hexanes) to give 371 mg (85%, two steps) of aldehyde 2.41 as a colorless oil. This material solidified after standing at \(-20\) °C overnight. TLC: \(R_f=0.42\) (SiO\(_2\), 1:4 EtOAc/hexanes); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\)
9.61 and 9.60 (2t, $J = 3.0$, 1H), 5.46 and 5.43 (2d, $J = 6.2$, 1H), 4.41 (dd, $J = 1.9$, 6.2, 1H), 4.15 and 3.81 (2d, $J = 3.8$, 1H), 3.52 and 3.44 (2t, $J = 9.8$, 1H), 3.14 – 3.02 (m, 2H), [3.02 and 2.99 (2d, $J = 2.8$), 2.80 and 2.78 (2d, $J = 3.0$) 1H total], 2.78 (app t, $J = 2.3$, 1H), 2.57 – 2.41 (m, 1H), 2.31 and 2.25 (2dd, $J = 7.4$, 15.1, 1H), 1.39 and 1.32 (2s, 9H), 0.76 (s, 9H), -0.01 and -0.05 (2s, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 199.49, 199.38, 153.51, 153.17, 140.62, 140.56, 118.93, 118.71, 80.95, 79.84, 64.05, 63.72, 61.57, 60.82, 53.43, 53.01, 52.73, 52.57, 50.56, 49.84, 45.19, 44.98, 28.96, 28.51, 28.46, 28.36, 25.65, 17.89, -4.55, -4.93, -4.96. HRMS (ESI-TOF) C$_{21}$H$_{35}$NO$_5$Si $m/z$ calcd for [M+H]$^+$ 410.2363; found 410.2356.

Aldehyde 2.43: To a solution of 2-allyl pyrrolidine 2.39 (491 mg, 1.60 mmol, 1.0 equiv.) in 7 mL acetonitrile was added Boc$_2$O (384 mg, 1.76 mmol, 1.1 equiv.), followed by DMAP (10 mg, 0.080 mmol, 0.05 equiv.). The solution was allowed to stir at rt overnight, then the solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO$_2$, 15% EtOAc/hexanes) to give 576 mg (80%) of mixed carbonic-carbamic anhydride 2.42 as a pale yellow oil. This material (1.27 mmol, 1.0 equiv.) was dissolved in 14.1 mL acetonitrile then 6.3 mL water was added, followed by NMO•H$_2$O (382 mg, 2.82 mmol, 2.2 equiv.) and OsO$_4$ (2.5 wt.% solution in t-BuOH, 710 µL, 0.0565 mmol, 0.045 equiv.). The resulting light brown solution was allowed to
stir at rt overnight before it was poured into a separatory funnel. The flask was rinsed with 30 mL EtOAc and the organic layer was washed once with 6 mL brine. The organic layer was dried with MgSO₄, filtered and the solvents were removed under reduced pressure to give 854 mg of an orange oil. This oil was dissolved in 14 mL of CH₂Cl₂ and NaIO₄/SiO₂ (0.68 mmol/g, 2.8 g, 1.90 mmol, 1.5 equiv.) was added. The resulting mixture was allowed to stir at rt for three hours, and then the silica was removed by filtration through Celite®. The filter cake was rinsed well with CH₂Cl₂, and then the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 15% EtOAc/hexanes) to give 547 mg (95%, two steps) of aldehyde 2.43 as a colorless oil. This material solidified after standing at –20 °C overnight. A single crystal suitable for X-ray crystallographic analysis was obtained from a Et₂O/hexanes diffusion crystallization. TLC: Rf=0.42 (SiO₂, 1:4 EtOAc/hexanes).
Allylic alcohol 2.50: A solution of TBS ether 2.40 (255 mg, 0.624 mmol, 1.0 equiv.) and p-TsOH•H₂O (131 mg, 0.687 mmol, 1.1 equiv.) in 3.12 mL DMSO was allowed to stir at rt for three days. The solution was diluted with Et₂O, poured into a separatory funnel and the organic layer washed once each with 1:1 water-saturated aqueous NaHCO₃, water, and brine. The organic layer was dried with MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 50% EtOAc/hexanes) to give 157 mg (86%) of allylic alcohol 2.50 as a colorless oil. TLC: Rf=0.36 (SiO₂, 1:1 EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 5.74 – 5.62 (m, 1H), 5.58 – 5.53 (m, 1H), 5.06 (d, J = 10.1, 1H), 5.05 – 4.98 (m, 1H), 4.45 – 4.35 (m, 1H), 4.14 (d, J = 3.8, 0.5H), 3.81 (d, J = 3.9, 0.5H), 3.52 (td, J = 1.1, 10.2, 0.5H), 3.44 (td, J = 1.3, 10.3, 0.5H), 3.20 (dd, J = 1.7, 3.4, 1H), 3.12 (tdd, J = 5.9, 7.6, 10.4, 1H), 2.65 (d, J = 7.7, 1H), 2.63 – 2.43 (m, 3H), 2.32 – 2.23 (m, 1H), 1.45 and 1.39 (2s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 153.89, 153.61, 141.55, 140.94, 133.92, 133.48, 119.46, 118.19, 118.14, 80.73, 79.71, 64.35, 63.83, 63.44, 63.17, 54.65, 54.07, 53.31, 53.21, 45.14, 44.94, 41.84, 40.51, 29.16, 28.66, 28.56; HRMS (ESI-TOF) C₁₆H₂₃NO₄ m/z calcd for [M+H]⁺ 294.1705; found 294.1701.
Enone 2.51: To a solution of TBS ether 2.40 (179 mg, 0.440 mmol, 1.0 equiv.) and p-TsOH•H₂O (84 mg, 0.440 mmol, 1.0 equiv.) in 2.2 mL DMSO was added IBX (616 mg, 2.20 mmol, 5.0 equiv.), and the resulting solution was allowed to stir at rt for three days, during which time a precipitate had formed. This mixture was diluted with Et₂O, poured into a separatory funnel and the organic layer washed once each with 1:1 water-saturated aqueous NaHCO₃, water, and brine. The organic layer was dried with MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 20 → 25% EtOAc/hexanes) to give 110 mg (86%) of enone 2.51 as a colorless oil. TLC: Rf=0.27 (SiO₂, 1:4 EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 5.85 – 5.79 (m, 1H), 5.59 – 5.47 (m, 1H), 5.15 – 5.05 (m, 2H), 4.57 (d, J = 4.1, 0.6H), 4.20 (d, J = 4.2, 0.4H), 3.74 (td, J = 1.6, 10.5, 0.4H), 3.64 (td, J = 1.6, 10.5, 0.6H), 3.46 – 3.38 (m, 1H), 3.36 (dd, J = 1.8, 4.0, 1H), 2.83 – 2.72 (m, 2H), 2.72 – 2.62 (m, 1H), 2.62 – 2.51 (m, 2H), 1.54 and 1.47 (2s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 195.02, 194.54, 159.93, 159.16, 153.71, 153.55, 131.24, 130.99, 121.01, 120.93, 118.56, 118.51, 81.52, 80.55, 65.36, 64.67, 54.04, 53.73, 53.68, 53.35, 46.16, 46.08, 42.34, 40.91, 29.26, 28.87, 28.76, 28.63; HRMS (ESI-TOF) C₁₆H₂₁NO₄ m/z calcd for [M+Na]+ 314.1368; found 314.1363.

Pyrroline 2.52: A solution of enone 2.51 (15.4 mg, 0.0529 mmol, 1.0 equiv.) in 530 µL t-BuOH was treated with t-BuOK (6 mg, 0.0529 mmol, 1.0 equiv.) and the solution
quickly took on a yellow color. The resulting yellow solution was allowed to stir at rt for 15 minutes before it was quenched with saturated aqueous NH₄Cl. The aqueous mixture was extracted three times with Et₂O, the combined organic extracts were dried with MgSO₄, filtered, and the solvent was removed under reduced pressure to give 15 mg (quant.) of pyrroline 2.52 as a pale yellow oil. TLC: Rf=0.59 (SiO₂, 1:2 EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 5.69 – 5.43 (m, 2H), 5.17 – 4.99 (m, 2H), 4.35 (d, J = 4.3, 0.5H), 4.27 – 4.08 (m, 1H), 4.06 (d, J = 4.2, 0.5H), 4.03 – 3.89 (m, 1H), 3.40 (d, J = 4.2, 1H), 3.38 – 3.17 and 3.12 – 3.03 (2m, 2H), 3.03 – 2.90 (m, 1H), 2.18 – 1.95 (m, 1H), 1.53 and 1.46 (2s, 9H).

Cyclic carbonate 2.53: A suspension of allylic alcohol 2.50 (173 mg, 0.589 mmol, 1.0 equiv.) and Cs₂CO₃ (1.92 g, 5.89 mmol, 10 equiv.) in 20 mL of acetonitrile was placed in a Parr vessel. The vessel was purged with CO₂ three times, and then put under 150 psi CO₂. The reaction was allowed to stir at rt for 24 hours, the purge and pressurization cycle was repeated, and then the reaction was allowed to stir at rt for a further 24 hours. The suspension was diluted with Et₂O, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 50% EtOAc/hexanes) to give 193 mg (97%) of cyclic carbonate 2.53 as a colorless oil that crystallized on standing at −20 °C, mp 119–122 °C. TLC: Rf=0.22 (SiO₂, 1:1 EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 5.78 – 5.70 (m, 1H), 5.63 (ddd, J = 8.4,
17.4, 33.6, 1H), 5.24 (dd, J = 4.2, 8.3, 1H), 5.06 (d, J = 15.7, 2H), 4.92 (d, J = 6.1, 1.6H),
4.61 (s, 0.4H), 3.66 (t, J = 10.4, 0.4H), 3.53 (td, J = 1.9, 10.5, 0.6H), 3.31 – 3.17 (m, 1H),
2.85 (dd, J = 7.5, 13.9, 1.6H), 2.68 (dtdd, J = 1.1, 2.6, 10.6, 14.5, 1H), 2.52 – 2.42 (m,
1H), 2.38 (s, 0.4H), 2.03 (dd, J = 7.4, 13.9, 0.6H), 1.97 (dd, J = 7.9, 13.8, 0.4H), 1.47 and
1.43 (2s, 9H); 13C NMR (126 MHz, CDCl3) δ 154.58, 153.98, 151.06, 149.41, 132.48,
132.09, 120.08, 119.79, 113.43, 81.72, 80.60, 75.58, 75.22, 71.85, 71.56, 71.49, 70.20,
66.58, 66.50, 45.74, 45.42, 42.79, 42.06, 29.67, 29.58, 28.66, 28.58; HRMS (ESI-TOF)
C17H23NO6 m/z calcd for [M+H]+ 338.1604; found 338.1598.

Diene 2.54: A solution of enone 2.51 (105 mg, 0.360 mmol, 1.0 equiv.) in 14 mL of
MeOH was allowed to cool to 0 °C before hydrazine (57 µL, 1.80 mmol, 5.0 equiv.) and
AcOH (720 µL) were added. The resulting clear solution was allowed to stir at 0 °C for
20 minutes, during which time the solution took on a yellow color, at rt for 90 minutes,
then at 65 °C overnight. The resulting yellow solution was allowed to cool to rt before
water and saturated aqueous NaHCO3 were added. The aqueous mixture was extracted
three times with EtOAc, then the combined organic extracts were washed with brine,
dried with MgSO4, filtered, and the solvent was removed under reduced pressure. The
residue was purified by flash chromatography (SiO2, 33 → 50% EtOAc/hexanes) to give
63 mg (63%) of diene 2.54 as a pale yellow oil. TLC: Rf=0.36 (SiO2, 1:2
EtOAc/hexanes); 1H NMR (400 MHz, CDCl3) δ 6.05 (dd, J = 5.2, 9.5, 1H), 6.00 – 5.85
(m, 1H), 5.81 (dd, J = 3.8, 8.0, 1H), 5.77 – 5.64 (m, 1H), 5.15 – 4.93 (m, 2H), 4.50 and 4.21 (2d, J = 5.7, 1H), 3.76 and 3.63 (2td, J = 2.3, 10.3, 1H), 3.47 – 3.34 (m, 1H), 2.70 – 2.49 (m, 2H), 2.49 – 2.26 (m, 2H), 1.52 and 1.46 (2s, 9H).

E.3 Experimental for Chapter 3

\[ \text{Boc-} \beta \text{-alanine (3.7)} \]

\[ \text{Boc-} \beta \text{-Keto ester 3.8: Under a blanket of inert gas, solid } N\text{-Boc-} \beta \text{-alanine (3.7)} (24.31 g, 128.5 mmol, 1.0 equiv.) was added in one portion to a suspension of 1,1'-carbonyldiimidazole (25 g, 154.2 mmol, 1.2 equiv.) in 350 mL THF in a 1 L round bottom flask via a powder funnel, which was rinsed with 25 mL THF. The resulting suspension was allowed to stir under a stream of inert gas for one hour, during which time carbon dioxide evolved and the reaction mixture became a homogeneous, yellow solution, then a septum and argon balloon were placed on the flask. The yellow reaction solution was allowed to stir three hours further before a mixture of MgCl\textsubscript{2} (325 mesh, 12.23 g, 128.5 mmol, 1.0 equiv.) and methyl potassium malonate (40.13 g, 257.0 mmol, 2.0 equiv.) solids were added under a blanket of inert gas in one portion via a powder funnel, which was rinsed with 25 mL THF. A septum and argon balloon were placed on the flask and the suspension was allowed to stir vigorously overnight (slow gas evolution) before 250 mL water and 150 mL 1 M HCl were added. The resulting yellow, biphasic solution (aqueous layer pH approx. 7) was poured into a 2 L separatory funnel, followed by 1 L EtOAc, using some to rinse the reaction flask. The aqueous layer was} \]
removed and the organic layer was washed with 150 mL 1 M HCl, 150 mL brine, dried with MgSO$_4$, filtered, and concentrated under reduced pressure to give, after azeotropic removal of the remaining EtOAc with three 200 mL portions of hexanes, 33 g of β-keto ester 3.8 as a faint yellow liquid, which was taken on without further purification. TLC: $R_f$=0.24 (SiO$_2$, 1:2 EtOAc/hexanes); IR (film) 3397, 2978, 1748, 1714, 1520, 1439, 1367, 1324, 1252, 1170 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 5.05 (br s, 1H), 3.62 (s, 3H), 3.38 (s, 2H), 3.26 (q, $J=5.9$, 2H), 2.68 (t, $J=5.9$, 2H), 1.31 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 202.0, 167.1, 155.6, 79.0, 52.1, 48.8, 42.8, 34.8, 28.1; HRMS (ESI-TOF) C$_{11}$H$_{19}$NO$_5$ m/z calcd for [M+Na]$^+$ 268.1155; found 268.1151.

