Rearrangement and Cascade Reactions: New Synthetic Methods and the Total Synthesis of Diazonamide A

by

David Lee Waller

B. S. Chemistry, University of Georgia, 2001

Submitted to the Graduate Faculty of Arts and Sciences in partial fulfillment of the requirements for the degree of Doctor of Philosophy

University of Pittsburgh

2008
This dissertation was presented

by

David Lee Waller

It was defended on
February 13, 2008

and approved by

Professor Scott Nelson, Department of Chemistry
Professor Paul Floreancig, Department of Chemistry
Professor John Lazo, Department of Pharmacology

Dissertation Advisor: Professor Peter Wipf, Department of Chemistry
This dissertation describes the development of several cascade reactions and their application to the synthesis of structurally and/or biologically relevant molecules. We successfully developed a three-step, one-pot carboalumination-Claisen rearrangement-addition reaction, which provides complex allylic alcohols from simple starting materials. While attempting to extend this methodology to nitrogen-containing substrates, a tandem hydrozirconation-iminium ion addition reaction was developed that allows simple access to functionalized isoindolinones. An oxidative rearrangement of enol ethers to spiroketals was developed, contributing an unusual approach to these highly sought after functionalities. Finally, an approach to the complex natural product diazonamide A was investigated with the intention of applying the Chan rearrangement. Eventually, the complexities of total synthesis forbid the use of the Chan rearrangement, and an alternative pathway was developed that led to the application of a cascade acyl chloride-oxazoline ring scission to install critical components of diazonamide.
Acknowledgments

A Ph.D. is greater than the sum of its parts, and certainly greater than what appears within this document. It is an experience, and comprises the fullest meaning of “the journey is its own reward”. I gratefully acknowledge Professor George Majetich of the University of Georgia for starting me down this road and introducing me to the beautiful world of molecules.

Graduate school has been an outstanding experience, and I thank Prof. Peter Wipf for continually raising the bar, providing endless knowledge and for allowing me to be a part of the diazonamide story. I also would like to thank Professors Nelson, Floreancig, Lazo, Brummond and Wilcox for serving on committees at various points. I would like to thank the numerous co-workers with whom I have interacted with in fruitful ways over the years. We have learned much about life and science, and I hope that you learned something from me. Additionally, I would like to thank Bayer, Roche, Merck, NIH and NSF (and hence the U. S. taxpayer) for funding over the years.

Finally, I would like to express my love and admiration for my parents, two amazing people who let me become whatever I wanted to be, and supported me every step of the way. My brother and grandmothers have also been unbelievably supportive over the years, and kept me close to home despite the distance. As I head to Harvard with my beloved siamese cat Bailey, I look forward to more wonderful experiences and people like those here in Pittsburgh.
# TABLE OF CONTENTS

## 1. WATER ACCELERATED CASCADE REACTIONS .......................................................... 1

1.1 INTRODUCTION .................................................................................................. 1

1.1.1 Carboalumination of Alkynes ..................................................................... 1
1.1.2 The Nature of Water/Alane Mixtures ....................................................... 6
1.1.3 The Claisen Rearrangement ...................................................................... 8

1.2 RESULTS AND DISCUSSION ........................................................................... 12

1.2.1 Proof-of-Concept Studies ......................................................................... 12
1.2.2 Optimization Studies ............................................................................... 13
1.2.3 Synthesis and Cascade Reaction of Carboxyl-Substituted Vinyl Ethers 15
1.2.4 Synthesis and Cascade Reactions of Alkoxy Propenols............................ 17
1.2.5 Synthesis and Cascade Reactions of Alkylated Vinyl Ethers.................... 21
1.2.6 Synthesis and Cascade Reactions of Phenethyl-Substituted Vinyl Ethers... 24
1.2.7 Stereochemistry of the Cascade Process.................................................. 28
1.2.8 Conversion of 1,6-Diene to Cyclopentene .............................................. 33
1.2.9 [1,3] vs [3,3] Rearrangement.................................................................... 34
1.2.10 Conclusions............................................................................................... 35

## 2. AZA-COPE REARRANGEMENTS AND N-ACYL IMINIUM ION CHEMISTRY. 36
2.1 INTRODUCTION ..................................................................................................... 36
   2.1.1 Aza-Cope Rearrangements ........................................................................ 36
2.2 RESULTS AND DISCUSSION ................................................................................. 37
   2.2.1 Preliminary Investigations ......................................................................... 37
   2.2.2 Carboalumination Studies on Lactam-based Substrates and Medium Ring Formation ................................................................. 44
   2.2.3 Intermolecular Alkenylation of N-Acyl Iminium Ions ....................... 52
   2.2.4 Conclusions .................................................................................................. 61
3. SPRIOKETALS VIA OXIDATIVE REARRANGEMENT OF ENOL ETHERS ...... 63
   3.1 INTRODUCTION ....................................................................................................... 63
      3.1.1 Barton’s Proposal for the Biosynthesis of Acutumine ..................... 63
   3.2 RESULTS AND DISCUSSION ........................................................................ 67
4. TOTAL SYNTHESIS OF DIAZONAMIDE A ............................................................... 76
   4.1 INTRODUCTION ............................................................................................. 76
      4.1.1 Isolation and Structure ........................................................................ 76
      4.1.2 Biological Activity ................................................................................ 79
      4.1.3 Previous Total Syntheses ....................................................................... 80
   4.2 RESULTS AND DISCUSSION ........................................................................ 90
      4.2.1 Previous Work Towards Diazonamide A in the Wipf group .......... 90
      4.2.2 Retrosynthetic Analysis ........................................................................ 92
      4.2.3 Preparation of Aniline 4-51 ................................................................. 95
      4.2.4 Incorporation of Tyrosine Backbone and Installation of C10 Quaternary Center ................................................................. 96
4.2.5  Installation of Diazonamide’s Central Oxazole ................................. 107
4.2.6  Conclusions ....................................................................................... 118

5.  EXPERIMENTAL SECTION ........................................................................ 119

5.1  WATER ACCELERATED CASCADE REACTIONS .................................. 120
5.2  AZA-COPE REARRANGEMENTS AND N-ACYL IMINUM ION CHEMISTRY ................................................................. 147
5.3  SPIROKETALS VIA OXIDATIVE REARRANGEMENT OF ENOL ETHERS ........................................................................ 175
5.4  ENANTIOSELECTIVE TOTAL SYNTHESIS OF DIAZONAMIDE A .. 185

APPENDIX A ................................................................................................ 210
APPENDIX B ................................................................................................ 217
APPENDIX C ................................................................................................ 224
APPENDIX D ................................................................................................ 230
BIBLIOGRAPHY ....................................................................................... 241
LIST OF TABLES

Table 1-1. Cascade carboalumination/Claisen rearrangement optimization. .............................. 14
Table 1-2. Summary of results of the cascade reaction with carboxyl group-containing substrates. ................................................................. 16
Table 1-3. Summary of results of cascade reactions of alkoxy propenol derivatives................... 19
Table 1-4. Summary of results of the cascade reaction of alkylated allyl vinyl ethers. ............. 24
Table 1-5. Summary of results of the cascade reaction of phenethyl-substituted vinyl ethers... 28
Table 2-1. Optimization of the intermolecular alkenylation of acyl-iminium ions to generate isoindolinones. ................................................................. 55
Table 2-2. Addition of various alkenyl nucleophiles to generate isoindolinones.................... 56
Table 2-3. Addition of trisubstituted alkenyl alanes to provide isoindolinones 2-56 and 2-57... 58
Table 4-1. Enantioselective Heck cyclization to set the C10 quaternary center of diazonamide A. 0
LIST OF SCHEMES

Scheme 1-1. Zirconium-catalyzed carboalumination. ................................................................. 1
Scheme 1-2. Initially proposed mechanism of zirconium-catalyzed carboalumination. .......... 2
Scheme 1-3. Revised and generally accepted mechanism of carboalumination. .................... 3
Scheme 1-4. Attempted crossover experiment demonstrating that Cp₂ZrCl(Me) is not the active methylating agent in zirconium-catalyzed carboalumination. ........................................................... 3
Scheme 1-5. Mechanism of thermal isomerization resulting in anti-carboalumination. ......... 4
Scheme 1-6. The Negishi carboalumination and the water-accelerated carboalumination discovered by Wipf and Lim. ............................................................................................................................ 5
Scheme 1-7. Proposed oxo-bridged intermediate responsible for water related rate enhancement of carboalumination............................................................................................................................. 6
Scheme 1-8. The reaction of AlMe₃ with water. ........................................................................... 7
Scheme 1-9. Proposed structures of aluminoxanes........................................................................ 8
Scheme 1-10. The Claisen rearrangement and the numbering of the allylic vinyl ether system... 8
Scheme 1-11. The possible boat (1-22) and chair (1-23) conformations of the Claisen rearrangement. ................................................................................................................................................. 9
Scheme 1-12. Proposed transition states of the Claisen rearrangement. ................................. 9
Scheme 1-13. The aromatic Claisen rearrangement promoted by water-activated alane......... 10
Scheme 1-14. Tandem Claisen rearrangement/carboalumination in the presence of Erker's catalyst.
........................................................................................................................................................... 11
Scheme 1-15. Structures of okaramine J and azadirachtin. ................................................................. 11
Scheme 1-16. Proposed three-step cascade reaction to form allylic alcohols. ............................... 12
Scheme 1-17. Proof-of-concept experiment. ....................................................................................... 13
Scheme 1-18. Preparation of carboxyl group containing substrates................................................. 15
Scheme 1-19. Proposed fragmentation mechanism of ester 1-35 during the cascade reaction.. 17
Scheme 1-20. Preparation of alkoxy propenol derivatives. ............................................................... 18
Scheme 1-21. Fragmentation pathway leading to 1-45/1-46. .............................................................. 20
Scheme 1-22. Deprotection of 1-47................................................................................................. 20
Scheme 1-23. Preparation of 1-51. ................................................................................................. 21
Scheme 1-24. Preparation of 1-53 via alkene isomerization. ........................................................... 22
Scheme 1-25. Preparation of 1-56 via Cu-catalyzed coupling. ......................................................... 23
Scheme 1-26. Preparation of allylic alcohol 1-64.............................................................................. 25
Scheme 1-27. Preparation of hydrocinnamate derivatives 1-65 and 1-67................................. 26
Scheme 1-28. Preparation of allylic alcohol 1-69.............................................................................. 26
Scheme 1-29. X-ray analysis of ester 1-77 and 1-38 confirm the syn,syn-configuration for the major diastereomers. .................................................................................................................. 29
Scheme 1-30. Proposed mechanism for cascade reaction. .............................................................. 30
Scheme 1-31. Control reactions for test of stereochemical integrity of the aldehyde intermediate. 3
Scheme 1-32. Control experiments establish the beneficial effect of water on the diastereoselectivity of the addition process. .................................................................................................................. 33
Scheme 1-33. Preparation of cyclopentenes by ring closing metathesis......................................... 34
Scheme 1-34. [1,3] Rearrangement of cyclopropylmethyl vinyl ether 1-85. ....................... 35

Scheme 2-1. Aza-Cope rearrangement to access 2-4 in Overman’s synthesis of gelsemine. ..... 36

Scheme 2-2. Aza-Cope rearrangement to furnish allene 2-8. ........................................ 37


Scheme 2-4. Preparation and reactions of model substrate 2-11. .............................. 39

Scheme 2-5. Preparation of alkyl-branched substrate 2-15. ........................................ 40

Scheme 2-6. Attempted reactions of alkyl branched substrate 2-15. ............................ 40

Scheme 2-7. Preparation of phthalimide substrate 2-18. ........................................ 41

Scheme 2-8. Attempted reactions of phthalimide substrate 2-18. .............................. 41

Scheme 2-9. Attempted carboalumination of 2-18. ............................................... 42

Scheme 2-10. Attempted aza-Cope rearrangement of hydroxy lactam 2-17. .................. 42

Scheme 2-11. Preparation of 2-20. ................................................................. 43

Scheme 2-12. Attempted aza-Cope rearrangement of acetoxy lactam 2-20.................... 43

Scheme 2-13. Attempted carboalumination of 2-20 .................................................. 44

Scheme 2-14. Preparation of 2-24, containing a three carbon spacer between amide and alkyne. 45

Scheme 2-15. Reaction of 2-24 under carboalumination conditions ............................... 45

Scheme 2-16. Preparation of 2-26. ................................................................. 46

Scheme 2-17. Attempted carboalumination of tertiary alcohol 2-27 .............................. 46

Scheme 2-18. Proposed cascade cyclization sequence ..................................................... 47

Scheme 2-19. Preparation and model reaction of 2-31 .............................................. 48

Scheme 2-20. Preparation of lactam 2-33. ............................................................... 48

Scheme 2-21. Attempted cascade cyclization of 2-33 .............................................. 49

Scheme 2-22. Preparation of phenoxy lactam 2-34 .............................................. 49
Scheme 4-11. Macrolactamization in Nicolaou's first total synthesis of diazonamide A .......... 86
Scheme 4-12. Nicolaou's use of Witkop-type cyclization to form lower macrocycle and completion of diazonamide A ................................................................................................................................................................. 87
Scheme 4-13. Formation of the C10 quaternary center in Nicolaou's second total synthesis of diazonamide A .................................................................................................................................................................................................................. 88
Scheme 4-14. SmI2-mediated heteropinacol macrocyclization in Nicolaou's second total synthesis of diazonamide A .................................................................................................................................................................................................................. 89
Scheme 4-15. Harran's key oxidative cyclization in his total synthesis of diazonamide A ...... 89
Scheme 4-16. Magnus' O- to C-aryl migration to form the C10 quaternary center in his formal synthesis of diazonamide A ........................................................................................................................................................................................................... 90
Scheme 4-17. Enantioselective Heck cyclization reported by Wipf as an approach to the originally proposed structure of diazonamide A ........................................................................................................................................................................................................... 91
Scheme 4-18. Wipf's Chan rearrangement approach to the indole bis-oxazole motif in diazonamide A ........................................................................................................................................................................................................... 92
Scheme 4-19. Retrosynthetic analysis for diazonamide A .................................................. 94
Scheme 4-20. Requirement for aniline fragment to be selectively activated by Pd(0) .......... 95
Scheme 4-21. Preparation of aniline 4-51 utilizing an N- to C-silane transfer ....................... 96
Scheme 4-22. Retrosynthetic analysis for key intermediate 4-47 ......................................... 96
Scheme 4-23. Hydrostannylation of 4-56 and iodination of stannane 4-57 ......................... 97
Scheme 4-24. Preparation of ester 4-63 ................................................................................ 98
Scheme 4-25. Condensation of aniline 4-51 with ester 4-63 ............................................... 99
Scheme 4-26. Preparation of the O-benzyl protected ester 4-69 ........................................ 100
Scheme 4-27. Attempted condensation of aniline 4-51 with ester 4-69 ............................. 101
Scheme 4-28. Preparation of ester 4-72 containing the \((E)\) alkene geometry and attempted condensation with aniline 4-51. ......................................................................................................................... 102

Scheme 4-29. Possible intermediate required for successful amidation of esters of type 4-63. 103

Scheme 4-30. Preparation of vinyl iodide 4-76. ................................................................. 104

Scheme 4-31. Carboxylation of vinyl iodide 4-76 to prepare key ester 4-77. .................... 104

Scheme 4-32. Condensation of aniline 4-51 with ester 4-77 and subsequent elaboration to key Heck cyclization precursor 4-79. .............................................................................................................. 105

Scheme 4-33. Debromination observed during attempted reduction of oxindole 4-80. .......... 108

Scheme 4-34. Reduction of oxindole 4-80 with DIBAL. ...................................................... 109

Scheme 4-35. Oxidative cleavage of alkene 4-82 and unexpected decarboxylation during attempted oxidation of aldehyde 4-83. .................................................................................................................................. 110

Scheme 4-36. Revised retrosynthetic analysis for diazonamide A. ........................................ 111

Scheme 4-37. Attempted addition to aldehyde 4-83. ............................................................ 112

Scheme 4-38. Preparation of oxazoline 4-94. ....................................................................... 113

Scheme 4-39. Hydrolysis of oxazoline 4-94 and attempted deformylation of 4-95. .......... 114

Scheme 4-40. Installation of valine residue through acylation of oxazoline 4-94. ............... 115

Scheme 4-41. Oxidation of alcohol 4-98 and cyclodehydration to key oxazole 4-99. ............ 116

Scheme 4-42. Alternative substrates to proceed to the late stages of the synthesis. .......... 116

Scheme 4-43. Preparation of isocyanide 4-104. ................................................................... 117

Scheme 4-44. Preparation of oxazoline 4-105 and subsequent acylation. ......................... 118
ABBREVIATIONS

Ac  acetyl
AlR₃  trialkylaluminum
Boc  tert-butyloxycarbonyl
Bn  benzyl
Cbz  benzyloxycarbonyl
dba  dibenzyldineacetone
DBU  1,8-diazabicyclo[5.4.0]undec-7-ene
d,l-CSA  d,l-camphorsulfonic acid
DIAD  diisopropylazodicarboxylate
DIPEA  diisopropylethylamine
DMAP  4-dimethylaminopyridine
dppb  diphenylphosphinobutane
dr  diastereomeric ratio
EDCI  1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee  enantiomeric excess
IBCF  isobutyl chloroformate
KHMDS  potassium hexamethyldisilazide
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>LHMDS</td>
<td>lithium hexamethyldisilazide</td>
</tr>
<tr>
<td><em>m</em>-CPBA</td>
<td><em>meta</em>-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Mes</td>
<td>mesityl</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>NMM</td>
<td><em>N</em>-methyl morpholine</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>Piv</td>
<td>pivaloyl</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBDPS</td>
<td><em>tert</em>-butyldiphenylsilyl</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Ts</td>
<td><em>p</em>-toluenesulfonyl</td>
</tr>
</tbody>
</table>
WATER ACCELERATED CASCADE REACTIONS

1.1 INTRODUCTION

1.1.1 Carboalumination of Alkynes

Some of the earliest accounts of the carbometallation of alkynes appeared around 1970 and included metals such as Mg,\textsuperscript{1} Rh,\textsuperscript{2} and Cu.\textsuperscript{3} An preliminary report detailing carboalumination appeared in 1960,\textsuperscript{4} demonstrating the reaction of acetylene with triethylaluminum at 60 °C. Of all of these carbometallations, the method which proved most general was carbocupration,\textsuperscript{5} until the catalytic carboalumination was published. The zirconium-catalyzed carboalumination of alkynes (Scheme 1-1) was discovered by Negishi and co-workers in 1978.\textsuperscript{6}

\[
\text{R=â–—} \xrightarrow{\text{AlMe}_3, \text{cat. Cp}_2\text{ZrCl}_2} \text{R} = \equiv \text{AlMe}_2
\]

Scheme 1-1. Zirconium-catalyzed carboalumination.

The carboalumination of alkynes is one of the most versatile methods for the preparation of olefins with defined geometry. Terminal alkynes give excellent regioselectivity, often greater than 95:5 in favor of terminal metallation. Internal symmetrical alkynes also give excellent stereoselectivity.\textsuperscript{7} The mechanism of carbometallation was initially thought to involve carbozirconation by MeZrCp\textsubscript{2}Cl, followed by transmetallation to Al (Scheme 1-2).\textsuperscript{8}
Scheme 1-2. Initially proposed mechanism of zirconium-catalyzed carboalumination.

Subsequent mechanistic investigations weakened support for the carbozirconation/transmetallation mechanism. A mixture of Me$_2$AlCl-Cp$_2$ZrCl$_2$ was also found to be a good methylating agent, although no Cl-Me exchange could be observed by NMR. The formation of MeCp$_2$ZrCl would be necessary for the mechanism in Scheme 1-2 to be valid. NMR data clearly indicated the reversible Cl-Me exchange between Zr and Al in mixtures of AlMe$_3$-Cp$_2$ZrCl$_2$. These data led to a revision of the proposed mechanism of carboalumination to a Zr-assisted direct Al-C bond addition to the alkyne (Scheme 1-3).
Furthermore, when a 1:1 mixture of AlEt₃ and Cl(Me)ZrCp₂ was treated with 1-heptyne, only 1-7 and 1-8 were isolated in a combined 93% yield, with only trace amounts of the product derived from methylalumination formed (Scheme 1-4).

A solvent effect is also observed in the zirconium-catalyzed carboalumination of alkynes. The relative rate of the reaction decreases on going from 1,2-dichloroethane to chlorobenzene to benzene, following the general trend of the dielectric constants of the solvents (ε = 10.4, 5.6, and 2.3,
respectively). This observation is in agreement with the existence of the highly polarized intermediate 1-5.

A complementary method that furnishes the products of a net anti-carbometallation has been reported recently. Homopropargyl alcohols as well as their one carbon homologues undergo standard zirconium-catalyzed carboaluminatation, but when heated, the products of an anti-carbometallation were isolated. Negishi has proposed a thermal isomerization through bis-alane intermediate 1-10. Methyl transfer to aluminum and reformation of the olefin generates metallacycle 1-12, the masked product of anti-carboalumination of the alkyne (Scheme 1-5). Good yields and excellent anti/syn selectivities are observed (>98:2). It is interesting that this isomerization is thermally induced. Without heating, only syn-carbometallation products are isolated.

Scheme 1-5. Mechanism of thermal isomerization resulting in anti-carboalumination.

Vinyl alanes resulting from carboaluminations of alkynes can be transformed in a variety of ways, making them versatile intermediates. The Al of the resulting vinyl alane can be readily exchanged with H(D), Hg, B, Zr, trapped with epoxides, chloroformates, and imines.
or coupled to vinyl\textsuperscript{15} or aryl halides.\textsuperscript{16} Carboalumination has found recent utility in the synthesis of the carotenoids\textsuperscript{17} and the insect juvenile hormones I and II.\textsuperscript{18}

In 1993, Wipf and Lim reported dramatic rate enhancing effects of water on carboaluminations.\textsuperscript{13} Standard Negishi carboalumination of 1-octyne proceeds in 3 hours at room temperature to yield a 95:5 mixture of regioisomers following aqueous acidic workup (Scheme 1-6). Addition of stoichiometric amounts of water allows for the same carboalumination to proceed at -70 °C within minutes. Yields and selectivities are identical to those reported by Negishi.\textsuperscript{3}

\begin{center}
\begin{tabular}{c c c c c c}
 & & & & & \\
\text{nC}_6\text{H}_{13} & \rightarrow & \text{nC}_6\text{H}_{13} & \rightarrow & \text{nC}_6\text{H}_{13} & + \\
& & & & & \\
 & & & & & \\
1) AlMe\textsubscript{3} & \text{Cp}_2ZrCl\textsubscript{2} & \rightarrow & Me & \text{Me} & \\
& & & & & \\
& & & & & \\
2) H\textsubscript{3}O\textsuperscript{+} & & & & & \\
& & & & & \\
23 °C & 3-24 h & & & & \\
& & & & & \\
\end{tabular}
\end{center}

\textbf{Scheme 1-6.} The Negishi carboalumination and the water-accelerated carboalumination discovered by Wipf and Lim.

The vinyl alane intermediates obtained from the water-accelerated carboalumination can be manipulated in the same fashion as standard carbometallation intermediates. The structure of the active carboaluminating reagent, however, remains elusive. The origin of the rapid rate acceleration also remains in doubt. Wipf proposed the oxo-bridged dimer 1-15 (Scheme 1-7) as the catalytically active species, although its existence at temperatures above 0 °C was questionable at the time of
publication. More recent results from the Wipf group\textsuperscript{19,20} indicate that temperature is not a factor in the rate enhancement.

Scheme 1-7. Proposed oxo-bridged intermediate responsible for water related rate enhancement of carboalumination.

1.1.2 The Nature of Water/Alane Mixtures

The composition of mixtures of alkylalalanes and water is the subject of considerable research.\textsuperscript{21} This effort is largely funded by the polymer industry because these mixtures are known to efficiently co-promote olefin polymerization in the presence of group 4 metallocenes.\textsuperscript{22} Methylaluminoxane (MAO) is, by far, the most popular and effective polymerization co-catalyst. MAO has been known to promote the polymerization of monomers since the early 1960s.\textsuperscript{23} MAO is generated by the controlled hydrolysis of AlMe\textsubscript{3}, forming the Al-O-Al linkage with the extrusion of CH\textsubscript{4} gas. This relates it to the accelerated carboalumination conditions developed by Wipf and Lim. Although the structure and reactivity of MAO is highly dependent on the method of preparation,\textsuperscript{24} MAO most likely approximates the nature of the mixtures formed when water-accelerated carboalumination conditions are generated in the laboratory. Despite its widespread use, little is known about its structure or physical properties. MAO is, however, known to be an equilibrating mixture of oligomers with an average molecular weight of 1100.\textsuperscript{25} Substantial efforts have been made to acquire information about the structure of MAO and related systems with \textsuperscript{27}Al NMR, mass
spectrometry, and computational methods. These efforts have generated some concrete findings, but are plagued by inconsistencies associated with the handling of MAO. The reaction of water and alkyl alanes (Scheme 1-8) has been followed by NMR and reported to be dependant on temperature, with full consumption of the water protons occurring around 0 °C.

\[
\text{AlMe}_3 + \text{H}_2\text{O} \rightarrow \text{(MeAlO)}_n + \text{CH}_4
\]

**Scheme 1-8.** The reaction of AlMe₃ with water.

It should be noted that these NMR experiments were performed in diethyl ether, and the reaction was followed by observing the proton resonances of the alkyl groups on aluminum. It is generally accepted that MAO is *always* contaminated with free AlMe₃ (if it is removed, the MAO oligomer will release more AlMe₃) and contains a constant Me/Al ratio of 1.5. Multinuclear NMR investigations have shown that four-coordinate aluminum centers predominate in MAO, although some three-coordinate centers do exist. All of the oxygen atoms in MAO are believed to be three-coordinate. About 15-20% of the methyl groups of MAO are believed to be bridging between Al atoms in a rapidly exchanging fashion and these methyl groups participate in reactions which activate metallocenes for catalytic olefin polymerization.

The Lewis acidity of the reagent has been proposed to be very similar to that of AlMe₃. This acidity has been attributed to either free AlMe₃ or open sites on oligomeric aluminoxanes. The actual structures which most commonly are postulated for MAO are shown in Scheme 1-9. Cyclic 6-membered fused rings (1-16) of varying length and 4-membered rings (1-17) were observed by X-ray diffraction. More recently, Sinn and co-workers have proposed structures representing the *tetramer* of 1-18, which is based on the *tert*-butyl monomer 1-19 which has been observed by X-ray
diffraction. Thus, the structure of MAO can be drawn as a collection of rapidly equilibrating oligomers which contain acidic sites that participate in chemical reactions.


1.1.3 The Claisen Rearrangement

The Claisen rearrangement of allyl vinyl ethers (1-20 $\rightarrow$ 1-21, Scheme 1-10) was discovered in 1912.\textsuperscript{35} Since this initial report, it has become one of the most utilized methods for introducing molecular complexity.\textsuperscript{36}

Scheme 1-10. The Claisen rearrangement and the numbering of the allylic vinyl ether system.
The Claisen rearrangement is a concerted, non-synchronous pericyclic reaction that shows a strong preference for a chair-like transition state. Calculations have estimated the stability of the chair transition state (1-23) over the boat transition state (1-22) of allyl vinyl ether to be 6.6 Kcal/mol (Scheme 1-11).\textsuperscript{38} The preference for the chair-like transition state can, however, be overridden by conformational constraints.

![Scheme 1-11](image)

**Scheme 1-11.** The possible boat (1-22) and chair (1-23) conformations of the Claisen rearrangement.

In most cases, the electronic structure of the transition state is thought to range from a number of limiting electronic distributions (1-25, 1-26) which can be derived from the traditional aromatic transition state (1-24)(Scheme 1-12). However, the electronic structure of the transition state continues to be debated since it is highly dependant on substitution.\textsuperscript{39}

![Scheme 1-12](image)

**Scheme 1-12.** Proposed transition states of the Claisen rearrangement.

The Claisen rearrangement benefits thermodynamically from the scission of a C-O $\sigma$-bond and two C-C $\pi$-bonds and the formation of a new C-O $\pi$-bond, a new C-C $\sigma$-bond and a new C-C $\pi$-
bond. This benefit of roughly 20 kcal/mol is derived mainly from the conversion of the C-C \( \pi \)-bond into a C-O \( \pi \)-bond.

The synthetic utility of the Claisen rearrangement has been well documented over the 105 years since its discovery. Advances have been made steadily over the years, including the study of the metal-promoted rearrangement. Protic as well as Lewis acids were found to effectively promote the Claisen rearrangement and other closely related [3,3] sigmatropic rearrangements. Aluminum has proven to be a most effective and widely used metal for the promotion of the Claisen rearrangement.\textsuperscript{40} In a recent example, Wipf and co-workers reported an accelerated aromatic Claisen rearrangement using water-activated alanes (Scheme 1-13).\textsuperscript{40(b)}

\begin{equation}
\begin{array}{c}
\text{1-27} \\
\text{1) AlMe}_3 \ (4 \text{ eq}) \ \text{H}_2\text{O} \ (1 \text{ eq}) \\
\text{2) H}_3\text{O}^+ \text{ } 94\% \\
\text{1-28}
\end{array}
\end{equation}

**Scheme 1-13.** The aromatic Claisen rearrangement promoted by water-activated alane.

Recently, transition metals have found increased use for the catalysis of the Claisen rearrangement, including highly diastereoselective and enantioselective variants.\textsuperscript{41} A testament to the utility of the Claisen rearrangement and its variants is its continued use in tandem methodology and in the synthesis of complex natural products. For example, Wipf and co-workers reported a tandem aromatic Claisen rearrangement/catalytic asymmetric carboalumination (Scheme 1-14) utilizing water-activated alane and Erker’s catalyst.\textsuperscript{42}
Scheme 1-14. Tandem Claisen rearrangement/carboalumination in the presence of Erker's catalyst.

Ganesan and co-workers recently completed the total synthesis of okaramine J using an aza-Claisen rearrangement (Scheme 1-15). An advanced intermediate in a total synthesis of the complex natural product azadirachtin was accessed using a microwave-assisted Claisen rearrangement.

1.2 RESULTS AND DISCUSSION

1.2.1 Proof-of-Concept Studies

Based on results of the Wipf group on water-accelerated processes, a cascade involving a water-accelerated carboalumination and an *aliphatic* Claisen rearrangement was envisioned. Since the aliphatic Claisen rearrangement gives rise to an aldehyde, vinyl addition should follow rearrangement, thereby comprising a cascade reaction (Scheme 1-16). This proposed sequence will form three new C-C bonds by converting an achiral allyl vinyl ether into an allylic alcohol containing three contiguous stereocenters.

![Scheme 1-16. Proposed three-step cascade reaction to form allylic alcohols.](image)

The initial proof-of-concept reaction was performed with cinnamyl vinyl ether (1-30). Treatment of the carboalumination product of 1-hexyne with 1-30 in CH₂Cl₂ at -78 °C gave a 42% yield of 1-31a and 1-31b as a 1:1 mixture of diastereomers (Scheme 1-17). The desired product was
accompanied by substantial amounts of 1-32, which was characterized by $^1$H NMR and mass spectroscopy.

Scheme 1-17. Proof-of-concept experiment.

1.2.2 Optimization Studies

Optimization of the cascade reaction was performed with cinnamyl vinyl ether (1-30) and 1-hexyne. The initial goal was to increase the yield of 1-31 by suppressing the formation of 1-32, derived from methyl addition to the aldehyde (Table 1-1). It was postulated that the large excess of AlMe$_3$ (5 eq) present in the reaction mixture was responsible for the methyl addition to the aldehyde. Reduction of the equivalents of both AlMe$_3$ and H$_2$O to 2.2 and 1.1, respectively (Entry 1), suppressed the undesired methyl addition to nearly undetectable levels. Further reduction to 2 equivalents of AlMe$_3$ and 1 equivalents H$_2$O (Entry 2) furnished the desired product in 60% yield with no evidence of the methyl transfer by-product; however some hydrolysis of the starting vinyl ether was indicated by TLC analysis.
Table 1-1. Cascade carboalumination/Claisen rearrangement optimization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>AlMe$_3$ (eq)</th>
<th>H$_2$O (eq)</th>
<th>Solvent</th>
<th>Yield$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.2</td>
<td>1.1</td>
<td>CH$_2$Cl$_2$</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>2.05</td>
<td>1.0</td>
<td>CH$_2$Cl$_2$</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>0.75</td>
<td>CH$_2$Cl$_2$</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>0.5</td>
<td>CH$_2$Cl$_2$</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>2.5</td>
<td>1.25</td>
<td>CH$_2$Cl$_2$</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>2.2</td>
<td>2.25</td>
<td>CH$_2$Cl$_2$</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>2.25</td>
<td>0.56</td>
<td>CH$_2$Cl$_2$</td>
<td>61</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>1</td>
<td>ClCH$_2$CH$_2$Cl</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td>2.25</td>
<td>1.2</td>
<td>Toluene</td>
<td>48</td>
</tr>
</tbody>
</table>

$^a$ Carboalumination performed at 0 °C in the presence of 10 mol % Cp$_2$ZrCl$_2$. $^b$ 1-30 added at -78 °C and allowed to warm to ambient temperature. $^c$ dr = 1:1.

Reduction of the amount of AlMe$_3$ to levels below 2 equivalents resulted in no reaction or only a trace of conversion (Entries 3 and 4). Raising the amount of AlMe$_3$ to 2.5 equivalents and H$_2$O to 1.25 equivalents had little effect on the yield (Entry 5).

With the conditions optimized for vinyl ether 1-30, the amount of water added to the reaction was further investigated. Equimolar amounts of AlMe$_3$ and H$_2$O gave a very slow reaction and lowered the yield substantially (Entry 6). Interestingly, good yields were obtained with substoichiometric amounts of H$_2$O (Entry 7); however, this was unique to simple unfunctionalized allyl vinyl ethers. The optimum stoichiometry was 2 equivalents of AlMe$_3$ and 1 equivalent of H$_2$O, with a yield of approximately 60%. No change in the rate of the reaction in CH$_2$Cl$_2$ was observed...
with the exception of a large amount of water, which slowed the reaction. The reaction proved to be somewhat sensitive to solvent. Conducting the entire reaction in dichloroethane showed no benefit over dichloromethane (Entry 8). When toluene was used as a solvent, the rearrangement/addition step was very slow and gave a yield of only 50% (Entry 9). Therefore, dichloromethane was chosen as the solvent of choice for this transformation. To extend the method to a synthetically useful state, the scope of the cascade was examined and the results are discussed below.

1.2.3 Synthesis and Cascade Reaction of Carboxyl-Substituted Vinyl Ethers

The first group of substrates tested with the optimized conditions contained a carboxyl group. Acid 1-34 was prepared in 95% yield by treating the sodium salt of cinnamyl alcohol with betaine 1-33, according to the method of Büchi (Scheme 1-18).

\[
\begin{align*}
\text{Ph} & \quad \text{OH} \\
\rightarrow & \quad \text{1) NaH, THF} \\
 & \quad \text{2) } \text{PhOH} \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{TMSCHN}_2 & \quad \text{MeOH/benzene} \\
\rightarrow & \quad 20\% \\
\text{Ph} & \quad \text{O} \\
\text{1-34} & \quad 95\% \\
\end{align*}
\]

Scheme 1-18. Preparation of carboxyl group containing substrates.
Treatment of 1-34 with TMSCHN$_2$ in methanolic benzene$^{46}$ furnished methyl ester 1-35 in quantitative yield. Acid 1-34 was also coupled with dimethyl amine using standard coupling methods to give the corresponding dimethyl amide 1-36 in a modest 48% yield (Scheme 1-18).

These substrates were submitted to the cascade reaction, with the results summarized in Table 1-2. Acid 1-34 was incompatible with the reaction conditions, resulting in immediate decomposition with no recovery of any starting material (Table 1-2, Entry 1).

**Table 1-2.** Summary of results of the cascade reaction with carboxyl group-containing substrates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Products (major:minor)$^a$</th>
<th>Yield (%) (dr)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-34</td>
<td>i</td>
<td>Decomposition</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1-35</td>
<td>ii</td>
<td>MeO 1-37</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>1-36</td>
<td>iii</td>
<td>1-38 1-39</td>
<td>10 (5:1)</td>
</tr>
</tbody>
</table>

Reaction Conditions: (i) 5 eq AlMe$_3$, 2.5 eq H$_2$O, 10 mol % Cp$_2$ZrCl$_2$, 2 eq hexyne (ii) 2.5 eq AlMe$_3$, 1.25 eq H$_2$O, 10 mol % Cp$_2$ZrCl$_2$, 2 eq hexyne (iii) 10 eq AlMe$_3$, 4 eq H$_2$O, 10 mol % Cp$_2$ZrCl$_2$, 2 eq hexyne. $^a$ Shown as major (left):minor (right). $^b$ Determined by integration of the $^1$H NMR spectrum of the product mixture.

When ester 1-35 was submitted to the reaction, only dienoate 1-37 (37%) and cinnamyl alcohol (47%) were isolated (Table 1-2, Entry 2). Dienoate 1-37 is the result of vinyl alane addition into the $\alpha,\beta$-unsaturated ester with subsequent elimination of cinnamyl alkoxide (Scheme 1-19). This result demonstrated the incompatibility of good Michael acceptors with the water-activated vinyl alanes.
Scheme 1-19. Proposed fragmentation mechanism of ester 1-35 during the cascade reaction.

Amide 1-36 was submitted to the cascade reaction and required 10 and 4 equivalents of AlMe₃ and H₂O, respectively, for any reaction to occur. The reaction proceeded in very low yield (10%) but with a diastereoselectivity of 5:1 (Table 1-2, Entry 3). This lack of reactivity could be due to the highly aggregated AlMe₃/H₂O mixtures that coordinate to the amide oxygen and thus block the reactive Lewis acidic sites of aluminum.

1.2.4 Synthesis and Cascade Reactions of Alkoxy Propenols

The next class of substrates tested were derived from allylic alcohols. Ester 1-35 was reduced with DIBAL-H to give a low yield of the desired allyl alcohol 1-40 (31%) and cinnamyl alcohol, resulting from 1,4-reduction and subsequent expulsion of alkoxide ion. A wide variety of reducing agents were screened but DIBAL-H proved to be the most effective (Scheme 1-20).
Scheme 1-20. Preparation of alkoxy propenol derivatives.

The allylic alcohol 1-40 was treated with NaH followed by CH₃I to provide methyl ether 1-41 in 97% yield. 1-40 was also silylated with TIPSCI in the presence of imidazole and DMAP to furnish silyl alcohol 1-42 in 93% yield (Scheme 1-20).

Allylic alcohol 1-40 was submitted to the standard cascade reaction conditions, i.e. 4 equivalents of AlMe₃ and 2 equivalents of H₂O. The reaction proceeded to completion within 10 min and led to rearrangement products 1-43 and 1-44 in 30% yield and 10:1 diastereoselectivity (Table 1-3, Entry 1). The configuration of the major diastereomer (1-43) was determined to be all syn by x-ray analysis of a derivative (vide infra). The low yield can be attributed to multiple background reactions taking place, as indicated by TLC and GC analysis. Two identifiable side-reactions were the hydrolysis of the starting vinyl ether and methyl addition to the intermediate aldehyde.
Table 1-3. Summary of results of cascade reactions of alkoxy propenol derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Products (major:minor) (^a)</th>
<th>Yield (%) (dr) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-40</td>
<td>i</td>
<td><img src="Ph" alt="OH" />O=C=C=C(C4H9)OH</td>
<td><img src="Ph" alt="OH" />O=C=C=C(C4H9)OH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><img src="Ph" alt="1-43" />O=C=C=C(C4H9)OH</td>
<td><img src="Ph" alt="1-44" />O=C=C=C(C4H9)OH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><img src="Ph" alt="1-45" />O=C=C=C(C4H9)OH</td>
<td><img src="Ph" alt="1-46" />O=C=C=C(C4H9)OH</td>
</tr>
<tr>
<td>2</td>
<td>1-41</td>
<td>ii</td>
<td><img src="Ph" alt="1-47" />O=C=C=C(C4H9)OH</td>
<td><img src="Ph" alt="1-48" />O=C=C=C(C4H9)OH</td>
</tr>
<tr>
<td>3</td>
<td>1-42</td>
<td>iii</td>
<td><img src="Ph" alt="1-49" />O=C=C=C(C4H9)OH</td>
<td><img src="Ph" alt="1-50" />O=C=C=C(C4H9)OH</td>
</tr>
</tbody>
</table>

Reaction Conditions: (i) 4 eq AlMe\(_3\), 2 eq H\(_2\)O, 10 mol % Cp\(_2\)ZrCl\(_2\), 2 eq hexyne (ii) 2.1 eq AlMe\(_3\), 1 eq H\(_2\)O, 10 mol % Cp\(_2\)ZrCl\(_2\), 2 eq phenylacetylene (iii) 2.1 eq AlMe\(_3\), 1 eq H\(_2\)O, 10 mol % Cp\(_2\)ZrCl\(_2\), 2 eq hexyne. \(^a\) Shown as major (left):minor (right). \(^b\) Determined by integration of the \(^1\)H NMR spectrum of the product mixture.

Methyl ether 1-41 failed to undergo the desired process, instead giving only decomposition products, and 1-45 and 1-46 were isolated in 12% combined yield (Table 1-3, Entry 2). These compounds are derived from the process shown in Scheme 1-21. Coordination and elimination of the methoxy group generated the oxocarbenium ion 1-49. Readdition of the vinyl alane in a conjugate fashion into 1-49 generated intermediate 1-50 which underwent the cascade Claisen rearrangement-vinyl alane addition.
Scheme 1-21. Fragmentation pathway leading to 1-45/1-46.

Although an interesting process, cleavage of this type renders ether moieties with sterically accessible oxygen atoms incompatible with the Lewis acidic water-activated alane. The bulky TIPS ether 1-42 did not suffer from this problem. Allyl vinyl ether 1-42 underwent the cascade reaction in good yield (60%) and in high diastereoselectivity (10:1) to provide the monoprotected alcohols 1-47 and 1-48 (Table 1-3, Entry 3). To assign the stereochemistry of 1-47, it was desilylated with TBAF to furnish the corresponding diol which had spectral data identical to 1-43, confirming its stereochemistry as all syn (Scheme 1-22).

Scheme 1-22. Deprotection of 1-47.
1.2.5 Synthesis and Cascade Reactions of Alkylated Vinyl Ethers

Allylic vinyl ethers which bear alkyl substitution at the 1 and/or 2 position are difficult to prepare. However, isopropenyl ether 1-51 was prepared via Hg(II)-catalyzed alcohol exchange with 2-methoxypropene, in 45% yield (Scheme 1-23).

\[
\text{Ph}=\text{CH} \xrightarrow{\text{Hg(OAc)}_2} \text{Ph}=\text{CH}-\text{O} \xrightarrow{45\%} 1-51
\]

Scheme 1-23. Preparation of 1-51.

One of the most mild and selective methods for the formation of allylic vinyl ethers is the alkene isomerization method of Frauenrath. This method uses Ni-centered catalysts, usually NiCl₂(dppb), which must be activated with Li(Et)₃BH. Generally, stereoselectivities are 95:5 or greater and there is a good regioselectivity for terminal olefins. Bis-allyl ether 1-52 was constructed by alkylation of the sodium salt of cinnamyl alcohol in 97% yield (Scheme 1-24). Treatment of bis-allyl ether 1-52 and catalytic NiCl₂(dppb) in THF with catalytic Li(Et)₃BH generated the Ni-H containing catalyst necessary to effect terminal olefin isomerization. Vinyl ether 1-53 was isolated in 50% yield in a 94:6 ratio in favor of the (Z)-isomer.

A recent addition to the literature on the preparation of allylic vinyl ethers by Buchwald and co-workers demonstrated the copper-mediated coupling of vinyl iodides and bromides with alcohols.\textsuperscript{49} The process is catalytic and the olefin geometry is retained throughout the process. The conversion does require the presence of commercially available phenanthroline 1-55. Yields are variable, but the reaction scales very well. This chemistry was used for the synthesis of butyl-substituted vinyl ether 1-56. Vinyl iodide 1-54\textsuperscript{50} was coupled to cinnamyl alcohol in the presence of CuI, CsCO\(_3\), and 1-55. After heating the mixture for 24 hours, a low 17% yield of vinyl ether 1-56 was obtained as a pure geometric (\(E,E\))-isomer (Scheme 1-25).
Scheme 1-25. Preparation of 1-56 via Cu-catalyzed coupling.

With the alkyl substituted vinyl ethers in hand, 1-51 was submitted to the standard conditions, affording tertiary alcohols 1-57 and 1-58 in 75% yield but in poor diastereoselectivity of 3:2 (Table 1-4, Entry 1). Vinyl ether 1-53 underwent the cascade rearrangement/addition in 65% yield and with a 10:1 diastereoselectivity, partially derived from the mixture of olefins that went into the reaction, therefore this is indicative of a highly diastereoselective process (Table 1-4, Entry 2). Butyl-substituted vinyl ether 1-56 also underwent the cascade rearrangement/addition in 90% yield and good diastereoselectivity, although a third diastereomer was present according to $^1$H NMR analysis. (Table 1-4, Entry 3).
Table 1-4. Summary of results of the cascade reaction of alkylated allyl vinyl ethers.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Products (major:minor)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield (%) (dr)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1-51</td>
<td>i</td>
<td><img src="image1.png" alt="image" /></td>
<td>75 (3:2)</td>
</tr>
<tr>
<td>2</td>
<td>1-53</td>
<td>ii</td>
<td><img src="image2.png" alt="image" /></td>
<td>65 (10:1)</td>
</tr>
<tr>
<td>3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1-56</td>
<td>iii</td>
<td><img src="image3.png" alt="image" /></td>
<td>90 (10:1:0.8)</td>
</tr>
</tbody>
</table>

Reaction Conditions: (i) 2.1 eq AlMe₃, 1 eq H₂O, 10 mol % Cp₂ZrCl₂, 2 eq hexyne  
(ii) 2.1 eq AlMe₃, 1 eq H₂O, 10 mol % Cp₂ZrCl₂, 2 eq phenylacetylene  
(iii) 2.1 eq AlMe₃, 1 eq H₂O, 10 mol % Cp₂ZrCl₂, 2 eq hexyne.  
<sup>a</sup> Shown as major (left):minor (right).  
<sup>b</sup> Determined by integration of the ¹H NMR spectrum of the product mixture.  
<sup>c</sup> Major and minor diastereomers are unassigned.  
<sup>d</sup> Minor diastereomers are unassigned as indicated.

1.2.6 Synthesis and Cascade Reactions of Phenethyl-Substituted Vinyl Ethers

All of the examples presented thus far demonstrate the cascade reaction on substrates based on the cinnamyl alcohol moiety. A series of substrates based on allylic alcohol 1-64 was synthesized to demonstrate the chemistry with alkyl substitution at the 6-position of the allylic vinyl ether system. Allylic alcohol 1-64 was synthesized according to a literature protocol (Scheme 1-26).<sup>51</sup> Horner-Wadsworth-Emmons olefination of hydrocinnamaldehyde furnished enoate 1-63 in 72%
yield as a single geometric isomer (\(E\)). Reduction of 1-63 with DIBAL proceeded in quantitative yield to give the desired \((E,E)\)-allylic alcohol 1-64.

![Scheme 1-26. Preparation of allylic alcohol 1-64.](image)

Using previous methods, a series of analogous substrates were synthesized. Alcohol 1-64 underwent Hg(II)-catalyzed alcohol exchange with ethyl vinyl ether in a moderate 47% yield to give vinyl ether 1-65 (Scheme 1-27). Allylic alcohol 1-64 was coupled to betaine to furnish the unstable acid 1-66. This acid was immediately coupled with dimethyl amine (EDCI, DMAP) to yield the dimethyl amide 1-67 in 36% overall yield.

To access allylic alcohol 1-69, 1-64 was condensed with ethyl propiolate in the presence of Et$_3$N to give an 81% yield of the (E,E)-ester 1-68 (Scheme 1-28, geometry assigned based on $J = 12.5$ Hz for $\alpha$-hydrogen). Ester 1-68 was directly subjected to DIBAL reduction, from which only the (E)-allylic alcohol 1-69 was isolated in 45% yield, along with alcohol 1-64, derived from 1,4-reduction and elimination of alkoxide.

Vinyl ether 1-65 underwent the cascade reaction in 78% yield to furnish a 3:2 mixture of separable diastereomers, 1-70 and 1-71 (Table 1-5, Entry 1). Allylic alcohol 1-69 provided diols 1-72 and 1-73 in 17% yield as a 10:0.8:0.5 mixture of diastereomers (Table 1-5, Entry 2). The lower yield can be attributed to the significant number of side-products formed in this reaction. Once again, amide 67 failed to undergo the desired reaction until the equivalents of AlMe₃ and H₂O were raised to 10 and 4, respectively, furnishing amide alcohols 1-74 and 1-75 in 34% yield as a 10:4:1 mixture of diastereomers (Table 1-5, Entry 3). These examples demonstrate that alkyl-substituted allyl vinyl ethers undergo the cascade reaction as effectively as the aryl-substituted derivatives.
Table 1-5. Summary of results of the cascade reaction of phenethyl-substituted vinyl ethers.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Products (major:minor)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield (%) (dr)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1-65</td>
<td>i</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><img src="Ph" alt="OH" /> 1-70 <img src="Ph" alt="OH" /> 1-71</td>
<td>78 (5:3)</td>
</tr>
<tr>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1-69</td>
<td>ii</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><img src="Ph" alt="OH" /> 1-72 <img src="Ph" alt="OH" /> 1-73</td>
<td>17 (10:0.8:0.5)</td>
</tr>
<tr>
<td>3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1-67</td>
<td>iii</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reaction Conditions: (i) 2.1 eq AlMe<sub>3</sub>, 1 eq H<sub>2</sub>O, 10 mol% Cp<sub>2</sub>ZrCl<sub>2</sub>, 2 eq phenylacetylene (ii) 4 eq AlMe<sub>3</sub>, 2 eq H<sub>2</sub>O, 10 mol% Cp<sub>2</sub>ZrCl<sub>2</sub>, 2 eq phenylacetylene (iii) 10 eq AlMe<sub>3</sub>, 4 eq H<sub>2</sub>O, 10 mol% Cp<sub>2</sub>ZrCl<sub>2</sub>, 2 eq hexyne. <sup>a</sup> Shown as major (left):minor (right). <sup>b</sup> Determined by integration of the <sup>1</sup>H NMR spectrum of the product mixture. <sup>c</sup> Major and minor diastereomers are unassigned. <sup>d</sup> Minor diastereomers are unassigned as indicated.

1.2.7 Stereochemistry of the Cascade Process

In order to assign the relative configuration of the major diastereomers, diol 1-76, the product of the cascade reaction of 1-40 with phenylacetylene, was derivatized to its mono-<i>p</i>-bromobenzoyl ester 1-77, and shown by x-ray diffraction to be all syn (Scheme 1-29). In addition to mono-benzoate 1-77, a 75% yield of the bis-benzoate was also obtained, but the latter was not
diastereomically pure and therefore unsuitable for analysis. Additionally, amide 1-38 (see Table 1-2) was assigned as the all syn diastereomer by X-ray diffraction.

Scheme 1-29. X-ray analysis of ester 1-77 and 1-38 confirm the syn,syn-configuration for the major diastereomers.

The all syn configuration of the major diastereomer formed in the cascade process can be explained by a chair-like transition state for the accelerated Claisen rearrangement (Scheme 1-30). The resulting aldehyde (or ketone) is then subjected to a highly selective Felkin-Anh addition of the vinyl alane, directed by the α-stereocenter. After aldehyde 1-78 is formed, addition takes place with the most bulky substituent orthogonal to the carbonyl π-bond. This conformation
follows the Felkin-Anh model and allows the nucleophile to assume a Bürgi-Dunitz trajectory for attack onto the carbonyl group,\textsuperscript{55} resulting in the observed \textit{syn} stereochemistry (1-79).

Scheme 1-30. Proposed mechanism for cascade reaction.

In the addition of alkylaluminum reagents to aldehydes, a 6-membered transition state is generally preferred over a 4-membered transition state when more than one equivalent of AlR\textsubscript{3} is employed.\textsuperscript{56} In the present case, chelation control in the addition can be ruled out since substrates 1-40 and 1-42 gave identical diastereomers (\textit{vide supra}). The stereodirecting effect of the newly formed aldehyde \(\alpha\)-stereocenter, in combination with the steric demand of the oligomeric alane nucleophile,\textsuperscript{57} leads to a high overall induction in the carbonyl addition step. Further support for the significance of steric effects is provided by the poor diastereoselectivity of substrates that lack an \(\alpha\)-
stereocenter. Poor diastereoselectivity is also observed if the intermediate is a ketone, such as 1-51, which is known to exhibit diminished, substituent dependent complexation to aluminum Lewis acids compared to aldehydes.\(^{58}\)

It is possible that the intermediate aldehyde 1-78 might epimerize under the reaction conditions, leading to decreased product diastereomeric ratio; therefore, it was attempted to isolate this intermediate and compare it to the product of a thermal Claisen rearrangement with a substrate of known configuration. Allyl vinyl ether 1-53, when subjected to microwave heating,\(^{59}\) underwent a [3,3] sigmatropic rearrangement in 10 min to yield aldehyde 1-80 in 60% yield as a 10:1 mixture of diastereomers (Scheme 1-31).\(^{60}\) Conversely, attempts to quench a cascade carboalumination-Claisen rearrangement-vinyl alane addition reaction before the allyl vinyl ether was consumed resulted only in recovered starting material and final cascade reaction products. Presumably, nucleophilic addition to the intermediate aldehyde was too rapid for preparative isolation. However, the addition of alkyl alanes to carbonyl groups is slower than vinyl transfer, and when the reaction with an alkyl aluminoxane was quenched prematurely, aldehyde 1-80 was isolated in 55% yield. A 9:1 diastereoselectivity was observed in this reaction, and the configuration of 1-80 was identical to the aldehyde obtained by thermal rearrangement, thus indicating that \(\alpha\)-epimerization during the cascade reaction was unlikely.
Scheme 1-31. Control reactions for test of stereochemical integrity of the aldehyde intermediate.

