

**PART A: 5- AND 6-MEMBERED HYDRAZIDES AS POTENTIAL
CATALYSTS FOR DIELS-ALDER CYCLOADDITIONS**

**PART B: SYNTHESIS OF ISOCAMPHOLENIC ACID
DERIVATIVES FROM CAMPHOR STARTING MATERIALS**

**PART C: APPLICATIONS FOR THE SYNTHESIS OF
MULTISUBSTITUTED OLEFINS FROM β -CHLORO- α -IODO- α , β -
UNSATURATED ESTERS**

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ABSTRACT

Part A: Synthesis of 5- and 6-Membered Camphor-Based Hydrazides as Organocatalysts for Cycloaddition Reactions

The favorable environmental and reactivity qualities of organocatalysts are contributing to the popularization of this method for the acceleration of enantioselective reactions. Research in our group has been focused on the synthesis of camphor-derived hydrazide based organocatalysts for enantioselective cycloaddition processes. Recent results suggest that the presence of an exocyclic electron withdrawing group on the hydrazide moiety, as well as the incorporation of the hydrazide moiety into a 6-membered ring, may have a beneficial effect on the kinetics of the catalysts. A variety of camphor-based cyclic hydrazides have been synthesized and tested in Diels-Alder reactions, varying both the ring size and placement of the electron withdrawing group.

ABSTRACT

Part B: Synthesis of Isocampholenic Acids by the Rearrangement of Camphor Derivatives

A variety of substituted isocampholenic acid derivatives have been prepared by rearrangement of the camphor skeleton of a variety of tertiary alcohols derived from ketopininc acid. The reaction is highly reliable and retains the stereochemical information from the camphor scaffold. This rearrangement represents an efficient way to prepare synthetically useful isocampholenic acids. Mechanistic experiments show that the rearrangement does not involve exogenous water and that a short-lived carbocation is implicated in the reaction.

ABSTRACT

Part C: Diastereoselective Formation of Quaternary Centers from Stereodefined Trisubstituted Alkenes

Previous work in our laboratory has focused on the preparation of single-isomer tri- and tetra-substituted olefins. This methodology has been used in the construction of a variety of alkenyl esters in good to excellent yields. These alkenyl esters could then be transformed into the corresponding 3,3-disubstituted allyl boronates in a stereocontrolled fashion. There are a limited number of methods available to prepare single isomer 3,3-disubstituted allyl boronates, which can be important precursors in the stereoselective preparation of all-carbon quaternary centers. Our methodology has therefore been applied to the construction of single isomer 3,3-disubstituted allyl boronates and subsequently used in the stereoselective generation of all-carbon quaternary centers by the reaction of these allyl boronates with aldehydes.

LIST OF SCHEMES

Scheme 1. Use of proline as an organocatalyst in intramolecular aldol reaction.	1
Scheme 2. Thiourea catalyzed enantioselective hydrocyanation reaction.....	2
Scheme 3. Use of squaramide catalyst 3 in conjugate addition reactions.	2
Scheme 4. Kinetic resolution of <i>trans</i> -1,2-acetamidocyclohexanol (5) with peptide catalyst 4.	3
Scheme 5. β -hairpin containing octapeptide with greater selectivity in a kinetic resolution reaction.	3
Scheme 6. Stereochemical model for kinetic resolution reaction.....	4
Scheme 7. Enantioselective synthesis of brominated biaryl 8 by peptide catalysis.	5
Scheme 8. Chiral phosphoric acid 9 as an organocatalyst for Mannich-type reactions.	6
Scheme 9. Michael addition facilitated by derivative 10.	6
Scheme 10. Synthesis of an intermediate of (+)-grandisol utilizing bifunctional Brønsted acid/base catalyst 11.	7
Scheme 11. Energy diagram showing the principle behind A) HOMO activation, B) SOMO activation, and C) LUMO activation.	9
Scheme 12. Use of MacMillan catalyst 12 to affect the α -fluorination of aldehydes.	10
Scheme 13. General catalytic cycle for enamine derivatives.	11
Scheme 14. Trienamine activation in Diels-Alder reaction by proline-derived catalyst 13.....	11
Scheme 15. Stereochemical rationale for trienamine derivative 14.	12
Scheme 16. Enantioselective α -allylation with catalyst 15 via SOMO catalysis.....	12
Scheme 17. Proposed catalytic cycle for SOMO activation with organocatalyst 15.	13
Scheme 18. Rationale behind LUMO activation.	14
Scheme 19. Seminal reaction in iminium catalysis involving MacMillan catalyst 17.....	14
Scheme 20. General catalytic cycle for iminium activation.	15
Scheme 21. Diels-Alder reaction between cyclopentadiene and <i>p</i> -benzoquinone.	15
Scheme 22. FMO description of normal electron demand Diels-Alder reaction	16
Scheme 23. FMO description of inverse electron demand Diels-Alder reaction.	16
Scheme 24. The influence of orbital coefficients on the regiochemical outcome of the Diels-Alder reaction.	17
Scheme 25. <i>Endo</i> and <i>Exo</i> diastereomers arising from a normal electron demand DA cycloaddition. ...	18
Scheme 26. Activation of Diels-Alder reaction by Lewis acids.....	19

Scheme 27. Synthesis of imidazolidinone catalysts.	19
Scheme 28. Origin of enantiocontrol with imidazolidinone organocatalysts	20
Scheme 29. Key Diels-Alder reaction-iminium cyclization cascade sequence en route to (-)-vincorine catalyzed by chiral amine 17.	20
Scheme 30. Diels-Alder reaction between cyclopentadiene and (<i>E</i>)-cinnamaldehyde catalyzed by diaryl prolinol derivative 18.....	21
Scheme 31. Thought process behind the design of more nucleophilic iminium catalysts.	22
Scheme 32. Energetic consequences of the α -heteroatom effect in raising the energy of the HOMO of a hydrazine derivative.	23
Scheme 33. Attempted scaffolds for hydrazine-based catalysts.....	23
Scheme 34. Hydrazide catalyst 19 in the Diels-Alder reaction between (<i>E</i>)-cinnamaldehyde and cyclopentadiene.	24
Scheme 35. Originally proposed catalyst architectures.	24
Scheme 36. Additional catalyst architectures incorporating the hydrazine moiety in a simpler scaffold.	25
Scheme 37. “Privileged” 5-membered ring hydrazides based on camphor architecture.....	25
Scheme 38. Optimized reaction conditions utilizing 22 as catalyst.	25
Scheme 39. Proposed model for enantiocontrol with catalyst 22.....	26
Scheme 40. Evaluation of both diastereomers of conformationally rigid methyl-phenyl catalysts.	27
Scheme 41. Use of catalyst 22 in 1,3-dipolar cycloadditions of nitrones.	28
Scheme 42. Unsuccessful transformations using catalyst 22.	28
Scheme 43. Hydrazide containing achiral catalysts investigated by Tomkinson <i>et al.</i>	29
Scheme 44. Organocatalytic addition of azomethine ylides to aldehydes using 30.....	31
Scheme 45. Possible reaction model leading to enantioselective formation of the <i>exo</i> product.....	32
Scheme 46. Potential reaction model for addition of azomethine ylides to aldehydes facilitated by catalyst 22.	32
Scheme 47. Synthesis of azomethine ylide 31.	32
Scheme 48. Conversion of <i>exo/endo</i> aldehyde mixture to alcohols.....	34
Scheme 49. DL-proline catalyzed addition of azomethine ylides to aldehydes as a control reaction.....	34
Scheme 50. Diels-Alder reaction employing 6-membered hydrazide catalysts possessing an exocyclic electron withdrawing group.....	35
Scheme 51. Proposed general structures for chiral 6-membered hydrazide catalysts possessing an exocyclic electron withdrawing group.....	35
Scheme 52. Synthesis of 6-membered hydrazide catalyst 33.....	36

Scheme 53. Diels-Alder cycloaddition catalyzed by 33.....	37
Scheme 54. Synthesis of derivative 38.....	40
Scheme 55. Enantiospecific synthesis of 41.....	42
Scheme 56. Retrosynthesis of racemic catalyst 46.....	43
Scheme 57. Attempted synthesis of derivative 45.....	43
Scheme 58. Attempted one-pot cyclization/electron withdrawing group installation.....	43
Scheme 59. Attempted synthesis of 45 using dimesylate 53.....	44
Scheme 60. Attempted treatment of 53 with hydrazine hydrate followed by electron withdrawing group installation.	44
Scheme 61. Retrosynthetic analysis for potential catalyst 54 starting with C2-symmetric 57.....	44
Scheme 62. Attempted synthesis of racemic 54.	45
Scheme 63. Proposed synthesis for diastereopure catalyst 66.	45
Scheme 64. Retrosynthetic analysis for potential racemic catalyst 67.....	46
Scheme 65. Attempted synthesis of potential catalyst 67.	46
Scheme 66. Attempted deprotection/cyclization of derivative 73.....	47
Scheme 67. Attempted deprotonation/cyclization of derivative 73.....	47
Scheme 68. Variations of ring size/electron withdrawing group placement for camphor based hydrazides.....	48
Scheme 69. Retrosynthetic analysis for derivatives of general structure 74.....	49
Scheme 70. Synthesis of alkene 82.	50
Scheme 71. Attempted hydroboration of 82.....	50
Scheme 72. Synthesis of 80 via hydroboration of protected derivative 81.	50
Scheme 73. Attempted conversion of alcohol 85 to bromoketone 79.....	51
Scheme 74. Synthesis of bromoketone 79 from protected intermediate 80.	51
Scheme 75. Attempted formation of 86 from bromoketone 79.....	51
Scheme 76. Formation of hydrazone 87 from alcohol 85.	52
Scheme 77. Structure proposed for product 88.	54
Scheme 78. Potential mechanism for formation of 88.	55
Scheme 79. Retrosynthetic plan for the synthesis of derivatives with general structure 75.	55
Scheme 80. Synthesis of 6-membered hydrazide 98 from 80.	56

Scheme 81. Efficiency and enantioselectivity of derivatives 99 in Diels-Alder reactions	57
Scheme 82. Synthesis of diastereomers 100 and 101	58
Scheme 83. Retrosynthetic analysis for derivative 104.....	61
Scheme 84. Synthesis of derivative 104.....	61
Scheme 85. Retrosynthetic plan for 5-membered camphor-based hydrazides.....	63
Scheme 86. Synthesis of bromoketone 110.....	63
Scheme 87. Attempted cyclization of crude hydrazone 111.	64
Scheme 88. Synthesis of iodoketone 113.	66
Scheme 89. Attempted cyclization of 116 after removal of the –Boc group.	71
Scheme 90. Attempted cyclization/electron withdrawing group installation of deprotected derivative 118.	71
Scheme 91. Synthesis of desired cyclized product 117.....	73
Scheme 92. Reduction of 117 with sodium cyanoborohydride to obtain 121.....	73
Scheme 93. Successful control of iminium geometry by 23.	82
Scheme 94. Hypothesized unsuccessful control of iminium geometry by 121-124.	82
Scheme 95. Reactive conformations calculated for the iminiums arising from catalysts 123 and 124. ..	83
Scheme 96. Reactive conformations calculated from iminium ions 127-135.....	83
Scheme 97. Synthesis of 136.....	86
Scheme 98. Synthesis of 137.....	87
Scheme 99. Synthesis of derivative 138.....	88
Scheme 100. Reactive conformations calculated for iminium ions 140-142.....	89
Scheme 101. Retrosynthetic plan for phenyl disubstituted camphor derivative 143.	90
Scheme 102. Synthesis of diphenyl derivative 145.....	90
Scheme 103. Attempted mesylation of 145.....	91
Scheme 104. Reduction of 144/byproduct mixture.	97
Scheme 105. Possible formation of hydrazone 148.	98
Scheme 106. Derivative 150 as a potential substrate for hydrazone formation/cyclization.....	99
Scheme 107. Previous catalyst design 23 and proposed improved design 153.....	100
Scheme 108. Retrosynthetic plan for the synthesis of a derivative 154.....	100

Scheme 109. Cyclopentanoid compounds obtained from treatment of 9,10-dibromocamphor with base.	147
Scheme 110. Intermediate lactone 166 implicated in the formation of hydroxyacid 165.....	148
Scheme 111. Preparation of hydrindenone derivative 167 from methyl ester 164.	148
Scheme 112. Diastereoselective alkylation of lactone 166 and subsequent transformation to chiral synthons of type 168.....	149
Scheme 113. Attack of preferred conformation of enolate on electrophile.....	149
Scheme 114. Formal synthesis of California red scale pheromone 172 via isocampholenic acid derivative 163.	150
Scheme 115. Products synthesized via isocampholenic acid intermediates.....	150
Scheme 116. Synthesis of cyclopentene carboxylic acids via 4-substituted camphor derivatives.....	151
Scheme 117. Breakage of the C1-C2 bond in camphor by photolysis.	151
Scheme 118. Photolysis of C1-C2 bond in camphor oxime 178 to give α -campholenic nitrile 177.	151
Scheme 119. Production of α -campholenic acid from the sodium salt of camphorsulfonic acid.....	151
Scheme 120. Natural products synthesized from camphorsulfonic acid via an α -campholenic acid derivative.	152
Scheme 121. Obtention of α -campholenic acid derivative 183 from camphor oxime derivative 184...	152
Scheme 122. Conversion of camphor oxime derivative 185 into campholenic acid derivative 186 en route to Balduilin (187).	153
Scheme 123. Catalytic hydrosilylation of camphor oxime to obtain α -campholanic amine 188.....	153
Scheme 124. Diastereoselective synthesis of (+)-trans- α -campholanic acid derivatives by DGPTI....	154
Scheme 125. Proposed mechanism for the transformation of camphor-based derivatives 189 to campholanic acid derivatives 190.....	154
Scheme 126. Attempted synthesis of an intermediate for a potential organocatalyst resulting in byproduct formation.	155
Scheme 127. Control reaction suggesting hydrazide is not involved in the rearrangement process.....	155
Scheme 128. Attempted derivatization reaction to determine the identity of the byproduct.	156
Scheme 129. Synthesis of diaryl substituted alcohols from (+)-ketopinic acid.	157
Scheme 130. Possible pathways for rearrangement of diaryl substituted alcohols to isocampholenic acids.	159
Scheme 131. Methyl ester 216 formed exclusively when methanol used as an external nucleophile. ..	160
Scheme 132. Crossover experiment performed between methyl ether 217 and alcohol 209.....	160
Scheme 133. Application to the construction of 218 from dimethyl alcohol 219.....	161

Scheme 134. Attempted synthesis of dibenzyl substituted isocampholenic acid 221.....	161
Scheme 135. Preparation of differentially substituted alcohol 224 and subsequent rearrangement.	162
Scheme 136. Distortion of tetrasubstituted olefins bearing all-carbon linked groups.....	178
Scheme 137. Regioisomers and stereoisomers possible from carbometallation processes.....	179
Scheme 138. Use of organozinc reagent 226 to obtain vinylzinc intermediate 227, which was post-functionalized to tetrasubstituted olefin 228.	180
Scheme 139. Synthesis of tetrasubstituted alkene 229 from alkynyl thioether 230.	181
Scheme 140. Synthesis of tetrasubstituted olefins bearing all different alkyl groups via a key carbozirconation reaction.....	182
Scheme 141. General structures for olefin templates used in the construction of tetrasubstituted olefins.	182
Scheme 142. Use of an electronic bias to install remaining groups onto dihalogenated olefin template to make tetrasubstituted olefins.	183
Scheme 143. Use of a stereo-enriched dihalogenated acyclic olefin template to form a tetrasubstituted olefin.	183
Scheme 144. Synthesis of tetrasubstituted olefins via <i>in situ</i> generated ketenes.	184
Scheme 145. Generation of β -chloro- α -iodo- α , β -unsaturated ester templates.....	184
Scheme 146. Determination of alkene geometry.....	185
Scheme 147. Electrophilic addition mechanism proposed to explain formation of single isomer.....	185
Scheme 148. Representative example of the sequential Sonogashira couplings to obtain tetrasubstituted olefins.	186
Scheme 149. Sonogashira reaction followed by Suzuki-Miyaura coupling to obtain tetrasubstituted olefin 238.....	186
Scheme 150. Use of sequential Suzuki-Miyaura couplings to produce tetrasubstituted olefin 239 from precursor 240.	186
Scheme 151. Optimal conditions to produce β -chloro derivative 241 using S-Phos as ligand.....	187
Scheme 152. Small ligand facilitates formation of tetrasubstituted olefin 243 in second Suzuki-Miyaura coupling.	187
Scheme 153. Use of alkyl-Suzuki cross coupling reaction to obtain tetrasubstituted derivatives 244. .	187
Scheme 154. Formation of an unexpected trisubstituted olefin 245.	188
Scheme 155. Proposed catalytic cycle to account for formation of trisubstituted olefin 245.	188
Scheme 156. Unoptimized formation of trisubstituted olefins 247 directly from alkynyl ester 249.	189
Scheme 157. Use of small ligand to provide derivative 247 only in good yield.....	189

Scheme 158. Proposed catalytic cycle for production of trisubstituted olefins from alkynyl esters.....	190
Scheme 159. Optimal conditions in the synthesis of a trisubstituted olefin 252 bearing alkyl groups..	190
Scheme 160. Optimized alkyl-Suzuki couplings onto alkynyl esters.	191
Scheme 161. Synthesis of tamoxifen by carbolithiation of diphenylacetylene.....	192
Scheme 162. Stereoselective synthesis of tamoxifen using benzoyl germane 254 and alkynoate 255..	192
Scheme 163. Bergman Cyclization on tetrasubstituted olefins 256.	193
Scheme 164. Proposed pathway leading to octyl ring product.....	194
Scheme 165. Four general strategies for the enantioselective production of quaternary centers	195
Scheme 166. General methods to create acyclic all-carbon quaternary centers	196
Scheme 167. Preparation of trisubstituted allyl boronates as precursors for quaternary center forming reactions.....	197
Scheme 168. Addition of allyl boronate 258 to aldehydes.....	198
Scheme 169. Proposed transition state leading to formation of quaternary carbon containing products.	198
Scheme 170. Enantioselective preparation of all-carbon quaternary centers using allyl boronates.....	198
Scheme 171. Proposed transition state to explain stereoselectivity in reaction with 261.	199
Scheme 172. Tandem carbocupration/electrophilic trapping of alkyneates to make 2-alkoxycarbonyl allyl boronates.....	199
Scheme 173. Use of 2-alkoxycarbonyl allyl boronates in γ -lactonization reactions.....	199
Scheme 174. Preparation of 3,3-disubstituted allylboranes.	200
Scheme 175. Enantioselective synthesis of all-carbon quaternary centers using tartrate ester derivatives of 3,3-disubstituted allyl boranes.....	200
Scheme 176. Stereodefined 3,3-disubstituted allyl trichlorosilanes in the enantioselective formation of quaternary centers	201
Scheme 177. One-pot preparation of quaternary centers via geminally disubstituted allyl zinc species possessing a chelating sulfoxide group.	201
Scheme 178. Proposed transition state for the formation of quaternary centers from allyl zinc species stabilized by a sulfoxide group	202
Scheme 179. Preparation of disubstituted allylborane nucleophiles from single isomer trisubstituted olefins.	203
Scheme 180. Oxidation/reduction sequence for producing a mixture of diastereomers.	205
Scheme 181. Attempted preparation of phenyl substituted alkenyl boronate 294.	208
Scheme 182. Attempted reduction of ester 301.....	208

Scheme 183. Attempted addition of a secondary alkyl borane to an alkynyl ester template	208
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LIST OF TABLES

Table 1. Comparison of catalytic activity of amine containing scaffolds in a Diels-Alder reaction.....	29
Table 2. Acid scan for addition of aldehydes to azomethine ylides.	33
Table 3. Crystallization conditions attempted in order to preferentially crystallize one diastereomeric salt. ¹	37
Table 4. Attempted formation of Mosher amide from 33.	38
Table 5. Attempted coupling of 33 to Boc-protected amino acids.	39
Table 6. Crystallization conditions for derivative 38 using tartaric acid.....	41
Table 7. Hydrazone formation with <i>t</i> -butyl carbazate	47
Table 8. Attempted cyclization of 87.	52
Table 9. Diels-Alder reactions employing 137 as a catalyst.	57
Table 10. Diels-Alder reactions employing 100 as catalyst.	59
Table 11. Diels-Alder reactions employing 101 as catalyst.	60
Table 12. Diels-Alder reactions employing 104 as catalyst.	62
Table 13. Attempted hydrazone formation/cyclization with 110.	64
Table 14. Attempted hydrazone formation to give derivatives of type 111.	65
Table 15. Attempted hydrazone formation with H ₂ NNH ₂ •HX as nucleophile.	67
Table 16. Use of hydrazides to obtain the corresponding hydrazone 115.....	69
Table 17. Addition of various bases to 116 in an attempt to provide cyclized product 117.	70
Table 18. Attempted one-pot hydrazone formation/cyclization to obtain 120.....	72
Table 19. Optimization of reduction to give 121.....	74
Table 20. Conditions attempted for Diels-Alder reactions using 121 as catalyst.....	75
Table 21. Synthesis of derivatives 122-124 as potential catalysts for Diels-Alder reactions.....	76
Table 22. 122 as a catalyst in the Diels-Alder reaction between (<i>E</i>)-cinnamaldehyde and cyclopentadiene.	77
Table 23. 123 as a catalyst in the Diels-Alder reaction between (<i>E</i>)-cinnamaldehyde and cyclopentadiene.	79
Table 24. 124 as a catalyst in the Diels-Alder reaction between (<i>E</i>)-cinnamaldehyde and cyclopentadiene.	80
Table 25. Energy differences between <i>E</i> and <i>Z</i> iminium ions for compounds 125-135.	85

Table 26. 136 as a catalyst in the Diels-Alder reaction between (<i>E</i>)-cinnamaldehyde and cyclopentadiene.	86
Table 27. 137 in the Diels-Alder reaction between (<i>E</i>)-cinnamaldehyde and cyclopentadiene.....	87
Table 28. 138 in the Diels-Alder reaction between (<i>E</i>)-cinnamaldehyde and cyclopentadiene.....	88
Table 29. Solvent scans for attempted formation of cyclic hydrazone 144 from alcohol 145.	92
Table 30. Temperature scans for attempted formation of cyclic hydrazone 144 from alcohol 145.....	93
Table 31. Attempts to make cyclic hydrazone 144 with Lewis acids.	94
Table 32. Acid scans for attempted formation of cyclic hydrazone 144 from alcohol 145.	95
Table 33. Effects of pre-mixing the acids with the hydrazides for attempted formation of cyclic hydrazone 144 from alcohol 145.	96
Table 34. Adjustments to ratio of acid:hydrazide in hopes to obtain a larger amount of 144.....	97
Table 35. Attempted cyclization reactions of 148.....	98
Table 36. Attempted conditions to install carbamate group on (+)-ketopinic acid (105).	101
Table 37. Various amination conditions attempted for derivative 161.	103
Table 38. Attempted reductive amination of 162 from a mixture of 161 and 162.....	105
Table 39. Rearrangement of diaryl substituted alcohols 193-202 to obtain isocampholenic acids.....	158
Table 40. Use of Lewis acids to facilitate condensation between allylboronates and aldehydes.....	204
Table 41. Condensation of aldehydes with disubstituted allylboronate 278.	207
Table 42. Condensation of various trisubstituted allyl boron nucleophiles with <i>p</i> -cyanobenzaldehyde	209

LIST OF FIGURES

Figure 1. a) ^1H NMR and b) ^{13}C NMR of compound 88	53
Figure 2. INADEQUATE spectrum and predicted structure of mystery product 192.	156
Figure 3. X-ray ORTEP image of 192.....	157
Figure 4. ^1H NMR spectra of adduct 283 and diastereomeric mixture 284.....	205

LIST OF ABBREVIATIONS

Ac	acetyl
AUC	area under the curve
$[\alpha]_D$	optical rotation, sodium lamp
HOAc	acetic acid
Bn	benzyl
br	broad
CDI	carbonyldiimidazole
cm	centimeter
d	doublet
DCE	dichloroethane
DCM	dichloromethane
dd	doublet of doublet
DMF	<i>N,N</i> -dimethylformamide
DIPEA	<i>N,N</i> -diisopropylethylamine
DNB	dinitrobenzene
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EEDQ	2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
ee	Enantiomeric excess
EI	electron impact
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
Et ₂ O	diethylether
FU	Fluorescence unit
HOBT	1-hydroxybenzotriazole
HPLC	High performance liquid chromatography
Hz	hertz
λ	wavelength
iPr	isopropyl
IR	infrared spectroscopy
m	multiplet
M	molar

Me	methyl
MeOH	methanol
MHz	megahertz
mmol	millimoles
MS	mass spectrometry
nm	nanometer
NMR	nuclear magnetic resonance
p	pentet
Ph	phenyl
pmol	picomoles
ppm	parts per million
q	quartet
R _f	retention factor
rt	room temperature
s	singlet
sln	solution
t	triplet
TBAF	tetrabutylammonium fluoride
TBS	<i>t</i> -butyldimethylsilyl
TCA	trichloroacetic acid
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

TABLE OF CONTENTS

PART A: 5- AND 6-MEMBERED HYDRAZIDES AS POTENTIAL CATALYSTS FOR DIELS-ALDER CYCLOADDITIONS.....	1
INTRODUCTION	1
Non-Covalent Catalysis	1
Hydrogen bonding Catalysts	1
Catalysts exploiting ionic interactions.....	5
Covalent Catalysis	7
Enamine Catalysis	9
Iminium Catalysis	13
Diels-Alder Reaction and Iminium Catalysis	15
The α -effect and iminium catalysis	21
Effect of ring-size and electron withdrawing group placement on cyclic hydrazides.....	28
RESULTS AND DISCUSSION FOR SYNTHESIS OF HYDRAZIDE-BASED ORGANOCATALYSTS FOR CYCLOADDITION REACTIONS.....	31
Catalytic Addition of Aldehydes to Azomethine Ylides	31
Synthesis of 6-Membered Cyclic Hydrazides Possessing Exocyclic Electron Withdrawing Groups	35
Racemic Synthesis of Potential Catalysts With Resolution of Enantiomers	35
Attempted Synthesis of Chiral Catalysts Obtained From Chiral Starting Materials	42
Variation of Electron Withdrawing Group Placement and Ring Size of Camphor-Based Cyclic Hydrazides	48
6-Membered Camphor-Based Hydrazides Possessing an Exocyclic Electron Withdrawing Group.....	49
6-Membered Camphor-Based Hydrazides Possessing an Endocyclic Electron Withdrawing Group	55
5-Membered Camphor-Based Hydrazides Possessing Both Exo- and Endocyclic Electron Withdrawing Groups	61
Future Directions	63
5- Membered Camphor-Based Hydrazides Possessing An Exocyclic Electron Withdrawing Group	63
Future Directions	99
Design of a potential camphor-based hydrazide organocatalyst possessing a different architecture.....	99

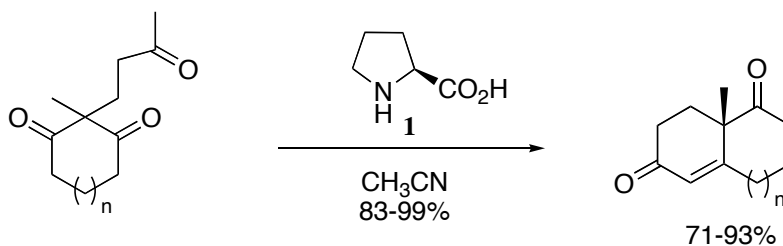
Future Directions	106
EXPERIMENTAL SECTION FOR HYDRAZIDE-BASED ORGANOCATALYSTS	107
Computational Methods	134
REFERENCES	142
PART B: SYNTHESIS OF ISOCAMPHOLENIC ACID DERIVATIVES FROM CAMPHOR STARTING MATERIALS.....	147
INTRODUCTION	147
RESULTS AND DISCUSSION FOR FACILE SYNTHESIS OF ISOCAMPHOLENIC ACIDS VIA REARRANGEMENT OF CAMPHOR DERIVATIVES	155
Future Directions	162
EXPERIMENTAL SECTION	163
REFERENCES	176
PART C: APPLICATIONS FOR THE SYNTHESIS OF MULTISUBSTITUTED OLEFINS FROM β - CHLORO- α -IODO- α , β -UNSATURATED ESTERS	178
INTRODUCTION	178
Carbometallation of Alkynes	179
Functionalization of Existing Alkene Templates	182
Synthesis of tri- and tetrasubstituted olefins from β -chloro- α -iodo- α , β -unsaturated esters	184
Applications of methodologies providing access to highly substituted alkenes	191
Applications of methodology providing single isomer multisubstituted olefins as precursors in other transformations	193
Stereocontrolled synthesis of trisubstituted olefins for the construction of all-carbon quaternary centers	195
RESULTS AND DISCUSSION FOR STEREOCONTROLLED PREPARATION OF QUATERNARY CARBON CENTERS VIA SINGLE ISOMER TRISUBSTITUTED OLEFINS.....	203
Future Directions	210
EXPERIMENTAL SECTION FOR STEREOCONTROLLED PREPARATION OF QUATERNARY CARBON CENTERS VIA SINGLE ISOMER TRISUBSTITUTED OLEFINS.....	211
REFERENCES	230
APPENDIX: SPECTRA	233

PART A: 5- AND 6-MEMBERED HYDRAZIDES AS POTENTIAL CATALYSTS FOR DIELS-ALDER CYCLOADDITIONS

INTRODUCTION

Organocatalysis refers to the use of non-metallic small molecules for the acceleration of organic reactions. An early report of an organocatalytic reaction was in 1912 involving the use of cinchona alkaloids to facilitate the addition of HCN to aldehydes.¹ This particular organocatalyst, however, resulted in low enantioselectivities. The key pioneering reaction of enantioselective organocatalysis was the proline (**1**)-catalyzed intramolecular aldol reaction independently developed by two pharmaceutical companies (Scheme 1).²

Scheme 1. Use of proline as an organocatalyst in intramolecular aldol reaction.



Enantioselective organocatalysis allows the preparation of intermediates that are important in the synthesis of medically relevant molecules.³ There are a few different types of organocatalysts that can be split into two major categories: non-covalent catalysis and covalent catalysis.

NON-COVALENT CATALYSIS

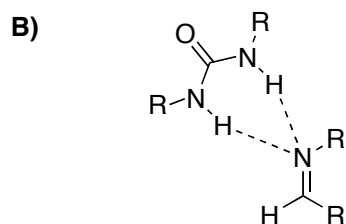
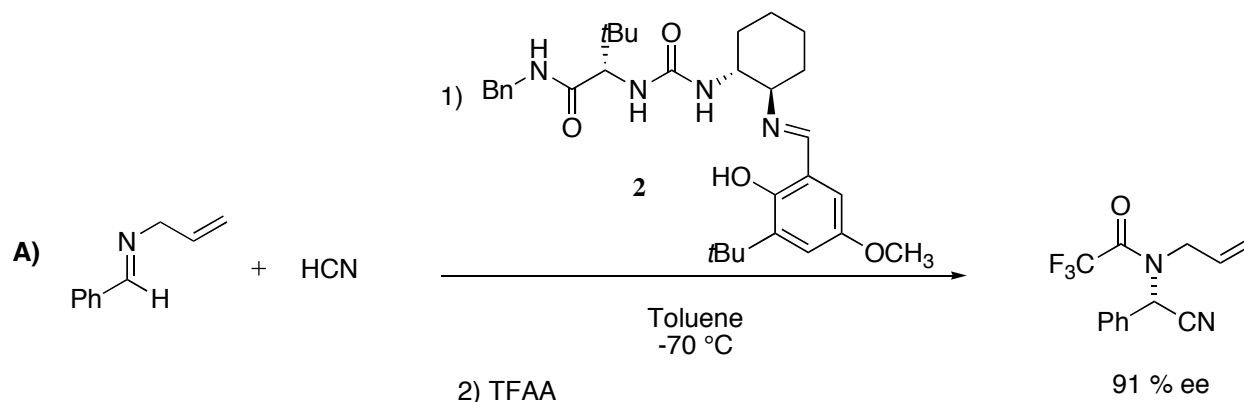
Organocatalysts that impart enantioselectivity to organic reactions by exploiting intermolecular interactions often act through non-covalent catalysis. Such processes comprise those exploiting hydrogen-bonds or ionic interactions in order to achieve enantiomerically enriched products.

HYDROGEN BONDING CATALYSTS

The organocatalysts utilizing hydrogen-bonding as a means of achieving enantioselectivity include urea and thiourea-based catalysts⁴ and squaramides.⁵ One particular example of urea-based catalysis is the enantioselective hydrocyanation reactions of aliphatic and aromatic imines using **2** (Scheme 2, A).⁶

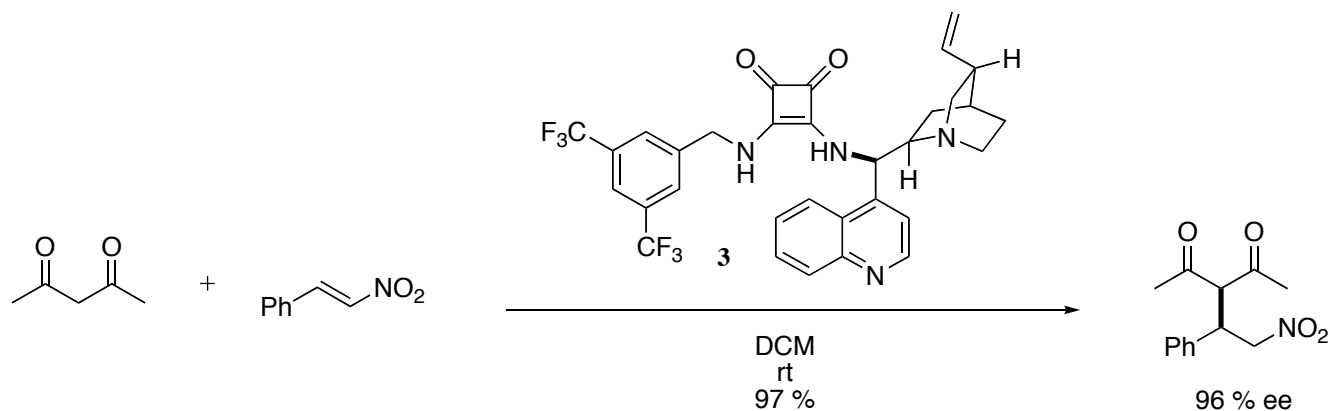
A dual hydrogen-bonding interaction was implicated in the transition state in order to explain the observed enantioselectivity (Scheme 2, B).⁷

Scheme 2. Thiourea catalyzed enantioselective hydrocyanation reaction.



The use of these chiral urea and thiourea organocatalysts in enantioselective reactions inspired another class of hydrogen-bonding organocatalysts called squaramides to be developed.^{5b} The rigidity of the squaramide motif coupled with its ability to participate in hydrogen-bonding led to the synthesis and application of catalysts such as **3** in enantioselective transformations (Scheme 3).⁸

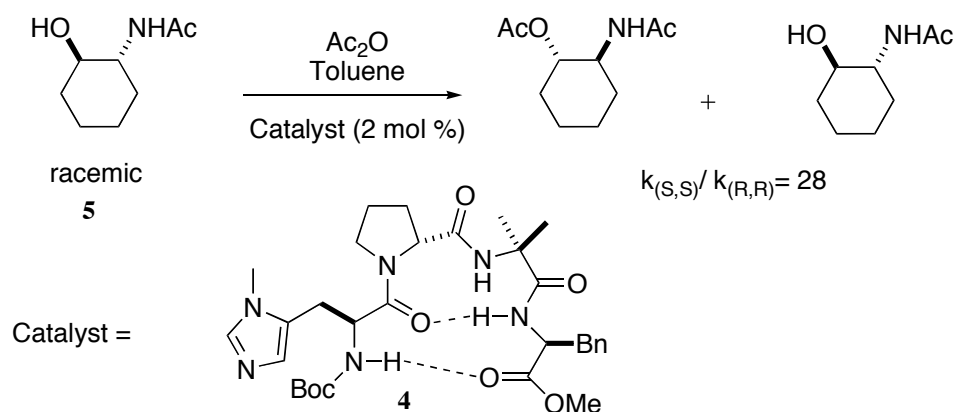
Scheme 3. Use of squaramide catalyst 3 in conjugate addition reactions.



Another interesting class of catalysts that utilize hydrogen-bonding to aid in the stereocontrol of a reaction are Miller's peptide catalysts.^{9,10} Inspired by the way enzymes catalyze reactions, Miller's

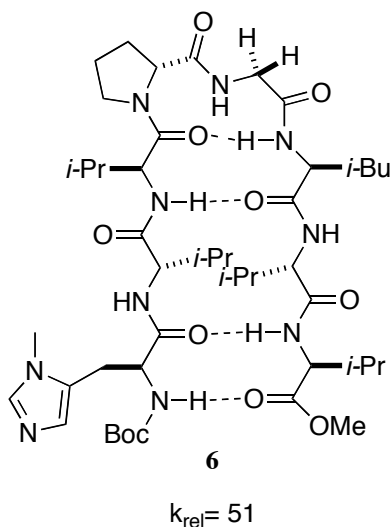
peptides are essentially designed to act as a mini enzyme. In order to use peptides as stereoselective catalysts, there has to be some rigidity present. With that in mind, Miller designed peptides that have a specific secondary structure in order to control the conformation of the peptide. He chose to use a histidine residue as a nucleophilic site on the peptide, and therefore catalysts such as **4** were used initially in acylation reactions in the kinetic resolution of *trans*-1,2-acetamidocyclohexanol (**5**), (Scheme 4).

Scheme 4. Kinetic resolution of *trans*-1,2-acetamidocyclohexanol (5**) with peptide catalyst **4**.**



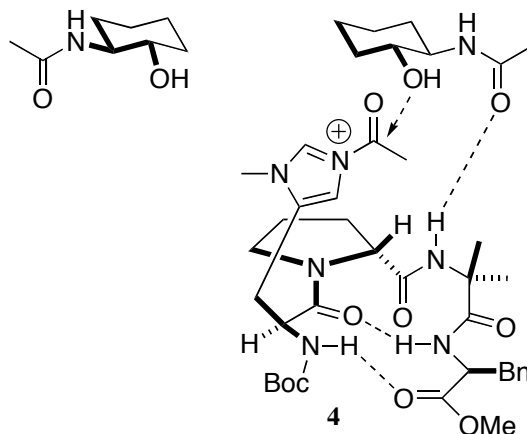
Increased selectivity could be obtained upon rigidification of the catalyst's secondary structure. This was demonstrated by the synthesis of octapeptides that contained a bias to form β -hairpins, such as **6** (Scheme 5).

Scheme 5. β -hairpin containing octapeptide with greater selectivity in a kinetic resolution reaction.



The stereochemical rationale for this reaction involves the preferential attack of the enantiomer that is capable of hydrogen bonding with a particular section of the peptide backbone. The –NHAc group interacts with the backbone, whereas the –OH attacks the acyl group on the histidine nitrogen (Scheme 6).

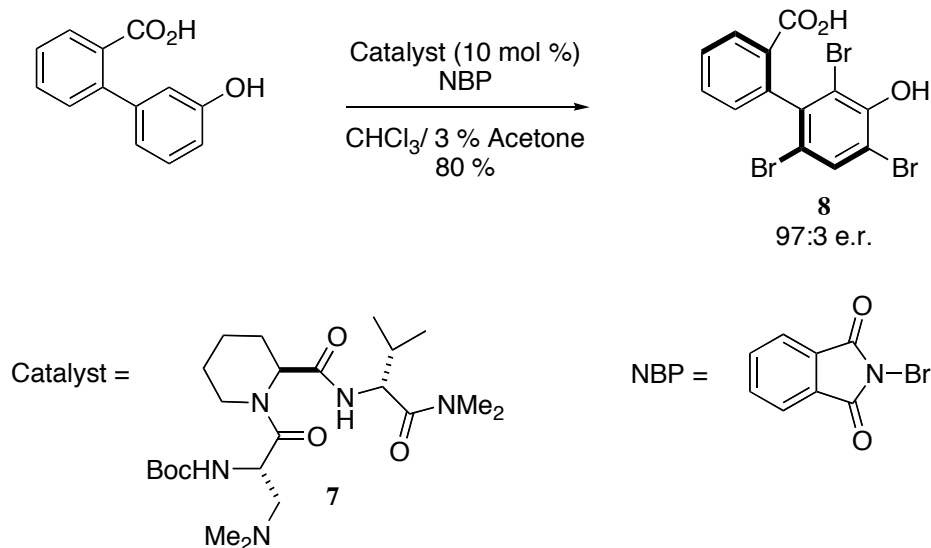
Scheme 6. Stereochemical model for kinetic resolution reaction.



This methodology was also applied in a variety of reactions such as enantioselective phosphorylation, conjugate addition, and Morita-Baylis-Hillman reactions.⁹ More recently, Miller's peptide organocatalysts have been used in reactions such as enantioselective epoxidation,¹¹ allenolate additions to *N*-acyl imines,¹² desymmetrization of a Bis(phenol),¹³ and the chemo and enantioselective oxidation of indoles.¹⁴

These catalysts have also been used to control a different type of stereochemistry, where compounds exhibit axial chirality. These types of compounds are called atropisomers, and contain a stereogenic unit that is not an sp³ hybridized carbon atom. Biaryl compounds commonly exhibit this type of chirality. Miller designed a peptide catalyst **7** that was able to produce chiral non-racemic brominated biaryl compounds from racemic biaryls (Scheme 7).¹⁵

Scheme 7. Enantioselective synthesis of brominated biaryl **8 by peptide catalysis.**



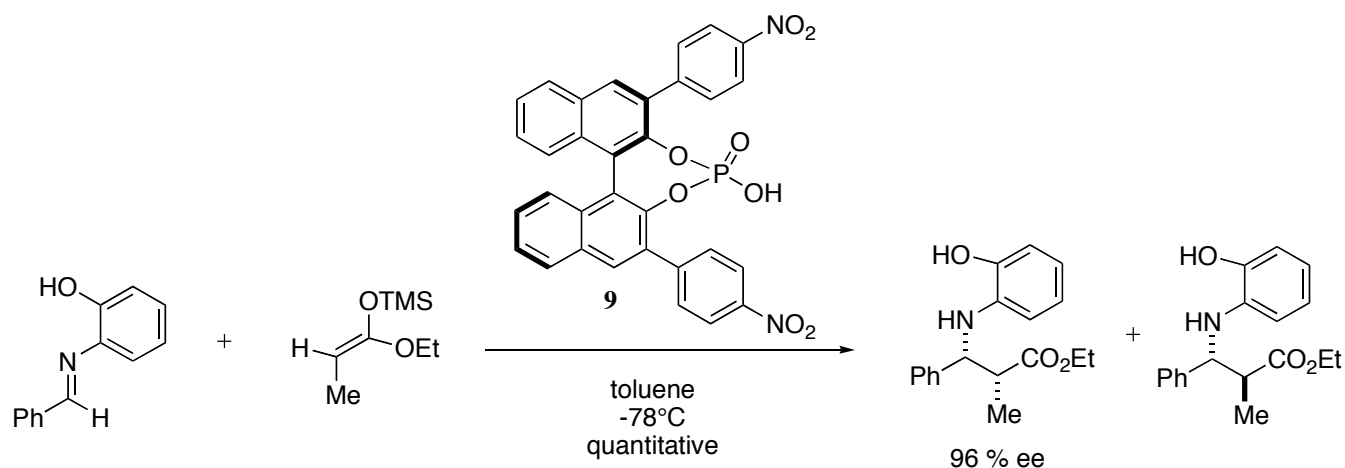
This catalyst gave high enantiomeric ratios and good yields for the transformation, providing the first example of an organocatalyst capable of controlling an atropisomeric process.

CATALYSTS EXPLOITING IONIC INTERACTIONS

In addition to organocatalysts exploiting hydrogen-bonding to infer enantioselectivity on their products, there are a variety of organocatalysts that participate in ionic interactions in order to influence the stereochemical outcome of a reaction. An example of such catalysts are Brønsted acid and base organocatalysts. These catalysts exploit ionic interactions in order to impart stereocontrol on a reaction.¹⁶ Brønsted acid organocatalysts consist of chiral phosphoric acids,¹⁷ phosphoramides,¹⁸ carboxylic acids,¹⁹ and sulfonic acids.²⁰ These catalysts activate the electrophilic partner in a reaction by protonation.

A pioneering example of the use of chiral Brønsted acid organocatalysts in enantioselective transformations involved chiral phosphoric acids (Scheme 8).²¹

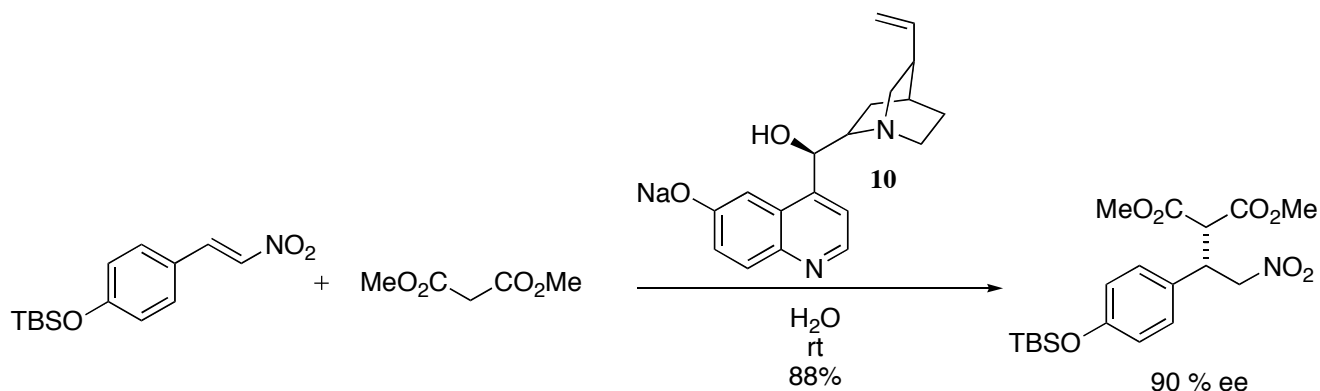
Scheme 8. Chiral phosphoric acid **9 as an organocatalyst for Mannich-type reactions.²¹**



The optimal phosphoric acid in this particular study was derivative **9**, which provided the *syn* product in 96 % ee. The stereocontrol with these phosphoric acid organocatalysts is thought to arise from the formation of an iminium salt generated by proton transfer from the phosphoric acid derivative. The phosphate counterion would remain in proximity to the iminium, and the naphthyl groups would shield the phosphate counterion, resulting in enantioselective induction.

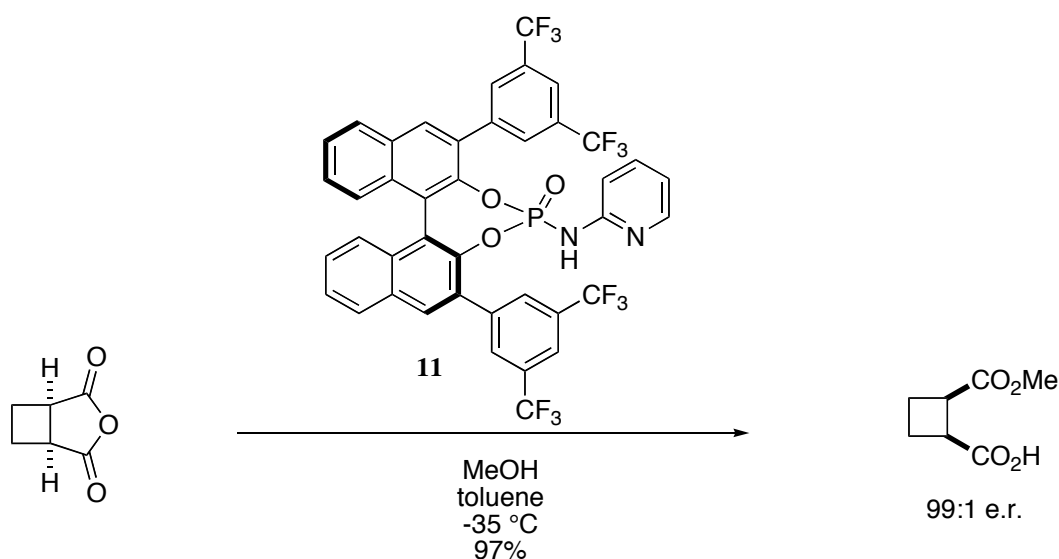
In addition to chiral Brønsted acid organocatalysts being utilized in enantioselective transformations, chiral Brønsted base organocatalysts have also been employed. An example of Brønsted base organocatalysts are catalysts based on cinchona alkaloids.²² These types of catalysts operate by either partially or fully abstracting an acidic hydrogen from a nucleophilic substrate, and as a result, controlling the subsequent nucleophilic attack. An example of such a catalyst is derivative **10** (Scheme 9) capable of controlling a Michael addition with a high degree of stereocontrol.²³

Scheme 9. Michael addition facilitated by derivative **10.**



The idea of Brønsted acid and base organocatalysts was combined to create bifunctional catalysts, whereby the electrophilic partner in the reaction is activated by the Brønsted acid moiety on the catalyst, and a Brønsted base moiety activates the nucleophilic partner in the reaction. This type of activation was inspired by the way enzymes function in biological systems. An example of such a chiral bifunctional organocatalyst is phosphoramidate **11** (Scheme 10).²⁴ This catalyst was successfully used in alcoholysis reactions, including that shown in Scheme 10, which provided an intermediate in the synthesis of the sex pheromone (+)-grandisol.

Scheme 10. Synthesis of an intermediate of (+)-grandisol utilizing bifunctional Brønsted acid/base catalyst 11.



The phosphoramidate hydrogen was proposed to be the electrophile-activating Brønsted acid, whereas the pyridine nitrogen would act as the nucleophile-activating Brønsted base.

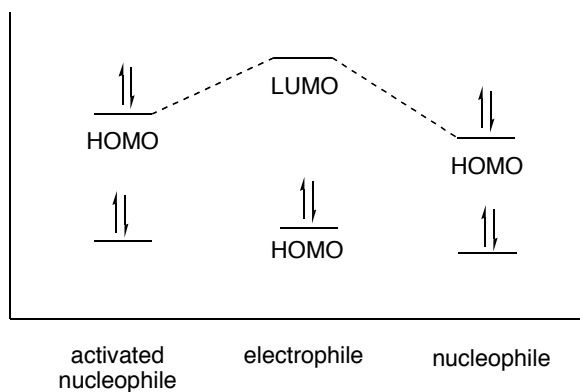
COVALENT CATALYSIS

In addition to the non-covalent organocatalysts highlighted, another prominent method of enantioselective organocatalysis is through the use of covalent catalysis. A key sub-category of covalent catalysis involves aminocatalysis, which involves the use of chiral amines as organocatalysts in enantioselective transformations. Chiral amine catalysts can impart stereocontrol in a reaction by either the formation of an enamine or an iminium ion.

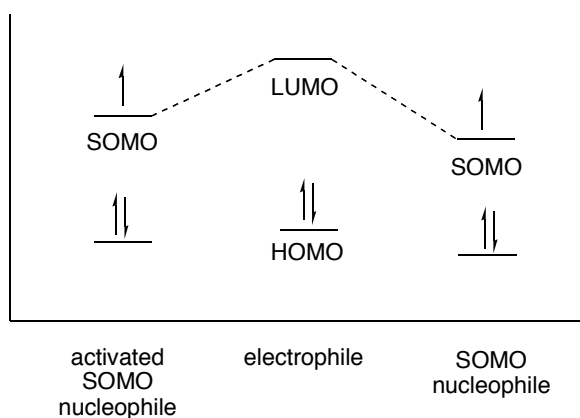
There are three different activation modes when chiral amine catalysts are involved. These are the highest molecular orbital (HOMO) activators (Scheme 11, A),²⁵ the singly occupied molecular orbital (SOMO) activators (Scheme 11, B),²⁶ and the lowest unoccupied molecular orbital (LUMO) activators (Scheme 11, C).²⁷ Formation of an enamine from a chiral amine catalyst can allow for either HOMO or SOMO activation, depending on the conditions required. Formation of an iminium ion allows for LUMO activation of the substrate.

Scheme 11. Energy diagram showing the principle behind A) HOMO activation, B) SOMO activation, and C) LUMO activation.

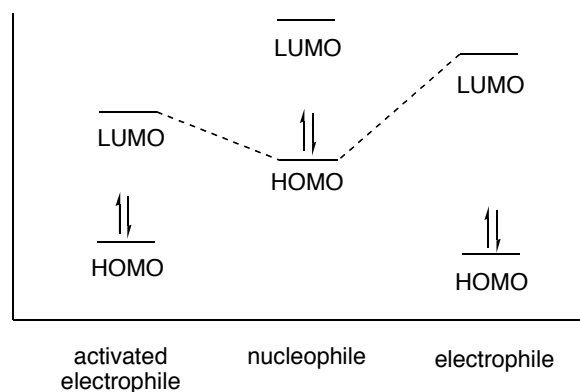
A) HOMO Activation



B) SOMO Activation



C) LUMO Activation



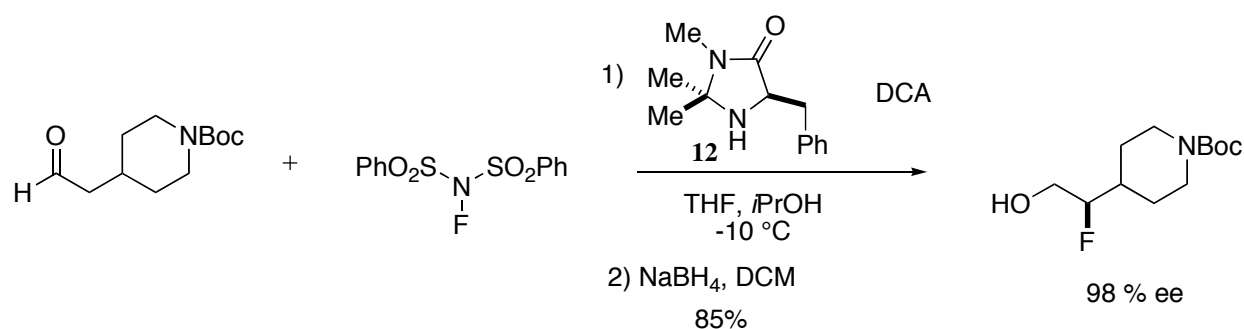
ENAMINE CATALYSIS

The first enamine organocatalyst discovered was proline, when it was applied to an intramolecular aldol reaction.² There are now a variety of organocatalysts that participate in reactions that proceed

through an intermediate enamine to provide stereocontrol in numerous reactions.²⁸ The nucleophilic component in nucleophilic addition reactions, as well as nucleophilic substitution reactions, have been activated through formation of an enamine intermediate via a chiral amine catalyst. Carbonyl compounds in aldol reactions,²⁹ imines in Mannich reactions,³⁰ azodicarboxylates,³¹ nitrosobenzene,³² and C=C Michael acceptors³³ have been the electrophilic partners in these reactions.

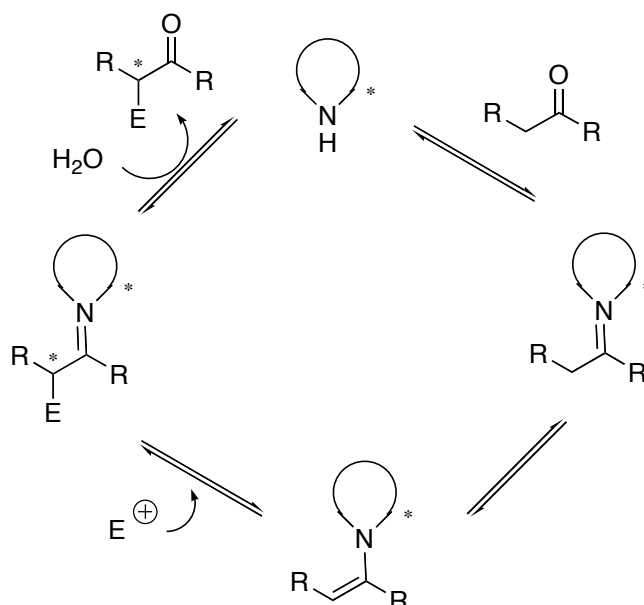
Nucleophilic substitution reactions can also be accomplished by utilizing enamine catalysis. Such reactions include the α -alkylation of aldehydes,³⁴ and the α -halogenation of aldehydes (Scheme 12).³⁵

Scheme 12. Use of MacMillan catalyst 12 to affect the α -fluorination of aldehydes.^{35b}



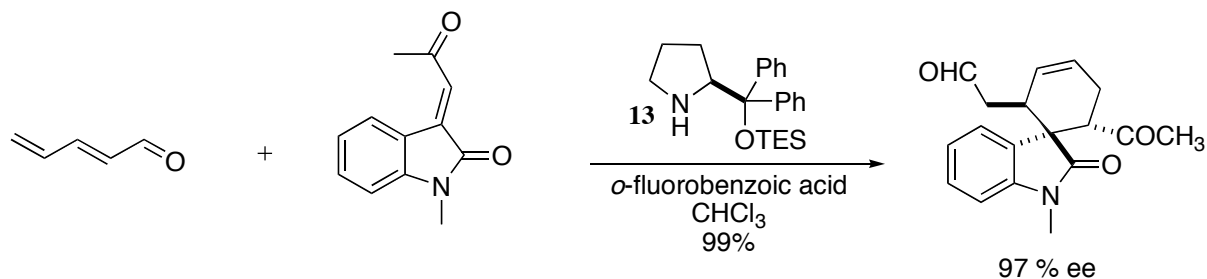
A general catalytic cycle for processes proceeding through enamine catalysis³⁶ is shown in Scheme 13. The initial formation of an iminium species lowers the LUMO energy of the system, facilitating α -deprotonation. The resulting enamine can then attack an electrophile, transferring any stereochemical information from the starting amine ultimately to the product.

Scheme 13. General catalytic cycle for enamine derivatives.



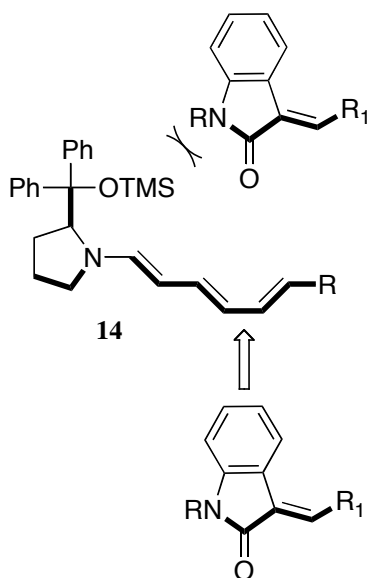
The concept of HOMO activation by enamine formation has been extended to the application of dienamines³⁷ and trienamines³⁸ in enantioselective organocatalysis. These derivatives allowed the remote transfer of stereochemical information from the amine catalyst ultimately used (Scheme 14).

Scheme 14. Trienamine activation in Diels-Alder reaction by proline-derived catalyst 13.³⁸



The proposed explanation for the regio-, diastereo-, and enantioselectivity of the trienamine activation pathway was rationalized by the authors as a combination of steric and electronic effects. The diastereoselectivity was rationalized by the stabilizing effect of secondary orbital interactions in the transition state leading to the *endo* diastereomer. The regioselectivity was rationalized based on maximization of the charge interaction and orbital overlap for the HOMO of the diene and LUMO of the dienophile. The enantioselectivity was thought to be a result of steric interactions between the chiral amine portion and the incoming dienophile, whereby the top face of the trienamine is blocked by the diaryl moiety (Scheme 15).

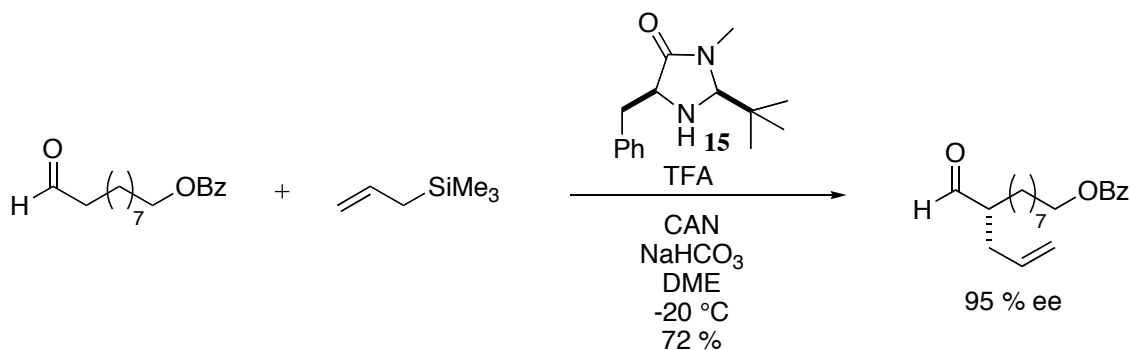
Scheme 15. Stereochemical rationale for trienamine derivative 14.



These trienamines could also be used in a tandem trienamine-enamine reaction to obtain structurally more complex compounds.

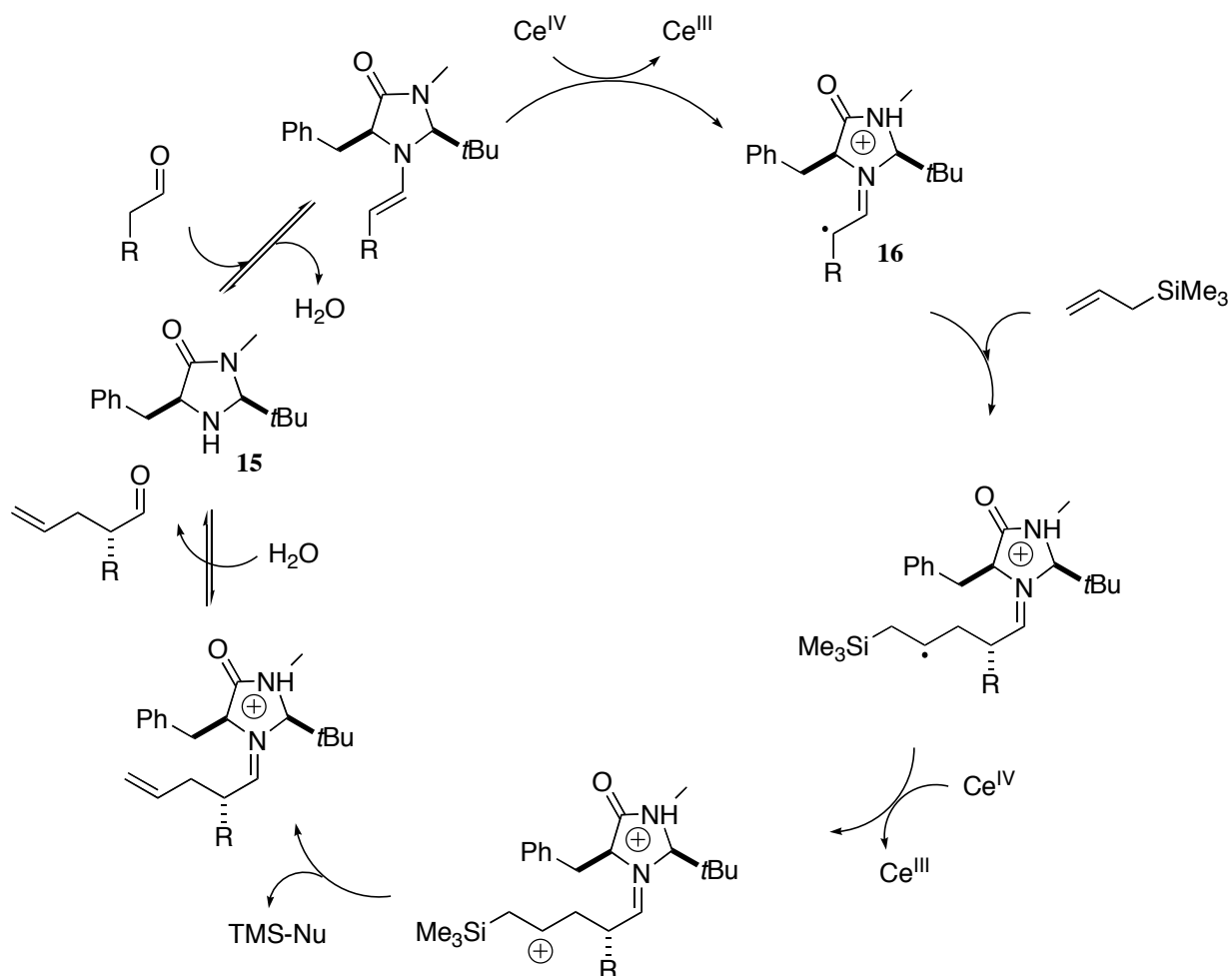
Enamines can also be further transformed into intermediates which undergo SOMO activation by the addition of an oxidant that can remove one electron from the enamine.²⁶ This additional activation mode can provide access to compounds that are not easily obtained from enamine activation, such as α -allyl aldehydes and α -aryl aldehydes. High enantioselectivities can be observed using a chiral catalyst acting under the SOMO mode of activation (Scheme 16).

Scheme 16. Enantioselective α -allylation with catalyst 15 via SOMO catalysis.



The mechanism of SOMO catalysis was investigated, and the following catalytic cycle was proposed (Scheme 17).³⁹

Scheme 17. Proposed catalytic cycle for SOMO activation with organocatalyst **15.³⁹**

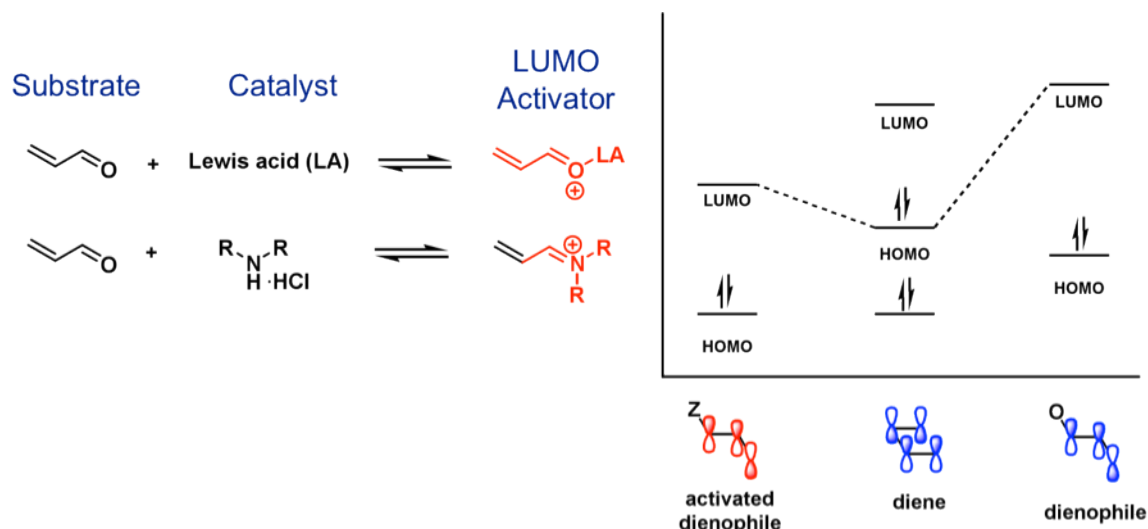


The enantioselectivity in this process arose from the approach of the allylsilane from the bottom face of the enamine radical cation species. This could occur due to the conformational restrictions on the enamine radical cation **16**, which hold the three π -electron system in an *E*-enamine conformation directed away from the bulky groups.³⁵

IMINIUM CATALYSIS

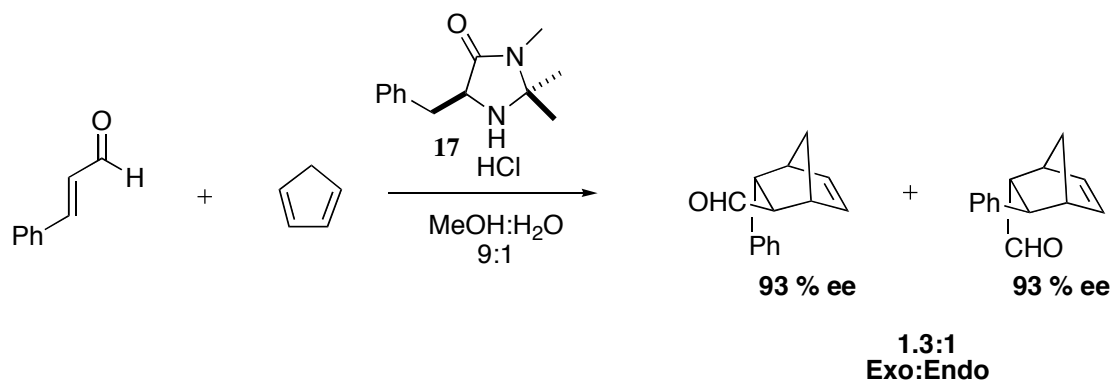
Aside from the HOMO-raising enamines or SOMO generating enamines, another mode of activation commonly used in enantioselective organocatalysis is the LUMO lowering iminium formation reaction. The idea behind the catalysis by this pathway, is that by lowering the energy of the LUMO of an electrophilic reaction partner, the energy gap between this electrophile LUMO and the HOMO of a nucleophilic reaction partner would decrease, thereby facilitating the reaction (Scheme 18).

Scheme 18. Rationale behind LUMO activation.



The seminal reactions for enantioselective iminium catalysis involve MacMillan catalyst **17** (Scheme 19).²⁷ This catalyst was used in Diels-Alder reactions to afford the *exo* and *endo* products enantioselectively.

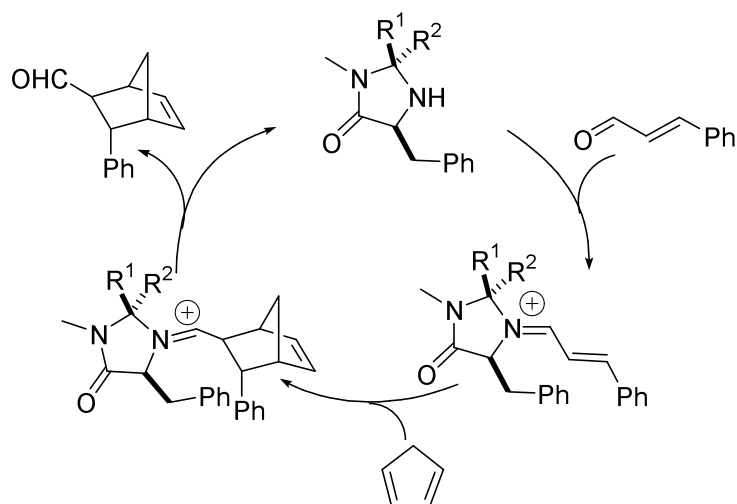
Scheme 19. Seminal reaction in iminium catalysis involving MacMillan catalyst 17.



This type of catalysis has since been applied toward a variety of reactions which are accelerated by the formation of an iminium species, such as 1,3-dipolar cycloadditions,⁴⁰ conjugate additions,⁴¹ epoxidations,⁴² cyclopropanations,⁴³ and conjugate reductions.⁴⁴

The proposed catalytic cycle involves three major steps: iminium formation, reaction with nucleophilic partner, and hydrolysis (Scheme 20).

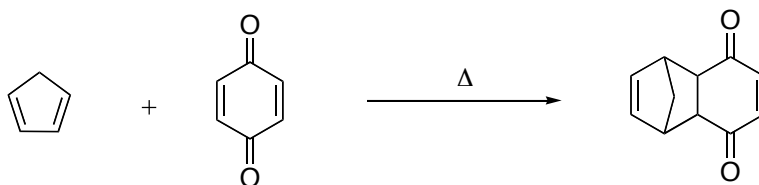
Scheme 20. General catalytic cycle for iminium activation.



DIELS-ALDER REACTION AND IMINIUM CATALYSIS

The Diels-Alder reaction is a widely used reaction for forming carbon-carbon bonds in organic synthesis.⁴⁵ The structure of the products of a Diels-Alder reaction (Scheme 21) were first elucidated in 1928 by Otto Diels and Kurt Alder,⁴⁶ who were subsequently awarded the Nobel prize in chemistry.

Scheme 21. Diels-Alder reaction between cyclopentadiene and *p*-benzoquinone.

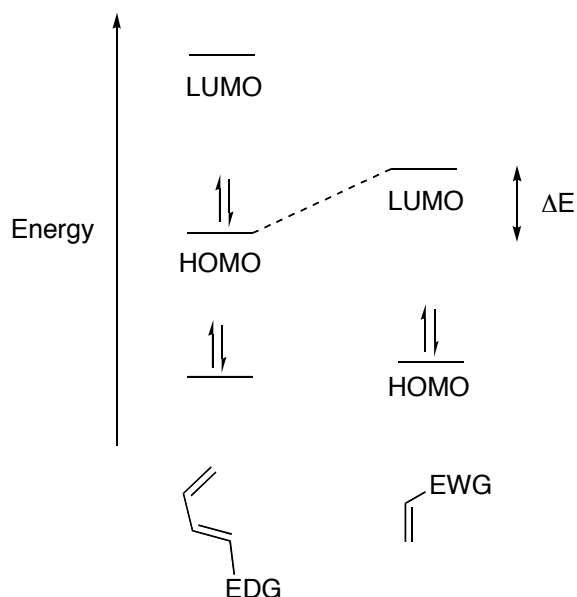


The Diels-Alder reaction can allow up to four contiguous stereocenters to be simultaneously generated, which can be useful in the synthesis of complex natural products.

There are two species involved in the Diels-Alder reaction, one of these, the diene, is a conjugated 4π electron compound, and the other, the dienophile, is a 2π electron species.

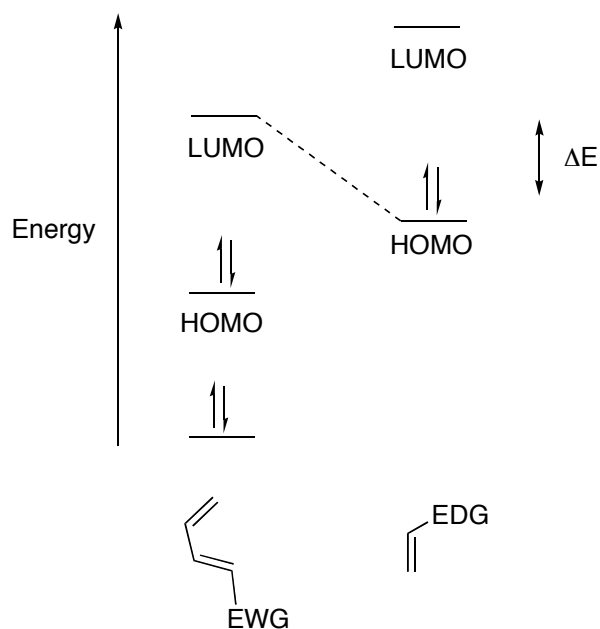
The FMO description of the normal electron demand Diels-Alder cycloaddition involves the HOMO of the diene overlapping the LUMO of the dienophile (Scheme 22).

Scheme 22. FMO description of normal electron demand Diels-Alder reaction



A situation can exist where the HOMO of the dienophile overlaps with the LUMO of the diene, and this is termed an “inverse” electron demand Diels-Alder reaction (Scheme 23).

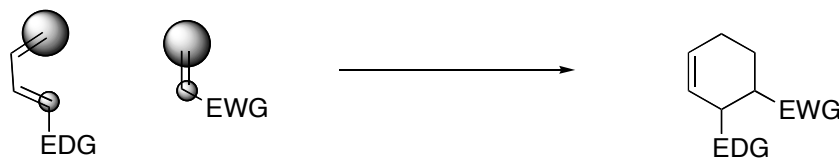
Scheme 23. FMO description of inverse electron demand Diels-Alder reaction.



Most Diels-Alder cycloadditions are normal electron demand. With Diels-Alder cycloadditions involving unsymmetrical reagents, there are aspects of regio- and stereo-control to be considered. The regiochemical outcome of Diels-Alder reactions can be predicted using the orbital coefficients associated with the diene and dienophile. These orbital coefficients are determined by the substituents in each partner. If electron donating groups are present on the diene component, they can influence the size

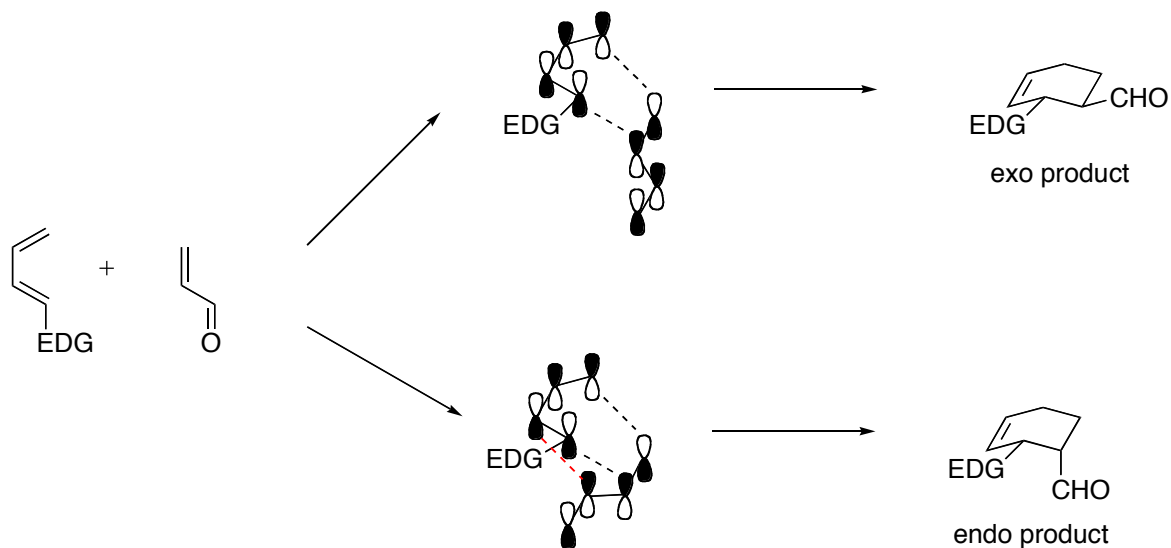
of the orbital coefficients on the terminal atoms. The influence of an electron donating group would increase the size of the terminal atom's orbital coefficients in the diene HOMO. For the dienophile LUMO, the presence of an electron withdrawing group can increase the size of the terminal atom's orbital coefficient. The atoms with the larger orbital coefficients would overlap, which would result in a specific regiochemical outcome (Scheme 24).

Scheme 24. The influence of orbital coefficients on the regiochemical outcome of the Diels-Alder reaction.



Another consideration for Diels-Alder cycloadditions is the stereochemical outcome of the reaction. Whereas the regiochemical outcome depends on the orientation of the terminal atoms of the diene and dienophile with respect to each other, the diastereoselectivity depends on the relative facial selectivity of the reactants.⁴⁶ If, during the course of the reaction, the electron withdrawing group of the dienophile is oriented toward the diene, the *endo* diastereomer is obtained. If the electron withdrawing group is oriented away from the diene, the *exo* diastereomer is obtained. Under kinetic control, the *endo* product is generally preferred, even though there is an increased amount of steric interactions in this diastereomer compared to the *exo* diastereomer. This phenomenon was thought to arise from secondary orbital interactions⁴⁷ in the transition state leading to the *endo* product, which would be a stabilizing event (Scheme 25).

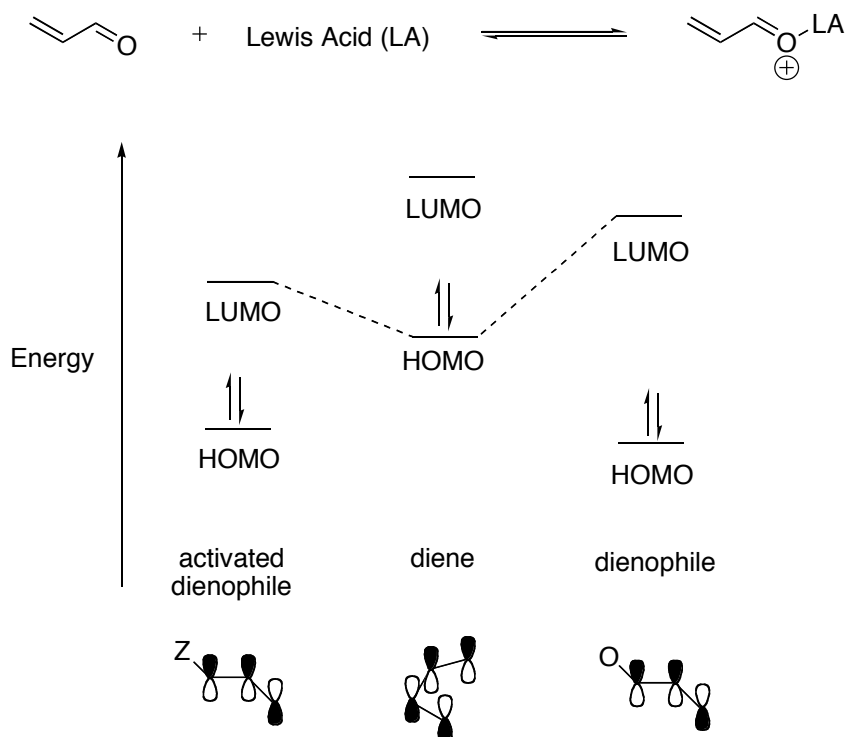
Scheme 25. *Endo* and *Exo* diastereomers arising from a normal electron demand DA cycloaddition.



The second aspect of the stereochemical outcome of a Diels-Alder reaction involving unsymmetrical components is the enantioselectivity. The enantioselectivity of Diels-Alder reactions is dictated by the absolute facial selectivity of both reactants. The facial exposure can be controlled by either chiral auxiliaries⁴⁸ or organocatalysts.²⁷

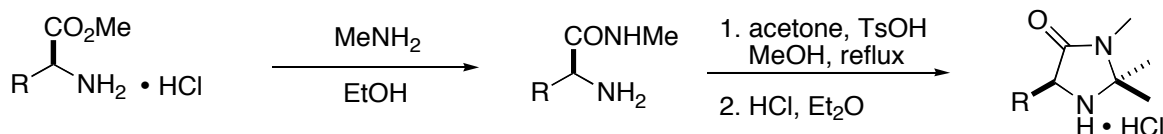
In order for most Diels-Alder cycloadditions to be carried out under mild conditions, they need to be activated.⁴⁹ This activation can be achieved by the use of Lewis acids.⁵⁰ The way in which Lewis acids activate Diels-Alder reactions is by complexing with the electron withdrawing group on the dienophile, and lowering the energy of the LUMO (Scheme 26).

Scheme 26. Activation of Diels-Alder reaction by Lewis acids.



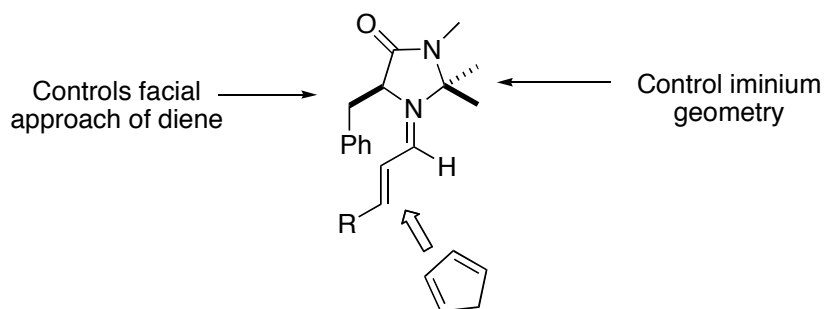
One way to activate Diels-Alder reactions and impart enantioselectivity is by the use of chiral amine catalysts.⁵¹ Pioneering work in this area was done by MacMillan *et al* (Scheme 19).³³ The synthesis of the imidazolidinone catalysts is relatively straightforward, consisting of a condensation between methylamine and the methyl ester of an amino acid salt, with subsequent cyclization using acetone, followed by precipitation of the HCl salt (Scheme 27).

Scheme 27. Synthesis of imidazolidinone catalysts.



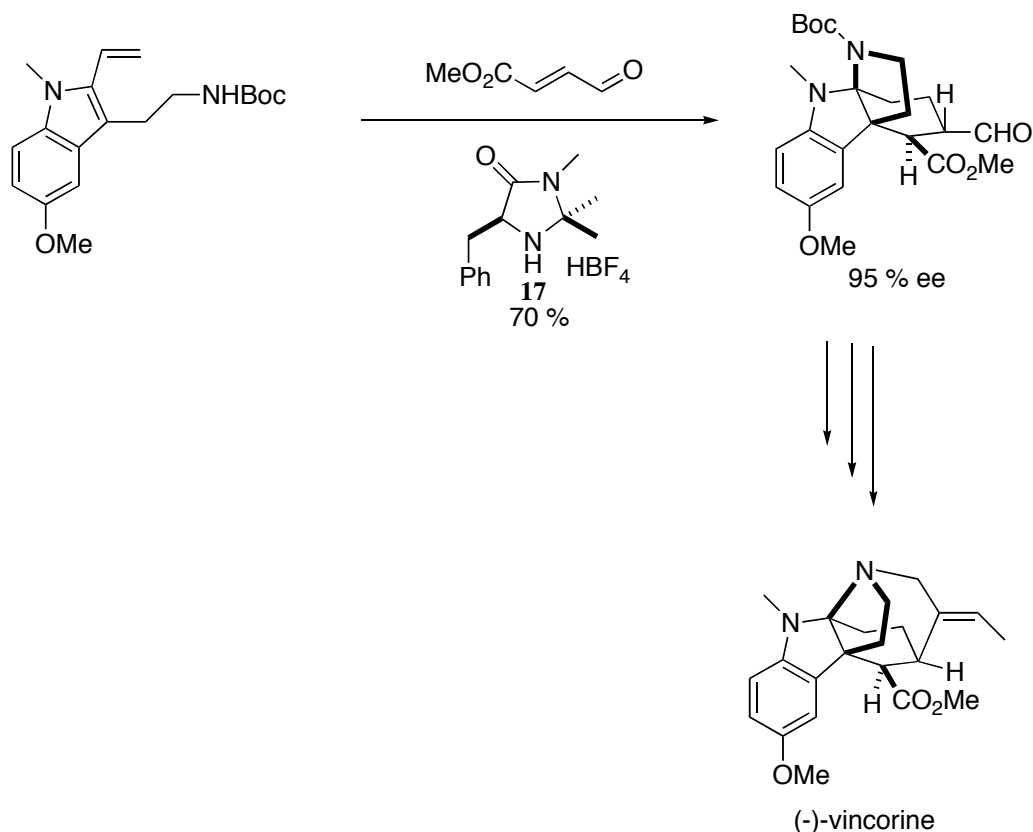
The proposed origin of enantioselectivity with such imidazolidinone catalysts in Diels-Alder reactions arises from two control elements built into the catalyst, which affect 1) iminium geometry, and 2) facial selectivity of the diene. The former is thought to be controlled by the avoidance of non-bonding interactions between the olefin of the dienophile and the geminal methyl groups. This would allow selective formation of the (*E*)-iminium. The approach of the diene is thought to be controlled by the benzyl group on the catalyst, which would shield one face of the dienophile (Scheme 28).³³

Scheme 28. Origin of enantiocontrol with imidazolidinone organocatalysts



This catalyst has been used in the construction of complex molecular targets such as (-)-vincorine, an alkaloid of interest in medicinal chemistry (Scheme 29).⁵²

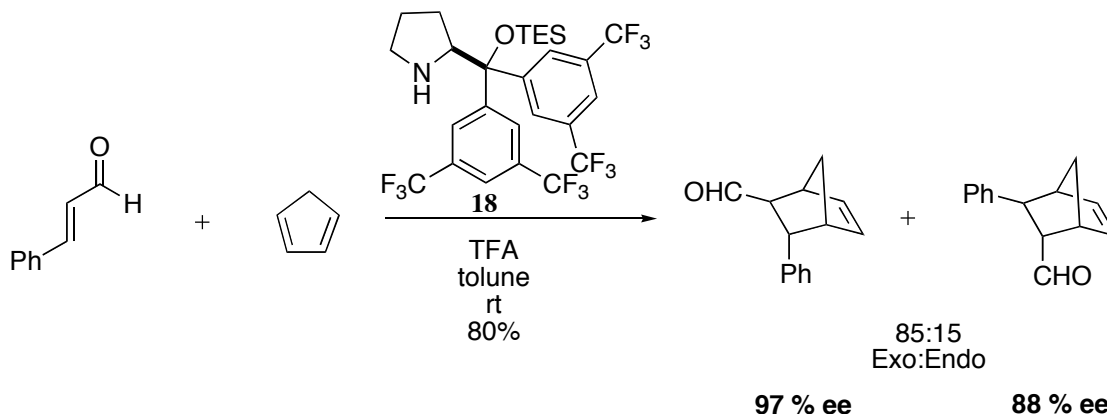
Scheme 29. Key Diels-Alder reaction-iminium cyclization cascade sequence en route to (-)-vincorine catalyzed by chiral amine 17.



The synthesis was carried out in 9 steps with the key step accomplished in 70 % yield and 95 % ee via secondary amine catalyzed Diels-Alder reaction-iminium cyclization cascade sequence.

In addition to MacMillan's imidazolidinone catalysts, diaryl prolinol derivatives have also shown success in affording Diels-Alder products enantioselectively via iminium catalysis.⁵³ These catalysts typically showed preference for the *exo* diastereomer, but afforded both *endo* and *exo* products with high enantioselectivities (Scheme 30).

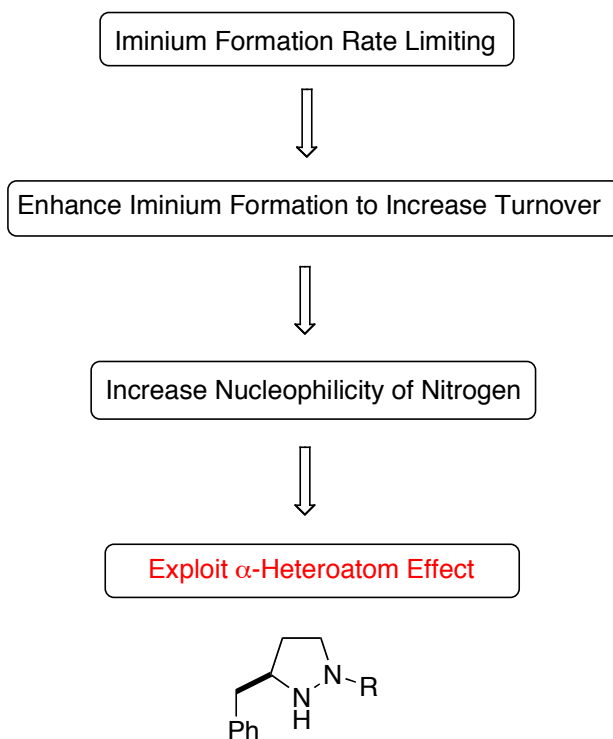
Scheme 30. Diels-Alder reaction between cyclopentadiene and (*E*)-cinnamaldehyde catalyzed by diaryl prolinol derivative 18.



THE α -EFFECT AND IMINIUM CATALYSIS

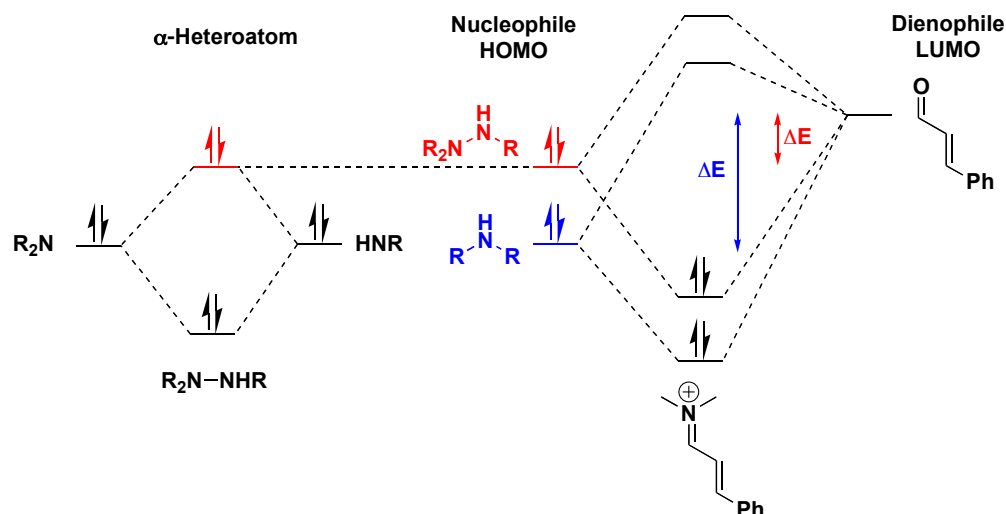
It was previously hypothesized in the Ogilvie group, that the relatively long reaction times typically associated with catalysts involved in iminium formation⁵⁴ could be shortened by examining the catalytic cycle of iminium formation and making a modification to the catalyst architecture that would accelerate the rate determining step.⁵⁵ At the time, the rate determining step was thought to be the iminium formation step, based on an observation by MacMillan that one of the imidazolidinone catalysts with a more accessible lone pair showed an increase in rate and selectivities.⁵⁶ With this observation, our group had rationalized that if the chiral amine catalyst had a more nucleophilic nitrogen, the iminium formation step could be accelerated, thereby increasing the rate of the whole process. It was envisioned that the increase in nucleophilicity could be achieved by exploiting a phenomenon called the α -heteroatom effect (Scheme 31).

Scheme 31. Thought process behind the design of more nucleophilic iminium catalysts.



The α -heteroatom effect⁵⁷ results when there are two heteroatoms side-by-side. The orbitals containing the non-bonding electrons on each of the heteroatoms overlap, creating a new molecular orbital that is higher in energy.⁵⁸ This new molecular orbital is the HOMO of the compound, and has a smaller energy gap with the LUMO of the dienophile, which facilitates overlap (Scheme 32). This smaller energy gap should result in an increased rate for the reaction. Another way to describe the α -heteroatom effect involves the fact that the lone pairs on the nitrogen atoms are higher in energy due to electron repulsion.

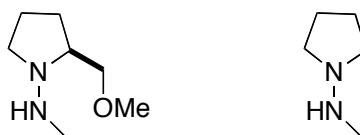
Scheme 32. Energetic consequences of the α -heteroatom effect in raising the energy of the HOMO of a hydrazine derivative.



Toward that end, the Ogilvie group had set out on an arduous journey to create a catalyst architecture possessing the hydrazine moiety that would be capable of achieving great reactivity and enantioselectivity.

After examining the effect of simple acyclic hydrazines and a hydroxylamine on their ability to catalyze the Diels-Alder reaction, it was decided to proceed with the hydrazide moiety.⁵⁵ Attempts to incorporate this moiety into a scaffold capable of enantioselective induction proved difficult at first. The use of a proline-type scaffold was initially investigated, with no successful synthesis being realized (Scheme 33).

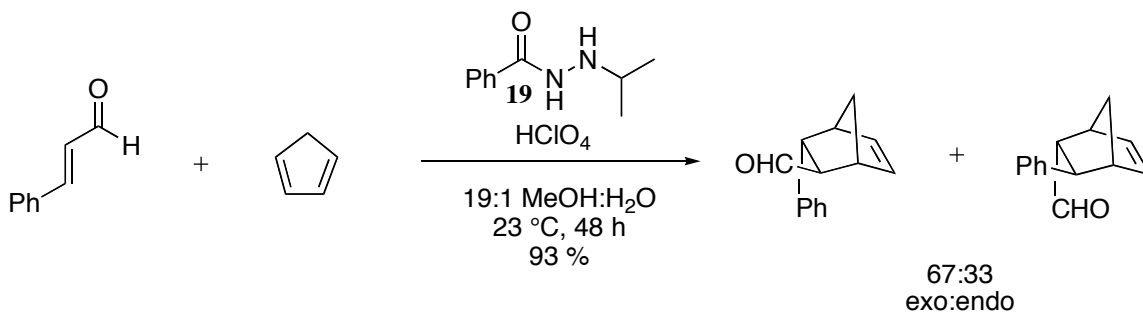
Scheme 33. Attempted scaffolds for hydrazine-based catalysts.



It was then hypothesized that perhaps the use of an electron withdrawing group on the nitrogen next to the nucleophilic nitrogen would confer ease of handling due to increased stability. A potential additional benefit would be that with an electron withdrawing group present, the LUMO energy of the resulting iminium ion can be lower in energy with respect to the LUMO energy of the hydrazine derived iminium ion. This could have the effect of accelerating the Diels-Alder reaction with a hydrazide derivative compared to a hydrazine derivative.

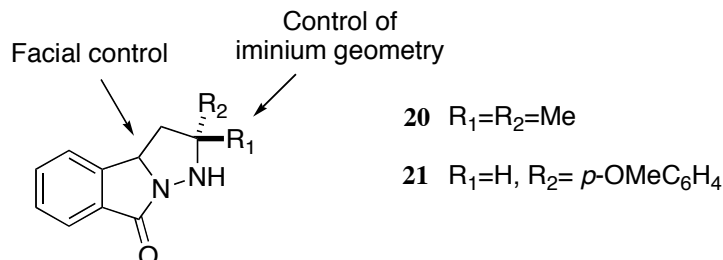
This hypothesis that hydrazides had the potential to catalyze the Diels-Alder reaction was subsequently published by Tomkinson *et al.*,⁵⁹ which showed that the use of hydrazide **58** with perchloric acid as a co-catalyst provided Diels-Alder adducts in 93 % yield (Scheme 34).

Scheme 34. Hydrazide catalyst 19 in the Diels-Alder reaction between (*E*)-cinnamaldehyde and cyclopentadiene.



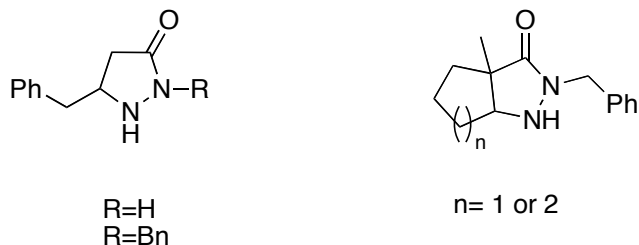
The investigation of various scaffolds containing a hydrazide moiety that could be capable of enantioselective induction began. The first scaffold investigated was tricyclic derivatives **20** and **21** (Scheme 35). The hydrazide would be incorporated into a conformationally rigid bicyclic structure, where it was thought that the facial bias would be achieved by the cup-like shape formed by the two rings, and the groups next to the nucleophilic nitrogen would control iminium geometry. Structures like these would therefore address the two elements that affect enantioselectivity in hydrazide catalyzed Diels-Alder cycloadditions.

Scheme 35. Originally proposed catalyst architectures.



Unfortunately, the synthesis of these derivatives was unsuccessful, so other architectures were examined, which were based on a simpler scaffold (Scheme 36).

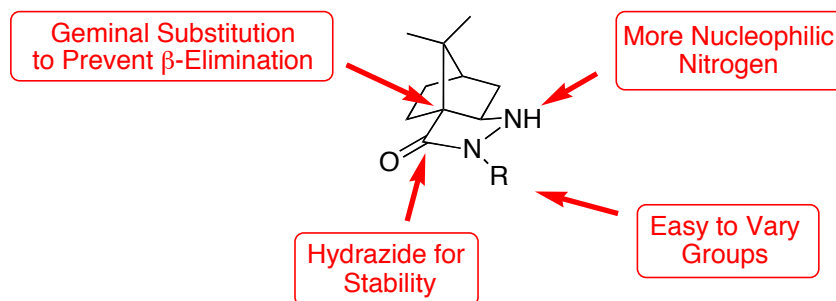
Scheme 36. Additional catalyst architectures incorporating the hydrazine moiety in a simpler scaffold.



These catalysts were able to be synthesized relatively efficiently in their racemic versions, however, upon testing in Diels-Alder reactions, they showed very low conversions to the corresponding adducts, and hence, were useless as catalysts.

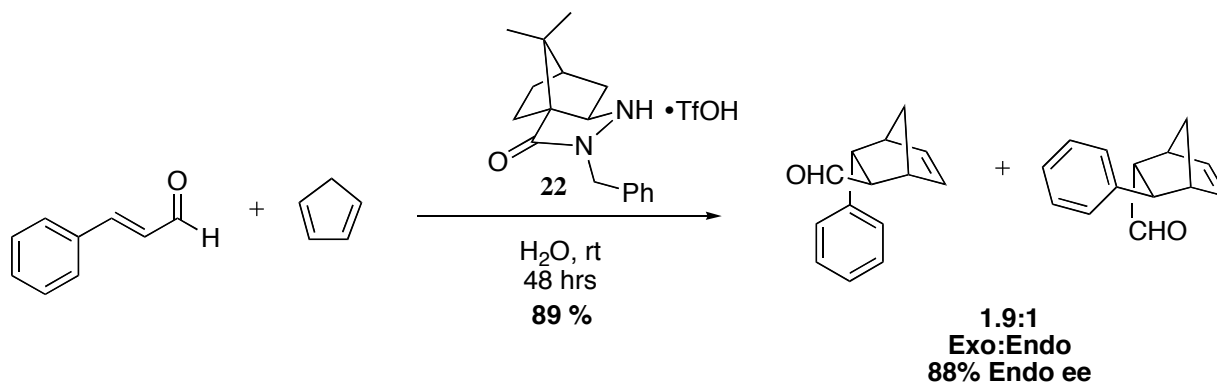
Our lab next began an intensive literature investigation into other potential catalyst architectures, and ended up choosing a camphor-based architecture for the anticipated benefits in terms of selectivity and catalyst stability (Scheme 37).

Scheme 37. “Privileged” 5-membered ring hydrazides based on camphor architecture.



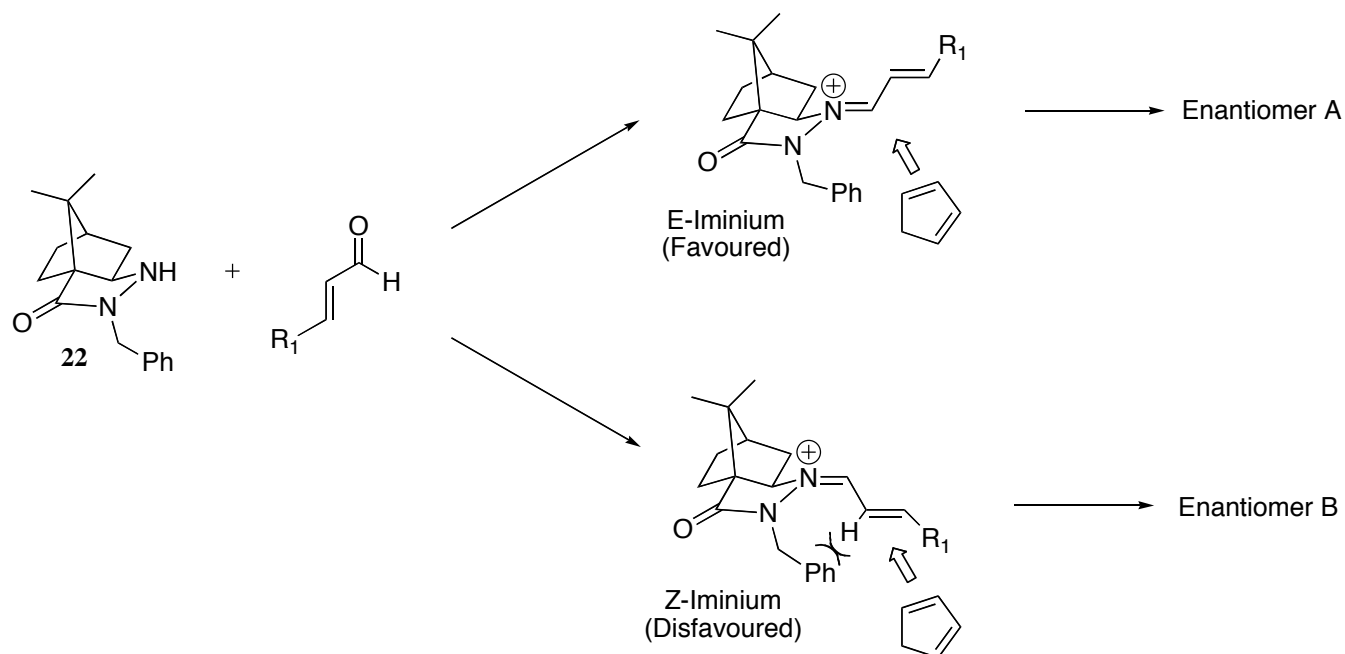
Various R groups next to the nucleophilic nitrogen were tried, along with co-catalysts and solvents, and the reaction was optimal with a benzyl as the R group (**22**), with the reaction being performed in water with triflic acid as co-catalyst (Scheme 38).⁶⁰

Scheme 38. Optimized reaction conditions utilizing **22 as catalyst.**



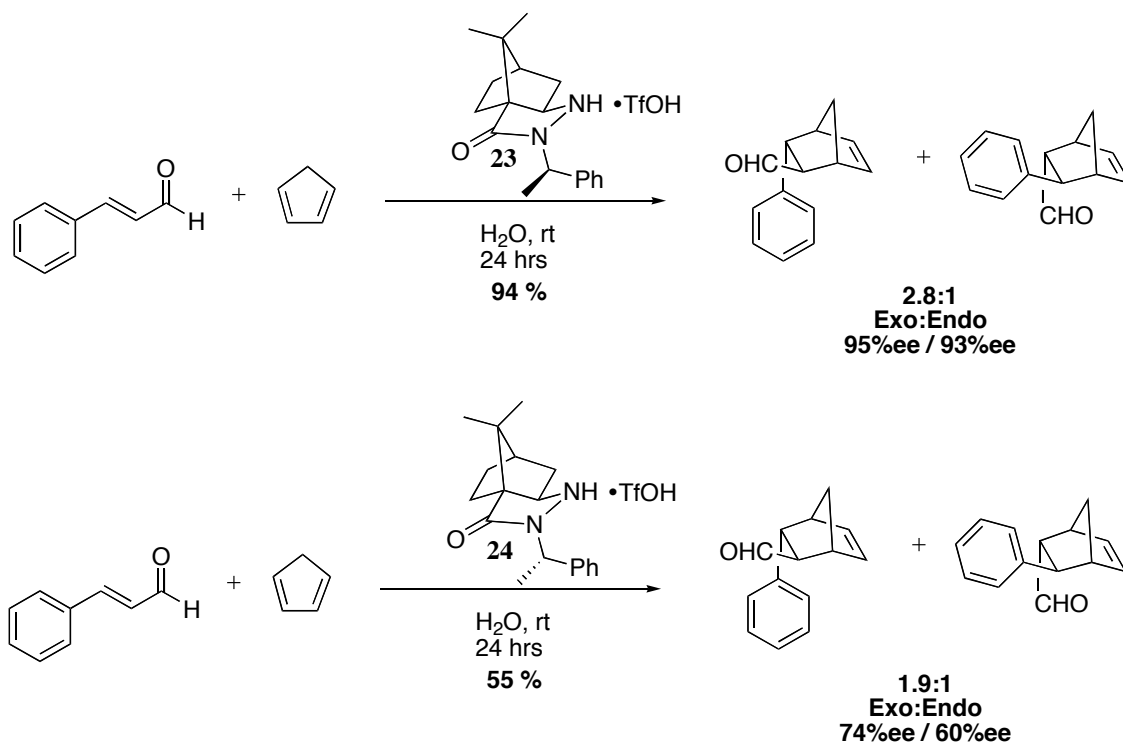
The proposed model for the observed enantioselectivity was based on the benzyl group on the nitrogen adjacent to the nucleophilic nitrogen as a control for the iminium geometry, favoring the formation of the (*E*)-iminium (Scheme 39). The camphor skeleton controls the facial attack of the cyclopentadiene, giving rise to the observed enantioselectivity.

Scheme 39. Proposed model for enantiocontrol with catalyst 22.



The enantioselectivity and reactivity were further improved by the introduction of a methyl-phenyl group, resulting in a conformationally rigid organocatalyst.⁶¹ The synthesis and evaluation of both possible diastereomers was carried out, and it was found that diastereomer **23** was a better catalyst (Scheme 40).

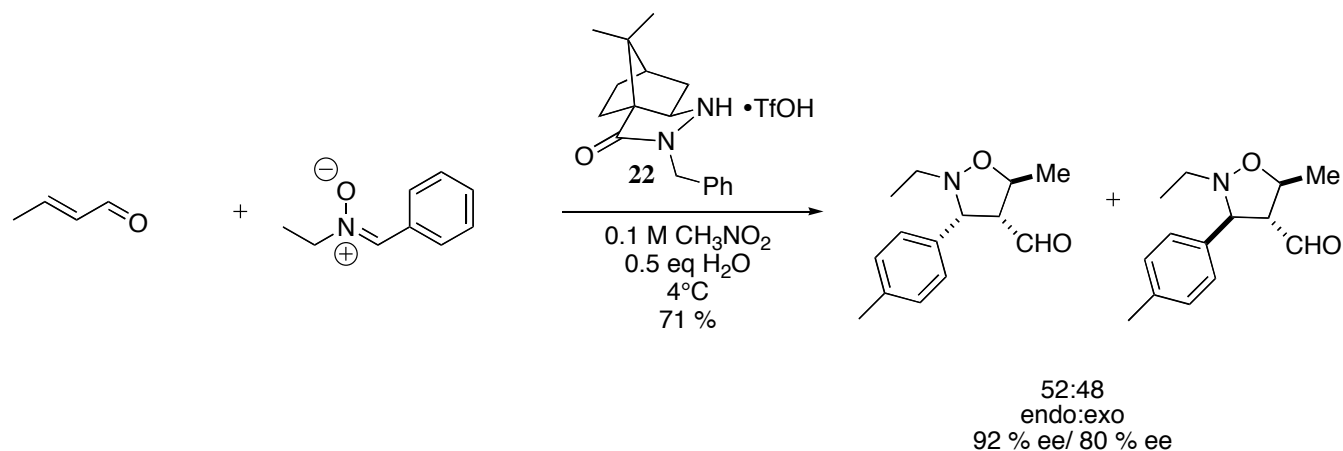
Scheme 40. Evaluation of both diastereomers of conformationally rigid methyl-phenyl catalysts.



This experimental result was supported computationally using a dihedral driver experiment of the C-N-CO dihedral angle of the iminium ions of the corresponding catalysts **23** and **24** for both diastereomers.⁵⁵ The successful diastereomer displayed one clear conformation that was lowest in energy, whereas the iminium ion derived from the less successful diastereomer **24** showed a few different energy minima, resulting in less enantioselectivity.

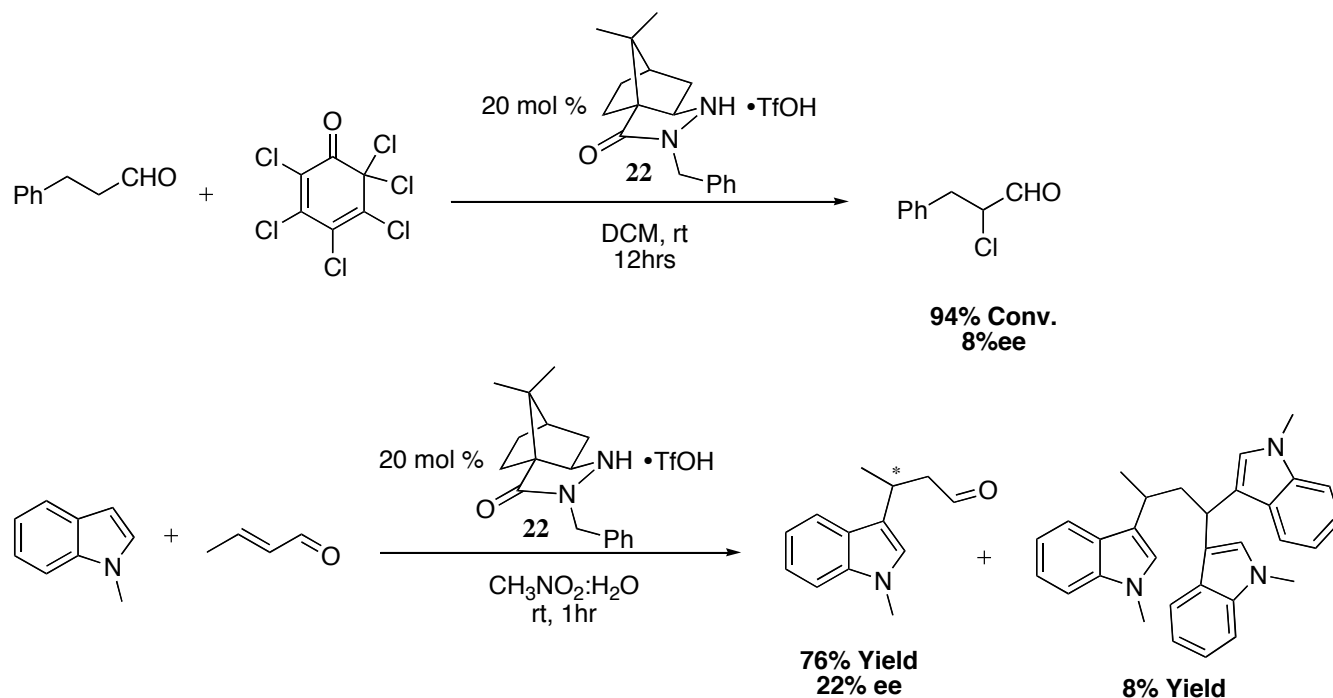
The success of these camphor-derived hydrazides in the Diels-Alder cycloadditions prompted an investigation into the scope of these catalysts with respect to other enantioselective transformations. It was found that catalyst **22** was, in fact, successful in catalyzing the 1,3-dipolar cycloadditions of nitrones (Scheme 41).⁶²

Scheme 41. Use of catalyst 22 in 1,3-dipolar cycloadditions of nitrones.



Despite the success of these camphor-based cyclic hydrazides in Diels-Alder cycloadditions and 1,3-dipolar cycloadditions, they were not useful enantioselective catalysts for other transformations attempted, such as the α -chlorination of aldehydes,⁶³ or the alkylation of indoles⁶⁴ (Scheme 42).

Scheme 42. Unsuccessful transformations using catalyst 22.



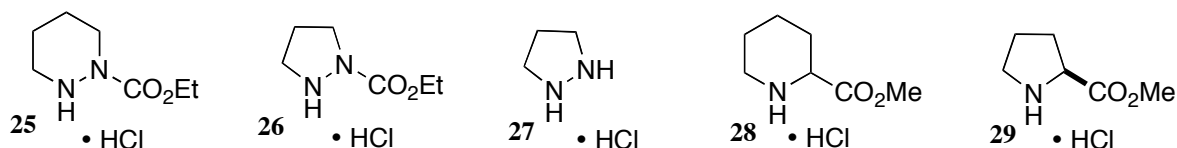
These results prompted further investigation into optimizing the catalyst architecture.

EFFECT OF RING-SIZE AND ELECTRON WITHDRAWING GROUP PLACEMENT ON CYCLIC HYDRAZIDES

In 2009, Tomkinson *et al* were investigating the effect of both the ring-size and the incorporation of either an endo or exocyclic electron withdrawing group on the hydrazide moiety, and its effect on the

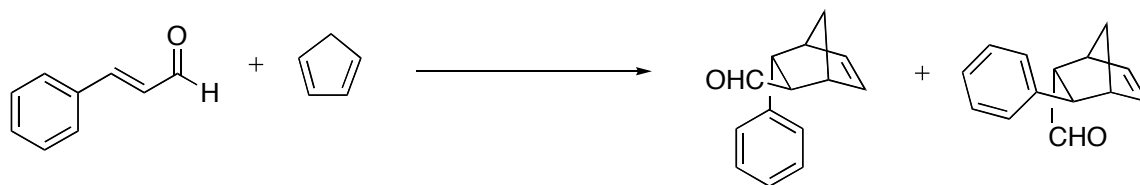
reactivity of these catalysts.⁶⁵ They investigated simple achiral amine, hydrazine, and hydrazide catalysts such as **25-29**, possessing varying ring sizes and electron withdrawing group placement (Scheme 43).

Scheme 43. Hydrazide containing achiral catalysts investigated by Tomkinson *et al.*



They compared the reactivity of each, and found that for hydrazide organocatalysts, the incorporation of the hydrazide moiety in a 6-membered ring with an exocyclic electron withdrawing group was beneficial for reactivity in the Diels-Alder reaction between (*E*)-cinnamaldehyde and cyclopentadiene (Table 1, entry 1).

Table 1. Comparison of catalytic activity of amine containing scaffolds in a Diels-Alder reaction.⁶⁵



Entry	Catalyst	Time (h)	endo:exo	Yield (%)
1	25	6	32:68	99
2	26	24	33:67	38
3	27	24	55:45	15
4	28	6	40:60	3
5	29	6	30:70	62

Incorporation of the hydrazide into a 5-membered ring with an exocyclic electron withdrawing group was detrimental in terms of yield and reaction length (Table 1, entry 2). The yield was even further diminished upon use of a hydrazine instead of a hydrazide (Table 1, entry 3). Removal of the α -heteroatom in the 6-membered ring derivatives resulted in an even worse result, where the derivative had negligible catalytic activity (Table 1, entry 4). Using proline methyl ester as a catalyst resulted in an improved yield for the short reaction time (Table 1, entry 5). These results suggested that for scaffolds

containing α -heteroatoms, such as hydrazides, catalytic activity is increased when the hydrazide is incorporated into a 6-membered ring with the electron withdrawing group being held outside the ring. In the case of amines, where no α -heteroatom is present, 5-membered ring scaffolds performed better than 6-membered ones. This is consistent with the success of Macmillan's catalyst and proline-derived catalysts in Diels-Alder reactions.

Efforts were made to rationalize these results by performing DFT calculations on the iminium ions formed upon reaction with the catalyst and the aldehyde. The calculated LUMO of the iminium ions for derivative **25** and **26** were consistent with experimental results obtained (E_{LUMO} **26** = -6.20 eV, E_{LUMO} **25** = -6.38 eV). When applied to the amine derivatives **28** and **29**, however, the model broke down, giving an equal E_{LUMO} of -6.35 eV for each, inconsistent with experimental results.

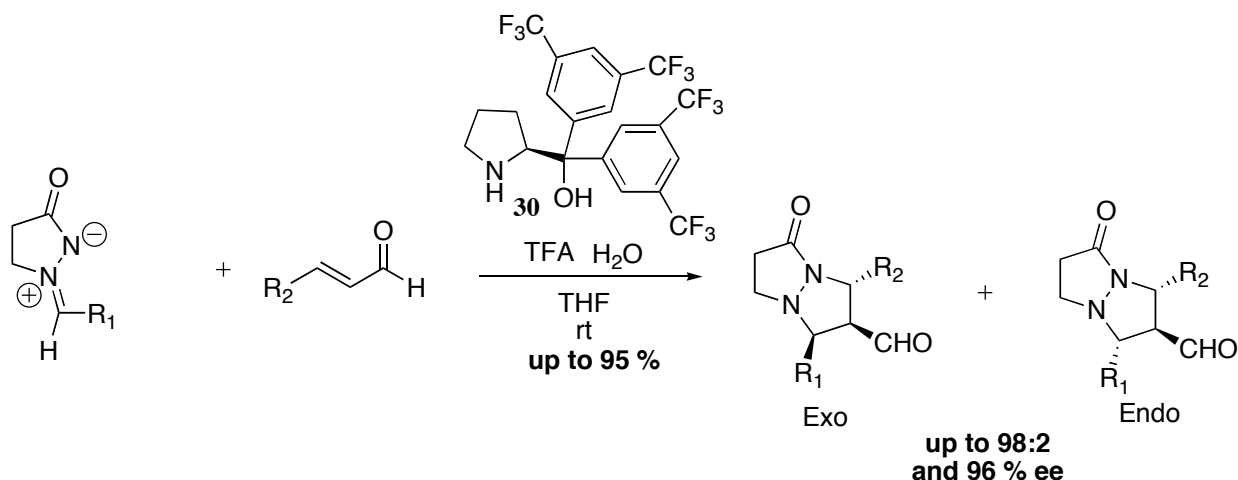
The observation that changing the ring size and electron withdrawing group placement for hydrazide catalysts can have an effect on catalyst activity led us to examine the effects of modification of our camphor based hydrazide catalysts.

RESULTS AND DISCUSSION FOR SYNTHESIS OF HYDRAZIDE-BASED ORGANOCATALYSTS FOR CYCLOADDITION REACTIONS

CATALYTIC ADDITION OF ALDEHYDES TO AZOMETHINE YLIDES

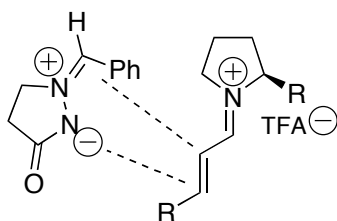
The previous success^{60,61,62} of the camphor-based hydrazone catalyst **22** in cycloaddition reactions prompted us to explore the use of this catalyst in other cycloaddition reactions. It has been shown⁶⁶ that chiral secondary amine catalysts based on proline, such as **30**, can be used to facilitate the addition of aldehydes to azomethine ylides (Scheme 44).

Scheme 44. Organocatalytic addition of azomethine ylides to aldehydes using 30.



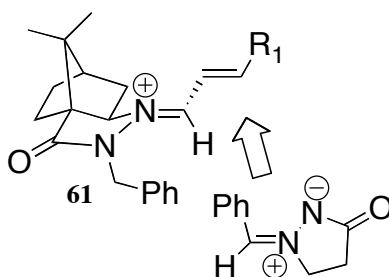
The rationale for the high diastereoselectivity obtained was that the process was likely proceeding through the transition state shown in Scheme 45, which would lead to the exo diastereomer. The high enantioselectivity was thought to be obtained from the bottom-approach of the azomethine ylide on the iminium species, due to the fact that the top approach would be hindered by the bulky aryl groups on the catalyst portion (Scheme 45).

Scheme 45. Possible reaction model leading to enantioselective formation of the exo product.



Recognizing that our previous successful catalyst **22** could operate under a similar mechanism (Scheme 46), with the camphor backbone acting as the blocking group that would give rise to enantioselectivity, we decided to investigate the use of our catalyst in such a process.

Scheme 46. Potential reaction model for addition of azomethine ylides to aldehydes facilitated by catalyst **22.**



As a test substrate, the azomethine ylide **31** was synthesized via condensation of benzaldehyde with the pyrazolidinone **32**⁶⁶ (Scheme 47). This azomethine ylide was then reacted with (*E*)-crotonaldehyde in the presence of camphor-based catalyst **22** and various acids (Table 2).

