Distribution Agreement:

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submissions of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature

______________________  _____________
Véronique Martin          Date
Explorations of Metallocarbene and Metallonitrene Reactive Intermediate Chemistry for the Development of Synthetically Useful New Reactions

By

Véronique Martin
Doctor of Philosophy
Chemistry

________________________
Simon B. Blakey, Ph. D.
Advisor

________________________
Frank E. McDonald, Ph. D.
Committee Member

________________________
Lanny S. Liebeskind, Ph. D.
Committee Member

Accepted:

________________________
Lisa A. Tedesco, Ph. D.
Dean of the James T. Laney School of Graduate Studies

Date
Explorations of Metallocarbene and Metallonitrène Reactive Intermediate Chemistry for the Development of Synthetically Useful New Reactions

By

Véronique Martin
Diplôme d’ingénieur, Ecole Supérieure de Chimie Physique Electronique de Lyon, 2006

Advisor: Simon B. Blakey, Ph.D.

An abstract of
A dissertation submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry 2010
Abstract

Explorations of Metallocarbene and Metallonitrene Reactive Intermediate Chemistry for the Development of Synthetically Useful New Reactions

By

Véronique Martin

This dissertation outlines our efforts on three different projects focusing on the synthesis of metallocarbene and metallonitrene intermediates for the development of new reactions. Part I focuses on a proposed novel carbohydroxylation reaction through an osmium (VIII) alkylidene intermediate. We were able to synthesize a series of unprecedented high oxidation state osmium alkylidene complexes by reaction of bisimido osmium (VIII) complexes with bulky electron ylides. We also demonstrated that these alkylidenes undergo a [3+2] reaction with nitrones to generate an alkene product. Part II focuses on the expansion of the substrate scope of our newly developed metallonitrene/ alkyne reaction. In the context of C-N bond formation, we were able to demonstrate that this reaction is versatile and leads to the formation of new C-C, C-N and C-O bonds to give rise to a variety of complex products from relatively simple starting materials. This work has led us to explore the mechanism of this reaction and allowed us to hypothesize on the nature of the reactive intermediate. In addition, we also studied the chemoselectivity of different Rh(II) catalysts. Part III focuses on our efforts towards the concise synthesis of (+)-actinobolin through a key selective C-H insertion step to form a 6-membered ring product. We propose to impart this unusual selectivity through the careful choice of protecting groups on the C5-C6 diol. So far, protection as the acetonide leads to the formation of cyclobutanone products. Protection with electron-withdrawing groups and exploring the selectivity of Rh(II) catalysts is now the focus of this project.
Explorations of Metallocarbene and Metallonitrene Reactive Intermediate Chemistry for
the Development of Synthetically Useful New Reactions

By

Véronique Martin
Diplôme d’ingénieur, Ecole Supérieure de Chimie Physique Electronique de Lyon, 2006

Advisor: Simon B. Blakey, Ph.D.

A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy
in Chemistry
2010
Acknowledgments

These five years at Emory would not have been possible without a number of people. First and foremost, I must thank my advisor, Dr Blakey, for his mentoring and guidance throughout these years. It took some time but looking back I am now able to see how much I have learned thanks to you. I would also like to thank my committee members Dr Liebeskind, Dr McDonald and Dr Padwa for their helpful advice. I must also thank other members of the department. Dr Wu’s and Dr Wang’s input with anything related to NMR was essential through the years but especially on the first project I worked. Ann Dasher makes our life also much easier. Thanks to them.

Being one of the first students in the Blakey lab, I have sometimes felt like a guinea pig so I can not thank enough the members of the lab next door, aka the McDonald lab members, especially Omar, Matt and Claney, who have not only always been great neighbors but also served as our senior group members in our early years. They were always there if we needed some help. My own lab members, especially Aaron, Clay and Danny, have also made this experience enjoyable. Thank you for that.

Having an ocean between me and my friends and family has not always been easy but I am grateful for their support, even though I know they are all disappointed that I’m not coming back. Finally, despite his crazy ways, I don’t think I would have made it through grad school without Ricardo, thank you.
Table of Contents

Part I: Synthesis and Reactivity of Osmium (VIII) Alkylidene Complexes. .............. 1

1. Chapter One: Introduction. .................................................................................. 1

   1.1. Difunctionalization of Olefins in Total Synthesis ........................................... 1

   1.2. A Proposed Carbohydroxylation Reaction ..................................................... 3

   1.3. Difunctionalization of Olefins using Osmium Reagents ......................... 3

       1.3.1 Dihydroxylation of Olefins ................................................................. 3

       1.3.2 Aminohydroxylation of Olefins ............................................................ 5

       1.3.3 Diamination of Olefins .......................................................................... 7

   1.4. Imido Osmium Complexes ............................................................................. 8

   1.5. High Oxidation State Alkylidene Complexes .............................................. 11

   1.6. Theoretical studies ....................................................................................... 14

2. Chapter Two: Results and Discussion ................................................................ 16

   2.1. Initial Approach: Diazo Compounds as Alkylidene Transfer Reagents ...... 16

   2.2. Various Approaches for the Synthesis of Osmium (VIII) Alkylidene Complexes ............................................................................................................. 17

       2.2.1 Results with Osmium Tetroxide.............................................................. 18

       2.2.2 Introduction of Imido Ligands ................................................................. 19

       2.2.3 Synthesis of Phosphorous Ylides ........................................................... 20

       2.2.4 Results with Monoimido Complex 8 ...................................................... 23

       2.2.5 Results with Bisimido Complexes 6 and 14 ......................................... 23

       2.2.6 Results with Trisimido Complexes 9 and 12 ........................................ 25
2.2.7 Reaction Optimization................................................................. 27
2.3. Approaches to Stabilize The Alkylidene Complex ......................... 28
  2.3.1 Modification of the Imido Ligand............................................. 28
  2.3.2 Polymerization of the Phosphorous Ylide................................. 30
  2.3.3 Intramolecular Approach....................................................... 33
2.4. Investigations into the Reactivity of the Alkylidene Complex .......... 36
  2.4.1 Reactivity with Olefins....................................................... 37
  2.4.2 Alternative Trapping Reagents.............................................. 37
  2.4.3 Reaction with Nitrones....................................................... 38
2.5. Conclusions. ............................................................................... 39
3. Chapter Three: Experimentals .......................................................... 41
  3.1. Materials and Methods: General Information................................. 41
  3.2. General Procedures. .................................................................. 42
  3.3. Procedures and Compound Characterization.................................. 43
Part II: Studies on the versatility of metallonitrene/ alkyne cascade reactions .... 58
4. Chapter Four: Introduction ................................................................ 58
  4.1. N-containing Compounds in Chemistry.......................................... 58
  4.2. The Chemistry of Metallonitrenes................................................ 59
    4.2.1 Aziridination ........................................................................ 59
    4.2.2 C-H Amination. .................................................................... 62
  4.3. Dirhodium(II) Paddlewheel Complexes. ........................................ 65
  4.4. Metallonitrene Chemistry and Metallocarbene Chemistry: a Comparison.... 69
  4.5. Development of a metallonitrene/ alkyne cascade reaction................ 70
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5.1</td>
<td>Proposed reaction.</td>
<td>70</td>
</tr>
<tr>
<td>4.5.2</td>
<td>Metallonitrene/Alkyne Cascade Reactions: Preliminary results.</td>
<td>71</td>
</tr>
<tr>
<td>4.5.3</td>
<td>Reaction Scope.</td>
<td>72</td>
</tr>
<tr>
<td>4.5.4</td>
<td>Nature of the Reactive Intermediate.</td>
<td>73</td>
</tr>
<tr>
<td>5.1</td>
<td>Chapter Five: Results and Discussion.</td>
<td>74</td>
</tr>
<tr>
<td>5.2</td>
<td>Preliminary Results.</td>
<td>74</td>
</tr>
<tr>
<td>5.2.1</td>
<td>Synthesis of the Starting Homopropargylic Sulfamate Esters.</td>
<td>75</td>
</tr>
<tr>
<td>5.2.2</td>
<td>Alternative Route to Access the Homopropargylic Esters.</td>
<td>77</td>
</tr>
<tr>
<td>5.2.3</td>
<td>Elongation of the Tether Between the Alkyne and the Nucleophile.</td>
<td>79</td>
</tr>
<tr>
<td>5.3</td>
<td>Cyclization Reactions with π-Nucleophiles.</td>
<td>81</td>
</tr>
<tr>
<td>5.3.1</td>
<td>Formation of 7,5-Ring Systems.</td>
<td>81</td>
</tr>
<tr>
<td>5.3.2</td>
<td>Formation of 7,6-Ring Systems.</td>
<td>83</td>
</tr>
<tr>
<td>5.3.3</td>
<td>Nature of the Reactive Intermediate.</td>
<td>86</td>
</tr>
<tr>
<td>5.4</td>
<td>Synthesis of Pyrrolidine Substrates.</td>
<td>87</td>
</tr>
<tr>
<td>5.5</td>
<td>Efforts to Develop an Enantioselective Version of Our Metallonitrene/Alkyne Reaction.</td>
<td>88</td>
</tr>
<tr>
<td>5.5.1</td>
<td>Enantioselectivity studies of the metallonitrene/alkyne oxonium ylide cascade with substrate 50.</td>
<td>89</td>
</tr>
<tr>
<td>5.5.2</td>
<td>Enantioselectivity studies of the metallonitrene/alkyne cyclopropanation cascade with substrate 18.</td>
<td>90</td>
</tr>
<tr>
<td>5.5.3</td>
<td>Enantioselectivity studies of the metallonitrene/alkyne cyclopropanation cascade with substrates 29 and 30.</td>
<td>91</td>
</tr>
</tbody>
</table>
5.6. Tuning the Selectivity via Catalyst Development

5.6.1 Objectives of Catalyst Development

5.6.2 Carbamates as Nitrene Precursors in the Metallonitrene/Alkyne Reaction

5.6.3 Chemoselectivity Studies With Rh(II) Tetracarboxylate Complexes

5.6.4 Chemoselectivity Studies With a Rh(II) Tetracarboxamidate Catalyst

5.6.5 Catalyst Design

5.6.6 Synthesis of Ligand 69

5.6.7 Chemoselectivity Studies With Newly Developed Catalyst 76

5.7. Conclusions

6. Chapter Six: Experimentals

6.1. Materials and Methods: General information

6.2. General Procedures

6.3. Procedures and Compound Characterization

6.4. X-Ray Crystallography

Part III: Studies towards the synthesis of (+)-Actinobolin

7. Chapter Seven: Introduction

7.1. Actinobolin and Bactobolin

7.1.1 Actinobolin: Isolation, Characterization and Biological Activity

7.1.2 Bactobolin: a Related Compound

7.2. Syntheses of (+)-actinobolin and (-)-bactobolin

7.2.1 Syntheses of (+)-actinobolin via a Diels Alder reaction

7.2.2 Weinreb’s Approach to (+)-Actinobolin and (-)-Bactobolin
7.3. Approach to (+)-Actinobolin and Our Interest in this Natural Product ...... 193

7.3.1 Retrosynthetic Analysis ................................................................. 193

7.3.2 Amino-oxygenation of an Alkene .................................................... 194

7.3.3 Regio- and Diastereoselective C-H Insertion Reaction ....................... 195

7.3.4 Retrosynthesis of α-Diazo β-Ketoester 45 ....................................... 198

8. Chapter Eight: Results and Discussion .................................................. 199

8.1. Diastereoselectivity of the Mukaiyama Aldol Reaction ............................ 199

8.1.1 Mukaiyama Aldol Reactions with Diene 51 and α-Heterosubstituted
    Aldehydes ......................................................................................... 199

8.1.2 (-)-Pestalotin 52 and epi-Pestalotin 53 as a Model System ..................... 200

8.1.3 Determination of the Diastereoselectivity in a Model System ................. 202

8.2. First Approach to (+)-Actinobolin using the Electron-Withdrawing Group
    Strategy .................................................................................................. 203

8.2.1 Determination of the diastereoselectivity with α-hydroxyaldehyde 61 .... 203

8.2.2 Moving forward with the synthesis of (+)-actinobolin ......................... 204

8.2.3 Switching protecting group for the synthesis of α-diazo β-ketoester 45 .... 206

8.2.4 Changing the order of addition of the electron-withdrawing protecting
    group ...................................................................................................... 209

8.3. Second Approach to the Synthesis of (+)-Actinobolin using the Acetonide
    Protecting Group Strategy .................................................................... 211

8.3.1 Synthesis of α-diazo β-ketoester 77 .................................................. 211

8.3.2 Cyclization reaction of α-diazo β-ketoester 77 .................................... 212

8.3.3 Synthesis and cyclization reaction of α-diazo β-ketoester 82 .................. 213
8.3.4 Alternative strategies................................................................. 216

8.4. Conclusions and Future Work......................................................... 218

9. Chapter Nine: Experimentals........................................................... 220

9.1. Materials and Methods : General information............................... 220

9.2. General Procedures....................................................................... 221

9.3. Procedures and Compound Characterization................................. 223

10. References....................................................................................... 256
Table of Schemes

Scheme 1.1: Difunctionalization of olefins using osmium-derived reagents. .................... 2
Scheme 1.2: The Sharpless dihydroxylation reaction. .................................................... 5
Scheme 1.3: Regioselective aminohydroxylation reactions. ........................................ 6
Scheme 1.4: Diamination reactions of olefins. ............................................................... 7
Scheme 1.5: Methods for the synthesis of osmium imido complexes. ............................ 9
Scheme 1.6: Muñiz and Schrock’s approaches to the synthesis of complexes 8, 6, 9, 12 and 14 ....................................................................................................................... 10
Scheme 1.7: Synthesis of complex 18 .............................................................................. 12
Scheme 1.8: Synthesis of high oxidation state complexes 20 and 25 ............................ 13
Scheme 1.9: Synthesis of complexes 19 and 22. ............................................................ 14
Scheme 1.10: Reaction profile of the reaction of ethylene with an osmium alkylidene. .... 15
Scheme 2.1: Diazo compounds as alkylidene transfer reagents. .................................... 16
Scheme 2.2: Systematic study on the influence of imido ligands. .................................... 17
Scheme 2.3: Preliminary results with bisimido and trisimido complexes. ....................... 19
Scheme 2.4: Synthesis of ylide 39. .................................................................................. 21
Scheme 2.5: Synthesis of phosphonium salt 42 ............................................................. 21
Scheme 2.6: First hint of alkylidene formation. ............................................................... 22
Scheme 2.7: Proposed mechanism for the formation of the aldehyde product. .............. 25
Scheme 2.8: Improved route for the synthesis of complex 14. ....................................... 29
Scheme 2.9: Variations on the imido ligand. ................................................................ 30
Scheme 2.10: Reaction of complex 60 with ylide 50 leads to the formation of aldehyde 61 ................................................................. 30

Scheme 2.11: Introduction of a polymer bound phosphine reagent. ......................... 31

Scheme 2.12: Synthesis of ROM polymer 66 ......................................................... 32

Scheme 2.13: Reaction of polymer 66 with complexes 6 and 14 leads to the formation of aldehyde 61 ................................................................. 32

Scheme 2.14: Intramolecular trapping of the alkylidene ...................................... 33

Scheme 2.15: Synthesis of iodide 69 .................................................................. 34

Scheme 2.16: Alternative route to form the phosphonium salt. ......................... 35

Scheme 2.17: Alternative route for the intramolecular trapping of the alkylidene. .... 35

Scheme 2.18: Synthesis of ylide 80 .................................................................. 36

Scheme 2.19: Reaction of ylide 80 with complex 14 ............................................. 36

Scheme 2.20: Reaction of the in-situ formed alkylidene 81 formed from complex 6 and ylide 50 with a variety of olefins ................................................................. 37

Scheme 2.21: Reaction of the in-situ formed alkylidene 81 formed from complex 6 and ylide 50 with alternative trapping reagents ......................................................... 38

Scheme 2.22: Reaction of alkylidene 81 with a 1,3-dipole ...................................... 38

Scheme 2.23: Proposed mechanism for the formation of alkene 83 ..................... 39

Scheme 4.1: Existing metallonitrene chemistry. .................................................. 59

Scheme 4.2: Copper catalyzed intermolecular aziridination reactions .................. 60

Scheme 4.3: Alternative nitrene sources ............................................................ 61

Scheme 4.4: Rhodium catalyzed aziridination reactions ..................................... 61

Scheme 4.5: Rhodium catalyzed intramolecular C-H amination reactions .......... 63
Scheme 4.6: Examples of intermolecular C-H amination reactions. .................................. 64
Scheme 4.7: Enantioselective C-H amination reactions. .................................................. 65
Scheme 4.8: Reactions with Rh(II) paddlewheel complexes. ......................................... 68
Scheme 4.9: Metallonitrene chemistry vs metallocarbene chemistry. ............................ 69
Scheme 4.10: Proposed metallonitrene/ alkyne metathesis reaction. ............................. 70
Scheme 4.11: Odom’s precedent. .................................................................................... 70
Scheme 4.12: Initial result of the reaction of 1 with a Rh(II) catalyst. ............................. 71
Scheme 4.13: Proposed mechanism for the formation of imine 2 .................................... 72
Scheme 4.14: Scope of the metallonitrene/ alkyne cascade reaction. ............................... 73
Scheme 5.1: Preliminary results with π-nucleophiles ..................................................... 74
Scheme 5.2: Retrosynthetic analysis for the formation of homopropargylic sulfamate esters. .................................................................................................................... 75
Scheme 5.3: Attempts to couple alkynes 10 and 14 with iodides 11, 12 and 13 .......... 76
Scheme 5.4: Competitive elimination reaction ............................................................... 76
Scheme 5.5: Strategy for an alternative route ............................................................... 77
Scheme 5.6: Synthesis of ketone 16 and aldehyde 17 ................................................... 77
Scheme 5.7: Synthesis of sulfamate esters 18 and 20 ..................................................... 78
Scheme 5.8: Reaction of aldehyde 17 with phosphonium salt 22 .................................. 79
Scheme 5.9: Synthesis of sulfamate ester 28 ............................................................... 80
Scheme 5.10: Synthesis of sulfamate esters 29, 30 and 31 ........................................... 80
Scheme 5.11: Cyclization of sulfamate ester 18 ........................................................... 81
Scheme 5.12: Attempts to cyclize sulfamate ester 20 .................................................... 82
Scheme 5.13: Cyclization of sulfamate ester 31 ........................................................... 83
Scheme 5.14: Proposed mechanism for the formation of compound 36. .................. 83
Scheme 5.15: Cyclization of sulfamate esters 29 and 30 ....................................... 86
Scheme 5.16: Nature of the reactive intermediate .................................................... 87
Scheme 5.17: Synthesis of a pyrrolidine product through SO₃ extrusion and nucleophilic
  displacement of iodide from oxathiazepane 47 .................................................. 88
Scheme 5.18: Development of a one-pot procedure for the synthesis of pyrrolidine 49
  from oxathiazepane 47 ...................................................................................... 88
Scheme 5.19: Competition between C-H amination and metallonitrene/ alkyne
  cyclization ........................................................................................................... 94
Scheme 5.20: Regioselectivity of C-H amination reactions ........................................... 95
Scheme 5.21: Regioselectivity in metallonitrene/ alkyne cascade reactions .................. 95
Scheme 5.22: Carbamates display no reactivity in the metallonitrene/ alkyne cascade
  reaction ................................................................................................................ 96
Scheme 5.23: Synthesis of sulfamate ester 56 .......................................................... 97
Scheme 5.24: Synthesis of carbamates 60 and 61 ...................................................... 97
Scheme 5.25: Cyclization of sulfamate ester 56 and carbamates 60 and 61 with Rh₂.esp₂.
  .......................................................................................................................... 98
Scheme 5.26: Diastereoselective reduction of imine 65 ................................................. 100
Scheme 5.27: Synthesis of the esp ligand ................................................................. 103
Scheme 5.28: Retrosynthetic analysis for the synthesis of 69 ..................................... 104
Scheme 5.29: First route attempted for the synthesis of novel ligand 69 ................... 105
Scheme 5.30: Alternative route for the synthesis of 72 ............................................. 105
Scheme 5.31: Synthesis of novel catalyst 76 ............................................................ 106
Scheme 7.1: Retrosynthetic analysis of Ohno’s approach to (+)-actinobolin 1. ........... 185
Scheme 7.2: Synthesis of diene 4. ................................................................. 185
Scheme 7.3: Synthesis of cyclohexene 8 via a Diels-Alder reaction. ...................... 186
Scheme 7.4: Synthesis of γ-lactam 15. ............................................................. 187
Scheme 7.5: Final steps of Ohno’s synthesis of (+)-actinobolin. ........................ 187
Scheme 7.6: Retrosynthetic analysis of Kozikowski’s approach to (+)-actinobolin. 188
Scheme 7.7: Synthesis of minor diastereomer 23 via a Diels-Alder reaction. ............. 188
Scheme 7.8: Retrosynthetic analysis of Weinreb’s approach to (+)-actinobolin. ........ 189
Scheme 7.9: Synthesis of bridged lactone 29. ................................................... 190
Scheme 7.10: Synthesis of diol 30. ................................................................... 190
Scheme 7.11: Final stages of Weinreb’s synthesis of (+)-actinobolin. .................... 191
Scheme 7.12: Weinreb’s approach to (-)-bactobolin. .......................................... 192
Scheme 7.13: Approach to (+)-actinobolin. ....................................................... 193
Scheme 7.14: Copper catalyzed olefin aminoacetoxylation reactions. ..................... 194
Scheme 7.15: Intramolecular C-H insertion reactions. ........................................... 196
Scheme 7.16: Selective 6-membered formation via intramolecular C-H insertion ....... 196
Scheme 7.17: Retrosynthesis of α-diazo β-ketoester 45. .................................... 198
Scheme 8.1: Felkin-Ahn control needed in the Mukaiyama aldol step. ..................... 199
Scheme 8.2: Precedent for the use of diene 51 in Mukaiyama aldol reactions. ........... 200
Scheme 8.3: Hagawari’s synthesis of pestalotin 52 and epi-pestalotin 53. .......... 201
Scheme 8.4: Determination of the diastereoselectivity in a model system. ................. 202
Scheme 8.5: Synthesis of β-ketoester 60. ......................................................... 204
Scheme 8.6: Synthesis of enol ether 59. ................................................................ 204
Scheme 8.7: Attempts at a selective deprotection of bis silyl ether 65......................... 206
Scheme 8.8: Attempts at synthesizing alcohol 67 via a selective deprotection............. 207
Scheme 8.9: Attempts to synthesize aldehyde 69.................................................. 207
Scheme 8.10: Synthesis of alcohol 70 and determination of the diastereoselectivity. ... 208
Scheme 8.11: Formation of lactol 73 and attempts at its opening through acetate protection. ........................................................................................................... 209
Scheme 8.12: Introduction of the acetate protecting group earlier in the synthesis. ..... 210
Scheme 8.13: Use of diene 76 in the aldol step to prevent subsequent lactol formation.210
Scheme 8.14: Formation of alcohol 78 and determination of the diastereoselectivity. 211
Scheme 8.15: Synthesis of α-diazo β-ketoester 77. .................................................. 212
Scheme 8.16: Cyclization of α-diazo β-ketoester 77 leading to the formation of ketone 81. ....................................................................................................................... 213
Scheme 8.17: Synthesis of α-diazo β-ketoester 82. .................................................. 214
Scheme 8.18: Cyclization of α-diazo β-ketoester 82 leading to the formation of cyclobutanone 84.............................................................. 214
Scheme 8.19: Variation of the reaction conditions for the cyclization of α-diazo β-ketoester 82. .............................................................. 216
Scheme 8.20: Formation of alkene 86................................................................. 217
Scheme 8.21: Protection of the C-6 alcohol as a pivaloate ester. .............................. 217
Table of Figures.

Figure 1.1: Vicinal hydroxy-alkyl motif in natural products.................................................. 2
Figure 1.2: Known osmium imido complexes........................................................................... 8
Figure 1.3: Examples of high oxidation state alkylidene complexes...................................... 11
Figure 2.1: Survey of the phosphonium salts examined. ......................................................... 20
Figure 4.1: Examples of N-containing herbicides and active pharmaceutical agents.............. 58
Figure 4.2: General structures of dirhodium(II) paddlewheel complexes............................. 66
Figure 4.3: Examples of Rh(II) tetracarboxylate complexes.................................................. 66
Figure 4.4: Examples of Rh(II) tetracarboxylate complexes.................................................. 67
Figure 4.5: Examples of Rh(II) complexes with bridged ligands........................................... 68
Figure 5.1: Extension of the substrate scope. ........................................................................... 75
Figure 5.2: Determination of the relative stereochemistry of compound 35...................... 82
Figure 5.3: Explanation for the facial selectivity of the reduction and determination of the relative stereochemistry of compound 41................................................................. 85
Figure 5.4: Structural features of Rh$_2$(esp)$_2$ and Rh$_2$(tfacam)$_4$. ................................... 102
Figure 5.5: Structure of novel catalyst 68. ............................................................................. 103
Figure 7.1: (+)-actinobolin and (-)-bactobolin...................................................................... 183
Figure 7.2: First protecting group strategy using a small electron-withdrawing group at C-5 and a sterically demanding group at C-6. ............................................................. 197
Figure 7.3: Second protecting group strategy using an acetonide protecting group.............. 197
Figure 8.1: Diagnostic proton shifts for pestalotin 52 and epi-pestalotin 53......................... 201
Figure 8.2: Transition state for the formation of cyclobutanones 81 and 84....................... 215
Table of Tables

Table 2.1: Reaction of phosphonium salt 31 with osmium tetroxide. ......................... 18
Table 2.2: Reaction of monoimido complex 8 with a variety of phosphorous ylides. ..... 23
Table 2.3: Reaction of bisimido complex 6 with a variety of phosphorous ylides......... 24
Table 2.4: Reaction of bisimido complex 14 with a variety of phosphorous ylides ....... 24
Table 2.5: Reaction of trisimido complex 9 with a variety of phosphorous ylides. ....... 25
Table 2.6: Reaction of trisimido complex 12 with a variety of phosphorous ylides. ....... 26
Table 2.7: Best conditions for the formation of an alkylidene. .................................. 27
Table 2.8: \(^1\)H and \(^{13}\)C chemical shifts of known alkylidene complexes. ............ 28
Table 5.1: Cyclization of sulfamate ester 28: optimization studies on the selectivity of the cyclization and reductions steps ................................................................. 84
Table 5.2: Enantioselectivity studies of the metallonitrene/ alkyne oxonium ylide cascade with substrate 50 ........................................................................................................ 90
Table 5.3: Enantioselectivity studies of the metallonitrene/ alkyne cyclopropanation cascade with substrate 18 ..................................................................................................... 91
Table 5.4: Enantioselectivity studies of the metallonitrene/ alkyne cyclopropanation cascade with substrate 29 ..................................................................................................... 92
Table 5.5: Enantioselectivity studies of the metallonitrene/ alkyne cyclopropanation cascade with substrate 30 ..................................................................................................... 93
Table 5.6: Optimization studies with Rh\(_2\)(TPA)\(_4\). ......................................................... 99
Table 5.7: Optimization studies with Rh\(_2\)(tfacam)\(_4\). .................................................... 101
Table 5.8: Optimization studies with novel catalyst 76. ............................................. 107
Table 8.1: Optimization studies of the aldol step. .............................................................. 205
### Abbreviations

- **pABSA**  
  *para-*acetamidobenzenesulfonyl azide
- **Ac**  
  acetyl
- **Ada**  
  adamantyl
- **AIBN**  
  azobisisobutyronitrile
- **APCI**  
  atmospheric pressure chemical ionization
- **AQN**  
  *tert*-butoxycarbonyl
- **Bn**  
  benzyl
- **br**  
  broad
- **Bz**  
  benzoyl
- **Cbz**  
  benzyloxycarbonyl
- **CDI**  
  1,1'-carbonyldiimidazole
- **d**  
  doublet
- **DBU**  
  dibenzylideneacetone
- **DCC**  
  *N*-[*N*'-dicyclohexylcarbodiimide
- **DCE**  
  1, 2-dichloroethane
- **DCM**  
  dichloromethane
- **DDQ**  
  2,3-dichloro-5,6-dicyanobenzoquinone
- **DIBAL-H**  
  diisobutylaluminum hydride
- **DHP**  
  dihydropyran
- **DHQ**  
  dihydroquinine
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHQD</td>
<td>dihydroquinidine</td>
</tr>
<tr>
<td>DMA</td>
<td>N,N-dimethylacetamide</td>
</tr>
<tr>
<td>DMAP</td>
<td>N,N-dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMPU</td>
<td>N,N-dimethyl-N,N-propylene urea</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>d.r.</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>e.e.</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>equiv.</td>
<td>equivalent</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoric triamide</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectroscopy</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>L.A.</td>
<td>Lewis acid</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>LiHMDS</td>
<td>lithium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>mmol</td>
<td>millimole</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>NMO</td>
<td><em>N</em>-methylmorpholine <em>N</em>-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per Million</td>
</tr>
<tr>
<td>PCC</td>
<td>Pyridinium Chlorochromate</td>
</tr>
<tr>
<td>PHAL</td>
<td>Phthalazine</td>
</tr>
<tr>
<td>Piv</td>
<td>Pivaloate</td>
</tr>
<tr>
<td>PPTS</td>
<td>Pyridinium <em>para</em>-Toluenesulfonate</td>
</tr>
<tr>
<td>q</td>
<td>Quartet</td>
</tr>
<tr>
<td>qn</td>
<td>Quintet</td>
</tr>
<tr>
<td>RT</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>SES</td>
<td>Trimethylsilylyethylsulfonyl</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>TBS</td>
<td><em>tert</em>-Butyldimethylsilyl</td>
</tr>
<tr>
<td>TBDPS</td>
<td><em>tert</em>-Butyldiphenylsilyl</td>
</tr>
<tr>
<td>TES</td>
<td>Triethylysilyl</td>
</tr>
<tr>
<td>tf</td>
<td>Trifluoromethanesulfonyle</td>
</tr>
<tr>
<td>tfa</td>
<td>Trifluoroacetate</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>tfacam</td>
<td>Trifluoroamidate</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>Tetrahydropyran</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>Acronym</td>
<td>Name</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------</td>
</tr>
<tr>
<td>TPA</td>
<td>triphenylacetate</td>
</tr>
<tr>
<td>Ts</td>
<td><em>para</em>-toluenesulfonyl</td>
</tr>
</tbody>
</table>
Part I: Synthesis and Reactivity of Osmium (VIII)

Alkylidene Complexes.


1.1. Difunctionalization of Olefins in Total Synthesis.

The field of natural product synthesis has experienced spectacular advances in the last few decades.\(^1\) Installing multiple functionalities in a single chemical step has allowed for the efficient construction of molecular complexity, but identifying such disconnections has remained a challenge.\(^2\) For some motifs, for example a \(\beta\)-hydroxyketone (as seen in Octalactin B and Mycalolide B, Figure 1.1), there are obvious disconnections - in this case, an aldol reaction.\(^3\) For other motifs however, such a general disconnection is not as straightforward. Vicinal hydroxyl-alkyl moieties are present in a variety of molecules, as illustrated in Figure 1.1. Being able to introduce these two functionalities, by oxidation of an alkene, for example, would represent an efficient way of building such a motif.
Indeed, oxidative reaction of alkenes is a powerful pathway to vicinal difunctionalization and has been extensively developed to introduce various motifs such as vicinal diols or diamines. Such methods usually employ metals such as Pd, Ru, Mn. Osmium-derived reagents have also been used for the conversion of olefins into vicinal diols (Scheme 1.1, eq. 1) or amino alcohols (eq. 2) as well as diamino-compounds (eq. 3).

Scheme 1.1: Difunctionalization of olefins using osmium-derived reagents.
1.2. A Proposed Carbohydroxylation Reaction.

Inspired by all three difunctionalization reactions using osmium reagents, we envisioned that the same type of [3+2] cycloaddition might take place between a species such as 1 and an olefin to generate, after reductive cleavage, an unprecedented carbohydroxylation product 2 (eq. 4). In order for this transformation to occur, it must proceed through an intermediate such as osmium (VIII) alkylidene 1. At the onset of the project, this proposed alkylidene was, to the best of our knowledge, unprecedented. If synthesized, it would represent the highest oxidation state late transition metal alkylidene complex known.

Thus before embarking on such a project, a thorough review of osmium promoted olefin difunctionalization reactions and of high oxidation state alkylidene complexes was warranted.

1.3. Difunctionalization of Olefins using Osmium Reagents.

1.3.1 Dihydroxylation of Olefins.

The osmium-mediated dihydroxylation reaction of olefins, also known as the Sharpless dihydroxylation reaction, is a well-known reaction and has been extensively studied.\(^5\) It was first introduced using stoichiometric osmium tetroxide.\(^6\) The discovery that the addition of pyridine increased the rate of the reaction (i.e. ligand acceleration
effect) as well as the fact that NMO could be used as a stoichiometric osmium reoxidant led to the development of a catalytic and enantioselective version of this reaction.\textsuperscript{7} The mechanism for this reaction proceeds through a concerted \([3+2]\) pathway leading to the formation of glycolate product 3, which is then funneled through the catalytic cycle (Scheme 1.2).\textsuperscript{8}

The enantiomeric excess of diol products formed under catalytic conditions was initially observed to be lower than those obtained under stoichiometric conditions. These observations were explained by the presence of a secondary catalytic cycle in which the olefin adds to glycolate 4, as shown in scheme 1.2, in the absence of a chiral ligand.\textsuperscript{8b} This problem was solved by performing the reaction under biphasic conditions with catalytic quantities of osmium (VI) and potassium hexacyanoferrate as a reoxidant.\textsuperscript{9} Under these conditions, the osmylation takes place in the organic phase leading to 3, which then undergoes hydrolysis, releasing the diol and the ligand in the organic phase and the osmium (VI) in the aqueous phase, before it can be reoxidized to 5. This reaction has proven extremely versatile and leads to the formation of \textit{cis}-vicinal diols with a preference for electron-rich olefins (eq. 5).
1.3.2 Aminohydroxylation of Olefins.

The related aminohydroxylation reaction is also well established, though the asymmetric version is more recent.\textsuperscript{5c} It also proceeds \textit{via} a similar mechanism under biphasic conditions with catalytic osmium (VI) salts which form imido osmium (VIII) complexes \textit{in situ}.\textsuperscript{10} Chiral cinchona alkaloid ligands and nitrene precursors are also necessary for the transformation, the latter serving as both a nitrogen source and a reoxidant in the reaction.

Issues of chemo- (dihydroxylation \textit{vs} aminohydroxylation) and regioselectivity come to mind when examining the aminohydroxylation reaction. In terms of chemoselectivity, it has been shown that the addition of a tertiary amine increases the
chemoselectivity in favor of the aminohydroxylation reaction.\textsuperscript{11} It is believed that this is due to the fact that the amine changes the overall arrangement of the ligands around the metal allowing for easy nitrogen transfer (\textit{vide infra}). On the other hand, the low regioselectivity of the addition to unsymmetrical olefins can be a drawback for this reaction. Several factors have been shown to influence the regioselectivity: alkene substitution, ligand-substrate interactions and to some extent alkene polarization. In a number of cases, though, good regioselectivity can be obtained. Indeed, in general the nitrogen prefers to add at the less substituted end of the alkene due to the greater steric demand of the substituted imidoosmium moiety (\textit{Os=NR}) relative to the unsubstituted oxo-counterpart (\textit{Os=O}). In addition, it has been shown that the selectivity of the addition can be reversed by changing the chiral ligand used in the reaction, as shown in Scheme 1.3.\textsuperscript{12}

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme13.png}
\end{center}

\textbf{Scheme 1.3:} Regioselective aminohydroxylation reactions.

This reaction has also proven to be fairly versatile allowing the use of a variety of nitrene precursors and has a preference for terminal or \textit{E}-1,2-substituted olefins.
1.3.3 Diamination of Olefins.

In contrast to the dihydroxylation and the aminohydroxylation reactions, diamination of olefins using osmium reagents remains relatively underdeveloped.\textsuperscript{13} It was first reported by Sharpless in the late 1970’s and the main difference between this transformation and the previous two is that this reaction requires pre-formed bis or trisimido osmium complexes (such as 6, Scheme 1.4).\textsuperscript{13a} These reagents react with an olefin to form a stable osmamidazolidine complex (such as 7) that cannot be cleaved by \textit{in situ} hydrolysis, thus requiring a stoichiometric amount of osmium.\textsuperscript{14} In addition, the imido ligands increase the electron density at the metal center, preventing the coordination of a chiral ligand. Therefore other techniques need to be developed to make this reaction asymmetric and this has hampered its development.

Scheme 1.4: Diamination reactions of olefins.

Recent work by Muñiz and co-workers has shown that \textit{E}-substituted, electron-poor olefins can efficiently undergo diamination reactions and that these reactions tolerate functional groups such as free ketones and amines (unlike the parent
dihydroxylation and aminohydroxylation reactions) (Scheme 1.4). They also employed chiral auxiliaries, such as (-)-8-phenylmenthol, on the olefin with some success to impart selectivity (up to 95:5 diastereoselectivity, eq.7). However, this transformation continues to require stoichiometric amounts of osmium reagents, which limits its applicability.

1.4. Imido Osmium Complexes.

As mentioned previously, a major aspect of the diamination reaction is the necessity to pre-synthesize bis and trisimido osmium (VIII) complexes. The first imido osmium complexes were isolated in the late 1950s. Since then, there have been only a limited number of osmium imido complexes reported (Figure 1.2).

![Figure 1.2: Known osmium imido complexes.](image)

Traditionally, the monoimido complex can be synthesized directly from osmium tetroxide and the corresponding amine in organic or aqueous media (eq. 8 and Scheme 1.5).
Bis and trisimido complexes are synthesized either from the preformed monoimido complex or directly by the reaction of OsO₄ with phosphorous ylides (Scheme 1.5).¹³a, ¹⁵-¹⁶

Scheme 1.5: Methods for the synthesis of osmium imido complexes.

Muñiz and Schrock have both recently developed more efficient routes.¹⁷ The former has developed a route to directly synthesize the mono, bis and trisimido osmium complexes 8, 6 and 9 by reaction of osmium tetroxide with TMS-\(N\)-tert-butylamine (Scheme 6, eq. 9).¹⁷a On the other hand, Schrock reacted osmium tetroxide with (2,6-di-iso-propyl)phenylisocyanate to form an osmium (VI) complex 16 which was then either oxidized to trisimido osmium complex 12 or reduced to bisimido bisphosphine osmium complex 17. Complex 17 can then be re-oxidized to form bisoxo bisimido osmium complex 14 (Scheme 1.6).¹⁷b
Scheme 1.6: Muñiz and Schrock’s approaches to the synthesis of complexes 8, 6, 9, 12 and 14.

All of these crystalline compounds are air and moisture stable when kept at 0°C in the dark. They are also stable to column chromatography. However, a significant drawback for the synthesis of these complexes is the fact that, for stability reasons, it is necessary to have tertiary substituents on the nitrogen or, in the case of aniline derived ligands, a 2,6 substitution pattern. Otherwise, the substituents undergo hydride transfer causing osmium reduction and degradation of the complex.

As mentioned previously, the introduction of imido ligands around the metal increases its electron density because of the lone pair donation from each nitrogen of the imido ligand. This gives these complexes unique structural features. Monoimido complex 8 displays a nearly tetrahedral coordination sphere around the metal and an almost linear imido ligand suggesting that it is a 6 electron donor leading to an osmium center with a formal 18 electron count. However in the presence of a tertiary amine, the...
complex becomes trigonal bipyramidal with the amine *trans* to the imido ligand. The ligand is no longer linear but bent and functions now as a 4 electron donor.

In the case of bisimido complex 8, the two imido ligands are not equivalent. While one is almost linear, the other ligand is bound to the metal center with an angle of 155° (Os-N-C), meaning that the two ligands are 6 and 4 electron donors respectively making the overall electron count of the osmium 18 once again.

### 1.5. High Oxidation State Alkylidene Complexes.

While the first high oxidation state transition metal alkylidene complex (18, Figure 1.3) was synthesized in 1974, this type of complex has grown in popularity only since the 1980s when it was discovered that they can serve as efficient catalysts for olefin metathesis.\(^20\) A variety of high oxidation state alkylidene complexes has been synthesized and it is important to note that they all contain early and mid transition metals (Figure 1.3).\(^21\)

![Figure 1.3: Examples of high oxidation state alkylidene complexes.](image)
Indeed even though tantalum complex 18 is inactive towards metathesis, tungsten and molybdenum complexes are active catalysts and have become widely developed, the latter being more functional group tolerant.\textsuperscript{20a} One of the most famous examples is Schrock’s molybdenum alkylidene 20. High oxidation state rhenium (VII) alkylidenes (such as 21) have also been synthesized as well as ruthenium alkylidenes (such as ruthenium (IV) complex 22) though these complexes are not in a high oxidation state.\textsuperscript{21-22}

Complex 18 was synthesized by intramolecular $\alpha$-hydrogen abstraction (Scheme 1.7). Since this initial discovery, several routes for the synthesis of these complexes have been developed, based on the structural features necessary to their stability. Indeed, all of these high oxidation state complexes share some common features. All have electron demanding alkoxide ligands to stabilize the complex. They also all contain sterically bulky imido ligands to avoid bimolecular decomposition and thus serving as “protecting groups” for the formation of the complex.\textsuperscript{20a}

![Scheme 1.7: Synthesis of complex 18.](image)

The first approach developed relied on alkylidyne intermediate 23 and generated the alkylidene moiety through proton transfer from the amido nitrogen to the alkylidyne carbon (Scheme 1.8, eq. 11).\textsuperscript{23a} A more efficient route was developed through the generation of intermediate 24 and intramolecular $\alpha$-hydrogen abstraction to generate the alkylidene moiety (eq. 12).\textsuperscript{23b}
Scheme 1.8: Synthesis of high oxidation state complexes 20 and 25.

It is also noteworthy that Grubbs has developed a synthesis via alkylidene transfer from phosphorous ylide 26 to form imido complex 19 (Scheme 1.9, eq. 13). This reaction is sensitive to steric congestion around the metal and the nature of the ylide. The Grubbs group has also shown that diazo compounds can serve as alkylidene transfer reagents to synthesize ruthenium alkylidene complexes (eq. 14). Finally, it is important to note that these complexes undergo decomposition in various ways including via reduction of the metal and bimolecular decomposition.
1.6. Theoretical studies.

Although a trisoxo osmium (VIII) alkylidene has not yet been synthesized, the Frenking and Holthausen group has conducted some theoretical studies on this compound.26 As shown in Scheme 1.10, the [3+2] addition of ethylene across CH₂=Os=O is predicted to be both kinetically and thermodynamically favored over the addition of ethylene across O=Os=O. It should also be noted that the authors predicted that the alkylidene complex could also isomerize to a more stable osmaoxirane compound 27 albeit with a significant energy barrier (36.3 kcal/mol).

Thus, these studies demonstrate that not only should our proposed reaction be possible but it should be favored over any other type of reaction once the osmium (VIII) alkylidene is formed.
Scheme 1.10: Reaction profile of the reaction of ethylene with an osmium alkylidene.

The following chapter will describe our studies toward the synthesis of osmium (VIII) oxo-alkylidene complexes and our investigation of their reactivity.
2. Chapter Two: Results and Discussion

2.1. Initial Approach: Diazo Compounds as Alkylidene Transfer Reagents.

Our initial approach to the synthesis of a high oxidation state osmium alkylidene complex was to use diazo compounds as alkylidene transfer reagents, mimicking Grubbs’ approach to the synthesis of ruthenium alkylidene complexes. Dr Hussaini investigated the reaction of various diazo compounds with several osmium (VI) sources but was only able to isolate alkene 28 resulting from the dimerization of the diazo 29 (Scheme 2.1). However, high resolution mass spectrometry of the reaction mixture suggested that the desired alkylidene complex 30 was present in the reaction.

![Scheme 2.1: Diazo compounds as alkylidene transfer reagents.](image)

In spite of this exciting preliminary result, Dr Hussaini was never able to isolate any products other than compound 28 from the reaction mixture. We therefore turned our attention to another approach for the synthesis of a high oxidation state osmium alkylidene complex. Based on previously mentioned reports that phosphorous ylides
can be used as alkylidene transfer reagents (Scheme 1.9, eq. 13) and the fact that imido ligands can be efficiently introduced on the osmium metal center through an aza-Wittig reaction (vide supra), we decided to investigate the use of phosphorous ylides to generate an osmium (VIII) alkylidene complex.


Keeping in mind the structural features that have been found to be essential for the stability and reactivity of known high oxidation state alkylidene complexes (i.e. electron withdrawing alkoxide ligands and sterically encumbered imido ligands), we hypothesized that oxo ligands could mimic the electron-withdrawing perfluoro alkoxide ligands.\textsuperscript{20a} We therefore decided to do a systematic study on the influence of the number of imido ligands around the metal (Scheme 2.2).

Scheme 2.2: Systematic study on the influence of imido ligands.
2.2.1 Results with Osmium Tetroxide.

We began our investigation by looking at the reaction of osmium tetroxide with a small phosphonium salt 31. *In situ* deprotonation was followed by addition of an olefin to the mixture. Several olefins, solvents and conditions were investigated, as shown in table 2.1.

$$
\text{R} = \text{H, OMe, Br, \text{Me}}_2\text{C} \quad \text{Ph} = \text{Ph, } \text{Bn}
$$

![Diagram](image-url)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Olefin</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>0</td>
<td>[CH=CH][O][Bn]</td>
<td>Olefin recovered</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>0</td>
<td>[CH=CH][O][Bn]</td>
<td>Olefin recovered</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>0</td>
<td>Styrene</td>
<td>Olefin recovered</td>
</tr>
<tr>
<td>4</td>
<td>Pyridine</td>
<td>-78</td>
<td>Styrene</td>
<td>Phosphonium salt recovered</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>-78</td>
<td>Styrene</td>
<td>Dihydroxylation product isolated</td>
</tr>
<tr>
<td>6</td>
<td>Toluene</td>
<td>-78</td>
<td>Decene</td>
<td>Olefin recovered</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>-78</td>
<td>Styrene</td>
<td>Unidentified product</td>
</tr>
</tbody>
</table>

**Table 2.1:** Reaction of phosphonium salt 31 with osmium tetroxide.

It soon appeared that osmium tetroxide was too reactive. Even at low temperature the mixture of osmium and ylide immediately turned black and the only compound isolated after column chromatography was unreacted olefin. It should be noted however, that, in solvents where the phosphonium salt was not soluble (entry 5), a dihydroxylation product was isolated. This result led us to conclude that a reaction between the ylide and osmium tetroxide did indeed take place but was probably too quick for any intermediate to react with an olefin before it decomposed. Thus, it seemed that osmium tetroxide was too electrophilic and that, as predicted, imido ligands were potentially necessary to
stabilize any intermediate formed. Additionally, we decided to broaden the scope of the phosphorous ylides used, keeping in mind that a more sterically hindered and more electron rich ylide might help stabilize an alkylidene intermediate.

2.2.2 Introduction of Imido Ligands.

We began our investigation into the influence of imido ligands with complexes 6 and 9, easily accessible from osmium tetroxide (vide supra). Reaction of these complexes with a mixture of phosphonium salt 32 and base followed by addition of methyl trans cinnamate led to the isolation of products 33, 34 and 35 (Scheme 2.3). These osmamidazolidines correspond to a diamination reaction.27

Scheme 2.3: Preliminary results with bisimido and trisimido complexes.

Therefore, to avoid any competing reaction, we decided to stop adding an olefin to the mixture and concentrate on synthesizing and isolating the desired alkylidene complex. In addition, it also appeared that these reactions remained very rapid and realizing that an alkylidene intermediate might not be stable to column chromatography, we also decided to follow these reactions by $^1$H NMR.
With this new approach in mind, we decided to expand the scope of the osmium complexes that we were using. Thus, we synthesized complexes 14 and 12 which are sterically and electronically different from the complexes previously used (Figure 1.2).\textsuperscript{17b} We were also interested in looking at the influence of the phosphonium salts.

### 2.2.3 Synthesis of Phosphorous Ylides.

We decided to explore a wide range of phosphonium salts as shown in Figure 2.1 varying both the size and the electronic. Inspired by tungsten alkylidene complexes (such as complex 19) in which the oxygen of an ortho methoxy group acts as an extra ligand to stabilize the complex, we choose to add 41 to our survey of salts. In addition, we decided to also include 2,4,6-trisubstituted benzylic phosphonium salt 42. We hypothesized that increasing the steric bulk might improve the stability of any alkylidene intermediate formed.

![Survey of the phosphonium salts examined.](image)

**Figure 2.1:** Survey of the phosphonium salts examined.

Compound 39 was synthesized by reaction of hydrazone with mercury (II) oxide as shown in Scheme 2.4.\textsuperscript{28}
Scheme 2.4: Synthesis of ylide 39.

Compound 42 was not a known phosphonium salt, however the synthesis of the alcohol precursor 44 had already been developed in our laboratory (Scheme 2.5). Esterification of 2,4,6 tri-iso-propylbenzoic acid gave compound 45 that was reduced to alcohol 44. This was followed by bromination and reaction of 46 with PPh₃ to give salt 42.

Scheme 2.5: Synthesis of phosphonium salt 42.

With the phosphonium salts in hand, we began to investigate their reactivity towards osmium imido complexes by forming the ylide in situ followed by addition of the complex. We examined several bases (NaO'Bu, nBuLi, LiHMDS) as well as different solvents (C₆D₆, d₈-THF, CD₂Cl₂) and temperatures (-78 °C to 60 °C). It soon appeared that the phosphorous ylide formation was actually slower than anticipated. With a longer
reaction time (overnight) for the ylide formation, we were delighted to observe the formation of a peak at 15.4 ppm by $^1$H NMR when phosphonium salt 42 was reacted with complex 14 in CD$_2$Cl$_2$ (Scheme 2.6).

Scheme 2.6: First hint of alkyldene formation.

Considering that known alkyldene complexes have characteristically downfield shifts for both the alkyldene proton and carbon, this result hinted at alkyldene formation. However, the reactions remained complex and difficult to follow by NMR. We realized that in order to simplify the NMR spectrum and have a better understanding of what was happening, we should isolate and purify the phosphorous ylides rather than generate them in situ.

This proved to be more difficult than anticipated. The first procedure attempted involved refluxing the salt in THF with an excess of base (NaH). Even though there seemed to be a reaction occurring since the reaction mixtures turned bright orange, we were not able to isolate the ylide. The product appeared to be reprotonating very quickly, most likely due to heavy atmospheric humidity. In order to avoid this, we switched solvent (toluene) and minimized contact with air by doing the reactions in sealed vials and doing the workup, evaporation of solvent and recrystalization in a glovebox. Ultimately, the optimal conditions were found to be with NaNH$_2$ in refluxing toluene.
With this method in hand, we were able to purify all of the phosphorous ylides and follow the reactions more clearly by NMR. This proved to be essential and enabled us to do a systematic study on the influence of both the imido ligands and the ylides.

2.2.4 Results with Monoimido Complex 8.

With this complex, all the reactions turned immediately black and the only product isolated was the aldehyde of the corresponding ylide as shown in Table 2.2.

![Reaction diagram](image)

**Table 2.2**: Reaction of monoimido complex 8 with a variety of phosphorous ylides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ylide</th>
<th>Solvent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCHPPh₂, 47</td>
<td>C₆D₆</td>
<td>PhCHO</td>
</tr>
<tr>
<td>2</td>
<td>o-OMePhCHPPh₂, 48</td>
<td>C₆D₆</td>
<td>o-OMePhCHO</td>
</tr>
<tr>
<td>3</td>
<td>(Ph)₂CPPPh₂, 39</td>
<td>CD₂Cl₂, pyridine</td>
<td>(Ph)₂CO</td>
</tr>
<tr>
<td>4</td>
<td>BuCHPPh₂, 49</td>
<td>C₆D₆</td>
<td>BuCHO</td>
</tr>
<tr>
<td>5</td>
<td>2,4,6-iPr₃PhCHPPh₂, 50</td>
<td>C₆D₆</td>
<td>2,4,6-iPr₃PhCHO</td>
</tr>
<tr>
<td>6</td>
<td>2,6-F₂PhCHPPh₂, 51</td>
<td>C₆D₆</td>
<td>2,6-F₂PhCHO</td>
</tr>
</tbody>
</table>

2.2.5 Results with Bisimido Complexes 6 and 14.

Reactions with complexes 6 and 14 (Tables 2.3 and 2.4) gave two major hits (entries 5 and 6 in Table 2.3 and entries 5 and 6 in Table 2.4) for which there was a clear indication by formation of a peak at 14.20 ppm (entry 5, Table 2.3) on the ¹H NMR spectrum that the alkylidene species was formed (and at 15.25 for entry 6, Table 2.3 and 14.53 and 15.39 ppm for entries 5 and 6, Table 2.4). However, it then slowly decomposed to the aldehyde corresponding to the ylide. This decomposition product can be explained
by isomerization of the alkylidene as shown in Scheme 2.7. This isomerization was predicted in the theoretical studies on the addition of ethylene to an osmium alkylide \((\text{vide supra})\) (Scheme 1.10).

