EFFORTS TOWARDS SYNTHESES OF MARINE NATURAL PRODUCTS

by

Benjamin Charles Loosley

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Abstract

This thesis describes work attempting to synthesize and derivatize marine natural products. Chapter 1 outlines a brief history of natural products chemistry. It explains why modern medicines are commonly derived from natural sources using historical examples. It also explains why natural products chemists have turned to organisms in the oceans for exploration into new and unique molecular frameworks and biological activities.

Chapter 2 describes the work done towards total synthesis of the marine natural product cladoniamide G. The successful approach involves coupling a halogenated 2,2-bisindole with an unsymmetric, tricarbonyl electrophile. It also describes work towards synthesis of analogues, including attempts to glycosylate the natural product.

Chapter 3 is the first chapter that discusses work towards total synthesis of a second marine natural product, nahuoic acid A. This chapter focuses on synthesis of a linear cycloaddition precursor that resembles an intermediate in the presumed biosynthetic pathway. The work in this chapter culminates in attempts at a Diels-Alder reaction to form a cis-decalin system.

Chapter 4 also focuses on work towards total synthesis of nahuoic acid A. However, the work in this chapter uses a Diels-Alder reaction to form a cis-decalin system early, and then focuses on the challenges of functionalizing the decalin. Four general approaches to functionalization are investigated: conjugate additions, nucleophilic substitutions, sigmatropic rearrangements, and metal catalyzed cycloisomerizations.
Lay Summary

There is an increasing need to find new drugs for cancer treatment. The majority of drugs currently available to treat cancer are based on compounds found in nature. These natural compounds are often produced in small amounts, by organisms that grow in small populations. Chemical synthesis is often the best method to obtain large quantities of these natural compounds that can also avoid over-harvesting and destruction of habitats.

Recently, researchers at UBC discovered two sets of natural compounds that have the ability to kill cancer cells. These sets were named the cladoniamides and the nahuoi acids. These compounds are produced in minuscule quantities, causing a supply problem. This thesis describes my efforts to synthesize large quantities of these compounds for development into drugs for cancer treatment.
Preface

A portion of the research reported in Chapter 2 was published in 2013: Benjamin C. Loosley, Raymond J. Andersen, and Gregory R. Dake. “Total Synthesis of Cladoniamide G.” *Org. Lett.*, 2013, 15 (5), 1152–1154. I wrote the first draft of the manuscript, which was heavily edited by Dr. Gregory Dake and Dr. Raymond Andersen. The experimental portion of the manuscript and chapter 2 of this thesis were written by me. I performed all synthetic procedures and was responsible for nearly all of the characterization. Sugar derivative 2.81 was borrowed from the Withers lab. Spectra of some of the intermediates in the synthesis of brominated analogues of cladoniamide G were collected by Mala Milanese.

The work in chapters 3 and 4 remains unpublished. I performed all synthetic procedures and was responsible for nearly all of the characterization. X-Ray crystallographic analysis was performed by Spencer Serin.
Table of Contents

Abstract ........................................................................................................................................... ii
Lay Summary ................................................................................................................................... iii
Preface .............................................................................................................................................. iv
Table of Contents ............................................................................................................................. v
List of Tables ...................................................................................................................................... x
List of Figures .................................................................................................................................... xi
List of Schemes ................................................................................................................................. xiii
List of Abbreviations and Symbols ................................................................................................. xvii
Acknowledgements ......................................................................................................................... xxv
Dedication .......................................................................................................................................... xxvi

Chapter 1: Introduction to Marine Natural Products Chemistry ..................................................... 1
  1.1 A Brief History of Natural Products Chemistry ................................................................. 1
  1.2 Development of Medicinal Chemistry ................................................................................. 2
    1.2.1 Natural Product Analogue Creation ........................................................................... 3
  1.3 Modern Natural Products Chemistry ................................................................................. 4
    1.3.1 Analytical Techniques ............................................................................................... 4
    1.3.2 Synthetic Methods ......................................................................................................... 5
  1.4 Marine Natural Products as Therapeutics ........................................................................... 6
  1.5 Cancer Therapeutics ............................................................................................................. 8
    1.5.1 A Brief History of Cancer Therapeutics ................................................................... 8
    1.5.2 Natural Products as Cancer Therapeutics ................................................................. 9
1.5.3 Marine Natural Products as Cancer Therapeutics........................................................................... 9
1.6 Reasons for Total Synthesis of Marine Natural Products............................................................. 10
1.7 Focus of This Thesis .......................................................................................................................... 11

Chapter 2: Total Synthesis of Cladoniamide G and Related Compounds ................................. 12
2.1 Introduction....................................................................................................................................... 12
2.1.1 2,2’-Bisindole Natural Products.................................................................................................. 12
2.1.2 Isolation of Cladoniamides ......................................................................................................... 13
2.1.3 Biosynthesis of Cladoniamides .................................................................................................... 14
2.2 Initial Goals of the Project ................................................................................................................ 15
2.3 Retrosynthetic Analysis .................................................................................................................... 16
2.4 Total Synthesis of Cladoniamide G ................................................................................................. 16
2.4.1 Synthesis of Deshalo-Indolotryptoline Core............................................................................. 16
2.4.2 Synthesis of 5,5’-Dichloroindolotryptoline Core .................................................................... 20
2.4.3 Synthesis of an Unsymmetric Vicinal Tricarbonyl ................................................................. 24
2.4.4 Completion of Total Synthesis of Cladoniamide G ................................................................. 26
2.5 Attempted Glycosylation of Cladoniamide G .............................................................................. 27
2.5.1 Attempted Glycosylation Using Basic Conditions ................................................................. 28
2.5.2 Attempted Glycosylation Using Acidic and Neutral Conditions ........................................ 29
2.5.3 Attempted Glycosylation of Cladoniamide G’s Synthetic Intermediates ............................ 29
2.6 Synthesis of Cladoniamide G Analogue....................................................................................... 30
2.6.1 Attempted Synthesis of Deschloro-Cladoniamide G ............................................................. 30
2.6.2 Attempted Synthesis of Cladoniamide G’s Fluorinated Analogue....................................... 30
2.6.3 Synthesis of Cladoniamide G’s Bromine Analogue ............................................................... 31
Chapter 3: Studies Towards Synthesis of Nahuoic Acid A Through a Late Stage Diels-Alder Reaction

3.1 Introduction

3.1.1 Isolation of Nahuoic Acids

3.1.2 Proposed Biosynthesis of Nahuoic Acids

3.1.3 Structural Determination of the Nahuoic Acids

3.1.4 Biological Activity of Nahuoic Acid A

3.2 Retrosynthetic Analysis of Nahuoic Acid A

3.3 Attempted Synthesis of Nahuoic Acid A Fragments

3.4 Synthesis of a Linear IMDA Precursor

3.5 Synthesis of Macrocyclic IMDA Precursor

3.5.1 Using the Total Synthesis of Superstolide A as Inspiration

3.5.2 Using the Total Synthesis of Phomopsidin as Inspiration

3.5.2.1 Attempted Macrocyclization Through Lactonization

3.5.2.2 Attempted Macrocyclization Through Cross-Coupling

3.5.2.3 Attempted Macrocyclization Through Olefination
3.5.2.4 Attempting Macrocyclization With a Minimally Functionalized Carbon Skeleton ......................................................... 79

3.6 Analysis of Results and Restructuring of the Hypothesis.......................................................... 82

3.7 Experimental.......................................................................................................................... 83

Chapter 4: Studies Towards Synthesis of Nahuoic Acid A Through an Early Stage Diels-Alder Reaction ........................................................................................................ 140

4.1 Retrosynthetic Analysis for Nahuoic Acid A Using an Early Stage Diels-Alder Reaction .................................................................................................................. 140

4.2 Previous Work in the Dake Lab.................................................................................................. 141

4.3 Synthesis and Derivatization of cis-Decalin Compounds......................................................... 142

4.3.1 Analysis of Potential Methods for Stereoselective C-C Bond Formation ......................... 142

4.3.2 Synthesis of cis-Decalin Compounds for Exploration of Stereoselective C-C Bond Forming Reactions ........................................................................................................ 143

4.3.3 Conjugate Addition Strategy For C-C Bond Formation ..................................................... 145

4.3.4 Sn’ Displacement Strategy For C-C Bond Formation ......................................................... 146

4.3.5 [3,3]-Sigmatropic Rearrangement Strategy For C-C Bond Formation ............................... 148

4.3.6 Metal Catalyzed Cycloisomerization Strategy For C-C Bond Formation ......................... 150

4.3.6.1 Synthesis of Substrates For Metal Catalyzed Cycloisomerization ................................. 151

4.3.6.2 Attempted Metal Catalyzed Cycloisomerizations ....................................................... 152

4.4 Conclusion ............................................................................................................................. 154

4.5 Experimental ........................................................................................................................ 155

4.5.1 X-Ray Crystallography ..................................................................................................... 175

Chapter 5: Conclusion and Future Work....................................................................................... 176
5.1 Conclusions and Future Work for Chapter 2 .......................................................... 176
5.2 Conclusions and Future Work for Chapters 3 and 4 ................................................. 176

Bibliography .................................................................................................................. 178

Appendices ...................................................................................................................... 186

Appendix A General Experimental .................................................................................. 186
Appendix B Selected Spectra .......................................................................................... 187
  B.1 Selected Spectra for Chapter 2 ................................................................................ 188
  B.2 Selected Spectra for Chapter 3 ................................................................................ 203
  B.3 Selected Spectra for Chapter 4 ................................................................................ 254
List of Tables

Table 2.1: Wolff-Kishner reductions quenching with different methylating agents .................. 21
Table 2.2: Attempted indolocarbazole formation by amide activation................................. 23
Table 3.1: IC₅₀ data for nahuoc acid A and analogues towards SETD8................................. 55
Table 3.2: Conditions for attempted Stille coupling reactions on ester 3.112 to form macrocycle
3.113........................................................................................................................................... 77
Table 4.1: Attempted cycloisomerization conditions for 1,6-enyne 4.63................................. 152
Table 4.2: Attempted cycloisomerization conditions for 1,6-enyne 4.67................................. 153
Table 4.3: Attempted cycloisomerization conditions for 1,6-enyne 4.65................................. 153
Table 4.4: X-ray Data Collection and Refinement Details for 4.28, 4.29, and 4.32............... 175
List of Figures

Figure 1.1: Examples of bioactive natural products isolated between 1804 and 1855 .............................. 1

Figure 1.2: a) Number of alkaloid natural products discovered from the beginning of natural products chemistry until the 1960s. b) Two extremely complex natural products isolated in recent history. ........................................................................................................................................ 2

Figure 1.3: Pathways of medicinal chemistry development from salicin to acetylsalicylic acid ... 3

Figure 1.4: Chronological development of anesthetics derived from cocaine. The colored boxes show retained pharmacophores ........................................................................................................................................ 4

Figure 1.5: Structures of the first clinically approved drugs based on marine natural products .... 6

Figure 1.6: Structures of halichondrin B, and selected clinically approved drugs based on marine natural products ........................................................................................................................................... 7

Figure 1.7: Selected structures of marine natural products with uncommon atom incorporation .. 8

Figure 1.8: Structures of the chemical weapon mustard gas and the chemotherapeutic mustine... 8

Figure 1.9: Marine natural products that show antitumor activities ....................................................... 9

Figure 2.1: Common indole-containing structural motifs in natural products......................... 12

Figure 2.2: Bisindole natural products with interesting biological activities ......................... 12

Figure 2.3: Structures of cladinamides A - G ....................................................................................... 13

Figure 2.4: Selected literature reported methods to form vicinal tricarbonyl compounds .......... 24

Figure 2.5: Intermediates of final step in total synthesis. a) $^1$H NMR spectrum of crude 2.71. b) $^1$H NMR spectrum of crude 2.72. ........................................................................................................................................ 26

Figure 2.6: Structures of cladinamide G, rebeccamycin aglycone, and rebeccamycin ............ 27

Figure 2.7: Future targets for the cladinamide project................................................................. 32
Figure 3.1: Examples of polyketide natural products from bacterial sources............................. 50
Figure 3.2: Examples of polyketide natural products containing a decalin motif ...................... 50
Figure 3.3: Structures of nahuoic acids A - E, each containing a cis-decalin and a polyol side chain.............................................................................................................................................. 51
Figure 3.4: COSY, HMBC, ROESY, and J coupling data used to establish structure of nahuoic acid A\textsuperscript{53} ........................................................................................................................................................................ 53
Figure 3.5: Pictorial model for compression of DNA into nucleosomes and chromosomes\textsuperscript{111} .... 53
Figure 3.6: a) Inhibition of HMTs by nahuoic acid A, b) Lineweaver Burk plots indicating SAM competitive inhibition\textsuperscript{53} ........................................................................................................................................................................ 54
Figure 3.7: Possible products of an intramolecular Diels-Alder reaction on substrate 3.15 ........ 55
Figure 3.8: Explanation for selectivity of Grignard addition by Felkin-Ahn model ...................... 59
Figure 3.9: Rationalization for 1,3-anti products based on Evans' polar model\textsuperscript{153} .............. 63
Figure 4.1: a) Pictorial representation of the side view of the B ring of sulfite 4.41 and b) Chem3D model of sulfite 4.41........................................................................................................................................................................ 148
Figure 4.2: ORTEP representation of the solid state of structure 4.28 (50% probability ellipsoids) ........................................................................................................................................................................ 157
Figure 4.3: ORTEP representation of the solid state of structure 4.29 (50% probability ellipsoids) ........................................................................................................................................................................ 159
Figure 4.4: ORTEP representation of the solid state of structure 4.32 (50% probability ellipsoids) ........................................................................................................................................................................ 162
List of Schemes

Scheme 2.1: Biosynthesis of cladoniamides proposed by Andersen and Ryan.......................... 14
Scheme 2.2: Retrosynthetic steps for cladoniamide G starting from 5,5’-dichloroindigo ........ 16
Scheme 2.3: Proposed mechanism for Clemmensen type reduction of indigo to 2,2’-bisindole
2.30.................................................................................................................. 17
Scheme 2.4: Reactivity studies of 2,2’-bisindole derivatives................................................. 18
Scheme 2.5: Attempts to form indolotryptolines by a) Lewis acidic conditions and b) basic
conditions........................................................................................................... 19
Scheme 2.6: Synthesis of 5,5’-dichlorobisindole 2.27......................................................... 20
Scheme 2.7: Unintentional synthesis of diamide 2.52.............................................................. 22
Scheme 2.8: Potential mechanism for indolocarbazole formation through amide activation ..... 22
Scheme 2.9: Synthesis of unsymmetric vicinal tricarbonyl 2.70............................................. 25
Scheme 2.10: Completing the synthesis of cladoniamide G ................................................. 26
Scheme 2.11: a) Glycosylation of rebeccamycin precursor by Danishefsky and b) attempted
glycosylation of cladoniamide G and protected cladoniamide G in the Dake lab............... 28
Scheme 2.12: Attempted glycosylations of cladoniamide G using a) Mitsunobu-type conditions
and b) gold catalyzed conditions pioneered by Yu90................................................... 29
Scheme 2.13: Attempted formation of deschloro-cladoniamide G 2.84 ............................... 30
Scheme 2.14: Synthesis of bromine analogue of cladoniamide G 2.90................................. 31
Scheme 3.1: Proposed biosynthesis of nahuoic acid A through a series of condensations and
cycloaddition........................................................................................................ 52
Scheme 3.2: Retrosynthetic analysis for nahuoic acid A......................................................... 57
Scheme 3.3: Synthesis of aldehyde 3.29 using three separate methods ........................................ 57

Scheme 3.4: Synthesis of acetonide 3.25 completing the synthesis of a protected polyol side chain......................................................................................................................................................................................... 58

Scheme 3.5: Determining relative configuration of epoxidation reaction by Rychnovsky's acetonide method .......................................................................................................................................................................................................................................................... 60

Scheme 3.6: Two methods for preparation of vinyl iodide 3.34 starting from either a) propargyl alcohol or b) diethyl methylmalonate .......................................................................................................................................................................................................................................................................................................................... 60

Scheme 3.7: Synthesis of unsaturated aldehyde 3.41 ................................................................. 61

Scheme 3.8: Synthesis of aldehyde 3.45 using a Nagao aldol reaction ...................................... 61

Scheme 3.9: Major E1cB side product of Nagao aldol reaction ................................................. 62

Scheme 3.10: Diastereoselective addition of final substituents on IMDA precursor ............... 63

Scheme 3.11: Synthesis of oxazolidinone 3.53 ........................................................................... 64

Scheme 3.12: Synthesis of second IMDA precursor 3.57 and attempted IMDA reaction ........ 65

Scheme 3.13: Syntheses a) of enol silyl ether 3.63 and b) silyl ketene acetal 3.65 ...................... 66

Scheme 3.14: Rationalization for 1,2-syn outcome in a VMAR .................................................... 67

Scheme 3.15: Synthesis of α,β-unsaturated carbonyls for IMDA via VMARs ......................... 68

Scheme 3.16: Synthesis of IMDA precursors lacking a C-8 methyl group ................................ 69

Scheme 3.17: Retrosynthetic analysis for nahuoic acid A inspired by the synthesis of superstolide A172 .................................................................................................................................................................................................................................................................................................................. 70

Scheme 3.18: Synthesis of aldehyde 3.88 .................................................................................... 71

Scheme 3.19: Mechanism for zirconium catalyzed carboalumination, quenching with an epoxide electrophile .............................................................................................................................................................................................................................................................................................................. 71

Scheme 3.20: Attempted synthesis of a macrocyclic IMDA precursor .................................... 72
Scheme 3.21: Retrosynthetic analysis of nahuoic acid A using synthesis of phomopsidin as inspiration\textsuperscript{180} ........................................................................................................................................ 73

Scheme 3.22: Synthesis of macrolactonization precursor 3.107 ........................................................................ 74

Scheme 3.23: Saponification and attempted macrolactonization ........................................................................... 75


Scheme 3.25: Attempted macrocyclization through Stille cross-coupling .................................................................. 76

Scheme 3.26: Synthesis of phosphonate 3.118 ........................................................................................................ 78

Scheme 3.27: Attempted removal of tetrahydropyran protecting group ................................................................. 79

Scheme 3.28: Selected steps from Nakada’s synthesis of phomopsidin\textsuperscript{180} ....................................................... 79

Scheme 3.29: Synthesis of macrocyclization precursor mimicking steps used in the synthesis of phomopsidin ............................................................................................................................................. 81

Scheme 4.1: Retrosynthetic analysis for nahuoic acid A using an early stage Diels-Alder reaction ................................................................................................................................................................................. 140

Scheme 4.2: Dr. Andrew Beekman’s synthetic work towards nahuoic acid A using a) S\textsubscript{N}2’ displacement and b) 1,4-addition reactions ........................................................................................................... 141

Scheme 4.3: Potential methods of stereoselective C-C bond formation using b) 1,4-addition of an intramolecular nucleophile, b) S\textsubscript{N}’ displacement by an intramolecular nucleophile, c) [3,3]-sigmatropic rearrangement reactions, or d) metal catalyzed intramolecular cycloisomerization. ......................................................................................................................................................... 142

Scheme 4.4: a) DA reaction to synthesize cis-decalin core and b) derivatization into various oxidation states for future functionalization reactions ................................................................................................................ 143

Scheme 4.5: Formation of unusual by-product during workup ................................................................................. 144
Scheme 4.6: Attempted C-C bond forming reactions by conjugate addition .......................................................... 145
Scheme 4.7: Attempted intramolecular S_N' displacement with acetate or β-ketoester nucleophiles
........................................................................................................................................................................ 146
Scheme 4.8: Synthesis of carbonate and sulfite compounds for potential S_N' reactions ........... 147
Scheme 4.9: a) Synthesis of diol 4.7 and b) attempted [3,3]-sigmatropic rearrangements ...... 149
Scheme 4.10: One possible mechanism for a metal catalyzed 1,6-enyne cycloisomerization ... 150
Scheme 4.11: Failed attempts to functionalize less hindered alcohol of diol 4.7 ....................... 151
Scheme 4.12: Reaction of diol 4.7 with alkynylsilanes ................................................................. 151
Scheme 5.1: Potential route for synthesis of the core of nahuoic acid A ................................. 177
<table>
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<tr>
<th>Abbreviation</th>
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<tr>
<td>*</td>
<td>antibonding orbital</td>
</tr>
<tr>
<td>°</td>
<td>degree</td>
</tr>
<tr>
<td>18-c-6</td>
<td>18-crown-6</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>Å</td>
<td>angstrom</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
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<td>Anal.</td>
<td>analysis</td>
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<tr>
<td>BHT</td>
<td>butylated hydroxytoluene</td>
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<td>br.</td>
<td>broad</td>
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<td>Bu</td>
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<td>ca</td>
<td>circa</td>
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<td>COSY</td>
<td>homonuclear correlation spectroscopy</td>
</tr>
<tr>
<td>Cp</td>
<td>cyclopentadienyl</td>
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</table>
cryst  crystal
Cy  cyclohexyl
d  doublet or deuterium
Δ  heating to reflux
δ  chemical shift
DA  Diels-Alder
dba  dibenzylideneacetone
DBU  1,8-diazabicyclo[5.4.0]undec-7-ene
DCC  \( N,N' \)-dicyclohexylcarbodiimide
decomp  decomposition
DIAD  diisopropyl azodicarboxylate
DIBALH  diisobutylaluminum hydride
DMAP  4-dimethylaminopyridine
DMF  \( N,N' \)-dimethylformamide
DMP  Dess-Martin periodinane
DMPU  \( N,N' \)-dimethylpropylene urea
DMSO  dimethyl sulfoxide
DNA  deoxyribonucleic acid
dppb  1,4-bis(diphenylphosphino)butane
dr  diastereomeric ratio
\( E \)  entgegen
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<tr>
<td>e.g.</td>
<td>Latin: exempli gratia, English: for example</td>
</tr>
<tr>
<td>E⁺</td>
<td>electrophile</td>
</tr>
<tr>
<td>E₁cB</td>
<td>elimination unimolecular conjugate base</td>
</tr>
<tr>
<td>EDCI</td>
<td>1-ethyl-3-(3-dimethylaminopropyl)carbodiimide</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EE</td>
<td>ethoxylethyl</td>
</tr>
<tr>
<td>eq. or equiv.</td>
<td>equivalent(s)</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>etc.</td>
<td>Latin: et cetera, English: and the rest</td>
</tr>
<tr>
<td>EWG</td>
<td>electron withdrawing group</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>HSQC</td>
<td>heteronuclear single quantum coherence</td>
</tr>
<tr>
<td>HTS</td>
<td>high-throughput screening</td>
</tr>
<tr>
<td>HWE</td>
<td>Horner-Wadsworth-Emmons</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>i</td>
<td>iso</td>
</tr>
<tr>
<td>i.e.</td>
<td>Latin: id est, English: that is</td>
</tr>
<tr>
<td>IBX</td>
<td>2-iodoxybenzoic acid</td>
</tr>
<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>half maximal inhibitory concentration</td>
</tr>
<tr>
<td>IMDA</td>
<td>intramolecular Diels-Alder</td>
</tr>
<tr>
<td>imid.</td>
<td>imidazole</td>
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<tr>
<td>int</td>
<td>internal</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>Ka</td>
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<tr>
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<td>Lewis acid</td>
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<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
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<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LG</td>
<td>leaving group</td>
</tr>
<tr>
<td>M</td>
<td>molar</td>
</tr>
<tr>
<td>m</td>
<td>meta</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>m / z</td>
<td>mass to charge ratio</td>
</tr>
<tr>
<td>m.p.</td>
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<tr>
<td>mCPBA</td>
<td>meta-chloroperbenzoic acid</td>
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<td>Abbreviation</td>
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<td>normal</td>
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<td>naphthalene</td>
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<td>national cancer institute</td>
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<tr>
<td>NMO</td>
<td>N-methylmorpholine N-oxide</td>
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<td>NMP</td>
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<td>NMR</td>
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<tr>
<td>PCNA</td>
<td>proliferating cell nuclear antigen</td>
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<td>PG</td>
<td>protecting group</td>
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Ph  phenyl
PhD  doctor of philosophy
Pic  picolinate
PKS  polyketide synthase
PPTS  pyridinium para-toluenesulfonate
Pr  propyl
pyr.  pyridine
θ  angle
q  quartet
quin  quintet
R  rectus
R  any atom
r.t.  room temperature
Red-Al  sodium bis(2-methoxyethoxy)aluminumhydride
Ref.  reference
reflns  reflections
ROESY  rotating-frame Overhauser effect spectroscopy
S  sinister
s  singlet (NMR) or second (time)
σ  sigma orbital or background (X-ray)
SAM  S-adenosyl methionine
SAR  structure activity relationship
sat.  saturated
SCUBA  self-contained underwater breathing apparatus
SEM  [2-(trimethylsilyl)ethoxy]methyl
sext  sextet
SM  starting material
S\textsubscript{N}2  second-order nucleophilic substitution
S\textsubscript{N}2\textsuperscript{'}  second-order nucleophilic allylic substitution
syst  system
t  triplet
t  tertiary
T  Tesla
TADA  trans-annular Diels-Alder
TBAF  tetra-normal-butylammonium fluoride
TBS  tertiary-butyldimethylsilyl
TC  thiophene-2-carboxylate
\textit{tert}  tertiary
Tf  trifluoromethanesulfonyl (triflyl)
THF  tetrahydrofuran
TIPS  triisopropylsilyl
TLC  thin layer chromatography
<table>
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<tr>
<td>TMP</td>
<td>2,2,6,6-tetramethylpiperidine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetra-normal-propylammonium perruthenate</td>
</tr>
<tr>
<td>Ts</td>
<td>toluenesulfonyl (tosyl)</td>
</tr>
<tr>
<td>UBC</td>
<td>University of British Columbia</td>
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<tr>
<td>VMAR</td>
<td>vinylogous Mukaiyama aldol reaction</td>
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<tr>
<td>Z</td>
<td>zusammen</td>
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Acknowledgements

This work could not have been completed without the help of many people. If I have interacted with you in any meaningful way, then trust me, it was not forgotten, I truly appreciate it, and this is me thanking you here. However, “since brevity is the soul of wit, and tediousness the limbs and outward flourishes, I will be brief.”

Dr. Gregory Dake, your support over the years has been invaluable. Dr. Raymond Andersen, thank you for the opportunities you gave me. I’d still like to play a round of golf with the two of you.

Special thanks to those who are made of D-amino acids, those with LUMOs and HOMOs, those who are umpolung synthons, and those who have a penchant for beers and bicycles.
for Carolyn
Chapter 1: Introduction to Marine Natural Products Chemistry

1.1 A Brief History of Natural Products Chemistry

Natural products are organic, secondary metabolites produced by living organisms that are not required for an organism’s survival. All metabolites need energy to biosynthesize, so organisms expending energy to produce these metabolites must gain some evolutionary advantage to offset the energy expenditure. These advantages are manifested as chemical defenses against predators, chemical weapons against prey, or communicative markers. Often, natural products act selectively towards a competitor in the organism’s habitat.

Natural products often affect signal transduction and biochemical pathways, which can cause many different physiological responses. For centuries humans have tried to harness the beneficial responses caused by natural products. It is well documented that ancestral peoples all over the world experimented with plants and fungi that provided therapeutic value. Examples include Native American peoples using the salvia plant to aid in childbirth, Ayurvedic people using the camelthorn plant to treat anorexia and constipation (and many more ailments), and Polynesian people using kava root to induce a numbing and relaxing effect. In each case the observed effects were due to chemicals synthesized by the organism: natural products.

Figure 1.1: Examples of bioactive natural products isolated between 1804 and 1855

salicylic acid, \textit{genus: Salix}
morphine, \textit{genus: Papaver}
quiline, \textit{genus: Cinchona}
ocaine, \textit{genus: Erythroxyllum}
Most early discoveries of natural products (examples in figure 1.1) were either simple molecules constituting a significant fraction of the organic matter (salicylic acid, $1.1^7$), or a chemical purified by acidification and crystallization (alkaloids such as morphine, $1.2^8$, quinine, $1.3^9$, and cocaine, $1.4^{10}$). As scientific knowledge and techniques improved, so too did the ability to isolate and characterize natural products. This culminated in a boom in natural products discovery in the mid-20th century (figure 1.2).$^{11}$ Modern natural products chemists can characterize complex molecules containing more than 100 stereogenic centers, with molecular weights over 3000 Daltons (e.g. maitotoxin, $1.5^{12}$ and palytoxin, $1.6^{13}$).

![Figure 1.2: a) Number of alkaloid natural products discovered from the beginning of natural products chemistry until the 1960s. b) Two extremely complex natural products isolated in recent history.](image)

### 1.2 Development of Medicinal Chemistry

Once chemists discovered the natural product responsible for an observed physiological effect, they could synthesize analogues and derivatives of the natural product. These analogues and derivatives exhibited both enhanced and diminished biological activities, demonstrating that
changing the substituents on a molecule could alter the physiological response. Synthesizing analogues and identifying which ones were suitable for therapeutic use became a core tenet of medicinal chemistry.

1.2.1 Natural Product Analogue Creation

Figure 1.3: Pathways of medicinal chemistry development from salicin to acetylsalicylic acid

One well known story of medicinal chemistry is that of Aspirin (acetylsalicylic acid, 1.8, figure 1.3). After centuries of people in Eurasia and North America using willow bark as an analgesic, in 1828 chemists isolated salicin (1.7) and demonstrated that salicin could react in air to form salicylic acid (1.1), the active component of willow bark. While salicylic acid could act as an analgesic, those who used the drug often felt undesired side effects. To explore potential therapeutic benefits of compounds similar to salicylic acid, chemists at the dye and drug company Bayer began to synthesize analogues and test them on human subjects. One particular analogue: acetylsalicylic acid (1.8) provided similar analgesic effects to salicylic acid (1.1), while minimizing the undesired side effects. In 1899, Bayer marketed acetylsalicylic acid as “Aspirin” to treat headaches, pain, and inflammation.

A similar story materialized for procaine (1.9) and lidocaine (1.10, figure 1.4). For centuries, people indigenous to South America used leaves of the shrub Erythroxylon coca for their anesthetic properties. In 1855 scientists isolated the natural product responsible for these properties, cocaine (1.4). It was initially used as an anesthetic, but discovery of its toxic properties
precluded widespread use. Chemists attempting to improve the anesthetic properties and reduce the toxic properties of cocaine were able to identify the pharmacophores and synthesize compounds that accomplished this: procaine in 1904 and lidocaine in 1943.

![Figure 1.4: Chronological development of anesthetics derived from cocaine. The colored boxes show retained pharmacophores.](image)

Using bioactive natural products as a starting point for drug development has proven an effective method for discovery of new therapeutics. In fact, approximately 40% of drugs used in clinics today are natural products, natural product derivatives, or synthetic drugs inspired by natural products.

### 1.3 Modern Natural Products Chemistry

#### 1.3.1 Analytical Techniques

In the past, characterizing a molecular structure required multigram quantities of products, largely for degradation studies. Today, many technologies are available to separate, purify, and characterize a chemical compound. The advent of chromatographic methods (regular and reverse phase, size-exclusion, ion exchange, etc.), and mechanized instruments (high performance liquid chromatography) have allowed for effective separation and isolation of chemicals that make up only a small percentage of the organic fraction (micrograms of metabolite per kilogram of organism).
The methods for characterization have also improved. Nuclear magnetic resonance (NMR) spectroscopy can often provide sufficient data to elucidate a molecular structure. Most modern NMR spectroscopy methods only require micrograms of material. Also, new NMR techniques for probing certain structural elements are always under development. High resolution mass spectrometers (HRMS) can often indirectly provide the molecular formula of a compound using only micrograms of material.

The increased number and availability of biological assays has allowed scientists to screen natural products for a broader range of activity over time. The improved limits of detection for these assays has provided the potential to discover bioactive natural products that constitute a smaller fraction of the overall organic content, and that tend to display high potency. High-throughput screening (HTS) has led to the discovery of a number of drug leads by combining these improved assays with natural product libraries, modern robotics, and data processing software.

1.3.2 Synthetic Methods

The task of synthesizing complex natural products is a main driving force for development in organic chemistry. New methodologies to form challenging functional groups and stereogenic centers are constantly being developed to accommodate the task of natural product synthesis. Methods have arisen to determine stereochemical information of natural products through synthesis of derivatives (e.g. Mosher ester analysis or Rychnovsky’s acetonide method). Research into synthetic methods has led to theories that help explain molecular reactivity and advancement in the field of chemical biology. E. J. Corey described natural products research as “an engine for organic chemistry”.22

The ability to synthesize complex molecules is ever-improving. New reagents and reaction procedures supplant older methods for a variety of reasons: the reaction could proceed in
a higher yield, with greater specificity, or with less waste. New methods may reduce total cost of materials, involve a simpler apparatus, or use less toxic reagents. The plethora of methods available today provide the theoretical ability to synthesize almost any organic molecule, given enough time and effort.

1.4 Marine Natural Products as Therapeutics

The search for natural products was mostly limited to terrestrial organisms until the 1950s. With the advent of SCUBA technology, scientists were able to explore marine environments to collect new and interesting organisms such as algae, tunicates, sponges, and nudibranchs. The biodiversity in the vast, unexplored oceans was an opportunity to find new drug candidates through natural products research.

![Structures of the first clinically approved drugs based on marine natural products](image)

**Figure 1.5: Structures of the first clinically approved drugs based on marine natural products**

Investigation into organic extracts from the sponge *Tethya crypta* led to the discovery of spongothymidine (1.11, figure 1.5), a molecule with anticancer and antiviral properties. Significant clinical research and testing led to the first approved drugs based on a marine natural product in 1969: ara-A (1.12) and ara-C (1.13). In 1986, the FDA approved the spongothymidine-related compound AZT (1.14) for treatment of HIV and AIDS.

Since the discovery of nucleosides 1.11 - 1.13, research on marine natural products has led to several drugs that are approved for clinical use. Examples include eribulin (1.16), trabectedin
(1.17), and ziconotide (1.18, figure 1.6). Eribulin is an anticancer drug that was approved by the United States Food and Drug Administration (FDA) in 2010. It is a structural analogue of the marine natural product halichondrin B (1.15), a compound discovered in the sponge Halichondria okadai in 1986. Trabectedin is a marine natural product discovered in the tunicate Ecteinascidia turbinata. Researchers at the University of Illinois determined its structure in 1984. The FDA approved trabectedin for treatment of soft tissue sarcomas in 2015. Ziconotide is a polypeptide isolated from the cone snail Conus magnus in the 1980s. The FDA approved ziconotide for treatment of chronic pain in 2004. These and other examples are proving that exploring the ocean can be a viable method for discovering drug leads.

Figure 1.6: Structures of halichondrin B, and selected clinically approved drugs based on marine natural products

Exploring the vast biodiversity of marine natural products can lead to the discovery of new biosynthetic pathways. Oceans contain large amounts of dissolved elements not available to
terrestrial organisms in appreciable quantities. As a result, unique structures with uncommon atom incorporation can occur (1.19 - 1.21, figure 1.7).29–32

![Figure 1.7: Selected structures of marine natural products with uncommon atom incorporation](image)

### 1.5 Cancer Therapeutics

#### 1.5.1 A Brief History of Cancer Therapeutics

Treatment of cancer with chemical agents emerged as a field in the 1940s. After chemical weapons attacks in World War I, scientists noticed that mustard gas (1.22, figure 1.8) had the ability to slow or reduce mitosis of fast-dividing cell lines.33 Investigating the possible therapeutic benefits of this novel strategy for killing cancer cells led to the first chemotherapeutic cancer treatment: a nitrogen mustard called mustine (1.23).34,35

![Figure 1.8: Structures of the chemical weapon mustard gas and the chemotherapeutic mustine](image)

Since that seminal discovery, a massive increase in research has resulted in several chemotherapeutics coming to market. These drugs are helping people live longer and often provide a permanent cure, depending on the type of cancer.36 Still, chemotherapy does not provide a cure for all types of cancers, and patients undergoing chemotherapy often encounter a wide range of negative side effects. As such, there is significant room for improvement of chemotherapeutic agents. Governments and private organizations spend billions of dollars each year on cancer research to address these problems.37
1.5.2 Natural Products as Cancer Therapeutics

Although there have been many advances in the field of cancer research, scientists still use natural products as inspiration for the search into new cancer drugs because they have historically yielded the best results. As stated above, natural products and their derivatives accounted for roughly 40% of all drugs approved between 1981–2014. However, natural product scaffolds were the basis for 70% of all small molecules used for cancer treatment.

1.5.3 Marine Natural Products as Cancer Therapeutics

![Chemical structures of hemiasterlin, discodermolide, and bryostatin 1]

Figure 1.9: Marine natural products that show antitumor activities

Marine natural products have provided antitumor drug candidates such as halichondrin B (1.15, figure 1.6), hemiasterlin (1.24), discodermolide (1.25), and bryostatin 1 (1.26) (figure 1.9). Each of these molecules has a different mode of action, but each has helped advance understanding of how small molecules can inhibit cancer cell growth. Continuing research in this field may provide drug leads for incurable cancers, and may uncover new modes of action for killing cancer cells.
1.6 Reasons for Total Synthesis of Marine Natural Products

Despite the reasons outlined above for investigating marine natural products, supply of marine natural products often suffers due to the serious drawback of low titer. To make matters more difficult, a SCUBA diver is limited in the amount of organism that they can collect. Additionally, scaling up organism growth with aquaculture can be challenging, time consuming, and expensive. For example, only 0.4 mg of halichondrin B (1.15, figure 1.6) was isolated per kg of wild sponge. Using aquaculture to grow the sponge in bulk was very costly, and yielded only 30 – 60% of the halichondrin content compared to wild sponges.

A solution to the supply problem of halichondrin B came about by using synthesis and structure activity relationship (SAR) studies. Researchers were able to determine that only the right hand side of the molecule was necessary for antitumor activity. This led to the drug eribulin (1.16), a somewhat simpler synthetic problem to solve than halichondrin B.

The story of bryostatin 1 (1.26, figure 1.9) is another example of synthesis overcoming the problems related to poor titer. One kg (wet weight) of the bryozoan Bugula neritina yielded only 1.5 mg of bryostatin 1. When the national cancer institute (NCI) was first interested in pursuing bryostatin 1 as a drug candidate, scientists collected 14 tons of animal off the coast of California to yield only 18 grams of bryostatin 1. Investigation into commercial aquaculture allowed production of 100 – 200 g of bryostatin 1 per year at a cost of $700,000. While this expensive solution might produce enough compound for clinical testing, it does not provide enough for SAR studies to improve the pharmacokinetic properties of the drug. Syntheses of various bryostatins and analogues have helped researchers discover a truncated structure that still contains the pharmacophore.
The total synthesis of natural products is often the best way to confirm the proposed structures. Structure elucidation of natural products is prone to error. From 2006 to 2010, approximately 1000 new marine natural products were reported each year. In the same period, approximately 25 structures of marine natural products were misassigned each year. Possible errors include incorrect chemical formula, incorrect constitution, and incorrect configuration. These errors can create incorrect proposals for biosynthetic pathways, and can waste the time and money of those attempting to synthesize the natural product or investigate SAR.

