Synthesis of Frondosin B Analogs via Rhodium Catalyzed Carbonyl Ylide Cycloaddition

A dissertation presented to
the faculty of
the College of Arts and Sciences of Ohio University

In partial fulfillment
of the requirements for the degree
Doctor of Philosophy

John H. Bougher

May 2015

© 2015 John H. Bougher. All Rights Reserved.
This dissertation titled
Synthesis of Frondosin B Analogs via Rhodium Catalyzed Carbonyl Ylide Cycloaddition

by

JOHN H. BOUGHER

has been approved for
the Department of Chemistry and Biochemistry

and the College of Arts and Sciences by

Mark C. McMills
Associate Professor of Chemistry and Biochemistry

Robert Frank
Dean, College of Arts and Sciences
ABSTRACT

BOUGHER, JOHN H., Ph.D., May 2015, Chemistry

Synthesis of Frondosin B Analogs via Rhodium Catalyzed Carbonyl Ylide Cycloaddition

Director of Dissertation: Mark C. McMills

Carbonyl and azomethine ylides can be useful tools in organic synthesis. By proceeding through a carbonyl or azomethine ylide, rhodium catalyzed cycloaddition reactions can result in the formation of bridged oxygen or nitrogen heterocycles.

The 8-oxa-6-azabicyclo[3.2.1]octane and 6-oxa-8-azabicyclo[3.2.1]octane cores are important parts of numerous natural product scaffolds. These scaffolds include Ribasine, Himalayamine, Ribasidine, and Norribasine. Ribasine is the parent compound of a class of alkaloids that all have the indanobenzapine core. These alkaloids are biogenetically related to the isoquinoline alkaloids. The 8,14-epoxy-indano[2,1-c][2]benzapine ring may promote biological activity.

Frondosins have shown promising bioactivity profiles. They have been shown to inhibit binding of interleukin-8 (IL-8) to its receptor as well as protein kinase C. These natural products have also exhibited HIV-inhibitory activity in anti-HIV assays. We herein report an approach towards the synthesis of analogs of Frondosin B via a rhodium catalyzed diazo decomposition reaction to form a carbonyl ylide intermediate, which then proceeds through a cycloaddition pathway to form the desired synthetic product.

The core structures of these natural products can be obtained via intermolecular or intramolecular cycloaddition routes mediated by metal catalyzed decomposition of diazo-
substituted precursors. These routes make the syntheses of these cores faster and more efficient.
DEDICATION

To my amazing wife, Alexandria
ACKNOWLEDGMENTS

I would like to thank my Ph.D advisor, Dr. Mark C. McMills for having me in his group. I have grown a lot since I started at Ohio University, both as a chemist and as a person. Thank you for all of your guidance in not only chemistry related issues, but as well as in my career aspirations. The knowledge and skills you have provided me with will help me in my career later in life.

I would also like to thank my undergraduate advisor at Allegheny College, Dr. PJ Persichini for showing me that organic chemistry can be fun and encouraging me to continue my education.

I am also thankful for all of the current and past members of the McMills’ group. I would like to thank Dr. Jason Stengel for, even though we only overlapped for a little time, showing me how real organic chemistry was performed. I would also like to thank Dr. Oksana Pavlyuk for showing me new laboratory techniques. I would like to thank Alicia Frantz for some great conversations and company in the lab. I would finally like to thank all of the undergraduate students who have helped me in my years here.

I would like to thank all of my committee members, Dr. Jeffrey Rack, Dr. Peter Coschigano, and Dr. Bergmeier for taking the time to be here today and looking through my dissertation.

I would like to thank the Department of Chemistry and Biochemistry for all that you have done and all of the help you have given me. Special thanks go out to Carolyn Khurshid, Marlene Jenkins, Rollie Merriman, Aaron Dillon and many others.
I would like to thank my family for always supporting me in all of my endeavors. I would not have been able to make it this far without your support.

Finally, I would like to thank my wonderful wife, Alexandria Bougher. You have shown me what true happiness is. I know our long-distance relationship has been difficult at times, but it is now over. Thanks for all of your love and support throughout this entire process.

I would like the acknowledge Ohio University and Biomolecular Innovation and Technology (BMIT) Group for financial support.
TABLE OF CONTENTS

Abstract ............................................................................................................................... 3
Dedication ........................................................................................................................... 5
Acknowledgments ............................................................................................................... 6
List of Schemes ................................................................................................................. 10
List of Figures ................................................................................................................... 15
List of Abbreviations ........................................................................................................ 17
Chapter 1: Introduction ..................................................................................................... 21
Chapter 2: Background ..................................................................................................... 32
  2.1 The reactivity of carbonyl ylides .......................................................................... 32
  2.2 Intermolecular carbonyl ylide cycloaddition reactions ......................................... 36
  2.3 Intramolecular carbonyl ylide cycloaddition reactions ......................................... 38
  2.4 Azomethine Ylides ................................................................................................ 40
  2.5 Previous Syntheses of Ribasine ............................................................................ 44
  2.6 The Frondosins ...................................................................................................... 47
Chapter 3: Syntheses of 8-oxa-6-azabicyclo[3.2.1]octane and 6-oxa-8-azabicyclo[3.2.1]octane .................................................................................................... 59
  3.1 Background ........................................................................................................... 59
  3.2 Model Studies ....................................................................................................... 61
  3.3 Phthalic anhydride/cuprate synthesis of 8-oxa-6-azabicyclo[3.2.1]octane ............... 67
  3.4 Imine synthesis of 8-oxa-6-azabicyclo[3.2.1]octane ............................................ 72
Chapter 4: Syntheses towards Frondosin B analogs ......................................................... 77
  4.1 Background ........................................................................................................... 77
  4.2 Indene synthesis towards a desoxy-Frondosin B analog ....................................... 78
  4.3 Benzofuran synthesis towards Frondosin B .......................................................... 98
  4.4 Salicylaldehyde approach towards the benzofuran ester .................................... 104
  4.5 Epoxyolefin synthesis ......................................................................................... 105
  4.6 Faveline analog synthesis ................................................................................... 110
  4.7 Stetter reaction approach towards Frondosin B analog ...................................... 113
Chapter 5: Other Projects ................................................................................................ 119
5.1 Albomycin: Synthesis of a C7N amino acid subunit ........................................ 119
5.2 Synthesis of 1-(azetidin-1-yl)-2-diazoethan-1-one ........................................ 125
Experimental ........................................................................................................... 130
References ............................................................................................................... 160
Appendix: Selected NMR Spectra ........................................................................ 169
# LIST OF SCHEMES

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Catalytic cycle to generate carbonyl ylides</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>Padwa’s tandem cyclization-cycloaddition reaction</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>Early Ibata work</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>Padwa’s synthesis of the ribasine core through intermolecular addition of C-N multiple bonds</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>McMills’ synthesis of a phorbol analogue</td>
<td>39</td>
</tr>
<tr>
<td>6</td>
<td>Padwa’s synthesis of brevicomins</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>Padwa’s use of azomethine ylides in synthesis</td>
<td>41</td>
</tr>
<tr>
<td>8</td>
<td>McMills’ use of an azomethine ylide in the formation of a simple precursor to quinocarcin</td>
<td>41</td>
</tr>
<tr>
<td>9</td>
<td>Synthesis of a simple precursor to quinocarcin</td>
<td>42</td>
</tr>
<tr>
<td>10</td>
<td>Ollero’s synthesis of Ribasine</td>
<td>45</td>
</tr>
<tr>
<td>11</td>
<td>Padwa’s synthesis of the ribasine-like core</td>
<td>46</td>
</tr>
<tr>
<td>12</td>
<td>Dominguez approach towards Ribasine</td>
<td>47</td>
</tr>
<tr>
<td>13</td>
<td>Ovaska approach to Frondosin B</td>
<td>49</td>
</tr>
<tr>
<td>14</td>
<td>Flynn used a Stille-Heck approach to Frondosin B</td>
<td>50</td>
</tr>
<tr>
<td>15</td>
<td>Flynn’s multicomponent coupling approach to Frondosin B</td>
<td>51</td>
</tr>
<tr>
<td>16</td>
<td>MacMillan’s enantioselective synthesis of (+)-Frondosin B</td>
<td>52</td>
</tr>
<tr>
<td>17</td>
<td>Winne’s concise synthesis of Frondosin B</td>
<td>53</td>
</tr>
<tr>
<td>18</td>
<td>Li’s approach to (+/-) Frondosin B</td>
<td>54</td>
</tr>
</tbody>
</table>
Scheme 19: Wright’s approach to Frondosin B ............................................................. 55
Scheme 20: Trauner’s approach using palladium towards Frondosin B. ...................... 57
Scheme 21: Nevado’s approach to Frondosin B using a gold catalyst ....................... 57
Scheme 22: Synthesis for model studies................................................................. 63
Scheme 23: Synthetic route to alcohol derivative ...................................................... 64
Scheme 24: Synthesis to bisprotected aldehyde ....................................................... 65
Scheme 25: Synthetic route to oxime 119 ................................................................. 66
Scheme 26: Synthetic route to diazo compound 121............................................... 67
Scheme 27: Proposed synthesis of the 8-oxa-6-azabicyclo[3.2.1]octane core .............. 69
Scheme 28: Phthalic anhydride approach to the 8-oxa-6-azabicyclo[3.2.1]octane core 70
Scheme 29: Preparation of a Grignard-copper reagent ............................................ 71
Scheme 30: Proposed synthesis of 8-oxa-6-azabicyclo[3.2.1]octane via the imine pathway .......................................................................................................................... 73
Scheme 31: Attempts to perform a coordinated deprotonation of imine 135 .............. 75
Scheme 32: Retrosynthesis towards a desoxy-Frondosin B analog ......................... 78
Scheme 33: Attempt to make indene carboxylic acid ............................................. 79
Scheme 34: Mechanism for carboxylation via oxalyl bromide ................................ 79
Scheme 35: Synthesis of indene carboxylic acid .................................................... 80
Scheme 36: Fischer esterification ............................................................................. 80
Scheme 37: Acid chloride approach to ester 151 ..................................................... 81
Scheme 38: Synthesis of 4-hydroxybutan-2-one ..................................................... 82
Scheme 39: Attempt to make diazocarbonyl 153 ..................................................... 83
Scheme 40: Mechanism for the mono-brominated product 159 ........................................ 83
Scheme 41: Mechanism of the di-brominated product 160 ........................................ 83
Scheme 42: Attempt to make diazocarbonyl 156 .......................................................... 84
Scheme 43: β-elimination product ............................................................................... 85
Scheme 44: Deprotonation of five-membered ring ....................................................... 85
Scheme 45: Final steps towards the desoxy-Frondosin B analog ................................. 86
Scheme 46: Synthetic route to enolether 168 .............................................................. 86
Scheme 47: β-elimination mechanism ......................................................................... 87
Scheme 48: Proposed synthesis towards the desoxy-Frondosin B analog ................. 87
Scheme 49: Final steps towards the synthesis of the desoxy-Frondosin B analog ...... 88
Scheme 50: Attempts to make enolate ........................................................................ 90
Scheme 51: Attempt to make desoxy-Frondosin B analog beginning with
    dimethylcyclohexanone ....................................................................................... 90
Scheme 52: Synthesis of diazobromide ..................................................................... 92
Scheme 53: Synthesis of indene ester ....................................................................... 93
Scheme 54: Synthesis of acid chloride ..................................................................... 94
Scheme 55: DCC coupling to synthesize ester 186 ...................................................... 94
Scheme 56: Ester 186 via a Mitsunobu reaction ......................................................... 95
Scheme 57: First attempt to make diazocarbonyl 190 .............................................. 95
Scheme 58: Second attempt to make diazocarbonyl 190 ........................................... 96
Scheme 59: Final steps towards the Frondosin B analog ........................................... 97
Scheme 60: Retrosynthesis towards a Frondosin B analog ........................................ 98
Scheme 61: Synthesis of the benzofuran piece .............................................................. 99
Scheme 62: Willgerodt-Kindler rearrangement mechanism to form thioamide 197... 100
Scheme 63: Mechanism for bromination reaction ....................................................... 102
Scheme 64: Mechanism towards amide ....................................................................... 103
Scheme 65: Mechanism towards enamine ................................................................... 104
Scheme 66: Salicylaldehyde approach to the benzofuran ester ............................. 105
Scheme 67: Synthesis of epoxolefin ........................................................................... 106
Scheme 68: New route to the epoxolefin ................................................................. 107
Scheme 69: Weinreb amide approach to epoxolefin .............................................. 109
Scheme 70: Synthesis of TBS-protected alcohol 231 ............................................ 110
Scheme 71: Ring opening of epoxide to provide bromohydrin 233 ..................... 111
Scheme 72: Possible E1cB elimination mechanism .............................................. 112
Scheme 73: Attempts to couple bromohydrin 232 and aryl bromide 231 .......... 112
Scheme 74: Final steps towards the Faveline analog ............................................ 113
Scheme 75: Formation of the benzofuran via a Stetter reaction ............................ 114
Scheme 76: Grignard addition to 242 ................................................................. 115
Scheme 77: Model reaction of ethynylmagnesium bromide and 242 .......... 115
Scheme 78: Grignard attack, elimination, diazotization, and cycloaddition .......... 116
Scheme 79: Proposed albomycin biosynthetic pathway and functions of alb 7 enzyme120
Scheme 80: Proposed synthesis of the C7N Unit ..................................................... 120
Scheme 81: Aldehyde synthesis of L-arabinose ....................................................... 121
Scheme 82: Aldehyde synthesis from gluconolactone ........................................... 123
Scheme 83: Protected lactam formation ................................................................. 124

Scheme 84: Original synthesis of 1-(azetidin-1-yl)-2-diazoethan-1-one .................. 126

Scheme 85: Coupling reactions ............................................................................ 128

Scheme 86: New route to 1-(azetidin-1-yl)-2-diazoethan-1-one .............................. 129
### LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Palitoxin and 68 stereogenic centers</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>R and S enantiomers of Thalidomide</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>Diagram showing chemistry as the central science</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>Highlighted are the 8-oxa-6-azabicyclo[3.2.1]octane (left) and the 6-oxa-8-azabicyclo[3.2.1]octane (right) substructures</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>Natural products containing the 8-oxa-6-azabicyclo[3.2.1]octane substructure</td>
<td>28</td>
</tr>
<tr>
<td>6</td>
<td>Natural products containing the 6-oxa-8-azabicyclo[3.2.1]octane substructure</td>
<td>29</td>
</tr>
<tr>
<td>7</td>
<td>Structures of Frondosins A-E</td>
<td>29</td>
</tr>
<tr>
<td>8</td>
<td>General disconnection of 8-oxa-6-azabicyclo[3.2.1]octane and 6-oxa-8-azabicyclo[3.2.1]octane</td>
<td>31</td>
</tr>
<tr>
<td>9</td>
<td>Carbonyl ylides</td>
<td>32</td>
</tr>
<tr>
<td>10</td>
<td>Reactions of carbonyl ylides</td>
<td>33</td>
</tr>
<tr>
<td>11</td>
<td>Rhodium catalysts used for carbonyl ylide generation</td>
<td>35</td>
</tr>
<tr>
<td>12</td>
<td>Possible mechanism for the formation of the aziridine product</td>
<td>43</td>
</tr>
<tr>
<td>13</td>
<td>Structures of the Frondosins</td>
<td>48</td>
</tr>
<tr>
<td>14</td>
<td>Natural products containing the 8-oxa-6-azabicyclo[3.2.1]octane core</td>
<td>59</td>
</tr>
<tr>
<td>15</td>
<td>Natural products containing the 6-oxa-8-azabicyclo[3.2.1]octane core</td>
<td>60</td>
</tr>
<tr>
<td>16</td>
<td>Core structures of synthetic targets</td>
<td>60</td>
</tr>
<tr>
<td>17</td>
<td>Retrosynthesis for the 8-oxa-6-azabicyclo[3.2.1]octane core</td>
<td>60</td>
</tr>
<tr>
<td>18</td>
<td>Retrosynthesis for the 8-oxa-6-azabicyclo[3.2.1]octane core</td>
<td>61</td>
</tr>
</tbody>
</table>
Figure 19. Retrosynthesis for the 6-oxa-8-azabicyclo[3.2.1]octane core ................. 61

Figure 20. Retrosyntheses for the 8-oxa-6-azabicyclo[3.2.1]octane and the 8-oxa-6-
azabicyclo[3.2.1]octane cores ................................................................................. 68

Figure 21. Retrosynthetic scheme for the imine pathway to the 8-oxa-6-
azabicyclo[3.2.1]octane scaffold ........................................................................... 72

Figure 22. Structures of Frondosins A-E .................................................................. 77

Figure 23. Structure of the C7N Unit of Albomycin ............................................. 119

Figure 24. 1-(azetidin-1-yl)-2-diazoethan-1-one .................................................. 125
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alb 7</td>
<td>Albomycin 7 enzyme</td>
</tr>
<tr>
<td>BHBr₂-SMe₂</td>
<td>dibromoborane dimethylsulfide</td>
</tr>
<tr>
<td>Boc₂O</td>
<td>di-tert-butyl dicarbonate</td>
</tr>
<tr>
<td>BTMA-Br₃</td>
<td>benzyl trimethylammonium bromide</td>
</tr>
<tr>
<td>CSA</td>
<td>camphorsulfonic acid</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazobicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DEAD</td>
<td>diethyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAD</td>
<td>dimethyl acetylenedicarboxylate</td>
</tr>
<tr>
<td>DMAP</td>
<td>dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>2,2-DMP</td>
<td>2,2-dimethoxypropane</td>
</tr>
<tr>
<td>DMP</td>
<td>Dess-Martin periodinane</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>Et₂O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>HATU</td>
<td>(1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate)</td>
</tr>
<tr>
<td>IBX</td>
<td>2-iodoxybenzoic acid</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Name</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropyl amide</td>
</tr>
<tr>
<td>Li(t-BuO)_3AlH</td>
<td>tri-tert-butoxylium aluminum hydride</td>
</tr>
<tr>
<td>mCPBA</td>
<td>meta-chloroperbenzoic acid</td>
</tr>
<tr>
<td>Me₂TiCl₂</td>
<td>dimethyl titanium dichloride</td>
</tr>
<tr>
<td>Me₂Zn</td>
<td>dimethyl zinc</td>
</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>MeMgBr</td>
<td>methyl magnesium bromide</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>MOMCl</td>
<td>chloromethyl methyl ether</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>n-butyllithium</td>
</tr>
<tr>
<td>NaHMDS</td>
<td>sodium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NCS</td>
<td>N-chlorosuccinimide</td>
</tr>
<tr>
<td>NEt₃</td>
<td>triethylamine</td>
</tr>
<tr>
<td>NMP</td>
<td>N-methyl-2-pyrrolidone</td>
</tr>
<tr>
<td>p-ABSA</td>
<td>para-acetamidobenzenesulfonyl azide</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>Pd(PPh₃)₂Cl₂</td>
<td>bis(triphenylphosphine) palladium(II) chloride</td>
</tr>
<tr>
<td>Pd(PPh₃)₄</td>
<td>tetrakis(triphenylphosphine) palladium</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Chemical Name</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------</td>
</tr>
<tr>
<td>PfBr</td>
<td>9-bromo9-phenylfluorene</td>
</tr>
<tr>
<td>pTSA</td>
<td><em>para</em>-toluenesulfonic acid</td>
</tr>
<tr>
<td>pTsOH</td>
<td><em>para</em>-toluenesulfonic acid</td>
</tr>
<tr>
<td>RCM</td>
<td>ring closing metathesis</td>
</tr>
<tr>
<td>Rh$_2$(acam)$_4$</td>
<td>dirhodium(II) tetraacetamide</td>
</tr>
<tr>
<td>Rh$_2$(OAc)$_4$</td>
<td>dirhodium(II) tetraacetate</td>
</tr>
<tr>
<td>Rh$_2$(OHex)$_4$</td>
<td>dirhodium(II) tetrahexanoate</td>
</tr>
<tr>
<td>Rh$_2$(pfb)$_4$</td>
<td>dirhodium(II)tetrakis(perfluorobutyrate)</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>sec-BuLi</td>
<td><em>sec</em>-butyllithium</td>
</tr>
<tr>
<td>SOCl$_2$</td>
<td>thionyl chloride</td>
</tr>
<tr>
<td>T3P</td>
<td>2,4,6-Tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide</td>
</tr>
<tr>
<td>TBAF</td>
<td><em>tert</em>-butylammonium fluoride</td>
</tr>
<tr>
<td>TBDPSCl</td>
<td><em>tert</em>-butyldiphenylsilyl chloride</td>
</tr>
<tr>
<td>TBSCl</td>
<td><em>tert</em>-butyldimethylsilyl chloride</td>
</tr>
<tr>
<td>TBSOTf</td>
<td><em>tert</em>-butyldimethylsilyl trifluoromethane</td>
</tr>
<tr>
<td>t-BuLi</td>
<td><em>tert</em>-butyllithium</td>
</tr>
<tr>
<td>TEA</td>
<td>triethylamine</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TiCl$_4$</td>
<td>titanium(IV) chloride</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilane</td>
</tr>
<tr>
<td>TMSCl</td>
<td>trimethylsilyl chloride</td>
</tr>
</tbody>
</table>
CHAPTER 1: INTRODUCTION

Methodology development has changed significantly over the past half century. Organic chemists used to focus research efforts on synthesizing natural products just for the challenge of making structurally complex molecules. With the advancements in organic chemistry, however, such efforts are now in the minority. Scientists are now motivated to make molecules and their analogs that have specific molecular function and biological activity instead.\(^1\) To ensure these molecules have the appropriate biological activity, stereochemistry has become a major focus for chemists. An example of this achievement is the incredible synthesis of palitoxin, which has 68 defined stereocenters. (Figure 1)\(^2\)
Rather than completing a complex natural product synthesis, more recent targets are molecules that control the active centers of biological systems. These include molecules that bind to enzymes, receptors, transport and channel proteins, and ribosomes. These are generally what are considered small molecules, with molecular weights of less than 500 amu.