![Reaction Scheme](image)

**Table 2.3:** Reaction of bisimido complex 6 with a variety of phosphorous ylides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ylide</th>
<th>Solvent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃PPh₂, 52</td>
<td>CD₂Cl₂</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>PhCH₂PPh₂, 47</td>
<td>C₆D₆</td>
<td>complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>o-OMePhCH₂PPh₂, 48</td>
<td>C₆D₆</td>
<td>aldehyde</td>
</tr>
<tr>
<td>4</td>
<td>(Ph)₂CPPh₂, 39</td>
<td>C₆D₆</td>
<td>complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>3BuCH₂PPh₂, 49</td>
<td>C₆D₆</td>
<td>carbene transforming into aldehyde 1:0.9*</td>
</tr>
<tr>
<td>6</td>
<td>2,4,6-Pr₂PhCH₂PPh₂, 50</td>
<td>C₆D₆</td>
<td>carbene transforming into aldehyde 1:1.6*</td>
</tr>
<tr>
<td>7</td>
<td>2,6-F₂PhCH₂PPh₂, 51</td>
<td>C₆D₆</td>
<td>complex mixture</td>
</tr>
</tbody>
</table>

* initial ratio carbene to aldehyde.

![Reaction Scheme](image)

**Table 2.4:** Reaction of bisimido complex 14 with a variety of phosphorous ylides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ylide</th>
<th>Solvent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃PPh₂, 52</td>
<td>CD₂Cl₂</td>
<td>aldehyde</td>
</tr>
<tr>
<td>2</td>
<td>PhCH₂PPh₂, 47</td>
<td>C₆D₆</td>
<td>aldehyde</td>
</tr>
<tr>
<td>3</td>
<td>o-OMePhCH₂PPh₂, 48</td>
<td>C₆D₆</td>
<td>aldehyde</td>
</tr>
<tr>
<td>4</td>
<td>(Ph)₂CPPh₂, 39</td>
<td>CD₂Cl₂</td>
<td>complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>3BuCH₂PPh₂, 49</td>
<td>C₆D₆</td>
<td>carbene transforming into aldehyde 1:0.5*</td>
</tr>
<tr>
<td>6</td>
<td>2,4,6-Pr₂PhCH₂PPh₂, 50</td>
<td>C₆D₆</td>
<td>carbene transforming into aldehyde 1:1*</td>
</tr>
<tr>
<td>7</td>
<td>2,6-F₂PhCH₂PPh₂, 51</td>
<td>C₆D₆</td>
<td>complex mixture</td>
</tr>
<tr>
<td>8</td>
<td>3PrCH₂PPh₂, 53</td>
<td>CD₂Cl₂</td>
<td>aldehyde</td>
</tr>
</tbody>
</table>

* initial ratio carbene to aldehyde.
Scheme 2.7: Proposed mechanism for the formation of the aldehyde product.

2.2.6 Results with Trisimido Complexes 9 and 12.

Finally, when trisimido osmium complexes 9 and 12 (Tables 2.5 and 2.6) were subjected to a variety of phosphorous ylides, we either observed the formation of the imine corresponding to the ylide (formed through the same mechanism as for the formation of the aldehyde) or the ylide remained unreacted.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ylide</th>
<th>Solvent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCHPPh3, 47</td>
<td>C6D6</td>
<td>slow reaction</td>
</tr>
<tr>
<td>2</td>
<td>α-OCH3PhCHPPh3, 48</td>
<td>C6D6</td>
<td>slow reaction</td>
</tr>
<tr>
<td>3</td>
<td>t-BuC(PPh3), 49</td>
<td>C6D6</td>
<td>slow reaction</td>
</tr>
<tr>
<td>4</td>
<td>2,4,6-t-Pr3PhCHPPh3, 50</td>
<td>C6D6</td>
<td>slow reaction</td>
</tr>
<tr>
<td>5</td>
<td>2,6-F2PhCHPPh3, 51</td>
<td>C6D6</td>
<td>slow reaction</td>
</tr>
</tbody>
</table>

Table 2.5: Reaction of trisimido complex 9 with a variety of phosphorous ylides.
Examining tables 2.2 to 2.6, several trends were observed. It seems that the formation of the alkylidene complex was influenced by both steric and electronic factors. With respect to the osmium complexes, it is clear that the monoimido complex 8 (Table 2.2) was too reactive and when reacted with an ylide, there was immediate decomposition to the aldehyde. On the contrary, trisimido complexes 9 and 12 (Tables 2.5 and 2.6) were relatively unreactive. It was the bisoxo-bisimido complexes 6 and 14 (Tables 2.3 and 2.4) that had the right balance.

Regarding the various ylides, it seems that relatively bulky, electron rich ylides, such as 49 and 50, react with both type of bis oxo osmium complexes. However, the intermediate was to be more stable when the bulkier ylide 50 reacted with the smaller osmium complex 6 or when smaller ylide 49 reacted with bulkier complex 14. Electron poor ylide 51 gave complex mixtures with both osmium complexes whereas ylides 52 and 53 (which are smaller than 49) and also have alpha hydrogens immediately gave the aldehyde decomposition product. As for bulky ylide 39 it gave complex mixtures that were extremely hard to analyze.

Table 2.6: Reaction of trisimido complex 12 with a variety of phosphorous ylides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ylide</th>
<th>Solvent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃PPh₃, 52</td>
<td>CD₂Cl₂</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>PhCHPPh₃, 47</td>
<td>C₆D₆</td>
<td>imine</td>
</tr>
<tr>
<td>3</td>
<td>o-OMePhCHPPh₃, 48</td>
<td>C₆D₆</td>
<td>slow reaction to Os(VI)</td>
</tr>
<tr>
<td>4</td>
<td>tBuCHPPh₃, 49</td>
<td>C₆D₆</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>2,4,6-iPr₃PhCHPPh₃, 50</td>
<td>C₆D₆</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>2,6-F₂PhCHPPh₃, 51</td>
<td>C₆D₆</td>
<td>imine</td>
</tr>
<tr>
<td>7</td>
<td>tPrCHPPh₃, 53</td>
<td>CD₂Cl₂</td>
<td>imine</td>
</tr>
</tbody>
</table>
Therefore, we decided to concentrate on the two ylides that gave the best results and tried to stabilize the alkylidene intermediate by changing the reaction conditions in order to isolate it and fully characterize it.

2.2.7 Reaction Optimization

A variety of solvents and temperatures were tested. The best results were obtained in dichloromethane in which the alkylidene was initially the major product and could be seen by NMR for more than six hours as shown (Table 2.7).

![Chemical structure](image)

**Table 2.7**: Best conditions for the formation of an alkylidene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R’</th>
<th>δ H₆ (ppm)</th>
<th>alkyldene:aldehyde[^a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ᵉBu</td>
<td>2,4,6-iPr₃Ph</td>
<td>15.25</td>
<td>1:1.3</td>
</tr>
<tr>
<td>2</td>
<td>ᵉBu</td>
<td>ᵉBu</td>
<td>14.20</td>
<td>2.3:1</td>
</tr>
<tr>
<td>3</td>
<td>2,6-iPr₂Ph</td>
<td>2,4,6-iPr₃Ph</td>
<td>15.39</td>
<td>1.4:1</td>
</tr>
<tr>
<td>4</td>
<td>2,6-iPr₂Ph</td>
<td>ᵉBu</td>
<td>14.53 (54)</td>
<td>4.0:1</td>
</tr>
</tbody>
</table>

[^a]: Initial ratio, measured by ¹H NMR.

We were nonetheless able to further characterize alkylidene complex 54. By conducting the reaction at -50 °C, we could stabilize the alkylidene and observe a ¹³C NMR signal at 286.1 ppm, consistent with our assignment as an osmium alkylidene carbon signal and in agreement with the ¹³C NMR signal of known alkylidene complexes (Table 2.8).[^23b, 24]
Table 2.8: $^1$H and $^{13}$C chemical shifts of known alkylidene complexes.

<table>
<thead>
<tr>
<th>Complex</th>
<th>$^1$H (ppm)</th>
<th>$^{13}$C (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19, $R'$=Me</td>
<td>10.81</td>
<td>240.2</td>
</tr>
<tr>
<td>20, $R$=Me, $R'$=CMe$_2$(CF$_3$)$_2$</td>
<td>12.06</td>
<td>288.2</td>
</tr>
</tbody>
</table>

The alkylidene was also clearly identified by HRMS with a signal (-ESI) at 611.3068 corresponding to [M-OH]$^-$ . Finally IR studies revealed the loss of strong absorption signals at 874 and 885 cm$^{-1}$ (symmetric and anti-symmetric Os=O in an MO$_2$ system) and a new weak signal at 991 cm$^{-1}$ (Os=O). This shift is consistent with the replacement of a weak π–donor oxo ligand with a strong π-acceptor alkylidene ligand.

2.3. Approaches to Stabilize The Alkylidene Complex.

Having failed to stabilize the alkylidene complex by optimizing the reaction conditions, we became interested in looking at other ways to either isolate or observe more clearly the alkylidene complex. We hypothesized that this might be possible by modifying its structural features. We envisioned several approaches to achieve this and the first modification we examined was changing the imido ligands around the metal.

2.3.1 Modification of the Imido Ligand.

In an effort to develop a more efficient route for the synthesis of complex 14 (vide supra, eq. 10), we were inspired by Sharpless’ early methods to synthesize osmium imido complexes using phosphorous ylides. Thus based on known procedures,
diazotization of 2,6-diisopropylaniline with NaNO₂ and subsequent displacement with NaN₃ led to the formation of azide 55, which was then reacted with PPh₃ to form iminophosphorane 56. Reaction of this compound with osmium tetroxide gave us the desired complex 14 (Scheme 2.8).

Scheme 2.8: Improved route for the synthesis of complex 14.

With this method in hand, we synthesized several other iminophosphoranes, including 57, 58 and 59 varying the size and electronics of the imido ligand (Scheme 2.9). However, other than compound 57, which is very similar to the original iminophosphorane 56, the reactions of compounds 58 and 59 with osmium tetroxide did not yield the expected compounds. It is possible that these compounds are not stable to silica.
Reaction of complex 60 with phosphorous ylide 50 did not improve the stability of the alkylidene and we observed immediate formation of aldehyde 61.

Scheme 2.10: Reaction of complex 60 with ylide 50 leads to the formation of aldehyde 61.

2.3.2 Polymerization of the Phosphorous Ylide.

At this stage, we decided to concentrate on attempting to see more clearly the alkylidene complex by NMR. We hypothesized that by having an ylide attached to a solid support, a simple filtration of the reaction mixture would eliminate all phosphorous
residues and thus make the $^1$H NMR easier to analyse. Attempts at reacting compound 46 and neopentyl iodide with polymer-bound PPh$_3$ were unsuccessful with the halides remaining unreactive. However, Barrett and co-workers have developed a ROMPgel-supported triphenyl phosphine 62 (Scheme 2.11). Compound 62 has been successfully applied to a variety of transformations with an easy work-up.

**Scheme 2.11:** Introduction of a polymer bound phosphine reagent.

Compound 62 was synthesized according to literature procedures by coupling 4-bromoiodobenzene with norbornadiene followed by reaction of the resulting bromide 63 with chlorodiphenylphosphine (Scheme 2.12). Compound 62 was submitted to standard reaction conditions with bromide 46 and neopentyl iodide to form phosphonium salts 64 and 65 respectively. Reaction of 64 with Grubbs’ second generation catalyst yielded the desired ROM polymer 66, which was characterized by $^1$H NMR and compared to similar known compounds. However reaction with 65 did not give the expected polymer product 67.
**Scheme 2.12:** Synthesis of ROM polymer 66.

Polymer 66 was then submitted to the standard ylide formation conditions. The ylide was not isolated but was instead directly reacted with osmium complexes 6 and 14 (Scheme 2.13). The polymer residue was then crashed out with ether and eliminated by filtration. Unfortunately, $^1$H NMR of the residual reaction mixture only showed formation of aldehyde 61 with no trace of the intermediate alkylidene.

**Scheme 2.13:** Reaction of polymer 66 with complexes 6 and 14 leads to the formation of aldehyde 61.
2.3.3 Intramolecular Approach.

Since we had not been able to either stabilize the alkylidene complex enough to avoid its decomposition to the aldehyde or have a clearer NMR spectrum, we turned our attention to another approach. Taking all of our results into consideration, it appeared that a neopentyl-like group alpha to the alkylidene is necessary for its formation. In addition, we hypothesized that trapping the alkylidene in situ in an intramolecular reaction with an olefin would lead to the formation of a stable fused ring system (Scheme 2.14). Thus, we wanted to avoid isolating the alkylidene and concentrate instead on isolating a more stable product that would provide direct evidence of alkylidene formation.

Scheme 2.14: Intramolecular trapping of the alkylidene.

We therefore undertook the synthesis of the desired salt 68 with a neopentyl-like group containing a terminal alkene. The iodide precursor (compound 69 in Scheme 2.15) of 68 was synthesized according to literature procedures. Addition of 4-bromobutene to the enolate of methyl isobutyrate led to the formation of ester 70. This was followed by reduction to alcohol 71 and substitution with iodide to form the desired compound 69 (Scheme 2.15).
Unfortunately, the reaction of 69 with PPh₃ did not yield the desired phosphonium salt 72. Depending on the temperature, the compound either decomposed or did not react. We examined the influence of the leaving group by installing either a bromide or a tosylate moiety (73 and 74 in Scheme 2.16). However neither of these compounds reacted with PPh₃. This is probably due to the fact these compounds are sterically hindered. We therefore turned our attention to a more nucleophilic phosphine ((p-OMePh)₃P). Reaction of (p-OMePh)₃P with iodide 69 gave the desired compound 75 but it could not be purified. The corresponding ylide was nonetheless synthesized through the standard procedure, however it too was difficult to purify. Considering that the purity of the ylide is essential for the formation of the alkylidene (vide supra), we left this route aside and concentrated on an alternative route.
Thus, in order to avoid a sterically hindered neopentyl group, we replaced it with an aromatic group that still fulfilled the desired criteria of not having any alpha protons \textit{(vide supra)} (Scheme 2.17).

\textbf{Scheme 2.16}: Alternative route to form the phosphonium salt.

\textbf{Scheme 2.17}: Alternative route for the intramolecular trapping of the alkylidene.

To that effect, alcohol 76 was protected as the THP acetal 77 that was then reacted with vinyl magnesium bromide followed by deprotection to give alcohol 78 (Scheme 2.18).\textsuperscript{34} This was followed by bromide formation and reaction with PPh\textsubscript{3} to give phosphonium salt 79. Standard conditions were used to form ylide 80.
Scheme 2.18: Synthesis of ylide 80.

Ylide 80 was then reacted with complex 14 (Scheme 2.19). Following the reaction by $^1$H NMR allowed us to observe the formation of the alkylidene (peak at 16.2 ppm), however none of the desired product was isolated from the reaction mixture.

Scheme 2.19: Reaction of ylide 80 with complex 14.

2.4. **Investigations into the Reactivity of the Alkylidene Complex**

As we were attempting to isolate the alkylidene, we were also interested in studying its reactivity. While it does decompose to the aldehyde corresponding to the ylide over time, with the right combination of osmium complex and phosphorous ylide (such as complex 14 and compound 49) we were able to observe the alkylidene 54 (Table 2.7) for several hours. We therefore hypothesized that this lifetime was sufficient for us
to investigate the reactivity of the newly formed alkylidene with a variety of small organic molecules.

2.4.1 Reactivity with Olefins.

In the context of our proposed carboxyhydroxylation reaction (*vide supra*), we were mostly interested in the reactivity of the alkylidene towards olefins. We examined a variety of electronically and sterically diverse olefins (Scheme 2.20). However, none of the attempted reactions gave the desired results. In all cases, the olefin remained unreacted.

Scheme 2.20: Reaction of the *in-situ* formed alkylidene 81 formed from complex 6 and ylide 50 with a variety of olefins.

2.4.2 Alternative Trapping Reagents.

Having been unsuccessful with olefins, we turned our attention to potentially more reactive trapping reagents (Scheme 2.21). Alkynes, allenes and reactive dienes such as Danishefsky’s diene were tested but none showed any reactivity with the alkylidene.
Scheme 2.21: Reaction of the in-situ formed alkylidene 81 formed from complex 6 and ylide 50 with alternative trapping reagents.

2.4.3 Reaction with Nitrones.

We then decided to investigate even more reactive trapping reagents such as 1,3 dipoles. To our delight, reaction of alkylidene 81 formed from complex 6 and ylide 50 with nitrone 82 led to the formation of alkene 83 in 40 % yield.\(^{35}\)

Scheme 2.22: Reaction of alkylidene 81 with a 1,3-dipole.

Our proposed mechanism for this transformation is a [3+2] cycloaddition between alkylidene 81 and nitrone 82 leading to osmacycle 84. Compound 84 can then undergo cycloreversion leading to alkene 83 and a more stable osmium (VI) species. Control
experiments show that phosphorous ylide 50 remains unreactive in the presence of nitrona 83 without osmium complex 6 consistent with alkylidene 81 as an intermediate in the reaction.

Scheme 2.23: Proposed mechanism for the formation of alkene 83.

2.5. Conclusions.

We began this project with the hypothesis that an osmium (VIII) alkylidene complex could undergo a [3+2] addition with an olefin to give a carbohydroxylation product. Inspired by the existing [3+2] cycloaddition reaction of olefins involving osmium derived reagents as well as known high oxidation state alkylidene complexes, we were able to synthesize a series of unprecedented high oxidation state osmium (VIII) alkylidene complexes by reaction of osmium imido complexes with phosphorous ylides.

We were able to show that the formation of the alkylidene is dependant on both the structure of the starting osmium complex and that of the reacting phosphorous ylide. In terms of the osmium complex, two bulky imido ligands are needed. In terms of phosphorous ylides, bulky electron rich ylides with no alpha protons are preferred. These
alkylidene complexes are however not stable and decompose overtime to the aldehyde corresponding to the starting ylide.

Finally, we demonstrated that while the newly formed alkylidene did not react with olefins to give the originally proposed product, they do indeed react with a nitrone in a [3+2] fashion to give an alkene product.

3.1. Materials and Methods: General Information.

$^1$H and $^{13}$C NMR spectra were recorded on a Varian Inova 600 spectrometer (600 MHz $^1$H, 150 MHz $^{13}$C) and a Varian Inova 400 spectrometer (400 MHz $^1$H, 100 MHz $^{13}$C) at room temperature in CDCl$_3$ with internal CHCl$_3$ as the reference (7.26 ppm for $^1$H and 77.23 ppm for $^{13}$C). Chemical shifts (δ values) were reported in parts per million (ppm) and coupling constants (J values) in Hz. Multiplicity is indicated using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sep = septet, m = multiplet, b = broad signal. Infrared (IR) spectra were recorded from 4000-400 cm$^{-1}$ using Thermo Electron Corporation Nicolet 380 FT-IR spectrometer. High resolution mass spectra were obtained using a Thermo Electron Corporation Finigan LTQFTMS (at the Mass Spectrometry Facility, Emory University). We acknowledge the use of shared instrumentation provided by grants from the NIH and the NSF. Melting points (m.p.) were uncorrected and measured on a Fisher-Johns melting point apparatus. Analytical thin layer chromatography (TLC) was performed on precoated glass backed EMD 0.25 mm silica gel 60 plates. Visualization was accomplished with UV. Flash column chromatography was carried out using EMD Geduran® silica gel 60 (40-63 μm).

All reactions were conducted with anhydrous solvents in oven dried or flame-dried and argon-charged glassware. Anhydrous solvents were purified by passage through activated alumina using a Glass Contours solvent purification system unless otherwise noted. Solvents used in workup, extraction and column chromatography were used as received.
from commercial suppliers without prior purification. All reagents were purchased from Sigma-Aldrich and used as received unless otherwise noted. 2,4,6-Tri-iso-propylbenzoic acid and N-α-diphenyl nitrone were purchased from Alfa Aesar and used as received.

3.2. General Procedures.

**General procedure A for the preparation of phosphorous ylides:** In a MBraun Lab Master 130 glovebox under an atmosphere of dry nitrogen, the starting phosphonium salt (1 equiv.) and NaNH₂ (5 equiv.) were dissolved in toluene (0.3 M) in a Schlenk tube. The tube was sealed and taken out of the glovebox. The resulting orange mixture was stirred at reflux overnight then allowed to reach room temperature. The tube was returned to the glovebox and the mixture was filtered through celite and concentrated in vacuo. The resulting solid was recrystallized in cold pentane to afford orange crystals.

**General procedure B for the preparation of alkylidene complexes:** In a MBraun Lab Master 130 glovebox under an atmosphere of dry nitrogen, the starting bisimido osmium complex (1 equiv.) was dissolved in CD₂Cl₂ (0.05 M) and transferred to an NMR tube. A solution of the starting ylide (1 equiv.) in CD₂Cl₂ (0.05 M) was added, and the NMR tube was sealed with a rubber septum. The tube was removed from the glovebox, and the reaction was monitored by ¹H NMR. The first data were collected after 5 min and showed complete consumption of the starting osmium complex with concomitant formation of osmium alkylidene.
General procedure C for the preparation of azides: \( \text{NaNO}_2 \) (2 equiv.) in water was added dropwise to a solution of the starting amine (1.0 equiv.) in a mixture of \( \text{EtOH/H}_2\text{O/H}_2\text{SO}_4 \) (0.15 M, 1:1:0.2) at 0 ºC. The reaction was left to stir at 0 ºC for 1 h then \( \text{NaN}_3 \) (2.2 eq) in water was added. The reaction mixture was stirred at 0 ºC for 2 h then poured into ice cold water. The mixture was then extracted with DCM, dried over \( \text{MgSO}_4 \) and concentrated in vacuo. No further purification was needed.

General procedure D for the preparation of iminophosphoranes: A solution of the starting azide (1.5 equiv.) in DCM (0.4 M) was added dropwise to a solution of \( \text{PPh}_3 \) (1.0 equiv.) in DCM at room temperature. The reaction mixture was left to stir at RT overnight. The reaction mixture was then concentrated in vacuo and cold pentane was slowly added. After a few minutes in the freezer a precipitate formed. It was filtered, washed with cold pentane and dried under high vacuum.

General procedure E for the preparation of bisimido-bisoxo complexes: The starting iminophosphorane (2 equiv.) was slowly added to a solution of \( \text{OsO}_4 \) (1 equiv.) in DCM (0.2 M). The reaction mixture was heated to reflux for several hours then it was allowed to reach room temperature and loaded on a silica column. Purification via flash chromatography afforded the desired complex, which can be crystallized from pentane.

3.3. Procedures and Compound Characterization.

Ylides \( 47^{35b}, 48^{36}, 52^{37} \) and \( 53^{38} \) were prepared according to general procedure A and their \( ^1\text{H} \) NMR spectra matched those reported in the literature.
Preparation of ethyl-2,4,6-tri-iso-propylbenzoate 45:

2,4,6-Tri-iso-propylbenzoic acid (1.00 g, 4.03 mmol) was dissolved in toluene (12.5 mL) in a 25 mL round bottom flask. Ethanol (0.59 mL, 21.76 mmol) was added followed by concentrated sulfuric acid (0.03 mL, 0.48 mmol). A Dean-Stark apparatus was installed and filled with toluene (13 mL). The resulting solution was stirred at reflux for 24 hours, then was allowed to reach room temperature and cooled to 0 ºC. Anhydrous potassium carbonate (1.5 g, 10.8 mmol) was added and the mixture was stirred vigorously for five minutes before being filtered through celite and concentrated in vacuo. Ester 45 was obtained as a colorless oil (1.04 g, 94% yield) and used without further purification in the next step; \( R_f \) 0.85 (2:1 hexanes/EtOAc); \textbf{IR} (thin film, cm\(^{-1}\)) 2961, 1726, 1463, 1251, 1075; \textbf{\( ^1H \) NMR} (CDCl\(_3\), 600 MHz) \( \delta \) 7.01(s, 2H), 4.38 (q, 2H, \( J = 7.2 \) Hz), 2.84-2.92 (m, 3H), 1.37 (t, 3H, \( J = 7.2 \) Hz), 1.25 (d, 12H, \( J = 4.8 \) Hz), 1.24 (d, 6H, \( J = 5.4 \) Hz); \textbf{\( ^{13}C \) NMR} (CDCl\(_3\), 150 MHz) \( \delta \) 171.1, 150.3, 144.9, 130.8, 121.0 60.9, 34.6, 31.6, 24.3, 24.1, 14.7; \textbf{HRMS} (+ESI) calculated for C\(_{18}\)H\(_{29}\)O\(_2\) 277.2168, found 277.21634 [M+H]\(^+\).
Preparation of (2,4,6-tri-iso-propylphenyl)methanol 44:

LiAlH4 (1.89 mL, 3.78 mmol, 2M solution in THF) was added dropwise to a solution of ethyl-2,4,6-tri-iso-propylbenzoate 45 (1.04 g, 3.78 mmol) in THF (10 mL) at 0 °C. The resulting solution was stirred at reflux for 20 hours. The mixture was allowed to cool to 0 °C and a saturated solution of Rochelle’s salt (15 mL) was carefully added. The mixture was extracted with Et2O (3× 20 mL), washed with brine (2× 10 mL), dried over MgSO4 and concentrated in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc) afforded alcohol 44 as a white solid (0.79 g, 90 % yield); Rf 0.55 (3:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 3220, 2959, 1604, 1456, 1004, 874; ¹H NMR (CDCl3, 600 MHz) δ 7.04 (s, 2H), 4.78 (d, 2H, J = 4.8 Hz), 3.37 (sep, 2H, J = 6.6 Hz), 2.88 (sep, 1H, J = 7.2 Hz), 1.28 (d, 12 H, J = 6.6 Hz), 1.20 (d, 6H, J = 7.2 Hz); ¹³C NMR (CDCl3, 100 MHz) δ 149.2, 148.1, 131.8, 121.5, 57.5, 34.6, 29.5, 24.8, 24.2; m.p. 89-90 ºC; HRMS (+ESI) calculated for C₁₆H₂₅ 217.1956, found 217.19557 [M-OH]+.

Preparation of 2-(bromomethyl)-1,3,5-tri-iso-propylbenzene 46:

Dimethylsulfide (0.24 mL, 3.20 mmol) was added dropwise to a solution of N-bromosuccinimide (0.69 g, 3.85 mmol) in DCM (10 mL) at 0 °C. The reaction mixture
was then cooled to -20 °C and a solution of (2,4,6-tri-iso-propylphenyl)methanol 44 (0.50 g, 2.14 mmol) in DCM (10 mL) was added dropwise. The resulting yellow solution was stirred for 3 hours at 0 °C. The mixture was diluted with pentane (40 mL) and poured into ice water. The organic layer was washed with brine (2 × 20 mL), filtered through silica and concentrated in vacuo to obtain bromine 46 as a colorless oil (0.61 g, 96 % yield); \( R_f \) 0.89 (3:1 hexanes/EtOAc); IR (thin film, cm\(^{-1}\)) 2958, 1606, 1458, 1215, 877; \( ^1H \) NMR (CDCl\(_3\), 600 MHz) \( \delta \) 7.00 (s, 2H), 4.67 (s, 2H), 3.30 (sep, 2H, \( J = 6.6 \) Hz), 2.87 (sep, 1H, \( J = 6.6 \) Hz), 1.29 (d, 12 H, \( J = 6.6 \) Hz), 1.24 (d, 6H, \( J = 6.6 \) Hz); \( ^{13}C \) NMR (CDCl\(_3\), 100 MHz) \( \delta \) 149.8, 148.3, 128.8, 121.7, 34.5, 29.5, 28.3, 24.4, 24.1; HRMS (+APCI) calculated for C\(_{16}H_{25}\) 217.1956, 217.19501 found [M-Br]\(^+\).

**Preparation of triphenyl-(2,4,6-tri-isopropylbenzyl)phosphonium bromide 42:**

![Reaction Scheme](image)

2-(Bromomethyl)-1,3,5-tri-iso-propylbenzene 46 (3.37 g, 11.35 mmol) and triphenylphosphine (3.27 g, 12.48 mmol) were dissolved in toluene (40 mL). The resulting mixture was stirred at reflux for 24 hours. The reaction was allowed to reach room temperature and the product was precipitated by addition of cold pentane. Filtration followed by washing with pentane (10 mL) and drying under high vacuum afforded phosphonium salt 42 as a white solid (6.20 g, 98 % yield); IR (thin film, cm\(^{-1}\)) 2954, 1604, 1435, 1105, 750; \( ^1H \) NMR (CDCl\(_3\), 600 MHz) \( \delta \) 7.79 (m, 3H), 7.62 (m, 6H), 7.52 (m, 6H), 6.86 (s, 2H), 5.15 (d, 2H, \( J_{H-P} = 13.2 \) Hz), 2.84 (sep, 1H, \( J = 6.6 \) Hz), 2.57 (sep,
2H, J = 6.6 Hz), 1.22 (d, 6 H, J = 6.6 Hz), 0.78 (bs, 12 H); 13C NMR (CDCl₃, 150 MHz) δ 150.4 (d, J_C-P = 4.2 Hz), 148.8, 135.3, 134.5 (d, J_C-P = 10.4 Hz), 130.4 (J_C-P = 12.4 Hz), 122.2, 118.4, 117.9, 34.4, 31.4, 25.4, 25.0, 24.3; m.p. 225-227 °C; HRMS (+ESI) calculated for C₃₄H₄₀P⁺ 479.2862, found 479.28510 [M⁺].

**Preparation of ylide 50:**

Prepared according to general procedure A using triphenyl-(2,4,6-triisoproylbenzyl)phosphonium bromide 42 (0.53 g, 0.95 mmol). Recrystallization in cold pentane afforded ylide 50 as orange crystals (0.23 g, 50 % yield); ¹H NMR (C₆D₆, 400 MHz) δ 7.60-7.70 (m, 6H), 7.25 (s, 2H), 6.90-7.05 (m, 9H), 3.70 (sep, 2H, J = 6.8 Hz), 2.95 (sep, 1H, J = 7.2 Hz), 2.4 (d, 2H, J_H-P = 15.0 Hz), 1.35 (d, 6 H, J = 7.2 Hz), 1.15 (d, 12H, J = 6.8 Hz).

**Preparation of ylide 49:**

Prepared according to general procedure A using neopentyl phosphonium iodide 38 (0.58g, 1.26 mmol) to afford ylide 49 as orange crystals (0.21g, 50% yield); ¹H NMR (C₆D₆, 400 MHz) δ 7.80-7.84 (m, 6H), 7.04-7.16 (m, 9H), 1.41 (s, 9 H), 1.14 (d, 1H, J_H-P = 14.4 Hz).
Preparation of phosphonium salt 43:

2,6-difluorobenzylbromide (0.500 g, 2.42 mmol) and PPh₃ (0.697 g, 2.66 mmol) were dissolved in toluene (5 mL) and the resulting solution was heated to reflux for 18 h. It was then cooled to room temperature and the white precipitate was filtered, washed with cold toluene and dried under high vacuum to afford phosphonium salt 43 as an amorphous white solid (1.10 g, 97% yield); IR (thin film, cm⁻¹) 3403, 3054, 1623, 1589, 1469, 1437, 1110, 989, 747, 726, 690; ¹H NMR (300 MHz, CDCl₃) δ 7.82-7.75 (m, 9H), 7.68-7.62 (m, 6H), 7.27 (m, 2H), 6.73 (t, 1H, J = 8.0 Hz), 5.36 (d, 2H, J = 14.0 Hz); ¹³C NMR (CDCl₃, 150 MHz) δ 161.3 (d, J_{C-F} = 250 Hz), 135.5, 134.2 (d, J_{C-P} = 10.4 Hz), 130.4 (d, J_{C-P} = 12.3 Hz), 117.3 (d, J_{C-F} = 84.6 Hz), 111.9 (d, J = 20.7 Hz), 21.3 (d, J_{C-P} = 51.6 Hz); HRMS (+APCI) calculated for C₂₅H₂₀F₂P⁺ 389.1265 found 389.1265 [M⁺].

Preparation of ylide 51:

Prepared according to general procedure A using phosphonium salt 43 (0.08 g, 0.17 mmol) to afford ylide 51 as orange crystals (0.045 g, 68% yield); ¹H NMR (C₆D₆, 400 MHz) δ 7.71-7.62 (m, 5H), 7.37-7.34 (m, 1H), 7.04-6.91 (m, 9H), 6.75-6.67 (m, 2H), 6.22-6.15 (m, 1H).
Preparation of alkylidene 54:

Prepared according to general procedure B using bis(2,6-di-iso-propylphenylimino)-dioxo-osmium 14 (0.010 g, 0.02 mmol) and ylide 49 (0.006 g, 0.02 mmol); $^1$H NMR (CD$_2$Cl$_2$, 400 MHz) $\delta$ 14.53 (s, 1H), 7.15 (d, 2H, $J$ = 7.6 Hz), 7.10 (d, 2H, $J$ = 8.0 Hz), 4.0 (sep, 2H, $J$ = 6.8 Hz), 3.40 (sep, 2H, $J$ = 6.8 Hz), 1.24 (s, 9H), 1.22 (d, 12H, $J$ = 6.8 Hz), 1.18 (d, 12H, $J$ = 6.8 Hz Hz); HRMS (–ESI) calculated for C$_{29}$H$_{43}$N$_2$O 611.3041, found 611.3048 [M-OH]$^-$. The formation of alkylidene 54 was accompanied by the formation of pivalaldehyde in an initial ratio of 4:1.

Azide 55$^{30}$ and 2-azido-1,3,5-trimethylbenzene$^{40}$ was prepared according to general procedure C and its characterization match the one reported in the literature.

Preparation of azide 85:

Prepared according to general procedure C using 2,6-dichloroaniline (0.677 g, 4.18 mmol) to afford azide 85 as a yellow oil (0.784 g, 100 % yield); IR (thin film, cm$^{-1}$) 2927, 2100, 1576, 1562, 1436, 1305; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.30 (d, 2H, $J$=8.4...
Hz), 7.05 (t, 1H, J = 8.0 Hz); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$ 130.6, 129.1, 130.0, 126.5; HRMS (+APCI) calculated for C$_6$H$_4$Cl$_2$N 159.9721, found 159.9714 [M-N$_2$+H]$^+$.

**Preparation of azide 86:**

Prepared according to general procedure C using 2-trifluoromethylaniline (0.500 g, 3.10 mmol) to afford azide 86 as a yellow oil (0.578 g, 100 % yield); IR (thin film, cm$^{-1}$) 2127, 2099, 1587, 1493, 1457, 1314, 1292, 1126, 1112; $^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ 7.66 (d, 1H, $J$ = 7.8 Hz), 7.60 (t, 1H, $J$ = 7.8 Hz), 7.30 (d, 1H, $J$ = 8.4 Hz), 7.25 (t, 1H, $J$ = 7.8 Hz); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$ 138.7, 133.3, 127.5 (q, $J_{C-F}$ = 2.4 Hz), 124.6, 124.1, 122.3, 119.6; HRMS (+APCI) calculated for C$_6$H$_5$NF$_3$ 160.0374, found 160.0369 [M-N$_2$+H]$^+$.

Iminophosphorane 56$^{41}$ was prepared according to general procedure D and its characterization match the data reported in the literature.

**Preparation of iminophosphorane 57:**

Prepared according to general procedure D using 2-azido-1,3,5-trimethylbenzene$^{40}$ (0.165 g, 1.02 mmol) to afford iminophosphorane 57 as a yellow powder (0.254 g, 63 % yield);
IR (thin film, cm⁻¹) 3054, 2908, 1476, 1433, 1333, 1106; ¹H NMR (300 MHz, C₆D₆) δ 7.51-7.37 (m, 9H), 7.33-7.27 (m, H), 6.58 (s, 2H), 2.07 (s, 3H), 1.81 (s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 144.3, 133.7, 132.9, 132.6 (d, J_C,P = 8.9 Hz), 131.4, 128.6 (d, J_C,P = 4.8 Hz), 128.4 (d, J_C,P = 11.7 Hz), 127.9, 21.3, 20.8; HRMS (+APCI) calculated for C₂₇H₂₇NP 398.1881, found 396.1874 [M+H]⁺.

Preparation of iminophosphorane 58:

Prepared according to general procedure D using azide 85 (0.784 g, 4.18 mmol) to afford iminophosphorane 58 as a yellow powder (0.989 g, 56 % yield); IR (thin film, cm⁻¹) 3056, 1467, 1435, 1341, 1111, 692; ¹H NMR (300 MHz, CDCl₃) δ 7.79-7.72 (m, 6H), 7.54-7.48 (m, 3H), 7.46-7.39 (m, 6H), 7.12 (dd, 2H, J = 8.0, 1.3 Hz), 6.56 (td, 1H, J = 7.9, 2.0 Hz); ¹³C NMR (300 MHz, CDCl₃) δ 148.8, 132.8 (d, J_C,P = 9.8 Hz), 132.6, 131.9, 131.8 (d, J_C,P = 8.7 Hz), 131.6, 128.4 (d, J_C,P = 12.6 Hz), 127.9; HRMS (+APCI) calculated for C₂₄H₁₉NCl₂P 422.0632, found 422.0627 [M+H]⁺.

Preparation of iminophosphorane 59:

Prepared according to general procedure E using azide 86 (0.500 g, 3.10 mmol) to afford iminophosphorane 59 as a pink powder (0.933 g, 71 % yield); IR (thin film, cm⁻¹) 3058,
1599, 1482, 1457, 1437, 1358, 1313, 1299, 1107; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.80-7.75 (m, 9H), 7.70-7.65 (m, 1H), 7.55-7.44 (m, 6H), 6.98 (t, 2H, $J = 7.6$ Hz), 6.63 (t, 1H, $J = 7.6$), 6.48 (d, 1H, $J = 8.4$ Hz); $^{13}$C NMR (300 MHz, CDCl$_3$) δ 150.4, 132.8 (d, $J_{C,P} = 9.6$ Hz), 132.3(q, $J_{C,F} = 9.6$ Hz), 131.9, 131.8, 131.3, 130.7, 128.8(d, $J_{C,F} = 11.7$ Hz), 127.0, 122.8, 116.2; HRMS (+APCI) calculated for C$_{25}$H$_{20}$NF$_3$P 422.1285, found 422.1276 [M+H]$^+$. Bisoxobisimido complex 14$^{17b}$ was prepared according to general procedure E and its characterization match the data reported in the literature.

**Preparation of complex 60:**

Prepared according to general procedure E using iminophosphorane 57 (0.202 g, 0.511 mmol) to afford complex 60 as a purple powder (0.035g, 28 % yield); $^1$H NMR (400 MHz, CDCl$_3$) δ 6.4 (s, 2H), 2.19 (s, 6H), 2.00 (s, 3H); HRMS (+ESI) calculated for C$_{18}$H$_{23}$N$_2$O$_2$Os 491.1374, found 491.1362 [M+H]$^+$. 

\[
\text{Me} \quad \text{Me} \\
\text{N=PPPh$_3$} \\
\text{Me} \quad \text{Me} \\
\text{O} \quad \text{O} \\
\text{R=2,4,6-MePh} \\
\text{60} \\
\text{Os} \\
\text{Os} \\
\text{NR} \\
\text{Me} \quad \text{Me} \\
\text{N=PPPh$_3$} \\
\text{Me} \quad \text{Me} \\
\text{O} \quad \text{O} \\
\text{R=2,4,6-MePh} \\
\text{60} \
\]
Preparation of phosphorous salt 64:

Bromine 46 (1.26 g, 4.23 mmol) was added to a solution of phosphine 62\textsuperscript{32} (1.50 g, 4.23 mmol) in toluene (30 mL). The reaction mixture was heated to reflux for 48 h. It was then cooled to 0 °C. The resulting solid was filtered, washed with cold toluene and dried under high vacuum to yield phosphonium salt 64 as a white solid (1.96 g, 71 % yield);

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.77 (t, 2H, J = 3.6 Hz), 7.68 (td, 4H, J = 4, 1.8 Hz), 7.52-7.40 (m, 8H), 6.85 (s, 2H), 6.25 (dd, 1H, J = 3.6, 1.8 Hz), 6.20 (dd, 1H, J = 3.6, 1.8 Hz), 5.12 (d, 2H, J = 10 Hz), 3.02 (s, 1H), 2.94 (s, 1H), 2.84 (sep, 1H, J = 4.0 Hz), 2.78 (t, 1H, J = 4.0 Hz), 2.58 (sep, 1H, J = 4.0 Hz), 1.73-1.58 (m, 2H), 1.49 (s, 2H), 1.22 (d, 6H, J = 4.0 Hz), 0.78 (bs, 12 H).

Preparation of phosphorous salt 65:

Neopentyl iodide (0.65 mL, 4.9 mmol) and phosphine 62\textsuperscript{32} (1.2 g, 3.3 mmol) were mixed together in a sealed flask. The reaction mixture was heated to 125 °C for 60 h. It was then cooled to room temperature and the resulting solid was recrystallized in a 1: 10 mixture of DCM and toluene to afford phosphonium salt 65 as a white amorphous solid (0.75 g, 41 % yield);

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 8.35-8.05 (m, 4H), 7.96 (s, 2H, J = 8.0, 7.6
Hz), 7.79-7.50 (m, 6H), 7.57 (dd, 2H, J = 7.6, 2.0 Hz), 6.25 (dd, 1H, J = 4.0, 2.0 Hz), 6.19 (dd, 1H, J = 4.0, 2.0 Hz), 3.92 (d, 2H, J = 12 Hz), 3.10 (s, 2H), 2.94 (s, 1H), 2.78 (t, 1H, J = 6.0 Hz), 1.73-1.67 (m, 2H), 1.52-1.48 (m, 2H), 1.2 (s, 9H).

**Polymerization of phosphorous salt 66:**

Grubb’s 2\textsuperscript{nd} generation catalyst (0.043 g, 0.051 mmol) was added to a solution of salt 64 (1.00 g, 1.53 mmol) in degassed DCM (8 mL). The resulting solution was heated to 50 °C for 90 min. It was then cooled to room temperature and ethyl vinyl ether (2 mL) was added. The reaction mixture was stirred at room temperature for 30 min then NaHCO\textsubscript{3} (0.094 g, 1.12 mmol) was added, followed by P(CH\textsubscript{2}OH)\textsubscript{4}Cl (0.16 mL, 80 % wt in H\textsubscript{2}O). The reaction mixture was heated to 50 °C for 18 h. The reaction mixture was then allowed to reach room temperature and extracted with H\textsubscript{2}O (3 × 5 mL) and the aqueous phase was washed with DCM (3 × 5 mL). The combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{3}, and concentrated \textit{in vacuo}. The polymer was then recrystallized with a mixture of DCM/Et\textsubscript{2}O; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.80-7.20 (m, 14H), 6.80 (s, 2H), 5.40-4.80 (m, 4H), 2.95-2.35 (m, 6H), 2.05-1.8 (m, 2H), 1.15-1.05 (m, 8H), 0.95-0.50 (bs, 12H); \textsuperscript{31}P NMR (161 MHz, CDCl\textsubscript{3}) δ 17.47 (bs).
Preparation of triflate 74:

Tf₂O (1.4 mL, 8.2 mmol) was added to a solution of alcohol 87\textsuperscript{33} (1.0 g, 7.8 mmol) and 2,6-lutidine (0.95 mL, 8.2 mmol) in DCM (40 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 30 min. Saturated aq. NH₄Cl (20 mL) was then added. The mixture was extracted with DCM (3 × 60 mL). The combined organic extracts were washed with NaHCO₃ (2 × 20 mL) and brine (2 × 20 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (4:1 Pentane/DCM) afforded triflate 74 as a yellow oil (1.5 g, 78 % yield); Rₚ = 0.9 (2:1, pentane/DCM); IR (thin film, cm⁻¹) 2970, 1642, 1410, 1198, 1143, 931, 612; \textsuperscript{1}H NMR (600 MHz, CDCl₃) δ 5.82-5.75 (m, 1H), 5.03 (d, 1H, J = 17.4 Hz), 4.96 (d, 1H, J = 10.8 Hz), 4.22 (s, 2H), 2.06-2.02 (m, 2H), 1.43-1.40 (m, 2H), 1.00 (s, 6H); \textsuperscript{13}C NMR (150 MHz, CDCl₃) δ 138.4, 120.5 (q, Jₐₕ = 317 Hz), 115.0, 84.8, 37.5, 34.8, 28.2, 23.6.

Preparation of phosphorous salt 75:

Iodide 69\textsuperscript{33} (0.40 g, 1.7 mmol) and P(pOMeC₆H₄)₃ (0.40 g, 1.1 mmol) were mixed together in a sealed flask. The mixture was heated to 135 °C for 48 h. The reaction mixture was cooled to room temperature and the solid was dissolved with DCM. The solvent was then evaporated to afford the impure phosphonium salt 75 as a white solid.
(0.44 g, 67 % yield crude); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.68-7.59 (m, 6H), 7.21-7.12 (m, 6H), 5.86-5.79 (m, 1H), 5.06-4.93 (m, 2H), 3.92 (s, 9H), 3.03 (d, 2H, $J$ = 15 Hz), 2.09-1.97 (m, 2H), 1.52-1.46 (m, 2H), 1.05 (s, 6H). All attempts to purify salt 75 by column chromatography or recrystallization failed.

**Preparation of phosphonium salt 79:**

\[
\begin{align*}
\text{PPh}_3 (0.593 \text{ g}, 2.26 \text{ mmol}) & \text{ was added to a solution of bromine 88$^{34}$ (0.239 g, 1.13 mmol) in toluene (10 mL). The reaction mixture was heated to reflux for 18h. It was then cooled to room temperature and the solid was filtered, washed with cold toluene and dried under high vacuum to afford phosphonium salt 88 as a white powder (0.490 g, 92 % yield);} \\
\text{1H NMR} (400 \text{ MHz, } \text{CDCl}_3) & \delta 7.81-7.76 (m, 3H), 7.69-7.60 (m, 12H), 7.24-7.17 (m, 2H), 7.10 (t, 1H, $J$ = 4.0 Hz), 5.55-5.42 (m, 1H), 5.33 (d, 2H, $J$ = 20 Hz), 4.96 (dd, 1H, $J$ = 12, 2.0 Hz), 4.78 (dd, 1H, $J$ = 24, 2.0 Hz), 2.62 (d, 2H, $J$ = 8.0 Hz).
\end{align*}
\]

**Preparation of ylide 80:**

\[
\begin{align*}
\text{PPh}_3 (0.593 \text{ g}, 2.26 \text{ mmol}) & \text{ was added to a solution of bromine 88$^{34}$ (0.239 g, 1.13 mmol) in toluene (10 mL). The reaction mixture was heated to reflux for 18h. It was then cooled to room temperature and the solid was filtered, washed with cold toluene and dried under high vacuum to afford phosphonium salt 88 as a white powder (0.490 g, 92 % yield);} \\
\text{1H NMR} (400 \text{ MHz, } \text{CDCl}_3) & \delta 7.81-7.76 (m, 3H), 7.69-7.60 (m, 12H), 7.24-7.17 (m, 2H), 7.10 (t, 1H, $J$ = 4.0 Hz), 5.55-5.42 (m, 1H), 5.33 (d, 2H, $J$ = 20 Hz), 4.96 (dd, 1H, $J$ = 12, 2.0 Hz), 4.78 (dd, 1H, $J$ = 24, 2.0 Hz), 2.62 (d, 2H, $J$ = 8.0 Hz).
\end{align*}
\]

Prepared according to general procedure A using phosphorous salt 79 (0.100 g, 0.211 mmol) to ylide 80 as orange crystals (0.020 g, 43 % yield); $^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ 7.75-7.69 (m, 6H), 7.26 (d, 1H, $J$= 4.0 Hz), 7.06-6.91 (m, 12H), 6.76-6.72 (m 1H), 6.40-
6.29 (m, 1H), 5.28 (dd, 1H, J= 20, 2.0 Hz), 5.5 (dd, 1H, J = 12, 2.0 Hz), 3.69 (d, 1H, J = 8.0 Hz).

**Preparation of alkene 83:**

In a MBraun Lab Master 130 glovebox under an atmosphere of dry nitrogen, ylide 50 (0.10 g, 0.21 mmol) dissolved in toluene (2 mL) was added to a solution of bis(tert-butylimino)-dioxo-osmium 6 (0.08 g, 0.21 mmol) in toluene (2 mL). N-α-diphenyl nitrone (0.04 g, 0.21 mmol) 82 was added and the resulting red solution was stirred at room temperature for 18 hours outside of the glovebox. The reaction mixture was concentrated in vacuo and purified by flash chromatography (8:1, 4:1, 2:1, 1:1, 1:2 hexanes/DCM) to afford compound 83 as a colorless oil (0.03g, 40% yield); Rf 0.83 (4:1 hexanes/ CH2Cl2); IR (thin film, cm⁻¹) 2957, 2924, 2886, 1459, 692; \(^1\text{H NMR}\) (CDCl₃, 400 MHz) δ 7.51 (d, 2H, J = 7.2 Hz), 7.39 (t, 2H, J = 7.2 Hz), 7.29 (t, 1H, J = 7.2 Hz), 7.20 (d, 1H, J = 16.4 Hz), 6.50 (d, 1H, J = 16.8 Hz), 3.28 (sep, 2H, J = 6.4 Hz), 2.91 (sep, 1H, J = 6.8 Hz), 1.28 (d, 6H, J = 6.8 Hz), 1.21 (d, 12H, J = 6.4 Hz); \(^{13}\text{C NMR}\) (CDCl₃, 100 MHz) δ 147.9, 146.9, 137.8, 134.6, 133.2, 128.9, 127.7, 127.2, 126.5, 120.8, 34.5, 30.4, 29.9, 24.3, 24.2; \text{HRMS} (ESI) calculated for C₂₃H₃₁ 307.2426, found 307.2359 [M+H]⁺.
Part II: Studies on the versatility of metallonitrene/alkyne cascade reactions.


4.1. N-containing Compounds in Chemistry.

N-containing molecules form the core of life as amino-acids and are also found in numerous natural products as well as in a variety of man-made molecules such as herbicides or active pharmaceutical agents (Figure 4.1). Methods to form C-N bonds are therefore of the utmost importance. Indeed when efficient and practical methods have been developed (for example the Buchwald-Hartwig amination), they are often rapidly adopted by the synthetic community, illustrating the fact that there is still a need for new C-N bond forming methodologies.42

![Figure 4.1: Examples of N-containing herbicides and active pharmaceutical agents.](image)

The ability to selectively introduce N-containing functionality into simple organic substrates represents an attractive strategy for the construction of such molecules. Among
the different methods available to date, the use of metallonitrenes stands out as a particularly efficient method to incorporate \(N\)-containing functionality. Indeed, metallonitrenes have been shown to be efficient in both olefin aziridination and C-H amination (Scheme 4.2).\(^{43}\)

\[
\begin{align*}
\text{aziridination} & \\
M = \text{Ru, Mn, Ag, Cu, Rh} & \\
C-\text{H insertion}
\end{align*}
\]

**Scheme 4.1:** Existing metallonitrene chemistry.

### 4.2. The Chemistry of Metallonitrenes.

#### 4.2.1 Aziridination.

Aziridines are valuable synthetic intermediates for the synthesis of \(N\)-containing molecules because their regio- and stereoselective ring opening by nucleophiles allows for the formation of a variety of functionalized amines.\(^{44}\) In addition, the aziridine functionality is present in a number of natural products, several of which have interesting biological properties.\(^{45}\) Thus, the field of aziridine synthesis has attracted a lot of attention.

