HIGHLY SELECTIVE AUXILIARY-MEDIATED ACETATE ALDOL ADDITIONS
AND PROGRESS TOWARDS THE TOTAL SYNTHESIS OF (−)-BREVENAL

Mariam Shamszad

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Approved by,

Michael T. Crimmins
Jeffrey S. Johnson
Cynthia K. Schauer
Joesph L. Templeton
Marcey L. Waters
ABSTRACT

Mariam Shamszad

Highly Selective Auxiliary-Mediated Acetate Aldol Additions and Progress Towards the Total Synthesis of (−)-Brevenal

(Under the direction of Michael T. Crimmins)

The development of a highly selective acetate aldol addition using chlorotitanium enolates of novel mesityl-substituted N-acetyloxazolidinethione and N-acetylthiazolidinethione auxiliaries is herein described. This method proceeds in high yields and diastereoselectivity for aliphatic, aromatic, α, β-unsaturated, and non-racemic aldehydes, efficiently generating the β-hydroxycarbonyl subunit, prevalent in polyketide-derived natural products.

Efforts towards the total synthesis of the marine pentacyclic polyether, (−)-brevenal, are also described. (−)-Brevenal has been found to counteract the toxic effects of the brevetoxins, a family of molecules also produced by Karenia brevis, alleviating respiratory distress. A highly convergent route to (−)-brevenal is herein illustrated in which a Horner-Wadsworth-Emmons reaction is used to couple two key complex cyclic ether fragments. In addition, an asymmetric glycolate alkylation/ring-closing metathesis strategy has been employed to synthesize two of the five rings.
# TABLE OF CONTENTS

LIST OF TABLES ........................................................................................................ vi
LIST OF SCHEMES .................................................................................................... vii
LIST OF FIGURES ...................................................................................................... ix
LIST OF ABBREVIATIONS .......................................................................................... x

Chapter

1. DEVELOPMENT OF A HIGHLY SELECTIVE ACETATE ALDOL ADDITION .................................................................................................................. 1

   A. Background ........................................................................................................ 2

      (i) Asymmetric Aldol Additions Using Chiral Auxiliaries ......................... 2

      (ii) Previous Advances in the Acetate Aldol Addition .............................. 4

   B. Asymmetric Acetate Aldol Additions Using Mesityl-Substituted Auxiliaries .................................................................................................................. 5

      (i) Acetate Aldol Additions Using a Mesityl-Substituted Oxazolidinethione ....................................................................................................................... 7

      (ii) Acetate Aldol Additions Using a Mesityl-Substituted Thiazolidinethione ..................................................................................................................... 11

   C. Iterative Aldol Additions Using a Mesityl-Substituted Thiazolidinethione ......................................................................................................................... 17

   D. Summary ........................................................................................................... 18

   E. References ......................................................................................................... 19

2. PROGRESS TOWARDS THE TOTAL SYNTHESIS OF (−)-BREVENAL ................................................................................................................................. 22
A. Background ......................................................................................................................... 22
  (i) Isolation and Biological Activity of (−)-Brevenal .................................................. 22
  (ii) Previous Synthetic Efforts ......................................................................................... 24
B. Studies Towards the Total Synthesis of (−)-Brevenal ........................................ 29
  (i) Retrosynthetic Analysis ............................................................................................ 29
  (ii) Application of the Acetate Aldol Methodology to the Synthesis of the AB-Ring Fragment .......................................................................................................................... 30
  (iii) Revised Synthesis of the AB-Ring Fragment .......................................................... 40
  (iv) Coupling of the AB-Ring and E-Ring Fragments .................................................. 47
  (v) Attempts at D-Ring Formation ................................................................................... 49
  (vi) Revised Retrosynthesis of (−)-Brevenal ................................................................. 54
C. Summary .......................................................................................................................... 55
D. References ......................................................................................................................... 56

3. EXPERIMENTAL INFORMATION AND NMR SPECTRA FOR CHAPTER 1 ................................................................. 61

4. EXPERIMENTAL INFORMATION AND NMR SPECTRA FOR CHAPTER 2 ................................................................. 143
LIST OF TABLES

Table 1.1 Evans' propionate aldol addition .................................................. 2
Table 1.2 Acetate aldol additions of N-acetyloxazolidinethione 4 ............ 8
Table 1.3 Acetate aldol additions of N-acetyloxazolidinethione 14 .......... 11
Table 1.4 Acetate aldol additions of N-acetylthiazolidinethione 25 .......... 14
Table 1.5 Attempts at selectivity reversal ..................................................... 16
Table 2.1 Attempts at enone reduction ......................................................... 34
Table 2.2 Attempts at D-ring formation ......................................................... 51
LIST OF SCHEMES

Scheme 1.1 Racemic synthesis of $N$-acetyloxazolidinethione 4 .................. 7
Scheme 1.2 Initial enantioselective route .................................................. 9
Scheme 1.3 Enantioselective synthesis of $N$-acetyloxazolidinethione 14 .......................... 10
Scheme 1.4 Attempts at thiazolidinethione formation ................................. 12
Scheme 1.5 Initial attempts at $N$-acetylthiazolidinethione 21 .................... 12
Scheme 1.6 Enantioselective synthesis of $N$-acetylthiazolidinethione 25 .......................... 13
Scheme 1.7 Condensed route to thiazolidinethione 24 ................................. 14
Scheme 1.8 Iterative aldol additions .......................................................... 17
Scheme 2.1 Sasaki’s synthesis of the AB-ring exo olefin 36 .......................... 26
Scheme 2.2 Sasaki’s synthesis of the DE-ring enol phosphate 37 .......................... 27
Scheme 2.3 Sasaki’s synthesis of the pentacyclic polyether core .......................... 28
Scheme 2.4 Completion of Sasaki’s synthesis of (–)-brevenal ........................ 29
Scheme 2.5 Synthesis of aldehyde 75 .......................................................... 31
Scheme 2.6 Synthesis of $\beta$-ketophosphonate 74 ........................................ 32
Scheme 2.7 Acetate aldol addition with $N$-acetylthiazolidinethione 25 .......................... 32
Scheme 2.8 Synthesis of A-ring enol ether 87 .............................................. 33
Scheme 2.9 Attempt at A-ring enol ether formation ...................................... 35
Scheme 2.10 Revised synthesis of A-ring enol ether ..................................... 35
Scheme 2.11 Second revised synthesis of the A-ring enol ether ...................... 36
Scheme 2.12  Epoxidation-methylation attempt ........................................... 37
Scheme 2.13  Attempts at mixed acetal formation ........................................... 39
Scheme 2.14  Synthesis of enol ether 112 ...................................................... 42
Scheme 2.15  Epoxidation-methylation sequence ........................................... 43
Scheme 2.16  Synthesis of mixed acetal 128 .................................................. 43
Scheme 2.17  Synthesis of A-ring pyran 131 .................................................. 44
Scheme 2.18  Synthesis of alcohol 133 ............................................................ 45
Scheme 2.19  Synthesis of bicycle 137 ............................................................ 46
Scheme 2.20  Completion of AB-ring fragment 68 .......................................... 47
Scheme 2.21  Synthesis of E-ring aldehyde 69 ............................................... 48
Scheme 2.22  Coupling of the AB-ring and E-ring fragments ......................... 49
Scheme 2.23  Attempts at one-pot D-ring formation ....................................... 49
Scheme 2.24  Attempts at D-ring formation ..................................................... 50
Scheme 2.25  Attempts at D-ring formation ..................................................... 51
Scheme 2.26  Attempts at D-ring formation ..................................................... 52
Scheme 2.27  Synthesis of hydroxy ketone 163 .............................................. 53
Scheme 2.28  Attempts at D-ring formation ..................................................... 54
LIST OF FIGURES

Figure 1.1  Representative acetate aldol addition .............................................. 2
Figure 1.2  Propionate aldol additions ................................................................. 3
Figure 1.3  Proposed transition states for propionate aldol additions .............. 4
Figure 1.4  Selected auxiliaries developed for the acetate aldol addition ............. 5
Figure 1.5  Possible transition states of propionate and acetate aldol additions .................................................. 6
Figure 1.6  X-ray structure of N-acetyloxazolidinethione 14 ..................... 10
Figure 1.7  Possible transition states to account for the observed stereochemistry .............................................. 15
Figure 2.1  The brevetoxins ........................................................................ 23
Figure 2.2  (−)-Brevenal ............................................................................. 24
Figure 2.3  Sasaki’s retrosynthetic analysis ......................................................... 25
Figure 2.4  Original retrosynthetic analysis of (−)-brevenal ........................... 30
Figure 2.5  Original retrosynthetic analysis of AB-ring fragment 68 .................. 30
Figure 2.6  Possible mechanism for formation of triol 105 .............................. 38
Figure 2.7  Literature precedent for epoxidation-methylation sequence .......................................................... 40
Figure 2.8  Proposed substrate for epoxidation-methylation sequence .................. 40
Figure 2.9  Revised retrosynthetic analysis of AB-ring fragment 68 .................... 41
Figure 2.10 Revised retrosynthetic analysis of (−)-brevenal ............................. 55
### LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>9-BBN</td>
<td>9-Borabicyclononane</td>
</tr>
<tr>
<td>AcCl</td>
<td>Acetyl chloride</td>
</tr>
<tr>
<td>BF$_3$·Et$_2$O</td>
<td>Boron trifluoride etherate</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>BnBr</td>
<td>Benzyl bromide</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxycarbonyl</td>
</tr>
<tr>
<td>Bu$_2$BOTf</td>
<td>Dibutylboron triflate</td>
</tr>
<tr>
<td>cod</td>
<td>Cyclooctadiene</td>
</tr>
<tr>
<td>CSA</td>
<td>Camphorsulfonic acid</td>
</tr>
<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-Dichloro-5,6-dicyanobenzoquinone</td>
</tr>
<tr>
<td>(DHQ)$_2$PHAL</td>
<td>Hydroquinine 1,4-phthalazinediyl diether</td>
</tr>
<tr>
<td>Dibal</td>
<td>Diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylamino pyridine</td>
</tr>
<tr>
<td>DMDO</td>
<td>Dimethyl dioxirane</td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N$-Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>EtSH</td>
<td>Ethanethiol</td>
</tr>
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</table>
Et$_3$SiH  Triethylsilane
G2  Grubbs’ 2nd generation catalyst
HMPA  Hexamethylphosphoramide
$i$-Bu$_2$AlH  Diisobutylaluminum hydride
imid.  Imidazole
$i$-Pr$_2$NEt  Diisopropylethylamine
KHMDS  Potassium hexamethyldisilazide
KO$t$-Bu  Potassium tert-butoxide
LiDBB  Lithium di-tert-butylbiphenyl
$m$-CPBA  meta-Chloroperoxybenzoic acid
Me  Methyl
MeOH  Methanol
Me$_2$PhSiH  Dimethylphenylsilane
Mes  Mesityl
MPM  4-Methoxybenzyl
$n$-BuLi  n-Butyllithium
NIS  N-Iodosuccinamide
NaHMDS  Sodium hexamethyldisilazide
NMM  N-Methylmorpholine
NMO  N-Methylmorpholine-N-oxide
NMP  N-Methyl pyridinone
$n$-Pr  n-Propyl
NSP  Neurotoxic shellfish poisoning
<table>
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<tr>
<th>Abbreviation</th>
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<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PMB</td>
<td>4-Methoxybenzyl</td>
</tr>
<tr>
<td>PMBOCH₂Cl</td>
<td>1-((chloromethoxy)methyl)-4-methoxybenzene</td>
</tr>
<tr>
<td>p-TsOH</td>
<td>para-Toluenesulfonic acid</td>
</tr>
<tr>
<td>py</td>
<td>pyridine</td>
</tr>
<tr>
<td>SAA</td>
<td>Sharpless asymmetric aminohydroxylation</td>
</tr>
<tr>
<td>Sc(OTf)₃</td>
<td>Scandium (III) trifluoromethanesulfonate</td>
</tr>
<tr>
<td>(Sia)₂BH</td>
<td>Siamylborane</td>
</tr>
<tr>
<td>TAS-F</td>
<td>tris(dimethylamino)sulfonyl difluorotrimethylsilicate</td>
</tr>
<tr>
<td>TBAF</td>
<td>tert-Butylammonium fluoride</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-Butyldiphenylsilyl</td>
</tr>
<tr>
<td>TBDPSCI</td>
<td>tert-Butyldiphenylsilyl chloride</td>
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</tr>
<tr>
<td>TBSOTf</td>
<td>tert-Butyldimethylsilyl trifluoromethanesulfonate</td>
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<tr>
<td>t-BuLi</td>
<td>tert-Butyllithium</td>
</tr>
<tr>
<td>TEMPO</td>
<td>2,2,6,6-Tetramethylpiperidine-1-oxyl</td>
</tr>
<tr>
<td>Tf₂O</td>
<td>Trifluoromethanesulfonic anhydride</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>TfOH</td>
<td>Trifluoromethanesulfonic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TiCl₄</td>
<td>Titanium tetrachloride</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>TIPS</td>
<td>Triisopropylsilyl</td>
</tr>
<tr>
<td>TIPSCI</td>
<td>Triisopropylsilyl chloride</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TMSCI</td>
<td>Trimethylsilyl chloride</td>
</tr>
<tr>
<td>TPAP</td>
<td>Tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>VSSC</td>
<td>Voltage sensitive sodium channels</td>
</tr>
<tr>
<td>Zn(OTf)₂</td>
<td>Zinc trifluoromethanesulfonate</td>
</tr>
</tbody>
</table>
Chapter 1

Development of a Highly Selective Acetate Aldol Addition

On the basis of the seminal report of Evans and coworkers on the use of boron enolates of N-acyloxazolidinones for highly diastereoselective syn-propionate aldol additions,\textsuperscript{1} auxiliary-mediated asymmetric aldol additions have become one of the most valuable methods for the construction of carbon-carbon bonds.\textsuperscript{2-4} In particular, the asymmetric aldol addition has played a significant role in the synthesis of the β-hydroxycarbonyl subunit, prevalent in polyketide-derived natural products.\textsuperscript{5} While high stereocontrol of this reaction can be achieved through the use of chiral ligands and chiral catalysts, auxiliary-based aldol additions remain a valuable and widely employed method. Although many auxiliaries have been developed to promote the asymmetric propionate aldol addition, minimal diastereoselectivity is attained when these auxiliaries are applied to the acetate aldol addition. This chapter will outline the recent advances we have made in the development of highly selective acetate aldol additions using the chlorotitanium enolates of mesityl-substituted N-acetyloxazolidinethione and N-acetyltiazolidinethione auxiliaries (Figure 1.1).
A. Background

(i) Asymmetric Aldol Additions Using Chiral Auxiliaries

The chiral auxiliary-mediated asymmetric aldol addition has been the focus of extensive research over the years, becoming an invaluable method in organic synthesis. In 1981, the pioneering studies of Evans and coworkers established that the use of boron enolates of N-acyloxyazolidinones resulted in a highly diastereoselective propionate aldol addition, via a dipole-minimized transition state (Table 1.1). While this dibutylboron trflate mediated aldol addition is a widely used and well accepted method, it suffers from several limitations: 1) oxazolidinones can be difficult to remove on certain substrates, 2) dibutylboron trflate is more expensive than other Lewis acids and must be freshly distilled prior to use, and 3) an extra step of oxidative workup is required to hydrolyze the dibutylboronates.

**Table 1.1. Evans’ propionate aldol addition.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Yield</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(CH$_3$)$_2$CHCHO</td>
<td>78%</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>2</td>
<td>(CH$_3$)$_2$CHCH$_2$CHO</td>
<td>75%</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>3</td>
<td>PhCHO</td>
<td>88%</td>
<td>&gt;99:1</td>
</tr>
</tbody>
</table>
Since this seminal work, intensive research has led to the development of a large number of chiral auxiliaries that give rise to syn- or anti-propionate aldol products in high yields and excellent diastereoselectivities. In particular, previous work in the Crimmins laboratory has led to the development of highly diastereoselective auxiliary-based propionate aldol additions\textsuperscript{6-8} and anti-selective glycolate aldol additions\textsuperscript{9} through the use of chlorotitanium enolates of $N$-acyloxazolidinethiones and $N$-acylthiazolidinethiones. With respect to the propionate aldol addition, the “Evans” syn and “non-Evans” syn products can both be obtained from the same enantiomer of the chiral auxiliary simply by altering the nature and stoichiometry of the Lewis acid and amine base (Figure 1.2). Specifically, one equivalent each of titanium tetrachloride, (−)-sparteine as the base, and $N$-methyl-2-pyrolidinone (NMP), provides “Evans” syn aldol adducts with selectivities ranging from 97:3 to >99:1. The “non-Evans” syn aldol adducts are attainable with oxazolidinethiones and thiazolidinethiones by altering the stoichiometry of titanium tetrachloride and/or the amine base. The difference in facial selectivity in the aldol additions is believed to be the result of a switch
between chelated and nonchelated transition states, in which the presence of
NMP breaks chelation between the sulfur of the thiocarbonyl of the auxiliary and
titanium, leading to a dipole-minimized, non-chelated transition state, giving rise
to the “Evans” syn aldol adduct (Figure 1.3). Without NMP, the reaction proceeds
through a chelated transition state, giving rise to “non-Evans” syn aldol adducts.
The auxiliaries can then be removed reductively or cleaved by a nucleophilic acyl
substitution to reveal the β-hydroxycarbonyl subunit.

(ii) Previous Advances in the Asymmetric Acetate Aldol Addition

While the development of the asymmetric propionate aldol addition has
reached high levels of success over the years, the advancement of an analogous
method towards an auxiliary-based asymmetric acetate aldol addition has proven
to be a more elusive task; the same auxiliaries that have been successful for
other types of aldol additions result in reduced diastereoselectivity for the acetate
aldol addition, particularly for aliphatic aldehydes. For example, the dibutylboryl
enolate of Evans’ valine-derived acetyl oxazolidinone gives a 52:48 ratio of
diastereomers with isobutyraldehyde and a 72:28 ratio with acetaldehyde when
used for acetate aldol additions.\(^1\) A number of chiral auxiliaries have been
developed in an effort to improve the diastereoselectivity of acetate-type aldol additions involving the use of tin,\textsuperscript{10} lithium,\textsuperscript{11,12} boron,\textsuperscript{13,14} and titanium\textsuperscript{15,16,17,18} chiral acetate enolates (Figure 1.4). These methods, however, suffer from several limitations: 1) the necessity of expensive reagent and/or metals, 2) low reaction temperature (lower than -100 °C), 3) narrow substrate scope, 4) lengthy preparation of the auxiliary, and 5) modest diastereoselectivity. These shortcomings have thereby limited the utility of the asymmetric acetate aldol addition in synthetic applications. To date, the highly hindered auxiliaries recently advanced by Phillips\textsuperscript{17} and Sammakia\textsuperscript{18} provide the most consistent high levels of diastereoselectivity.

![Figure 1.4. Selected auxiliaries developed for the acetate aldol addition.](image)

**B. Asymmetric Acetate Aldol Additions Using Mesityl-Substituted Auxiliaries**

The diminished diastereoselectivity of the acetate aldol addition, in comparison to the high levels of diastereoselectivity attainable for propionate
aldol additions, has been attributed to the lack of substitution at the \( \alpha \)-carbon of the enolate, which is believed to function as an important stereocontrol element. In the propionate aldol addition, it is believed that a chair transition state is preferred over the boat transition state due to the disfavored interactions between the methyl group of the \( \alpha \)-carbon of the enolate and the hydrogen of the aldehyde and between the hydrogen of the \( \alpha \)-carbon and the “R” group of the aldehyde (Figure 1.5). In the case of the acetate aldol addition, because there is no longer a methyl group present at the \( \alpha \)-carbon, the preference for one transition state over the other no longer exists, thereby causing a lack of stereocontrol in the reaction.

![Figure 1.5: Possible transition states of propionate and acetate aldol additions](image)

In an attempt to overcome this issue, we have investigated more sterically encumbered chiral auxiliaries to improve the selectivity of acetate aldol additions using the chlorotitanium enolates of mesityl-substituted \( N \)-acetyloxazolidinethione and \( N \)-acetylthiazolidinethione chiral auxiliaries. Mesityl-substituted auxiliaries were chosen due to the restricted rotational freedom about the bond between the aromatic ring and the benzylic carbon.\(^{19,20}\) This was expected to compensate for
the lack of substitution at the α-carbon and lead to a more ordered transition state, thereby increasing the diastereoselectivity.

(i) Acetate Aldol Additions Using a Mesityl-Substituted Oxazolidinethione

Before investigating an enantioselective synthetic route to the desired mesityl-substituted \( N \)-acetyloxazolidinethione, a racemic version was first developed to test the auxiliary’s performance in the acetate aldol addition. Dihydroxylation of commercially available trimethylstyrene gave diol 1, which, upon exposure to Ritter conditions\(^{21}\) followed by hydrolysis, afforded amino alcohol 2 (Scheme 1.1). Treatment with thiophosgene and triethylamine led to the formation of oxazolidinethione 3, and subsequent exposure to acetyl chloride and triethylamine provided the desired \( N \)-acetyloxazolidinethione 4.

![Scheme 1.1. Racemic synthesis of \( N \)-acetyloxazolidinethione 4.](image)

With the acetylated auxiliary in hand, studies on the acetate aldol addition commenced. Initially, \( N \)-acetyloxazolidinethione 4 was treated with titanium tetrachloride (1 equiv) and diisopropylethylamine (1 equiv) followed by addition of aldehyde (1.2 equiv). A variety of aldehydes were screened under these reaction conditions, providing moderate yields and high diastereomeric ratios for several
aldehydes (Table 1.2). While high selectivities were obtained for several aldehydes (entries 3-6), the diastereomeric ratios were not consistent for all aldehydes screened. In addition, it was necessary to improve upon the modest yields. By modifying the stoichiometry of titanium tetrachloride (2 equiv) and diisopropylethylamine (2 equiv), higher yields and consistently high diastereoselectivities were obtained (Table 1.2). The mesityl-substituted auxiliary performed well with aromatic aldehydes (entry 6), aliphatic aldehydes (2-5), and α, β-unsaturated aldehydes (entry 1). Under these optimized conditions, the yields ranged from 71% to 86% with diastereomeric ratios of 92:8 to 99:1. An added benefit to the high diastereoselectivities was the ability to cleanly separate the diastereomers via column chromatography.