3-carboxybenzenesulfonyl azide: 3-(chlorosulfonyl)benzoic acid (50 g, 226 mmol, 1.0 equiv.) was added in one portion to 660 mL acetone in a 2 L round bottom flask via a powder funnel, which was rinsed with 50 mL acetone. To the resulting light brown solution was added a solution of sodium azide (18.4 g, 284 mmol, 1.25 equiv.) in 120 mL water, followed by approximately 20 to 30 mL water to make the reaction mixture homogeneous. The light brown solution was allowed to stir for two hours before most of the acetone was removed under reduced pressure leaving a brown residue. Approximately 1500 mL of water were added to the flask, followed by a few mL’s of concentrated HCl (solution pH < 2). The precipitate was collected in a 150 mL sintered glass funnel, rinsed well with water and three portions of hexanes in the funnel, and then dried by pulling air through the funnel for one hour, followed by drying under high vacuum overnight to give 41 g (80%) of 3-carboxybenzenesulfonyl azide as an off-white,
powdery solid. IR (film) 3100-2200, 2135, 1913, 1734, 1265, 1177 cm⁻¹; ¹H NMR (500 MHz, CDCl₃/DMSO-d₆) δ 11.41 (br s, 1H), 8.58 (t, J = 1.6, 1H), 8.35 (ddd, J = 1.3, 1.5, 7.8, 1H), 8.07 (ddd, J = 7.9, 2.0, 1.2, 1H), 7.67 (t, J = 7.9, 1H); ¹³C NMR (126 MHz, CDCl₃/DMSO-d₆) δ 166.1, 138.7, 135.6, 132.9, 130.8, 129.8, 128.6; HRMS (ESI-TOF) C₇H₅N₃O₄S m/z calcd for [M-H]- 225.9928; found 225.9926.

α-Diazo-β-keto ester 3.9: Under a blanket of inert gas, 3-carboxybenzenesulfonyl azide (32.11 g, 141.3 mmol, 1.1 equiv.) was added in one portion to a solution of β-keto ester 3.8 (33 g, 128.5 mmol, 1.0 equiv.) in 450 mL acetonitrile in a 1 L round bottom flask via a powder funnel, which was rinsed with 50 mL acetonitrile. Triethylamine (54 mL, 385.4 mmol, 3.0 equiv.) was added dropwise via a pressure equalizing addition funnel over 30 minutes, and the resulting yellow-orange solution was allowed to stir for one hour before the solvent was removed under reduced pressure. To the foamy, yellow-orange residue was added a stirbar and 800 mL 1:1 Et₂O/water. After allowing the mixture to stir well for several minutes, the resulting biphasic solution was poured into a 2 L separatory funnel, and then the flask was rinsed with 500 mL 4:1 Et₂O/water and 400 mL Et₂O. The aqueous layer was removed and the organic layer was washed with 300 mL 2:1 saturated NaHCO₃ solution/water and 300 mL 2:1 saturated NH₄Cl solution/water. The organic layer was dried with MgSO₄, filtered, and concentrated under reduced pressure to give 35 g of α-diazo-β-keto ester 3.9 as a viscous yellow liquid that was taken on without further purification. TLC: Rf=0.31 (SiO₂, 1:2 EtOAc/hexanes); IR (film) 3390, 2978, 2139,
1715, 1652, 1514, 1438 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.03 (br s, 1H), 3.77 (s, 3H), 3.39 (s, 2H), 3.37 (q, J = 5.9, 2H), 2.97 (t, J = 5.9, 2H), 1.35 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 191.5, 161.4, 155.6, 78.9, 76.0, 52.1, 40.6, 35.3, 28.2; HRMS (ESI-TOF) C₁₁H₁₇N₃O₅ m/z calcd for [M+Na]⁺ 294.1060; found 294.1056.

\[ \text{N-Boc-3-keto proline methyl ester 3.10} \]

Rh₂(OAc)₄ (284 mg, 0.642 mmol, 0.005 equiv.) was added to a pale yellow solution of α-diazo-β-keto ester 3.9 (34.9 g, 128.5 mmol, 1.0 equiv.) in 1300 mL of toluene in a 2 L round bottom flask, which was then fitted with a reflux condenser and placed into a preheated 100 °C oil bath under a stream of inert gas (no septum). The green mixture was allowed to heat at 85–90 °C until nitrogen gas evolution ceased (approximately 30 minutes) and then was allowed to cool to rt. The solvent was removed under reduced pressure, then under high vacuum, and the green residue was then treated with 500 mL hexanes and the solvent was again removed under reduced pressure and high vacuum. To remove the Rh₂(OAc)₄, the green residue was diluted with Et₂O and filtered through Celite®, rinsing well with Et₂O, and the solvent was evaporated under reduced pressure to give 29 g (93%) of N-Boc-3-keto proline methyl ester 3.10 as pale yellow oil, which solidified when azeotroped with hexanes or placed in the freezer. This material is sufficiently pure to be taken on without any further purification, but can be purified by stirring the crude product with 1:1 Et₂O/hexanes, collecting the solid by filtration, evaporation of the filtrate, and repeating the sequence. An analytical sample was obtained by flash column chromatographic purification (SiO₂,
1:3 EtOAc/hexanes) to give a colorless powder, mp 55–56 °C. TLC: $R_f$=0.32 (SiO$_2$, 1:2 EtOAc/hexanes); IR (film) 2977, 1775, 1746, 1707, 1395, 1239, 1163 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 4.55 and 4.47 (2 s, 1H total), 3.93 – 3.75 (m, 5H), 2.67 (t, $J$ = 7.6, 2H), 1.47 and 1.40 (2 s, 9H total); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 204.6, 166.7, 153.7, 81.1, 65.6, 65.2, 52.9, 42.1, 41.5, 37.1, 36.4, 28.1; HRMS (ESI-TOF) C$_{11}$H$_{17}$NO$_5$ m/z calcd for [M+Na]$^+$ 266.0999; found 266.0990.

Allyl keto proline 3.11: A mixture of [Pd(π-allyl)Cl]$_2$ (12 mg, 0.0305mmol, 0.01 equiv.) and rac-BINAP (20 mg, 0.0320 mmol, 0.0105 equiv.) in 8 mL toluene was allowed to stir at rt for 15 minutes, then allyl acetate (495 µL, 4.57 mmol, 1.5 equiv.) was added and the resulting mixture was allowed to stir at rt for 15 minutes. The resulting solution was allowed to cool to –30 °C, then a solution of N-Boc-3-keto proline methyl ester 3.10 (741 mg, 3.05 mmol, 1.0 equiv.) in 8 mL toluene was added in one portion. After the resulting mixture was allowed to stir at –30 °C for 5-10 minutes, $t$-BuOK (410 mg, 3.66 mmol, 1.2 equiv.) was added and the resulting yellow-green mixture was allowed to stir at –30 °C overnight, after which time saturated NH$_4$Cl solution was added and the mixture was allowed to warm to rt. The biphasic solution was poured into a separatory funnel, Et$_2$O was added and the organic layer was removed. The aqueous phase was extracted four times with Et$_2$O, the combined organic extracts dried with MgSO$_4$, and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (SiO$_2$, 1:4 → 1:3 EtOAc/hexanes) to give 641 mg (74%) of allyl β-keto ester 3.11 as a
colorless oil that crystallized on standing at –20 °C. TLC: $R_f$=0.49 (SiO$_2$, 1:1 EtOAc/hexanes); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.66 – 5.41 (m, 1H), 5.16 – 4.98 (m, 2H), 3.93 – 3.74 (m, 1H), 3.74 – 3.66 (m, 3H), 3.66 – 3.47 (m, 1H), 3.27 – 2.71 (m, 2H), 2.70 – 2.57 (m, 1H), 2.46 (ddd, $J$ = 6.4, 9.4, 18.9, 1H), 1.51 – 1.37 (m, 9H).

Primary alcohol 3.13: A solution of $i$-Pr$_2$NH (745 µL, 5.29 mmol, 1.5 equiv.) in 10 mL THF was allowed to cool to 0 °C, then $n$-BuLi (1.6 M in hexanes, 3.3 mL, 5.29 mmol, 1.5 equiv.) was added dropwise over 15 minutes by syringe pump. The resulting solution was allowed to stir at 0 °C for 30 minutes, then was allowed to cool to –78 °C before a solution of β-keto ester 3.11 (1 g, 3.53 mmol, 1.0 equiv.) in 2.5 mL THF was added dropwise over 15 minutes by syringe pump, followed by a rinse with 1 mL THF to ensure complete addition of 3.11. The resulting pale yellow solution was allowed to stir at –78 °C for one hour, during which time the solution became a pale yellow suspension. LAH (1.0 M in Et$_2$O, 5.3 mL, 5.29 mmol, 1.5 equiv.) was then added dropwise over 15 minutes by syringe pump, and the resulting pale yellow suspension was allowed to stir at –78 °C for 45 minutes before the flask was placed in an ice bath. After 10 minutes in the ice bath, the cold reaction mixture was quenched by the slow addition of 3 mL EtOAc, followed by 200 µL water, 400 µL 10% aqueous NaOH, and 600 µL water. The reaction mixture was removed from the ice bath and allowed to warm to rt over 30 minutes, then MgSO$_4$ was added. The resulting slurry was allowed to stir well at rt for 30 minutes, then it was filtered, and the filter cake was rinsed well with EtOAc. The filtrate was
concentrated under reduced pressure and the residue was purified by flash chromatography (SiO₂, 25 → 30 → 35 → 40 → 45% EtOAc/hexanes) to give 740 mg (82%) of primary alcohol 3.13 as a pale yellow oil. TLC: Rf=0.41 (SiO₂, 2:1:1 Et₂O/hexanes/CH₂Cl₂).

Phosphonoacetate 3.14: A solution of primary alcohol 3.13 (740 mg, 2.90 mmol, 1.0 equiv.) and DMAP (35 mg, 0.290 mmol, 0.1 equiv.) in 17 mL CH₂Cl₂ was allowed to cool to 0 °C, and then diethylphosphonoacetic acid (700 μL, 4.35 mmol, 1.5 equiv.) was added, followed by EDC (835 mg, 4.35 mmol, 1.5 equiv.). The resulting colorless solution was allowed to stir at 0 °C for 15 minutes, then at rt for 45 minutes before the solvent was removed under reduced pressure. The residue was diluted with 30 mL Et₂O and 20 mL 2% HCl, and then poured into a separatory funnel, rinsing the flask with 50-60 mL Et₂O. The aqueous layer was removed and the organic layer was washed with saturated aqueous NaHCO₃, dried with MgSO₄, filtered, and concentrated under reduced pressure to give 1.24 g (quant.) of phosphonoacetate 3.14 as a colorless oil. This material was taken on without further purification. TLC: Rf=0.19 (SiO₂, 2:1:1 Et₂O/hexanes/CH₂Cl₂).
Lactone 3.15: A solution of phosphonoacetate 3.14 (1.24 g, 2.9 mmol, 1.0 equiv.) in 29 mL MeCN was treated with LiCl (246 mg, 5.8 mmol, 2.0 equiv.), followed by i-Pr_{2}NEt (1 mL, 5.8 mmol, 2.0 equiv.) dropwise over a few minutes. The resulting mixture was allowed to stir at rt overnight, then the solvent was removed under reduced pressure. The residue was diluted with 30 mL Et_{2}O and 20 mL water, and then poured into a separatory funnel, rinsing the flask with 50-60 mL Et_{2}O. The aqueous layer was removed and the organic layer was washed with 2% HCl, dried with MgSO_{4}, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_{2}, 25 → 30 → 35 → 40% EtOAc/hexanes) to give 755 mg (93%, two steps) of lactone 3.15 as a pale yellow oil. TLC: R_{f}=0.59 (SiO_{2}, 2:1:1 Et_{2}O/hexanes/CH_{2}Cl_{2}).

Propargyl alcohol 3.16: A solution TBS propargyl ether (380 mg, 2.17 mmol, 2.2 equiv.) in 1.7 mL toluene was allowed to cool to −78 °C before NaHMDS (0.6 M in toluene, 3.30 mL, 1.98 mmol, 2.0 equiv.) was added dropwise over five minutes. The resulting pale yellow solution was allowed to stir at −78 °C for 30 minutes, then a solution of β-keto ester 3.11 (280 mg, 0.988 mmol, 1.0 equiv.) in 5 mL toluene was added dropwise over 15 minutes via syringe pump. The resulting pale yellow solution was allowed to slowly warm to −40 °C over 90 minutes, after which time saturated NH_{4}Cl solution was added and the mixture was allowed to warm to rt. The biphasic solution was poured into a separatory funnel, EtOAc was added and the organic layer was removed. The aqueous
phase was extracted four times with EtOAc, the combined organic extracts dried with MgSO₄, and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (SiO₂, 1:4 → 1:3 EtOAc/hexanes) to give 283 mg (63%) of propargyl alcohol 3.16 as a pale yellow oil that crystallized on standing at –20 °C. TLC: Rf=0.43 (SiO₂, 1:2 EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 6.36 – 6.09 (m, 1H), 5.28 – 5.04 (m, 2H), 4.27 (s, 2H), 3.82 and 3.70 (2ddd, J = 2.7, 8.5, 10.9, 1H), 3.71 and 3.70 (2s, 3H), 3.57 – 3.47 (m, 1H), 3.32 and 3.18 (2dd, J = 5.0, 15.1, 1H), 2.96 and 2.91 (2s, 1H), 2.80 and 2.73 (2dd, J = 9.2, 15.1, 1H), 2.51 – 2.30 (m, 1H), 2.05 (ddd, J = 3.0, 6.5, 9.0, 1H), 1.42 and 1.39 (2s, 9H), 0.88 (s, 9H), 0.08 (s, 6H).

cis-Alllylic alcohol 3.17: A solution of propargyl alcohol 3.16 (100 mg, 0.220 mmol, 1.0 equiv.) in 10 mL EtOAc was treated with Lindlar’s catalyst (5% Pd/CaCO₃/Pb, 36 mg) and the resulting mixture was allowed to stir well under one atmosphere of hydrogen gas for two hours. Argon was then bubbled through the mixture to purge the hydrogen gas. The resulting mixture was filtered through Celite®, the filter cake was rinsed well with EtOAc, and the solvent was evaporated to give 102 mg (quant.) of cis-allylic alcohol 3.17 as a colorless oil. TLC: Rf=0.43 (SiO₂, 1:2 EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 6.12 – 5.75 (m, 1H), 5.57 (dt, J = 5.3, 12.6, 1H), 5.39 (tt, J = 1.5, 12.6, 1H), 5.18 – 4.92 (m, 2H), 4.39 – 4.22 (m, 2H), 3.80 – 3.36 (m, 6H), 3.03 – 2.76 (m, 1H), 2.25 – 1.80 (m, 3H), 1.41 and 1.38 (2s, 9H), 0.90 and 0.89 (2s, 9H), 0.09 and 0.08 (2s, 6H).
Enone 3.18: To a vial containing 220 mg of flame-dried, powdered 4Å molecular sieves was added cis-allylic alcohol 3.17 (100 mg, 0.219 mmol, 1.0 equiv.) and finely ground PCC (237 mg, 1.10 mmol, 5.0 equiv.). The solid mixture was diluted with 1.1 mL CH₂Cl₂, and the initially orange mixture quickly took on a brown color. The resulting brown mixture was allowed to stir at rt overnight before it was diluted with Et₂O. This mixture was filtered through Celite®, the filter cake was rinsed well with Et₂O, and the solvents were evaporated. The residue was purified by flash chromatography (SiO₂, 10 → 20% EtOAc/hexanes) to give 46 mg (45%, two steps) of enone 3.18 as a pale yellow oil. TLC: R_f=0.48 (SiO₂, 1:2 EtOAc/hexanes).

