

An Iterative Synthesis of Oligo-Vinyl Ethers and Applications Thereof

by

Katherine Davies
B.Sc., University of Victoria, 2007

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of the Requirements for the Degree of

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in the Department of Chemistry

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Supervisory Committee

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Abstract

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An iterative protocol is a highly efficient strategy for the generation of large, complex molecules that has been applied in many different subfields of organic synthesis. The use of a tandem or cascade reaction is also an effective approach for the rapid introduction of molecular complexity into a system since the number of steps requiring independent optimization is greatly reduced. With the aim of creating new synthetic strategies to efficiently gain access to stereochemically complex small molecules, we envisioned the use of short iterative protocols to prepare reactive oligomers to which a diverse range of cascade cyclization processes could be applied.

In an attempt to minimize reaction optimization and chromatographic purification steps during the development of our small molecule precursors, we first developed an iterative synthesis based on a conjugate addition/reduction sequence that has allowed us to access a diverse series of oligo-vinyl ether intermediates. Significantly, both the addition and reduction steps proceed in near-quantitative yield, and reaction co-products can be removed without column chromatography. At the same time, most of our vinyl ether intermediates are stable to silica gel, and so analytically pure samples can be prepared when desired. Except for when very sterically demanding substrates are employed as electrophiles, the intermediates are isolated as single geometrical isomers. We also developed an improved synthesis of a previously intractable class of alkynoate starting materials (4-aryl-2-butynoates) to ensure a diverse range of easily accessible monomeric building blocks were available for our use.

With this effective iterative route in hand, we have several interesting small molecule targets at our disposal. We first applied our iterative route to synthesize oxygen-containing analogues of juvenile hormone III. These mono- and bis-vinyl ethers are currently undergoing biological testing (in collaboration with Dr. Steve Perlman and Dr. Michael Horst), and early results show promise as ecologically degradable insect control agents.

We also developed an unprecedented 6-*endo*/5-*exo* radical cascade reaction across bis-vinyl ethers which proceeds in good yield, high diastereoselectivity, and excellent regiochemical control. This reaction represents the first cascading radical cyclization ever reported for a bis-vinyl ether system and validates our iterative approach to molecular complexity.

Table of Contents

| | |
|--|-------|
| Supervisory Committee | ii |
| Abstract..... | iii |
| Table of Contents..... | v |
| List of Tables | ix |
| List of Schemes..... | x |
| List of Figures..... | xiv |
| List of Abbreviations and Symbols..... | xvi |
| Acknowledgements..... | xxiii |
| Dedication..... | xxiv |
| Chapter 1: Introduction..... | 1 |
| 1.0.0 Iterative Synthesis..... | 1 |
| 1.1.0 Iterative Synthesis of Biomolecules | 3 |
| 1.1.1 Polyamino Acids..... | 9 |
| 1.1.2 Oligonucleotides | 11 |
| 1.1.3 Oligosaccharides..... | 12 |
| 1.1.4 Summary..... | 19 |
| 1.2.0 Iterative Protocols in the Synthesis of Other Organic Molecules..... | 20 |
| 1.2.1 Dendrimers..... | 21 |
| 1.2.2 Oligoarenes | 23 |
| 1.2.3 [4n + 2]Annulenes | 26 |
| 1.2.4 Aliphatic Molecules..... | 26 |
| 1.2.5 Belt and Ribbon Shaped Molecules..... | 31 |
| 1.2.6 Polyketides..... | 34 |
| 1.2.7 Polyethers..... | 39 |
| 1.2.8 Iterative Cross-Coupling Reactions..... | 43 |
| 1.2.9 Iterative Ring Expansions..... | 51 |
| 1.3.0 Summary & Objectives..... | 53 |
| 1.3.1 Iterative Synthesis Design..... | 53 |

| | |
|---|-----|
| Chapter 2: Iterative Synthesis Development & Optimization | 56 |
| 2.0.0 Iterative Synthesis Development | 56 |
| 2.1.0 Synthetic Preparation of Starting Material Building Blocks | 57 |
| 2.1.1 Optimization of Benzyl Alkyne Synthesis..... | 63 |
| 2.1.2 Scope of the Reaction | 66 |
| 2.1.3 Summary of Coupling Methodology to access Benzyl Alkynes (12)..... | 70 |
| 2.2.0 Conjugate Addition Optimization..... | 71 |
| 2.3.0 Reduction Optimization..... | 75 |
| 2.4.0 Summary and Concluding Remarks | 81 |
| Chapter 3: Analogues of Juvenile Hormone III | 83 |
| 3.0.0 Introduction..... | 83 |
| 3.1.0 Synthesis of Juvenile Hormone III Analogues | 86 |
| 3.1.1 Synthesis of Bis-Vinyl Ether Analogues (39)..... | 86 |
| 3.1.2 Synthesis of Mono-Vinyl Ether Analogues (40) | 88 |
| 3.2.0 Stability of Analogues in Moist Air and Water | 89 |
| 3.2.1 Stabilities of Bis-Vinyl Ether Analogues..... | 90 |
| 3.2.2 Stabilities of Mono-Vinyl Ether Analogues | 96 |
| 3.2.3 Summary of Vinyl Ether Analogue Stabilities | 99 |
| 3.3.0 Biological Assays | 101 |
| 3.3.1 Biological Assays in Insects | 102 |
| 3.3.2 Biological Assays in Crustaceans | 104 |
| Chapter 4: Radical Cyclizations across Bis-Vinyl Ethers..... | 105 |
| 4.0.0 Introduction..... | 105 |
| 4.1.0 Initial Radical Cyclization Attempt..... | 111 |
| 4.2.0 Alternate Radical Cyclization Attempt..... | 119 |
| 4.3.0 Substrate Scope..... | 130 |
| 4.4.0 Mechanistic Analysis..... | 136 |
| 4.4.1 Mechanistic Studies on the 6-endo/5-exo Radical Cascade: Part I..... | 143 |
| 4.4.2 Mechanistic Studies on the 6-endo/5-exo Radical Cascade: Part II | 151 |
| 4.5.0. Summary..... | 155 |
| Chapter 5: Experimental | 157 |

| | |
|--|-----|
| 5.0.0 General Remarks..... | 157 |
| 5.0.1 General Experimental Remarks..... | 157 |
| 5.0.2 Materials | 157 |
| 5.0.3 Instrumentation | 158 |
| 5.1.0 General Experimental Procedures | 159 |
| 5.1.1 General Benzyl Halide and Terminal Alkyne Coupling Procedure..... | 159 |
| 5.1.2 General Conjugate Addition Procedure..... | 159 |
| 5.1.3 General DIBAL-H Reduction Procedure..... | 160 |
| 5.1.4 General LiAlH ₄ /LiAlD ₄ Reduction Procedure..... | 160 |
| 5.1.5 General Methoxymethyl Chloride Protection Procedure..... | 161 |
| 5.1.6 General TBAF Deprotection Procedure..... | 161 |
| 5.1.7 General Methylation Procedure | 161 |
| 5.1.8 General Benzylation Procedure | 162 |
| 5.1.9 General Parikh-Doering Oxidation Procedure..... | 162 |
| 5.1.10 General Thiol-Catalyzed Radical-Mediated Cyclization Procedure..... | 163 |
| 5.1.11 General Radical-Mediated Cyclization Procedure..... | 163 |
| 5.1.12 General Protodestannylation Procedure..... | 163 |
| 5.1.13 General IBX Oxidation Procedure..... | 164 |
| 5.1.14 General Wittig Reaction Procedure | 164 |
| 5.2.0 Compounds Pertaining to Chapter 2..... | 165 |
| 5.2.1 Experimental Data for 4-Aryl-2-Butynoates (12)..... | 165 |
| 5.3.0 Compounds Pertaining to Chapter 3..... | 171 |
| 5.3.1 Experimental Data for Bis-Vinyl Ethers 39 | 171 |
| 5.3.2 Experimental Data for Mono-Vinyl Ethers 40 | 174 |
| 5.3.3 Experimental Data for Conjugate Addition Synthetic Intermediates 42 | 177 |
| 5.3.4 Experimental Data for Reduction Synthetic Intermediates 43 | 180 |
| 5.4.0 Compounds Pertaining to Chapter 4 Section 4.1.0..... | 183 |
| 5.4.1 Experimental Data for Synthetic Intermediates 23 and 25 | 183 |
| 5.4.2 Experimental Data for Synthetic Intermediates 24 and 26 | 185 |
| 5.4.3 Experimental Data for Synthetic Intermediates 67 and 69 | 186 |
| 5.4.4 Experimental Data for Synthetic Intermediates 68 and 70 | 188 |

| | |
|---|-----|
| 5.4.5 Experimental Data for Synthetic Intermediate 72 | 189 |
| 5.4.6 Experimental Data for Cyclization Product 76b | 190 |
| 5.5.0 Compounds Pertaining to Chapter 4 Section 4.2.0 & 4.3.0..... | 191 |
| 5.5.1 Experimental Data for Synthetic Intermediates 78, 80, 85a, 87a, and 98 | 191 |
| 5.5.2 Experimental Data for Synthetic Intermediates 79, 81, 86a, and 88a | 201 |
| 5.5.3 Experimental Data for Synthetic Intermediates 82, 83, and 90a | 210 |
| 5.5.4 Experimental Data for Synthetic Intermediate 89 | 217 |
| 5.5.5 Experimental Data for Cyclization Products 91, 94, 95, and 115a | 217 |
| 5.5.6 Experimental Data for Protodestannylation Products 93a, 96, or 97a | 227 |
| 5.6.0 Experiments Pertaining to Chapter 4 Section 4.4.0 | 231 |
| 5.6.1 Experimental Data for Addition Synthetic Intermediates 78h and 80k | 231 |
| 5.6.2 Experimental Data for Synthetic Intermediates 79 and 81 | 232 |
| 5.6.3 Experimental Data for Synthetic Intermediates 82 and 83 | 234 |
| 5.6.4 Experimental Data for IBX Oxidation Product 117 | 236 |
| 5.6.5 Experimental Data for Diene 118 | 237 |
| 5.6.6 Experimental Data for Cyclization Products 91, 94, 95, and 115 | 237 |
| 6.0.0 References..... | 243 |
| Appendix 1: Chapter 2 Spectral Data | 259 |
| Appendix 2: Chapter 3 Spectral Data | 271 |
| Appendix 3: Chapter 4 Section 4.1.0 – 4.3.0 Spectral Data | 285 |
| Appendix 4: Chapter 4 Section 4.4.0 Spectral Data | 312 |
| Appendix 5: Publications and Presentations..... | 321 |

List of Tables

| | |
|---|-----|
| Table 1. Optimization of reaction conditions for coupling 4-benzyloxybenzyl chloride (11a) with methyl propiolate (7a) in the presence of 1.0 eq of copper (I) iodide. | 64 |
| Table 2. Variation of the benzyl halide coupling partner (11)..... | 67 |
| Table 3. Variation of the alkyne coupling partner (7). | 69 |
| Table 4. Phosphine catalyst optimization for conjugate addition of 1a to 2a | 72 |
| Table 5. Stability tests of 26a to determine the level of acid sensitivity in our oligo-vinyl ether systems. | 77 |
| Table 6. Stabilities of bis-vinyl ether analogues of JH-III..... | 91 |
| Table 7. Stabilities of mono-vinyl ether analogues of JH-III. | 96 |
| Table 8. Iterative synthesis of bis-vinyl ether substrates. | 130 |
| Table 9. Iterative synthesis of bis-vinyl ether substrates. | 132 |
| Table 10. Methylation of bis-vinyl ether substrates..... | 134 |
| Table 11. Radical cyclization across bis-vinyl ethers. | 135 |

List of Schemes

| | |
|--|----|
| Scheme 1. Iterative fatty acid biosynthesis..... | 4 |
| Scheme 2. Iterative biosynthesis of the terpene squalene..... | 7 |
| Scheme 3. Biosynthesis of lanosterol from the triterpene squalene. | 8 |
| Scheme 4. General scheme for Merrifield solid-phase peptide synthesis. | 10 |
| Scheme 5. Iterative synthesis of DNA..... | 11 |
| Scheme 6. Automated solid-phase oligosaccharide synthesis..... | 14 |
| Scheme 7. A one-pot synthesis of Globo H, a hexasaccharide..... | 16 |
| Scheme 8. Iterative synthesis of branched oligosaccharides via a fluoruous tag strategy.. | 18 |
| Scheme 9. Iterative synthesis of dendrites..... | 21 |
| Scheme 10. An iteratively synthesized fifth generation polyamine dendrimer..... | 22 |
| Scheme 11. Iterative preparation of a phenylacetylene dendrimer..... | 23 |
| Scheme 12. Iterative convergent-divergent synthesis of oligoarenes..... | 24 |
| Scheme 13. Iterative synthesis of oligophenylene rods via Suzuki coupling strategy. | 25 |
| Scheme 14. A building-block approach to $[4n + 2]$ annulenes..... | 26 |
| Scheme 15. Iterative synthesis of polyspiro cyclic aliphatic linkages..... | 27 |
| Scheme 16. Alternate iterative pathway to polyspiro four-membered ring linkages. | 28 |
| Scheme 17. Stepwise synthesis of bi- and tricyclohexyl derivatives..... | 29 |
| Scheme 18. Iterative synthesis of terminally substituted dispiranes..... | 30 |
| Scheme 19. Synthesis of kohnkene via iterative Diels-Alder cycloadditions. | 31 |
| Scheme 20. Iterative synthesis of double-stranded molecules..... | 33 |
| Scheme 21. Alternate route to the iterative construction of molecular ribbons..... | 34 |
| Scheme 22. Generation of polyketides via iterative asymmetric aldol reactions. | 35 |
| Scheme 23. Iterative synthesis of di- and triketides on a solid support..... | 36 |
| Scheme 24. Iterative assembly of extended polypropionates to generate polyketides. | 37 |
| Scheme 25. Iterative approach to polycyclic ether segments of gamberic acids A – D... | 40 |
| Scheme 26. General iterative approach to <i>trans</i> -fused polycyclic ether skeletons..... | 41 |
| Scheme 27. Polyether synthesis via epoxide-opening cascades. | 42 |

| | |
|--|----|
| Scheme 28. (a) Generation of mono protected benzenediboronic acid derivatives. (b) Pd-catalyzed Suzuki-Miyaura cross-coupling reaction. | 45 |
| Scheme 29. Synthesis of boron-substituted oligoarene derivatives..... | 46 |
| Scheme 30. General one-step iterative synthesis of oligoarenes..... | 47 |
| Scheme 31. Iterative synthesis of the vacidin A core. | 49 |
| Scheme 32. Iterative synthesis of (-)-peridinin..... | 50 |
| Scheme 33. Tandem conjugate addition/[3,3] rearrangement to nitrogen heterocycles.. | 51 |
| Scheme 34. Iterative ring expansion towards the synthesis of fluvirucinine A ₂ | 52 |
| Scheme 35. General reaction for the preparation of propiolate starting materials. | 57 |
| Scheme 36. Preparation of monomeric building blocks 2d and 2e | 59 |
| Scheme 37. Literature methods to gain access to benzyl-substituted species (12)..... | 60 |
| Scheme 38. General reaction schemes for the alkylation of benzyl halides..... | 61 |
| Scheme 39. Initial benzyl halide and terminal alkyne coupling results..... | 63 |
| Scheme 40. Phosphine catalyzed addition of an alcohol (1a) to an alkyne (2a). | 71 |
| Scheme 41. Proposed mechanism for the catalyzed addition of 1 to 2 | 72 |
| Scheme 42. Application of second conjugate addition to access bis-vinyl ether 25 | 73 |
| Scheme 43. Initial DIBAL-H reduction conditions to access alcohol 24a | 76 |
| Scheme 44. LiAlH ₄ reduction conditions to access 24 from 23 | 78 |
| Scheme 45. Desired LiAlH ₄ reduction of bis-vinyl ether 25a to 26a | 78 |
| Scheme 46. Possible mechanism accounting for the regeneration of 24a | 79 |
| Scheme 47. Mechanism for the DIBAL-H promoted reduction of 25 to 26 | 80 |
| Scheme 48. DIBAL-H promoted reduction of the ester function to an alcohol. | 80 |
| Scheme 49. Summary for the iterative route to a library of oligo-vinyl ethers. | 81 |
| Scheme 50. Iterative synthesis of the bis-vinyl ether juvenile hormone III mimics..... | 87 |
| Scheme 51. Synthesis of the mono-vinyl ether juvenile hormone mimics..... | 89 |
| Scheme 52. Water-promoted Claisen rearrangement using glyco-vinyl ether substrates. | 93 |
| Scheme 53. Primary decomposition pathway for the bis-vinyl ethers (39)..... | 93 |
| Scheme 54. Mechanistic pathway for Claisen rearrangement/elimination of 39 to 49 | 94 |
| Scheme 55. Mechanistic decomposition pathway for hydrolysis of 39f to 1b | 95 |
| Scheme 56. Mechanistic pathway for Claisen rearrangement of 40 to 51 | 97 |
| Scheme 57. Decomposition pathways for the mono-vinyl ethers (40)..... | 97 |

| | |
|---|-----|
| Scheme 58. General mechanistic decomposition pathway of 40 to 53a | 98 |
| Scheme 59. General mechanistic decomposition pathway for the hydrolysis of 53a | 99 |
| Scheme 60. Summary of new synthetic strategy to access (poly)cyclic targets. | 105 |
| Scheme 61. Retrosynthetic analysis of desired acyl radical precursor. | 112 |
| Scheme 62. Iterative synthesis of TBS protected alcohol vinyl ethers. | 113 |
| Scheme 63. Preparation of mono-vinyl ethers for oxidation to carboxylic acid. | 114 |
| Scheme 64. Preparation of bis-vinyl ethers for oxidation to carboxylic acids. | 114 |
| Scheme 65. An unexpected rearrangement from a PDC oxidation. | 115 |
| Scheme 66. Conversion of an alcohol to an acyl selenide. | 116 |
| Scheme 67. First radical cyclization attempt from an acyl radical. | 117 |
| Scheme 68. A thiol-catalyzed acyl radical cyclization. | 118 |
| Scheme 69. Iterative synthesis of alkyne vinyl ethers. | 120 |
| Scheme 70. Methylation of mono-vinyl ethers 79 | 121 |
| Scheme 71. Methylation of bis-vinyl ethers 81 | 121 |
| Scheme 72. Iterative synthesis of tris- and tetrakis-vinyl ethers. | 122 |
| Scheme 73. (a) Benzylation of vinyl ether 81a . (b) Methylation of vinyl ether 86a | 123 |
| Scheme 74. Radical cyclization onto mono-vinyl ether 82b | 123 |
| Scheme 75. Radical cyclization onto mono-vinyl ether 82a | 124 |
| Scheme 76. Effects of low <i>E:Z</i> selectivity on outcome of radical cyclization reaction.. | 125 |
| Scheme 77. Protodestannylation reaction conditions to convert 91a to 93a | 126 |
| Scheme 78. Radical cyclizations across bis-vinyl ethers. | 126 |
| Scheme 79. Protodestannylation reaction conditions. | 128 |
| Scheme 80. Proposed mechanism for the generation of transesterification product 98 . 133 | |
| Scheme 81. Proposed mechanism for the radical cascade. | 139 |
| Scheme 82. A 5- <i>exo-trig</i> / β -scission product. | 142 |
| Scheme 83. Preparation of cyclopropyl derivative 82c | 144 |
| Scheme 84. Cyclopropyl derivative radical cascade reaction. | 145 |
| Scheme 85. Potential outcomes of cyclopropyl derivative radical cascade reaction. | 147 |
| Scheme 86. Preparation of diene 118 | 148 |
| Scheme 87. Potential outcomes of diene radical cascade reaction. | 149 |
| Scheme 88. Diene derivative radical cascade reaction. | 150 |

| | |
|---|-----|
| Scheme 89. Final work needing to be completed for cyclopropyl derivative 119 | 151 |
| Scheme 90. Generation of deuterated incorporated analogues. | 152 |
| Scheme 91. Synthesis of deuterated incorporated analogues. | 153 |
| Scheme 92. Deuterium incorporated radical cascade reactions. | 154 |
| Scheme 93. Synthesis of triphenyltin deuteride. | 155 |
| Scheme 94. Marrying iterative synthesis to cascade radical cyclizations. | 155 |

List of Figures

| | |
|--|----|
| Figure 1. The basic principle of iterative synthesis. | 1 |
| Figure 2. The basic principle of branched iterative synthesis..... | 2 |
| Figure 3. Iterative polyketide biosynthesis. | 5 |
| Figure 4. The terpene isoprene rule. | 6 |
| Figure 5. Tetraterpene β -carotene containing 8 isoprene units..... | 6 |
| Figure 6. Possible stereochemical outcomes in the synthesis of carbohydrates..... | 13 |
| Figure 7. General structures of peptoids, oligocarbamates, and oligoureas. | 20 |
| Figure 8. Applications of the iterative Diels-Alder reaction. (a) Methylene-bridged beltenes. (b) Linear [<i>n</i>]beltene synthons. (c) Molecular tweezers. | 32 |
| Figure 9. (a) Complex polyketide leading to spiroacetal subunit of (b) spongistatin 1.... | 38 |
| Figure 10. The gamberic acids A – D..... | 39 |
| Figure 11. A boron masking strategy. (a) A 1,8-diaminonaphthalene masking group. (b) A Pd-catalyzed ICC strategy. (c) Oligoarenes prepared using this methodology. | 44 |
| Figure 12. (a) General reaction for the generation of MIDA boronates. (b) Small subset of available MIDA boronate building blocks..... | 48 |
| Figure 13. General iterative synthetic plan..... | 54 |
| Figure 14. An iterative based strategy on an unusual vinyl ether template. | 55 |
| Figure 15. General outline of our two-step iterative synthesis. | 56 |
| Figure 16. Preparation of monomeric building blocks 2a – 2c | 58 |
| Figure 17. General structure of a 4-aryl butynoate (12). | 59 |
| Figure 18. Isomerization of benzyl-substituted propiolates to the corresponding allene. 61 | |
| Figure 19. Accessible small molecule heterocycles from acetylenic esters and ketones. 62 | |
| Figure 20. Possible mechanism for the generation of benzyl alkynes (12). | 66 |
| Figure 21. Summary of developed copper-mediated coupling methodology..... | 70 |
| Figure 22. Summary of propiolates available for the addition step..... | 74 |
| Figure 23. Summary of alcohols available for the addition iteration. | 75 |
| Figure 24. Structures of the insect juvenile hormones 0 – III. | 83 |
| Figure 25. Structural analogues of JH-III used as insect control agents..... | 84 |

| | |
|--|-----|
| Figure 26. Structures of juvenile hormone III, <i>S</i> -methoprene, and methyl farnesoate..... | 85 |
| Figure 27. General structure of target juvenile hormone III analogues 39 and 40 | 86 |
| Figure 28. Alkynoate building blocks utilized in the synthesis of JH-III mimics. | 88 |
| Figure 29. Decomposition of vinyl ether 39a via method A. | 92 |
| Figure 30. Summary of general electronic trends observed for vinyl ether analogues... | 100 |
| Figure 31. Analogues of juvenile hormone III selected for biological assays..... | 101 |
| Figure 32. General experimental set-up for the <i>Drosophila melanogaster</i> assay..... | 102 |
| Figure 33. Preliminary insect assay results..... | 103 |
| Figure 34. Baldwin's rules for favored and disfavored ring closures. | 107 |
| Figure 35. Cyclization pathways dependent on the vinyl ether substitution. | 109 |
| Figure 36. Potential cyclization pathways for our oligo-vinyl ether systems..... | 111 |
| Figure 37. Retrosynthetic analysis of desired vinyl radical precursor..... | 119 |
| Figure 38. ¹ H NMR spectrum of 94a | 127 |
| Figure 39. The nOe interactions observed for compounds 96a , 97a , and 96b | 129 |
| Figure 40. Examples of hexahydrofuropyrans present in the literature. ^{125,145} | 137 |
| Figure 41. Proposed basis of regioselectivity. | 141 |
| Figure 42. Rational for observed diastereoselectivity..... | 143 |
| Figure 43. Retrosynthetic analysis of target radical trap precursor 119 | 146 |

List of Abbreviations and Symbols

| | |
|---------------------|--------------------------------------|
| ^1H NMR | proton nuclear magnetic resonance |
| ^{13}C NMR | carbon-13 nuclear magnetic resonance |
| α | alpha |
| Å | angstroms |
| Ac | acetyl |
| acac | acetylacetonate |
| ACCN | 1,1'-azobis(cyclohexanecarbonitrile) |
| AcOH | acetic acid |
| AIBN | 2,2'-azobisisobutyronitrile |
| aq | aqueous |
| Ar | aryl |
| β | beta |
| br | broad |
| Bu | butyl |
| Bn | benzyl |
| Bz | benzoyl |
| Boc | <i>tert</i> -butyloxycarbonyl |
| °C | degrees Celsius |
| calcd | calculated |
| cat | catalytic |
| Cbz | benzyloxycarbonyl |

| | |
|------------------|--|
| cm ⁻¹ | wavenumbers |
| CoA | coenzyme A |
| conc | concentrated |
| COSY | ¹ H – ¹ H correlation spectroscopy |
| Cy | cyclohexyl |
| d | doublet |
| δ | chemical shift |
| Δ | reflux |
| dba | dibenzylideneacetone |
| DCC | <i>N,N'</i> -dicyclohexylcarbodiimide |
| dd | doublet of doublets |
| ddd | doublet of doublet of doublets |
| DEPT | distortionless enhancement by polarization transfer |
| DIBAL-H | diisobutylaluminum hydride |
| DMAP | 4-dimethylaminopyridine |
| DMF | <i>N,N</i> -dimethylformamide |
| DMP | Dess-Martin periodinane |
| DMSO | dimethyl sulfoxide |
| DNA | deoxyribonucleic acid |
| DPPF | 1,1'-bis(diphenylphosphino)ferrocene |
| dr | diastereomeric ratio |
| dt | doublet of triplets |
| dtd | doublet of triplet of doublets |

| | |
|-------------------|---|
| ee | enantiomeric excess |
| e.g. | for example |
| eq | equivalents |
| Et | ethyl |
| Et ₃ N | triethylamine |
| etc | etcetera |
| g | grams |
| h | hours |
| H ⁺ | acid |
| HMBC | heteronuclear multiple bond correlation |
| HSQC | heteronuclear single quantum coherence |
| hν | light |
| HRMS | high resolution mass spectrometry |
| Hz | Hertz, s ⁻¹ |
| IBX | 2-iodoxybenzoic acid |
| ICC | iterative cross-coupling |
| i.e. | that is |
| <i>i</i> Pr | <i>isopropyl</i> |
| IR | infrared |
| IUPAC | International Union of Pure and Applied Chemistry |
| <i>J</i> | coupling constant |
| JH | juvenile hormone |
| kbar | kilobar |

| | |
|----------------|------------------------------------|
| kDa | kiloDalton |
| KHMDS | potassium bis(trimethylsilyl)amide |
| L | litre |
| Lev | levulinoyl |
| LHMDS | lithium hexamethyldisilazide |
| lit. | literature |
| M | molar |
| m | multiplet |
| <i>m</i> | meta |
| <i>m/z</i> | mass to charge ratio |
| M ⁺ | molecular ion |
| <i>m</i> CPBA | <i>m</i> -chloroperbenzoic acid |
| Me | methyl |
| mg | milligrams |
| MHz | megaHertz |
| MIDA | <i>N</i> -methyliminodiacetic acid |
| min | minutes |
| mL | millilitres |
| μL | microliters |
| mmol | millimoles |
| mol | moles |
| M | molar |
| mM | millimolar |

| | |
|----------------------|--|
| μM | micromolar |
| MOM | methoxymethyl |
| Ms | methansulfonyl |
| MS | mass spectrometry |
| <i>n</i> | straight chain |
| n/a | not applicable |
| NBz | <i>para</i> -nitrobenzoyl |
| n.d. | not determined |
| NIS | <i>N</i> -iodosuccinimide |
| nM | nanomolar |
| nOe | nuclear Overhauser effect |
| Nu | nucleophile |
| <i>o</i> | ortho |
| [O] | an oxidative step |
| <i>o</i> ClBn | <i>ortho</i> -chlorobenzyl |
| OPP | allyl pyrophosphate |
| ox. | oxidation |
| <i>p</i> | para |
| p. | page |
| PCC | pyridinium chlorochromate |
| PDC | pyridinium dichromate |
| Pd(dba) ₂ | bis(dibenzylideneacetone)palladium (0) |
| PG | protecting group |

| | |
|-------|---|
| Ph | phenyl |
| pH | potential hydrogen |
| PhH | benzene |
| PhMe | toluene |
| Piv | pivaloyl |
| PMP | <i>para</i> -methoxyphenyl |
| pp. | pages |
| ppm | parts per million |
| PPTS | pyridinium <i>p</i> -toluenesulfonate |
| pyr | pyridine |
| qd | quartet of doublets |
| R | generalized substituent |
| RNA | ribonucleic acid |
| r.t. | room temperature |
| rxn | reaction |
| s | singlet |
| SOMO | singly occupied molecular orbital |
| SPhos | 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl |
| SPS | solvent purification system |
| t | triplet |
| td | triplet of doublets |
| tdd | triplet of doublet of doublets |
| tdt | triplet of doublet of triplets |

| | |
|-------------------------|---|
| temp | temperature |
| ttd | triplet of triplet of doublets |
| <i>t</i> or <i>tert</i> | tertiary |
| TBAF | <i>tetrabutylammonium fluoride</i> |
| TBHP | <i>tert</i> -butyl hydroperoxide |
| TBDPS | <i>tert</i> -butyldiphenylsilyl |
| TBS | <i>tert</i> -butyldimethylsilyl |
| Tf | triflyl (trifluoromethanesulfonyl) |
| THF | tetrahydrofuran |
| THP | tetrahydropyran |
| TIPS | triisopropylsilyl |
| tlc | thin layer chromatography |
| TMS | trimethylsilyl |
| Tol | tolyl (<i>para</i> -methylphenyl) |
| Troc | trichloroethyloxycarbonyl |
| Ts | <i>p</i> -toluenesulfonyl |
| UV | ultraviolet |
| vs | versus |
| XPhos | 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl |
| ~ | approximately |

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Dedication

~ For Daniel ~

Chapter 1: Introduction

1.0.0 Iterative Synthesis

Iterative or repetitive synthesis is a term that describes the stepwise synthesis of molecules through the repeated use of similar reaction sequences.¹ In general, an iterative synthesis consists of the addition of a monomeric unit followed by an activation (or deprotection) of a previously unreactive functional group thereby enabling the iteration to be repeated (Figure 1). This reaction sequence can be repeated n number of times with the molecule growing by (at least) one monomer unit at the end of each iteration.

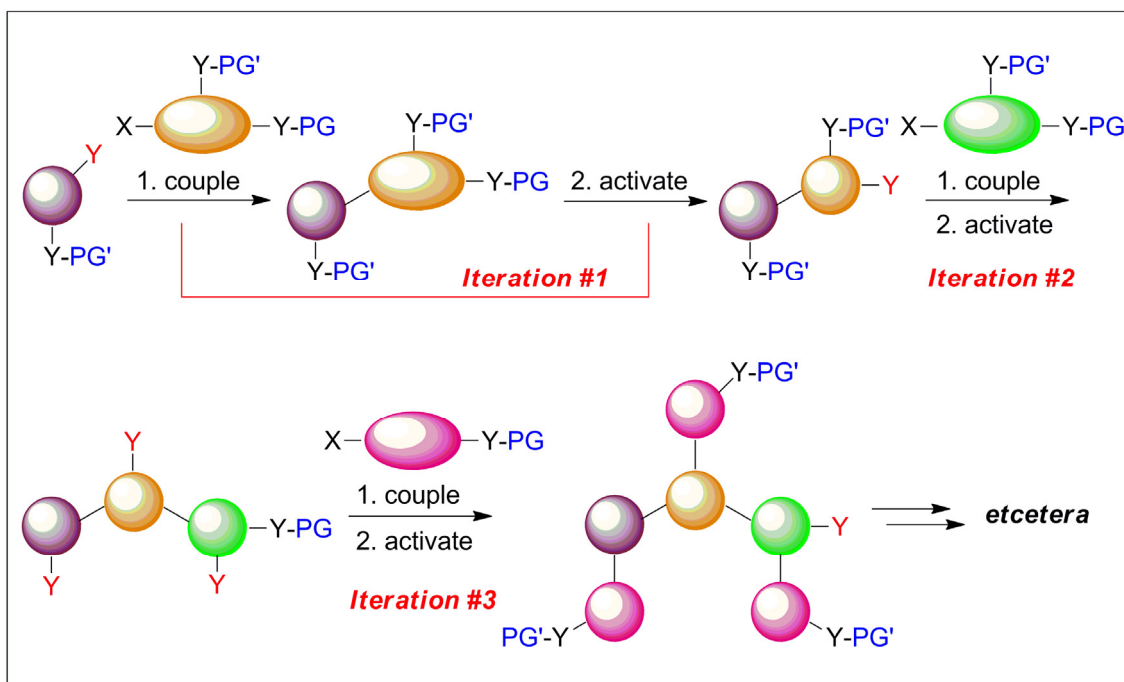


Figure 1. The basic principle of iterative synthesis.

Depending on the functionalities of the initial molecule, this process can in theory be used not only to expand the size of the molecule in one uniform (and predictable) direction (Figure 1) but rather in several (possibly less predictable) directions (Figure 2).²

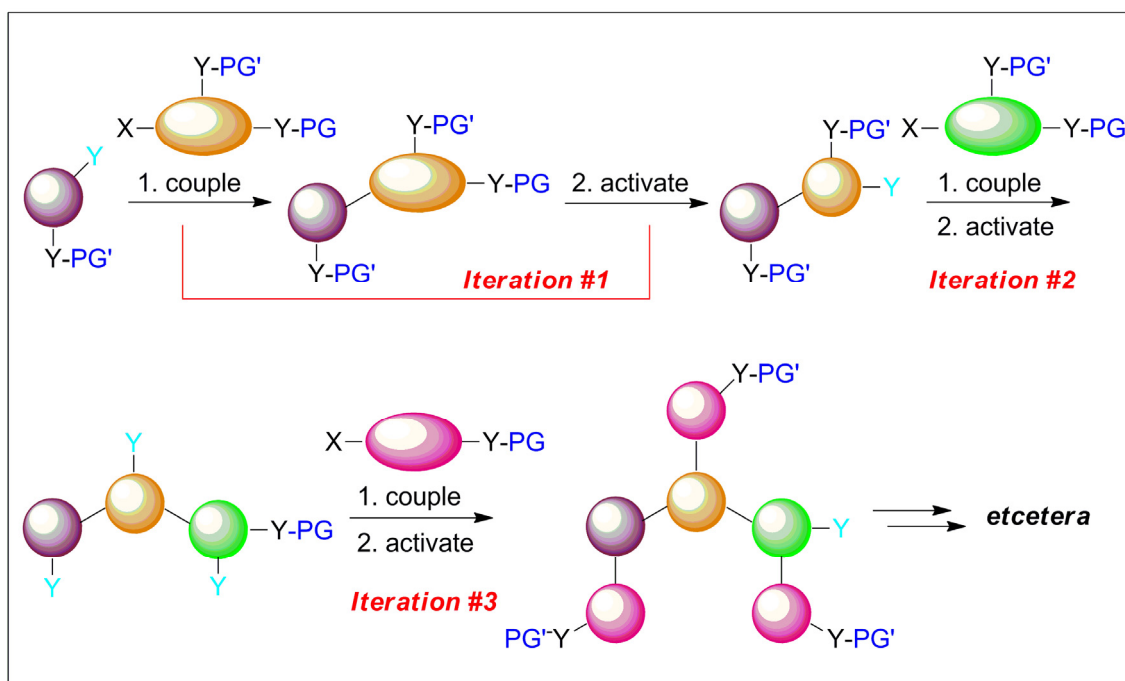
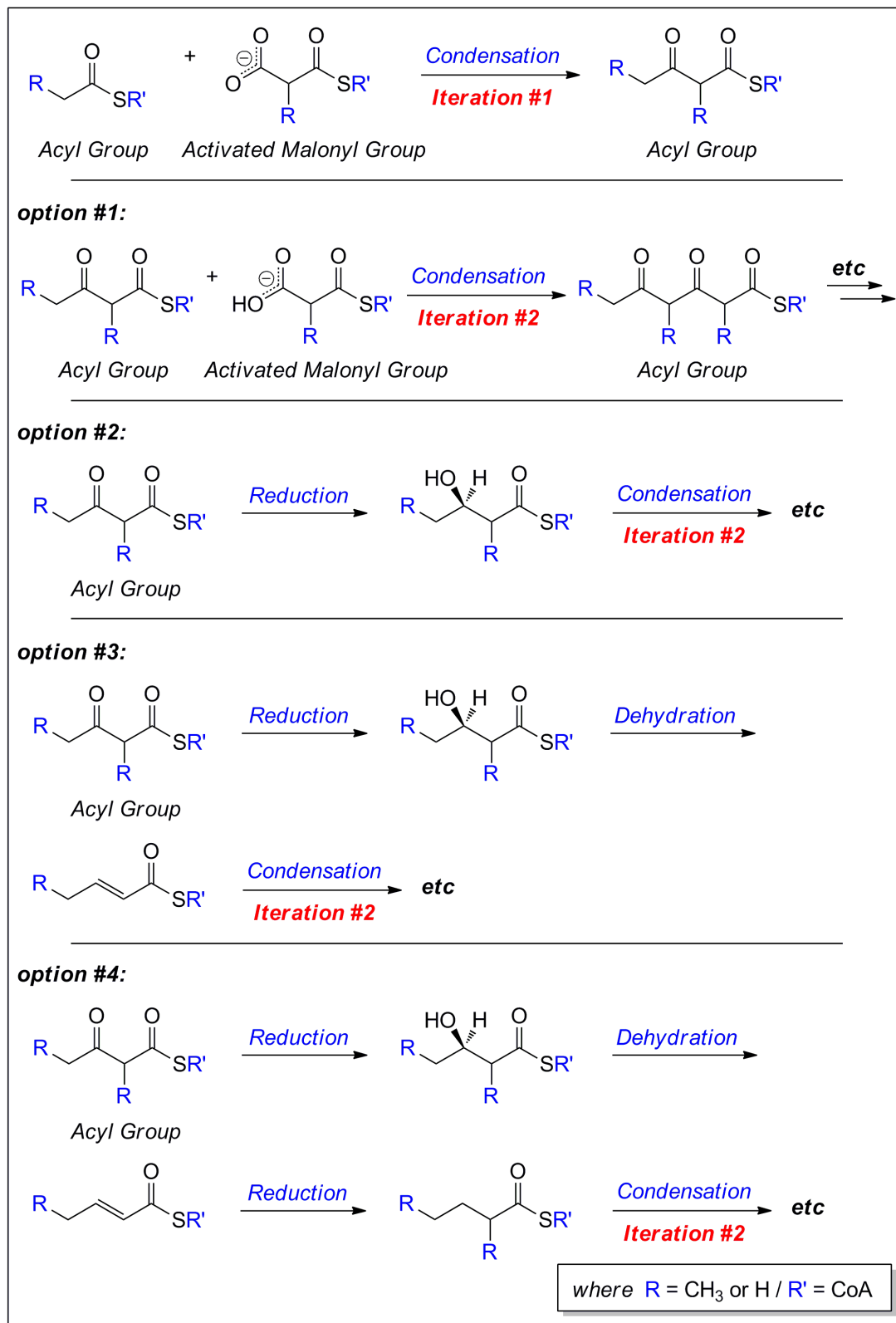


Figure 2. The basic principle of branched iterative synthesis.

Iterative strategies in synthetic chemistry are highly sought after since each round of synthesis (each iteration) uses the same building blocks, coupling reactions, and functional groups thereby minimizing the amount of time, money, and effort required to cleanly access large molecules. In an ideal iterative synthesis the coupling step (step #1) would allow for a variety of readily available and inexpensive building blocks to be utilized. The key iterative steps (coupling and activation) would be predictable and reliable, allowing for application towards natural product synthesis and subsequent increase in scale. In addition, the handling, separation, and purification of various intermediates and final products should be facile and high yielding (>95% yield per step), even with an array of different functional groups present. Finally, the iterative sequence would ideally be amenable to solid-phase synthesis and automation.^{1,3} Herein we review the development of iterative synthesis in the last half century and the application of this technique to the synthesis of structurally complex small molecules.

1.1.0 Iterative Synthesis of Biomolecules

Nature employs a simple ‘building block approach’ to making most molecules found in living systems. This includes important primary metabolites (such as proteins, nucleic acids, and carbohydrates), the synthesis of which will be discussed later, as well as secondary metabolites. The biosynthesis of fatty acid and polyketide secondary metabolites through an iterative series of Claisen-type condensations to assemble linear chains is one such example (Scheme 1).⁴



Scheme 1. Iterative fatty acid biosynthesis.

After the first condensation (iteration #1), the resulting acyl group can undergo one of four pathways: a second condensation reaction on the resulting β -dicarbonyl (option #1), a reduction of the ketone to an alcohol followed by a condensation reaction (option #2), a reduction, dehydration to a double bond, and subsequent condensation reaction (option #3), or finally reduction, dehydration, and reduction (to remove the alcohol) followed by a condensation reaction (option #4). In nature this process is catalyzed by a multi-enzyme complex (or condensing enzyme) and can proceed through any of the pathways shown in Scheme 1 in order to lengthen the molecule by two carbon atoms per iteration (Figure 3).

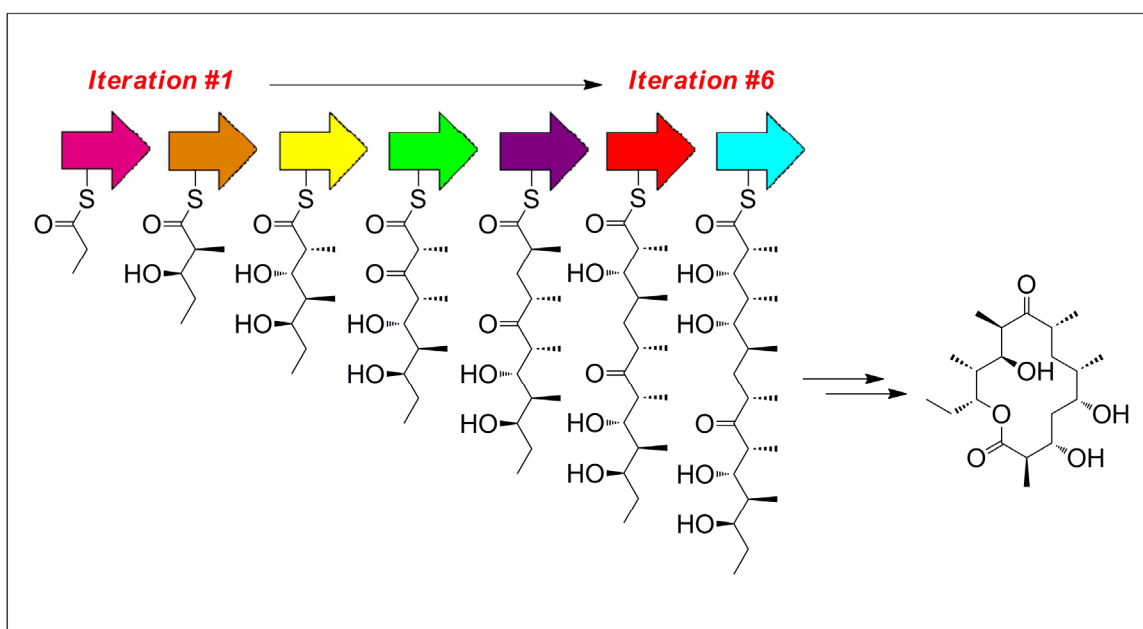


Figure 3. Iterative polyketide biosynthesis.

Once molecules are synthesized to the correct size and architecture, they can be cyclized to give other natural products such as antibiotics.

Terpenes and steroids are another structurally diverse family of natural products where nature employs iterative means in the biosynthesis of these important scaffolds. Although they are highly varied, all terpenes are related through the isoprene rule, whereby terpenoids are made up of C5 monomer units analogous to isoprene (2-methyl-1,3-butadiene) connected head-to-tail (Figure 4).⁵

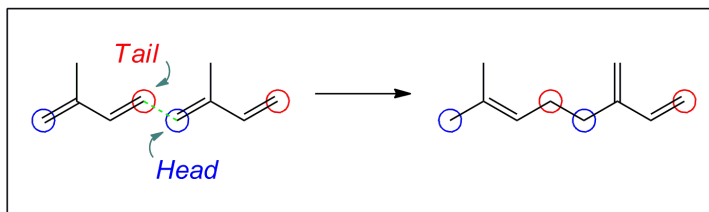


Figure 4. The terpene isoprene rule.

Terpenes are classified based on the number of isoprene units they contain. For example, β -carotene, a major dietary source of vitamin A, is a tetraterpene containing eight isoprene units (Figure 5).

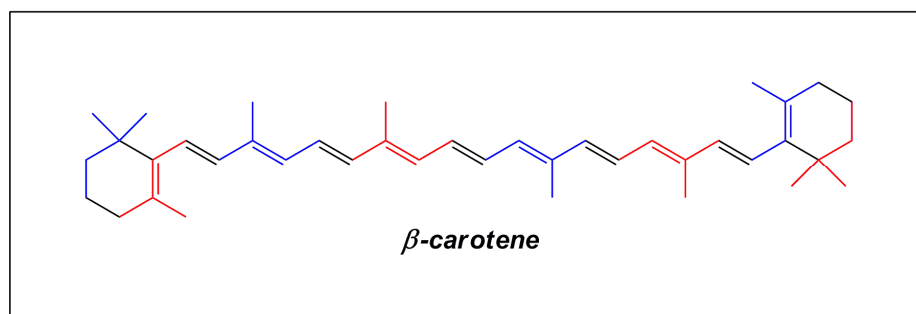
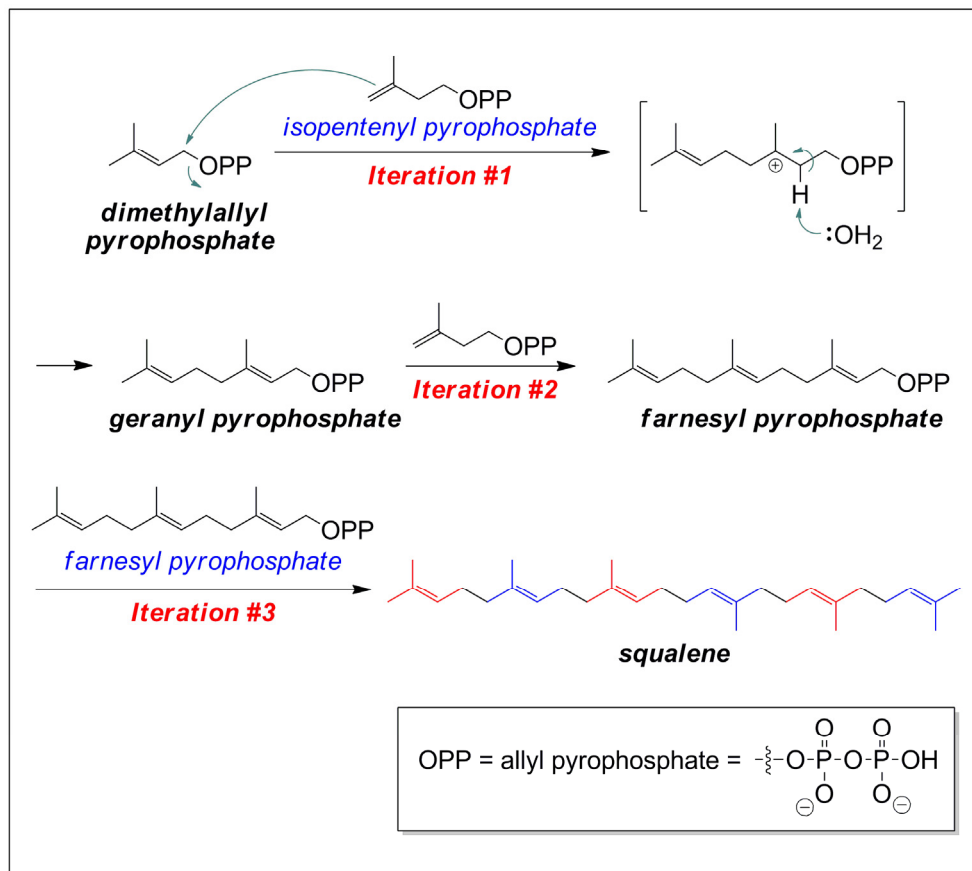


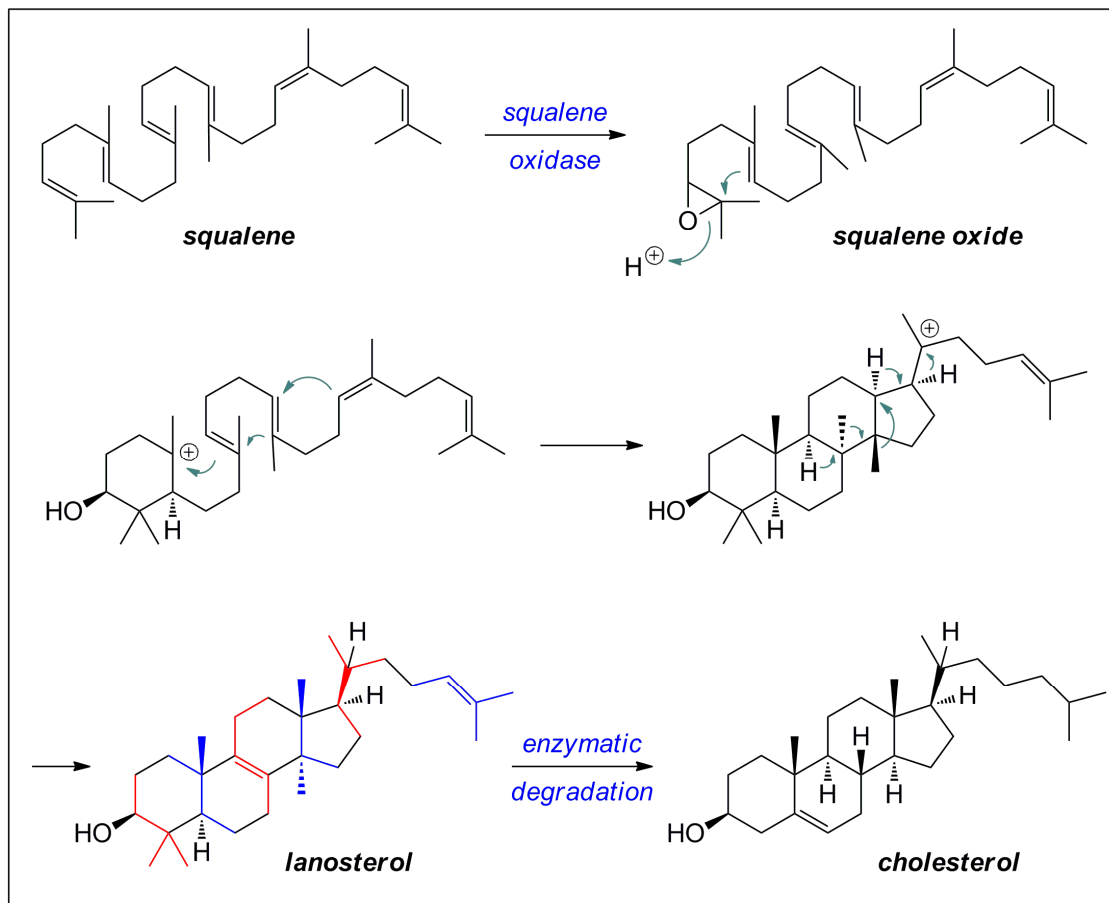
Figure 5. Tetraterpene β -carotene containing 8 isoprene units.

Nature, however, does not utilize isoprene itself in the biosynthesis of terpenes but rather isoprene pyrophosphate derivatives. For example, the iterative synthesis of squalene, a precursor from which all triterpenes (containing six isoprene units) and steroids arise, is made from the two isoprene derivatives isopentyl pyrophosphate and dimethylallyl pyrophosphate (Scheme 2).^{5a}



Scheme 2. Iterative biosynthesis of the terpene squalene.

Steroids, which are heavily modified triterpenes, are biosynthesized from squalene via enzyme-catalyzed epoxidation to give squalene oxide, followed by a cation-olefin cascade and rearrangement to generate lanosterol (Scheme 3).^{5a}



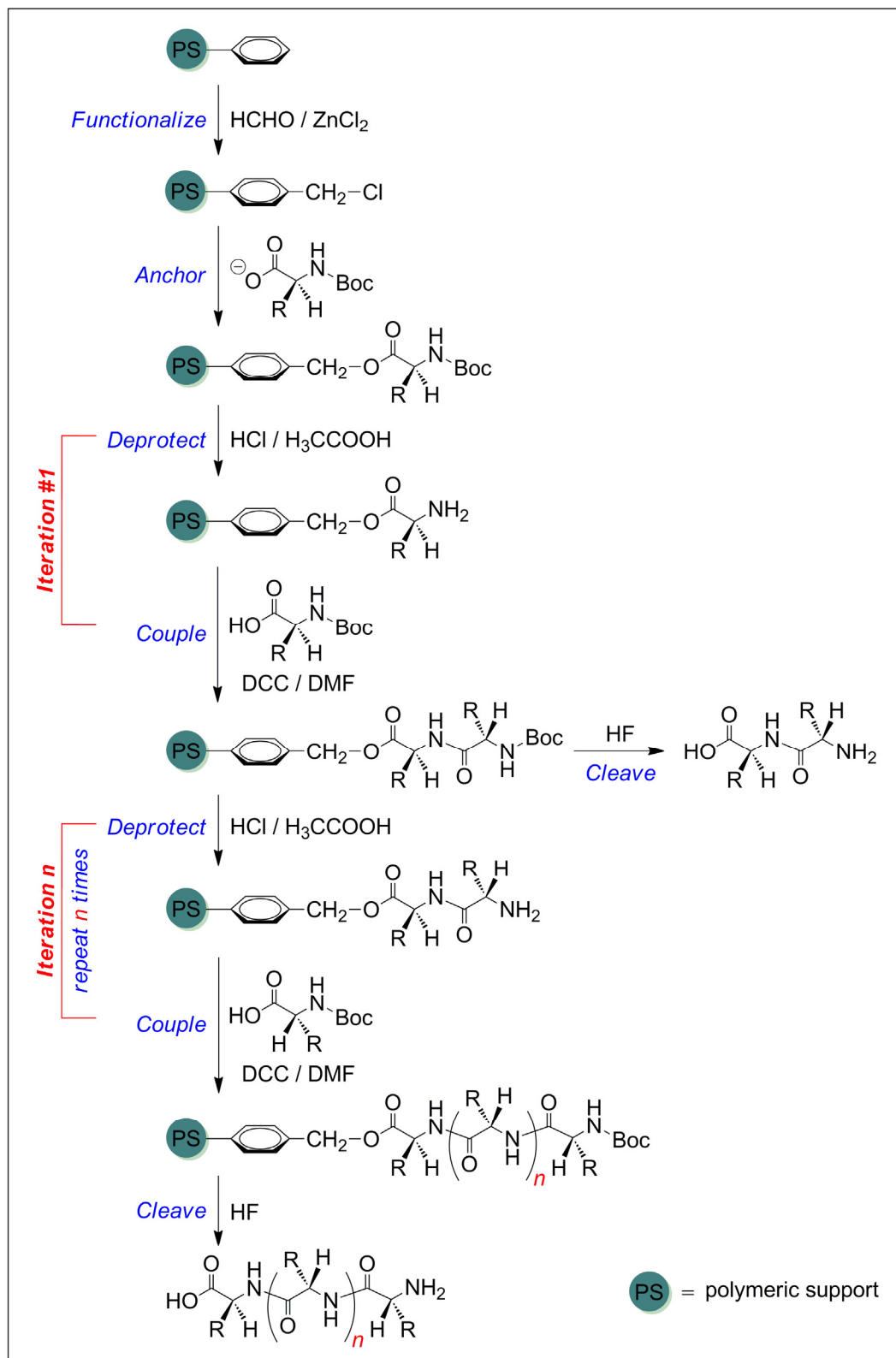
Scheme 3. Biosynthesis of lanosterol from the triterpene squalene.

Lanosterol is then further degraded by other enzymes to yield cholesterol, an important intermediate from which a variety of different steroids can be enzymatically obtained.

Due to the successful development of solid-phase synthesis techniques in the 1960s, we can now routinely replicate Nature's building block strategy in excellent yields for the synthesis of the three major classes of biopolymers including polyamino acids (i.e. peptides and proteins),⁶ oligonucleotides (i.e. DNA and RNA),⁷ and to a growing extent oligosaccharides.⁸ In each of these cases, a simple and efficient iterative coupling of pre-assembled building blocks is utilized in a fully automated fashion.

1.1.1 Polyamino Acids

As originally described by Merrifield,^{6b} in solid-phase peptide synthesis the *C*-terminal end of a protected amino acid is attached to an insoluble solid support (Scheme 4). The *N*-terminal end then undergoes *n* rounds of a two-step iteration whereby the amino acid is deprotected and lengthened. By having a solid support, excess reagents used to drive the reaction to completion can simply be washed away.

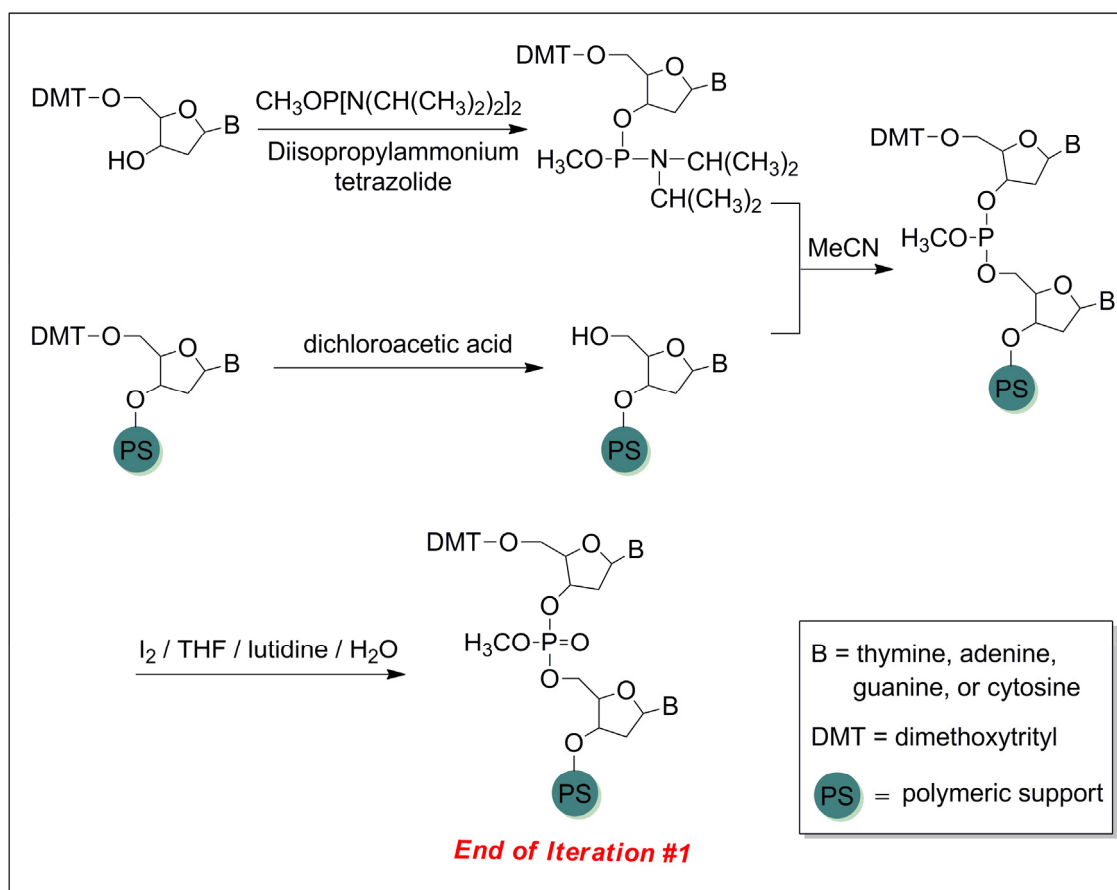


Scheme 4. General scheme for Merrifield solid-phase peptide synthesis.

This process contributes to increased yields by eliminating unnecessary optimization, isolation, and purification of intermediates.^{6b} The use of an automated synthesizer also allows for these iterative steps to be repeated quickly and efficiently to assemble a peptide chain of the desired size.

1.1.2 Oligonucleotides

The solid-phase synthesis for peptides invented by Merrifield^{6b} was also applied to the synthesis of oligonucleotides, enabling a variety of DNA and RNA sequences to be synthesized rapidly and in high yields (Scheme 5).⁷



Scheme 5. Iterative synthesis of DNA.

The general synthesis of DNA (or RNA) utilizes protected nucleotides as monomer units and either phosphite triester (as shown in Scheme 5) or phosphotriester chemistry to lengthen the chain in the 3' to 5' direction. Once the chain is extended iteratively to the correct size, the product is cleaved from the solid support, deprotected, and isolated to give the desired oligonucleotide in high purity.

1.1.3 Oligosaccharides

Of the three major classes of biomolecules (proteins, nucleic acids, and carbohydrates), carbohydrates are the most difficult to synthesize. Unlike polyamino acids and oligonucleotides, oligosaccharides require selectivity not only for the location of the glycosidic bond but also for the anomeric configuration as two potential stereoisomers (α or β) are possible (Figure 6a).

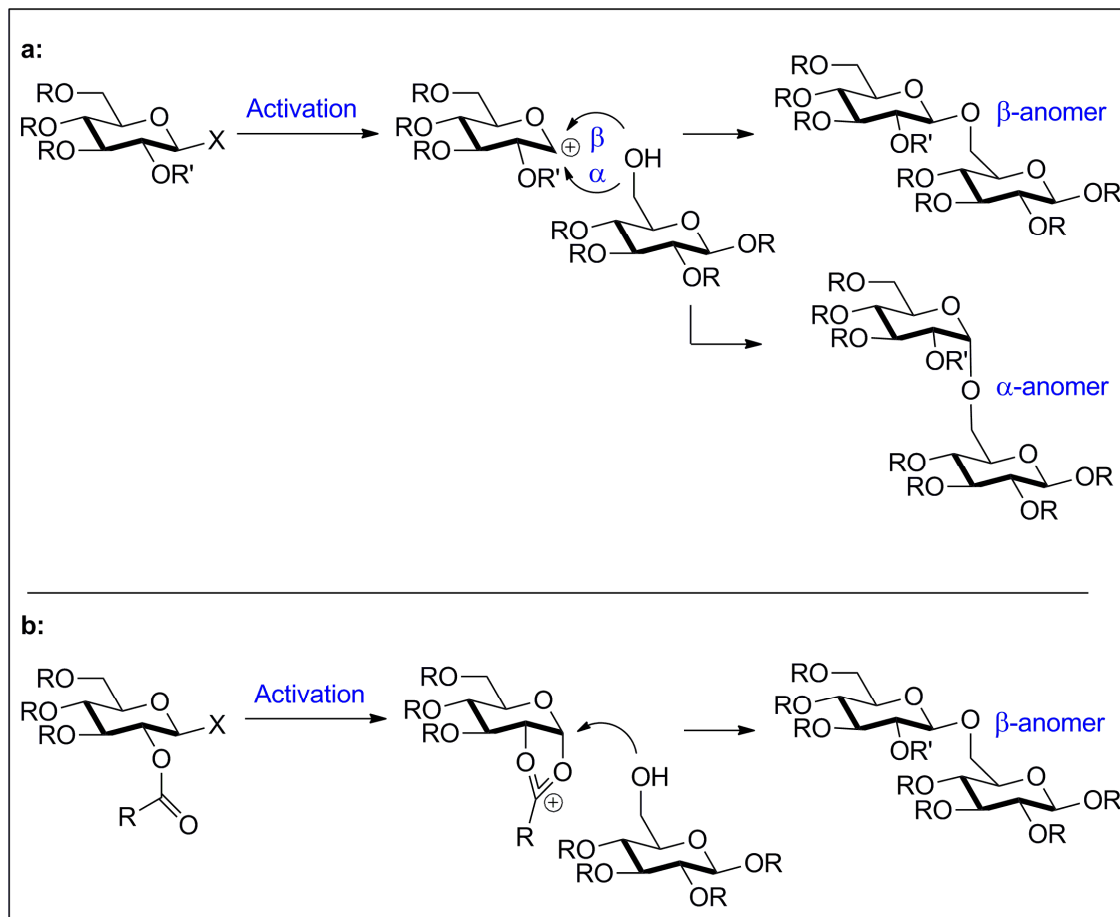
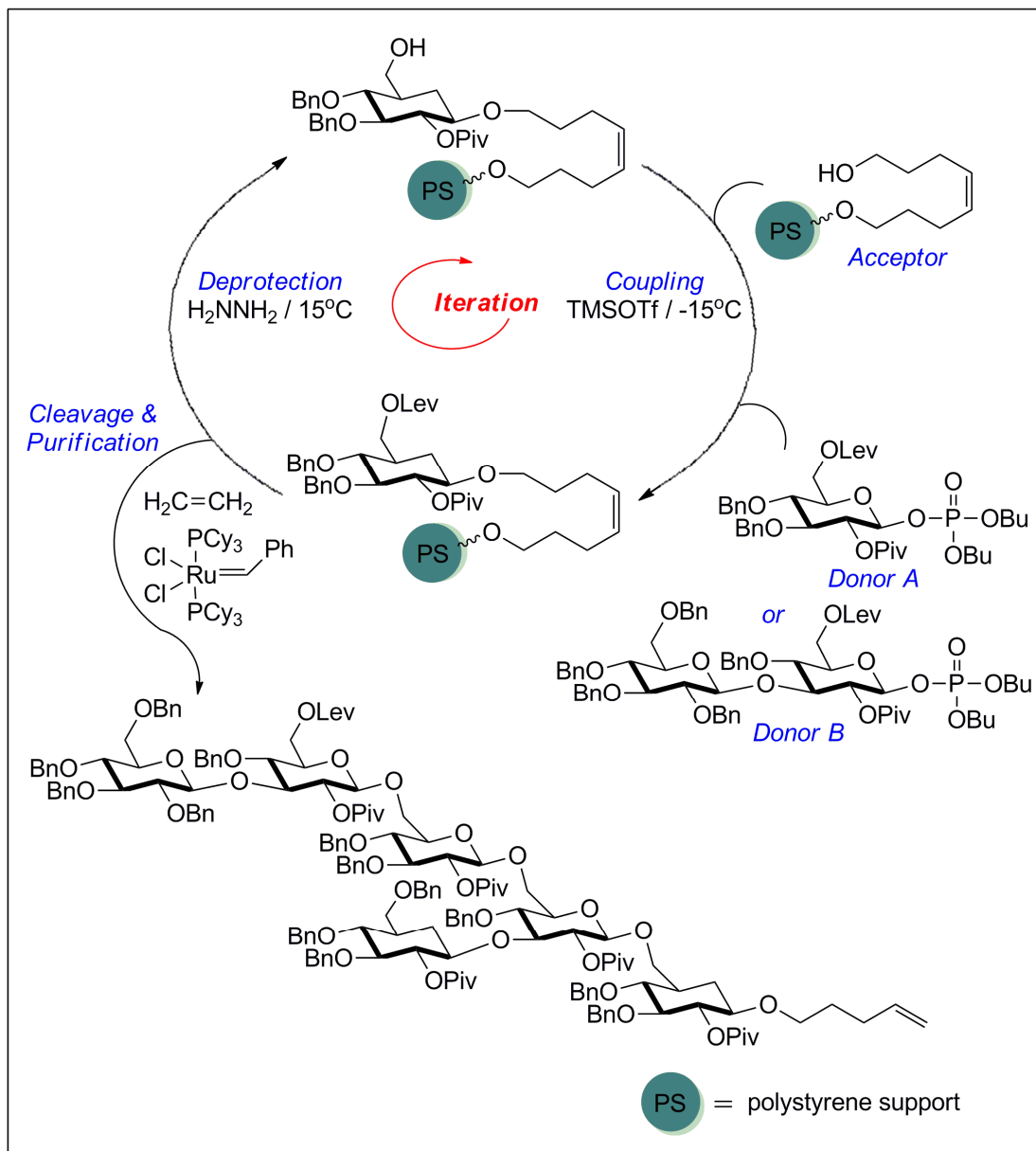


Figure 6. Possible stereochemical outcomes in the synthesis of carbohydrates.

To circumvent this issue, participating groups (e.g. esters) and solvent effects are used to control the formation of the desired stereoisomer (Figure 6b).⁹

Oligosaccharides are also typically branched rather than linear and therefore require orthogonal protecting groups for each hydroxyl (and therefore multiple selective protection and deprotection steps).

Solid-phase⁸⁻¹⁰ approaches that utilize a modified peptide synthesizer and one-pot^{8,11} methods have been established by several research groups. Seeberger and co-workers developed a solid support synthesis based on automated peptide synthesis (Scheme 6).⁸

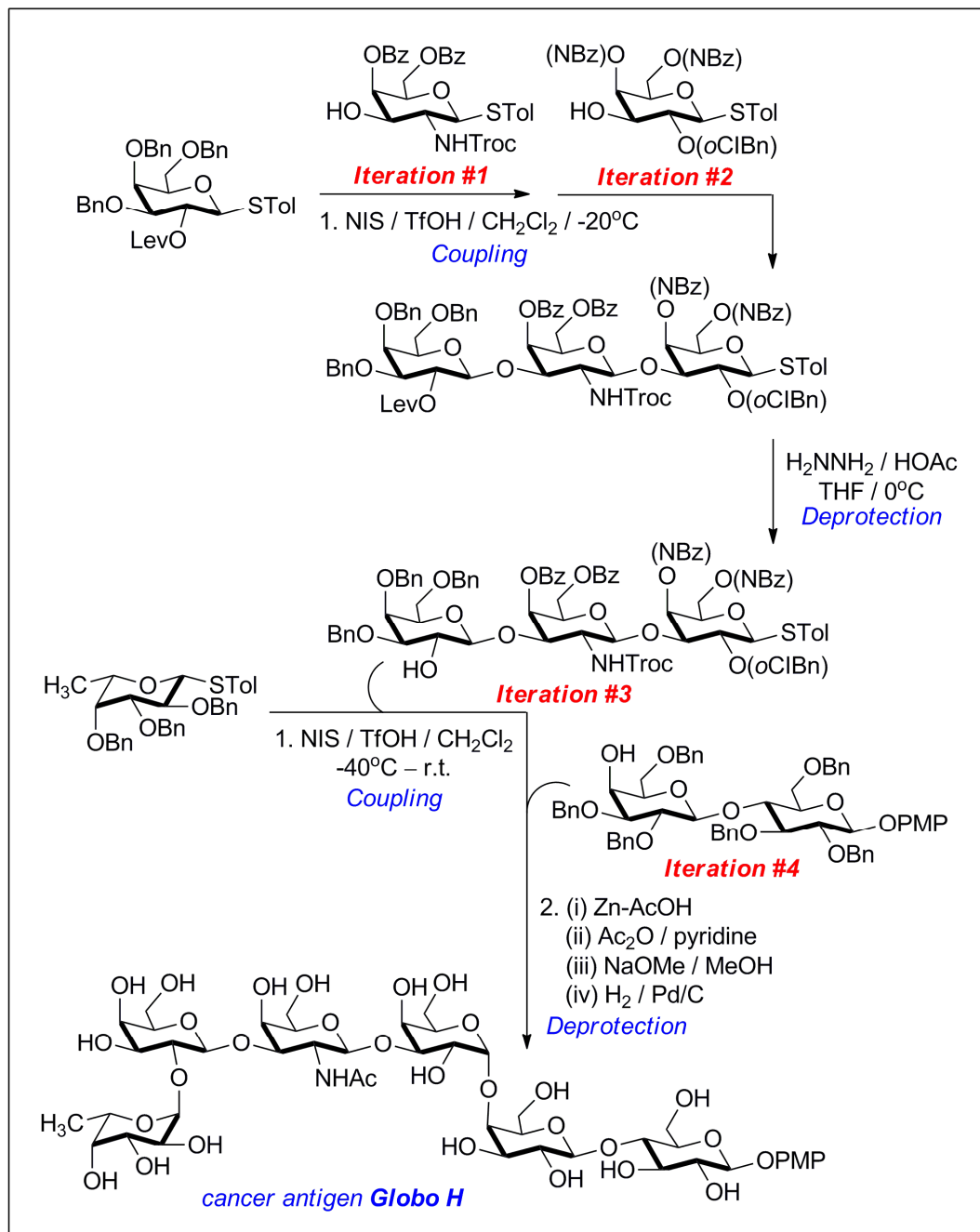


Scheme 6. Automated solid-phase oligosaccharide synthesis.

With the nucleophilic acceptor hydroxyl group exposed on solid support, a reactive glycosylating agent (**Donor A** or **Donor B**) is delivered in solution (coupling step). After the oligosaccharide is purified by washing the soluble side products away, the temporary protecting group is removed revealing another hydroxyl group ready for a second round of iteration (deprotection step). Large, branched oligosaccharides have been generated

using this technique, albeit a large excess of sugar donors is required at each coupling step to obtain reasonable reaction rates.

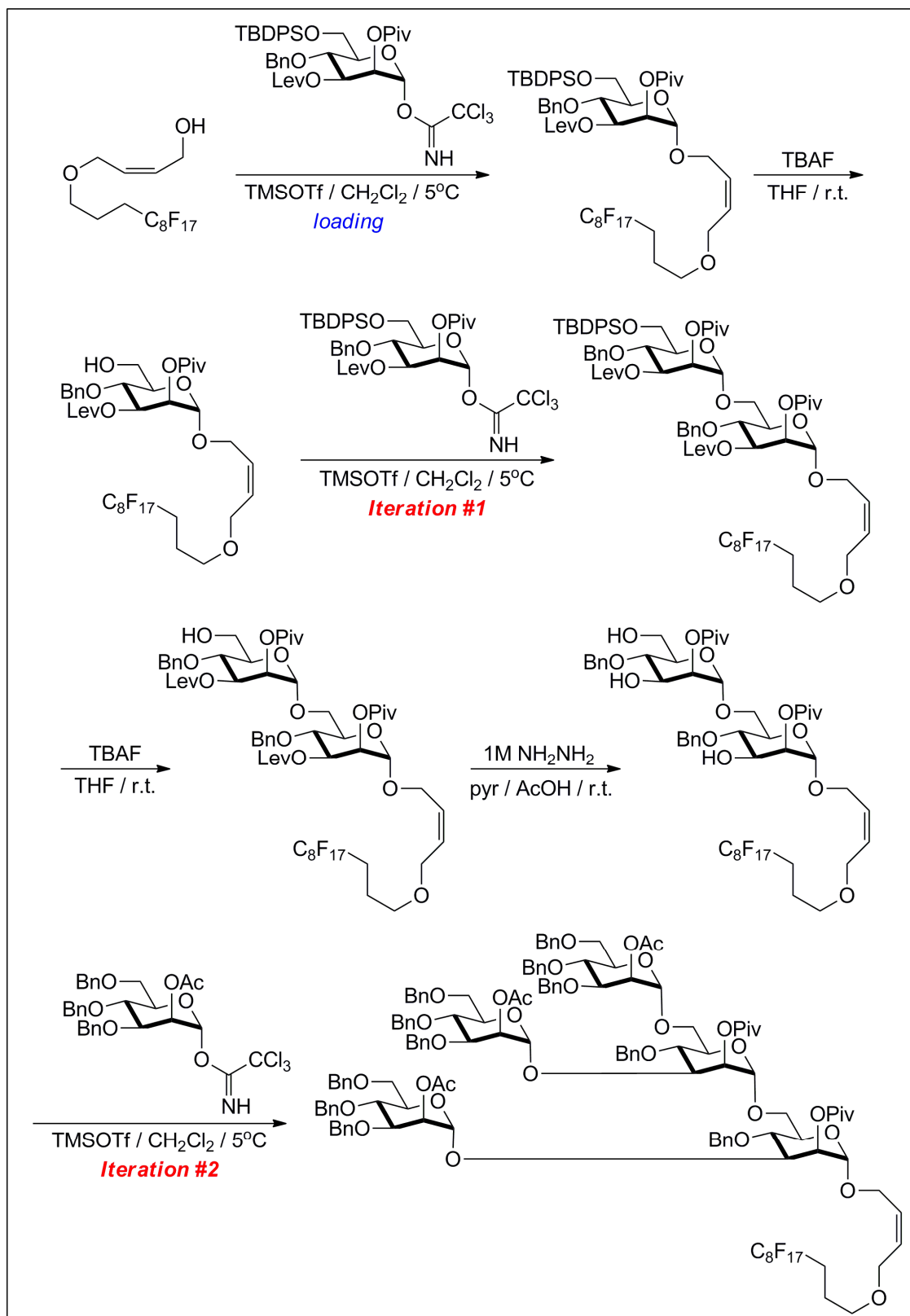
Utilizing a different approach, Wong and co-workers elegantly exploited two separate one-pot programmable strategies to synthesize the hexasaccharide Globo H, an antigen on prostate and breast cancer cells (Scheme 7).¹¹



Scheme 7. A one-pot synthesis of Globo H, a hexasaccharide.

In this synthetic strategy, the required building blocks are added into the “pot” in a specific sequence, with the most reactive monomer being added first. Aside from the final deprotection/isolation step, no work-up is required allowing for oligosaccharides containing three to six monosaccharides to be assembled very rapidly and efficiently.¹¹

Enzymatic methods¹² and solution-phase automated iterative syntheses¹³ have also been designed, with the latter taking advantage of key hydroxyl protecting group strategies and a fluoros affinity tag (Scheme 8).



Scheme 8. Iterative synthesis of branched oligosaccharides via a fluororous tag strategy.

The fluorous-tag proved quite advantageous in this synthetic strategy in that it was soluble in most organic solvents (used for glycosylation and protection/deprotection reactions) but also selectively adsorbed to a solid support to allow for easy purification.

All synthetic strategies mentioned above represent important advances made in this field leading toward the streamlining of oligosaccharide synthesis. Several groups have shown that it is now possible to transfer many solution and solid-phase chemistries to an automated synthesizer. The ease of oligosaccharide access has and will continue to have a huge impact to the field of glycobiology in the years to come.

1.1.4 Summary

Using this Nature-inspired building block approach has allowed for the simplification and acceleration of multi-step biomolecule syntheses. Due to these advances in synthetic techniques, research in the area of biomolecules has developed significantly to the point where investigating new molecular functions is now the primary focus. In addition, creation of libraries of organic oligomers with potentially useful pharmaceutical properties including oligocarbamates,¹⁴ peptoids,¹⁵ and oligoureas¹⁶ by repeated coupling to amino-functionalized supports has shown that iterative methods can be employed in combinatorial chemistry (Figure 7).^{10a,17}

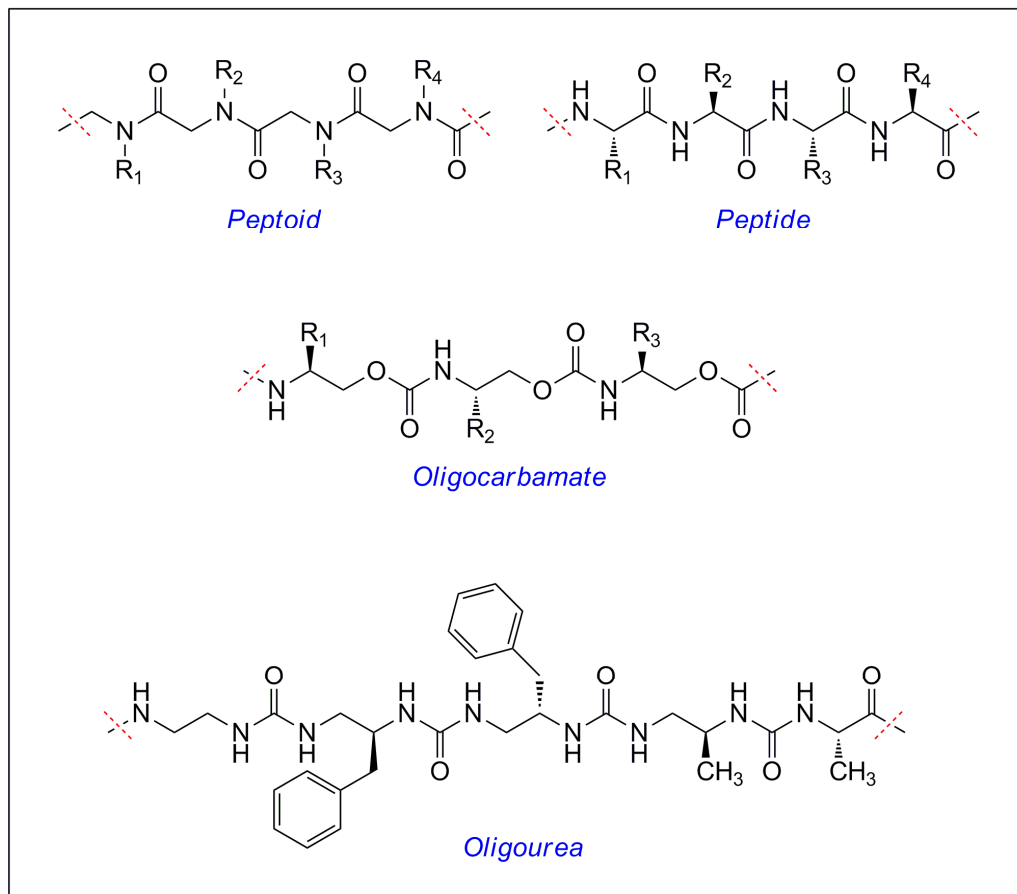


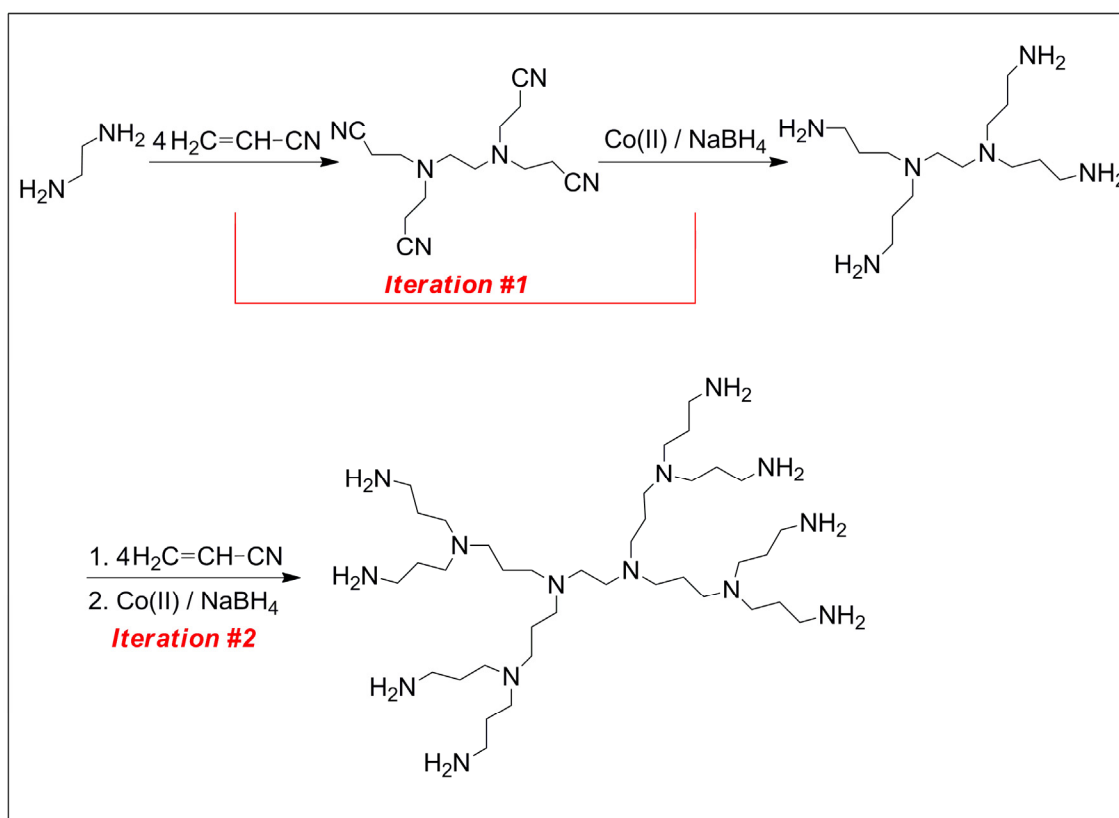
Figure 7. General structures of peptoids, oligocarbamates, and oligoureas.

1.2.0 Iterative Protocols in the Synthesis of Other Organic Molecules

Oligonucleotides, polypeptides, and oligosaccharides can now all be prepared quickly by simple oligomerization of suitably protected versions of their constituent monomers. In stark contrast to this efficient and high yielding synthetic platform, the synthesis of structurally complex small molecules remains non-systemized. This shortfall can be attributed to the complex nature of most small molecule secondary metabolite natural products. There have, however, been some excellent contributions to this field that have helped stimulate more interest in the application of iterative protocols to organic synthesis.¹

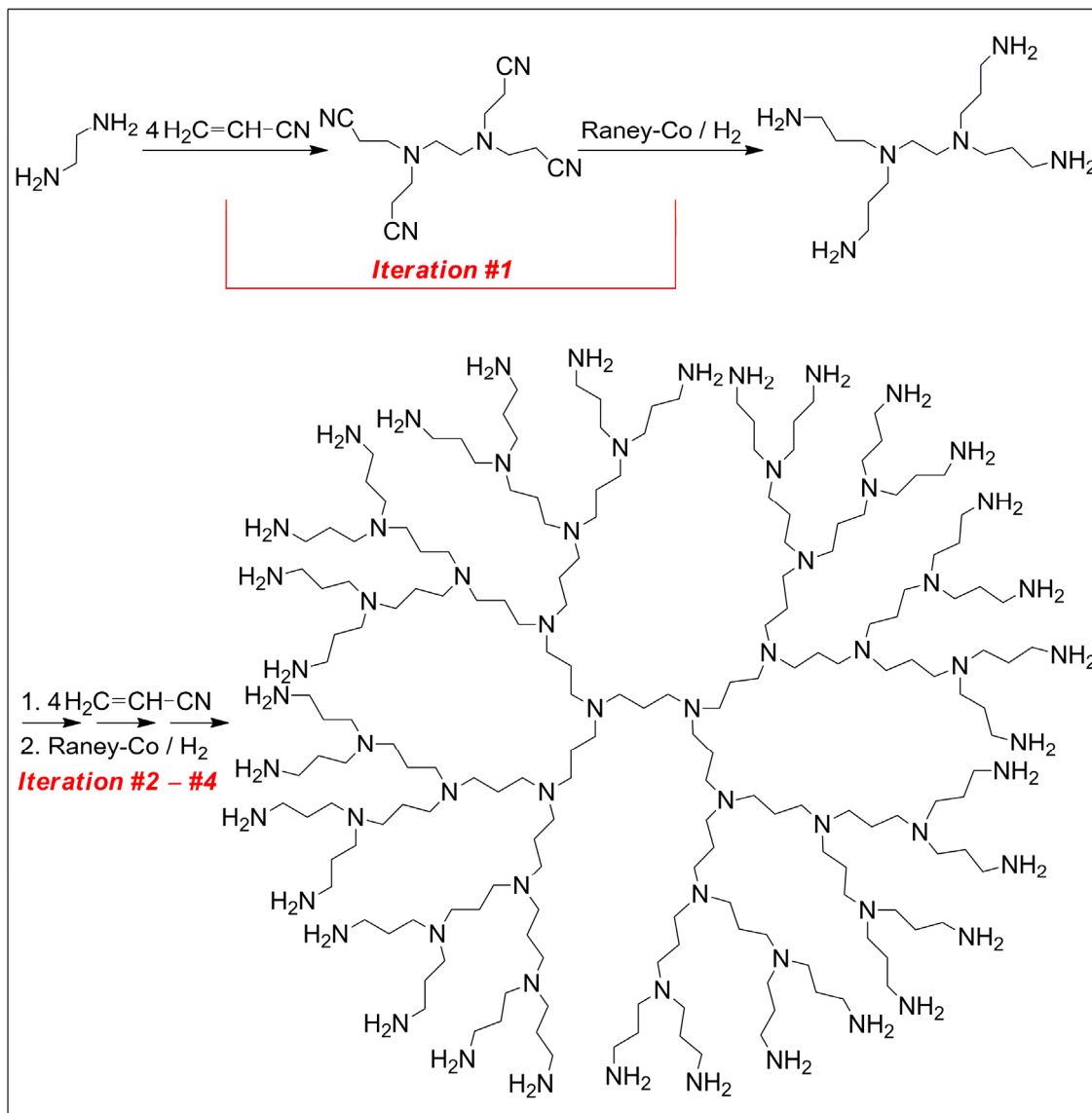
1.2.1 Dendrimers

In the late 1970s, Vögtle and co-workers¹⁸ prepared a series of dendritic molecules through a divergent two-step iteration sequence using identical monomeric building blocks (Scheme 9). These hyperbranched polymers are an important class of molecules with potential applications in drug delivery,¹⁹ gene delivery,²⁰ and sensors.²¹



Scheme 9. Iterative synthesis of dendrites.

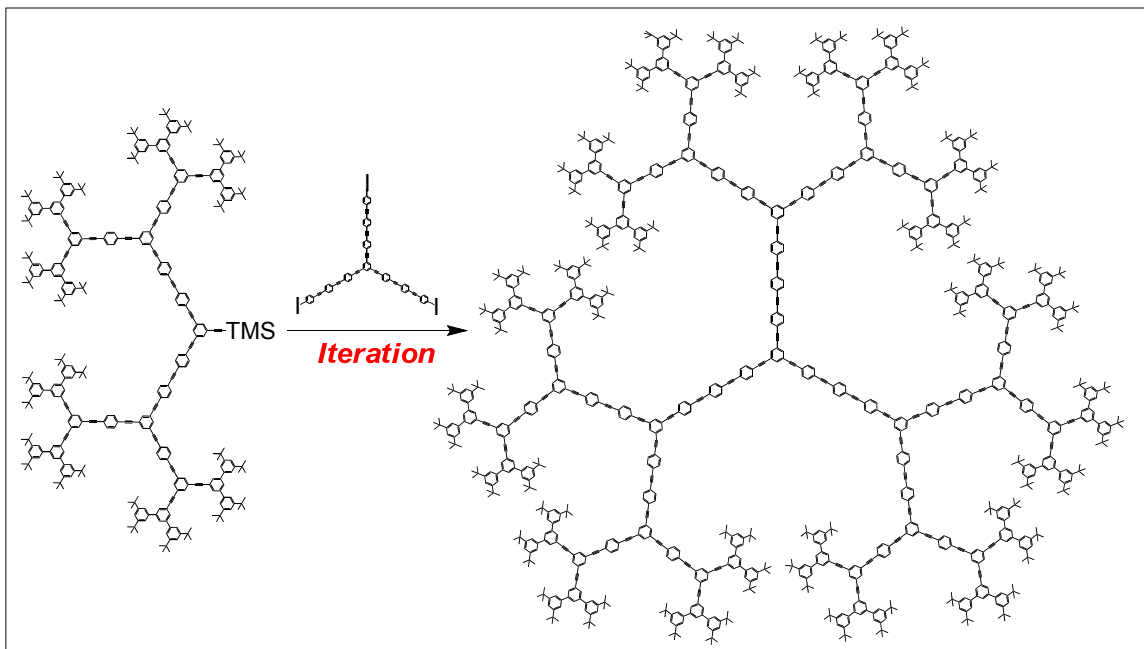
With this new iterative methodology, researchers were able to access a plethora of new dendrimers.²² In 1993, Meijer and co-workers²³ applied this methodology to synthesize a fifth generation dendrimer in large (kilogram scale) quantities and high purity (Scheme 10).



Scheme 10. An iteratively synthesized fifth generation polyamine dendrimer.

Although work in this field was originally aimed at the development of divergent syntheses where the dendritic molecule is built from a central focal point outwards with the number of peripheral groups dependent on the branching multiplicity, convergent-iterative syntheses in this field have also been used.²⁴ Proceeding in the opposite direction, a convergent-iterative synthesis builds the molecule from the surface inwards to a focal point. By building dendrimers in this fashion, one avoids the potential for incomplete conversion of the reactive functional groups and possible defects inside the

structure as the molecule grows to the desired size.²⁵ This latest direction of dendrimer synthesis expands the various synthetic pathways available in this field and in turn has led to a variety of hyperbranched molecules including large 18 kDa hydrocarbon dendrimers (Scheme 11).²⁶

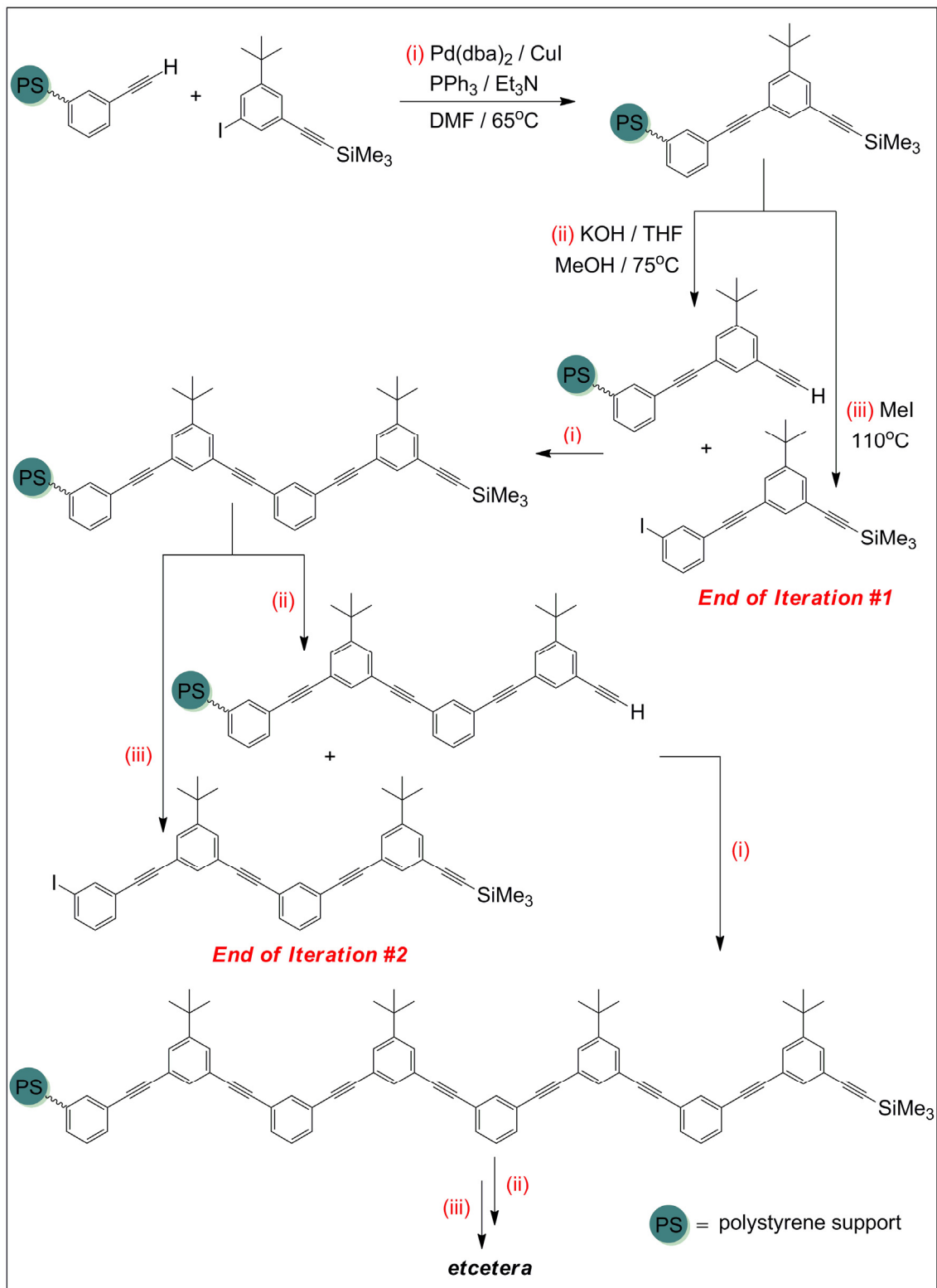


Scheme 11. Iterative preparation of a phenylacetylene dendrimer.

As this field continues to grow and gain popularity, so too does the array of functionalities available in the iterative dendrimer synthetic tool box.^{2,22c}

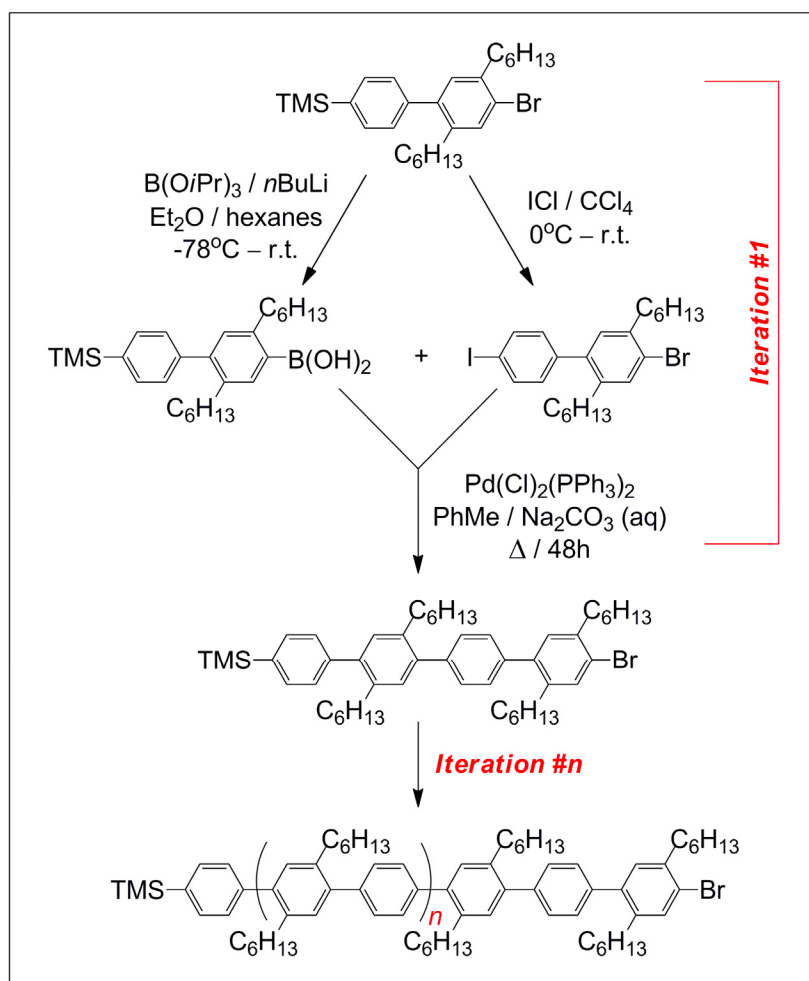
1.2.2 Oligoarenes

A second area where repetitive synthesis has been successfully integrated involves the iterative cross-coupling of bifunctional aromatics to prepare oligoarenes. These well-defined oligomeric sequences are valuable models for understanding the physical and electronic properties of their corresponding polymer analogues.²⁷ The iterative divergent-convergent synthesis involves the repeated cross-coupling of terminal acetylenes with aryl iodides (Scheme 12).²⁸



Scheme 12. Iterative convergent-divergent synthesis of oligoarenes.

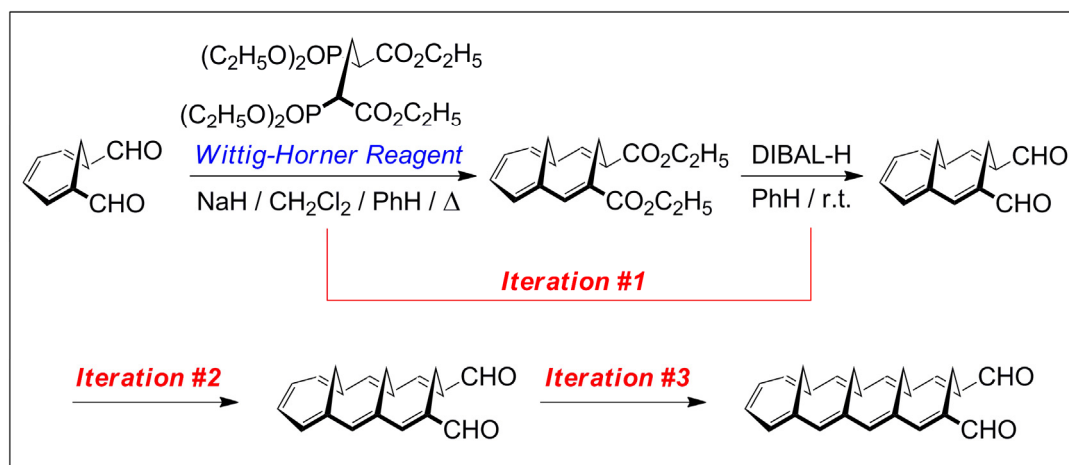
This methodology is highly efficient due to the chemo-orthogonality of the trimethylsilyl protecting group and the polystyrene support which can both be selectively removed. Among other approaches,²⁹ exponential growth of oligophenylenes has also been reported via a direct triazene link to a polystyrene support,^{28b} an efficient Suzuki coupling of similar monomers utilizing either a trimethylsilyl or bromine group at the terminus of an oligophenylene (Scheme 13),³⁰ and finally a stepwise synthesis of substituted oligophenylene vinylene systems.³¹



Scheme 13. Iterative synthesis of oligophenylene rods via Suzuki coupling strategy.

1.2.3 [4n + 2]Annulenes

Hoping to gain deeper insight into the Hückel rule, Vogel and co-workers³² reported in the early 1980s the synthesis of CH₂ bridged [4n + 2]annulenes by a building block approach (Scheme 14). They focused on the *all-syn* bridge configuration which is geometrically favourable for the occurrence of aromatic character.³³

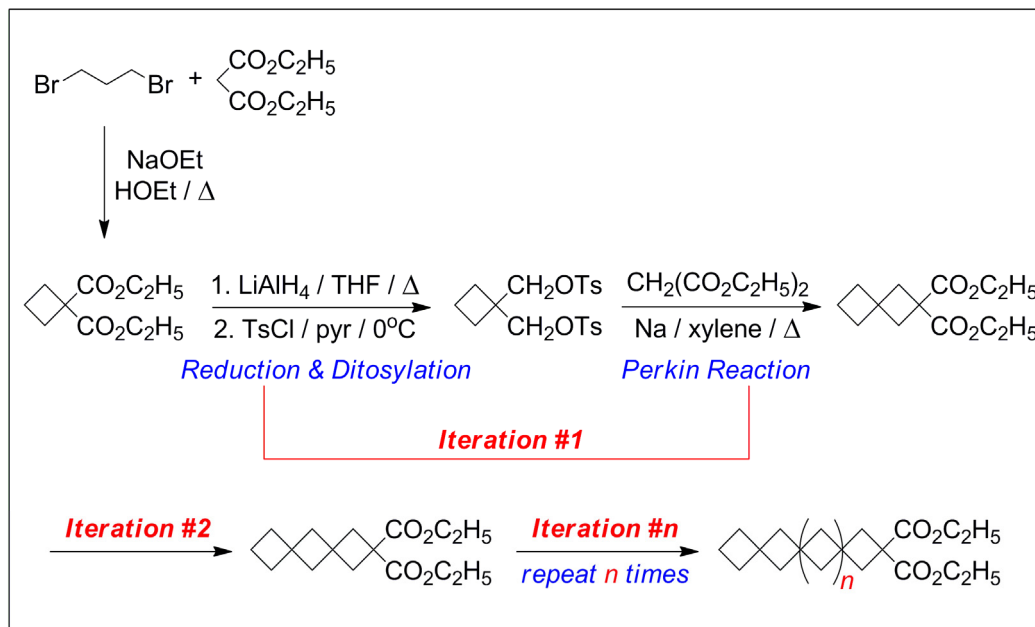


Scheme 14. A building-block approach to [4n + 2]annulenes.

By way of a two-step iterative sequence through a Wittig-Horner reaction and a DIBAL-H reduction, researchers were able to cleanly synthesize the *all-syn* tetracyclic dicarbonyl.³²

1.2.4 Aliphatic Molecules

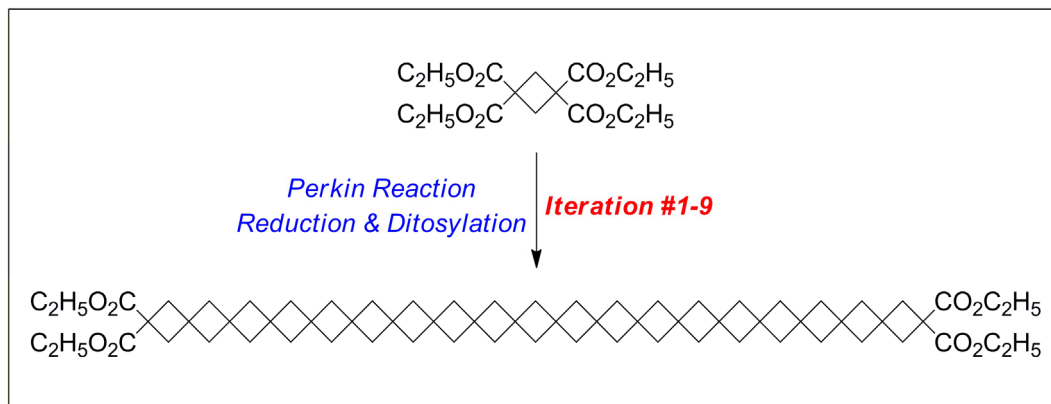
Easy access to linear aliphatic molecules via synthetic pathways with repeating reaction sequences is highly sought after due to the diverse range of applications that these compounds are involved in. Based upon earlier work done by Rice and Grogan³⁴ and by Buchta and Geibel,³⁵ Menger and Ding³⁶ utilized an iterative synthesis of polyspiro linkages with four-membered rings to access rigidified hydrocarbon chains (Scheme 15).



Scheme 15. Iterative synthesis of polyspiro cyclic aliphatic linkages.

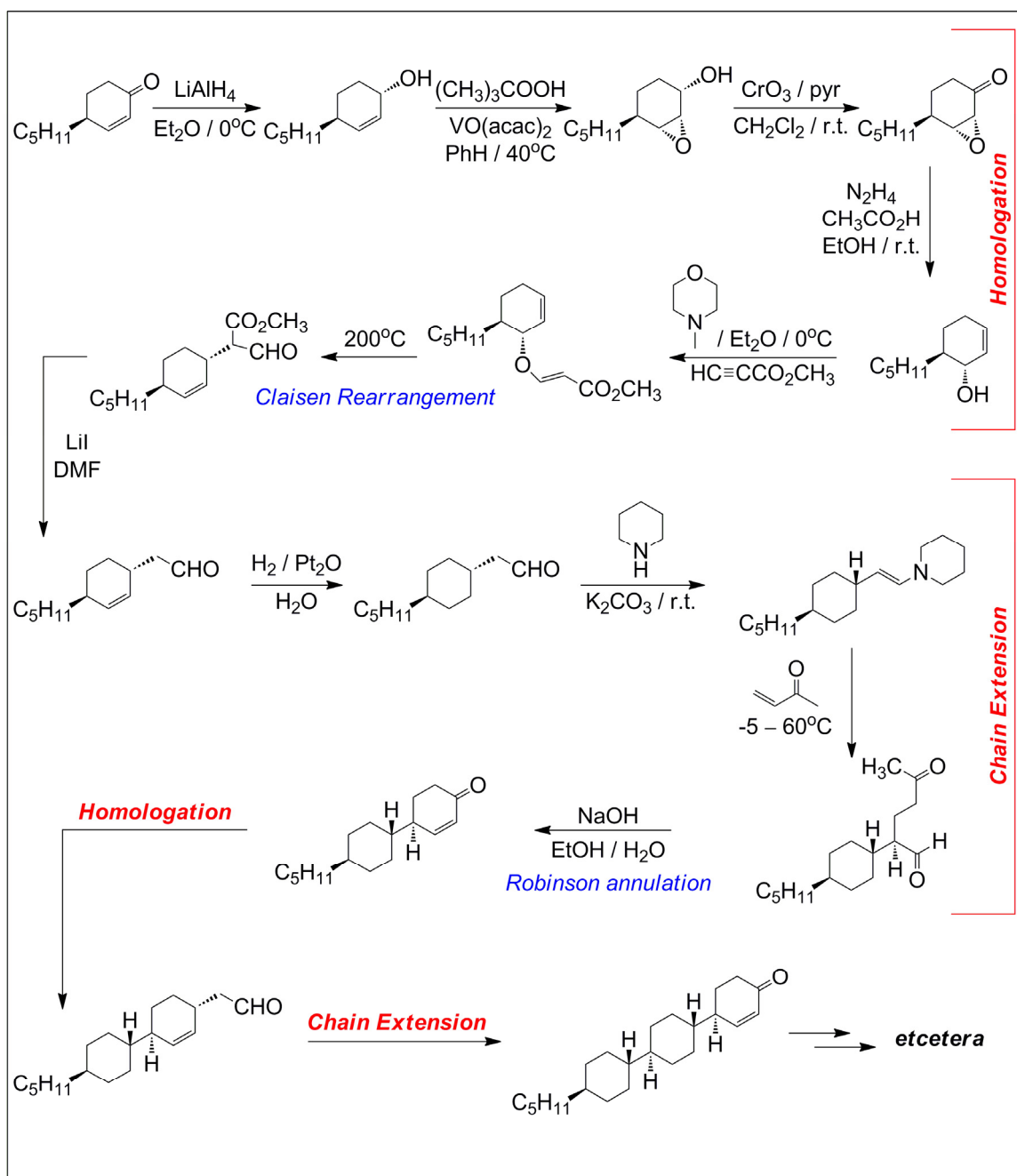
The three-step iterative sequence goes through a reduction of the diester to give a dialcohol, ditosylation of the alcohols, and finally a Perkin cyclization. Once in hand, these hydrophobic chains were used to help study the disorganization of micellar chains and the effects on surfactants if the chains were forced to remain unbent.³⁶

In a similar synthetic sequence, Buchta and Merk³⁷ showed that these polyspiro linkages could be expanded simultaneously on both sides of the growing molecule (Scheme 16).



Scheme 16. Alternate iterative pathway to polyspiro four-membered ring linkages.

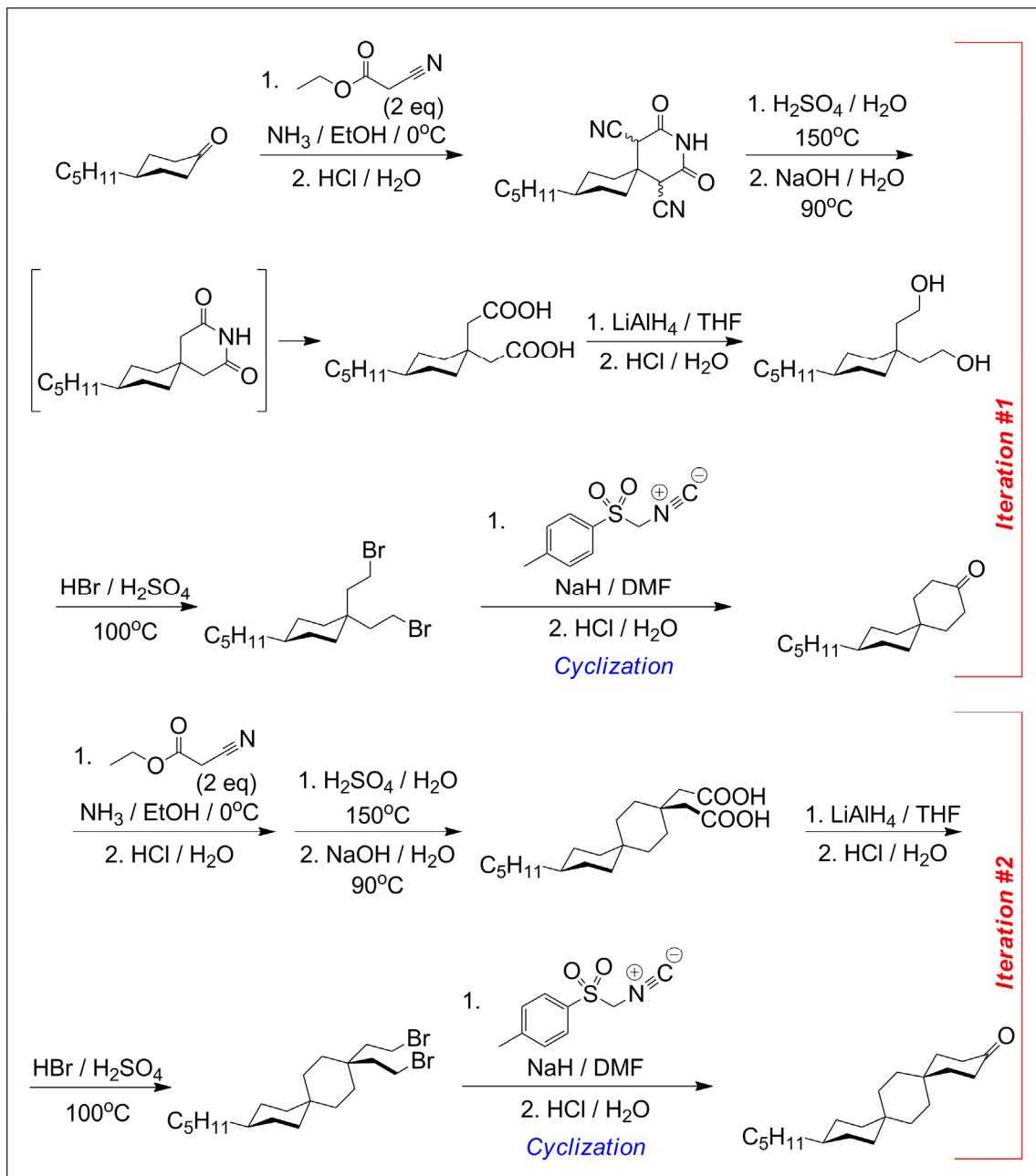
Another area in this field is the iterative synthesis of bi- and tercyclohexyl derivatives as liquid crystals which have been applied to many electronic displays since the late 1980s (Scheme 17).³⁸



Scheme 17. Stepwise synthesis of bi- and tricyclohexyl derivatives.

Based on work done by Grogan and co-workers³⁹ with six-membered ring spiro compounds, Vögtle and co-workers⁴⁰ have also contributed to the field of liquid crystals

by introducing a stepwise synthesis of terminal substituted dispiranes in which the ring units are directly connected by a common carbon atom (Scheme 18).

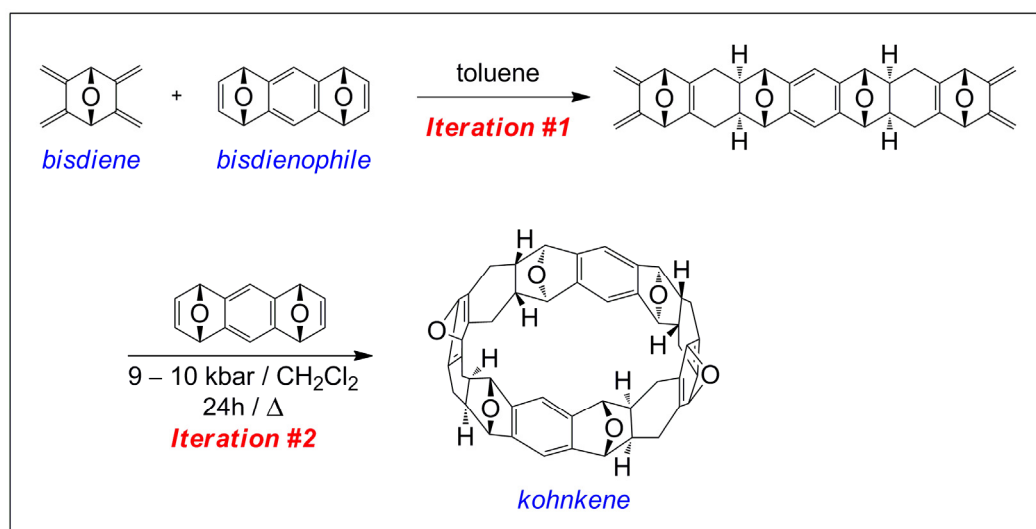


Scheme 18. Iterative synthesis of terminally substituted dispiranes.

Starting from 4-pentylcyclohexanone, this synthesis goes through a two-step iteration sequence, with a cyclization during the second iteration as a key step.

1.2.5 Belt and Ribbon Shaped Molecules

The synthesis of rigid macrocycles with accessible, well-defined cavities of different sizes is a significant area of interest in supramolecular chemistry. These compounds, known as ribbon and belt shaped molecules, are used in the investigation of non-covalent interactions to better understand molecular recognition and enzyme activities. Stoddart and co-workers⁴¹ first reported the use of a repeated Diels-Alder reaction to access a variety of polyunsaturated hydrocarbons including beltenes, collarenes, and cyclacenes (Scheme 19).



Scheme 19. Synthesis of kohnkene via iterative Diels-Alder cycloadditions.