**Table 1.2. Acetate aldol additions of N-acetyloxazolidinone 4.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Yield</th>
<th>1.0 eq TiCl₄</th>
<th>1.0 eq i-Pr₂EtN</th>
<th>2.0 eq TiCl₄</th>
<th>2.0 eq i-Pr₂EtN</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>PhCH₂-CHO</td>
<td>66%</td>
<td>88:12</td>
<td>71%</td>
<td>94:6</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(CH₂)₂CHO</td>
<td>61%</td>
<td>76:24</td>
<td>77%</td>
<td>95:5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>n-PrCHO</td>
<td>77%</td>
<td>94:6</td>
<td>86%</td>
<td>94:6</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(CH₂)₂CHO</td>
<td>61%</td>
<td>94:6</td>
<td>86%</td>
<td>92:8</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>EtCHO</td>
<td>60%</td>
<td>92:8</td>
<td>84%</td>
<td>99:1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>PhCHO</td>
<td>42%</td>
<td>96:4</td>
<td>86%</td>
<td>96:4</td>
<td></td>
</tr>
</tbody>
</table>

With a successful diastereoselective acetate aldol addition in hand, investigations into an enantioselective synthetic route of the auxiliary commenced. It was initially proposed that an efficient route for the synthesis of
the desired $N$-acyloxyazolidinethione would begin with a Sharpless asymmetric aminohydroxylation (SAA)$^{22}$ of trimethylstyrene to form the Boc-protected amino alcohol 6 (Scheme 1.2). Subsequent removal of the Boc group, formation of the auxiliary and ultimate acylation would lead to the formation of the desired $(S)$-$N$-acyloxyazolidinethione 9 in four steps. The SAA of trimethylstyrene, however, was sluggish and the highest yield obtained, despite various optimization attempts, did not exceed 21%. This result is consistent with the findings of O’Brien and coworkers, who determined that the presence of ortho-substituents is detrimental to the SAA of styrene derivatives.$^{23}$

**Scheme 1.2.** Initial enantioselective synthetic route.

Since the SAA approach to the desired $N$-acyloxyazolidinethione was unsuccessful, efforts were then focused on the employment of tert-butylsulfinamide methodology developed by Ellman (Scheme 1.3).$^{24-26}$ Imine 11 was prepared via the copper sulfate-mediated condensation of $(R)$-(+)-2-methyl-2-propanesulfinamide 10 and (4-methoxybenzyloxy)acetaldehyde. Addition of mesitylmagnesium bromide to imine 11 afforded a single diastereomer of the protected amino alcohol 12. The addition of the mesityl group occurs from the Re
face of the imine due to coordination between magnesium and the PMB ether.

Concomitant acid-catalyzed removal of the sulfinyl and PMB groups provided amino alcohol 13. Finally, formation of the auxiliary followed by acylation yielded (R)-N-acetyloxazolidinethione 14. The stereochemistry of oxazolidinone 14 was confirmed by X-ray crystallography (Figure 1.6).

As with the racemic variant of the acylated auxiliary, enolization of 14 with titanium tetrachloride (2 equiv) and diisopropylethylamine (2 equiv), followed by addition of the aldehyde (1.2 equiv), resulted in a highly diastereoselective acetate aldol addition across a wide range of aldehydes (Table 1.3). Once again, this protocol was amenable to aliphatic, aromatic, and α, β-unsaturated aldehydes. The stereochemistry of the addition was determined by reductive
cleavage of the adduct obtained in entry 4 to afford (S)-4-methyl-pentane-1,3-diol, as confirmed by polarimetry.27

Table 1.3. Acetate aldol additions of N-acetylthiazolidinethione 14.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Yield</th>
<th>dr (15:16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH=CHCHO</td>
<td>72%</td>
<td>93:7</td>
</tr>
<tr>
<td>2</td>
<td>(CH₃)₂CHCHO</td>
<td>84%</td>
<td>96:4</td>
</tr>
<tr>
<td>3</td>
<td>n-PrCHO</td>
<td>85%</td>
<td>95:5</td>
</tr>
<tr>
<td>4</td>
<td>(CH₃)₂C₆H₄CHO</td>
<td>88%</td>
<td>94:6</td>
</tr>
<tr>
<td>5</td>
<td>EtCHO</td>
<td>78%</td>
<td>95:5</td>
</tr>
<tr>
<td>6</td>
<td>PhCHO</td>
<td>89%</td>
<td>96:4</td>
</tr>
</tbody>
</table>

(ii) Acetate Aldol Additions Using a Mesityl-Substituted Thiazolidinethione

With a highly diastereoselective acetate aldol addition using a mesityl-substituted N-acetylthiazolidinethione in hand, efforts then shifted towards the formation of a mesityl-substituted N-acetylthiazolidinethione. A major advantage of using thiazolidinethiones over oxazolidinethiones lies in the ease with which thiazolidinethiones can be directly converted to a variety of functional groups, such as aldehydes, amides, β-ketophosphonates, and β-ketoesters, whereas conversions of oxazolidinethiones are limited.8,28 All attempts, however, to convert amino alcohol 13 into mesityl-substituted thiazolidinethione 17 using LeCorre’s standard protocol29 were unsuccessful (Scheme 1.4); the reaction afforded a mixture of thiazolidinethione 17 and oxazolidinethione 14, with 14 being the major product, and the products formed were susceptible to
decomposition in the reaction mixture. Attempts to optimize the reaction included 1) lowering the reaction temperature by refluxing in solvents with lower boiling points, 2) increasing the amount of carbon disulfide to favor thiazolidinethione formation, and 3) adding solvents, such as dioxane, to prevent the oxazolidinethione intermediate from precipitating out of the reaction mixture. Despite these efforts, the highest yield of thiazolidinethione 17 obtained was only 40%.

Because oxazolidinethione 14 was the major product obtained under LeCorre’s conditions from amino alcohol 13, investigations into the formation of thiazolidinethione 17 from an amino thiol instead of an amino alcohol were explored (Scheme 1.5). Imine 18 was generated from the condensation of (R)-(-)-2-methyl-2-propanesulfonamide 10 and (4-methoxybenzylthio)acetaldehyde. Treatment with mesitylmagnesium bromide gave protected amino thiol 19 as a single diastereomer. At this point, concomitant deprotection of the sulfinyl and
PMB groups was attempted, however, none of the conditions examined were able to remove the PMB group. Another difficulty with this route was the preparation of (4-methoxybenzylthio)acetaldehyde due to its instability. For these reasons, further investigations into this route were abandoned.

Next, investigations into the formation of the desired mesityl-substituted thiazolidinethione from an amino halide were explored (Scheme 1.6). Condensation of \((R)-(+)\)-2-methyl-2-propanesulfinamide 10 with chloroacetaldehyde provided imine 22, which upon exposure to mesitylmagnesium bromide provided sulfinyl-protected amino halide 23 as a single diastereomer. It is important to note that, in this case, addition of the mesityl group occurs from the Si face of the imine due to the lack of coordination between magnesium and chlorine.\(^{25}\) Removal of the sulfinyl group under acidic conditions then afforded the amino halide, which was successfully converted to the desired mesityl-substituted thiazolidinethione 24 using LeCorre’s protocol. Treatment with acetyl chloride and sodium hydride then gave mesityl-substituted \(N\)-acetylthiazolidinethione 25.

![Scheme 1.6. Enantioselective synthesis of \(N\)-acetylthiazolidinethione 25.](image-url)
Because the Grignard addition of mesitylmagnesium bromide provided a single diastereomer of the sulfinyl-protected amino halide, this reaction could be quenched with hydrochloric acid, neutralized, and directly treated with carbon disulfide and aqueous potassium hydroxide to directly access thiazolidinethione 24, shortening the reaction sequence (Scheme 1.7).

Enolization of N-acetylthiazolidinethione 25 under optimized reaction conditions (1.1 equiv titanium tetrachloride and 1.1 equiv diisopropylethylamine) followed by addition of the aldehyde (1.0 equiv) resulted in highly diastereoselective acetate aldol additions (Table 1.4). It was found that when excess aldehyde was used in these reactions, a decrease in diastereoselectivity was observed. Aliphatic, aromatic, and α, β-saturated aldehydes were amenable to this procedure and all diastereomers prepared have been completely separable by flash column chromatography. The stereochemistry of the aldol

![Scheme 1.7. Condensed route to thiazolidinethione 24.](image)

**Table 1.4. Acetate aldol additions of N-acetylthiazolidinethione 25.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Yield</th>
<th>dr (26:27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCHO=CHO</td>
<td>79%</td>
<td>96:4</td>
</tr>
<tr>
<td>2</td>
<td>(CH₃)₂CHCHO</td>
<td>94%</td>
<td>97:3</td>
</tr>
<tr>
<td>3</td>
<td>α-PrCHO</td>
<td>92%</td>
<td>97:3</td>
</tr>
<tr>
<td>4</td>
<td>(CH₃)₂CHCHO</td>
<td>95%</td>
<td>98:2</td>
</tr>
<tr>
<td>5</td>
<td>EtCHO</td>
<td>90%</td>
<td>95:5</td>
</tr>
<tr>
<td>6</td>
<td>PhCHO</td>
<td>94%</td>
<td>94:6</td>
</tr>
</tbody>
</table>
adducts was determined by reductive cleavage of the adduct obtained in entry 4 to afford \((R)\)-4-methyl-pentane-1,3-diol, as confirmed by polarimetry.\(^{27}\)

The observed stereochemistry in the acetate aldol reactions can be explained by two possible models (Figure 1.7). The enolization conditions in these acetate aldol additions are analogous to those employed in “non-Evans” syn-aldol additions for propionates. The propionate aldol additions are believed to proceed via a chelated transition state;\(^6\) therefore, diastereoselectivity would arise from the preference of the “R” group of the aldehyde to occupy the pseudoequatorial position to avoid a 1,3-diaxial interaction with both the auxiliary and one of the methyl groups on the mesityl group. Other possible transition states, such a nonchelated boat, cannot be ruled out. Further studies are necessary to distinguish which transition state is operational in these reactions.

![Figure 1.7. Possible transition states to account for the observed stereochemistry.](image)
Under the optimized reaction conditions, the acetate aldol addition using mesityl-substituted \( N \)-acetylthiazolidinethione 25 gives the “\textit{syn}” acetate aldol adduct as the major diastereomer. We next investigated whether the “\textit{anti}” acetate aldol adduct could be accessed from the same enantiomer of the auxiliary. In the case of the propionate aldol addition, one benefit of using a thiazolidinethione auxiliary is the ability to access both the “Evans” \textit{syn} and “non-Evans” \textit{syn} aldol adducts by altering the stoichiometry of titanium tetrachloride and/or the amine base (Figure 1.2, vide supra). The presence of \( N \)-methyl pyrrolidinone (NMP), or an excess of (−)-sparteine, has been shown to break chelation between titanium and the auxiliary, resulting in the formation of the “non-Evans” \textit{syn} propionate aldol adduct.\(^6\)

To investigate whether this selectivity reversal would be feasible for the acetate aldol addition, several experiments were run to see if the “\textit{anti}” acetate aldol adduct could be obtained in the presence of NMP and (−)-sparteine (Table 1.5). Despite optimization attempts, the “\textit{anti}” acetate aldol adduct was only obtained in modest yield and diastereoselectivity.

\[
\begin{array}{|c|c|c|c|c|c|}
\hline
\text{Entry} & \text{Eq } TiCl}_4 & \text{Eq (−)-sparteine} & \text{Eq NMP} & \text{Yield} & \text{dr} \\
\hline
1 & 1.0 & 2.2 & - & 54\% & 72:28 \\
2 & 1.0 & 1.2 & 1.3 & 56\% & 74:26 \\
3 & 1.0 & 1.0 & 1.0 & 56\% & 73:27 \\
\hline
\end{array}
\]

\(\text{Table 1.5. Attempts at selectivity reversal.}\)
C. Iterative Aldol Additions Using a Mesityl-Substituted Thiazolidinethione

To explore the utility of the acetate aldol addition in more stereochemically complex substrates, the application of the mesityl-substituted N-acetyltiazolidinethione in double diastereoselective aldol additions\(^\text{30}\) using nonracemic aldehydes was investigated. Aldol adducts from both acetate aldol additions (\(30a\)) and propionate aldol additions (\(30b\)) underwent a \(t\)-butyldimethylsilyl protection of the \(\beta\)-hydroxyl group, followed by reductive cleavage of the thiazolidinethione auxiliary, revealing enantiopure aldehydes \(31a\) and \(31b\) (Scheme 1.8). These nonracemic aldehydes were then subjected to acetate aldol additions with both enantiomers of the mesityl-substituted thiazolidinethione (\(21\) and \(25\)) to provide aldol adducts \(32a\), \(32b\), \(33a\) and \(33b\) in high yields and excellent diastereoselectivities. The presence of an \(\alpha\)-substituent
on the aldehyde led to a drop in yield when the original enolization conditions were applied (1.1 equiv N-acetylthiazolidinethione, 1.1 equiv titanium tetrachloride, and 1.1 equiv diisopropylethylamine). The yield increased significantly when a slight excess of enolate was employed (1.5 equiv N-acetylthiazolidinethione, 1.5 equiv titanium tetrachloride, and 1.5 equiv diisopropylethylamine). Because diastereoselectivity was high in all cases, this demonstrates that the selectivity of these acetate aldol additions is influenced by auxiliary control rather than substrate control.

D. Summary

This chapter has described the concise synthesis of highly hindered oxazolidinethione and thiazolidinethione auxiliaries bearing mesityl directing groups that achieve high levels of diastereoselectivity for acetate aldol additions employing aliphatic, aromatic, and α, β-unsaturated aldehydes. In addition, these auxiliaries also provide excellent double diastereoselection in the acetate aldol addition of nonracemic aldehydes. This methodology finds wide application in the synthesis of a variety of polyketide-derived natural products, and has already been successfully applied to the total synthesis of (−)-pironetin. Efforts towards the application of this acetate aldol methodology to the total synthesis of (−)-brevenal will be discussed in the following chapter.
E. References


Chapter 2

Progress Towards the Total Synthesis of (−)-Brevenal

A. Background

(i) Isolation and Biological Activity of (−)-Brevenal

Marine polycyclic ether natural products have received much attention over the years due to their unique and highly complex molecular architecture, in addition to their diverse and potent biological activities.\(^1\)\(^-\)\(^3\) Cyclic polyethers, such as the ciguatoxins\(^4\) and maitotoxin\(^5\), are representative secondary metabolites produced by marine phytoplankton. A number of bioactive polyether natural products have been isolated from the marine dinoflagellate *Karenia brevis*, the organism responsible for toxic red tides along Florida’s Gulf Coast. The most well-known compounds isolated from *K. brevis* are a family of neurotoxins called the brevetoxins (Figure 2.1). The brevetoxins are responsible for massive kills of fish and marine animals such as dolphins and manatees. The red tides can also affect humans when the brevetoxins have become aerosolized in sea spray or bioaccumulated in shellfish. Inhaled brevetoxins cause respiratory irritation and breathing difficulties in sensitive populations.\(^6\) At high concentrations, ingested brevetoxins lead to a collection of symptoms commonly referred to as neurotoxic shellfish poisoning (NSP).\(^7\)
The brevetoxins bind with high affinity to site 5 of voltage sensitive sodium channels (VSSC) in neurons. Binding of brevetoxins to tissues containing VSSC results in membrane depolarization, repetitive firing, and increased sodium currents. Investigations using voltage clamp experiments indicate that brevetoxins activate VSSC by prolonging mean open time, inhibiting channel inactivation, thus extending the duration of sodium currents across the membrane.

Interestingly, the same organism which produces these potentially deadly toxins also produces a compound that displays antagonistic activity against the brevetoxins. This compound, brevenal, has been shown to competitively displace titrated dihydrobrevetoxin-B from VSSC in rat brain synaptosomes in a dose-dependent manner, alleviating the toxic effects of brevetoxins in vivo. More importantly, picomolar concentrations of brevenal were found to increase tracheal mucus velocity to the same degree as that observed with millimolar

![Figure 2.1: The brevetoxins.](image-url)
concentrations of a sodium channel blocker, amiloride, which is used in the
treatment of the debilitating lung disorder cystic fibrosis.\textsuperscript{15} As such, brevenal
represents a potential lead for the development of novel therapeutic agents for
the treatment of mucociliary dysfunction associated with cystic fibrosis and other
lung disorders.

(−)-Brevenal (34, Figure 2.2) was
isolated in 2004 by Baden and coworkers.
The structure of brevenal was disclosed
based on 2D NMR studies; however, the
absolute chemistry remained to be established. Brevenal is characterized by its
pentacyclic polyether core arranged with four methyl and two hydroxyl groups,
and its heavily substituted left-hand \((E,E)\)-dienal side chain. The first total
synthesis and absolute configuration was reported by Sasaki and coworkers in
2006.\textsuperscript{16} To date, this is the only reported total synthesis of brevenal.

\textit{(ii) Previous Synthetic Efforts}

Sasaki and coworkers first reported the total synthesis of brevenal (34) in
2006, however, in 2008, they reported a revised, concise synthetic entry to the
pentacyclic polyether core.\textsuperscript{17} Their retrosynthetic plan is depicted in Figure 2.3, in
which the pentacyclic core 35 could be rapidly accessed from a Suzuki-Miyaura
coupling\textsuperscript{18,19} of the AB-ring \textit{exo}-olefin 36 and the DE-ring enol phosphate 37,
followed by subsequent construction of the C-ring by a mixed
thioacetalization/methylation sequence. The AB-ring \textit{exo}-olefin 36 was
retrosynthetically divided into alkylborate 38 and B-ring enol phosphate 39 based
on a further application of the Suzuki-Miyaura coupling/mixed thioacetalization strategy. Finally, the D-ring enol phosphate was traced back to the E-ring 40 via lactonization of the D-ring. This two-fold use of the Suzuki-Miyaura coupling/mixed thioacetalization strategy resulted in a highly convergent synthesis of brevenal. Employment of this strategy allowed Sasaki and coworkers to access (−)-brevenal with 46 steps in the longest linear sequence.

Figure 2.3. Sasaki’s retrosynthetic analysis.

The synthesis of the AB-ring exo-olefin 36 began with iodination of alcohol 41, followed by lithiation with t-butyllithium in the presence of B-MeO-9-BBN to generate the alkylborate, which was then coupled with enol phosphate 39 to afford enol ether 42 (Scheme 2.1). Selective hydroboration, followed by oxidation
of the resultant alcohol gave ketone 43. Removal of the MPM group and subsequent treatment with ethanethiol and zinc triflate provided the mixed thioacetal, which was displaced with the angular methyl group via a one-pot oxidation/methylation protocol,\textsuperscript{21} giving rise to bicycle 44. Removal of the benzyl groups and protection of the resultant primary alcohol as the TIPS ether gave alcohol 45, which was regioselectively eliminated by a one-pot procedure\textsuperscript{22} to yield olefin 46. After various protecting group manipulations, a dihydroxylation of the olefin furnished diol 47 as a single diastereomer. Protection of the diol and cleavage of the TIPS group gave the alcohol, which was iodinated and subsequently treated with potassium \( t \)-butoxide to afford the AB-ring exo-olefin 36.

The synthesis of the DE-ring enol phosphate 37 commenced with the regioselective opening of the known epoxide 48,\textsuperscript{23} readily available from 1,5-pentanediol in five steps (Scheme 2.2). The resultant diol 49 underwent selective sulfonylation of the primary alcohol, then epoxidation under basic conditions.
Epoxide 50 was then allylated with allylmagnesium bromide, and the free hydroxyl group was protected as the benzyl ether. A Wacker oxidation delivered methyl ketone 51, 24 and deprotection of the MPM group followed by attachment of an acrylate unit led to the \( \beta \)-alkoxyacrylate. Treatment with samarium (II) iodide furnished the lactone 52 as a single diastereomer, which underwent reduction followed by Wittig methylation to afford alcohol 53. In four steps, 53 was converted to diol 54, which was converted to the lactone via a direct oxidative cyclization. 25 Enolization then generated the DE-ring enol phosphate 37.

Assembly of the AB-ring \textit{exo}-olefin 36 and the DE-ring enol phosphate 37 and subsequent construction of the C-ring was accomplished according to Sasaki’s Suzuki-Miyaura coupling-based strategy (Scheme 2.3). 19 Stereoselective hydroboration of 36 using 9-BBN-H generated an alkylborane, which was reacted with 37 in the presence of cesium carbonate and \( \text{Pd(PPh}_3)_4 \) to furnish enol ether 55 as a single stereoisomer. Hydroboration of the enol ether proceeded stereoselectively to give the alcohol, which underwent oxidation to
give ketone 56 as a single stereoisomer. Cleavage of the PMB and silyl groups, mixed thioacetalization, and ensuing silylation of the resultant unprotected hydroxyl group delivered mixed thioacetal 57. The thioethyl group was then oxidized and displaced with a methyl nucleophile in a one-pot manner,21 giving rise to the pentacyclic polyether, which then underwent debenzylolation26 to give alcohol 58.

Having constructed the pentacyclic polyether core, efforts were then focused on the construction of the left-hand side chain (Scheme 2.4). Dess-Martin oxidation27 of alcohol 58 to the aldehyde followed by treatment with Ohira-Bestmann reagent28,29 produced a terminal alkyne, which was then methylated to provide alkyne 59. The robust TBS groups were replaced with easily removable TES ethers. Regioselective silylcupration delivered the desired vinylsilane 60 in approximately 9:1 regioselectivity. Conversion of 60 to the vinyl iodide30, followed by a Stille coupling31 with vinyl stannane 61 proceeded smoothly to furnish (E, E)-diene 62 as a single stereoisomer. After protection of the allylic alcohol as the TBDPS ether, the primary TES ether was selectively removed to give alcohol 63. Introduction of the right-hand (Z)-diene side chain was performed via Nicolaou’s
Thus, 63 was oxidized and then subjected to a Wittig olefination using ylide 64. Subsequent treatment with hydrogen peroxide led to conjugated (Z)-diene 65. Global deprotection of the silyl groups followed by selective oxidation of the allylic alcohol completed the synthesis of (−)-brevenal (34).