One oft-overlooked benefit of undertaking the challenge of total synthesis is that it forces the creation of new solutions to the problems encountered, whether it be bond formation, asymmetric induction, or development of entirely new reactive mechanisms. Newly-created methods expand the toolbox of synthesis and can facilitate shorter total syntheses or provide easier access to targets through semi-synthesis.

1.7 Focus of This Thesis

The focus of this thesis is on synthesis of marine natural products found to be cytotoxic towards cancer cells, whose supply is minimal enough to preclude further medicinal chemistry studies. Chapter 2 focuses on the total synthesis of cladoniamide G and its analogues and derivatives. Chapters 3 and 4 focus on the various approaches explored in an attempt to synthesize nahuoic acid A. Both of these molecules were isolated in the Andersen lab at UBC. They each contain uncommon structural motifs that present challenges for total synthesis efforts.
Chapter 2: Total Synthesis of Cladoniamide G and Related Compounds

2.1 Introduction

2.1.1 2,2’-Bisindole Natural Products

The 2,2-bisindole skeleton (figure 2.1) is a common structural motif in natural products. These natural products are known to derive from a variety of marine and terrestrial organisms and can exist in a number of arrangements including indolocarbazoles (2.5) and indolotryptolines (2.6).

Figure 2.1: Common indole-containing structural motifs in natural products

Many compounds containing a 2,2’-bisindole framework have shown interesting biological activity profiles (figure 2.2) including staurosporine (2.7) (IC\text{50} value of 2.7 nM for protein kinase C inhibition),\textsuperscript{54–56} K252a (2.8) (IC\text{50} value of 20 nM for protein kinase C inhibition),\textsuperscript{57}

Figure 2.2: Bisindole natural products with interesting biological activities
rebeccamycin (2.9) (IC\textsubscript{50} value of 0.7 \(\mu\)M against HCT-116 cancer cells),\textsuperscript{58} and BE-54017 (2.10) (IC\textsubscript{50} value of 0.24 \(\mu\)M against P388 cancer cells).\textsuperscript{59} Work studying these natural products and their analogues has led to indolocarbazole compounds entering clinical trials.\textsuperscript{60}

2.1.2 Isolation of Cladoniamides

In 2008, the Andersen group reported the isolation and structural elucidation of a new class of indolotryptoline alkaloids, the cladoniamides (figure 2.3).\textsuperscript{52} The cladoniamides were isolated from extracts of \textit{Streptomyces uncialis}, an actinobacteria harbored within the lichen \textit{Cladonia uncialis}, found near the Pitt River in British Columbia. They were purified by size exclusion chromatography and HPLC. Structure elucidation was done using two-dimensional NMR spectroscopy, high resolution mass spectroscopy, and X-ray crystallography in the case of cladonamide A (2.11).

![Figure 2.3: Structures of cladoniamides A - G](image)

Compounds within the cladoniamide family differ by the number of carbon atoms (21 or 22), the position of functional groups, oxidation level, and halogen substitution. The presence of chloride substituents has been suggested to be a critical prerequisite for biological activity, as cladonamide G (2.17), is cytotoxic against MCF-7 breast cancer cells (10 \(\mu\)g/mL in vitro), whereas cladonamide F (2.16) lacks this activity. Similarly, cladonamide A (2.11) possesses potent
activity (8.8 ng/mL) against human colon cancer HCT-116 cells, while cladonamide C (2.13) does not.  

2.1.3  Biosynthesis of Cladoniamides

![Scheme 2.1: Biosynthesis of cladoniamides proposed by Andersen and Ryan](image)

A characteristic difference between the indolotryptoline and the indolocarbazole alkaloid classes is the relative orientation of the bisindole subunit; i.e. one of the indole fragments is flipped within the indolotryptoline (figure 2.1). Ryan reported the biogenetic gene cluster for the cladoniamides that suggests they arise biosynthetically through tryptophan dimer 2.21 (scheme
2.1), a known biosynthetic precursor to the well-described indolocarbazole class of natural products (e.g. staurosporine, 2.7 and rebeccamycin, 2.9)\textsuperscript{56,63–66}. In the case of the cladoniamides, dimer 2.21 is oxidized to tri-ol 2.24, which can ring-open at the center ring, rotate along the horizontal axis of the bisindole, and finally ring-close to form the indolotryptoline unit seen in the cladoniamides. Transformation from cladoniamides A - C (2.11 - 2.13) to cladoniamides D - G (2.14 - 2.17) occurs by hydrolysis of the succinimide followed by decarboxylation and oxidation. The difference between cladoniamides D (2.14) and E (2.15), and cladoniamides F (2.16) and G (2.17), is the direction of succinimide hydrolysis.

### 2.2 Initial Goals of the Project

When this work began, no cladoniamide syntheses had been reported in the literature. There was interest in developing a synthetic approach to the cladoniamides that would enable simple manipulations to generate a set of structural analogs with increased cytotoxicity towards cancer cell lines.

I also wanted to be able to glycosylate the natural product. Considering the biological activities of glycosylated natural products staurosporine (2.7) and rebeccamycin (2.9) (figure 2.2) and that activities of bisindole natural products can increase after glycosylation\textsuperscript{67}, I anticipated that glycosylation of the cladoniamides could increase their cytotoxicity and/or specificity.\textsuperscript{68,69}

Cladoniamide G (2.17) was selected as a target to provide a context for an initial tactical approach because, at the onset of this work, it showed the most significant biological activity. The lessons learned during this study could then be utilized in second generation approaches to other, more synthetically challenging natural and artificial compounds.
2.3 Retrosynthetic Analysis

My retросynthetic analysis of cladoniamide G (2.17) involved establishing the central ring connecting the two indole partners at a late stage of the synthesis (scheme 2.2). Condensation between an electrophilic synthon as represented by “E⁺⁺” and the C2-C2’ bisindole 2.27 would generate the carbon skeleton. Established indigo dye chemistry would construct the key C2-C2’ bisindole 2.27.⁷⁰

\[
\text{cladoniamide G, 2.17} \rightarrow \text{E}^+ + \text{Cl} \rightarrow \text{2.27} \rightarrow \text{2.28}
\]

Scheme 2.2: Retrosynthetic steps for cladoniamide G starting from 5,5’-dichloroindigo

5,5’-Dichloroindigo (2.28) is an expensive starting material (ca. $200 CAD per gram), so initial experiments to establish the feasibility of this approach were undertaken using indigo (2.29) (ca. $1 CAD per gram) as the starting material.⁷¹

2.4 Total Synthesis of Cladoniamide G

2.4.1 Synthesis of Deshalo-Indolotryptoline Core

The 2,2’-bisindole-acetate 2.30 is available from the chemical reduction of indigo (2.29) using tin metal, acetic anhydride, and acetic acid in a Clemmensen-type reduction (scheme 2.3).⁷² In this reaction, one ketone on indigo is reduced by two equivalents of tin metal to form anion 2.36, which can be quenched by acetic anhydride to form acetate 2.30. The reaction of indigo could be monitored by observing the reaction mixture’s color change from blue to yellow/brown. Once
the blue solid has disappeared from the reaction flask, acetic acid could be added to quench the reaction mixture.

Scheme 2.3: Proposed mechanism for Clemmensen type reduction of indigo to 2,2'-bisindole 2.30

Significant effort was required to transform the acetate group on 2.30 into a methyl ether (scheme 2.4) because the saponification intermediate would rapidly decompose. Fortunately, I found that transformation to ether 2.37 could take place in 51% yield through saponification *in situ* using tetrabutylammonium hydroxide in the presence of methyl iodide. Methyl ether 2.37 was identified by *¹H NMR* spectroscopy due to the distinct change of an acetate singlet (δ 2.54) to a methyl ether singlet (δ 4.19).
Scheme 2.4: Reactivity studies of 2,2'-bisindole derivatives

Early experiments had demonstrated the propensity for electrophiles to react at C-3 of the desoxygenated indole on 2.30. For example, acyl chlorides only reacted at C-3 of the desoxygenated indole when refluxing in ethyl acetate to provide acylation products 2.38 and 2.39. Analysis of the $^1$H NMR spectrum determined C-3 as the site of new bond formation; the well resolved C-3 proton ($\delta 6.66$ for 2.30) disappeared after reactions with various electrophiles, while the other aromatic protons remained in product spectra. Unfortunately, acylation products 2.38 and 2.39 were insoluble in common solvents, and attempted manipulations to form indolotryptolines (like 2.40) were unsuccessful. Search for another approach led to diethyl 2-oxomalonate (2.41). This strong electrophile contained the correct number of carbons in the correct oxidation states for transformation into cladonamide G. Reactions of bisindoles 2.30 or 2.37 with diethyl 2-oxomalonate (2.41) in refluxing ethyl acetate led to carbonyl addition product 2.42 or 2.43 in 82% and 90% yields respectively. These products contained two distinct ethyl residues in the $^1$H NMR spectrum, likely due to restricted rotation of the ester groups.
Attempts to construct the lactam ring of the indolotryptoline core by Lewis acid activation of 2.42 using boron trifluoride diethyl etherate were unsuccessful (scheme 2.5). However, it was noted through spectroscopic and spectrometric experiments on the reaction products, that under these conditions, dehydrative and oxidative cyclizations to form polycycles 2.44 and 2.45 took place. Instead, treatment of 2.43 with DBU generated the desired β-ester lactam 2.46 in 53% yield, observed by loss of an ethoxy residue in both the $^1$H NMR and MS spectral analysis. This transformation was also possible using alkoxide bases but with diminished yields compared to using DBU.

![Scheme 2.5: Attempts to form indolotryptolines by a) Lewis acidic conditions and b) basic conditions](image)

The sequence of experiments in schemes 2.4 and 2.5 demonstrated the means to convert the acetate within 2.30 to a methyl ether before lactam formation, and the need for basic conditions to generate the lactam ring within 2.46. With this information in hand, studies using 5-chloroindole as a starting material began.
2.4.2 Synthesis of 5,5'-Dichloroindolotryptoline Core

Commercially available 5-chloroindole (2.47) was converted to 3-acetoxy-5-chloroindole (2.48) by initial iodination followed by an iodide acetate exchange process promoted by silver (I) (Scheme 2.6). Subjecting acetate 2.48 to sodium hydroxide in ethanol led to the formation of 5,5'-dichloroindigo (2.28), which could be isolated as a deep blue powder. The reduction of 2.28 using tin metal, as previously used for indigo (scheme 2.3), led to a disappointing 22% yield of bisindole 2.49. I speculated that the low yield is a result of tin addition into the C-Cl bonds. To circumvent the problems associated with the tin reaction, a Wolff-Kishner type reduction was undertaken using hydrazine hydrate in the presence of NaOH, and then quenching with Ac₂O to afford acetate 2.49 in 88% yield, a 4-fold improvement. Using the procedure established above (scheme 2.4), the saponification and methylation of chloroindole acetate 2.49 resulted in methyl ether 2.27, but only in 23% yield. Attempts to improve the yields by altering reaction conditions or methyl electrophiles were unsuccessful. In response, a one-pot procedure was developed that
utilizes the reduction of indigo compounds using hydrazine and NaOH with a methyl electrophile quench (table 2.1). These experiments showed that dimethyl sulfate could quench the reaction resulting in direct formation of methyl ether 2.27 in 34% yield. This reaction required optimization of reaction temperature and time due to the formation of multi-methylated by-products, which were a significant detriment to total yield and created issues with purification. Still, compared to the previous 2-step procedure, this was a 7-fold improvement in yield alone.

**Table 2.1: Wolff-Kishner reductions quenching with different methylating agents**

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</tr>
<tr>
<td>2</td>
<td>MeOTf</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>trimethyloxonium tetrafluoroborate</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>methyl fluorosulfonate</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>Me₂SO₄</td>
<td>34%</td>
</tr>
</tbody>
</table>

Reaction of methyl ether 2.27 with diethyl 2-oxomalonate (2.41) in refluxing ethyl acetate gave C-3 addition product 2.50 (scheme 2.7). Once again, loss of the distinct C-3 signal in the ¹H NMR spectrum (δ 6.89 for 2.27) helped confirm bond formation at C-3. Treatment of 2.50 with DBU then generated indolocarbazole 2.51. Interestingly, the reaction of indolocarbazole 2.51 with methylamine generated diamide 2.52 in 88% yield instead of the natural product. This was seen in the ¹H NMR spectrum by noting the two indole N-H peaks (δ 9.44, 9.08) and the two methyl amide singlets at (δ 2.60, 2.59), which integrated to 6 hydrogens together. Diamide formation was further confirmed by MS. I expected that limiting the amount of methylamine would allow for the
formation of cladoniamide G, regardless of the site selectivity of the nucleophilic attack by

Scheme 2.7: Unintentional synthesis of diamide 2.52
methylamine, but limiting the quantity of methylamine to 1 equivalent or less produced diamide 2.52 and unreacted indolocarbazole 2.51. Using hindered nucleophiles (such as N-benzylmethylamine), modifying solvents, or modifying temperatures was not successful.

Scheme 2.8: Potential mechanism for indolocarbazole formation through amide activation
To resolve this problem, I attempted to convert diamide 2.52 into an indolocarbazole through electrophilic activation of an amide (scheme 2.8). In this proposed reaction, addition of triflic anhydride to diamide 2.52 in the presence of pyridine could form iminium 2.54, which could then be attacked intramolecularly by the indole nitrogen to form cladoniamide G 2.17 after work up. However, trying to react diamide 2.52 or its O-TBS ether derivative 2.56 using amide activation conditions reported in the literature was unsuccessful (table 2.2). The reactions formed decomposition products at or above room temperature. Decomposition was fast for diamide 2.52, while O-TBS diamide 2.56 appeared to slowly desilylate into diamide 2.52 before decomposing further to intractable mixtures.

Table 2.2: Attempted indolocarbazole formation by amide activation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Base</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.52</td>
<td>pyridine</td>
<td>CH₂Cl₂, r.t.</td>
<td>decomp.</td>
</tr>
<tr>
<td>2</td>
<td>2.52</td>
<td>2-Cl-pyridine</td>
<td>CH₂Cl₂, r.t.</td>
<td>decomp.</td>
</tr>
<tr>
<td>3</td>
<td>2.52</td>
<td>2-Cl-pyridine</td>
<td>CH₂Cl₂, -78 °C</td>
<td>decomp.</td>
</tr>
<tr>
<td>4</td>
<td>2.52</td>
<td>2-OMe-pyridine</td>
<td>CH₂Cl₂, -78 °C</td>
<td>decomp.</td>
</tr>
<tr>
<td>5</td>
<td>2.52</td>
<td>3-Br-pyridine</td>
<td>CH₂Cl₂, -78 °C</td>
<td>decomp.</td>
</tr>
<tr>
<td>6</td>
<td>2.52</td>
<td>2,6-di-‘Bu-4-Me-pyridine</td>
<td>CH₂Cl₂, -78 °C</td>
<td>decomp.</td>
</tr>
<tr>
<td>7</td>
<td>2.56</td>
<td>pyridine</td>
<td>CH₂Cl₂, r.t.</td>
<td>decomp.</td>
</tr>
<tr>
<td>8</td>
<td>2.56</td>
<td>2-Cl-pyridine</td>
<td>CH₂Cl₂, r.t.</td>
<td>decomp.</td>
</tr>
<tr>
<td>9</td>
<td>2.56</td>
<td>2-Cl-pyridine</td>
<td>CH₂Cl₂, -78 °C</td>
<td>partial decomp.</td>
</tr>
<tr>
<td>10</td>
<td>2.56</td>
<td>2-OMe-pyridine</td>
<td>CH₂Cl₂, -78 °C</td>
<td>partial decomp.</td>
</tr>
<tr>
<td>11</td>
<td>2.56</td>
<td>3-Br-pyridine</td>
<td>CH₂Cl₂, -78 °C</td>
<td>partial decomp.</td>
</tr>
<tr>
<td>12</td>
<td>2.56</td>
<td>2,6-di-‘Bu-4-Me-pyridine</td>
<td>CH₂Cl₂, -78 °C</td>
<td>partial decomp.</td>
</tr>
</tbody>
</table>
2.4.3 Synthesis of an Unsymmetric Vicinal Tricarbonyl

At this point, I decided to return to reactions of 2,2'-bisindole 2.27 with tricarbonyl electrophiles. Attempting to append on a symmetric tricarbonyl and then desymmetrize resulting products was unsuccessful so the new goal was to create an unsymmetric vicinal tricarbonyl to react with 2,2'-bisindole 2.27.

![Diagram of tricarbonyl synthesis](image)

Figure 2.4: Selected literature reported methods to form vicinal tricarbonyl compounds

There are many reported methods for synthesis of vicinal tricarbonyl compounds (figure 2.4). The general strategies include: coupling a chlorooxoacetate (2.57) with an acetyl tin (2.58) or silyl reagent (2.59),\textsuperscript{79,80} oxidizing a phosphorus ylide (2.60),\textsuperscript{81} or oxidizing the \(\alpha\) carbon of a malonate derivative (2.61 - 2.63).\textsuperscript{82-86} In my hands, the first two strategies were not amenable the functionality required to synthesize cladoniamide G 2.17, leaving central carbon oxidation as the
remaining strategy. Oxidation of diazo compounds and malonate monoamides proved difficult, but ozonolysis of alkylidenes (2.63) showed promise.

![Scheme 2.9: Synthesis of unsymmetric vicinal tricarbonyl 2.70](image)

A known Knoevenagel condensation between diethyl malonate (2.65) and benzaldehyde (2.66) produced diester 2.67 (scheme 2.9). Next, saponification with lithium hydroxide generated carboxylic acid 2.68. Generating Vilsmeier-Haack reagent in situ with oxalyl chloride and DMF transformed acid 2.68 into an acyl chloride species that was reacted with Boc protected methylamine to generate carbamate 2.69. Oxidative cleavage of carbamate 2.69 with ozone generated, after workup with triphenylphosphine unsymmetric tricarbonyl 2.70.

Tricarbonyl 2.70 and similar compounds are very electrophilic and must be used promptly. For this reason, oxidative cleavage of carbamate 2.69 with ozone did not work when using methanol as a co-solvent because it would form the methanol adduct. During storage, these compounds converted to carbonyl hydrates over the course of days. On substrates without the steric hindrance of the Boc group, this conversion was much quicker.
2.4.4 Completion of Total Synthesis of Cladoniamide G

Scheme 2.10: Completing the synthesis of cladoniamide G

The reaction of chlorinated bisindole 2.27 with tricarbonyl 2.70 proceeded in ethyl acetate at reflux (scheme 2.10). Examination of the reaction mixture after 12 h using preparatory TLC and $^1$H NMR spectroscopy resulted in a gratifying observation: cladoniamide G 2.17 was a significant product along with unreacted bisindole 2.27, the expected product 2.71, and the carbamate-removed intermediate 2.72 (figure 2.5). Disappearance of C-3 signal in the $^1$H NMR spectrum

![Diagram](image)

Figure 2.5: Intermediates of final step in total synthesis. a) $^1$H NMR spectrum of crude 2.71. b) $^1$H NMR spectrum of crude 2.72.
(δ 6.89) identified the products as C-3 adducts. The product lacking a carbamate group (2.72) was identified by the lack of a Boc singlet (δ ~ 1.4), and the N-methyl amide peak changing from a singlet to a doublet while shifting upfield (δ 3.11 to 2.98). It appeared that once carbonyl addition product 2.71 formed in situ, it first underwent spontaneous Boc deprotection and then formed the lactam ring. This order of events is the best explanation for the mixture of products observed.

Extending the reaction time between bisindole 2.27 and tricarbonyl 2.70 to 72 hours led to higher conversion of starting materials to 2.17, isolated in 81% yield. This synthetic material shared All 1H NMR and 13C NMR spectroscopic data with those of the natural compound.

In summary, access to synthetic cladoniamide G was achieved using a sequence with a low step count (9 steps, 5 in the longest linear sequence, 15% from 5-chloroindole, 2.47, 27% from dimethyl malonate, 2.65).

2.5 Attempted Glycosylation of Cladoniamide G

As stated in 2.2, a goal of this project was to glycosylate cladoniamide G (2.17) because of the hypothesis that doing so may increase activity or potency of the natural product in biological systems. I looked to the glycosylation of rebeccamycin (2.9) for inspiration (scheme 2.11) since rebeccamycin aglycone (2.66) and cladoniamide G (2.17) share significant functionality (figure 2.6), and might react in similar ways.

Figure 2.6: Structures of cladoniamide G, rebeccamycin aglycone, and rebeccamycin
2.5.1 Attempted Glycosylation Using Basic Conditions

Scheme 2.11: a) Glycosylation of rebeccamycin precursor by Danishefsky and b) attempted glycosylation of cladoniamide G and protected cladoniamide G in the Dake lab

In work towards synthesis of rebeccamycin (2.9) in the Danishefsky lab, they deprotonated indole 2.74 using sodium hydride, and then added glycal epoxide 2.75 to form N-glycoside 2.76 (scheme 2.11). I attempted glycosylation of cladoniamide G (2.17) using a near identical procedure (different glycal), but was unsuccessful. Exploration of bases ("BuLi, MeLi, LDA) and epoxide electrophiles (other glycals, glycidyl ethers, aliphatic epoxides) were also unsuccessful. I hypothesized that the free alcohol on 2.17 was being deprotonated instead of the indole. To fix this, I protected 2.17 as O-TBS ether 2.77 and subjected this substrate to glycosylation conditions. Unfortunately, addition of base to TBS ether 2.77 appeared to cause elimination of silanol.
2.5.2 Attempted Glycosylation Using Acidic and Neutral Conditions

Scheme 2.12: Attempted glycosylations of cladoniamide G using a) Mitsunobu-type conditions and b) gold catalyzed conditions pioneered by Yu.\(^90\)

To overcome the problems caused by basic media, glycosylation was also attempted using Lewis acidic conditions,\(^91\)--\(^93\) but this also led to intractable mixtures. Next, I experimented with more neutral conditions (scheme 2.12). Mitsunobu-type conditions\(^94\) did not cause any reaction, even after stirring for days in boiling solvent. Conditions developed by Yu using glycosyl ortho-alkynylbenzoate 2.83 and a gold catalyst\(^90,95,96\) were also unable to provide the glycosylation product 2.82.

2.5.3 Attempted Glycosylation of Cladoniamide G’s Synthetic Intermediates

In light of the troubles with glycosylating cladoniamide G directly, I ran glycosylation experiments on indole-containing intermediates from the total synthesis in the hopes that a
glycosylated intermediate could be carried through using the same sequence. Unfortunately, glycosylation using C-3 unsubstituted indoles (e.g. bisindole 2.27) failed, likely due to competition for reaction at C-3 leading to by-products and decomposition.

2.6 Synthesis of Cladoniamide G Analogues

2.6.1 Attempted Synthesis of Deschloro-Cladoniamide G

With a method for the total synthesis of cladoniamide G, I began synthesis of analogues using similar chemical transformations. To this end, I mixed reduced indigo 2.37 with vicinal tricarbonyl 2.70 in refluxing ethyl acetate in an attempt to synthesize deschloro-cladoniamide G 2.84 (scheme 2.13). Instead, $^1$H NMR and MS spectra provided evidence that dehydrated species 2.85 was made, indicating that the chlorine atoms may stabilize the molecule. Product 2.85 could not be fully characterized because it was nearly insoluble in all common NMR solvents. More than 1000 scans were necessary to obtain a $^1$H NMR spectra with a reasonable signal to noise ratio.

![Scheme 2.13: Attempted formation of deschloro-cladoniamide G 2.84](image)

2.6.2 Attempted Synthesis of Cladoniamide G’s Fluorinated Analogue

In an effort to synthesize fluorine analogues of cladoniamide G, I first prepared 5,5’-difluoroindigo and 6,6’-difluoroindigo through established procedures. Unfortunately, reduction of either difluoroindigo using any methods described above gave low yields (ca. 1 - 3%).
Furthermore, products were difficult to isolate purify. For these reasons, attempts to synthesize fluorine analogues of cladoniamide G were abandoned.

### 2.6.3 Synthesis of Cladoniamide G’s Bromine Analogue

**Scheme 2.14: Synthesis of bromine analogue of cladoniamide G 2.90**

Fortunately, synthesis of a bromine analogue by the newly discovered route was possible (scheme 2.14). The synthesis began with transformation of 5-bromoindole (2.86) into 5,5’-dibromoindigo (2.88) under known conditions. Wolff-Kishner-type reduction of 5,5’-bromoindigo followed by dimethyl sulfate quench gave bisindole 2.89. Stirring bisindole 2.89 with tricarbonyl 2.70 in refluxing ethyl acetate provided the bromine analogue of cladoniamide G 2.90 in 71% yield. NMR spectra of 2.90 looked very similar to those of cladoniamide G 2.17, but HMRS confirmed formation of the brominated analogue.

### 2.7 Conclusion and Future Directions

At this point, I wanted to test synthetic cladoniamide G 2.17, its bromine analogue 2.83, and some synthetic intermediates against cancer cell lines, but the collaborators who tested the original cladoniamide extracts had stopped growing the relevant cell lines and could not test the synthetic compounds.
Figure 2.7: Future targets for the cladoniamide project

Deprotonation or elimination of the tertiary alcohol on cladoniamide G appeared to impede glycosylation reactions (section 2.5). One method to circumvent the problem of elimination is using structures like 2.91 (figure 2.7) for glycosylation reactions, provided R can later be transformed into an oxygen atom.

Another future direction of the cladoniamide project would be to synthesize the iodine analogue of cladoniamide G (2.92). When the collaborators are once again able to test for cytotoxicity against the relevant cell lines, investigating a possible trend in halogen bonding could provide insight into further SAR.
2.8 Experimental

General experimental (see Appendix A)

1H,1'H-[2,2'-Biindol]-3-yl acetate (2.30)

1H,1'H-[2,2'-biindol]-3-yl acetate (2.30) was prepared by the methods of Sato\textsuperscript{72,97–99} and Bergman.\textsuperscript{74,75} All \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectroscopic data matched reported values.

3-Methoxy-1H,1'H-2,2'-biindole (2.37)

To a solution of 1H,1'H-2,2'-biindol-3-yl acetate (2.30) (1.78 g, 6.1 mmol) in THF (100 mL) was added aqueous tetrabutylammonium hydroxide (1.6 M, 4.0 mL, 6.1 mmol) and iodomethane (0.38 mL, 6.1 mmol). The reaction mixture was stirred for 18 h and then diluted with ethyl acetate (100 mL). The organic layer was collected and washed with H\textsubscript{2}O (50 mL) and brine (50 mL), dried over sodium sulfate, and concentrated \textit{in vacuo}. The residue was purified by flash column chromatography on silica gel (4:1 hexanes/ethyl acetate) to afford 2.37 (815 mg, 3.1 mmol, 51%) as a pale green solid.

Data for 2.37: IR \textnu 3413, 3051, 1335, 735 cm\textsuperscript{-1}; HRMS (ESI) Anal. Calcd. for C\textsubscript{17}H\textsubscript{14}N\textsubscript{2}O \textit{m} / \textit{z} 261.1028 [M-H]\textsuperscript{-}, found 261.1031; \textsuperscript{1}H NMR (300MHz, CDCl\textsubscript{3}) \textdelta 9.50 (s, 1H), 8.04 (s, 1H), 7.75
(d, J = 7.8 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.36 - 7.15 (m, 6H), 6.66 (d, J = 1.1 Hz, 1H), 4.19 (s, 3H); $^{13}$C NMR (75MHz, CDCl$_3$) δ 137.1, 136.5, 134.5, 130.2, 128.4, 123.1, 122.3, 121.3, 120.3, 120.2, 119.9, 118.1, 117.9, 111.6, 110.9, 97.4, 61.6

**Chloroacetate 2.38**

Chloroacetate **2.38** was prepared by the method of Moody.$^{100}$ All $^1$H NMR and $^{13}$C NMR spectroscopic data matched reported values.

**Dichloroacetate 2.39**

Dichloroacetate **2.39** was prepared by the method of Moody.$^{100}$ All $^1$H NMR and $^{13}$C NMR spectroscopic data matched reported values.
Diethyl 2-(3'-acetoxy-1H,1'H-2,2'-biindol-3-yl)-2-hydroxymalonate (2.42)

To a solution of 1H,1'H-2,2'-biindol-3-yl acetate (2.30) (500 mg, 1.7 mmol) in ethyl acetate (15 mL) was added diethyl 2-oxomalonate (0.53 mL, 3.4 mmol). The reaction mixture was stirred at reflux. After 3 h, the mixture was cooled, concentrated _in vacuo_, and chromatographed directly on silica gel (3:1 hexanes/ethyl acetate) to afford 2.42 (652 mg, 1.4 mmol, 82%) as a pale green solid.

Data for 2.42: IR £ 3348, 3287, 1746, 744 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₂₅H₂₄N₂O₇ m/z 487.1481 [M-Na]^+; found 487.1481; ^1H NMR (300MHz, CDCl₃) δ 9.40 (s, 1H), 8.97 (s, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.48 - 7.34 (m, 3H), 7.27 - 7.20 (m, 2H), 7.19 - 7.10 (m, 2H), 4.55 (s, 1H), 4.00 - 4.22 (m, 4H), 2.44 (s, 3H), 1.11 (t, J = 7.1 Hz, 6H); ^13C NMR (75MHz, CDCl₃) δ 170.4, 135.8, 133.7, 127.5, 127.2, 126.3, 123.8, 123.2, 121.2, 120.9, 120.8, 120.1, 119.3, 117.6, 112.0, 111.7, 110.0, 78.5, 63.6, 21.1, 13.9
Diethyl 2-hydroxy-2-(3'-methoxy-1H,1'H-2,2'-biindol-3-yl)malonate (2.43)

![Chemical structure](image)

To a solution of 3-methoxy-1H,1'H-2,2'-biindole (2.37) (260 mg, 1.0 mmol) in ethyl acetate (10 mL) was added diethyl 2-oxomalonate (0.30 mL, 2.0 mmol). The reaction mixture was stirred at reflux. After 3 h, the mixture was cooled, concentrated in vacuo, and chromatographed directly on silica gel (3:1 hexanes/ethyl acetate) to afford 2.43 (392 mg, 0.90 mmol, 90%) as a green solid.

Data for 2.43: IR $\tilde{\nu}$ 3365, 29.78, 1737, 741 cm$^{-1}$; HRMS (ESI) Anal. Calcd. for C$_{24}$H$_{24}$N$_2$O$_6$ m / z 437.1713 [M-H]$^+$, found 437.1710; $^1$H NMR (300MHz, CDCl$_3$) $\delta$ 9.67 (s, 1H), 9.55 (s, 1H), 7.70 (d, $J = 7.7$ Hz, 1H), 7.47 - 7.41 (m, 2H), 7.38 - 7.34 (m, 1H), 7.25 - 7.19 (m, 2H), 7.16 - 7.09 (m, 2H), 4.67 (s, 1H), 4.36 - 4.14 (m, 4H), 4.11 (s, 3H), 1.16 (t, $J = 6.6$ Hz, 6H); $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ 170.3, 137.9, 135.4, 134.2, 125.9, 123.2, 122.4, 120.6, 120.3, 119.8, 119.2, 118.0, 117.1, 112.0, 111.1, 106.8, 78.3, 63.2, 61.9, 13.8
Pentacycle 2.46

To a solution of diethyl 2-hydroxy-2-(3'-methoxy-1H,1'H-2,2'-biindol-3-yl)malonate (2.43) (80 mg, 0.18 mmol) in THF (3 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (30 μL, 0.20 mmol). After stirring for 3 hours at 22 °C, the reaction mixture was concentrated in vacuo and chromatographed directly on silica gel (3:1 hexanes/ethyl acetate) to afford 2.46 (37 mg, 95 μmol, 53%) as a green solid.

Data for 2.46: IR ν 3419, 1757, 1685, 740 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₂₂H₁₈N₂O₅ m/z 389.1137 [M⁻H]⁻, found 389.1132; ¹H NMR (300MHz, CDCl₃) δ 8.86 (s, 1H), 8.55 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.49 - 7.10 (m, 5H), 4.69 (s, 1H), 4.30 (s, 3H), 4.29 – 4.11 (m, 2H), 1.11 (t, J = 7.1 Hz, 3H); ¹³C NMR (75MHz, CDCl₃) δ 170.8, 167.1, 139.8, 137.6, 134.4, 126.7, 125.4, 124.8, 124.6, 124.4, 123.6, 121.3, 119.4, 118.8, 116.9, 115.3, 111.4, 107.5, 75.9, 63.3, 61.1, 13.9

5-Chloro-1H-indol-3-yl acetate (2.48)

5-Chloro-1H-indol-3-yl acetate (2.48) was prepared by the method of Tanoue.⁷⁰ All ¹H NMR and ¹³C NMR spectroscopic data matched reported values.
**5,5’-Dichloroindigo (2.28)**

![Diagram of 5,5’-Dichloroindigo (2.28)](image)

5,5’-Dichloroindigo (2.28) was prepared by the method of Tanoue. All \(^1\)H NMR and \(^{13}\)C NMR spectroscopic data matched reported values.

**5,5’-Dichloro-1H,1'H-2,2'-biindol-3-yl acetate (2.49)**

**Method 1: Use of tin as reducing agent**

![Diagram of 5,5’-Dichloro-1H,1'H-2,2'-biindol-3-yl acetate (2.49)](image)

To a solution of 5,5’-dichloroindigo (2.28) (2.4 g, 7.0 mmol) in acetic acid (70 mL) and acetic anhydride (70 mL) was added tin (16.0 g, 135 mmol). The reaction mixture was stirred at 65 °C for 3 h and subsequently cooled to 22 °C. After 12 h, the reaction mixture was filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (4:1 hexanes/ethyl acetate) to afford 2.49 (540 mg, 1.5 mmol, 22 %) as a pale blue solid.

**Method 2: Use of hydrazine as reducing agent**

To a solution of 5,5’-dichloroindigo (2.28) (200 mg, 0.60 mmol) in ethanol (10 mL) and aqueous sodium hydroxide (2 M, 10 mL) was added hydrazine hydrate (0.15 mL, 3.0 mmol). The reaction mixture was stirred at reflux for 4 h, then cooled to 0 °C and charged with acetic anhydride (3 mL). After 12 h, the reaction mixture was concentrated *in vacuo*. The resulting residue was charged with
ethyl acetate (20 mL) and sat. NaHCO₃ (until effervescence ceased). The organic layer was collected and the aqueous layer further extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine (20 mL) and dried over sodium sulfate. The dried organic layer was concentrated in vacuo and the residue chromatographed on silica gel (4:1 hexanes/ethyl acetate) to afford 2.49 (190 mg, 0.53 mmol, 88%) as a pale green solid.

Data for 2.49: IR ν 3430, 3361, 1739, 792 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₁₈H₁₂Cl₂N₂O₂ m/z 357.0198 [M-H]⁻, found 357.0194; ¹H NMR (300MHz, DMSO-d₆) δ 11.67 (s, 1H), 11.38 (s, 1H), 7.70 (d, J = 1.9 Hz, 1H), 7.55 (d, J = 8.7 Hz, 1H), 7.52 (d, J = 1.8 Hz, 1H), 7.48 (d, J = 8.7 Hz, 1H), 7.19 (dt, J = 7.8, 1.8 Hz, 2H), 6.93 (d, J = 1.4 Hz, 1H), 2.53 (s, 3H); ¹³C NMR (75MHz, DMSO-d₆) δ 169.7, 135.9, 132.7, 130.1, 129.7, 126.0, 124.9, 123.1, 122.7, 122.5, 121.8, 119.8, 117.4, 113.8, 113.6, 100.8, 21.4

5,5'-Dichloro-3-methoxy-1H,1'H-2,2'-biindole (2.27)

Method 1: Conversion from 5,5'-dichloroindigo

To a solution of 5,5'-dichloroindigo (2.28) (1.65 g, 5.0 mmol) in ethanol (75 mL) and aqueous sodium hydroxide (2 M, 75 mL) was added hydrazine hydrate (1.22 mL, 25 mmol). The reaction mixture was stirred at reflux for 4 h, then cooled to 0 °C and charged with dimethyl sulfate (5.85 mL, 50 mmol). After 16 h, the reaction mixture was diluted with ethyl acetate (50 mL) and H₂O (50 mL). The organic layer was washed with brine (50 mL) and dried over sodium sulfate. The
dried organic layer was concentrated in vacuo and the residue chromatographed on silica gel (8:1:1 hexanes/ethyl acetate/dichloromethane) to afford 2.27 (565 mg, 1.7 mmol, 34%) as a pale green solid.

**Method 2: Saponification of ester**

![Chemical structure of 2.49](image)

To a solution of 5,5'-dichloro-1H,1'H-2,2'-biindol-3-yl acetate (2.49) (225 mg, 0.63 mmol) in THF (10 mL) was added aqueous tetrabutylammonium hydroxide (1.6 M, 0.42 mL, 0.67 mmol) and iodomethane (60 μL, 0.96 mmol). The reaction mixture was stirred for 18 h and then diluted with ethyl acetate (10 mL). The organic layer was collected and washed with H₂O (10 mL) and brine (10 mL), dried over sodium sulfate, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (4:1 hexanes/ethyl acetate) to afford 2.27 (46 mg, 0.14 mmol, 23%) as a pale green solid.

Data for 2.27: IR ν 3443, 3417, 787 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₁₇H₁₂Cl₂N₂O m / z 329.0248 [M-H], found 329.0241; ¹H NMR (300MHz, DMSO-d₆) δ 11.33 (s, 1H), 11.17 (s, 1H), 7.69 (d, J = 1.8 Hz, 1H), 7.62 (d, J = 1.8 Hz, 1H), 7.55 (d, J = 8.7 Hz, 1H), 7.38 (d, J = 8.7 Hz, 1H), 7.12 (dt, J = 8.7, 1.8 Hz, 2H), 6.89 (d, J = 1.8 Hz, 1H), 4.04 (s, 3H); ¹³C NMR (75MHz, DMSO-d₆) δ 136.3, 135.8, 132.9, 129.7, 124.6, 124.2, 121.9, 119.7, 119.3, 117.3, 113.8, 113.7, 99.1, 61.8, 40.9, 40.6, 40.3, 40.0, 39.7, 39.5, 39.2
Diethyl 2-(5,5'-dichloro-3'-methoxy-1H,1'H-2,2'-biindol-3-yl)-2-hydroxymalonate (2.50)

To a solution of 5,5'-dichloro-3-methoxy-1H,1'H-2,2'-biindole (2.27) (600 mg, 1.8 mmol) in ethyl acetate (30 mL) was added diethyl 2-oxomalonate (1.0 mL, 6.5 mmol). The reaction mixture was then heated to reflux. After 3 h, the mixture was cooled, concentrated in vacuo, and chromatographed directly on silica gel (8:1:1 hexanes/ethyl acetate/dichloromethane) to afford 2.50 (713 mg, 1.4 mmol, 78%) as a pale green solid.