Scheme 47. Synthesis of azomethine ylide **31.**

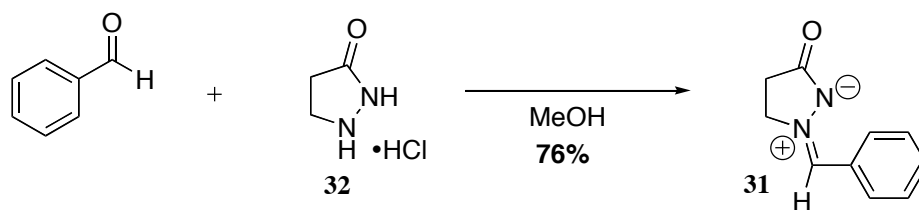
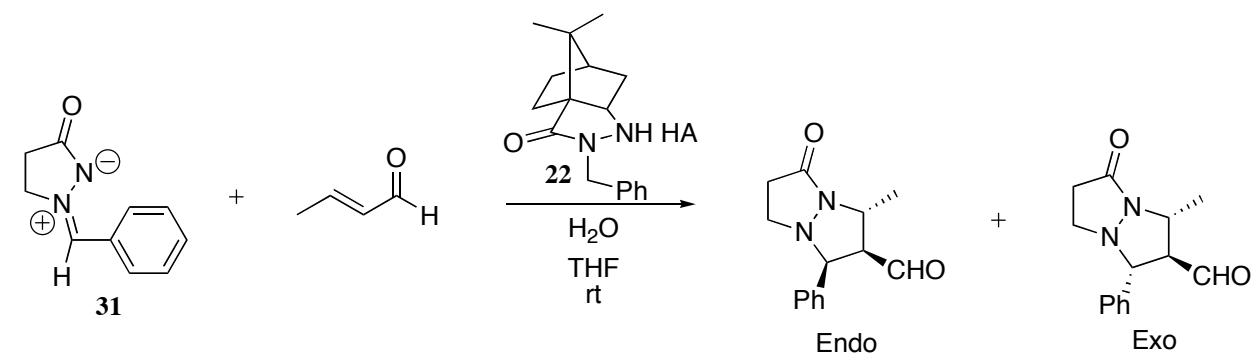


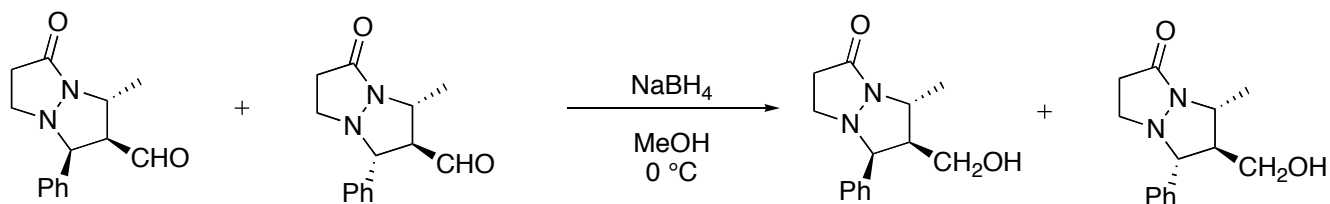
Table 2. Acid scan for addition of aldehydes to azomethine ylides.

Entry	HA	Exo:Endo	Yield (%)
1	TFA	N/A	0
2	PNBA	2.2:1	7
3	CSA	2.2:1	6
4	HClO ₄	1.6:1	7
5	none	3.9:1	9

Previous reports for the iminium catalyzed version of this reaction using chiral secondary amine catalysts showed an improvement in yield and reaction time with the use of acid additives.⁶⁶ For our catalyst, the addition of TFA as an acid proved detrimental to the reaction, resulting in no product being observed (entry 1). The addition of *p*-nitrobenzoic acid (PNBA) and camphorsulfonic acid (CSA) gave similar exo:endo ratios of 2.2:1, and similar low yields (entries 2 and 3). Although a similar yield was obtained with perchloric acid as an additive, the exo:endo ratio dropped to 1.6:1 (entry 4). The best exo:endo ratio was achieved when no additive was present, at 3.9:1, with a miniscule improvement in yield (entry 5).

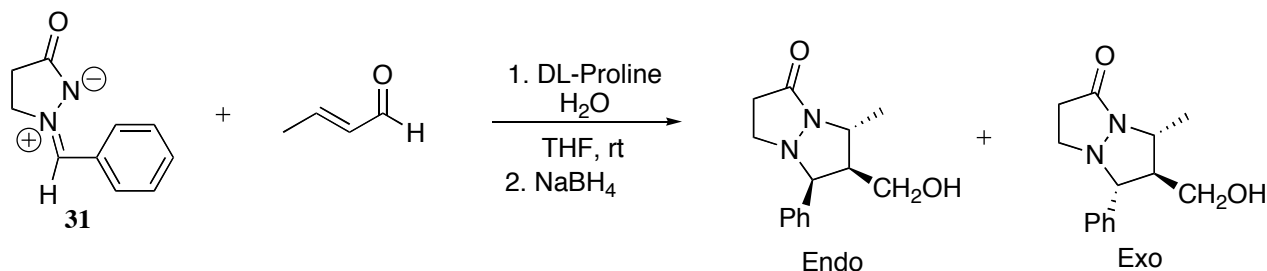
Although the yields obtained in all cases were very low, we decided to investigate whether the exo and endo diastereomers obtained were enantioenriched. Toward this end, the exo/endo mixture of aldehydes obtained (Table 2, entry 5) were converted to their corresponding alcohol (Scheme 48).

Scheme 48. Conversion of *exo/endo* aldehyde mixture to alcohols.



This was done in order to evaluate the enantiomeric excess via HPLC on a chiral stationary phase. A control reaction was also performed, in which DL-proline was used as a catalyst to effect the cycloaddition, and the presumably racemic mixture of *exo/endo* aldehydes was reduced to the corresponding alcohols (Scheme 49).

Scheme 49. DL-proline catalyzed addition of azomethine ylides to aldehydes as a control reaction.

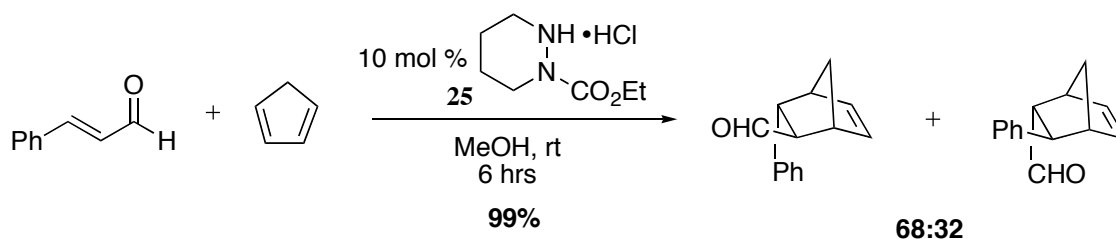


Despite the different HPLC conditions tried, we were unable to resolve each of the isomers in the mixture satisfactorily to determine the enantiomeric excess from this reaction with the equipment that was available. Due to the low yields obtained in this process, we decided to terminate this study. We turned our focus instead onto making novel organocatalysts for the Diels-Alder cycloaddition reaction, one in which catalyst **22** had seen much success. A structure-activity study had surfaced in the literature that led to synthetic attempts at various catalyst architectures in hopes of producing a rapid and enantioselective organocatalyst for the Diels-Alder reaction.

SYNTHESIS OF 6-MEMBERED CYCLIC HYDRAZIDES POSSESSING EXOCYCLIC ELECTRON WITHDRAWING GROUPS

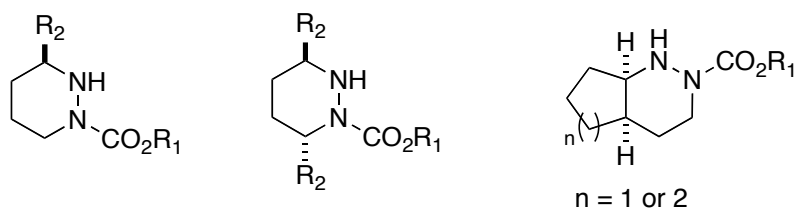
The study done by Tomkinson *et. al.*⁶⁵, which found an acceleration in the rate of hydrazide catalyzed Diels-Alder cycloadditions when cyclic 6-membered hydrazides possessing an exocyclic electron withdrawing group such as **25** were employed (Scheme 50), inspired us to investigate the synthesis and use of chiral derivatives of these catalysts in Diels-Alder reactions.

Scheme 50. Diels-Alder reaction employing 6-membered hydrazide catalysts possessing an exocyclic electron withdrawing group.



These chiral derivatives would require a relatively bulky group on the carbon α -to the nucleophilic nitrogen, in order to have the best chance of transferring the stereochemical information to the products (Scheme 51). We envisioned two strategies for the synthesis of these chiral derivatives: a racemic synthesis involving a chiral resolution step, and a synthesis involving chiral starting materials.

Scheme 51. Proposed general structures for chiral 6-membered hydrazide catalysts possessing an exocyclic electron withdrawing group.



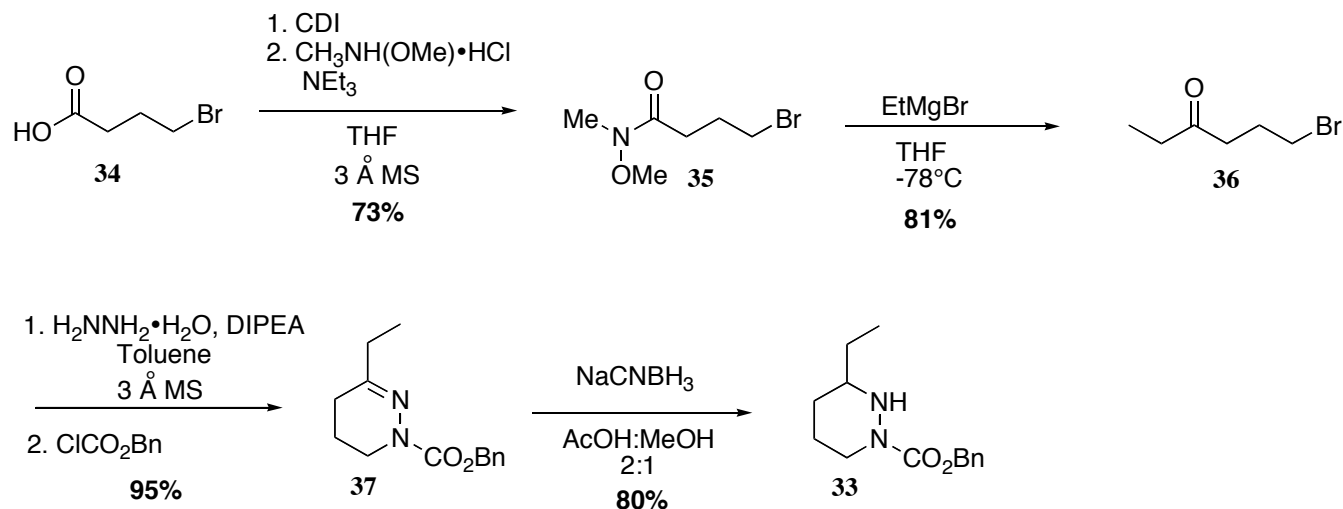
RACEMIC SYNTHESIS OF POTENTIAL CATALYSTS WITH RESOLUTION OF ENANTIOMERS

Our first approach to synthesizing chiral derivatives of the Tomkinson catalyst was to make the catalyst as a racemic mixture, and subsequently perform a resolution to obtain pure enantiomers. We envisioned that addition of a chiral acid to the cyclic hydrazide would produce a diastereomeric salt capable of crystallizing with the appropriate choice of solvent. The diastereomeric salt could then be isolated and washed with base to obtain the free cyclic hydrazide as one enantiomer. This catalyst would

then be used in Diels-Alder cycloadditions, and the enantiomeric excess of the products would be evaluated.

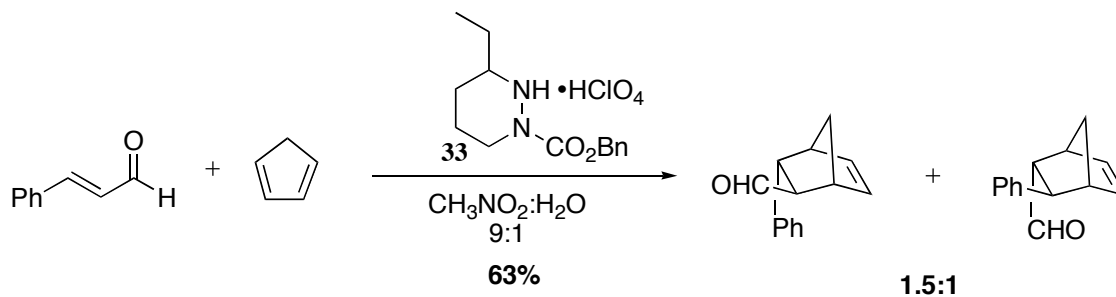
The first derivative chosen was racemic compound **33** (Scheme 52). The synthesis of **33** commenced by treatment of 4-bromobutyric acid (**34**) with $\text{CH}_3\text{NH}(\text{OMe})\cdot\text{HCl}$ under standard coupling conditions to obtain the Weinreb amide **35** in 73% yield. A Grignard reaction was then performed with ethylmagnesium bromide to obtain the bromoketone **36** in 81% yield. Hydrazone formation and cyclization was then carried out with hydrazine hydrate in toluene under basic conditions. The electron withdrawing group installation was subsequently accomplished in a one-pot procedure with benzyl chloroformate to obtain the derivative **37** in a 95% yield over the two steps. Reduction of **37** with sodium cyanoborohydride resulted in an 80% yield of potential catalyst **33**.

Scheme 52. Synthesis of 6-membered hydrazide catalyst 33.



We decided to first evaluate whether **33** was capable of catalyzing Diels-Alder reactions, before investing effort into the resolution of enantiomers. Derivative **33** did, indeed, catalyze the Diels-Alder cycloaddition between (*E*)-cinnamaldehyde and cyclopentadiene in an unoptimized yield of 63 % under the conditions employed (Scheme 53).

Scheme 53. Diels-Alder cycloaddition catalyzed by 33.



Confident that **33** could, in fact, act as a catalyst in Diels-Alder cycloadditions, we set out to find conditions in which a successful resolution of enantiomers could be performed. A variety of chiral acids were used along with different solvents in an attempt to crystallize one diastereomeric salt preferentially (Table 3).

Table 3. Crystallization conditions attempted in order to preferentially crystallize one diastereomeric salt.¹

	Camphorsulfonic acid (CSA)	Mandelic acid (MA)	Tartaric acid (TA)	Dibenzoyl tartaric acid (DBTA)
Methyl-<i>t</i>-butyl ether (MTBE)	crystals	-	crystals	-
MeOH	-	-	-	-
CH₃CN	-	-	crystals	-
EtOAc	-	-	crystals	-
CHCl₃	-	crystals	crystals	-
Toluene	-	crystals	crystals	-

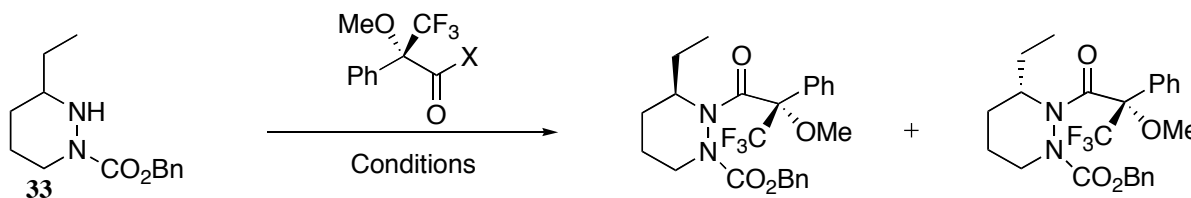
The use of CSA as a chiral acid produced crystals only in methyl *tert*-butyl ether (MTBE), while the use of mandelic acid (MA) produced crystals in both CHCl_3 and toluene. Tartaric acid (TA) ended up giving crystals in all solvents tried except methanol, and the use of dibenzoyl tartaric acid (DBTA) resulted in no crystals in any of the solvents tried.

Once these crystals were obtained, we planned to perform a base wash and determine the enantiomeric excess of the resulting freebase. Prior to doing this, we needed to have a method of determining the enantiomeric excesses of the freebases obtained from each crystallization condition.

To start, we decided to try out derivatization reactions that would create a second stereocenter in the molecule, resulting in a diastereomeric mixture that could be seen by NMR analysis. This would allow us to relatively quickly determine the enantiomeric ratio of the freebases obtained from each set of crystals produced. To test the derivatization reactions, we used the racemate of the catalyst **33** as a control to ensure that 1) the derivatization reaction would work, and 2) that the diastereomeric products of this reaction could both be clearly identified by NMR.

Toward this end, we first attempted to synthesize the Mosher amides of racemic **33** due to the relative ease of determining the enantiomeric excess by ^{19}F NMR (Table 4).⁶⁷

Table 4. Attempted formation of Mosher amide from **33.**

			
Entry	X	Conditions	Yield (%)
1	-Cl	NEt_3 DCM	0
2	-Cl	NEt_3 , DMAP DMF 100 °C	0
3	-OH	DCC, DMAP, HOBt DCM	0

Unfortunately, no reaction was observed when the (*R*)-(-)-Mosher acid chloride was used either alone or with the assistance of DMAP and heat (entries 1 and 2). The use of (*S*)-(-)-Mosher acid under peptide coupling conditions also did not yield any product (entry 3).

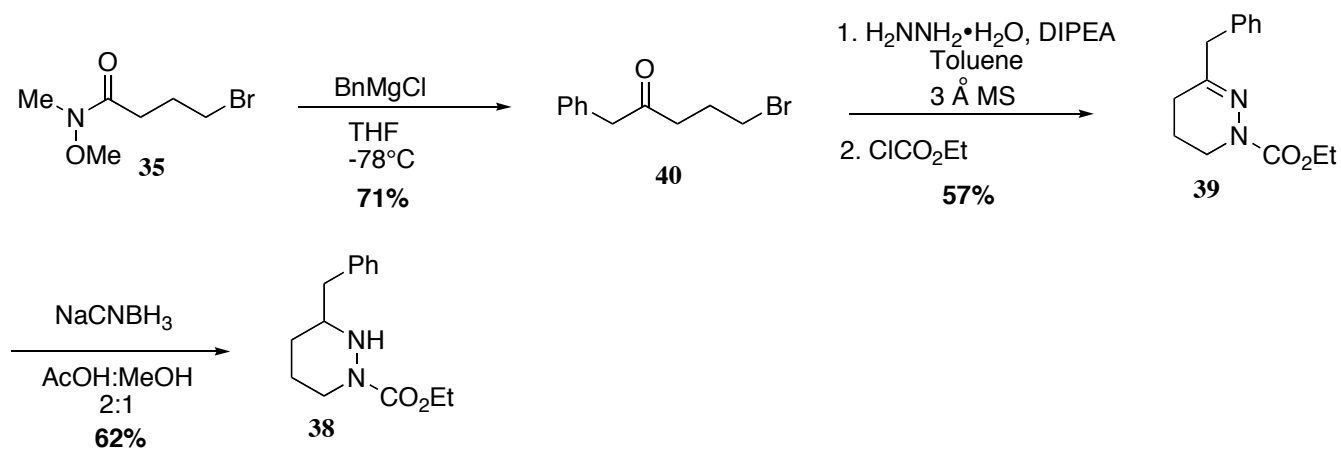
With these results, we decided to attempt coupling of **33** with some Boc-protected amino acids in hopes that the issue with the Mosher amide formation was due to steric effects associated with the quaternary center α -to the carbonyl (Table 5). These Boc-protected amino acids were chosen such that they contained functionality that would give characteristic ^1H NMR signals, to aid in identifying the two diastereomers in the spectrum. Both Boc-protected phenylalanine and alanine were employed, with no product observed in either case (Table 5, entries 1 and 2).

Table 5. Attempted coupling of 33 to Boc-protected amino acids.

Entry	R	Yield (%)
1	-Bn	0
2	-Me	0

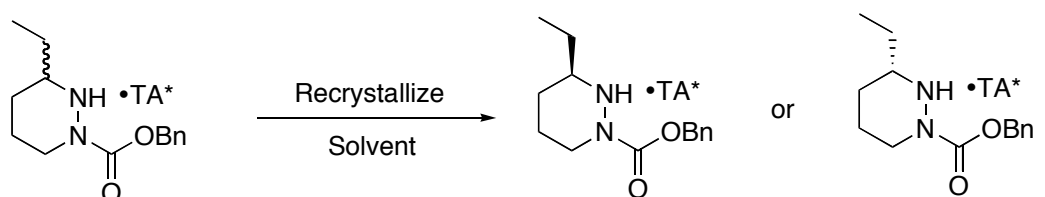
Although the synthesis of catalyst **33** was relatively quick and efficient, the difficulty of finding a method to determine catalyst ee was unfavorable. We decided to instead pursue a similar derivative **38**, possessing the larger benzyl group on the carbon α to the key nucleophilic nitrogen on the catalyst whose synthesis mirrors that described for **33** (Scheme 54).

Scheme 54. Synthesis of derivative 38.⁶⁸



After a failed attempt at a simple acylating reaction between benzoyl chloride and racemic **38**, it was determined that the free secondary nitrogen was too sterically hindered to participate in derivatization reactions. We therefore decided to attempt separation of the enantiomers by chiral HPLC. The racemic catalyst was subjected to various crystallization conditions using tartaric acid as the chiral acid with some success (Table 6). Toward this end, the crystals obtained were washed with base, then subjected to HPLC on a chiral stationary phase (CHOD column, 5 % *i*PrOH/hexanes, 1 mL/min) to determine enantiomeric excess.

Table 6. Crystallization conditions for derivative 38 using tartaric acid.⁶⁸



Entry	Solvent	Result	ee (%) ^a
1	CHCl ₃	Crystals	0
2	Toluene	Crystals	0
3	EtOAc	Crystals	0
4	DCE	Crystals	35
5	MeOH	No Crystals	N/A
6	CH ₃ CN	No Crystals	N/A
7	MTBE	Crystals	0
8	EtOH	No Crystals	N/A
9	DCM	Crystals	0
10	Dioxane	Crystals	0
11	<i>i</i> PrOH	No Crystals	N/A
12	Benzene	No Crystals	N/A
13	Cyclohexane	Crystals	0
14	Acetone	Crystals	0
15	CCl ₄	Crystals	0

^a Enantiomeric excess determined after conversion of the diastereomeric salt to the freebase compound.

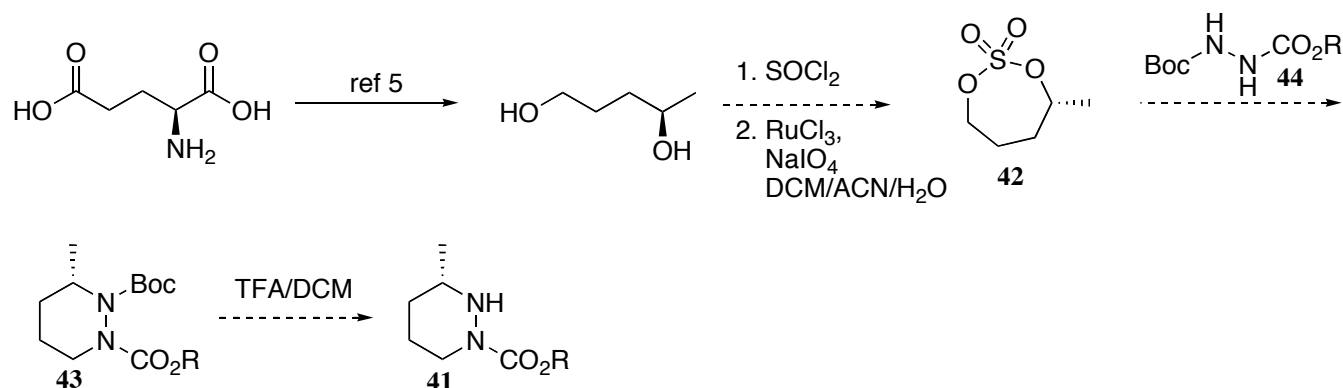
Despite the many crystallization conditions tried, all except one gave 0 % ee of the freebase. When crystals were obtained from dichloroethane (DCE), using tartaric acid as the chiral acid, a 35 % ee was obtained from the recrystallization process. This ee could not be improved, and we therefore decided that a process involving resolution of enantiomers may not be best suited for these types of catalysts.

ATTEMPTED SYNTHESIS OF CHIRAL CATALYSTS OBTAINED FROM CHIRAL STARTING MATERIALS⁶⁹

Due to the fact that there was little success in resolving racemic catalysts **33** and **38**, we decided to take a different approach toward the synthesis of chiral 6-membered hydrazides possessing an exocyclic electron withdrawing group. This approach involved starting with chiral materials that are readily available. The advantage to this method, is that the stereogenic unit can be introduced at the beginning of the synthesis, and may result in a more efficient synthesis of these catalysts.

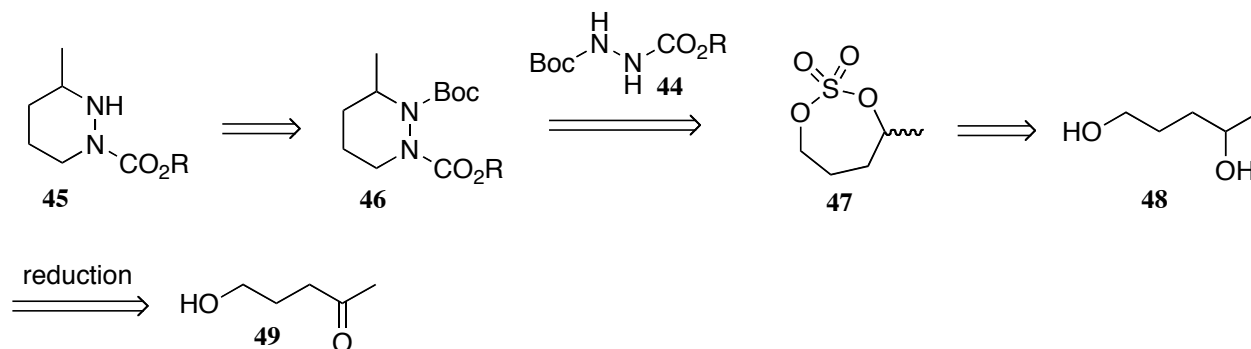
An example of such a derivative that can be obtained from chiral starting material, is **41** (Scheme 55). It has been reported⁷⁰ that intermediate **42** can be obtained as a single enantiomer, which would, in turn, allow us to obtain **43** as a single enantiomer upon S_N2 displacement by the hydrazide **44**. Deprotection of **43** would give rise to potential chiral catalyst **41**.

Scheme 55. Enantiospecific synthesis of **41**.



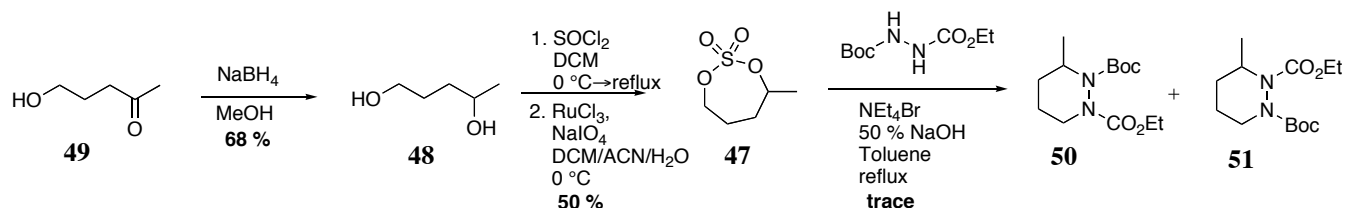
We chose to first explore the synthesis of **45**, the racemic derivative of **41** (Scheme 56). We wanted to try out the synthesis racemically first, before moving to a synthesis involving precious chiral materials. We imagined that **46** could be obtained from attack of hydrazide **44** on intermediate **47**. Intermediate **47** could be obtained from diol **48**, arising from reduction of ketone **49**.

Scheme 56. Retrosynthesis of racemic catalyst **46**.

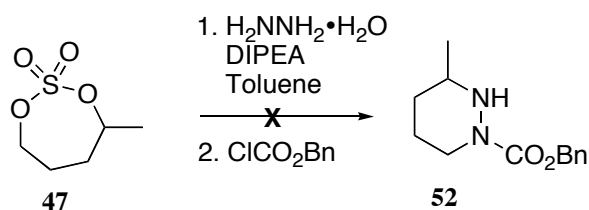


The reduction of ketone **49** proceeded smoothly as expected using NaBH_4 , to give the resulting diol in 68 % yield (Scheme 57). This diol was then converted into derivative **47** using a procedure described in the literature⁷¹ in a 50 % yield. Attempts to introduce the hydrazide under phase-transfer conditions led to a trace amount of a mixture of products (Scheme 57). We believed this was indeed a mixture of isomers **50** and **51**, because of the presence of two multiplets corresponding to the ring hydrogen α to the methyl group, with chemical shifts consistent with protons next to a nitrogen atom. Treating with hydrazine hydrate and subsequent installation of the electron withdrawing group led to no product formation (Scheme 58).

Scheme 57. Attempted synthesis of derivative **45**.



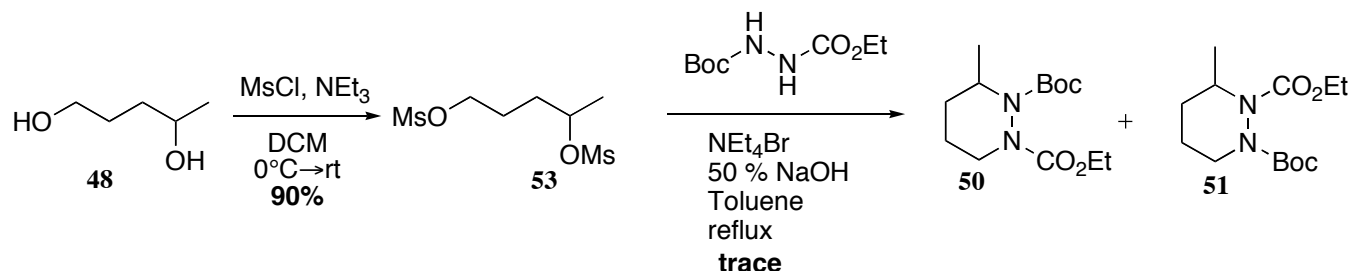
Scheme 58. Attempted one-pot cyclization/electron withdrawing group installation.



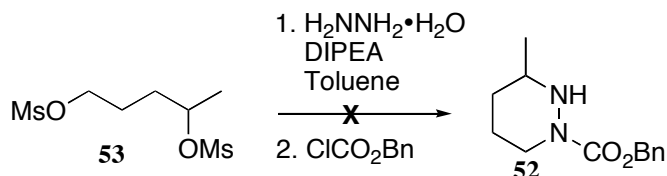
We next decided to employ a different set of leaving groups, and therefore methanesulfonyl groups were used in place of the cyclic sulfone derivative **47** (Scheme 59). Toward this end, derivative **48** was converted to the dimesylate **53** in 90 % yield. This product was then treated under similar conditions as described before to obtain what appeared to be a mixture of isomers from the phase transfer reaction

(Scheme 59), and no observable product from the reaction with hydrazine hydrate (Scheme 60). The apparent mixture of isomers was subjected to deprotection, however, a sufficient quantity of the pure derivative **45** could not be obtained.

Scheme 59. Attempted synthesis of **45 using dimesylate **53**.**

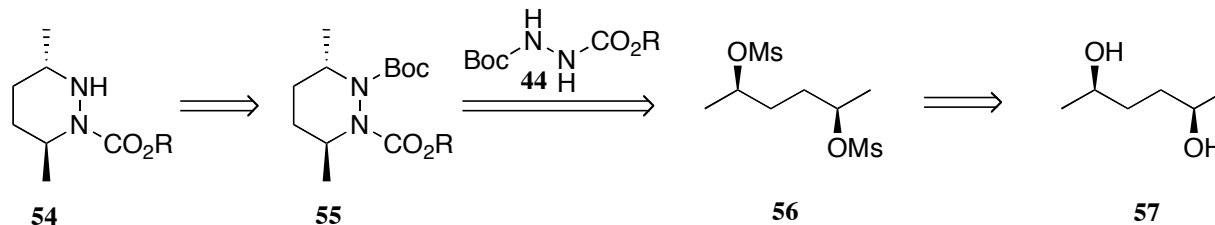


Scheme 60. Attempted treatment of **53 with hydrazine hydrate followed by electron withdrawing group installation.**



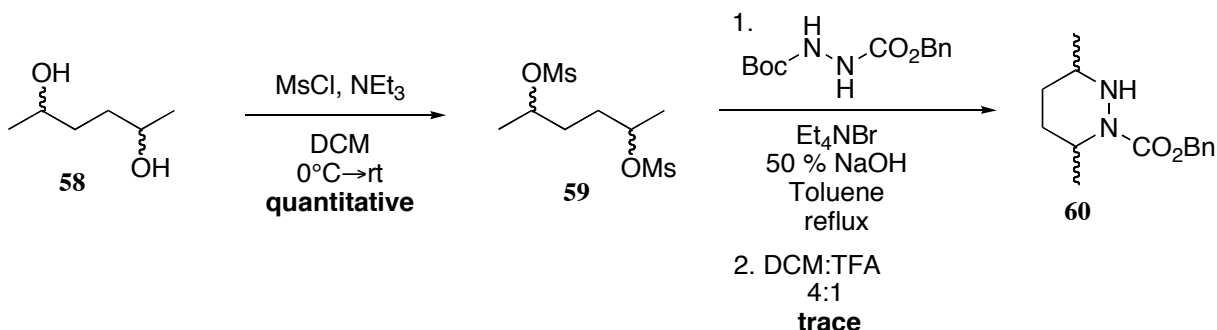
Due to the unsuccessful reaction of **92** with hydrazine hydrate, and the apparent isomer formation for the phase-transfer reaction, we decided to explore the synthesis of a catalyst **54** in which the starting material possessed C2-symmetry (Scheme 61). This way, the approach of the hydrazide would not be as significant, because either approach would lead to the same enantiomer. The cyclic hydrazide formation to give **55** could be accomplished by the same phase-transfer conditions described for derivative **45**, and the dimesylate **56** could be obtained from commercially available diol **57**.

Scheme 61. Retrosynthetic analysis for potential catalyst **54 starting with C2-symmetric **57**.**



Initially, we planned to do the synthesis in a non-enantioselective manner, to ensure that the process would be efficient (Scheme 62).

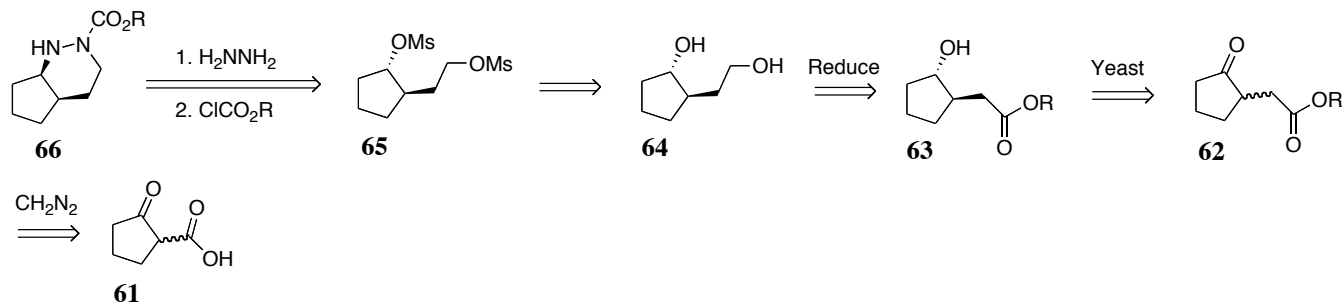
Scheme 62. Attempted synthesis of racemic 54.



The racemic *syn* diol **58** was converted smoothly to the dimesylate **59**, which was then reacted with the hydrazide under phase transfer conditions. This produced an intermediate, which was immediately subjected to deprotection with TFA/DCM to provide a trace amount of **60**. Unfortunately, the efficiency of the last step could not be improved, so this route was abandoned.

Lastly, we decided to investigate the synthesis of a chiral 6-membered hydrazide that would possess a “cup-shape”. It was believed that the diastereomerically pure catalyst could be obtained via the route shown in Scheme 63. The carboxylic acid **61** would be converted to **62** via a homologation reaction. The key diastereoselective reduction would be performed on the γ -ketoester **62** by baker’s yeast, to obtain derivative **63**.⁷² Subsequent reduction of the ester functionality to the diol **64** would set the stage for conversion of the alcohol groups to good leaving groups such as the dimesylate **65**. This compound would then be reacted with hydrazine, followed by an alkyl chloroformate to obtain the potential catalyst **66**.

Scheme 63. Proposed synthesis for diastereopure catalyst 66.



In order to evaluate whether **66** would be a good catalyst, the synthesis of the racemic version of this derivative (**67**) was first examined. The retrosynthetic analysis involved the use of a different strategy to

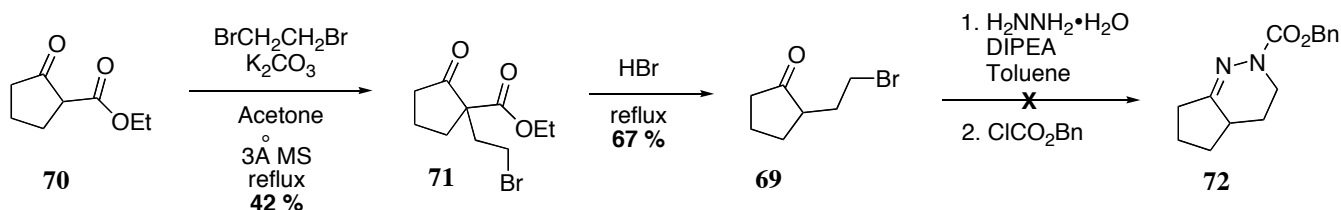
install the hydrazide portion (Scheme 64). The key hydrazone formation/cyclization step to form **68** would utilize intermediate **69**, which could, in turn, be obtained ultimately from material **70** by a known procedure.⁷³

Scheme 64. Retrosynthetic analysis for potential racemic catalyst 67.

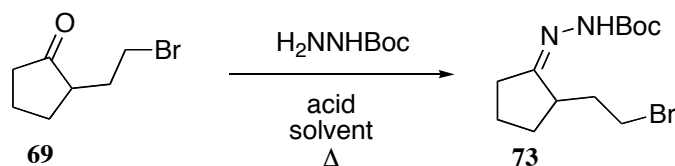


The synthesis began with the conversion of the β -ketoester **70** into the alkylated derivative **71** in 42% yield (Scheme 65). Hydrolysis of the ester was accomplished by refluxing in HBr, in 67% yield. A one-pot hydrazone formation/cyclization procedure to form **72** was attempted using hydrazine hydrate followed by benzyl chloroformate.

Scheme 65. Attempted synthesis of potential catalyst 67.

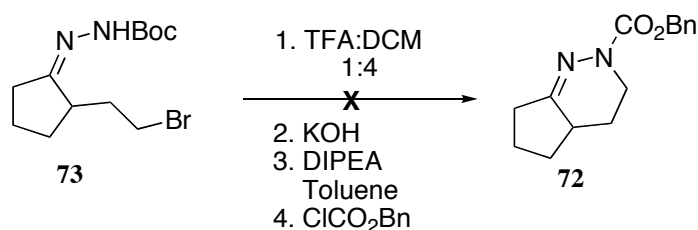


Disappointingly, no product was observed from this reaction, despite our previous success with the one-pot hydrazone formation/cyclization on a similar derivative. We then decided to form the hydrazone in a separate step, using a Boc-protected hydrazide due to the expected increased stability and ease of purification of the resulting hydrazone. The Boc protecting group would be removed, and the compound subjected to cyclization conditions and electron withdrawing group installation. Toward this end, hydrazone formation with *t*-butyl carbazate was attempted under neutral and acidic conditions (Table 7).

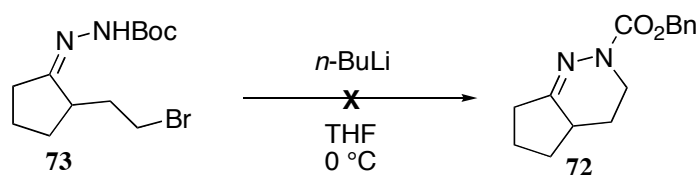
Table 7. Hydrazone formation with *t*-butyl carbazate

Entry	Acid	Solvent	Result
1	TsOH•H ₂ O	benzene	0 % yield
2	none	toluene	0 % yield
3	none	hexanes	crude product

Heating an acid in benzene, or no acid in toluene resulted in decomposition (entries 1 and 2). The use of hexanes as solvent in neutral conditions led to a product whose spectral characteristics resembled those expected for **73**, yet could not be satisfactorily purified. This product was immediately put under deprotection/cyclization conditions, in hopes of obtaining **72** (Scheme 66).

Scheme 66. Attempted deprotection/cyclization of derivative 73.

Unfortunately, we could not obtain any product with the sequential deprotection/cyclization steps, so we decided to attempt the cyclization with an organolithium base, in hopes that the intermediate **72** could be obtained in this manner (Scheme 67).

Scheme 67. Attempted deprotonation/cyclization of derivative 73.

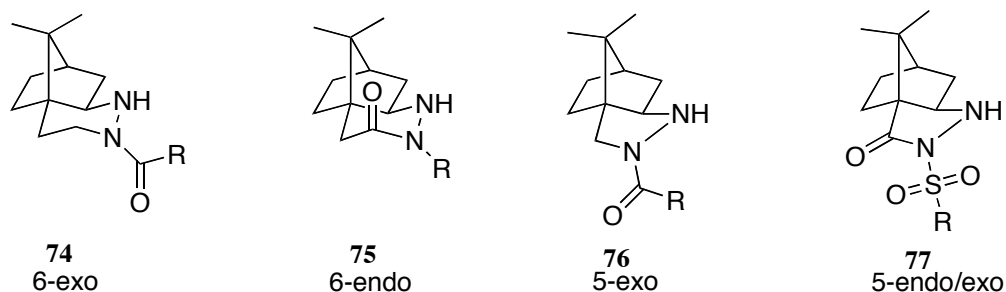
Sadly, only decomposition was observed, and the racemic synthesis of this type of potential catalyst was abandoned. We then decided to revisit our camphor-based hydrazides that had been successfully synthesized and applied in enantioselective Diels-Alder reactions in the past. We realized that we could use the camphor skeleton framework as an easily accessible element to influence reaction

enantioselectivity for derivatives in which we vary the ring size and electron withdrawing group placement of the hydrazide moiety.

VARIATION OF ELECTRON WITHDRAWING GROUP PLACEMENT AND RING SIZE OF CAMPHOR-BASED CYCLIC HYDRAZIDES

The extreme variations in efficiency of achiral cyclic hydrazide catalysts for Diels-Alder reactions noted by Tomkinson *et al*⁶⁵, led us to re-examine our own camphor-based hydrazide catalyst. We were interested in performing variations on both the size of the ring that the hydrazide was incorporated into, as well as the placement of the electron withdrawing group; in particular whether the electron withdrawing group was *endo* or *exocyclic*. We envisioned that four variations of ring size and electron withdrawing group placement could be performed, maintaining the camphor backbone (Scheme 68).

Scheme 68. Variations of ring size/electron withdrawing group placement for camphor based hydrazides.



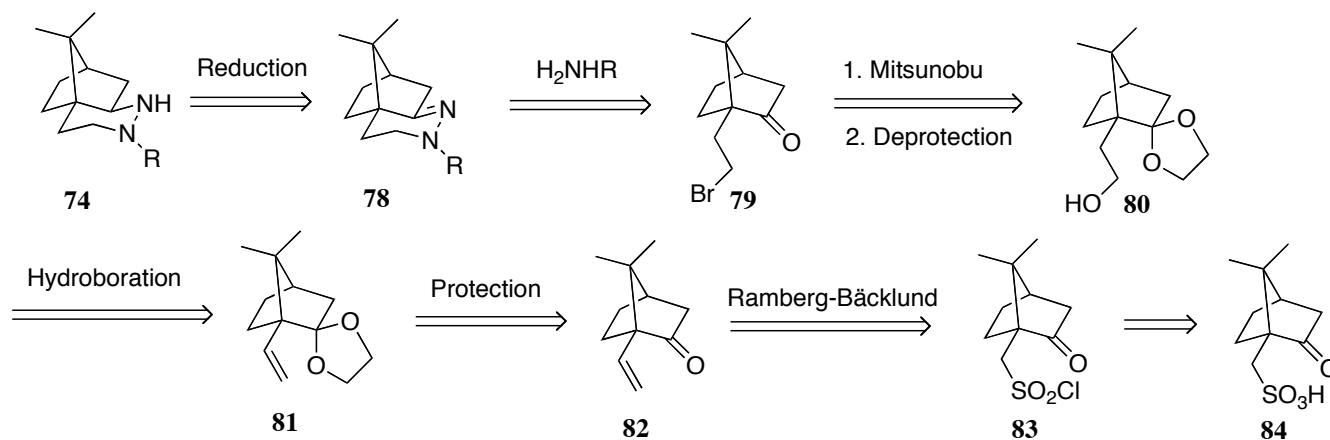
The first variation involves the synthesis of a 6-membered hydrazide possessing an exocyclic electron withdrawing group (**74**), the second, an endocyclic electron withdrawing group (**75**). The third variation involved a 5-membered derivative possessing an exocyclic electron withdrawing group (**76**). The last variation we wanted to explore was the incorporation of both an endo and exocyclic electron withdrawing group on a five membered ring scaffold (**77**). We hoped that a change in the electron withdrawing group placement or ring size would lead to increased catalyst efficiency and a broader applicability to other reactions.

6-MEMBERED CAMPHOR-BASED HYDRAZIDES POSSESSING AN EXOCYCLIC ELECTRON WITHDRAWING GROUP

The results by Tomkinson *et al*⁶⁵ suggest that a hydrazide incorporated into a 6-membered ring, and possessing an exocyclic electron withdrawing group, would show increased efficiency over derivatives with 5-membered ring hydrazides, regardless of electron withdrawing group placement. We were very interested in synthesizing a chiral 6-membered hydrazide with an exocyclic electron withdrawing group, and our previous efforts toward synthesizing chiral derivatives with relative structural simplicity had not been fruitful.

As an alternate way to obtain a chiral 6-membered hydrazide possessing an exocyclic electron withdrawing group, we decided to explore the synthesis of derivatives containing a camphor backbone. The precursors for this type of derivative could be obtained from the chiral pool, therefore the chiral information would be built in from the start. Our retrosynthetic plan for such derivatives involved multiple manipulations of functionality around the camphor backbone, and was quite lengthy (Scheme 69).

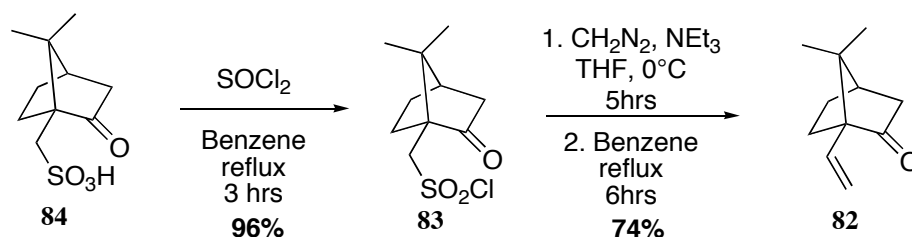
Scheme 69. Retrosynthetic analysis for derivatives of general structure 74.



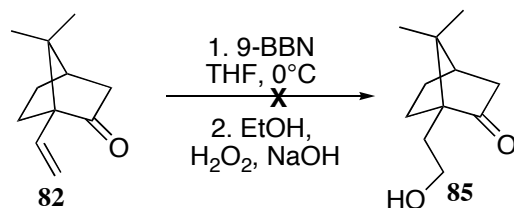
We imagined that derivative 74 could be obtained via reduction of the cyclic hydrazone 78. One-pot hydrazone formation/cyclization involving bromoketone 79 should give rise to 78. The bromoketone 79 could, in turn, be obtained by Mitsunobu-type conversion of the alcohol on 80, followed by deprotection. Alcohol 80 could be obtained by using variations on synthetic procedures previously reported⁷⁴, ultimately starting from camphorsulfonic acid (84).

The synthesis of these derivatives commenced with the conversion of camphorsulfonic acid (**84**) to the sulfonyl chloride **83** in 96 % yield. This intermediate was then subjected to a Ramberg-Bäcklund⁷⁵ reaction with subsequent decomposition of the episulfone to give rise to alkene **82** in 74 % yield over the two steps (Scheme 70). Initially, we attempted to perform a hydroboration on compound **82** to obtain the corresponding alcohol **85** (Scheme 71). Despite reports of previous success with this procedure,⁷⁶ in our hands, the keto alcohol product **85** could not be obtained, and instead, a crude byproduct whose spectral characteristics did not match those reported⁷⁶ for **85** was observed. This byproduct was present in the reaction mixture even after only 30 minutes of reaction time.

Scheme 70. Synthesis of alkene **82**.

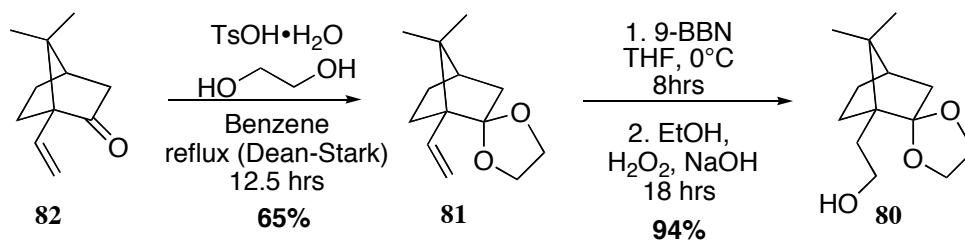


Scheme 71. Attempted hydroboration of **82**.



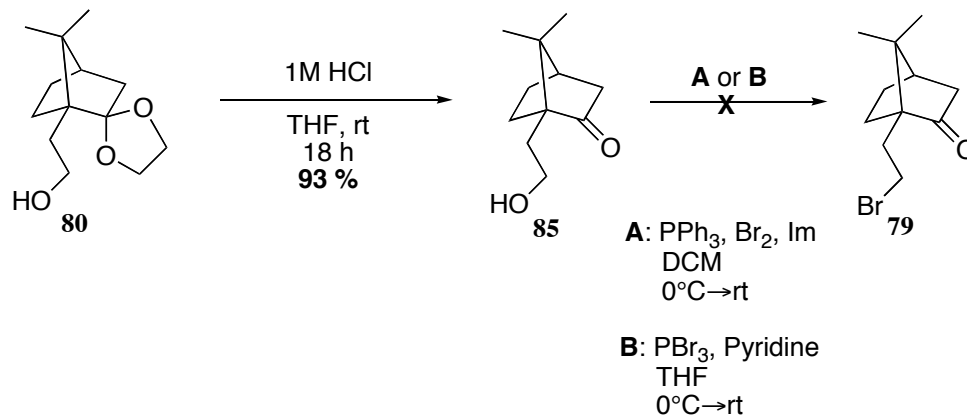
We then discovered a different paper^{74b} in which the hydroboration was performed after the ketone carbonyl on **82** was protected by conversion to the acetal **81**. We therefore synthesized **81** in 65 % yield, and subsequently performed the hydroboration on this derivative, which gave the desired protected alcohol **80** in 94 % yield (Scheme 72).

Scheme 72. Synthesis of **80** via hydroboration of protected derivative **81**.



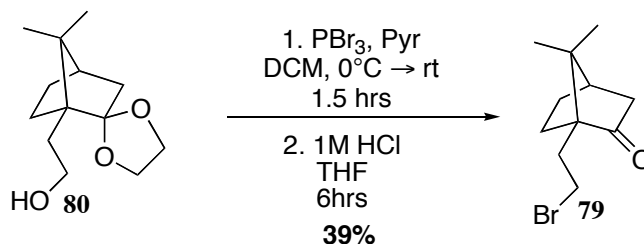
The protected alcohol **80** was then deprotected to obtain **85** in 93 % yield. The Mitsunobu-type bromination of this derivative under two different conditions led to complete decomposition (Scheme 73).

Scheme 73. Attempted conversion of alcohol 85 to bromoketone 79.



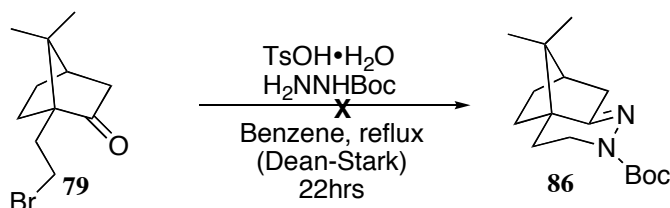
Due to our previous troubles with reactions performed in the presence of the free ketone functionality, we decided to attempt the bromination on the protected derivative **80** (Scheme 74). Thankfully, the use of PBr₃ under basic conditions allowed the preparation of **79** in 39 % yield after deprotection.

Scheme 74. Synthesis of bromoketone 79 from protected intermediate 80.



Attempted hydrazone formation/cyclization with *t*-butyl carbazate under acid catalysis resulted in no reaction by TLC analysis (Scheme 75).

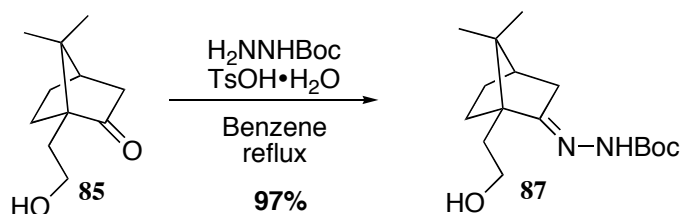
Scheme 75. Attempted formation of 86 from bromoketone 79.



We were surprised to discover that the hydrazone formation on derivative **79** was not an easy process. We originally thought that perhaps the ketone functionality in **79** was too hindered, although similarly hindered ketones have successfully been converted to hydrazones in the past.⁷⁷ We wondered whether a

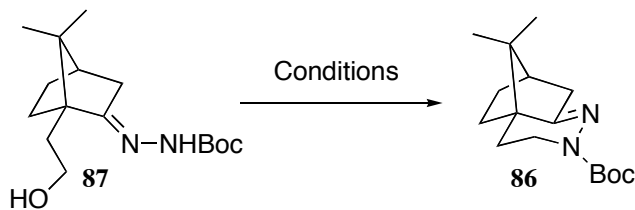
group that is capable of hydrogen bonding could be used in place of the bromine group in **79**. Fortunately, we had an intermediate on hand to test this theory (**85**). Indeed, when **85** was subjected to the same hydrazone forming conditions as **79**, the corresponding hydrazone **87** was obtained in 97 % yield (Scheme 76).

Scheme 76. Formation of hydrazone **87 from alcohol **85**.**



Excited by this result, we decided to attempt the cyclization of **87** after converting the alcohol to a better leaving group (Table 8).

Table 8. Attempted cyclization of **87.**

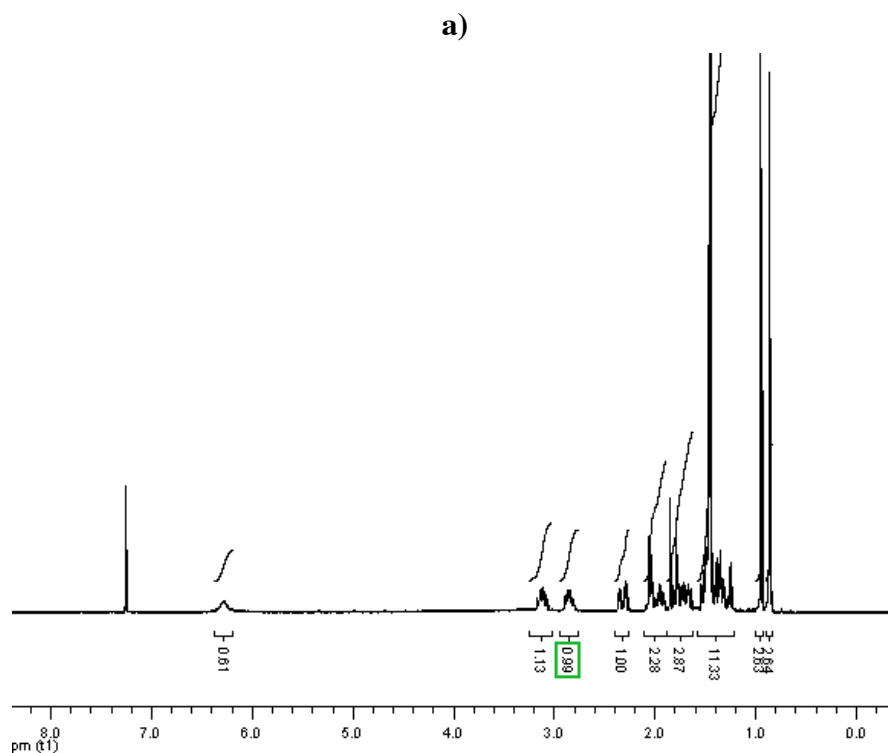


Entry	Conditions	Result
1	PPh ₃ , DIAD THF, rt 4 hrs	88
2	PPh ₃ , DIAD (premixed) THF 0°C to rt 18hrs	88
3	PPh ₃ , CBr ₄ THF, rt 3 days	88 and SM
4	PBr ₃ , Pyr THF, 0°C to rt 1 hr	decomposition
5	MsCl, NEt ₃ DCM, 0°C to rt 2hrs	88 and mesylated 87

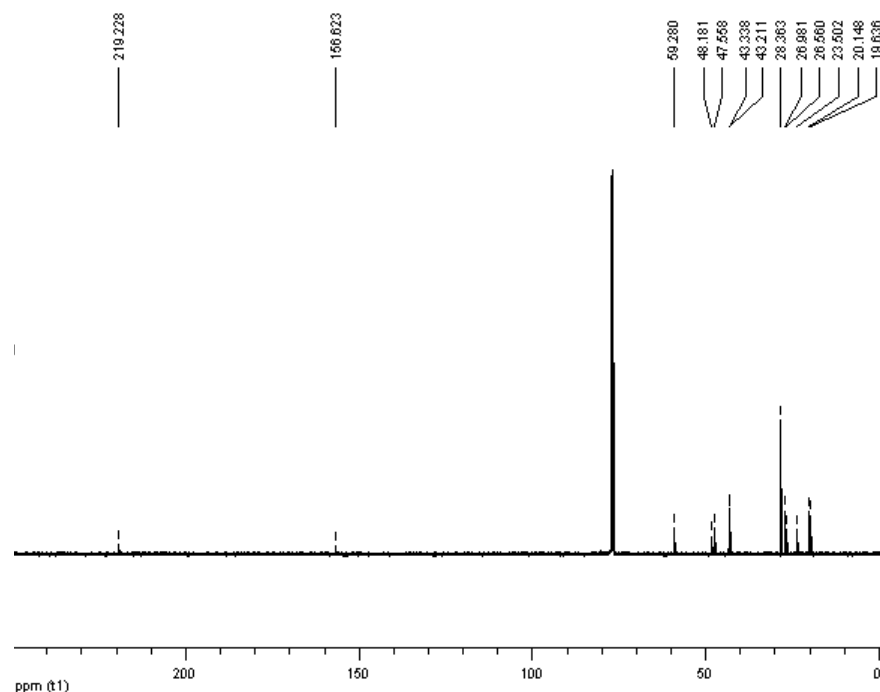
The use of a Mitsunobu reaction employing triphenylphosphine and diisopropyl azodicarboxylate (DIAD) resulted in the formation of a product **88** that did not match spectral characteristics of the desired derivative **86** (entry 1). Premixing the triphenylphosphine and DIAD with hopes that the attack of the free alcohol on **87** would be facilitated by the presence of a pre-activated electrophile gave the same product **88** (entry 2). We then attempted to obtain the cyclized product through the intermediacy of a bromide leaving group. Toward this end, triphenylphosphine was used along with carbon tetrabromide, and a mixture of product **88** and starting material was obtained (entry 3). Attempting bromination using the previously successful PBr₃/Pyridine conditions only afforded decomposition of this substrate (entry 4). When we attempted to obtain the cyclized product through the intermediacy of a mesylate leaving group, a mixture of the mesylated derivative was obtained along with **88** (entry 5).

We then set out to determine the identity of this product **88**, in case it had a structure that could be useful in our studies. The presence of a broad singlet at ~6.30 ppm in the ¹H NMR suggested that this molecule could potentially contain an amide hydrogen (Figure 1, a).

Figure 1. a) ¹H NMR and b) ¹³C NMR of compound 88

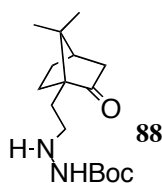


b)



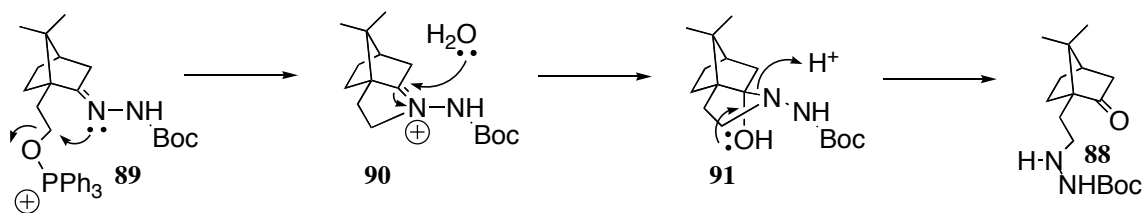
The Boc group was identified in the spectrum, as well as some signals characteristic to the camphor backbone. With this information, we gathered that the hydrazide was still present on the camphor backbone, but was not in its original place. The ^{13}C NMR spectrum provided some key additional information (Figure 1, b). Specifically, the presence of two signals were observed from this spectrum, one at 219.2 ppm, the other at 156.6 ppm, suggesting that there were two carbonyls; one of which was conjugated. This allowed us to come up with a structure for **88**, incorporating the key elements from the ^1H and ^{13}C NMR spectra, as well as examining the substrate and reaction conditions (Scheme 77).

Scheme 77. Structure proposed for product 88.



We believed that this product could arise from attack of the imine nitrogen on activated derivative **89**, to form the 5-membered species **90** (Scheme 78). Hydrolysis of the resulting iminium via **91** would give **88**.

Scheme 78. Potential mechanism for formation of **88**.

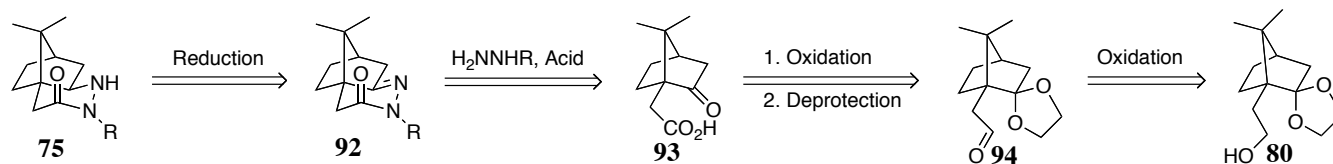


The structure of **88** unfortunately was not overly suitable for conversion into desired derivative **86**. The difficulty of obtaining **86** from hydrazone **87** led us to abandon that strategy as a way of obtaining **86**. The difficulty of hydrazone formation on bromoketone **79** and similar derivatives examined, prompted us to investigate the use of an endocyclic electron withdrawing group on a hydrazide in a 6-membered ring. We imagined that this would be synthetically simpler, due to the fact that the catalyst could be obtained in a similar fashion to the way **22** was obtained, only starting from homoketopinic acid rather than ketopinic acid.

6-MEMBERED CAMPHOR-BASED HYDRAZIDES POSSESSING AN ENDOCYCLIC ELECTRON WITHDRAWING GROUP

In light of the difficulty of obtaining 6-membered camphor-based hydrazides containing exocyclic electron withdrawing groups, we decided to move on with a study of 6-membered derivatives with endocyclic electron withdrawing groups. Such 6-membered hydrazides were not included in Tomkinson's original study,⁶⁵ so we were interested in how these derivatives would behave in cycloaddition reactions. The proposed retrosynthetic plan for such derivatives started from intermediate **80**, whose synthesis was described in Scheme 72.

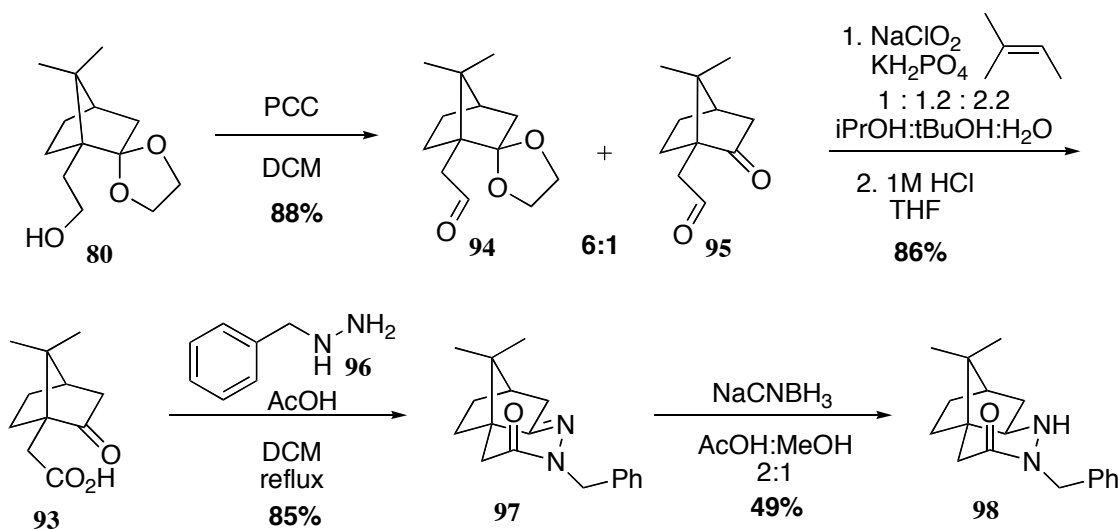
Scheme 79. Retrosynthetic plan for the synthesis of derivatives with general structure **75**.



We envisioned yet again that **75** could be obtained from the reduction of cyclic hydrazone **92**. **92** could be produced by hydrazone formation/cyclization of homoketopinic acid (**93**). This key intermediate could be obtained from oxidation of the alcohol **80** via the aldehyde **94**, and subsequent deprotection to afford **93**.

The synthesis of derivatives of type **75** commenced with the oxidation of alcohol **80** with PCC to afford a 6:1 mixture of the corresponding protected and deprotected aldehydes **94** and **95** in 88 % combined yield (Scheme 80). This mixture was then oxidized by a Pinnick oxidation, and subsequent deprotection afforded homoketopinic acid (**93**) in 86 % yield. Gratifyingly, hydrazone formation and immediate cyclization occurred with hydrazine **96** and acetic acid as catalyst to give **97** in 85 % yield. Reduction of **97** with sodium borohydride afforded the desired derivative **98** in 49 % yield.

Scheme 80. Synthesis of 6-membered hydrazide **98 from **80**.**



Once **98** was obtained, we examined its ability to act as an enantioselective catalyst for Diels-Alder reactions, using the common test reaction between (*E*)-cinnamaldehyde and cyclopentadiene^{65,78} (Table 9). The use of triflic acid as a co-catalyst in H₂O:THF (9:1) resulted in a moderate conversion of 52 %, and low enantioselectivities of both the endo and exo products (entry 1). Changing the solvent to brine⁷⁹ did not provide an improvement in either conversion or enantioselectivity (entry 2). The use of perchloric acid as a co-catalyst improved the conversion to 78 %, however, low enantioselectivities were still obtained (entry 3). Using trichloroacetic acid⁷⁹ provided a moderate conversion of 56 % with low enantioselectivities (entry 4).

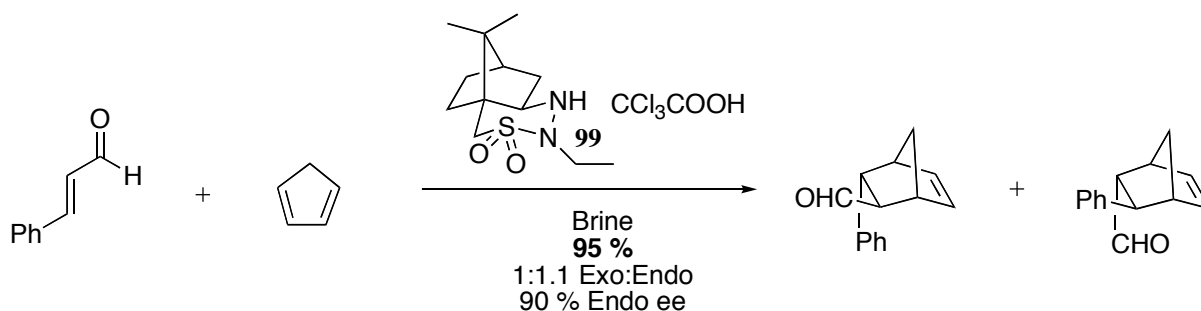
Table 9. Diels-Alder reactions employing 137 as a catalyst.

Reaction scheme showing (E)-cinnamaldehyde reacting with cyclopentadiene in the presence of catalyst **98** and a co-catalyst in a solvent to yield endo and exo bicyclic aldehyde products.

Entry	Co-Catalyst	Solvent	Conversion	Endo:Exo	Endo ee	Exo ee
1	TfOH	H ₂ O:THF (9:1)	52%	1:1.7	34%	38%
2	TfOH	Brine	46%	1:1.8	29%	31%
3	HClO ₄	H ₂ O:THF (9:1)	78%	1:1.9	33%	29%
4	TCA	Brine	56%	1:1.6	33%	27%

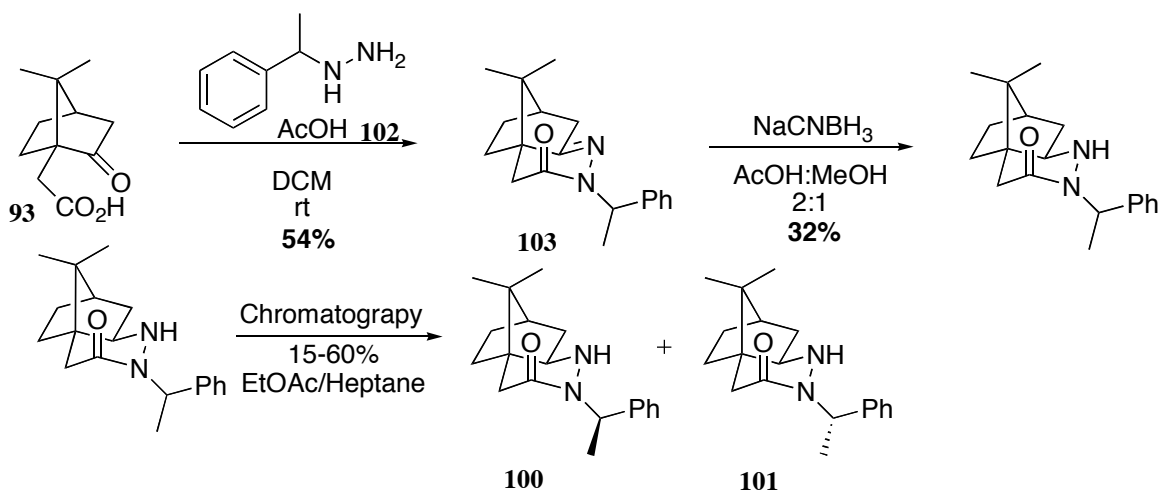
We were shocked and appalled at the low conversions and enantioselectivities obtained, as it was reported that derivatives possessing a sulfonyl group in place of the carbonyl with similar structures (**99**), were enantioselective catalysts for Diels-Alder reactions⁷⁹ (Scheme 81).

Scheme 81. Efficiency and enantioselectivity of derivatives 99 in Diels-Alder reactions⁷⁹



We also did not expect the ring size to have such a large role in the enantioselectivity of the process. Nevertheless, we decided to synthesize diastereomers **100** and **101** as a last ditch effort toward an enantioselective camphor-based 6-membered hydrazide with an endocyclic electron withdrawing group (Scheme 82).

Scheme 82. Synthesis of diastereomers **100** and **101**.



We decided to synthesize these derivatives due to the fact that our previous most successful catalyst **23** possessed a methyl-phenyl group which was shown to make a large contribution to enantioselectivity (Scheme 40).⁶¹ We accomplished the synthesis by treating homoketopinic acid (**93**) with racemic hydrazide **102** to obtain the resulting cyclic hydrazone **103** in 54 % yield. This derivative was then reduced with sodium cyanoborohydride to provide the mixture of diastereomers **100** and **101** in 32 % yield. At that point, it was possible to separate the diastereomers by flash chromatography to obtain the two individual compounds for testing. The first diastereomer **100** was used in the test Diels-Alder reaction between (*E*)-cinnamaldehyde and cyclopentadiene (Table 10). The use of triflic acid in either water or 9:1 H₂O:THF resulted in poor conversions (entries 1 and 2). Switching the co-catalyst to perchloric acid in H₂O:THF (9:1) resulted in no improvement in conversion (entry 3). The enantioselectivities were not examined, due to the poor conversions obtained.

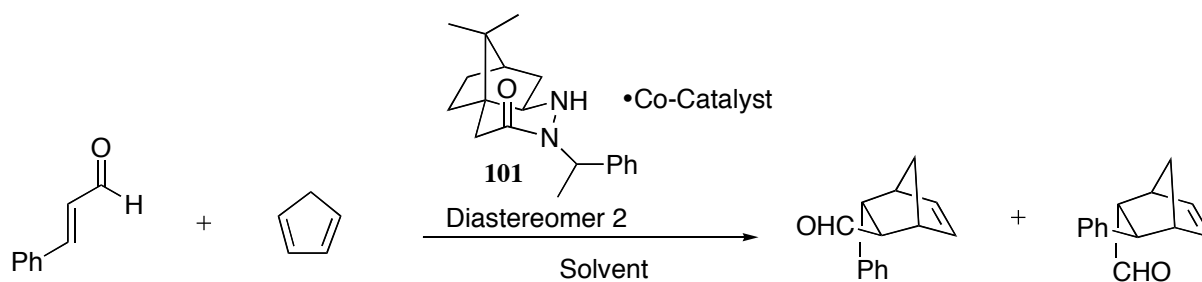
Table 10. Diels-Alder reactions employing **100 as catalyst.**

Reaction scheme: Cinnamaldehyde + Cyclopentadiene $\xrightarrow[\text{Solvent}]{\text{Diastereomer 100, Co-Catalyst}}$ Bicyclic aldehyde products (Endo:Exo ratio).

Entry	Co-Catalyst	Solvent	Conversion	Endo:Exo
1	TfOH	H ₂ O	4%	1:1.2
2	TfOH	H ₂ O:THF (9:1)	4%	1:1.4
3	HClO ₄	H ₂ O:THF (9:1)	5%	1:1.2

The diastereomer **101** showed similar inefficient reactions (Table 11). Again, when triflic acid was used in either H₂O or H₂O:THF (9:1), poor conversions were obtained (entries 1 and 2). These results were also not improved with perchloric acid as a catalyst (entry 3). Due to the poor conversions obtained with this diastereomer, the enantioselectivities were not determined. The poor conversions in the case of both of the diastereomers may be due to sterically hindered environment around the key nucleophilic nitrogen of the catalyst.

Table 11. Diels-Alder reactions employing 101 as catalyst.

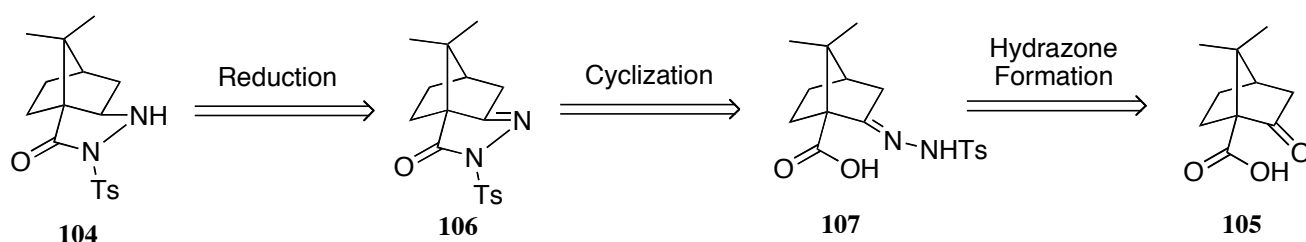
				
Entry	Co-Catalyst	Solvent	Conversion	Endo:Exo
1	TfOH	H ₂ O	4%	1:1.2
2	TfOH	H ₂ O:THF (9:1)	4%	1:1.4
3	HClO ₄	H ₂ O:THF (9:1)	5%	1:1.2

The surprisingly poor results obtained from the 6-membered camphor-based hydrazides possessing endocyclic electron withdrawing groups, allowed us to conclude that there was a detrimental effect on reaction efficiency when such derivatives were employed, using a carbonyl as the electron withdrawing group. We then decided to pursue the synthesis of 5-membered derivatives possessing both an endocyclic electron withdrawing group and an exocyclic electron withdrawing group. We thought that perhaps these types of catalysts would perform better in Diels-Alder reactions, due to our previous success in using a 5-membered ring catalyst **22**.

5- MEMBERED CAMPHOR-BASED HYDRAZIDES POSSESSING BOTH EXO- AND ENDOCYCLIC ELECTRON WITHDRAWING GROUPS

We decided to attempt the synthesis of a camphor-based hydrazide containing both an *exo*- and endocyclic electron withdrawing group (**104**). We were curious as to whether an advantage in the kinetics and enantioselectivity of the process would be gained if such derivatives were employed in Diels-Alder reactions. We envisioned a retrosynthetic sequence starting ultimately from (+)-ketopininc acid (**105**) inspired by a report on the synthesis of camphor derivatives for alternate applications⁸⁰ (Scheme 83).

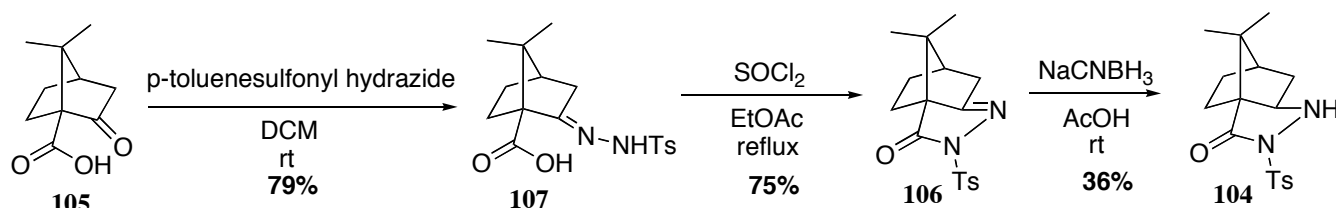
Scheme 83. Retrosynthetic analysis for derivative 104.



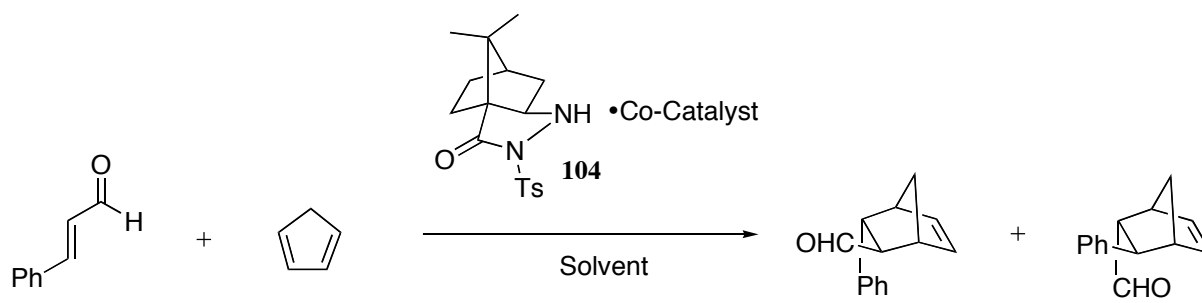
The desired derivative **104** was anticipated to be obtained from cyclic hydrazide **106** via a sodium cyanoborohydride reduction. Cyclization of **107** facilitated by thionyl chloride was expected to give the cyclic hydrazide **106**. The acyclic hydrazide **107** would be obtained from (+)-ketopininc acid (**105**).

The synthesis of derivative **104** began by the formation of the hydrazide **107** using *p*-toluenesulfonyl hydrazide in 79 % yield (Scheme 84). Cyclization of hydrazide **107** was achieved with thionyl chloride in refluxing ethyl acetate in a 75 % yield. Subsequent reduction of this cyclic hydrazide was accomplished in 36 % yield to give **104**.

Scheme 84. Synthesis of derivative 104.



The ability of **104** to act as an enantioselective catalyst for Diels-Alder reactions was examined by testing a few conditions (Table 12).

Table 12. Diels-Alder reactions employing 104 as catalyst.

Entry	Co-Catalyst	Solvent	Conversion	Endo:Exo	Endo ee	Exo ee
1	TfOH	H ₂ O:THF (9:1)	15%	1:1.3	nd	nd
2	HClO ₄	H ₂ O:THF (9:1)	26%	1:1	4%	0%

The conversions in both conditions tested were sub-optimal, and therefore, these were the only conditions attempted. In general, solvent and co-catalyst effects do not affect conversions to an extent that could rectify the issue of the low conversions obtained. The use of triflic acid as catalyst resulted in a dismal 15 % conversion, and therefore the resulting enantioselectivities were not determined (entry 1). The acid was then changed to perchloric acid, with a similar low conversion of 26 %, however, the enantioselectivities were determined in this case (entry 2). The endo and exo derivatives were formed with essentially no enantioselectivity with this catalyst. This may be due to the fact that there was no significantly large group attached α -to the iminium nitrogen. This derivative would therefore most likely allow for both the (*E*) and (*Z*) iminiums to form an approximately equal amount of the time, resulting in practically no enantioselectivity. The poor conversions may be a result of the two electron withdrawing groups inductively limiting the nucleophilicity of the key iminium forming nitrogen.

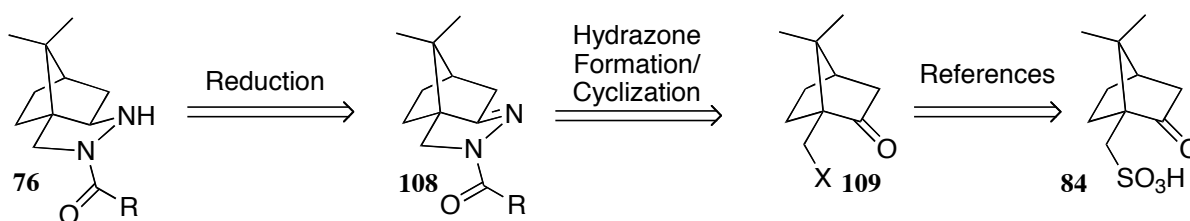
FUTURE DIRECTIONS

In order to increase conversions, electron withdrawing groups that are less strong than the carbonyl and sulfonyl groups could be used, in varying combinations. To increase the enantioselectivities, catalysts could be synthesized such that the endo and exocyclic electron withdrawing groups are both carbonyl groups. This would allow for the potential use of chelating agents in order to hold the “R” group in space such that it blocks the formation of the *Z*-iminium. This would presumably lead to an increase in enantioselectivity.

5- MEMBERED CAMPHOR-BASED HYDRAZIDES POSSESSING AN EXOCYCLIC ELECTRON WITHDRAWING GROUP

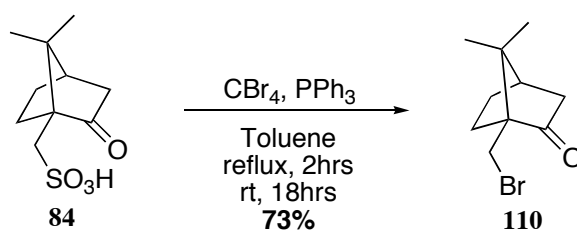
Our previously successful catalyst **22** contained the hydrazide in a 5-membered ring possessing an endocyclic electron withdrawing group. We wanted to investigate the efficiency of similar 5-membered hydrazides possessing an exocyclic electron withdrawing group in Diels-Alder cycloadditions. The retrosynthetic plan for **76** involved the reduction of the cyclic hydrazone **108**, which could be obtained by hydrazone formation/cyclization (Scheme 85). This presumably could be accomplished using halo ketone **109**. This halo ketone could be obtained directly from commercially available (+)-camphorsulfonic acid (**84**).⁸¹

Scheme 85. Retrosynthetic plan for 5-membered camphor-based hydrazides.



Initially, we chose a bromo ketone **110** as the haloketone we wanted to employ (Scheme 86). The synthesis of this bromoketone occurred smoothly in 73 % yield when a $\text{CBr}_4/\text{PPh}_3$ ^{81b} system was used.

Scheme 86. Synthesis of bromoketone 110.



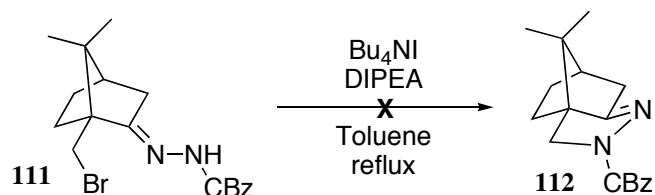
We then attempted the one-pot hydrazone formation/cyclization step under a few different conditions (Table 13).

Table 13. Attempted hydrazone formation/cyclization with 110.

Entry	R	Base	Solvent	Electrophile	Result
1	-H	-	-	-	NR
2	-H	-	H ₂ O:AcOH (9:1)	-	NR
3	-Boc	K ₂ CO ₃	Mesitylene	-	NR
4	-H	DIPEA	Toluene	ClCO ₂ Bn	crude 111

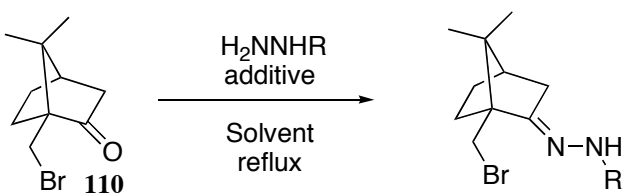
Using hydrazine hydrate as solvent resulted in no product being observed (entry 1). Using a stoichiometric amount of hydrazine hydrate in H₂O:AcOH (9:1) resulted in a 0 % yield of product as well (entry 2). The use of *t*-butyl carbazate as nucleophile with potassium carbonate as base, did not show any progress from starting material (entry 3). Employing hydrazine hydrate with DIPEA as base in toluene, followed by introduction of benzyl chloroformate led to uncyclized hydrazone **111**. This uncyclized hydrazone was then immediately subjected to cyclization conditions by refluxing in toluene with tetrabutyl ammonium iodide as a means of increasing the leaving group ability (Scheme 87). Unfortunately, no product was obtained from this.

Scheme 87. Attempted cyclization of crude hydrazone 111.



This result prompted us to examine the hydrazone formation and cyclization steps separately. Toward this end, conditions focused specifically on the hydrazone formation step were developed (Table 14).

Table 14. Attempted hydrazone formation to give derivatives of type 111.

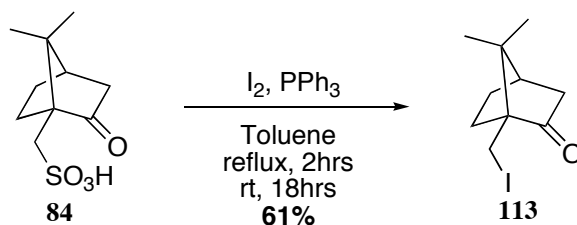


Entry	R	Additive	Solvent	Result
1	-H	AcOH (cat)	MeOH	NR
2	-Boc	-	Hexanes	NR
3	-Boc	-	Toluene	NR
4	-Boc	-	Mesitylene	NR
5	-Boc	-	<i>i</i> PrOH	NR

Initially, bromoketone **110** was subjected to hydrazine hydrate in refluxing methanol with catalytic acetic acid (entry 1). The addition of an acid catalyst should activate the carbonyl for attack by the nucleophilic hydrazine. Despite these conditions, only starting material was observed in this reaction. We then decided to change the nucleophile to *t*-butyl carbazate in hopes of eliminating the electron withdrawing group installation step. Reaction of this nucleophile in hexanes had been previously shown⁸² to give the corresponding hydrazone on cyclic ketones. We therefore attempted to use the *t*-butyl carbazate in hexanes to obtain our desired hydrazone, with no success (entry 2). Changing the solvent to higher-boiling solvents such as toluene and mesitylene, also did not produce any reaction (entries 3 and 4). We thought that a protic solvent may facilitate the reaction by hydrogen bonding to the carbonyl, and decided to try isopropanol (entry 5). This also gave absolutely no reaction.

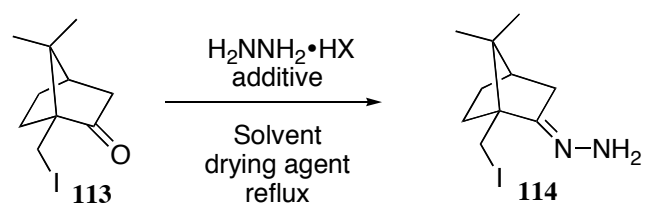
The results obtained suggested that hydrazone formation was difficult using hydrazides under the conditions tried. We had reason to believe that we had, however, obtained a hydrazone using hydrazine hydrate, but that cyclization of this was more difficult. To address the potential difficulty of cyclization, we decided to start with iodoketone **113**, which possessed a better leaving group than the bromoketone **110**. Toward this end, the iodoketone **113** was synthesized in 61 % yield following a literature procedure^{81a} (Scheme 88).

Scheme 88. Synthesis of iodoketone 113.



We decided to first focus on the hydrazone forming reactions, and to deal with the cyclization conditions later. This way, we remained focused on one problem at a time. Toward this end, iodoketone **113** was subjected to various hydrazone forming conditions using hydrazine as a nucleophile (Table 15). We chose to focus on hydrazine itself, because it should be more nucleophilic than hydrazides, giving us a better chance at obtaining the desired hydrazone **114**.

Table 15. Attempted hydrazone formation with $\text{H}_2\text{NNH}_2\cdot\text{HX}$ as nucleophile.



$\text{H}_2\text{NNH}_2\cdot\text{HX}$
additive

Solvent
drying agent
reflux

113 → 114

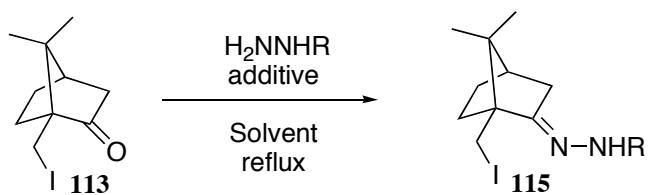
Entry	X	Additive	Solvent	Drying Agent	Result
1	-Cl	DIPEA	MeOH	-	NR
2	-Cl	-	MeOH	3 Å MS	NR
3	-OH	-	MeOH	3 Å MS	NR
4	-OH	-	MeOH	MgSO_4	NR
5	-OH	-	MeOH	-	NR
6	-OH	$\text{TsOH}\cdot\text{H}_2\text{O}$	MeOH	3 Å MS	NR
7	-OH	$\text{TsOH}\cdot\text{H}_2\text{O}$ (excess)	MeOH	-	NR
8	-OH	AcOH	MeOH	3 Å MS	NR
9	-OH	AcOH	DCM	3 Å MS	NR
10	-OH	DIPEA	Toluene ^a	3 Å MS	NR
11	-OH	$\text{TsOH}\cdot\text{H}_2\text{O}$, $\text{CH}(\text{OCH}_3)_3$	Benzene	-	NR
12	-OH	$\text{TsOH}\cdot\text{H}_2\text{O}$	$\text{CH}(\text{OCH}_3)_3$	-	NR
13	-OH	-	- ^a	-	Decomposition
14	-OH	AcOH	- ^a	-	Decomposition

^a reaction performed at room temperature

Initially, we decided to use $\text{H}_2\text{NNH}_2\cdot 2\text{HCl}$ with a base (DIPEA) in methanol to produce free hydrazine that would then attack the carbonyl (entry 1). Unfortunately, no reaction was observed. We then thought that perhaps keeping the reaction mixture acidic would aid in activating the carbonyl for attack (entry 2). This also did not produce a reaction. We then decided to switch to hydrazine hydrate as the nucleophile, because we have had success using this reagent in the past with related reactions. Hence, hydrazine hydrate was employed in methanol with 3 Å molecular sieves as drying agent (entry 3). A reaction failed to occur in this case. We then decided to investigate the role of the drying agent by

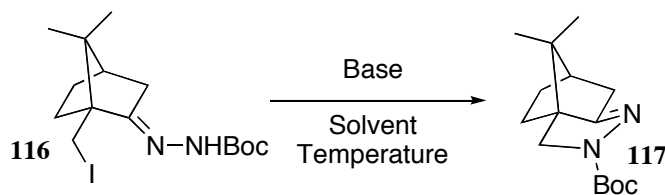
switching it to magnesium sulfate, and subsequently leaving a drying agent out entirely (entries 4 and 5). Only starting material was observed in these cases as well. We wondered whether the addition of acid would activate the carbonyl of the iodoketone **113** enough to produce some reaction. Toward this end, we decided to investigate different acids. The use of *p*-toluene sulfonic acid in both a catalytic amount and in excess did not result in any observed reaction (entries 6 and 7). Switching the acid to acetic acid and employing molecular sieves in an attempt to drive product formation also did not produce a reaction (entry 8). Switching the solvent to DCM while using acetic acid did not help (entry 9). A reaction was then attempted at room temperature, in case the issue was that some product was being formed in the reaction, but decomposed with heat. Toward this end, a reaction was performed in toluene with 3 Å molecular sieves as drying agent, under basic conditions at room temperature (entry 10). No product formation was observed. We then decided to focus on increasing the reactivity of the carbonyl group. In order to do this, we imagined that we could attempt to convert the carbonyl to the more reactive dimethylacetal compound using trimethyl orthoformate to accomplish this. Toward this end, iodoketone **113** was used with *p*-toluenesulfonic acid with trimethyl orthoformate in benzene, and in trimethyl orthoformate as solvent (entries 11 and 12). No reaction of the iodoketone was observed, suggesting that the carbonyl was not overly reactive. We wondered if switching the solvent to hydrazine hydrate would drive product formation due to the sheer excess of nucleophile present in the reaction mixture. Toward this end, iodoketone **113** was added to hydrazine hydrate under both neutral and acidic conditions (entries 13 and 14). In both instances, decomposition was observed. This decomposition led us to question the overall stability of a hydrazone such as **114**. With the free -NH_2 group, we wondered if oxidation was taking place, resulting in a decomposition process. This prompted us to examine the addition of hydrazides to **113**, in order to obtain the corresponding hydrazone **115**. This would have an additional advantage in that the electron withdrawing group would already be installed. Toward this end, some hydrazides were examined (Table 16).

Table 16. Use of hydrazides to obtain the corresponding hydrazone 115.



Entry	R	Additive	Solvent	Result
1	-C(O)Ph	DIPEA	DMF	NR
2	-Boc	AcOH	EtOH	NR
3	-Boc	TsOH•H ₂ O	Benzene	20 % yield

Refluxing iodoketone **113** with benzoic hydrazide under basic conditions in DMF resulted in no reaction (entry 1). We then wondered if benzoic hydrazide was not a nucleophilic enough hydrazide, and therefore switched to the carbamate-containing *t*-butyl carbazate. We examined the use of this hydrazide in ethanol under acetic acid catalysis, with no product observed (entry 2). We then switched the solvent to benzene, and the acid to *p*-toluenesulfonic acid, and, gratifyingly, observed product **116**, albeit in a low yield (entry 3). Although this yield was low, it gave us material to work with for the testing of cyclization conditions (Table 17). Our first strategy involved the addition of base to deprotonate the amide nitrogen and increase its nucleophilicity. We expected this deprotonated nitrogen to attack the carbon containing the iodide leaving group, which would result in the cyclized product **117**.

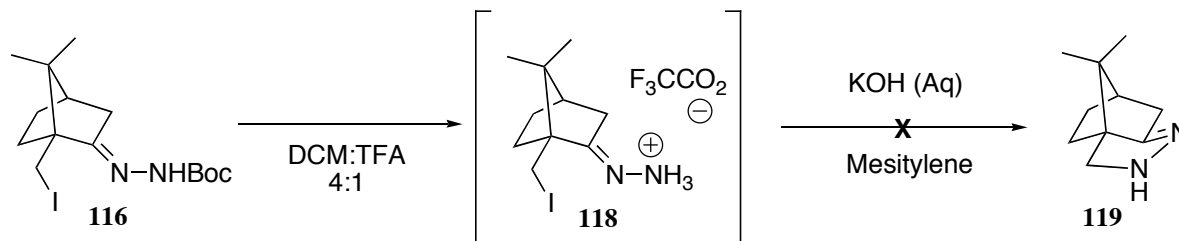
Table 17. Addition of various bases to 116 in an attempt to provide cyclized product 117.

Entry	Base	Solvent	Temperature	Result
1	<i>n</i> -BuLi	THF	-78 °C	NR
2	LiHMDS	THF	-78 °C-reflux	NR
3	LiHMDS	DMF	0 °C-100 °C	NR
4	NaH	THF	0 °C-rt	NR
5	NaH	DMF	rt-100 °C	NR
6	NaH	DMSO	rt-100 °C	NR
7	50 % NaOH	Toluene	reflux	NR
8	50 % NaOH	Dioxane	reflux	NR
9	KO ^t Bu	<i>t</i> BuOH	reflux	NR

We initially decided to try organolithium bases, due to the fact that they are among the stronger bases to be used synthetically. We started by using *n*-butyllithium in THF at -78 °C (entry 1). No reaction was observed. We then examined lithium hexamethyldisilazide (LiHMDS) in both THF and DMF (entries 2 and 3). In both cases, the reagent was added at low temperature, and brought to reflux in an attempt to push the reaction along. No reaction was observed in either case. We then decided to try other types of bases, in hopes that we would obtain cyclized product from one of these choices. Sodium hydride was used in THF, DMF, and DMSO, with no reaction being observed in any case (entries 4-6). We then wondered whether performing the reaction with the use of an aqueous base would assist in the cyclization reactions. Toward this end, 50 % NaOH was used as base in both dioxane and toluene (entries 7 and 8). In each case, no reaction was observed. The last base we decided to try was potassium *tert*-butoxide in *tert*-butanol as solvent at reflux. Again, no reaction was observed.

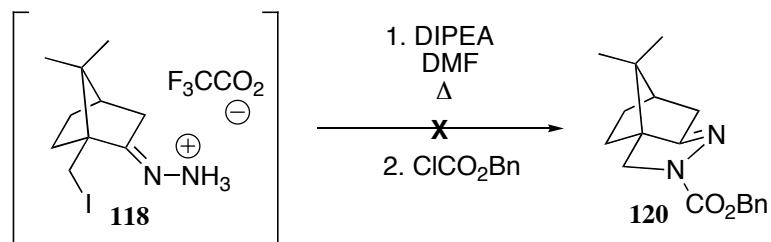
Due to the lack of cyclization under basic conditions, we next attempted to remove the –Boc group first, with a subsequent cyclization step. Toward this end, the –Boc was removed with 4:1 DCM:TFA, and subjected to cyclization conditions (Scheme 89).

Scheme 89. Attempted cyclization of 116 after removal of the –Boc group.

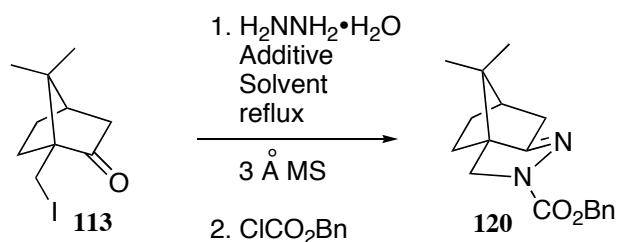


Unfortunately, refluxing in mesitylene under basic conditions did not afford cyclized product **119**. We decided that attempting to install the electron withdrawing group right away may increase our chance at isolating a cyclic product, due to the increased stability expected of such derivatives compared to hydrazones of type **119**. Therefore, we attempted to cyclize **118** by heating in DMF under basic conditions, and subsequently cooling to room temperature and adding benzyl chloroformate (Scheme 90). This also led to no observed cyclized product.

Scheme 90. Attempted cyclization/electron withdrawing group installation of deprotected derivative 118.



Due to the difficulties associated with cyclizing derivative **118**, we decided to attempt a one-pot hydrazone formation/cyclization procedure with hydrazine hydrate, in case the use of hydrazine hydrate in previous reactions resulted in an unstable product (Table 18).

Table 18. Attempted one-pot hydrazone formation/cyclization to obtain 120.

Entry	Additive	Solvent	Result
1	DIPEA	Mesitylene	NR
2	AcOH (0.5 eq)	DMF ^a	Decomposition
3	TsOH (0.1 eq)	DMF ^a	Decomposition

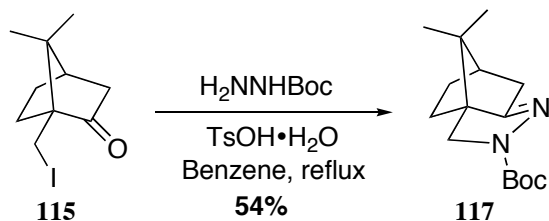
^aDIPEA added immediately before introduction of ClCO_2Bn

We initially performed the experiment under basic conditions in refluxing mesitylene (entry 1). This resulted in no reaction. We then switched to acidic conditions in hopes of promoting the hydrazone formation, upon which the reaction would be made basic in order to facilitate cyclization. Toward this end, acetic acid and *p*-toluenesulfonic acid were used in DMF, followed by addition of DIPEA for cyclization (entries 2 and 3). Unfortunately, this procedure only led to decomposition of starting material.

Once these results were obtained, we had decided to go back and revisit the hydrazone **115**, with the intention of examining other cyclization conditions. The reaction to make **115** was allowed to stir longer (48 hours) in this particular instance, and we noticed a major spot below **115** upon TLC analysis. We decided to determine what this spot was, and, upon characterization, we were ecstatic to find that the spectra matched that expected for the cyclized product **117** (Scheme 91). The main indication that the cyclization occurred was due to the chemical shift in the ^{13}C NMR of the $-\text{CH}_2$ next to the bridgehead that was attached to an iodine in the starting material, and a nitrogen in the product. The characteristic upfield nature of carbons attached to iodine atoms in the ^{13}C NMR provided us with a comparison of the starting material (containing a C-I bond) to the anticipated cyclized product (containing a C-N bond). Indeed, the upfield $-\text{CH}_2$ signal (3.6 ppm) in the ^{13}C NMR disappeared in place of a signal whose shift was consistent with that of a carbon attached to a nitrogen (46.1 ppm). In the proton NMR, the doublets

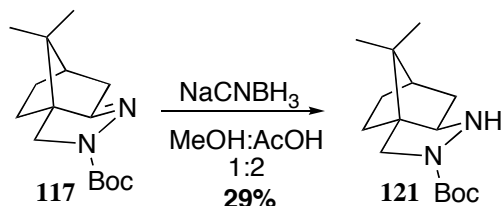
corresponding to the $-\text{CH}_2$ attached to the iodine atom shifted from 3.31 and 3.11 ppm, respectively, in **117**, to 3.61 and 3.46 ppm respectively, in **117**. These results strongly suggested that the cyclization had occurred, and this was later confirmed by the mass spectrum of **117**.

Scheme 91. Synthesis of desired cyclized product 117.

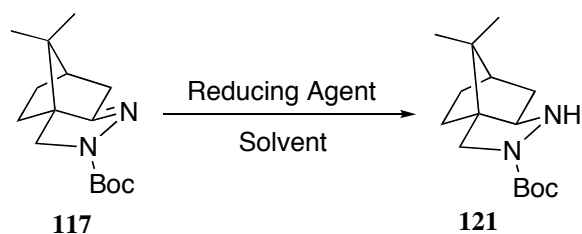


With this compound in hand, we decided to do a reduction with sodium cyanoborohydride, which had been previously shown⁵⁵ to be successful in reducing similar hydrazones (Scheme 92).

Scheme 92. Reduction of 117 with sodium cyanoborohydride to obtain 121.



The desired hydrazide **121** was obtained when sodium cyanoborohydride was used in AcOH:MeOH (2:1), although only a 29 % yield was obtained. We wished to optimize this yield, and therefore examined other reducing conditions (Table 19).

Table 19. Optimization of reduction to give 121.

Entry	Reducing Agent	Solvent	Result
1	H ₂ , PtO ₂	MeOH	NR
2	H ₂ , Pd/C	MeOH	NR
3	H ₂ , Pd/C (55 % wet with water)	MeOH	NR
4	HCO ₂ NH ₄ , Pd/C	MeOH	NR
5	TsNHNH ₂ , NaOAc	THF:H ₂ O (1:1)	NR
6	NaBH ₄	MeOH	NR
7	NaBH(OAc) ₃	MeOH	NR
8	NaBH(OAc) ₃	MeOH:AcOH (2:1)	NR
9	NaBH ₃ CN	MeOH:AcOH (2:1)	51 % ^a

^a Acidic work-up followed by basification with NaOH pellets and extraction

The use of hydrogen sources with different metal catalysts was examined first. The combination of hydrogen and platinum dioxide in methanol resulted in no reaction (entry 1). Switching the catalyst to Pd/C that was either dry or wetted with 55 % water did not produce any reaction (entries 2 and 3). We then decided to examine different hydrogen sources. Transfer hydrogenation using Pd/C as a catalyst did not produce a reaction (entry 4). Using a diimide reduction⁸³ employing *p*-toluenesulfonyl hydrazide and sodium acetate did not result in any reaction (entry 5). We then examined borohydride reducing agents, starting with sodium borohydride, which did not produce a reaction (entry 6). Using sodium triacetoxyborohydride under neutral or acidic conditions also did not lead to a reaction (entries 7 and 8). Finally, we re-examined the use of sodium cyanoborohydride, wondering if the low yield was, in fact, due to an inefficient work up. Indeed, a more reasonable 51 % yield was obtained when sodium

cyanoborohydride was used in 2:1 MeOH:AcOH with an acidic work-up followed by extraction of the product under basic conditions.

Settling with the most efficient sodium cyanoborohydride reduction, we were able to try **121** out in Diels-Alder cycloadditions. Toward this end, **121** was employed as a catalyst in the reaction between (*E*)-cinnamaldehyde and cyclopentadiene (Table 20).

Table 20. Conditions attempted for Diels-Alder reactions using **121 as catalyst.**

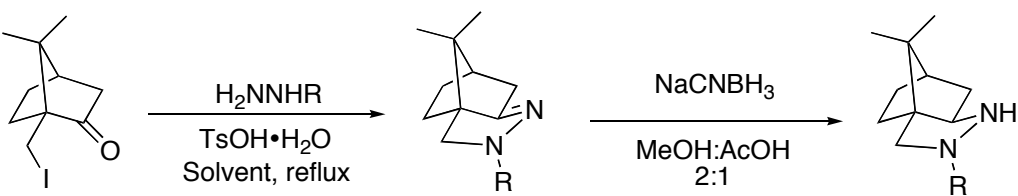
Reaction scheme: (*E*)-cinnamaldehyde + cyclopentadiene $\xrightarrow[\text{Solvent}]{\text{121 (Boc-protected bicyclic amine) • Co-Catalyst}}$ endo/exo bicyclic aldehyde products.

Entry	Co-Catalyst	Solvent	Conversion	Endo:Exo	Endo ee	Exo ee
1	TfOH	H ₂ O	12%	1:1.6	17%	1%
2	TfOH	H ₂ O:CH ₃ NO ₂ (9:1)	14%	1:2	14%	3%
3	TfOH	H ₂ O:THF (9:1)	38%	1:2	30%	16%
4	HClO ₄	H ₂ O:THF (9:1)	12%	1:1.5	21%	12%
5	HClO ₄	H ₂ O:THF (1:9)	4%	1:2	nd	nd
6	HClO ₄	MeOH:H ₂ O (9:1)	20%	1:1.2	3%	10%
7	HCl	H ₂ O:THF (9:1)	18%	1:2	11%	9%

The first co-catalyst examined was triflic acid. This co-catalyst was examined in water, 9:1 water:nitromethane, and 9:1 water:THF (entries 1-3). In the first two cases, very low conversions were obtained, accompanied by low enantioselectivities. In the case of water:THF (9:1), a 38% conversion was obtained, with slightly better ee's of 30% for endo and 16% for exo (entry 3). Changing the co-catalyst to perchloric acid did not improve the conversions or enantioselectivities (entries 4-6), even when the solvent was mostly composed of MeOH, which can sometimes be beneficial in these cycloaddition reactions⁶⁵ (entry 6). The use of hydrochloric acid as a co-catalyst led to both low conversions and low enantioselectivities.

Due to the fact that both low conversions and ee's were obtained across the board, we hypothesized that this was due to the acid lability of the –Boc group in the catalyst. Since our conditions required an acid co-catalyst,⁵⁵ we prepared various other derivatives in an attempt to increase both conversion and ee's (Table 21).

Table 21. Synthesis of derivatives 122-124 as potential catalysts for Diels-Alder reactions.

				
Entry	R	Solvent	Yield of Hydrazone	Yield of Product
1	-CBz	<i>i</i> PrOH	53 %	50 %
2	-C(O)Ph	EtOH	38 %	74 %
3	-C(O) <i>p</i> -OMe-C ₆ H ₄	<i>i</i> PrOH	82 %	41 %

The first compound synthesized was another carbamate derivative, in which the electron withdrawing group was –CBz (entry 1). The hydrazone formation/cyclization was optimal when performed in isopropanol, and the yield of the cyclic hydrazone was 53%. The cyclic hydrazone was reduced with sodium cyanoborohydride as the optimal reducing agent, to afford the corresponding derivative **122** in

50% yield. We then synthesized an aromatic amide compound in which the cyclic hydrazone was obtained in 38% yield, and reduction to the desired derivative **123** proceeded in 74% yield. The *p*-methoxy derivative of **123** was then synthesized with 82% yield of the cyclic hydrazone, and 41% yield of the desired product **124**.

The derivatives **122-124** prepared above were then each tested in Diels-Alder reactions. To start, **122** was used as a catalyst for the reaction of (*E*)-cinnamaldehyde and dicyclopentadiene (Table 22).

Table 22. 122 as a catalyst in the Diels-Alder reaction between (*E*)-cinnamaldehyde and cyclopentadiene.

Reaction scheme: (*E*)-cinnamaldehyde + cyclopentadiene $\xrightarrow[\text{Solvent}]{\text{122 (CBz), Co-Catalyst}}$ endo/exo bicyclic aldehydes.

Entry	Co-Catalyst	Solvent	Conversion	Endo:Exo	Endo ee	Exo ee
1	HClO ₄	H ₂ O	84%	1:2	28%	1%
2	HClO ₄	H ₂ O:CH ₃ NO ₂ (9:1)	77%	1:2.4	23%	1%
3	HClO ₄	H ₂ O:THF (9:1)	71%	1:2	30%	5%
4	HClO ₄	MeOH:H ₂ O (9:1)	73%	1:1.9	6%	14%
5	HClO ₄	Brine	81%	1:2	26%	0%
6	HClO ₄	CF ₃ CH ₂ OH:H ₂ O (9:1)	100%	1:1.9	1%	14%

The co-catalyst chosen for these reactions was perchloric acid, due to the original massive improvement in reaction conversion of 84 % using **122** in water compared to **121** (entry 1). Although

the conversion was high, the endo ee was still a dismal 28 %, and the exo product showed virtually no enrichment. Different combinations of water with various solvents were examined next, to see if the enantioselectivity would be increased. Toward this end, 9:1 water:nitromethane was used, with a good conversion of 77 %, however a similar ee of 23 % was obtained for the endo product, and essentially no ee for the exo product was observed (entry 2). A water:THF system was explored, resulting in a conversion of 71 % and an endo ee of 30 %, with a 5 % exo ee, only a miniscule improvement in ee over the condition with water alone as solvent (entry 3). A 9:1 mixture of MeOH:H₂O was used, resulting in a similar conversion of 73 %, and terrible ee's, where the endo ee was actually worse (6 %) than the exo ee (14 %) for once (entry 4). The solvent was then switched to brine, where an 81 % conversion was realized, with a 26 % ee for the endo product, and no ee for the exo product (entry 5). The last solvent tried was trifluoroethanol:water (9:1)⁸⁴, which resulted in an excellent quantitative conversion (entry 6). The ee, however, was devastatingly low for both the endo and exo products.

Although **122** provided much better conversions than **121**, in every condition tried, the ee's were sub-optimal. We wondered whether a catalyst in which the large group potentially sat closer to the key nitrogen would improve the ee's of this process. Toward this end, we synthesized aromatic amide derivative **123** and subjected it to Diels-Alder cycloaddition conditions (Table 23).

Table 23. 123 as a catalyst in the Diels-Alder reaction between (*E*)-cinnamaldehyde and cyclopentadiene.

Reaction scheme: (*E*)-cinnamaldehyde + cyclopentadiene $\xrightarrow[\text{Solvent}]{\text{123, Co-Catalyst}}$ endo-bicyclic aldehyde + exo-bicyclic aldehyde

Entry	Co-Catalyst	Solvent	Conversion	Endo:Exo	Endo ee	Exo ee
1	TfOH	H ₂ O	78%	1:2	19%	1%
2	HClO ₄	H ₂ O:CH ₃ NO ₂ (9:1)	82%	1:2.1	20%	8%
3	HClO ₄	H ₂ O:THF (9:1)	83%	1:1.7	36%	18%
4	HClO ₄	MeOH:H ₂ O (9:1)	89%	1:2.4	3%	18%
5	HClO ₄	Brine	83%	1:1.7	28%	16%
6	HClO ₄	DMSO	38%	1:2.1	12%	7%

The first co-catalyst tried was triflic acid, in water as the solvent (entry 1). This led to a 78 % conversion, with only a 19 % endo ee, and practically no ee for the exo product. The co-catalyst was then switched to perchloric acid, with slightly better results. In the first case using perchloric acid in water:nitromethane (9:1), an 82 % conversion was obtained with a 20 % endo ee, and a low exo ee of 8 % (entry 2). The solvent was then switched to 9:1 water:THF. This gave rise to a similar conversion of 83 % and an improved endo ee of 36 % (entry 3). The exo ee also improved to 18 % with this solvent system. MeOH:H₂O (9:1) was then used, to give a conversion of 89 %, with a poor endo ee of 3 % and an exo ee of 18 % (entry 4). Using brine as solvent led to an 83 % conversion and 28 % endo ee, with a

16 % exo ee (entry 5). Attempts to perform the reaction in DMSO led to a poor conversion of 38 %, along with poor ee's of 12 % for the endo product and 7 % for the exo product (entry 6).

Since comparable ee's to **122** were obtained, we wondered whether substitution on the phenyl ring would have an influence on the reactive conformation. Toward this end, we synthesized a derivative containing a methoxy group on the aryl ring (**124**). This methoxy group was thought to rigidify the carbonyl group through increased resonance participation. This was thought to result in a conformation in which the aryl ring was positioned in order to have the most influence on iminium geometry. This derivative **124** was then subjected to the test conditions (Table 24).

Table 24. 124 as a catalyst in the Diels-Alder reaction between (*E*)-cinnamaldehyde and cyclopentadiene.

Entry	Co-Catalyst	Solvent	Conversion	Endo:Exo	Endo ee	Exo ee
1	TfOH	H ₂ O	50%	1:2.1	22%	2%
2	HClO ₄	H ₂ O	33%	1:2	28%	0%
3	HClO ₄	H ₂ O:THF (9:1)	70%	1:1.9	33%	24%
4	HClO ₄	Brine	76%	1:1.8	32%	20%

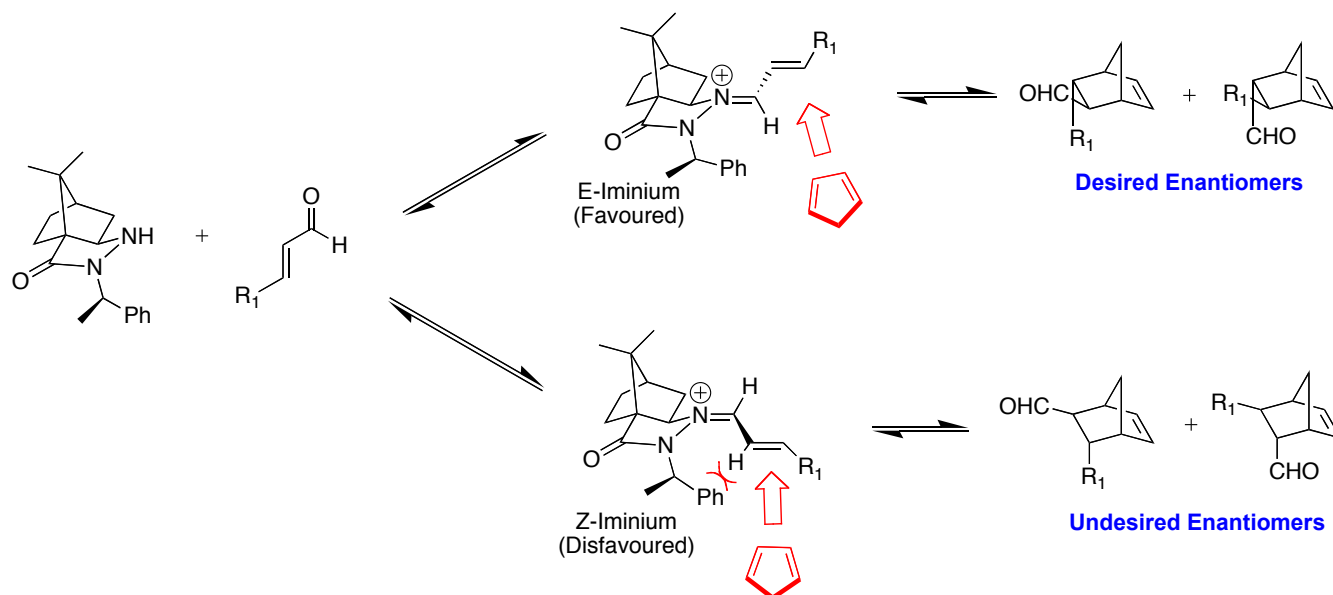
The use of triflic acid as a catalyst in water was examined first (entry 1). This resulted in a 50 % conversion and poor ee's of 22 % for the endo product and 2 % for the exo product. The co-catalyst was then switched to perchloric acid, and a few different aqueous solvents were tried. The first solvent was

water only, which resulted in a 33 % conversion and a 28 % endo ee, with no exo ee (entry 2). A water THF (9:1) mixture was then tried, resulting in an improved 70 % conversion and 33 % endo ee with a 24 % exo ee (entry 3). We then tried to do the reaction in brine, with a 76 % conversion and 32 % endo ee, with a 20 % exo ee (entry 4).

Since the conversions decreased with respect to the cases where **123** was used, and the enantioselectivity was just as low, we came to the conclusion that the methoxy group did not have a positive influence on the reactive conformation of the catalyst. This frustration led us to try to determine why the enantioselectivities were this poor compared to previous catalyst **22**.

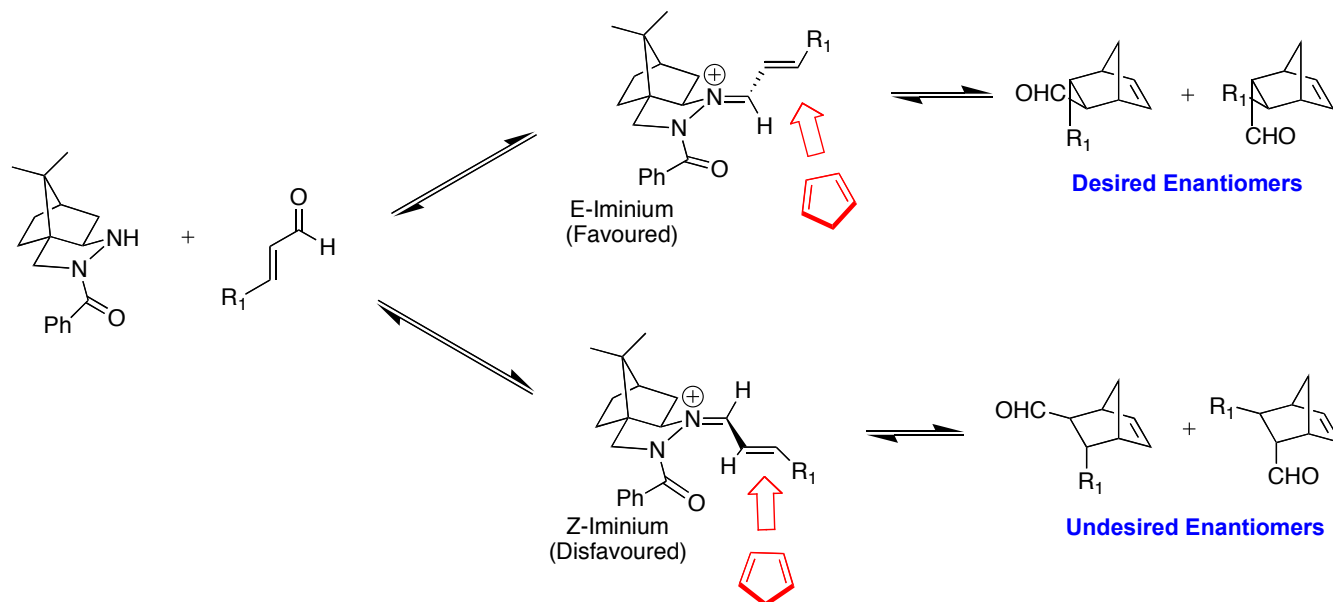
In order to get to the bottom of this, we decided to do some preliminary computational investigations. Toward this end, dihedral driver calculations were performed with the Gaussian '09 suite of programs using the PM3 semi-empirical level of theory. The first derivatives examined were compounds **121-124**. We knew from previous results⁵⁵ that the geometry of the iminium ion played a major role in the enantioselectivity of the process (Scheme 93). If there is a mixture of (*E*) and (*Z*) geometries for the iminium ions, there should be a mixture of enantiomers obtained. The success of our previously developed catalyst (**23**) relied on the alkyl group on the nitrogen neighboring the nitrogen involved with the iminium ion, blocking the (*Z*)-iminium from forming, resulting predominantly in the (*E*)-isomer. This, in turn, resulted in higher selectivity (Scheme 93).

Scheme 93. Successful control of iminium geometry by 23.



From this information, we hypothesized that the “R” group on our newly synthesized catalysts was not sitting in the proper position to influence the iminium geometry to a large degree (Scheme 94).

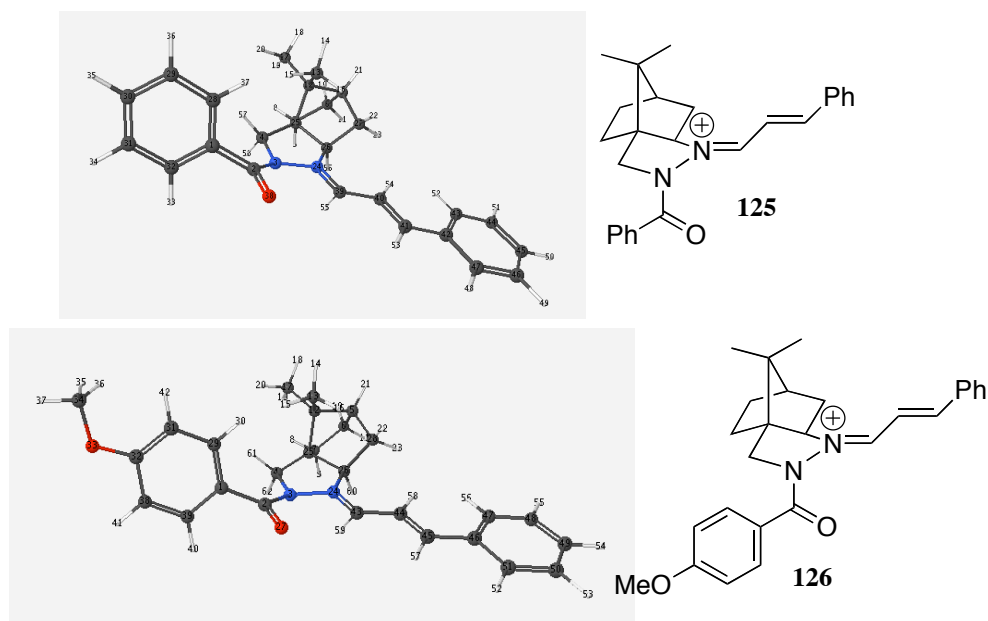
Scheme 94. Hypothesized unsuccessful control of iminium geometry by 121-124.