This stereoselective two-step iterative synthesis utilizes readily available starting materials to form the macropolycyclic belt-like compound kohnkene with 20 stereogenic centers. The high stereoselectivity of this synthesis was attributed to the stereospecificity, regioselectivity, and *endo* stereoselectivity of the Diels-Alder reaction.⁴²

Iterative Diels-Alder syntheses have also been utilized for all-carbon methylene bridged beltene (Figure 8a),⁴³ linear precursors for $[n]$ beltene (Figure 8b),⁴⁴ and for the

synthesis of molecular tweezers as synthetic receptors in host-guest chemistry (Figure 8c).⁴⁵

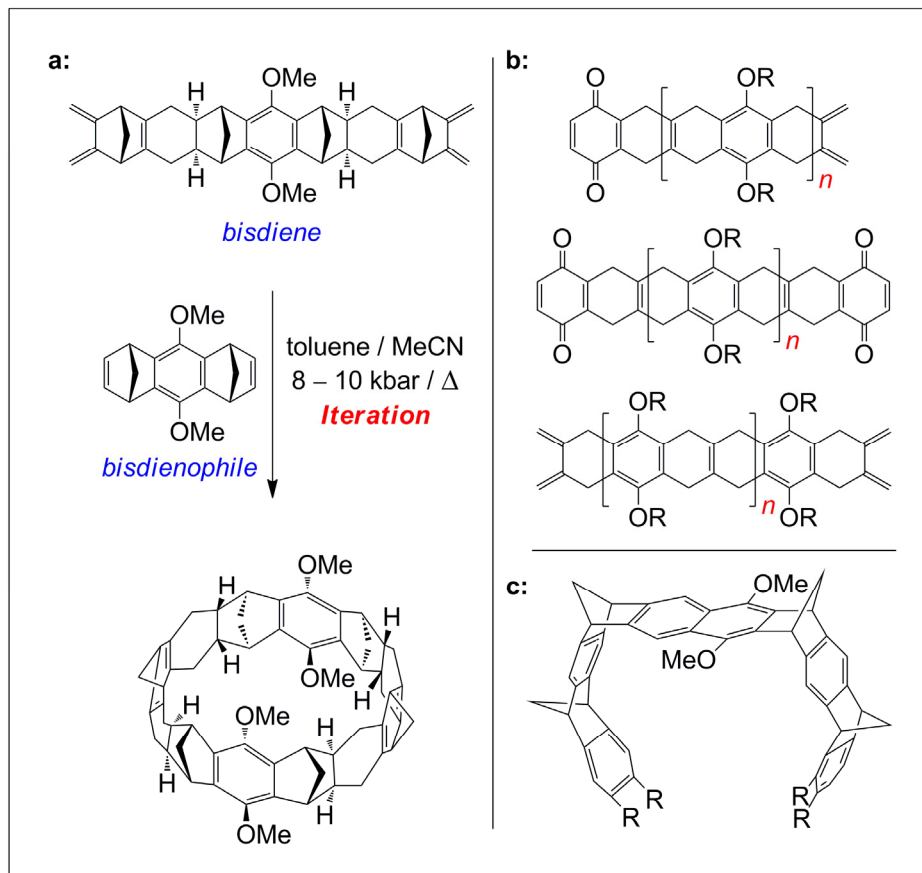
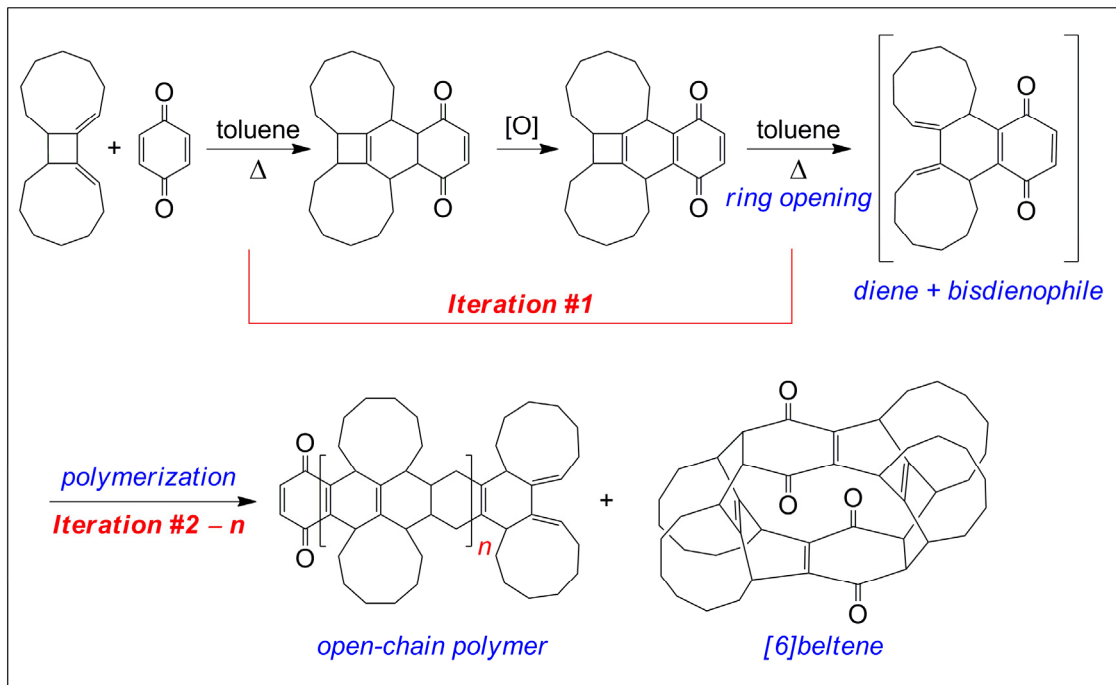


Figure 8. Applications of the iterative Diels-Alder reaction. (a) Methylene-bridged beltene. (b) Linear $[n]$ beltene synthons. (c) Molecular tweezers.

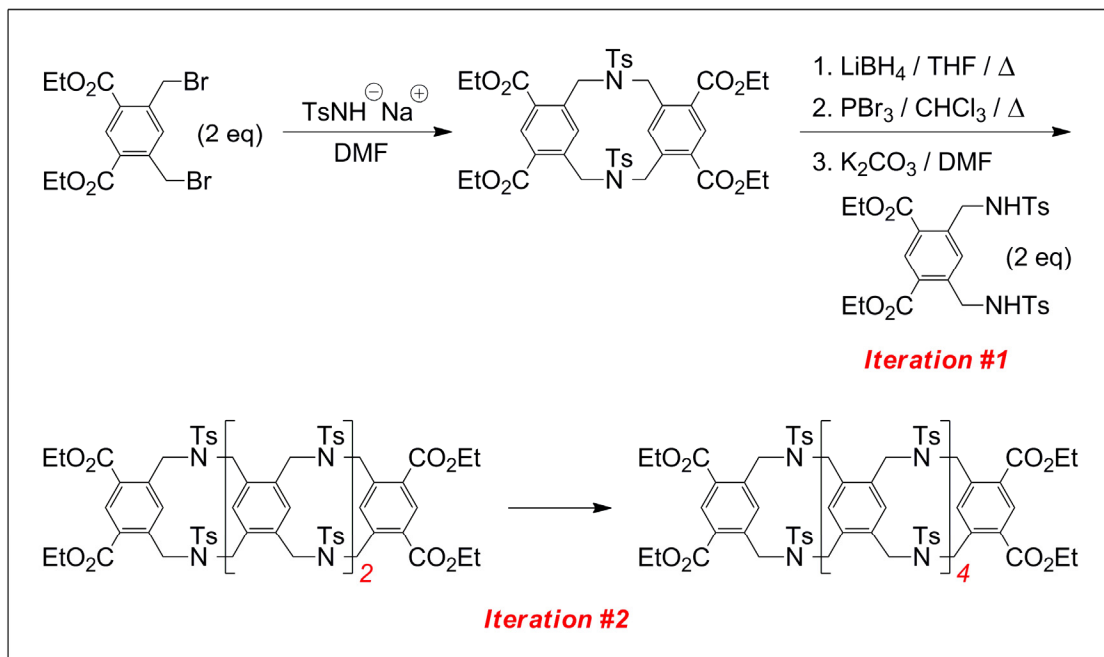
Utilizing the iterative Diels-Alder chemistry established by Stoddart and co-workers,⁴¹ Schlüter and co-workers⁴⁶ developed a route to access two double-stranded molecules: a $[6]$ beltene derivative and its corresponding open-chain polymer (Scheme 20).



Scheme 20. Iterative synthesis of double-stranded molecules.

By altering the dilution of the final reaction, they were able to control the distribution of products; higher dilutions lead to approximately 80% of the [6]beltene (20% of the open chain polymer) while lower dilutions lead to approximately 70% of the open chain polymer (30% of the [6]beltene).

An alternate iterative synthetic route to access new ribbon and belt-shaped molecules was developed by Vögtle and co-workers (Scheme 21).⁴⁷

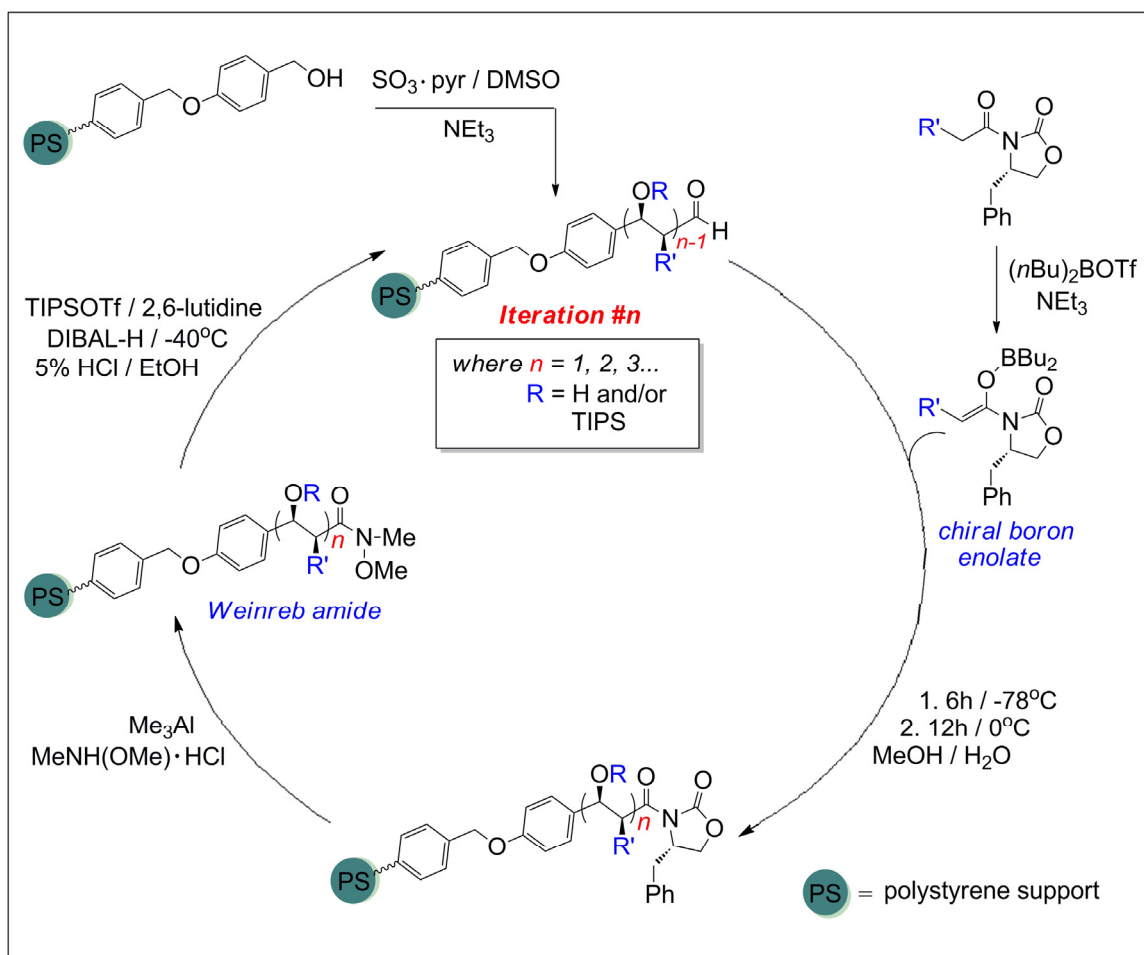


Scheme 21. Alternate route to the iterative construction of molecular ribbons.

They utilized tetrafunctionalized arenes and cyclophane monomers to synthesize ribbon type molecules that elongate by two benzene units with each iteration and have also been able to access cyclophanes containing nine benzene units⁴⁸ as well as other aromatic systems including pyridinophanes.⁴⁹

1.2.6 Polyketides

Polyketides are a broad class of bioactive molecules that display antibiotic, antifungal, immunosuppressant, antitumor, and other important biological activities.⁵⁰ By utilizing a sequence of stereocontrolled aldol reactions to mimic the stereoregulated chain growth involved in the biosynthesis of natural polyketides, the assembly of diverse unnatural polyketide libraries can be envisioned. Based on procedures developed by Evans and co-workers⁵¹ as well as by Nahm and Weinreb,⁵² Reggelin and Brenig⁵³ developed an iterative asymmetric aldol synthesis on a solid support (Scheme 22).

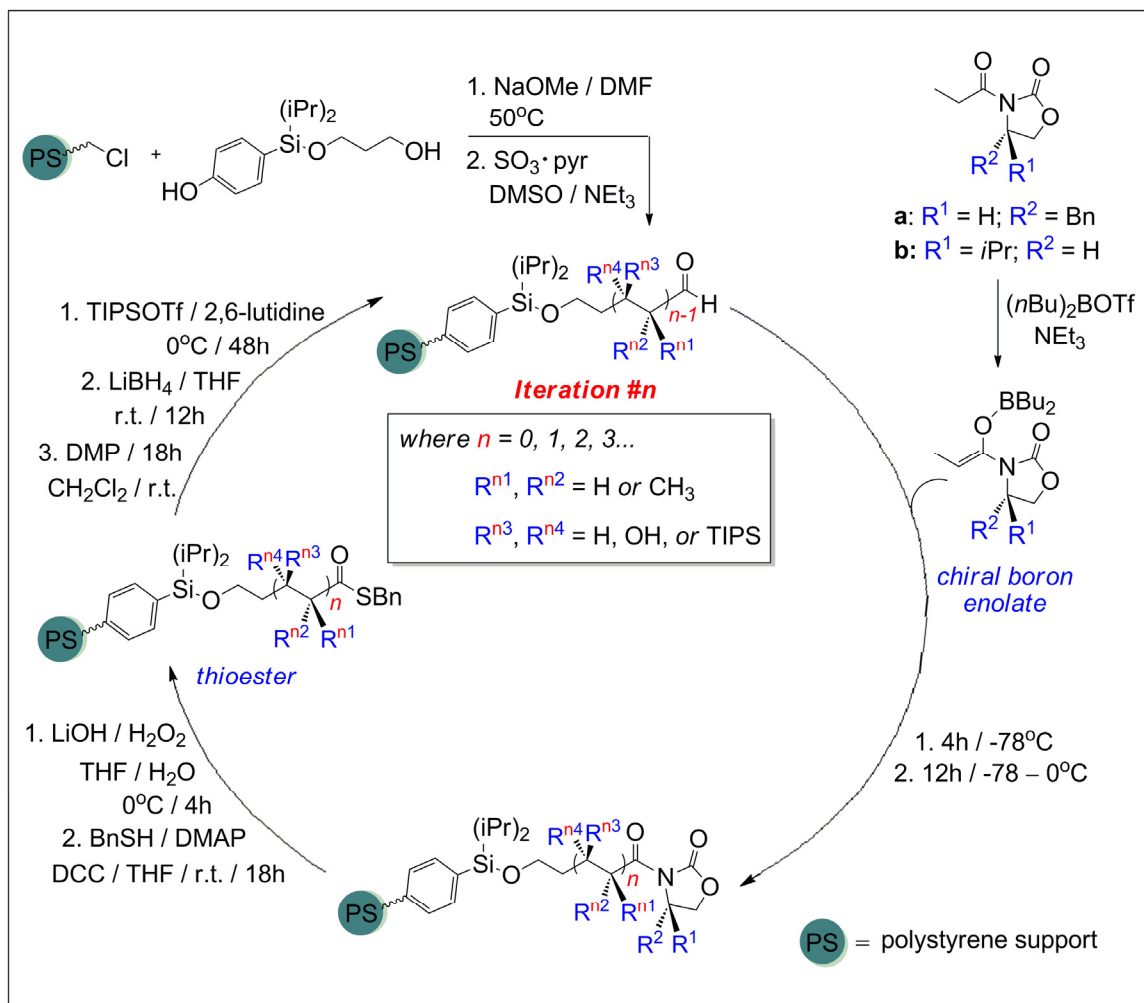


Scheme 22. Generation of polyketides via iterative asymmetric aldol reactions.

This iterative aldol reaction based on chiral boron enolates and Weinreb amides allowed this group to build diversification through not only a pool of monomeric units but also through the absolute configuration at the newly created stereogenic centers and modification of the sidechain functionality (R').

Based on their initial solid support work, Reggelin and co-workers⁵⁴ developed a second iterative synthesis to access a diverse library of chiral di- and triketides (Scheme 23). Two major changes were introduced into their new protocol to aid in feasibility issues. First, by replacing the Weinreb amide by a thioester as the aldehyde precursor, they bypassed difficulties associated with re-establishing the aldehyde functionality. Second,

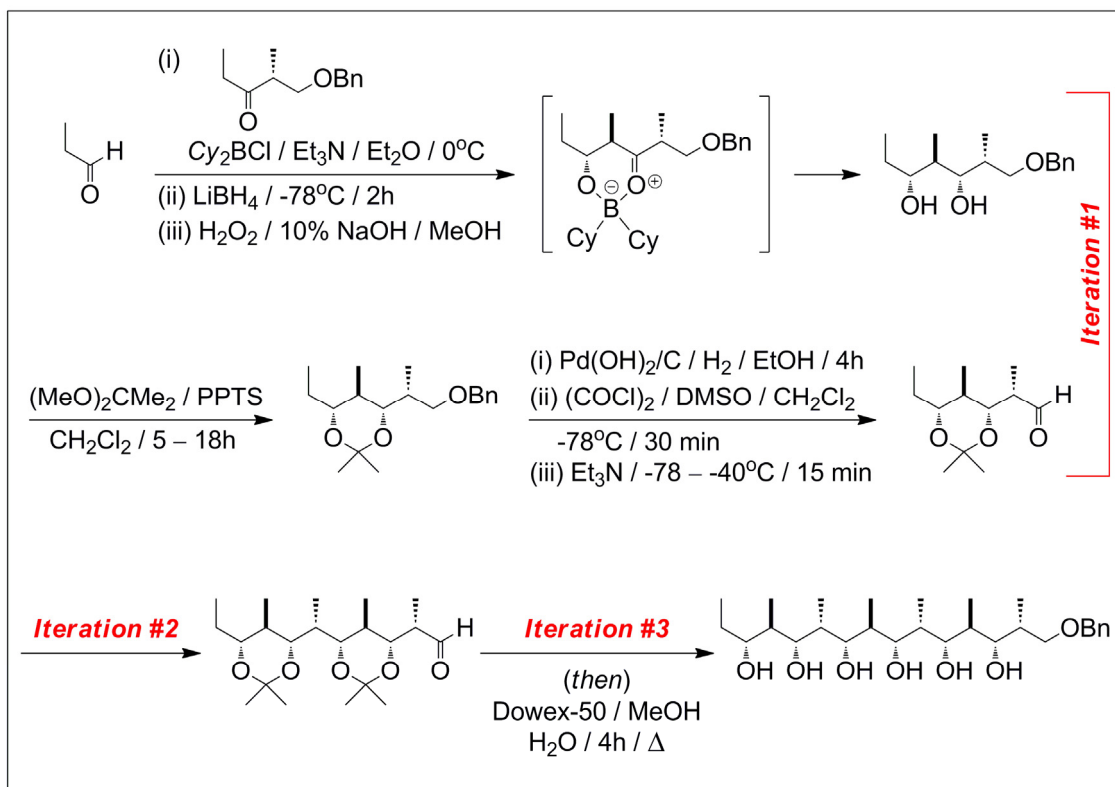
they developed a new fluoride ion cleavable tether which acts as a much more flexible and suitable linker.



Scheme 23. Iterative synthesis of di- and triketides on a solid support.

Since the late 1990s, several other research groups have developed a variety of solid-phase methods that may be applicable for the generation of diverse polyketide libraries.⁵⁵

Taking a different synthetic approach, Paterson and Scott⁵⁶ developed an iterative synthetic route that does not employ a solid-phase support. Instead, they utilized a boron-mediated aldol reaction of an ethyl ketone to an aldehyde followed by *in situ* reduction to give the 1,3-*syn* diol (Scheme 24).



Scheme 24. Iterative assembly of extended polypropionates to generate polyketides.

With the diol in hand, the iterative protocol is completed by hydrogenolysis of the benzyl ether followed by Swern oxidation to give an aldehyde, which may be used in the subsequent iteration sequence. With this iterative protocol in place, Paterson and Scott expanded the scope of their sequence by introducing structural diversity through stereochemical changes of the aldol bond construction (*syn* vs *anti*) and by varying the substitution and absolute configuration of their ketone building blocks. These changes helped expand the diverse range of novel polyketides available through this powerful iterative strategy.⁵⁶⁻⁵⁷

More recently, Paterson and co-workers⁵⁸ cleverly showed how an iterative solid-phase synthesis of polyketides could be applied to the synthesis of complex natural products (Figure 9).

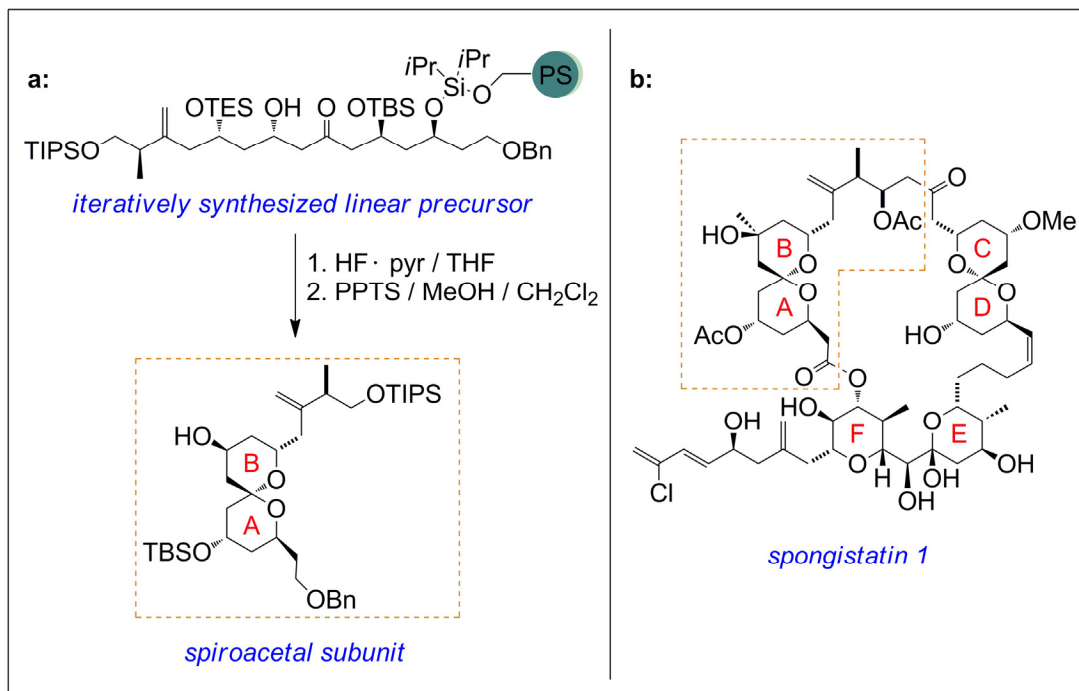


Figure 9. (a) Complex polyketide leading to spiroacetal subunit of (b) spongistatin 1.

By relying on asymmetric boron-mediated aldol reactions, researchers were able to utilize their developed solid-phase methodology to selectively synthesize a linear precursor of spongistatin 1. Subsequent cleavage of the polyketide from the resin and *in situ* spiroacetalisation led to the spiroacetal subunit of spongistatin 1 in 5% overall yield (over 7 steps). This group showed that by utilizing a wide variety of starting units, a large, diverse pool of linear polyketide sequences and in turn spiroacetal scaffolds can be accessed.⁵⁸

1.2.7 Polyethers

The potent biological activity of structurally interesting natural products of marine origin has stimulated substantial interest in the pursuit of “ladder”-type polyether natural products. Over the past two decades, a variety of strategies⁵⁹ including several elegant iterative routes⁶⁰ to access these structurally complex and toxic molecules have been developed.

Evans and co-workers⁶¹ reported an iterative approach to fused polycyclic ethers to access segments of the biologically important gamberic acids A – D (Figure 10) via intramolecular acyl radical cyclizations.

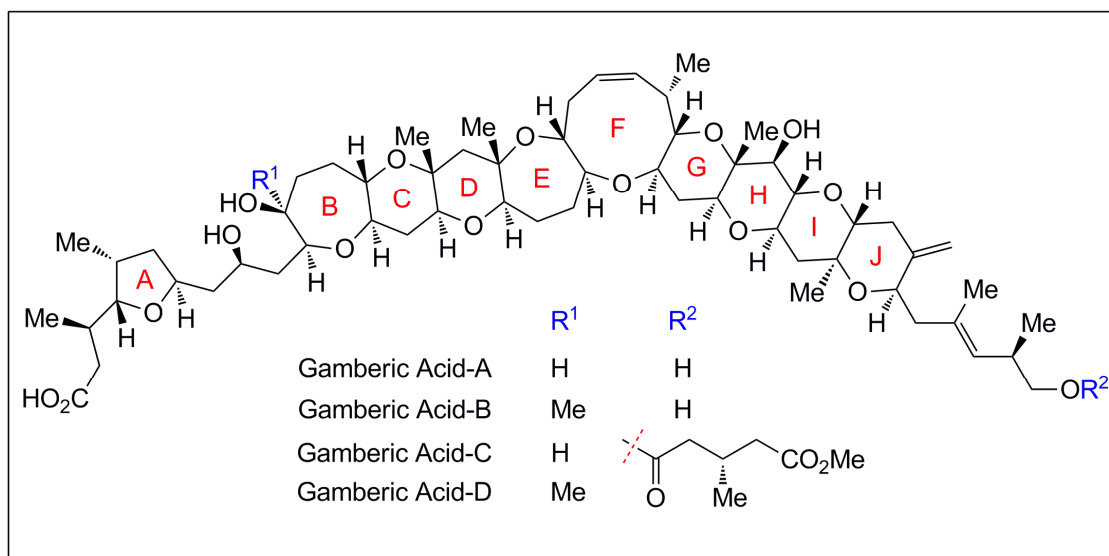
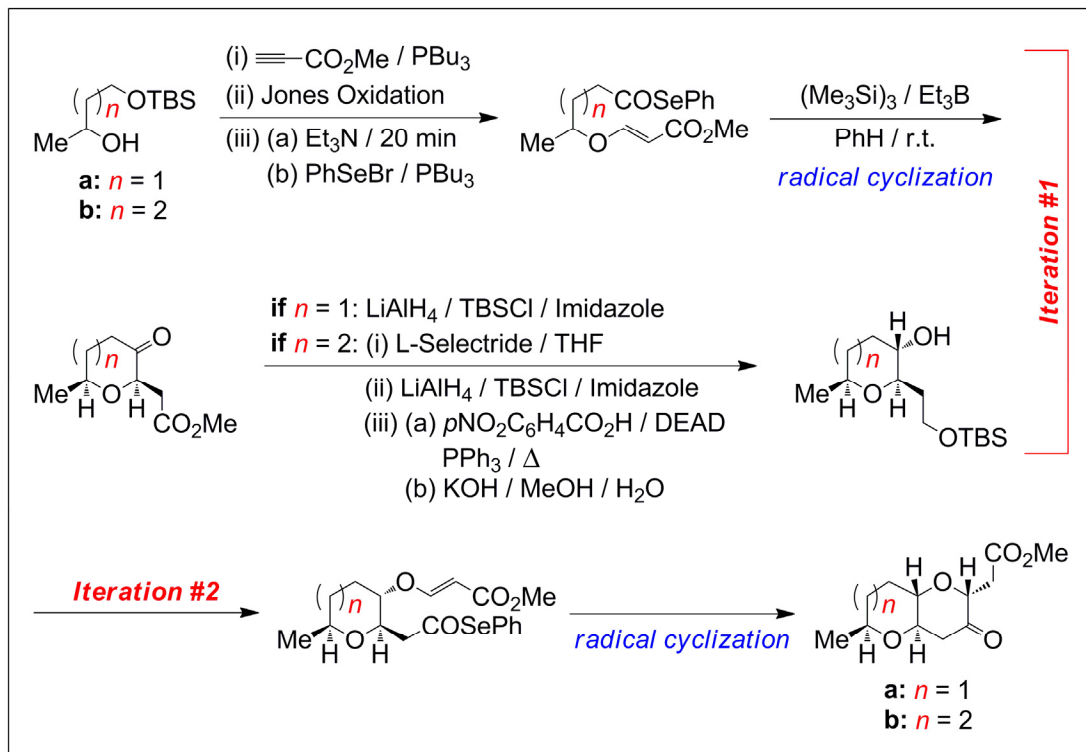


Figure 10. The gamberic acids A – D.

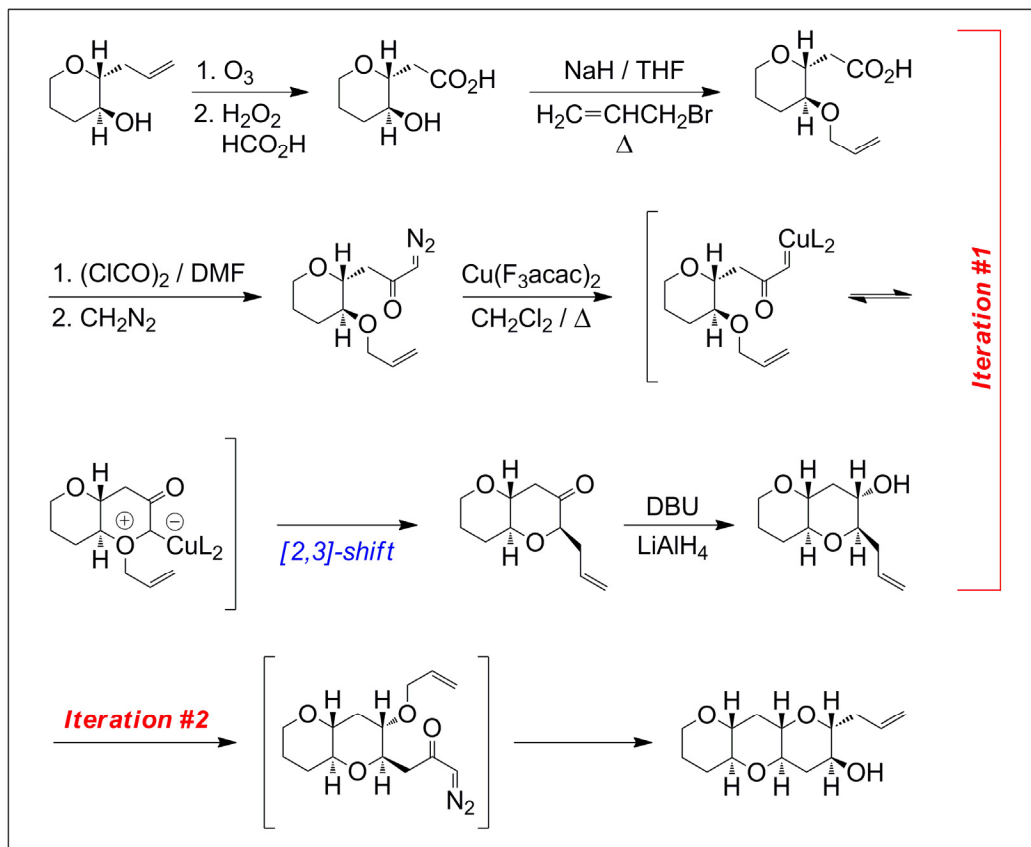
The two portions of the molecule this group targeted were the key left hand **BC** segment and right hand **IJ** segment. A two-step iterative sequence was used in conjunction with a radical cyclization to synthesize the desired segments (Scheme 25).⁶¹



Scheme 25. Iterative approach to polycyclic ether segments of gamberic acids A – D.

Although they were unable to cleanly reduce the larger ring ($n = 2$) with a straightforward LiAlH₄ reduction due to inseparable mixtures of epimeric alcohols, Evans and co-workers circumvented these difficulties by an alternate, more lengthy reduction procedure involving L-selectride reduction (step i), LiAlH₄ reduction (step ii), a Mitsunobu inversion of the *cis*-alcohol (step iii), and finally an alkaline hydrolysis (step iiib) to give the desired *trans*-alcohol.⁶¹

Marmsäter and West⁶² developed a novel strategy towards the general synthesis of a *trans*-fused polycyclic ether skeleton based on the iterative generation and rearrangement of cyclic oxonium ylides (Scheme 26).

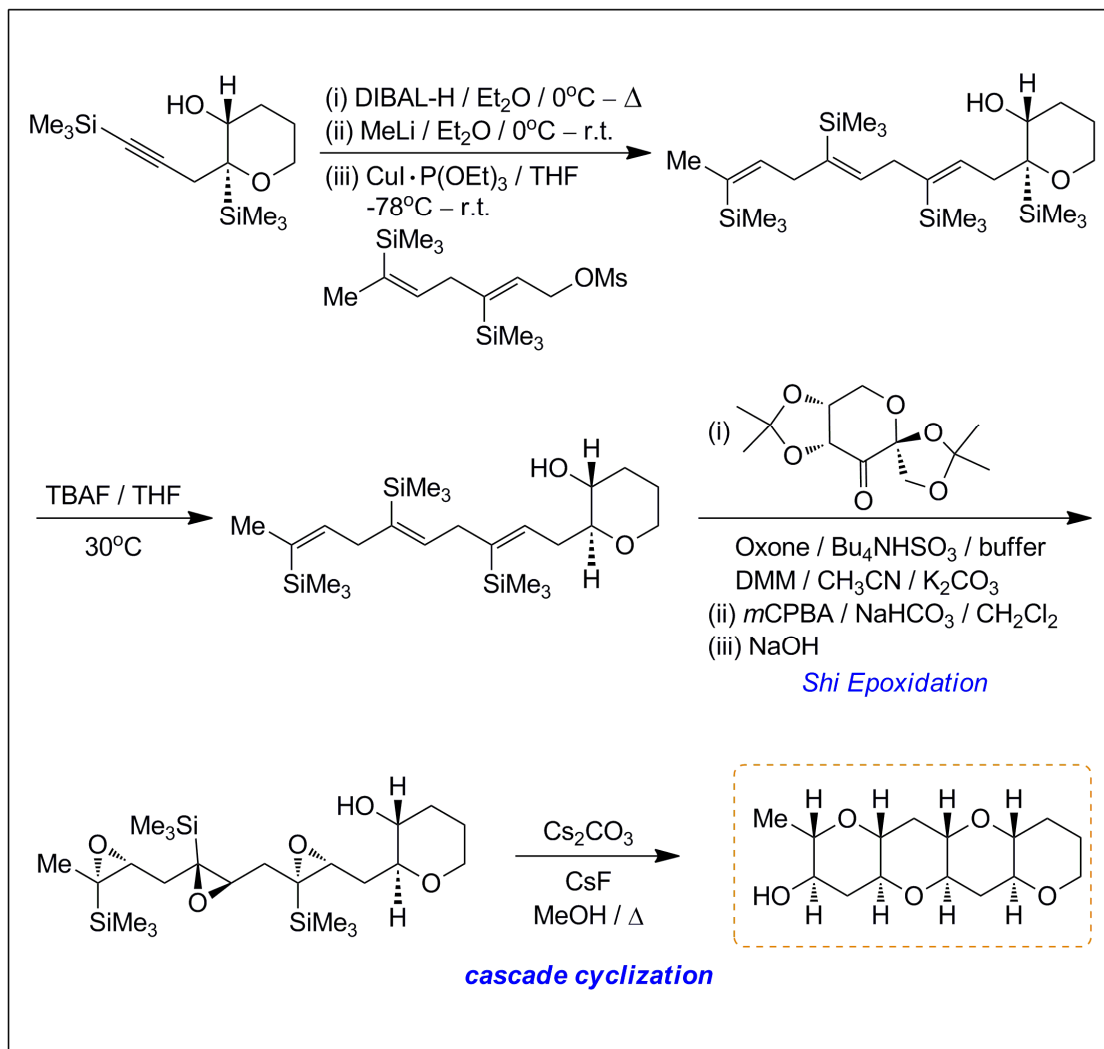


Scheme 26. General iterative approach to *trans*-fused polycyclic ether skeletons.

Their two-step iterative synthesis begins with the formation of a diazoketone from a hydroxypyran via ozonolysis with oxidative work-up, allyl ether formation, and finally conversion to the acid chloride followed by treatment with diazomethane. Using a copper (II) catalyst, they then induced an oxonium ylide/[2,3]-shift step followed by reduction of the ketone to give them a suitable alcohol precursor to begin the next round of iterative synthesis.

One of the more traditional synthetic routes to access “ladder”-type polyether natural products is through a cascade of epoxide-opening events from polyepoxide starting materials. Although many impressive synthetic cascades have been accomplished,⁶³ these syntheses have all required the use of directing groups that are not removed at the end of the synthesis to control the regioselectivity of the epoxide opening. In addition, the four-ring system (a tetrad of THP rings) that is found in most ladder polyether natural products

has not been synthesized using these methodologies. Recently, however, Jamison and co-workers⁶⁴ reported an epoxide-opening cascade reaction that yields up to a tetrad of THP rings and contains no directing groups at the end of the cascade (Scheme 27).



Scheme 27. Polyether synthesis via epoxide-opening cascades.

Utilizing their previously reported Me₃Si-based strategy to synthesize THP polyether subunits,⁶⁵ they were able to successfully pair this methodology with a Shi epoxidation,⁶⁶ a Brønsted base (Cs₂CO₃), and a fluoride source (CsF) to remove the SiMe₃ directing groups to generate the dyad, triad, and the first THP tetrad (shown in Scheme 27), each in one epoxide-opening cascade sequence.

1.2.8 Iterative Cross-Coupling Reactions

In recent years, one of the greatest contributions to the repetitive synthesis of small, complex molecules has been the development of iterative cross-coupling reactions. This type of reaction has allowed researchers to gain quick and easy access to new varieties of the molecules mentioned above including poly- and oligoarene derivatives, polyene systems, polyketides, and other small molecule natural products.^{3,67}

Suginome and co-workers⁶⁸ were the first to develop a masking/unmasking strategy to control the reactivity of organoboronic acids in an iterative Suzuki-Miyaura cross-coupling reaction (Figure 11). By utilizing a 1,8-diaminonaphthalene masking group (Figure 11a) that can be easily installed, is stable during the coupling reaction, and easy to remove, this group was able to perform a simple two-step iteration sequence (Figure 11b) to access a variety of oligoarene derivatives (Figure 11c).

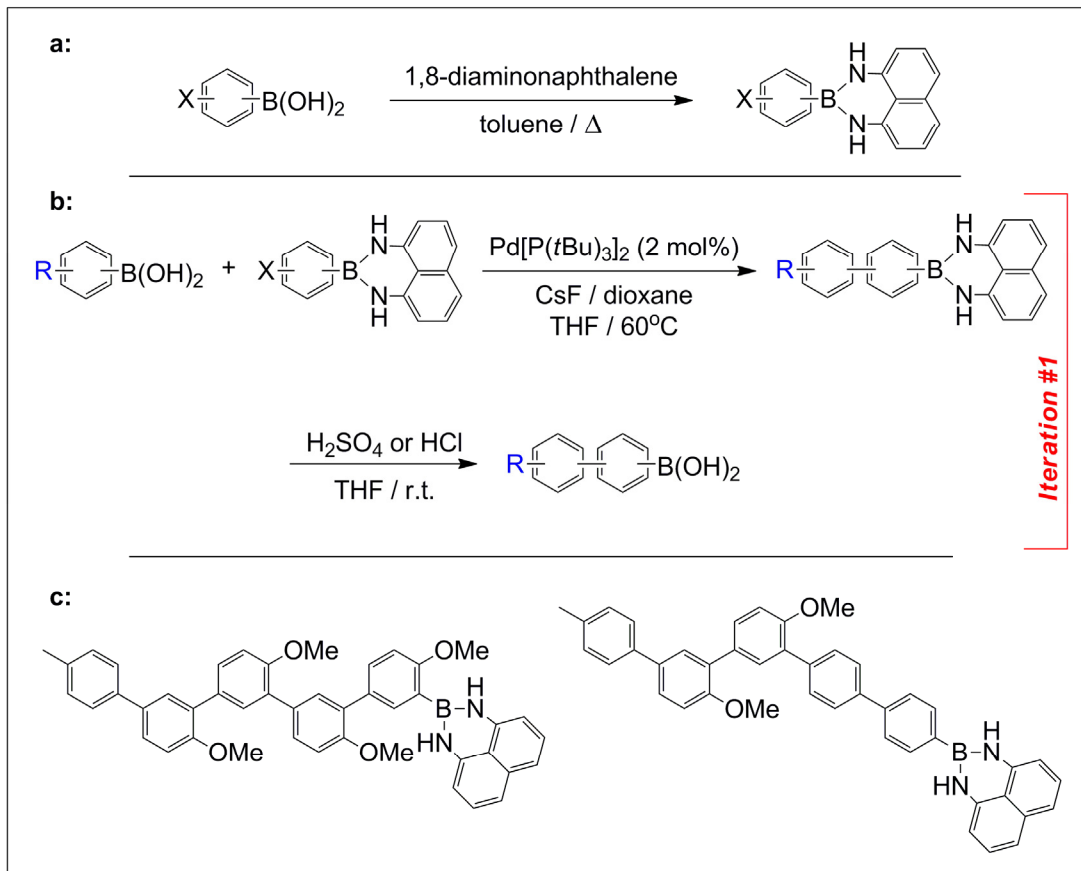
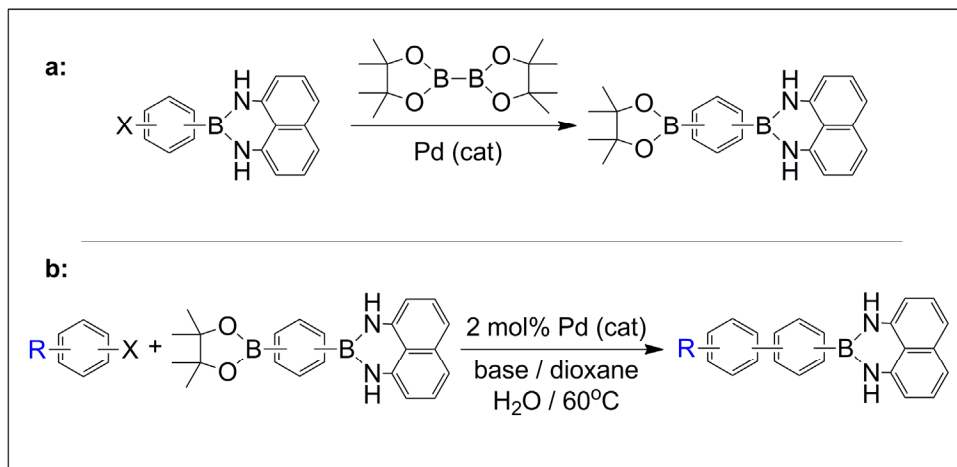


Figure 11. A boron masking strategy. (a) A 1,8-diaminonaphthalene masking group. (b) A Pd-catalyzed ICC strategy. (c) Oligoarenes prepared using this methodology.

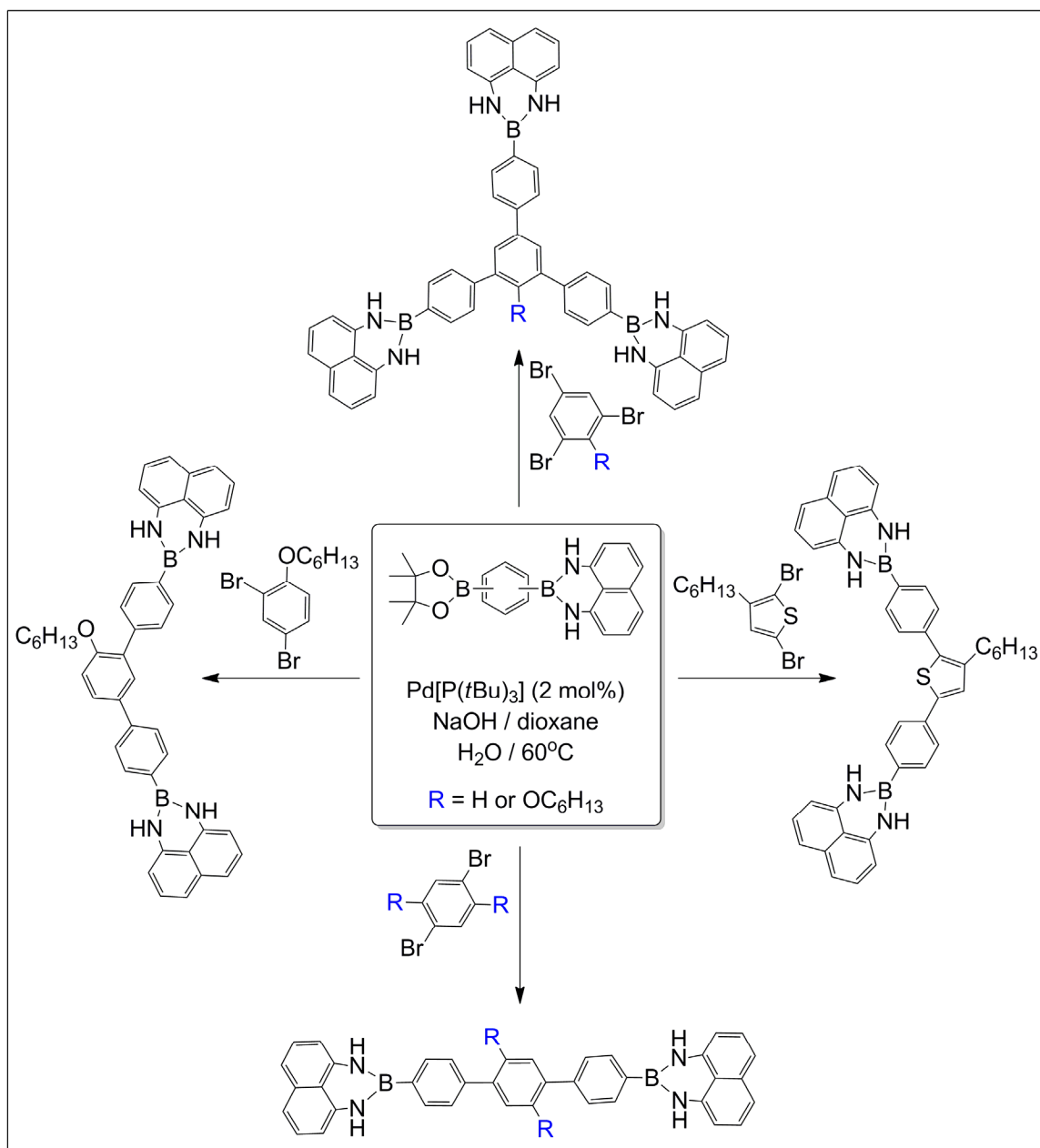
They attributed the observed stability of the masked boronic acid to the π -electron donation of the nitrogen atoms on the 1,8-diaminonaphthalene which decreases the Lewis acidity of the boron center.⁶⁸

As an extension of their iterative methodology, Suginome and co-workers⁶⁹ reported a new system in which benzenediboronic acid derivatives were mono protected (Scheme 28).



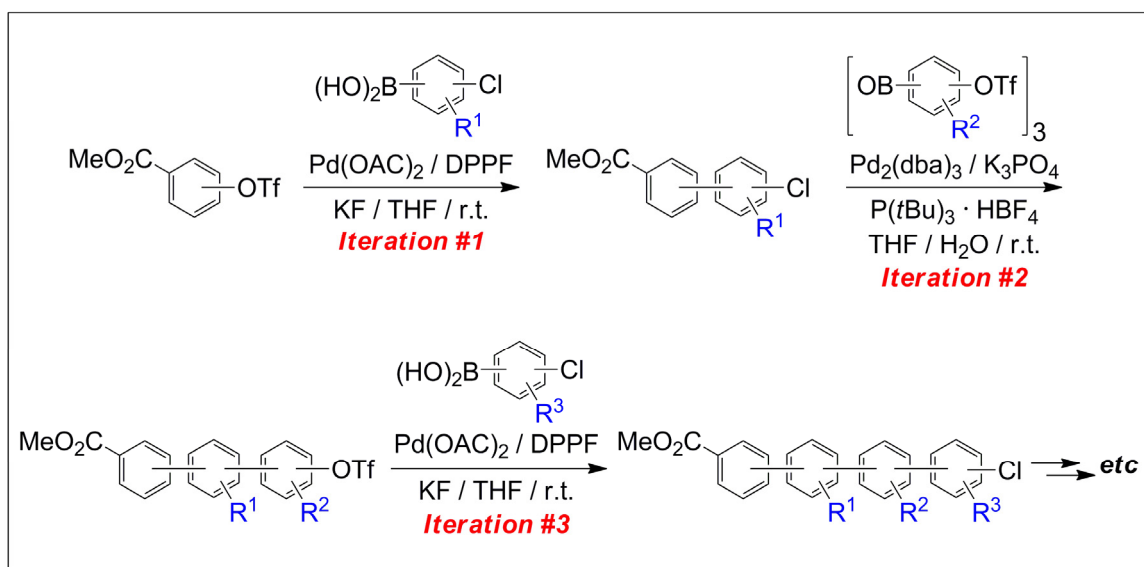
Scheme 28. (a) Generation of mono protected benzenediboronic acid derivatives. (b) Pd-catalyzed Suzuki-Miyaura cross-coupling reaction.

By selectively masking one of the boronyl groups with their 1,8-diaminonaphthalene protecting group, they were able to successfully complete an iterative Suzuki-Miyaura cross-coupling reaction with one boronyl group remaining intact. This new divalent cross-coupling reaction expands the scope and availability of organoboron compounds that can be applied to their iterative methodology and in turn expands the array of accessible oligoarene derivatives (Scheme 29).



Scheme 29. Synthesis of boron-substituted oligoarene derivatives.

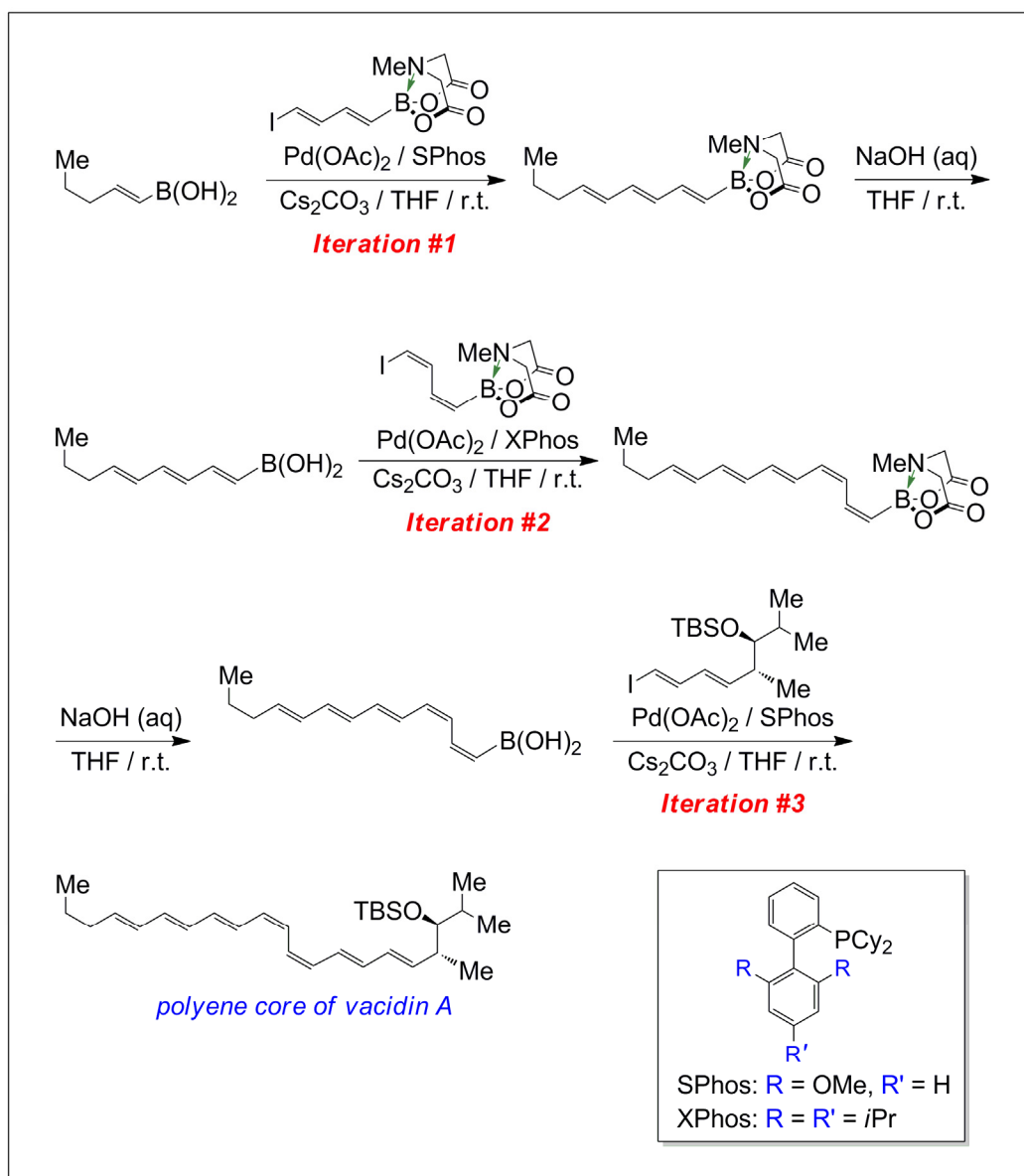
More recently Manabe and co-workers⁷⁰ developed a clever one-step iteration sequence based on work done by Fu and co-workers⁷¹ that removes the need for functional group transformation prior to the next elongation reaction (Scheme 30).



Scheme 30. General one-step iterative synthesis of oligoarenes.

Their sequence is the first reported for the chemoselective Suzuki-Miyaura cross-coupling of chloroarenes with OTf decorated phenylboronic acids (isolated as the boroxine). By alternating Pd catalytic reaction conditions and coupling partners (a chlorophenylboronic acid in iteration #1/3 and a phenylboronic acid bearing a TfO group in iteration #2), the molecule can be selectively elongated by one benzene unit in every step. All of this hinges on having chemo-orthogonal catalytic conditions for the chloroarenes and the aryl triflates respectively. This clever one-step iterative sequence reduces the number of overall steps required to synthesize the desired oligoarene target, making the synthesis very quick and efficient.

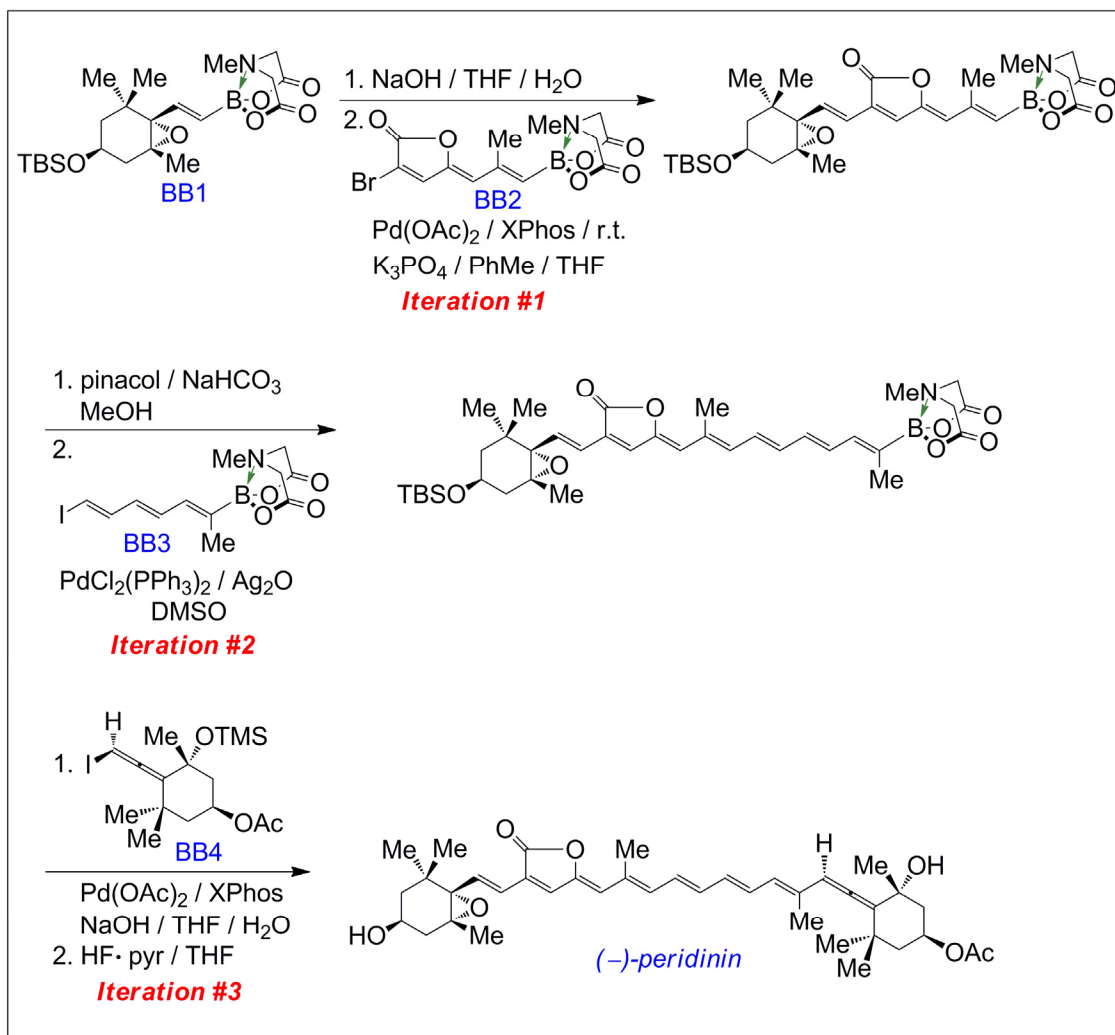
As illustrated above, boronic acids are useful building blocks in organic synthesis. However, unmasking the protected boronic acid in the strategies shown thus far requires harsh conditions (such as H₂SO₄ or HCl) that can be incompatible with structurally complex organic products. To overcome these limitations, Burke and co-workers⁷² developed a series of *N*-methyliminodiacetic acid (MIDA) boronates⁷³ (Figure 12) that are unreactive under cross-coupling conditions, benchtop stable (stable neat, under air, at room temperature), compatible with chromatography, available on kilogram scale,



Scheme 31. Iterative synthesis of the vacidin A core.

In this first synthesis to reach the heptane core of vacidin A (Scheme 31), the Burke group was able to highlight the flexibility of their iterative sequence by targeting a natural product that contains both *cis* and *trans* double bonds, an unusual feature of polyene systems.^{74c} In a second example (Scheme 32), Burke and co-workers were able to access the natural product (–)-peridinin from four key building blocks (BB1 – BB4), each

containing all of the required functionality preinstalled with the right stereochemistry and in the correct oxidation states.^{75a}

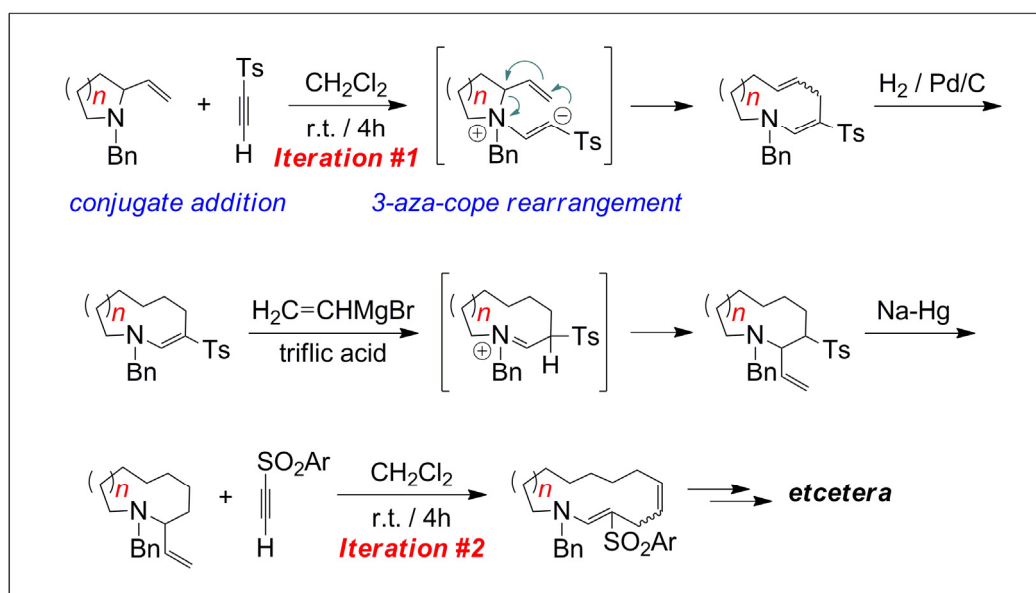


Scheme 32. Iterative synthesis of (-)-peridinin.

These are a few of many syntheses accomplished by Burke and co-workers as proof for the efficiency of their new platform. As new and more diverse building blocks become available, the variety of small molecules accessible through iterative cross-coupling will continue to expand.

1.2.9 Iterative Ring Expansions

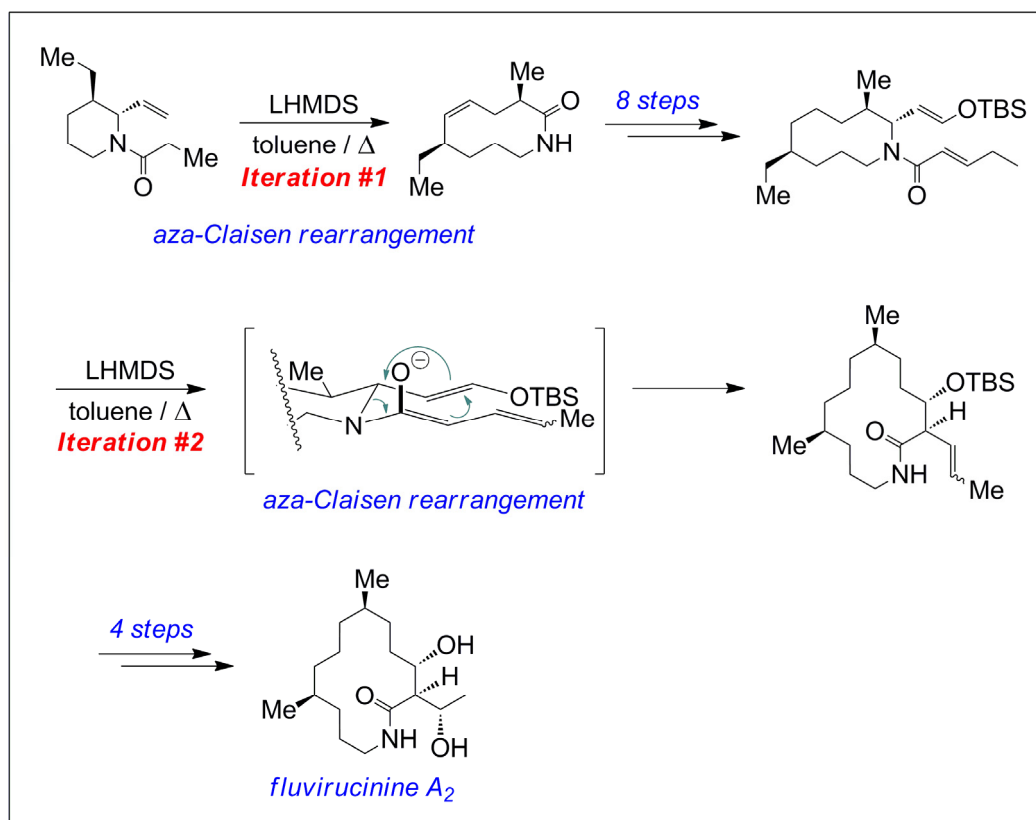
The efficient synthesis of medium-sized lactam alkaloids and macro-lactam alkaloids is highly sought after due to the diverse range of biological activities that many of these compounds possess. Although either linear or cyclic precursors can be utilized in the case of macrolide synthesis, there is a big advantage in making use of cyclic precursors as one avoids the need for high dilution in order to circumvent intermolecular condensations. In an early review by Masamune and co-workers,⁷⁶ the ring “growing” of macrolides using diazomethane and medium-ring cyclanones was described. Beckwith and co-workers⁷⁷ later applied a radical process for the ring expansion of ketones by one or more carbon atoms. To access libraries of substituted α,β -unsaturated and saturated medium-ring lactones, Rousseau and co-workers⁷⁸ created an iterative one-carbon ring enlargement from easily obtainable n -membered lactone precursors. More recently, Back and co-workers⁷⁹ developed a clever iterative ring expansion that utilizes tandem conjugate additions and 3-aza-Cope rearrangements of tertiary allyl amines or cyclic α -vinylamines with acetylenic sulfones (Scheme 33).



Scheme 33. Tandem conjugate addition/[3,3] rearrangement to nitrogen heterocycles.

This iterative process, in which the product of one ring expansion is converted into a new cyclic α -vinyl amine and undergoes a second conjugate addition and [3,3] rearrangement, led to an array of medium and large-ring nitrogen heterocycles.

Finally, Suh and co-workers⁸⁰ have reported a novel iterative ring expansion strategy leading to the first total synthesis and structural confirmation of fluvirucinine A₂.



Scheme 34. Iterative ring expansion towards the synthesis of fluvirucinine A₂.

Their efficient and versatile ring expansion strategy utilized a highly stereo- and regioselective amide enolate induced vinylogous aza-Claisen rearrangement as a key iterative step. Although applied to a very specific natural product target, in the future this iterative strategy is likely to provide access to a plethora of macrolactam skeletons rapidly and with a variety of functionalization.

1.3.0 Summary & Objectives

As established above, iterative strategies can constitute a useful means to access efficiently a diverse range of complex small molecules. Herein, we report our contribution to the field of iterative synthesis, including two applications deriving from these protocols.

1.3.1 Iterative Synthesis Design

Although the synthesis of small molecules remains highly non-systemized due to the complex nature of most natural products, the achievements presented in section 1.2 demonstrate the versatility of iterative protocols and represent major steps towards automation in organic synthesis. In order to further advance this field, however, the development and utilization of new, high yielding synthetic methods is required.

As such, we sought to make our contribution to this synthetic area through the development of a new iterative/cascade protocol that takes into account the following constraints:

- (a) Target compounds must be easily synthesized through repetitive, simple, and high yielding synthetic steps (as for the synthesis of peptides and nucleic acids).
- (b) A large selection of simple monomeric building blocks should be available, allowing for the inclusion of an array of different functionality into our systems.
- (c) No more than two steps per iteration should be required, allowing for quick and efficient synthesis of our target compounds.
- (d) Target compounds must be available in sufficient quantity and diversity, allowing for libraries of substrates to be synthesized.
- (e) Although chromatography should be accessible, it should not be required until the end of our synthetic process.

- (f) Target compounds should be designed in such a way that a variety of orthogonal cascade methodologies could be applied, leading to a broad range of products.
- (g) Finally, the chemistry should be portable to solid-phase.

Figure 13 outlines a general synthetic plan for the development of our iterative synthesis.

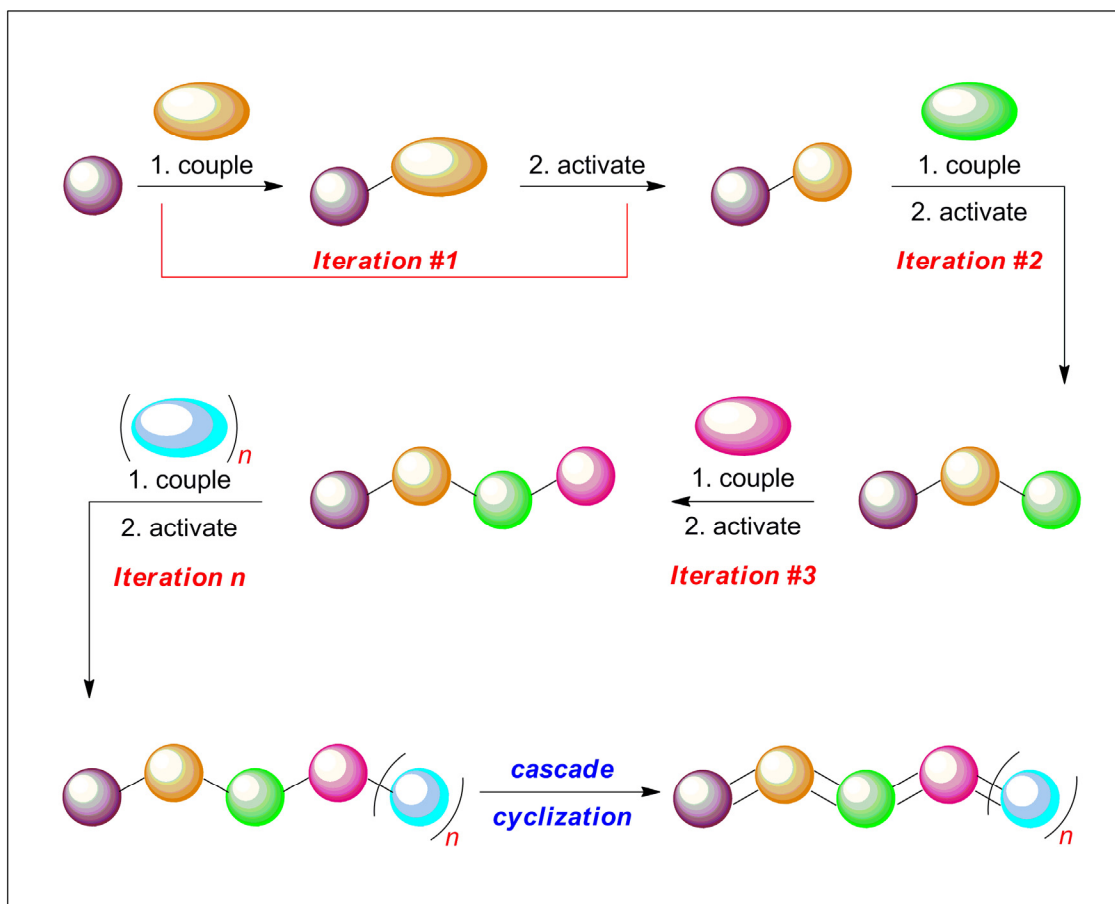


Figure 13. General iterative synthetic plan.

Constraint (f) represents a key goal for our research. We endeavoured to develop an iterative protocol that would permit the assembly of oligomers (of size n , Figure 13) that could be transformed via cascade cyclization into a variety of complex structures.

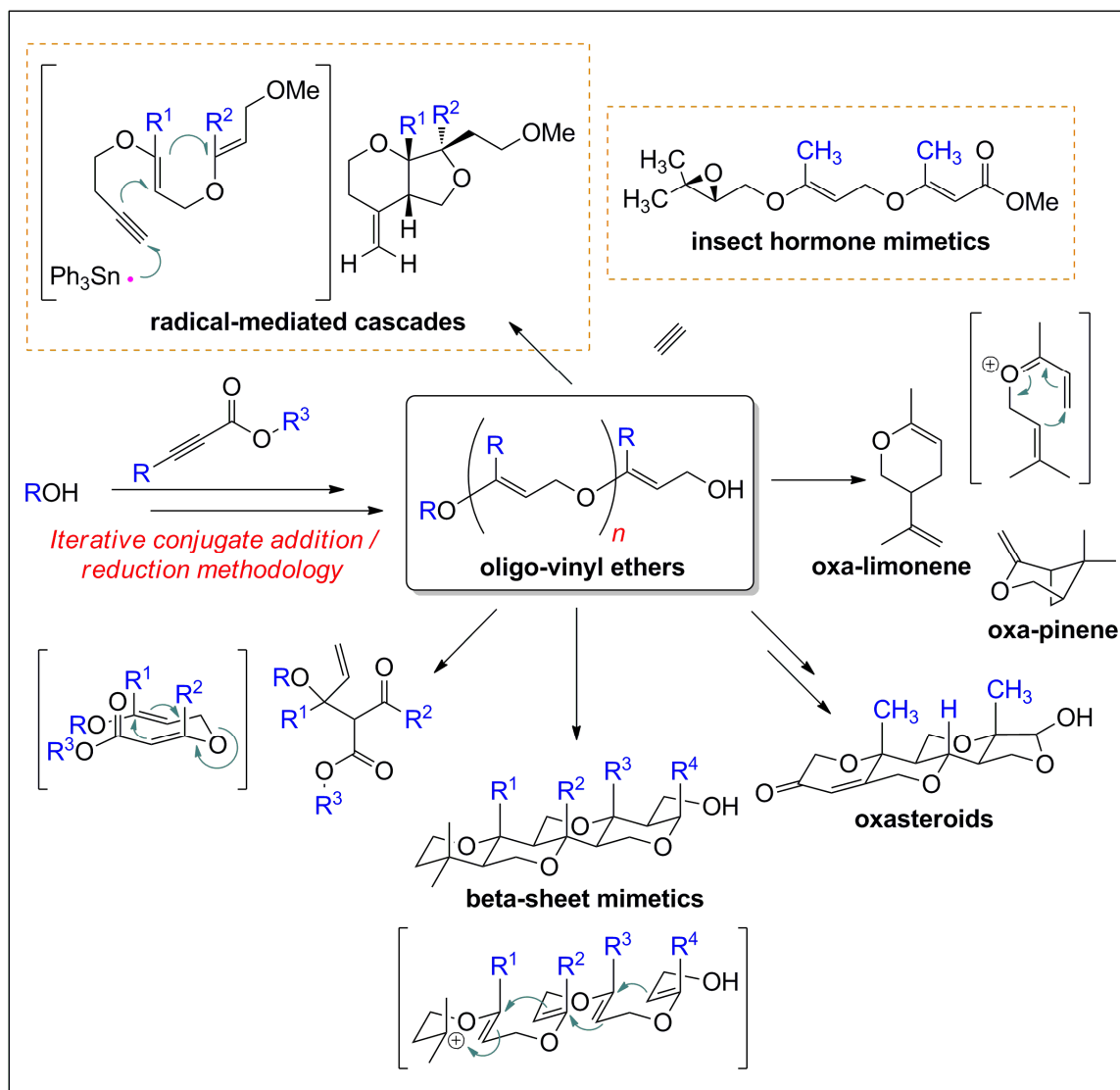


Figure 14. An iterative based strategy on an unusual vinyl ether template.

We therefore chose to focus our efforts on the iterative synthesis of oligo-vinyl ethers (Figure 14) as a variety of orthogonal cascade methodologies could be envisioned leading to a diverse range of products.

Chapter 2: Iterative Synthesis Development & Optimization

2.0.0 Iterative Synthesis Development

As discussed in Chapter 1, an iterative approach is a highly efficient strategy for the generation of large, complex molecules that has been applied in many different subfields of organic synthesis. Utilizing this approach can help minimize reaction optimization and chromatographic purification steps which in turn will help increase the speed, effectiveness, and overall yield of the synthesis.

We targeted for the development of a two-step iterative approach that utilizes a conjugate addition/reduction sequence leading to a series of oligo-vinyl ethers (Figure 15).

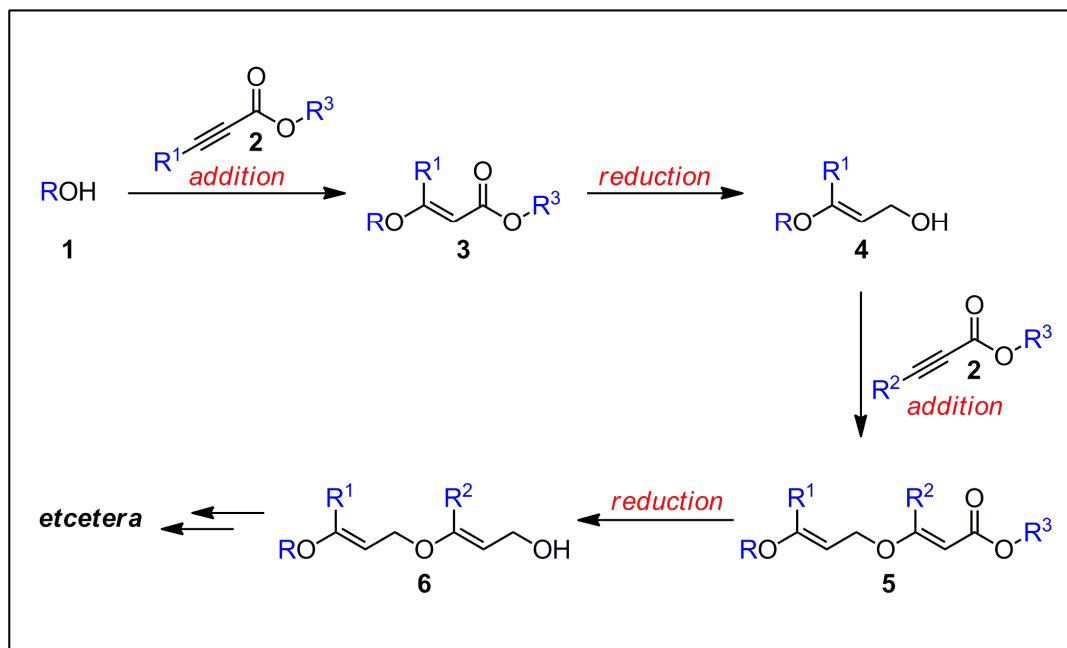


Figure 15. General outline of our two-step iterative synthesis.

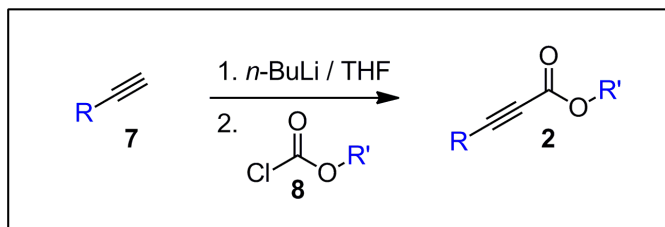
The products from this sequence should be amenable to a variety of cascade cyclization pathways. In addition, substituted vinyl ether systems of the type described here were

virtually unseen in the literature prior to our work; for that reason any chemistry that we apply to these systems should be relatively novel. However, due to the absence of these systems in the chemical literature, there were several concerns that needed to be addressed:

- (1) Are oligo-vinyl ethers stable and if so under what conditions? More specifically, are these systems benchtop stable? Are they compatible with a variety of solvents (reaction and NMR) and will they be stable under thermal reaction conditions? Finally, if in fact they are stable to our reaction conditions will purification by column chromatography be accessible?
- (2) Can we access mild, chromatography-free conditions?
- (3) Can we selectively make or cleanly isolate only one isomer (*E* vs *Z*)?

2.1.0 Synthetic Preparation of Starting Material Building Blocks

For our iterative synthesis to have broad application the addition step must allow for a variety of readily available and inexpensive building blocks to be utilized, thus enabling an array of different functionality into our systems. Many alkyl- and aryl-substituted propiolates (**2**) are commercially available or are easily accessible through a simple reaction between a terminal alkyne (**7**) and a chloroformate (**8**, Scheme 35).⁸¹



Scheme 35. General reaction for the preparation of propiolate starting materials.

This straightforward reaction is generally high yielding and has allowed us to access a variety of alkyl- and aryl-substituted propiolates (**2**) utilized throughout this body of work (Figure 16).

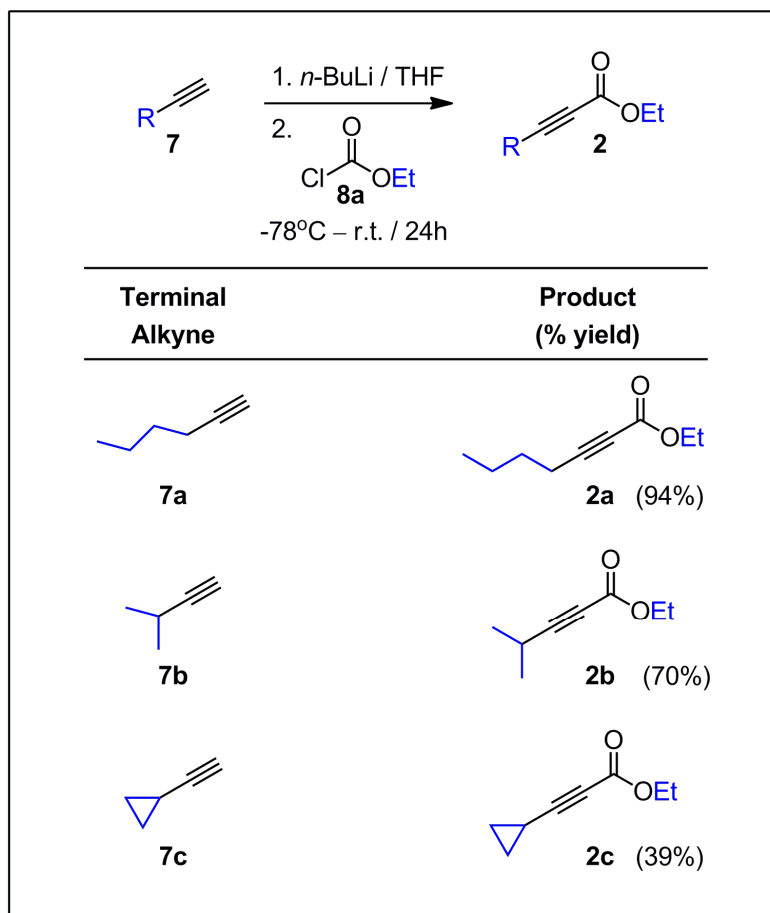
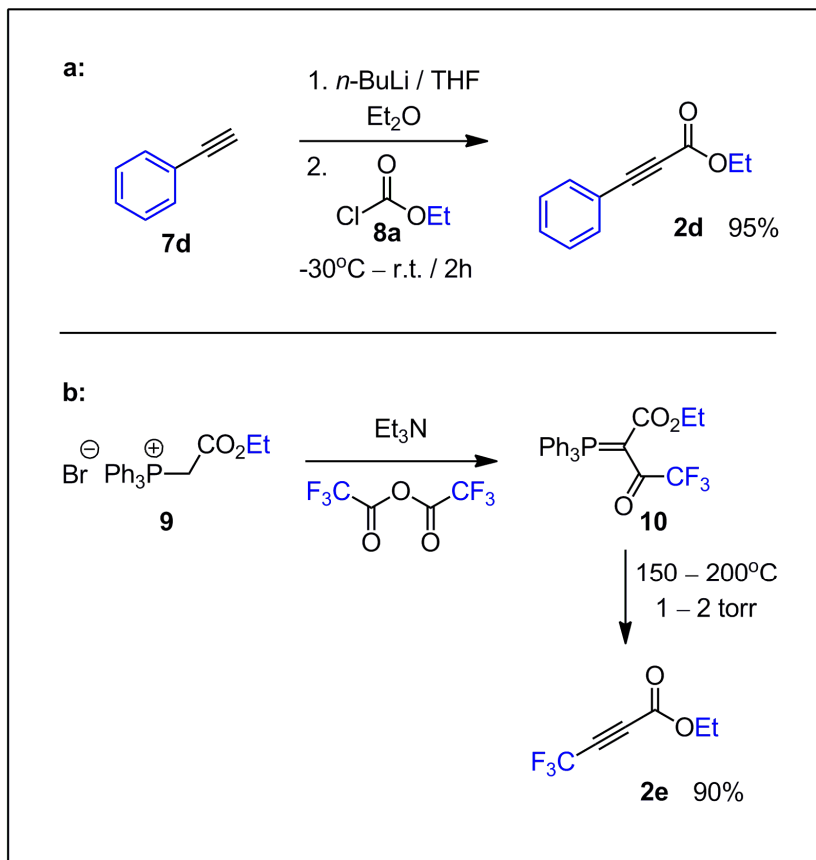


Figure 16. Preparation of monomeric building blocks 2a – 2c.

Other literature preparations were used to access specific substituted propiolates when the above reaction sequence was determined not to be suitable including 3-phenyl-2-propynoic acid ethyl ester (**2d**, Scheme 36a)⁸² and ethyl 4,4,4-trifluoro-2-butynoate (**2e**, Scheme 36b).⁸³



Scheme 36. Preparation of monomeric building blocks 2d and 2e.

For the preparation of 4-aryl butynoates (**12**, Figure 17), however, there were no procedures suitable for our needs.

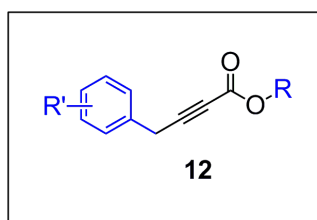
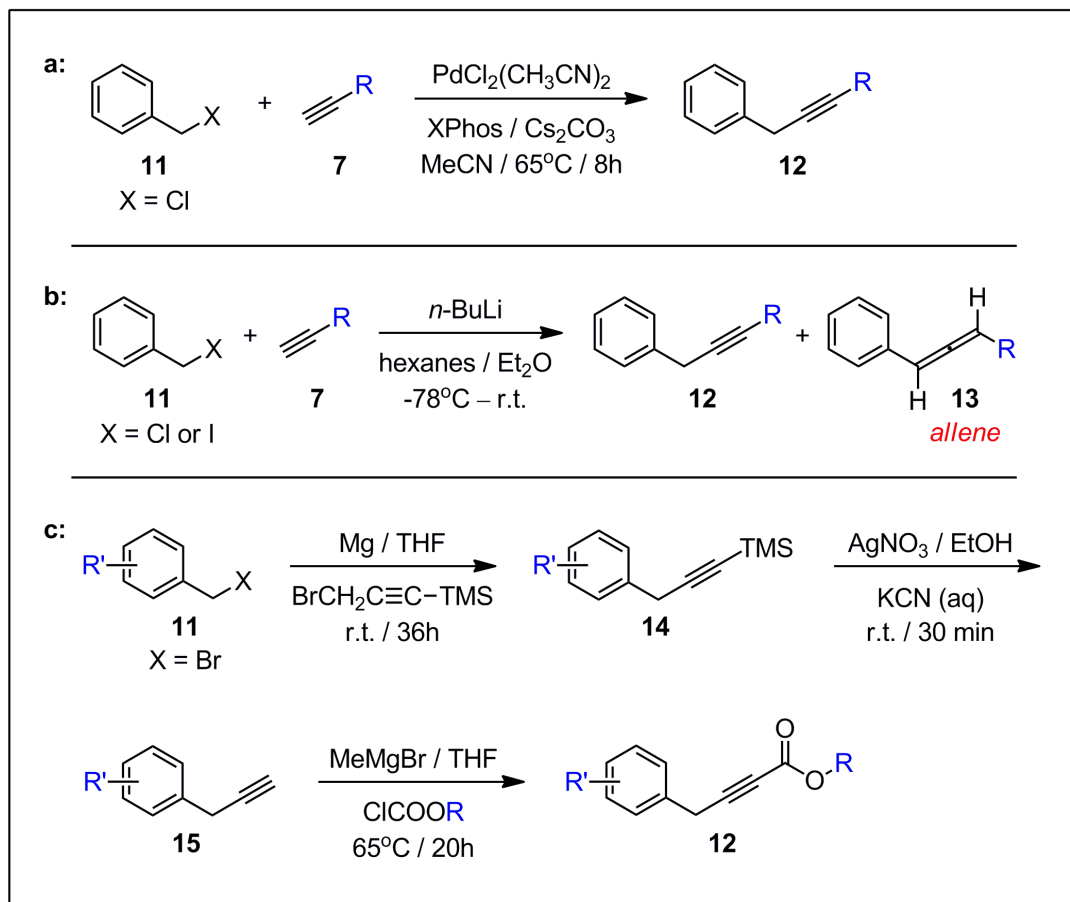


Figure 17. General structure of a 4-aryl butynoate (12).

Benzyl-substituted species such as **12** have previously been difficult to prepare and generally require the use of palladium catalysts (Scheme 37a),⁸⁴ lithiation (Scheme

37b),⁸⁵ or lengthy synthetic strategies (Scheme 37c)⁸⁶ in conjunction with expensive, less readily available ligands and/or high heat conditions.



Scheme 37. Literature methods to gain access to benzyl-substituted species (12).

The challenging nature of benzyl alkynes is also reinforced by the fact that one, they contain a rather acidic center which might prove incompatible with the above methods and two, they are more prone (compared to alkyl- and aryl-substituted propiolates) to isomerization to the corresponding allenes (**13**), known to form mixtures of unwanted products (Figure 18).^{84c,87}

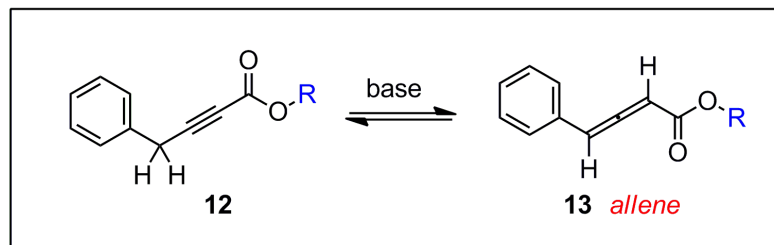
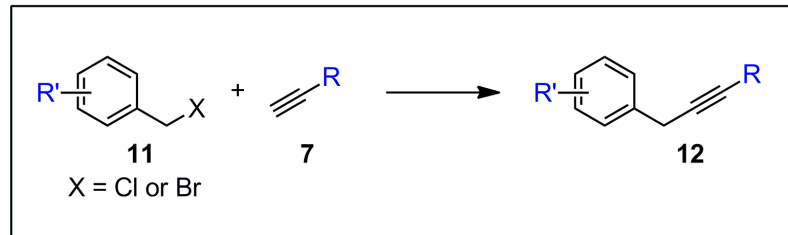


Figure 18. Isomerization of benzyl-substituted propiolates to the corresponding allene.

These factors have contributed to the limited utility of 4-aryl-2-butynoates (**12**) in the synthesis of complex heterocyclic small molecules.

As such, we set out to develop a new methodology which provides a straightforward protocol to access many variations of **12** through the direct coupling of a benzyl halide (**11**) with a terminal alkyne (**7**) with relative ease and under mild conditions (Scheme 38).⁸⁸



Scheme 38. General reaction schemes for the alkylation of benzyl halides.

Although having access to various 4-aryl butynoates (**12**) was important for the building blocks in this project, substituted acetylenic esters and ketones are also useful as precursors in the parallel synthesis of small-molecule heterocycles (furans (**16**),⁸⁹ pyrazoles (**17**),⁹⁰ 1,2,3-triazoles (**18**),⁹¹ 2-pyridones (**19**),⁹² pyrimidines (**20**),⁹³ pyrroles (**21**),⁹⁴ and pyridines (**22**)⁹⁵) of interest to the pharmaceutical industry (Figure 19).

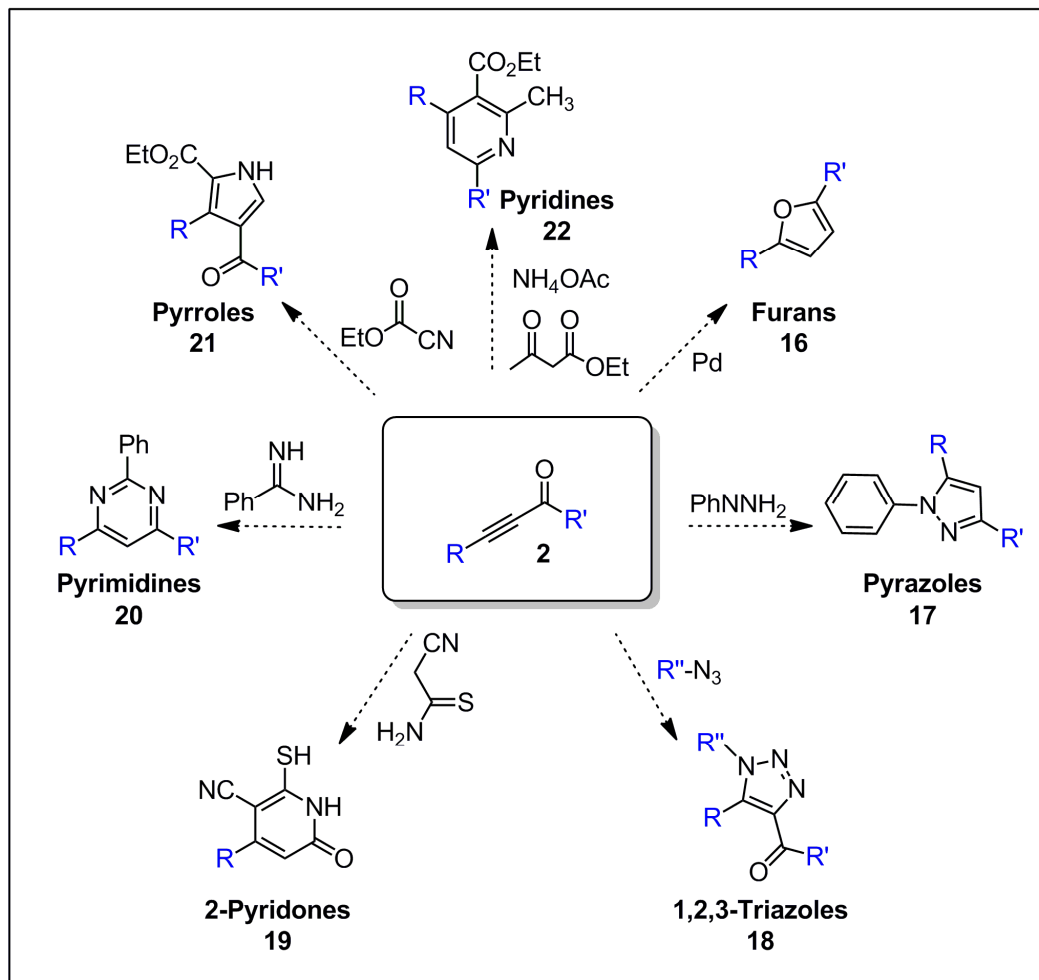
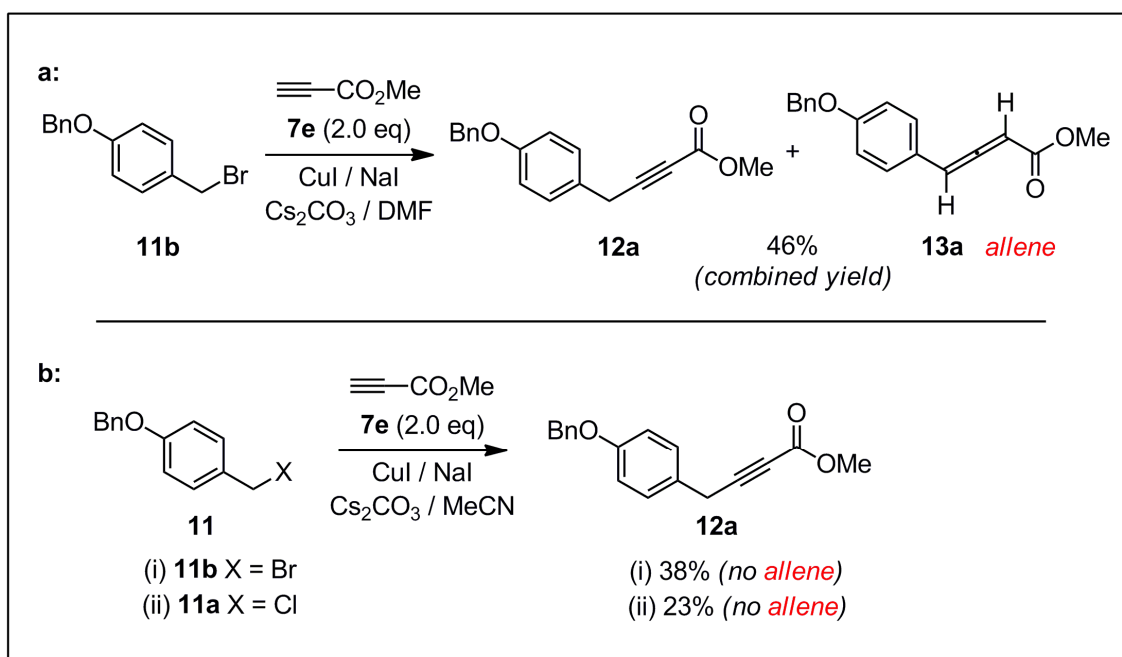


Figure 19. Accessible small molecule heterocycles from acetylenic esters and ketones.

Given the utility of these heterocycles, it is surprising that the reactions leading to products **16** – **22** in Figure 19 have only been accomplished using alkyl- and aryl-substituted propiolates. Therefore, our new methodology could potentially be proven useful not only for our own synthetic needs but also for the generation of new small-molecule heterocyclic products.⁹⁶

2.1.1 Optimization of Benzyl Alkyne Synthesis

Inspired by literature reports for the copper-mediated addition of terminal alkynes to allyl⁹⁷ or propargyl⁹⁸ halides, we first investigated whether the reaction of *p*-(benzyloxy)benzyl bromide (**11b**) and methyl propiolate (**7e**) to give the 4-aryl-2-butynoate **12a** would be possible under similar conditions (Cs₂CO₃, CuI, NaI, DMF).⁹⁸ From this reaction we observed the desired 4-aryl-2-butynoate (**12a**) along with its corresponding allene (**13a**) in a combined yield of 46% (Scheme 39a).



Scheme 39. Initial benzyl halide and terminal alkyne coupling results.

By changing the solvent to acetonitrile (Scheme 39b), we were able to prevent the formation of the undesired allene, although the yield remained low (38%). After further experimentation, we discovered that *p*-(benzyloxy)benzyl chloride (**11a**) also couples to methyl propiolate (**7e**) albeit in poorer yield (23%, Table 1, entry 1). This, however, was a promising result as benzyl chlorides are more readily available commercially and are more benchtop stable than benzyl bromides.

From these preliminary results, initial optimization of the methodology progressed using the cheaper 4-benzyloxybenzyl chloride (**11a**) with methyl propiolate (**7e**, Table 1).

Table 1. Optimization of reaction conditions for coupling 4-benzyloxybenzyl chloride (11a**) with methyl propiolate (**7a**) in the presence of 1.0 eq of copper (I) iodide.**

Reaction scheme: 4-benzyloxybenzyl chloride (**11a**) reacts with methyl propiolate (**7e**, 2.0 eq) in the presence of CuI (1.0 eq) and a base to yield 4-benzyloxybenzyl propiolate (**12a**).

| entry | base (eq) | additive | solvent | temp / time | conversion (%) ^{a,b} |
|-----------|--|--------------------------|---------------------------|-------------------|-------------------------------|
| 1 | Cs ₂ CO ₃ (1.0) | Nal | MeCN | r.t. / 24h | 25 (23) |
| 2 | Cs ₂ CO ₃ (1.0) | Nal | THF | r.t. / 24h | <5 |
| 3 | Cs ₂ CO ₃ (1.0) | Nal | 1:1 MeCN:H ₂ O | r.t. / 24h | 20 |
| 4 | Cs ₂ CO ₃ (1.0) | Nal | MeCN | r.t. / 48h | 36 |
| 5 | Cs ₂ CO ₃ (1.0) | Nal | MeCN | 40°C / 24h | 80 (75) ^c |
| 6 | Na ₂ CO ₃ (1.0) | Nal | MeCN | r.t. / 24h | 59 |
| 7 | K ₂ CO ₃ (1.0) | Nal | MeCN | r.t. / 24h | 88 |
| 8 | K ₂ CO ₃ (1.0) | Nal + Bu ₄ NI | MeCN | r.t. / 24h | 94 (91) ^d |
| 9 | K ₂ CO ₃ (1.0) | Nal | MeCN | 40°C / 4h | 98 (96) ^d |
| 10 | K ₂ CO ₃ (2.0) | Nal | MeCN | 40°C / 4h | 100 (95) ^d |
| 11 | K₂CO₃ (2.0) | none | MeCN | r.t. / 24h | 99 (99) |
| 12 | K ₂ CO ₃ (2.0) | none | MeCN | r.t. / 24h | 62 ^e |
| 13 | K ₂ CO ₃ (2.0) | none | MeCN | 40°C / 24h | 100 (92) |

^aPercent conversion was measured by ¹H NMR. ^bNumbers in parentheses refer to isolated yield. ^cThe isolated product for this entry was contaminated with unidentified impurities. ^dThe isolated product for this entry was contaminated with traces of allene. ^e1.2 eq of methyl propiolate were used.

As shown in Table 1, acetonitrile (entry 1) was a better solvent than both THF (entry 2) and 1:1 acetonitrile/water (entry 3). A longer reaction time (entry 4) was not as effective for the conversion to product as was an increase in temperature to 40°C (entry 5),

although the latter isolated product was contaminated with unidentified impurities. Changing the base to sodium carbonate (entry 6) and subsequently potassium carbonate (entry 7) both had very positive impacts on the conversion to products. Addition of the phase-transfer catalyst tetrabutylammonium iodide (entry 8) again provided an improvement to the overall yield. However, a small amount of allene could be detected. The use of potassium carbonate at varying equivalents with elevated temperatures (entries 9 and 10) likewise led to higher yields; final products, however, were still contaminated with small amounts of allene.

Finally, we found that removing the sodium iodide additive and increasing the amount of potassium carbonate (entries 11 and 13) allowed for the isolation of clean product in excellent yield at both room temperature and at 40°C with no detectable (by ^1H NMR) allenic impurity. We also tried reducing the amount of alkyne used in the reaction from 2.0 equivalents to 1.2 equivalents (entry 12). This, however, resulted in a drastic decrease in the percent conversion to the desired product (**12a**).

In summary, the reaction conditions from Table 1 entry 11 (K_2CO_3 , CuI, MeCN, 24h, r.t.) were determined to be the most optimal for coupling 4-benzyloxybenzyl chloride (**11a**) with methyl propiolate (**7e**). As such, this set of reaction conditions was designated as method A and utilized for assessing the scope of our coupling reaction.

Based on mechanistic studies of similar Cu(I)-catalyzed bond forming reactions,^{97b,99} Figure 20 depicts a plausible reaction mechanism for the coupling of terminal alkynes (**7**) with benzyl halides (**11**).

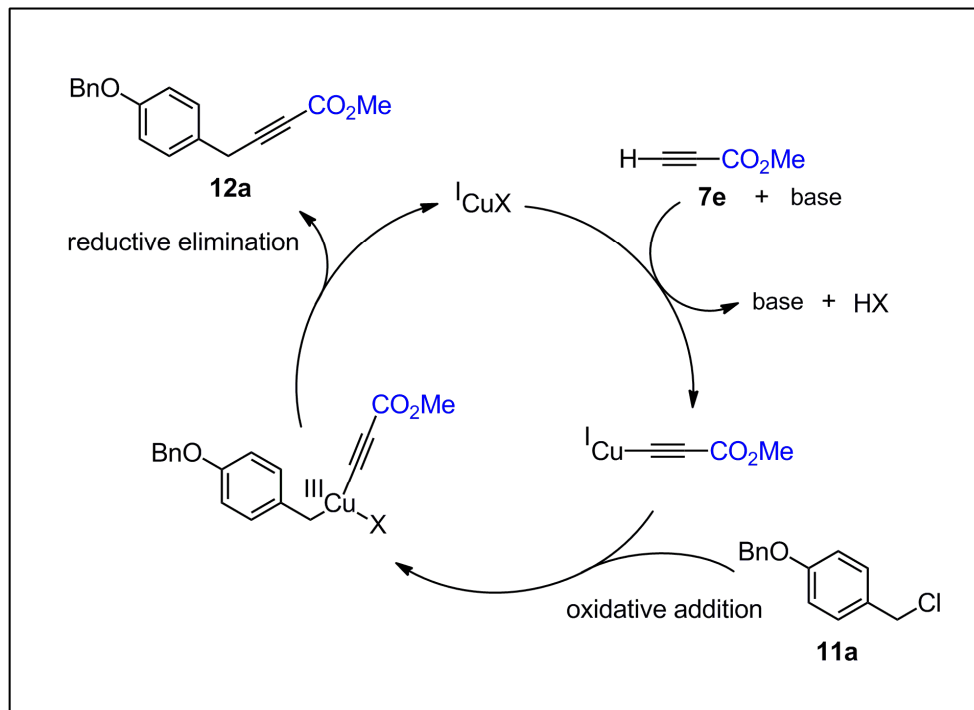


Figure 20. Possible mechanism for the generation of benzyl alkynes (12).

In the first-step of this catalytic cycle, oxidative addition of a benzyl halide (**11a**) to a Cu(I) alkyne species generates an unstable Cu(III) complex. This then undergoes reductive elimination to give the desired coupling product (**12a**).

2.1.2 Scope of the Reaction

Once these initial reaction conditions were optimized (method A), we explored the reactivity of an assortment of benzyl halides (**11**) with methyl propiolate (**7e**) as the coupling partner (Table 2).

Table 2. Variation of the benzyl halide coupling partner (11).

| entry | benzyl halide | method ^{a,b} | product | allene (%) ^c | isolated yield (%) |
|-------|---------------|-----------------------|------------|-------------------------|--------------------|
| 1 | | A | 12a | <1 | 99 |
| 2 | | A | 12a | <1 | 99 |
| 3 | | B | 12b | <1 | 75 ^d |
| 4 | | B | 12c | <1 | 83 |
| 5 | | B | 12d | 1 | 91 |
| 6 | | B | 12e | 3 | 90 |
| 7 | | B | 12f | 2 | 45 |
| 8 | | B | 12g | 13 | 87 |
| 9 | | A / B | 12h | n.d. | <10 |

^aMethod A: K₂CO₃ (2.0 eq), CuI (1.0 eq), r.t. ^bMethod B: K₂CO₃ (1.0 eq), CuI (1.0 eq), Bu₄Ni (1.0 eq), 40°C. ^cPercentage allene contaminant estimated by ¹H NMR integration. ^dOnly 10 mol% CuI was used.

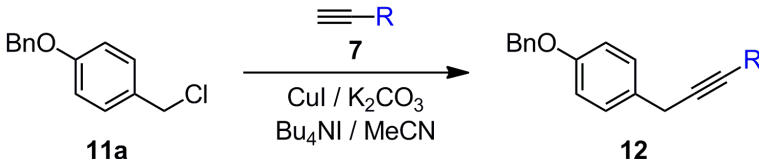
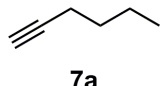

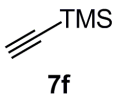
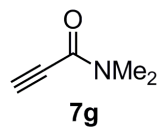
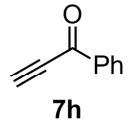
With the exception of benzyl halides *p*-(benzyloxy)benzyl chloride (**11a**, entry 1) and *p*-(benzyloxy)benzyl bromide (**11b**, entry 2), we obtained low percent conversions of reactants to products under method A conditions (e.g. when method A was applied to benzyl halide **11d**, only a 25% conversion to **12c** was observed). However, we found that heating the reaction mixture to 40°C and introducing the phase-transfer catalyst tetrabutylammonium iodide increased the rate of reaction (e.g. 83% isolated yield for **12c** was obtained) without promoting isomerization to the allene. This second set of reaction conditions (K₂CO₃, CuI, Bu₄NI, MeCN, 24h, 40°C) was therefore termed method B and was applied to the reactions in entries 3 – 9 of Table 2.

Overall we found that we could use a variety of electron-neutral or electron-rich benzyl chlorides and bromides in our coupling reaction with methyl propiolate (Table 2, entries 1 – 7). Other than benzyl halides **11a** and **11b** (entries 1 and 2), method B afforded much higher yields for the remainder of the substrates with relatively low levels of allene present. Under method B reaction conditions we were also able to successfully utilize substoichiometric quantities of copper iodide (10 mol%) for the benzyl halide **11c** to obtain **12b** in 75% isolated yield. In comparison, under method A conditions when substoichiometric quantities of copper iodide (10 mol%) were used for benzyl halide **11a**, only 6% conversion to **12a** was observed.

The coupling reaction was determined to be very tolerant towards a large variety of substituted benzyl halides including ortho-substituted substrates (entry 4), bulky meta-substituted substrates (entry 5), and benzyl halides containing a free hydroxyl group (entry 7). On the other hand, the reaction was less tolerant of electron-withdrawing substituents; product **12g** obtained from coupling *p*-chlorobenzyl chloride (**11h**) and methyl propiolate (**7e**) was shown to contain ~13% of the corresponding allene. Similarly, attempted coupling of methyl propiolate (**7e**) with *o*-fluorobenzyl chloride **11i** (entry 9) led to complex mixtures of products.

Finally, to determine the scope of this methodology the coupling of 4-benzyloxybenzyl chloride (**11a**) with various alkyne coupling partners (**7**) was explored by Wulff group summer undergraduate student Ryan Abel (Table 3).

Table 3. Variation of the alkyne coupling partner (7).

|  | | | | | |
|--|--|---|------------|-------------------------|--------------------|
| entry | alkyne | conditions ^a | product | allene (%) ^b | isolated yield (%) |
| 1 |  7a | 2.0 eq K ₂ CO ₃ 40°C / 4d | 12i | <1 | 68 |
| 2 |  7d | 1.0 eq K ₂ CO ₃ 40°C / 4d | 12j | <1 | 83 |
| 3 |  7f | 2.0 eq K ₂ CO ₃ 40°C / 24h | 12k | <1 | 99 |
| 4 |  7g | 1.0 eq K ₂ CO ₃ 40°C / 4d | 12l | <1 | 62 |
| 5 |  7h | 1.0 eq K ₂ CO ₃ 40°C / 24h | 12m | <1 | 60 |

^aCuI (1.0 eq) and Bu₄NI (1.0 eq) were added to all reactions. ^bPercentage allene contaminant estimated by ¹H NMR integration.

Surprisingly, this coupling strategy was successfully applied to more electron-rich alkynes such as **7a** (entry 1) and **7f** (entry 3) in reasonable yields. In addition, we were able to apply our methodology to a few representative acetylenic arenes (**7d**, entry 2), amides (**7g**, entry 4),¹⁰⁰ and ketones (**7h**, entry 5)¹⁰¹ all in equally reasonable yields. In addition, by increasing the length of the reaction times, we were able to obtain higher yields and more pure crude products which in turn simplified final product purification.

2.1.3 Summary of Coupling Methodology to access Benzyl Alkynes (**12**)

In summary, we have developed an efficient copper-mediated coupling of commercially available benzyl halides (**11**) to terminal alkynes (**7**), gaining access to a variety of 4-aryl-2-butynoates and related synthetic building blocks (**12**, Figure 21).

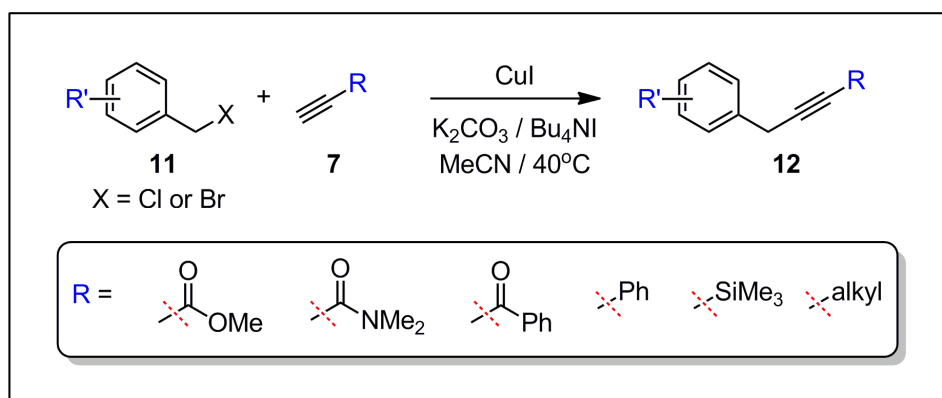
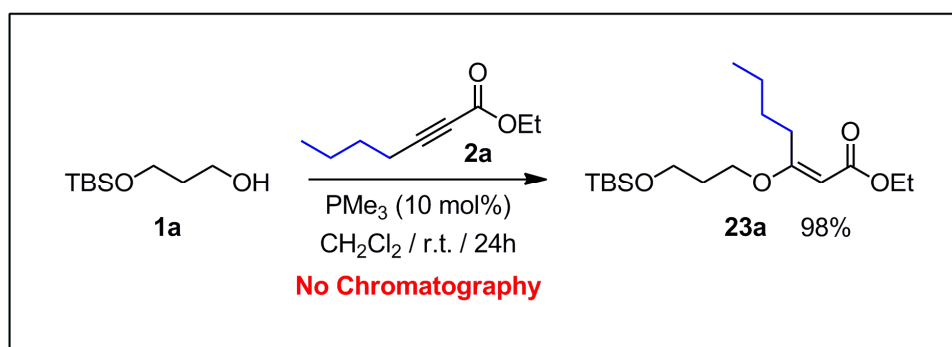


Figure 21. Summary of developed copper-mediated coupling methodology.

We have demonstrated that the reaction proceeds under mild conditions (at or below 40°C), requires only inexpensive reagents, and is relatively insensitive to small quantities of moisture. This methodology has proven effective not only for the development of starting materials for our iterative synthetic route but also for the synthesis of more substituted benzyl alkynes used in the synthesis of complex small molecules.⁹⁶

2.2.0 Conjugate Addition Optimization

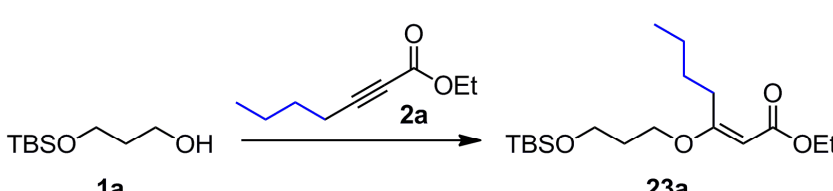
With a wide range of monomeric building blocks now at our disposal, we set out to optimize our iterative sequence. Building on chemistry by Inanaga and co-workers,¹⁰² we first attempted a conjugate addition of 1.0 equivalent of an alcohol (**1**, specifically **1a** for early optimization purposes) to 1.0 equivalent of a propiolate derivative (**2**, specifically **2a** for early optimization purposes) in dichloromethane using 10 mol% trimethylphosphine (Scheme 40).



Scheme 40. Phosphine catalyzed addition of an alcohol (1a) to an alkyne (2a).

Various concentrations of the phosphine catalyst were tested (1 – 10 mol%); however 10 mol% was determined to be the most optimal to maximize yield (Table 4).

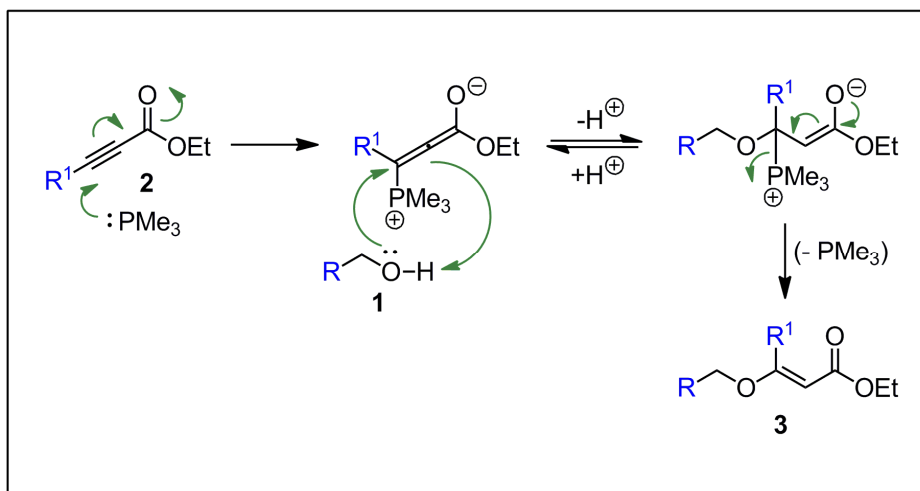
Table 4. Phosphine catalyst optimization for conjugate addition of 1a to 2a.



| entry | mol% PMe ₃ | solvent | temperature | time | % conversion |
|-------|-----------------------|---------------------------------|-------------|------|--------------|
| 1 | 1 mol% | CH ₂ Cl ₂ | r.t. | 24h | 0% |
| 2 | 5 mol% | CH ₂ Cl ₂ | r.t. | 24h | 50% |
| 3 | 10 mol% | CH ₂ Cl ₂ | r.t. | 24h | 100% |

Following the addition, filtration through basic alumina was found to remove any phosphine impurities present, providing clean ester product (**23**) with no chromatography required, generally high yields (greater than 90%), and good selectivity for the *E* isomer.

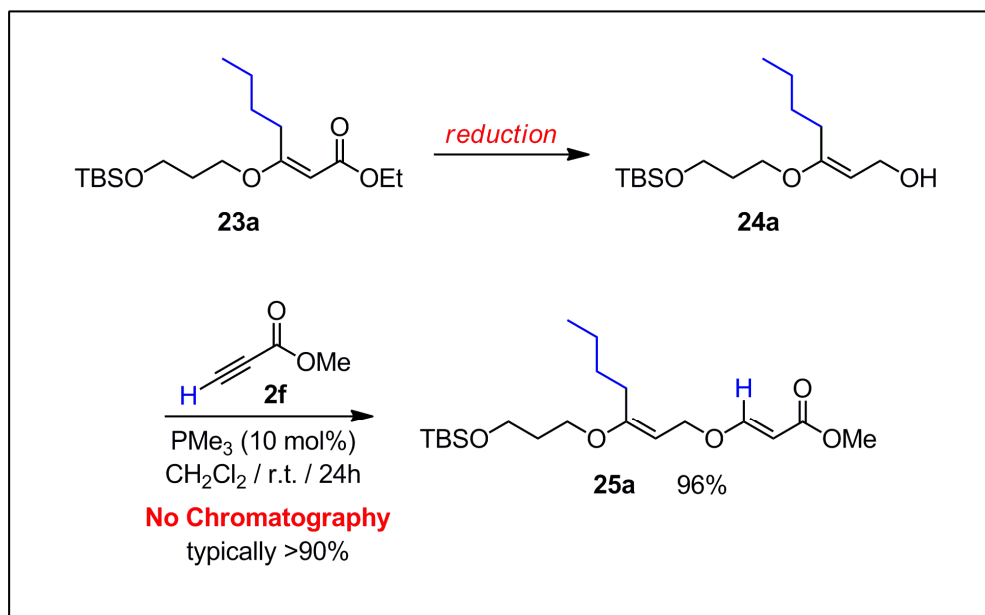
As shown in Scheme 41, it is thought that trimethylphosphine first attacks the β -carbon of the propiolate derivative (**2**) to give a phosphonium enolate intermediate.¹⁰²



Scheme 41. Proposed mechanism for the catalyzed addition of 1 to 2.

Conjugate addition of the alcohol (**1**) followed by elimination of the phosphine (to be recycled as a catalyst) affords the desired product **3**.

Following reduction of ester **23a** to alcohol **24a** (*vide infra*), we successfully completed a second conjugate addition to access bis-vinyl ether systems (**25**) in excellent yield (>90%, Scheme 42).



Scheme 42. Application of second conjugate addition to access bis-vinyl ether **25**.

We successfully expanded the scope of the reaction over what was originally reported¹⁰² and were able to demonstrate the flexibility of this methodology by using several different propiolates; methyl propiolate (**2f**, $R^1 = \text{H}$), ethyl 2-butynoate (**2g**, $R^1 = \text{CH}_3$), ethyl 2-heptynoate (**2a**, $R^1 = \text{butyl}$), phenyl-propionic acid ethyl ester (**2d**, $R^1 = \text{phenyl}$), and our newly synthesized 4-aryl-2-butynoates (**12**, $R^1 = \text{benzyl}$) all gave exclusively the *E* isomer (Figure 22).