Data for 2.50: IR $\nu$ 3352, 2934, 1733, 795 cm$^{-1}$; HRMS (ESI) Anal. Calcd. for C$_{24}$H$_{22}$Cl$_2$N$_2$O$_6$ m/z 505.0933 [M-H]$^+$, found 505.0929; $^1$H NMR (300MHz, CDCl$_3$) $\delta$ 9.71 (s, 1H), 9.69 (s, 1H), 7.55 (d, $J = 1.9$ Hz, 1H), 7.38 (d, $J = 1.9$ Hz, 1H), 7.18 (d, $J = 8.7$ Hz, 1H), 7.14 (d, $J = 8.7$ Hz, 1H), 7.07 (dt $J = 8.7$, 1.5 Hz, 2H), 5.25 (s, 1H), 4.36 – 4.17 (m, 4H), 3.99 (s, 3H), 1.19 (t, $J = 7.1$ Hz, 6H); $^{13}$C NMR (75MHz, CDCl$_3$) $\delta$ 170.1, 137.2, 133.9, 132.5, 130.1, 126.8, 126.2, 125.6, 123.8, 122.9, 121.2, 118.9, 118.0, 117.2, 113.2, 112.3, 107.0, 78.3, 63.5, 62.0, 13.9
**Dichloro-pentacycle 2.51**

To a solution of diethyl 2-(5,5'-dichloro-3'-methoxy-1H,1'H-2,2'-biindol-3-yl)-2-hydroxymalonate (2.50) (460 mg, 0.91 mmol) in THF (20 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (160 µL, 1.1 mmol). After 2 h, the reaction mixture was concentrated *in vacuo* and chromatographed directly on base-washed silica gel (2:1 hexanes/ethyl acetate) to afford 2.51 (320 mg, 0.70 mmol, 77%) as a solid.

Data for 2.51: IR ν 3413, 1753, 1682, 807 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₂₂H₁₆Cl₂N₂O₅ m/z 457.0358 [M-H]⁻, found 457.0364; ¹H NMR (300MHz, DMSO-d₆) δ 11.77 (s, 1H), 8.41 (d, J = 8.9 Hz, 1H), 7.95 (s, 1H), 7.59 - 7.47 (m, 3H), 7.31 (s, 1H), 7.22 (d, J = 8.9 Hz, 1H), 4.21 (s, 3H), 4.20 – 3.97 (m, 2H), 0.98 (t, J = 7.1 Hz, 3H); ¹³C NMR (75MHz, DMSO-d₆) δ 169.3, 167.4, 138.3, 136.9, 131.9, 129.4, 126.7, 125.7, 125.2, 124.9, 124.8, 123.1, 118.8, 118.3, 117.3, 116.6, 114.0, 108.5, 75.7, 61.9, 61.6, 13.8
Dimethylmalonamide 2.52

To a solution of 2.51 (103 mg, 0.22 mmol) in THF (5 mL) was added methylamine in THF (2 M, 1.0 mL, 2.0 mmol). After 12 h, the reaction mixture was concentrated *in vacuo* and chromatographed directly on silica gel (3:1 hexanes/ethyl acetate) to afford 2.52 (94 mg, 0.20 mmol, 88%) as a solid.

Data for 2.52: IR ν 3315, 2935, 1676, 726 cm⁻¹; HRMS (ESI) Anal. Calcd. for C_{22}H_{20}Cl_{2}N_{4}O_{4} m / z 497.0759 [M−Na]+, found 497.0757; ¹H NMR (300MHz, CDCl₃) δ 9.44 (s, 1H), 9.08 (s, 1H), 7.55 (s, 1H), 7.37 (s, 1H), 7.31 (q, J = 4.5 Hz, 2H), 7.18 (d, J = 8.7 Hz), 7.14 – 7.05 (m, 3H), 5.89 (s, 1H), 3.83 (s, 3H), 2.60 (s, 3H), 2.59 (s, 3H); ¹³C NMR (75MHz, CDCl₃) δ 171.1, 137.9, 133.9, 132.4, 129.7, 127.3, 126.5, 125.6, 123.2, 121.2, 118.8, 117.5, 117.1, 112.9, 112.4, 111.2, 77.7, 76.8, 76.5, 62.0, 26.9
O-TBS dimethylmalonamide 2.56

![Chemical structure](image)

To a solution of dimethylmalonamide 2.52 (200 mg, 0.42 mmol) in THF (5 mL) was added pyridine (0.50 mL, 6.2 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (0.10 mL, 0.44 mmol). After 3 h, the reaction mixture was concentrated *in vacuo* and directly chromatographed directly on silica gel (3:1 hexanes/ethyl acetate) to afford 2.56 (210 mg, 0.36 mmol, 85%) as a solid.

Data for 2.56: IR $\nu$ 3321, 2930, 1678, 732 cm$^{-1}$; HRMS (ESI) Anal. Calcd. for C$_{28}$H$_{34}$Cl$_2$N$_4$O$_4$Si $m/z$ 611.1624 [M-Na]$^+$, found 611.1618; $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 10.52 (s, 1H), 9.47 (s, 1H), 7.65 (d, $J =$ 1.7 Hz, 1H), 7.53 (d, $J =$ 2.0 Hz, 1H), 7.42 (q, $J =$ 4.8 Hz, 2H), 7.27 (d, $J =$ 8.5 Hz, 1H), 7.30 (d, $J =$ 8.5 Hz, 1H), 7.15 (dd, $J =$ 2.0, 8.5 Hz, 2H), 4.04 (s, 3H), 2.81 (s, 3H), 2.80 (s, 3H), 0.75 (s, 9H), 0.11 (s, 6H); $^{13}$C NMR (101MHz, CDCl$_3$) $\delta$ 172.2, 137.3, 133.8, 132.2, 130.6, 127.1, 125.3, 123.6, 123.1, 118.9, 118.5, 117.6, 112.9, 112.2, 110.6, 79.8, 62.4, 26.9, 26.1, 18.9, -3.2
Diethyl 2-benzylidemalonate 2.67

\[
\text{EtO} \quad \begin{array}{c}
\text{O} \\
\text{CO} \\
\text{COEt}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{Et}
\end{array} + \begin{array}{c}
\text{H} \\
\text{C} = \text{C} \\
\text{Et}
\end{array} \quad \rightarrow \quad \text{EtO} \quad \begin{array}{c}
\text{O} \\
\text{CO} \\
\text{Ph}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{Et}
\end{array}
\]

Diethyl 2-benzylidemalonate 2.67 was prepared by the method of Smith. All $^1$H NMR and $^{13}$C NMR spectroscopic data matched reported values.

(Z)-2-(Ethoxycarbonyl)-3-phenylacrylic acid (2.68)

\[
\text{EtO} \quad \begin{array}{c}
\text{O} \\
\text{CO} \\
\text{COEt}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{Et}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{Et}
\end{array} \quad \begin{array}{c}
\text{Ph}
\end{array} \quad \rightarrow \quad \text{HO} \quad \begin{array}{c}
\text{O} \\
\text{CO} \\
\text{Et}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{Et}
\end{array} \quad \begin{array}{c}
\text{O} \\
\text{Et}
\end{array} \quad \begin{array}{c}
\text{Ph}
\end{array}
\]

(Z)-2-(Ethoxycarbonyl)-3-phenylacrylic acid (2.68) was prepared by the method of Deprez. All $^1$H NMR and $^{13}$C NMR spectroscopic data matched reported values.

Methyl 2-(tert-butoxycarbonyl(methyl)carbamoyl)-3-phenylacrylate (2.69)

\[
\text{C(OH)} \quad \begin{array}{c}
\text{O} \\
\text{Ph}
\end{array} \quad \begin{array}{c}
\text{O}
\end{array} \quad \rightarrow \quad \text{C(OH)} \quad \begin{array}{c}
\text{O} \\
\text{Ph}
\end{array} \quad \begin{array}{c}
\text{O}
\end{array} \quad \begin{array}{c}
\text{N}
\end{array} \quad \begin{array}{c}
\text{Boc}
\end{array}
\]

To a stirred solution of (Z)-2-(methoxycarbonyl)-3-phenylacrylic acid (2.68) (1.01 g, 4.9 mmol) in CH$_2$Cl$_2$ (30 mL) at 0 °C was added dimethylformamide (50 μL) and oxalyl chloride (0.50 mL, 5.9 mmol). After 1 h the mixture concentrated in vacuo to afford a yellow residue. The residue was diluted with CH$_2$Cl$_2$ (30 mL) and cooled to 0 °C. To this stirred solution was added tert-butyl methylcarbamate (640 mg, 4.9 mmol) which was stirred for 12 hours while warming to 22 °C.
After concentration *in vacuo*, the residue was purified by flash column chromatography on silica gel (4:1 hexanes/ethyl acetate) to afford **2.69** (1.22 g, 3.8 mmol, 78%) as an oil.

Data for **2.69**: IR ν 1724, 1668, 1630, 1141 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₁₇H₂₁NO₅ m/z 342.1317 [M-Na]⁺, found 342.1318; ¹H NMR (300MHz, CDCl₃) δ 7.55 (s, 1H), 7.31 (s, 5H), 3.82 - 3.72 (m, 3H), 3.63 (s, 1 H), 3.06 - 3.27 (m, 3 H), 1.44 (s, 2 H), 1.36 (s, 7 H); ¹³C NMR (75MHz, CDCl₃) δ 69.3, 168.3, 164.7, 164.4, 153.2, 152.3, 143.1, 138.4, 134.0, 133.2, 131.4, 130.5, 130.1, 130.0, 129.5, 129.4, 129.2, 128.9, 128.0, 84.3, 83.8, 52.7, 52.4, 51.7, 32.0, 31.1, 27.9, 27.7

**Methyl 3-((tert-butoxycarbonyl)(methyl)amino)-2,3-dioxopropanoate (2.70)**

![Chemical structure of 2.69 and 2.70]

To a stirred solution of methyl 2-((tert-butoxycarbonyl)(methyl)carbamoyl)-3-phenylacrylate (2.69) (700 mg, 2.2 mmol) in CH₂Cl₂ (25 mL) at -78 °C was bubbled O₃ until the solution became blue. The solution was then sparged with N₂ until the blue color disappeared. Triphenylphosphine (580 mg, 2.2 mmol) was then added to the solution which stirred for 2 h. The mixture was then concentrated *in vacuo* and the resulting residue purified by flash column chromatography on silica gel (4:1 hexanes/ethyl acetate) to afford **2.70** (302 mg, 1.2 mmol, 56%) as an oil.

Data for **2.70**: IR ν 1772, 1736, 1719, 1694 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₁₀H₁₅NO₆ m/z 268.0797 [M-Na]⁺, found 268.0804; ¹H NMR (300MHz, CDCl₃) δ 3.88 (s, 3H), 3.15 (s, 3H), 1.47 (s, 9H); ¹³C NMR (75MHz, CDCl₃) δ 176.4, 167.6, 158.9, 154.1, 86.8, 77.7, 76.8, 53.5, 29.5, 27.8
Cladoniamide G (2.17)

To a stirred solution of 5,5'-dichloro-3-methoxy-1H,1'H-2,2'-biindole (2.27) (140 mg, 0.42 mmol) in ethyl acetate (30 mL) was added methyl 3-(tert-butoxycarbonyl(methyl)amino)-2,3-dioxopropanoate (2.70) (208 mg, 0.85 mmol). The reaction mixture was then heated to reflux. After 72 h, the mixture was cooled and filtered to afford a pale green solid. The solid was washed with EtOAc (20 mL) and Et₂O (20 mL) to give cladoniamide G (2.17) (152 mg, 0.34 mmol, 81%).

Data for 2.17: HRMS (ESI) Anal. Calcd. for C_{21}H_{15}Cl_{2}N_{3}O_{4} m / z 442.0361 [M-H]⁻, found 442.0354; ¹H NMR (300MHz, DMSO-d₆) δ 11.66 (s, 1H), 8.71 (q, J = 4.7 Hz, 1H), 8.39 (d, J = 8.8 Hz, 1H), 7.92 (d, J = 1.9 Hz, 1H), 7.71 (d, J = 1.9 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.48 (dd, J = 8.8, 1.9 Hz, 1H), 7.22 (s, 1H), 7.20 (dd, J = 8.8, 1.9 Hz, 1H), 4.19 (s, 3H), 2.66 (d, J = 4.7 Hz, 3H); ¹³C NMR (75MHz, DMSO-d₆) δ 169.7, 168.8, 137.7, 136.9, 131.7, 129.1, 126.3, 125.7, 125.2, 124.9, 124.7, 122.9, 118.6, 117.5, 117.1 113.8, 118.6, 110.6, 76.1, 61.6, 25.8

5-Bromo-1H-indol-3-yl acetate (2.87)

5-Bromo-1H-indol-3-yl acetate (2.87) was prepared by the method of Tanoue.⁷⁰ All ¹H NMR and ¹³C NMR spectroscopic data matched reported values.
5,5’-Dibromoindigo (2.88)

5,5’-Dibromoindigo (2.88) was prepared by the method of Tanoue.\(^7\) All \(^1\)H NMR and \(^13\)C NMR spectroscopic data matched reported values.

Cladoniamide G – bromine analogue (2.90)

To a stirred solution of 5,5’-dibromo-3-methoxy-1H,1’H-2,2’-biindole (2.89) (142 mg, 0.34 mmol) in ethyl acetate (30 mL) was added methyl 3-(tert-butoxycarbonyl(methyl)amino)-2,3-dioxopropanoate (2.70) (200 mg, 0.79 mmol). The reaction mixture was then heated to reflux. After 72 h, the mixture was cooled and filtered to afford a pale green solid. The solid was washed with EtOAc (20 mL) and Et\(_2\)O (20 mL) to give the bromine analogue of cladoniamide G (2.90) (129 mg, 0.24 mmol, 71%).

Data for 2.90: IR \(\nu\) 3421, 3188, 3094, 2942, 1704, 1669, 801 cm\(^{-1}\); HRMS (ESI) Anal. Calcd. for C\(_{21}\)H\(_{14}\)Br\(_2\)N\(_3\)O\(_4\) \(m/z\) 529.5391 [M-H], found 529.9354; \(^1\)H NMR (300MHz, DMSO-\(d_6\)) \(\delta\) 11.66 (s, 1H), 8.71 (q, \(J = 4.2\) Hz, 1H), 8.33 (d, \(J = 8.7\) Hz, 1H), 8.04 (d, \(J = 1.8\) Hz, 1H), 7.84 (d, \(J = \ldots\)
1.8 Hz, 1H), 7.60 (dd, J = 8.7, 1.8 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.31 (dd, J = 8.6, 1.7 Hz, 1H), 7.22 (s, 1H), 4.19 (s, 3H), 2.66 (d, J = 4.6 Hz, 3H); $^{13}$C NMR (75MHz, DMSO-d$_6$) δ 169.7, 168.8, 137.6, 137.1, 132.1, 129.1, 126.1, 125.4, 124.7, 121.6, 121.3, 117.5, 117.3, 117.2, 114.2, 112.8, 110.5, 76.2, 61.6, 25.8
Chapter 3: Studies Towards Synthesis of Nahuoic Acid A Through a Late Stage Diels-Alder Reaction

3.1 Introduction

Polyketides are a group of natural products biosynthesized through a series of condensations of simple thioester units. They were originally named “polyketenes” because scientists believed they were a polymer of ketene. The name was later changed “polyketides”. Many classes of polyketides have been discovered, including macrolides such as pikromycin (3.1) and epothilone A (3.2), and tetracyclines such as oxytetracycline (3.3, figure 3.1).

Figure 3.1: Examples of polyketide natural products from bacterial sources

Polyketide natural products contain many structures and functionalities, but one structural motif is uncommon when considering all known polyketides: the decalin. Polyketide natural products that contain a decalin (figure 3.2) have demonstrated a wide range of biological effects including antibacterial, antifungal, and anticancer properties.

Figure 3.2: Examples of polyketide natural products containing a decalin motif
3.1.1 Isolation of Nahuoic Acids

In 2012, the Andersen group reported the isolation and structural elucidation of a new decalin containing polyketide natural product, nahuoic acid A (3.8, figure 3.3).\textsuperscript{53} In 2015, the Qi group published the structures of nahuoic acids B - E (3.9 - 3.12)\textsuperscript{107} which were also published by the Andersen group shortly thereafter.\textsuperscript{108} Each of these novel molecules contained an unprecedented carbon skeleton, which included a cis-decalin moiety and a polyol side chain.

The only difference between the skeletons of nahuoic acids A - C (3.8 - 3.10) and nahuoic acids D and E (3.11, 3.12) is an extra acetate subunit in the polyol side chains of nahuoic acids D and E.

![Structures of nahuoic acids A - E](image)

**Figure 3.3: Structures of nahuoic acids A - E, each containing a cis-decalin and a polyol side chain**

The molecules were isolated from *Streptomyces* sp. found in marine sediment near Padana Nahua, Papua New Guinea. Pans of bacteria were grown before the organic material was extracted with ethyl acetate. The extract was fractionated and purified by size exclusion chromatography and HPLC providing nahuoic acids A - E.\textsuperscript{53,107,108}
3.1.2 Proposed Biosynthesis of Nahuoic Acids

The nahuoic acids appear to originate from polyketide synthase (PKS) enzymes. Beginning with an isobutyrate subunit at the terminus of the polyol side chain (scheme 3.1), a series of propionate and acetate condensation reactions form the carbon backbone. Once the linear polyketide has been synthesized, formation of the decalin might occur through an intramolecular cycloaddition. A Diels-Alderase enzyme possibly aids this cycloaddition.

![Scheme 3.1: Proposed biosynthesis of nahuoic acid A through a series of condensations and cycloaddition](image)

3.1.3 Structural Determination of the Nahuoic Acids

Many techniques were used to characterize the nahuoic acids. High resolution mass spectrometry was used to determine the molecular formula. Carbon and hydrogen connectivities were largely determined by $^1$H, $^{13}$C, COSY, HSQC, and HMBC NMR spectroscopy, with some of the relative configuration being established with $J$ coupling data and ROESY NMR spectroscopy (figure 3.4). The remainder of the relative and absolute configurations of alcohols were determined by formation of acetonides and by Mosher ester analysis.
3.1.4 Biological Activity of Nahuoic Acid A

3.1.4.1 Introduction to Histone Methyltransferases (HMTs)

Deoxyribonucleic acid (DNA) must be compressed to fit inside a cell nucleus. Compression of DNA begins by wrapping it around histone proteins into structures called nucleosomes (figure 3.5). Further compacting with other proteins will provide the structure of the chromosome. DNA transcription is necessary for proper cell function, but before that can happen, the DNA, and by extension the nucleosomes, have to be “unwrapped”. If the histones become altered in some way, this unwrapping process may fail and DNA transcription may fail.110

Histone methyl transferase enzymes modify histone proteins by methylating nitrogen on lysine or arginine residues using cofactor S-adenosyl methionine (SAM). Methylation of histones
has been shown to play a role in gene expression, cell maturation and mitosis, and DNA methylation.\textsuperscript{110,112} Mutation of HMTs is linked to many diseases including cancer.\textsuperscript{113}

SETD8 is a HMT that has a primary function of methylating the nitrogen of lysine 20 of histone 4.\textsuperscript{108} SETD8 has also been shown to methylate lysine 248 of proliferating cell nuclear antigen (PCNA)\textsuperscript{114} and lysine 382 of tumor suppressor protein p53.\textsuperscript{115} SETD8 is found to be overexpressed in some cancers, and abnormal methylation by SETD8 can lead to cancer in humans.\textsuperscript{114} For these reasons, finding a SETD8 inhibitor may prove useful for development of an anticancer therapeutic.

3.1.4.2 Inhibition of SETD8 By Nahuoic Acid A

Nahuoic acid A (3.8) is the first known SAM competitive inhibitor of SETD8 (figure 3.6) and displayed the highest selectivity for SETD8 of any known inhibitor.\textsuperscript{116,117} Part A of figure 3.6 shows how SETD8 is the only HMT greatly inhibited by nahuoic acid A, even at high concentrations. Part B shows concentration of SAM affects activity, while concentration of histone does not. This indicates that nahuoic acid A is binding competitively with SAM.

![Figure 3.6: a) Inhibition of HMTs by nahuoic acid A, b) Lineweaver Burk plots indicating SAM competitive inhibition\textsuperscript{53}](image-url)
Table 3.1: IC$_{50}$ data for nahuoic acid A and analogues towards SETD8

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC$_{50}$ (µM)</th>
<th>Hill Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>nahuoic acid A (from old batch)</td>
<td>8</td>
<td>1.4</td>
</tr>
<tr>
<td>7,17-diacetylnahuoic acid A</td>
<td>11</td>
<td>1.6</td>
</tr>
<tr>
<td>nahuoic acid A</td>
<td>12</td>
<td>1.4</td>
</tr>
<tr>
<td>methyl ester of nahuoic acid A</td>
<td>16</td>
<td>1.3</td>
</tr>
<tr>
<td>17-acetylnahuoic acid A</td>
<td>17</td>
<td>1.3</td>
</tr>
<tr>
<td>pentaacetate of nahuoic acid A</td>
<td>21</td>
<td>1.5</td>
</tr>
<tr>
<td>7-acetylnahuoic acid A</td>
<td>26</td>
<td>1.4</td>
</tr>
</tbody>
</table>

To explore SAR of nahuoic acid A, the Andersen lab synthesized analogues and tested for inhibition of SETD8 (table 3.1). Nahuoic acid A and each of the analogues all possessed similar activities towards SETD8. These results raised questions about certain structure activity relationships. For instance, which hydroxyl/methyl groups were necessary and was the configuration important? Would a minimal cis-decalin with an identical polyol side chain retain activity? Would formation of a macrolactone affect activity? With less than milligram quantities available from the Andersen lab, the goal was to answer some of these questions through synthesis.

3.2 Retrosynthetic Analysis of Nahuoic Acid A

3.2.1 Analysis of an Intramolecular Diels-Alder Reaction

Figure 3.7: Possible products of an intramolecular Diels-Alder reaction on substrate 3.15

Intramolecular Diels-Alder (IMDA) reactions of linear precursors such as 3.15 can form 4 possible decalin products (3.16 - 3.19, figure 3.7). Outcomes occurring through either the exo or endo transition states have both been described in natural product literature. Figure 3.2 shows two
examples: phomopsidin (3.4, via an exo transition state) and tanzawaic acid A (3.5, via an endo transition state).

If the biosynthesis of nahuoic acid does proceed through an IMDA (scheme 3.1), it would need to occur via an exo transition state to create the cis-decalin structure. Furthermore, the electron withdrawing carbonyl group, whether in the form of carboxylic acid or ester, is likely activating the molecule for Diels-Alder reactivity.

Although formation of a cis-decalin is not typically favored (exo transition states are usually disfavored), the possible formation of a mixture of products was an ideal scenario because I wanted to investigate the SAR of multiple stereoisomers.

The majority of decalin containing natural products contain trans-decalin moieties. Of the remaining cis-decalin natural products, few contain a methyl group at the ring junction. This may be indicative that formation of cis-decalins containing a methyl group at the ring junction is challenging. Despite the anticipated challenges, I still expected that a biomimetic synthesis was possible by first creating a linear precursor and then undergoing an IMDA reaction.118–122

3.2.2 Retrosynthetic Analysis for a Linear Precursor to an IMDA

Beginning with an IMDA disconnection results in a linear polyketide precursor (scheme 3.2). This theoretical disconnection simplified the synthetic task since the reactions and techniques to synthesize polyketide type molecules have been extensively researched.123

Linear polyketide 3.20 could be pieced together in a convergent manner using stereoselective crotylation, cross metathesis, and carboalumination chemistry. Aldehyde 3.23 could be synthesized by a Sonogashira coupling and an enantioselective aldol reaction leading back to known vinyl iodide 3.24. Epoxide 3.25 could come from known aldehyde 3.26 after allylation and epoxidation reactions.
Scheme 3.2: Retrosynthetic analysis for nahuoic acid A

Following the completion of this thesis, a study was published that successfully uses a very similar retrosynthetic approach.\textsuperscript{124}

3.3 Attempted Synthesis of Nahuoic Acid A Fragments

3.3.1 Synthesis of a Protected Polyol Side Chain

Scheme 3.3: Synthesis of aldehyde 3.29 using three separate methods
Scheme 3.3 shows the synthesis of the side chain precursor, beginning with the well described Evans syn aldol to form oxazolidinone 3.28. Due to the many examples in the literature I attempted a few methods to create aldehyde 3.29. There were two general strategies: oxazolidinone 3.28 was either converted to a Weinreb amide and then reduced, or oxazolidinone 3.28 was reduced to a primary alcohol and then oxidized to aldehyde 3.29.

Method A from scheme 3.3 gave the highest yields. In this method, oxazolidinone 3.28 was first transformed into a Weinreb amide in 84% yield using trimethylaluminum as a Lewis acid. This step also allowed recovery of the chiral auxiliary in 93% yield. Following this, TBS protection of the secondary alcohol using TBSOTf occurred in high yield. Reducing the resulting Weinreb amide using diisobutylaluminum hydride (DIBALH) gave aldehyde 3.29.

Scheme 3.4: Synthesis of acetonide 3.25 completing the synthesis of a protected polyol side chain

Aldehyde 3.29 reacted with allyl Grignard to provide known alcohol 3.30 with a modest dr of 3:1 (scheme 3.4). The observed diastereoselectivity could be explained by the Felkin-Ahn model (figure 3.8). The diastereomers were separable by chromatography.
Figure 3.8: Explanation for selectivity of Grignard addition by Felkin-Ahn model

Epoxidation of alcohol 3.30 with mCPBA gave a 1:1 mixture of product diastereomers, which were also separable by chromatography. Investigating epoxidation methods for a more diastereoselective reaction was unsuccessful (vanadium catalysts, Shi epoxidation conditions,\textsuperscript{132} Sharpless epoxidation conditions\textsuperscript{133}). Ultimately, I rationalized that a lack of diastereoselectivity was beneficial because a small library of diastereomers would prove useful when investigating SAR. To complete the protection of the polyol side chain, and at the same time confirm the configuration of the Grignard products, TBS protecting group of epoxide 3.31 was removed using TBAF, and the resulting diol reacted with 2,2-dimethoxypropane to form acetonide 3.25.

Rychnovsky’s acetonide method is a derivatization method that helps determine the relative configuration of 1,3-diols.\textsuperscript{21} According to this method the $^{13}$C NMR spectroscopy signal ($\delta$ 99.0) for the acetonide carbon of 3.25 proved that the diol had 1,3-syn configuration.

The relative configuration of epoxide 3.31 was also determined by Rychnovsky’s acetonide method (scheme 3.5). After opening epoxide 3.31 using LAH, the resulting diol was once again reacted with 2,2-dimethoxypropane to form acetonide 3.32. Crude product showed a $^{13}$C NMR signal for the acetonide carbon ($\delta$ 100.2) that confirmed 1,3-anti stereochemistry.
Scheme 3.5: Determining relative configuration of epoxidation reaction by Rychnovsky's acetonide method

With a small cache of acetonide 3.25 synthesized, and absolute configuration of all chiral centers confirmed, focus turned to synthesis of a potential IMDA precursor.

3.4 Synthesis of a Linear IMDA Precursor

Scheme 3.6: Two methods for preparation of vinyl iodide 3.34 starting from either a) propargyl alcohol or b) diethyl methylmalonate

To build an IMDA precursor, I chose (E)-vinyl iodide 3.34 as the starting material and synthesized it using two literature reported methods (scheme 3.6). While carboalumination of propargyl alcohol 3.33 (scheme 3.6a) was a relatively simple, one-pot procedure, yields of this reaction were never raised above 30%. A more successful route began with diethyl methylmalonate 3.35 (scheme 3.6b). Deprotonated malonate was added to iodoform and then the intermediate subjected to decarboxylation and elimination conditions using hydroxide forming (E)-carboxylic acid 3.36. This acid was then reduced with LAH to afford (E)-vinyl iodide 3.34. Although the latter pathway had more steps, it was a technically easier process and provided a greater overall yield of 3.34.
Scheme 3.7: Synthesis of unsaturated aldehyde 3.41

Standard polyketide chemistry was used to elongate the linear chain (scheme 3.7). Vinyl iodide 3.34 underwent a Sonogashira coupling with TMS acetylene\textsuperscript{139,140} followed by oxidation with manganese dioxide to arrive at known aldehyde 3.37.\textsuperscript{141} This aldehyde was then reacted with stabilized Wittig reagent 3.38 in an (E)-selective olefination process to form ester 3.39. The ester was then transformed to aldehyde 3.41 in a two-step process starting with reduction to alcohol 3.40 using Dibal-H and subsequent oxidation with manganese dioxide. Throughout these reactions, experimental success was determined by the location of the vinyl proton(s) with \textsuperscript{1}H NMR spectroscopy. Changing the electronic withdrawing or donating ability of neighboring functional groups resulted in dramatic shifts of the vinyl resonances (e.g. $\delta$ 5.97 and 5.44 for alcohol 3.40 to $\delta$ 6.71 and 5.82 for aldehyde 3.41).

Scheme 3.8: Synthesis of aldehyde 3.45 using a Nagao aldol reaction
With aldehyde 3.41 in hand, the next step was to add an acetate equivalent in a stereoselective manner through an aldol reaction (scheme 3.8). Acetate equivalents can often be difficult to use in aldol reactions, especially when attempting to impart a significant level of diastereoselectivity.\textsuperscript{142–144} After some experimentation, success came using a Nagao aldol reaction.\textsuperscript{144–146} In this reaction, chiral thiazolidinethione 3.42 (the acetate equivalent) was added to aldehyde 3.41 using 1-ethylpiperidine as a base, and tin(II) trifluoromethanesulfonate as a Lewis acid activator. The desired product was obtained in a high diastereomeric ratio and good yield. In addition to a 59\% yield of desired aldol product 3.43, 30\% of aldehyde 3.41 was recovered which could be recycled. The relative configuration was presumed to agree with literature precedent and was not strictly assigned. The Nagao aldol product 3.43 was then protected as a TBS ether 3.44, and then the chiral auxiliary removed using DIBALH to form aldehyde 3.45 in high yield. \textsuperscript{1}H NMR spectroscopy of aldehyde 3.45 gave a clear signal of aldehyde proton (\(\delta 9.73\)) and signals of the two diastereotopic protons (\(\delta 2.66\) and 2.43), each a doublet of doublet of doublets. Throughout these steps, the products were easy to visually identify because all thiazolidinethione containing compounds were bright yellow.

\begin{center}
\includegraphics[width=\textwidth]{Scheme3.9.png}
\end{center}

**Scheme 3.9: Major E\textsubscript{1cB} side product of Nagao aldol reaction**

When trying to optimize aldol reaction conditions, I observed that altering reaction times, equivalents, and temperatures all resulted in increased E\textsubscript{1cB} side reaction to give conjugated thiazolidinthione 3.46 (scheme 3.9). In fact, all reactions on compounds containing a thiazolidinthione group required careful observation to avoid the facile E\textsubscript{1cB} side reaction.
Scheme 3.10: Diastereoselective addition of final substituents on IMDA precursor

To stereoselectively add the final alcohol and methyl substituents to the IMDA precursor, I used an asymmetric Roush crotylation (scheme 3.10).\textsuperscript{147–150} Reacting aldehyde 3.45 with (Z)-crotylboronate 3.47\textsuperscript{150} provided homoallylic alcohol 3.48. \textsuperscript{1}H NMR spectroscopy analysis of crude product showed a modest 4:1 ratio of diastereomers, which is surprising due to the fact that reagent control matched substrate control to favor the product shown.\textsuperscript{151–153}

Figure 3.9: Rationalization for 1,3-anti products based on Evans' polar model\textsuperscript{153}
The observed diastereoselectivity could be explained by the Evans polar model (figure 3.9). This model minimizes electrostatic and steric repulsions to predict the outcome of a nucleophilic attack on a \( \beta \)-chiral aldehyde. According to this model, conformation B is disfavored because of dipole alignment, conformation C is disfavored because of torsional strain, while conformation A minimizes both factors resulting in a 1,3-anti product.

At this point, [4+2] cycloaddition reactions were attempted on homoallylic alcohol 3.48. Screening of a variety of Lewis acids (AlClMe\(_2\), AlCl\(_2\)Me, AlCl\(_3\), AlBr\(_3\), BF\(_3\)-OEt\(_2\), Sc(OTf)\(_3\), SnCl\(_4\)) provided either decomposition products or returned starting material. Heating 3.48 in a variety of solvents (toluene, xylenes, xylene and water, 1,2-dichlorobenzene, diglyme, trifluorotoluene) up to 400 °C, using heat baths and microwave irradiation also failed to produce cycloaddition products such as 3.49. To increase potential [4+2] reactivity, experiments were undertaken to form electron deficient homoallylic alcohol 3.50. I attempted to transform the terminal alkene of homoallylic alcohol 3.48 to an EWG by cross metathesis, oxidation, and hydroboration reactions, but this alkene appeared to be unreactive. Using more forcing conditions only increased decomposition rates.

![Scheme 3.11: Synthesis of oxazolidinone 3.53](image)
To synthesize an IMDA precursor with a more reactive dienophile, a second iteration was attempted using Evans syn aldol conditions (scheme 3.11).\textsuperscript{125} Once again starting with Nagao aldol product 3.43, the secondary alcohol was first protected as a TIPS ether before removing the chiral auxiliary with DibalH to afford aldehyde 3.51. The (Z)-boron enolate of oxazolidinone 3.52, reacted with aldehyde 3.51 to afford Evans aldol product, which was protected as TBS ether 3.53. \textsuperscript{154-156} Despite the modest yields, these steps added all the correct IMDA precursor substituents with correct configurations.

Scheme 3.12: Synthesis of second IMDA precursor 3.57 and attempted IMDA reaction

To transform the imide moiety of 3.53 into an alkene for an IMDA reaction, the chiral auxiliary was removed using lithium borohydride (scheme 3.12) and resulting alcohol 3.54 oxidized to aldehyde 3.55 using Dess-Martin periodinane (DMP).\textsuperscript{157,158} The mass of aldehyde 3.55
was confirmed by HRMS as well as displaying characteristic aldehyde resonances in $^1$H NMR (δ 9.63) and $^{13}$C NMR (δ 204.4) spectroscopy.

Aldehyde 3.55 was elaborated into a potential Diels-Alder substrate using Still-Gennari modified Horner-Wadsworth-Emmons (HWE) olefination conditions to provide unsaturated ester 3.57. Despite these conditions often favoring Z-alkene products, the reaction gave an intractable mixture of isomers that could not be fully characterized. Nonetheless, $^1$H NMR spectroscopy indicated formation of carbonyl-conjugated E and Z alkenes (δ 6.3 - 5.6, $J = 11 - 16$ Hz) and methyl esters (singlets at δ ~3.7), and MS showed a signal matching the mass of desired product 3.57, so I presumed that a mixture of E and Z isomers was synthesized. Ester 3.57 was reacted using thermal and Lewis acid conditions similar to those listed above for substrate 3.48 on page 64. Unfortunately, there was no sign of a cycloaddition product 3.58 under all conditions attempted so an even more reactive IMDA precursor was sought.

Scheme 3.13: Syntheses a) of enol silyl ether 3.63 and b) silyl ketene acetal 3.65

A more direct approach to synthesize α,β-unsaturated carbonyl compounds similar to ester 3.57 was desired so I began exploring vinylogous Mukaiyama aldol reactions (VMARs). To
this end, two known VMAR nucleophiles, enol silyl ether 3.63\textsuperscript{164} and silyl ketene acetal 3.65\textsuperscript{165} were synthesized according to reported procedures (scheme 3.13). TBS protection of (Z)-2-butene-1,4-diol 3.59, followed by DMP oxidation, Wittig olefination, and isomerization with cobalt catalyst 3.62 provided enol silyl ether 3.63. Synthesis of silyl ketene acetal 3.65 was more straightforward, using a one-pot procedure starting from methyl (E)-2-pentenoate 3.64. Stereochemistry of the γ,δ-alkene was important because studies indicated that a (Z)-γ,δ-alkene would react to preferentially form 1,2-syn products\textsuperscript{163,166}, which would be the desired outcome (scheme 3.14).

**Scheme 3.14: Rationalization for 1,2-syn outcome in a VMAR**

A recent study by Kalesse showed that using bulky Lewis acids (such as tris(pentafluorophenyl)borane) will more likely go through a syn-clinal transition state than an anti-periplanar transition state\textsuperscript{163,167}. Of the syn-clinal transition state possibilities, B is sterically disfavored due to interaction with the bulky Lewis acid. Favored transition state A provides the predicted 1,2-syn product 3.67.

Reacting VMAR nucleophiles enol silyl ether 3.63\textsuperscript{161,162} or silyl ketene acetal 3.65\textsuperscript{165} with aldehyde 3.45 (scheme 3.15) both yielded mixtures of isomers that were challenging to separate and characterize, but were largely identified by new signals in the \textsuperscript{1}H NMR spectra. The unsaturated aldehyde product 3.68 displayed characteristic aldehyde (δ 9.55) and conjugated,
trans-alkene \( \delta 6.89 \) (dd, \( J = 15.8, 7.2 \) Hz), \( 6.15 \) (ddd, \( J = 15.8, 7.8, 1.2 \) Hz)] resonances. The unsaturated methyl ester product 3.69 displayed characteristic methyl ester (singlet, \( \delta 3.75 \)) and conjugated, trans-alkene \( \delta 6.99 \) (dd, \( J = 15.8, 7.8 \) Hz), \( 5.87 \) (dd, \( J = 15.8, 1.2 \) Hz)] resonances. Literature precedent indicated that 1,2-syn and 1,3-anti stereochemistry should be the major outcomes\(^{166}\) (schemes 3.10 and 3.14), but neither was confirmed due to lack of material. Still, the primary goal at this point was to synthesize a decalin, so the IMDA precursors 3.68 and 3.69 were subjected to thermal and Lewis acid conditions similar to those listed above for substrate 3.48 page 64, and once again, no evidence of cycloaddition products 3.70 or 3.71 was observed. The only tractable product from all reactions attempted was from a retro-VMAR to resupply aldehyde 3.45.

\[
\begin{align*}
\text{Scheme 3.15: Synthesis of } \alpha,\beta\text{-unsaturated carbonyls for IMDA via VMARs}
\end{align*}
\]

With all these IMDA reaction attempts failing, I surmised that the methyl group at carbon-8 (3.68 or 3.69, scheme 3.15) was preventing the cycloaddition by sterically hindering the interaction between diene and dienophile. Thus, removing the C-8 methyl group could increase the chance of successful cycloaddition reactions.\(^{168-171}\)
Elaboration of aldehyde 3.37 to an IMDA precursor (scheme 3.16) proceeded in a similar manner to that described above. Olefination with stabilized Wittig reagent 3.72 formed unsaturated ester 3.73. A two-step reduction-oxidation procedure formed aldehyde 3.74 in good yield. Once again, Nagao aldol conditions were employed to add an acetate unit stereoselectively, after which TBS protection and removal of the chiral auxiliary gave aldehyde 3.76. This aldehyde was reacted with VMAR nucleophiles in a similar fashion to that shown in scheme 3.15, and once again, these reactions provided an intractable mixture of isomers. However, since they were all reasonable probes for IMDA reactivity, the diastereomers were left unseparated and once again subjected to IMDA reaction conditions listed above for substrate 3.48 page 64. Unfortunately, there was still no sign of cycloaddition reactivity under all attempted conditions.