Aziridines are the \(N\)-equivalent of epoxides and the first aziridines were synthesized by mimicking the cytochrome P-450 catalyzed oxygen transfer from iodosylbenzene to organic substrates.\(^{46}\) Thus, it was found that the analogous nitrene transfer could be done using sulfonyliminoiodinanes (such as TsN=IPh) in the presence of a variety of catalysts
including Mn(III)- and Fe(III)-prophyrins and Rh$_2$(OAc)$_4$.\textsuperscript{47} With these early results in mind, it was the Evans group that developed the formal nitrine transfer to olefins with TsN=IPh into a synthetically useful reaction by using Cu(I) and Cu(II) salts as catalysts (Scheme 4.2).\textsuperscript{48} In parallel with the Jacobsen group, they were also able to show that these reactions can be enantioselective when using bis(oxazoline) and chiral diimine ligands.\textsuperscript{49} The substrate scope of these reactions was however limited to styrene-derived substrates.

\begin{align*}
\text{Ph} = \text{PhI} = \text{NTs} & \quad \xrightarrow{\text{Cu(acac)}_2} \quad \text{Ph} - \text{NTs} \\
(5 \text{ eq.}) & \quad (1 \text{ eq.}) & \quad 95 \%
\end{align*}

\begin{align*}
\text{Ph} - \text{COPh} & \quad + \quad \text{PhI} = \text{NTs} & \quad \xrightarrow{\text{CuOTf-L}_1^-} \quad \text{Ph} - \text{NTs} \\
(1 \text{ eq.}) & \quad (2 \text{ eq.}) & \quad 64 \%, 97 \% \text{ e.e.}
\end{align*}

\begin{align*}
\text{Ph} & \quad + \quad \text{PhI} = \text{NTs} & \quad \xrightarrow{\text{CuOTf-L}_2^-} \quad \text{Ph} - \text{NTs} \\
(1 \text{ eq.}) & \quad (1.5 \text{ eq.}) & \quad 75 \%, > 98 \% \text{ e.e.}
\end{align*}

\textbf{Scheme 4.2:} Copper catalyzed intermolecular aziridination reactions.

The demonstration by Dauban and Dodd that the nitrine source is not limited to TsN=IPh has helped improve the synthetic utility of the aziridination reaction. They were able to show that iminoiodinanes derived from aliphatic sulfonamides (such as SesN=IPh) can be synthesized and isolated (Scheme 4.3).\textsuperscript{50} However, iminoiodinanes are often troublesome to prepare and difficult to handle. This made the discovery that they can be generated \textit{in situ} from a variety of molecules, including sulfonamides and
sulfamates esters in the presence of iodosylbenzene or PhI(OAc)$_2$, a breakthrough$^{51}$ This has greatly increased the substrate scope of the aziridination reaction and has led the way to intramolecular aziridination.

\[
\text{Ph} + \text{PhI} = \text{NSes} \quad \xrightarrow{\text{CuOTf}} \quad \text{Ph} \text{NSes} \\
\text{Ph} \text{= NSES} \quad \text{CuOTf} \quad 4 \text{ Å mol. sieves} \quad 68 \%
\]

**Scheme 4.3:** Alternative nitrene sources.

In addition to Cu(I) salts, Rh(II) catalysts are also efficient for the aziridination of olefins. It was observed that C-H amination is a competitive process with Rh(II) catalysts$^{43}$ However the Du Bois group has demonstrated that Rh(II) tetracarboxamide catalysts (such as Rh$_2$(tfacam)$_4$) allow for the selective aziridination of a variety of olefins (Scheme 4.4)$^{52}$

\[
\text{Ph} + \text{Me} + \text{H}_2\text{NSO}_2\text{CCl}_3 \quad \xrightarrow{\text{PhI(OAc)$_2$, MgO, Rh$_2$(tfacam)$_4$}} \quad \text{Ph} \text{NSO}_2\text{CH}_2\text{CCl}_3 \\
\text{Ph} = \text{NSES} \quad \text{CuOTf} \quad 85 \%
\]

**Scheme 4.4:** Rhodium catalyzed aziridination reactions.
4.2.2 C-H Amination.

Due to the ubiquity of the C-H bond in organic substrates, C-H amination reactions represent an attractive alternative to traditional C-N bond formation methodologies, especially since it does not require a pre-installed functional group. However, the ability to generate a species capable of inducing selective C-H functionalization remained, until recently, a challenge. C-H amination was usually observed as a side reaction in the aziridination of olefins but efforts in the past decade have allowed for its development as a selective intra- and intermolecular process using a variety of metals such as Rh, Ru, Cu and Ag.43, 53

Inspired by early reports from Breslow and Gellman, the Du Bois group demonstrated that intramolecular C-H amination reactions were possible using Rh(II) catalysts and in situ formation of the iminoiodinane from carbamate and sulfamate esters in a stereo- and regioselective fashion.53a Carbamates form 5-membered ring oxazolidinone products exclusively whereas sulfamate esters form 6-membered ring oxathiazinane products, which are versatile synthons (Scheme 4.5). Their work allowed for the field to flourish.

Additionally, the Du Bois group greatly expanded the scope of these reactions with the development a new bridged Rh(II) tetracarboxylate catalyst, which they named Rh2.esp2, allowing for the use of sulfamides, ureas and guanidines as nitrone precursors with low catalyst loadings.54
Although extensively studied, intermolecular C-H amination reactions have suffered for many years from several drawbacks including a limited substrate scope and the need for large excesses of substrate relative to oxidant.43 These limitations have been partially over-come and there have been reports of successful intermolecular C-H amination reactions with a variety of catalysts including Mn-porphyrins and Rh(II) tetracarboxylates (Scheme 4.6).53c, 54-55
Likewise, the development of enantioselective C-H amination with synthetically useful levels of selectivity has remained a challenge. However, recent efforts have demonstrated that C-H amination reactions can be achieved in a highly enantioselective fashion using a variety of catalysts and substrates for both intra- and intermolecular C-H amination (Scheme 4.7).
4.3. Dirhodium(II) Paddlewheel Complexes.

Among the variety of catalysts used for aziridination and C-H amination reactions are Rh(II) tetracarboxylates and tetracarboxamidates. These catalysts belong to a larger family of dirhodium(II) paddlewheel complexes. This family includes a wide variety of stable complexes, both chiral and achiral, known to catalyze a broad range of reactions including carbene and nitrene chemistry. They all share some unique structural features.

Indeed, all the dirhodium(II) paddlewheel complexes consists of a dirhodium core surrounded by four equatorial $\mu_2$-ligands and two labile axial ligands and held together by a single bond between the two rhodium nuclei (Figure 4.2). Each rhodium has an
octahedral geometry and the catalytically active sites are considered to be in the axial positions, with the lantern-shape structure remaining intact during the reaction.

**Figure 4.2:** General structures of dirhodium(II) paddlewheel complexes.

Several types of ligands for these complexes have been developed: carboxylates, phosphonates and carboxamidates, the most common being the carboxylates. A variety of achiral Rh(II) tetracarboxylate catalysts are known and more interestingly chiral Rh(II) tetracarboxylate catalysts with prolinate and phthalimide derived ligands have also been extensively developed (Figure 4.3).\(^{57}\)

**Figure 4.3:** Examples of Rh(II) tetracarboxylate complexes.

A variety of chiral tetracarboxamidate catalysts have been also developed with four major class of ligands: 2-oxopyrrolidine, 2-oxozolidinone, N-acylimidazolidin-2-one and acetidinone derived ligands (Figure 4.4).\(^{58}\) In addition, the tetracarboxamidate complexes are of overall \(C_2\)-symmetry with a \textit{cis} (2,2) configuration in which two nitrogen and two
oxygen atoms are attached to each rhodium center in a *cis* fashion. These catalysts are also more electron rich due to the relative basicity of the ligand.

![Diagram of Rh(II) tetracarboxylate complexes]

**Figure 4.4**: Examples of Rh(II) tetracarboxylate complexes.

The advantage of these catalysts and the reason for the development of such a variety of ligands is the fact that the structure of these complexes strongly influences the type of reaction they catalyze. This is very well exemplified with the carbene chemistry (Scheme 4.8). Thus, while Rh(II) tetraprolinate catalysts are extremely effective for the intermolecular cyclopropanation with aryl or vinyldiazoacetates, Rh(II) phthalimide derived catalysts excel at intramolecular C-H insertion. On the other hand, Rh(II) carboxamidate catalysts are the catalysts of choice for intramolecular cyclopropanation.
Scheme 4.8: Reactions with Rh(II) paddlewheel complexes.

A common decomposition pathway for these catalysts is through ligand exchange. This has necessitated the development of bridged ligands which provide more rigid structures that are less prone to ligand exchange (Figure 4.5).\textsuperscript{54, 57}

Figure 4.5: Examples of Rh(II) complexes with bridged ligands.

As described in section 4.1, the chemistry of metallonitrenes revolves around two reactions: aziridination and C-H amination reactions. This stands in sharp contrast to the related metallocarbene chemistry. Not only have metallocarbenes been shown to perform cyclopropanation and C-H insertion reactions but they also catalyze a wide range of other reactions (Scheme 4.9).  

![Scheme 4.9: Metallonitrene chemistry vs metallocarbene chemistry.](image)

This observation has prompted us to explore the reactivity of metallonitrenes and their ability to catalyze a range of C-N bond forming reactions. Given the importance of the C-N bond in nature and the need for new reactions for C-N bond formation, we hypothesized that these metallonitrene species were a good entryway into C-N bond
formation development. We were especially interested in the reactivity of metallonitrenes towards alkynes.

4.5. Development of a metallonitrene/alkyne cascade reaction.

4.5.1 Proposed reaction.

At the onset of this project, we envisioned that a metallonitrene species could undergo a metathesis reaction with an alkyne, mechanistically mirroring the ene/ynetype (Scheme 4.10). This would generate a new C-N double bond as well as a reactive carbene species that could cascade into secondary transformations.

![Scheme 4.10: Proposed metallonitrene/alkyne metathesis reaction.](image)

In considering this reaction, we noticed that the Odom group had recently reported such a reaction using a stable molybdenum imido complex and a strained alkyne to generate a stable molybdenum alkylidene complex (Scheme 4.11).

![Scheme 4.11: Odom’s precedent.](image)
While this result is interesting, when thinking of catalysts for our transformation we realized that it was important to focus on transition metals known to support reactive metallonitrenes and reactive metallocarbenes. We were especially drawn to the Rh(II) paddlewheel complexes as the Padwa group has reported that these complexes are capable of catalyzing analogous metallocarbene/ alkyne cascade reactions.\(^\text{63}\)

### 4.5.2 Metallonitrene/ Alkyene Cascade Reactions: Preliminary results.

Aaron Thornton in our group was able to show that when test substrate 1, containing a sulfamate ester with an alkyne positioned six atoms away from the nitrogen atom and a benzyl ether tether to trap the transient carbene, was exposed to an oxidant in the presence of catalytic \(\text{Rh}_2(\text{TPA})_4\) it reacted to form a bicyclic imine product 2 (Scheme 4.12).\(^\text{64}\) Though this product could be isolated, it displayed a propensity to hydrolyze on silica gel leading us to adopt a reductive work-up for subsequent reactions.

**Scheme 4.12:** Initial result of the reaction of 1 with a Rh(II) catalyst.

Mechanistically, formation of a seven membered ring by cyclization at the distal carbon of the alkyne precludes a [2+2] metathesis mechanism.
Thus, we propose that the alkyne attacks the electrophilic nitrene intermediate 3 generating transient vinyl cation 4 (Scheme 4.13). This species could undergo a 1,3-metal shift and be in equilibrium with metallocarbene 5. This is followed by formation of oxonium ylide 6 and 1,2 benzyl migration furnishes product 2.

4.5.3 Reaction Scope.

While this result was unexpected and did not match our proposed reaction, it revealed unprecedented reactivity for a metallonitrene species and led to the diastereoselective formation of new C-N, C-O and C-C bonds in a single step. This prompted us to investigate the scope of this reaction.

Aaron’s work demonstrated that this intramolecular metallonitrene/alkyne cascade reaction was effective for the cyclization of a variety of sulfamate esters derived for homopropargylic alcohols (Scheme 4.14).64 Indeed, 7,5 and 7,6 bicyclic ring systems were readily assembled and both benzyl and allyl units were transferred in the cascade process. In addition, alkyl and aryl were tolerated at either end of the alkyne and the imine can be reduced or trapped with Grignard reagents in situ diastereoselectively. In all cases, the cyclization occurred at the distal carbon of the alkyne.
4.5.4 Nature of the Reactive Intermediate.

Having established the viability of a metallonitrene/ alkyne cascade reaction, we decided to focus our attention on the nature of the reactive intermediate (transient vinyl cation 4 or the isomeric α-iminometallocarbene 5, Scheme 4.13) and its potential for cascading into a diverse range of C-C, C-O and C-N bond forming reactions. In doing so, we were particularly interested in the reactivity of the intermediate with π-nucleophiles.

The following chapter will describe our efforts to study the nature of the reactive intermediate as well as our efforts to expand the synthetic potential of our newly developed reaction.
5. Chapter Five: Results and Discussion.

5.1. Preliminary Results.

Preliminary results by Aaron Thornton had demonstrated that it was possible to use \(\pi\)-nucleophiles for the cascade termination reaction. Thus, having an alkene tethered to the alkyne led to the formation of a cyclopropanation product 7 (eq. 1, Scheme 5.1), whereas a tethered phenyl ring led to the formation of Friedel-Crafts type product 8 (eq. 2, Scheme 5.1).\(^4\)

![Scheme 5.1: Preliminary results with \(\pi\)-nucleophiles.](image)

We wanted to determine the scope of these transformations in terms of the substitution pattern of the alkene nucleophile as well as the type of functional groups tolerated (Figure 5.2). In addition, we were also interested in whether a heteroaromatic nucleophile, such as a furan, could engage in a cascade termination process.
Figure 5.1: Extension of the substrate scope.

5.2. Synthesis of the Starting Homopropargylic Sulfamate Esters.

5.2.1 Initial Approach.

The desired homopropargylic sulfamate esters were envisioned to arise from the corresponding alcohols 9 which in turn would be synthesized by nucleophilic displacement of the corresponding iodide with terminal alkyne 10 (Scheme 5.2).

Scheme 5.2: Retrosynthetic analysis for the formation of homopropargylic sulfamate esters.

However, when either compound 11 or 12 was reacted with the lithium anion of alkyne 10 the desired reaction was not observed and the starting alkyne 10 was recovered (Scheme 5.3). A variety of conditions were investigated, including different protecting groups on the homopropargylic alcohol as well as different solvent mixtures and additives but none afforded the desired product. When β-iodoethylfuran 13 was subjected
to the reaction conditions, the desired product 15 was isolated in 8 % yield along with starting alkyne 14.

Scheme 5.3: Attempts to couple alkynes 10 and 14 with iodides 11, 12 and 13.

We hypothesized that the lack of desired reactivity could be attributed to an elimination reaction occurring, leading to stable, conjugated products (Scheme 5.4). This was further supported by our inability to recover any of the starting iodide suggesting the formation of volatile butadiene derivatives.

Scheme 5.4: Competitive elimination reaction.
5.2.2 Alternative Route to Access the Homopropargylic Esters.

To avoid the elimination problem, an alternative route was envisioned through a 1,4 Michael addition of alkyne 14 on the appropriate α,β-unsaturated carbonyl compound (Scheme 5.5). The resulting carbonyl could then be functionalized through known olefination reactions such as a Wittig reaction.

Scheme 5.5: Strategy for an alternative route.

To our delight, the reaction of methyl vinyl ketone with alkyne 14 in the presence of catalytic [RuCl₂(p-cymene)]₂ yielded the desired ketone 16 in 57 % yield (Scheme 5.6). In addition, the reaction of acrolein with alkyne 14 also produced the desired product 17 in 39 %.

Scheme 5.6: Synthesis of ketone 16 and aldehyde 17.
With ketone \( \text{16} \) in hand, we proceeded with the synthesis of sulfamate ester \( \text{18} \). Reaction with methylenetriphenylphosphine afforded olefin \( \text{19} \) in 55 % yield (Scheme 5.7) and was followed by deprotection of the alcohol moiety with TBAF and formation of sulfamate ester \( \text{18} \). Sulfamate ester \( \text{20} \) was synthesized in a similar fashion from silyl ether \( \text{21} \), which in turn was accessed from aldehyde \( \text{17} \) through a Horner-Wadsworth-Emmons reaction.

![Scheme 5.7: Synthesis of sulfamate esters 18 and 20.](attachment:image.png)

In an effort to introduce an electron rich substituent, a Wittig reaction was performed with aldehyde \( \text{17} \) and phosphonium salt \( \text{22} \) (Scheme 5.8). However, the reaction gave an inseparable mixture of \( \text{cis} \) and \( \text{trans} \) olefins \( \text{23} \). Given these separation difficulties, we undertook the synthesis of similar substrates with a longer tether length (\textit{vide infra}).
5.2.3 Elongation of the Tether Between the Alkyne and the Nucleophile.

In addition to investigating the formation of 7,5 fused ring systems, we were also interested in accessing 7,6 ring systems, as had been previously done for the oxomium ylide cascade termination process. To that effect, it was necessary to install an extra carbon between the alkyne and the tethered nucleophile. We hypothesized that this extra carbon would enable us to use the initial approach envisioned for the synthesis of the desired homopropargylic sulfamate esters (Scheme 5.2). We reasoned that the extra carbon would favor the nucleophilic displacement of iodide over its elimination.

Indeed, subjecting the lithium anion of alkyne 24 to iodide 25 in a THF/ DMPU mixture afforded the desired alkene 26 (Scheme 5.9). The yield for this reaction was initially between 40 and 50 %, however with longer reaction times and a higher ratio of DMPU in THF (from 4:1 to 3:1) we were able to increase the yield to 63 % (and above 80 % for other substrates, Scheme 5.10). With 26 in hand, deprotection of the THP acetal produced alcohol 27 that was subjected to standard sulfamate ester formation conditions to give compound 28.
We were able to synthesize sulfamate esters 29, 30, and 31 in a similar fashion from iodides 32, 33 and 34 (Scheme 5.10).

Scheme 5.10: Synthesis of sulfamate esters 29, 30 and 31.
5.3. Cyclization Reactions with π-Nucleophiles.

5.3.1 Formation of 7,5-Ring Systems.

Reaction of sulfamate ester 18 under standard cyclization conditions, i.e. 2 mol % of Rh$_2$(esp)$_2$ with 1.1 equivalents of PhI(OAc)$_2$ in CH$_2$Cl$_2$ followed by reductive work up with NaBH$_4$, led to the clean formation of a single compound 35 in 85 % yield (Scheme 5.11).

![Scheme 5.11: Cyclization of sulfamate ester 18.](image)

Compound 35 was fully characterized by 1D and 2D NMR experiments and its relative stereochemistry was determined by NOE experiments (Figure 5.2). Irradiation of H$_a$ produced key NOE interactions with all the protons on the same side of the molecule while irradiation of the cyclopropane protons produced NOE interactions with the protons on the other side of the molecule. Thus, the facial selectivity of the imine reduction can be explained by the steric congestion of the adjacent cyclopropane that block the bottom face.
On the other hand, reaction of sulfamate ester 20 under standard conditions only led to the formation of a mixture of unidentified products (Scheme 5.12). This result is consistent with the results obtained by Aaron Thornton in his studies on the substrate scope of the Friedel-Crafts termination reaction. He determined that an electron-withdrawing group on the aromatic tether significantly decreased the yield of the reaction. Thus, our observations suggest that electron-poor π-nucleophiles are not as reactive in our metallonitrene/alkyne cascade reaction.

Scheme 5.12: Attempts to cyclize sulfamate ester 20.
5.3.2 Formation of 7,6-Ring Systems.

Reaction of sulfamate ester 31 under standard conditions led to the formation of an unstable $\alpha,\beta,\gamma,\delta$-unsaturated aldehyde product 36 in 47 % yield (Scheme 5.13).

![Scheme 5.13: Cyclization of sulfamate ester 31.]

Although initially surprising, this product is consistent with a cyclopropanation/rearrangement reaction on the furan and such a reaction is preceded in the carbene chemistry literature (Scheme 5.14). Thus, the proposed mechanism for the formation of product 36 involves the initial cyclization of the alkyne with the metallonitrene species 37, followed by cyclopropanation of the pendant alkene leading to the formation of a 7,6 fused ring system 38 which rearranges through a ring expansion to produce 36.

![Scheme 5.14: Proposed mechanism for the formation of compound 36.]

More interestingly, when sulfamate ester 28 was submitted to the standard cyclization conditions two products were isolated (Table 5.1). Compound 39, the expected product, was produced in 47 % yield along with compound 41, identified by X-ray crystallography as a regioisomer of 39, in 39 % (Entry 1). Indeed, compound 41 is the product resulting from the initial cyclization of the metallonitrene species onto the proximal carbon of the alkyne and was obtained as a 1.1: 1 mixture of diastereomers.

![Catalyst Structures](image)

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Reduction</th>
<th>39 (%)</th>
<th>40 (%)</th>
<th>41 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh₂(esp)₂</td>
<td>DCM</td>
<td>RT</td>
<td>NaBH₄, MeOH, RT</td>
<td>47</td>
<td>0</td>
<td>39</td>
</tr>
<tr>
<td>Rh₂(esp)₂</td>
<td>DCM</td>
<td>-20</td>
<td>NaBH₄, MeOH, RT</td>
<td>66</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>Rh₂(OAc)₄</td>
<td>DCE</td>
<td>75</td>
<td>NaBH₄, MeOH, RT</td>
<td>28</td>
<td>0</td>
<td>58</td>
</tr>
<tr>
<td>Rh₂(esp)₂</td>
<td>DCM</td>
<td>-25</td>
<td>DIBAL-H, -25 °C</td>
<td>10</td>
<td>39</td>
<td>24</td>
</tr>
</tbody>
</table>

Table 5.1: Cyclization of sulfamate ester 28: optimization studies on the selectivity of the cyclization and reductions steps.

A short study showed that 2 mol % of Rh₂(esp)₂ with 1.1 equivalents of Phl(OAc)₂ in CH₂Cl₂ were still the optimal conditions but carrying out the reaction at -30 °C allowed for the formation of compound 39 in 66 % (Entry 2). Interestingly, using Rh₂(OAc)₄ in DCE at 75 °C inverted the selectivity and compound 41 was obtained in 58 % yield (Entry 3). In addition, it was found that using DIBAL-H instead of NaBH₄ during the reductive work-up favored the formation of the other diastereomer 40, albeit with modest selectivity (4:1 in favor of compound 40). This can be explained by the
structure of 7,6-bicyclic imine 42 where an axial hydride delivery will be favored for a small hydride reagent whereas an equatorial delivery will be preferred with a larger reductant to avoid 1,3-diaxial interactions. However, the presence of the cyclopropane offers some steric congestion on the bottom face, explaining why the selectivity with DIBAL-H is lower (Figure 5.3). In addition, the relative stereochemistry of diastereomer 41 was determined by NOE experiments. Irradiation of Hₐ produced NOE interactions with all the protons on the face opposite to that of the cyclopropane. The stereochemistry of diastereomer 40 was deduced from its characterization and comparison to compound 41.

Figure 5.3: Explanation for the facial selectivity of the reduction and determination of the relative stereochemistry of compound 41.

As for sulfamate esters 29 and 30, both afforded the desired products 43 and 44 in 70 % and 42 % yield respectively (Scheme 5.15). In addition, the reaction with sulfamate ester 30 also produced regioisomer 45 in 21 % yield. More importantly, for both substrates the geometry of the olefin was transferred onto the cyclopropane (as determined by X-Ray crystallography), suggesting that the cyclopropanation step takes place in a concerted fashion.
Scheme 5.15: Cyclization of sulfamate esters 29 and 30.

5.3.3 Nature of the Reactive Intermediate.

These results led us to reconsider the nature of the reactive intermediate. We had initially hypothesized that the intermediate was best represented as a vinyl cation 4 that may be in equilibrium with its isomeric α-iminometallocarbene 5 (Scheme 4.13). Aaron’s results with aromatic tethers have led us to exclude the later species as a reactive intermediate. On the other hand, the fact that the initial cyclization of the metallonitrene species with the alkyne can occur on both the proximal and distal carbon led us to hypothesize that the intermediate was more accurately represented as a highly strained, electrophilic rhodium bound azirine-like species 45. As has been shown with the related aziridine chemistry, the sulfamate ester tether imparts a strong bias for nucleophilic attack at the internal position of the azirine. However, in cases where the tether length prevents efficient orbital overlap between the nucleophile and the internal position of the aziridine, the attack occurs on the other carbon to form the alternate regioisomer, as is the
case with sulfamate esters 28 and 30. Computational studies will be necessary to gain a better understanding of the exact nature of the reactive intermediate, such as whether vinyl cations 4 and 46 are discrete intermediates, but additional results further in this chapter are in agreement with our mechanistic hypothesis.

**Scheme 5.16**: Nature of the reactive intermediate.

5.4. *Synthesis of Pyrrolidine Substrates.*

Having established that a variety of complex products can be synthesized from relatively simple starting materials using our metallonitrene/ alkyne reaction, we were interested in demonstrating that these oxathiazepane products are useful synthetic intermediates.

It has been shown that nitrogen acylation of cyclic sulfamates activates them towards nucleophilic displacement of sulfur trioxide. Thus, we were able to demonstrate that after protection with CbzCl, reaction of 47 with NaI in acetone produced iodide 48 by sulfur trioxide extrusion in 61 % yield (Scheme 5.17). Reaction of 48 with NaH in THF led to ring closure to give pyrrolidine-derived product 49 in 52 % yield.
Scheme 5.17: Synthesis of a pyrrolidine product through SO$_3$ extrusion and nucleophilic displacement of iodide from oxathiazepane 47.

We were also able to show that this two-step sequence can be achieved in one pot by carrying out the reaction in DMF to obtain pyrrolidine 49 in 57 % yield (Scheme 5.18).

Scheme 5.18: Development of a one-pot procedure for the synthesis of pyrrolidine 49 from oxathiazepane 47.

5.5. Efforts to Develop an Enantioselective Version of Our Metallonitrene/Alkyne Reaction.

With an effective method for the formation of a variety of C-N bonds established, we became interested in developing an enantioselective version of our metallonitrene/alkyne reaction. Thus far, this transformation had been done with an achiral catalyst generating one diastereomer. Given the diversity of dirhodium(II) paddlewheel
complexes available, we hypothesized that we could use this to our advantage and investigate the influence of the type of ligands around the metal on imparting enantioselectivity on our reaction.\textsuperscript{59} In addition, considering that the regioselectivity of the initial cyclization step was somewhat dependant on the tethered nucleophile, we reasoned that the enantioselectivity might also be influenced by the nucleophile. We therefore decided to investigate the reactivity of several substrates, with different tethered nucleophiles, with a variety of Rh(II) catalysts.

5.5.1 Enantioselectivity studies of the metallonitrene/ alkyne oxonium ylide cascade with substrate 50.

When sulfamate ester 50\textsuperscript{64} was subjected to a variety of Rh(II) catalysts (Table 5.2), it displayed modest reactivity with all the catalysts tested to give the expected cyclization product 51 in all cases, except with Rh\textsubscript{2}(S-nap)\textsubscript{4}. With the latter, the only product 52 isolated from the reaction mixture corresponded to that of a C-H amination reaction at the propargylic position.
Table 5.2: Enantioselectivity studies of the metallonitrene/alkyne oxonium ylide cascade with substrate 50.

Thus with substrate 50, the best enantioselectivity observed was of 56 % e.e. with Rh$_2$(S-biTISP)$_2$.

5.5.2 Enantioselectivity studies of the metallonitrene/alkyne cyclopropanation cascade with substrate 18.

When examining the reactivity of sulfamate ester 18, with a different nucleophilic tether, it appeared that it too yielded the expected cyclized compound 35 with modest levels of selectivity (Table 5.3).
Table 5.3: Enantioselectivity studies of the metallonitrene/ alkyne cyclopropanation cascade with substrate 18.

In this case though, the enantioselectivity was significantly lower and Rh₂(S-biTISP)₂ and Rh₂(S-DOSP)₄ were equally selective (22 % e.e. and 25 % e.e. respectively). In addition, with this substrate Rh₂(S-nap)₄ was capable of catalyzing the reaction to give product 35 in 39 % yield and only 9 % e.e.

5.5.3 Enantioselectivity studies of the metallonitrene/ alkyne cyclopropanation cascade with substrates 29 and 30.

Having observed the influence of the tether length on the outcome of the cyclization cascade (vide supra), we wanted to investigate its influence on the enantioselectivity. Thus, in addition to sulfamate ester 18 we also employed sulfamate esters 29 and 30 with Rh(II) chiral catalysts.

As shown in tables 5.4 and 5.5, the reactions with both sulfamate esters 29 and 30 were enantioselective with all the catalysts tested. However, as observed with substrate
50, the reactions with Rh₂(S-nap)₄ yielded the products resulting from C-H amination at the propargylic position (with trace amounts of desired cyclized product 43 for substrate 29). In addition, the enantioselectivity for all the reactions remained low and while the best results were obtained with Rh₂(S-DOSP)₄ for substrate 29 (33 % e.e.), it was Rh₂(S-biTISP)₂ that gave the best result (40 % e.e.) for substrate 30.

![Diagram of the reaction](image)

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>e.e (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh₂(S-DOSP)₄</td>
<td>DCM</td>
<td>42</td>
<td>33</td>
</tr>
<tr>
<td>Rh₂(S-DOSP)₄</td>
<td>Hexanes</td>
<td>n. r.</td>
<td>n.d.</td>
</tr>
<tr>
<td>Rh₂(S-DOSP)₄</td>
<td>Toluene</td>
<td>33</td>
<td>30</td>
</tr>
<tr>
<td>Rh₂(S-biTISP)₂</td>
<td>DCM</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>Rh₂(S-PTAD)₄</td>
<td>DCM</td>
<td>56</td>
<td>18</td>
</tr>
<tr>
<td>Rh₂(S-nap)₄</td>
<td>DCM³</td>
<td>traces²</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

*³ reaction done with Ph=O and 3Å MS
² C-H amination product also observed.

Table 5.4: Enantioselectivity studies of the metallonitrene/ alkyne cyclopropanation cascade with substrate 29.
In light of all of these results, it appears that the enantioselectivity of the metallonitrene/alkyne cascade reaction is extremely substrate dependant. None of the chiral catalysts studied were particularly reactive towards our reaction. Given that Rh(II) paddlewheel complexes are known to be tuned towards a very specific type of reaction (vide supra), these results are not surprising.

Therefore, we decide to devote our efforts to developing a catalyst that would be specifically tuned towards the metallonitrene/alkyne cascade reaction.

**Table 5.5:** Enantioselectivity studies of the metallonitrene/alkyne cyclopropanation cascade with substrate 30.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>44 (%)</th>
<th>e.e. 44 (%)</th>
<th>53 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh₂(S-DOSP)₄</td>
<td>45</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Rh₂(S-biTISP)₂</td>
<td>12</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Rh₂(S-PTAD)₄</td>
<td>40</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rh₂(S-nap)₄*</td>
<td>0</td>
<td>0</td>
<td>&lt; 10</td>
</tr>
</tbody>
</table>

* reaction done with Ph=O and 3Å MS
5.6. Tuning the Selectivity via Catalyst Development.

5.6.1 Objectives of Catalyst Development.

As we turned our attention to catalyst development, we had two objectives in mind. We wanted to develop a catalyst that was chemoselective for our metallonitrene/alkyne reaction and we were interested in expanding the scope of the nitrene precursors employed.

Intramolecular competition experiments are an excellent way to directly compare the chemoselectivity of any given catalyst. Thus, we became interested in adding a level of complexity in the substrates investigated by adding a carbon between the alkyne and the tethered nitrene source (Scheme 5.19). In that case, a C-H insertion amination reaction becomes a competitive pathway to the metallonitrene/alkyne cascade reaction and as stated earlier, such substrates allow for the direct comparison of a catalyst’s chemoselectivity.

Scheme 5.19: Competition between C-H amination and metallonitrene/alkyne cyclization.
Carbamates are known nitrene precursors. They undergo regioselective C-H amination reactions to form 5-membered ring oxazolidines (Scheme 5.20). In addition to forming synthetically useful products, it has been shown that carbamates can also be pre-oxidized (X=OTs). This avoids the use of an external oxidant in the reaction and can allow for substrates with sensitive functionalities to be used. With this in mind, we became interested in whether carbamates could be used as nitrene precursors in the metallonitrene/ alkyne cascade reaction.

Scheme 5.20: Regioselectivity of C-H amination reactions.

5.6.2 Carbamates as Nitrene Precursors in the Metallonitrene/ Alkyne Reaction.

Having observed mostly cyclization at the distal alkyne carbon to form 7-membered ring with sulfamate ester, we hypothesized that, similarly to C-H amination chemistry, carbamates might cyclize to afford 6-membered ring product (Scheme 5.21).

Scheme 5.21: Regioselectivity in metallonitrene/ alkyne cascade reactions.
However, so far we have been unable to observe any kind of reactivity with carbamates under a variety of conditions including using both pre-oxidized and non pre-oxidized carbamates and investigating different Rh(II) catalysts (Scheme 5.22).

\[
\text{Rh(II): Rh}_2(\text{esp})_2, \text{Rh}_2(\text{TPA})_4, \text{Rh}_2(\text{tfacam})_4
\]

**Scheme 5.22:** Carbamates display no reactivity in the metallonitrene/ alkyne cascade reaction

We hypothesized that these failures might be to the fact that, with only one carbon between the alkyne and the carbamate, once the nitrene forms it cannot align properly with the alkyne to react (as shown in 55, Scheme 5.22). Thus, we envisioned that adding a carbon might allow for better alignment and this brought us back to the initial chemoselectivity study that we intended to do (*vide supra*).

### 5.6.3 Chemoselectivity Studies With Rh(II) Tetracarboxylate Complexes.

In order to evaluate the chemoselectivity of Rh(II) catalysts towards the metallonitrene/ alkyne reaction, sulfamate ester 56 was synthesized using a route previously developed for similar substrates (Scheme 5.23). Sonogashira coupling of 2-iodobenzylalcohol with alkyne 57 produced alcohol 58 in 80 % yield. Reaction with allyl bromide yielded allyl ether 59 in 81 % yield. Deprotection of silyl ether 59 was followed by sulfamate ester formation to produce compound 56 in 84 %.
Scheme 5.23: Synthesis of sulfamate ester 56.

Carbamates 60 and 61 were synthesized in a similar fashion from alcohol 62 (Scheme 5.24).

Scheme 5.24: Synthesis of carbamates 60 and 61.

With sulfamate ester 56 in hand, the first catalyst to be investigated was Rh$_2$(esp)$_2$, which is the catalyst of choice for our cyclization reaction. However, it only produced C-H amination product 63 in 37 % yield (Scheme 5.25). Considering that this catalyst has been tuned for C-H amination reactions, this result is not surprising.
When carbamates 60 and 61 were subjected to the reaction conditions, they both displayed significantly reduced reactivity. After 48h we were able to isolate only trace amounts of C-H amination product 64 with carbamate 60. We therefore decided to concentrate our efforts on investigating the chemoselectivity with sulfamate ester 56.

![Scheme 5.25: Cyclization of sulfamate ester 56 and carbamates 60 and 61 with Rh₂(esp)₂.](image)

Moving on to another catalyst, Rh₂(TPA)₄, which has been reported to be more reactive towards π-bonds,70 we were able to isolate not only cyclized product 65 and the C-H amination product 63 but also a product corresponding to the aziridination of the alkene 66. The formation of 8-membered ring product 65 was initially surprising. We had hypothesized that the formation of a 7-membered ring (such as 54, Scheme 5.19) would be favored. However this result is consistent with the formation an azirene intermediate with the nucleophile attacking at the internal position leading to the unusual selective
formation of an 8-membered ring product (Scheme 5.16). Noticing that the reductive work-up with NaBH₄ was yielding both diastereomers and thus hampering the clean isolation of the cyclized product, we opted to forgo such a work-up in order to facilitate the optimization studies (Table 5.6). These showed that the C-H amination product 63 remained the major product in the reaction.

![Chemical structure diagram]

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DCM</td>
<td>RT</td>
<td>25 %</td>
<td>1: trace: 0</td>
</tr>
<tr>
<td>DCM</td>
<td>40 °C</td>
<td>72 %</td>
<td>3.4: 0.7: 1</td>
</tr>
<tr>
<td>CF₂C₆H₅</td>
<td>RT</td>
<td></td>
<td>2.2: 0.55: 1</td>
</tr>
<tr>
<td>CF₂C₆H₅</td>
<td>40 °C</td>
<td>83 %</td>
<td>2.6: 1.3: 1</td>
</tr>
</tbody>
</table>

**Table 5.6: Optimization studies with Rh₂(TPA)₄.**

In addition, a brief survey of reagents showed that a reductive work-up with L-selectride at -78 °C allowed for the exclusive formation of diastereomer 67. Its configuration was determined by NOE experiments (Scheme 5.26) corresponding to the reduction with a large reductant occurring on the opposite side of the allyl moiety. The lack of selectivity with NaBH₄ can be explained by the increased ring size. With an 8-membered ring, even though the allyl group does offer some steric bias, with a small reductant it appears not to be enough.
Despite being a step in the right direction, the results with Rh$_2$(TPA)$_4$ were not satisfactory and ultimately we decided to investigate a different type of ligand on the Rh(II) catalyst.

5.6.4 Chemoselectivity Studies With a Rh(II) Tetracarboxamidate Catalyst.

Rh$_2$(tfacam)$_4$, a tetracarboxamidate Rh(II) catalyst, has also been shown to display an enhanced reactivity towards π bonds.$^{52}$ We therefore decided it would a good candidate for our chemoselectivity studies.

To our delight, Rh$_2$(tfacam)$_4$ was indeed more selective in favor of the metallonitrene/ alkyne cascade reaction. We decided to embark into a brief optimization study, exploring a variety of solvents and oxidants (Table 5.7).
Table 5.7: Optimization studies with Rh$_2$(tfacam)$_4$.

The best selectivity was obtained in CH$_2$Cl$_2$ at 40 °C with a 4:1 ratio in favor of the metallonitrene/alkyne cascade product 65 in 51% overall yield (Entry 2, Table 5.7). Albeit better, this selectivity remained too low to be synthetically useful. We realized that in order to improve the selectivity we had to design a catalyst specifically tuned towards our reaction.

5.6.5 Catalyst Design.

In order to design a new catalyst tuned towards the metallonitrene/alkyne cascade reaction, we first considered the features of the two catalysts, Rh$_2$(esp)$_2$ and Rh$_2$(tfacam)$_4$, that have been successful for the metallonitrene/alkyne reaction.
Figure 5.4: Structural features of Rh$_2$(esp)$_2$ and Rh$_2$(tfacam)$_4$.

Rh$_2$(esp)$_2$, which has been a very successful catalyst for reactions where chemoselectivity was not an issue, has two bridged dicarboxylate ligands (Figure 5.4). To further increase the stability of this catalyst, a gem-dimethyl group was installed at the alpha position of the carboxylate moiety.$^{54}$ Rh$_2$(tfacam)$_4$, on the other hand, possesses four carboxamidate ligands. The increased electron density at the metal center provided by the amide functionality can increase the capacity of the metal for backbonding to the π-acidic nitrene but it also lowers their oxidation potential thus favoring a one-electron oxidation to a Rh$^{2+}$/Rh$^{3+}$ dimer in the presence of hypervalent iodine oxidants. However, the donating capacity of the carboxamidate ligand can be attenuated by an electron-withdrawing α-trifluoromethyl substituent also increasing the oxidation potential of the complex.$^{52,58}$

Thus, we hypothesized that a catalyst 68 with two bridged dicarboxamidate ligands would favor the desired reaction. In addition, to tune the electronics and help stabilize the catalyst we envisioned that we could replace the gem-dimethyl group by a gem-difluoro or gem-bis(trifluoromethyl) group.
5.6.6 Synthesis of Ligand 69.

In order to design a route for the synthesis of ligand 69, we considered the synthesis of the esp ligand (Scheme 5.27). However, reactions of 1,3-bis(chloromethyl)benzene with the appropriate cyano or ester reagents were not pursued due to the strong aptitude of the fluoride substituent to undergo elimination to more stable alkene or carbene compounds when α to a cation.\(^7\)

![Scheme 5.27: Synthesis of the esp ligand.](image-url)
Instead, we envisioned ligand 69 arising from non-fluoronated diester 70 since there a number of literature precedent for the sequential or direct electrophilic difluorination α to ester groups (Scheme 5.28).

\[\begin{align*}
\text{H}_2\text{N} & \quad \text{F} \quad \text{F} \quad \text{F} \quad \text{NH}_2 \\
\text{O} & \quad \text{MeO} \quad \text{F} \quad \text{F} \quad \text{OH}_2 \quad \text{F} \\\n\text{O} & \quad \text{OMe} \quad \text{F} \quad \text{F} \quad \text{O} \\
\text{OMe} & \quad \text{MeO} \quad \text{F} \quad \text{F} \quad \text{OMe} \quad \text{F} \quad \text{OH}_2 \quad \text{F} \\
\text{MeO} & \quad \text{OMe} \quad \text{F} \quad \text{F} \quad \text{OMe} \quad \text{F} \quad \text{OH}_2 \quad \text{F} \\
\text{O} & \quad \text{OTBS} \quad \text{TBS} \quad \text{O} \\
\text{O} & \quad \text{OTBS} \quad \text{TBS} \quad \text{O} \\
\text{LiHMDS}, & \quad (\text{PhSO}_2)_2\text{NF} \quad \text{THF, 61%} \\
\text{OTBS} & \quad \text{TBS} \quad \text{O} \\
\text{KHMD} & \quad (\text{PhSO}_2)_2\text{NF} \quad \text{THF/Toluene, 57%} \\
\text{MnBr}_2 & \quad \text{THF/Toluene, 70%} \\
\text{O} & \quad \text{OTBS} \quad \text{TBS} \quad \text{O} \\
\end{align*}\]

**Scheme 5.28:** Retrosynthetic analysis for the synthesis of 69.

Compound 71 was synthesized by a Heck reaction of 1,3-dibromobenzene with methyl acrylate followed by hydrogenation of the olefins to give saturated diester 70 (Scheme 5.29). At this stage, we attempted to introduce the gem-difluoro moiety. We investigated conditions developed for the sequential addition of the fluoride substituents as well as conditions developed for a direct difluorination reaction. However in both cases the reactions were low yielding, with the best yield of 13% obtained for a direct difluorination reaction to give 71, and mixtures of mono- and di-fluorination products
were obtained. In addition these products were difficult to separate by column chromatography.

Scheme 5.29: First route attempted for the synthesis of novel ligand 69.

We therefore turned our attention to an alternative route. In the course of discussions with the Du Bois group, we realized that they had been directing their investigations towards the synthesis of the same novel ligand. They had discovered that adding a meta tert-butyl group increases the solubility of diamide 72 thus facilitating its purification. In addition, by using a Reformatsky reaction as the key disconnection they had been able to develop a synthetic route for this ligand (Scheme 5.30).

Scheme 5.30: Alternative route for the synthesis of 72.
Thus we were able to synthesize 72 starting with 5-(t-butyl)isophthalic acid (Scheme 5.31). Reduction to the alcohol was followed by reoxidation to afford dialdehyde 73. A Reformatsky reaction generated β-hydroxyester 74. A Barton deoxygenation reaction produced diester 75 that was reacted with NH₃ in methanol to yield the desired ligand 72. Finally, ligand exchange with Rh₂(tfa)₄ in DCE at 150 °C afforded catalyst 76.

**Scheme 5.31:** Synthesis of novel catalyst 76.

### 5.6.7 Chemoselectivity Studies With Newly Developed Catalyst 76.

With this new catalyst in hand, we went ahead and tested it as a catalyst for the cyclization cascade with substrate 56 to determine its selectivity. As shown in Table 5.8, despite remaining more reactive towards π-bonds, the chemoselectivity with this catalyst
is only of 1.6:1 in favor of the metallonitrene/ alkyne cascade product 67. This selectivity is significantly lower than the one (4:1) obtained with Rh$_2$(tfacam)$_4$ and therefore remained not synthetically useful.

![chemical structure](image)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>T (°C) reaction</th>
<th>T (°C) reduction</th>
<th>Oxidant</th>
<th>Yield (%)</th>
<th>63 vs 67</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCM</td>
<td>RT</td>
<td>-78</td>
<td>Phl(OAc)$_2$</td>
<td>35</td>
<td>1: 1.6</td>
</tr>
<tr>
<td>DCM</td>
<td>40</td>
<td>-78</td>
<td>Phl(OAc)$_2$</td>
<td>33</td>
<td>1: 1.6</td>
</tr>
<tr>
<td>Toluene</td>
<td>RT</td>
<td>-78</td>
<td>Phl(OAc)$_2$</td>
<td>17</td>
<td>1: 1.4</td>
</tr>
<tr>
<td>Toluene</td>
<td>40</td>
<td>-78</td>
<td>Phl(OAc)$_2$</td>
<td>27</td>
<td>1: 2</td>
</tr>
<tr>
<td>CF$_3$-Tol</td>
<td>40</td>
<td>-30</td>
<td>Phl(OAc)$_2$</td>
<td>17</td>
<td>1: 1.3</td>
</tr>
<tr>
<td>Benzene</td>
<td>40</td>
<td>5</td>
<td>Phl(OAc)$_2$</td>
<td>20</td>
<td>1: 2.2</td>
</tr>
<tr>
<td>DCM</td>
<td>40</td>
<td>-78</td>
<td>Phl(OPiv)$_2$</td>
<td>22</td>
<td>1: 1</td>
</tr>
<tr>
<td>DCM</td>
<td>40</td>
<td>-78</td>
<td>Phl=O</td>
<td>18</td>
<td>1: 1.9</td>
</tr>
<tr>
<td>DCM</td>
<td>40</td>
<td>-78</td>
<td>Phl(OCl(O)CPh$_3$</td>
<td>25</td>
<td>1.5: 1</td>
</tr>
</tbody>
</table>

Table 5.8: Optimization studies with novel catalyst 76.

5.7. Conclusions.

Having established the viability of metallonitrene/ alkyne cascade reactions, we became interested in studying the nature of the reactive intermediate by exploring the versatility of this newly developed reaction.

We were able to show that π-nucleophiles can react in this cascade reaction to generate cyclopropanation products. 1,1 disubstituted olefins as well as 1,2 cis and trans
olefins react to generate complex 7,5,3 and 7,6,3 products from relatively simple starting materials. Heteroaromatic tethers such as furans are also reactive nucleophiles. In some cases, we observe the formation of a regioisomeric product. These results suggest that the regioselectivity of the initial cyclization is dependent on the nature of the nucleophilic tether. This led us to revisit the structure of the reactive intermediate and propose that it is more accurately represented as a highly strained, rhodium bound azirine. In addition, the geometry of the olefin is conserved in the reaction suggesting a concerted process.

Having demonstrated the versatility of the metallonitrene/alkyne cascade reaction, we became interested in developing an enantioselective version of this reaction. A survey of known Rh(II) chiral tetracarboxylate and tetracarboxamidate catalysts indicated that the enantioselectivity of the reaction is highly substrate dependent. Since none of the catalysts tested were able to impart useful levels of selectivity, we decided to focus on developing a catalyst tuned towards the metallonitrene/alkyne reaction.

During the course of our investigations, we were able to conclude that tetracarboxamidate catalysts are chemoselective with a ratio of 4 to 1 in favor of the cyclized product over the product resulting from C-H amination.

Future directions for this project include continuing to expand on the versatility of the reaction and continuing to explore catalysts for the design of a chemoselective catalyst.


$^1$H and $^{13}$C NMR spectra were recorded on a Varian Inova 600 spectrometer (600 MHz $^1$H, 150 MHz $^{13}$C) or a Varian Inova 400 spectrometer (400 MHz $^1$H, 100 MHz $^{13}$C) at room temperature in CDCl$_3$ with internal CHCl$_3$ as the reference (7.26 ppm for $^1$H and 77.23 ppm for $^{13}$C). Chemical shifts ($\delta$ values) were reported in parts per million (ppm) and coupling constants ($J$ values) in Hz. Multiplicity is indicated using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, b = broad signal. Infrared (IR) spectra were recorded using Thermo Electron Corporation Nicolet 380 FT-IR spectrometer. High resolution mass spectra were obtained using a Thermo Electron Corporation Finigan LTQFTMS (at the Mass Spectrometry Facility, Emory University). We acknowledge the use of shared instrumentation provided by grants from the NIH and the NSF. Melting points (mp) were taken using a Fisher-Johns melting point apparatus and are not corrected. Analytical thin layer chromatography (TLC) was performed on precoated glass backed EMD 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light or ethanolic anisaldehyde, followed by heating. Flash column chromatography was carried out using EMD Geduran® silica gel 60 (40-63 $\mu$m).

All reactions were conducted with anhydrous solvents in oven dried or flame-dried and argon charged glassware. Anhydrous solvents were purified by passage through activated alumina using a Glass Contours solvent purification system unless otherwise noted.
Benzene, DMA, and DMF were dried over activated 4 Å molecular sieves. Acetone was purified by distillation from CaCl₂. Solvents for workup, extraction and column chromatography were used as received from commercial suppliers. All reagents were purchased from Sigma-Aldrich and used as received unless otherwise noted. Bisacetoxyiodobenzene was dried under vacuum (0.02 mmHg) for 12 hours prior to use. Pyridine, pyrrolidine, 2,6 lutidine, and DMPU were purified by distillation from calcium hydride. [RuCl₂(p-cymene)₂]₂ was purchased from Strem. Rhodium catalysts were purchased from Sigma-Aldrich and used as received.

6.2. General Procedures.

General procedure A for the preparation of sulfamate esters: Formic acid (2.5 equiv.) was added to neat chlorosulfonyl isocyanate (2.5 equiv.) at 0 °C with stirring. The resulting white solid was dissolved in MeCN (2.0 M). The resulting solution was warmed to room temperature and stirred for 14 h. The reaction mixture was cooled to 0 °C and a solution of the starting alcohol (1.0 equiv.) and 2,6 lutidine (2.5 equiv.) in DMA (1.4 M) was added dropwise. The resulting mixture was warmed to room temperature and stirred until thin layer chromatography indicated complete consumption of starting material. H₂O and EtOAc were added. The organic phase was collected and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography as indicated afforded the desired sulfamate ester.
General procedure B for the preparation of homopropargylic alcohols: PPTS (0.4 equiv.) was dissolved in EtOH (0.1 M). The starting THP protected alcohol (1.0 equiv.) was added and the resulting solution was heated to 55 °C until thin layer chromatography indicated complete consumption of starting material. The reaction mixture was cooled to room temperature and concentrated in vacuo. Purification by flash chromatography as indicated afforded the desired homopropargylic alcohol.

General procedure C for oxathiazepane synthesis: Sulfamate ester (1.0 equiv.), PhI(OAc)$_2$ (1.1 equiv.) and Rh$_2$(esp)$_2$ (2 mol %) were combined in a 2 dram vial and capped with a teflon lined septum. CH$_2$Cl$_2$ (0.175 M) was added and the reaction was stirred under argon at room temperature until thin layer chromatography indicated complete consumption of starting material. The reaction mixture was cooled to 0 °C before MeOH (0.178 M) and NaBH$_4$ (3.0 equiv.) were added. The resulting mixture was warmed to room temperature and stirred until thin layer chromatography indicated complete consumption of the sulfamoyl imine intermediate. SiO$_2$ was added and the resulting mixture was concentrated in vacuo. The silica was then eluted with CH$_2$Cl$_2$/Et$_2$O (1:1). The eluent was concentrated in vacuo and the residue was purified by flash chromatography as indicated.