Since the addition of water to mixtures of alane and zirconocene leads to a significant rate increase in the alkyne carboalumination, the potential accelerating effect of water in the aldehyde addition was probed. Treatment of aldehyde 1-80 at -78 °C with vinyl alane 1-81, prepared via Negishi carboalumination in the absence of water, led in less than 1 min to addition product 1-59 as a modest 3:1 mixture of diastereomers (Scheme 1-32). In the presence of stoichiometric quantities of water, the vinyl alane also rapidly added to this aldehyde, but in 8:1 diastereocntrol. These results indicate that, while no measurable rate enhancement in the already fast 1,2-addition is gained at -78 °C from the addition of water, the larger aluminoxane cluster acting as a bulky nucleophile in the 1,2-addition or a tighter transition state leads indeed to improved facial selectivity in the carbonyl addition step.
Scheme 1-32. Control experiments establish the beneficial effect of water on the diastereoselectivity of the addition process.

1.2.8 Conversion of 1,6-Diene to Cyclopentene

As a practical demonstration of the synthetic potential of this new cascade reaction, a 10:1:0.8 mixture of the 1,6-dienes 1-61 and 1-62 was converted to cyclopentenol 1-83 in the presence of ruthenium catalyst 1-82 (Scheme 1-33). These substituted cyclopentenones have found use in the preparation of carbocyclic nucleosides, some of which are potent antiviral agents lacking the labile anomeric linkage that increases susceptibility to degradative enzymes such as phosphorylases.
Scheme 1-33. Preparation of cyclopentenes by ring closing metathesis.

1.2.9 [1,3] vs [3,3] Rearrangement.

The [1,3] sigmatropic rearrangement of allyl vinyl ethers can compete with the [3,3] sigmatropic shift\textsuperscript{36a} especially in the presence of strong Lewis acids and with substrates that favor allyl cation intermediates.\textsuperscript{65} While reaction products in the cascade process derived from [1,3] rearrangement have not been observed, this process is feasible under the typical reaction conditions. To attempt to observe the [1,3] rearrangement, cyclopropylmethyl vinyl ether 1-85 was prepared in high yield from alcohol 1-84 by a Hg(II)-mediated vinyl ether exchange. Indeed, 1-85 was smoothly converted into allylic alcohol 1-88 under the cascade conditions (Scheme 1-34). The conversion of 1-85 to 1-88 appears to be the first case of a [1,3] sigmatropic rearrangement of a cyclopropane analog of an allyl vinyl ether.\textsuperscript{66}
Scheme 1-34. [1,3] Rearrangement of cyclopropylmethyl vinyl ether 1-85.

1.2.10 Conclusions

A rapid diastereoselective three-step cascade carboalumination-Claisen rearrangement-carbonyl addition process leading to 1,6-diene functionalities containing allylic alcohols with up to three contiguous stereocenters has been developed. The stoichiometric quantities of water that are used as an additive increase the rate of the [3,3] sigmatropic rearrangement as well as the diastereoselectivity of the carbonyl addition. The resulting products are readily converted to substituted cyclopentenes. The cascade strategy has also been extended to a sequence involving a [1,3] sigmatropic shift.
2. AZA-COPE REARRANGEMENTS AND N-ACYL IMINIIUM ION CHEMISTRY

2.1 INTRODUCTION

2.1.1 Aza-Cope Rearrangements

The studies on Claisen rearrangements promoted by water-activated alanes described in the previous chapter prompted an investigation into whether the same strategy could be used to promote other sigmatropic rearrangements. The aza-Cope rearrangement is a closely related sigmatropic process which has been extensively utilized in synthesis. For example, Overman and co-workers have used the aza-Cope rearrangement to form intermediate ketone 2-4 during their synthesis of gelsemine (Scheme 2-1).67

![Scheme 2-1. Aza-Cope rearrangement to access 2-4 in Overman’s synthesis of gelsemine.](image_url)
The aza-Cope rearrangement is known to be catalyzed by acids and bases. Krantz and co-workers have used protic acids as promoters of sigmatropic processes which form allenes. As shown in Scheme 2-2, when aminal 2-5 was treated with formic acid, iminium ion formation followed by sigmatropic rearrangement furnished the allenyl lactam 2-8 after workup.


2.2 RESULTS AND DISCUSSION

2.2.1 Preliminary Investigations

Although there are examples to the contrary, a common problem with the aza-Cope rearrangement is prolonged reaction times. It was anticipated that water-activated alane could dramatically increase the rates of these reactions. Extending on some models by Krantz, an acidic cascade would generate an iminium ion from an aminal using water-activated alane (Scheme 2-3).
The iminium ion would then undergo an aza-Cope rearrangement and be trapped by addition of a methyl group from the alane, generating an allene.


Initial exploration of the water-activated, alane-promoted aza-Cope rearrangement reaction began with preparation of methoxylactam 2-11, accessible in three steps from succinimide. Mitsunobu alkylation with alcohol 2-9 proceeded in 42% yield to furnish imide 2-10 which was readily reduced with NaBH₄ (Scheme 2-4). The crude corresponding hydroxy lactam was subjected to acid-catalyzed methanol exchange to provide the model lactam 2-11 in 45% yield. Lactam 2-11 was added to a −78 °C solution of AlMe₃ (3 eq.) and H₂O (1.5 eq.). After 24 h at room temperature, only lactam 2-12 and starting material could be observed by ¹H NMR (Scheme 2-4). All of the exploratory reactions towards the aza-Cope rearrangement were studied by ¹H NMR analysis of the crude reaction mixtures.⁷⁰
Scheme 2-4. Preparation and reactions of model substrate 2-11.

The formation of 2-12 indicated that the desired ionization was occurring, however addition of a methyl group from AlMe₃ was quenching the iminium ion needed for sigmatropic rearrangement. The elimination of the methoxy group was extremely slow at room temperature, contrary to the reactivity observed with water-activated alane in other reaction manifolds. The studies of Hart and co-workers on iminium ion sigmatropic rearrangements suggested that substitution at the nitrogen bearing *exo*-carbon in pyrrolidones can promote the aza-Cope rearrangement.⁷¹ Thus, branched methoxy lactam 2-15 was explored. This compound was prepared in an analogous fashion to methoxylactam 2-11. Mitsunobu alkylation of succinimide with secondary alcohol 2-13 proceeded sluggishly to provide imide 2-14 in a 32% yield (Scheme 2-5). The imide was reduced with sodium borohydride and converted to its corresponding methoxy lactam 2-15 in 56% yield over two steps as a 1:1 mixture of diastereomers.
Scheme 2-5. Preparation of alkyl-branched substrate 2-15.

Addition of 2-15 to a mixture of AlMe₃ (3 eq.) and H₂O (1.5 eq.) provided, after 24 h at room temperature, only recovered starting material (Scheme 2-6). A water-accelerated zirconium-catalyzed carboalumination was attempted on methoxy lactam 2-15, however after 24 h at room temperature, only starting material was recovered. The lack of reactivity indicated that the succinimide scaffold was unsuitable for this chemistry.

Scheme 2-6. Attempted reactions of alkyl branched substrate 2-15.

Before the rate of the sigmatropic rearrangement vs. methyl addition could be addressed, iminium ion formation had to occur. Therefore, a more ideal substrate would include a more
activated leaving group. An analogous phthalimide derivative seemed promising since the site of elimination would now be activated by both the amide nitrogen and the aromatic ring.

The alkyl branched methoxy lactam 2-18 was selected as the next target substrate. Mitsunobu alkylation of phthalimide with secondary alcohol 2-13 provided the alkylated imide 2-16 in a low 20% yield (Scheme 2-7). Sodium borohydride reduction of imide 2-16 proceeded in moderate yield to provide hydroxy lactam 2-17 as a 1:1 mixture of diastereomers. Acid mediated methanol exchange with hydroxy lactam 2-17 furnished methoxylactam 2-18 in 76% yield.

\[
\begin{align*}
\text{NH} & \quad \text{O} \\
& \quad \text{O} \\
& \quad \text{PPh}_3, \text{DIAD} \\
& \quad \text{THF} \\
& \quad 20\% \\
\text{2-13} & \quad \text{HO} \\
\text{NaBH}_4, \text{MeOH} & \quad 68\% \\
\text{dr 1:1} \\
\text{MeOH, d,l-CSA} & \quad 76\% \\
\text{R} & \quad \text{OH (2-17)} \\
\text{R} & \quad \text{OMe (2-18)}
\end{align*}
\]

**Scheme 2-7.** Preparation of phthalimide substrate 2-18.

Treatment of methoxy lactam 2-18 with AlMe₃ (3 eq.) and H₂O (1.5 eq.) in CH₂Cl₂ returned only starting material. Increasing both the stoichiometry between AlMe₃ and H₂O and the overall equivalents did not impart any detectable conversion (Scheme 2-8).

\[
\begin{align*}
\text{OMe} & \quad \text{AlMe}_3 (3-10 \text{ eq}) \\
\text{H}_2\text{O (1.5-4 \text{ eq})} & \quad \text{CH}_2\text{Cl}_2 \\
\text{No Reaction}
\end{align*}
\]

**Scheme 2-8.** Attempted reactions of phthalimide substrate 2-18.
Again, a water-accelerated zirconium-catalyzed carboalumination was attempted on methoxylactam 2-18. Conditions which employed AlMe₃ (3 eq.), H₂O (1.5 eq.), and catalytic zirconocene dichloride led only to starting material (Scheme 2-9). This time, an increase in AlMe₃ and H₂O (6 and 2 eq., respectively) furnished a low conversion to olefin 2-19.

![Scheme 2-9. Attempted carboalumination of 2-18.](image)

In the absence of any evidence of iminium ion formation, a change in the leaving group was investigated. Hydroxy lactam 2-17, an intermediate in the preparation of methoxy lactam 2-18, was tested under the standard conditions (3 eq. AlMe₃ and 1 eq. H₂O). Unfortunately, only starting material was observed by NMR (Scheme 2-10).

![Scheme 2-10. Attempted aza-Cope rearrangement of hydroxy lactam 2-17.](image)

The acylation of hydroxy lactam 2-17 was completed to provide a substrate more prone to undergo elimination (Scheme 2-11).³²
Acetoxy lactam 2-20 was added to a solution of AlMe₃ (4 eq.) and H₂O (1 eq.) (Scheme 2-12). After 5 min at room temperature, NMR analysis indicated only alkylated lactam 2-21, derived from elimination and addition of a methyl group onto the iminium ion.

The rapid formation of 2-21 in high yield indicated that the desired type of reactivity was demonstrated by the substrate. Unfortunately, no sigmatropic rearrangement had occurred. The same reaction was then studied in the presence of zirconocene dichloride. Acetoxy lactam 2-20 was added to a solution of AlMe₃ (3 eq.), H₂O (1 eq.), and catalytic zirconocene dichloride (Scheme 2-13). Again, after 5 min at room temperature, only lactam 2-21 was formed.
These results indicated that an elimination process, followed by a sigmatropic rearrangement seemed unlikely to occur given the high nucleophilicity of the water-activated alane. The lifetime of the iminium ion would have to be sufficiently long to allow for the sigmatropic rearrangement to occur. Given the rapid addition to the iminium ion at low temperatures, this tandem reaction manifold was abandoned.

2.2.2 Carboalumination Studies on Lactam-based Substrates and Medium Ring Formation

The investigations of the water-activated alane-promoted aza-Cope rearrangement raised some intriguing questions about the reactivity of water-activated alane and the scope of water-accelerated carboalumination. Previous work has clearly demonstrated that these reagents were highly Lewis acidic, yet no elimination/iminium ion formation was observed with substrates known to undergo acid-mediated elimination. Further, the resistance to carboalumination that the lactam-based substrates demonstrated was quite unusual. This prompted an investigation into whether proximity to Lewis basic functionality affects carboalumination.

Towards this end, methoxy lactam 2-24, which contained a three-carbon spacer between the alkyne and amide functionality, was synthesized (Scheme 2-14). Mitsunobu alkylation of
phthalimide with alkynol 2-22 gave the alkylated imide 2-23 in 81% yield. Sodium borohydride reduction followed by acid-mediated methanol exchange furnished the methoxylactam 2-24 in 91% over two steps.

Scheme 2-14. Preparation of 2-24, containing a three carbon spacer between amide and alkyne.

The addition of 2-24 to a solution of AlMe₃ (3 eq.) and H₂O (1 eq.) returned only starting material after 24 h at room temperature. The addition of 2-24 to a solution of AlMe₃ (3 eq.) and H₂O (1 eq.) and catalytic zirconocene dichloride furnished a mixture of starting material (84%) and carboalumination product 2-25 (16%) by NMR analysis (Scheme 2-15).

Scheme 2-15. Reaction of 2-24 under carboalumination conditions.

Since carboalumination was observed at a slow rate, and no elimination occurred, the next step was the synthesis of tertiary alcohol 2-26 to investigate its effect on elimination. Thus, addition of MeMgBr to imide 2-23 proceeded smoothly to furnish 2-26 (Scheme 2-16).

When hydroxy lactam 2-26 was added to a solution of AlMe_3 (3 eq.), H_2O (1 eq.) and catalytic zirconocene dichloride, NMR analysis of the reaction mixture after 24 h indicated approximately 10% carboalumination (2-27) with only starting material remaining (Scheme 2-17). Thus, the tertiary hydroxy group was not any more reactive towards elimination than the secondary hydroxyl group.

Scheme 2-17. Attempted carboalumination of tertiary alcohol 2-27.

Subsequently, the alkyne was tethered further away from the central region of the substrate. A longer tether might also provide a novel method to form medium or large rings which contain olefins of defined geometry by a three step, one pot operation: carboalumination, elimination and vinyl alane addition (Scheme 2-18). Preliminary investigations into this method began by constructing a precursor which would be cyclized to form a 9-membered ring.
Scheme 2-18. Proposed cascade cyclization sequence.

Alcohol 2-29 was synthesized by the isomerization of the commercially available hept-3-yne-1-ol with the KAPA reagent\textsuperscript{73} in 85% yield (Scheme 2-19). Imide 2-30 was then constructed by Mitsunobu alkylation of phthalimide with alkynol 2-29, which proceeded in 82% yield. This material was submitted to standard carboalumination conditions, AlMe\textsubscript{3} (3 eq.), H\textsubscript{2}O (1 eq.) and zirconocene dichloride (10 mol%); however, only methyl addition to the imide was observed.
Imide 2-30 was reduced with sodium borohydride, followed by methanol exchange to give methoxylactam 2-33 in 40% overall yield (Scheme 2-20).

Treatment of a solution of AlMe3 (3 eq.), H2O (1 eq.) and zirconocene dichloride (10 mol%) with methoxylactam 2-33 returned only starting material with no evidence for elimination or carboalumination (Scheme 2-21).

It was anticipated that a phenoxy group would be a better leaving group. This lead to the synthesis of lactam 2-34. Treatment of 2-32 with SOCl₂ and catalytic DMF furnished the corresponding unstable chloride, which was immediately treated with phenol in the presence of triethylamine to yield phenoxy lactam 2-34 in 34% yield (Scheme 2-22).⁷⁴

Scheme 2-22. Preparation of phenoxy lactam 2-34.

Addition of 2-34 to a solution of AlMe₃ (3 eq.), H₂O (1 eq.) and zirconocene dichloride (10 mol%) furnished alkylated lactam 2-35 (10%), starting material (52%), and decomposition products (Scheme 2-23).
Scheme 2-23. Attempted cascade cyclization of 2-34.

These experiments demonstrated that the functionality present in these substrates was inhibiting the usually fast carboalumination. It was postulated that the amide group was inhibiting carbometallation, and a series of GC experiments were performed to test this hypothesis. An alkyne, which was known to undergo rapid water-accelerated carboaluminations, was submitted to the standard water-accelerated carboalumination conditions in the presence of lactam 2-33. A control experiment demonstrated that the carboalumination of heptyne with AlMe₃ (3 eq.), H₂O (1 eq.), and Cp₂ZrCl₂ (10 mol %) proceeded to completion in under 5 min at low temperatures (-78 °C to -25 °C) to furnish a 97:3 mixture of regioisomers by GC (Scheme 2-24).

Scheme 2-24. GC control experiment of the water-accelerated carboalumination of heptyne.

Conducting the identical experiment in the presence of 1 eq. of methoxylactam 2-33 dramatically inhibited carboalumination, with only 4.4% of heptyne undergoing conversion after 1 h (Scheme 2-25).
Scheme 2-25. GC analysis of the water-accelerated carboalumination of heptyne in the presence of 2-33.

One possibility for this inhibition is that highly Lewis basic functionality coordinates to AlMe₃ oligomers, thus inhibiting alkyne carboalumination. This could explain why one equivalent of lactam can inhibit 3 equivalents of AlMe₃.

Due to the lack of reactivity in the carboalumination approach, hydrozirconation was chosen as an alternative, known to be quite tolerant of diverse functionality.⁷⁵ Pivaloate lactam 2-36 was synthesized in an attempt to increase the rate of elimination. Unfortunately, when lactam 2-33 or 2-36 was treated with Cp₂ZrHCl, only the corresponding alkene was recovered (Scheme 2-26). Treatment of the intermediate alkenylzirconocene with AgClO₄ or trimethylaluminum also provided no desired cyclization products. Highly concentrated reaction mixtures or prolonged heating resulted only in slow methyl group addition. Possibly, the ring strain present in the desired products is too high to allow the reaction to proceed under these conditions.
Scheme 2-26. Attempted hydrozirconation and medium ring formation.

2.2.3 Intermolecular Alkenylation of N-Acyl Iminium Ions

Since the intramolecular cyclizations proved elusive, we turned our attention toward an alternative construction of these systems starting with an intermolecular addition process. Intermolecular alkenylation of N-acyliminium ions can often require harsh reaction conditions such as extended periods of heating, or unusual anomeric leaving groups (Scheme 2-27).
Scheme 2-27. Selected literature examples of intermolecular alkenylation.

An exception to this trend is the mild intermolecular addition of alkenyl boronates reported by Batey. For example, when aminal 2-42 was treated with alkenyl boronate 2-43 and BF₃•Et₂O, addition product 2-44 was isolated in 99% yield as a > 98:2 ratio of diastereomers (Scheme 2-28).

Scheme 2-28. Alkenylation with alkenyl boronates.

For model purposes, lactams 2-46 to 2-48 were chosen, bearing methoxy, acetoxy and pivaloyl leaving groups, respectively. Each of these substrates was made using standard procedures (Scheme 2-29).
Scheme 2-29. Preparation of model lactams.

The hydrozirconation of terminal alkynes was first explored as a method to generate alkenyl nucleophiles (Table 2-1). Hydrozirconation of 1-hexyne, followed by treatment with silver perchlorate\(^{79}\) and lactam 2-46 yielded only a trace of addition product after 24 h at rt (entry 1, Table 2-1). Transmetallation to dimethylzinc also proved unsuccessful (entry 2, Table 2-1). Gratifyingly, hydrozirconation-transmetallation to trimethylaluminum\(^{80}\) generated an alkenylalane that reacted with lactam 2-46 in a moderate 43\% yield (entry 3, Table 2-1). The leaving group ability was further increased by using acetate 2-47; however, product 2-49 was only formed in 30\% yield while the remaining starting material was consumed (entry 4, Table 2-1). Attempts to perform this reaction in THF or toluene led to recovered starting material. Pivaloate 2-48, when treated with the \textit{in situ} generated alane, provided hexenyl isoindolinone 2-49 in 81\% yield without any observed isomerization of the alkene moiety (entry 5, Table 2-1). Attempts to achieve this transformation under cationic conditions with silver perchlorate led to complex mixtures, seemingly arising from
alkene isomerization (entry 6, Table 2-1). The mild conditions under which the addition proceeds and the ability to utilize readily available alkynes and pivaloate iminium ion precursors encouraged further exploration.

**Table 2-1.** Optimization of the intermolecular alkenylation of acyl-iminium ions to generate isoindolinones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Yield (2-49, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-46</td>
<td>i</td>
<td>trace&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>2-46</td>
<td>ii</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>2-46</td>
<td>iii</td>
<td>43&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>2-47</td>
<td>iii</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>2-48</td>
<td>iii</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>2-48</td>
<td>i</td>
<td>ND&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Reaction Conditions: (i) AgClO₄  (ii)Me₂Zn (iii) Me₃Al.  <sup>a</sup> Product was formed as a mixture of alkene isomers.  <sup>b</sup> Starting material observed after 12 h.  ND = not determined.

Among the numerous methods known for the synthesis of substituted isoindolinones, only a few examples of Heck-type coupling install an alkenyl moiety at the 3-position. The synthesis of
isoindolinones presents significant opportunities for preparing biologically active molecules as well. Isoindolinones demonstrate a remarkably wide array of biological activities, including anti-inflammatory, antihypertensive, antipsychotic, vasodilatory, and antileukemic effects.

The modularity of the current approach warranted further investigation into the substrate scope of this process. As shown in Table 2-2, silyl ether, carbamate, and sulfonamide functionalities are well tolerated, generating functionalized isoindolinones in a high yielding, one-pot procedure.

Table 2-2. Addition of various alkenyl nucleophiles to generate isoindolinones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R (alkyne)</th>
<th>Product [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₄H₉</td>
<td>2-49 [81]</td>
</tr>
<tr>
<td>2</td>
<td>c-C₆H₁₁</td>
<td>2-50 [79]</td>
</tr>
<tr>
<td>3</td>
<td>CH₂CH₂OTBDPS</td>
<td>2-51 [71]</td>
</tr>
<tr>
<td>4</td>
<td>CH₂CH₂N(CO₂Me)Ts</td>
<td>2-52 [62]</td>
</tr>
</tbody>
</table>

To further probe the scope of this reaction, succinimide-derived pivaloate 2-54 was synthesized from dimethyl succinic anhydride (2-53) and subjected it to the optimized conditions (Scheme 2-30). Addition product 2-55 was isolated in 83% yield which bodes well for the extension of the cyclic iminium ion alkenylation methodology toward a broad class of heterocyclic electrophiles.
Scheme 2-30. Preparation of 2-55.

The use of trisubstituted alkenes was also investigated in this transformation. Although the lactam functionality had prevented an intramolecular addition, pre-forming the alkenylalane under water-accelerated conditions, followed by addition of 2-48, provided isoindolinones 2-56 and 2-57 in 77% yield after only 15 minutes (Table 2-3).
Table 2-3. Addition of trisubstituted alkenyl alanes to provide isoindolinones 2-56 and 2-57.

\[
\begin{array}{ccc}
\text{Entry} & \text{R} & \text{Product [%]} \\
1 & \text{C}_4\text{H}_9 & 2-56 [77] \\
2 & \text{Ph} & 2-57 [77]^a \\
\end{array}
\]

\(^a\) Product contains ~5% of a carbometallation regioisomer.

Since this strategy provided a rapid access toward alkenyl-functionalized phthalimides, the initial goal of generating medium rings was revisited. As a model system, alkyne 2-59 was prepared by alkylation of alkynol 2-22, and allyl-pivaloate 2-61 was synthesized using the standard method (Scheme 2-31).

\[
\text{Ph} = \text{Br} + \text{Me}_3\text{Al}, \text{Cp}_2\text{ZrCl}_2, \text{H}_2\text{O} \rightarrow 2-48
\]

Scheme 2-31. Preparation of alkyne 2-59 and pivaloate 2-61.
Subsequently, 2-60 and 2-61 were subjected to the hydrozirconation-transmetallation conditions to generate 2-62 in 55% yield accompanied by considerable amounts of methyl addition side product (Scheme 2-32). It should be noted that carboalumination of 2-59 failed and the rate of addition for the alkenylalane generated via the transmetallation reaction was retarded due to the presence of the ether functionality. With 2-62 in hand, conditions were screened to form the desired 12-membered macrocycle. Although ring closing metathesis methodology has been found to perform well for the synthesis of a variety of macrocycles, a rapid formation of the undesired 5-membered ring 2-63 was observed. Increasing dilution, change of metathesis catalyst, addition of Ti(OiPr)$_4$, or varying solvents did not influence the reaction pathway.

Scheme 2-32. Preparation of 2-62 and attempted macrocyclization via alkene metathesis.
Due to the ease of formation of pyrrolizidine 2-63, a more generalized synthesis of this compound was explored. Addition of hexenylalane to 2-61 furnished diene 2-64, which smoothly underwent the metathesis in 75% yield to furnish pyrrolizidine 2-63 (Scheme 2-33).

Scheme 2-33. Preparation of 2-63.

To access the desired medium ring systems through this approach, imide 2-66 was prepared via Mitsunobu alkylation (Scheme 2-34). Reduction of 2-66 and acylation proceeded in 76% over the two steps to provide 2-67.

Scheme 2-34. Preparation of pivaloate 2-67.
The synthesis of fused azepines was achieved from indolinone 2-68, prepared from 2-67 and 1-hexyne in 72% yield (Scheme 2-35). Ring closing metathesis of 2-68 proved to be problematic in CH₂Cl₂ with several ruthenium catalysts, yielding only starting material or decomposition products. Addition of Ti(OPr)₄ in toluene at room temperature resolved these issues and yielded 67% of 2-69. Possible deactivation of the metathesis intermediate by the neighboring amide carbonyl could explain the difficulty in this transformation. While not fully optimized, these reactions provide proof of concept for the conversion of our phthalimide substrates to structurally diverse tricyclic products.

Scheme 2-35. Synthesis of azepine 2-69 via ring-closing metathesis.

2.2.4 Conclusions

In situ generated alkenylalanes constitute versatile nucleophiles for additions to N-acyliminium ions. While direct intramolecular cyclization strategies suffer from inhibition of the carboalumination reaction by Lewis basic functional groups, preforming alkenylalanes via hydrozirconation-transmetallation or carboalumination and subsequent addition to the lactam acetal substrates yields functionalized isoindolinones. This method applies easily prepared or
commercially available starting materials that provide opportunities for diversification at numerous points and yields synthetically useful heterocyclic products in a one-pot transformation. Further elaboration of the alkenyl heterocycles through the use of ring closing metathesis leads to tricyclic products that are common motifs in natural products and drug-like molecules.
3. SPIROKETALS VIA OXIDATIVE REARRANGEMENT OF ENOL ETHERS

3.1 INTRODUCTION

3.1.1 Barton’s Proposal for the Biosynthesis of Acutumine

Acutumine (3-1, Scheme 3-1) is a chlorinated tetracyclic alkaloid whose isolation was first reported in 1929.\(^92\) Although the structure was initially misassigned, a series of chemical and X-ray structures established the correct structure of acutumine in 1967.\(^93\)

![Scheme 3-1. Barton's proposed biosynthetic precursor of acutumine (3-1).](image)

Shortly thereafter, Sir Derek Barton proposed a biosynthesis for the spiro-fused vinylogous ester moiety of acutumine.\(^94\) In this proposal, Barton suggested spirodienone 3-2 as a possible biosynthetic branching point (Scheme 3-1). As shown in Scheme 3-2, Barton proposed that double epoxidation of 3-3 followed by a hydrolytic Favorskii-type rearrangement would give acid 3-5.
Decarboxylation and epoxide opening affords allylic diol 3-6, which is only a single oxidation level below vinylogous ester 3-7.

![Chemical structures and reaction arrows]

Scheme 3-2. Proposed mechanistic conversion of 3-3 to 3-7.

Barton’s proposal contained several interesting components, including the Favorskii-type ring contraction. At the time of publication, it was the first proposed Favorskii rearrangement in a biosynthesis. Since Barton’s proposal, the Favorskii rearrangement has rarely been proposed in biosynthetic sequences, and has therefore been controversial. In 1975, the Favorskii rearrangement was proposed by Simpson during the biosynthesis of pyrone containing polyketides. For example, a polyketide such as 3-8 with a non-specified leaving group (LG) was proposed to undergo a hydrolytic Favorskii-type rearrangement to furnish the branched polyketide 3-9 (Scheme 3-3).95
Scheme 3-3. Proposed Favorskii-type rearrangement to generate branched polyketides.

A similar rearrangement was postulated by Kakinuma to account for the unusual 17-membered carbocyclic ring system in the lankacidin antibiotics. Macrocycle 3-10 was proposed to undergo a non-specific oxidation to the cyclopropanone intermediate 3-11, which would be opened with hydroxide to effect a one-carbon ring contraction and furnish acid 3-12 (Scheme 3-4).96

Scheme 3-4. Proposed Favorskii-type rearrangement to effect ring contraction in a polyketide.

The Favorskii-type rearrangement has recently been proposed by Wright to account for carbon deletions in the biosynthesis of the polyketide shellfish toxins DTX-1 and DTX-2. Wright proposed that an α-diketone, such as 3-13, would undergo intramolecular closure to furnish cyclopropanone 3-14 (Scheme 3-5).97 Attack by a peroxide and collapse of the peroxy-ketal 3-15 generates ketone 3-16 after the extrusion of CO₂.
Scheme 3-5. Wright’s proposed Favorskii-type rearrangement to effect carbon deletion in polyketide natural products.

Barton’s proposal represented a key unsolved problem (or unconfirmed proposal) in natural product chemistry. Combined with our interest in densely oxygenated natural products, we began investigations into this hypothesis. An examination of the literature reveals a previous attempt to model the Barton proposal in 1984. The Matoba group treated enone 3-17 with m-CPBA in refluxing trichloroethane and assigned the product as 3-18 (Scheme 3-6). Based on the results presented herein, it appears that compound 3-18 was incorrectly assigned.

Scheme 3-6. Attempted modeling of Barton’s proposal by Matoba.
3.2 RESULTS AND DISCUSSION

Due to the ready access to dienones of type 3-3 in Barton’s proposed biosynthesis, this hypothetical ring contraction provides an attractive entry to the acutumine skeleton. Our first approach to model this proposal began with dienone 3-19 (Scheme 3-7). Epoxidation of 3-19 provided epoxyketone 3-20, a theoretical intermediate in Barton’s proposed biosynthesis. When 3-20 was treated with 3 equivalents of m-CPBA buffered by Na$_2$HPO$_4$, we expected that the intermediate bis-epoxide would undergo Barton’s proposed cascade, however we isolated only epoxy lactone 3-21 in 80% yield as a single diastereomer, which was characterized by X-ray crystallography. It was determined that the crude diastereoselectivity of the reaction in the absence of a basic workup was only 2:1, although this mixture equilibrated to a single diastereomer after washing with aqueous NaHCO$_3$.

![Scheme 3-7: Preparation of model epoxy ketone 3-20 and attempted rearrangement.](image)

In order to prepare another substrate for experimentation, epoxy alcohol 3-22 was prepared from intermediate 3-20 by the addition of MeLi, which proceeded in 91% yield (Scheme 3-8). With a small collection of substrates in hand, the scope of the oxidative rearrangement was probed.
Scheme 3-8. Preparation of ketone 3-22.

Enone 3-17 lacking the epoxide underwent rearrangement to lactone 3-23 in 75% yield, while five-membered enone 3-24 was converted to lactone 3-25 in only 35% yield, although the reaction does generate a tetrasubstituted carbon (Scheme 3-9). To ascertain whether the carbonyl functionality was needed to facilitate rearrangement, 3-22 was submitted to the oxidative rearrangement and was converted to hemiacetal 3-26 in only 21% yield as a single diastereomer, which was characterized by X-ray crystallography. The above preliminary results were obtained by Corey R. J. Stephenson while working as a graduate student in the Wipf group.
A proposal for the oxidative rearrangement of 3-17 is outlined in Scheme 3-10. The epoxy ether intermediate 3-27 opens to the alkoxy carbocation 3-28 in the presence of a proton donor. This species is then intercepted by another equivalent of peracid to give peroxy ketal 3-29. A methyl ether assisted acyl shift generates the seven-membered lactone 3-30 which can undergo a ring contraction to generate the product lactone ester 3-23, which is epimerizable at the α-position to the ester moiety, resulting in the thermodynamically more stable equatorial ester after basic workup and isolation. This sequence constitutes a net addition of two oxygen atoms concomitant with a skeletal rearrangement.101
Due to their occurrence in many biologically active molecules, the potential formation of acetals and ketals such as 3-18 appeared to offer convenient access to these motifs. There are several known methods for the formation of spiroketals, many based on the cyclization of hydroxy ketones. For example, in Marshall’s synthesis of a fragment of tautomycin, ketone 3-31 was converted through in-situ deprotection of the silyl ethers and subsequent intramolecular ketalization to 3-32 in 92% yield (Scheme 3-11).

A similar method was used by Kiyota’s group during their approach to spirofungins A and B. When bisketal 3-33 was subjected to acidic conditions, the deprotected secondary hydroxy
group underwent transketalization in 82% overall yield to furnish the spiroketal 3-34 as the major product (Scheme 3-12).

![Scheme 3-12](image)

**Scheme 3-12.** Acid-promoted transketalization to form 3-34 by Kiyota.

Forsyth and co-workers took a different approach during their approach to a family of fly pheromones. For example, ketone 3-35 was treated with CSA in methanol to induce deprotection of the silyl ethers (Scheme 3-13). A solvent switch to benzene facilitated double Michael addition of the hydroxy groups to provide the spiroketal 3-36 in 70% yield.

![Scheme 3-13](image)

**Scheme 3-13.** Tandem Michael addition to form ketal 3-36 by Forsyth.

Although many ketalization methods proceed under dehydrating or oxidative conditions, Jorgenson and co-workers have reported a hetero Diels-Alder pathway mediated by copper catalysis. Upon treatment with chiral copper catalyst 3-39, ketoester 3-37 and vinyl ether 3-38 underwent cycloaddition in 84% yield to provide ester 3-40 as the major product in 74% ee (Scheme 3-14). The epimer at the ketal center constituted the remaining material.
Scheme 3-14. Copper-catalyzed enantioselective cycloaddition to form ketal 3-40 by Jorgenson.

Although the oxidative rearrangement of 3-22 proceeded in low yield (as shown in Scheme 3-9), it was hypothesized that masking the free alcohol as a cyclic ether would improve the efficiency of the reaction by avoiding the formation of sensitive hemiacetals. Toward this end, cyclopentanone was treated with 5-lithio-2,3-dihydrofuran according to a protocol by Paquette,\textsuperscript{108} which furnished an intermediate tertiary allylic alcohol which could be rearranged under acidic catalysis to the spirocyclic ketone 3-41 in 65\% yield overall (Scheme 3-15). At this stage, all that was required to set up the oxidative rearrangement was O-alkylation of the corresponding enolate of 3-41. Following treatment with KHMDS, addition of DMF and dimethylsulfate furnished the methyl enol ether 3-42 in 83\% yield. When 3-42 was submitted to the oxidative rearrangement, the volatile spiroketal 3-43 was obtained as the sole product in 52\% yield.
Scheme 3-15. Preparation of spiroether 3-42 and rearrangement to spiroketal 3-43.

Seeking to expand this spiroketal methodology, methyl enol ethers 3-44, 3-46 and androsterone-based 3-48 were prepared in an identical fashion to 3-42. When 3-44 was submitted to the rearrangement, volatile spiroketal 3-45 was isolated in 48% yield as a modest 2:1 mixture of diastereomers (Scheme 3-16). Methyl enol ether 3-46 smoothly underwent rearrangement in 53% yield, and 3-47 was isolated as a single diastereomer. Additionally, 3-48 was converted to pentacyclic spiroketal 3-49 in 76% yield as a single diastereomer. The configurations of 3-45, 3-47, and 3-49 were assigned in analogy to 3-21 and 3-26, which were characterized by X-ray analysis.
Scheme 3-16. Oxidative rearrangement of various enol ethers to spiroketsals.

In conclusion, an efficient oxidative rearrangement of alkyl enol ethers to lactone and spiroketal esters has been demonstrated. This method allows rapid access to these common structural subunits under relatively mild conditions. Although this investigation was inspired by Barton’s proposal for the biosynthesis of acutumine, no experimental support for the dienone diepoxide rearrangement was achieved. It appears that α-epoxy ethers of type 3-27 prefer alternative rearrangements to a migratory ring contraction. The recent isolation of acutudaurin (3-54, Scheme 3-17),\textsuperscript{110} a possible precursor of acutumine-type natural products, lends support to a modified biosynthetic pathway. As shown in scheme 3-17, the tricarbonyl tyrosine dimer 3-50 can be envisioned as a direct precursor of acutumine (3-1) after oxidation and benzilic acid rearrangement (3-51 to 3-52), followed by decarboxylation to generate the cyclopentanone subunit
3-53. This pathway is supported by experimental observations in the literature,\textsuperscript{111} and the oxygenation pattern on spirocycle 3-54 is in good agreement with the structure of acutudaurin.

\[
\begin{align*}
\text{Acutumine (3-1)} & \xrightarrow{\text{Modified Biosynthetic Pathway}} \text{3-50} \\
\text{3-51} & \xrightarrow{\text{Oxidation & Rearrangement}} \text{3-52} \xrightarrow{-\text{CO}_2} \text{3-53}
\end{align*}
\]

\textbf{Scheme 3-17.} Revised biosynthetic proposal for acutumine (3-1).
4. TOTAL SYNTHESIS OF DIAZONAMIDE A

4.1 INTRODUCTION

4.1.1 Isolation and Structure

The diazonamides (4-1 and 4-2, Scheme 4-1) were isolated in 1991 from *Diazona angulata*, a rare marine ascidian found in the coastal caves of Siquijor island, Philippines. The structure of diazonamide A was assigned as 4-3 by \(^1\)H NMR analysis and spectral similarity to diazonamide B (4-2). The first and only synthesis of 4-3 was reported 10 years later by Harran and revealed a structural misassignment. Harran then proposed 4-1 as the correct structure of diazonamide A based on the reported X-ray data and \(^1\)H NMR studies of related compounds. Nearly two years later, Nicolaou reported the first total synthesis of diazonamide A, and confirmed 4-1 as the correct structure.
Scheme 4-1. Originally proposed and revised structures of diazonamide A and B.

The diazonamides possess unique structures which include ten rings spanning two macrocyclic domains (Scheme 4-2). These domains are anchored by the C10 quaternary center, which lies deep within the core of the molecule. Three biaryl bonds link together the lower polyaromatic domain that exists as a single atropisomer. Additionally, the diazonamides were the first natural products isolated to contain the bis-indole, bis-oxazole motif.
Scheme 4-2. Ring lettering and perspective view of diazonamide A.

As part of his structural reassignment, Harran suggested a biosynthetic pathway for 4-1. The complex structure of diazonamide A was proposed to be derived from five simple components, along with multiple oxidation state changes (Scheme 4-3).

Scheme 4-3. Biosynthetic origin of diazonamide A as proposed by Harran.
4.1.2 Biological Activity

Diazonamide A possesses not only a tremendously complex structure, but is also significantly cytotoxic. Initial assays revealed IC$_{50}$ values against HCT-116 human colon carcinoma and B-16 murine melanoma cell lines of less than 15 ng/mL, with diazonamide B less potent.$^{113}$ Assays at the National Cancer Institute indicated that diazonamide A had a mean GI$_{50}$ of 4.9 nM against a standardized panel of human cancer cell lines.$^{114}$ Cruz-Montseratte reported detailed studies which indicated that 4-1 arrests cells at the G2/M phase of the cell cycle through inhibition of tubulin assembly.$^{116}$ The Nicolaou group also tested diazonamide A (and its C37 epimer) against six human cancer cell lines, four of which were standard: 1A9 human ovarian carcinoma, PC-3 human prostate carcinoma, MCF-7 human breast carcinoma, and A549 human lung carcinoma.$^{117}$ Two were drug-resistant cell lines from 1A9 parental cells, one with a multidrug resistant phenotype due to high expression of the drug-efflux pump P-glycoprotein (PGP) and the other Taxol-resistant because of an acquired $\beta$-tublin mutation. Diazonamide A demonstrated IC$_{50}$ values of 2-5 nM against every cell line except the multidrug resistant cell line, suggesting that diazonamide is a substrate for PGP. The C37 epimer of diazonamide was 3- to 5-times less potent. Interestingly, diazonamide A and its C37 epimer were active against the taxol-resistant cell line, suggesting that diazonamide had a binding site on tublin distinct from taxol. Recently, Harran reported that diazonamide A blocks mitotic spindle assembly through binding to ornithine $\delta$-amino transferase (OAT).$^{118}$ To confirm the mechanism, it was demonstrated using RNAi that OAT knockdown “blocks cell division and causes cell death, the effects largely phenocopying diazonamide A treatment”. This study revealed a new role for OAT in mitosis and makes it a target for drug development.
Harran has also reported that diazonamide analog 4-7, which lacks chlorination, is as potent as diazonamide A against multiple cancer types, yet displays no toxicity (Scheme 4-4). Analog 4-7 demonstrated anti-cancer activity in animals with xenografted tumors that was comparable to taxanes or vinca alkaloids. Mice treated with 4-7 demonstrated no weight loss, no change in appearance, and no evidence of white-blood cell loss. This exciting result suggests that 4-7 could have potential in a clinical setting.

Scheme 4-4. Diazonamide analog developed by Harran.

4.1.3 Previous Total Syntheses

Diazonamide attracted the attention of the synthesis community immediately, and several groups have reported progress toward its total synthesis. Despite this intense effort, only two groups have reported successful total syntheses, and one has reported a formal synthesis. Only the work resulting in total (or formal) syntheses will be addressed here.

The Harran group approached the originally proposed structure of diazonamide by utilizing a Heck macrocyclization to construct triarylalkene 4-9 from 4-8 (Scheme 4-5). This brought together
the components of diazonamide’s macrolactam ring, but still required some skeletal rearrangement to install the C10 quaternary center.

\[
\begin{align*}
\text{4-8} & \quad \text{4-9} \\
\text{Pd}_2(\text{dba})_3 (3 \text{ mol }%) & \quad \text{Ag}_3\text{PO}_4 \\
\text{P(}t\text{-Bu)}_2 & \quad \text{THF, 75 }^\circ\text{C} \\
\text{(6 mol %)} & \quad \text{82\% (brsm)} 
\end{align*}
\]

**Scheme 4-5.** Macrocyclic Heck cyclization utilized during Harran’s synthesis of the originally proposed structure of diazonamide A.

Following protection of the free phenol, Harran dihydroxylated alkene 4-10 to provide diol 4-12 in excellent yield and diastereoselectivity (Scheme 4-6).\textsuperscript{114} Treatment of diol 4-12 with \(p\)-TsOH in toluene initiated a ring-contracting pinacol rearrangement to furnish aldehyde 4-13, containing the proper architecture required for the macrolactam region of diazonamide.
Scheme 4-6. Key dihydroxylation and pinacol rearrangement in Harran's total synthesis of the originally proposed structure of diazonamide A.

After converting aldehyde 4-13 to indole-containing 4-14, Harran utilized a photochemical Witkop-type cyclization to forge the C16-C18 bond in ~ 35% yield (Scheme 4-7). This transformation is proposed to proceed through intermediates 4-16 and 4-17, with a final aromatization to furnish the product. This operation completed the polyaromatic lower domain of diazonamide and provided a unique approach to the biaryl linkage between the D and E rings of diazonamide.
Scheme 4-7. Witkop-type cyclization developed by Harran to form C16-C18 bond.

Harran converted 4-15 to the proposed structure for diazonamide A through 6 steps (Scheme 4-8). Upon completion, 4-3 neither matched the reported data for diazonamide nor was stable for significant periods of time. Upon comparison of the reported spectral data for diazonamide as well as the X-ray data, Harran proposed 4-1 (See Scheme 4-1) as the correct structure of diazonamide A.\textsuperscript{115} Once again, a total synthesis of 4-1 would be required to confirm this assignment.
Scheme 4-8. Final conversion of Witkop product 4-15 to the originally proposed structure of diazonamide A.

The Nicolaou group had been working towards diazonamide when the structure revision was published by Harran. A revised strategy toward the complex elements of the diazonamide skeleton began by adding oxazole dianion 4-20 to isatin 4-19, which proceeded in 73% yield and provided a 1:1 mixture of diastereomers (Scheme 4-9). 116

Scheme 4-9. Formation of key tertiary alcohol 4-21 in Nicolaou’s first total synthesis of diazonamide A.
Upon treatment with p-TsOH, a mixture of tertiary alcohol 4-21 and N-Cbz-Tyr-OMe furnished triaryl lactam 4-22 in 47% yield and as a 1:1 mixture of diastereomers (Scheme 4-10). This transformation installed the critical C10 quaternary center, although only half of the material had the configuration required for the natural product.

![Diagram of chemical structures](image)

Scheme 4-10. Formation of C10 center during Nicolaou's first total synthesis of diazomamide A.

Having installed diazomamide’s C10 center, Nicolaou then turned to closing the macrolactam region of the molecule. With amino acid 4-23 in hand, macrocyclization proceeded in 36% yield, since only the correct diastereomer required for diazomamide cyclized (Scheme 4-11). Material containing the incorrect configuration was reported to dimerize or oligomerize.
Scheme 4-11. Macrolactamization in Nicolaou's first total synthesis of diazonamide A.

With one of the major domains in place, Nicolaou turned to Harran’s method to form the lower, polyaromatic domain. Compound 4-25, when irradiated at 200 nm, underwent the Witkop-type cyclization to furnish 4-26 in 33% yield (Scheme 4-12). The low yield reflects the highly strained nature of the large rings being formed. After 5 more straightforward steps, the Nicolaou group completed the first total synthesis of diazonamide A, confirming Harran’s revised structure (4-1).
Scheme 4-12. Nicolaou's use of Witkop-type cyclization to form lower macrocycle and completion of diazonamide A.

Shortly after the Nicolaou group confirmed the assignment of diazonamide A, they reported another approach which also resulted in a successful total synthesis. The key C10 quaternary center was formed through a two-step hydroxymethylation of oxindole 4-27 (Scheme 4-13). As in their first synthesis, the Nicolaou group chose to form the C10 center in a non-selective fashion.
Scheme 4-13. Formation of the C10 quaternary center in Nicolaou's second total synthesis of diazonamide A.

Oxindole 4-28 was readily converted to the oxime 4-29 through a biaryl coupling at the C16-C18 bond, which set the stage for a hetero-pinacol macrocyclization. Following treatment with SmI₂, the macrocyclization proceeds smoothly to yield amino alcohol 4-30 in excellent yield (Scheme 4-14). This approach allows for a convergent approach to the polyaromatic core of diazonamide A. The Nicolaou group carried out the remaining macrolactamazation and structural elaboration to complete a second total synthesis of diazonamide A.
**Scheme 4-14.** SmI$_2$-mediated heteropinacol macrocyclization in Nicolaou's second total synthesis of diazonamide A.

The Harran group continued their investigations into the revised structure of diazonamide and published an extremely efficient approach in 2003.\textsuperscript{122} Readily prepared 4-31, when treated with PhI(OAc)$_2$, underwent oxidative cyclization to form 4-32 in 20-25% yield as a single diastereomer (Scheme 4-15). Despite the low yield, this represents the most effective approach to diazonamide reported to date. Harran carried 4-32 on to complete his total synthesis of diazonamide A, utilizing the Witkop-type macrocyclization to append the remainder of the molecule.

**Scheme 4-15.** Harran's key oxidative cyclization in his total synthesis of diazonamide A.
In 2007, Magnus reported a formal synthesis of diazonamide A, intercepting an intermediate in Nicolaou’s first synthesis. Magnus’ approach relied on a thermal O- to C-aryl migration. Specifically, when 4-33 was refluxed in CHCl₃, migration of the aryl ring to form 4-34 in quantitative yield as an 84:16 ratio of diastereomers (only major is drawn, Scheme 4-16). A formal synthesis required 3 synthetic operations to reach macrolactam 4-24 (see Scheme 4-11).

**Scheme 4-16.** Magnus’ O- to C-aryl migration to form the C10 quaternary center in his formal synthesis of diazonamide A.

### 4.2 RESULTS AND DISCUSSION

#### 4.2.1 Previous Work Towards Diazonamide A in the Wipf group

Diazonamide presented a difficult problem, and therefore an exciting opportunity to construct a complex array of heterocycles within a dense, rigid framework. Additionally, its potent biological activity encouraged work in the Wipf group directed at the originally proposed (incorrect) structure.
An approach based upon an enantioselective Heck cyclization was reported in 1998 and is shown in Scheme 4-17. Ester 4-35 underwent Heck cyclization to furnish model lactone 4-36 in 47% yield, but only 19% ee. This transformation established a model for generating the C10 quaternary center, although the structure revision would render this approach unusable.

Scheme 4-17. Enantioselective Heck cyclization reported by Wipf as an approach to the originally proposed structure of diazamamide A.

Additional work in the Wipf group developed a method for installing the central oxazole of the diazamamide skeleton utilizing a Chan-type rearrangement. The key to this approach was the rapid preparation of the α-amino ketone motif required for the central oxazole. Towards this end, Boc-imide 4-37 was treated with LDA to furnish the intermediate anion 4-38 (Scheme 4-18). Immediate acyl migration resulted in aminoketone 4-39 in 78% yield. Subsequent deprotection, coupling to Cbz-protected valine and cyclodehydration provided the bis-oxazole 4-40 in 41% over the three steps, and provided a model for constructing this region of the molecule once the C10 quaternary center had been formed.
Scheme 4-18. Wipf's Chan rearrangement approach to the indole bis-oxazole motif in diazonamide A.

4.2.2 Retrosynthetic Analysis

The planned approach to diazonamide A centered on forming the C10 center using an enantioselective Heck cyclization. In the retrosynthetic sense, diazonamide can be stripped of its adorning acyl- and chlorine substituents, and opened at the peptide bond to furnish 4-41 (Scheme 4-19). Cleavage through the indole-indole biaryl axis and central oxazole excises valine and reveals Chan-rearrangement product 4-42. Rupture of the aminal linkage and hydrolytic cleavage of the
peptide bond reveals the key C10 anchored acid 4-44 and known indole-oxazole fragment 4-45. Acid 4-44 is accessible from Heck cyclization product 4-46 through oxidative cleavage of an alkene. The required Heck precursor 4-47 is easily deconstructed as the condensation product of an ester (4-48) and a functionalized aniline 4-49.
Scheme 4-19. Retrosynthetic analysis for diazonamide A.
4.2.3 Preparation of Aniline 4-51

An ideal aniline fragment would allow for selective insertion of palladium during the Heck cyclization, and allow a handle for the palladium-mediated formation of the indole-indole biaryl linkage later in the synthesis (Scheme 4-20). Aniline 4-51 was chosen as a suitable target since the halogen substituents would be relatively stable during synthetic operations (as opposed to a triflate), yet provide sufficient reactivity in a complex system.

![Scheme 4-20](image)

**Scheme 4-20.** Requirement for aniline fragment to be selectively activated by Pd(0).

Perusal of the literature revealed a single method for constructing mixed 2,6-dihaloanilines, consisting of 5 to 7 steps and requiring tedious separation throughout the sequence. Furthermore, compound 4-51 itself had never been reported, indicating potential difficulty in its preparation. Therefore, a new preparation was developed utilizing an N- to C-silyl transfer reaction. Commercially available 2,6-dibromoaniline (4-52) was doubly silylated to provided 4-53 in 99% yield (Scheme 4-21). Treatment with 2 eq of s-BuLi generated intermediate lithiate 4-54 which induced migration of one silyl group from nitrogen, which furnished the key differentially substituted aniline 4-55 upon acidic workup. This crude material rapidly underwent iododesilylation with ICl to provide the desired aniline 4-51 in 90% yield over the two steps. This approach has

95
proven to be very scalable, and a simple recrystallization of 4-51 makes the final purification simple and effective.

\[ \text{BrNH}_2 \text{Br} \overset{\text{LDA, TMSCI}}{\text{THF, -78 °C}} \text{100%} \]
\[ \rightarrow \text{Me}_3\text{Si}N\text{SiMe}_3 \]
\[ \rightarrow \text{BrNH}_2 \text{TMS} \]
\[ \rightarrow \text{ICl} \text{CH}_2\text{Cl}_2, -78 °C \]
\[ \rightarrow \text{90% over two steps} \]

**Scheme 4-21.** Preparation of aniline 4-51 utilizing an N- to C-silane transfer.

### 4.2.4 Incorporation of Tyrosine Backbone and Installation of C10 Quaternary Center

As shown in Scheme 4-22, ester 4-48 was required to complete the synthesis of the key Heck cyclization precursor. An sp\(^2\)-sp\(^2\) coupling was initially employed to access to this fragment.

**Scheme 4-22.** Retrosynthetic analysis for key intermediate 4-47.
Toward this end, iodoenoate 4-58 was prepared from ethyl ester 4-56 beginning with a palladium-catalyzed hydrostannylation to furnish crude stannane 4-57 followed by iododestannylation in 68% yield (Scheme 4-23).128

![Scheme 4-23. Hydrostannylation of 4-56 and iodination of stannane 4-57.](image)

Preparation of the coupling partner for 4-58 began with Boc protection of L-Tyr-OMe-HCl to furnish 4-60 (Scheme 4-24). Reduction of crude 4-60 with LiBH4 followed by protection of the amino alcohol as the isopropylidene aminal generated 4-61 in 70% over the three steps. Subsequent protection of the crude phenol as the MOM-ether furnished the desired coupling partner 4-62 in 91% yield. A Negishi coupling was employed to couple 4-62 and 4-58.129 Thus, directed ortho-lithiation with n-BuLi followed by transmetallation to zinc generated an arylzinc reagent that smoothly underwent cross-coupling with vinyl iodide 4-58 in the presence of Pd(PPh3)4 to furnish enoate 4-63 in 76% yield.130
Scheme 4-24. Preparation of ester 4-63.