**Scheme 2.4. Completion of Sasaki’s synthesis (−)-brevenal.**

**B. Studies Towards the Total Synthesis of (−)-Brevenal**

(i) Retrosynthetic Analysis

Our original retrosynthetic analysis (Figure 2.4) envisioned a highly convergent approach to brevenal, wherein the left- and right-hand unsaturated side chains are installed late-stage. The pentacyclic polyether core was envisaged to arise from a Horner-Wadsworth-Emmons coupling of the AB-ring β-ketophosphonate 68 and the E-ring aldehyde 69 to give enone 67, followed by an
acid-catalyzed cyclodehydration to close the D-ring, generating tetracycle 66. Closure of the C-ring would then provide the brevenal pentacyclic core.

(ii) Application of the Acetate Aldol Methodology to the Synthesis of the AB-Ring Fragment.

Initial efforts towards the total synthesis of (−)-brevenal focused on the construction of the AB-ring β-ketophosphonate 68, in which our newly developed acetate aldol methodology, discussed in the previous chapter, would serve as a key step. The first proposed retrosynthetic plan for the synthesis of 68 is outlined in Figure 2.5. β-Ketophosphonate 68 was expected to arise from methyl ester 70.

Figure 2.5. Original retrosynthetic analysis of AB-ring fragment 68.
The B-ring would be formed via an intramolecular Michael addition of alcohol 71, which in turn will stem from enol ether 72. The enol ether would arise from a one-pot enone reduction, TMS deprotection, and cyclodehydration of enone 73, which would be generated from a Horner-Wadsworth-Emmons coupling of β-ketophosphonate 74 and aldehyde 75. β-ketophosphonate 74 and aldehyde 75 would be accessed from an acetate aldol adduct, and a propionate aldol adduct, respectively.

The synthesis of aldehyde 75 began with a highly diastereoselective “Evans” syn propionate aldol addition\(^3\) between phenylalanine-derived \(N\)-propionylthiazolidinethione 76 and aldehyde 77 (Scheme 2.5). The resultant aldol adduct 78 was protected as the TMS ether, and the auxiliary underwent reductive cleavage to furnish the desired aldehyde 75.

![Scheme 2.5, Synthesis of aldehyde 75](image)

Efforts were then focused on the synthesis of β-ketophosphonate 74 (Scheme 2.6). The key step to 74 involved an acetate aldol addition using mesityl-substituted \(N\)-acetyltiazolidinethione 21,\(^3\) discussed in the previous chapter. Thus, \(N\)-acetyltiazolidinethione 21 underwent an acetate aldol addition with aldehyde 79, synthesized in four steps from commercially available (\(R\))-benzylglycidyl ether (81). The addition proceeded in high yield, however, very poor diastereoselectivity was observed. It was expected that this aldol addition
would be a “matched” case, in that the acetate aldol addition results in “syn” acetate aldol adducts, and the presence of an α-silyl ether on the aldehyde would lead to the Felkin-Anh\textsuperscript{35,36} product, giving rise to the stereochemistry observed in aldol adduct 80. Poor diastereoselectivity, however, suggested that perhaps this aldol addition was a “mismatched” case.

To test this hypothesis, the opposite enantiomer of the auxiliary, N-acetylthiazolidinethione 25, underwent an acetate aldol addition with aldehyde 79, furnishing adduct 84 in excellent yield and diastereoselectivity (Scheme 2.7). The high diastereoselectivity suggested that this reaction is perhaps proceeding through chelation control, resulting in the anti-Felkin product. To prevent chelation, the TBS group on aldehyde 79 was replaced with a TIPS group, as bulky silyl groups are generally understood to be poor coordinators. This, however, still resulted in poor diastereoselectivity, most likely due to the presence of titanium tetrachloride causing the reaction to
At this point, the synthetic route to the AB-ring β-ketophosphonate was modified by performing the acetate aldol addition with cinnamaldehyde instead of aldehyde 79 (Scheme 2.8). This would not alter the retrosynthetic strategy outlined in Figure 2.3 as the styrene moiety could be cleaved via ozonolysis then subjected to a vinyl addition, TBS deprotection, and acetonide protection to access the necessary right-hand side chain of protected diol 71 (Figure 2.5, vide supra). The acetate aldol addition was carried out with N-acetyltimizolidinethione 21 and cinnamaldehyde, providing “syn” acetate aldol adduct 85 with excellent diastereoselectivity. Upon treatment with TBSOTf and 2,6-lutidine, the free hydroxyl group was protected as the TBS ether, and the auxiliary was the displaced with lithiodimethyl methylphosphonate to afford β-ketophosphonate 86.37,38 A Horner-Wadsworth-Emmons coupling of 86 and aldehyde 75, synthesized in Scheme 2.5, in the presence of barium hydroxide gave enone 87.39 A one-pot enone reduction, TMS deprotection, and cyclodehydration, using Wilkinson’s catalyst followed by the addition of pyridinium p-toluenesulfonate (PPTS),40,41 was then attempted to access the A-ring enol ether 88, however, this
reaction proved to be unsuccessful.

To circumvent this problem, the enone reduction, TMS deprotection, and cyclodehydration reactions were carried out stepwise. The enone reduction proved to be difficult in that a variety of reaction conditions were employed resulting in either decomposition or no reaction (Table 2.1). Eventually, it was found that diisobutylaluminum hydride and hexamethyolphosphoramide, in the presence of a catalytic amount of methyl copper, furnished ketone 89 in high yield (entry 6).

Table 2.1. Attempts at enone reduction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagents</th>
<th>Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Ph3P)2RhCl, Me-PhSiH</td>
<td>toluene, 50 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>(Ph3P)2CuH2</td>
<td>toluene, 23 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>NiCl2·6H2O, NaBH4</td>
<td>MeOH, H2O, 23 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>LiBH4</td>
<td>MeOH, Et2O, 0 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>5</td>
<td>i-Bu2AlH, HMPA</td>
<td>THF, 0 °C</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>i-Bu2AlH, HMPA, MeCu (cat.)</td>
<td>THF, -50 °C</td>
<td>94%</td>
</tr>
</tbody>
</table>

Ketone 89 was then treated with PPTS and heat to induce removal of the TMS ether followed by subsequent cyclodehydration to produce the A-ring enol ether 88 (Scheme 2.9). This reaction, however, only led to decomposition of the starting material; therefore, the TMS group was removed in the presence of ammonium fluoride and methanol to reveal hydroxy ketone 90. Treatment of 90 with PPTS was expected to give rise to enol ether 88; however, conjugated triene 91 was obtained instead. It is believed that under acidic conditions, the TBS ether acts as a leaving group, whereby the cation being generated is stabilized.
by the styrene component.

To prevent the formation of the undesired triene, it was necessary to remove the styrene component from the substrate. To do this, the acetate aldol addition was revisited using crotonaldehyde instead of cinnamaldehyde, generating adduct 92 in good yield and excellent diastereoselectivity (Scheme 2.10). In the same manner depicted in Scheme 2.8, aldol adduct 92 was
converted to hydroxy ketone 95 in five steps. Upon treatment with PPTS to generate the desired enol ether 96, the undesired conjugated triene 97 was once again obtained as the major product. This time, it was thought that having a terminal olefin instead of an internal olefin would prevent elimination of the TBS ether.

To do this, the acetate aldol addition was revisited once again using acrolein instead of crotonaldehyde (Scheme 2.11). Aldol adduct 98 was furnished in high yield and excellent diastereoselectivity. As before, the free hydroxyl group was protected as the TBS ether and the thiazolidinethione was displaced to afford β-ketophosphonate 99. The ensuing Horner-Wadsworth-Emmons coupling of 99 and aldehyde 75 generated enone 100 in high yield, which was then subjected to a 1,4-reduction followed by TMS deprotection with ammonium
fluoride to provide hydroxy ketone 101. At this point, the necessary cyclodehydration reaction was attempted. In the presence of PPTS, the desired enol ether 102 was obtained in a 1:1 mixture with conjugated triene 103. Upon examination of various cyclodehydration conditions, it was found that enol ether 102 could be obtained in excellent yield in the presence of phosphorus pentoxide, a reagent commonly used to effect various cyclizations.\textsuperscript{44,45} Under these conditions, no formation of triene 103 was observed.

With the desired A-ring enol ether in hand, efforts then focused on an epoxidation-methylation sequence to access A-ring pyran 104 using methodology developed by Rainier (Scheme 2.12).\textsuperscript{46,47} It was hoped that treatment of enol ether 102 with dimethyl dioxirane\textsuperscript{48} (DMDO) would chemoselectively form the epoxide on the olefin of the enol ether from the less hindered face of the six-membered ring. In the same pot, the solvent would then be removed under an argon purge and a large excess of trimethyl aluminum would be added to coordinate to the epoxide and selectively deliver a methyl group to the bottom face of the pyran to generate alcohol 104. Treatment with DMDO did indeed lead to the selective formation of the desired epoxide without

\textbf{Scheme 2.12: Epoxidation-methylation attempt.}
any side reactions with the terminal olefin. Addition of trimethylaluminum, however, did not yield the desired alcohol; rather, 2D NMR studies and mass spectrometry revealed the formation of triol 105. To confirm that alcohol 104 was not being formed, the product obtained from the epoxidation-methylation reaction was subjected to an acetate protection. The NMR of the product obtained showed the presence of two acetate groups, suggesting that more than one free hydroxyl group was present in the starting material. While triol 105 has three free hydroxyl groups instead of two, one of the hydroxy groups is tertiary, and thereby more difficult to protect.

A possible mechanism for the formation of triol 105 is depicted in Figure 2.6. It is believed that after treatment with DMDO, the epoxide was being opened by the action of adventitious water rather than that of trimethyl aluminum, leading to the formation of acetal 107. Addition of a large excess of trimethyl aluminum would then generate oxocarbenium cation 108. Addition of a methyl nucleophile into the resultant oxocarbenium cation would then furnish triol 105.

Figure 2.6. Possible mechanism for formation of triol 105.

At this point, a variety of alterations were made to the reaction conditions to avoid the presence of water and it was found that “acetone-free” DMDO
successfully avoided formation of the undesired triol 105. The desired product, however, was only obtained in modest yield (58%) and no diastereoselectivity was observed. One possible explanation for the lack of diastereoselectivity could be attributed to coordination of trimethyl aluminum to the TBS ether, causing the methyl group to be delivered to either face of the oxocarbenium. To avoid this problem, we next investigated an acid-catalyzed opening of the epoxide to form mixed acetal 109 (Scheme 2.13). If successful, the methoxy group could later be displaced for a methyl group. Enol ether 102 was first treated with DMDO to form the epoxide. The solvent was then removed under an argon purge and methanol, followed by a catalytic amount of PPTS, was added. These reaction conditions, however, resulted in no reaction. The reaction was then attempted with a stronger acid, camphorsulfonic acid (CSA), to promote the epoxide opening, but this resulted only in deprotection of the TBS protecting group. The TBS group was then replaced with the bulkier TIPS protecting group to give enol ether 110, which was treated with DMDO followed by CSA and methanol. This reaction resulted in a mixture of unidentifiable products.
Due to the difficulties encountered with this epoxidation-methylation strategy, we concluded that a substrate more similar to that of Rainier would be necessary to overcome this step in the synthesis (Figure 2.7). To do so would involve moving the protected hydroxyl group of the right-hand side chain farther away from the reaction site by revising the synthetic strategy of the AB-ring fragment to no longer include the acetate aldol addition. The new target enol ether for the epoxidation-methylation sequence is shown in Figure 2.8.

(iii) Revised Synthesis of the AB-Ring Fragment

The revised retrosynthesis of the AB-ring β-ketophosphonate 68 is illustrated in Figure 2.9, in which the key step is no longer an acetate aldol addition. Rather, the revised retrosynthesis relies on the glycolate alkylation/ring-closing metathesis strategy, developed in the Crimmins laboratory, to access medium-ring ethers. The AB-ring fragment 68 is expected to arise from nitrile 113. The seven-membered B-ring will be formed via a ring-closing metathesis reaction of diene 114, which will stem from an alkylation of glycolate 115 followed
by conversion of the oxazolidinone to the olefin. Enol ether 112 will arise from the 1,4-reduction and TMS deprotection of enone 116, which will be generated from the Horner-Wadsworth-Emmons coupling of aldehyde 75 and β-ketophosphonate 117.

The revised synthesis of the AB-ring fragment 68 began with synthesis of enol ether 112, to test its performance in Rainier’s epoxidation-methylation reaction (Scheme 2.14). Commercially available 1,4-butanediol underwent monobenzylation followed by a Jones’ oxidation to afford carboxylic acid 118. Conversion to the methyl ester under acidic conditions followed by displacement of the auxiliary with lithiodimethyl methylphosphonate then furnished β-ketophosphonate 117. β-ketophosphonate 117 and aldehyde 75 were coupling via a Horner-Wadsworth-Emmons reaction to give enone 116, which then underwent a 1,4-reduction followed by TMS deprotection to provide hydroxy ketone 119. It should be noted that the acidic workup of the enone reduction resulted in partial loss of the TMS group; therefore, the crude mixture of products
was treated with ammonium fluoride, resulting in complete removal of the TMS group, and the yield was calculated over two steps. The resultant hydroxy ketone 119 was exposed to phosphorus pentoxide to induce cyclodehydration to form the A-ring enol ether 112; however, these reaction conditions provided inconsistent results, sometimes providing 112 in high yield and other times resulting in no reaction. Cyclodehydration using PPTS in the presence of molecular sieves was examined and gave the desired enol ether 112 in moderate yield (42-60%) in addition to unreacted starting material. In the presence of a stronger acid, such as CSA, enol ether 112 was obtained in excellent yield.

With the necessary enol ether 112 in hand, efforts then focused on the epoxidation-methylation reaction to afford alcohol 120 (Scheme 2.15). Upon addition of DMDO, enol ether 112 underwent facile conversion to the corresponding epoxide. After the solvent switch, exposure to trimethylaluminum provided alcohol 120 in poor yield and low diastereoselectivity. An acid-catalyzed opening of the epoxide in the presence of methanol was then attempted. Mixed acetal 121 was obtained as a single diastereomer.
With the successful formation of mixed methyl acetal 121, we then decided to make the right-hand side chain one carbon shorter so as to ease the manipulation of the side chain later in the synthesis (Scheme 2.16). To do this, a synthesis identical to that depicted in Scheme 2.14 was employed, with the exception that 1,3-propanediol was used in place of 1,4-butanediol. From 1,3-propanediol, enol ether 127 was obtained in eight steps. Upon exposure to the epoxidation-acetalization reaction conditions, mixed methyl acetal 128 was obtained in good yield, as a single diastereomer.

Scheme 2.16. Synthesis of mixed acetal 128.
At this point, it was necessary to displace the methoxy group of mixed acetal 128 and install the angular methyl, generating pyran 129 (Scheme 2.17). Exposure of 128 to trimethyl aluminum in the presence of boron trifluoride etherate was expected to furnish pyran 129; however, these conditions resulted only in the recovery of starting material. It was thought that protecting the free hydroxyl group might be necessary for the success of the reaction. Therefore, the free hydroxyl group was protected as the TES ether. The methylation reaction was then attempted, once again resulting in no reaction. We then turned to Nicolaou’s strategy for accessing medium-ring systems via cyclizations of hydroxy dithioketals.\textsuperscript{21} Thus, enol ether 127 was converted to the epoxide, which was opened in the presence of zinc triflate and ethanethiol furnishing mixed thioacetal 130. Initially, replacement of the thioethyl group for the methyl group was attempted via the one-pot procedure utilized by Sasaki in the presence of the free hydroxyl group,\textsuperscript{21} generating pyran 129 in modest yield. In an effort to increase the yield, the free hydroxyl group was protected as the TES ether. Exposure to \textit{m}-CPBA followed by trimethyl aluminum gave the desired pyran 131.
in high yield as a single diastereomer.

With the necessary methyl group in place, the synthesis of the AB-ring fragment 68 continued (Scheme 2.18). Pyran 131 was subjected to hydrogenation conditions to reductively cleave the benzyl ether. These conditions, however, led to partial removal of the TES protecting group in addition to the benzyl group. Benzyl cleavage was thus realized in the presence of sodium naphthalenide\textsuperscript{53} to give the desired alcohol, which was oxidized under Swern conditions\textsuperscript{54} to furnish aldehyde 132. A Wittig methylenation\textsuperscript{55} followed by cleavage of the TES ether\textsuperscript{56} then ensued, affording alcohol 133. It was found that PPTS was not a strong enough acid for the TES cleavage and that CSA was a better choice. CSA in the presence of methanol led to partial cleavage of the TIPS protecting group as well. Using a larger nucleophile such as ethanol alleviated this problem, providing alcohol 133 in high yield, with only a negligible amount of TIPS deprotection observed.

With alcohol 133 in hand, our glycolate alkylation/ring-closing metathesis strategy\textsuperscript{49} was applied to construct the seven-membered B-ring (Scheme 2.19). Alcohol 133 was transformed to the glycolic acid in the presence of sodium hydride and bromoacetic acid. In one pot, the resultant acid was converted to the mixed pivalic anhydride and treated in situ with the lithium salt of (R)-4-benzyl-2-
oxazolidinone to produce acyl oxazolidinone 115. Treatment of the sodium enolate of 115 with bromoacetonitrile resulted in a highly diastereoselective glycolate alkylation to furnish the nitrile. The highest yield obtained, however, was only 52% due to the presence of an unidentifiable byproduct which was formed during the enolization process. All attempts to optimize this reaction, including lowering the reaction temperature and screening various bases for enolization, were unsuccessful. The oxazolidinone was then cleaved to afford alcohol 134, which was oxidized to the aldehyde under Swern conditions. It should be noted that oxidation of 134 with Dess-Martin periodinane gave much lower yields due to decomposition. At this point, a methylene Wittig reaction was performed to generate diene 114, however, the presence of the nitrile facilitated elimination, thus reforming alcohol 133. Attempts at methylenation with the Tebbe reagent led to decomposition. To prevent elimination, the methylene Wittig reaction was performed using crystallized, salt-free methylenetriphenylphosphorane, thereby giving rise to the desired diene 114. Upon exposure to Grubbs’ 2nd generation catalyst, the seven-membered B-ring was formed providing bicycle 135.

Scheme 2.19: Synthesis of bicycle 137.
With the AB-ring core formed, completion of the fragment commenced (Scheme 2.20). Olefin 135 underwent dihydroxylation to furnish the diol as a single diastereomer, which was then protected in the presence of PPTS and 2-methoxypropene to afford acetonide 113. The nitrile was then converted to the β-ketophosphonate by reduction to the aldehyde, followed by addition of lithiodimethyl methylphosphonate to give the β-hydroxyphosphonate, and then oxidation with Dess-Martin periodinane to furnish AB-ring β-ketophosphonate fragment 68 with 27 steps in the longest linear sequence.

(iv) Coupling of the AB-Ring and E-Ring Fragments

With the AB-ring β-ketophosphonate 68 in hand, we were then ready to proceed with the coupling of 68 with the E-ring aldehyde 69. Aldehyde 69 has been synthesized by Dr. Anita Mattson for the synthesis of hemibrevetoxin B (Scheme 2.21). Taking advantage of the Kobayashi lactate aldol addition, superquat 136 was used to prepare aldol adduct 137. The auxiliary was converted to the methyl ester and the free hydroxyl group was protected as the TES ether to give ester 138, which was converted to aldehyde 139 in two steps. After methylenation, the TES group was removed using t-butylammonium fluoride to furnish alcohol 140, which was converted to glycolyl oxazolidinone 141.
via the glycolic acid. Alkylation with bromoacetonitrile followed by cleavage of the auxiliary then furnished alcohol 142. Oxidation to the aldehyde under Swern conditions, followed by vinyl addition gave allylic alcohols 144 and 145 as a 5:1 mixture of diastereomers, which were both subjected to Grubbs’ 2nd generation catalyst to provide the E-ring alcohols 146 and 147. The undesired diastereomer 146 could be converted to 147 via a two step oxidation/reduction sequence. The free alcohol was protected as the TES ether and the nitrile was then reduced with diisobutylaluminum hydride to generate the E-ring aldehyde 69 in 16 steps.

With both the AB-ring β-ketophosphonate and the E-ring aldehyde available, a Horner-Wadsworth-Emmons coupling between the fragments ensued, furnishing enone 67 in excellent yield (Scheme 2.22).
(v) Attempts at D-Ring Formation

With fragments 68 and 69 successfully coupled, efforts then focused on the formation of the seven-membered D-ring enol ether. The original plan to synthesize the D-ring was to utilize the one-pot enone reduction, TES deprotection, and cyclodehydration strategy (Scheme 2.23). While this strategy has been successful for the formation of six-membered cyclic enol ethers, there are no examples in the literature in which a seven-membered cyclic enol ether is formed via this protocol. Treatment of enone 67 with Wilkinson’s catalyst and dimethylphenylsilane cleanly gave the silyl enol ether, however, addition of PPTS slowly led to formation of TES deprotected ketone 149, with no trace of desired
enol ether 66, despite much care taken to avoid the presence of water in the reaction. Stronger acids, such as CSA and p-TsOH were also used; however, only TES deprotected ketone 149 was obtained.