If the “R” group was positioned away from the iminium nitrogen, only the carbonyl would be able to influence iminium conformation. Since the carbonyl group was relatively small, we did not imagine it would have a substantial effect on iminium geometry.

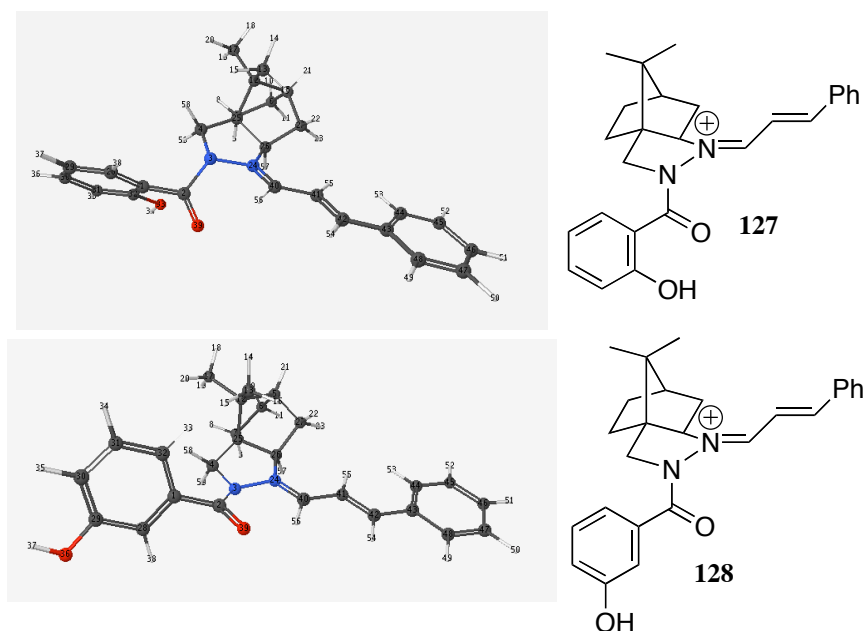
The calculations performed on iminium ions **125** and **126** arising from catalysts **123** and **124** did, indeed, show that the carbonyl group was held closer to the iminium in the reactive conformation (Scheme 95).

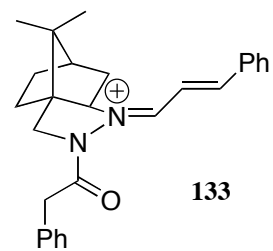
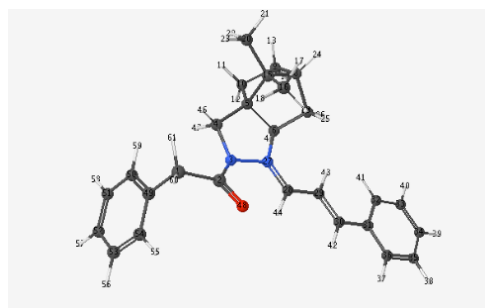
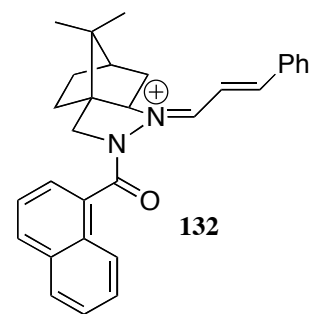
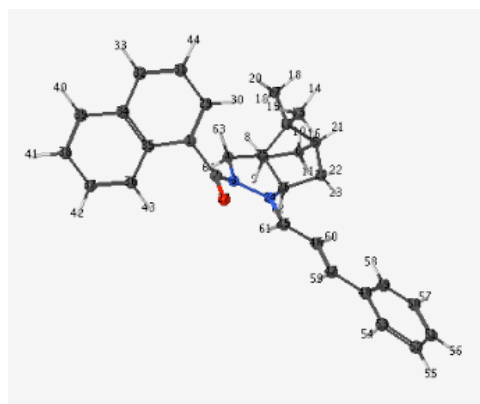
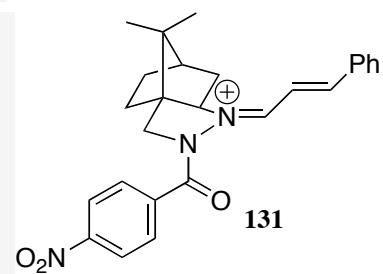
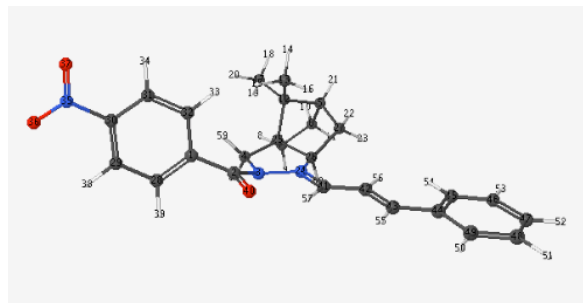
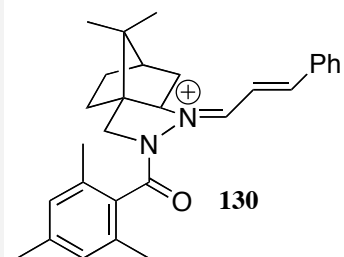
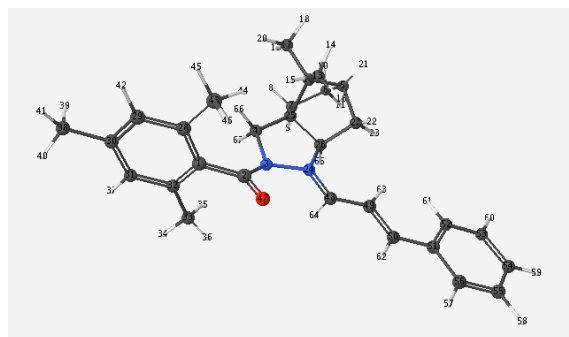
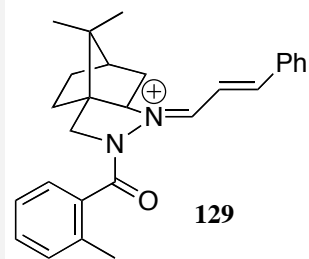
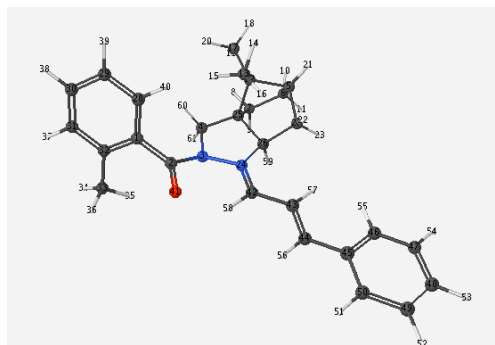
Scheme 95. Reactive conformations calculated for the iminiums arising from catalysts 123 and 124.



We then decided to perform calculations on the iminium ions of various other derivatives that could be synthesized relatively quickly (Scheme 96).

Scheme 96. Reactive conformations calculated from iminium ions 127-135.





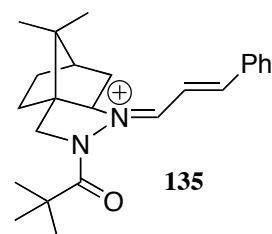
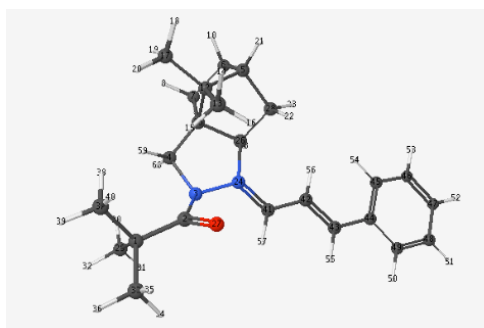
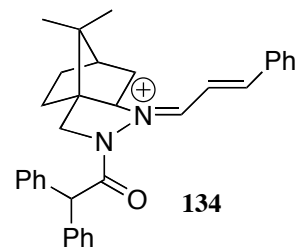
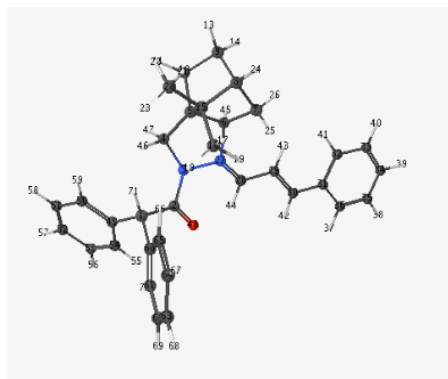
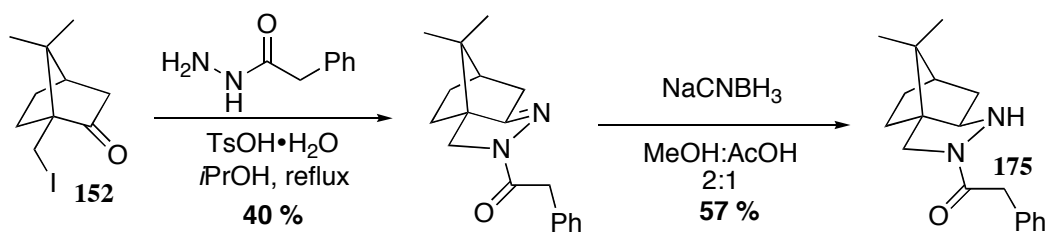


Table 25. Energy differences between *E* and *Z* iminium ions for compounds 125-135.

Compound	Lowest Energy Conformation for <i>E</i> -Iminium (kcal/mol)	Lowest Energy Conformation for <i>Z</i> -Iminium (kcal/mol)	Energy Difference (kcal/mol)
125	209.7	210.3	0.6
126	170.4	170.8	0.4
127	164.9	164.7	0.2
128	164.3	165.3	1.0
129	201.4	200.6	0.8
130	182.4	181.4	1.0
131	208.1	209.0	0.9
132	228.2	228.9	0.7
133	204.4	205.2	0.8
134	235.1	236.1	1.0
135	162.0	162.0	0.0

With this set of compounds, we identified **136**, **137**, and **138** as potential enantioselective catalysts, arising from iminium ions **133**, **134**, and **135**, respectively. Although there was questionable proximity of the large groups to the iminium ion, we decided to synthesize these derivatives anyway, because the calculations were preliminary and therefore may not be completely accurate. The first derivative synthesized was **136** (Scheme 97).

Scheme 97. Synthesis of 136.



The cyclized hydrazone in this case was obtained in 40 % yield. The sodium cyanoborohydride reduction proceeded in 57 % yield to give the desired derivative **136**. This compound was then tested in Diels-Alder reactions under various conditions (Table 26).

Table 26. 136 as a catalyst in the Diels-Alder reaction between (*E*)-cinnamaldehyde and cyclopentadiene.

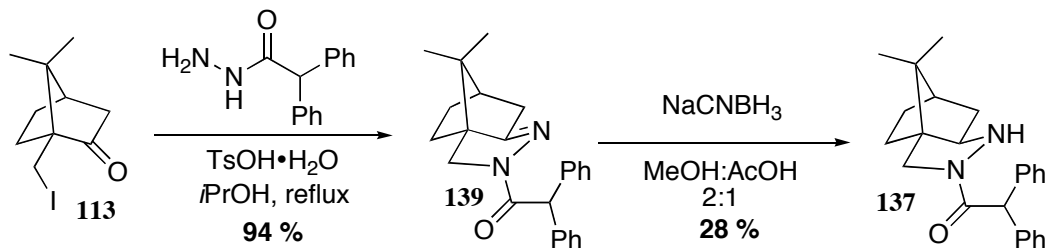
Entry	Co-Catalyst	Solvent	Conversion	Endo:Exo	Endo ee	Exo ee
1	HClO ₄	H ₂ O:CH ₃ NO ₂ (9:1)	5%	1.3:1	nd	nd
2	HClO ₄	H ₂ O:THF (9:1)	3%	1:1	nd	nd
3	HClO ₄	MeOH:H ₂ O (9:1)	17%	1.6:1	nd	nd
4	HClO ₄	Brine	26%	1:1.2	nd	nd

The co-catalyst chosen for these reactions was perchloric acid, as it, on average, had had the best performance with the catalysts of similar structure. The first solvent chosen was water:nitromethane (9:1), which led to a poor 5 % conversion (entry 1). Due to the low conversion, we did not examine the ee of this process. Using water:THF as solvent gave a similar poor yield of 3 % (entry 2). Changing the solvent composition to 9:1 MeOH:water produced a slightly better conversion of 17 % (entry 3). The

best conversion obtained with this catalyst was 26 %, using brine as solvent (entry 4). We decided that this catalyst was not efficient enough to pursue any farther, and moved on.

We next synthesized **137** in hopes that we could obtain better conversions and ee's (Scheme 98).

Scheme 98. Synthesis of 137.



This derivative was then subjected to Diels-Alder reactions (Table 27).

Table 27. 137 in the Diels-Alder reaction between (*E*)-cinnamaldehyde and cyclopentadiene.

Entry	Co-Catalyst	Solvent	Conversion	Endo:Exo	Endo ee	Exo ee
1	TfOH	H ₂ O:THF (9:1)	16%	2:1	12%	4%
2	HClO ₄	H ₂ O:THF (9:1)	0%	N/A	N/A	N/A
3	HClO ₄	Brine	14%	1.7:1	8%	6%

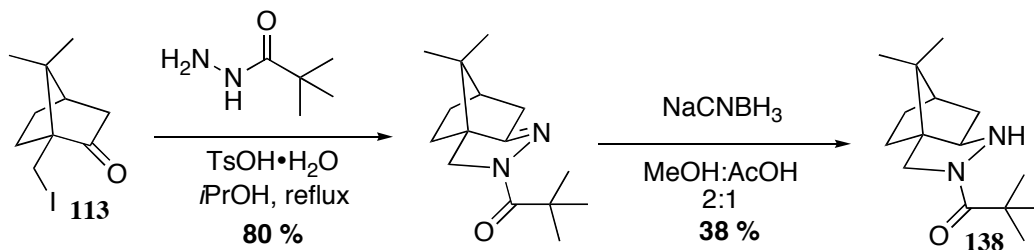
We decided to try triflic acid as a co-catalyst, in case it ended up being superior for this derivative. The solvent chosen to use with this co-catalyst was water:THF (9:1). Under these conditions only a 16 % conversion was obtained (entry 1). The ee in this case was determined, and ended up being 12 % for the endo product, and 4 % for the exo product. We next chose to examine perchloric acid as a co-catalyst in the same solvent system as above. This led to no conversion to product observed (entry 2).

The last condition we tried was to pair perchloric acid with brine, which resulted in a 14 % conversion and low ee's of 8 % and 6 % for the endo and exo product, respectively.

The low conversions obtained could be rationalized by the apparent ease of oxidation of **137** to hydrazone **139**, as evidenced by NMR analysis. During the collection of the ^{13}C spectrum, the compound **137** had already partially oxidized to the corresponding hydrazone **139**. This oxidation would render the catalyst inactive. This oxidation problem may also be to blame for the low conversions and ee's observed for derivative **136**, which is similar in structure.

Lastly, we synthesized **138** (Scheme 99).

Scheme 99. Synthesis of derivative 138.



This compound was also subjected to the test Diels-Alder reaction with sub-optimal results (Table 28).

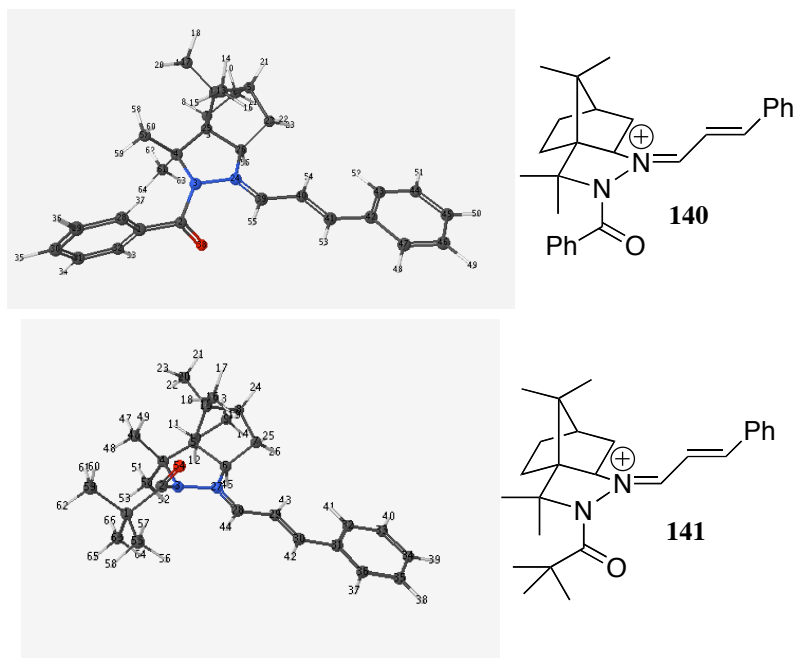
Table 28. 138 in the Diels-Alder reaction between (*E*)-cinnamaldehyde and cyclopentadiene.

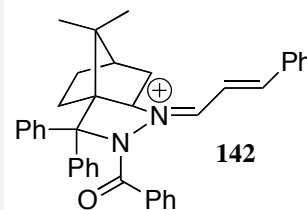
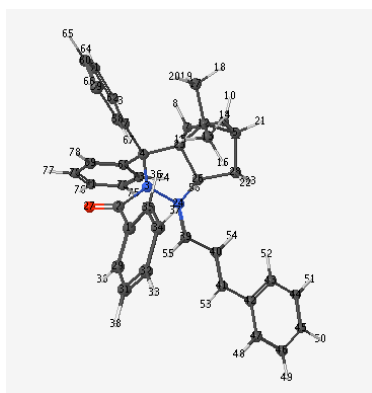
Entry	Co-Catalyst	Solvent	Conversion	Endo:Exo	Endo ee	Exo ee
1	HClO ₄	H ₂ O:THF (9:1)	33%	2:1	22%	14%
2	HClO ₄	Brine	44%	1.9:1	21%	14%

Perchloric acid was used as a catalyst in both cases. The first solvent tried was water:THF (9:1). This experiment resulted in a 33 % conversion (entry 1). The ee's obtained were 22 % and 14 % for the endo and exo products, respectively. The solvent was then switched to brine, and a small improvement in conversion to 44 % was obtained (entry 2). The ee, however, remained relatively unchanged at 21 % and 14 % for the endo and exo products, respectively.

The failure of these catalysts led us to consider a means to “force” the R group to occupy the space that we wanted it to. We imagined that the substitution of the camphor backbone at the position α to the nitrogen carrying the electron withdrawing group would cause the R group to sample space on the iminium side of the molecule. This, in turn, should allow this group to have significant control over iminium geometry. Toward this end, we performed calculations on a few different disubstituted derivatives (Scheme 100). These derivatives were chosen for their synthetic feasibility. Calculations to determine the low energy conformations for the (*Z*)-iminium ions failed, due to bad geometry in each case.

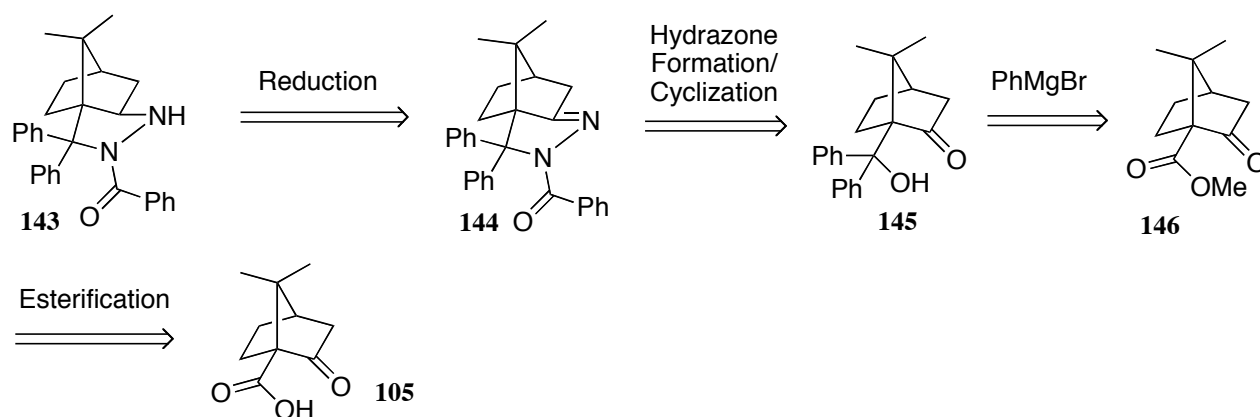
Scheme 100. Reactive conformations calculated for iminium ions 140-142.





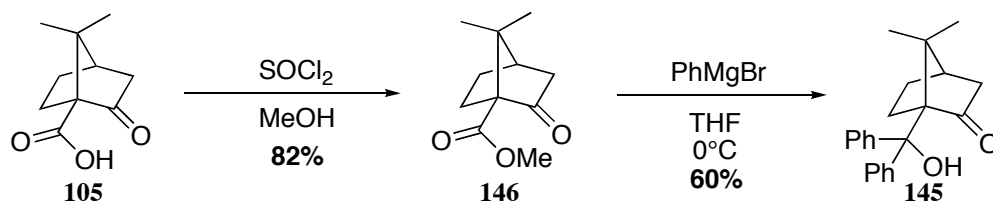
The promising result obtained from the diphenyl substituted derivative **142** prompted us to set out to synthesize the corresponding catalyst **143** for this compound. The fact that there was now substitution on the camphor backbone, required the synthesis to be re-designed. Toward this end, the following retrosynthetic plan was proposed (Scheme 101).

Scheme 101. Retrosynthetic plan for phenyl disubstituted camphor derivative 143.



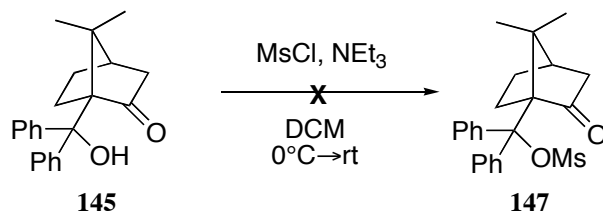
It was envisioned that the desired diphenyl derivative **143** could arise from reduction of the cyclic hydrazone compound **144**. This, in turn, could be obtained from hydrazone formation/cyclization of derivative **145** with the appropriate hydrazide and choice of conditions. The diphenyl alcohol **145** could be prepared by a literature procedure starting from (+)-ketopinic acid (**105**). We then set out to accomplish this synthesis (Scheme 102).

Scheme 102. Synthesis of diphenyl derivative 145.



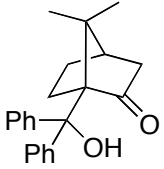
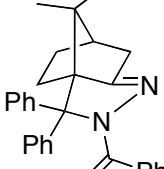
The methyl ester **146** was prepared in an 82 % yield from (+)-ketopinic acid by stirring in methanol with thionyl chloride. This methyl ester was then subjected to Grignard reaction, in which phenylmagnesium bromide was used in excess to provide the alcohol **145** in 60 % yield. At this point, we were contemplating the best way to add the hydrazide to alcohol **145**. We were unsure of how readily the cyclization would occur with the alcohol functionality in **145**. We decided to first try and convert the alcohol into a good leaving group in order to increase the chances of the hydrazone formation/cyclization occurring in one step. Toward this end, we attempted a mesylation reaction to give **147** (Scheme 103).

Scheme 103. Attempted mesylation of 145.



Unfortunately, only starting material was isolated from this process. Due to the fact that this seemingly facile reaction was difficult, we decided to examine the hydrazone formation reaction first in hopes that the cyclization would also occur under the acidic conditions necessary for hydrazone formation. Toward this end, a variety of conditions were tried. The first set of conditions explored was intended to identify the type of solvent that could be used (Table 29).

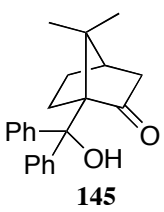
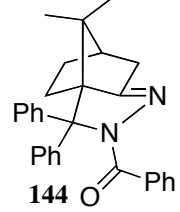
Table 29. Solvent scans for attempted formation of cyclic hydrazone **144 from alcohol **145**.**

 145 $\xrightarrow[\text{Solvent, Temp}]{\text{H}_2\text{NNHC(O)Ph (2 Eq)} \atop \text{TsOH}\cdot\text{H}_2\text{O (2 Eq)}}$  144			
Entry	Solvent	Temp	Result
1	<i>i</i> PrOH	reflux	NR
2	MeOH	160 °C	NR
3	DMF	210 °C	SM and Byproduct
4	Heptane	90 °C	Byproduct
5	THF	180 °C	5:1 Byproduct:Product
6	DCM	140 °C	4 % isolated yield

p-Toluenesulfonic acid was chosen due to the previous success of this acid in forming hydrazones with similar derivatives. The first solvent investigated was isopropanol, which led to no reaction at reflux (entry 1). No reaction was also observed with methanol in the microwave reactor at 160 °C (entry 2). When the reaction was performed in DMF in the microwave reactor at 210 °C, a mixture of starting material and a product whose spectra did not match that expected for either an acyclic hydrazone or cyclic hydrazone **144** was obtained (entry 3). This same byproduct was obtained exclusively when the reaction was performed in heptane at 90 °C in the microwave reactor (entry 4). The use of THF in the microwave reactor at 180 °C did produce a compound which matched that expected for cyclic hydrazone **144**, however, it was obtained in a 5:1 ratio of byproduct:**144** (entry 5). The amount of the byproduct formed made it very difficult to obtain a clean sample of the anticipated product **144**, and it could therefore not be isolated from this particular reaction. Performing the reaction in DCM at 140 °C in the microwave reactor allowed us to obtain enough product that we could painstakingly free it from the death grip of the byproduct, albeit in a useless 4 % yield (entry 6).

Wondering if the temperature may play a role in the byproduct formation, we decided to perform a scan of the most successful reaction conditions at different temperatures, in hopes that the byproduct formation would be suppressed at lower temperatures (Table 30).

Table 30. Temperature scans for attempted formation of cyclic hydrazone **144 from alcohol **145**.**

 145 $\xrightarrow[\text{DCM, Temp}]{\text{H}_2\text{NNHC(O)Ph (2 Eq)} \\ \text{TsOH}\cdot\text{H}_2\text{O (2 Eq)}}$  144		
Entry	Temperature (°C)	Result
1	50	NR
2	70	Mostly SM
3	90	Mostly SM
4	110	SM, P and Byprod
5	130	Mostly Byprod and 12 % yield of 144

Performing the reaction at only 50 °C in the microwave reactor did not result in anything other than starting material being observed (entry 1). Increasing the temperature to both 70 and 90 °C produced only a trace of the byproduct, with mostly starting material being observed (entries 2 and 3). When the temperature was increased to 110 °C, a mixture of starting material, byproduct, and product was obtained (entry 4). Performing the reaction at 130 °C resulted in disappearance of the starting material, however a substantial amount of byproduct was obtained along with the product (entry 5). In this case, purification was performed by preparatory TLC multiple times to obtain 12 % of the clean cyclic hydrazone **144**. The difficult purification and low yield warranted further investigations for the suppression of byproduct formation.

These results led us to conclude that varying the temperature of the reaction was not going to influence the distribution between the byproduct and product to a large degree. The next parameter that we wanted to explore involved the choice of acid. We wondered whether a different acid would enable us to obtain the cyclic hydrazone preferentially. There were reports⁸⁵ in the literature that suggested imine formation on the same alcohol **145** could be performed using $\text{BF}_3 \cdot \text{OEt}_2$ in toluene at reflux. We decided to attempt to mimic these conditions with our hydrazide in hopes of obtaining the corresponding hydrazone, whether it cyclized or not (Table 31).

Table 31. Attempts to make cyclic hydrazone 144 with Lewis acids.

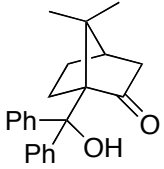
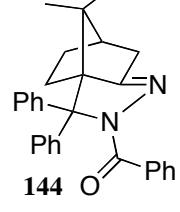
Entry	Acid	Temp	Result
1	$\text{BF}_3 \cdot \text{OEt}_2$	reflux	Byproduct
2	$\text{BF}_3 \cdot \text{OEt}_2$	reflux ^a	Byproduct
3	$\text{BF}_3 \cdot \text{OEt}_2$	170°C ^a	Byproduct
4	AlMe_3	reflux	SM and Byproduct

^a $\text{BF}_3 \cdot \text{OEt}_2$ premixed with hydrazide

The attempted repetition of the imine forming reaction conditions on **145** led to complete formation of the byproduct (entry 1). Attempting to first pre-mix the acid and the hydrazide also resulted in complete byproduct formation (entry 2). Pre-mixing the acid and hydrazide and subjecting the reaction mixture to a higher temperature in the microwave reactor also produced only the byproduct (entry 3). Attempting to switch to a different Lewis acid reported⁸⁵ did not assist in suppressing byproduct formation (entry 4).

With these results, we realized that Lewis acids would not work under the conditions that we required for hydrazone formation in our case. At this point, we decided to test different Brønsted acids to see if we could find one that provided an improvement in yield of the cyclized hydrazone **144** (Table 32).

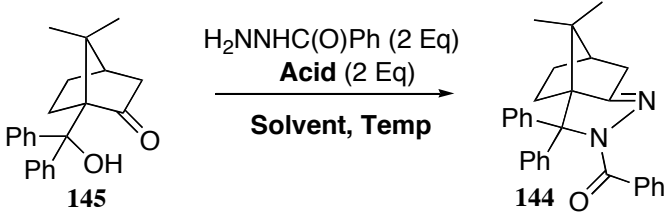
Table 32. Acid scans for attempted formation of cyclic hydrazone 144 from alcohol 145.

 145 $\xrightarrow[\text{Solvent, Temp}]{\text{H}_2\text{NNHC(O)Ph (2 Eq)} \atop \text{Acid (2 Eq)}}$  144				
Entry	Acid	Solvent	Temperature	Result
1	AcOH	DCM	140°C	NR
2	AcOH (4eq)	DCM	140°C	NR
3	HCl	DCM	140°C	NR
4	HCl	DMF	210°C	NR
5	TFA	DCM	140°C	Byproduct only

The first acid we wanted to try was acetic acid, as it is much weaker than triflic acid or any of the Lewis acids tried (entry 1). This resulted in no reaction when 2 equivalents were used. When we increased the equivalents to 4 eq, we also saw no reaction (entry 2). Changing the acid to HCl did not produce a reaction in either DCM or DMF (entries 3 and 4). The use of trifluoroacetic acid resulted in exclusive formation of the byproduct (entry 5).

Upon obtaining these results, we wondered if it would be beneficial to pre-mix the acid and hydrazide, in order to treat **145** with the corresponding salts. Toward this end, some acids, which were pre-mixed with the hydrazide, were examined (Table 33).

Table 33. Effects of pre-mixing the acids with the hydrazides for attempted formation of cyclic hydrazone 144 from alcohol 145.



Entry	Acid	Solvent	Temperature (°C)	Result
1	TsOH•H ₂ O	DCM	140	Mostly Byproduct
2	TsOH•H ₂ O	DCM	140	3:1 Byproduct:Product
3	HCl	DCM	140	NR
4	HCl	THF	180	NR
5	CSA	DCM	140	NR
6	TFA	DCM	140	NR

Premixing TsOH•H₂O with the hydrazide in DCM did not produce a significant benefit, as mostly byproduct was observed (entry 1). Attempts to pre-heat TsOH•H₂O with the hydrazide led to a 3:1 byproduct:product ratio (entry 2). Premixing HCl in both DCM and THF led to no reaction (entries 3 and 4). The use of both CSA and TFA premixed with the hydrazide also led to no reaction (entries 5 and 6).

We next wondered whether we could adjust the ratio of the acid:hydrazide in order to obtain an optimal ratio of product:byproduct. Thus, TsOH•H₂O was used in conjunction with the hydrazide in varying ratios (Table 34).

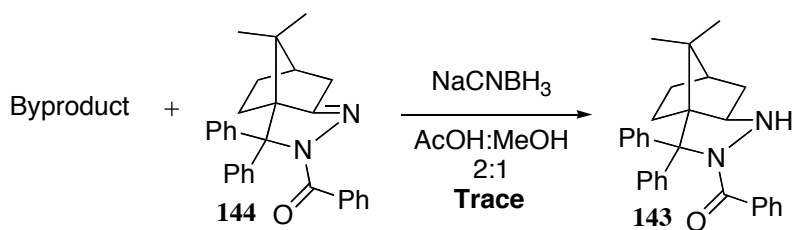
Table 34. Adjustments to ratio of acid:hydrazide in hopes to obtain a larger amount of 144.

Entry	Equivalents	Solvent	Temperature	Result
1	1.0	DCM	140 °C	NR
2	1.8	DCM	140 °C	2.7:1 Byproduct:Product
3	0.2	iPrOH	180 °C	SM, S _N 1 attack of iPrOH
4	0.2	Toluene	170 °C	NR

The reduction of equivalents of TsOH•H₂O to 1 eq, led to no reaction (entry 1). Increasing to 1.8 equivalents showed an improvement in the ratio of byproduct:product to 2.7:1, however, the amount of byproduct was still problematic for purification (entry 2). Changing the solvent to isopropanol and using a catalytic amount of acid resulted in mostly starting material, with some observed material resulting from S_N1 attack of isopropanol (entry 3). Using the same catalytic amount of acid in toluene resulted in no reaction (entry 4).

The small amount of cyclic hydrazone **144** was taken along with the byproduct that was difficult to separate, and subjected to reduction with sodium cyanoborohydride (Scheme 104). The desired product **143** was obtained, however, in only a trace amount.

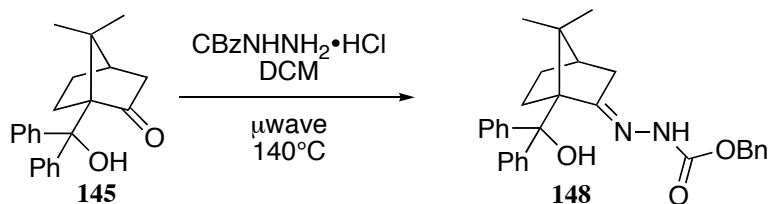
Scheme 104. Reduction of 144/byproduct mixture.



Due to the difficulty of obtaining hydrazone **144** free of the high amount of byproduct contamination, catalyst **143** could not be tested in Diels-Alder reactions.

We wondered if a different hydrazide would be more reactive and result in a suppression of byproduct formation. Toward this end, alcohol **145** was reacted with CBzNHNH₂ (Scheme 105).

Scheme 105. Possible formation of hydrazone **148.**



Originally, it had seemed that we obtained **148** in 69 % yield. This product was then used in the following cyclization reactions (Table 35).

Table 35. Attempted cyclization reactions of **148.**

Entry	Conditions	Result
1	PPh ₃ , DEAD Toluene, 0°C-rt	Complex mixture
2	PPh ₃ , DIAD Toluene, 0°C-rt	Unidentified Product
3	PPh ₃ , DIAD ^a Toluene, 0°C-rt	complex mixture
4	PPh ₃ , CBr ₄ THF, rt	NR

^a pre-mixed at room temperature

Attempts to cyclize this presumed acyclic hydrazide with triphenylphosphine and diethylazodicarboxylate (DEAD) resulted in a complex mixture of products that was difficult to identify (entry 1). Changing the reagent to diisopropylazodicarboxylate (DIAD) resulted in the isolation of a product whose NMR spectra did not match that of cyclized hydrazone **149** (entry 2). It was difficult to determine what, exactly this product was. Attempts to obtain the right product **149** by pre-mixing the

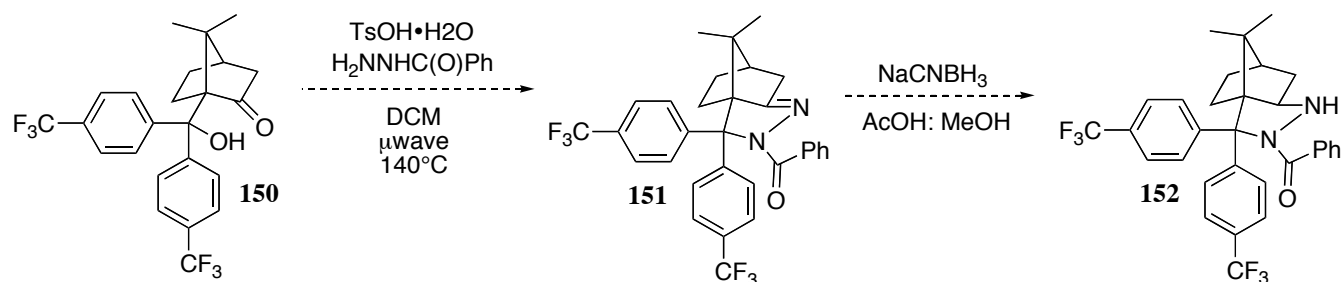
triphenylphosphine and DIAD resulted in a complex mixture of products (entry 3). Attempting to brominate and subsequently cyclize were also fruitless (entry 4). It was later discovered that the precursor **148**, was, in fact, never formed in the first place, due to a more careful examination of the spectral data obtained, and upon the discovery of the identity of the byproduct from reactions with **145** (Part B).

The production of the byproduct in the reactions involving alcohol **145** led to the downfall of this synthetic route. The low amounts of cyclic hydrazone **144** led to an insufficient amount of material for testing in Diels-Alder cycloadditions.

FUTURE DIRECTIONS

The presence of the pesky byproduct in all of the reactions in which cyclic hydrazone **144** was obtained heavily thwarted efforts to test the ultimate compound **143** in Diels-Alder reactions. Once the identity of this byproduct was known (Part C), we could imagine attempting the hydrazone formation/cyclization steps with a disubstituted aryl derivative **150** in which electron withdrawing groups are placed on the aryl rings to hopefully decrease the byproduct formation (Scheme 106). If derivative **150** could be successfully converted to **151** under optimal conditions, this compound could be reduced to give **152**, which would then be tested in Diels-Alder reactions.

Scheme 106. Derivative 150 as a potential substrate for hydrazone formation/cyclization.

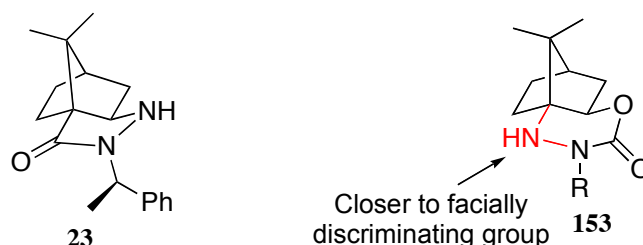


DESIGN OF A POTENTIAL CAMPHOR-BASED HYDRAZIDE ORGANOCATALYST POSSESSING A DIFFERENT ARCHITECTURE

Due to our difficulties in obtaining an effective catalyst by slight modifications of our previously successful architecture, we felt that a re-design may be in order. We decided to focus on the key nitrogen involved in iminium formation. In the original catalyst **22**, this nitrogen is placed β to the

bridgehead carbon containing the major facially discriminating group (Scheme 107). The other important enantiocontrolling group is the “R” group attached to the nitrogen α -to the key iminium nitrogen. This group will dictate which face of the dienophile is exposed by influencing the iminium geometry. Considering these two important control elements for enantioselectivity with camphor-based hydrazide catalysts, we decided to design a derivative **153** (Scheme 107) which we imagined may provide an improvement in enantioselectivity and versatility.

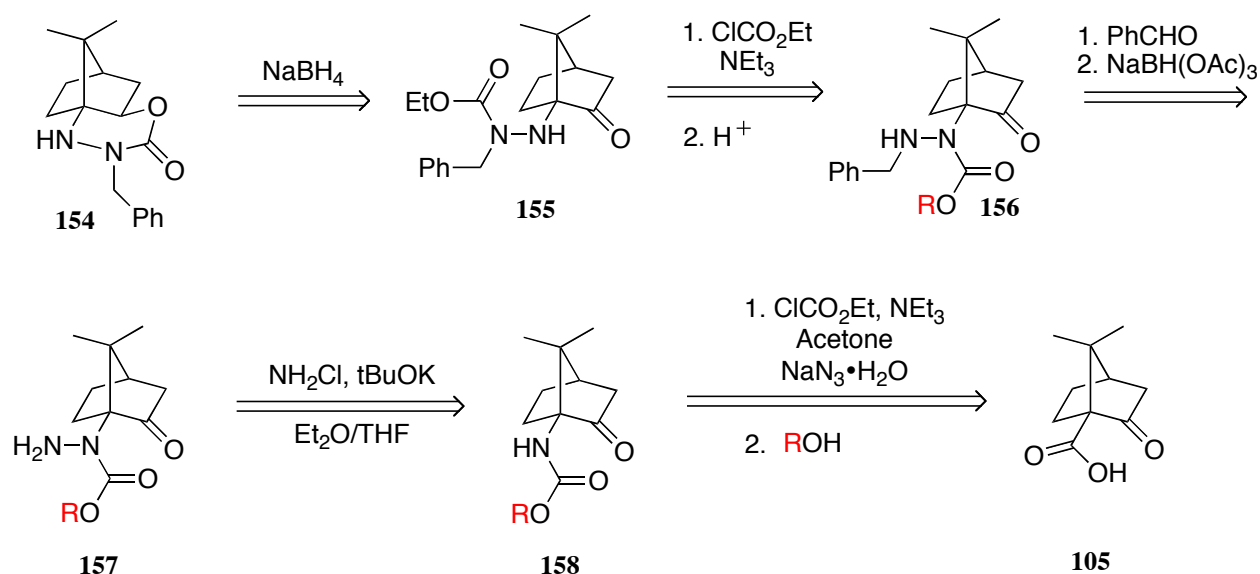
Scheme 107. Previous catalyst design **23 and proposed improved design **153**.**



We envisioned that placing the nitrogen involved in iminium formation closer to the camphor bridgehead would impart an even tighter control on the enantioselectivity of the process. The nitrogen α -to this key nitrogen would still possess the “R” group responsible for enantiocontrol.

The synthetic sequence for derivatives of type **153** would be quite different from the previous derivatives of type **23**. The retrosynthetic plan for such is shown in Scheme 108.

Scheme 108. Retrosynthetic plan for the synthesis of a derivative **154.**



The retrosynthetic plan relied on the reduction of the ketone in derivative **155**, which we hoped would subsequently attack the ester group, providing the cyclized compound **154**. The key ester functionality would be installed on the protected derivative **156**, which would immediately be deprotected to obtain **155**. The benzyl group would be installed via reductive amination on derivative **157**. This derivative **157**, would, in turn, be synthesized with an amination reaction performed on derivative **158**. A Curtius rearrangement using (+)-ketopinic acid would provide derivative **158**.

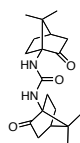
The synthesis commenced with the Curtius rearrangement of (+)-ketopinic acid (**105**), and subsequent trapping with an appropriate nucleophile (Table 36).

Table 36. Attempted conditions to install carbamate group on (+)-ketopinic acid (105**).**

Entry	Reagents	Solvent	R	Result
1	(PhO) ₂ P(O)N ₃	Toluene	<i>t</i> -Bu	isocyanate 159
2	NaN ₃ , ClCO ₂ Et	Acetone ^a	<i>t</i> -Bu	isocyanate 159
3	(PhO) ₂ P(O)N ₃	Toluene	-CH ₂ (CH)CH ₂	dimer byproduct 160
4	(PhO) ₂ P(O)N ₃	Toluene	-CH ₂ CH ₂ TMS	89 % yield

^a Reaction performed at room temperature

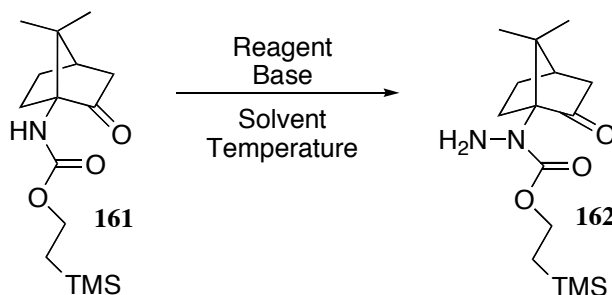
^b Proposed structure of dimer byproduct **160**:



We first performed the reaction by refluxing (+)-ketopinic acid with diphenylphosphoryl azide in toluene to form the isocyanate (entry 1). We attempted to trap this isocyanate with *t*-butanol to obtain derivative **158**. Unfortunately, only the isocyanate **159** was isolated from this reaction. Simultaneously, we tried using a different azide in the form of sodium azide along with ethyl chloroformate⁸⁶ in acetone at room temperature (entry 2). This process also led to isolation of only isocyanate **159** after attempted

trapping with *t*-butanol. We then realized that perhaps *t*-butanol was too sterically hindered to attack the isocyanate **159**, and decided to use different alcohol nucleophiles, as this group would eventually be removed in the synthesis anyway. Toward this end, we decided to try allyl alcohol as nucleophile using diphenylphosphoryl azide to form the isocyanate (entry 3). In this case, we did not observe any of the desired product, but rather, a product that we believed was dimeric product **160**. We believed that this product could arise from water being present in the reaction mixture. Finally, we decided to try switching the nucleophile to TMS-ethanol, with great success (entry 4). We obtained the desired derivative **161** in 89 % yield.

Once the optimal condition was obtained for the synthesis of **161**, we decided to approach the amination reaction. This reaction proved to be a difficult feat (Table 37).

Table 37. Various amination conditions attempted for derivative 161.

Entry	Reagent	Base	Solvent	Temp	Result
1	NH ₂ Cl	KOtBu	THF	Rt	Trace
2	NH ₂ Cl	NaOH	THF	Rt	0%
3	NH ₂ Cl	K ₂ CO ₃	THF	Rt	0%
4	NH ₂ Cl	NaH	THF	Rt	Trace
5	NH ₂ Cl	NaOH ^a	THF	Rt	Trace
6	NOBF ₄ ^b	Pyridine	CH ₃ CN	-30°C-rt	0%
7	NBzONH ₂	NaH	Dioxane	60°C-rt	0%
8	NBzONH ₂	NaH	DMF	60°C	Trace
9	Ph ₂ P(O)ONH ₂	<i>n</i> -BuLi	THF	-78°C-rt	0%
10	Ph ₂ P(O)ONH ₂	NaH	DMF	60°C-rt	Trace
11	Ph ₂ P(O)ONH ₂	NaH	DMF	60°C	Trace
12	Ph ₂ P(O)ONH ₂	NaH	Dioxane	60°C-rt	0%
13	Ph ₂ P(O)ONH ₂ ^c	NaH	DMF	60°C	43%
14	Ph ₂ P(O)ONH ₂ ^c	NaH	DMF	100°C	58% ^d

^a Tetrabutylammonium bromide used as phase transfer catalyst

^b Attempt to form the nitroso compound, and subsequently reduce

^c Reagents added all at once

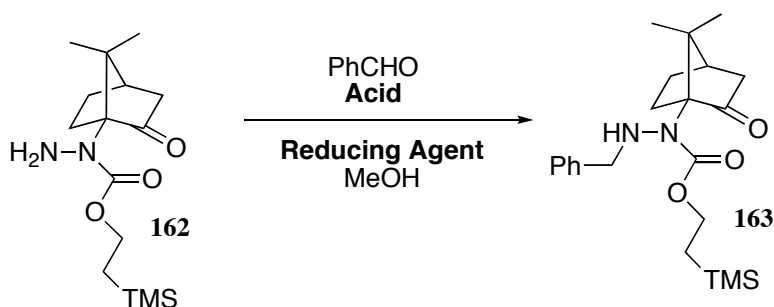
^d Product present as a mixture with starting material

The use of NH₂Cl as an aminating reagent with potassium *t*-butoxide as base⁸⁷ resulted in only a trace amount of product being observed at room temperature (entry 1). We wondered whether the use of a different base would increase the yield of product, and so we switched the base to sodium hydroxide (entry 2). The use of this base led to no observed product. We then tried potassium bicarbonate as a

weaker base, with no reaction being observed (entry 3). Using sodium hydride allowed us to obtain product again, albeit, in a trace amount (entry 4). Employing phase transfer conditions with sodium hydroxide as base, and tetrabutylammonium bromide as a phase-transfer catalyst also resulted in a trace amount of product being formed (entry 5). We then decided to change the aminating reagent, in hopes that we could obtain the nitroso compound and subsequently reduce down to the hydrazide. Toward this end, we employed NOBF_4 with pyridine as base in acetonitrile⁸⁸, unfortunately with no success (entry 6). We then examined whether nitrobenzylhydroxylamine would be a suitable aminating reagent. This reagent was used in conjunction with sodium hydride in either dioxane or DMF (entries 7 and 8). These conditions produced a trace amount of product (entry 7), although no reaction was observed in DMF (entry 8). We next examined diphenylphosphinylhydroxylamine⁸⁹ as an aminating reagent. We first attempted the reaction with *n*-BuLi as base, which gave no reaction observed (entry 9). When the base was changed to sodium hydride in DMF, a trace amount of product was observed upon heating and subsequently cooling to room temperature for the introduction of the aminating reagent (entry 10). When the aminating reagent was added with continued heating at 60 °C, the same result was obtained (entry 11). Switching the solvent to dioxane produced no reaction (entry 12). When the reagents were added all at once, not allowing the starting material to pre-heat with base, better results were obtained. In DMF at 60 °C, the product was isolated in 43 % yield as a mixture with starting material (entry 13). When the reaction temperature was increased to 100 °C, a 58 % yield of product was isolated along with starting material.

Although the amination reaction resulted in a mixture of aminated **162** and non-aminated **161** under the most optimal conditions employed, we decided to take this mixture and put it into the following reaction. We felt that the non-aminated **161** would not interfere with the reductive amination step, due to the very decreased nucleophilicity of the carbamate nitrogen compared to the free hydrazide nitrogen. Toward this end, the mixture of **161** and **162** was subjected to reductive amination conditions (Table 38).

Table 38. Attempted reductive amination of 162 from a mixture of 161 and 162.



Entry	Acid	Reducing Agent	Result
1	-	NaBH ₄	complex mixture
2	AcOH	NaBH(OAc) ₃	complex mixture
3	TsOH•H ₂ O ^a	-	complex mixture

^a Attempt to isolate the hydrazone and subsequently reduce

The conditions attempted for the reductive amination step proved to be non-ideal. The attempted condensation of benzaldehyde with hydrazide **162** under neutral conditions with subsequent reduction by sodium borohydride provided a complex mixture of products that could not be satisfactorily purified by column chromatography (entry 1). The same situation was observed when acetic acid was used to catalyze the hydrazone formation step, along with sodium triacetoxyborohydride as reducing agent (entry 2). An attempt to form and isolate just the hydrazone with the intention of reducing it in a separate pot also provided a mixture of products (entry 3).

FUTURE DIRECTIONS

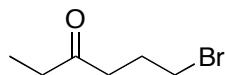
The complex mixture of products obtained from the reductive amination conditions suggested that considerable work would be required to identify proper conditions. Further investigations should focus on the hydrazone formation step, using different acids/solvents to provide the pure hydrazone. At this point, the reduction step can be examined. Once this chemistry is worked out, the electron withdrawing group shuffle can be performed, followed by reduction of the secondary carbonyl on the camphor backbone and hopefully cyclization. It is foreseeable that this last step may require the most optimization.

Once the synthesis is complete, these derivatives could be tested in Diels-Alder reactions, and evaluated for their catalytic ability and enantioselectivity.

EXPERIMENTAL SECTION FOR HYDRAZIDE-BASED ORGANOCATALYSTS

General Methods

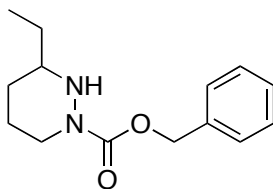
Reactions were performed under nitrogen in oven-dried glassware equipped with a magnetic stirbar and a rubber septum. Solvents were freshly distilled prior to use as follows: THF over sodium/benzophenone, toluene and methylene chloride over calcium hydride. All reagents were used without further purification unless otherwise indicated. Reactions were monitored by TLC analysis using aluminum plates (250 μm thickness) precoated with silica gel 60 F254. TLC plates were visualized using ultraviolet light and potassium permanganate. Flash chromatography was carried out on 230-400 mesh silica gel 60, or preparatory TLC glass plates precoated with silica gel (Si250F). ^1H and ^{13}C NMR spectra were acquired on a 300 MHz, 400 MHz, or 500 MHz spectrometer in the specified solvent. Infrared spectra were acquired on a FTIR spectrometer. High resolution mass spectra were obtained using an Analytical Concept spectrometer. Melting points were determined using an Electrothermal Meltemp apparatus and are uncorrected. Optical rotations were determined using a Rudolph Research Analytical AUTOPOL III automatic polarimeter.



6-Bromohexan-3-one (36)

4-Bromobutyric acid (2.00 g, 12.0 mmol) was weighed directly into a 250 mL round bottom flask containing a stir bar. Molecular sieves (3 Å) were added, and an atmosphere of nitrogen was established. Dry THF (50 mL) was then introduced, followed by carbonyl diimidazole (CDI) (2.52 g, 15.6 mmol) and the reaction mixture stirred at room temperature for 20 minutes. At this time, $\text{CH}_3\text{NH}(\text{OMe})\cdot\text{HCl}$ (1.40 g, 14.4 mmol) was added, followed by triethylamine (3.34 mL, 24.0 mmol). The resulting mixture was stirred at room temperature for 18 hours, before being diluted with ether (50 mL). The organic layer was subsequently washed with 10 % HCl (50 mL), saturated NaHCO_3 (25 mL), and brine (25 mL), then dried over MgSO_4 , filtered, and concentrated to obtain the Weinreb amide **35** as a pale yellow oil (1.84 g, 73 %). ^1H NMR (CDCl_3 , 300 MHz) 3.71 (s, 3H), 3.51 (t, J = 6.3 Hz, 2H), 3.18

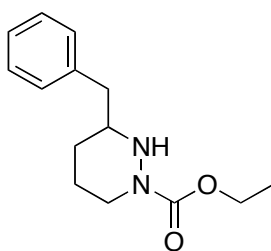
(s, 3H), 2.63 (t, J = 6.9 Hz, 2H), 2.19 (p, J = 6.6 Hz, 2H). This material was used without further purification in the subsequent Grignard reaction. Weinreb amide **35** (3.15 g, 15.0 mmol) was placed in a 250 mL round bottom flask under inert atmosphere. Dry THF (50 mL) was then added via syringe, and the mixture brought to -78 °C in a dry ice/acetone bath. At this point, 1.0 M EtMgBr (23 mL, 22.5 mmol) was added dropwise over 20 minutes. The resulting mixture was stirred at -78 °C for 10 additional minutes, before being warmed to 0 °C for 1.5 hours. A 5 % solution of ammonium chloride (50 mL) was used to quench the reaction, followed by dropwise addition of 1 M HCl (20 mL). The mixture was then diluted with ether (50 mL) and the organic phase washed with 1 M HCl (3 x 25 mL), saturated NaHCO₃ (25 mL), brine (25 mL), then dried over MgSO₄, filtered, and concentrated to obtain the title compound as a pale yellow oil (2.18 g, 81 %). Spectra matched those previously reported for this compound.⁹⁰ **¹H NMR** (CDCl₃, 400 MHz) 3.45 (t, J = 6.8 Hz, 2H), 2.61 (t, J = 6.8 Hz, 2H), 2.45 (q, J = 7.2 Hz, 2H), 2.13 (p, J = 6.8 Hz, 2H), 1.06 (t, J = 7.2 Hz, 3H).



Benzyl 3-ethylpiperazine-1-carboxylate (33)

6-Bromohexan-3-one (137 mg, 0.77 mmol) was dissolved in dry toluene (8 mL) in a 25 mL round bottom flask under inert atmosphere. Molecular sieves (3 Å) were added, followed by H₂NNH₂•H₂O (70 µL, 1.53 mmol) via microsyringe. DIPEA (0.40 mL, 2.31 mmol) was then added, and the resulting mixture stirred at room temperature for 18 hours. At this point, the reaction was brought to 0 °C in an ice bath, and benzyl chloroformate (0.27 mL, 1.93 mmol) was added via syringe. The resulting mixture was stirred for 2 hours at 0 °C, and subsequently diluted with ethyl acetate (20 mL). The organic layer was then washed with a citric acid solution at pH 4 (3 x 10 mL), saturated NaHCO₃ (10 mL), and brine (10 mL). Drying over MgSO₄, filtering, and concentrating gave the crude cyclic hydrazone **37** as a pale yellow oil. This compound was purified by flash chromatography (20 % EtOAc/hexanes) to afford the product as a clear oil (179.4 mg, 95 %). **¹H NMR** (CDCl₃, 400 MHz) 7.42-7.20 (m, 5H), 5.23 (s, 2H),

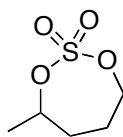
3.63-3.60 (m, 2H), 2.24 (q, J = 7.6 Hz, 2H), 2.08 (dd, J = 6.8 Hz, 2H), 1.82-1.76 (m, 2H), 1.07 (t, J = 7.6 Hz, 3H). The cyclic hydrazone **37** (155 mg, 0.63 mmol) was subsequently placed under inert atmosphere, and dissolved in a mixture of methanol (2.1 mL) and acetic acid (4.2 mL). NaCNBH_3 (396 mg, 6.30 mmol) was added in four portions over one hour, and the reaction mixture stirred at room temperature for 18 hours. 10 % HCl (20 mL) was added to quench the reaction, and the resulting mixture diluted with DCM (20 mL). The aqueous layer was then basified with NaOH pellets ($\text{pH} > 11$), and extracted with DCM (3 x 20 mL). The combined organic phases were washed with brine, dried over MgSO_4 , filtered, and concentrated to obtain the crude material. Purification by flash chromatography (10-20 % EtOAc/ hexanes) provided the title compound as a colorless oil (88.9 mg, 57 %). **^1H NMR** (CDCl_3 , 300 MHz) 7.39-7.28 (m, 5H), 5.19 (d, J = 12.4 Hz, 1H), 5.14 (d, J = 12.4 Hz, 1H), 4.10-4.02 (m, 1H), 3.04 (ddd, J = 13.2, 13.2, 2.8 Hz, 1H), 2.65-2.56 (m, 1H), 1.83-1.74 (m, 1H), 1.72-1.63 (m, 1H), 1.59-1.17 (m, 4H), 0.94 (t, J = 7.6 Hz, 3H); **^{13}C NMR** (CDCl_3 , 100 MHz) 155.1 (C), 136.5 (C), 128.3 (CH), 127.9 (CH), 127.7 (CH), 67.3 (CH_2), 58.6 (CH_2), 45.0 (CH_2), 30.1 (CH_2), 26.8 (CH_2), 9.9 (CH_3); **IR (neat)** 2969, 2937, 1698 cm^{-1} ; **MS** (EI) 247.1 (M-H); **HRMS** (EI) Calcd for $\text{C}_{14}\text{H}_{19}\text{N}_2\text{O}_2$ (M-H) 247.1447, found 247.1401.



ethyl 3-benzylpiperazine-1-carboxylate (38)

5-bromo-1-phenylpentan-2-one (**40**, 550mg, 2.30 mmol), was prepared according to a procedure similar to that described above for **36**, and dissolved in dry toluene (25 mL). This solution was added to a separate, dry 100 mL round bottom flask containing molecular sieves (3 Å). $\text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O}$ (0.22 mL, 4.60 mmol) was added, followed by DIPEA (1.9 mL, 6.80 mmol) and the reaction mixture stirred for 18 hours at room temperature. At this point, the mixture was cooled to 0 °C in an ice bath, and ethyl chloroformate (0.51 mL, 5.70 mmol) was added via syringe. The resulting mixture was stirred for

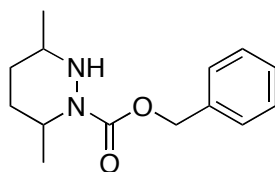
another 18 hours before being diluted with ethyl acetate (50 mL). The organic phase was washed with a citric acid solution (3 x 25 mL), saturated NaHCO₃ (25 mL), and brine (25 mL) before being dried over MgSO₄, filtered and concentrated *in vacuo* to obtain the crude cyclic hydrazone **39**. This crude material was subjected to flash chromatography (30 % EtOAc/hexanes) to obtain a pale yellow oil (321 mg, 57 %). ¹H NMR (CDCl₃, 400 MHz) 7.35-7.20 (m, 5H), 4.32 (q, *J*=7.2 Hz, 2H), 3.67-3.63 (m, 2H), 3.60 (s, 2H), 2.02 (dd, *J*= 6.4 Hz, 2 H), 1.83-1.75 (m, 2H), 1.36 (t, *J*= 7.2 Hz, 3H). This compound **39** (321 mg, 1.31 mmol) was immediately dissolved in AcOH (11 mL) and MeOH (6 mL) in a 50 mL round bottom flask under nitrogen atmosphere. NaCNBH₃ (820 mg, 13.1 mmol) was introduced in four portions over one hour, and the resulting mixture stirred for 18 hours at room temperature. The reaction was then quenched by the addition of 2N NaOH, until the mixture was basic (pH >11), and diluted with DCM (25 mL). The aqueous phase was extracted with DCM (3 x 25 mL), then the combined organic phases were washed with brine (25 mL), dried over MgSO₄, filtered, and concentrated *in vacuo* to obtain the crude product. This was dissolved in ether (25 mL), and extracted with 10 % HCl (50 mL). The aqueous phase was then basified with KOH pellets until basic (pH >11), extracted with DCM (3 x 50 mL), and the resulting combined organic phases washed with brine (25 mL). The solution was then dried over MgSO₄, filtered, and concentrated *in vacuo* to obtain the title compound as a clear oil (175.6 mg, 54 %). ¹H NMR (CDCl₃, 400 MHz) 7.34-7.19 (m, 5H), 4.18-3.98 (m, 3H), 3.08-2.90 (m, 2H), 2.68 (ddd, *J*= 7.6, 7.6, 4.4 Hz, 2H), 1.79-1.72 (m, 1H), 1.71-1.64 (m, 1H), 1.54-1.44 (m, 1H), 1.43-1.33 (m, 1H), 1.19 (t, *J*= 6.4 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) 155.3 (C), 137.8 (C), 129.1 (CH), 128.5 (CH), 126.5 (CH), 61.7 (CH₂), 57.9 (CH), 44.8 (CH₂), 40.7 (CH₂), 30.6 (CH₂), 14.6 (CH₃); IR (neat) 1695 cm⁻¹; HRMS (EI) Unable to obtain a satisfactory spectrum.



4-Methyl-1,3,2-dioxathiepane 2,2-dioxide (**47**)

Pentane-1,4-diol (100 mg, 0.96 mmol) was dissolved in DCM (7 mL) in a 25 mL round bottom flask. A reflux condensor was attached, and the solution brought to 0 °C in an ice bath. Thionyl chloride (90

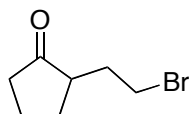
μL , 1.25 mmol) was added and the reaction mixture subsequently allowed to warm to room temperature for 30 minutes. At this point, the mixture was brought to reflux for two hours. The mixture was cooled to room temperature and concentrated on a rotary evaporator. DCM (2 mL), MeCN (3 mL), and H_2O (6 mL) were added, and the mixture brought to 0 °C in an ice bath. $\text{RuCl}_3 \cdot \text{H}_2\text{O}$ (2 mg, 0.01 mmol) was added, followed by NaIO_4 (411 mg, 1.92 mmol) and the reaction mixture warmed to room temperature and allowed to stir for 16 hours. The mixture was then diluted with ether (20 mL) and washed with water (20 mL) before being dried over MgSO_4 , filtered and concentrated *in vacuo* to obtain the crude product. Filtering through a silica pad eluting with 1:1 EtOAc/hexanes and subsequent flash chromatography (20 % EtOAc/hexanes) provided the title compound as a clear oil⁷¹ (80 mg, 50 %). **¹H NMR** (CDCl_3 , 400 MHz) 4.83-4.74 (m, 1H), 4.48 (ddd, J = 12.0, 12.0, 1.2 Hz, 1H), 4.38-4.32 (m, 1H), 2.20-2.05 (m, 1H), 2.03-1.88 (m, 3H), 1.43 (d, J = 6.4 Hz, 3H).



benzyl 3,6-dimethylpiperazine-1-carboxylate (60)

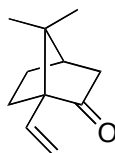
2,5-dimethanesulfonylhexanediol⁹¹ (774 mg, 2.82 mmol) in toluene (10 mL) was added to a 50 mL round bottom flask containing 1-benzyl-2-*tert*-butyl hydrazine-1,2-dicarboxylate⁹² (500 mg, 1.88 mmol). Et_4NBr (7.9 mg, 0.034 mmol) was added to the mixture, followed by a 50 % solution of NaOH in water (5 mL). A reflux condenser was attached, and the resulting mixture heated to reflux for 1.5 hours. The mixture was cooled to room temperature, and diluted with EtOAc (50 mL). The organic phase was washed with saturated NaHCO_3 (25 mL), water (25 mL) and brine (25 mL), dried over MgSO_4 , filtered and concentrated *in vacuo* to obtain the crude Boc-protected catalyst. Flash chromatography (40 % EtOAc/hexanes) provided the Boc-protected catalyst (8 mg, 1 %), which was immediately subjected to deprotection in dry DCM (0.4 mL) with TFA (0.1 mL). The reaction mixture was stirred for 1 hour at room temperature, then diluted with EtOAc (10 mL) and water (10 mL). The organic phase was washed with concentrated KOH (10 mL), and the aqueous phase was subsequently

extracted with EtOAc (2 x 10 mL). The combined organic phases were dried over MgSO_4 , filtered, and concentrated *in vacuo* to obtain a trace amount of the title compound as a clear residue. $^1\text{H NMR}$ (CDCl_3 , 400 MHz) 7.41-7.27 (m, 5H), 5.20 (d, J = 12.8 Hz, 1H), 5.15 (d, J = 12.4 Hz, 1H), 4.49-4.38 (m, 1H), 2.88-2.75 (m, 1H), 1.83-1.68 (m, 1H), 1.57-1.37 (m, 3H), 1.25 (d, J = 6.8 Hz, 3H), 1.07 (d, J = 6.0 Hz, 3H). There was an insufficient amount of product for further characterization.



2-(2-bromoethyl)cyclopentanone (69)

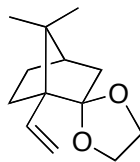
To a 250 mL round bottom flask containing molecular sieves (3 Å) was added acetone (64 mL) followed by ethyl 2-oxocyclopentanecarboxylate (1.89 mL, 12.8 mmol). Potassium bicarbonate (5.3 g, 38.4 mmol) and dibromoethane (6.6 mL, 76.8 mmol) were added, and the reaction mixture heated to reflux for 6 hours, then stirred at room temperature for 18 hours. The solids were filtered off, rinsing with acetone, and the eluant concentrated *in vacuo* to give ethyl 1-(2-bromoethyl)-2-oxocyclopentanecarboxylate as a crude mixture. Flash chromatography (3:1 Hexanes/Ether) provided the pure product as a pale yellow oil (1.82g, 55 %). $^1\text{H NMR}$ (CDCl_3 , 400 MHz) 4.18 (q, J = 7.2 Hz, 2H), 3.51 (ddd, J = 14.8, 9.6, 5.2 Hz, 1H), 3.35 (ddd, J = 15.2, 10.8, 5.2 Hz, 1H), 2.57-2.40 (m, 3H), 2.35-2.25 (m, 1H), 2.17 (ddd, J = 16.4, 10.8, 5.2 Hz, 1H), 2.09-1.89 (m, 3H), 1.26 (t, J = 7.2 Hz, 3H). This material (1.39 g, 5.31 mmol) was then subjected to decarboxylation by dissolving in HBr (5.59 mL). The mixture was heated to reflux for 30 minutes, then allowed to cool to room temperature and diluted with ether (50 mL). The organic phase was washed with saturated NaHCO_3 (25 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo* to obtain the crude product which was filtered through a silica pad using 3:2 hexanes/ether as the eluant. This provided the title compound as a pale yellow oil⁹³ (684 mg, 67 %). $^1\text{H NMR}$ (CDCl_3 , 400 MHz) 3.61-3.56 (m, 1H), 3.49-3.43 (m, 1H), 2.40-2.25 (m, 4H), 2.19-1.99 (m, 2H), 1.88-1.74 (m, 2H), 1.56-1.44 (m, 1H).



(+)-(1*S*,4*R*)-1-ethenyl-7,7-dimethylbicyclo[2.2.1]heptan-2-one (82)

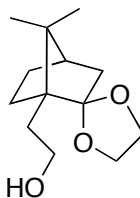
Diazomethane Preparation: Distilled water (30 mL) was added to a 125 mL Erlenmeyer flask, and cooled to 0 °C in an ice bath. KOH pellets (12 g) were added and stirred at 0 °C until dissolved. The solution was transferred to a 1 L plastic bottle containing a stir bar, and 100 mL of ether was added. The resulting mixture was cooled to 0 °C in an ice bath, and *N*-Nitroso-*N*-methyl urea (7 g) was added in four portions, with 5 minutes wait between additions. The solution was stirred at 0 °C for 15 minutes after the last addition, and subsequently frozen at -78 °C in a dry ice/acetone bath for 20 minutes. Collection of the ether layer by filtering through cotton gave a bright yellow solution (~ 0.16 M).

This 0.16 M diazomethane solution (75 mL, 11.8 mmol) was placed in a dry 250 mL round bottom flask, and brought to 0 °C in an ice bath. Triethylamine (1.43 mL, 10.2 mmol) was then added. Camphorsulfonyl chloride **83** (1.97 g, 7.87 mmol) was then added dropwise over 1.5 hours via syringe pump as a solution in dry THF (20 mL). The reaction was subsequently stirred at 0 °C for 5 hours. The white precipitate was filtered off through a cotton plug, and the solvent evaporated under air flow in the fumehood until the yellow color disappeared. At this point, the remaining solvent was evaporated with a rotary evaporator to obtain the episulfone as a pale yellow oil that was used immediately dissolved in benzene (30 mL) and heated to reflux for 6 hours. The reaction mixture was then cooled to room temperature, and concentrated *in vacuo*. Flash chromatography (20 % EtOAc/hexanes) provided the title compound⁹⁴ as a waxy solid (952 mg, 74 %). ¹H NMR (CDCl₃, 400 MHz) 5.81 (dd, *J*= 17.6, 10.8 Hz, 1H), 5.39 (dd, *J*= 11.2, 1.6 Hz, 1H), 5.22 (dd, *J*= 18.0, 2.0 Hz, 1H), 2.45 (ddd, *J*= 18.4, 4.8, 2.4 Hz, 1H), 2.14 (dd, *J*= 4.0, 4.0 Hz, 1H), 2.08-1.96 (m, 2H), 1.91 (d, *J*= 18.0 Hz, 1H), 1.53-1.38 (m, 2H), 0.94 (s, 3H), 0.93 (s, 3H).



(1S, 4R)-1-ethenyl-7,7-dimethylspiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolane] (81)

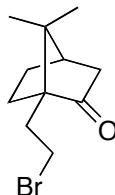
Compound **82** (50 mg, 0.30 mmol) was added to a 10 mL round bottom flask and dissolved in benzene (4 mL). Ethylene glycol (25 μ L, 0.46 mmol) was added, followed by TsOH $\cdot$ H₂O (11.4 mg, 0.06 mmol) and a condenser and Dean-Stark apparatus were attached. The mixture was refluxed for 18 hours, introducing additional ethylene glycol (25 μ L, 0.46 mmol) after 12 hours. At this point, the mixture was cooled to room temperature and diluted with benzene (50 mL). The organic layer was washed with water (25 mL), saturated NaHCO₃ (25 mL), and brine (25 mL), dried over MgSO₄, filtered, and concentrated *in vacuo* to obtain the crude product. Purification by flash chromatography (2 % EtOAc/hexanes) provided the title compound⁹⁵ as a clear oil (40.3 mg, 65 %). ¹H NMR (CDCl₃, 300 MHz) 6.02 (dd, *J*= 17.7, 11.1 Hz, 1H), 5.16 (dd, *J*= 11.1, 2.1 Hz, 1H), 5.08 (dd, *J*= 17.7, 2.1 Hz, 1H), 3.97-3.66 (m, 4H), 2.16 (ddd, *J*= 13.5, 3.9, 3.9 Hz, 1H), 1.96-1.88 (m, 1H), 1.82-1.57 (m, 3H), 1.48 (d, *J*= 13.5 Hz, 1H), 1.33-1.21 (m, 1H), 1.12 (s, 3H), 0.77 (s, 3H).



(1S, 4R)-7,7-dimethyl-spiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolane]-1-ethanol (80)

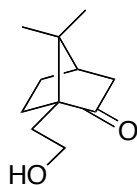
A solution of **81** (321 mg, 1.54 mmol) in dry THF (16 mL) was added to a dry 100 mL round bottom flask. The solution was brought to 0 °C in an ice bath, a 0.5 M solution of 9-BBN in THF (4.62 mL, 2.31 mmol) was added, and the reaction allowed to warm to room temperature over 8 hours. The resulting mixture was then cooled to 0 °C once again, and EtOH (0.31 mL, 5.39 mmol), 6 M NaOH (2.44 mL, 9.5 mmol), then 30 % H₂O₂ (4.88 mL) were added, and the solution stirred for 18 hours at room temperature. At this point, ether (50 mL) was added, and the organic layer washed with water (2 x 25 mL), brine (25 mL), dried over MgSO₄, filtered, and concentrated *in vacuo* to give the crude product.

Purification by flash chromatography (15 % EtOAc/hexanes) provided the title compound⁹⁶ as a clear oil (327 mg, 94 %). ¹H NMR (CDCl₃+K₂CO₃, 300 MHz) 4.02-3.85 (m, 3H), 3.81-3.59 (m, 3H), 2.61 (t, *J*= 6.0 Hz, 1H), 2.05-1.89 (m, 3H), 1.83-1.68 (m, 2H), 1.57-1.45 (m, 1H), 1.37 (d, *J*= 12.9 Hz, 1H), 1.34-1.17 (m, 2H), 1.02 (s, 3H), 0.85 (s, 3H).



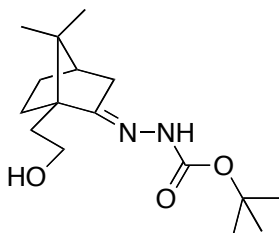
(1S, 4R)-1-(2-bromoethyl)-7,7-dimethyl-bicyclo[2.2.1]heptan-2-one (79)

To a dry 25 mL round bottom flask was added **80** (166.9 mg, 0.73 mmol) as a solution in dry DCM (8 mL). The mixture was cooled to 0 °C in an ice bath, and dry pyridine (0.18 mL, 2.19 mmol) was added, followed by PBr₃ (104 μL, 1.11 mmol). The resulting mixture was allowed to warm to room temperature over 1.5 hours. At this point, ether (50 mL) was added and the organic phase washed with 10 % HCl (25 mL), saturated NaHCO₃ (25 mL), and brine (25 mL), dried over MgSO₄, filtered, and concentrated *in vacuo* to give the crude protected product as an off-white solid. This was immediately dissolved in THF (1.65 mL) containing 1 M HCl (3.30 mL), and the resulting mixture was stirred at room temperature for 6 hours. Ether (50 mL) was added, and the organic phase washed with saturated NaHCO₃ (2 x 25 mL) and brine (25 mL), dried over MgSO₄, filtered, and concentrated *in vacuo* to give the crude product. Flash chromatography (5 % EtOAc/hexanes) provided the title compound⁹⁷ as a white solid (70.4 mg, 39 %). ¹H NMR (CDCl₃, 400 MHz) 3.84 (ddd, *J*= 14.4, 9.2, 4.8 Hz, 1H), 3.34 (ddd, *J*= 14.8, 9.6, 5.2 Hz, 1H), 2.32 (ddd, *J*= 18.4, 4.4, 4.4 Hz, 1H), 2.14 (ddd, *J*= 13.6, 12.4, 5.2 Hz, 1H), 2.06 (dd, *J*= 4.4, 4.4 Hz, 1H), 2.02-1.91 (m, 1H), 1.84-1.73 (m, 3H), 1.54-1.45 (m, 1H), 1.37 (ddd, *J*= 12.4, 9.6, 3.6 Hz, 1H), 0.95 (s, 3H), 0.88 (s, 3H).



(1S, 4R)-1-(2-hydroxyethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (85)

To a 250 mL round bottom flask containing **80** (680 mg, 3.00 mmol) was added THF (10 mL). 1 M HCl (20 mL) was added and the reaction mixture stirred at room temperature for 18 hours. The mixture was then diluted with ether (50 mL), and the organic layer washed with saturated NaHCO₃ (25 mL) and brine (25 mL), dried over MgSO₄, filtered, and concentrated to give the crude product. Purification by flash chromatography (40 % EtOAc/hexanes) afforded **85** as a clear oil⁹⁸ (467.5 mg, 86 %). ¹H NMR (CDCl₃, 400 MHz) 3.78-3.65 (m, 2H), 2.87 (s, 1H), 2.41 (ddd, *J* = 18.4, 4.4, 4.4 Hz, 1H), 2.13 (dd, *J* = 4.4 Hz, 4.4 Hz, 1H), 2.04-1.95 (m, 1H), 1.88 (d, *J* = 18.4 Hz, 1H), 1.84-1.71 (m, 2H), 1.61 (ddd, *J* = 14.0, 9.2, 4.8 Hz, 1H), 1.48-1.38 (m, 2H), 0.94 (s, 3H), 0.90 (s, 3H).

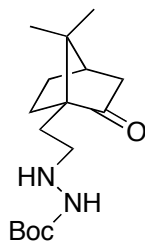


***tert*-butyl-2-(1-(2-hydroxyethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazinecarboxylate (87)**

To a 10 mL round bottom flask containing **85** was added benzene (3 mL) followed by *t*-butyl carbazate (70 mg, 0.52 mmol) and TsOH•H₂O (3 mg, 0.018 mmol). The reaction mixture was then heated to reflux for 8 hours. The mixture was then diluted with benzene (50 mL), and the organic layer washed with a citric acid solution (25 mL), saturated NaHCO₃ (25 mL), and brine (25 mL), dried over MgSO₄, filtered, and concentrated to obtain a white solid. Purification by flash chromatography (40 % EtOAc/hexanes) afforded **87** as a white solid (100.8 mg, 97 %). ¹H NMR (CDCl₃, 400 MHz) 8.10 (s, 1H), 5.68 (s, 1H), 3.80-3.62 (m, 2H), 2.40-2.29 (m, 1H), 1.99 (dd, *J* = 4.4, 4.4 Hz, 1H), 1.94-1.76 (m, 3H), 1.70-1.59 (m, 2H), 1.57-1.40 (m, 1H), 1.49 (s, 9H), 1.29-1.18 (m, 1H), 0.87 (s, 3H), 0.77 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) 164.6 (C), 59.4 (CH₂), 56.7 (C), 48.8 (C), 44.1 (CH), 33.2 (CH₂), 30.6

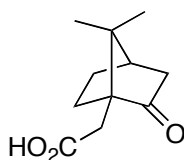
(CH₂), 29.7 (CH₂), 28.2 (CH₃), 27.2 (CH₂), 19.7 (CH₃), 18.7 (CH₃); **IR** (neat) 3223, 2968, 1733 cm⁻¹;

HRMS (EI) Unable to obtain a satisfactory spectrum. **Mp** 174-176 °C.



***tert*-butyl-2-(2-(7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)ethyl)hydrazinecarboxylate (88)**

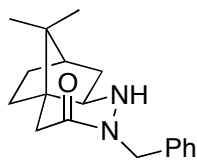
To a dry 10 mL round bottom flask was added **87** (20 mg, 0.07 mmol) followed by dry THF (1 mL). Triphenylphosphine (53 mg, 0.20 mmol) was added, and the reaction brought to 0 °C in an ice bath. Diisopropyl azodicarboxylate (DIAD) (40 µL, 0.20 mmol) was added, and the reaction mixture stirred at 0 °C for 4.5 hours. The mixture was then diluted with EtOAc (50 mL), washed with water (25 mL) and brine (25 mL), dried over MgSO₄, filtered, and concentrated to obtain a crude pale yellow oil. Purification by flash chromatography (20 % EtOAc/hexanes) provided the product as a clear oil (8.2 mg, 40 %). **¹H NMR** (CDCl₃, 300 MHz) 6.29 (s, 1H), 3.20-3.06 (m, 1H), 2.92-2.78 (m, 1H), 2.32 (ddd, *J*= 18.0, 4.2, 3.0 Hz, 1H), 2.10-1.89 (m, 2H), 1.82 (d, *J*= 18.0 Hz, 1H), 1.82-1.63 (m, 2H), 1.55-1.43 (m, 1H), 1.46 (s, 9H), 1.41-1.29 (m, 2H), 0.95 (s, 3H), 0.86 (s, 3H); **¹³C NMR** (CDCl₃, 100 MHz) 219.2 (C), 156.6 (C), 59.3 (C), 48.2 (CH₂), 47.6 (C), 43.3 (CH₂), 43.2 (CH), 28.4 (CH₃), 26.9 (CH₂), 26.5 (CH₂), 23.5 (CH₂), 20.1 (CH₃), 19.6 (CH₃); **IR** (neat) 3331, 2926, 1747, 1697 cm⁻¹; **MS** (EI) 296.2 (M⁺); **HRMS** (EI) Calcd for C₁₆H₂₈N₂O₃ (M⁺) 296.2100, found 296.2119.



(1*S*, 4*R*)-7,7-dimethyl-2-oxo-bicyclo[2.2.1]heptane-1-acetic acid (93)

To a 250 mL round bottom flask containing **80** (3.09 g, 13.6 mmol) was added dry DCM (90 mL). PCC (7.36 g, 34.1 mmol) was added, and the reaction stirred at room temperature for one hour. Ether (10 mL) was added dropwise, and the mixture filtered through a celite pad, rinsing with copious amounts of ether. The filtrate was then concentrated *in vacuo* and flash chromatography (20 %

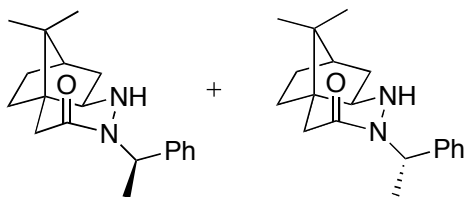
EtOAc/hexanes) afforded a 6:1 mixture of the corresponding protected and deprotected aldehydes (2.59 g, 88% combined). The entirety of this mixture was immediately subjected to Pinnick oxidation, the product was dissolved in *i*PrOH (27 mL) and *t*BuOH (32 mL), the mixture cooled to 0 °C in an ice bath, and 2-methyl-2-butene (16.4 mL, 155.2 mmol) was added via syringe. In a separate 150 mL beaker containing a stir bar was added KH₂PO₄ (16.2 g, 119.4 mmol) followed by distilled water (59.5 mL). NaClO₂ (10.8 g, 119.4 mmol) was then introduced, and the mixture stirred at room temperature until a deep yellow color was obtained (20 minutes). This solution was then added to the first mixture, and the reaction stirred at 0 °C for 1.5 hours before being diluted with EtOAc (100 mL). The organic layer was washed with 10 % HCl (50 mL), followed by brine (50 mL). Drying over MgSO₄, filtering, and concentrating *in vacuo* afforded the protected acid which was immediately subjected to deprotection by dissolving in THF (20 mL) and 1 M HCl (40 mL). The mixture was stirred at room temperature for 1 hour, then diluted with ether (100 mL). The organic phase was washed with water (2 x 50 mL) and brine (50 mL), dried over MgSO₄, filtered, and concentrated to afford the crude product. Purification by flash chromatography (30 % EtOAc/hexanes) provided the pure acid **93**⁹⁹ as a clear oil (2.02 g, 86 %). ¹H NMR (CDCl₃, 300 MHz) 2.60 (d, *J*= 14.7 Hz, 1H), 2.47 (ddd, *J*= 18.9 Hz, 5.1, 2.1 Hz, 1H), 2.26 (d, *J*= 14.4 Hz, 1H), 2.18-2.15 (m, 1H), 2.09-1.94 (m, 4H), 1.74-1.63 (m, 1H), 1.48-1.38 (m, 1H), 1.00 (s, 3H), 0.91 (s, 3H).



4-Benzyl-11,11-dimethyl-4,5-diaza-tricyclo[6.2.1.0^{1,6}]undecan-3-one (98**)**

To a 25 mL round bottom flask containing **93** (219 mg, 1.12 mmol) was added dry DCM (5 mL). In a separate 100 mL flask, benzyl hydrazine (227 mg, 1.66 mmol) was dissolved in DCM (6 mL) and this solution was transferred to the solution containing **93**. AcOH (13 µL, 0.22 mmol) was added via microsyringe, and the solution stirred at room temperature for 18 hours. Heating to reflux for 6 hours was then necessary to complete the reaction. The mixture was concentrated on a rotary evaporator and

subjected to flash chromatography (15 % EtOAc/hexanes) to obtain the cyclized hydrazone **97** as a pale yellow oil (269 mg, 85 %). **¹H NMR** (CDCl₃, 300 MHz) 7.30-7.20 (m, 5H), 5.00 (d, *J*= 15.0 Hz, 1H), 4.80 (d, *J*= 14.7 Hz, 1H), 2.60 (ddd, *J*= 17.4, 3.3, 3.3 Hz, 1H), 2.51 (d, *J*= 17.1 Hz, 1H), 2.40 (d, *J*= 17.4 Hz, 1H), 2.06-1.87 (m, 3H), 1.70-1.54 (m, 2H), 1.30 (ddd, *J*= 12.9, 8.7, 5.4 Hz, 1H), 0.92 (s, 6H). This material **97** (21.9 mg, 0.078 mmol) was immediately dissolved in MeOH (0.66 mL) and AcOH (1.32 mL), and NaBH₃CN (49 mg, 0.78 mmol) was added in four portions over 1.5 hours. The resulting mixture was stirred at room temperature for 18 hours. Additional NaBH₃CN (49 mg, 0.78 mmol) was added in two portions over 3 hours, and the reaction mixture stirred for 18 hours. At this point, 2N NaOH (5 mL) was added, followed by additional NaOH pellets until the pH was basic (> 11). The mixture was then diluted with DCM (50 mL), and the aqueous layer extracted with DCM (3 x 50 mL). The combined organics were washed with brine (50 mL), dried over MgSO₄, filtered, and concentrated to obtain the crude product. Flash chromatography (10 % EtOAc/hexanes with 1 % NEt₃) provided the corresponding product **98** as translucent crystals (10.8 mg, 49 %). **¹H NMR** (CDCl₃, 300 MHz) 7.33-7.21 (m, 5H), 4.83 (d, *J*= 14.4 Hz, 1H), 4.44 (d, *J*= 14.1 Hz, 1H), 3.80 (s, 1H), 2.87-2.77 (m, 1H), 2.50 (d, *J*= 17.7 Hz, 1H), 2.39 (d, *J*= 17.7 Hz, 1H), 1.82-1.51 (m, 5H), 1.28 (ddd, *J*= 12.3, 9.3, 3.3 Hz, 1H), 1.19-1.07 (m, 1H), 0.97 (s, 3H), 0.86 (s, 3H); **¹³C NMR** (CDCl₃, 100 MHz) 171.7 (C), 137.4 (C), 128.5 (CH), 128.3 (CH), 127.3 (CH), 65.9 (CH), 51.9 (CH₂), 49.7 (C), 47.2 (C), 43.9 (CH), 34.9 (CH₂), 34.6 (CH₂), 32.0 (CH₂), 26.9 (CH₂), 20.6 (CH₃), 20.5 (CH₃); **IR** (neat) 1662 cm⁻¹; **HRMS** (EI) Unable to obtain a satisfactory spectrum; **Mp** 72-74 °C; **[α]_D** +7.8 (*c* 1.00, MeOH).

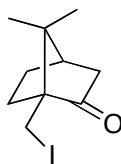


11,11-Dimethyl-4-((*R*)-1-phenyl-ethyl)-4,5-diaza-tricyclo[6.2.1.0^{1,6}]undecan-3-one +

11,11-Dimethyl-4-((*S*)-1-phenyl-ethyl)-4,5-diaza-tricyclo[6.2.1.0^{1,6}]undecan-3-one (100** and **101**)**

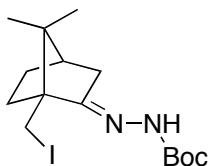
To a 250 mL round bottom flask containing **93** (1.93g, 9.8 mmol) was added a solution of 2-(1-phenylethyl)hydrazine⁵⁵ (2.0 g, 14.7 mmol) in dry DCM (60 mL). AcOH (0.11 mL, 1.96 mmol) was added, and the solution stirred at room temperature for 18 hours. At this point, an additional amount of 2-(1-phenylethyl)hydrazine (333 mg, 2.45 mmol) was added, and the reaction mixture stirred for an additional 24 hours. The mixture was concentrated on a rotary evaporator and flash chromatography (40 % EtOAc/hexanes) was performed to remove the excess hydrazine. The entirety of the resulting hydrazone was then dissolved in toluene (35 mL) in a dry 100 mL round bottom flask. The mixture was heated to reflux for 18 hours, and the solvent removed under reduced pressure. Flash chromatography (10-40 % EtOAc/hexanes) provided the cyclic hydrazone as a pale yellow oil (1.42 g, 54 %). This material was subsequently reduced by dissolving in dry MeOH (17 mL) and AcOH (33 mL). NaBH₃CN (3.31 g, 53.0 mmol) was then added in four portions, waiting 10 minutes between additions. The resulting mixture was stirred at room temperature for 18 hours, and subsequently quenched by the addition of 2 N NaOH (50 mL), and NaOH pellets until the pH was basic (> 11). The mixture was then diluted with DCM (50 mL) and the aqueous phase extracted with DCM (3 x 50 mL). The combined organic layers were then washed with brine (100 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Flash chromatography (20-50 % EtOAc/hexanes) provided **diastereomer 1** as a clear oil (135 mg, 9 %). ¹H NMR (CDCl₃, 400 MHz) 7.37-7.22 (m, 5H), 5.83 (q, *J* = 7.2 Hz, 1H), 3.19 (d, *J* = 12.8 Hz, 1H), 2.82 (ddd, *J* = 14.8, 9.2, 6.0 Hz, 1H), 2.46 (d, *J* = 17.2 Hz, 1H), 2.38 (d, *J* = 17.6 Hz, 1H), 1.82-1.68 (m, 3H), 1.65-1.55 (m, 2H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.31-1.24 (m, 1H), 1.21-1.12 (m, 1H), 0.91 (s, 3H), 0.84 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) 171.3 (C), 141.1 (C), 128.3 (CH), 127.5 (CH), 127.2 (CH), 67.1 (CH), 52.2 (CH), 49.6 (C), 47.2 (C), 43.8 (CH), 34.8 (CH₂), 34.6 (CH₂), 32.4 (CH₂), 26.9 (CH₂),

20.6 (CH₃), 15.7 (CH₃); **IR** (neat) 1649 cm⁻¹; **MS** (EI) 298.2 (M⁺); **HRMS** (EI) Calcd for C₁₉H₂₆N₂O (M⁺) 298.2045, found 298.2049; [α]_D -206.3 (c 1.00, MeOH). **Diastereomer 2** as a white solid (106.1 mg, 7 %). **¹H NMR** (CDCl₃, 400 MHz) 7.43-7.16 (m, 5H), 5.73 (q, *J* = 7.2 Hz, 1H), 3.53 (d, *J* = 11.6 Hz, 1H), 2.44 (d, *J* = 17.2 Hz, 1H), 2.29 (d, *J* = 17.2 Hz, 1H), 2.22-2.14 (m, 1H), 1.72-1.59 (m, 2H), 1.59-1.50 (m, 2H), 1.48-1.39 (m, 1H), 1.43 (d, *J* = 7.2 Hz, 3H), 1.08-0.92 (m, 2H), 0.99 (s, 3H), 0.79 (s, 3H); **¹³C NMR** (CDCl₃, 100 MHz) 172.0 (C), 141.2 (C), 128.0 (CH), 127.6 (CH), 127.2 (CH), 66.6 (CH), 52.0 (CH), 49.7 (C), 47.2 (C), 43.8 (CH), 34.6 (CH₂), 34.4 (CH₂), 32.5 (CH₂), 26.7 (CH₂), 20.7 (CH₃), 20.5 (CH₃), 16.7 (CH₃); **IR** (neat) 1654 cm⁻¹; **MS** (EI) 298.2 (M⁺); **HRMS** (EI) Calcd for C₁₉H₂₆N₂O (M⁺) 298.2045, found 298.2046; **Mp** 132-134 °C. [α]_D +76.9 (c 1.00, MeOH).



1-(iodomethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (113)

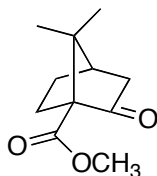
To a dry 250 mL round bottom flask was added (+)-camphorsulfonic acid (2.00 g, 8.61 mmol). Dry toluene (50 mL) was added, followed by triphenylphosphine (11.3 g, 43.05 mmol). The reaction mixture was protected from light by wrapping in aluminum foil. Iodine (4.37 g, 17.2 mmol) was added, and the reaction mixture heated to reflux for 1.5 hours, then stirred at room temperature for 18 hours. The mixture was then diluted with benzene (100 mL), washed with water (3 x 50 mL), dried over MgSO₄, filtered, and concentrated *in vacuo* to provide the crude product. Purification by flash chromatography (100 % benzene) afforded compound **113**^{81a} as a white powder (1.46 g, 61 %). **¹H NMR** (CDCl₃, 400 MHz) 3.31 (d, *J* = 10.8 Hz, 1H), 3.11 (d, *J* = 10.8 Hz, 1H), 2.43-2.37 (m, 1H), 2.16 (dd, *J* = 4.0, 4.0 Hz, 1H), 2.05-1.88 (m, 2H), 1.91 (d, *J* = 18.4 Hz, 1H), 1.66-1.57 (m, 1H), 1.45-1.34 (m, 1H), 1.07 (s, 3H), 0.90 (s, 3H).



***tert*-butyl-2-(1-(iodomethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-ylidene)hydrazinecarboxylate**

(116)

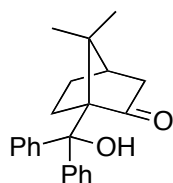
To a dry 100 mL round bottom flask was added **113** (530 mg, 1.91 mmol) as a solution in benzene (25 mL). *tert*-Butyl carbazate (302 mg, 2.29 mmol) was then added, followed by TsOH•H₂O (36 mg, 0.19 mmol), and the mixture heated to reflux for 24 hours. The white precipitate produced during the course of the reaction was removed by filtration, rinsing with copious amounts of ether, and the filtrate was washed with saturated NaHCO₃ (50 mL) and brine (50 mL). The organic layer was then dried over MgSO₄, filtered, and concentrated *in vacuo* to obtain the crude product. Purification by flash chromatography gave rise to **116** as a white solid (151 mg, 45 % brsm). ¹H NMR (CDCl₃, 400 MHz) 7.20 (s, 1H), 3.61 (d, *J*= 10.4 Hz, 1H), 3.29 (d, *J*= 10.8 Hz, 1H), 2.31 (ddd, *J*= 16.4, 4.0, 4.0 Hz, 1H), 2.09 (ddd, *J*= 12.4, 12.4, 4.0 Hz, 1H), 2.04 (dd, *J*= 4.4, 4.4 Hz, 1H), 1.96-1.85 (m, 1H), 1.79 (d, *J*= 16.4 Hz, 1H), 1.62-1.53 (m, 1H), 1.50 (s, 9H), 1.24 (ddd, *J*= 12.8, 9.2, 4.0 Hz, 1H), 1.07 (s, 3H), 0.81 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) 80.9 (C), 53.8 (C), 49.4 (C), 45.3 (CH), 32.7 (CH₂), 32.5 (CH₂), 28.3 (CH₃), 27.1 (CH₂), 20.2 (CH₃), 19.7 (CH₃), 3.6 (CH₂); IR (neat) 1714, 1688 cm⁻¹; MS (EI) 292.0 (M-C₅H₈O₂); HRMS (EI) Calcd for C₁₀H₁₇N₂I (M-C₅H₈O₂) 292.0436, found 292.0436; Mp 162-164 °C.



Methyl 7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-carboxylate (146)

Methanol (30 mL) was stirred in a 100 mL round bottom flask and cooled to 0 °C using an ice bath. Thionyl chloride (4 mL, 54.9 mmol) was then slowly added via syringe. To this solution was introduced (S)-(+)-ketopinic acid¹⁰⁰ in four portions, waiting five minutes between additions. The resulting reaction mixture was stirred at 0 °C for 4 hours, allowed to warm to room temperature over 18 hours, and then concentrated under reduced pressure using a rotary evaporator. The resulting residue

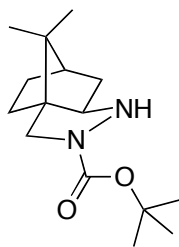
was diluted with ethyl acetate (50 mL). Water (50 mL) was added and the phases were separated. The aqueous phase was extracted once more with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (100 mL), and brine (100 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (5 to 20% EtOAc in hexanes) to afford **146** as white needles (2.09 g, 98 %). ^1H NMR (300 MHz, CDCl_3) δ 3.73 (s, 3H), 2.51 (ddd, J = 18.3, 3.9, 3.9 Hz, 1H), 2.40-2.27 (m, 1H), 2.09 (dd, J = 4.2, 4.2 Hz, 1H), 2.07-1.95 (m, 1H), 1.93 (d, J = 18.3 Hz, 1H), 1.77 (ddd, J = 13.8, 9.6, 5.1 Hz, 1H), 1.39 (ddd, J = 12.3, 9.3, 4.2 Hz, 1H), 1.13 (s, 3H), 1.06 (s, 3H). Spectral data matched those previously reported.¹⁰¹



1-(hydroxydiphenylmethyl)-7,7-dimethylbicyclo[2.2.1] heptan-2-one (145)

Magnesium turnings (1.2 g, 51.2 mmol) and a few small crystals of I_2 were placed under a nitrogen atmosphere in a 100 mL round bottom flask equipped with a condenser. The flask was then warmed gently using a heat gun to vaporize the iodine, and the apparatus allowed to stand until the color of the iodine vapor disappeared. Into this flask was introduced one half of a solution of bromobenzene (4.5 mL, 42.7 mmol) in dry THF (30 mL). The solution was stirred until an exothermic reaction was observed, bringing it to reflux. As the reflux began to subside, the other half of the bromobenzene solution was added, and the reaction was heated to reflux for 1 hour using a heating mantle, and then cooled to 0 °C in an ice bath. Methyl ester **146** (1.37g, 6.48 mmol) was then introduced in one portion and the resulting mixture stirred at 0 °C for 1 hour. The reaction was quenched with a saturated solution of ammonium chloride (20 mL). Water (50 mL) was then added and the resulting mixture was then extracted twice with EtOAc (50 mL portions). The combined organic extracts were washed with brine (50 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. Pure **145** (924 mg, 60 %) was obtained as clear crystals after recrystallization from 1:4 EtOAc:hexanes. ^1H NMR (300 MHz, CDCl_3) δ 7.53-

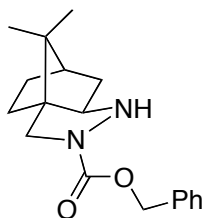
7.15 (m, 10H), 3.82 (s, 1H), 2.57-2.45 (m, 2H), 2.29 (ddd, $J = 13.8, 9.6, 5.1$ Hz, 1H), 1.99-1.87 (m, 1H), 1.97 (d, $J = 18.6$ Hz, 1H), 1.78 (dd, $J = 4.8, 4.8$ Hz, 1H), 1.42 (ddd, $J = 12.0, 9.3, 3.9$ Hz, 1H), 1.07 (s, 3H), 0.27 (s, 3H). Spectral data matched those previously reported.¹⁰²



10,10-Dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decane-3-carboxylic acid *tert*-butyl ester (121**)**

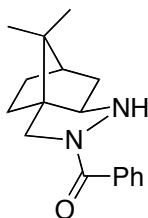
To a dry 10 mL round bottom flask containing **113** (58.4 mg, 0.21 mmol) was added benzene (3 mL). *tert*-Butyl carbazate (139 mg, 1.05 mmol) was added, followed by TsOH•H₂O (4 mg, 0.021 mmol), and the mixture heated to reflux for 46 hours. Benzene (50 mL) was added and the organic layer washed with saturated NaHCO₃ (25 mL) and brine (25 mL). The organic phase was then dried over MgSO₄, filtered, and concentrated. Purification by flash chromatography (15 % EtOAc/hexanes) provided the cyclized hydrazone **117** as a white powder (36 mg, 65 %). ¹H NMR (CDCl₃, 400 MHz) 3.61 (d, $J = 11.2$ Hz, 1H), 3.46 (d, $J = 11.6$ Hz, 1H), 2.57 (ddd, $J = 17.6, 4.0, 2.0$ Hz, 1H), 2.10 (dd, $J = 4.0, 4.0$ Hz, 1H), 2.03 (d, $J = 17.6$ Hz, 1H), 1.98-1.85 (m, 2H), 1.70-1.62 (m, 1H), 1.52 (s, 9H), 1.36-1.28 (m, 1H), 0.96 (s, 3H), 0.89 (s, 3H). The cyclic hydrazone **117** (100 mg, 0.38 mmol) was subsequently dissolved in MeOH (2.7 mL) and AcOH (1.3 mL) in a 25 mL round bottom flask under nitrogen atmosphere. NaCNBH₃ (238 mg, 3.78 mmol) was added in four portions over one hour, and the mixture stirred at room temperature for 18 hours. The reaction was quenched with 10 % HCl (5 mL) and allowed to stir for 30 minutes. The mixture was then poured into a separatory funnel and washed with ether (10 mL). The aqueous phase was then basified with NaOH pellets (pH > 11), and extracted with DCM (3 x 25 mL). The combined organics were then washed with brine (25 mL), dried over MgSO₄, filtered, and concentrated to obtain pure **121** (52.1 mg, 51 %). ¹H NMR (CDCl₃, 300 MHz) 3.87 (s, 1H), 3.36 (d, $J = 11.1$ Hz, 1H), 3.30 (d, $J = 11.4$ Hz, 1H), 3.20 (dd, $J = 8.1, 3.9$ Hz, 1H), 1.96-1.74 (m, 4H), 1.64 (dd, $J = 13.2, 8.7$ Hz, 1H), 1.47 (s, 9H), 1.31-1.19 (m, 2H), 1.04 (s, 3H), 0.91 (s, 3H); ¹³C NMR (CDCl₃, 75

MHz) 154.4 (C), 79.9 (C), 69.5 (CH), 58.7 (C), 46.4 (CH), 46.3 (CH₂), 45.8 (C), 35.4 (CH₂), 29.7 (CH₂), 28.5 (CH₃), 26.8 (CH₂), 21.3 (CH₃), 20.5 (CH₃); **IR** (neat) 3274, 2959, 1685 cm⁻¹; **MS** (EI) 266.2 (M⁺); **HRMS** (EI) Calcd for C₁₅H₂₆N₂O₂ (M⁺) 266.1994, found 266.1988; **Mp** 74-76 °C.



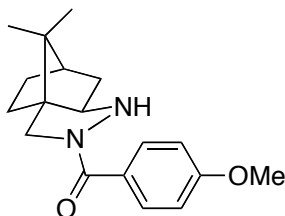
10,10-Dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decane-3-carboxylic acid benzyl ester (122)

Cyclic hydrazone of **122** was prepared according to a procedure similar to that described for **121**, using **113** (1.00 g, 3.60 mmol), benzyl hydrazinecarboxylate (1.50 g, 9.00 mmol), TsOH•H₂O (137 mg, 0.72 mmol), and *i*PrOH (40 mL) to afford the cyclic hydrazone (564 mg, 53 %) as a clear oil after flash chromatography (20 % EtOAc/hexanes). **¹H NMR** (CDCl₃, 300 MHz) 7.44-7.30 (m, 5H), 5.32-5.10 (m, 2H), 3.69 (d, *J* = 11.4 Hz, 1H), 3.54 (d, *J* = 11.4 Hz, 1H), 2.58 (ddd, *J* = 17.7, 3.9, 1.8 Hz, 1H), 2.15-1.88 (m, 4H), 1.74-1.64 (m, 1H), 1.43-1.34 (m, 1H), 0.98 (s, 3H), 0.90 (s, 3H). The cyclic hydrazone (564 mg, 1.89 mmol) was then subjected to reduction using a procedure similar to that described for **121** to afford **122** (285 mg, 50 %) as a clear oil. **¹H NMR** (CDCl₃, 400 MHz) 7.43-7.27 (m, 5H), 5.21 (d, *J* = 9.2 Hz, 1H), 5.14 (d, *J* = 12.4 Hz, 1H), 3.50 (d, *J* = 11.2 Hz, 1H), 3.44 (d, *J* = 11.2 Hz, 1H), 3.40-3.34 (m, 1H), 2.17-2.05 (m, 1H), 1.98-1.77 (m, 3H), 1.70 (dd, *J* = 13.2, 8.4 Hz, 1H), 1.32-1.23 (m, 2H), 1.06 (s, 3H), 0.92 (s, 3H); **¹³C NMR** (CDCl₃, 100 MHz) 136.6 (C), 128.5 (CH), 128.4 (CH), 128.2 (C), 128.1 (CH), 77.2 (CH), 67.3 (CH₂), 46.7 (CH₂), 46.5 (CH), 46.0 (C), 35.2 (CH₂), 29.7 (CH₂), 26.8 (CH₂), 21.2 (CH₃), 20.6 (CH₃); **IR** (neat) 3272, 2880, 1694 cm⁻¹; **MS** (EI) 300.2 (M⁺); **HRMS** (EI) Calcd for C₁₈H₂₄N₂O₂ (M⁺) 300.1838, found 300.1848; [α]_D +7.5 (*c* 1.00, MeOH).



(10,10-Dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-3-yl)-phenyl-methanone (123)

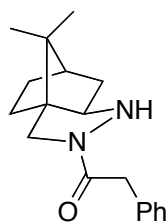
Cyclic hydrazone of **123** was prepared according to a procedure similar to that described for **121**, using **113** (20 mg, 0.07 mmol), benzoic hydrazide (49 mg, 0.36 mmol), TsOH•H₂O (3 mg, 0.014 mmol), and EtOH (3 mL) to afford the cyclic hydrazone (7.1 mg, 38 %) as a clear oil after flash chromatography (20 % EtOAc/hexanes). ¹H NMR (CDCl₃, 300 MHz) 7.84-7.81 (m, 2H), 7.46-7.36 (m, 3H), 3.94 (d, *J*= 12.9 Hz, 1H), 3.77 (d, *J*= 12.9 Hz, 1H), 2.59 (ddd, *J*= 17.7, 3.9, 2.1 Hz, 1H), 2.18 (dd, *J*= 4.2 Hz, 4.2 Hz, 1H), 2.08 (d, *J*= 17.7 Hz, 1H), 2.08-1.95 (m, 2H), 1.76-1.69 (m, 1H), 1.49-1.37 (m, 1H), 1.04 (s, 3H), 0.92 (s, 3H). The cyclic hydrazone (165 mg, 0.61 mmol) was then subjected to reduction using a procedure similar to that described for **121** to afford **123** (122 mg, 74 %) as a clear oil. ¹H NMR (DMSO-*d*₆, 400 MHz) Mixture of rotamers: 7.67-7.26 (m, 5H), 5.39 (d, *J*= 5.8 Hz, 1H), 3.68 (d, *J*= 12.4 Hz, 1H), 3.43 (d, *J*= 12.4 Hz, 1H), 3.21-3.11 (m, 1H), 1.99-1.67 (m, 4H), 1.58-1.47 (m, 1H), 1.30-1.15 (m, 2H), 1.08 (s, 0.6H), 0.99 (s, 2.4H), 0.91 (s, 2.4H), 0.79 (s, 0.6H); ¹³C NMR (CDCl₃, 100 MHz) Mixture of rotamers: 135.7 (C), 130.0 (CH), 128.3 (CH), 127.7 (CH), 127.5 (C), 71.0 (CH), 67.0 (CH₂), 58.1 (C), 48.9 (CH₂), 46.7 (CH), 46.4 (CH), 46.0 (CH₂), 36.1 (CH₂), 34.7 (CH₂), 29.6 (CH₂), 26.8 (CH₂), 21.2 (CH₃), 20.7 (CH₃); IR (neat) 3264, 2955, 2879, 1614 cm⁻¹; MS (EI) 270.2 (M⁺); HRMS (EI) Calcd for C₁₇H₂₂N₂O (M⁺) 270.1732, found 270.1738; [α]_D -4.5 (c 1.00, MeOH).



(10,10-Dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-3-yl)-(4-methoxy-phenyl)-methanone (124)

Cyclic hydrazone of **124** was prepared according to a procedure similar to that described for **121**, using **113** (500 mg, 1.80 mmol), 4-methoxybenzoic hydrazide (746 mg, 4.49 mmol), TsOH•H₂O (68

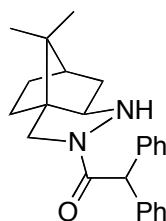
mg, 0.36 mmol), and *i*PrOH (18 mL) to afford the cyclic hydrazone (440 mg, 82 %) as an off-white powder after flash chromatography (20 % EtOAc/hexanes). **¹H NMR** (CDCl₃, 300 MHz) 7.89-7.85 (m, 2H), 6.91-6.87 (m, 2H), 3.91 (d, *J*= 12.6 Hz, 1H), 3.82 (s, 3H), 3.75 (d, *J*= 12.9 Hz, 1H), 2.58 (ddd, *J*= 17.7, 4.2, 2.7 Hz, 1H), 2.16 (dd, *J*= 3.9, 3.9 Hz, 1H), 2.07 (d, *J*= 17.7 Hz, 1H), 2.00 (m, 2H), 1.69 (m, 1H), 1.41 (m, 1H), 1.02 (s, 3H), 0.90 (s, 3H). The cyclic hydrazone (206 mg, 0.69 mmol) was then subjected to reduction using a procedure similar to that described for **121** to afford **124** (85.3 mg, 41 %) as a white flaky powder after flash chromatography (30 % EtOAc/hexanes + 1% NEt₃). **¹H NMR** (DMSO-*d*₆, 400 MHz) 7.74-7.64 (m, 2H), 6.98-6.85 (m, 2H), 5.36 (d, *J*= 10.8 Hz, 1H), 3.78 (s, 3H), 3.64 (d, *J*= 12.0 Hz, 1H), 3.44 (d, *J*=12.4 Hz, 1H), 3.21-3.09 (m, 1H), 1.95-1.68 (m, 4H), 1.53 (dd, *J*= 12.4, 8.4 Hz, 1H), 1.29-1.16 (m, 2H), 0.99 (s, 3H), 0.89 (s, 3H); **¹³C NMR** (DMSO-*d*₆, 100 MHz) 160.3 (C), 130.6 (CH), 128.3 (C), 127.9 (C), 112.5 (CH), 69.5 (CH), 55.1 (CH₃), 45.9 (CH), 45.6 (CH₂), 35.2 (CH₂), 29.3 (CH₂), 26.4 (CH₂), 20.8 (CH₃), 20.3 (CH₃); **IR** (neat) 3279, 1601 cm⁻¹; **MS** (EI) 300.2 (M⁺); **HRMS** (EI) Calcd for C₁₈H₂₄N₂O₂ (M⁺) 300.1838, found 300.1846; **Mp** 164-166 °C; [α]_D -13.4 (*c* 1.00, MeOH).



1-(10,10-Dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-3-yl)-2-phenyl-ethanone (136)

Cyclic hydrazone of **136** was prepared according to a procedure similar to that described for **121**, using **113** (416 mg, 1.50 mmol), 2-phenylacetic hydrazide (562 mg, 3.74 mmol), TsOH•H₂O (57 mg, 0.30 mmol), and *i*PrOH (10 mL) to afford the cyclic hydrazone (172 mg, 40 %) as a clear oil after flash chromatography (20 % EtOAc/hexanes). **¹H NMR** (CDCl₃, 300 MHz) 7.35-7.18 (m, 5H), 3.99 (d, *J*= 14.4 Hz, 1H), 3.91 (d, *J*= 14.4 Hz, 1H), 3.75 (d, *J*= 12.6 Hz, 1H), 3.54 (d, *J*= 12.6 Hz, 1H), 2.59 (ddd, *J*= 17.7, 4.2, 2.1 Hz, 1H), 2.17 (dd, *J*= 4.2, 4.2 Hz, 1H), 2.09 (d, *J*= 17.7 Hz, 1H), 2.02-1.90 (m, 2H), 1.69-1.58 (m, 1H), 1.43-1.33 (m, 1H), 0.99 (s, 3H), 0.88 (s, 3H). The cyclic hydrazone (123 mg, 0.43

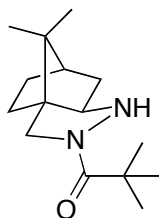
mmol) was then subjected to reduction using a procedure similar to that described for **121** to afford **136** (70 mg, 57 %) as a clear oil after flash chromatography (30 % EtOAc/hexanes + 1% NEt₃). **¹H NMR** (DMSO-d₆, 400 MHz) 7.34-7.15 (m, 5H), 5.23 (d, *J* = 11.6 Hz, 1H), 3.73 (d, *J* = 14.8 Hz, 1H), 3.62 (d, *J* = 14.8 Hz, 1H), 3.48 (d, *J* = 12.4 Hz, 1H), 3.18 (m, 2H), 1.82 (m, 4H), 1.60 (dd, *J* = 12.4, 8.4 Hz, 1H), 1.24 (d, *J* = 9.6 Hz, 1H), 1.20 (d, *J* = 10.4 Hz, 1H), 0.94 (s, 3H), 0.86 (s, 3H); **¹³C NMR** (DMSO-d₆, 100 MHz) 169.3 (C), 136.2 (C), 129.4 (CH), 128.0 (CH), 126.0 (CH), 68.9 (CH), 57.7 (C), 45.9 (CH), 45.6 (C), 44.8 (CH₂), 39.5 (CH₂), 35.5 (CH₂), 29.2 (CH₂), 26.4 (CH₂), 20.8 (CH₃), 20.1 (CH₃); **IR (neat)** 3507, 3251, 2879, 1646 cm⁻¹; **MS (EI)** 284.2 (M⁺); **HRMS (EI)** Calcd for C₁₈H₂₄N₂O (M⁺) 284.1889, found 284.1873.



1-(10,10-Dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-3-yl)-2,2-diphenyl-ethanone (137)

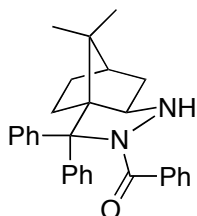
Cyclic hydrazone of **137** was prepared according to a procedure similar to that described for **121**, using **113** (400 mg, 1.44 mmol), 2, 2-diphenylacetic hydrazide (814 mg, 3.60 mmol), TsOH•H₂O (55 mg, 0.30 mmol), and *i*PrOH (20 mL) to afford the cyclic hydrazone (486 mg, 94 %) as a clear oil after flash chromatography (15 % EtOAc/hexanes). **¹H NMR** (CDCl₃, 300 MHz) 7.52-7.18 (m, 10H), 5.93 (s, 1H), 3.80 (d, *J* = 12.9 Hz, 1H), 3.59 (d, *J* = 12.6 Hz, 1H), 2.55 (ddd, *J* = 18.0, 4.5, 2.1 Hz, 1H), 2.15 (dd, *J* = 3.9, 3.9 Hz, 1H), 2.05 (d, *J* = 17.7 Hz, 1H), 2.05-1.89 (m, 2H), 1.63-1.57 (m, 1H), 1.40-1.33 (m, 1H), 0.99 (s, 3H), 0.84 (s, 3H). The cyclic hydrazone (486 mg, 1.36 mmol) was then subjected to reduction using a procedure similar to that described for **121** to afford **137** (137 mg, 28 %) as a clear oil after performing an acid-base extraction to eliminate impurities. **¹H NMR** (CDCl₃, 400 MHz) 7.39-7.27 (m, 8H), 7.24-7.17 (m, 2H), 5.69 (s, 1H), 3.58 (d, *J* = 12.4 Hz, 1H), 3.50 (d, *J* = 12.4 Hz, 1H), 3.17-3.11 (m, 1H), 1.98-1.74 (m, 4H), 1.69-1.61 (m, 1H), 1.31-1.19 (m, 2H), 0.91 (s, 3H); **¹³C NMR** Unable to obtain

due to decomposition; **IR** (neat) 1638 cm^{-1} ; **MS** (EI) 358.2 (M-2H); **HRMS** (EI) Calcd for $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}$ (M-2H) 358.2045, found 358.2046.



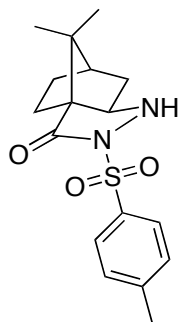
1-(10,10-Dimethyl-3,4-diaza-tricyclo[5.2.1.0^{1,5}]dec-3-yl)-2,2-dimethyl-propan-1-one (138)

Cyclic hydrazone of **138** was prepared according to a procedure similar to that described for **121**, using **113** (500 mg, 1.80 mmol), pivaloyl hydrazide (522 mg, 4.49 mmol), $\text{TsOH}\cdot\text{H}_2\text{O}$ (68 mg, 0.36 mmol), and *i*PrOH (18 mL) to afford the cyclic hydrazone (356 mg, 80 %) as a white solid after flash chromatography (10 % EtOAc/hexanes). **¹H NMR** (CDCl_3 , 300 MHz) 3.73 (d, J = 12.6 Hz, 1H), 3.54 (d, J = 12.6 Hz, 1H), 2.57 (ddd, J = 17.7, 4.2, 2.1 Hz, 1H), 2.15 (dd, J = 4.2, 4.2 Hz, 1H), 2.07 (d, J = 17.4 Hz, 1H), 1.95 (m, 2H), 1.58 (m, 1H), 1.39 (m, 1H), 1.30 (s, 9H), 0.99 (s, 3H), 0.86 (s, 3H). The cyclic hydrazone (187 mg, 0.75 mmol) was then subjected to reduction with a procedure similar to that described for **121** to afford **138** (71 mg, 38 %) as a white solid after performing an acid-base extraction to eliminate impurities. **¹H NMR** (CDCl_3 , 400 MHz) 3.61 (d, J = 12.4 Hz, 1H), 3.54 (s, 1H), 3.30 (d, J = 12.4 Hz, 1H), 3.09-2.98 (m, 1H), 1.99-1.77 (m, 4H), 1.70 (dd, J = 12.8, 8.4 Hz, 1H), 1.33-1.18 (m, 2H), 1.25 (s, 9H), 1.04 (s, 3H), 0.92 (s, 3H); **¹³C NMR** (CDCl_3 , 100 MHz) 46.9 (CH_2), 46.4 (CH), 45.8 (C), 39.1 (C), 34.0 (CH_2), 34.0 (C), 29.9 (CH_2), 26.9 (CH_3), 26.8 (CH_2), 21.5 (CH_3), 20.8 (CH_3); **IR** (neat) 1623 cm^{-1} ; **MS** (EI) 250.2 (M^+); **HRMS** (EI) Calcd for $\text{C}_{15}\text{H}_{26}\text{N}_2\text{O}$ (M^+) 250.2045, found 250.2033. **Mp** 97-99 °C.



(10,10-Dimethyl-3,4-diaza-4-diphenyl-tricyclo[5.2.1.0^{1,5}]dec-3-yl)-phenyl-methanone (143)

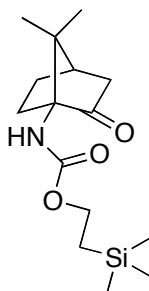
Benzyl hydrazide (16 mg, 0.12 mmol) was added to a 2 mL microwave vial. Dry DCM (1.5 mL) was added via syringe, followed by TsOH•H₂O (23 mg, 0.12 mmol). The resulting solution was heated in the microwave for 10 minutes at 50 °C. The reaction was cooled to room temperature, and compound **145** (20 mg, 0.06 mmol) was added. The resulting mixture was then heated in the microwave for 30 minutes at 140 °C. The reaction mixture was cooled to room temperature, then diluted with DCM (50 mL). The organic phase was washed with saturated NaHCO₃ (25 mL) then dried over MgSO₄, filtered, and concentrated to obtain an inseparable mixture (~ 3:1) of the cyclized hydrazone **144** and a byproduct (22.3 mg). The material (~7.4 mg of **144**, 0.02 mmol) was subsequently reduced using a procedure similar to that described for **121** to obtain a trace amount of the title compound as a clear residue after both flash chromatography (5-20 % EtOAc/hexanes) and preparatory thin layer chromatography (40 % EtOAc/hexanes). **¹H NMR** (CDCl₃, 400 MHz) 8.06-7.99 (m, 2H), 7.55-7.46 (m, 3H), 7.30-7.10 (m, 10H), 2.97 (dd, *J*= 15.2, 4.0 Hz, 1H), 2.74 (dd, *J*= 15.2, 11.2 Hz, 1H), 2.45-2.31 (m, 2H), 2.25-2.16 (m, 1H), 1.89-1.79 (m, 1H), 1.51-1.39 (m, 2H), 1.02 (s, 3H), 0.87 (s, 3H); **¹³C NMR** (CDCl₃, 100 MHz) 147.8 (C), 142.4 (C), 135.9 (C), 131.5 (CH), 129.6 (CH), 128.9 (CH), 128.3 (CH), 128.0 (CH), 127.8 (CH), 126.7 (CH), 126.3 (CH), 126.0 (CH), 124.0 (C), 77.2 (CH), 49.8 (CH), 44.9 (C), 31.4 (CH₂), 27.8 (CH₂), 26.9 (CH₃), 25.9 (CH₂), 22.8 (CH₃); **IR (neat)** 2927 cm⁻¹; **MS** (EI) 420.2 (M-2H); **HRMS** (EI) Calcd for C₂₉H₂₈N₂O (M-2H) 420.2202, found 420.2193.