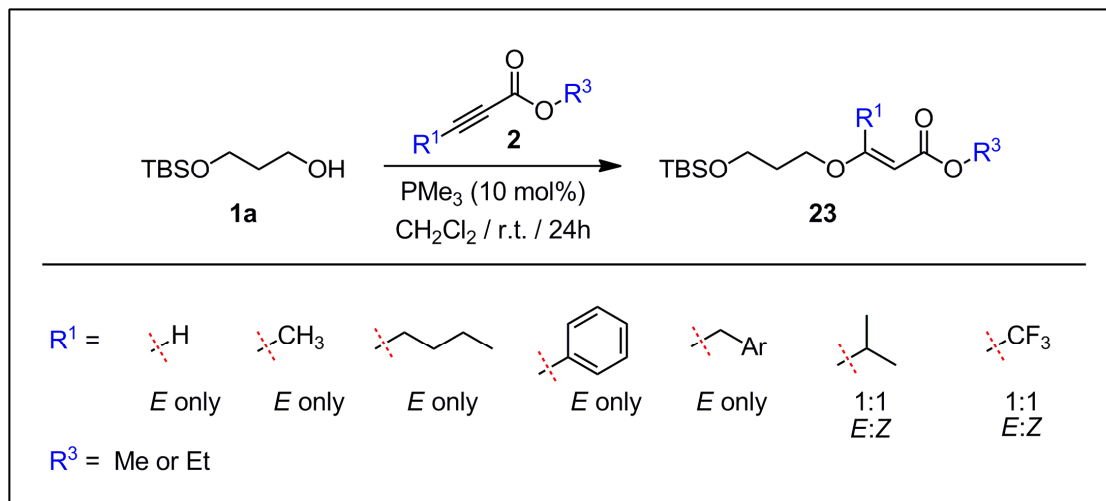


Figure 22. Summary of propiolates available for the addition step.

However, with more hindered electrophiles such as ethyl 4-methyl-2-pentynoate (**2b**, $\text{R}^1 = i\text{Pr}$),* or ethyl 4,4,4-trifluoro-2-butynoate (**2e**, $\text{R}^1 = \text{CF}_3$), the *E:Z* selectivity was substantially eroded; in such cases, the two isomers were separated chromatographically using triethylamine-treated silica gel before proceeding to the next step in the iterative sequence.

Although initial optimization of the conjugate addition step was carried out using a TBS-protected diol (**1a**), we were also able to expand the scope of the reaction by using several different alcohols (**1a** – **1e**, Figure 23).

* Conjugate addition optimization of substrates **2b** (to **1a**) and **1e** (to various propiolates **2**) was completed by Wulff group graduate student Natasha O'Rourke.

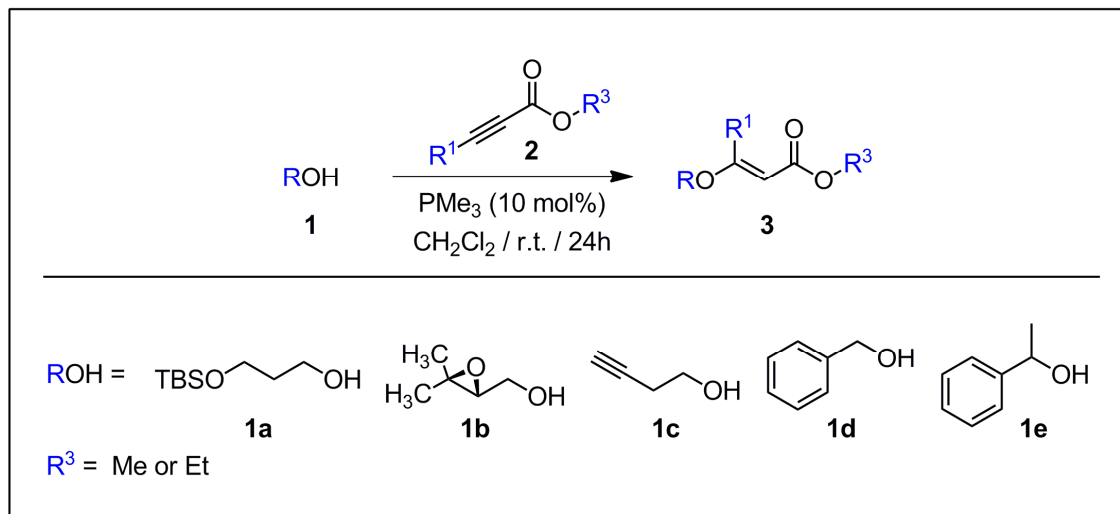


Figure 23. Summary of alcohols available for the addition iteration.

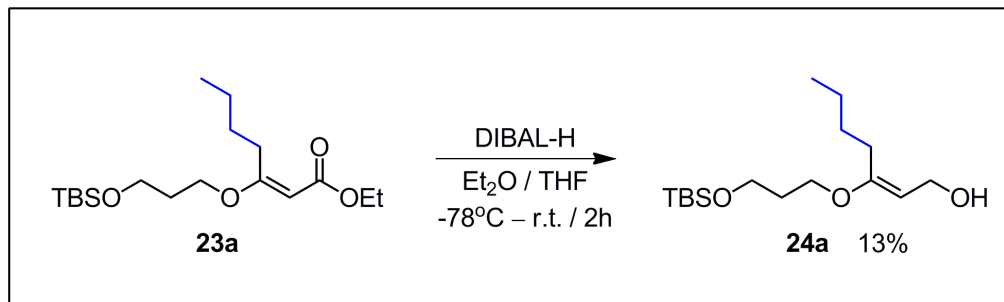
To our delight, the conjugate addition was compatible with a variety of alcohol starting materials (**1**) including hindered alcohols such as the 1-phenyl ethanol (**1e**)* and potentially reactive alcohols such as (3,3-dimethyloxiranyl)methanol (**1b**). The flexibility of this conjugate addition allowing for a large range of selected alcohols (**1**) and propiolates (**2**) broadens the scope and potential applications of our iterative synthesis. A more in depth discussion into specific combinations of alcohols (**1**) and propiolates (**2**) used will be provided in later chapters.

2.3.0 Reduction Optimization

In the next step of our iterative synthesis, diisobutylaluminum hydride promoted reduction of the ester function (**23**) was expected to afford the desired alcohol (**24**). However, initial attempts to reduce ester **23** to the corresponding alcohol (**24**) proved to be quite challenging.

Early reduction optimization was completed on substrate **23a**, where $\text{R}^1 = \text{butyl}$. We first attempted a DIBAL-H promoted reduction of **23a** to **24a** in a diethyl ether/THF solvent

system and with a temperature range of -78°C to room temperature over 2 hours (Scheme 43).



Scheme 43. Initial DIBAL-H reduction conditions to access alcohol 24a.

Although tlc analysis of the crude reaction mixture indicated complete consumption of starting material (**23a**), low yields were consistently obtained ($<14\%$) following column chromatography. After careful analysis of the crude product by tlc, we noted that when dissolved in CDCl_3 (the NMR solvent we were then using) a new spot would begin to appear on the tlc plate whereas when the product was dissolved in hexanes/ethyl acetate, only one spot (desired product) appeared. In addition, we also observed that if column chromatography was sufficiently slow, the product began to decompose (as shown by multiple spots following tlc analysis). These findings indicated to us that our vinyl ether intermediates were acid sensitive. As such, all future NMR samples for all oligo-vinyl ethers were run in deuterated acetone (acetone-d_6) and all silica gel used in column chromatography for these systems was pre-treated with triethylamine.

To determine the level of acid sensitivity in our oligo-vinyl ether systems, we took bis-vinyl ether **26a** through a series of stability tests (Table 5).

Table 5. Stability tests of 26a to determine the level of acid sensitivity in our oligo-vinyl ether systems.

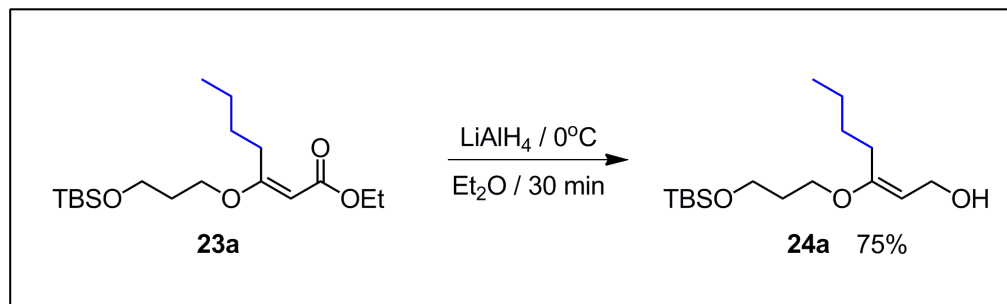
26a

| entry | NMR solvent | additive | result |
|-------|------------------------|-------------|---------------------|
| 1 | acetone-d ₆ | HCl (conc) | decomposed (<5 min) |
| 2 | acetone-d ₆ | HCl (10%) | decomposed (<1h) |
| 3 | acetone-d ₆ | acetic acid | stable (>1 week) |

Bis-vinyl ether **26a** decomposed very rapidly in acetone-d₆ with one drop of concentrated HCl present (<5 min). With one drop of 10% HCl, the bis-vinyl ether decomposed more slowly, however was still completely decomposed after 1 hour. Finally, when one drop of acetic acid was added to an acetonic solution of **26a**, the bis-vinyl ether was stable, even after one week at room temperature.

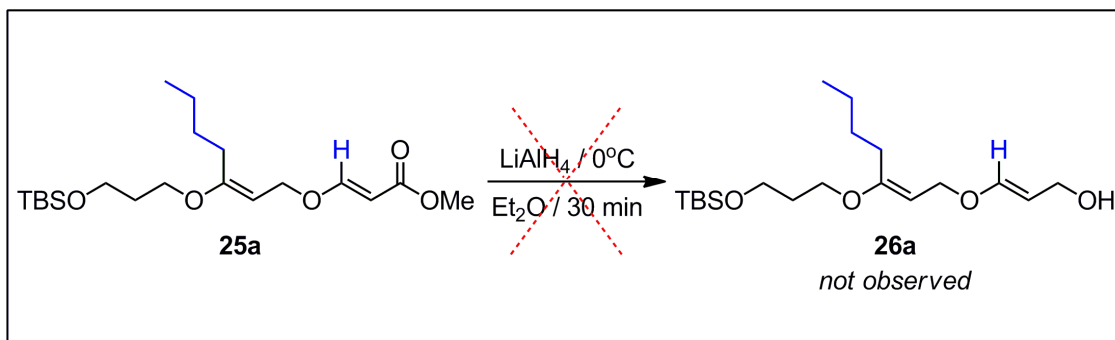
With this acid sensitivity knowledge in hand, we repeated the same reaction as shown in Scheme 43 using our updated purification and NMR conditions. Although a higher yield was obtained with the implemented changes, overall final yields were still very low (the best result was 28%).

Unable to increase the yield any further, we turned our attention to a lithium aluminum hydride reduction to convert **23a** to **24a** (Scheme 44).



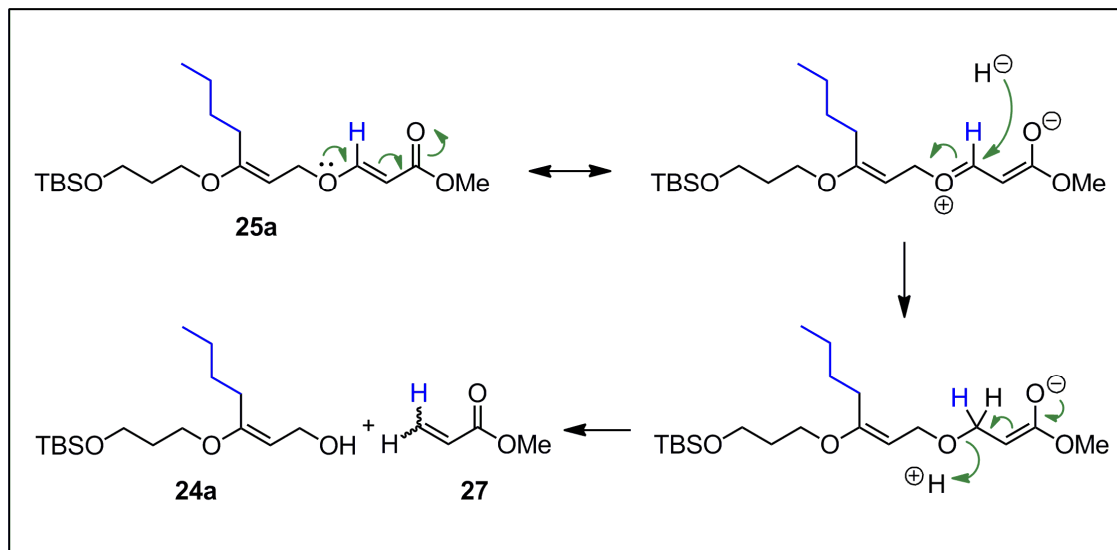
Scheme 44. LiAlH₄ reduction conditions to access 24 from 23.

In diethyl ether at 0°C over 30 minutes we obtained a reproducible yield of 75%. When the same set of conditions was applied to the bis-vinyl ether **25a**, however, no desired product (**26a**) was isolated (Scheme 45).



Scheme 45. Desired LiAlH₄ reduction of bis-vinyl ether 25a to 26a.

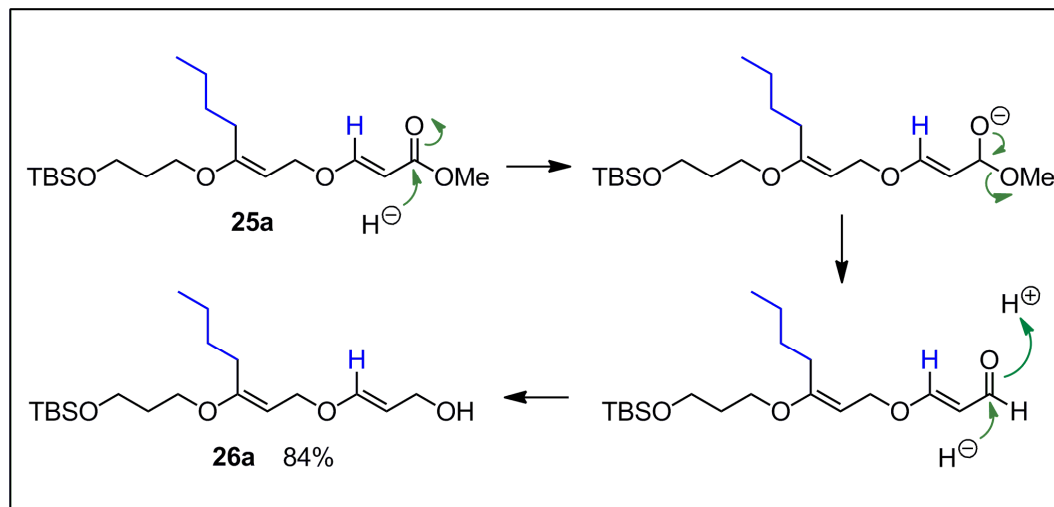
Rather than forming the desired alcohol product **26a**, the crude ¹H NMR spectrum indicated that a different alcohol was being formed with the segment of the molecule coming from the second conjugate addition missing (i.e. the R² = H fragment). After column chromatography, alcohol **24a** was cleanly isolated. Further investigation and optimization using various solvents (THF, diethyl ether, and hexanes), led us to discover that more polar solvents appear to favour an undesired hydride addition/β-elimination to provide product **24a** and likely **27**, although **27** was not isolated due to volatility issues (Scheme 46).



Scheme 46. Possible mechanism accounting for the regeneration of 24a.

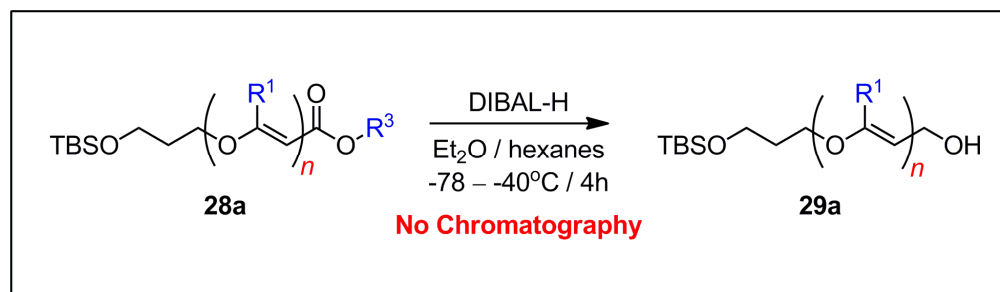
Under LiAlH_4 conditions with the bis-vinyl ether systems, no result other than isolation of **24a** could be obtained. Reduction of **25a** using lithium borohydride (LiBH_4) or sodium borohydride (NaBH_4) was also attempted. Unfortunately, under both sets of these reducing conditions only starting material **25a** was isolated.

We therefore returned our attention to the DIBAL-H promoted reduction of **25a** to **26a**. It was quickly discovered that by maintaining the reaction temperature at a constant -78°C (rather than letting the solution warm to room temperature) and by using a less polar solvent system (diethyl ether/hexanes) for the reaction, we were able to control where hydride attack occurred on the carbonyl group and obtain the desired alcohol product (**26a**) in good yield (84%, Scheme 47).



Scheme 47. Mechanism for the DIBAL-H promoted reduction of 25 to 26.

Further optimization revealed that the most optimal temperature range (to maximize yield while minimizing unwanted decomposition) was -78°C to -40°C over a 4 hour reaction period (Scheme 48).

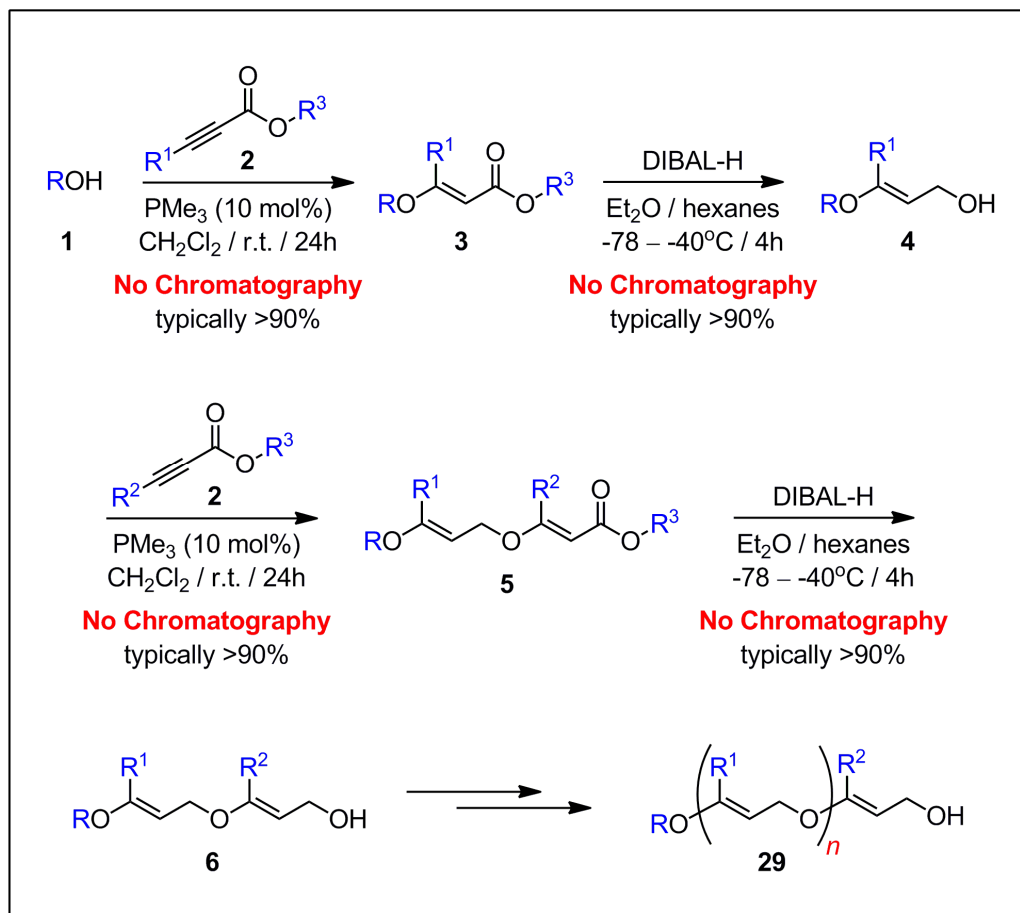


Scheme 48. DIBAL-H promoted reduction of the ester function to an alcohol.

After the reduction is complete, most aluminum based by-products could be removed with an aqueous work-up and filtration. Once again, although column chromatography is accessible for these systems, it was often not required, and high yields were generally achieved. This same set of reaction conditions was successfully applied to all oligo-vinyl ether systems attempted in this body of work (mono, bis, tris, etc.).

2.4.0 Summary and Concluding Remarks

Now that this chemistry is established, the addition and reduction steps can in principle be repeated as many times as desired to afford a series of oligo-vinyl ethers of varying lengths (**29**, Scheme 49).



Scheme 49. Summary for the iterative route to a library of oligo-vinyl ethers.

We were able to address all of our initial concerns, particularly our ability to access these species selectively, with mild, chromatography-free conditions. This iterative addition/reduction sequence could also form the basis for an automated or semi-automated assembly of oligo-vinyl ethers due to the lack of chromatographic purification steps required during this reaction sequence.

With a plethora of simple, easily-accessible starting material options, we now have an excellent starting point from which to apply some unique chemistry to these oligo-vinyl ether systems to generate interesting, complex small molecules (through cascade reactions) and other desirable targets.

Chapter 3: Analogues of Juvenile Hormone III

3.0.0 Introduction

Juvenile hormones (JH-0 – JH-III, Figure 24) are a class of hormones that play an important role in insect physiology by helping to regulate insect development,¹⁰³ reproduction,¹⁰⁴ and caste differentiation.¹⁰⁵ The concentration of juvenile hormone present during the growth cycle of an insect dictates the progression from larva to pupa to adult.¹⁰⁶

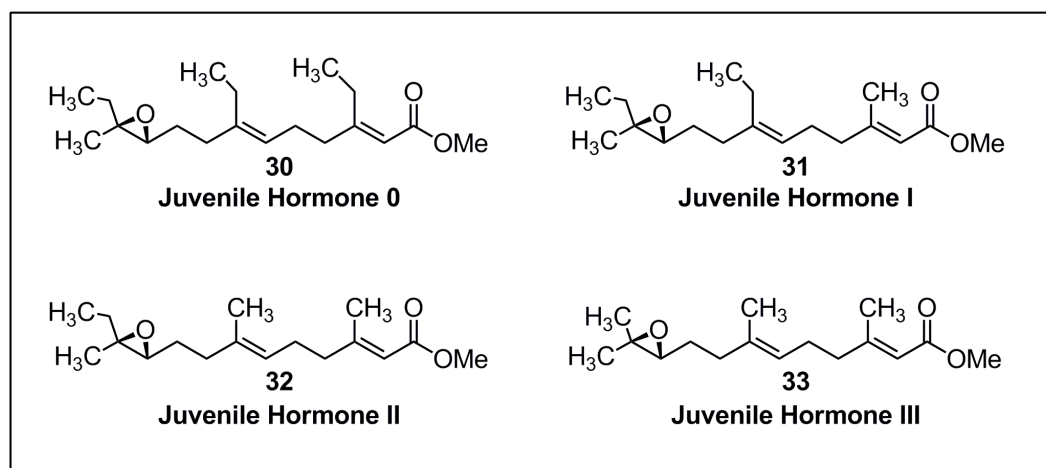


Figure 24. Structures of the insect juvenile hormones 0 – III.

While JH-0 – JH-II have only been found in Lepidoptera (butterflies and moths),¹⁰⁷ JH-III is found in most species of insects and is therefore considered to be the most important of these hormones.

For an insect to progress from larva to pupa and eventually to the adult stage, concentrations of juvenile hormone must be very low.¹⁰⁶ As such, structural analogues of JH-III (Figure 25) are now widely used as insect control agents. The presence of these

hormone mimics triggers impaired development which eventually leads to fatal morphological abnormalities.¹⁰⁶

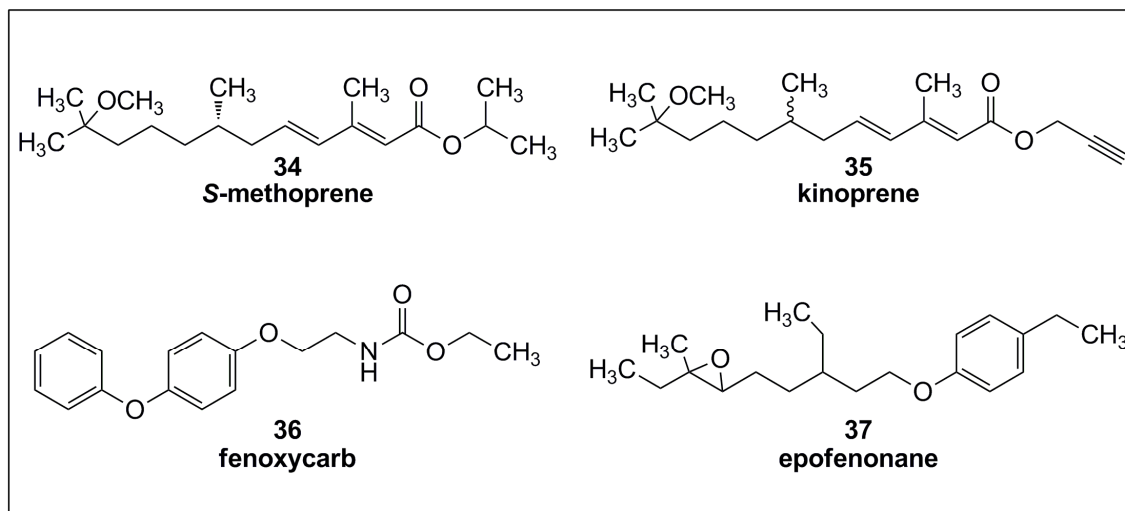


Figure 25. Structural analogues of JH-III used as insect control agents.

The most commercially relevant of these insect control agents is the *S*-enantiomer of methoprene. Commercialized in the 1970s, *S*-methoprene was the first successfully implemented biorational insecticide as it does not control target pests through direct toxicity but rather interferes with an insect's life cycle, preventing it from reaching maturity.¹⁰⁸

Although it is non-toxic to both mammals and birds, *S*-methoprene has been proven to be very active against an extensive range of insect pests and is now widely used for the control of mosquitoes, fire and pharaoh ants, Indian meal and tobacco moths, beetles, fleas (eggs and larvae), and flies (in agriculture).^{106,109} Unfortunately research has shown that *S*-methoprene is acutely toxic to certain species of fish, shrimp, and crabs,¹¹⁰ although no conclusive evidence has been provided as to the threat that this pesticide would have to these species in their natural environment. A link between methoprene use and deformities in amphibians has also been postulated,¹¹¹ however this remains controversial.¹¹²

Of perhaps greater ecological concern, methoprene has been shown to have toxic effects at very low concentrations on larval and adult crustaceans.¹¹³ In addition, anecdotal evidence suggests that there is a possible link between methoprene use and fatal abortive moults in lobsters.¹¹³ This may be due to mimicry by methoprene of the crustacean hormone methyl farnesoate.¹¹⁴ Methyl farnesoate is the non-epoxidized precursor of juvenile hormone III that is thought to play similar roles in crustaceans to the juvenile hormones in insects (Figure 26).¹¹⁵

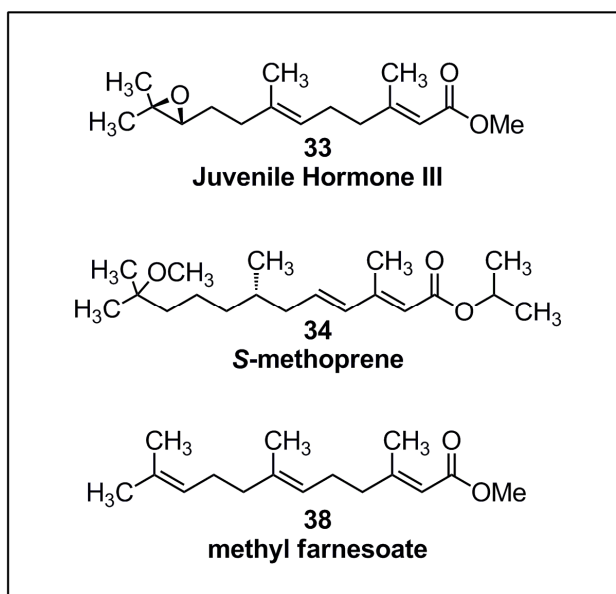


Figure 26. Structures of juvenile hormone III, S-methoprene, and methyl farnesoate.

Although methoprene can be degraded both microbially¹¹⁶ and photochemically,¹¹⁷ it is lipophilic and chemically robust. As a result, following its transport from treated water supplies, methoprene bioaccumulates at the bottom of the ocean where larval and juvenile crustaceans develop. Studies have shown that methoprene concentrates up to 125-fold over the surrounding sea water in the hepatopancrease (critical to homeostasis), nervous and gonadal tissue, and epidermal cells of adult crustaceans leading to increased morbidity and mortality.¹¹³ Given these results indicating the tissue susceptibility in crustaceans to methoprene, it seems that a more rapidly degradable analogue of juvenile hormone III might be useful for certain applications.

With this in mind, we set out to synthesize a variety of bis- and mono-vinyl ether analogues of juvenile hormone III (Figure 27) using the (iterative) protocols discussed in the previous section, hypothesizing that inclusion of the sensitive vinyl ether function would make the target compounds more prone to decomposition.¹¹⁸

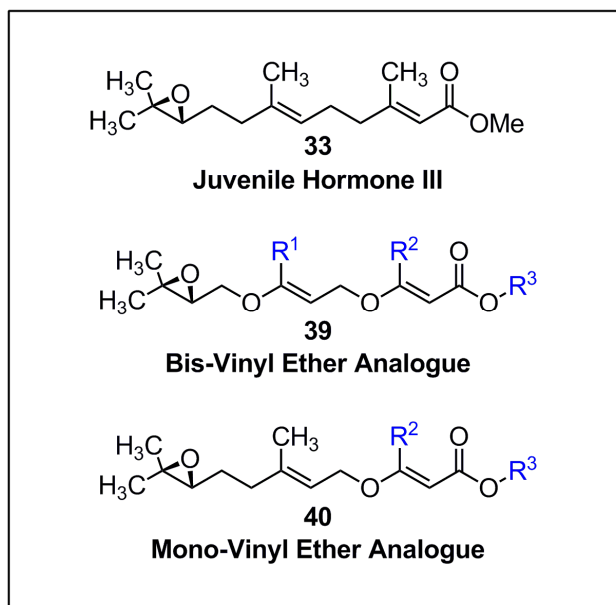
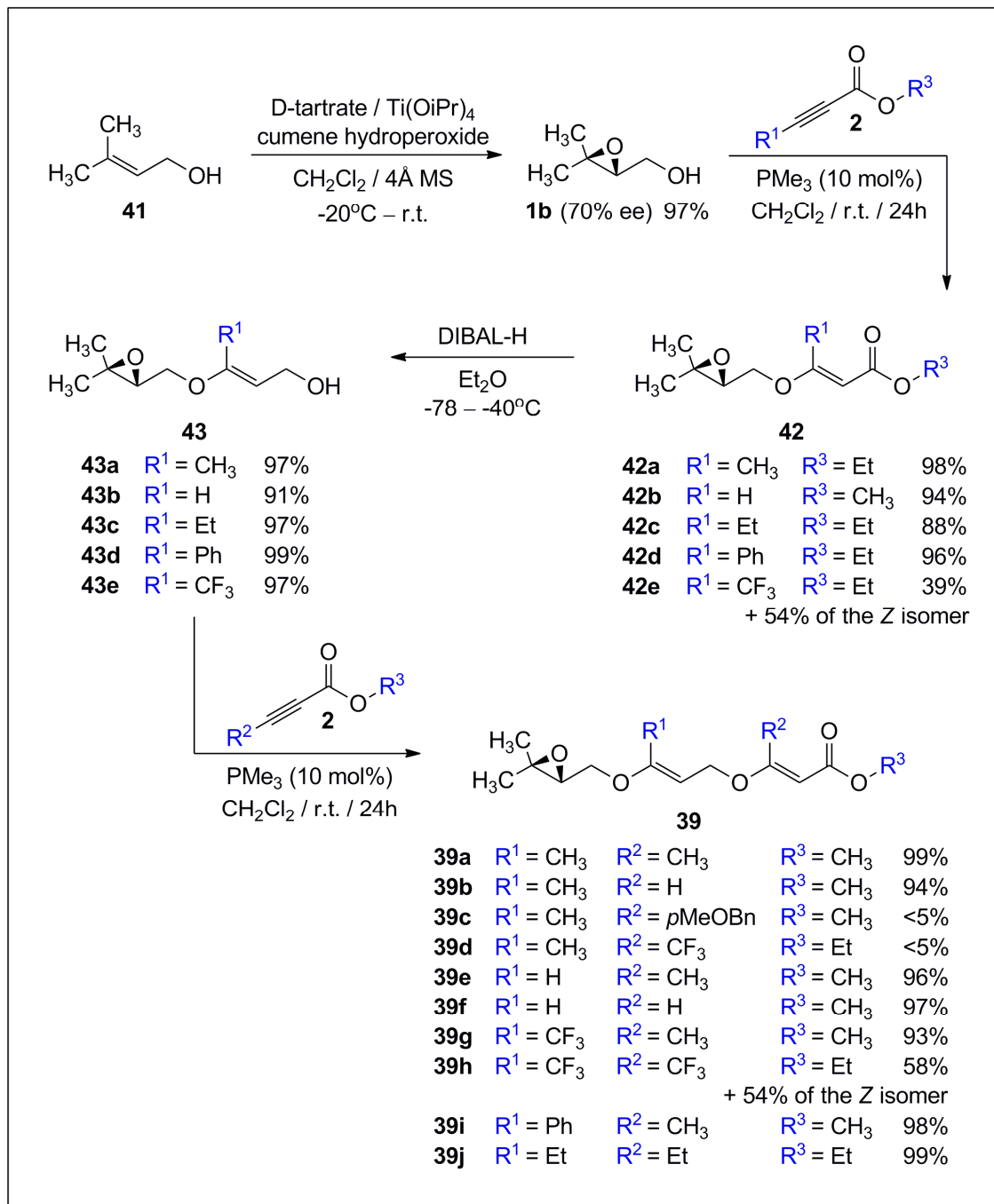


Figure 27. General structure of target juvenile hormone III analogues 39 and 40.

3.1.0 Synthesis of Juvenile Hormone III Analogues

3.1.1 Synthesis of Bis-Vinyl Ether Analogues (39)

We first synthesized a series of bis-vinyl ether analogues **39** through our iterative conjugate addition¹⁰²/reduction/conjugate addition sequence using the epoxy alcohol **1b**¹¹⁹ and a variety of methyl or ethyl alkynoates **2** (Scheme 50).



Scheme 50. Iterative synthesis of the bis-vinyl ether juvenile hormone III mimics.

Alkyne **2g** was purchased from Acros Organics while **2f** and **2h** were available commercially from Sigma-Aldrich. Alkynoates **2d**,⁸² **2e**,⁸³ and **12a**⁸⁸ were prepared following protocols presented in Chapter 2 (Figure 28).

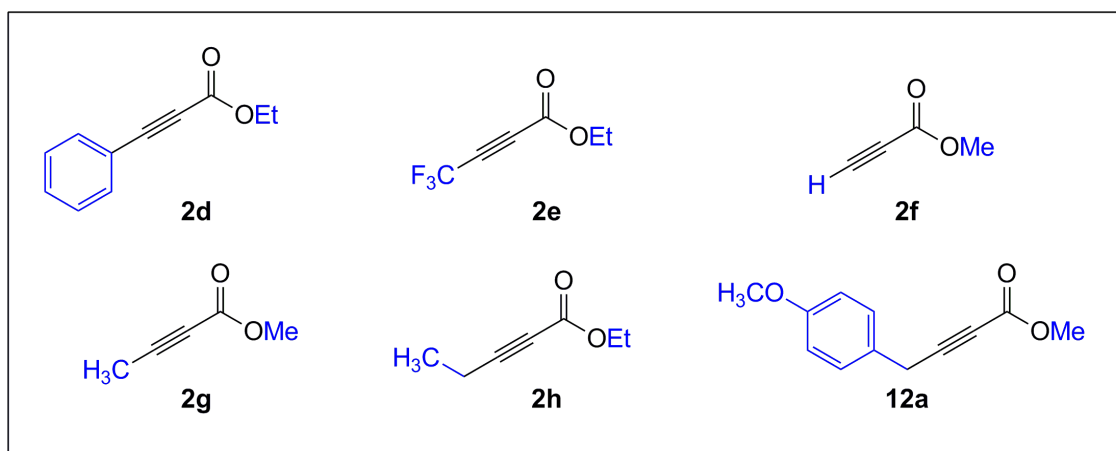
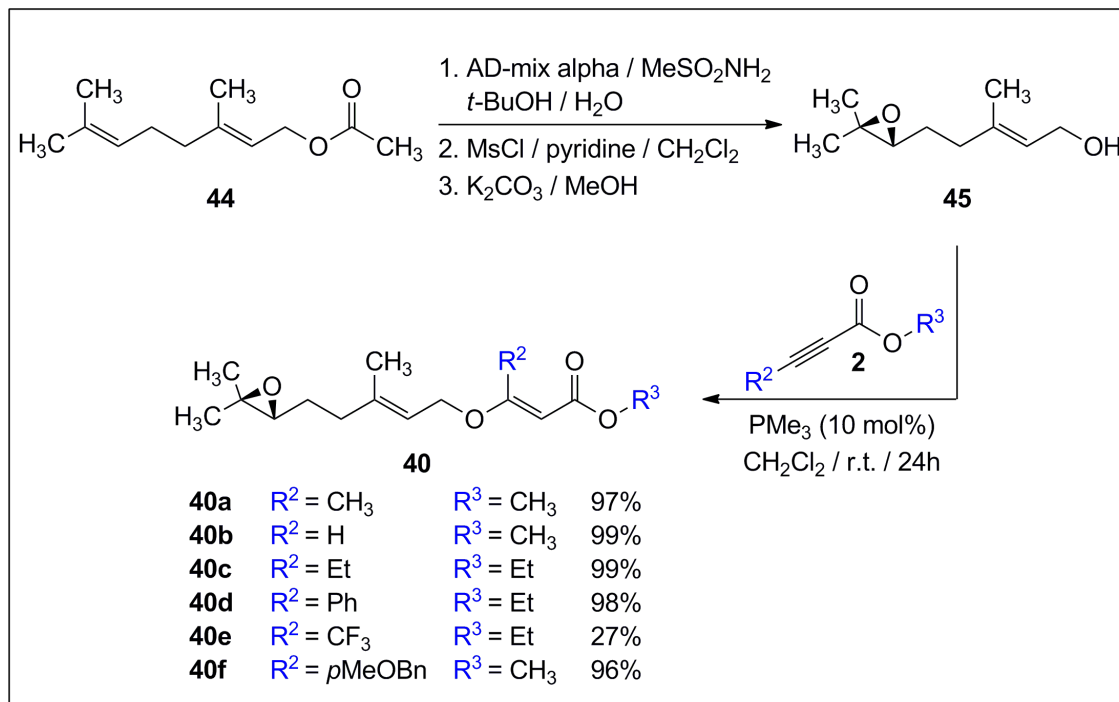


Figure 28. Alkyne building blocks utilized in the synthesis of JH-III mimics.

The individual conjugate addition and reduction steps were generally high yielding and in almost all cases a single geometrical isomer (*E, E*) was isolated for each of the target compounds. In the specific case of conjugate additions to ethyl 4,4,4-trifluoro-2-butynoate (**2e**, leading to the generation of **42e** or **39h**), a mixture of geometrical isomers was formed. This result is consistent with our initial iterative synthesis development (summarized in Figure 22) where we observed that conjugate additions to **2e** ($R = CF_3$) and **2b** ($R = iPr$) give mixtures of geometrical isomers; when taken together it suggests that the *E:Z* mixtures are due to steric effects although we cannot rule out electronic factors. These isomers could, however, be cleanly separated through column chromatography to give the desired *E* product. With the exception of **39c** and **39d**, all of the bis-vinyl ether analogues reported in Scheme 50 were sufficiently stable for purification by flash column chromatography over triethylamine-treated silica gel.

3.1.2 Synthesis of Mono-Vinyl Ether Analogues (**40**)

To provide a wide range of vinyl ether analogues, we also synthesized a series of mono-vinyl ethers (**40**) using the same phosphine-mediated conjugate addition¹⁰² of alkynes **2** (Figure 28) to the known epoxy alcohol **45** (Scheme 51).¹²⁰



Scheme 51. Synthesis of the mono-vinyl ether juvenile hormone mimics.

Once again we observed high yields for all synthesized compounds (>95%) with the exception of the trifluoromethyl-substituted analogue **40e**. We attribute the instability (and therefore low yield) of this compound as well as the complete instability of bis-vinyl ether **39d** to the large electronic mismatch between the electron-rich ‘western’ olefin (between C-6 and C-7, e.g. $R^1 = \text{CH}_3$ for the bis-vinyl ether system) and the very electron-poor ‘eastern’ olefin (between C-2 and C-3, e.g. $R^2 = \text{CF}_3$, present in both the mono- and bis-vinyl ether systems). These and other electronic trends will be discussed in more detail in section 3.2.3. Finally, like the bis-vinyl ether substrates, all of the mono-vinyl ether analogues in Scheme 51 were sufficiently stable for purification by flash column chromatography over triethylamine-treated silica gel.

3.2.0 Stability of Analogues in Moist Air and Water

Simple, less substituted bis-vinyl ethers (where $R = \text{H}$, e.g. compound **46**, Scheme 52) have previously been reported in the literature.^{121,122} More complex bis-vinyl ether

systems of the type described here (**39**) are unknown. For that reason, we felt it was important to undertake careful examination of their stability before proceeding with any biological assays. In addition, we felt it was essential to gain a well-rounded understanding of the physical and chemical properties of these oligo-vinyl ethers to aid in substrate selection in future Wulff group projects.

Insect-control experiments are typically conducted in either warm, humid growth chambers (mimicking a tropical environment) or in water (for water-breeding species like mosquitos). As such, we sought to characterize the behaviour of our vinyl ether compounds under similar conditions.

3.2.1 Stabilities of Bis-Vinyl Ether Analogues

Stability measurements were completed by Dr. Jeremy Wulff. Three different methods were used when assessing the stabilities of our juvenile hormone analogues. In the first method, referred to here as method A, compounds were dissolved in deuterated acetone (along with 4,4'-dibromobiphenyl as an internal standard) and deposited onto several watch glasses. After allowing the solvent to evaporate for 1 hour in a fume hood, the watch glasses were transferred to a cell-culture incubator maintained at 37°C, 5% CO₂, and >90% relative humidity. Periodically a watch glass was removed from the incubator and the sample composition was evaluated by ¹H NMR.

In the second method, which we refer to from here on as method B, compounds were dissolved in a 1:1 mixture of deuterated methanol and D₂O and left at room temperature. Periodically, the samples were evaluated by ¹H NMR.

Finally, for the third method, referred to here as method C, compounds were dissolved in a 1:1 mixture of deuterated methanol and acidified (with H₂SO₄) D₂O and left at room temperature. Again, samples were evaluated at regular intervals by ¹H NMR. Method C

was only applied to the more stable mono-vinyl ethers, since even neutral aqueous conditions were sufficient to rapidly decompose the bis-vinyl ether substrates.

We first applied method A to each of the bis-vinyl ether analogues (Table 6).

Table 6. Stabilities of bis-vinyl ether analogues of JH-III.

| Product | | | | $t_{1/2}$ | |
|------------|----------------------------------|----------------------------------|----------------------------------|-----------------------|-----------------------|
| | | | | method A ^a | method B ^b |
| 39a | R ¹ = CH ₃ | R ² = CH ₃ | R ³ = CH ₃ | 17h | <5 min |
| 39b | R ¹ = CH ₃ | R ² = H | R ³ = CH ₃ | 3.5h | <5 min |
| 39c | R ¹ = CH ₃ | R ² = <i>p</i> MeOBn | R ³ = CH ₃ | — ^e | — ^e |
| 39d | R ¹ = CH ₃ | R ² = CF ₃ | R ³ = Et | — ^e | — ^e |
| 39e | R ¹ = H | R ² = CH ₃ | R ³ = CH ₃ | 39h | 28 min |
| 39f | R ¹ = H | R ² = H | R ³ = CH ₃ | >24h ^c | 73 min ^d |
| 39g | R ¹ = CF ₃ | R ² = CH ₃ | R ³ = CH ₃ | >14d | n/a ^f |
| 39h | R ¹ = CF ₃ | R ² = CF ₃ | R ³ = Et | >14d | n/a ^f |
| 39i | R ¹ = Ph | R ² = CH ₃ | R ³ = CH ₃ | >14d | n/a ^f |
| 39j | R ¹ = Et | R ² = Et | R ³ = Et | 60h | <5 min |

^a Method A: 37°C, 5% CO₂, >90% relative humidity
^b Method B: 1:1 CD₃OD:D₂O, room temperature
^c Monitoring was complicated by volatility of the substrate
^d Decomposition occurred via hydrolysis
^e Sufficiently pure compound was not available for testing
^f The substrate was insoluble in 1:1 CD₃OD:D₂O

Figure 29 shows the change in the ¹H NMR spectrum (normalized to the concentration of internal standard) for bis-vinyl ether **39a** (decomposing to the Claisen rearrangement product **48a**) over time.

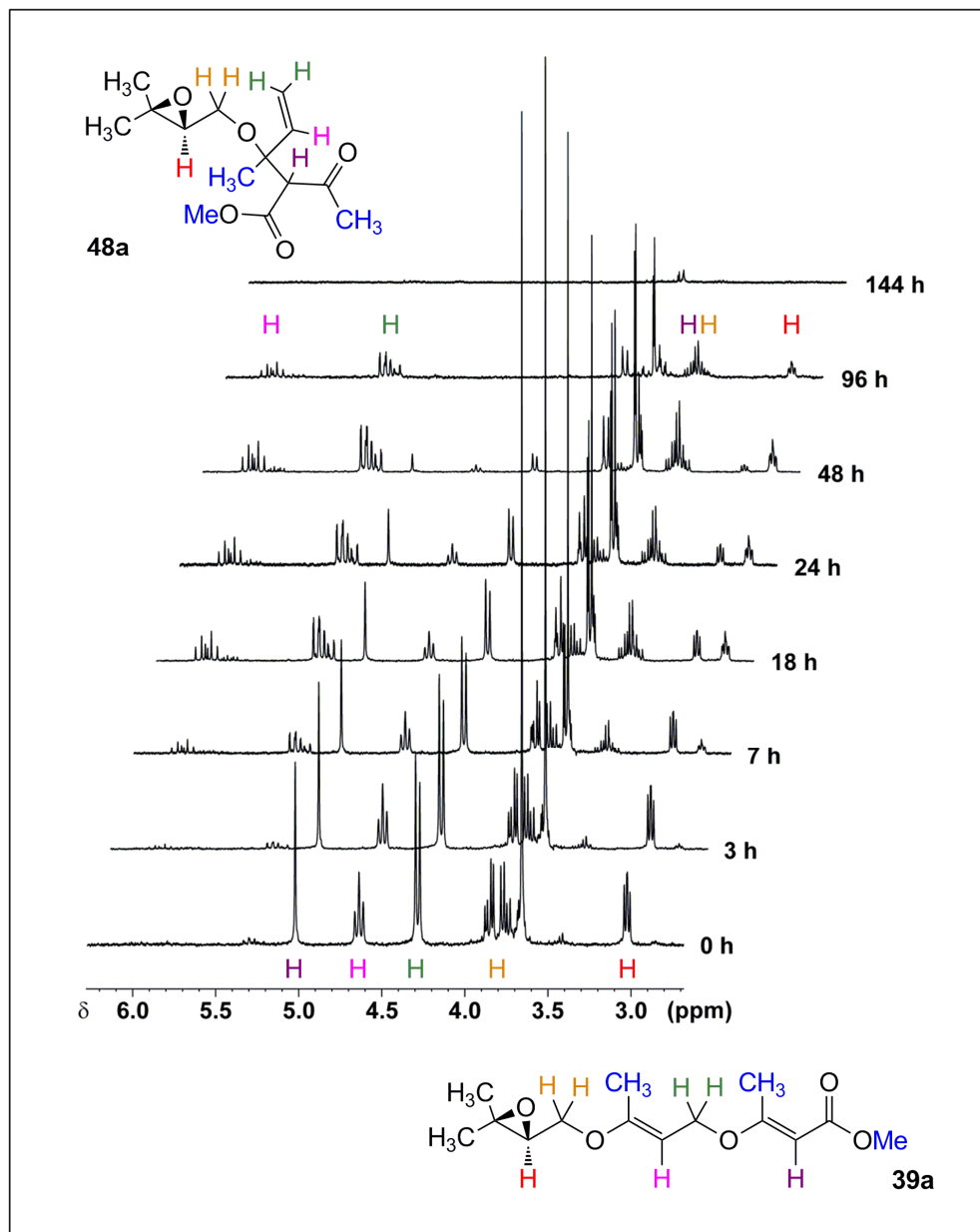
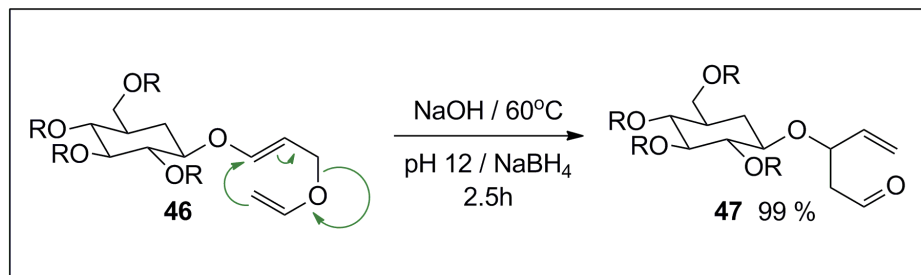


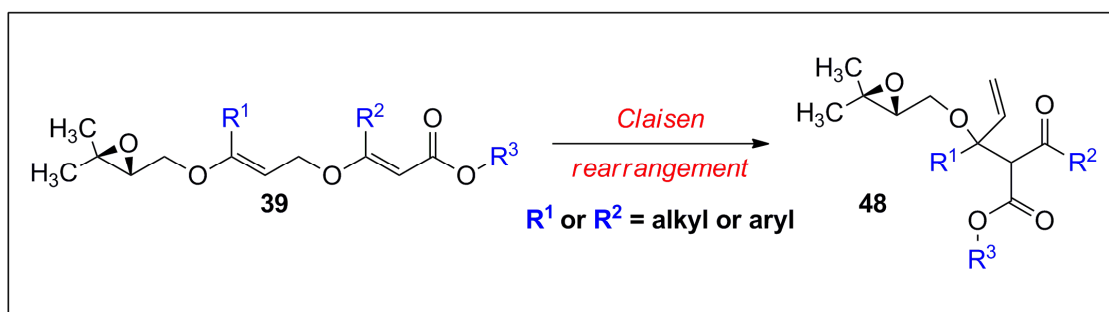
Figure 29. Decomposition of vinyl ether 39a via method A.

Claisen rearrangement of less substituted bis-vinyl ethers under aqueous conditions and moderate temperatures have been previously reported by Lubineau and co-workers,¹²¹ and were attributed to hydrophobic effects (Scheme 52).



Scheme 52. Water-promoted Claisen rearrangement using glyco-vinyl ether substrates.

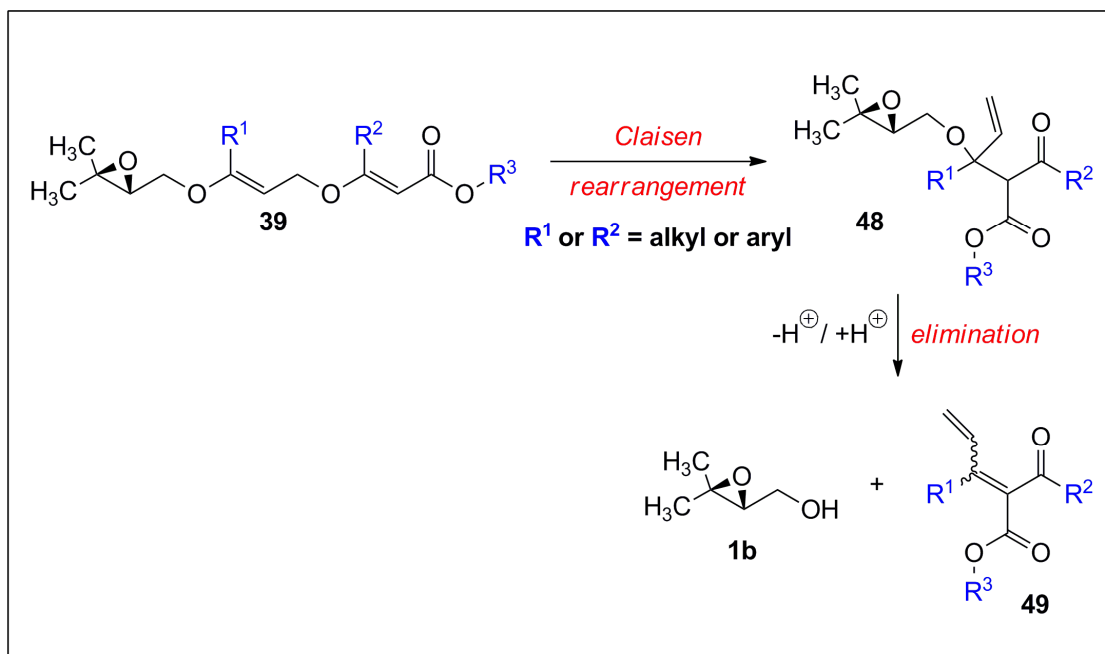
In a similar fashion, our substrate (**39a**) smoothly underwent Claisen rearrangement to afford ketone **48a** ($R^1 = R^2 = R^3 = \text{CH}_3$) with a half-life of 17 hours, the structure of which was confirmed by ^1H NMR, ^{13}C NMR, and HRMS (Scheme 53).



Scheme 53. Primary decomposition pathway for the bis-vinyl ethers (39**).**

Significantly, continued monitoring of the reaction showed that **48a** decomposed even further into volatile by-products, such that after 144 hours (1 week) the ^1H NMR spectrum showed mostly just the internal standard. We ruled out simple evaporation of **48a** (MW = 270 g/mol) under these conditions by the fact that **40a** (MW = 268 g/mol) was not lost in an identical assay (Table 7). The long-term incubation of **39a** in 1:1 $\text{CD}_3\text{OD}/\text{D}_2\text{O}$ led to the appearance of olefinic signals at 7.1 ppm (dd, $J = 17, 11$ Hz) and 6.6 ppm (dd, $J = 17, 11$ Hz). These signals are consistent with the formation of two geometric isomers of a conjugated diene and led to the identification of **49a** ($R^1 = R^2 = R^3 = \text{CH}_3$, structure confirmed by HRMS) along with several other species, suggesting that during the final decomposition step elimination of the epoxy alcohol starting material

takes place to generate volatile by-products **49** and **1b**, which are then lost under the conditions of method A (Scheme 54). To some extent, this satisfies the goal of this project, which was to generate juvenile hormone III analogues which were not environmentally accumulative.

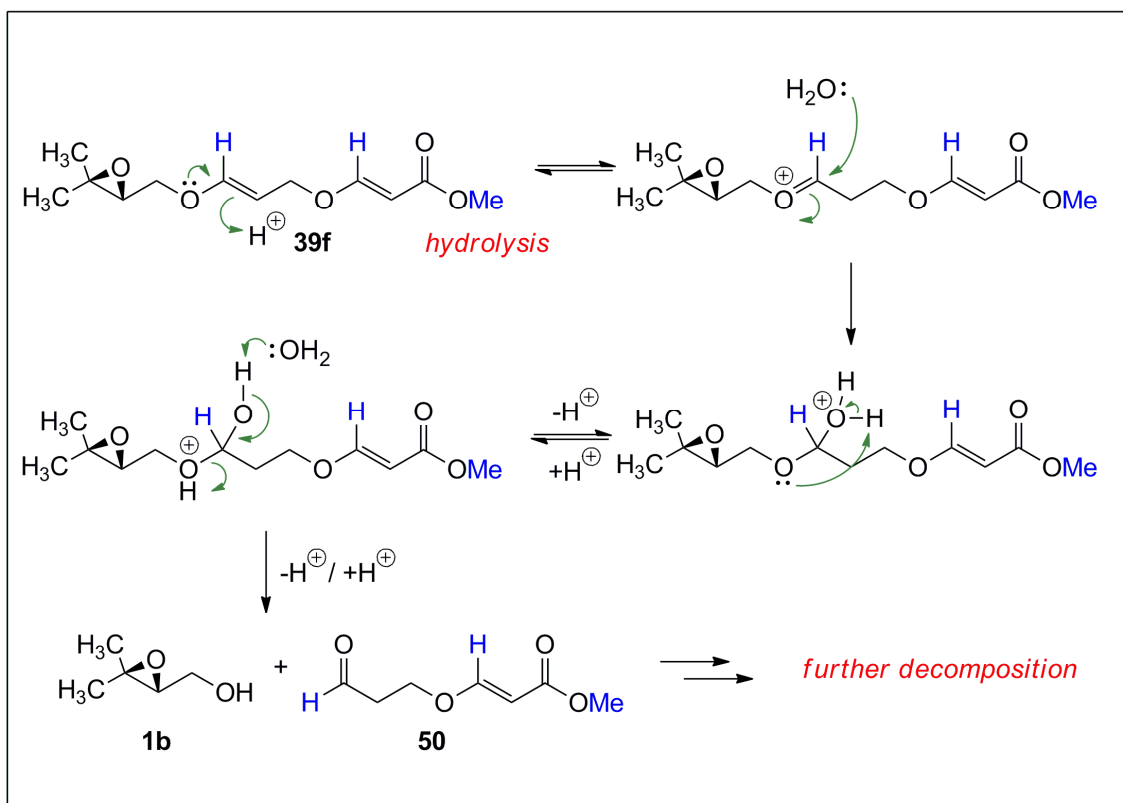


Scheme 54. Mechanistic pathway for Claisen rearrangement/elimination of 39 to 49.

Under the conditions of method A, we obtained a wide range of stabilities for our bis-vinyl ethers (Table 6). Compounds **39b** (3.5 hours), **39e** (39 hours), and **39j** (60 hours) all decomposed similarly to **39a** (Scheme 54) while **39g**, **39h**, and **39i** were robust (stable for >14 days) under the method A conditions. As such, we applied our second set of decomposition conditions (method B) to test the stability of our bis-vinyl ether analogues in aqueous solution.

As was observed for method A, under the conditions of method B (Table 6) compounds **39a**, **39b**, **39e**, and **39j** decomposed via Claisen rearrangement, but with greatly accelerated rates (minutes instead of hours). Unfortunately aqueous stabilities for **39g**, **39h**, and **39i** could not be evaluated as the compounds were insoluble in 1:1

CD₃OD/D₂O. This immiscibility with water may in fact be playing a role in the observed stabilities of **39g**, **39h**, and **39i** using the method A decomposition conditions. Under the conditions of method A and B, Claisen rearrangement was not observed for substrate **39f** ($R^1 = R^2 = \text{H}$, $R^3 = \text{CH}_3$). Instead, this substrate underwent vinyl ether hydrolysis in aqueous solution to regenerate the epoxy alcohol starting material (**1b**, Scheme 55).



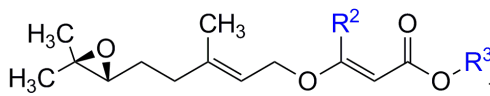
Scheme 55. Mechanistic decomposition pathway for hydrolysis of 39f to 1b.

The presumed aldehydic co-product (**50**) from this hydrolysis reaction was not observed in large amounts, likely due to further decomposition.

3.2.2 Stabilities of Mono-Vinyl Ether Analogues

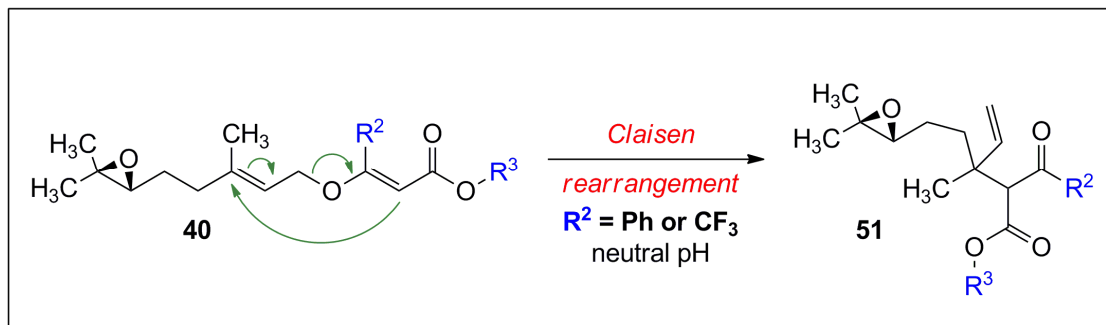
The same decomposition trials as those used for the bis-vinyl ether series were then carried out for the mono-vinyl ether analogue series (**40**, Table 7).

Table 7. Stabilities of mono-vinyl ether analogues of JH-III.

| Product |  | | $t_{1/2}$ | | |
|------------|---|---------------------|--------------------------|--------------------------|--------------------------|
| | | | method A ^a | method B ^b | method C ^c |
| 40a | $R^2 = \text{CH}_3$ | $R^3 = \text{CH}_3$ | >14d | >14d | 3h ^e |
| 40b | $R^2 = \text{H}$ | $R^3 = \text{CH}_3$ | >14d | >14d | >14d |
| 40c | $R^2 = \text{Et}$ | $R^3 = \text{Et}$ | >14d | >14d | 2.5h ^e |
| 40d | $R^2 = \text{Ph}$ | $R^3 = \text{Et}$ | 8.8d ^d | 21h ^d | 2.7h ^e |
| 40e | $R^2 = \text{CF}_3$ | $R^3 = \text{Et}$ | 14h ^d | <5 min ^d | <5 min ^d |
| 40f | $R^2 = p\text{MeOBn}$ | $R^3 = \text{CH}_3$ | >14d | >14d | 21h ^e |

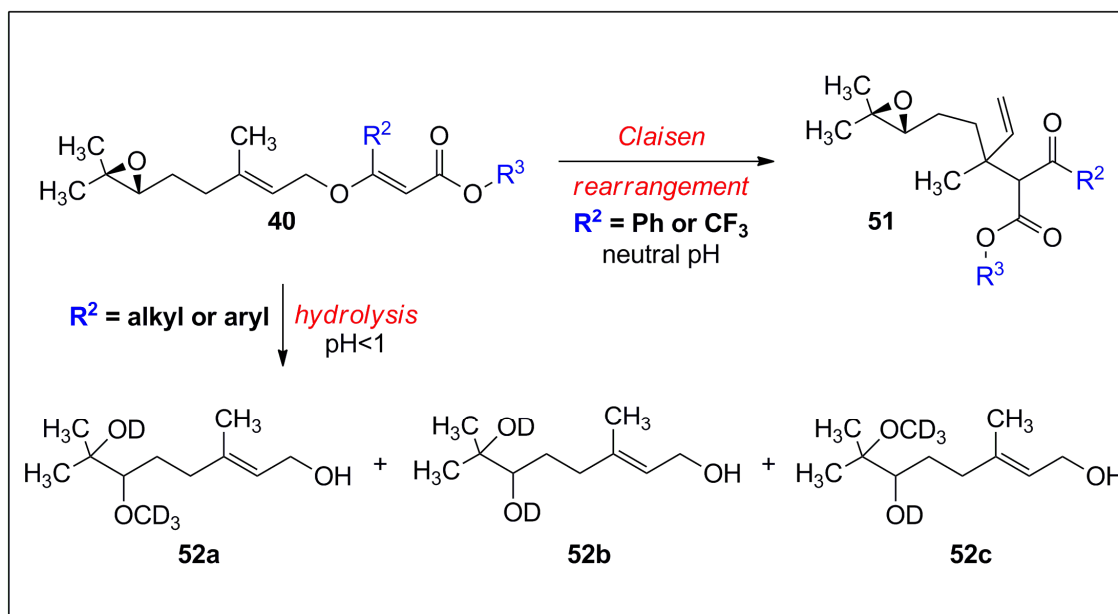
^a Method A: 37°C, 5% CO₂, >90% relative humidity
^b Method B: 1:1 CD₃OD:D₂O, room temperature
^c Method C: 1:1 CD₃OD:D₂O, pH<1, room temperature
^d Decomposition occurred mostly via Claisen rearrangement
^e Decomposition occurred mostly by vinyl ether hydrolysis

Under both sets of conditions (method A and B), analogues **40a**, **40b**, **40c**, and **40f** were stable with half-lives of greater than 14 days. Substrate **40d** decomposed slowly via Claisen rearrangement while **40e** underwent more rapid decomposition through the same pathway (Scheme 56).



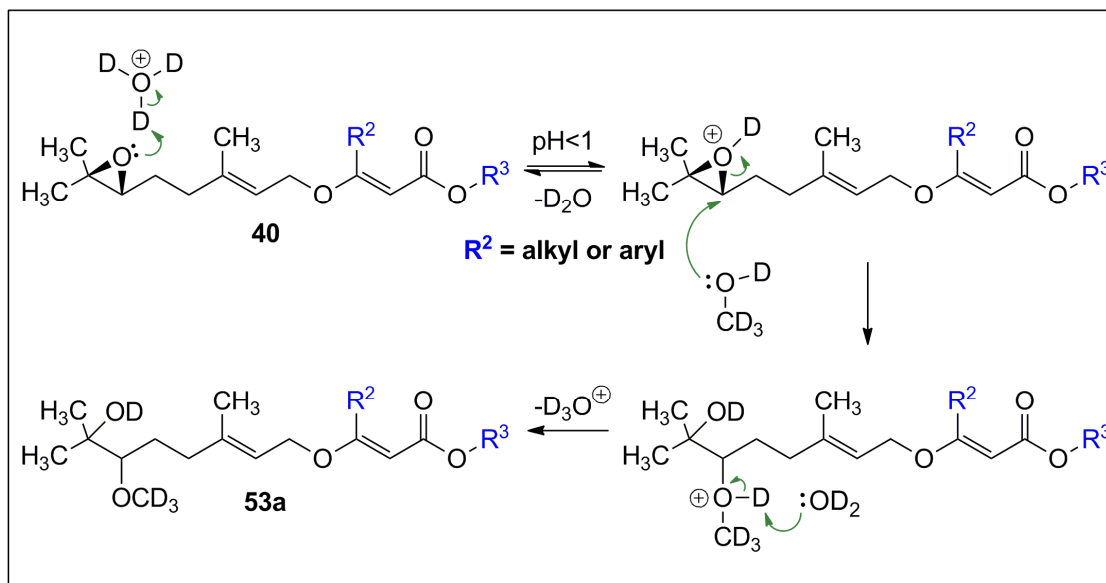
Scheme 56. Mechanistic pathway for Claisen rearrangement of 40 to 51.

To further evaluate the stabilities of the more robust mono-vinyl ether analogue series, we subjected the substrates to the acidic (pH<1) method C conditions (Scheme 57).



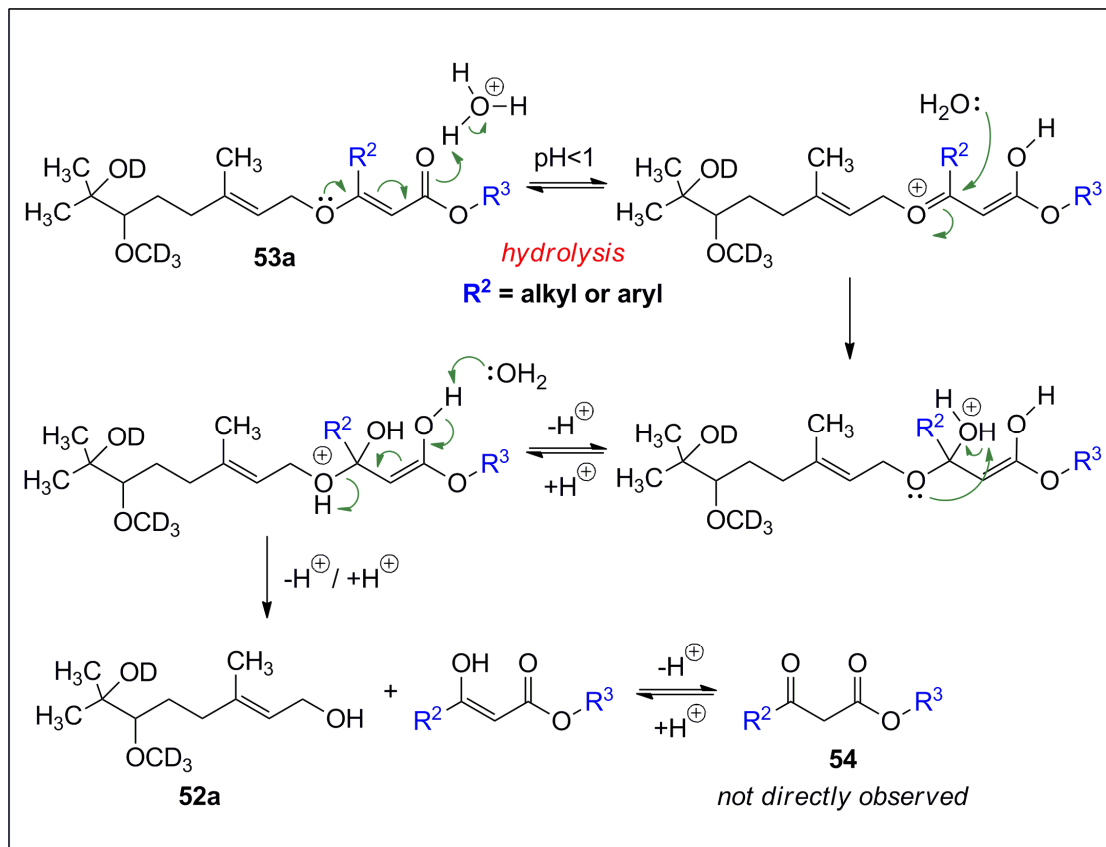
Scheme 57. Decomposition pathways for the mono-vinyl ethers (40).

Although small amounts of Claisen rearrangement products were still detected, under these more forcing conditions (method C) we primarily obtained vinyl ether hydrolysis products (**52a** – **52c**). Under these conditions, the epoxide also opened rapidly, with a half-life of less than 5 minutes (Scheme 58).



Scheme 58. General mechanistic decomposition pathway of 40 to 53a.

The vinyl ether groups, however, hydrolyzed with an analytically convenient range of rates (method C, Table 7) from 2.4 hours to greater than 14 days (Scheme 59).



Scheme 59. General mechanistic decomposition pathway for the hydrolysis of **53a**.

3.2.3 Summary of Vinyl Ether Analogue Stabilities

Overall our bis- and mono-vinyl ether analogues of juvenile hormone III exhibited a wide range of stabilities with half-lives ranging from minutes to weeks under assay conditions that have some relevance to real world scenarios. Decomposition occurred by either Claisen rearrangement or vinyl ether hydrolysis, depending on the nature of the substituents (steric and electronic factors associated with the substituents) and the assay conditions employed.

The large electronic mismatch between the electron-rich ‘western’ olefin (between C-6 and C-7, e.g. $R^1 = \text{CH}_3$) and very electron-poor ‘eastern’ olefin (between C-2 and C-3, e.g. $R^2 = \text{CF}_3$) made the bis-vinyl ether substrate **39d** too unstable to isolate and accounts

for the very low yields observed for the mono-vinyl ether substrate **40e** (Figure 30a). On the other hand, small electronic mismatches between an electron-rich ‘western’ olefin and an electron-poor ‘eastern’ olefin (or an electron-neutral ‘western’ olefin and a very electron-poor ‘eastern’ olefin) accelerated to different degrees the rate of Claisen rearrangement observed in our vinyl ether systems (Figure 30b). For example, **39a** reacts much faster than **40a**, **40e** reacts much faster than **40a**, and **39g** is more stable than **39a**.

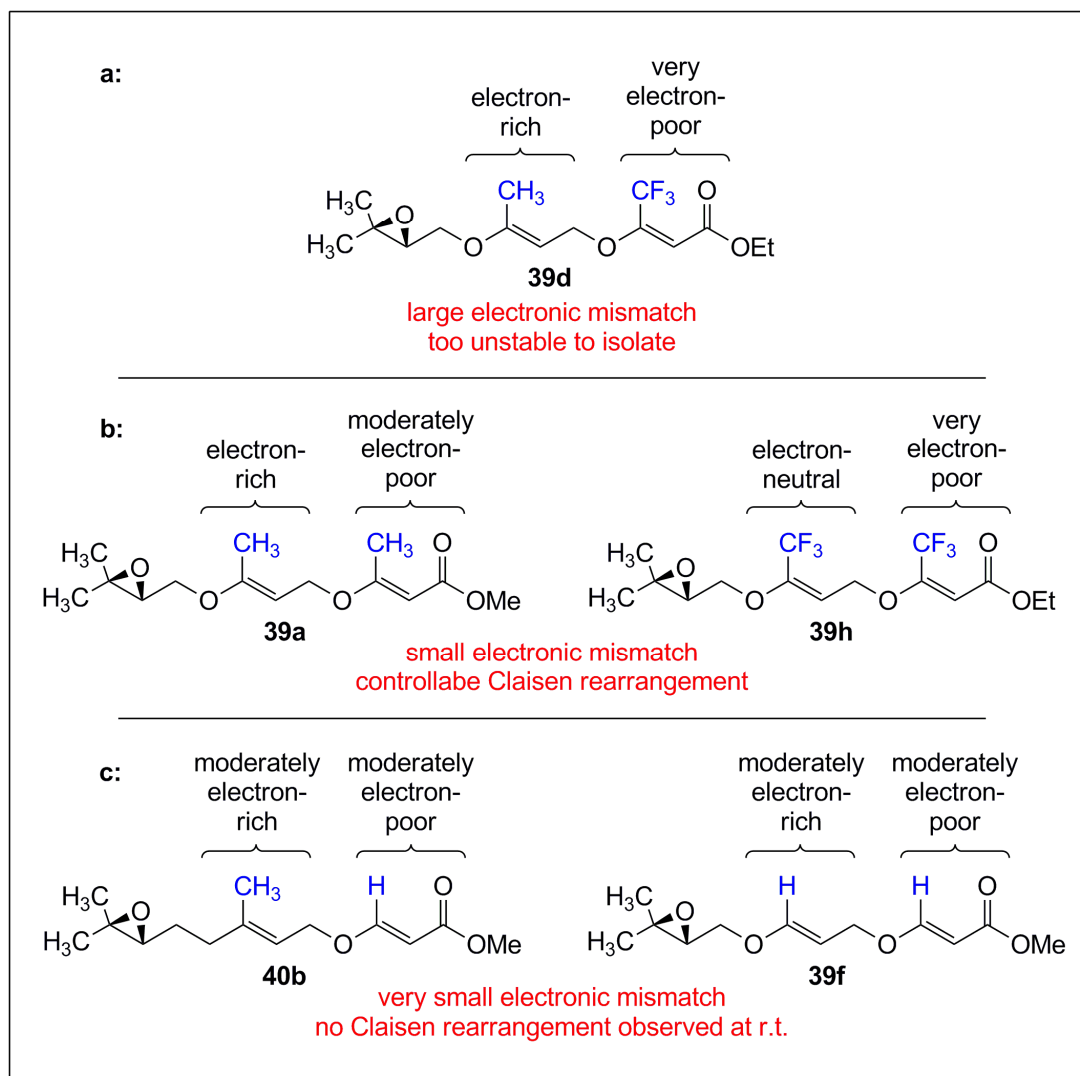


Figure 30. Summary of general electronic trends observed for vinyl ether analogues.

In the cases where very little or no electronic mismatch was present between the two olefins (e.g. **39f**, **40a**, **40b**, **40c**, and **40f**) no Claisen rearrangement was observed, or in cases where Claisen rearrangement was sufficiently slow (e.g. **40d**) decomposition occurred via vinyl ether hydrolysis (Figure 30c). More electron-rich vinyl ether analogues generally hydrolyzed faster (e.g. under method C conditions **40c**>**40a**>**40b**). However, a lack of water solubility for the more lipophilic substrates (e.g. **40d** and **40f**) likely contributed to reducing the rate of hydrolysis for some substrates.

To the best of our knowledge, the observed trends for our bis-vinyl ether systems are not reported elsewhere. As such, they will be a very useful precedent for the exploitation of vinyl ethers for other synthetic applications we wish to attempt.

3.3.0 Biological Assays

With knowledge of the relative stabilities of our candidate juvenile hormone III mimics, we took two analogues (**39a** and **40a**) forward for testing in a series of biological assays using juvenile hormone III as a positive control (Figure 31).

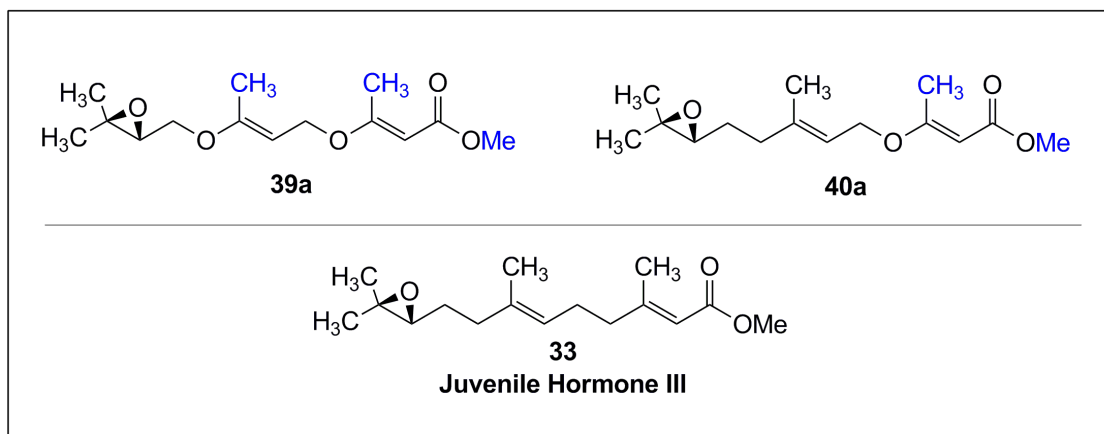


Figure 31. Analogues of juvenile hormone III selected for biological assays.

3.3.1 Biological Assays in Insects

In collaboration with Dr. Steve Perlman from the University of Victoria, Department of Biology, we first set up a series of biological assays to test our compound's function in *Drosophila melanogaster* (the common fruit fly). *Drosophila melanogaster* is one of the most regularly used model organisms in biology due to the fact that the species is easy to take care of, breeds quickly, and can lay many eggs in a short period of time (females can lay up to 100 eggs per day).¹²³

Following a procedure by Riddiford and co-workers,¹²⁴ we tested each of our compounds through feeding experiments. Using a mushroom based agar media, we set up 4 experiments, each with a different compound: bis-vinyl ether **39a**, mono-vinyl ether **40a**, JH-III, and finally a vehicle control (with no compound). For each experiment (consisting of 5 trials), 2 μL of a 10 mg/mL solution of the test compound in acetone was deposited on approximately 5 mL of the mushroom agar diet to give the insects a diet containing 4 ppm of compound (Figure 32).

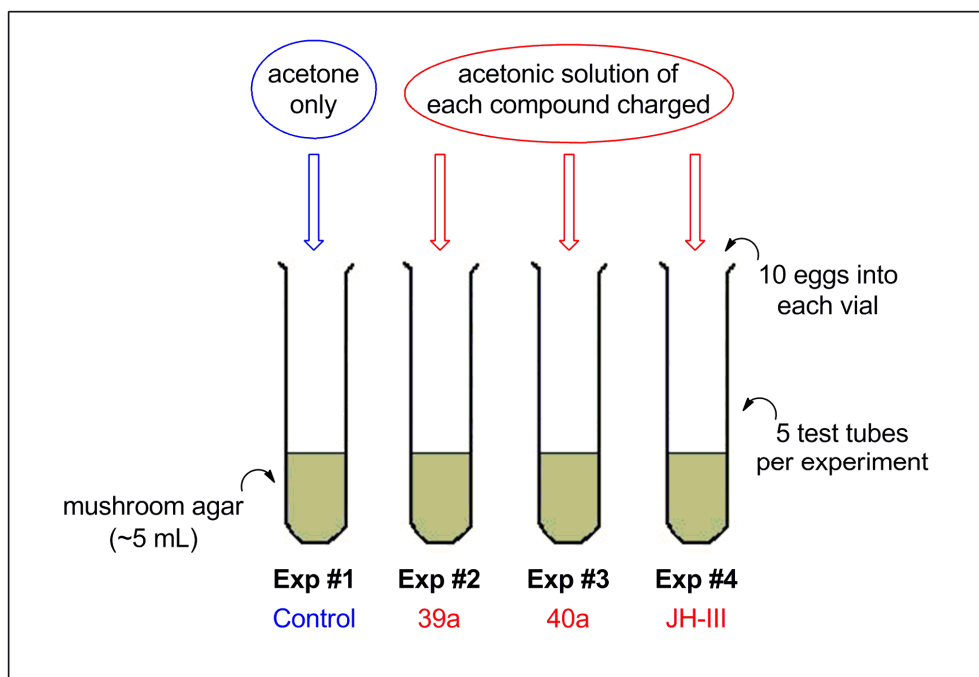


Figure 32. General experimental set-up for the *Drosophila melanogaster* assay.

The small volume of acetone was allowed time to evaporate after which 10 *Drosophila melanogaster* eggs were added to each vial. The tubes were then loosely covered with aluminium foil and carefully monitored to determine the number of eggs that developed from larva to pupa and eventually to the adult stage.

Figure 33 shows the preliminary results for our first round of insect assays.

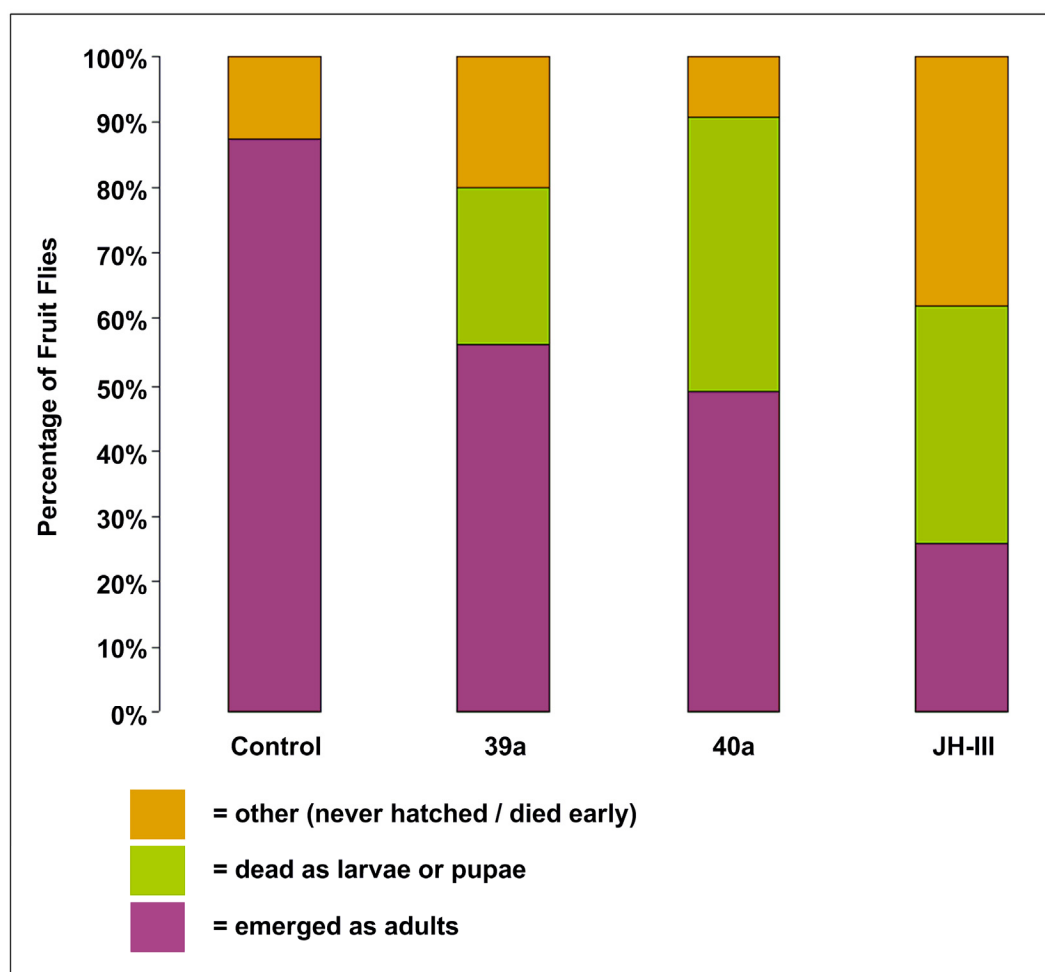


Figure 33. Preliminary insect assay results.

In the control experiment, 13% of fruit flies did not hatch (other) while the remaining 87% emerged as adults. Gratifyingly, analogues **39a** and **40a** showed similar trends to JH-III with 20%, 9%, and 38% of fruit flies not hatching, 24%, 42%, and 36% dying

around the pupal stage, and 56%, 49%, and 26% emerging as adults for **39a**, **40a**, and JH-III respectively.

These results are quite promising given that this was our first attempt at an insect assay. Wulff group undergraduate student Steven Wong is now currently working very closely with Dr. Perlman to develop a reliable assay to give us consistent and statistically significant results. They are currently investigating different methods to deposit the compound into the tubes (direct addition on top vs pre-mixing the compound with the agar media), compound concentration, types of agar media (mushroom, banana, and cornmeal based media), the ideal species of fruit fly (*Drosophila melanogaster*, *Drosophila funebris*, and *Drosophila immigrans*), and the solvent used (acetone vs ethanol). We have also now introduced *S*-methoprene as an additional positive control in these insect assays and envision generating a series of vinyl ether analogues based on the *S*-methoprene motif.

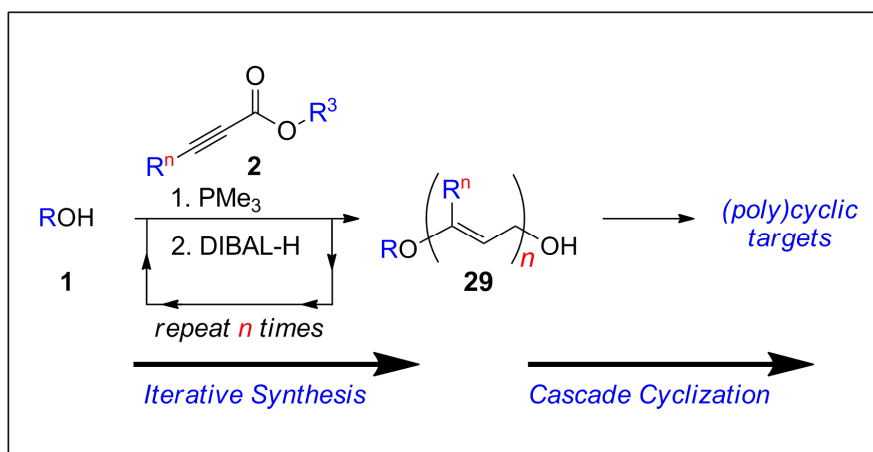
3.3.2 Biological Assays in Crustaceans

In collaboration with Dr. Michael Horst from Mercer University, Department of Biochemistry and through the University of Maine marine laboratory in Walpole, our compounds (**39a** and **40a**) are also being tested to see their effects on larval and juvenile lobsters. These tests are currently ongoing, and we are hoping to get preliminary results by the end of the 2012 year.

Chapter 4: Radical Cyclizations across Bis-Vinyl Ethers

4.0.0 Introduction

As is the case with iterative synthetic protocols, the use of a tandem or cascade reaction is an efficient strategy for the rapid introduction of molecular complexity into a system since the number of steps requiring independent optimization is greatly reduced. With the aim of creating new synthetic strategies to efficiently gain access to complex small molecules, we envisioned the use of short iterative protocols to prepare reactive oligomers to which cascade cyclization processes could be applied (Scheme 60).



Scheme 60. Summary of new synthetic strategy to access (poly)cyclic targets.

By combining these inherently complementary strategies, we anticipated the ability to access a variety of stereochemically rich (poly)cyclic targets, of potential interest to medicinal chemistry programs.¹²⁵ As such, we decided to pursue an iterative protocol to access a variety of oligo-vinyl ethers; a synthetic target for which we expected a diverse range of cascade cyclization reactions to be amenable (Figure 14).

Because cascade cyclizations have become ubiquitous in organic synthesis, there are several strategies to choose from including transition-metal catalyzed cyclizations, cation-olefin cyclizations, and radical initiated cyclizations.¹²⁶ Due to the relatively mild reaction conditions which allow for a wide range of functionality on the substrates as well as the lack of any Lewis acid species (which could cause problems with our electron-rich vinyl ether substrates), we chose to start our initial investigation into our oligo-vinyl ether cascade reactions with a radical-mediated cyclization.

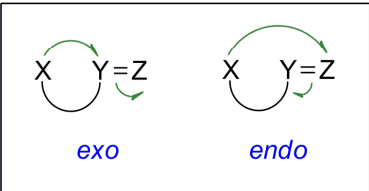
Cyclizations involving carbon-, oxygen-, and nitrogen-centered radicals are all possible for radical-mediated cascade reactions.¹²⁷ Given the types of products we were generating from our iterative protocol, however, we chose to focus our attention on the carbon-centered radicals. For a carbon-centered approach, radicals are routinely accessed from alkyl halides (Br or I), nitro compounds, acyl species (such as an acyl selenide), vinyl halides, or by addition of another radical species to an alkyne. We recognized that as optimization of our vinyl ether radical cyclization conditions proceeded, the type of radical precursor used might need to be altered. Given the flexibility as to the variety of alcohols (**1**) that are accessible with our conjugate addition/reduction methodology, however, we felt that several different radical precursors should be attainable synthetically depending on our needs.

Cascading cyclizations across substituted oligo-vinyl ether systems (of the type generated from our newly developed iterative protocol) are virtually unseen in the literature prior to our work. Baldwin's rules (Figure 34)¹²⁸ can provide some guidance for helping to predict possible outcomes for general cyclization reactions.

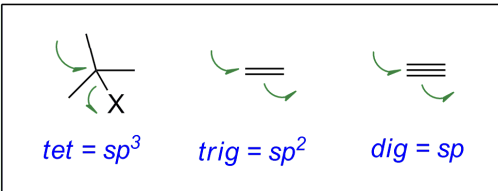
Baldwin's Rules for Ring Closure

Dis/Favored Cyclization Pathway for 3- to 7-Membered Rings

| Type of Cyclization | 3 | 4 | 5 | 6 | 7 |
|---------------------|---|---|---|---|---|
| exo-tet | ✓ | ✓ | ✓ | ✓ | ✓ |
| endo-tet | | | ✗ | ✗ | |
| exo-trig | ✓ | ✓ | ✓ | ✓ | ✓ |
| endo-trig | ✗ | ✗ | ✗ | ✓ | ✓ |
| exo-dig | | ✗ | ✓ | ✓ | ✓ |
| endo-dig | ✓ | ✓ | ✓ | ✓ | ✓ |



exo endo



tet = sp^3 trig = sp^2 dig = sp

Figure 34. Baldwin's rules for favored and disfavored ring closures.

Three factors are involved in classifying the type of cyclization that is occurring; ring size, *exo* versus *endo* attack, and hybridization at the site of attack. *Exo* indicates that the breaking bond is outside of the formed ring while *endo* means that the breaking bond is inside of the new ring.

A second well-known set of guidelines for radical reactions was also developed by Beckwith:¹²⁹

- (i) *Intramolecular addition under kinetic control in lower alkenyl and alkynyl radicals and related species occurs preferentially in the exo-mode.* This guideline indicates that *exo* ring closure is kinetically favored (over the *endo* process) when

the chain between the radical and unsaturated system contains five linking carbons or less.

- (ii) *Substituents on an olefinic bond disfavor homolytic addition at the substituted position.* This point suggests that the rate of an *exo* cyclization (1,5-cyclization) is greatly retarded (and can be overwritten) by the presence of a substituent at the internal position of the alkene.
- (iii) *Homolytic cleavage is favored when the bond concerned lies close to the plane of an adjacent semi-occupied orbital or of an adjacent filled nonbonding or π -orbital.* This stereoelectronic guideline is relevant to cyclizations because *endo* radicals often cannot acquire the required orbital overlap due to ring constraints whereas *exo* radicals can.
- (iv) *1,5-Ring closures of substituted hex-5-enyl and related radicals are stereoselective: 1- or 3-substituted systems afford mainly cis-disubstituted products, whereas 2- or 4-substituted systems give mainly trans-products.* The stereoselectivity observed in 2-, 3-, or 4-substituted 5-hexenyl radicals has been ascribed to the effects of orbital symmetry (i.e. conformational preferences of the chair-like transition state¹²⁹ with substituents preferentially occupying pseudoequatorial positions).¹³⁰

In both Baldwin's and Beckwith's rules, reactions that are predicted to be unfavorable are not completely forbidden but rather are expected to cyclize at a relatively slow rate compared to the faster (kinetically favored) reactions.

In addition to these general guidelines, an analysis of mechanistically related cyclizations (either unsubstituted mono-vinyl ethers, all carbon polyene systems, or carbon radical cyclizations onto sp^2 or sp centers) reported in the chemical literature suggests a strong dependence on the nature of the substituents (**R**) that are directly attached to the alkene bonds participating in the cyclization process (Figure 35).

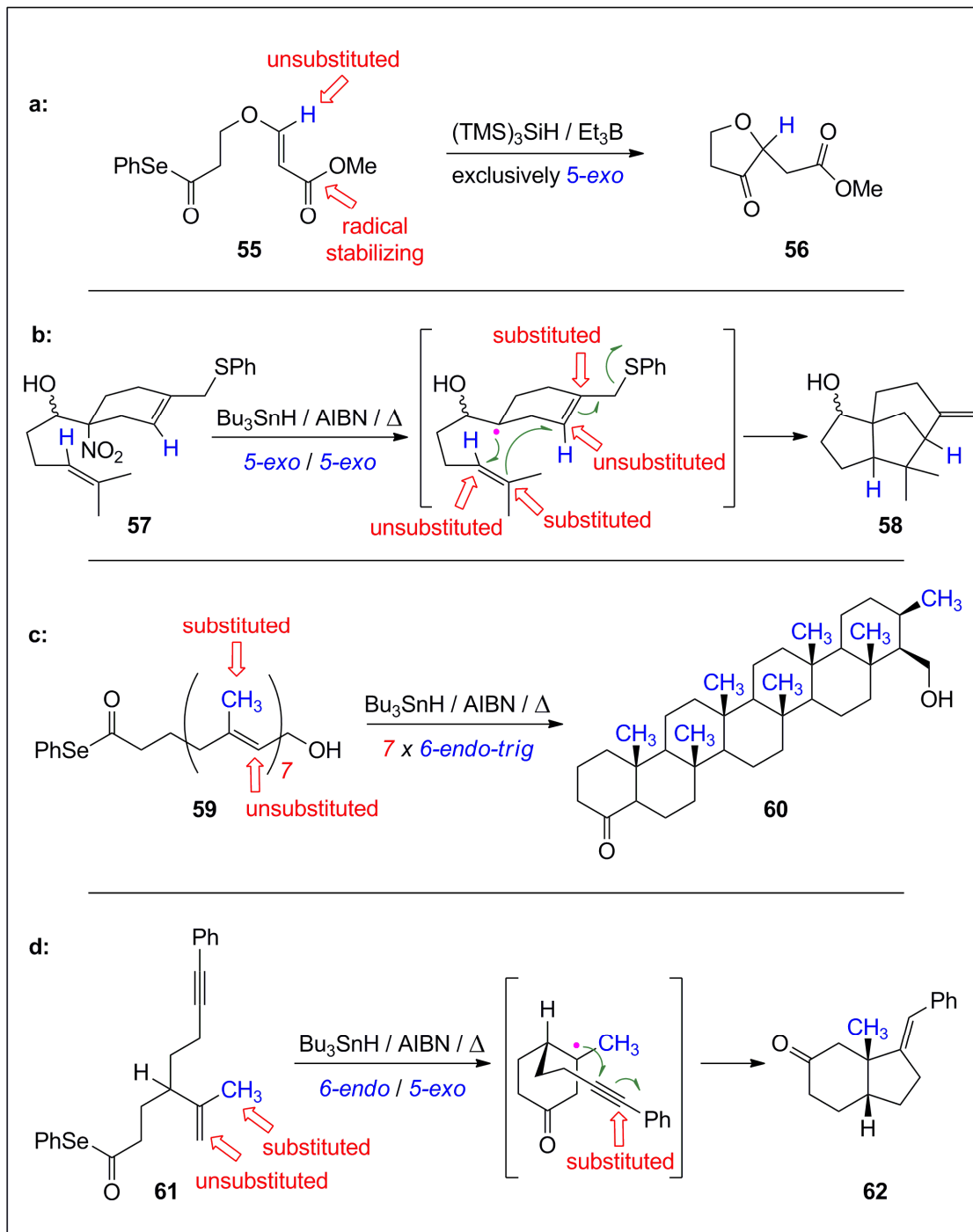


Figure 35. Cyclization pathways dependent on the vinyl ether substitution.

For example, work by Evans and co-workers has shown that mono-substituted vinyl ethers (e.g. **55**, where $R = H$) typically cyclize predominantly through a 5-*exo* pathway (Figure 35a).¹³¹ Figure 35b shows an example of a system (**57**) where although the

radical cascade has two mechanistic options available (either through a *5-exo* pathway attacking the less substituted end of an sp^2 center or a *6-endo* route onto the more substituted end of the double bond), the primary mode of cyclization is through a *5-exo/5-exo* cascade (preferentially cyclizing onto the less substituted end of each double bond).¹³²

In a similar fashion (but opposite cyclization pathway), the Pattenden group established that more substituted alkenes (e.g. all-*E* polyene selenoates such as **59**, where each alkene bears an extra methyl ($R = CH_3$) substituent) can undergo radical-mediated cascade polycyclizations exclusively through a *6-endo* pathway (again preferentially cyclizing onto the less substituted end of each double bond) with excellent regio- and stereoselective control to yield large polycycles such as **60** up to seven rings in size (Figure 35c).¹³³ Finally, Figure 35d shows an example of a radical cascade where the final cyclization process exclusively undergoes a *5-exo* pathway onto the less substituted end of the double bond.¹³⁴

With these literature examples and Baldwin and Beckwith's rules in mind, we set out to investigate possible iterative synthesis/cascade radical cyclization strategies across our oligo-vinyl ether substrates in the hopes of generating interesting, stereochemically complex polycyclic molecules.

For our oligo-vinyl ether systems, we foresaw two possible cyclization pathways: either a *6-endo-trig* cyclization or a *5-exo-trig* cyclization (Figure 36).

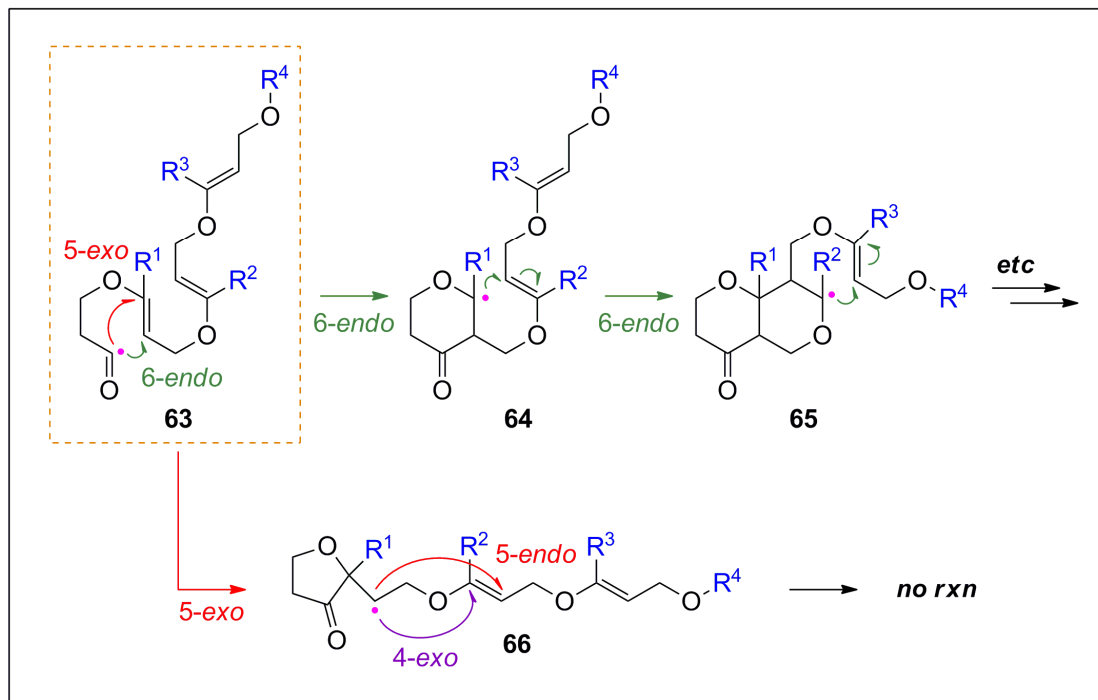


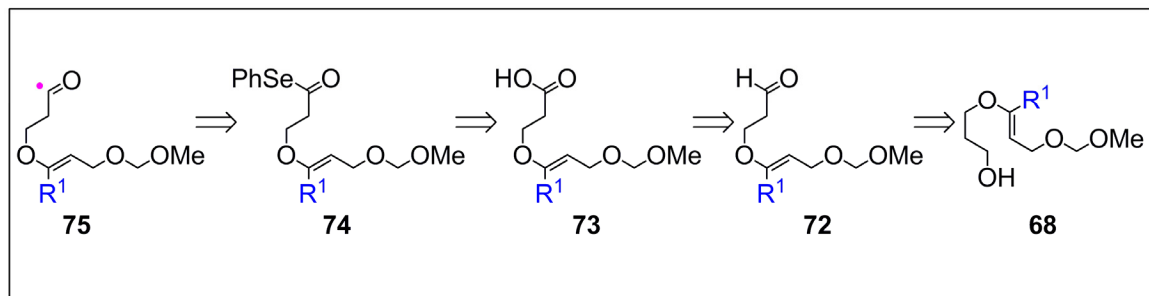
Figure 36. Potential cyclization pathways for our oligo-vinyl ether systems.

The *6-endo-trig* cyclization can (theoretically) propagate along our linear vinyl ether framework (i.e. **63** → **64** → **65** → *etc*) resulting in a successful cascade reaction, while the corresponding *5-exo-trig* cyclization (i.e. **63** → **66**) would likely be terminating, in that the subsequent *5-endo-trig* cyclization would likely be disfavored. While a *4-exo-trig* cyclization would be allowed (in principle) by both Baldwin's and Beckwith's guidelines, this also seems unlikely to proceed at a sufficient rate to permit a cascade cyclization to take place. With this in mind, we were interested in strategies to bias the system toward *6-endo* cyclization pathways over the corresponding *5-exo* trajectories, possibly through the introduction of substituents at the R positions.

4.1.0 Initial Radical Cyclization Attempt

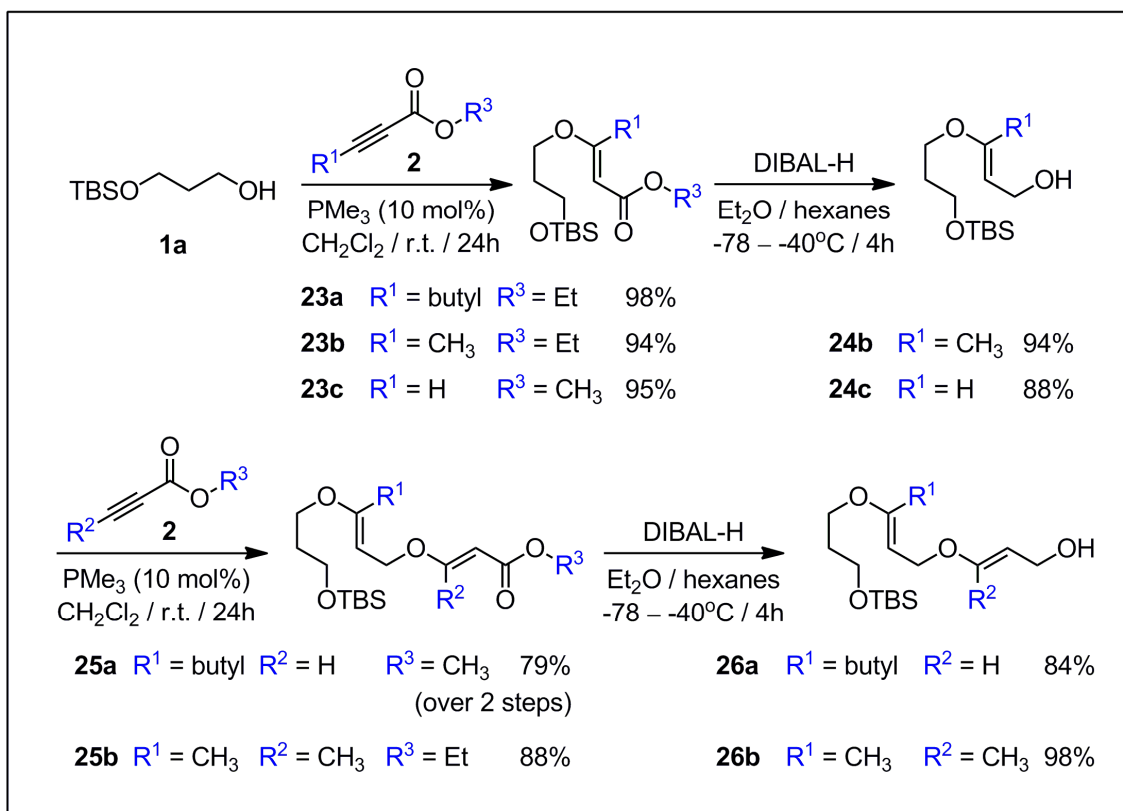
Prior to our work, there were no examples of cascading radical cyclizations across bis-vinyl ethers. As such, we initially focused our synthetic optimization on the simplest

system available (a mono-vinyl ether). Our first strategy to initiate the cascade radical cyclization sequence was through an acyl radical precursor (**74**, Scheme 61).¹³⁵



Scheme 61. Retrosynthetic analysis of desired acyl radical precursor.

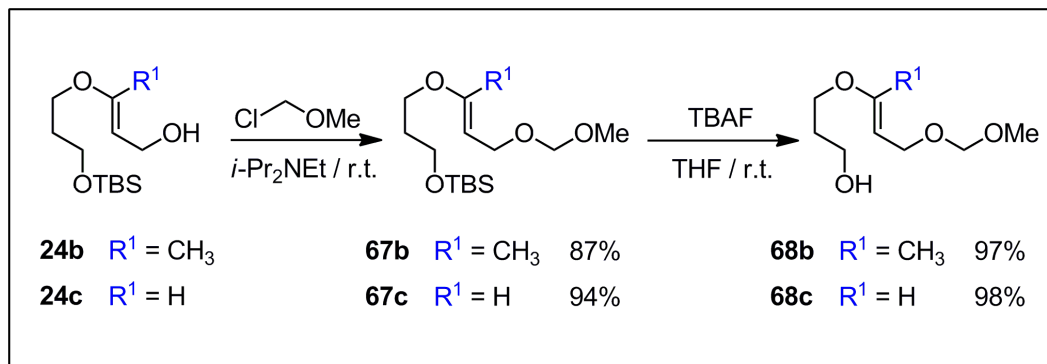
We proposed synthesizing acyl selenide **74** through a series of oxidations; either one reaction to give us the carboxylic acid (**73**) directly from the alcohol (**68**) or a stepwise procedure through an aldehyde intermediate (**72**). To gain access to the required vinyl ether alcohol **68**, we envisioned utilizing protected alcohol **1a** in our conjugate addition/reduction methodology (Scheme 62).



Scheme 62. Iterative synthesis of TBS protected alcohol vinyl ethers.

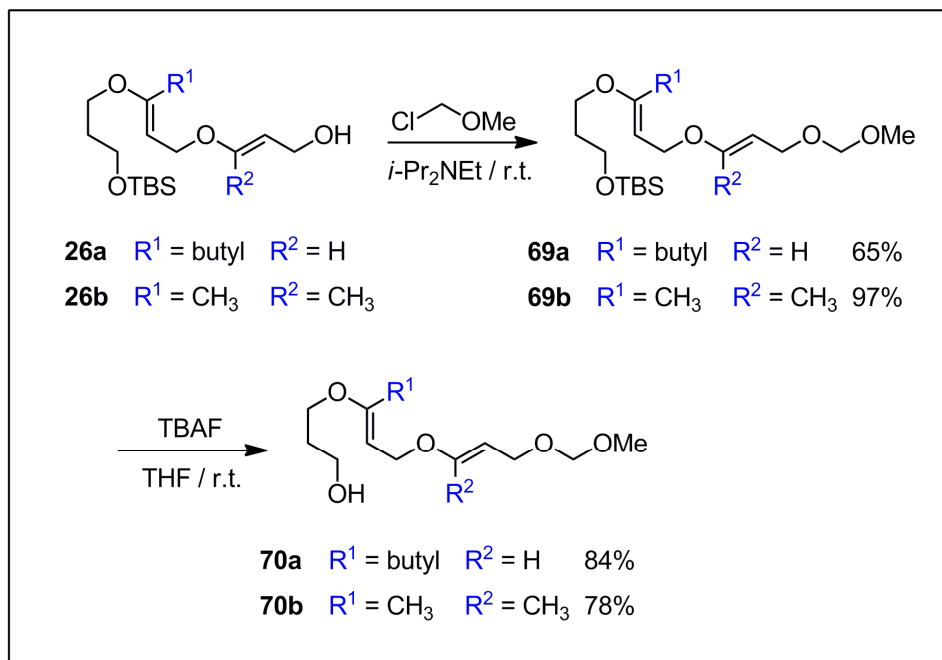
Both the addition and reduction steps yielded relatively pure material (ca. 90% purity by ^1H NMR). The products **23** – **26** could also be successfully purified over triethylamine-treated silica to afford product ($\geq 95\%$ purity) in consistently good yields.

As shown in the retrosynthetic analysis (Scheme 61), to gain access to an acyl selenide, oxidation of the alcohol (**68**) to a carboxylic acid (**73**) was required, followed by selenation to the acyl selenide (**74**). After the reduction step, the unprotected alcohol (**24** or **26**) was protected as the corresponding methoxymethyl ether (**67** or **69**) to allow for synthetic manipulation on the other alcohol present in the molecule (Scheme 63 and Scheme 64).



Scheme 63. Preparation of mono-vinyl ethers for oxidation to carboxylic acid.

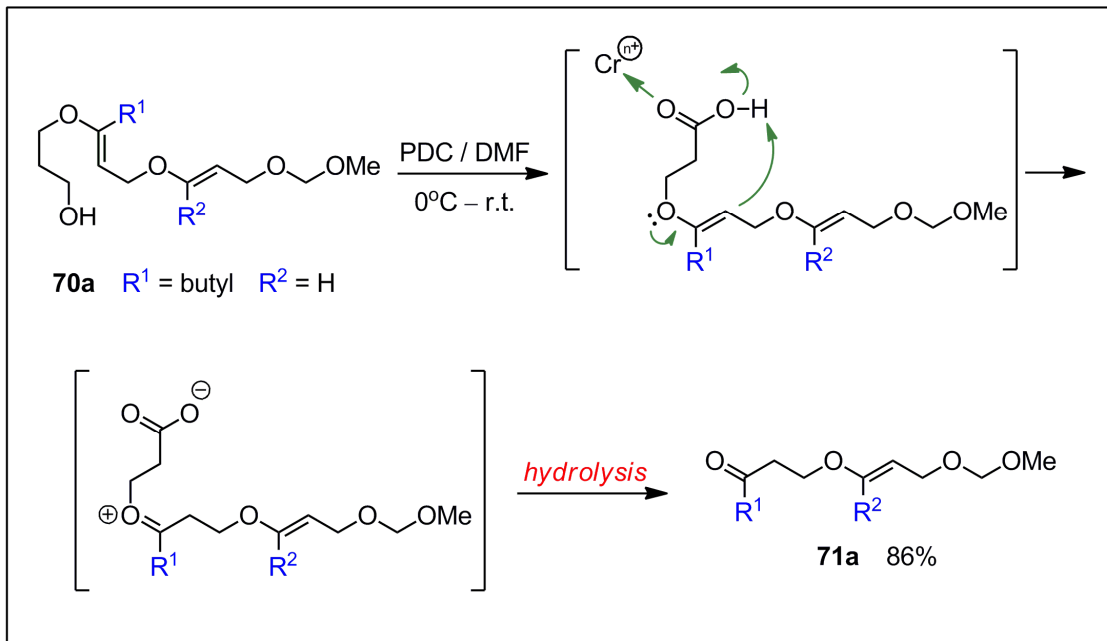
Deprotection of the TBS protected alcohol (**67** or **69**) via *tetrabutylammonium* fluoride afforded alcohols **68** or **70** (Scheme 63 and Scheme 64). After each protection/deprotection step, purification by column chromatography using triethylamine treated-silica gel provided clean products in good yields.



Scheme 64. Preparation of bis-vinyl ethers for oxidation to carboxylic acids.

At this stage we had the alcohol functional group (**68** or **70**) required to form an acyl radical synthon (or equivalent) to allow for the radical cyclization to be initiated.

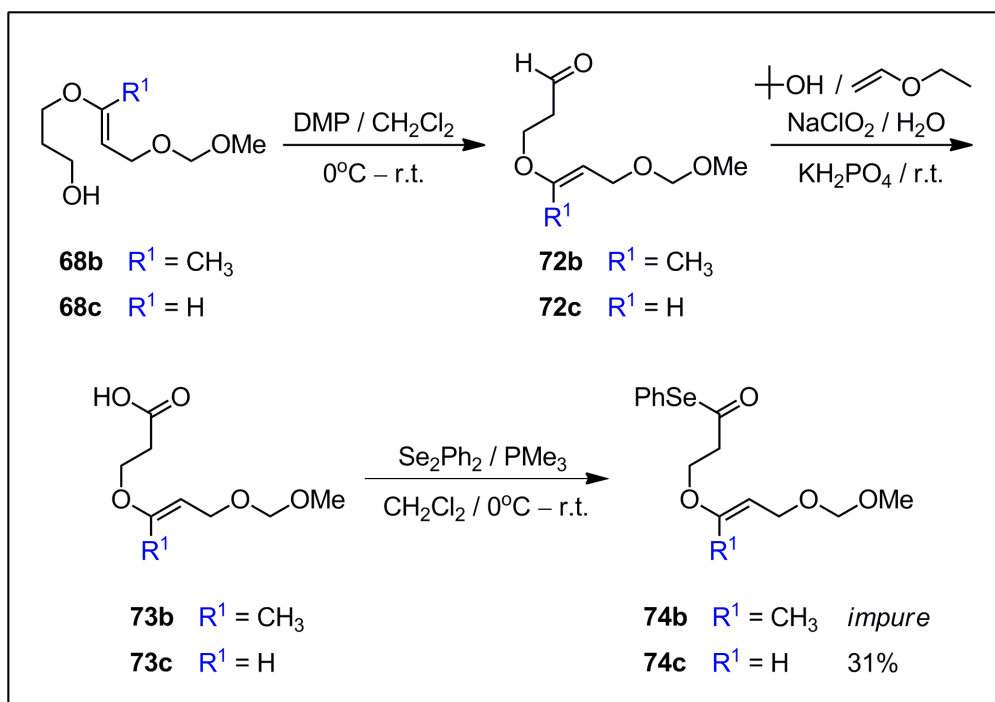
Early attempts to access an acyl radical proved to be challenging. We initially tried to form an acyl selenide via a carboxylic acid.¹³⁶ The first attempt involved conversion of the alcohol (**70a**) directly to a carboxylic acid using pyridinium dichromate and DMF.¹³⁷ Although we believe that the carboxylic acid did form, it was not observed in the isolated product. After some investigation, it was determined that an unexpected rearrangement was occurring via intramolecular delivery of a proton from the newly formed carboxylic acid to yield a new ketone product (**71a**, Scheme 65). We ruled out the possibility of an intramolecular proton transfer given that substrate **26a** was stable for over one week in a solution of acetone- d_6 and acetic acid (Table 5).



Scheme 65. An unexpected rearrangement from a PDC oxidation.

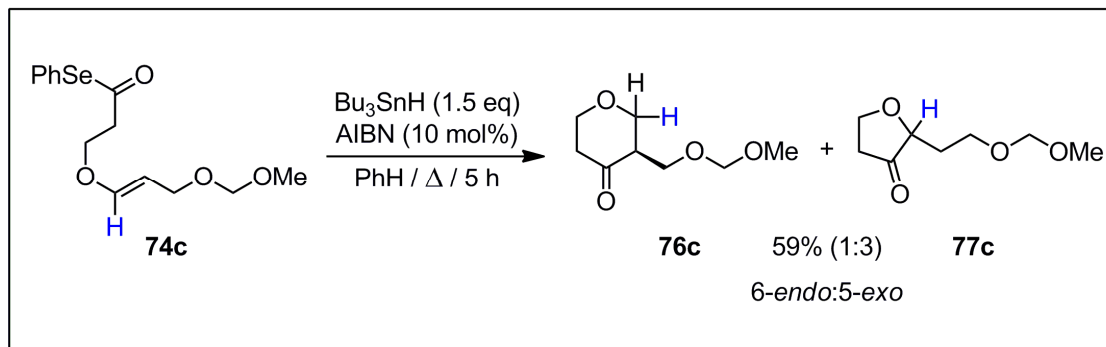
Although this type of rearrangement was not observed for Pattenden's all-carbon polyene systems (**59**), this result was not surprising to us given that alkene **70a** is more electron rich due to the presence of oxygen in the carbon skeleton.¹³⁶

The second attempt involved conversion of the alcohol (**68**) first to an aldehyde (**72**) via a Dess-Martin Periodane oxidation¹³⁸ followed by a Pinnick oxidation¹³⁹ to yield the desired carboxylic acid (**73**, Scheme 66). Instead of using the traditional 2-methyl-2-butene as a sacrificial alkene in the Pinnick oxidation, we utilized a more electron rich alkene (ethyl vinyl ether) to ensure that any hypochlorite ions (HOCl) being produced in this reaction would successfully be scavenged to avoid any reaction with our electron-rich vinyl ethers (**72** or **73**).



Scheme 66. Conversion of an alcohol to an acyl selenide.