Our next strategy was to replace the TES protecting with the more labile TMS protecting group to facilitate the deprotection step to generate the necessary free hydroxyl group for the pending cyclodehydration. Thus β-ketophosphonate 68 was coupled with the TMS protected E-ring aldehyde to give enone 150. Once again, only TMS deprotected ketone 149 was obtained (Scheme 2.24). Removal of the TMS group prior to the enol ether formation step was also attempted. Treatment of enone 150 with HF-pyridine gave the desired alcohol 151. The alcohol had to be taken on without purification as exposure to deactivated silica gel led to a Michael addition of the free hydroxyl group into the enone. Subjection to the one-pot enone reduction and cyclodehydration protocol led to decomposition, most likely due to the instability of 151.
At this point, the one-pot enone reduction and cyclodehydration strategy was abandoned. Enone 67 was subjected to a hydrogenation to reduce both olefins and cleave the two benzyl ethers, generating diol 152 (Table 2.2). Various solvents, acids, and temperatures were screened to effect the cyclodehydration of 152, however, only the formation of TES deprotected ketone 149 or decomposition occurred.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Solvent</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPTS</td>
<td>Toluene</td>
<td>50°</td>
</tr>
<tr>
<td>2</td>
<td>PPTS</td>
<td>Benzene</td>
<td>50°</td>
</tr>
<tr>
<td>3</td>
<td>CSA</td>
<td>Toluene</td>
<td>50°</td>
</tr>
<tr>
<td>4</td>
<td>CSA</td>
<td>Benzene</td>
<td>50°, vacuum aspirator</td>
</tr>
</tbody>
</table>

Lewis acids were also screened in an attempt to form the D-ring enol ether (Scheme 2.25). TMS triflate, in the presence of trimethylsilane, has been shown to induce a reductive cyclization to access the seven-membered C-ring of
Fujiwara’s synthesis of hemibrevetoxin B. A variation of this protocol was attempted, resulting in decomposition, most likely due to loss of the acetonide. Cyclizations with additional Lewis acids, such as bismuth tribromide and scandium triflate, were also carried out, also resulting in decomposition.

We next investigated accessing the D-ring enol ether via cyclization of dimethyl ketal 156 or dithioketal 157 (Scheme 2.26). Formation of the dimethyl ketal was first attempted in the presence of PPTS, methanol, and trimethyl orthoformate, resulting only in the decomposition of the starting material. Ketalization was also attempted using Noyori’s protocol, also resulting in decomposition. It is believed that these conditions were not amenable to the presence of the acetonide on ketone 154. Dithioketalization of 154 was successful, albeit low yielding; however, attempts at cyclization to access mixed thioacetal 158 were met with failure.
Due to the incompatibility of many of the cyclodehydration conditions with the acetonide protecting group, our next strategy was to replace the acetonide with two benzyl groups (Scheme 2.27). To do this, diol 159 was treated with sodium hydride and benzyl bromide, generating the dibenzyl protected diol 160 in modest yield, in addition to the monoprotected product. Diol 160 then underwent reduction of the nitrile and the resultant aldehyde was converted to β-hydroxyphosphonate 161. The modest yield of this reaction can be attributed to the steric bulk associated with the benzyl group closest to the reaction site. Finally, oxidation with Dess-Martin periodinane furnished AB-ring β-ketophosphonate 162. A Horner-Wadsworth-Emmons coupling with E-ring aldehyde 163 gave enone 164 which was then subjected to a 1,4-reduction using Wilkinson’s catalyst and PPTS to give TMS deprotected hydroxy ketone 165. Treatment with Fujiwara’s conditions to induce a cyclodehydration to form the D-ring enol ether 166 only led to decomposition of the starting material.
It was thought that the Bn-protected allylic alcohol in the E ring was causing stability issues of ketone 165 in the presence of a Lewis acid, therefore, the olefin was reduced using Crabtree’s catalyst to give ketone 167 (Scheme 2.28). Cyclodehydration under Fujiwara’s conditions once again resulted in decomposition. Treatment of 167 with PPTS or CSA to induce cyclodehydration only led to recovery of starting material.

(vi) Revised Retrosynthesis of (−)-Brevenal

Due to the failures associated with formation of the D-ring enol ether, the retrosynthetic plan for (−)-brevenal was then revised (Figure 2.10). The revised plan involves coupling of AB-ring aldehyde 173 with E-ring β-ketophosphonate 172 to give enone 171. Following a 1,4-reduction, the acetonide will then be removed and an acid-catalyzed cyclodehydration will ensue to form the six-membered C-ring enol ether 170. Manipulation of the enol ether to give ketone 169 followed by formation of the D-ring via acetalization will give the
pentacyclic polyether core. Installation of the left- and right-hand side chains will then furnish (−)-brevenal (34). This sequence is analogous to that used in the Crimmins synthesis of the BCDE fragment of brevetoxin A. This work will be reported in due course.

C. Summary

The asymmetric propionate aldol addition using the chlorotitanium enolates of acylthiazolidinethiones has been successfully applied in our efforts towards the total synthesis of (−)-brevenal. The glycolate alkylation/ring-closing metathesis strategy has also been effective in the synthesis of both the AB-ring and E-ring fragments. The AB-ring β-ketophosphonate has been synthesized in 27 steps in the longest linear sequence, and the E-ring aldehyde has been prepared in 16 linear steps. If the synthesis proceeds as planned in the revised route (Figure 2.10), (−)-brevenal will be constructed with a longest linear sequence of 34 steps.
D. References


Chapter 3

Experimental Information and NMR spectra for Chapter 1

Methods and Materials: Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer and values reported in cm\(^{-1}\). Proton and carbon nuclear magnetic resonance (1H and 13C NMR) spectra were recorded on the Bruker 400 (1H at 400 MHz; 13C at 100 MHz). Optical rotations were determined using a Jasco P1010 polarimeter. Thin layer chromatography (TLC) was conducted on silica gel F254 TLC plates purchased from Scientific Adsorbents, Inc. Flash column chromatography was carried out using silica gel (32 to 63 µm) purchased from Scientific Adsorbents, Inc. Diethyl ether (Et\(_2\)O), tetrahydrofuran (THF), dichloromethane (CH\(_2\)Cl\(_2\)), and toluene were dried by being passed through a column of neutral alumina under nitrogen immediately prior to use. Alkylamines were distilled from calcium hydride immediately prior to use. Mesitylmagnesium bromide was synthesized using standard Grignard techniques from 2-bromomesitylene. (R)-(+)-2-methyl-2-propanesulfinamide and (S)-(−)-2-methyl-2-propanesulfinamide were prepared using Ellman’s procedure.\(^1\) All other reagents and solvents were used as received from the manufacturer. All air and water sensitive reactions were

performed in flasks flame dried under positive flow argon and conducted under an argon atmosphere.

**Imine 11:** To a dry 25 mL round-bottom flask, under argon, was added (R)-(+)-2-methyl-2-propanesulfinamide (0.715 g, 5.90 mmol) and 12 mL of CH₂Cl₂. Anhydrous CuSO₄ (2.07 g, 13.0 mmol) was added in one portion followed by (4-methoxy-benzyloxy)-acetaldehyde (1.17 g, 6.49 mmol). The reaction mixture was stirred at room temperature for 24 h, filtered through a pad of celite, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (25% EtOAc/Hex to 35% EtOAc/Hex) to provide the product as a pale yellow oil (1.67 g, 85%). ¹H NMR (400 MHz, CDCl₃): δ 1.17 (s, 9H), 3.76 (s, 3H), 4.33 (s, 2H), 4.52 (s, 2H), 6.85 (d, 2H, J = 8.4 Hz), 7.24 (d, 2H, J = 8.4), 8.07 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 22.3, 55.1, 56.8, 70.8, 72.8, 113.8, 129.1, 129.4, 159.4, 166.7. IR (film): 2959, 2866, 1633, 1613, 1514, 1363, 1249, 1175 cm⁻¹. ESI-MS: C₁₄H₂₁NO₃S [M+H] calc. 284.4, found 284.2. [α]²⁶D = -173° (c = 1.25, CH₂Cl₂).

**Protected amino alcohol 12:** To a dry 250 mL round-bottom flask, under argon, was added imine 11 (4.00 g, 14.1 mmol) and 71 mL of toluene and the
flask was cooled to −78 °C. To this solution was slowly added mesitylmagnesium bromide (5.0 equiv), prepared from 4.30 g Mg turnings (0.18 mol), 24.0 mL 2-bromomesitylene (0.17 mol) and 80 mL of dry ether. The mixture was stirred for 2 h at −78 °C upon which the reaction was quenched with saturated ammonium chloride. The layers were separated and the aqueous layer was extracted with ethyl acetate (2x). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (40% EtOAc/Hex to 70% EtOAc/Hex) to provide a single diastereomer of the product as a yellow oil (5.40 g, 95%). ¹H NMR (400 MHz, CDCl₃): δ 1.19 (s, 9H), 2.23 (s, 3H), 2.39 (s, 6H), 3.51 (dd, 1H, J = 4.0, 10.0 Hz), 3.78 (s, 3H), 3.95 (t, 1H, J = 10.4 Hz), 4.11 (s, 1H), 4.51 (ABq, 2H, J_AB = 11.6 Hz, ∆ν_AB = 75.9 Hz), 5.12 (ddd, 1H, J = 10.4, 3.6, 1.2 Hz), 6.80 (s, 2H), 6.87 (d, 2H, J = 8.4 Hz), 7.26 (d, 2H, J = 8.8 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 20.7, 20.9, 22.5, 52.7, 54.8, 55.1, 69.8, 72.0, 113.7, 129.3, 129.4, 129.7, 140.0, 137.2, 137.8, 159.2. IR (film): 3277, 2955, 2866, 1612, 1513, 1464, 1363, 1249, 1174 cm⁻¹. ESI-MS: C₂₃H₃₃NO₃S [M+H] calc. 404.6, found 404.2. [α]D²⁵ = -86.1° (c = 1.65, CH₂Cl₂).

Amino alcohol 13: To a dry 250 mL round-bottom flask, under argon, was added protected amino alcohol 12 (4.50 g, 11.2 mmol) in 23 mL of MeOH.
To this solution was added 4 N HCl/dioxane (28.0 mL, 112.0 mmol) and the solution was stirred for 1 h at room temperature. The solution was then concentrated under reduced pressure. The residue was dissolved in ether and 4 N NaOH (200 mL) was slowly added while stirring. The layers were separated and the aqueous layer was extracted with ether (2x). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (80% EtOAc/Hex to 10% MeOH/CH$_2$Cl$_2$) to provide the amino alcohol as a pale yellow solid (1.52 g, 76%).$^1$H NMR (400 MHz, CDCl$_3$): δ 2.25 (s, 3H), 2.40 (s, 6H), 2.60 (brs, 3H), 3.62 (dd, 1H, J = 4.0, 10.8 Hz), 3.83 (t, 1H, J = 12.0 Hz), 4.47 (dd, 1H, J = 4.8, 10.0 Hz), 6.83 (s, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 20.6, 21.2, 53.9, 64.6, 130.3, 134.8, 136.2, 136.6. IR (film): 3364, 3300, 2954, 2920, 2867, 1610, 1455, 1378, 1249 cm$^{-1}$. ESI-MS: C$_{11}$H$_{17}$NO [M+H] calc. 180.3, found 180.2. $[\alpha]_{D}^{25}$ = -25.9° (c = 0.40, CH$_2$Cl$_2$).

(R)-4-mesityloxazolidinethione: To a dry 250 mL round-bottom flask, under argon, was added amino alcohol 13 (4.86 g, 27.1 mmol) in 97 mL of CH$_2$Cl$_2$. To this solution was added triethylamine (9.4 mL, 67.8 mmol) and the solution was cooled to 0 °C. Thiophosgene (2.1 mL, 27.1 mmol) was diluted in 2
mL of CH$_2$Cl$_2$ and added slowly to the reaction vessel. The reaction mixture was stirred for 30 min at 0 °C and then quenched with 10% NaHSO$_4$. After warming to room temperature, the layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2x). The combined organic layers were washed with 1 M NH$_4$OH, followed by saturated NaCl, dried over NaSO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (30% EtOAc/Hex) to provide the product as a pale yellow foam (5.1 g, 85%). The product was crystallized by triturating with hexanes. $^1$H NMR (400 MHz, CDCl$_3$): δ 2.25 (s, 3H), 2.34 (s, 6H), 4.53 (dd, 1H, J = 8.8, 8.8 Hz), 4.96 (dd, 1H, J = 9.2, 10.8 Hz), 5.64 (dd, 1H, J = 8.8, 10.8 Hz), 6.87 (s, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 20.3, 20.7, 55.6, 74.9, 129.1, 131.0, 136.9, 138.7, 189.3. IR (film): 3382, 3184, 2971, 2923, 1610, 1505, 1269, 1174, 1146 cm$^{-1}$. ESI-MS: C$_{12}$H$_{15}$NOS [M+H] calc. 222.3, found 222.1, [M+Na] calc. 244.3, found 244.1. [α]$_D^{25}$ = -5.3° (c = 3.0, CH$_2$Cl$_2$).

![Structure of ONS](image)

**(R)-N-acetyloxazolidinethione 14:** To a dry 500 mL round-bottom flask, under argon, was added the oxazolidinethione (7.82 g, 35.3 mmol) and 176 mL of CH$_2$Cl$_2$. The solution was cooled to 0 °C and triethylamine (9.8 mL, 70.6 mmol) was added. The reaction mixture was stirred for 15 min at 0 °C and acetyl
chloride (3.8 mL, 53.0 mmol) was slowly added. The mixture was stirred for 15 min at 0 °C, then warmed to room temperature and stirred for 20 min. The reaction was quenched with 10% NaHSO$_4$ and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (2x) and the combined organic layers were dried over NaSO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (15% EtOAc/Hex) to provide the product as a yellow foam (7.53 g, 81%). The foam was dissolved in CH$_2$Cl$_2$ and a crystal of the racemic N-acetyloxazolidinethione was used as a seed to induce crystallization. $^1$H NMR (400 MHz, CDCl$_3$): δ 2.26 (s, 6H), 2.46 (s, 3H), 2.78 (s, 3H), 4.39 (dd, 1H, J = 7.6, 8.8 Hz), 4.86 (dd, 1H, J = 10.0, 10.8 Hz), 6.10 (dd, 1H, J = 7.2, 10.8 Hz), 6.87 (s, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 19.4, 20.4, 20.6, 26.3, 57.9, 71.5, 129.6, 130.3, 131.7, 134.7, 137.2, 138.0, 170.7, 186.3. IR (film): 3009, 2971, 2920, 2867, 1707, 1611, 1483, 1415, 1372, 1341, 1311, 1239, 1181 cm$^{-1}$. ESI-MS: C$_{14}$H$_{17}$NO$_2$S [M+H] calc. 264.2, found 264.1. [$\alpha$]$^\text{D}_{25}$ = +75.3°(c = 5.55, CH$_2$Cl$_2$).

**Typical aldol procedure using N-acetyloxazolidinethione:** To a dry 25 mL round-bottom flask, under argon, was added N-acetyloxazolidinethione 14 (0.263 g, 1.00 mmol) and 5 mL of CH$_2$Cl$_2$. The flask was cooled to −40 °C and titanium tetrachloride (neat, 0.22 mL, 2.00 mmol) was added and the reaction mixture was stirred for 5 min. Diisopropylethylamine (0.35 mL, 2.00 mmol) was then added and the solution was stirred for 2 h at −40 °C and was then cooled to
−78 °C, whereupon the freshly distilled aldehyde (n eat, 1.2 mmol) was added. The mixture was stirred for 4 h at −78 °C, then quenched with half saturated ammonium chloride and warmed to room temperature. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2x). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (20% EtOAc/Hex). Yields and diastereoselectivities are listed in Table 1.

\[
\begin{align*}
\text{(R)-3-hydroxy-1-((R)-4-mesityl-2-thioxooxazolidin-3-yl)pentan-1-one:} \\
\text{^1H NMR (400 MHz, CDCl}_3\text{): } &\delta 0.94 \text{ (dd, 3H, } J = 7.2, 7.6 \text{ Hz), } 1.48\text{-}1.60 \text{ (band, 2H), } \\
&2.25 \text{ (s, 6H), } 2.46 \text{ (s, 3H), } 2.88 \text{ (brs, OH), } 3.36 \text{ (dd, 1H, } J = 2.4, 17.6 \text{ Hz), } 3.51 \text{ (dd, 1H, } J = 9.2, 17.6 \text{ Hz), } 3.91 \text{ (m, 1H), } 4.39 \text{ (dd, 1H, } J = 7.2, 9.2 \text{ Hz), } 4.88 \text{ (dd, 1H, } J = 9.6, 10.8 \text{ Hz), } 6.12 \text{ (dd, 1H, } J = 7.2, 10.8 \text{ Hz), } 6.86 \text{ (s, 1H), } 6.87 \text{ (s, 1H).} \\
\text{^13C NMR (100 MHz, CDCl}_3\text{): } &\delta 9.73, 19.5, 20.5, 20.7, 29.2, 44.5, 58.1, 69.0, 71.8, \\
&129.7, 130.3, 131.8, 134.7, 137.0, 138.1, 173.5, 185.9. \text{ IR (film): } 3472, 2967, \\
&2919, 2875, 1703, 1612, 1487, 1456, 1395, 1369, 1340, 1304, 1196 \text{ cm}^{-1}. \text{ ESI-MS: } C_{17}H_{23}NO_3S \text{ [M+H] calc. 322.4, found 322.2, [M+Na] calc. 344.4, found 344.1. } \alpha^{25}_D = +21.5^\circ (c = 3.7, \text{ CH}_2\text{Cl}_2). \end{align*}
\]
**(R)-3-hydroxy-1-((R)-4-mesityl-2-thioxooxazolidin-3-yl)hexan-1-one**: 

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.91 (dd, 3H, $J = 6.8, 10.8$ Hz), 1.37-1.52 (bands, 4H), 2.52 (s, 6H), 2.46 (s, 3H), 2.88 (s, 1H), 3.35 (dd, 1H, $J = 2.4, 18.0$ Hz), 3.51 (dd, 1H, $J = 9.6, 18.0$ Hz), 3.99 (dd, 1H, $J = 7.2, 9.2$ Hz), 4.38 (dd, 1H, $J = 9.2, 10.8$ Hz), 6.12 (dd, 1H, $J = 7.2, 10.8$ Hz), 6.86 (s, 1H), 6.87 (s, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 13.8, 18.5, 19.4, 20.5, 20.6, 38.3, 44.9, 58.1, 67.4, 71.7, 129.7, 130.3, 131.7, 134.7, 137.0, 138.1, 173.5, 185.9. IR (film): 3458, 2958, 2929, 2871, 1705, 1611, 1395, 1370, 1341, 1199, 1161 cm$^{-1}$. ESI-MS: C$_{18}$H$_{25}$NO$_3$S [M+H] calc. 336.5, found 336.2, [M+Na] calc. 358.5, found 358.2. $[\alpha]_{D}^{23} = +24.3^\circ (c = 3.00, \text{CH}_2\text{Cl}_2)$.

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**S)-3-hydroxy-1-((R)-4-mesityl-2-thioxooxazolidin-3-yl)-4-methylpentan-1-one**: 

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.94 (dd, 6H, $J = 5.6, 6.8$ Hz), 1.71-1.76 (m, 1H), 2.25 (s, 6H), 2.46 (s, 3H), 2.75 (d, 1H, $J = 4.8$ Hz), 3.32 (dd, 1H, $J = 2.0, 17.6$ Hz), 3.56 (dd, 1H, $J = 10.0, 17.6$ Hz), 3.77 (m, 1H), 4.39 (dd, 1H, $J = 7.2,$
9.2 Hz), 4.87 (dd, 1H, J = 9.6, 11.2 Hz), 6.12 (dd, 1H, J = 7.2, 11.2 Hz), 6.86 (s, 2H). $^{13}$C NMR (100 MHz, CDCl₃): δ 17.7, 18.4, 19.6, 20.6, 20.7, 33.1, 42.1, 58.2, 71.8, 72.5, 76.7, 129.8, 130.4, 131.8, 134.8, 137.1, 138.2, 174.0, 186.1. IR (film): 3473, 2962, 2923, 2875, 1704, 1611, 1482, 1465, 1394, 1370, 1341, 1308, 1198, 1161 cm⁻¹. ESI-MS: C₁₈H₂₅NO₃S [M+H] calc. 336.5, found 336.2, [M+Na] calc. 358.5, found 358.2. [α]$_{23}^{23}$D = +12.3° (c = 3.65, CH₂Cl₂).

(enantio-3-hydroxy-1-((enantio)-4-mesityl-2-thioxooxazolidin-3-yl)-5-methylhexan-1-one: $^1$H NMR (400 MHz, CDCl₃): δ 0.89 (t, 6H, J = 6.8 Hz), 1.19 (ddd, 1H, J = 4.0, 8.8, 12.8 Hz), 1.52 (ddd, 1H, J = 5.2, 9.2, 14.4 Hz), 1.76-1.81 (bands, 1H), 2.26 (s, 6H), 2.47 (s, 3H), 2.83 (s, 1H), 3.32 (dd, 1H, J = 2.0, 17.6 Hz), 3.51 (dd, 1H, J = 9.6, 18.0 Hz), 4.05-4.08 (m, 1H), 4.39 (dd, 1H, J = 7.2, 9.2 Hz), 4.88 (dd, 1H, J = 9.6, 10.8 Hz), 6.13 (dd, 1H, J = 7.2, 11.2 Hz), 6.87 (s, 1H), 6.88 (s, 1H). $^{13}$C NMR (100 MHz, CDCl₃): δ 19.5, 20.5, 20.7, 21.8, 23.1, 24.2, 45.3, 45.4, 58.1, 65.8, 71.8, 129.7, 130.4, 131.8, 134.7, 137.0, 138.1, 173.6, 185.9. IR (film): 3448, 2955, 2923, 2869, 1704, 1611, 1487, 1466, 1395, 1370, 1340, 1199, 1161 cm⁻¹. ESI-MS: C₁₉H₂₇NO₃S [M+H] calc. 350.5, found 350.2, [M+Na] calc. 372.5, found 372.2. [α]$_{24}^{24}$D = +36.1° (c = 1.5, CH₂Cl₂).
(S)-3-hydroxy-1-((R)-4-mesityl-2-thioxooxazolidin-3-yl)-3-phenylpropan-1-one: \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 2.22 (s, 3H), 2.27 (s, 3H), 2.48 (s, 3H), 3.58 (dd, 1H, J = 2.4, 17.6 Hz), 3.93 (dd, 1H, J = 9.6, 17.6 Hz), 4.41 (dd, 1H, J = 7.6, 9.6 Hz), 4.87 (dd, 1H, J = 9.6, 10.8 Hz), 5.13 (dd, 1H, J = 2.8, 10.0 Hz), 6.13 (dd, 1H, J = 7.2, 11.2 Hz), 6.85 (s, 1H), 6.89 (s, 1H), 7.27-7.35 (bands, 5H).