10,10-Dimethyl-3-(toluene-4-sulfonyl)-3,4-diaza-tricyclo[5.2.1.0^{1,5}]decan-2-one (104)

To a dry 50 mL round bottom flask was added (+)-ketopinic acid (500 mg, 2.74 mmol). Dry DCM (10 mL) was added, followed by 4-methylbenzenesulfonylhydrazide (767 mg, 4.10 mmol). The mixture was stirred at room temperature for 18 hours, and subsequently diluted with water (25 mL) and DCM (50 mL). The aqueous layer was then extracted with DCM (3 x 50 mL), and the combined organics dried over MgSO₄, filtered, and concentrated to obtain the crude product. Purification by flash chromatography (40 % EtOAc/hexanes) afforded the acyclic hydrazone **107** as a white solid (756 mg, 79 %). ¹H NMR (CDCl₃, 400 MHz) 7.82-7.80 (m, 2H), 7.36-7.34 (m, 2H), 2.50 (ddd, *J*= 17.6, 3.2, 3.2 Hz, 1H), 2.46-2.37 (m, 1H), 2.43 (s, 3H), 2.10-2.02 (m, 2H), 1.97 (d, *J*= 18.0 Hz, 1H), 1.69-1.63 (m, 1H), 1.35-1.27 (m, 1H), 1.19 (s, 3H), 0.79 (s, 3H). This material (756 mg, 2.15 mmol) was then subjected to cyclization in a 100 mL round bottom flask under nitrogen atmosphere. A 3-way valve was attached, and ethyl acetate (25 mL) was added via syringe. Thionyl chloride (0.63 mL, 8.63 mmol) was added via syringe, and the apparatus fitted with a reflux condenser. The mixture was refluxed for 4 hours, and subsequently quenched with water (25 mL). The aqueous phase was then extracted with ethyl acetate (3 x 50 mL), and the combined organics dried over MgSO₄, filtered, and concentrated to obtain the cyclized hydrazone **106** as a white powder (539 mg, 75 %). ¹H NMR (CDCl₃, 400 MHz) 7.94-7.92 (m, 2H), 7.33-7.30 (m, 2H), 2.59 (ddd, *J*= 17.6, 3.2, 3.2 Hz, 1H), 2.43 (s, 3H), 2.26-2.19 (m, 2H), 2.16 (d, *J*= 18.0 Hz, 1H), 2.12-2.05 (m, 1H), 1.72 (ddd, *J*= 13.6, 9.6, 4.4 Hz, 1H), 1.48 (ddd, *J*= 13.2, 9.2, 4.4 Hz, 1H), 1.12 (s, 3H), 0.63 (s, 3H). This material (539 mg, 1.62 mmol) was subsequently reduced according to a procedure similar to that described for **121** to afford the product **104** as a white solid (195 mg, 36 %) after flash chromatography (15 % EtOAc/hexanes). ¹H NMR (CDCl₃, 400 MHz) 7.96-7.91

(m, 2H), 7.35-7.29 (m, 2H), 3.49 (dd, J = 8.0, 4.4 Hz, 1H), 2.44 (s, 3H), 2.12-2.00 (m, 2H), 1.90-1.80 (m, 2H), 1.66 (dd, J = 13.2, 8.4 Hz, 1H), 1.27-1.14 (m, 2H), 0.94 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (CDCl₃, 100 MHz) 172.2 (C), 145.3 (C), 134.6 (C), 129.5 (CH), 128.5 (CH), 64.7 (CH), 59.0 (C), 52.6 (C), 47.3 (CH), 36.5 (CH₂), 29.0 (CH₂), 26.6 (CH₂), 21.7 (CH₃), 20.6 (CH₃), 19.8 (CH₃); **IR** (neat) 3323, 3300, 1759, 1745 cm⁻¹; **HRMS** (EI) Unable to obtain satisfactory spectrum; **Mp** 128-130 °C.



2-(trimethylsilyl)ethyl 7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-ylcarbamate (161)

To a dry 10 mL round bottom flask under inert atmosphere was added (+)-ketopinic acid (50 mg, 0.27 mmol). Dry toluene (3 mL) was added, followed by NEt₃ (0.08 mL, 0.54 mmol). (PhO)₂P(O)N₃ (0.09 mL, 0.41 mmol) was added via syringe, and the mixture heated to reflux for 1.5 hours. The mixture was cooled to room temperature, and TMS-EtOH (0.19 mL, 1.35 mmol) was added via syringe. The reaction was heated to reflux once again for 18 hours. EtOAc (50 mL) was added, and the organic phase washed with 10 % NaOH (25 mL), then dried over MgSO₄, filtered, and concentrated to obtain the crude product. Purification by flash chromatography (10-50 % EtOAc/hexanes) provided the title compound **161** as a clear oil (71.6 mg, 89 %). ^1H NMR (CDCl₃, 400 MHz) 5.15 (s, 1H), 4.16-4.07 (m, 2H), 3.09-2.95 (m, 1H), 2.41 (ddd, J = 18.4, 4.4, 3.6 Hz, 1H), 2.19-2.08 (m, 1H), 2.04 (dd, J = 4.8, 4.8 Hz, 1H), 2.01 (d, J = 18.8 Hz, 1H), 1.49-1.32 (m, 2H), 1.21 (s, 3H), 1.02-0.94 (m, 2H), 0.84 (s, 3H), 0.03 (s, 9 H); ^{13}C NMR (CDCl₃, 100 MHz) 213.6 (C), 72.3 (C), 62.8 (CH₂), 47.8 (C), 41.3 (CH₂), 40.3 (CH), 26.4 (CH₂), 20.9 (CH₃), 19.1 (CH₃), 17.6 (CH₂), -1.5 (CH₃); **IR** (neat) 2955, 2361, 1729, 1509 cm⁻¹; **MS** (EI) 297.2 (M⁺); **HRMS** (EI) Calcd for C₁₅H₂₇NO₃Si (M⁺) 297.1760, found 297.1705; [α]_D -20.6° (c 1.00, MeOH).



General Procedure for Diels Alder Reactions: (1*R*, 2*R*, 3*R*, 4*S*)-3-phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde and (1*S*, 2*S*, 3*S*, 4*R*)-3-phenylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde

To a 10 mL round bottom flask containing **123** (17.2 mg, 0.06 mmol) under an atmosphere of nitrogen was added THF (0.1 mL). Water (0.9 mL) was added, followed by a 1.16 M solution of HClO₄ in water (55 μ L, 0.06 mmol). Distilled (*E*)-cinnamaldehyde (40 μ L, 0.32 mmol) was added, followed by freshly distilled cyclopentadiene (0.07 mL, 0.96 mmol). The resulting mixture was stirred for 48 hours at room temperature. The mixture was then diluted with ether (25 mL), and the aqueous phase was extracted twice more with ether (2 x 25 mL). The organic phases were combined and washed with brine (25 mL), dried over MgSO₄, filtered, and concentrated to obtain the crude product as a pale yellow oil (52.3 mg, 83 % conversion). *Endo/Exo* ratios were determined by examining the aldehyde protons in the ¹H NMR spectra. Enantiomeric excesses were determined by conversion of the aldehydes into the corresponding (R, R)-hydrobenzoin acetals.⁵⁵

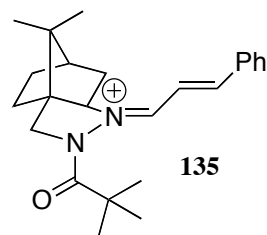
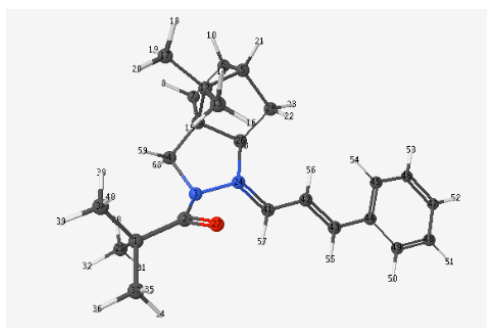
General Procedure for Addition to Azomethine Ylides: (1*S*, 2*R*, 3*R*)-3-methyl-5-oxo-1-phenylhexahydropyrazolo[1,2-*a*]pyrazole-2-carbaldehyde and (1*R*, 2*R*, 3*R*)-3-methyl-5-oxo-1-phenylhexahydropyrazolo[1,2-*a*]pyrazole-2-carbaldehyde

To a 4 mL screw cap vial under inert atmosphere was added **22** (9 mg, 0.034 mmol). THF (1 mL) was added, followed by water (10 μ L). *p*-nitrobenzoic acid (5 mg, 0.034 mmol) was added, followed by **31**¹⁰³ (30 mg, 0.17 mmol). (*E*)-crotonaldehyde (0.03 mL, 0.34 mmol) was added, and the reaction mixture stirred at room temperature for 48 hours. The mixture was then diluted with EtOAc (25 mL), washed with water (25 mL), dried over MgSO₄, filtered, and concentrated to obtain the crude products. *Endo/Exo* ratios were determined by comparison of the aldehyde signals in the ¹H NMR of the crude products. The compounds were then purified by flash chromatography (90-100 % EtOAc/hexanes) and

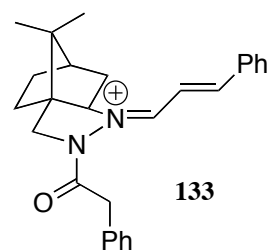
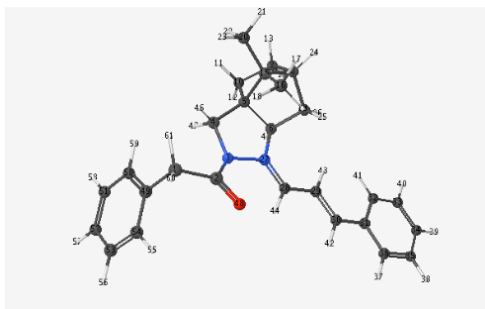
subjected to reduction with NaBH₄ to obtain the corresponding alcohols. The enantiomeric excesses of these alcohols could be determined by chiral HPLC (10 % *i*ProH/hexanes, 0.1 % DEA, 1 mL/min, CHOD column).

COMPUTATIONAL METHODS

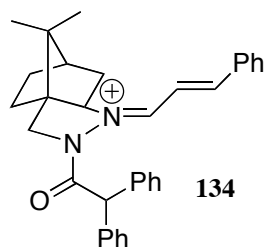
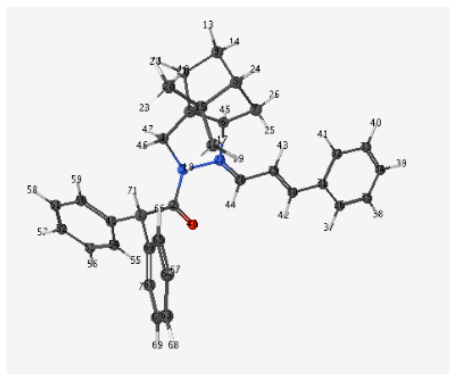
Calculations for the dihedral driver experiments were carried out at the PM3 semi-empirical level of theory using the Gaussian '09 suite of programs. The energy of the conformations produced from rotating about the C-N-C(O)-C bond for each derivative was measured in order to find the dihedral angle that produced the lowest energy conformations.



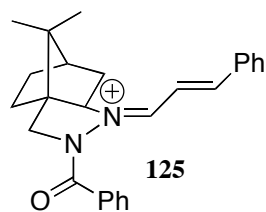
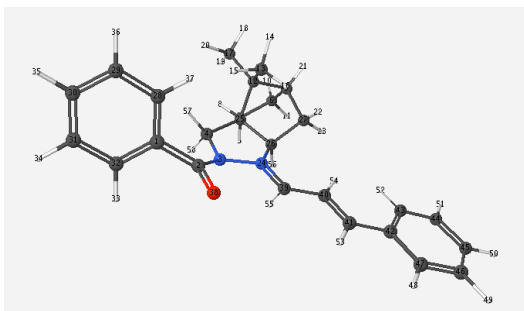
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-119.99986	169.6346431
-90.00003	169.3899144
-60.00007	164.9094966
-29.99998	162.7320386
-0.00013	163.3344478
0.0001	163.6733029
29.99996	162.8010647
59.99994	162.0668786
89.99988	165.1228498
119.9999	165.8821363
149.9999	168.2541222
179.9999	171.6677739



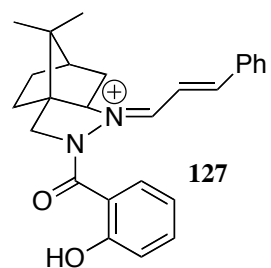
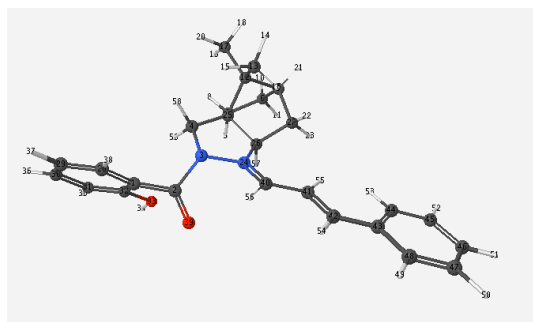
Dihedral Angle	Energy (kCal/mol)
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-120.00007	211.5083521
-89.99999	210.0839055
-59.9999	208.4712061
-29.99989	206.8271312
0.00002	205.2771827
0.0001	205.0010786
29.99992	204.3861192
59.99994	204.9069521
89.99989	206.5635772
119.99993	207.6868192
149.9999	209.8580021



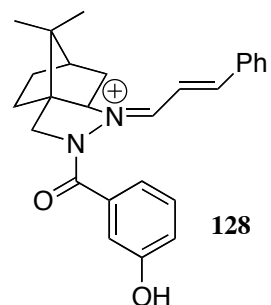
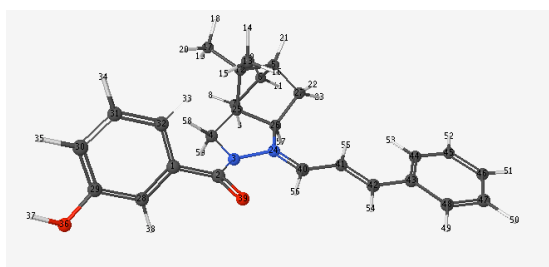
Dihedral Angle	Energy (kCal/mol)
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-120.00002	240.6561683
-89.99992	239.8780566
-59.99993	239.0434689
-29.99994	237.3178178
-0.00008	237.0291634
0.00006	235.1152595
29.99994	235.6925682
59.99991	235.3725384
89.9999	237.4872454
119.99991	238.516361
149.99992	240.7063691
179.9999	242.017864



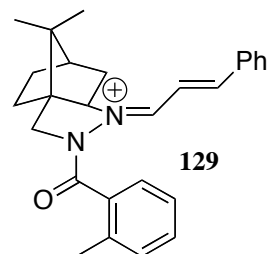
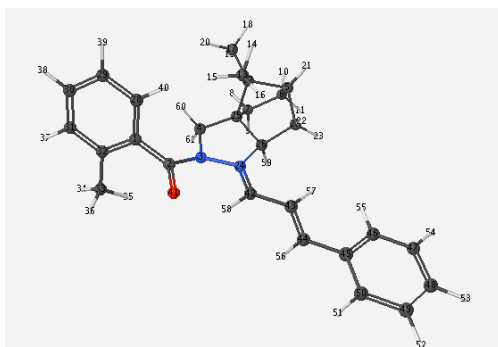
Dihedral Angle	Energy (kCal/mol)
-180	214.9533792
-150	213.9807395
-120.00004	214.212918
-90.00009	216.2711492
-59.99997	216.3527254
-29.99996	215.0914313
0.00011	209.6948496
0.00013	209.6948496
29.99993	210.3662848
59.99994	210.6737644
89.9999	212.6880699
119.99993	214.6521747
150	214.8216022



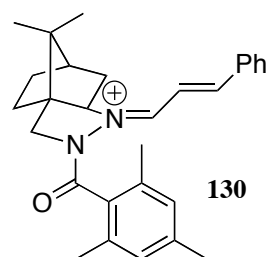
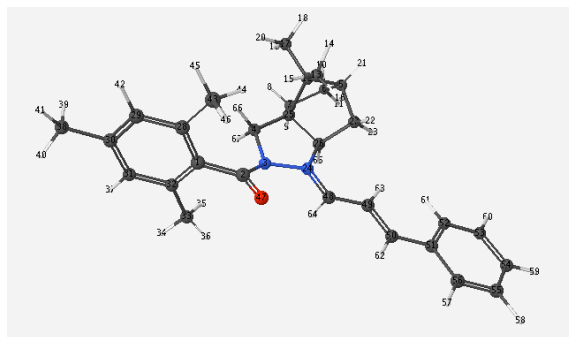
Dihedral Angle	Energy (kCal/mol)
-150.00004	170.08645
-119.99999	169.2518623
-89.99991	167.3505086
-59.99995	165.4993555
-30.00005	164.9596974
-0.00007	165.9888129
-0.00005	165.9888129
29.99989	167.645438
60.00002	169.358539
89.99993	169.6785688
120.00011	169.7099443
149.99994	169.6597435
179.9999	170.1366507



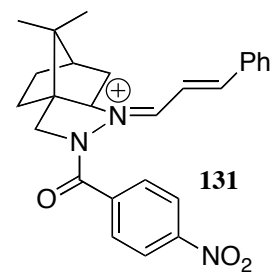
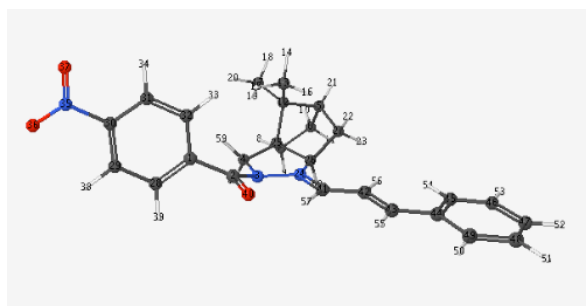
Dihedral Angle	Energy (kCal/mol)
-179.9999	169.8542715
-150	168.1599958
-120.00009	168.8565314
-90.00007	170.9775135
-60.00006	171.146941
-29.99994	170.0111488
0.00007	164.7588943
0.00013	164.3133626
29.99993	165.1102996
59.9999	165.7064337
89.99993	168.172546
119.99996	168.8251559
149.9999	170.8269112



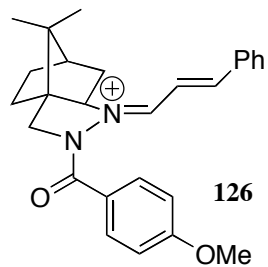
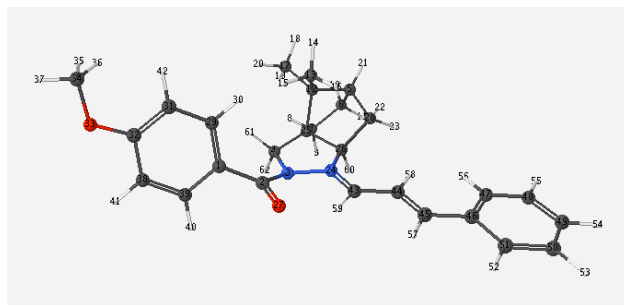
Dihedral Angle	Energy (kCal/mol)
-180	205.892142
-150	205.7729152
-120.00003	206.7330048
-90.00001	206.5761274
-60.00002	207.5926928
-29.99989	206.4443504
0.00007	201.3552484
0.0001	201.3552484
29.99992	202.1019847
59.9999	202.5977172
89.99993	203.6770335
119.99992	205.4466103
150	206.7706553



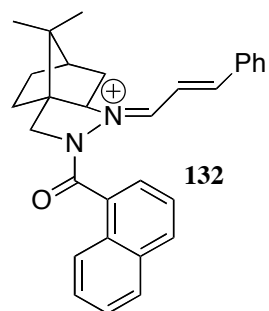
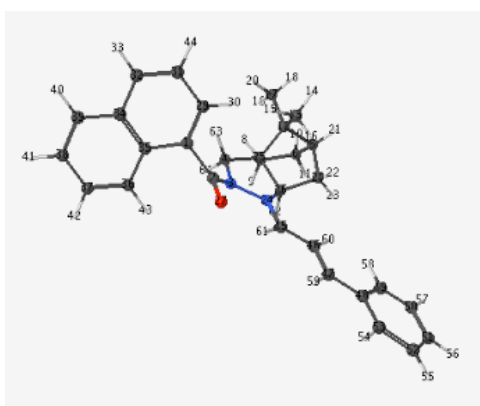
Dihedral Angle	Energy (kCal/mol)
-150.00004	187.6002401
-119.99994	188.3344262
-90.00007	189.576895
-59.99994	190.1228283
-29.99993	188.7862331
0.00008	183.2076736
0.00008	183.232774
29.99994	182.4170117
59.99997	182.8688185
89.99992	184.688596
119.99991	188.2591251
150.00005	189.5141441
180	187.4370877



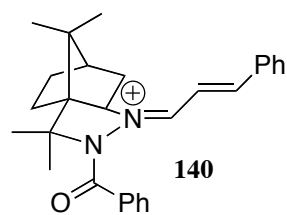
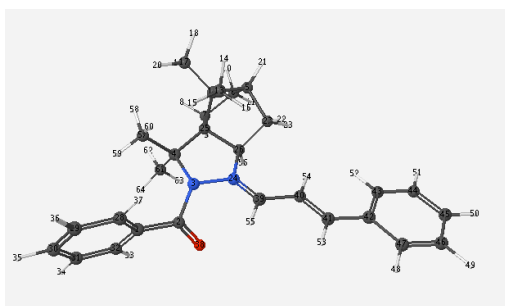
Dihedral Angle	Energy (kCal/mol)
-179.99994	213.8615127
-150	212.7508209
-120.00009	213.1587021
-90.00006	215.3612604
-59.99995	215.2859593
-29.99994	213.6293342
0.00011	208.1072506
0.00012	208.1072506
29.99999	208.6594589
59.99993	208.9543884
89.99994	211.3765751
119.99993	213.4473564
150	213.7109104



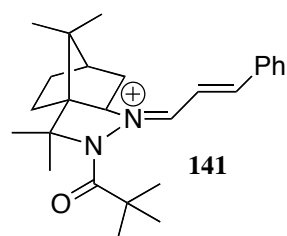
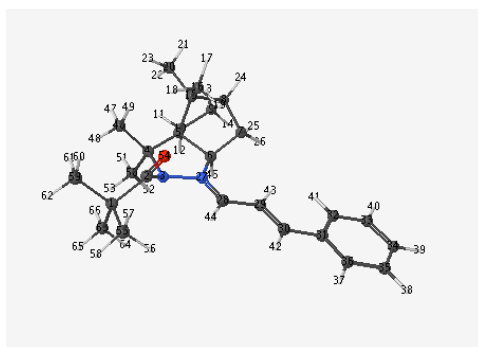
Dihedral Angle	Energy (kCal/mol)
-179.99995	175.6650094
-150	174.7362954
-120.00008	174.911998
-90.00008	176.9074782
-60.00001	177.1145564
-29.99994	176.0666155
0.00011	170.3813794
0.00011	170.682584
29.99993	171.2159671
59.99994	171.2975433
89.99994	173.0733952
119.99994	175.0061245
150	175.2822286



Dihedral Angle	Energy (kCal/mol)
-179.99999	232.241266
-150	232.3165671
-120	234.3998986
-89.99998	233.6029616
-60.00004	235.479215
-29.9999	233.2703815
-0.00009	230.3712876
0.00009	228.1624542
29.99996	228.8903652
59.99992	229.4362985
89.99992	230.5407152
119.99999	233.2829317
149.9999	233.0444781

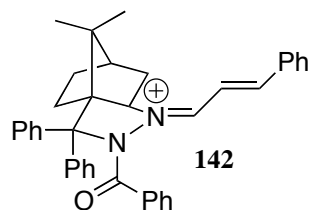
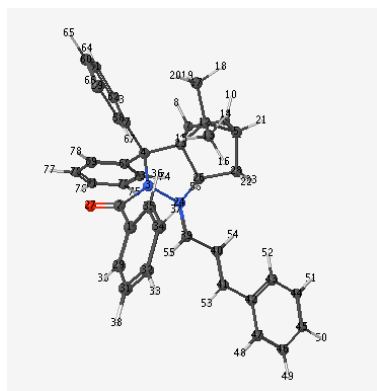


Dihedral Angle	Energy (kCal/mol)
-179.99995	209.1551914
-150	207.3856147
-119.99989	205.4842609
-90	204.1664909
-59.99996	202.4408398
-30.00013	204.4425951
-0.00006	203.8715615
-0.00003	203.8715615
30.00005	203.7272343
59.99989	204.2104166
89.99993	203.9594128
119.99991	205.9235175
149.9999	207.674269



Dihedral Angle	Energy (kCal/mol)
-179.99991	169.4777658
-149.9997	161.7719491
-119.99992	157.1974048
-90.00017	155.4968541
-60.0002	156.877375
-30.00008	160.3851531
0	161.3389675
0.00004	161.3326925
30.0001	160.2345508
60.00032	156.4192931
90.00019	154.2041845
119.9998	157.4546837

149.9997 164.2819871



Dihedral Angle	Energy (kCal/mol)
-179.99985	288.4786673
-150	284.8328371
-120.0003	287.7256559
-90.00025	294.4713831
-60.00039	298.2427152
-30.00019	301.7755936
-0.00014	288.5665187
0.00004	286.6588898
29.99989	287.2299234
59.99998	286.9914698
89.99983	287.2236483
119.99995	289.9219392
149.9997	293.3795165

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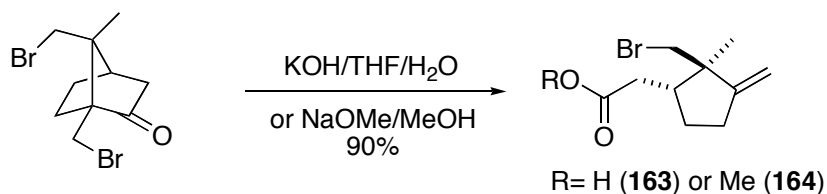
PART B: SYNTHESIS OF ISOCAMPHOLENIC ACID DERIVATIVES FROM CAMPHOR STARTING MATERIALS

INTRODUCTION

The use of starting materials from the chiral pool is a common strategy in order to obtain stereoenriched materials in synthesis.¹ Camphor-based starting materials have been widely used as chiral pool starting materials in the synthesis of natural products, chiral auxiliaries, organocatalysts, and ligands.² The benefit of using camphor based materials in the synthesis of natural products comes from the ability of the camphor skeleton to rearrange, producing another carbon skeleton in a stereospecific way. This can provide access to stereochemically pure advanced intermediates in natural product synthesis.

One particular type of rearrangement of the camphor skeleton involves cleavage of the C1-C2 bond of 9,10-dibromocamphor compounds to give cyclopentanoid compounds under basic conditions (Scheme 109).³

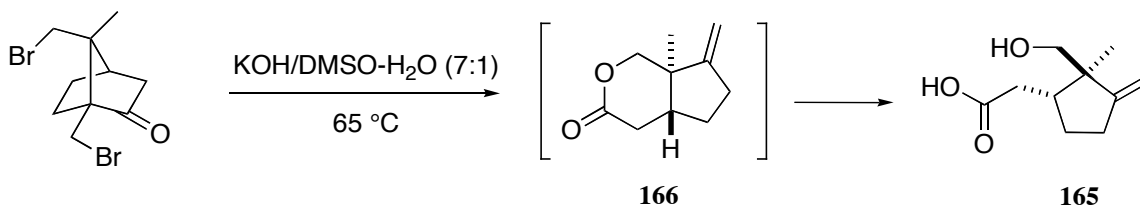
Scheme 109. Cyclopentanoid compounds obtained from treatment of 9,10-dibromocamphor with base.



This rearrangement proceeded in good yield to provide ring cleavage of the C1-C2 bond in the camphor starting material, while producing the cyclopentane carboxylic acid **163** containing an exocyclic double bond. Alternatively, cleavage of the C1-C2 bond in dibromocamphor derivatives with sodium methoxide provided methyl ester **164**. When the reaction temperature was increased to 65 °C and performed in a DMSO-water mixture, the corresponding hydroxy-acid **165** was formed. This reaction was thought to proceed via formation of an intermediate lactone **166**, that would subsequently

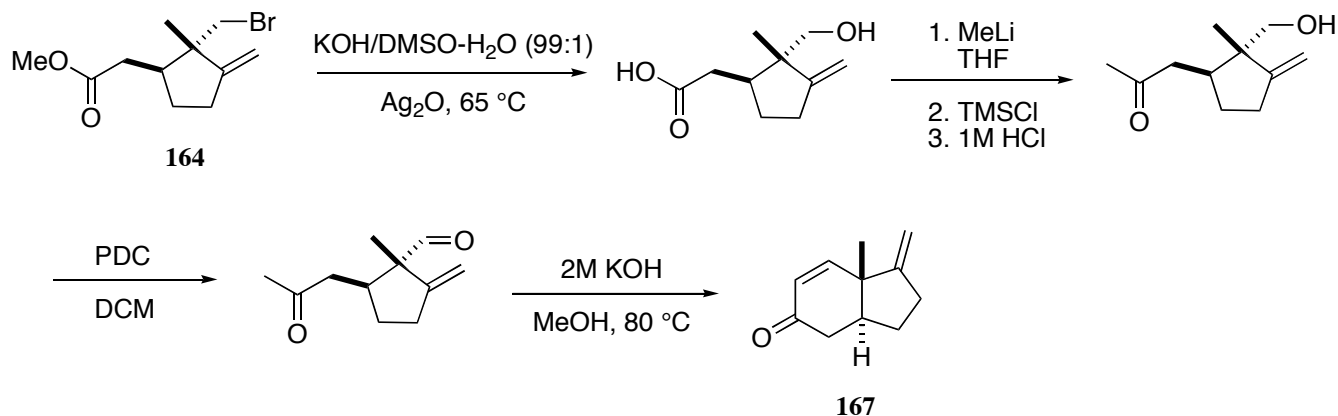
be hydrolyzed to the corresponding acid (Scheme 110). This lactone could be isolated when the amount of water present in the reaction was kept low, and the reaction mixture was not heated.

Scheme 110. Intermediate lactone 166 implicated in the formation of hydroxyacid 165.



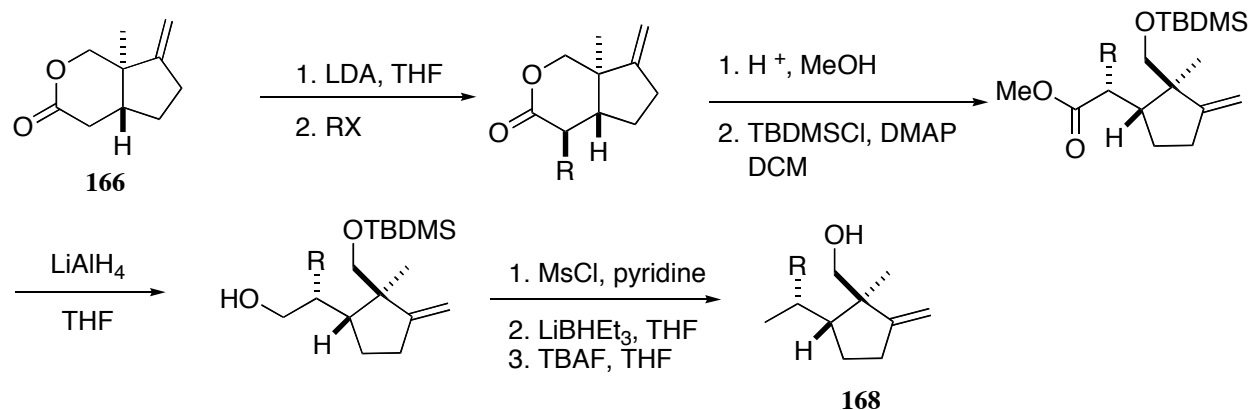
Further transformations of these synthetically useful compounds were showcased, starting with the methyl ester **164**. This derivative was transformed into hydrindenone **167** using a few more steps (Scheme 111).^{3b} The hydrindenone **167** could act as an enantiodefined precursor for common steroid systems.

Scheme 111. Preparation of hydrindenone derivative 167 from methyl ester 164.



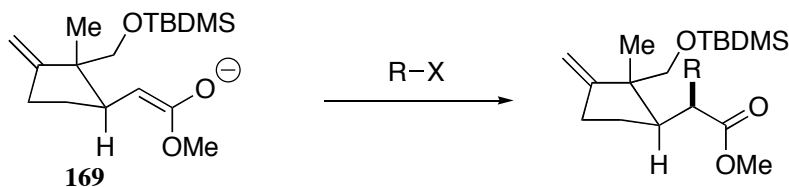
Another application of this methodology involves the manipulation of the lactone derivative **166** to provide access to more advanced chiral intermediates en route to steroids containing functionalized side chains.^{3c} Lactone **166** was shown to be able to be diastereoselectively alkylated with different electrophilic agents. This key alkylation step could provide access to diastereopure precursors for steroids with functionalized side chains. The authors used either allyl bromide, methyl iodide, or 2-methylallyl iodide as alkylating agents, and subsequently transformed these diastereopure alkylated lactones into the more advanced chiral synthons **168** (Scheme 112).

Scheme 112. Diastereoselective alkylation of lactone **166 and subsequent transformation to chiral synthons of type **168**.**



Similar transformations were also carried out with hydroxyacid **165**, after protection of the hydroxyl group with a TBDMS group, and conversion of the carboxylic acid functionality to the corresponding methyl ester. The diastereoselectivity of the subsequent alkylation step was rationalized by attack on the electrophile occurring on the less hindered face of the preferred conformation **169** of the ester enolate (Scheme 113).

Scheme 113. Attack of preferred conformation of enolate on electrophile.

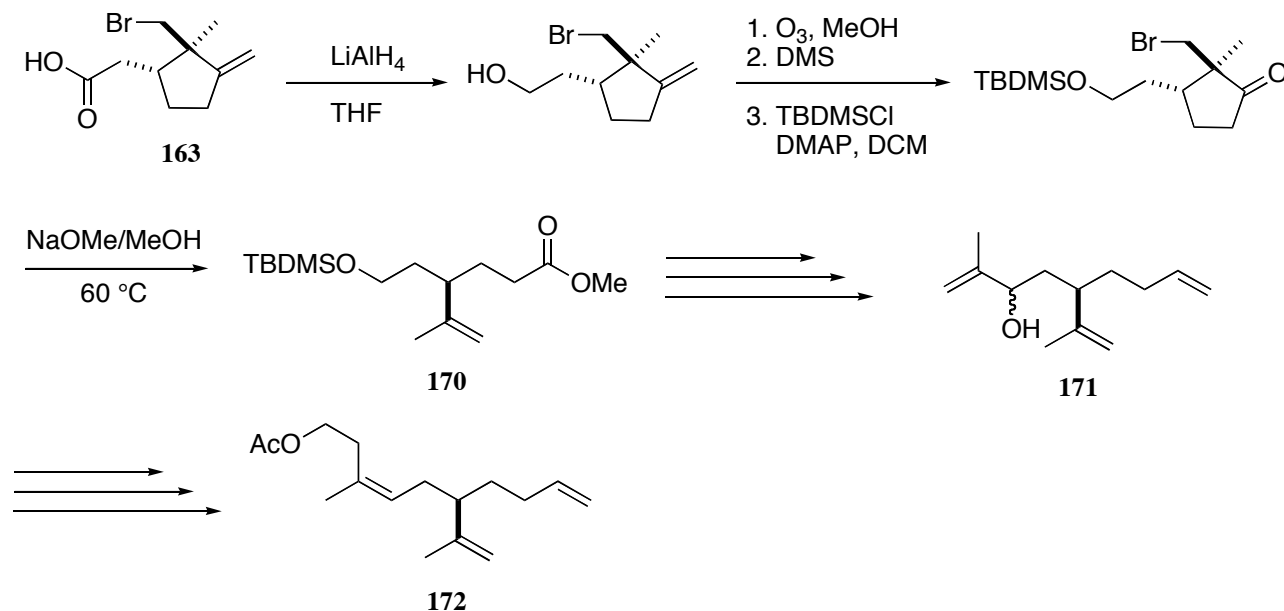


These advanced chiral synthons, produced originally from camphor starting materials, are convenient starting points for the stereoselective construction of D-ring steroid systems, with the addition of a side chain established using an enolate alkylation step.

The first example of a synthesis using these isocampholenic acid derivatives, employed the bromo acid **163**, which could be obtained from the cleavage of the C1-C2 bond in 9,10-dibromocamphor using this transformation. A precursor to one of the sex pheromones of the female California red scale was synthesized, using (+)-camphor as the source of chirality.^{3d} The isocampholenic acid derivative **163**, obtained by the basic ring cleavage of 9,10-dibromocamphor, was ultimately reduced from the carboxylic acid to the alcohol, which was subjected to ozonolysis to cleave the exocyclic alkene functionality (Scheme 114). A key ring opening reaction via methanolysis of the corresponding ketone

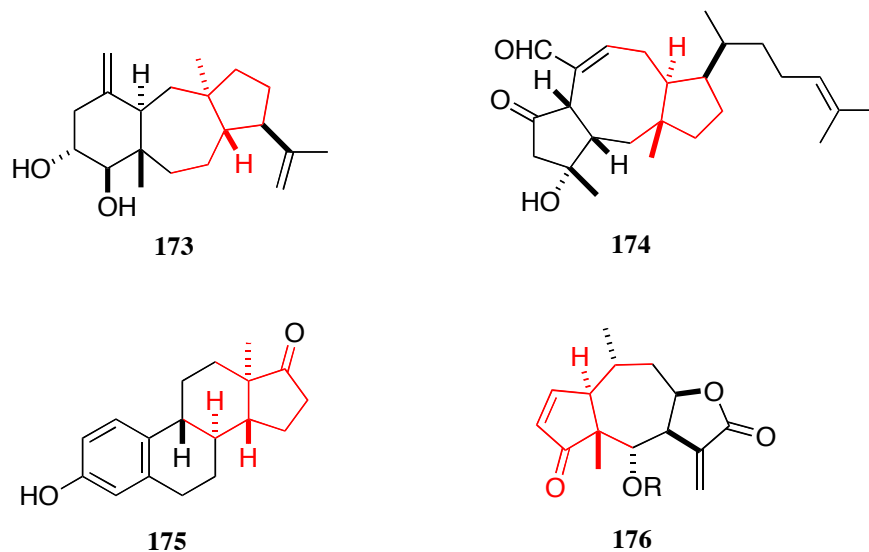
provided acyclic derivative **170**, which underwent further transformation to the California red scale pheromone precursor **171**. The remaining steps to California red scale pheromone had been previously reported from the identical intermediate.⁴

Scheme 114. Formal synthesis of California red scale pheromone 172 via isocampholenic acid derivative 163.



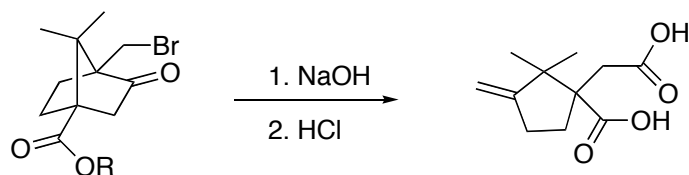
This methodology has subsequently been employed in such syntheses as: the dolastane diterpene (-)-clavulara-1,(15),17-dien-3,4-diol (**173**),⁵ the sesterterpene (+)-ophiobolin C (**174**)⁶, the steroid ent-estrone (**175**)⁷, and formal syntheses of a variety of the sesquiterpenoid tricyclic lactones in the class of the pseudoguaianolides such as the helenanolides (**176**)⁸, (Scheme 115).

Scheme 115. Products synthesized via isocampholenic acid intermediates.



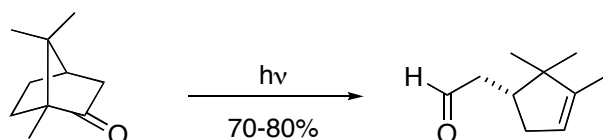
The synthesis of isocampholenic acid derivatives by a similar mechanism to that described by Money was carried out with racemic 4-substituted camphor starting materials (Scheme 116).⁹ A variety of cyclopentene carboxylic acids were synthesized in this fashion.

Scheme 116. Synthesis of cyclopentene carboxylic acids via 4-substituted camphor derivatives.



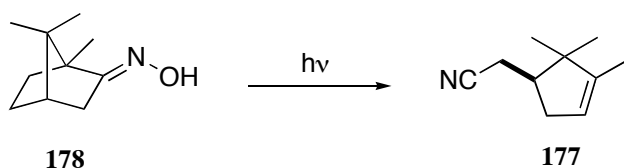
The transformation of camphor derivatives into campholenic acids has also been accomplished by a variety of methods. The conversion of camphor to α -campholenic aldehyde can be undertaken by photolysis of the C1-C2 bond (Scheme 117).¹⁰

Scheme 117. Breakage of the C1-C2 bond in camphor by photolysis.



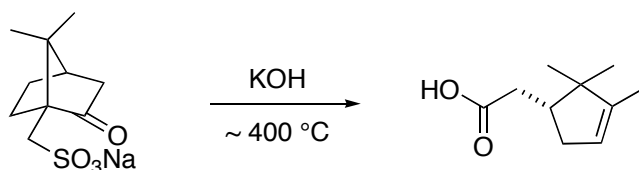
The Beckmann fragmentation of camphor oxime by photolysis was shown to give rise to the α -campholenic nitrile **177** (Scheme 118).¹¹

Scheme 118. Photolysis of C1-C2 bond in camphor oxime 178 to give α -campholenic nitrile 177.



The transformation of camphor derivatives into campholenic acids has been most commonly accomplished by treating salts of camphorsulfonic acid with KOH at 400 °C (Scheme 119).¹²

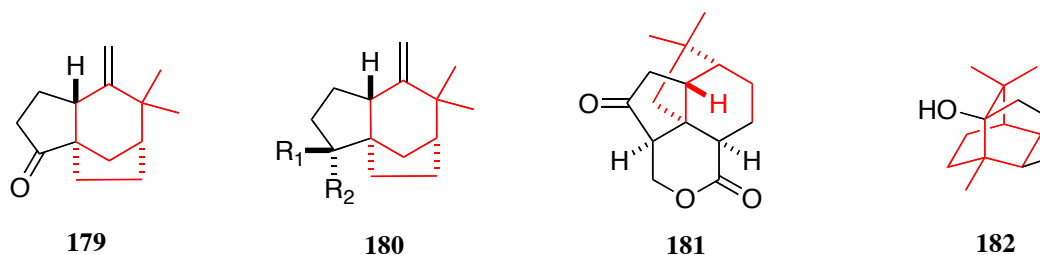
Scheme 119. Production of α -campholenic acid from the sodium salt of camphorsulfonic acid.



The mechanism for this reaction was thought to proceed via an isocampholenic acid intermediate, in which the double bond was in the exocyclic position, followed by base-catalyzed isomerization to

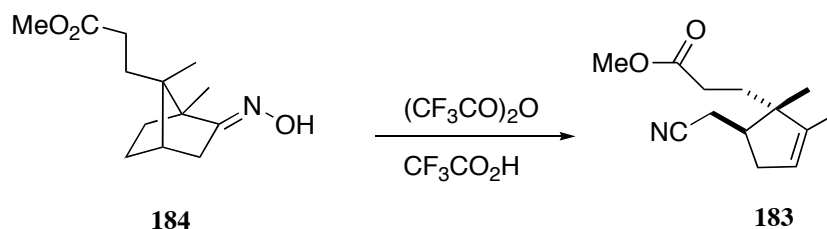
obtain the more stable endocyclic double bond.¹² This rearrangement of the camphor skeleton to α -campholenic acid derivatives has been used in the synthesis of natural products such as the zizaane sesquiterpenes¹³ (-)-khusimone (**179**), (+)-zizanoic acid (**180**), and (-)-epizizanoic acid, the sesquiterpene (-)-quadron (**181**),¹⁴ and (+)-norpatchoulenol (**182**)¹⁵ (Scheme 120).

Scheme 120. Natural products synthesized from camphorsulfonic acid via an α -campholenic acid derivative.



An alternative approach to α -campholenic acid derivatives starting from camphor-based starting materials involves the use of camphor oxime derivatives in a Beckmann fragmentation (Scheme 121). This derivative can be treated with trifluoroacetic anhydride (TFAA) and trifluoroacetic acid (TFA) to obtain the corresponding α -campholenic acid derivative **183**.¹⁶

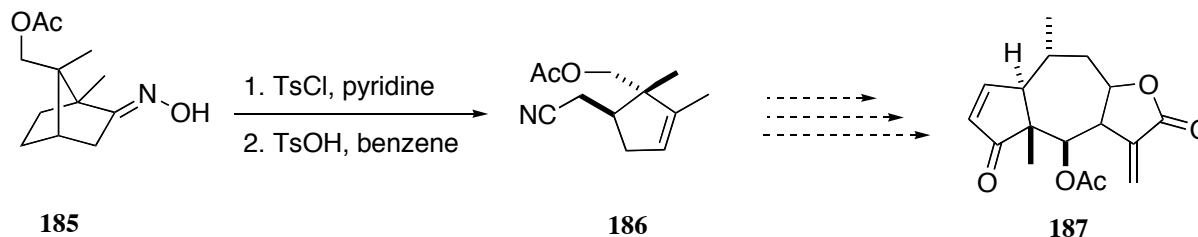
Scheme 121. Obtention of α -campholenic acid derivative 183 from camphor oxime derivative 184.



This derivative was further elaborated to obtain more advanced intermediates for use in the preparation of steroids.

Another way to convert camphor oxime derivatives to the corresponding campholenic acid derivatives is by treatment with *p*-toluene sulfonyl chloride (TsCl), followed by *p*-toluene sulfonic acid (TsOH). This strategy was used to construct an advanced intermediate in the synthesis of the pseudoguaianolide Balduilin (Scheme 122).¹⁷

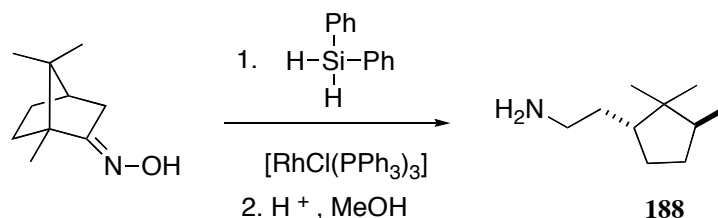
Scheme 122. Conversion of camphor oxime derivative 185 into campholenic acid derivative 186 en route to Balduilin (187).



Cleavage of the C1-C2 bond of camphor derivatives to obtain α -campholanic acids can also be accomplished. α -Campholanic acids can be converted to their corresponding alkyl esters, which tend to have fruity or floral scents that are of interest to the fragrance industry.¹⁸ These derivatives can be obtained from the corresponding α -campholenic acids via hydrogenation, however, this tends to lead to mixtures of diastereomers.¹⁹

Another method for synthesizing α -campholanic acids from camphor starting materials involves the hydrosilylation of camphor oxime using a rhodium catalyst to obtain the corresponding α -campholanic amine **188** (Scheme 123).²⁰

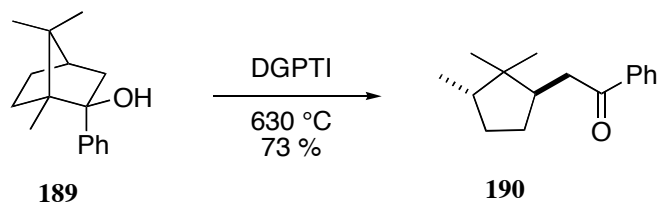
Scheme 123. Catalytic hydrosilylation of camphor oxime to obtain α -campholanic amine 188.



These products were produced in low yields, however, alongside *endo* and *exo* bornylamine byproducts.

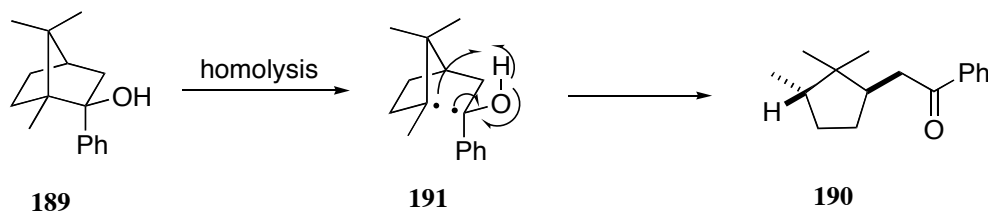
A more recent method of synthesizing α -campholanic acids from camphor based starting materials involves dynamic gas phase thermoisomerization (DGPTI).¹⁸ In this method, the camphor-based starting material **189** was heated to 630 °C in a flow reactor system, to provide (+)-trans- α -campholanic acid derivatives **190** in good yields and high diastereoselectivities (Scheme 124).

Scheme 124. Diastereoselective synthesis of (+)-trans- α -campholanic acid derivatives by DGPTI.



The mechanism for this process was proposed to be that shown in Scheme 125. A diradical species **191** is formed via thermal homolysis of the C1-C2 bond of the camphor derivative. This radical then rearranges to the ketone product **190**.

Scheme 125. Proposed mechanism for the transformation of camphor-based derivatives **189 to campholanic acid derivatives **190**.**

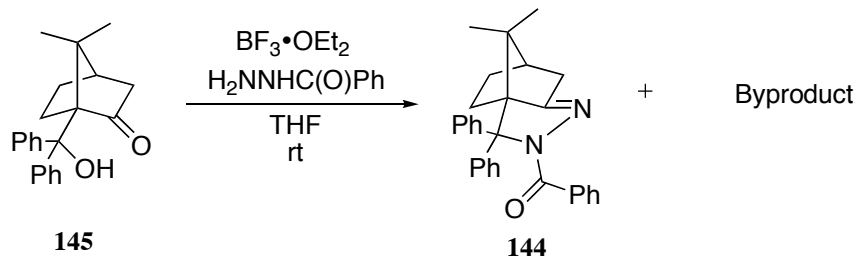


The synthetic value of these campholanic acid intermediates suggests that methods which facilitate access to these compounds are highly desirable.

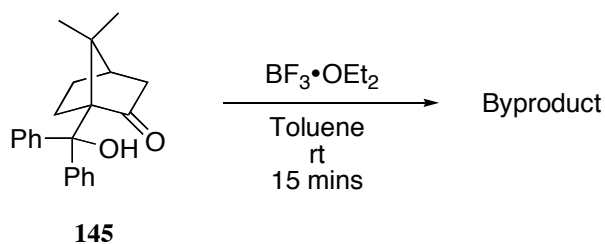
RESULTS AND DISCUSSION FOR FACILE SYNTHESIS OF ISOCAMPHOLENIC ACIDS VIA REARRANGEMENT OF CAMPHOR DERIVATIVES

During our investigations into the construction of disubstituted catalysts such as **143** in an attempt to improve the enantioselectivity of our 5-membered camphor-based hydrazide organocatalysts, we came across a problematic reaction. We wanted to obtain diphenyl substituted derivative **144** by heating the starting alcohol **145** in the presence of an acid (Scheme 126). What we initially thought was the cyclized hydrazone **144** by TLC analysis, turned out to be a compound whose spectral characteristics did not match those expected for the cyclic hydrazone. There were only 10 aromatic protons seen in the ^1H NMR, suggesting that the hydrazide never did add to the carbonyl. This was confirmed by a control reaction performed in the absence of the hydrazide (Scheme 127).

Scheme 126. Attempted synthesis of an intermediate for a potential organocatalyst resulting in byproduct formation.



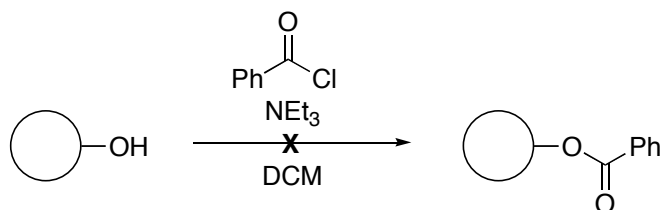
Scheme 127. Control reaction suggesting hydrazide is not involved in the rearrangement process.



The spectral data from the product of the control reaction matched that of the reaction employing the hydrazide, confirming that the hydrazide was not involved in the formation of the byproduct. We then set out to determine the identity of this byproduct. A variety of spectral data were obtained for this compound, however, the identity still could not be conclusively determined. A derivatization reaction was also attempted, with the assumption that the unknown compound was an alcohol (Scheme 128).

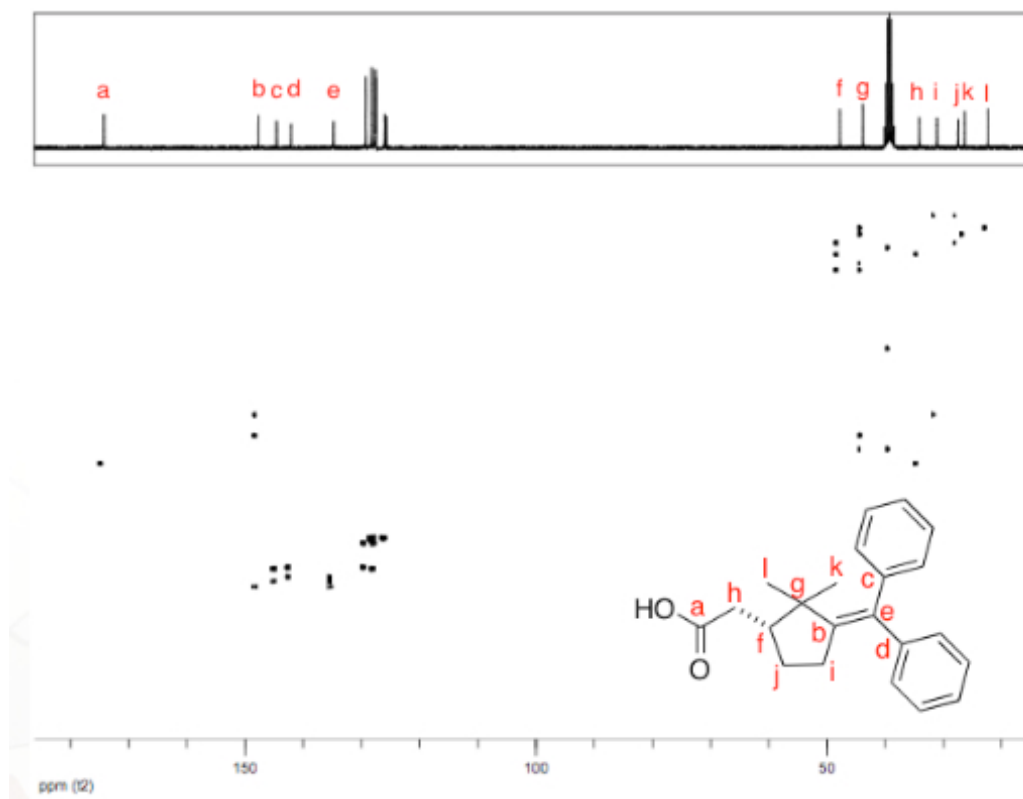
This reaction proved unsuccessful, so we decided to attempt the acquisition of an INADEQUATE spectrum, as well as an X-ray crystal structure to identify the product.

Scheme 128. Attempted derivatization reaction to determine the identity of the byproduct.



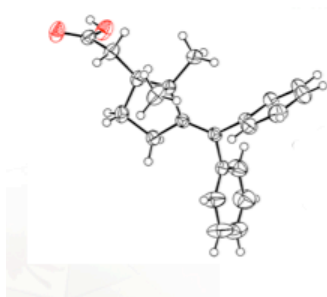
The results of the INADEQUATE spectrum suggested **192** as the structure for this mystery product, resulting from a rearrangement of the starting diaryl substituted alcohol (Figure 2).

Figure 2. INADEQUATE spectrum and predicted structure of mystery product 192.



Suitable crystallization conditions were subsequently found, which allowed us to procure an X-ray crystal structure of the product, which matched the proposed structure obtained by the INADEQUATE analysis (Figure 3).

Figure 3. X-ray ORTEP image of 192.



Due to the high efficiency of this process, we decided to investigate the substrate scope. Toward this end, a variety of diaryl substituted alcohols were synthesized (Scheme 129).²¹ This was achieved by treating ketopinic acid (**105**) with thionyl chloride in methanol to obtain the corresponding methyl ester **146**. This derivative was then converted into the various diaryl substituted alcohols **193-202** by exposure to the appropriate Grignard reagent. Treatment of the diaryl substituted alcohols thus obtained with $\text{BF}_3 \cdot \text{OEt}_2$ provided the corresponding rearranged products **203-212** in high yields (Table 39).

Scheme 129. Synthesis of diaryl substituted alcohols from (+)-ketopinic acid.

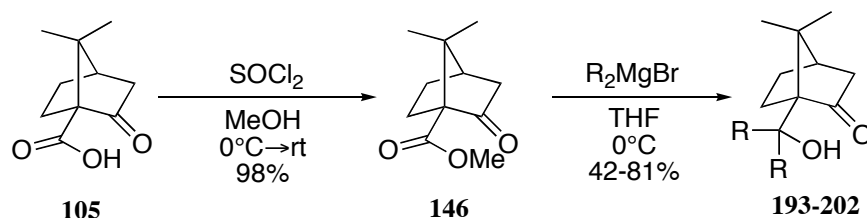
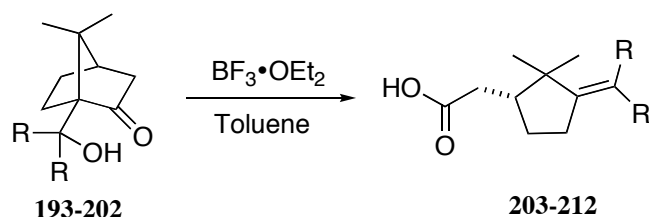


Table 39. Rearrangement of diaryl substituted alcohols 193-202 to obtain isocampholenic acids.^a

Entry	R (product)	Yield (%) ^b
1	Ph (192)	96
2	4-F-C ₆ H ₄ (203)	96
3	4-CH ₃ -C ₆ H ₄ (204)	80
4	3-CH ₃ -C ₆ H ₄ (205)	89
5	4- ^t Bu-C ₆ H ₄ (206)	76
6	4-CF ₃ -C ₆ H ₄ (207)	84 ^c
7	4-OMe-C ₆ H ₄ (208)	80
8	3-OMe-C ₆ H ₄ (209)	79
9	2-OMe-C ₆ H ₄ (210)	62
10	2-Naphthyl (211)	65 ^d
11	2-Thiophenyl (212)	93

^a Reaction conditions: BF₃•OEt₂ (1.0 equiv), Toluene, room temperature, 15 minutes

^b Isolated yield

^c Reaction required 48 hours to complete

^d Dichloromethane used in place of toluene

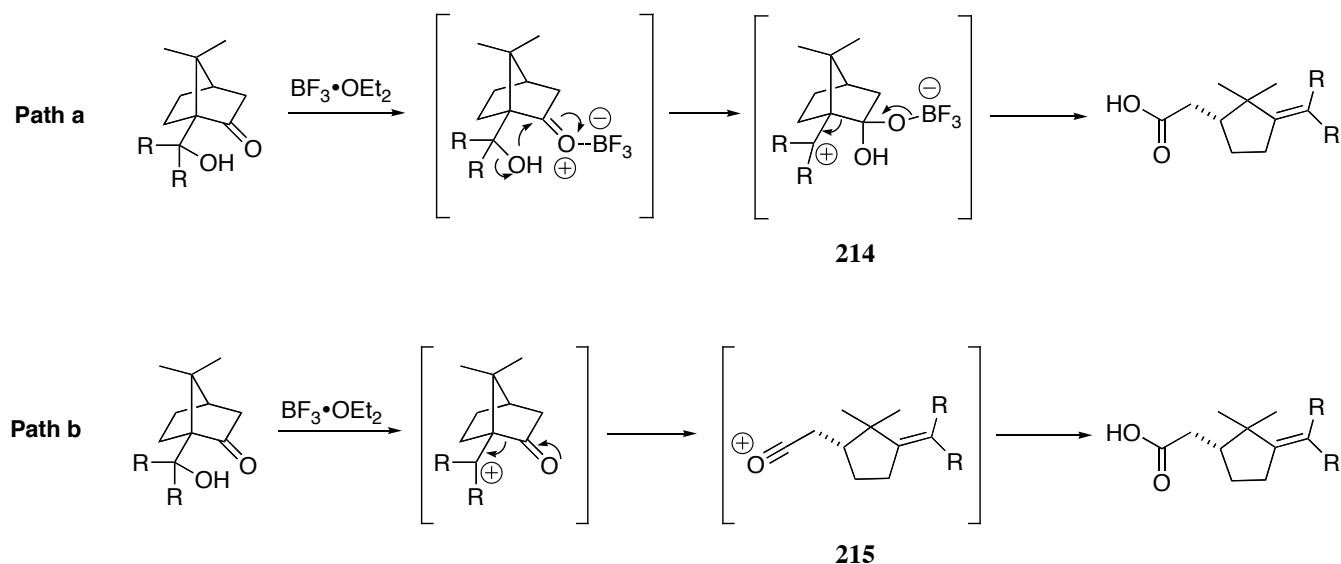
The reactions occurred rapidly (15 minutes) in good to excellent yields to afford the corresponding isocampholenic acids. The presence of fluoro-substituted aryl rings was well tolerated, and produced the resulting isocampholenic acid in a yield similar to the unsubstituted case (entry 1 and 2). The methyl substituted aryl rings were synthesized as both the *meta* and *para* derivatives, and resulted in good yields as well (entry 3 and 4). Attempted synthesis of the *ortho* methyl diaryl substituted alcohol proved unsuccessful, most likely due to steric hindrance between the methyl group and the camphor skeleton. Tertiary alkyl substitution on the aryl rings also did not significantly alter the yield of the rearrangement (entry 5). The effect of electron withdrawing aryl substituents on the process was investigated by synthesizing a –CF₃ substituted derivative. The yield of the rearrangement was not significantly affected, however, the reaction required 48 hours to complete (entry 6). The effect of electron donating aryl substituents as well as the regiochemistry of aryl ring substitution was explored by synthesizing a variety of methoxy substituted derivatives (entries 7-9). The yield of the *ortho* substituted derivative

was slightly diminished, most likely due to steric encomberment. Larger aromatic groups such as dinaphthyl substituted alcohols could also be employed in the reaction (entry 10), as well as diheteroaryl substituted alcohols (entry 11).

The mechanism of this rearrangement was then investigated. We hypothesized that the reaction proceeded through a carbocationic intermediate that subsequently rearranged to provide the isocampholenic acids. This hypothesis was generated due to the fact that a differentially substituted alcohol **213** gave a mixture of isomers upon rearrangement (Scheme 130).

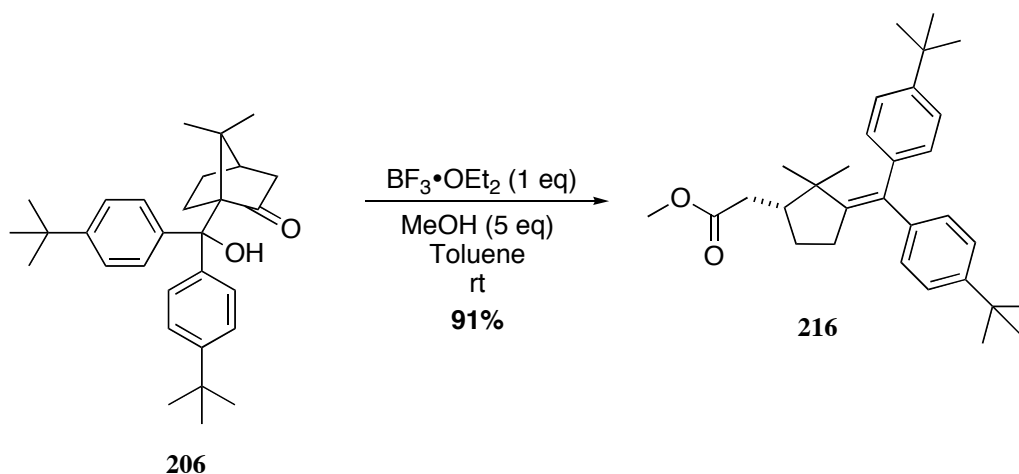
Initially, it was unclear whether the reaction proceeded via the formation of a hemiacetal species **214** (Scheme 130, path a) or through the formation of an acylium species **215** (Scheme 130, path b). If the reaction was proceeding via hemiacetal species **214**, it was assumed that the hydroxyl group would attack shortly after leaving to form the hemiacetal. If an acylium species was involved, it was assumed that the presence of an external nucleophile would significantly impact the product distribution.

Scheme 130. Possible pathways for rearrangement of diaryl substituted alcohols to isocampholenic acids.



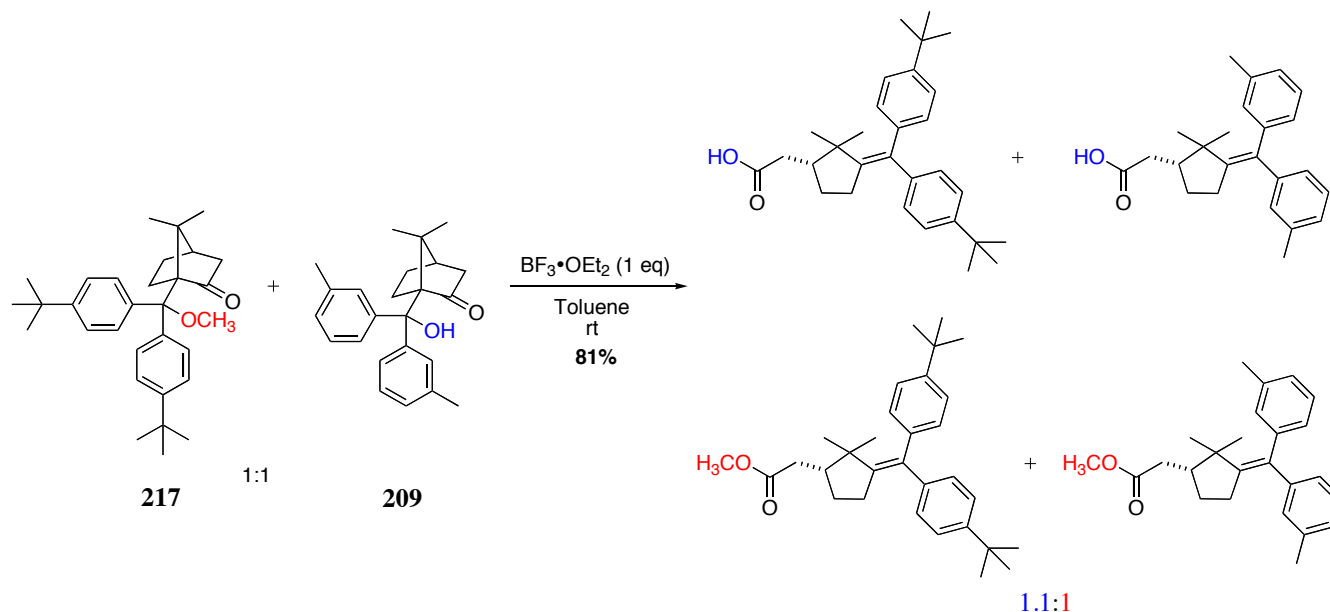
To differentiate between the two pathways, 5 equivalents of methanol was added to a toluene solution of alcohol **206**, and treated with $\text{BF}_3 \cdot \text{OEt}_2$ (Scheme 131). This resulted in the production of the corresponding methyl ester **216** in 91 % yield, suggesting the process did indeed proceed through an acylium ion (Scheme 130, path b).

Scheme 131. Methyl ester 216 formed exclusively when methanol used as an external nucleophile.



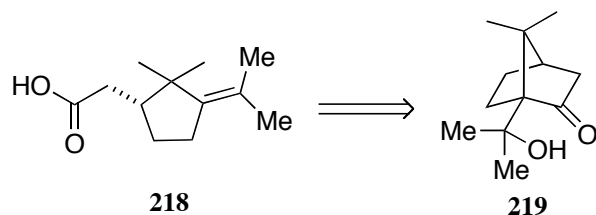
To further validate this hypothesis, a crossover experiment was performed, whereby methyl ether **217** (prepared from alcohol **206** by a Williamson ether synthesis) and alcohol **209** were combined in a 1:1 ratio and subjected to the standard reaction conditions (Scheme 132). This resulted in a 1.1:1 mixture of the corresponding acids and esters in a combined 81 % yield. This result was consistent with a reaction that proceeded via a rearrangement of the carbocation species to form an acylium species **215**, which was then attacked by the appropriate nucleophile.

Scheme 132. Crossover experiment performed between methyl ether 217 and alcohol 209.



The application of this methodology toward the synthesis of dialkyl isocampholenic acid derivatives such as **218** proved more challenging than initially anticipated. Dimethyl alcohol **219** was completely consumed upon reaction with $\text{BF}_3 \cdot \text{OEt}_2$, however, a mixture of products was obtained. (Scheme 133).

Scheme 133. Application to the construction of 218 from dimethyl alcohol 219.

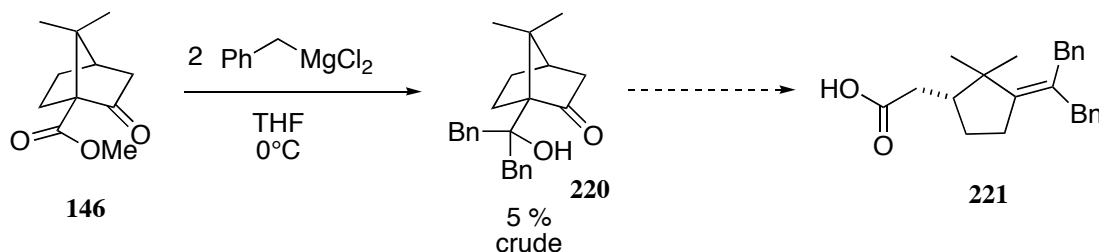


The presence of the desired product in the mixture was suggested by resonances in the ¹H NMR spectrum. We attempted to isolate this product by conversion of the acid to a methyl ester, in hopes that this ester would be easier to isolate than the acid precursor. This transformation was accomplished by treating the mixture containing acid **218** with diazomethane. Unfortunately, the methyl ester obtained still could not be separated from the other products.

We next attempted to determine if the other products were being formed subsequent to the formation of the desired product. If this was the case, quenching of the reaction mixture after a shorter time period could help eliminate or reduce the amount of the byproducts formed. To test this, we ran the reaction for one minute, as well as five minutes. In the case of the reaction time of one minute, only the starting alcohol was present in the mixture. After five minutes, the starting alcohol, desired product, and byproducts were all present in the reaction mixture. This suggests that the rate of byproduct formation is similar to the rate of formation for the desired product.

In an attempt to recover some reactivity for alkyl derivatives, we decided to try to synthesize a dibenzyl derivative (Scheme 134). Unfortunately, the disubstituted alcohol precursor **220** proved difficult to prepare due to an inefficient, low yielding reaction.

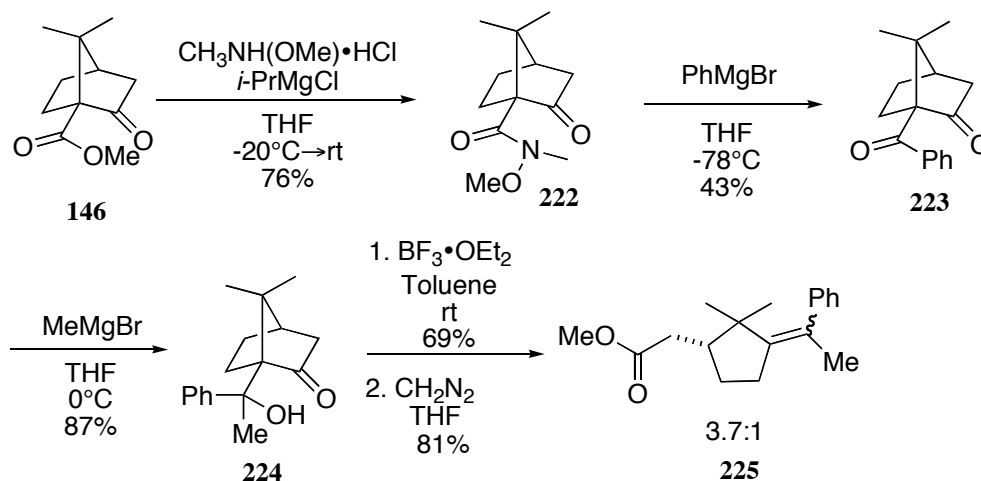
Scheme 134. Attempted synthesis of dibenzyl substituted isocampholenic acid 221.



We next examined whether a differentially substituted derivative could be prepared. Toward this end, Weinreb amide **222** was prepared from methyl ester **146** (Scheme 135). This amide was then treated

with excess PhMgBr in THF at -78 °C to obtain the corresponding ketone **223**. This product was then treated with excess CH₃MgBr at 0 °C to obtain differentially substituted alcohol **224** as a single isomer. Upon treatment with BF₃•OEt₂, rapid rearrangement occurred, and the resulting mixture was immediately treated with diazomethane to obtain the methyl ester **225**. This material was obtained as a 3.7:1 mixture of isomers. This result is consistent with the rearrangement proceeding through a stepwise mechanism such as that shown in Scheme 130, path b.

Scheme 135. Preparation of differentially substituted alcohol 224 and subsequent rearrangement.



Future Directions

The successful construction of intermediates which bear similarity to those used in the synthesis of natural products provides an avenue to be explored in the future with regards to attempts toward the synthesis of natural product targets.

EXPERIMENTAL SECTION

General Methods

Reactions were performed under nitrogen in oven-dried glassware equipped with a magnetic stirbar and a rubber septum. Solvents were freshly distilled prior to use as follows: THF over sodium/benzophenone and toluene over calcium hydride. $\text{BF}_3 \cdot \text{OEt}_2$ was freshly distilled before each use. All other reagents were used without further purification unless otherwise indicated. Reactions were monitored by TLC analysis using aluminum plates (250 μm thickness) precoated with silica gel 60 F254. TLC plates were visualized using ultraviolet light and potassium permanganate. Flash chromatography was carried out on 230-400 mesh silica gel 60, or preparatory TLC glass plates precoated with silica gel (Si250F). ^1H and ^{13}C NMR spectra were acquired on a 300 MHz, 400 MHz, or 500 MHz spectrometer in the specified solvent. Infrared spectra were acquired on a FTIR spectrometer. High resolution mass spectra were obtained using an Analytical Concept spectrometer. Melting points were determined using an Electrothermal Meltemp apparatus and are uncorrected. Optical rotations were determined using a Rudolph Research Analytical AUTOPOL III automatic polarimeter.

Methyl 7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-carboxylate (**146**)

Methanol (30 mL) was stirred in a 100 mL round bottom flask and cooled to 0 °C using an ice bath. Thionyl chloride (4 mL, 54.9 mmol) was then slowly added via syringe. To this solution was introduced (*S*)-(+)-ketopinic acid²² in four portions, waiting five minutes between additions. The resulting reaction mixture was stirred at 0 °C for 4 hours, allowed to warm to room temperature over 18 hours, and then concentrated under reduced pressure using a rotary evaporator. The resulting residue was diluted with ethyl acetate (50 mL). Water (50 mL) was added and the phases were separated. The aqueous phase was extracted once more with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (100 mL), and brine (100 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (5 to 20% EtOAc in hexanes) to afford **146** as white needles (2.09 g, 98 %). ^1H NMR (300 MHz, CDCl_3) δ 3.73 (s, 3H), 2.51 (ddd, J = 18.3, 3.9, 3.9 Hz, 1H), 2.40-2.27 (m, 1H), 2.09 (dd, J =

4.2, 4.2 Hz, 1H), 2.07-1.95 (m, 1H), 1.93 (d, J = 18.3 Hz, 1H), 1.77 (ddd, J = 13.8, 9.6, 5.1 Hz, 1H), 1.39 (ddd, J = 12.3, 9.3, 4.2 Hz, 1H), 1.13 (s, 3H), 1.06 (s, 3H). Spectral data matched those previously reported.²³

***N*-methoxy-*N*-7,7-trimethyl-2-oxobicyclo[2.2.1]heptane-1-carboxamide (222)**

To a solution of **146** (200 mg, 1.02 mmol) in dry THF (10 mL) was added CH₃NH(OMe)•HCl (160 mg, 1.63 mmol). The resulting mixture was cooled to -20 °C and *i*PrMgCl (2.6 mL, 5.10 mmol) was added via syringe. After warming to 0 °C over 5 hours, the reaction was quenched by the addition of saturated ammonium chloride (5 mL). The aqueous phase was then extracted twice with methyl *tert*-butyl ether (20 mL portions), and the organic extracts combined, dried over MgSO₄, filtered, and concentrated on a rotary evaporator. Column chromatography (15-30 % EtOAc/hexanes) provided pure **222** as a white powder (153 mg, 67 %). Mp 46-48 °C; $[\alpha]_D$ = + 26.5° (c 0.62, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 3.67 (s, 3H), 3.23 (s, 3H), 2.51 (ddd, J = 18.4, 5.2, 3.6 Hz, 1H), 2.38-2.28 (m, 1H), 2.15-1.98 (m, 3H), 1.94 (d, J = 18.0 Hz, 1H), 1.46-1.39 (m, 1H), 1.21 (s, 3H), 1.14 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 211.1 (C), 169.9 (C), 67.5 (C), 60.6 (CH₃), 50.1 (C), 43.8 (CH₃), 43.7 (CH₂), 32.6 (CH), 27.1 (CH₂), 26.7 (CH₂), 21.6 (CH₃), 20.4 (CH₃); IR (neat) 1741, 1623 cm⁻¹; MS (EI) 225.1 (M⁺); HRMS (EI) Calcd for C₁₂H₁₉NO₃ (M⁺) 225.1365, found 225.1342.

1-benzoyl-7,7-dimethylbicyclo[2.2.1]heptan-2-one (223)

To a solution of amide **222** (128 mg, 0.57 mmol) in dry THF (5 mL) at -78 °C was added a freshly prepared solution of PhMgBr in THF (0.61 mL, 0.85 mmol). The resulting mixture was allowed to warm to room temperature over 12 hours, and then quenched by the addition of saturated ammonium chloride (5 mL). The mixture was then diluted with EtOAc (20 mL), washed with 10% HCl (10 mL), saturated NaHCO₃ (10 mL), and brine (10 mL), dried over MgSO₄, filtered, and concentrated on a rotary evaporator. Column chromatography (5 % EtOAc/hexanes) provided pure **223** as a white powder (59.3 mg, 43 %). Mp 60-62 °C; $[\alpha]_D$ = - 23.1° (c 0.62, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.80-7.75 (m, 2H), 7.52-7.36 (m, 3H), 2.63 (ddd, J = 18.6, 4.8, 3.3 Hz, 1H), 2.32-1.98 (m, 4H), 2.06 (d, J = 18.3 Hz, 1H), 1.55-1.43 (m, 1H), 1.24 (s, 3H), 1.12 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 213.1 (C), 200.2 (C), 139.1 (C), 131.9 (CH), 128.9 (CH), 128.0 (CH), 73.2 (C), 50.0 (C), 44.4 (CH₂), 44.3

(CH), 28.9 (CH₂), 26.8 (CH₂), 21.8 (CH₃), 20.1 (CH₃); IR (neat) 1733, 1658 cm⁻¹; MS (EI) 242.1 (M⁺); HRMS (EI) Calcd for C₁₆H₁₈O₂ (M⁺) 242.1307, found 242.1308.

1-(1-hydroxy-1-phenylethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (224)

To a solution of ketone **223** (59 mg, 0.24 mmol) in dry THF (5 mL) at 0 °C was added a solution of 3.0 M MeMgBr in Et₂O (0.24 mL, 0.73 mmol). The reaction mixture was allowed to warm to room temperature, and stirred at this temperature for 2 hours. The reaction was then quenched with saturated ammonium chloride (5 mL), and the aqueous phase extracted twice with EtOAc (20 mL portions). The combined organic phases were washed with brine (20 mL), dried over MgSO₄, filtered, and concentrated on a rotary evaporator. Column chromatography (3 % EtOAc/hexanes) provided **224** as fine white needles (53.8 mg, 87 %). Mp 79-81 °C; [α]_D = - 98.9° (c 0.74, CH₂Cl₂); ¹H NMR (300 MHz, C₆D₆) δ 7.62-7.55 (m, 2H), 7.19-7.05 (m, 3H), 4.07 (s, 1H), 2.14-2.03 (m, 1H), 1.89-1.77 (m, 1H), 1.71 (s, 3H), 1.45 (d, *J* = 18.3 Hz, 1H), 1.45-1.33 (m, 1H), 1.25-1.14 (m, 2H), 0.95 (s, 3H), 0.77 (ddd, *J* = 17.7, 9.0, 3.6 Hz, 1H), 0.00 (s, 3H); ¹³C NMR (100 MHz, C₆D₆) δ 145.3 (C), 127.5 (CH), 126.9 (CH), 126.8 (CH), 74.6 (C), 67.3 (C), 48.1 (C), 44.7 (CH), 43.4 (CH₂), 28.2 (CH₃), 26.6 (CH₂), 25.7 (CH₂), 21.8 (CH₃), 20.9 (CH₃); IR (neat) 3393, 1717 cm⁻¹; MS (EI) 258.2 (M⁺); HRMS (EI) Calcd for C₁₇H₂₂O₂ (M⁺) 258.1620, found 258.1617.

Methyl-2-((*R*)-2,2-dimethyl-3-(1-phenylethylidene)cyclopentyl)acetate (225)

To a solution of **224** (97 mg, 0.38 mmol) in dry toluene (4 mL) was added a solution of 0.65M BF₃•OEt₂ (0.10 mL, 0.76 mmol) under nitrogen. The mixture was stirred at room temperature for 15 minutes, and the reaction was then quenched by the addition of water (10 mL). The resulting mixture was extracted twice with EtOAc (20 mL portions). The combined organic extracts were washed with brine (20 mL) dried over MgSO₄, filtered, and concentrated *in vacuo* to provide compound the isocampholenic acid without need for further purification (3.7:1 mixture of isomers, 67.6 mg, 69 %) as a clear syrup. This product was immediately dissolved in dry THF (2 mL), and a solution of freshly prepared diazomethane in Et₂O (2.6 mL, 1.77 mmol) was added dropwise until the yellow color persisted. The solvent was then evaporated, and the resulting residue purified by column chromatography (3-6 % EtOAc/hexanes) to obtain the title compound as a 3.7:1 mixture of isomers (57

mg, 81 %). ^1H NMR (300 MHz, C_6D_6) δ 7.20-7.01 (m, 5.4H), 3.37 (s, 0.9H), 3.35 (s, 2.1H), 2.38-1.89 (m, 6.9H), 1.79 (dd, J = 1.5, 1.5 Hz, 2.4H), 1.36-1.21 (m, 0.6H), 1.23 (s, 0.6H), 0.89 (s, 0.6H), 0.71 (s, 2.2H), 0.68 (s, 2.3H); ^{13}C NMR (100 MHz, C_6D_6) δ 173.2 (C), 145.0 (C), 144.7 (C), 128.8 (CH), 127.7 (CH), 126.0 (CH), 50.7 (CH_3), 50.6 (CH_3), 49.3 (CH), 48.5 (CH), 44.3 (C), 44.2 (C), 34.5 (CH_2), 34.3 (CH_2), 32.5 (CH_2), 30.3 (CH_2), 29.0 (CH_2), 27.8 (CH_2), 26.7 (CH_3), 26.3 (CH_3), 24.4 (CH_3), 22.6 (CH_3), 20.7 (CH_3), 20.5 (CH_3); IR (neat) 1735 cm^{-1} ; MS (EI) 272.2 (M^+); HRMS (EI) Calcd for $\text{C}_{18}\text{H}_{24}\text{O}_2$ (M^+) 272.1776, found 272.1773.

General procedure for the synthesis of diaryl alcohols

1-(hydroxydiphenylmethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (145)

Magnesium turnings (1.2 g, 51.2 mmol) and a few small crystals of I_2 were placed under a nitrogen atmosphere in a 100 mL round bottom flask equipped with a condenser. The flask was then warmed gently using a heat gun to vaporize the iodine, and the apparatus allowed to stand until the color of the iodine vapor disappeared. Into this flask was introduced one half of a solution of bromobenzene (4.5 mL, 42.7 mmol) in dry THF (30 mL). The solution was stirred until an exothermic reaction was observed, bringing it to reflux. As the reflux began to subside, the other half of the bromobenzene solution was added, and the reaction was heated to reflux for 1 hour using a heating mantle, and then cooled to $0\text{ }^\circ\text{C}$ in an ice bath.

Methyl ester **146** (1.37g, 6.48 mmol) was then introduced in one portion and the resulting mixture stirred at $0\text{ }^\circ\text{C}$ for 1 hour. The reaction was quenched with a saturated solution of ammonium chloride (20 mL). Water (50 mL) was then added and the resulting mixture was then extracted twice with EtOAc (50 mL portions). The combined organic extracts were washed with brine (50 mL), dried over MgSO_4 , filtered, and concentrated *in vacuo*. Pure **145** (924 mg, 60 %) was obtained as clear crystals after recrystallization from 1:4 EtOAc:hexanes. ^1H NMR (300 MHz, CDCl_3) δ 7.53-7.15 (m, 10H), 3.82 (s, 1H), 2.57-2.45 (m, 2H), 2.29 (ddd, J = 13.8, 9.6, 5.1 Hz, 1H), 1.99-1.87 (m, 1H), 1.97 (d, J = 18.6 Hz, 1H), 1.78 (dd, J = 4.8, 4.8 Hz, 1H), 1.42 (ddd, J = 12.0, 9.3, 3.9 Hz, 1H), 1.07 (s, 3H), 0.27 (s, 3H). Spectral data matched those previously reported.²⁴

1-(bis(4-fluorophenyl)(hydroxy)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (193)

Prepared from **146** (100 mg, 0.51 mmol) using a procedure similar to that described for **145**. Column chromatography (5 % EtOAc/hexanes) provided the title compound as clear crystals (142 mg, 78 %). Mp 138-140 °C; $[\alpha]_D = -145.7^\circ$ (c 1.03, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.48-7.28 (m, 4H), 7.02-6.86 (m, 4H), 3.76 (s, 1H), 2.51 (ddd, $J = 18.6, 5.1, 3.0$ Hz, 1H), 2.48-2.37 (m, 1H), 2.21 (ddd, $J = 13.5, 9.3, 4.8$ Hz, 1H), 2.02-1.88 (m, 1H), 1.97 (d, $J = 18.6$ Hz, 1H), 1.79 (dd, $J = 4.8, 4.8$ Hz, 1H), 1.43 (ddd, $J = 12.6, 9.6, 3.9$ Hz, 1H), 1.03 (s, 3H), 0.32 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 162.9 (d, $J = 35$ Hz, C), 160.4 (d, $J = 35.4$ Hz, C), 142.7 (d, $J = 1.9$ Hz, C), 140.3 (d, $J = 2.7$ Hz, C), 130.8 (d, $J = 7.8$ Hz, CH), 129.8 (d, $J = 7.4$ Hz, CH), 114.1 (d, $J = 2.2$ Hz, CH), 113.9 (d, $J = 2.2$ Hz, CH), 79.2 (C), 68.1 (C), 50.2 (C), 44.5 (CH), 43.5 (CH₂), 26.8 (CH₂), 25.6 (CH₂), 22.7 (CH₃), 21.9 (CH₃); IR (neat) 3548, 1719 cm⁻¹; MS (EI) 260.1 (M⁺ -C₆H₅F); HRMS (EI) Calcd for C₁₆H₁₇FO₂ (M⁺ -C₆H₅F) 260.1213, found 260.1237.

1-(hydroxydi-*p*-tolylmethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (194)

Prepared from **146** (100 mg, 0.51 mmol) using a procedure similar to that described for **145**. Column chromatography (3 % EtOAc/hexanes) provided the title compound as clear needles (118 mg, 67 %). Mp 98-100 °C; $[\alpha]_D = -180.6^\circ$ (c 0.96, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.34 (d, $J = 8.1$ Hz, 2H), 7.25 (d, $J = 8.4$ Hz, 2H), 7.08 (d, $J = 7.8$ Hz, 2H), 7.02 (d, $J = 8.4$ Hz, 2H), 3.73 (s, 1H), 2.57-2.43 (m, 2H), 2.33 (s, 3H), 2.29 (s, 3H), 2.24 (ddd, $J = 14.1, 9.3, 4.5$ Hz, 1H), 1.95 (d, $J = 18.6$ Hz, 1H), 1.96-1.86 (m, 1H), 1.76 (dd, $J = 4.8, 4.8$ Hz, 1H), 1.40 (ddd, $J = 12.3, 9.3, 3.9$ Hz, 1H), 1.05 (s, 3H), 0.30 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 144.4 (C), 141.7 (C), 136.3 (C), 136.2 (C), 128.9 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 79.5 (C), 68.1 (C), 50.1 (C), 44.5 (CH), 43.5 (CH₂), 26.9 (CH₂), 25.6 (CH₂), 22.7 (CH₃), 21.8 (CH₃), 20.9 (CH₃), 20.8 (CH₃); IR (neat) 3530, 1716 cm⁻¹; MS (EI) 348.2 (M⁺); HRMS (EI) Calcd for C₂₄H₂₈O₂ (M⁺) 348.2089, found 348.2070.

1-(hydroxydi-*m*-tolylmethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (195)

Prepared from **146** (100 mg, 0.51 mmol) using a procedure similar to that described for **145**. Column chromatography (3 % EtOAc/hexanes) provided the title compound as clear crystals (116 mg, 66 %).

Mp 124-126 °C; $[\alpha]_D = -188.8^\circ$ (c 0.99, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.45-7.00 (m, 8H), 3.86 (s, 1H), 2.61-2.46 (m, 2H), 2.37 (s, 3H), 2.35-2.23 (m, 1H), 2.31 (s, 3H), 1.99 (d, $J = 18.6$ Hz, 1H), 1.99-1.89 (m, 1H), 1.79 (dd, $J = 4.5, 4.5$ Hz, 1H), 1.44 (ddd, $J = 12.3, 9.3, 3.9$ Hz, 1H), 1.09 (s, 3H), 0.30 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 147.1 (C), 144.3 (C), 136.7 (C), 136.6 (C), 129.7 (CH), 128.7 (CH), 127.5 (CH), 127.4 (CH), 127.0 (CH), 126.9 (CH), 126.1 (CH), 125.6 (CH), 79.8 (C), 68.1 (C), 50.2 (C), 44.5 (CH), 43.5 (CH₂), 26.9 (CH₂), 25.6 (CH₂), 22.7 (CH₃), 21.8 (CH₃), 21.7 (CH₃), 21.6 (CH₃); IR (neat) 3569, 1719 cm⁻¹; MS (EI) 348.2 (M⁺); HRMS (EI) Calcd for C₂₄H₂₈O₂ (M⁺) 348.2089, found 348.2109.

1-(bis(4-*tert*-butylphenyl)(hydroxy)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (196)

Prepared from **146** (100 mg, 0.51 mmol) using a procedure similar to that described for **145**. Column chromatography (3 % EtOAc/hexanes) provided the title compound as white needles (127 mg, 58 %). Mp 162-164 °C; $[\alpha]_D = -116.3^\circ$ (c 1.02, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.49-7.21 (m, 8H), 3.82 (s, 1H), 2.58-2.45 (m, 2H), 2.25 (ddd, $J = 13.8, 9.3, 4.5$ Hz, 1H), 1.95 (d, $J = 18.6$ Hz, 1H), 2.00-1.85 (m, 1H), 1.76 (dd, $J = 4.5, 4.5$ Hz, 1H), 1.40 (ddd, $J = 12.9, 9.6, 3.9$ Hz, 1H), 1.32 (s, 9H), 1.29 (s, 9H), 1.05 (s, 3H), 0.25 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 149.7 (C), 149.3 (C), 144.1 (C), 141.4 (C), 128.7 (CH), 127.8 (CH), 124.1 (CH), 123.9 (CH), 79.4 (C), 68.2 (C), 50.1 (C), 44.5 (CH), 43.6 (CH₂), 34.3 (C), 34.2 (C), 31.4 (CH₃), 31.3 (CH₃), 26.9 (CH₂), 25.6 (CH₂), 22.5 (CH₃), 21.4 (CH₃); IR (neat) 3483, 1718 cm⁻¹; MS (EI) 432.3 (M⁺); HRMS (EI) Calcd for C₃₀H₄₀O₂ (M⁺) 432.3028, found 432.3075.

1-(bis(4-(trifluoromethyl)phenyl)(hydroxy)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (197)

Prepared from **146** (500 mg, 2.55 mmol) using a procedure similar to that described for **145**. Column chromatography (5 % EtOAc/hexanes) provided the title compound as clear crystals (972 mg, 81 %). Mp 148-150 °C; $[\alpha]_D = -137.9^\circ$ (c 1.13, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.64-7.54 (m, 4H), 7.49 (s, 4H), 3.86 (s, 1H), 2.53 (ddd, $J = 18.8, 4.8, 2.8$ Hz, 1H), 2.49-2.43 (m, 1H), 2.32-2.23 (m, 1H), 2.02-1.92 (m, 1H), 1.99 (d, $J = 18.8$ Hz, 1H), 1.83 (dd, $J = 4.8, 4.8$ Hz, 1H), 1.47 (ddd, $J = 12.8, 9.2, 3.6$ Hz, 1H), 1.07 (s, 3H), 0.30 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 150.3 (C), 147.7 (C), 129.2 (CH),

128.4 (CH), 124.5 (q, $J = 3.7$ Hz, CH), 124.3 (q, $J = 3.7$ Hz, CH), 79.5 (C), 67.9 (C), 50.3 (C), 44.4 (CH), 43.3 (CH₂), 26.8 (CH₂), 25.6 (CH₂), 22.8 (CH₃), 21.9 (CH₃); IR (neat) 3542, 1716 cm⁻¹; MS (EI) 456.2 (M⁺); HRMS (EI) Calcd for C₂₄H₂₂F₆O₂ (M⁺) 456.1524, found 456.1557.

1-(hydroxybis(4-methoxyphenyl)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (198)

Prepared from **146** (500 mg, 2.55 mmol) using a procedure similar to that described for **145**. Column chromatography (7-10 % EtOAc/hexanes) provided the title compound as a clear syrup (614 mg, 63 %). $[\alpha]_D = -155.9^\circ$ (c 1.29, CH₂Cl₂); ¹H NMR (400 MHz, C₆D₆) δ 7.62-7.46 (m, 4H), 6.79-6.71 (m, 4H), 3.92 (s, 1H), 3.31 (s, 3H), 3.29 (s, 3H), 2.29-2.17 (m, 1H), 2.21 (ddd, $J = 18.0, 4.8, 2.8$ Hz, 1H), 1.99 (ddd, $J = 14.0, 9.6, 4.8$ Hz, 1H), 1.58 (d, $J = 18.0$ Hz, 1H), 1.60-1.51 (m, 1H), 1.30 (dd, $J = 4.8, 4.8$ Hz, 1H), 0.99 (s, 3H), 0.95 (ddd, $J = 12.8, 9.2, 3.6$ Hz, 1H), 0.31 (s, 3H); ¹³C NMR (100 MHz, C₆D₆) δ 159.0 (C), 158.8 (C), 140.2 (C), 138.0 (C), 131.0 (CH), 129.9 (CH), 112.8 (CH), 112.7 (CH), 79.6 (C), 68.4 (C), 54.7 (CH₃), 54.6 (CH₃), 50.0 (C), 44.7 (CH), 43.6 (CH₂), 26.9 (CH₂), 25.8 (CH₂), 22.8 (CH₃), 22.2 (CH₃); IR (neat) 3527, 1719 cm⁻¹; MS (EI) 380.2 (M⁺); HRMS (EI) Calcd for C₂₄H₂₈O₄ (M⁺) 380.1988, found 380.2008.

1-(hydroxybis(3-methoxyphenyl)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (199)

Prepared from **146** (100 mg, 0.51 mmol) using a procedure similar to that described for **145**. Column chromatography (5 % Et₂O/toluene) provided the title compound as a clear syrup (135 mg, 70 %). $[\alpha]_D = -153.7^\circ$ (c 0.29, CH₂Cl₂); ¹H NMR (300 MHz, C₆D₆) δ 7.53 (s, 1H), 7.40 (dd, $J = 2.1, 2.1$ Hz, 1H), 7.28-7.22 (m, 1H), 7.09-6.99 (m, 3H), 6.69-6.61 (m, 2H), 3.96 (s, 1H), 3.33 (s, 3H), 3.29 (s, 3H), 2.33 (ddd, $J = 14.4, 12.0, 3.6$ Hz, 1H), 2.13 (ddd, $J = 18.6, 5.1, 3.0$ Hz, 1H), 2.08-1.99 (m, 1H), 1.58-1.45 (m, 1H), 1.50 (d, $J = 18.3$ Hz, 1H), 1.25 (dd, $J = 4.5, 4.5$ Hz, 1H), 0.97 (s, 3H), 0.87 (ddd, $J = 12.6, 9.3, 3.6$ Hz, 1H), 0.32 (s, 3H); ¹³C NMR (100 MHz, C₆D₆) δ 159.4 (C), 149.4 (C), 146.8 (C), 124.4 (CH), 128.1 (CH), 121.9 (CH), 121.5 (CH), 116.2 (CH), 114.9 (CH), 112.1 (CH), 111.9 (CH), 79.9 (C), 68.4 (C), 54.7 (CH₃), 54.6 (CH₃), 50.1 (C), 44.6 (CH), 43.3 (CH₂), 26.9 (CH₂), 25.9 (CH₂), 22.8 (CH₃), 21.9 (CH₃); IR (neat) 3512, 1719 cm⁻¹; MS (EI) 380.2 (M⁺); HRMS (EI) Calcd for C₂₄H₂₈O₄ (M⁺) 380.1988, found 380.1997.

1-(hydroxybis(2-methoxyphenyl)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (200)

Prepared from **146** (200 mg, 1.02 mmol) using a procedure similar to that described for **145**. Recrystallization from 3:1 hexanes/EtOAc provided the title compound as a clear crystals (164 mg, 42 %). $[\alpha]_D = -43.1^\circ$ (c 0.51, CH₂Cl₂); ¹H NMR (500 MHz, (CD₃)₂SO, 145 °C) δ 7.67-7.63 (m, 1H), 7.52-7.48 (m, 1H), 7.18-7.08 (m, 2H), 6.92-6.75 (m, 4H), 5.00 (s, 1H), 3.40 (s, 3H), 3.25 (s, 3H), 2.66-2.58 (m, 1H), 2.45-2.38 (m, 1H), 2.17 (ddd, $J = 14.0, 9.5, 5.0$, 1H), 1.90-1.83 (m, 1H), 1.89 (d, $J = 18.0$ Hz, 1H), 1.72 (dd, $J = 4.5, 4.5$ Hz, 1H), 1.36 (ddd, $J = 11.5, 9.5, 4.0$ Hz, 1H), 1.04 (s, 3H), 0.70 (s, 3H); ¹³C NMR (125 MHz, (CD₃)₂SO, 145 °C) δ 213.4, 156.5, 156.4, 135.3, 134.9, 129.5, 128.5, 126.8, 126.3, 118.5, 118.1, 113.0, 112.6, 79.8, 68.1, 54.9, 54.7, 49.6, 44.2, 42.9, 25.4, 22.4, 21.7; IR (neat) 3517, 1734 cm⁻¹; MS (EI) 380.2 (M⁺); HRMS (EI) Calcd for C₂₄H₂₈O₄ (M⁺) 380.1988, found 380.2011.

1-(hydroxy(naphthalen-2-yl)(naphthalen-3-yl)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (201)

Prepared from **146** (100 mg, 0.51 mmol) using a procedure similar to that described for **145**. Column chromatography (3 % EtOAc/hexanes) provided the title compound as a white fluffy powder (111 mg, 52 %). Mp 228-230 °C $[\alpha]_D = -266.8^\circ$ (c 0.40, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.18-8.11 (m, 1H), 7.98-7.96 (m, 1H), 7.88-7.58 (m, 7H), 7.51-7.42 (m, 4H), 7.34-7.28 (m, 1H), 4.04 (s, 1H), 2.70-2.47 (m, 3H), 2.08 (d, $J = 18.8$ Hz, 1H), 2.01-1.89 (m, 1H), 1.81 (dd, $J = 4.8, 4.8$ Hz, 1H), 1.53-1.47 (m, 1H), 1.18 (s, 3H), 0.22 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 143.8 (C), 141.8 (C), 132.5 (C), 132.3 (C), 132.2 (C), 132.1 (C), 128.6 (CH), 128.5 (CH), 128.2 (CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 126.9 (CH), 126.7 (CH), 126.5 (CH), 126.0 (CH), 125.9 (CH), 125.7 (CH), 80.3 (C), 68.2 (C), 50.3 (C), 44.6 (CH), 43.5 (CH₂), 26.9 (CH₂), 25.8 (CH₂), 22.9 (CH₃), 22.0 (CH₃); IR (neat) 3513, 1710 cm⁻¹; MS (EI) 420.2 (M⁺); HRMS (EI) Calcd for C₃₀H₂₈O₂ (M⁺) 420.2089, found 420.2099.

1-(hydroxydi(thiophen-2-yl)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (202)

Prepared from **146** (140 mg, 0.71 mmol) using a procedure similar to that described for **145**. Column chromatography (3 % EtOAc/hexanes) provided the title compound as a charcoal powder (160 mg, 68 %). Mp 112-114 °C $[\alpha]_D = -147.8^\circ$ (c 0.97, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.24-7.12 (m, 4H), 6.98-6.91 (m, 2H), 4.33 (s, 1H), 2.63-2.41 (m, 2H), 2.09-1.94 (m, 2H), 1.90 (d, $J = 18.3$ Hz, 1H), 1.83

(dd, $J=4.5, 4.5$ Hz, 1H), 1.44-1.33 (m, 1H), 0.98 (s, 3H), 0.58 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.5 (C), 148.2 (C), 126.5 (CH), 126.3 (CH), 125.5 (CH), 124.1 (CH), 124.0 (CH), 68.5 (C), 49.6 (C), 44.7 (CH), 43.3 (CH_2), 26.6 (CH_2), 26.2 (CH_2), 21.5 (CH_3), 21.2 (CH_3); IR (neat) 3448, 1712 cm^{-1} ; MS (EI) 332.1 (M^+); HRMS (EI) Calcd for $\text{C}_{18}\text{H}_{20}\text{O}_2\text{S}_2$ (M^+) 332.0905, found 332.0907.

General Procedure for the synthesis of isocampholenic acid derivatives, 2-((*R*)-2,2-dimethyl-3-(diphenylmethylene)cyclopentyl)acetic acid (192**)**

To a solution of **145** (1.06 g, 3.31 mmol) in dry toluene (30 mL) was added $\text{BF}_3 \cdot \text{OEt}_2$ (0.49 mL, 4.00 mmol). The mixture was stirred at room temperature for 15 minutes, and the reaction was then quenched by the addition of water (20 mL). The resulting mixture was extracted twice with EtOAc (30 mL portions). The combined organic extracts were washed with brine (20 mL) dried over MgSO_4 , filtered, and concentrated *in vacuo* to provide compound **192** as a white powder (1.02g, 96%). Mp 138-140 $^\circ\text{C}$; $[\alpha]_{\text{D}} = -126.3^\circ$ (c 0.51, CH_2Cl_2); ^1H NMR (300 MHz, C_6D_6) δ 7.21-6.96 (m, 10H), 2.31-2.21 (m, 2H), 2.19-2.05 (m, 2H), 1.95 (dd, $J=14.7, 10.5$ Hz, 1H), 1.89-1.76 (m, 1H), 1.24-1.09 (m, 1H), 0.78 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 180.7 (C), 148.3 (C), 145.3 (C), 142.9 (C), 136.3 (C), 129.9 (CH), 128.6 (CH), 128.5 (CH), 126.5 (CH), 126.3 (CH), 48.5 (CH), 44.8 (C), 34.8 (CH_2), 31.9 (CH_2), 28.3 (CH_2), 26.8 (CH_3), 22.9 (CH_3); IR (neat) 1693 cm^{-1} ; MS (EI) 320.2 (M^+); HRMS (EI) Calcd for $\text{C}_{22}\text{H}_{24}\text{O}_2$ (M^+) 320.1776, found 320.1791.

2-((*R*)-3-(bis(4-fluorophenyl)methylene)-2,2-dimethylcyclopentyl)acetic acid (203**)**

Prepared from **193** (25 mg, 0.07 mmol) using a procedure similar to that described for **192** to obtain the title compound as a clear syrup (24.6 mg, 96 %). $[\alpha]_{\text{D}} = -108.6^\circ$ (c 0.48, CH_2Cl_2); ^1H NMR (400 MHz, C_6D_6) δ 6.88-6.69 (m, 8H), 2.21 (dd, $J=14.8, 3.2$, 1H), 2.15-2.03 (m, 3H), 1.96 (dd, $J=14.8, 10.8$, 1H), 1.88-1.78 (m, 1H), 1.21-1.08 (m, 1H), 0.69 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 180.3 (C), 163.0 (d, $J=28.8$ Hz, C), 160.6 (d, $J=28.4$ Hz, C), 149.6 (C), 140.8 (d, $J=3.2$ Hz, C), 138.5 (d, $J=3.3$ Hz, C), 133.9 (C), 131.3 (d, $J=7.6$ Hz, CH), 130.0 (d, $J=7.7$ Hz, CH), 115.4 (d, $J=21.0$ Hz, CH), 114.9 (d, $J=21.0$ Hz, CH), 48.5 (CH), 44.7 (C), 34.7 (CH_2), 31.9 (CH_2), 28.2 (CH_2), 26.8 (CH_3), 22.8 (CH_3); IR (neat) 1701 cm^{-1} ; MS (EI) 356.2 (M^+); HRMS (EI) Calcd for $\text{C}_{22}\text{H}_{22}\text{F}_2\text{O}_2$ (M^+) 356.1588, found 356.1583.

2-((R)-2,2-dimethyl-3-(di-*p*-tolylmethylene)cyclopentyl)acetic acid (204)

Prepared from **194** (33 mg, 0.10 mmol) using a procedure similar to that described for **192** to obtain the title compound as a white sticky solid (26.8 mg, 80 %). Mp 80-82 °C; $[\alpha]_D = -86.3^\circ$ (c 0.41, CH₂Cl₂); ¹H NMR (400 MHz, C₆D₆) δ 7.17-7.09 (m, 4H), 6.96 (d, *J* = 7.6 Hz, 2H), 6.92 (d, *J* = 7.6 Hz, 2H), 2.40-2.33 (m, 2H), 2.22-2.11 (m, 2H), 2.10 (s, 3H), 2.07 (s, 3H), 1.94 (dd, *J* = 14.4, 10.4 Hz, 1H), 1.91-1.83 (m, 1H), 1.25-1.13 (m, 1H), 0.85 (s, 3H), 0.82 (s, 3H); ¹³C NMR (100 MHz, C₆D₆) δ 180.6 (C), 148.0 (C), 142.8 (C), 140.4 (C), 136.2 (C), 135.7 (C), 135.4 (C), 129.9 (CH), 129.3 (CH), 128.8 (CH), 128.5 (CH), 48.6 (CH), 44.8 (C), 34.8 (CH₂), 32.0 (CH₂), 28.3 (CH₂), 26.7 (CH₃), 22.7 (CH₃), 20.8 (CH₃), 20.7 (CH₃); IR (neat) 1702 cm⁻¹; MS (EI) 348.2 (M⁺); HRMS (EI) Calcd for C₂₄H₂₈O₂ (M⁺) 348.2089, found 348.2140.

2-((R)-2,2-dimethyl-3-(di-*m*-tolylmethylene)cyclopentyl)acetic acid (205)

Prepared from **195** (31 mg, 0.09 mmol) using a procedure similar to that described for **192** to obtain the title compound as clear needles (27.6 mg, 89 %). Mp 100-102 °C; $[\alpha]_D = -94.4^\circ$ (c 0.50, CH₂Cl₂); ¹H NMR (400 MHz, C₆D₆) δ 7.13-7.02 (m, 6H), 6.85 (d, *J* = 7.6 Hz, 2H), 2.42-2.28 (m, 2H), 2.25-2.11 (m, 2H), 2.09 (s, 3H), 2.06 (s, 3H), 1.96 (dd, *J* = 14.8, 10.8 Hz, 1H), 1.91-1.83 (m, 1H), 1.27-1.14 (m, 1H), 0.85 (s, 3H), 0.83 (s, 3H); ¹³C NMR (100 MHz, C₆D₆) δ 180.6 (C), 147.9 (C), 145.5 (C), 143.1 (C), 137.9 (C), 137.4 (C), 136.5 (C), 130.6 (CH), 129.1 (CH), 128.6 (CH), 127.9 (CH), 127.3 (CH), 127.1 (CH), 127.0 (CH), 125.7 (CH), 48.6 (CH), 44.8 (C), 34.9 (CH₂), 31.9 (CH₂), 28.3 (CH₂), 26.9 (CH₃), 23.0 (CH₃), 21.5 (CH₃), 21.4 (CH₃); IR (neat) 1700 cm⁻¹; MS (EI) 348.2 (M⁺); HRMS (EI) Calcd for C₂₄H₂₈O₂ (M⁺) 348.2089, found 348.2083.

2-((R)-3-(bis(4-*tert*-butylphenyl)methylene)-2,2-dimethylcyclopentyl)acetic acid (206)

Prepared from **196** (25 mg, 0.06 mmol) using a procedure similar to that described for **192** to obtain the title compound as a white powder (19 mg, 76 %). Mp 176-178 °C; $[\alpha]_D = -86.1^\circ$ (c 0.53, CH₂Cl₂); ¹H NMR (400 MHz, C₆D₆) δ 7.28-7.21 (m, 8H), 2.49-2.34 (m, 2H), 2.22-2.10 (m, 2H), 2.01-1.92 (m, 1H), 1.91-1.82 (m, 1H), 1.21-1.16 (m, 1H), 1.19 (s, 9H), 1.18 (s, 9H), 0.87 (s, 3H), 0.84 (s, 3H); ¹³C NMR (100 MHz, C₆D₆) δ 180.3 (C), 149.0 (C), 148.6 (C), 148.2 (C), 142.7 (C), 140.3 (C), 136.1 (C), 129.8

(CH), 128.4 (CH), 125.5 (CH), 124.9 (CH), 48.6 (CH), 44.8 (C), 34.8 (CH₂), 34.4 (C), 34.3 (C), 32.2 (CH₂), 31.5 (CH₃), 28.4 (CH₂), 27.0 (CH₃), 23.1 (CH₃); IR (neat) 1701 cm⁻¹; MS (EI) 432.3 (M⁺); HRMS (EI) Calcd for C₃₀H₄₀O₂ (M⁺) 432.3028, found 432.3042.

2-((R)-3-(bis(4-(trifluoromethyl)phenyl)methylene)-2,2-dimethylcyclopentyl)acetic acid (207)

Prepared from **197** (300 mg, 0.64 mmol) using a procedure similar to that described for **192**. Column chromatography (15-30% EtOAc/hexanes) provided the title compound as a pale yellow powder (253 mg, 84 %). Mp 60-62 °C; [α]_D = -89.3° (c 0.52, CH₂Cl₂); ¹H NMR (400 MHz, C₆D₆) δ 7.35 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 2.18 (dd, *J* = 14.8, 3.2 Hz, 1H), 2.11-1.91 (m, 4H), 1.86-1.76 (m, 1H), 1.18-1.05 (m, 1H), 0.61 (s, 3H), 0.59 (s, 3H); ¹³C NMR (100 MHz, C₆D₆) δ 180.7 (C), 150.7 (C), 147.6 (C), 145.5 (C), 133.4 (C), 130.2 (CH), 129.2 (q, *J* = 32.2 Hz, C), 128.8 (CH), 128.8 (q, *J* = 32.0 Hz, C), 125.8 (q, *J* = 3.7 Hz, CH), 125.2 (q, *J* = 3.7 Hz, CH), 124.9 (q, *J* = 270.1 Hz, C), 124.8 (q, *J* = 270.2 Hz, C), 48.3 (CH), 44.9 (C), 34.7 (CH₂), 31.7 (CH₂), 28.1 (CH₂), 26.6 (CH₃), 22.7 (CH₃); IR (neat) 1705 cm⁻¹; MS (EI) 456.2 (M⁺); HRMS (EI) Calcd for C₂₄H₂₂F₆O₂ (M⁺) 456.1524, found 456.1523.

2-((R)-3-(bis(4-methoxyphenyl)methylene)-2,2-dimethylcyclopentyl)acetic acid (208)

Prepared from **208** (26 mg, 0.07 mmol) using a procedure similar to that described for **192** to obtain the title compound as a pale yellow syrup (22 mg, 80 %). [α]_D = -104.5° (c 1.09, CH₂Cl₂); ¹H NMR (400 MHz, C₆D₆) δ 7.13-7.08 (m, 4H), 6.00-6.72 (m, 4H), 3.30 (s, 3H), 3.28 (s, 3H), 2.47-2.33 (m, 2H), 2.24 (dd, *J* = 14.8, 3.2 Hz, 1H), 2.20-2.12 (m, 1H), 1.99 (dd, *J* = 14.4, 10.4 Hz, 1H), 1.95-1.86 (m, 1H), 1.28-1.16 (m, 1H), 0.88 (s, 3H), 0.83 (s, 3H); ¹³C NMR (100 MHz, C₆D₆) δ 180.3 (C), 158.6 (C), 158.4 (C), 148.3 (C), 138.2 (C), 135.7 (C), 135.5 (C), 131.0 (CH), 129.7 (CH), 114.0 (CH), 113.6 (CH), 54.7 (CH₃), 54.6 (CH₃), 48.7 (CH), 44.8 (C), 34.9 (CH₂), 32.2 (CH₂), 28.4 (CH₂), 27.0 (CH₃), 23.1 (CH₃); IR (neat) 1701 cm⁻¹; MS (EI) 380.2 (M⁺); HRMS (EI) Calcd for C₂₄H₂₈O₄ (M⁺) 380.1988, found 380.1982.

2-((R)-3-(bis(3-methoxyphenyl)methylene)-2,2-dimethylcyclopentyl)acetic acid (209)

Prepared from **209** (87 mg, 0.23 mmol) using a procedure similar to that described for **192** to obtain the title compound as a clear syrup (69 mg, 79 %). [α]_D = -101.8° (c 1.20, CH₂Cl₂); ¹H NMR (400 MHz,

C₆D₆) δ 7.10-7.01 (m, 2H), 6.99-6.96 (m, 2H), 6.91-6.82 (m, 2H), 6.64-6.58 (m, 2H), 3.28 (s, 3H), 3.26 (s, 3H), 2.43-2.29 (m, 2H), 2.19 (dd, J = 14.8, 3.6 Hz, 1H), 2.15-2.07 (m, 1H), 1.94 (dd, J = 14.8, 10.8 Hz, 1H), 1.88-1.80 (m, 1H), 1.23-1.10 (m, 1H), 0.86 (s, 3H), 0.81 (s, 3H); ¹³C NMR (100 MHz, C₆D₆) δ 180.3 (C), 159.7 (C), 148.3 (C), 146.6 (C), 144.2 (C), 136.0 (C), 129.7 (CH), 129.0 (CH), 122.5 (CH), 120.9 (CH), 116.1 (CH), 114.7 (CH), 111.8 (CH), 111.6 (CH), 54.7 (CH₃), 54.6 (CH₃), 48.6 (CH), 34.8 (CH₂), 31.9 (CH₂), 28.2 (CH₂), 26.8 (CH₃), 22.9 (CH₃); IR (neat) 1701 cm⁻¹; MS (EI) 380.2 (M⁺); HRMS (EI) Calcd for C₂₄H₂₈O₄ (M⁺) 380.1988, found 380.1967.

2-((*R*)-3-(bis(2-methoxyphenyl)methylene)-2,2-dimethylcyclopentyl)acetic acid (210)

Prepared from **200** (30 mg, 0.08 mmol) using a procedure similar to that described for **192** to obtain the title compound as a white powder (19 mg, 62 %). Mp 182-184 °C; [α]_D = -24.6° (c 0.29, CH₂Cl₂); ¹H NMR (500 MHz, (CD₃)₂SO, 145 °C) δ 7.33-7.22 (m, 2H), 7.18-7.07 (m, 2H), 6.94-6.80 (m, 4H), 3.78 (s, 3H), 3.76 (s, 3H), 2.32-2.24 (m, 1H), 2.15-2.06 (m, 2H), 2.03-1.94 (m, 2H), 1.84-1.75 (m, 1H), 1.35-1.24 (m, 1H), 0.82 (s, 6H); ¹³C NMR (100 MHz, C₆D₆) δ 180.5 (C), 180.4 (C), 157.5 (C), 156.5 (C), 156.3 (C), 149.3 (C), 149.1 (C), 133.7 (C), 132.5 (CH), 132.2 (CH), 130.9 (CH), 130.5 (CH), 120.9 (CH), 120.7 (CH), 119.9 (CH), 119.7 (CH), 111.3 (CH), 110.8 (CH), 110.7 (CH), 55.0 (C), 54.9 (C), 54.6 (C), 54.5 (C), 48.7 (CH), 48.4 (CH), 44.9 (C), 44.6 (C), 35.1 (CH₂), 34.8 (CH₂), 31.5 (CH₂), 31.3 (CH₂), 28.3 (CH₂), 27.9 (CH₂), 24.3 (CH₃), 22.5 (CH₃), 22.4 (CH₃), 21.2 (CH₃), 1.3 (CH₃); IR (neat) 1707 cm⁻¹; MS (EI) 380.2 (M⁺); HRMS (EI) Calcd for C₂₄H₂₈O₄ (M⁺) 380.1988, found 380.1975.

2-((*R*)-2,2-dimethyl-3-((naphthalen-2-yl)(naphthalen-3-yl)methylene)cyclopentyl)acetic acid (211)

Prepared from **201** (35 mg, 0.08 mmol) using a procedure similar to that described for **192** to obtain the title compound as a clear syrup (23 mg, 65 %). [α]_D = -143.2° (c 0.60, CH₂Cl₂); ¹H NMR (400 MHz, C₆D₆) δ 7.84-7.81 (m, 1H), 7.76-6.73 (m, 1H), 7.68-7.52 (m, 6H), 7.39-7.33 (m, 2H), 7.27-7.18 (m, 4H), 2.50-2.30 (m, 2H), 2.24-2.13 (m, 2H), 1.99 (dd, J = 11.7, 8.4 Hz, 1H), 1.93-1.84 (m, 1H), 1.29-1.16 (m, 1H), 0.85 (s, 3H), 0.82 (s, 3H); ¹³C NMR (100 MHz, C₆D₆) δ 179.7 (C), 149.5 (C), 142.6 (C), 140.4 (C), 136.0 (C), 134.3 (C), 133.6 (C), 132.6 (C), 132.6 (C), 128.8 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.4 (CH), 127.2 (CH), 126.3 (CH),

126.2 (CH), 125.9 (CH), 125.8 (CH), 48.6 (CH), 45.0 (C), 34.6 (CH₂), 32.1 (CH₂), 28.4 (CH₂), 26.9 (CH₃), 23.1 (CH₃); IR (neat) 1699 cm⁻¹; MS (EI) 420.2 (M⁺); HRMS (EI) Calcd for C₃₀H₂₈O₂ (M⁺) 420.2089, found 420.2106

2-((*R*)-2,2-dimethyl-3-(di(thiophen-2-yl)methylene)cyclopentyl)acetic acid (212)

Prepared from **202** (47 mg, 0.14 mmol) using a procedure similar to that described for **192** to obtain the title compound as a turquoise powder (44 mg, 93 %). Mp 76-78 °C; [α]_D = -130.5° (c 0.57, CH₂Cl₂); ¹H NMR (400 MHz, C₆D₆) δ 6.89 (dd, *J* = 4.8, 0.8 Hz, 1H), 6.86 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.78 (dd, *J* = 3.2, 1.2 Hz, 1H), 6.73 (dd, *J* = 4.0, 1.6 Hz, 1H), 6.70 (dd, *J* = 4.8 Hz, 2.8 Hz, 1H), 6.69 (dd, *J* = 4.8, 2.8 Hz, 1H), 2.70-2.49 (m, 2H), 2.17 (dd, *J* = 14.8, 3.2 Hz, 1H), 2.11-2.01 (m, 1H), 1.96-1.85 (m, 2H), 1.28-1.16 (m, 1H), 0.81 (s, 3H), 0.76 (s, 3H); ¹³C NMR (100 MHz, C₆D₆) δ 179.8 (C), 154.2 (C), 147.3 (C), 142.8 (C), 126.4 (CH), 126.3 (CH), 125.9 (CH), 125.5 (CH), 124.8 (CH), 121.2 (CH), 48.1 (CH), 46.2 (C), 34.4 (CH₂), 33.7 (CH₂), 28.1 (CH₂), 25.8 (CH₃), 22.2 (CH₃); IR (neat) 1699 cm⁻¹; MS (EI) 332.1 (M⁺); HRMS (EI) Calcd for C₁₈H₂₀O₂S₂ (M⁺) 332.0905, found 332.0925.

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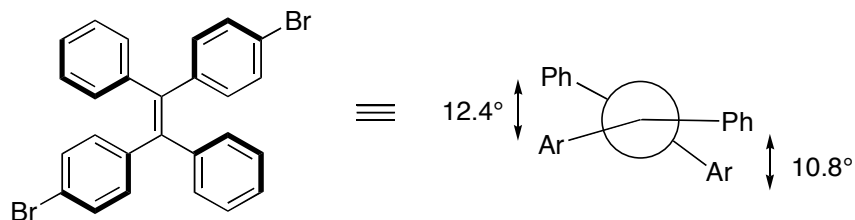
PART C: APPLICATIONS FOR THE SYNTHESIS OF MULTISUBSTITUTED OLEFINS FROM β -CHLORO- α -IODO- α , β -UNSATURATED ESTERS

INTRODUCTION

Tetrasubstituted olefins are present in a variety of natural products,¹ pharmaceuticals,² and other bioactive compounds.³ Many of these tetrasubstituted olefins bear four different carbon-linked groups. Therefore, methods to install all-carbon linked tetrasubstituted olefins in a stereocontrolled fashion is highly desirable. The synthesis of such tetrasubstituted olefins is generally made challenging by the congested nature of the resulting double bond. With four different all-carbon groups attached to the olefin, eclipsing interactions are experienced in the products, which are destabilizing for these products, as well as the transition states leading to them.

In order to relieve the torsional strain associated with these eclipsing interactions, in severe cases, the olefin can become distorted (Scheme 136). This distortion can be as much as 12° off planarity.⁴

Scheme 136. Distortion of tetrasubstituted olefins bearing all-carbon linked groups.⁴

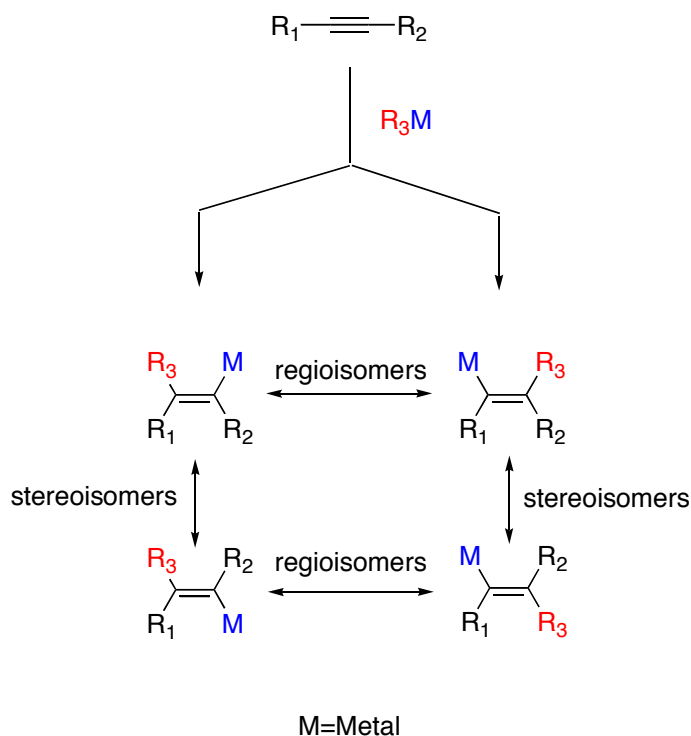


Due to this unnatural distortion, the synthesis of all-carbon linked tetrasubstituted olefins can be difficult energetically. In addition to the difficulty of obtaining tetrasubstituted olefins in general, there also exists the problem of obtaining these olefins in a stereocontrolled fashion. In the synthesis of olefins, both the regio- and stereochemistry have to be considered. These can be difficult to control, but there do exist ways of synthesizing both regio- and stereochemically pure all-carbon linked tetrasubstituted olefins.