When R^1 was a proton, both oxidations were successful. This allowed us to attempt an initial cyclization reaction by converting the carboxylic acid (**73c**) to an acyl selenide¹⁴⁰ using diphenyl diselenide and PMe_3 to afford **74c** in a 31% overall yield (unoptimized), followed by initiation and cyclization using azobisisobutyronitrile and tributylstannane to give **76c** and **77c** in a 1:3 ratio (Scheme 67).¹³⁶



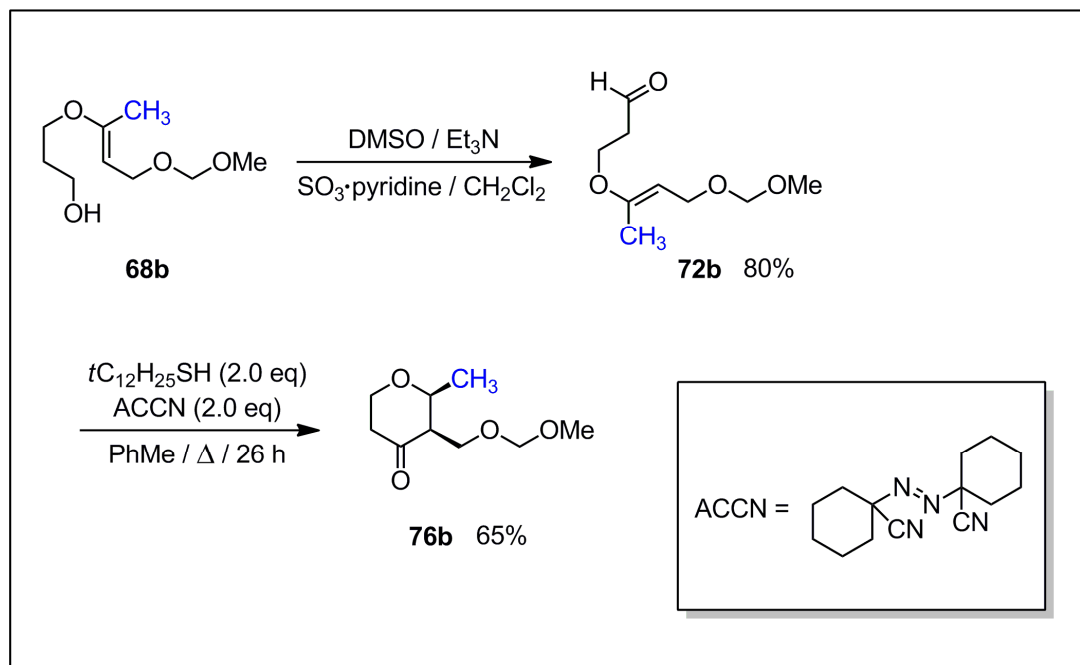
Scheme 67. First radical cyclization attempt from an acyl radical.

The fact that we obtained any 6-*endo* cyclization product (**76c**) in this attempt was unexpected, given that all previously reported acyl radical cyclizations onto vinyl ethers with 2 unsubstituted positions (on either end of the double bond involved in the cyclization) were reported to yield exclusively 5-*exo* products (Figure 35a).¹³¹ This boded well for our future studies, in which we would introduce additional substitution at the 5-position, thus favoring the larger (6-*endo*) ring size (Figure 35b).¹³⁵

We then turned our focus to optimization of the methyl substituent (**68b**), as literature precedent indicated that having a bulkier methyl at the R^1 position has a significant impact on determining the regiochemical outcome of various cyclizations and should favor the six-membered ring.¹³⁵⁻¹³⁷ When the same oxidation conditions were applied to alcohol **68b**, the products from the reaction were very unstable and many inseparable side products were visible by proton NMR. This instability is likely due to the presence of a more electron rich vinyl group, a result of replacing the proton at the R^1 position with a methyl group. Consequently, other oxidation conditions needed to be investigated in order to carry forward a variety of oligo-vinyl ether substrates cleanly for several steps.

After further optimization, it was determined that a Parikh-Doering oxidation¹⁴¹ of **68b** to the corresponding aldehyde (**72b**) was the most optimal and high yielding set of reaction conditions. However, conversion of the aldehyde **72b** to the carboxylic acid **73b** was still not achievable. As such, we decided to explore the use of an aldehyde as an acyl radical

precursor utilizing the reaction conditions developed by Tomioka and co-workers. (Scheme 68).¹⁴²



Scheme 68. A thiol-catalyzed acyl radical cyclization.

When two equivalents each of *tert*-dodecane thiol and ACCN in refluxing toluene were stirred with **72b** for 26 hours, 6-*endo* product **76b** was exclusively obtained; a result which is consistent with outcomes for related systems.¹⁴³ By using this alternate route, we removed two full steps from the synthesis (Pinnick oxidation and selenation) and allowed for purification of the cyclized product after only one oxidation step.

While initial results for the mono-vinyl ether systems were promising, when the optimized oxidation reaction conditions were applied to the bis-vinyl ether **70b**, results were inconsistent. Unfortunately clean oxidized product could not be consistently made or cleanly isolated. As such, a new synthetic strategy was required to initiate the cascade radical cyclization sequence.

4.2.0 Alternate Radical Cyclization Attempt

Although we were able to use an acyl radical to initiate our radical cyclization process, the chemistry required to gain access to the acyl radical precursor (**72** or **74**) was challenging due to the sensitive nature of our vinyl ether systems. Given the variety of radical initiators available, we thought that a vinyl radical would allow for easier synthetic access to the necessary radical precursor, allowing us to circumvent unnecessary oxidation or reduction reactions (Figure 37).

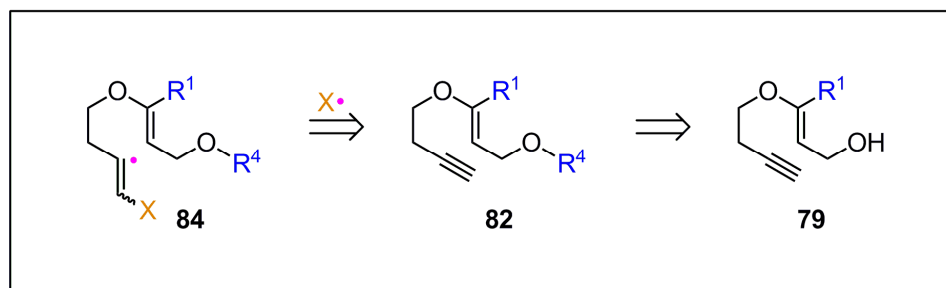
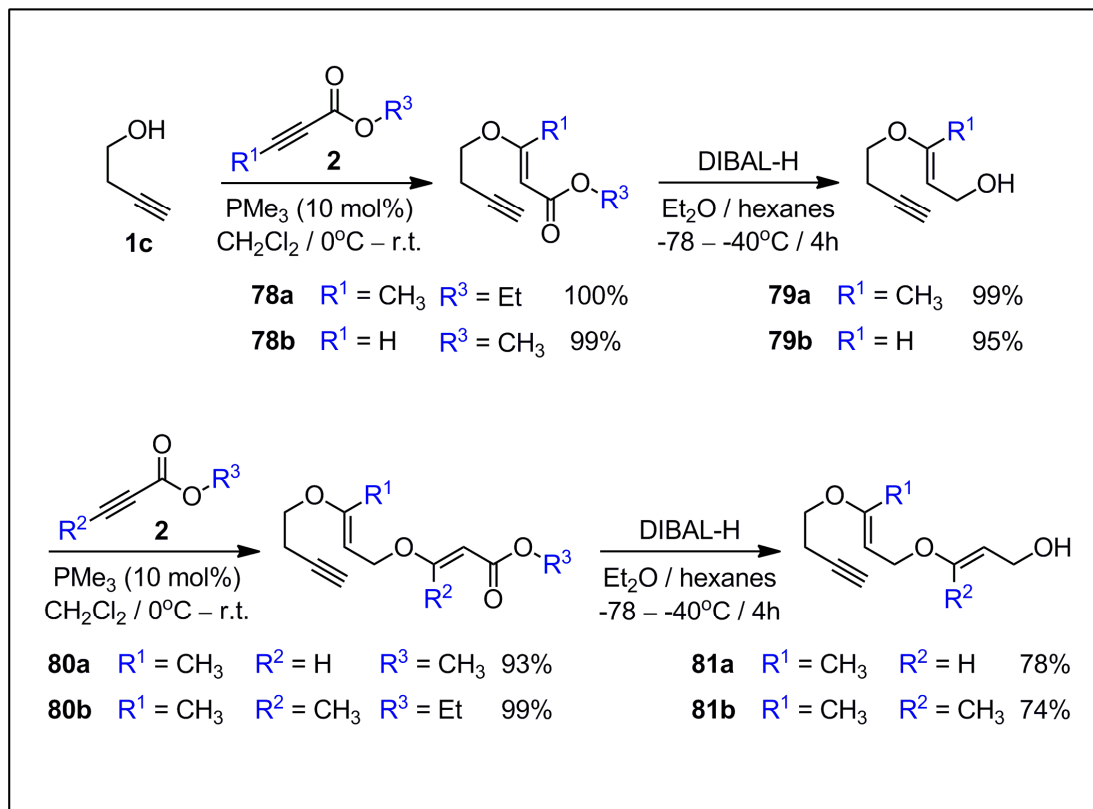


Figure 37. Retrosynthetic analysis of desired vinyl radical precursor.

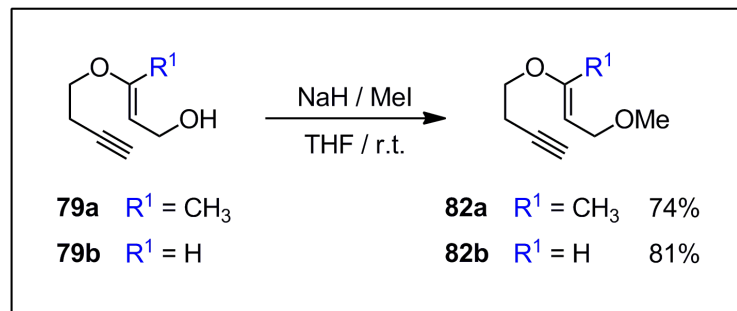
For our new strategy to initiate the cascading radical cyclization sequence, we wanted to keep the synthesis as efficient as possible by minimizing the number of steps necessary once the final reduction in our iterative sequence was completed. We therefore took an alternate approach and utilized alkyne **1c** as our starting material alcohol (Scheme 69).¹⁴⁴



Scheme 69. Iterative synthesis of alkyne vinyl ethers.

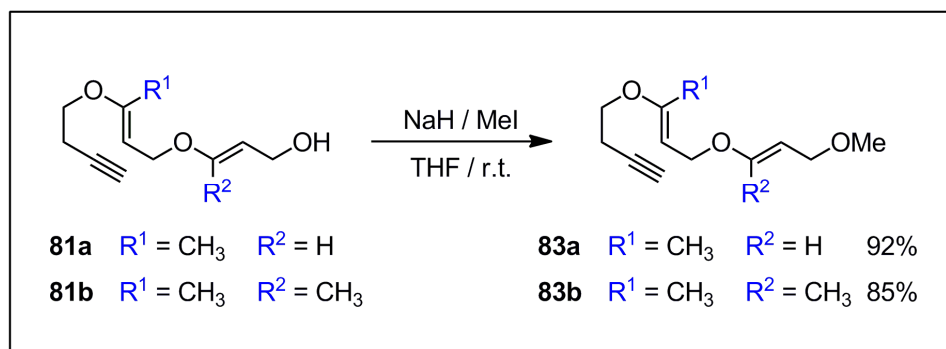
Similar to the TBS protected alcohol, the addition and reduction steps yielded relatively pure crude material and the vinyl ether products (**78** – **81**) could be cleanly purified over triethylamine-treated silica to afford product ($\geq 95\%$ purity) in good yields. Unlike previously used alcohols, however, better *E:Z* selectivity was obtained for the conjugate addition step if the reaction temperature was run from 0°C to room temperature over 24 hours.

This new sequence requires no oxidation steps and therefore the alcohol (**79** or **81**) need not necessarily be protected. At the same time, we were unsure of the stability of the alcohol under radical cyclization conditions. We therefore chose to protect the alcohol with a methyl group (Scheme 70 and Scheme 71).



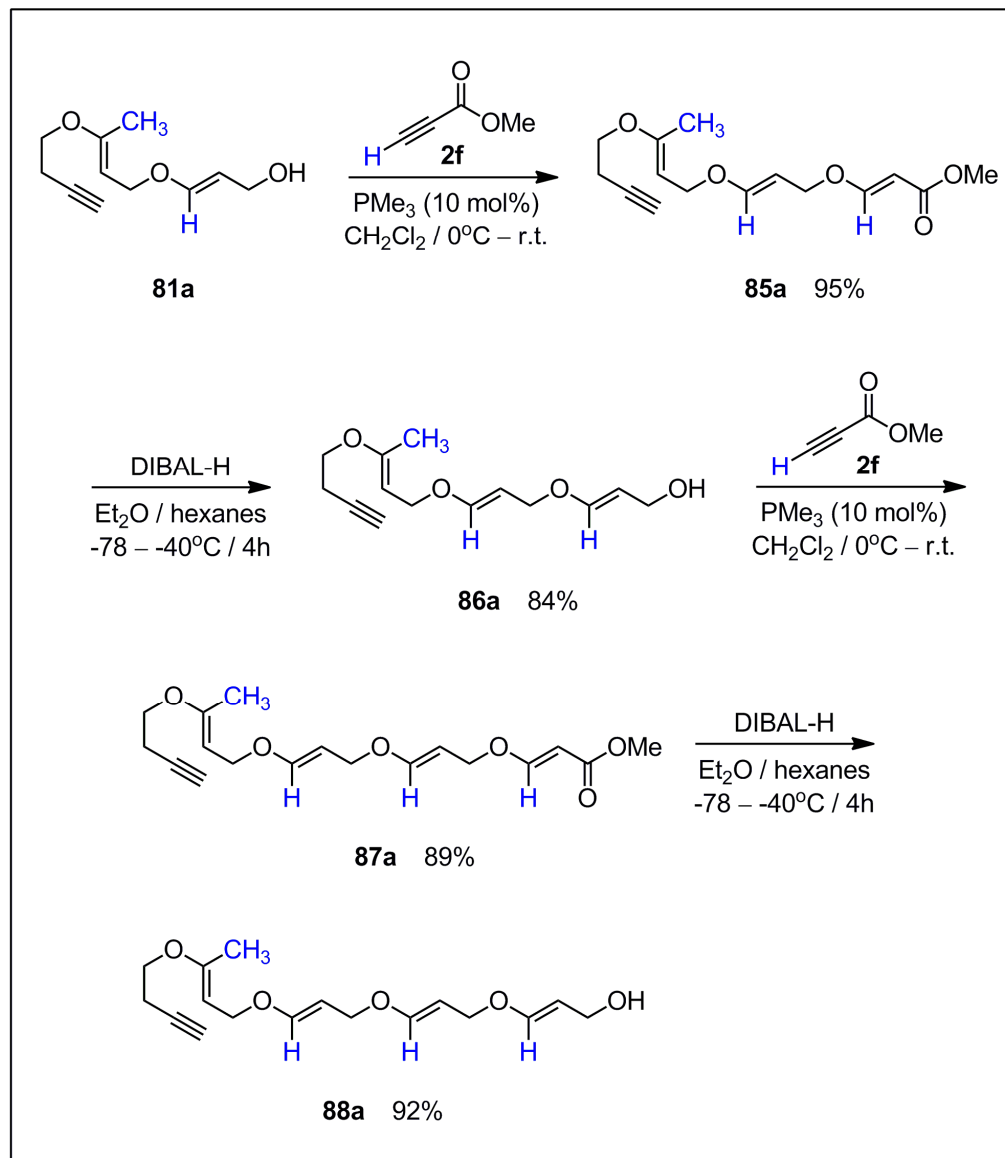
Scheme 70. Methylation of mono-vinyl ethers 79.

Methylation using sodium hydride (60% w/w) in THF at room temperature afforded very clean products (**82** and **83**) after column chromatography over triethylamine-treated silica gel with relatively good yields, even for the more sensitive bis-vinyl ether systems (Scheme 71).



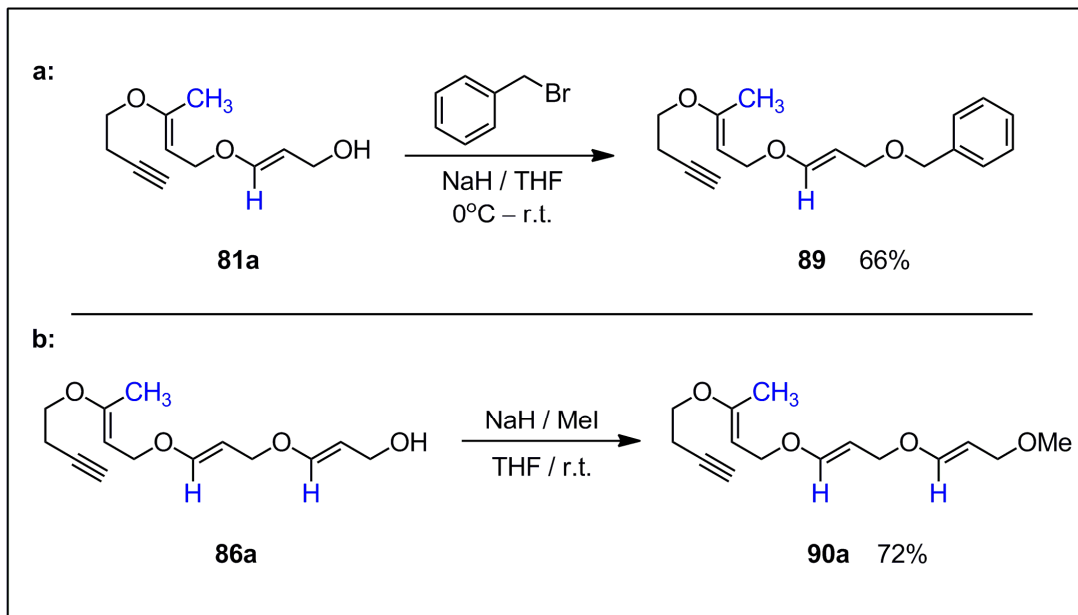
Scheme 71. Methylation of bis-vinyl ethers 81.

As a proof of concept, we sought to ensure that our iterative protocol could be applied to more than two iterative sequences (i.e. to generate oligo-vinyl ether systems larger than bis-vinyl ethers). To our great satisfaction, we were able to generate the tris-vinyl ether (**86a**) and tetrakis-vinyl ether (**88a**) very cleanly and in good yields (Scheme 72).



Scheme 72. Iterative synthesis of tris- and tetrakis-vinyl ethers.

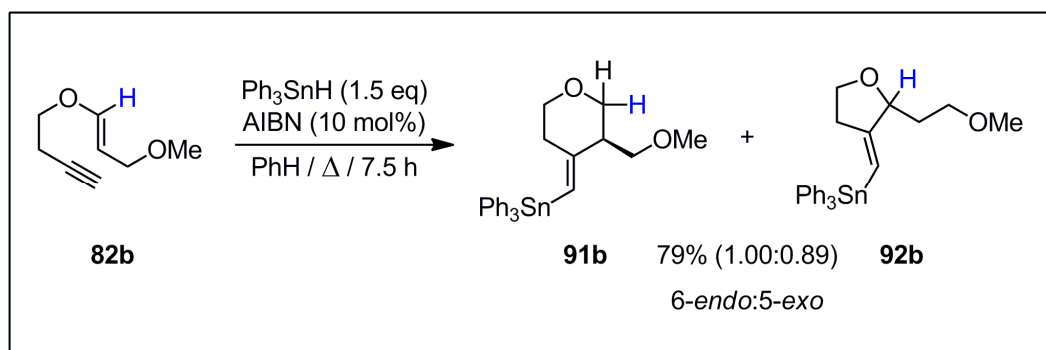
We also applied a benzyl protecting group to the bis-vinyl ether **81a** (Scheme 73a) as well as the standard methylation procedure to the larger tris-vinyl ether **86a** in order to have a greater diversity of substrates to utilize in our radical cascade cyclizations (Scheme 73b).



Scheme 73. (a) Benzylation of vinyl ether 81a. (b) Methylation of vinyl ether 86a.

Again, we were very encouraged to discover that both reactions could be accomplished cleanly, with column chromatography over triethylamine-treated silica successfully applied to both systems.

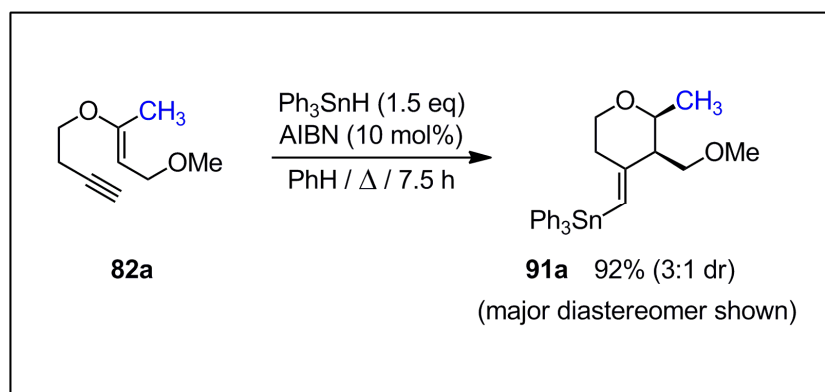
Analogous to our earlier cyclization attempts with acyl radicals, we initially investigated the reactivity of the mono-vinyl ether systems (Scheme 74).



Scheme 74. Radical cyclization onto mono-vinyl ether 82b.

When a solution of triphenyltin hydride and AIBN in benzene was added over 6 hours by syringe pump to a refluxing solution of alkyne **82b** in benzene (followed by an additional 1.5 hours of heating) at a final concentration of 8 mM, **91b** and **92b** were obtained in a 1.00:0.89 ratio and good overall yield (79%). If the triphenyltin hydride/AIBN solution was added too quickly to the refluxing alkyne solution, uncyclized product **109** (Scheme 76) was isolated due to rapid hydrogen atom abstraction from the excess triphenyltin hydride present in solution (see section 4.4.2 for further mechanistic details).

Again we theorized that introducing additional substitution at the R^1 position would favor the larger (6-*endo*) ring size. Consistent with our previous cyclization attempt, when these same radical cyclization conditions were applied to alkyne **82a**, we obtained exclusively the 6-*endo* product **91a** in excellent yield (Scheme 75).

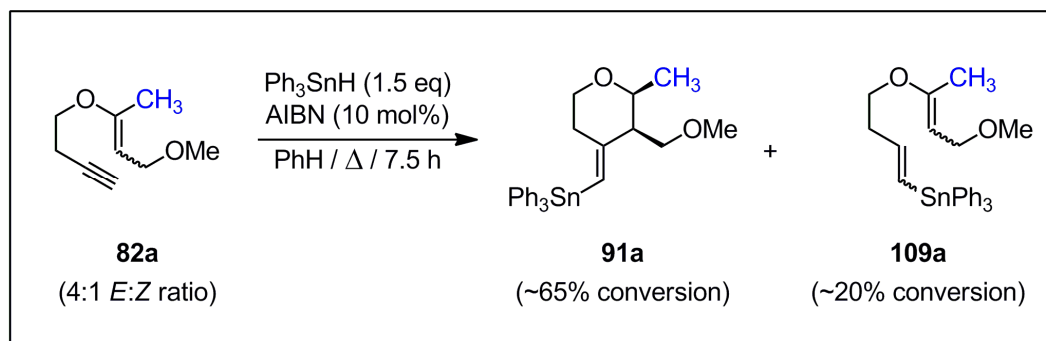


Scheme 75. Radical cyclization onto mono-vinyl ether 82a.

With this knowledge in hand, subsequent cascading reactions were carried out exclusively with either an alkyl or aryl substituent at the R^1 position to ensure that the first ring closing event generated a 6-membered ring.

As previously mentioned, it was determined that better *E:Z* selectivity was obtained for the conjugate addition step if the reaction temperature was run from 0°C to room temperature. When initially starting these mono-vinyl ether cyclizations, conjugate

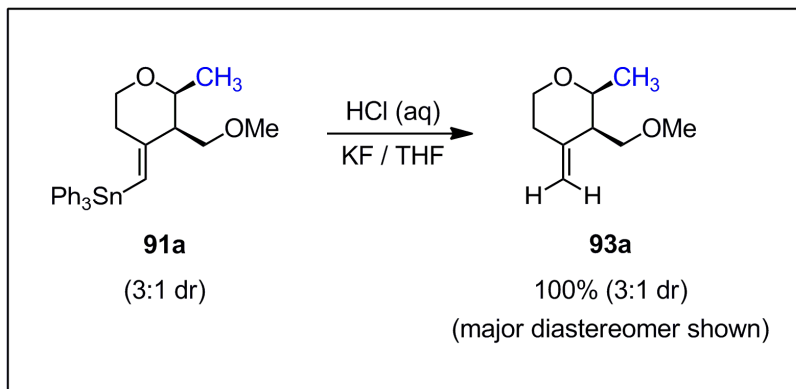
additions were being run at room temperature (as optimized in previous projects). However, it was observed that high levels of the *Z* isomer present in **82a** led to very low conversion to product (**91a**). For example, a 4:1 *E:Z* ratio in **82a** gave only a 65% conversion to **91a**, along with what appeared to be alkene **109a** (Scheme 76).



Scheme 76. Effects of low *E:Z* selectivity on outcome of radical cyclization reaction.

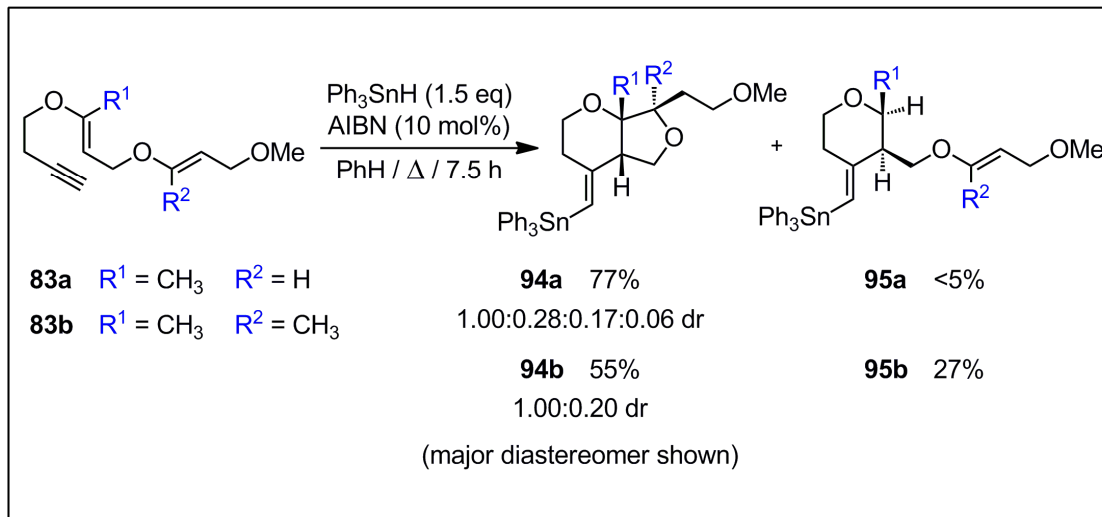
When the amount of *Z* isomer present for **82a** was reduced (through temperature optimization of the conjugate addition) to >20:1 *E:Z*, the percent conversion and overall yield of the reaction increased to obtain 91% of the final product (**91a**, Scheme 75). These results are consistent with the hypothesis that the *Z* vinyl ether does not cyclize under these reaction conditions or it cyclizes slowly. Unfortunately these results could not be fully confirmed as **109a** could not be cleanly isolated. However, all future conjugate addition reactions were carried out using the newly optimized conjugate addition conditions to minimize the amount of (unreactive) *Z* isomer present (see Table 8 and Table 9 for reported *E:Z* ratios).

Removal of the triphenyltin group was also cleanly accomplished in excellent yield using 15% HCl and potassium fluoride in THF (Scheme 77).



Scheme 77. Protodestannylation reaction conditions to convert 91a to 93a.

When radical cascade cyclization conditions were applied to our bis-vinyl ether systems (**83**) an interesting result was obtained (Scheme 78).



Scheme 78. Radical cyclizations across bis-vinyl ethers.

When R^2 was a proton (**83a**), the cascade cyclization went exclusively through a 6-endo-trig/5-exo-trig reaction to provide **94a** in good yield. Alternatively, when R^2 was a methyl group (**83b**)[†] a mixture of 6-endo-trig/5-exo-trig (**94b**) and monocyclic 6-endo-trig

[†] This specific radical cyclization was uniquely run at a concentration of 1.6 mM while all other radical cyclizations were run at a concentration of 8 mM. See Table 11 (section 4.3.0) for further details.

product (**95b**) was obtained, presumably owing to increased steric hindrance for the final bond-forming step (although the diastereoselectivity of the reaction was greatly improved for the formation of **94b**).

The presence of minor isomers visible in the proton and carbon NMR spectra made the assignment of the relative stereochemistry of **94** quite difficult; **94a** (Figure 38) was approximately a 4:1 ratio of major isomers (1.00:0.28 dr), each of which could be further resolved by NMR into a mixture of secondary geometrical isomers (0.17:0.06 dr) while **94b** was only a 5:1 ratio of major isomers (1.00:0.20 dr). In addition, the presence of tin satellites created an extra level of difficulty when analyzing the ^1H NMR spectrum.

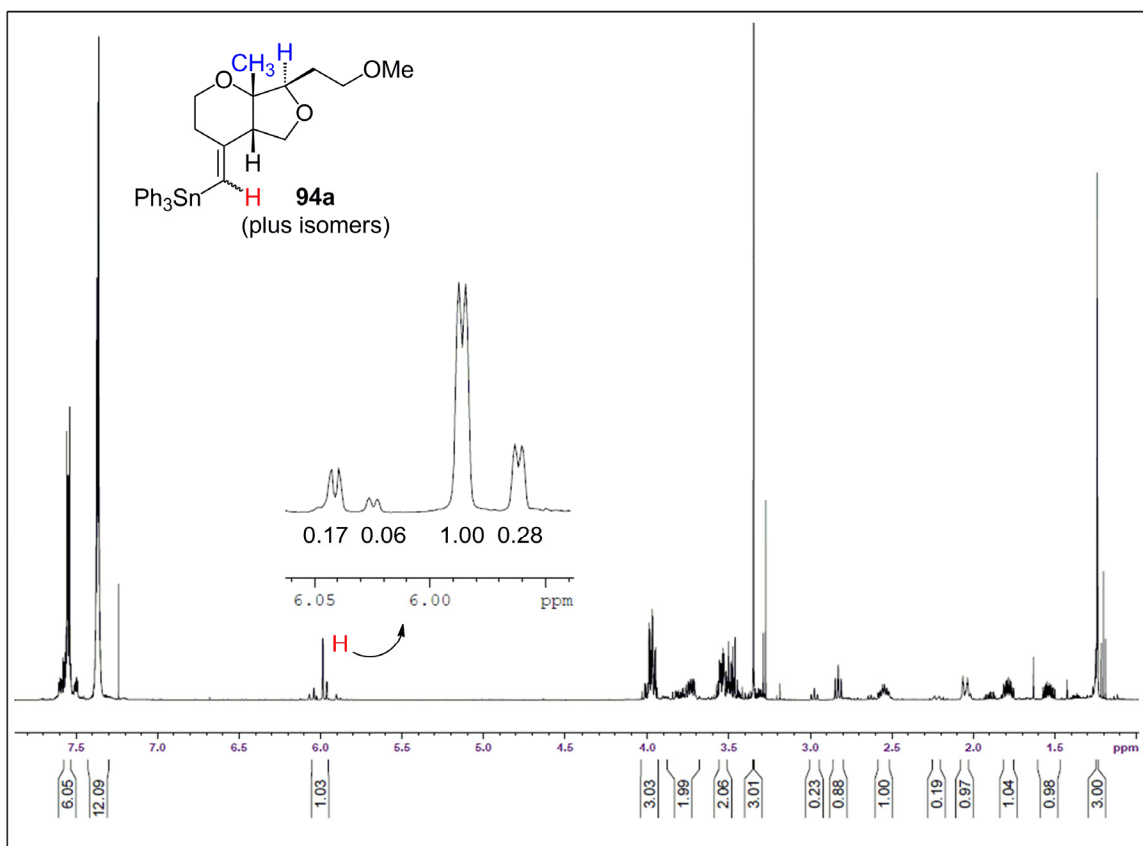
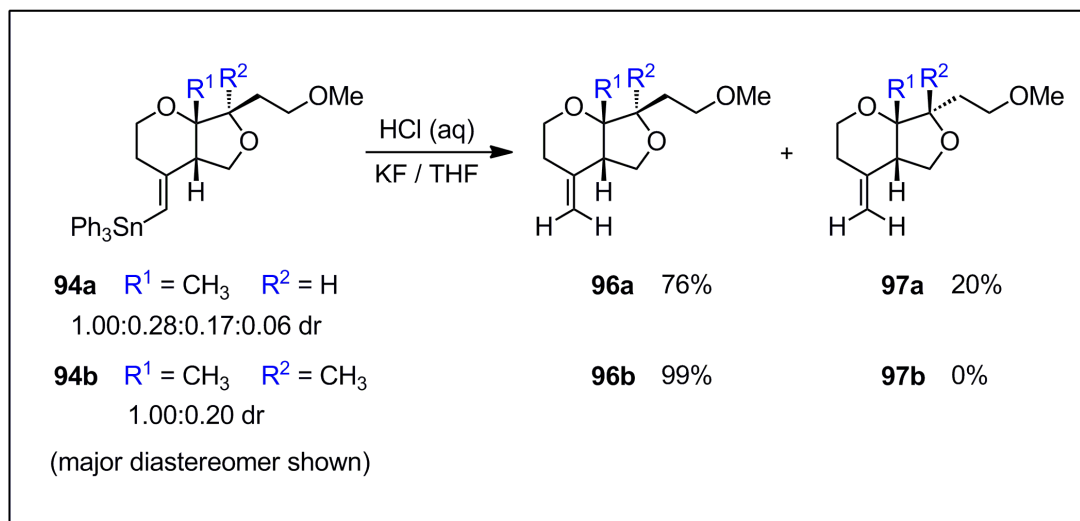


Figure 38. ^1H NMR spectrum of **94a**.

Therefore, to simplify the overall structure and assignment of the final products, we applied our protodestannylation conditions (aqueous HCl and KF) to remove the triphenyltin species (Scheme 79).



Scheme 79. Protodestannylation reaction conditions.

Assignment of relative stereochemistry to each of the final products (**96** and **97**) was accomplished with 2D NMR methods (COSY, NOESY, HSQC, HMBC – see Appendix 3). Interestingly, destannylation of **94a** afforded both possible diastereomers of product (**96a** (Figure 39a) and **97a** (Figure 39b), again in a 4:1 ratio) in high overall yield (combined yield of 96%) while destannylation of **94b** provided a single diastereomer of product (**96b**, Figure 39c) in excellent yield (99%).

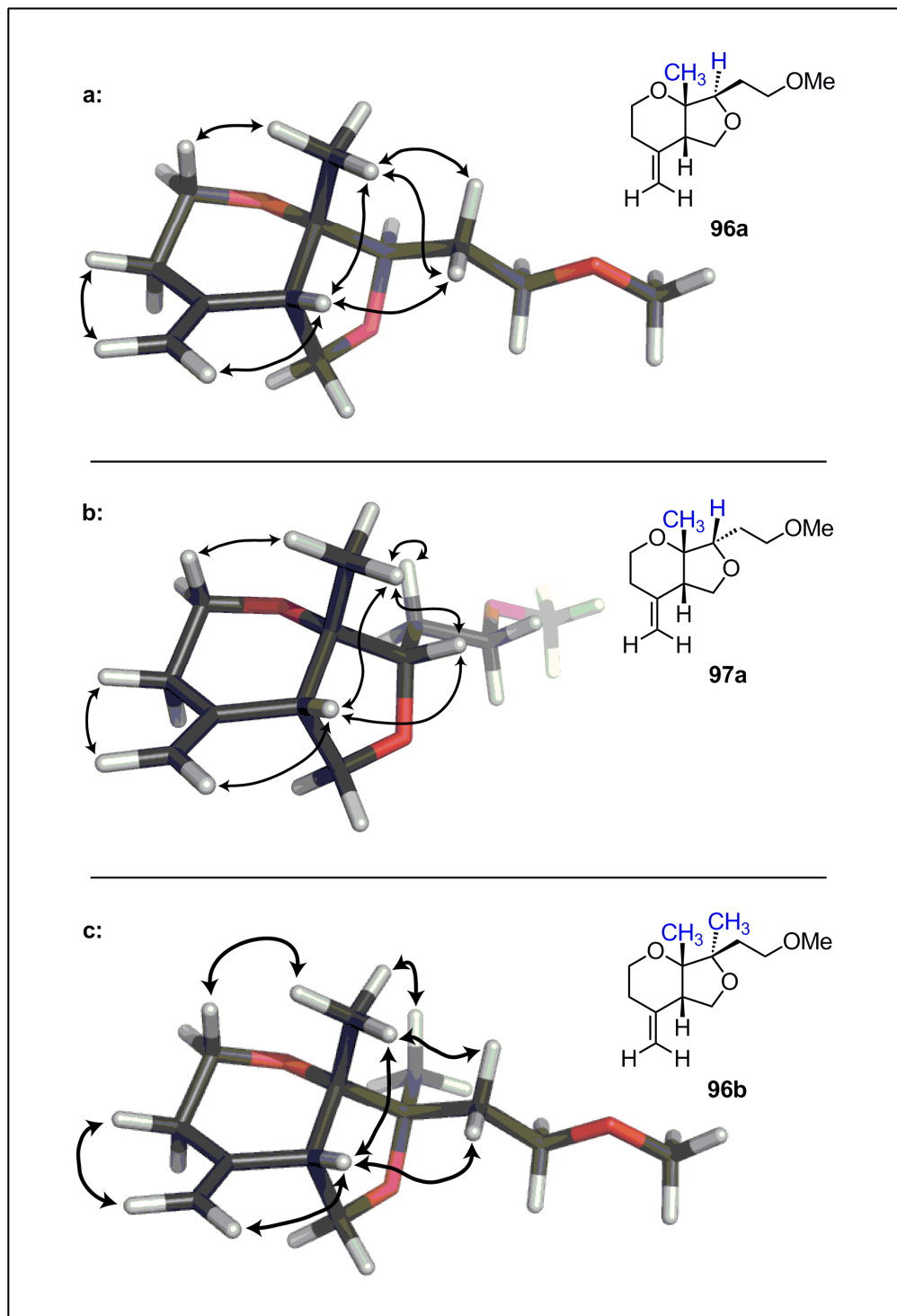


Figure 39. The nOe interactions observed for compounds 96a, 97a, and 96b.

Figure 39 presents structural representations of compounds **96a**, **97a**, and **96b** and provides arrows to specify which ^1H - ^1H correlations were observed in the COSY and NOESY 2D NMR analysis. These results indicated to us that the bicyclic structure **94b** was in fact formed as a single diastereomer and that the minor isomer observed by ^1H NMR was due to a second geometric isomer at the double bond.

4.3.0 Substrate Scope

With these initial radical cyclization results in hand, we wanted to determine the scope of our radical cyclization reaction and investigate whether different vinyl ether properties (R group size and electronics) would have an effect on the outcome of the cascade cyclization. As such, we applied our iterative protocol to a series of differentially substituted bis-vinyl ether analogues (Table 8 – Table 10).

Table 8. Iterative synthesis of bis-vinyl ether substrates.

| entry | R^1 | R^3 | substrate | addition yield | ($E:Z$) | substrate | reduction yield | ($E:Z$) |
|-------|----------------------|-----------------|------------|----------------|-----------|------------|-----------------|-----------|
| 1 | CH ₃ | Et | 78a | 100% | >20:1 | 79a | 99% | >20:1 |
| 2 | H | CH ₃ | 78b | 99% | 7:1 | 79b | 95% | >20:1 |
| 3 | Et | Et | 78c | 96% | 7:1 | 79c | 89% | >20:1 |
| 4 | Ph | Et | 78d | 69% | 5:1 | 79d | 95% | 8:1 |
| 5 | CH ₂ OTHP | CH ₃ | 78e | 73% | 3:1 | 79e | 92% | 3:1 |
| 6 | CF ₃ | Et | 78f | 38% | | 79f | 91% | >20:1 |

+ 59% Z isomer

The first conjugate addition of alkyne **1c** to propiolate **2** was generally high yielding and had good selectivity for the *E* isomer (**78**, Table 8). As was the case in previous chapters, when a more sterically demanding substituent was present at the R^1 position (e.g. $R^1 = CF_3$, entry 6) the *E:Z* selectivity was substantially eroded; the two isomers were, however, cleanly separated chromatographically before proceeding. DIBAL-H reduction of **78** to **79** also occurred very cleanly and in excellent yields (typically >90%). The improved *E:Z* ratio that is consistently observed after the DIBAL-H reduction suggests the possibility that isomerization of the double bond from the *Z* (minor) product to the *E* (major) product might be occurring.

The second round of conjugate additions also typically afforded clean products in high yields and good selectivity (Table 9).

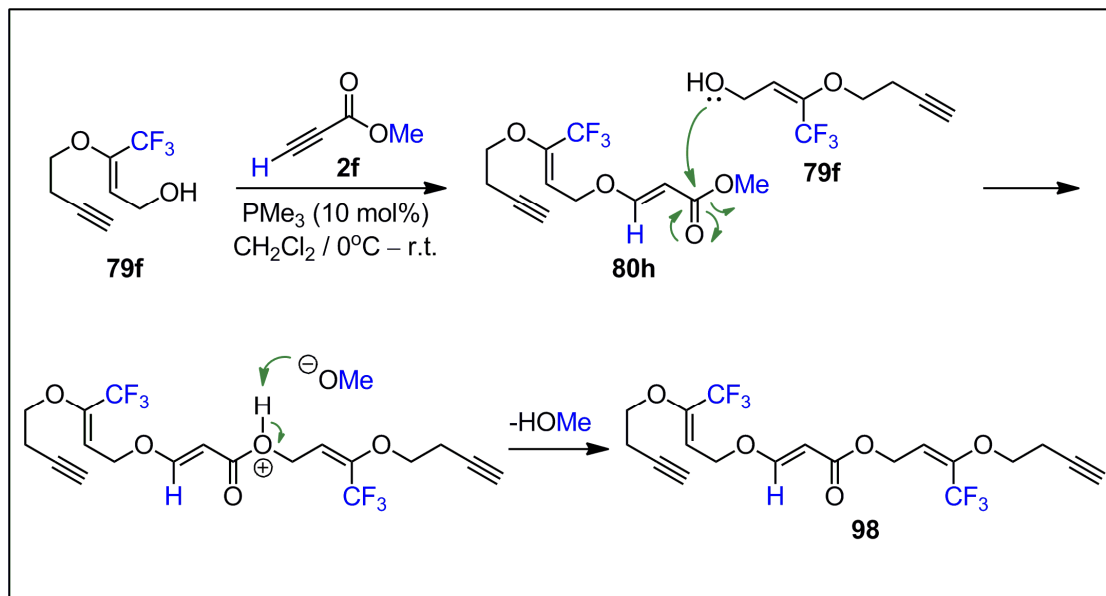
Table 9. Iterative synthesis of bis-vinyl ether substrates.

| entry | R ¹ | R ² | R ³ | substrate | addition yield | (E:Z) ^a | substrate | reduction yield | (E:Z) ^a |
|-------|----------------------|-----------------|-----------------|------------|------------------|--------------------|------------|-----------------|--------------------|
| 1 | CH ₃ | H | CH ₃ | 80a | 93% | 20:1 | 81a | 78% | >20:1 |
| 2 | CH ₃ | CH ₃ | Et | 80b | 99% | 20:1 | 81b | 74% | >20:1 |
| 3 | Et | H | CH ₃ | 80c | 99% | 20:1 | 81c | 75% | >20:1 |
| 4 | Et | Et | Et | 80d | 68% | 20:1 | 81d | 86% | >20:1 |
| 5 | Ph | H | CH ₃ | 80e | 98% | 14:1 | 81e | 90% | >20:1 |
| 6 | Ph | CH ₃ | Et | 80f | 99% | >20:1 | 81f | 97% | >20:1 |
| 7 | CH ₂ OTHP | H | CH ₃ | 80g | 92% | 4:1 | 81g | 82% | 3:1 |
| 8 | CF ₃ | H | CH ₃ | 80h | 64% ^b | 14:1 | 81h | 77% | >20:1 |
| 9 | CF ₃ | CH ₃ | Et | 80i | 99% | 13:1 | 81i | 97% | 9:1 |
| 10 | CF ₃ | CF ₃ | Et | 80j | 41% | | 81j | 84% | 9:1 |

+ 58% Z isomer

^aThe E:Z ratio refers to the ratio of the all-E product to all other adducts. ^bIsolated along with 22% of the transesterification product **98**.

Again the *E:Z* selectivity was significantly eroded when a more hindered electrophile was present at the R² position (e.g. R² = CF₃, entry 10) and the two isomers were cleanly separated before proceeding. An unexpected transesterification product (**98**) was also cleanly isolated (entry 8, where R¹ = CF₃, R² = H), the structure of which was confirmed by HRMS and NMR spectroscopy (Scheme 80).



Scheme 80. Proposed mechanism for the generation of transesterification product **98**.

Depending on the substitution at the R^1 and R^2 positions, bis-vinyl ethers **80** were occasionally prone to unwanted Claisen rearrangements. These unwanted rearrangements mirrored the observed reactivity described in Chapter 3 (Figure 30) where an electronic mismatch between an electron-rich R^1 group and an electron-poor R^2 group (or an electron-neutral R^1 group and a very electron-poor R^2 group) accelerated to different degrees the rate of the Claisen rearrangement observed in our vinyl ether systems. To minimize the electronic mismatch between R groups, we focused our methodology on substrates that contained an alkyl group or proton at the R^2 position. After DIBAL-H reduction of **80** to alcohol **81**, Claisen rearrangement was no longer observed.

Methylating reaction conditions were then applied to alcohol substrates (**81**) to yield our final cyclization precursors (**83**) again in relatively good yields and *E:Z* selectivity (Table 10).

Table 10. Methylation of bis-vinyl ether substrates.

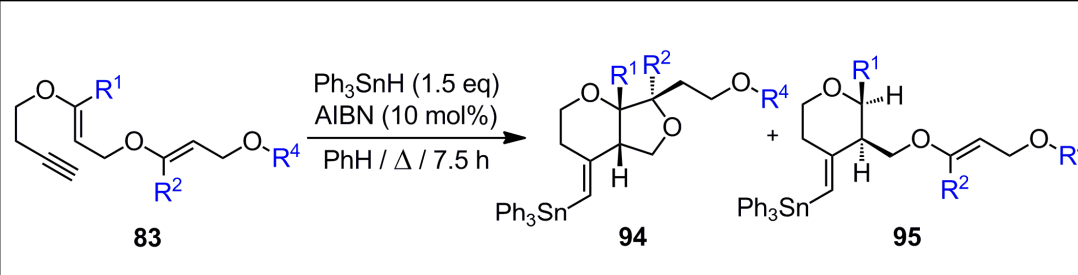
| entry | R ¹ | R ² | substrate | methylation yield | (<i>E</i> : <i>Z</i>) ^a |
|-------|----------------------|-----------------|------------|-------------------|--------------------------------------|
| 1 | CH ₃ | H | 83a | 92% | 8:1 |
| 2 | CH ₃ | CH ₃ | 83b | 85% | >20:1 |
| 3 | Et | H | 83c | 72% | 20:1 |
| 4 | Et | Et | 83d | 69% | >20:1 |
| 5 | Ph | H | 83e | 96% | >20:1 |
| 6 | Ph | CH ₃ | 83f | 99% | >20:1 |
| 7 | CH ₂ OTHP | H | 83g | 94% | 3:1 |
| 8 | CF ₃ | H | 83h | 43% | >20:1 |
| 9 | CF ₃ | CH ₃ | 83i | 86% | 7:1 |
| 10 | CF ₃ | CF ₃ | 83j | 46% | >20:1 |

^aThe *E*:*Z* ratio refers to the ratio of the all-*E* product to all other adducts.

To ensure pristine material was obtained prior to radical cyclization, all products (**78** – **83**) were purified over triethylamine-treated silica.

With this array of methylated bis-vinyl ethers (**83**) in hand, each substrate was subjected to identical radical cyclization conditions (Table 11).

Table 11. Radical cyclization across bis-vinyl ethers.



| entry | substrate | R ¹ | R ² | R ⁴ | concentration | yield (dr) ^a | |
|-------|------------|----------------------|-----------------|-----------------|---------------|---------------------------|--------------------------|
| | | | | | | 94 | 95 |
| 1 | 83a | CH ₃ | H | CH ₃ | 8 mM | 94a 77% (4:1) | — ^b |
| 2 | 83b | CH ₃ | CH ₃ | CH ₃ | 8 mM | 94b 33% (5:1) | 95b 54% (4:1) |
| 3 | 83b | CH ₃ | CH ₃ | CH ₃ | 1.6 mM | 94b 55% (5:1) | 95b 27% (3:1) |
| 4 | 83c | Et | H | CH ₃ | 8 mM | 94c 76% (8:1) | — ^b |
| 5 | 83d | Et | Et | CH ₃ | 8 mM | — ^b | 95d 67% (2:1) |
| 6 | 83e | Ph | H | CH ₃ | 8 mM | 94e 80% (4:1) | — ^b |
| 7 | 83f | Ph | CH ₃ | CH ₃ | 8 mM | — ^b | 95f 72% (12:1) |
| 8 | 83g | CH ₂ OTHP | H | CH ₃ | 8 mM | 94g 67% (2:1) | — ^b |
| 9 | 83h | CF ₃ | H | CH ₃ | 8 mM | 94h 64% (7:1) | — ^b |
| 10 | 81a | CH ₃ | H | H | 8 mM | 94i 81% (1.4:1) | — ^b |
| 11 | 89 | CH ₃ | H | Bn | 8 mM | 94j 74% (2.7:1) | — ^b |

^aReported values refer to the ratio between the major observed product and the next most abundant species. ^bProduct was not observed in >10% yield.

Not surprisingly, the reaction leading exclusively to bicycle **94** was most efficient for substrates in which the R^2 group was a proton (Table 11, entries 1, 4, 6, 8, and 9) whereas substrates bearing bulkier alkyl groups at the R^2 position were more resistant to bicycle formation (Table 11, entries 2, 3, 5, and 7).

In the case of bis-vinyl ether **83b** where a mixture of bicyclic and monocyclic products was obtained, the use of higher dilution (1.6 mM, Table 11, entry 3) afforded more of the bicyclic product **94b** with two adjacent quaternary centers (vs monocyclic product **95b**) compared to the standard dilution of 8 mM (Table 11, entry 2). Further increasing the size of the substituents at the R^2 position (Table 11, entries 5 and 7) blocked the formation of **94** such that only monocyclic products **95d** and **95f** were isolated. In the case of **83d**, however, small amounts of product (<5% by ^1H NMR) with signals indicative of bicyclic product were present in the crude material. Unfortunately, no bicyclic product for this substrate could be cleanly isolated.

Finally, in place of the terminal methyl ether the presence of either a free hydroxyl group (Table 11, entry 10) or a benzyl protecting group (Table 11, entry 11) did not adversely affect the yield of the final products **94i** or **94j**. However, in both cases the diastereoselectivity was eroded.

4.4.0 Mechanistic Analysis

Hexahydrofurofurans of the type described here have potential applications toward the synthesis of biologically active compounds as these molecules and oxidized forms thereof have been utilized in medicinal chemistry programs¹²⁵ and also comprise the core structures of several natural products (Figure 40).¹⁴⁵ As such, we considered the factors that underpin the regio- and stereochemical control in our radical cascade since the compounds we are generating have potential applications towards some medicinally related compounds.

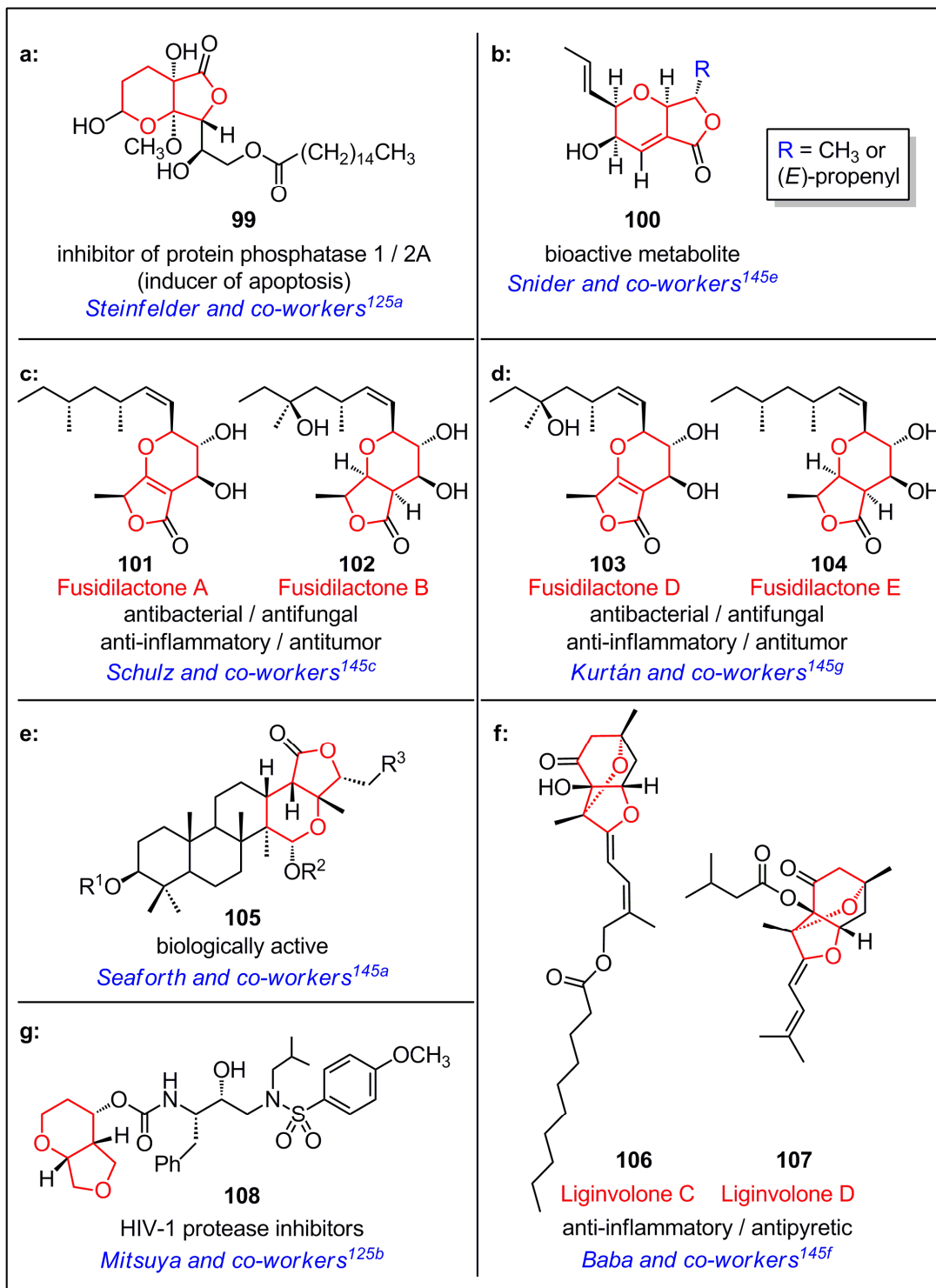
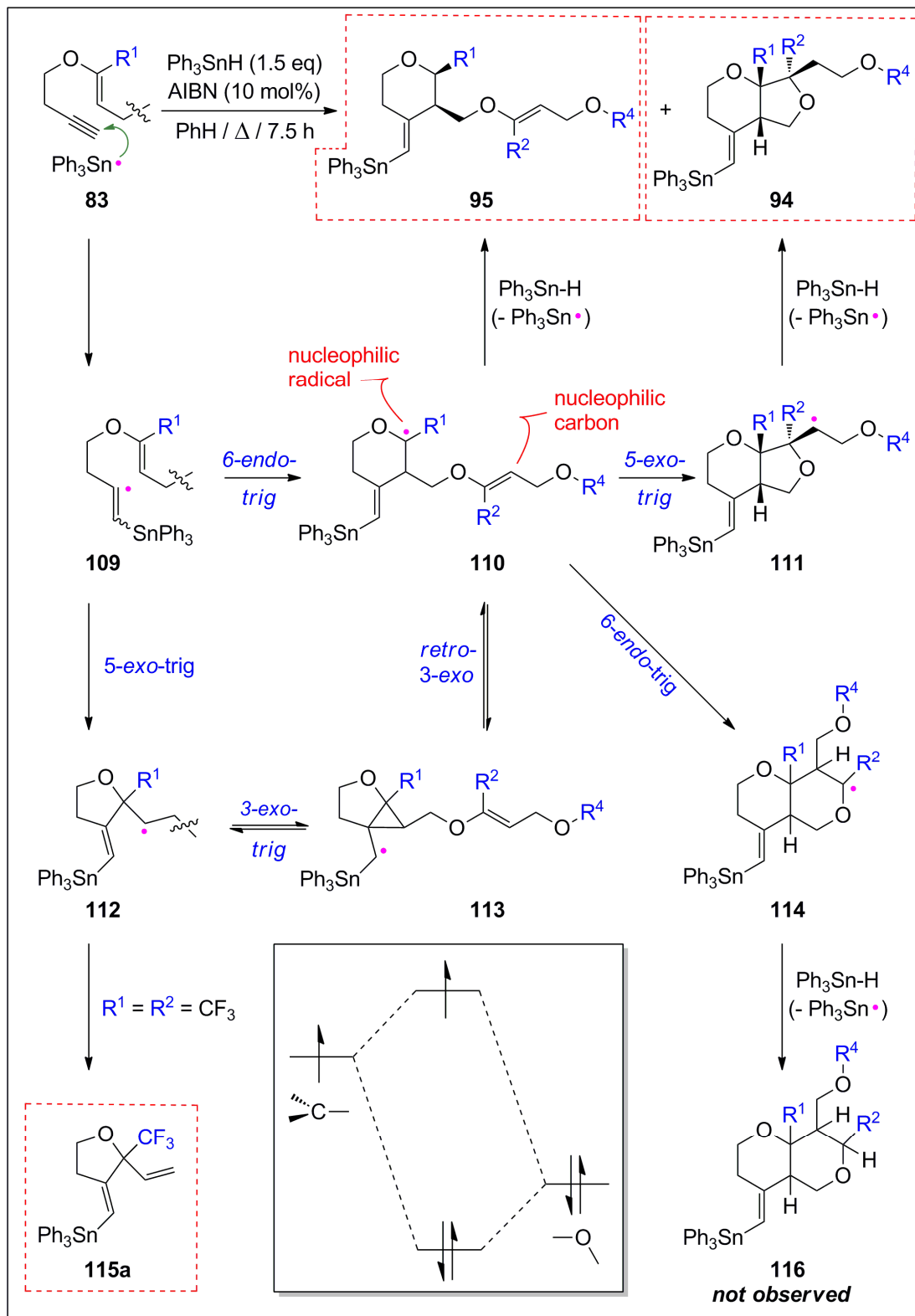


Figure 40. Examples of hexahydrofuroprans present in the literature.^{125,145}

As depicted in Figure 35, the Pattenden group showed that all-carbon polyenes (**59**) that are structurally related to our oligo-vinyl ether systems reliably react through a series of *6-endo-trig* cyclizations to generate large steroid like polycycles (**60**), a fact that has been attributed to steric control.^{133,135-136} Since methyl ether **82b** generated both the 5- and 6-membered ring products (**91b** and **92b**, Scheme 74) while methyl ether **82a** afforded exclusively the 6-membered ring product (**91a**, Scheme 75), it appears that steric control is likewise important for our analogous vinyl ether substrates, although electronic factors presumably play a role as well.

As depicted in Scheme 81, there are several possible mechanistic pathways (and synthetic outcomes) available from our bis-vinyl ether systems when our standard radical cyclizations conditions are applied.



Scheme 81. Proposed mechanism for the radical cascade.

In contrast to radical cascades on structurally related all-carbon polyene systems (which typically react through a series of *6-endo-trig* cyclizations),^{133,135} the cascade cyclization described here proceeds via an unusual *6-endo-trig/5-exo-trig* route, presumably owing to electronic factors associated with the vinyl ether scaffold.¹³⁶ After the first cyclization event is complete, electron donation from the adjacent oxygen atom to the radical-bearing carbon increases the energy of the SOMO, thereby enhancing the nucleophilicity of the radical in intermediate **110** (Scheme 81).¹⁴⁶ As such, although a second *6-endo-trig* cyclization (to yield intermediate **114**) would be favored on steric grounds (particularly for derivatives of substrate **83b**), this pathway is disfavored electronically as it would require the nucleophilic radical of intermediate **110** to add to the nucleophilic end of the vinyl ether function. This electronic mismatch might be sufficient to drive the regiochemical switch that we observe here, where addition to the more hindered but less nucleophilic end of the vinyl ether function results in a *5-exo-trig* cyclization to afford intermediate **111** (Figure 41).¹⁴⁷

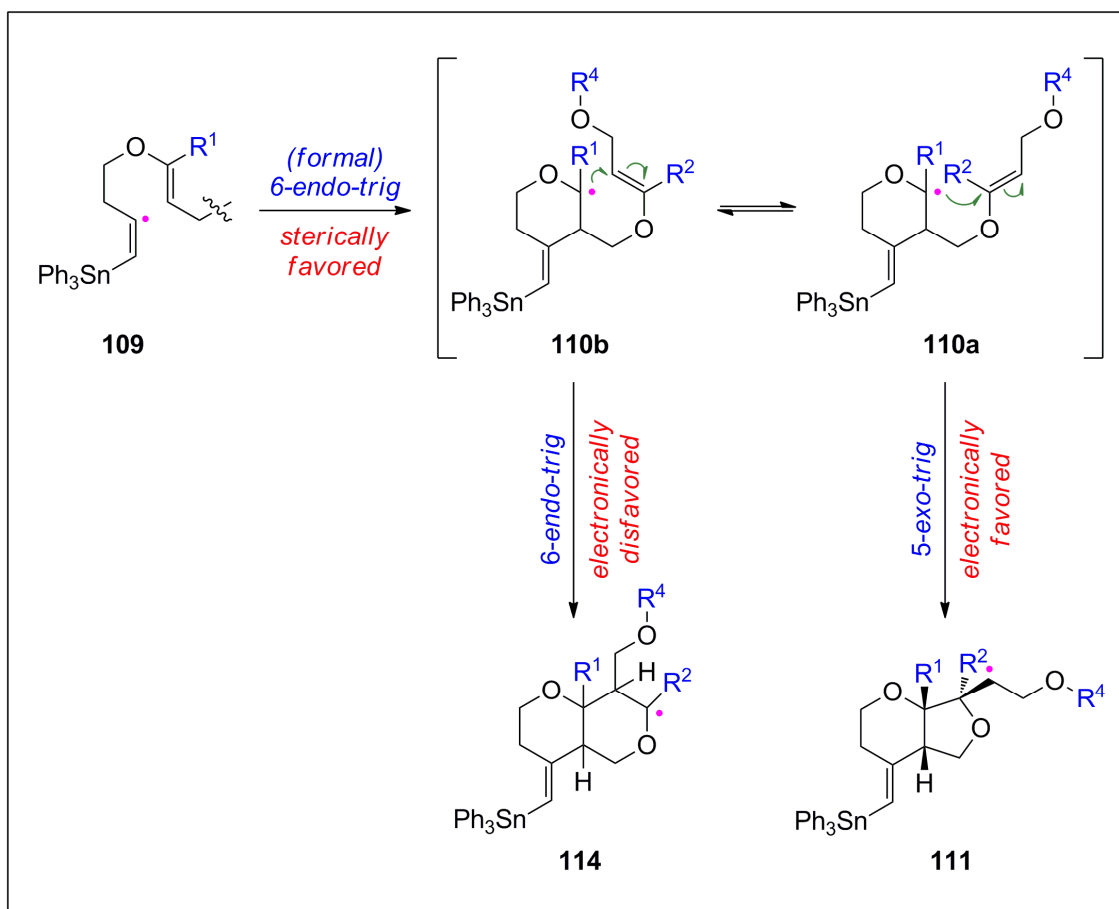
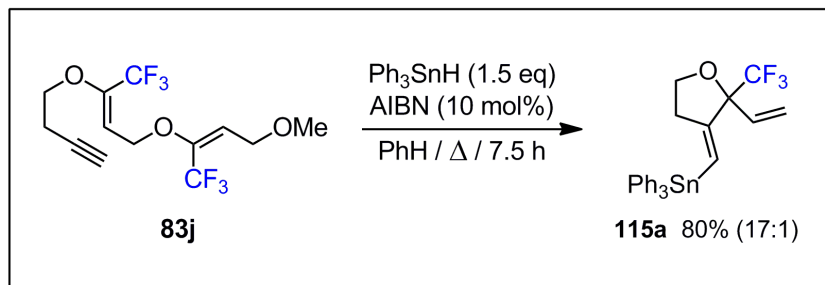


Figure 41. Proposed basis of regioselectivity.

However, this electronic explanation was called into question by one atypical result from our list of methyl ethers (Table 10) that were subjected to our radical cyclization conditions. When methyl ether **83j** ($R^1 = R^2 = CF_3$) was treated under identical conditions to those in Table 11, compound **115a** was exclusively isolated very cleanly and in good yield (Scheme 82). This product appears to originate from a 5-*exo* attack, followed by β -scission.



Scheme 82. A 5-*exo-trig*/β-scission product.

There are several reports in the literature where perceived 6-*endo-trig* cyclizations are determined to proceed through an initial 5-*exo-trig* cyclization, followed by rearrangement to a more thermodynamically stable 6-*endo* product.¹⁴⁸ The isolation of **115a** suggests the possibility that all of our cascading radical cyclizations shown in Table 11 may likewise arise through an initial 5-*exo-trig* cyclization (to intermediate **112**) followed by a 3-*exo* (**113**)/retro-3-*exo* rearrangement to the apparent 6-*endo* intermediate **110** (Scheme 81). Methyl ether **83h** (where $R^1 = \text{CF}_3$ and $R^2 = \text{H}$) is similar to **83j** but less primed to undergo β-scission due to the presence of a proton at the R^2 position. This substrate cyclized in good yield to product **94h** (entry 9, Table 11), a result that supports the 5-*exo* addition/rearrangement hypothesis, although a direct 6-*endo-trig* cyclization cannot be ruled out for other substrates (see section 4.4.1 for details on our ongoing mechanistic studies on the 6-*endo*/5-*exo* radical cascade).

If this 5-*exo* process predominates for the first ring-closing event, the second ring closure (i.e. **110** → **94**, Scheme 81) no longer requires any additional explanation since the product of 5-*exo* addition in this case (**111**) has no mechanistic pathway available to convert to the 6-*endo* product (**114**).

A high level of diastereoselectivity was observed for our radical cyclization process, particularly for the generation of **94b**. We attributed this selectivity to the orientation of the allylic ether side chain during the final cyclization event preferentially away from the tetrahydro-2*H*-pyran core (represented by intermediate **110c**, Figure 41).

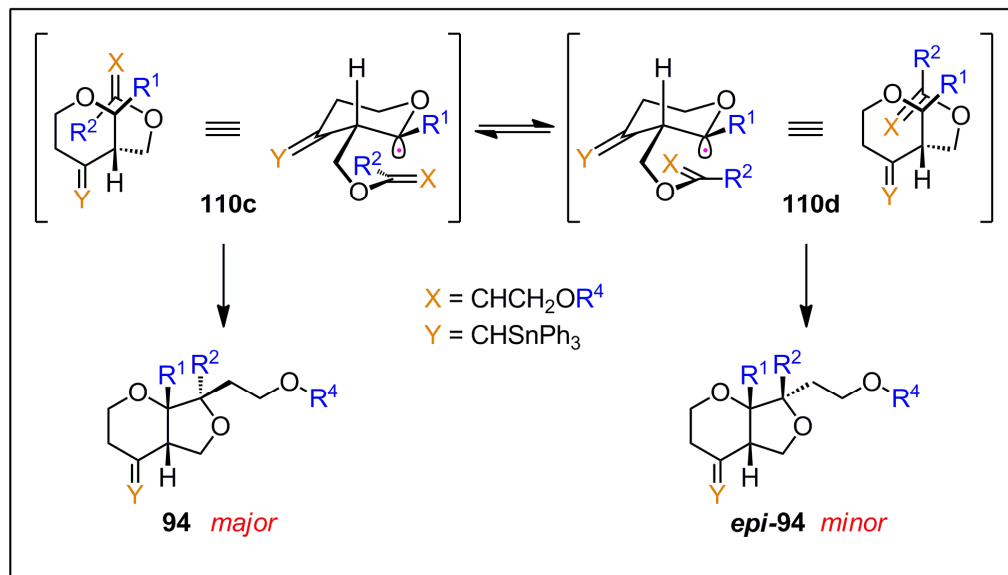


Figure 42. Rational for observed diastereoselectivity.

This rational is supported by the cascade cyclization results presented in Table 11. An increase in selectivity of **94b** (one diastereomer after protodestannylation) over **94a** (a 4:1 mixture of diastereomers after protodestannylation) was observed, perhaps due to a bulkier methyl group in the R^2 position being more easily accommodated *anti* to the R^1 substituent. When a bulky protecting group was introduced into the R^1 position (as was the case for the THP protected alcohol of substrate **94g**), a decrease in selectivity was observed (2:1), suggesting that the THP group may present an obstacle for the allylic ether. This model for the final cyclization step may also account for why substituents larger than a methyl group are not tolerated at the R^2 position, and therefore generate exclusively the monocyclic product **95**.

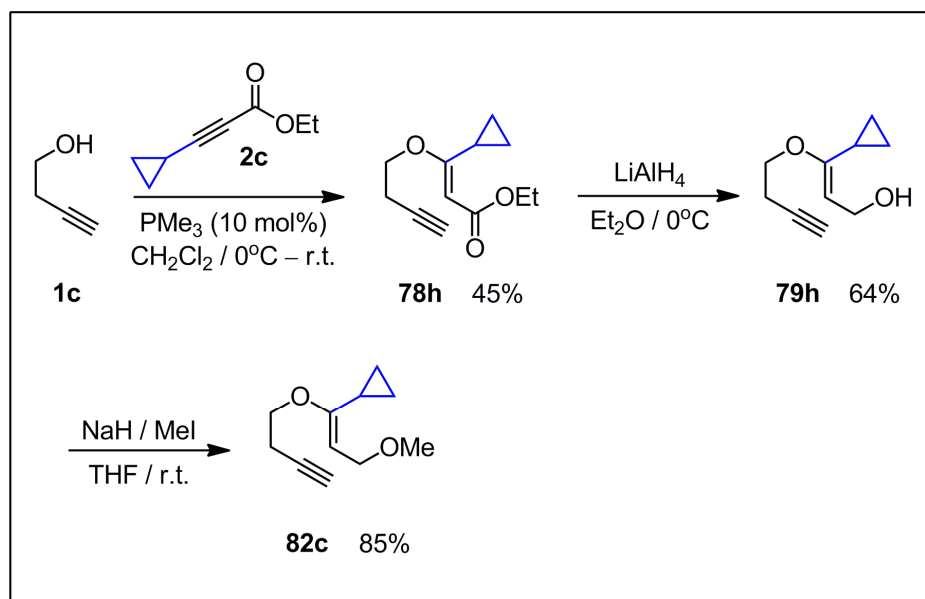
4.4.1 Mechanistic Studies on the 6-endo/5-exo Radical Cascade: Part I

Given the ambiguity as to the general mechanistic pathway for the first ring closing event in our cascade cyclization process, we wanted to clarify which mechanism was in fact taking place for all of our vinyl ether substrates: either a direct 6-endo-*trig* cyclization to intermediate **110** or a 5-*exo-trig* cyclization followed by a 3-*exo/retro-3-exo*

rearrangement sequence to **110** (Scheme 81). This work is ongoing in the Wulff group; preliminary results are reported here.

In an effort to probe the mechanistic route for the first ring closing event, a series of radical-trapping experiments using vinyl ether cyclopropyl derivatives were envisioned since cyclopropyl derivatives have been extensively used as radical clocks and mechanistic probes for a variety of systems.¹⁴⁹ We initially chose a simple cyclopropyl group as it was less likely to undergo spontaneous ring-opening (compared to the fast ring-opening diphenylcyclopropyl group) in the absence of a radical intermediate.¹⁵⁰

We first wanted to demonstrate that this strategy would be applicable for our vinyl-ether systems and that the cyclopropyl ring would open when the radical intermediate was present. As such, we used our conjugate addition/reduction protocol to synthesize methyl ether **82c** (Scheme 83).

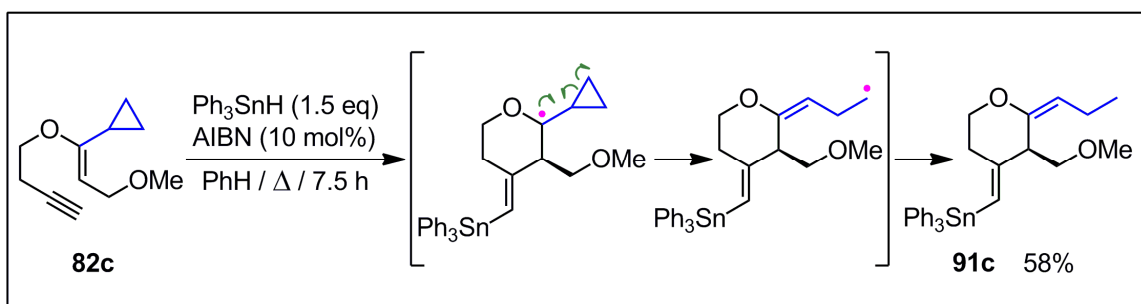


Scheme 83. Preparation of cyclopropyl derivative 82c.

The conjugate addition proceeded smoothly, albeit in poorer than usual yield. This is likely due to sensitivity of the cyclopropyl group (both in the starting material **2c** and

addition product **78h**). Alcohol **79h** likewise proved somewhat unstable (completely decomposing within 12 hours of its formation), which was problematic for the ‘lengthy’ 4 hour DIBAL-H reduction. As such, we opted for the faster lithium aluminum hydride reduction (1 hour reaction time) to give alcohol **79h** which we immediately methylated to **82c**.

To this methyl ether **82c**, we applied our standard radical cyclization conditions used throughout this body of work (Scheme 84).



Scheme 84. Cyclopropyl derivative radical cascade reaction.

To our delight, when **82c** was treated with triphenyltin hydride and AIBN, the cyclopropyl group ring-opened to give the 6-*endo* product **91c** in 58% yield.

With this initial result in hand, we wanted to synthesize a second cyclopropyl derivative (**119**) from alcohol **79a** that would determine whether or not a 5-*exo*-derived radical intermediate (i.e. intermediate **112** in Scheme 81 and Scheme 85) was being formed (Figure 43).

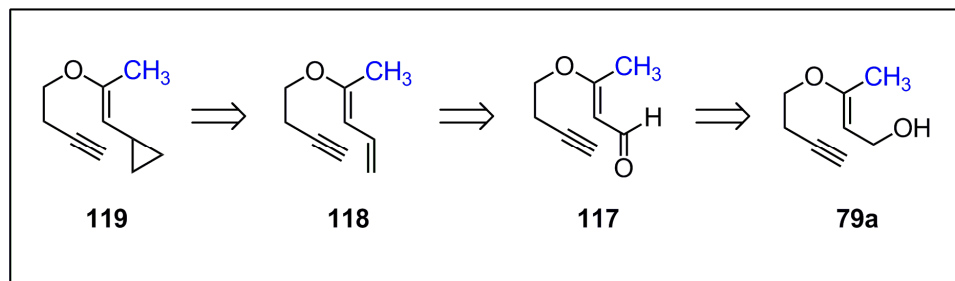
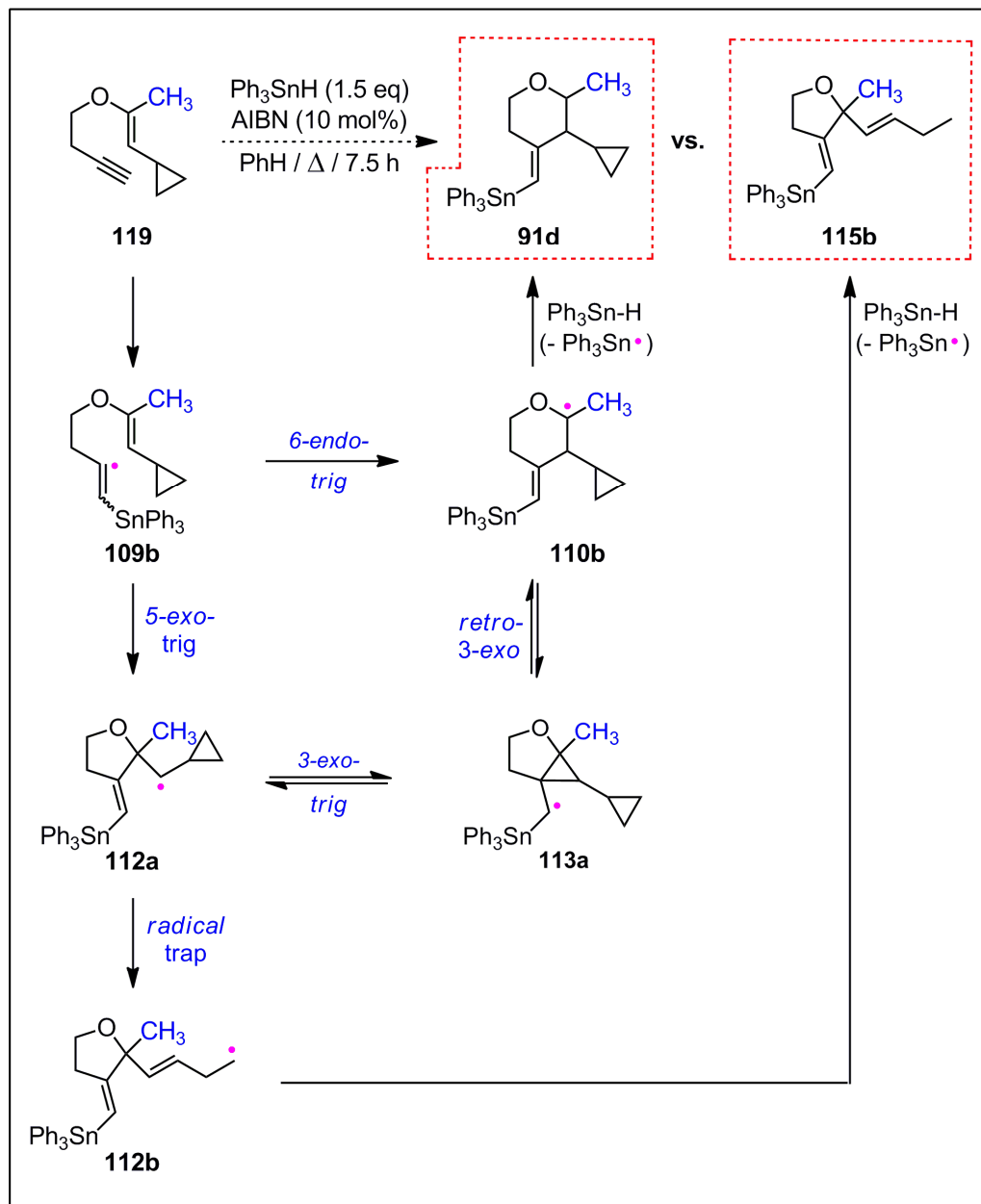


Figure 43. Retrosynthetic analysis of target radical trap precursor 119.

When radical cyclization conditions are applied to cyclopropyl derivative **119**, we would expect to obtain the *5-exo-trig* product **115b** (where the radical has been trapped by the cyclopropane opening), product **91d**, or a combination thereof (Scheme 85).

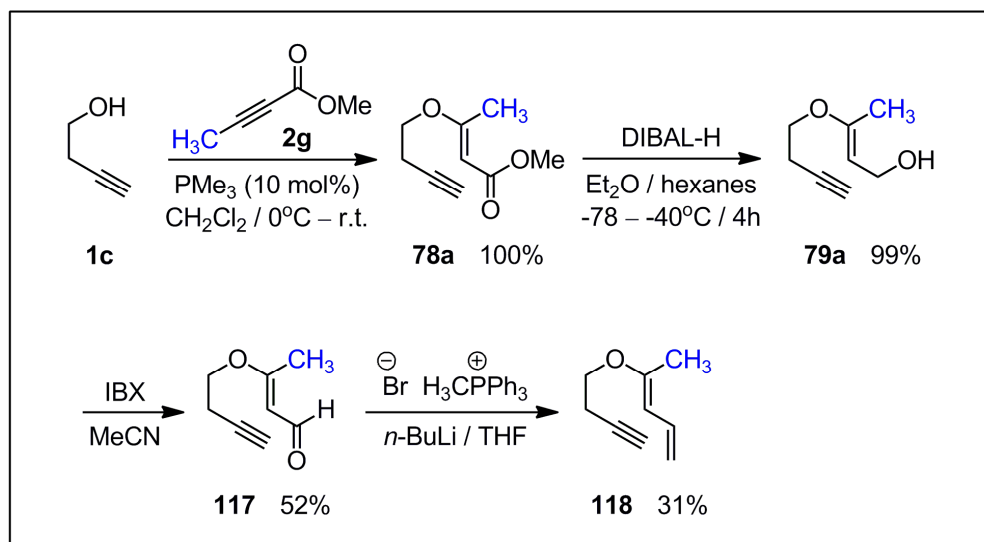


Scheme 85. Potential outcomes of cyclopropyl derivative radical cascade reaction.

If **91d** is the only isolated product, however, our question as to which mechanistic route is occurring will not have been answered. This is because there are two possible pathways to access **91d**; either through a direct 6-endo-trig cyclization or through the postulated 5-exo-trig cyclization followed by a 3-exo/retro-3-exo rearrangement sequence. Other groups have determined the rate of cyclopropane ring opening (k_r) at

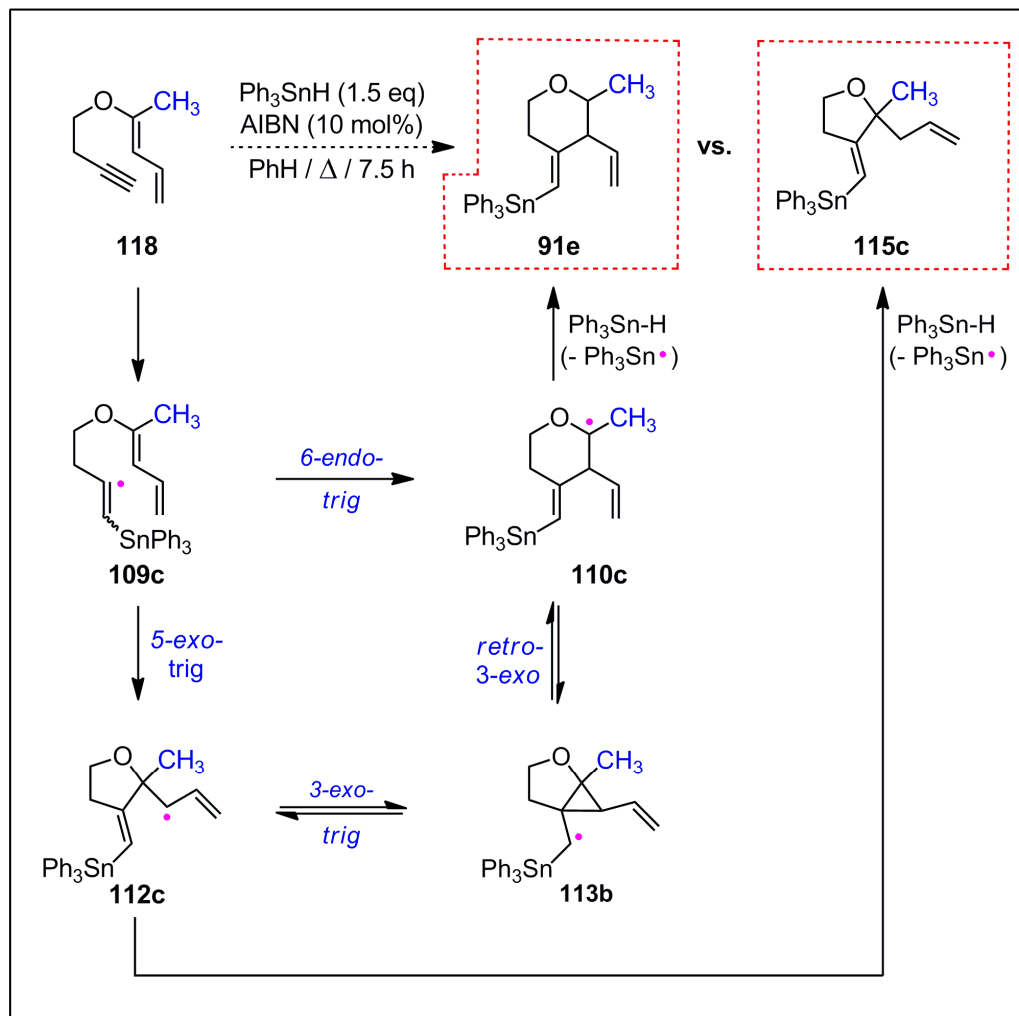
25°C to be from $1.0 \times 10^8 \text{ s}^{-1}$ to $1.2 \times 10^8 \text{ s}^{-1}$ while the rate of a 3-*exo*/retro-3-*exo* rearrangement sequence to be anywhere from $1.3 \times 10^4 \text{ s}^{-1}$ to $9.0 \times 10^8 \text{ s}^{-1}$ at 80°C (depending on the system).^{148b,149} Based on these rates, we decided to start with the cyclopropane ring to see (if in fact we are going through this alternate mechanistic route) whether the ring will open at 97°C (PhH reflux temperature) to give us at a minimum a mixture of **91d** and **115b** as some confirmation to the presence of intermediate **112a**. If no conclusive results can be obtained, we will then turn our attention to the less stable (but faster ring opening) diphenylcyclopropyl ring, which has a ring opening rate of $4 \times 10^{11} \text{ s}^{-1}$.^{149a}

From previously synthesized alcohol **79a** we were able to successfully apply an IBX oxidation¹³⁸ to give us aldehyde **117** cleanly and in reasonable yield, followed by Wittig reaction to provide diene **118** (Scheme 86).



Scheme 86. Preparation of diene 118.

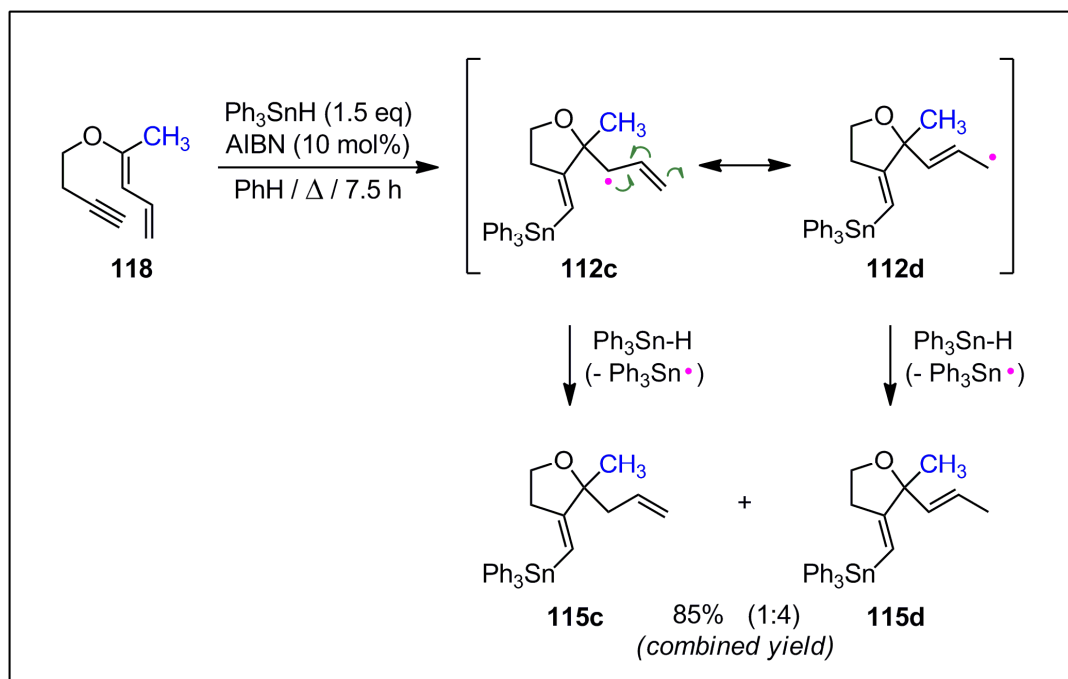
Due to initial synthetic difficulties in accessing **119**, we decided to apply our standard radical cascade reaction to the diene **118** to determine if **115c**, **91e**, or a mixture thereof would be obtained (Scheme 87).



Scheme 87. Potential outcomes of diene radical cascade reaction.

As with the cyclopropane derivative **119** (Scheme 85), isolation of **115c** would provide evidence in support of the hypothesis that our radical cyclizations are going through an indirect *5-exo-trig* cyclization followed by a *3-exo/retro-3-exo* rearrangement sequence. If, however, **91e** were the only isolated product, our question as to which mechanistic route is occurring will not have been answered.

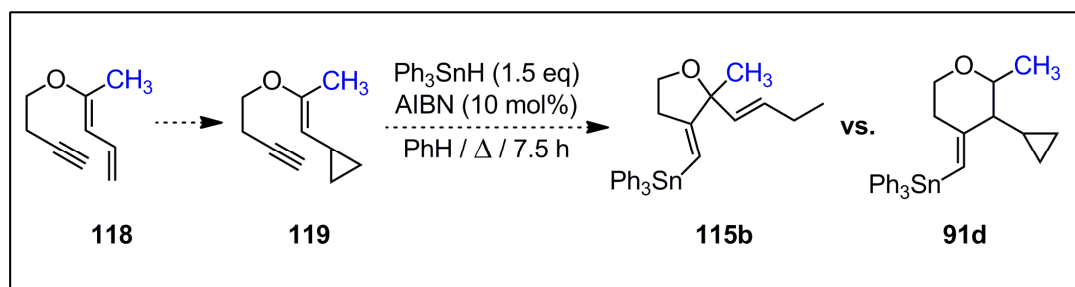
Application of our radical cyclization conditions to diene **118** was completed by Wulff group member Natasha O'Rourke. Surprisingly, we obtained exclusively the *5-exo* product as a mixture of positional isomers (**115c** and **115d**) in good overall yield (Scheme 88).



Scheme 88. Diene derivative radical cascade reaction.

This result supports the hypothesis that our systems are not going through a direct 6-*endo-trig* cyclization to intermediate **110** but rather through an indirect 5-*exo-trig* cyclization followed by a 3-*exo*/retro-3-*exo* rearrangement sequence.

As a final proof that our systems are in fact reacting through this indirect synthetic route, we would like to complete a radical cyclization on derivative **119**. As such, Wulff group graduate student Natasha O'Rourke is currently synthesizing **119** from **118** (Scheme 89).

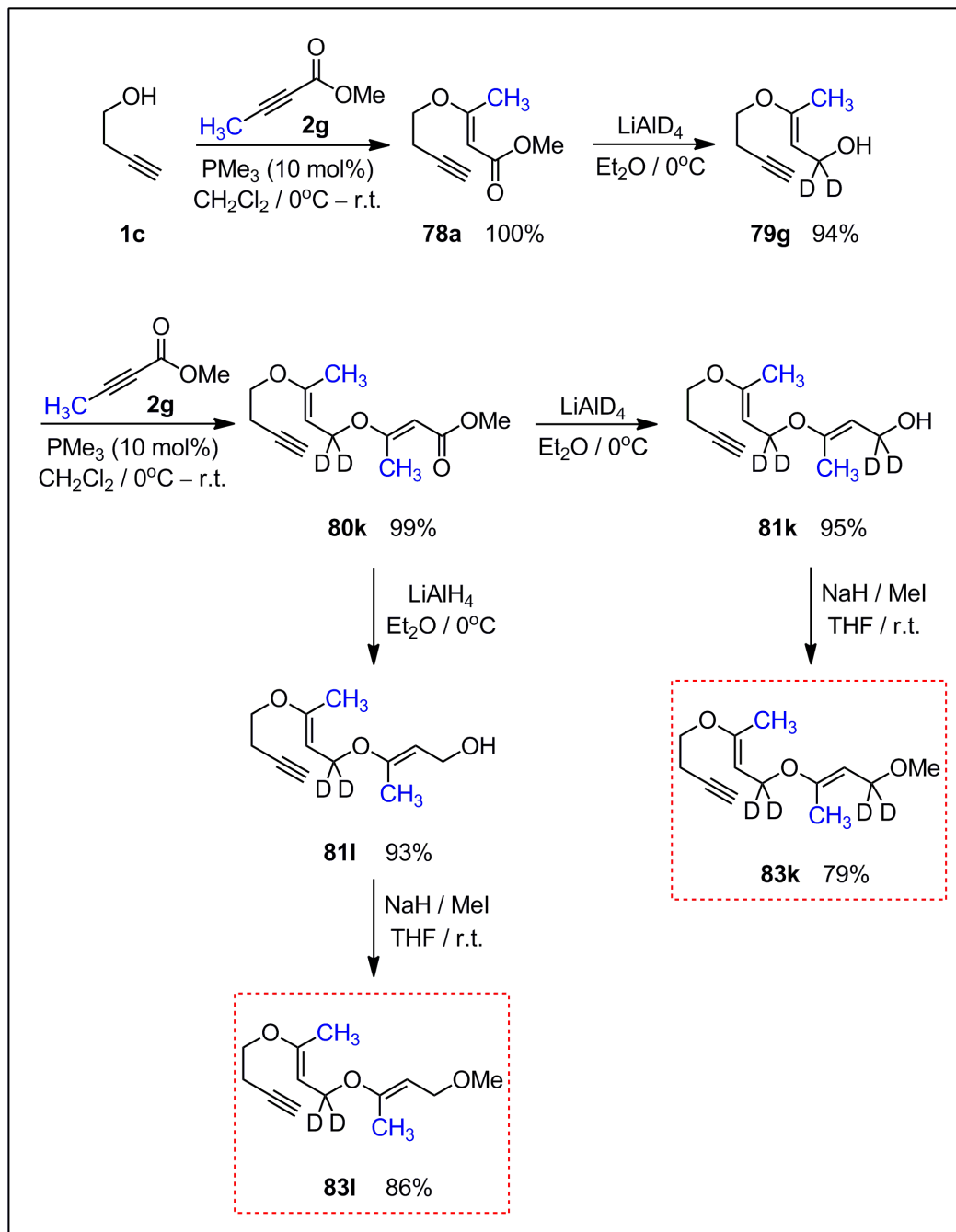


Scheme 89. Final work needing to be completed for cyclopropyl derivative 119.

Once this cyclopropane derivative is in hand, she will apply our radical cyclization conditions to determine if we can successfully trap the radical after the initial 5-*exo* cyclization (via cyclopropane ring opening to give **115b**) before the 3-*exo*/retro-3-*exo* cyclization takes place to give product **91d**.

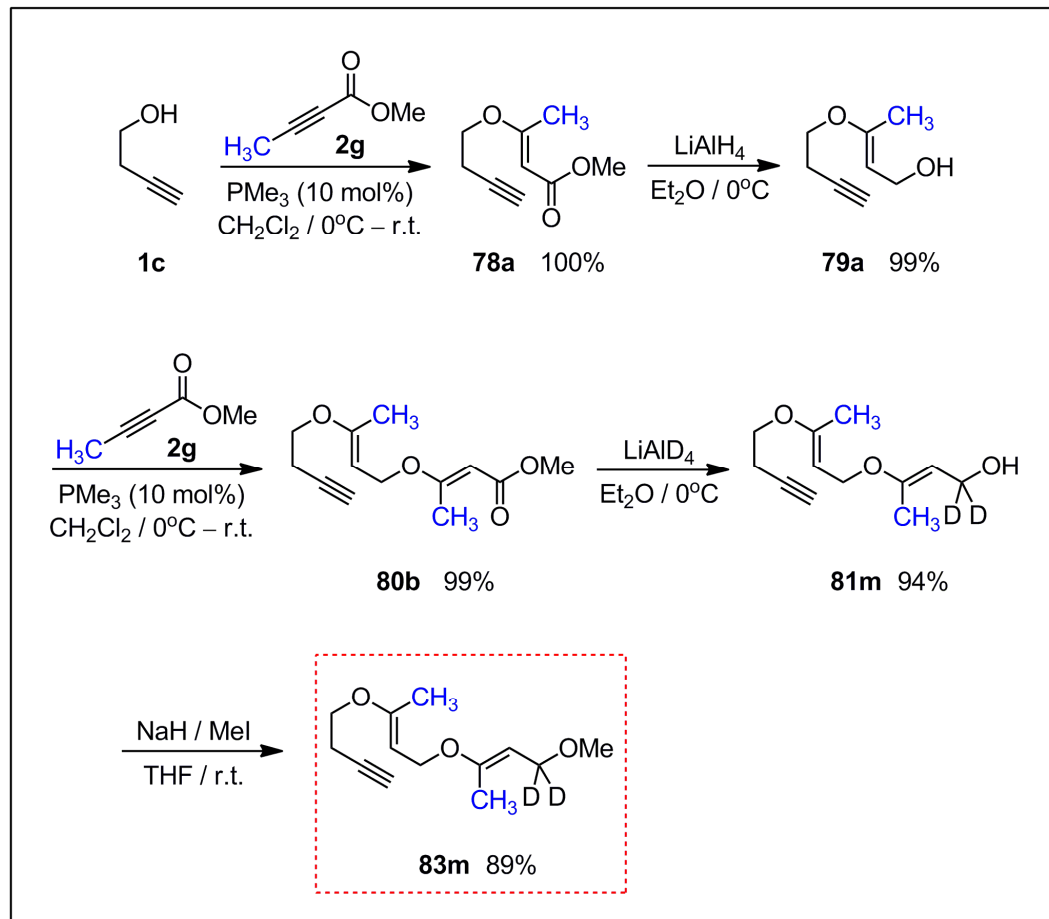
4.4.2 Mechanistic Studies on the 6-*endo*/5-*exo* Radical Cascade: Part II

Whether isolating the bicyclic product **94** or the monocyclic product **95**, the final step in the catalytic cycle is abstraction of a hydrogen atom from triphenyltin hydride. Due to the nature of our vinyl ether analogues, we were initially concerned that hydrogen abstraction might occur from either of the two positions next to the oxygen atoms on the bis-vinyl ether scaffold (either by an intramolecular or intermolecular process, although the intramolecular process is less likely) as the resulting radicals would be highly stabilized. To investigate this possibility, we first prepared a series of deuterated bis-vinyl ether analogues with 2 or 4 deuterium atoms present at the appropriate positions (Scheme 90 and Scheme 91).



Scheme 90. Generation of deuterated incorporated analogues.

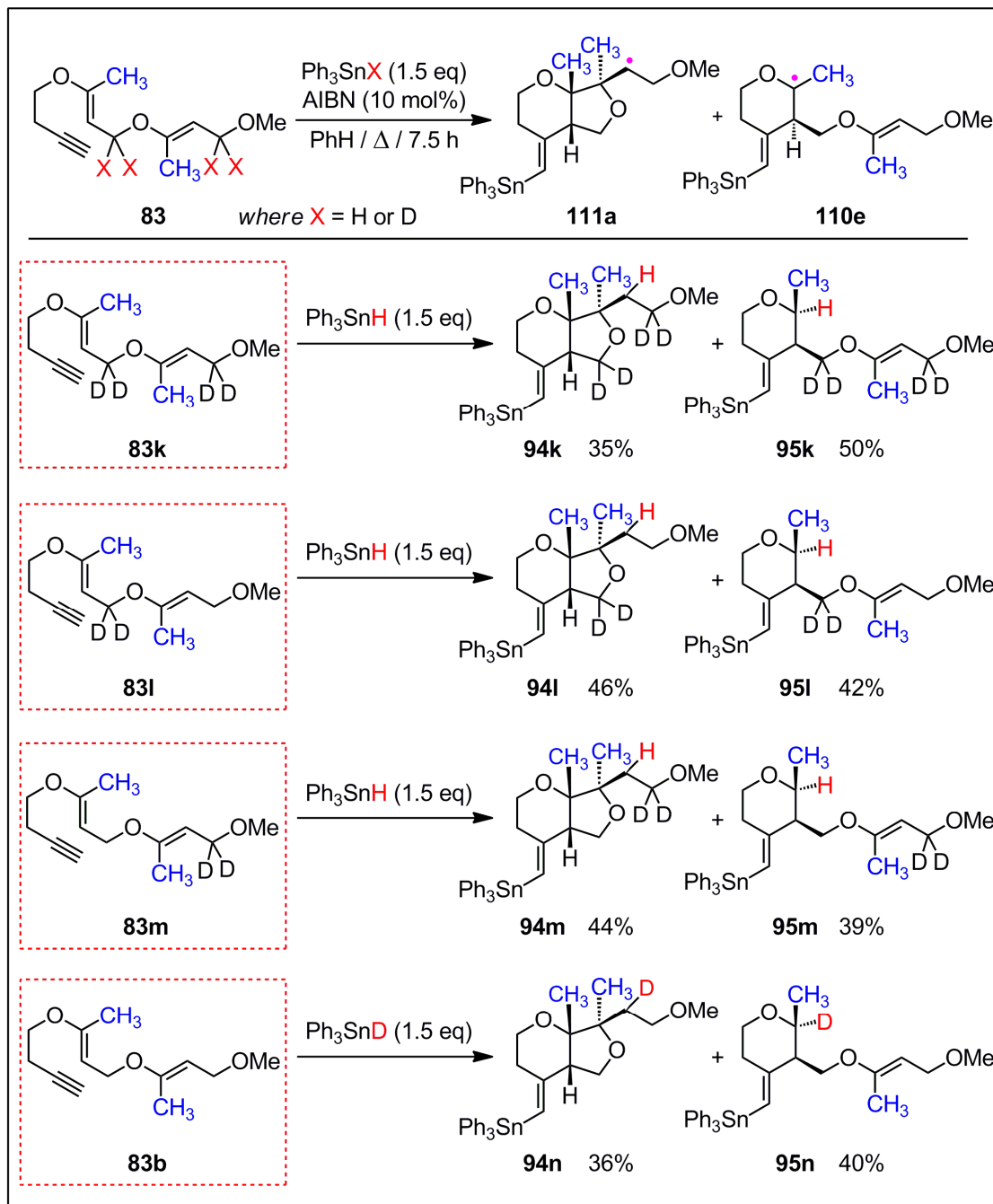
To accomplish this, DIBAL-H promoted reduction, the second step in our iterative protocol, was successfully replaced with a lithium aluminum deuteride reduction to introduce deuterium atoms at the desired positions. Full deuteration at the specified sites on our vinyl ether substrates was confirmed through NMR and HRMS experiments.



Scheme 91. Synthesis of deuterated incorporated analogues.

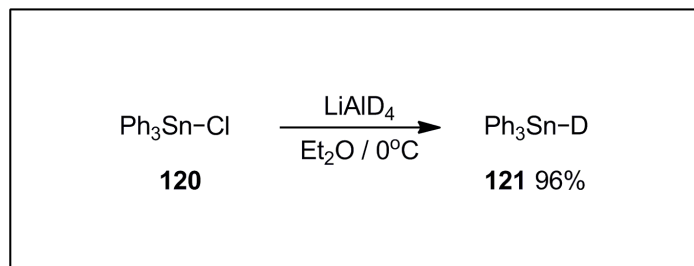
As was the case with our earlier addition/reduction sequences, all of the reactions to generate our deuterated analogues were high yielding and relatively clean, although column chromatography with triethylamine-treated silica gel was used to ensure that perfect material was isolated prior to radical cyclization.

When each of the deuterated bis-vinyl ether analogues (**83k**, **83l**, and **83m**) was subjected to our standard radical cyclization conditions, no deuterium scrambling was observed (Scheme 92).



Scheme 92. Deuterium incorporated radical cascade reactions.

To confirm that the hydrogen atom was therefore being delivered by triphenyltin hydride, the deuterated version, triphenyltin deuteride (**121**), was synthesized by treatment of triphenyltin chloride (**120**) and lithium aluminum deuteride in diethyl ether at 0°C and was isolated in excellent yield (Scheme 93).

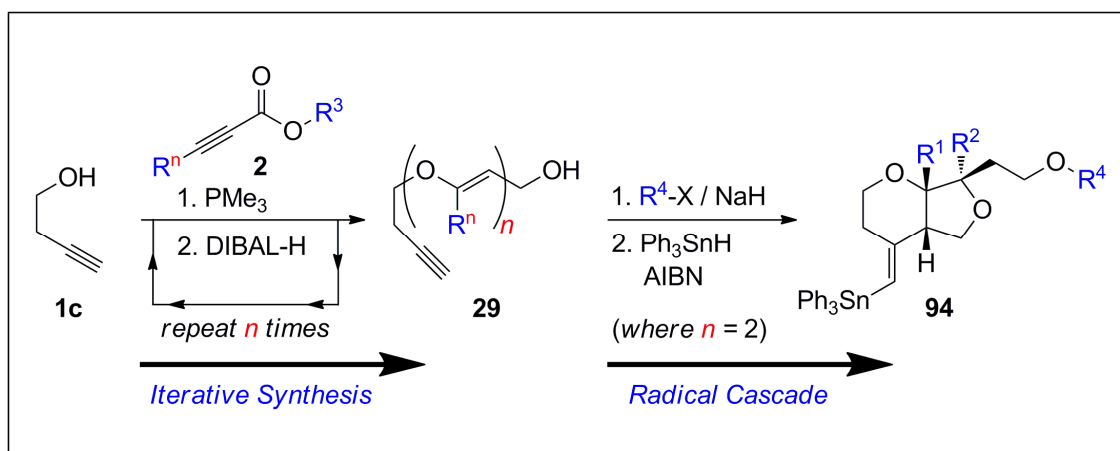


Scheme 93. Synthesis of triphenyltin deuteride.

The use of triphenyltin deuteride (with analogous substrate **83b**) led to quantitative deuteration (confirmed by NMR and HRMS experiments) at the expected positions for both the bicyclic product (**94n**) and the monocyclic product (**95n**, Scheme 92). With this final result, we can conclude that the intermediate open-shell species formed during the reaction (**110** or **111**) are not prone to hydrogen atom migration and that the final step in the catalytic cycle is in fact abstraction of a hydrogen atom from triphenyltin hydride.

4.5.0. Summary

Overall, we discovered the first cascade cyclization across bis-vinyl ether substrates, which are themselves iteratively synthesized from simple building blocks (Scheme 94).



Scheme 94. Marrying iterative synthesis to cascade radical cyclizations.

We explored the scope of the reaction and synthesized some functionally complex bicycles with good overall yields and diastereomeric ratios (Table 11). Mechanistic studies were also completed which point to an initial *5-exo-trig* cyclization (to intermediate **112**) followed by a *3-exo/retro-3-exo* rearrangement sequence (to intermediate **110**) rather than a direct *6-endo-trig* cyclization to intermediate **110**. Finally, we confirmed that the last step in the catalytic cycle for our radical mediated reaction is the specific delivery of a hydrogen atom from triphenyltin hydride.

Chapter 5: Experimental

5.0.0 General Remarks

5.0.1 General Experimental Remarks

All reactions were performed in single-neck, flame-dried, round-bottom flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Liquid reagents were transferred via glass microsyringe. Solvents were transferred via syringe with a stainless steel needle. Organic solutions were concentrated at 35°C by rotary evaporation under vacuum. Analytical thin layer chromatography (tlc) was performed using aluminum plates pre-coated with silica gel (0.20 mm, 60 Å pore-size, 230 – 400 mesh, Macherey-Nagel) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light or a *p*-anisaldehyde indicator solution and heat. Flash-column chromatography was performed as described by Still et al.,¹⁵¹ employing silica gel (60 Å, 63-200 μM, Caledon).

5.0.2 Materials

Commercial solvents and reagents were used as received with the following exceptions. Tetrahydrofuran was dried by distillation over sodium and benzophenone. Dichloromethane, diethyl ether, and methanol were dried by passage through alumina in a commercial solvent purification system (SPS) unless otherwise stated. Benzene was distilled over calcium hydride.

5.0.3 Instrumentation

Proton nuclear magnetic resonance spectra (^1H NMR) were recorded at either 300 MHz or 500 MHz at 23°C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane, and are referenced to residual protium in the NMR solvent ($\text{CD}_3\text{C}(\text{O})\text{CD}_3$, δ 2.05; CDCl_3 , δ 7.26). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sext = sextet, m = multiplet and/or multiple resonances, br = broad, app = apparent), coupling constant in Hertz, and integration. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at either 75 MHz or 125 MHz at 23°C. Carbon chemical shifts are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($\text{CD}_3\text{C}(\text{O})\text{CD}_3$, δ 29.85; CDCl_3 , δ 77.22). Infrared (IR) spectra were obtained using a Perkin Elmer 1000 FT-IR spectrometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad). Optical rotation data was obtained using a Rudolph Research Autopol III Automatic Polarimeter. Concentrations for optical rotation measurements are reported as grams of substrate per milliliter of solvent. Mass spectra were obtained at the University of British Columbia Chemistry Mass Spectrometry Facility or the University of Victoria Mass Spectrometry Facility and Proteomics Centre.

5.1.0 General Experimental Procedures

5.1.1 General Benzyl Halide and Terminal Alkyne Coupling Procedure

Terminal alkyne **7** (2.00 mmol) was added via microsyringe to a stirring mixture of benzyl halide **11** (1.00 mmol), copper (I) iodide (1.00 mmol), and potassium carbonate (2.00 mmol) in dry acetonitrile (2 mL). The resulting slurry was stirred at room temperature for 24 hours. The reaction mixture was then diluted with saturated aqueous ammonium chloride (~5 mL) and extracted with diethyl ether (2 x ~20 mL). The combined organic layers were dried using anhydrous sodium sulfate and passed through a filter to remove the drying agent. The filtrate was concentrated in vacuo and purified by flash-column chromatography (hexanes-ethyl acetate, gradient), to afford **12** as a clear, yellow oils.

5.1.2 General Conjugate Addition Procedure

A solution of alkyne **2** (1.00 mmol) in dry dichloromethane (3 mL) was added at room temperature or 0 °C via cannula to a stirring mixture of alcohol **1** (1.00 mmol) and trimethylphosphine (1.0 M solution in THF, 0.10 mmol) in dry dichloromethane (2 mL). The resulting solution was allowed to warm to room temperature while stirring for 24 hours. The solvent was partially evaporated and the residue was re-suspended in diethyl ether (~30 mL). The resulting mixture was stirred for 2 minutes then filtered through a thin layer of basic alumina. The filtrate was concentrated in vacuo and purified by flash-column chromatography (triethylamine-treated silica gel, hexanes-ethyl acetate, 40:1 to 1:2 gradient), to afford esters as clear, colorless to yellow oils.

5.1.3 General DIBAL-H Reduction Procedure

A solution of diisobutylaluminum hydride (1.0 M solution in hexanes, 2.20 mmol) was added dropwise via syringe to a stirring mixture of ester (1.00 mmol) in diethyl ether[‡] (5 mL) at -78°C. After 1 hour the reaction flask was moved to a -40°C bath. After a further 3 hours, the reaction mixture was poured into a vigorously stirring mixture of Rochelle's salt (0.5 M, 100 mL), diethyl ether (100 mL), and glycerol (0.2 mL/mmol DIBAL-H). Vigorous stirring was continued for 1 hour. The reaction mixture was then extracted with diethyl ether (2 x ~50 mL). The combined organic layers were dried over anhydrous sodium sulfate and passed through a filter to remove the drying agent. The filtrate was concentrated in vacuo and purified by flash-column chromatography (triethylamine-treated silica gel, hexanes-ethyl acetate, 40:1 to 1:2 gradient), to afford alcohols as clear, colorless to yellow oils.

5.1.4 General LiAlH₄/LiAlD₄ Reduction Procedure

Lithium aluminum hydride or lithium aluminum deuteride (2.00 mmol) was added portion-wise to a stirring mixture of ester (1.00 mmol) in diethyl ether (8 mL) at 0°C. After 30 min, the reaction was quenched with 10% KOH (~15 mL) and extracted with diethyl ether (2 x ~20 mL). The combined organic layers were dried over anhydrous sodium sulfate and passed through a filter to remove the drying agent. The filtrate was concentrated in vacuo and purified by flash-column chromatography (triethylamine-treated silica gel, hexanes-ethyl acetate, 20:1 to 1:2 gradient), to afford alcohols as clear, light yellow oils.

[‡] The attempted use of rigorously dried diethyl ether caused the DIBAL-H reduction to repeatedly fail, suggesting that traces of water are required for successful conversion. We found that the use of commercially available bulk-quantity diethyl ether, drawn straight from the 4L bottle, gave the most consistent results.

5.1.5 General Methoxymethyl Chloride Protection Procedure

Methoxymethyl chloride (1.25 mmol) was added dropwise to a stirring mixture of alcohol **24** or **26** (1.00 mmol) and *N,N*-diisopropylethylamine (5 mL) at room temperature. After 24 hours, the reaction was quenched with saturated aqueous ammonium chloride (~15 mL) and extracted with diethyl ether (2 x ~20 mL). The combined organic layers were dried over anhydrous sodium sulfate and passed through a filter to remove the drying agent. The filtrate was concentrated in vacuo and purified by flash-column chromatography (triethylamine-treated silica gel, hexanes-ethyl acetate, 9:1 to 4:1 gradient), to afford **67** or **69** as clear, yellow-tinted oils.

5.1.6 General TBAF Deprotection Procedure

Tetrabutylammonium fluoride (1.25 mmol) was added dropwise to a stirring mixture of protected alcohol **67** or **69** (1.00 mmol) and dry THF (5 mL) at room temperature. After 3 hours, the reaction was quenched with 0.5 M Rochelle's salt (~5 mL) and extracted with diethyl ether (2 x ~20 mL). The combined organic layers were dried over anhydrous sodium sulfate and passed through a filter to remove the drying agent. The filtrate was concentrated in vacuo and purified by flash-column chromatography (triethylamine-treated silica gel, hexanes-ethyl acetate, 4:1 to 1:2 gradient), to afford **68** or **70** as clear, yellow-tinted oils.

5.1.7 General Methylation Procedure

Iodomethane (3.00 mmol) was added dropwise via syringe to a stirring mixture of alcohol **79**, **81**, or **86a** (1.00 mmol) in THF (3 mL) at 0°C. Sodium hydride (60% w/w in mineral oil, 2.00 mmol) was added in one portion to the reaction mixture and the resulting white slurry was allowed to warm to room temperature while stirring for 24 hours. The reaction was quenched with sat. aq. NH₄Cl (~5 mL) and 10% KOH (~15 mL) and extracted with diethyl ether (2 x ~20 mL). The combined organic layers were dried over anhydrous

sodium sulfate and passed through a filter to remove the drying agent. The filtrate was concentrated in vacuo and purified by flash-column chromatography (triethylamine-treated silica gel, hexanes-ethyl acetate, 40:1 to 1:2 gradient), to afford the corresponding methyl ethers **82**, **83**, or **90a** as clear, colorless to yellow oils.

5.1.8 General Benzylation Procedure

Sodium hydride (95% dry, 1.10 mmol) was added in one portion to a stirring mixture of alcohol **81a** (1.00 mmol) in THF (1 mL) at 0°C. After 10 minutes of mixing, benzyl bromide (1.00 mmol) was added via syringe to the reaction mixture and the resulting yellow slurry was allowed to warm to room temperature with stirring over 24 hours. The reaction was quenched with brine (~15 mL) and extracted with diethyl ether (3 x ~20 mL). The combined organic layers were dried over anhydrous sodium sulfate and passed through a filter to remove the drying agent. The filtrate was concentrated in vacuo and purified by flash-column chromatography (triethylamine-treated silica gel, hexanes-ethyl acetate, 20:1 to 1:2 gradient), to afford the corresponding benzyl ether **89**.

5.1.9 General Parikh-Doering Oxidation Procedure

Sulfur trioxide pyridine (16.00 mmol) was added portion-wise at 0°C to a stirring mixture of alcohol **68b** (1.00 mmol) and triethylamine (20.00 mmol) in a 1:1 mixture of DMSO/CH₂Cl₂ (26 mL). The resulting solution was allowed to warm to room temperature while stirring for 5 hours. The reaction was diluted with diethyl ether (30 mL), washed with brine and water (~30 mL each) and extracted with diethyl ether (3 x ~30 mL). The combined organic layers were dried (very quickly) over anhydrous sodium sulfate and passed through a filter to remove the drying agent. The filtrate was concentrated in vacuo to afford the corresponding aldehyde **72b**.

5.1.10 General Thiol-Catalyzed Radical-Mediated Cyclization Procedure

A deoxygenated solution of *tert*-dodecane thiol (2.00 mmol), aldehyde **72b** (1.00 mmol), and 1,1'-azobis(cyclohexanecarbonitrile) (2.00 mmol) in benzene (37 mL) was stirred at reflux (~90°C) under a positive pressure of argon. After 24 hours, the reaction mixture was concentrated in vacuo and purified by flash-column chromatography (hexanes-ethyl acetate, 10:1 to 1:1 gradient) to afford cyclized product **76b**.

5.1.11 General Radical-Mediated Cyclization Procedure

A solution of triphenyltin hydride (1.50 mmol) and azobisisobutyronitrile (0.10 mmol) in deoxygenated benzene (10 mL) was added via syringe pump (in a rubber-free plastic syringe) over 6 hours to a refluxing solution of enyne **81a**, **82**, **83**, **89**, or **118** (1.00 mmol) in deoxygenated benzene (115 mL). The resulting solution was stirred at reflux for an additional 1.5 hours. The reaction mixture was then concentrated in vacuo and purified by flash-column chromatography (hexanes-ethyl acetate, 40:1 to 1:2 gradient) to afford cyclized product **91**, **94**, **95**, or **115**.

5.1.12 General Protodestannylation Procedure

A 15% HCl (15 mL) solution was added to a stirring mixture of stannane **91a**, **94a**, or **94b** (1.00 mmol) in THF (15 mL). The resulting solution was stirred at room temperature for 48 hours. A saturated aqueous KF solution (15 mL) was then added and the resulting mixture was stirred for 10 minutes. The reaction mixture was then extracted with diethyl ether (2 x ~20 mL). The combined organic layers were dried over anhydrous sodium sulfate and filtered through a thin layer of KF (s). The filtrate was concentrated in vacuo and purified by flash-column chromatography (hexanes-ether, 20:1 to 4:1 gradient), to afford the terminal alkene **93a**, **96a**, **96b**, or **97a**.

5.1.13 General IBX Oxidation Procedure

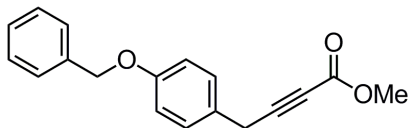
2-Iodoxybenzoic acid (1.50 mmol) was added portion wise to a stirring mixture of alcohol **79a** (1.00 mmol) in acetonitrile (3 mL) at room temperature. After 4 hours, the reaction mixture was diluted with brine (5 mL) and extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate and passed through a filter to remove the drying agent. The filtrate was concentrated in vacuo and purified by flash-column chromatography (triethylamine-treated silica gel, hexanes-ethyl acetate, 9:1 to 1:2 gradient), to afford **117** as a clear, light yellow oil.