Molecules that pharmaceutical companies deem feasible are pushed into what are called clinical trials. Initially there is the so-called “Phase 0” which is the data the pharmaceutical company collects before selecting a molecule to move forward. Phase 0
consists of pharmacodynamics and pharmacokinetics. There are typically four phases to clinical trials. Phase 1 typically consists of a screen for safety. On average, about 40% of molecules that enter clinical trials fail Phase 1, meaning they were not safe for human beings. If a drug fails a phase, it does not move forward. Phase 2 is used to establish the efficacy of the drug versus a placebo. This phase is also used to establish if there is a significant upgrade over similar drugs already on the market. Phase 3 is the final confirmation of safety and efficacy. This phase is typically larger than Phase 2 and uses a lot more patients. The fourth and final phase, Phase 4, is used as sentry studies during sales. This phase is used to establish additional information, including optimal use, the benefits and also the risks involved with using the drug. Overall, it may take anywhere from eight to fifteen years for the molecule to make it from the laboratories of the pharmaceutical company to being approved by the Food & Drug Administration (FDA) after clinical trials. If these molecules make it through clinical trials, they could become drugs that would help people throughout the world.

Many of the recent discoveries in organic chemistry have not been solitary, revolutionary discoveries. They have rather been the result of cumulative, small steps, which have been the result of the increasing number of scientists in the world. Numerous reactions, including, but not limited to, the aldol, Beckmann, Claisen, Cope, Diels-Alder, Mannich, Michael, Wittig, 1,3-dipolar cycloadditions, dithiane methodology, ortho metallation, pinacol condensation and nucleophilic substitution have all been advanced to higher levels, but very few new methods have
been produced. Most of the reactions have focused on catalytic modifications, diastereoselectivity, enantioselectivity, and in-situ multi-step sequences.

With the advent of negative drug interactions from racemic mixtures of synthetic material, attention has focused away from synthesizing racemic mixtures of compounds that provide multiple activities. Attention is now focused on the preparation of one specific enantiomer that can elicit very specific biological activity without causing unwanted side effects. Biological systems also react differently to enantiomers. One enantiomer of a drug may cure a disease or relieve symptoms; the opposite antipode (enantiomer) may be toxic to the person. An example of the problems that can be caused due to a racemic mixture of a drug was the use of Thalidomide, which was first marketed in Germany in 1957. Thalidomide was a racemic mixture and was used to alleviate pain and morning sickness in pregnant women. Once the women gave birth though, the babies were born with deformed and sometimes missing limbs. As a result of these birth defects the structure of Thalidomide had to be examined to determine the cause.

Thalidomide has one chiral center and has an S-enantiomer and an R-enantiomer (Figure 2). The R enantiomer is a fairly safe drug that produces sedative benefits, but the S enantiomer is the compound that caused the birth defects. A dangerous fact about Thalidomide though, is that even if only the safe R enantiomer of the drug was taken, it racemizes. Due to this devastating outcome of the racemization of Thalidomide, the Food and Drug Administration (FDA) banned the drug in 1961.
The FDA has restrictions on the registration of racemic drugs due to the possibility of adverse reactions to specific enantiomers. These restrictions have changed the ways pharmaceutical companies need to operate and the use of these enantiomerically pure reactions is very beneficial. Recent synthetic processes have provided chemists with straightforward approaches to the synthesis of small enantiomerically pure compounds through the use of chiral catalytic reactions to produce chirality products from achiral starting materials. Chemists have also determined methods to provide drugs on an industrial scale. During this entire process, scientists have gained a better understanding of the intermolecular interactions involved in all of these reactions performed on very large scales.

Chemists have always been fascinated by nature’s complex synthetic achievements. Nature also provides a significant challenge to make these natural molecules synthetically. Nature has figured out a way to make these molecules in a chiral way, so it is the job of chemists to develop reactions that only produce one enantiomer over another.

Chemistry is a central science; meaning chemistry is everywhere people look. Chemistry is important for all of the other natural sciences as well. The lines defining

---

**Figure 2: R and S enantiomers of Thalidomide**

![R-thalidomide](image1.png) ![S-thalidomide](image2.png)

(R)-thalidomide  (S)-thalidomide
each of these natural sciences are beginning to blur between the different sciences and create interdisciplinary sciences. Organic methodology development is at the heart of chemistry. Chemistry methods need to be improved upon as well as new methods need to be developed in order for more complex molecules to be made. Since chemistry is everywhere people look, organic methodology is at the center of other natural sciences and interdisciplinary sciences as well (Figure 3).

![Diagram showing chemistry as the central science.](image)

Innovative methodology needs to be developed for the synthesis of complex heterocyclic compounds, which include natural products like Ribasine and the frondosins. Syntheses for heterocyclic compounds are important because heterocycles are located in all areas of chemistry. Heterocycles make up the biggest and most varied group of organic compounds.\(^2^2\) Heterocycles are mainly found in biologically active sites. They are synthesized by plants and animals to be used as poisons or coloring agents along with many other uses.\(^2^2\) An example of how heterocycles are necessary for life is the heme found in red blood cells.\(^2^2\) A heme is a heterocycle that complexes an iron atom, which
allows for the transport of oxygen through our bodies. Chlorophyll A, which is very similar to heme, is another example of a heterocycle coordinating a magnesium atom to have plants turn carbon dioxide into breathable oxygen.\textsuperscript{22} The building blocks of life, DNA and RNA are also very complex arrangements of a very large amount of heterocycles.\textsuperscript{22} Without heterocycles, life would not exist in its present form.

Heterocycles are also found outside of biological systems. Nitrogen-containing heterocycles tethered to graphene have been used as catalysts for oxygen reduction in fuel cells.\textsuperscript{23} Nitrogen containing heterocycles have also been used to generate energetic salts.\textsuperscript{24} These energetic salts have the potential to be used as either explosives or propellants in the future.\textsuperscript{24}

Complex heterocyclic system containing nitrogen include 8-oxa-6-azabicyclo[3.2.1]octane and 6-oxa-8-azabicyclo[3.2.1]octane and are found in compounds such as Ribasine and Solidaline (Figure 4).
The 8-oxa-6-azabicyclo[3.2.1]octane scaffold is part of numerous natural products including Ribasine, Himalayamine, and Zoanthamine (Figure 5).

Figure 5: Natural Products containing the 8-oxa-6-azabicyclo[3.2.1]octane substructure.

Ribasine is a natural product isolated from the *Fumariaceae* plant in 1983. It is the parent of a class of alkaloids that all contain the indanobenzepine core. These alkaloids are biogenetically related to the isoquinoline alkaloids. Himalayamine is also a part of this class of alkaloids. The core structure of these molecules, which is the N,O five membered ring in each structure, may help promote biological activity.

The 6-oxa-8-azabicyclo[3.2.1]octane scaffold is also a component of several natural products including azasugars, β-glucosidase inhibitors, Solidaline, and the precursor intermediate of deoxygulonojirimycin (Figure 6).
Figure 6: Natural products containing the 6-oxa-8-azabicyclo[3.2.1]octane substructures.

The frondosins (Figure 7) are a family of oxacyclic heterocyclic sesquiterpenes collected from a marine sponge displaying promising bioactive profiles. The five structurally related analogs have been shown to inhibit the binding of interleukin-8 (IL-8) to either its native receptor or protein kinase C. These natural products have also exhibited HIV-inhibitory activity in HIV assays.

Figure 7: Structures of Frondosins A-E
After examination of the previous syntheses of these molecules, it becomes evident that it is necessary to investigate new routes to these target molecules. A more efficient and quicker pathway to the core structure of these molecules is needed. Also, truncated structures need to be tested to see if biological activity can be obtained using just the core structure. The focus of our project will be to synthesize Frondosin B analogs that we hypothesize could have specific biological activity. In order for us to do this, we will eventually need to make specific molecules with the stereochemistry defined. Although there are a number of synthetic approaches and novel synthetic solutions to the frondosin family, none of these pathways proceed through a \([3+2]\)-cycloaddition reaction provided through rhodium catalyzed diazo decomposition using a carbonyl ylide. Our analysis of the core 8-oxa-6-azabicyclo[3.2.1]octane and 6-oxa-8-aza[3.2.1]octane structures and the Frondosin family provides that the general scaffold can be synthesized by using carbonyl as well as azomethine ylides utilizing either intermolecular or intramolecular \([3+2]\)-cycloaddition reactions provided through rhodium catalyzed diazo decomposition.

Carbonyl and azomethine ylides are noted for generating 5-, 6-, and 7-membered heterocycles in an efficient stereocontrolled manner. We will see if this pathway can be used to generate the core scaffold of Frondosin B.
Figure 8: General disconnection of 8-oxa-6-azabicyclo[3.2.1]octane and 6-oxa-8-azabicyclo[3.2.1]octane.
CHAPTER 2: BACKGROUND

2.1 The reactivity of carbonyl ylides.

Carbonyl ylides have become an indispensable tool in the synthetic chemist’s arsenals. These highly reactive dipolar intermediates have been utilized since their introduction in the 1960’s.\textsuperscript{30} Ylides can be formed when the lone pair of electrons of a carbonyl reacts with a carbenoid moiety generated from a diazocarbonyl in the presence of a dirhodium catalyst. The concomitant loss of nitrogen results in the formation of the carbonyl ylide, an overall neutral intermediate that contains charged atoms within the structure. The atomic charges make for a highly reactive intermediate that is able to undergo a number of synthetically useful transformations.\textsuperscript{30} These transformations include [2,3]-rearrangements, C-H/N-H insertion reactions and [3+2]-cycloaddition reactions. The use of carbonyl ylides can provide a novel pathway toward the formation of 8-oxa-6-azabicyclo[3.2.1]octane substructures that are difficult to synthesize. The ylide cycloaddition can occur owing to the dipolar nature of the carbonyl ylide (Figure 9).

\begin{center}
\begin{tikzpicture}
\node[draw, rectangle] (a) {\textbf{Figure 9: Carbonyl ylides.}\textsuperscript{30}};
\end{tikzpicture}
\end{center}

Carbonyl ylides (1) such as those in Figure 10 are in equilibrium with a corresponding epoxide (2), which is the result of an intramolecular cyclization reaction. Epoxides such as 2 are sometimes used as precursors for the formation of the carbonyl
ylides (Figure 10).\textsuperscript{30} Substituted ethers (3) can also be formed through concerted rearrangements and proton transfers. Carbonyl ylides, once formed, can further participate in [3+2]-dipolar cycloaddition reactions. Cycloaddition reactions of these types, shown in Figure 10, may be one of the most efficient and effective reactions available to the organic chemist because they can form carbon-carbon bonds similar in efficiency to the Diels-Alder reaction. In the presence of olefins and alkynes, the carbonyl ylide serves as the 1,3-dipolar intermediate and will result in many interesting oxacycles (4).\textsuperscript{30}

Carbonyl ylides (5) are prepared via a catalytic cycle beginning with a diazoketone (6). A rhodium catalyst is introduced and the diazoketone goes through a rhodium catalyzed diazo decomposition to give an electrophilic metal stabilized carbene

\begin{align*}
\text{R}_1\text{O}\text{R}_2\text{R}_3\text{R}_4 & \quad \text{R}_1\text{O}\text{R}_2\text{R}_3\text{R}_4^2 \quad \text{X-Y} \quad \text{R}_1\text{O}\text{Y}\text{R}_3\text{R}_4 \\
\text{R}_3 \text{or} \text{R}_4 = \text{Ketone} \quad \text{or} \quad \text{Ester} \quad & \quad \text{A=B} \\
\text{R}_1\text{O}_{\text{R}_2\text{R}_3\text{R}_4} & \quad \text{A-B}
\end{align*}

Figure 10: Reactions of carbonyl ylides.\textsuperscript{30}
(7) and loss of nitrogen gas. The metal stabilized carbene is attacked by the nucleophilic oxygen of the carbonyl, which then proceeds to the carbonyl ylide (Scheme 1).\textsuperscript{31}

Scheme 1: Catalytic cycle to generate carbonyl ylides.\textsuperscript{31}

The catalyst used to generate a carbonyl ylide is usually rhodium, or another organometallic based compound. The bridging ligands can be interchanged based on the need for selectivity or reactivity (Figure 11). Rhodium is a d\textsuperscript{7} transition metal and has a propensity to form rhodium-rhodium metal bonds. These types of catalysts typically have four ligands in a paddlewheel formation. In Figure 11, dirhodium(II) tetraacetate (Rh\textsubscript{2}(OAc)\textsubscript{4}) gives a good balance of reactivity and selectivity. As reactivity increases, selectivity decreases and as selectivity increases, reactivity decreases. Figure 11 shows
how one can move towards a more reactive catalyst or a more selective catalyst. In Figure 11, dirhodium(II) tetrakis(perfluorobutyrate) \( (\text{Rh}_2\text{pfb}_4) \) is the most reactive because the perfluorobutyrate bridging ligand is the most electron withdrawing, making the catalyst overall, more electrophilic, hence more reactive. Dirhodium(II) tetraacetamide \( (\text{Rh}_2\text{acam}_4) \) is the most selective because the acetamidate bridging ligand is electron donating, therefore making the catalyst overall less electrophilic and less reactive.\(^{32}\)

\[ \text{Increasing Reactivity} \]

\[ \text{Increasing regio- and stereoselectivity} \]

*Figure 11: Rhodium catalysts used for carbonyl ylide generation.*\(^{32}\)

Carbonyl ylides can be formed through a number of carbonyl derivatives including ketones, esters and amides as well as several other C=O equivalents. Padwa and others have developed a number of approaches to the preparation and utilization of carbonyl ylides in both inter- and intramolecular fashion that uses a tandem cyclization-cycloaddition method (Scheme 2).\(^{33}\) Regitz was one of the first to develop the required
diazo group transfer to a carbonyl group. This allows the carbonyl ylide to form when introduced to a rhodium catalyst. Decomposition of diazoketone (8) in the presence of rhodium acetate resulted in an electrophilic rhodium stabilized metallocarbenoid intermediate that undergoes attack by the lone pair of electrons of the oxygen of the carbonyl. This results in the formation of the carbonyl ylide (9). In the reaction provided, a reactive acetylene such as DMAD was added to the carbonyl ylide in order to trap the 1,3-dipolar intermediate. This resulted in the formation of the oxabicyclo[3.2.1]heptane nucleus (10) in good chemical yield.

![Scheme 2: Padwa's tandem cyclization-cycloaddition reaction](image)

2.2 Intermolecular carbonyl ylide cycloaddition reactions.

Ibata et al. produced a number of early studies that utilized carbonyl ylides as a synthetic tool for cycloaddition reactions. Their main focus was a carbonyl ylide derived from an aromatic ester (11) used for an intermolecular cycloaddition reaction with various dipolarophiles to provide the formation of cycloadducts (12-14) (Scheme 3).
One of the first instances of the addition of a heterocyclic olefinic dipolarophile, in this case an imine or nitrile to a carbonyl ylide, was described in Padwa’s synthesis of a straightforward ribasine-like scaffold. He first synthesized a model of the simple ribasine core using a substituted benzylidene imine as the dipolarophile (Scheme 4).
Scheme 4: Padwa’s synthesis of the ribasine core through intermolecular addition of C-N multiple bonds.\(^{36}\)

The cycloadduct of the benzylidine imine and the diazoketone (15) provided scaffold (16). The reaction was completely regiospecific, but both the endo and exo products were formed in an 8:1 ratio favoring the endo product.\(^{30}\) Also in Scheme 4, Padwa used Mander’s reagent (methyl cyanoformate) as the dipolarophile. The addition of this reagent resulted in the formation of racemic product (17).

2.3 Intramolecular carbonyl ylide cycloaddition reactions.

Intramolecular variants of the carbonyl ylide cycloaddition reactions have been used in the synthesis of several complex natural products and interesting scaffolds. The McMills group utilized a tandem ylide formation/dipolar cycloaddition reaction sequence in the synthesis of several phorbol analogs.\(^{37}\) The use of this methodology can allow for easier analogue formation with additional functionality easily prepared. McMills utilized
the ether bridge formed during the cycloaddition reaction to effect generation of the quaternary alcohol function of phorbol. The ether opening was effected via generation of the samarium enolate of the pendant keto-ether (Scheme 5).\textsuperscript{37}

\[ \text{Scheme 5: McMills’ synthesis of a phorbol analogue.}^{37} \]

The yield of this simple tricyclic phorbol analogue (19) was >90%, and was formed as a single diastereomer. X-ray crystallography also showed the correct relative stereochemical formation of C\textsubscript{8}, C\textsubscript{9}, and C\textsubscript{10}.

Padwa used an intramolecular carbonyl ylide cycloaddition reaction in conjunction with an aldehyde as the dipolarophile to synthesize a series of the substituted brevicomin analogs. The brevicomins are a family of natural products derived from the Western Pine Beetle and serve as an aggregation pheromone (Scheme 6).\textsuperscript{38}
The oxo-brevicomin derivative (20) was prepared in a 60% yield of a mixture of exo- and endo- isomers from a diazohexanedione. Dithioketalization of the bicycle adduct ketone followed by Raney nickel reduction of the resulting dithioketal, provided the formation of a mixture of the exo- and endo- brevicomins (21) in good chemical yield. Padwa has used a number of other dipolarophiles in a similar manner to create other useful natural products.$^{38}$

2.4 Azomethine Ylides

Azomethine ylides are unique synthetic tools for the formation of carbon-nitrogen bonds through cycloaddition. The azomethine ylide formed can be used in the preparation of various nitrogen-containing rings.$^{39}$ Despite this subject not receiving the same attention as carbonyl ylides, it is an additional powerful technique to generate C-N bonds. Padwa provided an interesting example in 1989 of using an azomethine ylide in the formation of an interesting azatricyclic analog (25). He begins with diazoketone (22) in the presence of DMAD and rhodium acetate to afford the carbonyl ylide (23), which then isomerizes to furnish the azomethine ylide (24). He named this process a dipole cascade. After the addition of a dipolarophile and an \textit{in situ} alkoxy 1,3-shift, he
proceeded to get the tricyclic structure (25) (Scheme 7). This also showcases some of the difficulties using this methodology. The stabilized azomethine ylide is the reactive species rather than the initially formed carbonyl ylide.

Scheme 7: Padwa’s use of azomethine ylides in synthesis.39

Another example of the use of azomethine ylide intermediates from the McMills group was the formation of a simple precursor to quinocarcin (Scheme 8).40

Scheme 8: McMills’ use of an azomethine ylide in the formation of a simple precursor to quinocarcin.40
The synthesis (Scheme 9) proceeded from commercially available tetrahydroisoquinoline acid (26) where the nitrogen had been protected as the BOC carbamate. The acid was transformed into an aldehyde through a two-step procedure of reduction with borane, then oxidation with PCC to provide the aldehyde. Oxamination of the aldehyde resulted in formation of oxime 27. The BOC group was removed, then diketene was added to provide for the subsequent formation of the α-diazoamide. The diazo group was introduced using p-ABSA to provide the substrate (28) needed for the diazo decomposition reaction. 28 was reacted with the methyl acrylate as the dipolarophile and a catalytic amount of dirhodium tetraacetate to yield the resulting simple quinocarcin precursor in trace amounts. The major product of the reaction was the aziridine (29). The aziridine was the major reaction product regardless of the reaction conditions. As an example, the aziridine was generated whether the reaction was performed at room temperature or at -78°C.