Preparation of t-butyl((6-(furan-3-yl)hex-3-yn-1-yl)oxy)dimethylsilane 15:

\[
\text{n-BuLi (1.65 mL, 1.6 M in hexanes, 2.65 mmol) was added dropwise to a solution of 1-}
\]
\[(t\text{-Butyldimethylsilyloxy})\text{-3-butyne 14 (0.514 g, 2.80 mmol) in THF (2.5 mL) at -78 °C.}
\]
\[The resulting solution was warmed to -5 °C over 15 min and 3-(2-iodoethyl)furan (0.620 g, 2.80 mmol) was added followed by HMPA (0.46 mL, 2.80 mmol). The reaction mixture was then heated to 40 °C and stirred for 20 h. The reaction mixture was cooled to room temperature and saturated aq. NH}_4\text{Cl (2 mL) was then added. The mixture was extracted with Et}_2\text{O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over MgSO}_4\text{ and concentrated in vacuo. Purification by flash chromatography (10:1 \rightarrow 1:1 pentane/DCM) afforded product 15 as a yellow oil (0.066 g, 8 % yield); R}_f\text{ 0.5 (1:1 pentane/DCM); }^1\text{H NMR (CDCl}_3\text{, 400 MHz) }\delta\text{ 7.35 (s, 1H), 7.22 (s, 1H), 6.32 (s, 1H), 3.66 (t, 2H, }J = 8.0 \text{ Hz), 2.60 (t, 2H, }J = 8.0 \text{ Hz), 2.39-2.31 (m, 4H), 0.90 (s, 9H), 0.03 (s, 6H).}
\]
Preparation of 8-(t-butyldimethylsilyloxy)oct-5-yn-2-one 16:

Pyrrolidine (0.09 mL, 1.09 mmol) was added to a solution of [RuCl₂(p-cymene)₂]₂ (0.166 g, 0.272 mmol) in benzene (22 mL). The mixture was stirred at room temperature for 10 min. 1-(t-Butyldimethylsilyloxy)-3-butyne 14 (1.00 g, 5.43 mmol) was added dropwise followed by methyl vinyl ketone (1.32 mL, 16.3 mmol). The resulting mixture was heated to 60 °C for 14 h then cooled to room temperature and concentrated in vacuo. Purification by flash chromatography (20:1 → 9:1 hexanes/EtOAc) afforded product 16 as a yellow oil (0.785 g, 57% yield); Rₐ 0.63 (3:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 2954, 2928, 2856, 1719, 1361, 1254, 1101, 836; ¹H NMR (CDCl₃, 600 MHz) δ 3.67 (t, 2H, J = 7.2 Hz), 2.63 (t, 2H, J = 6.6 Hz), 2.40 (td, 2H, J = 7.2, 1.8 Hz), 2.35-2.32 (m 2H), 2.17 (s, 3H), 0.90 (s, 9H), 0.1 (s, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 207.2, 79.8, 77.8, 62.4, 43.0, 30.1, 26.1, 23.3 18.5, 13.6, -5.1; HRMS (+ESI) calculated for C₁₄H₂₇O₂Si 255.1780, found 255.1774 [M+H]⁺.

Preparation of 1-(t-Butyldimethylsilyloxy)-7-methyloct-7-en-3-yn 19:

8-(t-Butyldimethylsilyloxy)oct-5-yn-2-one 16 (0.100 g, 0.393 mmol) was added to a solution of methylenetriphenylphosphine (0.127 g, 0.452 mmol) in THF (1.5 mL) at 0 °C.
The resulting solution was warmed to room temperature, stirred for 1.5 h and then quenched with aq. HCl (10 %, 2 mL). The mixture was extracted with Et$_2$O (3 × 3 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography (20:1 → 10:1 pentane/CH$_2$Cl$_2$) afforded alkene 19 as a yellow oil (0.054 g, 55 % yield); $R_f$ 0.43 (10:1 pentane/CH$_2$Cl$_2$); IR (thin film, cm$^{-1}$) 2928, 2856, 1472, 1255, 1102; $^1$H NMR (CDCl$_3$, 600 MHz) δ 4.73 (d, 2H, $J = 23.4$ Hz), 3.69 (t, 2H, $J = 7.8$ Hz), 2.37 (m, 2H), 2.28 (m, 2H), 2.20 (t, 2H, $J = 7.8$ Hz), 1.73 (s, 3H), 0.9 (s, 9H), 0.1 (s, 6H); $^{13}$C NMR (CDCl$_3$, 150 MHz) δ 144.6, 110.8, 81.1, 77.4, 62.6, 37.3, 26.1, 23.4, 22.6, 18.6, 17.8, -5.1; HRMS (+APCI) calculated for C$_{15}$H$_{29}$OSi 253.1988, found 253.1985 [M+H]$^+$.  

**Preparation of 7-methyloct-7-en-3-yn-1-ol 77:**  

TBAF (2.46 mL, 1.0M in THF, 2.46 mmol) was added dropwise to a solution of 1-(t-butyldimethylsilyloxy)-7-methyloct-7-en-3-yn 19 (0.207 g, 0.821 mmol) in THF (3 mL) at 0 °C. The resulting solution was warmed to room temperature and stirred for 2.5 h. Saturated aq. NH$_4$Cl (5 mL) was then added. The mixture was extracted with Et$_2$O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc) afforded alcohol 77 as a colorless oil (0.059 g, 52 % yield); $R_f$ 0.79 (3:1 hexanes/EtOAc); IR (thin film, cm$^{-1}$) 3341, 2916, 1650, 1449, 1044; $^1$H NMR (CDCl$_3$, 400 MHz) δ 4.75 (d, 2H, $J = 18.0$ Hz), 3.65 (q, 2H, $J = 6.0$ Hz), 2.41 (m, 2H), 2.31 (m,
2H), 2.21 (t, 2H, \( J = 6.8 \) Hz), 1.92 (t, 1H, \( J = 6.0 \) Hz), 1.73 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 144.7, 111.0, 82.3, 77.1, 61.5, 37.2, 23.4, 22.3, 17.6; HRMS (+ESI) calculated for C\(_9\)H\(_{15}\)O 139.1123, found 139.1114 [M+H]\(^+\).

**Preparation of sulfamate Ester 18:**

![Reaction scheme]

Prepared according to general procedure A using 7-methyloct-7-en-3-yn-1-ol 77 (0.059 g, 0.428 mmol). Purification by flash chromatography (2:1 \( \rightarrow \) 1:1 hexanes/EtOAc) afforded sulfamate ester 18 as a pale yellow oil (0.057 g, 61 % yield); \( R_f \) 0.77 (1:1 hexanes/EtOAc); IR (thin film, cm\(^{-1}\)) 3380, 3284, 2920, 1556, 1360, 1177; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 4.85 (s, 2H), 4.75 (d, 2H, \( J = 19.2 \) Hz), 4.25 (t, 2H, \( J = 6.8 \) Hz), 2.63 (tt, 2H, \( J = 6.8, 2.0 \) Hz), 2.29 (m, 2H), 2.19 (t, 2H, \( J = 7.2 \) Hz), 1.73 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 144.4, 111.0, 82.7, 74.9, 69.4, 36.9, 22.5, 19.9, 17.5; HRMS (-ESI) calculated for C\(_9\)H\(_{14}\)NO\(_3\)S 216.0694, found 216.0700 [M-H]\(^-\).

**Preparation of 7-(t-butyldimethylsilyloxy)hept-4-ynal 17:**

![Reaction scheme]

\( n\)-BuLi (2.04 mL, 1.6 M in hexanes, 3.26 mmol) was added dropwise to a solution of 1-(t-Butyldimethylsilyloxy)-3-butyne 14 (0.600 g, 3.26 mmol) in THF (8 mL) at -15 °C. The reaction mixture was stirred at -15 °C for 30 min. Cul (0.684 g, 3.58 mmol) was
added and the resulting mixture was stirred at -15 °C for 1.5 h then cooled to -45 °C. TMSI (0.44 mL, 3.26 mmol) was added followed by acrolein (0.22 mL, 3.26 mmol). The resulting mixture was stirred at -45 °C for 2 h. Saturated aq. NH₄Cl (5 mL) was then added. The mixture was extracted with Et₂O (3 × 5 mL). The combined organic extracts were washed with Na₂S₂O₃ (2 × 3 mL) and brine (1 × 3 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (95:5 → 10:1 hexanes/EtOAc) afforded aldehyde 17 as a yellow oil (0.305 g, 39 % yield); Rf 0.85 (20:1 hexanes/EtOAc); H NMR (CDCl₃, 400 MHz) δ 9.78 (s, 1H), 3.67 (t, 2H, J = 7.2.4 Hz), 2.62 (t, 2H, J = 6.8 Hz), 2.49-2.46 (m, 2H), 2.34 (tt, 2H, J = 7.6, 2.0 Hz), 0.89 (s, 9H), 0.07 (s, 6H).

**Preparation of (E)-methyl 9-(t-butyldimethylsilyloxy)non-2-en-6-ynoate 21:**

LiCl (0.209 g, 4.94 mmol) were added to a solution of methyl 2-(dimethoxyphosphoryl)acetate (0.71 mL, 4.94 mmol) in MeCN (4.4 mL), followed by DBU (0.64 mL, 4.28 mmol). The reaction mixture was stirred at room temperature for 10 min then aldehyde 17 (0.790 g, 3.29 mmol) in MeCN (4.4 mL) was added dropwise. The resulting mixture was stirred at room temperature for 2 h. H₂O (5 mL) was then added. The mixture was extracted with Et₂O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over Na₂SO₃ and concentrated in vacuo. Purification by flash chromatography (40:1 → 20:1 hexanes/EtOAc) afforded alkene 21 as a
colorlessw oil (0.537 g, 55 % yield); \( R_f \) 0.66 (5:1 hexanes/EtOAc); IR (thin film, cm\(^{-1}\)) 2952, 2927, 2854, 1728, 1471, 2=1435, 1104, 836; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 6.98 (dt, 1H, \( J = 16, 4.8 \) Hz), 5.85 (d, 1H, \( J = 16 \) Hz), 3.74 (s, 3H), 3.66 (t, 2H, \( J = 8.0 \) Hz), 2.41-2.25 (m, 6H), 0.90 (s, 9H), 0.05 (s, 6H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 167.1, 147.6, 122.0, 79.7, 78.4, 62.4, 51.7, 31.8, 26.1, 23.3, 18.5, 17.9, -5.6.

**Preparation of (E)-methyl 9-hydroxynon-2-en-6-ynoate 78:**

\[ \text{TBAF (5.6 mL, 5.63 mmol)} \text{ added to a solution of} \text{ 21 (0.556 g, 1.88 mmol) in THF (6mL) at 0 °C. The resulting solution was stirred at room temperature for 3h. Saturated aq. NH}_4\text{Cl (3 mL)} \text{ was then added. The mixture was extracted with Et}_2\text{O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over MgSO}_4 \text{ and concentrated in vacuo. Purification by flash chromatography (20:1 → 1:1 hexanes/EtOAc) afforded alcohol 78 as a yellow oil (0.167 g, 49 % yield); R}_f \text{ 0.26 (2:1 hexanes/EtOAc); IR (thin film, cm}^{-1}\text{) 3430, 2950, 1720, 1658, 1435, 1272, 1158, 1039;}} \]

\(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 6.97 (dt, 1H, \( J = 15.6, 6.0 \) Hz), 5.87 (d,1H, \( J = 15.6 \) Hz), 3.72 (s, 3H), 3.66 (t, 2H, \( J = 6.0 \) Hz), 2.42-2.32 (m, 6H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 167.1, 147.4, 122.1, 80.7, 78.1, 61.5, 51.7, 31.7, 23.3, 17.9; HRMS (+ESI) calculated for C\(_{10}\)H\(_{15}\)O\(_3\) 183.1021, found 183.1011 [M+H]\(^+\).
Preparation of sulfamate ester 20:

Prepared according to general procedure A using 78 (0.167 g, 0.917 mmol). Purification by flash chromatography (3:1 → 1:1 hexanes/EtOAc) afforded sulfamate ester 20 as a pale yellow oil (0.192 g, 80 % yield); Rf 0.32 (1:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 3305, 3270, 1705, 1367, 1181; $^1$H NMR (CDCl₃, 400 MHz) δ 7.06 (dt, 1H, J = 15.6, 6.4 Hz), 5.87 (dt, 1H, J = 15.6, 1.6 Hz), 5.31 (bs, 2H), 4.24 (t, 2H, J = 6.4 Hz), 3.74 (s, 3H), 2.60 (tt, 2H, J = 6.4, 2.0 Hz) 2.41-2.31 (m, 4H); $^{13}$C NMR (CDCl₃, 100 MHz) δ 167.7, 147.9, 122.1, 80.8, 77.4, 68.8, 51.9, 31.2, 19.8, 17.9; HRMS (+ESI) calculated for C₁₀H₁₆N₂O₃S 262.0749, found 262.0743 [M+H]^+.

Preparation of 2-(non-8-en-3-ynyloxy)tetrahydro-2H-pyran 26:

$n$-BuLi (2.90 mL, 1.6 M in hexanes, 4.64 mmol) was added dropwise to a solution of 2-(but-3-ynyloxy)tetrahydro-2H-pyran 24 (0.715 g, 4.64 mmol) in a mixture of THF/DMPU (2.4:1, 17 mL) at -78 °C. The resulting solution was stirred at -78 °C for 1 h. 5-Iodopent-1-ene 25$^{75}$ (1.00 g, 5.10 mmol) was added. The reaction mixture was slowly warmed to room temperature over 6 h then stirred at room temperature for 10 h. Saturated aq. NH₄Cl (5 mL) was then added. The mixture was extracted with Et₂O (3 × 5 mL). The
combined organic extracts were washed with brine (2 × 3 mL), dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography (20:1 → 10:1 pentane/Et$_2$O) afforded the alkene 26 as a yellow oil (0.623 g, 63 % yield); $R_f$ 0.78 (5:1 hexanes/EtOAc); IR (thin film, cm$^{-1}$) 2938, 2871, 1440, 1122, 1033; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 5.75 (ddt, 1H, $J = 16.8, 10.4, 6.8$ Hz), 4.92-5.00 (m, 2H), 4.61 (t, 1H, $J = 3.2$ Hz), 3.82-3.88 (m, 1H), 3.76 (dt, 1H, $J = 9.6, 7.2$ Hz), 3.45-3.52 (m, 2H), 2.42 (tt, 2H, $J = 7.2, 2.4$ Hz), 2.10-2.15 (m, 4H), 1.77-1.85 (m, 1H), 1.64-1.72 (m, 1H), 1.45-1.60 (m, 6H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 138.1, 115.1, 98.8, 81.0, 77.2, 66.3, 62.2, 32.9, 30.7, 28.2, 25.6, 20.3, 19.5, 18.3; HRMS (+APCI) calculated for C$_{14}$H$_{23}$O$_2$ 223.1698, found 223.1667 [M+H]$^+$. 

**Preparation of non-8-en-3-yn-1-ol 27:**

Prepared according to general procedure B using 2-(non-8-en-3-ynloxy)tetrahydro-2H-pyran 26 (0.080 g, 0.360 mmol). Purification by flash chromatography (2:1 hexanes/EtOAc) afforded alcohol 27 as a colorless oil (0.039 g, 78 % yield); $R_f$ 0.39 (3:1 hexanes/EtOAc); IR (thin film, cm$^{-1}$) 3323, 2936, 2367, 2221, 1641, 1436, 1044; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 5.77 (ddt, 1H, $J = 16.8, 10.0, 6.8$ Hz), 4.94-5.04 (m, 2H), 3.66 (t, 2H, $J = 6.4$ Hz), 2.41 (tt, 2H, $J = 6.4, 2.4$ Hz), 2.11-2.19 (m, 4H), 1.98 (bs, 1H), 1.57 (qn, 2H, $J = 7.2$ Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$138.1, 115.3, 82.4, 76.8, 61.5, 33.0, 28.3, 23.3, 18.3; HRMS (+APCI) calculated for C$_9$H$_{15}$O 139.1123, found 139.1116 [M+H]$^+$. 
Preparation of sulfamate ester 28:

Prepared according to general procedure A using non-8-en-3-yn-1-ol 27 (0.332 g, 2.40 mmol). Purification by flash chromatography (4:1 → 2:1 hexanes/EtOAc) afforded sulfamate ester 28 as a light yellow oil (0.399 g, 76 % yield); \( R_f \) 0.44 (2:1 hexanes/EtOAc); \text{IR} \ (\text{thin film, cm}^{-1}) \ 3377, 3286, 2935, 1361, 1177; \text{^1H NMR} \ (\text{CDCl}_3, \ 400 \text{ MHz}) \ \delta \ 5.78 \ (\text{ddt, } 1 \text{H, } J = 16.8, 10.0, 6.8 \text{ Hz}), \ 4.96\text{-}5.05 \ (\text{m, } 4 \text{H}), \ 4.24 \ (\text{t, } 2 \text{H, } J = 6.8 \text{ Hz}), \ 2.62 \ (\text{tt, } 2 \text{H, } J = 6.8, 2.4 \text{ Hz}), \ 2.11\text{-}2.18 \ (\text{m, } 4 \text{H}), \ 1.57 \ (\text{qn, } 2 \text{H, } J = 7.2 \text{ Hz}); \text{^{13C NMR} \ (\text{CDCl}_3, \ 100 \text{ MHz}) \ \delta \ 138.1, 115.4, 82.8, 74.8, 69.4, 32.9, 28.1, 19.9, 18.2}; \text{HRMS} \ (\text{ESI}) \ \text{calculated for C}_{9}\text{H}_{14}\text{NO}_3\text{S} \ 216.0694, \ \text{found } 216.0701 \ [\text{M-H}]^-.

Preparation of (E)-2-(9-phenylnon-8-en-3-ynyloxy)tetrahydro-2H-pyran 79:

\( n\)-BuLi (14 mL, 1.52 M in hexanes, 21.3 mmol) was added dropwise to a solution of 2-(but-3-ynyloxy)tetrahydro-2H-pyran 24 (3.28 g, 21.3 mmol) in a mixture of THF/DMPU (3:1, 48 mL) at -78 °C. The resulting solution was stirred at -78 °C for 1 h. (E)-(5-iodopent-1-enyl)benzene 32 (3.86 g, 14.2 mmol) was added. The reaction mixture was stirred at -78 °C for 5 min then slowly warmed to room temperature and stirred for 18 h.
Saturated aq. NH₄Cl (30 mL) was then added. The mixture was extracted with Et₂O (3 × 30 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (5:1 → 4:1 hexanes/EtOAc) afforded alkene 79 as a colorless oil (3.44 g, 81 % yield); Rₓ 0.78 (5:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 2935, 2870, 1121, 1033; ¹H NMR (CDCl₃, 400 MHz) δ 7.25-7.32 (m, 4H), 7.16-7.20 (m, 1H), 6.39 (d, 1H, J = 16.0 Hz), 6.19 (dt, 1H, J = 15.6, 7.2 Hz), 4.64 (t, 1H, J = 3.2 Hz), 3.86-3.91 (m, 1H), 3.80 (dt, 1H, J = 9.6, 7.2 Hz), 3.48-3.55 (m, 2H), 2.47 (tt, 2H, J = 7.2, 2.4 Hz), 2.27-2.33 (m, 2H), 2.20 (tt, 2H, J = 7.2, 2.4 Hz), 1.50-1.80 (m, 8H); ¹³C NMR (CDCl₃, 100 MHz) δ 137.9, 130.6, 130.2, 128.7, 127.1, 126.1, 98.9, 81.7, 77.4, 66.4, 62.4, 32.2, 30.8, 28.8, 25.6, 20.5, 19.6, 18.4; HRMS (+ESI) calculated for C₂₀H₂₇O₂ 299.2011, found 299.2007 [M+H]⁺.

**Preparation of (E)-9-phenylnon-8-en-3-yn-1-ol 80:**

![Chemical structure](image)

Prepared according to general procedure B using (E)-2-(9-phenylnon-8-en-3-ynyl)oxy)tetrahydro-2H-pyran 79 (0.076 g, 0.254 mmol). Purification by flash chromatography (3:1 hexanes/EtOAc) afforded alcohol 80 as a colorless oil (0.034 g, 63 % yield); Rₓ 0.50 (1:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 3343, 3024, 2933, 1494, 1448; ¹H NMR (CDCl₃, 400 MHz) δ 7.27-7.35 (m, 4H), 7.17-7.21 (m, 1H), 6.41 (d, 1H, J = 16.0 Hz), 6.19 (dt, 1H, J = 15.6, 6.8 Hz), 3.68 (m, 2H), 2.42-2.46 (m, 2H), 2.28-2.33 (m, 2H), 2.23 (tt, 2H, J = 7.2, 2.4 Hz), 1.98 (bs, 1H), 1.67 (qn, 2H, J = 7.2 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 137.1, 130.7, 130.0, 128.7, 127.1, 126.1, 82.3, 77.0, 61.5, 32.2,
28.7, 23.3, 18.4; \textbf{HRMS} (+ESI) calculated for C$_{15}$H$_{19}$O 215.1436, found 215.1429 [M+H]$^+$. 

\textbf{Preparation of sulfamate Ester 29:}

Prepared according to general procedure A using (E)-9-phenylnon-8-en-3-yn-1-ol 80 (0.049 g, 0.231 mmol). Purification by flash chromatography (2:1 hexanes/EtOAc) afforded sulfamate ester 29 as a light yellow oil (0.051 g, 76 % yield); \textbf{Rf} 0.58 (1:1 hexanes/EtOAc); \textbf{IR} (thin film, cm$^{-1}$) 3381, 3286, 2927, 1364, 1181, 983, 967, 923; \textbf{$^1$H NMR} (CDCl$_3$, 400 MHz) $\delta$ 7.28-7.38 (m, 4H), 7.20-7.24 (m, 1H), 6.44 (d, 1H, $J$ = 15.6 Hz), 6.22 (dt, 1H, $J$ = 16.0, 7.2 Hz), 4.95 (bs, 2H), 4.27 (t, 2H, $J$ = 7.2 Hz), 2.66 (tt, 2H, $J$ = 7.2, 2.4 Hz), 2.30-2.35 (m, 2H), 2.34 (tt, 2H, $J$ = 7.2, 2.4 Hz), 1.69 (qn, 2H, $J$ = 7.2 Hz); \textbf{$^{13}$C NMR} (CDCl$_3$, 100 MHz) $\delta$ 137.8, 130.8, 129.9, 128.7, 127.2, 126.1, 82.8, 74.9, 69.4, 32.2, 28.5, 19.9, 18.3; \textbf{HRMS} (-ESI) calculated for C$_{15}$H$_{18}$NO$_3$S 292.1007, found 292.1014 [M-H]$^-$. 

\textbf{Preparation of (Z)-(5-iodopent-1-enyl)benzene 33:}

PPh$_3$ (1.94 g, 7.40 mmol) and imidazole (1.21 g, 9.87 mmol) were dissolved in THF (12 mL). I$_2$ (1.89 g, 7.40 mmol) was then added. The resulting dark orange mixture was stirred at room temperature for 5 min. (Z)-5-Phenylpent-4-en-1-ol 81$^{76}$ (1.00 g, 6.17
mmol) was added. The resulting mixture was stirred for 20 min and H₂O (10 mL) was added. The reaction was extracted with Et₂O (3 × 15 mL). The combined organic extracts were washed with brine (2 × 10 mL) and dried over MgSO₄. The mixture was filtered through silica gel and concentrated in vacuo to afford iodide 33 as a colorless oil (1.51 g, 90 % yield). The product was used without further purification; Rf 0.93 (2:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 3001, 1493, 1446, 1215, 696; ¹H NMR (CDCl₃, 400 MHz) δ 7.28-7.35 (m, 2H), 7.18-7.24 (m, 3H), 6.44 (d, 1H, J = 11.6 Hz), 5.57 (dt, 1H, J = 12.0, 7.6 Hz), 3.16 (t, 2H, J = 6.8 Hz), 2.41 (qd, 2H, J = 7.6, 1.6 Hz), 1.94 (qn, 2H, J = 7.6 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 130.6, 130.4, 128.9, 128.4, 126.9, 126.2, 33.9, 29.7, 6.3; HRMS (+APCI) calculated for C₁₁H₁₃I 272.0062, found 272.0050 [M]+.

Preparation of (Z)-2-(9-phenylnon-8-en-3-nyloxy)tetrahydro-2H-pyran 82:

\[
\begin{align*}
n-\text{BuLi} \quad \text{(1.31 mL, 1.6 M in hexanes, 2.00 mmol)} & \quad \text{was added dropwise to a solution of 2-(but-3-ynloxy)tetrahydro-2H-pyran 24 (0.369 g, 2.00 mmol)} \quad \text{in a mixture of THF/DMPU (4:1, 10 mL) at -78 °C. The resulting solution was stirred at -78 °C for 2 h. (Z)-(5-iodopent-1-enyl)benzene 33 (0.600 g, 2.21 mmol) was added. The reaction mixture was stirred at -78 °C for 10 min then slowly warmed to room temperature and stirred for 4 h. Saturated aq. NH₄Cl (5 mL) was then added. The mixture was extracted with Et₂O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (10:1 hexanes/EtOAc) afforded alkene 82 as a yellow oil (0.325 g, 54 % yield); Rf 0.49
\end{align*}
\]
(5:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 2938, 2870, 1441, 1352, 1121, 1031; \(^1\)H NMR (CDCl₃, 400 MHz) δ 7.27-7.35 (m, 4H), 7.20-7.24 (m, 1H), 6.42 (d, 1H, \(J = 11.6\) Hz), 5.64 (dt, 1H, \(J = 11.6, 7.2\) Hz), 4.62 (t, 1H, \(J = 2.8\) Hz), 3.85-3.91 (m, 1H), 3.77 (dt, 1H, \(J = 10.0, 7.2\) Hz), 3.48-3.53 (m, 2H), 2.39-2.45 (m, 4H), 2.19 (tt, 2H, \(J = 7.2, 2.4\) Hz), 1.49-1.84 (m, 8H); \(^{13}\)C NMR (CDCl₃, 100 MHz) δ 132.2, 129.7, 129.0, 128.3, 126.3, 98.9, 81.0, 77.5, 66.4, 62.4, 30.8, 29.4, 27.9, 25.6, 20.4, 19.7, 18.7; HRMS (+ESI) calculated C₂₀H₂₇O₂ 299.2011, found 299.2005 [M+H]+.

**Preparation of (Z)-9-phenylnon-8-en-3-yn-1-ol 83:**

Prepared according to general procedure B using (Z)-2-(9-phenylnon-8-en-3-ynyloxy)tetrahydro-2H-pyran 82 (0.370 g, 1.24 mmol). Purification by flash chromatography (2:1 hexanes/EtOAc) afforded alcohol 83 as a colorless oil (0.243 g, 91 % yield); \(R_f\) 0.60 (2:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 3345, 2931, 1493, 1446, 1433, 1042, 768, 698; \(^1\)H NMR (CDCl₃, 400 MHz) δ 7.28-7.36 (m, 4H), 7.21-7.25 (m, 1H), 6.45 (d, 1H, \(J = 12.0\) Hz), 5.65 (dt, 1H, \(J = 11.6, 7.2\) Hz), 3.63 (t, 2H, \(J = 6.4\) Hz), 2.43-2.47 (m, 2H), 2.39 (tt, 2H, \(J = 6.4, 2.4\) Hz), 2.20 (tt, 2H, \(J = 7.2, 2.4\) Hz), 2.04 (bs, 1H), 162-1.69 (m, 2H); \(^{13}\)C NMR (CDCl₃, 100 MHz) δ 137.7, 132.0, 129.7, 128.4, 128.2, 126.7, 82.0, 77.0, 61.4, 29.2, 27.8, 23.2, 18.5; HRMS (+ESI) calculated C₁₅H₁₉O 215.1436, found 215.1429 [M+H]+.
Preparation of sulfamate Ester 30:

![Chemical structure](image)

Prepared according to general procedure A using (Z)-9-phenylnon-8-en-3-yn-1-ol 83 (0.243 g, 1.13 mmol). Purification by flash chromatography (2:1 hexanes/EtOAc) afforded sulfamate ester 30 as a light yellow oil (0.230 g, 69 % yield); Rf 0.63 (2:1 hexanes/EtOAc); IR (thin film, cm\(^{-1}\)) 3382, 3284, 2931, 1554, 1493, 1363, 1180, 983.5, 920; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.28-7.36 (m, 4H), 7.22-7.25 (m, 1H), 6.45 (d, 1H, \(J=11.2\) Hz), 5.64 (dt, 1H, \(J=11.2, 7.6\) Hz), 5.08 (bs, 2H), 4.18 (t, 2H, \(J=6.8\) Hz), 2.58 (tt, 2H, \(J=7.2, 2.4\) Hz), 2.43 (qd, 2H, \(J=7.6, 1.6\) Hz), 2.19 (tt, 2H, \(J=7.2, 2.4\) Hz), 1.64 (qn, 2H, \(J=7.2\) Hz); \(^1\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) 137.7, 132.0, 129.8, 128.9, 128.3, 126.8, 82.6, 74.9, 69.2, 29.0, 27.8, 19.8, 18.4; HRMS (-ESI) calculated for C\(_{15}\)H\(_{18}\)NO\(_3\)S 292.1007, found 292.1015 [M-H]^-.

Preparation of 2-(7-(furan-3-yl)hept-3-ynoxy)tetrahydro-2H-pyran 84:

![Chemical structure](image)

\(n\)-BuLi (1.10 mL, 1.6 M in hexanes, 1.78 mmol) was added dropwise to a solution of 2-(but-3-ynoxy)tetrahydro-2H-pyran 24 (0.274 g, 1.78 mmol) in a mixture THF/DMPU (2.3:1, 10 mL) at -78 °C. The resulting solution was stirred at -78 °C for 45 min. 3-(Iodopropyl)furan 34\(^{77}\) (0.462 g, 1.96 mmol) was added. The reaction mixture was stirred at -78 °C for 5 min then slowly warmed to room temperature and stirred for 1.5 h.
Saturated aq. NH₄Cl (5 mL) was then added. The mixture was extracted with Et₂O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (10:1 hexanes/EtOAc) afforded alkene 84 as a yellow oil (0.242 g, 52 % yield); R_f 0.72 (5:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 2937, 2269, 1135, 1121, 1031; ¹H NMR (CDCl₃, 400 MHz) δ 7.31 (t, 1H, J = 1.6 Hz), 7.19 (s, 1H), 6.23 (d, 1H, J = 0.8 Hz), 4.62 (t, 1H, J = 3.2 Hz), 3.74-3.88 (m, 2H), 3.45-3.53 (m, 2H), 2.42-2.51 (m, 4H), 2.12-2.17 (m, 2H), 1.10-1.79 (m, 8H); ¹³C NMR (CDCl₃, 100 MHz) δ 142.8, 139.1, 124.3, 111.0, 98.8, 80.7, 77.5, 66.3, 62.2, 30.7, 29.2, 25.5, 23.7, 20.3, 19.5, 18.3; HRMS (+ESI) calculated for C₁₆H₂₃O₃ 263.1647, found 263.1640 [M+H]^+.

Preparation of 7-(furan-3-yl)hept-3-yn-1-ol 85:

Prepared according to general procedure B using 2-(7-(furan-3-yl)hept-3-ynyl)tetrahydro-2H-pyran 84 (0.242 g, 0.92 mmol). Purification by flash chromatography (4:1 hexanes/EtOAc) afforded alcohol 85 as a yellow oil (0.111 g, 67 %); R_f 0.56 (1:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 3357, 2935, 1501, 1044, 1024; ¹H NMR (CDCl₃, 400 MHz) δ 7.34 (t, 1H, J = 1.6 Hz), 7.22 (s, 1H), 6.26 (d, 1H, J = 0.8 Hz), 3.68 (t, 2H, J = 6.0 Hz), 2.51 (t, 2H, J = 7.6 Hz), 2.43 (tt, 2H, J = 6.0, 2.4 Hz), 2.19 (tt, 2H, J = 6.0, 2.4 Hz), 1.94 (bs, 1H), 1.74 (qn, 2H, J = 7.6 Hz); ¹³C NMR (CDCl₃, 100 MHz) δ 143.0, 139.2, 124.3, 111.1, 82.2, 77.1, 61.5, 29.3, 23.9, 23.3, 18.4; HRMS (+ESI) calculated for C₁₁H₁₅O₂ 179.1072, found 179.1064 [M+H]^+.
Preparation of sulfamate Ester 31:

Prepared according to general procedure A using 7-(furan-3-yl)hept-3-yn-1-ol 85 (0.111 g, 0.621 mmol). Purification by flash chromatography (1:1 hexanes/EtOAc) afforded sulfamate ester 31 as a yellow oil (0.143 g, 90 % yield); Rf 0.36 (3:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 3385, 2937, 1366, 1182; H NMR (CDCl₃, 400 MHz) δ 7.35 (t, 1H, J = 1.6 Hz), 7.23 (s, 1H), 6.27 (d, 1H, J = 0.8 Hz), 4.99 (bs, 2H), 4.25 (t, 2H, J = 7.2 Hz), 2.63 (tt, 2H, J = 7.2, 2.4 Hz), 2.51 (t, 2H, J = 7.6 Hz), 2.17 (tt, 2H, J = 6.8, 2.4 Hz), 1.73 (qn, 2H, J = 7.6 Hz); C NMR (CDCl₃, 100 MHz) δ 143.0, 139.2, 124.3, 111.1, 82.6, 75.1, 69.4, 29.1, 23.8, 19.6, 18.2; HRMS (-ESI) calculated for C₁₁H₁₄NO₄S 256.0644, found 256.0650 [M-H]⁻.

Preparation of oxathiazepane 35:

Prepared according to general procedure C using sulfamate ester 18 (0.056 g, 0.260 mmol). Purification by flash chromatography (4:1 → 1:1 hexanes/EtOAc) afforded oxathiazepane 35 as a white solid (0.048 g, 85 % yield); Rf 0.28 (2:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 3308, 2926, 2862, 1438, 1352, 1170; H NMR (CDCl₃, 400 MHz) δ 4.73 (d, 1H, J = 10.8 Hz), 4.38-4.46 (m, 2H), 3.90 (q, 1H, J = 10.4 Hz), 2.40 (dddd, 1H, J = 15.0, 10.0, 4.80, 1.2 Hz), 1.92 (dt, 1H, J = 13.6, 8.0 Hz), 1.79 (dd, 1H, J = 12.8, 8.0...
Hz), 1.61 (dt, 1H, \( J = 12.0, 8.0 \) Hz), 1.36 (dt, 1H, \( J = 15.2, 2.4 \) Hz), 1.13 (s, 3H), 0.92-1.03 (m, 1H), 0.79 (d, 1H, \( J = 5.6 \) Hz), 0.10 (d, 1H, \( J = 5.6 \) Hz); \( ^{13} \)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) 70.5, 59.5, 35.4, 32.5, 32.3, 29.1, 26.6, 18.0, 16.5; m.p. 110-111 °C; HRMS (-ESI) calculated for C\(_9\)H\(_{14}\)NO\(_3\)S 216.0694, found 216.0699 [M-H]\(^-\).

**Preparation of sulfamoyl imine 36:**

Sulfamate ester 31 (0.070 g, 0.27 mmol), PhI(OAc)\(_2\) (0.097 g, 0.300 mmol) and Rh\(_2\)(esp)\(_2\) (0.005 g, 0.005 mmol) were combined in a 2 dram reaction vial and capped with a teflon lined septum. CH\(_2\)Cl\(_2\) (1.55 mL) was added and the reaction was stirred under argon at room temperature for 40 min. The resulting solution was concentrated in vacuo. Purification by flash chromatography (1:1 \( \rightarrow \) 1:2 hexanes/CH\(_2\)Cl\(_2\)) afforded imine 36 as a yellow oil (0.032 g, 47 % yield); \( R_f \) 0.34 (1:2 hexanes/EtOAc); IR (thin film, cm\(^{-1}\)) 1669, 1598, 1362, 1177; \(^1\)H NMR (CDCl\(_3\), 600 MHz) \( \delta \) 10.05 (d, 1H, \( J = 6.4 \) Hz), 7.64 (s, 1H), 6.08 (d, 1H, \( J = 0.6 \) Hz), 4.42 (t, 2H, \( J = 6.4 \) Hz), 2.93 (t, 2H, \( J = 6.4 \) Hz), 2.77 (t, 2H, \( J = 7.2 \) Hz), 2.47 (t, 2H, \( J = 7.2 \) Hz), 2.04 (q, 2H, \( J = 7.2 \) Hz); \(^{13} \)C NMR (CDCl\(_3\), 150 MHz) \( \delta \) 190.0, 180.8, 152.8, 140.2, 137.0, 130.2, 70.4, 40.8, 35.9, 24.8; HRMS (-ESI) calculated for C\(_{11}\)H\(_{12}\)NO\(_4\)S 254.0487, found 254.0494 [M-H]\(^-\).
**Preparation of oxathiazepane 39 and oxathiazinane 41:**

Prepared according to general procedure C using sulfamate ester 28 (0.047 g, 0.217 mmol). The reaction was performed at -20 °C instead of room temperature. Purification by flash chromatography (5:1 → 2:1 hexanes/EtOAc) afforded oxathiazepane 39 as a white solid (0.030 g, 64 % yield); \( R_f \) 0.40 (2:1 hexanes/EtOAc); IR (thin film, cm\(^{-1}\)) 3247, 2938, 2867, 1445, 1331, 1178; \(^1\)H NMR (CDCl\(_3\), 600 MHz) \( \delta \) 4.53 (d, 1H, J = 10.8 Hz), 4.37 (td, 1H, J = 12.0, 1.2 Hz), 4.27 (dt, 1H, J = 12.6, 3.6 Hz), 3.64 (td, 1H, J = 11.4, 5.4 Hz), 2.52-2.58 (m, 1H), 1.97-2.03 (m, 1H), 1.85-1.86 (m, 1H), 1.53-1.57 (m, 1H), 1.24-1.34 (m, 2H), 1.19 (dq, 1H, J = 6.6, 2.4 Hz), 1.06-1.11 (m, 1H), 0.77-0.84 (m, 1H), 0.51 (dd, 1H, J = 6.0, 4.8 Hz), 0.33 (td, 1H, J = 5.4, 2.4 Hz); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz) \( \delta \) 69.6, 54.3, 40.7, 28.0, 26.9, 23.0, 22.9, 22.3, 16.0; m.p. 101-102 °C; HRMS (-ESI) calculated for C\(_9\)H\(_{14}\)NO\(_3\)S 216.0694, found 216.0701 [M-H]; and oxathiazinane 41 as a white solid (0.013 g, 27 % yield) obtained as a 1:0.8 mixture of diastereomers; \( R_f \) 0.51 (2:1 hexanes/EtOAc); IR (thin film, cm\(^{-1}\)) 3262, 2954, 1414, 1354, 1186, 1012; \(^1\)H NMR (CDCl\(_3\), 600 MHz) \( \delta \) 4.66-4.71 (m, 2H), 4.51-4.55 (m, 1.6H), 4.10 (d, 0.8H, J = 9.6 Hz), 3.95 (d, 1H, J = 9.6 Hz), 3.69-3.74 (m, 1H), 3.59-3.63 (m, 0.8H), 1.58-1.85 (m, 11.6H), 1.20-1.31 (m, 3.6H), 0.43-0.54 (m, 3.6H); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz) \( \delta \) 71.8, 60.6, 59.7, 31.5, 31.4, 28.6, 27.9, 27.8, 27.6, 27.4, 27.3, 22.5, 21.5, 20.9, 20.7, 11.8, 10.6; m.p. 102-103 °C; HRMS (-ESI) calculated for C\(_9\)H\(_{14}\)NO\(_3\)S 216.0694, found 216.0698 [M-H].
Preparation of oxathiazepane 40:

PhI(OAc)$_2$ (0.082 g, 0.25 mmol) and Rh$_2$(esp)$_2$ (0.004 g, 0.005 mmol) were combined in a 2 dram vial and capped with a teflon lined septum. CH$_2$Cl$_2$ (1.3 mL) was added and the mixture was cooled to -25 °C. Sulfamate ester 28 (0.046 g, 0.23 mmol) was then added and the resulting solution was stirred at -25 °C for 20 h. DIBAL-H (1.4 mL) was then added dropwise. The resulting mixture was stirred at -25 °C for 3 h then warmed to room temperature and a solution of Rochelle’s salts (5 mL) and EtOAc (10 mL) were added. The mixture was stirred for 20 h then extracted with EtOAc ($3 \times 5$ mL). The combined organic extracts were washed with brine ($2 \times 3$ mL), dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography (6:1 hexanes/EtOAc) afforded oxathiazepane 40 as a white solid (0.018 g, 39 % yield); IR (thin film, cm$^{-1}$) 3885, 2932, 1434, 1346, 1170, 753; $^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ 4.57 (d, 1H, $J = 9.1$ Hz), 4.37-4.34 (m, 1H), 4.27 (ddd, 1H, $J = 12.3, 6.1, 1.8$ Hz), 3.51 (td, 1H, $J = 10.2, 4.4$ Hz), 2.53-2.48 (m, 1H), 1.81-1.70 (m, 3H), 1.61-1.56 (m, 1H), 1.09-1.00 (m, 3H), 0.93-0.86 (m, 1H), 0.53 (dd, 1H, $J = 9.3, 5.3$ Hz), 0.37-0.35 (m, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 69.7, 54.8, 38.9, 29.6, 25.4, 22.5, 20.5, 18.7, 16.7; HRMS (-ESI) calculated for C$_9$H$_{14}$NO$_3$S 216.0694, found 216.0700 [M-H]$^-$; and oxathiazepanes 39 (0.005 g, 10 %) and 41 (0.011 g, 24 %), identical by $^1$H NMR and R$_f$ to previously prepared 39 and 41.
Preparation of oxathiazepane 43:

Sulfamate ester 29 (0.051 g, 0.175 mmol), PhI(OAc)\textsubscript{2} (0.061 g, 0.192 mmol) and Rh\textsubscript{2}(esp)\textsubscript{2} (0.003 g, 0.003 mmol) were combined in a 2 dram vial and capped with a teflon lined septum. CH\textsubscript{2}Cl\textsubscript{2} (1 mL) was added and the reaction was stirred under argon at room temperature for 30 min. The reaction mixture was cooled to -78 °C before MeOH (1 mL) and NaBH\textsubscript{4} (0.007 g, 0.175 mmol) were added. The resulting mixture was warmed to room temperature and stirred for 1h 30 min. SiO\textsubscript{2} was added and the resulting mixture was concentrated in vacuo. The silica was then eluted with CH\textsubscript{2}Cl\textsubscript{2}/Et\textsubscript{2}O (1:1). The eluent was concentrated in vacuo. Purification by flash chromatography (95:5 → 1:1 hexanes/EtOAc) afforded oxathiazepane 43 as a white solid (0.040 g, 70 %); R\textsubscript{f} 0.75 (1:1 hexanes/EtOAc); IR (thin film, cm\textsuperscript{-1}) 3293, 2939, 1428, 1354, 1335, 1171, 1066, 909, 702; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 600 MHz) δ 7.28-7.30 (m, 2H), 7.20-7.22 (m, 3H), 4.84 (d, 1H, J = 10.8 Hz), 3.87-3.94 (m, 2H), 3.76 (dt, 1H, J = 11.4, 6.0 Hz), 2.29 (ddd, 1H, J = 15.0, 10.8, 4.8 Hz), 2.13-2.18 (m, 1H), 2.06 (d, 1H, J = 6.6 Hz), 1.95-1.99 (m, 1H), 1.61-1.68 (m, 2H), 1.45 (qd, 1H, J = 6.6, 1.8 Hz), 1.25 (qd, 1H, J = 7.2, 2.4 Hz), 1.18 (dq, 1H, J = 15, 1.8 Hz), 1.08 (qd, 1H, J = 13.8, 1.6 Hz); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 150 MHz) δ 137.0, 128.8, 126.8, 119.4, 69.2 54.8, 34.7, 33.2, 32.2, 27.7, 25.0, 22.9, 22.6; m.p. 205-206 °C; HRMS (-ESI) calculated for C\textsubscript{15}H\textsubscript{18}NO\textsubscript{3}S 292.1007, found 292.1010 [M-H]\textsuperscript{-}. 
Preparation of oxathiazepane 44 and oxathiazinane 45:

Prepared according to general procedure C using sulfamate ester 30 (0.051 g, 0.17 mmol). The reaction was performed at -25 °C instead of room temperature. Purification by flash chromatography (9:1 → 1:1 hexanes/EtOAc) followed by preparatory thin layer chromatography (3:1 pentane/Et2O) afforded oxathiazepane 44 as a white solid (0.021 g, 42 % yield); Rf 0.23 (2:1 pentane/Et2O); IR (thin film, cm⁻¹) 3314, 2943, 2870, 1420, 1338, 1173; ¹H NMR (CDCl₃, 600 MHz) δ 7.43 (d, 2H, J = 7.8 Hz), 7.37 (t, 2H, J = 7.2 Hz), 7.24-7.27 (m, 1H), 4.76 (d, 1H, J = 10.2 Hz), 4.58 (td, 1H, J = 12.0, 2.4 Hz), 4.47 (dq, 1H, J = 12.0, 2.4 Hz), 3.37 (dq, 1H, J = 10.2, 5.4 Hz), 2.80 (ddd, 1H, J = 15.6, 12.0, 4.8 Hz), 2.16 (d, 1H, J = 10.2 Hz), 2.08-2.13 (m, 1H), 1.98 (qd, 1H, J = 6.0, 2.4 Hz), 1.51-1.57 (m, 2H), 1.45 (td, 1H, J = 10.2, 2.4 Hz), 1.21-1.29 (m, 2H), 0.34 (qd, 1H, J = 13.8, 2.4 Hz); ¹³C NMR (CDCl₃, 150 MHz) δ 136.8, 130.8, 129.4, 127.1, 70.7, 56.9, 43.4, 31.2, 28.9, 28.2, 25.6, 23.6, 18.2; m.p. 135-136 °C; HRMS (-ESI) calculated for C₁₅H₁₈NO₃S 292.1007, found 292.1013 [M-H]⁻; and oxathiazinane 45 as a white solid (0.011 g, 21 % yield); Rf 0.20 (2:1 pentane/Et2O); IR (thin film, cm⁻¹) 3259, 2924, 2858, 1412, 1356, 1188, 1015; ¹H NMR (CDCl₃, 600 MHz) δ 7.30 (t, 2H, J = 7.2 Hz), 7.23 (t, 1H, J = 7.2 Hz), 7.18 (d, 2H, J = 6.6 Hz), 4.75 (td, 1H, J = 13.8, 2.4 Hz), 4.60 (dd, 1H, J = 11.4, 4.8 Hz), 4.05 (d, 1H, J = 10.8 Hz), 3.79 (tq, 1H, J = 12.6, 3.0 Hz), 2.17 (d, 1H, J = 9.0 Hz), 2.00 (qd, 1H, J = 13.2, 5.4 Hz), 1.85-1.92 (m, 2H), 1.77-1.84 (m, 2H), 1.69
(dd, 1H, J = 9.0, 4.8 Hz), 1.64 (dd, 1H, J = 12.6, 8.4 Hz), 1.33-1.39 (m, 1H), 0.08-0.17 (m, 1H); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$ 136.6, 129.0, 128.7, 126.7, 71.8, 61.1, 37.5, 29.6, 27.8, 27.7, 26.4, 26.1, 23.1; m.p. 134-135 °C; HRMS (-ESI) calculated for C$_{15}$H$_{18}$NO$_3$S 292.1007, found 292.1010 [M-H]$^-$.

Preparation of oxathiazepane 47:

Oxathiazepane 39 (0.084 g, 0.386 mmol) in DME (2 mL) was added dropwise to a suspension of NaO$t$Bu (0.056 g, 0.579 mmol) in DME (1.75 mL). The resulting mixture was stirred at room temperature for 1.5 h. Benzyl chloroformate (0.14 mL, 0.965 mmol) was added and the reaction was stirred at room temperature for 16 h. Saturated aq. NH$_4$Cl (5 mL) was then added. The mixture was extracted with Et$_2$O (3 $\times$ 5 mL). The combined organic extracts were washed with brine (2 $\times$ 3 mL), dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography ($4:1 \rightarrow 3:1$ hexanes/EtOAc) afforded compound 47 as a white solid (0.108 g, 80 % yield); $R_f$ 0.63 (2:1 hexanes/EtOAc); IR (thin film, cm$^{-1}$) 2929, 1735, 1387, 1261, 1167; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 7.33-7.44 (m, 5H), 5.28 (s, 2H), 4.59 (td, 1H, J = 12.8, 1.2 Hz), 4.42 (dd, 1H, J = 11.2, 6.4 Hz), 4.34 (dt, 1H, J = 8.8, 3.2 Hz), 2.47 (tq, 1H, J = 12.8, 2.0 Hz), 1.68-1.95 (m, 3H), 1.43-1.59 (m, 2H), 1.25-1.38 (m, 1H), 1.16 (td, 1H, J = 5.6, 1.6 Hz), 0.97-1.03 (m, 2H), 0.58 (dd, 1H, J = 8.8, 5.6 Hz); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 152.8, 135.1, 128.8, 128.6,
128.1, 72.1, 69.5, 61.6, 39.5, 24.9, 23.0, 22.5, 22.2, 21.4, 16.3; m.p. 109-110 °C; HRMS (-ESI) calculated for C_{17}H_{20}NO_{5}S 350.1057, found 350.1066 [M-H].

**Preparation of iodide 48:**

A mixture of NaI (0.011 g, 0.072 mmol) and 47 (0.017 g, 0.048 mmol) in acetone (0.4 mL) was heated to 45 °C for 19 h. The reaction mixture then was cooled to room temperature and saturated aq. NH_{4}Cl (0.5 mL) was then added. The mixture was extracted with Et_{2}O (3 × 2 mL). The combined organic extracts were washed with brine (2 × 1 mL), dried over MgSO_{4} and concentrated in vacuo. Purification by flash chromatography (2:1 hexanes/EtOAc) afforded compound 48 as a yellow oil (0.012 g, 61 % yield); R_{f} 0.75 (2:1 hexanes/EtOAc); IR (thin film, cm\(^{-1}\)) 3329, 2928 2857, 1698, 1526, 1240, 1027; \(^{1}H\) NMR (CDCl\(_{3}\), 600 MHz) δ 7.39-7.36 (m, 4H), 7.35-7.31 (m, 1H), 5.10 (s, 2H), 4.64 (d, 1H, J = 8.4 Hz), 3.99 (td, 1H, J = 9.2, 5.8 Hz), 3.33 (td, 1H, J = 9.6, 4.7 Hz), 3.26 (q, 1H, J = 8.4 Hz), 2.27 (ddd, 1H, J = 14.3, 9.3, 4.8 Hz), 2.00-1.94 (m, 1H), 1.80-1.77 (m, 1H), 1.42-1.34 (m, 3H), 1.09-1.06 (m, 1H), 0.91-0.84 (m, 2H), 0.39 (dd, 1H, J = 9.1, 4.8 Hz), 0.27 (t, 1H, J = 5.1 Hz); \(^{13}C\) NMR (CDCl\(_{3}\), 150 MHz) δ 156.1, 136.7, 128.8, 128.4, 119.2, 66.9, 48.4, 42.0, 28.8, 26.0, 23.4, 21.2, 20.2, 14.7, 2.9; HRMS (+APCI) calculated for C_{17}H_{23}INO_{2} 400.0773, found 400.0771 [M+H].
Preparation of pyrrolidine 49:

A mixture of NaH (0.004 g, 0.088 mmol) and 48 (0.012 g, 0.029 mmol) in THF (0.3 mL) was heated to 35 °C for 1h. The reaction mixture was cooled to room temperature and saturated aq. NH₄Cl (0.5 mL) was then added. The mixture was extracted with Et₂O (3 × 2 mL). The combined organic extracts were washed with brine (2 × 1 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc) afforded compound 49 as a colorless oil (0.004 g, 52 % yield); Rₗ 0.68 (2:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 2928, 2863, 1699, 1414, 1352, 1104; ¹H NMR (d₆-DMSO, 600 MHz, 70°C) δ 7.29-7.39 (m, 5H), 5.09 (d, 1H, J = 12.6 Hz), 5.03 (d, 1H, J = 12.6 Hz), 3.62 (dd, 1H, J = 10.2, 8.4 Hz), 3.59 (dd, 1H, J = 12.0, 5.4 Hz), 3.34 (td, 1H, J = 10.8, 6.6 Hz), 2.37 (bs, 1H), 2.04 (td, 1H, J = 11.4, 9.0 Hz), 1.76 (qd, 1H, J = 8.4, 3.6 Hz), 1.57-1.62 (m, 1H), 1.40-1.46 (m, 3H), 1.37 (dd, 1H, J = 12.0, 7.2 Hz), 1.06-1.13 (m, 1H), 0.71 (t, 1H, J = 4.2 Hz), 0.22 (dd, 1H, J = 8.4, 4.8 Hz); ¹³C NMR (d₆-DMSO, 150 MHz, 70 °C) δ 154.7, 137.0, 128.0, 127.3, 127.1, 65.3, 56.3, 46.7, 31.1, 27.2, 23.6, 19.3, 16.7, 15.1, 10.4; HRMS (+APCI) calculated for C₁₇H₂₂NO₂ 272.1651, found 272.1645 [M+H]^+. 
Preparation of pyrrolidine 49 from oxathiazepane 47:

A mixture of compound 47 (0.108 g, 0.308 mmol) and NaI (68 mg, 0.462 mmol) in DMF (3.0 mL) was heated to 60 °C for 2.5 h. The reaction was cooled to room temperature and NaH (37 mg, 0.924 mmol, 60% dispersion in mineral oil) was added. The resulting mixture was stirred at room temperature for 1 h then heated to 40 °C for 1 h. The reaction mixture was cooled to room temperature and saturated aq. NH₄Cl (2 mL) was added. The reaction was extracted with Et₂O (3 × 2 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc) afforded pyrrolidine 49 as a colorless oil (0.048 g, 57 % yield) identical by ¹H NMR and Rf to previously prepared 49.