Propargyl keto proline 3.29: A suspension of sodium hydride (60% dispersion in mineral oil, 181 mg, 4.52 mmol, 1.1 equiv.) in 16 mL THF and 2 mL DMF was cooled to 0 ºC, then a solution of N-Boc-3-keto proline methyl ester 3.10 (1 g, 4.11 mmol, 1.0 equiv.) in 2 mL THF was added over 5 to 10 minutes, followed by a rinse with 1 mL THF. The resulting yellow suspension was allowed to stir at 0 ºC for 30 minutes before removing the flask from the ice bath. Propargyl bromide (80 wt.% in toluene, 440 µL, 4.93 mmol,
1.2 equiv.) was then added dropwise over five minutes, and the resulting orange-red suspension was allowed to stir at rt for 30 minutes before 5 mL saturated NH₄Cl solution and 10 mL water were added. The biphasic solution was poured into a 250 mL separatory funnel containing 100 mL water, the organic layer was removed, and the aqueous phase was extracted 4 x 25 mL Et₂O. The combined organic extracts were dried with MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 1:6:1 → 1:4:1 → 1:2:1 Et₂O/hexanes/CH₂Cl₂) to give 820 mg (71%) of propargyl keto proline 3.29 as small, colorless beads, mp 84–86 °C. TLC: Rᶠ=0.40 (SiO₂, 1:2 EtOAc/hexanes); IR 3289, 2978, 2360, 1774, 1743, 1706, 1386, 1255, 1147 cm⁻¹;¹H NMR (500 MHz, CDCl₃) δ 3.97 – 3.89 and 3.89 – 3.77 (2m, 2H total), 3.71 (s, 3H), 3.35 and 3.11 (dd and qd, J = 17.0, 2.6, 2H total), 2.86 – 2.64 (m, 2H), 1.97 and 1.94 (2t, J = 2.6, 1H total), 1.49 and 1.43 (2s, 9H total);¹³C NMR (126 MHz, CDCl₃) δ 206.9, 206.5, 167.4, 154.0, 153.4, 81.6, 81.1, 78.9, 78.2, 71.9, 71.6, 71.5, 70.9, 53.1, 42.8, 42.2, 36.5, 35.7, 28.3, 28.2; HRMS (ESI-TOF) C₁₄H₁₉N₂O₅ m/z calcd for [M+Na]⁺ 304.1155; found 304.1155.

Homoallylic alcohol 3.31: To a cooled a solution of propargyl keto proline 3.29 (1 g, 3.55 mmol, 1.0 equiv.) in 10.5 mL THF to −78 °C was added 2-methylallylmagnesium chloride (0.5 M in THF, 7.11 mL, 3.55 mmol, 1.0 equiv.) dropwise over 15 to 20 minutes via syringe pump. The resulting colorless solution was allowed to slowly warm to between −10 °C and 0 °C over 90 minutes, after which time 30 mL saturated NH₄Cl
solution was added and the mixture was allowed to warm to rt. The biphasic solution was poured into a 125 mL separatory funnel, 10 mL Et₂O was added and the organic layer was removed. The aqueous phase was extracted 4 x 15 mL Et₂O, the combined organic extracts dried with MgSO₄, and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (SiO₂, 1:4:1 → 1:3:1 → 1:2:1 → 1:1:1 Et₂O/hexanes/CH₂Cl₂) to give 1.09 g (91%) of homoallylic alcohol 3.31 as a colorless solid, mp 77–79 °C. TLC: Rf = 0.45 (SiO₂, 1:2 EtOAc/hexanes); IR (film) 3462, 3308, 2977, 2250, 2122, 1739, 1694, 1394, 1258, 1172 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 4.90 (s, 1H), 4.74 (s, 1H), 3.82 – 3.72 and 3.72 – 3.58 (2m, 4H total), 3.67 (s, 3H), 3.56 – 3.39 (m, 1H), [3.16 and 3.04 (2dd, J = 17.0, 2.3), 3.02 and 2.95 (2dd, J = 17.0, 2.6), 2H total], 2.72 (d, J = 15.5, 1H), 2.56 and 2.46 (2d, J = 13.4, 1H total), 2.14 – 2.02 (m, 2H), 1.99 – 1.91 (m, 1H), 1.88 (d, J = 13.7, 1H), 1.79 (s, 3H), 1.40 and 1.37 (2s, 9H total); ¹³C NMR (126 MHz, CDCl₃) δ 172.5, 172.3, 154.2, 153.4, 141.6, 141.4, 116.3, 116.1, 84.9, 83.9, 82.1, 81.6, 80.8, 80.2, 73.7, 73.5, 71.2, 71.0, 52.5, 45.9, 45.6, 44.2, 36.1, 35.5, 28.6, 28.4; HRMS (ESI-TOF) C₁₈H₂₇NO₅ m/z calcd for [M+Na]⁺ 360.1781; found 360.1778.

Epoxide 3.32: To a solution of homoallylic alcohol 3.31 (1 g, 2.96 mmol, 1.0 equiv.) in 30 mL CH₂Cl₂ was added VO(acac)₂ (40 mg, 0.148 mmol, 0.05 equiv.), and the resulting green solution was cooled to 0 °C before t-BuOOH (5.5 M in decane, 1.62 mL, 8.89 mmol, 3.0 equiv.) was added dropwise. After allowing the reddish-purple solution to stir at 0 °C for 15 minutes, the solution was allowed to warm to rt and stir at that temperature
overnight. The resulting yellow-orange solution was poured into a 125 mL separatory funnel, the flask was rinsed with 30 mL of CH$_2$Cl$_2$, 20 mL brine was added, the pale yellow organic layer was removed, and the aqueous layer was extracted 2 x 10 mL CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO$_2$, 1:4:1 → 1:3:1 → 1:2:1 → 1:1:1 Et$_2$O/hexanes/CH$_2$Cl$_2$) to give 832 mg (80%) of epoxide 3.32 as a colorless oil. When this oil was treated with a small amount of Et$_2$O, a colorless solid formed, which gave way to a colorless foam upon evaporation of the solvent. By scratching the sides of the flask, epoxide 3.32 could be isolated as a colorless powder, mp 83–88 °C. TLC: $R_f$=0.38 (SiO$_2$, 1:1 EtOAc/hexanes); IR (film) 3461, 3307, 2977, 1737, 1696, 1394, 1256, 1172 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 3.89 – 3.82 and 3.76 – 3.64 and 3.62 – 3.42 (3m, 6H total), 3.25 – 2.91 (m, 2H), 2.76 – 2.54 (m, 2H), 2.34 – 1.95 (m, 4H), 1.48 – 1.28 (m, 12H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 172.4, 154.2, 153.4, 85.4, 84.3, 81.9, 81.4, 80.9, 80.3, 73.9, 73.7, 71.1, 70.8, 56.0, 55.6, 52.6, 46.1, 45.8, 41.7, 36.5, 35.9, 28.6, 28.4; HRMS (ESI-TOF) C$_{18}$H$_{27}$NO$_6$ m/z calcd for [M+Na]$^+$ 376.1730; found 376.1716.

Vinylogous carbonate 3.33: To a three-neck 250 mL round bottom flask containing 80 mL of anhydrous methanol was added freshly sublimed yellow needles of 1,4-benzoquinone (475 mg, 4.39 mmol, 1.1 equiv.), followed by (MeCN)$_2$PdCl$_2$ (52 mg,
0.199 mmol, 0.05 equiv.) under a stream of inert gas delivered via a three-way adapter attached to the central neck of the flask. A balloon of carbon monoxide was attached to the three-way adapter, and then the flask was evacuated and refilled with carbon monoxide three times. While maintaining the reaction under 1 atm of carbon monoxide, the orange solution was allowed to cool to 0 °C before a solution of epoxide 3.32 (1.41 g, 3.99 mmol, 1.0 equiv.) in 36 mL methanol was added dropwise over several minutes, followed by a rinse with 4 mL methanol. The resulting solution was allowed to stir at 0 °C for 30 minutes before pouring the orange solution into a 2 L separatory funnel. The flask was rinsed 3 x 200 mL CH₂Cl₂, and then 800 mL 5% NaOH were added. The organic layer was removed, and the brown/black aqueous layer was extracted 3 x 100 mL CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered, and the solvent was removed under reduced pressure to give 1.48 g (90%) of vinylogous carbonate 3.33 as an off-white foam. This material was taken on without further purification as it partially decomposed when subjected to purification by flash chromatography on silica gel. However, an analytical sample was obtained by flash column chromatographic purification (SiO₂, 1:1 Et₂O/hexanes → 1:1:1 Et₂O/hexanes/CH₂Cl₂) to give vinylogous carbonate 3.33 as a colorless foam. TLC: Rf=0.42 (SiO₂, 1:1 EtOAc/hexanes); IR (film) 3482, 2980, 2953, 1747, 1699, 1652, 1437, 1394 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.32 (m, 1H), 3.96 – 3.69 (m, 3H), 3.71 (s, 3H), 3.64 (s, 3H), 3.43 – 3.22 (m, 2H), 2.71 (d, J = 4.6, 1H), 2.61 (d, J = 4.6, 1H), 2.41 – 1.97 (m, 2H), 1.49 – 1.36 (m, 12H); ¹³C NMR (126 MHz, CDCl₃) δ 172.6, 172.4, 169.7, 168.4, 168.2, 153.5, 152.6, 98.1, 97.0, 92.3, 92.0, 81.5, 81.0, 78.7, 76.5, 54.8, 53.5, 53.2, 51.1, 45.6, 45.4, 41.1, 40.8, 39.4, 38.8,
Ketone **3.25**: A solution of crude vinylogous carbonate **3.33** (276 mg, 0.671 mmol, 1.0 equiv.) in 6.7 mL THF and 670 µL water was cooled to 0 °C, then NaIO₄ (86 mg, 0.402 mmol, 0.6 equiv.) and H₂IO₆ (184 mg, 0.805 mmol, 1.2 equiv.) were added. The resulting solution was allowed to stir at 0 °C for 15 minutes, then at rt overnight, during which time sodium iodate precipitated. The resulting suspension was poured into a 60 mL separatory funnel, followed by 3.5 mL saturated aqueous NaHCO₃ solution, 7 mL water, and 10 mL Et₂O. The organic layer was removed and the aqueous layer was extracted 3 x 10 mL Et₂O. The organic extracts were dried over MgSO₄, filtered, and the solvent was removed under reduced pressure to give 270 mg of an off-white foam. This material was taken on without further purification as it significantly decomposed when subjected to purification by flash chromatography on silica gel. However, an analytical sample was obtained by flash column chromatographic purification (SiO₂, 1:1:1 → 2:1:1 Et₂O/hexanes/CH₂Cl₂ → Et₂O) to give ketone **3.25** as a colorless foam. TLC: *R*ᵣ=0.39 (SiO₂, 1:1 EtOAc/hexanes); IR (film) 3472, 2979, 2954, 2901, 2254, 1780-1650 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 5.18 (m, 1H), 3.89 – 3.53 (m, 6H), 3.50 (s, 3H), 3.24 – 3.11 (m, 1H), 2.78 and 2.74 (2d, *J* = 14.2 and 14.9, 1H total), 2.36 (dd, *J* = 13.9, 5.9, 1H), 2.14 and 2.13 (2d, *J* = 15.1 and 15.3, 1H total), 2.10 – 1.97 (m, 4H), 1.28 and 1.26 (2s, 9H
total); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 203.3, 203.0, 171.9, 169.1, 167.7, 153.0, 152.0, 96.7, 95.6, 91.8, 91.5, 80.9, 80.4, 75.5, 75.3, 52.8, 50.5, 45.9, 45.8, 45.0, 44.7, 39.2, 38.5, 32.7, 32.1, 31.5, 27.9; HRMS (ESI-TOF) C$_{19}$H$_{27}$NO$_8$ m/z calcd for [M+Na]$^+$ 420.1629; found 420.1622.

Bicyclic $\beta$-keto ester 3.27: Bu$_4$NOAc (405 mg, 1.34 mmol, 2.0 equiv.) was added to a solution of crude ketone 3.25 (270 mg, 0.671 mmol, 1.0 equiv.) in 13 mL THF at 0 °C, and the resulting yellow suspension was allowed to stir at rt for 30 minutes before removing most of the solvent under reduced pressure. To the residue was added 13 mL water, 2.6 mL 1 M NaOH, and 3 mL hexanes. The resulting biphasic solution was poured into a 30 mL separatory funnel, the organic layer was removed and the aqueous layer was washed 3 x 3 mL hexanes. To the aqueous layer was then added 10% HCl until the solution was acidic, and the aqueous layer was then extracted 5 x 15 mL Et$_2$O. The combined Et$_2$O extracts were dried over MgSO$_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO$_2$, 30 → 40 → 50 → 60 → 70% Et$_2$O/hexanes, all eluant containing 1% AcOH) to give 171 mg (64%, two steps) of bicyclic $\beta$-keto ester 3.27 as a colorless oil. TLC: $R_f$=0.34 (SiO$_2$, 1:1 EtOAc/hexanes + 1% AcOH); IR (film) 2978, 2954, 1749, 1701, 1663, 1618, 1448, 1393 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 10.76 (br s, 1H), 3.83 – 3.63 (m, 9H), 3.22 – 3.13 (m, 2H), 2.98 (d, $J = 18.8$, 0.4H), 2.82 (d, $J = 18.5$, 0.6H), 2.78 and 2.77 (2d,
J = 15.9 and 15.8, 1.5H total), 2.53 and 2.49 (2d, J = 15.8 and 15.9, 1H total), 2.41 – 2.32 (m, 1H), 2.13 – 1.96 (m, 5H), 1.41 and 1.38 (2s, 9H total); 13C NMR (126 MHz, CDCl3) δ 205.4, 205.2, 176.6, 175.8, 171.4, 168.9, 168.7, 153.4, 152.5, 99.3, 80.6, 80.2, 73.8, 73.6, 60.0, 58.7, 52.4, 52.3, 51.1, 51.0, 47.6, 47.5, 45.6, 45.4, 41.5, 40.4, 33.1, 32.6, 31.4, 28.2;

HRMS (ESI-TOF) C19H27NO8 m/z calcd for [M+H]+ 398.1809; found 398.1799.

Tricycle 3.34: A solution of β-keto ester 3.27 (100 mg, 0.252 mmol, 1.0 equiv.) in 5 mL THF was cooled to –78 °C, then NaHMDS (0.6 M in toluene, 1.26 mL, 0.755 mmol, 3.0 equiv.) was added dropwise. The resulting yellow solution was allowed to stir at –78 °C for 15 minutes, then at rt for 90 minutes. At rt, 3 mL 1 M NaHSO4 were slowly added to the yellow-orange suspension, the organic layer was removed and the aqueous layer (pH < 2) was extracted 4 x 1 mL EtOAc. The combined organic extracts were washed 3 x 1 mL brine, dried over Na2SO4, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO2, 30 → 40 → 50 → 60 → 70% Et2O/hexanes, all eluant containing 1% AcOH) to give, after azeotropic removal of AcOH with three portions of hexanes, 77 mg (84%) of tricycle 3.34 as a colorless powder, mp 135–139 °C. TLC: Rf=0.34 (SiO2, 1:1 EtOAc/hexanes + 1% AcOH); IR (film) 2980, 2716, 2360, 2341, 1772, 1734, 1717, 1661, 1447, 1406 cm⁻¹; ¹H NMR (500 MHz, CDCl3) δ 11.41 (s, 1H), 10.65 (br s, 1H), 5.38 (s, 1H), 3.79 (s, 3H), 3.65 (d, J = 18.7, 1H), 3.46 (dd, J = 10.7, 8.3, 1H), 3.19 (ddd, J = 12.2, 10.7, 6.3, 1H), 2.96 and 2.93
(2d, \(J = 18.7\) and 16.5, 2H total), 2.41 (dd, \(J = 13.0, 6.2, 1H\)), 2.37 (d, \(J = 16.5, 1H\)), 1.82 (dt, \(J = 12.7, 12.6, 8.3, 1H\)), 1.47 (s, 9H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 196.1, 173.0, 172.7, 169.0, 158.5, 103.5, 103.3, 83.6, 67.7, 56.2, 51.6, 47.0, 44.6, 38.7, 31.0, 28.2; HRMS (ESI-TOF) \(\text{C}_{18}\text{H}_{23}\text{NO}_{7}\) \(m/z\) calcld for [M+H]\(^+\) 366.1547; found 366.1533.