Scheme 9: Synthesis of a simple precursor to quinocarcin.
The group published a follow-up paper in which they determined that there were three possible mechanisms likely for the formation of the aziridine over the expected dipolarophile product (Figure 12). The first mechanistic possibility is the formation of the azomethine ylide which was formed after the addition of catalyst, which can then undergo attack from the anion to the carbon of the C=N bond and then quenches the positive charge of nitrogen to give the resulting aziridine (Figure 12). The second possible mechanism is the initial carbenoid formation, which then inserts directly into the C=N bond to give the resulting aziridine. Finally, a mechanism for a noncatalyzed process, which generated a triazole through a [2+3] cycloaddition reaction of azide. This mechanism provides for attack of
the diazo group to the oxime to give the resulting triazole 31 which further collapses to form the aziridine product with concomitant release of nitrogen gas.  

2.5 Previous Syntheses of Ribasine

Syntheses of ribasine have been completed by Ollero\textsuperscript{42}, Padwa\textsuperscript{36}, and Dominguez\textsuperscript{43}. The Ollero synthesis begins with a chiral aminolactone (32) subsequently alkylating with homopiperonyl bromide in the presence of sodium bis(trimethylsilyl)amide (NaHMDS) to give the lactone (33) in excellent chemical yield and diastereomeric purity (Scheme 10).\textsuperscript{42,44} This diastereomeric purity is due to the fact that the phenyl group must be in the axial position, therefore preventing attack on the same face of the molecule.
Scheme 10: Ollero’s synthesis of Ribasine.\textsuperscript{42, 44}

Hydrolysis with HCl of lactone 33 gave amino acid 34. Protection with 9-bromo-9-phenylfluorene (PfBr) and aromatic bromination with benzyltrimethylammonium
bromide (BTMA-Br$_3$) followed by condensation with formaldehyde gave the resulting oxazolidinone (35). Cyclization of oxazolidinone 35 was accomplished through butyllithium transmetallation of the bromide to give aminooxindanone (36). The lithium salt of ethyl dimethoxy-o-toluate was then reacted with aminooxindanone 36, resulting in the formation of lactone 37, which was further reduced to the hemiacetal (38) with DIBAL. Norribasine (39) was prepared by a [3+2] dipolar cycloaddition reaction via treatment of the hemiacetal 38 with trifluoroacetic acid, forming an oxonium ylide upon loss of H$_2$O. N-methylation of norribasine gave the desired ribasine (40) final product.

Padwa et al. has also used an intramolecular carbonyl ylide method to synthesize the non-nitrogen containing core structure of a compound similar to ribasine. They prepared α-diazo-β-(o-carboxyethoxy)-substituted aryl ketones and used them as model systems for the method to synthesize the aromatic core (Scheme 11).

\[ \textit{Scheme 11: Padwa’s synthesis of the ribasine-like core.} \]

The six-membered carbonyl ylide dipole (42) was formed from o-allyl-substituted diazo ketoesters (41) under dirhodium (II) catalysis to provide the desired ribasine core.
product (43). This method provides insight into the synthetic viability of the intramolecular cyclization-cycloaddition synthesis of the natural product ribasine.

Dominguez provided a racemic synthesis of Ribasine (Scheme 12). The synthesis began with the condensation of (1S,2S)-2-(Methylamino)-1-indanol (44) with \( o \)-bromomethylbenzoyl bromide (45) to provide the bromoalcohol 46. Bromoalcohol 46 was oxidized using PCC to give bromoketone 47. A Wittig reaction was then used to form the seven-membered ring compound 48. mCPBA was then used to give the racemic epoxide 49, which was then opened using LAH to give the corresponding alcohols 50.

Scheme 12: Dominguez approach towards Ribasine.

2.6 The Frondosins

The Frondosins (Figure 13) are a family of sesquiterpenes collected from a marine sponge displaying promising bioactive profiles. They have been shown to inhibit the binding of interleukin-8 (IL-8) to either its native receptor or protein kinase C. These natural products have also exhibited HIV-inhibitory activity in HIV assays. We report
herein an approach to the synthesis of Frondosin B analogs \textit{via} a rhodium catalyzed diazo-decomposition reaction, forming a carbonyl ylide intermediate, which proceeds through a cycloaddition path to form the desired cycloadduct.

Figure 13: Structures of the Frondosins.

The tetracyclic scaffold of the Frondosins is a synthetically challenging target due to the complex arrangement of the four rings. For Frondosin B alone, there have been over and handful of completed syntheses. Ovaska utilized a microwave assisted tandem 5-exo cyclization-Claisen rearrangement process to assemble the B-ring structure of Frondosin B (Scheme 13).\textsuperscript{29a} The key step is the alkyne formed oxo-claisen rearrangement which proceeds through transition state 51.
Flynn used a Stille-Heck reaction sequence to give the Frondosin B structure (Scheme 14). They proceeded through chloro-alkenyl triflate 52 with alkenyl tethered vinylstannane 53 as the Stille-Heck acceptor. The first step was to couple the two pieces together at the triflate and stannane positions to give the transition state 54. From this transition state, the molecule cyclizes to form the seven-membered ring of the Frondosin B scaffold to give scaffold 55.
Flynn also synthesized (+/-) frondosin B using a multicomponent coupling approach (Scheme 15). This approach began with the bromide 56 and reacting it with 3-methylbutenyne (57) in the presence of a palladium catalyst to give the o-alkynylphenolate 58 which then underwent heteroannulative coupling with bromide 59 to give product 60. 60 was then cyclized using a RCM reaction to give the core of frondosin B (61). The ketone was then converted to the gem-dimethyl group using Me₂TiCl₂ to give compound 62. Selective reduction of the least sterically hindered olefin gave compound 63 and demethylation of 63 with sodium ethylthiolate gave (+/-) frondosin B 64.

Scheme 14: Flynn used a Stille-Heck approach to get Frondosin B.
Enantioselective syntheses of Frondosin B have also been done. MacMillan used a very efficient five-step enantioselective total synthesis of (+)-Frondosin B (Scheme 16). The synthesis began with a benzofuran derived boronic acid (65) that was converted into the trifluoroborate salt (66) using Molander’s procedure. The trifluoroborate salt (66) was then reacted with crotonaldehyde using iminium catalysis to give aldehyde 67. Allylic alcohol 69 was obtained by reacting 67 with the vinyl lithium reagent, which was made by the Shapiro reaction of 68. The seven-membered ring was then closed using [Mo(CO)₆Br₂]₂ which proceeded through a π-allyl Friedel Crafts cyclization to give compound 70, which gave a 2.5:1 preference for the conjugated olefin. (+)-Frondosin B was then completed using boron tribromide in a demethylation reaction to give 71.
Scheme 16: MacMillan’s enantioselective synthesis of (+)-Frondosin B.\textsuperscript{29d}

Winne also had a very efficient synthesis for Frondosin B (Scheme 17). They used a recently developed (4+3) cycloaddition reaction between dienes and furfuryl alcohol as the key step in the synthesis of Frondosin B\textsuperscript{29c} They began with the fully functionalized benzofuran alcohol 72 and reacted it with titanium (IV) chloride and 1-vinyl-cyclohexene to give (+/-)-O-methyl frondosin B (73). The formal synthesis of frondosin B was completed using boron tribromide to give the demethylated product 74.\textsuperscript{29c}
The Li group also synthesized (+/-) frondosin B using a [4+3]-cycloaddition reaction between benzofuran allylic alcohols and dienes (Scheme 18).\textsuperscript{29f} They began with benzofuran 75 and reduced the ketone to the alcohol using sodium borohydride to give 76.\textsuperscript{29f} 76 was then reacted with diene 77 in a [4+3]-cycloaddition reaction using camphorsulfonic acid (CSA) to promote the reaction to give compound 78.\textsuperscript{29f} The double bond was migrated using pTsOH and demethylation was performed using boron tribromide to give (+/-) frondosin B (79).\textsuperscript{29f}
The Wright group achieved a synthesis of frondosin B based on a diastereoselective cycloaddition reaction of tetrabromocyclopropene and an annulated furan to provide a building block that could be used in the syntheses of both frondosin A and B (Scheme 19).\textsuperscript{29g} The synthesis began with commercially available ketone 80 and an asymmetric reduction was done using the (S,S)-Noyori transfer hydrogenation catalyst to give 81.\textsuperscript{29g} The alcohol was then protected and condensed with tetrabromocyclopropene to give compound 82 which can be used in both the synthesis of frondosin A and also of frondosin B.\textsuperscript{29g} 82 was then reacted in a Suzuki reaction to give 83. The annulated benzofuran 84 was then achieved through ring closure of the alcohol and the remaining bromide in the presence of stoichiometric copper(I) iodide. Wittig reaction of 84 and stereoselective hydrogenation of the resulting compound gave 85. 86 was achieved after deprotection and oxidation of the resulting alcohol. The ether bridge was opened using
tributylphosphine, which also allowed for deoxygenation to the olefin to give 87. Selective hydrogenation using palladium on carbon resulted in compound 88. 88 was then carried forward to give (+) frondosin B. The gem-dimethyl was put in place using Me₂TiCl₂, but also in the process, the methyl group on C₈ was inverted as it was later discovered had precedent in other natural product syntheses.²⁹g Finally, (-) frondosin B (89) was achieved using sodium ethylthiolate to demethylate and give the resulting alcohol.

Scheme 19: Wright’s approach to frondosin B.²⁹g
Other metals have been used in the synthesis of frondosin B. Trauner used palladium-catalyzed couplings to nucleophilic heteroarenes to give an enantioselective synthesis of (-)-frondosin B (Scheme 20).\textsuperscript{29h} This synthesis began with the R-configured alkyne 90 and the known aryl bromide 91 reacting in a Sonogashira coupling reaction to give compound 92. The alcohol was deprotected and the benzofuran 93 was formed using potassium carbonate in methanol effected saponification of the acetate followed by cyclization and iodination. 93 was alkylated with dimethoxylthiocyclohexadiene and hydrolyzed to give compound 94. NaHMDS and PhNTf\textsubscript{2} were used to form the enol triflate 95. The seven-membered ring was closed using Pd(PPh\textsubscript{3})\textsubscript{4} and Hunig’s base to give compound 96. Me\textsubscript{2}TiCl\textsubscript{2} was used to convert the ketone to the \textit{gem}-dimethyl compound 97. Demethylation using sodium ethylthiolate gave (-)-frondosin B (98).\textsuperscript{29h}
Scheme 20: Trauner’s approach using palladium towards frondosin B.\textsuperscript{29h}

Nevado used a gold-catalyzed stereocontrolled approach towards frondosin B (Scheme 21).\textsuperscript{29i} Pivaloate 99 was reacted with 6,6-dimethyl-1-vinyl cyclohexene (100) with a gold catalyst gave ketone 101, which has reported to be an intermediate on the way to frondosin B.\textsuperscript{29i}

Scheme 21: Nevado’s approach to frondosin B using a gold catalyst.\textsuperscript{29i}
Frondosin B is a very interesting and complex natural product that has been the target of numerous synthetic groups. Though it has been made in a variety of different ways, it still has not been made through a cycloaddition reaction that proceeds through a diazo decomposition reaction and forms a carbonyl ylide. We are attempting to synthesize frondosin B through this procedure in the hopes that a more efficient and quicker route can be discovered, which can possibly increase overall yield by decreasing the number of synthetic steps. Since we are also focusing on the truncated analogs of Frondosin B, we will have the truncated structures tested for biological activity to see if the cores are biologically active just like the parent compound.
CHAPTER 3: SYNTHESSES OF 8-OXA-6-AZABICYCLO[3.2.1]OCTANE AND 6-OXA-8-AZABICYCLO[3.2.1]OCTANE

3.1 Background

The 8-oxa-6-azabicyclo[3.2.1]octane and 6-oxa-8-azabicyclo[3.2.1]octane substructures are the core framework of several natural products. Some of the natural products containing the 8-oxa-6-azabicyclo[3.2.1]octane substructure include Ribasine (102), Himalayamine (103), Ribasidine (104), Norribasine (105) and Zoanthamine (106). (Figure 14)

\[
\begin{align*}
102 & \text{Ribasine, } R_1=R_2=H, R_3=\text{Me} \\
103 & \text{Himalayamine, } R_1=\text{OH}, R_2=H, R_3=\text{Me} \\
104 & \text{Ribasidine, } R_1=H, R_2=\text{OH}, R_3=\text{Me} \\
105 & \text{Norribasine, } R_1=R_2=R_3=H
\end{align*}
\]

Figure 14: Natural products containing the 8-oxa-6-azabicyclo[3.2.1]octane core.

Natural products that contain the 6-oxa-8-azabicyclo[3.2.1]octane substructure include a wide variety of compounds such as azasugars, β-glucosidase inhibitors, deoxygulonojirimycin and Solidaline (Figure 15).
The goal of this study was to synthesize truncated skeletons of the natural product cores, specifically the 8-oxa-6-azabicyclo[3.2.1]octane, 8-oxa-6-azabicyclo[3.2.1]octane and the 6-oxa-8-azabicyclo[3.2.1]octane core structures (Figure 16).

Figure 15: Natural products containing the 6-oxa-8-azabicyclo[3.2.1]octane core.$^{26h, 46}$

Figure 16: Core structures of synthetic targets.

Figure 17: Retrosynthesis for the 8-oxa-6-azabicyclo[3.2.1]octane core.
3.2 Model Studies

To determine if a cycloaddition process would be a viable synthetic pathway to form structures similar to the 8-oxa-6-azabicyclo[3.2.1]octane, a model study was developed without an aromatic ring attached as part of the core structure. These reactions were proposed in order to ensure the cycloaddition reactions could proceed, with more complex structures targeted for future work. The proposed synthesis is shown in Scheme 22. 2,4-pentandione (107) was used as the starting point for the synthesis of a simple aza bicycle intermediate. Base deprotonation provides enolate 108, which was reacted with 5-bromopentene (109) to give alkylated product (110). The terminal olefin of 110 was then oxidized via hydroboration to afford alcohol 111. The two carbonyl groups of 111 can be protected as the dithioketals using 1,3-propanedithiol, leaving the alcohol available to be oxidized to the aldehyde via a Swern oxidation generating product 112. The
aldehyde produced can be differentially protected as the oxo ketal 113 using ethylene glycol. The dithiane can be removed with NCS/silver nitrate conditions to provide a substrate amenable to diazotination with base and p-ABSA giving cyclization precursor 114. After deprotection of the aldehyde and formation of oxime 115, cyclization with rhodium acetate affords the final cycloadduct 116.
Scheme 22: Synthesis for model studies.

The synthesis of the tricycle (Scheme 23) began with 2,4-pentandione (107) and its deprotonation with sodium ethoxide, then reacting the subsequent enolate with 5-bromopentene to give alkylated dione 110. After 110 was isolated followed by
purification, substrate 110 was reacted with borane and hydrogen peroxide following a literature procedure\textsuperscript{47} to give the expected anti-Markovnikov alcohol 111 in moderate overall yields.

![Scheme 23: Synthetic route to alcohol derivative.](image)

With alcohol 111 in hand, our first attempt at protecting the carbonyl group with boron trifluoride diethyletherate and 1,3-propanedithiol\textsuperscript{48} to provide the bisthioketal compound 112. Unfortunately, none of the bisthioketal was obtained, only starting material and the mono-protected dithioketal were obtained. It was concluded that the bulkiness of the protecting group prohibited the bis-protection. After one ketone was protected as the dithioketal, the structure was too bulky for another dithioketal to be formed. After some literature searching, it was found that there are no instances of having a bis-dithioketal on these types of systems. A dithioketal protecting group works great when trying to protect a single ketone.\textsuperscript{48} A better approach would have been to perform the bis-1,3-dioxolane protection of the ketones. This could be performed using ethylene glycol and would not have the problem of steric hindrance of a bulky protecting group.\textsuperscript{55}
Alcohol 117 would then have to have been oxidized via a Swern oxidation\(^49\) to give the resulting aldehyde 112 (Scheme 24).

\[\text{Scheme 24: Synthesis to bisprotected aldehyde.}\]

Being unable to prepare the bisthioketal, we chose to prepare the diketoaldehyde 118 without protection, as the newly formed aldehyde should be more reactive than the ketones (Scheme 25). Swern oxidation\(^49\) did indeed prepare the diketoaldehyde in relatively low yield 38%, and gave a precursor that could potentially provide the requisite oxime dipolarophile. Diketoaldehyde 118 was then reacted with hydroxylamine hydrochloride and sodium carbonate to give the resulting methyloxime 119 in very poor yields.\(^53\) It was concluded by \(^1\)H NMR, that there was a mixture of oxime products showing that the aldehyde was not inherently more reactive over the ketone in oxime formation. In the \(^1\)H NMR, there was a visibly smaller aldehyde peak, indicating some reaction to the oxime occurred, but the aldehyde peak was still visible, meaning other oxime products generated from reacting with the ketones were formed. Since the reaction to form the oxime was not very efficient and starting material was scarce, we determined
it was not worthwhile to synthesize more starting material, so a different pathway was chosen.

Scheme 25: Synthetic route to oxime 119.

We determined that protection of the aldehyde could provide an additional pathway toward a similar synthetically viable intermediate (Scheme 26). Aldehyde 118 was subjected to ethylene glycol, p-toluenesulfonic acid and heated to give the resulting protected aldehyde 120 in low, but reproducible yields. With the purified protected aldehyde available, it was then subjected to Davies conditions for diazocarbonyl formation with p-acetamidobenzenesulfonyl azide and DBU to give the diazo product 121. Crude 1H NMR showed we had a mixture of the desired product as well as the bis-diazo compound. Since this reaction was not as selective as we had hoped, the project was discontinued in an effort to focus solely on forming the 8-oxa-6-azabicyclo[3.2.1]octane cores. While initially the model studies were viewed as meaningful supplemental data, it became apparent that they provided minimal information that was of value to the overall project.
3.3 Phthalic anhydride/cuprate synthesis of 8-oxa-6-azabicyclo[3.2.1]octane

The 8-oxa-6-azabicyclo[3.2.1]octane scaffold can be obtained via a rhodium catalyzed diazo decomposition reaction proceeding through an intramolecular carbonyl ylide cycloaddition pathway.\textsuperscript{37} Figure 20 shows our retrosynthetic assessment for both the 8-oxa-6-azabicyclo[3.2.1]octane and the 8-oxa-6-azabicyclo[3.2.1]octene cycloaddition products. In both cases, the final step contains a tethered dipolarophile. In the case of the 8-oxa-6-azabicyclo[3.2.1]octane, an imine or oxime provides a useful dipolarophile, while in the case of the 8-oxa-6-azabicyclo[3.2.1]octene, a nitrile can be used as the dipolarophile. One advantage of using the nitrile in the cycloaddition reaction is that the final product retains an imine in the product, allowing for further derivatization of the core.
Figure 20: Retrosyntheses for the 8-oxa-6-azabicyclo[3.2.1]octane and the 8-oxa-6-azabicyclo[3.2.1]octene cores.

Our first proposed synthesis towards the 8-oxa-6-azabicyclo[3.2.1]octane and 8-oxa-6-azabicyclo[3.2.1]octene core could begin with a cuprate addition to phthalic anhydride (122), with the resulting ketoacid 123 being reduced using lithium tri-tert-butoxyaluminum hydride to give the resulting aldehyde 124 (Scheme 27). It was postulated that the aldehyde would be acetoacylated and diazotized by the addition of ethyl diazoacetate, 2-iodoxybenzoic acid (IBX), and DBU to give the diazoketoester 125. The silicon protecting group could be removed using tert-butylammonium fluoride and the alcohol subsequently oxidized under Swern conditions to give aldehyde 126. The aldehyde was transformed into oxime 127 using methoxyamine...
hydrochloride. Once the oxime was in place, rhodium (II) tetraacetate could be used to give the final cycloaddition product 128.

Scheme 27: Proposed synthesis of the 8-oxa-6-azabicyclo[3.2.1]octane core.

The cuprate necessary for phthalate opening could be made from commercially available 5-bromopentanol (129), which could be subjected to tert-butylidimethylsilyl chloride (TBSCI), iodine and sodium thiosulfate to protect the alcohol of 130 in moderate yield (Scheme 28).
Scheme 28: Phthalic Anhydride approach to the 8-oxa-6-azabicyclo[3.2.1]octane core.

The TBS-protected alcohol could then be subjected to lithium metal, copper (I) iodide and phthalic anhydride to give the resulting carboxylic acid product 131. This type of cuprate is known as a Gilman reagent. These types of organocopper reagents are typically prepared from either copper (I) bromide or more preferably, copper (I) iodide and two equivalents of an alkyl lithium or Grignard species. This forms the homocuprate species known as a Gilman reagent. These types of reagents have two of the same alkyl group attached to the copper, with only one alkyl group being transferred in the reaction. These reagents are not stable and have to be prepared and used at cold temperatures. The desired product was not isolated as no reaction product was generated according to crude H\textsuperscript{1} NMR. Only starting material remained. It was concluded that the cuprate was not generated \textit{in situ} and no coupling of the two derivatives took place. Since the ring
opening of the phthalic anhydride could not be performed in a reasonable manner, another approach was attempted using new pathway.