5.1.14 General Wittig Reaction Procedure

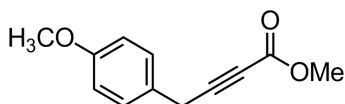
A solution of aldehyde **117** (1.00 mmol) in dry THF (3 mL) was added at -10°C via cannula to a stirring mixture of methyltriphenylphosphonium bromide (1.10 mmol) and *n*-butyllithium (1.10 mmol, 2.5 M in hexanes) in dry THF (4 mL). The resulting solution was stirred from -10°C to room temperature. After 1 hour, the reaction mixture was quickly diluted with water (5 mL) and extracted with diethyl ether (3 x 5 mL). The combined organic layers were dried over anhydrous sodium sulfate and passed through a filter to remove the drying agent. The filtrate was concentrated in vacuo and purified by flash-column chromatography (triethylamine-treated silica gel, hexanes-ethyl acetate, 20:1 to 1:2 gradient), to afford diene **118** as a clear, colorless oil.

5.2.0 Compounds Pertaining to Chapter 2[§]

5.2.1 Experimental Data for 4-Aryl-2-Butynoates (12)

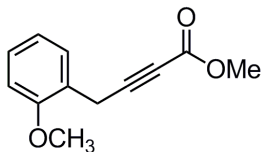


12a. $R_f = 0.72$ (hexanes-ethyl acetate, 2:1); $^1\text{H NMR}$ (CDCl_3) 7.45-7.30 (m, 5H), 7.22 (d, $J = 8.6$ Hz, 2H), 6.93 (d, $J = 8.6$ Hz, 2H), 5.04 (s, 2H), 3.76 (s, 3H), 3.66 (s, 2H); $^{13}\text{C NMR}$ (CDCl_3) 158.1 (C), 154.3 (C), 137.0 (C), 129.2 (CH), 128.7 (CH), 128.1 (CH), 127.6 (CH), 126.4 (C), 115.3 (CH), 87.3 (C), 74.4 (C), 70.2 (CH_2), 52.8 (CH_3), 24.3 (CH_2); IR (Neat, cm^{-1}) 2237 (m), 1714 (s); MS (EI) m/z (%) 280 (17.19), 91 (100.00), 65 (8.11); HRMS calcd for $\text{C}_{18}\text{H}_{16}\text{O}_3$ 280.10994, found 280.11003.

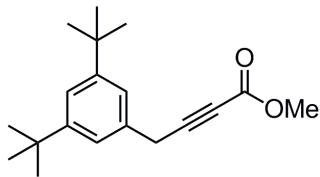


12b. $R_f = 0.34$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ (CDCl_3) 7.20 (d, $J = 8.8$ Hz, 2H), 6.83 (d, $J = 8.8$ Hz, 2H), 3.75 (s, 3H), 3.73 (s, 3H), 3.64 (s, 2H); $^{13}\text{C NMR}$ (CDCl_3) 158.8 (C), 154.2 (C), 129.1 (CH), 126.0 (C), 114.2 (CH), 87.3 (C), 74.3 (C), 55.3 (CH_3), 52.7 (CH_3), 24.1 (CH_2); IR (Neat, cm^{-1}) 2239 (m), 1716 (s); MS (EI) m/z (%) 204 (100.00), 189 (51.74), 145 (56.86); HRMS calcd for $\text{C}_{12}\text{H}_{12}\text{O}_3$ 204.07864, found 204.07881.

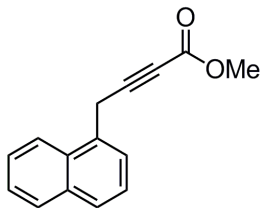
[§] For compounds **23** – **26**, see experimental section 5.4.0 (Compounds Pertaining to Chapter 4 Section 4.1.0) for experimental data.



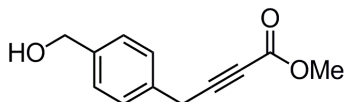
12c. $R_f = 0.69$ (hexanes-ethyl acetate, 2:1); $^1\text{H NMR}$ (CDCl_3) 7.33 (dt, $J = 7.4$ Hz, $J = 0.8$ Hz, 1H), 7.17 (td, $J = 8.7$ Hz, $J = 1.7$ Hz, 1H), 6.87 (td, $J = 7.5$ Hz, $J = 1.1$ Hz, 1H), 6.77 (dd, $J = 8.2$ Hz, $J = 0.8$ Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.63 (s, 2H); $^{13}\text{C NMR}$ (CDCl_3) 156.7 (C), 154.4 (C), 129.1 (CH), 128.6 (CH), 122.6 (C), 120.7 (CH), 110.3 (CH), 87.4 (C), 74.4 (C), 55.5 (CH_3), 52.7 (CH_3), 19.6 (CH_2); IR (Neat, cm^{-1}) 2240 (m), 1713 (s); MS (EI) m/z (%) 204 (100.00), 189 (44.75), 145 (66.05), 115 (67.27); HRMS calcd for $\text{C}_{12}\text{H}_{12}\text{O}_3$ 204.07864, found 204.07856.



12d. $R_f = 0.57$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ (CDCl_3) 7.34 (t, $J = 1.8$ Hz, 1H), 7.16 (d, $J = 1.8$ Hz, 2H), 3.78 (s, 3H), 3.73 (s, 2H), 1.34 (s, 18H); $^{13}\text{C NMR}$ (CDCl_3) 154.4 (C), 151.5 (C), 133.2 (C), 122.5 (CH), 121.4 (CH), 87.6 (C), 74.5 (C), 52.7 (CH_3), 31.6 (CH_3), 25.6 (CH_2); IR (Neat, cm^{-1}) 2240 (m), 1714 (s); MS (EI) m/z (%) 286 (39.67), 271 (100.00), 215 (75.99), 203 (32.41), 57 (89.32); HRMS calcd for $\text{C}_{19}\text{H}_{26}\text{O}_2$ 286.19328, found 286.19319.

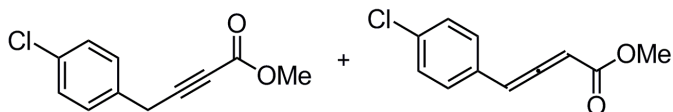


12e. ** $R_f = 0.47$ (hexanes-ethyl acetate, 4:1); major isomer. $^1\text{H NMR}$ (CDCl_3) 7.97-7.80 (m, 3H), 7.61-7.43 (m, 4H), 4.13 (s, 2H), 3.77 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3) 154.2 (C), 133.8 (C), 131.3 (C), 129.9 (C), 128.7 (CH), 128.3 (CH), 126.7 (CH), 126.2 (CH), 126.1 (CH), 125.7 (CH), 123.1 (CH), 86.5 (C), 75.4 (C), 52.8 (CH_3), 22.9 (CH_2); IR (Neat, cm^{-1}) 2240 (m), 1715 (s); MS (EI) m/z (%) 224 (37.48), 209 (13.17), 165 (100.00); HRMS calcd for $\text{C}_{15}\text{H}_{12}\text{O}_2$ 224.08373, found 224.08393.

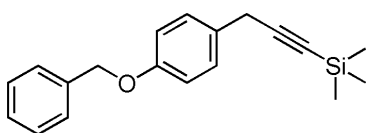


12f. $R_f = 0.15$ (hexanes-ethyl acetate, 2:1); $^1\text{H NMR}$ (CDCl_3) 7.30-7.33 (m, 4H), 4.66 (s, 2H), 3.77 (s, 3H), 3.73 (s, 2H), 1.91 (br s, 1H); $^{13}\text{C NMR}$ (CDCl_3) 154.2 (C), 140.0 (C), 133.5 (C), 128.3 (CH), 127.5 (CH), 86.8 (C), 74.6 (C), 65.0 (CH_2), 52.8 (CH_3), 24.8 (CH_2); IR (Neat, cm^{-1}) 2240 (m), 1713 (s); MS (EI) m/z (%) 204 (76.07), 175 (45.77), 115 (100.00), 107 (42.39); HRMS calcd for $\text{C}_{12}\text{H}_{12}\text{O}_3$ 204.07864, found 204.07877.

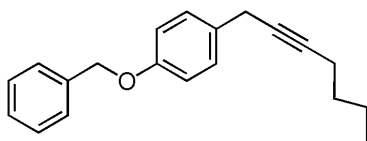
** 1-(chloromethyl)-naphthalene (**11f**) was purchased in 90% purity from Sigma-Aldrich. The remaining 10% of the material is 2-(chloromethyl)-naphthalene. As a result, the isolated product (**12e**) is contaminated with approximately 10% of the corresponding positional isomer.



12g. $R_f = 0.49$ (hexanes-ethyl acetate, 4:1); NMR analysis showed the product to be a 1:6 mixture of products; major isomer. ^1H NMR (CDCl_3) 7.27-7.15 (m, 4H), 3.72 (s, 3H), 3.71 (s, 2H); signals from the minor isomer were observed at 6.53 (d, $J = 6.3$ Hz, 1H), 5.97 (d, $J = 6.3$ Hz, 1H); ^{13}C NMR (CDCl_3) 154.0 (C), 133.1 (C), 132.5 (C), 129.1 (CH), 128.7 (CH), 85.9 (C), 74.8 (C), 52.7 (CH_3), 24.4 (CH_2); signals from the minor isomer were observed at 97.9 (C) and 91.9 (C); IR (Neat, cm^{-1}) 2240 (m), 1715 (s); MS (EI) m/z (%) 210 (34.85), 208 (100.00), 149 (87.90), 139 (92.82); HRMS calcd for $\text{C}_{11}\text{H}_9\text{O}_2^{35}\text{Cl}$ 208.02911, found 208.02919, for $\text{C}_{11}\text{H}_9\text{O}_2^{37}\text{Cl}$ 210.02616, found 210.02649.

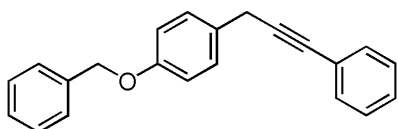


12j. $R_f = 0.76$ (hexanes-ethyl acetate, 4:1); ^1H NMR (CDCl_3 ; 250 MHz) 7.46-7.42 (m, 5H), 7.29 (d, $J = 8.6$ Hz, 2H), 6.97 (d, $J = 8.6$ Hz, 2H), 5.08 (s, 2H), 3.63 (s, 2H), 0.24 (s, 9H); ^{13}C NMR (CDCl_3) 157.5 (C), 137.0 (C), 128.7 (CH), 128.6 (C), 128.5 (CH), 127.8 (CH), 127.3 (CH), 114.8 (CH), 104.7 (C), 86.5 (C), 69.9 (CH_2), 25.2 (CH_2), 0.03 (CH_3); IR (Neat, cm^{-1}) 2175 (m); MS (EI) m/z (%) 294 (24.20), 91 (100.00), 65 (6.19); HRMS calcd for $\text{C}_{19}\text{H}_{22}\text{OSi}$ 294.14399, found 294.14377.

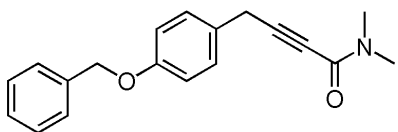


12k. $R_f = 0.73$ (hexanes-ethyl acetate, 4:1); ^1H NMR (CDCl_3) 7.36-7.12 (m, 7H), 6.83 (d, $J = 8.7$ Hz, 2H), 4.95 (s, 2H), 3.42 (t, $J = 3.0$ Hz, 2H), 2.17-2.08 (m, 2H), 1.47-1.27

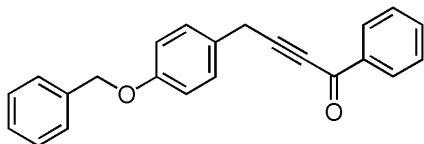
(m, 4H), 0.83 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (CDCl_3) 157.5 (C), 137.3 (C), 130.1 (C), 128.9 (CH), 128.7 (CH), 128.0 (CH), 127.6 (CH), 114.9 (CH), 82.5 (C), 78.0 (C), 70.2 (CH₂), 31.2 (CH₂), 24.4 (CH₂), 22.1 (CH₂), 18.7 (CH₂), 13.8 (CH₃); IR (Neat, cm^{-1}) 2931 (m), 1454 (m); MS (EI) m/z (%) 278 (20.83), 91 (100.00), 65 (7.49); HRMS calcd for $\text{C}_{20}\text{H}_{22}\text{O}$ 278.16707, found 278.16702.



12l. $R_f = 0.44$ (hexanes-ethyl acetate, 9:1); ^1H NMR (CDCl_3) 7.38-7.17 (m, 12H), 6.88 (d, $J = 8.8$ Hz, 2H), 4.99 (s, 2H), 3.69 (s, 2H); ^{13}C NMR (CDCl_3) 157.7 (C), 137.2 (C), 131.8 (CH), 129.2 (C), 129.1 (CH), 128.7 (CH), 128.4 (CH), 128.1 (CH), 127.9 (CH), 127.61 (CH), 123.9 (C), 115.1 (CH), 88.1 (C), 82.6 (C), 70.2 (CH₂), 25.1 (CH₂); IR (Neat, cm^{-1}) 2306 (w); MS (EI) m/z (%) 298 (22.23), 192 (10.26), 91 (100.00); HRMS calcd for $\text{C}_{22}\text{H}_{18}\text{O}$ 298.13577, found 298.13562.



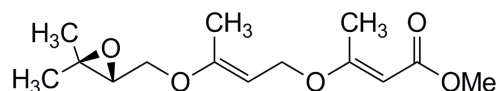
12m. $R_f = 0.22$ (hexanes-ethyl acetate, 2:1); ^1H NMR (CDCl_3) 7.36-7.20 (m, 5H), 7.15 (d, $J = 8.7$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 4.96 (s, 2H), 3.62 (s, 2H), 3.10 (s, 3H), 2.87 (s, 3H); ^{13}C NMR (CDCl_3) 157.9 (C), 154.6 (C), 137.0 (C), 129.1 (CH), 128.6 (CH), 128.0 (CH), 127.5 (CH), 127.2 (C), 115.2 (CH), 90.6 (C), 75.6 (C), 70.1 (CH₂), 38.4 (CH₃), 34.1 (CH₃), 24.5 (CH₂); IR (Neat, cm^{-1}) 2306 (w), 1644 (m); MS (EI) m/z (%) 293 (19.34), 91 (100.00), 72 (8.74); HRMS calcd for $\text{C}_{19}\text{H}_{19}\text{O}_2\text{N}$ 293.14158, found 293.14146.



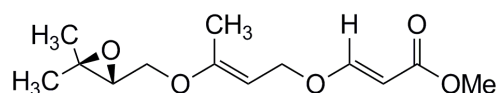
12n. $R_f = 0.14$ (hexanes-ethyl acetate, 9:1); $^1\text{H NMR}$ (CDCl_3) 8.05 (dd, $J = 8.5, 1.4$ Hz, 2H), 7.50 (tt, $J = 7.4, 1.4$ Hz, 1H), 7.41-7.18 (m, 9H), 6.88 (d, $J = 8.7$ Hz, 2H), 4.97 (s, 2H), 3.75 (s, 2H); $^{13}\text{C NMR}$ (CDCl_3) 178.2 (C), 158.1 (C), 137.0 (C), 136.9 (C), 134.1 (CH), 129.7 (CH), 129.2 (CH), 128.7 (CH), 128.7 (CH), 128.1 (CH), 127.6 (CH), 126.8 (C), 115.4 (CH), 94.0 (C), 81.1 (C), 70.2 (CH_2), 24.9 (CH_2); IR (Neat, cm^{-1}) 2254 (m), 1794 (w); MS (EI) m/z (%) 326 (13.66), 235 (10.97), 105 (25.39), 91 (100.00), 77 (13.53); HRMS calcd for $\text{C}_{23}\text{H}_{18}\text{O}_2$ 326.13068, found 326.13049.

5.3.0 Compounds Pertaining to Chapter 3

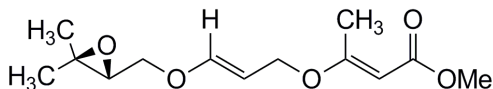
5.3.1 Experimental Data for Bis-Vinyl Ethers 39



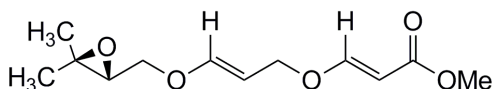
39a. Clear, colorless oil (99% yield, ~5% Claisen rearrangement product by ^1H NMR); $R_f = 0.79$ (hexanes-ethyl acetate, 1:1); ^1H NMR (CDCl_3) 5.00 (s, 1H), 4.62 (t, $J = 7.5$ Hz, 1H), 4.27 (d, $J = 7.6$ Hz, 2H), 3.84 (dd, $J = 10.8, 4.6$ Hz, 1H), 3.74 (dd, $J = 10.8, 6.0$ Hz, 1H), 3.64 (s, 3H), 3.01 (dd, $J = 6.0, 4.6$ Hz, 1H), 2.26 (s, 3H), 1.84 (s, 3H), 1.33 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (CDCl_3) 172.42 (C), 168.34 (C), 159.11 (C), 91.64 (CH), 90.90 (CH), 66.01 (CH_2), 65.13 (CH_2), 61.01 (CH), 58.01 (C), 50.69 (CH_3), 24.56 (CH_3), 19.21 (CH_3), 18.94 (CH_3), 16.50 (CH_3); IR (Neat, cm^{-1}) 2986 (s), 1709 (s), 1151 (s); $[\alpha]_D^{23} + 1.1$ (c 0.0028, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{22}\text{O}_5\text{Na}^+$ 293.1365, found 293.1359.



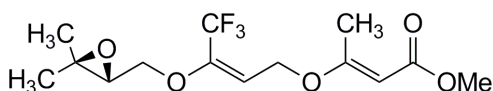
39b. Clear, yellow oil (94% yield); $R_f = 0.67$ (hexanes-ethyl acetate, 1:1); ^1H NMR (CDCl_3) 7.56 (d, $J = 12.7$ Hz, 1H), 5.19 (d, $J = 12.6$ Hz, 1H), 4.62 (t, $J = 7.7$ Hz, 1H), 4.35 (d, $J = 7.8$ Hz, 2H), 3.83 (dd, $J = 10.8, 4.5$ Hz, 1H), 3.73 (dd, $J = 10.8, 6.1$ Hz, 1H), 3.66 (s, 3H), 3.00 (dd, $J = 6.1, 4.5$ Hz, 1H), 1.86 (s, 3H), 1.32 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (CDCl_3) 168.25 (C), 162.18 (C), 159.98 (C), 96.37 (CH), 91.58 (CH), 67.93 (CH_2), 66.39 (CH_2), 60.95 (CH), 57.99 (C), 51.04 (CH_3), 24.54 (CH_3), 18.93 (CH_3), 16.54 (CH_3), 16.51 (CH_3); IR (Neat, cm^{-1}) 2979 (s), 1708 (m); $[\alpha]_D^{23} + 1.6$ (c 0.0025, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{20}\text{O}_5\text{Na}^+$ 279.1208, found 279.1229.



39e. Clear, colorless oil (96% yield); $R_f = 0.80$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 6.75 (d, $J = 12.7$ Hz, 1H), 5.11 (t, $J = 7.3$ Hz, 0.5H), 5.08 (t, $J = 7.5$ Hz, 0.5H), 5.06 (s, 1H), 4.30 (d, $J = 7.6$ Hz, 2H), 4.06 (dd, $J = 11.7, 3.9$ Hz, 1H), 3.78 (dd, $J = 11.4, 6.6$ Hz, 1H), 3.59 (s, 3H), 2.97 (dd, $J = 6.6, 3.9$ Hz, 1H), 2.23 (s, 3H), 1.29 (s, 6H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 172.50 (C), 168.45 (C), 152.73 (CH), 99.24 (CH), 91.56 (CH), 69.56 (CH_2), 67.01 (CH_2), 61.54 (CH), 57.94 (C), 50.66 (CH_3), 24.75 (CH_3), 19.16 (CH_3), 19.13 (CH_3); IR (Neat, cm^{-1}) 2986 (m), 1703 (s), 1148 (s); $[\alpha]_D^{23} + 6.7$ (c 0.0246, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{20}\text{O}_5\text{Na}^+$ 279.1208, found 279.1233.

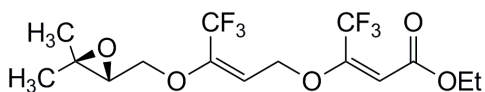


39f. Clear, light yellow oil (97% yield); $R_f = 0.76$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 7.57 (d, $J = 12.5$ Hz, 1H), 6.81 (d, $J = 12.5$ Hz, 1H), 5.22 (d, $J = 12.6$ Hz, 1H), 5.11 (t, $J = 7.7$ Hz, 0.5H), 5.09 (t, $J = 7.7$ Hz, 0.5H), 4.42 (d, $J = 7.9$ Hz, 2H), 4.07 (dd, $J = 11.6, 3.9$ Hz, 1H), 3.78 (dd, $J = 11.5, 6.6$ Hz, 1H), 3.61 (s, 3H), 2.97 (dd, $J = 6.5, 3.7$ Hz, 1H), 1.29 (s, 6H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 168.18 (C), 162.92 (CH), 153.34 (CH), 99.38 (CH), 97.04 (CH), 70.23 (CH_2), 69.64 (CH_2), 61.50 (CH), 57.94 (C), 50.95 (CH_3), 24.73 (CH_3), 19.10 (CH_3); IR (Neat, cm^{-1}) 2986 (m), 1704 (s), 1133 (s); $[\alpha]_D^{23} + 5.1$ (c 0.0108, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{18}\text{O}_5\text{Na}^+$ 265.1052, found 265.1039.

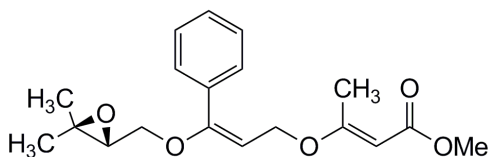


39g. Clear, light yellow oil (93% yield); $R_f = 0.79$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 5.50 (t, $J = 6.9$ Hz, 1H), 5.10 (s, 1H), 4.61 (dq, $J = 7.0, 4.2$ Hz, 2H), 4.26

(dd, $J = 11.3, 3.3$ Hz, 1H), 3.92 (dd, $J = 11.3, 6.8$ Hz, 1H), 3.60 (s, 3H), 3.06 (dd, $J = 6.8, 3.4$ Hz, 1H), 2.25 (s, 3H), 1.31 (s, 6H); ^{13}C NMR ($(\text{CD}_3)_2\text{CO}$) 172.06 (C), 168.31 (C), 146.60 (q, $J = 37.2$ Hz, C), 121.47 (q, $J = 272.62$ Hz, CF_3), 103.58 (CH), 92.13 (CH), 69.78 (CH_2), 62.97 (CH_2), 61.05 (CH), 58.26 (C), 50.88 (CH_3), 24.76 (CH_3), 19.14 (CH_3), 18.98 (CH_3); IR (Neat, cm^{-1}) 2985 (s), 1709 (s), 1146 (s); $[\alpha]_{\text{D}}^{23} + 4.1$ (c 0.0072, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{19}\text{F}_3\text{O}_5\text{Na}^+$ 347.1082, found 347.1091.

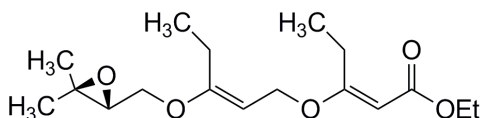


39h. Clear, yellow oil (58% yield + 42% of the *Z* isomer); $R_f = 0.53$ (hexanes-ethyl acetate, 1:1); ^1H NMR ($(\text{CD}_3)_2\text{CO}$) 5.75 (s, 1H), 5.58 (t, $J = 7.1$ Hz, 1H), 4.76 (dq, $J = 7.3, 3.9$ Hz, 2H), 4.30 (dd, $J = 11.3, 3.3$ Hz, 1H), 4.16 (q, $J = 7.1$ Hz, 2H), 3.96 (dd, $J = 11.3, 7.0$ Hz, 1H), 3.07 (dd, $J = 6.8, 3.3$ Hz, 1H), 1.31 (s, 6H), 1.24 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($(\text{CD}_3)_2\text{CO}$) 164.17 (C), 152.78 (q, $J = 36.0$ Hz, C), 148.04 (q, $J = 36.0$ Hz, C), 121.39 (q, $J = 234.8$ Hz, CF_3), 119.20 (q, $J = 252.82$ Hz, CF_3), 101.83 (CH), 100.33 (CH), 70.07 (CH_2), 64.86 (CH_2), 61.49 (CH_2), 60.98 (CH), 58.28 (C), 24.75 (CH_3), 19.23 (CH_3), 14.41 (CH_3); IR (Neat, cm^{-1}) 2986 (s), 1734 (s), 1150 (s); $[\alpha]_{\text{D}}^{23} + 2.1$ (c 0.0063, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{18}\text{F}_6\text{O}_5\text{Na}^+$ 415.0956, found 415.0951.



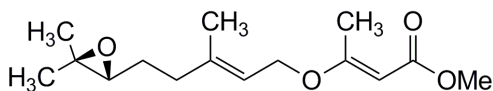
39i. Clear, light yellow oil (98% yield); $R_f = 0.90$ (hexanes-ethyl acetate, 1:1); ^1H NMR ($(\text{CD}_3)_2\text{CO}$) 7.58-7.56 (m, 2H), 7.45-7.38 (m, 3H), 5.60 (t, $J = 6.8$ Hz, 1H), 5.20 (s, 1H), 4.71 (d, $J = 6.9$ Hz, 2H), 3.94 (dd, $J = 11.7, 4.8$ Hz, 1H), 3.78 (dd, $J = 11.5, 6.5$ Hz, 1H), 3.60 (s, 3H), 3.07 (dd, $J = 6.3, 4.5$ Hz, 1H), 2.27 (s, 3H), 1.26 (s, 3H), 1.15 (s, 3H); ^{13}C NMR ($(\text{CD}_3)_2\text{CO}$) 172.52 (C), 168.45 (C), 157.94 (C), 135.56 (C), 129.89 (CH), 129.51

(CH), 127.34 (CH), 109.10 (CH), 91.83 (CH), 70.83 (CH), 63.97 (CH₂), 61.66 (CH₂), 58.19 (C), 50.72 (CH₃), 24.74 (CH₃), 19.14 (CH₃), 19.07 (CH₃); IR (Neat, cm⁻¹) 2985 (m), 1710 (s), 1146 (s); $[\alpha]_D^{23} + 4.7$ (*c* 0.0204, CH₂Cl₂); HRMS (ESI) calcd for C₁₉H₂₄O₅Na⁺ 355.1521, found 355.1506.



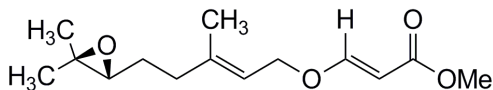
39j. Clear, yellow oil (100% yield, ~5% Claisen rearrangement product by ¹H NMR); R_f = 0.88 (hexanes-ethyl acetate, 1:1); ¹H NMR ((CD₃)₂CO) 5.02 (s, 1H), 4.75 (t, *J* = 7.7 Hz, 1H), 4.38 (d, *J* = 7.7 Hz, 2H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.99 (dd, *J* = 11.3, 3.8 Hz, 1H), 3.74 (dd, *J* = 11.2, 6.5 Hz, 1H), 3.00 (dd, *J* = 6.5, 3.8 Hz, 1H), 2.72 (q, *J* = 7.8 Hz, 2H), 2.26 (qd, *J* = 7.7, 2.6 Hz, 2H), 1.26 (s, 3H), 1.25 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 3H), 1.09 (t, *J* = 7.7 Hz, 3H), 1.06 (t, *J* = 7.6 Hz, 3H); ¹³C NMR ((CD₃)₂CO) 177.30 (C), 167.75 (C), 164.56 (C), 92.26 (CH), 91.01 (CH), 67.39 (CH₂), 65.58 (CH₂), 61.61 (CH), 59.45 (CH₂), 57.85 (C), 26.10 (CH₂), 24.78 (CH₂), 19.19 (CH₃), 14.76 (CH₃), 14.31 (CH₃), 12.94 (CH₃), 12.30 (CH₃); IR (Neat, cm⁻¹) 2977 (s), 1709 (s), 1052 (s); $[\alpha]_D^{23} + 8.4$ (*c* 0.0484, CH₂Cl₂); HRMS (ESI) calcd for C₁₇H₂₈O₅Na⁺ 335.1834, found 335.1841.

5.3.2 Experimental Data for Mono-Vinyl Ethers 40

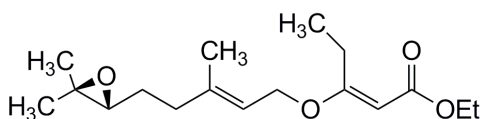


40a. Clear, light yellow oil (97% yield); R_f = 0.77 (hexanes-ethyl acetate, 1:1); ¹H NMR (CDCl₃) 5.41 (tq, *J* = 6.6, 1.3 Hz, 1H), 5.00 (s, 1H), 4.30 (d, *J* = 6.6 Hz, 2H), 3.64 (s, 3H), 2.68 (t, *J* = 6.2 Hz, 1H), 2.27 (s, 3H), 2.26-2.12 (m, 2H), 1.68 (s, 3H), 1.67-1.60 (m, 2H), 1.28 (s, 3H), 1.24 (s, 3H); ¹³C NMR (CDCl₃) 172.38 (C), 168.33 (C), 141.02 (C), 118.74 (CH), 90.99 (CH), 65.01 (CH₂), 63.85 (CH₂), 58.35 (C), 50.70 (CH₃), 36.14

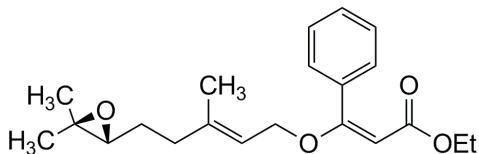
(CH₂), 27.03 (CH₂), 24.79 (CH₃), 19.12 (CH₃), 18.72 (CH₃), 16.59 (CH₃); IR (Neat, cm⁻¹) 2958 (m), 1714 (s), 1146 (s); [α]_D²³ + 4.2 (*c* 0.0116, CH₂Cl₂); HRMS (ESI) calcd for C₁₅H₂₄O₄Na⁺ 291.1572, found 291.1562.



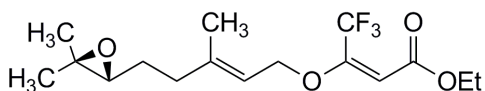
40b. Clear, yellow oil (99% yield); *R*_f = 0.71 (hexanes-ethyl acetate, 1:1); ¹H NMR (CDCl₃) 7.57 (d, *J* = 12.8 Hz, 1H), 5.40 (tq, *J* = 6.8, 1.3 Hz, 1H), 5.19 (d, *J* = 12.5 Hz, 1H), 4.37 (d, *J* = 7.8 Hz, 2H), 3.67 (s, 3H), 2.67 (t, *J* = 6.2 Hz, 1H), 2.19 (m, 2H), 1.70 (s, 3H), 1.68-1.61 (m, 2H), 1.28 (s, 3H), 1.24 (s, 3H); ¹³C NMR (CDCl₃) 168.21 (C), 162.27 (CH), 141.15 (C), 118.44 (CH), 96.41 (CH), 67.50 (CH₂), 63.78 (CH), 58.34 (C), 51.06 (CH₃), 36.16 (CH₂), 27.03 (CH₂), 24.79 (CH₃), 18.72 (CH₃), 16.63 (CH₃); IR (Neat, cm⁻¹) 2963 (s), 1714 (s), 1146 (s); [α]_D²³ + 3.6 (*c* 0.0130, CH₂Cl₂); HRMS (ESI) calcd for C₁₄H₂₂O₄Na⁺ 277.1416, found 277.1410.



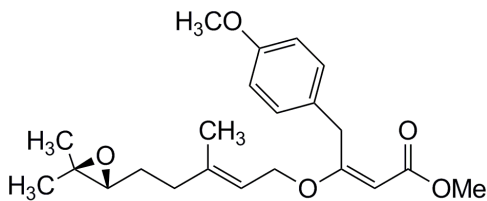
40c. Clear, colorless oil (99% yield); *R*_f = 0.73 (hexanes-ethyl acetate, 1:1); ¹H NMR (CDCl₃) 5.39 (tq, *J* = 6.5, 1.2 Hz, 1H), 4.91 (s, 1H), 4.26 (d, *J* = 6.6 Hz, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 2.74-2.64 (m, 3H), 2.26-2.08 (m, 2H), 1.67-1.59 (m, 5H), 1.26 (s, 6H), 1.22 (t, *J* = 7.6 Hz, 3H), 1.07 (t, *J* = 7.6 Hz, 3H); ¹³C NMR (CDCl₃) 176.98 (C), 167.54 (C), 140.82 (C), 118.91 (CH), 90.37 (CH), 64.89 (CH₂), 63.82 (CH), 59.20 (CH₂), 58.32 (C), 36.10 (CH₂), 27.01 (CH₂), 25.60 (CH₂), 24.78 (CH₃), 18.71 (CH₃), 16.57 (CH₃), 14.37 (CH₃), 11.89 (CH₃); IR (Neat, cm⁻¹) 2986 (m), 1708 (m); [α]_D²³ + 0.3 (*c* 0.0036, CH₂Cl₂); HRMS (ESI) calcd for C₁₇H₂₈O₄Na⁺ 319.1885, found 319.1909.



40d. Clear, light yellow oil (98% yield); $R_f = 0.87$ (hexanes-ethyl acetate, 1:1); ^1H NMR (CDCl_3) 7.53-7.51 (m, 2H), 7.41-7.34 (m, 3H), 5.56 (s, 1H), 5.51 (tq, $J = 7.0, 1.3$ Hz, 1H), 4.55 (d, $J = 7.0$ Hz, 2H), 4.18 (q, $J = 7.1$ Hz, 2H), 2.68 (t, $J = 6.3$ Hz, 1H), 2.22-2.08 (m, 2H), 1.64-1.59 (m, 2H), 1.54 (s, 3H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.28 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (CDCl_3) 167.61 (C), 165.29 (C), 140.92 (C), 135.41 (C), 130.21 (CH), 128.71 (CH), 127.47 (CH), 120.08 (CH), 101.21 (CH), 69.27 (CH), 63.86 (CH_2), 59.70 (CH_2), 58.33 (C), 36.16 (CH_2), 27.16 (CH_2), 24.83 (CH_3), 18.71 (CH_3), 16.41 (CH_3), 14.37 (CH_3); IR (Neat, cm^{-1}) 2984 (s), 1710 (s), 1164 (s); $[\alpha]_D^{23} + 4.2$ (c 0.0335, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{28}\text{O}_4\text{Na}^+$ 367.1885, found 367.1866.

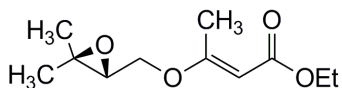


40e. Clear, light yellow oil (27% yield, ~5% Claisen rearrangement product by ^1H NMR); $R_f = 0.88$ (hexanes-ethyl acetate, 1:1); ^1H NMR (CDCl_3) 5.74 (s, 1H), 5.40 (tq, $J = 7.1, 1.3$ Hz, 1H), 4.72 (d, $J = 7.0$ Hz, 2H), 4.18 (q, $J = 7.2$ Hz, 2H), 2.63 (t, $J = 6.1$ Hz, 1H), 2.27 (s, 3H), 2.25-2.05 (m, 2H), 1.66 (s, 3H), 1.68-1.56 (m, 2H), 1.26-1.17 (m, 9H); ^{13}C NMR (CDCl_3) 164.99 (q, C), 163.66 (C), 142.89 (C), 118.87 (CH), 115.22 (q, CF_3), 102.67 (CH), 71.92 (CH), 63.81 (CH_2), 59.88 (CH_2), 58.39 (C), 36.15 (CH_2), 27.01 (CH_2), 24.73 (CH_3), 19.44 (CH_3), 18.67 (CH_3), 16.49 (CH_3); IR (Neat, cm^{-1}) 2986 (m), 1703 (s), 1148 (s); $[\alpha]_D^{23} + 4.2$ (c 0.0116, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{23}\text{F}_3\text{O}_4\text{Na}^+$ 359.1446, found 359.1444.

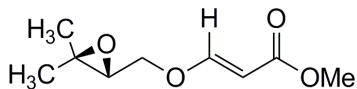


40f. Clear, colorless oil (96% yield); $R_f = 0.73$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ (CDCl_3) 7.23 (d, $J = 9.4$ Hz, 2H), 6.78 (d, $J = 8.7$ Hz, 2H), 5.37 (tq, $J = 6.4, 1.3$ Hz, 1H), 5.02 (s, 1H), 4.29 (d, $J = 6.6$ Hz, 2H), 4.01 (s, 2H), 3.75 (s, 3H), 3.67 (s, 3H), 2.67 (t, $J = 6.1$ Hz, 1H), 2.23-2.10 (m, 2H), 1.65-1.61 (m, 5H), 1.27 (s, 3H), 1.24 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3) 173.68 (C), 167.99 (C), 158.19 (C), 140.93 (C), 129.96 (C, CH), 118.78 (CH), 113.64 (CH), 91.12 (CH), 65.17 (CH_2), 63.82 (CH), 58.36 (C), 55.19 (CH_3), 50.84 (CH_3), 36.66 (CH_2), 36.09 (CH_2), 27.04 (CH_2), 24.81 (CH_3), 18.72 (CH_3), 16.58 (CH_3); IR (Neat, cm^{-1}) 2986 (s), 1708 (s), 1139 (s); $[\alpha]_D^{23} + 0.9$ (c 0.0059, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{30}\text{O}_5\text{Na}^+$ 397.1991, found 397.1967.

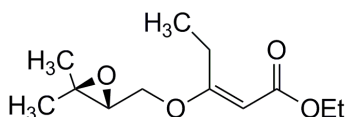
5.3.3 Experimental Data for Conjugate Addition Synthetic Intermediates 42



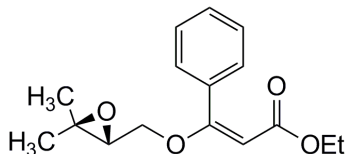
42a. Clear, yellow oil (98% yield); $R_f = 0.84$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ (CDCl_3) 4.98 (s, 1H), 4.10 (q, $J = 7.1$ Hz, 2H), 3.92 (dd, $J = 10.9, 4.3$ Hz, 1H), 3.78 (dd, $J = 11.0, 6.3$ Hz, 1H), 3.03 (dd, $J = 10.5, 4.3$ Hz, 1H), 2.29 (s, 3H), 1.34 (s, 3H), 1.28 (s, 3H), 1.23 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ (CDCl_3) 171.88 (C), 167.63 (C), 91.84 (CH), 67.14 (CH_2), 60.48 (CH), 59.40 (CH_2), 58.02 (C), 24.50 (CH_3), 18.93 (CH_3), 18.87 (CH_3), 14.36 (CH_3); IR (Neat, cm^{-1}) 2981 (m), 1710 (s), 1150 (s); $[\alpha]_D^{23} + 13.8$ (c 0.0058, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{18}\text{O}_4\text{Na}^+$ 237.1103, found 237.1092.



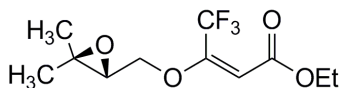
42b. Clear, light yellow oil (94% yield); $R_f = 0.72$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 7.61 (d, $J = 13.0$ Hz, 1H), 5.31 (d, $J = 12.6$ Hz, 1H), 4.28 (dd, $J = 11.8, 3.4$ Hz, 1H), 3.94 (dd, $J = 11.8, 7.1$ Hz, 1H), 3.63 (s, 3H), 3.02 (dd, $J = 7.0, 3.4$ Hz, 1H), 1.31 (s, 6H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 167.97 (C), 163.05 (CH), 97.68 (CH), 71.49 (CH_2), 61.20 (CH), 58.16 (C), 51.06 (CH_3), 24.71 (CH_3), 19.11 (CH_3); IR (Neat, cm^{-1}) 2986 (s), 1708 (s), 1145 (s); $[\alpha]_D^{23} + 15.0$ (c 0.0102, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_9\text{H}_{14}\text{O}_4\text{Na}^+$ 209.0790, found 209.0768.



42c. Clear, yellow oil (88% yield); $R_f = 0.91$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 5.05 (s, 1H), 4.14 (dd, $J = 11.2, 3.4$ Hz, 1H), 4.07 (q, $J = 7.0$ Hz, 2H), 3.83 (dd, $J = 11.1, 6.8$ Hz, 1H), 3.04 (dd, $J = 6.6, 3.4$ Hz, 1H), 1.32 (s, 6H), 1.21 (t, $J = 7.1$ Hz, 3H), 1.09 (t, $J = 7.6$ Hz, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 177.00 (C), 167.57 (C), 91.69 (CH), 68.72 (CH_2), 61.19 (CH), 59.59 (CH_2), 57.98 (C), 25.94 (CH_2), 24.74 (CH_3), 19.18 (CH_3), 14.72 (CH_3), 12.23 (CH_3); IR (Neat, cm^{-1}) 2984 (m), 1705 (s), 1149 (s); $[\alpha]_D^{23} + 3.3$ (c 0.0087, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{20}\text{O}_4\text{Na}^+$ 251.1259, found 251.1255.

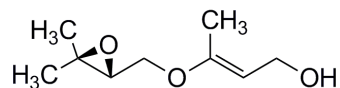


42d. Clear, light yellow oil (96% yield); $R_f = 0.76$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 7.73 (d, $J = 1.4$ Hz, 1H), 7.71 (d, $J = 1.8$ Hz, 1H), 7.48 (m, 3H), 5.74 (s, 1H), 4.34 (dd, $J = 11.4, 7.6$ Hz, 1H), 4.16 (q, $J = 7.2$ Hz, 2H), 4.10 (dd, $J = 6.5, 4.6$ Hz, 1H), 3.18 (dd, $J = 6.5, 4.6$ Hz, 1H), 1.30 (s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.21 (s, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 167.97 (C), 167.78 (C), 165.25 (C), 136.13 (C), 131.46 (CH), 129.54 (CH), 128.27 (CH), 128.16 (CH), 101.20 (CH), 73.53 (CH_2), 61.82 (CH), 60.16 (CH_2), 58.18 (C), 24.77 (CH_3), 19.11 (CH_3), 14.68 (CH_3); IR (Neat, cm^{-1}) 2980 (s), 1717 (s); $[\alpha]_{\text{D}}^{23} + 5.2$ (c 0.0169, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{20}\text{O}_4\text{Na}^+$ 299.1259, found 299.1247.

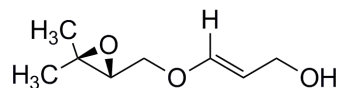


42e. Clear, light yellow oil (39% yield + 54% of the *Z* isomer); $R_f = 0.86$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ (CDCl_3) 5.40 (s, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 4.02 (dd, $J = 11.0, 4.0$ Hz, 1H), 3.86 (dd, $J = 11.0, 6.3$ Hz, 1H), 3.08 (dd, $J = 6.1, 4.2$ Hz, 1H), 1.36 (s, 3H), 1.30 (s, 3H), 1.27 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 164.21 (C), 153.77 (q, $J = 37.3$ Hz, C), 120.31 (q, $J = 275.5$ Hz, CF_3), 100.28 (CH), 71.20 (CH_2), 61.45 (CH_2), 60.75 (CH), 58.39 (C), 24.74 (CH_3), 19.23 (CH_3), 14.42 (CH_3); IR (Neat, cm^{-1}) 2986 (s), 1727 (s); $[\alpha]_{\text{D}}^{23} + 1.5$ (c 0.0072, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{15}\text{F}_3\text{O}_4\text{Na}^+$ 291.0820, found 291.0842.

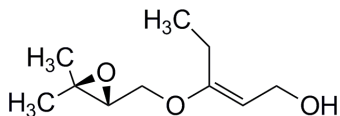
5.3.4 Experimental Data for Reduction Synthetic Intermediates 43



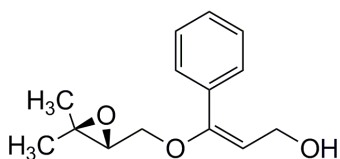
43a. Clear, light yellow oil (97% yield); $R_f = 0.30$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ (CDCl_3) 7.64 (t, $J = 7.7$ Hz, 1H), 4.07 (d, $J = 7.8$ Hz, 2H), 3.78 (dd, $J = 10.7, 4.4$ Hz, 1H), 3.68 (dd, $J = 11.0, 5.8$ Hz, 1H), 2.97 (dd, $J = 6.2, 4.7$ Hz, 1H), 1.82 (s, 3H), 1.72 (s, 1H), 1.29 (s, 3H), 1.24 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3) 156.93 (C), 97.09 (CH), 65.69 (CH_2), 61.18 (CH), 58.99 (CH_2), 58.04 (C), 24.54 (CH_3), 18.87 (CH_3), 16.17 (CH_3); IR (Neat, cm^{-1}) 3406 (br, m), 2980 (m); $[\alpha]_{\text{D}}^{23} + 13.1$ (c 0.0334, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_9\text{H}_{16}\text{O}_3\text{Na}^+$ 195.0997, found 195.1004.



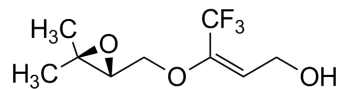
43b. Clear, colorless oil (91% yield); $R_f = 0.44$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 6.52 (d, $J = 12.9$ Hz, 1H), 5.04 (t, $J = 7.0$ Hz, 0.5H), 5.01 (t, $J = 7.0$ Hz, 0.5H), 3.97-3.94 (m, 3H), 3.70 (dd, $J = 11.5, 6.5$ Hz, 1H), 3.42 (t, $J = 5.3$ Hz, 1H), 2.94 (dd, $J = 6.6, 4.0$ Hz, 1H), 1.28 (s, 3H), 1.27 (s, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 149.29 (CH), 105.46 (CH), 69.08 (CH_2), 61.68 (CH), 60.08 (CH_2), 57.86 (C), 24.99 (CH_3), 19.10 (CH_3); IR (Neat, cm^{-1}) 3437 (br, m), 2985 (m); $[\alpha]_{\text{D}}^{23} + 7.6$ (c 0.0435, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_8\text{H}_{14}\text{O}_3\text{Na}^+$ 181.0841, found 181.0832.



43c. Clear, colorless oil (97% yield); $R_f = 0.32$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 4.66 (t, $J = 7.4$ Hz, 1H), 4.06 (dd, $J = 7.6, 5.5$ Hz, 2H), 3.88 (dd, $J = 11.1, 3.9$ Hz, 1H), 3.66 (dd, $J = 11.1, 6.3$ Hz, 1H), 2.97 (dd, $J = 6.3, 3.9$ Hz, 1H), 2.21 (qd, $J = 7.6, 3.2$ Hz, 2H), 1.29 (s, 3H), 1.28 (s, 3H), 1.04 (t, $J = 7.7$ Hz, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 160.94 (C), 98.45 (CH), 66.87 (CH_2), 61.75 (CH), 58.48 (CH_2), 57.82 (C), 25.02 (CH_3), 24.82 (CH_2), 19.20 (CH_3), 13.06 (CH_3); IR (Neat, cm^{-1}) 3402 (br, s), 2967 (s); $[\alpha]_D^{23} + 8.4$ (c 0.0567, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{18}\text{O}_3\text{Na}^+$ 209.1154, found 209.1132.



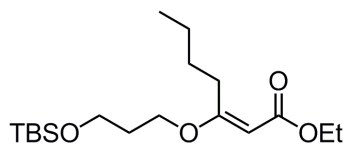
43d. Clear, colorless oil (99% yield); $R_f = 0.50$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 7.54-7.52 (m, 2H), 7.40-7.37 (m, 2H), 7.35-7.32 (m, 1H), 5.60 (t, $J = 6.8$ Hz, 1H), 4.37 (dd, $J = 6.6, 5.7$ Hz, 2H), 3.86 (dd, $J = 11.4, 4.8$ Hz, 1H), 3.74 (dd, $J = 11.3, 6.3$ Hz, 1H), 3.67 (t, $J = 5.6$ Hz, 1H), 3.05 (dd, $J = 6.5, 4.8$ Hz, 1H), 1.27 (s, 3H), 1.16 (s, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 54.80 (C), 136.41 (C), 129.38 (CH), 129.20 (CH), 126.90 (CH), 116.07 (CH), 70.70 (CH_2), 61.88 (CH), 58.17 (C), 57.29 (CH_2), 24.76 (CH_3), 19.07 (CH_3); IR (Neat, cm^{-1}) 3407 (br, m), 2299 (m); $[\alpha]_D^{23} + 13.3$ (c 0.0776, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{18}\text{O}_3\text{Na}^+$ 257.1154, found 257.1165.



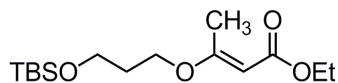
43e. Clear, yellow oil (97% yield); $R_f = 0.41$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ (CDCl_3) 5.13 (t, $J = 7.1$ Hz, 1H), 4.30 (d, $J = 6.9$ Hz, 2H), 3.92 (dd, $J = 11.0, 4.1$ Hz, 1H), 3.78 (dd, $J = 11.1, 6.3$ Hz, 1H), 3.02 (dd, $J = 6.0, 4.0$ Hz, 1H), 2.40 (s, 1H), 1.32 (s, 3H), 1.27 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3) 144.60 (q, $J = 36.6$ Hz, C), 120.4 (q, $J = 274.0$, CF_3), 107.24 (CH), 67.84 (CH_2), 60.50 (CH), 56.50 (CH_2), 56.35 (C), 24.39 (CH_3), 18.83 (CH_3); IR (Neat, cm^{-1}) 3456 (br, m), 2985 (m); $[\alpha]_D^{23} + 13.1$ (c 0.0334, CH_2Cl_2); HRMS (ESI) calcd for $\text{C}_9\text{H}_{13}\text{O}_3\text{F}_3\text{Na}^+$ 249.0714, found 249.0699.

5.4.0 Compounds Pertaining to Chapter 4 Section 4.1.0

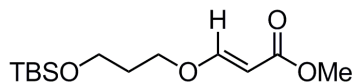
5.4.1 Experimental Data for Synthetic Intermediates 23 and 25



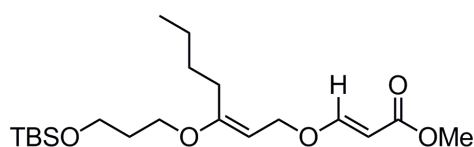
23a. Clear, light orange oil (98% yield); $R_f = 0.43$ (hexanes-ethyl acetate, 9:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 4.94 (s, 1H), 4.08 (q, $J = 7.1$ Hz, 2H), 3.79 (t, $J = 6.0$ Hz, 2H), 3.67 (t, $J = 5.9$ Hz, 2H), 2.69 (t, $J = 7.6$ Hz, 2H), 1.85 (m, 2H), 1.51 (m, 2H), 1.32 (m, 2H), 1.22 (t, $J = 7.1$ Hz, 3H), 0.87 (m, 3H), 0.85 (s, 9H), 0.00 (s, 6H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 176.38, 167.99, 90.85, 64.68, 59.46, 53.63, 35.05, 32.04, 26.10, 25.64, 22.73, 14.61, 14.23, 14.11, -5.23.



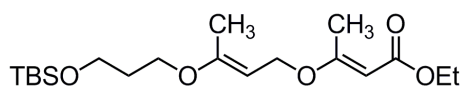
23b. Clear, light yellow oil (94% yield); $R_f = 0.70$ (hexanes-ethyl acetate, 2:1); $^1\text{H NMR}$ (CDCl_3) 5.00 (s, 1H), 4.10 (q, $J = 7.1$, 2H), 3.82 (t, $J = 6.1$ Hz, 2H), 3.70 (t, $J = 5.9$ Hz, 2H), 2.26 (s, 3H), 1.87 (q, $J = 6.0$ Hz, 2H), 1.24 (t, $J = 7.1$ Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H); $^{13}\text{C NMR}$ (CDCl_3) 172.53, 168.26, 91.32, 64.81, 59.86, 59.41, 31.92, 26.06, 19.24, 18.31, 14.60, -5.28.



23c. Clear, light yellow oil (95% yield); $R_f = 0.73$ (hexanes-ethyl acetate, 2:1). $^1\text{H NMR}$ (CDCl_3) 7.57 (d, $J = 12.6$ Hz, 1H), 5.16 (d, $J = 12.6$ Hz, 1H), 4.11 (q, $J = 7.1$ Hz, 2H), 3.90 (t, $J = 6.1$ Hz, 2H), 3.66 (t, $J = 5.8$ Hz, 2H), 1.84 (q, $J = 6.0$ Hz, 2H), 1.23 (t, $J = 7.1$ Hz, 3H), 0.84 (s, 9H), 0.00 (s, 6H).

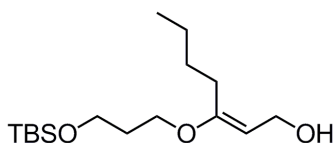


25a. Clear, light yellow oil (79% yield over two steps; DIBAL-H reduction (to **24a**) followed by second conjugate addition); $R_f = 0.51$ (hexanes-ethyl acetate, 9:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 7.52 (d, $J = 12.5$ Hz, 1H), 5.14 (d, $J = 12.6$ Hz, 1H), 4.68 (t, $J = 7.8$ Hz, 1H), 4.55 (d, $J = 7.7$ Hz, 2H), 4.05 (q, $J = 7.1$ Hz, 2H), 3.67 (m, 4H), 2.19 (t, $J = 7.4$ Hz, 2H), 1.81 (q, $J = 6.0$ Hz, 2H), 1.25-1.30 (m, 4H), 1.15 (t, $J = 7.1$ Hz, 3H), 0.82 (s, 9H), 0.00 (s, 6H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 167.89, 164.00, 163.06, 97.25, 92.38, 68.83, 64.15, 59.93, 59.88, 33.28, 30.87, 26.57, 24.23, 22.99, 14.81, 14.53, 14.34, -5.12.

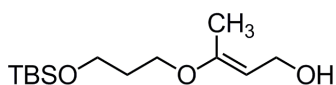


25b. Clear, yellow oil (88% yield); $R_f = 0.85$ (hexanes-ethyl acetate, 2:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 5.00 (s, 1H), 4.67 (t, $J = 7.5$ Hz, 1H), 4.34 (d, $J = 7.5$ Hz, 2H), 3.99 (q, $J = 7.1$ Hz, 2H), 3.71 (m, 4H), 2.17 (s, 3H), 1.80 (m, 2H), 1.79 (s, 3H), 1.15 (t, $J = 7.0$ Hz, 3H), 0.84 (s, 9H), 0.00 (s, 6H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 172.44, 167.98, 159.61, 92.30, 91.82, 66.01, 64.08, 60.10, 59.35, 32.85, 26.24, 19.29, 18.77, 16.68, 14.75, -5.30.

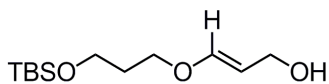
5.4.2 Experimental Data for Synthetic Intermediates 24 and 26



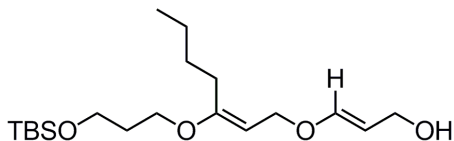
24a. Clear, light yellow oil (75% yield); $R_f = 0.13$ (hexanes-ethyl acetate, 9:1). ^1H NMR ($(\text{CD}_3)_2\text{CO}$) 4.61 (t, $J = 7.4$ Hz, 1H), 4.01 (m, 2H), 3.66 (m, 4H), 3.18 (t, $J = 5.4$ Hz, 1H), 2.11 (t, $J = 7.3$ Hz, 2H), 1.81 (q, $J = 6.1$ Hz, 2H), 1.41 (m, 2H), 1.24 (m, 2H), 0.86 (m, 3H), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($(\text{CD}_3)_2\text{CO}$) 159.71, 98.56, 63.64, 60.46, 58.79, 39.96, 33.22, 26.40, 24.24, 23.05, 14.59, 14.47, -5.10.



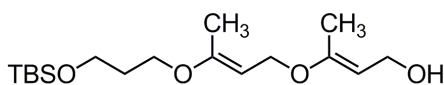
24b. Clear, light yellow oil (94% yield); $R_f = 0.51$ (hexanes-ethyl acetate, 2:1); ^1H NMR (CDCl_3) 4.68 (t, $J = 7.6$ Hz, 1H), 4.10 (m, 2H), 3.68 (m, 4H), 1.82 (m, 2H), 1.81 (s, 3H), 1.16 (m, 1H), 0.85 (s, 9H), 0.00 (s, 6H).



24c. Clear, light yellow oil (88% yield); $R_f = 0.39$ (hexanes-ethyl acetate, 2:1); ^1H NMR (CDCl_3) 6.45 (d, $J = 12.6$ Hz, 1H), 4.99 (m, 1H), 3.99 (d, $J = 7.3$ Hz, 2H), 3.75 (t, $J = 6.2$ Hz, 2H), 3.66 (t, $J = 6.0$ Hz, 2H), 1.81 (q, $J = 6.1$ Hz, 2H), 0.83 (s, 9H), 0.00 (s, 6H).

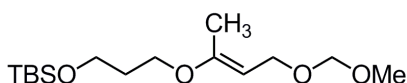


26a. Clear, light yellow oil (84% yield); $R_f = 0.26$ (hexanes-ethyl acetate, 9:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 6.40 (d, $J = 12.5$ Hz, 1H), 4.89 (m, 1H), 4.62 (t, $J = 7.6$ Hz, 1H), 4.17 (d, $J = 7.6$ Hz, 2H), 3.87 (d, $J = 7.0$ Hz, 2H), 3.70 (t, $J = 5.9$ Hz, 4H), 2.14 (t, $J = 7.4$ Hz, 2H), 1.80 (q, $J = 6.0$ Hz, 2H), 1.26 (m, 4H), 0.86 (m, 3H), 0.84 (s, 9H), 0.00 (s, 6H).

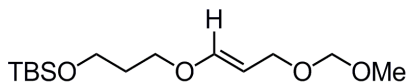


26b. Clear, light yellow oil (98% yield); $R_f = 0.85$ (hexanes-ethyl acetate, 2:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 4.64 (m, 2H), 4.14 (d, $J = 7.3$ Hz, 2H), 3.70 (m, 4H), 1.79 (m, 2H), 1.75 (s, 3H), 1.71 (t, $J = 6.1$ Hz, 3H), 0.84 (s, 9H), 0.00 (s, 6H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 158.11, 156.09, 98.51, 93.63, 64.08, 63.90, 60.19, 58.95, 32.93, 26.25, 19.46, 18.78, 16.63, -5.28.

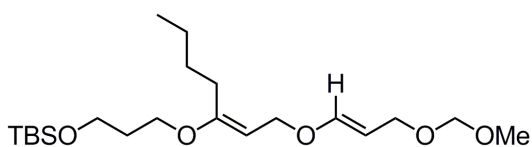
5.4.3 Experimental Data for Synthetic Intermediates 67 and 69



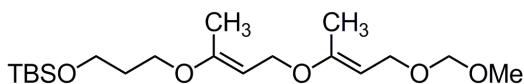
67b. Clear, light yellow oil (89% yield); $R_f = 0.59$ (hexanes-ethyl acetate, 2:1); $^1\text{H NMR}$ (CDCl_3) 4.59 (m, 3H), 4.05 (d, $J = 7.8$ Hz, 2H), 3.71 (m, 4H), 3.34 (s, 3H), 1.84 (m, 2H), 1.81 (s, 3H), 0.85 (s, 9H), 0.00 (s, 6H).



67c. Clear, light yellow oil (82% yield); $R_f = 0.58$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ (CDCl_3) 6.47 (d, $J = 12.6$ Hz, 1H), 4.88 (m, 1H), 4.59 (s, 2H), 3.94 (d, $J = 7.6$ Hz, 2H), 3.92 (t, $J = 6.2$ Hz, 2H), 3.66 (t, $J = 6.0$ Hz, 2H), 3.32 (s, 3H), 1.81 (q, $J = 6.1$ Hz, 2H), 0.84 (s, 9H), 0.00 (s, 6H).

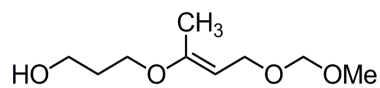


69a. Clear, light yellow oil (68% yield); $R_f = 0.48$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 6.46 (d, $J = 12.5$ Hz, 1H), 4.86 (m, 1H), 4.62 (t, $J = 7.6$ Hz, 1H), 4.49 (s, 2H), 4.21 (d, $J = 7.5$ Hz, 2H), 3.85 (d, $J = 7.2$ Hz, 2H), 3.70 (m, 4H), 3.21 (s, 3H), 2.15 (t, $J = 7.4$ Hz, 2H), 1.81 (q, $J = 6.3$ Hz, 2H), 1.25 (m, 4H), 0.86 (m, 3H), 0.84 (s, 9H), 0.00 (s, 6H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 162.52, 151.28, 100.69, 95.27, 93.44, 66.56, 65.39, 63.96, 60.31, 55.06, 39.97, 33.08, 26.56, 26.37, 24.22, 14.56, 14.33, -5.14.

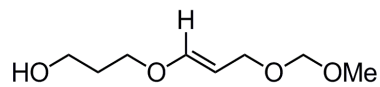


69b. Clear, light yellow oil (97% yield); $R_f = 0.38$ (hexanes-ethyl acetate, 9:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 4.60 (m, 2H), 4.49 (s, 2H), 4.16 (d, $J = 7.3$ Hz, 2H), 3.97 (d, $J = 7.6$ Hz, 2H), 3.70 (m, 4H), 1.79 (m, 2H), 1.74 (m, 4H), 0.84 (s, 9H), 0.00 (s, 6H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 158.26, 158.13, 95.07, 94.21, 93.49, 64.27, 63.92, 93.49, 64.27, 63.92, 63.72, 60.17, 54.94, 32.91, 26.23, 21.14, 19.49, 16.61, -5.23.

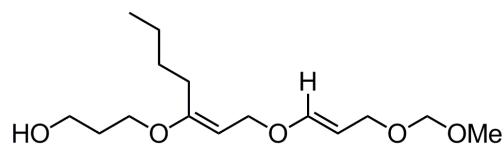
5.4.4 Experimental Data for Synthetic Intermediates 68 and 70



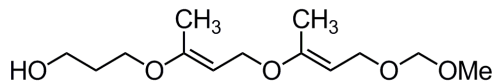
68b. Clear, light yellow oil (84% yield); $R_f = 0.22$ (hexanes-ethyl acetate, 1:2); $^1\text{H NMR}$ (CDCl_3) 4.59 (m, 3H), 4.04 (d, $J = 7.8$ Hz, 2H), 3.77 (t, $J = 6.0$ Hz, 2H), 3.70 (m, 2H), 3.33 (s, 3H), 2.48 (s, 1H), 1.88 (m, 2H), 1.82 (s, 3H).



68c. Clear, light yellow oil (72% yield); $R_f = 0.34$ (hexanes-ethyl acetate, 2:1); $^1\text{H NMR}$ (CDCl_3) 6.44 (d, $J = 12.6$ Hz, 1H), 4.85 (m, 1H), 4.54 (s, 2H), 3.90 (dd, $J = 0.8, 7.5$ Hz, 2H), 3.80 (t, $J = 5.9$ Hz, 2H), 3.67 (m, 2H), 3.28 (s, 3H), 1.83 (q, $J = 5.3$ Hz, 2H); $^{13}\text{C NMR}$ (CDCl_3) 150.79, 99.49, 94.84, 66.78, 64.74, 60.13, 55.16, 31.78.

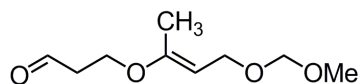


70a. Clear, light yellow oil (33% yield); $R_f = 0.15$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 6.52 (d, $J = 12.5$ Hz, 1H), 4.90 (m, 1H), 4.68 (t, $J = 7.6$ Hz, 1H), 4.55 (s, 2H), 4.27 (d, $J = 7.7$ Hz, 2H), 3.91 (d, $J = 7.4$ Hz, 2H), 3.77 (t, $J = 6.2$ Hz, 2H), 3.65 (t, $J = 6.1$ Hz, 2H), 3.27 (s, 3H), 2.19 (t, $J = 7.4$ Hz, 2H), 1.85 (q, $J = 6.3$ Hz, 2H), 1.45 (m, 2H), 1.32 (m, 2H), 0.87 (t, $J = 7.2$ Hz, 3H).

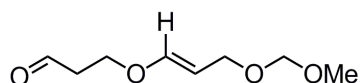


70b. Clear, light yellow oil (78% yield); $R_f = 0.12$ (hexanes-ethyl acetate, 2:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 4.65 (m, 2H), 4.54 (s, 2H), 4.20 (d, $J = 7.3$ Hz, 2H), 4.01 (d, $J = 7.7$ Hz, 2H), 3.77 (t, $J = 6.4$ Hz, 2H), 3.64 (t, $J = 6.1$ Hz, 2H), 3.27 (s, 3H), 1.84 (q, $J = 6.3$ Hz, 2H), 1.78 (m, 4H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 158.36, 158.16, 95.10, 94.22, 93.44, 64.50, 64.30, 63.74, 59.15, 54.94, 33.05, 16.58.

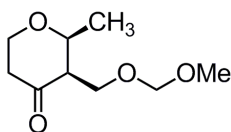
5.4.5 Experimental Data for Synthetic Intermediate 72



72b. Clear, yellow oil (47 % yield); $R_f = 0.19$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 9.73 (t, $J = 1.7$ Hz, 1H), 4.59 (m, 1H), 4.53 (s, 2H), 4.00 (m, 2H), 3.63 (t, $J = 6.2$ Hz, 2H), 3.27 (s, 3H), 2.22 (dt, $J = 1.7, 5.93$ Hz, 2H), 1.78 (s, 3H).



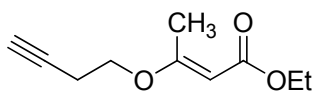
72c. Clear, light yellow oil (62% yield); $R_f = 0.15$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 9.63 (t, $J = 1.6$ Hz, 1H), 6.40 (d, $J = 12.7$ Hz, 1H), 4.82 (m, 1H), 4.43 (s, 2H), 3.96 (t, $J = 5.9$ Hz, 2H), 3.80 (dd, $J = 1.0, 7.4$ Hz, 2H), 3.15 (s, 3H), 2.6 (dt, $J = 1.4, 5.9$ Hz, 2H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 200.93, 150.95, 100.58, 95.27, 65.06, 63.61, 55.02, 43.70.

5.4.6 Experimental Data for Cyclization Product 76b

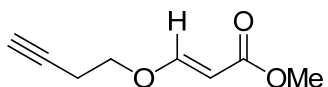
76b. Clear, yellow oil (65% yield); $R_f = 0.13$ (hexanes-ethyl acetate, 2:1); ^1H NMR (CDCl_3) 4.58 (d, $J = 6.7$ Hz, 1H), 4.56 (d, $J = 6.7$ Hz, 1H), 4.16 (ddd, $J = 11.4, 6.3, 4.6$ Hz, 1H), 4.02 (qd, $J = 6.6, 3.7$ Hz, 1H), 3.91 (dd, $J = 10.1, 8.8$ Hz, 1H), 3.76 (ddd, $J = 11.4, 9.3, 4.4$ Hz, 1H), 3.73 (dd, $J = 10.1, 6.9$ Hz, 1H), 3.32 (s, 3H), 2.80 (dddd, $J = 10.1, 8.8, 3.7, 1.4$ Hz, 1H), 2.62 (ddd, $J = 14.0, 9.4, 6.3$ Hz, 1H), 2.37 (dtd, $J = 14.0, 4.4, 1.4$ Hz, 1H), 1.21 (d, $J = 6.7$ Hz, 3H); ^{13}C (CDCl_3) 208.20 (C), 96.74 (CH_2), 75.31 (CH), 65.65 (CH_2), 63.85 (CH_2), 56.57 (CH_3), 55.72 (CH), 40.89 (CH_2), 17.12 (CH_3); IR (Neat, cm^{-1}) 2918 (s) 1709 (s), 1037 (s).

5.5.0 Compounds Pertaining to Chapter 4 Section 4.2.0 & 4.3.0

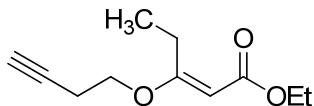
5.5.1 Experimental Data for Synthetic Intermediates 78, 80, 85a, 87a, and 98



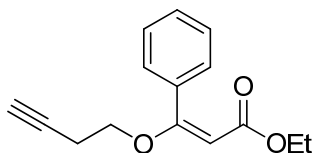
78a. Clear, light yellow oil (100% yield, 1.00:0.03 *E:Z*); $R_f = 0.93$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 5.05 (s, 1H), 4.07 (q, $J = 7.1$ Hz, 2H), 3.94 (t, $J = 6.3$ Hz, 2H), 2.63 (td, $J = 6.5, 2.7$ Hz, 2H), 2.44 (t, $J = 2.6$ Hz, 1H), 2.25 (s, 3H), 1.21 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 172.13 (C), 167.85 (C), 92.36 (CH), 81.16 (C), 71.23 (CH), 67.08 (CH_2), 59.59 (CH_2), 19.40 (CH_2), 18.83 (CH_3), 14.72 (CH_3); IR (Neat, cm^{-1}) 3295 (s), 3094 (w), 2980 (m), 2123 (w), 1709 (s), 1623 (s), 1143 (s); HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{14}\text{O}_3 + \text{H}^+$ 183.1021, found 183.1024.



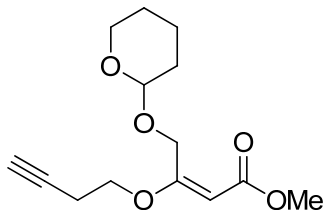
78b. Clear, orange-red oil (99% yield, 1.00:0.14 *E:Z*); $R_f = 0.74$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 7.59 (d, $J = 12.6$ Hz, 1H), 5.27 (d, $J = 12.6$ Hz, 1H), 4.06 (t, $J = 6.5$ Hz, 2H), 3.63 (s, 3H), 2.63 (td, $J = 6.5, 2.7$ Hz, 2H), 2.46 (t, $J = 2.8$ Hz, 1H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 168.00 (C), 162.98 (CH), 97.35 (CH), 80.91 (C), 71.53 (CH), 70.17 (CH_2), 51.06 (CH_3), 19.73 (CH_2); IR (Neat, cm^{-1}) 3293(s), 3093 (w), 2951 (m), 2122 (w), 1708 (s), 1627 (s), 1145 (s); HRMS (ESI) calcd for $\text{C}_8\text{H}_{10}\text{O}_3 + \text{H}^+$ 155.0708, found 155.0709.



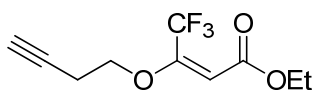
78c. Clear, yellow oil (96% yield, 1.00:0.15 *E:Z*); $R_f = 0.61$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 4.99 (s, 1H, major), 4.95 (s, 1H, minor), 4.16 (q, $J = 7.1$ Hz, 2H, minor), 4.07 (q, $J = 7.1$ Hz, 2H, major), 3.93 (t, $J = 6.5$ Hz, 2H), 2.74 (q, $J = 7.5$ Hz, 2H), 2.63 (td, $J = 6.5, 2.6$ Hz, 2H), 2.42 (t, $J = 2.6$ Hz, 1H), 1.31 (t, $J = 7.0$ Hz, 3H, minor), 1.21 (t, $J = 7.0$ Hz, 3H, major), 1.09 (t, $J = 7.5$ Hz, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 176.88 (C), 167.55 (C), 91.40 (CH), 81.18 (C), 71.16 (CH), 67.00 (CH_2), 59.48 (CH_2), 25.85 (CH_2), 19.39 (CH_2), 14.74 (CH_3), 12.23 (CH_3); IR (Neat, cm^{-1}) 3296 (m), 3090 (w), 2978 (s), 2123 (w), 1718 (s), 1623 (s), 1141 (s); HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{16}\text{O}_3 + \text{H}^+$ 197.1178, found 197.1175.



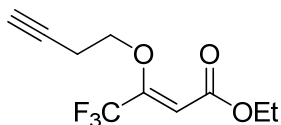
78d. Clear, light yellow oil (69% yield, 1.00:0.19 *E:Z*); $R_f = 0.58$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 7.78-7.74 (m, 2H), 7.49-7.45 (m, 3H), 5.72 (s, 1H, major), 5.64 (s, 1H, minor), 4.19 (t, $J = 6.7$ Hz, 2H), 4.16 (q, $J = 7.1$ Hz, 2H, major), 4.12 (q, $J = 7.0$ Hz, 2H, minor), 2.70 (td, $J = 6.7, 2.6$ Hz, 2H), 2.45 (t, $J = 2.7$ Hz, 1H), 1.35 (t, $J = 7.0$ Hz, 3H, minor), 1.27 (t, $J = 7.1$ Hz, 3H, major); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 167.31 (C), 165.31 (C), 136.16 (C), 131.42 (CH), 129.48 (CH), 128.21 (CH), 100.65 (CH), 81.57 (C), 72.27 (CH_2), 71.43 (CH), 60.16 (CH_2), 20.57 (CH_2), 14.68 (CH_3); IR (Neat, cm^{-1}) 3295 (s), 3061 (m), 2979 (s), 2121 (w), 1700 (s), 1617 (s), 1265 (s); HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{16}\text{O}_3 + \text{H}^+$ 245.1178, found 245.1172.



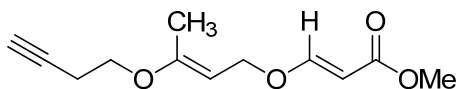
78e. Clear, light yellow oil (73% yield, 1.00:0.32 *E:Z*); $R_f = 0.31$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 5.19 (s, 1H, major), 5.18 (s, 1H, minor), 4.76-4.57 (m, 3H), 4.18 (t, $J = 6.7$ Hz, 1H, minor), 4.01 (t, $J = 6.5$ Hz, 1H, major), 3.90 (td, $J = 10.1, 3.1$ Hz, 1H), 3.74 (s, 3H, minor), 3.66 (s, 3H, major), 3.49 (dt, $J = 11.1, 4.1$ Hz, 1H), 2.70 (td, $J = 6.6, 2.4$ Hz, 2H, major), 2.57 (td, $J = 6.6, 2.4$ Hz, 2H, minor), 2.47 (t, $J = 2.4$ Hz, 1H, major), 2.44 (t, $J = 2.4$ Hz, 1H, minor), 1.87-1.51 (m, 6H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 171.66 (C, minor), 171.09 (C, major), 167.53 (C, major), 166.91 (C, minor), 99.25 (CH, minor), 99.05 (CH, major), 93.92 (CH, major), 93.17 (CH, minor), 81.35 (C, minor), 81.19 (C, major), 71.36 (CH, major), 71.28 (CH, minor), 67.53 (CH₂, minor), 67.42 (CH₂, major), 64.18 (CH₂, minor), 63.81 (CH₂, major), 62.38 (CH₂, minor), 61.94 (CH₂, major), 56.30 (CH₃, minor), 51.17 (CH₃, major), 31.15 (CH₂), 26.29 (CH₂), 19.80 (CH₂, minor), 19.73 (CH₂, major), 19.44 (CH₂); IR (Neat, cm^{-1}) 3272 (s), 3093 (w), 2947 (s), 2117 (w), 1713 (s), 1633 (s), 1145 (s); HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{20}\text{O}_5 + \text{Na}^+$ 291.1208, found 291.1205.



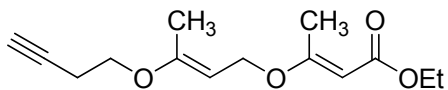
78f (*E* isomer). Clear, yellow oil (38% yield); $R_f = 0.41$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 5.69 (s, 1H), 4.16 (q, $J = 7.1$ Hz, 2H), 4.10 (t, $J = 6.4$ Hz, 2H), 2.72 (td, $J = 6.5, 2.7$ Hz, 2H), 2.47 (t, $J = 2.6$ Hz, 1H), 1.25 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 164.13 (C), 153.32 (q, $J = 36.0$ Hz, C), 120.23 (q, $J = 276.8$ Hz, CF₃), 99.85 (CH), 80.45 (C), 71.55 (CH), 68.97 (CH₂), 61.35 (CH₂), 19.13 (CH₂), 14.31 (CH₃); IR (Neat, cm^{-1}) 3308 (s), 3067 (w), 2985 (m), 2125 (w), 1732 (s), 1667 (s), 1148 (s); HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{11}\text{F}_3\text{O}_3 + \text{H}^+$ 237.0739, found 237.0741.



78f (Z isomer). Clear, yellow oil (59% yield); $R_f = 0.62$ (hexanes-ethyl acetate, 4:1); ^1H NMR ($(\text{CD}_3)_2\text{CO}$) 5.91 (s, 1H), 4.36 (t, $J = 6.6$ Hz, 2H), 4.22 (q, $J = 7.1$ Hz, 2H), 2.66 (td, $J = 6.6, 2.7$ Hz, 2H), 2.44 (t, $J = 2.7$ Hz, 1H), 1.28 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($(\text{CD}_3)_2\text{CO}$) 163.84 (C), 152.94 (q, $J = 33.8$ Hz, C), 120.74 (q, $J = 274.5$ Hz, CF_3), 103.85 (CH), 80.45 (C), 74.63 (CH_2), 71.47 (CH), 61.71 (CH_2), 20.39 (CH_2), 14.33 (CH_3); IR (Neat, cm^{-1}) 3305 (s), 3098 (w), 2986 (m), 2125 (w), 1734 (s), 1652 (s), 1147 (s); HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{11}\text{F}_3\text{O}_3 + \text{H}^+$ 237.0739, found 237.0742.

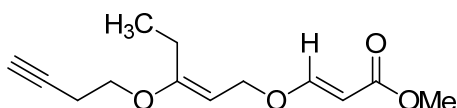


80a. Clear, yellow oil (93% yield, 1.00:0.05 *E:Z*); $R_f = 0.77$ (hexanes-ethyl acetate, 1:1); ^1H NMR ($(\text{CD}_3)_2\text{CO}$) 7.58 (d, $J = 12.6$ Hz, 1H), 5.23 (d, $J = 12.5$ Hz, 1H), 4.78 (t, $J = 7.8$ Hz, 1H), 4.51 (d, $J = 7.8$ Hz, 2H), 3.83 (t, $J = 6.7$ Hz, 2H), 3.62 (s, 3H), 2.58 (td, $J = 6.6, 2.7$ Hz, 2H), 2.41 (t, $J = 2.8$ Hz, 1H), 1.88 (s, 3H); ^{13}C NMR ($(\text{CD}_3)_2\text{CO}$) 168.24 (C), 163.12 (CH), 160.07 (C), 96.86 (CH), 93.00 (CH), 81.57 (C), 70.98 (CH), 68.90 (CH_2), 66.03 (CH_2), 50.94 (CH_3), 19.56 (CH_2), 16.59 (CH_3); IR (Neat, cm^{-1}) 3292 (s), 3091 (w), 2950 (m), 2122 (w), 1706 (s), 1621 (s); HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{16}\text{O}_4 + \text{Na}^+$ 247.0946, found 247.0941.

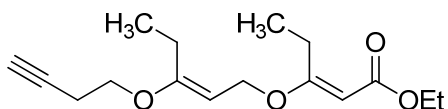


80b. Clear, orange oil (99% yield, 1.00:0.05 *E:Z*); $R_f = 0.72$ (hexanes-ethyl acetate, 1:1); ^1H NMR ($(\text{CD}_3)_2\text{CO}$) 5.07 (s, 1H), 4.75 (t, $J = 7.5$ Hz, 1H), 4.40 (d, $J = 7.6$ Hz, 2H), 4.07 (q, $J = 7.2$ Hz, 2H), 3.83 (t, $J = 6.7$ Hz, 2H), 2.58 (td, $J = 6.5, 2.7$ Hz, 2H), 2.42 (t, $J =$

2.6 Hz, 1H), 2.23 (s, 3H), 1.86 (s, 3H), 1.21 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ((CD_3) $_2\text{CO}$) 172.53 (C), 168.07 (C), 159.31 (C), 92.96 (CH), 91.91 (CH), 81.62 (C), 70.99 (CH), 65.95 (CH_2), 61.13 (CH_2), 59.45 (CH_2), 19.60 (CH_2), 19.17 (CH_3), 14.79 (CH_3), 14.36 (CH_3); IR (Neat, cm^{-1}) 3292 (s), 3087 (w), 2979 (s), 2122 (w), 1708 (s), 1619 (s); HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{20}\text{O}_4 + \text{Na}^+$ 275.1259, found 275.1266.

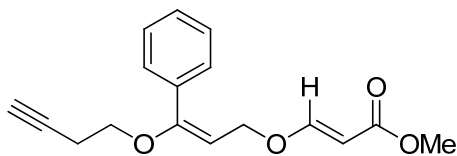


80c. Clear, light yellow oil (99% yield, 1.00:0.05 *E:Z*); $R_f = 0.38$ (hexanes-ethyl acetate, 4:1); ^1H NMR ((CD_3) $_2\text{CO}$) 7.59 (d, $J = 12.6$ Hz, 1H), 5.24 (d, $J = 12.6$ Hz, 1H), 4.72 (t, $J = 7.8$ Hz, 1H), 4.51 (d, $J = 3.5$ Hz, 2H), 3.82 (t, $J = 6.6$ Hz, 2H), 3.62 (s, 3H), 2.58 (td, $J = 6.6, 2.7$ Hz, 2H), 2.38 (t, $J = 2.7$ Hz, 1H), 2.25 (q, $J = 7.5$ Hz, 2H), 1.07 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR ((CD_3) $_2\text{CO}$) 168.26 (C), 164.97 (CH), 164.04 (C), 98.33 (CH), 92.14 (CH), 81.62 (C), 70.98 (CH), 68.60 (CH_2), 65.97 (CH_2), 51.02 (CH_3), 24.39 (CH_2), 19.58 (CH_2), 13.60 (CH_3); IR (Neat, cm^{-1}) 3294 (m), 3091 (w), 2949 (m), 2121 (w), 1712 (s), 1621 (s), 1130 (s), 1098 (s); HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{18}\text{O}_4 + \text{Na}^+$ 261.1103, found 261.1110.

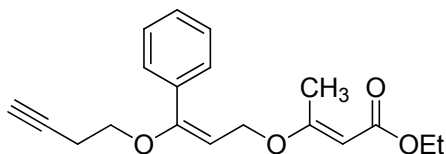


80d. Clear, colorless oil (68% yield); $R_f = 0.61$ (hexanes-ethyl acetate, 4:1); ^1H NMR ((CD_3) $_2\text{CO}$) 5.02 (s, 1H), 4.71 (t, $J = 7.6$ Hz, 1H), 4.38 (d, $J = 7.6$ Hz, 2H), 4.06 (q, $J = 7.1$ Hz, 2H), 3.82 (t, $J = 6.6$ Hz, 2H), 2.72 (q, $J = 7.5$ Hz, 2H), 2.58 (td, $J = 6.6, 2.7$ Hz, 2H), 2.40 (t, $J = 2.7$ Hz, 1H), 2.23 (q, $J = 7.5$ Hz, 2H), 1.21 (t, $J = 7.1$ Hz, 3H), 1.08 (t, $J = 7.5$ Hz, 3H), 1.06 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR ((CD_3) $_2\text{CO}$) 177.30 (C), 167.75 (C), 164.44 (C), 92.05 (CH), 90.99 (CH), 81.63 (C), 70.90 (CH), 65.92 (CH_2), 65.56 (CH_2), 59.45 (CH_2), 26.10 (CH_2), 24.42 (CH_2), 20.43 (CH_2), 19.57 (CH_3), 14.77 (CH_3), 14.43

(CH₃); IR (Neat, cm⁻¹) 3297 (m), 3063 (w), 2976 (m), 2117 (w), 1708 (s), 1615 (s), 1132 (s), 1083 (s); HRMS (ESI) calcd for C₁₆H₂₄O₄+Na⁺ 303.1572, found 303.1578.

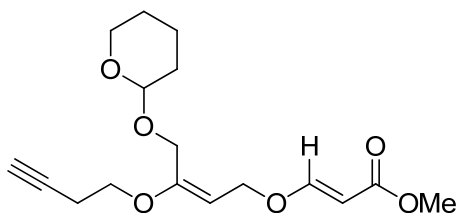


80e. Clear, light yellow oil (98% yield, 1.00:0.07 *E:Z*); *R*_f = 0.39 (hexanes-ethyl acetate, 4:1); ¹H NMR ((CD₃)₂CO) 7.65 (d, *J* = 12.5 Hz, 1H), 7.58-7.55 (m, 2H), 7.39-7.38 (m, 3H), 5.55 (t, *J* = 7.1 Hz, 1H, major), 5.54 (t, *J* = 7.1 Hz, 1H, minor), 5.35 (d, *J* = 12.5 Hz, 1H, minor), 5.33 (d, *J* = 12.6 Hz, 1H, major), 4.90 (d, *J* = 7.1 Hz, 2H, minor), 4.80 (d, *J* = 7.1 Hz, 2H, major), 3.83 (t, *J* = 6.5 Hz, 2H, major), 3.82 (t, *J* = 6.5 Hz, 2H, minor), 3.74 (s, 3H, minor), 3.63 (s, 3H, major), 2.57 (td, *J* = 6.5, 2.7 Hz, 2H), 2.45 (t, *J* = 2.6 Hz, 1H); ¹³C NMR ((CD₃)₂CO) 168.20 (C), 163.18 (CH), 158.30 (C), 135.43 (C), 129.99 (CH), 129.47 (CH), 127.51 (CH), 110.08 (CH, minor), 108.90 (CH, major), 97.48 (CH, minor), 97.19 (CH, major), 81.83 (C), 71.38 (CH), 69.63 (CH₂, major), 69.54 (CH₂, minor), 66.66 (CH₂, major), 59.08 (CH₂, minor), 51.04 (CH₃), 20.20 (CH₂); IR (Neat, cm⁻¹) 3303 (m), 3055 (m), 2950 (m), 2122 (w), 1703 (s), 1621 (s), 1136 (s); HRMS (ESI) calcd for C₁₇H₁₈O₄+Na⁺ 309.1103, found 309.1094.

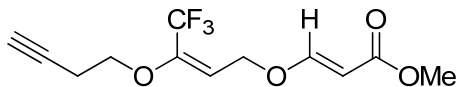


80f. Clear, light yellow oil (99% yield, 1.00:0.02 *E:Z*); *R*_f = 0.48 (hexanes-ethyl acetate, 4:1); ¹H NMR ((CD₃)₂CO) 7.59-7.55 (m, 2H), 7.43-7.40 (m, 3H), 5.56 (t, *J* = 6.8 Hz, 1H), 5.18 (s, 1H), 4.72 (d, *J* = 6.8 Hz, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.82 (t, *J* = 6.5 Hz, 2H), 2.55 (td, *J* = 6.5, 2.7 Hz, 2H), 2.27 (t, *J* = 2.7 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H); ¹³C NMR ((CD₃)₂CO) 172.33 (C), 168.04 (C), 157.52 (C), 135.57 (C), 129.85 (CH), 129.50

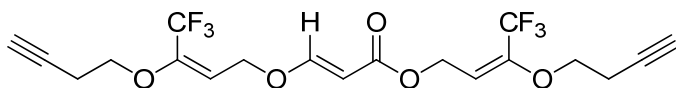
(CH), 127.38 (CH), 109.26 (CH), 92.25 (CH), 81.85 (C), 71.23 (CH), 69.57 (CH₂), 64.00 (CH₂), 59.52 (CH₂), 20.20 (CH₂), 19.14 (CH₃), 14.79 (CH₃); IR (Neat, cm⁻¹) 3294 (m), 3059 (m), 2977 (m), 2117 (w), 1708 (s), 1621 (s), 1142 (s); HRMS (ESI) calcd for C₁₉H₂₂O₄+Na⁺ 337.1426, found 337.1418.



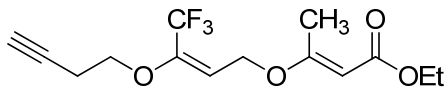
80g. Clear, light yellow oil (92% yield, 1.00:0.28 *E:Z*); *R_f* = 0.24 (hexanes-ethyl acetate, 4:1); ¹H NMR ((CD₃)₂CO) 7.61 (d, *J* = 12.6 Hz, 1H, major), 7.57 (d, *J* = 12.6 Hz, 1H, minor), 5.25 (d, *J* = 12.5 Hz, 1H, major), 5.24 (d, *J* = 12.6 Hz, 1H, minor), 4.95 (t, *J* = 7.7 Hz, 1H, major), 4.92 (t, *J* = 7.7 Hz, 1H, minor), 4.68 (t, *J* = 3.3 Hz, 1H, major), 4.64 (t, *J* = 3.3 Hz, 1H, minor), 4.62 (d, *J* = 7.6 Hz, 1H, minor), 4.61 (d, *J* = 7.6 Hz, 1H, major), 4.24 (d, *J* = 12.4 Hz, 1H, major), 4.23 (d, *J* = 12.2 Hz, 1H, minor), 4.10 (d, *J* = 12.2 Hz, 1H, major), 4.07 (d, *J* = 12.2 Hz, 1H, minor), 3.86 (t, *J* = 6.6 Hz, 2H), 3.82-3.77 (m, 1H), 3.62 (s, 3H, major), 3.58 (s, 3H, minor), 3.47 (dtd, *J* = 11.0, 4.6, 1.1 Hz, 1H), 2.60 (td, *J* = 6.6, 2.6 Hz, 2H, major), 2.56 (td, *J* = 6.6, 2.6 Hz, 2H, minor), 2.41 (t, *J* = 2.6 Hz, 1H, major), 2.35 (t, *J* = 2.6 Hz, 1H, minor), 1.84-1.46 (m, 6H); ¹³C NMR ((CD₃)₂CO) 168.19 (C), 163.11 (CH), 160.03 (C, minor), 158.93 (C, major), 98.31 (CH, minor), 98.26 (CH, major), 97.29 (CH, major), 97.10 (CH, major), 97.05 (CH, minor), 96.14 (CH, minor), 82.50 (C), 71.08 (CH), 68.15 (CH₂, minor), 68.08 (CH₂, major), 66.36 (CH₂), 64.22 (CH₂, minor), 64.02 (CH₂, major), 62.24 (CH₂), 55.15 (CH₃, minor), 50.99 (CH₃, major), 31.10 (CH₂), 26.20 (CH₂), 19.97 (CH₂, minor), 19.89 (CH₂, major), 19.64 (CH₂); IR (Neat, cm⁻¹) 3304 (m), 3053 (s), 2948 (s), 2123 (w), 1700 (s), 1621 (s), 1119 (s), 1028 (s); HRMS (ESI) calcd for C₁₇H₂₄O₆+Na⁺ 347.1471, found 347.1478.



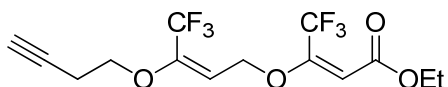
80h (major). Clear, colorless oil (64% yield, 1.00:0.07 *E:Z*); $R_f = 0.39$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 7.66 (d, $J = 12.6$ Hz, 1H), 5.44 (t, $J = 7.2$ Hz, 1H), 5.29 (d, $J = 12.6$ Hz, 1H), 4.79 (dq, $J = 7.4, 2.1$ Hz, 2H, minor), 4.71 (dq, $J = 7.3, 1.9$ Hz, 2H, major), 4.02 (t, $J = 6.5$ Hz, 2H), 3.75 (s, 3H, minor), 3.63 (s, 3H, major), 2.67 (td, $J = 6.5, 2.7$ Hz, 2H), 2.44 (t, $J = 2.7$ Hz, 1H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 167.94 (C), 164.42 (CH, minor), 162.44 (CH, major), 146.99 (q, $J = 35.1$ Hz, C), 121.31 (q, $J = 274.7$ Hz, CF_3), 103.90 (CH, minor), 102.93 (CH, major), 97.75 (CH, major), 96.17 (CH, minor), 80.74 (C), 71.39 (CH), 68.15 (CH_2), 65.62 (CH_2), 51.11 (CH_3), 19.28 (CH_2); IR (Neat, cm^{-1}) 3299 (s), 3047 (m), 2946 (m), 2121 (w), 1706 (s), 1624 (s), 1137 (s), 1046 (m); HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{13}\text{F}_3\text{O}_4 + \text{H}^+$ 279.0844, found 279.0839.



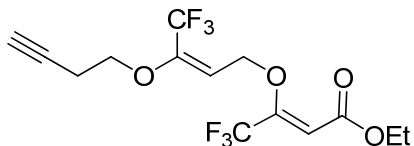
Transesterification product 98 formed along with 80h. Clear, colorless oil (22% yield); $R_f = 0.26$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 7.63 (d, $J = 12.6$ Hz, 1H), 5.46 (t, $J = 7.3$ Hz, 1H), 5.37 (t, $J = 7.4$ Hz, 1H), 5.31 (d, $J = 12.6$ Hz, 1H), 4.79 (dq, $J = 7.4, 2.0$ Hz, 2H), 4.72 (dq, $J = 7.3, 2.0$ Hz, 2H), 4.02 (t, $J = 6.5$ Hz, 2H), 3.98 (t, $J = 6.5$ Hz, 2H), 2.67 (td, $J = 6.5, 2.5$ Hz, 2H), 2.65 (td, $J = 6.5, 2.6$ Hz, 2H), 2.45 (t, $J = 2.6$ Hz, 1H), 2.44 (t, $J = 2.6$ Hz, 1H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 167.24 (C), 162.96 (CH), 146.57 (q, $J = 35.5$ Hz, C), 121.35 (q, $J = 270.8$ Hz, CF_3), 121.52 (q, $J = 270.2$ Hz, CF_3), 103.84 (CH), 102.83 (CH), 97.54 (CH), 80.74 (C), 71.39 (CH), 68.16 (CH_2), 68.04 (CH_2), 65.72 (CH_2), 58.00 (CH_2), 19.28 (CH_2); IR (Neat, cm^{-1}) 3299 (s), 3053 (m), 2957 (m), 2128 (w), 1717 (s), 1622 (s), 1132 (s); HRMS (ESI) calcd for $\text{C}_{19}\text{H}_{18}\text{F}_6\text{O}_5 + \text{Na}^+$ 463.0955, found 463.0945.



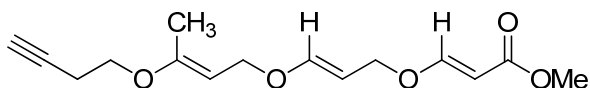
80i. Clear, orange oil (99% yield, 1.00:0.08 *E:Z*); $R_f = 0.58$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 5.44 (t, $J = 7.0$ Hz, 1H, major), 5.31 (t, $J = 76.8$ Hz, 1H, minor), 5.08 (s, 1H, major), 4.94 (s, 1H, minor), 4.85 (dq, $J = 6.8, 2.0$ Hz, 2H, minor), 4.61 (dq, $J = 7.0, 2.0$ Hz, 2H, major), 4.07 (q, $J = 7.1$ Hz, 2H), 4.01 (t, $J = 6.6$ Hz, 3H, major), 3.92 (t, $J = 6.6$ Hz, 3H, minor), 2.67 (td, $J = 6.7, 2.7$ Hz, 2H, major), 2.63 (td, $J = 6.7, 2.7$ Hz, 2H, minor), 2.44 (t, $J = 2.7$ Hz, 1H), 2.26 (s, 3H), 1.21 (t, $J = 7.0$ Hz, 3H, major), 1.20 (t, $J = 7.1$ Hz, 3H, minor); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 171.81 (C), 167.79 (C), 146.54 (q, $J = 35.4$ Hz, C), 121.43 (q, $J = 275.0$ Hz, CF_3), 103.26 (CH), 92.62 (CH), 80.76 (C), 71.39 (CH), 68.09 (CH_2), 62.88 (CH_2), 59.66 (CH_2), 20.07 (CH_2), 19.30 (CH_3), 14.72 (CH_3); IR (Neat, cm^{-1}) 3299 (s), 3053 (m), 2982 (m), 2117 (w), 1700 (s), 1623 (s), 1146 (s), 1051 (m); HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{17}\text{F}_3\text{O}_4 + \text{H}^+$ 307.1157, found 307.1150.



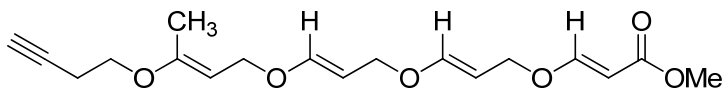
80j (*E* isomer). Clear, light yellow oil (41% yield); $R_f = 0.39$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 5.76 (s, 1H), 5.52 (t, $J = 7.3$ Hz, 1H), 4.76 (dq, $J = 7.3, 1.7$ Hz, 2H), 4.16 (q, $J = 7.1$ Hz, 2H), 4.05 (t, $J = 6.5$ Hz, 2H), 2.68 (td, $J = 6.5, 2.7$ Hz, 2H), 2.46 (t, $J = 2.7$ Hz, 1H), 1.25 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 164.08 (C), 152.85 (q, $J = 37.2$ Hz, C), 147.85 (q, $J = 36.0$ Hz, C), 121.22 (q, $J = 273.7$ Hz, CF_3), 120.20 (q, $J = 275.1$ Hz, CF_3), 101.45 (CH), 100.19 (CH), 80.70 (C), 71.40 (CH), 68.25 (CH_2), 64.74 (CH_2), 61.39 (CH_2), 19.26 (CH_2), 14.31 (CH_3); IR (Neat, cm^{-1}) 3311 (m), 3063 (w), 2986 (m), 2123 (w), 1725 (s), 1665 (s), 1141 (s); HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{14}\text{F}_6\text{O}_4 + \text{Na}^+$ 383.0694, found 383.0688.



80j (Z isomer). Clear, light yellow oil (58% yield); $R_f = 0.52$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 5.96 (s, 1H), 5.47 (t, $J = 7.6$ Hz, 1H), 5.03 (dq, $J = 7.6, 1.8$ Hz, 2H), 4.23 (q, $J = 7.1$ Hz, 2H), 4.03 (t, $J = 6.5$ Hz, 2H), 2.67 (td, $J = 6.5, 2.7$ Hz, 2H), 2.45 (t, $J = 2.7$ Hz, 1H), 1.28 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 163.89 (C), 152.57 (q, $J = 33.9$ Hz, C), 147.41 (q, $J = 35.0$ Hz, C), 121.24 (q, $J = 276.9$ Hz, CF_3), 120.71 (q, $J = 276.0$ Hz, CF_3), 104.63 (CH), 102.84 (CH), 80.69 (C), 71.39 (CH), 70.06 (CH₂), 68.18 (CH₂), 61.79 (CH₂), 19.24 (CH₂), 14.31 (CH₃); IR (Neat, cm^{-1}) 3311 (m), 3061 (w), 2986 (m), 2117 (w), 1726 (s), 1666 (s), 1135 (s); HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{14}\text{F}_6\text{O}_4 + \text{Na}^+$ 383.0694, found 383.0693.

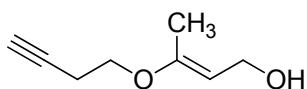


85a. Yellow solid (95% yield, 1.00:0.02 *E:Z*); $R_f = 0.32$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 7.59 (d, $J = 12.6$ Hz, 1H), 6.75 (d, $J = 12.6$ Hz, 1H), 5.21 (d, $J = 12.6$ Hz, 1H), 5.03 (dt, $J = 12.6, 7.8$ Hz, 1H), 4.73 (t, $J = 7.5$ Hz, 1H), 4.41 (d, $J = 7.7$ Hz, 2H), 4.34 (d, $J = 7.6$ Hz, 2H), 3.81 (t, $J = 6.7$ Hz, 2H), 3.61 (s, 3H), 2.57 (td, $J = 6.7, 2.7$ Hz, 2H), 2.41 (t, $J = 2.7$ Hz, 1H), 1.85 (s, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 168.22 (C), 162.97 (CH), 158.92 (C), 153.48 (CH), 98.73 (CH), 96.94 (CH), 93.79 (CH), 81.63 (C), 70.96 (CH), 70.63 (CH₂), 66.98 (CH₂), 65.88 (CH₂), 50.94 (CH₃), 19.58 (CH₂), 16.56 (CH₃); IR (Neat, cm^{-1}) 3300 (s), 3054 (m), 2950 (s), 2122 (w), 1705 (s), 1621 (s); HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{20}\text{O}_5 + \text{Na}^+$ 303.1208, found 303.1215.

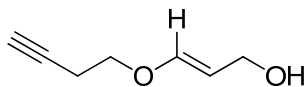


87a. Clear, light yellow oil (89% yield, 1.00:0.29 *E:Z*); $R_f = 0.19$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 7.57 (d, $J = 12.5$ Hz, 1H), 6.75 (d, $J = 12.5$ Hz, 1H, minor), 6.73 (d, $J = 12.5$ Hz, 1H, major), 6.66 (d, $J = 12.6$ Hz, 1H), 5.22 (d, $J = 12.5$ Hz, 1H), 5.08-4.98 (m, 2H, minor), 5.06-4.95 (m, 2H, major), 4.72 (t, $J = 7.4$ Hz, 1H), 4.40 (d, $J = 7.8$ Hz, 2H), 4.30 (d, $J = 7.5$ Hz, 2H), 4.22 (d, $J = 7.5$ Hz, 2H), 3.80 (t, $J = 6.6$ Hz, 2H), 3.64 (s, 3H, minor), 3.61 (s, 3H, major), 2.56 (td, $J = 6.6, 2.7$ Hz, 2H), 2.41 (t, $J = 2.7$ Hz, 1H), 1.84 (s, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 168.23 (C), 162.97 (CH), 158.92 (C, minor), 158.77 (C, major), 153.48 (CH, minor), 153.32 (CH, major), 152.46 (CH), 99.47 (CH), 98.79 (CH, major), 98.73 (CH, minor), 96.95 (CH), 93.91 (CH, major), 93.79 (CH, minor), 81.64 (C), 70.98 (CH), 70.60 (CH_2), 68.60 (CH_2), 66.98 (CH_2 , minor), 66.80 (CH_2 , major), 65.86 (CH_2), 51.78 (CH_3 , minor), 50.95 (CH_3 , major), 19.58 (CH_2), 16.57 (CH_3); IR (Neat, cm^{-1}) 3290 (s), 3070 (m), 2950 (s), 2117 (w), 1712 (s), 1621 (s), 1133 (s); HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{24}\text{O}_6 + \text{Na}^+$ 359.1471, found 359.1468.

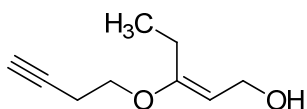
5.5.2 Experimental Data for Synthetic Intermediates 79, 81, 86a, and 88a



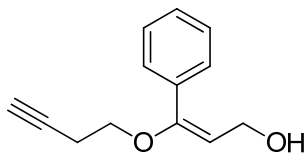
79a. Clear, light yellow oil (99% yield, 1.00:0.04 *E:Z*); $R_f = 0.43$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 4.69 (t, $J = 7.5$ Hz, 1H), 4.05 (dd, $J = 7.5, 5.6$ Hz, 2H), 3.75 (t, $J = 6.7$ Hz, 2H), 3.27 (t, $J = 5.5$ Hz, 1H), 2.54 (td, $J = 6.7, 2.7$ Hz, 2H), 2.40 (t, $J = 2.6$ Hz, 1H), 1.79 (s, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 155.78 (C), 99.10 (CH), 81.79 (C), 70.86 (CH), 65.51 (CH_2), 58.82 (CH_2), 19.63 (CH_2), 16.30 (CH_3); IR (Neat, cm^{-1}) 3372 (br, s), 3298 (s), 3071 (w), 2927 (s), 2121 (m), 1661 (s); LRMS (ESI) calcd for $\text{C}_8\text{H}_{12}\text{O}_2 + \text{Na}^+$ 163.1, found 163.1.



79b. Clear, colorless oil (95% yield, >1.00:0.05 *E:Z*); $R_f = 0.48$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 6.48 (d, $J = 12.7$ Hz, 1H), 5.00 (dt, $J = 14.0, 7.0$ Hz, 1H), 3.95 (ddd, $J = 6.9, 5.3, 1.0$ Hz, 2H), 3.79 (t, $J = 6.7$ Hz, 2H), 3.40 (t, $J = 5.5$ Hz, 1H), 2.52 (td, $J = 6.7, 2.8$ Hz, 2H), 2.40 (t, $J = 2.7$ Hz, 1H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 149.11 (CH), 105.33 (CH), 81.56 (C), 71.04 (CH), 67.90 (CH_2), 60.12 (CH_2), 19.78 (CH_2); IR (Neat, cm^{-1}) 3366 (br, s), 3294 (s), 3063 (w), 2927 (s), 2120 (w), 1651 (s).

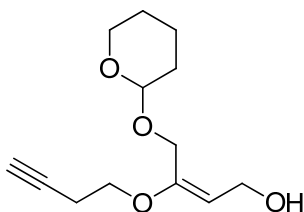


79c. Clear, light yellow oil (89% yield, >1.00:0.05 *E:Z*); $R_f = 0.09$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 4.64 (t, $J = 7.4$ Hz, 1H), 4.06 (dd, $J = 7.3, 4.6$ Hz, 2H), 3.75 (t, $J = 6.6$ Hz, 2H), 3.38 (t, $J = 4.5$ Hz, 1H), 2.54 (td, $J = 6.6, 2.6$ Hz, 2H), 2.38 (t, $J = 2.6$ Hz, 1H), 2.18 (q, $J = 7.5$ Hz, 2H), 1.03 (t, $J = 7.5$ Hz, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 160.75 (C), 98.32 (CH), 81.82 (C), 70.82 (CH), 65.48 (CH_2), 58.47 (CH_2), 24.15 (CH_2), 19.61 (CH_2), 13.01 (CH_3); IR (Neat, cm^{-1}) 3400 (br, s), 3298 (s), 3066 (w), 2937 (s), 2121 (w), 1659 (s), 1193 (s), 1099 (s); LRMS (ESI) calcd for $\text{C}_9\text{H}_{14}\text{O}_2 + \text{Na}^+$ 177.1, found 177.1.

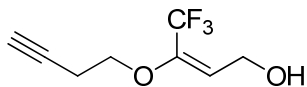


79d. Clear, light yellow oil (95% yield, 1.00:0.12 *E:Z*); $R_f = 0.09$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 7.55-7.48 (m, 2H), 7.41-7.33 (m, 3H), 5.57 (t, $J = 6.6$ Hz, 1H, major), 5.53 (t, $J = 6.6$ Hz, 1H, minor), 4.37 (dd, $J = 6.6, 5.7$ Hz, 2H, major), 4.33

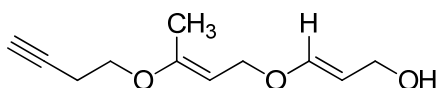
(dd, $J = 6.6, 5.7$ Hz, 2H, minor), 3.77 (t, $J = 6.7$ Hz, 2H), 3.61 (t, $J = 7.1$ Hz, 1H, major), 3.58 (t, $J = 7.1$ Hz, 1H, minor), 2.55 (td, $J = 6.7, 2.7$ Hz, 2H), 2.43 (t, $J = 2.7$ Hz, 1H); ^{13}C NMR ($(\text{CD}_3)_2\text{CO}$) 154.37 (C), 136.42 (C), 129.28 (CH), 129.16 (CH), 126.94 (CH), 116.22 (CH), 81.83 (C), 71.14 (CH), 69.49 (CH_2), 57.28 (CH_2), 20.23 (CH_2); IR (Neat, cm^{-1}) 3434 (br, m), 3303 (s), 3053 (s), 2985 (m), 2122 (w), 1654 (m), 1265 (s); HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{14}\text{O}_2 + \text{Na}^+$ 225.0891, found 225.0889.



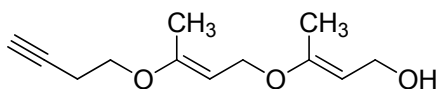
79e. Clear, light yellow oil (92% yield, 1.00:0.38 *E:Z*); $R_f = 0.06$ (hexanes-ethyl acetate, 4:1); ^1H NMR ($(\text{CD}_3)_2\text{CO}$) 4.92 (t, $J = 7.6$ Hz, 1H, major), 4.89 (t, $J = 7.6$ Hz, 1H, minor), 4.67 (t, $J = 3.3$ Hz, 1H, major), 4.63 (t, $J = 3.3$ Hz, 1H, minor), 4.19-4.067 (m, 4H), 3.87-3.78 (m, 1H), 3.79 (t, $J = 6.7$ Hz, 2H), 3.54-3.43 (m, 1H), 3.39 (t, $J = 5.6$ Hz, 1H, major), 3.36 (t, $J = 5.6$ Hz, 1H, minor), 2.56 (td, $J = 6.7, 2.6$ Hz, 2H, major), 2.50 (td, $J = 6.7, 2.6$ Hz, 2H, minor), 2.41 (t, $J = 2.6$ Hz, 1H, major), 2.39 (t, $J = 2.6$ Hz, 1H, minor), 1.84-1.45 (m, 6H); ^{13}C NMR ($(\text{CD}_3)_2\text{CO}$) 157.00 (C, minor), 155.93 (C, major), 104.22 (CH, major), 102.96 (CH, minor), 98.36 (CH, minor), 98.30 (CH, major), 82.13 (C), 71.39 (CH, major), 71.11 (CH, minor), 66.60 (CH_2 , minor), 66.32 (CH_2 , major), 64.44 (CH_2 , minor), 64.21 (CH_2 , major), 62.70 (CH_2 , minor), 62.50 (CH_2 , major), 58.51 (CH_2 , major), 58.38 (CH_2 , minor), 31.60 (CH_2), 26.67 (CH_2), 20.66 (CH_2 , minor), 20.29 (CH_2 , major), 20.03 (CH_2); IR (Neat, cm^{-1}) 3412 (br, s), 3289 (s), 3053 (w), 2942 (s), 2117 (w), 1661 (s), 1025 (s); HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{20}\text{O}_4 + \text{Na}^+$ 263.1259, found 263.1251.



79f. Clear, yellow oil (91% yield); $R_f = 0.09$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 5.31 (t, $J = 6.7$ Hz, 1H), 4.30-4.29 (m, 2H), 4.02 (t, $J = 4.9$ Hz, 1H), 3.92 (t, $J = 6.6$ Hz, 2H), 2.63 (td, $J = 6.6, 2.7$ Hz, 2H), 2.42 (t, $J = 2.7$ Hz, 1H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 143.66 (q, $J = 34.3$ Hz, C), 121.55 (q, $J = 274.7$ Hz, CF_3), 110.15 (CH), 80.93 (C), 71.23 (CH), 67.75 (CH_2), 56.45 (CH_2), 19.34 (CH_2); IR (Neat, cm^{-1}) 3361 (br, s), 3306 (s), 3061 (w), 2941 (m), 2123 (w), 1669 (s), 1136 (s); LRMS (ESI) calcd for $\text{C}_8\text{H}_9\text{F}_3\text{O}_2 + \text{Na}^+$ 217.0, found 217.1.

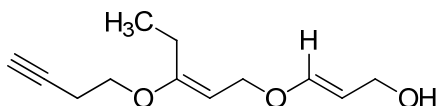


81a. Clear, yellow oil (78% yield, >1.00:0.05 *E:Z*); $R_f = 0.52$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 6.47 (d, $J = 12.5$ Hz, 1H), 5.00 (t, $J = 7.0$ Hz, 0.5H), 4.96 (t, $J = 7.0$ Hz, 0.5H), 4.70 (t, $J = 7.3$ Hz, 1H), 4.23 (d, $J = 7.5$ Hz, 2H), 3.94 (dd, $J = 6.9, 1.0$ Hz, 2H), 3.79 (t, $J = 6.7$ Hz, 2H), 3.35 (t, $J = 5.4$ Hz, 1H), 2.56 (td, $J = 6.7, 2.7$ Hz, 2H), 2.39 (t, $J = 2.7$ Hz, 1H), 1.83 (s, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 158.39 (C), 149.38 (CH), 104.85 (CH), 94.23 (CH), 81.67 (C), 70.98 (CH), 66.39 (CH_2), 65.82 (CH_2), 60.39 (CH_2), 19.61 (CH_2), 16.34 (CH_3); IR (Neat, cm^{-1}) 3376 (br, s), 3291 (s), 3061 (w), 2927 (s), 2121 (w), 1648 (s); HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{16}\text{O}_3 + \text{Na}^+$ 219.0997, found 219.0933.

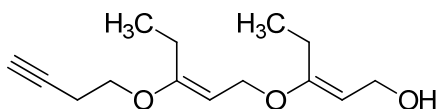


81b. Clear, yellow oil (74% yield, >1.00:0.05 *E:Z*); $R_f = 0.57$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 4.71 (t, $J = 7.4$ Hz, 2H), 4.19 (d, $J = 7.3$ Hz, 2H), 4.05 (dd, $J = 7.4, 5.6$ Hz, 2H), 3.80 (t, $J = 6.7$ Hz, 2H), 3.22 (t, $J = 5.4$ Hz, 1H), 2.56 (td, $J = 6.7, 2.7$

Hz, 2H), 2.41 (t, $J = 2.7$ Hz, 1H), 2.23 (s, 3H), 1.82 (s, 3H), 1.77 (s, 3H); ^{13}C NMR ((CD_3) $_2\text{CO}$) 157.84 (C), 156.09 (C), 98.66 (CH), 94.29 (CH), 81.70 (C), 70.95 (CH), 65.79 (CH $_2$), 63.99 (CH $_2$), 58.98 (CH $_2$), 19.62 (CH $_2$), 16.53 (CH $_3$); IR (Neat, cm^{-1}) 3372 (br, s), 3297 (s), 3051 (w), 2927 (s), 2122 (w), 1651 (s); HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{18}\text{O}_3 + \text{Na}^+$ 233.1154, found 233.1158.

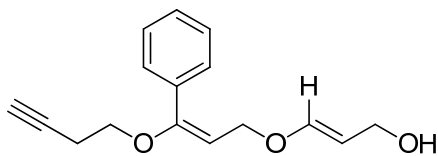


81c. Clear, light yellow oil (75% yield, >1.00:0.05 *E:Z*); $R_f = 0.09$ (hexanes-ethyl acetate, 4:1); ^1H NMR ((CD_3) $_2\text{CO}$) 6.47 (d, $J = 12.6$ Hz, 1H), 5.01 (t, $J = 7.1$ Hz, 1H), 4.96 (t, $J = 7.1$ Hz, 1H), 4.65 (t, $J = 7.6$ Hz, 1H), 4.23 (d, $J = 7.6$ Hz, 2H), 3.94 (ddd, $J = 7.0, 5.6, 1.0$ Hz, 2H), 3.79 (t, $J = 6.6$ Hz, 2H), 3.33 (t, $J = 5.6$ Hz, 1H), 2.56 (td, $J = 6.5, 2.7$ Hz, 2H), 2.39 (t, $J = 2.7$ Hz, 1H), 2.20 (q, $J = 7.5$ Hz, 2H), 1.06 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR ((CD_3) $_2\text{CO}$) 162.06 (C), 148.11 (CH), 103.61 (CH), 92.12 (CH), 80.44 (C), 69.64 (CH), 64.79 (CH $_2$), 64.51 (CH $_2$), 59.00 (CH $_2$), 24.71 (CH $_2$), 18.32 (CH $_2$), 11.63 (CH $_3$); IR (Neat, cm^{-1}) 3389 (br, s), 3293 (s), 3051 (w), 2937 (m), 2117 (w), 1651 (s), 1167 (s), 1098 (s); HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{18}\text{O}_3 + \text{Na}^+$ 233.1154, found 233.1151.

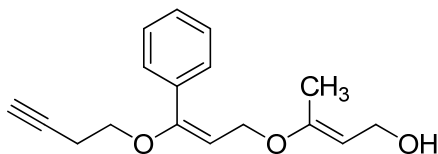


81d. Clear, light yellow oil (86% yield, >1.00:0.05 *E:Z*); $R_f = 0.13$ (hexanes-ethyl acetate, 4:1); ^1H NMR ((CD_3) $_2\text{CO}$) 4.67 (t, $J = 7.5$ Hz, 1H), 4.66 (t, $J = 7.5$ Hz, 1H), 4.18 (d, $J = 7.4$ Hz, 2H), 4.06 (dd, $J = 7.5, 5.3$ Hz, 2H), 3.80 (t, $J = 6.6$ Hz, 2H), 3.22 (t, $J = 5.3$ Hz, 1H), 2.57 (td, $J = 6.5, 2.7$ Hz, 2H), 2.40 (t, $J = 2.7$ Hz, 1H), 2.18 (q, $J = 7.6$ Hz, 2H), 2.17 (q, $J = 7.6$ Hz, 2H), 1.06 (t, $J = 7.6$ Hz, 3H), 1.02 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR ((CD_3) $_2\text{CO}$) 163.05 (C), 161.12 (C), 97.88 (CH), 93.38 (CH), 81.73 (C), 70.90 (CH), 65.75 (CH $_2$), 63.60 (CH $_2$), 58.63 (CH $_2$), 24.40 (CH $_2$), 24.36 (CH $_2$), 19.60 (CH $_2$), 13.16

(CH₃), 12.95 (CH₃); IR (Neat, cm⁻¹) 3432 (br, s), 3307 (s), 3064 (w), 2967 (m), 2117 (w), 1660 (s), 1099 (s); HRMS (ESI) calcd for C₁₄H₂₂O₃+Na⁺ 261.1467, found 261.1492.

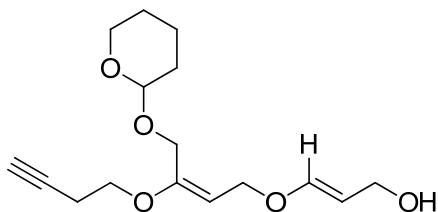


81e. Clear, light yellow oil (90% yield, >1.00:0.05 *E:Z*); R_f = 0.09 (hexanes-ethyl acetate, 4:1); ¹H NMR ((CD₃)₂CO) 7.57-7.54 (m, 2H), 7.41-7.38 (m, 3H), 6.53 (d, *J* = 12.6 Hz, 1H), 5.53 (t, *J* = 6.8 Hz, 1H), 5.06 (dt, *J* = 12.6, 7.1 Hz, 1H), 4.57 (d, *J* = 6.8 Hz, 2H), 3.97 (t, *J* = 6.5 Hz, 2H), 3.80 (t, *J* = 6.5 Hz, 2H), 3.36 (t, *J* = 5.2 Hz, 1H), 2.56 (td, *J* = 6.5, 2.6 Hz, 2H), 2.46 (t, *J* = 2.6 Hz, 1H); ¹³C NMR ((CD₃)₂CO) 156.73 (C), 149.37 (CH), 135.81 (C), 129.65 (CH), 129.45 (CH), 127.28 (CH), 110.85 (CH), 105.15 (CH), 81.86 (C), 71.37 (CH), 69.53 (CH₂), 64.52 (CH₂), 60.33 (CH₂), 20.20 (CH₂); IR (Neat, cm⁻¹) 3400 (br, s), 3294 (s), 3059 (m), 2955 (s), 2121 (w), 1652 (s), 1056 (s); HRMS (ESI) calcd for C₁₆H₁₈O₃+Na⁺ 281.1154, found 281.1151.