Mono-\textit{tert}-butyl malonate: Under a blanket of inert gas, a solution of Meldrum’s acid (50 g, 347 mmol, 1.0 equiv.) in 100 mL \(t\)-BuOH was allowed to heat at reflux overnight. The solution was concentrated under reduced pressure to give 55 g (quant.) of mono-\textit{tert}-butyl malonate as a colorless liquid.

\textit{tert}-Butyl \(\beta\)-keto ester: Under a blanket of inert gas, solid \(N\text{-Boc}\)-\(\beta\)-alanine (3.7) (17.37 g, 91.8 mmol, 1.0 equiv.) was added in one portion to a suspension of 1,1’-carbonyldiimidazole (17.86 g, 110 mmol, 1.2 equiv.) in 250 mL THF in a 1 L round bottom flask via a powder funnel, which was rinsed with 25 mL THF. The resulting suspension was allowed to stir under a stream of inert gas for one hour, during which time carbon dioxide evolved and the reaction mixture became a homogeneous, yellow solution, then a septum and argon balloon were placed on the flask. The yellow reaction solution was allowed to stir three hours further before MgCl\(_2\) (325 mesh, 10.5 g, 110 mmol, 1.2 equiv.) was added, followed by a solution of mono-\textit{tert}-butyl malonate (17.7
g, 110 mmol, 1.2 equiv.) in 25 mL THF. A septum and argon balloon were placed on the flask and the suspension was allowed to stir vigorously overnight (slow gas evolution) before 200 mL water and 100 mL 1 M HCl were added. The resulting yellow, biphasic solution (aqueous layer pH approx. 7) was poured into a 2 L separatory funnel, followed by 750 mL EtOAc, using some to rinse the reaction flask. The aqueous layer was removed and the organic layer was washed with 100 mL 1 M HCl, 100 mL brine, dried with MgSO\(_4\), filtered, and concentrated under reduced pressure to give, after azeotropic removal of the remaining EtOAc with three 200 mL portions of hexanes, 25.19 g (96%) of the desired tert-butyl \(\beta\)-keto ester as a faint yellow liquid, which was taken on without further purification. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 3.38 – 3.34 (m, 2H), 3.32 (d, \(J = 8.8\), 2H), 2.74 (t, \(J = 5.6\), 2H), 1.46 – 1.43 (m, 9H), 1.43 – 1.38 (m, 9H).

\[\text{Boc-} \text{NH-} \text{CH-} \text{CO-} \text{O'Bu} \rightarrow \text{Boc-} \text{NH-} \text{CH-N_2-} \text{CO-} \text{O'Bu}\]

tert-Butyl \(\alpha\)-diazo-\(\beta\)-keto ester: Under a blanket of inert gas, 3-carboxybenzenesulfonyl azide (22 g, 96.5 mmol, 1.1 equiv.) was added in one portion to a solution of tert-butyl \(\beta\)-keto ester (25.19 g, 87.7 mmol, 1.0 equiv.) in 330 mL acetonitrile in a 1 L round bottom flask via a powder funnel, which was rinsed with 30 mL acetonitrile. Triethylamine (37 mL, 263 mmol, 3.0 equiv.) was added dropwise via a pressure equalizing addition funnel over 30 minutes, and the resulting yellow-orange solution was allowed to stir for one hour before the solvent was removed under reduced pressure. To the foamy, yellow-orange residue was added a stirbar and 600 mL 1:1 Et\(_2\)O/water. After allowing the mixture to stir well for several minutes, the resulting biphasic solution was poured into a 2 L separatory funnel, and then the flask was rinsed with 400 mL 3:1 Et\(_2\)O/water and 300
mL Et₂O. The aqueous layer was removed and the organic layer was washed with 200 mL 2:1 saturated NaHCO₃ solution/water and 200 mL 2:1 saturated NH₄Cl solution/water. The organic layer was dried with MgSO₄, filtered, and concentrated under reduced pressure to give 23.4 g (85%) of the desired tert-butyl α-diazo-β-keto ester as a viscous yellow liquid that was taken on without further purification. ¹H NMR (500 MHz, CDCl₃) δ 5.00 (s, 1H), 3.41 (dd, J = 5.9, 11.7, 2H), 2.99 (t, J = 5.8, 2H), 1.50 (d, J = 0.7, 9H), 1.40 (s, 9H).

N-Boc-3-keto proline tert-butyl ester 3.35: Rh₂(OAc)₄ (165 mg, 0.373 mmol, 0.005 equiv.) was added to a pale yellow solution of tert-butyl α-diazo-β-keto ester (23.36 g, 128.5 mmol, 1.0 equiv.) in 750 mL of toluene in a 2 L round bottom flask, which was then fitted with a reflux condenser and placed into a preheated 100 °C oil bath under a stream of inert gas (no septum). The green mixture was allowed to heat at 85–90 °C until nitrogen gas evolution ceased (approximately 30 minutes) and then was allowed to cool to rt. The solvent was removed under reduced pressure, then under high vacuum, and the green residue was then treated with 500 mL hexanes and the solvent was again removed under reduced pressure and high vacuum. To remove the Rh₂(OAc)₄, the green residue was diluted with Et₂O and filtered through Celite®, rinsing well with Et₂O, and the solvent was evaporated under reduced pressure to give 19.6 g (92%) of N-Boc-3-keto proline tert-butyl ester 3.35 as pale yellow oil, which solidified when azeotroped with
hexanes or placed in the freezer. $^1$H NMR (500 MHz, CDCl$_3$) δ 4.41 and 4.33 (2s, 1H), 3.96 – 3.80 (m, 1H), 3.79 – 3.68 (m, 1H), 2.63 (t, $J$ = 7.5, 2H), 1.49 – 1.41 (m, 18H).

**tert-Butyl propargyl keto proline 3.37:** A solution of N-Boc-3-keto proline tert-butyl ester 3.35 (1.028 g, 3.60 mmol, 1.0 equiv.) and (R,R)-3.36 (39 mg, 0.036 mmol, 0.01 equiv.) in 24 mL o-xylene in a multi-jacketed, 100 mL round bottom flask was cooled to 0 °C with a Huber recirculating chiller. Propargyl bromide (80 wt.% in toluene, 482 μL, 4.32 mmol, 1.2 equiv.) was then added, followed by 18 mL of saturated aqueous K$_2$CO$_3$ that had been chilled in an ice bath. The resulting biphasic mixture was allowed to stir well at 0 °C for 24 hours before it was poured into a separatory funnel that contained saturated aqueous NH$_4$Cl and Et$_2$O. The organic layer was removed, and the aqueous phase was extracted three times with Et$_2$O. The combined organic extracts were dried with MgSO$_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO$_2$, 1:6:1 → 1:4:1 → 1:2:1 Et$_2$O/hexanes/CH$_2$Cl$_2$) to give 1.08 g (93%) of tert-butyl propargyl keto proline 3.37. TLC: $R_f$=0.37 (SiO$_2$, 1:4 EtOAc/hexanes); HPLC: Chiralpak AD-H column, hexanes/i-PrOH = 100:1, flow rate = 0.5 mL/min; $^1$H NMR (500 MHz, CDCl$_3$) δ 3.85 – 3.66 (m, 2H), 3.21 (dd, $J$ = 1.6, 17.1, 0.4H), 3.09 (dd, $J$ = 1.9, 17.1, 0.6H), 2.99 – 2.86 (m, 1H), 2.75 – 2.53 (m, 2H), 1.88 (d, $J$ = 9.5, 1H), 1.44 and 1.40 (2s, 9H), 1.35 and 1.33 (2s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 207.50, 206.99, 165.56, 153.84, 153.48, 82.98, 82.72, 81.33, 80.64, 79.28, 78.38,
72.39, 71.92, 71.29, 70.63, 42.73, 42.15, 36.38, 35.40, 28.22, 28.14, 27.63, 27.57, 23.49, 22.55; HRMS (ESI-TOF) C_{14}H_{19}NO_5 m/z calcd for [M+Na]^+ 346.1630; found 346.1625.

\[ \text{3.39} \quad \text{3.38} \]

\( \alpha \)-Diazo-\( \beta \)-keto ester \( \text{3.39} \): Under a blanket of inert gas, 3-carboxybenzenesulfonyl azide (13 g, 57 mmol, 1.1 equiv.) was added in one portion to a solution of Nazarov’s reagent (3.38) (7.39 g, 52 mmol, 1.0 equiv.) in 225 mL acetonitrile at 0 °C. Triethylamine (22 mL, 156 mmol, 3.0 equiv.) was added dropwise via a pressure equalizing addition funnel over 5-10 minutes, and the resulting yellow-orange solution was allowed to stir at 0 °C for one hour, then at rt for 90 minutes before the solvent was removed under reduced pressure. The foamy, yellow-orange residue was diluted with 500 mL Et_2O and 200 mL water. The resulting biphasic solution was poured into a 1 L separatory funnel, and the aqueous layer was removed. The organic layer was washed with 125 mL 4:1 saturated NaHCO_3 solution/water and 125 mL 4:1 saturated NH_4Cl solution/water. The organic layer was dried with MgSO_4, filtered, and concentrated under reduced pressure to give 7.32 g (84%) of the \( \alpha \)-diazo-\( \beta \)-keto ester \( \text{3.39} \) as a viscous yellow liquid that was taken on without further purification. TLC: \( R_f=0.41 \) (SiO_2, 1:4 EtOAc/hexanes); \(^1\)H NMR (300 MHz, CDCl_3) \( \delta \) 7.40 (ddd, \( J = 0.9, 10.4, 17.1, 1H \)), 6.42 (ddd, \( J = 0.9, 1.9, 17.1, 1H \)), 5.70 (ddd, \( J = 0.9, 1.9, 10.4, 1H \)), 4.29 (qd, \( J = 0.8, 7.1, 2H \)), 1.31 (td, \( J = 0.9, 7.1, 3H \)).
Diallylamine addition product 3.40: A solution of diallylamine (6 mL, 48.4 mmol, 1.0 equiv.) in 484 mL CH₂Cl₂ was treated with a solution of α-diazo-β-keto ester 3.39 (7.32 g, 43.5 mmol, 0.9 equiv.) in 30 mL CH₂Cl₂. The resulting light yellow solution was allowed to stir at rt for 90 minutes, then the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 20 → 28 → 36% EtOAc/hexanes) to give 10 g (87%) of diallylamine addition product 3.40 as a yellow liquid. TLC: \( R_f = 0.22 \) (SiO₂, 1:4 EtOAc/hexanes); \(^1H\) NMR (300 MHz, CDCl₃) \( \delta \) 5.80 (ddtd, \( J = 0.8, 6.5, 7.3, 10.1, 1H \)), 5.13 (tdt, \( J = 0.9, 2.0, 11.2, 2H \)), 4.27 (qd, \( J = 0.8, 7.1, 1H \)), 3.08 (d, \( J = 6.5, 2H \)), 3.00 (t, \( J = 7.2, 1H \)), 2.81 (t, \( J = 7.1, 1H \)), 1.30 (td, \( J = 0.9, 7.1, 2H \)).

\[ \text{N-Allyl-2-allyl keto proline 3.41: A solution of diallylamine addition product 3.40 (8.5 g, 32 mmol, 1.0 equiv.) in 500 mL benzene was degassed with three cycles of high vacuum/nitrogen refill, then Rh₂(OAc)₄ (142 mg, 0.32 mmol, 0.01 equiv.) was added. The resulting green mixture was allowed to heat at 85–90 °C for 45 minutes (the solution turned black during the first 15 minutes of heating, then returned to green) and then was allowed to cool to rt. The solvent was removed under reduced pressure, and then the residue was purified by flash chromatography (SiO₂, 10% EtOAc/hexanes) to give 6.35 g} \]
(83%) of N-allyl-2-allyl keto proline 3.41 as a pale yellow liquid. TLC: $R_f$=0.47 (SiO$_2$, 1:4 EtOAc/hexanes); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.79 (dddd, $J$ = 4.8, 7.8, 10.1, 17.2, 1H), 5.72 – 5.56 (m, 1H), 5.22 (dtd, $J$ = 1.2, 1.8, 17.1, 1H), 5.12 (dt, $J$ = 0.8, 1.7, 10.1, 1H), 5.04 (ddt, $J$ = 1.3, 2.2, 1.8, 4.2, 1H), 5.02 – 4.98 (m, 1H), 4.25 – 4.05 (m, 2H), 3.45 (ddt, $J$ = 1.8, 4.8, 13.9, 1H), 3.33 (td, $J$ = 1.5, 9.0, 1H), 2.93 (dd, $J$ = 7.7, 13.8, 1H), 2.88 (td, $J$ = 7.0, 9.3, 1H), 2.63 (ddt, $J$ = 1.2, 4.6, 7.3, 2H), 2.51 (dd, $J$ = 1.6, 7.0, 18.5, 1H), 2.39 – 2.24 (m, 1H), 1.24 (t, $J$ = 7.1, 3H).

E.4 Experimental for Chapter 4

Allyl ether 4.3: A mixture of β-keto ester 3.27 (16.7 mg, 0.0420 mmol, 1.0 equiv.) and K$_2$CO$_3$ (23 mg, 0.168 mmol, 4.0 equiv.) in 420 µL acetone was treated with allyl bromide (10 µL, 0.0840 mmol, 2.0 equiv.). The resulting mixture was allowed to heat at 65–70 °C in a sealed vial overnight. The mixture was allowed to cool to rt, saturated aqueous NH$_4$Cl was added, and the aqueous layer was extracted four times with Et$_2$O. The combined organic extracts were dried with MgSO$_4$, filtered, and the solvent was removed under reduced pressure to give 21 mg (quant.) of allyl ether 4.3 as a pale yellow oil. TLC: $R_f$=0.43 (SiO$_2$, Et$_2$O); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.94 (ddq, $J$ = 4.7, 9.7, 15.4, 1H), 5.38 (dtd, $J$ = 1.7, 3.1, 17.2, 1H), 5.25 (dddd, $J$ = 1.4, 2.9, 5.9, 10.4, 1H), 4.57 (pd, $J$ = 1.7, 4.6, 2H), 3.79 (dd, $J$ = 8.0, 17.7, 1.4H), 3.68 and 3.67 (2s, 6H), 3.61 (d, $J$ = 9.1, 3H).
0.6H), 3.27 – 3.10 (m, 2.5H), 2.96 (d, J = 17.6, 0.5H), 2.56 (d, J = 27.3, 0.5H), 2.48 – 2.36 (m, 1.5H), 2.00 and 2.01 (2s, 3H), 1.99 – 1.82 (m, 1H), 1.40 and 1.37 (2s, 9H), 1.23 (s, 1H).