There are a few other ways to make cuprate reagents. If time had allowed, a heterocuprate reagent could have been attempted. Since only one alkyl group is usually transferred in the desired reaction, a non-transferable group can be attached to the copper. These groups can include an alkyne, Ph$_2$P, R$_2$N, Me$_3$SiCh$_2$, PhS, t-BuO, and 2-thienyl.$^{61}$ These are not as reactive as Gilman reagents, but are more stable to use. Another way would have been to employ a cyanocuprate, otherwise known as a Lipshutz reagent. These have the benefit of being as reactive as Gilman reagents, but also have the stability of the heterocuprate reagents. Lipshutz reagents can be prepared using copper (I) cyanide and two equivalents of an alkyllithium species.$^{62}$ Lastly, a Grignard-copper reagent could have been used. Since we began with the commercially available 5-bromopentanol and protected the alcohol, the Grignard could have been made from compound 130. Once the Grignard (132) was formed, we could have used a catalytic amount of copper (I) iodide to form the Grignard-copper reagent which would react with phthalic anhydride to give the desired product 131 (Scheme 29).$^{63}$

![Scheme 29: Preparation of a Grignard-copper reagent.](image-url)
3.4 Imine synthesis of 8-oxa-6-azabicyclo[3.2.1]octane.

A second approach was attempted to prepare the 8-oxa-6-azabicyclo[3.2.1]octane core via a different pathway beginning with the azeotropic removal of water from the reaction of benzo[d][1,3]dioxole-5-carbaldehyde (133) and cyclohexylamine (134) (Figure 21).\(^{64}\)

![Figure 21: Retrosynthetic scheme for the imine pathway to the 8-oxa-6-azabicyclo[3.2.1]octane scaffold.](image)

The imine (135) could be deprotonated via a coordinated \(n\)-butyllithium procedure\(^ {65}\) followed by a quench with methyl chloroformate and the imine hydrolyzed with acid to give the resulting aldehyde 136 (Scheme 30). A Grignard made from the protected alcohol could be used to alkylate the aldehyde to give 137.\(^ {66}\) The alcohol could then be oxidized to the ketone (138) using N-chlorosuccinimide (NCS)\(^ {67}\) followed by TBAF deprotection\(^ {59}\) of the alcohol to give 139. The alcohol could be oxidized using PCC\(^ {68}\) and the resulting aldehyde (140) could be transformed into the oxime using methoxyamine hydrochloride\(^ {53}\) to give 141. 141 could then be treated under Davies conditions\(^ {52}\) with p-ABSA and DBU to give the diazo product 142 which could then be reacted with a rhodium catalyst to perform the final cycloaddition reaction.\(^ {37}\)
Scheme 30: Proposed synthesis of 8-oxa-6-azabicyclo[3.2.1]octane via the imine pathway.

Imine formation via azeotropic removal of water of benzo[d][1,3]dioxole-5-carbaldehyde (133) and cyclohexylamine (134) provided an excellent yield of the imine (135). Deprotonation of the 2-position of the substituted aromatic using n-butyllithium (n-BuLi), and then quenched with methyl chloroformate followed by hydrolytic conditions of the pendant imine with aqueous acid, but no acylated products were found. A second attempt was made using the stronger base, sec-BuLi followed by a quench with methyl chloroformate and then imine hydrolysis with acid, but again, the desired compound was not formed (Scheme 31). An attempt was made using tert-BuLi,
then following the same sequence, but no product was formed. Some literature reports have shown that chelation of the base using TMEDA assisted in the chelation/deprotonation protocol gave product in cases that did not work without the TMEDA. TMEDA was added in each of the three bases attempted. The reaction with n-BuLi, TMEDA and methyl chloroformate did produce small amounts of the desired product as evidenced by H NMR, but the yields were poor and non-reproducible. It was also found that the products tended to be difficult to separate. A better way to perform this experiment would have been to add the base to the reaction, and then quench with deuterium oxide to see if the deprotonation was happening. If the deprotonation were happening, then we would know that the imine hydrolysis was the problem. Another possible solution would be to add carbon dioxide rather than methyl chloroformate and see if the carboxylic acid were formed. This again would tell us if the deprotonation was happening as well as nucleophilic attack of the resulting anion. We did get a 14% yield in one instance with n-BuLi, TMEDA and methyl chloroformate, followed by acid to hydrolyze the imine. After several other attempts to reproduce this data, nothing could be obtained. It was concluded via H NMR that the problem was probably due to both the failure coordinately deprotonate the aromatic ring as well as the failure to hydrolyze the imine with acid.
After several attempts to synthesize the 8-oxa-6-azabicyclo[3.2.1]octane core scaffold, including a failed phthalic anhydride approach (Scheme 27) and the imine pathway (Scheme 30), it was concluded that a new natural product should be the focus of our research. The first approach towards the 8-oxa-6-azabicyclo[3.2.1]octane core scaffold using phthalic anhydride failed because a suitable cuprate could not be formed in situ to add into the phthalic anhydride to couple the two derivatives to give the required intermediate (Scheme 27). The second approach using an imine formation began with positive results with the formation of the imine proceeding in very good yields. This approach was hampered though by being unable to perform a coordinated deprotonation followed by imine hydrolysis. Numerous attempts were made to perform the coordinated deprotonation, including using various bases ranging from $n$-BuLi to $t$-BuLi, as well as

**Scheme 31: Attempts to perform a coordinated deprotonation of imine 135.**
including TMEDA as a way to increase the basicity, but nothing helped in the preparation of the advanced intermediate. Several attempts were made using literature precedent, but the hydrolyzed imine could not be obtained in reasonable yields to give the requisite intermediate (Scheme 31).

Model studies were also attempted in an effort to gain an understanding of how some of the reactions would proceed. Issues were encountered in protecting the diketone as the bis-dithioketal (Scheme 24). It was concluded that we only obtained the mono-protected dithioketal as well as recovered starting material. These model studies also were hampered by introduction of the diazo group using Davies conditions (Scheme 26). $^1$H NMR showed we had obtained the mono- as well as the bis-diazotized product in no apparent selectivity. Since there were various complications in the synthetic route of the model studies, they were abandoned to focus efforts on synthesizing core compounds of the 8-oxa-6-azabicyclo[3.2.1]octane and 6-oxa-8-azabicyclo[3.2.1]octane substructures.
CHAPTER 4: SYNTHESES TOWARDS FRONDOSIN B ANALOGS

4.1 Background

The Frondosins (Figure 22) are a family of sesquiterpenes collected from marine sponge *Dysidea frondosa* displaying promising bioactive profiles.\(^{29c}\) They have been shown to be inhibitors of interleukin-8 (IL-8). These types of inhibitors stop the inflammatory cascade and could possibly be used against autoimmune disorders.\(^{29h}\) These natural products have also exhibited HIV-inhibitory activity in HIV assays.\(^{70}\)

![Figure 22: Structures of Frondosins A-E](image)

We first chose to synthesize a desoxy-Frondosin B analog, similar to Frondosin C. The thought process was that we could make the desoxy analog first using indene as a starting material, then we could make a similar analog beginning with a benzofuran derivative. Synthesis of a desoxy-Frondosin B structure 143 was determined to be obtained from 145, which could be synthesized from diazobromide 146 which can be made in several steps from commercially available indene. The retrosynthesis can be seen in Scheme 32.
4.2 Indene synthesis towards a desoxy-frondosin B analog

Commercially available indene 149 was first subjected to oxalyl chloride in the hopes that it would yield the carboxylic acid indene 150. (Scheme 33) This reaction did not produce the desired product. The product was supposed to precipitate, but no precipitate was formed. This same reaction was also attempted using oxalyl bromide, but this reaction also did not produce the desired product, again failing to produce a precipitate. Crude $^1$H NMR only showed starting material for both of these reactions. This reaction would have to proceed through an acid chloride intermediate and then quenched with water to form the carboxylic acid. A possible problem with this reaction was the starting materials were not dry enough and had trace amounts of water in them, quenching the oxalyl chloride and oxalyl bromide before the acid chloride could be formed. A better way to make the indene carboxylic acid 150 would be to deprotonate and use carbon dioxide as the electrophile.
Indene (149) was subjected to with n-BuLi and solid carbon dioxide in THF\textsuperscript{72} to give the corresponding carboxylic acid 150 in 65\% yield and clean enough to carry forward without purification. (Scheme 35) Carboxylic acid 150 was converted to the acid chloride \textit{via} thionyl chloride to give 147 in good yields.\textsuperscript{73}
At this point, we could go 2 possible ways. We could use the acid chloride (147) and have an alcohol attack it to make the ester (151), or we could make the ester directly from the carboxylic acid (150) through a Fischer esterification. We thought it would be more useful to use the carboxylic acid 150 and convert it into the ester and shorten the sequence. Indene carboxylic acid 150 was heated with 10 mol% sulfuric acid and 4-hydroxybutan-2-one to give the ester 151 in 60% yield. (Scheme 36)

Acid chloride 147 was reacted with 4-hydroxybutan-2-one and triethylamine to give the resulting ester 151 in 69% yield. (Scheme 37)
4-hydroxybutan-2-one (152) could be synthesized starting with commercially available methyl 3-oxobutanoate (153) and performing a saponification reaction to give 3-oxobutanoic acid (154), which could then be protected using ethylene glycol to give the protected carboxylic acid 155 (Scheme 38). The carboxylic acid could then be reduced to the alcohol by using lithium aluminum hydride to give the resulting protected alcohol 156. The ketone could be deprotected using HCl to give 4-hydroxybutan-2-one. The saponification reaction of methyl 3-oxobutanoate was attempted and gave good yields of the resulting carboxylic acid, but this synthesis was abandoned since we found a supplier that sold the final product 152 at reasonable prices.
Scheme 38: Synthesis of 4-hydroxybutan-2-one.\textsuperscript{50, 76-77}

At this point in the procedure, there are several synthetic possibilities available to provide an electrophilic site as part of the substrate. In a first attempt, we could introduce a bromine atom to begin with and then diazotize $\alpha$ to the carbonyl moiety, or we could introduce the diazo center prior to placement of the bromine electrophile. For the introduction of the bromine atom first, ester 151 was subjected to bromine in methanol to generate the corresponding bromide 157.\textsuperscript{78} Bromide 157 could then be subjected to Davies conditions with p-ABSA and DBU to insert the diazo moiety $\alpha$ to the carbonyl providing the diazo-bromomethyl ketone 158 (Scheme 39).\textsuperscript{52} This reaction did not produce the brominated product. Rather, it seemed to give a mixture of inseparable products possibly including the mono- (159) (Scheme 40)\textsuperscript{79} and di-brominated (160) (Scheme 41)\textsuperscript{80} product of the five-membered ring.
In a second path, we could attempt to introduce the diazo moiety prior to bromination. (Scheme 42) In that event, ester 151 could be converted into the TMS
Enolether 161 by reacting 151 with lithium diisopropylamide (LDA) followed by trapping of the enolate with trimethylsilyl chloride (TMSCl).\textsuperscript{81}

Scheme 42: Attempt to make diazocarbonyl 156.\textsuperscript{52, 81-82}

Although the reaction provided some product by $^1$H NMR, the reaction had a number of side products. Some of these side products include what appeared to be the $\beta$-elimination product giving methyl vinyl ketone (162) (Scheme 43), other deprotonated products as the methylene unit on the five-membered ring will have approximately the same $\text{pK}_a$ as the $\beta$ protons of the carbonyl (Scheme 44), as well as an abundance of starting material, while providing only small amounts of the enolether necessary to continue. If the five-membered ring were deprotonated, any number of side products could be obtained, including intramolecular attack of the ketone to give an eight-membered ring, as well as intermolecular attack of itself.
Our pathway toward Frondosin B analogs, if the enolether were available, would be as follows. The TMS enolether 161 would react with N-bromosuccinimide (NBS) to provide bromide 157 which was then subjected to Davies conditions with p-ABSA and DBU to give the diazobromide 158.

Once diazobromide 158 was in hand, it could be subjected to the enolate of 3,3-dimethylocyclohexan-1-one (163) to give the penultimate product diazocarbonyl 164. Diazocarbonyl 164 could then be reacted with a rhodium (II) catalyst to give the cycloaddition product 165. The bridged oxygen could be cleaved to give the desoxy-Frondosin B analog 166 (Scheme 45).
With ongoing problems associated with brominating ester 151, a new route was devised subjecting the acid chloride of indene in a late step of the synthesis.

The synthesis began using commercially available 4-hydroxybutan-2-one 152 after protection of the hydroxyl functional group with TBSCI/imidazole. This reaction proceeded smoothly to provide the protected ketone 167, which was further subjected to LDA and the resulting enolate trapped with TMSCl to give enolether 168 (Scheme 46). Unfortunately, this reaction did not proceed as expected and no enolether was isolated. A possible suggestion as to why no enolether was isolated is that β-elimination occurred again giving methyl vinyl ketone (162) as the main product (Scheme 47).
If we would have isolated enolether 168, we would have brominated using NBS to provide α-bromomethyl compound 169. If bromide 169 were available, it would be reacted with p-ABSA and DBU to insert the diazo next to the carbonyl to give the diazocarbonyl 170, an issue we would struggle with included the regioselectivity of the diazocarbonyl formation. 3,3-dimethylcyclohexan-1-one could be deprotonated with sodium hydride to form the kinetic enolate and which was then reacted with bromide 170 to give compound 171, but would also result in a mixture of products. (Scheme 48)

One alternative to this strategy would be to make the sterically encumbered enolate through a cuprate addition of a methyl group ((CH₃)₂CuLi addition to 3-methyl cyclohexenone) and then trapping with TMS- or TBS-chloride. The TBS-protected
alcohol 171 could be deprotected using TBAF to restore the compound to alcohol 172. Alcohol 172 would finally be subjected to a base to form the alkoxide and then react with the acid chloride of indene (147) to give cyclization precursor 173 which could then be subjected to rhodium catalysis for ylide formation followed by cycloaddition. (Scheme 49)

Scheme 49: Final steps towards the synthesis of the desoxy-Frondosin B analog.

Since the original attempt to make the enolate using LDA and TMSCl did not work, other attempts were made (Scheme 50). The synthesis of the enolate was attempted using various bases including potassium bis(trimethylsilyl)amide (KHMDS) and LDA as well as various trapping agents including TBSCl and acetic anhydride, but no combination provided the trapped enolate. It was determined that a suitable amount of LDA was not formed in situ and the resulting trapped enolate was not formed in an isolable yield. Crude \(^1\)H NMR of the various reactions did show a very small amount of trapped enolate being formed, but nothing could be isolated. The final attempt was to trap the enolate and also brominate in one pot. KHMDS was used to deprotonate to form the enolate, TMSCl was used to trap the enolate and bromine was added to form the bromide
from the trapped enolate. Crude $^1$H NMR appeared to show the formation of the brominated product as the methyl peak shifted from 2.12 ppm downfield to 5.2 ppm due to the introduction of the bromine atom. The reaction did not appear to run to completion though, as only a small amount of the brominated product formed and not in enough yield to isolate. In all of these instances using strong bases LDA and KHMDS, $\beta$-elimination could be the reason no trapped enolate could be isolated. If $\beta$-elimination were to occur, methyl vinyl ketone would be the resulting product in the same manner that is shown in Scheme 47.

*Scheme 50: Attempts to make enolate.*

86
Another synthesis was devised using the more hindered enolether provided by conjugate addition to 3-methylcyclohexenone as the starting point. (Scheme 51)

\[ \text{Scheme 51: Attempt to make desoxy-Frondosin B analog beginning with dimethylcyclohexanone.}^{59,83,87} \]

The synthesis began using commercially available 3-methylcyclohex-2-en-1-one 174 to generate a highly substituted nucleophile. The nucleophile is prepared through a Michael addition to the enone to generate the gem dimethyl group, while providing the nucleophilic silyl enolether 175.\(^{83}\) Methyl magnesium bromide was first added to copper(I) iodide and lithium chloride to form the cuprate. 3-methylcyclohex-2-en-1-one was then added to the cuprate with TMSCl to yield the trapped enolate.\(^{83}\) Unfortunately, this did not occur. Our analysis of the \(^1\)H NMR data concluded that the cuprate did not form \textit{in situ}, therefore, the Michael addition could not occur. A small singlet was observed at 1.18 ppm indicating the methyl magnesium bromide added in a 1,2 fashion to
the carbonyl of 3-methylcyclohex-2-en-1-one to give 1,3-dimethylcyclohex-2-en-1-ol (176) rather than the desired product.

The reaction was attempted again, with TBSCl used as the trapping agent. Unfortunately, this reaction also did not proceed as anticipated to provide the silyl enolether 177. Again, $^1$H NMR showed a small peak indicating a 1,2-addition of methyl magnesium bromide to the carbonyl rather than a 1,4-addition. This indicated that the cuprate again, did not form in situ. The lack of formation of the cuprate in situ could be due to impure copper (I) iodide or traces of water in the copper (I) iodide. If there is water in the copper (I) iodide, the cuprate will not form. A possible solution to this problem includes using methyl lithium as a nucleophile to perform the Michael addition rather than the cuprate. Other possible solutions could be to use copper (I) bromide, rather than copper (I) iodide to form the Gilman reagent. A heterocuprate could be formed, using a non-transferable group along with the methyl that would need to be transferred. Finally, a Lipshutz copper reagent could be used. This is a cyanocuprate that has the reactivity of a Gilman reagent, but the stability of a heterocuprate. If the reaction were successful, addition of the diazo alkyl chain 178 would provide a cyclization precursor 179 to generate the desoxy-Frondosin. Titanium (IV) chloride could be used as a Lewis acid to promote coupling of the diazo alkyl chain 178 to the enolether 177. The final product could also be obtained by a one-pot deprotection of the enolether 177 using tert-butylammonium fluoride (TBAF) and reacting the enolate with the diazo alkyl chain 178 to provide the final desired product (179).
The substituted enolether \textbf{177} needed to react with diazobromide \textbf{178}. The synthesis of diazobromide \textbf{178} began with yellow mercuric oxide (\textbf{180}) being added to ethyl diazoacetate \textbf{181} to give the resulting mercury diazoacetate \textbf{182} as a yellow solid that precipitated out of solution in 50% yield that was very reproducible.\textsuperscript{88} Mercuryl diazoacetate \textbf{182} was then reacted with bromoacetyl bromide (\textbf{183}) to give the final diazo bromide compound \textbf{178} in a 69% yield that was also very reproducible and easily isolable (Scheme 52).\textsuperscript{88}

At this time, upon reanalyzing the project, it became apparent that this pathway would not yield the final product we were looking to achieve. In fact, the current pathway resulted in the electronics of the cycloaddition being reversed. Hence, we had to find a new synthetic pathway, which would provide the Frondosin B analog. A new synthesis was devised where we could change the electronics and allow the cycloaddition to proceed in the necessary fashion.

In a similar reaction sequence, the synthesis begins with commercially available indene (\textbf{149}). Indene reacts with n-BuLi followed by the addition of solid carbon dioxide “dry ice” to provide the carboxylic acid \textbf{150}.\textsuperscript{72} Rather than form the acid chloride as was part of the previous sequence, we chose to reduce the carboxylic acid using lithium
aluminum hydride to form alcohol 184. Alcohol 184 could be further reacted with acid chloride 185 to provide ester 186. (Scheme 53)

Scheme 53: Synthesis of indene ester.72,77

Acid chloride 185 could be synthesized from commercially available 4-hydroxybutan-2-one (152) and the ketone could be protected using ethylene glycol to give protected ketone 187.50 The primary alcohol could be oxidized to the carboxylic acid using Jones reagent to provide 188.89 Finally, the carboxylic acid moiety could be converted to acid chloride 185 using thionyl chloride (Scheme 54).73 The ethylene glycol protection and Jones oxidation worked as planned, but isolation of the acid chloride was problematic as no acid chloride could be recovered. After purification, only the carboxylic acid (188) was identified by $^1$H NMR. It was apparent that the acid chloride was not stable and was readily converted back into the carboxylic acid with any source of water, including moisture in the air.
Other ways ester 186 could be obtained could be through the use of coupling reagents such as N,N-dicyclohexylcarbodiimide (DCC), 2,4,6-Tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide (T3P) or 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU). The esterification of a carboxylic acid and an alcohol using DCC is known as a Steglich esterification. To make ester 186 using DCC, we would need to use carboxylic acid 188 and couple it with alcohol 184 (Scheme 55). The other reagents like T3P and HATU would work in the same fashion.