With ester 4-63 in hand, condensation of aniline 4-51 in the presence of AlMe₃ proceeded unreliably in 10-50% yield, and furnished only material lacking the MOM ether (Scheme 4-25). Unfortunately, any attempt to couple aniline 4-51 to any derivative of ester 4-63 was unsuccessful, including the acid, mixed anhydride, acyl fluoride and chloride.
Scheme 4-25. Condensation of aniline 4-51 with ester 4-63.

Given the clear lability of the MOM ether during the aluminum mediated condensation, the corresponding benzyl ether was prepared as shown in Scheme 4-26. Beginning with commercial 3-iodo-\(L\)-tyrosine (4-65), the free acid was converted to the methyl ester with \(\text{SOCl}_2\) in methanol. Subsequent Boc-protection of the nitrogen furnished 4-66. Crude ester 4-66 was reduced with \(\text{LiBH}_4\) and the resulting amino alcohol protected as the isopropylidene ketal to generate the phenol 4-67 in 92% yield over four steps. This crude phenol was then benzylated to provide 4-68 in 87% yield. Subsequent Stille coupling to stannane 4-57 proceeded in 73% yield to furnish the desired benzyl protected enoate 4-69.\(^{131}\)
Scheme 4-26. Preparation of the $O$-benzyl protected ester 4-69.

Ester 4-69 resisted aluminum-mediated condensation with aniline 4-51 under any set of stoichiometry, solvent or temperature conditions applied (Scheme 4-27). Given the necessity of this transformation, further optimization of the ester substrate was attempted. This time, the alkene geometry would be reversed to trans, moving the methyl group away from the sterically encumbering cis orientation.
Scheme 4-27. Attempted condensation of aniline 4-51 with ester 4-69.

Benzylated phenol 4-68 provided an ideal starting point for the preparation of the desired ester. Conversion of the iodide to the corresponding pinacol boronate ester 4-70 proceeded in 70% yield (Scheme 4-28). Subsequent Suzuki coupling with iodide 4-71 generated the desired trans ester 4-72 in 51% yield.¹³² Surprisingly, ester 4-72 also proved to be unreactive under any set of amidation conditions applied.
Scheme 4-28. Preparation of ester 4-72 containing the (E) alkene geometry and attempted condensation with aniline 4-51.

This result suggests that the MOM ether may be necessary for condensation to occur. It is conceivable that an in situ lactonization is required and that the lactone intermediate is the actual substrate undergoing amidation (Scheme 4-29). Additional concerns about material throughput
prompted a revised approach to this critical fragment that would include the MOM functionality, avoid tedious separations, and provide substantial amounts of material.

**Scheme 4-29.** Possible intermediate required for successful amidation of esters of type 4-63.

As before, carrying commercial 3-iodo-\(L\)-tyrosine (4-65) through to intermediate 4-67 and subsequent protection as the MOM ether generated 4-74. Crude MOM ether 4-74 underwent a Sonagashira coupling with propyne to furnish 4-75 which was pure enough to carry on crude (Scheme 4-30). This alkyne was hydrostannylated under palladium catalysis and the resulting alkenylstanne was iodinated to furnish alkenyiodide 4-76 in 71% yield over the 8 steps from 3-iodo-\(L\)-tyrosine. This approach allowed the installation of the desired alkenyl moiety in a very high-yielding sequence, although it was slightly longer than the previous approach. On large scale, the chemistry could be performed reliably with only a single purification of the alkenyliodide on SiO\(_2\), and proceeded in 70-80% over 8 steps, or about 97% per synthetic step. The operational benefits of this approach far outweighed the additional steps.
Scheme 4-30. Preparation of vinyl iodide 4-76.

With alkenyliodide 4-76 in hand, continued elaboration to the desired Heck cyclization precursor was required. Any attempt to perform lithium-halogen exchange on iodide 4-76 was met with failure. Therefore, a palladium-catalyzed carbonylation was performed in methanol, which gave rise to methyl ester 4-77 in 71% yield (Scheme 4-31).\textsuperscript{133,134}

Scheme 4-31. Carbonylation of vinyl iodide 4-76 to prepare key ester 4-77.
Ester 4-77 now contained all of the attributes that were presumed to aid the aluminum-mediated amidation: MOM-protection on the phenol, trans alkene geometry and the methyl (as opposed to ethyl) ester. Optimization of the amidation with ester 4-77 gave rise to anilide 4-78 in 67% yield, which varied only slightly on differing scales (Scheme 4-32). Double benzylation of anilide 4-78 furnished the desired Heck cyclization precursor 4-79 in 90% yield.

Scheme 4-32. Condensation of aniline 4-51 with ester 4-77 and subsequent elaboration to key Heck cyclization precursor 4-79.

The critical enantioselective Heck cyclization was investigated next.\textsuperscript{135} Initially employing Overman’s Ag-promoted conditions with rac-BINAP as the ligand and DMA as solvent provided the desired cyclization product 4-80 in 53% yield, with some evidence of decomposition, most likely from the prolonged heating (Entry 1, Table 4-1). Performing the reaction with (S)-BINAP and
reducing the reaction time provided an improved yield (63%) but the enantioselectivity (ee) was poor and some starting material remained (Entry 2).\textsuperscript{136} A switch to “base-promoted” conditions dramatically increased the yield to 97%, yet the ee remained at 30% (Entry 3). A switch to NMP as solvent dramatically increased the ee (60%) reduced the reaction time to \~3.5 h and provided an excellent yield (Entry 4). A decrease in ee from 60 to 50% was observed when (S)-Tol-BINAP was employed as the ligand (Entry 5). The temperature dependence of the cyclization was investigated next. Conducting the reaction at 95 °C required 6 h, and the ee dropped to 41% (Entry 6); however, at 135 °C the reaction proceeded in only 1h, and the ee was 55% (Entry 7). Thus, the optimal conditions chosen were (S)-BINAP as the ligand, PMP as the additive, NMP as solvent and a reaction temperature of \~110 °C. These conditions proved to be amenable to scale-up as demonstrated in entries 8-11, where increasingly larger scale reactions provided consistent yields and enantioselectivities. The optimized Heck cyclization did not perform at extreme levels of efficiency in terms of enantioselectivity, but effectively provided an average of 68% of the desired stereoisomer required for diazonamide A (based on the average yield and ee in Entries 8-11). Given the substantial challenges that were ahead in the synthesis, the optimized conditions would provide sufficient material throughput. Although attempts to confirm the relative stereochemistry of 4-80 by X-ray crystallography failed, the stereochemistry was assigned based on analogy to several similar substrates reported by Overman.\textsuperscript{136}
Table 4-1. Enantioselective Heck cyclization to set the C10 quaternary center of diazonamide A.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd Source</th>
<th>Ligand</th>
<th>Additive</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>time (h)</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>rac-BINAP</td>
<td>Ag&lt;sub&gt;3&lt;/sub&gt;PO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>DMA</td>
<td>100</td>
<td>20</td>
<td>53%</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>(S)-BINAP</td>
<td>Ag&lt;sub&gt;3&lt;/sub&gt;PO&lt;sub&gt;4&lt;/sub&gt;</td>
<td>DMA</td>
<td>95</td>
<td>12</td>
<td>68 + SM</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>b</td>
<td>(S)-BINAP</td>
<td>PMP</td>
<td>DMA</td>
<td>110</td>
<td>6</td>
<td>97</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>b</td>
<td>(S)-BINAP</td>
<td>PMP</td>
<td>NMP</td>
<td>110</td>
<td>3.5</td>
<td>99</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>b</td>
<td>(S)-Tol-BINAP</td>
<td>PMP</td>
<td>NMP</td>
<td>110</td>
<td>3.5</td>
<td>86</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>b</td>
<td>(S)-BINAP</td>
<td>PMP</td>
<td>NMP</td>
<td>95</td>
<td>6</td>
<td>97</td>
<td>41</td>
</tr>
<tr>
<td>7</td>
<td>b</td>
<td>(S)-BINAP</td>
<td>PMP</td>
<td>NMP</td>
<td>135</td>
<td>1</td>
<td>78</td>
<td>55</td>
</tr>
<tr>
<td>8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>b</td>
<td>(S)-BINAP</td>
<td>PMP</td>
<td>NMP</td>
<td>110</td>
<td>2.5</td>
<td>88</td>
<td>53</td>
</tr>
<tr>
<td>9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>b</td>
<td>(S)-BINAP</td>
<td>PMP</td>
<td>NMP</td>
<td>110</td>
<td>3.5</td>
<td>84</td>
<td>54</td>
</tr>
<tr>
<td>10&lt;sup&gt;d&lt;/sup&gt;</td>
<td>b</td>
<td>(S)-BINAP</td>
<td>PMP</td>
<td>NMP</td>
<td>110</td>
<td>3.5</td>
<td>87</td>
<td>54</td>
</tr>
<tr>
<td>11&lt;sup&gt;e&lt;/sup&gt;</td>
<td>b</td>
<td>(S)-BINAP</td>
<td>PMP</td>
<td>NMP</td>
<td>110</td>
<td>3.5</td>
<td>94</td>
<td>54</td>
</tr>
</tbody>
</table>

Reaction conditions: Pd source (10 mol %) (a = Pd<sub>2</sub>dba<sub>3</sub> or b = Pd<sub>2</sub>dba<sub>3</sub>•CHCl<sub>3</sub>), ligand (22 mol %), additive Ag<sub>3</sub>PO<sub>4</sub> (2 eq.) or PMP (4 eq.), ~0.1 M in degassed solvent.<sup>a</sup>Stereochemistry assigned by analogy to similar substrates reported for this transformation by Overman.<sup>136</sup> Reaction performed on 0.6 mmol scale.<sup>b</sup> Reaction performed on 3.52 mmol. Reaction performed on 4.76 mmol scale. Reaction performed on 5.03 mmol scale. Reaction performed on 0.6 mmol scale. Reaction performed on 3.52 mmol. Reaction performed on 4.76 mmol scale. Reaction performed on 5.03 mmol scale. Reaction performed on 0.6 mmol scale. Reaction performed on 3.52 mmol. Reaction performed on 4.76 mmol scale. Reaction performed on 5.03 mmol scale. Enantioselectivity determined by HPLC on a Chiracel OD column, 10% i-PrOH/hexanes, flow rate 1 mL/min.

### 4.2.5 Installation of Diazonamide’s Central Oxazole

With a reliable route to significant quantities of oxindole 4-80, the oxidative cleavage of its alkene was investigated, as this was our key fragment (see retrosynthetic analysis, Scheme 4-19). Not surprisingly, any attempted cleavage of the alkene in the presence of the lactam carbonyl resulted in decomposed material, presumably through decarboxylation. Therefore, the lactam would
be reduced to eliminate this undesired β-keto acid-type arrangement. Treatment of oxindole 4-80 with LAH in Et₂O or THF resulted in the desired reduction, along with unexpected debromination as indicated by ¹H NMR and MS analysis (Scheme 4-33, δ 6.46 (d, 1 H, J = 7.8 Hz, m/z = 631.5 ([M+H]+ for 4-81)).

![Scheme 4-33. Debromination observed during attempted reduction of oxindole 4-80.](image)

To circumvent the debromination issue, DIBAL was employed and delivered the desired hydroindole 4-82 in 77% yield (Scheme 4-34). Although this reaction was plagued by decomposition issues at room temperature, immediately heating the reaction mixture at reflux under concentrated conditions (~0.5 M) resulted in shorter reaction times and improved the recovery of the product.
Scheme 4-34. Reduction of oxindole 4-80 with DIBAL.

Hydroindole 4-82 was now ready to be converted to the corresponding acid through oxidative cleavage of the alkene. A two-step dihydroxylation-oxidative cleavage furnished the desired aldehyde 4-83 in 83% yield over the two steps (Scheme 4-35). Surprisingly, aldehyde 4-83 could not be converted to the corresponding acid under any conditions that were attempted, including: Cr- and Ru-based oxidants, O₃, Oxone®, NaClO₂, NaClO, and Br₂. The product of nearly all of these attempts was indole 4-85. Strictly controlling stoichiometry did not alter the reaction outcome to any detectable extent. The intermediacy of 4-84 is presumed to be the culprit in this decarboxylation. This result effectively terminated our Chan rearrangement approach to the central oxazole of diazonamide A, making aldehyde 4-83 a critical intermediate from which to proceed.
Scheme 4-35. Oxidative cleavage of alkene 4-82 and unexpected decarboxylation during attempted oxidation of aldehyde 4-83.

A revised approach to the α-amino ketone motif required for the central oxazole of diazonamide centered on an aldol-type addition of a glycine equivalent to aldehyde 4-83 (Scheme 4-36). This would allow for construction of the lower indole-containing subunit by appending 4-88 to the substrate.
Scheme 4-36. Revised retrosynthetic analysis for diazonamide A.

The literature revealed several suitable glycine equivalents, such as \textbf{4-90} and \textbf{4-91},\textsuperscript{137} which could serve as nucleophiles (Scheme 4-37). Any attempted addition of their corresponding enolates consistently returned only starting materials. Henry-type additions of nitroethane (\textbf{4-92}) or N-benzylphthalimide (\textbf{4-93}) also returned only starting materials. These results were somewhat surprising, but appear to be due to the sterically hindered nature of the aldehyde increasing the potential for retro-aldol fragmentation.
If retro-aldol fragmentation was indeed the obstacle to enolate addition, then \textit{in situ} trapping of the alkoxide intermediate would disable this pathway. Methyl isocyanoacetate was chosen since it contained a trapping function along with the desired $\alpha$-amino substitution. Indeed, upon treatment with DBU, a mixture of aldehyde \textbf{4-83} and methyl isocyanoacetate rapidly condensed to furnish oxazoline \textbf{4-94} in 99% yield as a mixture of several diastereomers (Scheme 4-38).
Scheme 4-38. Preparation of oxazoline 4-94.

In an effort to access the corresponding free amino alcohol, oxazoline 4-94 was hydrolyzed with dilute aqueous HCl to furnish formamide 4-95 in 99% yield (Scheme 4-39). Attempted deformylation of this substrate proved difficult, as the strongly acidic conditions typically applied rapidly decomposed the molecule. However, immediate deformylation with NaOMe furnished only the retro-aldol product 4-83 in 92% yield, which provided some indirect evidence that fragmentation of this delicate intermediate was indeed a favored pathway.
Scheme 4-39. Hydrolysis of oxazoline 4-94 and attempted deformylation of 4-95.

An alternative use of oxazoline 4-94 was required that would circumvent the formation of sensitive intermediates. Inspiration from N-acyl pyridine chemistry led to the attempted direct acylation of the oxazoline nitrogen with the acyl chloride derived from Fmoc-protected valine.\textsuperscript{138} When treated with Fmoc-Val-Cl, oxazoline 4-94 was rapidly consumed according to TLC analysis, presumably converted to chloroaminal 4-96 (Scheme 4-40). Hydrolytic workup of the reaction mixture revealed formate 4-97, which was immediately deformylated in basic methanol to provide alcohol 4-98 in 66% yield over the two steps as a mixture of several diastereomers. This method provided a rapid method to incorporate the valine residue required for diazonamide A. Unfortunately, the analytical data for 4-94 and subsequent intermediates is poorly resolved due to the mixtures of diastereomers present (melting ranges are also very large), although the $^1$H and $^{13}$C spectra are consistent with the assigned structures.
Scheme 4-40. Installation of valine residue through acylation of oxazoline 4-94.

With alcohol 4-98 in hand, cyclization of diazomamide’s central oxazole seemed within reach. Oxidation of the secondary alcohol with Dess-Martin periodinane furnished the corresponding crude ketone (structure tentatively assigned based on MS analysis) which was poised for cyclodehydration to 4-99, a substrate containing the fully functionalized quaternary center required for diazomamide A (Scheme 4-41). Unfortunately, under any of the cyclodehydration conditions applied including POCl₃, PPh₃/Cl₃CCl₃, PPh₃/BrCl₂CCl₂Br, Burgess reagent, and TsOH/toluene only decomposed or starting material was recovered. Mass analysis of the crude reaction mixtures indicates some partial loss of H₂O when POCl₃ in pyridine conditions are applied, but none of the desired oxazole has been recovered. This lack of reactivity has been observed by the Nicolaou and MacMillan groups in similar systems.¹³⁹
Several potential solutions to the oxazole cyclization problem remain to be explored. Although the issues preventing cyclodehydration in Scheme 4-41 are currently unknown, substrate 4-100 lacking ester substitution could be accessed by addition of allyl isocyanide to aldehyde 4-83. Conversely, polycycle 4-101 containing a fused H-ring may reduce the steric bulk around the C10 center and aid in cyclodehydration.

**Scheme 4-42.** Alternative substrates to proceed to the late stages of the synthesis.

Preliminary results toward an alternative cyclodehydration substrate have been achieved (although the structures are tentative until full characterization can be performed). Beginning with
cinnamyl bromide, displacement with NaN$_3$ yielded cinnamyl azide which was reduced with P(OMe)$_3$ and the resulting amine isolated as tosylate salt 4-102 in 87% overall (Scheme 4-43). Subsequent condensation with ethyl formate furnished formamide 4-103, which was dehydrated to the corresponding isocyanide 4-104 in 78% yield.

![Scheme 4-43. Preparation of isocyanide 4-104.](image)

The potassium anion of isocyanide 4-104 condensed with aldehyde 4-83 in 44% yield to furnish oxazoline 4-105 (Scheme 4-44). Acylation of the oxazoline with Fmoc-Val-Cl and subsequent hydrolysis provided alcohol 4-106 in only 15% yield (unoptimized). Alcohol 4-106 could be potentially be cyclized directly to the corresponding oxazoline and then oxidized to the desired oxazole. Conversely, it could be oxidized to the ketone and cyclodehydrated to the corresponding oxazole.
Scheme 4-44. Preparation of oxazoline 4-105 and subsequent acylation.

4.2.6 Conclusions

An approach to advanced intermediates for the synthesis of diazonamide has been developed that allows for the convenient preparation of multigram quantities of late stage material. Several key elements have been introduced, including the C10 quaternary center which was installed using an enantioselective Heck cyclization. Additionally, the valine residue has been efficiently introduced utilizing an N-acyl iminium ion cascade. The remainder of the molecule is fully functionalized in terms of appending the remainder of the diazonamide skeleton, and work continues toward this goal.
5. EXPERIMENTAL SECTION

All moisture sensitive reactions were performed under an N₂ atmosphere and all glassware was flame dried under vacuum prior to use. THF and Et₂O were dried by distillation over Na/benzophenone under a nitrogen atmosphere. Dry CH₂Cl₂ and Et₃N were obtained by distillation from CaH₂. All reactions were monitored by TLC analysis until the starting material had been consumed. Unless otherwise stated, solvents or reagents were used as received without further purification. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F-254 plates (particle size 0.040-0.055 mm, 230-400 mesh) and visualization was accomplished using UV light or by staining with basic KMnO₄ or anisaldehyde dye. NMR spectra were recorded at 300 MHz/75 MHz (¹H/¹³C NMR) in CDCl₃ unless otherwise stated on either a Bruker AVANCE 300 MHz or a Bruker QM-300 MHz spectrometer at 23 °C. Chemical shifts (δ) are reported in parts per million and the residual solvent peak was used as an internal standard (δ 7.261/77.0, ¹H/¹³C NMR). Data are reported as follows: Chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, s = sextet, m = multiplet, b = broad, app = apparent), integration, and coupling constant(s) (Hz). IR spectra were obtained on a Nicolet AVATAR 360 FT-IR E.S.P spectrometer. Mass spectra were obtained on a Micromass Autospec double focusing instrument. Melting points were determined using a Laboratory Devices Mel-Temp II and are uncorrected.
Authors note: Compounds 2-36, 2-48, 2-49, 2-50, 2-51, 2-52, 2-59, 2-61, 2-63, 2-69 and relevant precursors thereof were prepared by Joshua G. Pierce, University of Pittsburgh. Compounds 3-21, 3-23, 3-25, 3-26 and relevant precursors thereof were prepared by Corey R. J. Stephenson, University of Pittsburgh.

5.1 WATER ACCELERATED CASCADE REACTIONS

\[ \text{Ph} = \text{C} \quad \text{O} = \text{Ph} \]

1-((E)-3-(Vinyloxy)prop-1-enyl)benzene (1-30)\(^{140}\). To a solution of cinnamyl alcohol (5.80 g, 43.3 mmol) in ethyl vinyl ether (90 mL) at ambient temperature was added Hg(OAc)\(_2\) (5.11 g, 16.0 mmol). The reaction mixture was heated at reflux for 4 h, cooled, treated with K\(_2\)CO\(_3\) (2 g) and filtered through a pad of Al\(_2\)O\(_3\). The filtrate was concentrated, dissolved in hexanes (10 mL) and filtered through a 1.5 inch pad of SiO\(_2\). The filtrate was concentrated to provide allylic vinyl ether 1-30 (4.02 g, 25.1 mmol, 58%) as a colorless oil: \(^1\)H NMR \(\delta\) 7.51-7.33 (m, 5 H), 6.75 (d, 1 H, \(J = 16.0\) Hz), 6.64 (dd, 1 H, \(J = 14.3, 6.8\) Hz), 6.41 (dt, 1 H, \(J = 16.0, 5.8\) Hz), 4.47 (dd, 2 H, \(J = 5.9, 1.4\) Hz), 4.41 (dd, 1 H, \(J = 14.3, 2.1\) Hz), 4.20 (dd, 1 H, \(J = 6.8, 2.1\) Hz); \(^1\)C NMR \(\delta\) 151.3, 136.3, 132.6, 128.4 (2 C), 127.7, 126.4 (2 C), 124.2, 87.1, 68.6.
(E,3S*-5R*)-7-Methyl-3-phenylundeca-1,6-dien-5-ol (1-31a) and (E,3S*-5S*)-7-methyl-3-phenylundeca-1,6-dien-5-ol (1-31b). General Protocol A. To a -30 °C solution of AlMe₃ (540 mg, 7.35 mmol) and Cp₂ZrCl₂ (85.8 mg, 0.294 mmol) in CH₂Cl₂ (6 mL) was added H₂O (66.1 μL, 3.67 mmol) dropwise. The reaction mixture was warmed to ambient temperature and then cooled to 0 °C and treated with 1-hexyne (676 μL, 5.88 mmol). The mixture was stirred for 30 min, cooled to -78 °C, and treated with vinyl ether 1-30 (470 mg, 2.94 mmol) in CH₂Cl₂ (1.5 mL). The mixture was warmed to ambient temperature over 10 min and quenched with 1 M Rochelle’s salt (3 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL) and the combined organic layers were washed with brine, dried (MgSO₄), and concentrated. The residue was chromatographed on SiO₂ (hexanes/EtOAc, 5:1) to furnish alcohols 1-31a and 1-31b as a colorless oil which was a 1:1 mixture of inseparable diastereomers as indicated by ¹H NMR analysis: (1:1 mixture of diastereomers) IR (neat) 3334, 2956, 2929, 1452, 996, 913, 700 cm⁻¹; ¹H NMR δ 7.34-7.18 (m, 5 H), 6.03-5.92 (m, 1 H), 5.22-5.17 (m, 1 H), 5.11-5.02 (m, 2 H), 4.31-4.26 (m, 1 H), 3.49-3.39 (m, 1 H), 2.09-1.96 (m, 3 H), 1.88-1.74 (m, 1 H), 1.54 (2 br s, 3 H), 1.42-1.20 (m, 4 H), 0.94 (t, 1.5 H, J = 4.7 Hz), 0.91 (t, 1.5 H, J = 4.5 Hz); ¹³C NMR δ 143.8 (2 C), 142.3, 141.9, 139.5, 139.0, 128.4 (4 C), 127.6 (5 C), 127.2, 126.2 (2 C), 114.2, 114.0, 66.6, 66.4, 46.2, 46.1, 43.0, 42.9, 39.2 (2 C), 29.9 (2 C), 22.3 (2 C), 16.5 (2 C), 13.9 (2 C); MS (EI) m/z (rel intensity) 240 ([M-H₂O]⁺, 34), 201 (30), 183 (62), 155 (16), 117 (100); HRMS (EI) m/z calcd for C₁₈H₂₆O 258.1984, found 258.1982.

\[
\text{(E)-(Carboxyvinyl)trimethylammonium betaine (1-33).}^{141}\text{ To a mixture of ethyl propiolate (5.32 g, 54.0 mmol) in CH₂Cl₂ (3 mL) and H₂O (90 mL) at 5 °C was added Me₃N (25%}
\]
solution in water, 18.0 mL, 75.6 mmol) dropwise over 30 min. The temperature was kept under 30 °C during the addition. The mixture was warmed to ambient temperature and stirred for 3 h. The organic layer was separated and the aqueous layer was washed with CH₂Cl₂ (2 x 15 mL). The aqueous layer was azeotroped to dryness with 1,4-dioxane and the resulting solid washed with CH₃CN (10 mL). The solid cake was dried *in vacuo* for 24 h to provide betaine **1-33** (5.25 g, 40.4 mmol, 76%) as a beige powder: Mp 174.1-176.0 °C (dec., 1,4-dioxane); (lit. 176-177 °C (dec.)); \(^1\)H NMR δ 7.07 (d, 1 H, \(J = 13.8 \text{ Hz}\)), 6.57 (d, 1 H, \(J = 14.0 \text{ Hz}\)), 3.49 (s, 9 H).

\[
\text{Ph} = \overset{\text{O}}{\text{O}} \overset{\text{OH}}{\text{O}} (2E)-3-(\text{Cinnamyloxy})\text{acrylic acid (1-34).}^{111} \]

Hexane-washed NaH (830 mg, 34.6 mmol) was suspended in THF (40 mL) and cooled to 0 °C. A solution of cinnamyl alcohol (3.86 g, 28.8 mmol) in THF (40 mL) was added dropwise over 30 min and the reaction mixture was warmed to ambient temperature and stirred for 30 min. To this pink solution was added betaine **1-33** (4.70 g, 36.2 mmol) in one portion. The mixture was heated at reflux for 4 h, cooled to ambient temperature and treated with water (10 mL). The aqueous layer was washed with Et₂O (2 x 100 mL), acidified to pH 1 with 10.0 M hydrochloric acid, extracted with Et₂O (3 x 100 mL), dried (MgSO₄), and concentrated. The resulting white powder was dried at 0.1 mmHg for 24 h to furnish **1-34** (5.23 g, 25.6 mmol, 95%) as a white powder: Mp 139.0-141.9 °C (Et₂O); (lit. 140-141.5 °C); \(^1\)H NMR δ 12.00 (br s, 1 H), 7.73 (d, 1 H, \(J = 12.5 \text{ Hz}\)), 7.43-7.27 (m, 5 H), 6.69 (d, 1 H, \(J = 16.0 \text{ Hz}\)), 6.30 (dt, 1 H, \(J = 15.9, 6.2 \text{ Hz}\)), 5.29 (d, 1 H, 12.5 Hz), 4.58 (dd, 2 H, \(J = 6.0, 0.7 \text{ Hz}\)).
(2E)-Methyl 3-(cinnamyloxy)acrylate (1-35). A solution of acid 1-34 (500 mg, 2.45 mmol) in MeOH (5 mL) and benzene (19 mL) was treated at ambient temperature with TMSCHN$_2$ (2.0 M solution in hexanes, 1.72 mL, 3.43 mmol) and stirred for 90 min. The reaction mixture was concentrated and chromatographed on SiO$_2$ (hexanes/EtOAc, 3:1) to yield 1-35 (530 mg, 2.45 mmol, 99%) as a colorless oil: IR (neat) 1710, 1643, 1624, 1190, 1137, 967, 745 cm$^{-1}$; $^1$H NMR $\delta$ 7.62 (d, 1 H, $J = 12.6$ Hz), 7.42-7.19 (m, 5 H), 6.68 (d, 1 H, $J = 15.9$ Hz), 6.29 (dt, 1 H, $J = 15.9$, 6.0 Hz), 5.30 (d, 1 H, $J = 12.4$ Hz), 4.55 (dd, 2 H, $J = 6.1$, 1.2 Hz), 3.71 (s, 3 H); $^{13}$C NMR $\delta$ 168.1, 162.0, 135.8, 134.4, 128.6 (2 C), 128.3, 126.6 (2 C), 122.5, 96.9, 71.6, 51.1; MS (EI) m/z (rel intensity) 218 ([M]$^+$, 41), 200 (14), 158 (8), 129 (12), 117 (100), 91 (49); HRMS (EI) m/z calcd for C$_{13}$H$_{14}$O$_3$ 218.0942, found 218.0932.

(2E)-3-(Cinnamyloxy)-N,N-dimethylacrylamide (1-36). Acid 1-34 (1.08 g, 5.27 mmol), EDCI (1.31 g, 6.85 mmol), DMAP (64.3 mg, 0.53 mmol), and dimethylamine hydrochloride (1.07 g, 13.2 mmol) were combined in CH$_2$Cl$_2$ (10 mL) at ambient temperature and DIPEA (3.4 mL, 18.4 mmol) was added dropwise over 5 min. The reaction mixture was stirred for 30 h and quenched with H$_2$O (5 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (4 x 10 mL) and the combined organic extracts were washed with brine, dried (MgSO$_4$), filtered and concentrated. The resulting residue was chromatographed on SiO$_2$ (EtOAc) to give amide 1-36 (624 mg, 2.70 mmol, 48%) as a white solid: mp 58.4-59.6 °C (EtOAc); IR (KBr) 2931, 1651, 1591, 1495, 1449, 1254, 1119, 967, 746 cm$^{-1}$; $^1$H NMR $\delta$ 7.53 (d, 1 H, $J = 11.8$ Hz), 7.34-7.22 (m, 5 H), 6.60 (d, 1 H, $J = 15.9$ Hz), 6.22 (dt, 1 H, $J = 15.9$, 6.1 Hz), 5.67 (d, 1 H, $J = 11.8$ Hz), 4.48 (dd, 2 H, $J = 6.1$, 1.2 Hz), 2.93 (s, 6 H);
$^{13}$C NMR δ 166.9, 160.4, 135.7, 133.8, 128.4 (2 C), 127.9, 126.4 (2 C), 122.9, 96.4, 71.9, 36.9, 35.1; MS (EI) m/z (rel intensity) 231 ([M]$^+$, 12), 203 (21), 117 (100), 91 (36), 72 (15); HRMS (EI) m/z calcld for C$_{14}$H$_{17}$NO$_2$ 231.1260, found 231.1250.

(2$^E$,4$^E$)-Methyl 5-methylnona-2,4-dienoate (1-37). According to the general protocol A, AlMe$_3$ (206 mg, 2.88 mmol), Cp$_2$ZrCl$_2$ (33.6 mg, 0.115 mmol), H$_2$O (25.9 μL, 1.44 mmol), 1-hexyne (264 μL, 2.30 mmol) and ester 1-35 (250 mg, 1.15 mmol) afforded dienoate 37 (79 mg, 0.193 mmol, 37%) as a colorless oil: $^1$H NMR δ 7.58 (dd, 1 H, $J$ = 15.1, 11.6 Hz), 5.98 (d, 1 H, $J$ = 11.3 Hz), 5.77 (d, 1 H, $J$ = 15.1 Hz), 3.73 (s, 3 H), 2.13 (t, 2 H, $J$ = 7.2 Hz), 1.88 (br s, 3 H), 1.49-1.39 (m, 2 H), 1.36-1.24 (m, 2 H), 0.90 (t, 3 H, $J$ = 7.2 Hz); $^{13}$C NMR δ 168.0, 150.4, 141.2, 122.9, 118.1, 51.2, 39.8, 29.7, 22.3, 17.2, 13.8; MS (EI) 182 ([M]$^+$, 23), 167 (15), 151 (23), 125 (85), 111 (39).

(E,2$^S^*$,3$^S^*$)-3-Hydroxy-N,N-dimethyl-5-phenyl-2-((R*)-1-phenylallyl)hex-4-enamide (1-38) and (E,2$^S^*$,3$^R^*$)-3-hydroxy-N,N-dimethyl-5-phenyl-2-((R*)-1-phenylallyl)hex-4-enamide (1-39). According to the general protocol A, AlMe$_3$ (645 mg, 8.96 mmol), Cp$_2$ZrCl$_2$ (26.2 mg, 0.0896 mmol), H$_2$O (64.5 μL, 0.0896 mmol), phenylacetylene (197 μL, 1.79 mmol) and amide 1-36 (207 mg, 0.896 mmol) afforded, after chromatography on SiO$_2$ (hexanes/EtOAc, 3:1), hydroxy amides 1-
38 and 1-39 (31.9 mg, 0.0914 mmol, 10%) as a white solid which was a 5:1 mixture (1-38:1-39) of partially separable diastereomers by $^{1}$H NMR analysis of the crude reaction mixture. 1-38: Mp 142.8-145.9 °C (hexanes/EtOAc); IR (KBr) 3388, 3059, 3028, 2930, 1614, 1494, 1445, 1147, 1051, 760, 702 cm$^{-1}$; $^{1}$H NMR δ 7.33-7.22 (m, 10 H), 6.21 (ddd, 1 H, $J$ = 17.0, 10.0, 9.4 Hz), 5.72 (dd, 1 H, $J$ = 8.4, 1.3 Hz), 5.43 (d, 1 H, $J$ = 17.0 Hz), 5.33 (dd, 1 H, $J$ = 10.2, 1.5 Hz), 5.20 (d, 1 H, $J$ = 9.9 Hz, exchanges with D$_2$O), 4.87-4.80 (m, 1 H), 4.06 (dd, 1 H, $J$ = 9.5, 9.5 Hz), 3.05 (dd, 1 H, $J$ = 11.1, 2.7 Hz), 2.63 (s, 3 H), 2.48 (s, 3 H), 2.11 (d, 3 H, $J$ = 1.3 Hz); $^{13}$C NMR δ 174.3, 142.9, 141.6, 137.3, 135.6, 130.3, 128.3 (2 C), 128.2 (2 C), 127.9 (2 C), 127.2, 126.8, 125.7 (2 C), 118.2, 67.9, 49.9, 49.6, 37.4, 35.1, 16.2; MS (EI) m/z (rel intensity) 259 ([M-C$_3$H$_8$O$_2$N]$^{+}$, 34), 240 (21), 232 (32), 176 (12), 131 (15), 117 (63), 72 (100); HRMS (EI) m/z calcd for C$_{20}$H$_{19}$ [M-C$_3$H$_8$O$_2$N] 259.1487, found 259.1475. Characteristic data for 1-39: $^{1}$H NMR δ 7.50 (d, 2 H, $J$ = 7.0 Hz), 6.51 (dt, 1 H, $J$ = 17.0, 10.1 Hz), 3.90 (app t, 1 H, $J$ = 10.1 Hz), 3.25 (dd, 1 H, $J$ = 10.0, 8.5 Hz), 2.37 (s, 3 H), 1.90 (d, 3 H), 1.51 (s, 3 H).

(2E)-3-(Cinnamyloxy)prop-2-en-1-ol (1-40). A solution of ester 1-35 (10.2 g, 47.3 mmol) in CH$_2$Cl$_2$ (50 mL) was treated at -78 °C with DIBAL-H (1.0 M solution in hexanes, 99.2 mL, 99.2 mmol). The reaction mixture was allowed to warm to ambient temperature over 25 min and quenched with 1 M NaOH (10 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (5 x 35 mL). The combined organic layers were washed with water and brine, dried (MgSO$_4$), and concentrated. The residue was chromatographed on SiO$_2$ (Et$_2$O/hexanes, 3:1) to yield 1-40 (2.61 g, 13.7 mmol, 29%) as a white solid: Mp 49.5-51.4 °C (Et$_2$O/hexanes); IR (KBr) 3325, 2909, 2863, 1652, 1449, 1181, 971, 744 cm$^{-1}$; $^{1}$H NMR δ 7.41-7.25 (m, 5 H), 6.66 (d, 1 H, $J$ = 15.9 Hz), 6.57 (d, 1 H, $J$ = 12.6 Hz), 5.57 (d, 1 H, $J$ = 11.1 Hz), 5.35 (d, 1 H, $J$ = 17.0 Hz), 5.33 (dd, 1 H, $J$ = 10.2, 1.5 Hz), 5.20 (d, 1 H, $J$ = 9.9 Hz, exchanges with D$_2$O), 4.87-4.80 (m, 1 H), 4.06 (dd, 1 H, $J$ = 9.5, 9.5 Hz), 3.05 (dd, 1 H, $J$ = 11.1, 2.7 Hz), 2.63 (s, 3 H), 2.48 (s, 3 H), 2.11 (d, 3 H, $J$ = 1.3 Hz); $^{13}$C NMR δ 174.3, 142.9, 141.6, 137.3, 135.6, 130.3, 128.3 (2 C), 128.2 (2 C), 127.9 (2 C), 127.2, 126.8, 125.7 (2 C), 118.2, 67.9, 49.9, 49.6, 37.4, 35.1, 16.2; MS (EI) m/z (rel intensity) 259 ([M-C$_3$H$_8$O$_2$N]$^{+}$, 34), 240 (21), 232 (32), 176 (12), 131 (15), 117 (63), 72 (100); HRMS (EI) m/z calcd for C$_{20}$H$_{19}$ [M-C$_3$H$_8$O$_2$N] 259.1487, found 259.1475.
Hz), 6.30 (dt, 1 H, J = 15.9, 5.9 Hz), 5.13 (dt, 1 H, J = 12.5, 7.5 Hz) 4.42 (d, 2 H, J = 6.0 Hz), 4.07 (app t, 2 H, J = 5.7 Hz) 1.14 (t, 1 H, J = 5.6 Hz); $^{13}$C NMR δ 149.3, 136.1, 133.0, 128.4 (2 C), 127.8, 126.4 (2 C), 124.0, 103.4, 69.7, 60.2; MS (EI) m/z (rel intensity) 190 ([M]$^+$, 15), 172 (47), 159 (88), 117 (100), 91 (34); HRMS (EI) m/z calcd for C$_{12}$H$_{14}$O$_2$ 190.0993, found 190.0984.

Ph
\[\equiv\equiv\]
O
\[\equiv\equiv\]
OMe

1-((1E)-3-((E)-3-Methoxyprop-1-enyloxy)prop-1-enyl)benzene (1-41). To a suspension of NaH (30.3 mg, 1.26 mmol) in THF (3 mL) at ambient temperature was added a solution of alcohol 1-40 (200 mg, 1.05 mmol) in THF (2 mL). The reaction mixture was stirred at ambient temperature for 45 min and treated with CH$_3$I (164 μL, 2.63 mmol) over 3 min. The mixture was stirred at ambient temperature for 12 h and quenched with H$_2$O (1 mL). The aqueous layer was extracted with Et$_2$O (3 x 2 mL). The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), filtered and concentrated. The residue was chromatographed on SiO$_2$ (hexanes/EtOAc, 3:1) to yield methyl ether 1-41 (207 mg, 1.02 mmol, 97%) as a colorless oil: IR (neat) 3060, 2924, 2855, 2821, 1652, 1496, 1383, 1174, 1086, 967, 745 cm$^{-1}$; $^1$H NMR δ 7.42-7.28 (m, 5 H), 6.65 (d, 1 H, J = 16.0 Hz), 6.57 (d, 1 H, J = 12.6 Hz), 6.31 (dt, 1 H, J = 15.9, 5.9 Hz), 5.04 (dt, 1 H, J = 12.6, 7.4 Hz), 4.41 (dd, 2 H, J = 5.9, 1.3 Hz), 3.86 (dd, 2 H, J = 7.4, 0.8 Hz), 3.31 (s, 3 H); $^{13}$C NMR δ 149.9, 136.1, 132.8, 128.3 (2 C), 127.7, 126.3 (2 C), 123.9, 100.2, 69.7, 69.5, 56.8; MS (EI) m/z (rel intensity) 204 ([M]$^+$, 16), 186 (16), 172 (31), 159 (72), 148 (70), 131 (42), 117 (100), 91 (15); HRMS (EI) m/z calcd for C$_{12}$H$_{14}$O$_2$ [M-C$_2$H$_5$O] 159.0809, found 159.0797.

Ph
\[\equiv\equiv\]
O
\[\equiv\equiv\]
OTIPS

126
(2E)-3-(Cinnamyloxy)allyloxy)triisopropylsilane (1-42). A solution of imidazole (101 mg, 1.47 mmol), TIPSCl (235 μL, 1.10 mmol), and DMAP (13.4 mg, 0.112 mmol) in CH₂Cl₂ (3 mL) was cooled to 0 °C and treated with a solution of alcohol 1-40 (200 mg, 1.05 mmol) in CH₂Cl₂ (2 mL). The reaction mixture was warmed to ambient temperature, stirred for 4 h, and quenched with H₂O (1 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 2 mL) and the combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated. The residue was chromatographed on SiO₂ (hexanes/EtOAc, 9:1) to yield silyl ether 1-42 (338 mg, 0.974 mmol, 93%) as a colorless oil: IR (neat) 2942, 2891, 2865, 1672, 1652, 1463, 1283, 1181, 1054, 965, 690 cm⁻¹; ¹H NMR δ 7.40-7.24 (m, 5 H), 6.64 (d, 1 H, J = 16.0 Hz), 6.53 (d, 1 H, J = 12.6 Hz), 6.30 (dt, 1 H, J = 15.9, 5.9 Hz), 5.06 (dt, 1 H, J = 12.5, 6.6 Hz), 4.39 (dd, 2 H, J = 5.9, 1.3 Hz), 4.20 (dd, 2 H, J = 6.5, 1.2 Hz), 1.18-1.03 (m, 21 H); ¹³C NMR δ 147.8, 136.4, 132.9, 128.5 (2 C), 127.8, 126.5 (2 C), 124.4, 104.2, 69.7, 61.1, 18.0, 12.0; MS (EI) m/z (rel intensity) 347 ([M⁺], 9), 303 (27), 247 (24), 145 (6), 117 (100), 84 (25); HRMS (EI) m/z calcd for C₂₁H₃₄O₂Si 347.2406, found 347.2396.

\[
\text{(E,2R^*,3S^*)-5-Methyl-2-((R^*)-1-phenylallyl)non-4-ene-1,3-diol (1-43) and (E,2R^*,3R^*)-5-methyl-2-((R^*)-1-phenylallyl)non-4-ene-1,3-diol (1-44). According to general protocol A, AlMe₃ (2.12 g, 29.5 mmol), Cp₂ZrCl₂ (215 mg, 0.737 mmol), H₂O (265 μL, 14.7 mmol), 1-hexyne (1.69 mL, 14.7 mmol) and alcohol 1-40 (1.40 g, 7.37 mmol) afforded, after chromatography on SiO₂ (hexanes/EtOAc, 3:1), diols 1-43 and 1-44 (636 mg, 2.21 mmol, 30%) as a colorless oil which was a 10:1 mixture (1-43:1-44) of inseparable diastereomers as indicated by ¹H NMR analysis. 1-43: IR (neat) 3342, 2956, 2929, 1453, 1034, 915, 759, 700 cm⁻¹; ¹H NMR δ 7.33-7.18 (m, 5 H), 6.09 (dt, 1
H, J = 16.9, 9.8 Hz), 5.48 (d, 1 H, J = 8.5 Hz), 5.21 (d, 1 H, J = 17.1 Hz), 5.13 (dd, 1 H, J = 10.1, 1.2 Hz), 4.80-4.77 (m, 1 H), 3.93 (br d, 1 H, J = 11.1 Hz), 3.79 (t, 1 H, J = 9.6 Hz), 3.38-3.31 (m, 1 H), 2.92-2.90 (m, 1 H, exchanges with D2O), 2.56 (br d, 1 H, J = 4.1 Hz, exchanges with D2O), 2.02 (t, 2 H, J = 7.0 Hz), 1.81-1.71 (m, 1 H), 1.64 (s, 3 H), 1.46-1.36 (m, 2 H), 1.34-1.24 (m, 2 H), 0.91 (t, 3 H, J = 7.1 Hz); 13C NMR δ 142.6, 140.5, 138.6, 128.6 (2 C), 128.0 (2 C), 126.7, 126.4, 115.9, 70.3, 61.3, 49.3, 48.8, 39.3, 29.9, 22.3, 16.5, 13.9; MS (EI) m/z (rel intensity) 270 ([M-H2O]+, 18), 252 (52), 240 (52), 209 (36), 195 (61), 155 (56), 117 (100); HRMS (EI) m/z calcd for C19H26O [M-H2O]270.1984, found 270.1982. Characteristic data for 1-44: 1H NMR δ 5.39 (d, 1 H, J = 7.4 Hz), 2.41 (br d, 1 H, J = 3.4 Hz, exchanges with D2O); 13C NMR δ 143.1, 139.3, 138.4, 127.8, 70.5, 61.4, 49.6, 16.2.

\[
\begin{align*}
&\text{(2E,4R*},5S*,7E)-2,8-\text{Diphenyl-5-((R*)-1-phenylallyl)nona-2,7-dien-4-ol (1-45) and} \\
&\text{(2E,4S*},5S*,7E)-2,8-\text{diphenyl-5-((R*)-1-phenylallyl)nona-2,7-dien-4-ol (1-46). According to} \\
&\text{general protocol A, AlMe}_3\text{ (58.3 mg, 0.810 mmol), Cp}_2\text{ZrCl}_2\text{ (10.7 mg, 0.0368 mmol), H}_2\text{O (7.29} \\
&\mu\text{L, 0.405 mmol), phenylacetylene (101 }\mu\text{L, 0.920 mmol) and methyl ether 1-41 (75.0 mg, 0.368} \\
&\text{mmol) afforded, after chromatography on SiO}_2\text{ (hexanes/EtOAc, 5:1), alcohols 1-45 and 1-46 (18.0} \\
&\text{mg, 0.044 mmol, 12%) as a colorless oil which was an 8:1 mixture (1-45:1-46) of inseparable} \\
&\text{diastereomers as indicated by 1H NMR analysis: 1-45: 1H NMR δ 7.50-7.29 (m, 15 H), 6.38 (dt, 1} \\
&\text{H, J = 15.6, 9.8 Hz), 6.14 (dd, 1 H, J = 8.4, 1.3 Hz), 5.93-5.88 (m, 1 H), 5.37 (dd, 1 H, J = 16.8, 1.1} \\
&\text{Hz), 5.30 (dd, 1 H, J = 10.0, 1.7 Hz), 5.08-5.05 (m, 1 H), 3.73 (t, 1 H, J = 4.9 Hz), 2.59-2.49 (m, 1} \\
&\text{H).}
\end{align*}
\]
H), 2.41-2.28 (m, 2 H), 2.18 (d, 3 H, J = 1.2 Hz), 2.01 (s, 3 H), 1.82 (d, 1 H, J = 4.8 Hz, exchanges with D2O); MS (EI) m/z (rel intensity) 390 ([M-H2O]+, 43), 285 (41), 155 (79), 131 (89), 105 (96), 91 (100). Characteristic data for 1-46: 1H NMR δ 6.06 (dd, 1 H, J = 8.2, 1.3 Hz), 1.97 (d, 3 H, J = 1.2 Hz).

\[
\begin{align*}
\text{(E,2R*,3S*)-5-Methyl-2-((R*)-1-phenylallyl)non-4-ene-1-triisopropylsilyloxy-3-ol (1-47)}
\end{align*}
\]

and \((E,2R*,3R*)-5-methyl-2-((R*)-1-phenylallyl)non-4-ene-1-triisopropylsilyloxy-3-ol (1-48)\). According to general protocol A, AlMe₃ (39.1 mg, 0.258 mmol), Cp₂ZrCl₂ (7.53 mg, 0.0258 mmol), H₂O (4.64 μL, 0.258 mmol), 1-hexyne (59.4 μL, 0.517 mmol) and silyl ether 1-42 (89.4 mg, 0.258 mmol) afforded, after chromatography on SiO₂ (hexanes/EtOAc, 9:1), alcohols 1-47 and 1-48 (68.1 mg, 0.153 mmol, 60%) as a colorless oil which was a 10:1 mixture (1-47:1-48) of inseparable diastereomers as indicated by 1H NMR analysis. 1-47: IR (neat) 3508, 2929, 2866, 1464, 1071, 882, 700 cm⁻¹; 1H NMR δ 7.38-7.33 (m, 3 H), 7.28-7.24 (m, 2 H), 6.17 (dt, 1 H, J = 16.9, 9.8 Hz), 5.57 (d, 1 H, J = 8.2 Hz), 5.28 (d, 1 H, J = 17.0 Hz), 5.18 (dd, 1 H, J = 10.1, 1.2 Hz), 4.79 (td, 1 H, J = 8.1, 3.5 Hz), 4.10 (dd, 1 H, J = 10.2, 2.9 Hz), 3.92 (t, 1 H, J = 9.5 Hz), 3.84 (d, 1 H, J = 8.1 Hz, exchanges with D₂O), 3.65 (dd, 1 H, J = 10.1, 3.7 Hz), 2.09 (t, 2 H, J = 7.8 Hz), 1.93-1.86 (m, 1 H), 1.80 (s, 3 H), 1.54-1.44 (m, 2 H), 1.41-1.34 (m, 2 H), 1.06-1.04 (m, 21 H), 0.98 (t, 3 H, J = 7.2 Hz); 13C NMR δ 142.6, 140.7, 136.9, 128.5 (2 C), 128.2 (2 C), 127.6, 126.3, 115.9, 69.7, 62.9, 48.7, 48.6, 39.3, 29.8, 22.4, 17.9 (6 C), 16.4, 14.0, 11.7 (3 C); MS (EI) m/z (rel intensity) 444 ([M]+, 5), 401 (42), 383 (8), 309 (21), 253 (13), 117 (100); HRMS (EI) m/z calcd for C₂₈H₄₈O₂Si 444.3424, found 444.3408. Characteristic data for 1-48: 1H NMR δ 5.47 (d, 1 H, J = 7.6 Hz).
(E,2R*,3S*)-5-Methyl-2-((R*)-1-phenylallyl)non-4-ene-1,3-diol (1-43). To a solution of 1-47 and 1-48 (48.0 mg, 0.108 mmol) in THF (1.1 mL) at ambient temperature was added TBAF (1.0 M solution in THF, 216 μL, 0.216 mmol). The reaction mixture was stirred for 1 h and quenched with H2O (1 mL). The mixture was extracted with Et2O (3 x 3 mL) and the combined organic layers were washed with H2O, brine, dried (Na2SO4) and concentrated. The residue was chromatographed on SiO2 (hexanes/EtOAc, 5:1) to yield diol 1-43 (22.9 mg, 0.0795 mmol, 74%) as a colorless oil.

1-((E)-3-(Prop-1-en-2-yloxy)prop-1-enyl)benzene (1-51). To a solution of cinnamyl alcohol (1.00 g, 7.46 mmol) in isopropenyl methyl ether (3 mL) was added Hg(OAc)2 (1.19 g, 3.73 mmol) at ambient temperature. The mixture was allowed to stir for 30 h treated with solid K2CO3 (1 g) and filtered. The filtrate was evaporated and the residue chromatographed on SiO2 (hexanes/EtOAc, 9:1) to yield vinyl ether 1-51 (483 mg, 2.78 mmol, 45%) as a colorless oil: 1H NMR δ 7.45-7.28 (m, 5 H), 6.69 (d, 1 H, J = 15.9 Hz), 6.44-6.34 (m, 1 H), 4.41 (dd, 2 H, J = 6.0, 1.2 Hz), 3.96 (d, 2 H, J = 4.2 Hz), 1.92 (s, 3 H); 13C NMR δ 159.5, 136.6, 132.6, 128.5 (2 C), 127.7, 126.5 (2 C), 124.7, 81.8, 67.9, 21.0.
1-((E)-3-(Allyloxy)prop-1-enyl)benzene (1-52). To suspension of NaH (752 mg, 31.1 mmol) in THF (5 mL) at ambient temperature was added a solution of cinnamyl alcohol (3.00 g, 22.4 mmol) in THF (10 mL) dropwise over 10 min. The reaction mixture was stirred for 40 min, cooled to 0 °C, treated with allyl iodide (2.47 mL, 26.9 mmol) and warmed to ambient temperature and stirred overnight. The reaction mixture was quenched with H₂O (5 mL) and the aqueous layer extracted with hexanes/EtOAc (1:1, 3 x 25 mL). The combined organic layers were washed with H₂O, brine, dried (MgSO₄) and concentrated. The residue was chromatographed on SiO₂ (hexanes/EtOAC, 9:1) followed by Kugelrohr distillation to yield allyl ether 1-52 (3.90 g, 22.4 mmol, 97%) as a colorless oil: bp 82 °C (0.1 mmHg); ¹H NMR δ 7.44-7.24 (m, 5 H), 6.65 (d, 1 H, J = 15.9 Hz), 6.33 (dt, 1 H, J = 15.9, 5.9 Hz), 6.06-5.94 (m, 1 H), 5.36 (dd, 1 H, J = 17.1, 1.5 Hz), 5.25 (dd, 1 H, J = 10.4, 0.7 Hz), 4.17 (dd, 2 H, J = 5.8, 1.0 Hz), 4.06 (d, 2 H, J = 5.5 Hz); ¹³C NMR δ 136.5, 134.5, 132.0, 128.3 (2 C), 127.4, 126.2 (2 C), 125.8, 116.8, 70.8, 70.4.