Preparation of oxathiazepane 51:

Prepared according to general procedure C using sulfamate ester 50 (0.012 g, 0.034 mmol) and Rh₂(S-biTISP)₂ instead of Rh₂(esp)₂. The reaction was performed at 40 °C instead of room temperature. Purification by flash chromatography (9:1 → 1:1 hexanes/EtOAc) afforded oxathiazepane 51 as a white solid (0.004 g, 36 % yield, 56 %
Preparation of oxathiazepane 35:

Prepared according to general procedure C using sulfamate ester 18 (0.010 g, 0.046 mmol) and Rh$_2$(S-DOSP)$_4$ instead of Rh$_2$(esp)$_2$. Purification by flash chromatography (2:1 → 1:1 hexanes/EtOAc) afforded oxathiazepane 35 as white solid (0.004 g, 36 % yield), identical by $^1$H NMR and R$_f$ to previously prepared 35; GC (CHIRASIL DEX, 120 → 200 °C, 1 °C/min) t$_r$(maj) = 66.61 min, t$_r$(min) = 66.06 min.

Preparation of oxathiazepane 43:

Prepared according to general procedure C using sulfamate ester 29 (0.023 g, 0.085 mmol) and Rh$_2$(S-DOSP)$_4$ instead of Rh$_2$(esp)$_2$. Purification by preparatory thin layer chromatography (2:1 hexanes/EtOAc) afforded oxathiazepane 43 as a white solid (0.009 g, 42 % yield, 33 % e.e.), identical by $^1$H NMR and R$_f$ to previously prepared 43; HPLC (CHIRAPAK AS-H, 10 % IPA/hexanes, 1 mL/min) t$_r$(min) = 28.16 min, t$_r$(maj) = 37.48 min.
**Preparation of oxathiazepane 44:**

Prepared according to general procedure C using sulfamate ester 30 (0.012 g, 0.037 mmol) and Rh$_2$(S-biTISP)$_2$ instead of Rh$_2$(esp)$_2$. Purification by preparatory thin layer chromatography (3:1 pentane/Et$_2$O, done 3 times) afforded oxathiazepane 44 as a white solid (0.002 g, 12 % yield, 40 % e.e.), identical by $^1$H NMR and R$_f$ to previously prepared 44; **HPLC** (CHIRAPAK AS-H, 10 % IPA/hexanes, 1mL/min) $t_r$(min) = 29.25 min, $t_r$(maj) = 63.63 min.

**Preparation of alcohol 58:**

2-Iodobenzylalcohol (2.75 g, 11.8 mmol), Cul (0.08 g, 4.28 mmol) and Pd(PPh$_3$)$_3$Cl$_2$ (0.150 g, 0.214 mmol) were dissolved in a THF/Et$_3$N mixture (2.6:1, 55 mL). The resulting mixture was stirred at room temperature for 30 min then $t$-butyldimethyl(pent-4-yn-1-yl oxy)silane 57 (2.12 g, 10.7 mmol) was added. The reaction mixture was heated to 60 °C for 24h then cooled to room temperature. Saturated aq. NH$_4$Cl (40 mL) was then added. The reaction was extracted with Et$_2$O (3 × 20 mL). The combined organic extracts were washed with brine (2 × 15 mL), dried over MgSO$_4$ and concentrated *in vacuo.*
Purification by flash chromatography (40:1 → 5:1 hexanes/EtOAc) afforded the desired alcohol 58 as a yellow oil (2.60 g, 80 % yield); \( \text{Rf} \) 0.45 (5:1 hexanes/EtOAc); \( \text{IR} \) (thin film, cm\(^{-1}\)) 3353, 2952, 2928, 2856, 1471, 1256, 1103, 834; \(^1\text{H NMR} \) (CDCl\(_3\), 600 MHz) \( \delta \) 7.38-7.36 (m, 2H), 7.24 (t, 1H, \( J = 7.5 \) Hz), 7.17 (t, 1H, \( J = 7.6 \) Hz), 4.75 (s, 2H), 3.74 (t, 2H, \( J = 6.0 \) Hz), 2.98 (bs, 1H), 2.51 (t, 2H, \( J = 7.1 \) Hz), 1.79 (qn, 2H, \( J = 6.5 \) Hz), 0.91 (s, 9H), 0.07 (s, 6H); \(^{13}\text{C NMR} \) (CDCl\(_3\), 150 MHz) \( \delta \) 142.6, 132.1, 127.9, 127.2, 126.9, 121.9, 94.9, 78.3, 68.9, 63.7, 61.7, 31.9, 26.0, 18.4, 16.0, -5.2; \( \text{HRMS} \) (+APCI) calculated for C\(_{18}\)H\(_{29}\)O\(_2\)Si 305.1937, found 305.1929 [M+H]\(^+\).

**Preparation of silyl ether 59:**

\[ \begin{align*}
\text{58} & \overset{\text{OTBS}}{\xrightarrow{\text{NaH, nBu}_{4}\text{NI, THF}}} \text{59}
\end{align*} \]

58 (2.6 g, 8.53 mmol) was added dropwise to a suspension of NaH (0.511 g, 12.8 mmol) and \( n\text{Bu}_4\text{NI} \) (0.315 g, 0.853 mmol) in THF (28 mL) at 0°C. The resulting mixture was stirred at 0°C for 1 h then allyl bromide (0.94 mL, 11.1 mmol) was added. The resulting mixture was stirred at room temperature for 20 h then saturated aq. NH\(_4\)Cl (20 mL) was added. The reaction was extracted with Et\(_2\)O (3 × 20 mL). The combined organic extracts were washed with brine (2 × 15 mL), dried over MgSO\(_4\) and concentrated \textit{in vacuo}.

Purification by flash chromatography (40:1 hexanes/EtOAc) afforded the desired product 59 as a yellow oil (2.40 g, 81 % yield); \( \text{Rf} \) 0.82 (3:1 hexanes/EtOAc); \( \text{IR} \) (thin film, cm\(^{-1}\)) 2951, 2927, 1470, 1251, 1101, 883; \(^1\text{H NMR} \) (CDCl\(_3\), 600 MHz) \( \delta \) 7.49 (d, 1H, \( J = 7.7 \) Hz), 7.41 (dd, 1H, \( J = 7.6, 0.7 \) Hz), 7.30 (td, 1H, \( J = 7.6, 1.1 \) Hz), 7.21 (td, 1H, \( J = 7.5, \)
0.8 Hz), 6.01 (ddt, 1H, J = 17.2, 10.6, 5.4 Hz), 5.36 (dq, 1H, J = 17.2, 1.6 Hz), 5.25-5.22 (m, 1H), 4.71 (s, 2H), 4.11 (dt, 2H, J = 5.4, 1.2 Hz), 3.79 (t, 2H, J = 6.0 Hz), 2.56 (t, 2H, J = 7.0 Hz), 1.85 (q, 2H, J = 6.0 Hz), 0.94 (s, 9H), 0.11 (s, 6H); \(^{13}\text{C NMR}\) (CDCl\(_3\), 150 MHz) \(\delta 140.1, 135.0, 132.1, 127.8, 127.4, 127.2, 122.6, 117.0, 94.7, 78.5, 71.7, 70.4, 61.7, 32.0, 26.1, 18.5, 16.1, -5.2; \(^{1}\text{H NMR}\) (CDCl\(_3\), 600 MHz) \(\delta 7.41 (d, 1H, J = 7.7 \text{ Hz}, 1H), 7.36 (d, 1H, J = 7.2 \text{ Hz}), 7.24 (td, 1H, J = 7.2, 1.2 \text{ Hz}), 7.17 (td, 1H, J = 7.5, 1.1 \text{ Hz}), 5.98-5.91 (m, 1H), 5.30 (dq, 1H, J = 17.2, 1.6 Hz), 5.18 (dq, 1H, J = 10.4, 1.4 Hz), 4.81 (s, 2H), 4.04 (dt, 2H, J = 5.6, 1.4 Hz), 3.74 (t, 2H, J = 6.2 Hz), 2.60 (s, 1H), 2.52 (t, 2H, J = 7.0 Hz), 1.81 (qn, 2H, J = 6.6 Hz); \(^{13}\text{C NMR}\) (CDCl\(_3\), 150 MHz) \(\delta 139.6, 134.6, 131.9, 127.7, 127.5 127.1, 122.4,

**Preparation of alcohol 86:**

TBAF (21 mL, 1.0 M in THF, 21 mmol) was added to a solution of 59 (2.38 g, 6.92 mmol) in THF (23 mL) at 0 °C. The resulting solution was stirred at room temperature for 4 h. Saturated aq. NH\(_4\)Cl (15 mL) was then added. The mixture was extracted with Et\(_2\)O (3 \times 15 mL). The combined organic extracts were washed with brine (2 \times 10 mL), dried over MgSO\(_4\) and concentrated \textit{in vacuo}. Purification by flash chromatography (20:1 \(\rightarrow 1:1\) hexanes/EtOAc) afforded alcohol 86 as a yellow oil (1.12 g, 70 % yield); \(R_f\) 0.40 (2:1 hexanes/EtOAc); \(\text{IR}\) (thin film, cm\(^{-1}\)) 3384, 2930, 2864, 1484, 1448, 1072, 924, 759; \(^{1}\text{H NMR}\) (CDCl\(_3\), 600 MHz) \(\delta 7.41 (d, 1H, J = 7.7 \text{ Hz}, 1H), 7.36 (d, 1H, J = 7.2 \text{ Hz}), 7.24 (td, 1H, J = 7.2, 1.2 \text{ Hz}), 7.17 (td, 1H, J = 7.5, 1.1 \text{ Hz}), 5.98-5.91 (m, 1H), 5.30 (dq, 1H, J = 17.2, 1.6 Hz), 5.18 (dq, 1H, J = 10.4, 1.4 Hz), 4.81 (s, 2H), 4.04 (dt, 2H, J = 5.6, 1.4 Hz), 3.74 (t, 2H, J = 6.2 Hz), 2.60 (s, 1H), 2.52 (t, 2H, J = 7.0 Hz), 1.81 (qn, 2H, J = 6.6 Hz); \(^{13}\text{C NMR}\) (CDCl\(_3\), 150 MHz) \(\delta 139.6, 134.6, 131.9, 127.7, 127.5 127.1, 122.4,
117.0, 94.0, 78.5, 71.3, 70.1, 61.2, 31.3, 15.9; HRMS (+APCI) calculated for C$_{15}$H$_{19}$O$_2$ 231.1385, found 231.1376 [M+H]$^+$. 

**Preparation of sulfamate ester 56:**

![Image](image-url)

Prepared according to general procedure A using 86 (3.0 g, 13 mmol). Purification by flash chromatography (3:1 → 1:1 hexanes/EtOAc) afforded sulfamate ester 56 as a pale yellow oil (3.4 g, 84 % yield); R$_f$ 0.22 (2:1 hexanes/EtOAc); IR (thin film, cm$^{-1}$) 3310, 3279, 3077, 2858, 1363, 1178.928, 760; $^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ 7.40 (t, 2H, $J = 4.8$ Hz), 7.29 (t, 1H, $J = 5.2$ Hz), 7.23 (t, 1H, $J = 5.2$ Hz), 5.99-5.93 (m, 1H), 5.32 (d, 1H, $J = 12$ Hz), 5.23 (d, 1H, $J = 6.8$ Hz), 5.21 (bs, 2H), 4.65 (s, 2H), 4.39-4.37 (m, 2H), 4.07 (d, 2H, $J = 4.0$ Hz), 2.63 (t, 2H, $J = 4.4$ Hz), 2.04-2.0 (m, 2H); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$ 139.4, 134.7, 132.5, 128.7, 128.2, 127.8, 122.8, 117.9, 92.6, 79.9, 71.3, 70.6, 69.4, 27.4, 16.0; HRMS (+APCI) calculated for C$_{15}$H$_{20}$NO$_4$S 310.1113, found 310.1105 [M+H]$^+$. 

**Preparation of carbamate 60:**

![Image](image-url)

2,2,2-trichloroacetyl isocyanate (0.52 mL, 4.41 mmol) was added dropwise to a solution of alcohol 62 (0.795 g, 3.68 mmol) in DCM (11 mL) at 0 °C. The resulting mixture was
stirred at room temperature for 18 h and then concentrated in vacuo. The residue was dissolved in MeOH (8 mL) and K$_2$CO$_3$ (0.051 g, 0.368 mmol) was added. The resulting mixture was stirred at room temperature for 3.5 h. Saturated aq. NH$_4$Cl (5 mL) was then added. The mixture was extracted with Et$_2$O (3 × 10 mL). The combined organic extracts were washed with brine (2 × 5 mL), dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography (3:1 → 2:1 hexanes/EtOAc) afforded carbamate 60 as a yellow oil (0.80 g, 84 % yield); $R_f$ 0.68 (2:1 hexanes/EtOAc); IR (thin film, cm$^{-1}$) 3500, 3346, 2856, 1711, 1601, 1405, 1334, 1079, 760; $^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ 7.46 (d, 1H, $J = 7.8$ Hz), 7.39 (d, 1H, $J = 7.8$ Hz), 7.30 (t, 1H, $J = 6.6$ Hz), 7.21 (t, 1H, $J = 7.2$ Hz), 6.00-5.94 (m, 1H), 5.33 (dd, 1H, $J = 16.2$, 1.2 Hz), 5.21 (dd, 1H, $J = 10.2$, 1.2 Hz), 4.86 (bs, 2H), 4.66 (s, 2H), 4.25 (t, 2H, $J = 7.2$ Hz), 4.08 (d, 2H, $J = 5.4$ Hz), 2.78 (t, 2H, $J = 6.6$ Hz); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$ 156.8, 140.2, 135.0, 132.3, 128.3, 127.7, 127.4, 122.1, 117.2, 90.4, 79.8, 71.7, 70.3, 63.2, 20.6; HRMS (+APCI) calculated for C$_{15}$H$_{18}$NO$_3$ 260.1287, found 260.1280 [M+H]$^+$. 

**Preparation of hydroxyl-amine 87:**

![Chemical Structure](image)

CDI (0.83 g, 5.1 mmol) was added to a solution of alcohol 62 (1.0g, 4.6 mmol) in THF (23 mL). The resulting mixture was stirred for 24 h. Saturated aq. NH$_4$Cl (15 mL) was then added. The mixture was extracted with Et$_2$O (3 × 20 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over MgSO$_4$ and concentrated in vacuo.
vacuo. The residue was dissolved in pyridine (46 mL) and hydroxylamine hydrochloride (0.96 g, 14 mmol) was added. The resulting mixture was stirred for 20 h. Saturated aq. NH₄Cl (25 mL) was then added. The mixture was extracted with Et₂O (3 × 30 mL). The combined organic extracts were washed with brine (2 × 20 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (2:1 hexanes/EtOAc) afforded hydroxyl-amine 87 as a yellow oil (0.67 g, 53 % yield); Rf 0.39 (2:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 3400, 3328, 2852, 1713, 1599, 1406, 1399, 1222, 1076, 758; ¹H NMR (CDCl₃, 600 MHz) δ 7.45 (t, 1H, J = 7.2 Hz), 7.39 (d, 1H, J = 7.8 Hz), 7.30 (t, 1H, J = 6.6 Hz), 7. 21 (t, 1H, J = 7.8 Hz), 6.01-5.94 (m, 1H), 5.36-5.32 (m, 1H), 5.21 (d, 1H, J = 9.6 Hz), 4.81 (bs, 1H), 4.67 (s, 2H), 4.33 (bs, 1H), 4.25 (t, 2H, J = 7.2 Hz), 4.08-4.06 (m, 2H), 2.79-2.76 (m, 2H); ¹³C NMR (CDCl₃, 150 MHz) δ 156.8, 140.2, 134.9, 132.3, 128.3, 127.7, 127.4, 122.1, 117.2, 90.3, 79.8, 71.7, 70.3, 63.3, 20.6; HRMS (+APCI) calculated for C₁₅H₁₈NO₄ 276.1236, found 276,1229 [M+H]⁺.

**Preparation of N-tosyl-carbamate 61:**

TsCl (0.513 g, 2.69 mmol) was added to a solution of hydroxyl-amine 87 (0.673 g, 2.44 mmol) in Et₂O (25 mL). The resulting mixture was then cooled to 0°C and Et₃N (0.35 mL, 2.5 mmol) was added. The resulting mixture was then stirred at room temperature for 18 h. H₂O (15 mL) was then added. The organic extract was washed with brine (2 × 10 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash
chromatography (3:1 → 1:1 hexanes/EtOAc) afforded N-tosyl carbamate 61 as a yellow oil (0.488 g, 46 % yield); Rf 0.40 (2:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 2858, 1771, 1741, 1596, 1380, 1191, 1177, 1089; ¹H NMR (CDCl₃, 600 MHz) δ 8.56 (bs, 1H), 7.87 (d, 2H, J = 8.4 Hz), 7.39 (t, 2H, J = 7.8 Hz), 7.31-7.29 (m, 2H), 7.25-7.21 (m, 2H), 5.97-5.91 (m, 1H), 5.34-5.29 (m, 1H), 5.21-5.19 (m, 1H), 4.63 (s, 2H), 4.19 (t, 2H, J = 6.6 Hz), 4.04 (d, 2H, J = 5.4 Hz), 2.66 (t, 2H, J = 7.2 Hz), 2.43 (s, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 155.6, 146.3, 139.9, 134.8, 132.3, 130.0, 129.9, 129.7, 128.4, 128.2, 127.6, 122.1, 117.5, 89.3, 80.3, 71.3, 70.2, 64.6, 20.1; HRMS (+APCI) calculated for C₂₂H₂₄NO₆S 430.1324, found 430.1315 [M+H]⁺.

Preparation of oxathiazenane 63:

Prepared according to general procedure C using sulfamate ester 56 (0.061 g, 0.20 mmol). Purification by flash chromatography (4:1 hexanes/EtOAc) afforded oxathiazenane 63 as a yellow oil (0.022 g, 37 % yield); Rf 0.33 (2:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 3258, 2923, 2855, 1421,1369, 1351, 1186, 1064, 762; ¹H NMR (CDCl₃, 600 MHz) δ 7.48 (d, 1H, J = 7.7 Hz), 7.42 (dd, 1H, J = 7.8, 1.2 Hz), 7.38 (td, 1H, J = 7.6, 1.2 Hz), 7.26 (t, 1H, J = 7.8 Hz), 6.01-5.95 (m, 1H), 5.35 (dq, 1 H, J = 17.2, 1.6 Hz), 5.24 (dq, 1H, J = 10.4, 1.3 Hz), 4.82 (ddd, 1H, J = 11.4, 10.1, 3.3 Hz), 4.80-4.75 (m, 1H), 4.63 (s, 2H), 4.60 (ddd, 1H, J = 11.9, 4.8, 2.1 Hz), 4.46 (d, 1H, J = 9.9 Hz), 4.08 (dt, 2H, J = 5.6, 1.4 Hz), 2.24-2.09 (m, 2H); ¹³C NMR (CDCl₃, 150 MHz) δ 140.6, 134.8, 132.6,
Preparation of oxazolidine 64:

Prepared according to general procedure C using carbamate 60 \((0.05 \text{ g}, 0.19 \text{ mmol})\). Purification by flash chromatography \((4:1 \text{ hexanes/EtOAc})\) afforded oxazolidine 64 as a colorless oil; \(R_f 0.38 \) \((2:1 \text{ hexanes/EtOAc})\); \(\text{IR} \) (thin film, \(\text{cm}^{-1}\)) 3279, 2856, 1745, 1340, 1059, 760; \(\text{H NMR} \) \((\text{CDCl}_3, 600 \text{ MHz})\) \(\delta 7.48 \) (d, \(1 \text{ H}, J = 7.8 \text{ Hz}\)), 7.42 (d, \(1 \text{ H}, J = 7.7 \text{ Hz}\)), 7.37 (t, \(1 \text{ H}, J = 7.0 \text{ Hz}\)), 7.26 (t, \(1 \text{ H}, J = 7.8 \text{ Hz}\)), 5.97 (ddt, 1 H, \(J = 17.2, 10.6, 5.4 \text{ Hz}\)), 5.39 (s, 1H), 5.34 (dq, 1H, \(J = 17.2, 1.6 \text{ Hz}\)), 5.24 (dq, 1H, \(J = 10.4, 1.4 \text{ Hz}\)), 4.86 (dd, 1H, \(J = 8.4, 5.6 \text{ Hz}\)), 4.66 (t, 1H, \(J = 8.4 \text{ Hz}\)), 4.62 (s, 2H), 4.46 (dd, 1H, \(J = 8.4, 5.5 \text{ Hz}\)), 4.09 (dt, 2H, \(J = 6.0, 1.2 \text{ Hz}\)); \(\text{HRMS} \) (+APCI) calculated for \(\text{C}_{15}\text{H}_{18}\text{NO}_{4}\text{S} \) 308.0957, found 308.0950 [M+H]+.

Preparation of aziridine 66 and imine 65:

Sulfamate ester 56 \((0.047 \text{ g}, 0.15 \text{ mmol})\), PhI(OAc)₂ \((0.079 \text{ g}, 0.25 \text{ mmol})\) and \(\text{Rh}_2\text{(esp)}_2 \) \((0.005 \text{ g}, 0.006 \text{ mmol})\) were combined in a 2 dram vial and capped with a teflon lined
septum. CH$_2$Cl$_2$ (0.9 mL) was added and the mixture was stirred at 40 °C for 3.5 h. The mixture was then cooled to room temperature and concentrated *in vacuo*. Purification by flash chromatography (4:1 → 1:1 hexanes/EtOAc) afforded aziridine 66 as a colorless oil (0.005 g, 10 % yield); R$_f$ 0.38 (2:1 hexanes/EtOAc); IR (thin film, cm$^{-1}$) 2923, 2854, 1360, 1176, 923; $^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ 7.42 (dd, 1H, $J = 6.9$, 1.9 Hz), 7.32 (dd, 1H, $J = 7.2$, 1.6 Hz), 7.30-7.25 (m, 2H), 4.90 (d, 1H, $J = 11.1$ Hz), 4.81-4.74 (m, 2H), 4.57 (d, 1H, $J = 11.1$ Hz), 3.96 (dd, 1H, $J = 12.3$, 1.4 Hz), 3.41 (dd, 1H, $J = 12.3$, 5.9 Hz), 3.06-3.02 (m, 1H), 2.73 (ddd, 1H, $J = 17.2$, 8.1, 4.8 Hz), 2.67-2.62 (m, 2H), 2.41 (d, 1H, $J = 4.6$ Hz), 2.08-2.01 (m, 2H); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$ 139.4, 132.5, 129.8, 128.4, 128.3, 123.8, 92.1, 80.9, 72.9, 71.2, 67.6, 41.1, 29.9, 27.1, 15.7; HRMS (+APCI) calculated for C$_{15}$H$_{18}$NO$_4$S 308.0957, found 308.0953 [M+H]$^+$; and imine 65 as an colorless oil (0.007 g, 14 % yield); R$_f$ 0.26 (2:1 hexanes/EtOAc); $^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ 8.24 (d, 1H, $J = 8.1$ Hz), 7.54 (td, 1H, $J = 7.5$, 0.9 Hz), 7.39 (t, 1H, $J = 7.8$ Hz), 7.16 (d, 1H, $J = 7.5$ Hz), 5.84 (dddd, 1H, $J = 17.2$, 10.1, 7.2, 6.8 Hz), 5.26 (dd, 1H, $J = 17.1$, 1.3 Hz), 5.18 (d, 1H, $J = 10.2$ Hz), 4.85 (s, 2H), 4.56 (dt, 1H, $J = 11.7$, 4.0 Hz), 4.29 (td, 1H, $J = 16.8$, 4.2 Hz), 3.12 (dd, 1H, $J = 14.9$, 6.4 Hz), 2.86 (dd, 1H, $J = 14.9$, 7.5 Hz), 2.37-2.35 (m, 2H), 2.08-1.99 (m, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 173.3, 141.0, 134.2, 131.7, 130.4 129.6, 128.3, 124.2, 120.2, 83.7, 73.1, 61.5, 40.3, 33.7, 24.9; HRMS (+APCI) calculated for C$_{15}$H$_{18}$NO$_4$S 308.0957, found 308.0953 [M+H]$^+$; and oxathiazenane 63 (0.023 g, 48 % yield) identical by $^1$H NMR and R$_f$ to previously prepared 43.
Preparation of oxathiazepane 67:

L-selectride (0.16 mL, 0.16 mmol) was added to a solution of imine 65 (0.010 g, 0.04 mmol) in DCM (0.7 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 2.5 h. Saturated aq. NH₄Cl (1 mL) was then added. The mixture was extracted with Et₂O (3 × 1 mL). The combined organic extracts were washed with brine (2 × 0.5 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (2:1 hexanes/EtOAc) afforded oxathiazepane 67 as a colorless oil; Rf 0.30 (2:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 3284, 2923, 2852, 1453, 1352, 1174, 1083, 750; \(^1\)H NMR (CDCl₃, 600 MHz) δ 7.60 (d, 1H, J = 7.9 Hz), 7.32-7.29 (t, 1H, J = 7.2 Hz), 7.27-7.25 (m, 1H), 7.02 (d, 1H, J = 7.5 Hz), 5.89-5.82 (m, 1H), 5.21 (d, 1H, J = 10.2 Hz), 5.14 (d, 1H, J = 17.1 Hz), 4.86 (d, 1H, J = 16.0 Hz), 4.81-4.78 (m, 2H), 4.64 (d, 1H, J = 10.4 Hz), 4.53 (dt, 1H, J = 12.0, 6.4 Hz), 4.33 (ddd, 1H, J = 12.8, 9.1, 4.0 Hz), 2.36 (dd, 1H, J = 15.6, 6.4 Hz), 2.24-2.17 (m, 3H), 2.01-1.96 (m, 1H), 1.87 (dd, 1H, J = 15.0, 10.0 Hz); \(^{13}\)C NMR (CDCl₃, 150 MHz) δ 134.4, 132.3, 132.0, 127.8, 127.6, 126.0, 123.8, 119.6, 76.1, 72.6, 63.2, 58.2, 34.9, 31.3, 22.7; HRMS (+APCI) calculated for C₁₅H₂₀NO₄S 310.1113, found 310.1110 [M+H]^+.
Preparation of diester 71:

Diester 70 (0.15 g, 0.60 mmol) in THF (2 mL) was added to a solution of KHMDS (0.30 g, 1.5 mmol) in THF (5 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 1.5 h. (PhSO$_2$)$_2$NF (0.47 g, 1.5 mmol) in THF (2 mL) was then added dropwise. The resulting mixture was slowly warmed to room temperature and stirred for 20 h. Saturated aq. NaHCO$_3$ (5 mL) was then added. The mixture was extracted with DCM (3 × 8 mL). The combined organic extracts were washed with brine (2 × 5 mL), dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography (10:1 → 1:1 hexanes/EtOAc) afforded diester 71 as a white amorphous solid (0.023 g, 13 % yield); $R_f$ 0.23 (4:1 hexanes/EtOAc); $^1$H NMR (CDCl$_3$, 400 MHz) δ 7.35-7.18 (m, 4H), 3.80 (s, 6H), 3.37 (t, 4H, $J = 16$ Hz); $^{19}$F NMR (CDCl$_3$, 376 MHz) δ -115.3 (t, $J = 14.1$ Hz).

Preparation of dialdehyde 73:

A solution of 5-(t-butyl)isophthalic acid (4.0 g, 18 mmol) in THF 50 mL was cannulated into LAH (31.5 mL, 2.0M in THF, 63 mmol) at 0°C. The resulting mixture was warmed to room temperature and then heated to reflux for 5.5 h. The reaction mixture was then
cooled to 0°C and quenched by slow addition of H₂O (2.5 mL) followed by 3N NaOH (2.5 mL) and H₂O (7 mL). The mixture was then filtered over celite, washed with Et₂O and concentrated in vacuo. The resulting white solid was then taken to the next step without further purification.

A solution of the resulting alcohol (3.5 g, 18 mmol) in DCM (20 mL) was cannulated into a mixture of PCC (7.8 g 36 mmol) and celite (19 g) in DCM (80 mL) at 0°C. The resulting mixture was stirred at room temperature was 18 h then filtered over silica. The filtrate was concentrated in vacuo to afford aldehyde 73 as a white solid (2.66 g, 78 % yield over 2 steps); IR (thin film, cm⁻¹) 2962, 1750, 1591, 1456, 1218, 1146, 650; ¹H NMR (CDCl₃, 600 MHz) δ10.1 (s, 2H), 8.19-8.18 (m, 3H), 1.41 (s, 9H); ¹³C NMR (CDCl₃, 150 MHz) δ 191.7, 153.9, 137.2, 131.9, 129.3, 35.3, 31.3; HRMS (+APCI) calculated for C₁₂H₁₅O₂ 191.1072, found 191.1066 [M+H]⁺.

**Preparation of β-hydroxyester 74:**

A mixture of aldehyde 73 (1.51, 8.0 mmol) and ethyl 2-bromo-2,2-difluoroacetate (4.1 mL, 31.5 mmol) in THF (25 mL) was cannulated into a suspension of activated Zn (3.1 g, 47.3 mmol) in refluxing THT (95 mL). The mixture was maintained at reflux for 1.5 h then cooled to room temperature then 0 °C. Saturated aq. NH₄Cl (65 mL) was then added. The mixture was extracted with Et₂O (3 × 80 mL). The combined organic extracts were washed with brine (2 × 50 mL), dried over MgSO₄ and concentrated in vacuo.
Purification by flash chromatography (4:1 hexanes/EtOAc) afforded ketoester 74 as a colorless oil (3.19 g, 91 % yield); Rf 0.37 (2:1 hexanes/EtOAc); IR (thin film, cm\(^{-1}\)) 3468, 2966, 1756, 1312, 1075; \(^1\)H NMR (CDCl\(_3\), 600 MHz) \(\delta\) 7.47 (s, 2H), 7.34 (s, 1H), 5.20-5.14 (m, 2H), 4.31-4.27 (m, 4H), 2.88 (d, 2 H, J = 5.1 Hz), 1.29 (tdd, 6 H, J = 7.2, 2.5, 1.0 Hz), 1.39 (s, 9H); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz) \(\delta\) 163.7 (t, \(J_{\text{C-F}}\) = 31 Hz), 151.9, 134.7, 126.0, 124.5, 113.9 (t, \(J_{\text{C-F}}\) = 251 Hz), 74.1 (t, \(J_{\text{C-F}}\) = 27 Hz), 63.4, 35.0, 31.4, 14.0; HRMS (+ESI) calculated for C\(_{20}\)H\(_{26}\)O\(_6\)F\(_4\)Na 461.1558, found 461.1559 [M+Na]\(^{+}\).

**Preparation of diester 75:**

![Chemical Structure](image)

DBU (1.64 mL, 10.9 mmol) was added to a mixture of 74 ((874 g, 1.99 mmol) in DMF (50 mL) followed by CS\(_2\) (0.48 mL) 7.97 mmol). The resulting mixture was stirred at room temperature for 1 h then MeI (0.62 mL, 9.97 mmol) was added. The reaction mixture was stirred for 1 h and H\(_2\)O (40 mL) was then added. The mixture was extracted with Et\(_2\)O (3 \times 80 mL). The combined organic extracts were washed with brine (2 \times 50 mL), dried over MgSO\(_4\) and concentrated in vacuo. The residue was taken to the next step without purification (1.12 g, 91 % crude yield).

\(n\)Bu\(_3\)SnH (1.48 mL, 5.60 mmol) was added to a mixture of the previously obtained oil (1.12 g, 1.81 mmol) and AIBN (119 g, 0.723 mmol) in benzene (30 mL). The resulting mixture was heated to reflux for 3 h and H\(_2\)O (15 mL) was then added. The mixture was extracted with Et\(_2\)O (3 \times 20 mL). The combined organic extracts were washed with brine
(2 \times 15 \text{ mL}), dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo}. Purification by flash chromatography (40:1 \rightarrow 5:1 hexanes/EtOAc) afforded diester 75 as a yellow oil (0.494 g, 67 %); \textbf{IR} (thin film, cm\textsuperscript{-1}) 2963, 1759, 1604, 1292, 1220, 1183, 1069; \textbf{\textsuperscript{1}H NMR} (CDCl\textsubscript{3}, 600 MHz) \(\delta\) 7.19 (s, 2H), 6.97 (s, 1H), 4.23 (q, 4H, \(J = 7.1\) Hz), 3.35 (t, 4H, \(J = 16.4\) Hz), 1.30 (s, 9H), 1.25 (t, 6H, \(J = 7.1\) Hz); \textbf{\textsuperscript{13}C NMR} (CDCl\textsubscript{3}, 150 MHz) \(\delta\) 164.1 (t, \(J_{C-F} = 32\) Hz), 152.0, 130.8, 129.7, 127.3, 115.5 (t, \(J_{C-F} = 250\) Hz), 63.0, 41.2 (t, \(J_{C-F} = 23\) Hz), 34.7, 31.4, 14.0; \textbf{HRMS (+APCI)} calculated for C\textsubscript{20}H\textsubscript{27}O\textsubscript{4}F\textsubscript{4} 407.1845, found 407.1846 [M+H]\textsuperscript{+}.

\textbf{Preparation of diamide 72:}

\[
\begin{align*}
\text{NH}_3 (11 \text{ mL, 2.0M in MeOH, 21 mmol}) & \text{ was added to diester 75 (0.87 g, 2.1 mmol). The resulting mixture was stirred at room temperature for 12 h then a 10 \% NaCl solution (5 mL) was added. The mixture was extracted with EtOAc (3 \times 10 \text{ mL}). The combined organic extracts were washed with brine (2 \times 5 \text{ mL}), dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo}. The resulting solid was triturated with a 40:1 hexanes/EtOAc mixture to afford the desired amide 72 as a white solid (0.62 g, 84 \% yield); \textbf{IR} (thin film, cm\textsuperscript{-1}) 3324, 3190, 2955, 1691, 1604, 1432, 1247, 1175, 1092, 1067; \textbf{\textsuperscript{1}H NMR} (CDCl\textsubscript{3}, 600 MHz) \(\delta\) 7.23 (s, 2H), 7.02 (s, 1H), 6.1 (bs, 2H), 5.6 (bs, 2H), 3.39 (t, 2H, \(J = 16.8\) Hz), 1.30 (s, 9H); \textbf{\textsuperscript{13}C NMR} (d\textsubscript{6}-acetone, 150 MHz) \(\delta\) 166.5 (t, \(J_{C-F} = 27\) Hz), 152.0, 132.4, 130.8, 129.7, 127.3, 115.5 (t, \(J_{C-F} = 250\) Hz), 63.0, 41.2 (t, \(J_{C-F} = 23\) Hz), 34.7, 31.4, 14.0; \textbf{HRMS (+APCI)} calculated for C\textsubscript{20}H\textsubscript{27}O\textsubscript{4}F\textsubscript{4} 407.1845, found 407.1846 [M+H]\textsuperscript{+}.}
\end{align*}
\]
127.7, 118.3 (t, $J_{C-F} = 252$ Hz), 40.8 (t, $J^2_{C-F} = 25$ Hz), 35.1, 31.6; **HRMS** (+APCI) calculated for $C_{16}H_{21}O_2N_2F_4$ 349.1534, found 349.1536 $[M+H]^+$. 

**Preparation of complex 76:**

Amide 72 (0.212 g, 0.61 mmol) and Rh$_2$(tfa)$_4$ (0.192 g, 0.3 mmol) were dissolved in DCE (6 mL) in a sealed tube. The mixture was heated to 150 °C for 3.5 days. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. The resulting solid was recrystallized with acetone and heated to 50 °C to afford complex 76 as a blue-green solid (0.187 g, 71 % yield); **IR** (thin film, cm$^{-1}$) 3350, 2900, 1656, 1264, 1155; **$^1$H NMR** ($d_6$-acetone, 400 MHz) $\delta$ 7.41 (s, 1H), 7.20 (s, 2H), 5.58 (bs, 2H), 3.56-3.48 (m, 2H), 3.10-2.98 (m, 2H), 1.30 (s, 9H).

**6.4. X-Ray Crystallography.**

X-Ray crystallography for compound 41.
Table 1. Crystal data and structure refinement for 41.

<table>
<thead>
<tr>
<th>Identification code</th>
<th>41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C9 H10 N O3 S</td>
</tr>
<tr>
<td>Formula weight</td>
<td>212.24</td>
</tr>
<tr>
<td>Temperature</td>
<td>173(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54178 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>C2/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 32.858(3) Å          $\alpha$ = 90°.</td>
</tr>
<tr>
<td></td>
<td>b = 6.6744(6) Å          $\beta$ = 105.271(6)°.</td>
</tr>
<tr>
<td></td>
<td>c = 9.8990(7) Å          $\gamma$ = 90°.</td>
</tr>
<tr>
<td>Volume</td>
<td>2094.3(3) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>8</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.346 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>2.625 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>888</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.19 x 0.18 x 0.02 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>2.79 to 65.76°.</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-36≤h≤37, -7≤k≤6, -11≤l≤11</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>6036</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>1695 [R(int) = 0.0222]</td>
</tr>
<tr>
<td>Completeness to theta = 65.76°</td>
<td>93.4 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Semi-empirical from equivalents</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.9494 and 0.6354</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F^2</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>1695 / 6 / 144</td>
</tr>
<tr>
<td>Goodness-of-fit on F^2</td>
<td>1.184</td>
</tr>
<tr>
<td>Final R indices [I&gt;2sigma(I)]</td>
<td>R1 = 0.0544, wR2 = 0.1548</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0650, wR2 = 0.1613</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.576 and -0.366 e Å⁻³</td>
</tr>
</tbody>
</table>
Table 2. Atomic coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($\AA^2 \times 10^3$) for vim_4_153_1s. $U\text{eq}$ is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)</td>
<td>2840(1)</td>
<td>3870(5)</td>
<td>1779(3)</td>
<td>39(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>3194(1)</td>
<td>4107(5)</td>
<td>3102(3)</td>
<td>40(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>3588(1)</td>
<td>2978(5)</td>
<td>3013(3)</td>
<td>41(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>3965(1)</td>
<td>3145(7)</td>
<td>4253(4)</td>
<td>55(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>3931(2)</td>
<td>3126(8)</td>
<td>5735(4)</td>
<td>73(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>4312(3)</td>
<td>2223(17)</td>
<td>6574(9)</td>
<td>84(3)</td>
</tr>
<tr>
<td>C(7)</td>
<td>4635(5)</td>
<td>1900(30)</td>
<td>5660(20)</td>
<td>103(7)</td>
</tr>
<tr>
<td>C(8)</td>
<td>4372(5)</td>
<td>2200(40)</td>
<td>4099(18)</td>
<td>137(13)</td>
</tr>
<tr>
<td>C(5B)</td>
<td>4069(2)</td>
<td>5075(9)</td>
<td>5063(6)</td>
<td>80(2)</td>
</tr>
<tr>
<td>C(6B)</td>
<td>4520(4)</td>
<td>5090(20)</td>
<td>5538(18)</td>
<td>130(5)</td>
</tr>
<tr>
<td>C(7B)</td>
<td>4690(5)</td>
<td>2820(30)</td>
<td>5540(20)</td>
<td>116(8)</td>
</tr>
<tr>
<td>C(8B)</td>
<td>4364(6)</td>
<td>1960(30)</td>
<td>4222(18)</td>
<td>80(6)</td>
</tr>
<tr>
<td>N(1)</td>
<td>3485(1)</td>
<td>798(4)</td>
<td>2750(3)</td>
<td>37(1)</td>
</tr>
<tr>
<td>O(1)</td>
<td>3245(1)</td>
<td>1120(4)</td>
<td>184(2)</td>
<td>44(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>2965(1)</td>
<td>-1610(4)</td>
<td>1355(3)</td>
<td>50(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>2731(1)</td>
<td>1737(3)</td>
<td>1515(2)</td>
<td>38(1)</td>
</tr>
<tr>
<td>S(1)</td>
<td>3108(1)</td>
<td>398(1)</td>
<td>1352(1)</td>
<td>37(1)</td>
</tr>
</tbody>
</table>
Table 3. Bond lengths [Å] and angles [°] for 41.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length or Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)-O(3)</td>
<td>1.474(4)</td>
</tr>
<tr>
<td>C(1)-C(2)</td>
<td>1.513(4)</td>
</tr>
<tr>
<td>C(1)-H(1A)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(1)-H(1B)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(2)-C(3)</td>
<td>1.522(5)</td>
</tr>
<tr>
<td>C(2)-H(2A)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(2)-H(2B)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(3)-N(1)</td>
<td>1.500(4)</td>
</tr>
<tr>
<td>C(3)-C(4)</td>
<td>1.501(5)</td>
</tr>
<tr>
<td>C(3)-H(3)</td>
<td>1.0000</td>
</tr>
<tr>
<td>C(4)-C(5)</td>
<td>1.509(6)</td>
</tr>
<tr>
<td>C(4)-C(5B)</td>
<td>1.501(6)</td>
</tr>
<tr>
<td>C(5)-C(6)</td>
<td>1.439(9)</td>
</tr>
<tr>
<td>C(5)-C(5B)</td>
<td>1.581(8)</td>
</tr>
<tr>
<td>C(5)-H(5)</td>
<td>1.1258</td>
</tr>
<tr>
<td>C(6)-C(7)</td>
<td>1.581(19)</td>
</tr>
<tr>
<td>C(6)-H(6A)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(6)-H(6B)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(7)-C(8)</td>
<td>1.571(16)</td>
</tr>
<tr>
<td>C(5B)-C(6B)</td>
<td>1.432(14)</td>
</tr>
<tr>
<td>C(5B)-H(5B)</td>
<td>1.1512</td>
</tr>
<tr>
<td>C(6B)-C(7B)</td>
<td>1.614(18)</td>
</tr>
<tr>
<td>C(6B)-H(6B1)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(6B)-H(6B2)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(7B)-C(8B)</td>
<td>1.564(16)</td>
</tr>
<tr>
<td>N(1)-S(1)</td>
<td>1.618(3)</td>
</tr>
<tr>
<td>N(1)-H(1N)</td>
<td>0.8778</td>
</tr>
<tr>
<td>O(1)-S(1)</td>
<td>1.430(2)</td>
</tr>
<tr>
<td>O(2)-S(1)</td>
<td>1.421(3)</td>
</tr>
<tr>
<td>O(3)-S(1)</td>
<td>1.570(2)</td>
</tr>
<tr>
<td>O(3)-C(1)-C(2)</td>
<td>110.5(3)</td>
</tr>
</tbody>
</table>
O(3)-C(1)-H(1A)  109.8
C(2)-C(1)-H(1A)  109.6
O(3)-C(1)-H(1B)  109.3
C(2)-C(1)-H(1B)  109.6
H(1A)-C(1)-H(1B) 108.0
C(1)-C(2)-C(3)   111.7(3)
C(1)-C(2)-H(2A)  109.5
C(3)-C(2)-H(2A)  110.0
C(1)-C(2)-H(2B)  108.9
C(3)-C(2)-H(2B)  108.6
H(2A)-C(2)-H(2B) 108.0
N(1)-C(3)-C(4)   108.2(3)
N(1)-C(3)-C(2)   109.5(3)
C(4)-C(3)-C(2)   116.6(3)
N(1)-C(3)-H(3)   106.9
C(4)-C(3)-H(3)   107.5
C(2)-C(3)-H(3)   107.6
C(3)-C(4)-C(5)   122.7(3)
C(3)-C(4)-C(5B)  121.3(4)
C(5)-C(4)-C(5B)  63.4(3)
C(3)-C(4)-C(8)   116.4(7)
C(5)-C(4)-C(8)   112.8(8)
C(5B)-C(4)-C(8)  109.1(10)
C(3)-C(4)-C(8B)  118.0(7)
C(5)-C(4)-C(8B)  107.4(7)
C(5B)-C(4)-C(8B) 112.1(8)
C(8)-C(4)-C(8B)  7.7(18)
C(6)-C(5)-C(4)   106.8(5)
C(6)-C(5)-C(5B)  106.6(6)
C(4)-C(5)-C(5B)  58.6(3)
C(6)-C(5)-H(5)   133.2
C(4)-C(5)-H(5)   115.7
C(5B)-C(5)-H(5)  111.6
C(5)-C(6)-C(7)   109.9(9)
C(5)-C(6)-H(6A)  109.7
C(7)-C(6)-H(6A)  109.7
C(5)-C(6)-H(6B)  109.7
C(7)-C(6)-H(6B)  109.7
H(6A)-C(6)-H(6B)  108.2
C(8)-C(7)-C(6)  105.4(11)
C(4)-C(8)-C(7)  103.0(11)
C(6B)-C(5B)-C(4)  104.5(7)
C(6B)-C(5B)-C(5)  104.8(8)
C(4)-C(5B)-C(5)  58.1(3)
C(6B)-C(5B)-H(5B)  138.0
C(4)-C(5B)-H(5B)  109.2
C(5)-C(5B)-H(5B)  114.0
C(5B)-C(6B)-C(7B)  108.8(11)
C(5B)-C(6B)-H(6B1)  109.9
C(7B)-C(6B)-H(6B1)  109.9
C(5B)-C(6B)-H(6B2)  109.9
C(7B)-C(6B)-H(6B2)  109.9
H(6B1)-C(6B)-H(6B2)  108.3
C(8B)-C(7B)-C(6B)  100.5(12)
C(4)-C(8B)-C(7B)  101.3(11)
C(3)-N(1)-S(1)  113.3(2)
C(3)-N(1)-H(1N)  103.3
S(1)-N(1)-H(1N)  100.5
C(1)-O(3)-S(1)  114.0(2)
O(2)-S(1)-O(1)  119.62(15)
O(2)-S(1)-O(3)  105.40(14)
O(1)-S(1)-O(3)  108.35(13)
O(2)-S(1)-N(1)  109.50(15)
O(1)-S(1)-N(1)  107.69(15)
O(3)-S(1)-N(1)  105.41(13)

Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters (Å$^2 \times 10^3$) for 41. The anisotropic displacement factor exponent takes the form: -2π$^2$[ h$^2$a$^*$$^2$U$^{11}$ + ... + 2 h k a$^*$ b$^*$$^2$ U$^{12}$ ]

<table>
<thead>
<tr>
<th></th>
<th>U$^{11}$</th>
<th>U$^{22}$</th>
<th>U$^{33}$</th>
<th>U$^{23}$</th>
<th>U$^{13}$</th>
<th>U$^{12}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)</td>
<td>51(2)</td>
<td>26(2)</td>
<td>37(2)</td>
<td>0(1)</td>
<td>9(2)</td>
<td>6(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>55(2)</td>
<td>31(2)</td>
<td>33(2)</td>
<td>-3(1)</td>
<td>8(2)</td>
<td>2(2)</td>
</tr>
<tr>
<td>C(3)</td>
<td>52(2)</td>
<td>37(2)</td>
<td>32(2)</td>
<td>-3(1)</td>
<td>10(1)</td>
<td>-4(2)</td>
</tr>
<tr>
<td>C(4)</td>
<td>49(2)</td>
<td>66(3)</td>
<td>44(2)</td>
<td>-9(2)</td>
<td>5(2)</td>
<td>-3(2)</td>
</tr>
<tr>
<td>C(5)</td>
<td>77(3)</td>
<td>93(4)</td>
<td>41(2)</td>
<td>-5(2)</td>
<td>-2(2)</td>
<td>-15(3)</td>
</tr>
<tr>
<td>C(6)</td>
<td>85(7)</td>
<td>103(9)</td>
<td>49(5)</td>
<td>19(5)</td>
<td>-10(5)</td>
<td>11(6)</td>
</tr>
<tr>
<td>C(7)</td>
<td>82(10)</td>
<td>76(11)</td>
<td>115(12)</td>
<td>-14(9)</td>
<td>-38(8)</td>
<td>2(8)</td>
</tr>
<tr>
<td>C(8)</td>
<td>36(6)</td>
<td>240(30)</td>
<td>111(14)</td>
<td>-73(13)</td>
<td>-31(6)</td>
<td>59(10)</td>
</tr>
<tr>
<td>C(5B)</td>
<td>68(3)</td>
<td>90(4)</td>
<td>77(3)</td>
<td>-30(3)</td>
<td>8(2)</td>
<td>-21(3)</td>
</tr>
<tr>
<td>C(7B)</td>
<td>69(9)</td>
<td>128(19)</td>
<td>117(13)</td>
<td>-43(13)</td>
<td>-33(8)</td>
<td>22(10)</td>
</tr>
<tr>
<td>N(1)</td>
<td>49(2)</td>
<td>36(2)</td>
<td>26(1)</td>
<td>1(1)</td>
<td>9(1)</td>
<td>5(1)</td>
</tr>
<tr>
<td>O(1)</td>
<td>68(2)</td>
<td>42(2)</td>
<td>26(1)</td>
<td>-1(1)</td>
<td>16(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>78(2)</td>
<td>26(1)</td>
<td>45(1)</td>
<td>-2(1)</td>
<td>13(1)</td>
<td>-4(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>46(1)</td>
<td>32(1)</td>
<td>36(1)</td>
<td>1(1)</td>
<td>8(1)</td>
<td>-1(1)</td>
</tr>
<tr>
<td>S(1)</td>
<td>55(1)</td>
<td>28(1)</td>
<td>27(1)</td>
<td>-1(1)</td>
<td>10(1)</td>
<td>0(1)</td>
</tr>
</tbody>
</table>
Table 5. Hydrogen coordinates \( (x \times 10^4) \) and isotropic displacement parameters \( (\text{Å}^2 \times 10^3) \) for 41

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(1A)</td>
<td>2589</td>
<td>4624</td>
<td>1872</td>
<td>47</td>
</tr>
<tr>
<td>H(1B)</td>
<td>2928</td>
<td>4432</td>
<td>974</td>
<td>47</td>
</tr>
<tr>
<td>H(2A)</td>
<td>3099</td>
<td>3626</td>
<td>3915</td>
<td>48</td>
</tr>
<tr>
<td>H(2B)</td>
<td>3264</td>
<td>5547</td>
<td>3247</td>
<td>48</td>
</tr>
<tr>
<td>H(3)</td>
<td>3673</td>
<td>3496</td>
<td>2178</td>
<td>49</td>
</tr>
<tr>
<td>H(6A)</td>
<td>4245</td>
<td>919</td>
<td>6941</td>
<td>101</td>
</tr>
<tr>
<td>H(6B)</td>
<td>4440</td>
<td>3100</td>
<td>7380</td>
<td>101</td>
</tr>
<tr>
<td>H(6B1)</td>
<td>4610</td>
<td>5661</td>
<td>6494</td>
<td>156</td>
</tr>
<tr>
<td>H(6B2)</td>
<td>4637</td>
<td>5937</td>
<td>4910</td>
<td>156</td>
</tr>
<tr>
<td>H(1N)</td>
<td>3358</td>
<td>489</td>
<td>3399</td>
<td>45</td>
</tr>
<tr>
<td>H(5)</td>
<td>3602</td>
<td>3271</td>
<td>5867</td>
<td>44</td>
</tr>
<tr>
<td>H(5B)</td>
<td>3799</td>
<td>6205</td>
<td>4657</td>
<td>44</td>
</tr>
</tbody>
</table>
Table 6. Torsion angles [°] for 41.