These failures of linear substrates to undergo IMDA reactions prompted me to re-evaluate my strategy to elicit a cycloaddition reaction.
3.5 Synthesis of Macroyclic IMDA Precursor

3.5.1 Using the Total Synthesis of Superstolide A as Inspiration

After repeated indications that an IMDA reaction from a linear precursor would be challenging at best and impossible at worst (section 3.4), approach to the synthesis of an IMDA precursor was revised. A potential solution to the problem was inspired by the synthesis of superstolide A (3.81), which utilized a macrocyclic precursor that helped force diene/dienophile alignment, leading to a facile cycloaddition reaction to form a cis-decalin (scheme 3.17). This strategy could be adapted to the synthesis of nahuoic acid A, by first forming a macrocycle intermediate such as 3.83, that could come from a straight chain triene like 3.84. Modelling with Chem3D showed that macrocycle 3.83 had lower energy and higher π-orbital overlap compared to macrocycles formed with the other the alcohols on the polyol side chain. This retrosynthetic analysis was designed so that previously developed reactions and substrates could be re-used.
Scheme 3.18: Synthesis of aldehyde 3.88

The synthesis began with alcohol 3.40 (scheme 3.18). Removal of the TMS group gave free alkyne 3.85, that was used in a zirconium catalyzed carboalumination reaction to form diol 3.86 (details in scheme 3.19). Racemic benzyl glycidyl ether was chosen as the electrophilic quenching reagent because it was far cheaper than the enantioenriched starting material (ca. 30 times the cost for enantioenriched material).

Scheme 3.19: Mechanism for zirconium catalyzed carboalumination, quenching with an epoxide electrophile

According to work by Negishi\textsuperscript{173}, mixing zirconocene dichloride and trimethylaluminum creates a zirconium-aluminum complex where methyl and chloride ligands can rapidly interchange (scheme 3.19). This complex renders the aluminum electrophilic enough to bind to an alkyne, and subsequently undergo a migratory insertion to form a vinyl aluminum species (3.89). These vinyl
aluminum compounds can be isolated, and then subjected to \( n \)-butyl lithium to form an aluminate complex (3.90). These “ate” complexes are nucleophilic enough to add into epoxides, forming homoallylic alcohols (3.86).\textsuperscript{174–176}

Bis-TBS protection of diol 3.86 (scheme 3.18) followed by mono-deprotection with one equivalent of TBAF was found to be the optimal method for obtaining alcohol 3.87. Alcohol 3.87 was then oxidized to aldehyde 3.88 under Ley oxidation conditions.\textsuperscript{177,178}

Scheme 3.20: Attempted synthesis of a macrocyclic IMDA precursor

In continuing to build a macrocyclic IMDA precursor (scheme 3.20), 2-(3-bromopropyl)-1,3-dioxolane 3.92 was prepared from ethyl 4-bromobutanoate 3.91 via a known procedure.\textsuperscript{179} 2-(3-bromopropyl)-1,3-dioxolane 3.92 was then converted into the corresponding Grignard reagent and added to aldehyde 3.88 to provide Grignard addition product 3.93.

Forming the Grignard reagent was more challenging than expected. It would not form at concentrations less than 5 M. Furthermore, using 1,2-dibromoethane was the only method observed to sufficiently activate magnesium for this reaction. Initiation of the reaction also
required heating, yet once Grignard formation began, it was strongly exothermic, so switching to an ice bath with precise timing was required to prevent decomposition.

At this point, the goal was attachment of a pendant phosphonate to affect a HWE olefination reaction. Unfortunately, reactions to form phosphonate 3.94 either had low yields or were unsuccessful, so formation of macrocycle 3.95 was never achieved.

3.5.2 Using the Total Synthesis of Phomopsidin as Inspiration

Scheme 3.21: Retrosynthetic analysis of nahuoic acid A using synthesis of phomopsidin as inspiration

The total synthesis of phomopsidin (3.4) inspired another approach to a macrocyclic IMDA precursor (scheme 3.21). In the synthesis by Nakada, a trans-annular Diels-Alder (TADA) reaction of macrolactone 3.97 formed tricycle 3.96, with cis configuration across both ring junctions. The reaction occurred in 63% yield by refluxing macrocycle 3.97 in toluene for 24 hours, a fairly mild set of conditions. By analogy to this procedure, I hoped that macrocycle 3.99 could undergo a TADA reaction to form tricycle 3.98, which could be transformed into nahuoic acid A 3.8. The cyclization step to form macrocycle 3.99 could be a macrolactonization, a cross-coupling, or an olefination reaction.
3.5.2.1 Attempted Macrocyclization Through Lactonization

The initial strategy to synthesize macrocycle 3.99 envisioned cyclization through a macrolactonization step. Synthesis of a seco-acid began by transforming 4-pentyn-1-ol 3.100 to (E)-5-iodo-4-methyl-4-pentenal 3.101 using a known zirconium catalyzed carbometallation and oxidation protocol (scheme 3.22).

Ley oxidation conditions (TPAP, NMO) gave low yields (ca. 31%) due to the formation of side products. Using Swern oxidation conditions instead improved the yields of this reaction to 84%. (E)-5-iodo-4-methyl-4-pentenal 3.102 was then reacted with VMAR nucleophile 3.65 to afford vinyl iodide 3.103. 1H NMR analysis of the crude VMAR products showed only one diastereomer. This result agrees with research by Kalesse showing high 1,2-syn diastereoselectivity. Protection of the free alcohol on vinyl iodide 3.103 afforded protected vinyl iodide 3.104. Cross-coupling reactions were attempted on vinyl iodides 3.103 and 3.104, but only unprotected 3.103 showed promising reactivity. So, unprotected vinyl iodide 3.103 underwent Stille cross coupling with (Z)-3-(tributylstannyl)-2-buten-1-ol 3.106 (derived from 2-butyn-1-ol 3.105) to afford diene 3.107. Well dispersed vinyl protons in the

Scheme 3.22: Synthesis of macrolactonization precursor 3.107
$^1$H NMR spectrum ($\delta$ 6.98, 5.91, 5.67, and 5.49) allowed for easy characterization and confirmation of the cross-coupling reaction.

![H NMR spectrum](image)

Scheme 3.23: Saponification and attempted macrolactonization

To complete the macrolactonization, diene 3.107 was saponified to carboxylic acid 3.108, which was immediately subjected to well-established macrolactonization conditions.\textsuperscript{185–189} Unfortunately, these reactions gave no sign of having produced macrolactone 3.109.

3.5.2.2 Attempted Macrocyclization Through Cross-Coupling

![Scheme 3.24: Attempted Macrocyclization Through Cross-Coupling](image)

With the failure of the macrolactonization reactions, the next attempt to form macrocycle **3.99** was envisioned to occur via a cross-coupling reaction. This sequence began with vinyl iodide **3.103** (scheme 3.24). I hoped to avoid protection of the secondary alcohol because palladium cross-coupling reactions appeared more likely to succeed with a free alcohol (see scheme 3.22), but discovered that attempted esterification with EDCI formed lactone **3.110** in near quantitative yield.

Despite this undesired outcome, lactone **3.110** provided evidence of 1,2-syn configuration for the substituents on carbons 4 and 5. The coupling constants between hydrogen atoms on carbons 3, 4, and 5 were: $^3J_{H-C(3)-C(4)-H} = 6.1$ Hz and $^3J_{H-C(4)-C(5)-H} = 9.3$ Hz. Modelling 1,2-syn lactone **3.110** using Chem3D software shows the dihedral angle between hydrogen atoms on carbons 3 and 4 is $\sim 38^\circ$, while for hydrogen atoms on carbons 4 and 5 the dihedral angle is $\sim 47^\circ$. Modelling 1,2-anti lactone **3.111** shows hydrogen atoms on carbons 3 and 4 are nearly orthogonal ($\sim 84^\circ$), while hydrogen atoms on carbons 4 and 5 are nearly antiparallel ($\sim 171^\circ$). Using the Karplus equation $^{190}$, 1,2-syn lactone **3.110** would have coupling constants $^3J_{H-C(3)-C(4)-H} = 5 - 7$ Hz and $^3J_{H-C(4)-C(5)-H} = 8 - 10$ Hz, while 1,2-anti lactone **3.111** would have coupling constants $^3J_{H-C(3)-C(4)-H} = 1 - 3$ Hz and $^3J_{H-C(4)-C(5)-H} = 10 - 15$ Hz. These data helped confirm that the VMAR product **3.103** (scheme 3.22) had 1,2-syn configuration.

![Scheme 3.25: Attempted macrocyclization through Stille cross-coupling](image-url)
Instead of free alcohol 3.103, protected vinyl iodide 3.104 was saponified and then immediately reacted with (Z)-3-(tributylstannyl)-2-buten-1-ol 3.106 in the presence of EDCI to form ester 3.112. Unfortunately, macrocyclization through a Stille cross-coupling reaction was unsuccessful under all conditions attempted, even when using Stille coupling “enhancements”\textsuperscript{191–194} such as Cu(I), Cl\textsuperscript{−}, or F\textsuperscript{−} (table 3.2).

**Table 3.2: Conditions for attempted Stille coupling reactions on ester 3.112 to form macrocycle 3.113**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Additive(s)</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4}</td>
<td>THF</td>
<td>-</td>
<td>80</td>
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<tr>
<td>2</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4}</td>
<td>DMF</td>
<td>-</td>
<td>r.t.</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4}</td>
<td>DMF</td>
<td>-</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4}</td>
<td>DMF</td>
<td>CuI, CsF</td>
<td>r.t.</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4}</td>
<td>DMF</td>
<td>CuI, CsF</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4}</td>
<td>DMF</td>
<td>CuI, LiCl</td>
<td>r.t.</td>
</tr>
<tr>
<td>7</td>
<td>Pd(PPh\textsubscript{3})\textsubscript{4}</td>
<td>DMF</td>
<td>CuI, LiCl</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>Pd\textsubscript{2}(dba)\textsubscript{3}·CHCl\textsubscript{3}</td>
<td>DMF</td>
<td>CsF</td>
<td>r.t.</td>
</tr>
<tr>
<td>9</td>
<td>Pd\textsubscript{2}(dba)\textsubscript{3}·CHCl\textsubscript{3}</td>
<td>DMF</td>
<td>CsF</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>Pd\textsubscript{2}(dba)\textsubscript{3}·CHCl\textsubscript{3}</td>
<td>DMF</td>
<td>AsPh\textsubscript{3}</td>
<td>r.t.</td>
</tr>
<tr>
<td>11</td>
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<td>DMF</td>
<td>AsPh\textsubscript{3}</td>
<td>80</td>
</tr>
<tr>
<td>12</td>
<td>Cu(TC)</td>
<td>NMP</td>
<td>-</td>
<td>r.t.</td>
</tr>
</tbody>
</table>
3.5.2.3 Attempted Macrocyclization Through Olefination

With the failure of the Stille cross-coupling reactions, the next attempt to form macrocycle 3.99 was envisioned to occur through a HWE olefination reaction (scheme 3.26). This approach began with an Evans syn aldol reaction between oxazolidinone 3.52 and (E)-5-iodo-4-methyl-4-pentenal 3.102 followed by TBS protection of the secondary alcohol providing syn aldol product 3.114. Removing the chiral auxiliary with lithium borohydride provided primary alcohol 3.115, which was protected with 3,4-dihydro-2H-pyran to give acetal 3.116. While the tetrahydropyran was installed in high yield and was robust towards later transformations, it created an inseparable mixture of diastereomers that made spectra messy and characterization by NMR difficult. Nevertheless, acetal 3.116 underwent smooth palladium-free Stille coupling to afford diene 3.117, confirmed by HRMS. The primary alcohol on diene 3.117 was coupled with diethylphosphonoacetic acid to afford phosphonate 3.118. Its identity was confirmed by HRMS as well as a single, clean $^{31}$P NMR spectroscopy signal ($\delta$ 20.3).

Scheme 3.26: Synthesis of phosphonate 3.118
Scheme 3.27: Attempted removal of tetrahydropyran protecting group

Removal of the THP protecting group on 3.118 and isolation of primary alcohol 3.119 proved challenging. Standard THP cleavage conditions\textsuperscript{195} of stirring in ethanol with a catalytic amount of PPTS (scheme 3.27) partially removed the THP group (confirmed by MS), but the free alcohol 3.119 decomposed quickly and was never successfully isolated. Removal of the THP was attempted by several standard conditions\textsuperscript{196} but all were unsuccessful. Most of the reactions failed due to decomposition to intractable mixtures. This indicated that alcohol 3.119 might not be a stable compound.

3.5.2.4 Attempting Macrocyclization With a Minimally Functionalized Carbon Skeleton

Scheme 3.28: Selected steps from Nakada’s synthesis of phomopsidin\textsuperscript{180}
With all of the above macrocyclization reactions failing, I decided to follow the phomopsidin 3.4 synthesis more closely, using the minimum number of appendages attached to the carbon skeleton. In this way, I would build the macrocycle first, and functionalize it afterwards.

Scheme 3.28 shows the relevant parts of the total synthesis of phomopsidin. Using (S)-3-hydroxy-2-methylpropionate 3.120 as a starting material, (S)-5-methyltetrahydro-2H-pyran-2-one 3.121 could be synthesized in 5 steps. Following this, the lactone was transformed in Weinreb amide 3.122 with the primary alcohol protected as an ethoxyethyl ether. Addition of lithium (trimethylsilyl)acetylide to Weinreb amide 3.122, followed by diastereoselective reduction, alkyne deprotection, and alcohol protection gave TIPS protected propargyl alcohol 3.123. Hydroboration and Suzuki cross coupling followed by ester reduction provided allylic alcohol 3.124. This alcohol could be coupled with diethylphosphonoacetic acid, and then a sequence of ethoxyethyl ether protecting group removal, DMP oxidation, and HWE olefination at low concentration provided macrocycle 3.97. As stated above, this macrocycle could form tricycle 3.96 by refluxing in toluene.

Starting with (S)-5-methyltetrahydro-2H-pyran-2-one 3.121 would result in an epimer of nahuoic acid A, if transformed completely into the natural product (refer to structures of the natural products in scheme 3.21). Instead, to simplify the phomopsidin model as much as possible, tetrahydro-2H-pyran-2-one 3.125 was used as a starting material instead of (R)-5-methyltetrahydro-2H-pyran-2-one.

Opening of tetrahydro-2H-pyran-2-one 3.125 with N,O-dimethylhydroxylamine gave known Weinreb amide 3.126\textsuperscript{197} that could be protected as an ethoxyethyl ether to give Weinreb amide 3.127 (scheme 3.29). Once again, acetal protection led to messy spectra due to mixtures of diastereomers. Addition of lithium (trimethylsilyl)acetylide to Weinreb amide 3.127, followed by reduction, alkyne deprotection, and alcohol protection gave TIPS protected propargyl alcohol
3.128. While the synthesis of phomopsidin used a diastereoselective reduction, I wanted to keep
the study simple, so I used a racemic reduction with sodium borohydride instead. One benefit of
this procedure was that it also removed the alkynyl TMS protecting group in one step. TIPS
protected propargyl alcohol 3.128 underwent hydroboration, Suzuki cross coupling, and DIBALH
reduction to provide allylic alcohol 3.129. Coupling of this alcohol with diethylphosphonoacetic
acid using EDCI (instead of CBr$_4$/PPh$_3$) led to phosphonate 3.130 in good yield.

![Scheme 3.29: Synthesis of macrocyclization precursor mimicking steps used in the synthesis of
phomopsidin](image)

After this synthesis of phosphonate 3.130, reactions did not proceed as expected. Ethoxyethyl
removal with PPTS in ethanol caused significant decomposition. DMP oxidation gave
an insoluble, gooey product that was difficult to purify. Macrocyclization through olefination
attempts on this product (KHMDS in THF, or KHMDS and 18-c-6 in THF, or NaH in THF, or
KO'Bu in THF) mostly led to decomposition. The most promising results came from stirring in
acetonitrile (0.005 M) with DBU and lithium chloride.\textsuperscript{189,198} \textsuperscript{1}H NMR analysis of the crude reaction mixture showed olefination products, but mass spectrometry soon revealed the reaction had created minimal amounts of macrocycle \textbf{3.131} and a significant amount of diolide \textbf{3.132}. The two products were inseparable so macrocycle \textbf{3.131} could not be isolated or purified. In the hope that a cycloaddition reaction could occur across the diolide, this mixture was stirred in refluxing toluene, but this only led to decomposition.

From these results, I concluded that each substituent on structure \textbf{3.97} was absolutely vital to the successful TADA reaction to form intermediate \textbf{3.96} in the total synthesis of phomopsidin (scheme 3.21). This indicated that synthesis of tricycle \textbf{3.99} via a route inspired by the total synthesis of phomopsidin was disfavored, at best.

\section*{3.6 Analysis of Results and Restructuring of the Hypothesis}

Formation of \textit{cis}-decalin by a late stage Diels-Alder reaction had proved far more challenging than initially expected. Straight-chain precursors now seemed unlikely to fold in a way to create useful diene/dienophile interactions. Macrocycles that could force diene/dienophile interactions were difficult to synthesize, possibly due to strain. Even when mimicking a known procedure to form a macrocycle, results showed that substituents needed to exist in the correct orientation for a chance at success. Clearly, a new approach was needed.

Instead of using route where substituents were added early and \textit{cis}-decalin formation was late, an inverse approach was devised whereby a \textit{cis}-decalin was formed early in the synthesis and the substituents added afterwards. The details of these results can be found in chapter 4.
3.7 Experimental

General experimental (see Appendix A)

\((R)-4\text{-Benzyl-3-}((2R,3S)\text{-3-hydroxy-2,4-dimethylpentanoyl})\text{oxazolidin-2-one (3.28)}\)

\((R)-4\text{-Benzyl-3-}((2R,3S)\text{-3-hydroxy-2,4-dimethylpentanoyl})\text{oxazolidin-2-one (3.28)}\) was prepared by the methods of Evans.\(^{128,129}\) All \(^1\text{H NMR}\) and \(^{13}\text{C NMR}\) spectroscopic data matched reported values.

**Weinreb amide 3.133**

\(\text{Weinreb amide 3.133 was prepared by the methods of Evans.}^{128}\) All \(^1\text{H NMR}\) and \(^{13}\text{C NMR}\) spectroscopic data matched reported values.

**Silyl protected Weinreb amide 3.134**

\(\text{Silyl protected Weinreb amide 3.134 was prepared by the methods of Evans.}^{128}\) All \(^1\text{H NMR}\) and \(^{13}\text{C NMR}\) spectroscopic data matched reported values.
(2R,3S)-3-((tert-Butyldimethylsilyl)oxy)-2,4-dimethylpentanal (3.29)

(2R,3S)-3-((tert-Butyldimethylsilyl)oxy)-2,4-dimethylpentanal (3.29) was prepared by the methods of Evans. All \(^1\)H NMR and \(^{13}\)C NMR spectroscopic data matched reported values.

Silyl protected oxazolidinone 3.135

Silyl protected oxazolidinone 3.135 was prepared by the methods of Evans. All \(^1\)H NMR and \(^{13}\)C NMR spectroscopic data matched reported values.

(2S,3S)-3-((tert-Butyldimethylsilyl)oxy)-2,4-dimethylpentan-1-ol (3.136)

(2S,3S)-3-((tert-Butyldimethylsilyl)oxy)-2,4-dimethylpentan-1-ol (3.136) was prepared by the methods of Evans. All \(^1\)H NMR and \(^{13}\)C NMR spectroscopic data matched reported values.
(2R,3S)-3-((tert-Butyldimethylsilyl)oxy)-2,4-dimethylpentanal (3.29)

To a solution of (2S,3S)-3-((tert-butyldimethylsilyl)oxy)-2,4-dimethylpentan-1-ol (3.136) (125 mg, 0.51 mmol) in CH₂Cl₂ (5 mL) was added NaHCO₃ (213 mg, 2.5 mmol) and Dess-Martin periodinane (280 mg, 0.66 mmol). The mixture was stirred at room temperature for 3 hours before being filtered through a bed of silica gel, washing with solvent (3 x 5 mL 10:1 hexanes/diethyl ether). The collected solution was concentrated in vacuo to afford (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2,4-dimethylpentanal (3.29) (105 mg, 0.43 mmol, 84%) as a clear oil. All ¹H NMR and ¹³C NMR spectroscopic data matched reported values.¹²⁸

(2R,3S)-3-((tert-Butyldimethylsilyl)oxy)-2,4-dimethylpentanoic acid (3.137)

(2R,3S)-3-((tert-Butyldimethylsilyl)oxy)-2,4-dimethylpentanoic acid (3.137) was prepared by the methods of Evans¹²⁸,¹⁹⁹ All ¹H NMR and ¹³C NMR spectroscopic data matched reported values.
Silyl protected Weinreb amide 3.134

To a solution of crude (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2,4-dimethylpentanoic acid (3.137) (5.0 g, 19 mmol) in CH₂Cl₂ (110 mL) was added carbonyl diimidazole (3.0 g, 19 mmol) while stirring at 0 °C. The solution was stirred for 3 hours before addition of N,O-dimethylhydroxylamine hydrochloride (3.6 g, 38 mmol). The resulting mixture was stirred for 16 hours while warming to room temperature. The reaction was quenched with H₂O (50 mL) and the aqueous layer extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, and then concentrated in vacuo. The resulting residue was chromatographed on silica gel (5:1 to 2:1 hexanes/diethyl ether) to afford silyl protected Weinreb amide 3.134 (1.81 g, 6.0 mmol, 20% over 2 steps) as a clear oil.

Data for 3.134 matched that reported by Evans.¹²⁸

(4R,5S,6S)-6-((tert-Butyldimethylsilyl)oxy)-5,7-dimethyloct-1-en-4-ol (3.30)

To a solution of (2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2,4-dimethylpentanal (3.29) (100 mg, 0.41 mmol) in THF (5 mL) was added allylmagnesium chloride (0.42 mL, 1.0 M in Et₂O, 0.42 mmol) was added dropwise while stirring at -78 °C. After the mixture was stirred for 1 h, the reaction was quenched with saturated aqueous ammonium hydroxide (10 mL), and the solution
was warmed to room temperature. The mixture was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (25:1 hexanes/diethyl ether) to afford major diastereomer 3.30 (72 mg, 0.25 mmol, 61%) and minor diastereomer 3.30a (23 mg, 0.08 mmol, 19%), both as clear oils.

Data for the products matched that reported by Evans.¹²⁸

**Epoxides 3.31 and 3.31a**

To a solution of (4R,5S,6S)-6-((tert-butyldimethylsilyl)oxy)-5,7-dimethyloct-1-en-4-ol (3.30) (600 mg, 2.1 mmol) in CH₂Cl₂ (18 mL) was added meta-perchlorobenzoic acid (620 mg, 2.5 mmol) and the solution was stirred at room temperature for 16 hours. The reaction was quenched with saturated aqueous sodium thiosulfate (10 mL) and the aqueous layer extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (10 mL) and brine (10 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 hexanes/ethyl acetate) to afford diastereomer 3.31 (266 mg, 0.88 mmol, 42%) and diastereomer 3.31a (252 mg, 0.84 mmol, 40%), both as clear oils.

Data for 3.31: IR ν 3464, 2957, 2858, 836 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₁₆H₃₄O₃Si m/z 325.2175 [M-Na]+, found 325.2177; ¹H NMR (300 MHz, CDCl₃) δ 3.87 (td, J = 9.4, 3.6 Hz, 1H), 3.59 (dd, J = 4.9, 3.3 Hz, 1H), 3.17 - 3.05 (m, 1H), 2.81 (dd, J = 4.9, 4.1 Hz, 1H), 2.56 (dd, J =
4.9, 2.8 Hz, 1H), 2.36 (br. s, 1H), 1.94 - 1.77 (m, 2H), 1.67 (tq, J = 7.0, 3.4 Hz, 1H), 1.49 (ddd, J = 14.4, 6.8, 3.5 Hz, 1H), 0.95 - 0.85 (m, 18H), 0.09 (s, 3H), 0.07 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 79.9, 72.7, 50.6, 47.3, 40.6, 38.0, 33.1, 26.3, 19.1, 18.9, 18.6, 9.0, -3.2, -3.9

Data for 3.31a: IR $\nu$ 3464, 2957, 2858, 835 cm$^{-1}$; HRMS (ESI) Anal. Calcd. for C$_{16}$H$_{34}$O$_3$Si $m/z$ 325.2175 [M-Na]$^+$, found 325.2177; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.85 (dt, $J = 8.9, 3.9$ Hz, 1H), 3.55 (t, $J = 4.1$ Hz, 1H), 3.04 (dtd, $J = 6.8, 4.2, 2.8$ Hz, 1H), 2.75 (dd, $J = 4.8, 4.2$ Hz, 1H), 2.49 (dd, $J = 5.0, 2.7$ Hz, 1H), 2.39 (br. s, 1H), 1.92 - 1.52 (m, 4H), 0.94 - 0.83 (m, 18H), 0.05 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 79.2, 72.9, 50.9, 46.8, 40.8, 38.0, 32.9, 26.3, 19.3, 18.5, 18.5, 9.4, -3.3, -3.9

**Diol 3.138**

![Diol 3.138](image)

To a solution of silyl protected epoxide 3.31 (387 mg, 1.2 mmol) in THF (12 mL) was added tetrabutylammonium fluoride (1.4 mL, 1.0 M in THF, 1.4 mmol) while stirring at 0 °C. The solution was stirred for 2 hours while warming to room temperature. The reaction was quenched with H$_2$O (20 mL) and the aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (2:1 hexanes/ethyl acetate) to afford diol 3.138 (234 mg, 1.2 mmol, 97%) as a clear oil.

Data for 3.138: IR $\nu$ 3390, 2962, 969 cm$^{-1}$; HRMS (ESI) Anal. Calcd. for C$_{10}$H$_{20}$O$_3$ $m/z$ 211.1310 [M-Na]$^+$, found 211.1307; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.02 (ddd, $J = 9.4, 3.6, 1.9$ Hz, 1H), 3.56
To a solution of silyl protected epoxide 3.31a (285 mg, 0.94 mmol) in THF (10 mL) was added tetrabutylammonium fluoride (1.0 mL, 1.0 M in THF, 1.0 mmol) while stirring at 0 °C. The solution was stirred for 2 hours while warming to room temperature. The reaction was quenched with H₂O (20 mL) and the aqueous layer extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (2:1 hexanes/ethyl acetate) to afford diol 3.138a (160 mg, 0.85 mmol, 90%) as a clear oil.

Data for 3.138a: IR ν 3389, 2963, 970 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₁₀H₂₀O₃ \( m/z \) 211.1310 [M-Na]⁺, found 211.1312; \(^1\)H NMR (300 MHz, CDCl₃) δ 4.02 (ddd, \( J = 7.4, 5.7, 2.1 \) Hz, 1H), 3.40 (br. s, 1H), 3.35 (dd, \( J = 9.2, 2.1 \) Hz, 1H), 3.07 - 2.96 (m, 1H), 2.74 (dd, \( J = 4.6, 4.1 \) Hz, 1H), 2.49 (dd, \( J = 4.9, 2.6 \) Hz, 1H), 1.77 - 1.56 (m, 4H), 0.95 (d, \( J = 6.7 \) Hz, 3H), 0.85 (d, \( J = 7.2 \) Hz, 3H), 0.78 (d, \( J = 6.9 \) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl₃) δ 82.9, 75.2, 50.8, 46.9, 38.3, 37.8, 31.5, 19.7, 19.0, 4.6
To a solution of diol 3.138 (234 mg, 1.2 mmol) in CH$_2$Cl$_2$ (10 mL) was added 2,2-dimethoxypropane (0.5 mL, 4.1 mmol) and a catalytic amount of para-toluenesulfonic acid (5 mg, 0.03 mmol). The solution was stirred for 12 hours at room temperature before being concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 hexanes/diethyl ether) to afford diol 3.25 (278 mg, 1.2 mmol, 98%) as a clear oil.

Data for 3.25: IR $\tilde{\nu}$ 2960, 1201, 1010 cm$^{-1}$; HRMS (ESI) Anal. Calcd. for C$_{13}$H$_{24}$O$_3$ $m/z$ 251.1623 [M-Na]$^+$, found 251.1629; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.09 (ddd, $J = 9.3, 3.5, 2.4$ Hz, 1H), 3.33 (dd, $J = 9.6, 2.2$ Hz, 1H), 3.04 (dt, $J = 7.5, 3.2$ Hz, 1H), 2.77 (dd, $J = 4.9, 4.1$ Hz, 1H), 2.48 (dd, $J = 5.0, 2.7$ Hz, 1H), 1.93 (ddd, $J = 14.2, 9.4, 3.3$ Hz, 1H), 1.75 - 1.60 (m, 1H), 1.47 (qt, $J = 6.8, 2.3$ Hz, 1H), 1.41 (s, 3H), 1.38 (s, 3H), 1.28 - 1.17 (m, 1H), 0.93 (d, $J = 6.4$ Hz, 3H), 0.82 (d, $J = 6.7$ Hz, 3H), 0.78 (d, $J = 6.7$ Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 99.1, 79.5, 71.6, 50.1, 47.4, 37.0, 33.6, 30.2, 29.4, 19.9, 19.8, 17.6, 4.9

To a solution of diol 3.138a (160 mg, 0.85 mmol) in CH$_2$Cl$_2$ (10 mL) was added 2,2-dimethoxypropane (0.5 mL, 4.1 mmol) and a catalytic amount of p-toluenesulfonic acid (5 mg,
0.03 mmol). The solution was stirred for 12 hours at room temperature before being concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 hexanes/diethyl ether) to afford diol 3.25a (188 mg, 0.83 mmol, 97%) as a clear oil.

Data for 3.25a: IR ν 2960, 1201, 1010 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₁₃H₂₄O₃ m/z 251.1623 [M-Na]+, found 251.1623; ¹H NMR (300 MHz, CDCl₃) δ 3.97 (ddd, J = 7.9, 5.4, 2.3 Hz, 1H), 3.30 (dd, J = 9.5, 2.1 Hz, 1H), 3.03 - 2.92 (m, 1H), 2.72 (dd, J = 5.2, 4.1 Hz, 1H), 2.52 (dd, J = 5.1, 2.8 Hz, 1H), 1.82 (ddd, J = 14.1, 8.2, 5.4 Hz, 1H), 1.74 - 1.54 (m, 2H), 1.49 (qt, J = 6.8, 2.1 Hz, 1H), 1.37 (s, 3H), 1.36 (s, 3H), 0.91 (d, J = 6.4 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H), 0.77 (d, J = 6.7 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 99.0, 79.4, 70.5, 49.6, 47.0, 35.5, 32.9, 30.1, 29.4, 19.9, 19.7, 17.5, 4.9

**Acetonide 3.32**

To a solution of silyl protected epoxide 3.31 (8 mg, 0.03 mmol) in Et₂O (2 mL) was added lithium aluminum hydride (2 mg, 0.05 mmol) while stirring at 0 °C. The solution was stirred for 2 hours while warming to room temperature. The reaction was carefully quenched with H₂O dropwise, until effervescence had ceased. The mixture was dried with MgSO₄, filtered, and concentrated in vacuo. To the resulting residue, dissolved in CH₂Cl₂ (2 mL), was added 2,2-dimethoxypropane (0.15 mL, 1.2 mmol) and para-toluenesulfonic acid (5 mg, 0.03 mmol). The solution was stirred for 12 hours at room temperature before being concentrated in vacuo. The resulting residue was filtered through a silica gel plus (2:1 hexanes/diethyl ether eluent) to afford crude acetonide 3.32.
Data for 3.32: HRMS (ESI) Anal. Calcd. for C_{19}H_{40}O_{3}Si m/z 367.2644 [M-Na]^+, found 367.2641; 

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.91 (td, \(J = 9.2, 6.2\) Hz, 1H), 3.66 (dt, \(J = 8.8, 6.4\) Hz, 1H), 3.37 (dd, \(J = 5.9, 2.3\) Hz, 1H), 1.83 - 1.51 (m, 4H), 1.33 (d, \(J = 4.9\) Hz, 6H), 1.19 (d, \(J = 6.2\) Hz, 3H), 0.96 - 0.84 (m, 18H), 0.07 (s, 3H), 0.05 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 100.4, 76.4, 67.6, 63.0, 41.5, 39.5, 33.5, 30.6, 29.9, 26.4, 25.1, 24.7, 22.0, 19.6, 19.4, 18.8, 10.7, -3.5, -3.5

**Acetonide 3.32a**

\[ \begin{array}{c}
\text{OH} \\
\text{O} \\
\text{OH} \\
\text{OTBS} \\
\end{array} \quad \longrightarrow \quad \begin{array}{c}
\text{OH} \\
\text{O} \\
\text{OH} \\
\text{OTBS} \\
\end{array} \quad \longrightarrow \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{OTBS} \\
\end{array}
\]

To a solution of silyl protected epoxide 3.31a (8 mg, 0.03 mmol) in Et\(_2\)O (2 mL) was added lithium aluminum hydride (2 mg, 0.05 mmol) while stirring at 0 °C. The solution was stirred for 2 hours while warming to room temperature. The reaction was carefully quenched with H\(_2\)O dropwise, until effervescence had ceased. The mixture was dried with MgSO\(_4\), filtered, and concentrated \textit{in vacuo}. To the resulting residue, dissolved in CH\(_2\)Cl\(_2\) (2 mL), was added 2,2-dimethoxypropane (0.15 mL, 1.2 mmol) and \(p\)-toluenesulfonic acid (5 mg, 0.03 mmol). The solution was stirred for 12 hours at room temperature before being concentrated \textit{in vacuo}. The resulting residue was filtered through a silica gel plus (2:1 hexanes/diethyl ether eluent) to afford crude acetonide 3.32a.

Data for 3.32a: HRMS (ESI) Anal. Calcd. for C_{19}H_{40}O_{3}Si m/z 367.2644 [M-Na]^+, found 367.2640; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.95 (dqd, \(J = 11.6, 6.0, 1.0\) Hz, 1H), 3.73 (ddd, \(J = 11.5, 7.2, 2.3\) Hz, 1H), 3.43 (dd, \(J = 5.8, 2.7\) Hz, 1H), 1.83 - 1.70 (m, 1H), 1.66 - 1.48 (m, 3H), 1.40 (d, \(J = 8.2\) Hz, 6H), 1.18 (d, \(J = 6.2\) Hz, 3H), 0.95 - 0.83 (m, 18H), 0.05 (s, 3H), 0.04 (s, 3H); \(^{13}\)C
NMR (75 MHz, CDCl$_3$) δ 98.6, 76.8, 70.8, 65.4, 41.6, 37.2, 33.0, 30.6, 30.5, 29.9, 26.4, 22.7, 20.1, 19.7, 19.3, 18.7, 10.3, -3.5, -3.5

\[(E)-3\text{-Iodo-2-methylprop-2-en-1-ol (3.34)}\]

\[(E)-3\text{-Iodo-2-methylprop-2-en-1-ol (3.34)}\] was prepared by the methods of Menche.$^{136}$ All $^1$H NMR and $^{13}$C NMR spectroscopic data matched reported values.

\[(E)-3\text{-Iodo-2-methylprop-2-en-1-ol (3.34)}\]

\[(E)-3\text{-Iodo-2-methylprop-2-en-1-ol (3.34)}\] was prepared by the methods of Menche.$^{136}$ All $^1$H NMR and $^{13}$C NMR spectroscopic data matched reported values.

\[(E)-2\text{-Methyl-5-(trimethylsilyl)pent-2-en-4-yn-1-ol (3.140)}\]

\[(E)-2\text{-Methyl-5-(trimethylsilyl)pent-2-en-4-yn-1-ol (3.140)}\] was prepared by the methods of Motozaki.$^{139}$ All $^1$H NMR and $^{13}$C NMR spectroscopic data matched reported values.
(E)-2-Methyl-5-(trimethylsilyl)pent-2-en-4-ynal (3.37)

(E)-2-Methyl-5-(trimethylsilyl)pent-2-en-4-ynal (3.37) was prepared by the methods of Yoshino.\textsuperscript{141} All $^1$H NMR and $^{13}$C NMR spectroscopic data matched reported values.

**Ester 3.39**

To a stirring solution of aldehyde 3.37 (1.50 g, 9.0 mmol) in THF (100 mL) was added ylide 3.38 (3.72 g, 10.3 mmol). The mixture was then heated to 50 °C for 4 h and then cooled back to room temperature. A white solid was removed by filtration and the filtrate concentrated \textit{in vacuo}. The resulting residue was chromatographed on silica gel (10:1 hexanes/diethyl ether) to afford ester 3.39 (2.06 g, 8.2 mmol, 91%) as a clear oil.

Data for 3.39: IR ν 2961, 2130, 1706, 1248, 842 cm\textsuperscript{-1}; HRMS (ESI) Anal. Calcd. for C\textsubscript{14}H\textsubscript{22}O\textsubscript{2}Si m/z 273.1287 [M-Na]\textsuperscript{+}, found 273.1286; $^1$H NMR (300 MHz, CDCl\textsubscript{3}) δ 7.11 (s, 1H), 5.66 (s, 1H), 4.22 (q, $J = 7.1$ Hz, 2H), 2.13 (s, 3H), 2.05 (d, $J = 1.2$ Hz, 3H), 1.31 (t, $J = 7.1$ Hz, 3H), 0.22 (s, 9H)
Allylic alcohol 3.40

To a solution of ester 3.39 (1.70 g, 6.8 mmol) in toluene (60 mL) stirring at -78 °C was added diisobutylaluminum hydride (14.2 mL, 14.2 mmol, 1.0 M in hexanes). The solution was stirred for 90 minutes before quenching with methanol (5 mL) and Rochelle’s salt (20 mL, sat.). The aqueous phase was extracted with Et₂O (2 x 30 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (5:1 to 1:1 hexanes/diethyl ether) to afford alcohol 3.40 (1.34 g, 6.4 mmol, 95%) as a clear oil.