1-((1E)-3-(Prop-1-enyloxy)prop-1-enyl)benzene (1-53). To a solution of 1-52 (241 mg, 1.39 mmol) and NiCl₂(dppb)³² (77.3 mg, 0.139 mmol) in THF (700 μL) at -5 °C was added Li(Et)₃BH (1.0 M solution in THF, 139 μL, 0.139 mmol) dropwise. The reaction mixture was stirred for 25 min and filtered through basic Al₂O₃ (hexanes) and celite (hexanes). The filtrate was concentrated and the residue chromatographed on SiO₂ (hexanes/EtOAc, 20:1) to furnish vinyl ether 1-53 (120 mg, 0.690 mmol, 50%) as a 94:6 mixture of (Z:E) isomers (as indicated by ¹H NMR analysis) and starting material (103 mg, 0.592 mmol, 43%): (E,Z)-1-53: IR (neat) 3028, 2918, 2863, 1668, 1356, 1131, 1077, 966, 692 cm⁻¹; ¹H NMR δ 7.44-7.24 (m, 5 H), 6.65 (d, 1 H, J = 15.9 Hz), 6.32 (dt, 1 H, J = 15.9, 5.9 Hz), 6.06 (dq, 1 H, J = 6.2, 1.7 Hz), 4.48 (qd, 1 H, J = 6.8, 0.6 Hz), 4.44
(dd, 2 H, J = 5.8, 1.4 Hz), 1.66 (dd, 3 H, J = 6.8, 1.7 Hz); $^1$C NMR δ 145.0, 136.4, 132.6, 128.5 (2 C), 127.8, 126.5 (2 C), 125.3, 101.4, 72.2, 9.3; MS (EI) m/z (rel intensity) 174 ([M]$^+$, 17), 131 (11), 117 (100), 104 (12); HRMS (EI) m/z calcd for C$_{12}$H$_{14}$O 174.1045, 174.1050. Characteristic $^1$H NMR data for ($E,E$)-1-53: $^1$H NMR δ 1.60 (dd, 3 H, J = 6.7, 1.6 Hz).

(E)-1-Iodohex-1-ene (1-54). To a solution of 1-hexyne (4.10 g, 49.9 mmol) in $n$-heptane (10 mL) at ambient temperature was added DIBAL-H (1.0 M solution in hexanes, 50.0 mL, 50.0 mmol) dropwise with the temperature not rising above 40 °C. The reaction mixture was heated at 50 °C for 2 h. The $n$-heptane and hexane were distilled off and the residue was dissolved in THF (20 mL) and cooled to -78 °C. A solution of I$_2$ (14.1 g, 54.9 mmol) in THF (25 mL) was added dropwise. The reaction mixture was warmed to ambient temperature after the addition, quenched with 10% HCl until gas evolution ceased, poured into a slurry of 10% HCl and ice and extracted with pentane (3 x 20 mL). The combined organic layers were washed with sat. Na$_2$S$_2$O$_3$, sat. NaHCO$_3$, dried (MgSO$_4$), filtered and concentrated. The residue was distilled to furnish vinyl iodide 1-54 (6.92 g, 33.0 mmol, 66%) as a light yellow oil: bp 56-58 °C (2 mmHg), (lit.$^{59}$ 50-52 °C, 3 mmHg); $^1$H NMR δ 6.50 (dt, 1 H, J = 14.1, 7.2 Hz), 5.97 (dt, 1 H, J = 14.3, 1.3 Hz), 2.06-2.01 (m, 2 H), 1.42-1.27 (m, 4 H), 0.89 (t, 3 H, J = 4.9 Hz).

1-((1(E)-3-((E)-Hex-1-enyloxy)prop-1-enyl)benzene (1-56). A suspension of cinnamyl alcohol (2.00 g, 14.9 mmol), vinyl iodide 1-54 (1.57 g, 7.46 mmol), Cs$_2$CO$_3$ (3.64 g, 11.2 mmol), CuI (142 mg, 0.750 mmol) and 3,4,7,8-tetramethyl-1,10-phenanthroline (353 mg, 1.49 mmol) in
toluene (5 mL) was heated, open to air, at 80 °C for 24 h. The mixture was cooled and filtered through a pad of SiO₂, eluting with Et₂O (15 mL). The filtrate was concentrated and chromatographed on SiO₂ (hexanes/EtOAc, 9:1) to give allylic vinyl ether 1-56 (270 mg, 1.25 mmol, 17%) as a light yellow oil which was a single geometric isomer (E,E): IR (neat) 3057, 3027, 2956, 2925, 2854, 1671, 1651, 1449, 1166, 965, 735 cm⁻¹; ¹H NMR δ 7.53-7.36 (m, 5 H), 6.76 (d, 1 H, J = 16.0 Hz), 6.46-6.38 (m, 2 H), 5.00 (dt, 1 H, J = 12.5, 7.4 Hz), 4.46 (dd, 2 H, J = 5.8, 1.0 Hz), 2.07-2.03 (m, 2 H), 1.49-1.44 (m, 4 H), 1.03 (t, 3 H, J = 5.3 Hz); ¹³C NMR δ 145.5, 136.5, 132.6, 128.4 (2 C), 127.7, 126.4 (2 C), 124.9, 105.1, 69.7, 32.8, 27.3, 22.0, 13.9; MS (EI) m/z (rel intensity) 216 ([M]+, 11), 160 (45), 131 (14), 117 (100), 91 (24), 65 (5); HRMS (EI) m/z calcd for C₁₅H₂₀O₂ 216.1514, found 216.1515.

\[
\text{(E,4R*,6S*)-4-Methyl-2,6-diphenylocta-2,7-dien-4-ol (1-57) and (E,4S*,6S*)-4-methyl-2,6-diphenylocta-2,7-dien-4-ol (1-58).} \]

According to the general protocol A, AlMe₃ (131 mg, 1.82 mmol), Cp₂ZrCl₂ (25.3 mg, 0.0868 mmol), H₂O (15.6 μL, 0.868 mmol), phenylacetylene (190 μL, 1.74 mmol) and vinyl ether 1-51 (151 mg, 0.868 mmol) afforded, after chromatography on SiO₂ (hexanes/EtOAc, 5:1), alcohols 1-57 and 1-58 (189 mg, 0.647 mmol, 75%) as a colorless oil which was an 3:2 mixture (diastereomers unassigned) of inseparable diastereomers as indicated by ¹³C NMR analysis. Mixture of diastereomers: IR (neat) 3565, 3446, 2927, 1599, 1493, 1377, 914, 755, 699 cm⁻¹; ¹H NMR δ 7.36-7.19 (m, 10 H), 6.21-6.02 (m, 1 H), 5.78 (dd, 1 H, J = 10.3, 1.1 Hz), 5.17-5.03 (m, 2 H), 3.72-3.62 (m, 1 H), 2.30-2.19 (m, 5 H), 1.43 (2 s, 3 H); ¹³C NMR δ 144.9 (2 C), 144.7, 143.8, 143.2, 136.9, 136.7, 134.7, 134.5, 128.8 (2 C), 128.7 (2 C), 128.1 (4 C), 127.8 (2 C), 127.5, 127.3, 127.0, 126.8, 126.6, 126.4, 124.9, 105.1, 69.7, 32.8, 27.3, 22.0, 13.9; MS (EI) m/z (rel intensity) 216 ([M]+, 11), 160 (45), 131 (14), 117 (100), 91 (24), 65 (5); HRMS (EI) m/z calcd for C₁₅H₂₀O₂ 216.1514, found 216.1515.
According to the general protocol A, AlMe3 (31.3 mg, 0.434 mmol), Cp2ZrCl2 (6.04 mg, 0.0207 mmol), H2O (3.91 μL, 0.217 mmol), phenylacetylene (45.4 μL, 0.414 mmol) and vinyl ether \( 1-53 \) (36.0 mg, 0.207 mmol) afforded, after chromatography on SiO2 (hexanes/EtOAc, 5:1), alcohols \( 1-59 \) and \( 1-60 \) (39.3 mg, 0.135 mmol, 65%) as a colorless oil which was a 10:1 mixture \( (1-59:1-60) \) of inseparable diastereomers as indicated by ¹H NMR analysis. \( 1-59 \): IR (neat) 3393, 2974, 1637, 1493, 1451, 977, 757, 700 cm⁻¹; ¹H NMR δ 7.44-7.22 (m, 10 H), 6.04 (dt, 1 H, \( J = 17.5, 9.5 \) Hz), 5.89 (dd, 1 H, \( J = 8.2, 1.1 \) Hz), 5.13 (dd, 1 H, \( J = 7.4, 1.7 \) Hz), 5.08 (s, 1 H), 4.31-4.28 (m, 1 H), 3.42 (app t, 1 H, \( J = 9.3 \) Hz), 2.03-1.95 (m, 1 H), 1.85 (d, 3 H, \( J = 1.1 \) Hz), 1.39 (br s, 1 H, exchanges with D2O), 1.10 (d, 3 H, \( J = 6.8 \) Hz); ¹³C NMR δ 143.9, 143.1, 140.2, 136.3, 130.3, 128.6 (2 C), 128.2 (2 C), 127.8 (2 C), 127.1, 126.3, 125.8 (2 C), 115.8, 69.6, 53.5, 43.8, 16.2, 11.1; MS (EI) m/z (rel intensity) 292 ([M]⁺, 13), 274 (9), 147 (100), 117 (39); HRMS (EI) m/z calcd for C₂₁H₂₄O₂ 292.1827, found 292.1825. Characteristic data for \( 1-60 \): 0.84 (d, 3 H, \( J = 6.9 \) Hz).
(E,5S*,6R*)-8-Methyl-5-((R*)-1-phenylallyl)dodec-7-en-6-ol (1-61) and (E,5S*,6S*)-8-methyl-5-((R*S*)-1-phenylallyl)dodec-7-en-6-ol (1-62a/b). According to general protocol A, AlMe₃ (79.1 mg, 1.10 mmol), Cp₂ZrCl₂ (15.3 mg, 0.0523 mmol), H₂O (9.42 μL, 0.523 mmol), 1-hexyne (120 μL, 1.05 mmol) and vinyl ether 1-56 (113 mg, 0.523 mmol) afforded alcohols 1-61 and 1-62 (147 mg, 0.468 mmol, 90%) as a colorless oil which was a 10:1:0.8 mixture (1-61:1-62a/b) of inseparable diastereomers as indicated by ¹H NMR analysis of derivative 1-78. 1-61: IR (neat) 3444, 3062, 3027, 2928, 2858, 1635, 1600, 1454, 994, 701 cm⁻¹; ¹H NMR δ 7.34-7.20 (m, 5 H), 6.21 (dt, 1 H, J = 17.0, 9.9 Hz), 5.39 (dd, 1 H, J = 8.6 1.2 Hz), 5.19-5.00 (m, 2 H), 4.65-4.61 (m, 1 H), 3.45 (t, 1 H, J = 4.2 Hz), 2.02 (m, 2 H), 1.90-1.83 (m, 1 H), 1.59 (d, 3 H, J = 1.2 Hz), 1.46-1.14 (m, 8 H), 0.94 (t, 3 H, J = 7.1 Hz), 0.78 (t, 3 H, J = 6.1 Hz); ¹³C NMR δ 143.8, 141.5, 138.0, 128.4 (2 C), 128.0 (2 C), 126.3, 126.1, 115.2, 69.4, 52.9, 48.9, 39.3, 30.9, 29.8, 27.0, 22.9, 22.3, 16.4, 13.9, 13.8; MS (EI) m/z (rel intensity) 296 ([M-H₂O]+, 14), 239 (9), 197 (21), 179 (100), 155 (17), 127 (88); HRMS (EI) m/z calcd for C₂₂H₃₂ [M-H₂O] 296.2504, found 296.2502. Characteristic data for 1-62a: ¹H NMR δ 6.06-5.91 (m, 1 H), 4.21-4.17 (m, 1 H), 1.63 (d, 3 H, J = 1.2 Hz). Characteristic data for 1-62b: ¹H NMR δ 4.44-4.39 (m, 1 H). Characteristic data for 1-62a/b: ¹³C NMR δ 141.2, 125.4, 52.1, 31.9, 27.8.

(E)-Ethyl 5-phenylpent-2-enoate (1-63). To a suspension of NaH (1.95 g, 81.3 mmol) in THF (200 mL) at 0 °C was added triethylphosphonoacetate (16.0 mL, 80.8 mmol) over 10 min and the mixture was warmed to ambient temperature. After 15 min, the solution was cooled to 0 °C, hydrocinnamaldehyde (10.32 g, 77.0 mmol) was added dropwise over 10 min, and the mixture was
warmed to ambient temperature. After 14 h, the solution was poured into H₂O (100 mL) and extracted with EtOAc (4 x 20 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered, concentrated and the residue was chromatographed on SiO₂ (hexanes/EtOAc, 17:3) to yield (E)-1-63 (10.5 g, 51.5 mmol, 72%) as a colorless oil: ¹H NMR δ 7.34-7.18 (m, 5 H), 7.04 (dt, 1 H, J = 15.6, 6.8 Hz), 5.88 (dt, 1 H, J = 15.7, 1.4 Hz), 4.20 (q, 2 H, J = 7.1 Hz), 2.78 (t, 2 H, J = 7.3 Hz), 2.56-2.49 (m, 2 H), 1.30 (t, 3 H, J = 7.1 Hz); ¹³C NMR δ 166.2, 147.7, 140.5, 128.2 (2 C), 128.1 (2 C), 125.9, 121.7, 59.8, 34.1, 33.6, 14.0.

(E)-5-Phenylpent-2-en-1-ol (1-64).¹¹⁴ To a flask containing DIBAL-H (1.0 M solution in hexanes, 54.0 mL, 53.9 mmol) at -78 °C was added a solution of ester 1-63 (5.00 g, 24.5 mmol) in CH₂Cl₂ (30 mL) over 30 min. The reaction mixture was stirred at -78 °C for 30 min, treated with 1 M HCl (10 mL), and warmed to ambient temperature, and the solid salts were filtered off. The filtrate was extracted with CH₂Cl₂ (2 x 25 mL) and the combined organic layers were washed with brine, dried (MgSO₄), filtered, and concentrated. The residue was chromatographed on SiO₂ (hexanes/EtOAc, 5:1) to yield allylic alcohol 1-64 (3.97 g, 24.5 mmol, 100%) as a colorless oil: ¹H NMR δ 7.34-7.20 (m, 5 H), 5.79-5.65 (m, 2 H), 4.08 (d, 2 H, J = 5.0 Hz), 2.74 (t, 2 H, J = 15.6 Hz), 2.45-2.37 (m, 2 H), 2.07-2.00 (m, 1 H, exchanges with D₂O); ¹³C NMR δ 141.6, 131.9, 129.5, 128.3 (2 C), 128.2 (2 C), 125.8, 63.4, 35.4, 33.9.
1-(\((E\)-5-(Vinyl oxy)pent-3-enyl\)benzene (1-65). A solution of allylic alcohol 1-64 (158 mg, 0.975 mmol) in ethyl vinyl ether (4 mL) at ambient temperature was treated with Hg(OAc)$_2$ (208 mg, 0.653 mmol) and stirred for 24 h. K$_2$CO$_3$ (500 mg) was added and the mixture was filtered through Al$_2$O$_3$, eluting with hexanes (5 mL). The filtrate was concentrated and the residue was chromatographed on SiO$_2$ (hexanes/EtOAc, 9:1) to yield allylic vinyl ether 1-65 (86.0 mg, 0.457 mmol, 47%) as a colorless oil: IR (neat) 3027, 2926, 2857, 1635, 1613, 1496, 1454, 1320, 1196, 1049, 970, 699 cm$^{-1}$; $^1$H NMR $\delta$ 7.37-7.24 (m, 5 H), 6.52 (dd, 1 H, $J=$ 14.3, 6.8 Hz), 5.90-5.83 (m, 1 H), 5.76-5.69 (m, 1 H), 4.28 (dd, 1 H, $J=$ 14.3, 2.0 Hz), 4.23 (d, 2 H, $J=$ 5.8 Hz), 4.09 (dd, 1 H, $J=$ 6.8, 2.0 Hz), 2.79 (t, 2 H, $J=$ 7.3 Hz), 2.50-2.43 (m, 2 H); $^{13}$C NMR $\delta$ 151.4, 141.5, 134.3, 128.3 (2 C), 128.2 (2 C), 125.8, 125.3, 86.9, 68.7, 35.3, 34.0; MS (EI) $m/z$ (rel intensity) 144 ([M-C$_2$H$_4$O]$^+$, 14), 129 (7), 91 (100); HRMS (EI) $m/z$ calcd for C$_{11}$H$_{12}$ [M- C$_2$H$_4$O] 144.0939, found 144.0932.

(2E)-3-((E)-5-Phenylpent-2-enyloxy)-N,N-dimethylacrylamide (1-67). To a suspension of NaH (42.4 mg, 1.77 mmol) in THF (1.5 mL) at ambient temperature was added alcohol 1-64 (220 mg, 1.36 mmol) as a solution in THF (2.5 mL). The reaction mixture was stirred for 45 min, treated with betaine 1-33 (247 mg, 1.90 mmol) in one portion and heated at reflux for 14 h. The cooled mixture was poured into H$_2$O (20 mL) and the aqueous layer was washed with Et$_2$O (2 x 5 mL) and then acidified to pH = 4 with 10% HCl (~15 drops). The mixture was extracted with Et$_2$O (3 x 5 mL) and the combined organic layers were washed with H$_2$O, brine, dried (Na$_2$SO$_4$) and concentrated. The unstable crude acid 1-66 was added to a solution of EDCI (202 mg, 1.05 mmol), DMAP (9.98 mg, 0.0810 mmol), and dimethylamine hydrochloride (165 mg, 2.03 mmol) in CH$_2$Cl$_2$
(8 mL) at ambient temperature. DIPEA (564 μL, 3.24 mmol) was added dropwise over 5 min and the reaction mixture was stirred for 24 h and quenched with H₂O (2 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL) and the combined organic layers were washed with brine, dried (Na₂SO₄), concentrated and chromatographed on SiO₂ (hexanes/EtOAc, 1:4) to yield amide 1-67 (126 mg, 0.485 mmol, 36% over two steps) as a yellow oil: IR (neat) 3026, 2926, 1652, 1594, 1496, 1454, 1396, 1115, 968, 700 cm⁻¹; ¹H NMR δ 7.51 (d, 1 H, J = 11.8 Hz), 7.29-7.14 (m, 5 H), 5.82 (dt, 1 H, J = 15.4, 6.6 Hz), 5.67-5.58 (m, 2 H), 4.31 (d, 2 H, J = 6.1 Hz), 2.97 (br s, 6 H), 2.69 (t, 2 H, J = 7.3 Hz), 2.39-2.34 (m, 2 H); ¹³C NMR δ 167.1, 160.5, 141.2, 135.4, 128.2 (4 C), 125.7, 124.4, 96.2, 72.0, 37.0, 35.2, 35.0, 33.8; MS (EI) m/z (rel intensity) 259 ([M]+, 48), 231 (80), 216 (50), 188 (9), 115 (12), 91 (100); HRMS (EI) m/z calcd for C₁₆H₂₁NO₂ 259.1572, found 259.1557.

(2E)-3-((E)-5-Phenylpent-2-enyloxy)prop-2-en-1-ol (1-69). To a solution of ethyl propiolate (2.51 g, 25.6 mmol) and allylic alcohol 1-64 (4.36 g, 26.9 mmol) in CH₂Cl₂ (250 mL) at 0 °C was added Et₃N (4.28 mL, 30.7 mmol) dropwise over 15 min. The reaction mixture was stirred at ambient temperature for 14 h and quenched with 10% HCl (50 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 25 mL) and the combined organic layers were washed with 10% HCl, brine and dried (MgSO₄). The solution was filtered, concentrated and the residue was chromatographed on SiO₂ (hexanes/EtOAc, 5:1) to furnish ester 1-68 (5.67 g, 21.8 mmol, 81%) as a colorless oil which contained ~15% of an unknown impurity. This mixture was carried directly into the next step without further purification. A solution of ester 1-68 (1.51 g, 5.81 mmol) in toluene (12 mL) was cooled to -78 °C and treated dropwise over 5 min with a solution of DIBAL-H (1.0 M solution in hexanes, 12.8 mL, 12.8 mmol). The reaction mixture was stirred for 2 h at -78 °C,
warmed to ambient temperature, and quenched with 1 M Rochelle’s Salt (10 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 10 mL) and the combined organic layers were washed with brine, dried (MgSO$_4$), concentrated, filtered and chromatographed on SiO$_2$ (Et$_2$O/hexanes, 3:1) to yield alcohol 1-69 (573 mg, 2.63 mmol, 45%) as a colorless oil: IR (neat) 3361, 3061, 2924, 2859, 1652, 1496, 1175, 997, 747 cm$^{-1}$; $^1$H NMR $\delta$ 7.35-7.20 (m, 5 H), 6.50 (d, 1 H, $J$ = 12.6 Hz), 5.83 (dt, 1 H, $J$ = 15.4, 6.5 Hz), 5.65 (dt, 1 H, $J$ = 15.4, 6.0 Hz), 5.07 (dt, 1 H, $J$ = 12.6, 7.4 Hz), 4.20 (dd, 2 H, $J$ = 5.9, 0.7 Hz), 4.04 (d, 2 H, $J$ = 7.3 Hz), 2.75 (t, 2 H, $J$ = 7.3 Hz), 2.46-2.38 (m, 2 H), 2.30 (br s, 1 H, exchanges with D$_2$O); $^{13}$C NMR $\delta$ 149.2, 141.3, 134.4, 128.2 (2 C), 128.1 (2 C), 125.7, 125.1, 103.1, 69.7, 60.1, 35.1, 33.8; MS (EI) m/z (rel intensity) 218 ([M$^+$]+, 1), 169 (8), 145 (69), 144 (100), 129 (49); HRMS (EI) m/z calcd for C$_{11}$H$_{12}$ [M-C$_3$H$_6$O$_2$] 144.0939, found 144.0934.

![Chemical Structure](image_url)

$(E,4R^*,6S^*)$-6-Phenethyl-2-phenylocta-2,7-dien-4-ol (1-70) and $(E,4S^*,6S^*)$-6-phenethyl-2-phenylocta-2,7-dien-4-ol (1-71). According to the general protocol A, AlMe$_3$ (169 mg, 2.34 mmol), Cp$_2$ZrCl$_2$ (31.0 mg, 0.106 mmol), H$_2$O (21.0 $\mu$L, 1.17 mmol), phenylacetylene (257 $\mu$L, 2.34 mmol) and vinyl ether 1-65 (200 mg, 1.06 mmol) afforded, after chromatography on SiO$_2$ (hexanes/EtOAc, 5:1), alcohols 1-70 and 1-71 (major: 153 mg, 0.500 mmol, 47%, $R_f$ = 0.31, minor: 102 mg, 0.333 mmol, 31%, $R_f$ = 0.21) as colorless oils (diastereomers unassigned): Major diastereomer: IR (neat) 3376, 2924, 1495, 1453, 1029, 998, 913, 757, 697 cm$^{-1}$; $^1$H NMR $\delta$ 7.42-7.15 (m, 10 H), 5.80 (dd, 1 H, $J$ = 8.5, 1.3 Hz), 5.68 (dt, 1 H, $J$ = 15.9, 9.0 Hz), 5.19 (s, 1 H), 5.14 (dd, 1 H, $J$ = 7.2, 2.0 Hz), 4.66-4.57 (m, 1 H), 2.7 (ddd, 1 H, $J$ = 13.7, 10.4, 5.4 Hz), 2.57 (dd, 1 H, $J$ = 13.7, 10.2, 6.5 Hz), 2.43-2.33 (m, 1 H), 2.07 (d, 3 H, $J$ = 1.3 Hz), 1.81-1.45 (m, 4 H); $^{13}$C NMR $\delta$
142.9, 142.6, 142.2, 136.3, 131.0, 128.4 (2 C), 128.3 (2 C), 128.2 (2 C), 127.2, 125.8 (2 C), 125.6,
115.8, 66.9, 42.7, 40.3, 37.3, 33.5, 16.2; MS (EI) m/z (rel intensity) 306 ([M]+, 15), 288 (37), 201
(33), 183 (23), 147 (77), 129 (63), 105 (89), 91 (100); HRMS (EI) m/z calcld for C$_{22}$H$_{26}$O 306.1984,
found 306.1976. Minor diastereomer: IR (neat) 3346, 3061, 2922, 1495, 1453, 1029, 997, 913, 758
cm$^{-1}$; $^1$H NMR $\delta$ 7.40-7.16 (m, 10 H), 5.77-5.65 (m, 2 H), 5.11 (dd, 1 H, $J = 10.2$, 1.9 Hz), 5.04 (dd,
1 H, $J = 17.3$, 1.9 Hz), 4.64-4.56 (m, 1 H), 2.67 (dd, 1 H, $J = 13.8$, 10.3, 5.5 Hz), 2.54 (dd, 1 H, $J$
= 14.0, 10.1, 6.4 Hz), 2.18-2.06 (m, 1 H), 2.08 (d, 3 H, $J = 1.3$ Hz), 1.84-1.50 (m, 4 H); $^{13}$C NMR $\delta$
143.0, 142.8, 142.5, 130.5, 128.4 (2 C), 128.3 (3 C), 128.2 (2 C), 127.3, 125.9 (2 C), 125.7, 115.4,
67.5, 43.1, 40.9, 37.1, 33.3, 16.5; MS (EI) m/z (rel intensity) 306 ([M]$^+$, 18), 288 (14), 201 (23), 147
(100), 129 (63), 105 (96), 91 (100); HRMS (EI) m/z calcld for C$_{22}$H$_{26}$O 306.1984, found 306.1979.

\[
\begin{align*}
\text{Ph} & \quad \text{OH} \\
\text{Ph} & \quad \text{OH} \\
\text{OH} & \quad \text{Ph} \\
\text{OH} & \quad \text{Ph}
\end{align*}
\]

\((E,2R^*,3S^*)\)-5-Phenyl-2-((R$^*$)-5-phenylpent-1-en-3-yl)hex-4-ene-1,3-diol (1-72) and
\((E,2R^*,3S^*)\)-5-Phenyl-2-((R$^*$S$^*$)-5-phenylpent-1-en-3-yl)hex-4-ene-1,3-diol (1-73a/b).

According to general protocol A, AlMe$_3$ (373 mg, 5.17 mmol), Cp$_2$ZrCl$_2$ (37.7 mg, 0.129 mmol),
H$_2$O (46.6 $\mu$L, 2.59 mmol), phenylacetylene (284 $\mu$L, 2.59 mmol) and alcohol 1-69 (282 mg, 1.29
mmol) afforded, after chromatography on SiO$_2$ (hexanes/EtOAc, 2:1), diols 1-72 and 1-73 (72.0 mg,
0.214 mmol, 17%) as a colorless oil which was a 10:0.8:0.5 mixture of inseparable diastereomers as
indicated by $^1$H NMR analysis. 1-72: IR (neat) 3334, 2922, 1495, 1445, 1030, 999, 758, 697 cm$^{-1}$;
$^1$H NMR $\delta$ 7.40-7.15 (m, 10 H), 5.95 (dd, 1 H, $J = 9.8$, 1.2 Hz), 5.80 (dt, 1 H, $J = 17.0$, 9.2 Hz),
5.25-5.14 (m, 2 H), 4.89-4.83 (m, 1 H), 4.06-3.99 (m, 1 H), 3.91-3.83 (m, 1 H), 2.89 (t, 1 H, $J = 5.6$ Hz, exchanges with D$_2$O), 2.76-2.67 (m, 1 H), 2.52-2.38 (m, 3 H, one hydrogen exchanges with D$_2$O), 2.03 (d, 3 H, $J = 1.3$ Hz), 1.98-1.87 (m, 1 H), 1.63-1.49 (m, 2 H); $^{13}$C NMR $\delta$ 142.7, 142.3, 140.8, 136.8, 129.9, 128.3 (4 C), 128.2, 127.3, 125.8, 125.7, 116.7, 62.0, 49.3, 42.4, 33.9, 32.5, 16.2; MS (EI) $m/z$ (rel intensity) 336 ([M]$^+$, 54), 318 (83), 300 (61), 183 (15), 147 (54), 105 (62), 91 (100); HRMS (EI) $m/z$ calcd for C$_{23}$H$_{28}$O$_2$ 336.2089, found 336.2085. Characteristic data for 1-73a: $^1$H NMR $\delta$ 2.11 (d, 3 H, $J = 1.1$ Hz). Characteristic data for 1-73b: $^1$H NMR $\delta$ 2.09 (d, 3 H, $J = 1.3$ Hz).

(E,2$S^*$,3$S^*$)-3-Hydroxy-$N,N$-dimethyl-5-phenyl-2-((($R^*$)-5-phenylpent-1-en-3-yl)hex-4-enamide (1-74) and (E,2$S^*$,3$R^*$)-3-hydroxy-$N,N$-dimethyl-5-phenyl-2-((($R^*$)$S^*$)-5-phenylpent-1-en-3-yl)hex-4-enamide (1-75a/b). According to the general protocol A, AlMe$_3$ (27.7 mg, 0.385 mmol), Cp$_2$ZrCl$_2$ (1.12 mg, 0.00385 mmol), H$_2$O (2.77 $\mu$L, 0.154 mmol), phenylacetylene (8.53 $\mu$L, 0.0769 mmol) and amide 1-67 (10.0 mg, 0.0385 mmol) furnished, after chromatography on SiO$_2$ (hexanes/EtOAc 1:2), amide alcohols 1-74 and 1-75a/b (5.0 mg, 0.0133 mmol, 34%) as a light yellow oil which was a 100:43:13 mixture of inseparable diastereomers as indicated by $^1$H NMR analysis. 1-74: IR (neat) 3395, 2926, 1620, 1495, 1399, 1143, 917, 760, 699 cm$^{-1}$; $^1$H NMR $\delta$ 7.42 (m, 10 H), 6.10 (d, 1 H, $J = 8.8$ Hz), 5.78-5.63 (m, 1 H), 5.23-5.14 (m, 2 H), 4.82 (br t, 1 H, $J = 7.0$ Hz), 4.75 (d, 1 H, $J = 2.8$ Hz, exchanges with D$_2$O), 3.09 (s, 3 H), 2.96 (s, 3 H), 2.78-2.59 (m, 2 H), 2.54-2.39 (m, 1 H), 2.07 (s, 3 H), 1.89-1.79 (m, 1 H), 1.70-1.64 (m, 1 H), 1.56-1.41 (m, 1 H); $^{13}$C NMR $\delta$ 173.2, 143.1, 142.4, 140.7, 137.8, 128.4 (2 C), 128.3 (2 C), 127.2, 125.8, 125.7, 117.4, 70.0,
50.8, 44.5, 38.2, 35.7, 34.0, 33.6, 16.4; MS (EI) m/z (rel intensity) 377 ([M]+, 52), 286 (36), 232 (77), 126 (99), 91 (77); HRMS (EI) m/z calcd for C_{24}H_{31}NO_{2} 377.2355, found 377.2372. Characteristic data for **1-75a**: 1H NMR δ 5.92 (d, 1 H, J = 8.7 Hz), 5.38 (m, 2 H), 2.99 (s, 3 H), 2.94 (s, 3 H). Characteristic data for **1-75b**: 1H NMR δ 3.04 (s, 3 H), 2.90 (s, 3 H). Characteristic data for **1-75a/b**: 13C NMR δ 175.0, 142.8, 142.2, 138.8, 135.4, 130.3, 127.5, 48.9, 16.1.

![PhOH](PhOH)

(E,2R*,3S*)-5-Phenyl-2-((R*)-1-phenylallyl)hex-4-ene-1,3-diol (1-76). According to the general protocol A, AlMe_{3} (790 mg, 11.0 mmol), Cp_{2}ZrCl_{2} (91.4 mg, 0.313 mmol), H_{2}O (84.6 μL, 4.70 mmol), phenylacetylene (687 μL, 6.26 mmol) and alcohol **1-40** (595 mg, 3.13 mmol) afforded, after chromatography on SiO_{2} (hexanes/EtOAc, 4:1), diol **1-76** (222 mg, 0.721 mmol, 23%) as a colorless oil which was a 95:5 mixture of inseparable diastereomers as indicated by 1H NMR analysis. **1-76**: IR (neat) 3342, 3028, 1493, 1032, 700 cm⁻¹; 1H NMR δ 7.43-7.19 (m, 10 H), 6.14 (ddd, 1 H, J = 17.0, 10.0, 9.2 Hz), 6.10-6.06 (m, 1 H), 5.27 (ddd, 1 H, J = 17.0, 1.6, 0.9 Hz), 5.18 (dd, 1 H, J = 10.1, 1.2 Hz), 5.02-4.96 (m, 1 H), 4.00 (ddd, 1 H, J = 11.3, 3.8, 2.4 Hz), 3.87 (app t, 1 H, J = 9.7 Hz), 3.46-3.38 (m, 1 H), 2.54 (d, 1 H, J = 5.2 Hz, exchanges with D_{2}O), 2.46 (dd, 1 H, J = 6.8, 3.9 Hz, exchanges with D_{2}O), 2.07 (d, 3 H, J = 1.3 Hz), 1.94-1.86 (m, 1 H); 13C NMR δ 142.7, 142.3, 140.3, 136.2, 130.2, 128.6 (2 C) 128.2 (2 C), 128.0 (2 C), 127.2, 126.4, 125.7 (2 C), 116.2, 70.6, 61.3, 48.9, 48.7, 16.2; MS (EI) m/z (rel intensity) 308 ([M]+, 6), 290 (17), 260 (49), 215 (70), 117 (100); HRMS (EI) m/z calcd for C_{21}H_{24}O_{2} 308.1776, found 308.1788.
To a solution of diol 1-76 (67.0 mg, 0.217 mmol) and Et₃N (70.7 μL, 0.500 mmol) in CH₂Cl₂ (2.2 mL) at ambient temperature was added p-bromobenzoyl chloride (143 mg, 0.652 mmol). The reaction mixture was stirred for 12 h and quenched with H₂O (1 mL). The aqueous layer was extracted with CH₂Cl₂ (4 x 3 mL) and the combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated. The residue was chromatographed on SiO₂ (hexanes/EtOAc, 3:1) to furnish the corresponding bis-ester (110 mg, 0.163 mmol, 75%) and the mono-acylated alcohol 77 (20.0 mg, 0.0407 mmol, 18%) as colorless solids of which only the mono-acylated product was characterized as a single diastereomer. Mp 114.0-116.0 °C (CDCl₃/MeOH); IR (neat) 3502, 2920, 2851, 1718, 1590, 1271, 1012, 757 cm⁻¹; ¹H NMR δ 7.67 (d, 2 H, J = 8.6 Hz), 7.39 (d, 2 H, J = 7.4 Hz), 7.31-7.25 (m, 10 H), 6.19 (dt, 1 H, J = 16.8, 9.9 Hz), 6.01 (dd, 1 H, J = 8.3, 1.3 Hz), 5.26 (d, 1 H, J = 16.9 Hz), 5.18 (dd, 1 H, J = 10.0, 1.5 Hz), 4.99-4.96 (m, 1 H), 4.38 (d of AB, 1 H, J = 11.6, 6.9 Hz), 4.30 (d of AB, 1 H, J = 11.6, 4.3 Hz), 3.66 (t, 1 H, J = 9.6 Hz), 2.50-2.42 (m, 1 H), 2.04 (d, 3 H, J = 1.2 Hz), 1.83 (br s, 1 H, exchanges with D₂O); ¹³C NMR δ 165.7, 142.6, 142.2, 140.2, 136.4, 131.6 (2 C), 131.0 (2 C), 129.8, 128.7 (2 C), 128.3 (2 C), 127.9 (2 C), 127.7, 127.3, 126.8, 125.7 (2 C), 116.4, 68.4, 63.5, 50.5, 47.9, 16.2; MS (EI) m/z (rel intensity) 490 ([M-H]⁺, 15), 386 (51), 272 (26), 183 (67), 117 (100); HRMS (EI) m/z calcd for C₂₈H₂₆BrO₃ [M-H] 490.1144, found 490.1166.
(2R*,3R*)-2-Methyl-3-phenylpent-4-enal (1-80). A solution of vinyl ether 1-53 (5.0 mg, 0.0287 mmol) in MeOH-d₄ (1 mL) was heated at 140 °C in a microwave (150 W) for 10 min. The solvent was evaporated and the residue was chromatographed on SiO₂ (hexanes/EtOAc, 15:1) to furnish aldehyde 1-80 (3.0 mg, 0.0172 mmol, 60%) as a colorless oil which was an inseparable 10:1 mixture of diastereomers as indicated by ¹H NMR analysis. 1-80: IR (neat) 3082, 3028, 2977, 2875, 1724, 1493, 1453, 994, 919, 702 cm⁻¹; ¹H NMR δ 9.55 (d, 1 H, J = 2.4 Hz), 7.35-7.29 (m, 2 H), 7.25-7.17 (m, 3 H), 6.03-5.91 (m, 1 H), 5.16 (d, 1 H, J = 0.7 Hz), 5.11-5.07 (m, 1 H), 3.59 (app t, 1 H, J = 8.7 Hz), 2.87-2.72 (m, 1 H), 1.13 (d, 3 H, J = 7.0 Hz); ¹³C NMR δ 204.2, 141.3, 138.0, 126.8 (2 C), 116.9, 51.4, 50.4, 11.9; MS (EI) m/z (rel intensity) 174 ([M]+, 7), 159 (7), 131 (7), 117 (100). Characteristic data for minor diastereomer: ¹H NMR δ 9.70 (d, 1 H, J = 2.9 Hz); ¹³C NMR δ 204.6, 140.7, 139.0, 128.0, 116.3, 12.5.

(1R*,4S*,5R*)-5-Butyl-4-phenylcyclopent-2-enol (1-83a) and (1S*,4R*,5S*,5R*)-5-butyl-4-phenylcyclopent-2-enol (1-83b/c). To a solution of allylic alcohol 1-61/1-62 (41.0 mg, 0.130 mmol) in CH₂Cl₂ (2 mL) at room temperature was added Grubbs’ second generation catalyst ((1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)-dichloro-(phenylmethylene)-(tricyclohexylphosphine ) ruthenium) (11.1 mg, 0.0130 mmol). The reaction mixture was stirred for 4 h, the volatiles were evaporated, then CH₂Cl₂ (2 mL) and activated charcoal (100 mg) were added. The suspension was stirred for 12 h and filtered through SiO₂ (eluting with hexanes/EtOAc, 1:1, 5 mL). The filtrate was
evaporated and chromatographed on SiO2 (hexanes/EtOAc, 9:1) to yield cyclopentene 1-83 (26.0 mg, 0.110 mmol, 87%) as a colorless oil which was a 10:1:0.8 mixture of inseparable diastereomers as indicated by 1H NMR analysis. **1-83a**: IR (neat) 3331, 3058, 2956, 2925, 2856, 1601, 1492, 1454, 1075, 700 cm⁻¹; 1H NMR δ 7.42-7.24 (m, 5 H), 5.94 (dt, 1 H, J = 5.6, 2.0 Hz), 5.87 (dt, 1 H, J = 5.6, 1.5 Hz), 4.61 (dd, 1 H, J = 5.2, 1.5 Hz), 3.41 (dd, 1 H, J = 6.3, 1.8 Hz), 1.94-1.86 (m, 1 H), 1.71-1.60 (m, 2 H), 1.49-1.19 (m, 4 H), 0.90 (t, 3 H, J = 7.0 Hz); 13C NMR δ 144.7, 136.6, 133.8, 128.4 (2 C), 127.6 (2 C), 126.4, 83.2, 59.0, 56.7, 32.9, 29.9, 23.0, 14.0; MS (EI) m/z (rel intensity) 216 ([M-H2O]+, 24), 198 (25), 173 (40), 159 (90), 155 (78), 115 (48), 91 (100); HRMS (EI) m/z calcd for C15H18 [M-H2O] 216.1514, found 216.1513. Characteristic data for **1-83b**: 1H NMR δ 4.82 (d, 1 H, J = 5.8 Hz), 3.58 (d, 1 H, J = 7.0 Hz). Characteristic data for **1-83c**: 1H NMR δ 4.72 (dd, 1 H, J = 5.0, 2.0 Hz).

![](Ph\)

**1-(Cyclopropyl(vinlyloxy)methyl)benzene (1-85).** A solution of cyclopropyl alcohol 1-84 (1.00 g, 6.75 mmol) in ethyl vinyl ether (14 mL) at ambient temperature was treated with Hg(OAc)₂ (1.44 g, 4.52 mmol) and heated at reflux for 4 h. K₂CO₃ (1 g) was added and the mixture was filtered through Al₂O₃, eluting with hexanes (20 mL). The filtrate was concentrated and the residue was purified by chromatography on SiO₂ (hexanes/EtOAc/Et₃N, 95:4:1) to yield cyclopropyl vinyl ether 1-85 (1.11 g, 6.45 mmol, 96%) as a colorless oil: IR (neat) 3083, 3008, 1636, 1615, 1492, 1453, 1186, 1023, 865, 700 cm⁻¹; 1H NMR δ 7.43-7.32 (m, 5 H), 6.39 (dd, 1 H, J = 14.1, 6.6 Hz), 4.31 (dd, 1 H, J =14.1, 1.8 Hz), 4.25 (d, 1 H, J = 7.7 Hz), 4.02 (dd, 1 H, J = 6.6, 1.6 Hz), 1.37-1.26 (m, 1 H), 0.76-0.67 (m, 1 H), 0.60-0.53 (m, 2 H), 0.47-0.39 (m, 1 H); 13C NMR δ 150.7, 141.0,
128.3 (2 C), 127.6, 126.3 (2 C), 89.3, 85.1, 17.5, 3.8, 2.3; MS (EI) m/z (rel intensity) 174 ([M]+, 21), 156 (26), 131 (100), 115 (32); HRMS (EI) m/z calcd for C_{12}H_{14}O 174.1045, found 174.1038.

(E)-1-Cyclopropyl-5-methyl-1-phenyloct-4-en-3-ol (1-88). According to the general protocol A, AlMe₃ (288 mg, 4.00 mmol), Cp₂ZrCl₂ (29.2 mg, 0.100 mmol), H₂O (36.0 μL, 2.00 mmol), 1-pentyne (197 μL, 2.00 mmol) and cyclopropyl vinyl ether 1-85 (174 mg, 1.00 mmol) afforded, after chromatography on SiO₂ (hexanes/EtOAc, 5:1), alcohol 1-88 (136 mg, 0.527 mmol, 53%) as a colorless oily a 1:1 mixture of inseparable diastereomers as indicated by ¹H NMR analysis: (1:1 mixture of diastereomers) IR (neat) 3363, 3076, 2958, 2930, 2871, 1494, 1453, 1380, 1017, 742, 700 cm⁻¹; ¹H NMR δ 7.34-7.16 (m, 5 H), 5.18 (dd, 0.5 H, J = 8.5, 1.2 Hz), 5.13 (dd, 0.5 H, J = 9.0, 1.1 Hz), 4.31 (ddd, 0.5 H, J = 7.8, 6.5, 6.5 Hz), 4.25-4.16 (m, 0.5 H), 2.21-1.79 (m, 5 H), 1.48 (d, 1.5 H, J = 1.2 Hz), 1.47 (d, 1.5 H, J = 1.2 Hz), 1.45-1.33 (m, 2 H), 1.05-0.95 (m, 2 H), 0.89 (t, 1.5 H, J = 7.3 Hz), 0.86 (t, 1.5 H, J = 7.2 Hz), 0.65-0.54 (m, 1 H), 0.41-0.30 (m, 1 H), 0.29-0.19 (m, 1 H), 0.14-0.05 (m, 1 H); ¹³C NMR δ 145.5, 145.4, 139.3, 138.1, 128.3 (2 C), 127.6 (4 C), 126.1 (2 C), 66.7, 66.5, 47.4, 47.3, 44.6, 44.4, 41.7, 41.5, 20.8, 20.7, 17.9 (2 C), 16.4, 16.3, 13.7 (2 C), 5.5, 5.4, 4.0, 3.6; MS (EI) m/z (rel intensity) 258 ([M]+, 8), 240 (28), 215 (97), 131 (100), 113 (18); HRMS (EI) m/z calcd for C_{18}H_{26}O 258.1984, found 258.1971.
5.2 AZA-COPE REARRANGEMENTS AND N-ACYL IMINİUM ION CHEMISTRY

1-(But-3-ynyl)pyrrolidine-2,5-dione (2-10).\(^{145}\) To a solution of succinimide (2.17 g, 31.0 mmol), DEAD (3.47 mL, 31.0 mmol) and PPh\(_3\) (5.76 g, 31.0 mmol) in THF (31 mL) was added 3-butyn-1-ol (1.65 mL, 32.6 mmol) at 0 °C. The reaction mixture was warmed to ambient temperature and stirred for 36 h. The solvent was evaporated in vacuo, the residue was suspended in hexanes/EtOAc (1:1, 10 mL) and the mixture was filtered. The filtrate was allowed to stand for 12 h, filtered, dried (MgSO\(_4\)), and concentrated. The residue was chromatographed on SiO\(_2\) (hexanes/EtOAc, 1:5) to furnish imide 2-10 (1.37 g, 9.07 mmol, 42%) as a colorless oil: IR (neat) 3273, 2948, 1775, 1699, 1435, 1404, 1166, 1077, 821 cm\(^{-1}\); \(^1\)H NMR \(\delta\) 3.53 (t, 2 H, J = 7.1 Hz), 2.60 (s, 4 H), 2.36 (td, 2 H, J = 7.1, 2.7 Hz), 1.88 (t, 1 H, J = 2.5 Hz).

1-(But-3-ynyl)-5-methoxypyrrolidin-2-one (2-11). To a 0 °C solution of imide 90 (1.49 g, 9.87 mmol) in MeOH (20 mL) was added NaBH\(_4\) (375 mg, 9.87 mmol) in one portion. The reaction mixture was stirred for 1 h, the solvent was evaporated and the residue was partitioned between H\(_2\)O (10 mL) and CH\(_2\)Cl\(_2\) (10 mL). The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 10 mL), and the combined organic layers were washed with H\(_2\)O, brine, dried (Na\(_2\)SO\(_4\)), filtered and evaporated. The
residue was chromatographed on SiO₂ (EtOAc containing 1% Et₃N) to furnish the corresponding hydroxy lactam (920 mg, 6.01 mmol, 61%) as a colorless oil which was used directly in the next step. The reaction was repeated to generate material with identical results. A solution of the hydroxylactam (1.50 g, 9.87 mmol) in MeOH (90 mL) at ambient temperature was treated with TsOH (187 mg, 0.987 mmol) in one portion. The reaction mixture was stirred for 8 h and the MeOH was evaporated in vacuo. The residue was chromatographed on SiO₂ (EtOAc containing 1% Et₃N) to furnish methoxy lactam 2-11 (1.19 g, 7.13 mmol, 45% over two steps) as a colorless oil: IR (neat) 3249, 2118, 1697, 1420, 1171, 1076, 884 cm⁻¹; ¹H NMR δ 5.08 (dd, 1 H, J = 6.2, 1.4 Hz), 3.64 (ddd, 1 H, J = 13.4, 7.4, 5.7 Hz), 3.37-3.28 (m, 1 H), 3.28 (s, 3 H), 2.57-2.28 (m, 5 H), 2.23-2.10 (m, 1 H), 1.98 (t, 1 H, J = 2.4 Hz); ¹³C NMR δ 175.1, 90.6, 81.6, 69.7, 53.0, 39.4, 28.8, 23.9, 18.0; MS (EI) m/z (rel intensity) 167 ([M]+, 11), 151 (19), 135 (29), 96 (100); HRMS (EI) m/z calcd for C₉H₁₃NO₂ 167.0946, found 167.0946.

1-(But-3-ynyl)-5-methylpyrrolidin-2-one (2-12). Characteristic data: ¹H NMR δ 1.26 (d, 3 H, J = 7.4 Hz).

1-(Pent-4-yn-2-yl)pyrrolidine-2,5-dione (2-14). To a solution of succinimide (2.20 g, 22.2 mmol), 2-13 (2.20 mL, 22.2 mmol), and PPh₃ (5.83 g, 22.2 mmol) in THF (200 mL) at 0 °C was
added DEAD (3.52 mL, 22.2 mmol) dropwise over 10 min. The reaction mixture was stirred for 36 h, the solvent was removed in vacuo and the residue was dissolved in hexanes/EtOAc 1:1, 20 mL). The solids were filtered off the filtrate was evaporated. The residue was chromatographed on SiO2 (hexanes/EtOAc, 1:3) to furnish imide 2-14 (1.19 g, 7.21 mmol, 32%) as a colorless oil: IR (neat) 3276, 2984, 2942, 1773, 1693, 1371, 1183 cm\(^{-1}\); \(^1\)H NMR \(\delta\) 4.34-4.22 (m, 1 H), 2.74 (ddd, 1 H, \(J = 16.7, 9.2, 2.5\) Hz), 2.57 (s, 3 H), 2.46 (ddd, 1 H, \(J = 16.8, 6.6, 2.6\) Hz), 1.86 (t, 1 H, \(J = 2.6\) Hz), 1.29 (d, 3 H, \(J = 7.0\) Hz); \(^{13}\)C NMR \(\delta\) 176.9 (2 C), 80.3, 69.8, 46.5, 27.7 (2 C), 22.3, 16.8; MS (EI) \textit{m/z} 165 ([M\(^+\)], 15), 150 (14), 126 (100), 100 (48); HRMS (EI) \textit{m/z} calcd for C\(_9\)H\(_{11}\)NO\(_2\) 165.0790, found 165.0788.

\[\text{N} \quad \text{O} \quad \text{OMe} \]

\[\text{5-Methoxy-1-(pent-4-yn-2-yl)pyrrolidin-2-one (2-15).} \]

To a 0 °C solution of imide 2-14 (759 mg, 4.60 mmol) in MeOH (10 mL) was added NaBH\(_4\) (511 mg, 13.8 mmol) in one portion. The reaction mixture was stirred for 3 h and the solvent was removed in vacuo. The residue was partitioned between CH\(_2\)Cl\(_2\) (5 mL) and H\(_2\)O (5 mL) and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (5 x 5 mL). The combined organic layers were washed with brine, dried (MgSO\(_4\)) filtered and concentrated. The resulting crude hydroxylactam was immediately dissolved in MeOH (2 mL) and PPTS (49.3 mg, 0.196 mmol) was added. The mixture was stirred for 24 h at ambient temperature and the MeOH was removed in vacuo. The residue was partitioned between CH\(_2\)Cl\(_2\) (5 mL) and H\(_2\)O (5 mL) and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (4 x 5 mL). The combined organic layers were washed with brine, dried (Na\(_2\)SO\(_4\)), evaporated and the residue was chromatographed on SiO\(_2\) (hexanes/EtOAc, 1:1) to yield methoxylactam 2-15 (200 mg, 1.10 mmol,
As a colorless oil which was a 1:1 mixture of inseparable diastereomers as indicated by $^1$H NMR: IR (neat) 3251, 2980, 2829, 1697, 1418, 1376, 1075 cm$^{-1}$; $^1$H NMR $\delta$ 5.10 (dd, 0.5 H, $J = 5.7, 1.2$ Hz), 4.97 (dd, 0.5 H, $J = 5.9, 1.4$ Hz), 4.27-4.03 (m, 1 H), 3.27 (s, 1.5 H), 3.26 (s, 1.5 H), 2.71 (ddd, 0.5 H, $J = 16.6, 6.5, 2.7$ Hz), 2.62-2.25 (m, 4 H), 2.10-1.94 (m, 3.5 H), 1.37 (d, 1.5 H, $J = 6.9$ Hz), 1.33 (d, 1.5 H, $J = 6.9$ Hz); $^{13}$C NMR $\delta$ 175.0, 174.7, 89.7, 88.9, 81.6, 80.6, 70.1, 69.5, 52.3, 47.5, 46.7, 29.1, 28.9, 24.6, 23.9, 23.8, 23.6, 18.3, 16.6; MS (EI) $m/z$ (rel intensity) 181 ($[M]^+$, 15), 166 (10), 149 (32), 110 (100); HRMS (EI) $m/z$ calcd for C$_{10}$H$_{15}$NO$_2$ 181.1103, found 181.1108.

**2-(Pent-4-yn-2-yl)isoindoline-1,3-dione (2-16).** To a solution of phthalimide (3.24 g, 22.0 mmol), 2-13 (2.17 mL, 22.0 mmol), and PPh$_3$ (5.77 g, 22.0 mmol) in THF (50 mL) was added DIAD (4.33 mL, 22.0 mmol) at 0 °C. The reaction mixture was warmed to ambient temperature and stirred for 48 h. The solvent was removed in vacuo and the residue was dissolved in hexanes/EtOAc (1:1, 40 mL). The solids were filtered off and the filtrate was concentrated and chromatographed on SiO$_2$ (hexanes/EtOAc, 3:1) to yield imide 2-16 (939 mg, 4.41 mmol, 20%) as a white solid: Mp 97.3-99.9 °C (hexanes/EtOAc); IR (neat) 3281, 2923, 2120, 1773, 1706, 1467, 1360, 1025, 794, 719 cm$^{-1}$; $^1$H NMR $\delta$ 7.85-7.81 (m, 2 H), 7.75-7.70 (m, 2 H), 4.62-4.55 (m, 1 H), 2.95 (dd, 1 H, $J = 16.6, 2.4$ Hz), 2.70 (dd, 1 H, $J = 16.9, 2.5$ Hz), 1.91 (t, 1 H, $J = 2.3$ Hz), 1.54 (d, 3 H, $J = 7.2$ Hz); $^{13}$C NMR $\delta$ 168.2 (2 C), 133.9 (2 C), 131.8 (2 C), 123.2 (2 C), 80.7, 70.1, 46.4, 23.7, 18.0; MS (EI) $m/z$ (rel
intensity) 213 ([M]$^+$, 12), 198 (40), 174 (100), 147 (21), 130 (30), 102 (14); HRMS (EI) m/z calcd for C$_{13}$H$_{11}$NO$_2$ 213.0790, found 213.0783.