<table>
<thead>
<tr>
<th>Bond Sequence</th>
<th>Torsion Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(3)-C(1)-C(2)-C(3)</td>
<td>59.0(4)</td>
</tr>
<tr>
<td>C(1)-C(2)-C(3)-N(1)</td>
<td>-58.2(3)</td>
</tr>
<tr>
<td>C(1)-C(2)-C(3)-C(4)</td>
<td>178.5(3)</td>
</tr>
<tr>
<td>N(1)-C(3)-C(4)-C(5)</td>
<td>-84.3(5)</td>
</tr>
<tr>
<td>C(2)-C(3)-C(4)-C(5)</td>
<td>39.7(5)</td>
</tr>
<tr>
<td>N(1)-C(3)-C(4)-C(5B)</td>
<td>-160.8(4)</td>
</tr>
<tr>
<td>C(2)-C(3)-C(4)-C(5B)</td>
<td>-36.9(5)</td>
</tr>
<tr>
<td>N(1)-C(3)-C(4)-C(8)</td>
<td>62.2(14)</td>
</tr>
<tr>
<td>C(2)-C(3)-C(4)-C(8)</td>
<td>-173.8(14)</td>
</tr>
<tr>
<td>N(1)-C(3)-C(4)-C(8B)</td>
<td>53.8(9)</td>
</tr>
<tr>
<td>C(2)-C(3)-C(4)-C(8B)</td>
<td>177.8(9)</td>
</tr>
<tr>
<td>C(3)-C(4)-C(5)-C(6)</td>
<td>148.8(6)</td>
</tr>
<tr>
<td>C(5B)-C(4)-C(5)-C(6)</td>
<td>-99.5(6)</td>
</tr>
<tr>
<td>C(8)-C(4)-C(5)-C(6)</td>
<td>1.3(14)</td>
</tr>
<tr>
<td>C(8B)-C(4)-C(5)-C(6)</td>
<td>7.0(10)</td>
</tr>
<tr>
<td>C(3)-C(4)-C(5)-C(5B)</td>
<td>-111.7(5)</td>
</tr>
<tr>
<td>C(8)-C(4)-C(5)-C(5B)</td>
<td>100.8(13)</td>
</tr>
<tr>
<td>C(8B)-C(4)-C(5)-C(5B)</td>
<td>106.5(9)</td>
</tr>
<tr>
<td>C(4)-C(5)-C(6)-C(7)</td>
<td>7.8(11)</td>
</tr>
<tr>
<td>C(5B)-C(5)-C(6)-C(7)</td>
<td>-53.6(11)</td>
</tr>
<tr>
<td>C(5)-C(6)-C(7)-C(8)</td>
<td>-13.7(18)</td>
</tr>
<tr>
<td>C(3)-C(4)-C(8)-C(7)</td>
<td>-159.3(12)</td>
</tr>
<tr>
<td>C(5)-C(4)-C(8)-C(7)</td>
<td>-10(2)</td>
</tr>
<tr>
<td>C(5B)-C(4)-C(8)-C(7)</td>
<td>58.8(19)</td>
</tr>
<tr>
<td>C(8B)-C(4)-C(8)-C(7)</td>
<td>-55(9)</td>
</tr>
<tr>
<td>C(6)-C(7)-C(8)-C(4)</td>
<td>13(2)</td>
</tr>
<tr>
<td>C(3)-C(4)-C(5B)-C(6B)</td>
<td>-147.7(8)</td>
</tr>
<tr>
<td>C(5)-C(4)-C(5B)-C(6B)</td>
<td>98.6(9)</td>
</tr>
<tr>
<td>C(8)-C(4)-C(5B)-C(6B)</td>
<td>-8.0(14)</td>
</tr>
<tr>
<td>C(8B)-C(4)-C(5B)-C(6B)</td>
<td>-0.5(12)</td>
</tr>
<tr>
<td>C(3)-C(4)-C(5B)-C(5)</td>
<td>113.8(4)</td>
</tr>
<tr>
<td>C(8)-C(4)-C(5B)-C(5)</td>
<td>-106.6(11)</td>
</tr>
<tr>
<td>C(8B)-C(4)-C(5B)-C(5)</td>
<td>-99.0(8)</td>
</tr>
<tr>
<td>C(6)-C(5)-C(5B)-C(6B)</td>
<td>1.8(9)</td>
</tr>
</tbody>
</table>
C(4)-C(5)-C(5B)-C(6B)  -98.1(8)
C(6)-C(5)-C(5B)-C(4)  99.9(6)
C(4)-C(5B)-C(6B)-C(7B)  -21.7(15)
C(5)-C(5B)-C(6B)-C(7B)  38.5(15)
C(5B)-C(6B)-C(7B)-C(8B)  35.4(19)
C(3)-C(4)-C(8B)-C(7B)  170.8(11)
C(5)-C(4)-C(8B)-C(7B)  -45.3(15)
C(5B)-C(4)-C(8B)-C(7B)  22.4(16)
C(8)-C(4)-C(8B)-C(7B)  91(10)
C(6B)-C(7B)-C(8B)-C(4)  -32.3(17)
C(4)-C(3)-N(1)-S(1)  -174.9(2)
C(2)-C(3)-N(1)-S(1)  57.0(3)
C(2)-C(1)-O(3)-S(1)  -58.9(3)
C(1)-O(3)-S(1)-O(2)  170.0(2)
C(1)-O(3)-S(1)-O(1)  -60.8(2)
C(1)-O(3)-S(1)-N(1)  54.2(2)
C(3)-N(1)-S(1)-O(2)  -166.4(2)
C(3)-N(1)-S(1)-O(1)  62.0(3)
C(3)-N(1)-S(1)-O(3)  -53.5(2)

Symmetry transformations used to generate equivalent atoms:
Table 7. Hydrogen bonds for 41 [Å and °].

<table>
<thead>
<tr>
<th>D-H...A</th>
<th>d(D-H)</th>
<th>d(H...A)</th>
<th>d(D...A)</th>
<th>&lt;(DHA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1)-H(1N)...O(1)#1</td>
<td>0.88</td>
<td>2.18</td>
<td>3.012(3)</td>
<td>157.5</td>
</tr>
</tbody>
</table>

Symmetry transformations used to generate equivalent atoms:

#1 x, -y, z+1/2

X-Ray crystallography for compound 43

Table 1. Crystal data and structure refinement for 43
Identification code 43
Empirical formula C15 H19 N O3 S
Formula weight 293.37
Temperature 173(2) K
Wavelength 0.71073 Å
Crystal system Orthorhombic
Space group Pna2(1)
Unit cell dimensions a = 9.6700(2) Å  α = 90°.
b = 8.9639(2) Å  β = 90°.
c = 16.6568(3) Å  γ = 90°.
Volume 1443.83(5) Å³
Z 4
Density (calculated) 1.350 Mg/m³
Absorption coefficient 0.231 mm⁻¹
F(000) 624
Crystal size 0.20 x 0.18 x 0.18 mm³
Theta range for data collection 2.45 to 26.35°.
Index ranges -8<=h<=12, -9<=k<=11, -20<=l<=14
Reflections collected 10926
Independent reflections 2610 [R(int) = 0.0443]
Completeness to theta = 26.35° 99.9 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 0.9596 and 0.9553
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 2610 / 1 / 182
Goodness-of-fit on F² 1.004
Final R indices [I>2sigma(I)] R1 = 0.0346, wR2 = 0.0871
R indices (all data) R1 = 0.0373, wR2 = 0.0895
Absolute structure parameter 0.03(7)
Extinction coefficient 0.0113(13)
Largest diff. peak and hole 0.306 and -0.381 e.Å⁻³
Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for 43. U(eq) is defined as one third of the trace of the orthogonalized U^ij tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)</td>
<td>8833(2)</td>
<td>7711(3)</td>
<td>6854(1)</td>
<td>32(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>8456(3)</td>
<td>7829(3)</td>
<td>6050(2)</td>
<td>39(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>7592(3)</td>
<td>6798(3)</td>
<td>5700(2)</td>
<td>38(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>7113(3)</td>
<td>5626(3)</td>
<td>6154(2)</td>
<td>40(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>7494(3)</td>
<td>5484(3)</td>
<td>6954(1)</td>
<td>35(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>8347(2)</td>
<td>6536(2)</td>
<td>7318(1)</td>
<td>26(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>8656(2)</td>
<td>6363(2)</td>
<td>8194(1)</td>
<td>24(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>9636(2)</td>
<td>7362(2)</td>
<td>8658(1)</td>
<td>28(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>9250(3)</td>
<td>7872(3)</td>
<td>9500(1)</td>
<td>36(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>9657(3)</td>
<td>6749(3)</td>
<td>10143(2)</td>
<td>36(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>9185(2)</td>
<td>5170(2)</td>
<td>9921(1)</td>
<td>29(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>9972(2)</td>
<td>4636(2)</td>
<td>9178(1)</td>
<td>24(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>10036(2)</td>
<td>5752(2)</td>
<td>8498(1)</td>
<td>23(1)</td>
</tr>
<tr>
<td>C(14)</td>
<td>11173(2)</td>
<td>5485(2)</td>
<td>7887(1)</td>
<td>28(1)</td>
</tr>
<tr>
<td>C(15)</td>
<td>11116(2)</td>
<td>3981(2)</td>
<td>7475(1)</td>
<td>32(1)</td>
</tr>
<tr>
<td>N(1)</td>
<td>9363(2)</td>
<td>3205(2)</td>
<td>8894(1)</td>
<td>25(1)</td>
</tr>
<tr>
<td>O(1)</td>
<td>11494(2)</td>
<td>2789(2)</td>
<td>8038(1)</td>
<td>31(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>9466(2)</td>
<td>1110(2)</td>
<td>7961(1)</td>
<td>36(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>11087(2)</td>
<td>1147(2)</td>
<td>9094(1)</td>
<td>38(1)</td>
</tr>
<tr>
<td>S(1)</td>
<td>10309(1)</td>
<td>1937(1)</td>
<td>8500(1)</td>
<td>27(1)</td>
</tr>
</tbody>
</table>
Table 3. Bond lengths [Å] and angles [°] for 43__

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length [Å]</th>
<th>Angle [°]</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)-C(6)</td>
<td>1.388(3)</td>
<td></td>
</tr>
<tr>
<td>C(1)-C(2)</td>
<td>1.392(3)</td>
<td></td>
</tr>
<tr>
<td>C(1)-H(1)</td>
<td>0.9500</td>
<td></td>
</tr>
<tr>
<td>C(2)-C(3)</td>
<td>1.375(4)</td>
<td></td>
</tr>
<tr>
<td>C(2)-H(2)</td>
<td>0.9500</td>
<td></td>
</tr>
<tr>
<td>C(3)-C(4)</td>
<td>1.375(4)</td>
<td></td>
</tr>
<tr>
<td>C(3)-H(3)</td>
<td>0.9500</td>
<td></td>
</tr>
<tr>
<td>C(4)-C(5)</td>
<td>1.388(3)</td>
<td></td>
</tr>
<tr>
<td>C(4)-H(4)</td>
<td>0.9500</td>
<td></td>
</tr>
<tr>
<td>C(5)-C(6)</td>
<td>1.391(3)</td>
<td></td>
</tr>
<tr>
<td>C(5)-H(5)</td>
<td>0.9500</td>
<td></td>
</tr>
<tr>
<td>C(6)-C(7)</td>
<td>1.499(3)</td>
<td></td>
</tr>
<tr>
<td>C(7)-C(8)</td>
<td>1.516(3)</td>
<td></td>
</tr>
<tr>
<td>C(7)-C(13)</td>
<td>1.529(3)</td>
<td></td>
</tr>
<tr>
<td>C(7)-H(7)</td>
<td>1.0000</td>
<td></td>
</tr>
<tr>
<td>C(8)-C(13)</td>
<td>1.518(3)</td>
<td></td>
</tr>
<tr>
<td>C(8)-C(9)</td>
<td>1.522(3)</td>
<td></td>
</tr>
<tr>
<td>C(8)-H(8)</td>
<td>1.0000</td>
<td></td>
</tr>
<tr>
<td>C(9)-C(10)</td>
<td>1.522(3)</td>
<td></td>
</tr>
<tr>
<td>C(9)-H(9A)</td>
<td>0.9900</td>
<td></td>
</tr>
<tr>
<td>C(9)-H(9B)</td>
<td>0.9900</td>
<td></td>
</tr>
<tr>
<td>C(10)-C(11)</td>
<td>1.533(3)</td>
<td></td>
</tr>
<tr>
<td>C(10)-H(10A)</td>
<td>0.9900</td>
<td></td>
</tr>
<tr>
<td>C(10)-H(10B)</td>
<td>0.9900</td>
<td></td>
</tr>
<tr>
<td>C(11)-C(12)</td>
<td>1.530(3)</td>
<td></td>
</tr>
<tr>
<td>C(11)-H(11A)</td>
<td>0.9900</td>
<td></td>
</tr>
<tr>
<td>C(11)-H(11B)</td>
<td>0.9900</td>
<td></td>
</tr>
<tr>
<td>C(12)-N(1)</td>
<td>1.488(3)</td>
<td></td>
</tr>
<tr>
<td>C(12)-C(13)</td>
<td>1.512(3)</td>
<td></td>
</tr>
<tr>
<td>C(12)-H(12)</td>
<td>1.0000</td>
<td></td>
</tr>
<tr>
<td>C(13)-C(14)</td>
<td>1.518(3)</td>
<td></td>
</tr>
<tr>
<td>C(14)-C(15)</td>
<td>1.514(3)</td>
<td></td>
</tr>
<tr>
<td>C(14)-H(14A)</td>
<td>0.9900</td>
<td></td>
</tr>
<tr>
<td>C(14)-H(14B)</td>
<td>0.9900</td>
<td></td>
</tr>
<tr>
<td>C(15)-O(1)</td>
<td>1.468(3)</td>
<td></td>
</tr>
</tbody>
</table>
C(15)-H(15A) 0.9900
C(15)-H(15B) 0.9900
N(1)-S(1) 1.5996(18)
N(1)-H(1A) 0.8800
O(1)-S(1) 1.5775(16)
O(2)-S(1) 1.4220(16)
O(3)-S(1) 1.4312(17)
C(6)-C(1)-C(2) 120.3(2)
C(6)-C(1)-H(1) 119.8
C(2)-C(1)-H(1) 119.8
C(3)-C(2)-C(1) 121.0(2)
C(3)-C(2)-H(2) 119.5
C(1)-C(2)-H(2) 119.5
C(4)-C(3)-C(2) 119.0(2)
C(4)-C(3)-H(3) 120.5
C(2)-C(3)-H(3) 120.5
C(3)-C(4)-C(5) 120.5(3)
C(3)-C(4)-H(4) 119.7
C(5)-C(4)-H(4) 119.7
C(4)-C(5)-C(6) 120.9(2)
C(4)-C(5)-H(5) 119.6
C(6)-C(5)-H(5) 119.6
C(1)-C(6)-C(5) 118.2(2)
C(1)-C(6)-C(7) 123.6(2)
C(5)-C(6)-C(7) 118.2(2)
C(6)-C(7)-C(8) 124.07(19)
C(6)-C(7)-C(13) 122.26(18)
C(8)-C(7)-C(13) 59.79(13)
C(6)-C(7)-H(7) 113.5
C(8)-C(7)-H(7) 113.5
C(13)-C(7)-H(7) 113.5
C(7)-C(8)-C(13) 60.53(13)
C(7)-C(8)-C(9) 119.6(2)
C(13)-C(8)-C(9) 120.66(19)
C(7)-C(8)-H(8) 115.1
C(13)-C(8)-H(8)  115.1
C(9)-C(8)-H(8)  115.1
C(10)-C(9)-C(8)  112.73(19)
C(10)-C(9)-H(9A)  109.0
C(8)-C(9)-H(9A)  109.0
C(10)-C(9)-H(9B)  109.0
C(8)-C(9)-H(9B)  109.0
H(9A)-C(9)-H(9B)  107.8
C(9)-C(10)-C(11)  111.3(2)
C(9)-C(10)-H(10A)  109.4
C(11)-C(10)-H(10A)  109.4
C(9)-C(10)-H(10B)  109.4
C(11)-C(10)-H(10B)  109.4
H(10A)-C(10)-H(10B)  108.0
C(12)-C(11)-C(10)  109.65(18)
C(12)-C(11)-H(11A)  109.7
C(10)-C(11)-H(11A)  109.7
C(12)-C(11)-H(11B)  109.7
C(10)-C(11)-H(11B)  109.7
H(11A)-C(11)-H(11B)  108.2
N(1)-C(12)-C(13)  110.43(17)
N(1)-C(12)-C(11)  109.23(17)
C(13)-C(12)-C(11)  114.73(16)
N(1)-C(12)-H(12)  107.4
C(13)-C(12)-H(12)  107.4
C(11)-C(12)-H(12)  107.4
C(12)-C(13)-C(14)  115.28(16)
C(12)-C(13)-C(8)  119.20(19)
C(14)-C(13)-C(8)  116.89(17)
C(12)-C(13)-C(7)  116.72(17)
C(14)-C(13)-C(7)  117.83(19)
C(8)-C(13)-C(7)  59.68(13)
C(15)-C(14)-C(13)  114.72(18)
C(15)-C(14)-H(14A)  108.6
C(13)-C(14)-H(14A)  108.6
C(15)-C(14)-H(14B)  108.6
<table>
<thead>
<tr>
<th>Bond Length (Å)</th>
<th>108.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(14A)-C(14)-H(14B)</td>
<td>107.6</td>
</tr>
<tr>
<td>O(1)-C(15)-C(14)</td>
<td>110.46(18)</td>
</tr>
<tr>
<td>O(1)-C(15)-H(15A)</td>
<td>109.6</td>
</tr>
<tr>
<td>C(14)-C(15)-H(15A)</td>
<td>109.6</td>
</tr>
<tr>
<td>O(1)-C(15)-H(15B)</td>
<td>109.6</td>
</tr>
<tr>
<td>C(14)-C(15)-H(15B)</td>
<td>109.6</td>
</tr>
<tr>
<td>H(15A)-C(15)-H(15B)</td>
<td>108.1</td>
</tr>
<tr>
<td>C(12)-N(1)-S(1)</td>
<td>121.09(14)</td>
</tr>
<tr>
<td>C(12)-N(1)-H(1A)</td>
<td>119.5</td>
</tr>
<tr>
<td>S(1)-N(1)-H(1A)</td>
<td>119.5</td>
</tr>
<tr>
<td>C(15)-O(1)-S(1)</td>
<td>118.87(13)</td>
</tr>
<tr>
<td>O(2)-S(1)-O(3)</td>
<td>118.69(10)</td>
</tr>
<tr>
<td>O(2)-S(1)-O(1)</td>
<td>111.15(10)</td>
</tr>
<tr>
<td>O(3)-S(1)-O(1)</td>
<td>101.26(9)</td>
</tr>
<tr>
<td>O(2)-S(1)-N(1)</td>
<td>107.62(9)</td>
</tr>
<tr>
<td>O(3)-S(1)-N(1)</td>
<td>111.57(10)</td>
</tr>
<tr>
<td>O(1)-S(1)-N(1)</td>
<td>105.77(9)</td>
</tr>
</tbody>
</table>

Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters (Å² x 10³) for 43. The anisotropic displacement factor exponent takes the form: -2π² [ h² a*²U¹¹ + ... + 2 h k a* b* U¹² ]

<table>
<thead>
<tr>
<th></th>
<th>U¹¹</th>
<th>U²²</th>
<th>U³³</th>
<th>U²³</th>
<th>U¹³</th>
<th>U¹²</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)</td>
<td>35(1)</td>
<td>30(1)</td>
<td>31(1)</td>
<td>3(1)</td>
<td>2(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>44(1)</td>
<td>42(1)</td>
<td>30(1)</td>
<td>13(1)</td>
<td>5(1)</td>
<td>5(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>39(1)</td>
<td>50(2)</td>
<td>25(1)</td>
<td>3(1)</td>
<td>1(1)</td>
<td>15(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>43(1)</td>
<td>43(2)</td>
<td>33(1)</td>
<td>-4(1)</td>
<td>-6(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>42(1)</td>
<td>31(1)</td>
<td>32(1)</td>
<td>2(1)</td>
<td>-2(1)</td>
<td>-3(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>26(1)</td>
<td>27(1)</td>
<td>25(1)</td>
<td>3(1)</td>
<td>5(1)</td>
<td>9(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>28(1)</td>
<td>21(1)</td>
<td>25(1)</td>
<td>1(1)</td>
<td>3(1)</td>
<td>2(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>39(1)</td>
<td>18(1)</td>
<td>27(1)</td>
<td>0(1)</td>
<td>2(1)</td>
<td>-1(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>55(2)</td>
<td>24(1)</td>
<td>30(1)</td>
<td>-4(1)</td>
<td>3(1)</td>
<td>-1(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>52(2)</td>
<td>29(1)</td>
<td>27(1)</td>
<td>-4(1)</td>
<td>0(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>38(1)</td>
<td>25(1)</td>
<td>24(1)</td>
<td>2(1)</td>
<td>1(1)</td>
<td>-2(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>28(1)</td>
<td>20(1)</td>
<td>24(1)</td>
<td>0(1)</td>
<td>-2(1)</td>
<td>-2(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>26(1)</td>
<td>20(1)</td>
<td>23(1)</td>
<td>0(1)</td>
<td>-2(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(14)</td>
<td>28(1)</td>
<td>26(1)</td>
<td>29(1)</td>
<td>1(1)</td>
<td>2(1)</td>
<td>-2(1)</td>
</tr>
<tr>
<td>C(15)</td>
<td>31(1)</td>
<td>33(1)</td>
<td>31(1)</td>
<td>-2(1)</td>
<td>6(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>N(1)</td>
<td>23(1)</td>
<td>20(1)</td>
<td>31(1)</td>
<td>0(1)</td>
<td>3(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>O(1)</td>
<td>25(1)</td>
<td>28(1)</td>
<td>41(1)</td>
<td>-2(1)</td>
<td>4(1)</td>
<td>3(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>31(1)</td>
<td>29(1)</td>
<td>50(1)</td>
<td>-12(1)</td>
<td>-3(1)</td>
<td>-1(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>36(1)</td>
<td>28(1)</td>
<td>51(1)</td>
<td>4(1)</td>
<td>-6(1)</td>
<td>7(1)</td>
</tr>
<tr>
<td>S(1)</td>
<td>25(1)</td>
<td>21(1)</td>
<td>35(1)</td>
<td>-3(1)</td>
<td>-1(1)</td>
<td>1(1)</td>
</tr>
</tbody>
</table>
Table 5. Hydrogen coordinates (x \(10^4\)) and isotropic displacement parameters (Å\(^2\)x \(10^{-3}\)) for 43.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(1)</td>
<td>9426</td>
<td>8437</td>
<td>7086</td>
<td>38</td>
</tr>
<tr>
<td>H(2)</td>
<td>8801</td>
<td>8635</td>
<td>5738</td>
<td>46</td>
</tr>
<tr>
<td>H(3)</td>
<td>7331</td>
<td>6895</td>
<td>5153</td>
<td>46</td>
</tr>
<tr>
<td>H(4)</td>
<td>6515</td>
<td>4908</td>
<td>5918</td>
<td>48</td>
</tr>
<tr>
<td>H(5)</td>
<td>7169</td>
<td>4658</td>
<td>7257</td>
<td>42</td>
</tr>
<tr>
<td>H(7)</td>
<td>7843</td>
<td>6022</td>
<td>8517</td>
<td>29</td>
</tr>
<tr>
<td>H(8)</td>
<td>10139</td>
<td>8118</td>
<td>8327</td>
<td>33</td>
</tr>
<tr>
<td>H(9A)</td>
<td>9712</td>
<td>8835</td>
<td>9613</td>
<td>44</td>
</tr>
<tr>
<td>H(9B)</td>
<td>8239</td>
<td>8040</td>
<td>9525</td>
<td>44</td>
</tr>
<tr>
<td>H(10A)</td>
<td>9234</td>
<td>7041</td>
<td>10661</td>
<td>43</td>
</tr>
<tr>
<td>H(10B)</td>
<td>10674</td>
<td>6759</td>
<td>10211</td>
<td>43</td>
</tr>
<tr>
<td>H(11A)</td>
<td>9362</td>
<td>4484</td>
<td>10375</td>
<td>35</td>
</tr>
<tr>
<td>H(11B)</td>
<td>8179</td>
<td>5170</td>
<td>9810</td>
<td>35</td>
</tr>
<tr>
<td>H(12)</td>
<td>10945</td>
<td>4425</td>
<td>9347</td>
<td>29</td>
</tr>
<tr>
<td>H(14A)</td>
<td>11122</td>
<td>6275</td>
<td>7473</td>
<td>33</td>
</tr>
<tr>
<td>H(14B)</td>
<td>12078</td>
<td>5582</td>
<td>8160</td>
<td>33</td>
</tr>
<tr>
<td>H(15A)</td>
<td>10170</td>
<td>3803</td>
<td>7269</td>
<td>38</td>
</tr>
<tr>
<td>H(15B)</td>
<td>11760</td>
<td>3974</td>
<td>7013</td>
<td>38</td>
</tr>
<tr>
<td>H(1A)</td>
<td>8468</td>
<td>3054</td>
<td>8945</td>
<td>30</td>
</tr>
</tbody>
</table>
X-Ray crystallography for compound 44.

Table 1. Crystal data and structure refinement for 44.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>44</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C15 H19 N O3 S</td>
</tr>
<tr>
<td>Formula weight</td>
<td>293.37</td>
</tr>
<tr>
<td>Temperature</td>
<td>173(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>1.54178 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2(1)/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 7.3266(3) Å</td>
</tr>
<tr>
<td></td>
<td>b = 25.3593(12) Å</td>
</tr>
<tr>
<td></td>
<td>c = 8.0363(4) Å</td>
</tr>
<tr>
<td>Volume</td>
<td>1433.06(11) Å</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.360 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>2.070 mm⁻¹</td>
</tr>
</tbody>
</table>
F(000)  
624

Crystal size  
0.37 x 0.18 x 0.05 mm³

Theta range for data collection  
3.49 to 65.93°

Index ranges  
-8<=h<=8, -30<=k<=28, -9<=l<=9

Reflections collected  
10138

Independent reflections  
2412 [R(int) = 0.0265]

Completeness to theta = 65.93°  
96.5 %

Absorption correction  
Semi-empirical from equivalents

Max. and min. transmission  
0.9036 and 0.5147

Refinement method  
Full-matrix least-squares on F²

Data / restraints / parameters  
2412 / 0 / 185

Goodness-of-fit on F²  
1.068

Final R indices [I>2sigma(I)]  
R1 = 0.0345, wR2 = 0.1101

R indices (all data)  
R1 = 0.0400, wR2 = 0.1145

Largest diff. peak and hole  
0.185 and -0.386 e.Å⁻³
Table 2. Atomic coordinates (x $10^4$) and equivalent isotropic displacement parameters (Å$^2$x $10^3$) for 44. U(eq) is defined as one third of the trace of the orthogonalized U$ij$ tensor.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)</td>
<td>2230(2)</td>
<td>4291(1)</td>
<td>3967(2)</td>
<td>30(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>599(3)</td>
<td>4201(1)</td>
<td>4764(2)</td>
<td>37(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>1329(3)</td>
<td>3897(1)</td>
<td>6441(2)</td>
<td>47(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>1908(3)</td>
<td>3341(1)</td>
<td>6092(2)</td>
<td>44(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>3157(3)</td>
<td>3320(1)</td>
<td>4848(2)</td>
<td>40(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>2312(3)</td>
<td>3291(1)</td>
<td>2899(2)</td>
<td>37(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>255(3)</td>
<td>3202(1)</td>
<td>1998(2)</td>
<td>34(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>-708(3)</td>
<td>2779(1)</td>
<td>2471(2)</td>
<td>41(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>-2573(3)</td>
<td>2671(1)</td>
<td>1583(3)</td>
<td>47(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>-3526(3)</td>
<td>2978(1)</td>
<td>204(3)</td>
<td>46(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>-2589(3)</td>
<td>3393(1)</td>
<td>-312(2)</td>
<td>42(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>-723(3)</td>
<td>3502(1)</td>
<td>569(2)</td>
<td>37(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>3292(2)</td>
<td>3792(1)</td>
<td>373(2)</td>
<td>32(1)</td>
</tr>
<tr>
<td>C(14)</td>
<td>5225(3)</td>
<td>3901(1)</td>
<td>344(2)</td>
<td>39(1)</td>
</tr>
<tr>
<td>C(15)</td>
<td>5154(3)</td>
<td>4254(1)</td>
<td>190(3)</td>
<td>41(1)</td>
</tr>
<tr>
<td>N(1)</td>
<td>1569(2)</td>
<td>4573(1)</td>
<td>230(2)</td>
<td>33(1)</td>
</tr>
<tr>
<td>O(1)</td>
<td>2918(2)</td>
<td>5506(1)</td>
<td>275(2)</td>
<td>49(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>2134(2)</td>
<td>5085(1)</td>
<td>-71(2)</td>
<td>45(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>4832(2)</td>
<td>4803(1)</td>
<td>235(2)</td>
<td>39(1)</td>
</tr>
<tr>
<td>S(1)</td>
<td>2786(1)</td>
<td>5034(1)</td>
<td>177(1)</td>
<td>34(1)</td>
</tr>
</tbody>
</table>
Table 3. Bond lengths [Å] and angles [°] for 44.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length [Å]</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)-N(1)</td>
<td>1.472(2)</td>
</tr>
<tr>
<td>C(1)-C(13)</td>
<td>1.525(2)</td>
</tr>
<tr>
<td>C(1)-C(2)</td>
<td>1.523(2)</td>
</tr>
<tr>
<td>C(1)-H(1)</td>
<td>1.0000</td>
</tr>
<tr>
<td>C(2)-C(3)</td>
<td>1.514(3)</td>
</tr>
<tr>
<td>C(2)-H(2A)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(2)-H(2B)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(3)-C(4)</td>
<td>1.520(3)</td>
</tr>
<tr>
<td>C(3)-H(3A)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(3)-H(3B)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(4)-C(5)</td>
<td>1.534(3)</td>
</tr>
<tr>
<td>C(4)-H(4A)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(4)-H(4B)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(5)-C(13)</td>
<td>1.514(2)</td>
</tr>
<tr>
<td>C(5)-C(6)</td>
<td>1.516(3)</td>
</tr>
<tr>
<td>C(5)-H(5)</td>
<td>1.0000</td>
</tr>
<tr>
<td>C(6)-C(7)</td>
<td>1.495(3)</td>
</tr>
<tr>
<td>C(6)-C(13)</td>
<td>1.518(2)</td>
</tr>
<tr>
<td>C(6)-H(6)</td>
<td>1.0000</td>
</tr>
<tr>
<td>C(7)-C(8)</td>
<td>1.394(2)</td>
</tr>
<tr>
<td>C(7)-C(12)</td>
<td>1.396(2)</td>
</tr>
<tr>
<td>C(8)-C(9)</td>
<td>1.380(3)</td>
</tr>
<tr>
<td>C(8)-H(8)</td>
<td>0.9500</td>
</tr>
<tr>
<td>C(9)-C(10)</td>
<td>1.374(3)</td>
</tr>
<tr>
<td>C(9)-H(9)</td>
<td>0.9500</td>
</tr>
<tr>
<td>C(10)-C(11)</td>
<td>1.383(3)</td>
</tr>
<tr>
<td>C(10)-H(10)</td>
<td>0.9500</td>
</tr>
<tr>
<td>C(11)-C(12)</td>
<td>1.379(3)</td>
</tr>
<tr>
<td>C(11)-H(11)</td>
<td>0.9500</td>
</tr>
<tr>
<td>C(12)-H(12)</td>
<td>0.9500</td>
</tr>
<tr>
<td>C(13)-C(14)</td>
<td>1.526(2)</td>
</tr>
<tr>
<td>C(14)-C(15)</td>
<td>1.513(2)</td>
</tr>
<tr>
<td>C(14)-H(14A)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(14)-H(14B)</td>
<td>0.9900</td>
</tr>
<tr>
<td>Bond</td>
<td>Length</td>
</tr>
<tr>
<td>------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>C(15)-O(3)</td>
<td>1.473(2)</td>
</tr>
<tr>
<td>C(15)-H(15A)</td>
<td>0.9900</td>
</tr>
<tr>
<td>C(15)-H(15B)</td>
<td>0.9900</td>
</tr>
<tr>
<td>N(1)-S(1)</td>
<td>1.6007(14)</td>
</tr>
<tr>
<td>N(1)-H(1N)</td>
<td>0.80(2)</td>
</tr>
<tr>
<td>O(1)-S(1)</td>
<td>1.4240(13)</td>
</tr>
<tr>
<td>O(2)-S(1)</td>
<td>1.4271(14)</td>
</tr>
<tr>
<td>O(3)-S(1)</td>
<td>1.5541(13)</td>
</tr>
<tr>
<td>N(1)-C(1)-C(13)</td>
<td>109.96(13)</td>
</tr>
<tr>
<td>N(1)-C(1)-C(2)</td>
<td>110.94(14)</td>
</tr>
<tr>
<td>C(13)-C(1)-C(2)</td>
<td>114.48(13)</td>
</tr>
<tr>
<td>N(1)-C(1)-H(1)</td>
<td>107.0</td>
</tr>
<tr>
<td>C(13)-C(1)-H(1)</td>
<td>107.0</td>
</tr>
<tr>
<td>C(2)-C(1)-H(1)</td>
<td>107.0</td>
</tr>
<tr>
<td>C(3)-C(2)-C(1)</td>
<td>109.15(15)</td>
</tr>
<tr>
<td>C(3)-C(2)-H(2A)</td>
<td>109.9</td>
</tr>
<tr>
<td>C(1)-C(2)-H(2A)</td>
<td>109.9</td>
</tr>
<tr>
<td>C(3)-C(2)-H(2B)</td>
<td>109.9</td>
</tr>
<tr>
<td>C(1)-C(2)-H(2B)</td>
<td>109.9</td>
</tr>
<tr>
<td>H(2A)-C(2)-H(2B)</td>
<td>108.3</td>
</tr>
<tr>
<td>C(2)-C(3)-C(4)</td>
<td>110.76(14)</td>
</tr>
<tr>
<td>C(2)-C(3)-H(3A)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(4)-C(3)-H(3A)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(2)-C(3)-H(3B)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(4)-C(3)-H(3B)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(3A)-C(3)-H(3B)</td>
<td>108.1</td>
</tr>
<tr>
<td>C(3)-C(4)-C(5)</td>
<td>113.69(14)</td>
</tr>
<tr>
<td>C(3)-C(4)-H(4A)</td>
<td>108.8</td>
</tr>
<tr>
<td>C(5)-C(4)-H(4A)</td>
<td>108.8</td>
</tr>
<tr>
<td>C(3)-C(4)-H(4B)</td>
<td>108.8</td>
</tr>
<tr>
<td>C(5)-C(4)-H(4B)</td>
<td>108.8</td>
</tr>
<tr>
<td>H(4A)-C(4)-H(4B)</td>
<td>107.7</td>
</tr>
<tr>
<td>C(13)-C(5)-C(6)</td>
<td>60.13(11)</td>
</tr>
<tr>
<td>C(13)-C(5)-C(4)</td>
<td>120.43(15)</td>
</tr>
<tr>
<td>C(6)-C(5)-C(4)</td>
<td>121.99(16)</td>
</tr>
</tbody>
</table>
C(13)-C(5)-H(5)  114.5
C(6)-C(5)-H(5)  114.5
C(4)-C(5)-H(5)  114.5
C(7)-C(6)-C(5)  124.84(14)
C(7)-C(6)-C(13)  128.92(15)
C(5)-C(6)-C(13)  59.88(11)
C(7)-C(6)-H(6)  111.3
C(5)-C(6)-H(6)  111.3
C(13)-C(6)-H(6)  111.3
C(8)-C(7)-C(12)  117.50(17)
C(8)-C(7)-C(6)  120.22(16)
C(12)-C(7)-C(6)  122.02(15)
C(9)-C(8)-C(7)  121.02(18)
C(9)-C(8)-H(8)  119.5
C(7)-C(8)-H(8)  119.5
C(10)-C(9)-C(8)  120.63(17)
C(10)-C(9)-H(9)  119.7
C(8)-C(9)-H(9)  119.7
C(9)-C(10)-C(11)  119.41(19)
C(9)-C(10)-H(10)  120.3
C(11)-C(10)-H(10)  120.3
C(12)-C(11)-C(10)  120.16(18)
C(12)-C(11)-H(11)  119.9
C(10)-C(11)-H(11)  119.9
C(11)-C(12)-C(7)  121.25(16)
C(11)-C(12)-H(12)  119.4
C(7)-C(12)-H(12)  119.4
C(5)-C(13)-C(6)  59.99(11)
C(5)-C(13)-C(1)  117.66(13)
C(6)-C(13)-C(1)  123.64(14)
C(5)-C(13)-C(14)  116.93(14)
C(6)-C(13)-C(14)  115.35(14)
C(1)-C(13)-C(14)  113.28(14)
C(15)-C(14)-C(13)  114.39(15)
C(15)-C(14)-H(14A)  108.7
C(13)-C(14)-H(14A)  108.7
<table>
<thead>
<tr>
<th>Bond</th>
<th>Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(15)-C(14)-H(14B)</td>
<td>108.7</td>
</tr>
<tr>
<td>C(13)-C(14)-H(14B)</td>
<td>108.7</td>
</tr>
<tr>
<td>H(14A)-C(14)-H(14B)</td>
<td>107.6</td>
</tr>
<tr>
<td>O(3)-C(15)-C(14)</td>
<td>109.21(14)</td>
</tr>
<tr>
<td>O(3)-C(15)-H(15A)</td>
<td>109.8</td>
</tr>
<tr>
<td>C(14)-C(15)-H(15A)</td>
<td>109.8</td>
</tr>
<tr>
<td>O(3)-C(15)-H(15B)</td>
<td>109.8</td>
</tr>
<tr>
<td>C(14)-C(15)-H(15B)</td>
<td>109.8</td>
</tr>
<tr>
<td>H(15A)-C(15)-H(15B)</td>
<td>108.3</td>
</tr>
<tr>
<td>C(1)-N(1)-S(1)</td>
<td>122.13(12)</td>
</tr>
<tr>
<td>C(1)-N(1)-H(1N)</td>
<td>121.3(14)</td>
</tr>
<tr>
<td>S(1)-N(1)-H(1N)</td>
<td>113.1(14)</td>
</tr>
<tr>
<td>C(15)-O(3)-S(1)</td>
<td>119.29(11)</td>
</tr>
<tr>
<td>O(1)-S(1)-O(2)</td>
<td>116.86(8)</td>
</tr>
<tr>
<td>O(1)-S(1)-O(3)</td>
<td>103.83(8)</td>
</tr>
<tr>
<td>O(2)-S(1)-O(3)</td>
<td>111.30(7)</td>
</tr>
<tr>
<td>O(1)-S(1)-N(1)</td>
<td>114.81(8)</td>
</tr>
<tr>
<td>O(2)-S(1)-N(1)</td>
<td>107.16(8)</td>
</tr>
<tr>
<td>O(3)-S(1)-N(1)</td>
<td>101.85(7)</td>
</tr>
</tbody>
</table>

Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters (Å$^2 \times 10^3$) for 44. The anisotropic displacement factor exponent takes the form: 

$$-2\pi^2 [ h^2 a^* a U_{11}^{11} + \ldots + 2h k a^* b^* U_{12}^{12} ]$$

<table>
<thead>
<tr>
<th></th>
<th>$U_{11}$</th>
<th>$U_{22}$</th>
<th>$U_{33}$</th>
<th>$U_{23}$</th>
<th>$U_{13}$</th>
<th>$U_{12}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(1)</td>
<td>29(1)</td>
<td>32(1)</td>
<td>32(1)</td>
<td>1(1)</td>
<td>10(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>39(1)</td>
<td>35(1)</td>
<td>42(1)</td>
<td>0(1)</td>
<td>21(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>53(1)</td>
<td>56(1)</td>
<td>36(1)</td>
<td>1(1)</td>
<td>20(1)</td>
<td>-10(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>44(1)</td>
<td>48(1)</td>
<td>37(1)</td>
<td>15(1)</td>
<td>7(1)</td>
<td>-4(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>33(1)</td>
<td>37(1)</td>
<td>45(1)</td>
<td>12(1)</td>
<td>6(1)</td>
<td>6(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>36(1)</td>
<td>31(1)</td>
<td>45(1)</td>
<td>1(1)</td>
<td>14(1)</td>
<td>5(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>39(1)</td>
<td>30(1)</td>
<td>36(1)</td>
<td>-5(1)</td>
<td>13(1)</td>
<td>-1(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>49(1)</td>
<td>33(1)</td>
<td>39(1)</td>
<td>3(1)</td>
<td>10(1)</td>
<td>-4(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>53(1)</td>
<td>44(1)</td>
<td>41(1)</td>
<td>-1(1)</td>
<td>11(1)</td>
<td>-17(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>45(1)</td>
<td>50(1)</td>
<td>41(1)</td>
<td>-5(1)</td>
<td>7(1)</td>
<td>-9(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>54(1)</td>
<td>37(1)</td>
<td>32(1)</td>
<td>-2(1)</td>
<td>6(1)</td>
<td>-2(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>48(1)</td>
<td>30(1)</td>
<td>32(1)</td>
<td>-3(1)</td>
<td>13(1)</td>
<td>-5(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>28(1)</td>
<td>33(1)</td>
<td>35(1)</td>
<td>4(1)</td>
<td>9(1)</td>
<td>2(1)</td>
</tr>
<tr>
<td>C(14)</td>
<td>27(1)</td>
<td>43(1)</td>
<td>48(1)</td>
<td>3(1)</td>
<td>11(1)</td>
<td>5(1)</td>
</tr>
<tr>
<td>C(15)</td>
<td>29(1)</td>
<td>47(1)</td>
<td>50(1)</td>
<td>1(1)</td>
<td>18(1)</td>
<td>2(1)</td>
</tr>
<tr>
<td>N(1)</td>
<td>24(1)</td>
<td>35(1)</td>
<td>38(1)</td>
<td>8(1)</td>
<td>8(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>O(1)</td>
<td>56(1)</td>
<td>33(1)</td>
<td>61(1)</td>
<td>-1(1)</td>
<td>19(1)</td>
<td>-6(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>35(1)</td>
<td>62(1)</td>
<td>40(1)</td>
<td>16(1)</td>
<td>13(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>28(1)</td>
<td>43(1)</td>
<td>46(1)</td>
<td>6(1)</td>
<td>10(1)</td>
<td>-5(1)</td>
</tr>
<tr>
<td>S(1)</td>
<td>32(1)</td>
<td>35(1)</td>
<td>38(1)</td>
<td>7(1)</td>
<td>12(1)</td>
<td>-2(1)</td>
</tr>
</tbody>
</table>
Table 5. Hydrogen coordinates ($x \times 10^4$) and isotropic displacement parameters ($\AA^2 \times 10^3$) for 44

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(1)</td>
<td>3169</td>
<td>4526</td>
<td>4777</td>
<td>36</td>
</tr>
<tr>
<td>H(2A)</td>
<td>73</td>
<td>4544</td>
<td>4994</td>
<td>44</td>
</tr>
<tr>
<td>H(2B)</td>
<td>-428</td>
<td>4000</td>
<td>3948</td>
<td>44</td>
</tr>
<tr>
<td>H(3A)</td>
<td>324</td>
<td>3880</td>
<td>7045</td>
<td>56</td>
</tr>
<tr>
<td>H(3B)</td>
<td>2438</td>
<td>4083</td>
<td>7207</td>
<td>56</td>
</tr>
<tr>
<td>H(4A)</td>
<td>746</td>
<td>3130</td>
<td>5598</td>
<td>53</td>
</tr>
<tr>
<td>H(4B)</td>
<td>2607</td>
<td>3177</td>
<td>7206</td>
<td>53</td>
</tr>
<tr>
<td>H(5)</td>
<td>4373</td>
<td>3120</td>
<td>5300</td>
<td>48</td>
</tr>
<tr>
<td>H(6)</td>
<td>3146</td>
<td>3085</td>
<td>2343</td>
<td>44</td>
</tr>
<tr>
<td>H(8)</td>
<td>-70</td>
<td>2562</td>
<td>3419</td>
<td>49</td>
</tr>
<tr>
<td>H(9)</td>
<td>-3204</td>
<td>2381</td>
<td>1928</td>
<td>56</td>
</tr>
<tr>
<td>H(10)</td>
<td>-4817</td>
<td>2906</td>
<td>-390</td>
<td>55</td>
</tr>
<tr>
<td>H(11)</td>
<td>-3232</td>
<td>3604</td>
<td>-1276</td>
<td>50</td>
</tr>
<tr>
<td>H(12)</td>
<td>-92</td>
<td>3787</td>
<td>197</td>
<td>44</td>
</tr>
<tr>
<td>H(14A)</td>
<td>6058</td>
<td>4067</td>
<td>4498</td>
<td>47</td>
</tr>
<tr>
<td>H(14B)</td>
<td>5812</td>
<td>3561</td>
<td>3271</td>
<td>47</td>
</tr>
<tr>
<td>H(15A)</td>
<td>6367</td>
<td>4230</td>
<td>1597</td>
<td>49</td>
</tr>
<tr>
<td>H(15B)</td>
<td>4113</td>
<td>4140</td>
<td>893</td>
<td>49</td>
</tr>
<tr>
<td>H(1N)</td>
<td>470(30)</td>
<td>4583(8)</td>
<td>1780(30)</td>
<td>38(6)</td>
</tr>
</tbody>
</table>
Table 6. Torsion angles [°] for 44.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Torsion Angle [°]</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1)-C(1)-C(2)-C(3)</td>
<td>178.39(14)</td>
</tr>
<tr>
<td>C(13)-C(1)-C(2)-C(3)</td>
<td>53.23(19)</td>
</tr>
<tr>
<td>C(1)-C(2)-C(3)-C(4)</td>
<td>-66.8(2)</td>
</tr>
<tr>
<td>C(2)-C(3)-C(4)-C(5)</td>
<td>47.5(2)</td>
</tr>
<tr>
<td>C(3)-C(4)-C(5)-C(13)</td>
<td>-15.9(3)</td>
</tr>
<tr>
<td>C(3)-C(4)-C(5)-C(6)</td>
<td>-87.6(2)</td>
</tr>
<tr>
<td>C(13)-C(5)-C(6)-C(7)</td>
<td>-118.76(19)</td>
</tr>
<tr>
<td>C(4)-C(5)-C(6)-C(7)</td>
<td>-9.5(3)</td>
</tr>
<tr>
<td>C(4)-C(5)-C(6)-C(13)</td>
<td>109.27(18)</td>
</tr>
<tr>
<td>C(5)-C(6)-C(7)-C(8)</td>
<td>-51.5(2)</td>
</tr>
<tr>
<td>C(13)-C(6)-C(7)-C(8)</td>
<td>-128.53(19)</td>
</tr>
<tr>
<td>C(5)-C(6)-C(7)-C(12)</td>
<td>134.47(17)</td>
</tr>
<tr>
<td>C(13)-C(6)-C(7)-C(12)</td>
<td>57.4(2)</td>
</tr>
<tr>
<td>C(12)-C(7)-C(8)-C(9)</td>
<td>-1.6(3)</td>
</tr>
<tr>
<td>C(6)-C(7)-C(8)-C(9)</td>
<td>-175.93(17)</td>
</tr>
<tr>
<td>C(7)-C(8)-C(9)-C(10)</td>
<td>0.2(3)</td>
</tr>
<tr>
<td>C(8)-C(9)-C(10)-C(11)</td>
<td>1.1(3)</td>
</tr>
<tr>
<td>C(9)-C(10)-C(11)-C(12)</td>
<td>-1.0(3)</td>
</tr>
<tr>
<td>C(10)-C(11)-C(12)-C(7)</td>
<td>-0.5(3)</td>
</tr>
<tr>
<td>C(8)-C(7)-C(12)-C(11)</td>
<td>1.8(2)</td>
</tr>
<tr>
<td>C(6)-C(7)-C(12)-C(11)</td>
<td>175.98(16)</td>
</tr>
<tr>
<td>C(4)-C(5)-C(13)-C(6)</td>
<td>-111.79(19)</td>
</tr>
<tr>
<td>C(6)-C(5)-C(13)-C(1)</td>
<td>114.81(17)</td>
</tr>
<tr>
<td>C(4)-C(5)-C(13)-C(1)</td>
<td>3.0(3)</td>
</tr>
<tr>
<td>C(6)-C(5)-C(13)-C(14)</td>
<td>-105.14(17)</td>
</tr>
<tr>
<td>C(4)-C(5)-C(13)-C(14)</td>
<td>143.07(17)</td>
</tr>
<tr>
<td>C(7)-C(6)-C(13)-C(5)</td>
<td>112.36(19)</td>
</tr>
<tr>
<td>C(7)-C(6)-C(13)-C(1)</td>
<td>7.3(3)</td>
</tr>
<tr>
<td>C(5)-C(6)-C(13)-C(1)</td>
<td>-105.04(17)</td>
</tr>
<tr>
<td>C(7)-C(6)-C(13)-C(14)</td>
<td>-139.87(17)</td>
</tr>
<tr>
<td>C(5)-C(6)-C(13)-C(14)</td>
<td>107.77(17)</td>
</tr>
<tr>
<td>N(1)-C(1)-C(13)-C(5)</td>
<td>-147.51(15)</td>
</tr>
<tr>
<td>C(2)-C(1)-C(13)-C(5)</td>
<td>-21.8(2)</td>
</tr>
<tr>
<td>N(1)-C(1)-C(13)-C(6)</td>
<td>-76.75(19)</td>
</tr>
</tbody>
</table>
C(2)-C(1)-C(13)-C(6)  48.9(2)
N(1)-C(1)-C(13)-C(14)  71.03(18)
C(2)-C(1)-C(13)-C(14)  -163.29(15)
C(5)-C(13)-C(14)-C(15)  161.35(16)
C(6)-C(13)-C(14)-C(15)  93.69(19)
C(1)-C(13)-C(14)-C(15)  -56.9(2)
C(13)-C(14)-C(15)-O(3)  75.05(19)
C(13)-C(1)-N(1)-S(1)  -93.63(16)
C(2)-C(1)-N(1)-S(1)  138.71(12)
C(14)-C(15)-O(3)-S(1)  -98.35(15)
C(15)-O(3)-S(1)-O(1)  166.38(12)
C(15)-O(3)-S(1)-O(2)  -67.08(13)
C(15)-O(3)-S(1)-N(1)  46.83(13)
C(1)-N(1)-S(1)-O(1)  -69.04(15)
C(1)-N(1)-S(1)-O(2)  159.38(12)
C(1)-N(1)-S(1)-O(3)  42.43(14)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for 44 [Å and °].

<table>
<thead>
<tr>
<th>D-H...A</th>
<th>d(D-H)</th>
<th>d(H...A)</th>
<th>d(D...A)</th>
<th>&lt;(DHA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1)-H(1N)...O(2)#1</td>
<td>0.80(2)</td>
<td>2.18(2)</td>
<td>2.932(2)</td>
<td>156.7(19)</td>
</tr>
</tbody>
</table>

Symmetry transformations used to generate equivalent atoms:
#1 -x,-y+1,-z
Part III: Studies towards the synthesis of

(+)-Actinobolin.

7. Chapter Seven: Introduction.

7.1. Actinobolin and Bactobolin.

7.1.1 Actinobolin: Isolation, Characterization and Biological Acitivity.

In 1959, Haskell and Bartz reported the isolation of the novel natural product (+)-actinobolin 1, obtained from submerged, aerated broth cultures of a Streptomyces griseoviridus originating from a Georgia soil sample. In 1959, Haskell and Bartz reported the isolation of the novel natural product (+)-actinobolin 1, obtained from submerged, aerated broth cultures of a Streptomyces griseoviridus originating from a Georgia soil sample. Actinobolin was isolated as the crystalline sulfate salts and as the amorphous free base. Haskell and Bartz determined that this substance was a hydrophilic, amphoteric and water-soluble base that readily forms complexes with iron (III) and aluminum. Work by Struck et. al. determined that actinobolin has a molecular formula of C_{13}H_{20}N_{2}O_{6}. [79]

![Figure 7.1](image)

**Figure 7.1:** (+)-actinobolin and (-)-bactobolin.
Subsequently, a combination of degradation studies and spectroscopic methods by Munk and co-workers established the structure of actinobolin as shown in Figure 7.1 and it was later confirmed by X-Ray crystallography.\textsuperscript{80} Actinobolin is a small bicyclic β-ketolactone with a high level of functionality and five contiguous chiral centers.