CARBOMETALLATION OF ALKYNES

The most widely used method for obtaining tetrasubstituted olefins is by the carbometallation of alkynes.⁵ This process involves the reaction of an alkyne with an organometallic compound capable of adding to the alkyne. There are two major issues that these methodologies must address: 1) regiocontrol, and 2) stereocontrol (Scheme 137).

Scheme 137. Regioisomers and stereoisomers possible from carbometallation processes.



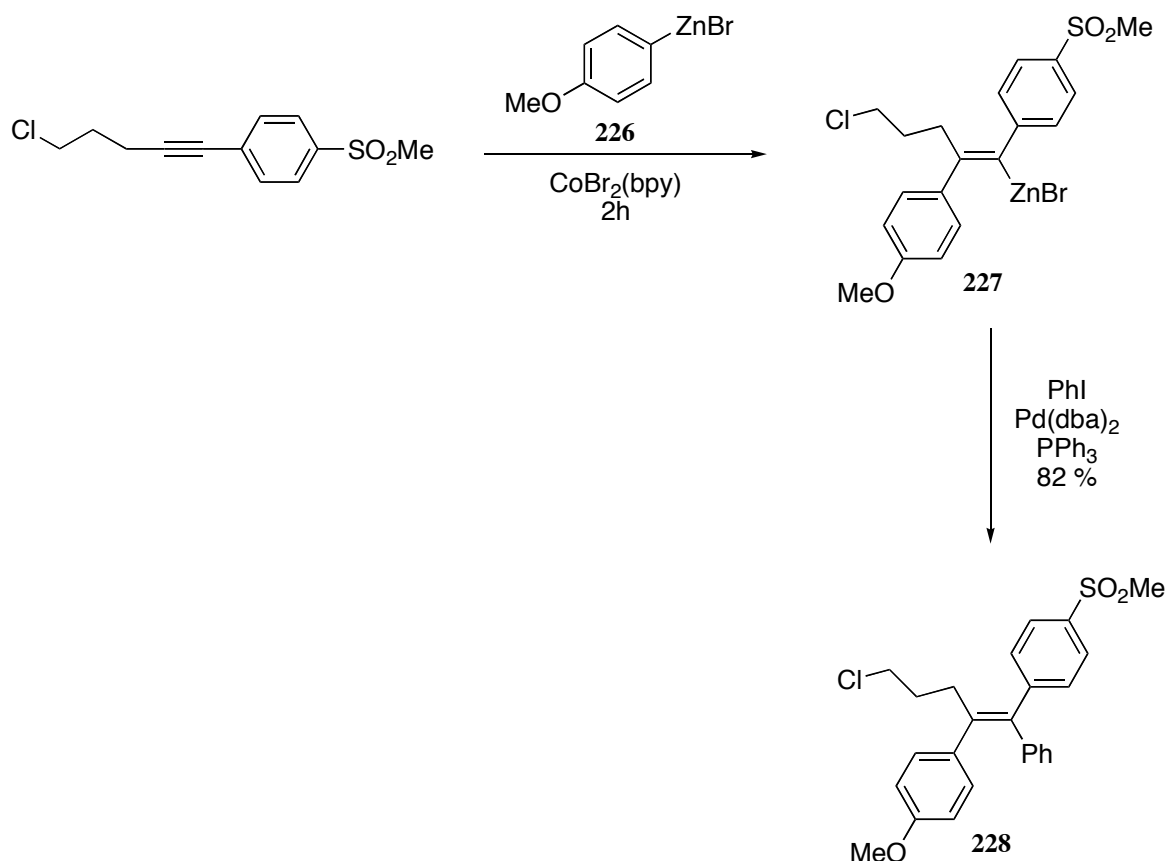
The regiochemical issue has been addressed by using directing groups, or by using symmetrical alkynes as substrates. Directing groups are the control method of choice, due to the increase in product scope that can be obtained. The directing groups can exert their influence by either sterics, electronics, or chelation.

The stereochemical issue has been addressed by the choice of organometallic reagent. Organometallic reagents can be selected such that the initial addition to the alkyne is stereospecific (either *syn* or *anti*addition), however, the subsequent coupling reaction can sometimes be problematic and lead to partial or complete inversion of the original stereospecificity from the organometallic addition.

The risk of inversion can be controlled by choice of the metal component of the organometallic reagent, substrate design, catalyst selection, or by performing the reaction at low temperatures.

The most common organometallic reagents used in the carbometallation of alkynes are organozincs, organocuprates, organoborons, organomagnesiums, and organozirconiums. Recently, organozinc reagents were used to stereoselectively form tri- and tetrasubstituted olefins from both terminal and internal alkynes under mild reaction conditions using cobalt catalysis (Scheme 138).⁶

Scheme 138. Use of organozinc reagent **226** to obtain vinylzinc intermediate **227**, which was post-functionalized to tetrasubstituted olefin **228**.

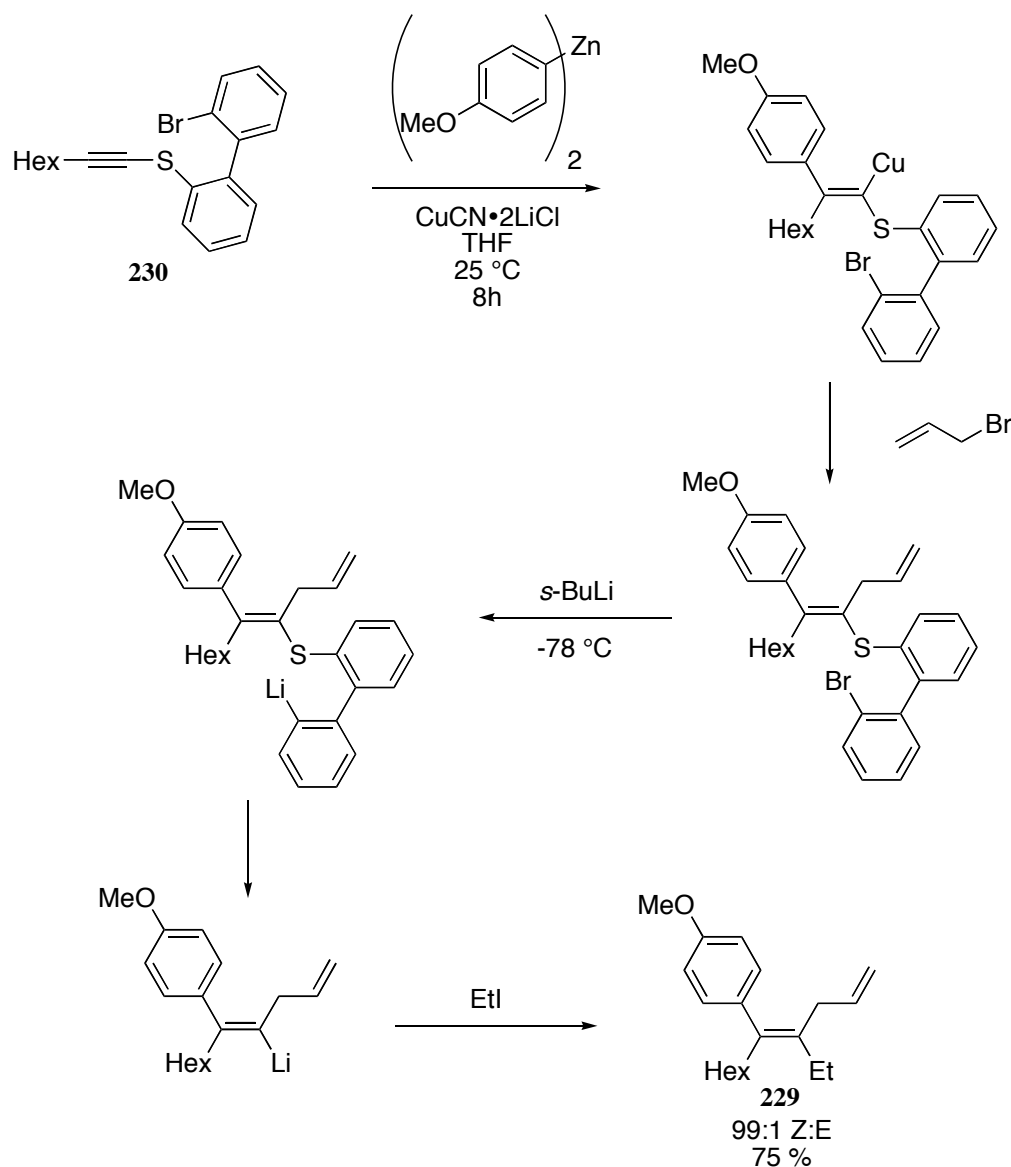


The trisubstituted olefins were obtained with yields up to 91 % using $\text{CoBr}_2(\text{bpy})$ as catalyst. The stereoselectivity was achieved due to the high preference of organozincs to add *syn*-selectively to internal alkynes in the presence of catalytic cobalt.⁷ These reaction tended to be relatively simple and reliable in comparison to other technologies employing organozinc reagents.

Carbocupration reactions have also recently been employed to obtain tetrasubstituted olefins in a stereoselective fashion.⁸ This methodology involved an activated alkyne in the formation of an alkynyl thioether, and the use of an organozinc reagent to effect the carbocupration reaction. The resulting alkenylcopper species would be trapped by an electrophile, to result in a tetrasubstituted alkenyl

thioether. Since the thioether moiety does not undergo nickel or palladium catalyzed cross coupling reactions,⁹ a novel sulfur-lithium exchange reaction was created by Knochel *et al* (Scheme 139). This sulfur-lithium exchange proceeded with the vinyl thioether functionality to provide the vinyl lithium species, which could be subsequently quenched by an electrophile.

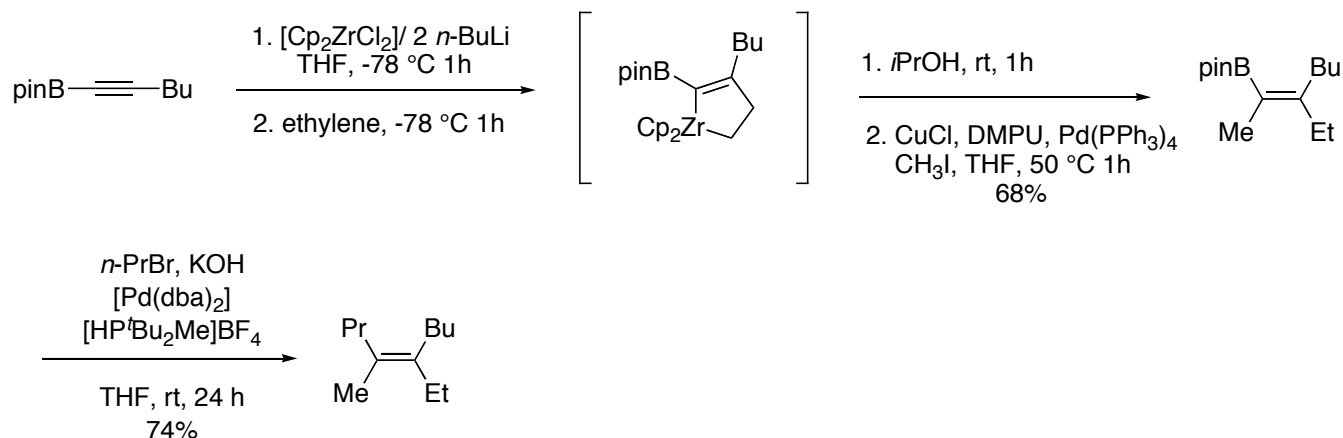
Scheme 139. Synthesis of tetrasubstituted alkene 229 from alkynyl thioether 230.



Carbozirconation has also recently been used in the stereoselective formation of tetrasubstituted olefins bearing all different carbon substituents.¹⁰ This technology utilizes alkynylboronates and [Cp₂ZrCl₂]/2-*n*-BuLi (the Negishi reagent) to form intermediate zirconacyclopentenes which can either be hydrolyzed for the eventual formation of trisubstituted alkenes, or selectively protonolyzed at the Zr-C(Sp³) bond to form intermediate zirconia species. These species could then be subjected to palladium

catalyzed cross coupling in the presence of CuCl followed by iodolysis to give the resulting trifunctionalized alkenylboronates. A Suzuki-Miyaura cross coupling reaction would then provide the tetraalkylated alkenes (Scheme 140).

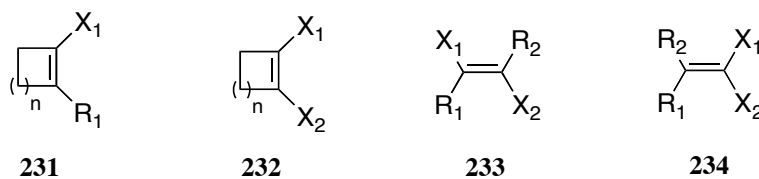
Scheme 140. Synthesis of tetrasubstituted olefins bearing all different alkyl groups via a key carbozirconation reaction.



FUNCTIONALIZATION OF EXISTING ALKENE TEMPLATES

Another method of preparing tetrasubstituted olefins involves the manipulation of existing olefins. Often, these pre-existing olefins have general structures **231** to **234**, where “x” is a halogen or pseudo-halogen (Scheme 141).

Scheme 141. General structures for olefin templates used in the construction of tetrasubstituted olefins.

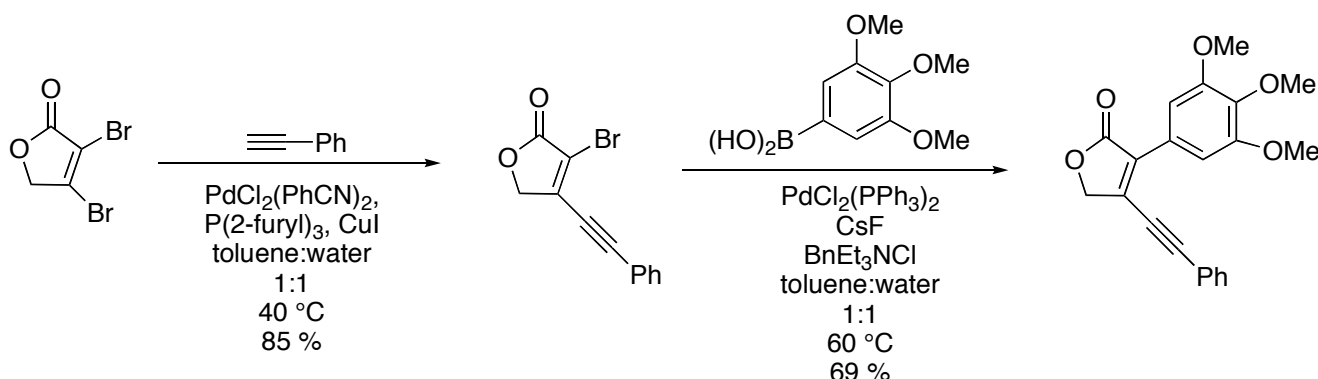


Methods involving these olefin templates often suffer the difficulty of generating the template in a stereocontrolled fashion. Often times, mixtures of stereo- and regioisomers are obtained.

The next challenge for synthesizing tetrasubstituted olefins in this manner is the introduction of the remaining groups onto the template under the right set of conditions. For halogen substituted templates, the tetrasubstituted olefins are often synthesized by either transition metal catalyzed cross coupling reactions or halogen-metal exchange followed by coupling with an organohalide.

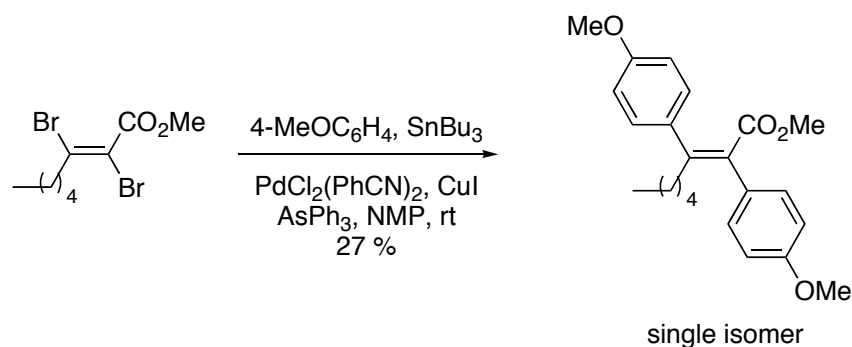
The issue with some methods is regioselectivity, because usually identical halides are present on the olefin template. Therefore, these methods either employ symmetrical substrates, or they have a means of distinguishing the two halogens from one another. These distinguishing means are usually either steric or electronic in nature, or a directing group is incorporated onto the substrate (Scheme 142).

Scheme 142. Use of an electronic bias to install remaining groups onto dihalogenated olefin template to make tetrasubstituted olefins.¹¹



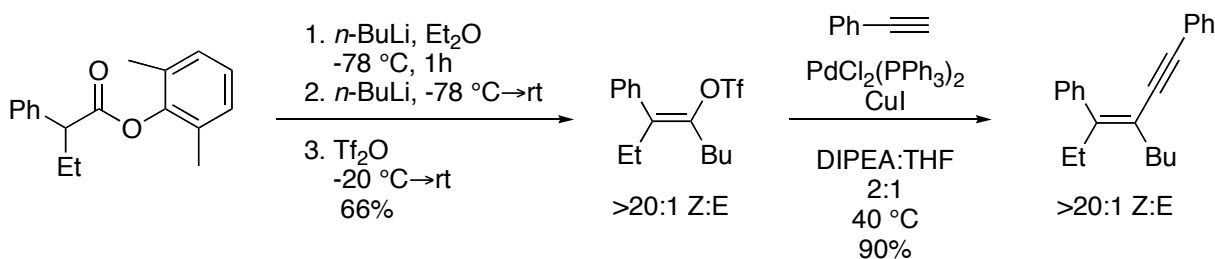
Another issue faced with the dihalogenated templates is the stereoselectivity of forming the tetrasubstituted olefins. Usually, cyclic templates are employed to overcome this issue. If acyclic templates are used, good stereoselectivity with respect to installing the remaining groups on the olefin can be obtained, as long as the starting template is a single isomer (Scheme 143).¹²

Scheme 143. Use of a stereo-enriched dihalogenated acyclic olefin template to form a tetrasubstituted olefin.



Recently, tetrasubstituted olefins were stereoselectively synthesized by ketene templates generated *in situ* (Scheme 144).¹³

Scheme 144. Synthesis of tetrasubstituted olefins via *in situ* generated ketenes.

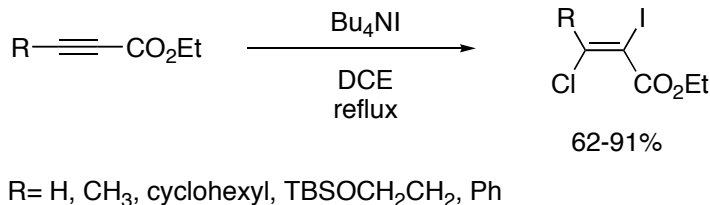


This method allowed for the template generation and tetrasubstituted alkene formation in two steps with good stereoselectivity of the resulting olefins.

SYNTHESIS OF TRI- AND TETRASUBSTITUTED OLEFINS FROM β -CHLORO- α -IODO- α , β -UNSATURATED ESTERS

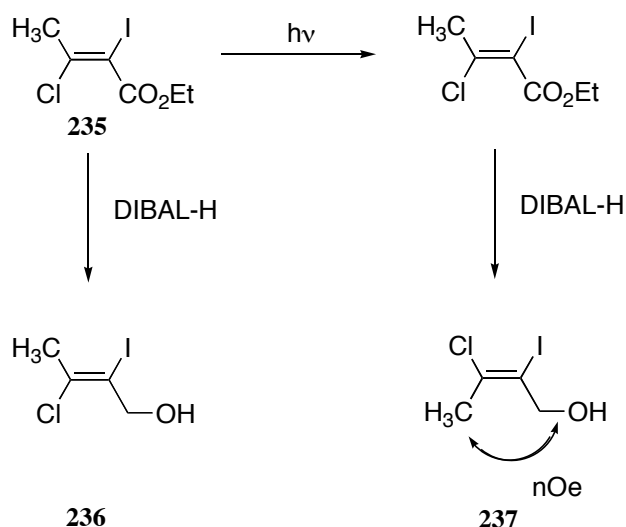
The generation of differentially halogenated alkene templates can be useful in the stereoselective construction of tetrasubstituted olefins, as different halogens generally show different reactivities in transition metal cross coupling reactions. A template containing different halogens was constructed efficiently and selectively by reacting NEt_4I and DCE with 2-alkynyl esters (Scheme 145).¹⁴

Scheme 145. Generation of β -chloro- α -iodo- α , β -unsaturated ester templates.



The chloro-iodo templates were generated in good to excellent yields as single isomers. The olefin template regiochemistry was confirmed by ¹³C NMR using template **235**, identifying the characteristic upfield shift of the carbon attached to the iodine atom. The olefin geometry was verified by photoisomerizing the alkene, reducing the ester to the alcohol with DIBAL-H, and performing nOe experiments (Scheme 146). A correlation was observed between the methyl and methylene of compound **236**, whereas this interaction was not present in compound **237**.

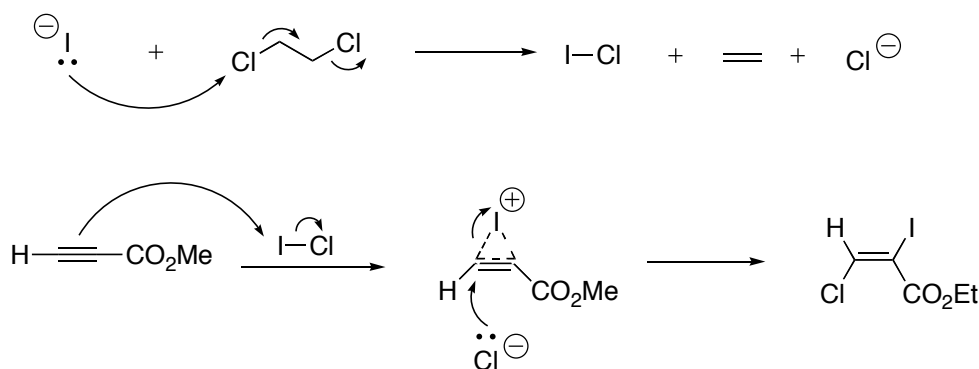
Scheme 146. Determination of alkene geometry.



The confirmation that the chloro-iodo template was indeed obtained as a single isomer made this methodology superior to similar transformations involving ICl, which tended to produce side products, *E/Z* mixtures, and lower yields.

The mechanism of this novel reaction was investigated next, in an attempt to explain why it was far superior to using ICl. An electrophilic addition mechanism was proposed to explain the selective formation of a single isomer (Scheme 147).¹⁵

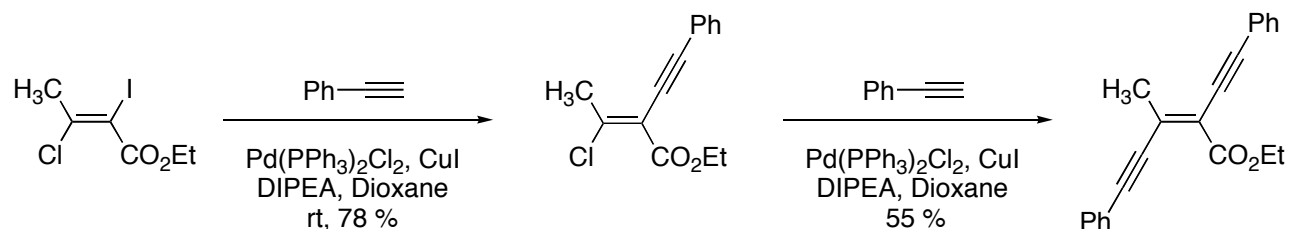
Scheme 147. Electrophilic addition mechanism proposed to explain formation of single isomer.



In this mechanism, ICl is generated in the reaction, but the key to the selectivity in this process arises from the fact that the NBu_4I is present in the mixture, and can complex with the ICl that is slowly generated. This was shown by a combination of the low reactivity of the $\text{Bu}_4\text{NI}/\text{DCE}$ system toward electrophilic aromatic substitution and the fact that slowly introducing ICl into a reaction mixture did not result in product selectivity.

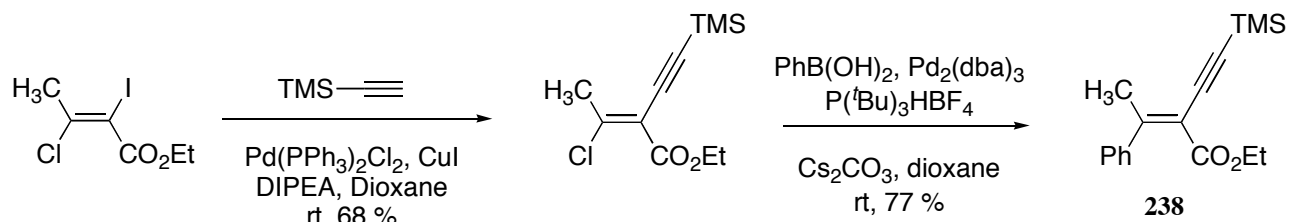
The first demonstration of the use of these chloro-iodo templates toward the synthesis of tetrasubstituted olefins involved sequential Sonogashira coupling reactions (Scheme 148).¹²

Scheme 148. Representative example of the sequential Sonogashira couplings to obtain tetrasubstituted olefins.



Sequential Sonogashira Suzuki-Miyaura coupling reactions could also be used on the chloro-iodo templates, to obtain aryl-substituted derivatives (Scheme 149).

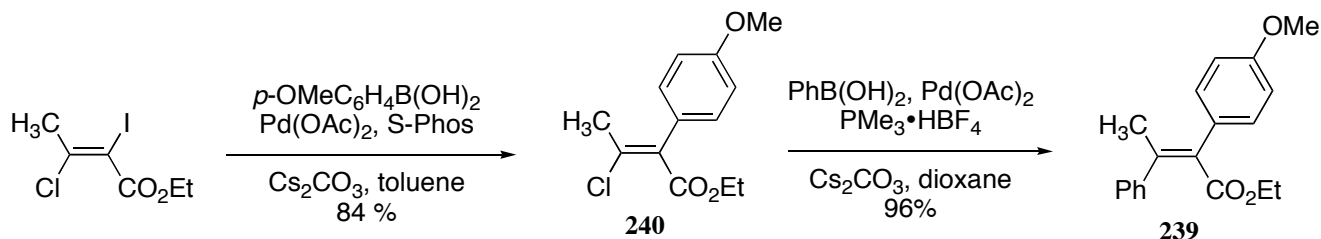
Scheme 149. Sonogashira reaction followed by Suzuki-Miyaura coupling to obtain tetrasubstituted olefin 238.



The higher reactivity of the C-I versus the C-Cl bond to oxidative insertion was key to the selectivity in this process, despite the fact that the iodine atom was in the α rather than the β -position with respect to the ester group, in which it was previously shown that the β -position was generally more reactive toward oxidative insertion.¹²

The use of sequential Suzuki-Miyaura couplings to provide tetrasubstituted olefins from chloro-iodo precursors was then demonstrated (Scheme 150).¹⁶

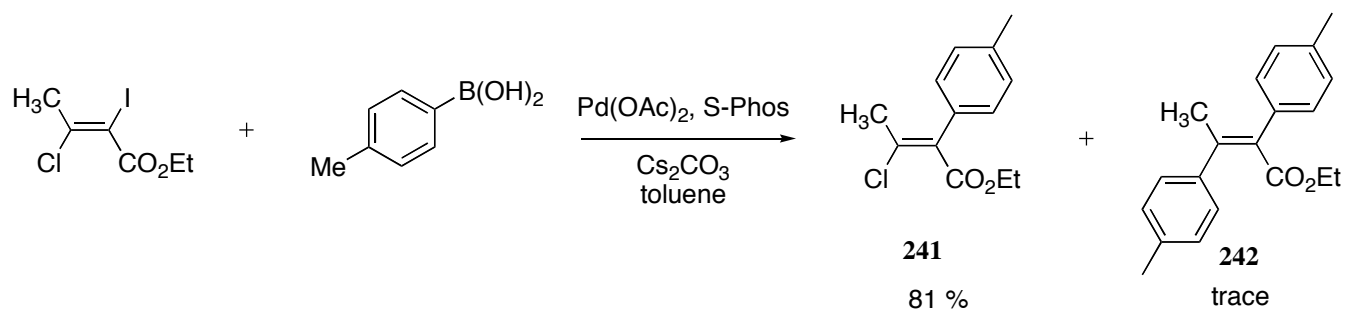
Scheme 150. Use of sequential Suzuki-Miyaura couplings to produce tetrasubstituted olefin 239 from precursor 240.



The effect of different reaction conditions on the formation of these tetrasubstituted olefins was extensively investigated. For the initial Suzuki coupling to obtain the β -chloro derivative **241**, it was

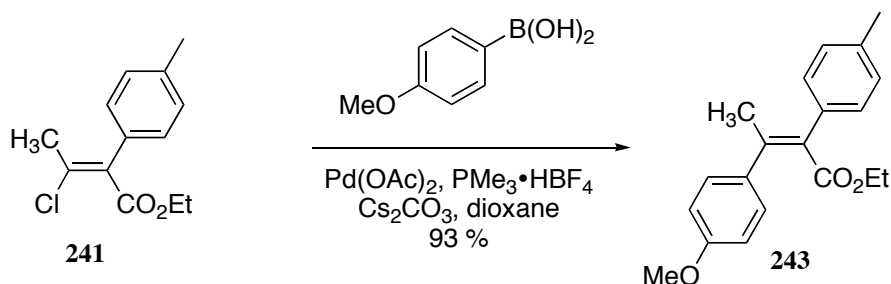
found that using $\text{Pd}(\text{OAc})_2$ as the palladium source in toluene as solvent with bulky ligand S-Phos produced the resulting derivative **241** the most cleanly, with only a trace of the double-coupled tetrasubstituted olefin **242** being formed (Scheme 151). The use of some other palladium sources and solvents led to lower conversions, whereas the use of other phosphine ligands, including Dave-Phos, which is closely related to S-Phos, produced lower overall conversions and higher amounts of the double-coupled tetrasubstituted olefin **242**.

Scheme 151. Optimal conditions to produce β -chloro derivative 241 using S-Phos as ligand.



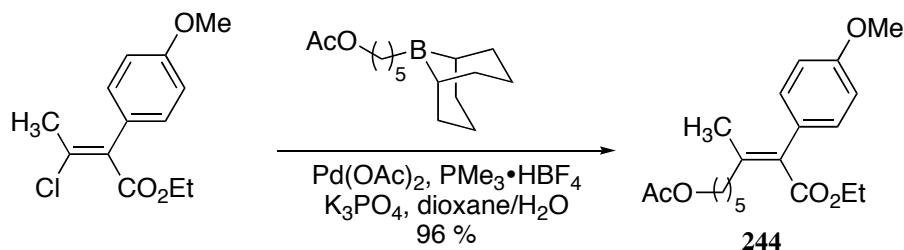
The conditions for the second Suzuki coupling were then investigated. It was found that small ligands were crucial to the generation of the tetrasubstituted olefins in high yields (Scheme 152).

Scheme 152. Small ligand facilitates formation of tetrasubstituted olefin 243 in second Suzuki-Miyaura coupling.



The methodology was then expanded to include the use of alkyl boranes in an alkyl-Suzuki cross coupling reaction to obtain tetrasubstituted olefins from β -chloro derivatives (Scheme 153).

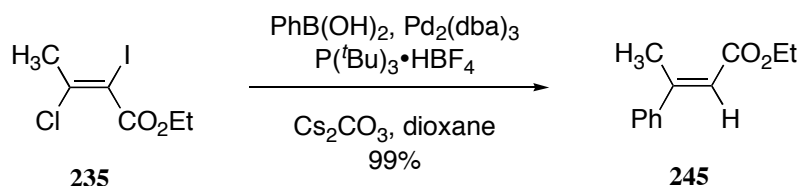
Scheme 153. Use of alkyl-Suzuki cross coupling reaction to obtain tetrasubstituted derivatives 244.



The choice of the reaction conditions for the formation of these tetrasubstituted olefins proved to be crucial to the success of the process.

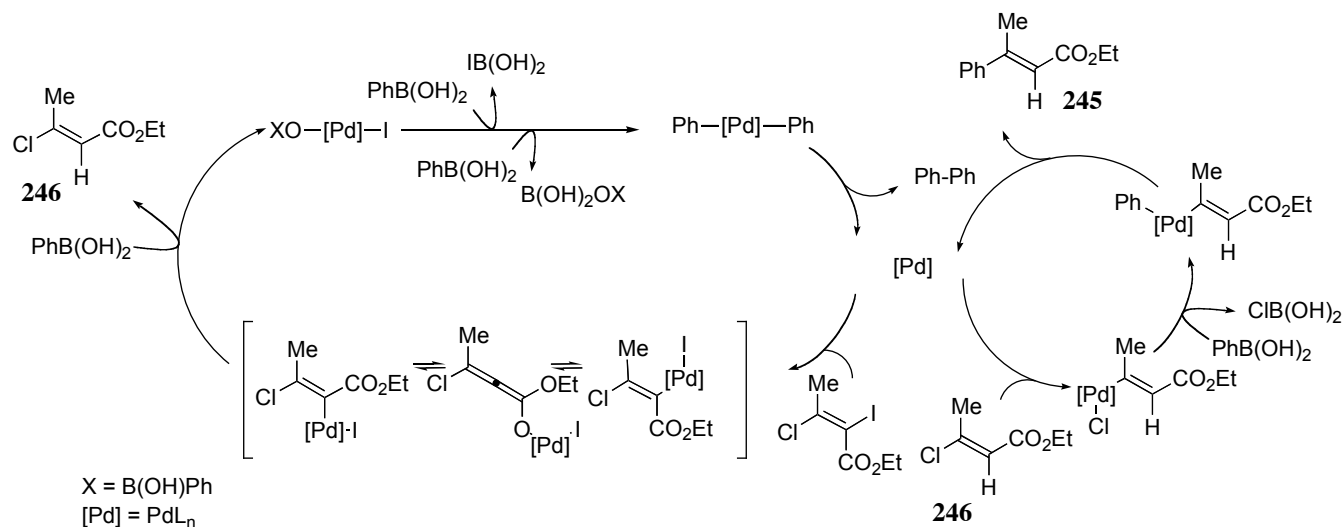
While investigating optimal conditions for tetrasubstituted olefin formation, another product was obtained in high yield instead of the anticipated tetrasubstituted olefin. This product was identified to be trisubstituted olefin **245** (Scheme 154).¹⁷

Scheme 154. Formation of an unexpected trisubstituted olefin **245.**



A variety of boronic acids could be coupled to the chloro-iodo derivative **235** to obtain the corresponding trisubstituted olefins. A catalytic cycle was proposed to account for the formation of trisubstituted olefins such as **245** from the chloro-iodo derivatives **235** (Scheme 155).

Scheme 155. Proposed catalytic cycle to account for formation of trisubstituted olefin **245.**

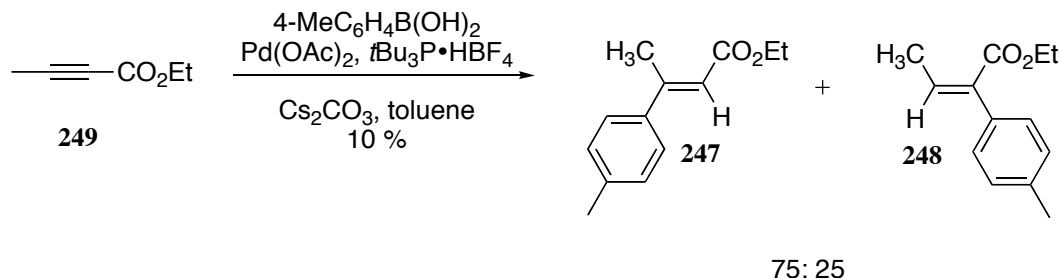


The involvement of two operative catalytic cycles was implicated in the formation of trisubstituted olefins like **245**. One cycle produced chloride **246**, which would undergo cross coupling reaction to obtain trisubstituted olefin **245** in the second cycle.

Upon investigating the mechanism for this transformation, it was found that when alkynes were directly treated with boronic acids under palladium catalysis, trisubstituted olefins such as **247** were

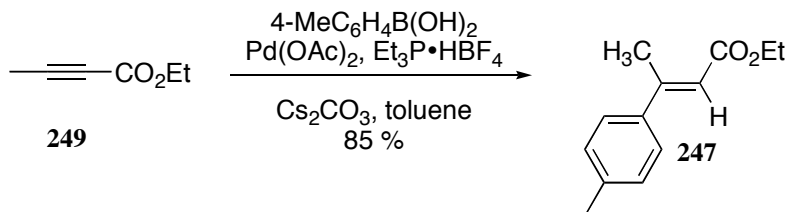
obtained stereoselectively, albeit in low yields and with the regioisomeric products such as **248** being observed (Scheme 156).

Scheme 156. Unoptimized formation of trisubstituted olefins **247 directly from alkynyl ester **249**.**



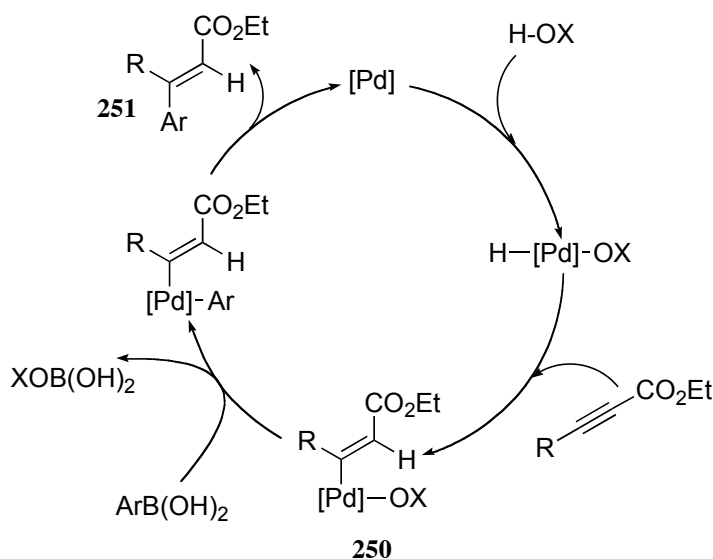
This result was still encouraging based on the fact that olefin **247** was formed stereoselectively, and also was the major regioisomer. Conditions were then investigated for the optimization of this reaction.¹⁸ It was discovered that the use of small ligands was crucial to the regioselectivity and yield issues (Scheme 157).

Scheme 157. Use of small ligand to provide derivative **247 only in good yield.**



The reaction was then expanded to produce a variety of trisubstituted alkenes, varying both the boronic acid and alkynyl ester components. A mechanism was proposed based on an investigation into the source of the hydrogen in these reactions, as well as similar methods previously proposed (Scheme 158).¹⁹

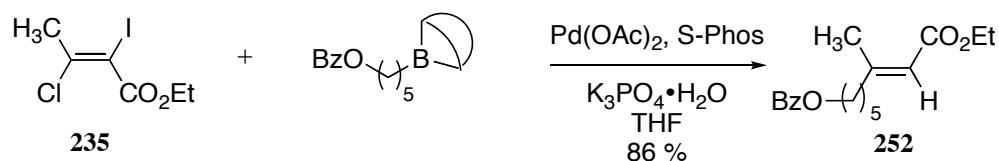
Scheme 158. Proposed catalytic cycle for production of trisubstituted olefins from alkynyl esters.



The first step was thought to involve the oxidative insertion of palladium into an OH bond such that a H-Pd-OX species was formed. This was suggested because an isotope effect was observed for hydrogen transfer, and that pinacol boronic esters did not undergo this process when water was absent from the reaction medium. A *syn*-carbopalladation into the triple bond of the alkynyl ester would follow the oxidative insertion to give a palladium intermediate **250**, which could transmetalate with the arylboronic acid, and reductively eliminate to obtain trisubstituted olefins **251**.

Single isomer trisubstituted olefins could also be prepared bearing alkyl groups using an alkyl Suzuki reaction.^{20,21} The first method explored for the preparation of these alkylated trisubstituted olefins involved starting from the chloro-iodo derivative **235**.²⁰ Optimal conditions were found using Pd(OAc)₂ as catalyst, S-Phos as ligand, and K₃PO₄•H₂O as base in THF (Scheme 159).

Scheme 159. Optimal conditions in the synthesis of a trisubstituted olefin **252 bearing alkyl groups.**

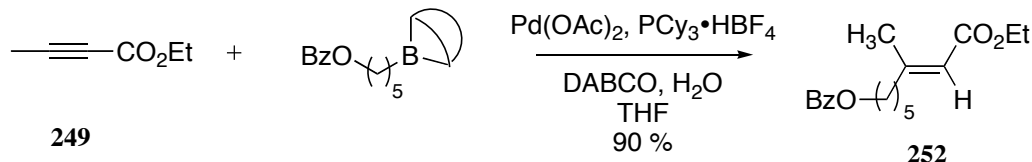


The source of hydrogen for the alkene and the origin of stereoselectivity was investigated by a series of mechanistic experiments. The experiments showed that the hydrogen source was the water associated

with the base, and the origin of stereoselectivity was a result of the hydrogen being incorporated at the iodo position first, followed by alkyl-Suzuki coupling to obtain single isomers of type **252**.

An expansion on this methodology used alkynyl esters directly with alkyl boranes to make the trisubstituted alkenes bearing alkyl groups.²¹ The optimal ligand was found to be PCy₃, and DABCO the optimal base for these transformations (Scheme 160).

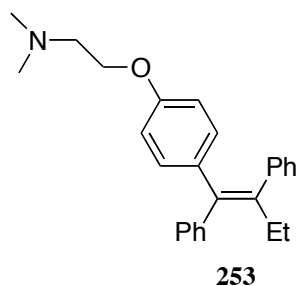
Scheme 160. Optimized alkyl-Suzuki couplings onto alkynyl esters.



A variety of alkyl trisubstituted olefins could be obtained with this method that would otherwise be difficult to make.

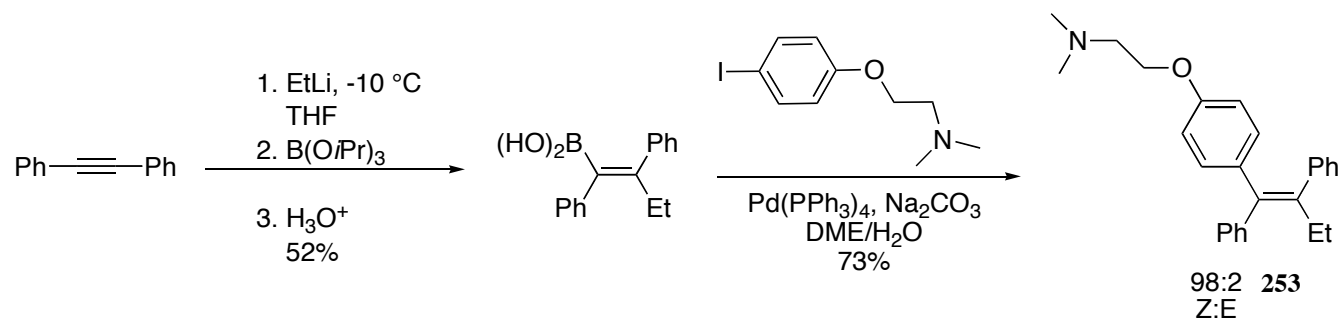
APPLICATIONS OF METHODOLOGIES PROVIDING ACCESS TO HIGHLY SUBSTITUTED ALKENES

The presence of highly substituted alkenes in natural products and pharmaceuticals provides a target for demonstrating a useful application of methodologies that achieve the synthesis of these moieties. One such target with biological importance is Tamoxifen (**253**).



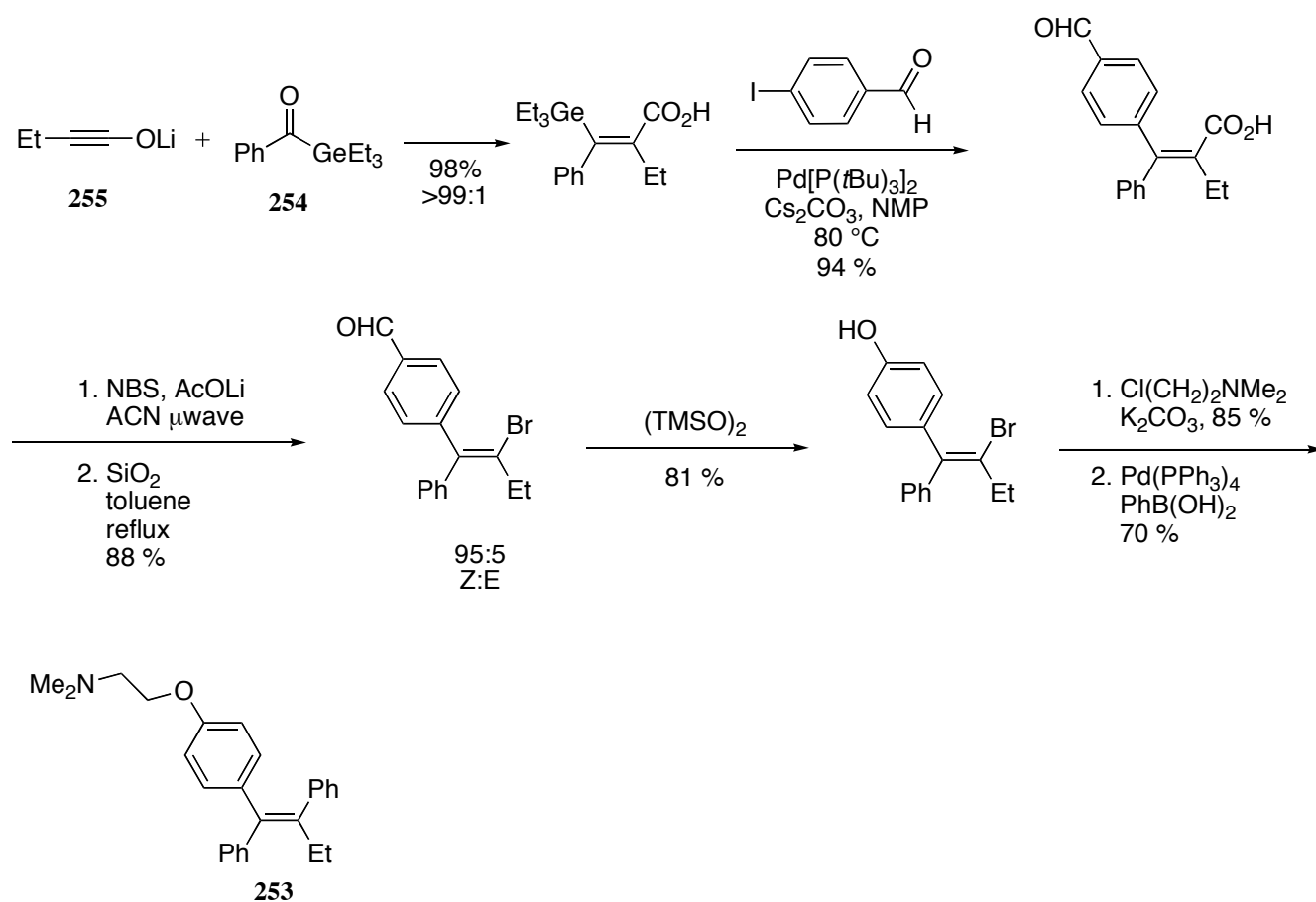
Tamoxifen is a selective estrogen receptor modulator (SERM) that is used in the treatment of estrogen-dependent breast cancer.²² Most of the successful stereoselective syntheses of tamoxifen have involved carbometallation of alkynes as a strategy.²³ An example of such a strategy is in the carbolithiation of diphenylacetylene (Scheme 161).^{2d}

Scheme 161. Synthesis of tamoxifen by carbolithiation of diphenylacetylene.



More recently, a strategy to construct tamoxifen from a benzoyl germane **254** and an alkynoate **255** was reported (Scheme 162).²⁴

Scheme 162. Stereoselective synthesis of tamoxifen using benzoyl germane **254 and alkynoate **255**.**

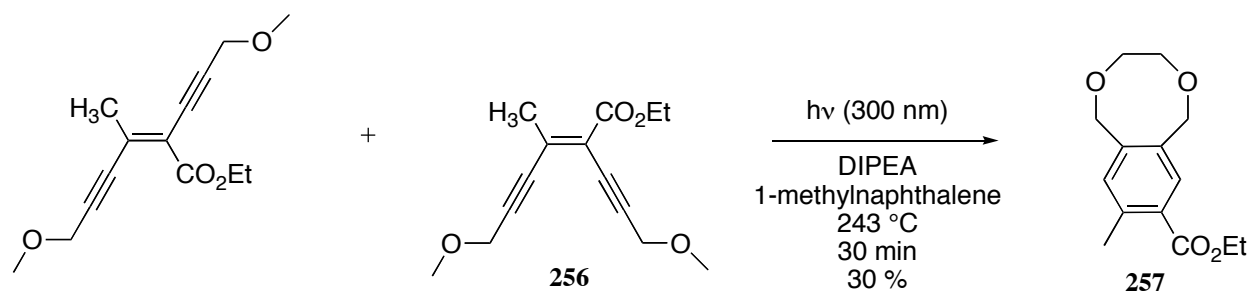


The stereoselective methods for constructing tamoxifen could be expanded by employing methodology developed in our lab.

APPLICATIONS OF METHODOLOGY PROVIDING SINGLE ISOMER MULTISUBSTITUTED OLEFINS AS PRECURSORS IN OTHER TRANSFORMATIONS

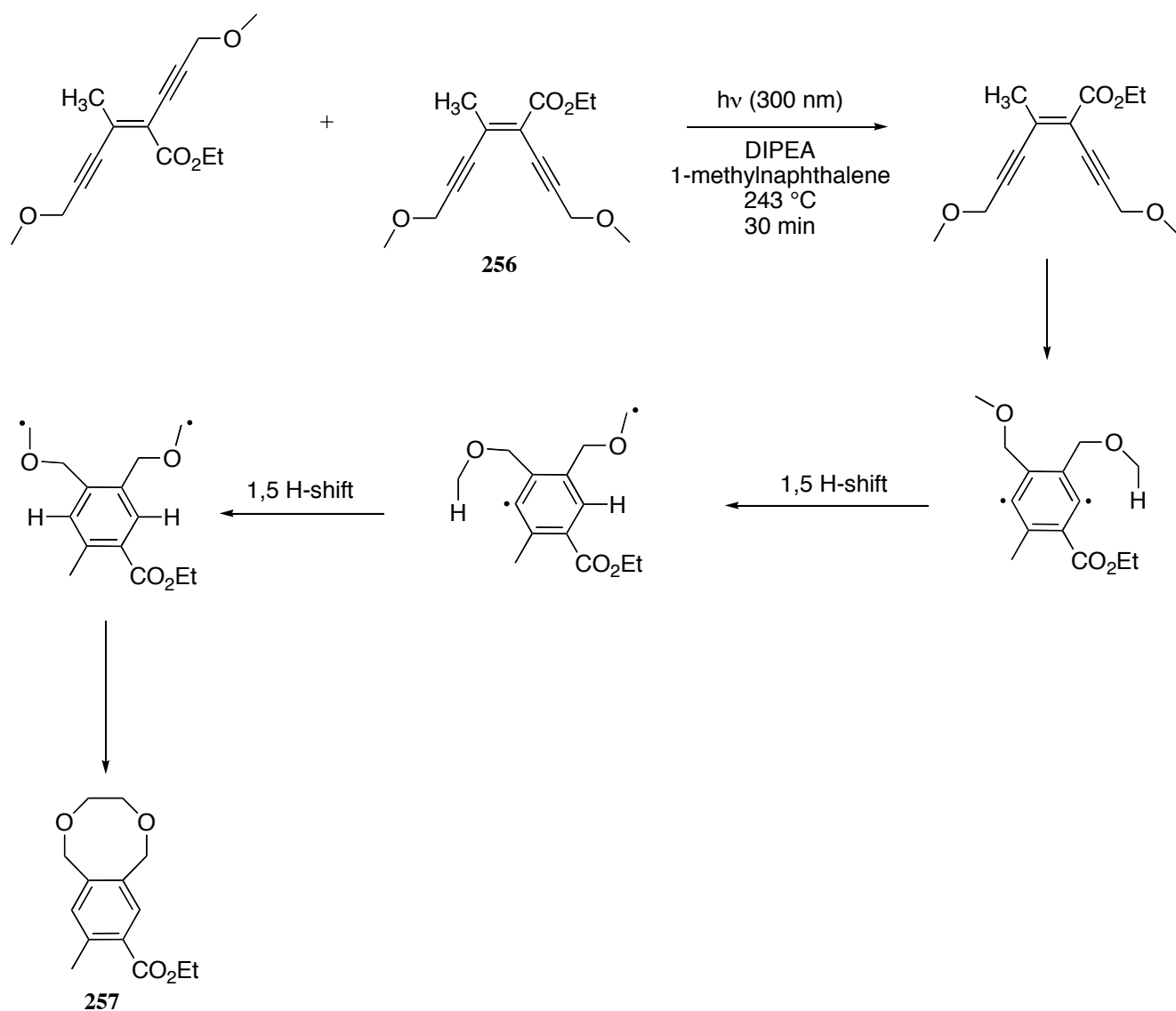
Recently, the technology developed in our lab has been applied toward the use of single isomer tetrasubstituted olefins in further synthetic transformations. One such example has been the Bergman cyclization of tetrasubstituted derivatives **256** to obtain fused aryl-cyclooctyl ring products (Scheme 163).²⁵

Scheme 163. Bergman Cyclization on tetrasubstituted olefins **256.**



The implication of two sequential 1,5-hydride shifts followed by a resulting radical-radical combination to form the 8-membered ring was used to explain the formation of product **257** (Scheme 164).

Scheme 164. Proposed pathway leading to octyl ring product.

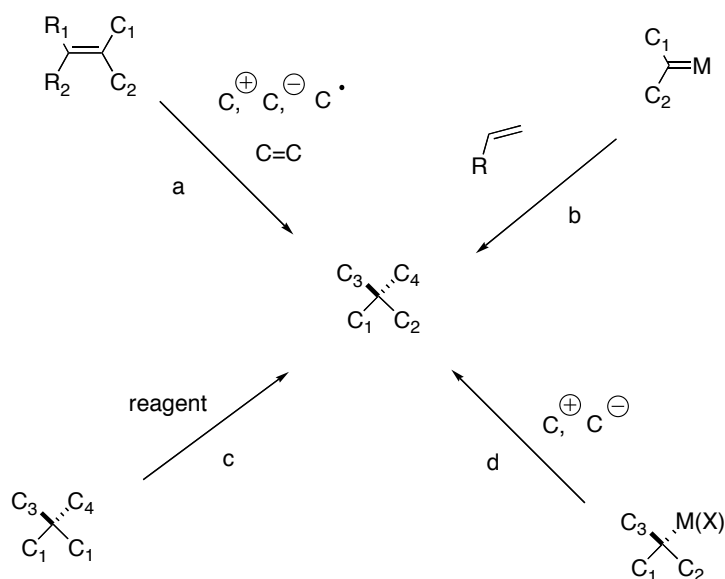


STEREOCONTROLLED SYNTHESIS OF TRISUBSTITUTED OLEFINS FOR THE CONSTRUCTION OF ALL-CARBON QUATERNARY CENTERS

Another potential synthetic use for single isomer multisubstituted olefins prepared with our methodology is in the synthesis of all-carbon quaternary centers. The enantioselective synthesis of all-carbon quaternary centers can be a very difficult transformation in organic synthesis. The stereochemical outcome of the quaternary centers can be controlled by efficient stereoinduction from the corresponding precursors.

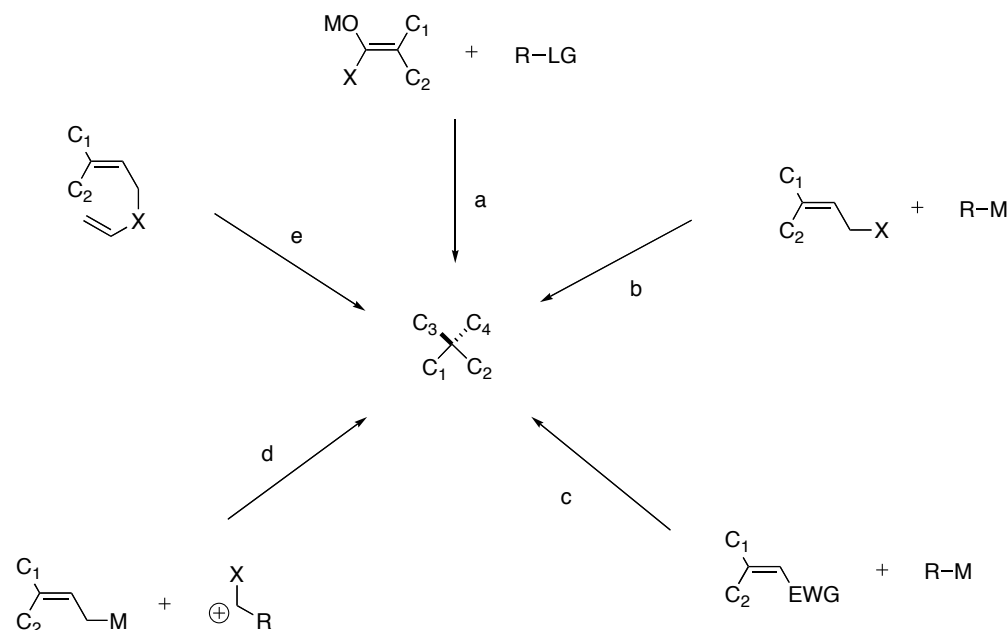
The methods available to construct quaternary centers in enantioselective fashion fall into four general categories (Scheme 165):²⁶ a) the use of a geminally disubstituted alkene precursor, in which an additional carbon substituent is added via a carbon-based reagent in the form of an electrophile, nucleophile, or radical; b) use of a carbene and an unsymmetrical olefin to afford simultaneous C-C bond formation, producing a cyclopropane; c) desymmetrization of a prochiral quaternary carbon, and; d) use of an optically active tertiary alkyl metal substrate, and stereospecifically reacting with a nucleophilic or electrophilic carbon.

Scheme 165. Four general strategies for the enantioselective production of quaternary centers



The first three categories are the most widely used for the enantioselective construction of quaternary centers. Method (a) is the most common for constructing quaternary centers in non-cyclic systems. This general strategy can be further broken up into five different types of methods for the stereoselective construction of acyclic compounds possessing all-carbon quaternary centers (Scheme 166).²⁷

Scheme 166. General methods to create acyclic all-carbon quaternary centers



These categories involve enantioselective alkylation reactions (path a),²⁸ allylic alkylation (path b),²⁹ conjugate addition (path c),³⁰ nucleophilic allylation (path d),³¹ and rearrangements of carbon skeletons (path e).³²

These methods all involve the transformation of sp² carbons to fully substituted sp³ carbons in a facially selective way. This often requires good control of *E/Z* geometry in the sp² hybridized precursor in order to observe good stereoselectivity in the final product. Therefore, methods that can produce the olefinic precursors in a stereocontrolled way, are valuable for the subsequent transformation of these olefins to stereogenic quaternary centers.

Nucleophilic allylation reactions (path d) have been important in the construction of these all-carbon quaternary centers. When stereodefined 3,3-disubstituted allyl metal species are employed, the reactions are generally stereospecific. This high reliability in the transfer of stereochemical information from the allyl metal species to the ensuing quaternary center makes these transformations a good choice in the synthesis of acyclic compounds containing quaternary centers.

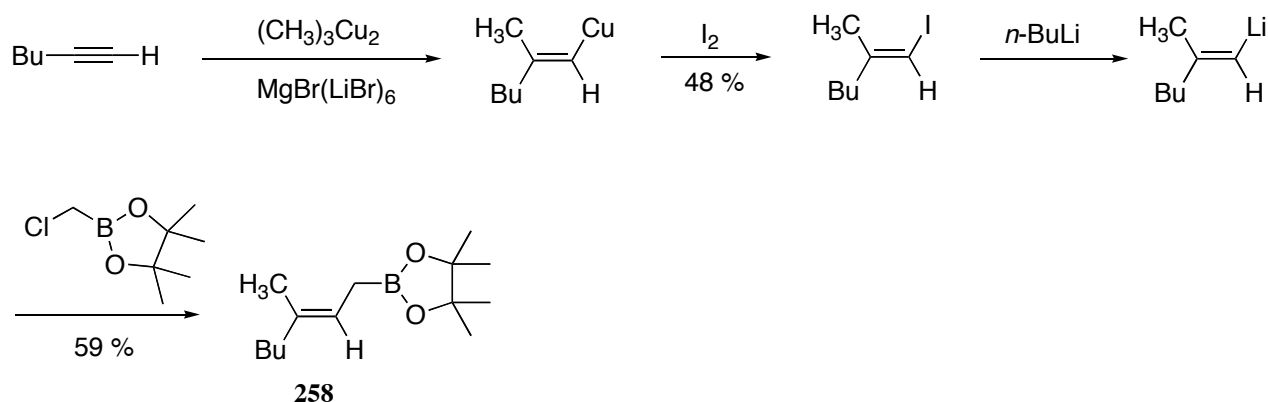
There is a relatively limited number of publications concerning the stereocontrolled preparation of 3,3-disubstituted allyl metal species. The stereoselective formation of these disubstituted species is imperative in the resulting stereoselectivity of the quaternary center formation process. In general, good

diastereoselectivity can be achieved by using geometrically pure 3,3-disubstituted allyl metal species in the construction of all-carbon quaternary centers.³³ The enantioselectivity can also be controlled by the use of chiral ligands on the metal, or by the use of a chiral catalyst.³⁴

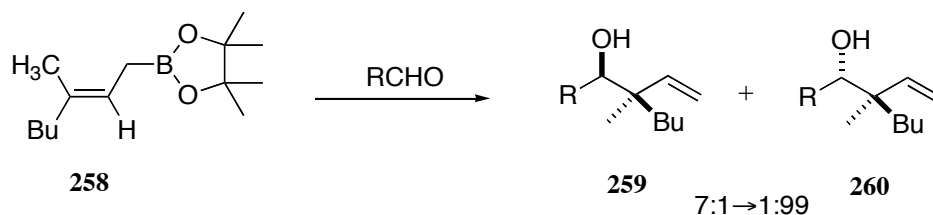
There are three main 3,3-disubstituted allyl species that have been used in the diastereoselective construction of quaternary centers: allyl boronates, allyl trichlorosilanes, and allyl zinc species.³⁵ The former two classes of reagents are generally stable to metallotropic equilibrium, that is, the alkene is configurationally stable. The allyl zinc derivatives are usually configurationally unstable, causing the alkene to isomerize between the *E* and *Z* alkenes, even at low temperatures.³⁶ The way that this metallotropic equilibrium has been slowed in the past is by chelating to the zinc species via a sulfoxide substituent on the alkene.³⁷

The use of allyl boronates for the construction of quaternary all-carbon centers was pioneered by Hoffmann and involved the transformation of single isomer trisubstituted olefins bearing an allylic boronic ester group to all-carbon quaternary centers.³³ In initial reports, the quaternary centers were generated from trisubstituted allyl boronates prepared from cuprate addition to an alkyne followed by an iodine quench, lithium-halogen exchange, and attack on a chloromethyl boronate (Scheme 167).²⁸

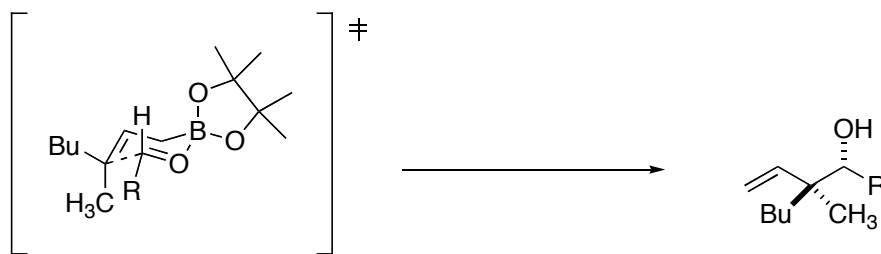
Scheme 167. Preparation of trisubstituted allyl boronates as precursors for quaternary center forming reactions.



The trisubstituted precursor was obtained in 95 % selectivity for the *E* isomer. This was then reacted with aliphatic and aromatic aldehydes with diastereoselectivities ranging from 7:1 to 99:1, with larger groups attached to the aldehyde giving better selectivity (Scheme 168).

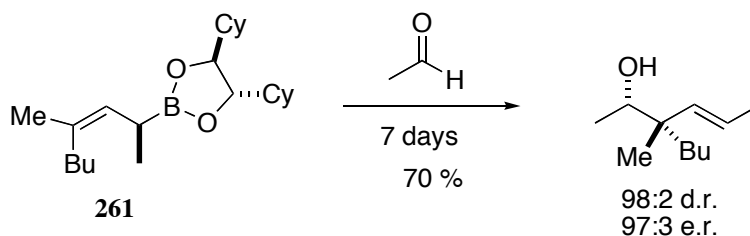
Scheme 168. Addition of allyl boronate 258 to aldehydes.

The proposed transition state for this process was a Zimmerman-Traxler³⁸ transition state, where it was rationalized that the group attached to the aldehyde occupied an equatorial position (Scheme 169). There was an erosion in selectivity that was realized for aliphatic aldehydes, which may have been due to the axial positioning of the aldehyde's R group.²⁶ This axial positioning was rationalized by the avoidance of two Gauche interactions arising from the presence of the geminal substituents on the alkene.³⁹

Scheme 169. Proposed transition state leading to formation of quaternary carbon containing products.

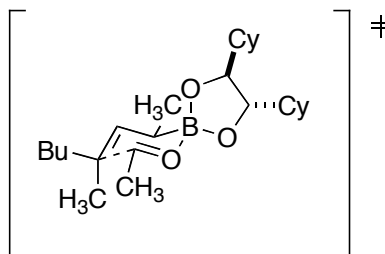
The only quaternary center formed with this methodology at the time was that possessed by compounds **259** and **260**. The reactions typically were carried out for 5-8 days to obtain yields in the range of 62-87 % with the aldehydes utilized.

The preparation of enantiomerically enriched alcohols containing all-carbon quaternary centers was then achieved by the use of diastereoenriched α -methyl allyl boronates **261** (Scheme 170).^{33b} Up to 97:3 enantiomeric ratio was achieved with this method.

Scheme 170. Enantioselective preparation of all-carbon quaternary centers using allyl boronates.

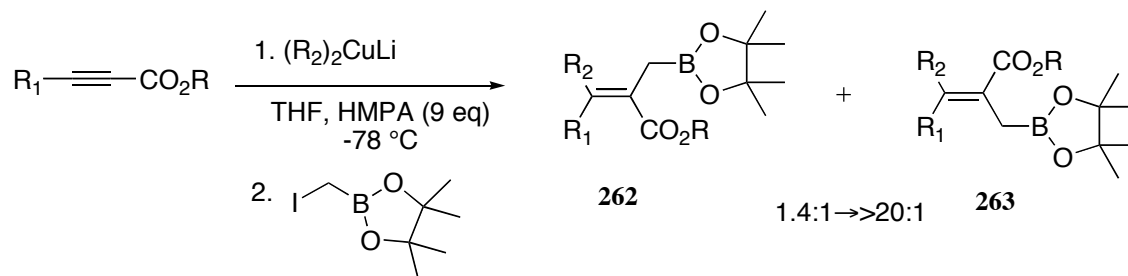
The proposed origin of stereoselectivity in this process was through a chair transition state where the α -methyl group of the allyl boronate occupies an equatorial position, in order to minimize A(1,3) strain (Scheme 171).⁴⁰

Scheme 171. Proposed transition state to explain stereoselectivity in reaction with 261.



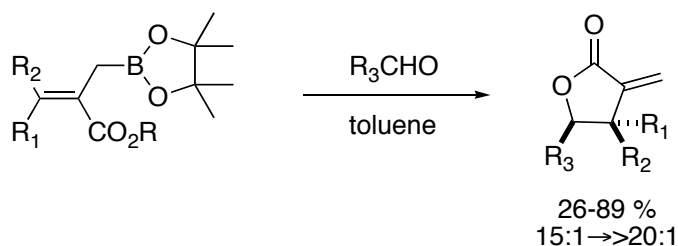
Another method used to prepare trisubstituted allyl boronates in a stereoselective fashion also involves the carbocupration of an alkyne, followed by trapping with a halomethyl boronate (Scheme 172).⁴¹

Scheme 172. Tandem carbocupration/electrophilic trapping of alkyneates to make 2-alkoxycarbonyl allyl boronates.



This technology produced 2-alkoxycarbonyl allyl boronates in yields up to 95 %, and selectivity of **262** to **263** ranging from nearly 1:1 up to >20:1. These derivatives were then used in γ -lactonization reactions to produce the γ -lactones in good diastereomeric ratios (Scheme 173).

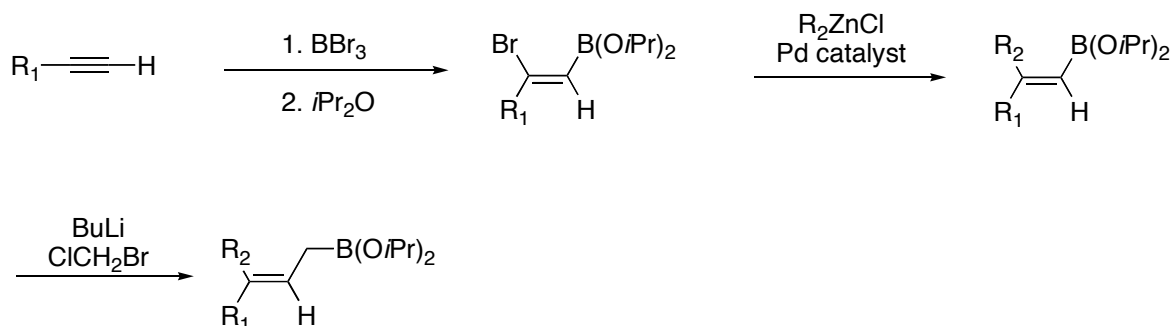
Scheme 173. Use of 2-alkoxycarbonyl allyl boronates in γ -lactonization reactions.



The γ -lactones were obtained in moderate to good yields and generally in a stereospecific manner.

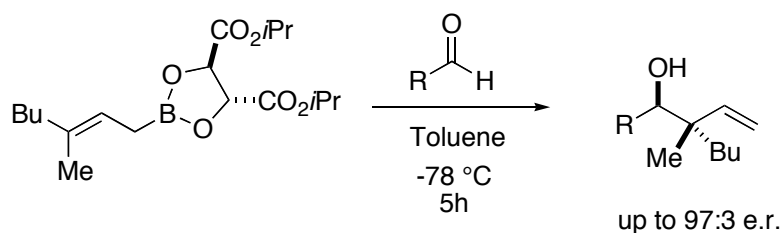
A third method reported for the stereoselective synthesis of 3,3-disubstituted allylborane derivatives involves the haloboration of alkynes, followed by a cross coupling reaction with alkyl zinc species and subsequent homologation reaction (Scheme 174).⁴²

Scheme 174. Preparation of 3,3-disubstituted allylboranes.



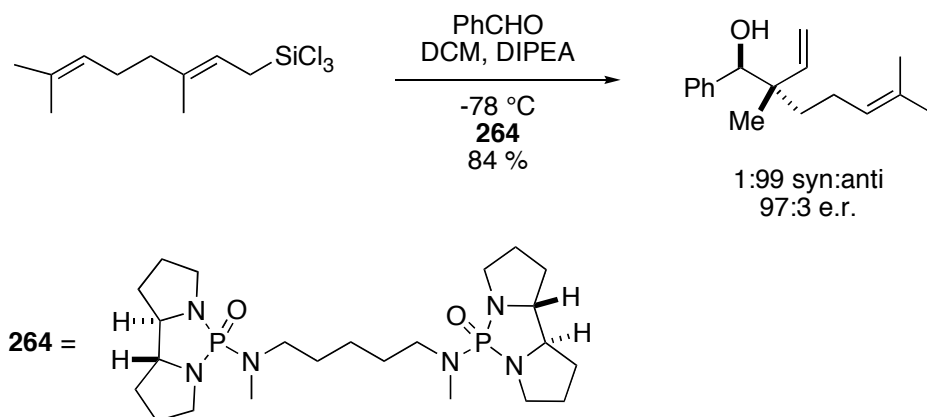
The quaternary center was then generated by reacting these allylboronates with aldehydes in diastereoselectivity up to 95 %. *n*-Butyl and methyl groups were demonstrated as R₁ and R₂, as well as phenyl, *n*-butyl quaternary centers. These diisopropoxy derivatives have been used to prepare quaternary all-carbon centers in enantiomeric ratios up to 97:3 (Scheme 175).⁴³

Scheme 175. Enantioselective synthesis of all-carbon quaternary centers using tartrate ester derivatives of 3,3-disubstituted allyl boranes



Another way to obtain all-carbon quaternary centers in a stereocontrolled way is by the use of allyl trichlorosilane reagents under chiral phosphoramidate catalysis.³⁴ Excellent diastereo- and enantioselectivity could be obtained for selected all-carbon quaternary center compounds (Scheme 176).

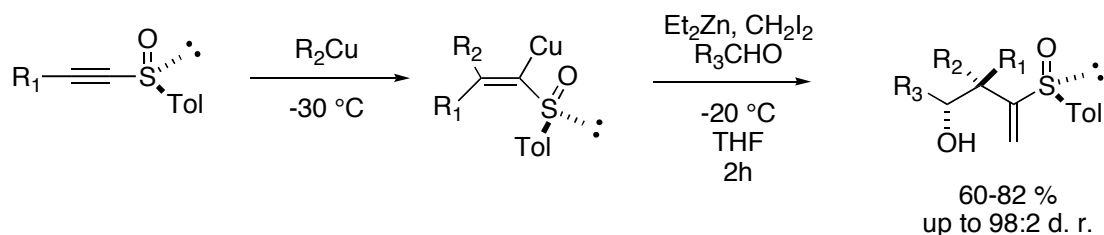
Scheme 176. Stereodefined 3,3-disubstituted allyl trichlorosilanes in the enantioselective formation of quaternary centers



A chair-like transition state was implicated in the reaction, leading to the diastereo- and enantioselectivity.^{34e} The geminally substituted allyl trichlorosilanes were prepared in 3 steps via carbometallation of an alkyne using trimethylaluminum and ZrCp_2Cl_2 .^{34c}

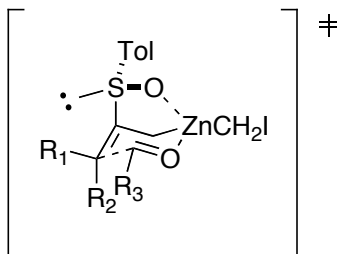
The last major type of 3,3-disubstituted allyl species that has been used in the enantioselective construction of quaternary centers is geminally substituted allyl zinc reagents.⁴⁴ These reagents can be prepared in a stereocontrolled way in one pot by carbocupration of an alkynyl sulfoxide followed by a zinc homologation reaction then the nucleophilic allylation reaction (Scheme 177).³⁷

Scheme 177. One-pot preparation of quaternary centers via geminally disubstituted allyl zinc species possessing a chelating sulfoxide group.



The transition state proposed for this process was chair-like in nature with the group attached to the aldehyde carbonyl occupying an equatorial position, while the oxygen from the sulfoxide chelated to the zinc, and the sulfoxide's lone pairs eclipsed the double bond, minimizing A(1,3) strain⁴⁵ (Scheme 178).

Scheme 178. Proposed transition state for the formation of quaternary centers from allyl zinc species stabilized by a sulfoxide group.



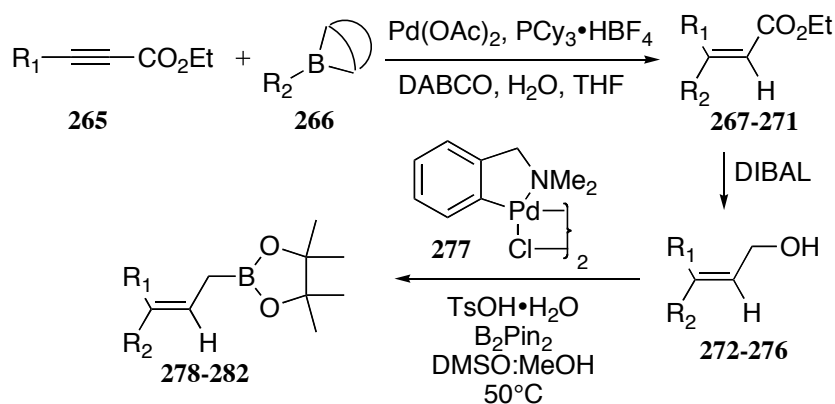
The stereoselective construction of tri- and tetrasubstituted olefins previously described in our laboratory can be applied in a variety of synthetic applications. One such application that was explored was the attempted synthesis of tamoxifen, which itself is a tetrasubstituted olefin. The methodology could also be applied to construct tri- or tetra-substituted precursors for the synthesis of quaternary carbon centers in a stereocontrolled fashion.

Specifically, the relatively few methods for synthesizing 3,3-disubstituted allylboronates in a stereocontrolled fashion speaks to the importance of methods that can be employed to make these special compounds. Methodology developed in our laboratory was applied toward the stereocontrolled generation of 3,3-allyl boronates, and their use in the diastereoselective formation of all carbon quaternary centers.⁴⁶

RESULTS AND DISCUSSION FOR STERECONTROLLED PREPARATION OF QUATERNARY CARBON CENTERS VIA SINGLE ISOMER TRISUBSTITUTED OLEFINS

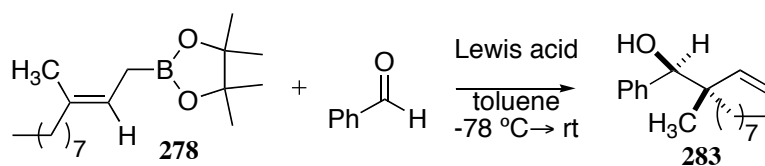
In order to prepare the single isomer substrates required for this study, the methodology previously described⁴⁷ in our lab was employed. Thus, alkynyl ester starting materials **265** were transformed into their alkenyl ester counterparts **266** using an alkyl borane **267-271** and palladium catalysis. The resulting alkenyl esters **267-271** were reduced with DIBAL-H to afford the vinyl alcohols **272-276**. These alcohols were then treated with bis(pinacolato)diboron in the presence of palladium catalyst **277** to afford the corresponding disubstituted allylborane nucleophiles **278-282** (Scheme 179)²¹.

Scheme 179. Preparation of disubstituted allylborane nucleophiles from single isomer trisubstituted olefins.



To demonstrate the addition of these allylborane nucleophiles to aldehydes, substrate **278** was reacted with benzaldehyde in toluene at $-78^\circ C$ to afford **283** in 64 % yield. A diastereomeric ratio of $> 30:1$ was observed for this adduct. This suggested that the stereointegrity of the starting olefin was being maintained in the product.

In order to improve the yield of the product and reaction time, it has been reported in the literature that the addition of a Lewis acid can assist the nucleophilic addition of allylboranes to aldehydes.^{41,48} In the interest of optimization, different Lewis acids were employed, with varying success (Table 40).

Table 40. Use of Lewis acids to facilitate condensation between allylboronates and aldehydes.^a

Entry	Lewis Acid	Yield (%) ^b	Selectivity (dr) ^c
1	None	64	>30 : 1
2	ZnCl ₂	60	>30 : 1
3	BF ₃ •OEt ₂	<5	
4	FeBr ₃	46	>30 : 1
5	TiCl ₄	39	>30 : 1
6	SnCl ₄	48	>30 : 1
7	AlCl ₃	72	>30 : 1 ^d
8	CSA	21	9 : 1

^a**Reagents and conditions:** 1.0 equiv of **278**, 2.4 equiv of benzaldehyde, 0.12 equiv of Lewis acid, toluene, -78 °C.

^bIsolated yields

^cDetermined by NMR

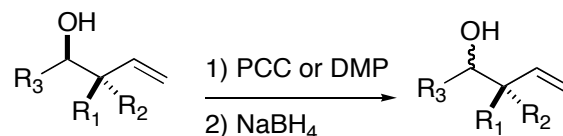
^dA ratio of 146:1 was measured by NMR integration.

The addition of ZnCl₂ did not show an improvement in yield compared to the case in which no Lewis acid was used (entries 1, 2). The addition of acids such as BF₃•OEt₂, FeBr₃, TiCl₄, and SnCl₄ resulted in a detrimental effect on the yield (entries 3-6). A slight improvement in yield and reaction speed was realized by using AlCl₃ as a catalyst (entry 7). Using a Brønsted acid⁴¹ decreased both the yield and selectivity of the process (entry 8).

The most efficient way to confirm that one diastereomer was selectively being produced was to compare the ¹H NMR signals for the alkene hydrogens of both diastereomers for each derivative made in this study. This required us to obtain a ¹H NMR spectrum of the other diastereomer to the one produced using our methodology. The most straightforward way to obtain this spectrum was by taking each product synthesized from our technology and subjecting it to an oxidation/reduction sequence. This

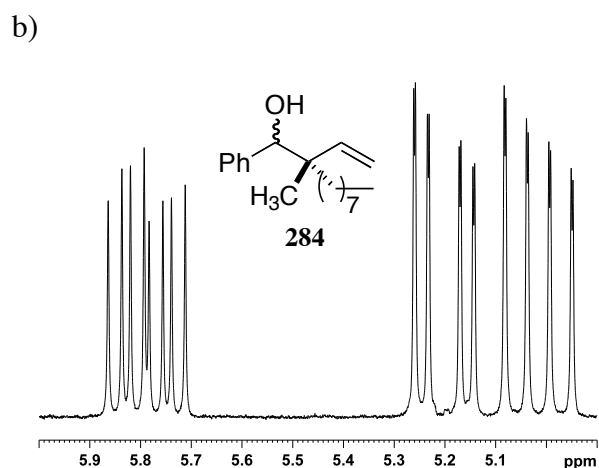
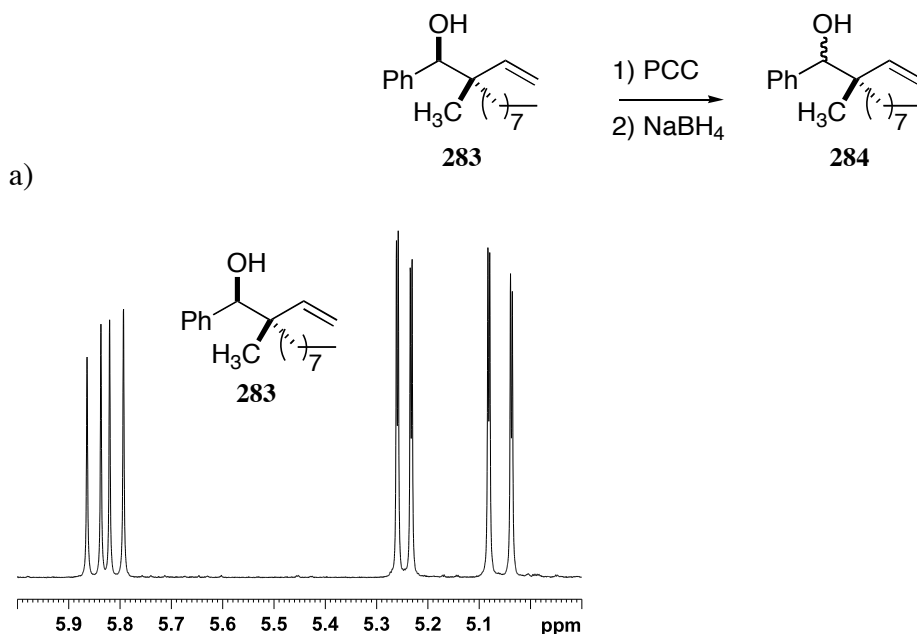
allowed us to obtain a mixture of diastereomers (Scheme 180), whose ^1H NMR spectrum could be compared to that of the original product obtained.

Scheme 180. Oxidation/reduction sequence for producing a mixture of diastereomers.

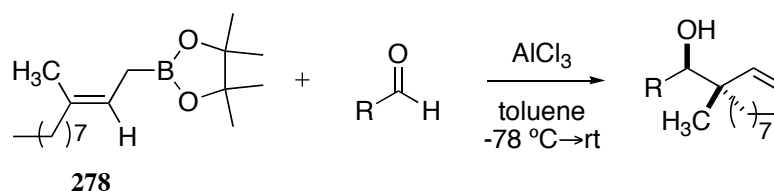


An example of the ^1H NMR spectra obtained before and after this process is shown in Figure 4. The area of absorption for the alkenyl hydrogens was clearly identified and integrated for all derivatives, allowing us to report our diastereomeric ratios with confidence.

Figure 4. ^1H NMR spectra of adduct 283 and diastereomeric mixture 284.



Once AlCl_3 was identified as the optimal Lewis acid⁴⁹, the scope of the aldehyde partner was explored (Table 41). The reaction tolerated both electron donating and electron withdrawing groups on the aromatic aldehydes, while still retaining the high diastereomeric ratios (entries 1-6). In general, the use of electron withdrawing groups on the aldehyde tended to lead to cleaner, higher yielding reactions. The one exception was the case of 3,5-bis(trifluoromethyl)benzaldehyde **289**, where the yield was slightly diminished (entry 6). This could be due to the propensity of that particular aldehyde to prefer the hydrate form over the aldehyde form, resulting in decreased reactivity. The use of aliphatic aldehydes led to a slight decrease in both yields and selectivity (entries 7, 8). No detectable product was obtained when heptanaldehyde was used as the aldehyde partner (entry 9). The use of 2-(benzylacetoxy)aldehyde resulted in a modest yield, however, the diastereoselectivity markedly decreased (entry 10).

Table 41. Condensation of aldehydes with disubstituted allylboronate **278.**

Entry ^a	R	Yield (%) ^b	Selectivity (dr) ^c
1	283 : Ph	72	>30:1
2	285 : (p-CF ₃)C ₆ H ₄	65	>30:1
3	286 : (p-NO ₂) C ₆ H ₄	78	>30:1
4	287 : (p-CN)C ₆ H ₄	82	>30:1
5	288 : (p-OMe)C ₆ H ₄	65	>30:1
6	289 : (m, m-(CF ₃) ₂)C ₆ H ₃	59	>30:1
7	290 : (CH ₂) ₂ Ph	41	25:1
8	291 : (CH ₂) ₃ OTIPS	66	29:1
9	292 : (CH ₂) ₅ CH ₃	0	
10	293 : (CH ₂)OBn	48	5.6:1

^a**Reagents and conditions:** 1.0 equiv of **278**, 2.4 equiv of aldehyde, 0.12 equiv of AlCl₃, toluene, -78 °C

^bIsolated yields

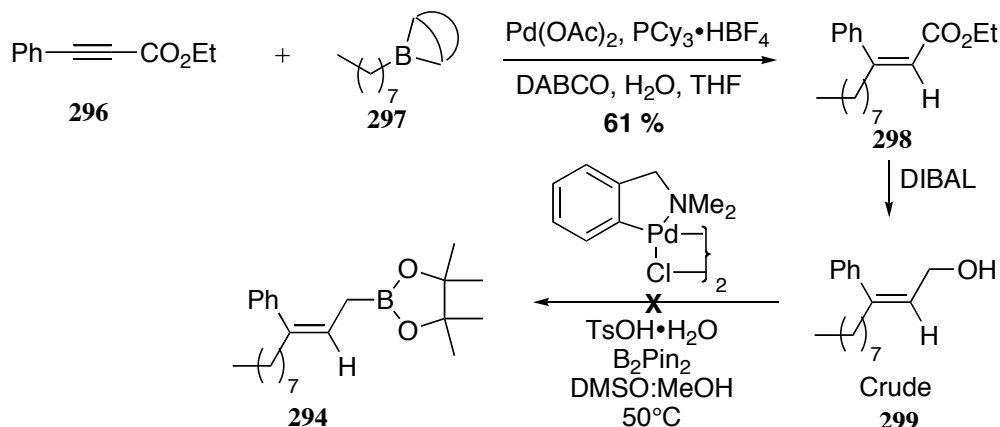
^cDetermined by NMR

The initial strategy for investigating the substrate scope of the allyl boronate nucleophiles was to explore the effect of phenyl substituted alkenyl boronates **294** and **295** on the reaction. In addition to broadening the substrate scope, alkenyl borane **295** could be prepared from an alternate methodology previously reported¹⁸ by our lab, resulting in a product which is the opposite diastereomer of the product from **294**.



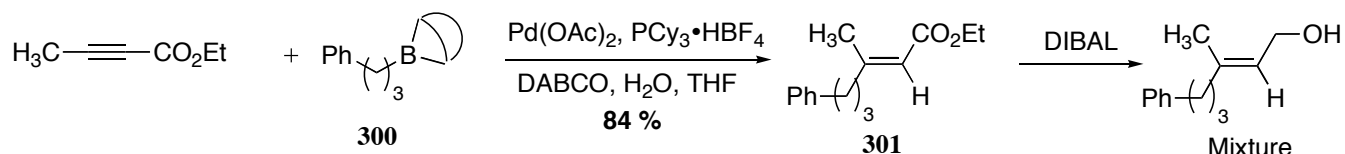
Toward this end, alkyne **296** was reacted with alkyl borane **297** to obtain the alkenyl ester **298** (Scheme 181). Subjection to reduction with DIBAL-H produced **299** as an inseparable mixture after repeated flash chromatography and preparatory thin layer chromatography. The preparation of the allylboronate was attempted with this mixture, however, no detectable product was obtained.

Scheme 181. Attempted preparation of phenyl substituted alkenyl boronate 294.



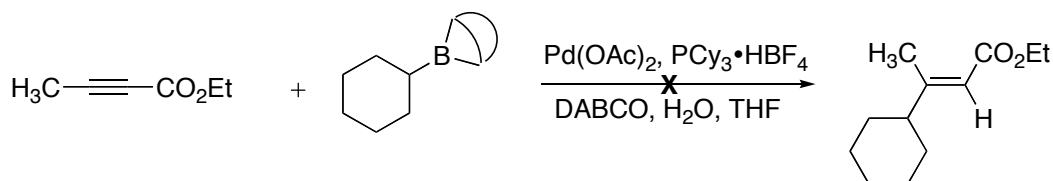
Due to the fact that the aryl substituted alkenyl boronates proved difficult to prepare, we attempted to introduce an alkyl spacer between the aryl group and the alkene using alkyl borane **300**. The ester **301** was prepared in 84 % yield as a single isomer, however, upon reduction, an inseparable mixture of products was obtained (Scheme 182).

Scheme 182. Attempted reduction of ester 301.



Attempts to add a secondary alkyl borane to an alkynyl ester to form the trisubstituted alkenyl ester template also proved unsuccessful (Scheme 183).

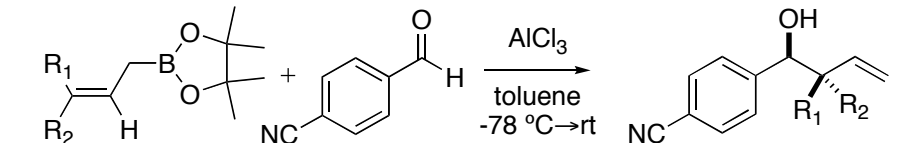
Scheme 183. Attempted addition of a secondary alkyl borane to an alkynyl ester template



The substrate scope investigation was carried on by utilizing exclusively alkyl substituted alkenyl boronates, as these derivatives proved to take part in much more efficient transformations (Table 42).

The aldehyde used in these studies was the best performing *p*-cyanobenzaldehyde from Table 41. Thus, the reaction tolerated simple alkyl substitution, as well as alcohol and silyl protecting groups (entries 1-3). The stereoselective preparation of the opposite diastereomer to **303** was realized by synthesizing the *E*-isomer allyl boronate **304** (entry 4). The diastereomeric ratios were exceptional for these silyl protected alcohol derivatives, with none of the opposite diastereomer detected by ¹H NMR analysis. The diastereomeric ratios in this case (for **303** and **304**) were verified by simply mixing the two products together and obtaining the corresponding ¹H NMR of the mixture for comparison. The reaction also tolerated secondary alkyl branching adjacent to the alkene, with excellent diastereoselectivity, however, a lower yield was obtained, most likely due to sterics (entry 5).

Table 42. Condensation of various trisubstituted allyl boron nucleophiles with *p*-cyanobenzaldehyde

				
Entry ^a	R ₁	R ₂	Yield (%) ^b	Selectivity (dr) ^c
1	287 : -CH ₃	-(CH ₂) ₇ CH ₃	82	>30:1
2	302 : -CH ₃	-(CH ₂) ₅ OH	66	>30:1
3	303 : -(CH ₂) ₄ OTIPS	-(CH ₂) ₇ CH ₃	75	One isomer
4	304 : -(CH ₂) ₇ CH ₃	-(CH ₂) ₄ OTIPS	78	One isomer
5	305 : -Cyclohexyl	-(CH ₂) ₇ CH ₃	35	One isomer

^aReagents and conditions: 1.0 equiv of **178-182**, 2.4 equiv of *p*-cyanobenzaldehyde, 0.12 equiv of AlCl₃, toluene, -78 °C

^bIsolated yields

^cDetermined by NMR

FUTURE DIRECTIONS

Due to the successful application of our methodology for forming trisubstituted olefins as single isomers in the stereoselective construction of all-carbon quaternary centers, future investigations would involve the use of chiral boron reagents to provide enantioselectivity in this reaction. This would allow the stereoselective generation of quaternary centers, which would be synthetically very useful in the total synthesis of medicinally relevant compounds. Examples of chiral allyl boron species have already been reported,²⁷ and so extension to the methodology described here should be relatively facile.

EXPERIMENTAL SECTION FOR STERECONTROLLED PREPARATION OF QUATERNARY CARBON CENTERS VIA SINGLE ISOMER TRISUBSTITUTED OLEFINS

General Methods:

Reactions were performed under nitrogen in oven-dried glassware equipped with a magnetic stirring bar and a rubber septum. THF was freshly distilled over sodium/benzophenone prior to use. All other reagents were used without further purification unless otherwise indicated. Reactions were monitored by TLC analysis using aluminum plates (250 μm thickness) pre-coated with silica gel 60 F254. TLC plates were visualized using ultraviolet light and potassium permanganate. Flash chromatography was carried out on 230-400 mesh silica gel 60, or preparatory TLC glass plates pre-coated with silica gel (Si250F). ^1H and ^{13}C NMR spectra were acquired on a 300 MHz, 400 MHz, or 500 MHz spectrometer in the specified solvent. Infrared spectra were acquired on a FTIR spectrometer. High resolution mass spectra were obtained using an Analytical Concept spectrometer. Melting points were determined using an Electrothermal Meltemp apparatus and are uncorrected.

(*Z*)-ethyl 3-phenylundec-2-enoate (**294**)

To a 50 mL round bottom flask under nitrogen atmosphere was added 1-octene (0.9 mL, 5.74 mmol), followed by a 0.5 M solution of 9-BBN in THF (11.5 mL, 5.74 mmol). The resulting mixture was stirred for 2.5 hours at room temperature. In a separate 100 mL round bottom flask, $\text{Pd}(\text{OAc})_2$ (94 mg, 0.05 mmol), DABCO (644 mg, 5.74 mmol), and $\text{PCy}_3 \cdot \text{HBF}_4$ (158 mg, 0.43 mmol) were added under nitrogen atmosphere. Dry THF (20 mL) was added, followed by H_2O (0.10 mL, 5.74 mmol). A solution of ethyl-2-butynoate (500 mg, 2.87 mmol) in dry THF (5 mL) under nitrogen atmosphere was introduced to the mixture via cannula. The borane prepared in the first solution was then introduced via cannula, and the resulting mixture stirred at room temperature for 18 hours. The mixture was then diluted with Et_2O (50 mL), washed with 10 % HCl (50 mL), saturated NaHCO_3 (30 mL), and brine (30 mL). The organic phase was then dried over MgSO_4 , filtered, and concentrated in vacuo. Flash chromatography (100% hexanes to 1 % EtOAc in hexanes) provided the ester **294** as a pale yellow oil (539.7 mg, 65 %). ^1H NMR (400 MHz, CDCl_3) δ 7.37-7.29 (m, 3H), 7.17-7.12 (m, 2H), 5.88-5.85 (m,

1H), 3.98 (q, J = 7.2 Hz, 2H), 2.43 (t, J = 7.2 Hz, 2H), 1.42-1.20 (m, 14H), 1.06 (t, J = 7.2 Hz, 3H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.1 (C), 140.4 (C), 127.8 (CH), 127.5 (CH), 127.1 (CH), 117.2 (CH), 59.8 (CH_2), 40.5 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 27.3 (CH_2), 22.7 (CH_2), 14.1 (CH_3), 13.9 (CH_3); IR (neat) 2935 cm^{-1} , 1720 cm^{-1} ; MS (EI) 288.2 (M^+); HRMS (EI) Calcd for $\text{C}_{19}\text{H}_{28}\text{O}_2$ (M^+) 288.2089, found 288.2104.

(E)-ethyl 3-methyl-6-phenylhex-2-enoate (297)

Prepared from ethyl-2-butyrate (300 mg, 2.67 mmol) using allylbenzene (1.06 mL, 8.02 mmol) according to a procedure similar to that described for **294** to afford **297** as a pale yellow oil (522 mg, 84 %). ^1H NMR (400 MHz, CDCl_3) δ 7.32-7.25 (m, 2H), 7.21-7.15 (m, 3H), 5.69-5.66 (m, 1H), 4.14 (q, J = 7.2 Hz, 2H), 2.61 (t, J = 7.6 Hz, 2H), 2.21-2.14 (m, 5H), 1.86-1.77 (m, 2H), 1.28 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 128.4 (CH), 128.4 (CH), 125.9 (CH), 115.8 (CH), 59.5 (CH_2), 40.4 (CH_2), 35.4 (CH_2), 29.1 (CH_2), 18.8 (CH_3), 14.4 (CH_3); IR (neat) 2935 cm^{-1} , 1710 cm^{-1} ; MS (EI) 232.1 (M^+); HRMS (EI) Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_2$ (M^+) 232.1463, found 232.1472.

General procedure for DIBAL reductions. (E)-3-methylundec-2-en-1-ol (272)

To a 100 mL round bottom flask under nitrogen atmosphere was added 1-octene (2.8 mL, 17.8 mmol), followed by a 0.5 M solution of 9-BBN in THF (36 mL, 17.8 mmol). The resulting mixture was stirred for 2.5 hours at room temperature. In a separate 250 mL round bottom flask, $\text{Pd}(\text{OAc})_2$ (300 mg, 0.45 mmol), DABCO (2.0 g, 17.8 mmol), and $\text{PCy}_3 \cdot \text{HBF}_4$ (490 mg, 1.34 mmol) were added under nitrogen atmosphere. Dry THF (20 mL) was added, followed by H_2O (0.32 mL, 17.8 mmol). A solution of ethyl-2-butyrate (1.0 g, 8.90 mmol) in dry THF (5 mL) under nitrogen atmosphere was introduced to the mixture via cannula. The borane prepared in the first solution was then introduced via cannula, and the resulting mixture stirred at room temperature for 18 hours. The mixture was then diluted with Et_2O (50 mL), washed with 10 % HCl (50 mL), saturated NaHCO_3 (30 mL), and brine (30 mL). The organic phase was then dried over MgSO_4 , filtered, and concentrated *in vacuo*. Flash chromatography (1 % EtOAc in hexanes) provided the ester (1.44 g), which was immediately dissolved in dry THF (50 mL)

under nitrogen atmosphere. The mixture was cooled to -78 °C, and a 1.0 M solution of DIBAL in THF (16 mL, 2.5 mmol) was introduced. The mixture was stirred at -78 °C until shown to be complete by TLC analysis, and then allowed to warm to room temperature. The reaction was then quenched with methanol (20 mL). The mixture was diluted with EtOAc and washed with 10 % HCl (50 mL). The aqueous phase was extracted with EtOAc (2 x 50 mL), and the combined organic extracts were washed with saturated NaHCO₃ (50 mL) and brine (50 mL) prior to being dried over MgSO₄, filtered, and concentrated *in vacuo* to afford **272** (1.10g, 68%) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 5.40 (t, *J*=6.8 Hz, 1H), 4.15 (d, *J*=7.2 Hz, 2H), 2.00 (t, *J*=7.6 Hz, 2H), 1.66 (s, 3H), 1.45-1.20 (m, 12H), 0.88 (t, *J*=6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 140.3 (C), 123.0 (CH), 59.4 (CH₂), 39.5 (CH₂), 31.9 (CH₂), 29.5 (CH₂), 29.3 (CH₂), 29.2 (CH₂), 27.7 (CH₂), 22.7 (CH₂), 16.2 (CH₃), 14.1 (CH₃); IR (neat) 3322 cm⁻¹, 2923 cm⁻¹, 2853 cm⁻¹; MS (EI) 184.3 (M⁺); HRMS (EI) Calcd for C₁₂H₂₄O (M⁺) 184.1827, found 184.1792.

(*E*)-3-methyl-8-(triisopropylsilyloxy)oct-2-en-1-ol (**273**)

Prepared from ethyl-2-butynoate (62 μL, 0.54 mmol) using a similar procedure to that described for **272**, employing triisopropyl(pent-4-enyloxy)silane (390 mg, 1.61 mmol) in place of 1-octene, to afford **273** (124 mg, 74%) as a pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 5.40 (tq, *J*=7.2, 1.2 Hz, 1H), 4.15 (d, *J*=7.2 Hz, 2H), 3.67 (t, *J*=6.8 Hz, 2H), 2.02 (t, *J*=8.0 Hz, 2H), 1.66 (s, 3H), 1.61-1.50 (m, 2H), 1.48-1.38 (m, 2H), 1.39-1.28 (m, 2H), 1.08-1.01 (m, 21H); ¹³C NMR (100 MHz, CDCl₃) δ 140.1 (C), 123.2 (CH), 59.4 (CH₂), 39.6 (CH₂), 32.9 (CH₂), 27.5 (CH₂), 25.5 (CH₂), 18.1 (CH₃), 16.2 (CH₃) 12.0 (CH); IR (neat) 3337 cm⁻¹, 2937 cm⁻¹, 2865 cm⁻¹; MS (EI) 271.2 (M-C₃H₇)⁺; HRMS (EI) Calcd for C₁₅H₃₁O₂Si (M-C₃H₇)⁺ 271.2093, found 271.2122.

(*Z*)-3-(4-(triisopropylsilyloxy)butyl)undec-2-en-1-ol (**274**)

Prepared from ethyl 7-(triisopropylsilyloxy)hept-2-ynoate (500 mg, 1.53 mmol) using a similar procedure to that described for **272**, to afford **274** (207 mg, 52%) as a clear oil. ¹H NMR (400 MHz,

CDCl₃) δ 5.40 (t, $J=7.2$ Hz, 1H), 4.15 (d, $J=6.8$ Hz, 2H), 3.68 (t, $J=6.0$ Hz, 2H), 2.08 (t, $J=7.6$ Hz, 2H), 2.01 (t, $J=8.0$ Hz, 2H), 1.57-1.22 (m, 18H), 1.09-1.01 (m, 19H), 0.88 (t, $J=7.2$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 144.5 (C), 123.4 (CH), 63.1 (CH₂), 59.3 (CH₂), 36.8 (CH₂), 32.9 (CH₂), 31.9 (CH₂), 30.1 (CH₂), 29.6 (CH₂), 29.5 (CH₂), 29.3 (CH₂), 28.0 (CH₂), 25.1 (CH₂), 22.7 (CH₂), 18.1 (CH₃), 14.1 (CH₃) 12.0 (CH); **IR** (neat) 3300 cm⁻¹, 2925 cm⁻¹, 2864 cm⁻¹; **MS** (EI) 355.3 (M-C₃H₇)⁺; **HRMS** (EI) Calcd for C₂₁H₄₃O₂Si (M-C₃H₇)⁺ 355.3032, found 355.3016.

(E)-3-(4-(triisopropylsiloxy)butyl)undec-2-en-1-ol (275)

Prepared from ethyl undec-2-ynoate (500 mg, 2.56 mmol) using a similar procedure to that described for **272**, employing (but-3-enyloxy)triisopropylsilane (2.2 g, 7.64 mmol) in place of 1-octene, to afford **275** (246 mg, 61%) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 5.39 (t, $J=6.8$ Hz, 1H), 4.15 (d, $J=6.8$ Hz, 2H), 3.68 (t, $J=6.0$ Hz, 2H), 2.07-2.01 (m, 4H), 1.60-1.19 (m, 18H), 1.12-1.02 (m, 19H), 0.88 (t, $J=7.2$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 144.4 (C), 123.4 (CH), 63.2 (CH₂), 59.3 (CH₂), 36.6 (CH₂), 32.7 (CH₂), 31.9 (CH₂), 30.3 (CH₂), 29.7 (CH₂), 29.5 (CH₂), 29.2 (CH₂), 28.9 (CH₂), 24.2 (CH₂), 22.7 (CH₂), 18.0 (CH₃), 14.1 (CH₃) 12.0 (CH); **IR** (neat) 3300 cm⁻¹, 2924 cm⁻¹, 2864 cm⁻¹; **MS** (EI) 355.2 (M-C₃H₇)⁺; **HRMS** (EI) Calcd for C₂₁H₄₃O₂Si (M-C₃H₇)⁺ 355.3032, found 355.2944.

(Z)-3-cyclohexylundec-2-en-1-ol (276)

Prepared from ethyl 3-cyclohexylpropiolate (746 mg, 4.14 mmol) using a similar procedure to that described for **272**, to afford **276** (229 mg, 36%) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 5.30 (tt, $J=6.9, 1.2$ Hz, 1H), 4.19 (d, $J=6.9$ Hz, 2H), 2.47-2.36 (m, 1H), 1.95 (t, $J=6.6$ Hz, 2H), 1.84-1.61 (m, 3H), 1.45-1.19 (m, 19H), 0.88 (t, $J=6.3$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 149.0 (C), 122.0 (CH), 58.8 (CH₂), 40.6 (CH), 32.5 (CH₂), 31.8 (CH₂), 31.6 (CH₂), 29.8 (CH₂), 29.6 (CH₂), 29.3 (CH₂), 28.9 (CH₂), 26.7 (CH₂), 26.1 (CH₂), 22.7 (CH₂), 14.1 (CH₃); **IR** (neat) 3300 cm⁻¹, 2924 cm⁻¹, 2854 cm⁻¹; **MS** (EI) 252.7 (M⁺); **HRMS** (EI) Calcd for C₁₇H₃₂O (M⁺) 252.2453, found 252.2425.

General procedure for the preparation of allyl boranate nucleophiles. 4,4,5,5-tetramethyl-2-((E)-3-methylundec-2-enyl)-1,3,2-dioxaborolane (278)

To a 25 mL round bottom flask containing **272** (81.7 mg, 0.44 mmol) equipped with a reflux condenser was added dry methanol (3 mL) followed by dry DMSO (3 mL) under inert atmosphere. TsOH•H₂O (4 mg, 0.02 mmol), B₂Pin₂ (223 mg, 0.88 mmol), and Di-μ-chlorobis[2-[(dimethylamino)methyl]phenyl-C,N]dipalladium(II) (6 mg, 0.01 mmol) were added, and the reaction mixture was stirred at 50 °C for 20 hours. Quenching with water (10 mL) was followed by extraction of the aqueous phase with Et₂O (3 x 10 mL). The combined organic extracts were then washed with water (10 mL) and brine (10 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Flash chromatography (1 % EtOAc in hexanes) provided **278** (105 mg, 81%) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 5.22 (t, *J*=7.6 Hz, 1H), 1.97 (t, *J*=7.6 Hz, 2H), 1.59 (d, *J*=7.6 Hz, 2H), 1.57 (s, 3H), 1.40-1.20 (m, 24H), 0.88 (t, *J*=6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 135.5 (C), 118.2 (CH), 83.0 (C), 37.9 (CH₂), 31.9 (CH₂), 29.6 (CH₂), 29.3 (CH₂), 29.2 (CH₂), 28.1 (CH₂), 24.7 (CH₃), 22.7 (CH₂), 15.8 (CH₃), 14.1 (CH₃); IR (neat) 2924 cm⁻¹, 2854 cm⁻¹; MS (EI) 294.2 (M⁺); HRMS (EI) Calcd for C₁₈H₃₅BO₂ (M⁺) 294.2730, found 294.2729.

(E)-6-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oct-6-en-1-ol (279)

Prepared from **273** (112.6 mg, 0.36 mmol) using a procedure similar to that described for **278** that provided **279** as a clear oil (63.2 mg, 65 %) after flash chromatography (10-30 % EtOAc in hexanes). ¹H NMR (400 MHz, CDCl₃) δ 5.23 (tq, *J*=7.6, 1.2 Hz, 1H), 3.63 (t, *J*=6.8 Hz, 2H), 1.99 (t, *J*=7.2 Hz, 2H), 1.62-1.51 (m, 5H), 1.45-1.36 (m, 2H), 1.35-1.27 (m, 2H), 1.26-1.21 (m, 14H); ¹³C NMR (100 MHz, CDCl₃) δ 134.9 (C), 118.6 (CH), 83.0 (C), 63.1 (CH₂), 39.4 (CH₂), 32.6 (CH₂), 27.6 (CH₂), 25.1 (CH₂), 24.8 (CH₃), 15.7 (CH₃); IR (neat) 3450 cm⁻¹, 2977 cm⁻¹, 2930 cm⁻¹, 2857 cm⁻¹; this compound would not produce a satisfactory mass spectrum.

(Z)-triisopropyl(5-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethylidene)tridecyloxy)silane (280)

Prepared from **274** (125 mg, 0.31 mmol) using a procedure similar to that described for **278** that provided **280** as a clear oil (47.5 mg, 30 %) after flash chromatography (1 % EtOAc in hexanes). **¹H NMR** (400 MHz, CDCl₃) δ 5.22 (t, *J*=8.0 Hz, 1H), 3.67 (t, *J*=6.4 Hz, 2H), 2.05-1.92 (m, 4H), 1.61 (d, *J*=7.6 Hz, 2H), 1.56-1.48 (m, 3H), 1.46-1.18 (m, 26H), 1.09-1.02 (m, 20H), 0.88 (t, *J*=7.2 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 139.5 (C), 118.5 (CH), 82.9 (C), 63.4 (CH₂), 36.9 (CH₂), 33.1 (CH₂), 29.6 (CH₂), 29.5 (CH₂), 29.4 (CH₂), 29.3 (CH₂), 28.3 (CH₂), 24.7 (CH₃), 24.3 (CH₂), 22.7 (CH₂), 18.1 (CH₃), 14.1 (CH₃), 12.0 (CH); **IR (neat)** 2925 cm⁻¹, 2865 cm⁻¹; **MS (EI)** 465.3 (M-C₃H₇)⁺; **HRMS (EI)** Calcd for C₂₇H₅₄BO₃Si (M-C₃H₇)⁺ 465.3935, found 465.3921.

(E)-3-(4-(triisopropylsilyloxy)butyl)undec-2-en-1-ol (281)

Prepared from **275** (136 mg, 0.34 mmol) using a procedure similar to that described for **278** that provided **281** as a clear oil (71.5 mg, 41 %) after flash chromatography (1 % EtOAc in hexanes). **¹H NMR** (400 MHz, CDCl₃) δ 5.22 (t, *J*=8.0 Hz, 1H), 3.66 (t, *J*=6.4 Hz, 2H), 2.02-1.93 (m, 4H), 1.84-1.36 (m, 6H), 1.61 (d, *J*=7.6 Hz, 2H), 1.35-1.18 (m, 23H), 1.11-1.01 (m, 20H), 0.88 (t, *J*=7.2 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 139.6 (C), 118.6 (CH), 83.0 (C), 63.4 (CH₂), 36.9 (CH₂), 32.8 (CH₂), 31.9 (CH₂), 29.9 (CH₂), 29.8 (CH₂), 29.7 (CH₂), 29.4 (CH₂), 28.3 (CH₂), 24.8 (CH₃), 24.5 (CH₂), 22.7 (CH₂), 18.1 (CH₃), 14.1 (CH₃), 12.1 (CH); **IR (neat)** 2925 cm⁻¹, 2865 cm⁻¹; **MS (EI)** 507.4 (M-H)⁺; **HRMS (EI)** Calcd for C₃₀H₆₀BO₃Si (M-H)⁺ 507.4405, found 507.4544.

General procedure for the condensation of allylboronate nucleophiles with aldehydes. (1*S, 2*S**)-2-methyl-1-phenyl-2-vinyldecan-1-ol (283)**

To a 10 mL round bottom flask containing **278** (50 mg, 0.17 mmol) was added dry toluene (2 mL). The resulting solution was cooled to -78 °C, and AlCl₃ (2.7 mg, 0.02 mmol) was added, followed by benzaldehyde (41 μL, 0.41 mmol). The mixture was then allowed to warm slowly to room temperature,

and stirred for 48 hours. The reaction was then re-cooled to -78 °C, and a 1.0 M solution of DIBAL in THF (0.82 mL, 0.82 mmol) was added in order to consume the excess aldehyde. The resulting mixture was stirred for 1 hour at -78 °C, and the reaction was then quenched by the addition of 10 % HCl (5 mL) and stirred for an additional hour. The mixture was then extracted with Et₂O (2 x 20 mL), and the combined organic extracts washed with saturated NaHCO₃ (20 mL), brine (20 mL), then dried over MgSO₄, filtered, and concentrated *in vacuo*. Flash chromatography (5 % EtOAc in hexanes) provided **283** (33.4 mg, 72 %) as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.23 (m, 5H), 5.85 (dd, *J*= 17.6, 10.8 Hz, 1H), 5.27 (dd, *J*= 10.8, 1.6 Hz, 1H), 5.08 (dd, *J*= 17.6, 1.6 Hz, 1H), 4.24 (s, 1H), 1.87 (s, 1H), 1.42-1.11 (m, 14 H), 0.89 (s, 3H), 0.87 (t, *J*= 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 144.2 (CH), 140.6 (C), 128.1 (CH), 127.5 (CH), 127.4 (CH), 115.7 (CH₂), 80.0 (CH), 45.9 (C), 37.7 (CH₂), 31.9 (CH₂), 30.4 (CH₂), 29.6 (CH₂), 29.3 (CH₂), 24.1 (CH₂), 22.7 (CH₂), 16.4 (CH₃), 14.1 (CH₃); IR (neat) 3455 cm⁻¹, 2924 cm⁻¹, 2854 cm⁻¹; MS (EI) 168.2 (M-C₇H₇O)⁺; HRMS (EI) Calcd for C₁₂H₂₄ (M- C₇H₇O)⁺ 168.1878, found 168.1861.

(1S*, 2S*)-1-(4-(trifluoromethyl)phenyl)-2-methyl-2-vinyldecan-1-ol (285)

Prepared from **278** (55.7 mg, 0.19 mmol) and 4-(trifluoromethyl)benzaldehyde (0.06 mL, 0.45 mmol) using a similar procedure to that described above for **283**, that provided **285** (42.2 mg, 65 %) as a clear oil after flash chromatography (4 % EtOAc in hexanes). ¹H NMR (400 MHz, CDCl₃) δ 7.61-7.52 (m, 2H), 7.45-7.37 (m, 2H), 5.82 (dd, *J*= 17.6, 10.8 Hz, 1H), 5.29 (dd, *J*= 10.8, 1.2 Hz, 1H), 5.09 (dd, *J*= 17.6, 1.2 Hz, 1H), 4.46 (s, 1H), 2.15 (s, 1H), 1.45-1.10 (m, 14 H), 0.88 (s, 3H), 0.88 (t, *J*= 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 144.5 (C), 143.6 (CH), 128.4 (CH), 124.3 (q, *J*= 3.8 Hz, CH), 124.2 (q, *J*= 270.1 Hz, C), 116.3 (CH₂), 79.4 (CH), 45.9 (C), 37.6 (CH₂), 31.8 (CH₂), 30.4 (CH₂), 29.6 (CH₂), 29.3 (CH₂), 24.0 (CH₂), 22.6 (CH₂), 16.2 (CH₃), 14.1 (CH₃); IR (neat) 3450 cm⁻¹, 2926 cm⁻¹, 2855 cm⁻¹, 1324 cm⁻¹; MS (EI) 323.2 (M-F)⁺; HRMS (EI) Calcd for C₂₀H₂₉F₂O (M- F)⁺ 323.2187, found 323.2179.

(1S*, 2S*)-2-methyl-1-(4-nitrophenyl)-2-vinyldecan-1-ol (286)

Prepared from **278** (55.5 mg, 0.18 mmol) and 4-nitrobenzaldehyde (68 mg, 0.45 mmol) using a similar procedure to that described above for **283**, that provided **286** (46.5 mg, 78 %) as a clear oil after flash chromatography (8 % EtOAc in hexanes). **¹H NMR** (400 MHz, CDCl₃) δ 8.19-8.13 (m, 2H), 7.50-7.43 (m, 2H), 5.81 (dd, *J*= 17.6, 10.8 Hz, 1H), 5.31 (dd, *J*= 10.8, 0.8 Hz, 1H), 5.08 (dd, *J*= 17.6, 1.2 Hz, 1H), 4.51 (s, 1H), 2.18 (s, 1H), 1.48-1.10 (m, 14 H), 0.87 (s, 3H), 0.86 (t, *J*= 7.2 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 147.9 (C), 147.2 (C), 143.1 (CH), 128.8 (CH), 122.5 (CH), 116.7 (CH₂), 79.1 (CH), 46.1 (C), 37.6 (CH₂), 31.8 (CH₂), 30.3 (CH₂), 29.5 (CH₂), 29.2 (CH₂), 23.9 (CH₂), 22.6 (CH₂), 16.2 (CH₃), 14.1 (CH₃); **IR (neat)** 3549 cm⁻¹, 2925 cm⁻¹, 2853 cm⁻¹, 1518 cm⁻¹, 1344 cm⁻¹; **MS (EI)** 320.2 (M+H)⁺; **HRMS (EI)** Calcd for C₁₉H₃₀NO₃ (M+H)⁺ 320.2225, found 320.2171.

4-((1S*, 2S*)-1-hydroxy-2-methyl-2-vinyldecyl)benzonitrile (287)

To a 10 mL round bottom flask containing **278** (57.1 mg, 0.19 mmol) was added dry toluene (2 mL). The resulting solution was cooled to -78 °C, and AlCl₃ (2.7 mg, 0.02 mmol) was added, followed by 4-cyanobenzaldehyde (61 mg, 0.46 mmol). The mixture was then allowed to slowly warm to room temperature, and stirred for 18 hours. The reaction was then quenched with 20 % NaHSO₃ (2 mL), and the resulting mixture was stirred for 20 minutes at room temperature, and subsequently extracted with Et₂O (2 x 20 mL). The combined organics were washed with saturated NaHCO₃ (20 mL), brine (20 mL), then dried over MgSO₄, filtered, and concentrated *in vacuo*. The title compound **287** (46.6 mg, 82 %) was obtained as a clear oil. **¹H NMR** (400 MHz, CDCl₃) δ 7.62-7.57 (m, 2H), 7.45-7.39 (m, 2H), 5.79 (dd, *J*= 17.2, 10.8 Hz, 1H), 5.29 (dd, *J*= 11.2, 1.6 Hz, 1H), 5.07 (dd, *J*= 17.6, 1.2 Hz, 1H), 4.45 (s, 1H), 2.19 (s, 1H), 1.43-1.09 (m, 14 H), 0.86 (t, *J*= 6.8 Hz, 3H), 0.85 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 145.9 (C), 143.3 (CH), 131.3 (CH), 128.8 (CH), 118.9 (C), 116.6 (CH₂), 111.2 (C), 79.3 (CH), 46.1 (C), 37.6 (CH₂), 31.9 (CH₂), 30.4 (CH₂), 29.6 (CH₂), 29.3 (CH₂), 24.1 (CH₂), 22.7 (CH₂), 16.3 (CH₃), 14.1

(CH₃); **IR** (neat) 3490 cm⁻¹, 2925 cm⁻¹, 2853 cm⁻¹, 2229 cm⁻¹; **MS** (EI) 300.2 (M+H)⁺; **HRMS** (EI) Calcd for C₂₀H₃₀NO (M+H)⁺ 300.2327, found 300.2351.

(1S*,2S*)-1-(4-methoxyphenyl)-2-methyl-2-vinyldecan-1-ol (288)

Prepared from **278** (47.6 mg, 0.16 mmol) and 4-methoxybenzaldehyde (47 μL, 0.39 mmol) using a similar procedure to that described above for **283**, that provided **288** (37.6 mg, 65 %) as a clear oil after flash chromatography (5 % EtOAc in hexanes). **¹H NMR** (400 MHz, CDCl₃) δ 7.25-7.19 (m, 2H), 6.88-6.82 (m, 2H), 5.84 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.25 (dd, *J* = 11.2, 1.6 Hz, 1H), 5.07 (dd, *J* = 17.6, 1.2 Hz, 1H), 4.38 (s, 1H), 3.81 (s, 3H), 1.99 (s, 1H), 1.41-1.09 (m, 14 H), 0.88 (s, 3H), 0.87 (t, *J* = 7.2 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 158.9 (C), 144.3 (CH), 132.7 (C), 129.1 (CH), 115.5 (CH₂), 112.9 (CH), 79.6 (CH), 55.2 (CH₃), 46.0 (C), 37.7 (CH₂), 31.9 (CH₂), 30.4 (CH₂), 29.6 (CH₂), 29.3 (CH₂), 24.1 (CH₂), 22.6 (CH₂), 16.2 (CH₃), 14.1 (CH₃); **IR** (neat) 3450 cm⁻¹, 2924 cm⁻¹, 2853 cm⁻¹; **MS** (EI) 286.2 (M-H₂O)⁺; **HRMS** (EI) Calcd for C₂₀H₃₀O (M-H₂O)⁺ 286.2297, found 286.2280.