3-Hydroxy-2-(pent-4-yn-2-yl)isoindolin-1-one (2-17). To a solution of imide 2-16 (245 mg, 1.15 mmol) in MeOH (4 mL) at ambient temperature was added NaBH$_4$ (46.0 mg, 1.15 mmol) portionwise. The reaction mixture was stirred for 3 h, treated with H$_2$O (1 mL) and extracted with CH$_2$Cl$_2$ (5 x 5 mL). The organic layers were washed with brine, dried (MgSO$_4$), concentrated and the residue was chromatographed on SiO$_2$ (hexanes/EtOAc, 1:1) to yield hydroxylactam 2-17 (167 mg, 0.777 mmol, 68%) as a white solid which was a 1:1 inseparable mixture of diastereomers as indicated by $^1$H NMR: Mp 95.0-95.5 °C (hexanes/EtOAc); IR (KBr) 3297, 1674, 1415, 1362, 1053, 747, 697 cm$^{-1}$; $^1$H NMR $\delta$ 7.67-7.63 (m, 1 H), 7.55-7.43 (m, 3 H), 5.97 (d, 0.5 H, J = 9.3 Hz), 5.93 (d, 0.5 H, J = 9.0), 4.44-4.23 (m, 1 H), 3.54 (d, 0.5 H, J = 10.9 Hz), 3.40 (d, 0.5 H, J = 11.3 Hz), 2.86-2.75 (m, 1 H), 2.67-2.57 (m, 1 H), 1.99 (t, 0.5 H, J = 2.7 Hz), 1.96 (t, 0.5 H, J = 2.7 Hz), 1.49 (d, 1.5 H, J = 3.5 Hz), 1.47 (d, 1.5 H, J = 3.5 Hz); $^{13}$C NMR $\delta$ 167.3, 167.2, 143.9, 143.8, 132.2 (2 C), 131.7, 131.6, 129.8 (2 C), 123.3, 123.2, 81.9, 81.7 (2 C), 81.6, 70.5, 70.3, 47.6, 47.2, 25.2, 24.0, 19.1, 17.8; MS (rel intensity) (EI) m/z 176 ([M-C$_3$H$_3$]$^+$, 92), 133 (100), 105 (18); HRMS (EI) m/z calcd for C$_{10}$H$_{10}$NO$_2$ [M-C$_3$H$_3$] 176.0712, found 176.0711.
3-Methoxy-2-(pent-4-yn-2-yl)isoindolin-1-one (2-18). To a solution of hydroxylactam 2-17 (620 mg, 2.88 mmol) in MeOH (5 mL) was added d,l-camphorsulfonic acid (116 mg, 0.288 mmol) in one portion. The reaction mixture was stirred at ambient temperature for 30 h and concentrated. The residue was dissolved in CH$_2$Cl$_2$ (10 mL) and washed with H$_2$O (5 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (4 x 15 mL) and the combined organic layers were washed with brine, dried (MgSO$_4$), and concentrated. The residue was chromatographed on SiO$_2$ (hexanes/EtOAc, 5:1) to yield methoxy lactam 2-18 (502 mg, 2.19 mmol, 76%) as a white solid which was a 1:1 mixture of inseparable diastereomers as indicated by $^1$H NMR: Mp 85.4-88.8 °C; IR (KBr) 3295, 2978, 2937, 2118, 1701, 1615, 1401, 1210, 1068, 748 cm$^{-1}$; $^1$H NMR $\delta$ 7.82-7.79 (m, 1 H), 7.60-7.47 (m, 3 H), 6.13 (s, 0.5 H), 6.02 (s, 0.5 H), 4.48-4.41 (app s, 0.5 H, $J$ = 7.2 Hz), 4.35-4.24 (app s, 0.5 H, $J$ = 7.2 Hz), 2.94 (s, 1.5 H), 2.90 (s, 1.5 H), 2.85 (ddd, 0.5 H, $J$ = 16.5, 7.7, 2.7 Hz), 2.71 (d, 0.5 H, $J$ = 2.6 Hz), 2.69 (d, 0.5 H, $J$ = 2.6 Hz), 2.53 (ddd, 0.5 H, $J$ = 16.6, 7.3, 2.7 Hz), 1.96 (t, 0.5 H, $J$ = 2.7 Hz), 1.94 (t, 0.5 H, $J$ = 2.7 Hz), 1.52 (d, 1.5 H, $J$ = 6.9 Hz), 1.45 (d, 1.5 H, $J$ = 6.9 Hz); $^{13}$C NMR $\delta$ 167.9, 167.7, 140.5, 140.2, 133.1, 132.8, 132.0 (2 C), 129.8 (2 C), 123.5, 123.2, 86.8, 86.0, 81.7, 81.0, 70.5, 69.9, 49.5, 49.0, 47.9, 47.2, 24.4, 24.0, 18.3, 17.7; MS (EI) m/z (rel intensity) 190 ([M-C$_2$H$_3$]$^+$, 11), 183 (17), 147 (45), 105 (64), 91 (100); HRMS (EI) m/z caled for C$_{12}$H$_{12}$NO$_2$ [M-C$_2$H$_3$] 190.0868, found 190.0866.

\[ \text{OMe} \]

3-Methoxy-2-(4-methylpent-4-en-2-yl)isoindolin-1-one (2-19). Characteristic data for 1:1 mixture of diastereomers: $^1$H NMR $\delta$ 4.78 (br s, 2 H), 4.71 (br s, 2 H), 1.81 (s, 3 H), 1.75 (s, 3 H).
1-Oxo-2-(pent-4-yn-2-yl)isoindolin-3-yl acetate (2-20). To a solution of hydroxylactam 2-17 (75.0 mg, 0.349 mmol) in pyridine (2 mL) at ambient temperature was added acetic anhydride (164 μL, 1.74 mmol) dropwise. The reaction mixture was stirred for 18 h, concentrated in vacuo, and the residue was dissolved in CH$_2$Cl$_2$ (10 mL) and washed with 10% HCl, brine and dried (MgSO$_4$). The solution was filtered, concentrated and the residue was chromatographed on SiO$_2$ (hexanes/EtOAc, 3:1) to furnish acetoxy lactam 2-20 (75.0 mg, 0.292 mmol, 84%) as a colorless oil which was a 1.5:1 mixture of inseparable diastereomers as indicated by $^1$H NMR analysis: IR (neat) 3294, 2926, 2119, 1740, 1712, 1402, 1229, 1013, 756 cm$^{-1}$; $^1$H NMR $\delta$ 7.82-7.76 (m, 1 H), 7.56-7.51 (m, 3 H), 7.24 (s, 0.5 H), 7.12 (s, 0.5 H), 4.48-4.39 (m, 0.5 H), 4.37-4.27 (m, 0.5 H), 2.81 (ddd, 0.5 H, $J$ = 16.7, 7.0, 2.7 Hz), 2.66 (dd, 1 H, $J$ = 6.9, 2.6 Hz), 2.51 (ddd, 0.5 H, $J$ = 16.7, 7.4, 2.6 Hz), 2.16 (s, 1.5 H), 2.14 (s, 1.5 H), 2.00 (t, 0.5 H, $J$ = 2.6 Hz), 1.97 (t, 0.5 H, $J$ = 2.6 Hz), 1.48 (d, 1.5 H, $J$ = 7.0 Hz), 1.43 (d, 1.5 H, $J$ = 7.0 Hz); $^{13}$C NMR $\delta$ 170.2 (2 C), 168.0, 167.8, 141.4, 141.3, 132.5 (2 C), 132.0, 131.8, 130.2 (2 C), 123.9, 123.7, 123.5 (2 C), 81.6, 81.1, 81.0, 80.5, 70.8, 70.3, 47.9, 47.3, 24.9, 24.2, 21.3 (2 C), 18.4, 17.6; MS (EI) $m/z$ (rel intensity) 257 ([M]$^+$, 12), 218 (62), 198 (20), 132 (100), 105 (19); HRMS (EI) $m/z$ calcd for C$_{15}$H$_{15}$NO$_3$ 257.1052, found 257.1050.
3-Methyl-2-(pent-4-yn-2-yl)isoindolin-1-one (2-21). Characteristic data for 1:1 mixture of diastereomers: $^1$H NMR $\delta$ 4.67 (q, 1 H, $J = 6.6$ Hz), 4.66 (q, 1 H, $J = 6.7$ Hz), 1.54 (d, 3 H, $J = 6.7$ Hz), 1.48 (d, 3 H, $J = 6.9$ Hz).

2-(Pent-4-ynyl)isoindoline-1,3-dione (2-23). To a solution of phthalimide (2.00 g, 13.6 mmol), 2-22 (1.27 mL, 13.6 mmol), and PPh$_3$ (3.57 g, 13.6 mmol) in THF (30 mL) was added DIAD (2.68 mL, 13.6 mmol) at 0 °C. The reaction mixture was warmed to ambient temperature and stirred for 36 h and the solvent was removed $\textit{in vacuo}$. The residue was dissolved in hexanes/EtOAc (1:1, 20 mL) and the solids were filtered off. The filtrate was concentrated and chromatographed on SiO$_2$ (hexanes/EtOAc, 4:1) to yield imide 2-23 (2.35 g, 11.0 mmol, 81%) as a white powder: Mp 89.9-91.7 °C (hexanes/EtOAc); IR 3268, 2942, 2115, 1772, 1708, 1399, 1122, 1018, 885, 722 cm$^{-1}$; $^1$H NMR $\delta$ 7.74-7.70 (m, 2 H), 7.65-7.60 (m, 2 H), 3.69 (t, 2 H, $J = 2.0$ Hz), 2.17 (td, 2 H, $J = 7.1$, 2.6 Hz), 1.88-1.78 (m, 3 H); $^{13}$C NMR $\delta$ 168.0 (2 C), 133.6 (2 C), 131.8 (2 C), 122.9 (2 C), 82.8, 68.9, 36.9, 27.0, 16.0; MS (EI) m/z (rel intensity) 213 ([M$^+$], 18), 212 (23), 185 (25), 160 (100), 148 (28), 130 (28); HRMS (EI) m/z calcd for C$_{13}$H$_{11}$NO$_2$ 212.0712, found 212.0708.
3-Methoxy-2-(pent-4-ynyl)isoindolin-1-one (2-24). To a solution of imide 2-23 (323 mg, 1.52 mmol) in MeOH (4 mL) at 0 °C was added NaBH₄ (45.5 mg, 1.14 mmol) in one portion. The reaction mixture was stirred for 30 min at 0 °C and at ambient temperature for 3 h, and quenched with H₂O (1 mL). The aqueous layer was extracted with CH₂Cl₂ (5 x 10 mL). The combined organic layers were washed with brine, dried (MgSO₄), and concentrated to furnish the crude hydroxylactam (323 mg, 1.50 mmol, 99%) which was used in the next step without further purification. To a solution of the crude hydroxylactam (323 mg, 1.50 mmol) in MeOH (5 mL) at ambient temperature was added d,l-camphorsulfonic acid (35.0 mg, 0.150 mmol). The reaction mixture was stirred for 48 h. The solvent was removed in vacuo and the residue was partitioned between CH₂Cl₂ (10 mL) and H₂O (10 mL). The aqueous layer was extracted with CH₂Cl₂ (5 x 10 mL) and the combined organic layers were washed with brine, dried (MgSO₄), and concentrated to furnish methoxy lactam 2-24 (315 mg, 1.38 mmol, 91% over two steps) as a colorless oil: IR (neat) 3294, 2935, 2116, 1705, 1413, 1373, 747, 696 cm⁻¹; ¹H NMR δ 7.77 (dd, 1 H, J = 6.9, 0.8 Hz), 7.57-7.44 (m, 3 H), 5.85 (s, 1 H), 3.79 (dd, 1 H, J = 14.5, 7.5, 7.5 Hz), 3.34 (ddd, 1 H, J = 14.1, 7.3, 7.3 Hz), 2.84 (s, 3 H), 2.23 (br t, 2 H, J = 7.1 Hz), 1.93-1.82 (m, 3 H); ¹³C NMR δ 167.6, 140.2, 132.9, 131.9, 129.8, 123.3 (2 C), 86.3, 83.0, 68.9, 49.1, 38.6, 26.7, 16.1; MS (EI) m/z (rel intensity) 228 ([M]+, 28), 214 (70), 198 (70), 170 (91), 146 (100), 132 (47); HRMS (EI) m/z calcd for C₁₄H₁₅NO₂ 228.1025, found 228.1025.
3-Methoxy-2-(4-methylpent-4-enyl)isoindolin-1-one (2-25). Characteristic data: $^1$H NMR $\delta$ 4.72 (br d, 2 H, $J = 8.0$ Hz), 1.72 (s, 3 H).

3-Hydroxy-3-methyl-2-(pent-4-ynyl)isoindolin-1-one (2-26). To a solution of imide 2-23 (100 mg, 0.469 mmol) in THF (5 mL) at -78 °C was added MeMgBr (3.0 M solution in ether, 187 $\mu$L, 0.563 mmol) dropwise over 3 min. The red reaction mixture was stirred at -78 °C for 1 h and was quenched with sat. NH$_4$Cl (2 mL). The THF was removed in vacuo and the residue was extracted with CH$_2$Cl$_2$ (4 x 5 mL). The combined organic layers were washed with brine, dried (Na$_2$SO$_4$), and concentrated to provide hydroxylactam 2-26 (108 mg, 0.469 mmol, 100%) as a light yellow oil which was used without further purification: IR (neat) 3296, 2982, 2936, 2116, 1681, 1409, 1141, 1080, 698 cm$^{-1}$; $^1$H NMR $\delta$ 7.52-7.50 (m, 2 H), 7.48-7.46 (m, 1 H), 7.41-7.33 (m, 1 H), 4.10 (s, 1 H, exchanges with D$_2$O), 3.46 (ddd, 1 H, $J = 14.9, 9.4, 5.8$ Hz), 3.12 (ddd, 1 H, $J = 15.2, 9.3, 6.0$ Hz), 2.22-2.16 (m, 2 H), 1.94 (t, 1 H, $J = 2.6$ Hz), 1.91-1.82 (m, 1 H), 1.80-1.70 (m, 1 H), 1.66 (s, 3 H); $^{13}$C NMR $\delta$ 167.2, 148.2, 132.2, 130.2, 129.3, 123.1, 121.5, 88.7, 83.7, 68.9, 37.7, 27.7, 24.3, 16.4; MS (EI) $m/z$ (rel intensity) 228 ([M-H]$^+$, 7), 214 (15), 186 (75), 160 (35), 147 (100), 130 (18); HRMS (EI) $m/z$ calcd for C$_{14}$H$_{15}$NO$_2$ 229.1103, found 229.1106.
3-Hydroxy-3-methyl-2-(4-methylpent-4-enyl)isoindolin-1-one (2-27). Characteristic data:

\[ ^1 \text{H NMR} \delta \ 4.70 \ (\text{br d, } 2 \text{ H, } J = 8.2 \text{ Hz}), 1.83 \ (\text{s, } 3 \text{ H}). \]

Hept-6-yn-1-ol (2-29). \[ ^{146} \] Li wire (483 mg, 69.6 mmol) was degreased with hexanes and pumped to dryness under vacuum. Diaminopropane (34.8 mL, 41.7 mmol) was added and the reaction mixture was stirred at 70 °C for 2 h, cooled to room temperature and treated with solid KOTBu (4.33 g, 42.9 mmol). The yellow solution was stirred for 20 min, treated with hept-3-yn-1-ol (1.36 mL, 10.7 mmol) and stirred for 2 h before being poured into H2O (150 mL). After addition of CH2Cl2 (20 mL), the aqueous layer was extracted with CH2Cl2 (5 × 10 mL) and the combined organic extracts were washed with brine and dried (MgSO4). After filtration and evaporation, the residue was distilled to furnish alcohol 2-29 (1.02 g, 9.12 mmol, 85%) as a colorless oil: Bp 96 °C (0.1 mmHg); \[ ^1 \text{H NMR} \delta \ 3.65 \ (t, 2 \text{ H, } J = 5.6 \text{ Hz}), 2.23-2.18 \ (\text{m, } 2 \text{ H}), 1.94 \ (t, 1 \text{ H, } J = 2.6 \text{ Hz}), 1.63-1.54 \ (\text{m, } 6 \text{ H}), 1.33 \ (\text{br s, } 1 \text{ H}). \]
2-(Hept-6-ynyl)isoindoline-1,3-dione (2-30). A solution of alcohol 2-29 (228 mg, 2.04 mmol), phthalimide (302 mg, 2.04 mmol), and PPh₃ (540 mg, 2.04 mg) in THF (20 mL) was cooled to 0 °C and treated with DIAD (403 μL, 2.04 mmol) over 5 min. The reaction mixture was warmed to ambient temperature and stirred for 56 h. The solvent was evaporated, the residue was dissolved in hexanes/EtOAc (1:1, 10 mL) and the solids were filtered off. The filtrate was concentrated and chromatographed on SiO₂ (hexanes/EtOAc, 5:1) to yield imide 2-30 (407 mg, 1.69 mmol, 82%) as a colorless oil: IR (neat) 3466, 3283, 2941, 2862, 2115, 1772, 1709, 1615, 1397, 1046, 720 cm⁻¹; ¹H NMR δ 7.84-7.79 (m, 2 H), 7.72-7.67 (m, 2 H), 3.67 (t, 2 H, J = 7.1 Hz), 2.17 (td, 2 H, J = 6.8, 2.6 Hz), 1.91 (t, 1 H, J = 2.6 Hz), 1.75-1.61 (m, 2 H), 1.58-1.51 (m, 2 H), 1.49-1.38 (m, 2 H); ¹³C NMR δ 168.3 (2 C), 133.8 (2 C), 132.1 (2 C), 123.1 (2 C), 84.2, 68.4, 37.7, 28.0, 27.9, 25.8, 18.2; MS (EI) m/z (rel intensity) 241 ([M]+, 11), 186 (6), 173 (10), 160 (100), 148 (31), 130 (29), 104 (27); HRMS (EI) m/z calcd for C₁₅H₁₅NO₂ 241.1103, found 241.1107.

2-(Hept-6-ynyl)-3-hydroxy-3-methylisoindolin-1-one (2-31). Characteristic data: ¹H NMR δ 1.64 (s, 3 H).

158
2-(Hept-6-ynyl)-3-methoxyisoindolin-1-one (2-33). To a 0 °C solution of imide 2-30 (40.0 mg, 0.166 mmol) in MeOH (4 mL) was added NaBH₄ (4.98 mg, 0.125 mmol). The reaction mixture was stirred at ambient temperature for 2.5 h, quenched with H₂O (1 mL) and the MeOH was removed in vacuo. The residue was extracted with CH₂Cl₂ (5 x 3 mL) and the combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated to provide crude the hydroxylactam 2-32 which was immediately dissolved in MeOH (4 mL), treated with d,l-camphorsulfonic acid (3.85 mg, 0.0166 mmol) and stirred for 16 h. The solvent was removed in vacuo and the residue was partitioned between H₂O (5 mL) and CH₂Cl₂ (5 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), concentrated and chromatographed on SiO₂ (hexanes/EtOAc, 4:1) to yield methoxy lactam 2-33 (17.0 mg, 0.0661 mmol, 40% over two steps) as a colorless oil: IR (neat) 3298, 2925, 2854, 2115, 1702, 1466, 1412, 1059, 746 cm⁻¹; ¹H NMR δ 7.84-7.80 (m, 1 H), 7.61-7.49 (m, 3 H), 5.88 (s, 1 H), 3.79 (ddd, 1 H, J = 15.6, 8.1, 7.3 Hz), 3.24 (ddd, 1 H, J = 14.0, 8.0, 6.3 Hz), 2.87 (s, 3 H), 2.19 (td, 2 H, J = 6.7, 2.6 Hz), 1.92 (t, 1 H, J = 2.6 Hz), 1.75-1.63 (m, 2 H), 1.62-1.43 (m, 4 H); ¹³C NMR δ 167.6, 140.3, 133.2, 131.9, 129.9, 123.4 (2 C), 86.2, 84.3, 68.4, 49.1, 39.3, 28.0, 27.6, 26.0, 18.3; MS (EI) m/z (rel intensity) 257 ([M⁺,18), 242 (17), 226 (20), 176 (66), 146 (100), 132 (39), 117 (21); HRMS (EI) m/z calcd for C₁₆H₁₉NO₂ 257.1416, found 257.1419.

2-(Hept-6-ynyl)-3-phenoxyisoindolin-1-one (2-24). A 0 °C solution of imide 2-30 (307 mg, 1.27 mmol) in MeOH (20 mL) was treated with NaBH₄ (36.3 mg, 0.953 mmol), warmed to
ambient temperature and stirred for 1 h. The reaction mixture was quenched with H₂O (10 mL) and the MeOH was removed in vacuo. The residue was extracted with CH₂Cl₂ (6 x 10 mL) and the combined organic layers washed with brine, dried (Na₂SO₄) and concentrated to yield crude hydroxylactam 2-32 as a colorless oil. A portion of the crude hydroxylactam (101 mg, 0.416 mmol) was immediately dissolved in THF (5 mL) at ambient temperature and treated with SOCl₂ (30.3 μL, 0.416 mmol) and DMF (1 drop) and stirred for 14 h. The volatiles were removed under reduced pressure and the residue was dried in vacuo for 12 h. The unstable crude chloride was obtained as a colorless oil and immediately dissolved in THF (4.1 mL) at ambient temperature. This solution was treated with phenol (58.0 mg, 0.620 mmol) and Et₃N (288 μL, 2.07 mmol) and stirred for 2 h. The reaction mixture was quenched with H₂O (1 mL) and the THF was removed in vacuo. The residue was extracted with CH₂Cl₂ (4 x 5 mL) and the combined organic layers were washed with brine, dried (Na₂SO₄), and concentrated. The residue was chromatographed on SiO₂ (hexanes/EtOAc, 3:1) to yield phenoxy lactam 2-34 (45.0 mg, 1.41 mmol, 34% over two steps) as a colorless oil: IR (neat) 3296, 2936, 2115, 1700, 1692, 780 cm⁻¹; ¹H NMR δ 7.85-7.79 (m, 1 H), 7.53-7.46 (m, 3 H), 7.33-7.27 (m, 2 H), 7.08-6.98 (m, 3 H), 6.42 (s, 1 H), 3.80 (dt, 1 H, J = 14.2, 7.4 Hz), 3.44 (ddd, 1 H, J = 14.0, 7.8, 6.4 Hz), 2.16 (td, 2 H, J = 6.7, 2.6 Hz), 1.91 (t, 1 H, J = 2.6 Hz), 1.78-1.61 (m, 2 H), 1.57-1.39 (m, 4 H); ¹³C NMR δ 167.4, 156.3, 141.3, 132.3, 132.0, 130.0, 129.7 (2 C), 123.5, 123.3, 123.1, 118.1 (2 C), 86.8, 84.2, 68.4, 40.0, 27.9, 27.6, 25.9, 18.2; MS (EI) m/z (rel intensity) 319 ([M]+, 70), 265 (28), 226 (100), 198 (8), 146 (52), 132 (65); HRMS (EI) m/z calcd for C₂₁H₂₁NO₂ 319.1572, found 319.1573.
2-(Hept-6-ynyl)-3-methylisoindolin-1-one (2-35). Characteristic data: $^1$H NMR $\delta$ 4.55 (q, 1 H, $J = 6.7$ Hz), 1.48 (d, 3 H, $J = 6.7$ Hz).

2-Benzyl-3-oxoisoindolin-1-yl pivaloate (2-48). To a solution of benzyl phthalimide (8.89 g, 37.5 mmol) in MeOH (130 mL) was added sodium borohydride (1.42 g, 37.5 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 2 h and carefully quenched with H$_2$O. The aqueous layer was extracted with EtOAc (2x) and the organic layer was separated, dried (MgSO$_4$) and concentrated. The residue was dried to yield a white solid which was carried on to the next step without further purification. To a solution of the crude reduced phthalamide (1.00 g, 4.20 mmol) in THF (30 mL) was added Et$_3$N (1.17 mL, 8.40 mmol) and pivaloyl chloride (621 $\mu$L, 5.04 mmol) at 0 °C and the reaction mixture was allowed to warm to rt and stirred at this temperature for 4 h. The mixture was quenched with sat. aq. NaHCO$_3$, extracted with EtOAc (2x), dried (MgSO$_4$) and concentrated. The residue was purified by chromatography on SiO$_2$ (EtOAc:Hex, 3:7) to yield 1.09 g (80% over 2 steps) of 2-48 as a colorless solid: mp 88.1 - 89.0 °C (CH$_2$Cl$_2$); IR (neat) 3419, 3062, 3031, 2973, 2934, 2872, 1717, 1408, 1276, 1122, 959, 751 cm$^{-1}$; $^1$H NMR $\delta$ 7.92-7.84 (m, 1 H), 7.61-7.53 (m, 2 H), 7.50-7.43 (m, 1 H), 7.38-7.22 (m, 5 H), 6.89 (s, 1 H), 5.01 (d, 1 H, $J = 15$ Hz), 4.44 (d, 1 H, $J = 15$ Hz), 1.13 (s, 9 H); $^{13}$C NMR $\delta$ 178.4, 167.9, 141.3, 136.8, 132.5, 131.9, 130.2, 161
(E)-2-Benzyl-3-(hex-1-enyl)isoindolin-1-one (2-49). General Protocol A. To a solution of 1-hexyne (60.5 μL, 0.526 mmol) in CH2Cl2 (1.5 mL) was added zirconocene hydrochloride (156 mg, 0.605 mmol) and the resulting suspension was stirred at rt for 10 min. The resulting yellow solution was cooled to 0 °C and Me3Al (1.0 M in CH2Cl2, 0.605 mL, 0.605 mmol) and 2-48 (85.0 mg, 0.263 mmol) were added. The mixture was warmed to rt and stirred at this temperature for 1 h, quenched with sat. aq. NH4Cl, and extracted with CH2Cl2. The organic layers were separated, dried (MgSO4) and concentrated. The residue was purified by chromatography on SiO2 (EtOAc:Hex, 3:7) to yield 65.1 mg (81%) of 2-49 as a colorless oil: IR (neat) 3479, 3031, 2927, 2857, 1694, 1615, 1400, 972 cm⁻¹; ¹H NMR δ 7.91-7.86 (m, 1 H), 7.56-7.42 (m, 2 H), 7.36-7.21 (m, 6 H), 5.90 (dt, 1 H, J = 15.0, 6.8 Hz), 5.30 (d, 1 H, J = 14.8 Hz), 5.09 (dd, 1 H, J = 15.2, 9.2 Hz), 4.70 (d, 1 H, J = 9.2 Hz), 4.17 (d, 1 H, J = 14.9 Hz), 2.13 (app q, 2 H, J = 6.7 Hz), 1.50-1.30 (m, 4 H), 0.94 (t, 3 H, J = 7.2 Hz); ¹³C NMR δ 167.9, 145.1, 138.3, 137.5, 131.8, 131.5, 128.6, 128.3, 127.3, 126.1, 123.6, 123.0, 62.7, 63.8, 31.8, 31.1, 22.1, 13.8; MS (EI) m/z (rel intensity) 305 ([M]⁺, 100), 248 (40), 237 (70), 214 (40); HRMS (EI) m/z calcd for C21H23NO 305.1780, found 305.1785.
(E)-2-Benzyl-3-(2-cyclohexylvinyl)isoindolin-1-one (2-50). According to general protocol A, cyclohexylacetylene (66.9 mg, 0.618 mmol), CH₂Cl₂ (1.5 mL), zirconocene hydrochloride (183 mg, 0.711 mmol), Me₃Al (1.0 M in CH₂Cl₂, 0.711 mL, 0.711 mmol) and 2-48 (100 mg, 0.309 mmol) afforded 80.8 mg (79%) of 2-50 as a colorless oil after purification on SiO₂ (EtOAc:Hex, 3:7): IR (neat) 3375, 3030, 2921, 2851, 2243, 1220, 1200, 1097, 844 cm⁻¹; ¹H NMR  δ 7.92-7.86 (m, 1 H), 7.54-7.41 (m, 2 H), 7.35-7.20 (m, 6 H), 5.85 (dd, 1 H, J = 15.3, 6.6 Hz), 5.28 (d, 1 H, J = 14.8 Hz), 5.02 (ddd, 1 H, J = 15.3, 9.2, 1.2 Hz), 4.67 (d, 1 H, J = 9.2 Hz), 4.18 (d, 1 H, J = 14.8 Hz), 2.14-1.96 (m, 1 H), 1.85-1.60 (m, 4 H), 1.42-1.00 (m, 6 H); ¹³C NMR  δ 167.9, 145.1, 144.1, 137.4, 131.8, 131.4, 128.5, 128.3, 128.2, 127.3, 123.6, 122.9, 62.8, 43.8, 40.3, 32.6, 26.0, 25.8; MS (EI) m/z (rel intensity) 331 ([M]+, 86), 248 (40), 237 (100); HRMS (EI) m/z calcd for C₂₃H₂₅NO 331.1936, found 331.1951.

(E)-2-Benzyl-3-(4-(tert-butyldiphenylsilyloxy)but-1-enyl)isoindolin-1-one (2-51). According to general protocol A, O-TBDPS-3-butynol (94.4 mg, 0.306 mmol), CH₂Cl₂ (1 mL), zirconocene hydrochloride (78.9 mg, 0.306 mmol), Me₃Al (1.0 M in CH₂Cl₂, 0.306 mL, 0.306
mmol) and 2-48 (50.0 mg, 0.153) afforded 57.6 mg (71%) of 2-51 as a colorless oil after purification on SiO2 (EtOAc:Hex, 2:8): IR (neat) 3450, 2930, 2857, 1692, 1111, 735, 701 cm⁻¹; ¹H NMR δ 7.92-7.86 (m, 1 H), 7.72-7.65 (m, 4 H), 7.53-7.35 (m, 9 H), 7.32-7.21 (m, 5 H), 5.96 (dt, 1 H, J = 15.3, 6.8 Hz), 5.27 (d, 1 H, J = 14.9 Hz), 5.16 (dd, 1 H, J = 15.1, 9.1 Hz), 4.71 (d, 1 H, J = 9.1 Hz), 4.16 (d, 1 H, J = 14.9 Hz), 3.77 (dt, 2 H, J = 6.3, 1.2 Hz), 2.37 (app q, 2 H, J = 6.6 Hz), 1.08 (s, 9 H); ¹³C NMR δ 168.0, 144.9, 137.5, 135.6, 134.8, 133.8, 131.9, 131.5, 129.7, 128.6, 128.4, 128.2, 127.7, 127.4, 123.6, 123.1, 63.2, 62.6, 43.9, 35.6, 26.9, 19.2; MS (EI) m/z (rel intensity) 532 ([M]+, 35), 488 (100), 474 (45), 306 (65), 252 (75); HRMS (EI) m/z calcd for C₃₅H₃₇NO₂Si 532.2664, found 532.2664.

{(E)-Methyl 4-(2-benzyl-3-oxoisindolin-1-yl)-but-3-enyl-(tosyl)-carbamate (2-52). According to general protocol A, methyl but-3-ynyl(tosyl)carbamate (174 mg, 0.618 mmol), CH₂Cl₂ (1.5 mL), zirconocene hydrochloride (183 mg, 0.711 mmol), Me₃Al (1.0 M in CH₂Cl₂, 0.711 mL, 0.711 mmol) and 2-48 (100 mg, 0.309) afforded 95.1 mg (62%) of 2-52 as a colorless oil after purification on SiO₂ (acetone:CH₂Cl₂, 0.3:9.7): IR (neat) 3467, 3032, 2957, 2245, 1735, 1686, 1359, 1168, 733 cm⁻¹; ¹H NMR δ 7.92-7.78 (m, 3 H), 7.56-7.41 (m, 2 H), 7.39-7.18 (m, 9 H), 5.93 (dt, 1 H, J = 15.2, 7.0 Hz), 5.26 (d, 1 H, J = 14.9 Hz), 5.21 (dd, 1 H, J = 15.1, 9.1 Hz), 4.73 (d, 1 H, J = 9.0), 4.18 (d, 1 H, J = 14.9 Hz), 3.95 (t, 2 H, J = 7.0 Hz), 3.69 (s, 3 H), 2.58 (app q, 2 H, J = 7.0 Hz), 2.43 (s, 3 H); ¹³C NMR δ 168.0, 152.8, 144.8, 144.6, 137.4, 136.5, 133.0, 131.7, 131.6, 129.7, 129.4,
128.6, 128.3, 128.3, 127.4, 123.6, 123.2, 62.3, 53.8, 46.5, 43.8, 32.9, 21.6; MS (EI) \(m/z\) (rel intensity) 504 ([M]^+, 50), 262 (40), 155 (100); HRMS (EI) \(m/z\) calcd for C_{28}H_{28}N_{2}O_{5}S 504.1719, found 504.1724.

\[
\text{1-benzyl-4,4-dimethyl-5-oxopyrrolidin-2-yl pivalate (2-54).} \quad \text{A mixture of 2,2-dimethylsuccinic anhydride (710 mg, 5.55 mmol) and benzyl amine (712 mg, 6.66 mmol, 1.2 eq) was heated over a bunsen burner for ~1 min. The cooled mixture was purified by chromatography on SiO\(_2\) (1:1 Hex/EtOAc) to furnish the corresponding imide (1.14 g, 95%) as a colorless oil: IR (neat) 2969, 2933, 1777, 1702, 1344, 1142, 709 cm\(^{-1}\); \(^1\)H NMR \(\delta\) 7.29-7.21 (m, 5 H), 4.57 (s, 2 H), 2.47 (s, 2 H), 1.22 (s, 6 H); \(^{13}\)C NMR \(\delta\) 182.5, 175.1, 135.8, 128.3 (2 C), 128.1 (2 C), 127.5, 43.2, 42.0, 39.7, 25.1 (2 C); MS (EI) \(m/z\) (rel intensity) 217 ([M]^+, 100), 174 (33), 133 (22); HRMS (EI) \(m/z\) calcd for C\(_{13}\)H\(_{15}\)NO\(_2\), found. A solution of this imide (1.14 g, 5.25 mmol) in MeOH (53 mL) was treated with NaBH\(_4\) (200 mg, 2.62 mmol, 1 eq) at ambient temperature. After 6 h, the reaction mixture was concentrated, the residue dissolved in CH\(_2\)Cl\(_2\) (50 mL) and treated with aq. NH\(_4\)Cl (aq.). The aqueous layer was separated and washed with CH\(_2\)Cl\(_2\) (2 x 25 mL) and the combined organic layers were dried (MgSO\(_4\)), filtered, concentrated and the resulting oil used without further purification. The crude oil was dissolved in CH\(_2\)Cl\(_2\) (50 mL) and treated sequentially with Et\(_3\)N (2.19 mL, 15.7 mmol, 3 eq), DMAP (128 mg, 1.05 mmol, 20 mol %) and pivaloyl chloride (1.29 mL, 10.5 mmol, 2 eq) at ambient temperature. After 6 h, the reaction mixture was quenched with 3 M HCl (aq., 10 mL) and the aqueous layer washed with CH\(_2\)Cl\(_2\) (3 x 15 mL). The combined organic layers were washed with H\(_2\)O, dried (MgSO\(_4\)), filtered, concentrated and the residue purified by}
chromatography on SiO\textsubscript{2} (2:1 Hex/EtOAc) to yield \textbf{2-54} (398 mg, 25\%) as a colorless oil: IR (neat) 2971, 1710, 1419, 707 cm\textsuperscript{-1}; \textsuperscript{1}H NMR \ddelta 7.33-7.21 (m, 5 H), 5.99 (d, 1 H, \textit{J} = 6.3 Hz), 4.74 (d, 1 H, \textit{J} = 14.4 Hz), 4.15 (d, 1 H, \textit{J} = 14.7 Hz), 2.14 (dd, 1 H, \textit{J} = 14.1, 6.3 Hz), 1.87 (d, 1 H, \textit{J} = 14.4 Hz), 1.32 (s, 3 H), 1.22 (s, 3 H), 1.10 (s, 9 H); \textsuperscript{13}C NMR \ddelta 180.6, 177.9, 136.6, 128.7 (2 H), 128.2 (2 H), 127.6, 82.1, 44.8, 41.5, 39.3, 38.7, 26.8 (3 C), 26.5, 25.6; MS (EI) \textit{m/z} (rel intensity) 303 ([M]\textsuperscript{+}, 36), 275 (15), 202 (85), 158 (46); HRMS (EI) \textit{m/z} calcd for C\textsubscript{18}H\textsubscript{25}NO\textsubscript{3} , found.

\begin{center}
\includegraphics[width=0.2\textwidth]{image}
\end{center}

\textbf{(E)-1-Benzyl-5-(hex-1-enyl)-3,3-dimethylpyrrolidin-2-one (2-55).} According to general protocol A, hexyne (9.77 mg, 0.119 mmol), CH\textsubscript{2}Cl\textsubscript{2} (1 mL), zirconocene hydrochloride (30.7 mg, 0.119 mmol), Me\textsubscript{3}Al (1.0 M in CH\textsubscript{2}Cl\textsubscript{2}, 0.119 mL, 0.119 mmol) and \textbf{2-54} (18.0 mg, 0.0593 mmol) afforded 14.0 mg (83\%) of \textbf{2-55} as a colorless oil after purification on SiO\textsubscript{2} (EtOAc:hex, 2.5:7.5): IR (neat) 2958, 2928, 2868, 1692, 1411, 1262, 972, 752 cm\textsuperscript{-1}; \textsuperscript{1}H NMR \ddelta 7.35-7.23 (m, 3 H), 7.21-7.13 (m, 2 H), 5.53 (dt, 1 H, \textit{J} = 15.0, 6.6 Hz), 5.16 (dd, 1 H, \textit{J} = 15.3, 9.0 Hz), 4.94 (d, 1 H, \textit{J} = 14.4 Hz), 3.88 (d, 1 H, \textit{J} = 14.4 Hz), 3.73 (app q, 1 H, \textit{J} = 7.8 Hz), 2.10-1.98 (m, 2 H), 1.99 (dd, 1 H, \textit{J} = 12.9, 7.2 Hz), 1.58 (dd, 1 H, \textit{J} = 12.9, 8.1 Hz), 1.42-1.28 (m, 4 H), 1.24 (s, 3 H), 1.11 (s, 3 H), 0.92 (t, 3 H, \textit{J} = 6.9 Hz); \textsuperscript{13}C NMR \ddelta 179.6, 137.2, 135.8, 129.8, 128.4, 128.3, 127.2, 56.9, 44.2, 42.0, 40.3, 31.8, 31.2, 25.5, 24.7, 22.2, 13.9; MS (EI) \textit{m/z} (rel intensity) 285 ([M]\textsuperscript{+}, 20), 228 (20), 175 (30), 91 (100); HRMS (EI) \textit{m/z} calcd for C\textsubscript{19}H\textsubscript{27}NO , found 285.2090.
**(E)-2-Benzyl-3-(2-methylhex-1-enyl)isoindolin-1-one (2-56).** General Protocol B. To a 30 °C solution of AlMe₃ (89.0 mg, 1.24 mmol) and Cp₂ZrCl₂ (9.00 mg, 0.0309 mmol) in CH₂Cl₂ (1.5 mL) was added H₂O (11.1 mg, 0.619 mmol) dropwise. The reaction mixture was warmed to ambient temperature, cooled to 0 °C, treated with 1-hexyne (71.0 μL, 0.619 mmol), stirred for 30 min and treated with 2-48 (100 mg, 0.309 mmol). The reaction mixture was warmed to rt and stirred at this temperature for 1 h, quenched with sat. aq. NH₄Cl, and extracted with CH₂Cl₂. The organic layers were separated, dried (MgSO₄) and concentrated. The residue was purified by chromatography on SiO₂ (EtOAc:Hex, 3:7) to yield 76.0 mg (77%) of 2-56 as a colorless oil: IR (neat) 2956, 2929, 2858, 1694, 1468, 1401, 749, 703 cm⁻¹; ¹H NMR δ 7.89-7.50 (m, 1 H), 7.53-7.40 (m, 2 H), 7.35-7.20 (m, 6 H), 5.31 (d, 1 H, J = 14.9 Hz), 5.06 (d, 1 H, J = 9.8), 4.81 (dq, 1 H, J = 9.8, 1.2 Hz), 4.09 (d, 1 H, J = 14.9 Hz), 2.07 (t, 2 H, J = 7.1 Hz), 1.67 (d, 3 H, J = 1.3 Hz), 1.50-1.22 (m, 4 H), 0.91 (t, 3 H, J = 7.2 Hz); ¹³C NMR δ 168.1, 145.7, 143.4, 137.5, 132.0, 131.4, 128.5, 128.2, 128.0, 127.3, 123.6, 122.8, 120.6, 57.9, 43.9, 39.3, 29.8, 22.2, 16.5, 13.8; MS (EI) m/z (rel intensity) 319 ([M⁺], 100), 221 (40); HRMS (EI) m/z calcd for C₂₂H₂₅NO 319.1936, found 319.1921.

**(E)-2-Benzyl-3-(2-phenylprop-1-enyl)isoindolin-1-one (2-57).** According to general protocol B, phenylacetylene (68.0 μL, 0.619 mmol), AlMe₃ (89.0 mg, 1.24 mmol), Cp₂ZrCl₂ (9.00
mg, 0.0309 mmol), CH$_2$Cl$_2$ (1.5 mL), H$_2$O (11.1 mg, 0.619 mmol) and 2-48 (100 mg, 0.309 mmol) afforded 81.0 mg (77%) of 2-57 as a colorless oil and a 95:5 mixture of regioisomers after purification on SiO$_2$ (EtOAc:Hex, 1:3): Major isomer: IR (neat) 3030, 2918, 1693, 1602, 1432, 1400, 1250, 749 cm$^{-1}$; $^1$H NMR $\delta$ 7.93 (dd, 1 H, $J = 6.3, 2.1$ Hz), 7.54-7.46 (m, 2 H), 7.35-7.26 (m, 11 H), 5.41 (dd, 1 H, $J = 9.6, 0.9$ Hz), 5.35 (d, 1 H, $J = 15.0$ Hz), 5.27 (d, 1 H, $J = 9.9$ Hz), 4.21 (d, 1 H, $J = 15.0$ Hz), 2.12 (d, 3 H, $J = 0.9$ Hz); $^{13}$C NMR $\delta$ 168.1, 145.0, 142.0, 141.3, 137.4, 132.0, 131.6, 128.6, 128.3, 127.8, 127.5, 125.8, 123.8, 123.7, 122.9, 58.2, 44.3, 16.3; MS (EI) $m/z$ (rel intensity) 339 ([M]$^+$, 41), 248 (47), 234 (77), 91 (100); HRMS (EI) $m/z$ calcd for C$_{24}$H$_{21}$NO 339.1623, found 339.1631. Minor isomer (characteristic peaks): $^1$H NMR $\delta$ 1.44 (d, 3 H, $J = 6.9$ Hz); $^{13}$C NMR $\delta$ 128.0, 121.9, 18.0.

\[
\text{(E)-(3-(Pent-4-ynyloxy)prop-1-enyl)benzene (2-59).} \]

To a solution of 4-pentyn-1-ol (4.03 mL, 43.3 mmol) in hexanes (75 mL) was added 50% NaOH (75 mL), TBAI (801 mg, 2.17 mmol) and cinnamyl bromide (8.97 g, 45.5 mmol). The reaction mixture was rapidly stirred for 10 h, the organic layer was separated, dried (MgSO$_4$) and concentrated. The residue was purified by chromatography on SiO$_2$ (EtOAc:Hex, 1:9) to yield 9.00 g (69%) of 2-59 as a colorless oil: IR (neat) 3298, 3027, 2951, 2854, 2117, 1478, 1365, 1111, 967 cm$^{-1}$; $^1$H NMR $\delta$ 7.44-7.37 (m, 2 H), 7.37-7.27 (m, 2 H), 7.27-7.21 (m, 1 H), 6.62 (d, 1 H, $J = 15.9$ Hz), 6.30 (dt, 1 H, $J = 15.9, 6.0$), 4.15 (dd, 2 H, $J = 6.0, 0.9$ Hz), 3.60 (t, 2 H, $J = 6.3$ Hz), 2.34 (dt, 2 H, $J = 7.2, 2.7$ Hz), 1.96 (t, 1 H, $J = 2.7$ Hz), 1.85 (app p, 2 H, $J = 6.6$ Hz); $^{13}$C NMR $\delta$ 136.5, 131.8, 128.3, 127.4, 126.2, 126.0, 83.7, 71.2, 68.5, 68.3, 28.5, 15.1; MS (EI) $m/z$ (rel intensity) 199 ([M]$^+$, 100), 186 (35), 173 (35), 131 (100); HRMS (EI) $m/z$ calcd for C$_{14}$H$_{16}$O 199.1123, found 199.1126.
2- Allyl-3-oxoisodolin-1-yl pivalate (2-61). To a solution of 2-allylisodolinone-1,3-dione (3.64 g, 19.4 mmol) in MeOH (100 mL) was added sodium borohydride (734 mg, 19.4 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 2 h and carefully quenched with H2O. The aqueous layer was extracted with EtOAc (2x) and the organic layer was separated, dried (MgSO4) and concentrated. The residue was dried to yield a white solid which was carried on to the next step without further purification. To a solution of the crude reduced phthalamide (3.60 g, 19.0 mmol) in THF (100 mL) was added Et3N (7.90 mL, 57.0 mmol) and pivaloyl chloride (2.81 mL, 22.8 mmol) at 0 °C and the reaction mixture was allowed to warm to rt and stirred at this temperature for 4 h. The mixture was quenched with sat. aq. NaHCO3, extracted with EtOAc (2x), dried (MgSO4) and concentrated. The residue was purified by chromatography on SiO2 (EtOAc:Hex, 2.5:7.5) to yield 4.40 g (83% over 2 steps) of 2-61 as a colorless oil: IR (neat) 2976, 1716, 1405, 1135, 753; ¹H NMR δ 7.88-7.80 (m, 1 H), 7.62-7.46 (m, 3 H), 6.99 (s, 1 H), 5.94-5.77 (m, 1 H), 5.29-5.15 (m, 2 H), 4.44 (dd, 1 H, J = 15.9, 5.1 Hz), 3.88 (dd, 1 H, J = 15.3, 6.6 Hz), 1.23 (s, 9 H) cm⁻¹; ¹³C NMR δ 178.3, 167.5, 141.2, 132.4, 132.4, 131.8, 130.0, 123.6, 123.5, 118.0, 80.9, 42.8, 39.0, 26.9; MS (El) m/z (rel intensity) 273 ([M]+, 60), 172 (100; HRMS (El) m/z calcd for C₁₆H₁₉NO₃ 273.1365, found 273.1358.
2-Allyl-3-((E)-5-(cinnamyloxy)pent-1-enyl)isoindolin-1-one (2-62). According to general protocol A, alkyne 2-59 (733 mg, 3.66 mmol), CH$_2$Cl$_2$ (10 mL), zirconocene hydrochloride (944 mg, 3.66 mmol), Me$_3$Al (1.0 M in CH$_2$Cl$_2$, 3.66 mL, 3.66 mmol) and 2-61 (500 mg, 1.83 mmol) (reaction time increased to 12 h) afforded 376 mg (55%) of 2-62 as a colorless oil after purification on SiO$_2$ (Acetone:CH$_2$Cl$_2$, 0.7:9.3): IR (neat) 2924, 2853, 1694, 1289, 1098, 746 cm$^{-1}$; $^1$H NMR $\delta$ 7.85 (d, 1 H, $J$ = 6.6 Hz), 7.57-7.20 (m, 8 H), 6.61 (d, 1 H, $J$ = 15.9 Hz), 6.29 (dt, 1 H, $J$ = 15.9, 6.0 Hz), 6.02 (dt, 1 H, $J$ = 13.8, 6.9 Hz), 5.90-5.73 (m, 1 H), 5.25-5.07 (m, 3 H), 4.87 (d, 1 H, $J$ = 9.0 Hz), 4.60 (ddd, 1 H, $J$ = 15.6, 4.5, 2.7 Hz), 4.15 (dd, 2 H, $J$ = 6.0, 1.2 Hz), 3.70 (dd, 1 H, $J$ = 15.3, 7.2 Hz), 3.53 (t, 2 H, $J$ = 6.3 Hz), 2.25 (app q, 2 H, $J$ = 6.9 Hz), 1.77 (app p, 2 H, $J$ = 7.8 Hz); $^{13}$C NMR $\delta$ 167.7, 144.9, 137.2, 136.6, 133.2, 132.3, 131.8, 131.4, 128.5, 128.3, 127.6, 126.7, 126.4, 126.1, 123.5, 122.9, 117.5, 71.5, 69.4, 62.9, 42.5, 29.2, 28.9; MS (ESI) $m/z$ (rel intensity) 396 ([M+Na]$^+$, 100), 307 (20), 297 (20); HRMS (ESI) $m/z$ calcd for C$_{25}$H$_{27}$NO$_2$Na 396.1939, found 396.1928
**3H-Pyrrolo[2,1-a]isoindol-5(9bH)-one (2-63).** To a solution of 2-62 (41.7 mg, 0.112 mmol) in CH₂Cl₂ (6 mL) was added Grubbs 2nd generation catalyst (4.75 mg, 5.60 mmol) and the red solution was heated at 50 °C for 1 h, cooled to rt and concentrated. The residue was purified by chromatography on SiO₂ (Acetone:CH₂Cl₂, 0.4:9.6) to yield 11.7 mg (61%) of 2-63 as a colorless oil: IR (neat) 2872, 1614, 1468, 1395, 1366, 1080, 746 cm⁻¹; ¹H NMR δ 7.74-7.66 (m, 2 H), 7.66-7.58 (m, 1 H), 7.54-7.45 (m, 1 H), 6.28-6.20 (m, 1 H), 6.08-5.99 (m, 1 H), 5.53 (app d, 1 H, J = 1.8 Hz), 4.57-4.43 (m, 1 H), 3.98-3.83 (m, 1 H); ¹³C NMR δ 175.4, 148.4, 133.6, 133.1, 131.9, 129.4, 129.2, 124.6, 124.0, 71.1, 52.0; MS (EI) m/z (rel intensity) 171 ([M⁺], 60), 160 (70), 130 (55), 105 (60), 83 (100); HRMS (EI) m/z calcd for C₁₁H₉NO 171.0684, found 171.0676.

\[ \text{O} \]
\[ \text{N} \]
\[ \text{C₄H₉} \]
\[ \text{CH₂CH₃} \]

**(E)-2-Allyl-3-(hex-1-enyl)isoindolin-1-one (2-64).** According to general protocol A, hexyne (420 µL, 3.66 mmol), CH₂Cl₂ (10 mL), zirconocene hydrochloride (944 mg, 3.66 mmol), Me₃Al (1.0 M in CH₂Cl₂, 3.66 mL, 3.66 mmol) and 2-61 (500 mg, 1.83 mmol) afforded 341 mg (73%) of 2-64 as a colorless oil after purification on SiO₂ (EtOAc:Hex, 3:7): IR (neat) 2957, 2926, 1697, 1468, 1396, 971, 748 cm⁻¹; ¹H NMR δ 7.83 (d, 1 H, J = 7.2 Hz), 7.57-7.38 (m, 2 H), 7.33 (d, 1 H, J = 7.5 Hz), 5.97 (dt, 1 H, J = 15.0, 6.9 Hz), 5.88-5.71 (m, 1 H), 5.22-4.97 (m, 3 H), 4.85 (d, 1 H, J = 9.3 Hz), 4.59 (dd, 1 H, J = 15.6, 4.5 Hz), 3.69 (dd, 1 H, J = 15.3, 7.2 Hz), 2.12 (app q, 2 H, J = 6.6 Hz), 1.48-1.28 (m, 4 H), 0.91 (t, 3 H, J = 6.9 Hz); ¹³C NMR δ 167.7, 145.0, 138.2, 133.1, 131.7, 131.4, 128.2, 126.0, 123.4, 122.9, 117.4, 62.9, 42.5, 31.8, 31.1, 27.0, 22.0, 13.8; MS (EI) m/z (rel
intensity) 255 ([M]$^+$, 30), 198 (100), 172 (55); HRMS (EI) m/z calcd for \( \text{C}_{17}\text{H}_{21}\text{NO}\ 255.1623 \), found 255.1627.

\[
\text{2-(Pent-4-eyl)isoindoline-1,3-dione (2-66). A solution of 4-penten-1-ol (2-65, 3.51 mL, 34.0 mmol), phthalimide (5.00 mg, 34.0 mmol), and PPh}_3\ (8.92\ g, 34.0\ mmol)\ in\ THF\ (220\ mL)\ was cooled to 0 °C and treated with DIAD (6.69 mL, 34.0 mmol) over 5 min. The reaction mixture was warmed to rt and stirred for 6 h. The solvent was evaporated, the residue was dissolved in EtOAc/hex (1:1, 100 mL) and the solids were filtered off. The filtrate was concentrated and chromatographed on SiO2 (EtOAc:hex, 1:5) to yield 6.44 g (88%) of imide 2-66 as a colorless oil: IR (neat) 3466, 3077, 2939, 1773, 1641, 1397, 995, 720 cm$^{-1}$; $^1$H NMR $\delta$ 7.88-7.81 (m, 2 H), 7.76-7.67 (m, 2 H), 5.90-5.73 (m, 1 H), 5.12-4.94 (m, 2 H), 3.70 (dt, 2 H, $J = 7.5, 4.5$ Hz), 2.20-2.07 (m, 2 H), 1.87-1.73 (m, 2 H); $^{13}$C NMR $\delta$ 168.1, 137.1, 133.7, 131.9, 122.9, 115.1, 37.3, 30.8, 27.4; MS (EI) m/z (rel intensity) 215 ([M]$^+$, 45), 173 (70), 160 (100), 148 (80), 130 (80), 104 (90); HRMS (EI) m/z calcd for \( \text{C}_{13}\text{H}_{13}\text{NO}_2\ 215.0946 \), found 215.0946.
3-Oxo-2-(pent-4-enyl)isoindolin-1-yl pivalate (2-67). To a solution of imide 2-66 (4.42 g, 20.5 mmol) in MeOH (100 mL) was added sodium borohydride (776 mg, 20.5 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 2 h and carefully quenched with H₂O. The aqueous layer was extracted with EtOAc (2x) and the organic layer was separated, dried (MgSO₄) and concentrated. The residue was dried to yield a white solid which was carried on to the next step without further purification. To a solution of the crude reduced phthalimide (4.23 g, 19.5 mmol) in THF (100 mL) was added Et₃N (8.15 mL, 58.5 mmol), pivaloyl chloride (3.61 mL, 29.3 mmol) and DMAP (119 mg, 0.975 mmol) at 0 °C and the reaction mixture was allowed to warm to rt and stirred at this temperature for 8 h. The mixture was quenched with sat. aq. NaHCO₃, extracted with EtOAc (2x), dried (MgSO₄) and concentrated. The residue was purified by chromatography on SiO₂ (EtOAc:Hex, 1:5) to yield 4.70 g (76% over 2 steps) of 2-67 as a colorless oil: IR (neat) 3077, 2974, 2873, 1739, 1641, 1618, 1208, 1141, 959, 751 cm⁻¹; ¹H NMR δ 7.67 (d, 1 H, J = 6.0 Hz), 7.49-7.32 (m, 3 H), 6.89 (s, 1 H), 5.79-5.58 (m, 1 H), 4.91 (d, 1 H, J = 17.1 Hz), 4.84 (d, 1 H, J = 10.5 Hz), 3.73-3.55 (m, 1 H), 3.27-3.09 (m, 1 H), 2.07-1.93 (m, 2 H), 1.77-1.50 (m, 2 H), 1.11 (s, 9 H); ¹³C NMR δ 178.2, 167.4, 140.9, 137.1, 132.0, 131.8, 129.8, 123.2, 123.1, 114.9, 80.8, 39.5, 38.7, 30.7, 27.1, 26.6; MS (EI) m/z (rel intensity) 301 ([M⁺], 15), 246 (45), 216 (65), 200 (85), 146 (85), 133 (65); HRMS (EI) m/z calcd for C₁₈H₂₃NO₃ 301.1678, found 301.1681.