Another way to make ester 186 would be to perform a Mitsunobu reaction. A Mitsunobu reaction couples an alcohol with a carboxylic acid using triphenylphosphine and diethyl azodicarboxylate (DEAD). To make ester 186, we would need to use
carboxylic acid 188 and alcohol 184 and subject those to triphenylphosphine and DEAD (Scheme 56).

\[ \text{Scheme 56: Ester 186 via a Mitsunobu reaction.}^{91} \]

If compound 186 were completed, two pathways could be envisioned to prepare the next crucial intermediate. The product could either be brominated first, followed by diazotization, or diazotization could be added prior to bromination. If we follow the initial bromination pathway, compound 186 could be subjected to acid hydrolysis of the ethylene ketal protecting group,\(^{92}\) then followed by bromination to provide the \(\alpha\)-bromomethyl ketone 189.\(^{78}\) Compound 189 could then be subjected to Davies diazotization protocol, p-ABSA/base to introduce the diazo moiety alpha to the carbonyl, forming bromo-diazo carbonyl 190.\(^{52}\) (Scheme 57)

\[ \text{Scheme 57: First attempt to make diazocarbonyl 190.}^{52, 78, 92} \]
Alternatively, introduction of the \(\alpha\)-diazocarbonyl group prior to bromination requires that compound 186 first be subjected to aqueous acid to deprotect the ethylene ketal\(^\text{92}\) and then subjected to Davies protocol to provide the \(\alpha\)-diazocarbonyl 191.\(^\text{52}\) Potassium bis(trimethylsilyl)amide could be used to make the enolate, which could be trapped using TMSCl to provide the diazo enolether compound 192.\(^\text{86a}\) Compound 192 could then be subjected to bromine to provide the bromo-diazo carbonyl 190.\(^\text{78}\) (Scheme 58)

\[
\text{Scheme 58: Second attempt to make diazocarbonyl 190.}^{\text{52, 78, 86a, 92}}
\]

This product (190) could then be subjected to the cuprate addition enolether product (177) used in an earlier sequence of 3,3-dimethylcyclohexan-1-one to give compound 193.\(^\text{83}\) Once completed, this compound provides a scaffold that can further be subjected to catalytic dirhodium catalysis. Initial ylide formation results from diazo decomposition followed by intramolecular cycloaddition of the resulting ylide that would result in formation of the pentacycle 194.\(^\text{37}\) Previous research in the McMills group has shown that the oxygen bridge is vulnerable to samarium diiodide opening resulting in the formation of the frondosin analog (195) (Scheme 59).\(^\text{37}\)
The actual synthesis started out fine with the indene (149) being converted into the carboxylic acid (150) by the same pathway as in the previous synthesis and in good yields.\(^\text{72}\) The reduction of the carboxylic acid to the alcohol (184) was problematic in that good yields could not be obtained and only small amounts of the indene alcohol 184 were obtained.\(^\text{77}\) Low yields could be due to the fact that the reagents were not dry enough to have the reaction proceed to completion. Any water present in the reaction could quench, or reduce the efficiency of LAH and the reduction cannot occur. At this point, other pathways towards Frondosin B analogs were brought to the forefront and those syntheses began in tandem while continuing this synthesis. Once the other syntheses showed more promise, this synthesis was abandoned to focus on the other syntheses.
4.3: Benzofuran Synthesis towards Frondosin B

At this juncture, it was decided that a completely new synthetic strategy was needed to synthesize these novel oxo- and carbocyclic compounds. It was decided to work on a series of analogs that include the benzofuran found in Frondosin B. This synthesis would proceed through the intermediacy of a brominated benzofuran ester and an epoxy-alkene, which once put together could then undergo a cycloaddition reaction to synthesize the Frondosin B analog.

Scheme 60: Retrosynthesis towards a Frondosin B analog.

In Scheme 60, our retrosynthetic analysis shows that we can start from a substituted benzofuran 196 followed by a lithium-halogen exchange to provide the
nucleophilic partner for the reactive epoxide (197). Once connected, the benzofuran olefin (198), with our needed diazocarbonyl in place can react under dirhodium catalysis to form an ylide (199), followed by intramolecular cycloaddition of the pendant olefin to form the oxobridged compound 200. The bridging oxygen can then be cleaved to prepare Frondosin B analog 201.37

The synthesis will be formed in several distinct sessions to provide all the necessary reactants.

Scheme 61: Synthesis of the benzofuran piece.78, 82, 93
The synthesis begins with preparation of thioamide 203 from commercially available acetylbenzofuran (202) and subjecting it to morpholine and sulfur (Scheme 61). This reaction proceeds through a Willgerodt-Kindler rearrangement (Scheme 62).

Scheme 62: Willgerodt-Kindler rearrangement mechanism to form thioamide 197.

The Willgerodt-Kindler rearrangement mechanism begins with the formation of the enamine 207. The enamine then attacks sulfur in the form of S8. The key step is the formation of the three-membered nitrogen-containing ring in 208, where the morpholine
unit is rearranged. After the rearrangement of the morpholine, formation of the thioamide 203 occurs (Scheme 62).\(^9\)

Thioamide 203 was then converted to carboxylic acid 204 by dissolving it in concentrated hydrochloric acid (HCl) and acetic acid, then heating the resulting mixture.\(^9\) The resulting carboxylic acid 204 could never be purified, but the \(^1\)H NMR of the crude reaction product showed conversion to the acid. The crude acid was carried forward using a Fischer esterification to form the corresponding ester (205) in low but manageable yields.\(^9\) Formation of the vinyl halide was attempted from the benzofuryl ester with both NBS\(^8\) and elemental bromine\(^7\), providing no appreciable amount of the vinyl bromide 206.

Our analysis of the results of these failed reactions are as follows. For the reaction with elemental bromine, the first step of the desired mechanism is the push of electrons from the oxygen of the benzofuran 205 through the alkene for attack of elemental bromine to give structure 209. The bromide ion in solution then deprotonates at the carbon with the bromine on it and reforms the double bond in 206. Crude \(^1\)H NMR shows that this did not occur. Crude \(^1\)H NMR shows that only a small amount of starting material remained, but a new peak arose at 4.85 ppm. This peak could be due to the formation of an alkene outside of the benzofuran ring, next to the ester in 211. The mechanism for this reaction would be deprotonation of the proton α to the ester (210) (Scheme 63). Crude \(^1\)H NMR also shows the disappearance of the original methylene unit.
As for the case with NBS as the brominating agent, our analysis of the $^1$H NMR showed some disappearance of the methylene unit again with a peak showing an alkene in that position as well. There was also an extra peak at 2.05 ppm, which could indicate the presence of the succinimide unit on the molecule in the form of an amide 212 (Scheme 64) or as an enamine 213 (Scheme 65). We concluded with this data that there is a mixture of the enamine as well as the amide as the resulting products.
Scheme 64: Mechanism towards amide.
4.4: Salicylaldehyde approach towards the benzofuran ester

An alternate route was devised to assemble the benzofuryl moiety in Scheme 66. This synthesis originated with salicylaldehyde (214) and reacted it with ethynyl magnesium bromide, providing the propargyl aromatic 215 in low yield. After several reactions, enough material had been collected to continue with the synthesis. Propargyl arene 215 could be converted into the desired benzofuran ester 205 by using palladium chemistry to form the benzofuryl moiety with PdI₂, methanol and carbon monoxide under pressure. This reaction was not attempted because of the use of high pressure carbon monoxide and the small amount of starting materials we would be able to run in a single
reaction. Also, the esterification of carboxylic acid 204 from Scheme 61 worked well and we could perform that reaction on a larger scale. Once the ester was in hand, the route is the same, first brominating, then making the diazo using p-ABSA to give the desired product.

\[
\text{Scheme 66: Salicylaldehyde approach to the benzofuran ester.}^{95-96}
\]

4.5: Epoxyolefin synthesis

Our analysis of the coupling partner provided a possible synthesis of an epoxide to couple, providing the ylide cyclization precursor.
To prepare epoxyolefin 197, bromoalcohol 216 was protected as its TBS ether (217), followed by Grignard formation and addition to acrolein. Unfortunately, acrolein has become an unavailable item of commerce. Our synthetic scheme is shown in 66. Grignard formation followed by 1,2-addition to the aldehyde of acrolein, would provide the heptenyl diol and protection of the primary alcohol would provide 218. Oxidation with NCS, gem-dimethylation with titanium or zinc reagents would form the dimethyl heptenyl alcohol 219. Deprotection with mineral acid or fluoride (F-) followed by oxidation to the aldehyde using PCC and finally Corey-Chaykovsky epoxidation would likely have generated the coupling epoxide (197) needed.
An alternate route was devised to make the epoxyolefin 197 compound (Scheme 68). Commercially available 3,4-dihydro-2H-pyran (220) was subjected to HCl to provide lactol 221 in good yields. Crude $^1$H NMR also shows the aldehyde peak for the open chain form of this structure. Vinylmagnesium bromide was added to the lactol to generate heptenyl diol 222. The allylic alcohol could be oxidized using manganese dioxide, since this reagent specializes in oxidizing allylic alcohols. The crude $^1$H NMR of the reaction mixture only showed the starting material and no oxidized product. Due to this fact, the primary alcohol of the diol was protected using TBSCl to provide the mono-protected allylic alcohol 224. The oxidation of the alcohol was troublesome. Manganese dioxide, PCC, Dess-Martin Periodinane (DMP), and Jones reagent were ineffective in oxidizing the allylic alcohol to the enone. In the case of the TMS- or TBS-protected primary alcohol, it was determined that bis protection or a gross mixture
of products resulted, meaning oxidation could not occur on the protected allylic alcohol. \(^1\)H NMR still only showed unoxidized starting material. The protection step was then attempted with the more bulky protecting reagent tert-butyldiphenylsilyl chloride (TBDPSCl) rather than TBSCl with the assumption that the more bulky group would selectively protect the primary alcohol over the secondary allylic alcohol. This proved not to be the case as a gross mixture of protected products again were found by \(^1\)H NMR. The oxidations were attempted again, but none of the oxidants provided the enone due to protection of the allylic alcohol. \(^1\)H NMR still showed the unoxidized starting material.

Looking back on this synthesis of the epoxyolefin, the troublesome step was the selective protection of the primary alcohol over the secondary alcohol. Since we used TBDPSCl as a group to selectively protect the primary alcohol versus the secondary allylic alcohol, this synthesis ran into problems because of two unprotected alcohols that could not selectively be protected. The rest of the synthesis would follow in a similar path as those previously delineated. Since this synthesis was troublesome, a new route was devised to overcome the selective protection problem.
An additional procedure (Scheme 69) was envisaged for the formation of the epoxyolefin 197 using a Weinreb amide as the electrophilic intermediate. This synthesis begins with commercially available δ-valerolactone (225) followed by opening the ester with the help of a Lewis acid, trimethylaluminum, and methoxymethylamine hydrochloride to form the Weinreb amide 226. This reaction proceeded, but with rather poor overall yield. The use of trimethylaluminum is precluded due to cost (3 equivalents required) and difficulty in large-scale reaction work-up. If the Weinreb amide 226 were available, the alcohol would be protected and then the protected Weinreb amide subjected to methylmagnesium bromide to form the α-β unsaturated ketone 224. Dimethyl titanium dichloride would be used to gem-dimethylate the ketone to give alkene 227. The alcohol would be deprotected using HCl and oxidized using PCC to provide
aldehyde 228. A Corey-Chaykovsky epoxidation would then be utilized to transform the aldehyde into the final epoxide intermediate (197).97b

4.6: Faveline analog synthesis

At this point, a route was devised to synthesize a truncated Faveline structure. This was due to the simplistic look and elimination of the furan ring from the Frondosin B analogs. This synthesis was performed in parallel with the other Frondosin B syntheses. Faveline and its methyl ether are isolated from the bark of the Brazilian plant Cnidoscolus Phyllacanthus. Faveline has shown activity against P-388 murine leukemia cells.100

The synthesis of the truncated frondosin analog faveline is provided through commercially available methyl 2-(2-bromophenyl)acetate (229). Reduction of the ester with lithium aluminum hydride was achieved to generate the primary alcohol 230.77 The primary alcohol was protected using TBSCI/imidazole to give the TBS protected alcohol 231 in good yields (Scheme 70).84

Scheme 70: Synthesis of TBS-protected alcohol 231.77, 84

Our simple coupling partner derived from 2-(hex-5-en-1-yl)oxirane (232) was subjected to dibromoborane dimethylsulfide to open the epoxide ring and to brominate alpha to the resulting alcohol, to give the bromohydrin 233 and its regioisomer 234 in
good yields with an 85:15 ratio for the desired product $\text{233}^{101}$. The alcohol of the bromohydrin was then protected with MOMCl to give the protected bromohydrin $\text{222}$ in excellent yields (Scheme 71).$^{102}$ The two regioisomers could not be separated and were both carried forward into the next reaction.

Scheme 71: Ring opening of epoxide to provide bromohydrin $\text{233}^{101-102}$

A bromo-lithium exchange was then attempted using n-BuLi, but with no apparent product. The lithium base was replaced with t-BuLi, but again, the exchange was not observed (Scheme 73).$^{103}$ Crude $^1\text{H}$ NMR showed the proteo product meaning a small amount of the lithium exchange did occur, but was being quenched with a proton source before it could attack the electrophilic epoxide. It could also be that the epoxide $\text{232}$ was not electrophilic enough for the lithium species to attack. Another option would be to use the aldehyde rather than the epoxide, to make the carbon more electrophilic. Another problem that could have occurred was an elimination reaction through an $E_{1cB}$ mechanism. Once the bromo-lithium exchange happened to give the resulting carbanion $\text{235}$, elimination could occur through the $E_{1cB}$ mechanism giving the diene product $\text{236}$ (Scheme 72).
The protected bromohydrin **233** was then coupled to the aryl bromide using tetrakistriphenylphosphine palladium, albeit in poor yields (Scheme 73). The poor yields of this coupling reaction could be due to the fact that both regioisomers of the bromohydrin were present in the reaction. This could reduce the efficiency of the palladium for catalyzing the reaction. This synthesis was abandoned due to the poor yields in the palladium coupling reaction. Starting material costs and availability, especially the oxirane, as well as the number of steps needed to get to the coupling step all played in a role in the decision to abandon this synthesis.

To continue the synthesis, deprotection of the silyl protecting group using TBAF would provide the alcohol. Oxidation of the resulting primary alcohol to the carboxylic acid using Jones reagent, followed by Fischer esterification procedure, would result in the formation of ester **237**. The diazo moiety would be introduced alpha to the carbonyl
of the ester using Davies conditions with p-ABSA and DBU. Deprotection of the MOM group would reveal an alcohol that could be oxidized to the necessary ketone in \(238\). At this point, we would have the required precursor needed to proceed with the ylide formation/cycloaddition reaction to give the final desired product. (Scheme 74)

![Scheme 74: Final steps towards the Faveline analog.](image)

4.7: Stetter reaction approach towards Frondosin B analog

Since the previous routes to the desired Frondosin products did not work. A new synthesis was devised to run parallel to the Faveline synthesis to the core structure of Frondosin B. This route uses a Stetter reaction to form the 5-membered oxygen-containing ring of the benzofuran.

In a final approach to Frondosin B and its analogs, commercially available methyl propiolate (\(239\)) was subjected to salicylaldehyde (\(214\)) in the presence of N-methyl morpholine to provide the ester (\(240\)) in very good yields. The five-membered ring was
then cyclized using an intramolecular Stetter reaction with thiazolium chloride (241) used as a catalyst.\textsuperscript{106} This reaction proceeded to give the benzofuran intermediate 242. (Scheme 75)

\textit{Scheme 75: Formation of the benzofuran via a Stetter reaction.}\textsuperscript{105-106}

With the benzofuran intermediate (242) obtained, it was subjected to a Grignard reagent 243 made from the epoxide attempted in an earlier sequence.\textsuperscript{97a} The epoxide would be opened using the same procedure as the previous synthesis by using dibromoborane dimethyl sulfide to provide the resulting bromohydrin (Scheme 71).\textsuperscript{102} The alcohol of the bromohydrin could be protected using TBSCI and the Grignard reagent 243 could be made from the resulting protected bromohydrin. The reaction of the Grignard reagent 243 and the benzofuran compound 242 did not go smoothly as no product could be obtained. It was determined that reaction of benzofuran 242 and Grignard 243 resulted in a gross mixture of products (Scheme 76). It is also possible that an E\textsubscript{1cB} elimination occurred on this substrate as well once the Grignard was made. This is very similar to the elimination in Scheme 72.
A model reaction was attempted using 242 and ethynyl magnesium bromide with the hopes that it would attack the ketone on the five-membered ring selectively over the ester functionality. $^1$H NMR of this model reaction showed that attack occurred not only at the ketone of the five-membered ring, but also at the ester as well, giving a gross mixture of products (Scheme 77).

The rest of the synthesis included elimination to form the olefin, which will greatly enhance the stability of the diazo, introduction of the diazo next to the carbonyl of the ester using Davies conditions, p-ABSA and DBU, followed by deprotection and
oxidation of the resulting alcohol to give 244. At this point, the required precursor for the rhodium-catalyzed reaction would be obtained. A rhodium catalyst could then be used to give the final desired product. (Scheme 78)

Scheme 78: Grignard attack, elimination, diazotization and cycloaddition.\(^{52, 97a, 107}\)

While both intermolecular and intramolecular approaches have been attempted, the advanced intermediates needed for the synthesis of truncated Frondosin B analogs have not been obtained in appreciative yields. In the case of the desoxy-Frondosin B analog, we ran into issues with formation of the silyl enolether. We could only obtain very small amounts of the enolether by \(^1\)H NMR and could not isolate it (Schemes 42, 46, & 50). We also had issues with cuprate formation and attack of 3-methylecyclohex-2-en-1-one (Scheme 51). It was determined that the cuprate did not form \textit{in situ} and rather, the Grignard reagent attacked in a 1,2 fashion rather than the 1,4-addition that was desired. Issues were also apparent in the formation of ester 186 through the use of an acid chloride. The required acid chloride could not be obtained, but if time had allowed, other attempts could have been made including using coupling reagents such as DCC (Scheme 55), T3P or HATU, as well as a Mitsunobu reaction (Scheme 56) to form ester 186.
In our attempts to make the benzofuran derivative, the reaction sequence began with a flourish as the thioamide 203 was obtained in good yields. This reaction proceeded through a Willgerodt-Kindler rearrangement to give the thioamide (Scheme 62). We had issues brominating the 5-membered ring later in the reaction sequence. It was determined that by using elemental bromine as a bromination agent, we ended up with the wrong elimination product. Rather than eliminating to form the vinyl bromide, it eliminated to give the $\alpha,\beta$-unsaturated ketone (Scheme 63). With the use of NBS as the brominating agent, it was determined that with ended up with a mixture of amide formation (Scheme 64) as well as enamine formation (Scheme 56), but not giving the desired product (Scheme 65). There was also the issue of the attempts at oxidation of the allylic alcohol. It was determined that there was a gross mixture of mono- and bis-protected alcohols as well as completely unoxidized starting material. The fact that two alcohols were present and selectivity of the primary over the secondary alcohol could not be obtained (Scheme 68). The last setback encountered was with the bromo/lithium exchange of the Faveline intermediate (Scheme 71). It was determined by $^1$H NMR that a small amount of the proteo compound was obtained, meaning that some bromo/lithium exchange did occur, but was immediately quenched by a proton source. It was also concluded that the epoxide may not have been electrophilic enough for the lithium species to attack and the aldehyde equivalent of the epoxyolefin should be attempted next. Another possibility is an elimination reaction that proceeds through an E$_{1cB}$ mechanism to give the dialkene product (Scheme 72).
Finally, in the Stetter reaction pathway, it was concluded that Grignard attack of the ketone on the five-membered ring did not solely occur. A model reaction attempted with ethynyl magnesium bromide showed a mixture of reaction products with attack of the Grignard reagent at the ketone of the 5-membered ring as well as the ester on the chain (Schemes 76 & 77). This resulted in a gross mixture of products that was not isolable.
CHAPTER 5: OTHER PROJECTS

5.1: Albomycin: Synthesis of a C7N amino acid subunit

Albomycin is an antibiotic that belongs to the class of sideromycins. Sideromycins are compounds that have iron carriers that are attached to antibiotic moieties. Albomycin has been shown to be active against bacteria that have a transport system that consists of ferric hydroxamate. Since albomycin is an iron carrier, bacteria with ferric hydroxamate will transport the antibiotic albomycin, until they die. Albomycin has been effective in clearing both Gram-positive and Gram-negative bacterial infections, which allows the immune system to remove any bacteria that is resistant to albomycin.\(^{109}\)

Amino penta-ol \textbf{245} (Figure 23) is one subunit of Albomycin 7, prepared biogenetically through the enzyme-catalyzed reaction between either serine and threose or xylose and glycine (Scheme 79).\(^{108}\)

\begin{center}
\textbf{Figure 23: Structure of the C7N Unit of Albomycin.}\(^{108}\)
\end{center}
Scheme 79: Proposed albomycin biosynthetic pathway and functions of alb 7 enzyme.\textsuperscript{108}

The synthesis of the C7N amino acid subunit is important for a determination of the enzymatic products of this antibiotic compound. Currently, a standard is needed to develop an assay regarding the production of the C7N amino acid and whether it is one of the products of the enzymatic reaction. The synthesis of this C7N amino acid is shown in Scheme 80.