(1S*,2S*)-1-(3,5-bis(trifluoromethyl)phenyl)-2-methyl-2-vinyldecan-1-ol (289)

Prepared from **278** (50 mg, 0.17 mmol) and 3,5-bis(trifluoromethyl)benzaldehyde (67 μL, 0.41 mmol) using a similar procedure to that described above for **283**, that provided **289** (40.9 mg, 59 %) as a clear oil after flash chromatography (3 % EtOAc in hexanes). **¹H NMR** (400 MHz, CDCl₃) δ 7.79-7.72 (m, 3H), 5.83 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.33 (dd, *J* = 10.8, 0.8 Hz, 1H), 5.09 (dd, *J* = 17.6, 1.2 Hz, 1H), 4.55 (s, 1H), 2.23 (s, 1H), 1.43-1.16 (m, 14 H), 0.87 (t, *J* = 6.8 Hz, 3H), 0.86 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 143.0 (C), 142.8 (CH), 130.7 (q, *J* = 33 Hz, C), 128.2 (q, *J* = 2.6 Hz, CH), 123.4 (q, *J* = 270.7 Hz, C), 121.4 (sep, *J* = 3.9 Hz, CH), 117.0 (CH₂), 78.9 (CH), 45.9 (C), 37.5 (CH₂), 31.8 (CH₂), 30.3 (CH₂), 29.5 (CH₂), 29.2 (CH₂), 23.9 (CH₂), 22.6 (CH₂), 16.2 (CH₃), 14.1 (CH₃); **IR** (neat) 3500 cm⁻¹, 2929 cm⁻¹, 2857 cm⁻¹, 1276 cm⁻¹, 1129 cm⁻¹; **MS** (EI) 168.2 (M-C₉H₄OF₆); **HRMS** (EI) Calcd for C₁₂H₂₄(M-C₉H₄OF₆) 168.1878, found 168.1876.

(3*R, 4*S**)-4-methyl-1-phenyl-4-vinyldodecan-3-ol (290)**

Prepared from **278** (50 mg, 0.17 mmol) and hydrocinnamaldehyde (54 μ L, 0.41 mmol) using a similar procedure to that described above for **283**, that provided **290** (20.9 mg, 41 %) as a clear oil after flash chromatography (4 % EtOAc in hexanes). **¹H NMR** (400 MHz, CDCl₃) δ 7.33-7.16 (m, 5H), 5.73 (dd, J = 17.6, 10.8 Hz, 1H), 5.20 (dd, J = 10.8, 1.2 Hz, 1H), 5.05 (dd, J = 17.6, 1.2 Hz, 1H), 3.31 (dd, J = 10.8, 2.0 Hz, 1H), 2.95 (ddd, J = 13.6, 10.4, 4.8 Hz, 1H), 2.67-2.57 (m, 1H), 1.87-1.76 (m, 1H), 1.67-1.54 (m, 1H), 1.41-1.06 (m, 14H), 0.95 (s, 3H), 0.89 (t, J = 6.8 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 144.4 (CH), 142.5 (C), 128.6 (CH), 128.3 (CH), 125.7 (CH), 115.1 (CH₂), 76.3 (CH), 45.0 (C), 37.3 (CH₂), 33.3 (CH₂), 32.8 (CH₂), 31.8 (CH₂), 30.5 (CH₂), 29.5 (CH₂), 29.3 (CH₂), 23.9 (CH₂), 22.6 (CH₂), 16.7 (CH₃), 14.1 (CH₃); **IR (neat)** 3450 cm⁻¹, 2924 cm⁻¹, 2853 cm⁻¹; **MS (EI)** 168.2 (M-C₉H₁₁O)⁺; **HRMS (EI)** Calcd for C₁₂H₂₄(M-C₉H₁₁O)⁺ 168.1878, found 168.1868.

(4*R, 5*S**)-5-methyl-1-(triisopropylsilyloxy)-5-vinyltridecan-4-ol (291)**

Prepared from **278** (100 mg, 0.34 mmol) and 4-(triisopropylsilyloxy)butanal (200 mg, 0.82 mmol) using a similar procedure to that described above for **283**, that provided **291** (42.4 mg, 30 %) as a clear oil after flash chromatography (2 % EtOAc in hexanes). **¹H NMR** (400 MHz, CDCl₃) δ 5.77 (dd, J = 18.0, 11.2 Hz, 1H), 5.15 (dd, J = 10.8, 1.6 Hz, 1H), 5.01 (dd, J = 17.6, 1.6 Hz, 1H), 3.80-3.68 (m, 2H), 3.31 (dd, J = 10.8, 1.6 Hz, 1H), 2.10 (s, 1H), 1.83-1.57 (m, 4H), 1.44-1.17 (m, 14H), 1.15-1.02 (m, 21H), 0.93 (s, 3H), 0.87 (t, J = 6.8 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 144.6 (CH), 114.4 (CH₂), 76.9 (CH), 63.5 (CH₂), 44.9 (C), 37.4 (CH₂), 31.9 (CH₂), 30.5 (CH₂), 30.2 (CH₂), 29.6 (CH₂), 29.4 (CH₂), 27.7 (CH₂), 23.9 (CH₂), 22.7 (CH₂), 18.0 (CH₃), 17.2 (CH₃), 14.1 (CH₃), 11.9 (CH); **IR (neat)** 3400 cm⁻¹, 2924 cm⁻¹, 2865 cm⁻¹; **MS (EI)** 369.3 (M-C₃H₇)⁺; **HRMS (EI)** Calcd for C₂₂H₄₅O₂Si(M-C₃H₇)⁺ 369.3189, found 369.3249.

(2S*,3S*)-1-(benzyloxy)-3-methyl-3-vinylundecan-2-ol (293)

Prepared from **278** (50 mg, 0.17 mmol) and 2-(benzyloxy)acetaldehyde (58 μ L, 0.41 mmol) using a similar procedure to that described above for **283**, that provided **293** (25.7 mg, 48 %) as a clear oil after flash chromatography (5 % EtOAc in hexanes). **¹H NMR** (400 MHz, CDCl₃) δ 7.38-7.27 (m, 5H), 5.85 (dd, J = 17.6, 10.8 Hz, 1H), 5.11 (dd, J = 10.8, 1.6 Hz, 1H), 4.98 (dd, J = 17.6, 1.2 Hz, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.53 (d, J = 11.6 Hz, 1H), 3.66-3.59 (m, 2H), 3.37 (t, J = 9.2 Hz, 1H), 2.35 (s, 1H), 1.48-1.15 (m, 14H), 0.96 (s, 3H), 0.88 (t, J = 6.8 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 143.5 (CH), 138.0 (C), 128.4 (CH), 127.7 (CH), 127.6 (CH), 113.7 (CH₂), 75.7 (CH), 73.3 (CH₂), 71.4 (CH₂), 42.8 (C), 37.3 (CH₂), 31.9 (CH₂), 30.4 (CH₂), 29.6 (CH₂), 29.3 (CH₂), 23.7 (CH₂), 22.7 (CH₂), 18.1 (CH₃), 14.1 (CH₃); **IR (neat)** 3400 cm⁻¹, 2955 cm⁻¹, 2925 cm⁻¹, 2854 cm⁻¹; **MS (EI)** 318.2 (M⁺); **HRMS (EI)** Calcd for C₂₁H₃₄O₂ (M⁺) 318.2559, found 318.2548.

4-((1S*, 2S*)-1,7-dihydroxy-2-methyl-2-vinylheptyl)benzonitrile (302)

Prepared from **279** (48.8 mg, 0.18 mmol) using a similar procedure to that described above for **287**, that provided **302** (32.6 mg, 66 %) as a clear oil after flash chromatography (40 % EtOAc/hexanes). **¹H NMR** (400 MHz, CDCl₃) δ 7.61-7.55 (m, 2H), 7.43-7.36 (m, 2H), 5.79 (dd, J = 17.6, 10.8 Hz, 1H), 5.27 (dd, J = 10.8, 1.2 Hz, 1H), 5.05 (dd, J = 17.6, 1.2 Hz, 1H), 4.44 (s, 1H), 3.58 (t, J = 6.8 Hz, 2H), 1.96 (s, 2H), 1.56-1.46 (m, 2H), 1.43-1.35 (m, 1H), 1.33-1.24 (m, 2H), 1.22-1.15 (m, 3H), 0.85 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 145.9 (C), 142.9 (CH), 131.2 (CH), 128.7 (CH), 118.8 (C), 116.5 (CH₂), 111.1 (C), 79.3 (CH), 62.8 (CH₂), 45.9 (C), 37.4 (CH₂), 32.5 (CH₂), 26.4 (CH₂), 23.7 (CH₂), 16.3 (CH₃); **IR (neat)** 3402 cm⁻¹, 2933 cm⁻¹, 2861 cm⁻¹, 2228 cm⁻¹; **MS (EI)** 142.1 (MH-C₈H₅NO)⁺; **HRMS (EI)** Calcd for C₉H₁₈O (MH-C₈H₅NO)⁺ 142.1358, found 142.1342.

4-((1S*, 2R*)-1-hydroxy-2-(4-(triisopropylsilyloxy)butyl)-2-vinyldecyl)benzonitrile (303)

Prepared from **280** (42 mg, 0.08 mmol) using a similar procedure to that described above for **287**, that provided **303** (30.9 mg, 75 %) as a clear oil after flash chromatography (5-10 % EtOAc/hexanes). **¹H**

NMR (400 MHz, CDCl₃) δ 7.61-7.54 (m, 2H), 7.38-7.33 (m, 2H), 5.60 (dd, J = 18.0, 11.2 Hz, 1H), 5.26 (dd, J = 11.2, 0.8 Hz, 1H), 4.99 (dd, J = 17.6, 0.8 Hz, 1H), 4.63 (s, 1H), 3.69-3.57 (m, 2H), 2.10 (s, 1H), 1.72-1.62 (m, 1H), 1.53-1.18 (m, 19H), 1.11-0.99 (m, 21H), 0.89 (t, J = 7.2 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 146.9 (C), 141.2 (CH), 131.2 (CH), 128.6 (CH), 118.9 (C), 116.6 (CH₂), 111.1 (C), 77.3 (CH), 62.9 (CH₂), 47.4 (C), 33.6 (CH₂), 32.6 (CH₂), 31.9 (CH₂), 31.6 (CH₂), 30.5 (CH₂), 29.6 (CH₂), 29.4 (CH₂), 23.2 (CH₂), 22.7 (CH₂), 19.8 (CH₂), 18.0 (CH₃), 14.1 (CH₃), 11.9 (CH); **IR (neat)** 3500 cm⁻¹, 2924 cm⁻¹, 2864 cm⁻¹, 2229 cm⁻¹; **MS** (EI) 470.3 (M-C₃H₇)⁺; **HRMS** (EI) Calcd for C₂₉H₄₈NO₂Si (M-C₃H₇)⁺ 470.3454, found 470.3432.

4-((1*S**, 2*S**)-1-hydroxy-2-(4-(triisopropylsilyloxy)butyl)-2-vinyldecyl)benzonitrile (304)

Prepared from **281** (65 mg, 0.13 mmol) using a similar procedure to that described above for **287**, that provided **304** (51 mg, 78 %) as a clear oil after flash chromatography (5 to 10 % EtOAc in hexanes). **¹H NMR** (400 MHz, CDCl₃) δ 7.61-7.55 (m, 2H), 7.38-7.32 (m, 2H), 5.59 (dd, J = 18.0, 11.2 Hz, 1H), 5.26 (dd, J = 10.8, 0.8 Hz, 1H), 4.98 (dd, J = 17.6, 1.2 Hz, 1H), 4.62 (s, 1H), 3.72 (t, J = 6.4 Hz, 2H), 2.12 (s, 1H), 1.75-1.66 (m, 1H), 1.61-1.33 (m, 5H), 1.31-1.12 (m, 14H), 1.09-0.98 (m, 21H), 0.87 (t, J = 7.2 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 146.9 (C), 141.3 (CH), 131.2 (CH), 128.6 (CH), 118.9 (C), 116.5 (CH₂), 111.1 (C), 77.3 (CH), 63.1 (CH₂), 47.4 (C), 33.7 (CH₂), 32.9 (CH₂), 31.8 (CH₂), 31.3 (CH₂), 30.4 (CH₂), 29.5 (CH₂), 29.3 (CH₂), 23.5 (CH₂), 22.6 (CH₂), 19.5 (CH₂), 18.0 (CH₃), 14.1 (CH₃), 12.0 (CH); **IR (neat)** 3487 cm⁻¹, 2926 cm⁻¹, 2864 cm⁻¹, 2229 cm⁻¹; **MS** (EI) 470.3 (M-C₃H₇)⁺; **HRMS** (EI) Calcd for C₂₉H₄₈NO₂Si (M-C₃H₇)⁺ 470.3454, found 470.3447.

4-((1*R**, 2*S**)-2-cyclohexyl-1-hydroxy-2-vinyldecyl)benzonitrile (305)

To a 25 mL round bottom flask containing **276** (229 mg, 0.91 mmol) equipped with a reflux condenser was added dry methanol (3 mL) followed by dry DMSO (3 mL) under inert atmosphere. TsOH•H₂O (4 mg, 0.02 mmol), B₂Pin₂ (461 mg, 1.81 mmol), and Di- μ -chlorobis[2-[(dimethylamino)methyl]phenyl-C,N]dipalladium(II) (13 mg, 0.02 mmol) were added, and the reaction mixture stirred at 50 °C for 20 hours. Quenching the reaction with water (10 mL) was followed by extraction of the aqueous phase with

Et₂O (3 x 10 mL). The combined organic extracts were then washed with water (10 mL) and brine (10 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Flash chromatography (1 % EtOAc/hexanes) provided the corresponding boronate (189 mg) as a clear oil. This material (55.9 mg, 0.15 mmol) was immediately condensed with 4-cyanobenzaldehyde using a procedure similar to that described above for **287** that afforded **305** (19.2 mg, 35%) after flash chromatography (5 to 10 % EtOAc in hexanes). ¹H NMR (400 MHz, CDCl₃) δ 7.58-7.53 (m, 2H), 7.41-7.36 (m, 2H), 5.73 (dd, *J*= 17.6, 11.2 Hz, 1H), 5.16 (dd, *J*= 11.2, 1.2 Hz, 1H), 4.89 (s, 1H), 4.76 (dd, *J*= 17.6, 1.2 Hz, 1H), 2.01 (s, 1H), 1.87-1.60 (m, 7H), 1.48-1.37 (m, 1H), 1.35-0.96 (m, 17H), 0.89 (t, *J*= 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 147.6 (C), 140.7 (CH), 130.9 (CH), 128.4 (CH), 118.9 (C), 116.2 (CH₂), 110.8 (C), 77.3 (CH), 49.9 (C), 40.2 (CH), 31.9 (CH₂), 30.9 (CH₂), 29.6 (CH₂), 29.5 (CH₂), 29.4 (CH₂), 27.9 (CH₂), 27.7 (CH₂), 27.3 (CH₂), 26.9 (CH₂), 26.7 (CH₂), 24.1 (CH₂), 22.7 (CH₂), 14.1 (CH₃); IR (neat) 3499 cm⁻¹, 2921 cm⁻¹, 2851 cm⁻¹, 2228 cm⁻¹; MS (EI) 284.2 (M-C₆H₁₁)⁺; HRMS (EI) Calcd for C₁₉H₂₆NO (M-C₆H₁₁)⁺ 284.2014, found 284.2019.

General procedure for the oxidation and reduction of quaternary carbon products. 2-methyl-1-phenyl-2-vinyldecan-1-ol (**284**)

To a 10 mL round bottom flask containing **283** (40.1 mg, 0.15 mmol) was added dry dichloromethane (2 mL) under inert atmosphere. Pyridinium chlorochromate (78 mg, 0.37 mmol) was then added and the reaction mixture was stirred at room temperature for 5 hours. Et₂O (1 mL) was then introduced, and the mixture was filtered through a celite pad, eluting with dichloromethane (50 mL). The filtrate was concentrated *in vacuo*, to afford the crude ketone which was dissolved in methanol (1 mL) and treated with sodium borohydride (7.6 mg, 0.20 mmol). The mixture was then quenched with 10 % HCl (5 mL), and subsequently diluted with Et₂O (20 mL). The organic phase was washed with saturated NaHCO₃ (10 mL), brine (10 mL), dried over MgSO₄, filtered, and concentrated *in vacuo*. Flash chromatography (5 % EtOAc in hexanes) provided **284** as a mixture of diastereomers (20.1 mg, 50 %). ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.23 (m, 5H), 5.84 (dd, *J*= 17.6, 10.8 Hz, 0.5H), 5.77 (dd, *J*= 17.6, 10.8 Hz, 0.5H), 5.27

(dd, J = 10.8, 1.2 Hz, 0.5H), 5.18 (dd, J = 10.8, 1.2 Hz, 0.5H), 5.08 (dd, J = 17.6, 1.2 Hz, 0.5H), 4.99 (dd, J = 17.6, 1.6 Hz, 0.5H), 4.44 (s, 0.5H), 4.42 (s, 0.5H), 1.85 (s, 1H), 1.44-1.11 (m, 14 H), 1.05 (s, 1.5H), 0.89 (s, 1.5H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.1 (CH), 142.9 (CH), 141.3 (C), 140.5 (C), 128.1 (CH), 127.8 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 115.7 (CH_2), 114.9 (CH_2), 80.8 (CH), 80.0 (CH), 45.9 (C), 45.3 (C), 37.6 (CH_2), 36.5 (CH_2), 31.9 (CH_2), 30.5 (CH_2), 30.4 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 24.1 (CH_2), 22.6 (CH_2), 19.1 (CH_3), 16.3 (CH_3), 14.1 (CH_3); IR (neat) 3453 cm^{-1} , 2923 cm^{-1} , 2852 cm^{-1} ; MS (EI) 168.2 ($\text{M-C}_7\text{H}_7\text{O}^+$); HRMS (EI) Calcd for $\text{C}_{12}\text{H}_{24}$ ($\text{M-C}_7\text{H}_7\text{O}^+$) 168.1878, found 168.1874.

1-(4-(trifluoromethyl)phenyl)-2-methyl-2-vinyldecan-1-ol (306)

To a 25 mL round bottom flask containing **285** (20.5 mg, 0.06 mmol) was added dichloromethane (1 mL). Dess-Martin Periodinane (38 mg, 0.09 mmol) was added and the reaction mixture stirred at room temperature for 15 minutes. Et_2O (5 mL) was then introduced, followed by saturated NaHCO_3 (2 mL) and 10 % NaHSO_3 (2 mL). The resulting mixture stirred until both layers were clear. At this point, the mixture was poured into a separatory funnel containing saturated NaHCO_3 (20 mL), and the aqueous phase was extracted with Et_2O (50 mL). The organic phase was subsequently dried over MgSO_4 , filtered, and concentrated *in vacuo* to obtain the crude ketone, which was dissolved in methanol (1 mL) and treated with sodium borohydride (10 mg, 0.25 mmol). The reaction was quenched with 10 % HCl (5 mL), and the aqueous phase extracted with Et_2O (50 mL). The organic phase was washed with saturated NaHCO_3 (20 mL), and brine (20 mL) prior to being dried over MgSO_4 , filtered, and concentrated *in vacuo* to obtain **306** as a mixture of diastereomers (14.5 mg, 71 %). ^1H NMR (400 MHz, CDCl_3) δ 7.59-7.53 (m, 2H), 7.45-7.36 (m, 2H), 5.82 (dd, J = 17.6, 10.8 Hz, 0.5H), 5.72 (dd, J = 17.6, 10.8 Hz, 0.5H), 5.30 (dd, J = 10.8, 1.2 Hz, 0.5H), 5.19 (dd, J = 10.8, 1.2 Hz, 0.5H), 5.10 (dd, J = 17.6, 0.8 Hz, 0.5H), 4.99 (dd, J = 17.6, 1.2 Hz, 0.5H), 4.50 (s, 0.5H), 4.47 (s, 0.5H), 2.08 (s, 1H), 1.43-1.10 (m, 14 H), 1.04 (s, 1.5H), 0.88 (s, 1.5H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.2 (C), 144.5 (C), 143.6 (CH), 142.3 (CH), 128.3 (CH), 128.1 (CH), 124.4 (q, J =3.7 Hz, CH), 124.3

(q, J = 3.7 Hz, CH), 116.4 (CH₂), 115.6 (CH₂), 80.1 (CH), 79.4 (CH), 45.9 (C), 45.4 (C), 37.6 (CH₂), 36.4 (CH₂), 31.8 (CH₂), 30.4 (CH₂), 30.3 (CH₂), 29.6 (CH₂), 29.3 (CH₂), 24.1 (CH₂), 24.0 (CH₂), 22.6 (CH₂), 18.8 (CH₃), 16.1 (CH₃), 14.1 (CH₃); **IR** (neat) 3450 cm⁻¹, 2927 cm⁻¹, 2855 cm⁻¹, 1324 cm⁻¹; **MS** (EI) 323.2 (M-F)⁺; **HRMS** (EI) Calcd for C₂₀H₂₉F₂O (M-F)⁺ 323.2187, found 323.2191.

2-methyl-1-(4-nitrophenyl)-2-vinyldecan-1-ol (307)

Prepared from **286** (21.5 mg, 0.07 mmol) using a procedure similar to that described for **306**, to obtain **307** as a mixture of diastereomers (7.7 mg, 35 %). **¹H NMR** (400 MHz, CDCl₃) δ 8.19-8.13 (m, 2H), 7.51-7.41 (m, 2H), 5.82 (dd, J = 17.6, 10.8 Hz, 0.5H), 5.71 (dd, J = 17.6, 10.8 Hz, 0.5H), 5.32 (dd, J = 10.8, 1.2 Hz, 0.5H), 5.20 (dd, J = 11.2, 1.2 Hz, 0.5H), 5.09 (dd, J = 17.6, 1.2 Hz, 0.5H), 4.97 (dd, J = 17.6, 1.2 Hz, 0.5H), 4.56 (d, J = 4.0 Hz, 0.5H), 4.52 (s, 0.5H), 2.17 (d, J = 2.0 Hz, 0.5H), 2.15 (d, J = 4.8 Hz, 0.5H), 1.45-1.14 (m, 14 H), 1.03 (s, 1.5H), 0.88 (s, 1.5H), 0.87 (t, J = 7.2 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 148.6 (C), 147.9 (C), 143.1 (CH), 142.0 (CH), 128.8 (CH), 128.6 (CH), 122.6 (CH), 122.5 (CH), 116.8 (CH₂), 115.9 (CH₂), 79.8 (CH), 79.1 (CH), 46.1 (C), 45.5 (C), 37.6 (CH₂), 36.5 (CH₂), 31.8 (CH₂), 30.4 (CH₂), 30.3 (CH₂), 29.6 (CH₂), 29.2 (CH₂), 24.0 (CH₂), 24.0 (CH₂), 22.6 (CH₂), 18.5 (CH₃), 16.2 (CH₃), 14.1 (CH₃); **IR** (neat) 3554 cm⁻¹, 2924 cm⁻¹, 2853 cm⁻¹, 1518 cm⁻¹, 1344 cm⁻¹; **MS** (EI) 168.2 (M-C₇H₆NO₃)⁺; **HRMS** (EI) Calcd for C₁₂H₂₄(M-C₇H₆NO₃)⁺ 168.1878, found 168.1855.

1-hydroxy-2-methyl-2-vinyldecyl)benzonitrile (308)

Prepared from **287** (19.1 mg, 0.06 mmol) using a procedure similar to that described for **206**, to obtain **308** as a mixture of diastereomers (6.2 mg, 32 %). **¹H NMR** (400 MHz, CDCl₃) δ 7.62-7.56 (m, 2H), 7.44-7.35 (m, 2H), 5.80 (dd, J = 18.0, 10.8 Hz, 0.5H), 5.69 (dd, J = 17.6, 10.8 Hz, 0.5H), 5.30 (dd, J = 10.8, 1.2 Hz, 0.5H), 5.19 (dd, J = 10.8, 1.2 Hz, 0.5H), 5.09 (dd, J = 17.6, 1.2 Hz, 0.5H), 4.96 (dd, J = 17.6, 1.2 Hz, 0.5H), 4.94 (s, 0.5H), 4.46 (s, 0.5H), 2.14 (s, 0.5H), 2.12 (s, 0.5H), 1.42-1.10 (m, 14 H), 1.01 (s, 1.5H), 0.87 (t, J = 6.4 Hz, 3H), 0.86 (s, 1.5H); **¹³C NMR** (100 MHz, CDCl₃) δ 146.6 (C), 145.9 (C), 143.3 (CH), 142.1 (CH), 131.3 (CH), 131.2 (CH), 128.8 (CH), 128.5 (CH), 118.9 (C), 116.6 (CH₂),

115.8 (CH₂), 111.2 (C), 111.1 (C), 79.9 (CH), 79.3 (CH), 46.1 (C), 45.5 (C), 37.6 (CH₂), 36.5 (CH₂), 31.8 (CH₂), 30.4 (CH₂), 30.3 (CH₂), 29.6 (CH₂), 29.3 (CH₂), 24.0 (CH₂), 23.9 (CH₂), 22.6 (CH₂), 18.6 (CH₃), 16.1 (CH₃), 14.1 (CH₃); **IR** (neat) 3498 cm⁻¹, 2924 cm⁻¹, 2853 cm⁻¹, 2228 cm⁻¹; **MS** (EI) 132.0 (M-C₁₂H₂₃)⁺; **HRMS** (EI) Calcd for C₈H₆NO (M-C₁₂H₂₃)⁺ 132.0449, found 132.0458.

1-(4-methoxyphenyl)-2-methyl-2-vinyldecan-1-ol (309)

Prepared from **288** (14.4 mg, 0.05 mmol) using a procedure similar to that described for **306**, to obtain **309** as a mixture of diastereomers (10.6 mg, 74 %). **¹H NMR** (400 MHz, CDCl₃) δ 7.24-7.16 (m, 2H), 6.89-6.81 (m, 2H), 5.84 (dd, *J*= 17.6, 10.8 Hz, 0.5H), 5.76 (dd, *J*= 17.6, 11.2 Hz, 0.5H), 5.25 (dd, *J*= 10.8, 1.6 Hz, 0.5H), 5.16 (dd, *J*= 10.8, 1.6 Hz, 0.5H), 5.07 (dd, *J*= 17.6, 1.6 Hz, 0.5H), 4.98 (dd, *J*= 17.6, 1.6 Hz, 0.5H), 4.39 (s, 0.5H), 4.38 (s, 0.5H), 3.81 (s, 3H), 1.96 (s, 1H), 1.40-1.09 (m, 14 H), 1.04 (s, 1.5H), 0.88 (s, 1.5H), 0.87 (t, *J*= 7.2 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 158.9 (C), 158.8 (C), 144.3 (CH), 143.1 (CH), 133.5 (C), 132.7 (C), 129.1 (CH), 128.8 (CH), 115.6 (CH₂), 114.9 (CH₂), 112.9 (CH), 112.8 (CH), 80.5 (CH), 79.6 (CH), 55.2 (CH₃), 46.1 (C), 45.4 (C), 37.8 (CH₂), 36.5 (CH₂), 31.9 (CH₂), 30.5 (CH₂), 30.4 (CH₂), 29.7 (CH₂), 29.3 (CH₂), 24.1 (CH₂), 22.7 (CH₂), 19.2 (CH₃), 16.3 (CH₃), 14.1 (CH₃); **IR** (neat) 3480 cm⁻¹, 2923 cm⁻¹, 2853 cm⁻¹; **MS** (EI) 286.2 (M-H₂O)⁺; **HRMS** (EI) Calcd for C₂₀H₃₀O (M-H₂O)⁺ 286.2297, found 286.2272.

4-methyl-1-phenyl-4-vinyldodecan-3-ol (310)

Prepared from **290** (27.5 mg, 0.09 mmol) using a procedure similar to that described for **306**, to obtain **310** as a mixture of diastereomers (20 mg, 73 %). **¹H NMR** (400 MHz, CDCl₃) δ 7.32-7.16 (m, 5H), 5.72 (dd, *J*= 18.0, 11.2 Hz, 0.5H), 5.68 (dd, *J*= 17.6, 10.8 Hz, 0.5H), 5.19 (dd, *J*= 10.8, 1.2 Hz, 0.5H), 5.13 (dd, *J*= 10.8, 1.2 Hz, 0.5H), 5.04 (dd, *J*= 18.0, 1.2 Hz, 0.5H), 4.99 (dd, *J*= 17.6, 1.2 Hz, 0.5H), 3.32 (dd, *J*= 3.6, 1.6 Hz, 0.5H), 3.29 (dd, *J*= 3.6, 1.6 Hz, 0.5H), 2.98-2.87 (m, 1H), 2.66-2.56 (m, 1H), 1.90-1.76 (m, 1H), 1.65-1.48 (m, 2H), 1.39-1.05 (m, 14H), 0.98 (s, 1.5H), 0.94 (s, 1.5H), 0.88 (t, *J*= 7.2 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 144.4 (CH), 143.6 (CH), 142.5 (C), 142.4 (C), 128.5 (CH), 128.4

(CH), 128.3 (CH), 128.3 (CH), 125.7 (CH), 125.7 (CH), 115.1 (CH₂), 114.6 (CH₂), 77.4 (CH), 76.4 (CH), 45.0 (C), 44.8 (C), 37.4 (CH₂), 37.2 (CH₂), 33.7 (CH₂), 33.3 (CH₂), 33.2 (CH₂), 32.8 (CH₂), 31.9 (CH₂), 30.5 (CH₂), 30.4 (CH₂), 29.6 (CH₂), 29.3 (CH₂), 23.9 (CH₂), 23.8 (CH₂), 22.6 (CH₂), 17.9 (CH₃), 16.7 (CH₃), 14.2 (CH₃); **IR** (neat) 3471 cm⁻¹, 2924 cm⁻¹, 2853 cm⁻¹; **MS** (EI) 168.2 (M-C₉H₁₁O)⁺; **HRMS** (EI) Calcd for C₁₂H₂₄(M-C₉H₁₁O)⁺ 168.1878, found 168.1896.

5-methyl-1-(triisopropylsilyloxy)-5-vinyltridecan-4-ol (311)

Prepared from **291** (28.9 mg, 0.07 mmol) using a procedure similar to that described for **206**, to obtain **311** as a mixture of diastereomers (21.3 mg, 74 %). **¹H NMR** (400 MHz, CDCl₃) δ 5.77 (dd, *J*= 17.6, 10.8 Hz, 0.5H), 5.72 (dd, *J*= 17.6, 10.8 Hz, 0.5H), 5.15 (dd, *J*= 10.8, 1.2 Hz, 0.5H), 5.10 (dd, *J*= 10.8, 1.6 Hz, 0.5H), 5.01 (dd, *J*= 17.6, 1.6 Hz, 0.5H), 4.98 (dd, *J*= 17.6, 1.6 Hz, 0.5H), 3.79-3.68 (m, 2H), 3.36-3.29 (m, 1H), 2.19 (d, *J*=5.6 Hz, 0.5H), 2.10 (d, *J*=3.6 Hz, 0.5H), 1.82-1.58 (m, 4H), 1.43-1.16 (m, 14H), 1.14-1.02 (m, 21H), 0.98 (s, 1.5H), 0.94 (s, 1.5H), 0.88 (t, *J*= 7.2 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 144.6 (CH), 144.2 (CH), 114.4 (CH₂), 113.8 (CH₂), 77.6 (CH), 76.9 (CH), 63.6 (CH₂), 63.5 (CH₂), 44.9 (C), 44.7 (C), 37.5 (CH₂), 37.4 (CH₂), 31.9 (CH₂), 30.6 (CH₂), 30.5 (CH₂), 30.3 (CH₂), 30.2 (CH₂), 29.6 (CH₂), 29.5 (CH₂), 29.3 (CH₂), 28.8 (CH₂), 27.7 (CH₂), 24.0 (CH₂), 23.9 (CH₂), 22.7 (CH₂), 18.0 (CH₃), 17.6 (CH₃), 17.2 (CH₃), 14.1 (CH₃), 11.9 (CH), 11.9 (CH); **IR** (neat) 3480 cm⁻¹, 2924 cm⁻¹, 2864 cm⁻¹; **MS** (EI) 369.3 (M-C₃H₇)⁺; **HRMS** (EI) Calcd for C₂₂H₄₅O₂Si (M-C₃H₇)⁺ 369.3189, found 369.3142.

1,7-dihydroxy-2-methyl-2-vinylheptyl)benzonitrile (312)

Prepared from **302** (19 mg, 0.07 mmol) using a procedure similar to that described for **306**, to obtain **312** as a mixture of diastereomers (7.3 mg, 38 %). **¹H NMR** (400 MHz, CDCl₃) δ 7.63-7.57 (m, 2H), 7.45-7.36 (m, 2H), 5.80 (dd, *J*= 17.6, 10.8 Hz, 0.5H), 5.70 (dd, *J*= 17.6, 10.8 Hz, 0.5H), 5.31 (dd, *J*= 10.8, 1.2 Hz, 0.5H), 5.19 (dd, *J*= 10.8, 1.2 Hz, 0.5H), 5.09 (dd, *J*= 17.6, 1.2 Hz, 0.5H), 4.96 (dd, *J*= 17.6, 1.2 Hz, 0.5H), 4.50 (s, 0.5H), 4.47 (s, 0.5H), 3.62 (t, *J*= 6.4 Hz, 2H), 1.61-1.48 (m, 2H), 1.44-1.15

(m, 6H), 1.01 (s, 1.5H), 0.87 (s, 1.5H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.5 (C), 145.8 (C), 143.1 (CH), 141.9 (CH), 131.3 (CH), 131.2 (CH), 128.8 (CH), 128.5 (CH), 118.8 (C), 116.7 (CH_2), 115.9 (CH_2), 111.3 (C), 111.1 (C), 79.9 (CH), 79.3 (CH), 62.9 (CH_2), 46.0 (C), 45.4 (C), 37.5 (CH_2), 36.4 (CH_2), 32.5 (CH_2), 26.5 (CH_2), 26.4 (CH_2), 23.8 (CH_2), 23.7 (CH_2), 18.5 (CH_3), 16.2 (CH_3); IR (neat) 3413 cm^{-1} , 2934 cm^{-1} , 2861 cm^{-1} , 2228 cm^{-1} ; MS (EI) 142.1 ($\text{MH-C}_8\text{H}_5\text{NO}^+$); HRMS (EI) Calcd for $\text{C}_9\text{H}_{18}\text{O}(\text{MH-C}_8\text{H}_5\text{NO})^+$ 142.1358, found 142.1369.

2-cyclohexyl-1-hydroxy-2-vinyldecyl)benzonitrile (313)

Prepared from **303** (9.6 mg, 0.03 mmol) using a procedure similar to that described for **306**, to obtain **313** as a mixture of diastereomers (6.0 mg, 63 %). ^1H NMR (400 MHz, CDCl_3) δ 7.60-7.53 (m, 2H), 7.43-7.36 (m, 2H), 5.87 (dd, $J=17.6, 10.8\text{ Hz}$, 0.15H), 5.73 (dd, $J=17.6, 11.2\text{ Hz}$, 0.85H), 5.29 (dd, $J=10.8, 0.8\text{ Hz}$, 0.15H), 5.16 (dd, $J=11.2, 0.8\text{ Hz}$, 0.85H), 4.93 (dd, $J=18.0, 1.2\text{ Hz}$, 0.15H), 4.92 (s, 0.15H), 4.89 (s, 0.85H), 4.76 (dd, $J=17.6, 0.8\text{ Hz}$, 0.85H), 2.03-1.49 (m, 8H), 1.47-0.98 (m, 18H), 0.89 (t, $J=6.8\text{ Hz}$, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 148.5 (C), 147.6 (C), 141.1 (CH), 140.7 (CH), 131.2 (CH), 131.0 (CH), 128.7 (CH), 128.4 (CH), 118.9 (C), 116.3 (CH_2), 116.2 (CH_2), 110.8 (C), 77.4 (CH), 77.2 (CH), 50.0 (C), 40.2 (CH), 31.9 (CH_2), 30.9 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 27.9 (CH_2), 27.8 (CH_2), 27.3 (CH_2), 26.9 (CH_2), 26.7 (CH_2), 24.1 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 14.2 (CH_3); IR (neat) 3489 cm^{-1} , 2921 cm^{-1} , 2851 cm^{-1} , 2228 cm^{-1} ; MS (EI) 235.2 ($\text{M-C}_8\text{H}_6\text{NO}^+$); HRMS (EI) Calcd for $\text{C}_{17}\text{H}_{31}(\text{M-C}_8\text{H}_6\text{NO})^+$ 235.2426, found 235.2429.

(1*S**,2*S**)-1-(3,5-bis(trifluoromethyl)phenyl)-2-methyl-2-vinyldecan-1-ol (314)

Prepared from **289** (5.1 mg, 0.03 mmol) using a procedure similar to that described for **306**, to obtain **314** as a mixture of diastereomers (3.3 mg, 80 %). ^1H NMR (400 MHz, CDCl_3) δ 7.81-7.70 (m, 6H), 5.83 (dd, $J=17.6, 10.8\text{ Hz}$, 1H), 5.71 (dd, $J=17.6, 10.8\text{ Hz}$, 1H), 5.33 (dd, $J=10.8, 0.8\text{ Hz}$, 1H), 5.21 (dd, $J=10.8, 0.8\text{ Hz}$, 1H), 5.09 (dd, $J=17.6, 0.8\text{ Hz}$, 1H), 4.60 (s, 1H), 4.55 (s, 1H), 2.24-2.13 (m, 2H), 1.46-1.14 (m, 28H), 0.99 (s, 3H), 0.87 (t, $J=6.8\text{ Hz}$, 6H), 0.86 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ

143.7 (C), 143.0 (C), 142.8 (CH), 141.8 (CH), 128.2 (q, $J = 2.4$ Hz, CH), 127.9 (q, $J = 3.3$ Hz, CH), 117.0 (CH₂), 116.2 (CH₂), 79.4 (CH), 78.9 (CH), 45.9 (C), 45.4 (C), 37.6 (CH₂), 36.5 (CH₂), 31.8 (CH₂), 30.3 (CH₂), 30.2 (CH₂), 29.5 (CH₂), 29.4 (CH₂), 29.3 (CH₂), 29.2 (CH₂), 23.9 (CH₂), 22.6 (CH₂), 18.2 (CH₃), 16.2 (CH₃), 14.1 (CH₃); **IR** (neat) 3500 cm⁻¹, 2928 cm⁻¹, 2857 cm⁻¹, 1276 cm⁻¹, 1129 cm⁻¹; **MS** (EI) 168.2 (M-C₉H₄OF₆); **HRMS** (EI) Calcd for C₁₂H₂₄(M-C₉H₄OF₆) 168.1878, found 168.1884.

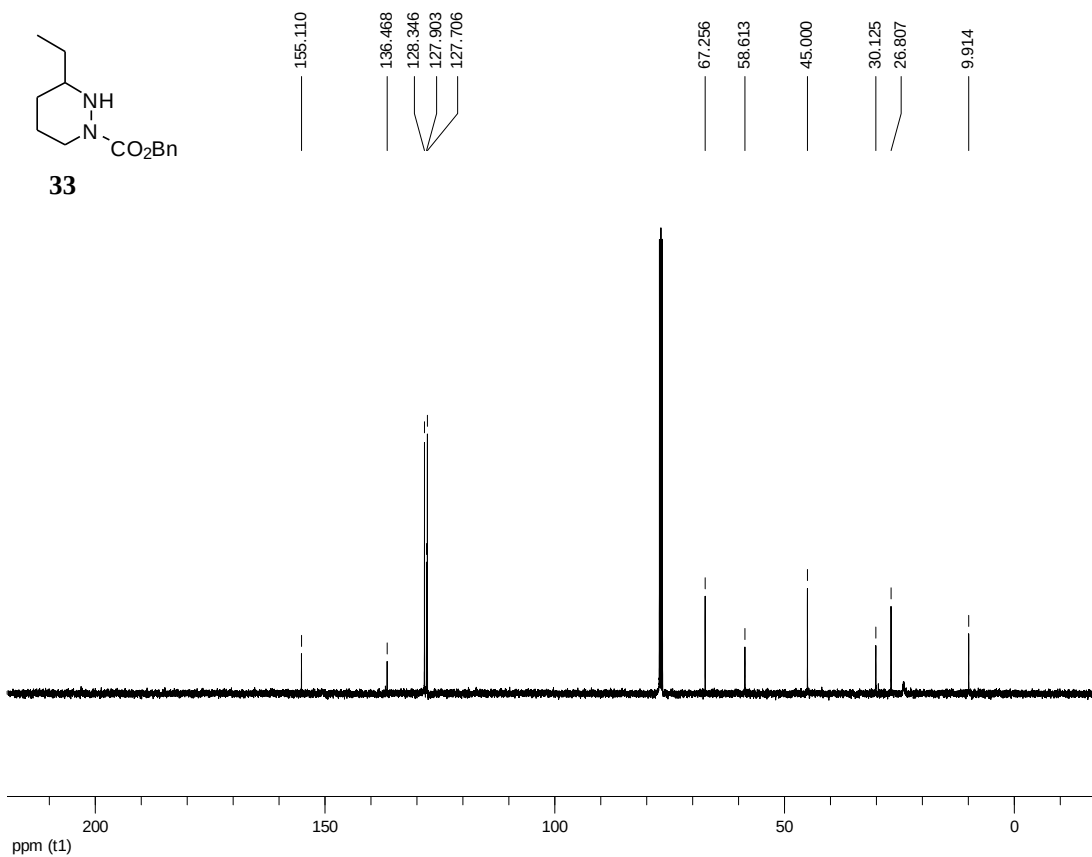
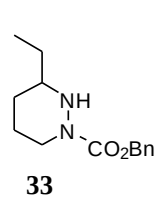
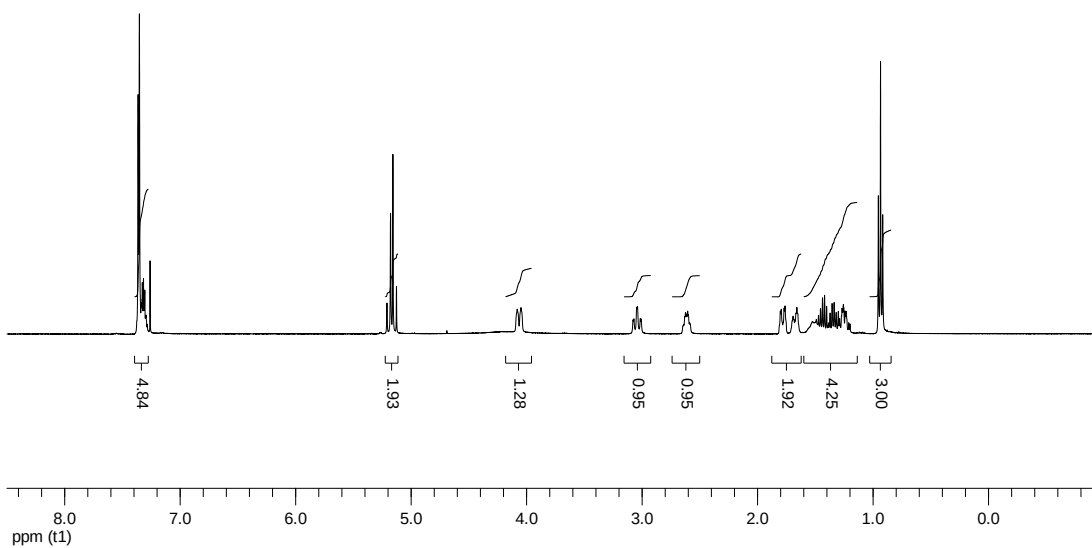
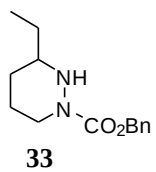
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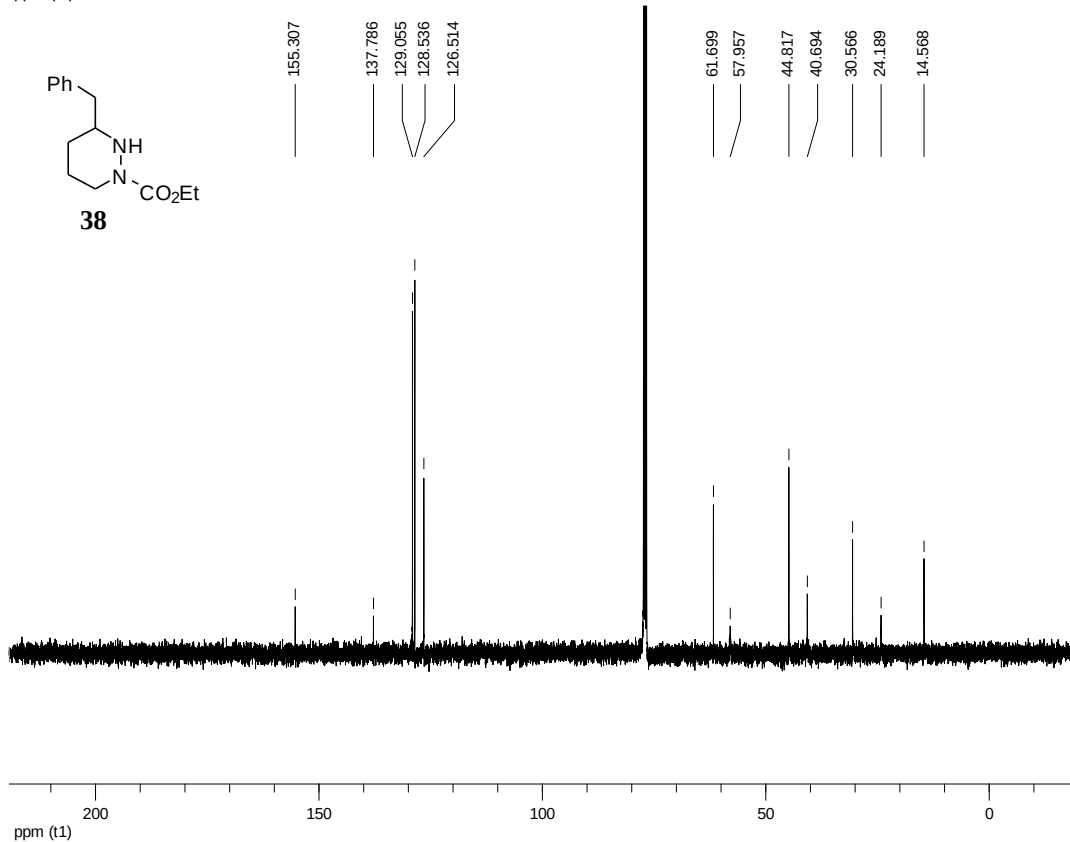
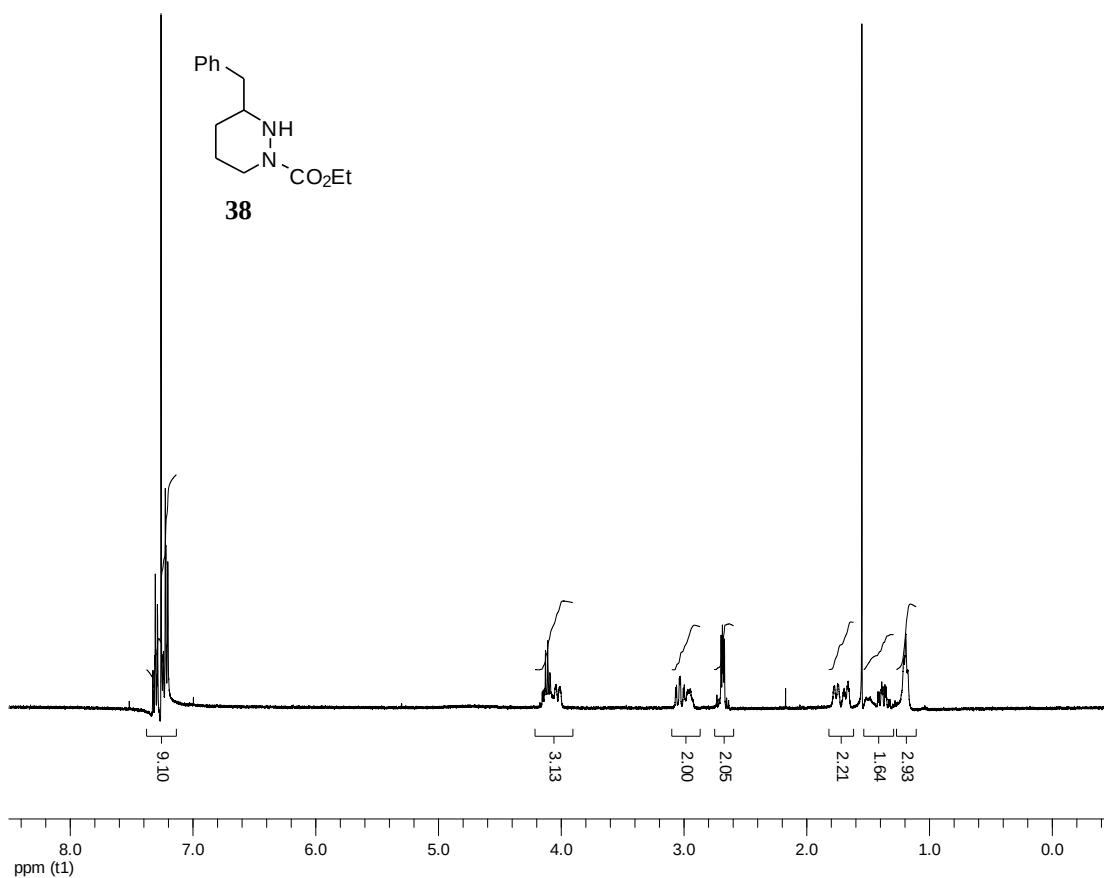
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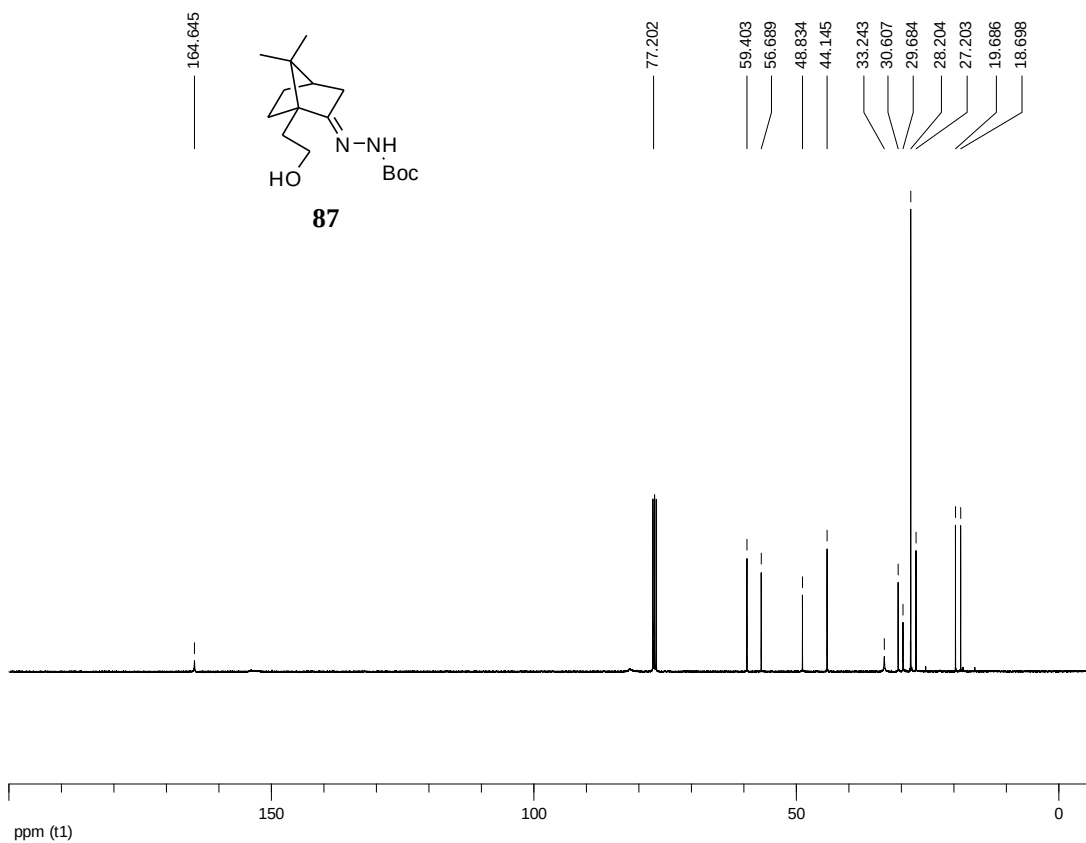
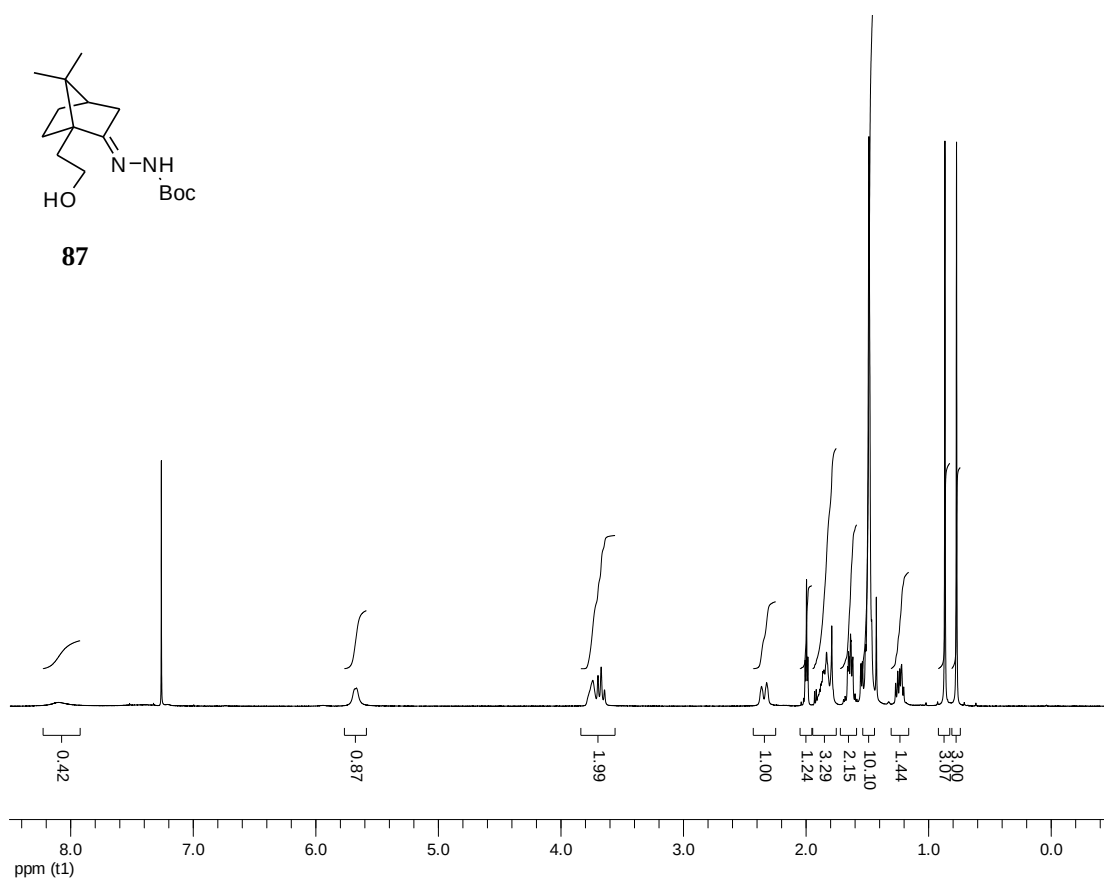
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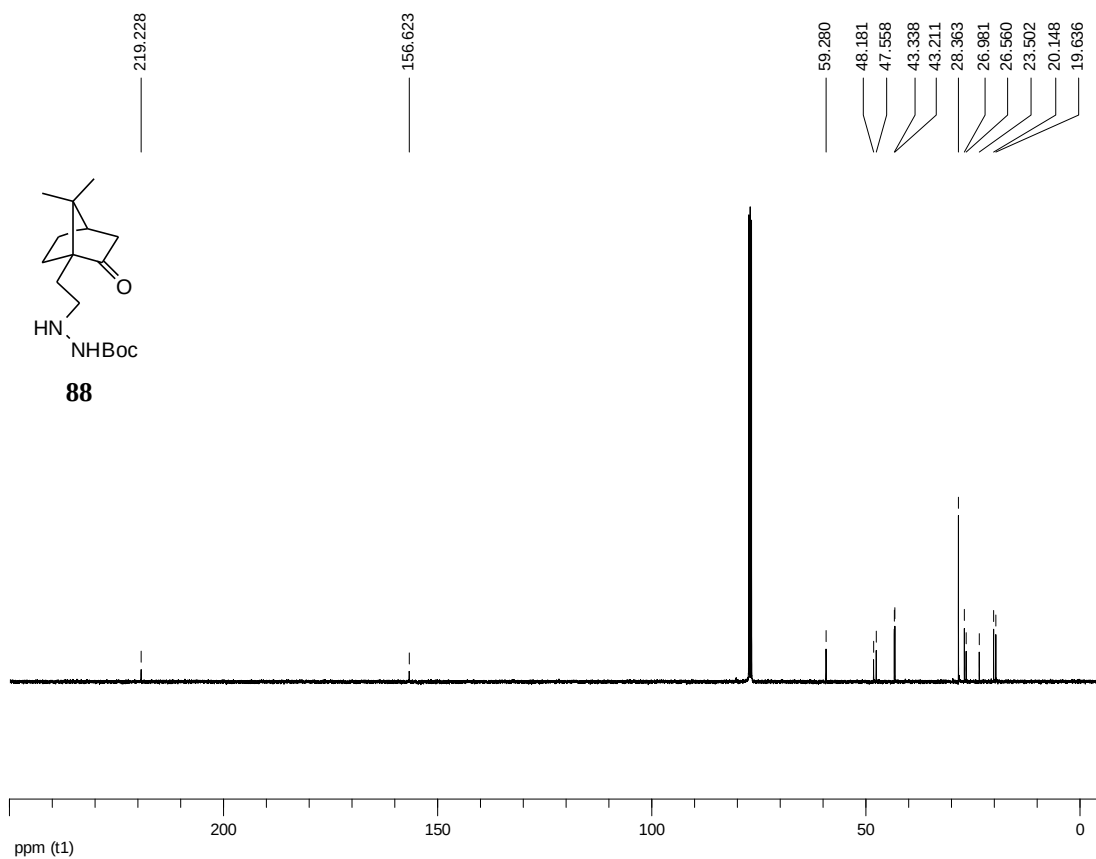
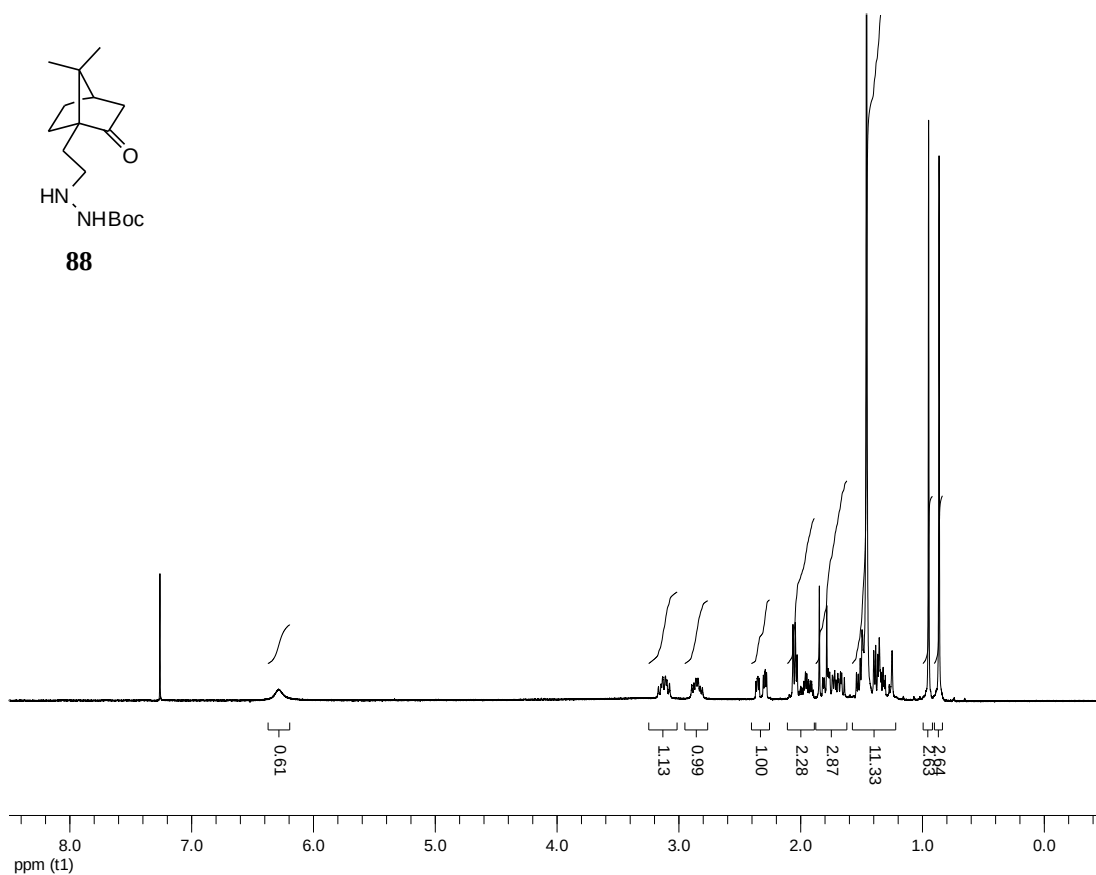
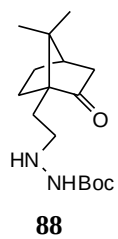
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- ⁴⁹ During the Lewis acid optimization studies, it came to our attention that certain impurities from the catalytic addition of alkyl boranes to the alkynes could interfere with the diastereoselectivity of the final products. It was therefore necessary to do preliminary flash chromatography on the resulting alkenyl esters obtained in the first step of the sequence in order to obtain highly diastereoenriched products.

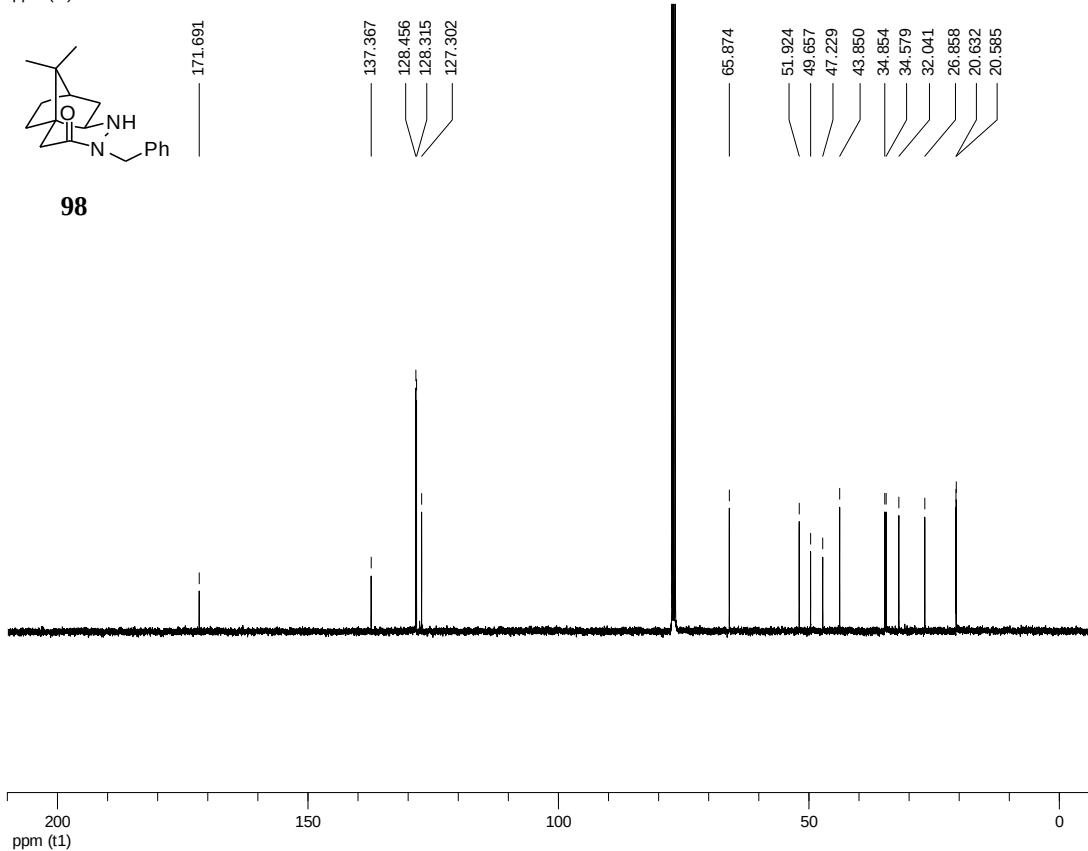
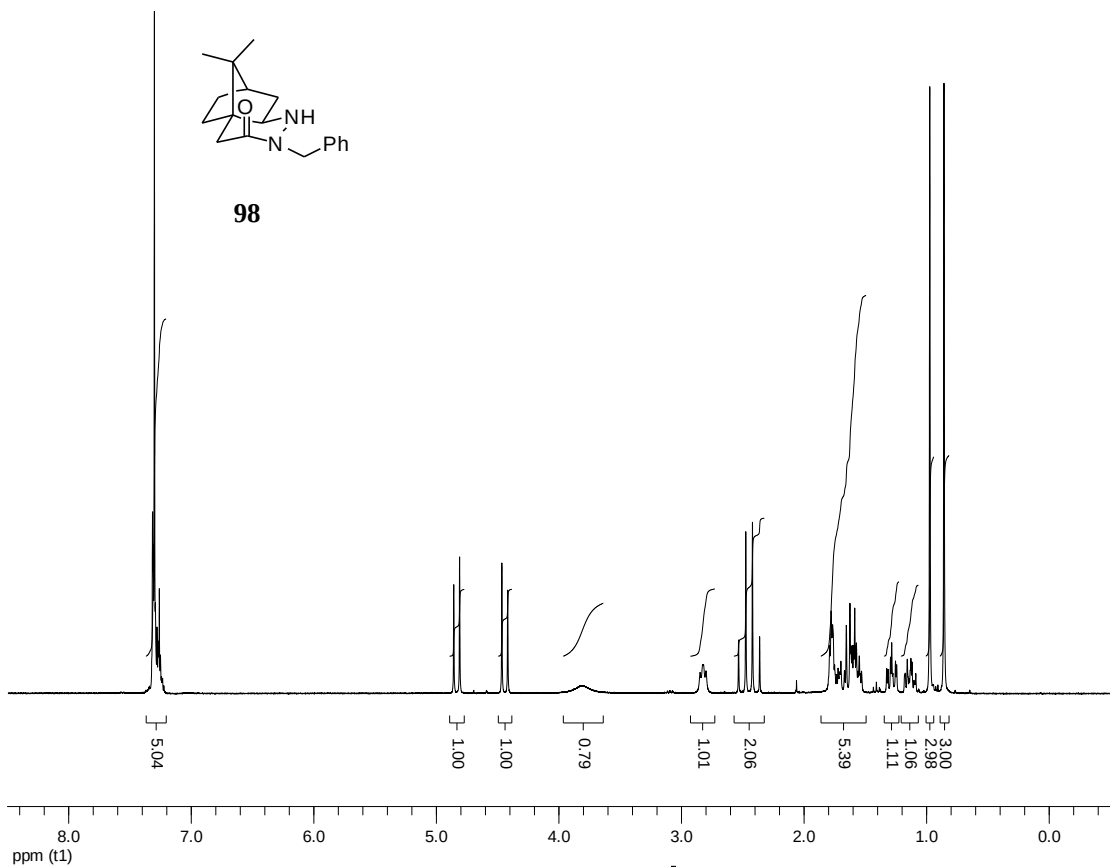
APPENDIX: SPECTRA

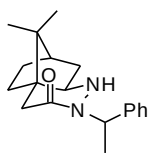






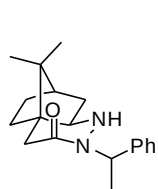
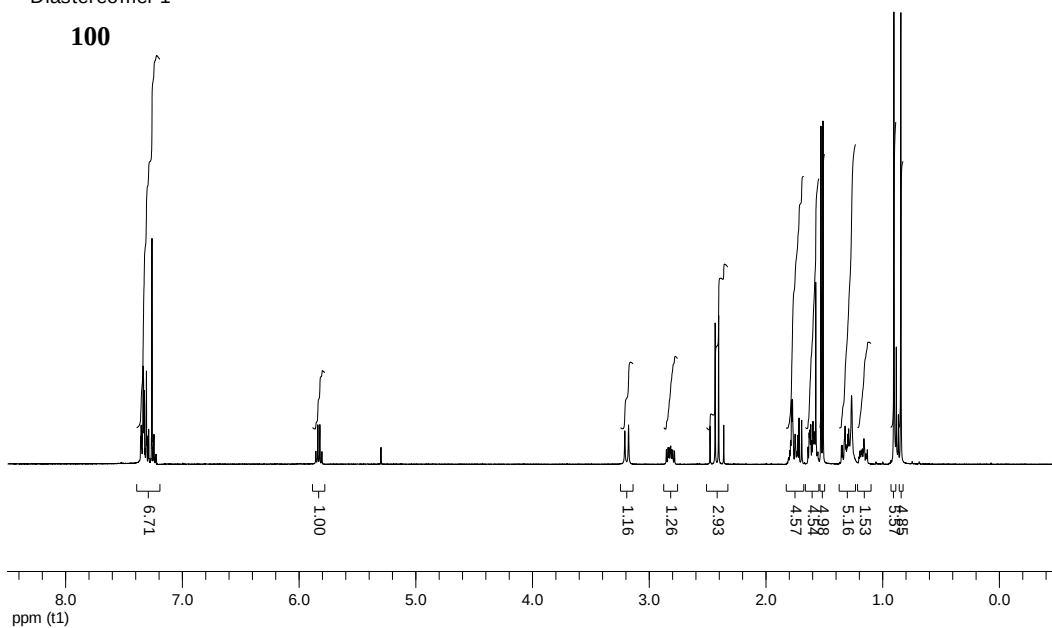






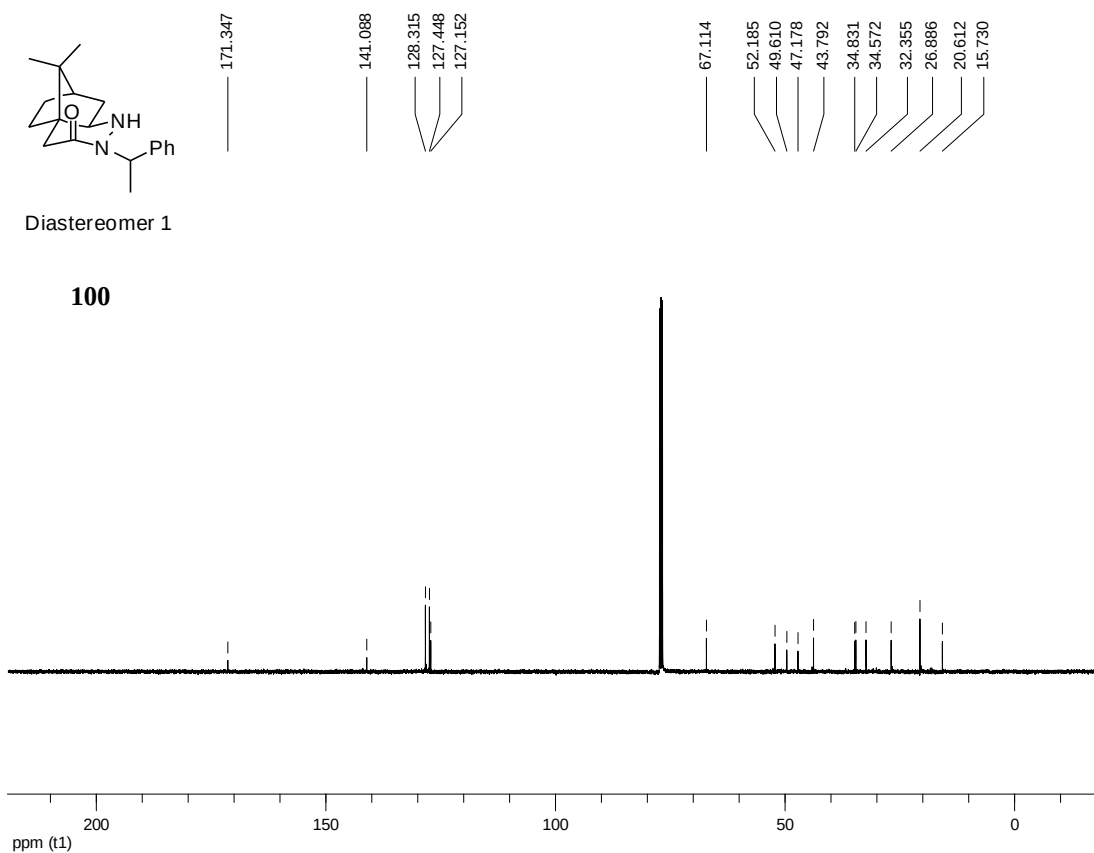
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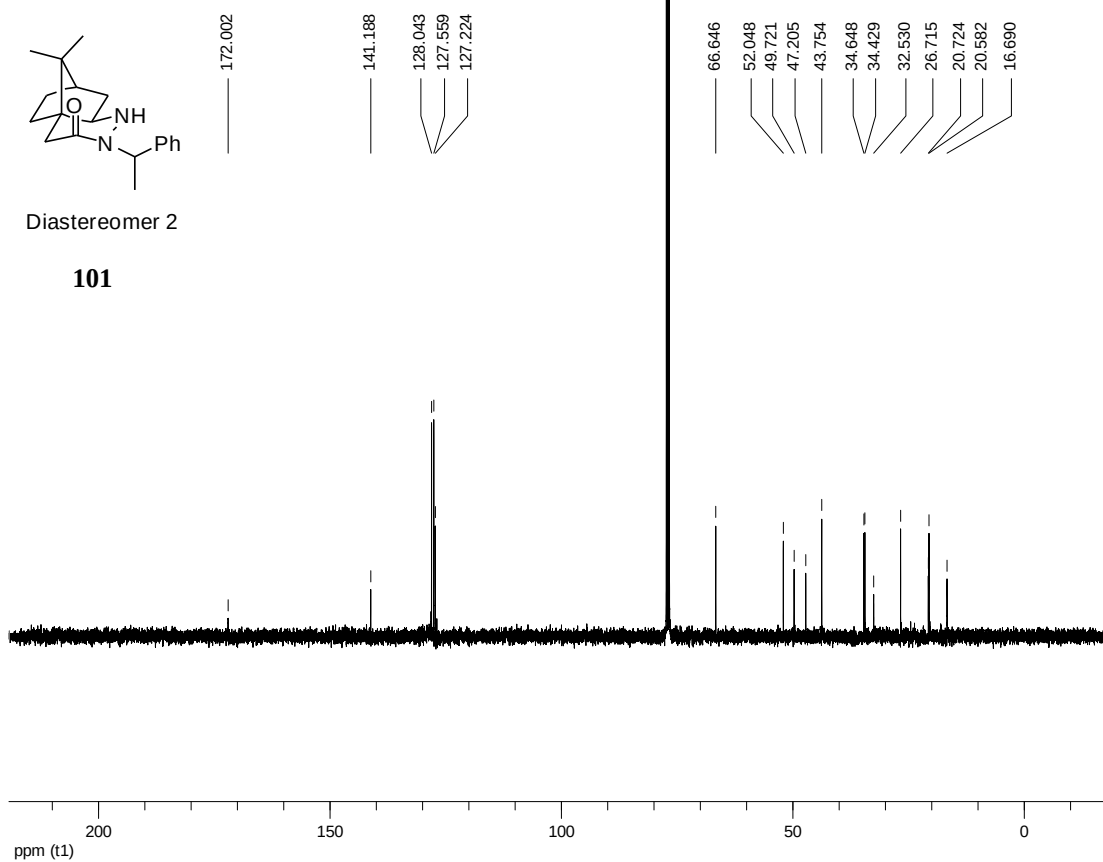
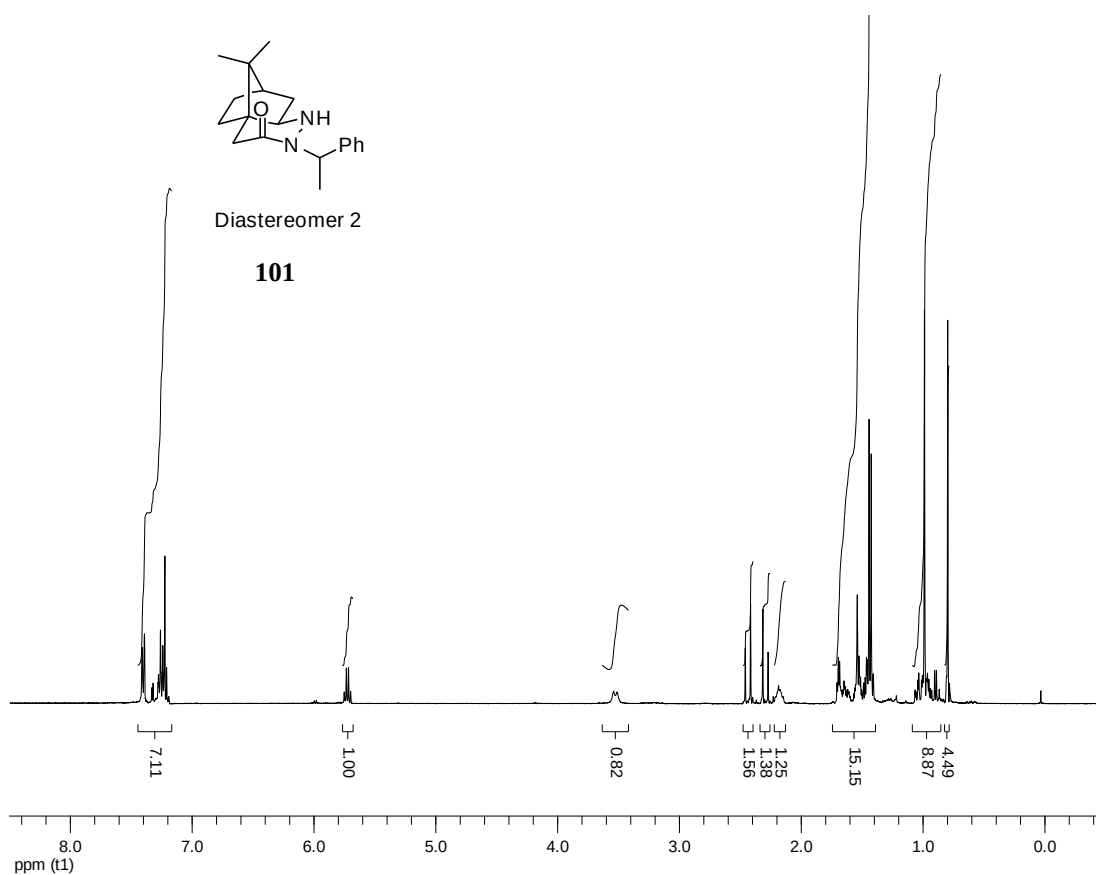
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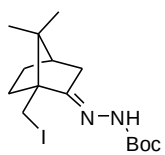


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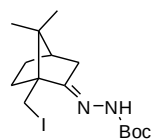
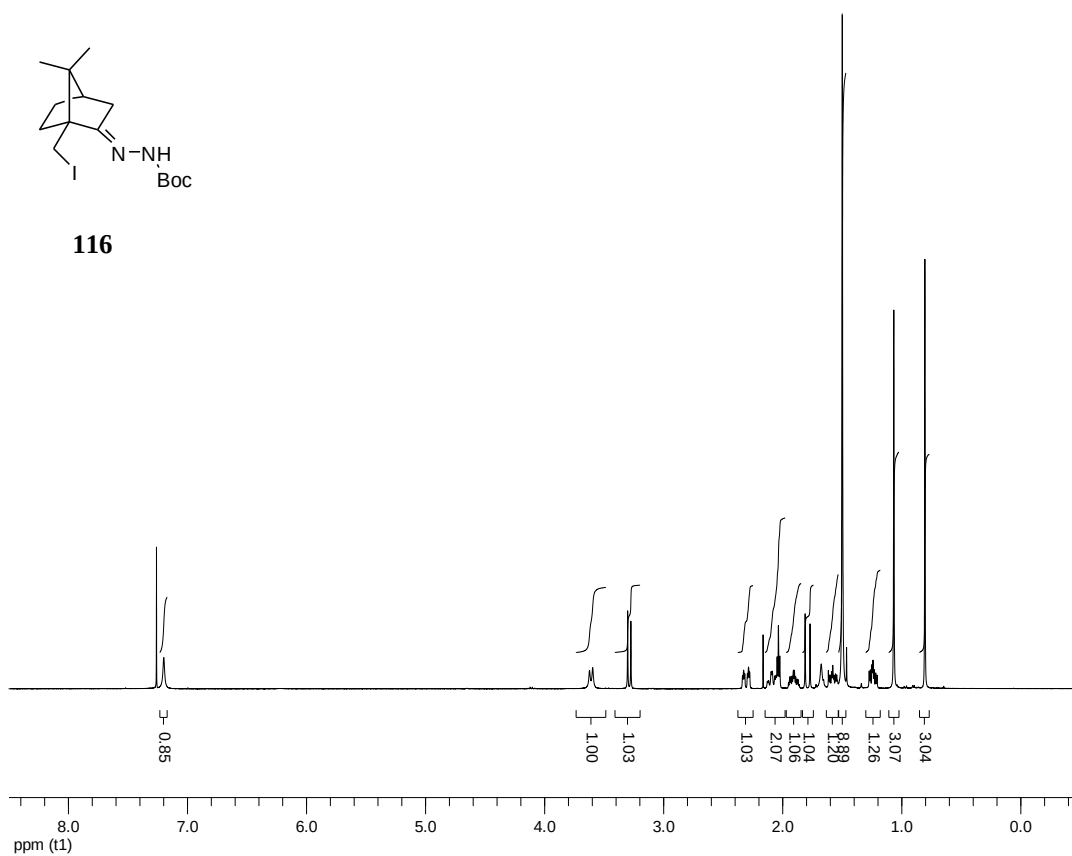
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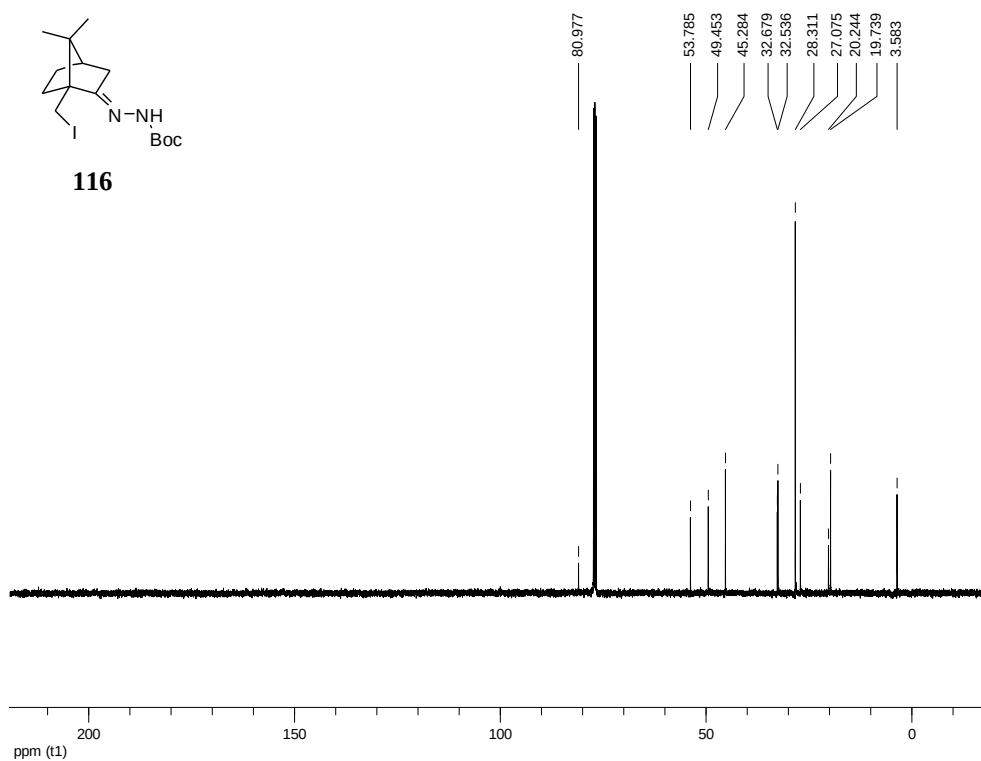


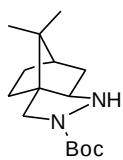


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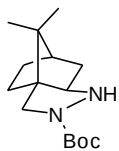
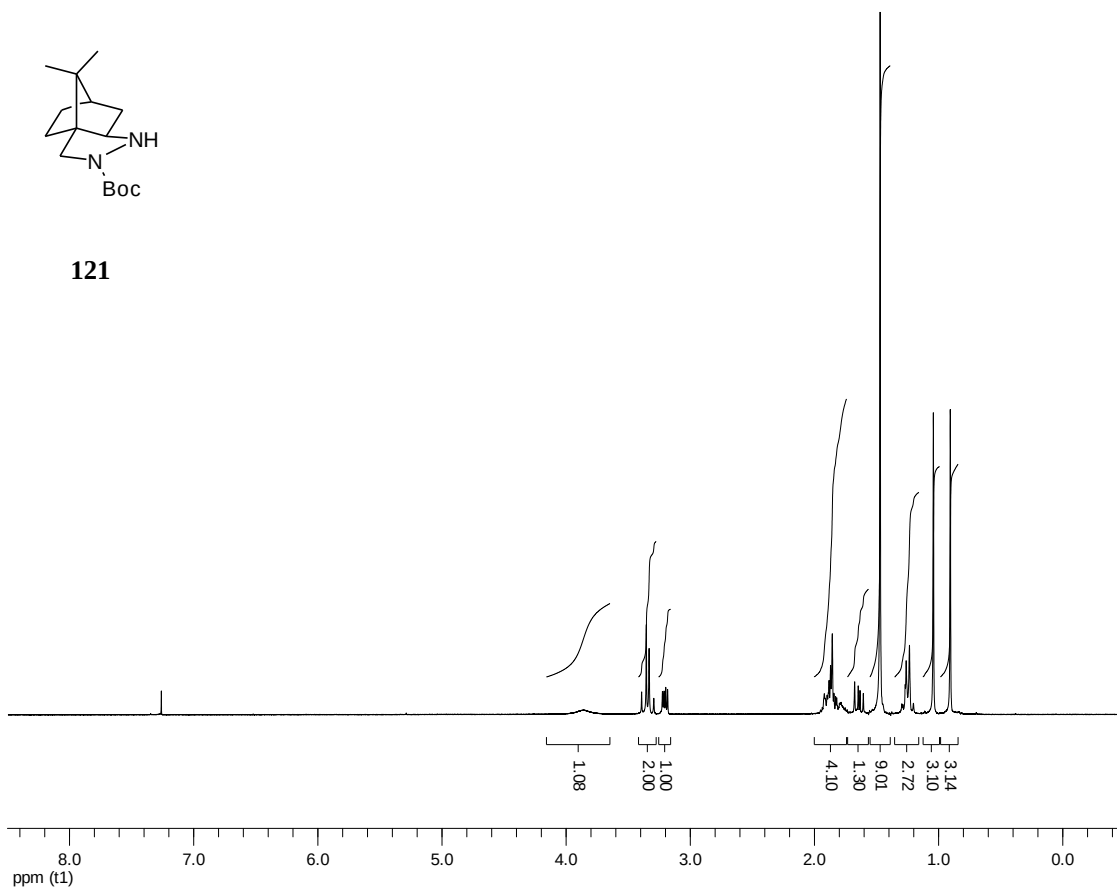


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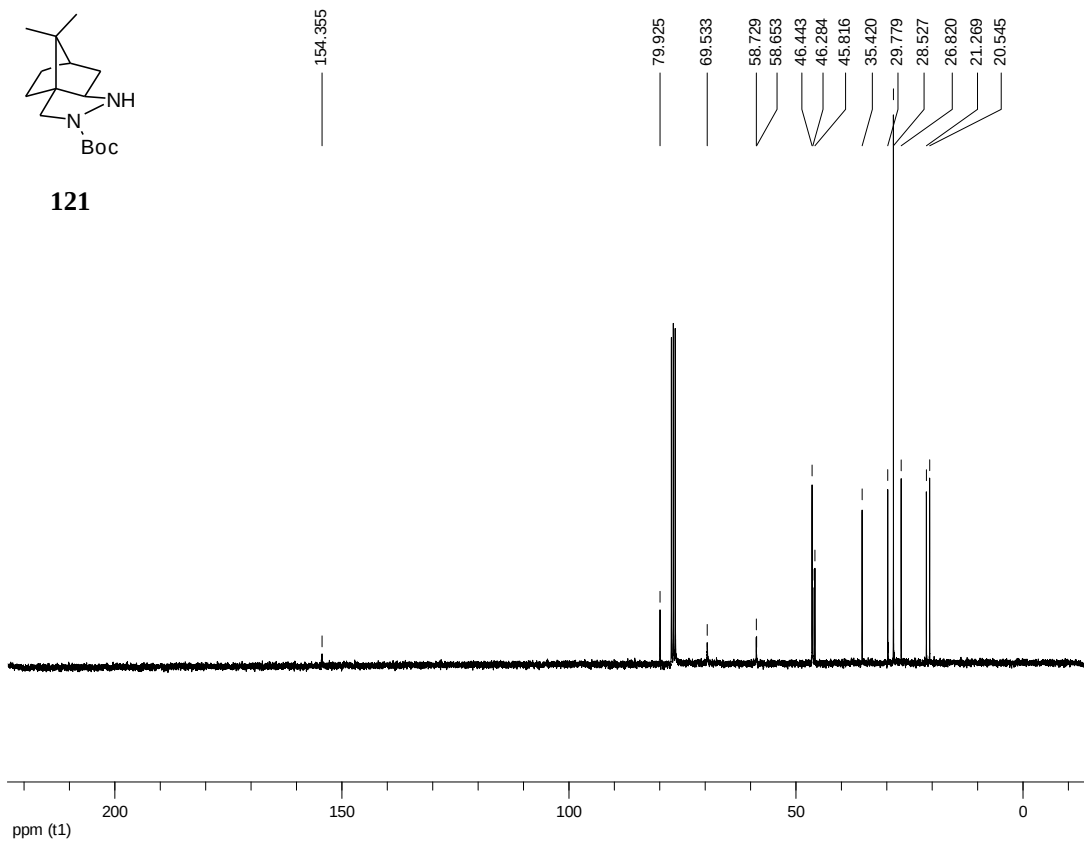


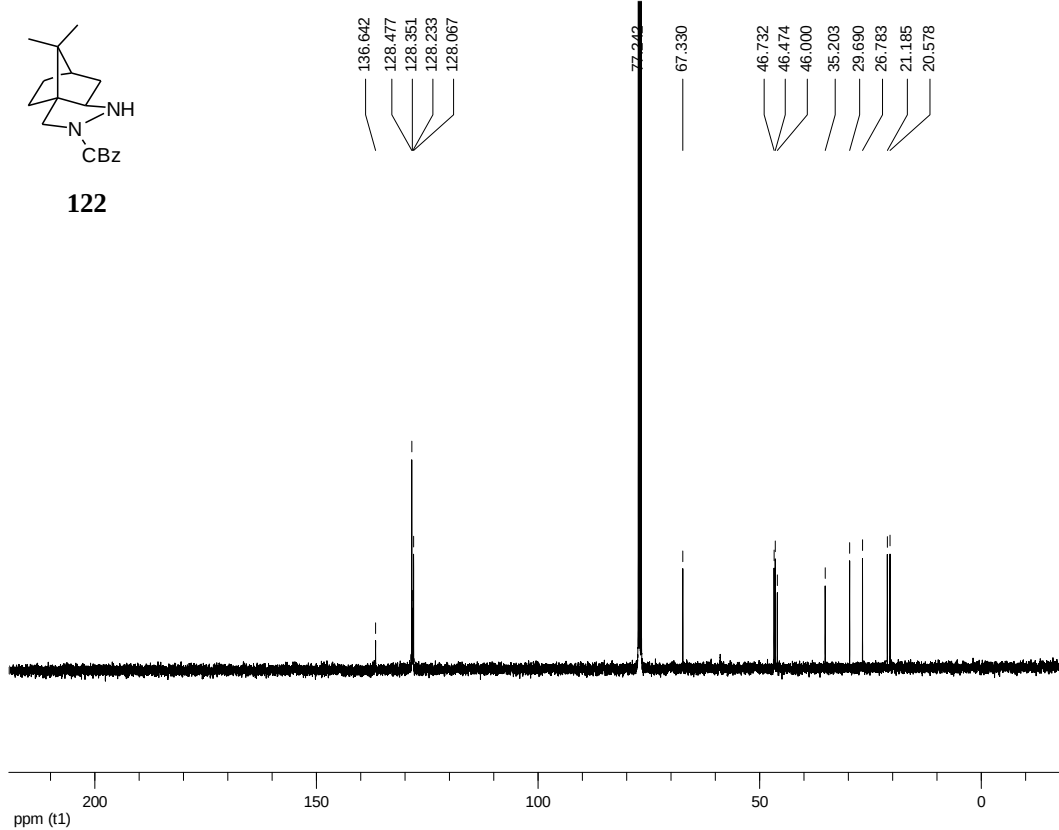
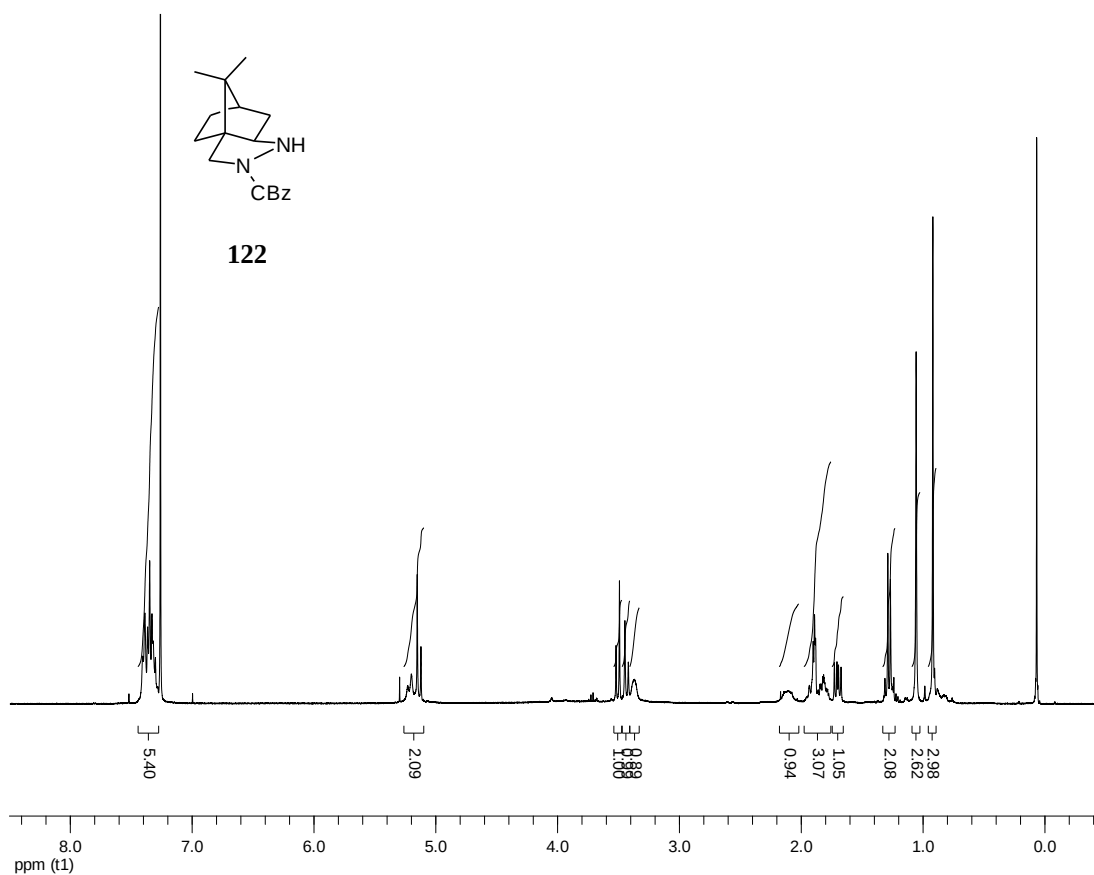


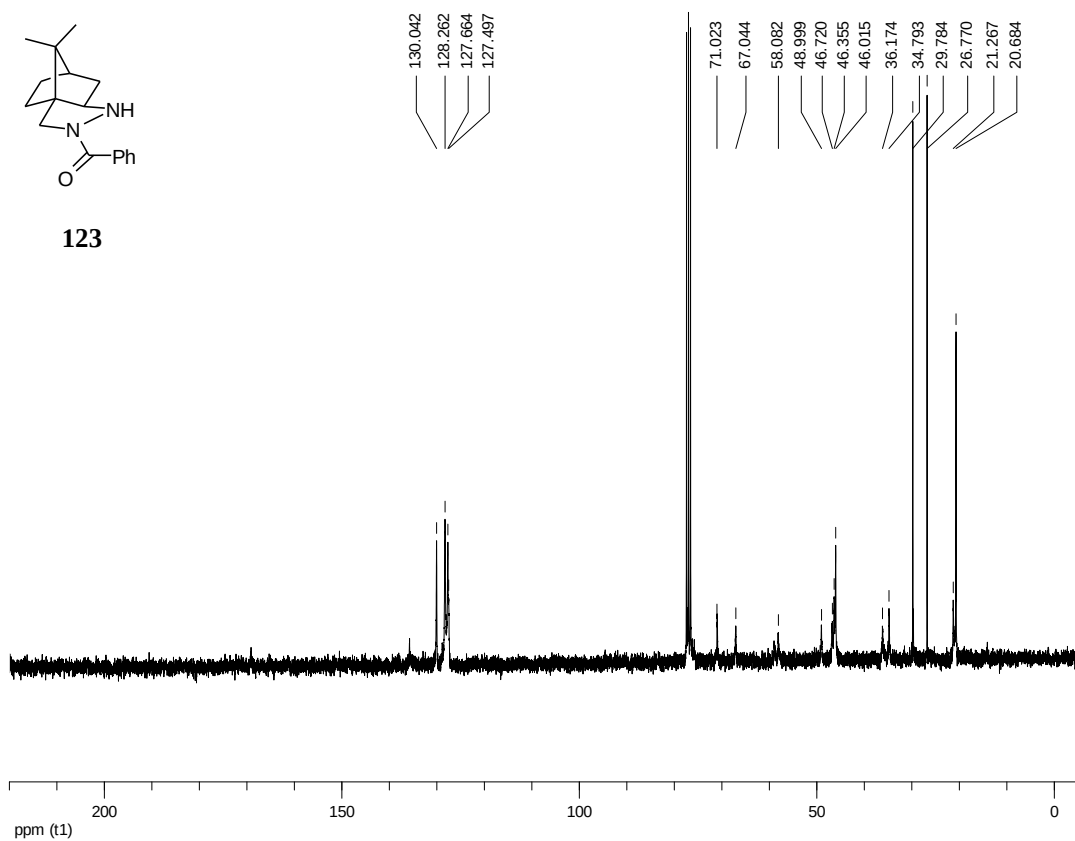
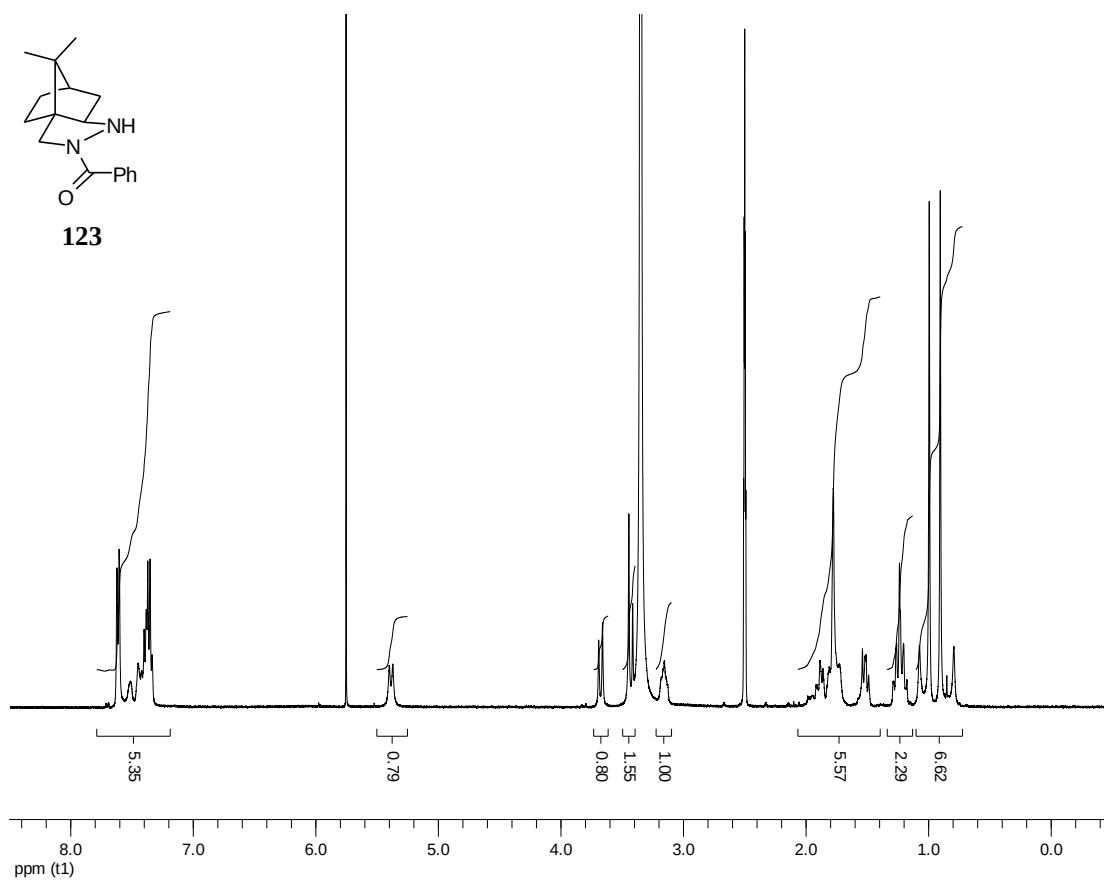
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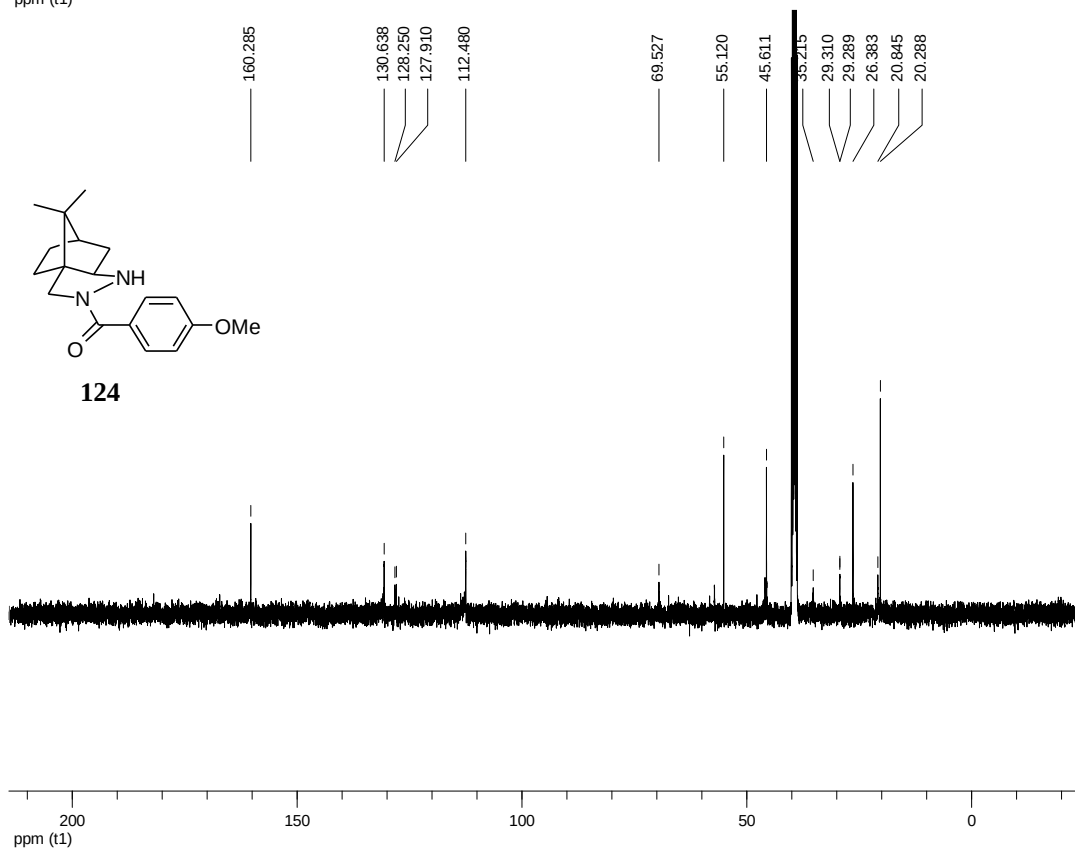
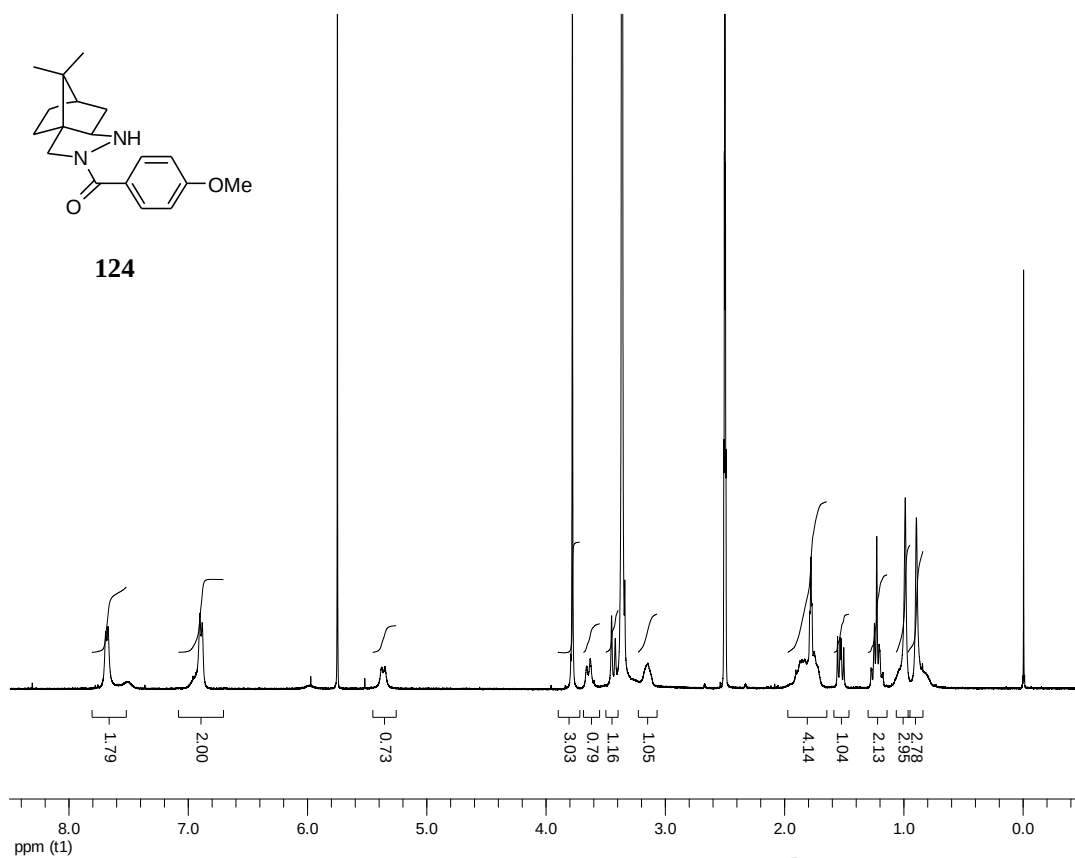


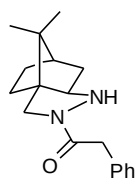
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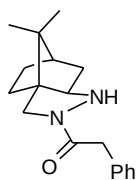
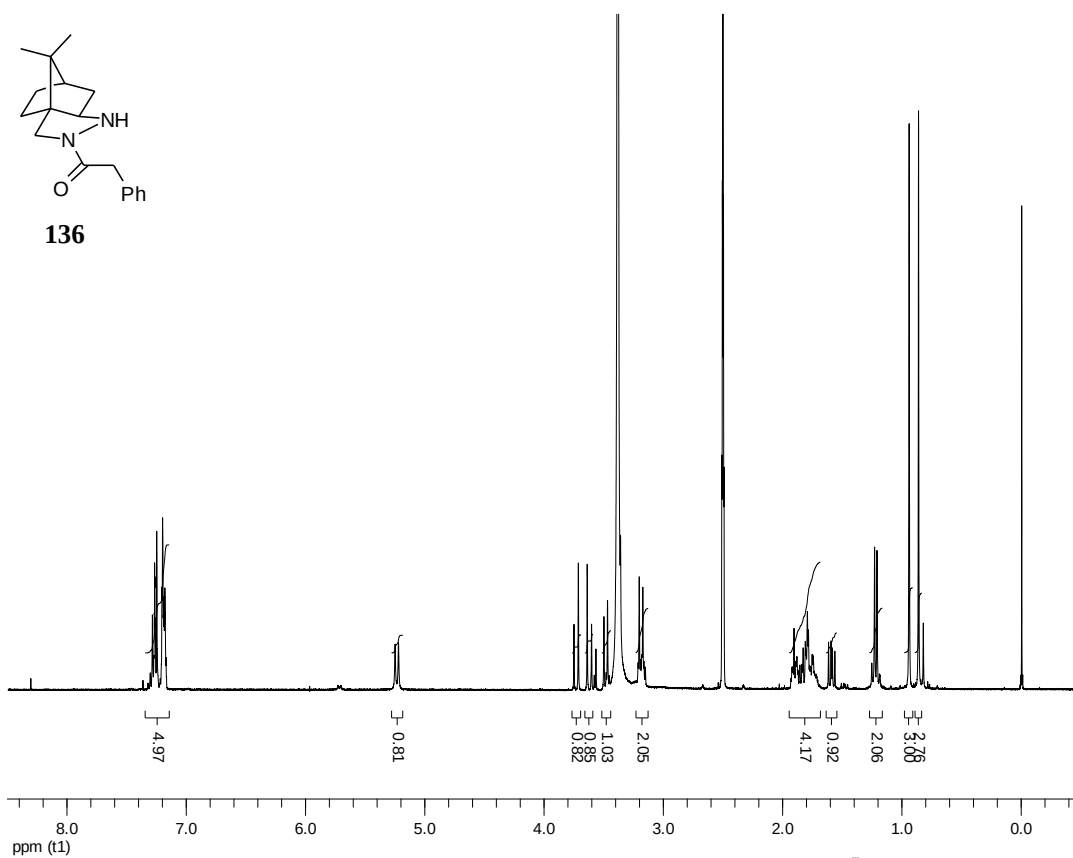




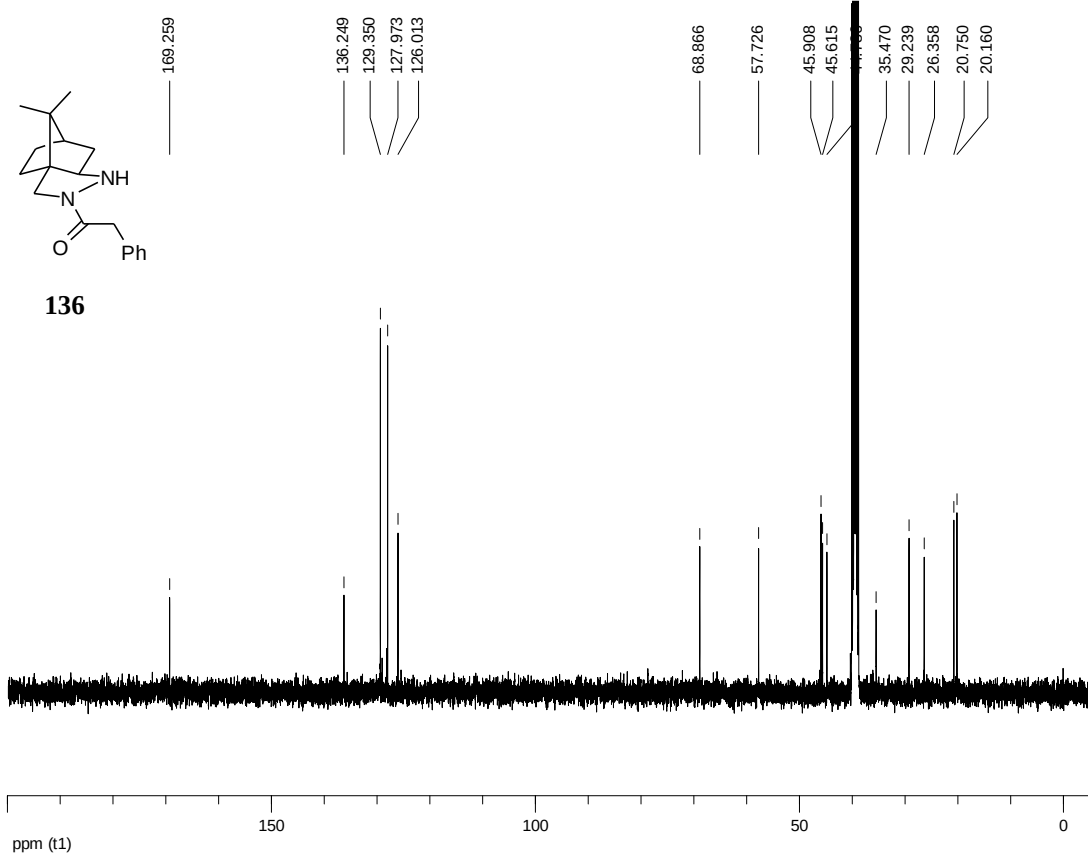


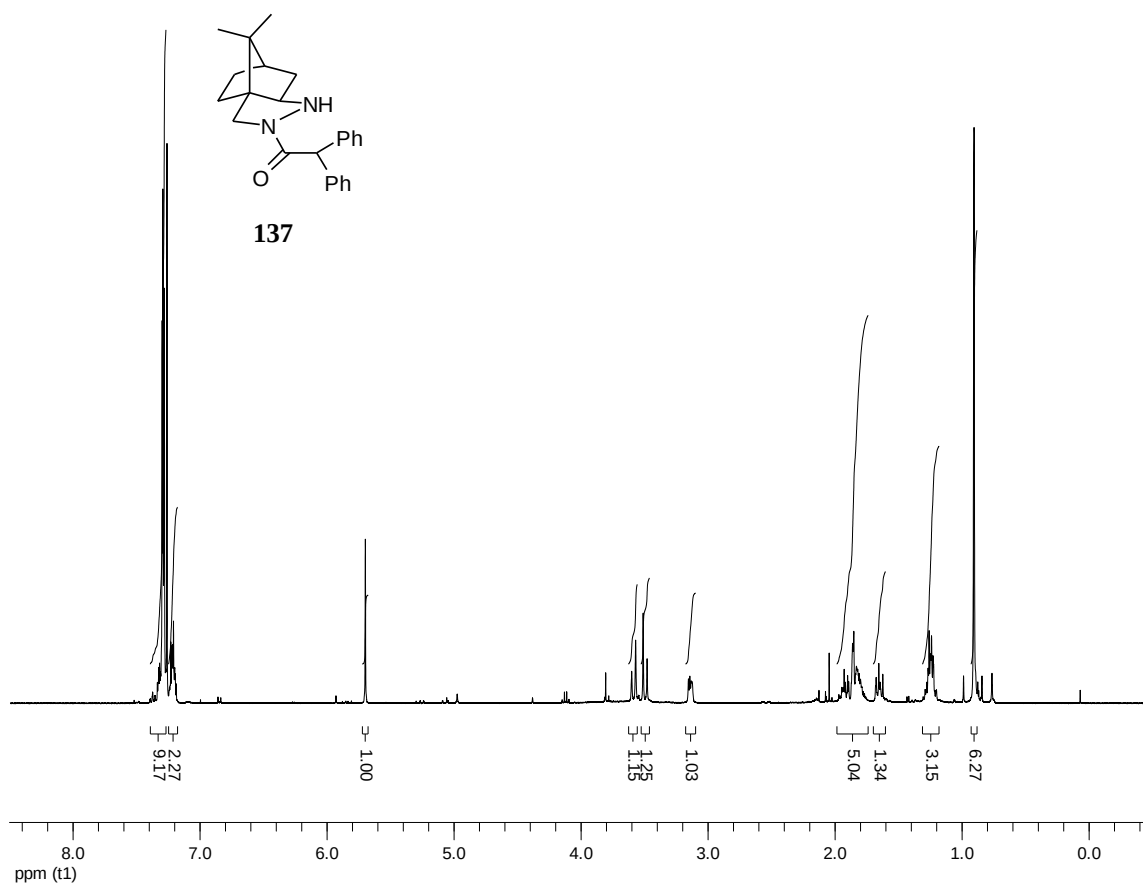


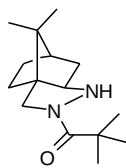
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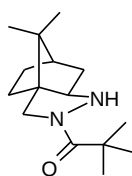
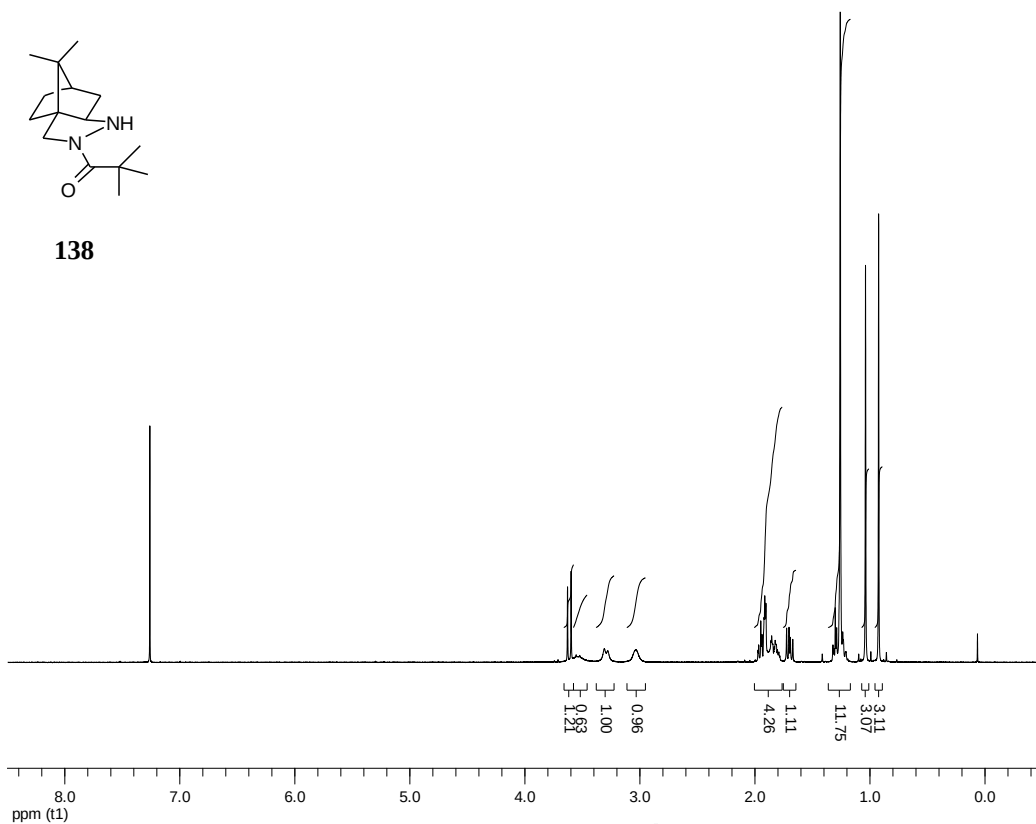
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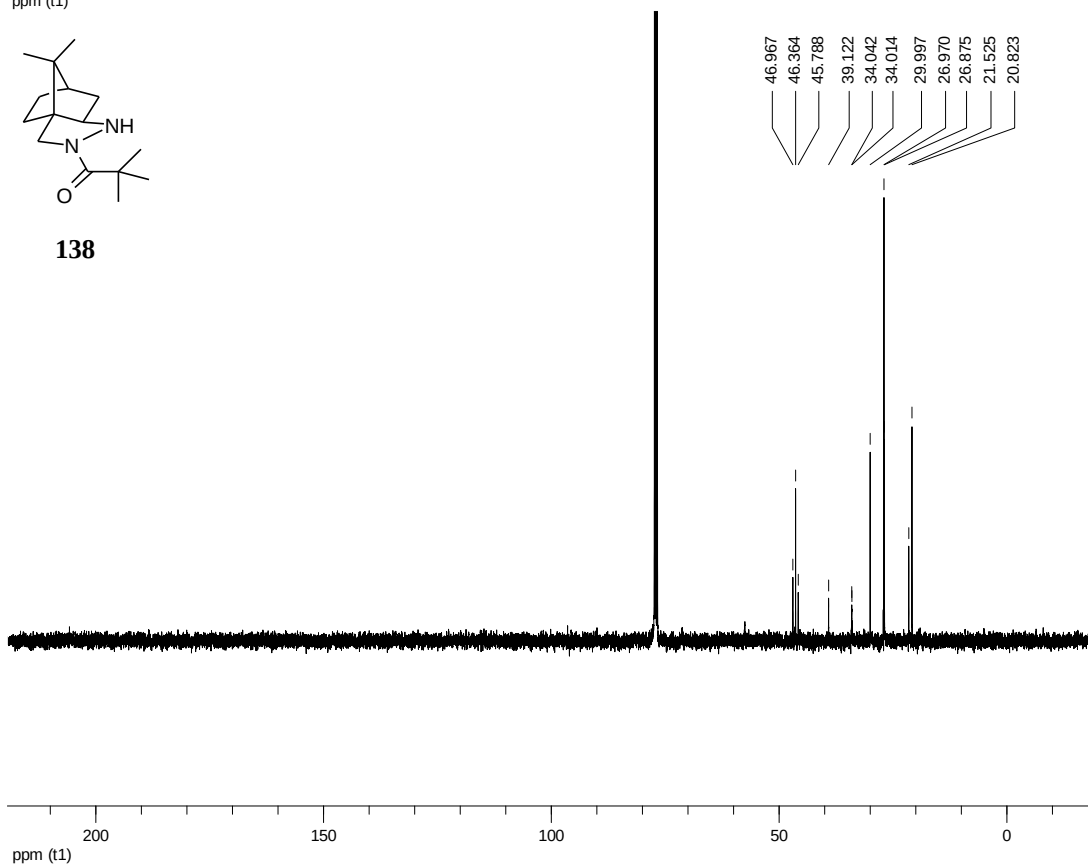