(E)-3-(Hex-1-enyl)-2-(pent-4-enyl)isoindolin-1-one (2-68). According to general protocol A, hexyne (420 μL, 3.66 mmol), CH₂Cl₂ (10 mL), zirconocene hydrochloride (944 mg, 3.66 mmol),
Me₃Al (1.0 M in CH₂Cl₂, 3.66 mL, 3.66 mmol) and 2-67 (552 mg, 1.83 mmol) afforded 368 mg (72%) of 2-68 as a colorless oil after purification on SiO₂ (EtOAc:Hex, 3:7): IR (neat) 3076, 2967, 2928, 2860, 1693, 1468, 1404, 972, 749 cm⁻¹; ¹H NMR δ 7.72 (d, 1 H, J = 7.5 Hz), 7.44-7.28 (m, 2 H), 7.23 (d, 1 H, J = 7.2 Hz), 5.94 (dt, 1 H, J = 14.4, 6.6 Hz), 5.80-5.63 (m, 1 H), 5.03-4.82 (m, 3 H), 4.75 (d, 1 H, J = 9.0 Hz), 3.83-3.65 (m, 1 H), 3.23-3.07 (m, 1 H), 2.13-1.93 (m, 4 H), 1.75-1.51 (m, 2 H), 1.42-1.19 (m, 4 H), 0.83 (t, 3 H, J = 6.9 Hz); ¹³C NMR δ 167.6, 144.6, 137.5, 137.3, 131.7, 131.0, 127.9, 126.2, 122.9, 122.6, 114.7, 39.4, 31.5, 30.8, 30.7, 27.3, 26.9, 21.8, 13.5; MS (EI) m/z (rel intensity) 283 ([M]+, 20), 228 (70), 160 (100), 146 (50), 76 (50); HRMS (EI) m/z calcld for C₁₉H₂₅NO 283.1936, found 283.1934.

(Z)-7,8,9,11a-Tetrahydro-5H-azepino[2,1-a]isoindol-5-one (2-69). To a solution of 37 (150 mg, 0.529 mmol) in toluene (100 mL) was added Ti(O̥Pr)₄ (157 μL, 0.529 mmol) and Grubbs 2nd generation catalyst (22.5 mg, 0.0265 mmol) and the red solution was stirred at rt for 12 h and concentrated. The residue was purified by chromatography on SiO₂ (Acetone:CH₂Cl₂, 0.4:9.6) to yield 70.7 mg (67%) of 2-69 as a colorless oil: IR (neat) 3024, 2926, 1680, 1469, 1419, 1298, 938, 709 cm⁻¹; ¹H NMR δ 7.76 (dd, 1 H, J = 6.9, 1.2 Hz), 7.58-7.51 (m, 1 H), 7.46 (app t, 2 H, 7.2 Hz), 6.13-6.02 (m, 1 H), 6.02-5.91 (m, 1 H), 4.49 (dd, 1 H, J = 11.4, 2.1 Hz), 4.26 (ddd, 1 H, J = 13.5, 6.6, 3.0 Hz), 3.22 (ddd, 1 H, J = 12.6, 9.6, 2.7 Hz), 2.81 (app ddd, 1 H, J = 15.9, 7.8, 2.4 Hz), 2.53-2.26 (m, 2 H), 2.25-2.09 (m, 1 H); ¹³C NMR δ 167.5, 145.9, 133.0, 132.7, 131.6, 128.8, 128.5, 123.5, 122.4, 60.6, 41.6, 35.2, 28.2; MS (EI) m/z (rel intensity) 199 ([M]+, 45), 145 (100), 117 (40), 90 (35); HRMS (EI) m/z calcld for C₁₃H₁₃NO 199.0997, found 199.0991.
5.3 SPIROKETALS VIA OXIDATIVE REARRANGEMENT OF ENOL ETHERS

(1R*,6R*)-3-Methoxy-5,5-dimethyl-7-oxabicyclo[4.1.0]hept-3-en-2-one (3-20). To a 40 °C solution of 3-19 (0.20 g, 1.3 mmol) in THF (30 mL) was added H2O2 (10 mL, 30% v/v in H2O) and K2CO3 (5 mL, 0.4 M in H2O). The reaction mixture was stirred for 6 h, diluted with EtOAc, washed with brine, dried (Na2SO4) and concentrated. The residue was purified by chromatography on SiO2 (4:1 hexanes/EtOAc) to afford 3-20 (0.11 g, 67%) as a colorless oil: IR (neat) 2965, 1694, 1627, 1205, 1158, cm⁻¹; ¹H NMR δ 5.23 (d, J = 2.5 Hz, 1 H), 3.54 (s, 1 H), 3.50 (d, J = 3.8 Hz, 1 H), 3.35 (dd, J = 3.8, 2.5 Hz, 1 H), 1.33 (s, 3 H), 1.20 (s, 3 H); ¹³C NMR δ 189.4, 146.8, 120.8, 61.2, 55.0, 54.8, 34.6, 28.3, 25.9; MS (EI) m/z (intensity) 168 ([M-H2O]⁺, 57), 153 (55), 125 (100); HRMS (EI) m/z calculated for C₉H₁₂O₃ [M-H₂O] 168.0786, found 168.0784.

(1R*,3S*,6R*)-Methyl-2,2-dimethyl-5-oxo-4,7-dioxabicyclo[4.1.0]heptane-3-carboxylate (3-21). General Protocol A. To a solution of 3-20 (35 mg, 0.21 mmol) in dry CH₂Cl₂ (2.0 mL) was added m-CPBA (0.15 g, 0.62 mmol, ~70 wt % m-CPBA) and Na₂HPO₄ (89 mg, 0.62 mmol) and the reaction mixture was stirred for 12 h, treated with 2-methyl-2-butene (0.10 mL of a 2 M solution in THF), stirred for 2 h, diluted with CH₂Cl₂ and washed with sat. NaHCO₃ (5x). The organic layer...
was dried (Na$_2$SO$_4$) and concentrated to afford **3-21** a colorless solid (42 mg, 80%, contaminated with 10% 3-chlorobenzoic acid). The material was purified by chromatography on SiO$_2$ (4:1 hexanes/EtOAc) for analysis: IR (neat) 2966, 1752, 1465, 1250, 1209, 907 cm$^{-1}$; NMR $\delta$ 4.81 (s, 1 H), 3.82 (s, 3 H), 3.64 (d, $J = 4.0$ Hz, 1 H), 3.32 (d, $J = 3.9$ Hz, 1 H), 1.37 (s, 3 H), 1.07 (s, 3 H); $^{13}$C NMR $\delta$ 167.5, 165.5, 78.6, 61.1, 52.7, 49.8, 34.9, 22.7, 17.8; MS (EI) $m/z$ (intensity) 141 ([M-CO$_2$Me]$^+$, 7), 84 (16); HRMS (EI) $m/z$ calculated for C$_7$H$_9$O$_3$ [M-CO$_2$Me] 141.0552, found 141.0550.

(1$^R$,2$^R$,6$^R$)-3-Methoxy-2,5,5-trimethyl-7-oxabicyclo[4.1.0]hept-3-en-2-ol (3-22). To a cooled (-78 °C) solution of **3-20** (28 mg, 0.17 mmol) in dry THF (4.0 mL) was added MeLi (0.19 mL, 0.30 mmol, 1.6 M in Et$_2$O). After 30 min, the reaction mixture was quenched with H$_2$O (1 mL) and extracted with Et$_2$O (3 x 5 mL). The combined organic layers were washed with H$_2$O, brine, dried (Na$_2$SO$_4$), filtered, and concentrated. The residue was purified by chromatography on SiO$_2$ (3:1 hexanes/EtOAc) to afford **3-22** (28 mg, 91%) as a colorless oil: IR (neat) 3479, 2962, 1667, 1469, 1212, 1162, 1059 cm$^{-1}$; $^1$H NMR $\delta$ 4.15 (d, $J = 2.3$ Hz, 1 H), 3.51 (s, 3 H), 3.32 (d, $J = 4.1$ Hz, 1 H), 3.06 (dd, $J = 4.3$, 2.1 Hz, 1 H), 1.42 (s, 3 H), 1.20 (s, 3 H), 1.09 (s, 3 H); $^{13}$C NMR $\delta$ 152.4, 100.4, 69.2, 61.1, 60.2, 54.5, 33.5, 27.7, 27.1, 25.2; MS (EI) $m/z$ (intensity) 184 ([M]$^+$, 17), 169 (44), 137 (13); HRMS (EI) $m/z$ calculated for C$_{10}$H$_{16}$O$_3$ 184.1099, found 184.1103.
**Methyl tetrahydro-3,3-dimethyl-6-oxo-2H-pyran-2-carboxylate (3-23).** According to General Protocol A, a solution of 3-17 (0.14 g, 0.97 mmol), m-CPBA (0.67 g, 2.7 mmol, ~70 wt % m-CPBA) and Na₂HPO₄ (0.39 g, 2.7 mmol) in CH₂Cl₂ (10 mL) afforded, after 12 h, 3-23 as a light yellow solid (0.13 g, 75%, contaminated with 15% 3-chlorobenzoic acid): IR (neat) 2965, 1751, 1469, 1204, 1159, 1080 cm⁻¹; ¹H NMR δ 4.53 (d, J = 1.4 Hz, 1 H), 3.79 (s, 3 H), 2.67, 2.60 (AB of ABMX, Jₐₐ = 18.8, Jₐₚ = 7.8 Hz, Jₐₓ = 4.3 Hz, 2 H), 1.89-1.79 (m, 1 H), 1.60 (dddd, J = 13.6, 5.7, 4.3, 1.4 Hz, 1 H), 1.20 (s, 3 H), 1.03 (s, 3 H); ¹³C NMR δ 169.5 (2C), 85.1, 52.3, 31.4, 31.0, 26.8, 25.3, 24.2; MS (EI) m/z (intensity) 171 ([M-CH₃]⁺, 3), 156 (70), 139 (88), 127(100); HRMS (EI) m/z calculated for C₉H₁₄O₄ 186.0892, found 186.0895.

![Methyl tetrahydro-2-methyl-5-oxofuran-2-carboxylate (3-25)](image)

**Methyl tetrahydro-2-methyl-5-oxofuran-2-carboxylate (3-25).** According to General Protocol A, a solution of 3-24 (0.11 g, 0.87 mmol) in CH₂Cl₂ (5.0 mL), m-CPBA (0.64 g, 2.6 mmol, ~70 wt % m-CPBA) and Na₂HPO₄ (0.37 g, 2.6 mmol) afforded, after 12 h, 3-25 (48 mg, 35%, corrected for 3-chlorobenzoic acid~10%) as a colorless solid: IR (neat) 2992, 2957, 1788, 1743, 1457, 1201, 1140 cm⁻¹; ¹H NMR δ 3.78 (s, 3 H), 2.73-2.48 (m, 3 H), 2.19-2.08 (m, 1 H), 1.65 (s, 3
H); $^{13}$C NMR $\delta$ 175.8, 172.1, 83.7, 52.9, 32.9, 28.3, 23.7; MS (EI) $m/z$ (intensity) 99 ([M-CO$_2$Me]$^+$, 48), 73 (100); HRMS (EI) $m/z$ calculated for C$_5$H$_7$O$_2$ [M-CO$_2$Me] 99.0446, found 99.0447.

(1$^R$,3$^S$,5$^S$,6$^R$)-Methyl-5-hydroxy-2,2,5-trimethyl-4,7-dioxabicyclo[4.1.0]heptane-3-carboxylate (3-26). According to General Protocol A, enol ether 3-22 (24 mg, 0.13 mmol) in CH$_2$Cl$_2$ (1.3 mL), Na$_2$HPO$_4$ (55 mg, 0.39 mmol) and m-CPBA (96 mg of ~70% m-CPBA) furnished, after 18 h and purification on SiO$_2$ (1:1 hexanes/EtOAc), ester 3-26 (5.6 mg, 20%) as a white solid which was a single diastereomer as indicated by $^1$H NMR: Mp 114.5-116.3 ºC (hexanes/EtOAc); IR (KBr) 3466, 2973, 1737, 1214, 1086, 920 cm$^{-1}$; $^1$H NMR $\delta$ 4.10 (s, 1 H), 3.75 (s, 3 H), 3.52 (s, 1 H), 3.33 (d, 1 H, $J$ = 3.8 Hz), 3.10 (d, 1 H, $J$ = 4.0 Hz), 1.64 (s, 3 H), 1.22 (s, 3 H), 1.00 (s, 3 H); $^{13}$C NMR $\delta$ 170.0, 92.4, 71.7, 63.4, 57.7, 51.8, 33.7, 26.5, 22.3, 18.5; MS (EI) $m/z$ (intensity) 198 ([M-H$_2$O]$^+$, 49), 156 (32), 139 (76), 114 (77); HRMS (EI) $m/z$ calculated for C$_{10}$H$_{14}$O$_4$ [M-H$_2$O] 198.0892, found 198.0891.

6-Methoxy-1-oxaspiro[4.5]dec-6-ene (3-42). General Protocol B. A solution of ketone 3-41 (155 mg, 1.01 mmol) in THF (3 mL) was added dropwise to a solution of KHMDS (241 mg, 1.21 mmol) in THF (7 mL) at -78 ºC. After 10 min, DMF (2.5 mL) was added. After 10 min, dimethylsulfate (254 mg, 2.01 mmol) was added and the reaction mixture was warmed to ambient
temperature over 4 h. Subsequently, sat. aq. NaHCO₃ (5 mL) was added and the aqueous layer was extracted with Et₂O (4 x 10 mL). The combined organic layers were washed with H₂O, brine, dried (Na₂SO₄), filtered, concentrated and purified on SiO₂ (85:15 pentane/Et₂O) to furnish enol ether 3-42 (155 mg, 0.923 mmol, 89%) as a volatile, colorless oil: IR (neat) 2948, 2875, 1717, 1601, 1441, 1367, 1224, 1060, 926 cm⁻¹; ¹H NMR δ 4.72 (dd, 1 H, J = 3.9, 3.9 Hz), 3.97-3.80 (m, 2 H), 3.51 (s, 3 H), 2.24-1.51 (m, 10 H); ¹³C NMR δ 156.9, 96.4, 81.2, 68.6, 54.2, 37.2, 35.1, 26.9, 23.9, 20.5; MS (EI) m/z (intensity) 168 ([M⁺], 43), 140 (40), 137 (37), 123 (52); HRMS (EI) m/z calculated for C₁₀H₁₆O₂ 168.1150, found 168.1151.

Methyl 1,6-dioxaspiro[4.5]decane-7-carboxylate (3-43). According to General Protocol A, enol ether 3-42 (100 mg, 0.595 mmol), Na₂HPO₄ (1.79 mmol, 246 mg) and m-CPBA (1.79 mmol, 411 mg of ~70% m-CPBA) in CH₂Cl₂ (6 mL) furnished, after 18 h and purification on SiO₂ (4:1 pentane/Et₂O), spiroketal ester 3-43 (62 mg, 0.31 mmol, 52%) as a colorless oil and a single diastereomer as indicated by ¹H NMR: IR (neat) 2951, 2882, 1760, 1738, 1456, 1439, 1201, 1011, 857 cm⁻¹; ¹H NMR (CD₂Cl₂) δ 4.38 (dd, 1 H, J = 12.1, 2.4 Hz), 3.89-3.83 (m, 2 H), 3.68 (s, 3 H), 2.08-1.96 (m, 2 H), 1.92-1.60 (m, 8 H); ¹³C NMR (CD₂Cl₂) δ 172.8, 106.9, 70.6, 67.7, 52.0, 38.1, 33.0, 28.5, 24.1, 20.5; MS (EI) m/z (rel intensity) 200 ([M⁺], 53), 184 (6), 172 (10), 141 (100), 114 (14); HRMS (EI) m/z calculated for C₁₀H₁₆O₄ 200.1049, found 200.1053.
6-Methoxy-10,10-dimethyl-1-oxaspiro[4.5]dec-6-ene (3-36). General Protocol C. A solution of 2,3-dihydrofuran in THF (90 mL) was treated with t-BuLi (10.7 mmol, 6.3 mL of a 1.7 M solution in pentane) at -78 °C. After 30 min, the reaction mixture was warmed to 0 °C for 30 min, recooled to -78 °C and treated with 2,2-dimethyl cyclopentanone. The reaction mixture was warmed to ambient temperature and quenched after 6 h with aq. NaHCO₃. The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organic layers washed with H₂O, brine, dried (Na₂SO₄), filtered, concentrated and the crude tertiary alcohol was used directly in the next step. A solution of the crude tertiary alcohol in CH₂Cl₂ (100 mL) was treated with Dowex-50X resin (4.71 g, 0.528 g/mmol) and stirred at ambient temperature for 24 h. The mixture was filtered, concentrated and the residue purified by chromatography on SiO₂ (4:1 hexanes/EtOAc) to furnish the α-spiroether ketone (1.32 g, 81% over two steps) as a colorless oil: IR (neat) 2965, 2872, 1717, 1462, 1056 cm⁻¹; ¹H NMR δ 3.88-3.79 (m, 1 H), 3.73-3.66 (m, 1 H), 2.82-2.72 (m, 1 H), 2.29-2.19 (m, 2 H), 1.93-1.66 (m, 6 H), 1.43-1.35 (m, 1 H), 0.96 (s, 3 H), 0.83 (s, 3 H); ¹³C NMR δ 212.1, 92.8, 68.7, 40.8, 37.3, 36.0, 26.3, 25.9, 23.1, 22.3, 21.9; MS (EI) m/z (intensity) 182 ([M⁺],30), 154 (8), 111 (63); HRMS (EI) m/z calculated for C₁₁H₁₈O₂ 182.1307, found 182.1299.

According to General Protocol B, the α-spiroether ketone (180 mg, 0.988 mmol), KHMDS (236 mg, 1.19 mmol), and Me₂SO₄ (249 mg, 1.98 mmol) furnished 3-44 (163 mg, 84%) as a colorless oil: IR (neat) 2926, 1662, 1464, 1215, 1122, 1054 cm⁻¹; ¹H NMR δ 4.56 (dd, 1 H, J = 3.8 Hz), 3.99-3.92 (m, 1 H), 3.78-3.71 (m, 1 H), 3.47 (s, 3 H), 2.08-1.63 (m, 10 H), 1.29 (ddd, 1 H, J = 12.9, 5.4, 5.4 Hz), 0.94 (s, 3 H), 0.86 (s, 3 H); ¹³C NMR δ 157.6, 93.6, 86.5, 69.8, 54.3, 37.6, 33.6,
(5S*,7S*)-Methyl 10,10-dimethyl-1,6-dioxaspiro[4.5]decane-7-carboxylate (3-45). According to General Protocol A, enol ether 3-44 (57 mg, 0.29 mmol), m-CPBA (200 mg of ~70% m-CPBA, 0.871 mmol) and Na2HPO4 (123 mg, 0.871 mmol) furnished, after 18 h and purification by chromatography on SiO2 (6:1 pentanes/Et2O), spiroketal 3-45 (32 mg, 48%) as a 2:1 mixture of diastereomers as indicated by NMR analysis: Major diastereomer: IR (neat) 2954, 2879, 1760, 1740, 1439, 1205, 1064 cm⁻¹; ¹H NMR δ 4.40 (dd, 1 H, J = 11.1, 3.6 Hz), 3.94-3.86 (m, 2 H), 3.73 (s, 3 H), 2.08-2.00 (m, 1 H), 1.96-1.62 (m, 6 H), 1.38-1.33 (m, 1 H), 1.07 (s, 3 H), 0.90 (s, 3 H); ¹³C NMR δ 172.9, 111.6, 69.3, 67.9, 51.9, 34.7, 34.1, 32.1, 25.4, 25.1, 23.9, 23.3; MS (EI) m/z (intensity) 228 ([M]+, 10), 213 (8), 198 (11), 169 (57), 142 (57); HRMS (EI) m/z calculated for C₁₀H₁₇O₂ [M-CO₂Me] 169.1229, found 169.1229. Characteristic data for minor diastereomer: ¹H NMR δ 4.17 (dd, 1 H, J = 5.1, 2.1 Hz), 3.74 (s, 3 H); ¹³C NMR δ 173.4, 112.1, 70.0, 68.7, 51.7, 35.1, 32.2, 31.0, 25.0, 24.8, 23.4, 21.4.

(571 mg, 2.86 mmol) and Me₂SO₄ (451 mg, 3.58 mmol) furnished, after chromatography on SiO₂
(3:1 hexanes/EtOAc), enol ether 3-46 (308 mg, 67%) as a colorless oil: IR (neat) 2941, 2864, 1647,
1370, 1214, 1053 cm⁻¹; ¹H NMR δ 4.80 (d, 1 H, J = 7.1 Hz), 3.92 (ddd, 1 H, J = 7.8, 7.8, 4.8 Hz),
3.72 (ddd, 1 H, J = 7.8, 7.8, 6.6 Hz), 3.41 (s, 3 H), 2.52-2.41 (m, 1 H), 2.22-1.34 (m, 10 H), 1.26-
1.19 (m, 1 H); ¹³C NMR δ 155.8, 101.9, 86.7, 68.3, 54.1, 44.9, 34.5, 34.0, 32.1, 31.8, 27.4, 23.7; MS
(EI) m/z (intensity) 194 ([M]⁺, 24), 162 (56), 153 (36), 135 (17); HRMS (EI) m/z calculated for
C₁₂H₁₈O₂ 194.1307, found 194.1311.

![Structural formula](image)

(1S*,4S*)-Methyldihydro-3'H-3-oxaspiro[bicyclo[3.2.1]octane-2,2'-furan]-4-carboxylate
(3-47). According to General Protocol A, 3-46 (303 mg, 1.56 mmol), m-CPBA (1.08 g of ~70% m-
CPBA, 4.68 mmol), and Na₂HPO₄ (664 mg, 4.68 mmol) furnished, after 18 h and purification by
chromatography on SiO₂ (3:1 hexanes/EtOAc), spiroketal 3-47 (187 mg, 53%) as a single
diastereomer as indicated by NMR analysis: IR (neat) 2950, 2872, 1759, 1733, 1201, 1043 cm⁻¹; ¹H
NMR δ 4.37 (s, 1 H), 3.93-3.85 (m, 2 H), 3.72 (s, 3 H), 2.41 (app t, 1 H, J = 5.1 Hz), 2.27 (app d, 1
H, J = 11.1 Hz), 2.16-1.99 (m, 3 H), 1.88-1.77 (m, 1 H), 1.73-1.62 (m, 3 H), 1.59-1.42 (m, 3 H); ¹³C
NMR δ 171.9, 110.1, 75.6, 67.5, 51.8, 42.8, 37.8, 36.3, 33.1, 26.3, 24.1, 23.4; MS (EI) m/z
(intensity) 226 ([M]⁺, 28), 138 (21), 108 (37); HRMS (EI) m/z calculated for C₁₂H₁₈O₄ 226.1205,
found 226.1203.
(1S,4aS,4bR,6aS,8R,10aS,10bS,12aS)-2,8-Dimethoxy-10a,12a-dimethyl-4a,4b,4',5,5'-
6,6a,7,8,9,10,10a,10b,11,12,12a-hexa-decahydro-3'H,4H-spiro-[chrysene-1,2'-furan] (3-48).

According to General Protocol C, androsterone (1.0 g, 3.44 mmol), 2,3-dihydrofuran (507 mg, 7.23 mmol), t-BuLi (4.5 mL of a 1.7 M solution in pentanes, 7.57 mmol), and Dowex 50X (1.82 g, 0.528 g/mmol) furnished, after chromatography on SiO₂ (6:1 hexanes/EtOAc), the α-spiroether ketone (754 mg, 61%) as a white solid and as a single diastereomer as determined by NMR analysis: Mp 196.8-198.5 °C (hexanes/EtOAc); IR (KBr) 3399, 2930, 2865, 1716, 1452, 1052, 732 cm⁻¹; ¹H NMR δ 3.99 (br s, 1 H), 3.72 (ddd, 1 H, J = 7.7, 7.0, 7.0 Hz), 3.57 (ddd, 1 H, J = 7.9, 6.8, 6.8 Hz), 2.86 (ddd, 1 H, J = 13.5, 13.5, 7.2 Hz), 2.38 (ddd, 1 H, J = 6.5, 6.1, 6.1 Hz), 2.17 (dd, 1 H, J = 5.6, 2.8 Hz), 2.04-1.99 (m, 1 H), 1.83-1.69 (m, 5 H), 1.63-1.08 (m, 15 H), 0.94-0.83 (m, 2 H), 0.69 (s, 3 H), 0.61 (s, 3 H); ¹³C NMR δ 211.3, 92.7, 68.5, 66.3, 53.3, 44.2, 43.3, 38.6, 37.0, 36.2, 36.0, 32.0, 31.3, 31.2 (2 C), 29.1, 28.7, 26.3, 25.7, 23.1, 20.1, 14.7, 11.0; MS (ESI) m/z (intensity) 383 ([M+Na]⁺, 38), 361 (86), 272 (15); HRMS (ESI) m/z calculated for C₂₃H₃₆O₅Na [M+Na] 383.2562, found 383.2545.

According to General Protocol B, the α-spiroether ketone (754 mg, 2.09 mmol), KHMDS (918 mg, 4.60 mmol) and Me₂SO₄ (1.05 g, 8.37 mmol) furnished, after chromatography on SiO₂ (6:1 hexanes/EtOAc), enol ether 3-48 (443 mg, 59%) as a white solid: Mp 157.1-158.5 °C (hexanes/EtOAc); IR (KBr) 2934, 1671, 1447, 1362, 1212, 1092 cm⁻¹; ¹H NMR δ 4.60 (dd, 1 H, J = 5.0, 1.0 Hz), 3.96 (ddd, 1 H, J = 7.7, 7.7, 2.6 Hz), 3.64-3.57 (m, 1 H), 3.46 (s, 3 H), 3.41 (br s, 1 H),
(1'R,3'S,4a'S,4b'R,6a'S,8'R,10a'S,10b'S,12a'S)-Methyl 18'-methoxy-10a',12a'-dimethyl octa-deca-hydro-3H-spiro-[furan-2,1'-naphtho-[2,1-f]-isochromene]-3'-carboxylate (3-49).

According to General Protocol A, enol ether 3-48 (443 mg, 1.24 mmol), m-CPBA (855 mg of ~70% m-CPBA, 3.72 mmol), Na₂HPO₄ (528 mg, 3.72 mmol) furnished, after 18 h and chromatography on SiO₂ (3:1 hexanes/EtOAc), spiroketal 3-49 (396 mg, 76%) as a colorless oil and as a single diastereomer by NMR: IR (neat) 2929, 1755, 1446, 1090, 732 cm⁻¹; ¹H NMR δ 4.38 (dd, 1 H, J = 12.4, 3.2 Hz), 3.92-3.75 (m, 2 H), 3.70 (s, 3 H), 3.41-3.40 (m, 1 H), 3.27 (s, 3 H), 2.04-1.98 (m, 1 H), 1.88-1.74 (m, 7 H), 1.68-1.09 (m, 14 H), 0.98 (s, 3 H), 0.91-0.81 (m, 2 H), 0.74 (s, 3 H); ¹³C NMR δ 172.9, 111.7, 75.4, 70.0, 67.7, 55.6, 53.1, 51.8, 42.9, 38.9, 38.8, 35.9, 35.0, 32.6, 32.4, 32.2, 31.5, 30.5, 28.5, 27.4, 25.1, 23.8, 19.7, 15.8, 11.3; MS (EI) m/z (intensity) 421 ([M+H]⁺, 27), 361 (51), 334 (80), 248 (100), 216 (95), 190 (87); HRMS (EI) m/z calculated for C₂₅H₄₁O₅ [M+H] 421.2954, found 421.2962.
2,6-Dibromo-N,N-bis(trimethylsilyl)benzenamine (4-53). A solution of 2,6-dibromoaniline 4-52 (15.7 g, 62.6 mmol) in THF (400 mL) was treated with LDA (34.4 mL of a 2M solution, 68.8 mmol) at -78 °C. After 5 min, TMSCl (9.53 mL, 75.1 mmol) was added. After 15 min, LDA (34.4 mL of a 2M solution, 68.8 mmol) was added and the reaction mixture was held at -78 °C for 20 min. TMSCl (9.53 mL, 75.1 mmol) was added and the reaction mixture was warmed to room temperature and quenched with aq. NaHCO₃ (~100 mL). The aqueous layer was washed with Et₂O (3 x 100 mL) and the combined organic layers were washed with H₂O, brine, dried (MgSO₄), filtered, concentrated and purified by chromatography on SiO₂ (hexanes) to furnish aniline 4-53 (24.6 g, 100%) as a colorless oil: IR (neat) 2953, 2898, 1422, 1251, 911 cm⁻¹; ¹H NMR δ 7.52 (d, 2 H, J = 8.0 Hz), 6.75 (t, 1 H, J = 8.0 Hz), 0.18 (s, 18 H); ¹³C NMR δ 132.2 (2C), 127.8, 125.6, 2.6 (6C); MS (El) m/z (rel intensity) 380 ([M-CH₃]⁺, 100, 301 (15); HRMS (El) m/z calcd for C₁₁H₁₈BrNSi₂ [M-CH₃] 377.9345, found 377.9334.
2-Bromo-6-iodobenzenamine (4-51). A solution of aniline 4-53 (24.6 g, 62.6 mmol) in THF (400 mL) was treated with s-BuLi (93.9 mL of a 1.4 M solution, 131.4 mmol) at -78 °C. After 15 min, the reaction mixture was warmed to 0 °C, treated with 3M HCl (aq, ~200 mL) and vigorously stirred for 1 h. The aqueous layer was extracted with Et₂O (3 x 100 mL) and the combined organic layers were washed with H₂O, brine, dried (Na₂SO₄), filtered and concentrated to yield crude aniline 4-55 which was immediately carried on to the next step. A solution of 4-55 (15.3 g, 62.6 mmol, based on 100% in previous reaction) in CH₂Cl₂ (340 mL) was cooled to -78 °C and treated with ICl (68.9 mL of a 1M solution, 68.9 mmol) over 30 minutes. The reaction mixture was warmed to 0 °C and quenched with Na₂S₂O₃ (aq, ~150 mL). The organic layer was washed with H₂O, brine, dried (Na₂SO₃), filtered, concentrated, and recrystallized from hexanes (3x) to furnish aniline 4-51 (16.8 g, 90% over two steps) as light brown needles: IR (neat) 3416, 3317, 1607, 1448, 1293, 1037, 754 cm⁻¹; ¹H NMR δ 7.59 (dd, 1 H, J = 8.1, 1.5 Hz), 7.40 (dd, 1 H, J = 7.8, 1.2 Hz), 6.33 (t, 1 H, J = 7.8 Hz), 4.59 (br s, 1 H); ¹³C NMR δ 144.1, 138.2, 132.8, 120.4, 107.3, 83.0; MS (ESI) m/z (rel intensity) 299 ([M+H]+, 15), 279 (31); HRMS (ESI) m/z calcd for C₆H₆BrIN [M+H]+ 297.8728, found 297.8715.

(E)-Ethyl 2-(tributylstanny1)but-2-enoate (4-57). A solution of ethyl propiolate 4-56 (4.44g, 39.6 mmol) in THF (200 mL, degassed) and Pd(PPh₃)₄ (915 mg, 0.792 mmol) at room temperature was treated with a solution of Bu₃SnH (11.7 mL, 43.55 mmol) in THF (40 mL, degassed) over 1 h. After 1.5 h, TLC analysis indicated consumption of the starting material, and the
solvent was evaporated and the residue dissolved in hexanes (~200 mL). After 1 h, the precipitates were filtered off and the filtrate concentrated. A small portion of this material could be purified by chromatography on SiO₂ (hexanes→9:1 hexanes/EtOAc) to provide stannane 4-57 (5:1 ratio of α:β regioisomers by ¹H NMR) as a colorless oil, which was carried on to the next step without further purification: IR 2957, 2926, 1708, 1461, 1180, 1036 cm⁻¹; ¹H NMR δ 6.16 (q, 1 H, J = 6.6 Hz), 4.14 (q, 2 H, J = 7.2 Hz), 2.00 (d, 3 H, J = 6.6 Hz), 1.53-1.42 (m, 6 H), 1.35-1.21 (m, 12 H), 0.98-0.82 (m, 12 H); ¹³C NMR δ 171.1, 147.9, 128.1, 59.9, 28.9, 27.2, 18.1, 14.3, 13.6, 10.2; HRMS (ESI) m/z calcd for C₁₈H₃₆O₂SnNa [M+Na] 427.1635, found 427.1637. Characteristic data for β isomer: ¹H NMR δ 5.95 (q, 1 H, J = 1.8 Hz), 2.38 (d, 1 H, J = 1.8 Hz); ¹³C NMR δ 136.9, 59.4, 9.4.

(E)-Ethyl 2-iodobut-2-enoate (4-58). The crude stannane residue was dissolved in THF (~250 mL) and treated with a solution of I₂ (13.7 g, 51.5 mmol) in THF (250 mL). After 30 min, TLC analysis indicated consumption of the stannane and the solvent was removed. The residue was dissolved in Et₂O (200 mL) and stirred with semisaturated KF for 1 h. Following, the solids were filtered off, and the aqueous layer extracted with Et₂O (3 x 100 mL). The combined organic layers were washed with H₂O, brine, dried (MgSO₄), filtered, concentrated, and the residue purified by chromatography on SiO₂ (95:5 hexanes/Et₂O) to provide iodide 4-58 (6.46 g, 68%) as a light yellow oil: IR 2981, 1713, 1368, 1220, 1027 cm⁻¹; ¹H NMR δ 6.98 (q, 1 H, J = 9.0 Hz), 4.25 (q, 2 H, J = 9.0 Hz), 1.99 (d, 3 H, J = 8.1 Hz), 1.32 (t, 3 H, J = 6.6 Hz); ¹³C NMR δ 163.8, 150.8, 85.5, 62.1,
19.3, 14.1; MS (EI) m/z (rel intensity) 240 ([M+H]+, 100), 212 (82), 195 (42); HRMS (EI) m/z calcd for C₆H₉O₂I 239.9647, found 239.9638.

(S)-tert-Butyl 4-(4-hydroxybenzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-61). A suspension of salt 4-59 (10.0 g, 43.2 mmol) and NaHCO₃ (7.25 g, 86.0 mmol) in THF/MeOH (200 mL/60 mL) was treated with Boc₂O (9.40 g, 43.2 mmol) at room temperature. After 24 h, the reaction mixture was concentrated and the residue dissolved in CH₂Cl₂ (~150 mL) and washed with H₂O, dried (MgSO₄), filtered, and concentrated to give crude 4-60 which was used without further purification. This crude material was dissolved in THF (200 mL) and treated with LiBH₄ (86.5 mL of a 2 M solution, 173 mmol) at 0 °C while vigorously stirring. After 6 h, 3M HCl was added dropwise and the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with H₂O, brine, dried (MgSO₄), filtered and concentrated to furnish the crude alcohol which was used without further purification. The crude alcohol was dissolved in dimethoxypropane/acetone (1:1, 160 mL) and treated with p-TsOH (821 mg, 4.32 mmol) at room temperature. After 4 h, the reaction mixture was poured into H₂O, and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered, concentrated and the solid recrystallized from hexanes (2x) to furnish phenol 4-61 (9.37 g, 70% over three steps) as a white powder: mp 104-106 °C (hexanes), lit. 107 °C; ¹H NMR
(S)-**tert-Butyl 4-(4-(methoxymethoxy)benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-62).** A suspension of NaH (568 mg of 60% NaH, 14.2 mmol) was degreased with hexanes and suspended in THF (~30 mL). A solution of phenol 4-61 (3.96 g, 12.9 mmol) in THF (~30 mL + 10 mL rinse) was added via cannula to the NaH at room temperature. After 30 min, the white solution was treated with TBAI (476 mg, 1.29 mmol) and MOMCl (2.55 mL, 33.5 mmol) was then added dropwise at 0 °C. After 12 h, H₂O was added to the reaction mixture and the aqueous layer was extracted with Et₂O (3 x 25 mL). The combined organic layers were washed with H₂O, brine, dried (Na₂SO₄), filtered, concentrated and purified by chromatography on SiO₂ (5:1 hexanes/EtOAc) to furnish MOM-ether 4-62 (4.12 g, 91%) as a colorless oil: IR 2978, 2934, 1698, 1388, 1078, 857 cm⁻¹; ¹H NMR (CD₃CN, 353 K) δ 7.15 (d, 2 H, J = 8.7 Hz), 6.97 (d, 2 H, J = 8.4 Hz), 5.14 (s, 2 H), 4.06-3.98 (m, 1 H), 3.83 (dd, 1 H, J = 9.0, 5.7 Hz), 3.73 (dd, 1 H, J = 9.0, 1.8 Hz), 3.43 (s, 3 H), 3.03 (dd, 1 H, J = 13.2, 3.6 Hz), 2.68 (dd, 1 H, J = 13.2, 9.6 Hz), 1.50 (s, 12 H), 1.45 (s, 3 H); ¹³C NMR (CD₃CN, 353 K) δ 157.4, 153.2, 133.6, 131.7 (2 C), 117.9 (2 C), 96.0, 94.9, 80.7, 67.4, 60.3, 56.5,
39.7, 29.1 (3 C), 27.7, 24.6; MS (ESI) m/z (rel intensity) 375 ([M+Na]+, 6), 322 (47), 224 (42);  
HRMS (ESI) m/z calcd for C_{19}H_{29}NO_{5}Na [M+Na] 374.1943, found 374.1956; [α]_D^{23} -19.2 (c 1.0, CH_{2}Cl_{2}).

(S)-tert-Butyl 4-(3-((Z)-1-(ethoxycarbonyl)prop-1-enyl)-4-(methoxymethoxy)benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-63). A solution of MOM-ether 4-62 (1.30 g, 3.71 mmol) and distilled TMEDA (600 μL, 3.98 mmol) in THF (12 mL) were treated with n-BuLi (3.06 mL of a 1.3 M solution, 3.98 mmol) at -78 °C. The yellow reaction mixture was warmed to room temperature for 45 min and recooled to 0 °C, and a solution of freshly fused ZnCl_{2} (560 mg, 4.11 mmol) in THF (~3 mL) was added via cannula. After 15 min at 0 °C, a solution of vinyl iodide 4-58 (636 mg, 2.65 mmol) and Pd(PPh_{3})_{4} (153 mg, 0.132 mmol) in THF (9 mL) was added via cannula and the reaction mixture was heated at 60 °C for 14 h. The cooled reaction mixture was treated with aq. NaHCO_{3} and the aqueous layer extracted with Et_{2}O (4 x 5 mL). The combined organic layers were washed with brine, dried (MgSO_{4}), filtered, concentrated and the residue purified by chromatography on SiO_{2} (3:1 hexanes/EtOAc) to furnish ester 4-63 (836 mg, 76% as a yellow oil: IR 2979, 2936, 1720, 1698, 1389, 1210, 1055 cm^{-1}; ^{1}H NMR (CD_{3}CN, 333 K) δ 7.12 (dd, 1 H, J = 9.0, 2.1 Hz), 7.07 (d, 1 H, J = 2.1 Hz), 7.00 (d, 1 H, J = 8.3 Hz), 6.24 (q, 1 H, J = 7.2 Hz), 5.07 (s, 2 H), 4.20 (q, 2 H, J = 6.9 Hz), 4.07-3.98 (m, 1 H), 3.87 (dd, 1 H, J = 9.0, 6.0 Hz), 3.76 (dd, 1 H, J =
(S,Z)-tert-Butyl-4-(3-(1-(2-bromo-6-iodophenylamino)-1-oxobut-2-en-2-yl)-4-hydroxy benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-64). A solution of AlMe₃ (297 mg, 0.998 mmol) in CH₂Cl₂ (1 mL) was treated with a solution of aniline 4-51 (297 mg, 0.998 mmol) in CH₂Cl₂ (1 mL) at 0°C. After 15 min, a white precipitate had formed. The reaction mixture was treated with a solution of ester 4-63 (154 mg, 0.333 mmol) in CH₂Cl₂ (2 mL) and warmed to ambient temperature. After 2 h, aq. Rochelle’s salt was added and the aqueous layer extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, concentrated and the residue purified by chromatography on SiO₂ (5:1 hex/EtOAc→3:1 hex/EtOAc) to provide anilide 4-64 (83 mg, 35%) as a colorless film which demonstrated hindered rotation by ¹H NMR, even at elevated temperatures: IR 3289, 2977, 1687, 1483, 1390, 1255 cm⁻¹; ¹H NMR (CD₃CN, 353 K, reported as seen) δ 7.88 (dd, 1 H, J = 8.7, 1.8 Hz), 7.66 (dd, 1 H, J = 8.4, 1.5 Hz),
7.60-7.30 (br s, 1 H), 7.17-7.04 (m, 3 H), 6.94-6.86 (m, 2 H), 4.19-4.04 (br s, 1 H), 3.91-3.75 (m, 2 H), 3.01 (dd, 1 H, J = 12.6, 4.8 Hz), 2.77 (dd, 1 H, J = 15.0, 10.2 Hz), 1.72 (d, 3 H, J = 6.6 Hz), 1.50-1.38 (m, 15 H); 13C NMR (CD3CN, 353 K, reported as seen) δ 167.5, 154.7, 153.2, 140.3, 139.9, 134.4, 133.6, 132.2, 131.7, 131.6, 124.5, 123.0, 117.7, 102.0, 94.9, 80.7, 67.8, 60.2, 39.7, 29.1 (3 C), 28.0, 24.8, 15.7; MS (ESI) m/z (rel intensity) 693 ([M+Na]+, 100), 592 (44); HRMS (ESI) m/z calcd for C27H32BrIN2O5Na [M+Na] 693.0437, found 693.0423; [α]D23 -8.7 (c 1.0, CH2Cl2).

(S)-tert-Butyl 4-(4-hydroxy-3-iodobenzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-67).

A solution of iodotyrosine (4-65, 49.2 mmol) in MeOH (350 mL) was treated with SOCl2 (35.9 mL, 492 mmol) over 30 min at 0 °C and then heated at 70 °C for 2 h. The volume of the reaction was reduced to about one-third in vacuo and the remaining solution poured into anhydrous Et2O (500 mL). The resulting white precipitate was filtered off, dried in vacuo, and used directly in the next step. A suspension of this white precipitate in THF/MeOH (300/120 mL) was treated with NaHCO3 (8.26 g, 98.3 mmol) and Boc2O (10.7 g, 49.2 mmol) at ambient temperature. After 24 h, the reaction mixture was concentrated to about one-third of its volume and partitioned between CH2Cl2 and H2O (200 mL/200 mL). The aqueous layer was extracted with CH2Cl2 (3 x 100 mL) and the combined organic layers washed with brine, dried (Na2SO4), filtered, and concentrated to provide ester 4-66 as a colorless oil that was used directly in the next step. A solution of 4-66 in THF (550 mL) was

192
treated dropwise with LiBH₄ (96.5 mL of a 2 M solution, 193 mmol) at 0 °C. The mixture was vigorously stirred and warmed to ambient temperature. After 4 h, aq. HCl was added until all additional LiBH₄ had been quenched. The aqueous layer was extracted with EtOAc (3 x 100 mL) and the combined organic layers washed with brine, dried (Na₂SO₄), filtered, and concentrated to provide the intermediate reduced ester as a colorless oil which was used directly without further purification. A solution of alcohol in acetone/2,2-dimethoxypropane (100 mL/100 mL) was treated with TsOH (918 mg, 4.82 mmol) at ambient temperature. After 1 h, aq. NaHCO₃ was added and the aqueous layer was extracted with EtOAc (4 x 100 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, concentrated, and the residue purified by chromatography on SiO₂ (3:1 hexanes/EtOAc) to provide phenol 4-67 (19.6 g, 93% over four steps) as a colorless oil: IR 3307, 2979, 2935, 1663, 1409, 1253, 1097 cm⁻¹; ¹H NMR (CD₃CN, 353 K) δ 7.57 (d, 1 H, J = 2.1 Hz), 7.08 (dd, 1 H, J = 8.1, 2.1 Hz), 7.03 (br s, 1 H), 6.84 (d, 1 H, J = 8.1 Hz), 4.03-3.94 (m, 1 H), 3.85 (dd, 1 H, J = 8.4, 6.0 Hz), 3.72 (dd, 1 H, J = 9.0, 1.5 Hz), 2.92 (dd, 1 H, J = 13.5, 3.6 Hz), 2.67 (dd, 1 H, J = 13.2, 9.0 Hz), 1.49 (s, 9 H), 1.47 (s, 3 H), 1.44 (s, 3 H); ¹³C NMR (CD₃CN, 353 K) δ 155.9, 153.2, 141.1, 133.9, 132.1, 116.3, 94.9, 84.8, 80.7, 67.4, 60.0, 38.8, 29.0 (3 C), 27.6, 24.4; MS (EI) m/z (rel intensity) 433 ([M]⁺, 19), 360 (17), 233 (53); HRMS (EI) m/z calcd for C₁₇H₂₄INO₄ 433.0750, found 433.0746; [α]D²³ -21.4 (c 1.0, CH₂Cl₂).
(S)- tert-Butyl-(3-((Z)-1-(ethoxycarbonyl)prop-1-enyl)-4-(benzyloxy)benzyl)-2,2-dimethyl oxazolidine-3-carboxylate (4-69). A solution of phenol 4-67 (7.69 g, 17.7 mmol) in THF (200 mL) was treated with NaH (1.06 g of 60% NaH in oil, 26.6 mmol) at 0 °C and the resulting slurry stirred for 30 min. TBAI (655 mg, 1.77 mmol) and BnBr (5.28 mL, 44.4 mmol) were added and the reaction mixture was warmed to ambient temperature. After 14 h, aq. NH₄Cl was added and the aqueous layer was extracted with Et₂O (3 x 50 mL). The combined organic layers were washed with H₂O, brine, dried (Na₂SO₄), filtered, concentrated and purified by chromatography on SiO₂ (6:1 hexanes/EtOAc) to proved benzyl ether 4-68 (8.04 g, 87%) as a yellow oil that was used directly in the next step. A solution of benzyl ether 4-68 (624 mg, 1.19 mmol), stannane 4-57 (438 mg, 1.08 mmol) and LiCl (138 mg, 3.24 mmol) were dissolved/suspended in DMF (3 mL). Pd(PPh₃)₄ (37.9 mg, 0.054 mmol) was added and the mixture was degassed by F-P-T (3 x). The reaction mixture was heated to 85 °C for 18 h. Following, the cooled reaction mixture was partitioned between H₂O and Et₂O (10 mL/10 mL). The aqueous layer was extracted with Et₂O (3 x 10 mL) and the combined organic layers were washed with H₂O, brine, dried (Na₂SO₄), filtered, concentrated and the residue purified by chromatography on SiO₂ (5:1 hexanes/EtOAc) to provide ester 4-69 as a colorless oil and approximately 2:1 mixture of regioisomers (α:β) by ¹H NMR: IR 2979, 2395, 1697, 1389, 1259, 1095, 1026 cm⁻¹; ¹H NMR (CD₃CN, 353 K, reported as seen) δ 7.56-7.30 (m, 4 H), 7.22-6.97 (m, 3 H), 6.96 (m, 1 H), 6.27 (q, 1 H, J = 7.2 Hz), 5.13-5.08 (m, 0.5 H), 5.07-5.03 (m, 1.5 H), 4.10 (q, 2 H, J = 7.2 Hz), 4.11-4.03 (m, 1 H), 3.93-3.84 (m, 1 H), 3.83-3.75 (m, 1 H), 3.12-2.98 (m, 1 H), 2.84-2.69 (m, 1 H), 2.48 (d, 1 H, J = 1.2 Hz), 2.08 (d, 2 H, J = 7.2 Hz), 1.58-1.48 (m, 15 H), 1.31 (t, 1 H, J = 7.2 Hz), 1.18 (t, 2 H, J = 7.2 Hz); ¹³C NMR (CD₃CN, 353 K) δ 168.6, 156.3, 153.4, 138.9, 138.2, 134.7, 132.8, 131.2, 129.9, 129.7 (2 C), 129.1, 128.9, 128.8 (2 C), 114.2, 95.1, 80.8, 72.0, 67.7, 61.3, 60.3, 39.6, 29.3 (3 C), 27.8, 25.0, 16.2, 14.9 ; MS (ESI) m/z (rel intensity) 532
([M+Na]$^+$, 4), 432 (100), 365 (14); HRMS (ESI) m/z calcd for C$_{30}$H$_{39}$NO$_6$Na [M+Na] 532.2675, found 532.2674; [α]$_D^{23}$ -14.7 (c 1.0, CH$_2$Cl$_2$).

(S)-$\alpha$-tert-Butyl-4-((E)-1-(methoxycarbonyl)prop-1-enyl)-4-(benzyloxy)benzyl)-2,2-dimethylloxazolidine-3-carboxylate (4-72). A solution of benzyl ether 4-68 (539 mg, 1.03 mmol), pinacolato diboron (288 mg, 1.13 mmol), PdCl$_2$dpf-CH$_2$Cl$_2$ (168 mg, 0.206 mmol), and KOAc (303 mg, 3.09 mmol) in DMSO (5 mL) was stirred for 12 h. Following, H$_2$O was added and the solution was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine, dried (Na$_2$SO$_4$), filtered, concentrated and the residue purified by chromatography in SiO$_2$ (1:1 hexanes/EtOAc) to proved boronate ester 4-70 (378 mg, 70%) as a colorless oil which was used directly in the next step. A solution of vinyl iodide 4-71 (147 mg, 0.65 mmol), boronate 4-70 (374 mg, 0.715 mmol), K$_2$CO$_3$ (155 mg, 1.12 mmol), and PdCl$_2$dpf-CH$_2$Cl$_2$ (45.9 mg, 0.056 mmol) in DME (6 mL) was heated at 50 °C for 8 h. The cooled reaction mixture was diluted with H$_2$O and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with H$_2$O, brine, dried (Na$_2$SO$_4$), filtered, concentrated and the residue purified by chromatography on SiO$_2$ (3:1 hexanes/EtOAc) to provide ester 4-72 (165 mg, 51%) as a colorless oil which demonstrated evidence of hindered rotation by $^1$H NMR, even at elevated temperatures: IR 2978, 2873, 1699, 1389, 1259, 736 cm$^{-1}$; $^1$H NMR (CD$_3$CN, 353 K) δ 7.40-7.33 (m, 3 H), 7.27-7.24 (m, 1 H), 7.19-7.13 (m, 2 H), 7.10-7.07 (m, 2 H), 7.05 (d, 1 H), 6.95-6.90 (m, 2 H), 6.50-6.45 (m, 1 H), 5.50-5.45 (m, 1 H), 4.30-4.25 (m, 1 H), 4.20-4.15 (m, 1 H), 2.00-1.95 (m, 2 H), 1.80-1.75 (m, 2 H), 1.70-1.65 (m, 2 H), 1.50-1.45 (m, 2 H), 1.30-1.25 (m, 2 H), 1.20-1.15 (m, 2 H), 1.10-1.05 (m, 2 H), 0.90-0.85 (m, 2 H), 0.85-0.80 (m, 2 H), 0.80-0.75 (m, 2 H).
7.10-6.99 (m, 2 H), 6.98-6.94 (m, 1 H), 5.05-5.01 (m, 2 H), 4.08-3.92 (m, 1 H), 3.89-3.81 (m, 1 H),
3.68 (s, 0.5 H), 3.63 (s, 2.5 H), 3.03 (dd, 1 H, J = 13.2, 3.0 Hz), 2.73 (dd, 1 H, J = 13.2, 9.6 Hz), 1.69 (d, 3 H, J = 6.9 Hz), 1.52-1.48 (m, 8 H), 1.48-1.43 (m, 7 H); 13C NMR
(CD3CN, 353 K) δ 168.6, 156.6, 153.2, 140.7, 138.9, 133.7, 132.2, 131.3, 129.7 (2 C), 129.6, 129.1,
128.7 (2 C), 126.4, 114.2, 94.9, 80.7, 71.6, 67.3, 60.2, 52.4, 39.5, 29.1 (3 C), 27.7, 24.7, 15.9; MS
(ESI) m/z (rel intensity) 518 ([M+Na]+, 100), 418 (100); HRMS (ESI) m/z calcd forC29H37NO6Na
[M+Na] 518.2519, found 518.2534; [α]D23 -16.3 (c 1.0, CH2Cl2).