Scheme 80: Proposed synthesis of the C7N Unit.\textsuperscript{108}
Our proposed synthesis of the penta-ol subunit begins with aldehyde (246) and protected lactam (247); combined in a tin-catalyzed Aldol reaction, followed by protection of the pendant alcohol formed with tert-butylidemethylsilyl chloride to provide product (248). Oxidation of the lactam unit with potassium permanganate, utilizing cation sequestration with 18-crown-6, followed by global deprotection of the acetonide groups with lithium hydroxide and finally sodium periodate was used as a last oxidant to give the desired C7N final product (245). The syntheses of aldehyde 246 and lactam 247 will be described in distinct sections. The aldehyde synthesis is shown in Scheme 81.

Scheme 81: Aldehyde Synthesis from L-arabinose.\(^\text{110}\)

Preparation of the aldehydic coupling partner began with L-arabinose (249). L-arabinose 249 was treated with hydrochloric acid while in the presence of propane-1,3-dithiol to provide dithiane (250)\(^\text{110}\) in decent yields. Three separate deprotection methods were attempted to provide the aldehyde necessary for further reaction. None of the methods provided any of the desired aldehyde (246). Our first generation was initiated through the alkylation of the dithiane moiety \(\text{via}\) the addition of iodomethane in acetonitrile in the presence of calcium carbonate.\(^\text{110}\) After several attempts, the reaction
showed no sign of aldehyde presence by $^1$H NMR spectroscopy, the crude reaction mixture did not show any aldehyde proton in the range of 9-11 ppm. The second cleavage method attempted was the addition of N-chlorosuccinimide (NCS) and silver nitrate in acetonitrile to provide the desired aldehyde (246). Again, $^1$H NMR did not show any signature aldehyde peak. Our third attempt to make the aldehyde was through the addition of copper(II) chloride and copper oxide in acetone to the dithiane (250). $^1$H NMR did not show the formation of any apparent aldehyde peak. Finally, the deprotection was attempted using acyl chloride, and sodium nitrite to give the desired product. Unfortunately, this method did not work as well. After some literature searching, it was found that dithioketals are notoriously difficult to deprotect and sometimes required very specific conditions that can change depending on the substrate. A better approach to this problem would have been to protect the aldehyde using ethylene glycol to give the resulting dioxolane, which can readily be removed with acid.

After four unsuccessful attempts to reveal the aldehyde through deprotection of the dithiane, another synthetic pathway was sought. The second generation began with a new carbohydrate, gluconolactone (Scheme 82).
Commercially available D-(+)/-glucono-1,5-lactone (251) was reacted with 2,2-dimethoxypropane (2,2-DMP) in the presence of a catalytic amount of p-toluenesulfonic acid (p-TSA) in acetone/methanol to generate bis-acetonide hydroxyester 252 in good yields.\textsuperscript{115a} Bis-acetonide hydroxyester 252 was reduced with lithium aluminum hydride (LAH) to provide diol 253.\textsuperscript{115a} Sodium periodate (in DCM), in the presence of sodium bicarbonate cleaved the diol formed in the prior reduction to generate aldehyde (246) albeit in relatively low overall yield.\textsuperscript{115b} The synthesis of the protected lactam is shown in Scheme 83.
To synthesize the pyrrole based silyl enolether, pyrrole (254) was oxidized with hydrogen peroxide in water to give lactam 255 in satisfactory chemical yield.\textsuperscript{116a} The resulting lactam was treated with di-tert-butyl dicarbonate (Boc\textsubscript{2}O) and catalytic dimethylaminopyridine (DMAP) in acetonitrile to give the Boc-protected lactam 256.\textsuperscript{116a} Unfortunately, this protection procedure provided none of the Boc-protected lactam needed. Since the t-butyl resonance of the protecting group did not appear in the $^1$H NMR spectrum, it was surmised that initial reaction conditions were not basic enough to deprotonate the nitrogen of the lactam and allow for formation of the Boc-protecting group. As a result, sodium hydride, a stronger base, was used to deprotonate the N-H of the lactam, providing the nucleophile needed to react with the Boc\textsubscript{2}O and allow formation of the protected lactam.\textsuperscript{116b} This reaction worked to provide a small amount of material that was combined over several runs to provide material for the subsequent step. The final step involved a base initiated deprotonation and subsequent trapping of the resulting
enolate with TBSCl. This reaction was performed with 2,6-lutidine and tert-butyldimethylsilyl trifluoromethane (TBSOTf)\cite{116a}. The reaction proceeded to give trace amounts of the desired product. The lack of significant amount of product was concluded to be due to the basicity of the conditions again. 2,6-lutidine was not basic enough to deprotonate and therefore could not form the enolate that needed to be trapped. If time had allowed, a stronger base would have been attempted to form the enolate, followed by trapping with TBSCl. Since appreciable amounts of material for the requisite aldehyde and protected lactam could not be obtained, the project was postponed, while a new project was started.

5.2: Synthesis of 1-(azetidin-1-yl)-2-diazoethan-1-one

![257]

**Figure 24: 1-(azetidin-1-yl)-2-diazoethan-1-one.**\cite{117}

Diazooacetamides, like 1-(azetidin-1-yl)-2-diazoethan-1-one (257) (Figure 24), have been expected to undergo photochemical or thermal Wolff rearrangements or C-H insertions.\cite{117} It was discovered that non-cyclic N,N-dialkyl containing diazoacetamides undergo the C-H insertion reaction, whereas cyclic amides suppress the insertion reactions and favor the Wolff rearrangements to ketenes.\cite{117}

1-(azetidin-1-yl)-2-diazoethan-1-one needed to be synthesized as a standard for spectroscopic identification of starting material prior to light induced carbene
formation.\textsuperscript{117} Despite the small nature of the molecule, it is a relatively difficult synthesis for several reasons, including the availability of azetidine. The sequence (Scheme 84) began with preparation of the precursor to succinimidyl diazoacetate from commercially available starting materials methylbenzenesulfonylhydrazide (258) and glyoxylic acid (259) being heated together with acid to generate the sulfonylhydrazono acid 260\textsuperscript{118}, followed by acid chloride formation with thionyl chloride to prepare glyoxylic acid chloride (p-toluenesulfonyl)hydrozone 261.\textsuperscript{118} The acid chloride provides the electrophilic center to add the hydroxysuccinimide moiety, providing the diazoacetate reagent needed to generate the azetidine diazomide.

\textit{Scheme 84: Original synthesis of 1-(azetidin-1-yl)-2-diazoethan-1-one.}\textsuperscript{118}

There were a number of difficulties found with this synthesis. Initial isolation of the acid chloride was especially difficult as only the carboxylic acid could be isolated. This could be due to the fact that water in solution of in the air came into contact with the acid chloride, therefore converting it back to the carboxylic acid. To remedy this
situation, the acid chloride was generated in situ, immediately reacted with N-hydroxysuccimide (262) followed by work-up to attempt to isolate the diazoacetate in a one-step procedure.\(^{119}\) It appears that this provided a small amount of the diazoacetate 263. Crude $^1$H NMR shows a broad peak at 5.13 ppm, which is the normal position for a proton directly bound to a diazocarbonyl group. The $^1$H NMR spectrum also shows peaks consistent with those of a tosyl group. The reaction yield was limited and purification of the diazoacetate difficult. It was surmised that the acid chloride was not being generated in situ due to wet solvent conditions.

We then attempted to couple the tosylhydrazono acetic acid (260) directly with N-hydroxysuccinimide (262) (Scheme 84). The tosylhydrazono acetic acid (260) was directly subjected to N-hydroxysuccinimide (262), using coupling reagent $N,N'$-Dicyclohexylcarbodiimide (DCC) to provide the diazoacetate 263.\(^{120}\) Again, this reaction failed to give the desired product. DCC coupling typically couples carboxylic acids and alcohols or amide to provide the corresponding ester or amide. Since the electronics of the N-hydroxysuccinimide are different than either an alcohol or an amide, the coupling reaction did not proceed. We chose instead to make the final product in a more direct fashion, subjecting the tosylhydrazono acetic acid (260) to azetidine (via the HCl salt) and DCC to give $N^\prime$-(2-(azetidin-1-yl)-2-oxoethylidene)-4-methylbenzenesulfonohydrazide (264).\(^{120}\) This reaction produced a low yield product, so we sought to find an additional pathway to the diazotized azetidine. DCC coupling gave a 12% yield showing the reaction did work, but that a better coupling reagent was needed.
If time had allowed, T3P or HATU would have been attempted to see if those coupling reagents would have given a better yield of the desired product.

Since none of these reactions provided a reasonable path to the diazoamide, a new synthesis was devised (Scheme 86). Beginning with commercially available methyl 3-chloro-3-oxopropanoate (265) and subjecting it to azetidine, the two partners were coupled to form the amide 266 in excellent chemical yields. Amide 266 was subjected to Davies conditions to prepare diazotized compounds by treatment with p-ABSA and triethylamine to give the diazo 267. Lithium or sodium hydroxide can be used to form the decarboxylated diazoamide (257) from the amidoester starting material. This reaction appears to be more promising for brevity and overall yield and is still under investigation.
Scheme 86: New route to 1-(azetidin-1-yl)-2-diazoethan-1-one.$^{52,121-122}$
EXPERIMENTAL

General materials and methods:

All reactions were carried out under a nitrogen atmosphere and anhydrous conditions unless otherwise noted. Acetonitrile (MeCN) was dried over calcium hydride and then distilled. Dichloromethane (DCM) and tetrahydrofuran (THF) were dried using Solv-Tek, Inc. column purification/drying system, which uses low-pressure nitrogen or argon gas to force solvents through various filter materials that remove moisture and impurities. Reagents purchased from commercial sources were used without further purification unless otherwise noted. Analytical TLC was performed on 0.25 mm silica gel (60 F254) plates purchased from EMD Chemicals, Inc. UV light and potassium permanganate solution (1.5 g KMnO4, 10 g K2CO3, 1.25 mL 10% NaOH in 200 mL H2O) as visualizing agents. Flash chromatography was carried out using Merck silica 60 (230-400 mesh). 1H NMR spectra were recorded at 300 MHz on a Bruker AVANCE-300 spectrometer. 13C NMR spectra were recorded at 75 MHz. Chemical shifts (δ) are quoted in parts per million (ppm) downfield from tetramethylsilane (TMS). Multiplicities are abbreviated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet or overlap of non-equivalent resonances; br, broad. Infrared spectra were obtained on a Shimadzu FTIR-8400 spectrometer as neat oils.
3-(pent-4-en-1-yl)pentane-2,4-dione (110)\textsuperscript{54}

2,4-pentanodione (1 g, 10 mmol) in 20 mL ethanol was cooled to 0°C and 5-bromopentene (1.49 g, 10 mmol) was added along with sodium ethoxide (680 mg, 10 mmol). The reaction was allowed to stir at 0°C for 2 hours, and then let warm to room temperature and let stir overnight. Dichloromethane was added and the mixture was washed with water, sodium bicarbonate and brine and the combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography eluting with 10% ethyl acetate in hexanes to give 3-(pent-4-en-1-yl)pentane-2,4-dione (574 mg, 34%). \textsuperscript{1}H NMR (300 MHz, CHLOROFORM-\textit{d}) \(\delta\) ppm 1.25 - 1.40 (m, 2 H) 1.42 - 1.54 (m, 2 H) 1.80 - 1.92 (m, 2 H) 2.19 (s, 6 H) 3.58 - 3.67 (m, 1 H) 4.95 - 5.13 (m, 2 H) 5.67 - 5.89 (m, 1 H).

3-(5-hydroxypentyl)pentane-2,4-dione (111)\textsuperscript{47}
A round-bottomed flask was charged with 5 mL THF and flushed with nitrogen. Borane (1 M in THF) (11.50 mg, 0.832 mmol) was added along with 3-(pent-4-en-1-yl)pentane-2,4-dione (140 mg, 0.832 mmol). Hydrogen peroxide (28.29 mg, 0.832 mmol) was then added and the reaction mixture was allowed to stir for one hour. Afterwards, sodium hydroxide was added to the mixture to destroy acidic materials. The mixture was washed with water, sodium bicarbonate and brine and the combined organic extracts were dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography eluting with 50% ethyl acetate in hexanes to give 3-(5-hydroxypentyl)pentane-2,4-dione (105 mg, 68%). $^1$H NMR (300 MHz, CHLOROFORM-d) δ ppm 1.26 - 1.32 (m, 2 H) 1.35 (br. s., 2 H) 2.10 (s, 6 H) 3.57 - 3.68 (m, 1 H) 4.65 - 5.11 (m, 1 H) with some buried protons.

(E)-6-acetyl-7-oxooctanal O-methyl oxime (119)

6-acetyl-7-oxooctanal (50 mg, 0.27 mmol) was placed in a round-bottomed flask with ethanol (1 mL) and methoxyamine hydrochloride (38 mg, 0.459 mmol) and heated to 55°C. A pre-made solution of sodium carbonate (20 mg) in 0.5 mL water was added via a dropping funnel over a period of 10 minutes. The mixture was stirred for 2.5 hours at 60°C, then filtered through a frit, washed with ethanol and evaporated. Water (1 mL) was
added and the mixture was stirred at 70°C for 1 hour, then let cool to room temperature. (E)-6-acetyl-7-oxooctanal O-methyl oxime (2 mg, 2%) was isolated by filtration and air dried. $^1$H NMR (300 MHz, CHLOROFORM-d) $\delta$ ppm 2.25 (s, 2 H) 2.46 (s, 6 H) 3.79 - 3.84 (m, 3 H) 6.88 (s, 1 H) with some buried protons.

3-(4-(1,3-dioxolan-2-yl)butyl)pentane-2,4-dione (120)

In a round-bottomed flask, 6-acetyl-7-oxooctanal (2 g, 10.86 mmol), ethylene glycol (674 mg, 10.86 mmol), 5 mL benzene and para-toluenesulfonic acid (1 mg, 0.005 mmol) were placed. The flask was attached to a Dean-Stark trap under a condenser. The reaction mixture was refluxed until close to the theoretical amount of water (0.2 mL) was collected. The mixture was cooled to room temperature, washed with 15% sodium hydroxide and water. The combined organic layers were dried over magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography eluting with 10% ethyl acetate in hexanes to give 3-(4-(1,3-dioxolan-2-yl)butyl)pentane-2,4-dione (879 mg, 35%). $^1$H NMR (300 MHz, CHLOROFORM-d) $\delta$ ppm 2.10 (s, 6 H) 3.80 - 4.05 (m, 4 H) 5.01 - 5.11 (m, 1 H) with some buried protons.
((5-bromopentyl)oxy)(tert-butyl)dimethylsilane (130)\textsuperscript{60}

To a stirred solution of 5-bromopentanol (100 mg, 0.598 mmol) and iodine (25 mg, 0.2 mmol) in dichloromethane (2 mL) was added tert-butyldimethylsilyl chloride (72 mg, 0.478 mmol) in dichloromethane (2 mL) dropwise over 5 minutes. After 1 hour, finely powdered sodium thiosulfate (180 mg, 1.138 mmol) was added and the mixture stirred for an additional 30 minutes. The mixture was filtered through a plug of silica and the filter cake was washed with dichloromethane (5-10 mL). The solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10% ethyl acetate in hexanes to give ((5-bromopentyl)oxy)(tert-butyl)dimethylsilane (111 mg, 66%). \textsuperscript{1}H NMR (300 MHz, CHLOROFORM-\textit{d}) \textsuperscript{δ} ppm 0.04 - 0.07 (m, 6 H) 0.86 - 0.88 (m, 9 H) 1.36 - 1.63 (m, 4 H) 1.73 - 1.93 (m, 2 H) 3.37 (td, \textit{J}=6.47, 4.06 Hz, 2 H) 3.51 - 3.68 (m, 2 H)

5-bromopentyl 4-methylbenzenesulfonate (130a)\textsuperscript{123}

A round-bottomed flask equipped with a rubber septum and a stir bar was charged with 5-bromopentanol (500 mg, 2.995 mmol) and dichloromethane (5 mL). The solution was cooled in an ice bath to 0°C while dimethylaminopyridine (18 mg, 0.14 mmol) and tosyl chloride (570 mg, 2.99 mmol) were added. Triethylamine (3.63 g, 35.85 mmol) in dichloromethane (5 mL) was added dropwise to the mixture at 0°C. The mixture was stirred for 2 hours and poured into a mixture of ice (5 mL), water (5mL) and 2M hydrochloric acid (2.5 mL). The aqueous layer was extracted with dichloromethane (5
mL) and the combined organic layers were washed with brine (2 x 5 mL), dried over magnesium sulfate and concentrated. The residue was purified by silica gel chromatography eluting with 20% ethyl acetate in hexanes to give 5-bromopentyl 4-methylbenzenesulfonate (721 mg, 75%). $^1$H NMR (300 MHz, CHLOROFORM-$d$) δ ppm 1.34 - 1.46 (m, 2 H) 1.55 - 1.67 (m, 2 H) 1.68 - 1.80 (m, 2 H) 2.38 (s, 3 H) 3.20 - 3.34 (m, 2 H) 3.97 (t, $J$=6.33 Hz, 2 H) 7.22 - 7.33 (m, 2 H) 7.72 (d, $J$=8.12 Hz, 2 H).

![Structure](image)

$^1$-(benzo[d][1,3]dioxol-5-yl)-N-cyclohexylmethanimine (134)$^{64}$

Piperonal (1 g, 6.66 mmol) and cyclohexylamine (790 mg, 7.99 mmol) were placed in a round-bottomed flask. The solution was distilled azeotropically by the literature procedure$^{124}$ and water was removed. The crude $^1$-(benzo[d][1,3]dioxol-5-yl)-N-cyclohexylmethanimine (1.37 g, 89%) was used in further syntheses. $^1$H NMR (300 MHz, CHLOROFORM-$d$) δ ppm 1.09 - 1.37 (m, 3 H) 1.40 - 1.53 (m, 2 H) 1.56 - 1.69 (m, 3 H) 1.70 - 1.82 (m, 2 H) 2.99 - 3.15 (m, 1 H) 5.90 (s, 2 H) 6.73 (d, $J$=7.93 Hz, 1 H) 7.01 (d, $J$=8.03 Hz, 1 H) 7.27 (s, 1 H) 8.11 (s, 1 H)

![Structure](image)

methyl 5-formylbenzo[d][1,3]dioxole-4-carboxylate (135)$^{65, 69a}$
n-BuLi (1M in hexanes) (0.5 mL, 0.4756 mmol) was added dropwise over 10 minutes to a stirred and cooled solution (-78°C) of 1-(benzo[d][1,3]dioxol-5-yl)-N-cyclohexylmethanimine (100 mg, 0.4324 mmol), TMEDA (55 mg, 0.4756 mmol) in THF (3.5 mL). The temperature was then raised to -20°C and stirred for 15 minutes. The temperature was cooled back down to -78°C and methyl chloroformate (0.67 mL, 0.8648 mmol) was added dropwise over 10 minutes, and then the cold bath was removed. Once the reaction mixture reached room temperature, 15% HCl (0.35 mL) was added. Stirring was continued for one hour and then the solution was concentrated. The residue was extracted with diethyl ether (2 x 10 mL). The combined organic extracts were washed with water (2 x 5 mL), saturated sodium bicarbonate (2 x 5 mL) and brine (5 mL) and dried over sodium sulfate. It was then concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 25% ethyl acetate in hexanes to give methyl 5-formylbenzo[d][1,3]dioxole-4-carboxylate (13 mg, 14%). $^1$H NMR (300 MHz, CHLOROFORM-d) δ ppm 3.87 (s, 3 H) 6.01 (s, 2 H) 7.19 (s, 1 H) 7.35 (d, $J$=7.84 Hz, 1 H) 9.75 (s, 1 H).