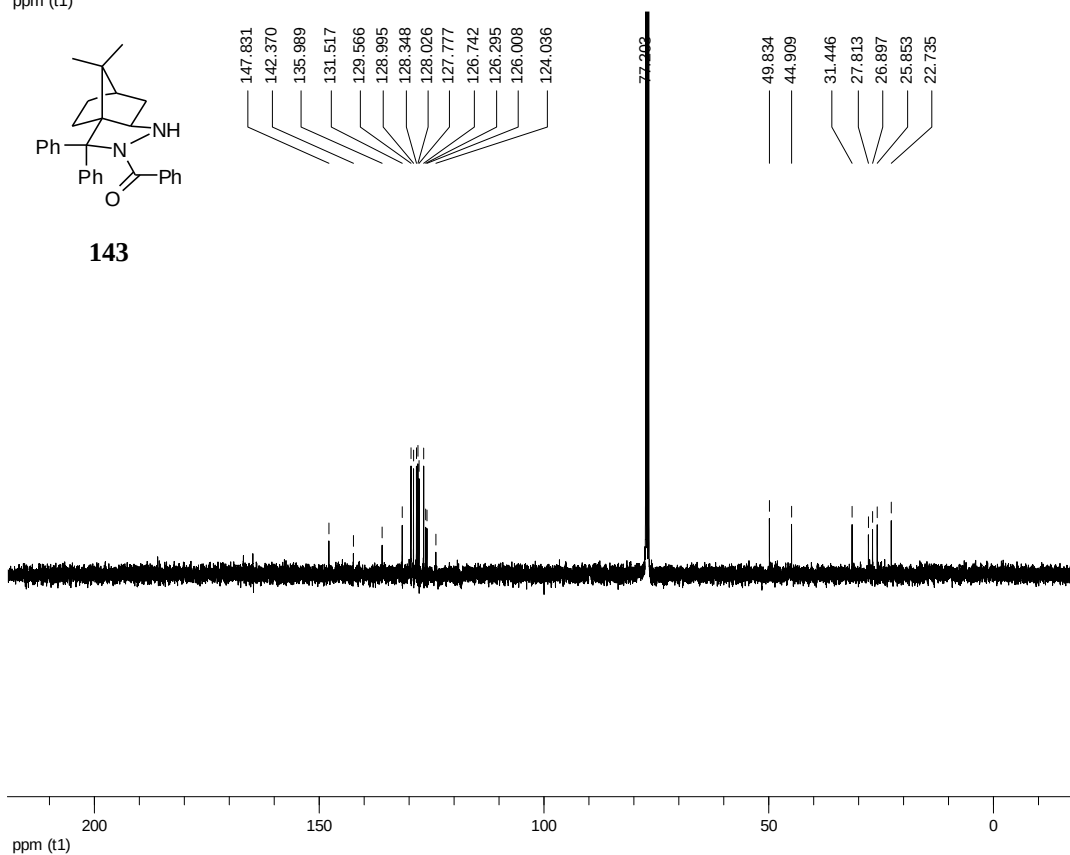
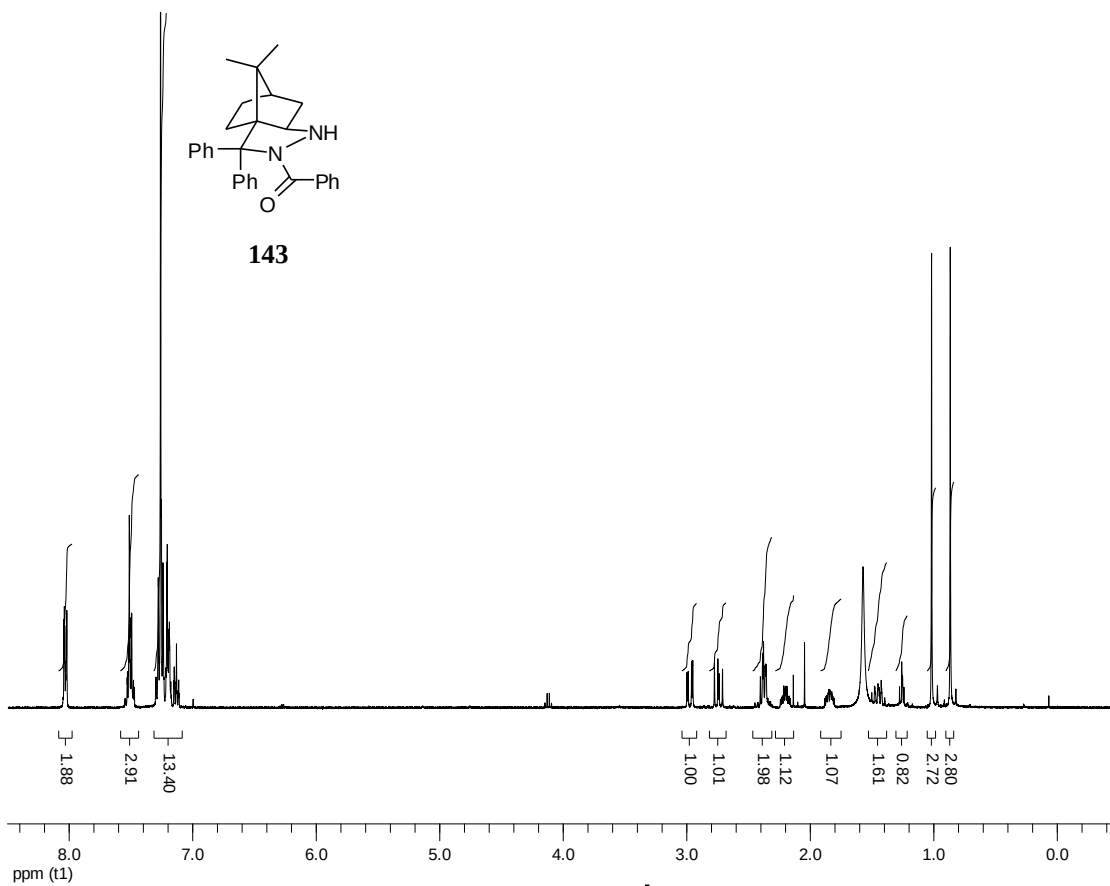


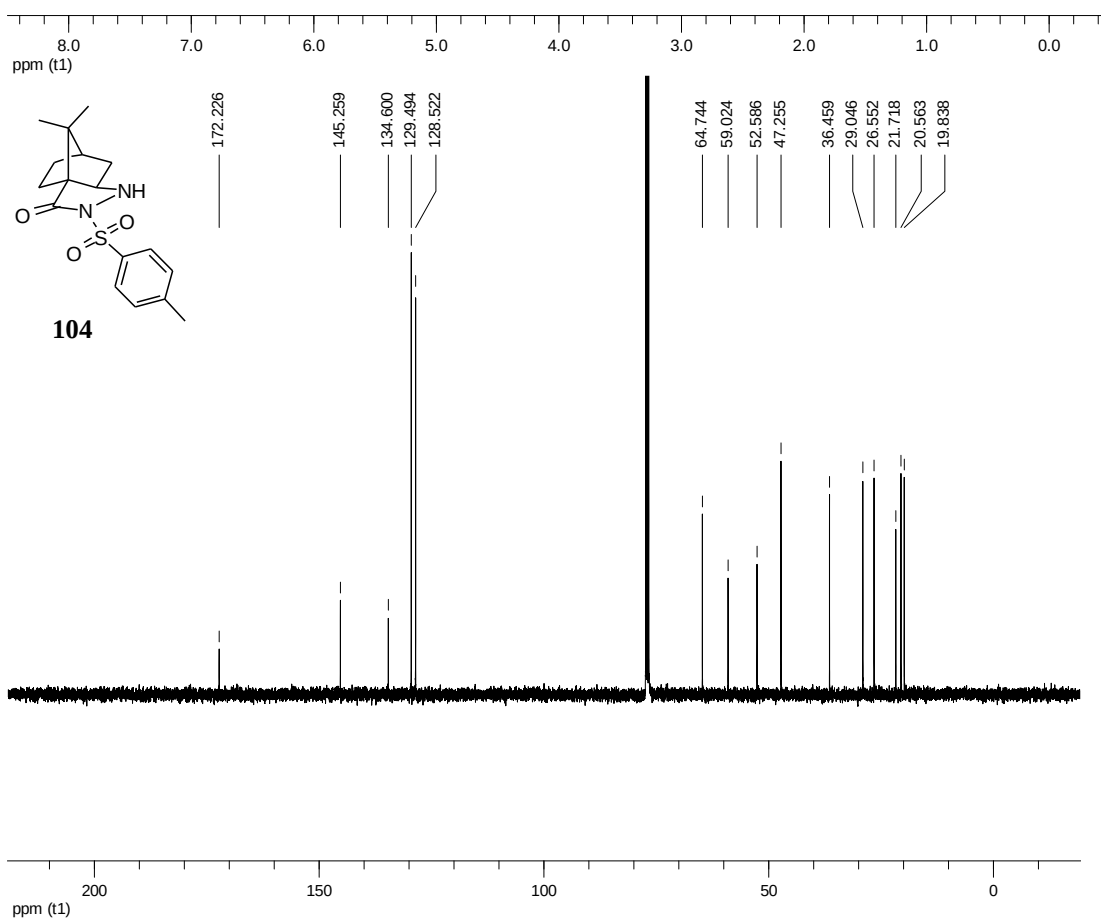
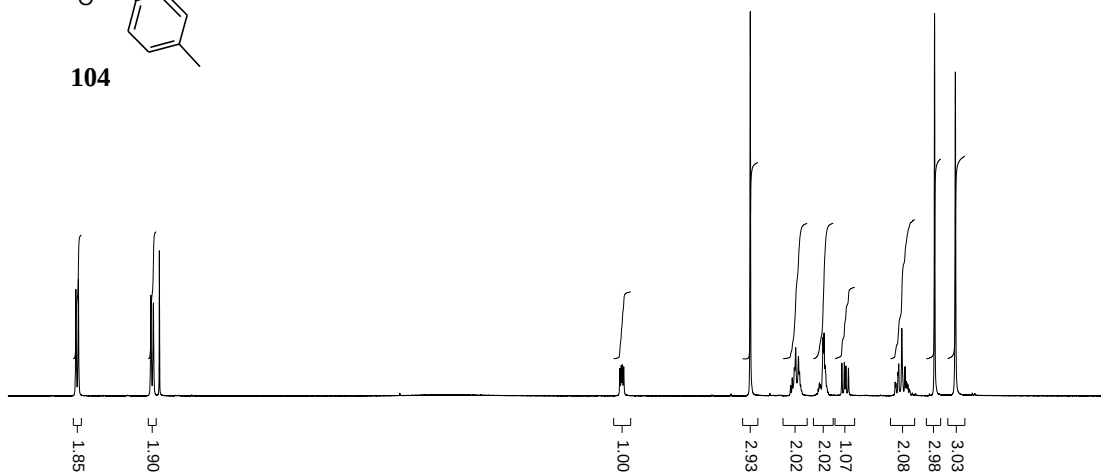
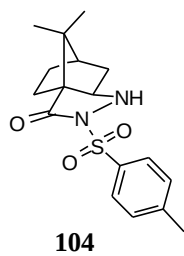
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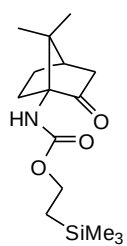


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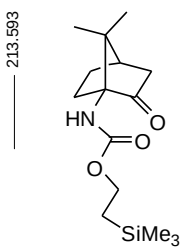
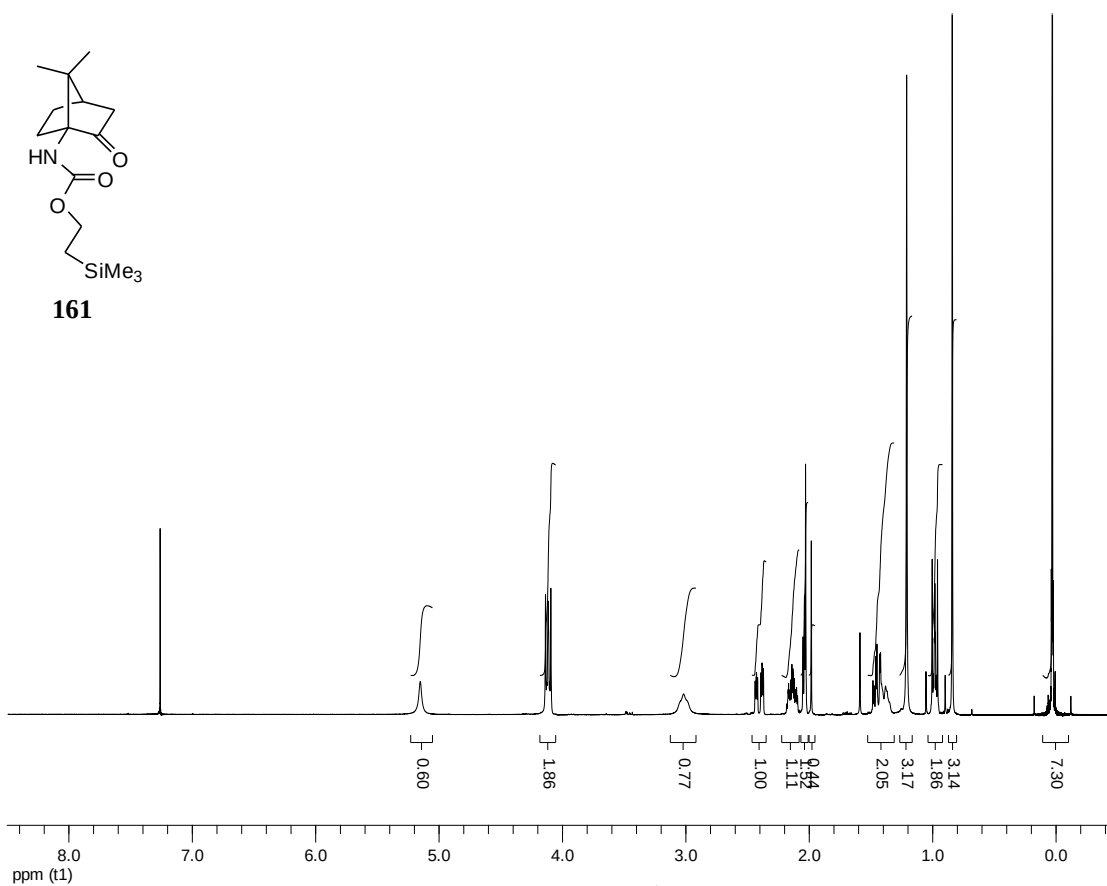




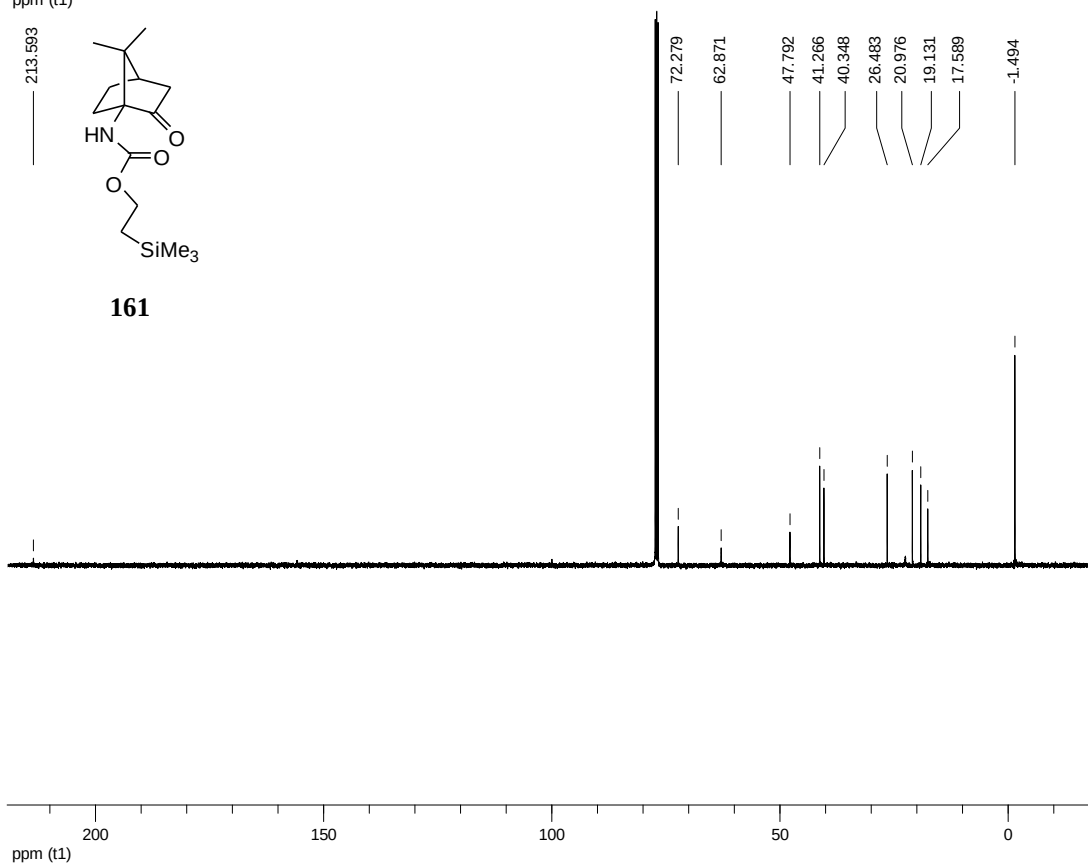


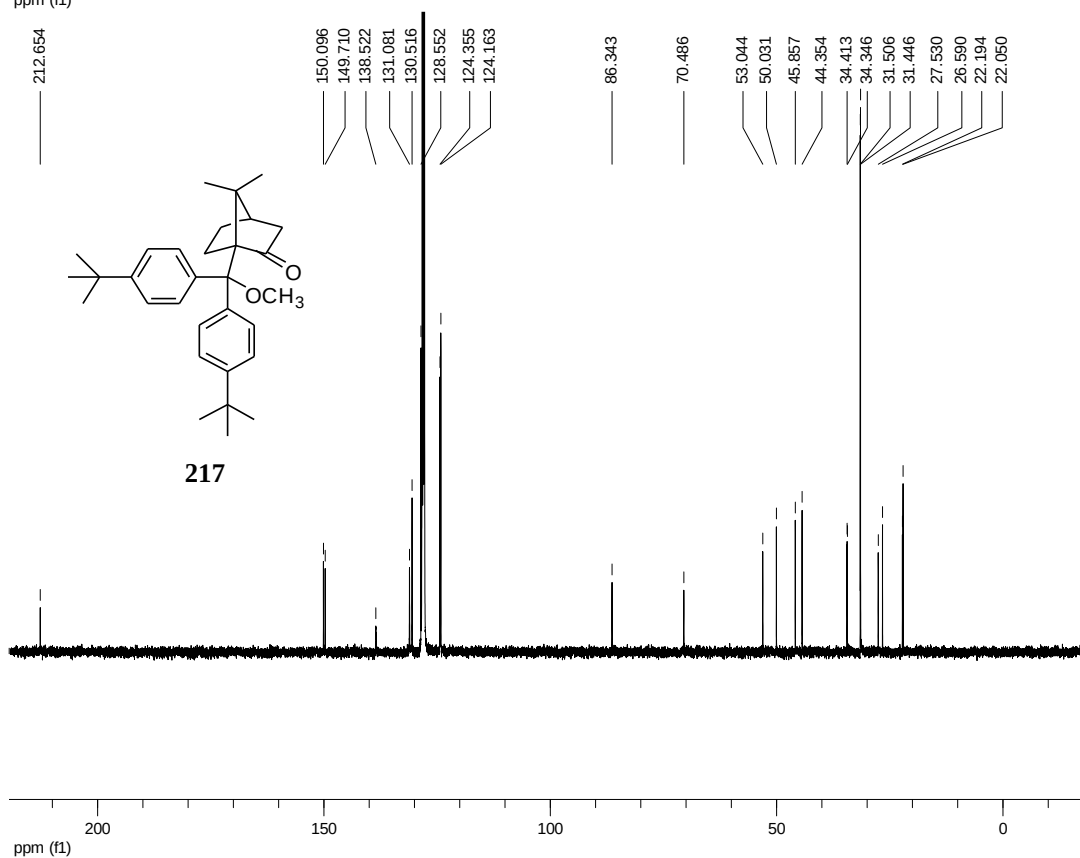
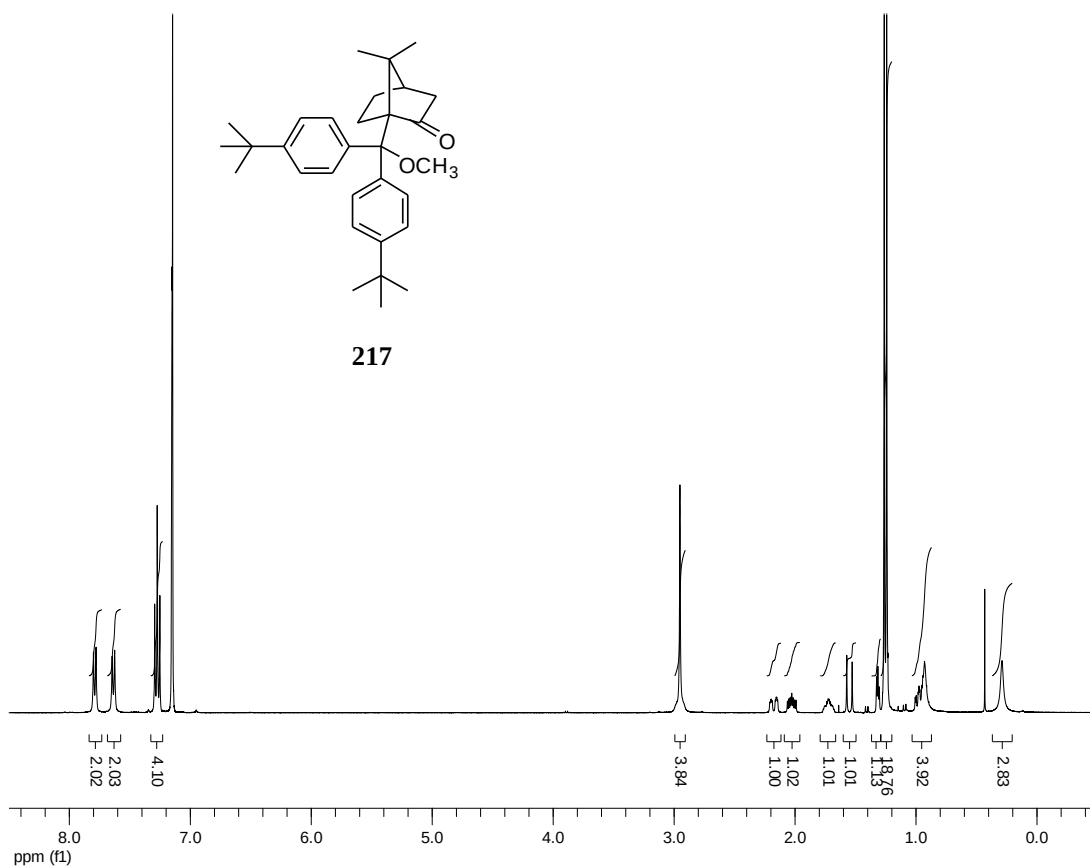


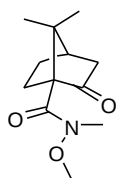
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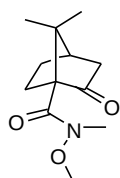
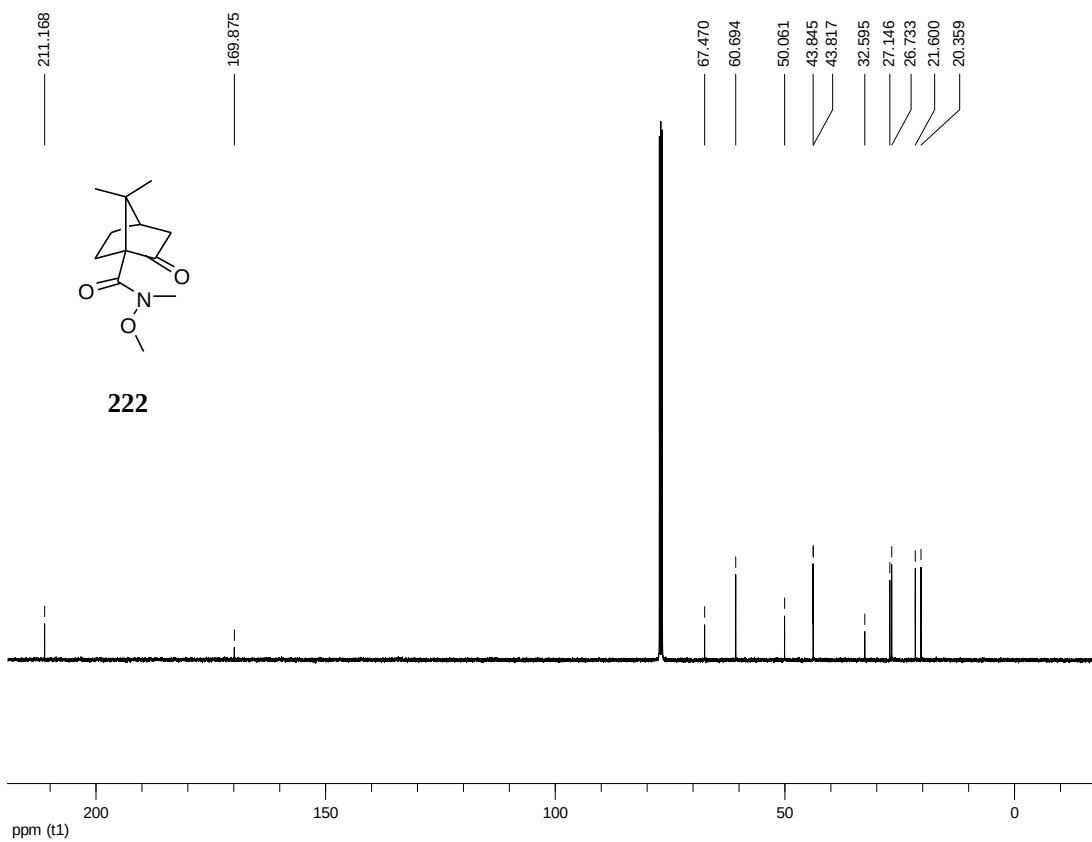
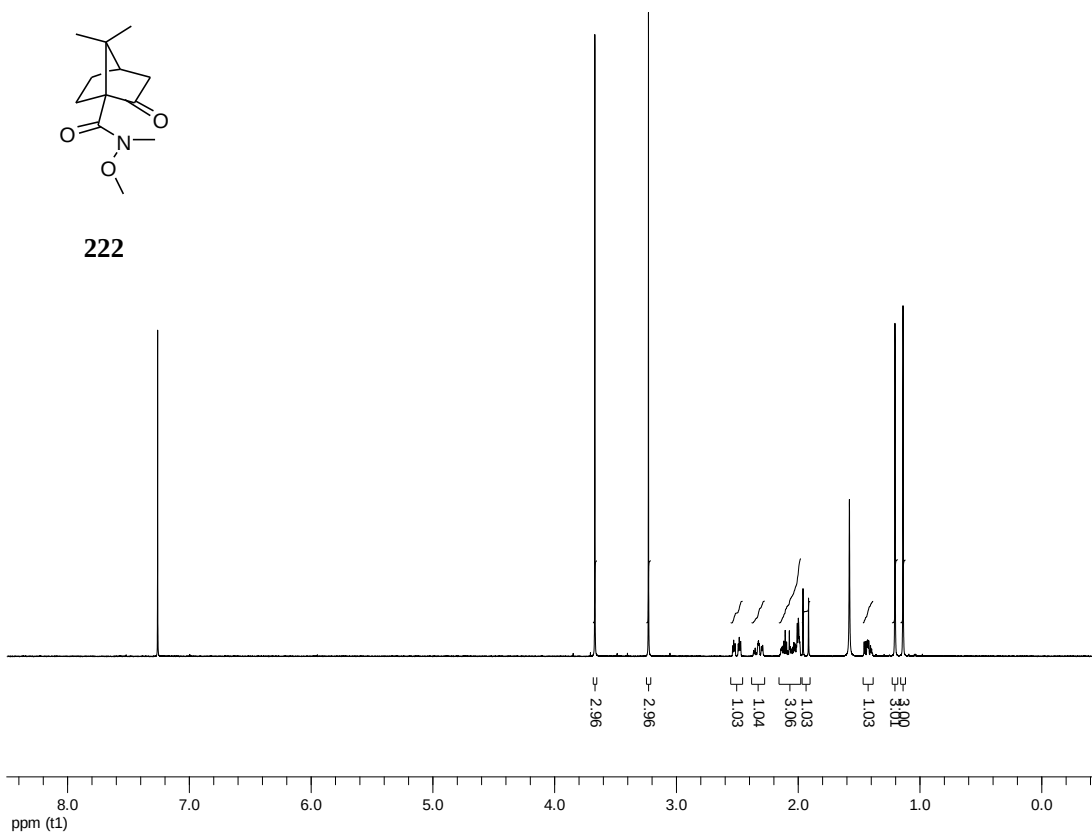
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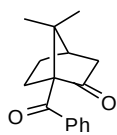




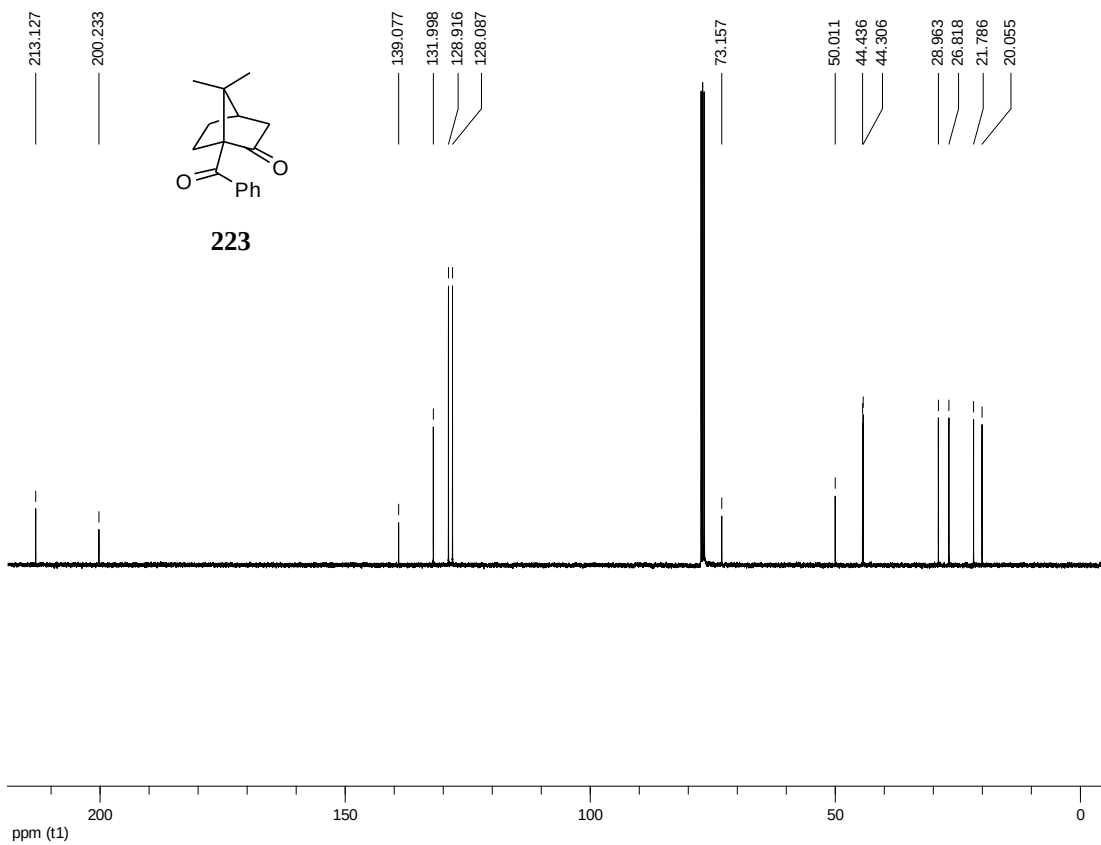
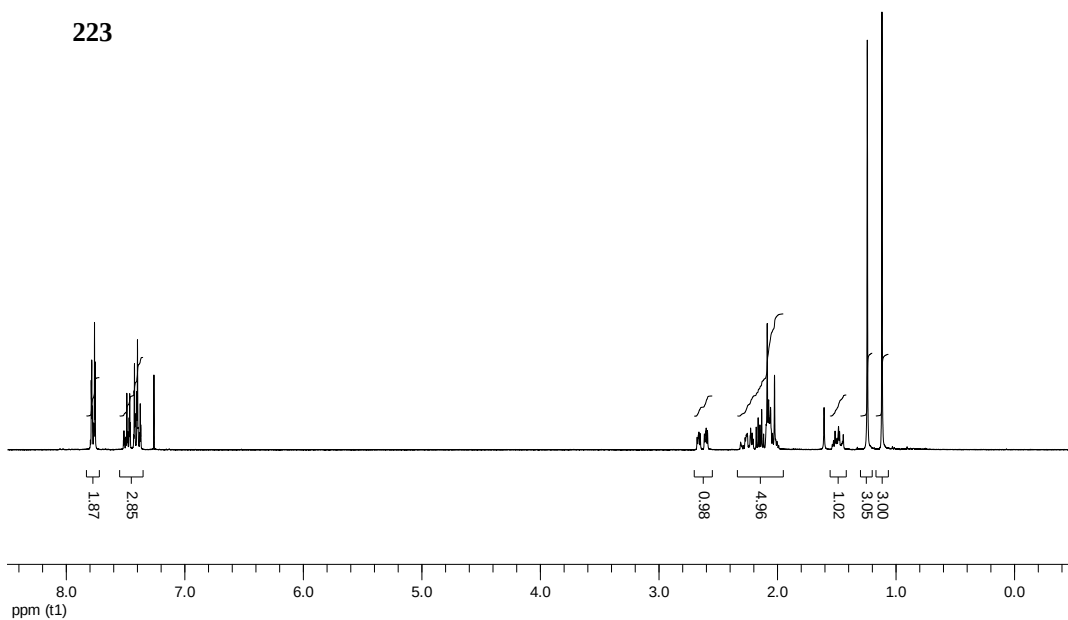
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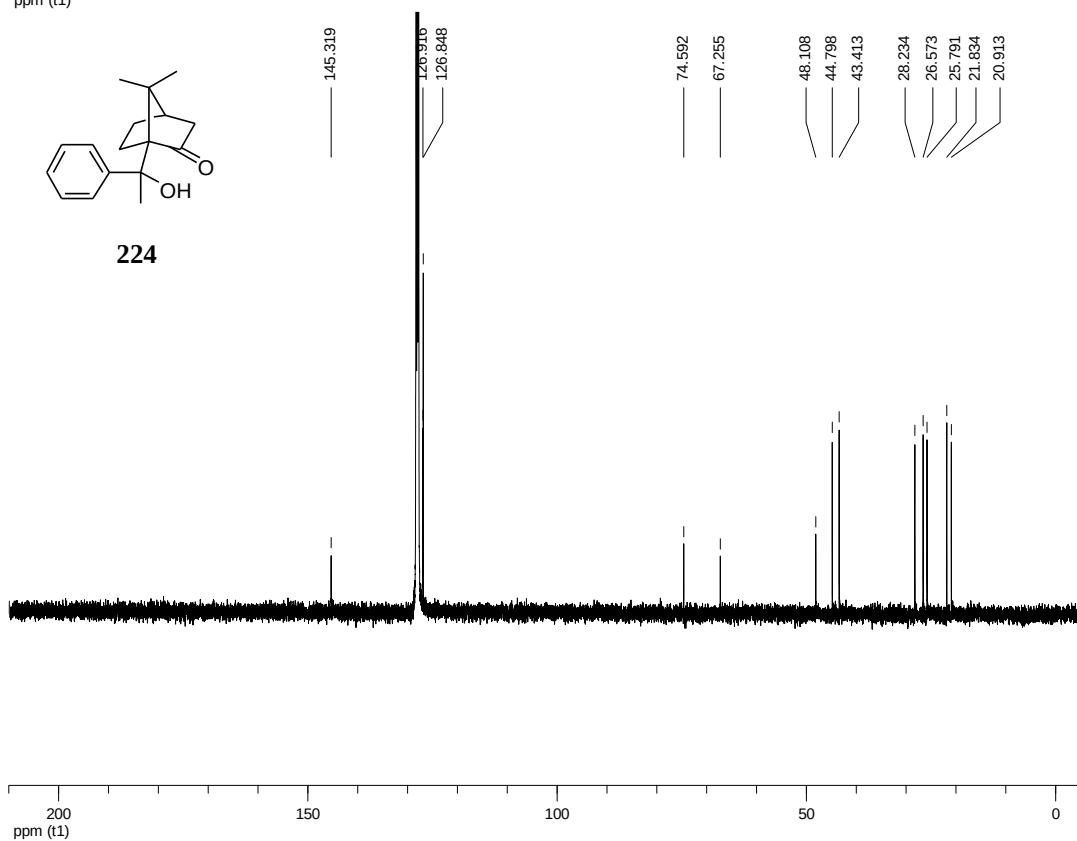
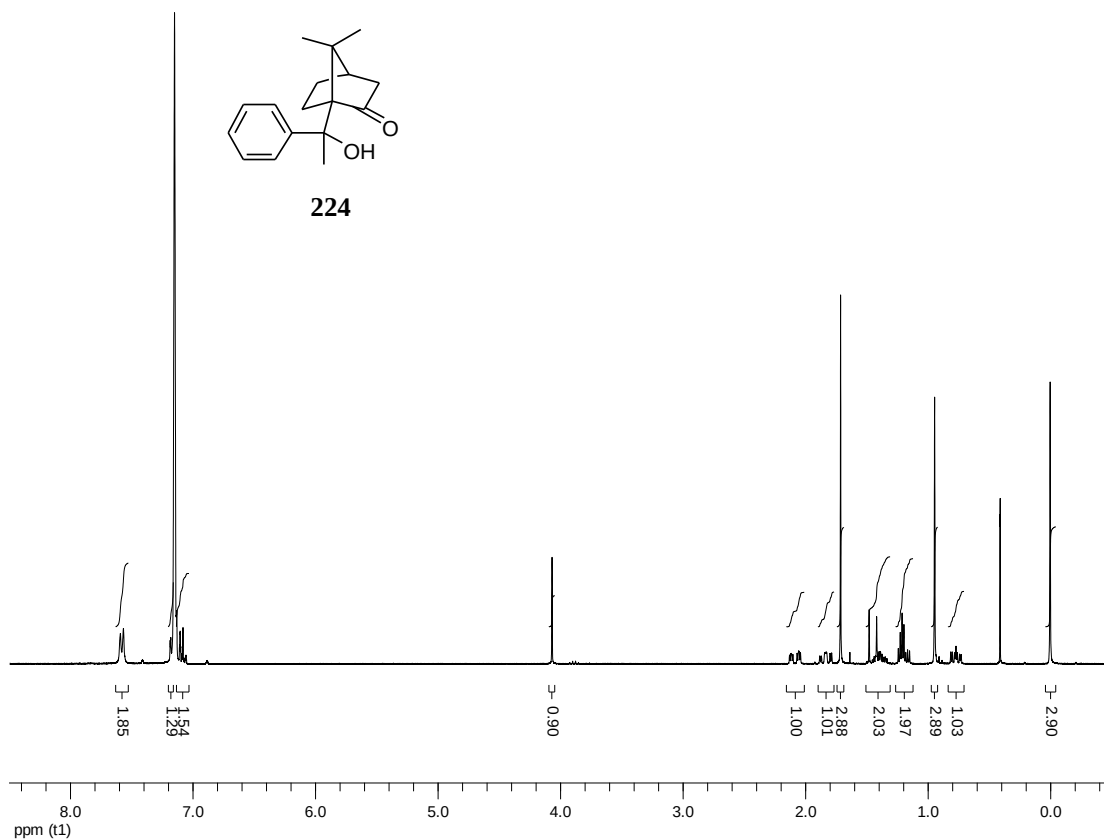


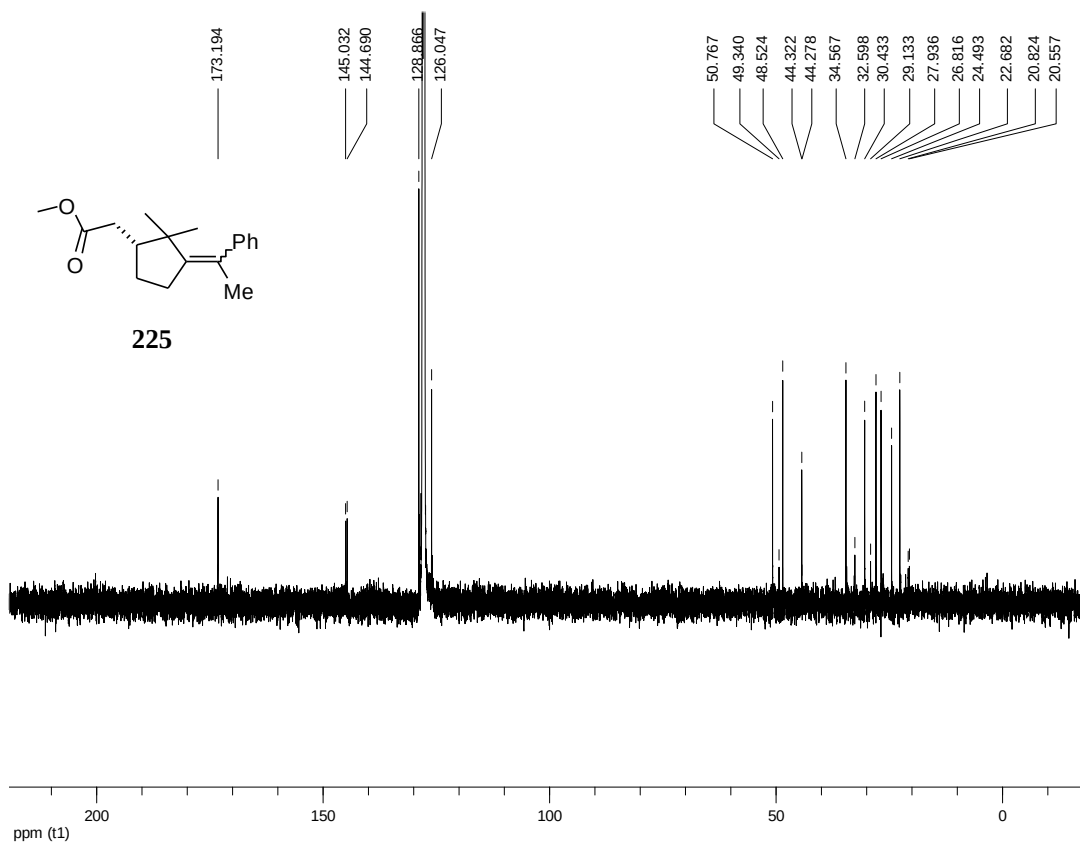
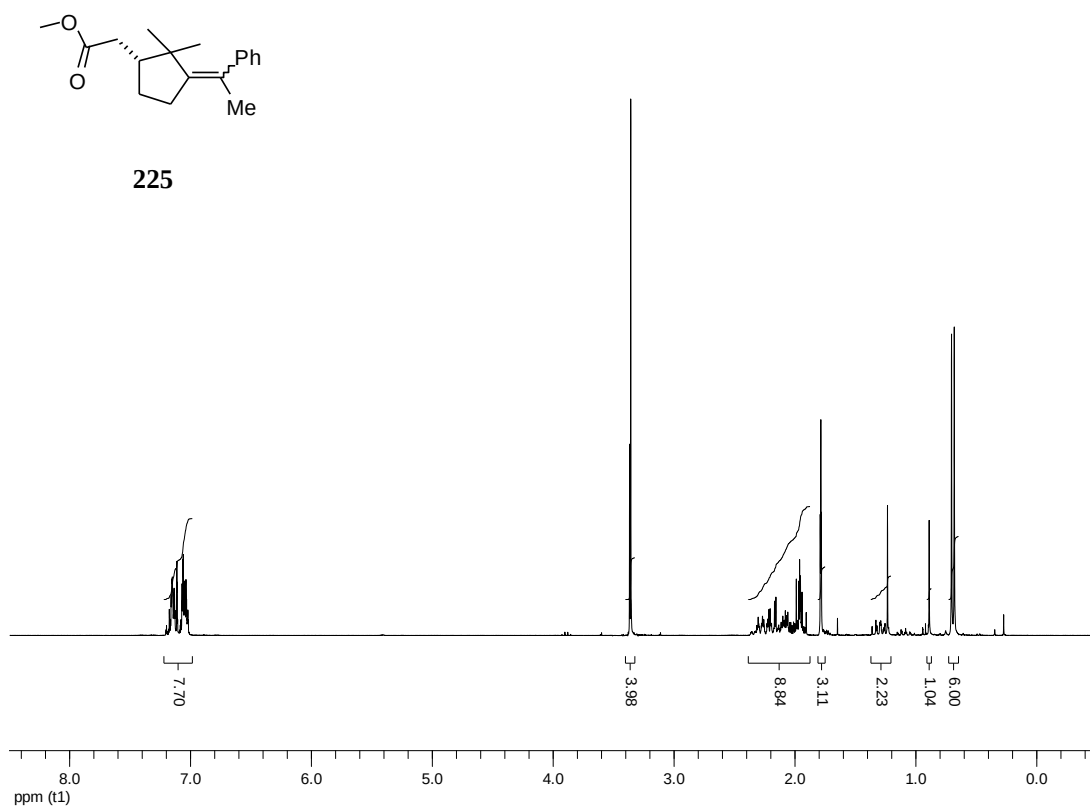
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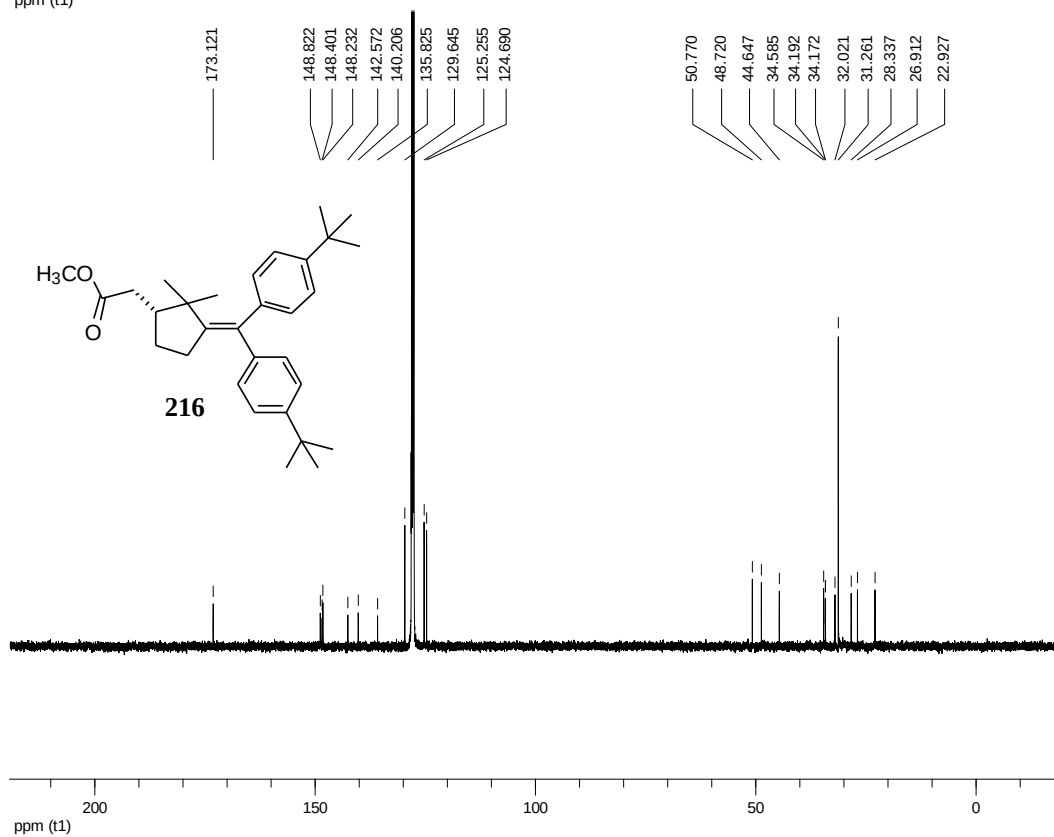
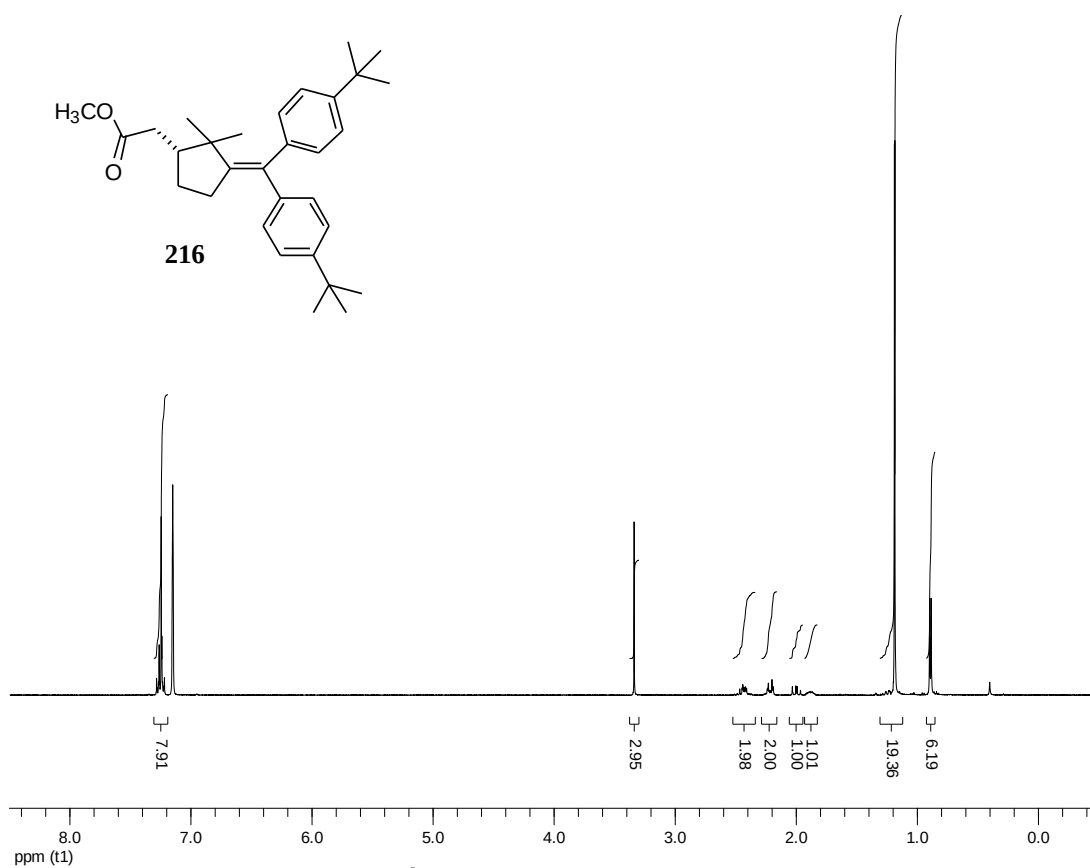


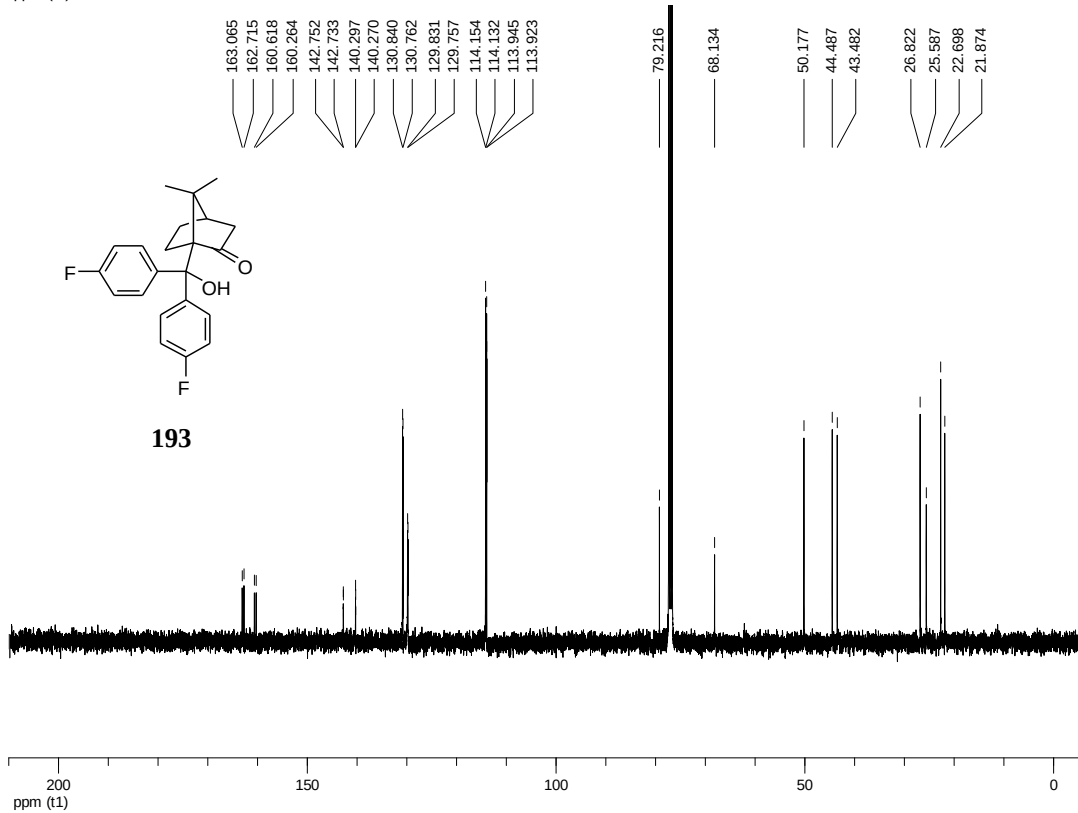
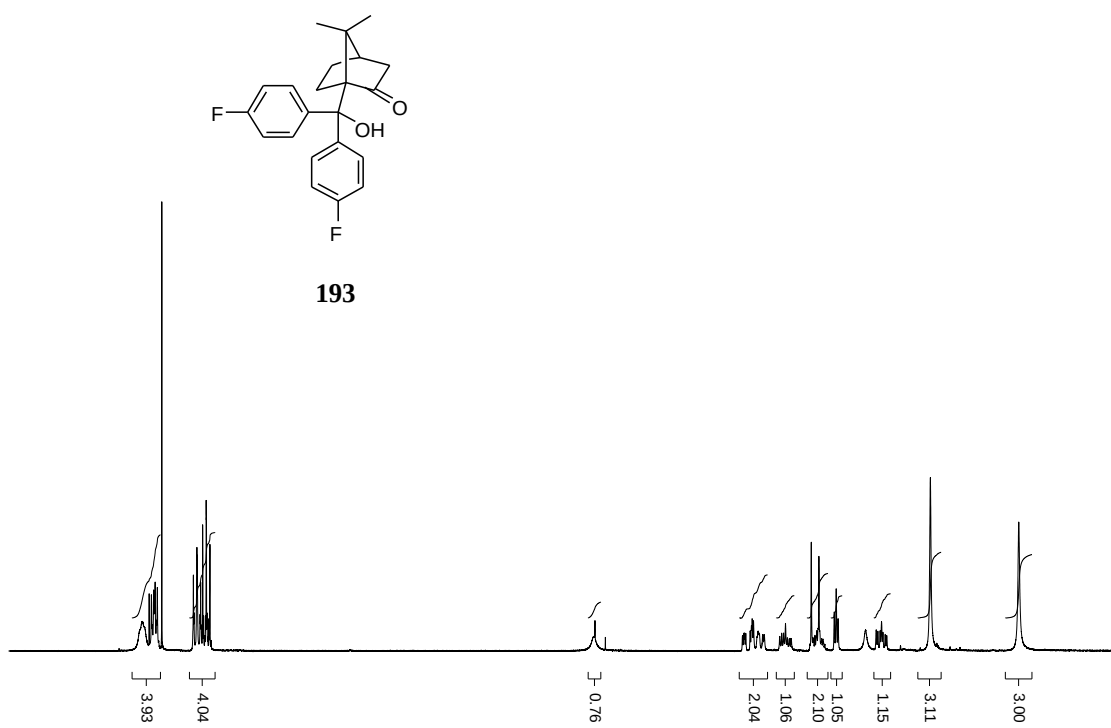
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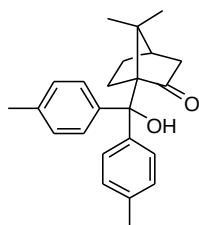




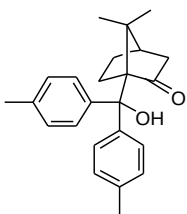
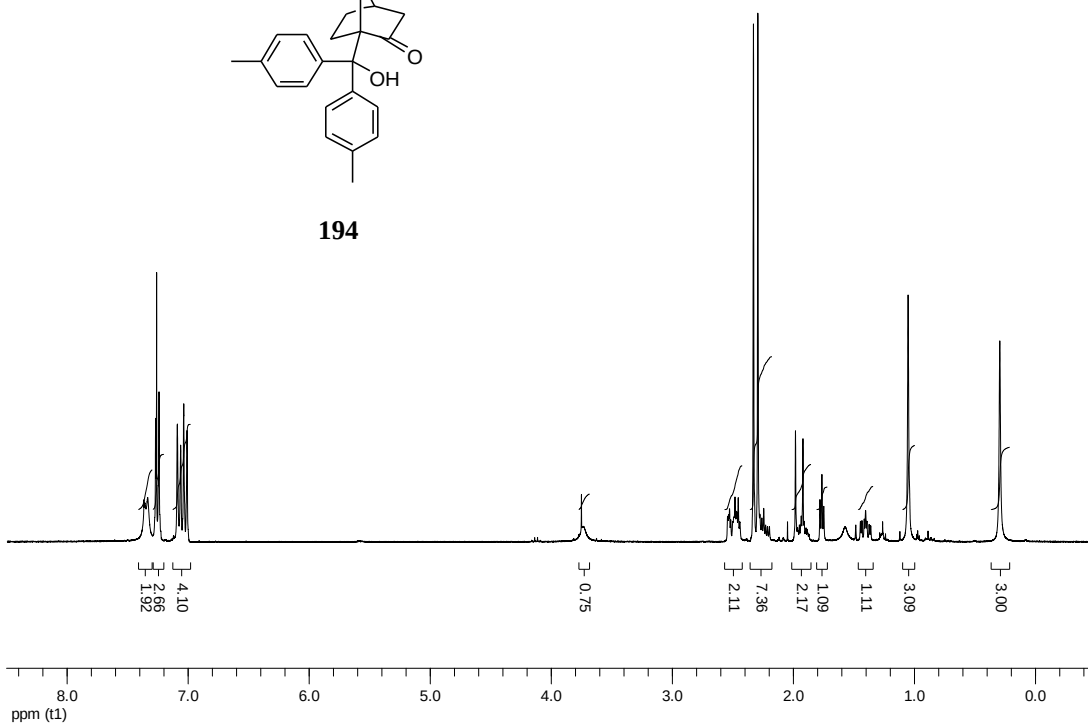




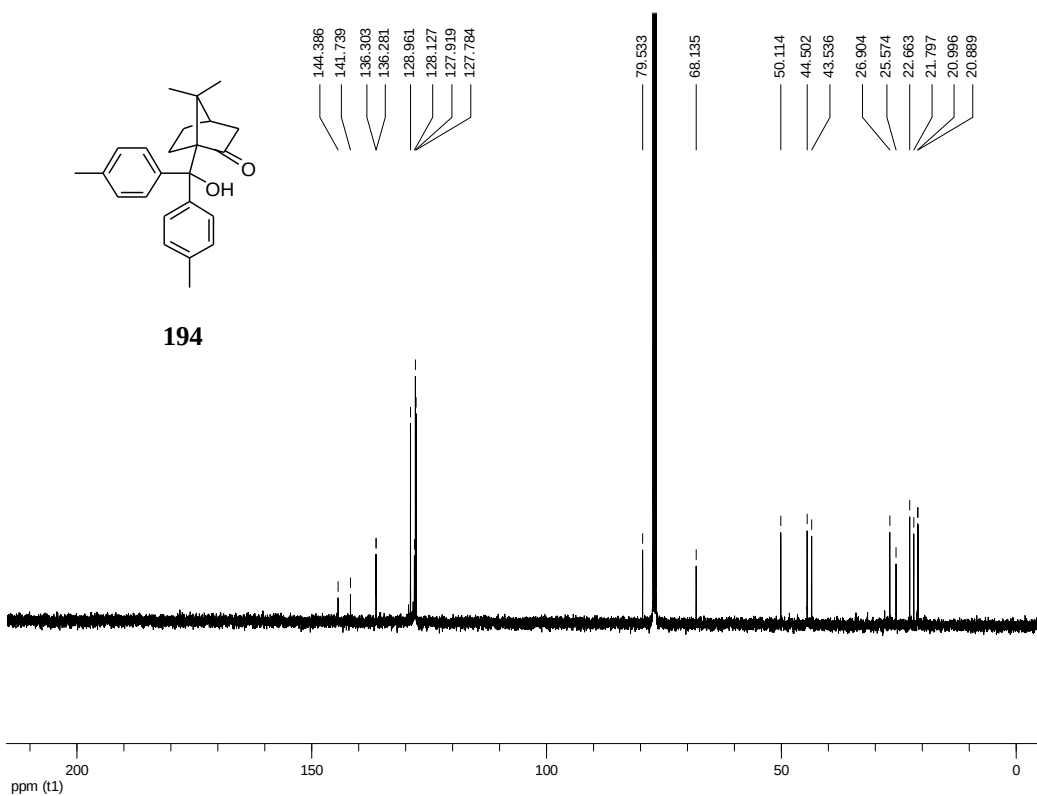


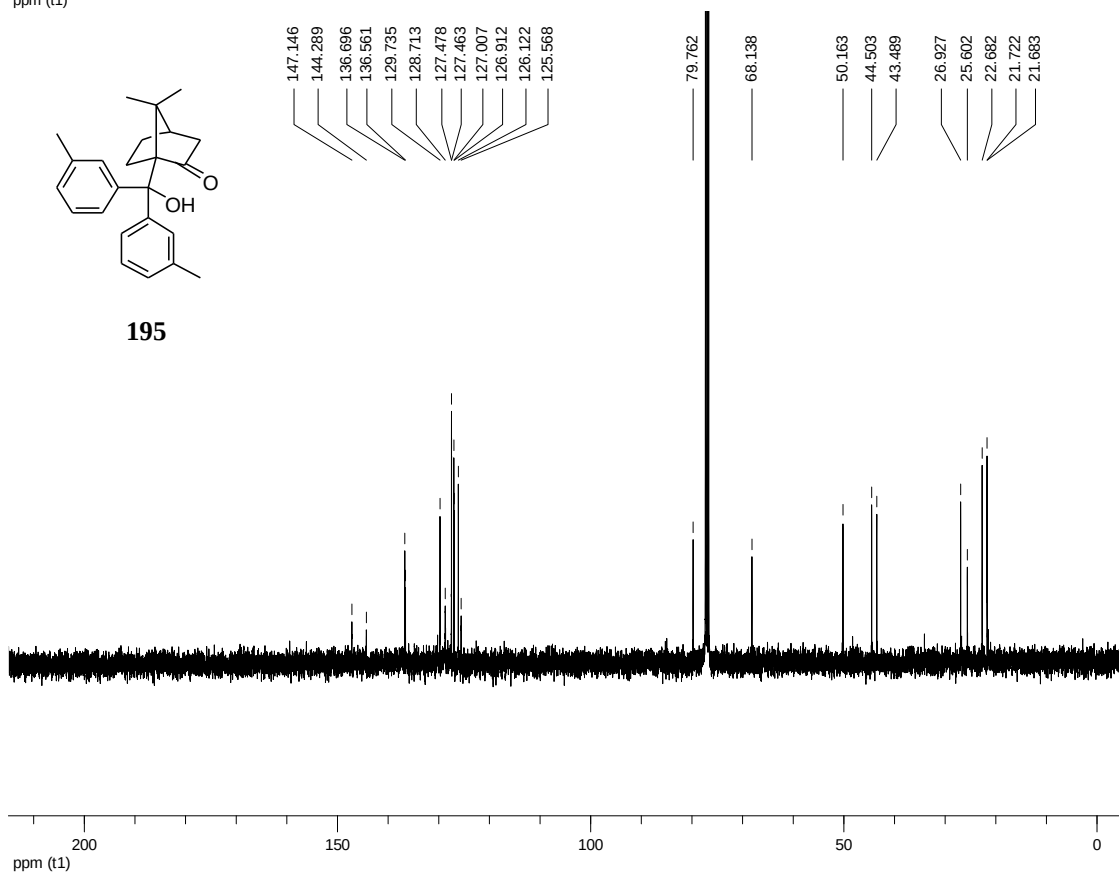
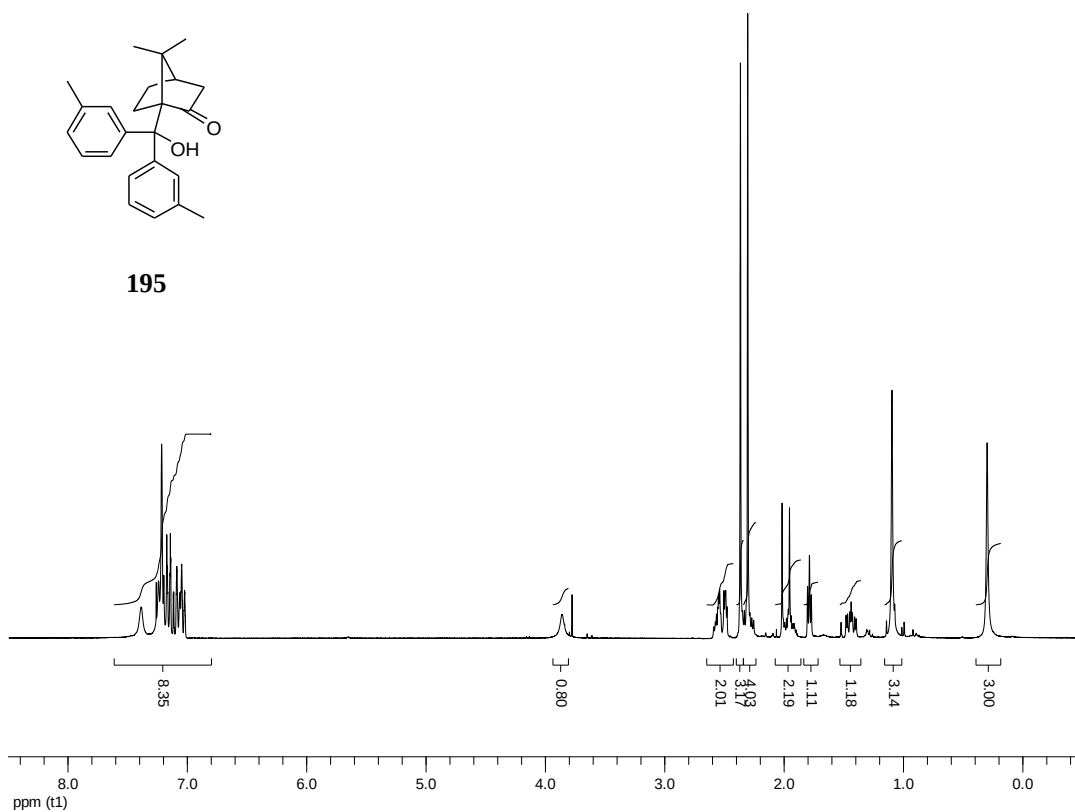


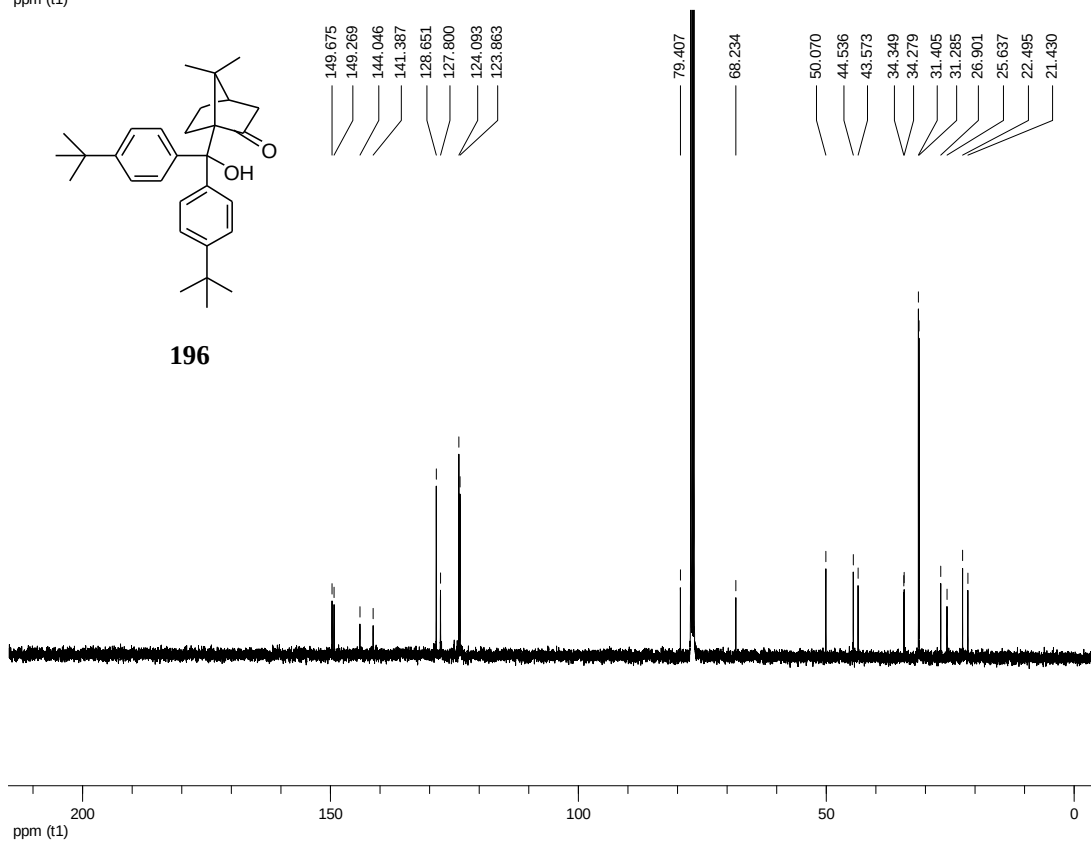
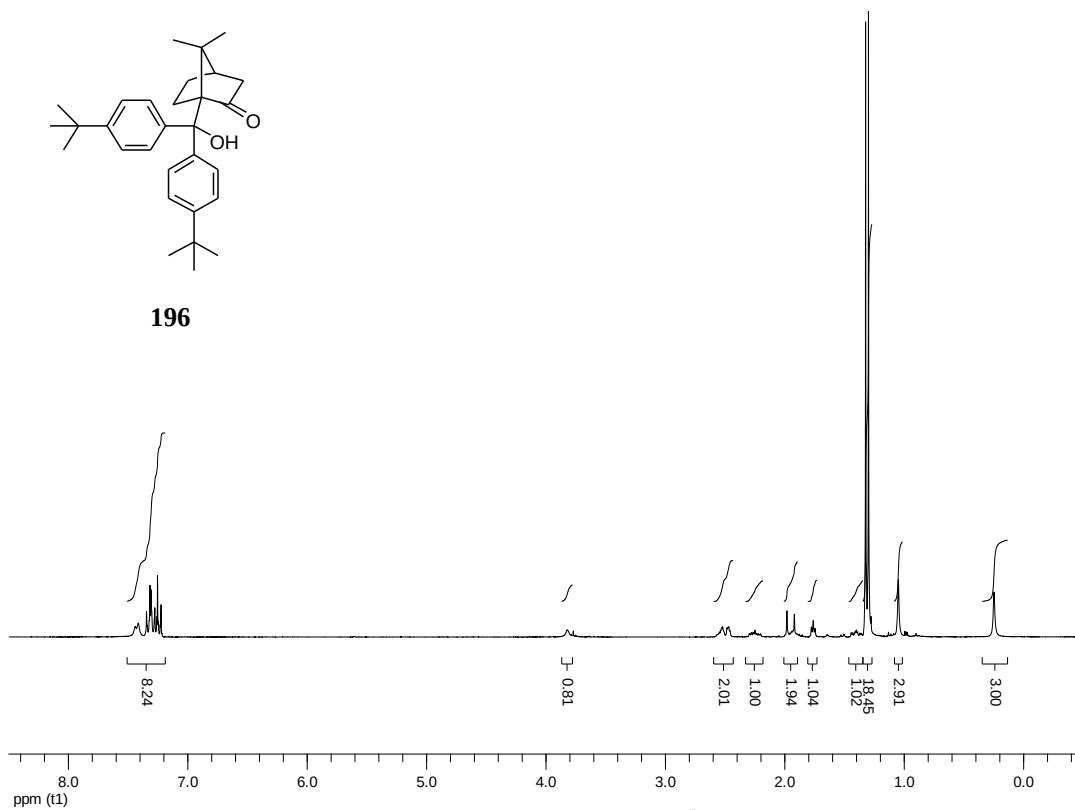
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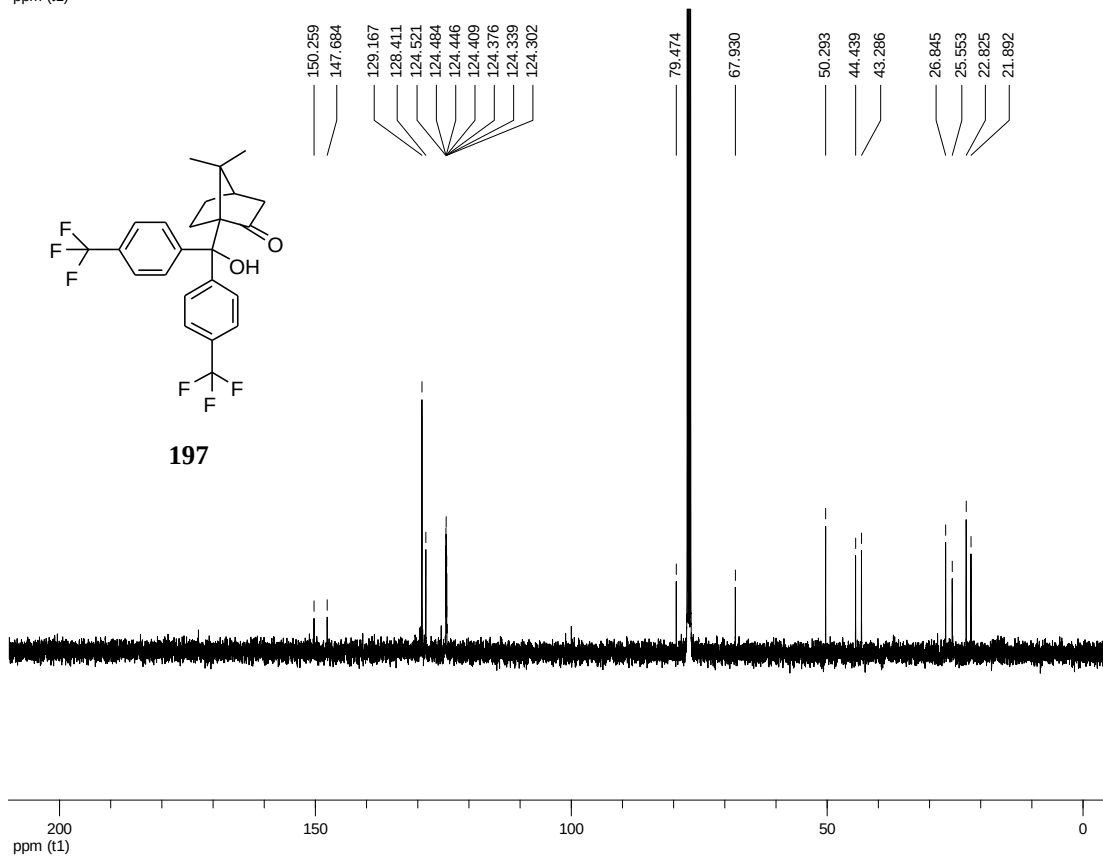
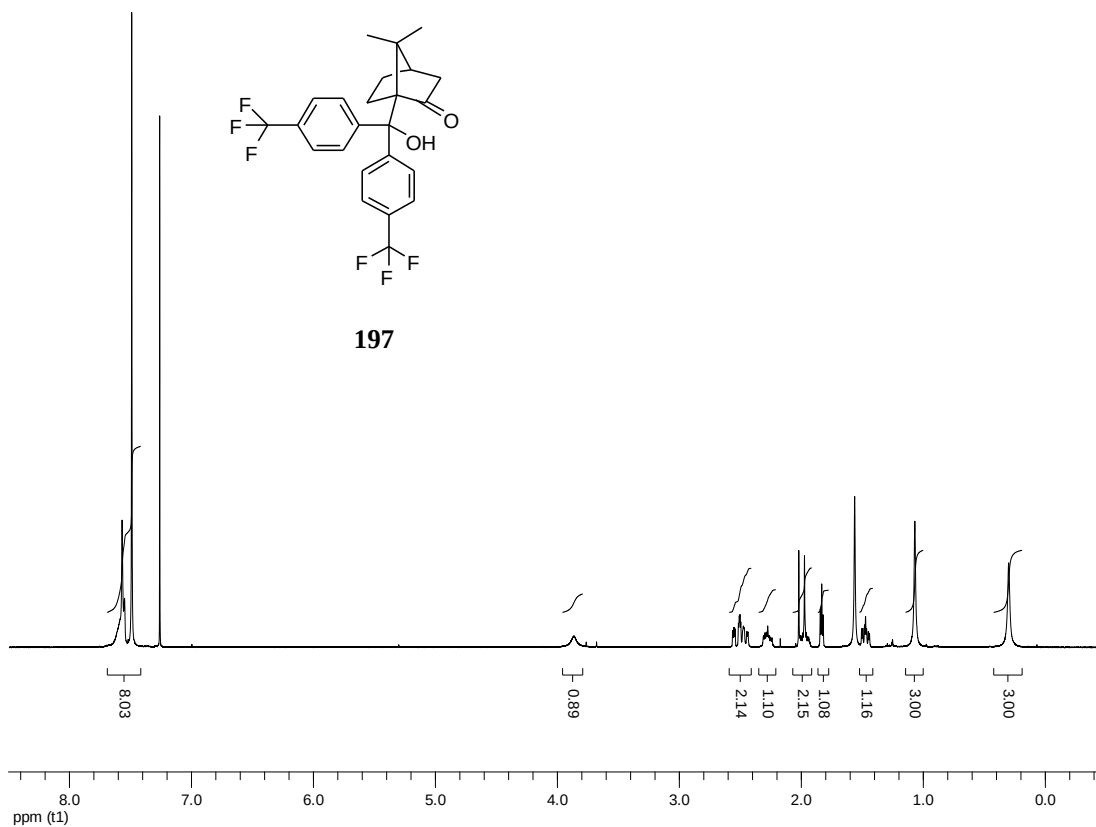


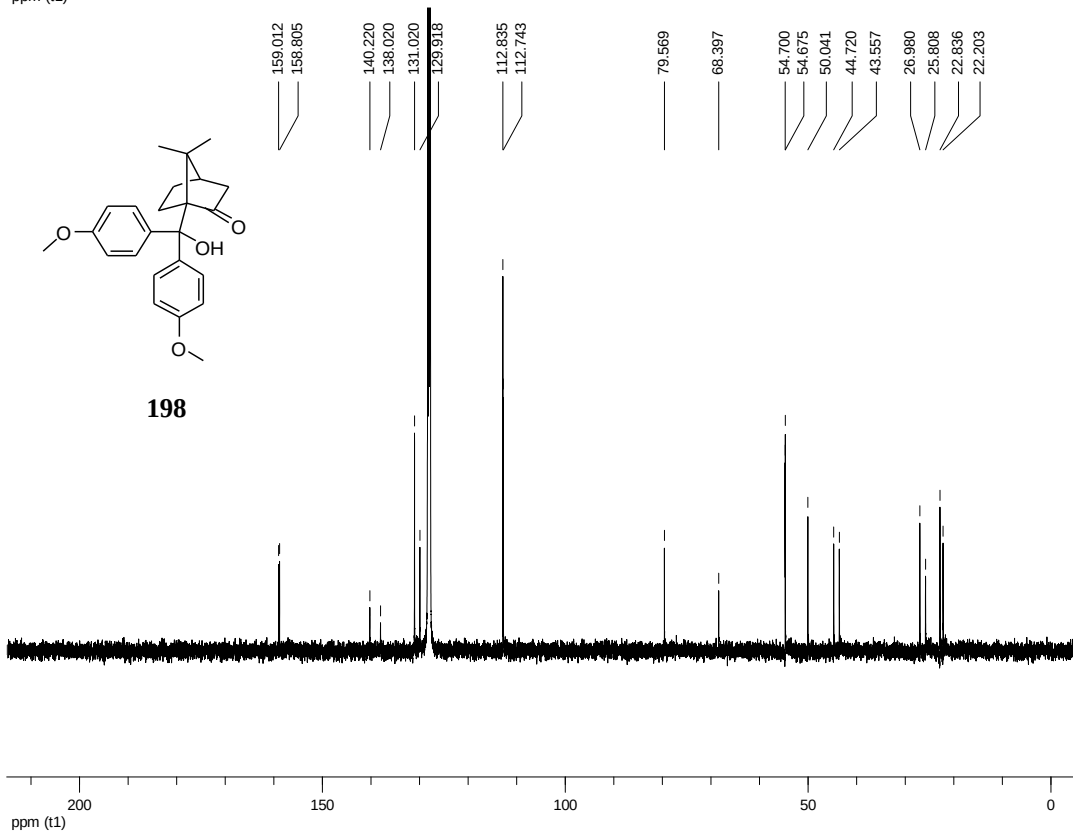
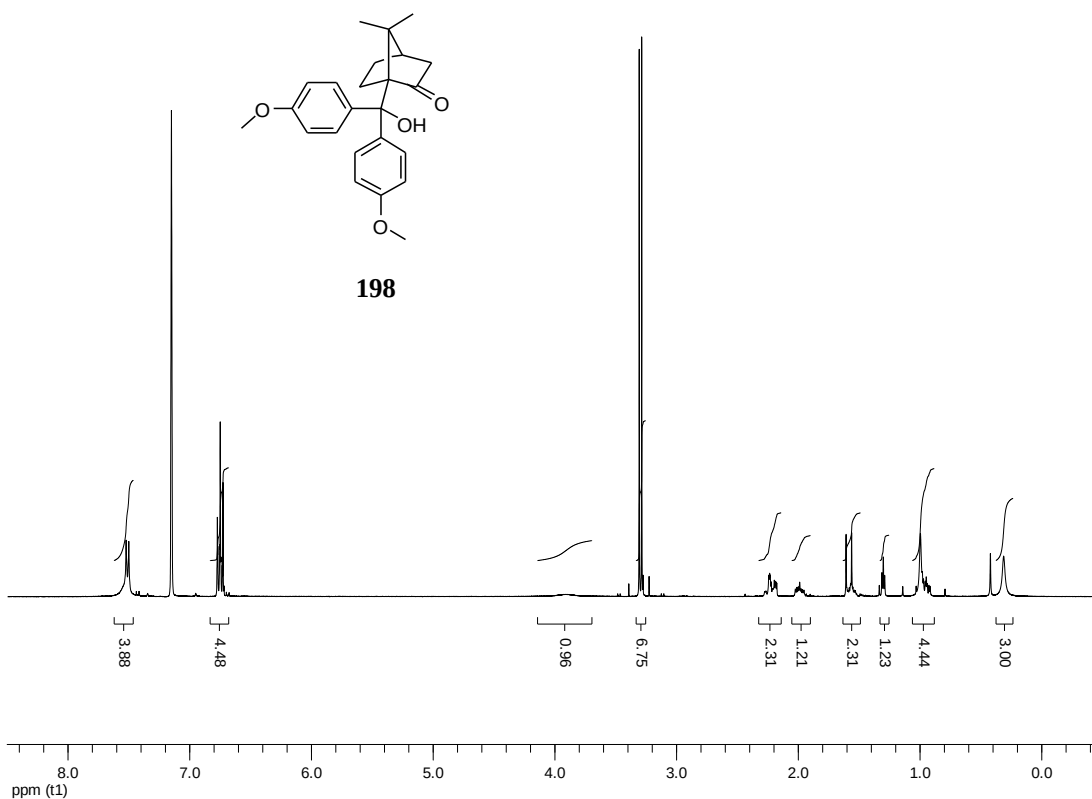
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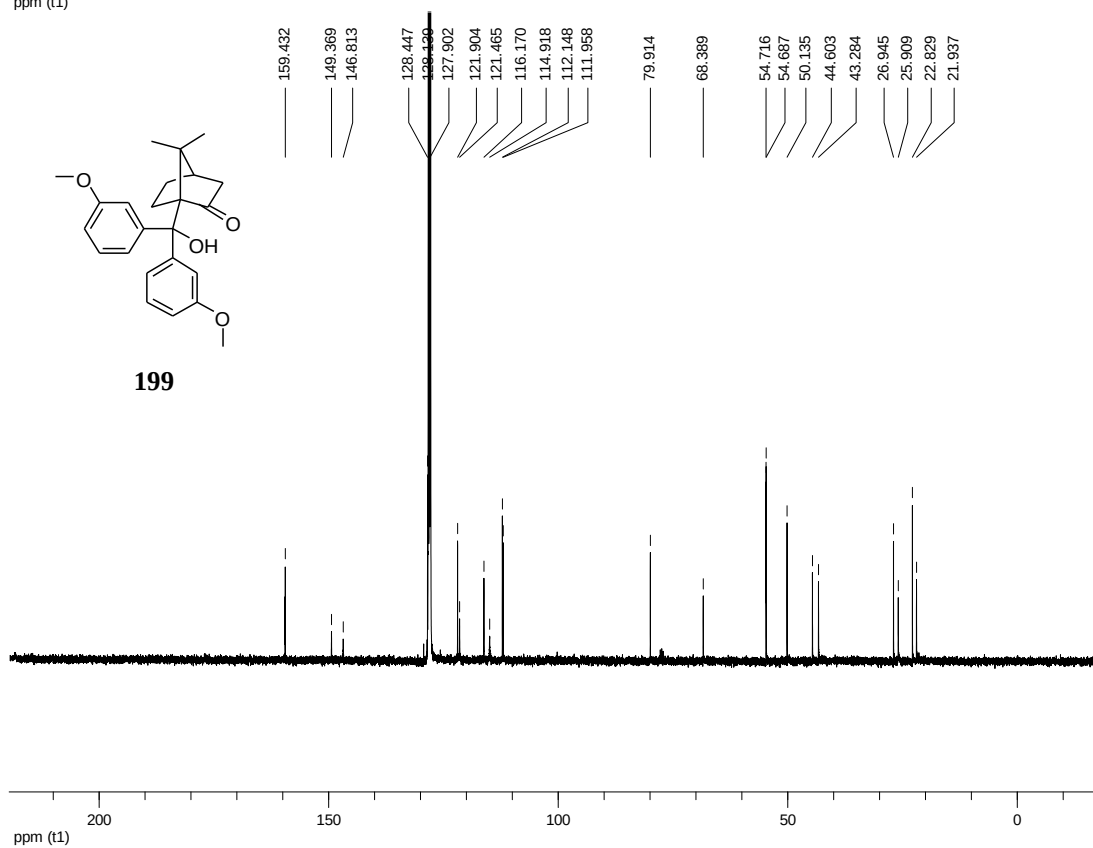
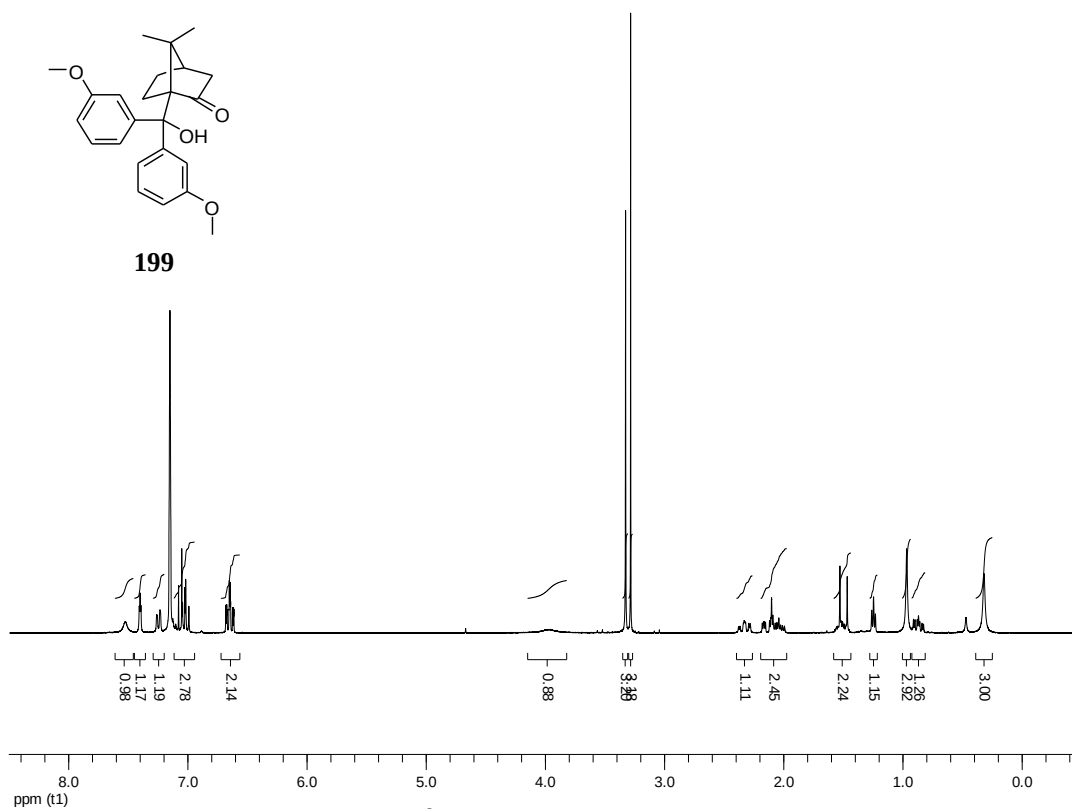


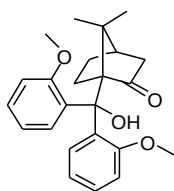




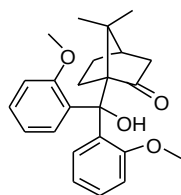
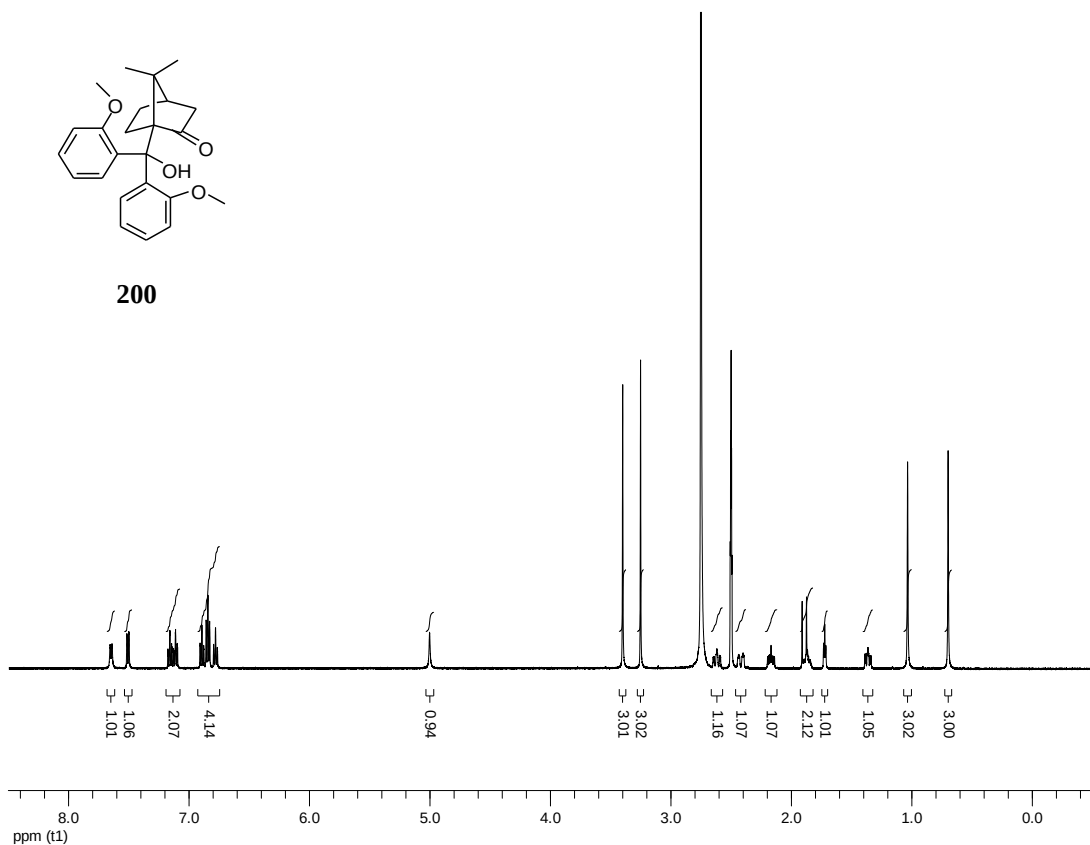




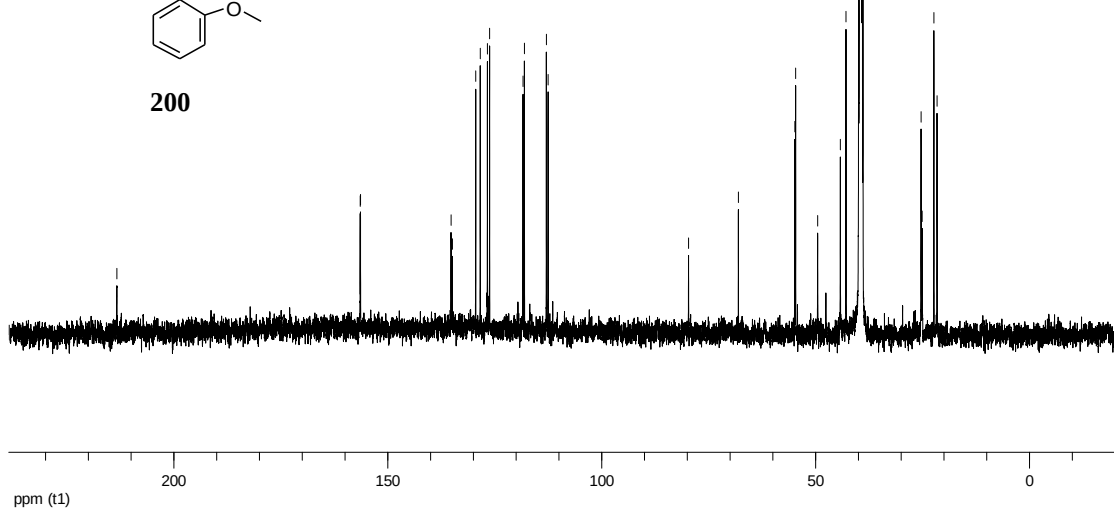


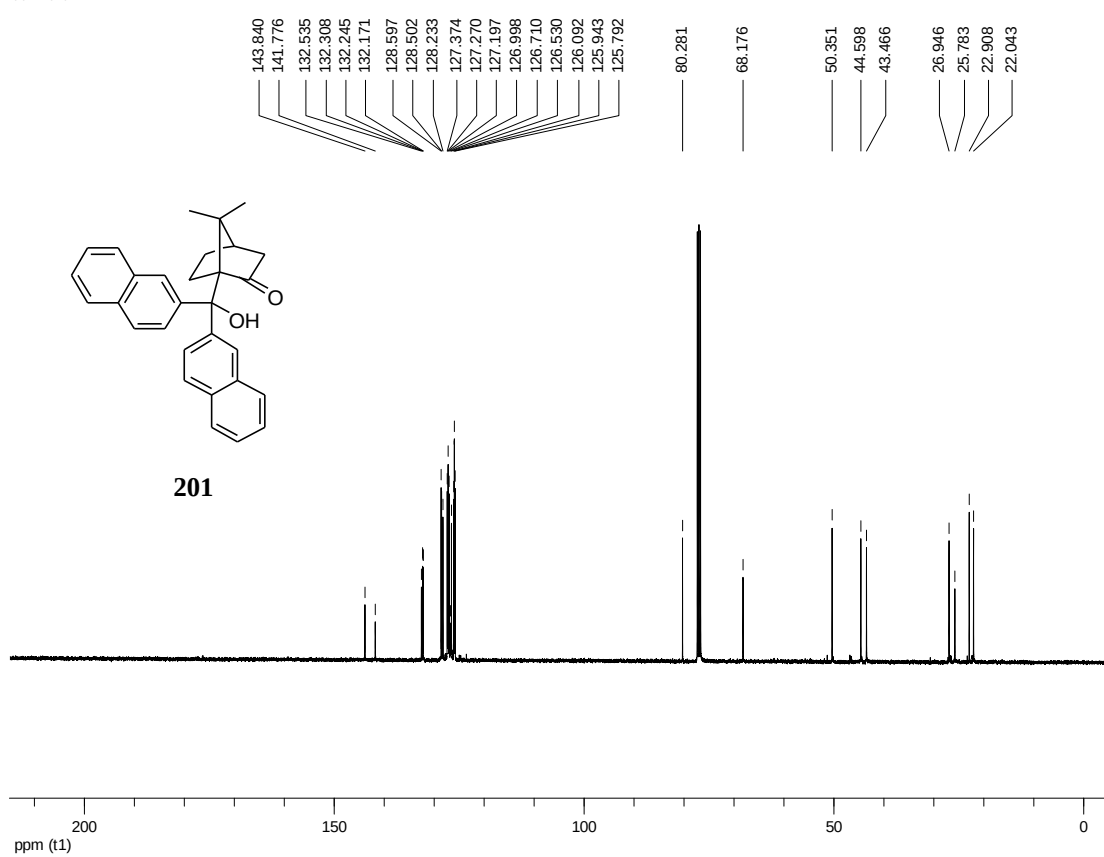
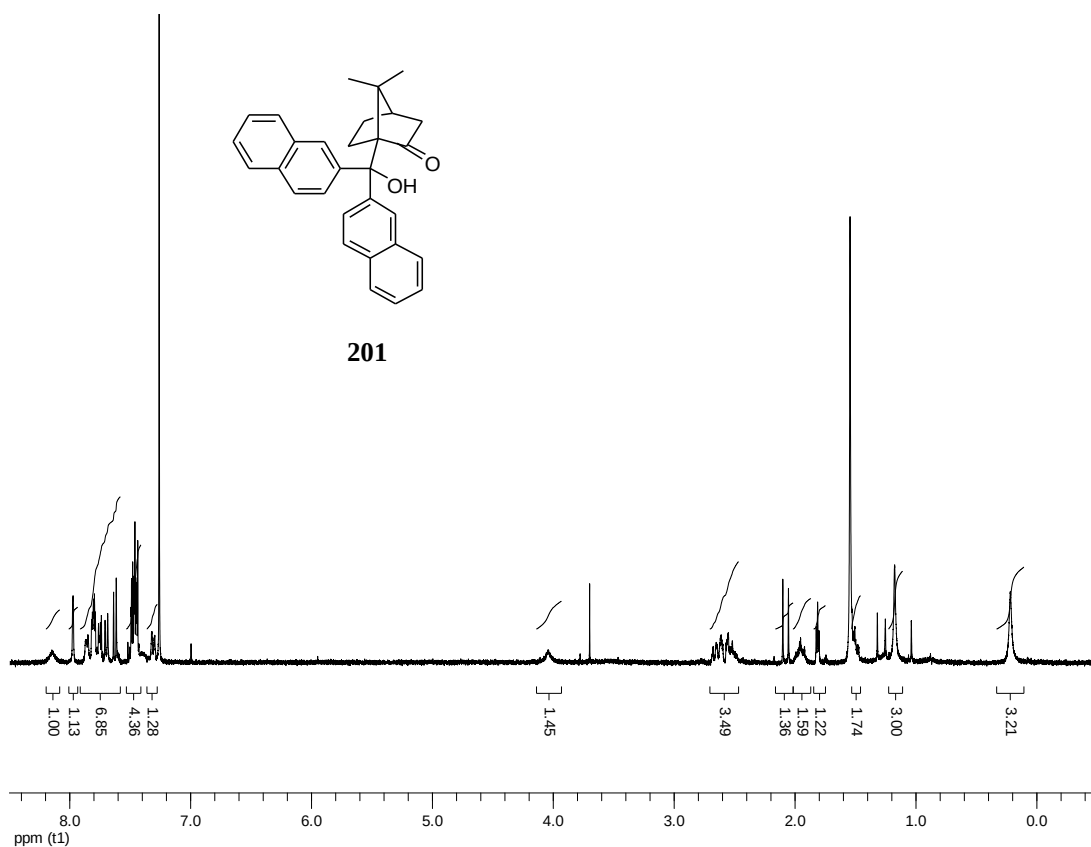


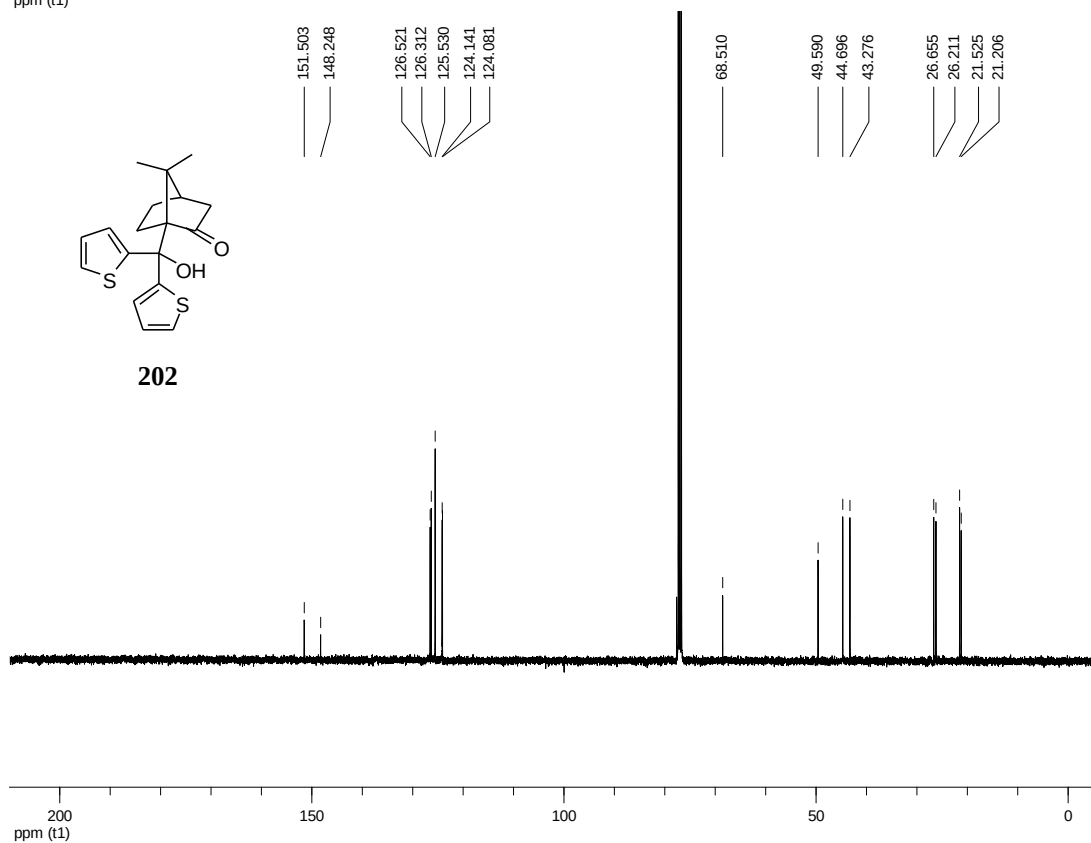
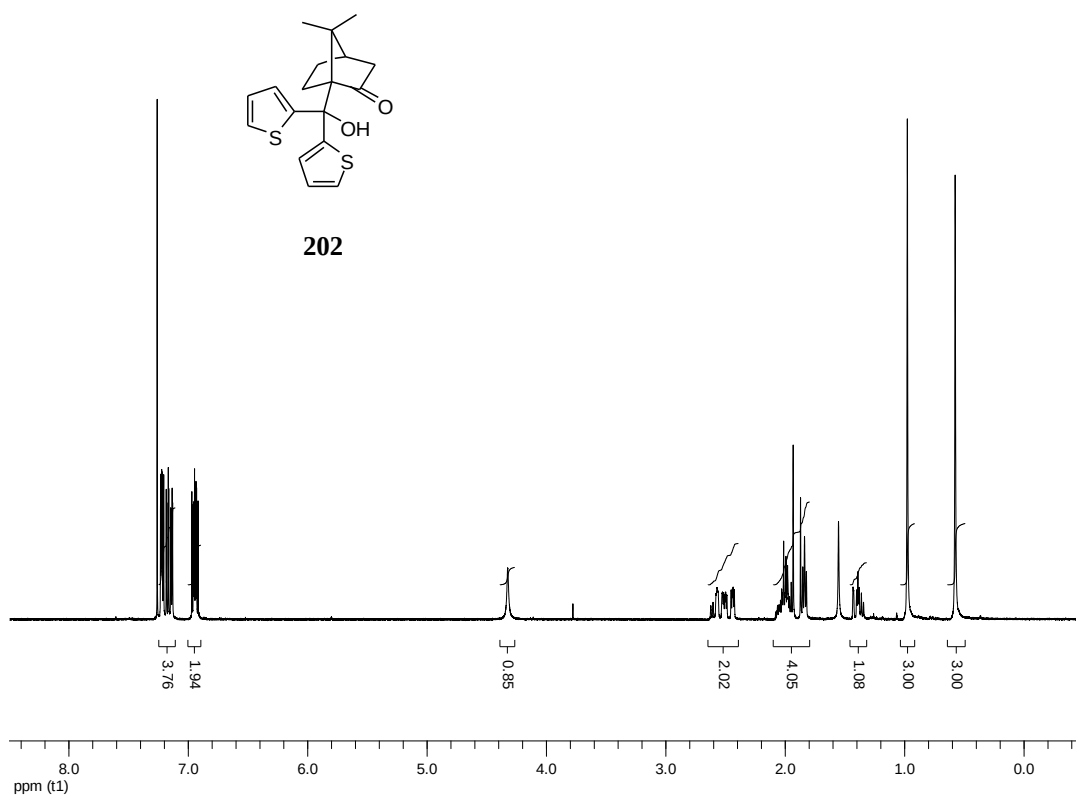
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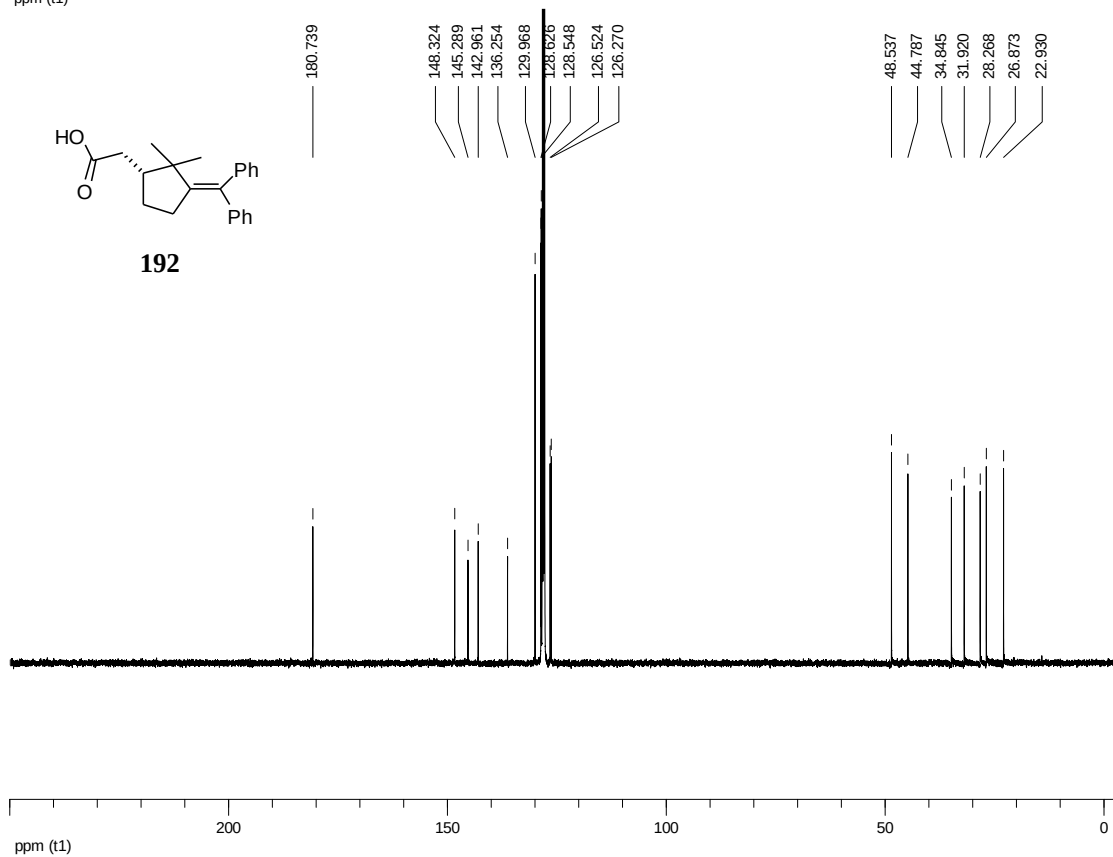
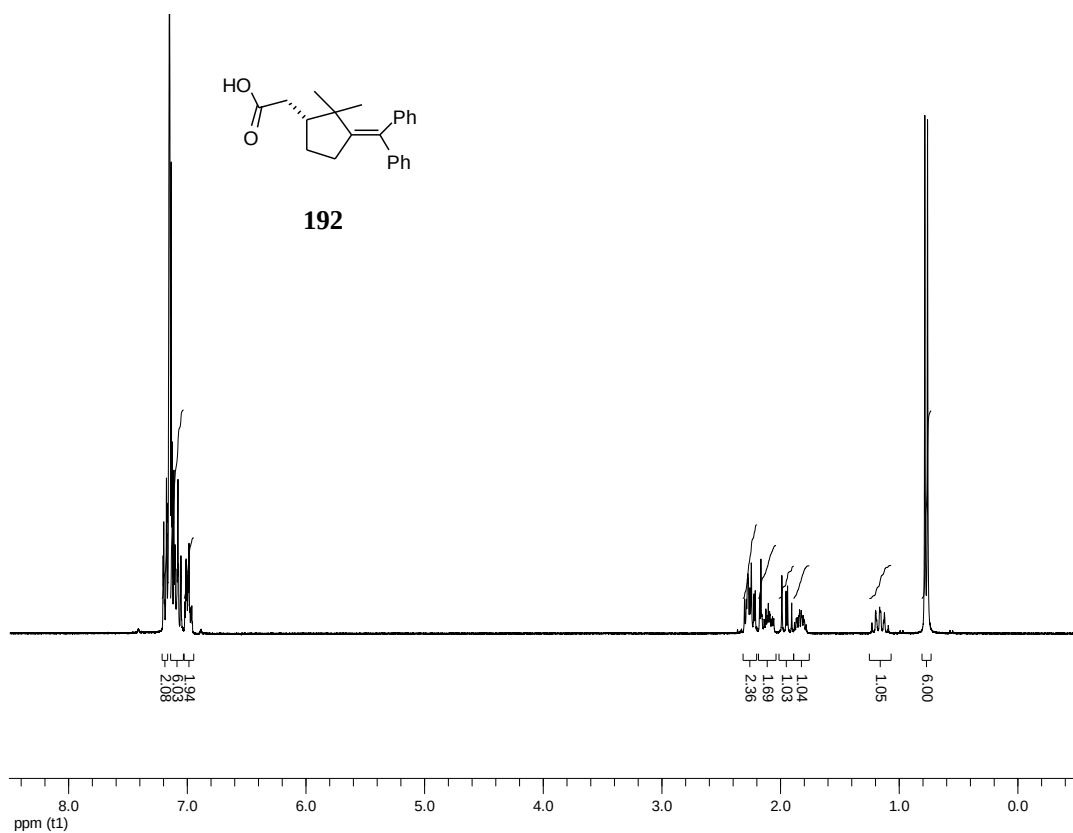


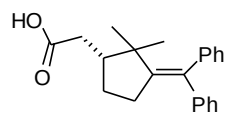
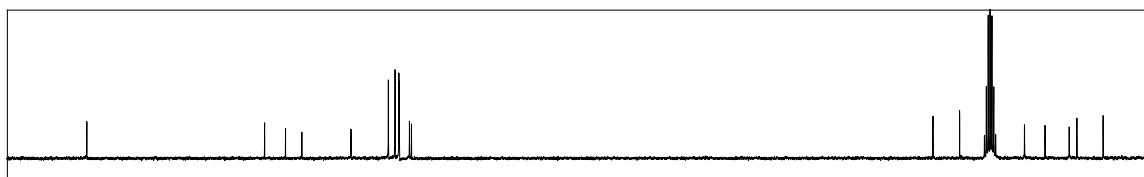
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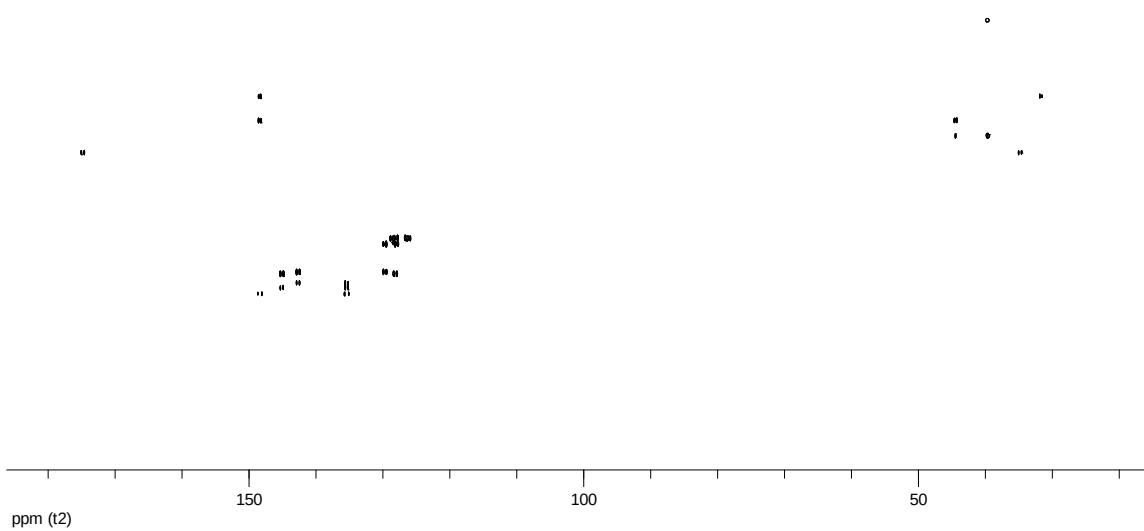


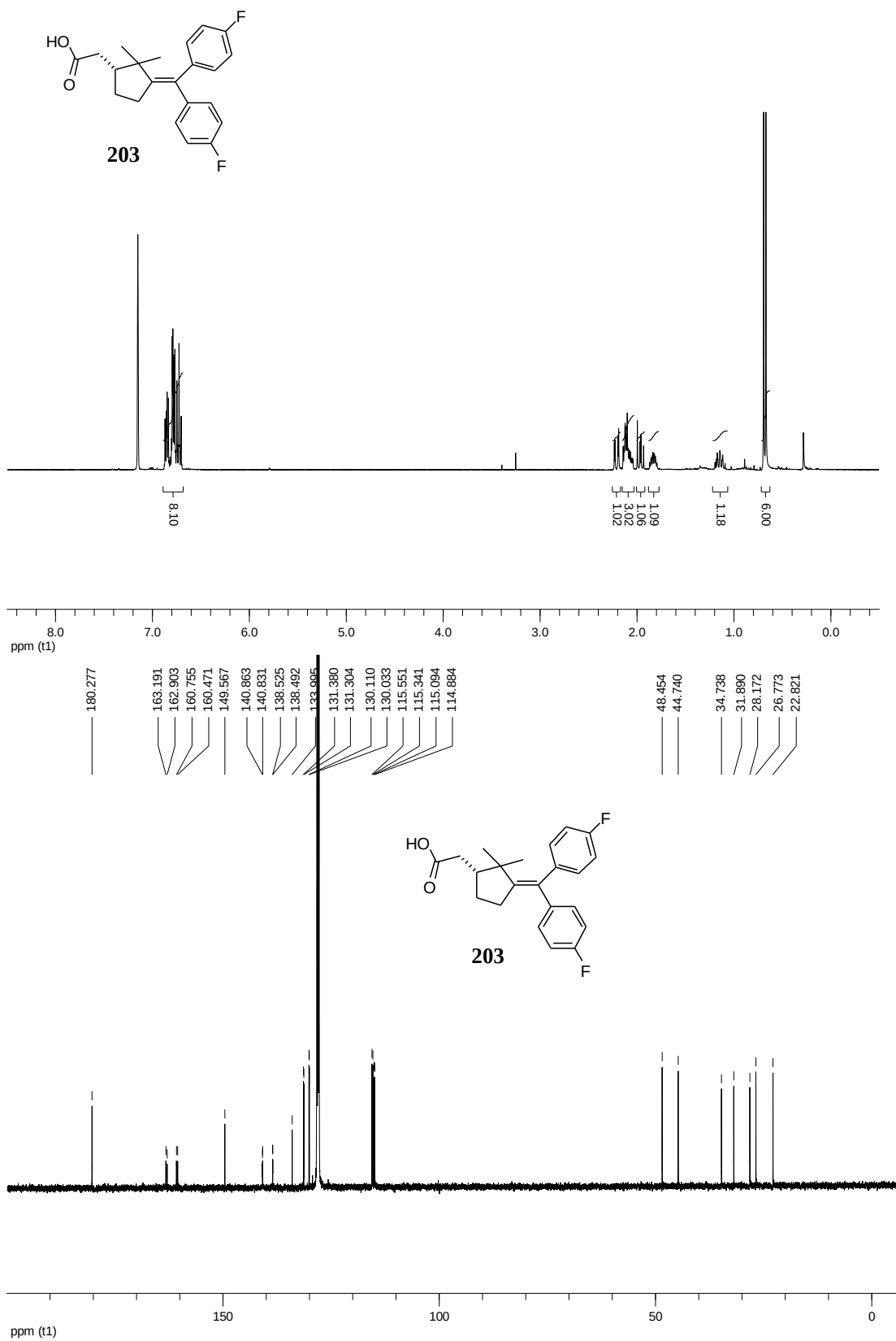


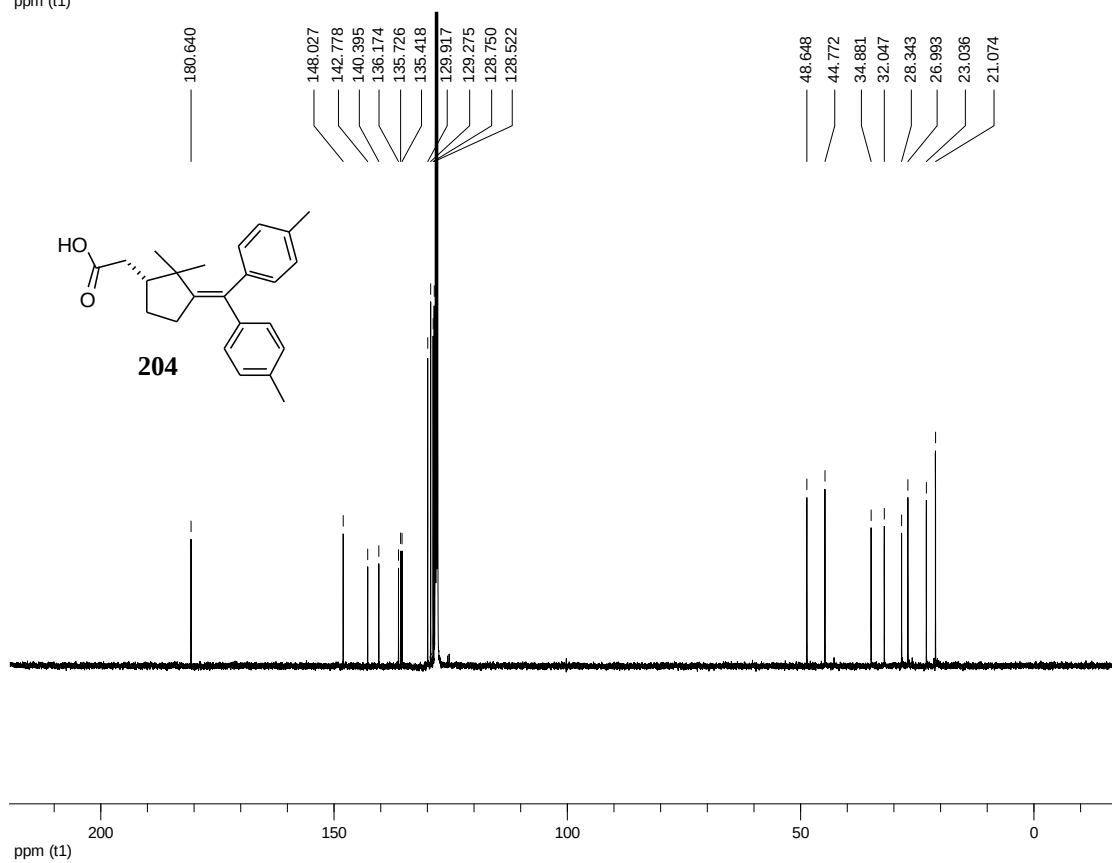
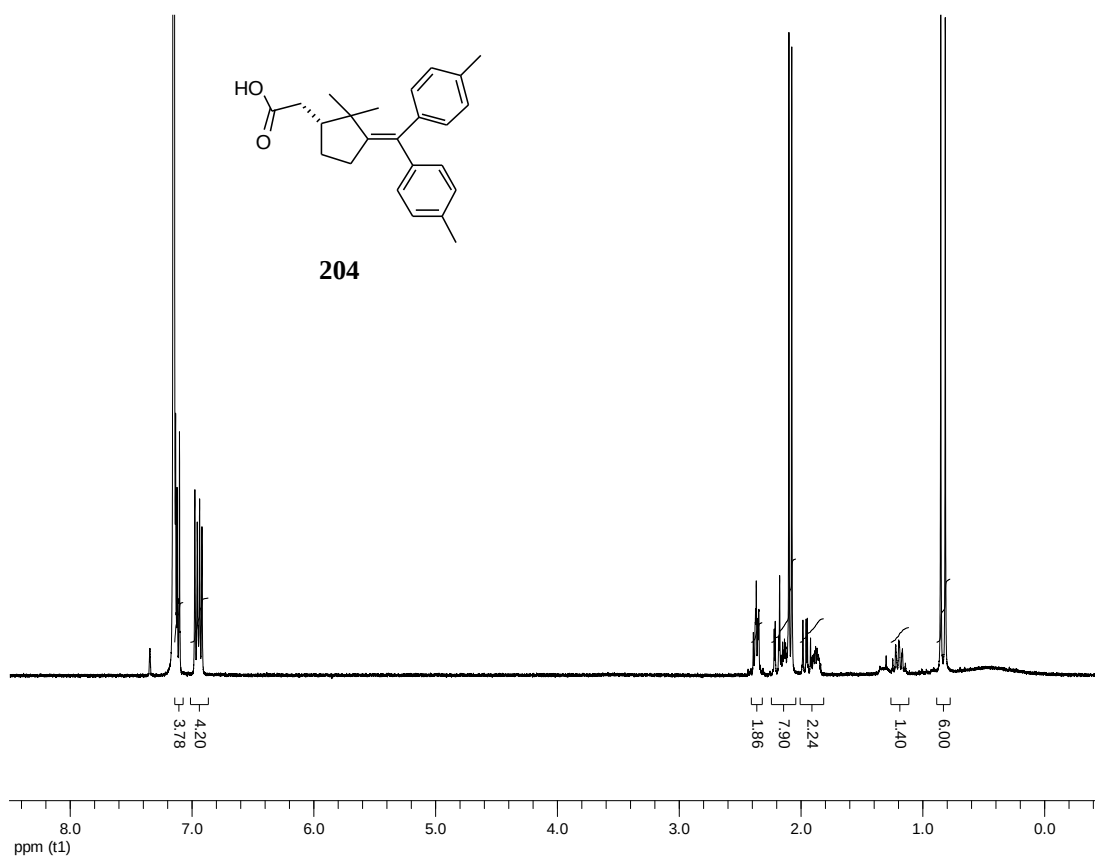