Data for 3.40: HRMS (ESI) Anal. Calcd. for C₁₂H₂₀OSi m/z 231.1181 [M-Na]+, found 231.1180; ¹H NMR (300 MHz, CDCl₃) δ 5.97 (s, 1H), 5.44 (s, 1H), 4.06 (s, 2H), 2.08 (s, 3H), 1.85 (s, 3H), 1.49 (br. s, 1H), 0.21 (s, 9H)

(2E,4E)-2,4-Dimethyl-7-(trimethylsilyl)hepta-2,4-dien-6-ynal (3.41)

To a stirring solution of allylic alcohol 3.40 (1.088 g, 5.2 mmol) in Et₂O (60 mL) was added manganese dioxide (2.27 g, 26.1 mmol). The mixture was stirred at room temperature for 16 h before filtering through celite. The filtrate was concentrated in vacuo and the resulting residue chromatographed on silica gel (15:1 hexanes/diethyl ether) to afford (2E,4E)-2,4-dimethyl-7-
(trimethylsilyl)hepta-2,4-dien-6-ynal (3.41) (777 mg, 3.7 mmol, 72%) as a clear oil which turned into a white solid when placed in a freezer.

Data for 3.41: HRMS (ESI) Anal. Calcd. for C_{12}H_{18}OSi m/z 229.1025 [M-Na]^+, found 229.1027; 1H NMR (300 MHz, CDCl$_3$) δ 9.40 (s, 1H), 6.71 (s, 1H), 5.82 (s, 1H), 2.22 (s, 3H), 1.97 (s, 3H), 0.21 (s, 9H); 13C NMR (75 MHz, CDCl$_3$) δ 195.5, 151.1, 146.6, 138.6, 117.5, 106.3, 102.6, 19.3, 11.1, 0.0

**Thiazolidinethione 3.43**

![Chemical Structure](image)

To a solution of tin (II) trifluoromethanesulfonate (242 mg, 0.58 mmol) in CH$_2$Cl$_2$ (5 mL) stirring at -45 °C was slowly added 1-ethylpiperidine (80 µL, 0.58 mmol) followed by thiazolidinethione 3.42 (100 mg, 0.48 mmol). This solution was stirred at this temperature for 4 h before addition of aldehyde 3.41 (100 mg, 0.48 mmol) dissolved in CH$_2$Cl$_2$ (2 mL). This solution was stirred for 90 minutes before the reaction was quenched with water (10 mL). The aqueous layer was extracted with Et$_2$O (3 x 5 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The resulting residue was chromatographed on silica gel (10:1 to 1:1 hexanes/diethyl ether) to afford desired thiazolidinethione 3.43 (116 mg, 0.29 mmol, 59%) and undesired thiazolidinethione 3.43a (2.0 mg, 0.005 mmol, 1%), both as yellow oils. A third fraction contained starting aldehyde 3.41 (30 mg, 30%).
Data for 3.43: IR ν 3402, 2961, 2128, 1690, 839 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₂₀H₃₁NO₂SiS₂ m/z 432.1463 [M-Na]⁺, found 432.1458; ¹H NMR (300 MHz, CDCl₃) δ 6.02 (s, 1H), 5.42 (s, 1H), 5.11 (t, J = 6.6 Hz, 1H), 4.57 (dd, J = 9.4, 2.1 Hz, 1H), 3.58 (dd, J = 17.4, 2.7 Hz, 1H), 3.50 (dd, J = 11.5, 7.9 Hz, 1H), 3.35 (dd, J = 17.4, 9.3 Hz, 1H), 3.02 (dd, J = 11.5, 0.8 Hz, 1H), 2.86 (br. s, 1H), 2.35 (sxt, J = 6.8 Hz, 1H), 2.04 (s, 3H), 1.84 (s, 3H), 1.05 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 7.1 Hz, 3H), 0.18 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 203.2, 172.7, 148.2, 139.1, 127.7, 109.9, 103.6, 100.8, 73.5, 71.7, 44.0, 31.0, 30.9, 20.3, 19.2, 18.0, 14.8, 0.2

Data for 3.43a: IR ν 3401, 2961, 2129, 1690, 840 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₂₀H₃₁NO₂SiS₂ m/z 432.1463 [M-Na]⁺, found 432.1461; ¹H NMR (300 MHz, CDCl₃) δ 6.01 (s, 1H), 5.43 (s, 1H), 5.17 (ddd, J = 7.6, 7.1, 0.9 Hz, 1H), 4.48 (dd, J = 9.4, 2.1 Hz, 1H), 3.64 (dd, J = 17.0, 9.7 Hz, 1H), 3.52 (dd, J = 11.5, 7.9 Hz, 1H), 3.36 (dd, J = 17.0, 2.9 Hz, 1H), 3.36 (br. s, 1H), 3.04 (dd, J = 11.4, 1.1 Hz, 1H), 2.36 (qd, J = 13.5, 6.8 Hz, 1H), 2.05 (d, J = 0.9 Hz, 3H), 1.86 (d, J = 1.1 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.20 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 203.4, 173.4, 148.3, 139.0, 128.0, 110.0, 103.6, 100.9, 74.3, 71.7, 43.8, 31.0, 30.9, 20.4, 19.3, 18.0, 14.7, 0.3, 0.2

TBS protected thiazolidinethione 3.44

![Diagram](image)

To a solution of thiazolidinethione 3.43 (71 mg, 0.17 mmol) in CH₂Cl₂ (5 mL) stirring at 0 °C was added 2,6-lutidine (100 µL, 0.87 mmol) followed by tert-butyldimethylsilyl...
trifluoromethanesulfonate (42 μL, 0.18 mmol). This solution was stirred at this temperature for 1 h before being concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 hexanes/diethyl ether) to afford protected thiazolidinethione 3.44 (90 mg, 0.17 mmol, 99%) as a yellow oil.

Data for 3.44: IR ν 2957, 2128, 1698, 836 cm⁻¹; HRMS (ESI) Anal. Calcd. for C_{26}H_{45}NO_{2}Si_{2}S_{2} m/z 546.2328 [M-Na]⁺, found 546.2324; ¹H NMR (300 MHz, CDCl₃) δ 5.93 (s, 1H), 5.40 (s, 1H), 4.98 (t, J = 6.9 Hz, 1H), 4.64 (dd, J = 8.8, 3.7 Hz, 1H), 3.86 (dd, J = 16.0, 8.8 Hz, 1H), 3.44 (dd, J = 11.3, 7.7 Hz, 1H), 3.01 (dd, J = 11.4, 0.8 Hz, 1H), 2.97 (dd, J = 15.9, 3.8 Hz, 1H), 2.37 (qd, J = 13.6, 6.8 Hz, 1H), 2.04 (d, J = 1.0 Hz, 3H), 1.81 (d, J = 1.0 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 0.83 (s, 9H), 0.19 (s, 9H), 0.03 (s, 3H), -0.02 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 203.1, 171.4, 148.3, 140.8, 128.0, 109.8, 103.6, 100.9, 75.9, 72.0, 44.8, 31.2, 31.0, 25.9, 20.2, 19.3, 18.2, 18.1, 14.0, 0.3, -4.5, -4.9

**Aldehyde 3.45**

To a solution of silyl protected thiazolidinethione 3.44 (600 mg, 1.14 mmol) in PhCH₃ (10 mL) stirring at -78 °C was added DIBALH (1.37 mL, 1.4 mmol, 1.0 M in hexanes). The solution was stirred at this temperature for 3 h before being quenched with Rochelle salt (10 mL, sat.). The aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica
gel (25:1 hexanes/diethyl ether) to afford desired aldehyde 3.45 (407 mg, 1.12 mmol, 98%) as a clear, colorless oil.

Data for 3.45: IR ν 2958, 2129, 1726, 837, 730 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₂₀H₃₆O₂Si₂ m/z 387.2152 [M-Na]⁺, found 387.2162; ¹H NMR (300 MHz, CDCl₃) δ 9.73 (dd, J = 2.8, 2.1 Hz, 1H), 5.98 (s, 1H), 5.41 (s, 1H), 4.53 (dd, J = 8.2, 3.8 Hz, 1H), 2.66 (ddd, J = 15.6, 8.3, 2.8 Hz, 1H), 2.43 (ddd, J = 15.4, 4.1, 2.1 Hz, 1H), 2.04 (d, J = 1.0 Hz, 3H), 1.80 (d, J = 1.0 Hz, 3H), 0.85 (s, 9H), 0.19 (s, 9H), 0.04 (s, 3H), -0.01 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 201.5, 148.1, 139.9, 127.9, 110.0, 103.5, 101.0, 74.4, 50.1, 25.9, 20.3, 18.3, 14.1, 0.2, -4.5, -5.0

**Conjugated triene 3.46**

To a solution of tin (II) trifluoromethanesulfonate (3.03 g, 7.3 mmol) in CH₂Cl₂ (60 mL) stirring at -45 °C was slowly added 1-ethylpiperidine (1.0 mL, 7.3 mmol) followed by thiazolidinethione 3.42 (1.23 g, 6.1 mmol). This solution was stirred at this temperature for 4 h before addition of aldehyde 3.41 (1.25 g, 6.1 mmol) dissolved in CH₂Cl₂ (5 mL). This solution was stirred for 5 hours before the reaction was quenched with water (20 mL). The aqueous layer was extracted with Et₂O (3 x 20 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated *in vacuo*. The resulting residue was chromatographed on silica gel (10:1 to 1:1 hexanes/diethyl ether) to afford conjugated triene 3.46 (709 mg, 1.8 mmol, 29%) as a yellow oil
Data for 3.46: HRMS (ESI) Anal. Calcd. for C_{20}H_{29}NO_{2}SiS_{2} \text{ m/z} 414.1358 [M-Na]^+, found 414.1361; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 7.46 (d, \( J = 15.1 \) Hz, 1H), 7.31 (dd, \( J = 15.1, 0.8 \) Hz, 1H), 6.34 (s, 1H), 5.61 (s, 1H), 5.05 (ddd, \( J = 8.2, 5.6, 2.6 \) Hz, 1H), 3.52 (dd, \( J = 11.4, 8.1 \) Hz, 1H), 3.10 (dd, \( J = 11.4, 2.7 \) Hz, 1H), 2.54 - 2.40 (m, 1H), 2.14 (d, \( J = 1.0 \) Hz, 3H), 2.02 (d, \( J = 1.0 \) Hz, 3H), 1.04 (d, \( J = 6.9 \) Hz, 3H), 0.99 (d, \( J = 7.2 \) Hz, 3H), 0.21 (s, 9H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \( \delta \) 202.6, 167.0, 149.7, 147.6, 141.3, 135.6, 120.2, 113.9, 104.1, 103.3, 72.2, 30.8, 27.0, 19.8, 19.2, 17.4, 0.1

Crottylboronate 3.47

\[
\begin{align*}
\text{3.141} &+ \text{3.142} + \text{3.143} \rightarrow \text{3.47}
\end{align*}
\]

Crottylboronate 3.47 was prepared by the methods of Roush.\textsuperscript{150} All \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectroscopic data matched reported values.

Homoallylic alcohol 3.48

To a flask containing 4 Å molecular sieves (1 g, powder) and toluene (40 mL) was added crottylboronate 3.47 (4.0 mL, 2.0 mmol, 0.5 M in PhCH\textsubscript{3}). This mixture was stirred for 30 minutes before the reaction mixture was cooled to -78 °C and aldehyde 3.45 (660 mg, 1.8 mmol) was added and subsequently stirred for 2 hours at this temperature. The reaction was then quenched with
aqueous NaOH (10 mL, 2.0 M) and allowed to warm to room temperature. The aqueous layer was extracted with Et₂O (3 x 20 mL). The combined organic layers were washed with aqueous NaHCO₃ (50 mL, sat.) and brine (2 x 30 mL) before being dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (50:1 to 10:1 hexanes/diethyl ether) to afford desired homoallylic alcohol 3.48 (296 mg, 0.70 mmol, 39%) as a clear, colorless oil.

Data for 3.48: HRMS (ESI) Anal. Calcd. for C₂₄H₄₄O₂Si₂ m/z 443.2778 [M-Na]⁺, found 443.2782; ¹H NMR (300 MHz, CDCl₃) δ 6.01 (s, 1H), 5.72 (ddd, J = 17.7, 10.0, 7.7 Hz, 1H), 5.41 (s, 1H), 5.11 - 5.00 (m, 2H), 4.31 (dd, J = 6.2, 3.3 Hz, 1H), 3.62 (dd, J = 8.1, 6.3 Hz, 1H), 2.68 (br. s, 1H), 2.29 - 2.18 (m, 1H), 2.06 (d, J = 1.0 Hz, 3H), 1.76 (d, J = 1.0 Hz, 3H), 1.72 (dd, J = 6.7, 1.8 Hz, 1H), 1.56 - 1.45 (m, 1H), 1.02 (d, J = 6.7 Hz, 3H), 0.90 (s, 9H), 0.20 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 148.7, 141.2, 140.6, 127.0, 115.3, 109.2, 103.8, 76.4, 71.7, 44.1, 39.2, 29.9, 26.0, 20.5, 18.4, 15.3, 15.2, 0.3, -4.6, -5.1

**TIPS protected thiazolidinethione 3.145**

To a solution of thiazolidinethione 3.144 (110 mg, 0.27 mmol) in CH₂Cl₂ (5 mL) stirring at 0 °C was added 2,6-lutidine (100 μL, 0.87 mmol) followed by triisopropylsilyl trifluoromethanesulfonate (144 μL, 0.54 mmol). This solution was stirred at this temperature for 1 h before being concentrated in vacuo. The resulting residue was chromatographed on silica gel
(10:1 hexanes/diethyl ether) to afford protected thiazolidinethione **3.145** (150 mg, 0.27 mmol, 99%) as a yellow oil.

Data for **3.145**: HRMS (ESI) Anal. Calcd. for C$_{29}$H$_{51}$NO$_2$Si$_2$S$_2$ m/z 588.2797 [M-Na]$^+$, found 588.2802; $^1$H NMR (300 MHz, CDCl$_3$) δ 5.91 (s, 1H), 5.39 (s, 1H), 4.96 (t, $J = 6.9$ Hz, 1H), 4.77 (t, $J = 6.4$ Hz, 1H), 3.86 (dd, $J = 15.9$, 7.2 Hz, 1H), 3.39 (dd, $J = 11.4$, 7.8 Hz, 1H), 3.20 (dd, $J = 15.9$, 5.8 Hz, 1H), 2.98 (d, $J = 11.4$ Hz, 1H), 2.32 (qd, $J = 13.5$, 6.8 Hz, 1H), 2.04 (s, 3H), 1.85 (s, 3H), 1.01 (s, 24H), 0.93 (d, $J = 6.9$ Hz, 3H), 0.19 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 203.0, 171.1, 148.3, 141.1, 128.1, 109.7, 103.6, 100.9, 75.6, 72.0, 45.2, 31.0, 20.2, 19.3, 18.2, 18.2, 18.1, 13.8, 12.5, 0.2

**Aldehyde 3.51**

To a solution of silyl protected thiazolidinethione **3.145** (153 mg, 0.27 mmol) in PhCH$_3$ (5 mL) stirring at -78 °C was added DIBALH (0.32 mL, 0.32 mmol, 1.0 M in hexanes). The solution was stirred at this temperature for 3 h before being quenched with Rochelle salt (10 mL, sat.). The organic layer was extracted with Et$_2$O (3 x 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated *in vacuo*. The resulting residue was chromatographed on silica gel (25:1 hexanes/diethyl ether) to afford desired aldehyde **3.51** (109 mg, 0.27 mmol, 99%) as a clear, colorless oil. Chiral auxiliary **3.42** could also be recovered (40 mg, 0.25 mmol, 92%) as a yellow oil. Aldehyde **3.51** was used immediately.
Data for 3.51: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.75 (t, $J = 2.7$ Hz, 1H), 6.03 (s, 1H), 5.41 (s, 1H), 4.63 (t, $J = 5.8$ Hz, 1H), 2.61 (dt, $J = 6.1$, 2.6 Hz, 2H), 2.04 (s, 3H), 1.83 (s, 3H), 1.07 - 1.00 (m, 21H), 0.19 (s, 9H)

**Evans aldol product 3.146**

![Evans aldol product 3.146](image)

To a flask containing (S)-(+) - 4-benzyl - 3 - propionyl - 2 - oxazolidinone 3.52 (63 mg, 0.27 mmol) stirring in CH$_2$Cl$_2$ (3 mL) at 0 °C was added dibutylboron trifluoromethanesulfonate (0.30 mL, 0.30 mmol, 1.0 M in CH$_2$Cl$_2$) and then triethylamine (0.5 mL, 3.5 mmol). The solution was then cooled to -78 °C and aldehyde 3.51 (110 mg, 0.27 mmol) dissolved in CH$_2$Cl$_2$ (1 mL) was added slowly. This solution was then stirred at -78 °C for 30 minutes before warming to 0 °C and stirring for an additional hour. The reaction mixture was quenched with pH 7 buffer solution (1 mL), methanol (5 mL), and hydrogen peroxide (5 mL, 30% aqueous soln.) and stirred for another hour at 0 °C. The mixture was then concentrated in vacuo. The aqueous layer was extracted with Et$_2$O (3 x 5 mL). The combined organic layers were washed with NaHCO$_3$ (10 mL, sat. aq.) and brine (10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 to 2:1 hexanes/diethyl ether) to afford Evans aldol product 3.146 (61 mg, 0.10 mmol, 35%) as a clear, colorless oil.

Data for 3.146: HRMS (ESI) Anal. Calcd. for C$_{36}$H$_{57}$NO$_5$Si$_2$ m/z 662.3673 [M-Na]$^+$, found 662.3672; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.39 - 7.27 (m, 3H), 7.25 - 7.15 (m, 2H), 6.08 (s, 1H), 5.42 (s, 1H), 4.68 (tdd, $J = 9.6$, 6.5, 3.3 Hz, 1H), 4.43 (t, $J = 4.3$ Hz, 1H), 4.26 - 4.08 (m, 3H), 3.76
(dq, J = 6.8, 4.0 Hz, 1H), 3.45 (br. s, 1H), 3.25 (dd, J = 13.2, 3.0 Hz, 1H), 2.77 (dd, J = 13.2, 9.6 Hz, 1H), 2.06 (s, 3H), 1.85 - 1.66 (m, 2H), 1.80 (s, 3H), 1.24 (d, J = 6.9 Hz, 3H), 1.05 (d, J = 4.1 Hz, 21H), 0.20 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 176.4, 153.3, 148.6, 140.3, 135.4, 129.6, 129.1, 127.5, 127.2, 109.3, 103.8, 100.5, 76.5, 68.7, 66.2, 55.4, 43.0, 39.0, 37.9, 20.4, 18.2, 18.2, 18.1, 18.1, 15.3, 12.5, 11.1, 0.3

**TBS protected Evans aldol product 3.53**

![Diagram of the reaction](image)

To a solution of Evans aldol product 3.146 (61 mg, 0.10 mmol) in CH$_2$Cl$_2$ (5 mL) stirring at room temperature was added 2,6-lutidine (33 µL, 0.30 mmol) followed by tert-butylidimethylsilyl trifluoromethanesulfonate (44 µL, 0.20 mmol). This solution was stirred for 1 h before being concentrated *in vacuo*. The resulting residue was chromatographed on silica gel (10:1 hexanes/diethyl ether) to afford desired TBS protected Evans aldol product 3.53 (71 mg, 0.090 mmol, 99%) as a colorless oil.

Data for 3.53: HRMS (ESI) Anal. Calcd. for C$_{42}$H$_{71}$NO$_5$Si$_3$ m / z 776.4538 [M-Na]$^+$, found 776.4530; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.39 - 7.26 (m, 3H), 7.24 - 7.17 (m, 2H), 5.96 (s, 1H), 5.43 (s, 1H), 4.56 (tdd, J = 9.7, 6.5, 3.2 Hz, 1H), 4.21 (dd, J = 9.1, 4.1 Hz, 1H), 4.18 - 4.07 (m, 2H), 3.94 - 3.82 (m, 2H), 3.30 (dd, J = 13.2, 3.0 Hz, 1H), 2.74 (dd, J = 13.2, 9.6 Hz, 1H), 2.05 (s, 3H), 2.03 - 1.94 (m, 1H), 1.84 (s, 3H), 1.82 - 1.73 (m, 1H), 1.24 (d, J = 6.9 Hz, 3H), 1.04 (s, 21H), 0.88 (s, 9H), 0.20 (s, 9H), 0.02 (s, 3H), -0.04 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 175.1, 153.2,
Alcohol 3.54

To a flask containing TBS protected Evans aldol product 3.53 (71 mg, 0.090 mmol) stirring at 0 °C in Et₂O (5 mL) and methanol (50 μL), added lithium borohydride and stirred at this temperature for 30 minutes before warming to room temperature and stirring for another 90 minutes. The reaction was quenched with water (1 mL), then dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 hexanes/diethyl ether) to afford desired alcohol 3.54 (52 mg, 0.089 mmol, 95%) as a colorless oil. Alcohol 3.54 was used immediately.

Data for 3.54: HRMS (ESI) Anal. Calcd. for C₃₂H₆₄O₃Si⁴ m/z 603.4061 [M-Na]+, found 603.4067;

¹H NMR (300 MHz, CDCl₃) δ 5.78 (s, 1H), 5.42 (s, 1H), 4.06 (dd, J = 8.9, 5.1 Hz, 1H), 3.69 (ddd, J = 9.3, 4.3, 1.8 Hz, 1H), 3.59 - 3.44 (m, 2H), 2.04 (s, 3H), 1.94 - 1.85 (m, 1H), 1.84 (s, 3H), 1.81 - 1.65 (m, 3H), 1.03 (s, 21H), 0.91 - 0.84 (m, 12H), 0.21 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H)
Aldehyde 3.55

To a flask containing alcohol 3.54 (51 mg, 0.089 mmol) in CH₂Cl₂ (2 mL) was added Dess-Martin periodinane (57 mg, 0.13 mmol) and the resulting mixture was stirred for 2 hours. The mixture was then filtered through silica gel, rinsing with Et₂O (20 mL) to afford aldehyde 3.55 (36 mg, 0.062 mmol, 71%) as a colorless oil.

Data for 3.55: HRMS (ESI) Anal. Calcd. for C₃₂H₆₂O₃Si₃ m/z 601.3904 [M-Na]⁺, found 601.3900; ¹H NMR (300 MHz, CDCl₃) δ 9.61 (s, 1H), 5.80 (s, 1H), 5.43 (s, 1H), 4.14 - 4.01 (m, 2H), 2.37 (dq, J = 6.9, 2.1 Hz, 1H), 2.05 (d, J = 1.1 Hz, 3H), 1.98 - 1.87 (m, 1H), 1.86 (d, J = 1.1 Hz, 3H), 1.84 - 1.74 (m, 1H), 1.10 (d, J = 6.9 Hz, 3H), 1.04 (s, 21H), 0.83 (s, 9H), 0.21 (s, 9H), 0.05 (s, 3H), -0.02 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 204.6, 148.0, 140.8, 128.6, 109.8, 103.5, 101.1, 76.6, 68.5, 50.4, 40.9, 31.8, 25.9, 22.9, 20.4, 18.3, 18.2, 18.1, 14.3, 13.3, 12.6, 6.5, 0.3, -3.8, -4.6

(Z)-4-((tert-Butyldimethylsilyl)oxy)-2-buten-1-ol (3.147)

(Z)-4-((tert-Butyldimethylsilyl)oxy)-2-buten-1-ol (3.147) was prepared by the methods of Shibasaki.¹⁶⁴ All ¹H NMR and ¹³C NMR spectroscopic data matched reported values.
(Z)-4-((tert-Butyldimethylsilyl)oxy)2-butenal (3.60)

(Z)-4-((tert-Butyldimethylsilyl)oxy)2-butenal (3.60) was prepared by the methods of Shibasaki.\textsuperscript{164} All \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectroscopic data matched reported values.

(Z)-\textit{tert}-Butyldimethyl(2,4-pentadien-1-yloxy)silane (3.61)

(Z)-\textit{tert}-Butyldimethyl(2,4-pentadien-1-yloxy)silane (3.61) was prepared by the methods of Shibasaki.\textsuperscript{164} All \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectroscopic data matched reported values.

\textit{tert}-Butyldimethyl(((1\textit{E},3\textit{Z})-1,3-pentadien-1-yloxy)silane (3.63)

\textit{tert}-Butyldimethyl(((1\textit{E},3\textit{Z})-1,3-pentadien-1-yloxy)silane (3.63) was prepared by the methods of Shibasaki.\textsuperscript{164} All \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectroscopic data matched reported values.

\textit{tert}-Butyl(((1\textit{Z},3\textit{Z})-1-methoxy-1,3-pentadien-1-yloxy)dimethylsilane (3.65)

\textit{tert}-Butyl(((1\textit{Z},3\textit{Z})-1-methoxy-1,3-pentadien-1-yloxy)dimethylsilane (3.65) was prepared by the methods of Kalesse.\textsuperscript{165} All \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectroscopic data matched reported values.
Conjugated aldehyde 3.68

To a flask containing aldehyde 3.45 (21 mg, 0.06 mmol) in CH$_2$Cl$_2$ (2 mL) and Et$_2$O (0.3 mL) stirring at -78 °C was added tert-butyldimethyl(((1E,3Z)-1,3-pentadien-1-yl)oxy)silane 3.63 (14 mg, 0.07 mmol) followed by boron trifluoride diethyl etherate (10 μL, 0.08 mmol). This solution was stirred at -78 °C for 2.5 hours before being quenched with H$_2$O (5 mL). The aqueous layer was extracted with Et$_2$O (3 x 5 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 hexanes/diethyl ether) to afford conjugated aldehyde 3.68 (13 mg, 0.03 mmol, 50%) as an oil.

Data for 3.68: HRMS (ESI) Anal. Calcd. for C$_{25}$H$_{44}$O$_3$Si$_2$ m/z 471.2727 [M-Na]$^+$, found 471.2726; $^1$H NMR (300 MHz, CDCl$_3$) δ 9.53 (d, $J = 7.9$ Hz, 1H), 6.87 (dd, $J = 15.9, 7.2$ Hz, 1H), 6.13 (ddd, $J = 15.8, 7.8, 1.3$ Hz, 1H), 6.05 (s, 1H), 5.42 (s, 1H), 4.33 (t, $J = 4.5$ Hz, 1H), 3.81 (ddd, $J = 9.6, 5.4, 2.2$ Hz, 1H), 2.59 - 2.50 (m, 1H), 2.07 (d, $J = 0.8$ Hz, 3H), 1.75 (s, 3H), 1.71 - 1.52 (m, 3H), 1.11 (d, $J = 6.7$ Hz, 3H), 0.91 (s, 9H), 0.21 (s, 9H), 0.08 (s, 3H), 0.02 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 194.2, 160.4, 148.3, 139.5, 133.0, 127.5, 109.7, 103.6, 100.9, 77.4, 76.4, 71.2, 43.1, 29.9, 26.1, 26.0, 20.5, 18.4, 15.5, 14.3, 0.3, -4.6, -5.1
Conjugated ester 3.69

To a flask containing aldehyde 3.45 (19 mg, 0.052 mmol) dissolved in Et$_2$O (1 mL) stirring at -78 °C was added tris(pentafluorophenyl)borane (27 mg, 0.052 mmol). To this solution was added tert-butyl(((1Z,3Z)-1-methoxy-1,3-pentadien-1-yl)oxy)dimethylsilane 3.65 (24 mg, 0.10 mmol) dissolved in Et$_2$O (0.3 mL) and iPrOH (30 μL) dropwise over 5 hours. After complete addition, the reaction was quenched with ammonium chloride (15 mL, sat. aq.) which caused a white solid to precipitate. The aqueous layer was extracted with Et$_2$O (2 x 10 mL). The combined organic layers were dried over MgSO$_4$, filtered and concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 to 5:1 hexanes/diethyl ether) to afford conjugated ester 3.69 (7 mg, 0.01 mmol, 28%) as a colorless oil.

Data for 3.69: IR ν 3514, 2956, 2858, 2130, 1727, 841 cm$^{-1}$; HRMS (ESI) Anal. Calcd. for C$_{26}$H$_{46}$O$_4$Si$_2$ m/z 501.2832 [M-Na]$^+$, found 501.2825; $^1$H NMR (300 MHz, CDCl$_3$) δ = 6.97 (dd, J = 15.8, 7.8 Hz, 1H), 5.89 (s, 1H), 5.85 (dd, J = 15.8, 1.2 Hz, 1H), 5.42 (s, 1H), 4.23 (dd, J = 9.0, 3.8 Hz, 1H), 3.73 (s, 3H), 3.46 (br. s, 1H), 2.49 - 2.36 (m, 1H), 2.09 - 2.03 (m, 3H), 1.83 - 1.78 (m, 3H), 1.77 - 1.49 (m, 3H), 1.08 (d, J = 6.9 Hz, 3H), 0.90 (s, 9H), 0.21 (s, 9H), 0.09 (s, 3H), 0.00 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 167.3, 151.3, 151.0, 148.2, 148.2, 141.0, 128.2, 128.1, 121.5, 121.4, 110.0, 109.9, 103.5, 101.2, 80.7, 80.5, 77.4, 74.4, 74.3, 51.7, 42.9, 42.8, 39.8, 30.5, 26.0, 20.3, 18.2, 15.2, 14.8, 14.0, 0.3, -4.1, -4.9
Ethyl (2E,4E)-4-methyl-7-(trimethylsilyl)-2,4-heptadien-6-ynoate (3.73)

To a stirring solution of aldehyde 3.37 (1.17 g, 7.0 mmol) in CH₂Cl₂ (70 mL) was added ethyl (triphenylphosphoranylidene)acetate (3.72) (2.45 g, 7.7 mmol). The mixture was stirred at room temperature for 12 hours. The solution was concentrated in vacuo and then charged with Et₂O (100 mL) resulting in formation of a white solid. The mixture was filtered and concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 hexanes/diethyl ether) to afford ethyl (2E,4E)-4-methyl-7-(trimethylsilyl)-2,4-heptadien-6-ynoate (3.73) (1.50 g, 6.3 mmol, 90%) as a clear oil.

Data for 3.73: IR ν 2960, 2133, 1713, 1620, 1165, 836 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₁₃H₂₀O₂Si m/z 259.1130 [M-Na]⁺, found 259.1126; ¹H NMR (300 MHz, CDCl₃) δ 7.23 (dd, J = 15.6, 0.5 Hz, 1H), 5.92 (dd, J = 15.6, 0.5 Hz, 1H), 5.76 (d, J = 0.8 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 1.98 (d, J = 1.0 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 0.16 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 166.8, 146.2, 145.9, 120.0, 117.5, 106.0, 102.6, 60.5, 15.0, 14.4, -0.1

(2E,4E)-4-Methyl-7-(trimethylsilyl)-2,4-heptadien-6-ynal (3.74)

To a solution of ethyl (2E,4E)-4-methyl-7-(trimethylsilyl)-2,4-heptadien-6-ynoate (3.73) (1.50 g, 6.3 mmol) in THF (45 mL) stirring at -78 °C was added diisobutylaluminum hydride (13.3 mL, 13
mmol, 1.0 M in hexanes). The solution was stirred for two hours before quenching with EtOAc (20 mL), ammonium chloride (20 mL, sat. aq.), and HCl (20 mL, 3 M). The aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (5:1 to 1:1 hexanes/diethyl ether) to afford a clear oil which was used immediately: In a flask, this clear oil was dissolved in CH₂Cl₂ (60 mL) and manganese dioxide (10.0 g, 115 mmol) was added with stirring. The mixture was stirred at room temperature for 2 h before filtering through celite. The filtrate was concentrated in vacuo and the resulting residue chromatographed on silica gel (50:1 to 10:1 hexanes/diethyl ether) to afford (2E,4E)-4-methyl-7-(trimethylsilyl)-2,4-heptadien-6-yenal (3.74) (903 mg, 4.7 mmol, 74% over 2 steps) as a clear oil which turned into a white solid when placed in a freezer.

Data for 3.74: IR ν 2961, 2731, 2127, 1677, 1606, 1126, 839 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₁₁H₁₆OSi m/z 215.0868 [M-Na]+, found 215.0868; ¹H NMR (300 MHz, CDCl₃) δ 9.54 (dd, J = 7.7, 3.1 Hz, 1H), 7.05 (dd, J = 15.6, 2.1 Hz, 1H), 6.18 (ddd, J = 15.7, 7.7, 3.1 Hz, 1H), 5.86 (s, 1H), 2.01 (d, J = 2.3 Hz, 3H), 0.18 (m, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 193.3, 193.3, 153.6, 146.0, 130.0, 119.3, 107.7, 102.4, 15.1, -0.1
Thiazolidinethione 3.148

To a solution of tin (II) trifluoromethanesulfonate (2.34 g, 5.6 mmol) in CH$_2$Cl$_2$ (50 mL) stirring at -45 °C was slowly added 1-ethylpiperidine (0.77 mL, 5.6 mmol) followed by thiazolidinethione 3.42 (950 mg, 4.5 mmol). This solution was stirred at this temperature for 4 h before addition of (2E,4E)-4-methyl-7-(trimethylsilyl)-2,4-heptadien-6-ynal (3.74) (900 mg, 4.7 mmol). This solution was stirred for 90 minutes before the reaction was quenched with water (50 mL). The aqueous layer was extracted with Et$_2$O (3 x 50 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 to 2:1 hexanes/diethyl ether) to afford desired thiazolidinethione 3.148 (1.20 g, 3.0 mmol, 65%) and undesired thiazolidinethione 3.148a (55 mg, 0.14 mmol, 3%), both as yellow oils.

Data for 3.148: IR ν 3405, 2961, 2126, 1690, 1161, 842 cm$^{-1}$; HRMS (ESI) Anal. Calcd. for C$_{19}$H$_{29}$NO$_2$SiS$_2$ m/z 418.1307 [M-Na]$^+$, found 418.1308; $^1$H NMR (300 MHz, CDCl$_3$) δ 6.34 (d, J = 15.6 Hz, 1H), 5.85 (dd, J = 15.6, 5.9 Hz, 1H), 5.50 (s, 1H), 5.14 (dt, J = 7.1, 1.0 Hz, 1H), 4.82 - 4.68 (m, 1H), 3.67 (dd, J = 17.6, 3.2 Hz, 1H), 3.51 (dd, J = 11.5, 7.9 Hz, 1H), 3.33 (dd, J = 17.4, 8.7 Hz, 1H), 3.03 (dd, J = 11.5, 1.0 Hz, 1H), 2.97 (br. s, 1H), 2.35 (qd, J = 13.5, 6.7 Hz, 1H), 2.00 (d, J = 1.0 Hz, 3H), 1.06 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.9 Hz, 3H), 0.20 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 203.2, 172.5, 147.5, 133.2, 132.2, 111.0, 103.5, 71.6, 68.7, 45.4, 31.0, 30.9, 19.3, 18.0, 15.5, 0.2
Data for 3.148a: IR ν 3297, 2961, 2126, 1686, 842 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₁₉H₂₉NO₂SiS₂ m/z 418.1307 [M-Na]⁺, found 418.1311; ¹H NMR (300 MHz, CDCl₃) δ 6.34 (d, J = 15.6 Hz, 1H), 5.84 (dd, J = 15.5, 5.8 Hz, 1H), 5.50 (s, 1H), 5.17 (ddd, J = 7.8, 6.5, 1.0 Hz, 1H), 4.73 - 4.63 (m, 1H), 4.03 (br. s, 1H), 3.65 (dd, J = 17.4, 9.0 Hz, 1H), 3.52 (dd, J = 11.5, 7.9 Hz, 1H), 3.40 (dd, J = 17.4, 3.6 Hz, 1H), 3.04 (dd, J = 11.4, 1.2 Hz, 1H), 2.35 (qd, J = 13.5, 6.8 Hz, 1H), 2.00 (d, J = 0.8 Hz, 3H), 1.09 - 0.95 (m, 6H), 0.20 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 203.3, 172.9, 147.5, 133.3, 132.3, 111.0, 103.5, 102.2, 71.6, 69.2, 45.2, 31.0, 30.9, 19.3, 18.6, 15.5, 0.2

Conjugated triene 3.149

To a solution of tin (II) trifluoromethanesulfonate (234 mg, 0.56 mmol) in CH₂Cl₂ (5 mL) stirring at -45 °C was slowly added 1-ethylpiperidine (77 µL, 0.56 mmol) followed by thiazolidinethione 3.42 (95 g, 0.47 mmol). This solution was stirred at this temperature for 4 h before addition of (2E,4E)-4-methyl-7-(trimethylsilyl)-2,4-heptadien-6-ynal 3.74 (90 mg, 0.47 mmol) dissolved in CH₂Cl₂ (2 mL). This solution was stirred for 3 hours before the reaction was quenched with water (10 mL). The aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 to 1:1 hexanes/diethyl ether) to afford conjugated triene 3.149 (106 mg, 0.28 mmol, 60%) as a yellow oil.
Data for 3.149: HRMS (ESI) Anal. Calcd. for C_{19}H_{27}NO_SiS_{2} m / z 400.1201 [M-Na]^+, found 400.1207; ¹H NMR (300 MHz, CDCl₃) δ 7.43 - 7.20 (m, 2H), 6.62 - 6.38 (m, 2H), 5.62 (s, 1H), 4.95 (dd, J = 8.1, 5.5, 2.6 Hz, 1H), 3.47 (dd, J = 11.4, 8.1 Hz, 1H), 3.04 (dd, J = 11.5, 2.6 Hz, 1H), 2.40 (sext, J = 6.6 Hz, 1H), 1.99 (s, 3H), 0.97 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H), 0.16 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 202.0, 166.5, 147.2, 143.7, 143.0, 128.7, 123.9, 114.5, 105.3, 103.3, 72.0, 31.5, 30.6, 22.6, 19.0, 17.1, 15.0, 14.1, -0.1

TBS protected thiazolidinethione 3.75

To a solution of thiazolidinethione 3.148 (100 mg, 0.25 mmol) in CH₂Cl₂ (5 mL) stirring at 0 °C was added 2,6-lutidine (60 µL, 0.51 mmol) followed by tert-butyldimethylsilyl trifluoromethanesulfonate (60 µL, 0.28 mmol). This solution was stirred at this temperature for 1 h before being concentrated in vacuo. The resulting residue was chromatographed on silica gel (25:1 hexanes/diethyl ether) to afford protected thiazolidinethione 3.75 (78 mg, 0.15 mmol, 61%) as a yellow oil.