\(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 19.5, 20.6, 20.7, 46.6, 58.2, 70.0, 71.8, 125.8, 127.7, 128.5, 129.8, 130.2, 131.9, 138.3, 142.2, 172.8, 185.9. IR (film): 3464, 2971, 2919, 1704, 1607, 1482, 1452, 1391, 1370, 1341, 1200, 1158 cm\(^{-1}\). ESI-MS: C\(_{21}\)H\(_{23}\)NO\(_3\)S [M+H] calc. 370.5, found 370.2, [M+Na] calc. 392.5, found 392.2. \([\alpha]^{26}_D = +53.7^\circ (c = 0.25, \text{CH}_2\text{Cl}_2)\).

(S,E)-3-hydroxy-1-((R)-4-mesityl-2-thioxooxazolidin-3-yl)-5-phenylpent-4-en-1-one: \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 2.24 (s, 6H), 2.45 (s, 3H), 3.04 (s, 1H), 3.53 (dd, 1H, J = 3.2, 17.6 Hz), 3.75 (dd, 1H, J = 8.8, 18.0 Hz), 4.37 (dd, 1H, J = 7.6, 9.2 Hz), 4.72 (m, 1H), 4.83 (dd, 1H, J = 9.6, 10.8 Hz), 6.09 (dd, 1H, J = 2.8, 9.2 Hz), 6.85 (s, 1H), 6.89 (s, 1H), 7.27-7.35 (bands, 5H).

\(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 19.5, 20.6, 20.7, 46.6, 58.2, 70.0, 71.8, 125.8, 127.7, 128.5, 129.8, 130.2, 131.9, 138.3, 142.2, 172.8, 185.9. IR (film): 3464, 2971, 2919, 1704, 1607, 1482, 1452, 1391, 1370, 1341, 1200, 1158 cm\(^{-1}\). ESI-MS: C\(_{21}\)H\(_{23}\)NO\(_3\)S [M+H] calc. 370.5, found 370.2, [M+Na] calc. 392.5, found 392.2. \([\alpha]^{26}_D = +53.7^\circ (c = 0.25, \text{CH}_2\text{Cl}_2)\).
7.2, 10.8 Hz), 6.21 (dd, 1H, J = 6.0, 16.0 Hz), 6.59 (d, 1H, J = 16.0 Hz), 6.79 (s, 1H), 6.87 (s, 1H), 7.23-7.35 (bands, 5H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 19.5, 20.6, 20.7, 44.9, 58.2, 68.5, 71.8, 126.5, 127.6, 128.4, 129.7, 130.2, 130.5, 131.8, 134.7, 136.3, 137.0, 138.2, 172.5, 185.8. IR (film): 3430, 3022, 2971, 2919, 2867, 1705, 1611, 1484, 1448, 1393, 1370, 1342, 1269, 1200, 1161 cm$^{-1}$. ESI-MS: C$_{23}$H$_{25}$NO$_3$S [M+H] calc. 396.2, found 396.2, [M+Na] calc. 418.2, found 418.2. [$\alpha$]$^{24}_D$ = +62.5° (c = 1.25, CH$_2$Cl$_2$).

**Imine 22:** To a dry 3-neck 1 L round-bottom flask, equipped with a mechanical stirrer and argon inlet, was added (R)-(+) 2-methyl-2-propanesulfinamide (20.00 g, 165 mmol) and 330 mL of CH$_2$Cl$_2$. Anhydrous CuSO$_4$ (165 g, 1.03 mol) was added in one portion followed by chloroacetaldehyde (198 mmol). The mixture was stirred at room temperature for 24 h. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography (15% EtOAc/Hex to 25% EtOAc/Hex) to provide the product as a pale yellow oil (26.14 g, 87%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.18 (s, 1H), 4.29 (d, 2H, J = 4.8 Hz), 7.99 (ddd, 1H, J = 0.8, 4.8, 4.8 Hz). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 22.2, 43.5, 57.4, 162.4. IR (film): 2979, 2963, 2928, 2903 2869, 1624, 1474, 1457, 1365, 1335, 1253, 1182, 1133 cm$^{-1}$. ESI-MS: C$_6$H$_{12}$ClNOS [M+H] calc. 182.7, found 182.0. [$\alpha$]$^{27}_D$ = -295° (c = 2.90, CH$_2$Cl$_2$).
(S)-4-mesitylthiazolidinethione 24: A dry 2 L round-bottom flask was charged with mesityl magnesium bromide (398 mmol, 5.0 equiv), prepared from 10.0 g Mg turnings (0.41 mol), 60.0 mL 2-bromomesitylene (0.40 mol) and 139 mL of dry ether. The flask was cooled to −78 °C and imine 22 (14.50 g, 79.6 mol, 1.0 equiv), dissolved in 265 mL of toluene, was slowly added to the solution and the reaction mixture was stirred for 3 h at −78 °C, quenched with 4 N HCl (199 mL, 796 mmol), warmed to room temperature and stirred for 3 h. The layers were separated, and the organic layer was extracted with H₂O (2x). The aqueous layers were combined and cooled to 0 °C, upon which 50% NaOH was slowly added, while stirring, until the pH reached 11. H₂O was added (approximately 500 mL, to prevent an emulsion from forming) and the solution was extracted with ether (3x). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was transferred to a 1 L round-bottom flask and 1 M KOH (398 mL, 398 mmol) was added. The reaction mixture was stirred for 10 min and carbon disulfide (24.0 mL, 398 mmol) was added. The reaction mixture was stirred for 30 min at room temperature, refluxed for 16 h, cooled to room temperature and extracted with CH₂Cl₂ (3x). The combined organic layers were dried over Na₂SO₄, filtered and concentrated
under reduced pressure. The crude product was purified by flash column chromatography (15% EtOAc/Hex to 100% CH$_2$Cl$_2$) to provide the product as a pale yellow solid (14.5 g, 77%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.26 (s, 3H), 2.39 (s, 6H), 3.63 (s, 1H), 3.65 (s, 1H), 5.83 (t, 1H, J = 10.4 H), 6.87 (s, 2H), 7.75 (brs, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 20.5, 20.8, 37.5, 63.6, 129.3, 130.8, 136.6, 138.6, 199.5. IR (film): 3333, 3130, 2965, 2923, 2858, 1610, 1482, 1383, 1288, 1218, 1134 cm$^{-1}$. ESI-MS: C$_{12}$H$_{15}$NS$_2$ [M+H] calc. 238.4, found 238.0. [$\alpha$]$^\circ$ = $+$139° (c = 0.25, CH$_2$Cl$_2$).

![Chemical Structure](image)

**(S)-N-acetylthiazolidinethione 25 :** To a dry 250 mL round-bottom flask, under argon, was added thiazolidinethione 24 (2.40 g, 10.1 mmol) and 51 mL THF. The solution was cooled to 0 ºC and 60% NaH in mineral oil (0.48 g, 12.1 mmol) was slowly added. The reaction mixture was stirred for 15 min at 0 ºC, and acetyl chloride (0.86 mL, 12.1 mmol) was added dropwise. The reaction mixture was stirred for 30 min at 0 ºC, upon which it was warmed to room temperature and allowed to stir for 2 h. The reaction was quenched with saturated ammonium chloride and the layers were separated. The aqueous layer was extracted with EtOAc (2x) and the combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (2% EtOAc/hexanes to 15% EtOAc/hexanes) to
provide N-acetylthiazolidinethione (2.63 g, 93%) as a yellow solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 2.26 (s, 3H), 2.41 (s, 6H), 2.70 (s, 3H), 3.34 (dd, 1H, $J = 10.0$, 11.2 Hz), 3.55 (dd, 1H, $J = 10.4$, 11.2 Hz), 6.36 (t, 1H, $J = 10.4$ Hz), 6.86 (s, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 20.2, 20.8, 27.7, 32.4, 67.9, 132.6, 137.7, 171.9, 201.4. IR (film): 3009, 2967, 2919, 2867, 1712, 1610, 1453, 1409, 1371, 1326, 1266, 1217, 1136 cm$^{-1}$. ESI-MS: C$_{14}$H$_{17}$NOS$_2$ [M+Na] calc. 302.1, found 302.2. $[\alpha]_{D}^{25} = + 81.0^\circ$ (c = 0.8, CH$_2$Cl$_2$).

**Typical aldol procedure using N-acetylthiazolidinethione:** To a dry 25 mL round-bottom flask, under argon, was added N-acetylthiazolidinethione 25 (0.307 g, 1.10 mmol) and 5.2 mL of CH$_2$Cl$_2$. The solution was cooled to $-78 \, ^\circ$C and titanium tetrachloride (neat, 0.12 mL, 1.10 mmol) was added and stirred for 5 min. Diisopropylethylamine (0.19 mL, 1.10 mmol) was added and the solution was stirred for 30 min at $-78 \, ^\circ$C, whereupon the freshly distilled aldehyde (neat, 1.0 mmol) was added dropwise. The mixture was stirred for 1 h at $-78 \, ^\circ$C, then quenched with half saturated ammonium chloride and warmed to room temperature. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2x). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10% EtOAc/Hex to 20% EtOAc/Hex). Yields and diastereoselectivities are listed in Table 2.
(S)-3-hydroxy-1-((S)-4-mesityl-2-thioxothiazolidin-3-yl)pentan-1-one: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.91 (dd, 3H, $J = 7.2$, 7.6 Hz), 1.41-1.54 (bands, 2H), 2.26 (s, 3H), 2.40 (s, 6H), 3.17 (dd, 1H, $J = 2.4$, 17.2 Hz), 3.33 (dd, 1H, $J = 9.6$, 11.2 Hz), 3.48-3.61 (bands, 2), 3.76-3.82 (bands, 1H), 6.38 (t, 1H, $J = 10.0$ Hz), 6.86 (s, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 9.73, 20.2, 20.8, 29.3, 32.5, 46.1, 68.0, 69.6, 132.6, 137.9, 175.0, 201.7. IR (film): 3439, 2964, 2924, 2875, 1704, 1610, 1456, 1371, 1325, 1258, 1177, 1129 cm$^{-1}$. ESI-MS: C$_{17}$H$_{23}$NO$_2$S$_2$ [M+Na] calc. 360.5, found 360.2. $[\alpha]^{26}_D = +101^\circ$ (c = 0.65, CH$_2$Cl$_2$).

(S)-3-hydroxy-1-((S)-4-mesityl-2-thioxothiazolidin-3-yl)hexan-1-one: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.88 (t, 3H, $J = 7.2$ Hz), 1.28-1.50 (bands, 4H), 2.25 (s, 3H), 2.40 (s, 6H), 2.81 (d, 1H, $J = 3.2$ Hz), 3.16 (dd, 1H, $J = 2.8$, 17.6 Hz), 3.33 (dd, 1H, $J = 9.6$, 11.2 Hz), 3.48-3.61 (bands, 2H), 3.87 (m, 1H), 6.38 (t, 1H, $J = 10.0$ Hz), 6.86 (s, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 13.9, 18.6, 20.2, 20.8, 32.5, 38.6, 46.6, 67.9, 68.0, 132.6, 137.9, 175.0, 201.7. IR (film): 3460, 2957, 2927, 2862, 1705, 1456, 1371, 1322, 1259, 1175, 1128 cm$^{-1}$. ESI-MS:
C_{18}H_{25}NO_{2}S_{2} [M+H] calc. 352.5, found 352.2, [M+Na] calc. 374.5, found 374.2.

$[\alpha]^{26}_{D} = +108^\circ$ (c = 0.25, CH$_2$Cl$_2$).

(R)-3-hydroxy-1-((S)-4-mesityl-2-thioxothiazolidin-3-yl)-4-methylpentan-1-one: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.90 (dd, 6H, J = 4.0, 6.8 Hz), 1.68 (m, 1H), 2.26 (s, 3H), 2.40 (s, 6H), 2.84 (brs, 1H), 3.13 (dd, 1H, J = 1.6, 16.8 Hz), 3.33 (dd, 1H, J = 9.6, 11.6 Hz), 3.51-3.67 (bands, 3H), 6.39 (t, 1H, J = 10.0 Hz), 6.86 (s, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 17.6, 18.3, 20.2, 20.8, 32.5, 33.2, 43.6, 68.1, 73.0, 132.6, 137.9, 175.4, 201.8. IR (film): 3460, 2960, 2927, 2873, 1698, 1610, 1463, 1371, 1326, 1258, 1178, 1128 cm$^{-1}$. ESI-MS: C$_{18}$H$_{25}$NO$_{2}$S$_{2}$ [M+H] calc. 352.5, found 352.2, [M+Na] calc. 374.5, found 374.2. $[\alpha]^{25}_{D} = +102^\circ$ (c = 0.55, CH$_2$Cl$_2$).

(S)-3-hydroxy-1-((S)-4-mesityl-2-thioxothiazolidin-3-yl)-5-methylhexan-1-one: $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.85 (dd, 6H, J = 6.4, 10.0 Hz), 1.10 (ddd, 1H, J = 4.4, 8.8, 3.2), 1.46 (dd, 1H, J = 5.2, 8.8, 14.4), 1.74 (m, 1H), 2.26 (s, 3H), 2.40 (s, 6H).
3H), 2.40 (s, 6H), 2.76 (brs, 1H), 3.15 (dd, 1H, J = 2.8, 17.2 Hz), 3.33 (dd, 1H, J = 9.6, 11.6 Hz), 3.47-3.62 (bands, 2H), 3.94 (m, 1H), 6.39 (t, 1H, J = 10.0 Hz), 6.86 (s, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 20.2, 20.7, 21.8, 23.2, 24.3, 32.5, 45.6, 47.1, 66.4, 68.0, 132.6, 137.8, 174.9, 201.6. IR (film): 3448, 2954, 2925, 2868, 1709, 1610, 1462, 1370, 1324, 1259, 1174, 1127 cm$^{-1}$. ESI-MS: C$_{19}$H$_{27}$NO$_2$S$_2$ [M+Na] calc. 388.6, found 388.3. [$\alpha$]$^{24}_{D}$ = +83.6° (c = 0.90, CH$_2$Cl$_2$).

![Chemical Structure](image)

(R)-3-hydroxy-1-((S)-4-mesityl-2-thioxothiazolidin-3-yl)-3-phenylpropan-1-one: $^1$H NMR (400 MHz, CDCl$_3$): δ 2.24 (s, 3H), 2.36 (s, 6H), 3.18 (brs, 1H), 3.27-3.38 (bands, 2H), 3.55 (dd, 1H, J = 11.2, 10.4 Hz), 3.91 (dd, 1H, J = 9.6, 17.6), 4.98 (dd, 1H, J = 2.4, 9.2 Hz), 6.36 (t, 1H, J = 10.0 Hz), 6.82 (s, 2H), 7.23-7.28 (bands, 5H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 20.3, 20.8, 32.5, 48.4, 68.1, 70.6, 125.8, 127.7, 128.5, 132.4, 137.9, 142.3, 174.0, 201.7. IR (film): 3437, 3030, 2968, 2919, 2869, 1706, 1610, 1493, 1483, 1454, 1371, 1325, 1257, 1183, 1129 cm$^{-1}$. ESI-MS: C$_{21}$H$_{23}$NO$_2$S$_2$ [M+H] calc. 386.6, found 386.2, [M+Na] calc. 408.6, found 408.3. [$\alpha$]$^{26}_{D}$ = +60.0° (c = 0.55, CH$_2$Cl$_2$).
(R,E)-3-hydroxy-1-((S)-4-mesityl-2-thioxothiazolidin-3-yl)-5-phenylpent-4-en-1-one: $^1$H NMR (400 MHz, CDCl$_3$): δ 2.20 (s, 3H), 2.35 (s, 6H), 2.87 (s, 6H), 3.28-3.33 (bands, 2H), 3.53 (dd, 1H, J = 10.4, 11.2 Hz), 3.76 (dd, 1H, J = 8.4, 17.2 Hz), 4.60 (m, 1H), 6.11 (dd, 1H, J = 6.0, 16.0 Hz), 6.35 (t, 1H, J = 10.0 Hz), 6.53 (d, 1H, J = 16.0 Hz), 6.77 (s, 2H), 7.19-7.31 (bands, 5H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 20.3, 20.8, 32.5, 46.8, 68.1, 69.0, 126.5, 127.7, 128.5, 129.8, 130.6, 132.4, 136.4, 137.9, 173.8, 201.7. IR (film): 3027, 2962, 2917, 2867, 1705, 1607, 1448, 1374, 1326, 1260, 1190, 1129 cm$^{-1}$. ESI-MS: C$_{23}$H$_{25}$NO$_2$S$_2$ [M+H] calc. 412.3, found 412.3, [M+Na] calc. 434.3, found 434.3. $[\alpha]_{D}^{26}$ = +20.2° (c = 0.20, CH$_2$Cl$_2$).

Protected aldol adduct: To a dry 100 mL round-bottom flask, under argon, was added aldol adduct 30a (1.90 g, 5.40 mmol) in 18 mL CH$_2$Cl$_2$. The flask was cooled to 0 °C and 2,6-lutidine (1.3 mL, 10.8 mmol) was added
followed by TBSOTf (1.49 mL, 6.48 mmol). The reaction mixture was stirred for 30 min at 0 °C and reaction progress was monitored by TLC. The reaction mixture was quenched with saturated sodium bicarbonate, warmed to room temperature, and extracted with CH$_2$Cl$_2$ (3x). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified via flash column chromatography (2% EtOAc/Hex to 10% EtOAc/Hex) to provide the product as a yellow solid (2.48 g, 98%). $^1$H NMR (400 MHz, CDCl$_3$): δ 0.00 (d, 6H, J = 0.8 Hz), 0.71 (d, 3H, J = 6.8 Hz), 0.76 (d, 3H, J = 6.8 Hz), 0.85 (s, 9H), 1.37 (m, 1H), 2.24 (s, 3H), 2.40 (s, 6H), 2.92 (dd, 1H, J = 6.4, 10.0 Hz), 3.30 (dd, 1H, J = 9.2, 11.2 Hz), 3.57 (dd, 1H, J = 10.8, 11.2 Hz), 3.73 (dd, 1H, J = 6.4, 18.0 Hz), 4.02 (ddd, 1H, J = 3.2, 6.4, 9.2 Hz), 6.36 (dd, 1H, J = 8.8, 10.0 Hz), 6.84 (s, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ -4.88, -4.89, 16.4, 18.1, 18.5, 20.3, 20.8, 25.6, 32.4, 32.8, 44.1, 68.0, 72.7, 132.9, 137.8, 140.4, 173.5, 201.2. IR (film): 2956, 2927, 2849, 1713, 1616, 1469, 1371, 1327, 1254, 1175, 1127 cm$^{-1}$. ESI-MS: C$_{24}$H$_{39}$NO$_2$S$_2$Si [M+H] calc. 466.8, found 466.3, [M+Na] calc. 488.6, found 488.3. $[\alpha]^{23}_D = +108^\circ$ (c = 0.10, CH$_2$Cl$_2$).

**Aldehyde 31a:** To a dry 100 mL round-bottom flask, under argon, was added the protected aldol adduct (0.75 g, 1.61 mmol) in 16 mL CH$_2$Cl$_2$. The flask was cooled to -78 °C, upon which DIBAL (1 M in hexanes) was added dropwise until the reaction mixture became colorless (~3.2 mL, 3.22 mmol). The reaction
mixture was immediately quenched with saturated potassium sodium tartrate, warmed to room temperature, and vigorously stirred for 1 h. 5 mL Et2O was added and the reaction mixture was stirred 5 min, then extracted with Et2O (3x). The combined organic layers were dried over Na2SO4 and concentrated under reduced pressure. The crude product was purified via flash column chromatography (2% EtOAc/Hex) to provide the product as a pale yellow oil (0.307 g, 83%). ¹H NMR (400 MHz, CDCl₃): δ 0.03 (d, 6H, J = 10.8 Hz), 0.85-0.92 (bands, 15H), 1.77 (m, 1H), 2.41 (ddd, 1H, J = 2.0, 4.4, 15.6 Hz), 2.50 (ddd, 1H, J = 2.8, 7.2, 15.6 Hz), 4.01 (ddd, 1H, J = 4.8, 4.8, 7.2 Hz), 9.79 (dd, 1H, J = 2.0, 3.2 Hz). ¹³C NMR (100 MHz, CDCl₃): δ -4.67, -4.56, 17.2, 18.0, 25.7, 34.0, 47.2, 72.4, 202.6. IR (film): 2958, 2931, 2888, 2858, 2718, 1728, 1472, 1388, 1370, 1254, 1218 cm⁻¹. ESI-MS: C₁₂H₂₆O₂Si [M+H] calc. 231.4, found 231.2. [α]²²°D = -4.54° (c = 1.05, CH₂Cl₂).