Actinobolin was originally found to be a broad-spectrum antibiotic, inhibiting the growth of both gram-positive and gram-negative bacteria.\textsuperscript{81} It was also found to have some antitumor and antileukemic activity while showing relatively low toxicity.\textsuperscript{82}

It was later reported that (+)-actinobolin has weak antineoplastic activity as well as dental cariostatic activity.\textsuperscript{83} It also has immunosuppressive effects and inhibits protein synthesis in mammalian cells.\textsuperscript{84}

### 7.1.2 Bactobolin: a Related Compound.

In 1979, a structurally related natural product, (-)-bactobolin 3 was isolated from \textit{Pseudomonas yoshitomiensis} Y-12278.\textsuperscript{85} It is identical to actinobolin except for a dichloromethyl group at C-3.\textsuperscript{86}

Bactobolin displays stronger antibacterial activity, more pronounced antileukemic activity and more potent antitumor activity.\textsuperscript{87} It also has a therapeutic effect on autoimmune encephalomyelitis.\textsuperscript{84b}
7.2. **Syntheses of (+)-actinobolin and (-)-bactobolin.**

7.2.1 Syntheses of (+)-actinobolin via a Diels Alder reaction.

Since their discoveries, actinobolin 1 and bactobolin 3 have attracted the attention of the synthetic community because of their biological activity and their interesting structural features. The first total synthesis of (+)-actinobolin was accomplished by Ohno and co-workers in 1984. 88

They envisioned (+)-actinobolin to arise from diene 4 via a key intramolecular Diels Alder reaction to access lactam 5, setting the correct stereochemistry at C-3, C-4 and C-4a (Scheme 7.1). In turn, they envisioned diene 4 to be synthesized from L-threonine.

![Scheme 7.1: Retrosynthetic analysis of Ohno’s approach to (+)-actinobolin 1.](image)

Thus, oxazoline 6 was accessed in several steps from L-threonine. Formation of the phosphonium salt followed by a Wittig reaction afforded diene 7 which after hydrolysis of the oxazoline and acylation produced diene 4 (Scheme 7.2).

![Scheme 7.2: Synthesis of diene 4.](image)
Thermolysis of compound 4 in benzene at 180 °C afforded the desired cycloadduct product 8 through transition state 9 (Scheme 7.3). The alternative transition state 10, which leads to the other diastereomer 11, is destabilized relative to 9 because of steric interactions between the vinylic proton and the large benzoyloxyethyl group.

**Scheme 7.3**: Synthesis of cyclohexene 8 via a Diels Alder reaction.

With compound 8 in hand, they proceeded to set the correct stereochemistry at C-5 and C-6 through olefin functionalization. To that effect, compound 12, which was accessed from cycloadduct 8, underwent iodolactonization to yield lactone 13 (Scheme 7.4). This was followed by formation of epoxide 14, and diaxial opening led to the formation of diol 15 which contains the five contiguous chiral centers of actinobolin.
Scheme 7.4: Synthesis of γ-lactam 15.

Activation of the system by attachment of a sulfonyl group to lactam 1, obtained in 5 steps from diol 15, allowed for the rearrangement of the γ-lactam to δ-lactone 17 to occur (Scheme 7.5). Simple functional group manipulations led to the formation of amine 18 which was transformed into (+)-actinobolin hydrochloride 1 by installation of the alanine residue. This first total synthesis of (+)-actinobolin was accomplished in 29 steps with a good overall yield.

Scheme 7.5: Final steps of Ohno’s synthesis of (+)-actinobolin.
In 1986, Kozikowski and co-workers reported the synthesis of (+)-actinobolin using an intermolecular Diels Alder strategy (Scheme 7.6).\(^{89}\)

**Scheme 7.6:** Retrosynthetic analysis of Kozikowski’s approach to (+)-actinobolin.

They envisioned actinobolin arising from the cyclization of diene 19 with a carboxy-ketene equivalent 20. In turn, diene 19 was also proposed to be synthesized from L-threonine. However, reaction of diene 19 with methyl propiolate led to the formation of the endo product 21 in a 1.7:1 ratio at 220 °C through transition state 22 (Scheme 7.7). The desired exo product 23, formed via transition state 24, was nonetheless converted to (+)-actinobolin in a total of 17 steps.

**Scheme 7.7:** Synthesis of minor diastereomer 23 via a Diels-Alder reaction.
This synthesis is the shortest to date but was hampered by a low overall yield due to the fact that the desired cycloadduct 23 was the minor product of the Diels Alder reaction.

7.2.2 Weinreb’s Approach to (+)-Actinobolin and (-)-Bactobolin.

In 1985, Weinreb and co-workers reported the second total synthesis of (+)-actinobolin. They subsequently demonstrated that they could access (-)-bactobolin through a common intermediate via a similar route.

They envisioned actinobolin to arise from cyclohexanone 25 (Scheme 7.8). In turn, ketone 25 would be synthesized from lactone 26 which would be the product of an intramolecular ene reaction of aldehyde 27.

![Scheme 7.8: Retrosynthetic analysis of Weinreb’s approach to (+)-actinobolin.](image)

Thus readily accessible glycolate 27 underwent a Lewis acid catalyzed ene cyclization to afford bridged lactone 28 (Scheme 7.9). Functional group manipulation led to the formation of cyclohexene 29.
This was followed by an epoxidation reaction producing a 1.5: 1 mixture of $\alpha$- and $\beta$-epoxides, which was inconsequential since diaxial opening of either epoxide afforded the same diol 30 (Scheme 7.10).

The bridged lactone was then opened to form Weinreb amide 31 (Scheme 7.11). Protection of the diol and reduction of the amide to the aldehyde was followed by a Cram chelation-controlled addition of methylmagnesium bromide to yield the desired alcohol 32 in 12:1 ratio of diastereomers. Alcohol 33 was synthesized from compound 32 through a series of straightforward steps and was treated with carbonyl diimidazole and NaH to produce enol lactone 34, presumably through enolate 35. Deprotection of the amine and introduction of the alanine residue afforded the natural product. This 18 step synthesis is one of the shortest to date. However, racemic compounds were used and a resolution was performed at the penultimate step with the introduction of Cbz-$L$-alanine.
Scheme 7.11: Final stages of Weinreb’s synthesis of (+)-actinobolin.

As mentioned previously, the Weinreb group was able to access (-)-bactobolin using the same strategy albeit with a different protecting group on the nitrogen (Scheme 7.12). Thus bridged lactone 28 was transformed into cyclohexene 36 that underwent epoxidation and diaxial opening to yield diol 37. Lactone opening and formation of a Weinreb amide were followed by the addition of methylmagnesium bromide to produce ketone 38. Cerium mediated addition of lithio dichloromethane onto ketone 38 led to the exclusive formation of desired alcohol 39. Formation of cyclic N-sulfonyl carbamate 40 followed by treatment with sodium methoxide produced the desired enol lactone 41 which was then converted into (-)-bactobolin 3. This was the first synthesis of (-) bactobolin and it was accomplished in only 17 steps.
Scheme 7.12: Weinreb’s approach to (-)-bactobolin.

Other syntheses of (+)-actinobolin include an approach by Ward starting from D-glucose through a novel [3+3] annulation and a more recent synthesis by the Chida group that involves the three component coupling of a functionalized cyclohexenone with vinyl cuprate and an aldehyde.\(^\text{92}\)

Finally, \(N\)-acetyldesalanylactinobolin 2 was synthesized, in an optically active form, by Rahman and Fraser-Reid \(\text{via}\) the Diels Alder reaction of a carbohydrate-derived dienophile with an oxygenated diene.\(^\text{93}\) It was also accessed, in a racemic form, by the Danishefsky group using a key siloxy Cope rearrangement.\(^\text{94}\)

Except for Weinreb’s and Kozikowski’s syntheses, all the approaches to (+)-actinobolin reported to date are lengthy. In addition, in the context of structure-activity-relationship studies, they are not easily amenable to analog synthesis. None of these syntheses allow for late stage variations at the C-3, C-5 and C-6 stereocenters such as introduction of different functional groups or inversion of the stereochemistry.

Thus, a concise approach to (+)-actinobolin that allows for the synthesis of analogs is of great interest and would represent an advance in the field.
7.3. Approach to (+)-Actinobolin and Our Interest in this Natural Product.

7.3.1 Retrosynthetic Analysis.

We envisioned (+)-actinobolin arising from the nucleophilic opening of oxathiazenane 42 with sulfur trioxide extrusion and inversion of the stereochemistry at C-5 (Scheme 7.13). Lactone 42 would, in turn, be the product of an amino-oxygenation reaction of alkene 43 to set the stereochemistry at C-3 and C-4. Hydrogenation of alkyne 44 would afford alkene 43. Finally we propose that a key C-H insertion reaction at the propargylic position of α-diazo β-ketoester 45 would produce cyclohexene 44 setting the stereochemistry at C-4a.

![Scheme 7.13: Approach to (+)-actinobolin.](image)

This concise proposed synthetic route would allow us to easy access analogs. Introduction of a variety of groups on the nitrogen is possible at a late stage. In addition,
inversion of the stereochemistry at C-3 and introduction of a variety of functional group at C-5 could also be done late in the synthesis.

7.3.2 Amino-oxygenation of an Alkene.

In addition to proposing a route amenable to analog synthesis, the opportunity to use an amino-oxygenation reaction developed in our lab is one of our key interests.\textsuperscript{95} We recently reported a copper catalyzed intramolecular olefin aminoacetoxylation reaction of sulfamate esters and nosyl substituted amines (Scheme 7.14).

![Scheme 7.14: Copper catalyzed olefin aminoacetoxylation reactions.](image)

This reaction was shown to be regio- and diastereoselective in most cases and can be carried out under relatively mild conditions. In addition, dialkylolefins showed anti addition of the nitrogen and acetate across the double bond, regardless of the olefin
geometry. Thus, a *cis* olefin geometry is necessary to impart the correct stereochemistry at C-3 and C-4 in the synthesis of (+)-actinobolin.

Given the importance of the 1,2 amino-alcohol motif in nature, its synthesis has drawn considerable research interest. Thus, a variety of methods have been reported to access such a motif. Should our copper catalyzed methodology prove unsuccessful for the synthesis of (+)-actinobolin, other methods, such as palladium catalyzed and copper catalyzed amino-oxygenation reactions, will be available.  

### 7.3.3 Regio- and Diastereoselective C-H Insertion Reaction.

As described in the retrosynthetic analysis of (+)-actinobolin, the key step in this proposed synthesis is a regio- and diastereoselective C-H insertion reaction to form a cyclohexene product 44. This reaction presents a number of challenges. First and foremost, C-H bonds *alpha* to a heteroatom capable of donating electron density are more reactive than allylic or propargylic C-H bonds. In addition, in intramolecular C-H insertion reactions, formation of a 5-membered ring is usually favored (Scheme 7.15). In general, regioselectivity in C-H insertion is controlled by steric, conformational and electronic factors. Catalyst choice can also have a profound influence on the regio- and diastereoselectivity.
The only example to date of the selective formation of a 6-membered ring over a 5-membered ring via intramolecular C-H insertion is found in Du Bois’ synthesis of tetrodotoxin (Scheme 7.16). In that case, they took advantage of conformational constraints allowing for the selective formation of a 6-membered ring.

Two separate strategies were envisioned to affect the regio- and diastereoselective C-H insertion reaction for the synthesis of (+)-actinobolin (Figures 7.2 and 7.3). Both strategies are based on the appropriate choice of diol protecting group. The first strategy
consists of placing a small, electron-withdrawing group at C-5, thus deactivating these C-H bonds for C-H insertion and disfavoring the formation of a 5-membered ring product (as shown with 47, Figure 7.2). In addition, the presence of a bulky protecting group on the alcohol moiety at C-6 should allow the group to be placed in an equatorial position in a chair conformation such as 46 to afford the desired diastereomer.

**Figure 7.2**: First protecting group strategy using a small electron-withdrawing group at C-5 and a sterically demanding group at C-6.

The second strategy consists of protecting the C-5,C-6 diol as the corresponding acetonide. In this case, in order to avoid forming a 5-5 *trans* fused system, the C-H bond cannot have the required alignment with the carbene, as shown in 48, disfavoring C-H insertion at C-5.

**Figure 7.3**: Second protecting group strategy using an acetonide protecting group.
7.3.4 **Retrosynthesis of α-Diazo β-Ketoester 45.**

The required α-diazo β-ketoester 45 is envisioned to arise from the corresponding ketoester 49, which in turn would be the product resulting from the Mukaiyama aldol reaction of hydroxyaldehyde 50 and Chan’s diene 51 (Scheme 7.17). Aldehyde 50 is proposed to arise from (R)-glycidol.

![Scheme 7.17: Retrosynthesis of α-diazo β-ketoester 45.](image)

The following chapter will describe our efforts to synthesize α-diazo β-ketoester 45 and our attempts at carrying out the proposed regio- and diastereoselective C-H insertion reaction using the two strategies described above.
8. Chapter Eight: Results and Discussion.

8.1. Diastereoselectivity of the Mukaiyama Aldol Reaction.

8.1.1 Mukaiyama Aldol Reactions with Diene 51 and α-Heterosubstituted Aldehydes.

To synthesize α-diazo β-ketoester 45, we envisioned carrying out a Mukaiyama aldol reaction between diene 51 and α-hydroxyaldehyde 50 to produce the 1,2-anti diol product (Scheme 8.1). In order to get the desired diastereoselectivity, the reaction has to take place under Felkin-Ahn control.

\[ \text{Felkin-Ahn control gives anti-diol.} \]

Scheme 8.1: Felkin-Ahn control needed in the Mukaiyama aldol step.

After a thorough study of the literature we realized that this type of reaction with Chan’s diene 51, when using an α-hydroxyaldehyde, is precedented for occurring under chelation control to afford the syn diol as the major diastereomer (Scheme 8.2). In cases where the anti diastereomer is formed as the major product, the yields are low. The only examples of Felkin-Ahn controlled Mukaiyama aldol reactions of this type were
found with \(\alpha\)-thio-, \(\alpha\)-amino- and \(\alpha\)-silylaldehydes. In these cases the *anti* product was formed.\(^{101}\)

Scheme 8.2: Precedent for the use of diene 51 in Mukaiyama aldol reactions.

Thus, we hypothesized that with a silyl protecting group on the alcohol we should be able to impart the correct diastereoselectivity. However, before embarking on the synthesis of (+)-actinobolin we decided to confirm this hypothesis on a model system.

8.1.2 \((-\)-Pestalotin 52 and *epi*-Pestalotin 53 as a Model System.

As stated previously, Hagawari and co-workers had demonstrated that a Mukaiyama aldol reaction between diene 51 and a variety of protected \(\alpha\)-hydroxyaldehydes, including benzyl protected \(\alpha\)-hydroxyaldehydes, proceeded under chelation control to afford the *syn* diol products (Scheme 8.2).\(^{100a}\) In order to unambiguously determine the stereochemistry of the products formed, the diols were
transformed into pestalotin 52 and epi-pestalotin 53 via lactones 54 and 55 (Scheme 8.3).100b

\[ \text{OTMS OTMS} + \text{OBn} \xrightarrow{L. A.} \text{OBn} \]

\[ \xrightarrow{\text{NaOH, THF}} \]

\[ \text{54} \]

\[ \xrightarrow{i. \text{Me}_2\text{SO}_4, \text{K}_2\text{CO}_3, \text{Acetone}} \]

\[ \xrightarrow{\text{ii. H}_2, \text{Pd/C, AcOEt}} \]

\[ \text{55} \]

\[ \text{Pestalotin 52} \]

\[ \text{epi-Pestalotin 53} \]

**Scheme 8.3:** Hagawari’s synthesis of pestalotin 52 and epi-pestalotin 53.

Pestalotin 52 and epi-pestalotin 53 can be differentiated by the diagnostic proton shifts of H-6 and H-1’ as shown in Figure 8.1. Therefore, we decided to use these two natural products as a model system for the Felkin-Ahn controlled Mukaiyama aldol reaction.

**Figure 8.1:** Diagnostic proton shifts for pestalotin 52 and epi-pestalotin 53.
8.1.3 Determination of the Diastereoselectivity in a Model System.

Synthesis of model $\alpha$-hydroxyaldehyde 56 commenced with the protection of 1,2-hexanediol with TBSCl. Selective deprotection of the primary silyl ether with HF-pyridine afforded alcohol 57 (Scheme 8.4). Alcohol 57 was then oxidized to $\alpha$-hydroxyaldehyde 56 with PCC in 94 % yield. Reaction of $\alpha$-hydroxyaldehyde 56 with diene 51 produced $\beta$-ketoester 58, which was transformed into enol ether 59. Its deprotection afforded epi-pestalotin 53 in a ratio of over 10:1 as determined by analysis of the $^1$H NMR spectrum.

Scheme 8.4: Determination of the diastereoselectivity in a model system.

Having determined that the Mukaiyama aldol reaction between diene 51 and a silyl protected $\alpha$-hydroxyaldehyde did indeed take place under Felkin-Ahn control and preceeded in good yield, we turned our attention to the synthesis of (+)-actinobolin.
8.2. **First Approach to (+)-Actinobolin using the Electron-Withdrawing Group Strategy.**

8.2.1 **Determination of the diastereoselectivity with α-hydroxyaldehyde 61.**

For our first approach to the synthesis of (+)-actinobolin, we decided to attempt using the electron-withdrawing protecting group on C-5 strategy (*vide supra*). To that effect, β-ketoester 60 had to be synthesized. However, before moving on with the synthesis we decided to confirm that the Mukaiyama aldol step with the desired α-hydroxyaldehyde 61 would afford the correct diastereoselectivity as it had with the model system.

Opening of racemic glycidol by the lithium anion of propyne in a THF/DMPU mixture afforded diol 62 in 55 % yield which was then converted into bis silyl ether 63 (Scheme 8.5). A brief survey of conditions, including CSA/MeOH, HCl/dioxane, PPTS/MeOH and TBAF/AcOH, determined that HF·pyridine in THF/pyridine at -30 °C were the optimal conditions to selectively deprotect the primary silyl moiety and produce alcohol 64 in 47 % yield. This was followed by oxidation to α-hydroxyaldehyde 61. Although initially performed with PCC, it was later found that a Swern oxidation gave the most reproducible yields (*vide infra*). With aldehyde 61 in hand, the Mukaiyama reaction was performed with diene 51 in the presence of 2.1 equivalents TiCl₄ to yield β-ketoester 60.
Hydrogenation of alkyne 60 was followed by lactonization and enol ether formation to produce silyl protected epi-pestalotin 59 (Scheme 8.6) with the same diagnostic doublet of triplets at 4.3 ppm, thus indicating that the aldol reaction had produced the desired anti diastereomer in over 10:1 diastereoselectivity.

Scheme 8.6: Synthesis of enol ether 59.

8.2.2 Moving forward with the synthesis of (+)-actinobolin.

Having determined the stereoselectivity of the aldol reaction, we moved forward with the synthesis of (+)-actinobolin. An optimization of the aldol reaction was first
accomplished (Table 8.1). A variety of conditions were examined, including order of addition, equivalents of diene and Lewis acid as well different solvents and various Lewis acids. It was found that the optimal conditions were either TiCl$_4$ in THF or Ti(OT$^3$Pr)$_2$Cl$_2$ in DCM to afford 60 in 64 % yield in an inseparable mixture with methyl acetoacetate (resulting from the hydrolysis of diene 51) as a side product.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Lewis acid</th>
<th>Eq. diene</th>
<th>Eq. L.A.</th>
<th>Order of addition</th>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>TiCl$_4$</td>
<td>3</td>
<td>2.1</td>
<td>Aldehyde/ L. A. to diene</td>
<td>DCM</td>
<td>43 %</td>
</tr>
<tr>
<td>TiCl$_4$</td>
<td>3</td>
<td>2.1</td>
<td>L. A. to aldehyde &amp; diene</td>
<td>DCM</td>
<td>28 %</td>
</tr>
<tr>
<td>TiCl$_4$</td>
<td>3</td>
<td>2.1</td>
<td>Diene to aldehyde &amp; L. A.</td>
<td>DCM</td>
<td>20 %</td>
</tr>
<tr>
<td>TiCl$_4$</td>
<td>1.5</td>
<td>1</td>
<td>Aldehyde/ L.A. to diene</td>
<td>DCM</td>
<td>59 %</td>
</tr>
<tr>
<td>TiCl$_4$</td>
<td>1.05</td>
<td>1</td>
<td>Aldehyde/ L.A. to diene</td>
<td>DCM</td>
<td>46 %</td>
</tr>
<tr>
<td>TiCl$_4$</td>
<td>1.5</td>
<td>0.25</td>
<td>Aldehyde/ L.A. to diene</td>
<td>DCM</td>
<td>37 %</td>
</tr>
<tr>
<td>TiCl$_4$</td>
<td>1.5</td>
<td>1</td>
<td>Aldehyde/ L.A. to diene</td>
<td>THF</td>
<td>64 %</td>
</tr>
<tr>
<td>TiCl$_4$</td>
<td>1.5</td>
<td>1</td>
<td>Aldehyde/ L.A. to diene</td>
<td>Toluene</td>
<td>56 %</td>
</tr>
<tr>
<td>BF$_3$0Et$_2$</td>
<td>1.5</td>
<td>1</td>
<td>Aldehyde/ L.A. to diene</td>
<td>DCM</td>
<td>49 %</td>
</tr>
<tr>
<td>TiCl$_2$(OT$^3$Pr)$_2$</td>
<td>1.5</td>
<td>1</td>
<td>Aldehyde/ L.A. to diene</td>
<td>DCM</td>
<td>64 %</td>
</tr>
</tbody>
</table>

Table 8.1: Optimization studies of the aldol step.

With alcohol 60 in hand, we attempted to introduce a sterically demanding TBDPS protecting group on C-6, as was necessary for the strategy proposed towards the regio- and diastereoselective C-H insertion reaction. However, with a relatively bulky TBS group at C-5, this turned out to be difficult (Scheme 8.7). With longer reaction times, we were able to isolate bis silyl ether 65 in only 36 % yield along with recovered starting material. We then turned our attention to the selective deprotection of the TBS
silyl ether at C-5, but all our attempts with a variety of conditions, including AcOH/THF/H₂O, HCl/THF and pTsOH/MeOH, were unsuccessful as the starting material remained unreactive.

![Chemical structure](image)

**Scheme 8.7**: Attempts at a selective deprotection of bis silyl ether 65.

We reasoned that once again the bulk of the TBS group was to blame. Thus, we decided to carry out the reaction sequence with a relatively smaller protecting group. To continue imparting Felkin-Ahn control in the Mukaiyama aldol reaction we choose to introduce a TES protecting group.

### 8.2.3 Switching protecting group for the synthesis of α-diazo β-ketoester 45.

We began our investigation into using a TES protecting group in place of a TBS group by carrying out the same approach for the synthesis of α-hydroxyaldehyde 61. In addition to switching protecting groups, we reasoned that in the C-H insertion step the chirality of the catalyst would influence the selectivity meaning that a chiral non-racemic α-diazo β-ketoester precursor was necessary. From then on, we worked with chiral non-racemic substrates by starting the reaction sequence with (R)-glycidol. Thus, bis TES
protected silyl ether 66 was synthesized (Scheme 8.8). However, due to the increased lability of the TES protecting group, the selective deprotection of the primary silyl ether to alcohol 67 could not be accomplished in useful yields, with a highest yield of 24 %.

Scheme 8.8: Attempts at synthesizing alcohol 67 via a selective deprotection.

Another approach was developed starting from PMB-protected glycidol (Scheme 8.9). Opening of the epoxide to produce alcohol 68 was followed by TES protection and deprotection of the PMB ether to afford alcohol 67. Oxidation of alcohol 67 to \( \alpha \)-hydroxyaldehyde 69 was problematic with all the methods attempted, including PCC, PDC, IBX, DMP and Parrikh-Doering oxidations. Indeed, aldehyde 69 is fairly unstable and, in general, could not be isolated cleanly. In cases when it was isolated cleanly enough to carry on the next step, the yields remained low (14 % with PCC).

Scheme 8.9: Attempts to synthesize aldehyde 69.

A literature precedent suggested that it should be possible to carry out a selective oxidative deprotection of bis silyl ether 66 to produce \( \alpha \)-hydroxyaldehyde 69 through a
Swern oxidation. This turned out to be the case and aldehyde 69 could be obtained in yields from 20 to 70 % (Scheme 8.10). Aldehyde 69 being relatively unstable, the following step was immediately carried out. Alcohol 70, obtained in 31 % using Ti(OiPr)2Cl2 in THF, was transformed into enol ether 71 and determined by analogy with the 1H NMR spectrum of enol ether 59 to have the desired anti configuration with good diastereoselectivity.

![Scheme 8.10: Synthesis of alcohol 70 and determination of the diastereoselectivity.]

Having confirmed the diastereoselectivity of the Mukaiyama aldol reaction, a bulky TBS protecting group was introduced at C-6 in quantitative yield (Scheme 8.11). At this stage it was possible to separate bis silyl ether 72 not only from methyl acetoacetate, but also from the minor diastereomer. A selective deprotection of the TES silyl ether moiety with an AcOH/THF/H2O mixture led to the formation of lactol 73. However, opening of lactol 73 and protection of the C-5 alcohol as the acetate using standard conditions could not be accomplished. The reaction produced a mixture of unidentified products.
Scheme 8.11: Formation of lactol 73 and attempts at its opening through acetate protection.

We therefore decide to attempt to introduce the acetate protecting group earlier in the synthetic route to avoid the formation of lactol 73.

8.2.4 Changing the order of addition of the electron-withdrawing protecting group.

In order to introduce an acetate protecting group earlier in the synthetic sequence, we used a similar route to that of alcohol 67 starting with PMB-protected glycidol (Scheme 8.12). Thus, protection of alcohol 68 as the acetate was followed by PMB ether deprotection with DDQ to afford alcohol 74. Once again, the oxidation step was troublesome. A variety of conditions were tested including Swern oxidation, DMP and TEMPO, but analysis of the crude $^1$H NMR revealed that these reactions afforded a mixture of unidentified products in addition to aldehyde 75 which was a minor product in the reaction. Fortunately, oxidation of alcohol 74 with TPAP afforded $\alpha$-
hydroxyaldehyde 75 in 67% yield but the subsequent aldol reaction with diene 51 did not produce the desired compound.

Scheme 8.12: Introduction of the acetate protecting group earlier in the synthesis.

We therefore, sought to find an alternative solution to avoid the formation of lactol 73. To that effect, we decided to pursue the strategy defined for the regio- and diastereoselective C-H insertion reaction by protecting the C-5,C-6 diol as the corresponding acetonide. In that case, the use of diene such as 76 in the aldol step would prevent the formation of the lactol (Scheme 8.13).

Scheme 8.13: Use of diene 76 in the aldol step to prevent subsequent lactol formation.

8.3.1 Synthesis of α-diazo β-ketoester 77.

In order to avoid the formation of a lactol once the alcohol moiety at C-5 is deprotected, we decided to use an alternative diene for the Mukaiyama aldol reaction (Scheme 8.14). Thus, α-hydroxyaldehyde 61 was subjected to diene 76 in the presence of BF₃·OEt₂ in DCM to afford alcohol 78 in 35% yield. The change of Lewis acid was based on literature precedents when using diene 76.¹⁰⁵ Alcohol 78 was treated with MeOH in refluxing toluene to afford β-ketoester 60, which was then transformed into enol ether 59. Analysis of the ¹H NMR spectrum indicated that the desired anti aldol product was the major product albeit in a ratio of only 1:0.6.

Scheme 8.14: Formation of alcohol 78 and determination of the diastereoselectivity.

Despite this decrease in selectivity, the mixture of diastereomers was carried through the rest of the synthesis. Thus, alcohol 78 was treated with HF·pyridine to reveal diol 79 (Scheme 8.15). This was followed by formation of the acetonide 80. Reaction
with MeOH in refluxing toluene followed by treatment with p-ABSA with Et$_3$N in MeCN afforded α-diazo β-ketoester 77 in 85 % yield over 2 steps.

Scheme 8.15: Synthesis of α-diazo β-ketoester 77.

8.3.2 Cyclization reaction of α-diazo β-ketoester 77.

With α-diazo β-ketoester 77 in hand, we were ready to investigate the regio- and diastereoselective C-H insertion step. Before investigating chiral catalysts, we decided to study the reactivity of α-diazo β-ketoester 77 with simpler achiral catalysts. Thus, reaction of α-diazo β-ketoester 77 with 2 mol% of Rh$_2$(OAc)$_4$ in DCM at room temperature afforded a mixture of compounds (Scheme 8.16). One of the two products was unstable and was not identified. However, the other product of the reaction was stable and through extensive NMR studies has been identified as butanone 81, corresponding to a C-H insertion at C-6. A DEPT analysis determined that the molecule contained 3 CH, 2 CH$_2$ and 4 CH$_3$. A $^1$H NMR spectrum and a COSY experiment revealed two deshielded methine protons coupling with two different sets of methylene
protons. These experiments excluded the formation of a 6-membered ring product. Finally, an IR spectrum revealed a C=O signal at 1772 cm$^{-1}$ consistent with the formation of 4-membered ring ketone. The stereochemistry of cyclobutanone 81 was determined by NOE experiments confirming that it was the desired anti diastereomer that had reacted.

![Scheme 8.16](image)

**Scheme 8.16**: Cyclization of α-diazo β-ketoester 77 leading to the formation of ketone 81.

### 8.3.3 Synthesis and cyclization reaction of α-diazo β-ketoester 82.

Having observed undesired reactivity at C-6, we hypothesized that more reactive C-H bonds at C-4a (actinobolin numbering) might allow for the desired C-H insertion reaction to occur. Thus, α-diazo β-ketoester 82, with allylic C-H bonds at C-4a instead of propargylic bonds, was synthesized starting from alcohol 83 via a similar route to that of the synthesis of 77 (Scheme 8.17).
α-Diazo β-ketoester 82 was then reacted with catalytic amounts of Rh$_2$(OAc)$_4$ in DCM at room temperature to afford cyclobutanone 84, corresponding once again to a C-H insertion at C-6. Butanone 84 was also characterized by NMR analysis, revealing the same coupling pattern, and its stereochemistry was confirmed by NOE experiments.

The carbenes generated from α-diazo β-ketoester 77 and 82 are very electron deficient due to the β-ketoester moiety, making them very reactive. We hypothesized that this increased reactivity might favor an early transition thus leading to the formation of
butanones \( \textbf{81} \) and \( \textbf{84} \), with the C-H insertion step resembling a hydride transfer. Indeed it appears that \( \alpha \)-diazo \( \beta \)-ketoester \( \textbf{77} \) and \( \textbf{82} \) can easily adopt a conformation allowing for easy hydride transfer (Figure 8.2). Having a less reactive carbene could favor a later transition state thus allowing for \( \alpha \)-diazo \( \beta \)-ketoester \( \textbf{77} \) and \( \textbf{82} \) to adopt the desired chair conformation to form more stable 6-membered ring products.

\[
\text{Figure 8.2: Transition state for the formation of cyclobutanones } \textbf{81} \text{ and } \textbf{84}.\]

To that effect, \( \alpha \)-diazo \( \beta \)-ketoester \( \textbf{82} \) was reacted with catalytic amounts of \( \text{Rh}_2(\text{OAc})_4 \) in DCM at -78 °C (Scheme 8.19). No reaction was observed at this temperature and when the reaction was warmed up, we observed formation of cyclobutanone \( \textbf{84} \) once the reaction had reached ambient temperature. In addition, \( \alpha \)-diazo \( \beta \)-ketoester \( \textbf{82} \) was reacted with catalytic amounts of \( \text{Rh}_2(\text{F}_2\text{-esp})_2 \), a more electron rich catalyst capable of making the intermediate carbene less electrophilic, in DCM at room temperature. However, the only product isolated from the reaction mixture was cyclobutanone \( \textbf{84} \).
**Scheme 8.19:** Variation of the reaction conditions for the cyclization of α-diazo β-ketoester 82.

### 8.3.4 Alternative strategies.

In addition to decreasing the electrophilicity of the carbene, we envisioned another alternative route to impart the correct regioselectivity on this key C-H insertion reaction by deactivating the C6-H bond for C-H insertion. To that effect, an electron-withdrawing protecting group at the C-6 alcohol must be introduced.

We decided to protect the C-5,C-6 diol as the carbonate instead of the acetonide. Diol 79 was treated with triphosgene to afford carbonate 85 in 55 % yield (Scheme 8.20). However, reaction of carbonate 85 with MeOH in toluene at 80 °C to produce the β-ketoester moiety led to the formation of a product tentatively assigned as alkene 86.
Another route was envisioned with the C-6 alcohol protected as a sterically demanding and electron deficient pivaloate ester. To that effect, alcohol 78 was subjected to PivCl to afford compound 87. The silyl ether was deprotected with HF·pyridine and the resulting alcohol was protected as the acetate 88. Compound 88 was then treated with MeOH in toluene to afford β-ketoester 89 followed by diazo formation to produce α-diazo β-ketoester 90. However the amount of α-diazo β-ketoester 90 obtained was too small to clearly follow its reaction with Rh₂(OAc)₄ in DCM.

Scheme 8.21: Protection of the C-6 alcohol as a pivaloate ester.
8.4. Conclusions and Future Work.

We envisioned a concise synthesis of (+)-actinobolin that would be amenable to analog synthesis and that features a key regio- and diastereoselective C-H insertion reaction to afford a cyclohexene product. We hypothesized that we should be able to impart this unusual selectivity through two different strategies involving the judicious choice of diol protecting group and catalyst.

We began working on the synthesis of (+)-actinobolin using the first strategy envisioned, *i.e.* having a small electron-withdrawing protecting group at C-5 to deactivate the position for C-H insertion and a sterically demanding protecting group at C-6 to induce the desired chair conformation. However, during the synthesis of the required α-diazo β-ketoester, the formation of lactol 73 prevented us from pursuing this route further.

We then moved on to an alternative route using a different diene that would prevent the formation of a lactol. For this route, we used the second strategy envisioned, *i.e.* protect the diol as the corresponding acetonide to prevent formation of a 5-membered ring using geometrical constraints. We were able to synthesize the required α-diazo β-ketoester compounds 77 and 82 but their reaction with a Rh(II) tetracarboxylate catalyst led to the formation of 4-membered ring ketones 81 and 84.

We hypothesized that the formation of these butanones should be prevented by either deactivation of the C5-bond or the formation of a more stable and less reactive carbene intermediate to favor a late transition state. Thus future work for this project includes exploring the reactivity of α-diazo β-ketoester 90 with a pivaloate group on the
C-6 alcohol moiety and the investigation of achiral and chiral Rh(II) catalysts with all of the α-diazo β-ketoesters synthesized to date.
Chapter Nine: Experimental.


$^1$H and $^{13}$C NMR spectra were recorded on a Varian Inova 600 spectrometer (600 MHz $^1$H, 150 MHz $^{13}$C) or a Varian Inova 400 spectrometer (400 MHz $^1$H, 100 MHz $^{13}$C) at room temperature in CDCl$_3$ with internal CHCl$_3$ as the reference (7.27 ppm for $^1$H and 77.23 ppm for $^{13}$C). Chemical shifts (δ values) were reported in parts per million (ppm) and coupling constants (J values) in Hz. Multiplicity is indicated using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, b = broad signal. Infrared (IR) spectra were recorded using Thermo Electron Corporation Nicolet 380 FT-IR spectrometer. High resolution mass spectra were obtained using a Thermo Electron Corporation Finigan LTQFTMS (at the Mass Spectrometry Facility, Emory University). We acknowledge the use of shared instrumentation provided by grants from the NIH and the NSF. Melting points (mp) were taken using a Fisher-Johns melting point apparatus and are not corrected. Analytical thin layer chromatography (TLC) was performed on precoated glass backed EMD 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light or ethanolic anisaldehyde, followed by heating. Flash column chromatography was carried out using EMD Geduran® silica gel 60 (40-63 µm).

All reactions were conducted with anhydrous solvents in oven dried or flame-dried and argon charged glassware. Anhydrous solvents were purified by passage through activated alumina using a Glass Contours solvent purification system unless otherwise noted.
Solvents for workup, extraction and column chromatography were used as received from commercial suppliers. All reagents were purchased from Sigma-Aldrich and used as received unless otherwise noted. Pyridine and Et$_3$N were purified by distillation from calcium hydride.

9.2. General Procedures.

**General procedure A for the preparation of bis-silyl ethers:** TBSCI (2.1 eq) or TESCl (2.1 equiv.) and imidazole (3.0 equiv.) were dissolved in DCM (0.5 M). The starting diol (1.0 equiv.) was then added and the resulting mixture was stirred at room temperature until thin layer chromatography indicated complete consumption of starting material. H$_2$O was added and the mixture was extracted with DCM. The combined organic extracts were washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. Purification by flash chromatography as indicated afforded the desired bis-silyl ether.

**General procedure B for the deprotection of PMB ethers:** The starting PMB ether (1.0 equiv.) was dissolved in a DCM/pH7 buffer mixture (2.5:1, 0.1 M). DDQ (1.2 equiv.) was then added and the resulting mixture was stirred at room temperature until thin layer chromatography indicated complete consumption of starting material. The reaction mixture was then diluted with Et$_2$O and saturated aq. NaHCO$_3$ was added. The mixture was extracted with Et$_2$O and the combined organic extracts were washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. Purification by flash chromatography as indicated afforded the desired alcohol.
General procedure C for the Swern oxidation: DMSO (8.8 eq) was slowly added to (COCl)$_2$ (4.4 equiv., 2.0 M in DCM) at -78 °C. The resulting mixture was stirred at -78 °C for 20 min then a solution of the starting alcohol (1.0 equiv.) in DCM (0.2 M) was added dropwise. The reaction mixture was stirred for 20 min at -78°C then warmed to -30 °C and stirred for 20 min. The mixture was then cooled back to -78 °C and Et$_3$N (15 equiv.) was added. The reaction mixture was then allowed to reach room temperature and H$_2$O was added. The mixture was extracted with DCM and the combined organic extracts were washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. Purification by flash chromatography as indicated afforded the desired aldehyde.

General procedure D for the Mukaiyama aldol reaction with diene 51: The starting aldehyde (1.0 equiv.) and TiCl$_4$ (1.0 equiv.) were added simultaneously to a solution of diene 51 (1.5 equiv.) in THF (0.3 M) at -78 °C. The resulting mixture was stirred at -78 °C until thin layer chromatography indicated complete consumption of starting material. A pH7 buffer solution was then added and the mixture was extracted with DCM. The combined organic extracts were washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. Purification by flash chromatography as indicated afforded the desired alcohol.

General procedure E for the preparation of α-diazo-β-ketoesters: The starting dioxanone (1.0 equiv.) was dissolved in toluene (0.3 M). MeOH (2.2 equiv.) was added and the resulting solution was heated to reflux until thin layer chromatography indicated complete consumption of starting material. The reaction mixture was then allowed to reach room temperature and concentrated *in vacuo*. The resulting residue was then
dissolved in MeCN (0.3 M) with pABSA (1.2 equiv.). Et₃N (1.2 equiv.) was added and the reaction mixture was stirred at room temperature until thin layer chromatography indicated complete consumption of starting material. Saturated aq. NH₄Cl was added and the reaction mixture was extracted with DCM. The combined organic extracts were washed with 10% KOH then saturated aq. NaHCO₃ and brine, dried over MgSO₄ and concentrated \textit{in vacuo}. Purification by flash chromatography as indicated afforded the desired α-diazo-β-ketoester.

\textbf{9.3. Procedures and Compound Characterization.}

\textbf{Preparation of bis-silyl ether 91:}

\[
\text{\begin{tikzpicture} 
\node (A) at (0,0) {OH}; \node (B) at (1,0) {OH}; \node (C) at (2,0) {OTBS}; \node (D) at (3,0) {OTBS}; \node (E) at (0,0.5) {OH}; \node (F) at (1,0.5) {OH}; \node (G) at (2,0.5) {OTBS}; \node (H) at (3,0.5) {OTBS}; \node (I) at (4,0) {91}; \draw [->] (A) -- (B); \draw [->] (B) -- (C); \draw [->] (C) -- (D); \draw [->] (D) -- (E); \draw [->] (E) -- (F); \draw [->] (F) -- (G); \draw [->] (G) -- (H); \draw [->] (H) -- (I); \end{tikzpicture}}
\]

Prepared according to general procedure A using 1,2-hexanediol (0.402 g, 3.34 mmol) to afford, without purification, the desired bis-silyl ether 91 as a colorless oil (1.14 g, 97 % yield); \(R_f\) 0.95 (5:1 hexanes/EtOAc); \textbf{IR} (thin film, cm\(^{-1}\)) 2954, 2928, 2857, 1468, 1252, 822, 771; \textbf{\(^1\)H NMR} (CDCl₃, 600 MHz) \(\delta\) 3.64 (qn, 1H, \(J = 5.4\) Hz), 3.51 (dd, 1H, \(J = 10.2, 5.4\) Hz), 3.41 (dd, 1H, \(J = 9.6, 6.6\) Hz), 1.34-1.25 (m, 6H), 0.89-0.88 (m, 21 H), 0.05 (s, 6H), 0.04 (s, 3H), 0.03 (s, 3H); \textbf{\(^{13}\)C NMR} (CDCl₃, 150 MHz) \(\delta\) 73.4, 67.7, 34.3, 27.6, 26.2, 26.1, 25.8, 23.1, 18.6, 18.4, -4.1, -4.6, -5.2, -5.3; \textbf{HRMS} (+APCI) calculated for C\(_{18}\)H\(_{43}\)O\(_2\)Si\(_2\) 347.2796, found 347.2794 [M+H]\(^+\).
Preparation of 2-((t-butyldimethylsilyl)oxy)hexan-1-ol 57:

An HF·pyridine solution (0.2 mL) was added to a solution of 91 (0.441 g, 0.133 mmol) in THF (3 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 2h. Saturated aq. NaHCO₃ (1 mL) was carefully added and the mixture was extracted with Et₂O (3 × 3 mL). The combined organic extracts were washed with brine, dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (40:1 hexanes/EtOAc) afforded alcohol 51 as a colorless oil (0.073 g, 25 % yield); Rf 0.80 (5:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 3375, 2954, 2928, 2857, 1463, 1253; ¹H NMR (CDCl₃, 600 MHz) δ 3.75-3.70 (m, 1H), 3.57-3.55 (m, 1H), 3.46-3.42 (m, 1H), 1.90 (t, 1H, J = 6.0 Hz), 1.32-1.24 (m, 6H), 0.90-0.88 (m, 12H), 0.08 (s, 6H); ¹³C NMR (CDCl₃, 150 MHz) δ 73.1, 66.5, 33.9, 31.8, 27.7, 26.1, 18.3, 14.2, -4.3, -4.4; HRMS (+APCI) calculated for C₁₂H₂₉O₂Si 233.1931, found 233.1931 [M+H]⁺.

Preparation of 2-((t-butyldimethylsilyl)oxy)hexanal 56:

Alcohol 57 (0.154 g, 0.661 mmol) was added to a solution of PCC (0.427 g, 1.98 mmol) in DCM (5 mL). The resulting mixture was stirred at room temperature for 3.5 h. Celite was then added and the mixture was filtered over silica. The filter cake was washed with DCM and the filtrate was concentrated in vacuo to afford aldehyde 56 as a yellow oil (0.143 g, 94 % yield); Rf 0.50 (5:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 2955, 2929,
2857, 1736, 1471, 1253, 1102; \(^1\)H NMR (CDCl\(_3\), 600 MHz) \(\delta\) 9.59 (d, 1H, \(J = 1.4\) Hz), 3.96 (ddd, 1H, \(J = 7.0, 5.6, 1.5\) Hz), 1.64-1.58 (m, 2H), 1.39-1.30 (m, 4H), 0.93 (s, 9H), 0.92-0.88 (m, 3H), 0.08 (s, 3H), 0.07 (s, 3H); \(^13\)C NMR (CDCl\(_3\), 150 MHz) \(\delta\) 204.8, 77.9, 32.5, 26.9, 25.9, 22.7, 18.4, 14.1, -4.4, -4.7; HRMS (+APCI) calculated for C\(_{12}\)H\(_{27}\)O\(_2\)Si 231.1775, found 231.1772 [M+H]\(^+\).

**Preparation of methyl 6-((t-butyldimethylsilyl)oxy)-5-hydroxy-3-oxodecanoate 58:**

Prepared according to general procedure D using aldehyde 56 (0.143 g, 0.619 mmol) and 3 equiv. of diene 51 and 2.1 equiv. of TiCl\(_4\). DCM was used instead of THF. Purification by flash chromatography (5:1 hexanes/EtOAc) afforded alcohol 58 as a colorless oil (0.184 g as a 2.5:1 mixture with methyl acetoacetate, 75 % yield); \(R_f\) 0.25 (4:1 hexanes/EtOAc); IR (thin film, cm\(^{-1}\)) 3566, 2955, 2930, 2858, 1748, 1713, 1254; \(^1\)H NMR (CDCl\(_3\), 600 MHz) \(\delta\) 4.01-3.99 (m, 1H), 3.72 (s, 3H), 3.70-3.66, (m, 1H), 3.51 (s, 2H), 2.69-2.61 (m, 2H), 1.55-1.30 (m, 6H), 0.87-0.85 (m, 12H), 0.13 (s, 6H); \(^13\)C NMR (CDCl\(_3\), 150 MHz) \(\delta\) 203.4, 167.6, 74.8, 70.5, 53.6, 50.0, 44.9, 32.5, 31.8, 27.4, 28.1, 23.0, 14.4, -4.2; HRMS (+APCI) calculated for C\(_{17}\)H\(_{35}\)O\(_5\)Si 347.2248, found 347.2244 [M+H]\(^+\).
Preparation of enol ether 59:

1.0 M NaOH (1 mL) was added to a solution of alcohol 58 (0.1837 g, 2.5:1 mixture with methyl acetoacetate) in THF (4 mL). The resulting mixture was stirred at room temperature for 30 min then 1M HCl (1 mL) was added. The mixture was extracted with Et₂O (2 × 3 mL). The combined organic extracts were washed with brine (2 × 1 mL), dried over MgSO₄ and concentrated in vacuo. The residue (0.098 g, 0.314 mmol) and K₂CO₃ (0.067 g, 0.486 mmol) were dissolved in acetone (3 mL). Me₂SO₄ (0.04 mL, 0.423 mmol) was then added and the resulting mixture was stirred at room temperature for 12 h. H₂O (1 mL) was added and the mixture was extracted with Et₂O (2 × 3 mL). The combined organic extracts were washed with brine (2 × 1 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc) afforded enol ether 59 as a colorless oil (0.103 g, 63 % yield over 2 steps); Rₜ 0.91 (1:1 hexanes/EtOAc); ¹H NMR (CDCl₃, 400 MHz) δ 5.12 (d, 1H, J = 1.2 Hz), 4.30 (dt, 1H, J = 10, 2.4 Hz), 3.94-3.95 (m, 1H), 3.74 (s, 3H), 2.82-2.78 (m, 1H), 2.32-2.21 (m, 1H), 1.53-1.22 (m, 6H), 0.82 (m, 12H), 0.04 (s, 6H); HRMS (+APCI) calculated for C₁₇H₃₃O₄Si 329.2143, found 329.2139 [M+H]+.
Preparation of *epi*-pestalotin 53:

![Chemical Structure](image.png)

TBAF (1.4 mL, 1.0M in THF, 0.481 mmol) was added to a solution of enol ether 59 (0.103 g, 0.314 mmol) in THF (2 mL) at 0 °C. The resulting mixture was stirred at room temperature for 4.5 h. Saturated aq. NH₄Cl (0.5 mL) was added. The mixture was extracted with Et₂O (3 × 2 mL). The combined organic extracts were washed with brine (2 × 1 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash chromatography (5:1 hexanes/EtOAc) afforded *epi*-pestalotin 53 as a colorless oil, which was characterized by \(^1\)H NMR and was found to be identical to the one reported in the literature.\(^{100b}\)

Preparation of *bis*-silyl ether 63:

![Chemical Structure](image.png)

Prepared according to general procedure A using diol 62 (0.761 g, 6.66 mmol) to afford, without purification, *bis*-silyl ether 63 as a colorless oil (2.18 g, 95 % yield); \(R_\text{f}\) 0.93 (5:1 hexanes/EtOAc); \(\text{IR}\) (thin film, cm\(^{-1}\)) 2954, 2928, 2856, 1471, 1463, 1252, 1116; \(^1\)H NMR (CDCl₃, 600 MHz) \(\delta\) 3.77-3.73 (m, 1H), 3.52 (dd, 1H, \(J = 5.7, 0.8\) Hz), 2.35 (ddt, 1H, \(J = 16.5, 5.5, 2.3\) Hz), 2.20-2.16 (m, 2H), 1.74 (t, 3H, \(J = 2.2\) Hz), 0.88 (s, 18H), 0.06 (s, 12H); \(^{13}\)C NMR (CDCl₃, 150 MHz) \(\delta\) 76.9, 76.3, 72.8, 67.0, 26.1, 26.0, 25.9,
18.5, 18.4, 18.2, 3.6, -3.4, -4.4, -5.2; **HRMS (+APCI)** calculated for C_{18}H_{39}O_{2}Si_{2} 343.2483, found 343.2480 [M+H]^+.

**Preparation of 2-((t-butyldimethylsilyl)oxy)hex-4-yn-1-ol 64:**

[Chemical structure diagram]

A HF·pyridine/pyridine/THF mixture (5:2:1, 5.8 mL) was added to a solution of 63 (0.500 g, 1.46 mmol) in THF (15 mL) at -30 °C. The resulting mixture was stirred at -30 °C for 2 days then at -20 °C for 3 days. Saturated aq. NaHCO₃ (10 mL) was carefully added and the mixture was extracted with Et₂O (3 × 20 mL). The combined organic extracts were washed with brine (2 × 15 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (40:1 → 5:1 hexanes/EtOAc) afforded alcohol 64 as a colorless oil (0.167 g, 47 % yield); Rₚ 0.50 (5:1 hexanes/EtOAc); **IR** (thin film, cm⁻¹) 3372, 2953, 2928, 2856, 1463, 1253, 1109; **¹H NMR** (CDCl₃, 600 MHz) δ 3.85-3.83 (m, 1H), 3.66 (dq, 1H, J = 8.3, 2.8 Hz), 3.57 (ddd, 1H, J = 11.3, 6.8, 4.7 Hz), 2.32 (dddd, 2H, J = 10.4, 7.8, 5.2, 2.6 Hz.), 1.93-1.91 (m, 1H), 1.75 (t, 3H, J = 2.4 Hz), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); **¹³C NMR** (CDCl₃, 150 MHz) δ 77.9, 75.6, 72.1, 66.0, 25.8, 24.3, 18.3, 3.7, -4.4, -4.6; **HRMS** (+APCI) calculated for C_{12}H_{25}O_{3}Si 229.1618, found 229.1620 [M+H]^+.
Preparation of 2-((t-butyldimethylsilyl)oxy)hex-4-ynal 61:

Prepared according to general procedure C using alcohol 64 (0.500 g, 2.19 mmol). Purification by flash chromatography (40:1 hexanes/EtOAc) afforded aldehyde 61 as a yellow oil (0.389 g, 78 % yield); \( R_f \) 0.80 (53:1 hexanes/EtOAc); \textbf{IR} (thin film, cm\(^{-1}\)) 2953, 2928, 2856, 1739, 1472, 1253, 1119; \textbf{\(^{1}\text{H NMR}\)} (CDCl\(_3\), 600 MHz) \( \delta \) 9.60 (s, 1H), 4.04 (t, 1H, \( J = 6.5 \) Hz), 2.49 (ddd, 1H, \( J = 16.6, 5.6, 2.8 \) Hz), 2.42-2.37 (m, 1H), 1.74 (t, 3H, \( J = 2.3 \) Hz), 0.89 (s, 9H), 0.10 (s, 6H); \textbf{\(^{13}\text{C NMR}\)} (CDCl\(_3\), 150 MHz) \( \delta \) 202.5, 78.5, 76.6, 74.2, 25.8, 23.5, 18.4, 3.6, -4.7; \textbf{HRMS} (+APCI) calculated for C\(_{12}\)H\(_{23}\)O\(_2\)Si 227.1462, found 227.1458 [M+H]+.