1H-indene-3-carboxylic acid (142)

To a solution of indene (50 mg, 0.43 mmol) in dry THF (2 mL) at -78°C was added n-BuLi (1M in hexanes) (0.47 mL, 0.47 mmol) over a period of 20 minutes under a nitrogen atmosphere. After being stirred at -78°C for 20 minutes, solid CO₂ was added
and the mixture stirred for another 20 minutes. The reaction mixture was acidified with
10% HCl and the solvent evaporated. To the residue was added 5% HCl, and the aqueous
layer was extracted with ethyl acetate. The organic layer was washed with brine and dried
over magnesium sulfate. The solvent was evaporated and the residue was treated with
hexane to give a solid. The solid was filtered, washed with hexane and dried under
reduced pressure to give 1H-indene-3-carboxylic acid (45 mg, 65%) as a yellow
crystalline solid that was used without further purification. 1H NMR (300 MHz,
CHLOROFORM-d) δ ppm 3.62 (s, 2 H) 7.33 (d, J=7.27 Hz, 1 H) 7.37 - 7.46 (m, 1 H)
7.53 (d, J=7.46 Hz, 1 H) 7.66 (s, 1 H) 8.11 (d, J=7.46 Hz, 1 H) (Missing one
exchangeable proton).

4-hydroxy-2-butanone (38 mg, 0.429 mmol) and triethylamine (87 mg, 0.858 mmol)
were dissolved in dry dichloromethane (3 mL) and stirred at 0°C for 2 hours. Afterwards,
1H-indene-3-carbonyl chloride (115 mg, 0.644 mmol) was dissolved in dry
dichloromethane and the solution was added to the mixture. The mixture was allowed to
stir overnight under nitrogen. The reaction mixture was washed with saturated
ammonium chloride, saturated sodium bicarbonate and then water. The combined organic
layers were dried over magnesium sulfate and the solvent was removed in vacuo. The
residue was purified by silica gel chromatography eluting with 75% petroleum ether in

---

3-oxobutyl 1H-indene-3-carboxylate (145){75}
ethyl acetate to give 3-oxobutyl 1H-indene-3-carboxylate (102 mg, 69%). $^1$H NMR (300 MHz, CHLOROFORM-$d$) δ ppm 2.17 (s, 3 H) 2.85 (t, $J$=6.28 Hz, 2 H) 4.52 (t, $J$=6.28 Hz, 2 H) 7.22 (br. s., 2 H) 7.24 - 7.33 (m, 2 H) 7.35 - 7.44 (m, 2 H) 7.92 (d, $J$=7.46 Hz, 1 H).

3-oxobutyl 1H-indene-3-carboxylate (145)$^{74}$

1H-indene-3-carboxylic acid (100 mg, 0.624 mmol) was placed in a round-bottomed flask along with 4-hydroxybutan-2-one (61 mg, 0.687 mmol) and 10 mol% sulfuric acid in dry THF (5 mL). The mixture was heated to reflux for 2 days. The mixture was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate, water and brine. The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with 30% ethyl acetate in hexanes to give 3-oxobutyl 1H-indene-3-carboxylate (86 mg, 60%). $^1$H NMR (300 MHz, CHLOROFORM-$d$) δ ppm 2.09 (s, 3 H) 3.56 (s, 2 H) 4.17 (t, $J$=5.90 Hz, 2 H) 4.38 (t, $J$=5.95 Hz, 2 H) 7.31 - 7.43 (m, 2 H) 7.47 - 7.55 (m, 2 H) 8.06 (d, $J$=7.46 Hz, 1 H).

3-oxobutanoic acid (148)$^{76}$
To a solution of methyl 3-oxobutanoate (1 g, 8.62 mmol) in dichloromethane/methanol (9:1) was added a methanolic solution of sodium hydroxide (3N) (4 eq). After 3 minutes of stirring, the solution became cloudy and the sodium salt of the carboxylic acid began to precipitate. The mixture was stirred until all of the ester was consumed to give a large amount of the white precipitate. The solvents were removed under vacuum, and the residue was diluted with water and the aqueous phase extracted with diethyl ether in order to isolate the alcohol and any unreacted ester. The aqueous phase was then cooled, acidified to pH 2 with dilute HCl and extracted with dichloromethane. The organic layers were combined and dried over magnesium sulfate and the solvent was removed in vacuo to provide 3-oxobutanoic acid (637 mg, 72%). The crude was used in further reactions.

\[ \text{\textsuperscript{1}H NMR (300 MHz, CHLOROFORM-d) } \delta \text{ ppm 2.26 (s, 3 H) 3.49 (s, 2 H) (missing 1 exchangeable proton).} \]

4-((tert-butyldimethylsilyl)oxy)butan-2-one (161)

4-hydroxybutan-2-one (100 mg, 1.13 mmol) was dissolved in dry dichloromethane (5 mL) with imidazole (231 mg, 3.39 mmol). The solution was cooled down to 0°C and tert-butyldimethylsilyl chloride (205 mg, 1.36 mmol) was added. The reaction was stirred for 2 hours. The reaction was quenched with water (5 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with 10% ethyl
acetate in hexanes to give 4-((tert-butyldimethylsilyl)oxy)butan-2-one (213 mg, 82%). $^1$H NMR (300 MHz, CHLOROFORM-$d$) δ ppm 0.00 (s, 6 H) 0.83 (s, 9 H) 2.12 (s, 3 H) 2.56 (t, $J$=6.23 Hz, 2 H) 3.83 (t, $J$=6.23 Hz, 2 H).

bis(1-diazo-2-ethoxy-2-oxoethyl)mercury (175)$^{88}$

Yellow mercuric oxide (100 mg, 0.462 mmol) was added over a period of 4 hours to ethyldiazoacetate (105 mg, 0.923 mmol) in diethyl ether at -10°C with vigorous stirring. After the yellow mercuric oxide was dissolved, magnesium sulfate (72 mg, 0.598 mmol) and diethyl ether (1 mL) were added to the reaction mixture. The mixture was slowly warmed to 0°C and maintained at 0°C for 20 hours. At this time, diethyl ether (1 mL) was added and the solid was filtered and washed with diethyl ether. The solvent was evaporated under reduced pressure to give bis(1-diazo-2-ethoxy-2-oxoethyl)mercury (98 mg, 50%) as a yellow solid. $^1$H NMR (300 MHz, CHLOROFORM-$d$) δ ppm 1.30 (t, $J$=7.18 Hz, 6 H) 4.24 (q, $J$=7.11 Hz, 4 H).

ethyl 4-bromo-2-diazo-3-oxobutanoate (177)$^{88}$

To a solution containing bis(1-diazo-2-ethoxy-2-oxoethyl)mercury (500 mg, 1.17 mmol) in dichloromethane (10 mL) under nitrogen at 0°C was added dropwise bromoacetyl
bromide (497 mg, 2.46 mmol) with vigorous stirring. After warming to room temperature, the mixture was stirred for an additional 30 minutes. The mercuric salts formed were decanted and the mixture was filtered through a plug of silica using diethyl ether as the eluent. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with 60% ethyl acetate in hexanes to give ethyl 4-bromo-2-diazo-3-oxobutanoate (189 mg, 69%). $^1$H NMR (300 MHz, CHLOROFORM-$d$) $\delta$ ppm 1.25 (t, $J=7.18$ Hz, 3 H) 3.89 (s, 2 H) 4.12 (q, $J=7.14$ Hz, 2 H).

![Chemical Structure](image)

**2-(benzofuran-2-yl)-1-morpholinoethane-1-thione (197)**

2-benzofuranylmethyl ketone (3.0 g, 18.7 mmol), morpholine (2.45 g, 28.1 mmol) and sulfur (6.59 mg, 20.6 mmol) were placed in a round-bottomed flask. The flask was heated to 80°C overnight. After cooling, methanol was added and the solid was collected via filtration to give 2-(benzofuran-2-yl)-1-morpholinoethane-1-thione (3.5 g, 72%). The solid product did not need purification. $^1$H NMR (300 MHz, CHLOROFORM-$d$) $\delta$ ppm 2.88 - 2.99 (m, 2 H) 3.78 - 3.85 (m, 2 H) 3.87 - 3.97 (m, 2 H) 4.36 - 4.44 (m, 2 H) 4.49 (s, 2 H) 6.67 (s, 1 H) 7.20 - 7.27 (m, 2 H) 7.44 (d, $J=7.55$ Hz, 1 H) 7.54 (d, $J=7.08$ Hz, 1 H).
2-(benzofuran-2-yl)acetic acid (198)\textsuperscript{93}

2-(benzofuran-2-yl)-1-morpholinoethane-1-thione (500 mg, 1.91 mmol) was dissolved in concentrated HCl and concentrated acetic acid. The solution was stirred at 80° C for 18 hours. The reaction was monitored by TLC. The solvent was evaporated in vacuo. The product was stirred in cold 1N HCl. The solid was filtered and washed with cold 1N HCl. The brown filter cake was purified by silica gel chromatography eluting with a gradient of 0-10% methanol in dichloromethane. Fractions were combined and concentrated to give 2-(benzofuran-2-yl)acetic acid (321 mg, 95%). \textsuperscript{1}H NMR shows the necessary peaks. \textsuperscript{1}H NMR (300 MHz, Acetone) $\delta$ ppm 3.70 - 3.72 (m, 2 H) 6.74 - 6.78 (m, 1 H) 6.87 - 7.06 (m, 1 H) 7.44 - 7.50 (m, 1 H) 7.56 - 7.63 (m, 1 H).

methyl 2-(benzofuran-2-yl)acetate (199)\textsuperscript{93}

2-(benzofuran-2-yl)acetic acid (500 mg, 2.84 mmol) was dissolved in methanol (17 mL) and concentrated sulfuric acid (3.3 mL). The mixture, which was originally a suspension, was stirred at reflux for 2 hours. A mixture consisting of water (3.3 mL), potassium hydroxide (0.11 g) and ethyl acetate (2 mL) was added. After mixing well, the organic layer was allowed to separate and was isolated. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were dried over sodium sulfate, filtered, and evaporated. The residue was purified by silica gel chromatography eluting with 40% ethyl acetate in hexanes to give methyl 2-(benzofuran-2-yl)acetate (150 mg, 28%). \textsuperscript{1}H
NMR (300 MHz, DMSO-$d_6$) δ ppm 3.33 (s, 2 H) 3.67 (s, 3 H) 6.79 (s, 1 H) 7.19 - 7.31 (m, 2 H) 7.53 (d, $J$=7.74 Hz, 1 H) 7.59 (d, $J$=7.08 Hz, 1 H).

2-(1-hydroxyprop-2-yn-1-yl)phenol (202)$^{95}$

Salicylaldehyde (3 g, 24.57 mmol) in dry THF (30 mL) was slowly added to a solution of ethynyl magnesium bromide (0.5 M in THF) (64 mL) at room temperature. This resulted in an exothermic reaction. After the reaction subsided, THF (30 mL) was added and the mixture was allowed to stir overnight at room temperature. The reaction was quenched with 1N HCl and filtered through Celite. Brine was added and extracted with ethyl acetate (3 x 25 mL) and dichloromethane (3 x 25 mL), dried over magnesium sulfate and concentrated. The residue was purified by silica gel chromatography eluting with 25% ethyl acetate in hexanes to give 2-(1-hydroxyprop-2-yn-1-yl)phenol (0.74 g, 20%). $^1$H NMR (300 MHz, CHLOROFORM-$d$) δ ppm 3.61 (s, 1 H) 5.82 - 5.90 (m, 1 H) 6.94 (s, 1 H) 7.37 - 7.43 (m, 1 H) 7.67 - 7.75 (m, 1 H) 7.77 - 7.85 (m, 1 H) (missing two exchangeable protons).

(4-bromobutoxy)(tert-butyl)dimethylsilane (205)$^{84}$

4-bromobutanol (1 g, 6.5 mmol) in acetonitrile (20 mL) was placed in a round-bottomed flask and triethylamine (2.26 mL, 13 mmol) was added. The mixture was cooled to 0°C
and tert-butyldimethylsilyl chloride (2.46 g, 16.3 mmol) was added and the mixture was allowed to warm to room temperature and stir overnight. Dichloromethane was added and the organic layers were washed with saturated aqueous sodium bicarbonate, water and brine. The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with 10% ethyl acetate in hexanes to give (4-bromobutoxy)(tert-butyl)dimethylsilane (1.37 g, 78%). \( ^1 \)H NMR (300 MHz, CHLOROFORM-\( d \)) \( \delta \) ppm 0.00 (s, 6 H) 0.82 (s, 9 H) 1.50 - 1.62 (m, 2 H) 1.69 - 1.88 (m, 2 H) 3.30 - 3.50 (m, 2 H) 3.55 (t, \( J = 6.23 \) Hz, 2 H).

\[ \text{tetrahydro-2H-pyran-2-ol (210)}^{98a} \]

An aqueous solution of cooled 1N HCl was added to a cooled (0°C) stirred sample of 2,3-dihydropyran (5 g, 59.44 mmol). The mixture was stirred at 0°C for 15 minutes before being warmed to room temperature and stirred for 1 hour. The mixture was then extracted with dichloromethane and the combined organic layers were washed with saturated aqueous sodium bicarbonate, water, brine, dried over magnesium sulfate and evaporated to give tetrahydro-2H-pyran-2-ol (2.04 g, 34%) as a pale yellow oil. The crude residue was not purified further. \( ^1 \)H NMR (300 MHz, CHLOROFORM-\( d \)) \( \delta \) ppm 1.66 - 1.95 (m, 6 H) 3.87 (ddd, \( J = 10.79, 7.06, 3.49 \) Hz, 2 H) 5.30 (s, 1 H).
hept-6-ene-1,5-diol (211)\textsuperscript{a}
tetrahydro-2\textit{H}-pyran-2-ol (4.492 g, 43.98 mmol) in dry THF (45 mL) was slowly added to a solution of vinyl magnesium bromide (1M in THF) (53 mL) at room temperature. This resulted in an exothermic reaction, which upon cooling resulted in the solidification of the reaction mixture. This was then treated further with dry THF (45 mL) and the suspension stirred vigorously for 16 hours. The reaction was quenched with 1N HCl and was filtered through Celite. Brine was added and the solution was extracted with ethyl acetate (3 x 25 mL) and dichloromethane (3 x 25 mL), dried over magnesium sulfate and concentrated to give an oil. The product was purified by silica gel chromatography eluting with 60\% ethyl acetate in petroleum ether to give hept-6-ene-1,5-diol (2.943 g, 51\%). Product was visualized with potassium permanganate stain. \textsuperscript{1}H NMR (300 MHz, CHLOROFORM-\textit{d}) $\delta$ ppm 1.54 - 1.70 (m, 6 H) 3.42 - 3.54 (m, 2 H) 3.98 - 4.14 (m, 1 H) 5.51 - 5.68 (m, 2 H) 5.82 (dd, $J$=10.39, 6.70 Hz, 1 H) (missing two exchangeable protons).

7-((\textit{tert}-butyldimethylsilyl)oxy)hept-1-en-3-ol (212)\textsuperscript{84}

hept-6-ene-1,5-diol (2.943 g, 22.61 mmol) was dissolved in DMF (36 mL) and was treated with imidazole (1.85 g, 27.13 mmol), followed by TBSCI (3.41 g, 22.61 mmol) at -5\textdegree C. After stirring overnight, diethyl ether (70 mL) and water (70 mL) were added. The organic layer was separated and the aqueous layer was further extracted with diethyl ether. The organic layers were washed with a 5\% lithium chloride solution to remove
DMF. After drying over magnesium sulfate, and evaporation of the solvent, the residue was purified by silica gel chromatography eluting with 12% diethyl ether in petroleum ether to give 7-((tert-butyldimethylsilyl)oxy)hept-1-en-3-ol (2.182 g, 40%). \(^1\)H NMR (300 MHz, CHLOROFORM-\(d\)) \(\delta\) ppm 0.06 (s, 6 H) 0.88 (s, 9 H) 1.55 - 1.69 (m, 6 H) 3.42 - 3.54 (m, 2 H) 5.51 - 5.67 (m, 2 H) 5.77 - 5.91 (m, 1 H) (Missing one exchangeable proton).

\[7-((\text{tert-butyldimethylsilyl})\text{oxy})\text{hept-1-en-3-ol (212a)}\]^{84}

hept-6-ene-1,5-diol (3.732 g, 28.67 mmol) was dissolved in DMF (40 mL) and was treated with imidazole (2.34 g, 34.4 mmol) followed by TBDPSCl (7.88 g, 28.67 mmol) at -5°C. After stirring overnight, diethyl ether (75 mL) and water (75 mL) were added. The organic layer was separated and the aqueous layer further extracted with diethyl ether. The combined organic layers were washed with a 5% lithium chloride solution to remove DMF. After drying over magnesium sulfate and evaporation of the solvent, the residue was purified by silica gel chromatography eluting with 10% diethyl ether in petroleum ether to give 7-((tert-butyldiphenylsilyl)oxy)hept-1-en-3-ol (3.74 g, 35%). \(^1\)H NMR (300 MHz, CHLOROFORM-\(d\)) \(\delta\) ppm 0.95 (s, 9 H) 1.47 - 1.61 (m, 6 H) 3.32 - 3.46 (m, 2 H) 3.87 - 4.03 (m, 1 H) 5.42 - 5.59 (m, 2 H) 5.67 - 5.84 (m, 1 H) 7.22 - 7.36 (m, 5 H) 7.60 (dd, \(J=7.13, 1.37\) Hz, 5 H) (missing one exchangeable proton).
δ-valerolactone (2 g, 19.98 mmol) was dissolved in dry benzene (80 mL) and trimethylaluminum (2M in toluene) (30 mL) was added at -10°C. N,O-dimethylhydroxylamine (2.92 g, 29.96 mmol) was then added and the reaction was allowed to stir for 30 minutes. Isopropanol was slowly added to the cold solution to quench the remaining trimethylaluminum. Dichloromethane was added and the organic layer was separated. The combined organic layers were washed with saturated aqueous sodium bicarbonate, water, brine and dried over magnesium sulfate. The solvent was removed in vacuo. The residue was purified by silica gel chromatography eluting with 75% ethyl acetate in hexanes to give 5-hydroxy-N-methoxy-N-methylpentanamide (314 mg, 10%). $^1$H NMR (300 MHz, CHLOROFORM-$d$) δ ppm 1.56 - 1.67 (m, 2 H) 1.68 - 1.80 (m, 2 H) 2.47 (t, $J$=6.85 Hz, 2 H) 3.18 (s, 3 H) 3.64 (t, $J$=6.18 Hz, 2 H) 3.68 (s, 3 H) (missing one exchangeable proton).

2-(2-bromophenyl)ethan-1-ol (219)

Lithium aluminum hydride (LAH) (89 mg, 2.35 mmol) was placed in a round-bottomed flask along with dry THF (20 mL). A reflux condenser was placed on the round-bottomed flask and a nitrogen line used. The slurry was cooled in an ice bath and a solution of
methyl 2-(2-bromophenyl)acetate (500 mgs, 1.96 mmol) in dry THF (20 mL) was added with stirring. The ice bath was removed and the mixture was refluxed for 3 days. The mixture was then cooled in an ice bath and excess LAH was decomposed by the addition of water (2 mL), 15% sodium hydroxide (2 mL) and water (6 mL). After stirring for another 20 minutes, the mixture was filtered with suction and the precipitate was washed with ether. The combined organic extracts were washed with water, brine and saturated sodium bicarbonate and dried over sodium sulfate and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with 10% ethyl acetate in hexanes to give 2-(2-bromophenyl)ethan-1-ol (85 mg, 22%). ¹H NMR (300 MHz, CHLOROFORM-d) δ ppm 1.55 (br. s., 1 H) 3.06 (t, J=6.70 Hz, 2 H) 3.91 (t, J=6.61 Hz, 2 H) 7.04 - 7.18 (m, 1 H) 7.21 - 7.40 (m, 2 H) 7.58 (d, J=7.93 Hz, 1 H).

(2-bromophenethoxy)(tert-butyl)dimethylsilane (220)

2-(2-bromophenyl)ethan-1-ol (2.082 g, 10.36 mmol) was dissolved in DMF (100 mL) and treated with imidazole (846 mgs, 12.43 mmol) followed by TBSCl (1.56 g, 10.36 mmol) at -5°C. After stirring overnight, ether (100 mL) and water (100 mL) were added. The organic layer was separated and the aqueous layer further extracted with ether. The organic layers were washed with 5% lithium chloride to remove DMF. After drying over sodium sulfate and evaporation of the solvent, the residue was purified by silica gel chromatography eluting with a gradient of 10-30% ethyl acetate in hexanes to give (2-
bromophenethoxy)(tert-butyl)dimethylsilane (1.057 g, 34%). $^1$H NMR (300 MHz, CHLOROFORM-$d$) δ ppm 0.00 (s, 6 H) 0.89 (s, 9 H) 3.00 (t, $J$=6.99 Hz, 2 H) 3.79 - 3.92 (m, 2 H) 7.02 - 7.15 (m, 1 H) 7.18 - 7.36 (m, 2 H) 7.54 (d, $J$=7.93 Hz, 1 H).