(3S,5R)-5-(tert-butyldimethylsilyloxy)-3-hydroxy-1-((S)-4-mesityl-2-thioxothiazolidin-3-yl)-6-methylheptan-1-one 32a: See “Typical aldol procedure using N-acetylthiazolidinethione.” One modification made to this procedure involves quenching with half-saturated sodium bicarbonate instead of ammonium chloride. The crude product was purified by flash column chromatography (5% EtOAc/Hex to 15% EtOAc/Hex) to provide the product as a
mixture of diastereomers (93% yield, 90:10 $d_r$) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.03 (s, 6H), 0.64 (d, 3H, $J = 6.8$ Hz), 0.81 (d, 3H, $J = 7.2$ Hz), 0.85 (s, 9H), 1.21-1.26 (bands, 1H), 1.39-1.45 (bands, 1H), 1.70 (m, 1H), 2.21 (s, 3H), 2.38 (s, 6H), 3.15 (dd, 1H, $J = 5.6, 17.6$ Hz), 3.30 (dd, 1H, $J = 10.0, 11.2$ Hz), 3.53-3.61 (bands, 2H), 3.67 (m, 1H), 4.07 (m, 1H), 6.36 (t, 1H, $J = 10.0$ Hz), 6.81 (s, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ -4.74, -4.41, 16.6, 17.2, 17.8, 20.2, 20.6, 25.7, 25.8, 32.3, 32.5, 37.3, 47.3, 67.0, 67.8, 75.7, 75.8, 132.5, 137.6, 173.7, 201.0. IR (film): 3481, 2956, 2928, 2895, 2856, 1708, 1611, 1577, 1462, 1370, 1329, 1258, 1177, 1129 cm$^{-1}$. ESI-MS: $C_{26}H_{43}NO_3S_2Si$ [M+H] calc. 510.8, found 510.4, [M+Na] calc. 532.8, found 532.4. $[\alpha]^{21}_D = +65.5^\circ$ (c = 0.45, CH$_2$Cl$_2$).

\[(3R,5R)-5-(tert-butyldimethylsilyloxy)-3-hydroxy-1-((R)-4-mesityl-2-thioxothiazolidin-3-yl)-6-methylheptan-1-one\ (33a):\] See “Typical aldol procedure using $N$-acetylthiazolidinethione.” One modification made to this procedure involves quenching with half-saturated sodium bicarbonate instead of ammonium chloride. The crude product was purified by flash column chromatography (5% EtOAc/Hex to 15% EtOAc/Hex) to provide the product as a mixture of diastereomers (91% yield, 95:5 $d_r$) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ -0.02 (s, 3H), 0.2 (s, 3H), 0.75 (d, 3H, 6.4 Hz), 0.82-0.90 (bands, 12H), 81
1.26-1.45 (bands, 2H), 1.75 (m, 1H), 2.23 (s, 3H), 2.39 (s, 6H), 3.14 (dd, 1H, J = 5.6, 16.8 Hz), 3.30 (t, 2H, J = 10.0 Hz), 3.45 (dd, 1H, J = 8.0 Hz, 17.2 Hz), 3.53-3.64 (bands, 2H), 4.08 (m, 1H), 6.35 (t, 1H, J = 10.0 Hz), 6.82 (s, 2H). 13C NMR (100 MHz, CDCl₃): δ -4.83, -4.74, 16.9, 17.7, 18.5, 20.1, 20.5, 25.7, 32.4, 32.9, 38.2, 47.3, 65.1, 67.7, 73.8, 73.9, 132.2, 137.3, 174.3, 200.9. IR (film): 3488, 2956, 2928, 2895, 2856, 1705, 1611, 1577, 1463, 1386, 1370, 1331, 1296, 1258, 1186, 1129 cm⁻¹. ESI-MS: C_{26}H_{43}NO_{3}S_{2}Si [M+H] calc. 510.8, found 510.4, [M+Na] calc. 532.8, found 532.3, [2M+Na] calc. 1041.8, found 1041.5. [α]$_{D}^{21}$ = -71.9° (c = 0.15, CH₂Cl₂).

**Protected aldol adduct:** To a dry 100 mL round-bottom flask, under argon, was added aldol adduct 30b (2.95 g, 5.40 mmol) in 29 mL CH₂Cl₂. The flask was cooled to 0 °C and 2,6-lutidine (2.0 mL, 17.5 mmol) was added followed by TBSOTf (2.41 mL, 10.5 mmol). The reaction mixture was stirred for 30 min at 0 °C and reaction progress was monitored by TLC. The reaction mixture was quenched with saturated sodium bicarbonate, warmed to room temperature, and extracted with CH₂Cl₂ (3x). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified via flash column chromatography (2% EtOAc/Hex to 10% EtOAc/Hex) to provide the product as a yellow solid (3.66 g, 94%). 1H NMR (400 MHz, CDCl₃): δ 0.06 (s,
3H), 0.07 (s, 3H), 0.82 (d, 3H, J = 6.8 Hz), 0.90 (s, 12H), 1.24 (d, 3H, J = 6.4 Hz),
1.63 (m, 1H), 2.87 (d, 1H, J = 11.6 Hz), 3.03 (dd, 1H, J = 4.8, 4.8 Hz), 3.21 (dd,
1H, J = 3.2, 12.8 Hz), 3.33 (dd, 1H, J = 7.2, 11.6 Hz), 3.88 (dd, 1H, J = 2.4, 7.2
Hz), 4.47 (m, 1H), 5.21 (dd, 1H, J = 3.6, 6.4, 10.4 Hz), 7.24-7.34 (bands, 5H).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.01 (s, 3H), 0.07 (s, 3H), 0.82 (d, 3H, J = 6.8 Hz),
1.63 (m, 1H), 2.87 (d, 1H, J = 11.6 Hz), 3.03 (dd, 1H, J = 4.8, 4.8 Hz), 3.21 (dd,
1H, J = 3.2, 12.8 Hz), 3.33 (dd, 1H, J = 7.2, 11.6 Hz), 3.88 (dd, 1H, J = 2.4, 7.2
Hz), 4.47 (m, 1H), 5.21 (dd, 1H, J = 3.6, 6.4, 10.4 Hz), 7.24-7.34 (bands, 5H).

Aldehyde 31b: To a dry 100 mL round-bottom flask, under argon, was
added the protected aldol adduct (0.60 g, 1.33 mmol) in 13 mL CH$_2$Cl$_2$. The flask
was cooled to -78 °C, upon which DIBAL (1 M in hexanes) was added dropwise
until the reaction mixture became colorless (~2.7 mL, 2.66 mmol). The reaction
mixture was immediately quenched with saturated potassium sodium tartrate,
warmed to room temperature, and vigorously stirred for 1 h. 5 mL Et$_2$O was
added and the reaction mixture was stirred 5 min, then extracted with Et$_2$O (3x).
The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under
reduced pressure. The crude product was purified via flash column
chromatography (2% EtOAc/Hex to 10% EtOAc/Hex) to provide the product as a
pale yellow oil (0.268 g, 82%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.01 (s, 3H), 0.07 (s, 3H), 0.82 (d, 3H, J = 6.8 Hz), 1.63 (m, 1H), 2.87 (d, 1H, J = 11.6 Hz), 3.03 (dd, 1H, J = 4.8, 4.8 Hz), 3.21 (dd, 1H, J = 3.2, 12.8 Hz), 3.33 (dd, 1H, J = 7.2, 11.6 Hz), 3.88 (dd, 1H, J = 2.4, 7.2 Hz), 4.47 (m, 1H), 5.21 (dd, 1H, J = 3.6, 6.4, 10.4 Hz), 7.24-7.34 (bands, 5H).
(s, 3H), 0.89-0.93 (bands, 15H), 1.09 (d, 3H, J = 8.0 Hz), 1.81 (m, 1H), 2.50 (m, 1H), 3.90 (t, 1H, J = 4.4 Hz), 9.78 (s, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ -4.21, -4.03, 8.59, 18.3, 19.7, 25.9, 32.2, 50.6, 76.4, 205.5. IR (film): 2958, 2884, 2858, 1728, 1472, 1387, 1254, 1100 cm$^{-1}$. ESI-MS: C$_{13}$H$_{28}$O$_2$Si [M+H] calc. 245.6, found 245.2, [M+Na] calc. 267.5, found 267.2. $[\alpha]^{22}_D = -59.1^\circ$ (c = 0.40, CH$_2$Cl$_2$).

![Chemical structure](image)

32b: To a dry 25 mL round-bottom flask, under argon, was added N-acetylthiazolidinethione 25 (0.474 g, 1.70 mmol) and 6 mL of CH$_2$Cl$_2$. The solution was cooled to −78 °C and titanium tetrachloride (neat, 0.19 mL, 1.70 mmol) was added and stirred for 5 min. Diisopropylethylamine (0.30 mL, 1.70 mmol) was added and the solution was stirred for 30 min at −78 °C, upon which the freshly prepared aldehyde (neat, 1.13 mmol) was added dropwise. The mixture was stirred for 1 h at −78 °C, then quenched with half saturated sodium bicarbonate and warmed to room temperature. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2x). The combined organic layers were dried over NaSO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5% EtOAc/Hex to 10% EtOAc/Hex) to provide the
product as a mixture of diastereomers (0.537 g, 91%, 97:3 \( dr \)) as a yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 0.02 (d, 6H, \( J = 10.0 \) Hz), 0.75 (d, 3H, \( J = 6.8 \) Hz), 0.84-0.93 (bands, 15H), 1.49 (m, 1H), 1.76 (m, 1H), 2.25 (s, 3H), 2.40 (s, 6H), 2.68 (s, 1H), 3.13 (dd, 1H, \( J = 3.6, 17.6 \) Hz), 3.34 (dd, 1H, \( J = 10.0, 11.6 \) Hz), 3.47 (dd, 1H, \( J = 4.0, 4.4 \) Hz), 3.55-3.68 (bands, 2H), 3.96 (m, 1H), 6.39 (t, 1H, \( J = 10.0 \) Hz), 6.85 (s, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) -3.96, -3.65, 9.86, 17.5, 18.4, 19.4, 20.2, 20.7, 26.1, 32.2, 32.4, 40.4, 45.1, 68.0, 70.5, 78.6, 132.1, 137.9, 174.8, 201.5. IR (film): 3545, 2956, 2928, 2856, 1705, 1611, 1462, 1371, 1329, 1257, 1178, 1128 cm\(^{-1}\). ESI-MS: C\(_{27}\)H\(_{45}\)NO\(_3\)S\(_2\)Si [M+H] calc. 524.9, found 524.3, [M+Na] calc. 546.9, found 546.3. \([\alpha]\)\(^{22}\)\(_D\) = +52.2\(^\circ\) (c = 0.70, CH\(_2\)Cl\(_2\)).

(3S,4S,5S)-5-(tert-butyldimethylsilyloxy)-3-hydroxy-1-((R)-4-mesityl-2-thioxothiazolidin-3-yl)-4,6-dimethylheptan-1-one 33b: To a dry 25 mL round-bottom flask, under argon, was added \( N \)-acetylthiazolidinethione 21 (0.419 g, 1.50 mmol) and 5 mL of CH\(_2\)Cl\(_2\). The solution was cooled to −78 °C and titanium tetrachloride (neat, 0.16 mL, 1.50 mmol) was added and stirred for 5 min. Diisopropylethylamine (0.26 mL, 1.50 mmol) was added and the solution was stirred for 30 min at −78 °C, upon which the freshly prepared aldehyde (neat, 1.0 mmol) was added dropwise. The mixture was stirred for 1 h at −78 °C, then
quenched with half saturated sodium bicarbonate and warmed to room temperature. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2x). The combined organic layers were dried over NaSO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (5% EtOAc/Hex to 10% EtOAc/Hex) to provide the product as a mixture of diastereomers (0.482 g, 92%, 92:8 $d$/$l$) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ -0.06 (s, 3H), 0.03 (s, 3H), 0.79 (d, 3H, $J = 6.8$ Hz), 0.85-0.92 (bands, 15H), 1.72 (m, 2H), 2.25 (s, 3H), 2.41 (s, 6H), 3.25-3.36 (bands, 3H), 4.46 (dd, 1H, $J = 9.6$, 16.8 Hz), 3.58 (dd, 1H, $J = 10.4$, 11.2 Hz), 3.72 (m, 2H), 6.34 (t, 1H, $J = 10.0$ Hz), 6.85 (s, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ -4.26, -4.11, 10.9, 18.3, 19.5, 19.6, 20.2, 20.7, 26.1, 32.2, 32.5, 41.4, 44.4, 68.1, 70.2, 76.3, 132.4, 137.7, 175.3, 201.7. IR (film): 3460, 2956, 2927, 2855, 1696, 1611, 1462, 1385, 1369, 1327, 1258, 1185, 1128 cm$^{-1}$. ESI-MS: C$_{27}$H$_{45}$NO$_3$S$_2$Si $[\text{M+H}]$ calc. 524.9, found 524.3, $[\text{M+Na}]$ calc. 546.9, found 546.3. $[\alpha]^{22}_D = -73.4^\circ$ (c = 0.30, CH$_2$Cl$_2$).
400 MHz, CDCl₃
100 MHz, CDCl₃
100 MHz, CDCl₃
$\left(\text{THF} \cdot \text{D}_{2} \text{O}\right)$

$100 \text{ MHz, CDCl}_3$

ppm
400 MHz, CDCl₃
Chapter 4

Experimental Information and NMR spectra for Chapter 2

Methods and Materials: Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer and values reported in cm\(^{-1}\). Proton and carbon nuclear magnetic resonance (\(^1\)H and \(^{13}\)C NMR) spectra were recorded on the Bruker 400 (\(^1\)H at 400 MHz; \(^{13}\)C at 100 MHz). Optical rotations were determined using a Jasco P1010 polarimeter. Thin layer chromatography (TLC) was conducted on silica gel F254 TLC plates purchased from Scientific Adsorbents, Inc. Flash column chromatography was carried out using silica gel (32 to 63 µm) purchased from Scientific Adsorbents, Inc. Diethyl ether (Et\(_2\)O), tetrahydrofuran (THF), dichloromethane (CH\(_2\)Cl\(_2\)), and toluene were dried by being passed through a column of neutral alumina under nitrogen immediately prior to use. Alkylamines were distilled from calcium hydride immediately prior to use. All other reagents and solvents were used as received from the manufacturer, unless otherwise specified. All air and water sensitive reactions were performed in flasks flame dried under positive flow argon and conducted under an argon atmosphere.
Aldol adduct 78: To a dry 1L round-bottom flask, under argon, was added N-acetylthiazolidinethione 76 (17.4g, 65.5 mmol) in 360 mL CH₂Cl₂. The solution was cooled to 0 °C and titanium tetrachloride (neat, 7.50 mL, 68.6 mmol) was added dropwise. The thick suspension was stirred for 5 min upon which (−)-sparteine was added (15.0 mL, 65.5 mmol). The dark red solution was stirred for 20 min at 0 °C, then cooled to -78 °C upon which N-methyl-2-pyrrolidinone (6.3 mL, 65.5 mmol) was added. The mixture was stirred 10 min at -78 °C and aldehyde 77 (neat, 17.6 g, 72.0 mmol) was added dropwise. The reaction mixture was stirred 1 h at -78 °C then warmed to 0 °C for 1 h upon which the reaction was quenched with half-saturated ammonium chloride. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2x). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (10% EtOAc/Hex to 25% EtOAc/Hex) to provide the product (34.0 g, 93%) as a yellow oil. ^1H NMR (400 MHz, CDCl₃): δ 1.06 (s, 21H), 1.27 (d, 3H, J = 6.8 Hz), 1.64 (m, 4H), 2.89 (d, 1H, J = 11.6 Hz), 3.05 (m, 1H), 3.25 (dd, 1H, J = 3.2 Hz, 12.8 Hz), 3.74 (m, 2H), 3.98 (m, 1H), 3.52 (m, 1H), 5.33 (m, 1H), 7.23 (m, 5H). ^13C NMR (100 MHz, CDCl₃): δ 10.8, 11.9, 18.0, 29.5, 31.8, 32.1, 36.7, 43.9, 63.5, 69.1, 72.4, 127.2, 128.9, 129.5, 136.5, 177.9, 201.2. IR (film): 3413, 3087, 3063, 2942, 2865, 2727, 1955, 1883, 1813, 1697, 1604, 1584, 1496, 1456, 1341,
1292, 1261, 1191, 1164 cm\(^{-1}\). ESI-MS: C\(_{26}H_{43}NO_3S_2Si\) [M+Na] calc. 532.3, found 532.3, [2M+Na] calc 1041.5, found 1041.5. \(\alpha\)\(^{21}\)\(D\) = -15.0° (c = 1.10, CH\(_2Cl_2\)).

**Protected aldol adduct:** To a dry 500 mL round-bottom flask, under argon, was added aldol adduct 78 (33.0 g, 64.7 mmol) in 129 mL CH\(_2Cl_2\). The solution was cooled to 0 °C upon which triethylamine (12.0 mL, 84.1 mmol) was added, followed by distilled trimethylsilyl chloride (9.9 mL, 77.7 mmol). 4-dimethylaminopyridine (0.396 g, 3.24 mmol) was added and the reaction mixture was stirred for 2 h at 0 °C. The reaction was quenched with saturated sodium bicarbonate and extracted with CH\(_2Cl_2\) (3x). The combined organic layers were dried over Na\(_2SO_4\), filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (100% Hex to 5% EtOAc/Hex to 10% EtOAc/Hex) to provide the product (34.8 g, 92%) as a yellow oil. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.12 (s, 9H), 1.06 (s, 21H), 1.24 (d, 6.8 Hz), 1.57 (m, 4H), 2.89 (d, 11.6 Hz), 3.33 (m, 2H), 3.69 (m, 2H), 3.99 (m, 1H), 4.56 (qn, 1H, J = 6.4 Hz), 5.17 (sp, 1H, J = 3.6 Hz), 7.32 (m, 5H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 0.44, 12.0, 12.8, 18.1, 29.2, 31.4, 32.2, 36.5, 44.8, 63.3, 69.6, 74.7, 127.2, 128.9, 129.5, 136.7, 177.0, 200.9. IR (film): 3028, 2943, 2892, 2865, 2725, 1699, 1496, 1456, 1363, 1341, 1292, 1252, 1191, 1164, 1104 cm\(^{-1}\). ESI-
Aldehyde 75: To a dry 1L round-bottom flask equipped with an addition funnel, under argon, was added the protected aldol adduct (25.1 g, 43.1 mmol) in 287 mL CH₂Cl₂. The yellow solution was cooled to -78 °C, upon which DIBAL (1 M in hexanes) was added dropwise until the reaction mixture became colorless (~86 mL, 86.2 mmol). The reaction mixture was immediately quenched with saturated potassium sodium tartrate, warmed to room temperature, and vigorously stirred for 1 h. 20 mL Et₂O was added and the reaction mixture was stirred 5 min, then extracted with Et₂O (3x). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified via flash column chromatography (5% EtOAc/Hex to 10% EtOAc/Hex) to provide the product as a pale yellow oil (13.1 g, 81%). ¹H NMR (400 MHz, CDCl₃): δ 0.08 (s, 9H), 1.04 (s, 24H), 1.52 (m, 4H), 2.42 (m, 1H), 3.67 (m, 2H), 4.11 (m, 1H), 9.71 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 0.31, 7.79, 11.9, 18.0, 29.4, 31.2, 51.5, 63.0, 71.9, 120.0, 204.9. IR (film): 2944, 2893, 2867, 2713, 1728, 1463, 1383, 1252, 1200, 1104 cm⁻¹. ESI-MS: C₁₉H₄₂O₃Si₂ [M+Na] calc. 397.2, found 397.2. [α]²⁰_D = -28.9° (c = 1.75, CH₂Cl₂).
**β-Ketophosphonate 124:** To a dry 2L round-bottom flask equipped with an addition funnel, under argon, was added dimethyl methylphosphonate (43 mL, 400 mmol) in 332 mL THF. The solution was cooled to -78 °C and n-BuLi (1.6 M, 247 mL, 395 mmol) was added dropwise. The white suspension was stirred 1h at -78 °C upon which methyl β-benzylxoypropionate (19.5 g, 100 mmol) was added in 168 mL THF. The reaction mixture was stirred 1 h -78 °C at which point it was quenched with saturated ammonium chloride and warmed to room temperature. The layers were separated and the aqueous layer was extracted with Et2O (3x). The combined organic layers were dried over Na2SO4, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (85% EtOAc/Hex to 100% EtOAc) to provide the product as a colorless oil (20.3 g, 71%). 1H NMR (400 MHz, CDCl3): δ 2.77 (t, 2H, J = 6.0 Hz), 3.02 (d, 2H, J = 22.4 Hz), 3.62 (m, 8H), 4.37 (s, 2H), 7.19 (m, 5H). 13C NMR (100 MHz, CDCl3): δ 40.8, 42.1, 43.9, 52.8, 52.9, 64.8, 73.0, 127.6, 128.3, 138.0, 200.2, 200.3. IR (film): 3474, 3062, 3030, 2956, 2856, 1715, 1496, 1455, 1397, 1368, 1259, 1185 cm⁻¹. ESI-MS: C13H19O5P [M+Na] calc. 309.1, found 309.1, [M+Cs] calc. 419.0, found 419.0, [2M+Na] calc. 595.2, found 595.2. [α]D₂₀ = +0.89° (c = 1.25, CH₂Cl₂).
The reaction mixture was stirred 1 h at room temperature and was then diluted with EtOAc and filtered over celite. The solution was washed with saturated sodium bicarbonate and the aqueous layer was extracted with EtOAc (4×). The combined organic layers were dried over Na₂SO₄, filtered, and then concentrated under reduced pressure. The crude product was purified via flash column chromatography (5% EtOAc/Hex to 10% EtOAc/Hex) to provide the product as a colorless oil (21.9 g, 90%).

**Enone 125:** To a dry 2L round-bottom flask, under argon, was added β-ketophosphonate 124 (18.2 g, 63.6 mmol) in 114 mL THF. To the solution was added anhydrous barium hydroxide (6.53 g, 38.1 mmol) and the mixture was stirred 30 min at room temperature. Aldehyde 75 (17.0 g, 45.4 mmol) was added in 126 mL of 40:1 THF:H₂O, followed by an additional 154 mL of 40:1 THF:H₂O. The reaction mixture was stirred 1 h at room temperature and was then diluted with EtOAc and filtered over celite. The solution was washed with saturated sodium bicarbonate and the aqueous layer was extracted with EtOAc (4x). The combined organic layers were dried over Na₂SO₄, filtered, and then concentrated under reduced pressure. The crude product was purified via flash column chromatography (5% EtOAc/Hex to 10% EtOAc/Hex) to provide the product as a colorless oil (21.9 g, 90%).