(S)-tert-Butyl-4-(3-iodo-4-(methoxymethoxy)benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-74). A solution of phenol 4-67 (24.3 g, 56.1 mmol) in THF (500 mL) was treated with NaH
(3.36 g of 60% NaH in grease, 84.0 mmol) portionwise at 0 °C. After 45 min, solid TBAI (2.07 g, 5.61 mmol) was added, followed by MOMCl (12.8 mL, 169 mmol) dropwise. After 6 h at room
temperature, the reaction was quenched by the addition of H2O and the aqueous layer was extracted with Et2O (3 x 100 mL). The combined organic layers were washed with H2O, brine, dried
(MgSO4), filtered, and concentrated. The bulk of the crude MOM ether was carried on crude, but an analytical sample was purified by chromatography on SiO2 (6:1 hexanes/EtOAc) to provide 4-74 as a colorless oil: IR (neat) 2976, 2930, 1697, 1388, 1241, 1085, 992 cm⁻¹; 1H NMR (DMSO-d6, 353 K) δ 7.60 (d, 1 H, J = 2.1 Hz), 7.15 (dd, 1 H, J = 8.4, 2.1 Hz), 7.02 (d, 1 H, J = 8.1 Hz), 5.19 (s, 2 H),
4.02-3.93 (m, 1 H), 3.84 (dd, 1 H, J = 9.0, 6.0 Hz), 3.69 (dd, 1 H, J = 9.0, 1.8 Hz), 3.43 (s, 3 H), 2.88
(S)-tert-Butyl 4-(4-(methoxymethoxy)-3-(prop-1-ynyl)benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-75). A solution of MOM-ether 4-74 (26.8 g, 56.1 mmol based on 100% from previous reaction), PdCl₂(PPh₃)₂ (787 mg, 1.12 mmol), and CuI (1.60 g, 8.4 mmol) was dissolved in CH₃CN/Et₂NH (400 mL/100 mL) and cooled to -20 °C. A cold-finger containing dry ice/acetone was attached to the flask and a 25 g (625 mmol) container of propyne was condensed into the reaction mixture. Following, the reaction mixture was warmed to room temperature, stirred for 12 h, and the volatile components evaporated. The residue was dissolved in boiling hexanes and then cooled to room temperature. The precipitates were filtered off (celite) and the orange filtrate was concentrated and carried to the next step without further purification. An analytical sample was purified by chromatography on SiO₂ (6:1 hexanes/EtOAc) to provide 4-75 as a colorless oil: IR (neat) 2978, 2234, 1740, 1701, 1078, 998 cm⁻¹; ¹H NMR (DMSO-d₆, 353 K) δ 7.15 (d, 1 H, J = 2.1 Hz), 7.08 (dd, 1 H, J = 8.7, 2.1 Hz), 7.02 (d, 1 H, J = 8.4 Hz), 5.17 (s, 2 H), 4.10-3.93 (m, 1 H), 3.83 (dd, 1 H, J = 9.0, 6.0 Hz), 3.68 (dd, 1 H, J = 9.0, 1.8 Hz), 3.42 (s, 3 H), 2.90 (dd, 1 H, J = 13.2, 3.6 Hz), 2.67 (dd, 1 H, J = 13.2, 8.7 Hz), 1.44 (s, 9 H), 1.42 (s, 3 H), 1.41 (s, 3 H); ¹³C NMR (DMSO-d₆, 353 K) δ 154.0, 150.8, 139.2, 133.5, 129.9, 114.9, 94.7, 92.8, 86.9, 78.7, 65.6, 57.7, 55.5, 37.0, 27.7 (3 C), 26.2, 23.4; MS (EI) m/z (rel intensity); HRMS (EI) m/z calcd for C₁₉H₂₈NO₅Na [M+ Na] 500.0910, found 500.0886; [α]D²³: -24.1 (c = 1.0, CH₂Cl₂).
Hz), 2.64 (dd, 1 H, $J = 13.2, 9$ Hz), 2.04 (s, 3 H), 1.45 (s, 9 H), 1.43 (s, 3 H), 1.41 (s, 3 H); $^{13}$C NMR (DMSO-d$_6$, 353 K) $\delta$ 155.6, 150.8, 133.3, 131.4, 129.3, 115.6, 114.0, 94.7, 92.7, 89.3, 78.7, 75.6, 65.6, 57.7, 55.2, 37.3, 27.7 (3 C), 26.3, 23.4, 3.5; MS (EI) $m/z$ (rel intensity) 390 ([M+H]$^+$, 8), 389 ([M]$^+$, 30), 200 (68); HRMS (EI) $m/z$ calcd for C$_{22}$H$_{31}$NO$_5$ 389.2202, found 389.2196; $\left[\alpha\right]_D^{23}$ -44.4 (c 1.0, CH$_2$Cl$_2$).

![Chemical Structure](image)

(S)-tert-Butyl 4-(3-((E)-1-iodoprop-1-enyl)-4-(methoxymethoxy)benzyl)-2,2-dimethyl oxazolidine-3-carboxylate (4-76). A solution of alkyne 4-75 (21.9 g, 56.1 mmol based on 100% from previous reaction) and PdCl$_2$(PPh$_3$)$_2$ (1.18 g, 1.68 mmol) in THF (220 mL, degassed) at room temperature was treated with a solution of Bu$_3$SnH (18.1 mL, 67.4 mmol) in THF (40 mL, degassed) dropwise. Once the addition was finished, the reaction mixture was evaporated and the residue dissolved in hexanes (~400 mL), filtered through celite, and the filtrate evaporated. The residue was dissolved in THF (300 mL) and treated with a solution of I$_2$ (18.5 g, 72.9 mmol) in THF (100 mL) over 30 min. Following, the reaction mixture was treated with aq. Na$_2$S$_2$O$_3$ and the aqueous layer was extracted with Et$_2$O (3 x 100 mL). The combined organic layers were washed with brine, dried (MgSO$_4$), filtered, concentrated and purified by chromatography on SiO$_2$ (6:1→3:1 hexanes/EtOAc, 3x) to provide vinyl iodide 4-76 (20.6 g, 71% over 8 steps) as a yellow oil: IR (neat) 2976, 1696, 1390, 1309, 1168, 1000, 923 cm$^{-1}$; $^1$H NMR (DMSO-d$_6$, 353 K) $\delta$ 7.10 (dd, 1 H, $J = 8.4, 2.1$ Hz), 198
7.02 (d, 1 H, $J = 8.4$ Hz), 6.95 (d, 1 H, $J = 2.1$ Hz) 6.51 (q, 1 H, $J = 6.9$ Hz), 5.18 (s, 2 H), 4.01-3.93 (m, 1 H), 3.85 (dd, 1 H, $J = 8.7$, 6.0 Hz), 3.70 (dd, 1 H, $J = 9.0$, 1.8 Hz), 3.43 (s, 3 H), 2.91 (dd, 1 H, $J = 13.2$, 3.3 Hz), 2.70 (dd, 1 H, $J = 13.5$, 9.0 Hz), 1.47 (s, 9 H), 1.45 (d, 3 H, $J = 6.6$ Hz), 1.41 (s, 3 H), 1.39 (s, 3 H); $^{13}$C NMR (DMSO-$d_6$, 353 K) $\delta$ 151.3, 150.8, 138.1, 130.9, 130.3, 130.2, 129.9, 114.9, 94.0, 92.8, 89.7, 78.7, 65.4, 57.7, 55.4, 37.2, 27.7 (3 C), 26.2, 23.4, 16.9; MS (ESI) $m/z$ (rel intensity) 540 ([M+Na]$^+$, 13), 500 (100), 430 (53); HRMS (ESI) $m/z$ calcd for C$_{22}$H$_{32}$INO$_5$Na 540.1223 [M+Na], found 540.1224; $[\alpha]_D^{23}$ -43.9 (c 1.0, CH$_2$Cl$_2$).

(S)-tert-Butyl 4-((E)-1-(methoxycarbonyl)prop-1-enyl)-4-(methoxymethoxy)benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-77). A solution of alkenyl iodide 4-76 (10.2 g, 19.7 mmol), DIPEA (13.7 mL, 78.9 mmol), PdCl$_2$(PPh$_3$)$_2$ (692 mg, 0.986 mmol), and MeOH (23.9 mL, 591 mmol) was purged with CO for 30 min and then heated at 60 °C under a balloon of CO for 8 h. The cooled reaction mixture was poured into brine (500 mL) and the mixture extracted with Et$_2$O (5 x 150 mL). The combined organic layers were washed with brine, dried (MgSO$_4$), filtered, concentrated, and the residue purified by chromatography on SiO$_2$ (5:1→3:1 hexanes/EtOAc) to furnish ester 4-77 (4.87 g, 55%) as a yellow oil: IR (neat) 2978, 1718, 1697, 1389, 1258, 1077 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$, 353 K) $\delta$ 7.12 (dd, 1 H, $J = 8.4$, 2.1 Hz), 7.05 (d, 1 H, $J = 8.4$ Hz), 7.01 (q, 1 H, $J = 6.9$ Hz), 6.88 (d, 1 H, $J = 2.1$ Hz), 5.05 (s, 2 H), 4.02-3.93 (m, 1 H), 3.85 (dd, 1 H, $J = 9.0$, 6.0 Hz), 3.70 (dd, 1 H, $J = 9.0$, 1.8 Hz), 3.43 (s, 3 H), 2.91 (dd, 1 H, $J = 13.2$, 3.3 Hz), 2.70 (dd, 1 H, $J = 13.5$, 9.0 Hz), 1.47 (s, 9 H), 1.45 (d, 3 H, $J = 6.6$ Hz), 1.41 (s, 3 H), 1.39 (s, 3 H); $^{13}$C NMR (DMSO-$d_6$, 353 K) $\delta$ 151.3, 150.8, 138.1, 130.9, 130.3, 130.2, 129.9, 114.9, 94.0, 92.8, 89.7, 78.7, 65.4, 57.7, 55.4, 37.2, 27.7 (3 C), 26.2, 23.4, 16.9; MS (ESI) $m/z$ (rel intensity) 540 ([M+Na]$^+$, 13), 500 (100), 430 (53); HRMS (ESI) $m/z$ calcd for C$_{22}$H$_{32}$INO$_5$Na 540.1223 [M+Na], found 540.1224; $[\alpha]_D^{23}$ -43.9 (c 1.0, CH$_2$Cl$_2$).
Hz), 3.72 (dd, 1 H, J = 9.0, 1.8 Hz), 3.62 (s, 3 H), 3.32 (s, 3 H), 2.95 (dd, 1 H, J = 13.2, 3.3 Hz), 2.69 (dd, 1 H, J = 13.2, 9.3 Hz), 1.65 (d, 3 H, J = 7.2 Hz), 1.46 (s, 9 H), 1.41 (s, 6 H); \(^{13}\)C NMR (DMSO-d\(_6\), 353 K) \(\delta\) 166.2, 152.8, 150.8, 138.8, 131.4, 131.1, 130.7, 129.2, 124.7, 114.6, 94.2, 92.8, 78.7, 65.4, 57.9, 55.0, 50.9, 37.3, 27.7 (3 C), 26.2, 23.4, 14.5; MS (ESI) m/z (rel intensity) 472 ([M+Na]\(^+\), 100), 416 (46); HRMS (ESI) m/z calcd for C\(_{24}\)H\(_{35}\)NO\(_7\)Na 472.2311 [M+Na], found 472.2291; [\(\alpha\)]\(_D\)\(^{23}\) -23.6 (c 1.0, CH\(_2\)Cl\(_2\)).

\((S,E)-tert-Butyl-4-(3-(1-(2-bromo-6-iodophenylamino)-1-oxobut-2-en-2-yl)-4-hydroxy benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-78)\). A solution of aniline 4-51 (9.55 g, 32.1 mmol) in CH\(_2\)Cl\(_2\) (60 mL) was added to a solution AlMe\(_3\) (2.31 g, 32.1 mmol, neat) in CH\(_2\)Cl\(_2\) (40 mL) at 0 °C. After 1 h at room temperature, a white precipitate had formed. A solution of ester 4-77 (4.80 g, 10.7 mmol) in CH\(_2\)Cl\(_2\) (60 mL) was added and the reaction mixture was immediately heated to reflux and held for 45 min. The cooled reaction mixture was treated slowly with aq. Rochelle’s salt and stirred for 3 h. The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 x 100 mL) and the combined organic layers were dried (MgSO\(_4\)), filtered, concentrated and purified by chromatography on SiO\(_2\) (3:1→2:1 hexanes/EtOAc) to provide the anilide 4-78 (3.82 g, 53%) as a white foam: mp 94.5-102.6 °C (CH\(_2\)Cl\(_2\)); IR (neat) 3284, 2978, 1686, 1482, 1390, 1256 cm\(^{-1}\); \(^1\)H NMR (DMSO-d\(_6\), 353 K) \(\delta\) 8.98 (br s, 1 H), 8.74 (s, 1 H), 7.87 (dd, 1 H, J = 8.1, 1.5 Hz), 7.66 (dd, 1 H, J = 9.0, 1.2
(S)-tert-Butyl 4-(3-((E)-1-(N-benzyl-N-(2-bromo-6-iodophenyl)carbamoyl)prop-1-enyl)-4-(benzyloxy)benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-79). A solution of anilide 4-78 (6.80 g, 10.1 mmol) in THF (100 mL) was treated with NaH (1.22 g of 60% NaH, 30.4 mmol) at 0 °C. After 30 min, the reaction mixture was treated with TBAI (374 mg, 1.01 mmol) and BnBr (6.01 mL, 50.6 mmol) and heated to 65 °C for 30 min. The cooled reaction mixture was quenched by the addition of H2O and the aqueous layer was extracted with Et2O (4 x 30 mL) and the combined organic layers were washed with brine, dried (MgSO4), filtered, concentrated and purified by chromatography on SiO2 (3:1 hexanes/EtOAc) to provide anilide 4-79 (7.24 g, 84%) as a white foam and several atropdiastereomers as indicated by 1H NMR analysis: mp 73.6-78.0 °C (CH2Cl2); IR (neat) 2977, 2934, 1696, 1653, 1434, 1388, 1254, 734 cm⁻¹; 1H NMR (DMSO-d6, 353 K, reported as
\[ \delta 7.58 \text{ (dd, 1 H, } J = 9.0, 3.9 \text{ Hz)}, \text{ 7.47-7.44 (m, 5 H), 7.43-7.25 (m, 3.5 H), 7.23-7.12 (m, 6 H),} \\
\text{7.08-7.01 (m, 1 H), 7.01-6.93 (m, 1 H), 6.93-6.84 (m, 1 H), 6.76-6.64 (m, 1.5 H), 6.58 (app q, 1 H, } J = 5.4 \text{ Hz), 6.35-6.23 (m, 1 H), 5.18 (s, 0.5 H), 5.00-4.92 (m, 2 H), 4.90-4.68 (m, 3 H), 4.05-3.97 (m,} \\
\text{1 H), 3.90-3.70 (m, 3 H), 3.66-3.58 (m, 1 H), 3.12-2.98 (m, 1 H), 2.89-2.68 (m, 1 H), 2.46-2.33 (m, 1 H), 1.69 (d, 1 H, } J = 7.5 \text{ Hz), 1.47 (s, 9 H), 1.47-1.45 (m, 2.5 H), 1.44 (s, 2 H), 1.41 (s, 1.5 H);} \\
\text{13C NMR (DMSO-d\textsubscript{6}, 353 K, reported as seen) } \delta 168.6, 153.9, 150.7, 141.5, 138.9, 136.8, 136.0, 134.8, \\
134.7, 133.0, 130.0, 129.8, 129.7, 129.0, 128.9, 128.8, 127.7, 127.5, 127.1, 127.0, 126.7, 126.5, \\
124.1, 122.7, 112.0, 102.2, 92.7, 78.6, 68.8, 65.3, 57.8, 57.8, 51.5, 37.4, 27.8, 36.4, 23.4, 14.1; \\
\text{HRMS (ESI) } m/z \text{ calcd for C}_{41}\text{H}_{45}\text{BrIN}_{2}\text{O}_{5} [M+H] 851.1557, \text{ found } 851.1592; [\alpha]_{D}^{23} -11.0 \text{ (c 0.5, CH}_{2}\text{Cl}_{2}).

(S)-\text{tert-Butyl-4-((S)-1-benzyl-7-bromo-2-oxo-3-vinylindolin-3-yl)-4-(benzyloxy)benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-80).} \text{ A mixture of amide 4-79 (3.00 g, 3.52 mmol),} \\
Pd\textsubscript{2}dba\textsubscript{3}-CHCl\textsubscript{3} (365 mg, 0.352 mmol), (S)-BINAP (483 mg, 0.775 mmol), and PMP (2.55 mL, 14.1 \text{ mmol}) in freshly distilled NMP (35 mL) was degassed (F-P-T, 3x). \text{ The reaction mixture was heated} \\
at 110 \degree C for 3.5 h, at which time HPLC indicated completion of the reaction. \text{ The cooled reaction} \\
mixture was poured into Et\textsubscript{2}O (50 mL) and H\textsubscript{2}O (50 mL). \text{ The aqueous layer was extracted with}
Et₂O (3 x 50 mL), and the combined organic layers were washed with H₂O (5x), brine, dried (MgSO₄), filtered, concentrated and purified by chromatography on SiO₂ (3:1 hexanes/EtOAc) to furnish oxindole 4-80 (2.14 g, 84%) as a white foam which was 77:23 mixture of diastereomers by HPLC: mp 77.5-84.2 °C (CH₂Cl₂); IR (neat) 2978, 2872, 1725, 1697, 1388, 1257, 1017, 738 cm⁻¹; ¹H NMR (DMSO-d₆, 353 K) δ 7.40-7.32 (m, 4 H), 7.30 (d, 1 H, J = 1.8 Hz), 7.26-7.12 (m, 4 H), 7.08-6.80 (m, 7 H), 6.30 (dd, 1 H, J = 17.4, 10.2 Hz), 5.40 (d, 1 H, J = 10.2), 4.93 (d, 1 H, J = 17.1 Hz), 4.85-4.71 (m, 3 H), 4.64 (d, 1 H, J = 16.8 Hz), 4.10-3.98 (m, 1 H), 3.88 (dd, 1 H, J = 9.0, 5.7 Hz), 3.76 (dd, 1 H, J = 9.0, 1.5 Hz), 3.05-2.98 (m, 1 H, signal obscured by H₂O contaminating DMSO), 2.78-2.68 (m, 1 H), 1.48 (s, 9 H), 1.47 (s, 3 H), 1.44 (s, 3 H); ¹³C NMR δ 176.7, 153.8, 150.8, 139.8, 137.8, 137.0, 135.7, 133.8, 132.9, 129.9, 129.8, 129.3, 128.0 (2 C), 127.8 (2 C), 127.6, 127.4, 127.3 (2 C), 126.2, 125.4 (2 C), 123.1, 123.0, 117.1, 112.2, 101.1, 92.8, 78.7, 69.6, 65.4, 58.0, 57.0, 43.0, 37.7, 27.8 (3 C), 26.4, 23.3; HRMS (ESI) m/z calcd for C₄₁H₄₃BrN₂O₅Na [M+Na] 745.2253, found 745.2269; [α]D 23 +86.9 (c 1.0, CH₂Cl₂).

(S)-tert-Butyl 4-(3-((S)-1-benzyl-7-bromo-3-vinylindolin-3-yl)-4-(benzyloxy)benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-82). A solution of oxindole 4-80 (5.05 g, 6.99 mmol) in THF (10 mL) was treated with DIBAL (28.0 mL of a 1 M solution, 28.0 mmol) at room temperature.
The reaction mixture was heated at reflux for 40 min and cooled to room temperature upon consumption of the starting material. The cooled reaction mixture was treated with aq. Rochelle’s salt and stirred for 3 h. The aqueous layer was extracted with Et₂O (3 x 30 mL) and the combined organic layers washed with brine, dried (MgSO₄), filtered, concentrated and purified by chromatography on SiO₂ (5:1 hexanes/EtOAc) to provide hydroindole 4-82 (3.78 g, 76%) as a white foam: mp 46.2-54.1 °C (CH₂Cl₂); IR (neat) 2977, 2933, 2873, 1697, 1388, 1095, 735 cm⁻¹; ¹H NMR (DMSO-d₆, 353 K) δ 7.34-7.18 (m, 9 H), 7.15-7.12 (m, 2 H), 7.08 (dd, 1 H, J = 8.4, 1.8 Hz), 7.05-7.00 (m, 1 H), 6.92 (d, 1 H, J = 1.8 Hz), 6.82 (dd, 1 H, J = 7.2, 1.2 Hz), 6.63 (dd, 1 H, J = 7.5, 7.5 Hz), 6.21 (dd, 1 H, J = 17.1, 10.5 Hz), 5.06 (dd, 1 H, J = 10.5, 0.9 Hz), 4.96 (d, 1 H, J = 11.7 Hz), 4.85 (d, 1 H, J = 12.0 Hz), 4.76 (app t, 2 H, J = 15.3 Hz), 4.34 (d, 1 H, J = 15.6 Hz), 3.98-3.78 (m, 1 H), 3.83-3.78 (m, 2 H), 3.68-3.60 (m, 2 H), 2.89 (dd, 1 H, J = 13.5, 3.6 Hz), 2.60 (dd, 1 H, J = 13.2, 9.0 Hz), 1.43 (s, 3 H), 1.42 (s, 9 H), 1.41 (s, 3 H); ¹³C NMR (DMSO-d₆, 353 K) δ 154.3, 150.7, 147.5, 142.8, 138.3, 137.5, 136.4, 132.3, 131.9, 129.2, 129.0, 128.6, 127.6(4) (2 C), 127.6(0) (2 C), 127.0, 126.9 (2 C), 126.8 (2 C), 126.2, 124.0, 119.0, 112.9, 112.3, 102.2, 92.7, 78.5, 69.4, 65.4, 64.3, 57.8, 53.5, 52.9, 37.7, 27.7 (3 C), 26.3, 23.3; MS (ESI) m/z (rel intensity) 711 ([M+H]⁺, 48), 709 ([M+H]⁺, 48), 574 (100); HRMS (ESI) m/z calcd for C₄₁H₄₆BrN₂O₄ 709.2641, found 709.2645; [α]D²³ -2.5 (c 1.0, CH₂Cl₂). Characteristic data for minor diastereomer: ¹H NMR (DMSO-d₆, 353 K) δ 6.81 (dd, 1 H, J = 7.2, 1.2 Hz), 6.62 (dd, 1 H, J = 7.5, 7.5 Hz), 5.07 (dd, 1 H, J = 10.5, 0.9 Hz), 4.33 (d, 1 H, J = 15.6 Hz); ¹³C NMR (DMSO-d₆, 353 K) δ 137.6, 129.0, 128.5, 123.9, 27.7.
(S)-tert-Butyl 4-(3-((R)-1-benzyl-7-bromo-3-formylindolin-3-yl)-4-(benzyloxy)benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-83). A solution of hydroindole 4-82 (3.76 g, 5.31 mmol) in THF/Acetone/pH 7 phosphate buffer (6/6/6 mL) was treated with NMO (1.06 g, 7.96 mmol) and OsO₄ (2.41 mL of a 0.33 M solution, 0.796 mmol) at room temperature. After 8 h, aq. NaHSO₃ was added and the mixture extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered, and concentrated. The crude residue was dissolved in THF/pH 7 phosphate buffer (25/5 mL) and treated with NaIO₄ (3.41 g, 15.9 mmol). After 40 min, the solution was diluted with brine, extracted with EtOAc (3 x 60 mL) and the combined organic layers washed with brine, dried (MgSO₄), filtered, concentrated, and the residue purified by chromatography on SiO₂ (4:1 hexanes/EtOAc) to furnish the aldehyde as a white foam and 3.3:1 mixture of diastereomers as indicated by ¹H NMR analysis: mp 56.0-63.2 °C (hexanes/EtOAc); IR (neat) 2977, 2933, 1728, 1696, 1388, 1256, 1094, 735 cm⁻¹; ¹H NMR (DMSO-d₆, 353 K) δ 9.64 (s, 1 H), 7.38 (dd, 1 H, J = 8.1, 0.9 Hz), 7.35-7.21 (m, 10 H), 7.16-7.07 (m, 3 H), 6.78 (dd, 1 H, J = 6.0, 2.1 Hz), 6.71 (dd, 1 H, J = 7.7, 7.7 Hz), 5.04 (d, 2 H, J = 2.4 Hz), 4.75 (d, 2 H, J = 2.4 Hz), 4.40 (d, 1 H, J = 0.8 Hz), 3.95-3.88 (m, 1 H), 3.83 (d, 1 H, J = 9.0 Hz), 3.65 (dd, 1 H, J = 8.7, 1.2 Hz), 3.36 (d, 1 H, J = 10.8 Hz), 2.86 (dd, 1 H, J = 13.2, 3.3 Hz), 2.63 (dd, 1 H, J = 13.5, 9.0 Hz), 1.41 (s, 3 H), 1.40 (s, 3 H), 1.38 (s, 9 H); ¹³C NMR (DMSO-d₆, 353 K) δ 195.1, 153.5,
150.7, 148.3, 137.9, 135.9, 134.0, 130.3, 129.8, 129.5, 128.9, 127.7(2) (2 C), 127.7(0) (3 C), 127.2, 126.9 (2 C), 126.8 (2 C), 126.4, 125.4, 119.5, 112.6, 102.6, 92.7, 78.5, 69.8, 65.4, 61.5, 60.4, 57.7, 52.7, 37.6, 27.6 (3 C), 26.2, 23.2; MS (ESI) m/z (rel intensity) 713([M+H]^+, 4), 711 ([M+H]^+, 4), 657 (74), 547 (100); HRMS (ESI) m/z calcd for C₄₀H₄₃BrN₂O₅ 711.2434, found 711.2488; \([\alpha]_D^{23}\) : -135.5 (c = 1.0, CH₂Cl₂). Characteristic data for minor diastereomer: \(^1\)H NMR (DMSO-d₆, 353 K) \(\delta\) 9.66 (s, 1 H), 1.45 (s, 3 H), 1.42 (s, 3 H); \(^{13}\)C NMR (DMSO-d₆, 353 K) \(\delta\) 195.2, 130.4, 130.0, 129.9, 129.3, 125.3, 112.7, 65.3, 61.5, 58.0, 37.8, 27.7, 26.3.

![Chemical Structure](image)

\textbf{(S)-**tert**-Butyl4-(3-(1-benzyl-7-bromo-1\textit{H}-indol-3-yl)-4-(benzyloxy)benzyl)-2,2-dimethyl oxazolidine-3-carboxylate (4-85).} Colorless oil: IR (neat) 2976, 2929, 1696, 1388, 1251, 1174 cm⁻¹

\(^1\)H NMR (DMSO-d₆, 353 K) \(\delta\) 7.66 (dd, 1 H, \(J = 6.9, 0.6\) Hz), 7.61 (s, 1 H), 7.37-7.30 (m, 2 H), 7.30-7.17 (m, 8 H), 7.16-7.11 (m, 2 H), 7.08-7.01 (m, 2 H), 6.96 (t, 1 H, \(J = 7.8\) Hz), 5.84 (s, 2 H), 5.07 (s, 2 H), 4.11-4.00 (m, 1 H), 3.88 (dd, 1 H, \(J = 8.7, 5.7\) Hz), 3.78 (dd, 1 H, \(J = 9.0, 1.8\) Hz), \(~3.02\) (dd, 1 H, signal obscured by H₂O contaminating DMSO), 2.73 (dd, 1 H, \(J = 13.2, 9.0\) Hz), 1.46 (s, 3 H), 1.43 (s, 3 H), 1.42 (s, 9 H); \(^{13}\)C NMR (DMSO-d₆, 353 K) \(\delta\) 153.9, 150.8, 138.6, 136.7,
Methyl 5-((R)-3-(S)-3-(tert-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)methyl)-2-(benzyloxy)phenyl]-1-benzyl-7-bromoindolin-3-yl)-4,5-dihydrooxazole-4-carboxylate (4-94). A solution of aldehyde 4-83 (2.75 g, 3.87 mmol) and methyl isocyanoacetate (1.06 mL, 11.6 mmol) in CH₂Cl₂ (40 mL) was treated with DBU (1.74 mL, 11.6 mmol) at room temperature. After 1 h, the volatiles were evaporated and the residue purified by chromatography on SiO₂ (1:1 hexanes/EtOAc) to furnish oxazoline 4-94 (3.10 g, 99%) as a white foam and a mixture of several diastereomers as indicated by ¹H NMR analysis: mp 73.1-82.9 °C (CH₂Cl₂); IR (neat) 2977, 1746, 1696, 1388, 1256, 1098, 738 cm⁻¹; ¹H NMR (DMSO-d₆, 353 K, reported as seen) δ 7.38-7.21 (m, 10 H), 7.17-7.10 (m, 4 H), 7.09-6.98 (m, 2 H), 6.81-6.75 (m, 0.3 H), 6.65-6.51 (m, 1 H), 5.62 (d, 0.6 H, J = 7.8 Hz), 5.49 (d, 0.4 H, J = 7.5 Hz), 5.06-4.72 (m, 3 H), 4.37 (dd, 0.3 H), 4.17-4.11 (m, 1 H), 4.30-3.89 (m, 1 H), 3.88-3.77 (m, 1 H), 3.74-3.58 (m, 3 H), 3.53 (s, 2.3 H), 3.80 (d, 0.4 H, J = 1.8 Hz), 2.94 (dd, 1 H, J =
13.2, 2.7 Hz), 2.71-2.59 (m, 1 H), 1.47-1.41 (m, 15 H); $^{13}$C NMR (DMSO-d$_6$, 353 K, reported as seen) δ 170.3, 169.9, 156.1, 155.8, 154.3, 154.2, 150.7, 148.8, 148.7, 138.1, 137.8, 135.9, 135.8, 133.5, 133.2, 133.0, 131.7, 130.4, 129.4, 129.3, 129.2, 128.7, 127.8, 127.7(6), 127.6, 127.3, 127.2(5), 127.2, 126.8, 126.7(6), 126.3, 126.2(5), 125.5, 123.5, 119.1, 119.0, 113.0, 112.8, 102.6, 101.9, 95.1, 92.7, 83.7, 82.8, 78.5, 69.8, 69.7, 68.8, 68.6, 65.4, 62.2, 57.9, 57.7, 53.7, 53.4, 53.2, 53.1, 51.5, 51.3, 37.8, 27.6, 26.2, 23.3; MS (ESI) m/z (rel intensity) 812 ([M+H]$^+$, 100), 810 ([M+H]$^+$, 100), 637 (100); HRMS (ESI) m/z calcd for C$_{44}$H$_{49}$BrN$_3$O$_7$ [M+H] 810.2754, found 810.2734; [$\alpha$]$_D^{23}$ +14.3 (c 1.0, CH$_2$Cl$_2$).

(S)-tert-Butyl 4-(3-(((R)-3-((S)-2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-methyl butanamido)-1-hydroxy-3-methoxy-3-oxopropyl)-1-benzyl-7-bromoindolin-3-yl)-4-(benzyloxy) benzyl)-2,2-dimethyloxazolidine-3-carboxylate (4-98). A solution of oxazoline 4-94 (870 mg, 1.08 mmol) in CH$_2$Cl$_2$ (5 mL) was treated with Fmoc-Val-Cl (577 mg, 1.61 mmol) at room temperature. After 1 h, a solution of Et$_3$N (300 µL, 2.15 mmol) and H$_2$O (39 µL, 2.15 mmol) in THF (0.5 mL) was added and the reaction mixture was stirred for 1 h. The volatile components were evaporated and the residue dissolved in MeOH (10 mL) and treated with KHCO$_3$ (215 mg, 2.15 mmol). After 1 h, the mixture was filtered, evaporated and the residue purified on SiO$_2$ (2:1
hexanes/EtOAc) to provide alcohol 4-98 (797 mg, 66%) as a colorless oil and a mixture of several diastereomers as indicated by $^1$H NMR analysis: \[ \text{IR (neat) 3345, 2924, 2853, 1696, 1453, 1389, 1247 cm}^{-1}; \]
$^1$H NMR (DMSO-d$_6$, 353 K, reported as seen) $\delta$ 7.85 (dd, 1.5 H, $J = 7.2, 3.9 \text{ Hz}$), 7.73 (d, 1.5 H, $J = 7.2 \text{ Hz}$), 7.44-7.25 (m, 12 H), 7.18-7.08 (m, 1.5 H), 7.05 (s, 1.5 H), 6.77 (d, 0.5 H), 6.67-6.58 (m, 0.5 H), 6.50 (t, 0.5 H, $J = 6.9 \text{ Hz}$), 6.32 (d, 0.5 H, $J = 9.0 \text{ Hz}$), 5.40-5.33 (m, 1 H), 5.12-4.93 (m, 2 H), 4.81-4.61 (m, 1 H), 4.50-4.25 (m, 3 H), 4.00-3.90 (m, 1.5 H), 3.83-3.62 (m, 3 H), 3.55-3.43 (m, 1.5 H), 3.39 (s, 0.5 H), 3.38-2.93 (m, 1 H), 2.58-2.41 (m, 1 H), 2.17-1.83 (m, 1 H), 1.51-1.42 (m, 15 H), 0.97-0.86 (m, 1.5 H), 0.85-0.68 (m, 4.5 H); $^{13}$C NMR (DMSO-d$_6$, 353 K, major resonances only, reported as seen) $\delta$ 170.9, 154.3, 150.7, 143.6, 143.4, 140.4, 140.3, 138.3, 136.3, 129.4, 129.0, 128.0, 127.7, 127.6, 127.5, 127.4(9), 127.3, 127.2, 127.1(7), 127.1, 127.0, 126.9, 126.6, 126.4, 126.3, 126.2, 124.6, 119.4, 118.1, 112.9, 101.8, 92.6, 78.5, 69.8, 65.8, 65.3, 59.4, 57.9, 55.7, 53.3, 53.0, 51.0, 46.6, 37.7, 30.0, 27.7, 26.3, 18.8, 18.3, 17.3; MS (ESI) $m/z$ (rel intensity) 1123 ([M+H]$^+$, 72), 1121 ([M+H]$^+$, 54); HRMS (ESI) $m/z$ calcd for C$_{63}$H$_{70}$BrN$_4$O$_{10}$ [M+H] 1121.4275, found 1121.4340; [$\alpha$]$_{D}^{23}$ -20.0 (c 0.1, CH$_2$Cl$_2$).
Table 1. Crystal data and structure refinement for dw1030u.

<table>
<thead>
<tr>
<th>Identification code</th>
<th>dw1030u</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{23}H_{27}NO_{2}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>349.46</td>
</tr>
<tr>
<td>Temperature</td>
<td>296(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2(1)</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 8.087(2) Å, ( \alpha = 90^\circ )</td>
</tr>
<tr>
<td></td>
<td>b = 6.2187(16) Å, ( \beta = 95.836(5)^\circ )</td>
</tr>
<tr>
<td></td>
<td>c = 19.865(5) Å, ( \gamma = 90^\circ )</td>
</tr>
<tr>
<td>Volume</td>
<td>993.8(4) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.168 Mg/m³</td>
</tr>
</tbody>
</table>
Absorption coefficient 0.074 mm\(^{-1}\)
F(000) 376
Crystal size 0.23 x 0.30 x 0.40 mm\(^3\)
Theta range for data collection 2.06 to 32.55°.
Index ranges 
-12<=h<=11, -9<=k<=9, -29<=l<=29
Reflections collected 12877
Independent reflections 6679 [R(int) = 0.0927]
Completeness to theta = 32.55° 96.3 %
Absorption correction Sadabs
Refinement method Full-matrix least-squares on F\(^2\)
Data / restraints / parameters 6679 / 1 / 242
Goodness-of-fit on F\(^2\) 0.920
Final R indices [I>2sigma(I)] R1 = 0.0721, wR2 = 0.1343
R indices (all data) R1 = 0.1736, wR2 = 0.1673
Absolute structure parameter 0.4(18)
Largest diff. peak and hole 0.335 and -0.243 e.Å\(^{-3}\)

Table 2. Atomic coordinates ( x 10\(^4\)) and equivalent isotropic displacement parameters (Å\(^2\) x 10\(^3\)) for dw1030u. 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>O(1)</td>
<td>-1923(2)</td>
<td>4938(4)</td>
<td>2711(1)</td>
<td>34(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>827(2)</td>
<td>6722(3)</td>
<td>2218(1)</td>
<td>33(1)</td>
</tr>
<tr>
<td>N(1)</td>
<td>31593(3)</td>
<td>4795(4)</td>
<td>2458(1)</td>
<td>27(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>2795(3)</td>
<td>4746(5)</td>
<td>4651(1)</td>
<td>32(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>3664(4)</td>
<td>5365(5)</td>
<td>5246(2)</td>
<td>38(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>3722(4)</td>
<td>4094(6)</td>
<td>5810(2)</td>
<td>42(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>2934(4)</td>
<td>2110(6)</td>
<td>5766(1)</td>
<td>40(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>2060(4)</td>
<td>1483(5)</td>
<td>5172(1)</td>
<td>33(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>1945(3)</td>
<td>2791(4)</td>
<td>4601(1)</td>
<td>26(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>9583(3)</td>
<td>2155(4)</td>
<td>3956(1)</td>
<td>24(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>879(4)</td>
<td>-231(5)</td>
<td>3805(2)</td>
<td>37(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>203(3)</td>
<td>3603(5)</td>
<td>3547(1)</td>
<td>25(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>-764(3)</td>
<td>3235(5)</td>
<td>2872(1)</td>
<td>27(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>414(3)</td>
<td>2966(5)</td>
<td>2314(1)</td>
<td>24(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>1508(3)</td>
<td>4949(5)</td>
<td>2326(1)</td>
<td>24(1)</td>
</tr>
</tbody>
</table>
Table 3. Bond lengths [Å] and angles [°] for dw1030u.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length</th>
<th>Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)-C(10)</td>
<td>1.428(3)</td>
<td></td>
</tr>
<tr>
<td>O(2)-C(12)</td>
<td>1.241(3)</td>
<td></td>
</tr>
<tr>
<td>N(1)-C(12)</td>
<td>1.337(3)</td>
<td></td>
</tr>
<tr>
<td>N(1)-C(14)</td>
<td>1.450(4)</td>
<td></td>
</tr>
<tr>
<td>N(1)-C(13)</td>
<td>1.453(4)</td>
<td></td>
</tr>
<tr>
<td>C(1)-C(2)</td>
<td>1.368(4)</td>
<td></td>
</tr>
<tr>
<td>C(1)-C(6)</td>
<td>1.395(4)</td>
<td></td>
</tr>
<tr>
<td>C(2)-C(3)</td>
<td>1.369(4)</td>
<td></td>
</tr>
<tr>
<td>C(3)-C(4)</td>
<td>1.387(5)</td>
<td></td>
</tr>
<tr>
<td>C(4)-C(5)</td>
<td>1.369(4)</td>
<td></td>
</tr>
<tr>
<td>C(5)-C(6)</td>
<td>1.391(4)</td>
<td></td>
</tr>
<tr>
<td>C(6)-C(7)</td>
<td>1.492(4)</td>
<td></td>
</tr>
<tr>
<td>C(7)-C(9)</td>
<td>1.320(4)</td>
<td></td>
</tr>
<tr>
<td>C(7)-C(8)</td>
<td>1.514(4)</td>
<td></td>
</tr>
<tr>
<td>C(9)-C(10)</td>
<td>1.501(4)</td>
<td></td>
</tr>
<tr>
<td>C(10)-C(11)</td>
<td>1.542(4)</td>
<td></td>
</tr>
<tr>
<td>C(11)-C(12)</td>
<td>1.516(4)</td>
<td></td>
</tr>
<tr>
<td>C(11)-C(15)</td>
<td>1.544(3)</td>
<td></td>
</tr>
</tbody>
</table>
C(15)-C(16)  1.500(4)
C(15)-C(18)  1.526(4)
C(16)-C(17)  1.311(4)
C(18)-C(23)  1.380(4)
C(18)-C(19)  1.388(4)
C(19)-C(20)  1.378(4)
C(20)-C(21)  1.383(5)
C(21)-C(22)  1.380(5)
C(22)-C(23)  1.374(4)
C(12)-N(1)-C(14) 118.3(3)
C(12)-N(1)-C(13) 124.3(3)
C(14)-N(1)-C(13) 117.3(2)
C(2)-C(1)-C(6) 120.9(3)
C(1)-C(2)-C(3) 121.1(3)
C(2)-C(3)-C(4) 119.0(3)
C(5)-C(4)-C(3) 120.1(3)
C(4)-C(5)-C(6) 121.5(3)
C(5)-C(6)-C(1) 117.4(2)
C(5)-C(6)-C(7) 122.0(3)
C(1)-C(6)-C(7) 120.6(2)
C(9)-C(7)-C(6) 121.4(3)
C(9)-C(7)-C(8) 122.6(3)
C(6)-C(7)-C(8) 116.0(2)
C(7)-C(9)-C(10) 127.8(3)
O(1)-C(10)-C(9) 111.0(2)
O(1)-C(10)-C(11) 111.0(2)
C(9)-C(10)-C(11) 110.8(2)
C(12)-C(11)-C(10) 107.6(2)
C(12)-C(11)-C(15) 109.4(2)
C(10)-C(11)-C(15) 113.4(2)
O(2)-C(12)-N(1) 120.9(3)
O(2)-C(12)-C(11) 118.1(2)
N(1)-C(12)-C(11) 121.0(3)
C(16)-C(15)-C(18) 111.6(2)
C(16)-C(15)-C(11) 110.7(2)
C(18)-C(15)-C(11) 110.4(2)

C(17)-C(16)-C(15) 124.4(3)

C(23)-C(18)-C(19) 118.7(3)

C(23)-C(18)-C(15) 121.6(3)

C(19)-C(18)-C(15) 119.7(3)

C(20)-C(19)-C(21) 120.6(3)

C(19)-C(20)-C(21) 120.1(3)

C(22)-C(21)-C(20) 119.3(3)

C(23)-C(22)-C(21) 120.4(3)

C(22)-C(23)-C(18) 120.8(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (Å²x 10³) for dw1030u. 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>U₁₂</th>
<th>U₁₃</th>
<th>U₂₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)</td>
<td>24(1)</td>
<td>44(1)</td>
<td>35(1)</td>
<td>0(1)</td>
<td>3(1)</td>
<td>10(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>30(1)</td>
<td>22(1)</td>
<td>46(1)</td>
<td>6(1)</td>
<td>1(1)</td>
<td>5(1)</td>
</tr>
<tr>
<td>N(1)</td>
<td>23(1)</td>
<td>23(1)</td>
<td>34(1)</td>
<td>0(1)</td>
<td>2(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>34(2)</td>
<td>24(2)</td>
<td>36(2)</td>
<td>6(1)</td>
<td>-2(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>36(2)</td>
<td>28(2)</td>
<td>49(2)</td>
<td>0(1)</td>
<td>-4(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>39(2)</td>
<td>51(2)</td>
<td>33(2)</td>
<td>-5(2)</td>
<td>-4(1)</td>
<td>-3(2)</td>
</tr>
<tr>
<td>C(4)</td>
<td>40(2)</td>
<td>50(2)</td>
<td>30(2)</td>
<td>9(2)</td>
<td>3(1)</td>
<td>0(2)</td>
</tr>
<tr>
<td>C(5)</td>
<td>36(2)</td>
<td>32(2)</td>
<td>32(2)</td>
<td>3(1)</td>
<td>6(1)</td>
<td>-4(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>23(1)</td>
<td>24(2)</td>
<td>31(1)</td>
<td>-1(1)</td>
<td>4(1)</td>
<td>2(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>25(1)</td>
<td>24(2)</td>
<td>25(1)</td>
<td>0(1)</td>
<td>8(1)</td>
<td>-1(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>48(2)</td>
<td>21(2)</td>
<td>43(2)</td>
<td>-1(1)</td>
<td>4(1)</td>
<td>-2(2)</td>
</tr>
<tr>
<td>C(9)</td>
<td>24(1)</td>
<td>25(2)</td>
<td>26(1)</td>
<td>-3(1)</td>
<td>6(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>26(1)</td>
<td>25(2)</td>
<td>30(2)</td>
<td>2(1)</td>
<td>5(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>24(1)</td>
<td>24(2)</td>
<td>24(1)</td>
<td>2(1)</td>
<td>2(1)</td>
<td>2(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>25(1)</td>
<td>25(2)</td>
<td>21(1)</td>
<td>-1(1)</td>
<td>3(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>29(2)</td>
<td>30(2)</td>
<td>71(2)</td>
<td>6(2)</td>
<td>6(2)</td>
<td>9(2)</td>
</tr>
<tr>
<td>C(14)</td>
<td>33(2)</td>
<td>33(2)</td>
<td>74(2)</td>
<td>7(2)</td>
<td>-3(2)</td>
<td>-9(2)</td>
</tr>
</tbody>
</table>

214
<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(1O)</td>
<td>-1290(60)</td>
<td>5700(80)</td>
<td>2540(20)</td>
<td>78(17)</td>
</tr>
<tr>
<td>H(1A)</td>
<td>2769</td>
<td>5640</td>
<td>4275</td>
<td>38</td>
</tr>
<tr>
<td>H(2)</td>
<td>4226</td>
<td>6672</td>
<td>5267</td>
<td>46</td>
</tr>
<tr>
<td>H(3)</td>
<td>4280</td>
<td>4553</td>
<td>6217</td>
<td>50</td>
</tr>
<tr>
<td>H(4)</td>
<td>3000</td>
<td>1204</td>
<td>6140</td>
<td>48</td>
</tr>
<tr>
<td>H(5)</td>
<td>1531</td>
<td>154</td>
<td>5149</td>
<td>39</td>
</tr>
<tr>
<td>H(8A)</td>
<td>278</td>
<td>-462</td>
<td>3369</td>
<td>56</td>
</tr>
<tr>
<td>H(8B)</td>
<td>324</td>
<td>-955</td>
<td>4145</td>
<td>56</td>
</tr>
<tr>
<td>H(8C)</td>
<td>1987</td>
<td>-788</td>
<td>3805</td>
<td>56</td>
</tr>
<tr>
<td>H(9)</td>
<td>281</td>
<td>5021</td>
<td>3695</td>
<td>30</td>
</tr>
<tr>
<td>H(10)</td>
<td>-1394</td>
<td>1897</td>
<td>2898</td>
<td>32</td>
</tr>
<tr>
<td>H(11)</td>
<td>1118</td>
<td>1704</td>
<td>2419</td>
<td>29</td>
</tr>
<tr>
<td>H(13A)</td>
<td>3681</td>
<td>2314</td>
<td>3077</td>
<td>65</td>
</tr>
<tr>
<td>H(13B)</td>
<td>5210</td>
<td>3091</td>
<td>2715</td>
<td>65</td>
</tr>
<tr>
<td>H(13C)</td>
<td>3795</td>
<td>1750</td>
<td>2314</td>
<td>65</td>
</tr>
<tr>
<td>H(14A)</td>
<td>3721</td>
<td>7607</td>
<td>2064</td>
<td>71</td>
</tr>
<tr>
<td>H(14B)</td>
<td>5278</td>
<td>6375</td>
<td>2405</td>
<td>71</td>
</tr>
<tr>
<td>H(14C)</td>
<td>4067</td>
<td>7538</td>
<td>2855</td>
<td>71</td>
</tr>
<tr>
<td>H(15)</td>
<td>-1141</td>
<td>4008</td>
<td>1487</td>
<td>32</td>
</tr>
<tr>
<td>H(16)</td>
<td>-1294</td>
<td>-506</td>
<td>1694</td>
<td>41</td>
</tr>
</tbody>
</table>

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for dw1030u.
<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>H(17A)</td>
<td>-3784</td>
<td>2383</td>
<td>1318</td>
</tr>
<tr>
<td>H(17B)</td>
<td>-4003</td>
<td>-162</td>
<td>1431</td>
</tr>
<tr>
<td>H(19)</td>
<td>481</td>
<td>5384</td>
<td>683</td>
</tr>
<tr>
<td>H(20)</td>
<td>2398</td>
<td>5025</td>
<td>-91</td>
</tr>
<tr>
<td>H(21)</td>
<td>3742</td>
<td>1770</td>
<td>-200</td>
</tr>
<tr>
<td>H(22)</td>
<td>3234</td>
<td>-1052</td>
<td>508</td>
</tr>
<tr>
<td>H(23)</td>
<td>1367</td>
<td>-666</td>
<td>1296</td>
</tr>
</tbody>
</table>
Table 1. Crystal data and structure refinement for dw1010.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>dw1010</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C_{28}H_{27}BrO_{3}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>491.41</td>
</tr>
<tr>
<td>Temperature</td>
<td>298(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 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></td>
</tr>
<tr>
<td>a</td>
<td>27.5495(14) Å</td>
</tr>
<tr>
<td>b</td>
<td>7.4365(4) Å</td>
</tr>
<tr>
<td>c</td>
<td>11.4908(6) Å</td>
</tr>
<tr>
<td>Volume</td>
<td>2341.6(2) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.394 Mg/m³</td>
</tr>
</tbody>
</table>
Absorption coefficient 1.783 mm\(^{-1}\)
F(000) 1016
Crystal size 0.10 x 0.10 x 0.40 mm\(^3\)
Theta range for data collection 2.23 to 32.58°.
Index ranges -41<=h<=40, -11<=k<=11, -16<=l<=17
Reflections collected 29664
Independent reflections 8292 [R(int) = 0.0781]
Completeness to theta = 32.58° 97.0 %
Absorption correction Sadabs
Refinement method Full-matrix least-squares on F\(^2\)
Data / restraints / parameters 8292 / 0 / 289
Goodness-of-fit on F\(^2\) 0.934
Final R indices [I>2sigma(I)] R1 = 0.0568, wR2 = 0.1237
R indices (all data) R1 = 0.1694, wR2 = 0.1610
Largest diff. peak and hole 0.823 and -0.283 e.Å\(^{-3}\)