Data for 3.75: IR ν 2955, 2128, 1698, 1249, 834, 777 cm⁻¹; HRMS (ESI) Anal. Calcd. for C_{25}H_{43}NO_SiS_{2} m / z 532.2172 [M-Na]^+, found 532.2178; ¹H NMR (300 MHz, CDCl₃) δ 6.25 (d, J = 15.6 Hz, 1H), 5.84 (dd, J = 15.5, 6.8 Hz, 1H), 5.46 (s, 1H), 5.02 (t, J = 6.7 Hz, 1H), 4.81 (dt, J = 6.9, 4.9 Hz, 1H), 3.70 (dd, J = 16.4, 7.9 Hz, 1H), 3.46 (dd, J = 11.5, 7.7 Hz, 1H), 3.20 (dd, J = 16.3, 4.5 Hz, 1H), 3.02 (dd, J = 10.2, 1.0 Hz, 1H), 2.37 (qd, J = 13.5, 6.8 Hz, 1H), 1.99 (d, J = 0.8
Hz, 3H), 1.05 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 0.85 (s, 9H), 0.20 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 203.0, 171.2, 147.7, 134.3, 132.7, 110.5, 103.6, 71.9, 70.7, 46.5, 31.2, 31.0, 26.0, 19.3, 18.3, 18.1, 15.5, 0.2, -4.1, -4.7

**Aldehyde 3.76**

To a solution of silyl protected TBS protected thiazolidinethione 3.75 (70 mg, 0.14 mmol) in PhCH₃ (10 mL) stirring at -78 °C was added DIBALH (0.16 mL, 0.16 mmol, 1.0 M in hexanes). The solution was stirred at this temperature for 3 h before being quenched with Rochelle salt (10 mL, sat. aq.). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 hexanes/diethyl ether) to afford desired aldehyde 3.76 (47 mg, 0.13 mmol, 98%) as a clear, colorless oil.

Data for 3.76: IR ν 2957, 2858, 2128, 1728, 839 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₁₉H₃₄O₂Si₂ m / z 373.1995 [M-Na]⁺, found 373.1989; ¹H NMR (300 MHz, CDCl₃) δ 9.76 (t, J = 2.2 Hz, 1H), 6.27 (d, J = 15.8 Hz, 1H), 5.80 (dd, J = 15.5, 6.4 Hz, 1H), 5.48 (s, 1H), 4.73 (q, J = 6.2 Hz, 1H), 2.65 (ddd, J = 15.9, 7.2, 2.6 Hz, 1H), 2.53 (ddd, J = 15.8, 4.8, 2.0 Hz, 1H), 1.99 (s, 3H), 0.87 (s, 9H), 0.20 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 201.4, 147.3, 133.6, 132.7, 110.9, 103.4, 102.3, 69.2, 51.8, 25.9, 18.3, 15.5, 0.2, -4.1, -4.8
(2E,4E)-2,4-Dimethyl-2,4-heptadien-6-yn-1-ol (3.85)

To a flask containing alcohol 3.40 (860 mg, 4.1 mmol) stirring in MeOH (40 mL) was added potassium carbonate (627 mg, 4.5 mmol) and the mixture stirred for 2 hours at room temperature. The mixture was then filtered and concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 to 1:1 hexanes/diethyl ether) to afford (2E,4E)-2,4-dimethyl-2,4-heptadien-6-yn-1-ol (3.85) (506 mg, 3.7 mmol, 90%) as a clear, colorless oil.

Data for 3.85: IR ν 3293, 2915, 1443, 1008 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₉H₁₃O m/z 137.0966 [M-Na]⁺, found 137.0968; ¹H NMR (300 MHz, CDCl₃) δ 5.98 (s, 1H), 5.40 (s, 1H), 4.07 (s, 2H), 3.24 (d, J = 2.3 Hz, 1H), 2.08 (s, 3H), 1.85 (s, 3H), 1.60 (br. s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 149.0, 138.7, 126.6, 108.4, 83.1, 82.1, 69.1, 20.2, 15.9

Alkyne 3.150

To a flask containing (2E,4E)-2,4-dimethyl-2,4-heptadien-6-yn-1-ol (3.85) (506 mg, 3.7 mmol) stirring in CH₂Cl₂ (40 mL) was added imidazole (380 mg, 5.6 mmol) and tert-butyldimethylsilyl chloride (613 mg, 4.1 mmol). The mixture was stirred for 2 hours at room temperature before being quenched with ammonium chloride (20 mL, sat. aq.). The aqueous layer was extracted with Et₂O (3 x 20 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in
vacuo. The resulting residue was chromatographed on silica gel (25:1 hexanes/diethyl ether) to afford alkyne 3.150 (909 mg, 3.6 mmol, 98%) as a clear, colorless oil.

Data for 3.150: IR ν 3313, 2930, 2857, 834, 775 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₁₅H₂₇OSi m/z 251.1831 [M-Na]⁺, found 251.1832; ¹H NMR (300 MHz, CDCl₃) δ 6.00 (s, 1H), 5.38 (s, 1H), 4.06 (s, 2H), 3.22 (d, J = 2.3 Hz, 1H), 2.08 (s, 3H), 1.79 (s, 3H), 0.92 (s, 9H), 0.07 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 149.4, 138.6, 125.4, 107.8, 82.7, 82.4, 68.6, 26.1, 20.3, 18.6, 15.6, -5.1

**Diol 3.86**

![Chemical structure](image)

To a flask containing zirconocene dichloride (1.18 g, 4.0 mmol) stirring in CH₂Cl₂ (25 mL) was added trimethylaluminum (12.2 mL, 24 mmol, 2.0 M in hexanes). The solution stirred for 15 minutes at room temperature before addition of (2E,4E)-2,4-dimethyl-2,4-heptadien-6-yn-1-ol (3.85) (160 mg, 1.2 mmol) dissolved in CH₂Cl₂ (20 mL). The resulting solution was stirred for 12 hours at room temperature before being concentrated in vacuo. The resulting residue was charged with pentanes (20 mL) and the solution was transferred to a second flask by cannula. The original flask was charged with pentanes and transferred twice more, leaving behind a white solid that was discarded. The flask containing pentanes was cooled to -78 °C with stirring and n-butyllithium (3.6 mL, 8.9 mmol, 2.5 M in hexanes) was added dropwise. This solution was stirred for 1 hour at this temperature before addition of benzyl glycidyl ether (0.32 mL, 1.5 mmol). The mixture was allowed to warm to room temperature and stir for an additional 2 hours before slowly quenching with HCl (80 mL, 0.5 M). The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined
organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 to 1:1 hexanes/ethyl acetate) to afford diol **3.86** (1.32 g, 4.2 mmol, 52%) as a clear, colorless oil.

Data for **3.86**: IR $\nu$ 3375, 2911, 2859, 1073, 697 cm$^{-1}$; HRMS (ESI) Anal. Calcd. for C$_{20}$H$_{28}$O$_3$ m / z 339.1936 [M-Na]$^+$, found 339.1938; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.39 - 7.26 (m, 5H), 5.92 (s, 1H), 5.78 (s, 1H), 5.36 (t, $J = 7.4$ Hz, 1H), 4.56 (s, 2H), 4.03 (s, 2H), 3.94 - 3.85 (m, 1H), 3.54 (dd, $J = 9.5$, 3.3 Hz, 1H), 3.40 (dd, $J = 9.5$, 7.2 Hz, 1H), 2.34 (t, $J = 6.8$ Hz, 2H), 2.15 (br. s, 2H), 1.88 (d, $J = 1.3$ Hz, 3H), 1.83 (d, $J = 1.3$ Hz, 3H), 1.76 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 138.1, 135.3, 135.3, 133.8, 132.5, 130.2, 128.6, 128.6, 128.0, 127.9, 125.3, 74.2, 73.6, 70.7, 69.5, 32.6, 19.0, 17.5, 15.6

**TBS protected diol 3.151**

![TBS protected diol 3.151](image)

To a flask containing diol **3.86** (100 mg, 0.32 mmol) stirring in CH$_2$Cl$_2$ (5 mL) was added 2,6-lutadiene (0.15 mL, 1.3 mmol) and tert-butyldimethylsilyl trifluoromethanesulfonate (0.14 mL, 0.66 mmol). The reaction was stirred for 2 hours before being concentrated in vacuo. The resulting residue was chromatographed on silica gel (50:1 hexanes/diethyl ether) to afford TBS protected diol **3.151** (115 mg, 0.21 mmol, 67%) as a clear, colorless oil.

Data for **3.151**: IR $\nu$ 2929, 2856, 1079, 832, 774 cm$^{-1}$; HRMS (ESI) Anal. Calcd. for C$_{32}$H$_{56}$O$_3$Si$_2$ m / z 567.3666 [M-Na]$^+$, found 567.3661; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.38 - 7.27 (m, 5H), 5.96 (s, 1H), 5.78 (s, 1H), 5.40 (t, $J = 7.4$ Hz, 1H), 4.55 (s, 2H), 4.09 (s, 2H), 3.94 (quin, $J = 5.6$ Hz,
1H), 3.44 (d, J = 5.4 Hz, 2H), 2.49 - 2.28 (m, 2H), 1.90 (d, J = 1.2 Hz, 3H), 1.79 (s, 3H), 1.78 (s, 3H), 0.96 (s, 9H), 0.91 (s, 9H), 0.11 (s, 6H), 0.08 (s, 6H); 13C NMR (75 MHz, CDCl3) δ 138.7, 134.8, 134.6, 133.7, 132.3, 129.1, 128.5, 127.8, 127.7, 126.2, 74.6, 73.5, 71.8, 69.2, 34.0, 26.2, 26.1, 19.1, 18.6, 18.4, 17.6, 15.4, -4.3, -4.5, -5.0

Alcohol 3.87

To a flask containing TBS protected diol 3.151 (110 mg, 0.20 mmol) stirring at 0 °C in THF (4 mL) was added tetrabutylammonium fluoride (0.20 mL, 0.20 mmol, 1.0 M in THF). The rose-colored solution was stirred at this temperature for 2 hours before being quenched with H2O (10 mL). The aqueous layer was extracted with Et2O (3 x 10 mL). The combined organic layers were dried over MgSO4, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 to 2:1 hexanes/diethyl ether) to afford alcohol 3.87 (50 mg, 0.12 mmol, 58%) as a clear, colorless oil as well as recovered TBS protected diol 3.151 (17 mg, 0.03 mmol, 15%).

Data for 3.87: IR ν 3343, 2928, 2856, 834, 775 cm⁻¹; HRMS (ESI) Anal. Calcd. for C26H42O3Si m/z 453.2801 [M-Na]⁺, found 453.2802; ¹H NMR (300 MHz, CDCl3) δ 7.38 - 7.27 (m, 5H), 5.94 (s, 1H), 5.79 (s, 1H), 5.40 (t, J = 7.4 Hz, 1H), 4.54 (s, 2H), 4.06 (s, 2H), 3.92 (quin, J = 5.7 Hz, 1H), 3.42 (d, J = 5.6 Hz, 2H), 2.47 - 2.27 (m, 2H), 1.89 (d, J = 1.3 Hz, 3H), 1.84 (d, J = 1.3 Hz, 3H), 1.77 (d, J = 0.7 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ¹³C NMR (75 MHz, CDCl3) δ 138.6, 135.0, 134.4, 134.2, 132.0, 130.5, 128.5, 127.8, 127.7, 126.5, 74.6, 73.5, 71.8, 69.7, 33.9, 26.1, 19.0, 18.3, 17.5, 15.6, -4.3, -4.5
Aldehyde 3.88

To a flask containing alcohol 3.87 (50 mg, 0.12 mmol) stirring in CH₂Cl₂ (3 mL) with molecular sieves (1 g, 4 Å, powder) was added 4-methylmorpholine-N-oxide (14 mg, 0.12 mmol) and tetrapropylammonium perruthenate (2 mg, 0.006 mmol). The mixture was stirred at room temperature for 1 hour before being filtered through silica gel, eluting with Et₂O (20 mL). The filtrate was concentrated in vacuo to afford aldehyde 3.88 (45 mg, 0.11 mmol, 95%).

Data for 3.88: IR ν 2929, 1675, 833, 775 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₂₆H₄₀O₃Si m/z 451.2644 [M-Na]⁺, found 451.2637; ¹H NMR (300 MHz, CDCl₃) δ 9.40 (s, 1H), 7.38 - 7.27 (m, 5H), 6.76 (s, 1H), 6.25 (s, 1H), 5.60 (t, J = 7.4 Hz, 1H), 4.53 (s, 2H), 3.94 (quin, J = 5.6 Hz, 1H), 3.48 - 3.35 (m, 2H), 2.51 - 2.32 (m, 2H), 2.10 (d, J = 1.0 Hz, 3H), 1.98 (d, J = 1.0 Hz, 3H), 1.83 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 196.2, 156.3, 143.0, 138.5, 136.1, 134.0, 132.1, 130.7, 128.5, 127.8, 127.7, 74.4, 73.6, 71.4, 34.0, 26.0, 18.3, 18.2, 17.2, 11.0, -4.3, -4.6

2-(3-Bromopropyl)-1,3-dioxolane (3.92)

2-(3-Bromopropyl)-1,3-dioxolane (3.92) was prepared by the methods of Maier.¹⁷⁹ All ¹H NMR and ¹³C NMR spectroscopic data matched reported values.
(3-(1,3-Dioxolan-2-yl)propyl)magnesium bromide (3.152)

To a flask containing 2-(3-bromopropyl)-1,3-dioxolane (3.92) (1.46 g, 7.5 mmol) stirring in THF (1.5 mL) was added 1,2-dibromoethane (0.13 mL, 1.5 mmol) and magnesium filings (365 mg, 15 mmol). This mixture was heated with a heat gun until effervescence began, and then immediately cooled to 0 °C. After stirring at 0 °C for 10 minutes, the mixture was allowed to warm to room temperature and stir for 3 hours. This solution of (3-(1,3-dioxolan-2-yl)propyl)magnesium bromide (3.152) was used immediately without further purification.

Alcohol 3.93

To a flask containing aldehyde 3.88 (40 mg, 0.09 mmol) stirring at -78 °C in THF (2 mL) was added (3-(1,3-dioxolan-2-yl)propyl)magnesium bromide (3.152) (0.18 mL, 0.9 mmol, 5 M in THF). The solution was allowed to warm to room temperature and stirred for 2 hours before being quenched with ammonium chloride (10 mL, aq. sat.). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 to 3:1 hexanes/ethyl acetate) to afford alcohol 3.93 (50 mg, 0.09 mmol, 99%) as a clear, colorless oil.
Data for 3.93: IR ν 3461, 2929, 2857, 833, 775 cm⁻¹; HRMS (ESI) Anal. Calcd. for C_{32}H_{52}O_{5}Si m/z 567.3482 [M-Na]^+; found 567.3478; \(^1\)H NMR (300 MHz, CDCl₃) δ 7.37 - 7.27 (m, 5H), 5.89 (s, 1H), 5.76 (s, 1H), 5.38 (t, J = 7.3 Hz, 1H), 4.86 (t, J = 4.7 Hz, 1H), 4.53 (s, 2H), 4.06 - 3.80 (m, 6H), 3.41 (d, J = 5.4 Hz, 2H), 2.45 - 2.25 (m, 2H), 1.86 (d, J = 1.2 Hz, 3H), 1.78 (d, J = 1.3 Hz, 3H), 1.75 (s, 3H), 1.74 - 1.57 (m, 6H), 0.88 (s, 9H), 0.05 (s, 6H); \(^{13}\)C NMR (75 MHz, CDCl₃) δ 138.7, 137.5, 134.4, 134.2, 132.0, 131.1, 128.5, 127.8, 127.7, 126.4, 104.7, 78.5, 74.6, 73.5, 71.8, 65.0, 65.0, 35.0, 33.9, 26.1, 20.6, 19.1, 18.3, 17.5, 13.3, -4.3, -4.5

\((E)-5\)-Iodo-4-methyl-4-penten-1-ol (3.101)

\((E)-5\)-Iodo-4-methyl-4-penten-1-ol (3.101) was prepared by the methods of Frost.\(^{182,183}\) All \(^1\)H NMR and \(^{13}\)C NMR spectroscopic data matched reported values.

\((E)-5\)-Iodo-4-methyl-4-pentenal (3.102)

\((E)-5\)-Iodo-4-methyl-4-pentenal (3.102) was prepared by the methods of MacMillan.\(^{183}\) All \(^1\)H NMR and \(^{13}\)C NMR spectroscopic data matched reported values.
Unsaturated ester 3.103

To a flask containing (E)-5-iodo-4-methyl-4-pentenal (3.102) (280 mg, 1.25 mmol) stirring at -78 °C in Et<sub>2</sub>O (12 mL) was added tris(pentafluorophenyl)borane (640 mg, 1.25 mmol). Silyl ketene acetal 3.65 (571 mg, 2.5 mmol) dissolved in Et<sub>2</sub>O (5 mL) and iPrOH (0.12 mL, 1.5 mmol) was added dropwise over a period of 6 hours while stirring at -78 °C and then the reaction was quenched with H<sub>2</sub>O (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (4:1 hexanes/ethyl acetate) to afford unsaturated ester 3.103 (402 g, 1.2 mmol, 95%) as a clear, colorless oil.

Data for 3.103: IR ν 3441, 2948, 1721, 1704, 1655, 1436, 1271 cm<sup>-1</sup>; HRMS (ESI) Anal. Calcd. for C<sub>12</sub>H<sub>19</sub>IO<sub>3</sub> m/z 361.0277 [M-Na]<sup>+</sup>, found 361.0272; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.90 (dd, J = 15.8, 7.8 Hz, 1H), 5.89 (q, J = 1.0 Hz, 1H), 5.82 (dd, J = 15.9, 1.3 Hz, 1H), 3.70 (s, 3H), 3.49 (ddd, J = 9.2, 5.3, 3.2 Hz, 1H), 3.22 (br. s, 1H), 2.46 - 2.16 (m, 3H), 1.79 (d, J = 1.0 Hz, 3H), 1.65 - 1.38 (m, 2H), 1.05 (d, J = 6.9 Hz, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 167.4, 151.2, 147.5, 121.4, 75.3, 73.9, 51.8, 42.7, 36.1, 32.3, 24.0, 14.1
TBS protected unsaturated ester 3.104

![Diagram of reaction]

To a flask containing unsaturated ester 3.103 (140 mg, 0.41 mmol) stirring at room temperature in DMF (3 mL) was added imidazole (250 mg, 3.7 mmol) and tert-butyldimethylsilyl chloride (75 mg, 0.50 mmol). The reaction was stirred for 16 hours before being quenched with H₂O (10 mL) and Et₂O (10 mL). The aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 hexanes/ethyl acetate) to afford protected ester 3.104 (183 mg, 0.41 mmol, 98%) as a clear, colorless oil.

Data for 3.104: IR ν 2951, 2858, 1726, 1257, 837, 775 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₁₈H₃₃IO₃Si m/z 475.1141 [M-Na]⁺, found 475.1144; ¹H NMR (300 MHz, CDCl₃) δ 6.99 (dd, J = 15.8, 7.3 Hz, 1H), 5.87 (q, J = 1.3 Hz, 1H), 5.81 (dd, J = 15.8, 1.4 Hz, 1H), 3.73 (s, 3H), 3.59 (td, J = 6.8, 4.7 Hz, 1H), 2.55 - 2.40 (m, 1H), 2.35 - 2.21 (m, 1H), 2.21 - 2.08 (m, 1H), 1.81 (d, J = 1.0 Hz, 3H), 1.61 - 1.41 (m, 2H), 1.02 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 167.2, 151.5, 148.0, 120.9, 75.0, 74.9, 51.6, 42.0, 35.6, 32.3, 26.1, 24.2, 18.3, 14.7, -4.2
(Z)-3-(Tributylstannyl)-2-buten-1-ol (3.106)

\[ \text{Z} - 3 - \text{(Tributylstannyl)} - 2 - \text{buten - 1 - ol} (3.106) \]

(Z)-3-(Tributylstannyl)-2-buten-1-ol (3.106) was prepared by the methods of Florencig.\(^{184}\) All \(^1\)H NMR and \(^{13}\)C NMR spectroscopic data matched reported values.

**Diene 3.107**

To a flask containing vinyl iodide 3.103 (13 mg, 0.04 mmol) and (Z)-3-(tributylstannyl)-2-buten-1-ol (3.106) (17 mg, 0.05 mmol) stirring in DMF (0.4 mL) was added tetrakis(triphenylphosphine)palladium (3 mg, 0.002 mmol), copper (I) iodide (1 mg, 0.004 mmol), and cesium fluoride (12 mg, 0.08 mmol). The reaction was stirred at room temperature for 12 hours before quenching with H\(_2\)O (5 mL) and CH\(_2\)Cl\(_2\) (5 mL). The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 5 mL). The combined organic layers were dried over MgSO\(_4\), filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (1:1 hexanes/ethyl acetate) to afford diene 3.107 (5 mg, 0.02 mmol, 44%) as a colorless oil.

Data for 3.107: IR \( v \) 3414, 2933, 1724, 1702, 1436, 1277, 1006 cm\(^{-1}\); HRMS (ESI) Anal. Calcd. for C\(_{16}\)H\(_{26}\)O\(_4\) \( m / z \) 305.1729 [M-Na]\(^+\), found 305.1722; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 6.96 (dd, \( J = 15.6, 7.9 \) Hz, 1H), 5.88 (dd, \( J = 15.6, 1.3 \) Hz, 1H), 5.64 (s, 1H), 5.46 (tt, \( J = 6.7, 1.3 \) Hz, 1H), 4.00 (d, \( J = 6.7 \) Hz, 2H), 3.74 (s, 3H), 3.58 (ddd, \( J = 9.0, 5.3, 3.3 \) Hz, 1H), 2.45 (qd, \( J = 13.2, 6.7 \) Hz, 1H).
Hz, 1H), 2.33 - 2.18 (m, 1H), 2.18 - 2.03 (m, 1H), 1.77 (s, 4H), 1.70 - 1.46 (m, 2H), 1.58 (br. s, 2H), 1.56 (d, \(J = 1.0\) Hz, 3H), 1.10 (d, \(J = 6.9\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 167.2, 151.3, 138.5, 136.7, 125.8, 124.4, 121.6, 74.4, 61.0, 51.8, 42.9, 36.2, 32.8, 24.2, 17.9, 14.4\)

**Lactone 3.110**

![Diagram of lactone formation](image)

To a flask containing unsaturated ester **3.103** (80 mg, 0.24 mmol) stirring in THF/MeOH (4 mL, 1:1) was added lithium hydroxide (2.4 mL, 2.4 mmol, 1 M in H\(_2\)O). The reaction was stirred at room temperature for 3 hours before being acidified with HCl (5 mL, 1 M). The aqueous layer was extracted with EtOAc (5 x 5 mL). The combined organic layers were dried over MgSO\(_4\), filtered, and concentrated *in vacuo*. The resulting unsaturated carboxylic acid **3.153** (80 mg) was used immediately without further purification.

Data for **3.153**: \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.04 (dd, J = 15.8, 7.8\) Hz, 1H), 6.27 (br. s, 2H), 5.93 (d, \(J = 0.8\) Hz, 1H), 5.86 (dd, 15.6, 0.8 Hz, 1H), 3.56 (ddd, \(J = 9.0, 5.1, 3.3\) Hz, 1H), 2.53 - 2.20 (m, 3H), 1.83 (s, 3H), 1.67 - 1.47 (m, 1H), 1.10 (d, \(J = 6.7\) Hz, 3H)

To a flask containing unsaturated carboxylic acid **3.153** (80 mg), (Z)-3-(tributylstannyl)-2-buten-1-ol **3.106** (175 mg, 0.48 mmol), and DMAP (37 mg, 0.30 mmol) stirring in CH\(_2\)Cl\(_2\) (2 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (55 mg, 0.29 mmol). The reaction was stirred at room temperature for 12 hours before being concentrated *in vacuo*. The resulting residue
was chromatographed on silica gel (10:1 hexanes/ethyl acetate) to afford lactone 3.110 (71 mg, 0.23 mmol, 98% over 2 steps) as a clear, colorless oil.

Data for 3.110: IR ν 2934, 1716, 1246, 1090, 822 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₁₁H₁₅IO₂
m/z 329.0015 [M-Na]+, found 329.0010; ¹H NMR (300 MHz, CDCl₃) δ 6.94 (dd, J = 9.7, 6.2 Hz, 1H), 5.98 - 5.93 (m, 2H), 4.35 (td, J = 9.3, 3.8 Hz, 1H), 2.56 - 2.25 (m, 3H), 2.02 - 1.86 (m, 1H), 1.85 (d, J = 1.0 Hz, 3H), 1.70 - 1.55 (m, 1H), 1.04 (d, J = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 164.6, 151.6, 146.7, 120.2, 79.2, 76.0, 35.2, 32.4, 29.8, 24.0, 11.6

**Unsaturated carboxylic acid 3.154**

![Unsaturated carboxylic acid 3.154](attachment:image.png)

To a flask containing unsaturated ester 3.104 (66 mg, 0.15 mmol) stirring in THF/MeOH (2 mL, 1:1) was added lithium hydroxide (1.5 mL, 1.5 mmol, 1 M in H₂O). The reaction was stirred at room temperature for 12 hours before being acidified with HCl (5 mL, 1 M). The aqueous layer was extracted with EtOAc (5 x 5 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting carboxylic acid 3.154 (60 mg) was used immediately without further purification.

Data for 3.154: ¹H NMR (300 MHz, CDCl₃) δ 10.08 (br. s, H), 7.12 (dd, J = 15.8, 7.1 Hz, 1H), 5.88 (s, 1H), 5.82 (dd, 15.8, 0.9 Hz, 1H), 3.61 (dt, J = 6.7, 4.8 Hz, 1H), 2.51 (sext, J = 6.2 Hz, 1H) 2.23 - 2.11 (m, 2H), 1.82 (s, 3H), 1.61 - 1.41 (m, 1H), 1.04 (d, J = 6.7 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H)
Vinyl tin 3.112

To a flask containing unsaturated carboxylic acid 3.154 (60 mg), (Z)-3-(tributylstannyl)-2-buten-1-ol (3.106) (110 mg, 0.30 mmol), and DMAP (37 mg, 0.30 mmol) stirring in CH₂Cl₂ (1 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (35 mg, 0.18 mmol). The reaction was stirred at room temperature for 24 hours before being concentrated in vacuo. The resulting residue was chromatographed on silica gel (40:1 to 5:1 hexanes/diethyl ether) to afford vinyl tin 3.112 (90 mg, 0.12 mmol, 79% over 2 steps) as a clear, colorless oil.

Data for 3.112: IR ν 2928, 2855, 1719, 1252, 835, 774 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₃₃H₆₃IO₃Si₂¹¹⁶Sn m / z 801.2506 [M-Na]⁺, found 801.2515; ¹H NMR (300 MHz, CDCl₃) δ 7.00 (dd, J = 15.9, 7.2 Hz, 1H), 6.23 (tq, J = 7.1, 1.7 Hz, 1H), 5.87 (d, J = 1.0 Hz, 1H), 5.81 (dd, J = 15.9, 1.3 Hz, 1H), 4.51 (d, J = 6.9 Hz, 2H), 3.59 (td, J = 6.4, 4.9 Hz, 1H), 2.53 - 2.40 (m, 1H), 2.34 - 2.08 (m, 2H), 1.97 (s, 3H), 1.81 (d, J = 0.8 Hz, 3H), 1.61 - 1.41 (m, 8H), 1.30 (qd, J = 14.6, 7.2 Hz, 6H), 1.05 - 0.84 (m, 24H), 0.04 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 166.5, 151.5, 148.2, 147.9, 134.0, 121.2, 74.9, 74.9, 66.5, 42.0, 35.6, 32.3, 29.3, 27.5, 27.3, 26.1, 24.2, 18.3, 14.7, 13.9, 10.3, -4.2
To a flask containing (S)-(+) 4-benzyl-3-propionyl-2-oxazolidinone (3.52) (1.42 g, 6.1 mmol) stirring in CH₂Cl₂ (40 mL) at 0 °C was added dibutylboron trifluoromethanesulfonate (7.3 mL, 7.3 mmol, 1.0 M in CH₂Cl₂) and then triethylamine (1.10 mL, 7.9 mmol). The solution was then cooled to -78 °C and a solution of (E)-5-iodo-4-methyl-4-pentenal (3.102) (1.5 g, 6.7 mmol) dissolved in CH₂Cl₂ (10 mL) was added slowly. This solution was then stirred at -78 °C for 30 minutes before warming to 0 °C and stirring for an additional hour. The reaction mixture was quenched with pH 7 buffer solution (20 mL), methanol (90 mL), and hydrogen peroxide (20 mL, 30% aqueous soln.) and stirred for another hour at 0 °C. The mixture was then concentrated in vacuo. The aqueous layer was extracted with Et₂O (2 x 50 mL). The combined organic layers were washed with NaHCO₃ (10 mL, sat. aq.) and brine (10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (2:1 hexanes/ethyl acetate) to afford Evans aldol product 3.155 (1.26 g, 2.8 mmol, 45%) as a clear, colorless oil.

Data for 3.155: HRMS (ESI) Anal. Calcd. for C₁₉H₂₄INO₄ m/z 480.0648 [M-Na]⁺, found 480.0643; ¹H NMR (300 MHz, CDCl₃) δ 7.35 - 7.21 (m, 3H), 7.20 - 7.13 (m, 2H), 5.91 (d, J = 0.9 Hz, 1H), 4.74 - 4.62 (m, 1H), 4.24 - 4.11 (m, 2H), 3.87 (td, J = 3.5, 9.0 Hz, 1H), 3.72 (dq, J = 3.1, 7.0 Hz, 1H), 3.19 (dd, J = 13.5, 3.2 Hz, 1H), 3.00 (br. s, 1H), 2.78 (dd, J = 13.3, 9.2 Hz, 1H), 2.58 - 2.20 (m, 2H), 1.81 (d, J = 0.8 Hz, 3H), 1.72 - 1.46 (m, 2H), 1.23 (d, J = 6.9 Hz, 3H); ¹³C NMR
(75 MHz, CDCl$_3$) δ 177.0, 153.0, 147.3, 135.0, 129.4, 128.9, 127.4, 75.3, 70.6, 66.2, 55.0, 42.3, 37.7, 35.8, 31.8, 23.9, 10.8

To a flask containing Evans aldol product 3.155 (1.16 g, 2.5 mmol) stirring at 0 °C in CH$_2$Cl$_2$ (25 mL) was added 2,6-lutidine (0.60 mL, 5.1 mmol) and then tert-butyldimethylsilyl trifluoromethanesulfonate (0.64 mL, 2.8 mmol). The reaction was allowed to warm to room temperature and stirred for 2 hours before being quenched with sodium bicarbonate (30 mL, sat. aq.). The aqueous layer was extracted with Et$_2$O (3 x 20 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (5:1 hexanes/ethyl acetate) to afford TBS protected Evans aldol product 3.114 (1.44 g, 2.5 mmol, 99%) as a clear, colorless oil.

Data for 3.114: IR ν 2857, 1779, 1700, 1208, 836, 775 cm$^{-1}$; HRMS (ESI) Anal. Calcd. for C$_{25}$H$_{38}$INO$_4$Si m/z 594.1513 [M-Na]$^+$, found 594.1505; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.38 - 7.27 (m, 3H), 7.24 - 7.19 (m, 2H), 5.90 (q, $J = 1.3$ Hz, 1H), 4.67 - 4.56 (m, 1H), 4.22 - 4.15 (m, 2H), 4.00 (q, $J = 5.6$ Hz, 1H), 3.92 - 3.82 (m, 1H), 3.28 (dd, $J = 13.3$, 3.1 Hz, 1H), 2.77 (dd, $J = 13.3$, 9.5 Hz, 1H), 2.37 - 2.13 (m, 2H), 1.83 (d, $J = 1.0$ Hz, 3H), 1.78 - 1.59 (m, 2H), 1.22 (d, $J = 6.9$ Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 175.2, 153.2, 148.0, 135.4, 129.6, 129.1, 127.5, 75.0, 72.6, 66.2, 55.9, 42.9, 37.8, 35.1, 33.7, 26.0, 24.3, 18.2, 12.2, -4.0, -4.6
To a flask containing TBS protected Evans aldol product 3.114 (666 mg, 1.2 mmol) stirring at 0 °C in THF (10 mL) was added lithium borohydride (38 mg, 1.7 mmol) and then MeOH (0.5 mL). The reaction was stirred for 3 hours before being quenched with H₂O (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 to 1:1 hexanes/diethyl ether) to afford desired alcohol 3.115 (376 mg, 0.94 mmol, 81%) as a clear, colorless oil.

Data for 3.115: HRMS (ESI) Anal. Calcd. for C₁₅H₃₁IO₂Si m/z 421.1036 [M-Na]⁺, found 421.1045; ¹H NMR (300 MHz, CDCl₃) δ 5.90 (q, J = 1.2 Hz, 1H), 3.73 (dt, J = 6.3, 3.2 Hz, 1H), 3.68 (dd, J = 10.5, 8.5 Hz, 1H), 3.51 (dd, J = 10.6, 5.3 Hz, 1H), 2.39 - 2.26 (m, 1H), 2.25 - 2.04 (m, 2H), 2.17 (br. s, 1H), 2.00 - 1.89 (m, 1H), 1.84 (d, J = 1.0 Hz, 3H), 1.65 - 1.56 (m, 2H), 0.89 (s, 9H), 0.82 (d, J = 6.9 Hz, 3H), 0.09 (s, 3H), 0.07 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 148.0, 75.2, 75.0, 65.9, 39.9, 36.6, 31.0, 26.1, 24.3, 12.3, -4.2, -4.2

To a flask containing alcohol 3.115 (40 mg, 0.10 mmol) stirring in CH₂Cl₂ (2 mL) was added 3,4-dihydro-2H-pyran (0.10 mL, 1.0 mmol) and pyridinium para-toluenesulfonate (5 mg, 0.02 mmol).
The reaction was stirred for 24 hours before being concentrated *in vacuo*. The resulting residue was chromatographed on silica gel (20:1 hexanes/diethyl ether) to afford protected alcohol **3.116** (48 mg, 0.10 mmol, 99%) as a clear, colorless oil.

Data for **3.116**: IR ν 2927, 2856, 1032, 836, 773 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₂₀H₃₉IO₃Si m/z 505.1611 [M-Na]⁺, found 505.1602; ¹H NMR (300 MHz, CDCl₃) δ 5.92 - 5.83 (m, 1H), 4.54 (q, J = 3.2 Hz, 1H), 3.90 - 3.64 (m, 3H), 3.59 - 3.44 (m, 2H), 3.33 (dd, J = 9.6, 6.5 Hz, 0.5H), 3.21 (dd, J = 9.7, 6.2 Hz, 0.5H), 2.37 - 2.13 (m, 2H), 2.04 - 1.89 (m, 1H), 1.83 (t, J = 1.2 Hz, 3H), 1.78 - 1.46 (m, 7H), 0.94 - 0.86 (m, 12H), 0.06 - 0.03 (m, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 148.5, 148.5, 99.1, 99.0, 74.6, 73.1, 72.8, 69.9, 69.8, 62.3, 62.3, 38.9, 38.9, 35.8, 35.6, 31.1, 30.9, 30.9, 26.1, 25.7, 24.3, 19.7, 18.3, 12.8, 12.7, -4.2, -4.2, -4.3

**Diene 3.117**

To a flask containing THP protected alcohol **3.116** (450 mg, 0.93 mmol) and (Z)-3-(tributylstannyl)-2-buten-1-ol (**3.106**) (340 mg, 0.93 mmol) stirring in NMP (10 mL) was added copper(I) thiophene-2-carboxylate (178 mg, 0.93 mmol). The reaction was stirred for 4 hours at room temperature before being filtered and concentrated *in vacuo*. The resulting residue was chromatographed on silica gel (5:1 to 2:1 hexanes-diethyl ether) to afford diene **3.117** (340 mg, 0.80 mmol, 85%) as a clear, colorless oil.

Data for **3.117**: IR ν 3402, 2930, 2856, 1023, 834 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₂₄H₄₆O₄Si m/z 449.3063 [M-Na]⁺, found 449.3078; ¹H NMR (300 MHz, CDCl₃) δ 5.54 (s, 1H), 5.39 (t, J =
6.5 Hz, 1H), 4.51 (d, J = 3.6 Hz, 1H), 3.94 (d, J = 6.7 Hz, 2H), 3.85 - 3.74 (m, 1H), 3.74 - 3.57 (m, 2H), 3.57 - 3.40 (m, 2H), 3.33 (dd, J = 9.6, 6.3 Hz, 0.5H), 3.17 (dd, J = 9.6, 6.3 Hz, 0.5H), 2.17 - 1.86 (m, 5H), 1.71 (s, 3H), 1.58 - 1.43 (m, 9H), 0.91 - 0.82 (m, 12H), 0.04 - 0.04 (m, 6H); ^13^C NMR (75 MHz, CDCl$_3$) δ 139.1, 139.1, 136.2, 125.7, 123.5, 99.0, 98.8, 73.5, 73.2, 69.8, 69.8, 62.1, 62.1, 60.8, 60.7, 38.7, 35.4, 35.3, 31.5, 31.5, 30.8, 30.8, 26.0, 25.6, 24.1, 19.5, 19.5, 18.2, 17.9, 12.9, 12.9, -4.2, -4.4, -4.4

**Phosphonate 3.118**

![Phosphonate 3.118](image)

To a flask containing diene 3.117 (200 mg, 0.47 mmol) stirring in CH$_2$Cl$_2$ (5 mL) was added diethylphosphonoacetic acid (184 mg, 0.94 mmol), DMAP (244 mg, 2.0 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (135 mg, 0.70 mmol). The reaction was stirred at room temperature for 14 hours before being concentrated *in vacuo*. The resulting residue was chromatographed on silica gel (3:1 to 1:1 hexanes/ethyl acetate) to afford phosphonate 3.118 (269 mg, 0.45 mmol, 95%) as a clear, colorless oil.