Preparation of methyl 6-((t-butyldimethylsilyl)oxy)-5-hydroxy-3-oxodec-8-ynoate 60:

Prepared according to general procedure D using aldehyde 61 (0.089 g, 0.393 mmol). Purification by flash chromatography (5:1 hexanes/EtOAc) afforded alcohol 60 (0.101 g, 2:1 mixture with methyl acetoacetate, 64 % yield); \( R_f \) 0.31 (5:1 hexanes/EtOAc); \textbf{IR} (thin film, cm\(^{-1}\)) 3529, 2953, 2928, 2855, 1744, 1713, 1437, 1149, 1105, 856, 776; \textbf{\(^{1}\text{H NMR}\)} (CDCl\(_3\), 600 MHz) \( \delta \) 4.16-4.14 (m, 1H), 3.75 (q, 1H, \( J = 4.8 \) Hz), 3.72 (s, 3H), 3.51 (s, 2H), 2.80-2.77 (m, 2H), 2.70 (dd, 1H, \( J = 18, 8.4 \) Hz), 2.37-2.27 (m, 2H), 1.74-1.73 (m, 3H), 0.87 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); \textbf{\(^{13}\text{C NMR}\)} (CDCl\(_3\), 150 MHz) \( \delta \) 203.2,
167.6, 78.1, 75.4, 73.7, 70.2, 52.5, 49.9, 44.7, 25.9, 23.7, 18.2, 3.7, -4.4, -4.6; HRMS (+APCI) calculated for C_{17}H_{31}O_{5}Si 343.1935, found 343.1932 [M+H]^+.

**Preparation of bis-silyl ether 75:**

Alcohol 60 (0.249 g, 0.726 mmol) was added to a solution of imidazole (0.444 g, 3.63 mmol) in DCM (0.7 mL). TBDPSCI (0.2 mL, 0.80 mmol) was then added and the resulting mixture was stirred at room temperature for 24h. MeOH (1.5 mL) was then added and the solution was concentrated in vacuo. Purification by flash chromatography (40:1 → 20:1 hexanes/EtOAc) afforded bis-silyl ether 65 as a colorless oil (0.150 g, 36 % yield); Rf 0.89 (5:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 2930, 2857, 1743, 1706, 1618, 1427, 1264, 1119, 699; ¹H NMR (CDCl₃, 600 MHz) δ 7.66-7.35 (m, 10H), 4.24-4.21 (m, 1H), 3.87-3.93 (m, 1H), 3.64 (s, 3H), 3.48 (s, 2H), 2.84 (dd, 1H, J = 17.4, 7.2 Hz), 2.58-2.26 (m, 3H), 1.76-1.75 (m, 3H), 1.08 (s, 18H), 0.15 (s, 6H); HRMS (+APCI) calculated for C_{33}H_{49}O_{5}Si_{2} 581.3113, found 581.3105 [M+H]^+.

**Preparation of bis-silyl ether 66:**

Prepared according to general procedure A using diol 62 (0.986 g, 3.39 mmol) to afford, without purification, bis-silyl ether 66 as a colorless oil (1.05 g, 91 % yield); Rf 0.92 (5:1
hexanes/EtOAc); **IR** (thin film, cm⁻¹) 2953, 2911, 2875 1458, 1238, 1118, 1078, 1004; **¹H NMR** (CDCl₃, 600 MHz) δ 3.77 (qn, 1H, J = 5.4 Hz), 3.58-3.52 (m, 2H), 2.42-2.37 (m, 1H), 2.25-2.21 (m, 1H), 1.77-1.76 (m, 3H), 0.98-0.94 (m, 18H), 0.61 (q, 12H, J = 8.4 Hz); **¹³C NMR** (CDCl₃, 150 MHz) δ 77.05, 76.45, 72.6, 66.5, 24.8, 7.0, 6.9, 5.1, 4.5, 3.7; **HRMS** (+APCI) calculated for C₁₈H₃₉O₂Si₂ 343.2483, found 343.2480 [M+H]⁺.

**Preparation of (S)-2-((triethylsilyl)oxy)hex-4-yn-1-ol 67:**

A HF-pyridine/pyridine/THF mixture (5:2:1, 2.4 mL) was added to a solution of 66 (0.500 g, 1.46 mmol) in THF (15 mL) at -20 °C. The resulting mixture was stirred at -20 °C for 1.5 h. Saturated aq. NaHCO₃ (10 mL) was carefully added and the mixture was extracted with Et₂O (3 × 20 mL). The combined organic extracts were washed with brine (2 × 15 mL), dried over MgSO₄ and concentrated *in vacuo*. Purification by flash chromatography (40:1 → 5:1 hexanes/EtOAc) afforded alcohol 67 as a colorless oil (0.30 g, 24 % yield); **Rf** 0.65 (5:1 hexanes/EtOAc); **IR** (thin film, cm⁻¹) 3410, 2953, 2913, 2876, 1458, 1238, 1108; **¹H NMR** (CDCl₃, 400 MHz) δ 3.88-3.82 (m, 1H), 3.67 (ddd, 1H, J = 11.1, 6.0, 3.7 Hz), 3.62-3.56 (m, 1H), 2.40-2.27 (m, 2H), 1.77 (t, 3H, J = 2.6 Hz), 0.96 (t, 9H, J = 8.0 Hz), 0.63 (q, 6H, J = 8.0 Hz); **HRMS** (+APCI) calculated for C₁₂H₂₃OSi 211.1513, found 211.1510 [M-H₂O]⁺.
Preparation of (S)-1-((4-methoxybenzyl)oxy)hex-4-yn-2-ol 68:

\[
\begin{align*}
\text{O} & \quad \text{PMB} \\
\text{Me} & \quad \text{Me} \\
\text{BuLi, BF}_3\cdot\text{OEt}_2 & \quad \text{THF} \\
\end{align*}
\]

Propyne (0.73 mL, 12.9 mL) was cannulated into a solution of \textit{n}BuLi (4.5 mL, 2.5M in hexanes, 11.3 mmol) in THF (10 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 1h then BF\textsubscript{3}·Et\textsubscript{2}O (1.3 mL, 10.3 mmol) was added. The mixture was stirred at -78 °C for 20 min then PMB protected glycidol (1.0 g, 5.15 mmol) was added. The resulting mixture was allowed to reach room temperature and stirred at room temperature for 18 h. Saturated aq. NaHCO\textsubscript{3} (8 mL) was then added. The mixture was extracted with Et\textsubscript{2}O (3 × 15 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo}. Purification by flash chromatography (3:1 → 1:1 hexanes/EtOAc) afforded alcohol 68 as a colorless oil (0.779 g, 65 % yield); \textit{R}_f 0.42 (3:1 hexanes/EtOAc); \textit{IR} (thin film, cm\textsuperscript{-1}) 3435, 2917, 2859, 1611, 1512, 1244, 1173, 1093; \textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\textit{\texti}
Preparation of (S)-triethyl((1-((4-methoxybenzyl)oxy)hex-4-yn-2-yl)oxy)silane 92:

Prepared according to general procedure A using alcohol 68 (0.779 g, 3.35 mmol), 1.1 equiv. of TESCl and 1.5 equiv. of imidazole. Purification by flash chromatography (40:1 hexanes/EtOAc) afforded product 92 as a colorless oil (1.13 g, 98 % yield); R_f 0.98 (3:1 hexanes/EtOAc); IR (thin film, cm\(^{-1}\)) 2952, 2910, 2874, 1612, 1512, 1245; \(^1\)H NMR (CDCl\(_3\), 600 MHz) \(\delta\) 7.30 (d, 2H, \(J = 8.4\) Hz), 6.90 (d, 2H, \(J = 8.4\) Hz), 4.51 (s, 2H), 3.94 (qn, 1H, \(J = 5.6\) Hz), 3.83 (s, 3H), 3.51 (dd, 1H, \(J = 9.8, 5.0\) Hz), 3.46 (dd, 1H, \(J = 9.7, 5.3\) Hz), 2.44 (ddd, 1H, \(J = 16.5, 6.3, 2.6\) Hz), 2.32 (ddd, 1H, \(J = 16.5, 5.7, 2.8\) Hz), 1.78 (t, 3H, \(J = 2.4\) Hz), 0.98 (t, 9H, \(J = 7.8\) Hz), 0.65 (qn, 6H, \(J = 8.4\) Hz); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz) \(\delta\) 159.3, 130.7, 1294, 113.8, 77.23, 76.1, 73.6, 73.2, 70.9, 55.4, 25.2, 7.0, 5.0, 3.7; HRMS (+APCI) calculated for C\(_{20}\)H\(_{33}\)O\(_3\)Si 349.2194, found 349.2190 [M+H]\(^+\).

Preparation of (S)-2-(((triethylsilyl)oxy)hex-4-yn-1-ol 67:

Prepared according to general procedure B using PMB ether 92 (0.827 g, 2.37 mmol). Purification by flash chromatography (20:1 hexanes/EtOAc) afforded alcohol 67 as a colorless oil (0.336 g, 66 % yield), identical to previously prepared 67 by \(^1\)H NMR and R_f.
Preparation of (S)-2-((triethylsilyl)oxy)hex-4-ynal 69:

Alcohol 67 (0.157 g, 0.688 mmol) added to a solution of PCC (0.296 g, 1.38 mmol) in DCM (15 mL). The resulting mixture was stirred at room temperature for 4h. Saturated aq. Na₂S₂O₃ (8 mL) was then added. The mixture was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over MgSO₄, filtered over celite and concentrated in vacuo. Purification by flash chromatography (20:1 → 5:1 hexanes/EtOAc) afforded aldehyde 69 as a yellow oil (0.22 g, 14 % yield); Rf 0.48 (5:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 2954, 2913, 2876, 1740, 1458, 1239, 1119; ¹H NMR (CDCl₃, 600 MHz) δ 9.53 (s, 1H), 3.97 (td, 1H, J = 6.0, 1.2 Hz), 2.43-2.41 (m, 1H), 2.38-2.32 (m, 1H), 1.68-1.67 (m, 3H), 0.92-0.87 (m, 9H), 0.60-0.56 (m, 6H); ¹³C NMR (CDCl₃, 150 MHz) 202.3, 78.3, 76.2, 73.8, 31.7, 23.5, 6.6, 5.8, 4.7.

Preparation of (S)-2-((triethylsilyl)oxy)hex-4-ynal 69:

Prepared according to general procedure C using bis-silylether 66 (0.350 g, 1.02 mmol). Purification by flash chromatography (20:1 → 5:1 hexanes/EtOAc) afforded aldehyde 69 as a yellow oil (0.162 g, 70 % yield), found to be identical to previously prepared 69 by ¹H NMR and Rf.
Preparation of (5\textit{R},6\textit{S})-methyl 5-hydroxy-3-oxo-6-((triethylsilyl)oxy)dec-8-ynoate 70:

Prepared according to general procedure D using aldehyde 69 (0.035 g, 0.155 mmol) and TiCl\textsubscript{2}(OiPr\textsubscript{2})\textsubscript{2} instead of TiCl\textsubscript{4}. Purification by flash chromatography (5:1 hexanes/EtOAc) afforded alcohol 70 as a colorless oil (0.017 g, 31 \% yield); \textit{R}\textsubscript{f} 0.22 (5:1 hexanes/EtOAc); \textbf{IR} (thin film, cm\textsuperscript{-1}) 3528, 2954, 2876, 1743, 1713, 1436, 1004; \textbf{\textit{1}H NMR} (CDCl\textsubscript{3}, 600 MHz) \textit{δ} 4.03-4.00 (m, 1H), 3.66-3.64 (m, 1H), 3.62 (s, 3H), 3.42 (s, 2H), 2.71 (dd, 1H, \textit{J} = 17.4, 3.6 Hz), 2.61 (dd, 1H, \textit{J} = 17.4, 9.0 Hz), 2.24-2.21 (m, 2H), 1.65-1.64 (m, 3H), 0.85 (t, 9H, \textit{J} = 8.4 Hz), 0.53 (q, 6H, \textit{J} = 7.8 Hz); \textbf{\textit{13}C NMR} (CDCl\textsubscript{3}, 150 MHz) \textit{δ} 202.9, 167.5, 77.7, 75.3, 73.6, 70.1, 52.1, 49.7, 30.0, 20.9, 6.7, 4.8, 3.4; \textbf{HRMS} (+APCI) calculated for C\textsubscript{17}H\textsubscript{29}O\textsubscript{4}Si 325.1830, found 325.1626 [M+H-H\textsubscript{2}O]\textsuperscript{+}.

Preparation of (5\textit{R},6\textit{S})-methyl-5-((t-butyldimethylsilyl)oxy)-3-oxo-6-((triethylsilyl)oxy)dec-8-ynoate 72:

TBSOTf (0.1 mL, 0.444 mmol) was added to a mixture of alcohol 70 (0.077 g, 0.222 mmol) and 2,6-lutidine (0.1 mL, 0.889 mmol) in DCM (5 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 1 h then allowed to reach room temperature. Saturated aq. NaHCO\textsubscript{3} (2 mL) was then added. The mixture was extracted with DCM (3 \times 5 mL).
The combined organic extracts were washed with brine (2 × 3 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (40:1 → 20:1 hexanes/EtOAc) afforded bis-silyl ether 72 as a colorless oil (0.100 g, 100 % yield); Rf 0.66 (5:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 2951, 2929, 2857, 1718, 1623, 1254, 1125; ¹H NMR (CDCl₃, 400 MHz) δ 4.35-4.31 (m, 1H), 3.78-3.75 (m, 1H), 3.72 (s, 3H), 3.49 (s, 2H), 2.73 (dd, 2H, J = 11.0, 5.7 Hz), 2.26-2.24 (m, 2H), 1.77 (t, 3H, J = 2.6 Hz), 0.96 (t, 9H, J = 8.0 Hz), 0.86 (s, 9H), 0.62 (q, 6H, J = 8.0 Hz), 0.10 (s, 3H), 0.07 (s, 3H); HRMS (+ESI) calculated for C₂₂H₄₄O₅Si₂Na 479.2617, found 479.2617 [M+Na]⁺.

Preparation of methyl 2-((4R,5S)-5-(but-2-yn-1-yl)-4-((t-butyldimethylsilyl)oxy)-2-hydroxytetrahydrofuran-2-yl)acetate 73:

![Diagram]

Bis-silylether 72 (0.103 g, 0.123 mmol) was dissolved in an AcOH/H₂O/THF mixture (3:1:3, 7 mL). The resulting solution was stirred at room temperature for 7 h. Saturated aq. NaHCO₃ (2 mL) was then added. The mixture was extracted with Et₂O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (20:1 → 5:1 hexanes/EtOAc) afforded lactol 73 as a colorless oil (0.067 g, 88 % yield) in a 1:0.6 mixture of diastereomers; ¹H NMR (CDCl₃, 600 MHz) δ 4.46-4.00 (m, 1.6H), 4.21 (dd, 1H, J = 10, 4.0 Hz), 3.98-3.94 (m, 0.6H), 3.74 (s, 1.8H), 3.69 (s, 3H), 2.96-2.84 (m, 1.6H), 2.46-2.30 (m, 3.6H), 2.24-2.21 (m, 2H), 2.14-1.91 (m, 2.2H), 1.78-1.75 (m, 4.8H),
0.95 (s, 9H), 0.94 (s, 5.4H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 1.8H), 0.03 (s, 1.8H);
**HRMS** (+APCI) calculated for C_{17}H_{29}O_{4}Si 325.1835, found 325.1826 [M+H-H_{2}O]^+.

**Preparation of (S)-1-((4-methoxybenzyl)oxy)hex-4-yn-2-yl acetate 93:**

Ac_{2}O (0.43 mL, 4.50 mmol) was added to a mixture of alcohol 68 (0.528 g, 2.25 mmol) and DMAP (0.825 g, 6.75 mmol) in DCM (10 mL). The resulting mixture was stirred at room temperature for 30 min. Saturated aq. NH_{4}Cl (5 mL) was then added. The mixture was extracted with DCM (3 × 8 mL). The combined organic extracts were washed with brine (2 × 5 mL), dried over MgSO_{4} and concentrated *in vacuo*. Purification by flash chromatography (3:1 → 1:1 hexanes/EtOAc) afforded acetate 93 as a colorless oil (0.448 g, 72 % yield); **R_{f}** 0.63 (2:1 hexanes/EtOAc); **IR** (thin film, cm⁻¹) 2919, 2859, 1736, 1612, 1513, 1236, 1033; **¹H NMR** (CDCl₃, 600 MHz) δ 7.21 (d, 2H, \(J = 8.4\) Hz), 6.83 (d, 2H, \(J = 8.4\) Hz), 4.99 (dt, 1H, \(J = 11.5, 5.6\) Hz), 4.45 (AB q, 1H, \(J = 16.7\) Hz), 3.75 (s, 3H), 3.56 (m, 2H), 2.49-2.39 (m, 2H), 1.99 (s, 3H), 1.70 (t, 3H, \(J = 2.4\) Hz); **¹³C NMR** (CDCl₃, 150 MHz) δ 170.4, 159.3, 130.1, 129.3, 113.8, 77.7, 74.0, 72.9, 71.2, 69.4, 55.3, 21.1, 14.2, 3.5; **HRMS** (+ESI) calculated for C_{16}H_{20}O_{4}Na 299.1254, found 299.1251 [M+Na]^+. 
Preparation of (S)-1-hydroxyhex-4-yn-2-yl acetate 74:

Prepared according to general procedure B using PMB ether 93 (0.561 g, 2.03 mmol). Purification by flash chromatography (2:1 → 1:1 hexanes/EtOAc) afforded alcohol 74 as a yellow oil (0.251 g, 79 % yield); \( R_f \) 0.29 (2:1 hexanes/EtOAc); \textbf{IR} (thin film, \text{cm}^{-1}) 3434, 2921, 1735, 1435, 1371, 1248, 1038; \textbf{\( ^1 \)}H NMR (CDCl\(_3\), 600 MHz) \( \delta \) 4.91-4.88 (m, 1H), 3.77 (qd, 2H, \( J = 13.8, 4.6 \text{ Hz} \)), 2.47-2.44 (m, 2H), 2.08 (s, 3H), 1.74 (td, 3H, \( J = 3.0, 0.6 \text{ Hz} \)); \textbf{\( ^{13} \)}C NMR (CDCl\(_3\), 150 MHz) \( \delta \) 171.0, 78.3, 73.8, 73.4, 63.5, 21.3, 20.8, 3.6; \textbf{HRMS} (+APCI) calculated for C\(_8\)H\(_{13}\)O\(_3\) 157.0859, found 157.0857 [M+H]\(^+\).

Preparation of (S)-1-oxohex-4-yn-2-yl acetate 75:

TPAP (0.023 g, 0.064 mmol) was added to a mixture of alcohol 74 (0.100 g, 0.64 mmol), NMO (0.113 g, 0.96 mmol) and 4Å molecular sieves (0.320 g) in DCM (1.5 mL). The resulting mixture was stirred at room temperature for 2h then loaded directly on a column. Purification by flash chromatography (3:1 hexanes/EtOAc) afforded aldehyde 75 as a colorless oil (0.066 g, 67 %); \textbf{\( ^1 \)}H NMR (CDCl\(_3\), 400 MHz) \( \delta \) 9.6 (s, 1H), 5.04-5.03 (m, 1H), 2.64-2.62 (m, 2H), 2.20 (s, 3H), 1.80-1.76 (m, 3H).
Preparation of 6-((2R,3S)-3-((t-butyldimethylsilyl)oxy)-2-hydroxyhept-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one 78:

BF₃·Et₂O (0.1 mL, 0.808 mmol) was added to a solution of aldehyde 61 (0.087 g, 0.385 mmol) in DCM (2 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 10 min then diene 76 (0.206 g, 0.962 mmol) was added. The mixture was stirred at -78 °C for 1 h. H₂O (1 mL) was then added and the mixture was extracted with DCM (3 × 3 mL). The combined organic extracts were washed with brine (2 × 2 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (10:1 → 3:1 hexanes/EtOAc) afforded alcohol 78 as a colorless oil (0.050 g, 35 % yield) as a 1:0.6 mixture of diastereomers which was carried through; Rₕ 0.30 (5:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 3465, 2998, 2928, 2856, 1721, 1635, 1390, 1272, 1202; ¹H NMR (CDCl₃, 600 MHz) δ 5.34 (s, 1H), 5.31 (s, 0.6H), 4.02-3.95 (m, 1.6H), 3.78-3.75 (m, 1H), 3.68-3.65 (m, 0.6H), 2.50-2.32 (m, 6.4H), 1.76-1.74 (m, 4.8H), 1.66 (s, 9.6H), 0.88 (s, 14.4H), 0.10-0.08 (m, 9.6H); ¹³C NMR (CDCl₃, 150 MHz) δ 169.3, 168.9, 161.4, 161.3, 160.7, 106.5, 95.3, 95.2, 78.5, 75.1, 74.0, 73.3, 71.3, 69.7, 38.8, 36.4, 25.9, 25.7, 25.5, 25.1, 24.9, 24.2, 23.5, 20.1, 3.4, -4.3, -4.6; HRMS (+APCI) calculated for C₁₉H₃₅O₅Si 369.2092, found 369.2088 [M+H]⁺.
Preparation of \((5R,6S)\)-methyl 5,6-dihydroxy-3-oxodec-8-ynoate 60:

MeOH (0.04 mL, 0.939 mmol) was added to a solution of alcohol 78 (0.065 g, 0.427 mmol) in toluene (3 mL). The resulting mixture was heated to reflux for 2 h. The reaction mixture was then allowed to reach room temperature and was concentrated \textit{in vacuo}. Purification by flash chromatography (5:1 hexanes/EtOAc) afforded alcohol 60, found to be identical to previously reported 60 by \(^1\)H NMR and \(R_f\).

Preparation of 6-((2R,3S)-2,3-dihydroxyhept-5-yn-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one 79:

HF-pyridine (2 mL) was added to a solution of alcohol 78 (0.144 g, 0.391 mmol) in THF (2 mL). The resulting mixture was stirred at room temperature for 2 h. Saturated aq. NaHCO\(_3\) (2 mL) was then added. The mixture was extracted with Et\(_2\)O (3 \(\times\) 5 mL). The combined organic extracts were washed with brine (2 \(\times\) 3 mL), dried over MgSO\(_4\) and concentrated \textit{in vacuo}. Purification by flash chromatography (3:1 \(\rightarrow\) 0:1 hexanes/EtOAc) afforded diol 79 as a colorless oil (0.080 g, 88 % yield); \(R_f\) 0.15 (3:1 hexanes/EtOAc); \textbf{IR} (thin film, cm\(^{-1}\)) 3408, 2919, 1703, 1631, 1391, 176, 1275, 1202; \(^1\)H NMR (CDCl\(_3\), 600 MHz) \(\delta\) 5.37 (s, 1H), 5.36 (s, 0.6H), 3.95-3.91 (m, 1.6H), 3.68-3.66 (m, 1H), 3.61-3.60.
(m, 0.6H), 2.59-2.34 (m, 9.6H), 1.82-1.79 (m, 4.8H), 1.70 (s, 9.6H); $^{13}$C NMR (CDCl$_3$, 150 MHz) δ 169.3, 168.9, 161.3, 106.9, 95.5, 79.6, 79.5, 74.5, 74.3, 73.3, 71.8, 70.8, 70.1, 38.5, 36.9, 25.9, 25.7, 25.5, 24.8, 23.2, 3.7; HRMS (+APCI) calculated for C$_{12}$H$_{19}$O$_5$ 255.1227, found 255.1221 [M+H]$^+$. 

**Preparation of 6-(((4$R$,5$S$)-5-(but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2,2-dimethyl-4H-1,3-dioxin-4-one 80:**

2,2-dimethoxypropane (0.03 mL, 0.235 mmol) and pTsOH (0.002 g, 0.008 mmol) were added to a solution of diol 79 (0.020 g, 0.078 mmol) in acetone (1 mL). The resulting mixture was stirred at room temperature for 30 min then Et$_3$N (0.2 mL) was added. The reaction mixture was concentrated in vacuo. Purification by flash chromatography (5:1 hexanes/EtOAc) afforded compound 80 as a colorless oil (0.019 g, 84%); R$_f$ 0.86 (3:1 hexanes/EtOAc); IR (thin film, cm$^{-1}$) 2987, 2921, 1730, 1637, 1377, 1205, 1065; $^1$H NMR (CDCl$_3$, 600 MHz) δ 5.39 (s, 0.6 H), 5.35 (s, 1H), 4.39 (ddd, 1H, $J = 10.0$, 6.0, 3.7 Hz), 4.25 (dt, 1H, $J = 8.6$, 5.6 Hz), 4.01 (td, 0.6H, $J = 8.3$, 3.4 Hz), 3.76 (td, 0.6H, $J = 7.5$, 4.8 Hz), 2.65 (dd, 0.6H, $J = 15.1$, 3.4 Hz), 2.58-2.53 (m, 1.6H), 2.48 (dd, 0.6H, $J = 5.5$, 2.7 Hz), 2.48-2.38 (m, 2.6H), 2.31-2.27 (m, 1H), 1.79-1.77 (m, 4.8H), 1.71 (s, 3.6H), 1.70 (s, 6H), 1.43 (s, 3H), 1.39 (s, 1.8H), 1.38 (s, 1.8H), 1.32 (s, 3H); $^{13}$C NMR (CDCl$_3$, 150 MHz) δ 168.8, 168.2, 161.2, 109.3, 108.9, 106.8, 95.4, 95.3, 78.7, 78.2, 76.9, 76.2,
Preparation of methyl 4-((4R,5S)-5-(but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-diazo-3-oxobutanoate 77:

Prepared according to general procedure E using compound 80 (0.092 g, 0.312 mmol). Purification by flash chromatography (5:1 hexanes/EtOAc) afforded α-diazo-β-ketoester 77 as a colorless oil (0.078 g, 85 % over 2 steps); Rf 0.72 (3:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 2954, 2922, 2853, 2136, 1724, 1657, 1437, 1217; ¹H NMR (CDCl₃, 400 MHz) δ 4.71 (dt, 1H, J = 8.0, 5.6 Hz), 4.35-4.28 (m, 1.6H), 3.84-3.79 (m, 5.4H), 3.31 (d, 0.6H, J = 8.8 Hz), 3.27 (d, 1H, J = 8.8Hz), 3.15-3.12 (m, 1H), 3.11-3.08 (m, 0.6H), 2.51-2.32 (m, 3.2H), 1.76 (td, 1.8H, J = 2.8, 1.2 Hz), 1.74 (td, 3H, J = 2.8, 1.2 Hz), 1.43 (s, 3H), 1.41 (s, 1.8H), 1.38 (s, 1.8H), 1.33 (s, 3H); HRMS (+APCI) calculated for C₁₄H₁₉O₅N₂ 295.1286, found 295.1286 [M+H]⁺.
Preparation of cyclobutanone 81:

\[ \alpha\text{-Diazo-}\beta\text{-ketoester } 77 \text{ (0.078 g, 0.265 mmol) and } \text{Rh}_2(\text{OAc})_4 \text{ (0.002 g, 0.005 mmol)} \]

were dissolved in DCM (0.9 mL). The resulting mixture was stirred at room temperature for 50 min then loaded directly on a column. Purification by flash chromatography (5:1 hexanes/EtOAc) afforded cyclobutanone 81 as a colorless oil (0.013 g, 18 %); \( R_f \) 0.48 (3:1 hexanes/EtOAc); \text{IR} \text{ (thin film, cm}^{-1}) 2922, 1772, 1743, 1437, 1288, 1076; \text{\textsuperscript{1}H NMR} (CDCl$_3$, 600 MHz) \( \delta \) 4.85 (d, 1H, \( J = 7.6 \text{ Hz} \)), 4.29-4.27 (m, 1H), 3.78 (s, 3H), 2.64 (ddd, 1H, \( J = 18, 7.6, 1.2 \text{ Hz} \), 1H), 2.48 (d, 1H, \( J = 18 \text{ Hz} \)), 2.37-2.33 (m, 1H), 2.05-2.00 (m, 1H), 1.78-1.76 (m, 3H), 1.40 (s, 6H); \text{\textsuperscript{13}C NMR} (CDCl$_3$, 150 MHz) \( \delta \) 205.6, 165.0, 86.0, 78.9, 77.8, 76.1, 73.0, 70.3, 53.0, 35.6, 23.8, 21.8, 19.9, 3.7.

Preparation of (S)-\( \text{t}-\text{butyl}((1\text{-((4-methoxybenzyl)oxy)hex-4-yn-2-yl)oxy})\text{-dimethylsilane} 83:

\[ \text{Prepared according to general procedure A using alcohol } 68 \text{ (2.78 g, 11.8 mmol), 1.1 equiv. of TBSCl and 1.5 equiv. of imidazole. Purification by flash chromatography (40:1 hexanes/EtOAc) afforded product } 83 \text{ as a colorless oil (3.20 g, 77 % yield); } R_f \text{ 0.78 (5:1 hexanes/EtOAc); IR (thin film, cm}^{-1}) 2953, 2928, 2855, 1612, 1513, 1463, 1247, 1119, 834; \text{\textsuperscript{1}H NMR} (CDCl$_3$, 600 MHz) \( \delta \) 7.26 (d, 2H, \( J = 8.4 \text{ Hz} \)), 6.87 (d, 2H, \( J = 8.4 \text{ Hz} \)), \]
4.47 (s, 2H), 3.91 (q, 1H, \( J = 6.0 \) Hz), 3.80 (s, 3H), 3.49-3.46 (dd, 1H, \( J = 10.2, 4.8 \) Hz), 3.42 (dd, 1H, \( J = 9.8, 5.5 \) Hz), 2.41-2.37 (m, 1H), 2.29-2.25 (m, 1H), 1.75 (t, 3H, \( J = 2.6 \) Hz), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); \(^{13}\text{C NMR}\) (CDCl\(_3\), 150 MHz) \( \delta \) 159.3, 130.8, 129.4, 113.9, 77.4, 76.4, 73.8, 73.2, 71.2, 55.4, 26.0, 25.2, 18.4, 3.7, -4.4; \(^{13}\text{C NMR}\) (+APCI) calculated for C\(_{20}\)H\(_{33}\)O\(_3\)Si 349.2194, found 349.2193 [M+H]\(^+\).

**Preparation of \((S,Z)-t\)-butyl(1-((4-methoxybenzyl)oxy)hex-4-en-2-yl)oxy)-dimethylsilane 94:**

A flask containing compound 93 (9.78 g, 28 mmol) and Lindlar’s catalyst (1.19 g, 0.561 mmol) in MeOH (200 mL) was purged with H\(_2\) then stirred for 18h under an atmosphere of H\(_2\). The reaction mixture was then filtered over silica and concentrated in vacuo to afford alkene 94 as a colorless oil (9.83 g, 100 %); \( R_f \) 0.78 (5:1 hexanes/EtOAc); \(^{1}\text{H NMR}\) (CDCl\(_3\), 600 MHz) \( \delta \) 7.26 (d, 2H, \( J = 8.5 \) Hz), 6.87 (d, 2H, \( J = 8.5 \) Hz), 5.53 (ddd, 1H, \( J = 6.0, 4.9, 1.1 \) Hz), 5.44 (ddd, 1H, \( J = 6.0, 3.4, 1.3 \) Hz), 4.46 (s, 2H), 3.86 (q, 1H, \( J = 5.4 \) Hz), 3.81 (s, 3H), 3.38-3.36 (m, 2H), 2.31-2.24 (m, 2H), 1.62 (d, 3H, \( J = 7.2 \) Hz), 0.90 (s, 9H), 0.06 (s, 6H); \(^{13}\text{C NMR}\) (CDCl\(_3\), 150 MHz) \( \delta \) 159.2, 130.8, 129.4, 126.6, 125.9, 113.9, 74.3, 73.2, 71.7, 55.4, 32.9, 26.1, 18.4, 13.2, -4.7; \(^{13}\text{C NMR}\) (+APCI) calculated for C\(_{20}\)H\(_{35}\)O\(_3\)Si 351.2359, found 351.2350 [M+H]\(^+\).
Preparation of (S,Z)-2-((t-butyldimethylsilyl)oxy)hex-4-en-1-ol 95:

![Chemical Structure](Image)

Prepared according to general procedure B using PMB ether 94 (2.25 g, 6.43 mmol). Purification by flash chromatography (20:1 hexanes/EtOAc) afforded alcohol 95 as a colorless oil (1.10 g, 74 % yield); Rf 0.50 (5:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 3396, 2953, 2928, 2884, 2856, 1472, 1252, 1101, 825, 774; ¹H NMR (CDCl₃, 600 MHz) δ 5.56-5.53 (m, 1H), 5.38-5.36 (m, 1H), 3.78-3.74 (m, 1H), 3.56-3.54 (m, 1H), 3.46-3.43 (m, 1H), 2.31-2.23 (m, 2H), 1.93 (bs, 1H), 1.61 (d, 3H, J = 6.6 Hz), 0.90 (s, 9H), 0.09 (s, 6H); ¹³C NMR (CDCl₃, 150 MHz) δ 126.6, 125.8, 72.9, 66.2, 31.9, 26.0, 18.3, 13.1, -4.3, -4.5; HRMS (+APCI) calculated for C₁₂H₂₅OSi 213.1669, found 213.1666 [M+H-H₂O]⁺.

Preparation of (S,Z)-2-((t-butyldimethylsilyl)oxy)hex-4-enal 96:

![Chemical Structure](Image)

Prepared according to general procedure C using alcohol 95 (0.283 g, 1.23 mmol). Purification by flash chromatography (20:1 → 5:1 hexanes/EtOAc) afforded aldehyde 96 as a yellow oil (0.200 g, 71 % yield); Rf 0.64 (5:1 hexanes/EtOAc); ¹H NMR (CDCl₃, 600 MHz) δ 9.59 (s, 1H), 5.62-5.57 (m, 1H), 5.43-5.39 (m, 1H), 3.98 (t, 1H, J = 7.2 Hz), 2.43-2.38 (m, 2H), 1.62 (d, 3H, J = 6.6 Hz), 0.91 (s, 9H), 0.07 (s, 6H); ¹³C NMR (CDCl₃, 150 MHz) δ 203.9, 127.3, 124.4, 77.7, 31.8, 30.7, 25.8, 22.8, 14.4, -4.6.
Preparation of 6-((2R,3S,Z)-2,3-dihydroxyhept-5-en-1-yl)-2,2-dimethyl-4H-1,3-dioxin-4-one 97:

BF₃·Et₂O (0.11 mL, 0.872 mmol) and diene 76 (0.373 g, 1.74 mmol) were added to a solution of aldehyde 96 (0.200 g, 0.872 mmol) in DCM (12 mL) at -78 °C. The resulting mixture was stirred at -78 °C for 45 min. H₂O (8 mL) was then added and the mixture was extracted with DCM (3 × 10 mL). The combined organic extracts were washed with brine (2 × 5 mL), dried over MgSO₄ and concentrated in vacuo. HF·pyridine (0.1 mL) was added to a solution of the residue in THF (3 mL). The resulting mixture was stirred at room temperature for 3 h. Saturated aq. NaHCO₃ (2 mL) was then added. The mixture was extracted with Et₂O (3 × 5 mL). The combined organic extracts were washed with brine (2 × 3 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (5:1 → 0:1 hexanes/EtOAc) afforded diol 97 as a colorless oil (0.099 g, 44 % yield over 2 steps) in a 1:0.6 mixture of diastereomers which was carried through; 

R_f 0.08 (2:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 3436, 2918, 1711, 1632, 1392, 1276, 1203, 1013; ¹H NMR (CDCl₃, 600 MHz) δ 5.72-5.67 (m, 1.6H), 5.45-5.41 (m, 1.6H), 5.37 (s, 1H), 5.35 (m, 0.6H), 3.91 (ddt, 1H, J = 9.8, 4.2, 2.8 Hz), 3.81-3.79 (m, 0.6H), 3.67 (dtd, 0.6H, J = 6.5, 4.3, 2.2 Hz), 3.53-3.51 (m, 1H), 2.53-2.23 (m, 9.6H), 1.72 (s, 9.6H), 1.68-1.65 (m, 4.8H); ¹³C NMR (CDCl₃, 150 MHz) δ 169.7, 169.3, 161.5, 128.6, 128.4, 125.3, 125.2, 106.9, 95.4, 73.8, 73.3, 71.1, 70.5, 38.7, 36.5, 31.5, 30.0, 25.6, 24.9, 13.3; HRMS (+APCI) calculated for C₁₃H₂₁O₅ 257.1384, found 257.1382 [M+H]^+. 
Preparation of 6-(((4R,5S)-5-((Z)-but-2-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2,2-dimethyl-4H-1,3-dioxin-4-one 98:

2,2-dimethoxypropane (0.14 mL, 1.16 mmol) and pTsOH (0.007 g, 0.004 mmol) were added to a solution of diol 97 (0.099 g, 0.387 mmol) in acetone (1 mL). The resulting mixture was stirred at room temperature for 30 min then Et₃N (0.2 mL) was added. The reaction mixture was concentrated in vacuo. Purification by flash chromatography (3:1 hexanes/EtOAc) afforded compound 98 as a colorless oil (0.075 g, 65%); Rₚ 0.81 (3:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 2988, 2934, 1732, 1638, 1390, 1377, 1273, 1206, 1012; \(^{1}H\) NMR (CDCl₃, 600 MHz) δ 5.64-5.60 (m, 1.6H), 5.44-5.37 (m, 2.2H), 5.34 (s, 1H), 4.34-4.31 (m, 1H), 4.20-4.18 (m, 1H), 3.88-3.83 (m, 0.6H), 3.74-3.71 (m, 0.6H), 2.49-2.31 (m, 5.4H), 2.23-2.20 (m, 1H), 1.71-1.69 (s, 9.6H), 1.65-1.62 (m, 4.8H), 1.45 (s, 3H), 1.38 (s, 3.6H), 1.33 (s, 3H); \(^{13}C\) NMR (CDCl₃, 150 MHz) δ 168.9, 168.2, 161.3, 127.4, 127.1, 125.0, 124.7, 109.0, 108.6, 106.9, 95.6, 95.4, 80.2, 74.2, 53.6, 37.5, 35.0, 31.8, 30.1, 28.6, 27.6, 27.3, 25.9, 25.8, 24.8, 24.6, 22.8, 14.3, 13.3; HRMS (+APCI) calculated for C₁₆H₂₅O₅ 297.1697, found 297.1694 [M+H]⁺.
Preparation of methyl 4-((4R,5S)-5-((Z)-but-2-en-1-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-diazo-3-oxobutanoate 82:

Prepared according to general procedure E using compound 98 (0.075 g, 0.253 mmol).

Purification by flash chromatography (5:1 hexanes/EtOAc) afforded α-diazo-β-ketoester 82 as a colorless oil (0.052 g, 69 % over 2 steps); Rf 0.76 (3:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 2924, 2138, 1720, 1654, 1437, 1264, 1061; $^1$H NMR (CDCl$_3$, 600 MHz) δ 5.59-5.56 (m, 1.6H), 5.48-5.39 (m, 1.6H), 4.65 (dt, 1H, J = 9.0, 5.4 Hz), 4.24-4.17 (m, 1.6H), 3.82 (s, 4.8H), 3.78 (q, 0.6H, J = 8.0 Hz), 3.28-3.20 (m, 1.6H), 2.98-2.91 (m, 1.6H), 2.38-2.20 (m, 3.2H), 1.63-1.61 (m, 4.8H), 1.44 (s, 3H), 1.41 (s, 3.6H), 1.36 (s, 3H); $^{13}$C NMR (CDCl$_3$, 150 MHz) δ 190.3, 189.8, 161.9, 127.1, 126.7, 125.7, 125.6, 125.1, 80.2, 76.2, 73.9, 52.4, 43.7, 41.2, 30.5, 29.9, 28.3, 28.0, 27.4, 27.3, 25.9, 14.4, 13.3; HRMS (+APCI) calculated for C$_{14}$H$_{21}$O$_3$N$_2$ 297.1445, found 297.1443 [M+H]$^+$.

Preparation of butanone 84:

α-diazo-β-ketoester 82 (0.064 g, 0.215 mmol) and Rh$_2$(OAc)$_4$ (0.002 g, 0.005 mmol) were dissolved in DCM (0.7 mL). The resulting mixture was stirred at room temperature
for 1 h then loaded directly on a column. Purification by flash chromatography (5:1 hexanes/EtOAc) afforded cyclobutanone 84 as a colorless oil (0.014 g, 24 %); Rf 0.48 (3:1 hexanes/EtOAc); Rf 0.61 (2:1 hexanes/EtOAc); IR (thin film, cm⁻¹) 2925, 1772, 1743, 1437, 1288, 1083; ¹H NMR (CDCl₃, 600 MHz) δ 5.59 (ddt, 1H, J = 11.5, 6.2, 1.6 Hz), 5.35-5.30 (m, 1H), 4.58 (d, 1H, J = 7.8 Hz), 4.18-4.15 (m, 1H), 3.77-3.76 (s, 3H), 2.60 (dd, 1H, J = 18, 7.2 Hz), 2.51 (dd, 1H, J = 17.4, 1.2 Hz), 2.14-2.03 (m, 2H), 1.60-1.58 (m, 3H), 1.41 (s, 3H), 1.39 (s, 3H); ¹³C NMR (CDCl₃, 150 MHz) δ 205.6, 164.8, 127.2, 123.8, 77.4, 76.3, 71.1, 52.8, 35.6, 29.1, 23.7, 19.7, 12.9; HRMS (+APCI) calculated for C₁₄H₂₁O₅ 269.1384, found 269.1379 [M+H]⁺.

Preparation of 6-(((4R,5S)-5-(but-2-yn-1-yl)-2-oxo-1,3-dioxolan-4-yl)methyl)-2,2-dimethyl-4H-1,3-dioxin-4-one 85:

Triphosgene (0.115 g, 0.388 mmol) added to a solution of diol 79 (0.082 g, 0.323 mmol) and pyridine (0.03 mL, 0.388 mmol) in DCM (1 mL). The reaction was stirred at room temperature for 2h. Saturated aq. NaHCO₃ (0.5 mL) was then added. The mixture was extracted with DCM (3 x 2 mL). The combined organic extracts were washed with brine (2 x 1 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (3:1 DCM/Et₂O) afforded carbonate 85 as a colorless oil (0.050 g, 55 % yield); ¹H NMR (CDCl₃, 400 MHz) δ 5.41 (s, 1.6H), 5.01 (ddd, 1H, J = 9.7, 7.4, 4.1 Hz), 4.81 (td, 1H, J = 7.4, 5.0 Hz), 4.73 (dd, 0.6H, J = 5.3, 1.9 Hz), 4.45-4.43 (m, 0.6H), 2.90-
2.61 (m, 6.4H), 1.80-1.77 (m, 4.8H), 1.70-1.70 (s, 9.6H); $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 165.4, 160.4, 153.3, 107.5, 96.7, 96.5, 81.2, 78.3, 77.2, 76.2, 75.2, 71.1, 38.1, 33.2, 25.8, 25.4, 24.9, 24.5, 24.4, 20.2, 3.6.

**Preparation of (Z)-methyl 3-oxodec-5-en-8-ynoate 86:**

MeOH (0.02 mL) was added to a solution of carbamate 85 (0.050 g, 0.179 mmol) in toluene (1 mL). The resulting solution was heated to 80 °C for 24h. The reaction was then allowed to reach room temperature and was concentrated in vacuo to afford alkene 86; $R_f$ 0.63 (3:1 hexanes/EtOAc); $^1$H NMR (CDCl$_3$, 400 MHz) δ 6.85 (dd, 1H, $J = 15.8$, 4.3 Hz), 6.63 (dd, 0.6H, $J = 15.5$, 4.8 Hz), 6.42 (dd, 1H, $J = 15.8$, 1.7 Hz), 6.08 (dt, 0.6H, $J = 15.5$, 1.6 Hz), 4.42-4.38 (m, 1.6H), 3.76 (s, 1.8H), 3.74 (s, 3H), 3.60 (s, 3.2H), 2.53-2.33 (m, 3.2H), 1.78-1.81 (m, 4.8H); $^{13}$C NMR (CDCl$_3$, 150 MHz) δ 192.1, 189.4, 173.4, 168.8, 167.9, 148.4, 139.8, 128.3, 124.4, 91.8, 79.9, 79.5, 74.2, 73.6, 69.9, 69.5, 66.1, 53.7, 28.0, 27.6, 15.5, 3.8.
Preparation of (2R,3S)-3-((t-butyldimethylsilyl)oxy)-1-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)hept-5-yn-2-yl pivalate 87:

PivCl (0.05 mL, 0.377 mmol) was added to a solution of diol 79 (0.132 g, 0.314 mmol, as 1:0.6 mixture of diastereomers) in DCM (1 mL) followed by pyridine (0.03 mL, 0.377 mmol). The reaction mixture was stirred at room temperature for 24 h. Saturated aq. NaHCO$_3$ (0.5 mL) was then added. The mixture was extracted with DCM (3 x 2 mL). The combined organic extracts were washed with brine (2 x 1 mL), dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography (5:1 DCM/Et$_2$O) afforded compound 87 as a colorless oil (0.075 g, 53 % yield); $R_f$ 0.50 (3:1 hexanes/EtOAc); IR (thin film, cm$^{-1}$) 2955, 1728, 1641, 1390, 1275, 1152; $^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ 5.25 (s, 1.6H), 5.23-5.22 (m, 0.6H), 5.11-5.07 (m, 1H), 3.92-3.89 (m, 1.6H), 2.70-2.67 (m, 1H), 2.61-2.52 (m, 1.2H), 2.40 (dd, 1H, $J = 15, 9.0$ Hz), 2.32-2.27 (m, 2.2H), 2.21-2.17 (m, 1H), 1.78-1.76 (m, 1.8H), 1.77-1.75 (m, 3H), 1.69 (s, 1.8H), 1.67 (s, 3H), 1.64 (s, 1.8H), 1.62 (s, 3H), 1.18 (s, 14.4H), 0.91 (s, 9H), 0.89 (s, 5.4H), 0.13 (s, 6H), 0.09 (s, 2.4H); $^{13}$C NMR (CDCl$_3$, 150 MHz) $\delta$ 177.5, 168.6, 161.1, 106.9, 95.3, 77.7, 75.8, 75.8, 72.4, 71.4, 71.0, 39.1, 33.3, 29.9, 27.3, 26.7, 25.9, 24.5, 22.7, 18.2, 3.7, -4.3, -4.7; HRMS (+ESI) calculated for C$_{24}$H$_{46}$O$_6$SiNa 475.2486, found 475.2478 [M+H]$^+$. 
Preparation of \((2R,3S)-1-(2,2\text{-dimethyl-4-oxo-4H-1,3-dioxin-6-yl})-3\text{-hydroxyhept-5-yn-2-yl pivalate 99:}\)

HF·pyridine (0.5 mL) was added to a solution of compound 87 (0.075 g, 0.166 mmol) in THF (1 mL). The resulting mixture was stirred at room temperature for 2h. Saturated aq. NaHCO₃ (1 mL) was then added. The mixture was extracted with Et₂O (3 × 3 mL). The combined organic extracts were washed with brine (2 × 1 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography (3:1 → 1:1 hexanes/EtOAc) afforded diol 99 as a colorless oil (0.017 g, 30 % yield); IR (thin film, cm⁻¹) 3444, 2968, 1729, 1635, 1392, 1277, 1204, 1151, 1014; \(^1\)H NMR (CDCl₃, 600 MHz) \(\delta\) 5.28 (s, 1H), 5.27 (s, 0.6H), 5.22-5.19 (m, 1H), 5.09-5.05 (m, 0.6H), 3.80-3.78 (m, 1.6H), 2.71 (dd, 0.6H, \(J = 15, 3.6H\)), 2.65-2.55 (m, 2.6H), 2.43-2.29 (m, 3.2H), 1.80-1.79 (m, 4.8H), 1.68 (s, 6H), 1.64 (s, 3.6H), 1.20 (s, 9H), 1.18 (s, 5.4H); \(^{13}\)C NMR (CDCl₃, 150 MHz) \(\delta\) 177.8, 168.0, 167.6, 161.0, 107.0, 95.6, 79.8, 79.4, 74.0, 71.7, 70.9, 70.8, 35.3, 34.9, 27.3, 25.5, 24.9, 3.7; HRMS (+APCI) calculated for C₁₈H₂₇O₆ 339.1802, found 339.1799 [M+H]⁺.
Preparation of (2R,3S)-3-acetoxy-1-(2,2-dimethyl-4-oxo-4H-1,3-dioxin-6-yl)hept-5-yn-2-yl pivalate 88:

\[
\text{Ac}_2\text{O} (0.01 \text{ mL}, 0.10 \text{ mmol}) \text{ was added to a mixture of alcohol } 99 \text{ (0.0168 g, 0.05 mmol) and DMAP (0.02 g, 0.143 mmol) in DCM (0.5 mL). The resulting mixture was stirred at room temperature for 30 min. Saturated aq. NH}_4\text{Cl (0.5 mL) was then added. The mixture was extracted with DCM (3 × 2 mL). The combined organic extracts were washed with brine (2 × 0.5 mL), dried over MgSO}_4\text{ and concentrated in vacuo. Purification by flash chromatography (3:1 → 1:1 hexanes/EtOAc) afforded compound 88 as a colorless oil (0.013 g, 68 % yield); }^{1}\text{H NMR} \text{ (CDCl}_3, 600 \text{ MHz}) \delta 5.41-5.34 \text{ (m, 1.6H), 5.30 (s, 1H), 5.26 (s, 0.6H), 5.10-5.04 \text{ (m, 1.6H), 2.63-2.43 \text{ (m, 6.4H), 2.10 (s, 3H), 2.08 (s, 1.8H), 1.78-1.75 (m, 4.8H), 1.70 (s, 6H), 1.66 (s, 3.6H), 1.20 (s, 9H), 1.18 (s, 5.4H); }^{13}\text{C NMR} \text{ (CDCl}_3, 150 \text{ MHz}) \delta 181.3, 177.3, 167.2, 166.8, 160.8, 107.1, 101.7, 95.8, 78.9, 72.8, 71.9, 71.8, 69.3, 69.2, 35.4, 30.3, 29.9, 27.3, 25.4, 25.1, 24.8, 21.3, 20.9, 3.7; }\text{HRMS (+ESI) calculated for } C_{20}H_{28}O_7Na 403.1727, \text{ found 403.1722 [M+Na]}^+.
\]
Preparation of (5R,6S)-methyl 6-acetoxy-3-oxo-5-(pivaloyloxy)dec-8-ynoate 89:

MeOH (0.01 mL, 0.935 mmol) was added to a solution of alcohol 88 (0.013 g, 0.034 mmol) in toluene (1 mL). The resulting mixture was heated to reflux for 2h. The reaction mixture was then allowed to reach room temperature and was concentrated in vacuo to afford β-ketoester 89 (0.006 g); ¹H NMR (CDCl₃, 600 MHz) δ 5.50-5.48 (m, 1.6H), 5.14-5.11 (m, 1.6H), 3.74 (s, 1.8H), 3.73 (s, 3H), 3.52-3.44 (m, 3.2H), 2.93-2.78 (m, 3.2H), 2.45-2.42 (m, 3.2H), 2.10 (s, 3H), 2.08 (s, 1.8H), 1.77-1.72 (m, 4.8H), 1.19 (s, 9H), 1.16 (s, 5.4H); HRMS (+ESI) calculated for C₁₈H₂₆O₇Na 377.1571, found 377.1566 [M+Na]⁺.

Preparation of (5R,6S)-methyl 6-acetoxy-2-diazo-3-oxo-5-(pivaloyloxy)dec-8-ynoate 90:

Et₃N (0.003 mL, 0.021 mmol) was added to a mixture of β-ketoester 89 (0.006 g, 0.017 mmol) and pABSA (0.005 g, 0.021 mmol) in MeCN (0.5 mL). The reaction mixture was stirred at room temperature for 2h. Saturated aq. NH₄Cl (0.5 mL) was added and the reaction mixture was extracted with DCM (3 × 2 mL). The combined organic extracts were washed with 10 % KOH (1 mL) then saturated aq. NaHCO₃ (11 mL) and brine (1 mL), dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography
as indicated afforded the desired α-diazo-β-ketoester 90; $^1$H NMR (CDCl$_3$, 600 MHz) δ 5.53-5.48 (m, 1.6H), 5.29-5.25 (m, 1.6H), 3.85 (s, 4.8H), 2.59-2.48 (m, 6.4H), 2.15 (s, 4.8H), 1.77-1.76 (m, 4.8H), 1.26 (s, 14.4H); HRMS (+ESI) calculated for C$_{18}$H$_{24}$O$_7$N$_2$Na 403.1476, found 403.1472 [M+Na]$^+$. 
10. References.