Table 2. Atomic coordinates ( x 10\(^4\)) and equivalent isotropic displacement parameters (Å\(^2\)x 10\(^3\)) for dw1010. 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>Br</td>
<td>364(1)</td>
<td>3815(1)</td>
<td>7864(1)</td>
<td>86(1)</td>
</tr>
<tr>
<td>O(1)</td>
<td>3060(1)</td>
<td>-2371(3)</td>
<td>8029(2)</td>
<td>56(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>2668(1)</td>
<td>1478(2)</td>
<td>6985(2)</td>
<td>44(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>2861(1)</td>
<td>3752(2)</td>
<td>8220(2)</td>
<td>53(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>1350(1)</td>
<td>-2520(4)</td>
<td>6244(2)</td>
<td>53(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>850(1)</td>
<td>-2459(5)</td>
<td>6037(3)</td>
<td>65(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>612(1)</td>
<td>-3271(5)</td>
<td>5067(3)</td>
<td>68(1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>880(1)</td>
<td>-4125(4)</td>
<td>4315(3)</td>
<td>67(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>1381(1)</td>
<td>-4195(4)</td>
<td>4508(3)</td>
<td>54(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>1632(1)</td>
<td>-3357(3)</td>
<td>5474(2)</td>
<td>41(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>2174(1)</td>
<td>-3421(3)</td>
<td>5685(2)</td>
<td>40(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>2421(1)</td>
<td>-2320(3)</td>
<td>6442(2)</td>
<td>43(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>2959(1)</td>
<td>-2307(3)</td>
<td>6781(2)</td>
<td>43(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>3239(1)</td>
<td>-701(3)</td>
<td>6347(2)</td>
<td>39(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>3795(1)</td>
<td>-1142(3)</td>
<td>6422(2)</td>
<td>43(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>4106(1)</td>
<td>256(3)</td>
<td>5888(2)</td>
<td>42(1)</td>
</tr>
<tr>
<td>Bond</td>
<td>Length [Å]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
<td>------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Br-C(26)</td>
<td>1.887(2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O(1)-C(9)</td>
<td>1.433(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O(2)-C(22)</td>
<td>1.326(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O(2)-C(21)</td>
<td>1.459(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O(3)-C(22)</td>
<td>1.208(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(1)-C(2)</td>
<td>1.376(4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(1)-C(6)</td>
<td>1.384(4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(2)-C(3)</td>
<td>1.372(4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(3)-C(4)</td>
<td>1.352(5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(4)-C(5)</td>
<td>1.375(4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(5)-C(6)</td>
<td>1.392(4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(6)-C(7)</td>
<td>1.489(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(7)-C(8)</td>
<td>1.330(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(7)-C(18)</td>
<td>1.511(4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(8)-C(9)</td>
<td>1.495(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(9)-C(10)</td>
<td>1.531(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C(10)-C(21)</td>
<td>1.513(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Bond lengths [Å] and angles [°] for dw1010.
C(10)-C(11)  1.561(3)
C(11)-C(19)  1.501(4)
C(11)-C(12)  1.516(3)
C(12)-C(17)  1.378(4)
C(12)-C(13)  1.382(4)
C(13)-C(14)  1.380(4)
C(14)-C(15)  1.361(4)
C(15)-C(16)  1.348(4)
C(16)-C(17)  1.389(4)
C(19)-C(20)  1.305(4)
C(22)-C(23)  1.487(3)
C(23)-C(24)  1.381(4)
C(23)-C(28)  1.385(3)
C(24)-C(25)  1.371(4)
C(25)-C(26)  1.382(4)
C(26)-C(27)  1.374(4)
C(27)-C(28)  1.382(3)
C(22)-O(2)-C(21) 115.96(19)
C(2)-C(1)-C(6) 121.5(3)
C(3)-C(2)-C(1) 120.7(3)
C(4)-C(3)-C(2) 118.7(3)
C(3)-C(4)-C(5) 121.3(3)
C(4)-C(5)-C(6) 121.3(3)
C(1)-C(6)-C(5) 116.5(3)
C(1)-C(6)-C(7) 122.0(2)
C(5)-C(6)-C(7) 121.5(2)
C(8)-C(7)-C(6) 121.6(2)
O(1)-C(9)-C(8) 110.2(2)
O(1)-C(9)-C(10) 110.2(2)
C(9)-C(10)-C(11)107.3(2)
\[ \begin{align*}
C(9)-C(10)-C(11) & \ 110.0(2) \\
C(19)-C(11)-C(12) & \ 108.2(2) \\
C(19)-C(11)-C(10) & \ 111.4(2) \\
C(12)-C(11)-C(10) & \ 115.2(2) \\
C(17)-C(12)-C(13) & \ 117.1(2) \\
C(17)-C(12)-C(11) & \ 120.8(2) \\
C(13)-C(12)-C(11) & \ 121.7(2) \\
C(14)-C(13)-C(12) & \ 121.4(3) \\
C(15)-C(14)-C(13) & \ 120.2(3) \\
C(16)-C(15)-C(14) & \ 119.8(3) \\
C(15)-C(16)-C(17) & \ 120.5(3) \\
C(12)-C(17)-C(16) & \ 121.0(3) \\
C(20)-C(19)-C(11) & \ 124.4(3) \\
O(2)-C(21)-C(10) & \ 109.25(19) \\
O(3)-C(22)-O(2) & \ 123.8(2) \\
O(3)-C(22)-C(23) & \ 123.6(2) \\
O(2)-C(22)-C(23) & \ 112.6(2) \\
C(24)-C(23)-C(28) & \ 119.2(2) \\
C(24)-C(23)-C(22) & \ 118.9(2) \\
C(28)-C(23)-C(22) & \ 121.8(2) \\
C(25)-C(24)-C(23) & \ 121.0(3) \\
C(24)-C(25)-C(26) & \ 118.8(3) \\
C(27)-C(26)-C(25) & \ 121.5(2) \\
C(27)-C(26)-Br & \ 119.5(2) \\
C(25)-C(26)-Br & \ 119.0(2) \\
C(26)-C(27)-C(28) & \ 118.9(2) \\
C(27)-C(28)-C(23) & \ 120.5(2)
\end{align*} \]

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters \((\text{Å}^2 \times 10^3)\) for dw1010. The anisotropic displacement factor exponent takes the form: 
\[-2\pi^2 [ h^2 a^* U_{11} + ... + 2 h k a^* b^* U_{12} ]\]

<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>Br37(1)</td>
<td>89(1)</td>
<td>136(1)</td>
<td>8(1)</td>
<td>23(1)</td>
<td>8(1)</td>
<td>221</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>---</td>
</tr>
<tr>
<td>O(1)</td>
<td>56(1)</td>
<td>55(1)</td>
<td>56(1)</td>
<td>6(1)</td>
<td>2(1)</td>
<td>-8(1)</td>
</tr>
<tr>
<td>O(2)</td>
<td>31(1)</td>
<td>38(1)</td>
<td>64(1)</td>
<td>-9(1)</td>
<td>7(1)</td>
<td>3(1)</td>
</tr>
<tr>
<td>O(3)</td>
<td>39(1)</td>
<td>45(1)</td>
<td>75(1)</td>
<td>-13(1)</td>
<td>-2(1)</td>
<td>-2(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>44(2)</td>
<td>61(2)</td>
<td>53(2)</td>
<td>-8(1)</td>
<td>6(1)</td>
<td>-11(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>47(2)</td>
<td>80(2)</td>
<td>71(2)</td>
<td>-9(2)</td>
<td>15(2)</td>
<td>-7(2)</td>
</tr>
<tr>
<td>C(3)</td>
<td>44(2)</td>
<td>73(2)</td>
<td>86(2)</td>
<td>3(2)</td>
<td>-2(2)</td>
<td>-7(2)</td>
</tr>
<tr>
<td>C(4)</td>
<td>58(2)</td>
<td>69(2)</td>
<td>68(2)</td>
<td>-4(2)</td>
<td>-19(2)</td>
<td>-10(2)</td>
</tr>
<tr>
<td>C(5)</td>
<td>63(2)</td>
<td>50(2)</td>
<td>49(2)</td>
<td>-2(1)</td>
<td>0(1)</td>
<td>-6(1)</td>
</tr>
<tr>
<td>C(6)</td>
<td>46(1)</td>
<td>37(1)</td>
<td>41(1)</td>
<td>2(1)</td>
<td>6(1)</td>
<td>-8(1)</td>
</tr>
<tr>
<td>C(7)</td>
<td>45(1)</td>
<td>38(1)</td>
<td>38(1)</td>
<td>3(1)</td>
<td>9(1)</td>
<td>-5(1)</td>
</tr>
<tr>
<td>C(8)</td>
<td>41(1)</td>
<td>33(1)</td>
<td>56(2)</td>
<td>-6(1)</td>
<td>10(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(9)</td>
<td>44(2)</td>
<td>37(1)</td>
<td>53(2)</td>
<td>-7(1)</td>
<td>6(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>C(10)</td>
<td>32(1)</td>
<td>37(1)</td>
<td>48(2)</td>
<td>-3(1)</td>
<td>6(1)</td>
<td>3(1)</td>
</tr>
<tr>
<td>C(11)</td>
<td>33(1)</td>
<td>45(2)</td>
<td>52(2)</td>
<td>0(1)</td>
<td>6(1)</td>
<td>7(1)</td>
</tr>
<tr>
<td>C(12)</td>
<td>33(1)</td>
<td>41(1)</td>
<td>52(2)</td>
<td>-5(1)</td>
<td>10(1)</td>
<td>7(1)</td>
</tr>
<tr>
<td>C(13)</td>
<td>41(2)</td>
<td>71(2)</td>
<td>64(2)</td>
<td>6(2)</td>
<td>5(1)</td>
<td>-11(1)</td>
</tr>
<tr>
<td>C(14)</td>
<td>64(2)</td>
<td>80(2)</td>
<td>64(2)</td>
<td>12(2)</td>
<td>14(2)</td>
<td>-7(2)</td>
</tr>
<tr>
<td>C(15)</td>
<td>49(2)</td>
<td>55(2)</td>
<td>90(3)</td>
<td>-6(2)</td>
<td>27(2)</td>
<td>-2(2)</td>
</tr>
<tr>
<td>C(16)</td>
<td>33(1)</td>
<td>52(2)</td>
<td>94(3)</td>
<td>-15(2)</td>
<td>5(2)</td>
<td>-3(1)</td>
</tr>
<tr>
<td>C(17)</td>
<td>38(1)</td>
<td>51(2)</td>
<td>62(2)</td>
<td>-8(1)</td>
<td>1(1)</td>
<td>8(1)</td>
</tr>
<tr>
<td>C(18)</td>
<td>54(2)</td>
<td>66(2)</td>
<td>59(2)</td>
<td>-19(2)</td>
<td>13(1)</td>
<td>-5(2)</td>
</tr>
<tr>
<td>C(19)</td>
<td>49(2)</td>
<td>50(2)</td>
<td>79(2)</td>
<td>-7(2)</td>
<td>24(2)</td>
<td>3(1)</td>
</tr>
<tr>
<td>C(20)</td>
<td>71(2)</td>
<td>51(2)</td>
<td>134(3)</td>
<td>0(2)</td>
<td>28(2)</td>
<td>15(2)</td>
</tr>
<tr>
<td>C(21)</td>
<td>30(1)</td>
<td>41(2)</td>
<td>68(2)</td>
<td>-3(1)</td>
<td>8(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>C(22)</td>
<td>36(1)</td>
<td>33(1)</td>
<td>45(2)</td>
<td>6(1)</td>
<td>6(1)</td>
<td>0(1)</td>
</tr>
<tr>
<td>C(23)</td>
<td>35(1)</td>
<td>32(1)</td>
<td>43(1)</td>
<td>4(1)</td>
<td>5(1)</td>
<td>1(1)</td>
</tr>
<tr>
<td>C(24)</td>
<td>45(2)</td>
<td>41(2)</td>
<td>57(2)</td>
<td>-5(1)</td>
<td>6(1)</td>
<td>2(1)</td>
</tr>
<tr>
<td>C(25)</td>
<td>49(2)</td>
<td>47(2)</td>
<td>67(2)</td>
<td>-4(1)</td>
<td>18(2)</td>
<td>10(1)</td>
</tr>
<tr>
<td>C(26)</td>
<td>33(1)</td>
<td>42(2)</td>
<td>73(2)</td>
<td>10(1)</td>
<td>10(1)</td>
<td>3(1)</td>
</tr>
<tr>
<td>C(27)</td>
<td>39(1)</td>
<td>47(2)</td>
<td>62(2)</td>
<td>0(1)</td>
<td>-1(1)</td>
<td>-3(1)</td>
</tr>
<tr>
<td>C(28)</td>
<td>43(1)</td>
<td>42(2)</td>
<td>50(2)</td>
<td>-4(1)</td>
<td>6(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 dw1010.
<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>H(1A)</td>
<td>3022</td>
<td>-3401</td>
<td>8257</td>
<td>83</td>
</tr>
<tr>
<td>H(1B)</td>
<td>1503</td>
<td>-1986</td>
<td>6917</td>
<td>63</td>
</tr>
<tr>
<td>H(2A)</td>
<td>670</td>
<td>-1860</td>
<td>6560</td>
<td>78</td>
</tr>
<tr>
<td>H(3A)</td>
<td>274</td>
<td>-3235</td>
<td>4930</td>
<td>82</td>
</tr>
<tr>
<td>H(4A)</td>
<td>723</td>
<td>-4677</td>
<td>3654</td>
<td>80</td>
</tr>
<tr>
<td>H(5A)</td>
<td>1556</td>
<td>-4813</td>
<td>3984</td>
<td>65</td>
</tr>
<tr>
<td>H(8A)</td>
<td>2239</td>
<td>-1466</td>
<td>6799</td>
<td>51</td>
</tr>
<tr>
<td>H(9A)</td>
<td>3094</td>
<td>-3400</td>
<td>6464</td>
<td>52</td>
</tr>
<tr>
<td>H(10A)</td>
<td>3120</td>
<td>-477</td>
<td>5526</td>
<td>47</td>
</tr>
<tr>
<td>H(11A)</td>
<td>3914</td>
<td>-1232</td>
<td>7253</td>
<td>52</td>
</tr>
<tr>
<td>H(13A)</td>
<td>3673</td>
<td>667</td>
<td>4395</td>
<td>70</td>
</tr>
<tr>
<td>H(14A)</td>
<td>4192</td>
<td>2519</td>
<td>3506</td>
<td>83</td>
</tr>
<tr>
<td>H(15A)</td>
<td>4934</td>
<td>3296</td>
<td>4460</td>
<td>76</td>
</tr>
<tr>
<td>H(16A)</td>
<td>5166</td>
<td>2183</td>
<td>6278</td>
<td>72</td>
</tr>
<tr>
<td>H(17A)</td>
<td>4653</td>
<td>302</td>
<td>7181</td>
<td>60</td>
</tr>
<tr>
<td>H(18A)</td>
<td>2772</td>
<td>-4731</td>
<td>5196</td>
<td>89</td>
</tr>
<tr>
<td>H(18B)</td>
<td>2356</td>
<td>-4540</td>
<td>4165</td>
<td>89</td>
</tr>
<tr>
<td>H(18C)</td>
<td>2311</td>
<td>-5974</td>
<td>5149</td>
<td>89</td>
</tr>
<tr>
<td>H(19A)</td>
<td>3807</td>
<td>-3042</td>
<td>5070</td>
<td>69</td>
</tr>
<tr>
<td>H(20A)</td>
<td>4146</td>
<td>-4261</td>
<td>7254</td>
<td>101</td>
</tr>
<tr>
<td>H(20B)</td>
<td>4111</td>
<td>-5398</td>
<td>6055</td>
<td>101</td>
</tr>
<tr>
<td>H(21A)</td>
<td>3317</td>
<td>838</td>
<td>7841</td>
<td>55</td>
</tr>
<tr>
<td>H(21B)</td>
<td>3362</td>
<td>1978</td>
<td>6704</td>
<td>55</td>
</tr>
<tr>
<td>H(24A)</td>
<td>2078</td>
<td>4779</td>
<td>9037</td>
<td>57</td>
</tr>
<tr>
<td>H(25A)</td>
<td>1253</td>
<td>5135</td>
<td>9147</td>
<td>64</td>
</tr>
<tr>
<td>H(27A)</td>
<td>973</td>
<td>1925</td>
<td>6351</td>
<td>60</td>
</tr>
<tr>
<td>H(28A)</td>
<td>1803</td>
<td>1525</td>
<td>6279</td>
<td>54</td>
</tr>
</tbody>
</table>
APPENDIX C

X-RAY DATA FOR COMPOUND 3-21

Table 1. Crystal data and structure refinement for grenon1t.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>compound9</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C9H12O5</td>
</tr>
<tr>
<td>Formula weight</td>
<td>200.19</td>
</tr>
<tr>
<td>Temperature</td>
<td>295(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>C 2/c</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>25.345(17) Å</td>
</tr>
<tr>
<td>b</td>
<td>6.038(4) Å</td>
</tr>
<tr>
<td>c</td>
<td>12.627(10) Å</td>
</tr>
<tr>
<td>Volume</td>
<td>1874(2) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>8</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.419 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.117 mm⁻¹</td>
</tr>
<tr>
<td>F(000)</td>
<td>848</td>
</tr>
</tbody>
</table>
Crystal size 0.28 x 0.18 x 0.12 mm$^3$
Theta range for data collection 1.66 to 25.00°.
Index ranges -30<=$h<=$25, -6<=$k<=$7, -15<=$l<=$15
Reflections collected 4776
Independent reflections 1647 [R(int) = 0.2741]
Completeness to theta = 25.00° 99.9 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 0.9861 and 0.9680
Refinement method Full-matrix least-squares on F$^2$
Data / restraints / parameters 1647 / 0 / 130
Goodness-of-fit on F$^2$ 1.132
Final R indices [I>2sigma(I)] R1 = 0.1225, wR2 = 0.2742
R indices (all data) R1 = 0.1859, wR2 = 0.3053
Largest diff. peak and hole 0.406 and -0.398 e.Å$^{-3}$

Table 2. Atomic coordinates (x 10$^4$) and equivalent isotropic displacement parameters (Å$^2$x 10$^3$) for greron1t. 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>O(1)</td>
<td>1875(2)</td>
<td>-1574(8)</td>
<td>5239(4)</td>
<td>44(1)</td>
</tr>
<tr>
<td>C(1)</td>
<td>1822(3)</td>
<td>0(12)</td>
<td>4631(5)</td>
<td>37(2)</td>
</tr>
<tr>
<td>O(2)</td>
<td>2379(2)</td>
<td>2448(8)</td>
<td>3728(4)</td>
<td>39(1)</td>
</tr>
<tr>
<td>C(2)</td>
<td>2157(3)</td>
<td>322(12)</td>
<td>3833(5)</td>
<td>34(2)</td>
</tr>
<tr>
<td>O(3)</td>
<td>1431(2)</td>
<td>1441(8)</td>
<td>4633(3)</td>
<td>36(1)</td>
</tr>
<tr>
<td>C(3)</td>
<td>1942(3)</td>
<td>1664(12)</td>
<td>2866(5)</td>
<td>34(2)</td>
</tr>
<tr>
<td>C(4)</td>
<td>1397(2)</td>
<td>2796(10)</td>
<td>2755(5)</td>
<td>25(2)</td>
</tr>
<tr>
<td>O(4)</td>
<td>437(2)</td>
<td>3109(9)</td>
<td>4097(6)</td>
<td>70(2)</td>
</tr>
<tr>
<td>O(5)</td>
<td>779(2)</td>
<td>6390(7)</td>
<td>3879(4)</td>
<td>39(1)</td>
</tr>
<tr>
<td>C(5)</td>
<td>1350(2)</td>
<td>3394(10)</td>
<td>3924(5)</td>
<td>27(2)</td>
</tr>
<tr>
<td>C(6)</td>
<td>1405(3)</td>
<td>4928(12)</td>
<td>2108(6)</td>
<td>46(2)</td>
</tr>
<tr>
<td>C(7)</td>
<td>958(3)</td>
<td>1207(12)</td>
<td>2174(6)</td>
<td>39(2)</td>
</tr>
<tr>
<td>C(8)</td>
<td>798(3)</td>
<td>4208(11)</td>
<td>3980(5)</td>
<td>30(2)</td>
</tr>
<tr>
<td>C(9)</td>
<td>281(3)</td>
<td>7423(14)</td>
<td>4022(7)</td>
<td>51(2)</td>
</tr>
</tbody>
</table>
Table 3. Bond lengths [Å] and angles [°] for grenon1t.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Length or Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)-C(1)</td>
<td>1.208(8)</td>
</tr>
<tr>
<td>C(1)-O(3)</td>
<td>1.320(8)</td>
</tr>
<tr>
<td>C(1)-C(2)</td>
<td>1.480(10)</td>
</tr>
<tr>
<td>O(2)-C(2)</td>
<td>1.421(8)</td>
</tr>
<tr>
<td>O(2)-C(3)</td>
<td>1.432(8)</td>
</tr>
<tr>
<td>C(2)-C(3)</td>
<td>1.456(9)</td>
</tr>
<tr>
<td>C(2)-H(2)</td>
<td>0.9800</td>
</tr>
<tr>
<td>O(3)-C(5)</td>
<td>1.465(8)</td>
</tr>
<tr>
<td>C(3)-C(4)</td>
<td>1.515(9)</td>
</tr>
<tr>
<td>C(3)-H(3)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(4)-C(7)</td>
<td>1.517(9)</td>
</tr>
<tr>
<td>C(4)-C(6)</td>
<td>1.527(9)</td>
</tr>
<tr>
<td>C(4)-C(5)</td>
<td>1.553(8)</td>
</tr>
<tr>
<td>O(4)-C(8)</td>
<td>1.169(8)</td>
</tr>
<tr>
<td>O(5)-C(8)</td>
<td>1.323(8)</td>
</tr>
<tr>
<td>O(5)-C(9)</td>
<td>1.456(8)</td>
</tr>
<tr>
<td>C(5)-C(8)</td>
<td>1.499(9)</td>
</tr>
<tr>
<td>C(5)-H(5)</td>
<td>0.9800</td>
</tr>
<tr>
<td>C(6)-H(6A)</td>
<td>0.9600</td>
</tr>
<tr>
<td>C(6)-H(6B)</td>
<td>0.9600</td>
</tr>
<tr>
<td>C(6)-H(6C)</td>
<td>0.9600</td>
</tr>
<tr>
<td>C(7)-H(7A)</td>
<td>0.9600</td>
</tr>
<tr>
<td>C(7)-H(7B)</td>
<td>0.9600</td>
</tr>
<tr>
<td>C(7)-H(7C)</td>
<td>0.9600</td>
</tr>
<tr>
<td>C(9)-H(9A)</td>
<td>0.9600</td>
</tr>
<tr>
<td>C(9)-H(9B)</td>
<td>0.9600</td>
</tr>
<tr>
<td>C(9)-H(9C)</td>
<td>0.9600</td>
</tr>
<tr>
<td>O(1)-C(1)-O(3)</td>
<td>118.9(6)</td>
</tr>
<tr>
<td>O(1)-C(1)-C(2)</td>
<td>122.9(7)</td>
</tr>
<tr>
<td>O(3)-C(1)-C(2)</td>
<td>118.1(6)</td>
</tr>
<tr>
<td>C(2)-O(2)-C(3)</td>
<td>61.4(4)</td>
</tr>
<tr>
<td>O(2)-C(2)-C(3)</td>
<td>59.7(4)</td>
</tr>
<tr>
<td>Bond</td>
<td>Angle (°)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>O(2)-C(2)-C(1)</td>
<td>119.2(6)</td>
</tr>
<tr>
<td>C(3)-C(2)-C(1)</td>
<td>119.0(6)</td>
</tr>
<tr>
<td>O(2)-C(2)-H(2)</td>
<td>115.8</td>
</tr>
<tr>
<td>C(3)-C(2)-H(2)</td>
<td>115.8</td>
</tr>
<tr>
<td>C(1)-C(2)-H(2)</td>
<td>115.8</td>
</tr>
<tr>
<td>C(1)-O(3)-C(5)</td>
<td>121.5(5)</td>
</tr>
<tr>
<td>O(2)-C(3)-C(2)</td>
<td>58.9(4)</td>
</tr>
<tr>
<td>O(2)-C(3)-C(4)</td>
<td>116.0(5)</td>
</tr>
<tr>
<td>C(2)-C(3)-C(4)</td>
<td>118.3(5)</td>
</tr>
<tr>
<td>O(2)-C(3)-H(3)</td>
<td>116.9</td>
</tr>
<tr>
<td>C(2)-C(3)-H(3)</td>
<td>116.9</td>
</tr>
<tr>
<td>C(4)-C(3)-H(3)</td>
<td>116.9</td>
</tr>
<tr>
<td>C(3)-C(4)-C(7)</td>
<td>107.7(5)</td>
</tr>
<tr>
<td>C(3)-C(4)-C(6)</td>
<td>107.4(5)</td>
</tr>
<tr>
<td>C(7)-C(4)-C(6)</td>
<td>112.2(5)</td>
</tr>
<tr>
<td>C(3)-C(4)-C(5)</td>
<td>107.3(5)</td>
</tr>
<tr>
<td>C(7)-C(4)-C(5)</td>
<td>112.9(5)</td>
</tr>
<tr>
<td>C(6)-C(4)-C(5)</td>
<td>109.1(5)</td>
</tr>
<tr>
<td>C(8)-O(5)-C(9)</td>
<td>115.3(5)</td>
</tr>
<tr>
<td>O(3)-C(5)-C(8)</td>
<td>103.2(5)</td>
</tr>
<tr>
<td>O(3)-C(5)-C(4)</td>
<td>111.2(5)</td>
</tr>
<tr>
<td>C(8)-C(5)-C(4)</td>
<td>114.3(5)</td>
</tr>
<tr>
<td>O(3)-C(5)-H(5)</td>
<td>109.3</td>
</tr>
<tr>
<td>C(8)-C(5)-H(5)</td>
<td>109.3</td>
</tr>
<tr>
<td>C(4)-C(5)-H(5)</td>
<td>109.3</td>
</tr>
<tr>
<td>C(4)-C(6)-H(6A)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(4)-C(6)-H(6B)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(6A)-C(6)-H(6B)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(4)-C(6)-H(6C)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(6A)-C(6)-H(6C)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(6B)-C(6)-H(6C)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(4)-C(7)-H(7A)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(4)-C(7)-H(7B)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(7A)-C(7)-H(7B)</td>
<td>109.5</td>
</tr>
<tr>
<td>C(4)-C(7)-H(7C)</td>
<td>109.5</td>
</tr>
<tr>
<td>H(7A)-C(7)-H(7C)</td>
<td>109.5</td>
</tr>
</tbody>
</table>
H(7B)-C(7)-H(7C) 109.5
O(4)-C(8)-O(5) 124.4(6)
O(4)-C(8)-C(5) 126.0(6)
O(5)-C(8)-C(5) 109.6(5)
O(5)-C(9)-H(9A) 109.5
O(5)-C(9)-H(9B) 109.5
H(9A)-C(9)-H(9B) 109.5
O(5)-C(9)-H(9C) 109.5
H(9A)-C(9)-H(9C) 109.5
H(9B)-C(9)-H(9C) 109.5

Symmetry transformations used to generate equivalent atoms:

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Anisotropic displacement parameters (Å²x 10³) for grenon1t. The anisotropic displacement factor exponent takes the form: -2π²[a*a*b*b* U₁₁ + ... + 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>O(1)</td>
<td>42(3)</td>
<td>41(3)</td>
<td>47(3)</td>
<td>16(2)</td>
<td>9(2)</td>
<td>9(2)</td>
</tr>
<tr>
<td>C(1)</td>
<td>38(4)</td>
<td>43(4)</td>
<td>27(4)</td>
<td>-3(3)</td>
<td>3(3)</td>
<td>4(4)</td>
</tr>
<tr>
<td>O(2)</td>
<td>22(2)</td>
<td>53(3)</td>
<td>43(3)</td>
<td>4(2)</td>
<td>10(2)</td>
<td>-6(2)</td>
</tr>
<tr>
<td>C(2)</td>
<td>31(3)</td>
<td>41(4)</td>
<td>31(4)</td>
<td>2(3)</td>
<td>7(3)</td>
<td>7(3)</td>
</tr>
<tr>
<td>O(3)</td>
<td>39(3)</td>
<td>38(3)</td>
<td>33(3)</td>
<td>5(2)</td>
<td>12(2)</td>
<td>1(2)</td>
</tr>
<tr>
<td>C(3)</td>
<td>25(3)</td>
<td>57(5)</td>
<td>23(3)</td>
<td>3(3)</td>
<td>10(3)</td>
<td>5(3)</td>
</tr>
<tr>
<td>C(4)</td>
<td>24(3)</td>
<td>30(4)</td>
<td>22(3)</td>
<td>-3(3)</td>
<td>8(3)</td>
<td>-4(3)</td>
</tr>
<tr>
<td>O(4)</td>
<td>37(3)</td>
<td>50(4)</td>
<td>138(6)</td>
<td>-9(3)</td>
<td>46(4)</td>
<td>-10(3)</td>
</tr>
<tr>
<td>O(5)</td>
<td>27(3)</td>
<td>32(3)</td>
<td>65(3)</td>
<td>1(2)</td>
<td>22(2)</td>
<td>3(2)</td>
</tr>
<tr>
<td>C(5)</td>
<td>23(3)</td>
<td>26(3)</td>
<td>33(4)</td>
<td>3(3)</td>
<td>8(3)</td>
<td>0(3)</td>
</tr>
<tr>
<td>C(6)</td>
<td>45(4)</td>
<td>48(5)</td>
<td>52(5)</td>
<td>15(4)</td>
<td>24(4)</td>
<td>18(4)</td>
</tr>
<tr>
<td>C(7)</td>
<td>41(4)</td>
<td>40(4)</td>
<td>35(4)</td>
<td>-7(3)</td>
<td>5(3)</td>
<td>0(4)</td>
</tr>
<tr>
<td>C(8)</td>
<td>31(4)</td>
<td>27(4)</td>
<td>34(4)</td>
<td>-6(3)</td>
<td>16(3)</td>
<td>-5(3)</td>
</tr>
<tr>
<td>C(9)</td>
<td>46(5)</td>
<td>46(4)</td>
<td>69(6)</td>
<td>0(4)</td>
<td>26(4)</td>
<td>20(4)</td>
</tr>
</tbody>
</table>
Table 5. Hydrogen coordinates ($x \times 10^4$) and isotropic displacement parameters ($A^2 \times 10^3$) forgrenon1t.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(2)</td>
<td>2382</td>
<td>-942</td>
<td>3732</td>
<td>41</td>
</tr>
<tr>
<td>H(3)</td>
<td>2034</td>
<td>1202</td>
<td>2189</td>
<td>41</td>
</tr>
<tr>
<td>H(5)</td>
<td>1623</td>
<td>4515</td>
<td>4236</td>
<td>33</td>
</tr>
<tr>
<td>H(6A)</td>
<td>1687</td>
<td>5885</td>
<td>2505</td>
<td>70</td>
</tr>
<tr>
<td>H(6B)</td>
<td>1060</td>
<td>5660</td>
<td>2001</td>
<td>70</td>
</tr>
<tr>
<td>H(6C)</td>
<td>1473</td>
<td>4578</td>
<td>1411</td>
<td>70</td>
</tr>
<tr>
<td>H(7A)</td>
<td>1048</td>
<td>651</td>
<td>1527</td>
<td>59</td>
</tr>
<tr>
<td>H(7B)</td>
<td>615</td>
<td>1969</td>
<td>1975</td>
<td>59</td>
</tr>
<tr>
<td>H(7C)</td>
<td>932</td>
<td>-6</td>
<td>2650</td>
<td>59</td>
</tr>
<tr>
<td>H(9A)</td>
<td>-17</td>
<td>7021</td>
<td>3424</td>
<td>77</td>
</tr>
<tr>
<td>H(9B)</td>
<td>324</td>
<td>9003</td>
<td>4041</td>
<td>77</td>
</tr>
<tr>
<td>H(9C)</td>
<td>209</td>
<td>6926</td>
<td>4695</td>
<td>77</td>
</tr>
</tbody>
</table>
APPENDIX D

X-RAY DATA FOR COMPOUND 3-26

Crystal Data

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>C10 H16 O5</td>
</tr>
<tr>
<td>Formula Weight</td>
<td>216.23</td>
</tr>
<tr>
<td>Crystal System</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P21/c (No. 14)</td>
</tr>
<tr>
<td>a, b, c [Å]</td>
<td>8.849(2) 15.512(3) 8.0902(17)</td>
</tr>
<tr>
<td>alpha, beta, gamma [deg]</td>
<td>90 101.154(19) 90</td>
</tr>
<tr>
<td>V [Å³]</td>
<td>1089.5(4)</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>D(calc) [g/cm³]</td>
<td>1.318</td>
</tr>
<tr>
<td>Mu(MoKa) [/mm]</td>
<td>0.106</td>
</tr>
<tr>
<td>F(000)</td>
<td>464</td>
</tr>
<tr>
<td>Crystal Size [mm]</td>
<td>0.00 x 0.00 x 0.00</td>
</tr>
</tbody>
</table>

Data Collection

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (K)</td>
<td>208</td>
</tr>
<tr>
<td>Radiation [Å]</td>
<td>MoKa 0.71073</td>
</tr>
<tr>
<td>Theta Min-Max [Deg]</td>
<td>2.3, 26.0</td>
</tr>
<tr>
<td>Dataset</td>
<td>-10: 10 ; -19: 17 ; -3: 9</td>
</tr>
<tr>
<td>Tot., Uniq. Data, R(int)</td>
<td>2284, 2132, 0.024</td>
</tr>
</tbody>
</table>
Observed data [I > 0.0 sigma(I)]

Refinement

Nref, Npar = 2132, 200
R, wR2, S = 0.0567, 0.1445, 1.03
w = 1/[s^2+(Fo^2+0.0554P)^2+0.8218P] where
P=(Fo^2+2Fc^2)/3

Max. and Av. Shift/Error = 0.00, 0.00
Min. and Max. Resd. Dens. [e/Ang^3] = -0.21, 0.25

Table S2 - Final Coordinates and Equivalent Isotropic Displacement Parameters of the non-Hydrogen atoms for: compound15P 21/c  R = 0.06

<table>
<thead>
<tr>
<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq) [Ang^2]</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1</td>
<td>0.2256(2)</td>
<td>0.79114(12)</td>
<td>0.1214(2)</td>
<td>0.0345(7)</td>
</tr>
<tr>
<td>O2</td>
<td>0.4175(2)</td>
<td>0.96400(11)</td>
<td>0.1784(2)</td>
<td>0.0283(6)</td>
</tr>
<tr>
<td>O3</td>
<td>0.3308(3)</td>
<td>1.11782(14)</td>
<td>0.2665(3)</td>
<td>0.0517(9)</td>
</tr>
<tr>
<td>O4</td>
<td>0.0822(2)</td>
<td>1.08403(14)</td>
<td>0.1849(3)</td>
<td>0.0468(8)</td>
</tr>
<tr>
<td>O5</td>
<td>0.4059(2)</td>
<td>0.88161(14)</td>
<td>-0.0649(3)</td>
<td>0.0346(7)</td>
</tr>
<tr>
<td>C1</td>
<td>0.2584(3)</td>
<td>0.97140(18)</td>
<td>0.1849(4)</td>
<td>0.0272(8)</td>
</tr>
<tr>
<td>C2</td>
<td>0.2162(3)</td>
<td>0.91172(18)</td>
<td>0.3232(3)</td>
<td>0.0283(8)</td>
</tr>
<tr>
<td>C3</td>
<td>0.2732(3)</td>
<td>0.82226(18)</td>
<td>0.2906(4)</td>
<td>0.0302(9)</td>
</tr>
<tr>
<td>C4</td>
<td>0.3866(3)</td>
<td>0.80822(18)</td>
<td>0.1848(4)</td>
<td>0.0316(9)</td>
</tr>
<tr>
<td>C5</td>
<td>0.4581(3)</td>
<td>0.88404(17)</td>
<td>0.1100(3)</td>
<td>0.0282(9)</td>
</tr>
<tr>
<td>C6</td>
<td>0.2323(3)</td>
<td>1.06554(18)</td>
<td>0.2173(3)</td>
<td>0.0305(9)</td>
</tr>
<tr>
<td>C7</td>
<td>0.2951(4)</td>
<td>0.9402(2)</td>
<td>0.4992(4)</td>
<td>0.0400(11)</td>
</tr>
<tr>
<td>C8</td>
<td>0.0419(4)</td>
<td>0.9064(2)</td>
<td>0.3095(5)</td>
<td>0.0415(11)</td>
</tr>
<tr>
<td>C9</td>
<td>0.6326(4)</td>
<td>0.8799(2)</td>
<td>0.1607(5)</td>
<td>0.0383(11)</td>
</tr>
<tr>
<td>C10</td>
<td>0.0405(6)</td>
<td>1.1718(3)</td>
<td>0.2188(7)</td>
<td>0.0604(16)</td>
</tr>
</tbody>
</table>
U(eq) = $\frac{1}{3}$ of the trace of the orthogonalized U Tensor

Table S3 - Hydrogen Atom Positions and Isotropic Displacement Parameters
for: compound15P 21/c       R = 0.06

<table>
<thead>
<tr>
<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(iso) [Å²]</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>0.201(3)</td>
<td>0.9564(17)</td>
<td>0.078(4)</td>
<td>0.025(7)</td>
</tr>
<tr>
<td>H3</td>
<td>0.270(3)</td>
<td>0.7838(16)</td>
<td>0.378(3)</td>
<td>0.012(6)</td>
</tr>
<tr>
<td>H4</td>
<td>0.453(3)</td>
<td>0.758(2)</td>
<td>0.202(3)</td>
<td>0.034(8)</td>
</tr>
<tr>
<td>H5O</td>
<td>0.462(4)</td>
<td>0.914(2)</td>
<td>-0.111(4)</td>
<td>0.045(10)</td>
</tr>
<tr>
<td>H7A</td>
<td>0.273(4)</td>
<td>0.901(2)</td>
<td>0.588(4)</td>
<td>0.054(10)</td>
</tr>
<tr>
<td>H7B</td>
<td>0.411(4)</td>
<td>0.942(2)</td>
<td>0.514(4)</td>
<td>0.049(9)</td>
</tr>
<tr>
<td>H7C</td>
<td>0.257(4)</td>
<td>1.001(2)</td>
<td>0.529(4)</td>
<td>0.059(10)</td>
</tr>
<tr>
<td>H8A</td>
<td>0.017(4)</td>
<td>0.863(2)</td>
<td>0.388(4)</td>
<td>0.047(9)</td>
</tr>
<tr>
<td>H8B</td>
<td>-0.004(3)</td>
<td>0.959(2)</td>
<td>0.339(4)</td>
<td>0.035(8)</td>
</tr>
<tr>
<td>H8C</td>
<td>-0.008(4)</td>
<td>0.889(2)</td>
<td>0.193(4)</td>
<td>0.044(9)</td>
</tr>
<tr>
<td>H9A</td>
<td>0.665(3)</td>
<td>0.8684(17)</td>
<td>0.282(4)</td>
<td>0.026(7)</td>
</tr>
<tr>
<td>H9B</td>
<td>0.666(4)</td>
<td>0.831(2)</td>
<td>0.110(4)</td>
<td>0.042(9)</td>
</tr>
<tr>
<td>H9C</td>
<td>0.677(4)</td>
<td>0.933(2)</td>
<td>0.127(4)</td>
<td>0.053(10)</td>
</tr>
<tr>
<td>H10A</td>
<td>0.074(5)</td>
<td>1.189(3)</td>
<td>0.332(6)</td>
<td>0.080(14)</td>
</tr>
<tr>
<td>H10B</td>
<td>-0.061(7)</td>
<td>1.175(3)</td>
<td>0.193(6)</td>
<td>0.111(19)</td>
</tr>
<tr>
<td>H10C</td>
<td>0.074(5)</td>
<td>1.207(3)</td>
<td>0.140(6)</td>
<td>0.092(17)</td>
</tr>
</tbody>
</table>

The Temperature Factor has the Form of Exp(-T) Where

232
The Temperature Factor has the Form of \( \exp(-T) \) Where
\[
T = 8*(\Pi^2)U*(\text{Sin(Theta)}/\text{Lambda})^2
\]
for Isotropic Atoms

\[
T = 2*(\Pi^2)\sum_{ij}(h(i)*h(j)*U(i,j)*A_{\text{star}(i)}*A_{\text{star}(j)}),
\]
for Anisotropic Atoms. \( A_{\text{star}(i)} \) are Reciprocal Axial Lengths and \( h(i) \) are the Reflection Indices.
Table S5 - Bond Distances (Angstrom) for: compound15P 21/c  R = 0.06

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>O1</td>
<td>-C3</td>
<td>1.436(4)</td>
<td>C5</td>
<td>-C9</td>
<td>1.520(5)</td>
</tr>
<tr>
<td>O1</td>
<td>-C4</td>
<td>1.442(3)</td>
<td>C1</td>
<td>-H1</td>
<td>0.94(3)</td>
</tr>
<tr>
<td>O2</td>
<td>-C1</td>
<td>1.424(3)</td>
<td>C3</td>
<td>-H3</td>
<td>0.93(2)</td>
</tr>
<tr>
<td>O2</td>
<td>-C5</td>
<td>1.432(3)</td>
<td>C4</td>
<td>-H4</td>
<td>0.97(3)</td>
</tr>
<tr>
<td>O3</td>
<td>-C6</td>
<td>1.201(4)</td>
<td>C7</td>
<td>-H7A</td>
<td>0.99(3)</td>
</tr>
<tr>
<td>O4</td>
<td>-C6</td>
<td>1.334(3)</td>
<td>C7</td>
<td>-H7B</td>
<td>1.01(4)</td>
</tr>
<tr>
<td>O4</td>
<td>-C10</td>
<td>1.451(5)</td>
<td>C7</td>
<td>-H7C</td>
<td>1.05(3)</td>
</tr>
<tr>
<td>O5</td>
<td>-C5</td>
<td>1.402(3)</td>
<td>C8</td>
<td>-H8A</td>
<td>0.98(3)</td>
</tr>
<tr>
<td>O5</td>
<td>-H5O</td>
<td>0.84(3)</td>
<td>C8</td>
<td>-H8B</td>
<td>0.96(3)</td>
</tr>
<tr>
<td>C1</td>
<td>-C2</td>
<td>1.552(4)</td>
<td>C8</td>
<td>-H8C</td>
<td>1.00(3)</td>
</tr>
<tr>
<td>C1</td>
<td>-C6</td>
<td>1.509(4)</td>
<td>C9</td>
<td>-H9A</td>
<td>0.98(3)</td>
</tr>
<tr>
<td>C2</td>
<td>-C7</td>
<td>1.525(4)</td>
<td>C9</td>
<td>-H9B</td>
<td>0.94(3)</td>
</tr>
<tr>
<td>C2</td>
<td>-C8</td>
<td>1.527(5)</td>
<td>C9</td>
<td>-H9C</td>
<td>0.97(3)</td>
</tr>
<tr>
<td>C2</td>
<td>-C3</td>
<td>1.517(4)</td>
<td>C10</td>
<td>-H10A</td>
<td>0.95(5)</td>
</tr>
<tr>
<td>C3</td>
<td>-C4</td>
<td>1.456(4)</td>
<td>C10</td>
<td>-H10B</td>
<td>0.88(6)</td>
</tr>
<tr>
<td>C4</td>
<td>-C5</td>
<td>1.516(4)</td>
<td>C10</td>
<td>-H10C</td>
<td>0.93(5)</td>
</tr>
</tbody>
</table>

Table S6 - Bond Angles (Degrees) for: compound15P 21/c  R = 0.06

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C3</td>
<td>-O1</td>
<td>-C4</td>
<td>60.77(18)</td>
<td>O2</td>
<td>-C1</td>
</tr>
<tr>
<td>C1</td>
<td>-O2</td>
<td>-C5</td>
<td>114.1(2)</td>
<td>C2</td>
<td>-C1</td>
</tr>
<tr>
<td>C6</td>
<td>-O4</td>
<td>-C10</td>
<td>116.4(3)</td>
<td>C6</td>
<td>-C1</td>
</tr>
</tbody>
</table>
O4  -C6  -C1  110.7(2)  H9B  -C9  -H9C  113(3)
O3  -C6  -O4  123.5(3)  O4  -C10  -H10A  114(3)

Table S6 - Bond Angles (Degrees) (continued)
for: compound15P 21/c  R = 0.06

O4  -C10  -H10B  107(3)  H10A  -C10  -H10C  115(4)
O4  -C10  -H10C  107(3)  H10B  -C10  -H10C  104(4)
H10A  -C10  -H10B  109(4)

Table S7 - Torsion Angles (Degrees)
for: compound15P 21/c  R = 0.06

C4  -O1  -C3  -C2  113.7(3)
C3  -O1  -C4  -C5  -110.9(3)
C5  -O2  -C1  -C2  71.6(3)
C5  -O2  -C1  -C6  -166.1(2)
C1  -O2  -C5  -O5  73.6(3)
C1  -O2  -C5  -C4  -45.9(3)
C1  -O2  -C5  -C9  -164.4(2)
C10  -O4  -C6  -O3  -2.5(4)
C10  -O4  -C6  -C1  177.1(3)
O2  -C1  -C2  -C3  -52.4(3)
O2  -C1  -C2  -C7  66.1(3)
O2  -C1  -C2  -C8  -169.4(2)
C6  -C1  -C2  -C3  -170.6(2)
C6  -C1  -C2  -C7  -52.1(3)
<table>
<thead>
<tr>
<th>Atom 1</th>
<th>Atom 2</th>
<th>Atom 3</th>
<th>Atom 4</th>
<th>Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>C6</td>
<td>-C1</td>
<td>-C2</td>
<td>-C8</td>
<td>72.4(3)</td>
</tr>
<tr>
<td>O2</td>
<td>-C1</td>
<td>-C6</td>
<td>-O3</td>
<td>-15.8(4)</td>
</tr>
<tr>
<td>O2</td>
<td>-C1</td>
<td>-C6</td>
<td>-O4</td>
<td>164.7(2)</td>
</tr>
<tr>
<td>C2</td>
<td>-C1</td>
<td>-C6</td>
<td>-O3</td>
<td>105.4(3)</td>
</tr>
<tr>
<td>C2</td>
<td>-C1</td>
<td>-C6</td>
<td>-O4</td>
<td>-74.2(3)</td>
</tr>
<tr>
<td>C1</td>
<td>-C2</td>
<td>-C3</td>
<td>-O1</td>
<td>-51.3(3)</td>
</tr>
<tr>
<td>C1</td>
<td>-C2</td>
<td>-C3</td>
<td>-C4</td>
<td>17.6(4)</td>
</tr>
<tr>
<td>C7</td>
<td>-C2</td>
<td>-C3</td>
<td>-O1</td>
<td>-171.8(2)</td>
</tr>
<tr>
<td>C7</td>
<td>-C2</td>
<td>-C3</td>
<td>-C4</td>
<td>-102.9(3)</td>
</tr>
<tr>
<td>C8</td>
<td>-C2</td>
<td>-C3</td>
<td>-O1</td>
<td>68.0(3)</td>
</tr>
<tr>
<td>C8</td>
<td>-C2</td>
<td>-C3</td>
<td>-C4</td>
<td>136.9(3)</td>
</tr>
<tr>
<td>O1</td>
<td>-C3</td>
<td>-C4</td>
<td>-C5</td>
<td>105.8(3)</td>
</tr>
<tr>
<td>C2</td>
<td>-C3</td>
<td>-C4</td>
<td>-O1</td>
<td>-102.7(3)</td>
</tr>
<tr>
<td>C2</td>
<td>-C3</td>
<td>-C4</td>
<td>-C5</td>
<td>3.1(4)</td>
</tr>
</tbody>
</table>

Table S7 - Torsion Angles (Degrees) (continued)
for: compound15P 21/c  R = 0.06

<table>
<thead>
<tr>
<th>Atom 1</th>
<th>Atom 2</th>
<th>Atom 3</th>
<th>Atom 4</th>
<th>Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1</td>
<td>-C4</td>
<td>-C5</td>
<td>-O2</td>
<td>77.8(3)</td>
</tr>
<tr>
<td>O1</td>
<td>-C4</td>
<td>-C5</td>
<td>-O5</td>
<td>-43.7(3)</td>
</tr>
<tr>
<td>O1</td>
<td>-C4</td>
<td>-C5</td>
<td>-C9</td>
<td>-167.0(2)</td>
</tr>
<tr>
<td>C3</td>
<td>-C4</td>
<td>-C5</td>
<td>-O2</td>
<td>8.9(4)</td>
</tr>
<tr>
<td>C3</td>
<td>-C4</td>
<td>-C5</td>
<td>-O5</td>
<td>-112.5(3)</td>
</tr>
<tr>
<td>C3</td>
<td>-C4</td>
<td>-C5</td>
<td>-C9</td>
<td>124.1(3)</td>
</tr>
<tr>
<td>Atom Pair</td>
<td>Distance (Å)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>--------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O1 .O2</td>
<td>3.160(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O1 .O5</td>
<td>2.778(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O1 .C10_b</td>
<td>3.308(6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O1 .C3_c</td>
<td>3.297(4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O2 .O3</td>
<td>2.646(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O2 .O1</td>
<td>3.160(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O2 .O5_d</td>
<td>3.095(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O3 .O5_d</td>
<td>3.092(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O3 .C7</td>
<td>3.386(4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O3 .O2</td>
<td>2.646(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O4 .C8</td>
<td>2.979(4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O5 .O1</td>
<td>2.778(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O5 .O3_d</td>
<td>3.092(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O5 .O2_d</td>
<td>3.095(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O1 .H8C</td>
<td>2.72(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O1 .H1</td>
<td>2.59(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O1 .H10B_a</td>
<td>2.91(5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O1 .H10B_b</td>
<td>2.73(5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O1 .H3_c</td>
<td>2.38(2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O2 .H5O_d</td>
<td>2.29(3)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
O2 .H7B       2.75(3)   H3 .H7A       2.49(4)  
O3 .H4_e      2.88(3)   H3 .H8A       2.57(4)  
O3 .H10A      2.67(5)   H3 .H10B_ a   2.49(6)  
O3 .H10C      2.69(5)   H3 .O1_h      2.38(2)  
O3 .H7B_f     2.77(3)   H3 .O5_h      2.83(3)  
O3 .H5O_d     2.47(3)   H3 .C4_h      2.88(2)  
O5 .H7A_g     2.84(3)   H4 .H9B       2.44(4)  

Table S8 - Contact Distances (Angstrom) (continued)  
for: compound15P 21/c   R = 0.06  
H4 .O3_i      2.88(3)   H8B .C6       2.98(3)  
H5O .H9C      2.45(5)   H8B .H7C      2.60(5)  
H5O .O2_d     2.29(3)   H8C .O1       2.72(3)  
H5O .O3_d     2.47(3)   H8C .H1       2.46(4)  
H5O .C6_d     3.01(4)   H9A .H4       2.53(4)  
H7A .O5_j     2.84(3)   H9A .H7C_f    2.55(4)  
H7A .H3       2.49(4)   H9B .H4       2.44(4)  
H7B .O2       2.75(3)   H9C .C1_d     3.07(3)  
H7B .O3_f     2.77(3)   H9C .C6_d     3.04(3)  
H7B .H7B_f    2.43(5)   H10A .O3      2.67(5)  
H7C .C6       2.68(3)   H10B .O1_k    2.91(5)  

239
Table S9 - Hydrogen Bonds (Angstrom, Deg) for: compound15P 21/c R = 0.06

<table>
<thead>
<tr>
<th>Bond</th>
<th>Distance (Å)</th>
<th>Angle (deg)</th>
<th>1st Distance (Å)</th>
<th>2nd Distance (Å)</th>
<th>3rd Distance (Å)</th>
<th>4th Distance (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O5 -- H5O .. O2</td>
<td>0.84(3)</td>
<td>2.29(3)</td>
<td>3.095(3)</td>
<td>160(3)</td>
<td>3.675</td>
<td></td>
</tr>
<tr>
<td>O5 -- H5O .. O3</td>
<td>0.84(3)</td>
<td>2.47(3)</td>
<td>3.092(3)</td>
<td>132(3)</td>
<td>3.675</td>
<td></td>
</tr>
<tr>
<td>C3 -- H3 .. O1</td>
<td>0.93(2)</td>
<td>2.38(2)</td>
<td>3.297(4)</td>
<td>167(2)</td>
<td>4.565</td>
<td></td>
</tr>
<tr>
<td>C8 -- H8B .. O4</td>
<td>0.96(3)</td>
<td>2.50(3)</td>
<td>2.979(4)</td>
<td>111(2)</td>
<td>.</td>
<td></td>
</tr>
</tbody>
</table>

Translation of Symmetry Code to Equiv.Pos

a = [ 2545.00 ] = -x,-1/2+y,1/2-z
b = [ 3575.00 ] = -x,2-y,-z
c = [ 4564.00 ] = x,3/2-y,-1/2+z
d = [ 3675.00 ] = 1-x,2-y,-z
e = [ 2655.00 ] = 1-x,1/2+y,1/2-z
f = [ 3676.00 ] = 1-x,2-y,1-z
g = [ 1554.00 ] = x,y,-1+z
h = [ 4565.00 ] = x,3/2-y,1/2+z
i = [ 2645.00 ] = 1-x,-1/2+y,1/2-z
j = [ 1556.00 ] = x,y,1+z
k = [ 2555.00 ] = -x,1/2+y,1/2-z
BIBLIOGRAPHY


20. Results appearing in this document.


39. For a discussion of these factors, see Ref. 36(a).


41. For reviews on the catalysis of the Claisen and Cope rearrangement, see (a) Lutz, R. P. *Chem. Rev.* **1984**, 84, 205. (b) Ref. 36 (b).


57. It is well accepted that aluminoxanes are highly aggregated species, forming clusters which have average molecular weights of about 1100 amu (in the case of methyl aluminoxane). Additionally, some of these clusters have been observed by X-ray crystallography. For


60. Configuration is based on a chair-like transition state: (a) Ziegler, F. E. Chem. Rev. 1988, 88, 1423. (b) Ref. 36a. (c) Ref. 52.


66. For the [1,3] sigmatropic rearrangement of the corresponding allyl vinyl ether, see:


70. Representative procedure for the attempted aza-Cope [or carboalumination] of **2-11** and related substrates: To a -30 °C solution of AlMe3 (58.1 mg, 0.802 mmol) in CH2Cl2 (2.6 mL) was added H2O (7.20 μL, 0.404 mmol) dropwise. The reaction mixture was warmed to room temperature and then cooled to -78 °C. Lactam **2-11** (45.0 mg, 0.269 mmol) was added dropwise as a solution in CH2Cl2 (1.25 mL) and the mixture was warmed to ambient temperature and stirred for 24 h. The solution was quenched with 1M Rochelle’s salt (2 mL) and the aqueous layer was extracted with CH2Cl2 (3 x 3 mL). The combined organic layers were washed with brine, dried (Na2SO4) and concentrated. The resulting crude residue was analyzed by 1H NMR and characteristic data are reported in the experimental part.


101. This net transformation has been reported only twice; in both cases upon treatment of enones with basic hydrogen peroxide for extended periods of time: Bhat, K. L.; Trivedi, G. Syn. Commun. 1982, 12, 585-93; Kocor, M.; Kurek, A.; Dabrowski, J. Tetrahedron 1969, 25, 4257.


109. See experimental part for protocols.


120. The synthetic efforts up to 2001 have been reviewed, see: Ritter, T.; Carreira, E. M. 


134. The product arising from reduction of the iodide was recovered in 5-10% yield, and had an R<sub>f</sub> identical to that of the iodide.


136. The term “ee” is used here to denote the degree of control exerted by the ligand during the cyclization. Technically, “diastereomeric excess (de)” should be used since there is a chiral center present in the molecule, although in this case, the chiral center has no stereochemical effect on the newly formed chiral center.