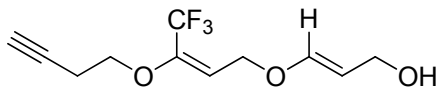


81f. Clear, light yellow oil (97% yield, >1.00:0.05 *E:Z*); R_f = 0.09 (hexanes-ethyl acetate, 4:1); ¹H NMR ((CD₃)₂CO) 7.58-7.54 (m, 2H), 7.41-7.38 (m, 3H), 5.57 (t, *J* = 6.6 Hz, 1H), 4.81 (t, *J* = 7.4 Hz, 1H), 4.55 (d, *J* = 6.6 Hz, 2H), 4.07 (dd, *J* = 7.4, 5.5 Hz, 2H), 3.80 (t, *J* = 6.5 Hz, 2H), 3.25 (t, *J* = 5.5 Hz, 1H), 2.55 (td, *J* = 6.5, 2.6 Hz, 2H), 2.46 (t, *J* = 2.6 Hz, 1H), 1.81 (s, 3H); ¹³C NMR ((CD₃)₂CO) 156.18 (C), 155.89 (C), 135.92 (C), 129.54 (CH), 129.44 (CH), 127.18 (CH), 111.24 (CH), 98.97 (CH), 81.85 (C), 71.32 (CH), 69.52 (CH₂), 62.38 (CH₂), 58.98 (CH₂), 20.21 (CH₂), 16.50 (CH₃); IR (Neat, cm⁻¹)

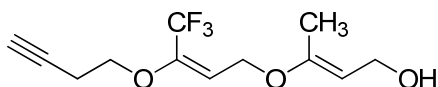
3428 (br, s), 3293 (s), 3053 (m), 2917 (s), 2117 (w), 1656 (s), 1056 (s); HRMS (ESI) calcd for $C_{17}H_{20}O_3+Na^+$ 295.1310, found 295.1313.



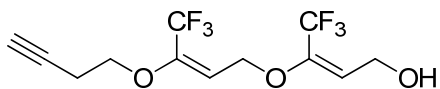
81g. Clear, light yellow oil (93% yield, 1.00:0.34 *E:Z*); $R_f = 0.03$ (hexanes-ethyl acetate, 4:1); 1H NMR ($(CD_3)_2CO$) 6.49 (d, $J = 12.6$ Hz, 1H, major), 6.46 (d, $J = 12.6$ Hz, 1H, minor), 4.99 (dt, $J = 12.3, 7.2$ Hz, 1H), 4.89 (t, $J = 7.4$ Hz, 1H, major), 4.86 (t, $J = 7.4$ Hz, 1H, minor), 4.66 (t, $J = 3.2$ Hz, 1H, major), 4.63 (t, $J = 3.5$ Hz, 1H, minor), 4.37 (d, $J = 7.4$ Hz, 2H, minor), 4.34 (d, $J = 7.4$ Hz, 2H, major), 4.19 (d, $J = 12.1$ Hz, 1H, major), 4.18 (d, $J = 12.1$ Hz, 1H, minor), 4.07 (d, $J = 12.1$ Hz, 1H, major), 4.04 (d, $J = 11.9$ Hz, 1H, minor), 3.95 (dd, $J = 7.1, 1.1$ Hz, 2H, minor), 3.93 (dd, $J = 7.1, 1.0$ Hz, 2H, major), 3.87-3.76 (m, 1H), 3.83 (t, $J = 6.6$ Hz, 2H, major), 3.81 (t, $J = 6.3$ Hz, 2H, minor), 3.47 (dtd, $J = 11.2, 4.4, 1.1$ Hz, 1H), 3.35 (t, $J = 5.6$ Hz, 1H), 2.58 (td, $J = 6.7, 2.7$ Hz, 2H, major), 2.53 (td, $J = 6.5, 2.7$ Hz, 2H, minor), 2.41 (t, $J = 2.7$ Hz, 1H, major), 2.36 (t, $J = 2.7$ Hz, 1H, minor), 1.85-1.45 (m, 6H); ^{13}C NMR ($(CD_3)_2CO$) 157.44 (C), 149.24 (CH), 105.10 (CH, major), 105.04 (CH, minor), 98.79 (CH), 98.14 (CH, minor), 98.08 (CH, major), 81.57 (C), 71.03 (CH), 66.16 (CH_2), 65.67 (CH_2 , minor), 65.61 (CH_2 , major), 64.06 (CH_2 , minor), 63.84 (CH_2 , major), 62.20 (CH_2), 60.32 (CH_2 , major), 60.18 (CH_2 , minor), 31.16 (CH_2), 26.22 (CH_2), 20.06 (CH_2 , minor), 19.92 (CH_2 , major), 19.56 (CH_2); IR (Neat, cm^{-1}) 3417 (br, s), 3286 (s), 3059 (w), 2941 (s), 2121 (w), 1653 (s), 1117 (s), 1025 (s); HRMS (ESI) calcd for $C_{16}H_{24}O_5+Na^+$ 319.1521, found 319.1512.



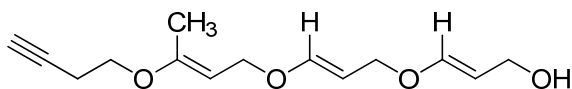
81h. Clear, light yellow oil (77% yield, >1.00:0.05 *E:Z*); $R_f = 0.06$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 6.49 (d, $J = 12.6$ Hz, 1H), 5.35 (t, $J = 6.9$ Hz, 1H), 5.03 (dt, $J = 12.6, 6.9$ Hz, 1H), 4.46 (dq, $J = 6.9, 2.1$ Hz, 2H), 3.98 (t, $J = 6.5$ Hz, 2H), 3.42 (t, $J = 5.5$ Hz, 1H), 2.65 (td, $J = 6.5, 2.7$ Hz, 2H), 2.44 (t, $J = 2.7$ Hz, 1H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 148.66 (CH), 145.69 (q, $J = 34.5$ Hz, C), 121.49 (q, $J = 274.5$ Hz, CF_3), 105.83 (CH), 104.83 (CH), 80.82 (C), 71.34 (CH), 67.99 (CH_2), 63.54 (CH_2), 60.08 (CH_2), 19.29 (CH_2); IR (Neat, cm^{-1}) 3411 (br, s), 3305 (s), 3047 (m), 2952 (m), 2117 (w), 1653 (s), 1135 (s); HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{13}\text{F}_3\text{O}_3 + \text{Na}^+$ 273.0714, found 273.0716.



81i. Clear, light yellow oil (97% yield, 1.00:0.11 *E:Z*); $R_f = 0.06$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 5.36 (t, $J = 6.7$ Hz, 1H, major), 5.30 (t, $J = 6.8$ Hz, 1H, minor), 4.71 (t, $J = 7.5$ Hz, 1H), 4.53 (dq, $J = 6.7, 2.1$ Hz, 2H, minor), 4.43 (dq, $J = 6.7, 2.1$ Hz, 2H, major), 4.06 (dd, $J = 7.2, 5.2$ Hz, 2H), 3.97 (t, $J = 6.5$ Hz, 2H), 3.36 (t, $J = 5.5$ Hz, 1H), 2.65 (td, $J = 6.6, 2.7$ Hz, 2H), 2.44 (t, $J = 2.7$ Hz, 1H), 1.84 (s, 3H, minor), 1.80 (s, 3H, major); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 155.55 (C), 145.35 (q, $J = 32.9$ Hz, C), 121.59 (q, $J = 275.2$ Hz, CF_3), 105.18 (CH), 99.43 (CH), 80.85 (C), 71.36 (CH), 67.95 (CH_2), 61.36 (CH_2), 58.80 (CH_2), 19.33 (CH_2), 16.38 (CH_3); IR (Neat, cm^{-1}) 3378 (br, s), 3306 (s), 3070 (w), 2916 (s), 2117 (w), 1666 (s), 1190 (s), 1137 (s); HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{15}\text{F}_3\text{O}_3 + \text{Na}^+$ 287.0871, found 287.0875.

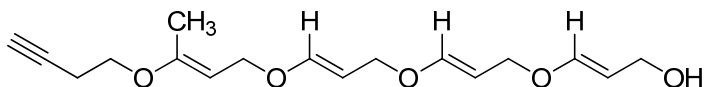


81j. Clear, yellow oil (84% yield, 1.00:0.11 *E:Z*); $R_f = 0.06$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 5.44 (t, $J = 7.0$ Hz, 1H), 5.36 (t, $J = 6.8$ Hz, 1H), 4.60 (dq, $J = 6.7$, 1.9 Hz, 2H, major), 4.45 (dq, $J = 6.1$, 1.9 Hz, 2H, minor), 4.31-4.26 (m, 2H), 4.02 (t, $J = 6.6$ Hz, 2H, major), 3.98 (s, 1H), 3.93 (t, $J = 6.6$ Hz, 2H, minor), 2.67 (td, $J = 6.5$, 2.7 Hz, 2H), 2.45 (t, $J = 2.7$ Hz, 1H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 146.87 (q, $J = 36.8$ Hz, C), 143.26 (q, $J = 35.2$ Hz, C), 121.73 (q, $J = 273.7$ Hz, CF_3), 121.35 (q, $J = 273.7$ Hz, CF_3), 110.75 (CH, major), 110.32 (CH, minor), 103.82 (CH, minor), 102.95 (CH, major), 80.75 (C), 71.36 (CH), 68.13 (CH_2), 63.51 (CH_2), 56.50 (CH_2), 19.28 (CH_2); IR (Neat, cm^{-1}) 3447 (br, m), 3299 (m), 3053 (s), 2977 (s), 2123 (w), 1669 (s), 1150 (s), 1076 (s).



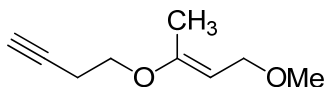
86a. Clear, yellow oil (84% yield, 1.00:0.28 *E:Z*); $R_f = 0.29$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 6.62 (d, $J = 12.6$ Hz, 1H), 6.46 (d, $J = 12.6$ Hz, 1H, minor), 6.45 (d, $J = 12.6$ Hz, 1H, major), 4.99 (td, $J = 7.7$, 3.1 Hz, 1H), 4.95 (dt, $J = 7.6$, 2.9 Hz, 1H), 4.72 (t, $J = 7.7$ Hz, 1H, major), 4.70 (t, $J = 7.7$ Hz, 1H, minor), 4.29 (d, $J = 7.5$ Hz, 2H, major), 4.29 (d, $J = 7.5$ Hz, 2H, minor), 4.12 (d, $J = 7.6$ Hz, 2H), 4.05 (dd, $J = 7.5$, 5.1 Hz, 2H, minor), 3.94 (ddd, $J = 7.2$, 4.7, 1.0 Hz, 2H, major), 3.80 (t, $J = 6.7$ Hz, 2H, major), 3.79 (t, $J = 6.7$ Hz, 2H, minor), 3.32 (t, $J = 5.4$ Hz, 1H, major), 3.28 (t, $J = 5.4$ Hz, 1H, minor), 2.56 (td, $J = 6.7$, 2.7 Hz, 2H, major), 2.54 (td, $J = 6.7$, 2.7 Hz, 2H, minor), 2.41 (t, $J = 2.7$ Hz, 1H, major), 2.40 (t, $J = 2.7$ Hz, 1H, minor), 1.84 (s, 3H, major), 1.79 (s, 3H, minor); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 158.71 (C), 151.91 (CH), 149.36 (CH, minor), 149.18 (CH, major), 104.96 (CH, major), 104.87 (CH, minor), 99.96 (CH, major), 99.09 (CH, minor), 94.23 (CH, minor), 93.97 (CH, major), 81.66 (C), 70.98 (CH), 68.00 (CH_2), 66.74 (CH_2 , major), 66.38 (CH_2 , minor), 65.86 (CH_2 , major), 65.82 (CH_2 , minor), 60.38 (CH_2 , minor), 60.34 (CH_2 , major), 19.60 (CH_2), 16.58 (CH_3); IR

(Neat, cm^{-1}) 3394 (br, s), 3290 (s), 3054 (m), 2926 (s), 2117 (w), 1651 (s), 1164 (s), 1077 (s); HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{20}\text{O}_4+\text{Na}^+$ 275.1259, found 275.1265.



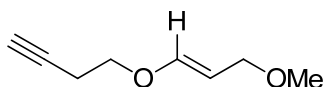
88a. Clear, light yellow oil (92% yield, 1.00:0.30 *E:Z*); $R_f = 0.19$ (hexanes-ethyl acetate, 4:1); ^1H NMR ($(\text{CD}_3)_2\text{CO}$) 6.65-6.56 (m, 3H), 6.47 (d, $J = 12.6$ Hz, 1H, minor), 6.44 (d, $J = 12.5$ Hz, 1H, major), 5.03-4.91 (m, 3H), 4.71 (t, $J = 7.6$ Hz, 1H, major), 4.69 (t, $J = 7.8$ Hz, 1H, minor), 4.28 (dd, $J = 7.6, 2.2$ Hz, 2H), 4.22 (d, $J = 7.5$ Hz, 2H, minor), 4.18 (d, $J = 7.5$ Hz, 2H, major), 4.12 (d, $J = 7.4$ Hz, 2H), 3.94 (ddd, $J = 6.3, 5.5, 0.8$ Hz, 2H), 3.80 (t, $J = 6.7$ Hz, 2H, major), 3.79 (t, $J = 6.7$ Hz, 2H, minor), 3.39 (t, $J = 5.5$ Hz, 1H, minor), 3.38 (t, $J = 5.5$ Hz, 1H, major), 2.56 (td, $J = 6.6, 2.7$ Hz, 2H), 2.39 (t, $J = 2.7$ Hz, 1H), 1.84 (s, 3H, major), 1.83 (s, 3H, minor); ^{13}C NMR ($(\text{CD}_3)_2\text{CO}$) 158.79 (C, major), 158.43 (C, minor), 152.24 (CH), 151.93 (CH, major), 151.76 (CH, minor), 149.43 (CH, minor), 149.25 (CH, major), 104.92 (CH, major), 104.82 (CH, minor), 100.05 (CH, major), 99.96 (CH, minor), 99.68 (CH), 94.22 (CH, minor), 93.96 (CH, major), 81.73 (C), 71.08 (CH), 68.39 (CH_2), 68.03 (CH_2 , major), 68.00 (CH_2 , minor), 66.82 (CH_2 , minor), 66.77 (CH_2 , major), 66.42 (CH_2 , minor), 65.87 (CH_2 , major), 60.37 (CH_2 , major), 60.24 (CH_2 , minor), 19.64 (CH_2), 16.68 (CH_3); IR (Neat, cm^{-1}) 3434 (br, s), 3305 (s), 3052 (m), 2976 (s), 2123 (w), 1647 (s), 1161 (s), 1077 (s); HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{24}\text{O}_5+\text{Na}^+$ 331.1521, found 331.1512.

5.5.3 Experimental Data for Synthetic Intermediates 82, 83, and 90a

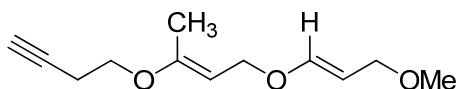


82a. Clear, light yellow oil (74% yield, $>1.00:0.05$ *E:Z*); $R_f = 0.79$ (hexanes-ethyl acetate, 1:1); ^1H NMR ($(\text{CD}_3)_2\text{CO}$) 4.62 (t, $J = 7.3$ Hz, 1H), 3.88 (d, $J = 7.6$ Hz, 1H),

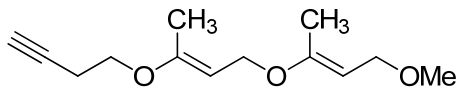
3.78 (t, $J = 6.7$ Hz, 2H), 3.21 (s, 3H), 2.55 (td, $J = 6.8, 2.7$ Hz, 2H), 2.40 (t, $J = 2.6$ Hz, 1H), 1.80 (s, 3H); ^{13}C NMR ($(\text{CD}_3)_2\text{CO}$) 157.14 (C), 95.36 (CH), 81.71 (C), 70.88 (CH), 68.90 (CH_2), 65.63 (CH_2), 56.93 (CH_3), 19.62 (CH_2), 16.47 (CH_3); IR (Neat, cm^{-1}) 3292 (s), 3072 (w), 2924 (s), 2122 (w), 1664 (s); HRMS (ESI) calcd for $\text{C}_9\text{H}_{14}\text{O}_2 + \text{H}^+$ 155.1072, found 155.1076.



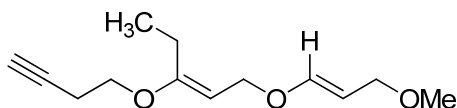
82b. Clear, colorless oil (81% yield, 1.00:0.39 *E:Z*); $R_f = 0.86$ (hexanes-ethyl acetate, 1:1); ^1H NMR ($(\text{CD}_3)_2\text{CO}$) 6.53 (d, $J = 12.9$ Hz, 1H), 4.91 (dt, $J = 12.9, 7.2$ Hz, 1H), 3.83 (t, $J = 6.7$ Hz, 2H), 3.78 (dd, $J = 7.6, 1.1$ Hz, 2H), 3.19 (s, 3H), 2.54 (td, $J = 6.7, 2.6$ Hz, 2H), 1.73 (t, $J = 2.6$ Hz, 1H); ^{13}C NMR ($(\text{CD}_3)_2\text{CO}$) 150.73 (CH), 101.45 (CH), 81.49 (C), 71.08 (CH), 70.16 (CH_2), 68.03 (CH_2), 56.79 (CH_3), 19.80 (CH_2); IR (Neat, cm^{-1}) 3290 (s), 3065 (w), 2923 (s), 2122 (w), 1651 (s); LRMS (ESI) calcd for $\text{C}_8\text{H}_{12}\text{O}_2 + \text{Na}^+$ 163.1, found 163.1.



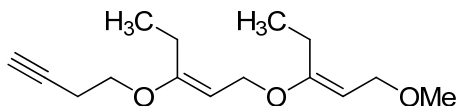
83a. Clear, yellow oil (92% yield, 1.00:0.12 *E:Z*); $R_f = 0.93$ (hexanes-ethyl acetate, 1:1); ^1H NMR ($(\text{CD}_3)_2\text{CO}$) 6.51 (d, $J = 12.8$ Hz, 1H), 4.91 (t, $J = 7.3$ Hz, 0.5H), 4.87 (t, $J = 7.3$ Hz, 0.5H), 4.71 (t, $J = 7.7$ Hz, 1H), 4.27 (d, $J = 7.5$ Hz, 2H), 3.82-3.76 (m, 4H), 3.18 (s, 3H), 2.56 (td, $J = 6.6, 2.8$ Hz, 2H), 2.40 (t, $J = 2.6$ Hz, 1H), 1.84 (s, 3H); ^{13}C NMR ($(\text{CD}_3)_2\text{CO}$) 158.52 (C), 150.96 (CH), 100.97 (CH), 94.10 (CH), 81.64 (C), 70.96 (CH), 70.45 (CH_2), 68.91 (CH_2), 65.84 (CH_2), 59.64 (CH_3), 19.59 (CH_2), 16.56 (CH_3); IR (Neat, cm^{-1}) 3291 (s), 3064 (w), 2926 (s), 2121 (w), 1651 (s); HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{18}\text{O}_3 + \text{Na}^+$ 233.1154, found 233.1162.



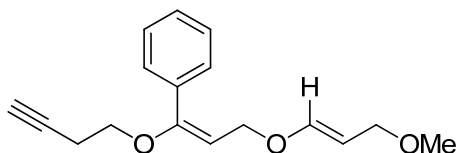
83b. Clear, yellow oil (85% yield, >1.00:0.05 *E:Z*); $R_f = 0.84$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 4.71 (t, $J = 7.2$ Hz, 1H), 4.63 (t, $J = 7.4$ Hz, 1H), 4.22 (d, $J = 7.4$ Hz, 2H), 3.88 (d, $J = 7.6$ Hz, 2H), 3.80 (t, $J = 6.8$ Hz, 2H), 3.21 (s, 3H), 2.56 (td, $J = 6.7, 2.7$ Hz, 2H), 2.40 (t, $J = 2.6$ Hz, 1H), 2.23 (s, 3H), 1.82 (s, 3H), 1.78 (s, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 157.94 (C), 157.67 (C), 94.90 (CH), 94.19 (CH), 81.68 (C), 70.93 (CH), 69.10 (CH_2), 65.80 (CH_2), 64.13 (CH_2), 56.87 (CH_3), 19.62 (CH_2), 16.71 (CH_3), 16.55 (CH_3); IR (Neat, cm^{-1}) 3292 (s), 3051 (w), 2926 (s), 2122 (w), 1654 (s); HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{20}\text{O}_3 + \text{H}^+$ 225.1491, found 225.1487.



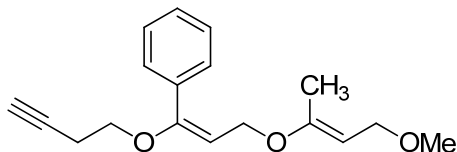
83c. Clear, light yellow oil (72% yield, 1.00:0.05 *E:Z*); $R_f = 0.45$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 6.52 (d, $J = 12.6$ Hz, 1H), 4.91 (dt, $J = 12.6, 7.4$ Hz, 1H), 4.66 (t, $J = 7.6$ Hz, 1H), 4.27 (d, $J = 7.6$ Hz, 2H), 3.79 (t, $J = 6.6$ Hz, 2H), 3.77 (dt, $J = 7.4, 1.0$ Hz, 2H), 3.18 (s, 3H), 2.57 (td, $J = 6.6, 2.7$ Hz, 2H), 2.39 (t, $J = 2.7$ Hz, 1H), 2.21 (q, $J = 7.5$ Hz, 2H), 1.06 (t, $J = 7.5$ Hz, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 163.45 (C), 150.97 (CH), 100.96 (CH), 93.26 (CH), 81.68 (C), 70.94 (CH), 70.46 (CH_2), 66.17 (CH_2), 65.79 (CH_2), 56.70 (CH_3), 24.35 (CH_2), 19.57 (CH_2), 12.89 (CH_3); IR (Neat, cm^{-1}) 3304 (m), 3051 (w), 2969 (m), 2117 (w), 1653 (s), 1169 (s), 1096 (s); HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{20}\text{O}_3 + \text{Na}^+$ 247.1310, found 247.1317.



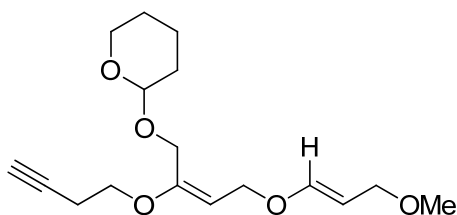
83d. Clear, light yellow oil (69% yield, >1.00:0.05 *E:Z*); $R_f = 0.53$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 4.68 (t, $J = 7.4$ Hz, 1H), 4.58 (t, $J = 7.5$ Hz, 1H), 4.21 (d, $J = 7.4$ Hz, 2H), 3.89 (d, $J = 7.5$ Hz, 2H), 3.80 (t, $J = 6.6$ Hz, 2H), 3.21 (s, 3H), 2.58 (td, $J = 6.5, 2.7$ Hz, 2H), 2.40 (t, $J = 2.7$ Hz, 1H), 2.19 (q, $J = 7.5$ Hz, 2H), 2.17 (q, $J = 7.5$ Hz, 2H), 1.06 (t, $J = 7.5$ Hz, 3H), 1.01 (t, $J = 7.5$ Hz, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 163.14 (C), 162.62 (C), 94.12 (CH), 93.29 (CH), 81.72 (C), 71.97 (CH), 68.79 (CH₂), 65.76 (CH₂), 63.73 (CH₂), 56.90 (CH₃), 24.43 (CH₂), 24.40 (CH₂), 19.58 (CH₂), 13.01 (CH₃), 12.92 (CH₃); IR (Neat, cm^{-1}) 3303 (m), 3053 (s), 2985 (m), 2117 (w), 1652 (m), 1155 (m); HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{24}\text{O}_3 + \text{Na}^+$ 275.1623, found 275.1617.



83e. Clear, light yellow oil (96% yield, 1.00:0.04 *E:Z*); $R_f = 0.44$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 7.44-7.42 (m, 2H), 7.41-7.37 (m, 3H), 6.58 (d, $J = 12.6$ Hz, 1H), 5.54 (t, $J = 6.8$ Hz, 1H), 4.98 (dt, $J = 12.6, 7.4$ Hz, 1H), 4.60 (d, $J = 6.8$ Hz, 2H), 3.81 (dd, $J = 7.4, 1.0$ Hz, 2H), 3.80 (t, $J = 6.5$ Hz, 2H), 3.19 (s, 3H), 2.56 (td, $J = 6.5, 2.7$ Hz, 2H), 2.45 (t, $J = 2.7$ Hz, 1H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 156.91 (C), 150.96 (CH), 135.78 (C), 129.69 (CH), 129.45 (CH), 127.30 (CH), 110.64 (CH), 101.25 (CH), 81.86 (C), 71.30 (CH), 70.36 (CH₂), 69.54 (CH₂), 64.62 (CH₂), 56.71 (CH₃), 20.20 (CH₂); IR (Neat, cm^{-1}) 3303 (m), 3053 (s), 2985 (m), 2117 (w), 1651 (s), 1079 (s); HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{20}\text{O}_3 + \text{Na}^+$ 295.1310, found 295.1316.

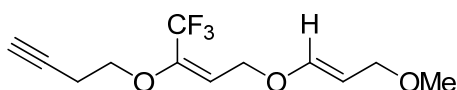


83f. Clear, light yellow oil (98% yield, 1.00:0.05 *E:Z*); $R_f = 0.47$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 7.54-7.42 (m, 2H), 7.41-7.34 (m, 3H), 5.57 (t, $J = 6.6$ Hz, 1H, major), 5.50 (t, $J = 6.7$ Hz, 1H, minor), 4.73 (t, $J = 7.5$ Hz, 1H), 4.58 (d, $J = 6.6$ Hz, 2H, major), 4.51 (d, $J = 6.7$ Hz, 2H, minor), 4.20 (d, $J = 6.7$ Hz, 2H, minor), 3.91 (d, $J = 7.5$ Hz, 2H, major), 3.81 (t, $J = 6.5$ Hz, 2H), 3.31 (s, 3H, minor), 3.22 (s, 3H, major), 2.56 (td, $J = 6.5, 2.7$ Hz, 2H), 2.44 (t, $J = 2.7$ Hz, 1H), 1.82 (s, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 157.47 (C), 156.32 (C), 135.90 (C), 129.57 (CH), 129.44 (CH), 127.19 (CH), 111.07 (CH), 95.21 (CH), 81.85 (C), 71.24 (CH), 69.54 (CH_2), 69.06 (CH_2), 62.47 (CH_2), 56.87 (CH_2), 20.20 (CH_2), 16.67 (CH_3); IR (Neat, cm^{-1}) 3299 (m), 3047 (m), 2923 (s), 2117 (w), 1653 (m), 1058 (s); HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{22}\text{O}_3 + \text{Na}^+$ 309.1467, found 309.1462.

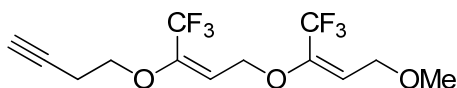


83g. Clear, light yellow oil (94% yield, 1.00:0.35 *E:Z*); $R_f = 0.16$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 6.54 (d, $J = 12.6$ Hz, 1H, major), 6.49 (d, $J = 12.6$ Hz, 1H, minor), 4.95-4.84 (m, 2H), 4.67 (t, $J = 3.3$ Hz, 1H, major), 4.63 (t, $J = 3.4$ Hz, 1H, minor), 4.39 (d, $J = 7.5$ Hz, 2H, minor), 4.38 (d, $J = 7.5$ Hz, 2H, major), 4.20 (d, $J = 12.2$ Hz, 1H, major), 4.19 (d, $J = 12.1$ Hz, 1H, minor), 4.08 (d, $J = 12.2$ Hz, 1H, major), 4.04 (d, $J = 12.0$ Hz, 1H, minor), 3.85-3.79 (m, 1H), 3.83 (t, $J = 6.6$ Hz, 2H), 3.77 (dd, $J = 7.4, 0.9$ Hz, 2H), 3.47 (dtd, $J = 11.3, 4.3, 0.9$ Hz, 1H), 3.23 (s, 3H, minor), 3.18 (s, 3H, major), 2.58 (td, $J = 6.6, 2.7$ Hz, 2H, major), 2.53 (td, $J = 6.6, 2.7$ Hz, 2H, minor), 2.41 (t, $J = 2.7$ Hz, 1H, major), 2.35 (t, $J = 2.7$ Hz, 1H, minor), 1.87-1.46 (m, 6H); $^{13}\text{C NMR}$

((CD₃)₂CO) 159.21 (C, minor), 158.13 (C, major), 151.42 (CH), 101.73 (CH, major), 101.67 (CH, minor), 99.18 (CH), 98.70 (CH, minor), 98.63 (CH, major), 82.11 (C), 71.58 (CH), 71.27 (CH₂), 66.73 (CH₂), 66.37 (CH₂, minor), 66.31 (CH₂, major), 64.64 (CH₂, minor), 64.43 (CH₂, major), 62.73 (CH₂), 57.26 (CH₃, major), 55.51 (CH₃, minor), 31.70 (CH₂), 26.78 (CH₂), 20.46 (CH₂), 20.11 (CH₂); IR (Neat, cm⁻¹) 3284 (m), 3061 (w), 2940 (s), 2121 (w), 1650 (s), 1119 (s), 1079 (s), 1029 (s); HRMS (ESI) calcd for C₁₇H₂₆O₅+Na⁺ 333.1678, found 333.1686.

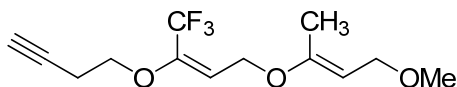


83h. Clear, light yellow oil (43% yield); *R_f* = 0.39 (hexanes-ethyl acetate, 4:1); ¹H NMR ((CD₃)₂CO) 6.54 (d, *J* = 12.6 Hz, 1H), 5.37 (t, *J* = 6.9 Hz, 1H), 4.94 (dt, *J* = 12.6, 7.3 Hz, 1H), 4.49 (dq, *J* = 6.9, 2.1 Hz, 2H), 3.99 (t, *J* = 6.5 Hz, 2H), 3.79 (dd, *J* = 7.3, 1.0 Hz, 1H), 3.19 (s, 3H), 2.66 (td, *J* = 6.5, 2.7 Hz, 2H), 2.45 (t, *J* = 2.7 Hz, 1H); ¹³C NMR ((CD₃)₂CO) 150.27 (CH), 145.79 (q, *J* = 35.2 Hz, C), 121.38 (q, *J* = 276.4 Hz, CF₃), 104.62 (CH), 101.97 (CH), 80.81 (C), 71.35 (CH), 70.11 (CH₂), 68.01 (CH₂), 63.62 (CH₂), 56.80 (CH₃), 19.29 (CH₂); IR (Neat, cm⁻¹) 3303 (m), 3053 (s), 2986 (s), 2125 (w), 1651 (s), 1144 (s); LRMS (ESI) calcd for C₁₂H₁₅F₃O₃+Na⁺ 287.1, found 287.2.

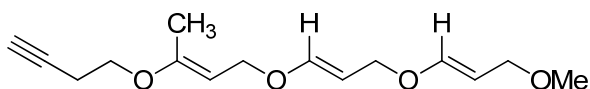


83i. Clear, light yellow oil (46% yield); *R_f* = 0.43 (hexanes-ethyl acetate, 4:1); ¹H NMR ((CD₃)₂CO) 5.45 (t, *J* = 7.1 Hz, 1H), 5.32 (t, *J* = 6.7 Hz, 1H), 4.63 (dq, *J* = 7.1, 1.9 Hz, 2H, major), 4.11 (dq, *J* = 6.7, 2.3 Hz, 2H), 4.02 (t, *J* = 6.5 Hz, 2H), 3.29 (s, 1H), 2.67 (td, *J* = 6.5, 2.7 Hz, 2H), 2.46 (t, *J* = 2.7 Hz, 1H); ¹³C NMR ((CD₃)₂CO) 146.01 (q, *J* = 34.9 Hz, C), 145.58 (q, *J* = 34.9 Hz, C), 121.50 (q, *J* = 274.5 Hz, CF₃), 121.33 (q, *J* = 274.5 Hz, CF₃), 106.96 (CH), 102.76 (CH), 80.75 (C), 71.37 (CH), 68.14 (CH₂), 66.47 (CH₂),

63.56 (CH₂), 57.89 (CH₃), 19.27 (CH₂); IR (Neat, cm⁻¹) 3303 (m), 3053 (s), 2986 (s), 2117 (w), 1671 (s), 1155 (s).



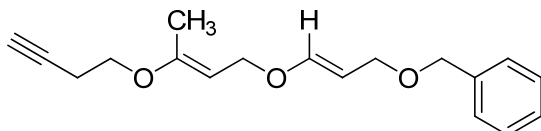
83j. Clear, light yellow oil (86% yield, 1.00:0.14 *E:Z*); *R_f* = 0.39 (hexanes-ethyl acetate, 4:1); ¹H NMR ((CD₃)₂CO) 5.40 (t, *J* = 6.6 Hz, 1H, major), 5.29 (t, *J* = 6.8 Hz, 1H, minor), 4.64 (t, *J* = 7.4 Hz, 1H), 4.55 (dq, *J* = 6.7, 2.1 Hz, 2H, minor), 4.46 (dq, *J* = 6.7, 2.2 Hz, 2H, major), 3.99 (t, *J* = 6.5 Hz, 2H, major), 3.95 (t, *J* = 6.6 Hz, 2H, minor), 3.89 (d, *J* = 7.4 Hz, 2H), 3.30 (s, 3H, minor), 3.21 (s, 3H, minor), 2.66 (td, *J* = 6.5, 2.7 Hz, 2H), 2.45 (t, *J* = 2.7 Hz, 1H), 1.87 (s, 3H, minor), 1.82 (s, 3H, major); ¹³C NMR ((CD₃)₂CO) 157.70 (C), 145.98 (q, *J* = 34.7 Hz, C), 122.19 (q, *J* = 276.6 Hz, CF₃), 105.63 (CH), 96.32 (CH), 81.41 (C), 71.92 (CH), 69.44 (CH₂), 68.57 (CH₂), 61.99 (CH₂), 57.52 (CH₃), 19.90 (CH₂), 17.13 (CH₃); IR (Neat, cm⁻¹) 3378 (br, s), 3306 (s), 3070 (w), 2916 (s), 2117 (w), 1666 (s), 1190 (s), 1137 (s); HRMS (ESI) calcd for C₁₃H₁₇F₃O₃+Na⁺ 301.1027, found 301.1031.



90a. Clear, light yellow oil (72% yield, 1.00:0.05 *E:Z*); *R_f* = 0.24 (hexanes-ethyl acetate, 4:1); ¹H NMR ((CD₃)₂CO) 6.63 (d, *J* = 12.7 Hz, 1H), 6.49 (d, *J* = 12.4 Hz, 1H), 4.98 (dt, *J* = 12.7, 7.6 Hz, 1H), 4.88 (dt, *J* = 12.76, 7.3 Hz, 1H), 4.72 (t, *J* = 7.6 Hz, 1H), 4.35 (d, *J* = 7.5 Hz, 2H, minor), 4.30 (d, *J* = 7.5 Hz, 2H, major), 4.16 (d, *J* = 7.5 Hz, 2H), 3.80 (t, *J* = 6.7 Hz, 2H), 3.76 (dd, *J* = 7.5, 0.9 Hz, 2H), 3.18 (s, 3H), 2.56 (td, *J* = 6.7, 2.6 Hz, 2H, major), 2.50 (td, *J* = 6.7, 2.6 Hz, 2H, minor), 2.41 (t, *J* = 2.6 Hz, 1H), 1.84 (s, 3H); ¹³C NMR ((CD₃)₂CO) 158.71 (C), 152.06 (CH), 150.78 (CH), 101.07 (CH), 99.84 (CH), 93.96 (CH), 81.63 (C), 70.95 (CH), 70.39 (CH₂), 68.14 (CH₂), 66.75 (CH₂), 65.86 (CH₂),

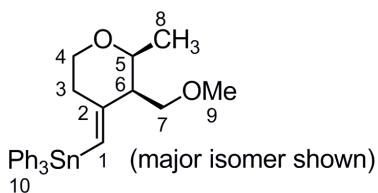
56.66 (CH₃), 19.58 (CH₂), 16.56 (CH₃); IR (Neat, cm⁻¹) 3304 (s), 3053 (s), 2985 (s), 2124 (w), 1652 (s), 1165 (s), 1079 (s); HRMS (ESI) calcd for C₁₅H₂₂O₄+Na⁺ 289.1416, found 289.1422.

5.5.4 Experimental Data for Synthetic Intermediate 89



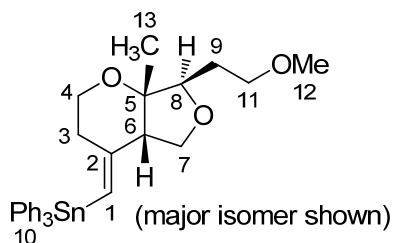
89. Clear, light yellow oil (66% yield, >1.00:0.05 *E:Z*); *R_f* = 0.55 (hexanes-ethyl acetate, 4:1); ¹H NMR ((CD₃)₂CO) 7.33 (d, *J* = 4.3 Hz, 2H), 7.31-7.23 (m, 3H), 6.54 (d, *J* = 12.6 Hz, 1H), 4.96 (dt, *J* = 12.5, 7.4 Hz, 1H), 4.72 (t, *J* = 7.6 Hz, 1H), 4.45 (s, 2H), 4.28 (d, *J* = 7.5 Hz, 2H), 3.93 (dd, *J* = 7.5, 0.9 Hz, 2H), 3.80 (t, *J* = 6.7 Hz, 2H), 2.56 (td, *J* = 6.6, 2.7 Hz, 2H), 2.41 (t, *J* = 2.7 Hz, 1H), 1.84 (s, 3H); ¹³C NMR ((CD₃)₂CO) 158.55 (C), 151.09 (CH), 140.17 (C), 129.01 (CH₂), 128.34 (CH₂), 128.01 (CH₂), 101.07 (CH), 94.11 (CH), 81.65 (C), 71.38 (CH₂), 70.97 (CH), 68.43 (CH₂), 66.55 (CH₂), 65.85 (CH₂), 19.60 (CH₂), 16.58 (CH₃); IR (Neat, cm⁻¹) 3296 (s), 3063 (s), 2926 (s), 2121 (w), 1651 (s), 758 (s), 694 (s); HRMS (ESI) calcd for C₁₈H₂₂O₃+Na⁺ 309.1467, found 309.1472.

5.5.5 Experimental Data for Cyclization Products 91, 94, 95, and 115a



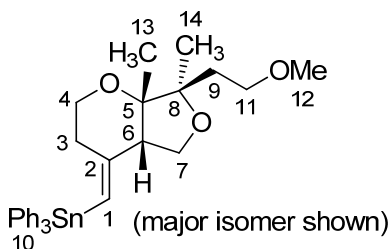
91a. Clear, light yellow oil (92% yield, 1.00:0.27 dr); *R_f* = 0.35 (hexanes-ethyl acetate, 4:1); ¹H NMR (CDCl₃) 7.68-7.50 (m, 6H, H₁₀), 7.38-7.36 (m, 9H, H₁₀), 5.96 (s, 1H, minor, H₁), 5.90 (s, 1H, major, H₁), 3.88 (ddd, *J* = 10.9, 5.6, 2.3 Hz, 1H, H₄), 3.75 (qd, *J*

= 6.6, 2.5 Hz, 1H, H5), 3.71 (dd, $J = 9.5, 6.6$ Hz, 1H, H7), 3.60 (dd, $J = 9.5, 7.5$ Hz, 1H, H7), 3.39 (s, 3H, H9), 3.33 (td, $J = 11.1, 3.0$ Hz, 1H, H4), 2.73 (td, $J = 6.9, 2.5$ Hz, 1H, H6), 2.40 (ddd, $J = 13.8, 12.8, 5.8$ Hz, 1H, H3), 2.10 (dt, $J = 13.8, 2.7$ Hz, 1H, H3), 1.33 (d, $J = 6.3$ Hz, 3H, minor, H8), 1.24 (d, $J = 6.6$ Hz, 3H, major, H8); ^{13}C NMR (CDCl_3) 158.80 (C, major, C2), 156.74 (C, minor, C2), 139.17 (C, C10), 136.88 (CH, C10), 128.94 (CH, C10), 128.57 (CH, C10), 118.26 (CH, major, C1), 117.74 (CH, minor, C1), 76.22 (CH, major, C5), 74.67 (CH, minor, C5), 71.87 (CH_2 , minor, C7), 70.39 (CH_2 , major, C7), 68.28 (CH_2 , C4), 58.81 (CH_3 , C9), 53.33 (CH, C6), 38.27 (CH_2 , minor, C3), 35.20 (CH_2 , major, C3), 19.17 (CH_3 , minor, C8), 18.18 (CH_3 , major, C8); IR (Neat, cm^{-1}) 3051 (m), 2981 (m), 1264 (s), 700 (s); HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{39}\text{O}_2\text{Sn}+\text{H}^+$ 503.1341, found 503.1346.

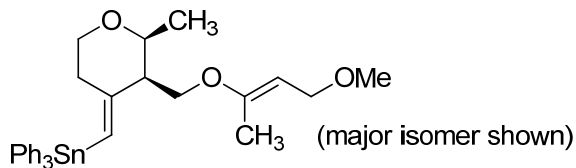


94a. Clear, yellow oil (77% yield, 1.00:0.28:0.17:0.06 dr); $R_f = 0.06$ (hexanes-ethyl acetate, 2 x 9:1); ^1H NMR (CDCl_3) 7.61-7.49 (m, 6H, H10), 7.38-7.35 (m, 9H, H10), 5.99 (s, 1H, H1), 3.95-3.85 (m, 2H, H7), 3.97 (dd, $J = 11.3, 2.6$ Hz, 1H, H8), 3.83-3.71 (m, 2H, H4), 3.58-3.46 (m, 2H, H11), 3.35 (s, 3H, H12), 2.98 (t, $J = 9.6$ Hz, 1H, H6, minor), 2.83 (t, $J = 9.5$ Hz, H6, major), 2.56 (tdd, $J = 13.2, 6.3, 1.5$ Hz, 1H, H3), 2.23 (dt, $J = 14.1, 1.1$ Hz, 1H, H3, minor), 2.05 (dt, $J = 14.1, 1.1$ Hz, 1H, H3, major), 1.78 (ttd, $J = 10.6, 5.6, 2.8$ Hz, 1H, H9), 1.54 (ttd, $J = 8.9, 7.3, 4.4$ Hz, 1H, H9), 1.24 (s, 3H, H13); ^{13}C NMR (CDCl_3) 153.84 (C, C2, minor), 153.11 (C, C2, major), 138.89 (C, C10), 136.98 (CH, C10), 129.27 (CH, C10), 128.85 (CH, C10), 123.39 (CH, C1, major), 123.17 (CH, C1, minor), 85.78 (CH, C8), 84.47 (C, C5), 70.14 (CH_2 , C11), 69.78 (CH_2 , C7), 62.62 (CH_2 , C4), 58.99 (CH_3 , C12), 57.93 (CH, C6, minor), 56.67 (CH, C6, major), 35.62 (CH_2 , C3, minor), 33.88 (CH_2 , C3, major), 32.74 (CH_2 , C9, major), 32.74 (CH_2 , C9,

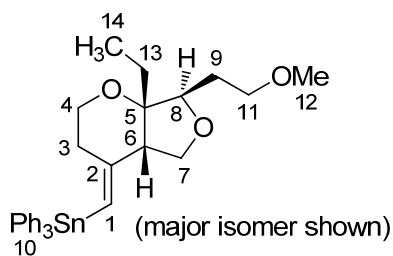
minor), 16.68 (CH₃, C13, minor), 16.23 (CH₃, C13, major); IR (Neat, cm⁻¹) 3063 (m), 2928 (s), 1662 (m), 1265 (s), 1074 (s), 736 (s), 700 (s); HRMS (ESI) calcd for C₃₀H₃₄O₃Sn+Na⁺ 581.1423, found 581.1435.



94b. Clear, light yellow oil (33% yield, 1.00:0.20 dr); R_f = 0.12 (hexanes-ethyl acetate, 2 x 9:1); ¹H NMR (CDCl₃) 7.59-7.48 (m, 6H, H10), 7.38-7.34 (m, 9H, H10), 5.92 (s, 1H, H1), 3.94 (t, *J* = 9.2 Hz, 1H, H7), 3.87 (t, *J* = 8.8 Hz, 1H, H7), 3.77 (dd, *J* = 11.6, 5.0 Hz, 1H, H4), 3.58-3.53 (m, 2H, H11), 3.48 (td, *J* = 12.2, 2.5 Hz, 1H, H4), 3.35 (s, 3H, H12), 3.15 (t, *J* = 9.5 Hz, 1H, H6), 2.54 (td, *J* = 12.8, 6.3 Hz, 1H, H3), 2.03 (d, *J* = 14.1 Hz, 1H, H3), 1.76-1.70 (m, 1H, H9), 1.66-1.62 (m, 1H, H9), 1.21 (s, 3H, H14), 1.16 (s, 3H, H13); ¹³C NMR (CDCl₃) 154.44 (C, C2), 138.95 (C, C10), 137.13 (CH, C10), 129.24 (CH, C10), 128.92 (CH, C10), 122.70 (CH, C1), 87.66 (C, C5), 84.32 (C, C8), 69.34 (CH₂, C11), 68.35 (CH₂, C7), 62.37 (CH₂, C4), 58.93 (CH₃, C12), 56.18 (CH, C6), 36.40 (CH₂, C9), 33.39 (CH₂, C3), 17.77 (CH₃, C14), 14.75 (CH₃, C13); IR (Neat, cm⁻¹) 3063 (m), 2931 (s), 1605 (m), 1115 (s), 1041 (s), 728 (s), 699 (s); HRMS (ESI) calcd for C₃₁H₃₆O₃Sn+H⁺ 573.1760, found 573.1754.

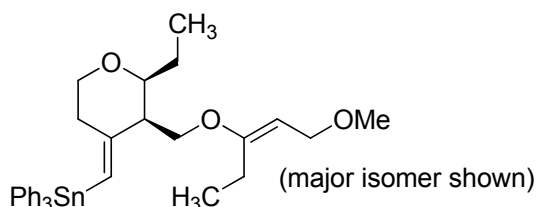


95b. Clear, light yellow oil (54% yield, 1.00:0.25 dr); $R_f = 0.56$ (hexanes-ethyl acetate, 2 x 4:1); $^1\text{H NMR}$ (CDCl_3) 7.61-7.49 (m, 6H), 7.37-7.33 (m, 9H), 5.88 (s, 1H), 4.66 (t, $J = 7.5$ Hz, 1H), 3.99 (dd, $J = 9.6, 6.5$ Hz, 1H), 3.92 (dd, $J = 7.5, 1.1$ Hz, 2H), 3.85 (dd, $J = 9.8, 7.7$ Hz, 2H), 3.73 (qd, $J = 6.7, 2.7$ Hz, 1H), 3.31 (s, 3H), 3.31-3.27 (m, 1H), 2.78 (td, $J = 7.3, 2.4$ Hz, 1H), 2.35 (tdd, $J = 12.9, 5.6, 1.0$ Hz, 1H), 2.04 (dt, $J = 13.7, 2.6$ Hz), 1.84 (s, 3H), 1.21 (d, $J = 6.6$ Hz, 3H); $^{13}\text{C NMR}$ (CDCl_3) 158.39 (C), 158.04 (C), 139.27 (C), 137.02 (CH), 129.15 (CH), 128.77 (CH), 119.03 (CH), 93.93 (CH), 76.27 (CH), 69.08 (CH_2), 68.60 (CH_2), 64.23 (CH_2), 57.57 (CH_3), 52.78 (CH), 35.03 (CH_2), 18.44 (CH_3), 16.75 (CH_3); IR (Neat, cm^{-1}) 3063 (s), 2932 (s), 1662 (m), 1074 (s), 1042 (s), 728 (s), 699 (s); HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{36}\text{O}_3\text{Sn}+\text{Na}^+$ 595.1580, found 595.1573.

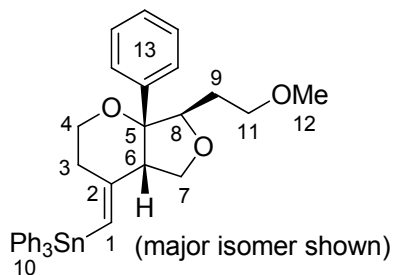


94c. Clear, light yellow oil (76% yield, 1.00:0.12 dr); $R_f = 0.34$ (hexanes-ethyl acetate, 2 x 4:1); $^1\text{H NMR}$ (CDCl_3) 7.61-7.50 (m, 6H, H10), 7.39-7.37 (m, 9H, H10), 5.96 (s, 1H, H1), 4.03-4.01 (m, 1H, H8), 4.02 (d, $J = 9.4$ Hz, 2H, H7), 3.74 (dd, $J = 11.0, 5.7$ Hz, 1H, H4), 3.57 (td, $J = 8.7, 4.3$ Hz, 1H, H11), 3.52 (t, $J = 9.0$ Hz, 1H, H11), 3.39 (td, $J = 11.9, 2.7$ Hz, 1H, H4), 3.36 (s, 3H, H12), 2.87 (t, $J = 9.4$ Hz, 1H, H6), 2.60 (tdd, $J = 13.2, 6.2, 1.1$ Hz, 1H, H3), 2.11-2.04 (m, 2H, H3/H13), 1.76 (dtd, $J = 13.1, 5.6, 2.0$ Hz, 1H, H9), 1.55-1.51 (m, 1H, H9), 1.32 (dq, $J = 14.9, 7.2$ Hz, 1H, H13), 0.89 (t, $J = 14.9$ Hz, 3H, H14); $^{13}\text{C NMR}$ (CDCl_3) 153.52 (C, C2), 138.91 (C, C10), 137.11 (CH, C10), 129.28 (CH, C10), 128.83 (CH, C10), 123.26 (CH, C1), 86.74 (C, C5), 83.87 (CH, C8), 70.11

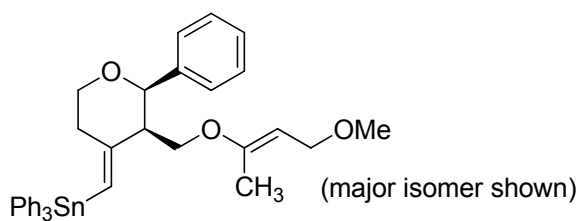
(CH₂, C11), 69.71 (CH₂, C7), 62.03 (CH₂, C4), 58.99 (CH₃, C12), 55.92 (CH, C6), 33.39 (CH₂, C3), 31.85 (CH₂, C9), 21.10 (CH₂, C13), 7.64 (CH₃, C14); IR (Neat, cm⁻¹) 3063 (m), 2928 (s), 1605 (m), 1117 (m), 1075 (s), 729 (s), 699 (s); HRMS (ESI) calcd for C₃₁H₃₆O₃Sn+Na⁺ 595.1590, found 595.1567.



95d. Clear, light yellow oil (67% yield, 1.00:0.56 dr); R_f = 0.66 (hexanes-ethyl acetate, 2 x 4:1); ¹H NMR (CDCl₃) 7.61-7.47 (m, 6H), 7.36-7.33 (m, 9H), 5.91 (s, 1H), 4.59 (t, *J* = 7.6 Hz, 1H), 3.92 (d, *J* = 7.6 Hz, 2H), 3.90-3.86 (m, 2H), 3.80 (dd, *J* = 9.6, 8.1 Hz, 1H), 3.53 (t, *J* = 7.6 Hz, 1H), 3.43-3.37 (m, 1H), 3.31 (s, 3H), 2.86 (td, *J* = 7.2, 2.0 Hz, 1H), 2.39 (td, *J* = 12.9, 6.1 Hz, 1H), 2.20 (q, *J* = 7.6 Hz, 2H), 2.04 (d, *J* = 14.2 Hz, 1H), 1.67-1.42 (m, 2H), 1.01 (t, *J* = 7.6 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (CDCl₃) 162.83 (C), 158.62 (C), 139.28 (C), 137.03 (CH), 129.15 (CH), 128.77 (CH), 118.97 (CH), 92.94 (CH), 82.55 (CH), 69.02 (CH₂), 68.73 (CH₂), 64.10 (CH₂), 57.54 (CH₃), 51.61 (CH), 35.25 (CH₂), 25.78 (CH₂), 23.99 (CH₂), 12.83 (CH₃), 10.79 (CH₃); IR (Neat, cm⁻¹) 3050 (s), 2929 (s), 1652 (m), 1074 (s), 737 (s), 700 (s); HRMS (ESI) calcd for C₃₃H₄₀O₃Sn+Na⁺ 623.1893, found 623.1907.

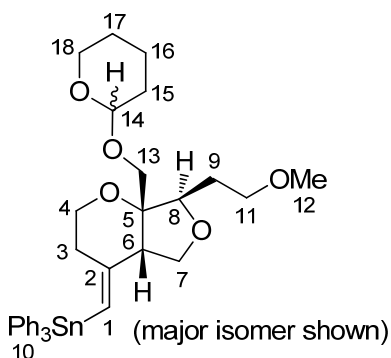


94e. Clear, light yellow oil (80% yield, 1.00:0.12 dr); $R_f = 0.40$ (hexanes-ethyl acetate, 2 x 4:1); $^1\text{H NMR}$ (CDCl₃) 7.47-7.36 (m, 10H, H10/H13), 7.35-7.25 (m, 10H, H10/H13), 6.15 (s, 1H, H1), 4.25 (dd, $J = 6.8, 3.0$ Hz, 1H, H8), 4.23 (dd, $J = 5.6, 2.9$ Hz, 1H, H7), 4.20 (t, $J = 8.3$ Hz, 1H, H7), 3.83 (t, $J = 9.3$ Hz, 1H, H6), 3.64 (dd, $J = 11.4, 6.0$ Hz, 1H, H4), 3.34 (td, $J = 7.1, 3.3$ Hz, 2H, H11), 3.23 (s, 3H, H12), 3.14 (td, $J = 11.7, 2.4$ Hz, 1H, H4), 2.64 (td, $J = 13.3, 6.5$ Hz, 1H, H3), 1.94 (d, $J = 14.1$ Hz, 1H, H3), 1.25-1.21 (m, 1H, H9), 1.09 (dtd, $J = 10.5, 7.7, 5.0$ Hz, 1H, H9); $^{13}\text{C NMR}$ (CDCl₃) 152.85 (C, C2), 138.82 (C, C10), 138.02 (C, C13), 137.24 (CH, C13), 136.97 (CH, C10), 129.20 (CH, C10), 129.01 (CH, C13), 128.78 (CH, C10), 127.98 (CH, C13), 123.85 (CH, C1), 88.73 (C, C5), 86.14 (CH, C8), 70.17 (CH₂, C11), 69.79 (CH₂, C7), 63.19 (CH₂, C4), 58.85 (CH₃, C12), 52.34 (CH, C6), 33.65 (CH₂, C9), 33.59 (CH₂, C3); IR (Neat, cm⁻¹) 3053 (m), 2923 (s), 1605 (m), 1113 (m), 1074 (s), 728 (s), 698 (s); HRMS (ESI) calcd for C₃₅H₃₆O₃Sn+Na⁺ 643.1580, found 643.1575.



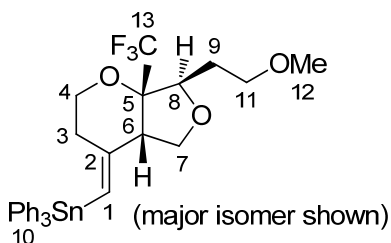
94f. Clear, light yellow oil (72% yield, 1.00:0.08 dr); $R_f = 0.74$ (hexanes-ethyl acetate, 2 x 4:1); $^1\text{H NMR}$ (CDCl₃) 7.69-7.49 (m, 6H), 7.39-7.29 (m, 14H), 6.04 (s, 1H), 4.69 (d, $J = 2.7$ Hz, 1H), 4.40 (t, $J = 7.6$ Hz, 1H), 4.09 (dd, $J = 10.9, 5.3$ Hz, 1H), 3.88-3.76 (m, 3H), 3.47-3.42 (m, 2H), 3.26 (s, 3H), 3.14-3.08 (m, 1H), 2.54 (tdd, $J = 13.2, 5.9$ Hz, 1H),

2.10 (dt, $J = 14.0, 1.2$ Hz), 1.70 (s, 3H); ^{13}C NMR (CDCl_3) 158.00 (C), 157.80 (C), 140.07 (C), 139.26 (C), 137.05 (CH), 129.19 (CH), 128.79 (CH), 128.53 (CH), 127.34 (CH), 125.23 (CH), 120.25 (CH), 93.57 (CH), 81.50 (CH), 69.41 (CH_2), 69.06 (CH_2), 63.54 (CH_2), 57.55 (CH_3), 53.86 (CH), 34.18 (CH_2), 16.56 (CH_3); IR (Neat, cm^{-1}) 3053 (s), 2986 (s), 1664 (m), 1075 (m), 737 (s), 704 (s); HRMS (ESI) calcd for $\text{C}_{36}\text{H}_{38}\text{O}_3\text{Sn}+\text{Na}^+$ 657.1736, found 657.1718.

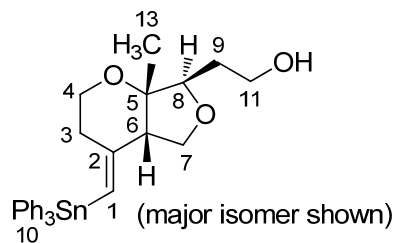


94g. Clear, light yellow oil (67% yield, 1.00:0.55:0.15:0.08 dr); $R_f = 0.24$ (hexanes-ethyl acetate, 2 x 4:1); ^1H NMR (CDCl_3) 7.55-7.45 (m, 6H, H10), 7.37-7.34 (m, 9H, H10), 5.96 (s, 1H, H1, major), 5.94 (s, 1H, H1, minor), 4.62 (t, $J = 3.3$ Hz, 1H, H14, minor), 4.62 (t, $J = 3.3$ Hz, 1H, H14, major), 4.07 (dd, $J = 12.1, 2.1$ Hz, 1H, H7), 4.05-4.01 (m, 1H, H7), 3.95 (dd, $J = 11.5, 2.7$ Hz, 1H, H8), 3.86-3.76 (m, 2H, H4), 3.71 (d, $J = 13.1$ Hz, 1H, H13), 3.67 (d, $J = 11.4$ Hz, 1H, H13), 3.60-3.44 (m, 42H, H11/H18), 3.33 (s, 3H, H12, minor), 3.31 (s, 3H, H12, major), 3.00 (t, $J = 9.2$ Hz, 1H, H6, major), 2.94 (t, $J = 9.2$ Hz, H6, minor), 2.56 (tdd, $J = 13.3, 6.3, 1.2$ Hz, 1H, H3), 2.38 (d, $J = 11.7$ Hz, 1H, H3, major), 2.37 (d, $J = 11.8$ Hz, 1H, H3, minor), 2.04-2.00 (m, 1H, H9, major), 1.99-1.94 (m, 1H, H9, minor), 1.92-1.88 (m, 1H, H9, minor), 1.85-1.76 (m, 1H, H9, major), 1.57-1.36 (m, 6H, H15/H16/H17); ^{13}C NMR (CDCl_3) 152.93 (C, C2), 138.61 (C, C10, minor), 138.61 (C, C10, major), 136.85 (CH, C10, major), 136.76 (CH, C10, minor), 129.27 (CH, C10, major), 129.06 (CH, C10, minor), 128.67 (CH, C10, minor), 128.64 (CH, C10, major), 122.98 (CH, C1), 99.22 (C, C14, minor), 99.01 (C, C14, major), 85.44 (C, C5, minor), 85.26 (C, C5, major), 85.02 (CH, C8, minor), 84.89 (CH, C8, major),

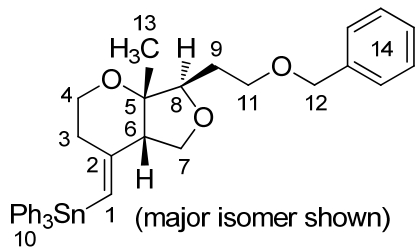
70.15 (CH₂, C11, major), 70.11 (CH₂, C11, minor), 69.80 (CH₂, C7, major), 69.77 (CH₂, C7, minor), 66.78 (CH₂, C13, minor), 65.79 (CH₂, C13, major), 62.10 (CH₂, C4, minor), 61.79 (CH₂, C4, major), 60.61 (CH₂, C18, major), 60.45 (CH₂, C18, minor), 58.66 (CH₃, C12, major), 58.53 (CH₃, C12, minor), 52.28 (CH, C6, minor), 52.16 (CH, C6, major), 31.27 (CH₂, C3, minor), 31.21 (CH₂, C3, major), 30.42 (CH₂, C15, major), 30.34 (CH₂, C15, minor), 29.94 (CH₂, C17, major), 29.70 (CH₂, C17, minor), 25.46 (CH₂, C9, major), 25.37 (CH₂, C9, minor), 19.21 (CH₃, C16, minor), 19.12 (CH₃, C16, major); IR (Neat, cm⁻¹) 3063 (m), 2928 (s), 1662 (m), 1265 (s), 1074 (s), 736 (s), 700 (s); HRMS (ESI) calcd for C₃₅H₄₂O₅Sn+Na⁺ 681.1847, found 681.1941.



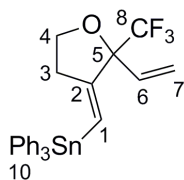
94h. Clear, light yellow oil (64% yield, 1.00:0.15:0.06:0.06 dr); R_f = 0.64 (hexanes-ethyl acetate, 2 x 4:1); ¹H NMR (CDCl₃) 7.58-7.46 (m, 6H, H10), 7.38-7.34 (m, 9H, H10), 6.01 (s, 1H, H1), 4.12 (t, *J* = 8.6 Hz, 1H, H4), 4.00 (d, *J* = 11.1 Hz, 1H, H8), 3.87-3.83 (m, 1H, H7), 3.76 (t, *J* = 9.4 Hz, 2H, H4/H7), 3.51-3.46 (m, 2H, H11), 3.33 (s, 3H, H12), 3.31 (t, *J* = 9.4 Hz, 1H, H6), 2.48 (tdd, *J* = 13.1, 5.6, 1.1 Hz, 1H, H3), 2.18 (dt, *J* = 14.7, 3.0 Hz, 1H, H3), 2.07-2.00 (m, 1H, H9), 1.90-1.80 (m, 1H, H9); ¹³C NMR (CDCl₃) 150.13 (C, C2), 138.52 (C, C10), 136.98 (CH, C10), 129.38 (CH, C10), 128.93 (CH, C10), 124.55 (CH, C1), 86.19 (CH, C8), 84.31 (q, *J* = 27.3 Hz, C, C5), 79.30 (q, *J* = 285.93 Hz, CF₃, C13), 70.71 (CH₂, C4), 69.81 (CH₂, C11), 65.55 (CH₂, C7), 58.90 (CH₃, C12), 49.31 (CH, C6), 33.10 (CH₂, C3), 29.86 (CH₂, C9); IR (Neat, cm⁻¹) 3058 (m), 2913 (s), 1605 (m), 1255 (m), 1071 (s), 727 (s), 697 (s); HRMS (ESI) calcd for C₃₀H₃₁O₃F₃Sn+Na⁺ 635.1140, found 635.1125.



94i. Clear, light yellow oil (81% yield, 1.00:0.71:0.17:0.15 dr); $R_f = 0.06$ (hexanes-ethyl acetate, 2 x 4:1); $^1\text{H NMR}$ (CDCl_3) 7.66-7.47 (m, 6H, H10), 7.39-7.37 (m, 9H, H10), 6.03 (s, 1H, H1, major), 6.01 (s, 1H, H1, minor), 4.10 (dd, $J = 11.0, 7.7$ Hz, 2H, H8), 4.03 (d, $J = 9.5$ Hz, 1H, H7, major), 4.01 (d, $J = 9.6$ Hz, 1H, H7, minor), 3.86-3.72 (m, 3H, H4/H11), 3.55 (td, $J = 12.0, 2.7$ Hz, 1H, H11, major), 3.49 (td, $J = 12.1, 2.3$ Hz, 1H, H11, minor), 2.96 (t, $J = 9.6$ Hz, 1H, minor, H6), 2.89 (t, $J = 9.4$ Hz, major, H6), 2.83-2.66 (m, 1H, H3, minor), 2.60 (tdd, $J = 13.4, 6.4, 1.1$ Hz, 1H, H3, major), 2.07 (d, $J = 14.1$ Hz, 1H, H3), 2.00-1.93 (m, 1H, H12), 1.80-1.71 (m, 1H, H9), 1.69-1.54 (m, 1H, H9), 1.26 (s, 3H, H13, minor), 1.25 (s, 3H, H13, major); $^{13}\text{C NMR}$ (CDCl_3) 153.39 (C, C2, minor), 152.61 (C, C2, major), 138.75 (C, C10), 136.89 (CH, C10), 129.22 (CH, C10), 128.80 (CH, C10), 123.78 (CH, C1, major), 123.37 (CH, C1, minor), 88.85 (CH, C8, major), 87.19 (CH, C8, minor), 84.41 (C, C5, major), 81.71 (C, C5, minor), 69.79 (CH₂, C7, major), 69.73 (CH₂, C7, minor), 62.87 (CH₂, C11, minor), 62.55 (CH₂, C11, major), 61.63 (CH₂, C4, major), 61.03 (CH₂, C4, minor), 57.52 (CH, C6, minor), 56.47 (CH, C6, major), 34.11 (CH₂, C3, major), 33.68 (CH₂, C3, minor), 31.05 (CH₂, C9, major), 30.62 (CH₂, C9, minor), 16.66 (CH₃, C13, minor), 16.01 (CH₃, C13, major); IR (Neat, cm^{-1}) 3468 (br, s), 3051 (s), 2973 (s), 1606 (m), 1074 (s), 737 (s), 699 (s); HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{32}\text{O}_3\text{Sn}+\text{Na}^+$ 567.1267, found 567.1271.

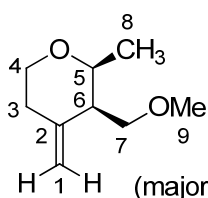


94j. Clear, light yellow oil (74% yield, 1.00:0.21:0.07:0.05 dr); $R_f = 0.38$ (hexanes-ethyl acetate, 2 x 4:1); $^1\text{H NMR}$ (CDCl_3) 7.60-7.48 (m, 6H, H10), 7.38-7.35 (m, 9H, H10), 7.33-7.30 (m, 4H, H14), 7.28-7.25 (m, 1H, H14), 5.97 (s, 1H, H1), 4.52 (d, $J = 3.5$ Hz, 2H, H12), 3.99 (dd, $J = 11.6, 2.5$ Hz, 1H, H8), 3.97 (dd, $J = 9.6, 2.6$ Hz, 2H, H7), 3.80 (dd, $J = 9.8, 2.9$ Hz, 1H, H4, minor), 3.73 (ddd, $J = 11.3, 6.7, 1.3$ Hz, 1H, H4, major), 3.69-3.63 (m, 1H, H11), 3.62 (t, $J = 7.7$ Hz, 1H, H11), 3.53 (td, $J = 11.8, 2.7$ Hz, H4, major), 3.46 (td, $J = 11.8, 2.7$ Hz, H4, minor), 2.97 (t, $J = 9.5$ Hz, 1H, H6, minor), 2.83 (t, $J = 9.5$ Hz, H6, major), 2.55 (tdd, $J = 13.1, 6.2, 1.5$ Hz, 1H, H3), 2.03 (dt, $J = 14.1, 1.0$ Hz, 1H, H3), 1.98-1.91 (m, 1H, H9, minor), 1.87-1.81 (m, 1H, H9, major), 1.58-1.54 (m, 1H, H9), 1.25 (s, 3H, H13, minor), 1.24 (s, 3H, H13, major); $^{13}\text{C NMR}$ (CDCl_3) 153.89 (C, C14, minor), 153.12 (C, C14, major), 138.90 (C, C10, major), 138.67 (C, C10, minor), 137.23 (CH, C10, minor), 136.98 (CH, C10, major), 129.27 (CH, C10, major), 129.19 (CH, C10, minor), 128.85 (CH, C10), 128.56 (CH, C14, major), 128.52 (CH, C14, minor), 127.91 (CH, C14, major), 127.82 (CH, C14, minor), 127.73 (CH, C14, major), 127.66 (CH, C14, minor), 123.40 (CH, major, C1), 122.98 (CH, minor, C1), 85.77 (CH, C8), 84.54 (C, C5), 73.46 (CH_2 , C12, major), 73.17 (CH_2 , C12, minor), 69.78 (CH_2 , C7, major), 69.61 (CH_2 , C7, minor), 67.96 (CH_2 , C11, minor), 67.90 (CH_2 , C11, major), 62.80 (CH_2 , C4, minor), 62.62 (CH_2 , C4, major), 57.93 (CH, C6, minor), 56.64 (CH, C6, major), 33.85 (CH_2 , C3, minor), 32.90 (CH_2 , C3, major), 29.91 (CH_2 , C9, major), 28.79 (CH_2 , C9, minor), 16.72 (CH_3 , C13, minor), 16.18 (CH_3 , C13, major); IR (Neat, cm^{-1}) 3053 (m), 2985 (s), 1652 (m), 1265 (s), 1074 (s), 739 (s), 704 (s); HRMS (ESI) calcd for $\text{C}_{36}\text{H}_{38}\text{O}_3\text{Sn}+\text{Na}^+$ 657.1736, found 657.1733.



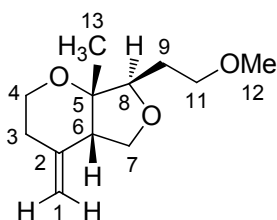
115a. Clear, light yellow oil (80% yield); $R_f = 0.78$ (hexanes-ethyl acetate, 2:1); ^1H NMR (CDCl_3) 7.55-7.48 (m, 6H, H10), 7.47-7.36 (m, 9H, H10), 6.43 (s, 1H, H1), 6.07 (dd, $J = 17.0, 10.6$ Hz, 1H, H6), 5.63 (d, $J = 17.0$ Hz, 1H, H7), 5.37 (d, $J = 10.6$ Hz, 1H, H7), 4.05 (q, $J = 8.2$ Hz, 1H, H4), 3.89 (q, $J = 7.7$ Hz, 1H, H4), 2.61 (dtd, $J = 15.8, 7.7, 2.4$ Hz, 1H, H3), 2.49 (dddd, $J = 15.9, 7.2, 6.6, 2.0$ Hz, 1H, H3); ^{13}C NMR (CDCl_3) 158.07 (C, C2), 137.84 (C, C10), 137.05 (CH, C10), 132.80 (CH, C6), 129.51 (CH, C10), 129.01 (CH, C10), 124.67 (q, $J = 287.0$ Hz, CF_3 , C8), 121.63 (CH, C1), 117.77 (CH_2 , C7), 85.26 (q, $J = 28.4$ Hz, C, C5), 67.75 (CH_2 , C4), 35.64 (CH_2 , C3); IR (Neat, cm^{-1}) 3047 (m), 2915 (s), 1146 (m), 1071 (m), 727 (s), 693 (s); HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{23}\text{OF}_3\text{Sn}+\text{Na}^+$ 551.0626, found 551.0635.

5.5.6 Experimental Data for Protodestannylation Products 93a, 96, or 97a

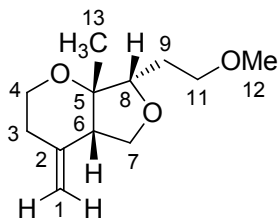


93a. Clear, light yellow oil (100% yield, 1.00:0.30 dr); $R_f = 0.18$ (hexanes-diethyl ether, 2 x 9:1); ^1H NMR (CDCl_3) 4.87 (t, $J = 1.3$ Hz, 1H, minor, H1), 4.80 (t, $J = 1.9$ Hz, 1H, H1), 4.77 (t, $J = 1.6$ Hz, 1H, major, H1), 3.99 (ddd, $J = 10.9, 5.6, 2.3$ Hz, 1H, major, H4), 3.90 (dt, $J = 10.9, 4.6$ Hz, 1H, minor, H4), 3.59 (qd, $J = 6.7, 3.0$ Hz, 1H, H5), 3.57 (dd, $J = 9.5, 6.2$ Hz, 1H, H7), 3.53 (dd, $J = 9.5, 8.2$ Hz, 1H, H7), 3.49-3.46 (m, 1H, minor, H4), 3.41 (td, $J = 11.1, 3.2$ Hz, 1H, major, H4), 3.32 (s, 3H, minor, H9), 3.31 (s, 3H, major, H9), 2.45 (td, $J = 7.2, 2.9$ Hz, 1H, major, H6), 2.36 (tdt, $J = 12.6, 5.6, 1.6$ Hz, 1H, major, H3), 2.24-2.23 (m, 2H, minor, H3/H6), 2.12-2.06 (m, 1H, minor, H3), 2.05 (dt, $J = 13.6,$

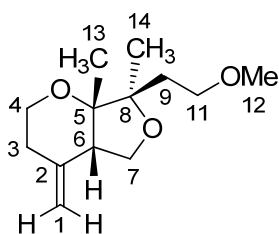
2.7 Hz, 1H, major, H3), 1.25 (d, $J = 6.3$ Hz, 3H, minor, H8), 1.17 (d, $J = 6.6$ Hz, 3H, major, H8); ^{13}C NMR (CDCl_3) 146.28 (C, major, C2), 144.90 (C, minor, C2), 109.83 (CH_2 , major, C1), 108.78 (CH_2 , minor, C1), 76.15 (CH, major, C5), 75.05 (CH, minor, C4), 71.53 (CH_2 , minor, C7), 70.19 (CH_2 , major, C7), 68.80 (CH_2 , major, C4), 59.05 (CH_3 , C9), 49.52 (CH, minor, C3), 48.83 (CH, major, C6), 35.96 (CH_2 , minor, C3/C6), 32.48 (CH_2 , major, C3), 19.51 (CH_3 , minor, C8), 18.32 (CH_3 , major, C8); IR (Neat, cm^{-1}) 3052 (m), 2982 (m), 1651 (m), 1264 (s), 1108 (s), 1091 (s), 1063 (m); HRMS (ESI) calcd for $\text{C}_9\text{H}_{16}\text{O}_2 + \text{H}^+$ 157.1229, found 157.1225.



96a. Clear, light yellow oil (76% yield); $R_f = 0.12$ (hexanes-diethyl ether, 2 x 4:1); ^1H NMR (CDCl_3) 4.90 (t, $J = 2.0$ Hz, 1H, H1), 4.84 (t, $J = 1.9$ Hz, 1H, H1), 3.93 (dd, $J = 10.0, 2.5$ Hz, 1H, H8), 3.92 (dd, $J = 10.1, 8.4$ Hz, 1H, H7), 3.86 (t, $J = 8.5$ Hz, 1H, H7), 3.85 (ddd, $J = 11.6, 6.0, 1.4$ Hz, 1H, H4), 3.64 (ddd, $J = 12.4, 11.4, 2.9$ Hz, 1H, H4), 3.53 (ddd, $J = 9.1, 8.4, 4.6$ Hz, 1H, H11), 3.47 (dt, $J = 9.2, 7.4$ Hz, 1H, H11), 3.33 (s, 3H, H12), 2.58 (dd, $J = 9.7, 9.1$ Hz, 1H, H6), 2.51 (tdt, $J = 13.2, 6.1, 1.9$ Hz, 1H, H3), 2.02 (dt, $J = 14.1, 1.9$ Hz, 1H, H3), 1.75 (ttt, $J = 10.6, 6.0, 2.8$ Hz, 1H, H9), 1.54-1.46 (m, 1H, H9), 1.16 (s, 3H, H13); ^{13}C NMR (CDCl_3) 140.58 (C, C2), 113.20 (CH_2 , C1), 85.82 (CH, C8), 84.05 (C, C5), 70.20 (CH_2 , C11), 69.40 (CH_2 , C7), 62.67 (CH_2 , C4), 58.99 (CH_3 , C12), 52.09 (CH, C6), 32.72 (CH_2 , C9), 31.06 (CH_2 , C3), 16.01 (CH_3 , C13); IR (Neat, cm^{-1}) 3073 (w), 2928 (s), 1647 (m), 1117 (s), 1082 (s), 1066 (m); HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{20}\text{O}_3 + \text{H}^+$ 213.1491, found 213.0977.



97a. Clear, light yellow oil (20% yield); $R_f = 0.18$ (hexanes-diethyl ether, 2 x 4:1); ^1H NMR (CDCl_3) 4.87 (t, $J = 2.0$ Hz, 1H, H1), 4.82 (t, $J = 1.9$ Hz, 1H, H1), 3.90 (d, $J = 9.7$ Hz, 1H, H7), 3.90 (d, $J = 9.6$ Hz, 1H, H7), 3.88 (dd, $J = 11.8, 5.1$ Hz, 1H, H4), 3.73 (dd, $J = 10.1, 2.8$ Hz, 1H, H8), 3.57 (ddd, $J = 12.6, 11.3, 2.6$ Hz, 1H, H4), 3.54-3.51 (m, 2H, H11), 3.34 (s, 3H, H12), 2.72 (t, $J = 9.6$ Hz, 1H, H6), 2.49 (tdt, $J = 13.4, 6.0, 1.8$ Hz, 1H, H3), 2.00 (dt, $J = 14.0, 1.3$ Hz, 1H, H3), 1.92-1.86 (m, 1H, H9), 1.78 (dtd, $J = 14.5, 7.6, 2.8$ Hz, 1H, H9), 1.16 (s, 3H, H13); ^{13}C NMR (CDCl_3) 141.23 (C, C2), 112.88 (CH_2 , C1), 85.03 (CH, C8), 81.23 (C, C5), 70.23 (CH_2 , C11), 69.22 (CH_2 , C7), 62.85 (CH_2 , C4), 58.91 (CH_3 , C12), 53.29 (CH, C6), 30.67 (CH_2 , C3), 28.63 (CH_2 , C9), 16.48 (CH_3 , C13); IR (Neat, cm^{-1}) 3074 (w), 2928 (s), 1647 (m), 1117 (s), 1082 (s), 1066 (m); HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{20}\text{O}_3 + \text{H}^+$ 213.1491, found 213.0977.

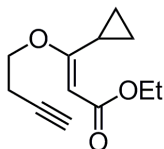


96b. Clear, light yellow oil (99% yield); $R_f = 0.19$ (hexanes-diethyl ether, 2 x 4:1); ^1H NMR (CDCl_3) 4.85 (t, $J = 2.0$ Hz, 1H, H1), 4.79 (t, $J = 1.9$ Hz, 1H, H1), 3.90 (dd, $J = 11.3, 6.0$ Hz, 1H, H4), 3.83 (dd, $J = 15.7, 8.9$ Hz, 1H, H7), 3.81 (dd, $J = 15.4, 9.2$ Hz, 1H, H7), 3.59 (ddd, $J = 12.5, 11.5, 2.7$ Hz, 1H, H4), 3.57-3.51 (m, 2H, H11), 3.33 (s, 3H, H12), 2.90 (t, $J = 9.4$ Hz, 1H, H6), 2.50 (tdt, $J = 13.3, 6.1, 1.9$ Hz, 1H, H3), 2.01 (dt, $J = 13.9, 1.1$ Hz, 1H, H3), 1.72-1.67 (m, 1H, H9), 1.63-1.58 (m, 1H, H9), 1.20 (s, 3H, H14), 1.09 (s, 3H, H13); ^{13}C NMR (CDCl_3) 141.84 (C, C2), 112.61 (CH_2 , C1), 87.62 (C, C5),

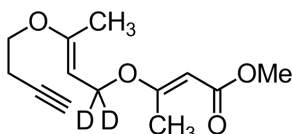
83.86 (C, C8), 69.37 (CH₂, C11), 67.90 (CH₂, C7), 62.45 (CH₂, C4), 58.94 (CH₃, C12), 51.49 (CH, C6), 36.38 (CH₂, C3), 30.58 (CH₂, C9), 17.71 (CH₃, C14), 14.49 (CH₃, C13); IR (Neat, cm⁻¹) 3047 (w), 2925 (s), 1647 (m), 1265 (s), 1109 (s), 1040 (m); HRMS (ESI) calcd for C₁₃H₂₂O₃+H⁺ 227.1647, found 227.1644.

5.6.0 Experiments Pertaining to Chapter 4 Section 4.4.0

5.6.1 Experimental Data for Addition Synthetic Intermediates 78h and 80k



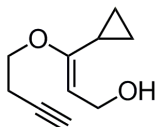
78h. Clear, colorless oil (45% yield); $R_f = 0.69$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 5.06 (s, 1H), 4.09 (q, $J = 7.2$ Hz, 2H), 3.88 (t, $J = 6.3$ Hz, 2H), 3.25 (tt, $J = 10.1, 8.4$ Hz, 1H), 2.57 (td, $J = 6.3, 2.7$ Hz, 2H), 2.43 (t, $J = 2.7$ Hz, 1H), 1.22 (t, $J = 7.1$ Hz, 3H), 0.97 (dq, $J = 5.7, 3.4$ Hz, 2H), 0.77 (dq, $J = 8.4, 3.5$ Hz, 2H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 174.49 (C), 168.29 (C), 91.74 (CH), 81.19 (C), 71.12 (CH), 66.68 (CH_2), 59.50 (CH_2), 19.27 (CH_2), 14.79 (CH_3), 12.01 (CH), 7.37 (CH_2); IR (Neat, cm^{-1}) 3300 (s), 3091 (m), 2954 (s), 2123 (w), 1702 (s), 1606 (s), 1146 (s), 1051 (s); HRMS (ESI) calcd for $\text{C}_{12}\text{H}_{16}\text{O}_3 + \text{H}^+$ 209.1178, found 209.1177.



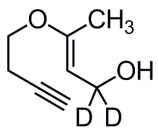
80k. Clear, orange oil (99% yield, 1.00:0.17 *E/Z*); $R_f = 0.09$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 5.06 (s, 1H), 4.74 (s, 1H, major), 4.68 (s, 1H, minor), 4.12 (q, $J = 7.1$ Hz, 2H, minor), 4.07 (q, $J = 7.1$ Hz, 2H, major), 3.82 (t, $J = 6.6$ Hz, 2H, major), 3.75 (t, $J = 6.6$ Hz, 2H, minor), 2.57 (td, $J = 6.7, 2.7$ Hz, 2H, major), 2.54 (td, $J = 6.7, 2.7$ Hz, 2H, minor), 2.41 (t, $J = 2.7$ Hz, 1H), 2.23 (s, 3H), 1.86 (d, $J = 0.8$ Hz, 3H, major), 1.79 (d, $J = 0.8$ Hz, 3H, minor), 1.26 (t, $J = 7.1$ Hz, 3H, minor), 1.21 (t, $J = 7.1$ Hz, 3H, major); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 172.56 (C), 168.07 (C), 159.38 (C), 92.80 (CH), 91.89 (CH), 81.62 (C), 70.99 (CH), 65.97 (CH_2), 65.35 (p, $J = 21.5$ Hz, CD_2), 59.45 (CH_3),

19.60 (CH₂), 19.18 (CH₃), 16.61 (CH₃), 14.79 (CH₃); IR (Neat, cm⁻¹) 3293 (s), 3078 (w), 2978 (s), 2122 (w), 1708 (s), 1660 (s), 1144 (s), 1064 (s); HRMS (ESI) calcd for C₁₄H₁₈O₄D₂+Na⁺ 277.1385, found 277.1383.

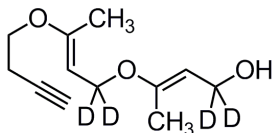
5.6.2 Experimental Data for Synthetic Intermediates 79 and 81



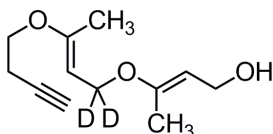
79h. Clear, light yellow oil (64% yield); *R_f* = 0.09 (hexanes-ethyl acetate, 4:1); ¹H NMR ((CD₃)₂CO) 4.71 (t, *J* = 7.5 Hz, 1H), 4.19 (dd, *J* = 7.4, 4.6 Hz, 2H), 3.69 (t, *J* = 6.5 Hz, 2H), 3.31 (t, *J* = 5.4 Hz, 1H), 2.48 (td, *J* = 6.5, 2.6 Hz, 2H), 2.38 (t, *J* = 2.6 Hz, 1H), 1.81 (tt, *J* = 10.0, 8.3 Hz, 1H), 0.77 (dq, *J* = 5.0, 3.6 Hz, 2H), 0.56 (dq, *J* = 8.4, 3.6 Hz, 2H); ¹³C NMR ((CD₃)₂CO) 157.43 (C), 98.70 (CH), 81.73 (C), 70.69 (CH), 65.28 (CH₂), 58.07 (CH₂), 19.43 (CH₂), 10.72 (CH), 4.89 (CH₂); IR (Neat, cm⁻¹) 3368 (br, s), 3300 (s), 3094 (m), 2928 (s), 2120 (w), 1651 (s), 1102 (s), 1052 (s); HRMS (ESI) calcd for C₁₀H₁₄O₂+Na⁺ 189.0891, found 189.0888.



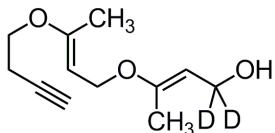
79g. Clear, light yellow oil (94% yield, 1.00:0.04 *E/Z*); *R_f* = 0.08 (hexanes-ethyl acetate, 4:1); ¹H NMR ((CD₃)₂CO) 4.54 (s, 1H), 3.61 (t, *J* = 6.7 Hz, 2H), 3.16 (s, 1H), 2.40 (td, *J* = 6.7, 2.7 Hz, 2H), 2.25 (t, *J* = 2.7 Hz, 1H), 1.65 (d, *J* = 0.8 Hz, 3H); ¹³C NMR ((CD₃)₂CO) 155.05 (C), 98.91 (CH), 81.81 (C), 70.90 (CH), 65.52 (CH₂), 58.15 (p, *J* = 21.6 Hz, CD₂), 19.64 (CH₂), 16.33 (CH₃); IR (Neat, cm⁻¹) 3355 (br, s), 3293 (s), 3069 (w), 2926 (s), 2103 (w), 1660 (s), 1079 (s).



81k. Clear, light yellow oil (95% yield, 1.00:0.23 *E/Z*); $R_f = 0.09$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 4.69 (s, 2H), 3.30 (t, $J = 6.6$ Hz, 2H, major), 3.75 (t, $J = 6.7$ Hz, 2H, minor), 3.24 (s, 1H, minor), 3.19 (s, 1H, major), 2.56 (td, $J = 6.7, 2.7$ Hz, 2H, major), 2.54 (td, $J = 6.7, 2.7$ Hz, 2H, minor), 2.40 (t, $J = 2.7$ Hz, 1H, major), 2.38 (t, $J = 3.0$ Hz, 1H, minor), 1.82 (d, $J = 0.7$ Hz, 3H, major), 1.79 (d, $J = 0.7$ Hz, 3H, minor), 1.77 (s, $J = 0.7$ Hz, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 157.91 (C), 156.18 (C), 98.45 (CH), 94.13 (CH), 81.70 (C), 70.95 (CH), 65.79 (CH₂), 63.36 (p, $J = 22.1$ Hz, CD₂), 58.30 (p, $J = 22.1$ Hz, CD₂), 19.63 (CH₂), 16.54 (CH₃); IR (Neat, cm⁻¹) 3372 (br, s), 3292 (s), 3070 (w), 2925 (m), 2101 (w), 1654 (s), 1073 (s); HRMS (ESI) calcd for C₁₂H₁₄O₃D₄+Na⁺ 237.1405, found 237.1407.

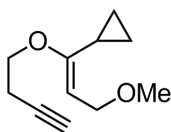


81l. Clear, light yellow oil (93% yield, 1.00:0.30 *E/Z*); $R_f = 0.09$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 4.71 (td, $J = 7.5, 0.8$ Hz, 1H), 4.69 (s, 1H), 4.05 (dd, $J = 7.5, 5.5$ Hz, 2H), 3.79 (t, $J = 6.6$ Hz, 2H, major), 3.75 (t, $J = 6.7$ Hz, 2H, minor), 3.26 (t, $J = 5.5$ Hz, 1H), 2.56 (td, $J = 6.7, 2.7$ Hz, 2H, major), 2.54 (td, $J = 6.7, 2.7$ Hz, 2H, minor), 2.40 (t, $J = 2.7$ Hz, 1H, major), 2.38 (t, $J = 2.4$ Hz, 1H, minor), 1.81 (d, $J = 0.8$ Hz, 3H, major), 1.79 (d, $J = 0.8$ Hz, 3H, minor), 1.77 (s, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 157.92 (C), 156.13 (C), 98.60 (CH), 94.13 (CH), 81.70 (C), 70.96 (CH), 65.79 (CH₂), 63.08 (p, $J = 21.6$ Hz, CD₂), 56.52 (CH₂), 19.64 (CH₂), 16.55 (CH₃); IR (Neat, cm⁻¹) 3361 (br, s), 3291 (s), 3047 (w), 2925 (s), 2123 (w), 1657 (s), 1073 (s); HRMS (ESI) calcd for C₁₂H₁₆O₃D₂+Na⁺ 235.1279, found 235.1280.

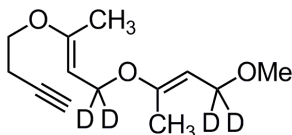


81m. Clear, light yellow oil (94% yield, 1.00:0.04 *E/Z*); $R_f = 0.09$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 4.73-4.68 (m, 2H), 4.19 (d, $J = 7.4$ Hz, 2H), 3.80 (t, $J = 6.7$ Hz, 2H), 3.16 (s, 1H), 2.56 (td, $J = 6.6, 2.7$ Hz, 2H), 2.40 (t, $J = 2.7$ Hz, 1H), 1.82 (s, 3H), 1.77 (d, $J = 0.7$ Hz, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 157.83 (C), 156.17 (C), 98.50 (CH), 94.30 (CH), 81.70 (C), 70.95 (CH), 65.79 (CH₂), 63.99 (CH₂), 58.32 (p, $J = 21.3$ Hz, CD₂), 19.63 (CH₂), 16.54 (CH₃); IR (Neat, cm⁻¹) 3366 (br, s), 3301 (s), 3047 (w), 2927 (s), 2102 (w), 1656 (s), 1077 (s); HRMS (ESI) calcd for C₁₂H₁₆O₃D₂+Na⁺ 235.1279, found 235.1275.

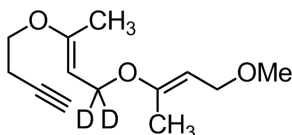
5.6.3 Experimental Data for Synthetic Intermediates 82 and 83



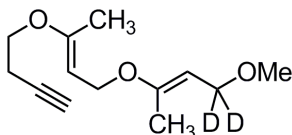
82c. Clear, light yellow oil (85% yield, 1.00:0.13 *E/Z*); $R_f = 0.57$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 4.64 (t, $J = 7.6$ Hz, 1H, major), 4.60 (t, $J = 7.6$ Hz, 1H, minor), 4.03 (d, $J = 7.6$ Hz, 2H, major), 4.02 (d, $J = 7.6$ Hz, 2H, minor), 3.73 (t, $J = 6.5$ Hz, 2H), 3.24 (s, 3H, major), 3.23 (s, 3H, minor), 2.49 (td, $J = 6.5, 2.7$ Hz, 2H), 2.37 (t, $J = 2.7$ Hz, 1H), 1.82 (tt, $J = 10.0, 8.3$ Hz, 1H), 0.80 (dq, $J = 5.0, 3.7$ Hz, 2H), 0.59 (dq, $J = 8.3, 3.7$ Hz, 2H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 159.45 (C, minor), 159.19 (C, major), 94.94 (CH, major), 94.34 (CH, minor), 81.67 (C), 70.75 (CH), 68.35 (CH₂, minor), 68.21 (CH₂, major), 65.45 (CH₂), 56.93 (CH₃, major), 56.86 (CH₃, minor), 19.49 (CH₂), 10.87 (CH, major), 10.81 (CH, minor), 5.03 (CH₂, major), 4.95 (CH₂, minor); IR (Neat, cm⁻¹) 3308 (s), 3093 (w), 2924 (s), 2122 (w), 1653 (s), 1104 (s), 1083 (s); HRMS (ESI) calcd for C₁₁H₁₆O₂+Na⁺ 203.1048, found 203.1049.



83k. Clear, yellow oil (79% yield, 1.00:0.08 *E/Z*); $R_f = 0.47$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 4.70 (s, 1H), 4.61 (s, 1H), 3.91 (t, $J = 6.7$ Hz, 2H, minor), 3.80 (t, $J = 6.7$ Hz, 2H, major), 3.20 (s, 3H, major), 3.19 (s, 3H, minor), 2.56 (td, $J = 6.7, 2.7$ Hz, 2H, major), 2.49 (td, $J = 6.7, 2.7$ Hz, 2H, minor), 2.40 (t, $J = 2.7$ Hz, 1H), 1.89 (d, $J = 1.0$ Hz, 3H, minor), 1.82 (d, $J = 0.8$ Hz, 3H, major), 1.78 (d, $J = 0.8$ Hz, 3H, major), 1.77 (d, $J = 0.8$ Hz, 3H, minor); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 158.01 (C), 157.75 (C), 94.69 (CH), 94.03 (CH), 81.69 (C), 70.93 (CH), 68.36 (p, $J = 21.1$ Hz, CD_2), 65.80 (CH_2), 63.50 (p, $J = 21.8$ Hz, CD_2), 56.76 (CH_3), 19.62 (CH_2), 16.71 (CH_3), 16.54 (CH_3); IR (Neat, cm^{-1}) 3291 (s), 3070 (w), 2925 (s), 2117 (w), 1653 (s), 1072 (s); HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{16}\text{O}_3\text{D}_4 + \text{Na}^+$ 251.1561, found 251.1564.

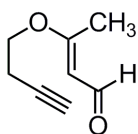


83l. Clear, yellow oil (86% yield, 1.00:0.10 *E/Z*); $R_f = 0.42$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 4.70 (s, 1H), 4.62 (td, $J = 7.5, 0.8$ Hz, 1H), 3.88 (d, $J = 7.4$ Hz, 2H), 3.80 (t, $J = 6.6$ Hz, 2H), 3.21 (s, 3H, major), 3.20 (s, 3H, minor), 2.56 (td, $J = 6.7, 2.7$ Hz, 2H, major), 2.49 (td, $J = 6.7, 2.7$ Hz, 2H, minor), 2.40 (t, $J = 2.7$ Hz, 1H), 1.89 (d, $J = 1.0$ Hz, 3H, minor), 1.82 (d, $J = 0.7$ Hz, 3H, major), 1.81 (d, $J = 0.8$ Hz, 3H, minor), 1.78 (s, 3H, major); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 158.02 (C), 157.68 (C), 94.86 (CH), 94.03 (CH), 81.69 (C), 70.95 (CH), 69.12 (CH_2), 65.81 (CH_2), 63.50 (p, $J = 21.6$ Hz, CD_2), 56.88 (CH_3), 19.63 (CH_2), 16.73 (CH_3), 16.56 (CH_3); IR (Neat, cm^{-1}) 3292 (s), 3070 (w), 2925 (s), 2117 (w), 1658 (s), 1077 (s); HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{18}\text{O}_3\text{D}_2 + \text{Na}^+$ 249.1436, found 249.1434.



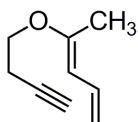
83m. Clear, yellow oil (89% yield, 1.00:0.11 *E/Z*); $R_f = 0.45$ (hexanes-ethyl acetate, 4:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 4.71 (t, $J = 7.3$ Hz, 1H), 4.61 (s, 1H), 4.31 (d, $J = 6.5$ Hz, 2H, minor), 4.31 (d, $J = 7.3$ Hz, 2H, major), 3.91 (t, $J = 6.7$ Hz, 2H, minor), 3.80 (t, $J = 6.7$ Hz, 2H, major), 3.20 (s, 3H, major), 3.19 (s, 3H, minor), 2.56 (td, $J = 6.7, 2.7$ Hz, 2H, major), 2.50 (td, $J = 6.7, 2.7$ Hz, 2H, minor), 2.40 (t, $J = 2.7$ Hz, 1H), 1.89 (d, $J = 1.0$ Hz, 3H, minor), 1.82 (s, 3H, major), 1.78 (d, $J = 0.8$ Hz, 3H, major), 1.77 (d, $J = 0.8$ Hz, 3H, minor); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 157.95 (C), 157.75 (C), 94.73 (CH), 94.20 (CH), 81.69 (C), 70.96 (CH), 68.37 (p, $J = 21.5$ Hz, CD_2), 65.81 (CH_2), 64.14 (CH_2), 56.79 (CH_3), 19.64 (CH_2), 16.73 (CH_3), 16.57 (CH_3); IR (Neat, cm^{-1}) 3291 (m), 3076 (w), 2926 (s), 2122 (w), 1656 (s), 1096 (s); HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{18}\text{O}_3\text{D}_2 + \text{H}^+$ 227.1616, found 227.1612.

5.6.4 Experimental Data for IBX Oxidation Product 117



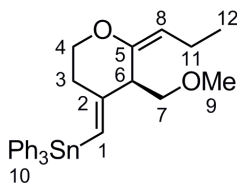
117. Clear, light yellow oil (52% yield); $R_f = 0.57$ (hexanes-ethyl acetate, 1:1); $^1\text{H NMR}$ ($(\text{CD}_3)_2\text{CO}$) 9.80 (d, $J = 7.4$ Hz, 1H), 5.36 (d, $J = 7.4$ Hz, 1H), 3.99 (t, $J = 12.9$ Hz, 2H), 2.65 (td, $J = 6.5, 2.7$ Hz, 2H), 2.46 (t, $J = 2.7$ Hz, 1H), 2.27 (s, 3H); $^{13}\text{C NMR}$ ($(\text{CD}_3)_2\text{CO}$) 190.36 (CH), 175.96 (C), 105.73 (CH), 81.09 (C), 71.42 (CH), 67.45 (CH_2), 19.38 (CH_2), 17.66 (CH_3); IR (Neat, cm^{-1}) 3304 (m), 3057 (m), 2958 (m), 2124 (w), 1703 (s), 1138 (m), 1060 (m); HRMS (ESI) calcd for $\text{C}_8\text{H}_{10}\text{O}_2 + \text{H}^+$ 139.0759, found 139.0759.

5.6.5 Experimental Data for Diene 118



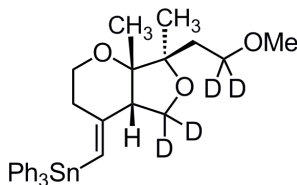
118. Clear, colorless oil (31% yield); $R_f = 0.88$ (hexanes-ethyl acetate, 1:1); ^1H NMR ($(\text{CD}_3)_2\text{CO}$) 6.44 (dt, $J = 16.7, 10.4$ Hz, 1H), 5.36 (d, $J = 10.7$ Hz, 1H), 4.96 (dd, $J = 16.7, 2.1$ Hz, 1H), 4.76 (dd, $J = 10.2, 2.1$ Hz, 1H), 3.83 (t, $J = 6.7$ Hz, 2H), 2.56 (td, $J = 6.7, 2.7$ Hz, 2H), 2.40 (t, $J = 2.7$ Hz, 1H), 1.89 (s, 3H); ^{13}C NMR ($(\text{CD}_3)_2\text{CO}$) 156.60 (C), 133.98 (CH), 111.40 (CH_2), 102.21 (CH), 81.58 (C), 70.98 (CH), 65.85 (CH_2), 19.68 (CH_2), 16.71 (CH_3); IR (Neat, cm^{-1}) 3304 (s), 3086 (w), 3053 (m), 2977 (s), 2123 (w), 1644 (s), 1113 (s), 1073 (s); HRMS (ESI) calcd for $\text{C}_9\text{H}_{12}\text{O}+\text{H}^+$ 137.0966, found 137.0963.

5.6.6 Experimental Data for Cyclization Products 91, 94, 95, and 115

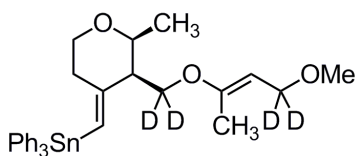


91c. Clear, light yellow oil (58% yield); $R_f = 0.59$ (hexanes-ethyl acetate, 2 x 9:1); ^1H NMR (CDCl_3) 7.62-7.50 (m, 6H, H10), 7.37-7.35 (m, 9H, H10), 5.94 (s, 1H, H1), 4.63 (t, $J = 7.1$ Hz, 1H, H8), 4.02 (ddd, $J = 10.5, 5.5, 2.8$ Hz, 1H, H4), 3.59 (d, $J = 7.6$ Hz, 2H, H7), 3.43 (td, $J = 11.0, 3.0$ Hz, 1H, H4), 3.39 (s, 3H, H9), 3.28 (t, $J = 7.5$ Hz, 1H, H6), 2.59 (dddd, $J = 14.3, 10.2, 5.4, 1.3$ Hz, 1H, H3), 2.19 (dt, $J = 14.3, 3.0$ Hz, 1H, H3), 2.11 (s, $J = 7.4$ Hz, 1H, H11), 2.04 (s, $J = 7.3$ Hz, 1H, H11), 0.95 (t, $J = 7.5$ Hz, 3H, H12); ^{13}C NMR (CDCl_3) 156.06 (C, C5), 150.75 (C, C2), 139.11 (C, C10), 137.03 (CH, C10), 129.16 (CH, C10), 128.77 (CH, C10), 119.75 (CH, C1), 112.30 (CH, C9), 74.76 (CH_2 , C7), 69.44 (CH_2 , C4), 58.98 (CH_3 , C8), 53.97 (CH, C6), 34.67 (CH_2 , C3), 18.06 (CH_2 ,

C11), 14.86 (CH₃, C12); IR (Neat, cm⁻¹) 3049 (m), 2974 (m), 1111 (s), 731 (s), 699 (s); HRMS (ESI) calcd for C₂₉H₃₂O₂Sn+Na⁺ 555.1328, found 555.1330.

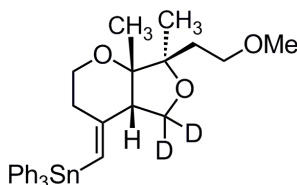


94k. Clear, light yellow oil (35% yield, 1.00:0.24 dr); R_f = 0.44 (hexanes-ethyl acetate, 2 x 4:1); ¹H NMR (CDCl₃) 7.63-7.44 (m, 6H), 7.380-7.34 (m, 9H), 5.92 (s, 1H), 3.77 (dd, *J* = 11.5, 5.1 Hz, 1H), 3.47 (td, *J* = 12.2, 2.3 Hz, 1H), 3.34 (s, 3H), 3.13 (s, 1H), 2.54 (tdd, *J* = 13.3, 6.2, 1.0 Hz, 1H), 2.03 (dt, *J* = 14.1, 1.0 Hz, 1H), 1.69 (s, 1H), 1.63 (s, 1H), 1.20 (s, 3H), 1.15 (s, 3H); ¹³C NMR (CDCl₃) 154.46 (C), 138.97 (C), 137.00 (CH), 129.26 (CH), 128.84 (CH), 122.69 (CH), 87.63 (C), 84.35 (C), 62.39 (CH₂), 58.88 (CH₃), 56.03 (CH), 36.24 (CH₂), 33.43 (CH₂), 17.79 (CH₃), 14.76 (CH₃); IR (Neat, cm⁻¹) 3063 (m), 2930 (s), 1605 (m), 1095 (s), 1074 (s), 730 (s), 699 (s); HRMS (ESI) calcd for C₃₁H₃₂O₃D₄Sn+H⁺ 577.2011, found 577.2003.

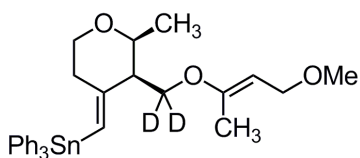


95k. Clear, light yellow oil (50% yield, 1.00:0.20 dr); R_f = 0.50 (hexanes-ethyl acetate, 2 x 4:1); ¹H NMR (CDCl₃) 7.66-7.46 (m, 6H), 7.37-7.33 (m, 9H), 5.88 (s, 1H), 4.66 (s, 1H), 3.85 (ddd, *J* = 10.9, 5.6, 2.0 Hz, 1H), 3.73 (qd, *J* = 6.6, 2.6 Hz, 1H), 3.31 (s, 3H), 3.30-3.28 (m, 1H), 2.78 (s, 1H), 2.35 (tdd, *J* = 12.7, 5.7, 0.9 Hz, 1H), 2.04 (dt, *J* = 14.0, 2.7 Hz), 1.85 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (CDCl₃) 158.38 (C), 158.10 (C), 139.26 (C), 137.01 (CH), 129.15 (CH), 128.76 (CH), 119.02 (CH), 93.72 (CH), 76.26 (CH), 68.60 (CH₂), 57.48 (CH₃), 52.60 (CH), 35.03 (CH₂), 18.44 (CH₃), 16.75

(CH₃); IR (Neat, cm⁻¹) 3058 (s), 2913 (s), 1657 (m), 1095 (s), 1071 (m), 728 (s), 698 (s); HRMS (ESI) calcd for C₃₁H₃₂O₃D₄Sn+H⁺ 577.2011, found 577.2023.

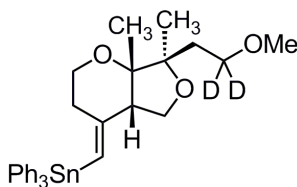


94I. Clear, light yellow oil (46% yield, 1.00:0.27 dr); R_f = 0.44 (hexanes-ethyl acetate, 2 x 4:1); ¹H NMR (CDCl₃) 7.64-7.44 (m, 6H), 7.38-7.34 (m, 9H), 5.92 (s, 1H), 3.77 (dd, *J* = 11.5, 5.1 Hz, 1H), 3.56 (t, *J* = 7.1 Hz, 2H), 3.48 (td, *J* = 12.3, 2.3 Hz, 1H), 3.35 (s, 3H), 3.13 (s, 1H), 2.52 (tdd, *J* = 13.1, 6.3, 1.2 Hz, 1H), 2.02 (dt, *J* = 14.1, 1.2 Hz, 1H), 1.77-1.68 (m, 2H), 1.21 (s, 3H), 1.15 (s, 3H); ¹³C NMR (CDCl₃) 154.47 (C), 138.97 (C), 136.99 (CH), 129.26 (CH), 128.84 (CH), 122.68 (CH), 87.64 (C), 84.36 (C), 69.35 (CH₂), 62.39 (CH₂), 58.95 (CH₃), 56.03 (CH), 36.45 (CH₂), 33.43 (CH₂), 17.79 (CH₃), 14.77 (CH₃); IR (Neat, cm⁻¹) 3063 (m), 2930 (s), 1605 (m), 1095 (s), 1074 (s), 730 (s), 699 (s); HRMS (ESI) calcd for C₃₁H₃₂O₃D₄Sn+H⁺ 575.1886, found 575.1887.

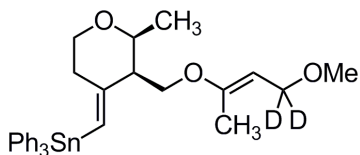


95I. Clear, light yellow oil (42% yield, 1.00:0.11 dr); R_f = 0.53 (hexanes-ethyl acetate, 2 x 4:1); ¹H NMR (CDCl₃) 7.66-7.46 (m, 6H), 7.38-7.32 (m, 9H), 5.88 (s, 1H), 4.67 (t, *J* = 7.5 Hz, 1H), 3.93 (d, *J* = 7.6 Hz, 2H), 3.86 (ddd, *J* = 10.9, 5.6, 2.1 Hz, 1H), 3.74 (qd, *J* = 6.4, 2.7 Hz, 1H), 3.31 (s, 3H), 3.30-3.28 (m, 1H), 2.77 (s, 1H), 2.35 (tdd, *J* = 12.7, 5.7, 1.0 Hz, 1H), 2.04 (dt, *J* = 12.7, 3.0 Hz), 1.85 (s, 3H), 1.21 (d, *J* = 6.7 Hz, 3H); ¹³C NMR (CDCl₃) 158.38 (C), 158.04 (C), 139.26 (C), 137.01 (CH), 129.14 (CH), 128.76 (CH), 119.02 (CH), 93.90 (CH), 76.26 (CH), 69.08 (CH₂), 68.60 (CH₂), 57.57 (CH₃), 52.61

(CH), 35.03 (CH₂), 18.56 (CH₃), 16.72 (CH₃); IR (Neat, cm⁻¹) 3052 (s), 2984 (s), 1661 (m), 1082 (s), 1075 (s), 733 (s), 703 (s); HRMS (ESI) calcd for C₃₁H₃₄O₃D₂Sn+H⁺ 575.1886, found 575.1883.

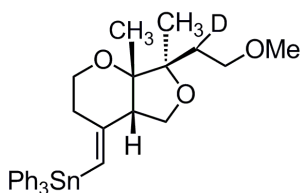


94m. Clear, light yellow oil (44% yield, 1.00:0.24 dr); R_f = 0.47 (hexanes-ethyl acetate, 2 x 4:1); ¹H NMR (CDCl₃) 7.64-7.44 (m, 6H), 7.38-7.33 (m, 9H), 5.92 (s, 1H), 3.94 (t, *J* = 9.2 Hz, 1H), 3.87 (t, *J* = 8.8 Hz, 1H), 3.77 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.48 (td, *J* = 12.2, 2.4 Hz, 1H), 3.34 (s, 3H), 3.15 (t, *J* = 9.2 Hz, 1H), 2.54 (tdd, *J* = 12.8, 6.2, 1.0 Hz, 1H), 2.02 (dt, *J* = 13.1, 1.0 Hz, 1H), 1.70 (s, 1H), 1.64 (s, 1H), 1.21 (s, 3H), 1.15 (s, 3H); ¹³C NMR (CDCl₃) 154.46 (C), 138.97 (C), 136.99 (CH), 129.26 (CH), 128.85 (CH), 122.72 (CH), 87.67 (C), 84.33 (C), 68.37 (CH₂), 62.39 (CH₂), 58.88 (CH₃), 56.20 (CH), 36.22 (CH₂), 33.41 (CH₂), 17.79 (CH₃), 14.77 (CH₃); IR (Neat, cm⁻¹) 3058 (m), 2916 (s), 1602 (m), 1093 (m), 1074 (s), 728 (s), 698 (s); HRMS (ESI) calcd for C₃₁H₃₄O₃D₂Sn+H⁺ 575.1886, found 575.1893.



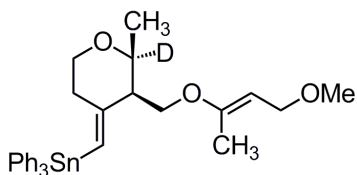
95m. Clear, light yellow oil (39% yield, 1.00:0.05 dr); R_f = 0.51 (hexanes-ethyl acetate, 2 x 4:1); ¹H NMR ((CD₃)₂CO) 7.71-7.52 (m, 6H), 7.44-7.37 (m, 9H), 5.95 (s, 1H), 4.69 (s, 1H), 4.06 (dd, *J* = 10.0, 6.5 Hz, 1H), 3.88 (dd, *J* = 10.0, 8.0 Hz, 1H), 3.84 (td, *J* = 5.7, 2.1 Hz, 1H), 3.73 (qd, *J* = 6.6, 2.7 Hz, 1H), 3.30 (td, *J* = 11.5, 2.8 Hz, 1H), 3.21 (s, 3H), 2.87 (td, *J* = 8.0, 2.5 Hz, 1H), 2.41 (tdd, *J* = 11.7, 5.7, 1.0 Hz, 1H), 2.14 (tdd, *J* = 12.6,

5.7, 1.0 Hz), 1.82 (d, $J = 0.8$ Hz, 3H), 1.21 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR ((CD_3) $_2\text{CO}$) 159.99 (C), 157.74 (C), 139.91 (C), 137.54 (CH), 129.87 (CH), 129.51 (CH), 118.65 (CH), 95.03 (CH), 76.85 (CH), 68.81 (CH_2), 64.76 (CH_2), 56.82 (CH_3), 53.38 (CH), 35.79 (CH_2), 18.56 (CH_3), 16.72 (CH_3); IR (Neat, cm^{-1}) 3058 (s), 2918 (s), 1653 (m), 1093 (s), 1071 (s), 728 (s), 698 (s); HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{34}\text{O}_3\text{D}_2\text{Sn}+\text{Na}^+$ 597.1705, found 597.1696.



94n. Clear, light yellow oil (36% yield, 1.00:0.30 dr); $R_f = 0.28$ (hexanes-ethyl acetate, 2 x 4:1); ^1H NMR (CDCl_3) 7.58-7.55 (m, 6H, H10, minor), 7.54-7.48 (m, 6H, H10, major), 7.38-7.34 (m, 9H, H10, major/minor), 5.98 (s, 1H, H1, minor), 5.92 (s, 1H, H1, major), 3.93 (t, $J = 9.2$ Hz, 1H, H7, major/minor), 3.87 (t, $J = 8.8$ Hz, 1H, H7, major/minor), 3.77 (dd, $J = 11.4, 6.0$ Hz, 1H, H4), 3.55 (d, $J = 7.8$ Hz, 2H, H11), 3.47 (td, $J = 12.0, 2.6$ Hz, 1H, H4, major/minor), 3.34 (s, 3H, H12, major), 3.26 (s, 3H, H12, minor), 3.14 (t, $J = 9.2$ Hz, 1H, H6, major), 3.09 (t, $J = 9.2$ Hz, 1H, H6, minor), 2.74 (tdd, $J = 13.5, 6.0, 1.7$ Hz, 1H, H3, minor), 2.74 (tdd, $J = 13.5, 6.3, 1.0$ Hz, 1H, H3, major), 2.22 (d, $J = 13.7$ Hz, 1H, H3, minor), 2.02 (d, $J = 14.1$ Hz, 1H, H3, major), 1.70 (t, $J = 7.2$ Hz, 0.5H, H9, major/minor), 1.61 (t, $J = 7.8$ Hz, 0.5H, H9, major/minor), 1.24 (s, 3H, H14, minor), 1.20 (s, 3H, H14, minor), 1.15 (s, 3H, H13, major), 1.09 (s, 3H, H13, minor); ^1D NMR (CHCl_3) 1.67 (s, br); ^{13}C NMR (CDCl_3) 155.14 (C, C2, minor), 154.46 (C, C2, major), 138.97 (C, C10, major), 138.92 (C, C10, minor), 137.06 (CH, C10, minor), 137.00 (CH, C10, major), 129.36 (CH, C10, minor), 129.26 (CH, C10, major), 128.94 (CH, C10, minor), 128.85 (CH, C10, major), 122.72 (CH, C1, major), 122.42 (CH, C1, minor), 87.61 (C, C5), 84.33 (C, C8), 69.30 (CH_2 , C11, major), 69.01 (CH_2 , C11, minor), 68.37 (CH_2 , C7, major), 67.48 (CH_2 , C7, minor), 62.66 (CH_2 , C4, minor), 62.40 (CH_2 , C4, major), 58.96 (CH_3 , C12, major), 58.76 (CH_3 , C12, minor), 56.20 (CH, C6, major), 53.16

(CH, C6, minor), 33.41 (CHD, C9), 29.92 (CH₂, C3), 17.76 (CH₃, C14, major), 17.55 (CH₃, C14, minor), 14.76 (CH₃, C13, major), 14.43 (CH₃, C13, minor); IR (Neat, cm⁻¹) 3051 (s), 2934 (s), 1606 (s), 1074 (s), 1041 (s), 732 (s), 699 (s); HRMS (ESI) calcd for C₃₁H₃₅O₃DSn+Na⁺ 596.1624, found 596.1625.



95n. Clear, light yellow oil (40% yield, 1.00:0.17 dr); $R_f = 0.53$ (hexanes-ethyl acetate, 2 x 4:1); ¹H NMR (CDCl₃) 7.66-7.46 (m, 6H), 7.37-7.33 (m, 9H), 5.88 (s, 1H), 4.67 (t, $J = 7.6$ Hz, 1H), 4.00 (dd, $J = 9.7, 6.5$ Hz, 1H), 3.93 (d, $J = 7.6$ Hz, 2H), 3.85 (dd, $J = 9.9, 7.6$ Hz, 2H), 3.33-3.27 (m, 1H), 3.32 (s, 3H), 2.78 (t, $J = 7.2$ Hz, 1H), 2.36 (tdd, $J = 12.8, 6.0, 1.0$ Hz, 1H), 2.05 (dt, $J = 12.8, 2.4$ Hz), 1.85 (s, 3H), 1.21 (s, 3H); ¹D NMR (CHCl₃) 3.72 (s, br); ¹³C NMR (CDCl₃) 158.38 (C), 158.04 (C), 139.26 (C), 137.01 (CH), 129.15 (CH), 128.76 (CH), 119.02 (CH), 93.93 (CH), 75.78 (t, $J = 20.7$ Hz, CD), 69.08 (CH₂), 68.54 (CH₂), 64.23 (CH₂), 57.57 (CH₃), 52.65 (CH), 35.05 (CH₂), 18.29 (CH₃), 16.73 (CH₃); IR (Neat, cm⁻¹) 3051 (s), 2933 (s), 1662 (m), 1074 (s), 1041 (s), 735 (s), 700 (s); HRMS (ESI) calcd for C₃₁H₃₅O₃DSn+Na⁺ 596.1624, found 596.1625.