Allyl carbonate 4.5: A solution of β-keto ester 3.27 (854 mg, 2.15 mmol, 1.0 equiv.) and DMAP (27 mg, 0.215 mmol, 0.1 equiv.) in 22 mL CH₂Cl₂ was allowed to cool to 0 °C, and then Et₃N (450 µL, 3.22 mmol, 1.5 equiv.) was added, followed by allyl chloroformate (274 µL, 2.58 mmol, 1.2 equiv.). The resulting solution was allowed to warm to rt over one hour, and then saturated aqueous NH₄Cl and Et₂O were added. The organic layer was removed, and then the aqueous layer was extracted five times with Et₂O. The combined organic extracts were dried with MgSO₄, filtered, and the solvent was removed under reduced pressure to give 1.0895 g (quant.) of allyl carbonate 4.5 as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 5.93 (ddtd, J = 1.5, 5.8, 10.4, 17.7, 1H), 5.43 – 5.33 (m, 1H), 5.29 (dtd, J = 1.2, 2.3, 10.4, 1H), 4.71 – 4.64 (m, 2H), 3.88 (dd, J = 9.0, 18.6, 1H), 3.83 – 3.62 (m, 1H), 3.69 (s, 6H), 3.22 (qdd, J = 2.6, 4.9, 6.0, 1H), 3.13 – 2.98 (m, 1.5H), 2.90 (d, J = 18.5, 0.5H), 2.62 (dd, J = 12.6, 17.2, 1H), 2.45 – 2.30 (m, 1H), 2.26 – 1.99 (m, 1H), 2.03 (d, J = 1.2, 3H), 1.40 and 1.36 (2s, 9H), 1.22 (s, 1H).
2-Allyl β-keto ester 4.4: A purple suspension of Pd$_3$dba$_3$ (98 mg, 0.107 mmol, 0.05 equiv.) in 25 mL THF was treated with (R,R)-4.6 (178 mg, 0.258 mmol, 0.12 equiv.) at rt. The resulting golden-orange solution was treated with a solution of allyl carbonate 4.5 (1.0895 g, 2.15 mmol, 1.0 equiv.) in 15 mL THF dropwise over several minutes, followed by a rinse with 4 mL THF. Immediately upon addition of this solution, the golden-orange reaction solution took on a green color. The resulting green solution was allowed to stir at rt overnight, during which time the reaction solution returned to a golden-orange color. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO$_2$, 40 → 50 → 60 → 70 → 80% Et$_2$O/hexanes) to give 440 mg (48%, two steps) of 2-allyl β-keto ester 4.4 as a colorless oil. TLC: $R_f$=0.53 (SiO$_2$, Et$_2$O); *epi*-4.4 TLC: $R_f$=0.48 (SiO$_2$, Et$_2$O); $^1$H NMR (300 MHz, CDCl$_3$) δ 6.10 – 5.90 (m, 1H), 5.05 – 4.91 (m, 2H), 3.84 – 3.64 (m, 2H), 3.75 and 3.73 (2s, 3H), 3.63 and 3.62 (2s, 3H), 3.60 – 3.48 (m, 1H), 2.95 – 2.74 (m, 2H), 2.70 – 2.37 (m, 4H), 2.22 and 2.21 (2s, 3H), 1.90 – 1.46 (m, 2H), 1.41 and 1.35 (2s, 9H), 1.22 (s, 1H), 0.95 – 0.70 (m, 1H).
Triketone 4.1: A solution of PdCl$_2$ (1 mg, 0.00457 mmol, 0.1 equiv.) and benzoquinone (5.5 mg, 0.0503 mmol, 1.1 equiv.) in 381 µL DMF and 76 µL water was treated with 2-allyl β-keto ester 4.4 (20 mg, 0.0457 mmol, 1.0 equiv.). The resulting orange solution was allowed to stir at rt overnight, and then 5% aqueous NaOH (2 mL) and Et$_2$O were added. The organic layer was removed, and then the aqueous layer was extracted five times with Et$_2$O. The combined organic extracts were washed three times with water, once with brine, and then dried with MgSO$_4$, filtered, and the solvent was removed under reduced pressure to give 21 mg (quant.) of triketone 4.1 as a colorless foam. TLC: $R_f$=0.30 (SiO$_2$, Et$_2$O); $^1$H NMR (300 MHz, CDCl$_3$) δ 4.16 – 3.90 (m, 1H), 3.75 (dd, $J = 3.1, 4.0, 7$H), 3.73 – 3.61 (m, 2H), 3.61 – 3.44 (m, 1H), 3.44 – 3.30 (m, 1H), 3.19 (dd, $J = 3.5, 17.5, 1$H), 2.99 – 2.39 (m, 7H), 2.17 (2s, 6H), 1.83 – 1.43 (m, 3H), 1.40 and 1.36 (2s, 9H).

Ynone 4.53: A solution of alkyne 4.52 (8 g, 57.1 mmol, 1.0 equiv.) in 180 mL THF was allowed to cool to −78 °C before n-BuLi (2.5 M in hexanes, 24 mL, 59.9 mmol, 1.05 equiv.) was added dropwise over five minutes. The resulting solution was allowed to stir at −78 °C for one hour, and then BF$_3$•OEt$_2$ (7.2 mL, 57.1 mmol, 1.0 equiv.) was added dropwise over five minutes. The resulting pale yellow solution was allowed to stir at −78 °C for 10 minutes before γ-butyrolactone (4.39 mL, 57.1 mmol, 1.0 equiv.) was added in one portion. This addition caused the pale yellow solution to initially become a colorless solution, then a colorless suspension after 5-10 minutes. The resulting suspension was
allowed to stir at –78 °C for 15 minutes (total time after the addition of γ-butyrolactone), then the flask was removed from the cooling bath. Once the mixture became homogeneous (approx. 30 minutes), 36 mL of 2:1 saturated NH₄Cl solution/water was added. The resulting biphasic mixture was poured into a 1 L separatory funnel that contained 200 mL water, and then the flask was rinsed with 100 mL water and 150 mL Et₂O. The organic layer was removed, and then the cloudy aqueous layer was extracted five times with Et₂O. The combined organic extracts were dried with MgSO₄, filtered, and the solvent was removed under reduced pressure to give the ynone 4.53, which was taken on without further purification. TLC: Rƒ=0.36 (SiO₂, 2:1 EtOAc/hexanes).

Propargyl ketal 4.54: A solution of ynone 4.53 from above (~57 mmol, 1.0 equiv.) in 570 mL MeOH was treated with CSA (663 mg 2.85 mmol, 0.05 equiv.) and trimethyl orthoacetate (11.4 mL, 89.6 mmol, 1.6 equiv.). The resulting solution was allowed to stir at rt for two hours, then the rust-colored solution was treated with Et₃N (650 µL, 4.66 mmol, 0.08 equiv.), which caused the solution to become pale yellow in color. The solvent was removed under reduced pressure, and then the residue was purified by flash chromatography (SiO₂, 20 → 30 → 40% EtOAc/hexanes, all eluant containing 1% Et₃N) to give 7 g (79%, 2 steps) of propargyl ketal 4.54 as a faint yellow liquid. TLC: Rƒ=0.49 (SiO₂, 2:1 EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 4.31 (d, J = 3.2, 2H), 4.04 – 3.93 (m, 1H), 3.87 (td, J = 0.8, 5.9, 8.2, 1H), 3.34 (d, J = 0.9, 3H), 2.29 – 2.15 (m, 2H), 2.15 – 1.88 (m, 2H), 1.80 (br s, 1H).
Propargyl bromide 4.7: A solution of propargyl ketal 4.54 (6.2 g, 39.7 mmol, 1.0 equiv.) in 200 mL THF was allowed to cool to –45 °C, and then MsCl (4.63 mL, 59.5 mmol, 1.5 equiv.) was added, followed by Et₃N (11 mL, 79.4 mmol, 2.0 equiv.). The resulting colorless mixture was allowed to stir at –45 °C for one hour, then the flask was placed in an ice bath and LiBr (17.2 g, 198 mmol, 5.0 equiv.) was added in one portion. The resulting orange mixture was allowed to stir at 0 °C for one hour, then at rt for 90 minutes. Water and Et₂O were then added, and the resulting biphasic mixture was poured into a 1 L separatory funnel. The organic layer was removed, and then the aqueous layer was extracted five times with Et₂O. The combined organic extracts were dried with MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 10% EtOAc/hexanes, all eluant containing 1% Et₃N) to give 7.05 g (81%) of propargyl bromide 4.7 as a faint yellow liquid. TLC: Rₓ=0.65 (SiO₂, 1:1 EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃) δ 3.98 (td, J = 6.2, 7.9, 1H), 3.93 (s, 2H), 3.87 (td, J = 5.9, 8.0, 1H), 3.34 (s, 3H), 2.27 – 2.14 (m, 2H), 2.14 – 1.89 (m, 2H).
Propargyl keto proline 4.8: A suspension of sodium hydride (60% dispersion in mineral oil, 446 mg, 11.2 mmol, 1.05 equiv.) in 40 mL THF and 5.3 mL DMF was allowed to cool to 0 °C, then a solution of N-Boc-3-keto proline methyl ester 3.10 (2.58 g, 10.6 mmol, 1.0 equiv.) in 5 mL THF was added over 5 to 10 minutes, followed by a rinse with 1 mL THF. The resulting yellow suspension was allowed to stir at 0 °C for 30 minutes before the flask was removed from the ice bath. Propargyl bromide 4.7 (2.56 g, 11.7 mmol, 1.1 equiv.) was then added in one portion, followed by a rinse with 1 mL THF, and the resulting orange-red suspension was allowed to stir at rt for one hour before saturated NH₄Cl solution and water were added. The biphasic solution was poured into a separatory funnel containing water, the organic layer was removed, and the aqueous phase was extracted four times with Et₂O. The combined organic extracts were dried with MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 1:6:1 → 1:4:1 → 1:2:1 Et₂O/hexanes/CH₂Cl₂) to give 3.6 g (89%) of propargyl keto proline 4.8 as a colorless oil. TLC: Rf=0.40 (SiO₂, 1:2 EtOAc/hexanes); ¹H NMR (400 MHz, CDCl₃) δ 3.97 – 3.87 (m, 2H), 3.87 – 3.77 (m, 2H), 3.70 (s, 3H), 3.53 – 3.29 (m, 0.5H), 3.27 – 3.24 (3s, 3H), 3.23 – 3.04 (m, 1.5H), 2.85 – 2.61 (m, 2H), 2.22 – 1.80 (m, 4H), 1.46 and 1.40 (2s, 9H).
Vinylogous ester: To a cooled a solution of propargyl keto proline 4.8 (1.7755 g, 4.65 mmol, 1.0 equiv.) in 20 mL THF at −78 °C was added allylmagnesium chloride (1.4 M in THF, 3.33 mL, 4.65 mmol, 1.0 equiv.) dropwise over 15 to 20 minutes via syringe pump. The resulting colorless solution was allowed to slowly warm to between −10 °C and 0 °C over 90 minutes, after which time 50 mL saturated NH₄Cl solution was added and the mixture was allowed to warm to rt. The biphasic solution was poured into a 125 mL separatory funnel, 10 mL water and 10 mL Et₂O were added, and then the organic layer was removed. The aqueous phase was extracted three times with 10 mL Et₂O, the combined organic extracts were dried with MgSO₄, and the solvent was evaporated under reduced pressure to give 2.1 g of the desired homoallylic alcohol. This material was dissolved in 45 mL wet acetone and the resulting solution was treated with PPTS (50 mg, 0.2 mmol, 0.05 equiv.). The resulting light yellow solution was allowed to stir at rt for 30 minutes, then 1 mL of Et₃N was added and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 40 → 50 → 60 → 70 → 80 → 100% EtOAc/hexanes, all eluant containing 1% Et₃N) to give 1.38 g (73%, two steps) of the desired vinylogous ester as a faint yellow liquid. ¹H NMR (300 MHz, CDCl₃) δ 5.81 (dd, J = 1.3, 2.1, 1H), 5.80 – 5.65 (m, 1H), 5.19 – 5.06 (m, 2H), 3.93 – 3.79 (m, 2H), 3.76 (s, 3H), 3.65 (t, J = 5.9, 2H), 3.40 – 3.23 (m, 1H), 2.56 (t, J = 6.7, 2H), 2.50 – 2.30 (m, 2H), 2.21 (dd, J = 6.2, 13.7, 1H), 2.15 – 2.01 (m, 2H), 1.93 – 1.77 (m, 2H), 1.66 (br s, 1H), 1.42 and 1.41 (2s, 9H).
Ketone 4.10: A solution of the above vinylogous ester (228 mg, 0.557 mmol, 1.0 equiv.), (MeCN)$_2$PdCl$_2$ (3 mg, 0.0111 mmol, 0.02 equiv.), and benzoquinone (61 mg, 0.557 mmol, 1.0 equiv.) in 4.64 mL THF and 928 µL water was allowed to stir at rt overnight. After the THF was removed under reduced pressure, 1 mL saturated NaHCO$_3$ solution and 5 mL EtOAc were added. The organic layer was removed, and then the aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed once with water, once with brine, and then dried with MgSO$_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO$_2$, 50 → 60 → 70 → 80 → 100% EtOAc/hexanes) to give 140 mg (60%) of ketone 4.10 as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) δ 5.84 – 5.66 (m, 1H), 3.94 – 3.72 (m, 2H), 3.70 and 3.68 (2s, 3H), 3.57 (td, $J = 2.9, 6.0$, 2H), 3.39 – 3.19 (m, 1H), 2.82 (dd, $J = 8.6, 15.3$, 1H), 2.67 – 2.40 (m, 4H), 2.26 – 2.13 (m, 2H), 2.12 (s, 3H), 1.85 – 1.70 (m, 2H), 1.36 and 1.35 (2s, 9H).

Diketone 4.11: A solution of ketone 4.10 (70 mg, 0.165 mmol, 1.0 equiv.) in 3.3 mL THF was treated with Cs$_2$CO$_3$ (107 mg, 0.329 mmol, 2.0 equiv.) and the resulting yellow
suspension was allowed to stir at rt for 48 hours. After the solvent was evaporated, 3.3 mL water was added and the resulting yellow solution was washed five times with Et₂O. The aqueous layer was acidified with 1 mL 1 N NaHSO₄ and extracted five times with EtOAc. The combined EtOAc extracts were dried with MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 50 → 75 → 100% EtOAc/hexanes) to give 51 mg (73%) of diketone 4.11 as a colorless foam. ¹H NMR (300 MHz, CDCl₃) δ 4.37 – 4.03 (m, 2H), 3.84 – 3.55 (m, 5H), 3.45 (dd, J = 12.4, 18.4, 1H), 3.24 – 3.07 (m, 2H), 3.04 – 2.76 (m, 2H), 2.64 – 2.44 (m, 2H), 2.14 – 1.97 (m, 7H), 1.61 (s, 1H), 1.49 – 1.40 (m, 2H), 1.39 and 1.36 (2s, 9H).