**α,β-unsaturated aldehyde 125:**

\[ \text{Enone 125: To a dry 2L round-bottom flask, under argon, was added } \beta-\text{ketophosphonate } 124 \text{ (18.2 g, 63.6 mmol) in 114 mL THF. To the solution was added anhydrous barium hydroxide (6.53 g, 38.1 mmol) and the mixture was stirred 30 min at room temperature. Aldehyde 75 (17.0 g, 45.4 mmol) was added in 126 mL of 40:1 THF:H₂O, followed by an additional 154 mL of 40:1 THF:H₂O. The reaction mixture was stirred 1 h at room temperature and was then diluted with EtOAc and filtered over celite. The solution was washed with saturated sodium bicarbonate and the aqueous layer was extracted with EtOAc (4x). The combined organic layers were dried over Na₂SO₄, filtered, and then concentrated under reduced pressure. The crude product was purified via flash column chromatography (5% EtOAc/Hex to 10% EtOAc/Hex) to provide the product as a colorless oil (21.9 g, 90%).} \]

**H NMR (400 MHz, CDCl₃):** δ 0.12 (s, 9H), 1.06 (s, 24H), 1.34-1.65 (bands, 4H), 2.45 (m, 1H), 2.89 (t, 2H, J = 6.4 Hz), 3.66 (m, 3H), 3.80 (t, 2H, J = 6.4 Hz), 4.53 (s, 2H), 6.11 (d, 1H, J = 16.4 Hz), 6.87 (dd, 1H, J = 7.6 Hz, 16.0 Hz), 7.39 (m, 5H).

**13C NMR (100 MHz, CDCl₃):** δ 0.48, 12.0, 14.7, 18.0, 29.2, 30.6, 40.0, 42.6, 63.3, 65.5, 73.2, 75.5, 127.6, 127.7, 128.4, 130.2, 138.2, 150.4, 198.5. IR (film): 3031, 2944, 2892, 2866, 2729, 2360, 1697, 1673, 1628, 1496, 1463, 1366, 1251, 1201, 1102 cm⁻¹. ESI-MS: C₃₀H₅₄O₄Si₂ [M+Na] calc. 557.4, found 557.4, [2M+Na] calc. 1091.8, found 1091.8. [α]²¹_D = -29.9° (c = 0.90, CH₂Cl₂).
Hydroxyketone 126:

i) To a dry 2L round-bottom flask, under argon, was added Cul (1.56 g, 8.18 mmol) in 400 mL THF. The solution was cooled to -50 °C and MeLi (1.6 M, 5.1 mL, 8.18 mmol) was added dropwise. The yellow suspension was stirred 5 min upon which freshly distilled HMPA (82 mL, 470 mmol) was added, followed by DIBAL (1 M, 106 mL, 106 mmol). The mixture was stirred 30 min at -50 °C, at which point enone 125 (21.9 g, 40.9 mmol) was added in 200 mL THF. The reaction mixture was stirred 1 h at -50 °C. The dry ice bath was removed and 100 mL 1N HCl was added. The mixture was diluted with Et₂O and allowed to stir for 5 min. The layers were separated and the organic layer was washed with 1 N HCl (2x) then with H₂O (2x). The combined organic layers were dried over MgSO₄, filtered, and then concentrated under reduced pressure. The crude product (a mixture of the TMS-protected ketone and TMS-deprotected ketone) was passed through a silica plug (10% EtOAc/Hex to 50% EtOAc/Hex) then taken on to the next step.

ii) To a dry 1 L round-bottom flask, under argon, was added the mixture of TMS-protected ketone and TMS-deprotected ketone (21.3 g) in 400 mL anhydrous MeOH. Ammonium fluoride (29.0 g, 793 mmol, 20 equiv.) was added and the reaction mixture was stirred 2 h at room temperature. The reaction was quenched with saturated sodium bicarbonate and diluted with Et₂O. The layers were separated and the organic layer was washed with brine. The
combined aqueous layers were extracted with CH$_2$Cl$_2$ (2x). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (100% Hex to 20% EtOAc/Hex to 50%EtOAc/Hex) to provide the product as a pale yellow oil (17.1 g, 90% over 2 steps). $^1$H NMR (400 MHz, CDCl$_3$): δ 0.89 (m, 3H), 1.08 (s, 21H), 1.38-1.88 (bands, 8H), 2.10 (m, 1H), 2.51 (m, 1H), 2.73 (m, 1H), 3.49-3.78 (bands, 4H), 4.10 (m, 1H), 4.53 (m, 3H), 7.29 (m, 5H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 10.9, 11.9, 12.0, 14.0, 18.0, 26.5, 26.6, 29.3, 29.6, 29.9, 30.1, 31.4, 38.1, 40.3, 41.5, 42.8, 63.5, 63.7, 65.4, 66.6, 71.0, 73.2, 73.4, 74.1, 96.0, 127.7, 128.4, 137.7, 209.8. IR (film): 3481, 2942, 2892, 2866, 2359, 1715, 1456, 1386, 1246, 1101 cm$^{-1}$. ESI-MS: C$_{27}$H$_{48}$O$_4$Si [M+Na] calc. 487.3, found 487.3, [2M+Na] calc. 951.6, found 951.6. $[\alpha]^{21}$D = +1.56° (c = 2.20, CH$_2$Cl$_2$).

**Enol ether 127:** To a dry 100 mL round-bottom flask, under argon, was added activated 4 Å powdered molecular sieves (30 mL), hydroxyketone 126 (1.59 g, 3.42 mmol), and 34 mL toluene. CSA (0.556 g, 0.7 mmol) was added and the reaction mixture was allowed to stir 2.5 h at room temperature. The reaction was quenched with triethylamine, filtered to remove the molecular sieves, and washed with saturated sodium bicarbonate. The layers were separated and the aqueous layer was extracted with Et$_2$O (2x). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure.
pressure. The crude product was purified via flash column chromatography (5%EtOAc/Hex doped with triethylamine) to provide the product as a colorless oil (1.45 g, 95%). The product was immediately carried on to the next step due to its instability. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.91 (m, 3H), 1.09 (s, 21H), 1.49-1.73 (bands, 5H), 1.92 (m, 1H), 2.22 (m, 1H), 2.35 (t, 2H, J = 6.4 Hz), 3.61 (t, 2H, J = 6.8 Hz), 3.67-3.82 (bands, 3H), 4.91 (s, 1H), 4.54 (s, 2H), 7.30 (m, 5H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 12.0, 13.5, 18.0, 27.0, 28.5, 29.3, 29.5, 34.8, 63.3, 68.1, 72.8, 78.0, 95.0, 127.4, 127.6, 128.3, 138.6, 150.1. IR (film): 2942, 2924, 2892, 2865, 1678, 1462, 1383, 1246, 1207, 1170, 1101 cm\(^{-1}\). ESI-MS: C\(_{27}\)H\(_{46}\)O\(_3\)Si [M+Na] calc. 469.3, found 469.3. \([\alpha]^{21}_D = -23.9^o\) (c = 2.25, CH\(_2\)Cl\(_2\)).

**Thioacetal 130:** To a dry 500 mL round-bottom flask, under argon, was added enol ether 127 (1.43 g, 3.20 mmol) in 32 mL CH\(_2\)Cl\(_2\). The solution was cooled to -78 °C upon which freshly prepared “aceto ne-free” DMDO\(^1\) (90 mL, 4.48 mmol) was added. TLC showed complete consumption of starting material. The dry ice bath was removed and the solvents were removed via an argon purge. 32 mL CH\(_2\)Cl\(_2\) was added and the solution was cooled to 0 °C. Ethanethiol (12 mL, 160 mmol) was added, followed by Zn(OTf)\(_2\) (0.116 g, 0.320 mmol). The reaction mixture was stirred 45 min at 0 °C, at which point the reaction was quenched with triethylamine. Excess ethanethiol was removed under an argon

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\(^1\)Crimmins, M. T.; McDougall, P. J.; Ellis, J. M. *Org. Lett.* 2006, 8, 4079.
purge and the remaining solvent was removed under reduced pressure. The crude product was purified via flash column chromatography (5% EtOAc/Hex doped with triethylamine to 10% EtOAc/Hex doped with triethylamine) to provide the product as a colorless oil (1.39 g, 83%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.94 (m, 3H), 1.07 (s, 21H), 1.23 (t, 4H, J = 7.6 Hz), 1.45-1.70 (bands, 5H), 1.90 (m, 1H), 2.05 (m, 3H), 2.32 (m, 2H), 3.63-3.81 (bands, 3H), 4.09 (m, 2H), 4.61 (m, 3H), 7.33 (m, 5H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 12.0, 12.8, 14.6, 18.8, 28.8, 29.9, 31.9, 35.1, 41.1, 63.3, 67.5, 69.1, 72.1, 73.5, 94.0, 128.0, 128.1, 128.6, 136.9. IR (film): 3413, 3090, 3063, 3032, 2958, 2941, 2892, 2866, 1731, 1455, 1386, 1258, 1210 cm$^{-1}$. ESI-MS: C$_{29}$H$_{52}$O$_4$SSi [M+Na] calc. 547.3, found 547.3, [2M+Na] calc. 1071.6, found 1071.6. $[\alpha]_{D}^{21} = -55.4^\circ$ (c = 0.30, CH$_2$Cl$_2$).

Protected thioacetal: To a dry 250 mL round-bottom flask equipped with an addition funnel, under argon, was added alcohol 130 (1.08 g, 2.06 mmol) in 21 mL THF. The solution was cooled to -78 °C and triethylsilyl chloride (2.1 mL, 12.3 mmol) was added. KHMDS (0.5 M, 25 mL, 12.6 mmol) was added dropwise. The reaction mixture was stirred 15 min at -78 °C upon which it was quenched with saturated sodium bicarbonate and warmed to room temperature. The layers were separated and the aqueous layer was extracted with Et$_2$O (2x) and the combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated.
under reduced pressure. The crude product was purified via flash column chromatography (100% Hex to 5% EtOAc/Hex to 10% EtOAc/Hex) to provide the product as a cloudy light yellow oil (1.27 g, 96%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.56 (m, 6H), 0.94 (t, 12H, $J = 8.0$ Hz), 1.09 (s, 21H), 1.23 (m, 7H), 1.39-1.65 (bands, 7H), 1.86 (brs, 2H), 2.20 (m, 2H), 2.38 (m, 4H), 3.72 (m, 4H), 3.96 (m, 1H), 4.04 (dd, 1H, $J = 1.2$ Hz, 11.6 Hz), 4.52 (m, 2H), 7.30 (m, 5H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 5.18, 6.91, 12.0, 12.8, 14.7, 18.0, 19.6, 28.8, 29.9, 32.1, 37.0, 39.3, 63.4, 66.7, 68.3, 72.1, 73.1, 92.1, 127.5, 127.8, 128.3, 138.6. IR (film): 3088, 3064, 3031, 2943, 2867, 2729, 2239, 1944, 1804, 1496, 1462, 1414, 1382, 1362, 1290, 1260, 1242, 1207, 1107 cm$^{-1}$. ESI-MS: C$_{35}$H$_{66}$O$_4$SSi$_2$ [M+Na]$^+$ calc. 661.4, found 661.4. $[^{\alpha}]^{20}_D = -0.51^\circ$ (c = 0.60, CH$_2$Cl$_2$).

**Protected pyran 131:** To a dry 1 L round-bottom flask, under argon, was added the thioacetal (4.36 g, 6.82 mmol) in 68 mL CH$_2$Cl$_2$. The solution was cooled to -78 °C and m-CPBA (purified by washing with pH 7.5 buffer, 6.12 g, 35.5 mmol) was added. The reaction mixture was stirred 2 h at -78 °C. The dry ice bath was replaced with an ice water bath and 3 portions of AlMe$_3$ (8 mL per aliquot, 28.0 mmol per aliquot) were added at 30 min intervals at 0 °C. 30 min after the last aliquot was added, an additional 3.7 mL AlMe$_3$ (13.0 mmol) was added. After stirring 30 min at 0 °C, the reaction was quenched slowly by dropwise addition of saturated potassium sodium tartrate. The mixture was
stirred vigorously overnight at which point it was extracted with CH$_2$Cl$_2$ (2x). The combined organic layers were dried over MgSO$_4$, filtered, the concentrated under reduced pressure. The crude product was purified via flash column chromatography (2% EtOAc/Hex to 5% EtOAc/Hex) to provide the product as a cloudy pale yellow oil (3.62 g, 90%). $^1$H NMR (400 MHz, CDCl$_3$): δ 0.57 (qr, 6H, J = 7.6 Hz, 15.6 Hz), 0.95 (t, 12H, J = 8.0 Hz), 1.08 (s, 21H), 1.12 (s, 3H), 1.22-1.60 (bands, 5H), 1.80 (m, 3H), 2.01 (m, 1H), 3.54 (m, 1H), 3.68 (m, 5H), 4.51 (s, 2H), 7.35 (m, 5H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 1.03, 5.21, 6.95, 12.0, 12.5, 15.1, 18.1, 29.2, 29.8, 32.9, 36.6, 40.4, 63.5, 66.4, 69.5, 71.0, 73.0, 76.4, 127.4, 127.7, 128.3, 138.8. IR (film): 3030, 2943, 2867, 1732, 1462, 1414, 1382, 1241, 1102 cm$^{-1}$. ESI-MS: C$_{34}$H$_{64}$O$_4$Si$_2$ [M+Na] calc. 615.4, found 615.4. $[^\alpha]_{D}^{20} = -5.42^\circ$ (c = 1.00, CH$_2$Cl$_2$).

**Hydroxypyran:** To a dry 500 mL round-bottom flask, under argon, was added benzyl ether 131 (3.61 g, 6.09 mmol) in 61 mL THF. The solution was cooled to 0 ºC and 61 mL 0.5 M Na/naphtholide (prepared by adding 1.04 g Na to a solution of 6.35 g naphthalene in 90 mL THF in a dry 250 mL round-bottom flask, under argon, cooled to 0 ºC and sonicating 2 h). TLC showed immediate consumption of starting material. The reaction was quenched with water and the layers were separated. The aqueous layer was extracted with Et$_2$O (2x) and the combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated.
under reduced pressure. The crude product was purified via flash column chromatography (2% EtOAc/Hex to 10% EtOAc/Hex) to provide the product as a colorless oil (2.61 g, 85%). $^1$H NMR (400 MHz, CDCl$_3$): δ 0.56 (m, 6H), 0.95 (m, 12H), 1.05 (s, 21H), 1.20 (s, 3H), 1.49-1.65 (bands, 5H), 1.81 (m, 4H), 3.66 (m, 4H), 3.82 (m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 5.14, 6.86, 12.0, 12.4, 15.3, 18.0, 29.2, 29.5, 32.5, 36.3, 41.1, 59.6, 63.2, 68.3, 71.7, 80.1, 128.3. IR (film): 3523, 2943, 2888, 2868, 1731, 1463, 1415, 1383, 1240, 1102 cm$^{-1}$. ESI-MS: C$_{27}$H$_{58}$O$_4$Si$_2$ [M+Na] calc. 525.3, found 525.3, [M+K] calc. 541.3, found 541.3, [2M+Na] calc. 1027.7, found 1027.7, [2M+K] calc. 1043.6, found 1043.6. $[\alpha]_{D}^{20} = -7.43^o$ (c = 0.80, CH$_2$Cl$_2$).

**Aldehyde 132:** To a dry 250 mL round-bottom flask equipped with an addition funnel, under argon, was added oxalyl chloride (2 M, 3.9 mL, 7.78 mmol) and 17 mL CH$_2$Cl$_2$. The solution was cooled to -78 °C and anhydrous DMSO (0.74 mL, 10.4 mmol) in 17 mL CH$_2$Cl$_2$ was added dropwise. The mixture was stirred 15 min at -78 °C upon which the alcohol (2.61 g, 5.19 mmol) in 18 mL CH$_2$Cl$_2$ was added dropwise. The reaction was stirred 30 min at -78 °C then triethylamine (neat, 3.6 mL, 26.0 mmol) was added dropwise. The mixture was stirred 30 min at -78 °C then 30 min at 0 °C upon which it was transferred to a separatory funnel and washed with 60 mL each of H$_2$O, 1 N HCl, saturated sodium bicarbonate, then brine. Each wash was back-extracted with CH$_2$Cl$_2$ (2x).
The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was passed through a short silica plug with 100% CH$_2$Cl$_2$, concentrated under reduced pressure, and then immediately subjected to the next reaction (2.56 g, 98%, yellow oil).

**TES protected olefin**: To a dry 200 mL round-bottom flask, under argon, was added methylenetriphenylphosphine bromide (7.29 g, 20.4 mmol) in 30 mL THF. The mixture was cooled to 0 °C and potassium tert-butoxide (1 M, 15 mL, 15.3 mmol) was added. The bright yellow mixture was stirred 30 min at 0 °C upon which aldehyde 132 (2.56 g, 5.11 mmol) was added in 21 mL THF. The reaction was stirred 30 min at 0 °C then quenched with water. The layers were separated and the aqueous layer was extracted with Et$_2$O (2x). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (2% EtOAc/Hex to 5% EtOAc/Hex) to provide the product as a colorless oil (2.31 g, 91%).  $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.58 (m, 6H), 0.96 (m, 12H), 1.07 (s, 24H), 1.23-1.55 (bands, 3H), 1.61 (m, 2H), 1.78 (m, 2H), 2.27 (dddd, 2H, $J = 7.2$ Hz, 13.6 Hz, 34.8 Hz, 48.4 Hz), 3.56 (m, 1H), 3.67 (m, 3H), 5.04 (m, 2H), 5.98 (ddd, 1H, $J = 7.2$ Hz, 17.2 Hz, 34.4 Hz).  $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 5.28, 6.93, 12.0, 12.5, 15.1, 18.0, 29.2, 29.8, 32.9, 36.9, 45.2, 63.5, 68.7, 71.1, 116.6, 134.9. IR (film): 3074, 2942, 2892, 2867, 2730, 1824, 1730, 1640, 1463, 1414, 1382, 156
1240, 1103 cm\(^{-1}\). ESI-MS: C\(_{28}\)H\(_{58}\)O\(_3\)Si\(_2\) [M+H] calc. 499.4, found 499.4, [M+Na] calc. 521.4, found 521.4. \([\alpha]\)\(^{20}_D\) = -5.17° (c = 1.05, CH\(_2\)Cl\(_2\)).

**Hydroxypyran 133:** To a 250 mL round-bottom flask was added the silyl ether (2.31 g, 4.63 mmol) in 46 mL 5:1 THF:H\(_2\)O. A solution of CSA in EtOH (0.1 M, 9 mL, 0.926 mmol) was added and the reaction mixture was stirred 3 h at room temperature. The reaction was quenched with saturated sodium bicarbonate and the layers were separated. The aqueous layer was extracted with Et\(_2\)O (2x) and the combined organic layers were dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (100% Hexanes to 10% EtOAc/Hex to 25% EtOAc/Hex) to provide the product as a very pale yellow oil (1.38 g, 78%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.92 (d, 3H, J = 7.2 Hz), 1.05 (s, 21H), 1.11 (s, 3H), 1.20-1.53 (bands, 3H), 1.64-1.85 (bands, 5H), 2.30 (ddd, 2H, J = 13.6 Hz, 21.6 Hz, 29.2 Hz), 3.55 (m, 1H), 3.67 (m, 3H), 5.07 (m, 2H), 5.98 (m, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 12.0, 12.3, 15.0, 18.0, 29.1, 29.7, 32.9, 36.1, 45.8, 63.4, 68.1, 71.3, 76.6, 117.2, 134.8. IR (film): 3371, 3074, 2942, 2892, 2866, 1640, 1464, 1383, 1246, 1220 cm\(^{-1}\). ESI-MS: C\(_{22}\)H\(_{44}\)O\(_3\)Si \([M+Na]\) calc. 407.3, found 407.3. \([\alpha]\)\(^{20}_D\) = -19.2° (c = 0.85, CH\(_2\)Cl\(_2\)).
Glycolic acid: To a dry 25 mL round-bottom flask, under argon, was added NaH (60% in mineral oil, 0.324 g, 8.10 mmol). The mineral oil was removed by washing with pentane. 1 mL THF was added and the mixture was cooled to 0 °C upon which a solution of bromoacetic acid (0.450 g, 3.24 mmol) in 1 mL THF dropwise. The mixture was stirred 10 min at 0 °C then 30 min at room temperature, and then cooled back to 0 °C. Alcohol 133 (1.04 g, 2.70 mmol) was added in 2 mL THF and the reaction mixture was warmed to room temperature. 1.4 mL DMF was added and the reaction was stirred 3 days at room temperature then quenched with saturated ammonium chloride. The layers were separated and the aqueous layer was acidified with 1 N HCl to pH = 1 then was extracted with Et₂O (3x). The combined aqueous layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (100% Hexanes to 15% EtOAc/Hex to 85% EtOAc/Hex) to provide the product as a light yellow oil (0.865 g, 72%, 84% brsm). ¹H NMR (400 MHz, CDCl₃): δ 0.92 (d, 3H, J = 7.2 Hz), 1.06 (m, 21H), 1.16 (s, 3H), 1.32-1.55 (bands, 3H), 1.60-1.87 (bands, 5H), 2.35 (dddd, 2H, J = 7.2 Hz, 14.0 Hz), 3.49 (dd, 1H, J = 5.2 Hz, 12.0 Hz), 3.60 (m, 1H), 3.69 (m, 2H), 4.10 (m, 2H), 5.04 (s, 1H), 5.08 (m, 1H), 5.93 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 12.0, 12.3, 16.0, 29.0, 29.6, 32.3, 32.5, 45.2, 63.4, 66.3, 71.3, 76.1, 77.4, 117.1, 134.6, 175.2. IR (film): 3079, 2942, 2892, 2866, 1733, 1640, 1464, 1383, 1245,
1129 cm\(^{-1}\). ESI-MS: C\(_{24}\)H\(_{46}\)O\(_{5}\)Si \([M+Na]\) calc. 465.3, found 465.3. \([\alpha]\)\(^{20}_D\) = -17.5° (c = 0.85, CH\(_2\)Cl\(_2\)).