Data for 3.118: IR ν 2932, 2857, 1737, 1255, 1023 cm$^{-1}$; HRMS (ESI) Anal. Calcd. for C$_{30}$H$_{57}$O$_8$PSi $m/z$ 627.3458 [M-Na]$^+$, found 627.3463; $^1$H NMR (300 MHz, CDCl$_3$) δ 5.45 (s, 1H), 5.26 (t, J = 6.8 Hz, 1H), 4.49 - 4.31 (m, 3H), 4.13 - 3.95 (m, 4H), 3.79 - 3.65 (m, 1H), 3.65 - 3.48 (m, 2H), 3.48 - 3.30 (m, 2H), 3.24 (dd, J = 9.5, 6.4 Hz, 0.5H), 3.08 (dd, J = 9.6, 6.3 Hz, 0.5H), 2.85 (s, 1H), 2.78 (s, 1H), 2.12 - 1.92 (m, 2H), 1.92 - 1.77 (m, 2H), 1.63 (s, 3H), 1.60 - 1.33 (m, 9H), 1.20 (t, J = 7.1 Hz, 6H), 0.86 - 0.72 (m, 12H), -0.03 - -0.12 (m, 6H); $^{13}$C NMR (75 MHz,
CDCl$_3$ $\delta$ 165.6, 165.5, 139.6, 139.5, 139.4, 139.4, 122.7, 119.7, 98.7, 98.5, 73.3, 73.0, 69.5, 69.5, 63.7, 62.5, 62.4, 61.8, 61.8, 38.6, 38.5, 35.2, 35.1, 35.0, 33.3, 31.2, 31.2, 30.6, 30.6, 25.8, 25.5, 23.9, 19.3, 18.0, 17.6, 16.3, 16.2, 12.7, 12.7, -4.4, -4.6, -4.7; $^{31}$P NMR (121 MHz, CDCl$_3$) $\delta$ 20.3

5-Hydroxy-N-methoxy-N-methylpentanamide (3.126)

5-Hydroxy-N-methoxy-N-methylpentanamide (3.126) was prepared by the methods of Molander.$^{197}$ All $^1$H NMR and $^{13}$C NMR spectroscopic data matched reported values.

7-(1-Ethoxyethoxy)-1-heptyn-3-ol (3.157)

To a flask containing 5-hydroxy-N-methoxy-N-methylpentanamide (3.126) (17.0 g, 106 mmol) stirring in CH$_2$Cl$_2$ (200 mL) was added ethyl vinyl ether (20.2 mL, 211 mmol) and pyridinium $p$-toluenesulfonate (1.30 g, 5.0 mmol). The reaction was stirred at room temperature for 12 hours before being quenched with H$_2$O (100 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 40 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (2:1 hexanes/ethyl acetate) to afford protected Weinreb amide 3.127 (21.1 g, 91 mmol, 86%) as a clear, colorless oil.
Data for 3.127: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.74 - 4.60 (m, 1H), 3.70 - 3.66 (m, 3H), 3.66 - 3.55 (m, 2H), 3.55 - 3.37 (m, 2H), 3.17 (s, 3H), 2.50 - 2.40 (m, 2H), 1.79 - 1.55 (m, 5H), 1.32 - 1.27 (m, 3H), 1.23 - 1.14 (m, 3H)

To a flask containing ethynyltrimethylsilane (15 mL, 110 mmol) stirring at -40 °C in THF (300 mL) was added n.butyl lithium (66 mL, 110 mmol, 1.6 M in hexanes). The reaction mixture was allowed to warm to 0 °C and stirred for 2 hours. The solution was then cooled to -10 °C and protected Weinreb amide 3.127 (21.0 g, 90 mmol) dissolved in THF (50 mL) was added slowly. This reaction was allowed to warm to 0 °C and stirred for an additional 3 hours before being quenched with ammonium chloride (200 mL, sat. aq.). The aqueous layer was extracted with Et$_2$O (3 x 50 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 to 1:1 hexanes/diethyl ether) to afford 7-(1-ethoxyethoxy)-1-(trimethylsilyl)-1-heptyn-3-one (3.156) (20.2 g, 75 mmol, 83%) as a clear, colorless oil.

Data for 3.156: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.67 (q, $J = 5.4$ Hz, 1H), 3.69 - 3.48 (m, 2H), 3.48 - 3.37 (m, 2H), 2.59 (t, $J = 7.3$ Hz, 2H), 1.81 - 1.54 (m, 5H), 1.29 (d, $J = 5.4$ Hz, 3H), 1.20 (t, $J = 7.1$ Hz, 3H), 0.23 (s, 9H)

To a flask containing 7-(1-ethoxyethoxy)-1-(trimethylsilyl)-1-heptyn-3-one (3.156) (1.50 g, 5.5 mmol) stirring at 0 °C in MeOH (50 mL) was added cerium(III) trichloride heptahydrate (2.3 g, 6.1 mmol) and sodium borohydride (315 mg, 8.3 mmol). The reaction was allowed to warm to room temperature and stir for 2 hours. The mixture was concentrated in vacuo and then diluted with H$_2$O (30 mL) and EtOAc (30 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL).
The combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 to 1:1 hexanes/ethyl acetate) to afford 7-(1-ethoxyethoxy)-1-heptyn-3-ol (3.157) (0.98 g, 4.9 mmol, 88%) as a clear, colorless oil.

Data for 3.157: IR $\nu$ 3418, 3307, 2940, 2869, 1128, 1081, 1054 cm$^{-1}$; HRMS (ESI) Anal. Calcd. for C$_{11}$H$_{20}$O$_3$ $m/z$ 223.1310 [M-Na]$^+$, found 223.1317; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.56 (q, $J = 5.4$ Hz, 1H), 4.22 (dq, $J = 6.0$, 1.3 Hz, 1H), 3.61 - 3.24 (m, 5H), 2.35 (d, $J = 2.3$ Hz, 1H), 1.69 - 1.32 (m, 6H), 1.17 (d, $J = 5.4$ Hz, 3H), 1.06 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 99.4, 85.2, 72.6, 64.9, 61.6, 60.6, 37.2, 29.3, 21.8, 19.7, 15.2

**TIPS protected alcohol 3.128**

To a flask containing 7-(1-ethoxyethoxy)-1-heptyn-3-ol (3.157) (13.0 g, 65 mmol) stirring in CH$_2$Cl$_2$ (400 mL) was added triethylamine (46 mL, 320 mmol) and triisopropylsilyl trifluoromethanesulfonate (18.3 mL, 68 mmol). The reaction was stirred at room temperature for 2 hours before being quenched with sodium bicarbonate (100 mL, sat. aq.). The aqueous layer was extracted with Et$_2$O (3 x 50 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (20:1 hexanes/diethyl ether) to afford TIPS protected alcohol 3.128 (22.0 g, 62 mmol, 95%) as a clear, colorless oil.
Data for 3.128: IR ν 2943, 2867, 1464, 1099, 1061, 822 cm⁻¹; HRMS (ESI) Anal. Calcd. for C_{20}H_{40}O_{3}Si m/z 379.2644 [M-Na]⁺, found 379.2651; ¹H NMR (300 MHz, CDCl₃) δ 4.67 (q, J = 5.3 Hz, 1H), 4.46 (dt, J = 6.2, 2.1 Hz, 1H), 3.72 - 3.56 (m, 2H), 3.56 - 3.36 (m, 2H), 2.36 (d, J = 2.1 Hz, 1H), 1.78 - 1.65 (m, 2H), 1.65 - 1.48 (m, 4H), 1.29 (d, J = 5.4 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H), 1.12 - 1.01 (m, 21H); ¹³C NMR (75 MHz, CDCl₃) δ 99.7, 99.7, 85.8, 72.3, 65.3, 65.2, 63.0, 60.8, 60.8, 38.8, 29.8, 21.9, 20.0, 18.2, 18.2, 15.5, 12.4

**Ethyl (Z)-3-iodo-2-butenoate (3.159)**

![Chemical structure of Ethyl (Z)-3-iodo-2-butenoate](image)

Ethyl (Z)-3-iodo-2-butenoate (3.159) was prepared by the methods of Piers.²⁰⁰ All ¹H NMR and ¹³C NMR spectroscopic data matched reported values.

**Phosphonate 3.130**

![Phosphonate reaction scheme](image)

To a flask containing 9-borabicyclo[3.3.1]nonane (6.8 g, 28 mmol) stirring in THF (120 mL) was added TIPS protected alcohol 3.128 (10.0 g, 28 mmol) dissolved in THF (60 mL). The resulting solution was stirred for 20 minutes at room temperature and then heated to reflux and stirred for an additional 2 hours. The reaction was then cooled to 0 °C and charged with benzaldehyde (2.9 mL, 28 mmol). This mixture was allowed to warm to room temperature and stirred for an additional
12 hours before being concentrated in vacuo. The resulting residue was dissolved in DMF (100 mL), THF (100 mL), and H₂O (10 mL). To this flask was added tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (400 mg, 0.39 mmol), triphenylarsine (900 mg, 2.9 mmol), potassium carbonate (7.8 g, 56 mmol), and ethyl (Z)-3-iodo-2-butenoate (3.159) (6.0 g, 25 mmol). The resulting mixture was stirred at room temperature for 48 hours before being diluted with H₂O (100 mL) and Et₂O (100 mL). The aqueous layer was extracted with Et₂O (3 x 50 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (10:1 to 4:1 hexanes/diethyl ether) to afford ester 3.160 (10.2 g, 22 mmol, 77%) as a clear, colorless oil.

To a flask containing ester 3.160 (10.2 g, 22 mmol) stirring at -78 °C in THF (200 mL) was added DIBALH (59 mL, 59 mmol, 1.0 M in hexanes). The reaction was allowed to warm to room temperature and stirred for 4 hours before being quenched with sodium hydroxide (100 mL, 2 M). The aqueous layer was extracted with Et₂O (3 x 50 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was chromatographed on silica gel (3:1 hexanes/diethyl ether) to afford alcohol 3.129 (9.0 g, 21 mmol, 97%) as a clear, colorless oil.

Data for 3.129: ¹H NMR (300 MHz, CDCl₃) δ 6.52 (d, J = 15.6 Hz, 1H), 5.74 (dd, J = 15.8, 6.5 Hz, 1H), 5.54 (t, J = 7.1 Hz, 1H), 4.67 (q, J = 5.4 Hz, 1H), 4.37 - 4.23 (m, 3H), 3.70 - 3.34 (m, 4H), 1.89 - 1.82 (m, 3H), 1.66 - 1.49 (m, 5H), 1.43 - 1.36 (m, 2H), 1.29 (d, J = 5.1 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H), 1.05 (s, 21H)
To a flask containing alcohol 3.129 (9.0 g, 21 mmol) stirring in CH₂Cl₂ (200 mL) was added
diethylphosphonoacetic acid (3.7 mL, 23 mmol), triethylamine (3.8 mL, 27 mmol), DMAP (330
mg, 2.7 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (4.8 g, 25 mmol). The
reaction was stirred at room temperature for 14 hours before being quenched with ammonium
chloride (100 mL, sat. aq.). The aqueous layer was extracted with EtOAc (3 x 50 mL). The
combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting
residue was chromatographed on silica gel (3:1 to 1:3 hexanes/ethyl acetate) to afford phosphonate
3.130 (9.0 g, 15 mmol, 71%) as a clear, colorless oil.

Data for 3.130: IR ν 2941, 2866, 1737, 1265, 1053, 124 cm⁻¹; HRMS (ESI) Anal. Calcd. for
C₃₀H₅₉O₈PSi m / z 629.3615 [M-Na]⁺, found 629.3610; ¹H NMR (300 MHz, CDCl₃) δ 6.46 (d, J
= 15.6 Hz, 1H), 5.74 (dd, J = 15.6, 6.7 Hz, 1H), 5.42 (t, J = 7.2 Hz, 1H), 4.73 (d, J = 7.2 Hz, 2H),
4.63 (q, J = 5.3 Hz, 1H), 4.29 (q, J = 5.9 Hz, 1H), 4.20 - 4.04 (m, 4H), 3.66 - 3.30 (m, 4H), 2.96
(s, 1H), 2.89 (s, 1H), 1.82 (s, 3H), 1.68 - 1.43 (m, 6H), 1.42 - 1.20 (m, 9H), 1.15 (t, J = 7.1 Hz,
3H), 1.01 (s, 21H); ¹³C NMR (75 MHz, CDCl₃) δ 165.8, 137.4, 136.5, 125.0, 122.0, 99.7, 73.7,
65.3, 65.2, 62.9, 62.8, 61.5, 60.8, 60.7, 38.7, 35.3, 33.5, 31.7, 30.1, 22.8, 21.6, 20.7, 20.0, 18.3,
18.3, 18.2, 18.2, 16.5, 16.4, 15.4, 14.2, 12.8, 12.5; ³¹P NMR (121 MHz, CDCl₃) δ 20.3, 20.1
Chapter 4: Studies Towards Synthesis of Nahuoic Acid A Through an Early Stage Diels-Alder Reaction

4.1 Retrosynthetic Analysis for Nahuoic Acid A Using an Early Stage Diels-Alder Reaction

Considering the difficulty encountered when trying to forming a cis-decalin through a late stage IMDA (chapter 3), a new approach was evaluated where the cis-decalin would be installed early in the synthesis and surrounding groups added afterwards. Scheme 4.1 shows the initial retrosynthetic approach.

Scheme 4.1: Retrosynthetic analysis for nahuoic acid A using an early stage Diels-Alder reaction

The decalin core of nahuoic acid A (3.8) and polyl side chain were once again envisioned to be connected through a zirconium catalyzed carboalumination reaction. Synthesis of diol 3.25 and similar structures was described in chapter 3. Cis-decalin 4.1 could be simplified to structure 4.2, which in turn could arrive from known Diels-Alder reaction between (1E,3E)-1-(tert-butyl(dimethyl)siloxy)-1,3-pentadiene (4.3) and 2,6-dimethylbenzoquinone (4.4). The exact functionality around the decalin 4.2 would be determined by successful reactions.
4.2 Previous Work in the Dake Lab

Scheme 4.2: Dr. Andrew Beekman’s synthetic work towards nahuoic acid A using a) S\(_{2}'\) displacement and b) 1,4-addition reactions

Dr. Andrew Beekman, a former member of the Dake lab, had attempted reactions along this route prior to my work (scheme 4.2). The work began with a known Diels-Alder process that established the \(cis\)-decalin core in step one.\(^{201–203}\) Following this, various transformations (such as S\(_{2}'\) displacement and 1,4-addition reactions)\(^{204}\) were attempted to convert the decalin’s substituents into ones resembling the substituents on nahuoic acid A (3.8). Unfortunately, the configurations constructed by these reactions were opposite to what was desired.
4.3 Synthesis and Derivatization of *cis*-Decalin Compounds

4.3.1 Analysis of Potential Methods for Stereoselective C-C Bond Formation

Scheme 4.3: Potential methods of stereoselective C-C bond formation using b) 1,4-addition of an intramolecular nucleophile, b) S_N' displacement by an intramolecular nucleophile, c) [3,3]-sigmatropic rearrangements, or d) metal catalyzed intramolecular cycloisomerization.

When I joined the project, the goal was to transform Diels-Alder adduct 4.14 into substituted *cis*-decalin 4.15. After looking over Dr. Beekman’s research, I decided to approach the problem of stereoselective C-C bond formation of substituents on the decalin, specifically the stereochemistry of the “R’” unit (4.15, scheme 4.3). Dr. Beekman’s work indicated that addition of external nucleophiles created the incorrect stereochemical outcome. To solve this problem, I chose methods to create this bond intramolecularly. The four main strategies identified were: conjugate addition using a tethered nucleophile, S_N’ displacement using a tethered nucleophile, [3,3]-sigmatropic rearrangements, or cycloisomerization of a tethered alkene or alkyne.
4.3.2 Synthesis of cis-Decalin Compounds for Exploration of Stereoselective C-C Bond Forming Reactions

Scheme 4.4: a) DA reaction to synthesize cis-decalin core and b) derivatization into various oxidation states for future functionalization reactions

The synthetic work began with preparation of (E)-(buta-1,3-dien-1-yloxy)(tert-butyl)dimethylsilane (4.25) from crotonaldehyde (4.24) under known conditions (scheme 4.4). I selected diene 4.25 for the DA reaction (instead of butadiene 4.5) to add another functional handle to the decalin, and because of its straightforward preparation. Stirring diene 4.25 with 2,6-dimethylbenzoquinone (4.4) in boiling toluene afforded cis-decalin 4.26 in high yield. These conditions also formed trans-decalin 4.27 over time, so careful monitoring of the reaction by TLC was necessary. Using diene 4.25 precluded the addition of a Lewis acid, but it also created a regioselectivity problem. The desired decalin 4.26 was formed in a 10:1 ratio to an undesired regioisomer (see experimental section), as determined by $^1$H NMR of the crude products.
After some experimentation, I discovered that chemoselective reduction of conjugated dione 4.26 was made possible by using specific reducing agents. For example, mixing dione 4.26 with sodium borohydride caused reduction of the more electron-deficient northern ketone to form enone 4.28. X-ray crystallographic analysis of enone 4.28 confirmed the selective reduction as well as the relative configuration of all chiral centers. Reaction of enone 4.28 with DIBALH resulted in diol 4.29. Despite isolation of diol 4.29 as a pure, crystalline solid, its NMR spectra were convoluted. Thankfully, X-ray crystallographic analysis confirmed the structure of diol 4.29.

Mixing dione 4.26 with DIBALH caused reduction of the less hindered southern ketone to form enone 4.30. $^1$H NMR spectra for enones 4.28 and 4.30 were similar, but each was identifiable by the chemical shift of the vinyl hydrogen (scheme 4.4b): $\delta$ 6.80 for enone 4.28 versus $\delta$ 5.80 for enone 4.30. Not surprisingly, each ketone reduction occurred by hydride attack from the convex face.

Mixing dione 4.26 with K-selectride caused reduction of the conjugated alkene to form a single isomer of dione 4.31. After some experimentation on dione 4.31, I realized that both mildly acidic and mildly basic conditions caused formation of trans-decalin species. This undesired result deterred pursuing the synthesis of nahuoic acid A through this intermediate.

**Scheme 4.5: Formation of unusual by-product during workup**
If diol 4.29 was allowed to sit in dilute acid during or after workup, tricyclic product 4.32 formed (scheme 4.5). NMR spectra of the product indicated shifting of an alkene (four alkene $^1$H resonances) and formation of a tertiary ether (three O-$^{13}$C resonances, but only two O-C-$^1$H resonances) but the exact structure was not immediately obvious. Luckily, crystallization of the product allowed confirmation of the structure by X-ray crystallographic analysis. This result confirmed that cis-decalins of this type had a propensity for trans-annular reactions, which needed accounting for when selecting reaction conditions.

4.3.3 Conjugate Addition Strategy For C-C Bond Formation

Scheme 4.6: Attempted C-C bond forming reactions by conjugate addition

Exploration of 1,4-addition chemistry began with enone 4.30. Attaching groups directly to the alcohol of enone 4.30 was problematic, possibly due to the alcohol being sterically hindered. To circumvent this problem, first the less hindered alcohol of diol 4.29 was acetylated to form 4.34, which was then oxidized with DMP. Much to my surprise, NMR and MS spectral analysis showed the reaction had formed enone 4.30. This result indicated that enone 4.30 was unusually hindered/strained and that conjugate addition with a tethered nucleophile might not be a viable pathway.
4.3.4  S_N’ Displacement Strategy For C-C Bond Formation

Scheme 4.7: Attempted intramolecular S_N’ displacement with acetate or \( \beta \)-ketoester nucleophiles

As shown in scheme 4.6, the less hindered alcohol of diol 4.29 could be acylated using acetic anhydride to form acetate 4.34. However, changing the acetylating agent to acetyl chloride produced unexpected \( \beta \)-ketoester 4.35 (confirmed by HRMS) as well as acetate 4.34 (scheme 4.7). Screening of Lewis acid and base combinations to cause an S_N’ reaction of acetate 4.34 and \( \beta \)-ketoester 4.35 came up unsuccessful. All conditions appeared to decompose the starting material without any sign of tricycle 4.37. To increase the potential for S_N’ displacement by creating a better leaving group, I tried to react the alcohol of acetate 4.34 or \( \beta \)-ketoester 4.35 with sulfonylating reagents (MsCl, TsCl, or Tf_2O). Unfortunately, no conditions showed any sign of sulfonylation products. This was a surprising result because Dr. Beekman was able to append picolinic acid to the northern alcohol of diol 4.7 (scheme 4.2).

The above reactions indicated that the bulky TBS protecting group on acetate 4.34 or \( \beta \)-ketoester 4.35 might be sterically hindering reactivity of the free alcohol. To solve this problem, the TBS group on acetate 4.34 was first removed using TBAF providing diol 4.38 in high yield.
Unfortunately, β-ketoester 4.35 decomposed when exposed to TBAF. Stirring diol 4.38 with either CDI or thionyl chloride gave cyclic carbamate 4.39 or sulfite 4.41, respectively. Sulfite 4.41 formed as a 7:4 mixture of inseparable diastereomers, but I expected that one or both of the diastereomers would show desired reactivity so they were moved forwards without further purification. Formation of carbamate 4.39 and sulfite 4.41 did not add any new hydrogens so confirmation of the structure came from HRMS and IR analysis. Carbamate 4.39 displayed a characteristic carbamate C=O stretch at 1774 cm⁻¹, while sulfite 4.41 displayed S=O stretches at 1238 and 1208 cm⁻¹.

Scheme 4.8: Synthesis of carbonate and sulfite compounds for potential Sₙ' reactions

Attempting to cause a Sₙ' reaction by deprotonation of carbamate 4.39 or sulfite 4.41 with a strong base (NaH, LDA, LiHMDS, KHMDS, LiTMP) through intermediates 4.40 and 4.42 was
unsuitable. The only isolable products of these reactions were diol 4.38 and what appeared to be deacetylation products (e.g. 4.44). To increase reactivity of the sulfite, I attempted to oxidize it to a sulfate under standard oxidizing conditions (RuCl₃ and NaIO₄). Interestingly, these conditions only affected the major sulfite diastereomer, forming what appeared to be product 4.45 (by ¹H NMR and MS spectral analysis), while leaving the minor diastereomer unreacted.

![Figure 4.1: a) Pictorial representation of the side view of the B ring of sulfite 4.41 and b) Chem3D model of sulfite 4.41](image)

These results indicated two things: first, the cis-decalin structure seemed to hinder reactions of atoms on the concave face of the molecule (figure 4.1). Second, there seemed to be poor overlap between the alkene pi bonding orbitals and C-O sigma antibonding orbital, making SN′ reactions difficult. Modelling sulfite 4.41 using Chem3D software showed an angle of 136° between the πC-C and σ*C-O orbitals.

### 4.3.5 [3,3]-Sigmatropic Rearrangement Strategy For C-C Bond Formation

To minimize the steric hindrance on the concave face of the cis-decalins, I decided to restart the synthesis of cis-decalin substrates using butadiene 4.5 as a starting material instead of (E)-(buta-1,3-dien-1-yloxy)(tert-butyl)dimethylsilane 4.25 (scheme 4.9). Mixing butadiene 4.5 and 2,6-dimethylbenzoquinone 4.4 in the presence of BF₃ etherate formed cis-decalin 4.6 in quantitative yield. A 2-step reduction sequence using sodium borohydride followed by DIBALH
(similar to conditions in scheme 4.4) formed diol 4.7 in high yield. After protection of the less hindered alcohol as TBS ether 4.46, I attempted reactions with the northern alcohol.

Subjecting TBS ether 4.46 to Johnson-Claisen conditions\textsuperscript{209,210} at temperatures up to 200 °C not only failed to provide ester 4.47, it failed to elicit any reaction whatsoever. Thinking that this was once again a problem of hindrance to atoms on the concave face, acetate 4.48 was synthesized to try Ireland-Claisen conditions instead.\textsuperscript{211–213} Deprotonation of acetate 4.48 with LDA followed by quenching with TMSCl succeeded in adding a silyl group to the molecule, but failed to cause a rearrangement reaction. At first, I assumed that rigidity of enol silyl ether 4.49 caused poor orbital overlap, preventing a [3,3]-sigmatropic rearrangement. However, close inspection of the \textsuperscript{1}H NMR spectrum revealed that \(\alpha\)-silyl ester 4.51 had actually formed instead of

Scheme 4.9: a) Synthesis of diol 4.7 and b) attempted [3,3]-sigmatropic rearrangements

Subjecting TBS ether 4.46 to Johnson-Claisen conditions\textsuperscript{209,210} at temperatures up to 200 °C not only failed to provide ester 4.47, it failed to elicit any reaction whatsoever. Thinking that this was once again a problem of hindrance to atoms on the concave face, acetate 4.48 was synthesized to try Ireland-Claisen conditions instead.\textsuperscript{211–213} Deprotonation of acetate 4.48 with LDA followed by quenching with TMSCl succeeded in adding a silyl group to the molecule, but failed to cause a rearrangement reaction. At first, I assumed that rigidity of enol silyl ether 4.49 caused poor orbital overlap, preventing a [3,3]-sigmatropic rearrangement. However, close inspection of the \textsuperscript{1}H NMR spectrum revealed that \(\alpha\)-silyl ester 4.51 had actually formed instead of

Scheme 4.9: a) Synthesis of diol 4.7 and b) attempted [3,3]-sigmatropic rearrangements

Subjecting TBS ether 4.46 to Johnson-Claisen conditions\textsuperscript{209,210} at temperatures up to 200 °C not only failed to provide ester 4.47, it failed to elicit any reaction whatsoever. Thinking that this was once again a problem of hindrance to atoms on the concave face, acetate 4.48 was synthesized to try Ireland-Claisen conditions instead.\textsuperscript{211–213} Deprotonation of acetate 4.48 with LDA followed by quenching with TMSCl succeeded in adding a silyl group to the molecule, but failed to cause a rearrangement reaction. At first, I assumed that rigidity of enol silyl ether 4.49 caused poor orbital overlap, preventing a [3,3]-sigmatropic rearrangement. However, close inspection of the \textsuperscript{1}H NMR spectrum revealed that \(\alpha\)-silyl ester 4.51 had actually formed instead of

Scheme 4.9: a) Synthesis of diol 4.7 and b) attempted [3,3]-sigmatropic rearrangements

Subjecting TBS ether 4.46 to Johnson-Claisen conditions\textsuperscript{209,210} at temperatures up to 200 °C not only failed to provide ester 4.47, it failed to elicit any reaction whatsoever. Thinking that this was once again a problem of hindrance to atoms on the concave face, acetate 4.48 was synthesized to try Ireland-Claisen conditions instead.\textsuperscript{211–213} Deprotonation of acetate 4.48 with LDA followed by quenching with TMSCl succeeded in adding a silyl group to the molecule, but failed to cause a rearrangement reaction. At first, I assumed that rigidity of enol silyl ether 4.49 caused poor orbital overlap, preventing a [3,3]-sigmatropic rearrangement. However, close inspection of the \textsuperscript{1}H NMR spectrum revealed that \(\alpha\)-silyl ester 4.51 had actually formed instead of
enol silyl ether 4.49. A lack of new alkene resonances and two new doublets (δ 1.93 and 1.82) showing geminal coupling (J = 11.8 Hz) indicated that the TMS group was bonded to carbon. Surprisingly, trying to synthesize enol silyl ether 4.49 using TMSOTf also led to α-silyl ester 4.51. Experiments to attach other groups for sigmatropic rearrangement reactions were unsuccessful so I moved on to the next best strategy: metal catalyzed cycloisomerization reactions.

### 4.3.6 Metal Catalyzed Cycloisomerization Strategy For C-C Bond Formation

![Scheme 4.10](image)

**Scheme 4.10: One possible mechanism for a metal catalyzed 1,6-enzyme cycloisomerization**

Cycloisomerization reactions are isomerization reactions that produce a cyclic isomer. The exact mechanism, and thus reaction product of a cycloisomerization, depends on the substrate, metal\textsuperscript{214–217}, and ligands\textsuperscript{218–220}. Stoichiometric additives can also affect reaction outcomes. For example, adding hydrides can form reduced products\textsuperscript{221–223}, adding carbon monoxide gas can form carbonylated product\textsuperscript{224–227}, and adding halogens can form halogenated products\textsuperscript{228–230}. Metals known to catalyze cycloisomerization reactions include: Pd, Pt, Rh, Ru, Co, Ti, Ir, Hg, Cr, Fe, Ni, Cu, Ag, Ga, and In\textsuperscript{214–217}.  

150
I wanted to investigate 1,6-enzyme cycloisomerizations on substrates such as 4.52 (scheme 4.10), with or without the use of additives. In this reaction, after the metal associates with unsaturated fragments (4.53), a metallacyclopentene with all-syn stereochemistry (4.54) can form through oxidative coupling. The metal can then abstract a β hydrogen to form a metal hydride (4.55) that can undergo reductive elimination to provide 1,4-diene 4.56, while regenerating the metal catalyst. X could be any linker such as: O, S, Si, CH₂, or a diester.

### 4.3.6.1 Synthesis of Substrates For Metal Catalyzed Cycloisomerization

**Scheme 4.11: Failed attempts to functionalize less hindered alcohol of diol 4.7**

Substrates synthesized for cycloisomerization reactions required a pendent alkene or alkyne moiety (scheme 4.3d). To accomplish this, I tried to react the less hindered alcohol of diol 4.7 with various electrophiles (some examples shown in scheme 4.11), most containing an alkyne or an alkene fragment. The majority of these reactions were unsuccessful, but the electrophiles that did show success were all silanes.

**Scheme 4.12: Reaction of diol 4.7 with alkynylsilanes**
Alkynyl silane 4.62 reacted with diol 4.7 to form 1,6-enyne 4.63, while the 1,6-enyne derived from alkynyl silane 4.64 was oxidized with DMP to afford enone 4.65. While the intermediate before DMP oxidation was also a 1,6-enyne, I also synthesized enone 4.65 to explore reactivity differences between cycloisomerizations with an electron rich alkene (4.63) versus an electron poor alkene (4.65) substrate. Silanes 4.62 and 4.64 were prepared fresh before each reaction.231,232

4.3.6.2 Attempted Metal Catalyzed Cycloisomerizations

With 1,6-enynes in hand, each was tested in parallel for cycloisomerization reactivity under conditions described in tables 4.1 - 4.3. Unfortunately, the majority of conditions either desilylated the starting materials or returned starting materials. One reaction (table 4.3, entry 2) did produce vinyl silane 4.71, but none showed any sign of a cycloisomerization reaction.

Table 4.1: Attempted cycloisomerization conditions for 1,6-enyne 4.63

<table>
<thead>
<tr>
<th>Entry</th>
<th>Precatalyst</th>
<th>Ligand</th>
<th>Additive</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd2(dba)3</td>
<td>dppb</td>
<td>Et3SiH</td>
<td>dioxane</td>
<td>80 °C</td>
<td>12 h</td>
<td>decomp</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)2</td>
<td>dppb</td>
<td>AcOH</td>
<td>PhCH3</td>
<td>90 °C</td>
<td>12 h</td>
<td>4.63 and 4.7</td>
</tr>
<tr>
<td>3</td>
<td>PtCl2</td>
<td>-</td>
<td>-</td>
<td>PhCH3</td>
<td>90 °C</td>
<td>12 h</td>
<td>4.7</td>
</tr>
<tr>
<td>4</td>
<td>[Ru(cymene)Cl2]2</td>
<td>-</td>
<td>-</td>
<td>PhCH3</td>
<td>110 °C</td>
<td>12 h</td>
<td>4.7</td>
</tr>
<tr>
<td>5</td>
<td>[Rh(cod)Cl]2</td>
<td>-</td>
<td>-</td>
<td>PhCH3</td>
<td>90 °C</td>
<td>12 h</td>
<td>4.7</td>
</tr>
<tr>
<td>6</td>
<td>Cr(CO)3Naphth</td>
<td>-</td>
<td>-</td>
<td>PhCH3</td>
<td>90 °C</td>
<td>12 h</td>
<td>4.63</td>
</tr>
<tr>
<td>7</td>
<td>Ti(O’Pr)4</td>
<td>-</td>
<td>CyMgBr</td>
<td>PhCH3</td>
<td>-78 - 70 °C</td>
<td>24 h</td>
<td>4.63</td>
</tr>
<tr>
<td>8</td>
<td>Cp2TiCl2</td>
<td>-</td>
<td>CyMgBr</td>
<td>PhCH3</td>
<td>-78 - 70 °C</td>
<td>24 h</td>
<td>4.63</td>
</tr>
</tbody>
</table>

†All reaction used 20 mg substrate, 50 mol% precatalysts and ligands, 2.0 eq. additives, and run at 0.1 M
Table 4.2: Attempted cycloisomerization conditions for 1,6-enyne 4.67

<table>
<thead>
<tr>
<th>Entry</th>
<th>Precatalyst</th>
<th>Ligand</th>
<th>Additive</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd$_2$(dba)$_3$</td>
<td>dppb</td>
<td>Et$_3$SiH</td>
<td>dioxane</td>
<td>80 °C</td>
<td>12 h</td>
<td>decomp</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>dppb</td>
<td>Et$_3$SiH and AcOH</td>
<td>dioxane</td>
<td>80 °C</td>
<td>12 h</td>
<td>4.67 and 4.7</td>
</tr>
<tr>
<td>3</td>
<td>PtCl$_2$</td>
<td>-</td>
<td>-</td>
<td>PhCH$_3$</td>
<td>90 °C</td>
<td>12 h</td>
<td>4.7</td>
</tr>
<tr>
<td>4</td>
<td>[Ru(cymene)Cl$_2$]$_2$</td>
<td>-</td>
<td>-</td>
<td>PhCH$_3$</td>
<td>110 °C</td>
<td>12 h</td>
<td>4.7</td>
</tr>
<tr>
<td>5</td>
<td>[Rh(cod)Cl]$_2$</td>
<td>-</td>
<td>-</td>
<td>PhCH$_3$</td>
<td>90 °C</td>
<td>12 h</td>
<td>4.7</td>
</tr>
<tr>
<td>6</td>
<td>Cr(CO)$_3$Naphth</td>
<td>-</td>
<td>-</td>
<td>PhCH$_3$</td>
<td>90 °C</td>
<td>12 h</td>
<td>4.67</td>
</tr>
<tr>
<td>7</td>
<td>Ti(O'Pr)$_4$</td>
<td>-</td>
<td>CyMgBr</td>
<td>PhCH$_3$</td>
<td>-78 - 70 °C</td>
<td>24 h</td>
<td>4.67</td>
</tr>
<tr>
<td>8</td>
<td>Cp$_2$TiCl$_2$</td>
<td>-</td>
<td>CyMgBr</td>
<td>PhCH$_3$</td>
<td>-78 - 70 °C</td>
<td>24 h</td>
<td>4.67</td>
</tr>
<tr>
<td>9</td>
<td>Cp$_2$TiCl$_2$</td>
<td>-</td>
<td>CyMgBr</td>
<td>PhCH$_3$</td>
<td>-78 - 70 °C</td>
<td>24 h</td>
<td>4.67</td>
</tr>
</tbody>
</table>

†All reaction used 20 mg substrate, 50 mol% precatalysts and ligands, 2.0 eq. additives, and run at 0.1 M

Table 4.3: Attempted cycloisomerization conditions for 1,6-enyne 4.65

<table>
<thead>
<tr>
<th>Entry</th>
<th>Precatalyst</th>
<th>Ligand</th>
<th>Additive</th>
<th>Solvent</th>
<th>Temp</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd$_2$(dba)$_3$</td>
<td>dppb</td>
<td>Et$_3$SiH</td>
<td>dioxane</td>
<td>80 °C</td>
<td>12 h</td>
<td>decomp</td>
</tr>
<tr>
<td>2</td>
<td>Pd$_2$(dba)$_3$</td>
<td>dppb</td>
<td>Et$_3$SiH and AcOH</td>
<td>dioxane</td>
<td>80 °C</td>
<td>12 h</td>
<td>4.71</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>dppb</td>
<td>Et$_3$SiH and AcOH</td>
<td>dioxane</td>
<td>80 °C</td>
<td>12 h</td>
<td>4.71</td>
</tr>
<tr>
<td>4</td>
<td>PtCl$_2$</td>
<td>-</td>
<td>-</td>
<td>PhCH$_3$</td>
<td>90 °C</td>
<td>12 h</td>
<td>4.65 and 4.70</td>
</tr>
<tr>
<td>5</td>
<td>[Ru(cymene)Cl$_2$]$_2$</td>
<td>-</td>
<td>-</td>
<td>PhCH$_3$</td>
<td>90 °C</td>
<td>12 h</td>
<td>4.70</td>
</tr>
<tr>
<td>6</td>
<td>[Rh(cod)Cl]$_2$</td>
<td>-</td>
<td>-</td>
<td>PhCH$_3$</td>
<td>90 °C</td>
<td>12 h</td>
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<tr>
<td>7</td>
<td>Cr(CO)$_3$Naphth</td>
<td>-</td>
<td>-</td>
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<td>90 °C</td>
<td>12 h</td>
<td>4.65</td>
</tr>
<tr>
<td>8</td>
<td>Ti(O'Pr)$_4$</td>
<td>-</td>
<td>CyMgBr</td>
<td>PhCH$_3$</td>
<td>-78 - 70 °C</td>
<td>24 h</td>
<td>4.65</td>
</tr>
<tr>
<td>9</td>
<td>Cp$_2$TiCl$_2$</td>
<td>-</td>
<td>CyMgBr</td>
<td>PhCH$_3$</td>
<td>-78 - 70 °C</td>
<td>24 h</td>
<td>4.65</td>
</tr>
</tbody>
</table>

†All reaction used 20 mg substrate, 50 mol% precatalysts and ligands, 2.0 eq. additives, and run at 0.1 M
4.4 Conclusion

Functionalization of a decalin by conjugate addition, $S_N'$ displacement, [3,3]-sigmatropic rearrangements, or cycloisomerization had all failed so at this point, another re-evaluation of the retrosynthesis seemed required to achieve the total synthesis of nahuoic acid A (3.8). An early stage DA reaction was an effective approach to synthesis of decalins but failed to agree with subsequent functionalization attempts. The inverse approach (chapter 3) was effective for functionalization of linear carbon chains, but failed to produce a decalin. Perhaps the approach that will succeed involves a combination of the two strategies.
4.5 Experimental

General experimental (see Appendix A)

\((E)-(\text{Buta-1,3-dien-1-yloxy})(\text{tert-butyl})\text{dimethylsilane (4.25)}\)

\[
\begin{align*}
\text{4.24} & \quad \xrightarrow{} \quad \text{4.25}
\end{align*}
\]

\((E)-(\text{Buta-1,3-dien-1-yloxy})(\text{tert-butyl})\text{dimethylsilane (4.25)}\) was prepared by the methods of Imagawa et. al.\textsuperscript{205} All \(^1\text{H}\) NMR and \(^{13}\text{C}\) NMR spectroscopic data matched reported values.