**1-bromooct-7-en-2-ol (222a)**

Dibromoborane dimethyl sulfide (4.4 mL, 4.4 mmol) was slowly added to a stirred solution of DCM and 1-bromooct-7-en-2-ol (1.0 g, 7.9 mmol) at room temperature under a nitrogen atmosphere. After 15 minutes, the intermediate dialkylborane was treated with water and the resulting bromohydrins were extracted with DCM, dried over magnesium sulfate and concentrated to give 1-bromooct-7-en-2-ol. The crude product was carried forward in other reactions. $^1$H NMR (300 MHz, CHLOROFORM-$d$) δ ppm 1.30 - 1.51 (m, 4 H) 1.54 - 1.66 (m, 2 H) 1.97 - 2.15 (m, 2 H) 2.21 (br. s., 1 H) 3.32 - 3.48 (m, 1 H) 3.50 - 3.62 (m, 1 H) 3.67 - 3.91 (m, 1 H) 4.86 - 5.12 (m, 2 H) 5.81 (ddt, $J$=17.02, 10.22, 6.68, 6.68 Hz, 1 H).

**8-bromo-7-(methoxymethoxy)oct-1-ene (222)**

1-bromooct-7-en-2-ol (1.0 g, 4.83 mmol) was dissolved in DCM and triethylamine (0.74 mL, 5.313 mmol) was added. After stirring at room temperature for 30 minutes, MOMCl (389 mgs, 4.83 mmol) was added and the mixture allowed to stir for 8 hours. The
reaction was quenched with water and the product extracted with DCM. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated in vacuo to give 8-bromo-7-(methoxymethoxy)oct-1-ene (982 mgs, 81%). The crude product was carried forward for further reactions. $^1$H NMR (300 MHz, CHLOROFORM-$d$) δ ppm 1.35 (br. s., 4 H) 1.47 - 1.70 (m, 3 H) 2.05 (d, $J$=6.04 Hz, 1 H) 3.30 - 3.41 (m, 4 H) 3.41 - 3.53 (m, 2 H) 3.64 - 3.83 (m, 1 H) 4.55 - 4.62 (m, 1 H) 4.63 - 4.76 (m, 1 H) 4.88 - 5.05 (m, 1 H) 5.67 - 5.88 (m, 1 H).

![Image of methyl (E)-3-(2-formylphenoxy)acrylate](image1)
methyl (E)-3-(2-formylphenoxy)acrylate (226)$^{105}$

N-methylmorpholine (248 mgs, 2.45 mmol) was added to a mixture of salicylaldehyde (5 g, 40.94 mmol), methyl propiolate (4.13 g, 49.13 mmol) and MeCN (50 mL). The solvent was removed after stirring overnight at room temperature to give methyl (E)-3-(2-formylphenoxy)acrylate (8.17 g, 97%). The crude product was carried forward. $^1$H NMR (300 MHz, CHLOROFORM-$d$) δ ppm 3.72 - 3.81 (m, 3 H) 5.67 (d, $J$=12.27 Hz, 1 H) 7.17 (d, $J$=8.31 Hz, 1 H) 7.34 (t, $J$=7.55 Hz, 1 H) 7.59 - 7.71 (m, 1 H) 7.87 (d, $J$=12.28 Hz, 1 H) 7.95 (dd, $J$=7.74, 1.51 Hz, 1 H) 10.39 (s, 1 H).

![Image of methyl 2-(3-oxo-2,3-dihydrobenzofuran-2-yl)acetate](image2)
methyl 2-(3-oxo-2,3-dihydrobenzofuran-2-yl)acetate (228)$^{106}$
A mixture of methyl (E)-3-(2-formylphenoxy)acrylate (1 g, 4.85 mmol), thiazolium chloride (131 mgs, 0.485 mmol) and DMF (10 mL) was evacuated and flushed with nitrogen and heated near reflux overnight. Toluene (100 mL) was added and the solution was washed with 5% ammonium hydroxide. The solution was separated and dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with 30% ethyl acetate in hexanes to give methyl 2-(3-oxo-2,3-dihydrobenzofuran-2-yl)acetate (420 mgs, 42%). $^1$H NMR (300 MHz, CHLOROFORM-d) δ ppm 2.74 (dd, $J=17.09$, 8.03 Hz, 1 H) 3.02 (dd, $J=17.00$, 3.59 Hz, 1 H) 3.60 - 3.67 (m, 3 H) 4.83 (dd, $J=8.12$, 3.59 Hz, 1 H) 6.99 - 7.11 (m, 2 H) 7.51 - 7.68 (m, 2 H).

\[ \text{5-(1,3-dithian-2-yl)-2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolane) (234)}^{110} \]

To a solution of L-arabinose (2g, 13.32 mmol) in 35% HCl (4 mL) was added propane 1,3-dithiol (1.28 mL, 12.7 mmol). The solution was stirred overnight at room temperature and then the mixture was poured into acetone (40 mL) at 0°C. After stirring at room temperature for 2 hours, the mixture was cooled to 0°C and 28% ammonium hydroxide (5 mL) was slowly added. The precipitate was removed by filtration and the filtrate concentrated. The residue was taken up with DCM/water (1:2, 30 mL) and the aqueous layer extracted with DCM (3 x 10 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated. The residue was purified by silica gel.
chromatography eluting with 50% ethyl acetate in dichloromethane to give 5-(1,3-dithian-2-yl)-2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolane) (1.77 g, 41%). $^1$H NMR (300 MHz, CHLOROFORM-$d$) δ ppm 1.36 (s, 3 H) 1.41 (s, 3 H) 1.46 (s, 3 H) 1.49 (s, 3 H) 2.08 (br. s., 2 H) 2.68 - 2.93 (m, 2 H) 3.04 (br. s., 2 H) 3.99 - 4.30 (m, 6 H).

methyl 2-hydroxy-2-(2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)acetate (236)$^{115a}$

p-toluenesulfonic acid (30 mg, 0.16 mmol) was added to a stirred suspension of gluconolactone (2 g, 11.16 mmol) in a mixture of 2,2-dimethoxypropane (3.4 g, 32.64 mmol), acetone (1.2 mL) and methanol (0.4 mL). The reaction was stirred under nitrogen for 4 days. Sodium bicarbonate (0.2 g) was added and the reaction mixture was stirred for 1 hour, then filtered through Celite. The solvent was removed in vacuo and the residue taken up with DCM (10 mL) and washed with water (1 mL). The aqueous phase was extracted with DCM (8 mL) and the combined organic extracts were dried over magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography eluting with 15% ethyl acetate in hexanes to give methyl 2-hydroxy-2-(2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)acetate (2.01 g, 62%). $^1$H NMR (300 MHz, CHLOROFORM-$d$) δ ppm 1.32 (s, 3 H) 1.34 (s, 3 H) 1.37 (s, 3 H) 1.40 (s, 3 H)
3.81 (s, 3 H) 3.93 - 4.16 (m, 4 H) 4.21 (d, J=7.27 Hz, 1 H) 4.29 - 4.36 (m, 1 H) (missing one exchangeable proton).

\[
\text{1-(2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)ethane-1,2-diol (237)}^{115a}
\]

To a stirred suspension of lithium aluminum hydride (LAH) (1.03 g, 27.14 mmol) in diethyl ether was added methyl 2-hydroxy-2-(2,2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)acetate (3.17 g, 11 mmol) dropwise at room temperature. The reaction mixture was heated to reflux overnight. The reaction mixture was cooled to 0°C and quenched with water (2 mL), 15% NaOH (2 mL), water (4 mL) and stirred for 1 hour at 0°C. The mixture was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with 75% ethyl acetate in hexanes to give 1-(2,2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)ethane-1,2-diol (1.07 g, 37%). \(^1\)H NMR (300 MHz, CHLOROFORM-d) δ ppm 1.28 (s, 3 H) 1.32 (s, 3 H) 1.35 (s, 3 H) 1.36 (br. s., 3 H) 3.66 - 3.76 (m, 2 H) 3.86 - 4.13 (m, 6 H) (missing two exchangeable protons).
2-hydroxy-2-(2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)acetaldehyde (230)\textsuperscript{115b}

1-(2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)ethane-1,2-diol (940 mg, 4.35 mmol) and sodium periodate (930 mg, 4.35 mmol) were placed in a round-bottomed flask with DCM (15 mL). The reaction was refluxed overnight. The next morning, sodium bicarbonate (0.5 g) was added. The solution was cooled and washed with water, saturated aqueous sodium bicarbonate, and brine. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography eluting with 25% ethyl acetate in hexanes to give 2-hydroxy-2-(2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)acetaldehyde (15 mg, 1.6%). \textsuperscript{1}H NMR (300 MHz, CHLOROFORM-\textit{d}) \textit{δ} ppm 1.28 (s, 3 H) 1.32 (s, 3 H) 1.35 (s, 3 H) 1.36 (s, 3 H) 3.67 - 3.77 (m, 2 H) 3.86 - 4.13 (m, 4 H) 7.53 - 18.21 (m, 0 H) 9.68 - 9.70 (m, 1 H) (missing one exchangeable proton).

\[ \text{1,5-dihydro-2H-pyrrol-2-one (239)} \textsuperscript{116a} \]

Pyrrole (3 g, 44.7 mmol) was dissolved in water (150 mL) and was refluxed in a round-bottomed flask with 30% hydrogen peroxide (6 g) and barium carbonate (0.9 g, 4.6 mmol) for 4 hours. Afterwards, excess oxidant was quenched by addition of lead (IV)
dioxide to the boiling solution. The solution was filtered and evaporated under reduced pressure avoiding heating above 50°C, until it reached a syrupy consistency. After treatment with dioxane and filtration, the filtrate was evaporated under reduced pressure. The residue was purified by silica gel chromatography eluting with 30% ethyl acetate in hexanes to give 1,5-dihydro-2H-pyrrol-2-one (1.37 g, 37%). $^1$H NMR (300 MHz, CHLOROFORM-d) δ ppm 3.57 - 3.75 (m, 2 H) 6.15 (d, $J=16.24$ Hz, 1 H) 7.15 (d, $J=16.05$ Hz, 1 H) 7.35 (br. s., 1 H).

**tert-butyl 2-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (240)**

60% sodium hydride (200 mg, 5.22 mmol) was placed in a round-bottomed flask along with dry hexanes (20 mL) under a nitrogen atmosphere. The mixture was stirred for 10 seconds, allowed to settle and the hexanes was removed. (repeat 2 more times). Dry THF (20 mL) and 1,5-dihydro-2H-pyrrol-2-one (400 mg, 4.8 mmol) were added to the flask. The reaction mixture was stirred at room temperature for 1 hour. Di-tert-butyldicarbonate (1.571 g, 7.2 mmol) was added and the mixture was allowed to stir overnight. The solution was quenched with brine and extracted with THF. The combined organic extracts were dried over magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography eluting with 10% ethyl acetate in hexanes to give tert-butyl 2-oxo-2,5-dihydro-1H-pyrrole-1-carboxylate (37 mg, 4.2%). $^1$H NMR (300 MHz, CHLOROFORM-d) δ ppm 3.57 - 3.75 (m, 2 H) 6.15 (d, $J=16.24$ Hz, 1 H) 7.15 (d, $J=16.05$ Hz, 1 H) 7.35 (br. s., 1 H).
MHz, CHLOROFORM-\textit{d}) \delta \text{ ppm } 1.58 (s, 9 H) 3.50 - 3.52 (m, 2 H) 7.34 - 7.36 (m, 1 H) (missing one buried proton).

\begin{center}
\includegraphics[width=1cm]{tbsoboc}
\end{center}

\textit{tert}-butyl 2-((\textit{tert}-butyldimethylsilyl)oxy)-1\textit{H}-pyrrole-1-carboxylate (231)\textsuperscript{116a}

To a solution of \textit{tert}-butyl 2-oxo-2,5-dihydro-1\textit{H}-pyrrole-1-carboxylate (350 mg, 1.91 mmol) in DCM (2 mL) was added 2,6-lutidine (0.6125 g, 5.72 mmol) and \textit{tert}-Butyldimethylsilyl trifluoromethane (0.56 g, 2.11 mmol) under nitrogen at room temperature. After the reaction stirred for 1 day, the solvent was removed in vacuo. The residue was purified by silica gel chromatography eluting with 50% ethyl acetate in benzene to give \textit{tert}-butyl 2-((\textit{tert}-butyldimethylsilyl)oxy)-1\textit{H}-pyrrole-1-carboxylate (13 mg, 2.3%). \textsuperscript{1}H NMR (300 MHz, CHLOROFORM-\textit{d}) \delta \text{ ppm } 0.00 (s, 6 H) 0.78 (s, 9 H) 0.82 (s, 9 H) 7.06 (s, 1 H) 7.09 (s, 1 H) 7.64 (t, \textit{J}=7.74 Hz, 1 H).

\begin{center}
\includegraphics[width=1cm]{tosyn}
\end{center}

\textbf{2-(2-tosylhydrazono)acetic acid (244)\textsuperscript{118}}

A solution of glyoxylic acid (50% in water) (6 mL) in water (54 mL) was placed in a round-bottomed flask and warmed in a steam bath to 60°C. This solution was then treated with a warm solution of p-toluenesulfonylhydrazide (10 g, 53.69 mmol) in 2M HCl (30 mL). The resulting mixture was heated in a steam bath with continuous stirring until all of the hydrazine, which was an oil, solidified. The reaction mixture was allowed to cool
to room temperature and then put in the refrigerator overnight. The solid was filtered, washed with cold water and allowed to dry for 2 days. The solid was dissolved in boiling ethyl acetate (50 mL), filtered and then carbon tetrachloride (100 mL) was added and the solution was allowed to cool. The solid was allowed to cool in the refrigerator overnight. The solid was collected and washed with a cold mixture of ethyl acetate and carbon tetrachloride (1:2 by volume). After drying, 2-(2-tosylhydrazono)acetic acid (9.74 g, 75%) was collected as a white crystalline solid. $^1$H NMR (300 MHz, CHLOROFORM-$d$) δ ppm 2.44 (s, 3 H) 7.32 (s, 1 H) 7.44 (d, $J$=8.03 Hz, 2 H) 7.82 (d, $J$=8.12 Hz, 2 H) (missing two exchangeable protons).

2,5-dioxopyrrolidin-1-yl 2-diazoacetate (247)\textsuperscript{119}

To a suspension of 2-(2-tosylhydrazono)acetic acid (500 mg, 2.06 mmol) in dry benzene was added thionyl chloride (0.3 mL, 4.13 mmol). The reaction mixture was heated to reflux with stirring for 2 hours. The reaction mixture was cooled immediately and the solvent removed in vacuo. The crude product was used for the next step. The acid chloride was dissolved in dry DCM and was added over 30 minutes to a stirred suspension of N-hydroxysuccinimide (261 mg, 2.27 mmol) and potassium carbonate (427 mg, 3.09 mmol) in dry DCM and maintained at 0°C. The resulting mixture was stirred at 0°C for 1 hour and then was warmed to room temperature and let stir for 3 hours. It was then filtered through Celite and the filtrate concentrated in vacuo to give 2,5-
dioxopyrrolidin-1-yl 2-diazoacetate (145 mg, 38%). $^1$H NMR (300 MHz, CHLOROFORM-$d$) $\delta$ ppm 2.80 - 2.84 (m, 4 H) 5.14 (br. s., 1 H).

$N'$-(2-(azetidin-1-yl)-2-oxoethylidene)-4-methylbenzenesulfonohydrazide (248)$^{120}$

A dry round-bottomed flask was charged with 2-(2-tosylhydrazono)acetic acid (100 mg, 0.413 mmol), azetidine HCl (39 mg, 0.413 mmol) and DCM (1 mL) under a nitrogen atmosphere. After cooling to 0°C, a solution of $N,N'$-Dicyclohexylcarbodiimide (DCC) (98 mg, 0.475 mmol) in DCM (1 mL) was added and the reaction was allowed to warm to room temperature while stirring overnight. The mixture was filtered through Celite, concentrated and purified by silica gel chromatography eluting with 50% ethyl acetate in hexanes to give $N'$-(2-(azetidin-1-yl)-2-oxoethylidene)-4-methylbenzenesulfonohydrazide (14 mg, 12%). $^1$H NMR (300 MHz, CHLOROFORM-$d$) $\delta$ ppm 2.38 (t, $J$=7.84 Hz, 2 H) 2.44 (s, 3 H) 4.13 (t, $J$=7.60 Hz, 2 H) 4.33 (t, $J$=7.79 Hz, 2 H) 6.74 (s, 1 H) 7.32 (d, $J$=8.21 Hz, 2 H) 7.83 (d, $J$=8.12 Hz, 2 H).

methyl 3-(azetidin-1-yl)-3-oxopropanoate (250)$^{121}$

methyl-3-chloro-3-oxopropanoate (500 mg, 3.66 mmol) was dissolved in dry DCM and was added over 30 minutes to a stirred suspension of azetidine HCl (209 mg, 3.66 mmol)
and potassium carbonate (1.26 g, 9.15 mmol) in dry DCM and maintained at 0°C. The resulting mixture was stirred at 0°C for 1 hour and then let warm to room temperature and let stir for 2 days. It was filtered, washed with DCM and the filtrate was concentrated in vacuo. The residue was purified by silica gel chromatography eluting with 25% ethyl acetate in hexanes to give methyl 3-(azetidin-1-yl)-3-oxopropanoate (498 mg, 86%). $^1$H NMR (300 MHz, CHLOROFORM-$d$) $\delta$ ppm 2.26 - 2.38 (m, 2 H) 3.22 (s, 2 H) 3.77 (s, 3 H) 4.07 - 4.16 (m, 2 H) 4.22 (t, $J=7.65$ Hz, 2 H).

methyl 3-(azetidin-1-yl)-2-diazo-3-oxopropanoate (251)$^{52}$

triethylamine (0.2 mL, 1.431 mmol) was added to a solution of methyl 3-(azetidin-1-yl)-3-oxopropanoate (75 mg, 0.477 mmol) and p-ABSA (172 mg, 0.715 mmol) in acetonitrile (2 mL) at 0°C under nitrogen. The reaction was allowed to warm to room temperature and stir overnight. The resulting suspension was filtered and washed with acetonitrile. The filtrate was concentrated in vacuo to 1/3 the initial volume. The remaining solution was diluted with diethyl ether and washed with water and brine. The organic layer was dried over sodium sulfate and concentrated. The residue was purified by silica gel chromatography eluting with 50% ethyl acetate in dichloromethane to give methyl 3-(azetidin-1-yl)-2-diazo-3-oxopropanoate (35 mg, 45%). $^1$H NMR (300 MHz, CHLOROFORM-$d$) $\delta$ ppm 2.29 (t, $J=7.65$ Hz, 2 H) 3.33 - 3.52 (m, 4 H) 3.79 (s, 3 H).
REFERENCES


4. How long does it take for a new drug to go through clinical trials?


22. Introduction to Heterocyclic Chemistry.


APPENDIX

SELECTED NMR SPECTRA
1-(pent-4-en-1-yl)pentane-2,4-dione.
173

Chemical Shift (ppm)

M03 (s)
M01 (m)
M02 (m)

17.85
5.18
1.00

Normalized Intensity

2.10
Chemical Shift (ppm) vs. Normalized Intensity

-3.49 ppm (M02)
-2.26 ppm (M02)
bis(1-diazo-2-ethoxy-2-oxoethyl)mercury.
Chemical Shift (ppm)

-1.0  0.0  0.5  1.0

0.05  0.10  0.15  0.20  0.25  0.30  0.35  0.40  0.45  0.50  0.55  0.60  0.65  0.70  0.75  0.80  0.85  0.90  0.95  1.00

Normalized Intensity

M01(s)  M02(d)  M03(d)  M04(m)  M05(s)  M06(m)  M07(m)  M08(m)  M09(m)

7.55  7.53  7.26  7.23  7.21  6.67  4.49  4.39  4.38  3.91  3.82  3.80  2.94  2.92  2.91
2-(benzofuran-2-yl)acetic acid.

Chemical Shift (ppm)

Normalized Intensity

M01(m) M02(m) M03(m) M04(m) M05(m) M06(m)
Methyl 2-(benzofuran-2-yl)acetate.
197
2.97 2.77 2.97 3.00
3.00 4.15 1.00 1.02
4.34 4.31 4.20 4.10 4.05 3.81
1.40 1.37 1.34 1.32

Chemical Shift (ppm)

Normalized Intensity
Chemical Shift (ppm)

Normalized Intensity
208
2.03 1.95 3.00 2.77 2.03

M02(s)  M01(s)  M03(t)  M04(m)  M05(m)

4.25 4.22 4.10 3.77 3.22

2.34 2.32 2.29

Chemical Shift (ppm)

Normalized Intensity

Normalized Intensity