**Glycolate 115:** To a dry 100 mL round-bottom flask, under argon, was added the glycolic acid (0.601 g, 1.36 mmol) in 10 mL THF. The solution was cooled to -78 °C and triethylamine (0.21 mL, 1.50 mmol) was added followed by dropwise addition of freshly distilled pivaloyl chloride (0.18 mL, 1.50 mmol). The mixture was warmed to 0 °C for 1 h then cooled back to -78 °C.

In a separate, dry 25 mL round-bottom flask, under argon, was added the oxazolidinone (0.211 g, 1.63 mmol) in 4.5 mL THF. The solution was cooled to -78 °C and n-BuLi (1.6 M, 0.98 mL, 1.56 mmol) was added dropwise. The mixture was stirred 1 h at -78 °C.

The lithiated oxazolidinone was added to the mixed anhydride at -78 °C. The reaction was stirred 1 h at -78 °C then 45 min at 0 °C upon which it was quenched with saturated ammonium chloride. The layers were separated and the aqueous layer was extracted with Et\(_2\)O (2x). The combined organic layers were dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (10% EtOAc/Hex to 25% EtOAc/Hex) to provide the product as a colorless oil (0.637 g, 85%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 0.87 (m, 9H), 1.01 (s, 21H), 1.06-1.21 (m, 5H), 1.32-1.53 (m, 3H), 1.58 (m, 1H), 1.65-1.87 (m, 3H), 2.33 (m, 3H), 3.38 (m, 1H), 3.54 (m,
1H), 3.64 (m, 2H), 4.03 (m, 1H), 4.21 (m, 1H), 4.30 (dd, 1H, J = 2.3 Hz, 8.4 Hz), 4.39 (m, 1H), 4.60 (m, 1H), 4.98 (s, 1H), 5.01 (m, 1H), 5.93 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ 11.9, 12.3, 14.5, 16.0, 17.8, 18.0, 28.1, 29.1, 29.7, 32.4, 32.6, 45.3, 58.1, 63.4, 68.9, 71.2, 76.2, 76.7, 117.0, 134.8, 154.0, 170.2. IR (film): 2966, 2942, 2896, 2866, 1785, 1722, 1639, 1464, 1389, 1302, 1257, 1210, 1100 cm$^{-1}$. ESI-MS: C$_{30}$H$_{55}$NO$_6$Si [M+Na] calc. 576.4, found 576.4, [2M+Na] calc. 1129.8, found 1129.8. $\alpha$$_{20}^D$ = +19.7$^o$ (c = 0.90, CH$_2$Cl$_2$).

**Nitrile:** To a dry 100 mL round-bottom flask, under argon, was added NaHMDS (0.83 M, 2.3 mL, 1.89 mmol) in 4 mL THF. The solution was cooled to -78 °C and glycolate 115 (0.697 g, 1.26 mmol) in 9 mL THF was added dropwise. The mixture was stirred 30 min at -78 °C upon which bromoacetonitrile was added (0.35 mL, 5.04 mmol) dropwise. The reaction was stirred 1 h at -78 °C then quenched with saturated ammonium chloride and warmed to room temperature. The layers were separated and the aqueous layer was extracted with Et$_2$O (2x). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (10% EtOAc/Hex to 15% EtOAc/Hex) to provide the product as a colorless oil (0.389 g, 52%). $^1$H NMR (400 MHz, CDCl$_3$): δ 0.90 (m, 6H), 0.95 (d, 3H, J = 6.8 Hz), 1.06 (m, 21H), 1.16 (s, 3H), 1.41 (m, 3H), 1.65 (m, 2H), 1.85 (m, 3H), 2.77 (m, 2H), 3.44 (dd, 1H, J = 4.8 Hz, 11.6 Hz), 3.57-3.75
(m, 3H), 4.32 (dd, 1H, J = 7.6 Hz, 10.4 Hz), 4.42 (m, 1H), 4.51 (m, 1H), 5.01 (m, 1H), 5.05 (s, 1H), 5.41 (m, 1H), 5.97 (m, 1H). 13C NMR (100 MHz, CDCl3): δ 12.0, 12.2, 14.8, 16.0, 17.8, 18.0, 23.0, 28.3, 29.0, 29.7, 32.1, 32.5, 44.8, 58.6, 63.4, 64.3, 69.6, 71.3, 75.6, 75.8, 116.8, 135.0, 153.8, 169.5. IR (film): 2962, 2942, 2896, 2866, 1781, 1720, 1464, 1389, 1248, 1207, 1105 cm⁻¹. ESI-MS: C32H56N2O6Si [M+Na] calc. 615.4, found 615.4, [M+Cs] calc. 725.3, found 725.3. [α]20°D = +37.0° (c = 0.30, CH2Cl2).

**Alcohol 134:** To a 50 mL round-bottom flask was added the oxazolidinone (0.386 g, 0.651 mmol) in 7 mL 3:1 THF:H2O. Sodium borohydride (0.037 g, 0.977 mmol) was added and the reaction was stirred 1 h at room temperature. The reaction was quenched with saturated sodium potassium tartrate and stirred 30 min at room temperature. The layers were separated and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were dried over Na2SO4, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (15% EtOAc/Hex to 30% EtOAc/Hex) to provide the product as a colorless oil (0.266 g, 87%). 1H NMR (400 MHz, CDCl3): δ 0.93 (d, 3H, J = 6.8 Hz), 1.06 (m, 21H), 1.13 (s, 3H), 1.32-1.55 (m, 3H), 1.62 (m, 1H), 1.72 (brrs, 1H), 1.85 (m, 4H), 2.31 (m, 2H), 2.58 (m, 2H), 3.52 (m, 1H), 3.68 (m, 6H), 5.05 (s, 1H), 5.10 (m, 1H), 6.01 (m, 1H). 13C NMR (100 MHz, CDCl3): δ 12.0, 12.4, 16.3, 18.0, 21.3, 29.0, 29.6, 32.5, 33.0, 45.3, 62.9, 63.4, 63.4, 65.9, 66.7, 68.2, 70.8, 71.8, 73.6, 75.2, 75.3, 108.6, 120.8, 123.1, 126.3, 130.5, 131.0, 135.0, 153.8, 169.5.
71.3, 72.8, 74.3, 75.8, 117.0, 117.6, 134.8. IR (film): 3464, 3074, 2942, 2893, 2866, 2253, 1725, 1639, 1464, 1384, 1245, 1223, 1100 cm⁻¹. ESI-MS: C₂₆H₄₉NO₄Si [M+Na] calc. 490.3, found 490.3. [α]¹⁹D = -10.5° (c = 1.10, CH₂Cl₂).

**Aldehyde:** To a dry 250 mL round-bottom flask equipped with an addition funnel, under argon, was added oxalyl chloride (2 M, 0.43 mL, 0.854 mmol) and 2 mL CH₂Cl₂. The solution was cooled to -78 °C and anhydrous DMSO (0.08 mL, 1.14 mmol) in 2 mL CH₂Cl₂ was added dropwise. The mixture was stirred 15 min at -78 °C upon which alcohol 134 (0.266 g, 0.569 mmol) in 2 mL CH₂Cl₂ was added dropwise. The reaction was stirred 30 min at -78 °C then triethylamine (neat, 0.40 mL, 2.85 mmol) was added dropwise. The mixture was stirred 30 min at -78 °C then 30 min at 0 °C upon which it was transferred to a separatory funnel and washed with 20 mL each of H₂O, 1 N HCl, saturated sodium bicarbonate, then brine. Each wash was back-extracted with CH₂Cl₂ (2x). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was passed through a short silica plug with 100% CH₂Cl₂, concentrated under reduced pressure, and then immediately subjected to the next reaction (0.251 g, 95%, yellow oil).
Diene 114:

Preparation of salt-free methylenetriphenylphosphorane: To a dry 50 mL round-bottom flask, under argon, was added 0.193 g 60% NaH, which was washed with pentane to remove the mineral oil, in 11 mL THF. To the solution was added 2.0 g methylenetriphenylphosphine bromide and the mixture was stirred overnight at room temperature, filtered, and then concentrated under reduced pressure. The ylide was store under argon until used.

Preparation of diene 114: To a dry 50 mL round-bottom flask, under argon, was added the ylide (0.208 g, 0.754 mmol) in 11 mL THF. The mixture was cooled to 0 °C and the aldehyde (0.251 g, 0.539 mmol) was added in 5 mL THF. The reaction was stirred 1 h at 0 °C the quenched with half-saturated sodium bicarbonate. The layers were separated and the aqueous layer was extracted with EtOAc (3x) (brine was used to break up any emulsion that may have formed). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Due to the instability of the product, the crude product was passed through a short silica plug (2% EtOAc/Hex doped with triethylamine to 5% EtOAc/Hex doped with triethylamine) to give the pure product (0.176 g, 70%), then taken on immediately to the next step.
**Bicycle 135:** To a dry 100 mL round-bottom flask, under argon, was added diene 114 (0.176 g, 0.379 mmol) in 38 mL degassed CH₂Cl₂. To this solution was added Grubb’s 2nd generation catalyst (0.016 g, 0.0190 mmol). The reaction mixture was stirred 3 h at room temperature, upon which it was opened to air and allowed to sit overnight at room temperature. The mixture was then concentrated under reduced pressure and the crude product was purified via flash column chromatography (5% EtOAc/Hex to 10% EtOAc/Hex) to give the purified product (0.136 g, 82%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): δ 0.95 (d, 3H, J = 6.8 Hz), 1.05 (m, 21H), 1.19 (s, 3H), 1.36-1.43 (m, 2H), 1.46-1.53 (m, 1H), 1.57-1.64 (m, 1H), 1.69-1.88 (bands, 3H), 2.32 (m, 2H), 2.59 (m, 2H), 3.45-3.77 (bands, 4H), 4.31 (m, 1H), 5.51-5.56 (m, 1H), 5.84 (m, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 12.0, 12.3, 15.9, 18.0, 25.3, 29.0, 29.6, 32.8, 34.8, 43.9, 63.3, 71.3, 74.3, 75.0, 80.5, 117.5, 130.1, 130.5. IR (film): 2958, 2940, 2888, 2866, 1728, 1463, 1383, 1276, 1102 cm⁻¹. ESI-MS: C₂₅H₄₅NO₅Si [M+Na] calc. 458.3, found 458.3. [α]¹⁹D = -41.0° (c = 0.05, CH₂Cl₂).

**Diol 159:** To a 100 mL round-bottom flask was added olefin 135 (0.132 g, 0.303 mmol) in 5 mL 4:1 acetone:H₂O. N-Methylmorpholine-N-oxide (0.089 g,
0.758 mmol) was added followed by osmium tetroxide (0.0151 mmol of a 20 mg/mL solution in water). The reaction was stirred overnight at room temperature upon which it was quenched with sodium sulfite (0.100 mg) and stirred 30 min at room temperature. EtOAc was added and the layers were separated. The aqueous layer was extracted with EtOAc (5x) and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (50% EtOAc/Hex to 85% EtOAc/Hex) to provide the product as a colorless oil (0.137 g, 96%). 

$^1$H NMR (400 MHz, CDCl₃): δ 0.95 (d, 3H, J = 7.2 Hz), 1.06 (m, 21H), 1.23 (s, 3H), 1.37-1.44 (m, 2H), 1.45-1.53 (m, 1H), 1.58-1.68 (m, 2H), 1.68-1.80 (m, 3H), 1.85 (m, 1H), 2.21 (m, 2H), 2.63 (dddd, 2H, J = 5.2 Hz, 16.8 Hz, 34.0 Hz), 2.77 (m, 1H), 3.68 (m, 4H), 3.91 (m, 2H), 4.15 (m, 1H). $^{13}$C NMR (100 MHz, CDCl₃): δ 12.0, 12.4, 16.4, 18.0, 23.9, 29.0, 29.5, 32.3, 33.8, 44.9, 63.4, 68.8, 70.9, 74.3, 76.0, 77.5, 117.7. IR (film): 3425, 2942, 2896, 2866, 1726, 1463, 1384, 1247, 1103 cm⁻¹. ESI-MS: C₂₅H₄₇NO₅Si [M+H] calc. 470.3, found 470.3, [M+Na] calc. 492.3, found 492.3, [M+Cs] calc. 602.2, found 602.2. $[\alpha]_{D}^{19} = -6.19°$ (c = 0.75, CH₂Cl₂).

**Acetonide 113:** To a dry 25 mL round-bottom flask, under argon, was added diol 159 (0.089 g, 0.189 mmol) and 3.3 mL 10:1 CH₂Cl₂:2-
methoxypropene. PPTS (0.019 g, 0.0758 mmol) was added and the mixture was stirred 45 min at room temperature. The reaction was quenched with saturated sodium bicarbonate and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (2x) and the combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (2% EtOAc/Hex to 5% EtOAc/Hex to 10% EtOAc/Hex) to provide the product as a pale yellow oil (0.074 g, 77%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.96 (d, 3H, J = 6.8 Hz), 1.05 (s, 21H), 1.14 (s, 3H), 1.32 (s, 3H), 1.41 (s, 3H), 1.43 (m, 2H), 1.50 (m, 2H), 1.57-1.92 (bands, 5H), 2.29 (m, 1H), 2.48 (dd, 1H, J = 8.0 Hz, 16.8 Hz), 2.76 (m, 1H), 3.45 (m, 1H), 3.67 (m, 4H), 3.92 (m, 1H), 4.50 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 12.0, 12.5, 14.4, 18.0, 22.9, 24.2, 27.3, 28.9, 29.6, 32.6, 33.5, 44.0, 63.4, 70.8, 73.6, 74.1, 76.6, 79.1, 83.4, 108.8, 117.8.

**Aldehyde:** To a dry 25 mL round-bottom flask, under argon, was added nitrile 113 (0.032 g, 0.0598 mmol) and 2 mL toluene. The solution was cooled to -78 °C and DIBAL (1 M, 0.12 mL, 0.120 mmol) was added dropwise. The reaction mixture was stirred 1 h at -78 °C and then quenched with saturated sodium potassium tartrate. The mixture was stirred vigorously at room temperature for 1 h. The layers were separated and the aqueous layer was
extracted with Et₂O (2x). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (5% EtOAc/Hex to 10% EtOAc/Hex) to provide the product as a pale yellow oil (0.030 g, 94%).

$^1$H NMR (400 MHz, CDCl₃): δ 0.98 (d, 3H, J = 7.2 Hz), 1.05 (s, 21H), 1.14 (s, 3H), 1.33 (s, 3H), 1.40 (s, 5H), 1.42-1.76 (bands, 7H), 1.86 (m, 1H), 1.94 (m, 1H), 2.28 (m, 1H), 2.58 (m, 1H), 2.78 (m, 1H), 3.47 (m, 1H), 3.68 (m, 1H), 3.94 (m, 2H), 4.50 (m, 1H), 9.80 (s, 1H).

$^{13}$C NMR (100 MHz, CDCl₃): δ 12.0, 12.5, 14.3, 18.0, 24.3, 27.3, 29.0, 32.7, 33.8, 44.2, 47.7, 63.4, 70.8, 73.8, 74.3, 76.2, 79.7, 83.0, 108.4, 200.6.

**β-hydroxyphosphonate:** To a dry 23 mL round-bottom flask, under argon, was added dimethyl methylphosphonate (0.05 mL, 0.468 mmol) in 1 mL THF. The solution was cooled to -78 °C and n-BuLi (1.6 M, 0.29 mL, 0.463 mmol) was added dropwise. The white suspension was stirred 1 h at -78 °C upon which the aldehyde (0.024 g, 0.0468 mmol) was added in 2 mL THF. The reaction mixture was stirred 1 h -78 °C at which point it was quenched with saturated ammonium chloride and warmed to room temperature. The layers were separated and the aqueous layer was extracted with Et₂O (3x). The combined organic layers were
dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified via flash column chromatography (100% EtOAc to 1% MeOH/EtOAc) to provide the product as a pale yellow oil (0.027 g, 90%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.97 (d, 3H, J = 7.2 Hz), 1.06 (s, 21H), 1.13 (s, 3H), 1.32 (s, 3H), 1.41 (m, 5H), 1.46-2.08 (bands, 12H), 2.24 (m, 1H), 3.43 (m, 1H), 3.60-3.72 (bands, 5H), 3.77 (m, 5H), 3.87 (m, 1H), 3.92 (m, 1H), 4.28 (m, 1H), 4.47 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 12.0, 12.6, 14.3, 18.0, 24.3, 27.4, 28.9, 29.6, 32.7, 33.9, 34.0, 44.3, 63.4, 70.7, 73.8, 74.1, 74.3, 79.8, 80.2, 81.1, 83.2, 108.2. IR (film): 3380, 2942, 2896, 2866, 1729, 1463, 1382, 1264, 1171 cm$^{-1}$. ESI-MS: C$_{31}$H$_{61}$O$_5$PSi $[M+H]$ calc. 637.4, found 637.4, [M+Na] calc. 659.4, found 659.4, [M+Cs] calc. 769.3, found 769.3. $[\alpha]_{D}^{19}$ = +15.0° (c = 0.07, CH$_2$Cl$_2$).

**β-ketophosphonate 68:** To a 50 mL round-bottom flask was added the β-hydroxyphosphonate (0.035 g, 0.0550 mmol) in 4 mL CH$_2$Cl$_2$ (wet). Sodium bicarbonate (0.046 g, 0.550 mmol) was added followed by Dess-Martin periodinane (0.059 g, 0.138 mmol). The reaction mixture was stirred 30 min at room temperature and then quenched with saturated 5:1 Na$_2$S$_2$O$_3$:NaHCO$_3$ and stirred 30 min at room temperature. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2x). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and then concentrated under reduced pressure. The crude
The product was purified via flash column chromatography (100% EtOAc to 1% MeOH/EtOAc) to provide the product as a colorless oil (0.033 g, 94%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.96 (d, 3H, $J =$ 6.8 Hz), 1.05 (s, 21H), 1.10 (s, 3H), 1.30 (s, 3H), 1.37 (s, 3H), 1.40-1.70 (bands, 6H), 1.83 (m, 1H), 1.91 (m, 2H), 2.23 (dd, 1H, $J =$ 6.4 Hz, 13.2 Hz), 2.75 (m, 1H), 2.92 (m, 1H), 3.14 (m, 2H), 3.44 (m, 1H), 3.65 (bands, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 3.89 (m, 2H), 4.46 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 12.0, 12.6, 14.3, 18.0, 24.3, 27.2, 28.9, 29.6, 32.6, 33.6, 41.8, 43.1, 44.1, 47.8, 53.0, 53.1, 63.4, 70.8, 73.8, 74.3, 77.1, 79.4, 82.8, 108.4, 200.2. IR (film): 2942, 2892, 2866, 1719, 1463, 1383, 1263, 1100 cm$^{-1}$. ESI-MS: C$_{31}$H$_{59}$O$_9$PSi [M+Na] calc. 657.3, found 657.3, [M+Cs] calc. 767.3, found 767.3. $\alpha$$_{D}^{20} = 13.4^\circ$ (c = 0.11, CH$_2$Cl$_2$).

**Enone 67:** To a dry 25 mL round-bottom flask, under argon, was added the $\beta$-ketophosphonate 68 (0.016 g, 0.0245 mmol) in 0.5 mL THF. To the solution was added anhydrous barium hydroxide (0.003 g, 0.0187 mmol) and the mixture was stirred 30 min at room temperature. Aldehyde 69 (0.012 g, 0.223 mmol) was added in 0.30 mL of 40:1 THF:H$_2$O, followed by an additional 0.33 mL of 40:1 THF:H$_2$O. The reaction mixture was stirred 1 h at room temperature and was then diluted with EtOAc and filtered over celite. The solution was washed with
saturated sodium bicarbonate and the aqueous layer was extracted with EtOAc (4x). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and then concentrated under reduced pressure. The crude product was purified via flash column chromatography (5% EtOAc/Hex to 10% EtOAc/Hex) to provide the product as a colorless oil (0.021 g, 91%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.67 (m, 6H), 1.00 (m, 12H), 1.08 (s, 21H), 1.13 (s, 3H), 1.27 (s, 4H), 1.33 (s, 3H), 1.39 (s, 3H), 1.41-2.00 (bands, 13H), 2.25 (m, 1H), 2.35 (m, 1H), 2.72-2.87 (bands, 3H), 3.57 (m, 4H), 3.68 (m, 3H), 3.86 (m, 1H), 3.94 (m, 1H), 4.01 (m, 1H), 4.14 (m, 1H), 4.41-4.53 (m, 5H), 5.65 (m, 2H), 6.21 (m, 1H), 6.95 (m, 1H), 7.30 (m, 10H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 5.10, 6.83, 12.1, 12.6, 14.3, 18.0, 20.2, 24.4, 26.7, 27.4, 29.0, 32.7, 33.7, 37.0, 43.6, 44.3, 63.5, 65.3, 70.2, 70.8, 72.9, 73.4, 74.1, 74.3, 79.7, 81.1, 82.7, 83.7, 85.3, 108.3, 127.3, 127.4, 127.6, 128.3, 133.1, 133.5, 136.8, 138.7, 139.1, 144.6, 197.8. IR (film): 2957, 2939, 2869, 2363, 2340, 1730, 1679, 1463, 1384, 1271, 1103 cm$^{-1}$. ESI-MS: C$_{61}$H$_{98}$O$_{10}$Si$_2$ [M+H] calc. 1047.6, found 1047.6, [M+Na] calc. 1069.6, found 1069.6. $[\alpha]_{D}^{19}=+6.25^\circ$(c = 0.20, CH$_2$Cl$_2$).
$\text{1.00} \quad \text{1.02} \quad \text{2.09} \quad \text{2.07} \quad \text{1.03} \quad \text{1.04} \quad 4.47 \quad 3.24 \quad 22.61 \quad 8.19$
$\text{TIPSO} - \text{Me}$

$400 \text{ MHz, CDCl}_3$
400 MHz, CDCl₃
TIPS-O-CH$_2$-CH$_2$-OH

400 MHz, CDCl$_3$
100 MHz, CDCl₃