Conjugated dione 4.26

\[
\begin{align*}
\text{4.25} & \quad + \quad \text{4.4} & \quad \xrightarrow{} & \quad \text{4.26} & \quad + \quad \text{4.27} & \quad + \quad \text{4.72}
\end{align*}
\]

To a sealable tube was added diene \textbf{4.25} (3.0 g, 16.3 mmol) and 2,6-dimethylbenzoquinone \textbf{4.4} (1.57 g, 11.5 mmol), each dissolved in PhCH\(_3\) (10 mL). A crystal of butylated hydroxytoluene (10 mg, 0.05 mmol) was added to the solution, before the tube was sealed and heated to 140 °C for 16 hours. The solution was concentrated \textit{in vacuo}, and the resulting residue was purified by flash column chromatography on silica gel (10:1 to 5:1 hexanes/diethyl ether) to afford conjugated dione \textbf{4.26} (3.22 g, 10.0 mmol, 87%) and \textit{trans}-decalin \textbf{4.27} (52 mg, 0.16 mmol, 1%) as oils.

Note: crude \(^1\text{H}\) NMR showed the desired product was formed in a 10:1 ratio to the undesired regioisomer \textbf{4.72}. The desired product \textbf{4.26} and undesired regioisomer \textbf{4.72} were inseparable, so complete data was not obtained for the undesired regioisomer \textbf{4.72}. 

155
Data for 4.26: IR ν 2930, 2857, 1678, 1051 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₁₈H₂₈O₃Si m/z 343.1705 [M-Na]⁺, found 343.1710; ¹H NMR (300 MHz, CDCl₃) δ 6.68 (q, J = 1.5 Hz, 1H), 5.80 (ddd, J = 10.2, 4.4, 2.6 Hz, 1H), 5.68 (tdd, J = 2.3, 4.9, 10.0 Hz, 1H), 3.90 (d, J = 5.4 Hz, 1H), 3.08 (ddd, J = 19.2, 4.5, 1.0 Hz, 1H), 2.86 (d, J = 7.4 Hz, 1H), 2.08 - 1.97 (m, 1H), 1.96 (d, J = 1.5 Hz, 3H), 1.29 (s, 3H), 0.72 (s, 9H), -0.06 (s, 3H), -0.14 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 203.1, 197.2, 149.0, 139.7, 127.8, 126.2, 71.7, 48.4, 25.9, 25.6, 20.4, 20.3, 16.6, -4.4, -5.0

Data for 4.27: IR ν 3032, 2930, 2857, 1686 cm⁻¹; HRMS (EI) Anal. Calcd. for C₁₈H₂₈O₃Si m/z 320.18077 [M⁺], found 320.18041; ¹H NMR (300 MHz, CDCl₃) δ 6.49 (q, J = 1.1 Hz, 1H), 5.72 (ddd, J = 7.5, 3.6, 1.8 Hz, 1H), 5.60 (dtd, J = 1.5, 3.9, 9.8 Hz, 1H), 4.21 (d, J = 5.5 Hz, 1H), 3.45 (dd, J = 5.6, 10.8 Hz, 1H), 2.30 (ddd, J = 1.7, 4.5, 5.7 Hz, 1H), 2.15 (ddt, J = 14.4, 8.1, 1.6 Hz, 1H), 1.84 (d, J = 1.7 Hz, 3H), 0.85 (s, 3H), 0.66 (s, 9H), -0.02 (s, 3H), -0.05 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 201.0, 200.5, 147.3, 137.1, 128.2, 126.8, 68.9, 45.1, 25.8, 22.6, 17.9, 17.9, 16.2, -3.8, -5.0

**Enone 4.28**

![Enone 4.28](image)

To a flask containing conjugated dione 4.26 (350 mg, 1.1 mmol) stirring in methanol (6 mL) at 0°C was slowly added sodium borohydride (41 mg, 1.1 mmol). The mixture was stirred for 5 minutes before being quenched with ammonium chloride (10 mL, sat.). The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over MgSO₄, filtered,
and concentrated \textit{in vacuo}. The resulting solid was practically pure enone \textbf{4.28} (330 mg, 1.0 mmol, 94%), however, it could be recrystallized in ethanol to afford clear colorless crystals (120 mg, 36% recovery).

Data for \textbf{4.28}: m.p. 119 - 120 °C; IR ν 3502, 2856, 1659, 1048 cm\(^{-1}\); HRMS (ESI) Anal. Calcd. for C\(_{18}\)H\(_{30}\)O\(_3\)Si \(m/z\) 345.1862 [M-Na]\(^+\), found 345.1855; \(^1\)H NMR (300 MHz, CD\textsubscript{3}Cl\(_3\)) δ 5.80 - 5.72 (m, 2H), 5.60 - 5.53 (m, 1H), 4.13 - 4.09 (m, 1H), 4.06 (s, 1H), 2.87 (s, 1H), 2.60 - 2.46 (m, 1H), 2.37 (dd, \(J = 8.0, 6.2\) Hz, 1H), 2.10 - 1.99 (m, 1H), 2.01 - 1.98 (m, 3H), 1.04 (s, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H); \(^{13}\)C NMR (75 MHz, CD\textsubscript{3}Cl\(_3\)) δ 200.2, 157.2, 128.3, 128.1, 125.4, 75.2, 73.4, 49.3, 42.6, 25.9, 25.6, 25.1, 21.7, 18.1, -3.8, -4.5

\[\text{Figure 4.2: ORTEP representation of the solid state of structure 4.28 (50\% probability ellipsoids)}\]
Diol 4.29

To a flask containing enone 4.28 (310 mg, 0.96 mmol) stirring in THF (10 mL) at -78 °C was added diisobutylaluminum hydride (1.9 mL, 1.9 mmol, 1.0 M in hexanes). The solution was stirred at this temperature for 10 minutes before being quenched with HCl (10 mL, 0.5 M). The aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (2:1 to 1:1 hexanes/diethyl ether) to afford diol 4.29 (272 mg, 0.84 mmol, 87%) as a white solid. The solid could be recrystallized in Et₂O to afford small prisms of diol 4.29 (250 mg, 92%).

Data for 4.29: m.p. 130 - 133 °C; IR ν 3420, 3028, 2857, 1059 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₁₈H₃₂O₃Si m/z 347.2018 [M-Na]+, found 347.2016; ¹H NMR (300 MHz, CDCl₃) δ 5.80 (ddt, J = 10.1, 2.9, 1.0, 1H), 5.49 (dq, J = 10.3, 2.8 Hz, 1H), 5.37 (s, 1H), 4.13 (s, 1H), 4.05 (s, 1H), 3.66 (s, 1H), 3.01 (s, 1H), 2.84 (s, 1H), 2.18 - 2.01 (m, 2H), 1.87 (q, J = 6.4 Hz, 2H), 1.74 (s, 3H), 0.93 (s, 3H), 0.85 (s, 9H), 0.08 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 135.5, 130.2, 128.0, 125.5, 74.5, 67.5, 40.7, 34.7, 31.6, 25.9, 24.3, 23.8, 20.7, 18.0, -3.9, -4.9
Enone 4.30

To a flask containing conjugated dione 4.26 (25 mg, 0.08 mmol) stirring in THF (1 mL) at -78 °C was added DIBALH (80 μL, 0.08 mmol, 1.0 M in hexanes). The solution was stirred at this temperature for 30 minutes before being quenched with Rochelle’s salt (5 mL, sat.). The aqueous layer was extracted with Et₂O (3 x 5 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (10:1 to 3:1 hexanes/diethyl ether) to afford enone 4.30 (24 mg, 0.07 mmol, 95%) as a white solid.

Data for 4.30: IR ν 3414, 2859, 1670, 1019 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₁₈H₃₀O₃Si m/z 345.1862 [M-Na]⁺, found 345.1862; ¹H NMR (300 MHz, CDCl₃) δ 6.77 (dq, J = 5.9, 1.2 Hz, 1H),
6.00 - 5.91 (m, 1H), 5.66 - 5.57 (m, 1H), 4.39 (d, J = 12.0 Hz, 1H), 4.04 - 3.93 (m, 2H), 2.39 - 2.22 (m, 3H), 1.79 (t, J = 2.3 Hz, 3H), 1.21 (s, 3H), 0.80 (s, 9H), 0.06 (s, 3H), -0.05 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 202.8, 144.4, 136.9, 130.3, 124.1, 70.9, 67.2, 47.1, 39.2, 25.9, 25.7, 22.1, 18.0, 16.7, -4.4, -5.3

**Dione 4.31**

![Dione 4.31](image)

To a flask containing conjugated dione 4.26 (170 mg, 0.53 mmol) stirring in THF (6 mL) at -78 °C was added K-selectride (0.53 mL, 0.53 mmol, 1.0 M in THF). The solution was stirred at this temperature for 2 hours before being quenched with water (10 mL). The aqueous layer was extracted with Et$_2$O (3 x 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (10:1 to 1:1 hexanes/diethyl ether) to afford dione 4.31 (142 mg, 0.44 mmol, 83%) as a white solid.

Data for 4.31: m.p. 85 - 89 °C; IR ν 3033, 2857, 1715, 1053 cm$^{-1}$; HRMS (ESI) Anal. Calcd. for C$_{18}$H$_{30}$O$_3$Si m / z 345.1862 [M-Na]$^+$, found 345.1868; $^1$H NMR (300 MHz, CDCl$_3$) δ 5.78 (ddd, J = 10.2, 4.8, 2.7 Hz, 1H), 5.67 - 5.58 (m, 1H), 4.11 (d, J = 5.1 Hz, 1H), 3.07 - 2.86 (m, 3H), 2.66 (dd, J = 18.9, 7.2 Hz, 1H), 2.42 (dd, J = 18.9, 13.2 Hz, 1H), 2.01 (ddt, J = 19.0, 7.2, 0.8 Hz, 1H), 1.18 (s, 3H), 1.12 (d, J = 6.4 Hz, 3H), 0.77 (s, 9H), 0.01 (s, 3H), -0.06 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 214.3, 207.2, 127.9, 125.8, 71.1, 51.1, 48.1, 42.7, 39.8, 26.0, 21.8, 20.3, 18.2, 13.6, -4.0, -4.9
To a flask containing enone 4.28 (500 mg, 1.6 mmol) stirring in THF (15 mL) at -78 °C was added diisobutylaluminum hydride (3.2 mL, 3.2 mmol, 1.0 M in hexanes). The solution was stirred at this temperature for 10 minutes before being quenched with HCl (15 mL, 0.5 M). The aqueous layer was extracted with Et₂O (3 x 15 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was placed in a refrigerator at 2 °C for 12 hours. This resulting residue was purified by flash column chromatography on silica gel (2:1 hexanes/diethyl ether) to afford tricycle 4.32 (184 mg, 0.96 mmol, 62%) as a white solid. The solid could be recrystallized in Et₂O to afford small prisms of tricycle 4.32 (110 mg, 60%).

Data for 4.32: m.p. 94 - 96 °C; IR ν 3398, 3024, 2890, 729 cm⁻¹; HRMS (EI) Anal. Calcd. for C₁₂H₁₆O₂ m/z 192.1150 [M]+, found 192.1150; ¹H NMR (300 MHz, CDCl₃) δ 5.89 - 5.80 (m, 1H), 5.66 (dd, J = 9.4, 2.2 Hz, 1H), 5.63 - 5.56 (m, 1H), 5.25 (dd, J = 9.2, 2.6 Hz, 1H), 3.97 - 3.91 (m, 1H), 3.67 (s, 1H), 2.75 (br. s., 1H), 2.57 - 2.51 (m, 1H), 2.36 - 2.23 (m, 1H), 1.92 (ddt, J = 18.2, 6.0, 1.4 Hz, 1H), 1.24 (s, 3H), 1.11 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 134.3, 131.9, 126.2, 125.6, 82.2, 80.0, 76.8, 45.8, 41.8, 28.0, 19.4, 15.8
Acetate 4.34

To a flask containing diol 4.29 (160 mg, 0.5 mmol) stirring in CH₂Cl₂ (5 mL) was added triethylamine (1.4 mL, 10 mmol), acetic anhydride (0.47 mL, 5 mmol), and DMAP (5 mg, 0.04 mmol). The solution was stirred for 16 hours before being quenched with HCl (10 mL, 1M). The aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were washed with NaHCO₃ (10 mL, sat.) and brine (10 mL). The organic layer was then dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (10:1 hexanes/ethyl acetate) to afford acetate 4.34 (130 mg, 0.36 mmol, 72%).
Data for 4.34: IR v 3566, 2857, 1736, 1239 cm\(^{-1}\); HRMS (ESI) Anal. Calcd. for C\(_{20}\)H\(_{34}\)O\(_4\)Si \(m / z\) 389.2124 [M-Na]\(^+\), found 389.2119; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.82 - 5.75 (m, 1H), 5.54 - 5.47 (m, 1H), 5.46 - 5.40 (m, 1H), 5.28 (s, 1H), 4.16 - 4.11 (m, 1H), 3.70 (s, 1H), 3.06 (s, 1H), 2.31 - 2.10 (m, 2H), 2.05 (s, 3H), 1.91 – 1.81 (m, 1H), 1.83 (t, \(J\) = 1.7 Hz, 3H), 0.98 (s, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 170.7, 136.2, 129.6, 129.3, 121.1, 73.3, 71.4, 41.1, 38.2, 26.0, 23.7, 23.6, 21.3, 21.1, 18.1, -3.9, -4.8

**Acetate 4.34 and \(\beta\)-ketoester 4.35**

![Diagram showing the transformation of 4.29 to 4.34 and 4.35](image)

To a flask containing diol 4.29 (300 mg, 0.92 mmol) stirring in CH\(_2\)Cl\(_2\) (10 mL) was added triethylamine (0.25 mL, 1.8 mmol), acetyl chloride (70 \(\mu\)L, 1.0 mmol), and DMAP (5 mg, 0.04 mmol). The solution was stirred for 24 hours before being quenched with water (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over MgSO\(_4\), filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (10:1 to 2:1 hexanes/ethyl acetate) to afford acetate 4.34 (160 mg, 0.44 mmol, 47%) and \(\beta\)-ketoester 4.35 (110 mg, 0.27 mmol, 29%) as well as recovered diol 4.29 (43 mg, 14%)

Data for 4.35: IR v 3563, 2857, 1739, 1717, 1061 cm\(^{-1}\); HRMS (ESI) Anal. Calcd. for C\(_{22}\)H\(_{36}\)O\(_5\)Si \(m / z\) 431.2230 [M-Na]\(^+\), found 431.2226; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 12.05 (s, 1H), 5.85 - 5.76
(m, 1H), 5.57 - 5.48 (m, 2H), 5.35 - 5.28 (m, 1H), 5.03 - 5.00 (m, 1H), 4.19 - 4.13 (m, 1H), 3.72 (s, 1H), 3.48 (s, 2H), 3.09 (s, 1H), 2.27 (s, 2H), 2.22 - 2.18 (m, 1H), 1.95 (s, 1H), 1.93 - 1.88 (m, 1H), 1.85 (t, J = 1.5 Hz, 3H), 1.00 (s, 3H), 0.96 - 0.91 (m, 8H), 0.90 (s, 1H), 0.86 (s, 1H), 0.80 - 0.79 (m, 1H), 0.14 (s, 3H), 0.13 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 200.6, 166.9, 136.7, 129.5, 129.3, 120.6, 76.0, 73.2, 72.7, 50.4, 41.1, 38.2, 30.4, 26.0, 23.7, 23.5, 21.4, 21.2, 18.1, -3.9, -4.8

Diol 4.38

To a flask containing acetate \(\text{4.34}\) (60 mg, 0.16 mmol) stirring in THF (2 mL) at 0 °C was added tetrabutylammonium fluoride (0.18 mL, 0.18 mmol, 1.0 M in THF). The solution was stirred at this temperature for 1 hour before being quenched with water (10 mL) and diluted with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over MgSO\(_4\), filtered, and concentrated \textit{in vacuo}. The resulting residue was purified by flash column chromatography on silica gel (2:1 hexanes/ethyl acetate) to afford diol \(\text{4.38}\) (37 mg, 0.15 mmol, 90%).

Data for \(\text{4.38}\): IR \(\nu\) 3451, 2878, 1718, 1238 cm\(^{-1}\); HRMS (ESI) Anal. Calcd. for C\(_{14}\)H\(_{20}\)O\(_{4}\) \(m / z\) 275.1259 [M-Na]\(^+\), found 275.1262; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.74 - 5.62 (m, 2H), 5.36 (s, 1H), 5.29 (s, 1H), 3.88 (s, 1H), 3.67 (s, 1H), 2.96 (br. s., 2H), 2.08 - 1.98 (m, 3H), 1.96 (s, 3H), 1.75 (s, 3H), 1.03 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 170.3, 130.0, 127.6, 120.8, 74.5, 72.4, 70.7, 39.9, 37.6, 24.3, 24.2, 22.6, 21.2, 20.4
Carbamate 4.39

To a flask containing diol 4.38 (90 mg, 0.36 mmol) stirring in PhCH₃ (3 mL) was added 1,1’-carbonyldiimidazole (64 mg, 0.39 mmol) and DMAP (5 mg, 0.04 mmol). The solution was heated to reflux and stirred for 14 hours. The solution was then cooled to room temperature and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (3:1 hexanes/diethyl ether) to afford diol 4.39 (75 mg, 0.27 mmol, 76%).

Data for 4.39: IR ν 2970, 1774, 1732, 1233 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₁₅H₁₈O₅ m/z 301.1052 [M-Na]⁺, found 301.1059; ¹H NMR (300 MHz, CDCl₃) δ 5.73 - 5.66 (m, 1H), 5.57 - 5.52 (m, 1H), 5.50 - 5.45 (m, 1H), 4.67 - 4.63 (m, 1H), 4.01 - 3.95 (m, 1H), 2.30 - 2.21 (m, 1H), 2.09 (s, 3H), 2.07 - 1.98 (m, 3H), 1.92 - 1.86 (m, 3H), 1.30 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.6, 153.5, 135.3, 131.5, 125.6, 123.9, 82.6, 79.1, 69.7, 38.1, 37.0, 25.6, 22.1, 21.2, 20.1
Sulfite 4.41

To a flask containing diol 4.38 (30 mg, 0.12 mmol) stirring in CH$_2$Cl$_2$ (1 mL) at 0 °C was added pyridine (0.97 mL, 12 mmol) followed by thionyl chloride (43 µL, 0.6 mmol). The solution was stirred at this temperature for 5 minutes before being quenched with water (5 mL) and diluted with EtOAc (5 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (4:1 hexanes/diethyl ether) to afford an inseparable mixture of both sulfur-diastereomers of diol 4.41 (32 mg, 0.11 mmol, 88%, dr ~7:4)

Data for 4.41: IR ν 2919, 1737, 1238, 1208 cm$^{-1}$; HRMS (ESI) Anal. Calcd. for C$_{14}$H$_{18}$O$_5$S m / z 321.0773 [M-Na]$^+$, found 321.0786; $^1$H NMR (300 MHz, CDCl$_3$) δ 6.15 - 6.07 (m, 1H), 5.86 (dt, $J$ = 9.7, 2.6 Hz, 1H), 5.62 - 5.56 (m, 1H), 5.55 - 5.49 (m, 1H) 4.59 - 4.55 (m, 1H), 4.52 (s, 1H), 2.34 - 2.12 (m, 2H), 2.12 (s, 3H), 2.09 - 1.97 (m, 1H), 1.85 (t, $J$ = 1.4 Hz, 3H), 1.28 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.6, 133.7, 132.2, 125.6, 125.0, 81.3, 69.9, 69.7, 39.5, 38.5, 23.6, 22.6, 21.3, 21.0
**Cis-decalin 4.6**

\[ \text{4.5} + \text{4.4} \rightarrow \text{4.6} \]

Cis-decalin 4.6 was prepared by the methods of Sugano et. al.\textsuperscript{204} All \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectroscopic data matched reported values.

**Alcohol 4.73**

\[ \text{4.6} \rightarrow \text{4.73} \]

Alcohol 4.73 was prepared by the methods of Sugano et. al.\textsuperscript{204} All \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectroscopic data matched reported values.

**Diol 4.7**

\[ \text{4.73} \rightarrow \text{4.7} \]

Diol 4.7 was prepared by the methods of Sugano et. al.\textsuperscript{204} All \textsuperscript{1}H NMR and \textsuperscript{13}C NMR spectroscopic data matched reported values.
TBS ether 4.46 was prepared by the methods of Sugano et. al.\textsuperscript{204}

Data for 4.46: IR ν 3460, 3022, 2857, 1073 cm\textsuperscript{-1}; HRMS (ESI) Anal. Calcd. for C\textsubscript{18}H\textsubscript{32}O\textsubscript{2}Si m/z 331.2069 [M-Na]\textsuperscript{+}, found 331.2072; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) δ 5.85 - 5.72 (m, 2H), 5.27 (s, 1H), 4.50 - 4.44 (m, 1H), 3.39 (s, 1H), 2.29 - 2.17 (m, 2H), 2.02 - 1.82 (m, 4H), 1.80 (s, 3H), 0.96 (s, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) δ 133.9, 128.0, 127.5, 125.6, 76.8, 68.3, 41.4, 36.5, 35.9, 27.3, 26.1, 24.0, 20.9, 18.4, -4.5, -4.6

Acetate 4.48

To a flask containing TBS ether 4.46 (30 mg, 0.097 mmol) stirring in CH\textsubscript{2}Cl\textsubscript{2} (2 mL) was added DMAP (100 mg, 0.82 mmol) followed by acetic anhydride (50 µL, 0.5 mmol). This now yellow solution was stirred at room temperature for 5 hours before being quenched with NaHCO\textsubscript{3} (5 mL, sat. aq.) and diluted with Et\textsubscript{2}O (5 mL). The aqueous layer was extracted with Et\textsubscript{2}O (3 x 5 mL). The combined organic layers were washed with HCl (5 mL), water (5 mL), and then brine (5 mL). The organic layer was dried over MgSO\textsubscript{4}, filtered, and concentrated \textit{in vacuo}. The resulting residue
was purified by flash column chromatography on silica gel (10:1 hexanes/diethyl ether) to afford acetate 4.48 (33 mg, 0.095 mmol, 98%).

Data for 4.48: IR ν 3022, 2857, 1735, 1236 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₂₀H₃₄O₃Si m/z 373.2175 [M-Na]⁺, found 373.2174; ¹H NMR (300 MHz, CDCl₃) δ 5.72 - 5.64 (m, 1H), 5.56 - 5.47 (m, 1H), 5.41 - 5.37 (m, 1H), 5.00 (s, 1H), 4.50 - 4.43 (m, 1H), 2.20 - 1.99 (m, 3H), 1.98 (s, 3H), 1.91 - 1.76 (m, 2H), 1.62 (t, J = 1.5 Hz, 3H), 1.00 (s, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.7, 130.7, 128.3, 127.2, 125.0, 76.3, 68.2, 41.6, 36.0, 36.0, 26.4, 26.1, 23.8, 21.3, 20.4, 18.4, -4.5, -4.6

α-Silyl acetate 4.51

To a flask containing acetate 4.48 (60 mg, 0.17 mmol) stirring in THF (2 mL) at 0 °C was added freshly prepared lithium diisopropylamide (1.8 mL, 0.18 mmol, 0.10 M). The solution was stirred at this temperature for 30 minutes before addition of trimethylsilyl chloride (24 μL, 0.19 mmol). This solution was allowed to warm to room temperature and subsequently stirred for 12 hours before being quenched with NaOH (5 mL, 2 M) and diluted with Et₂O (5 mL). The aqueous layer was extracted with Et₂O (3 x 5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL). The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (10:1 \( \text{hexanes/diethyl ether} \)).
hexanes/diethyl ether) to afford a 1:1 mixture of acetate 4.48 and a-silyl acetate 4.51 (60 mg, ~41% by mass).

Data for 4.51: IR ν 3022, 2857, 1736, 1717, 1238 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₃₂H₄₂O₃Si₂ m / z 445.2570 [M-Na]⁺, found 445.2570; ¹H NMR (300 MHz, CDCl₃) δ 5.73 - 5.64 (m, 1H), 5.57 - 5.48 (m, 1H), 5.42 - 5.36 (m, 1H), 5.00 (s, 1H), 4.50 - 4.42 (m, 1H), 2.19 - 1.99 (m, 3H), 1.98 (s, 3H), 1.91 (d, J = 11.8 Hz, 1H), 1.91 - 1.77 (m, 2H) 1.80 (d, J = 11.7 Hz, 1H), 1.65 - 1.61 (m, 3H), 1.00 (s, 3H), 0.90 (s, 9H), 0.10 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 173.7, 131.0, 128.2, 127.1, 125.4, 76.0, 68.4, 41.6, 36.0, 27.3, 26.5, 26.1, 23.8, 21.3, 20.6, 18.5, -0.9, -4.5, -4.5

**Chlorodimethyl((trimethylsilyl)ethynyl)silane (4.62)**

\[
\text{Cl}_2\text{Si} + \text{CH}_3\text{Si}(\text{TMS}) \rightarrow \text{Cl}_2\text{Si}(\text{TMS})
\]

To a flask containing trimethylsilylacetylene (5 mL, 36 mmol) stirring in hexanes (30 mL) at 0 °C was added "BuLi (28 mL, 38 mmol, 1.3 M in hexanes) slowly over 10 minutes. The solution was then warmed to room temperature and stirred for an additional hour. The resulting mixture was then slowly transferred by cannula to another flask containing dichlorodimethylsilane (4.4 mL, 36 mmol) stirring in THF (36 mL) at -78 °C. The cannula transfer took approximately 15 minutes. This new flask was then allowed to warm to room temperature and subsequently stirred for 16 hours. This mixture was concentrated *in vacuo* and then charged with hexanes (30 mL). The mixture was then distilled under vacuum. The first 30 mL of distillate were discarded, and the
remaining fraction was presumed to be chlorodimethyl((trimethylsilyl)ethynyl)silane (4.62). This fraction was used immediately without characterization.

1,6-Enyne 4.63

To a flask containing diol 4.7 (1.0 g, 5.1 mmol) and imidazole (1.05 g, 15.4 mmol) stirring in DMF (20 mL) was added chlorodimethyl((trimethylsilyl)ethynyl)silane (4.62) (2 g, 10 mmol). The solution was stirred at room temperature for 2 hours before being quenched with water (50 mL) and diluted with Et₂O (50 mL). The aqueous layer was extracted with Et₂O (3 x 25 mL). The combined organic layers were washed with water (25 mL) and brine (25 mL). The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (10:1 to 1:1 hexanes/ethyl acetate) to afford a 1,6-ynene 4.63 (250 mg, 0.72 mmol, 14%).

Data for 4.63: IR ν 3466, 3022, 2875, 829 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₁₉H₃₂O₂Si₂ m / z 371.1819 [M-Na]⁺, found 371.1816; ¹H NMR (300 MHz, CDCl₃) δ 5.85 - 5.70 (m, 2H), 5.36 - 5.21 (m, 1H), 4.70 - 4.41 (m, 1H), 3.41 - 3.34 (m, 1H), 2.26 - 2.15 (m, 2H), 2.04 - 1.88 (m, 3H), 1.80 - 1.74 (m, 3H), 1.36 - 1.22 (m, 2H), 0.95 (d, J = 7.5 Hz, 3H), 0.89 - 0.82 (m, 2H), 0.24 (d, J = 4.1 Hz, 3H), 0.15 (s, 6H), 0.08 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 134.3, 134.1, 128.0, 127.9, 127.4, 127.3, 125.4, 124.9, 111.4, 76.7, 76.7, 69.4, 68.0, 41.3, 40.6, 36.7, 36.5, 35.9, 27.4, 27.3, 26.6, 25.7, 23.8, 20.9, 20.9, 16.6, 14.3, 14.0, 1.7, 0.7, 0.7, 0.0, -0.1, -1.3, -1.4

171
Bromo(ethynyl)diisopropylsilane (4.64)

\[ \text{Cl-SiH} + \text{MgBr} + \text{NBS} \rightarrow \text{Br-Si-\equiv} \]

To a flask containing ethynylmagnesium bromide (11.7 mL, 5.8 mmol, 0.5 M in THF) stirring in THF (10 mL) at 0 °C was slowly added a solution of chlorodiisopropylsilane (0.92 mL, 2.7 mmol) in THF (4 mL). The solution was then warmed to room temperature and stirred for an additional 16 hours before quenching with water (5 mL). The THF was carefully removed in vacuo and the resulting mixture was charged with Et₂O (8 mL). The aqueous layer was extracted with Et₂O (2 x 4 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated to ~ 3 mL carefully in vacuo. The mixture was then distilled to afford ethynyldiisopropylsilane. This product was put into a flask with a stir bar and diluted in CH₂Cl₂ (30 mL). To this flask was added N-bromosuccinimide (1.13 g, 6.4 mmol) in portions over 20 minutes. This mixture was stirred for 30 minutes. At this point, bromo(ethynyl)diisopropylsilane (4.64) was presumed to have formed and was used without further purification or characterization.

1,6-Enyne 4.67

To a flask containing diol 4.7 (0.50 g, 2.9 mmol), triethylamine (0.9 mL, 6.4 mmol), and DMAP (5 mg, 0.04 mmol) stirring in CH₂Cl₂ (5 mL) was slowly added a solution of
bromo(ethynyl)diisopropylsilane (4.64) (~6mmol) in CH₂Cl₂ (30 mL). The mixture was stirred at room temperature for 2 hours before being quenched with ammonium hydroxide (10 mL, sat. aq.). The organic layer was washed with brine (20 mL). The organic layer was dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (10:1 to 1:1 hexanes/ethyl acetate) to afford a 1,6-enyne 4.67 (166 mg, 0.51 mmol, 20%).

1,6-enyne 4.67 was carried forwards without full characterization.

1,6-Enyne 4.65

To a flask containing 1,6-enyne 4.67 (50 mg, 0.16 mmol) stirring in CH₂Cl₂ (2 mL) was added Dess-Martin periodinane (72 mg, 0.17 mmol). The mixture was stirred at room temperature for 2 hours before being concentrated in vacuo. The resulting residue was purified by flash column chromatography on silica gel (5:1 hexanes/diethyl ether) to afford 1,6-enyne 4.65 (50 mg, 0.16 mmol, 100%).

Data for 4.65: IR ν 3028, 2868, 2032, 1672 cm⁻¹; HRMS (ESI) Anal. Calcd. for C₂₀H₃₀O₂Si m/z 353.1913 [M-Na]⁺, found 353.1906; ¹H NMR (300 MHz, CDCl₃) δ 6.66 (s, 1H), 5.76 - 5.66 (m, 1H), 5.66 - 5.57 (m, 1H), 4.63 - 4.51 (m, 1H), 2.49 (s, 1H), 2.47 - 2.36 (m, 1H), 2.23 - 1.99 (m, 3H), 1.78 (t, J = 1.5 Hz, 3H), 1.72 - 1.60 (m, 1H), 1.26 - 1.19 (m, 3H), 1.16 - 1.00 (m, 14H); ¹³C
NMR (75 MHz, CDCl$_3$) $\delta$ 203.4, 146.2, 132.4, 125.8, 125.3, 124.7, 124.3, 96.0, 84.8, 69.4, 46.7, 44.0, 31.7, 23.5, 20.6, 17.3, 17.3, 17.3, 16.4, 13.4, 13.2, 12.9, 12.8

**Vinyl silane 4.71**

To a flask containing 1,6-ényne 4.65 (20 mg, 0.061 mmol) stirring in toluene (0.6 mL) at room temperature was added tris(dibenzylideneacetone)dipalladium(0) (28 mg, 0.030 mmol), 1,4-bis(diphenylphosphino)butane (13 mg, 0.030 mmol), triethylsilane (20 $\mu$L, 0.12 mmol), and acetic acid (7 $\mu$L, 0.12 mmol). The mixture was heated to 80 °C and stirred at this temperature for 12 hours before being cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel (5:1 hexanes/diethyl ether) to afford vinyl silane 4.71 (15 mg, 0.045 mmol, 75%).

Data for 4.71: IR $\nu$ 2943, 2866, 1673, 1081 cm$^{-1}$; HRMS (ESI) Anal. Calcd. for C$_{20}$H$_{32}$O$_2$Si $m/z$ 355.2069 [M-Na]$^+$, found 355.2079; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.59 - 6.50 (m, 1 H), 6.20 - 6.02 (m, 2 H), 5.85 (dd, $J = 18.6$, 5.9 Hz, 1 H), 5.76 - 5.67 (m, 1 H), 5.67 - 5.56 (m, 1 H), 4.46 (dq, $J = 9.0$, 2.0 Hz, 1 H), 2.46 - 2.33 (m, 2 H), 2.20 - 2.00 (m, 2 H), 1.77 (dd, $J = 1.8$, 1.4 Hz, 3 H), 1.72 - 1.61 (m, 1 H), 1.22 (s, 3 H), 1.06 (s, 14 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 203.4, 146.7, 135.3, 133.3, 132.2, 125.6, 124.6, 68.4, 47.0, 44.0, 31.7, 23.7, 20.7, 17.7, 17.7, 17.7, 17.6, 16.5, 12.8, 12.7
4.5.1 X-Ray Crystallography

All single crystals were immersed in oil and mounted on a glass fiber. Data were collected on a Bruker X8 APEX II diffractometer with graphite-monochromated Mo Kα radiation. All structures were solved by Dr. Spencer Serin.

Table 4.4: X-ray Data Collection and Refinement Details for 4.28, 4.29, and 4.32

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<thead>
<tr>
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<td>T (K)</td>
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<td>1.000</td>
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\[ R₁ = \sum |F_o| - |F_c||/|\sum|F_o|. \]

\[ wR₂(F^2 \text{all data}) = \left\{ \frac{\sum w(F_o^2 - F_c^2)^2}{\sum w(F_o^2)^2} \right\}^{1/2} \]
Chapter 5: Conclusion and Future Work

Marine natural products chemistry research has led to the discovery of myriad molecules that show potential therapeutic value for humans. However, a major drawback when working with marine natural products is that it is difficult to obtain appreciable amounts of material for SAR and clinical studies. This work in this thesis attempts to solve that problem for cladonamide G (2.17) and nahuoic acid A (3.8) using synthesis.

5.1 Conclusions and Future Work for Chapter 2

Chapter 2 describes the successful synthesis of cladonamide G starting from 5-chloroindole (2.47). The convergent process contained a longest linear sequence of only 5 steps. A brominated analogue of cladonamide G (2.90) was also synthesized using a similar route. Glycosylation of cladonamide G was a goal at the onset of the project, although this was never achieved. This would be the area most interesting for future research. Masking the tertiary alcohol group of cladonamide G with different protecting groups, or exploring more esoteric glycosylation methods might hold the key to success.

Unfortunately, the project stalled due to the inability to test synthetic molecules in a bioassay. The ability to test these molecules’ cytotoxicity towards certain cancer cells may still provide SAR data points necessary to help create a new drug for cancer treatment.

5.2 Conclusions and Future Work for Chapters 3 and 4

Chapter 3 discusses an attempted synthesis of nahuoic acid A (3.8) through a putatively biomimetic route. While construction of linear and macrocyclic compounds was accomplished, the key cycloaddition step was never observed in any shape or form. One could argue that this is a strong indication that the molecule is formed by a “Diels-Alderase” enzyme.
Chapter 4 outlines the attempts to circumvent the cycloaddition problems encountered in chapter 3 by using a DA reaction early in the synthesis. While this approach was able to create a *cis*-decalin, the rigid, bowl-shaped conformation created challenges when trying to add substituents. Even though I was unable to synthesize molecules with the appropriate connectivity, I still believe that an early DA approach could encompass a method to synthesize nahuoic acid A. One potential route that was not explored is shown in scheme 5.1.

![Scheme 5.1: Potential route for synthesis of the core of nahuoic acid A](image)

Beginning with compound 5.1 (scheme 5.1), the route would use a conjugate addition followed by $\alpha$-substitution of the resulting carbonyl to form 5.2. These steps should provide the correct configurations of “$R$” and “$R'$”. Trifluoromethylsulfonylation of 5.2 followed by cross-coupling would result in structure 5.3, a *cis*-decalin that resembles the *cis*-decalin of nahuoic acid A. The biggest challenge would likely by synthesis of the non-trivial starting material 5.1.

As of June 2017, nahuoic acid A is still the only known SAM selective inhibitor of SETD8 so interest in the synthesis nahuoic acid A and its analogues remains high. The information learned during this project will be passed down to the next generation of graduate students in the Dake lab. Hopefully, the total synthesis of nahuoic acid A will be reported in due course.
Bibliography


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183
Appendices

Appendix A General Experimental

All reactions were performed under an atmosphere of dry nitrogen. Glassware was flame-dried prior to use. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Dichloromethane, pyridine, diisopropylamine, and triethylamine were distilled from calcium hydride prior to use. Toluene was distilled from sodium prior to use. Common reagents or materials were purchased from commercial sources and purified by standard distillation or recrystallization prior to use. Thin layer chromatography (TLC) was performed on DC-Fertigplatten SIL G-25 UV254 pre-coated TLC plates. Triethylamine-washed silica gel was stirred with triethylamine prior to packing and then sequentially flushed with polar solvent component and the solvent system of choice. Melting points (m.p.) were obtained using a Mel-Temp II apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin-Elmer FTIR instrument. Proton nuclear magnetic resonance (1H NMR) spectra and carbon nuclear magnetic resonance (13C NMR) spectra were recorded in deuterochloroform (CDCl3) and deuterated dimethyl sulfoxide (DMSO-d6) on 7.0 and 9.4 T Bruker NMR spectrometers. Chemical shifts are reported in parts per million and referenced to deuterochloroform (δ 7.26 1H NMR; 77.23 13C NMR) and deuterated dimethyl sulfoxide (δ 2.50 1H NMR; 39.51 13C NMR). Coupling constants (J values) are given in Hertz (Hz). Low resolution mass spectra were obtained with a Bruker Esquire-LC ion trap mass spectrometer equipped with an electrospray ionization source. High resolution mass spectra were recorded on a Waters/Micromass liquid chromatography tandem time of flight mass spectrometer equipped with an electrospray ionization source. X-ray crystallography measurements were made on either a Bruker APEX DUO diffractometer with cross-coupled multilayer optics Cu-Kα radiation or on a Bruker X8 APEX II diffractometer with graphite monochromated Mo-Kα radiation.
Appendix B  Selected Spectra

Numerical NMR data in the experimental sections was compiled using ACD Labs NMR processor, while Spectra in this appendix were mostly obtained using Bruker Topspin v3.5pl6. As a result, chemical shifts reported in the experimental sections throughout this thesis might differ from values shown in this appendix by ± 0.01 (¹H NMR) and ± 0.1 (¹³C NMR).
B.1 Selected Spectra for Chapter 2

Cladoniamide G 2.17

[Graph showing spectra with chemical structures and data]

100
95
90
85
80
75
70
65
60
55
50
45
40
3500 3000 2500 2000 1500 1000 650

% T

4000
B.2 Selected Spectra for Chapter 3
OTBS

3.151

OBn
B.3 Selected Spectra for Chapter 4