![Chemical Structure](image)

Enone 4.22: A solution of N-Boc-3-keto proline methyl ester 3.10 (6.31 g, 25.9 mmol, 1.0 equiv.) in 260 mL THF was evacuated and refilled with argon three times, then the flask was covered in aluminum foil and NaI (4.08 g, 27.2 mmol, 1.05 equiv.) was added. The resulting mixture was then treated with DBU (4.27 mL, 28.5 mmol, 1.1 equiv.) dropwise over several minutes. After 30 minutes at rt, the Wittig reagent (10.07 g, 28.5 mmol, 1.1 equiv.) was added in one portion and the resulting mixture was allowed to stir at rt overnight. The reaction mixture was poured into a 1 L separatory funnel that contained 250 mL Et₂O and 200 mL brine, and the flask was rinsed twice with 150 mL Et₂O. The aqueous layer was removed, the organic layer was washed once with 200 mL brine, and then the organic layer was dried with MgSO₄, filtered, and the solvent was
removed under reduced pressure. The residue was purified by flash chromatography 
(SiO$_2$, 25 → 33 → 40 → 50% EtOAc/hexanes) to give 4.61 g (63%) of enone 4.22 as a 
pale yellow oil. TLC: $R_f$=0.29 (SiO$_2$, 1:1 EtOAc/hexanes); $^1$H NMR (500 MHz, CDCl$_3$) 
$\delta$ 6.05 (dd, $J$ = 0.7, 1.4, 1H), 4.05 and 3.98 (2td, $J$ = 3.3, 10.2, 1H), 3.72 and 3.70 (2s, 
3H), 3.62 – 3.52 (m, 1H), 3.39 and 3.29 (2d, $J$ = 17.0, 1H), 2.97 – 2.78 (m, 2H), 2.57 and 
2.52 (2d, $J$ = 17.1, 1H), 1.46 and 1.40 (2s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 206.37, 
205.82, 176.14, 175.68, 171.38, 171.15, 154.86, 154.08, 127.51, 127.46, 81.16, 81.13, 
73.19, 73.14, 53.57, 51.26, 50.33, 48.27, 47.86, 34.88, 34.73, 31.80, 28.58, 28.45, 26.26, 
25.97, 25.49, 22.87, 14.34.

Bromo enone 4.23: A solution of enone 4.22 (4.33 g, 15.4 mmol, 1.0 equiv.) in 154 mL 
CH$_2$Cl$_2$ was allowed to cool to 0 °C before Br$_2$ (868 ml, 16.9 mmol, 1.1 equiv.) was 
added dropwise over 15 minutes. The resulting red solution was allowed to stir at 0 °C 
for 30 minutes, then Et$_3$N (3.22 mL, 23.1 mmol, 1.5 equiv.) was added dropwise over a 
few minutes. After the resulting yellow solution was allowed to stir at 0 °C for one hour, 
it was poured into a 250 mL separatory funnel that contained 75 mL brine. The organic 
layer was removed, the aqueous layer was washed three times with 25 mL CH$_2$Cl$_2$, and 
then the combined organic extracts were dried with MgSO$_4$, filtered, and the solvent was 
removed under reduced pressure. The residue was purified by flash chromatography 
(SiO$_2$, 5 → 15 → 25 → 35 → 45% EtOAc/hexanes) to give 5.26 g (95%) of bromo enone 
4.23 as a colorless oil. TLC: $R_f$=0.47 (SiO$_2$, 1:1:1 Et$_2$O/hexanes/CH$_2$Cl$_2$); $^1$H NMR (500
MHz, CDCl$_3$) δ 4.05 and 3.99 (2td, $J = 3.3$, 10.5, 1H), 3.72 and 3.70 (2s, 3H), 3.65 – 3.57 (m, 1H), 3.54 and 3.45 (2d, $J = 17.2$, 1H), 3.00 – 2.76 (m, 2H), 2.66 and 2.61 (2d, $J = 17.1$, 1H), 1.44 and 1.38 (2s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 198.55, 198.19, 171.88, 171.39, 170.40, 170.17, 154.76, 153.80, 121.82, 121.65, 81.47, 81.42, 72.31, 72.21, 53.78, 49.65, 48.79, 47.73, 47.40, 28.49, 28.38, 26.19, 25.86.

 Allylic alcohol 4.24: A solution of bromo enone 4.23 (1.15 g, 3.20 mmol, 1.0 equiv.) in 32 mL THF was allowed to cool to –78 °C before L-Selectride$^0$ (1.0 M in THF, 4.8 mL, 4.80 mmol, 1.5 equiv.) was added dropwise over 5-10 minutes. The resulting faint yellow solution was allowed to stir at –78 °C for one hour, then 50 mL saturated NH$_4$Cl solution was added and the biphasic mixture was allowed to warm to rt before it was poured into a 125 mL separatory funnel. The organic layer was removed, the aqueous layer was washed three times with 25 mL Et$_2$O, and then the combined organic extracts were dried with MgSO$_4$, filtered through a plug of SiO$_2$, and the solvent was removed under reduced pressure. This gave 980 mg (85%) of allylic alcohol 4.24 as a colorless oil. TLC: $R_t$=0.44 (SiO$_2$, 1:1:1 Et$_2$O/hexanes/CH$_2$Cl$_2$); $^1$H NMR (300 MHz, CDCl$_3$) δ 4.72 (dd, $J = 7.0$, 10.8, 1H), 3.98 – 3.84 (m, 1H), 3.77 (2s, 3H), 3.68 – 3.55 (m, 1H), 2.79 (d, $J = 14.1$, 0.27H), 2.67 (d, $J = 13.9$, 0.73H), 2.60 – 2.28 (m, 3H), 1.43 and 1.38 (2s, 9H). Epimer 4.24 could be prepared under Luche conditions (NaBH$_4$, CeCl$_3$$\cdot$7H$_2$O) in MeOH at –78 °C. TLC: $R_t$=0.33 (SiO$_2$, 1:1:1 Et$_2$O/hexanes/CH$_2$Cl$_2$); $^1$H NMR (500 MHz,
CDCl₃) δ 5.15 (s, 1H), 3.89 and 3.82 (2td, J = 1.7, 10.4, 1H), 3.68 (s, 4H), 3.51 (dd, J = 8.5, 17.9, 1H), 3.46 – 3.35 (m, 1H), 3.31 (dd, J = 5.8, 12.4, 1H), 2.77 (d, J = 3.9, 0.74H), 2.68 (d, J = 6.2, 0.26H), 2.54 (dd, J = 6.7, 14.9, 1H), 2.48 – 2.35 (m, 1H), 1.89 and 1.85 (2dd, J = 7.4, 12.4, 1H), 1.41 and 1.37 (2s, 9H).

Acrylate 4.26: A solution of N-Boc-3-keto proline methyl ester 3.10 (50 mg, 0.206 mmol, 1.0 equiv.) in 600 µL THF was allowed to cool to 0 °C before t-BuOK (1.0 M in THF, 226 µL, 0.226 mmol, 1.1 equiv.) was added. After 30 minutes at 0 °C, the phosphonium salt (111 mg, 0.247 mmol, 1.2 equiv.) was added in one portion and the resulting mixture was allowed to stir at rt overnight. The reaction mixture was diluted with Et₂O and brine, the organic layer was removed, and the aqueous layer was extracted three times with Et₂O. The combined organic extracts were dried with MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 25 → 33 → 40 → 50% EtOAc/hexanes) to give 40 mg (60%) of acrylate 4.26 as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 3.96 and 3.90 (2td, J = 2.0, 10.6, 1H), 3.72 (s, 3H), 3.68 (s, 3H), 3.64 – 3.49 (m, 1H), 3.20 – 2.96 (m, 2H), 2.96 – 2.73 (m, 2H), 2.61 (ddddd, J = 1.9, 5.1, 8.8, 10.6, 15.8, 1H), 2.08 – 1.83 (m, 1H), 1.42 and 1.37 (2s, 9H).
Allylic alcohol 4.27: To a cooled solution of acrylate 4.26 (40 mg, 0.123 mmol, 1.0 equiv.) in 2.46 mL THF at −78 °C was added allylmagnesium chloride (2.0 M in THF, 123 µL, 0.246 mmol, 2.0 equiv.) dropwise over 5-10 minutes. The resulting colorless solution was allowed to stir at −78 °C for 90 minutes, after which time saturated NH₄Cl solution was added and the mixture was allowed to warm to rt. The biphasic mixture was diluted with water and Et₂O were added, and then the organic layer was removed. The aqueous phase was extracted three times with Et₂O, the combined organic extracts were dried with MgSO₄, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (SiO₂, 20 → 30 → 40 → 50 → 60% EtOAc/hexanes) to give 39 mg (84%) of the allylic alcohol 4.27 as a colorless foam. ¹H NMR (500 MHz, CDCl₃) δ 5.83 – 5.56 (m, 2H), 5.17 – 4.97 (m, 4H), 3.85 and 3.79 (2td, J = 1.4, 10.1, 1H), 3.65 (s, 3H), 3.49 – 3.38 (m, 1H), 3.01 – 2.86 (m, 1H), 2.86 – 2.68 (m, 2H), 2.51 – 2.32 (m, 4H), 2.28 (dd, J = 7.4, 14.0, 1H), 2.17 (dd, J = 8.6, 13.7, 1H), 1.88 (s, 1H), 1.86 – 1.71 (m, 1H), 1.42 and 1.36 (2s, 9H).

Acid 4.28: A solution of allylic alcohol 4.27 (39 mg, 0.103 mmol, 1.0 equiv.) and 18-crown-6 (33 mg, 0.124 mmol, 1.2 equiv.) in 2 mL THF was allowed to cool to 0 °C before t-BuOK (1.0 M in THF, 114 µL, 0.114 mmol, 1.1 equiv.) was added. The resulting
solution was allowed to slowly warm to rt and stir at that temperature overnight. The reaction mixture was diluted with EtOAc and saturated NH₄Cl solution, the organic layer was removed, and the aqueous layer was extracted three times with EtOAc. The combined organic extracts were dried with MgSO₄, filtered, and the solvent was removed under reduced pressure to provide 34 mg (91%) of crude acid 4.28. ¹H NMR (500 MHz, CDCl₃) δ 5.93 – 5.58 (m, 2H), 5.25 – 4.96 (m, 4H), 3.88 and 3.75 (2t, J = 10.0, 1H), 3.68 (s, 0.4H), 3.53 – 3.39 (m, 1H), 3.03 – 2.88 (m, 1H), 2.83 (dd, J = 7.1, 13.8, 1.31H), 2.75 (dd, J = 6.1, 12.5, 0.69H), 2.57 – 2.37 (m, 4H), 2.33 (dd, J = 7.3, 14.0, 1H), 2.22 (dd, J = 8.6, 13.6, 1H), 1.96 – 1.71 (m, 1H), 1.46 and 1.41 (2s, 9H).

Allylic acetate 4.29: A solution of acrylate 4.26 (70 mg, 0.215 mmol, 1.0 equiv.) in 4 mL THF was allowed to cool to −78 °C before L-Selectride⁰ (1.0 M in THF, 645 µL, 0.645 mmol, 3.0 equiv.) was added dropwise over 5-10 minutes. The resulting faint yellow solution was allowed to stir at −78 °C for one hour, then was allowed to slowly warm to rt and stir at that temperature for one hour. The reaction mixture was diluted with EtOAc and saturated NH₄Cl solution, the organic layer was removed, and the aqueous layer was extracted three times with EtOAc. The combined organic extracts were dried with MgSO₄, filtered through a plug of SiO₂, and the solvent was removed under reduced pressure to provide 53 mg (83%) of the desired allylic alcohol. This material was dissolved in 1.8 mL CH₂Cl₂ along with DMAP (3 mg, 0.0178 mmol, 0.1 equiv.) and Et₃N (50 µL, 0.356 mmol, 2.0 equiv.), and the resulting solution was allowed to cool to 0 °C
before Ac₂O (26 μL, 0.267 mmol, 1.5 equiv.) was added. The resulting mixture was allowed to stir at 0 °C before water was added. The organic layer was removed, the aqueous layer was washed three times with CH₂Cl₂, and then the combined organic extracts were dried with MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 10 → 20 → 30 → 40% EtOAc/hexanes) to give 54 mg (89%) of allylic acetate 4.29 as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 4.66 (dd, J = 4.5, 13.4, 1H), 4.50 (d, J = 13.4, 1H), 3.88 and 3.82 (2td, J = 1.9, 10.2, 1H), 3.66 (s, 3H), 3.57 – 3.40 (m, 1H), 3.02 – 2.73 (m, 2H), 2.60 – 2.29 (m, 3H), 2.03 (s, 3H), 1.95 – 1.77 (m, 1H), 1.40 and 1.35 (2s, 9H).

Vinyl triflate 4.33: A solution of vinylogous carbonate 3.25 (773 mg, 1.95 mmol, 1.0 equiv.) in 20 mL wet THF was allowed to cool to 0 °C, then Cs₂CO₃ (951 mg, 2.92 mmol, 1.5 equiv.) was added. The resulting mixture was allowed to stir at rt for 3 hours before Comins’ reagent (4.32) (917 mg, 2.33 mmol, 1.2 equiv.) was added. The resulting suspension was allowed to stir at rt overnight, then was poured into a separatory funnel containing Et₂O and water. The organic layer was removed and the aqueous layer was extracted three times with Et₂O. The combined organic layers were dried with MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 0 → 10 → 20 → 30 → 40% EtOAc/hexanes) to give 815 mg (79%) of vinyl triflate 4.33 as a colorless oil. TLC: Rf=0.24 (SiO₂, 1:2
EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 3.90 (dd, J = 18.4, 21.3, 1H), 3.83 – 3.61 (m, 1H), 3.74 (2s, 3H), 3.68 (2s, 3H), 3.27 – 3.12 (m, 2H), 3.00 (2d, J = 18.4, 1H), 2.57 (t, J = 18.5, 1H), 2.35 (dd, J = 5.9, 12.9, 1H), 2.14 – 1.85 (m, 4H), 2.00 (2s, 3H), 1.38 and 1.34 (2s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 204.74, 204.61, 170.65, 170.58, 162.11, 162.02, 153.87, 153.46, 153.18, 152.32, 121.43, 121.09, 119.76, 117.21, 81.27, 80.88, 73.12, 72.97, 61.40, 60.13, 52.90, 52.79, 52.08, 52.03, 46.75, 46.60, 45.45, 45.25, 42.01, 40.89, 33.94, 33.39, 30.92, 28.37; HRMS (ESI-TOF) C₂₀H₂₆F₃NO₁₀S m/z calcd for [M+Na]⁺ 552.1127; found 552.1119.