6.0.0 References

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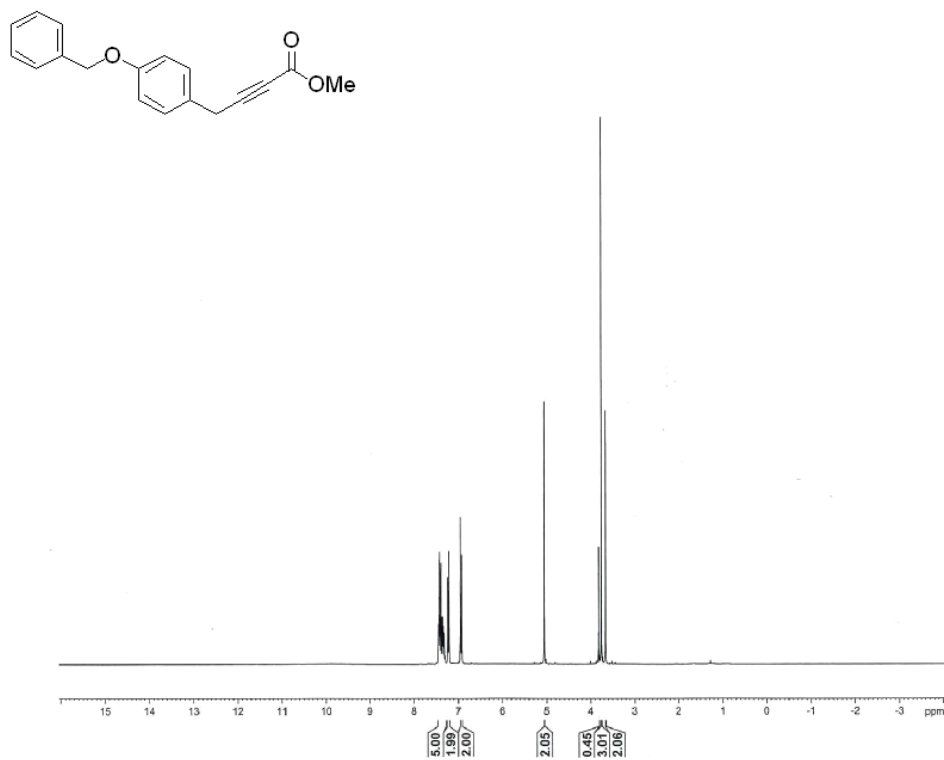
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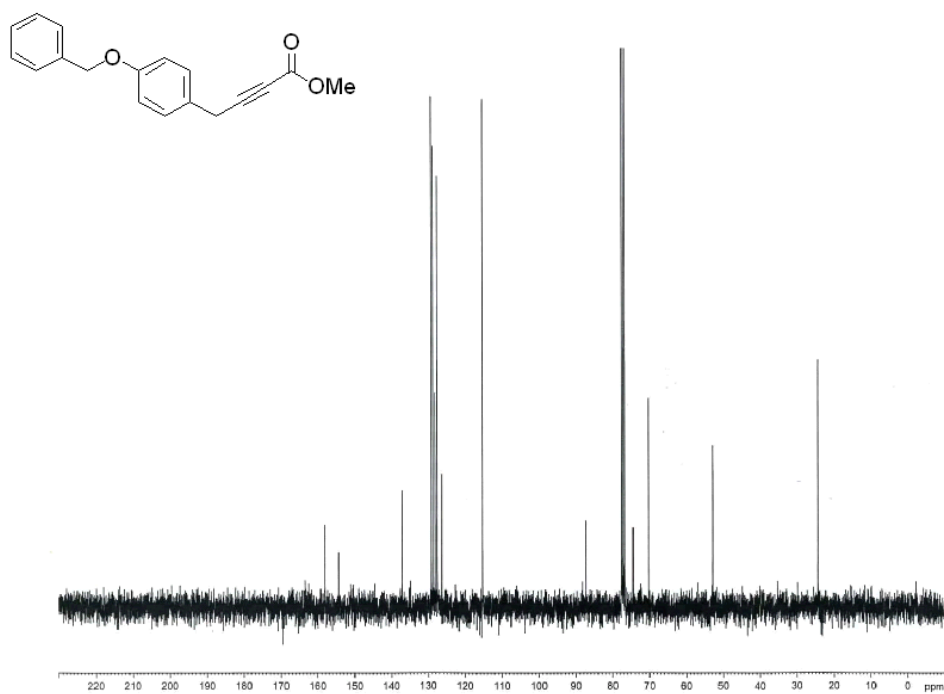
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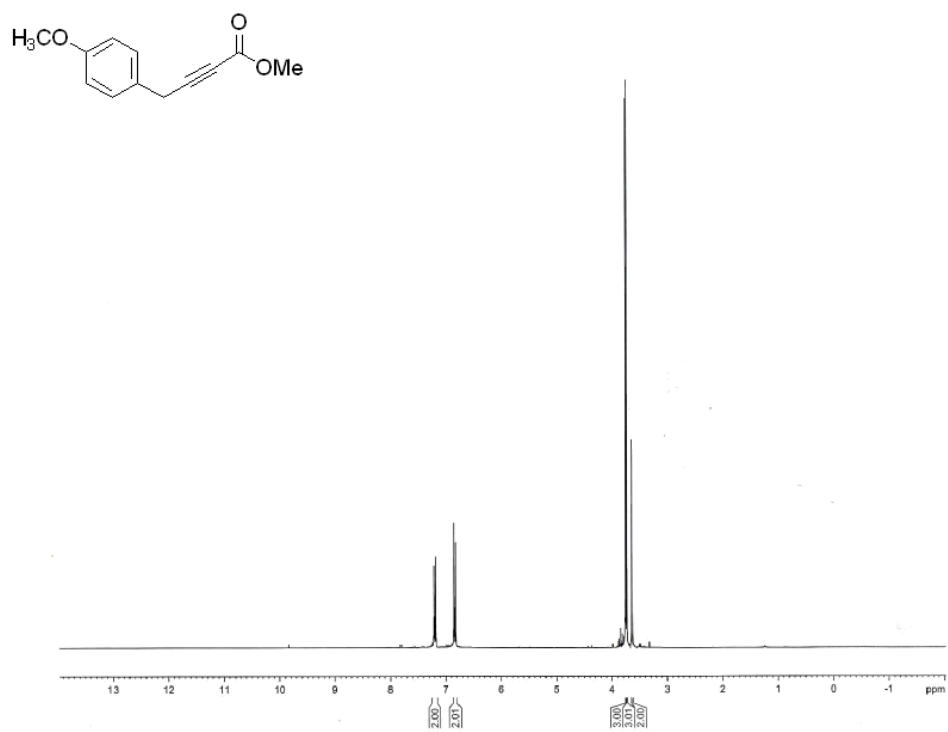
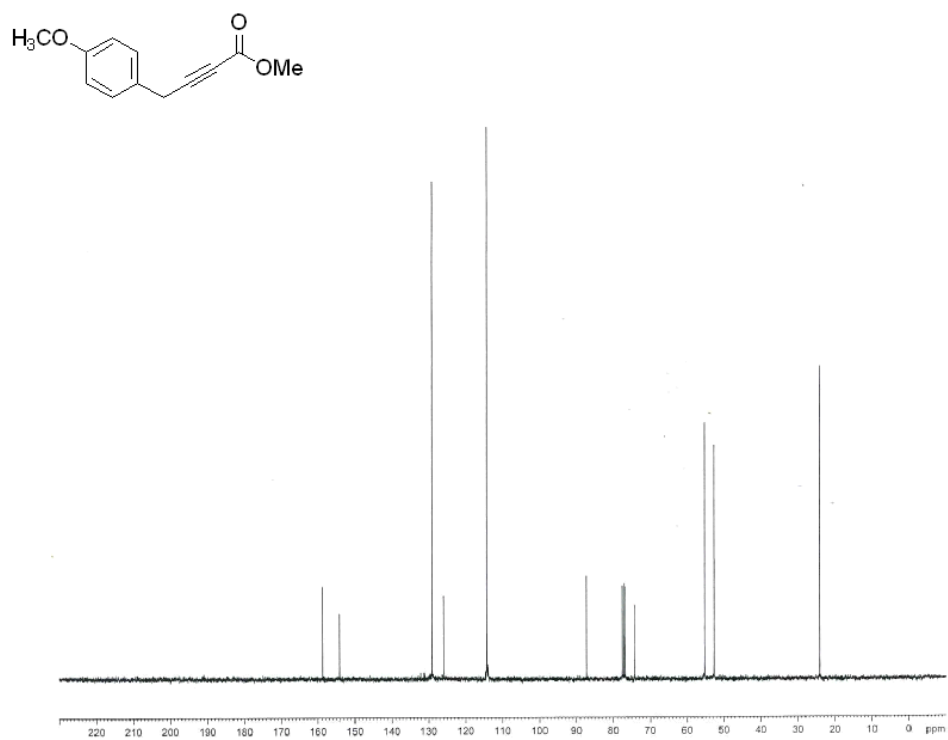
Appendix 1: Chapter 2 Spectral Data

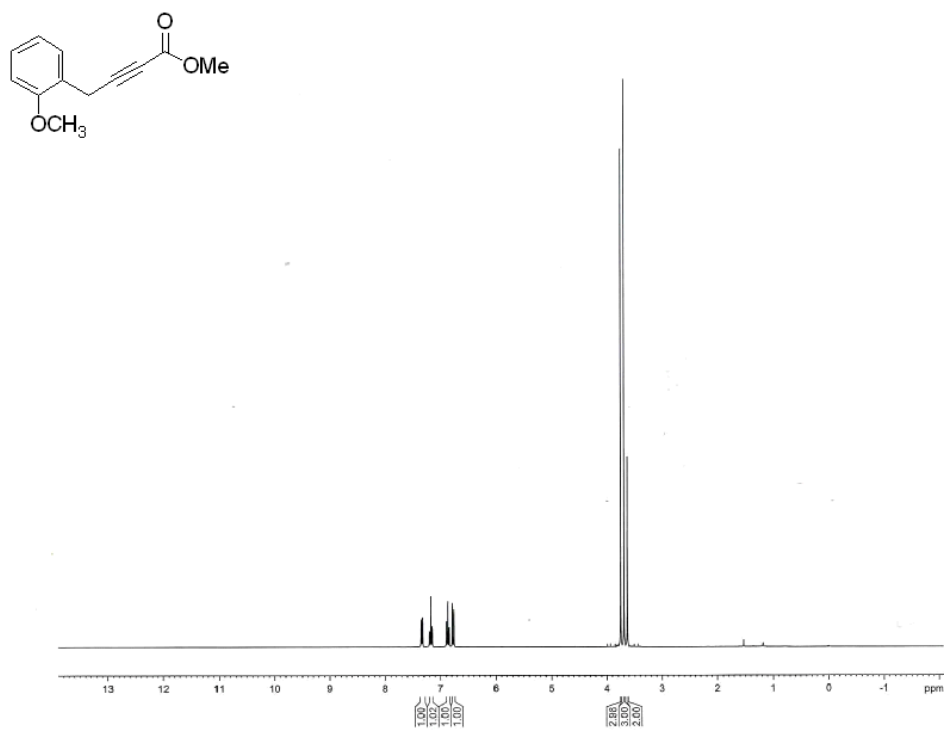
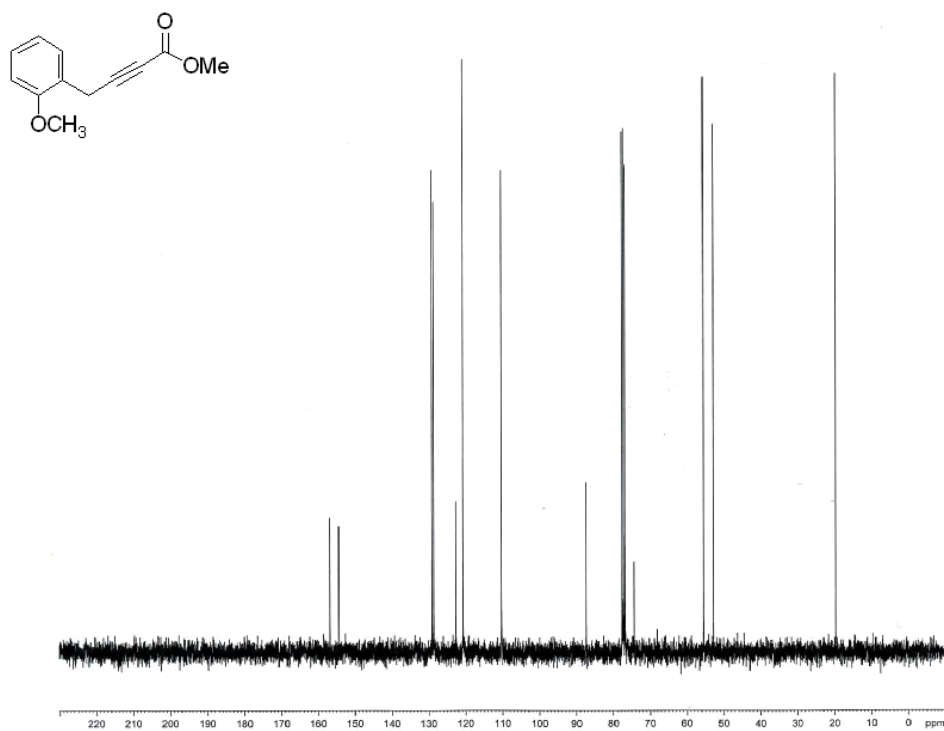
1. ^1H NMR Spectrum for **12a** in CDCl_3

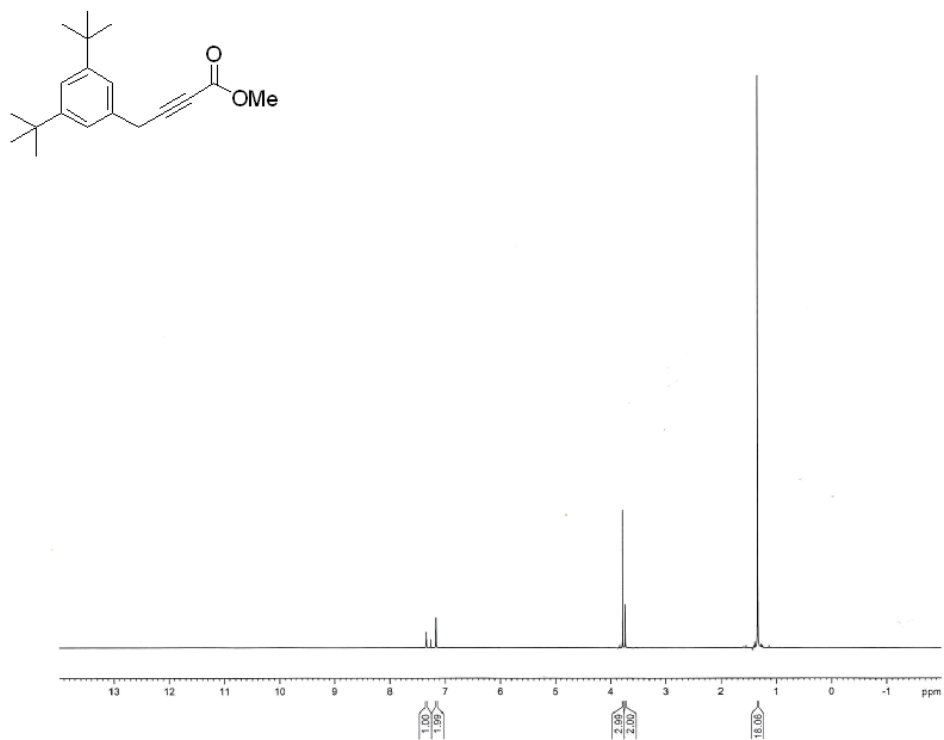
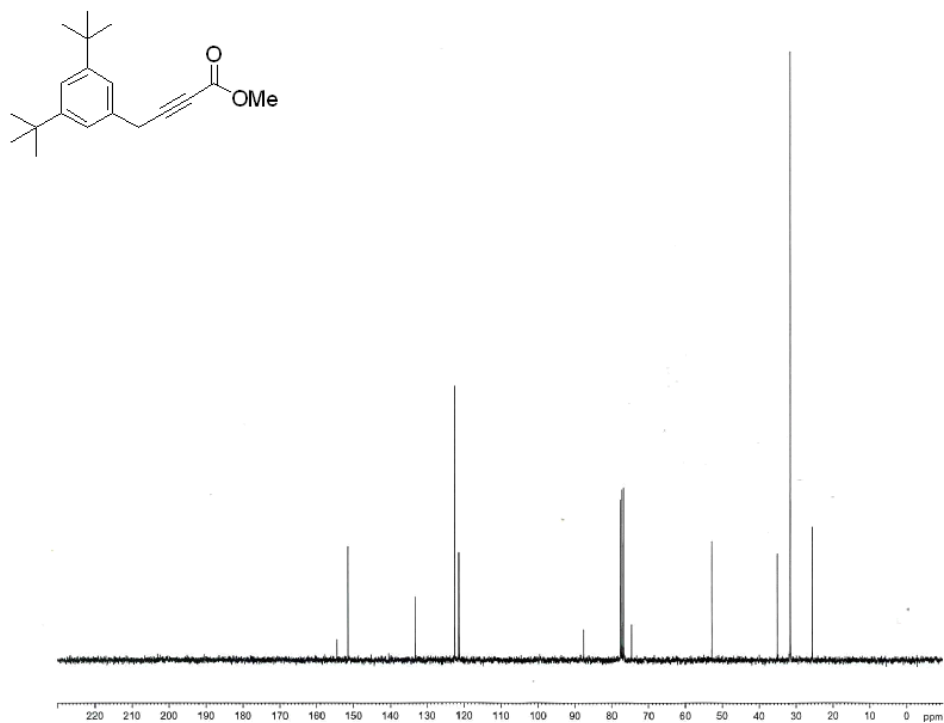


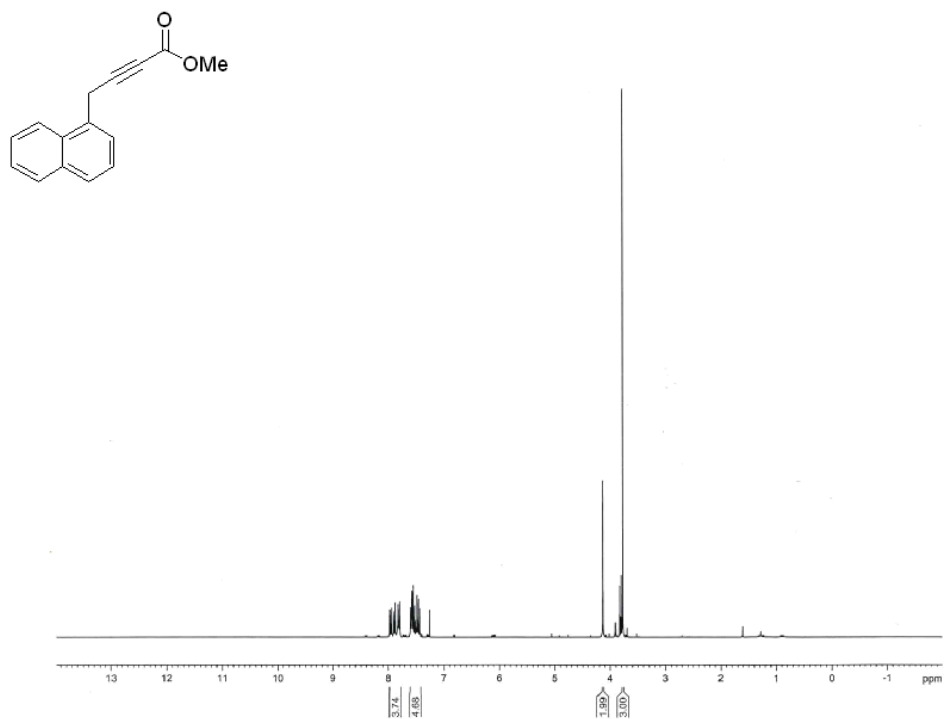
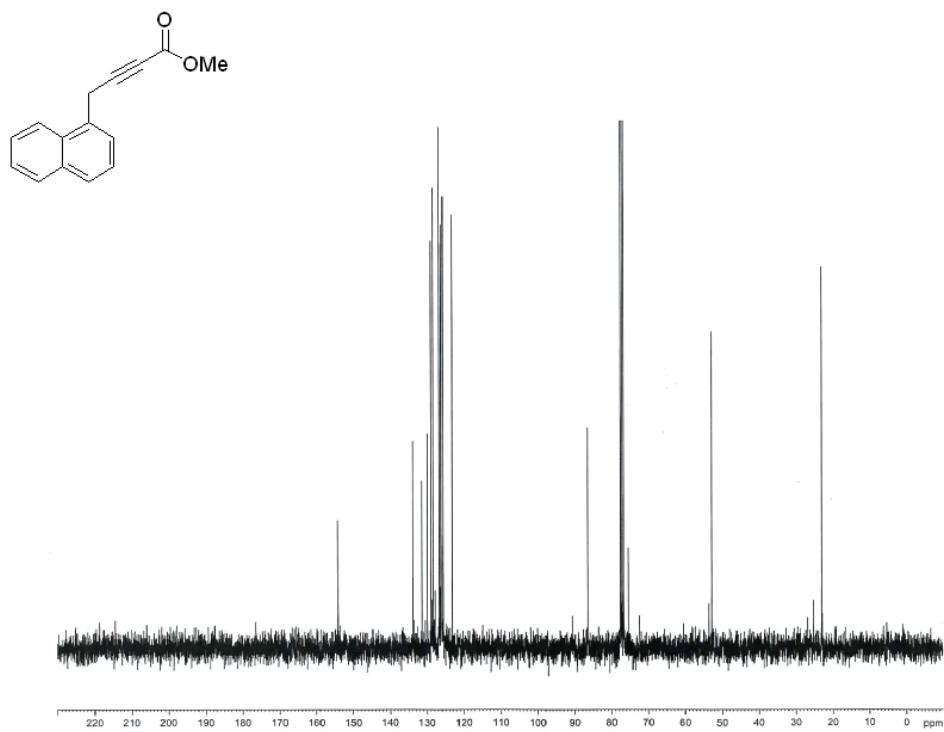
2. ^{13}C NMR Spectrum for **12a** in CDCl_3

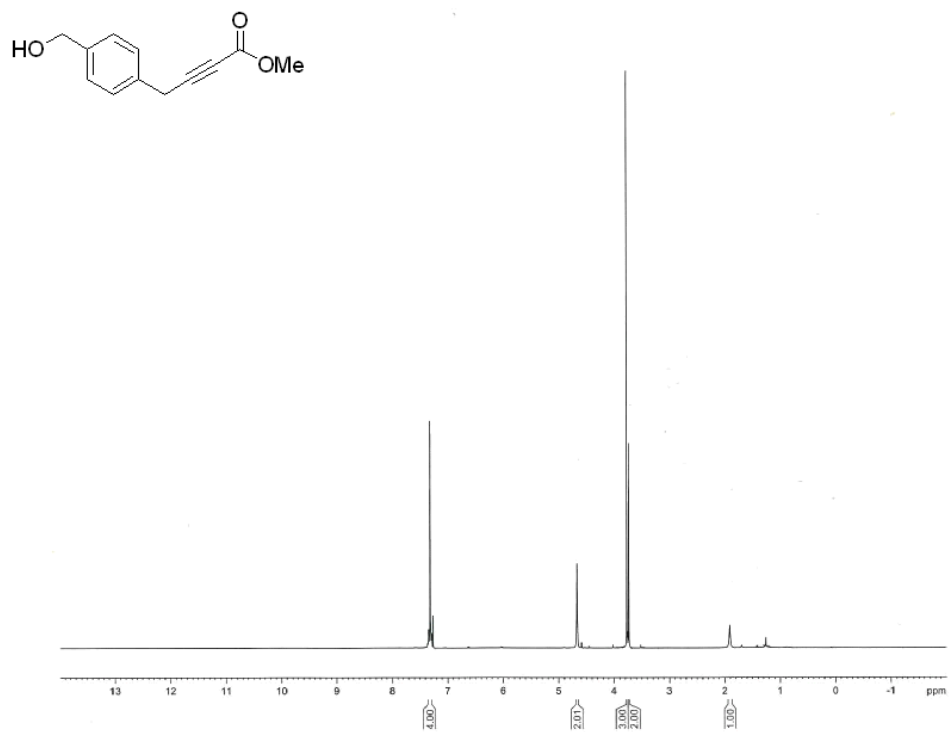
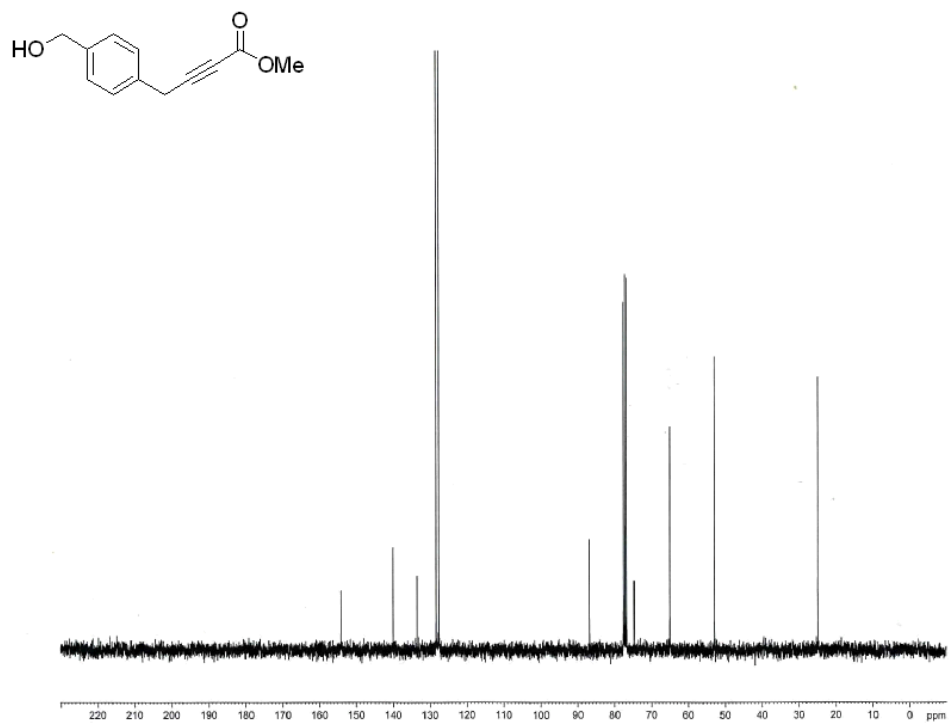


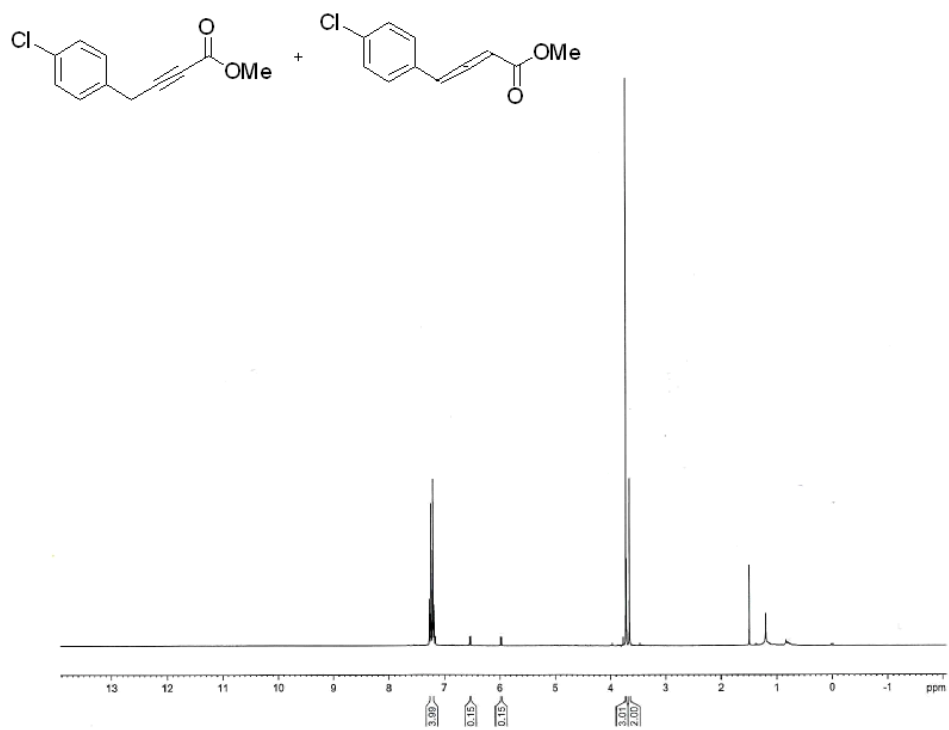
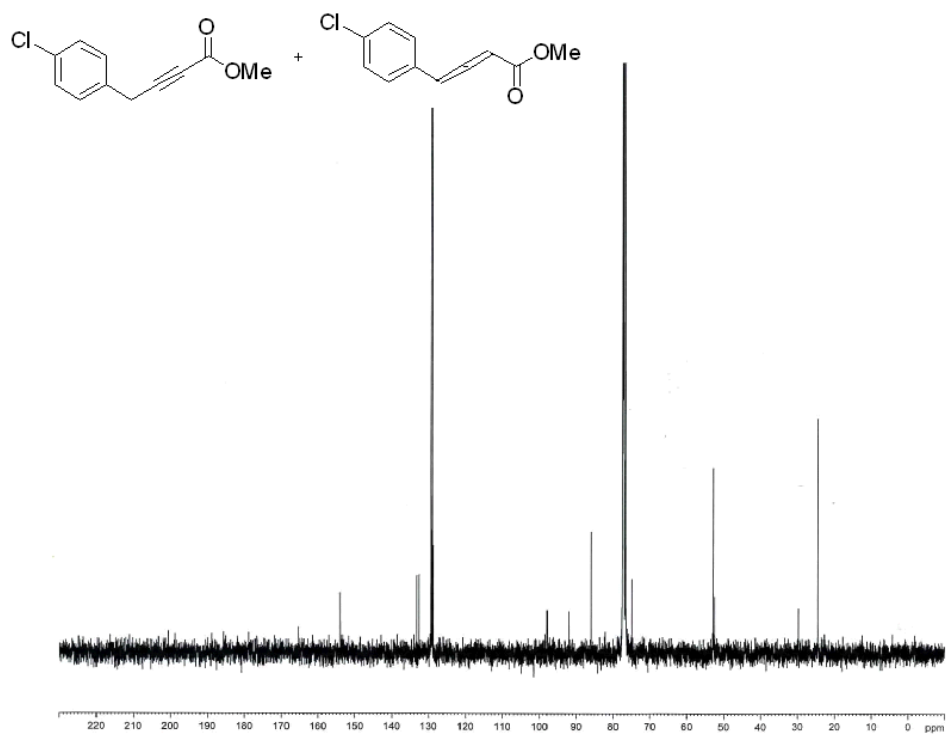
3. ^1H NMR Spectrum for **12b** in CDCl_3 4. ^{13}C NMR Spectrum for **12b** in CDCl_3 

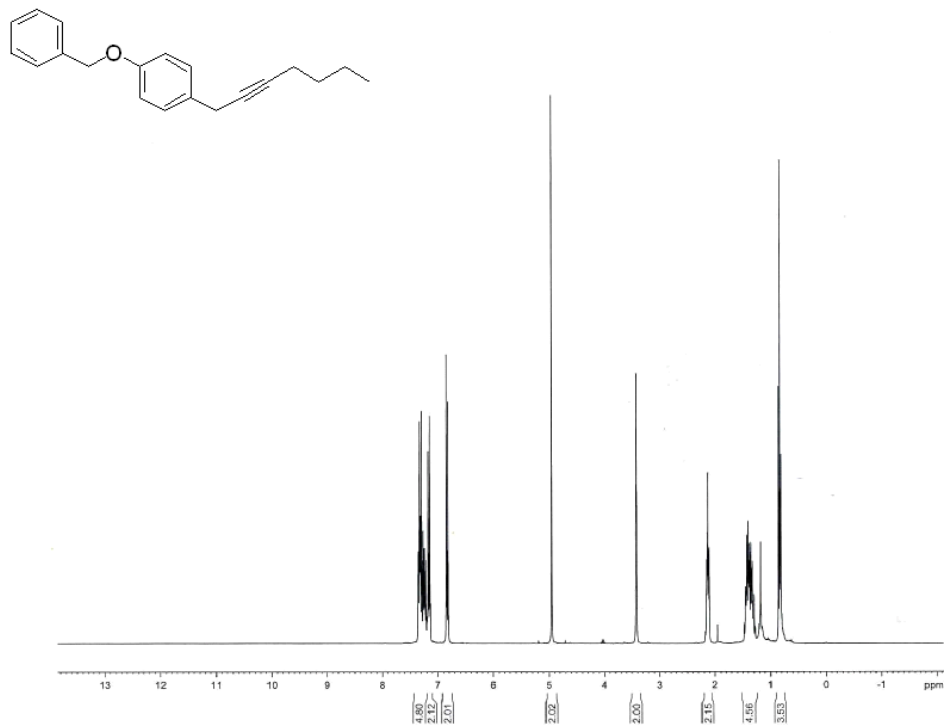
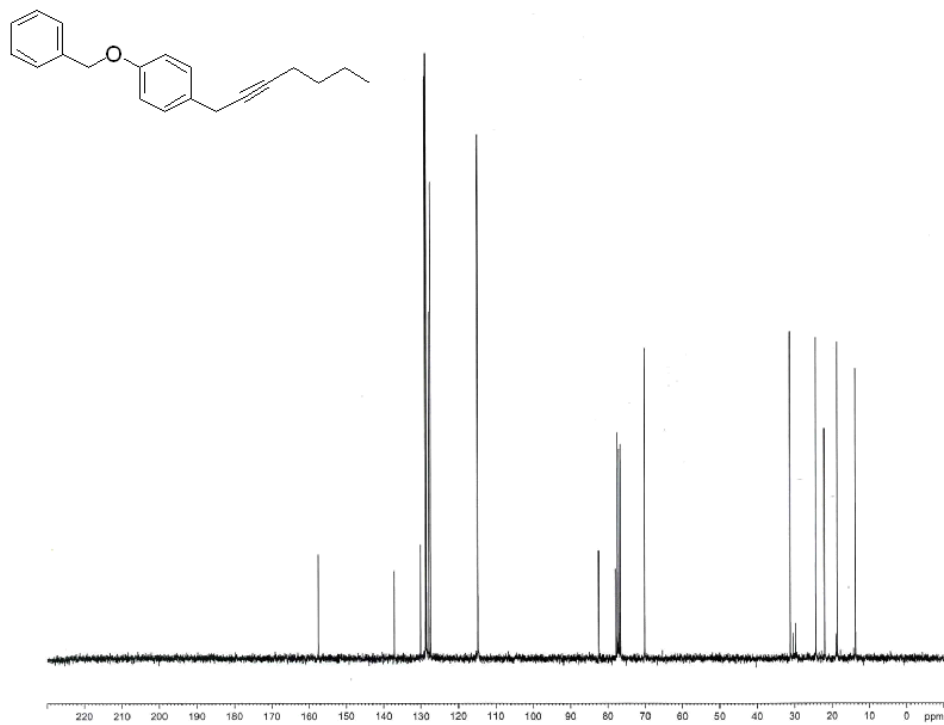
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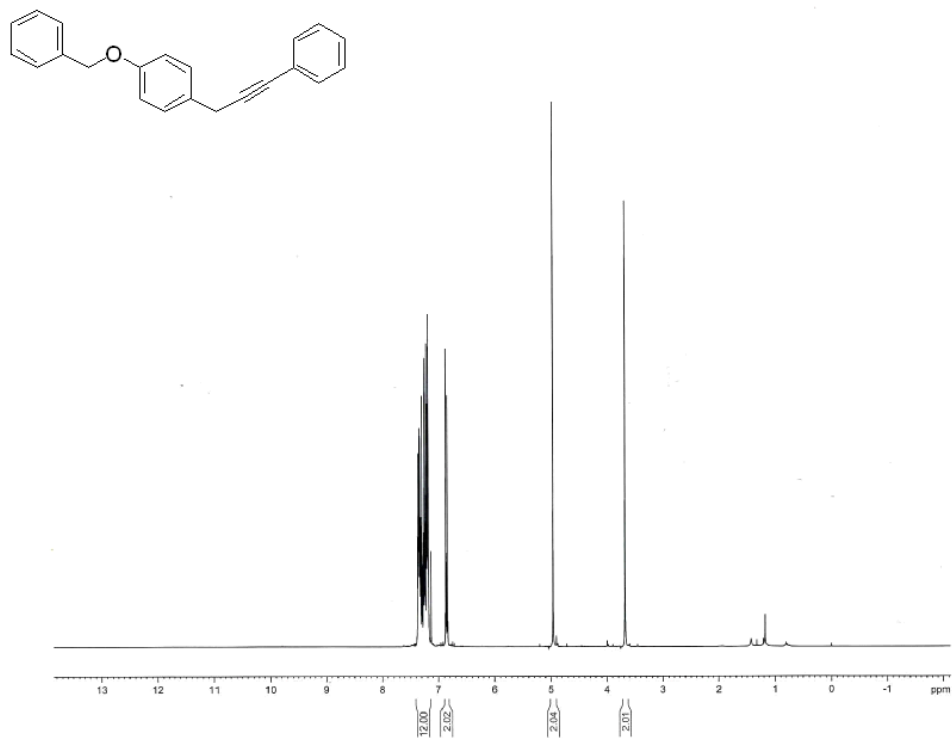
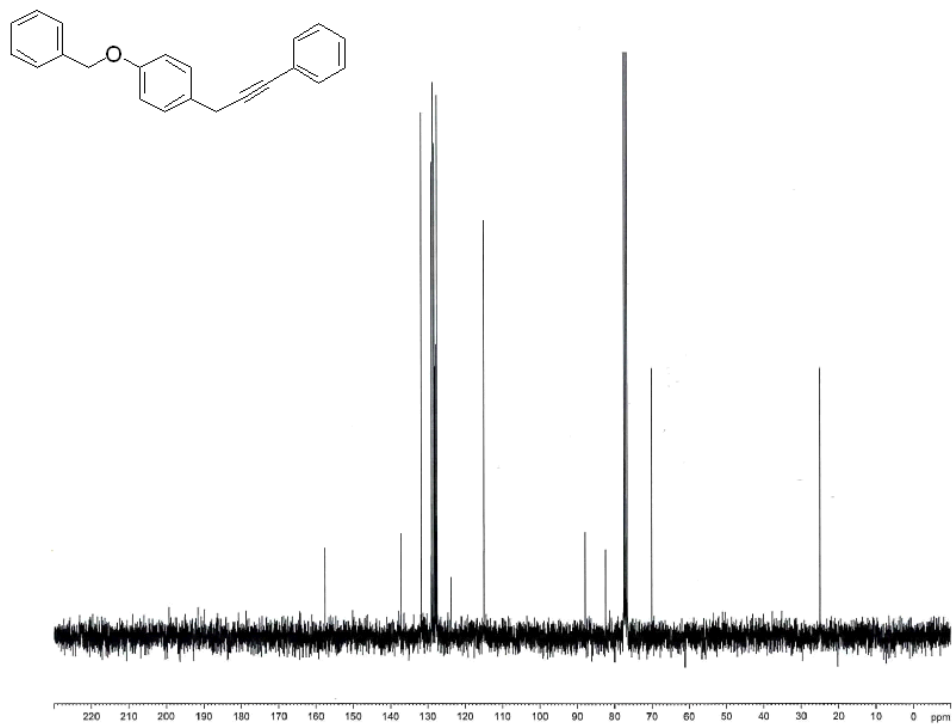
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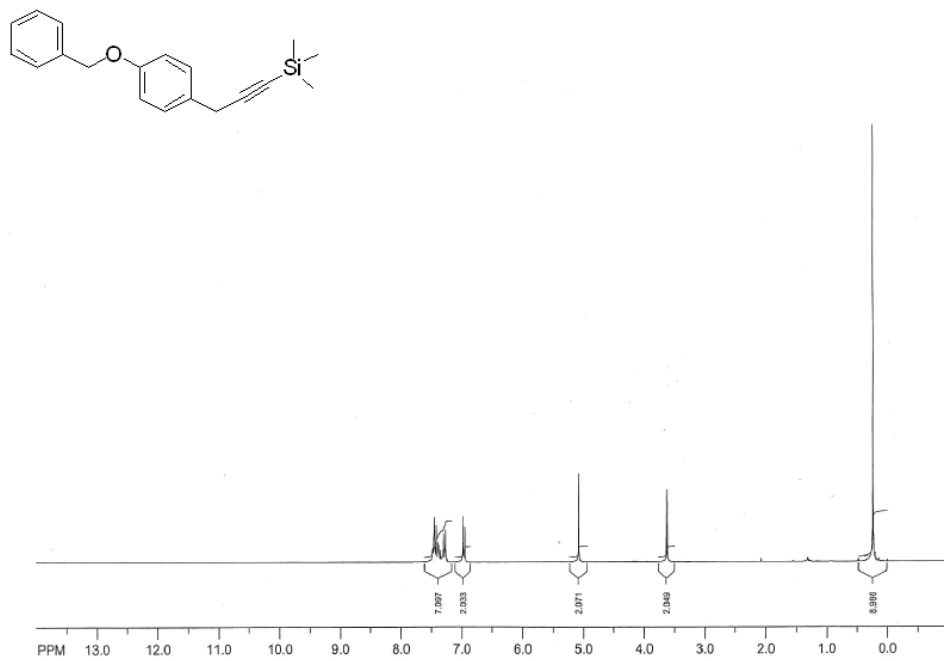
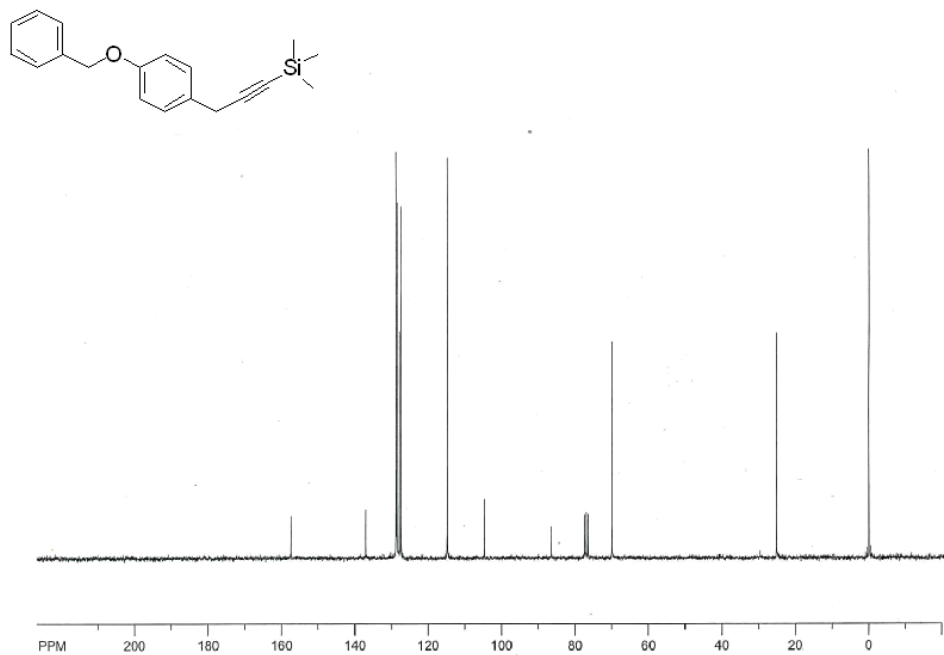
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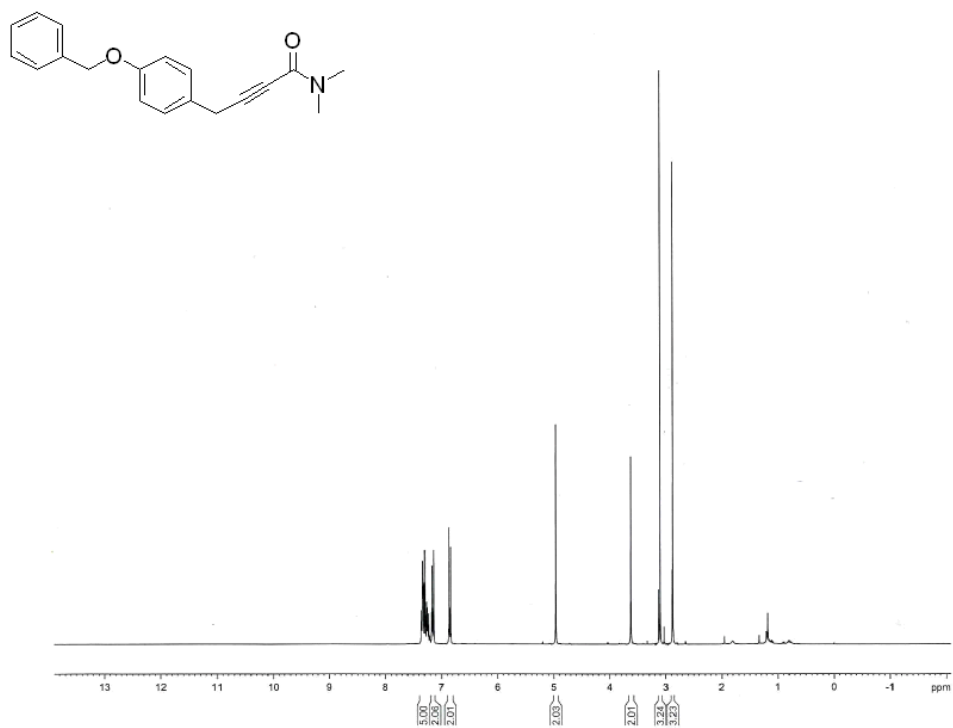
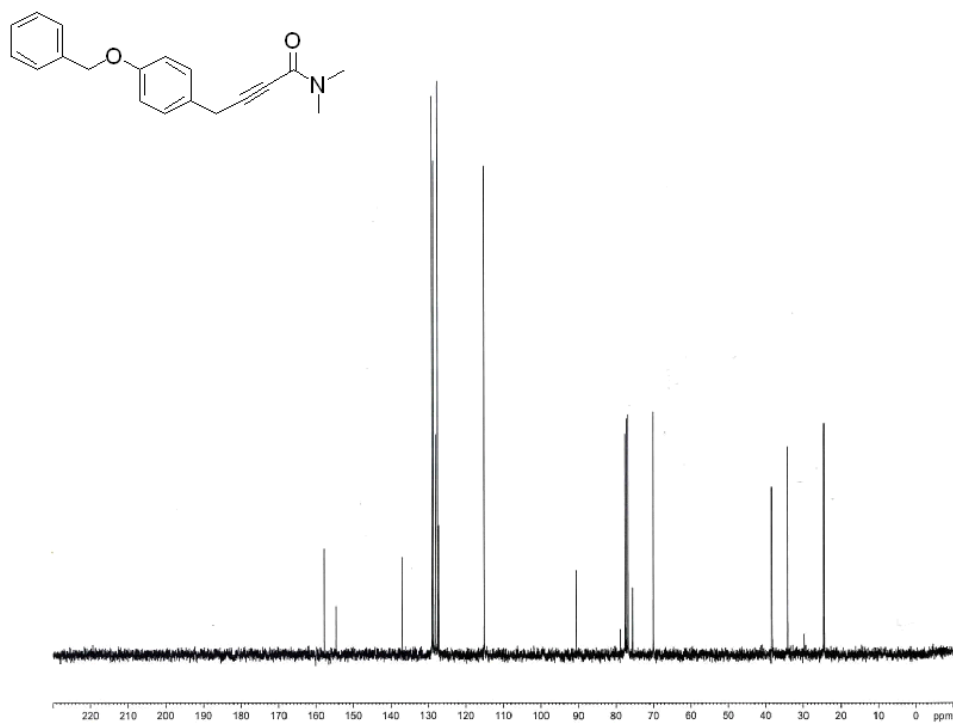
11. ^1H NMR Spectrum for **12f** in CDCl_3 12. ^{13}C NMR Spectrum for **12f** in CDCl_3 

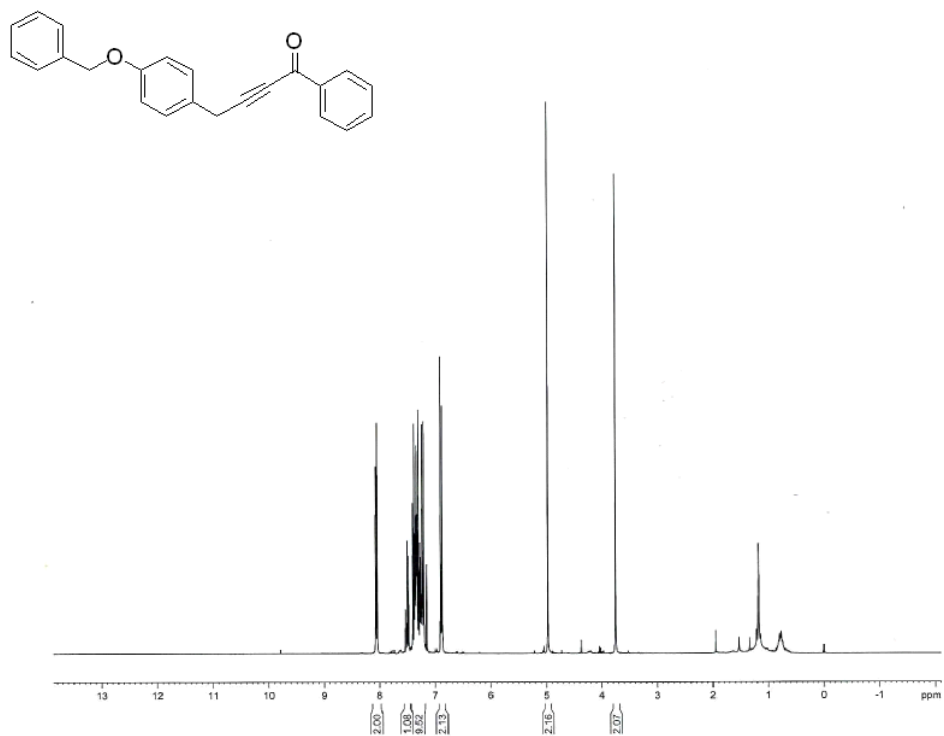
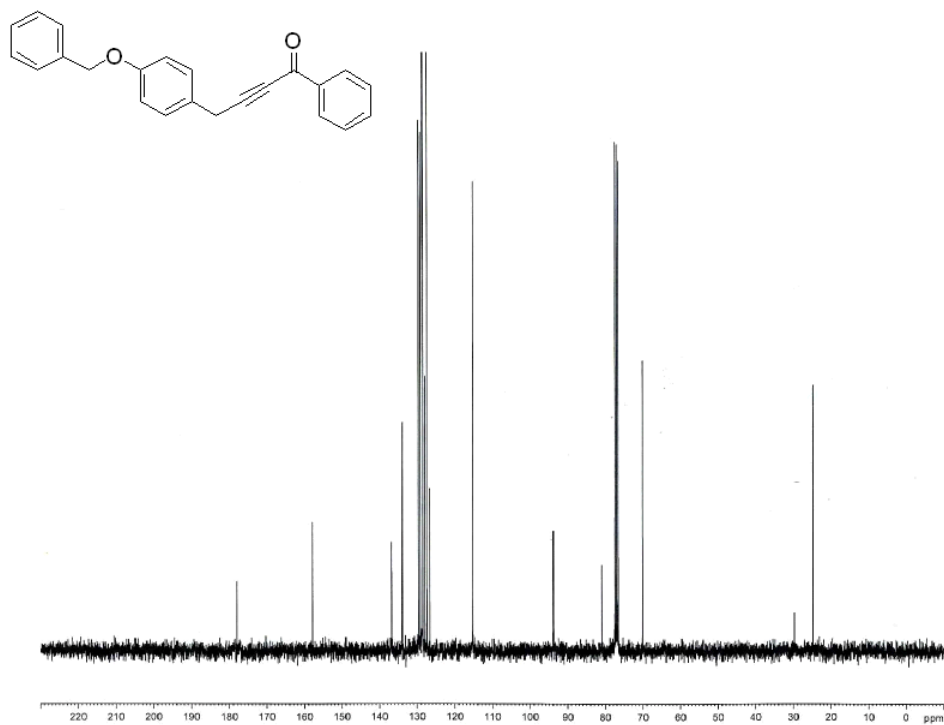
13. ^1H NMR Spectrum for **12g** in CDCl_3 14. ^{13}C NMR Spectrum for **12g** in CDCl_3 

15. ^1H NMR Spectrum for **12j** in CDCl_3 16. ^{13}C NMR Spectrum for **12j** in CDCl_3 

17. ^1H NMR Spectrum for **12k** in CDCl_3 18. ^{13}C NMR Spectrum for **12k** in CDCl_3 

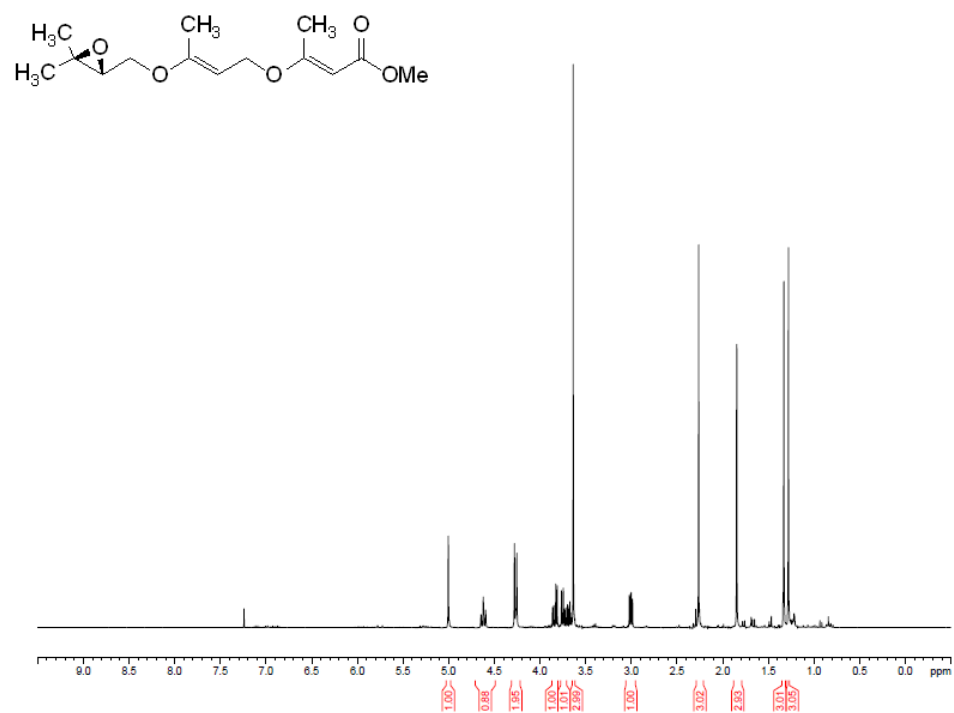
19. ^1H NMR Spectrum for **121** in CDCl_3 20. ^{13}C NMR Spectrum for **121** in CDCl_3 

21. ^1H NMR Spectrum for **12m** in CDCl_3 22. ^{13}C NMR Spectrum for **12m** in CDCl_3 

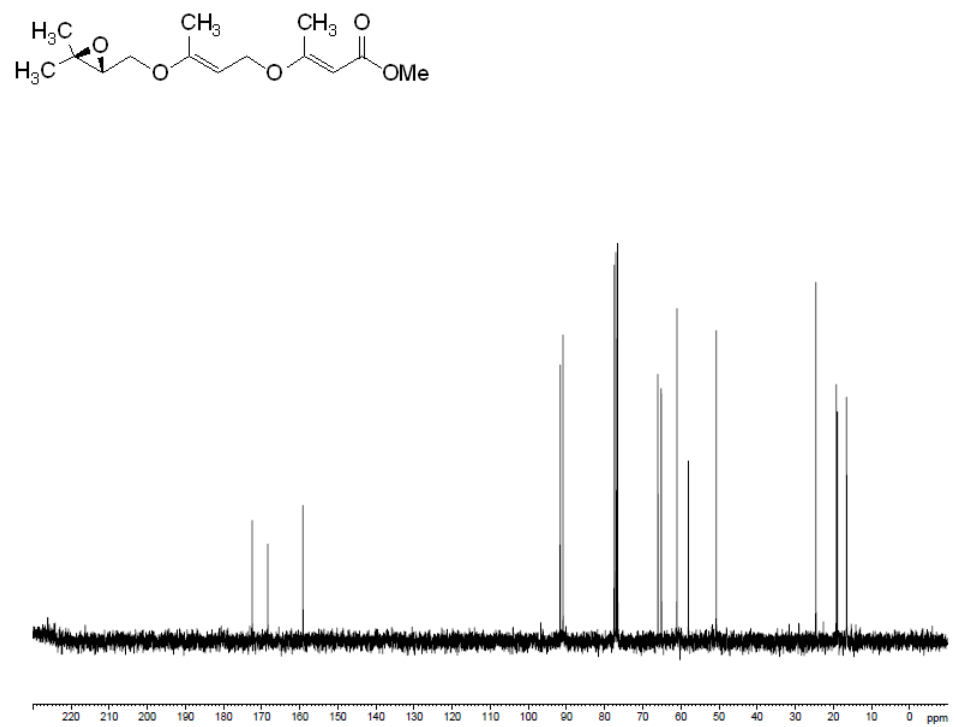
23. ^1H NMR Spectrum for **12n** in CDCl_3 24. ^{13}C NMR Spectrum for **12n** in CDCl_3 

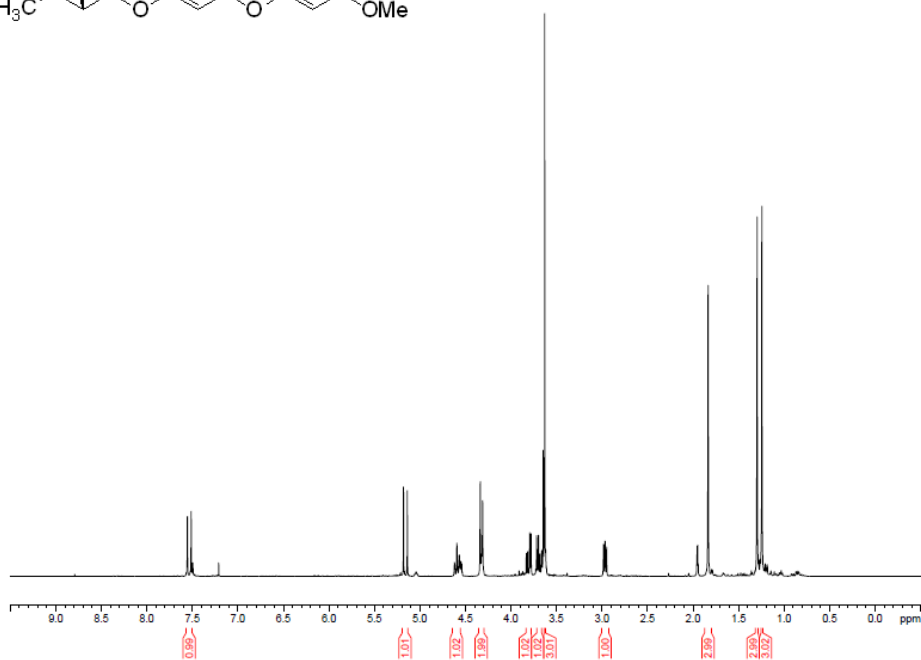
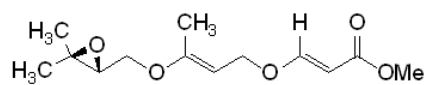
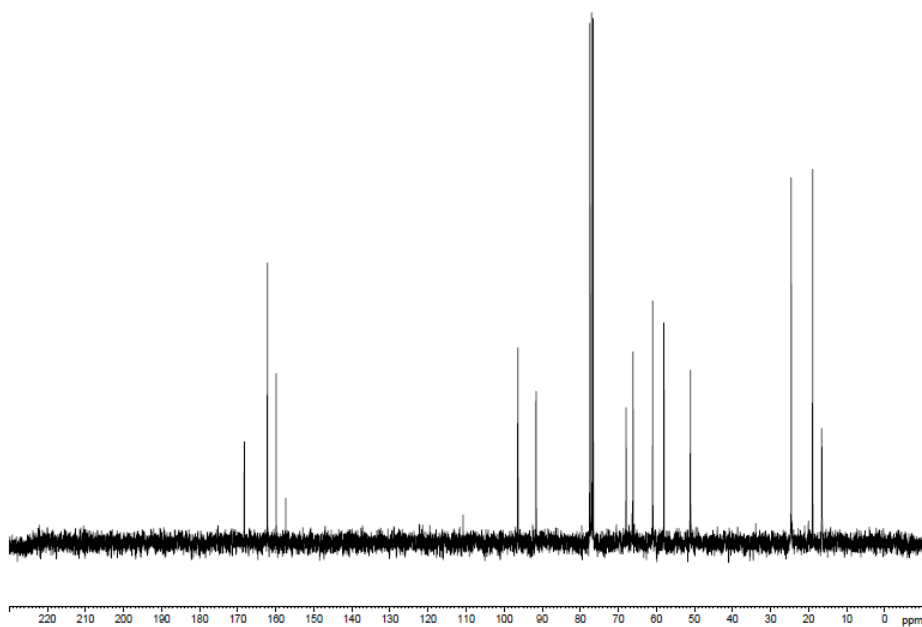
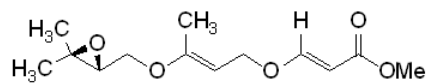
Appendix 2: Chapter 3 Spectral Data

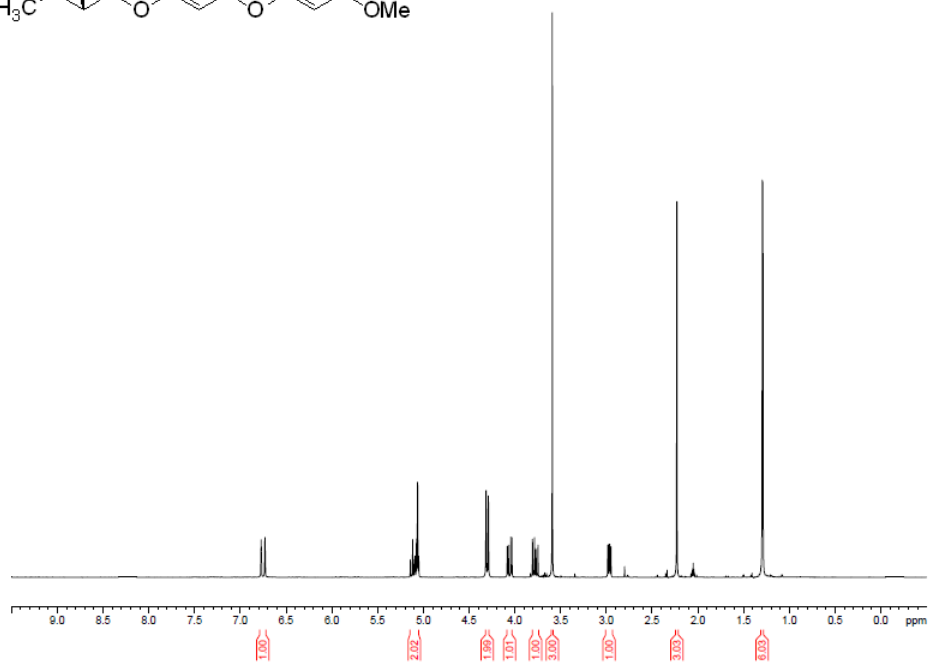
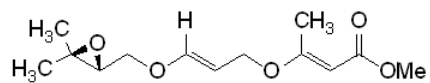
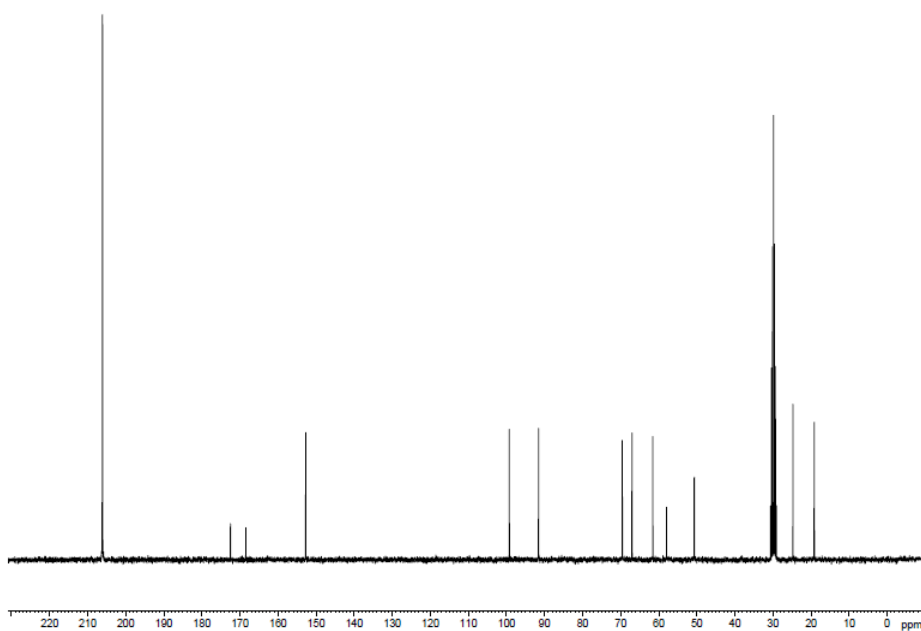
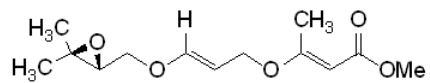
1. ^1H NMR Spectrum for **39a** in CDCl_3

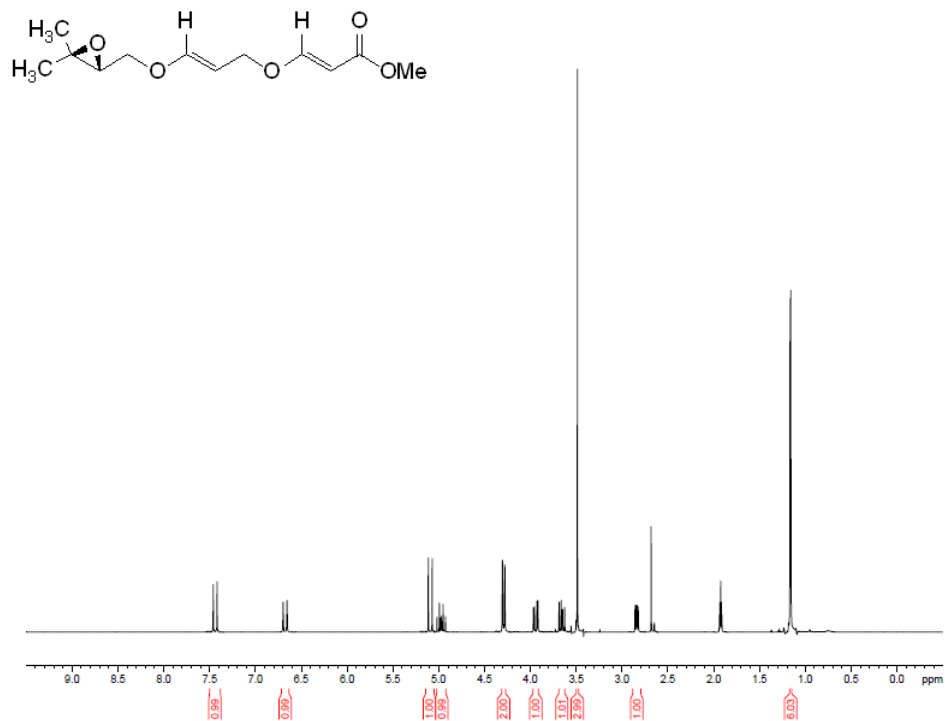
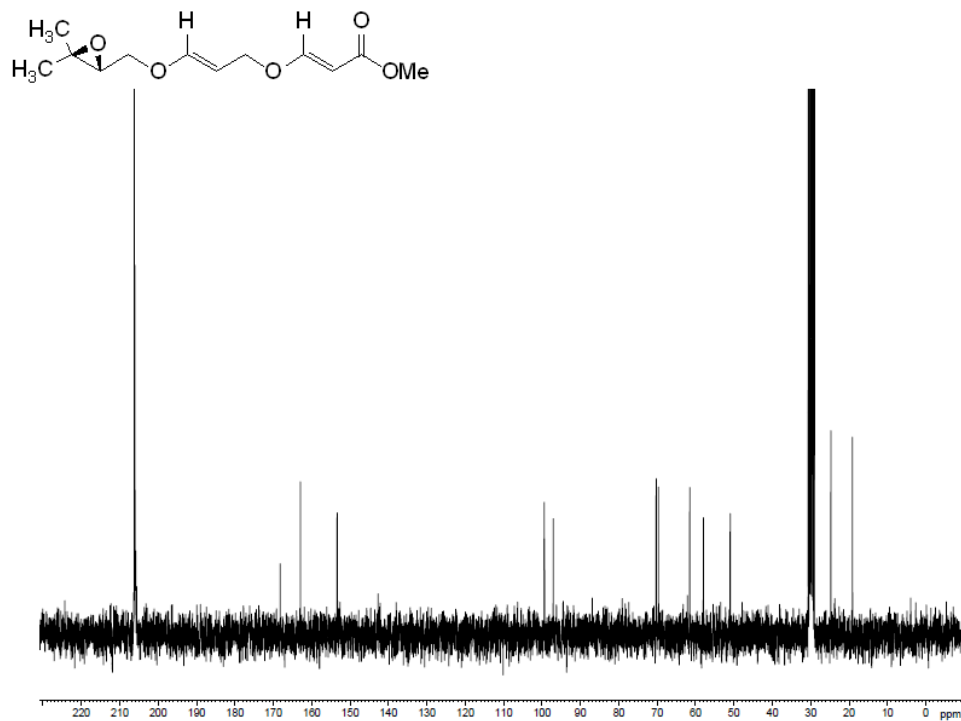


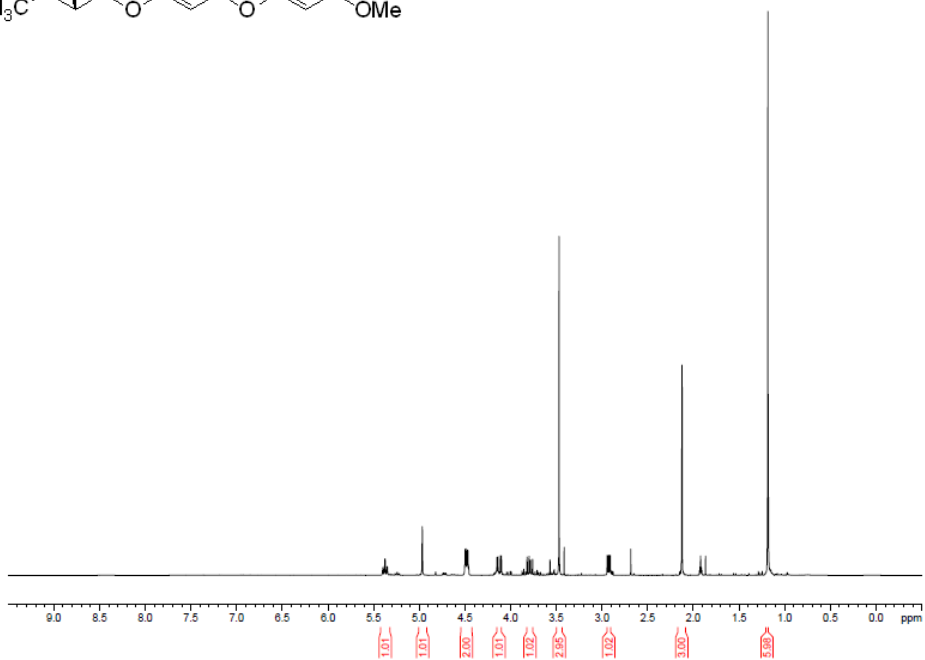
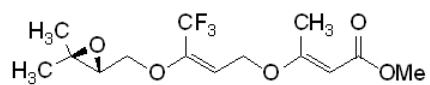
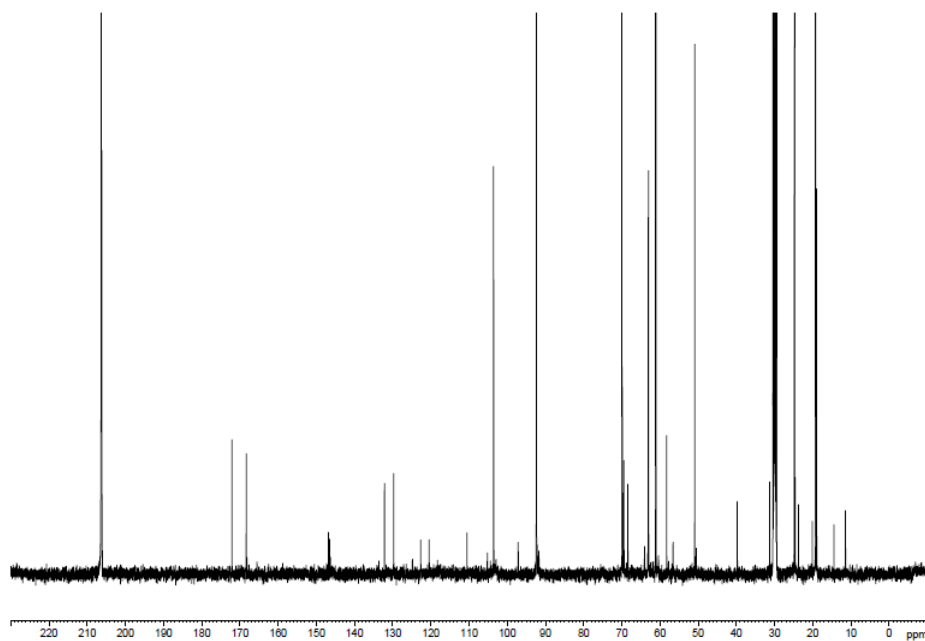
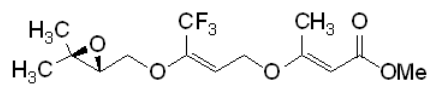
2. ^{13}C NMR Spectrum for **39a** in CDCl_3

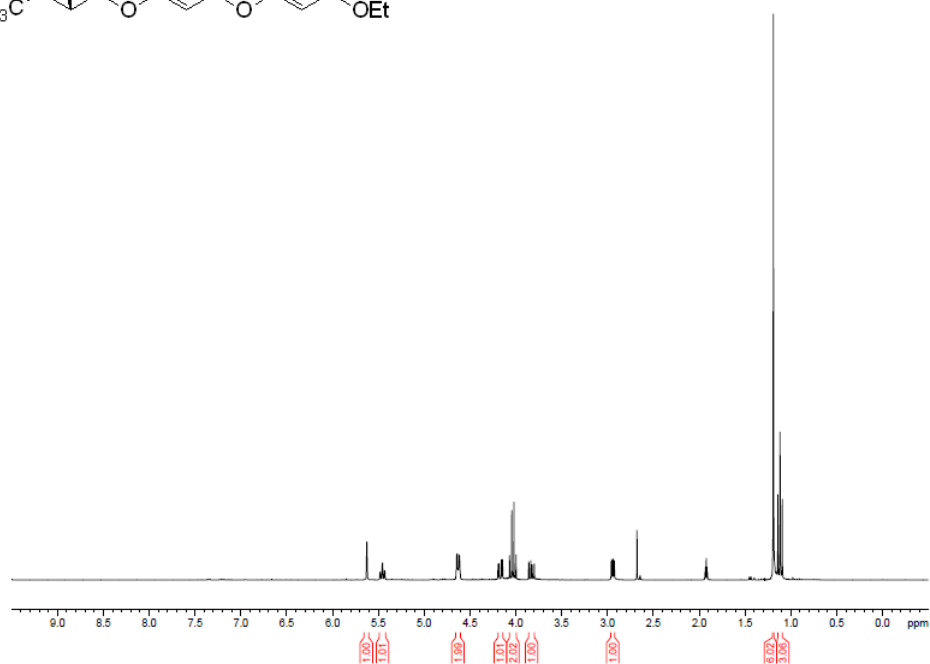
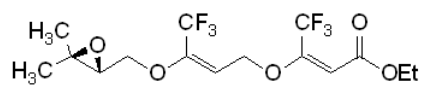
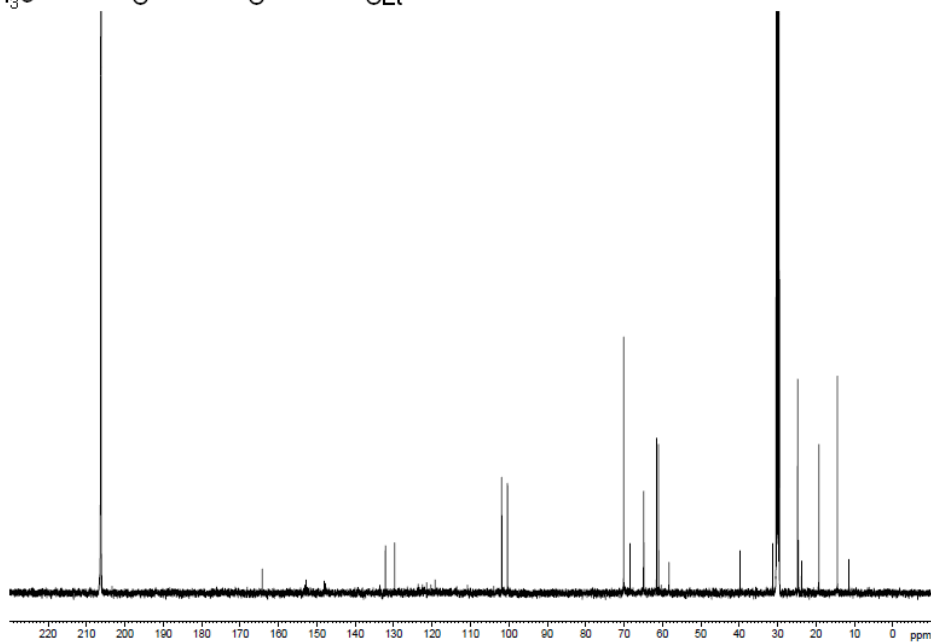
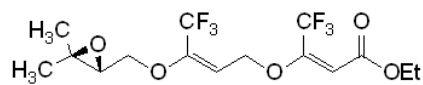


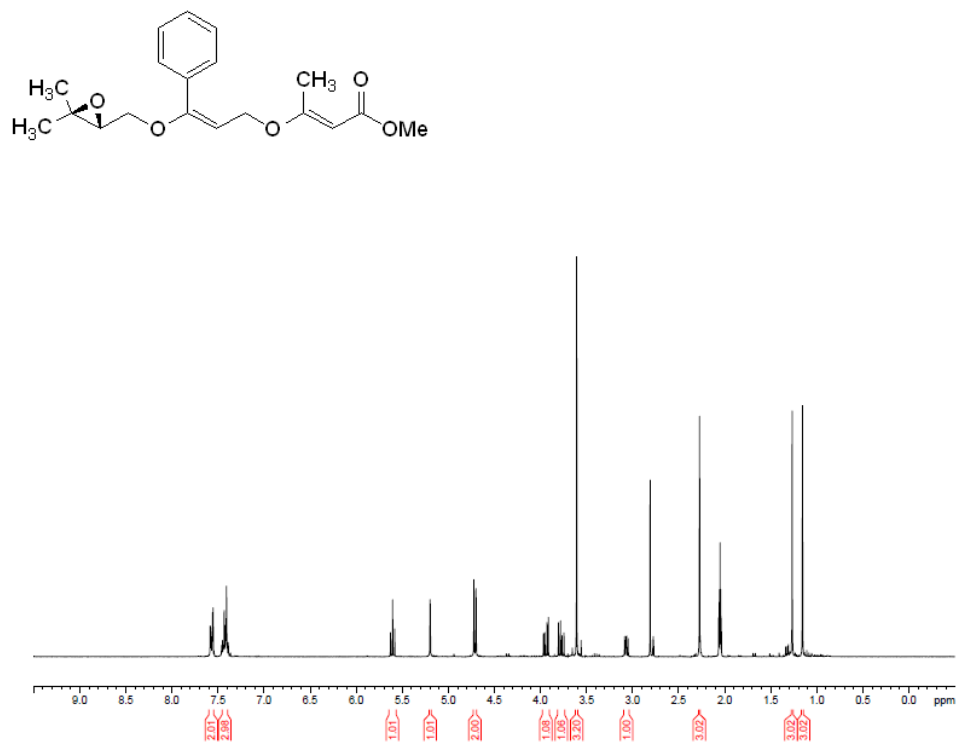
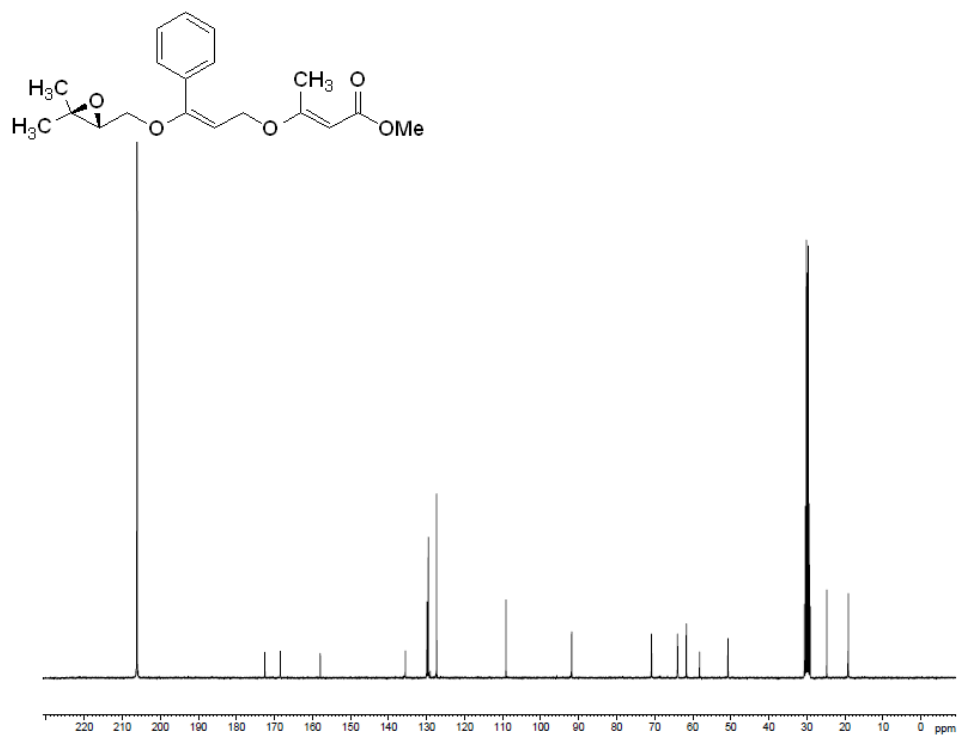
3. ^1H NMR Spectrum for **39b** in CDCl_3 4. ^{13}C NMR Spectrum for **39b** in CDCl_3 

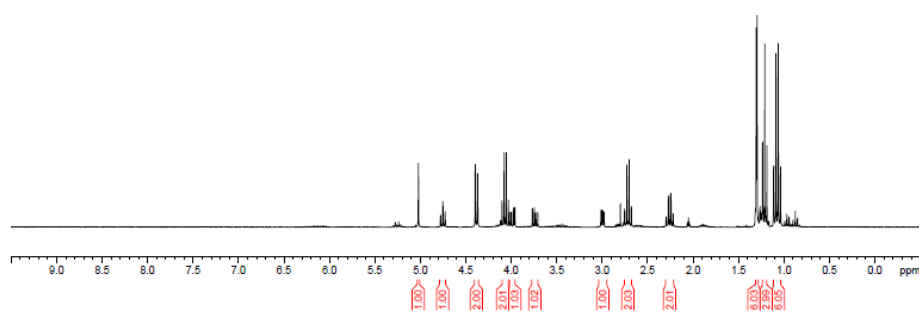
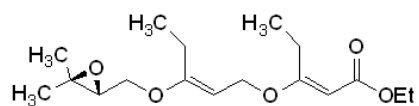
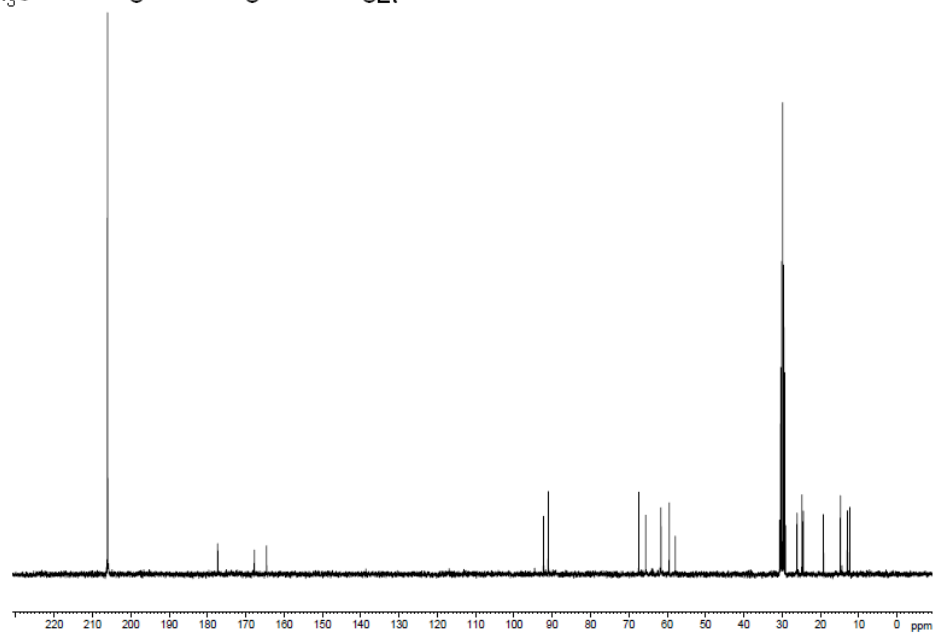
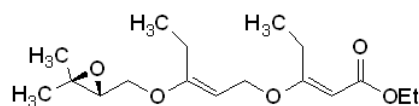
5. ^1H NMR Spectrum for **39e** in $(\text{CD}_3)_2\text{CO}$ 6. ^{13}C NMR Spectrum for **39e** in $(\text{CD}_3)_2\text{CO}$ 

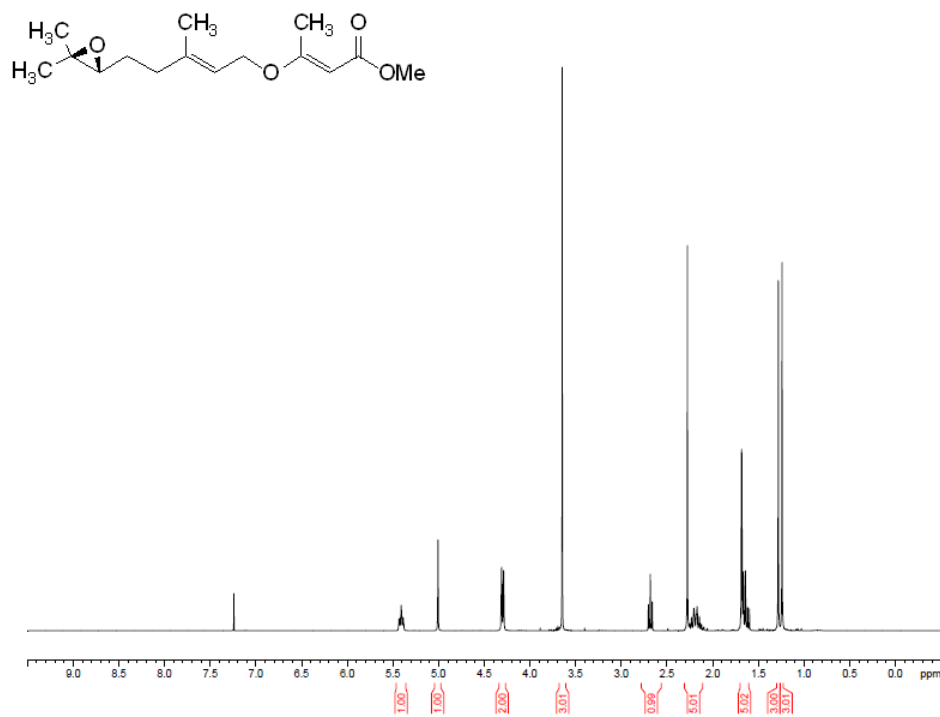
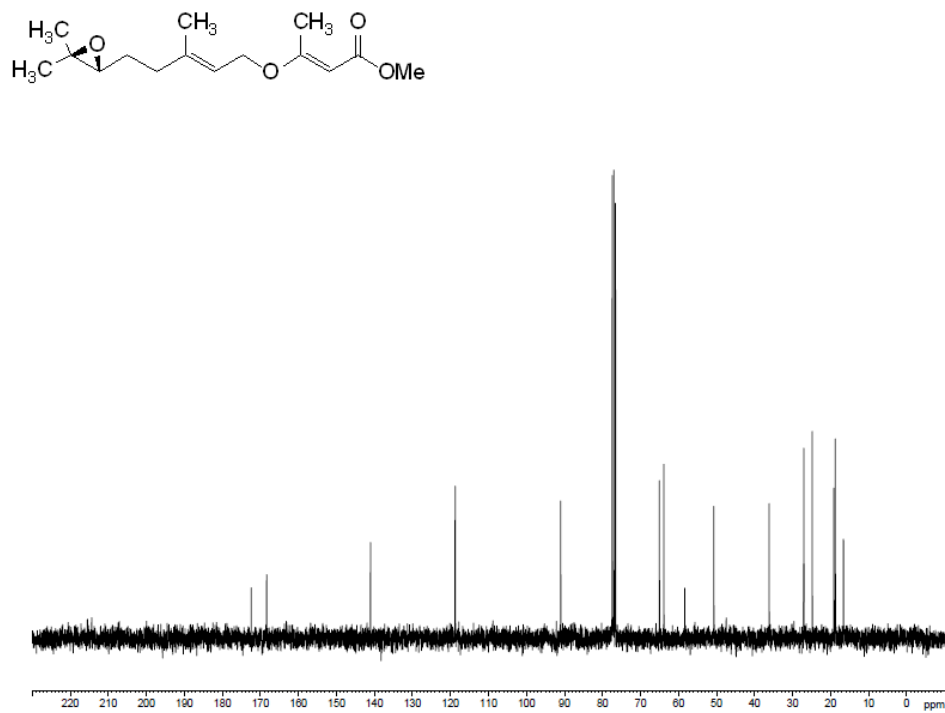
7. ^1H NMR Spectrum for **39f** in $(\text{CD}_3)_2\text{CO}$ 8. ^{13}C NMR Spectrum for **39f** in $(\text{CD}_3)_2\text{CO}$ 

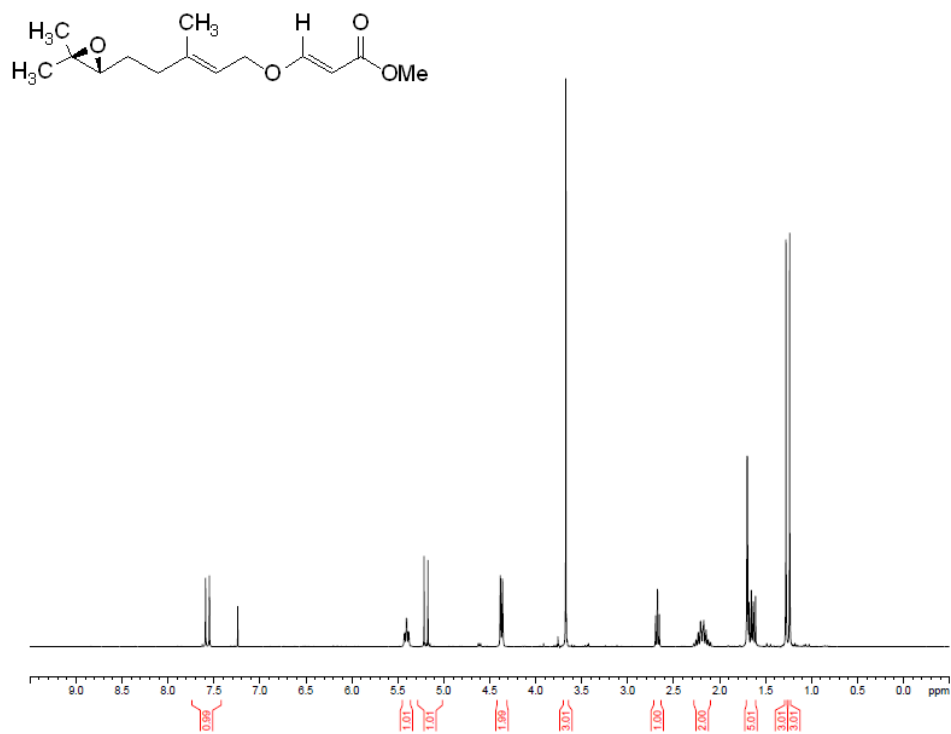
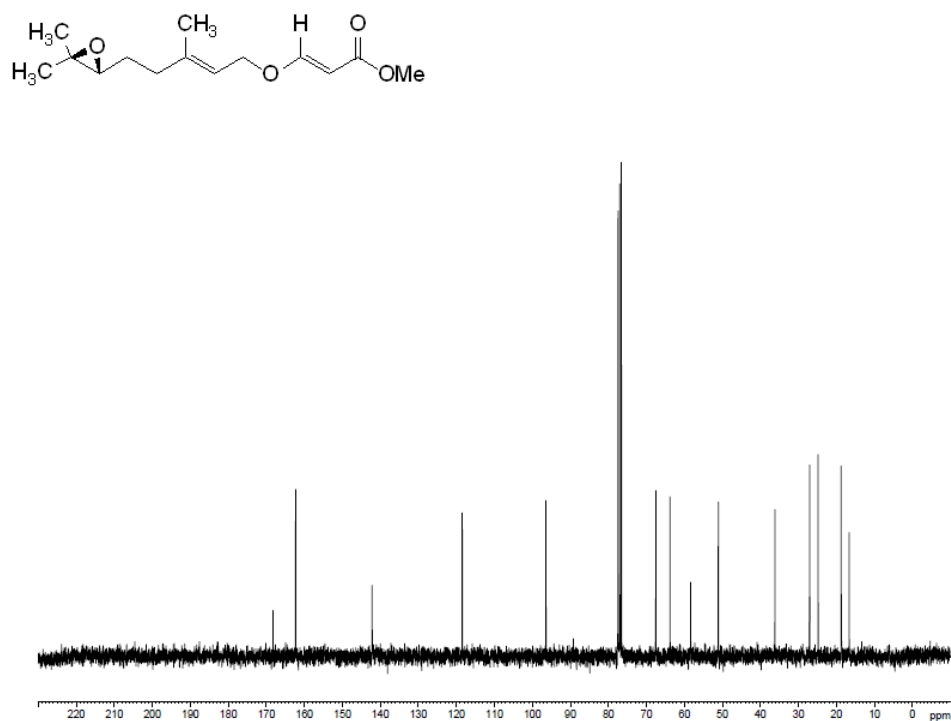
9. ^1H NMR Spectrum for **39g** in $(\text{CD}_3)_2\text{CO}$ 10. ^{13}C NMR Spectrum for **39g** in $(\text{CD}_3)_2\text{CO}$ 

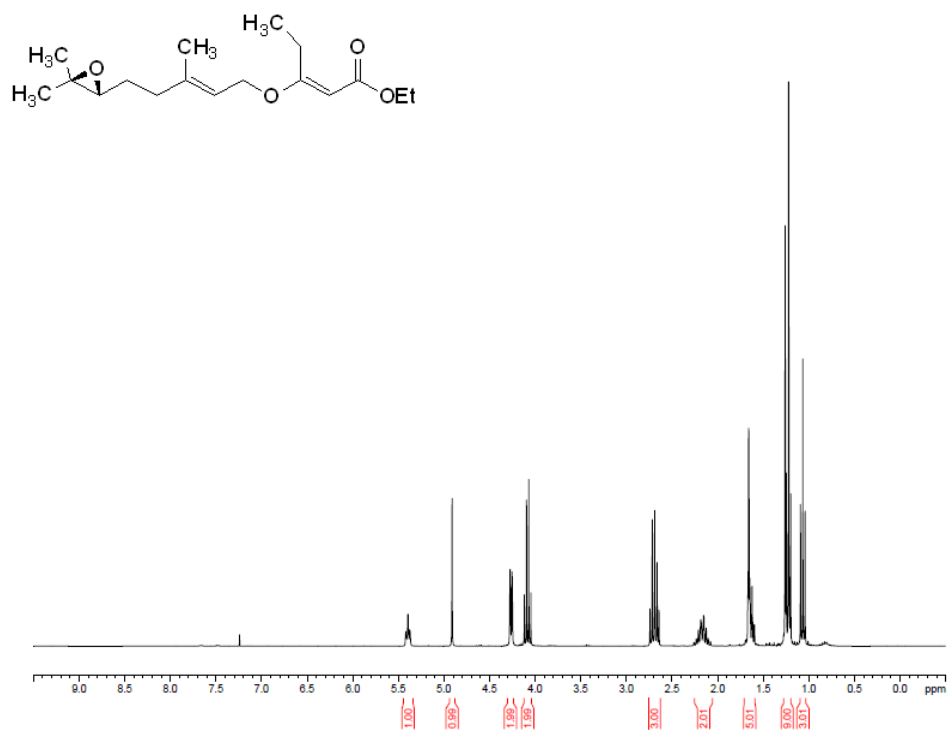
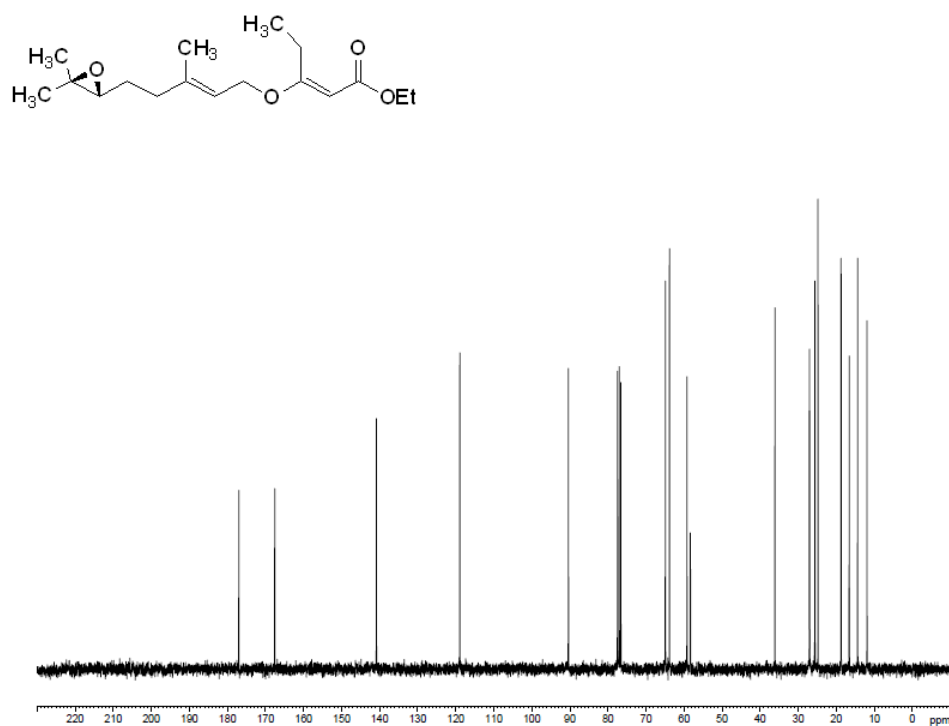
11. ^1H NMR Spectrum for **39h** in $(\text{CD}_3)_2\text{CO}$ 12. ^{13}C NMR Spectrum for **39h** in $(\text{CD}_3)_2\text{CO}$ 

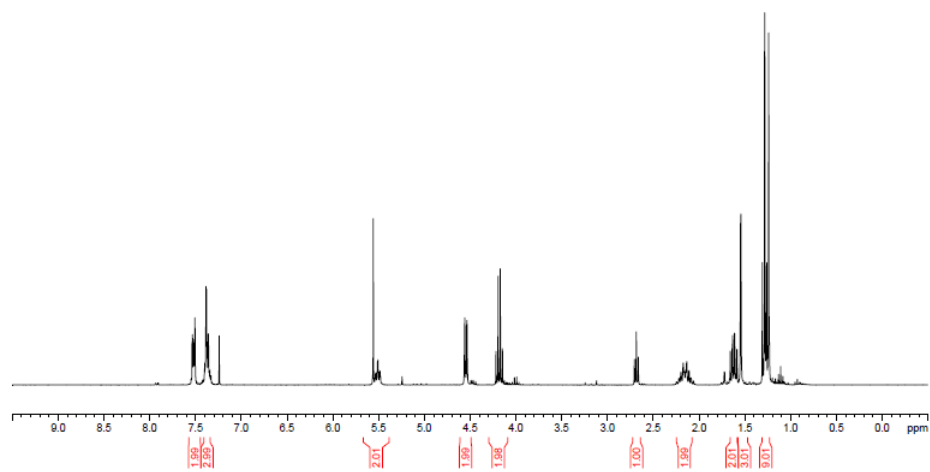
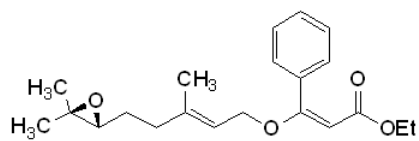
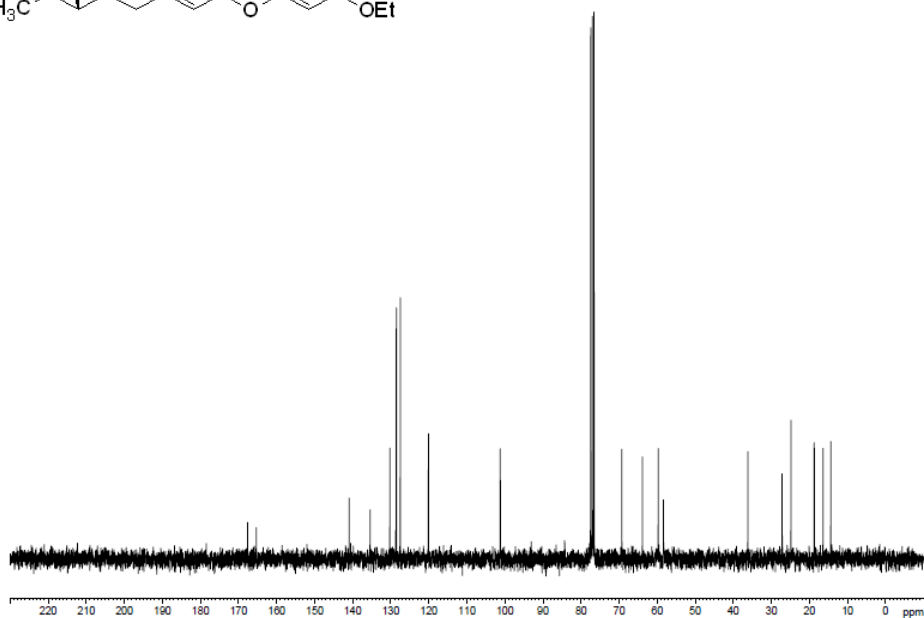
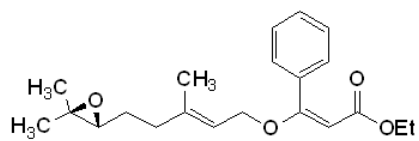
13. ^1H NMR Spectrum for **39i** in $(\text{CD}_3)_2\text{CO}$ 14. ^{13}C NMR Spectrum for **39i** in $(\text{CD}_3)_2\text{CO}$ 

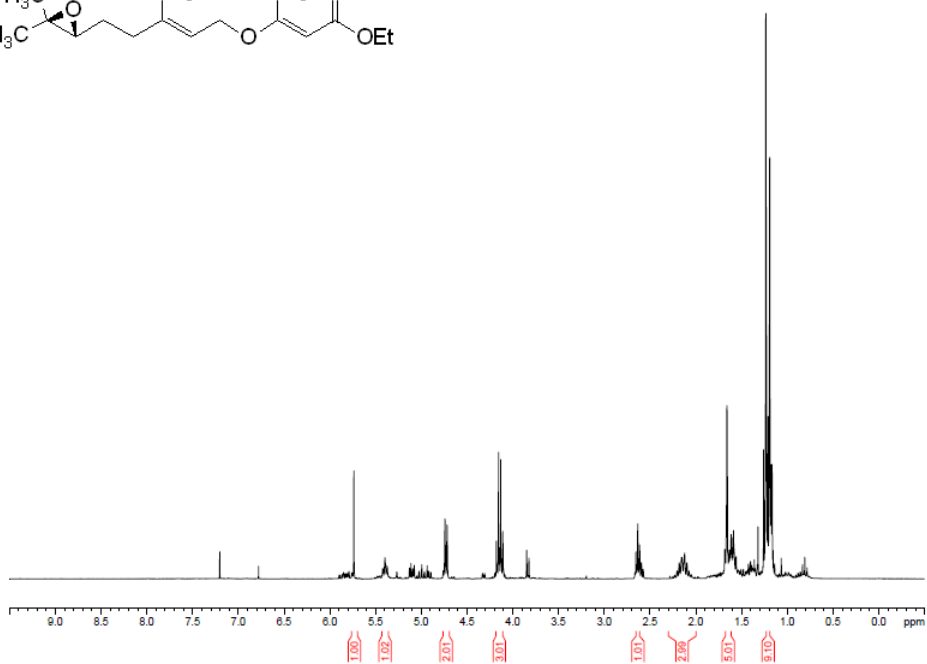
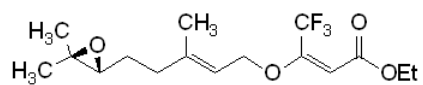
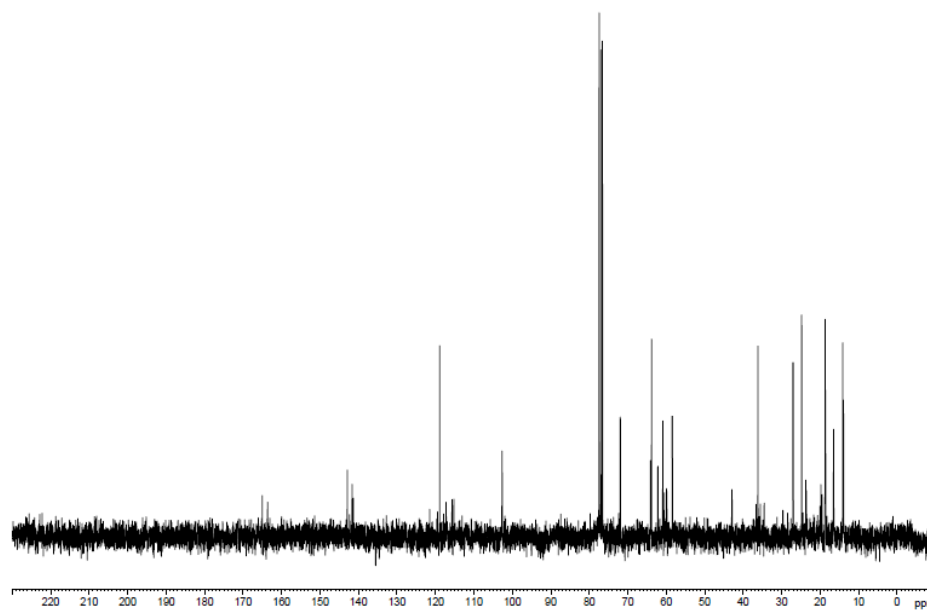
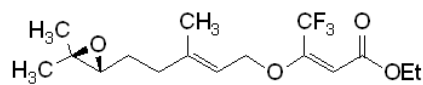
15. ^1H NMR Spectrum for **39j** in $(\text{CD}_3)_2\text{CO}$ 16. ^{13}C NMR Spectrum for **39j** in $(\text{CD}_3)_2\text{CO}$ 

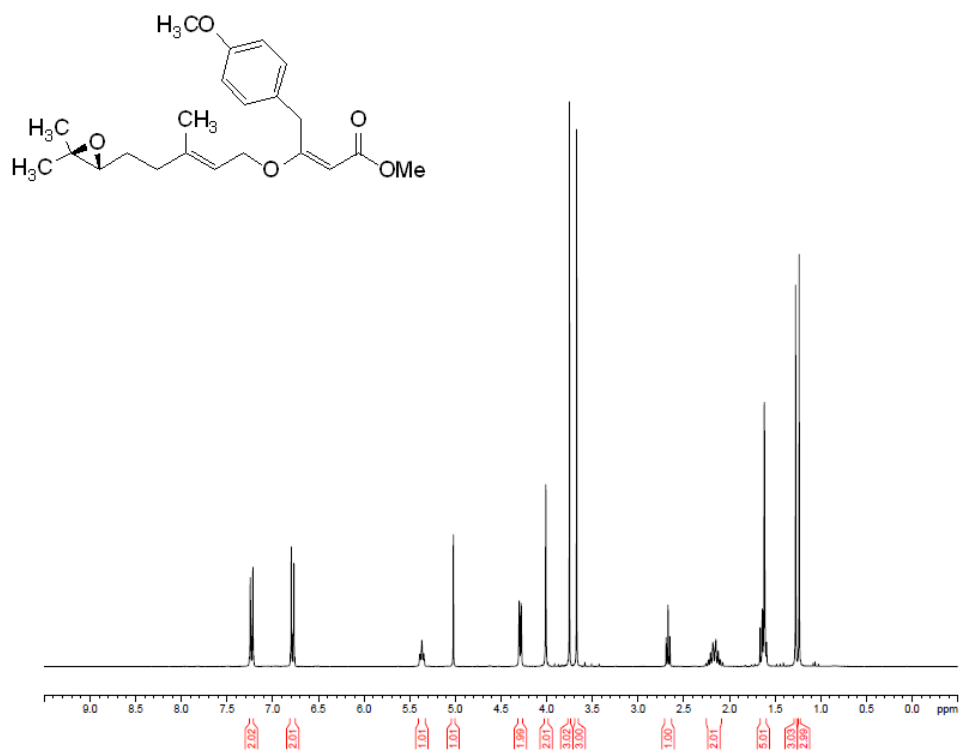
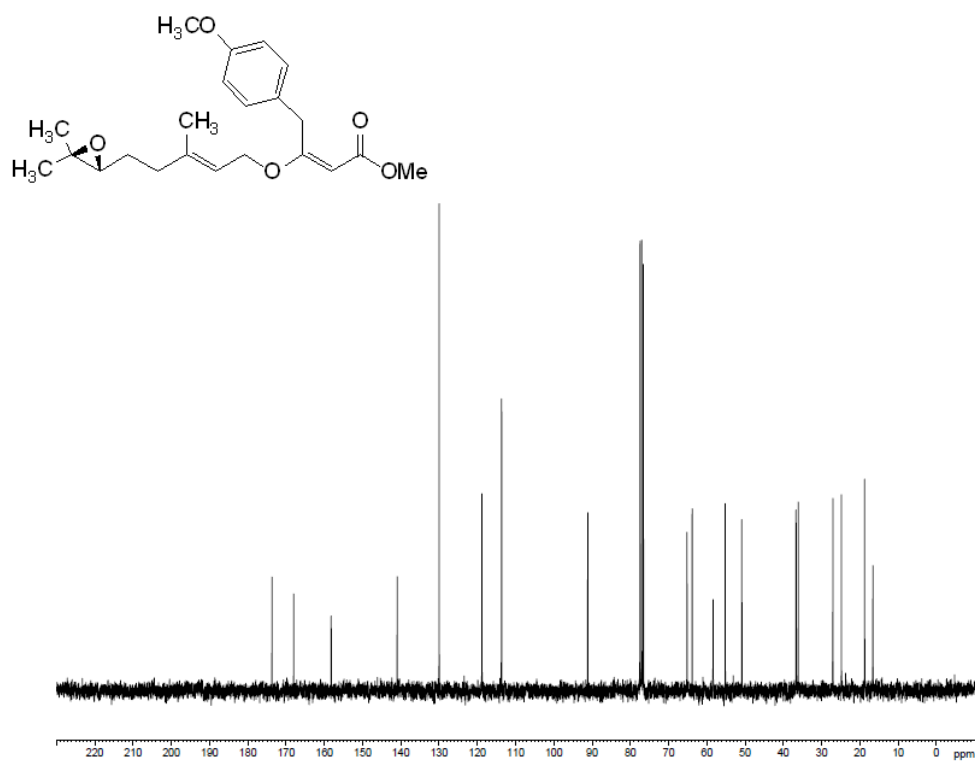
17. ^1H NMR Spectrum for **40a** in CDCl_3 18. ^{13}C NMR Spectrum for **40a** in CDCl_3 

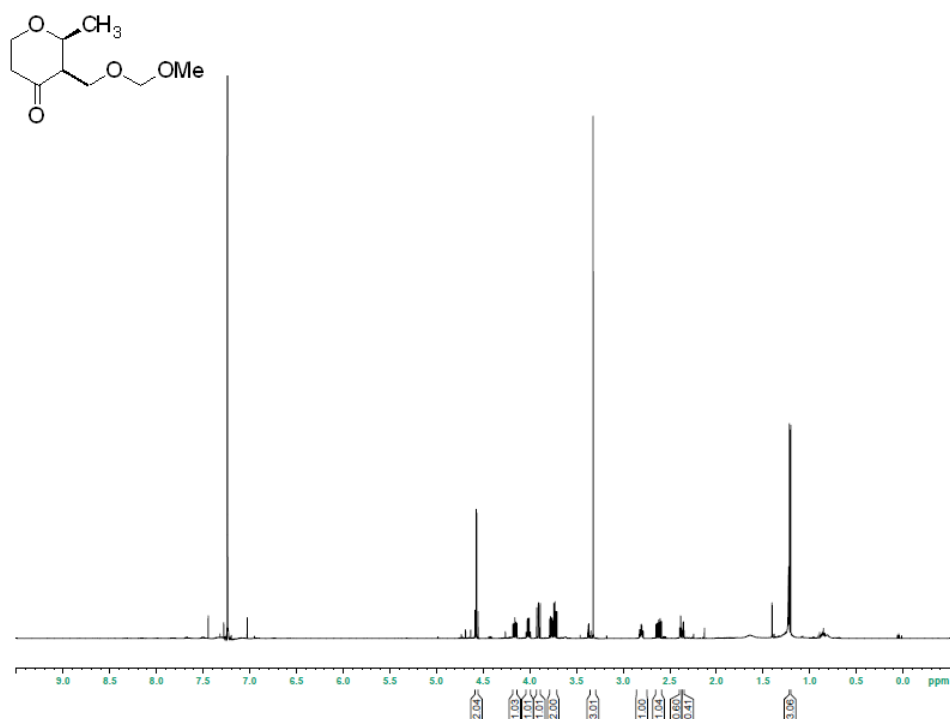
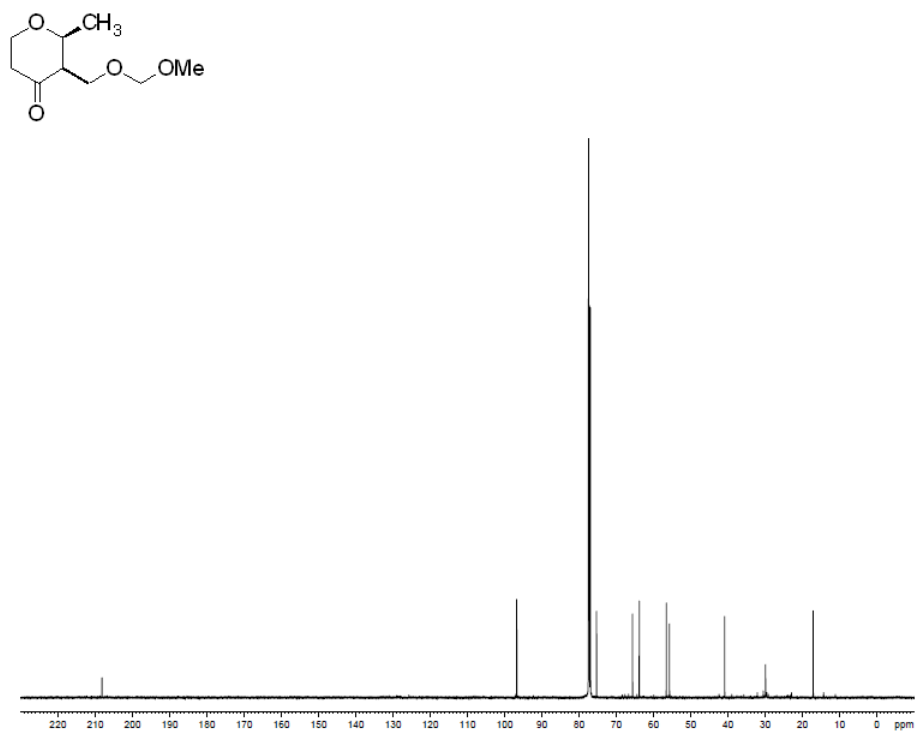
19. ^1H NMR Spectrum for **40b** in CDCl_3 20. ^{13}C NMR Spectrum for **40b** in CDCl_3 

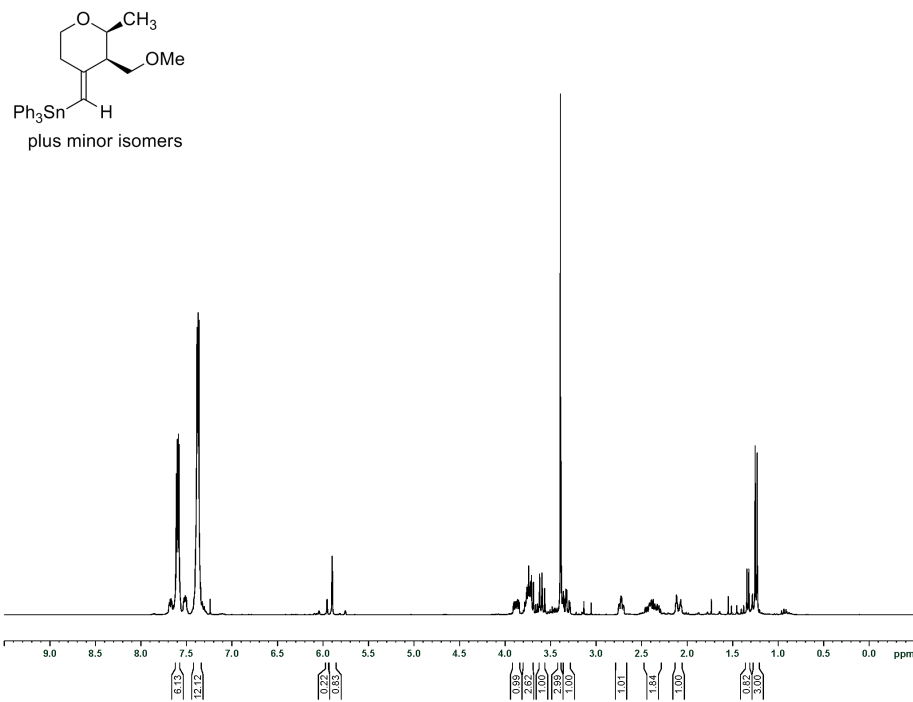
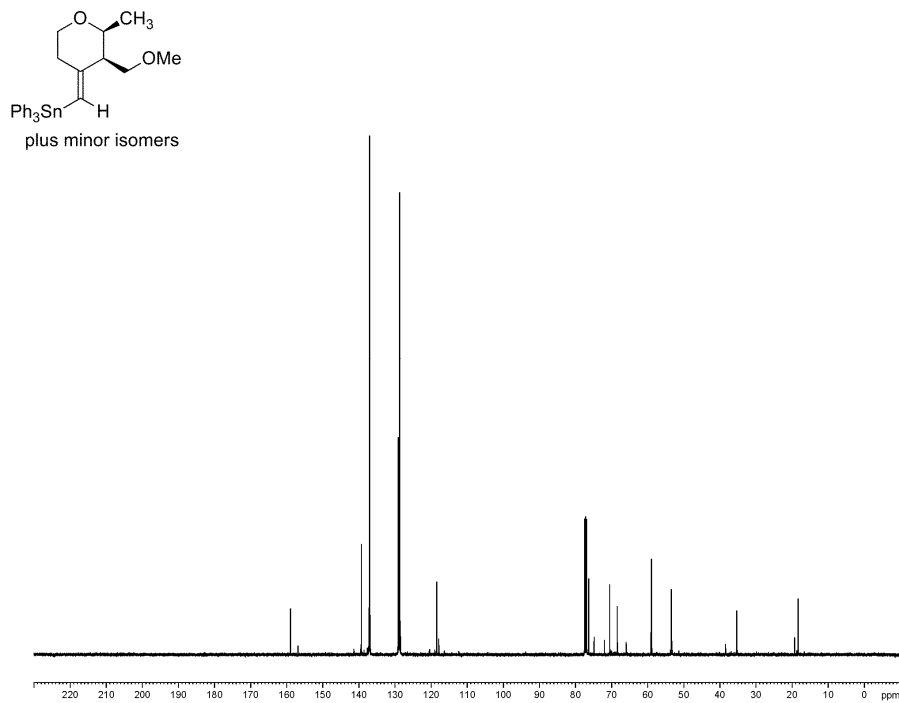
21. ^1H NMR Spectrum for **40c** in CDCl_3 22. ^{13}C NMR Spectrum for **40c** in CDCl_3 