Acrylate 4.34: Triethylamine (640 µL, 4.59 mmol, 3.0 equiv.) and formic acid (173 µl, 4.59 mmol, 3.0 equiv.) were added to a degassed solution of vinyl triflate 4.33 (810 mg, 1.53 mmol, 1.0 equiv.) and Pd[(PPh₃)₄] (89 mg, 0.0765 mmol, 0.05 equiv.) in 16 mL THF. The resulting solution was allowed to stir at 60 °C overnight then the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 0 → 10 → 20 → 30 → 40% EtOAc/hexanes) to give 542 mg (93%) of acrylate 4.34 as a colorless oil. TLC: Rf=0.23 (SiO₂, 1:2 EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 6.81 and 6.78 (2t, J = 2.6, 1H), 3.72 and 3.62 (2t, J = 9.3, 1H), 3.65 and 3.64 (2s, 6H), 3.52 and 3.48 (2dd, J = 2.2, 15.3, 1H), 3.11 – 3.03 (m, 1H), 3.00 and 2.97 (2d, J = 13.7, 1H), 2.94 and 2.79 (dd, J = 3.0, 19.3, 1H), 2.56 and 2.52 (2d, J = 16.8, 1H), 2.47 – 2.36 (m, 1H), 2.12 – 1.86 (m, 1H), 1.98 (s, 3H), 1.36 and 1.33 (2s, 9H); ¹³C NMR (126 MHz,
Ketal 4.38: Acrylate 4.34 (851 mg, 2.23 mmol, 1.0 equiv.) was dissolved in 8 mL CH₂Cl₂, then ethylene glycol (2 mL, approx. 10 equiv.), trimethylorthoformate (2 mL, approx. 5 equiv.), 2-ethyl-2-methyl-1,3-dioxolane (10 drops from a glass pipet), and CSA (52 mg, 0.223 mmol, 0.1 equiv.) were added successively. The resulting solution was allowed to heat at 55 °C overnight in a sealed vial. After the solution was allowed to cool to rt, Et₃N (63 µL, 0.446 mmol, 0.2 equiv.) was added and the solvent was removed under reduced pressure. The residue diluted with Et₂O and water, the organic layer was removed, and the aqueous layer was extracted three times with Et₂O. The organic layers were combined, washed with water and brine, then dried with MgSO₄, filtered, and the solvent was removed under reduced pressure to provide 903 mg (98%) of ketal 4.38, which was taken on without further purification. 

$^1$H NMR (500 MHz, CDCl₃) $\delta$ 6.62 and 6.60 (2t, $J = 2.5$, 1H), 3.85 – 3.48 (m, 6H), 3.64 and 3.65 (2s, 6H), 3.41 – 3.29 (m, 1H), 3.10 – 3.00 (m, 1H), 2.90 – 2.78 (m, 1H), 2.70 (dd, $J = 3.1$, 19.0, 1H), 2.03 and 2.02 (2d, $J = 15.3$, 1H), 1.96 – 1.83 (m, 2H), 1.34 and 1.33 (2s, 9H), 1.16 and 1.15 (2s, 3H); $^{13}$C NMR (126 MHz, CDCl₃) $\delta$ 171.78, 171.61, 164.83, 164.67, 153.61, 152.93, 141.74,

171
Acid 4.39: An aqueous solution of LiOH (1.0 M, 7.0 mL, 7.0 mmol, 3.3 equiv.) was added to a solution of ester 4.38 (898 mg, 2.11 mmol, 1.0 equiv.) in 7 mL THF and 7 mL methanol. The resulting pale yellow solution was allowed to heat at 60 °C for 24 hours. The solution was allowed to cool to rt before the THF and methanol were removed under reduced pressure. The resulting aqueous solution was treated with 10 mL EtOAc and 25 mL brine. Acetic acid (400 µL, 7.0 mmol, 3.3 equiv.) was then added to the resulting biphasic solution. The organic layer was removed and the aqueous layer was extracted four times with 10 mL EtOAc. The combined organic layers were dried with MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was azeotroped once with hexanes and dried under high vacuum to provide 842 mg (95%, two steps) of acid 4.39 as a colorless solid, mp 191–194 °C. This material was taken on without further purification. ¹H NMR (500 MHz, CDCl₃) δ 6.81 and 6.78 (2t, J = 2.4, 1H), 3.89 – 3.61 (m, 5H), 3.71 and 3.70 (2s, 3H), 3.42 (ddd, J = 1.9, 17.0, 19.0, 1H), 3.18 – 3.05 (m, 1H), 2.97 – 2.83 (m, 1.4H), 2.79 (dd, J = 3.2, 19.2, 0.6H), 2.13 – 1.85 (m, 3H), 1.40 and 1.38 (2s, 9H), 1.22 and 1.21 (2s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 171.83,
Barton ester 4.40: A solution of acid 4.39 (590 mg, 1.43 mmol, 1.0 equiv.) and DMAP (18 mg, 0.143 mmol, 0.1 equiv.) in 14 mL CH₂Cl₂ was treated with 2-mercaptopyridine N-oxide (201 mg, 1.58 mmol, 1.1 equiv.) and EDC (412 mg, 2.15 mmol, 1.5 equiv.). The resulting yellow solution was allowed to stir at rt overnight before the solvent was removed under reduced pressure. The residue was diluted with Et₂O and the organic layer was washed with once with water, once with saturated aqueous NH₄Cl, and once with saturated aqueous NaHCO₃. The organic layer was dried with MgSO₄, filtered, and concentrated under reduced pressure to give 594 mg (80%) of Barton ester 4.40 as a light yellow oil. This material was taken on without further purification. ¹H NMR (500 MHz, CDCl₃) δ 8.45 (d, J = 4.1, 0.2H), 7.69 – 7.42 (m, 4.4H), 7.18 (dd, J = 1.6, 6.9, 8.6, 1H), 6.61 (q, J = 6.6, 1H), 3.95 – 3.65 (m, 6H), 3.73 (s, 3H), 3.52 (dd, J = 2.0, 16.1, 19.5, 1H), 3.34 – 3.22 (m, 1H), 3.05 (dd, J = 3.1, 19.7, 0.5H), 2.99 – 2.89 (m, 1.5H), 2.13 – 1.88 (m, 4H), 1.42 and 1.40 (2s, 9H), 1.28 and 1.27 (2s, 3H).
Vinyl bromide 4.41: A solution of Barton ester 4.40 (594 mg, 1.14 mmol, 1.0 equiv.) and AIBN (57 mg, 0.342 mmol, 0.3 equiv.) in 7.5 mL BrCCl₃ was added dropwise over 30 minutes to 15 mL of BrCCl₃ maintained at 100 °C. Once the addition was complete, the reaction was allowed to heat five minutes more at 100 °C, then the solution was allowed to cool to rt and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 0→10→20→30% EtOAc/hexanes) to give 332 mg (65%, or 52% over two steps) of vinyl bromide 4.41 as a colorless oil. TLC: Rᵣ=0.34 (SiO₂, 1:2 EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 5.88 and 5.86 (2dd, J = 1.9, 3.3, 1H), 3.92 – 3.58 (m, 6H), 3.70 and 3.69 (2s, 3H), 3.26 and 3.21 (2dd, J = 1.8, 17.2, 1H), 3.15 – 3.01 (m, 1H), 2.78 and 2.64 (2dd, J = 3.4, 17.2, 1H), 2.24 – 2.13 (m, 1H), 2.12 – 1.86 (m, 3H), 1.40 and 1.38 (2s, 9H), 1.26 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 171.41, 171.18, 153.42, 152.93, 130.97, 130.49, 125.30, 108.52, 80.45, 80.04, 76.17, 76.11, 66.01, 64.78, 64.15, 63.97, 52.26, 52.18, 45.42, 45.24, 42.06, 41.84, 40.15, 39.06, 33.90, 33.10, 28.52, 25.48, 25.44; HRMS (ESI-TOF) C₁₉H₂₈BrNO₆ m/z calecd for [M+Na]⁺ 468.0998; found 468.0991.
Vinyl cyclobutanol 4.43: A solution of vinyl bromide 4.41 (105 mg, 0.235 mmol, 1.0 equiv.) in 2.4 mL THF was allowed to cool to –78 °C, then t-BuLi (1.7 M in pentane, 346 mL, 0.588 mmol, 2.5 equiv.) was added dropwise over five minutes. The resulting solution was allowed to stir at –78 °C for five minutes, then cyclobutanone (27 mL, 0.353 mmol, 1.5 equiv.) was added in one portion. The flask was removed from the cooling bath for five minutes before the reaction solution was quenched with saturated aqueous NaHCO₃. EtOAc was added, the organic layer was removed, and the aqueous layer was extracted four times with EtOAc. The combined organic layers were dried with MgSO₄, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 0 → 10 → 20 → 30 → 40 → 50% EtOAc/hexanes) to give 47 mg (46%) of vinyl cyclobutanol 4.43 and 42 mg (49%) of cyclopentene 4.44, both as colorless oils. Vinyl cyclobutanol 4.43: TLC: Rₜ=0.20 (SiO₂, 1:2 EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 5.56 and 5.52 (2s, 1H), 4.59 and 4.56 (2s, 1H), 3.90 – 3.81 (m, 1H), 3.81 – 3.70 (m, 2H), 3.70 – 3.50 (m, 1H), 3.61 (s, 3H), 3.23 (t, J = 15.7, 1H), 3.17 – 3.01 (m, 1H), 2.61 – 2.37 (m, 3H), 2.24 – 2.12 (m, 2H), 2.04 – 1.75 (m, 5H), 1.71 – 1.57 (m, 1H), 1.34 and 1.32 (2s, 9H), 1.08 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 172.15, 171.92, 153.54, 153.15, 146.99, 146.91, 124.39, 123.78, 109.05, 80.07, 79.62, 79.22, 79.15, 75.88, 75.79, 65.03, 64.40, 63.78, 62.88, 62.83, 51.84, 51.76, 45.44, 45.20, 44.16, 44.06, 40.25, 39.21, 38.38, 38.25, 36.97, 36.89, 34.65, 33.78, 28.49, 28.42, 25.36, 14.33, 14.24; HRMS (ESI-TOF) C₂₃H₃₅NO₇ m/z calcd for [M+Na]+ 460.2311; found 460.2308. Cyclopentene 4.44: TLC: Rₜ=0.46 (SiO₂, 1:2 EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 5.70 – 5.52 (m, 2H), 3.94 – 3.83 (m, 4H), 3.76 and 3.66 (2dd, J = 8.6, 10.3, 1H), 3.67 (s, 3H), 3.37 – 3.25 (m, 1H), 3.19 – 3.06.
(m, 1H), 2.78 and 2.66 (2dd, J = 2.3, 17.7, 1H), 2.15 – 1.82 (m, 4H), 1.53 and 1.51 (2d, J = 14.1, 1H), 1.39 and 1.36 (2s, 9H), 1.28 and 1.27 (2s, 3H).

Cyclopentanone 4.46: To a solution of vinyl cyclobutanol 4.43 (47 mg, 0.107 mmol, 1.0 equiv.) in 700 µL CDCl₃ was added VO(acac)₂ (3 mg, 0.0113 mmol, 0.1 equiv.) and the resulting green solution was treated with t-BuOOH (5.5 M in decane, 58 µL, 0.321 mmol, 3.0 equiv.). The resulting reddish-purple solution was allowed to stir at rt for one hour, then at 50 °C for five hours before the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 0 → 10 → 20 → 30 → 40 → 50% EtOAc/hexanes) to give 4 mg of a mixture of cyclopentanone 4.46 along with its methyl ketone analog as a colorless foam. ¹³C APT NMR (126 MHz, CDCl₃) δ 205.79, 205.68, 197.45, 197.29, 172.19, 172.12, 166.88, 166.06, 153.73, 152.98, 134.29, 134.19, 98.13, 83.37, 80.76, 80.58, 80.40, 76.51, 76.05, 75.85, 63.48, 62.22, 60.23, 52.59, 52.51, 52.20, 47.78, 46.94, 46.86, 46.39, 45.95, 45.68, 45.40, 38.57, 38.53, 38.06, 37.79, 35.04, 33.78, 33.70, 33.08, 32.67, 31.78, 31.41, 31.28, 29.92, 29.05, 28.60, 28.56, 28.51, 27.21, 23.18, 23.14, 22.87, 21.76, 17.14, 14.65, 14.42, 14.35, 11.98.
Vinyl squarate 4.47: A solution of vinyl bromide 4.41 (20 mg, 0.0448 mmol, 1.0 equiv.) in 500 mL THF was allowed to cool to −78 °C, then n-BuLi (2.5 M in hexanes, 22 mL, 0.0538 mmol, 1.2 equiv.) was added dropwise over five minutes. The resulting solution was allowed to stir at −78 °C for five minutes, then a solution of di-t-butyl squarate (16 mg, 0.0672 mmol, 1.5 equiv.) in 100 mL THF was added in one portion. The flask was removed from the cooling bath for five minutes before the reaction solution was quenched with saturated aqueous NaHCO₃. EtOAc was added, the organic layer was removed, and the aqueous layer was extracted four times with EtOAc. The combined organic layers were dried with MgSO₄, filtered, and the solvent was removed under reduced pressure to give 35 mg of crude vinyl squarate 4.47. ¹H NMR (500 MHz, CDCl₃) δ 5.98 (2s) and 5.72 (s, 1H total), 5.61 (ddd, J = 2.0, 3.4, 7.1) and 5.52 (ddd, J = 1.8, 2.9, 15.7, 1H total), 4.47 – 4.35 and 4.12 – 4.01 (2m, 1H), 4.01 – 3.71 (m, 4H), 3.71 – 3.55 (m, 1H), 3.66 and 3.65 (2s, 3H), 3.42 – 3.23 (m, 1H), 3.23 – 2.94 (m, 1H), 2.70 (td, J = 5.9, 12.8, 1H), 2.65 – 2.36 (m, 2H), 2.18 – 1.74 (m, 3H), 1.57 (s, 9H), 1.52 – 1.33 (m, 27H), 1.16 – 1.09 (m, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 188.80, 186.52, 186.46, 185.70, 183.23, 182.58, 172.08, 171.85, 167.36, 166.89, 165.57, 164.90, 153.68, 153.04, 140.81, 140.57, 140.17, 130.35, 130.10, 130.01, 129.92, 128.93, 128.31, 127.69, 108.88, 108.63, 89.09, 87.23, 85.39, 85.27, 84.67, 84.53, 83.80, 83.66, 83.63, 80.60, 80.30, 80.19, 80.13, 80.00, 79.59, 78.64, 78.56, 78.43, 64.85, 64.62, 64.29, 64.15, 64.03, 63.09, 62.89, 62.83, 51.96, 51.85, 45.84, 45.50, 45.29, 43.96, 43.87, 43.79, 40.87, 39.78, 35.68, 35.16,
34.31, 34.21, 29.10, 29.07, 29.04, 29.01, 28.85, 28.52, 26.05, 25.60, 25.49, 25.43; HRMS (ESI-TOF) C\textsubscript{31}H\textsubscript{47}NO\textsubscript{10} \textit{m/z} calcld for [M+Na]\textsuperscript{+} 616.3098; found 616.3091.