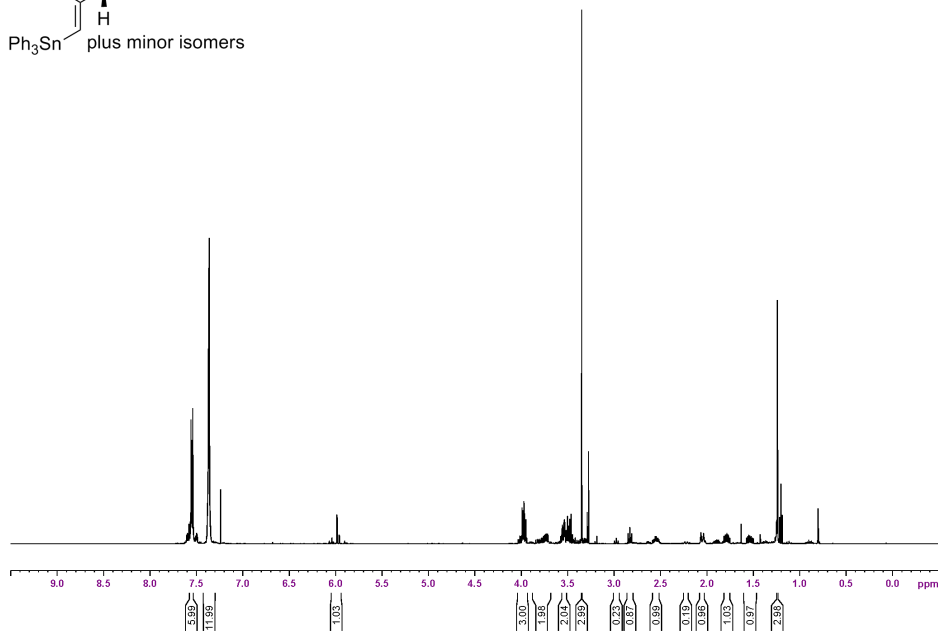
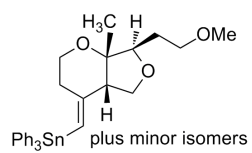
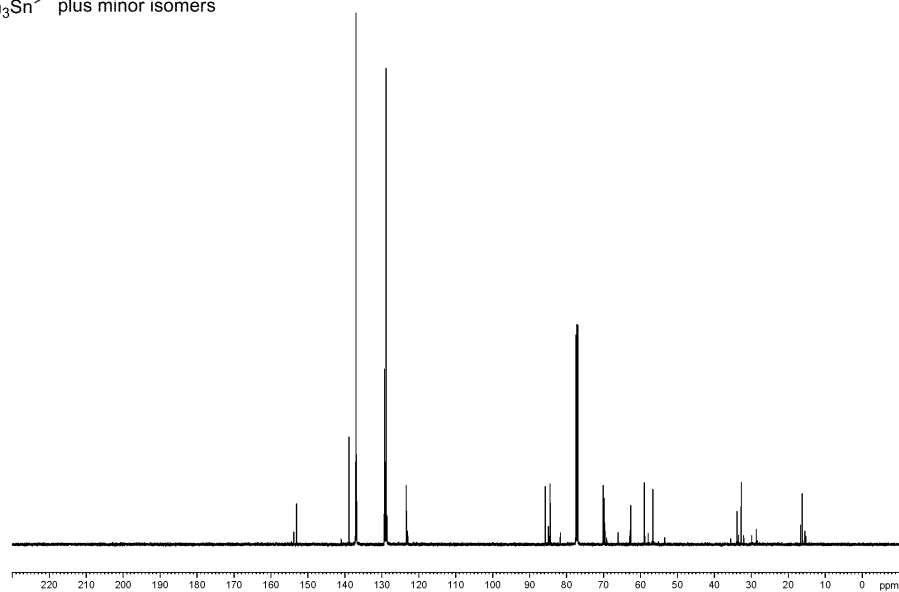
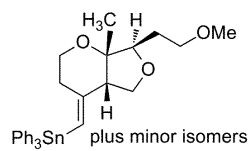
23. ^1H NMR Spectrum for **40d** in CDCl_3 24. ^{13}C NMR Spectrum for **40d** in CDCl_3 

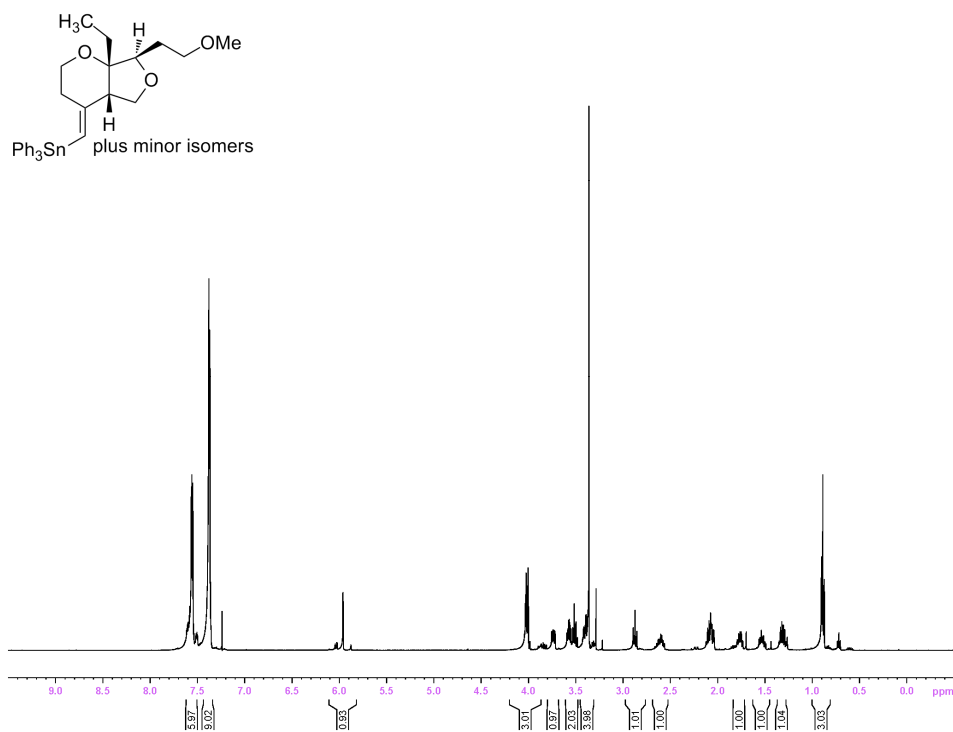
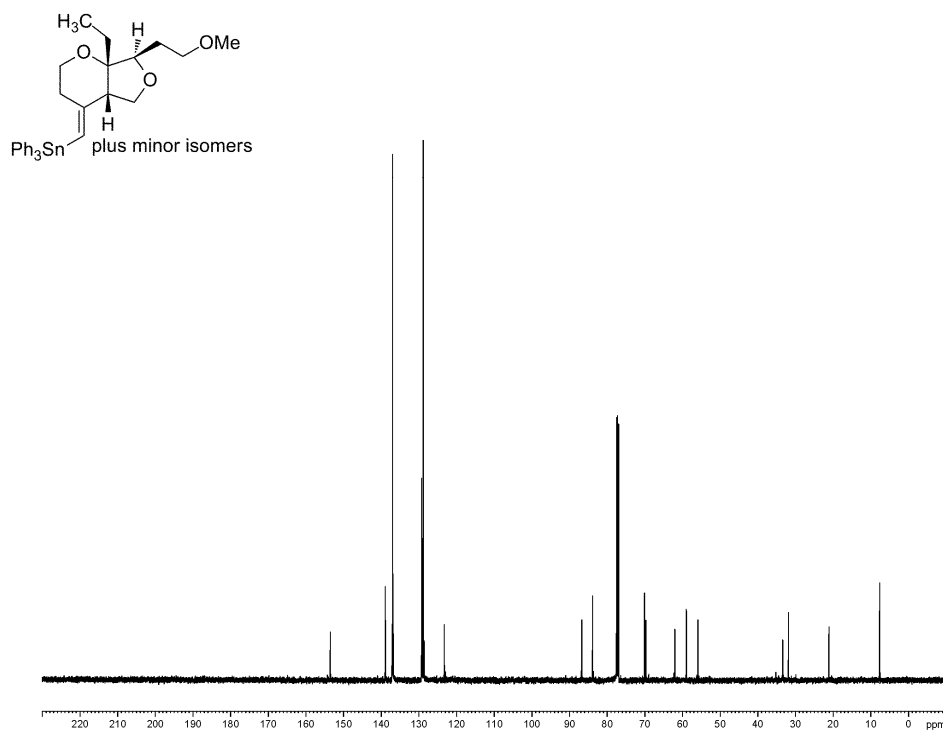
25. ^1H NMR Spectrum for **40e** in CDCl_3 26. ^{13}C NMR Spectrum for **40e** in CDCl_3 

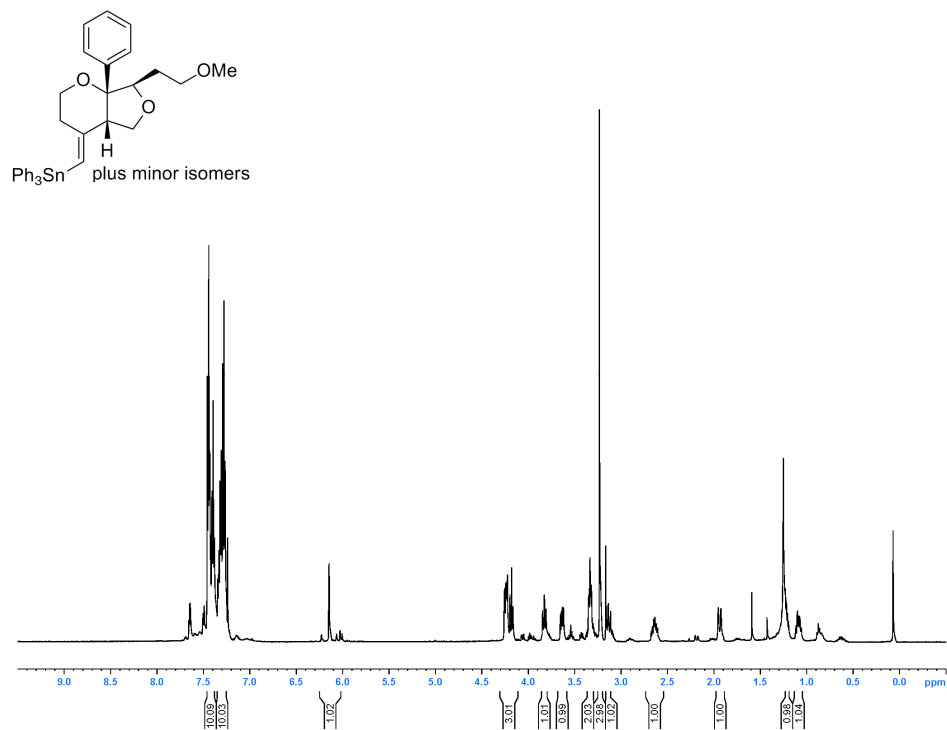
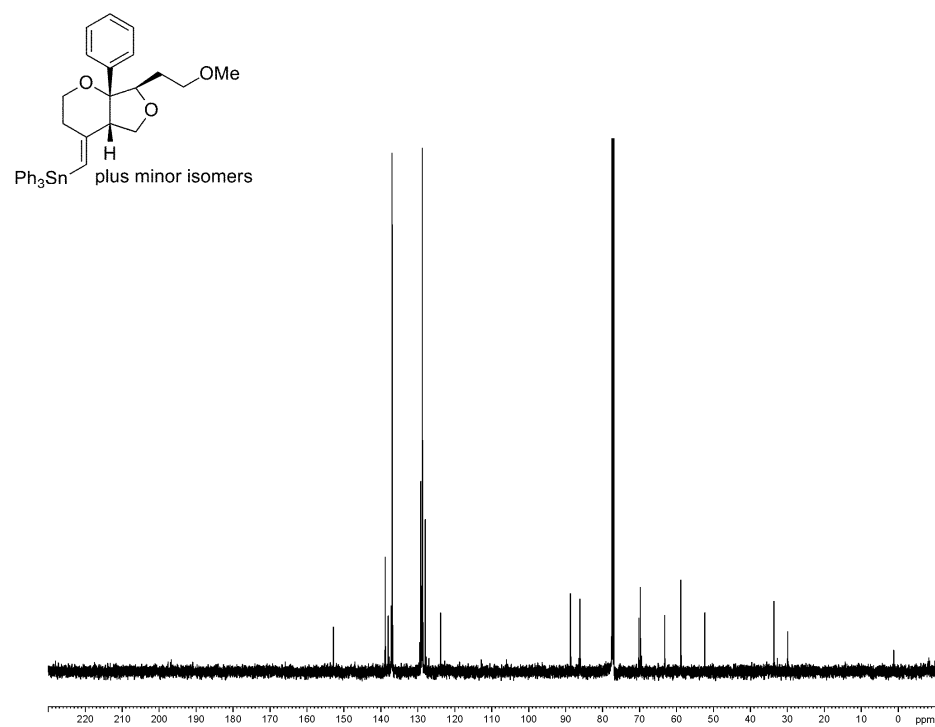
27. ^1H NMR Spectrum for **40f** in CDCl_3 28. ^{13}C NMR Spectrum for **40f** in CDCl_3 

Appendix 3: Chapter 4 Section 4.1.0 – 4.3.0 Spectral Data1. ^1H NMR spectrum for **76b** in CDCl_3 2. ^{13}C NMR spectrum for **76b** in CDCl_3 

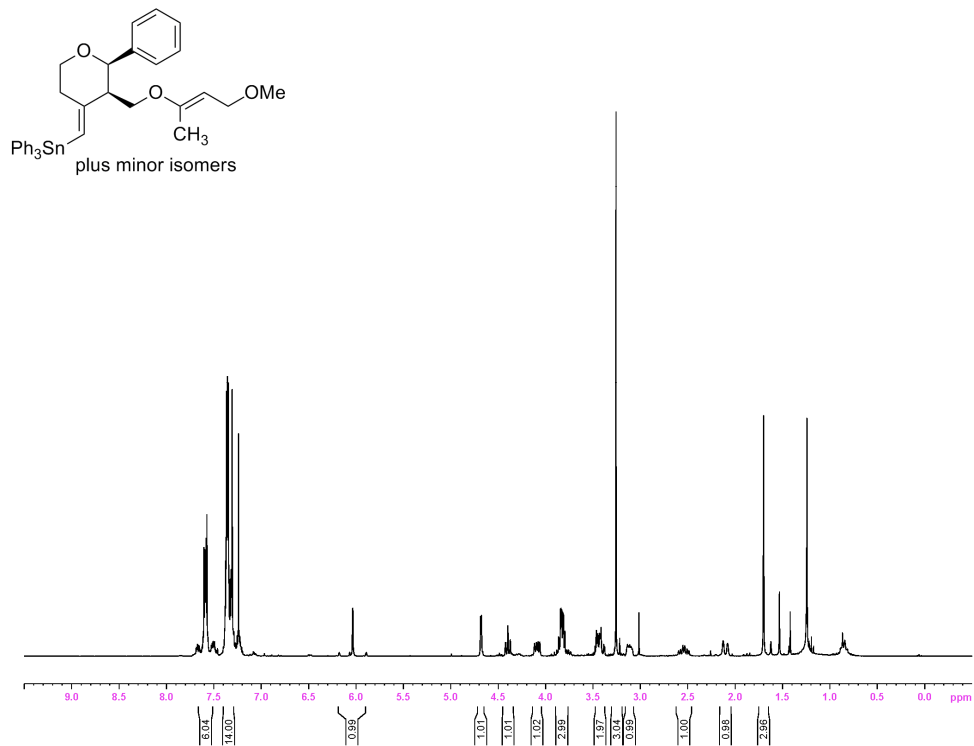
3. ^1H NMR spectrum for **91a** in CDCl_3 4. ^{13}C NMR spectrum for **91a** in CDCl_3 

5. ^1H NMR spectrum for **94a** in CDCl_3 6. ^{13}C NMR spectrum for **94a** in CDCl_3 

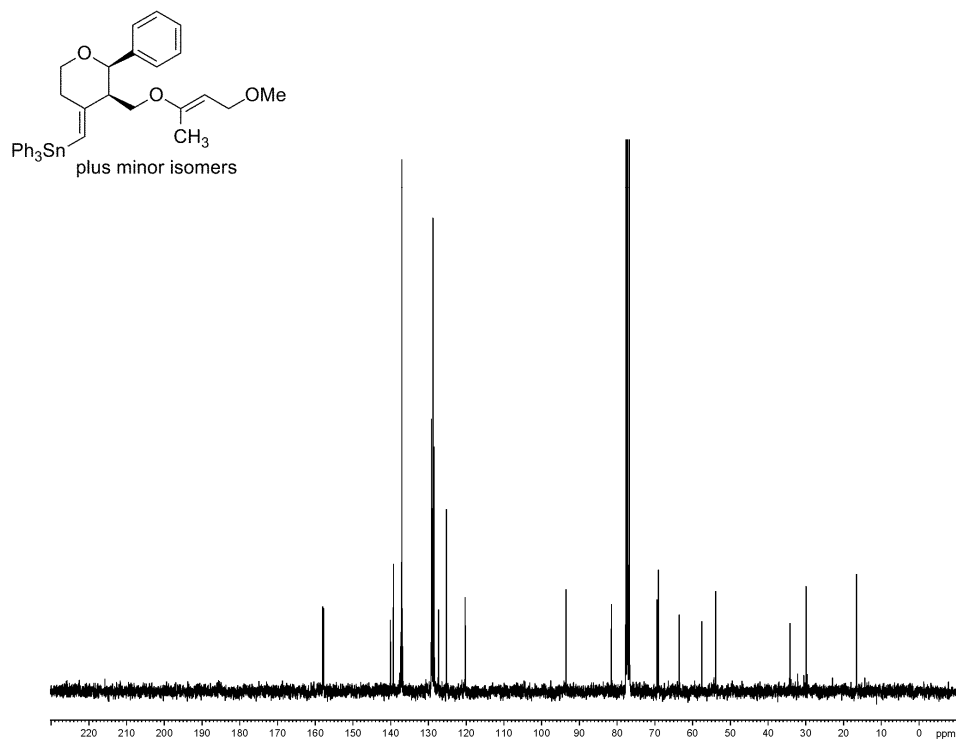
11. ^1H NMR spectrum for **94c** in CDCl_3 12. ^{13}C NMR spectrum for **94c** in CDCl_3 

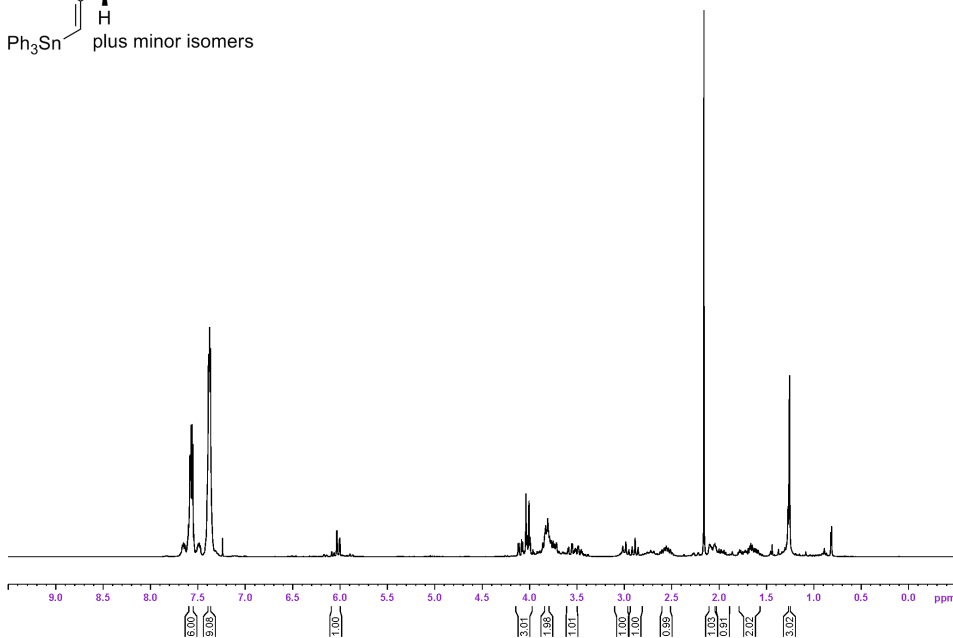
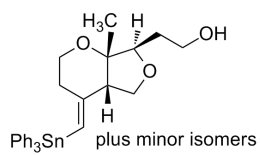
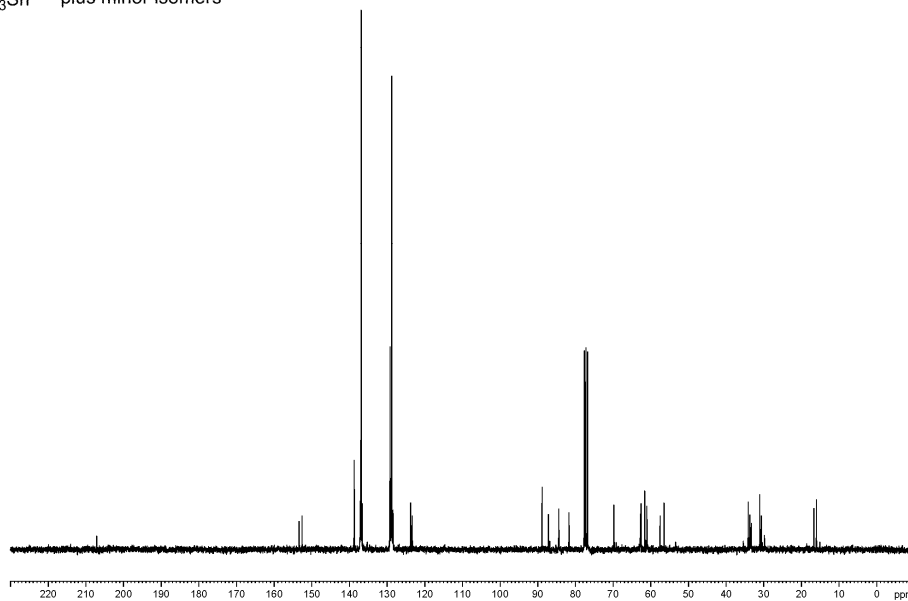
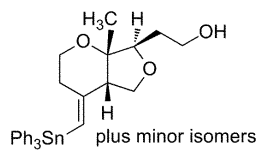
15. ^1H NMR spectrum for **94e** in CDCl_3 16. ^{13}C NMR spectrum for **94e** in CDCl_3 

17. ^1H NMR spectrum for **95f** in CDCl_3

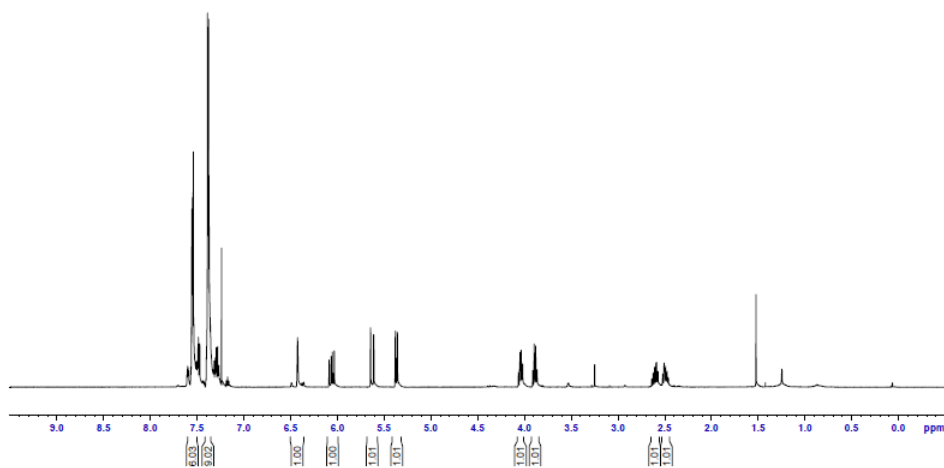
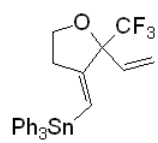


18. ^{13}C NMR spectrum for **95f** in CDCl_3

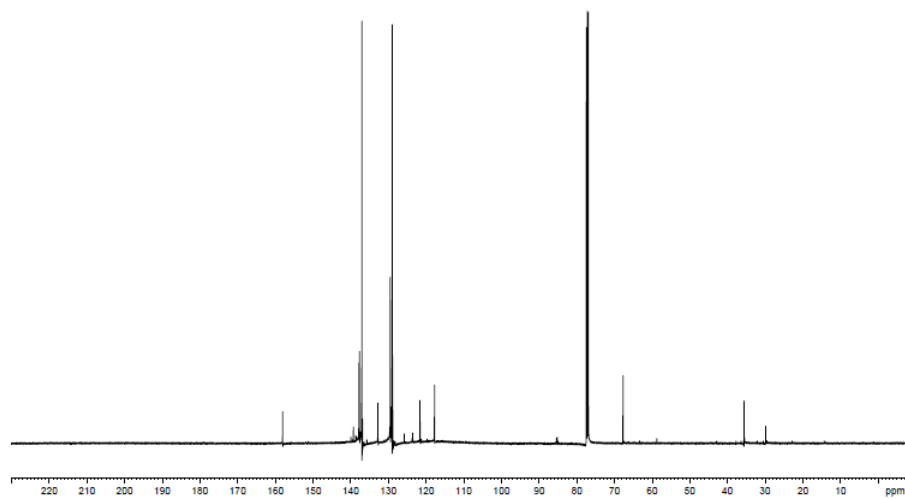
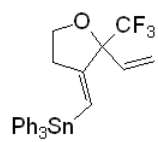


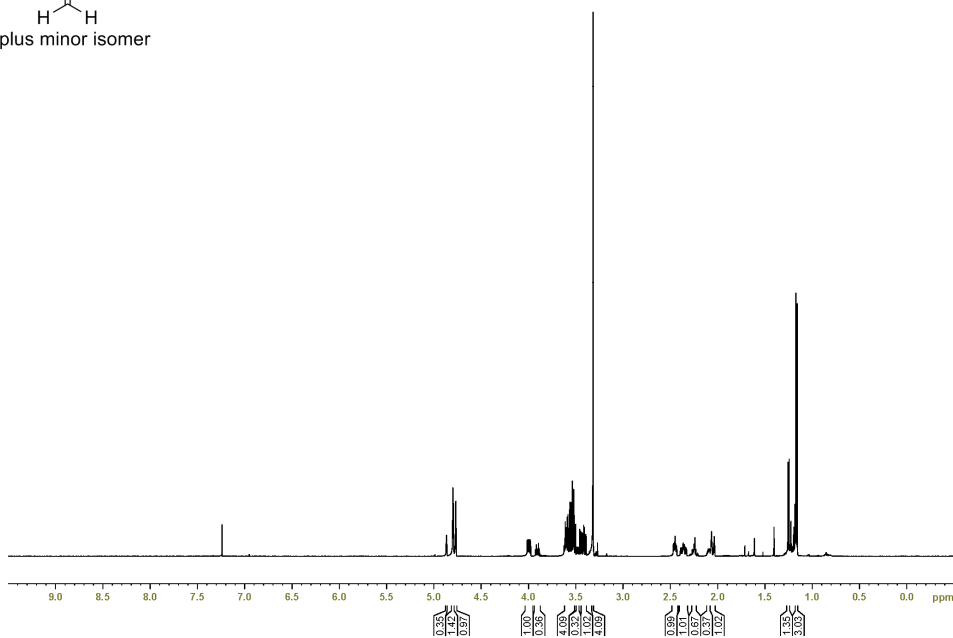
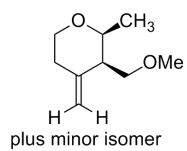
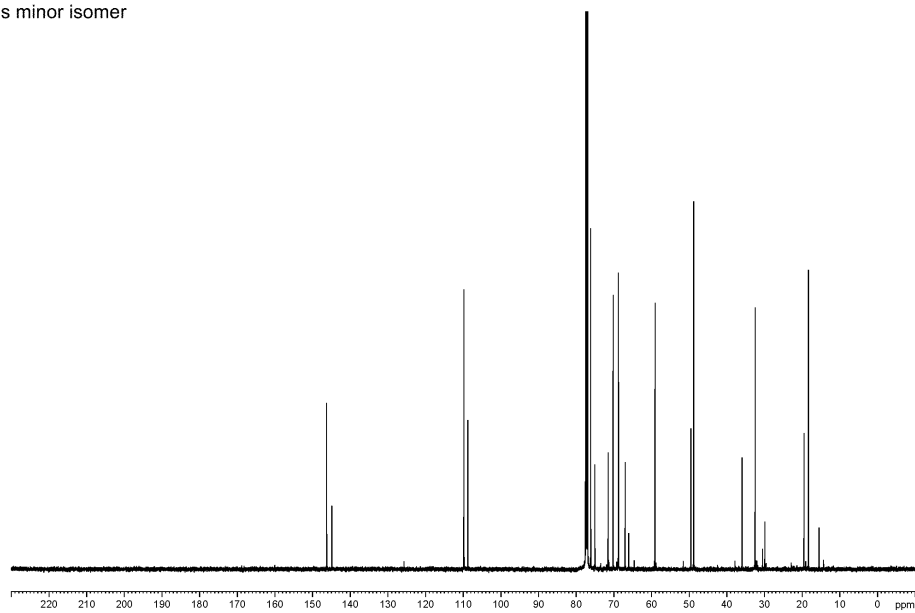
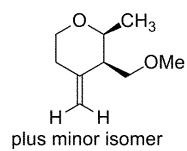
23. ^1H NMR spectrum for **94i** in CDCl_3 24. ^{13}C NMR spectrum for **94i** in CDCl_3 

27. ^1H NMR spectrum for **115a** in CDCl_3

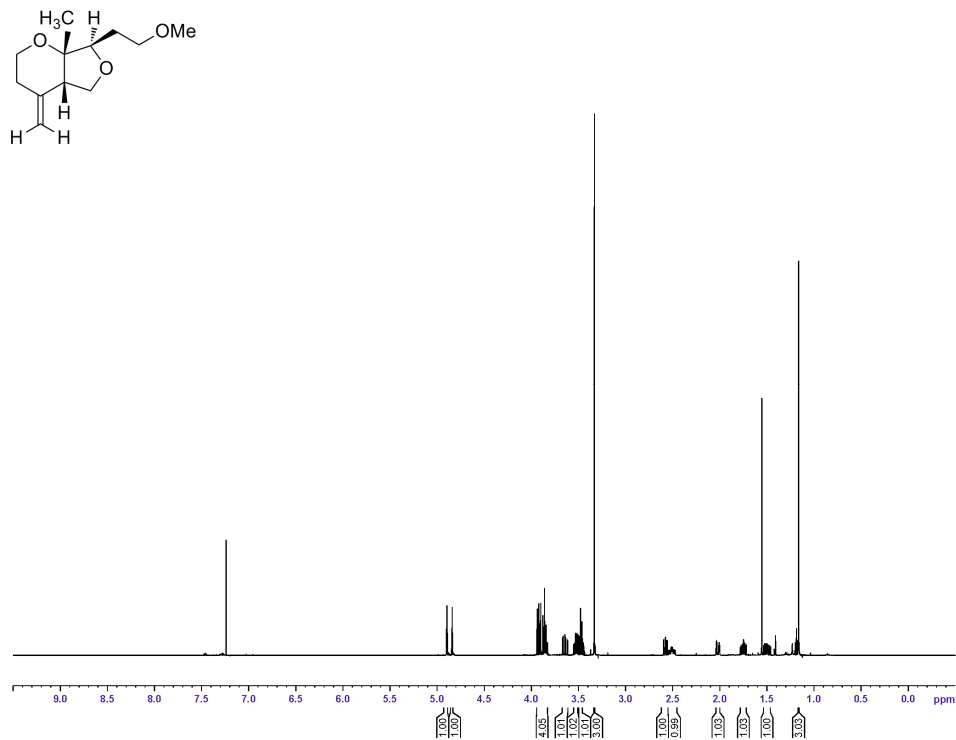


28. ^{13}C NMR spectrum for **115a** in CDCl_3

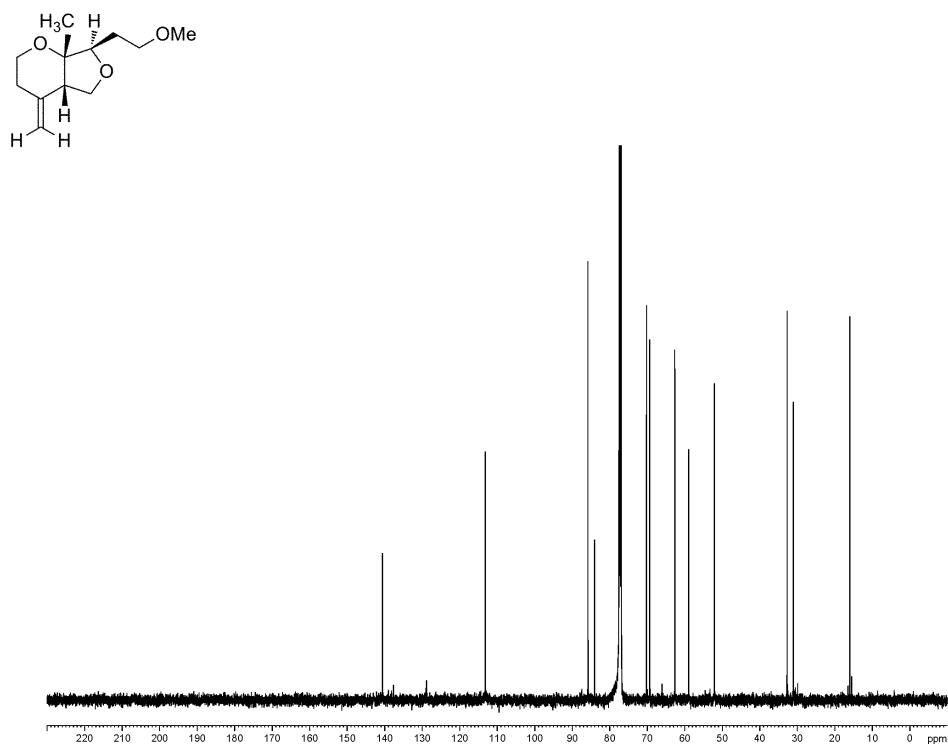


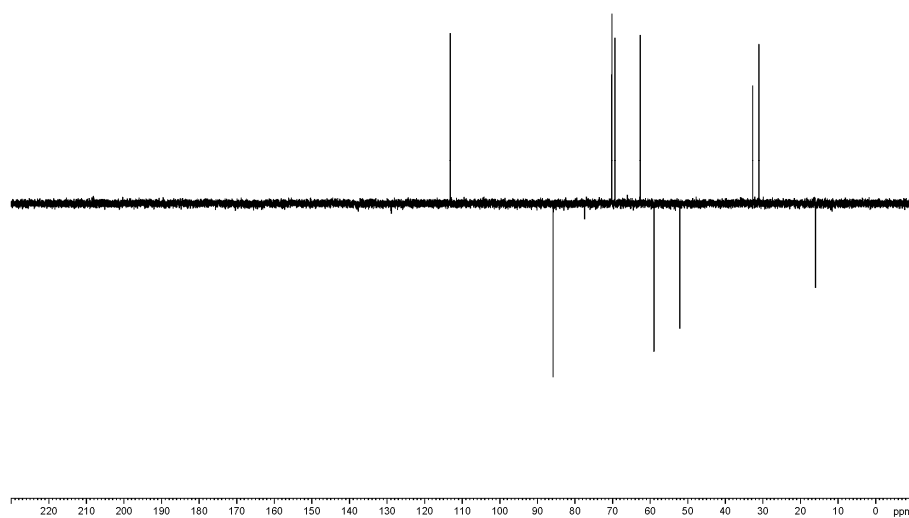
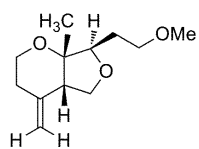
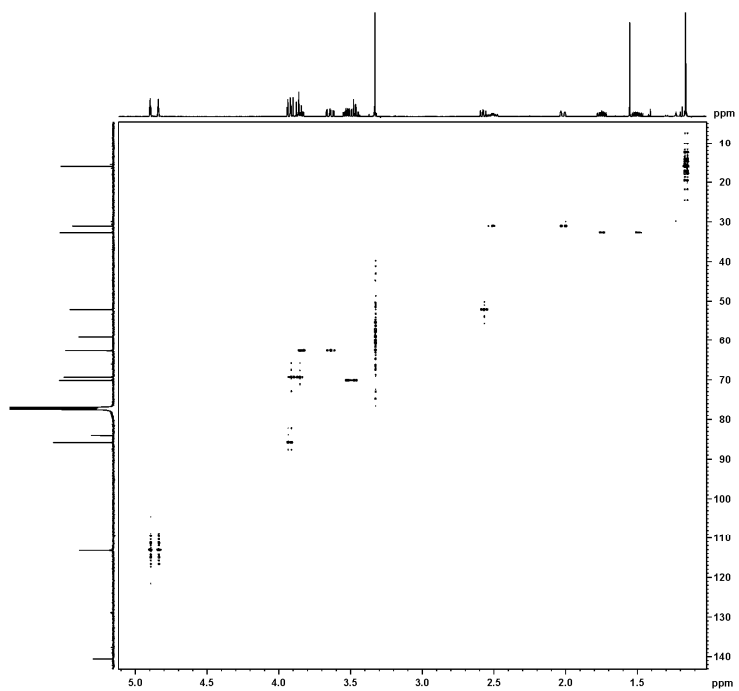
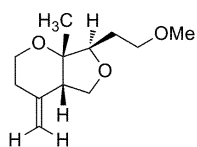
29. ^1H NMR spectrum for **93a** in CDCl_3 30. ^{13}C NMR spectrum for **93a** in CDCl_3 

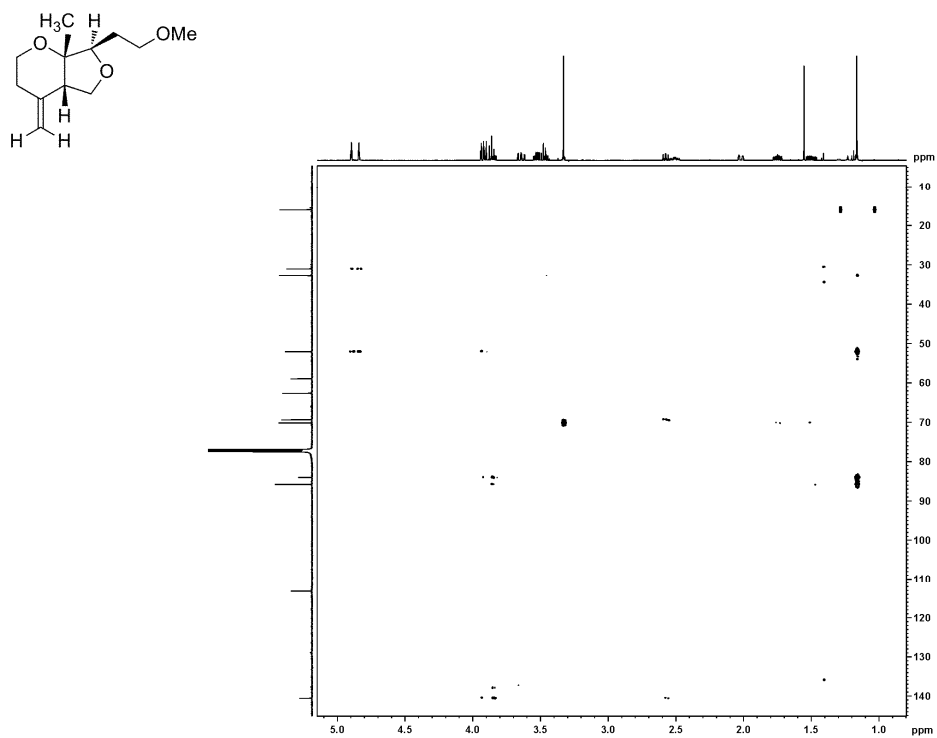
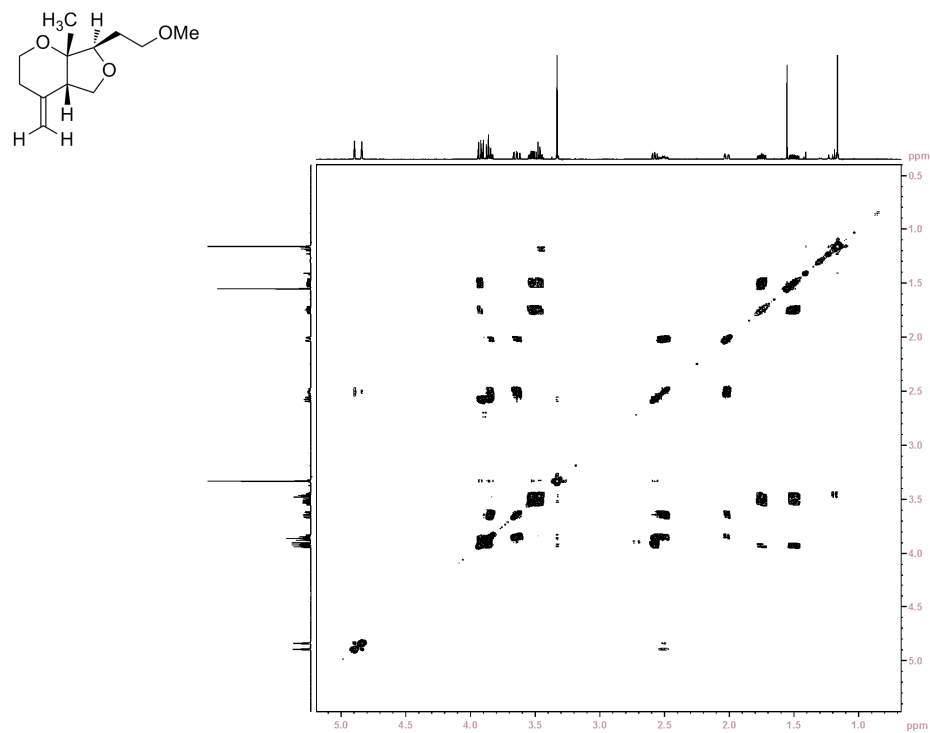
31. ^1H NMR spectrum for **96a** in CDCl_3

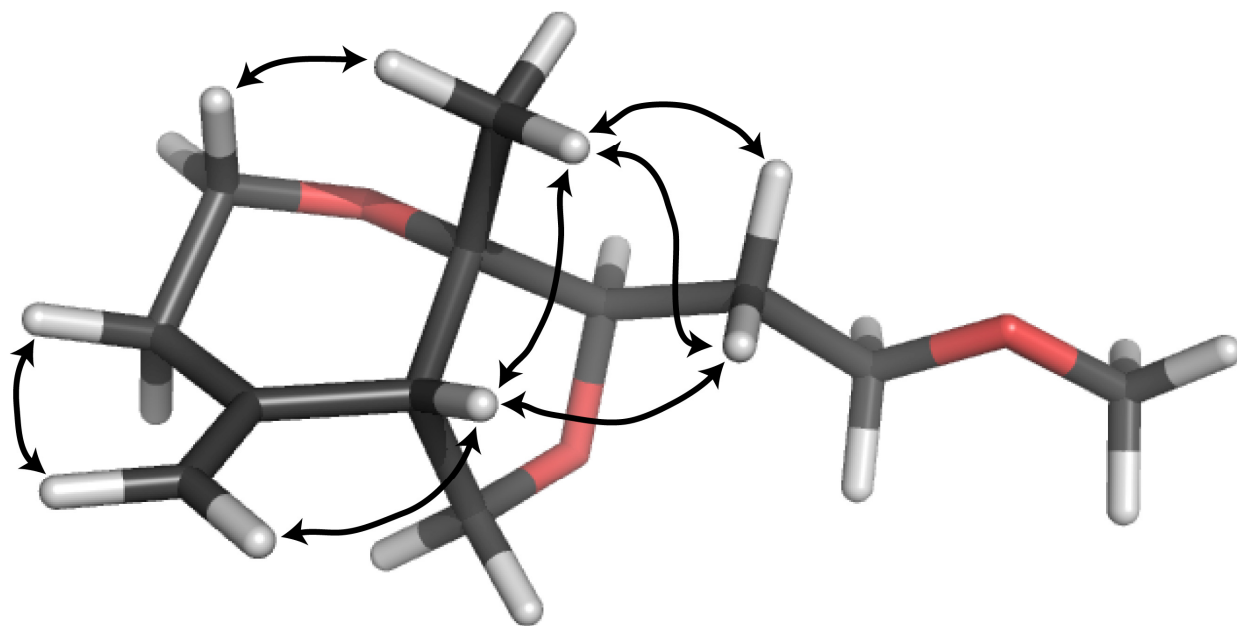
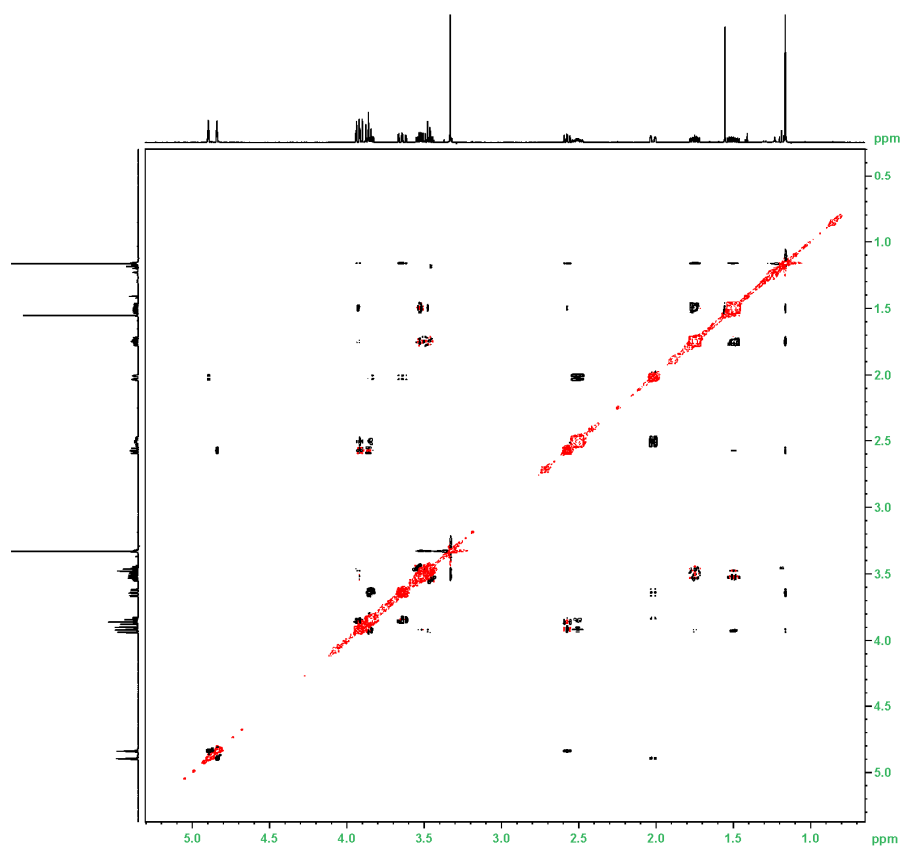
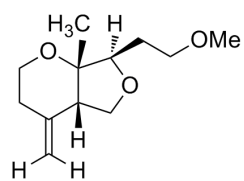


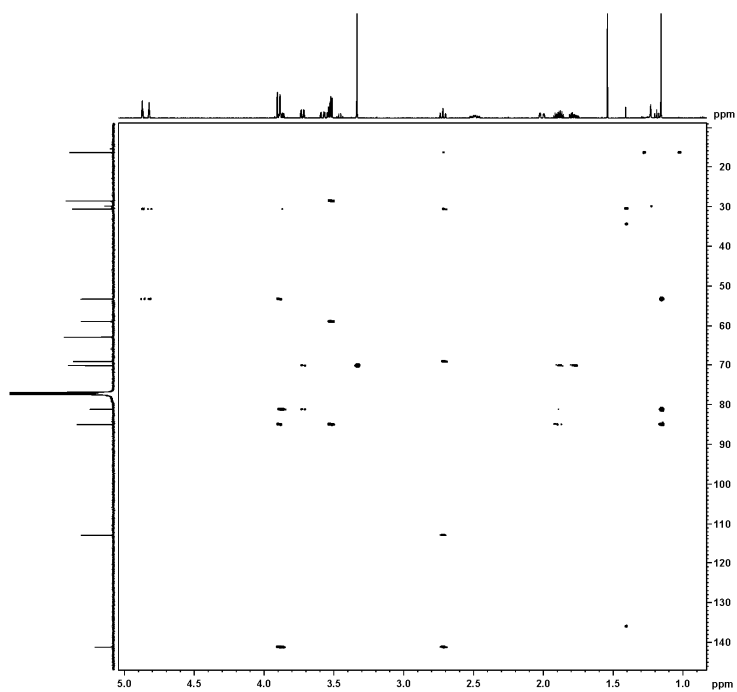
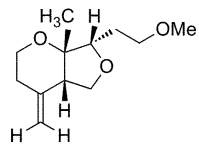
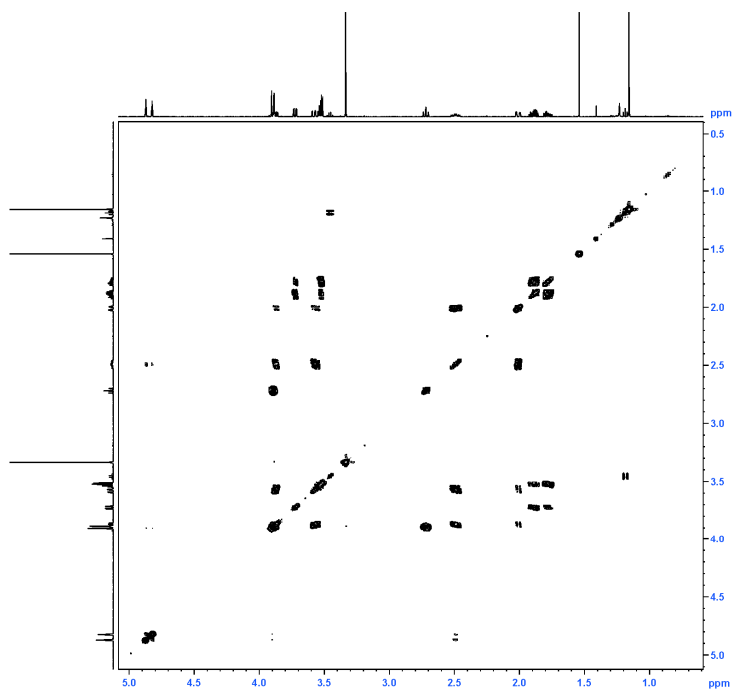
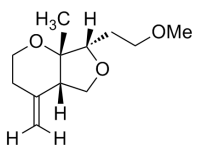
32. ^{13}C NMR spectrum for **96a** in CDCl_3

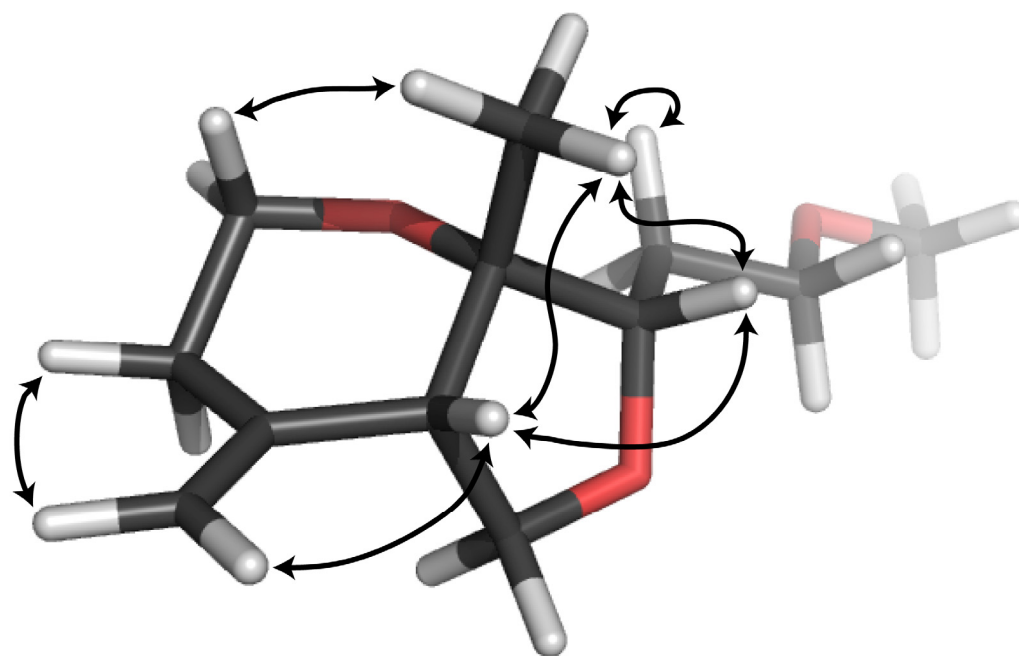
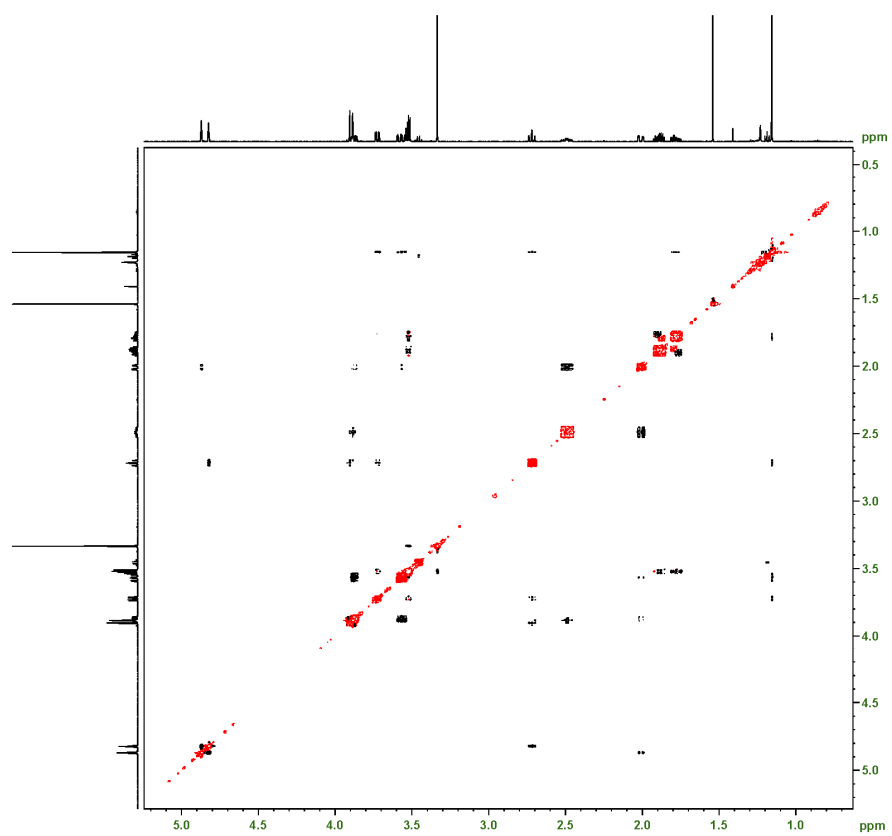
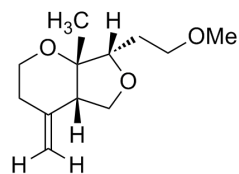


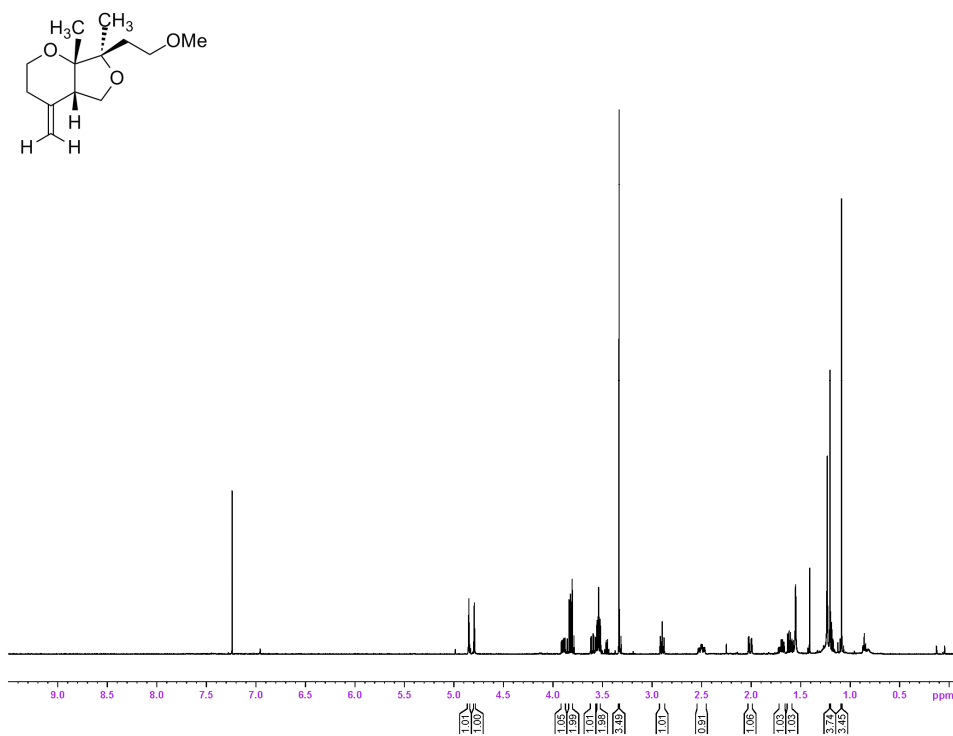
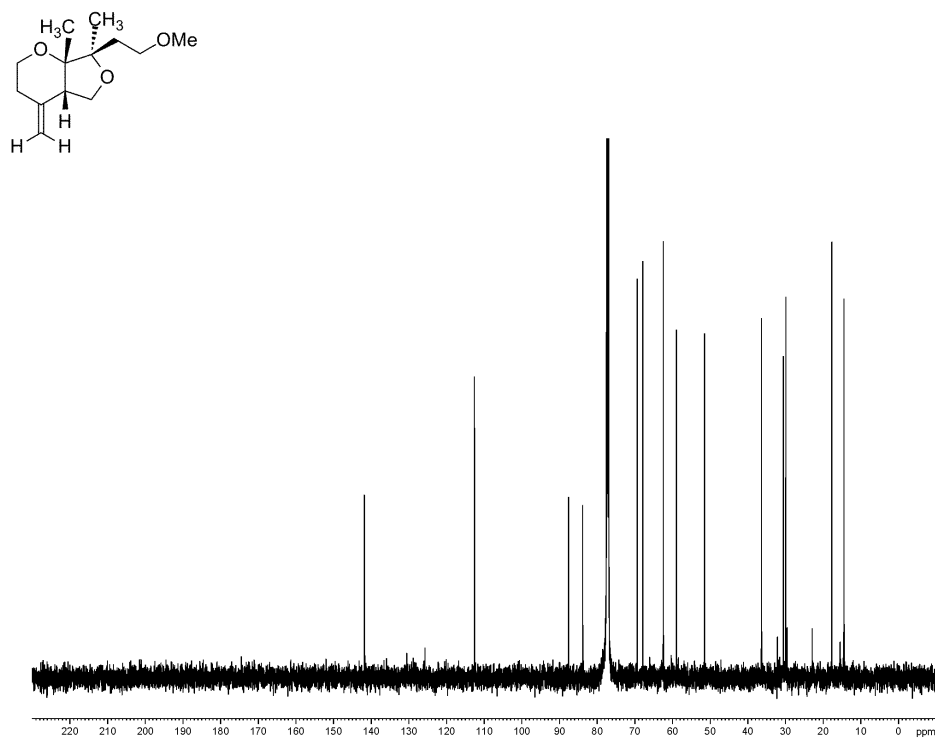
33. DEPT-135 spectrum for **96a** in CDCl₃34. HSQC spectrum for **96a** in CDCl₃

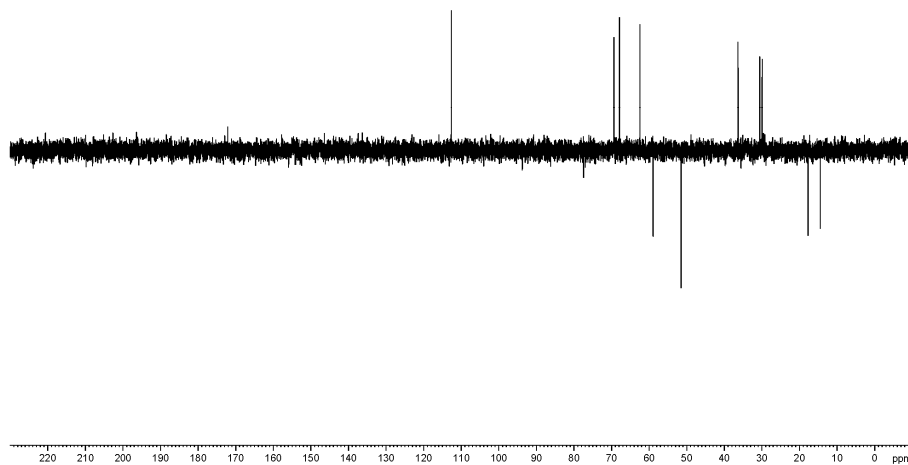
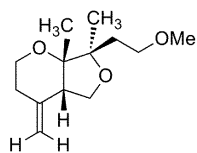
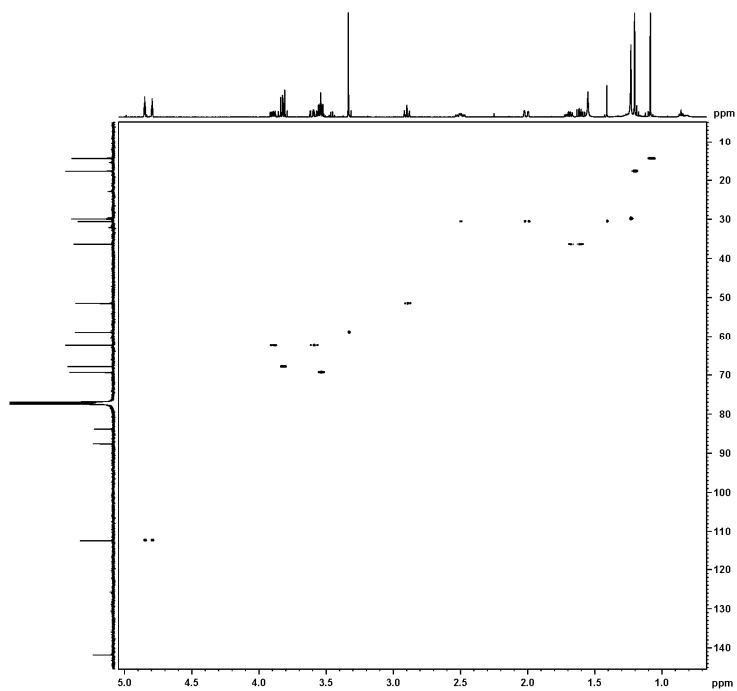
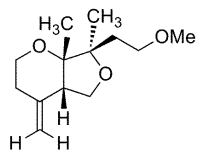
35. HMBC spectrum for **96a** in CDCl₃36. COSY spectrum for **96a** in CDCl₃

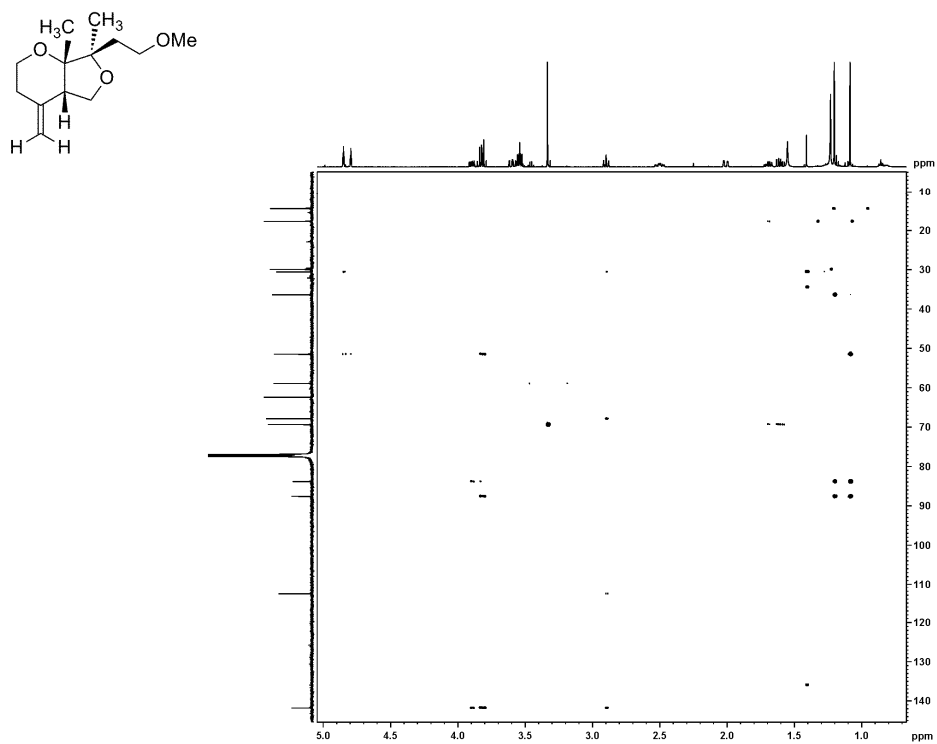
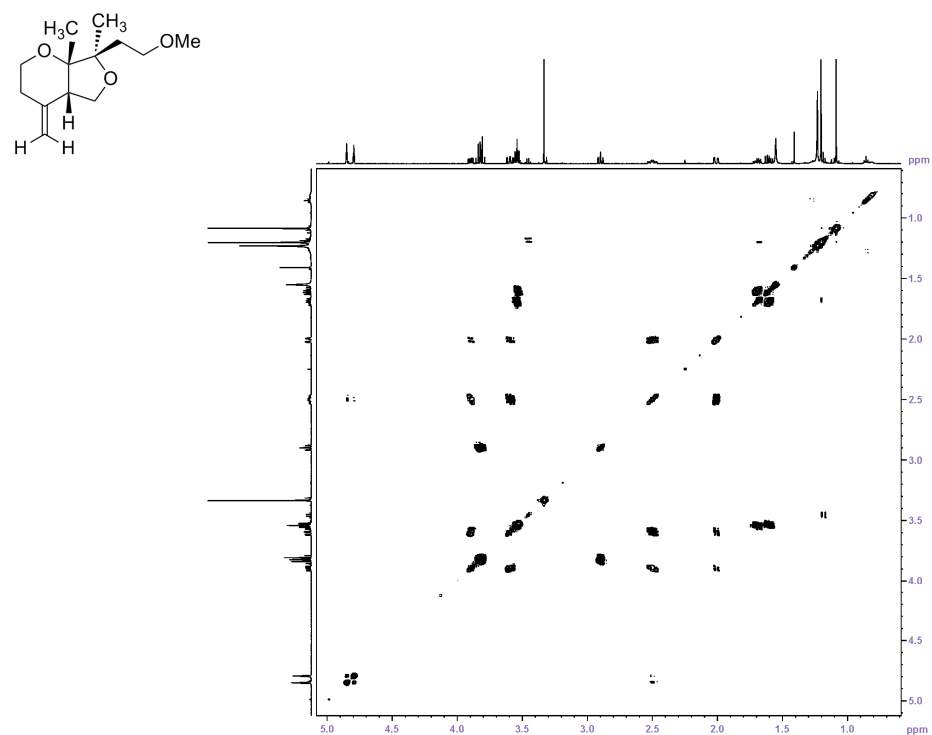
37. NOESY spectrum for **96a** in CDCl₃

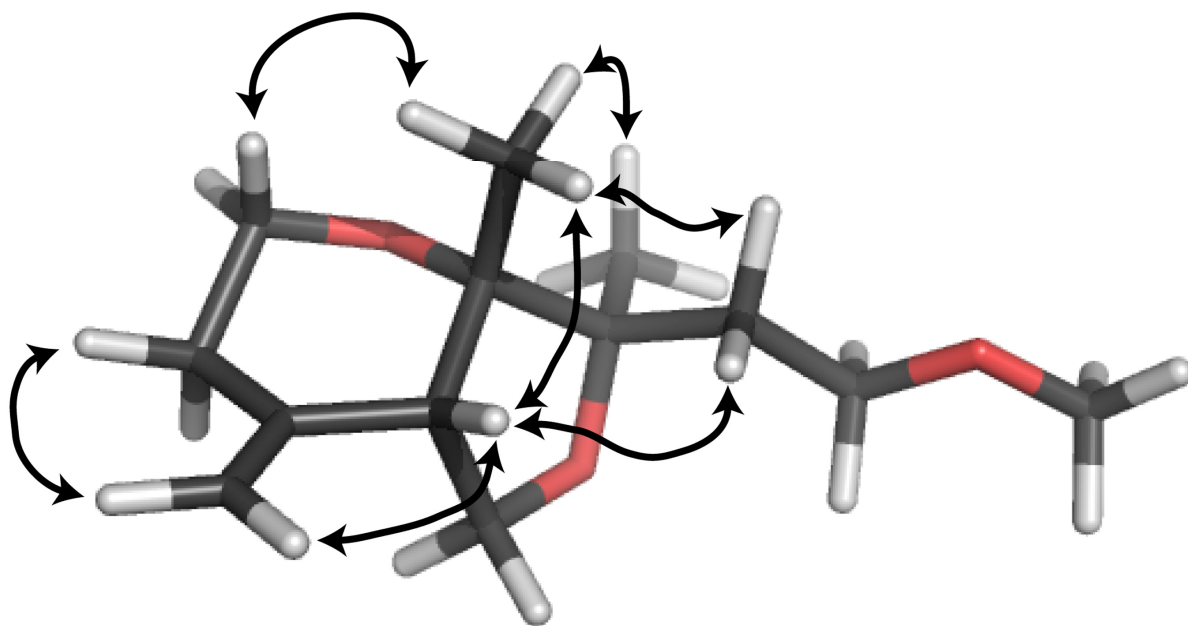
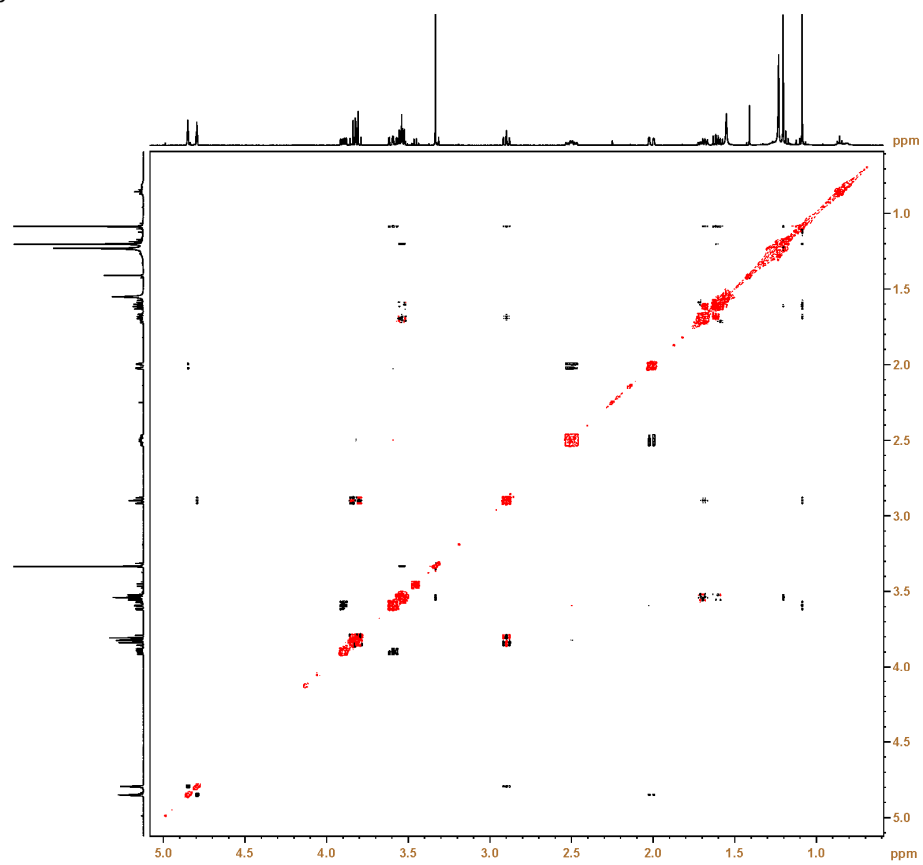
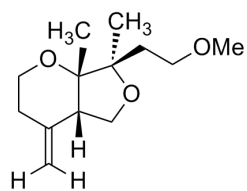
42. HMBC spectrum for **97a** in CDCl₃43. COSY spectrum for **97a** in CDCl₃

44. NOESY spectrum for **97a** in CDCl₃

45. ^1H NMR spectrum for **96b** in CDCl_3 46. ^{13}C NMR spectrum for **96b** in CDCl_3 

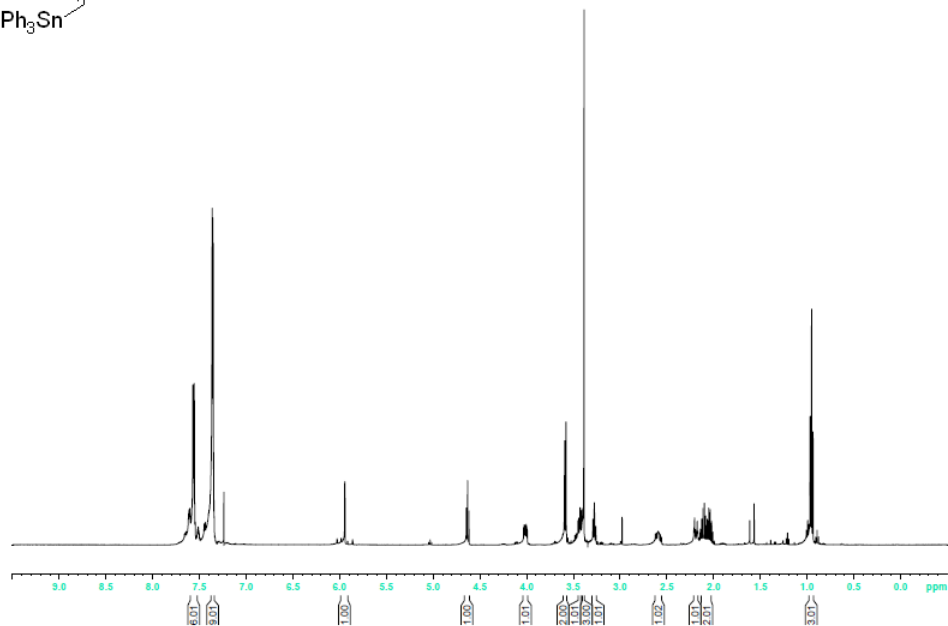
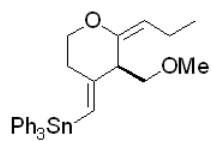
47. DEPT-135 spectrum for **96b** in CDCl₃48. HSQC spectrum for **96b** in CDCl₃

49. HMBC spectrum for **96b** in CDCl₃50. COSY spectrum for **96b** in CDCl₃

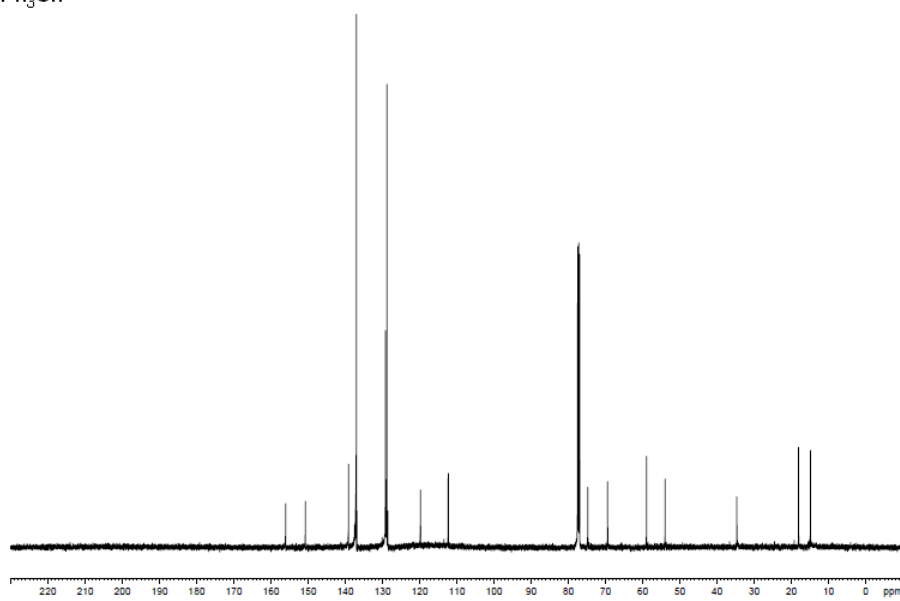
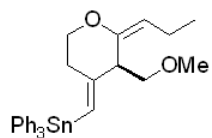
51. NOESY spectrum for **96b** in CDCl₃

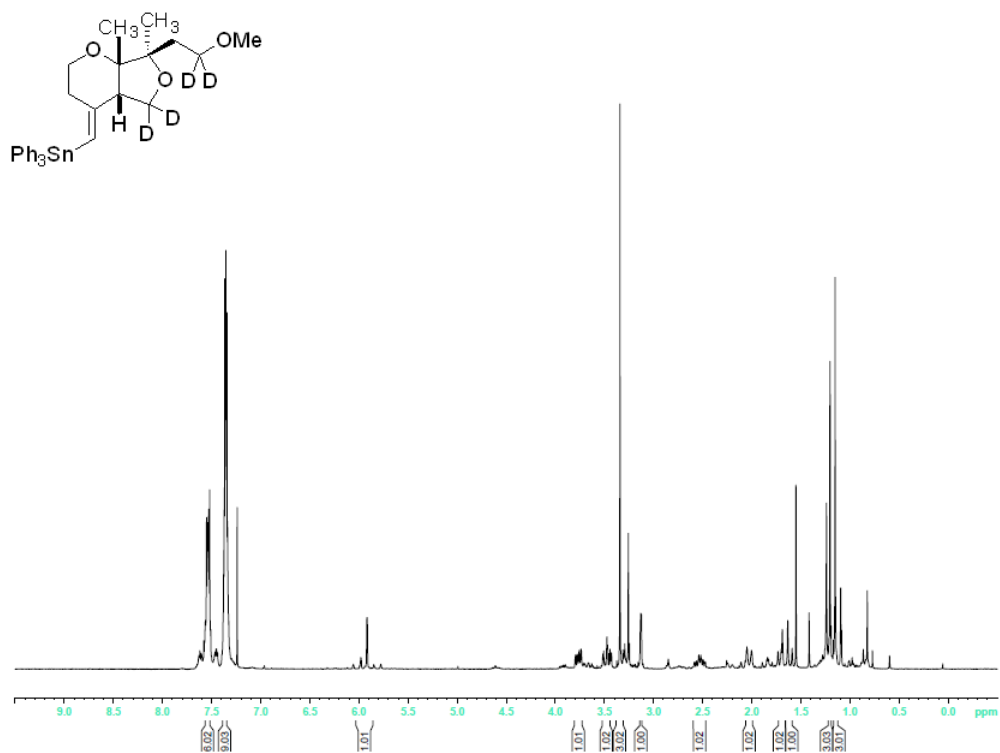
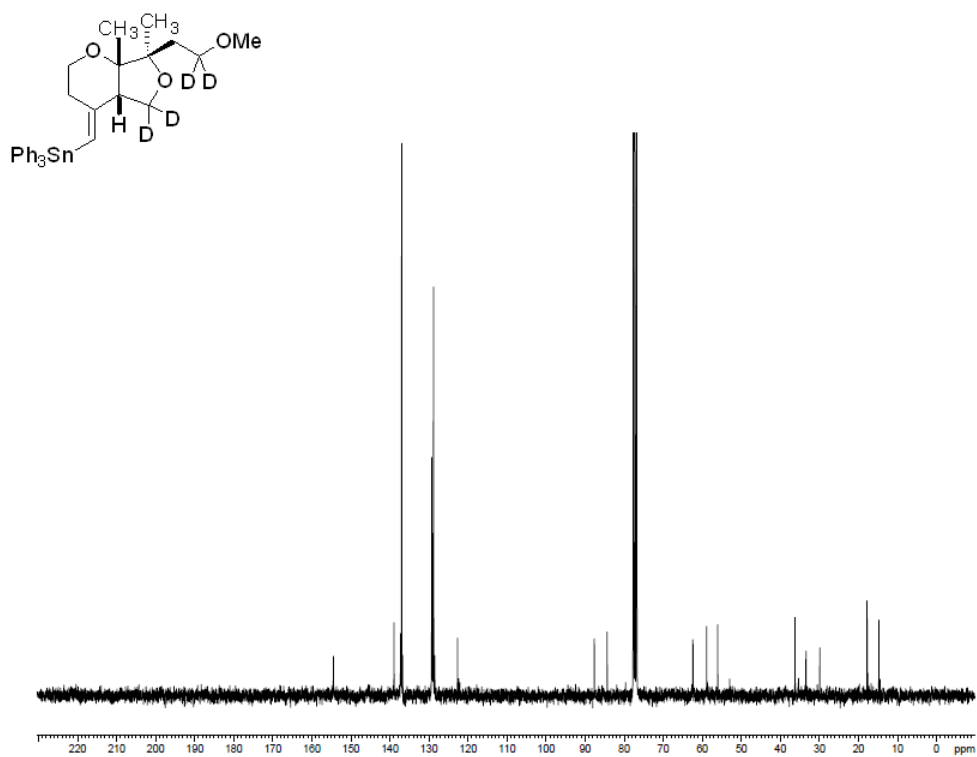
Appendix 4: Chapter 4 Section 4.4.0 Spectral Data

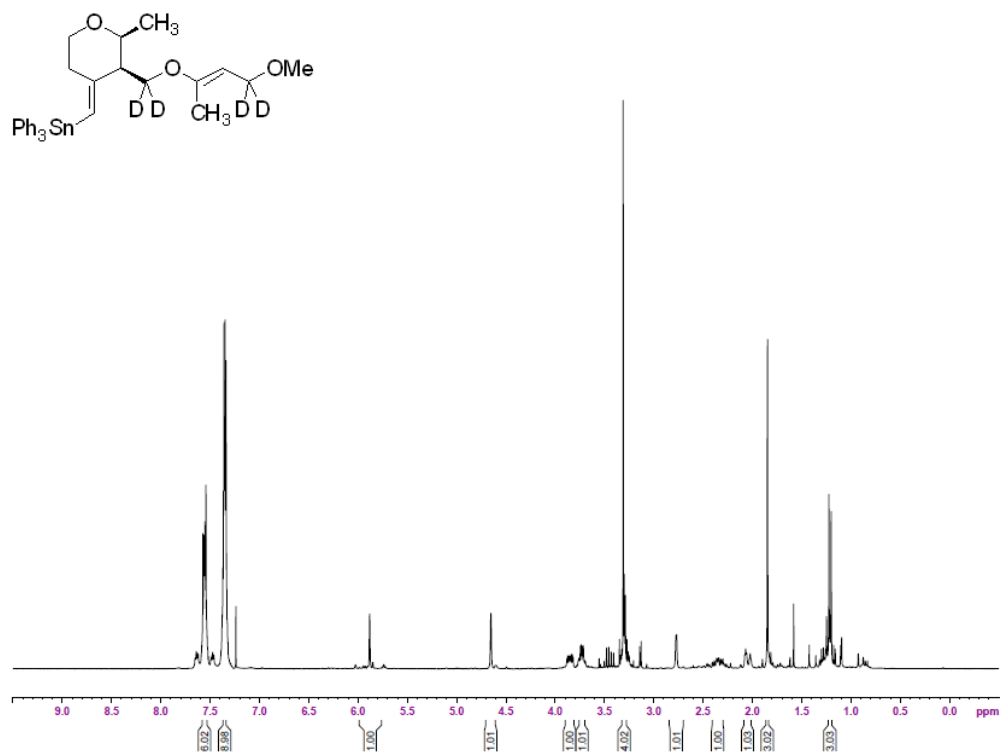
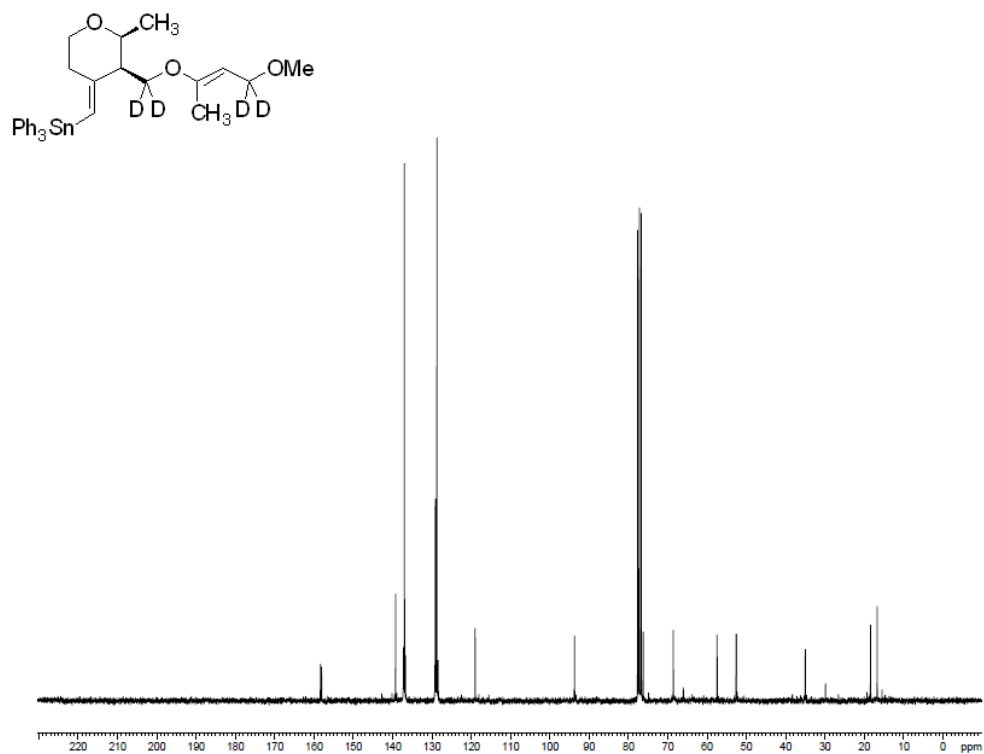
1. ^1H NMR spectrum for **91c** in CDCl_3



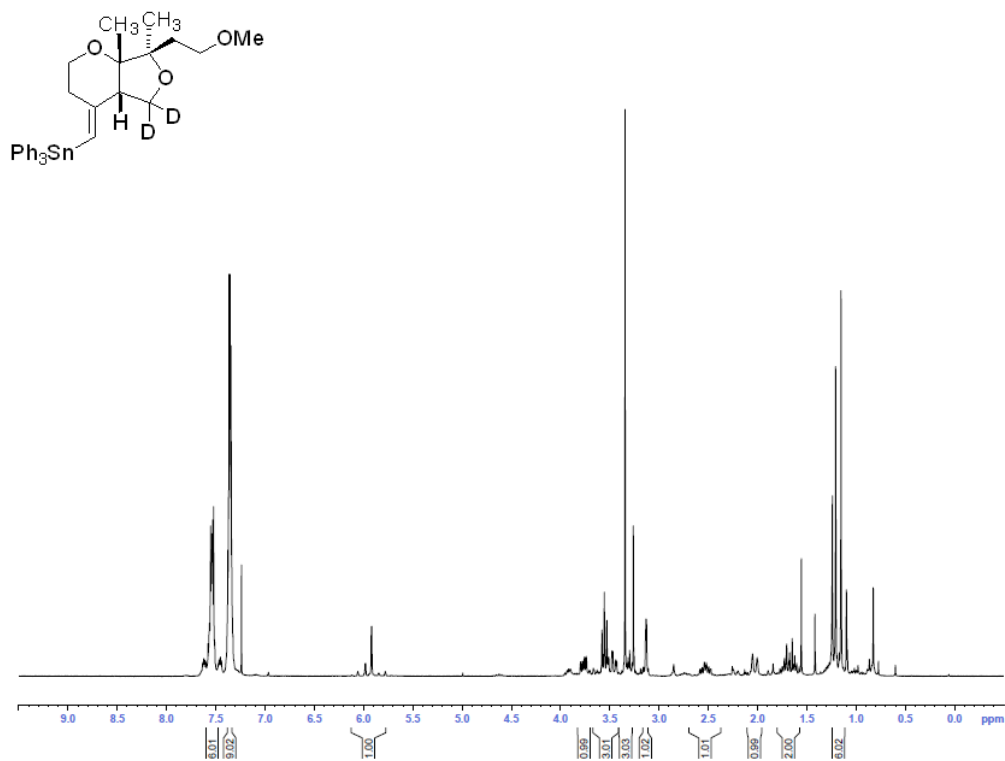
2. ^{13}C NMR spectrum for **91c** in CDCl_3



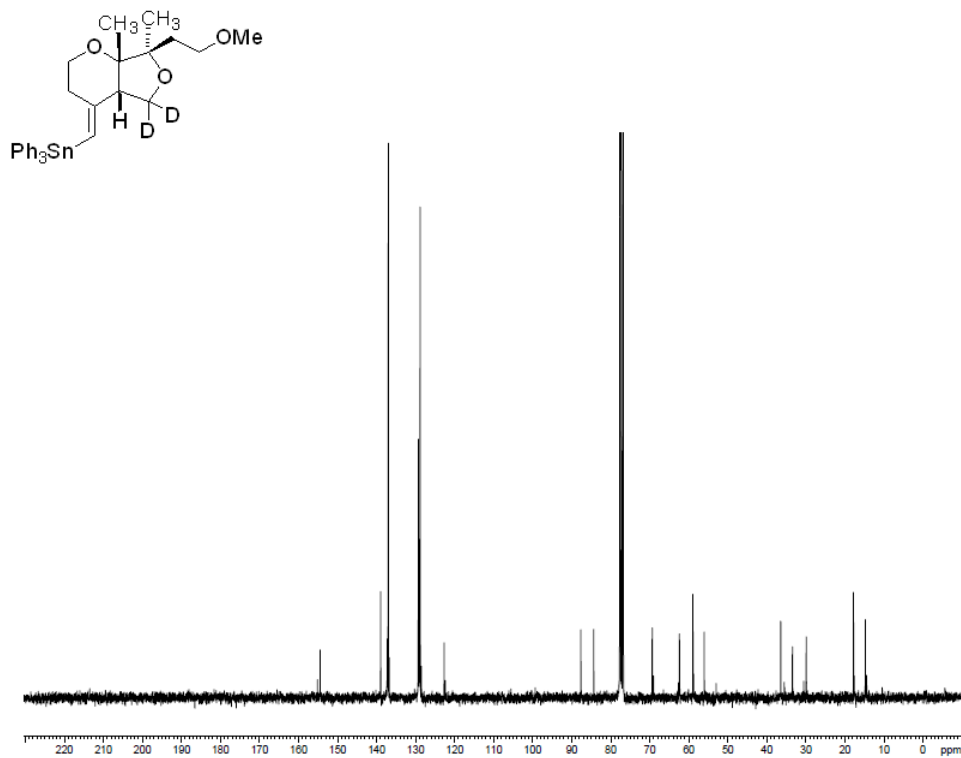
3. ^1H NMR spectrum for **94k** in CDCl_3 4. ^{13}C NMR spectrum for **94k** in CDCl_3 

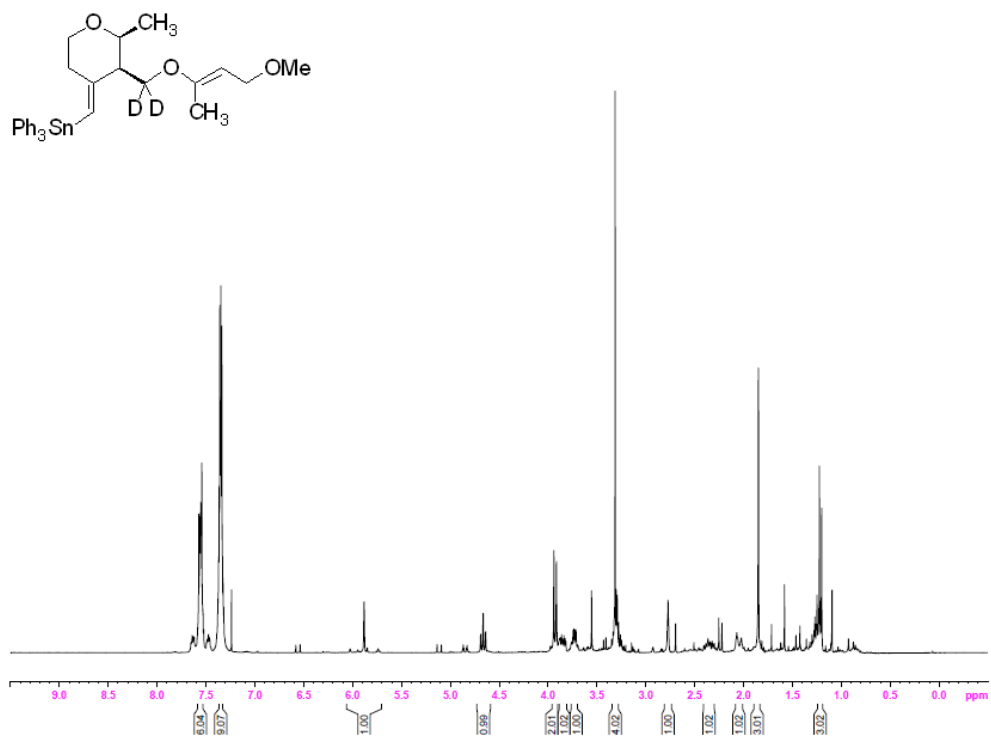
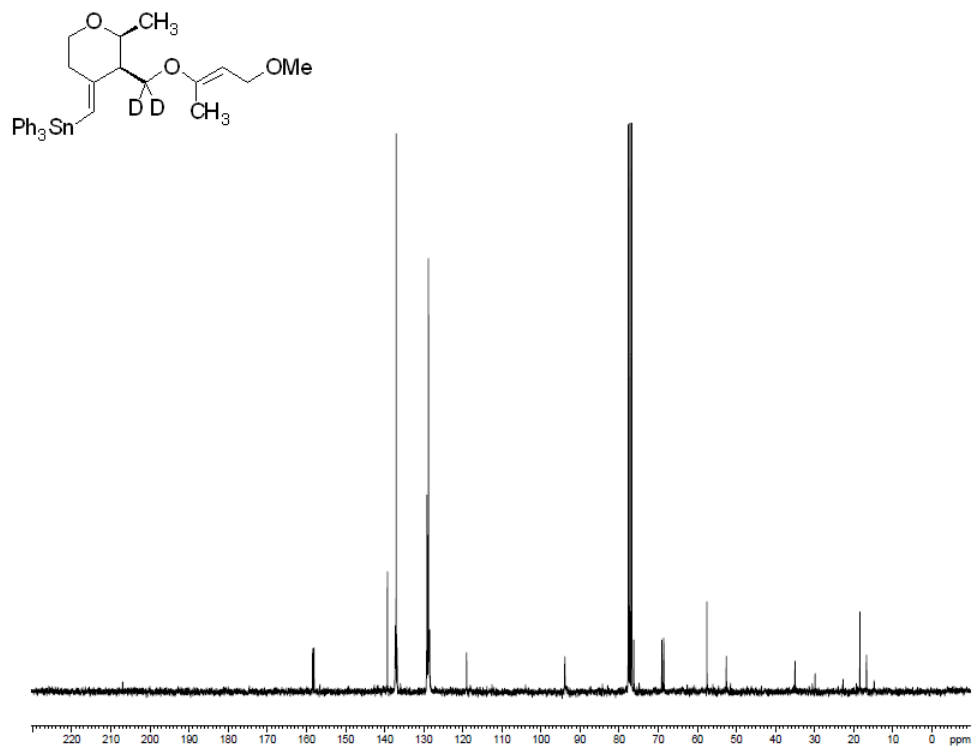
5. ^1H NMR spectrum for **95k** in CDCl_3 6. ^{13}C NMR spectrum for **95k** in CDCl_3 

7. ^1H NMR spectrum for **94I** in CDCl_3

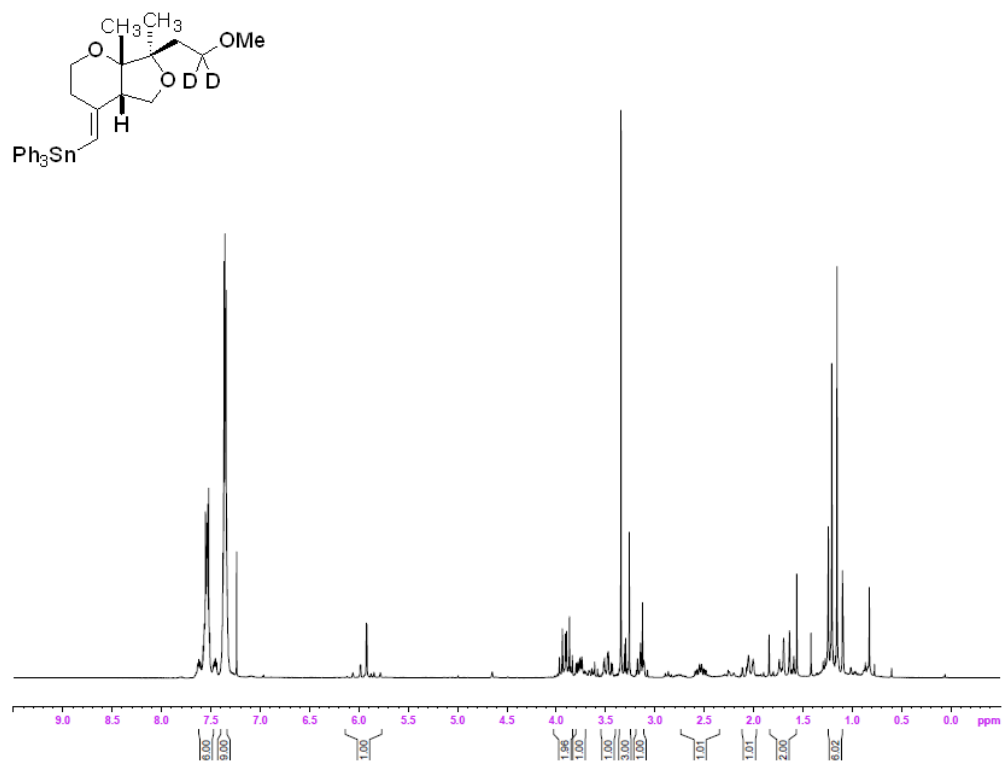


8. ^{13}C NMR spectrum for **94I** in CDCl_3

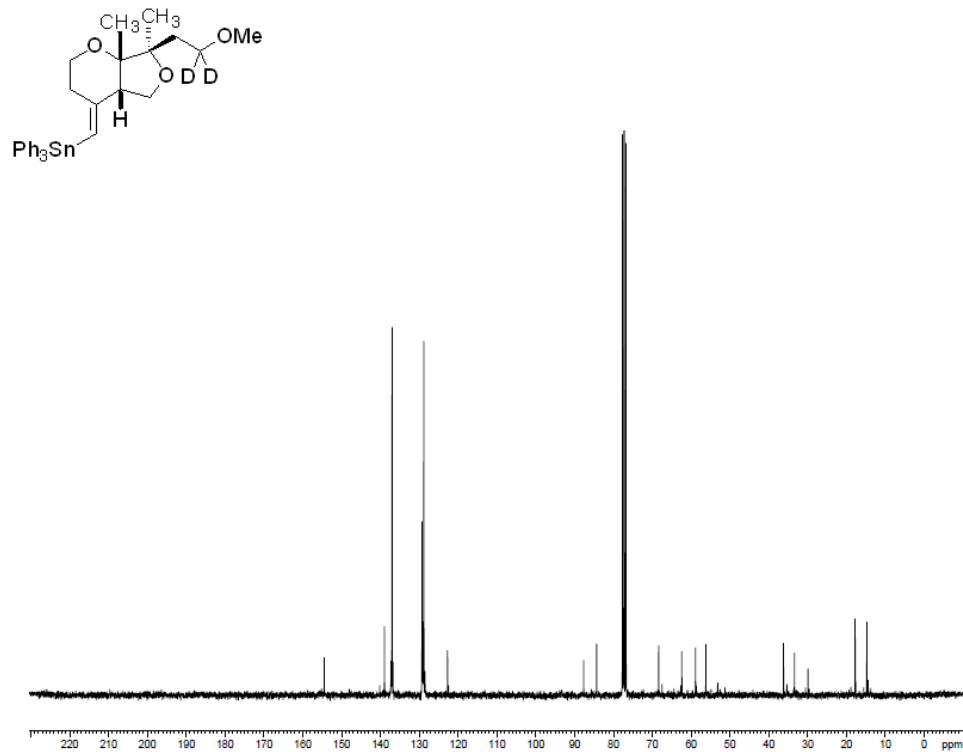


9. ^1H NMR spectrum for **951** in CDCl_3 10. ^{13}C NMR spectrum for **951** in CDCl_3 

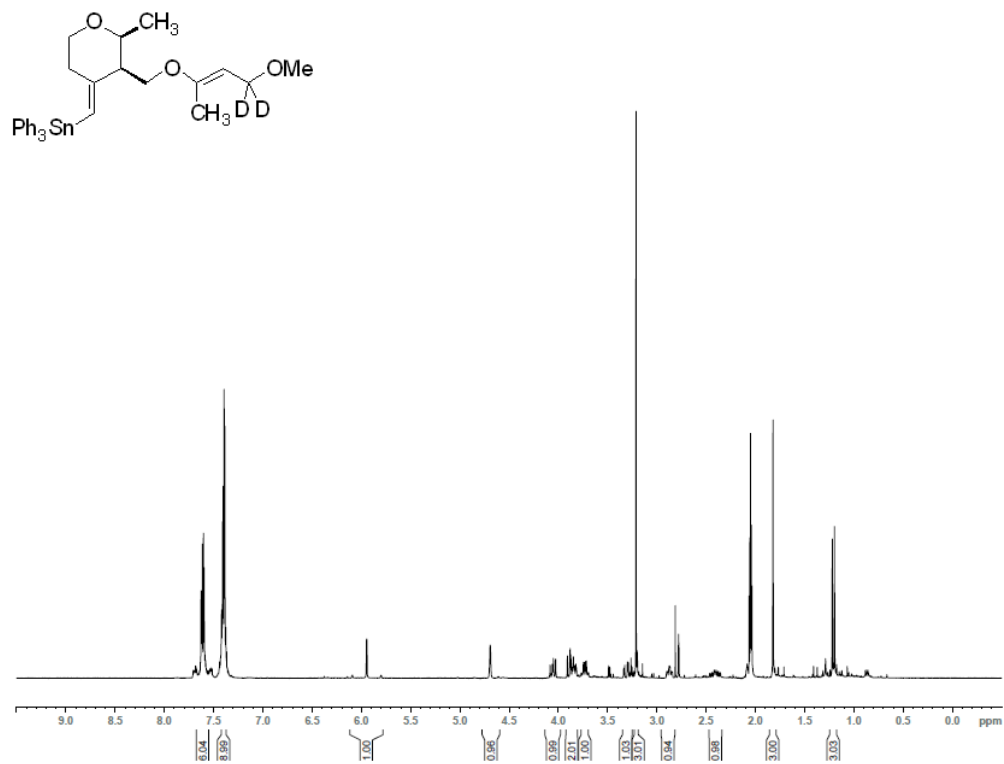
11. ^1H NMR spectrum for **94m** in CDCl_3



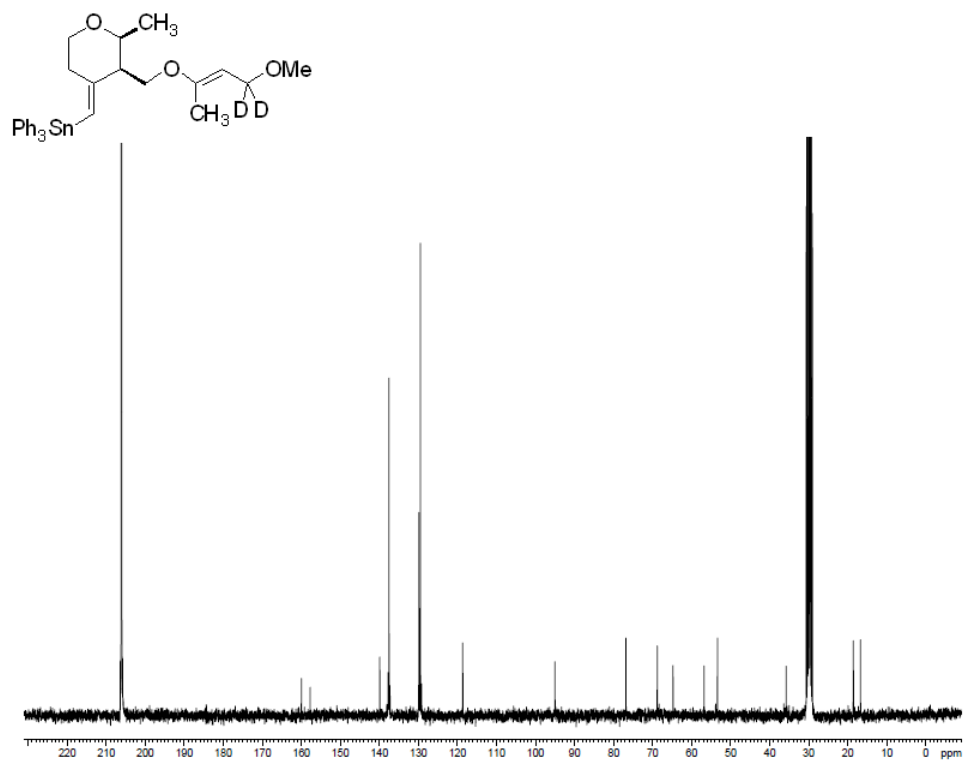
12. ^{13}C NMR spectrum for **94m** in CDCl_3



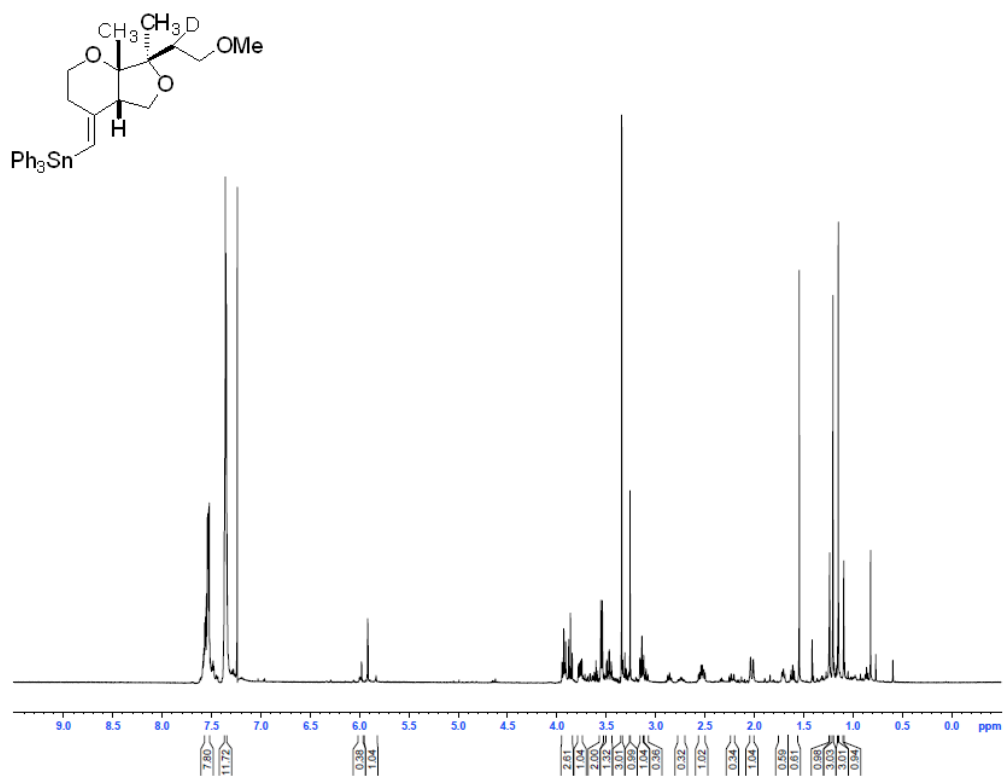
13. ^1H NMR spectrum for **95m** in CDCl_3



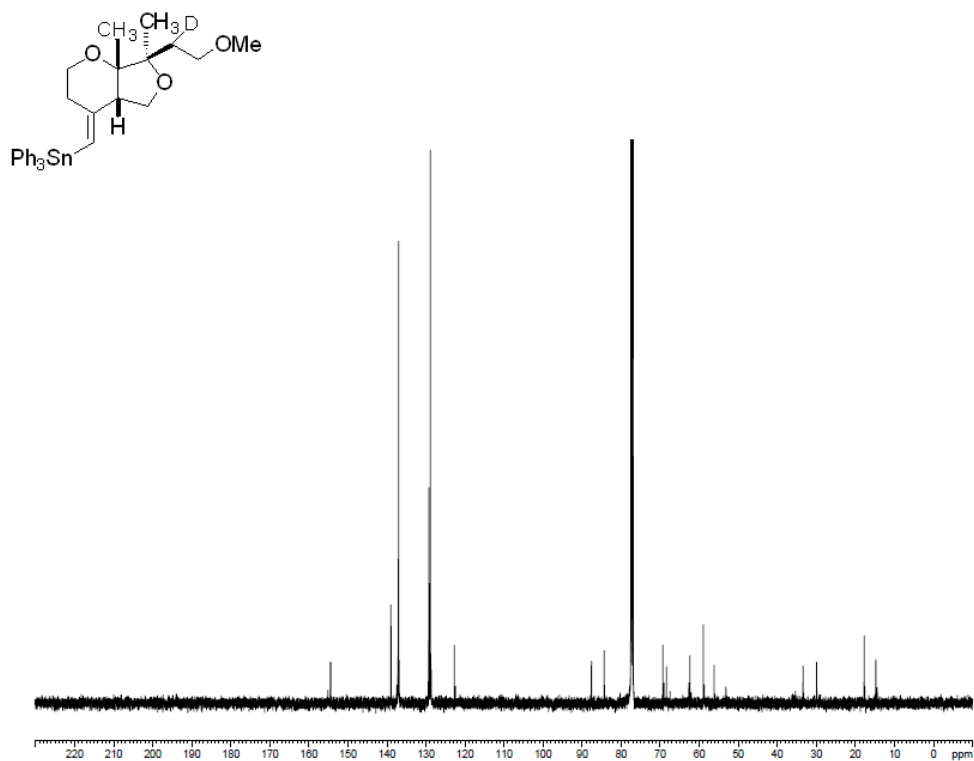
14. ^{13}C NMR spectrum for **95m** in CDCl_3



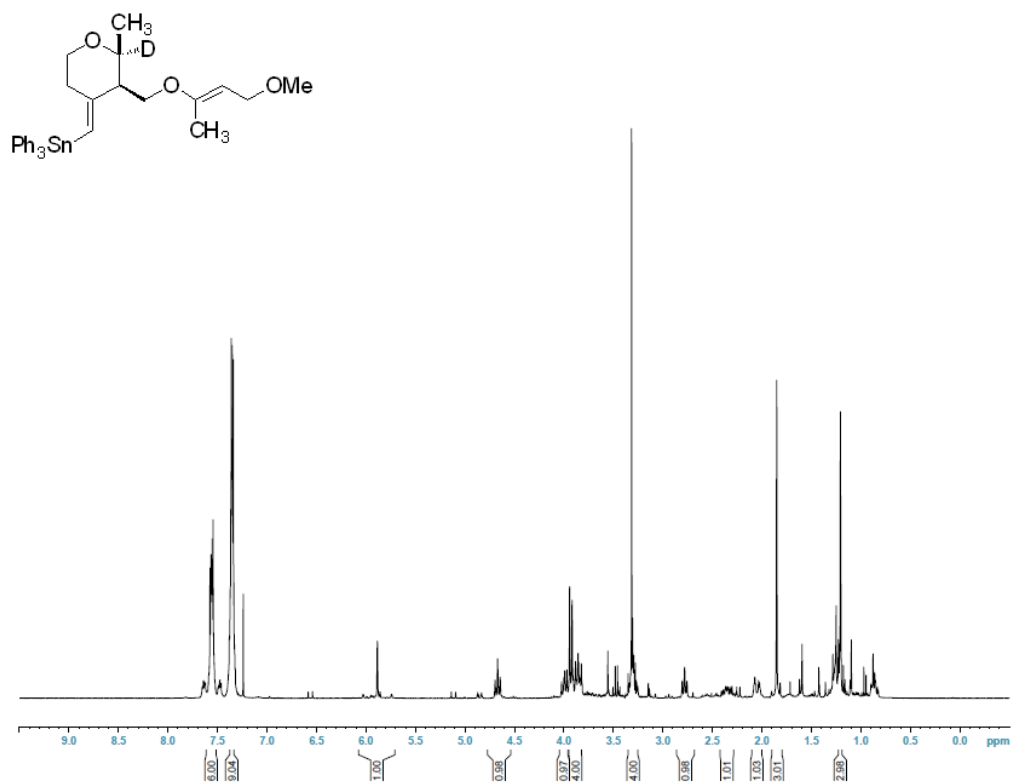
15. ^1H NMR spectrum for **94n** in CDCl_3



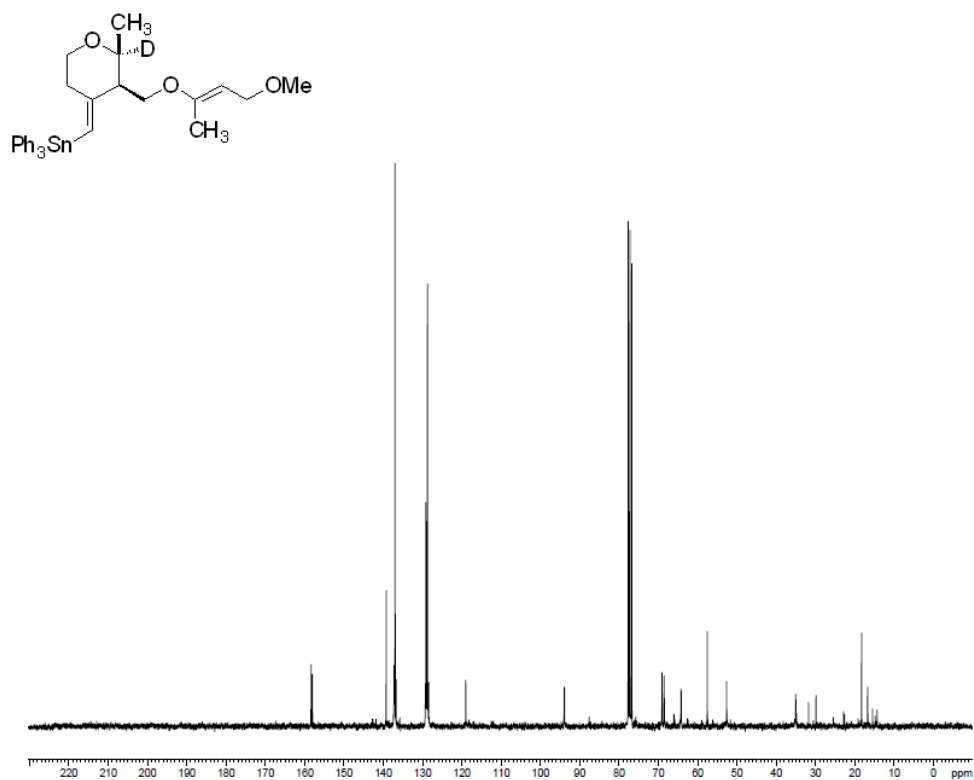
16. ^{13}C NMR spectrum for **94n** in CDCl_3



17. ^1H NMR spectrum for **95n** in CDCl_3



18. ^{13}C NMR spectrum for **95n** in CDCl_3



Appendix 5: Publications and Presentations

Research Publications:

- (3) **Davies, K. A.**; Wulff, J. E. Marrying Iterative Synthesis to Cascading Radical Cyclization: 6-endo/5-exo Radical Cascade across Bis-Vinyl Ethers. *Org. Lett.* **2011**, 13, 5552-5555.
- (2) **Davies, K. A.**; Kou, K. G. M.; Wulff, J. E. Oxygen-containing analogues of juvenile hormone III. *Tetrahedron Lett.* **2011**, 52(18), 2302-2305.
- (1) **Davies, K. A.**; Abel, R. C.; Wulff, J. E. An Operationally Simple Copper-Promoted Coupling of Terminal Alkynes with Benzyl Halides. *J. Org. Chem.* **2009**, 74(10), 3997-4000.

Conference Presentations:

- (3) Poster: **K. A. Davies**, N. F. O'Rourke, and J. E. Wulff. (2009). Synthesis of Novel Beta-Sheet Mimetics for the Inhibition of Protein-Protein Interactions. Presented at the Banff Symposium for Organic Chemistry, Banff, AB. October 31, 2009. *Received the Banff Organic Synthesis Poster Prize.*
- (2) Lecture: **K. A. Coopersmith**, and J. E. Wulff. (2009). An Iterative Approach to the Synthesis of Novel Beta-Sheet Mimetics for the Disruption of PD-1/PD-L1 Interactions in Pancreatic Cancer. Presented at the 2009 Volcano Conference in Chemical Biology, Seattle, WA. March 1, 2009.
- (1) Poster: **K. A. Coopersmith**, and J. E. Wulff. (2008). An Iterative Approach to the Synthesis of Pseudo-Steroidal Beta-Sheet Mimetics. Presented at the Canadian Society for Chemistry's 2008 National Meeting, Edmonton, AB. May 26, 2008. *Received the ChemComm Organic Synthesis Poster Prize.*