Extended conjugation product \textit{4.48}: To a solution of vinyl squarate \textit{4.47} (from above, approx. 0.045 mmol, 1 equiv.) in 700 \textmu L CDCl\textsubscript{3} was added VO(acac)	extsubscript{2} (1 mg, 0.00448 mmol, 0.1 equiv.) and the resulting green solution was treated with \textit{t}-BuOOH (5.5 M in decane, 25 \textmu L, 0.138 mmol, 3.0 equiv.). The resulting reddish-purple solution was allowed to stir at rt for six hours before the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO\textsubscript{2}, 0 \rightarrow 10 \rightarrow 20 \rightarrow 30 \rightarrow 40 \rightarrow 50\% EtOAc/hexanes) to give 12 mg (52%, two steps) of extended conjugation product \textit{4.48} as a colorless foam. \textit{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}) \textit{\delta} 7.06 – 6.90 (m, 1H), 3.87 – 3.78 (m, 1H), 3.78 – 3.60 (m, 3H), 3.72 and 3.71 (2s, 3H), 3.60 – 3.49 (m, 1H), 3.43 – 3.33 (m, 1H), 3.07 – 2.84 (m, 2H), 2.53 (t, \(J = 16.7\), 1H), 2.35 (td, \(J = 5.7, 12.4\), 1H), 2.14 – 1.92 (m, 2H), 1.64 (s, 9H), 1.40 and 1.39 (2s, 9H), 1.12 and 1.11 (2s, 3H).
Vinyl squarate 4.49: A solution of vinyl bromide 4.41 (20 mg, 0.0448 mmol, 1.0 equiv.) in 500 µL THF was allowed to cool to –78 °C, then n-BuLi (2.5 M in hexanes, 22 µL, 0.0538 mmol, 1.2 equiv.) was added dropwise over five minutes. The resulting solution was allowed to stir at –78 °C for five minutes, then a solution of dimethyl squarate (10 mg, 0.0672 mmol, 1.5 equiv.) in 100 µL THF was added in one portion. The flask was removed from the cooling bath for five minutes before the reaction solution was quenched with saturated aqueous NaHCO₃. EtOAc was added, the organic layer was removed, and the aqueous layer was extracted four times with EtOAc. The combined organic layers were dried with MgSO₄, filtered, and the solvent was removed under reduced pressure to give 24 mg of crude vinyl squarate 4.49. ¹H NMR (500 MHz, CDCl₃) δ [6.02, 5.96, 5.88, and 5.85 (4s, 1H total)], 5.71 and 5.60 (2ddd, J = 1.9, 2.9, 22.9, 1H), 4.13 and 4.12 (2s, 2H), 4.10 (s, 1H), 4.00 – 3.87 (m, 5H), 3.87 – 3.76 (m, 2H), 3.76 – 3.55 (m, 1H), 3.67 and 3.68 (2s, 3H), 3.42 – 3.26 (m, 1H), 3.19 – 2.96 (m, 1H), 2.72 – 2.58 (m, 1H), 2.58 – 2.20 (m, 2H), 2.05 – 1.61 (m, 2H), 1.42 – 1.34 (m, 9H), 1.18 – 1.12 (m, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 187.22, 186.13, 183.33, 182.74, 172.00, 171.80, 168.31, 168.02, 166.30, 165.70, 153.66, 153.18, 153.06, 140.27, 136.99, 134.50, 134.23, 134.20, 134.06, 129.47, 129.24, 128.60, 128.23, 109.78, 108.95, 108.63, 91.10, 86.91, 86.80, 85.61, 80.30, 80.10, 79.69, 78.69, 78.62, 78.51, 64.78, 64.57, 64.31, 64.14, 63.97, 63.77, 63.04, 62.91, 62.87, 62.82, 60.81, 60.67, 60.60, 58.64, 52.23, 52.01, 51.92, 45.82, 45.56, 45.30, 43.85, 43.72, 43.65, 40.85, 40.73, 39.77, 35.47, 35.14, 34.26, 28.56, 28.50, 26.03, 25.45, 25.31, 25.27; HRMS (ESI-TOF) C₂₅H₃₅NO₁₀ m/z calcd for [M+Na]⁺ 532.2159; found 532.2152.
Chlorination product 4.51: Vinyl squarate 4.49 (from above, approx. 0.045 mmol, 1 equiv.) was dissolved in 750 µL CDCl₃ and the vial was wrapped in aluminum foil before t-BuOCl (prepared fresh and stored over CaCl₂, 6 µL, 0.049 mmol, 1.1 equiv.) was added in one portion. The resulting solution was allowed to stir at rt for one hour, then at 55 °C for five hours before the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO₂, 0 → 10 → 20 → 30 → 40 → 50% EtOAc/hexanes) to give 3 mg of chlorination product 4.51 as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 5.67 (dd, J = 5.3, 7.0) and 5.59 (2d, J = 6.8, 1H total), 3.89 – 3.76 (m, 2H), 3.76 – 3.64 (m, 9H), 3.36 – 3.48 (m, 2H), 3.48 – 3.30 (m, 2H), 3.00 and 2.77 (2d, J = 15.4, 1H), 2.48 and 2.44 (2d, J = 13.2, 1H), 2.30 – 2.13 (m, 1H), 2.00 – 1.88 (m, 3H), 1.39 (m, 9H), 1.23 (s, 3H); ¹³C APT NMR (126 MHz, CDCl₃) δ 203.31, 203.23, 171.95, 171.80, 162.44, 162.38, 153.19, 152.38, 140.77, 140.70, 132.87, 132.60, 101.87, 101.85, 97.39, 97.35, 80.80, 80.30, 77.77, 77.65, 62.23, 61.01, 56.89, 56.38, 55.79, 55.72, 55.70, 54.97, 52.84, 52.74, 48.20, 48.07, 45.66, 45.48, 44.04, 42.32, 34.41, 33.87, 32.49, 30.16, 30.07, 29.93, 28.66, 28.58, 27.14.
E.5 NMR Spectra

2.17 (500 MHz, CDCl₃)
2.17
(126 MHz, CDCl₃)
2.18
(500 MHz, CDCl₃)
2.18 (126 MHz, CDCl₃)
2.19
(500 MHz, CDCl₃)

^H

OTBS

-500
0
500
1000
1500
2000
2500
3000
3500
4000
4500
5000
5500
6000
6500
7000
7500

0.00.51.01.52.02.53.03.54.04.55.05.56.06.57.07.58.0
f1 (ppm)
2.19
(126 MHz, CDCl₃)
2.22

(500 MHz, CDCl₃)
H₂C₂O₂C

OTBS

2.22

(126 MHz, CDCl₃)
2.23
(126 MHz, CDCl$_3$)
N\O\OTBS

2.25
(500 MHz, CDCl₃)
2.25
(126 MHz, CDCl₃)
2.38
(126 MHz, CDCl₃)
Boc

OTBS

2.40

(500 MHz, CDCl₃)
OTBS

Boc

2.40
(126 MHz, CDCl₃)
Boc
OTBS

2.41
(500 MHz, CDCl₃)
OTBS

2.41
(126 MHz, CDCl₃)
Boc

(OH)

N

Boc

2.50

(500 MHz, CDCl3)
Boc

2.50
(126 MHz, CDCl₃)
Boc

2.51

(500 MHz, CDCl₃)
\[
\text{\textbf{O N Boc}} \\
2.51 \\
(126 \text{ MHz, CDCl}_3)
\]
$2.52$

$(300 \text{ MHz, CDCl}_3)$
Boc

2.53
(500 MHz, CDCl₃)
2.53 (126 MHz, CDCl\textsubscript{3})
N
Boc
OH
2.54
(400 MHz, CDCl₃)
3.8
(500 MHz, CDCl₃)
3.8
(126 MHz, CDCl₃)
HO$_2$C
$\text{SO}_2\text{N}_3$

(500 MHz, CDCl$_3$/DMSO-d$_6$)
$\text{HO}_2\text{C} \xrightarrow{\text{SO}_2\text{N}_3} \text{HO}_2\text{C}$

$(126 \text{ MHz, CDCl}_3/\text{DMSO-d}_6)$
Boc-\text{N} \text{CH}_3

3.9
(500 MHz, CDCl$_3$)
3.9
(126 MHz, CDCl₃)
$\text{Boc}$

$\text{OCH}_3$

3.10
(126 MHz, CDCl$_3$)

![NMR spectrum]
3.11
(300 MHz, CDCl₃)
$\text{TBSO}^+\rightarrow\text{OH}$

$\text{H}_2\text{CO}_2\text{C} \rightarrow \text{Boc}$

3.16
(300 MHz, CDCl$_3$)
$\text{H}_3\text{CO}_2\text{C Boc}$

3.17

(300 MHz, CDCl$_3$)
N
H3CO2C Boc
O
3.29
(500 MHz, CDCl3)
\[
\text{N} \text{H}_3 \text{CO}_2 \text{C Boc} \text{O}_3 \text{Boc}
\]

3.29

(126 MHz, CDCl$_3$)
$\text{N} \text{H}_3 \text{CO}_2 \text{C} \ 	ext{Boc} \ 	ext{OH}$

3.31

(500 MHz, CDCl$_3$)
$\text{NHN} \text{CO}_2\text{C} \text{Boc}$

$3.31$

(126 MHz, CDCl$_3$)
\[
\text{N} \quad \text{H}_3 \text{CO}_2 \text{C Boc}
\]

3.32 (500 MHz, CDCl\text{3})
$\text{N} \quad \text{H}_3\text{CO}_2\text{C} \quad \text{Boc} \quad \text{O} \quad \text{H}_3$
3.33
(500 MHz, CDCl₃)
$$3.33$$

$$\text{(126 MHz, CDCl}_3\text{)}$$
3.25
(500 MHz, CDCl₃)
3.25 (126 MHz, CDCl₃)
3.27
(500 MHz, CDCl₃)
3.27 (126 MHz, CDCl₃)
$\text{H}_2\text{CO}$

3.34

(500 MHz, CDCl$_3$)
3.34
(126 MHz, CDCl₃)
Boc-NH\textsubscript{2}C\textsubscript{6}H\textsubscript{4}O\textsubscript{2}\textsubscript{Bu}

(500 MHz, CDCl\textsubscript{3})
$\text{N}{\text{Boc}}\text{O}{\text{tBu}}$

3.35

(500 MHz, CDCl$_3$)

\begin{align*}
\text{f1 (ppm)} & : \quad \text{0.0} \quad \text{0.5} \quad \text{1.0} \quad \text{1.5} \quad \text{2.0} \quad \text{2.5} \\
\text{δ (ppm)} & : \quad \text{7.5} \quad \text{8.0} \quad \text{8.5} \quad \text{9.0} \quad \text{9.5} \quad \text{10.0}
\end{align*}
NtBuO₂C Boc

3.37
(500 MHz, CDCl₃)
N\textsubscript{t}BuO\textsubscript{2}C Boc

3.37

(126 MHz, CDCl\textsubscript{3})
3.39
(300 MHz, CDCl₃)
3.40
(300 MHz, CDCl₃)
N3.41
(400 MHz, CDCl3)

\[
\begin{align*}
\text{f1 (ppm)} & \quad 0.0 \quad 0.5 \quad 1.0 \quad 1.5 \quad 2.0 \quad 2.5 \quad 3.0 \quad 3.5 \quad 4.0 \quad 4.5 \quad 5.0 \quad 5.5 \quad 6.0 \quad 6.5 \quad 7.0 \quad 7.5
\end{align*}
\]
\[
\begin{align*}
&\text{H}_3\text{CO}^+ \\
&\text{O} \\
&\text{N}^+ \text{Boc} \\
&\text{H}_3\text{CO}^+ \\
\end{align*}
\]

(300 MHz, CDCl₃)
4.4
(300 MHz, CDCl₃)
4.1
(300 MHz, CDCl₃)
$\text{HO}$

$\text{H}_2\text{CO}$

$4.54$

$(300 \text{ MHz, CDCl}_3)$
Br
\text{H}_2\text{CO}
\text{O}

4.7

(300 MHz, CDCl$_3$)
4.8
(400 MHz, CDCl₃)
4.10
(300 MHz, CDCl₃)
4.11
(300 MHz, CDCl₃)
N Boc
CO₂CH₃
O
4.22
(500 MHz, CDCl₃)
N\text{Boc} \text{CO}_2\text{CH}_3 \text{O} \quad 4.22 \\
(126 \text{ MHz, CDCl}_3)
N Boc
Br
CO₂CH₃
O
4.23
(126 MHz, CDCl₃)
-500
0
500
1000
1500
2000
2500
3000
3500
4000
4500
5000
5500
6000
6500
1 0.1 0
3 .27
0 .87
0 .30
1 .39
3 .16
1 .13
1 .00
N Boc
Br
CO₂CH₃
OH
epi-4.24
(500 MHz, CDCl₃)

<table>
<thead>
<tr>
<th>δ (ppm)</th>
<th>p.p.m.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>0.5</td>
</tr>
<tr>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>2.0</td>
<td>2.5</td>
</tr>
<tr>
<td>3.0</td>
<td>3.5</td>
</tr>
<tr>
<td>4.0</td>
<td>4.5</td>
</tr>
<tr>
<td>5.0</td>
<td>5.5</td>
</tr>
<tr>
<td>6.0</td>
<td>6.5</td>
</tr>
<tr>
<td>7.0</td>
<td>7.5</td>
</tr>
<tr>
<td>8.0</td>
<td>8.5</td>
</tr>
</tbody>
</table>
$\text{H}_3\text{CO}_2\text{C}$

$\text{CO}_2\text{CH}_3$

$\text{N}^{\text{Boc}}$

$4.26$

$(300 \text{ MHz, CDCl}_3)$
257
N\_Boc
CO\_2H
HO
4.28
(500 MHz, CDCl\_3)
$\text{AcO} \quad \text{CO}_2\text{CH}_3 \quad 4.29$

(300 MHz, CDCl$_3$)
$\text{CH}_3\text{CO}_2\text{CH}_3\text{O}^\text{OTf}\text{N}^\text{Boc}\text{H}_3\text{CO}$

$\delta$ (ppm, CDCl$_3$)

0.00 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0 5.5 6.0 6.5 7.0 7.5 8.0 8.5 9.0 9.5 10.0

0 500 1000 1500 2000 2500

4.33 (500 MHz, CDCl$_3$)
$CH_3CO_2CH_3O\text{OTf}\text{N}\text{Boc}H_3CO\text{O}$

4.33

(126 MHz, CDCl₃)
4.34
(500 MHz, CDCl₃)
4.34 (126 MHz, CDCl₃)
4.38
(500 MHz, CDCl₃)
4.38
(126 MHz, CDCl₃)
4.39
(500 MHz, CDCl₃)
4.39 ppm
(126 MHz, CDCl₃)
(500 MHz, CDCl₃)
Br

\( \text{CH}_2 \text{CO}_2\text{CH}_3 \text{N Boc} \) (500 MHz, CDCl\(_3\))

\( 4.41 \)

\((\text{ppm})\)

-100
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
1300
1400

3.1 2
9.7 1
3.5 4
1.0 9
1.0 3
1.0 2
1.0 0
8.3 6
0.8 4
CH₃\(\text{CO}_2\text{CH}_3\)

4.43

(126 MHz, CDCl₃)
\[
\text{CH}_2\text{CO}_2\text{CH}_3
\]

Boc

4.44

(500 MHz, CDCl\textsubscript{3})
4.46
(500 MHz, CDCl₃)

[Chemical Structure Image]
\[\text{OH} \quad \text{N-Boc} \quad \text{CH}_3 \quad \text{CO}_2\text{CH}_3\]

4.46

(126 MHz, CDCl$_3$)
$\text{CH}_3\text{CO}_2\text{CH}_3\text{N}$

BocO

O

O

H

O
Ot-Bu
t-BuO

4.47

(126 MHz, CDCl$_3$)
$^{13}C$ NMR spectrum of the compound 4.48 (500 MHz, CDCl$_3$)
(500 MHz, CDCl₃)
$\text{H}_2\text{CO}$

$\text{O}$

$\text{OCH}_3$

$\text{H}$

$\text{O}$

$\text{N}$

$\text{Boc}$

$\text{O}$

$\text{O}$

$\text{H}$

$\text{O}$

$\text{OCH}_3$

$\text{H}_3\text{CO}$

$\text{N}$

$\text{Boc}$

$4.49$

(126 MHz, CDCl$_3$)
4.51
(500 MHz, CDCl₃)
4.51
(126 MHz, CDCl₃)