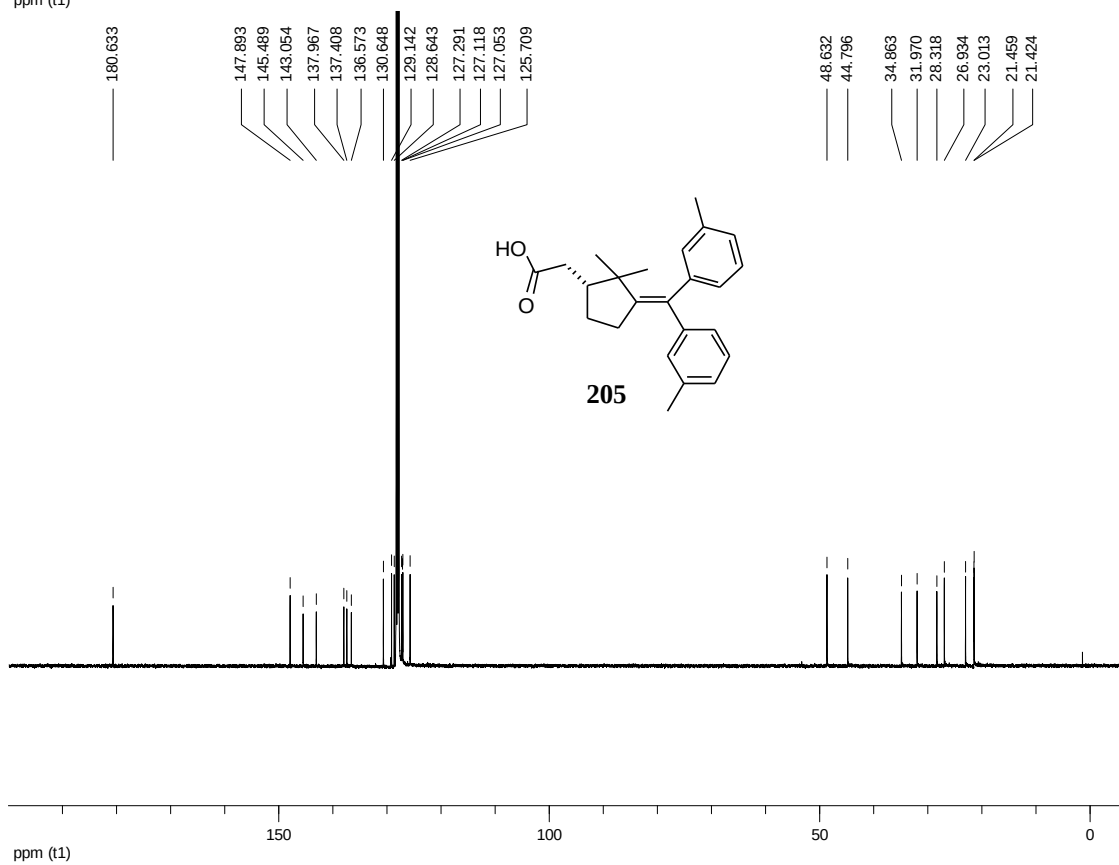
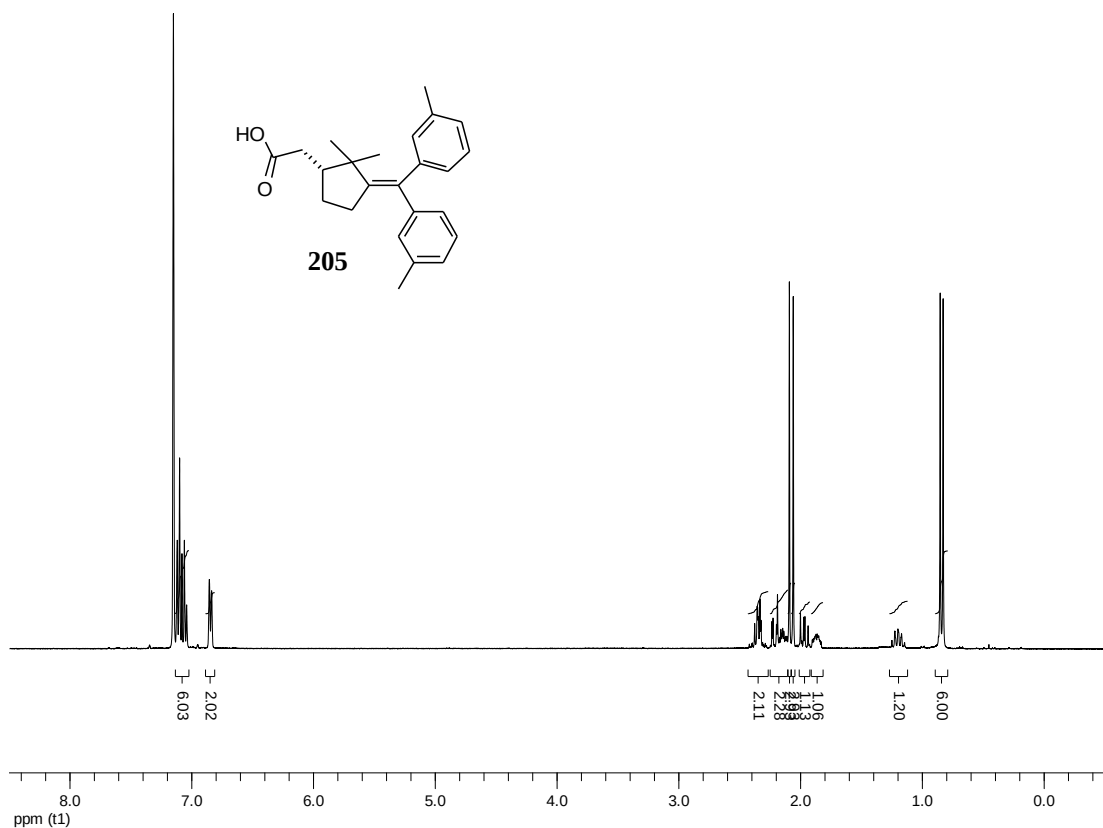


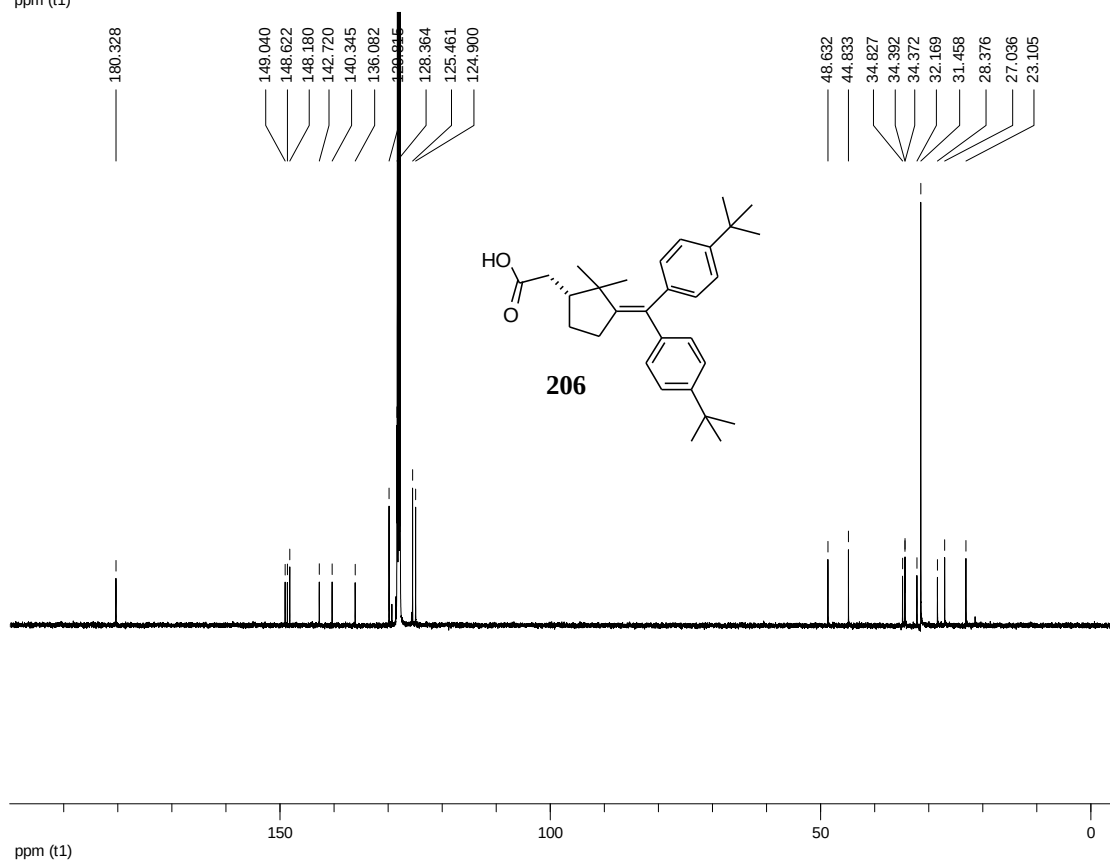
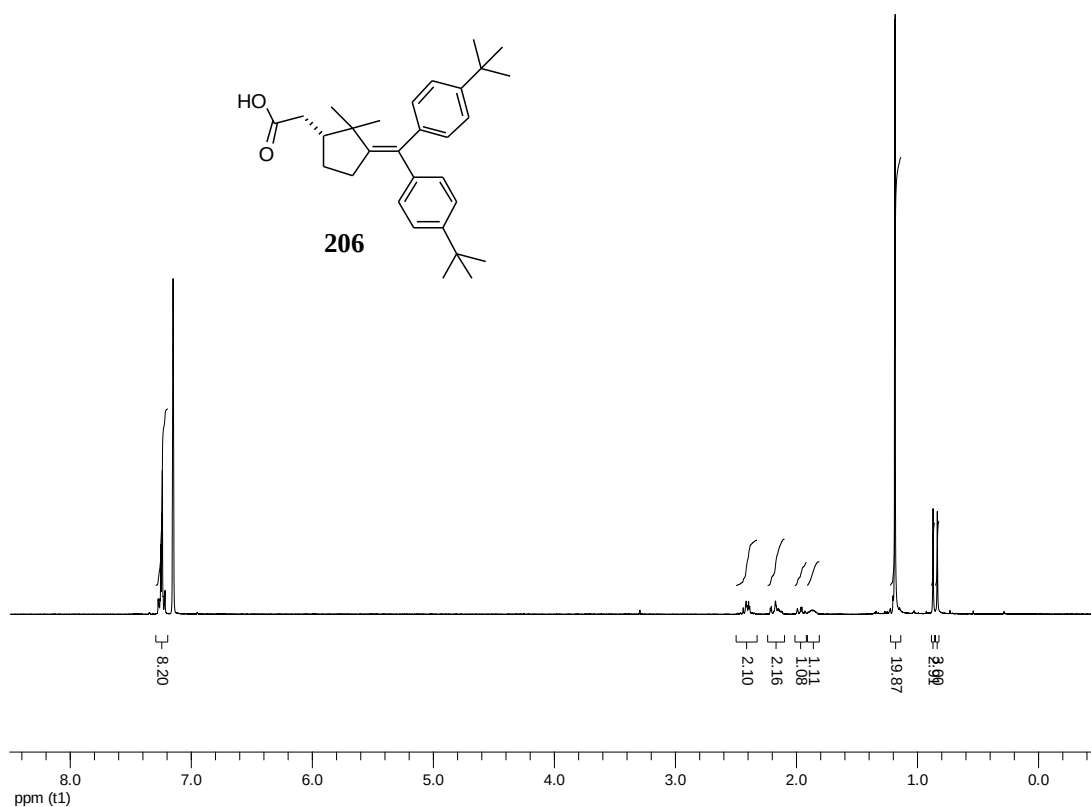
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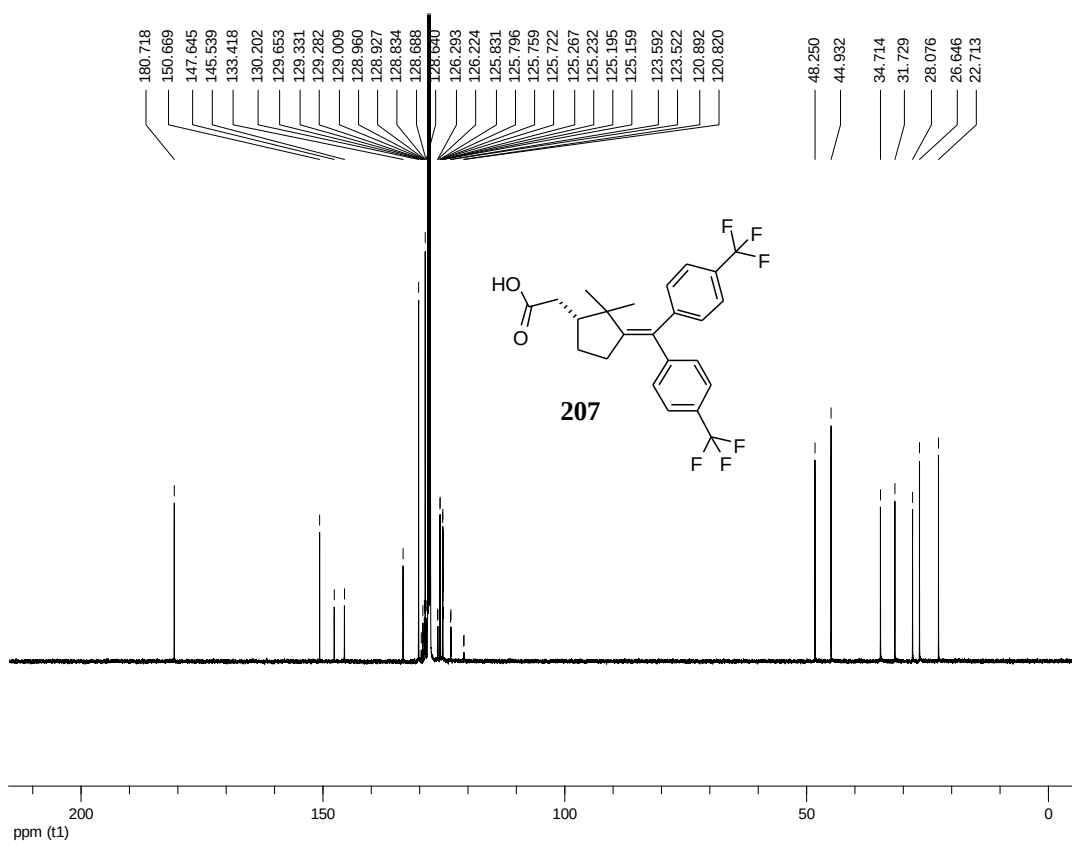
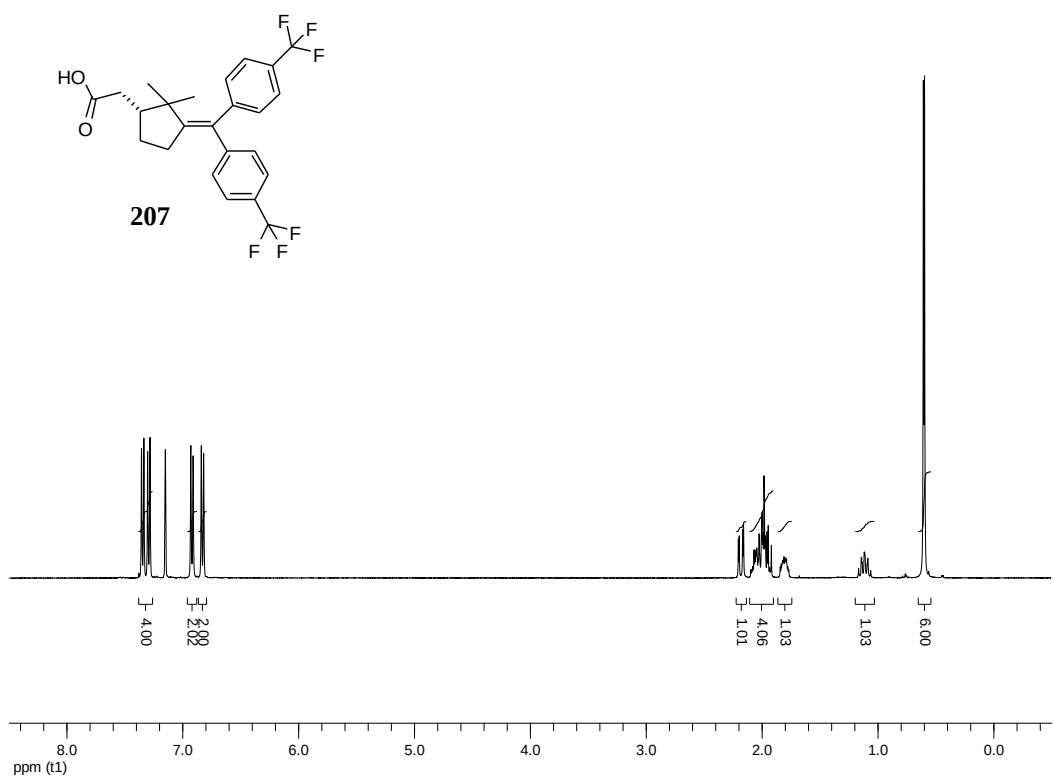


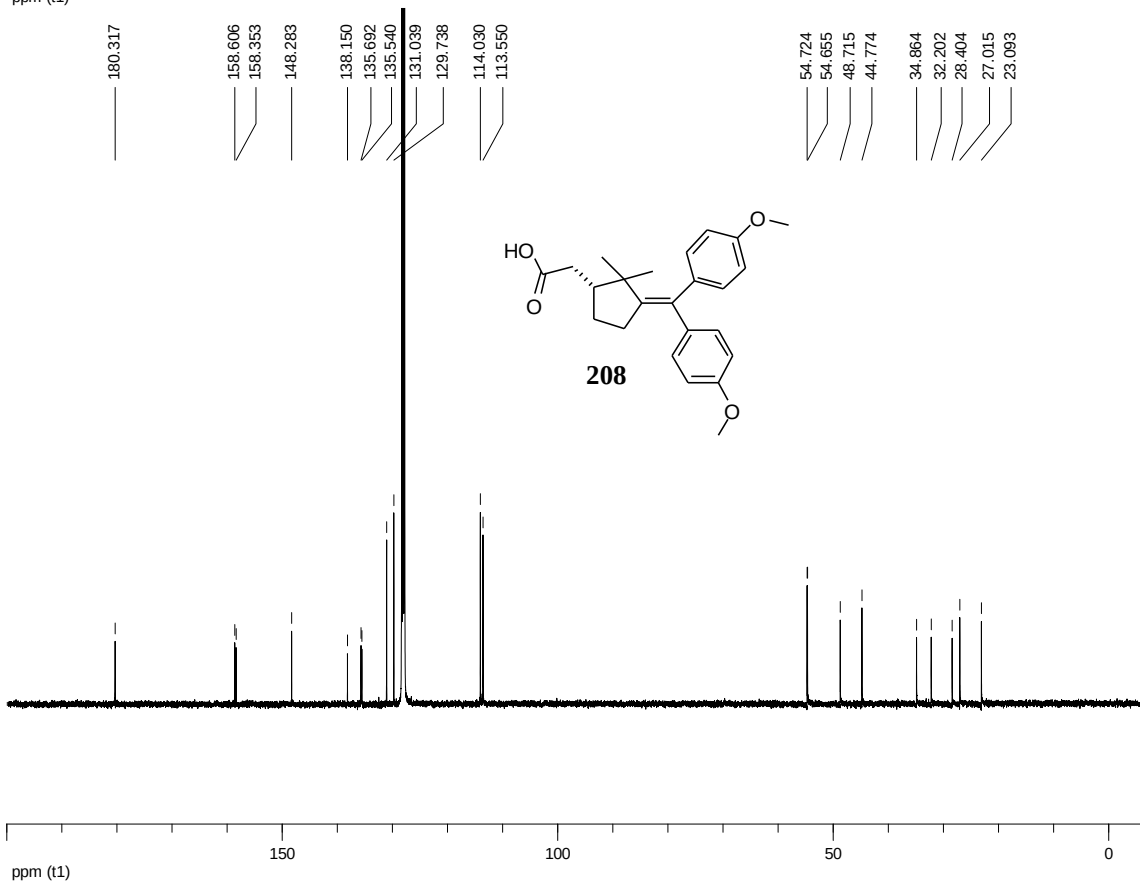
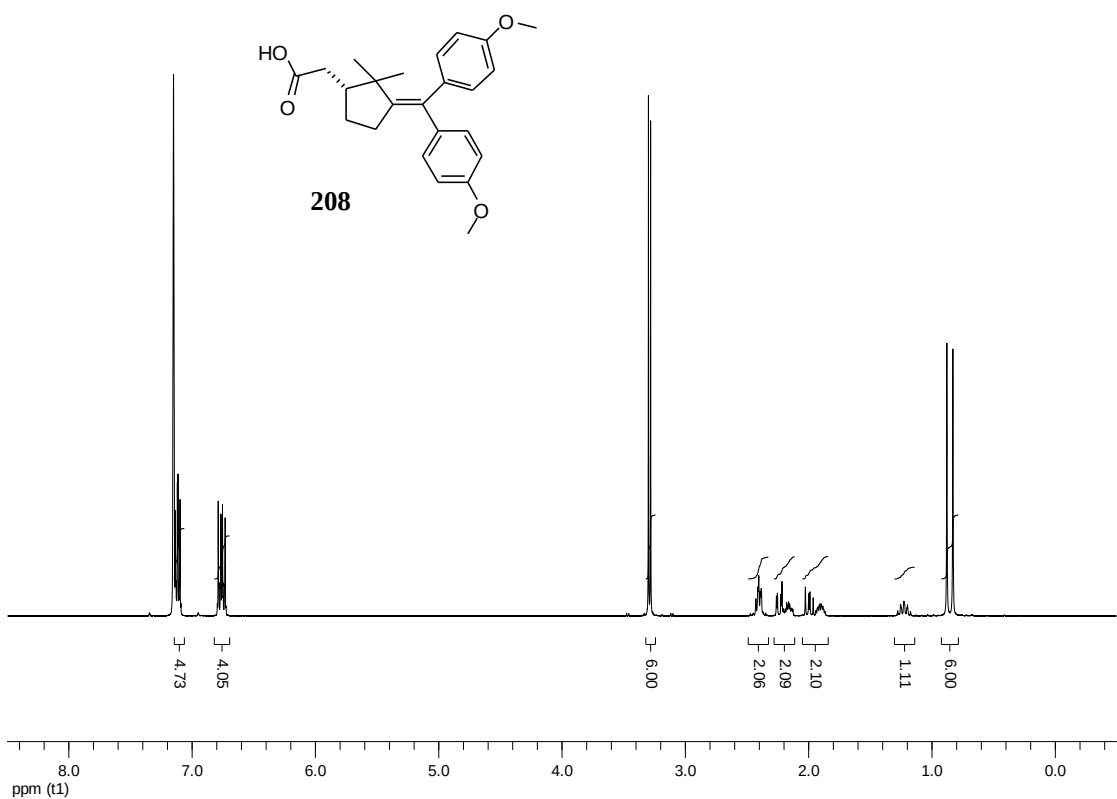


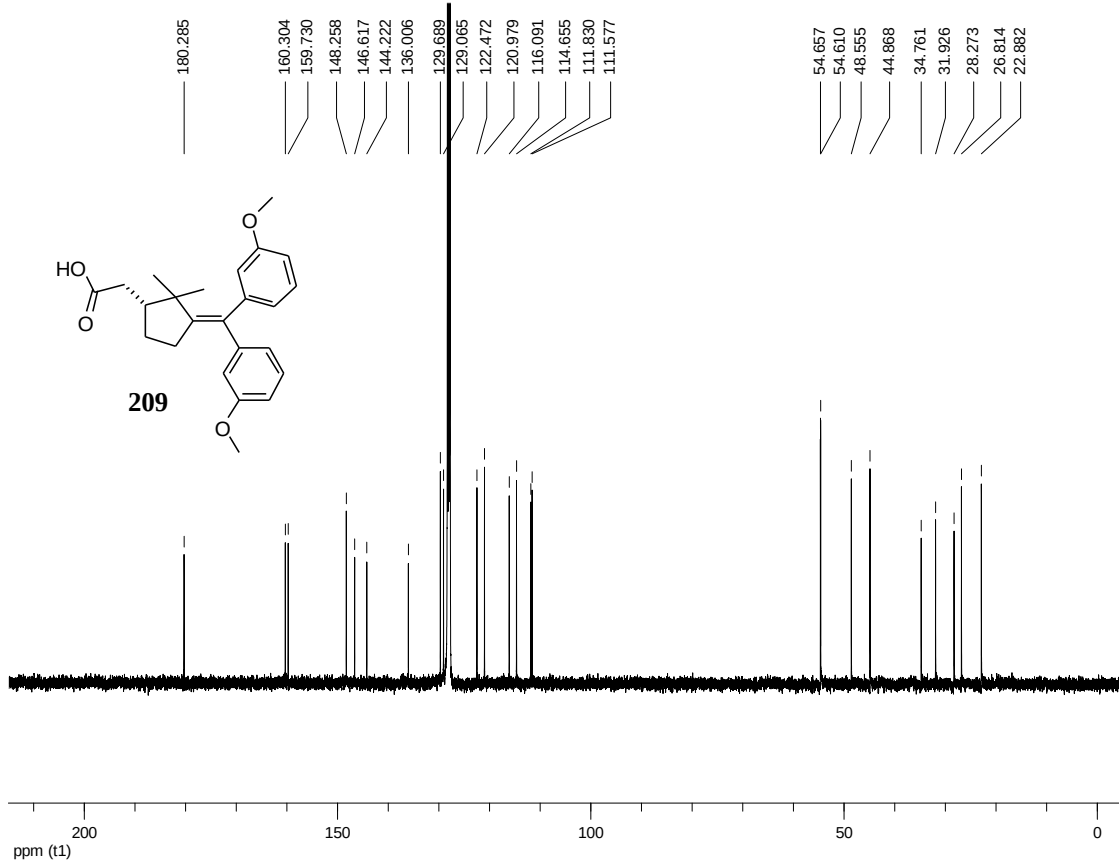
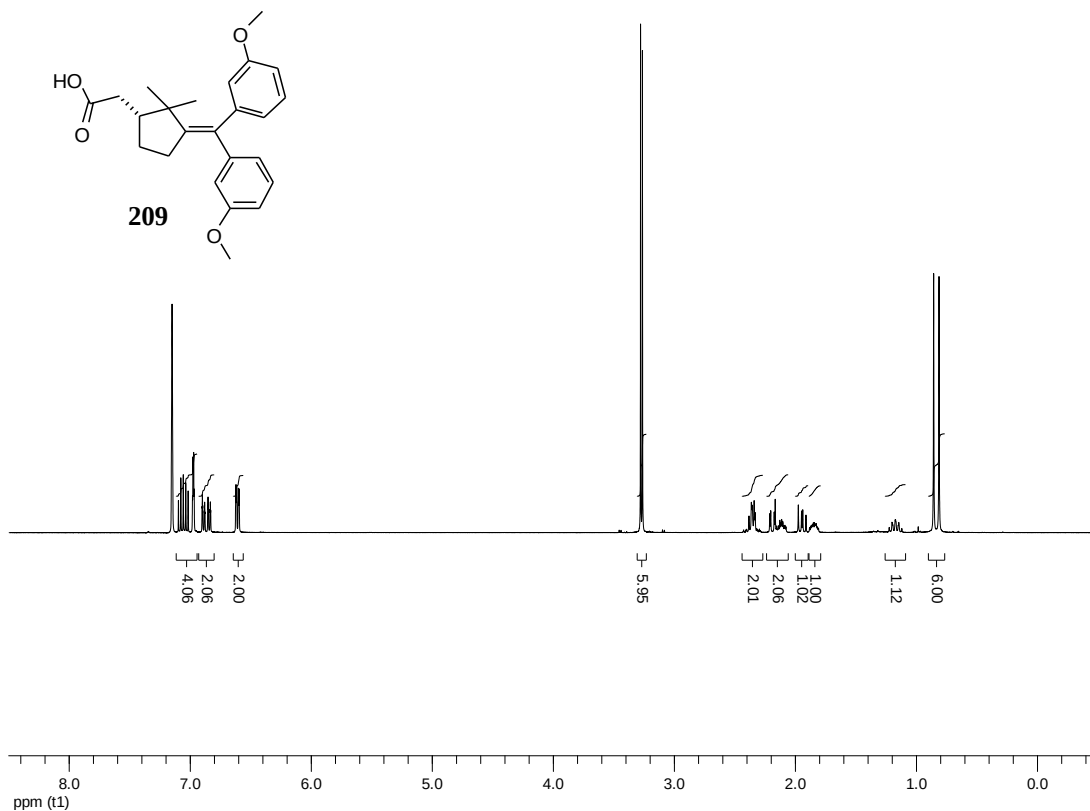


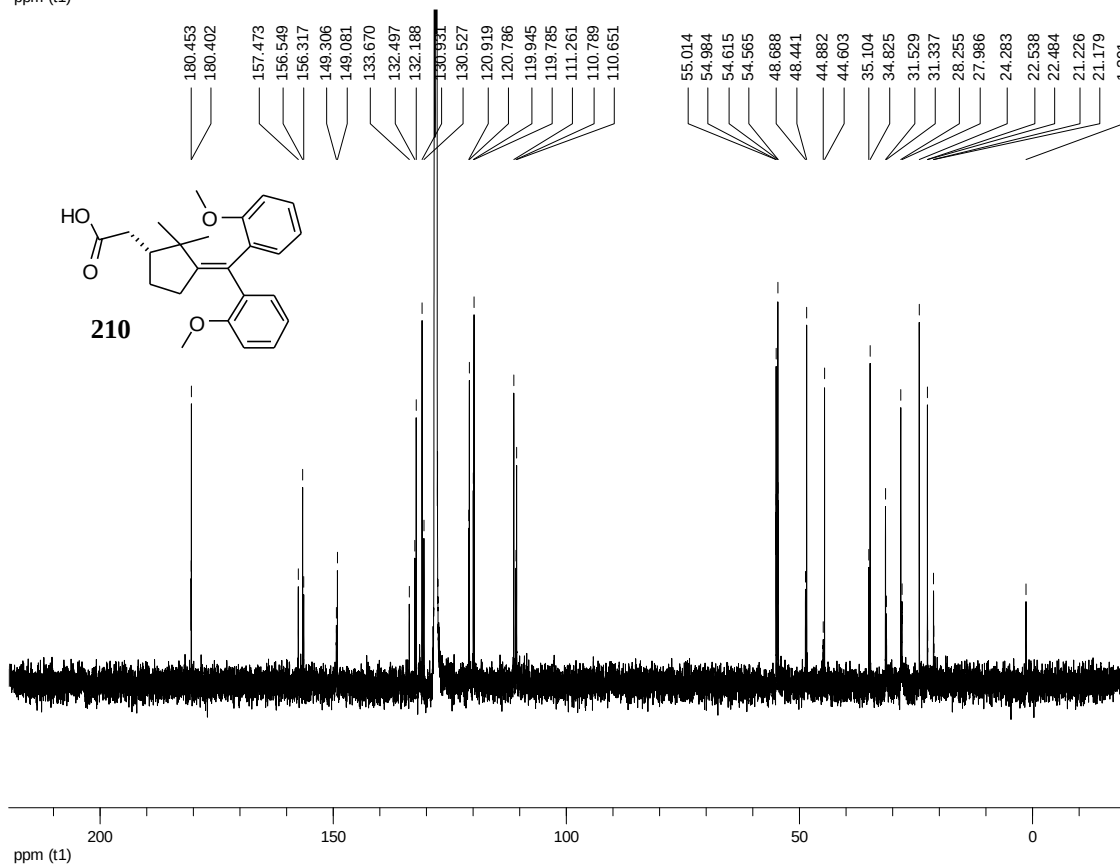
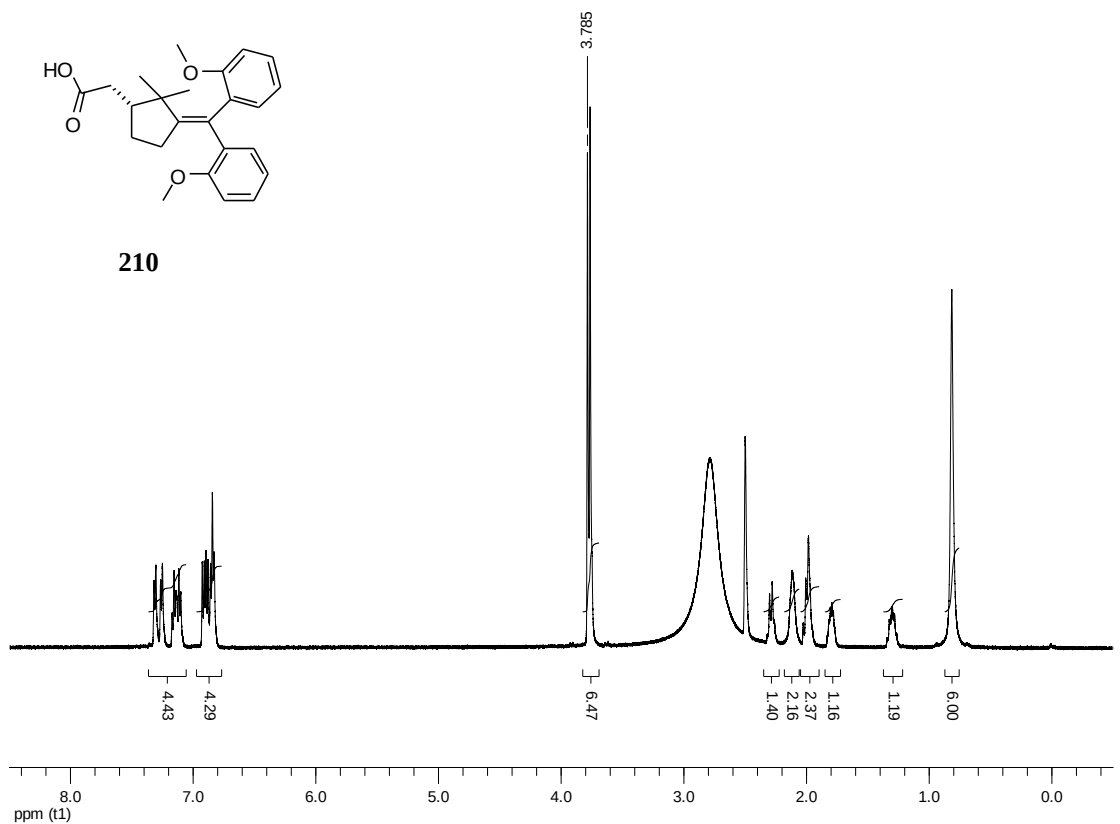


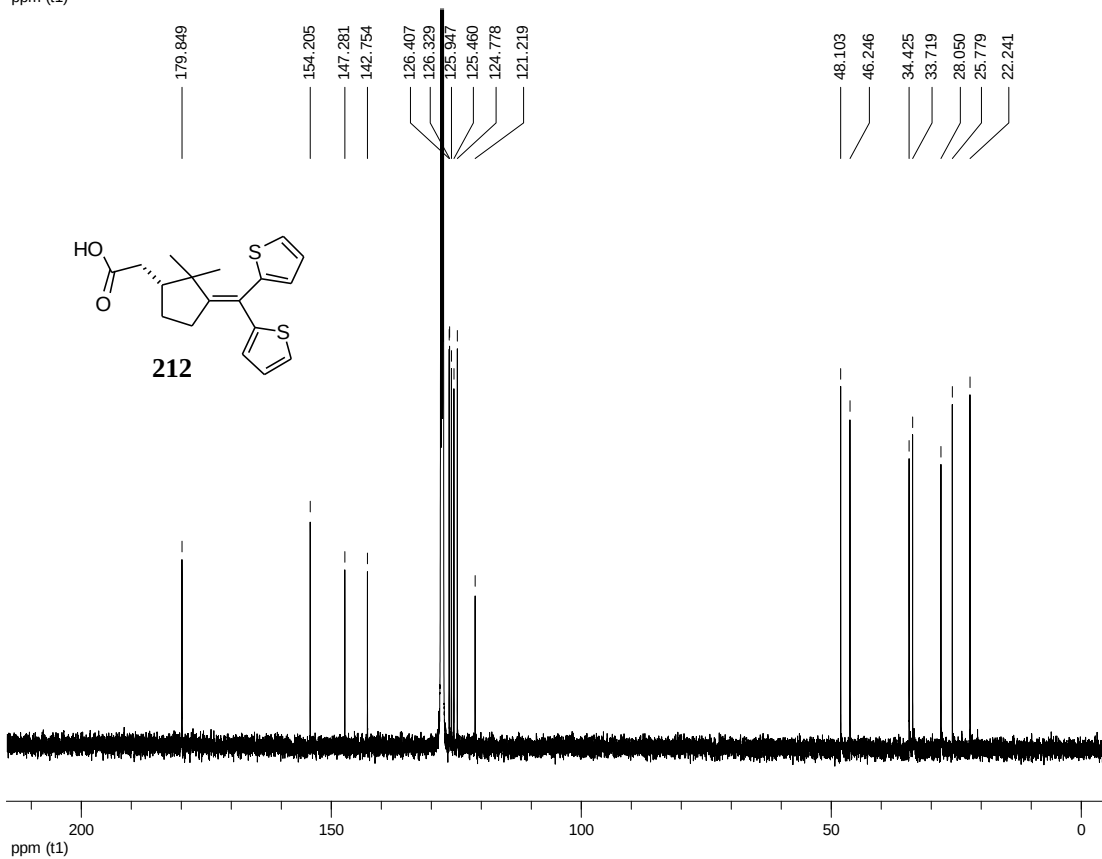
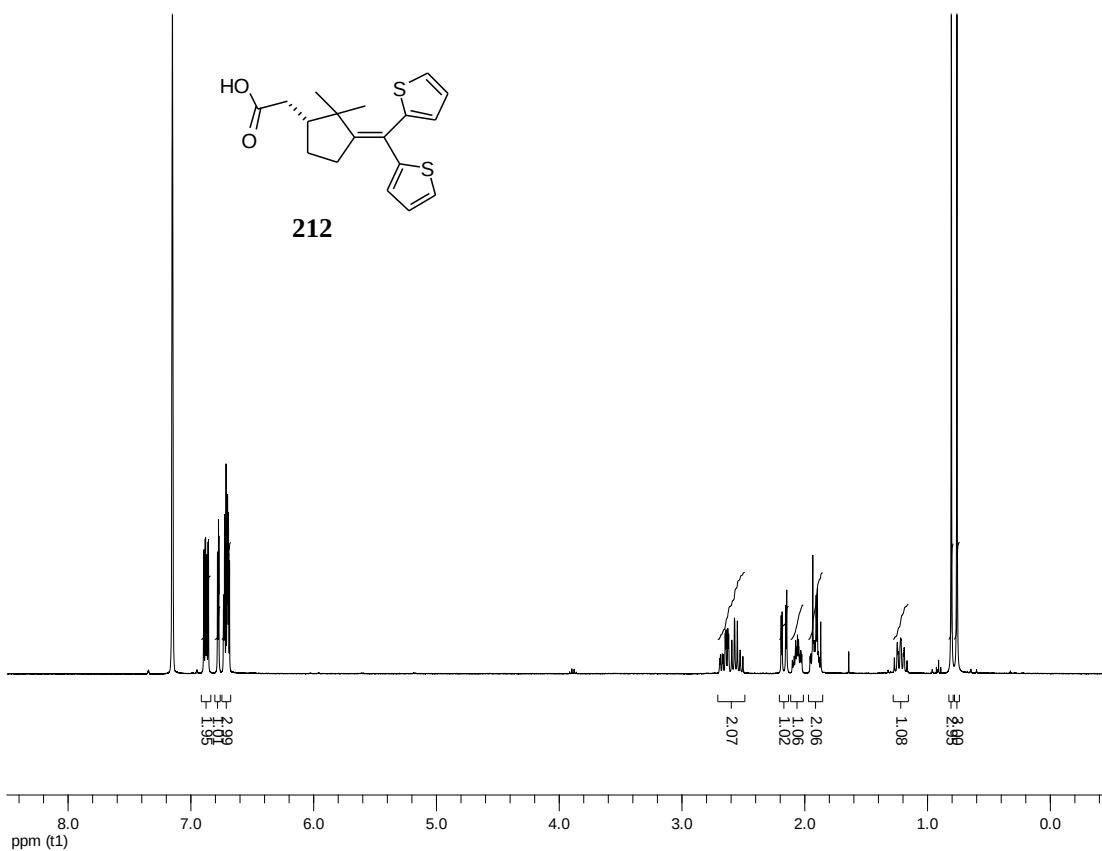


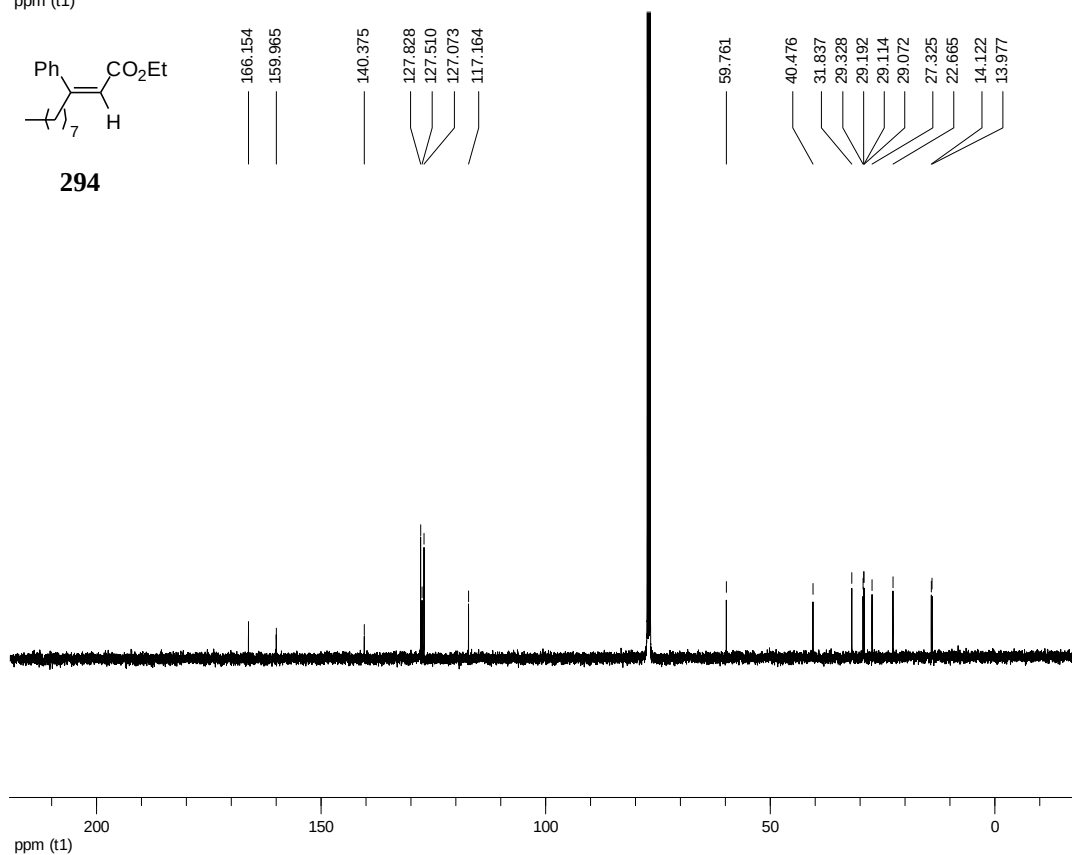
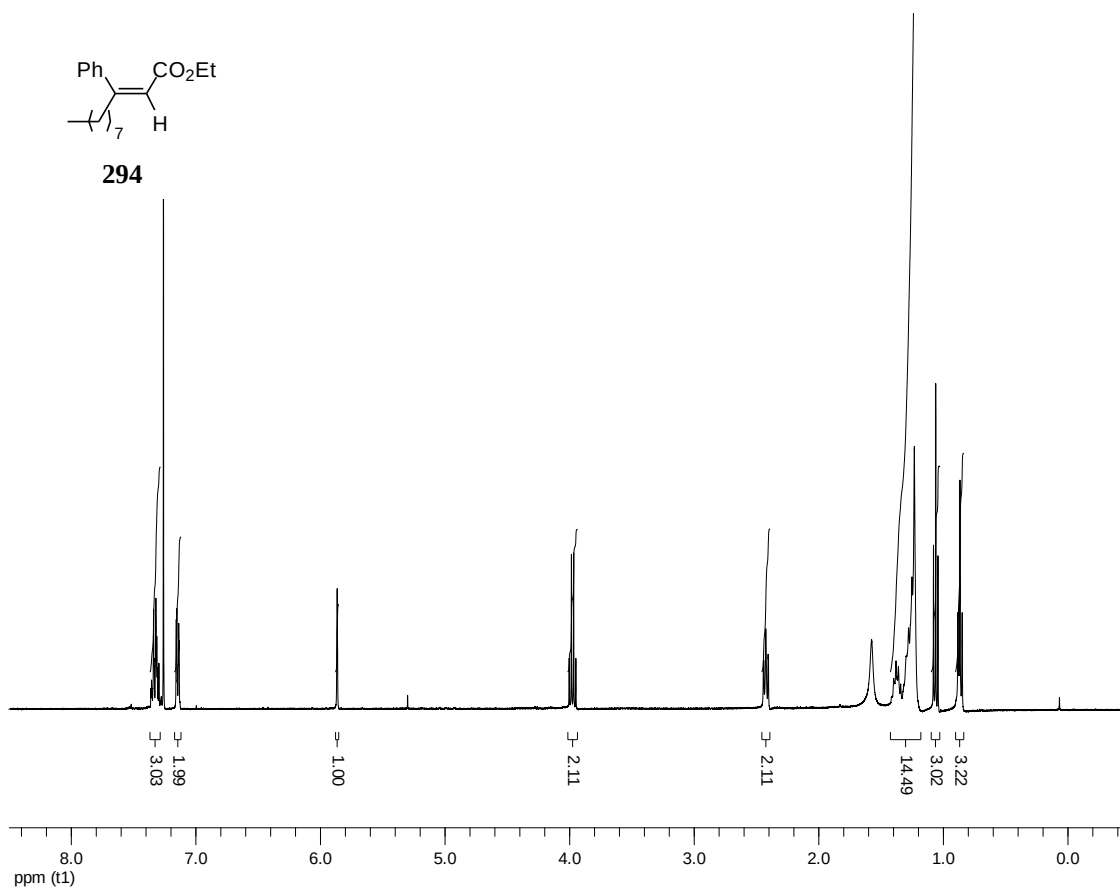


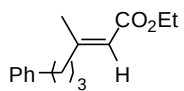




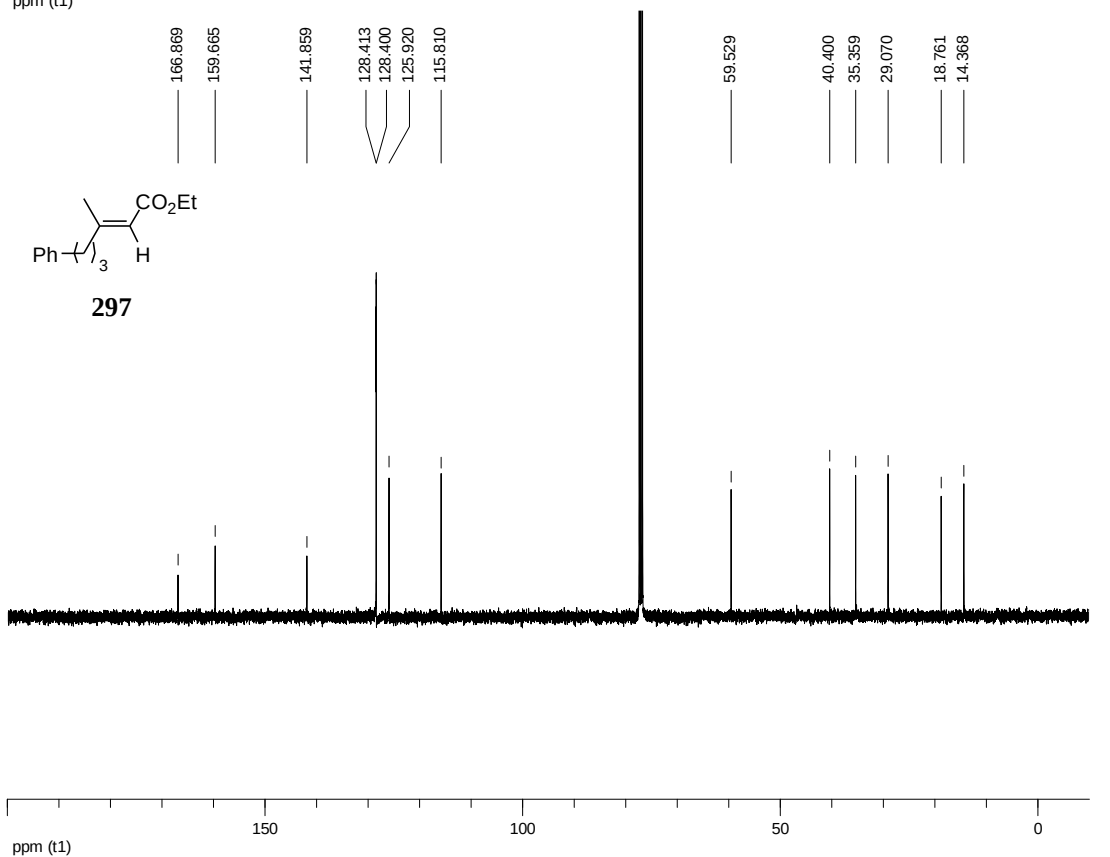
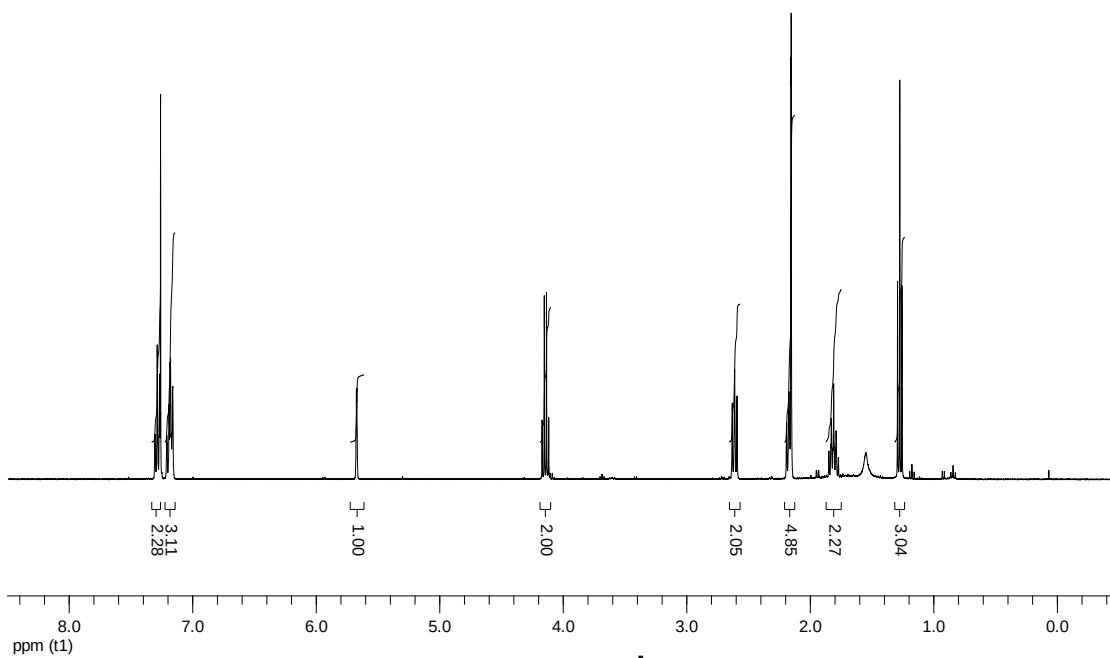


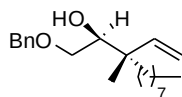




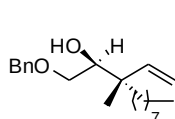
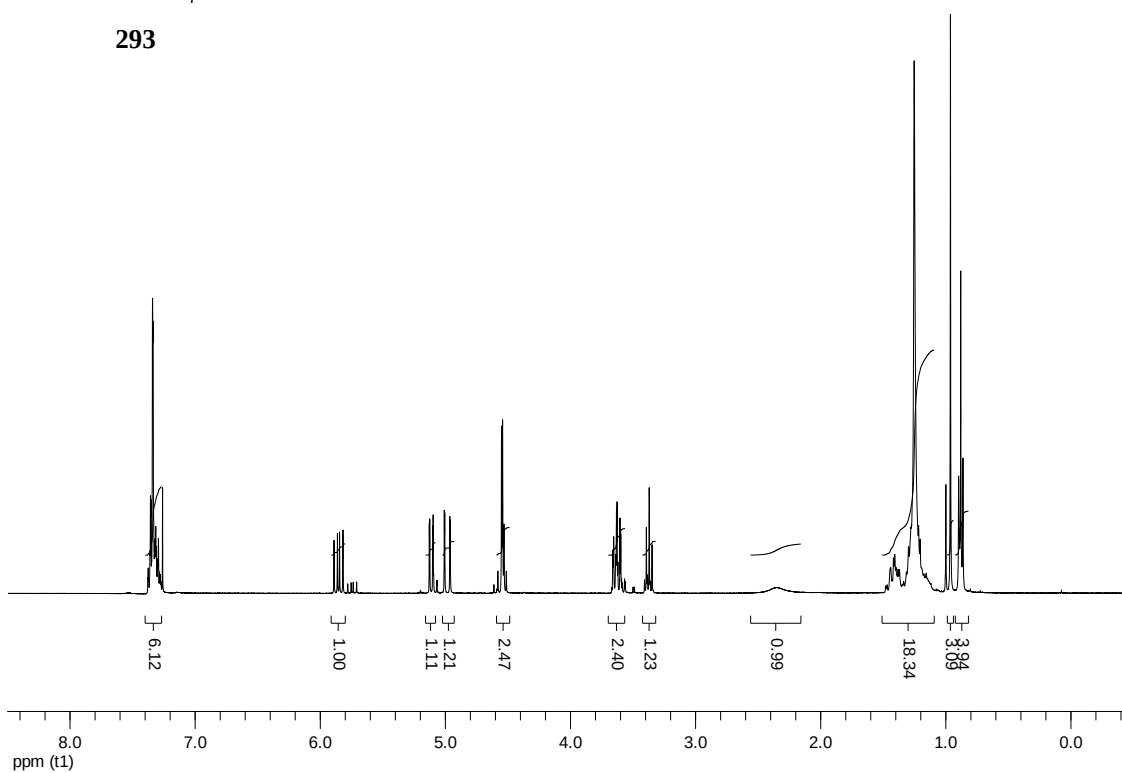


297

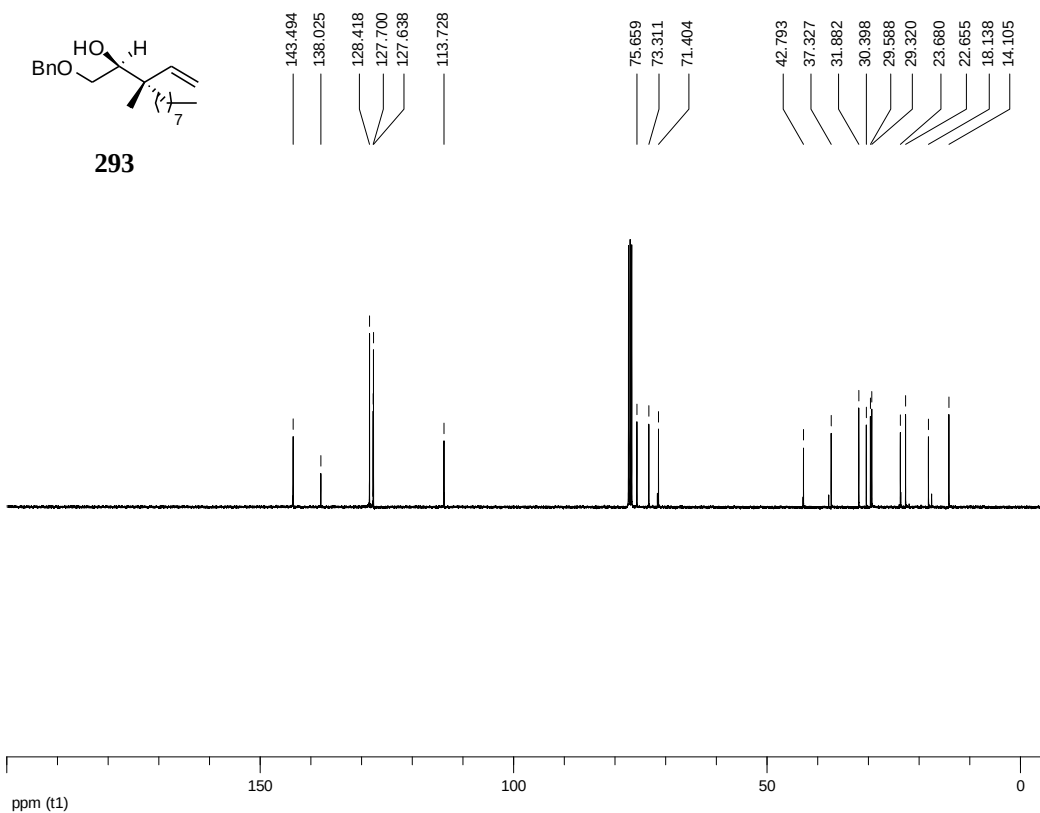


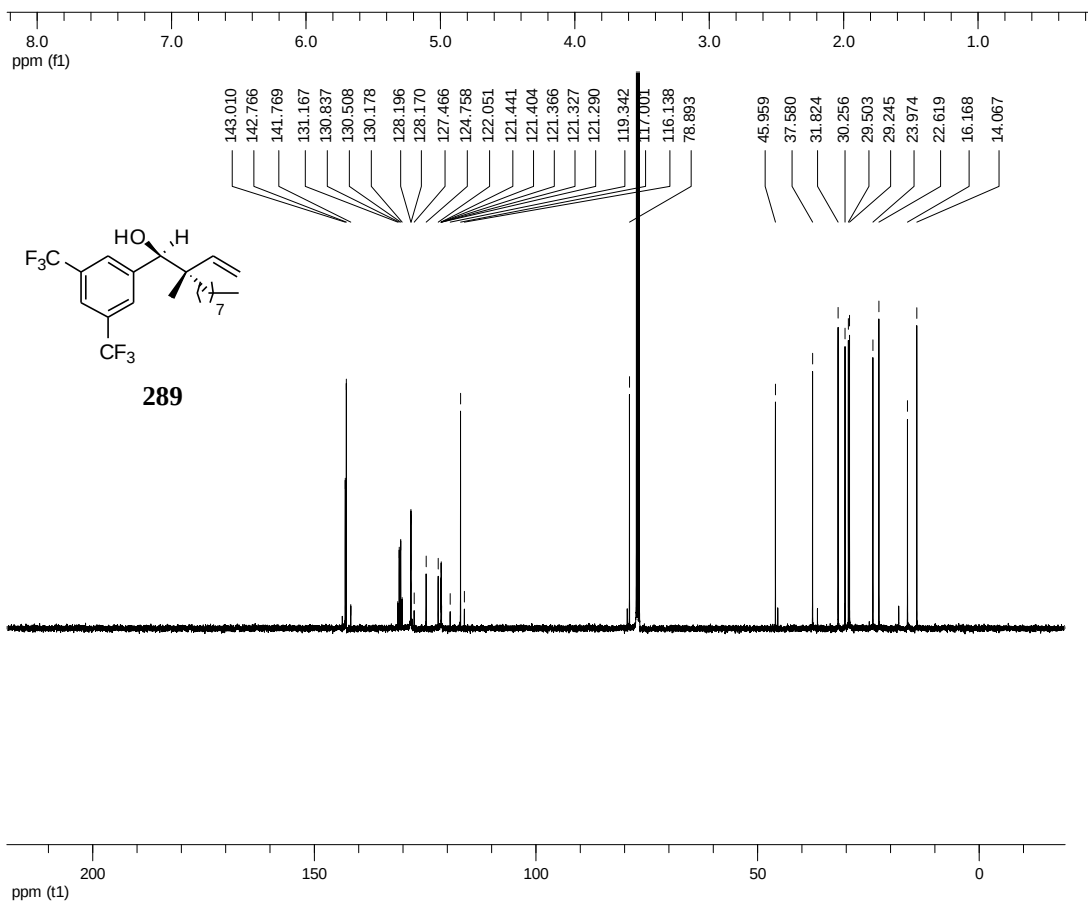
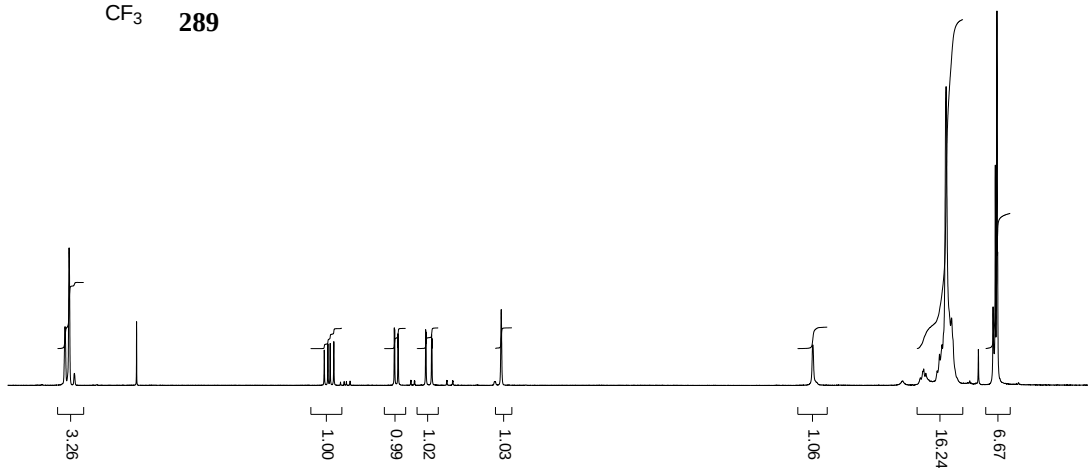
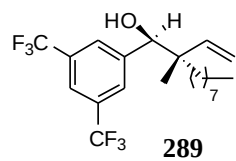


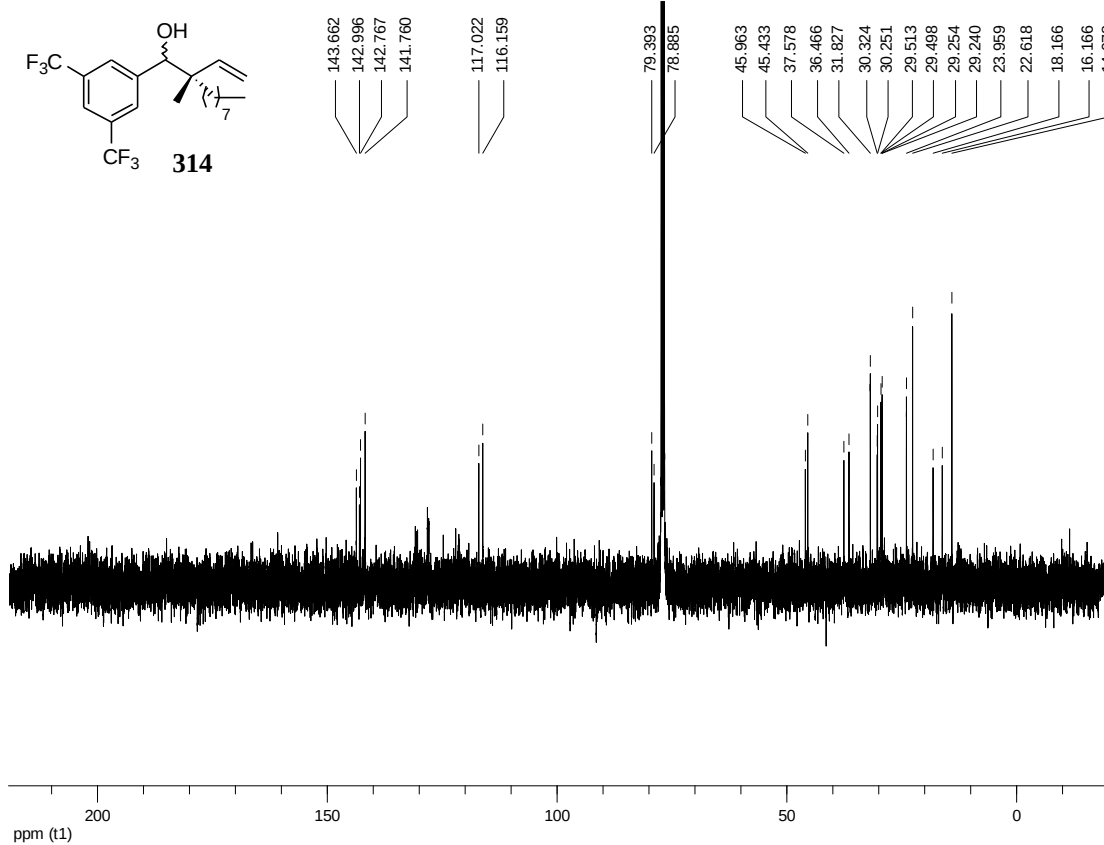
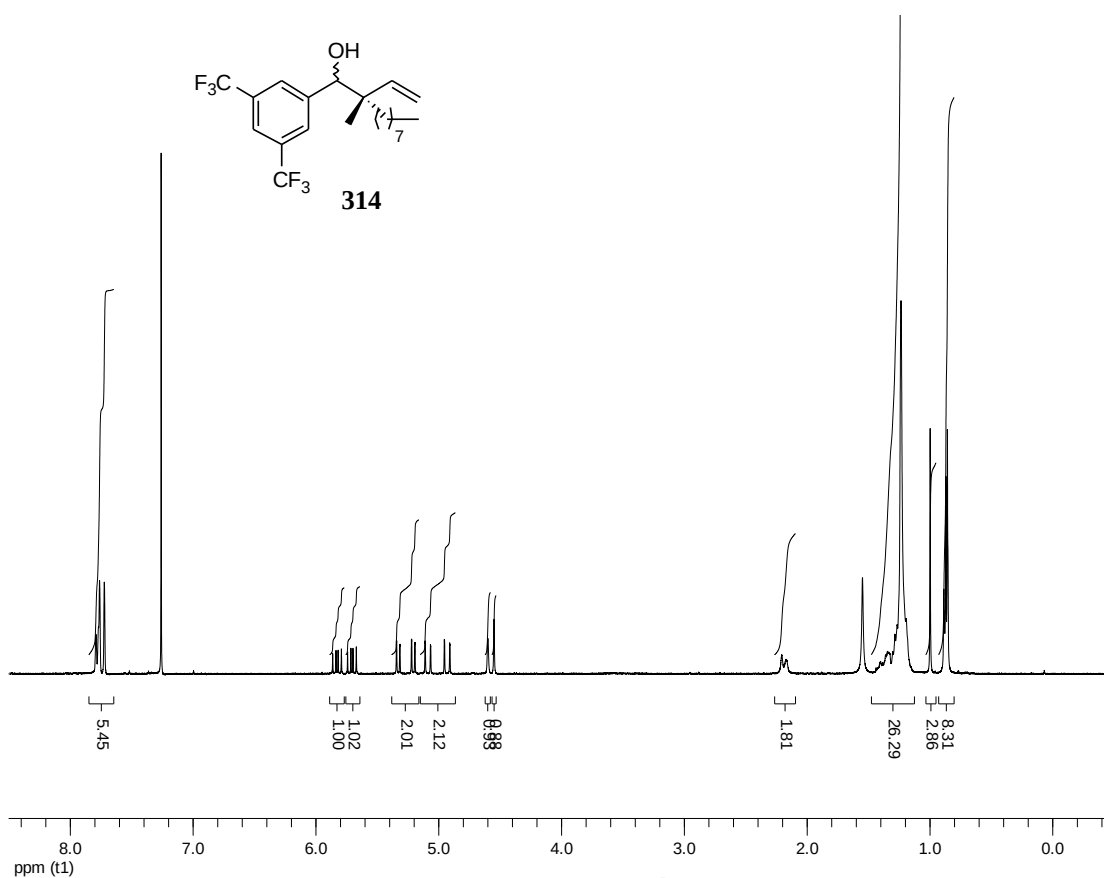
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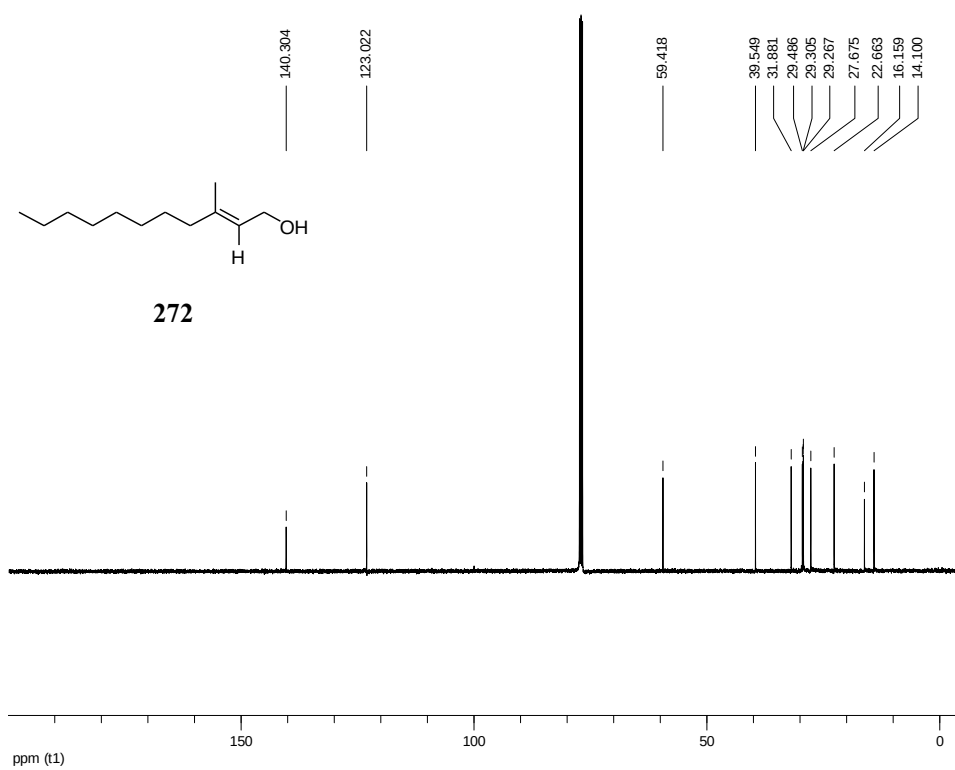
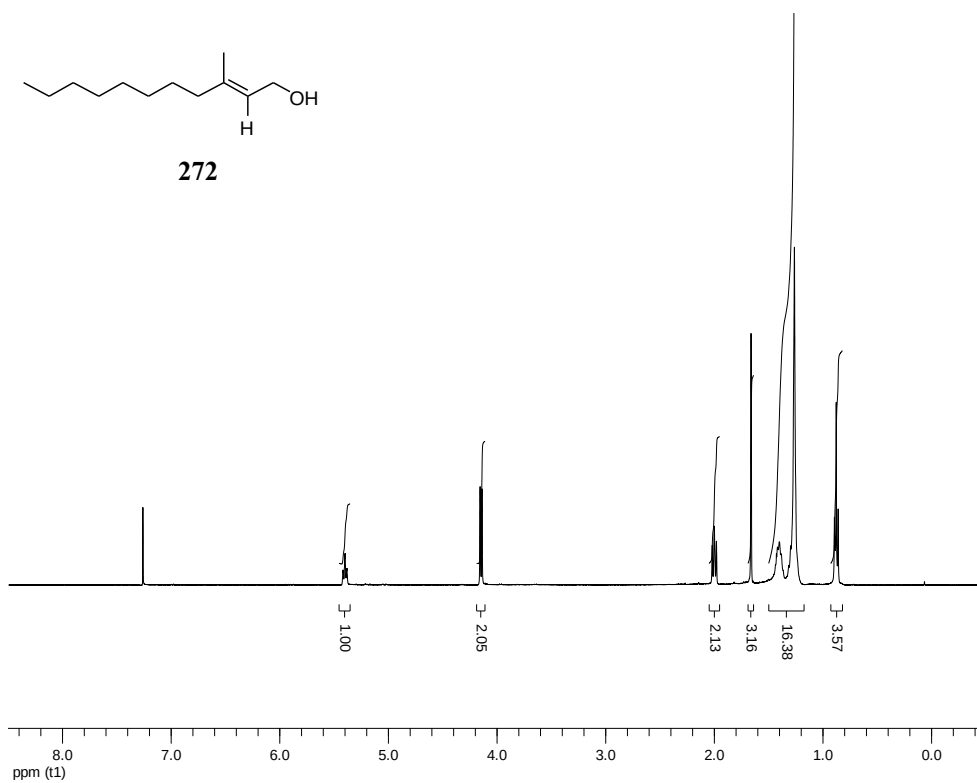


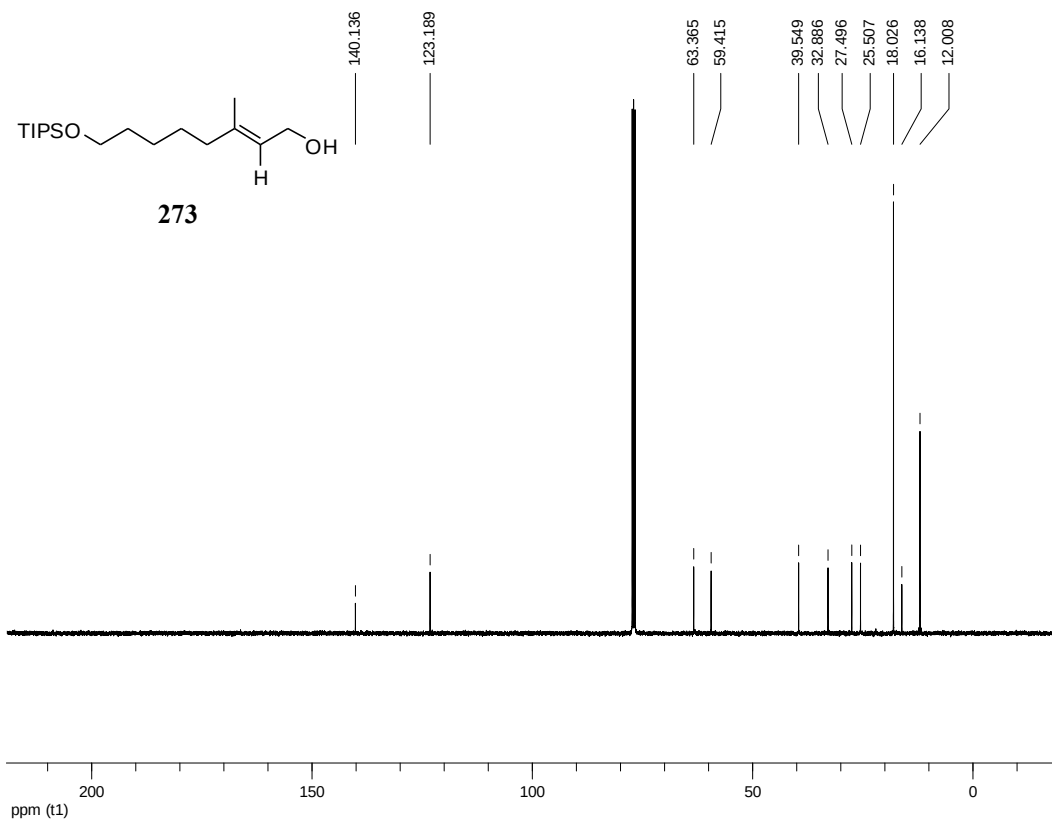
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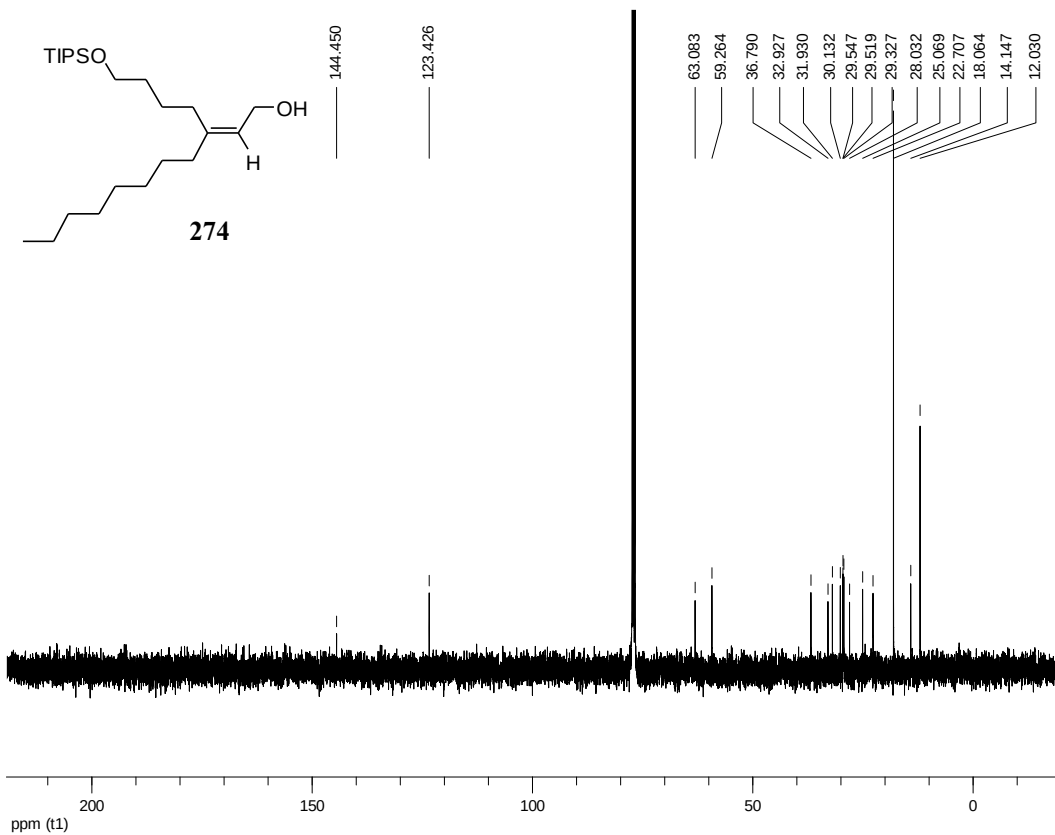


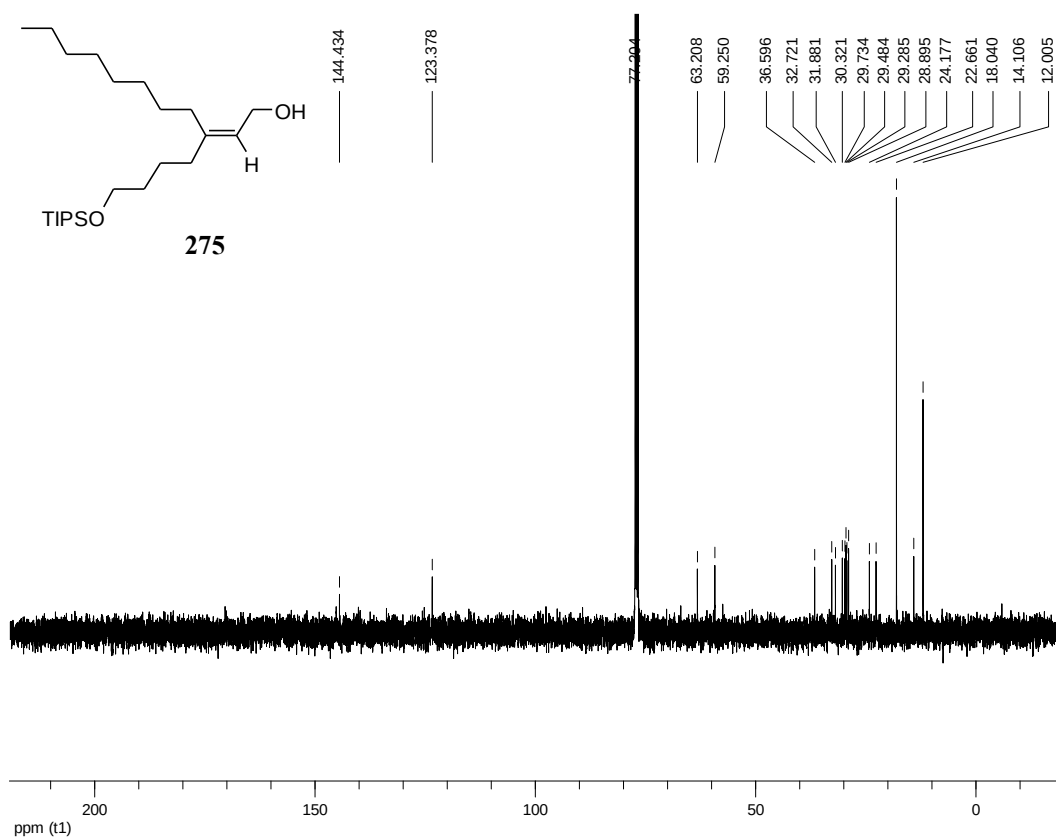
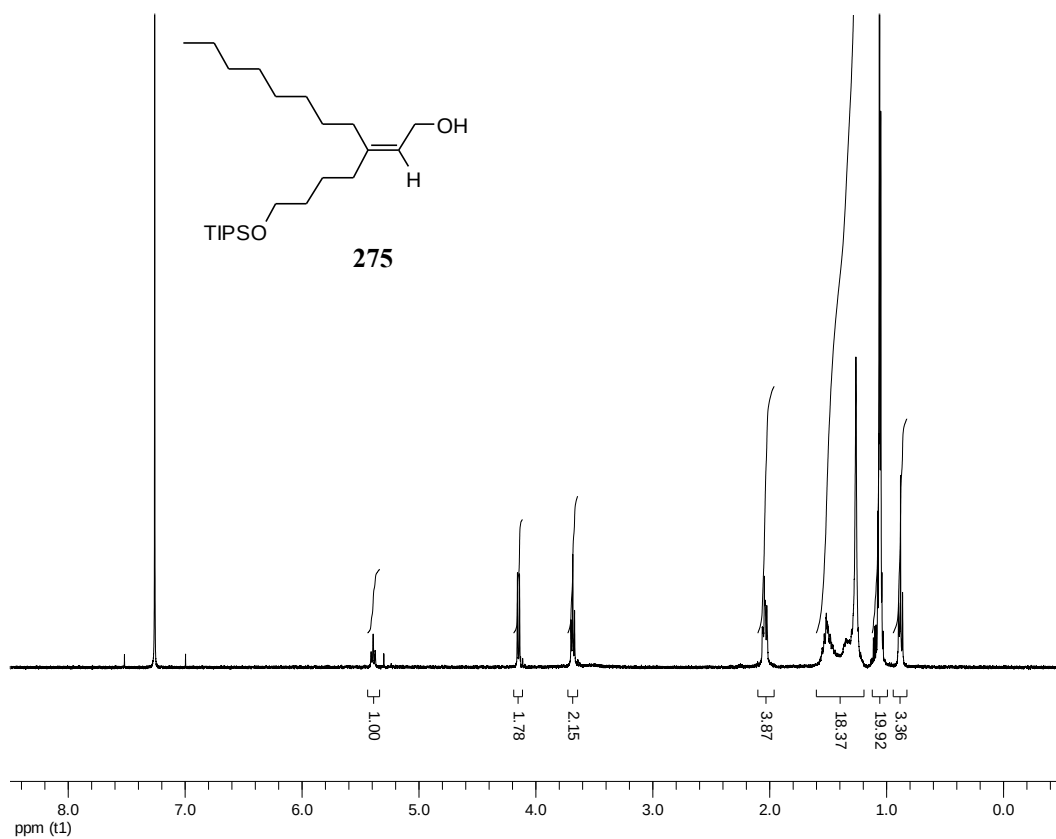


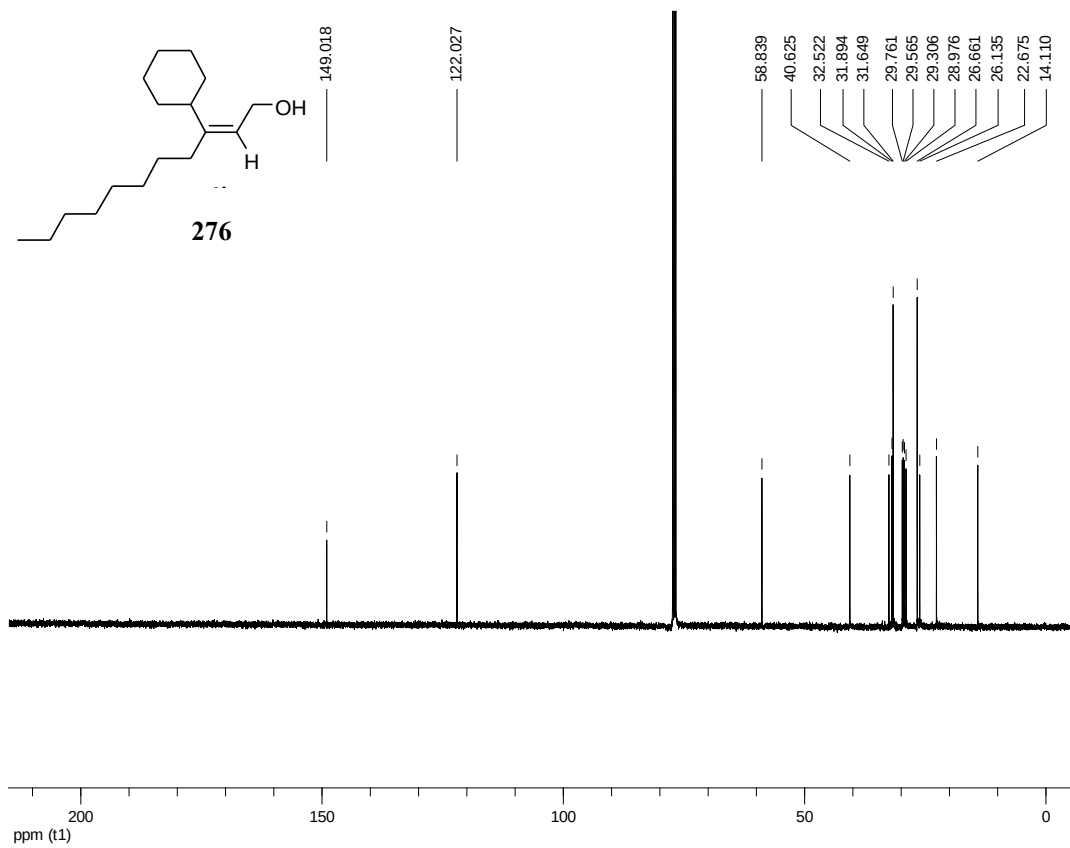
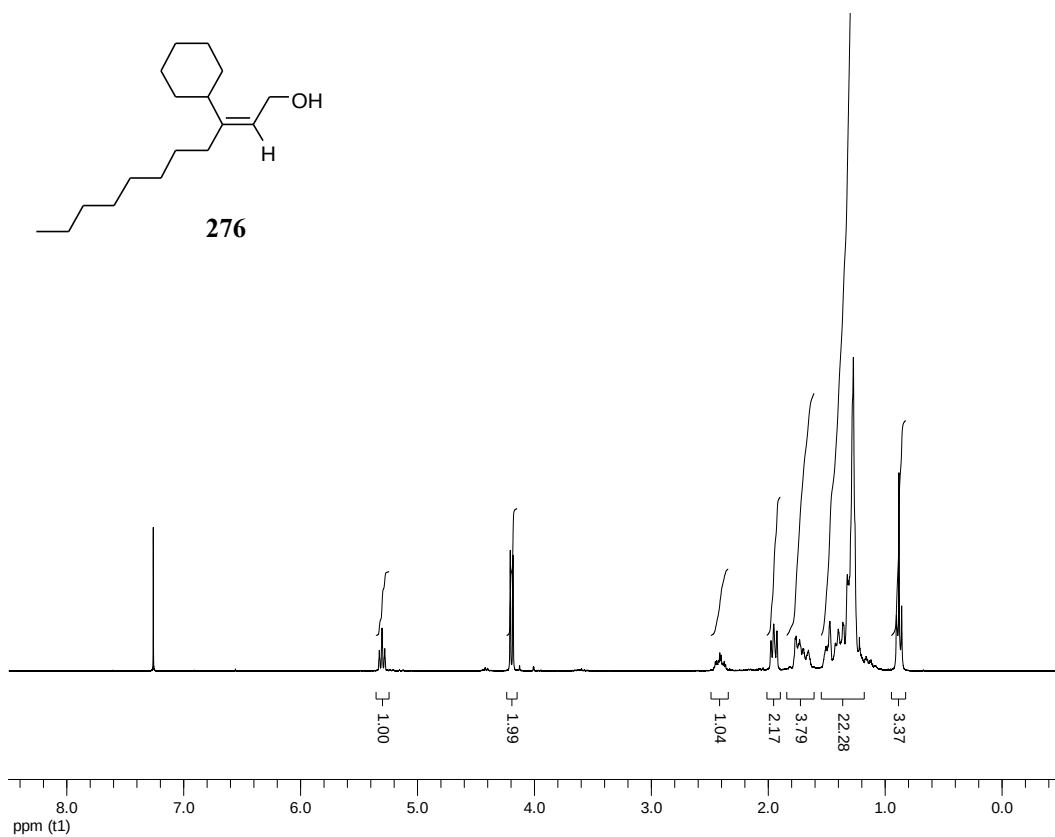


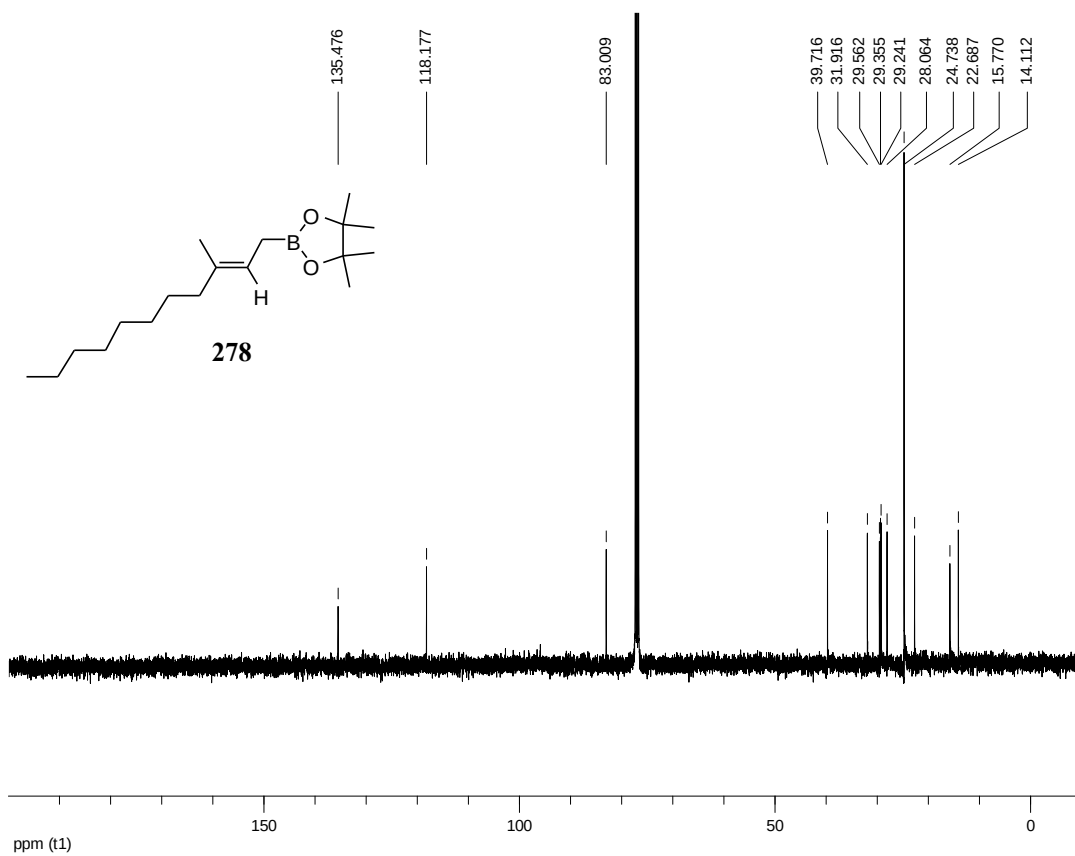
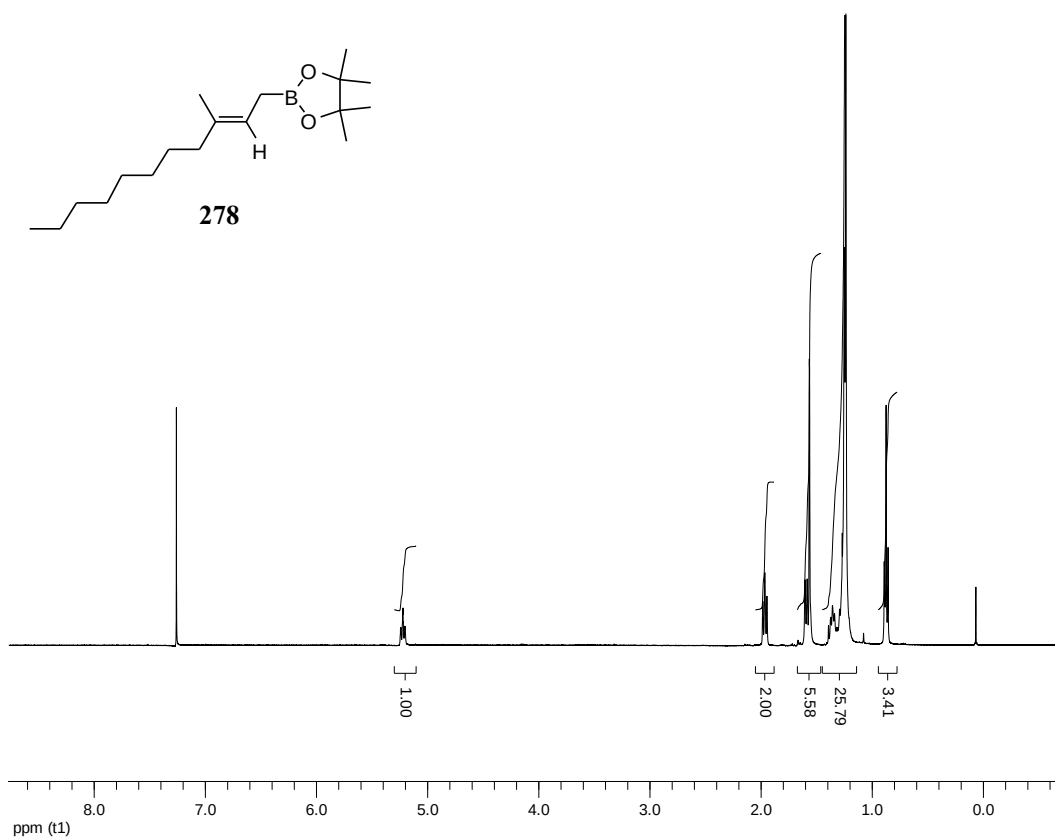


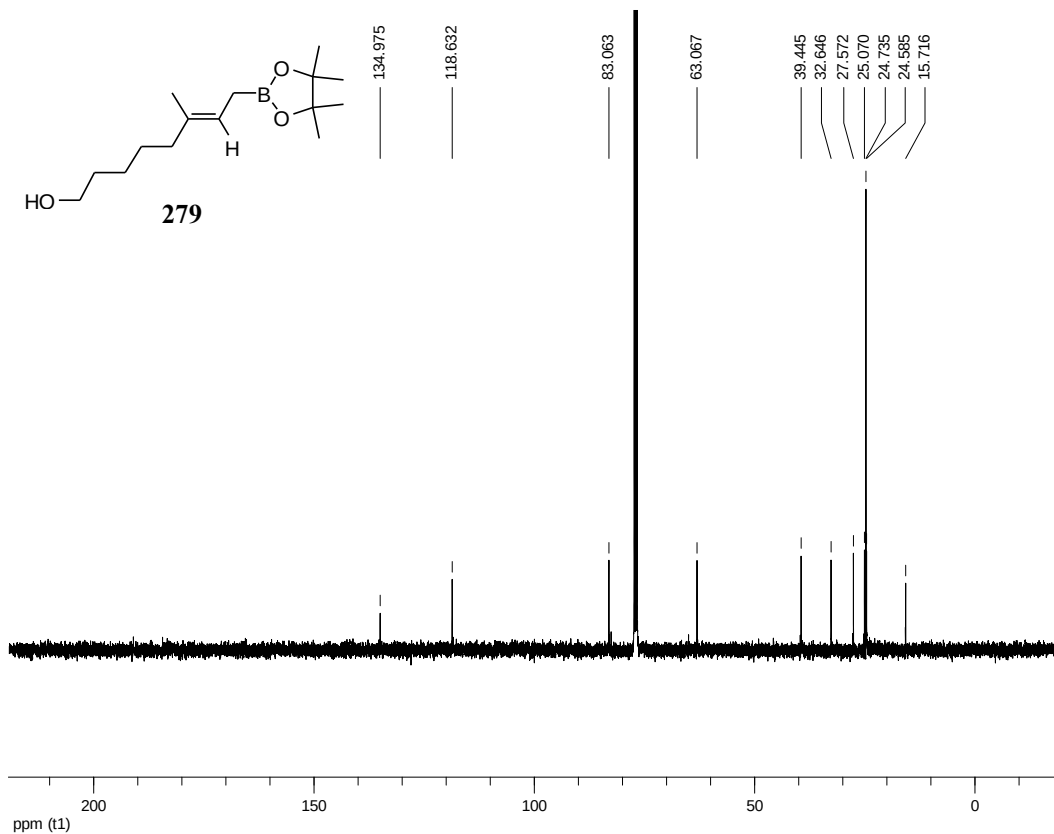
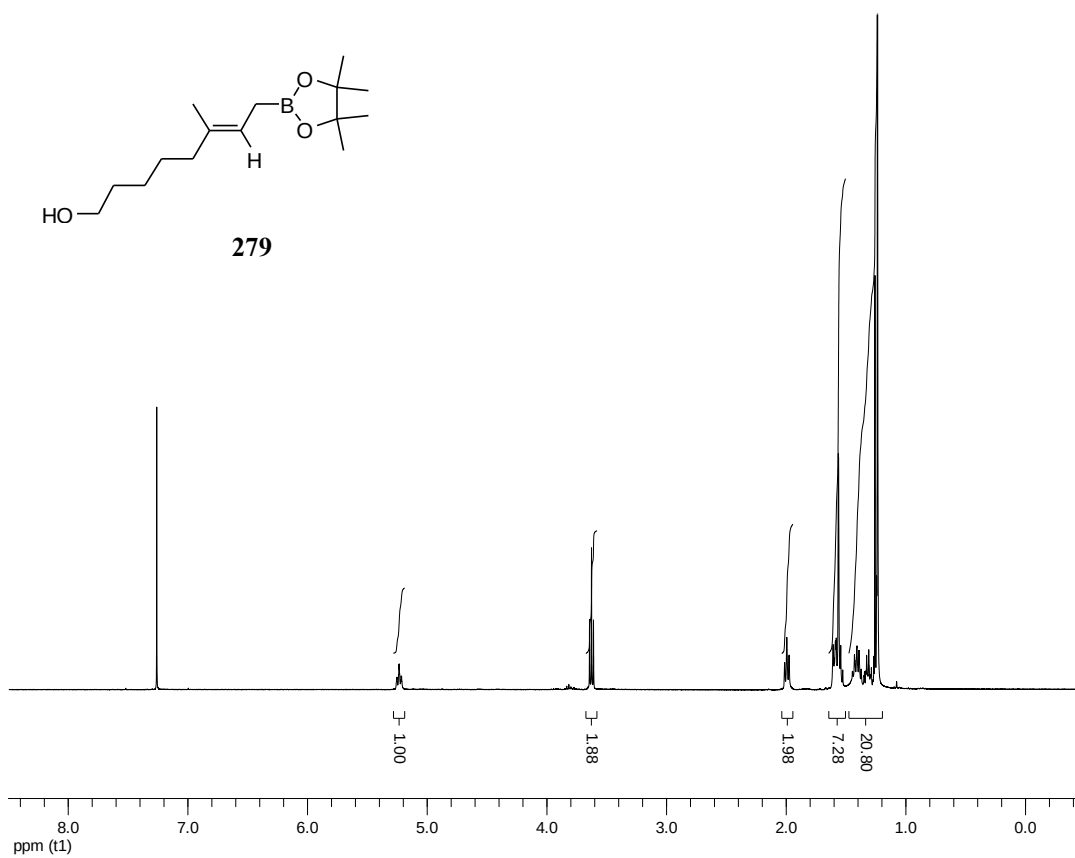


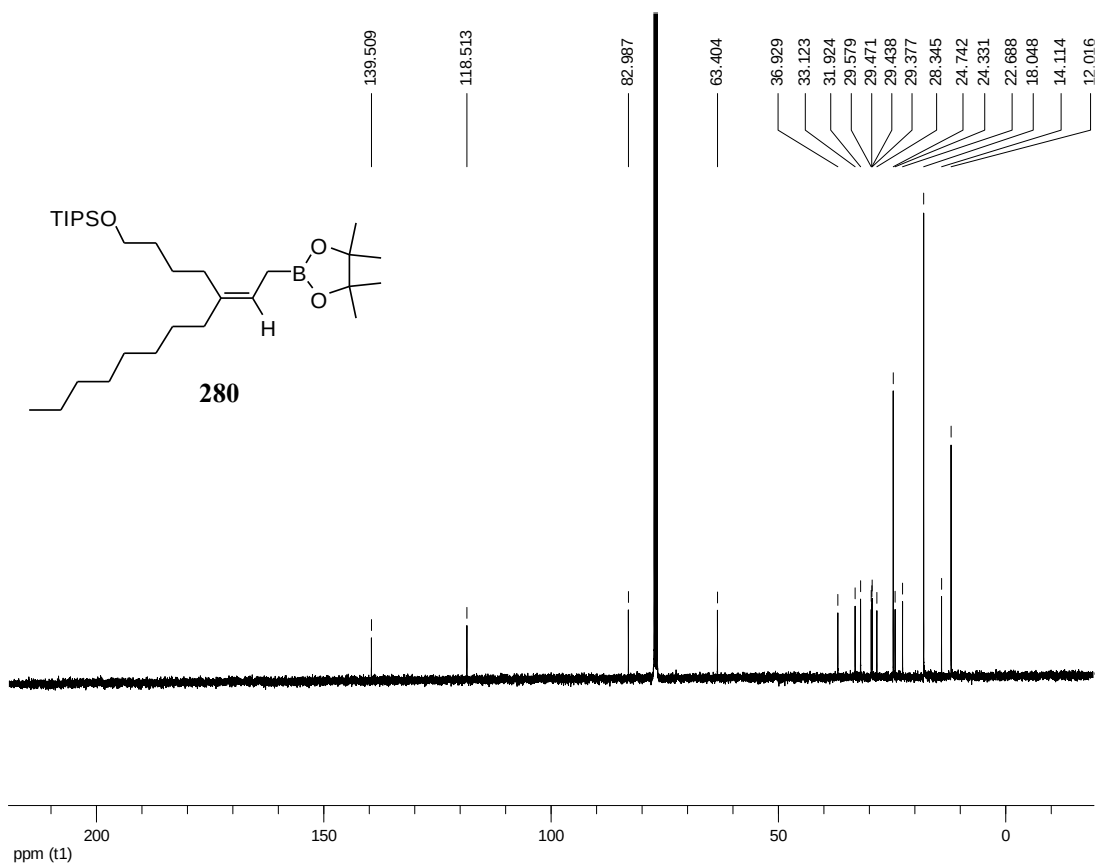
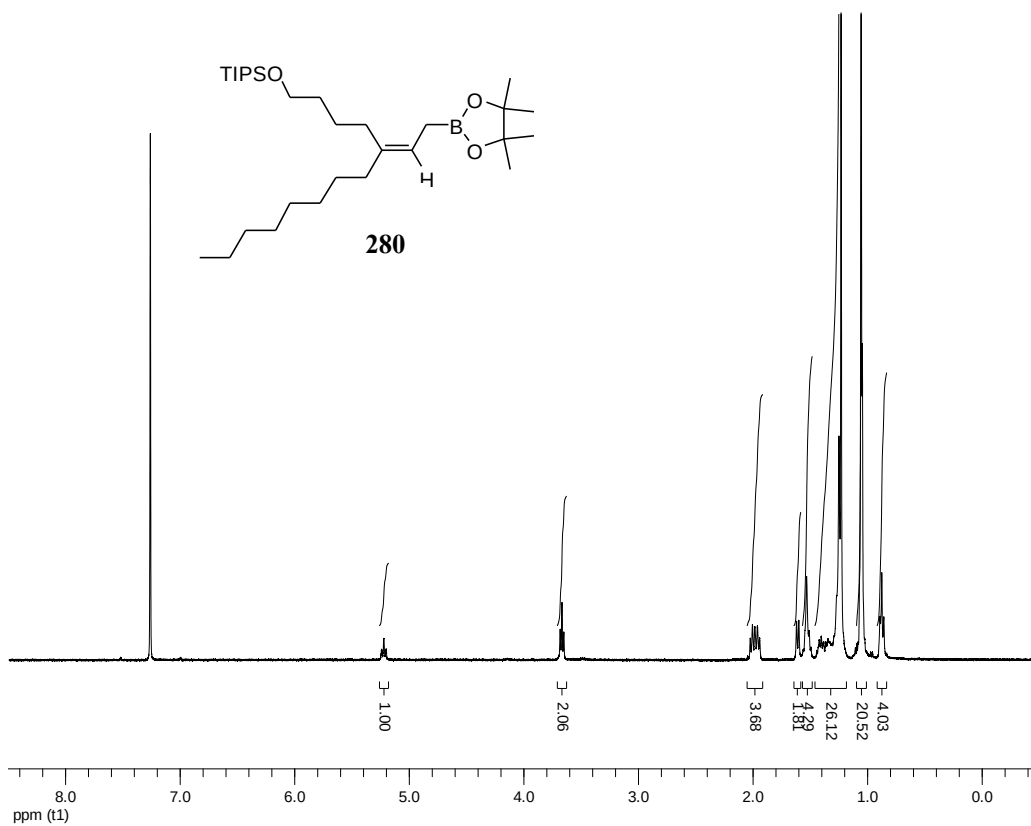


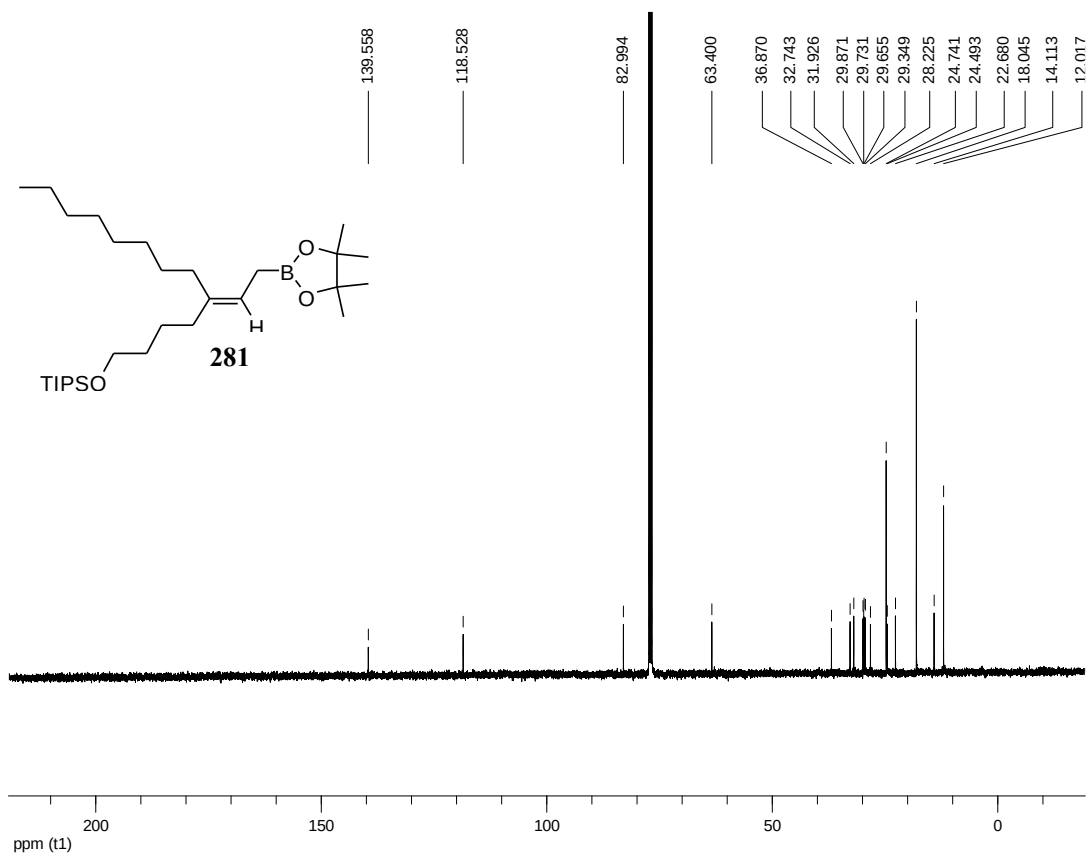
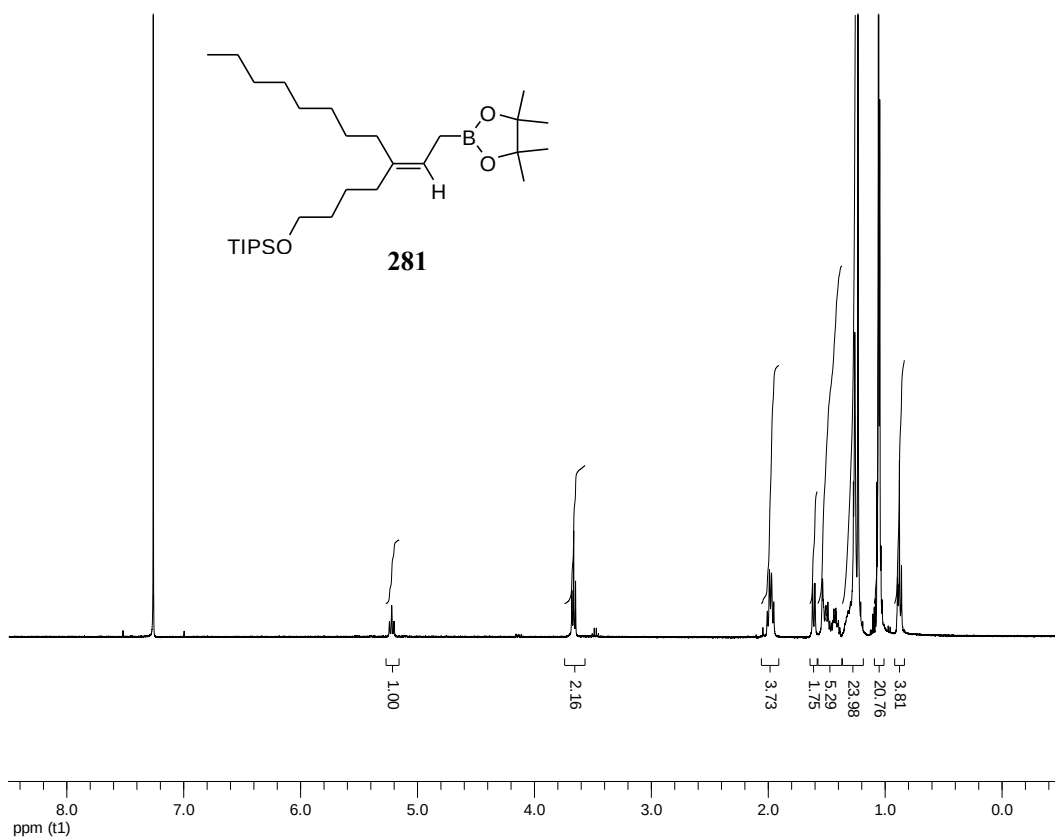


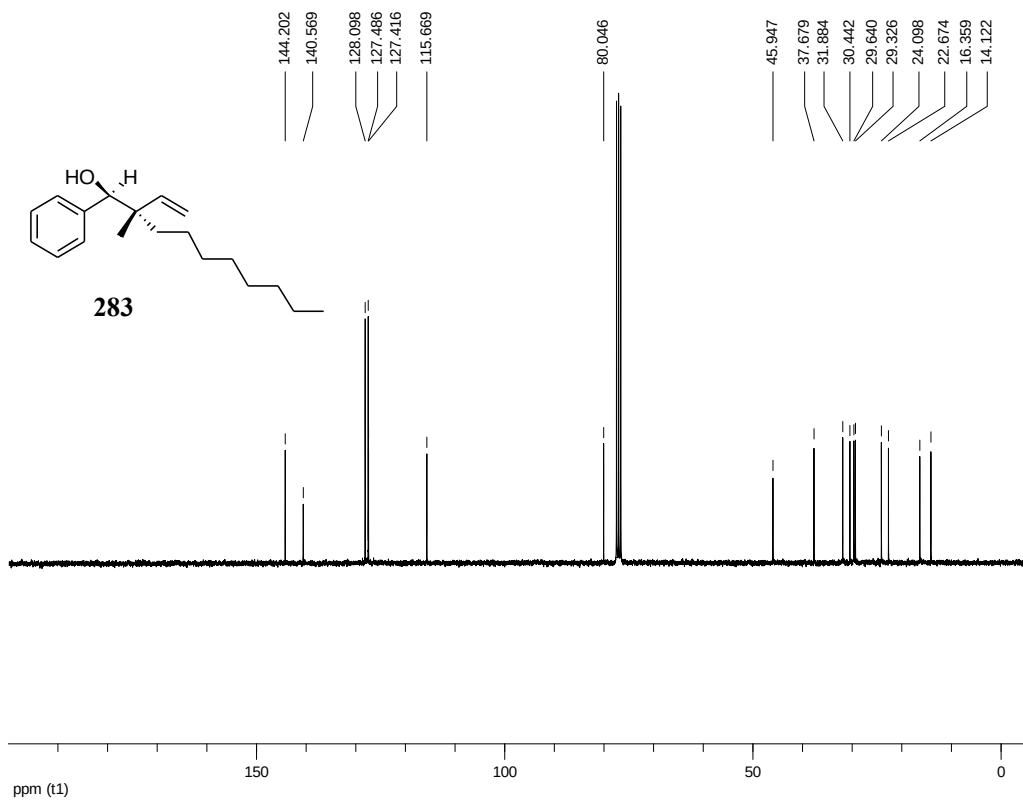
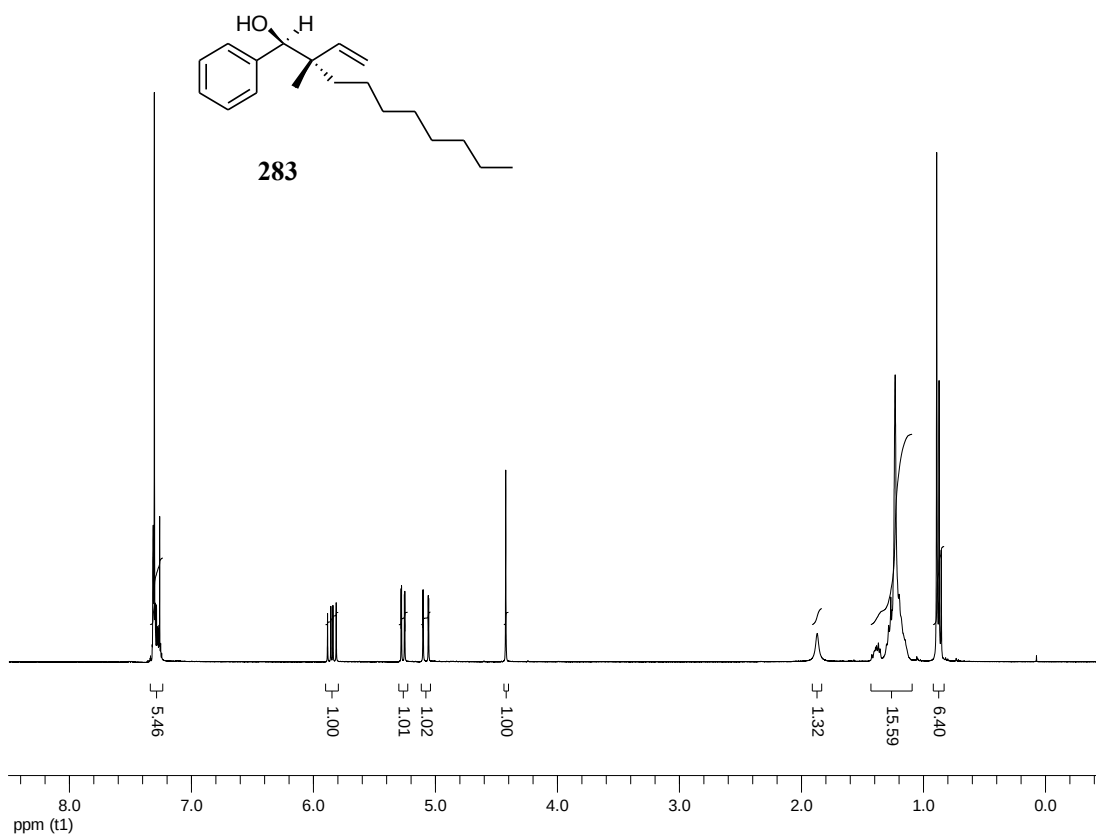


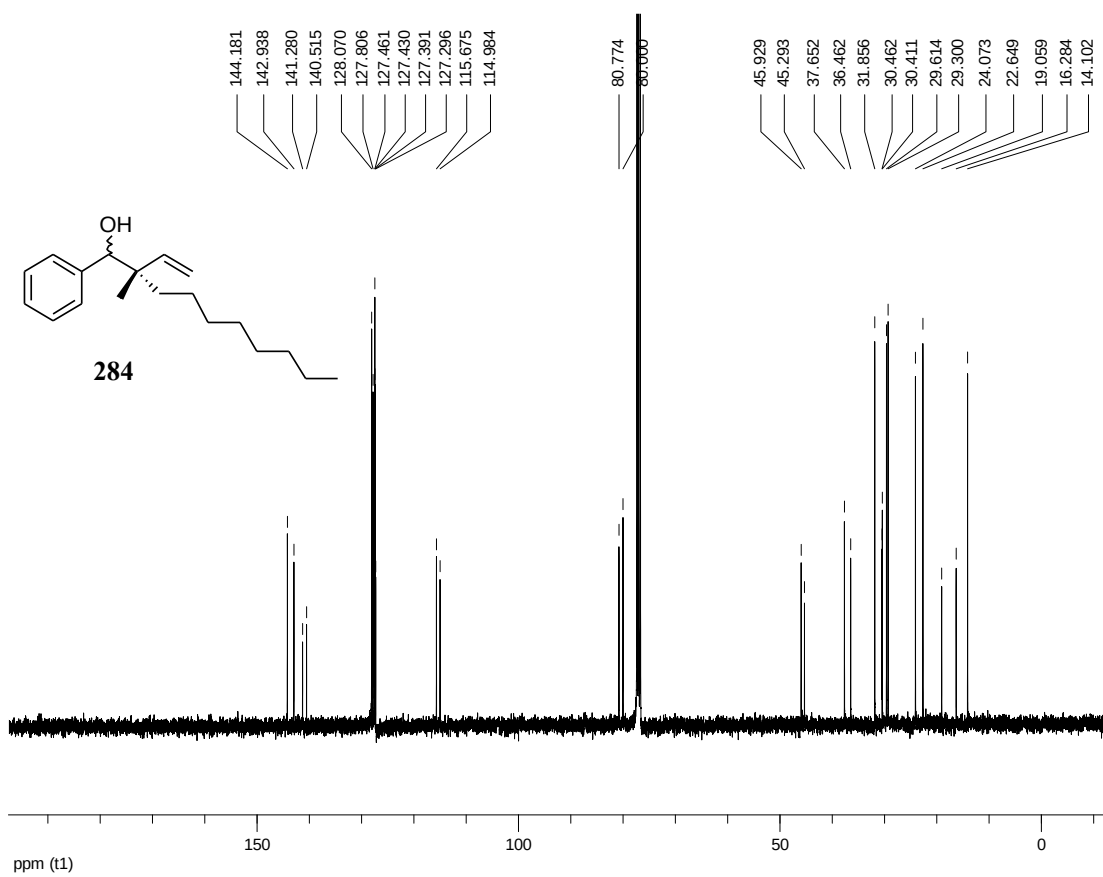
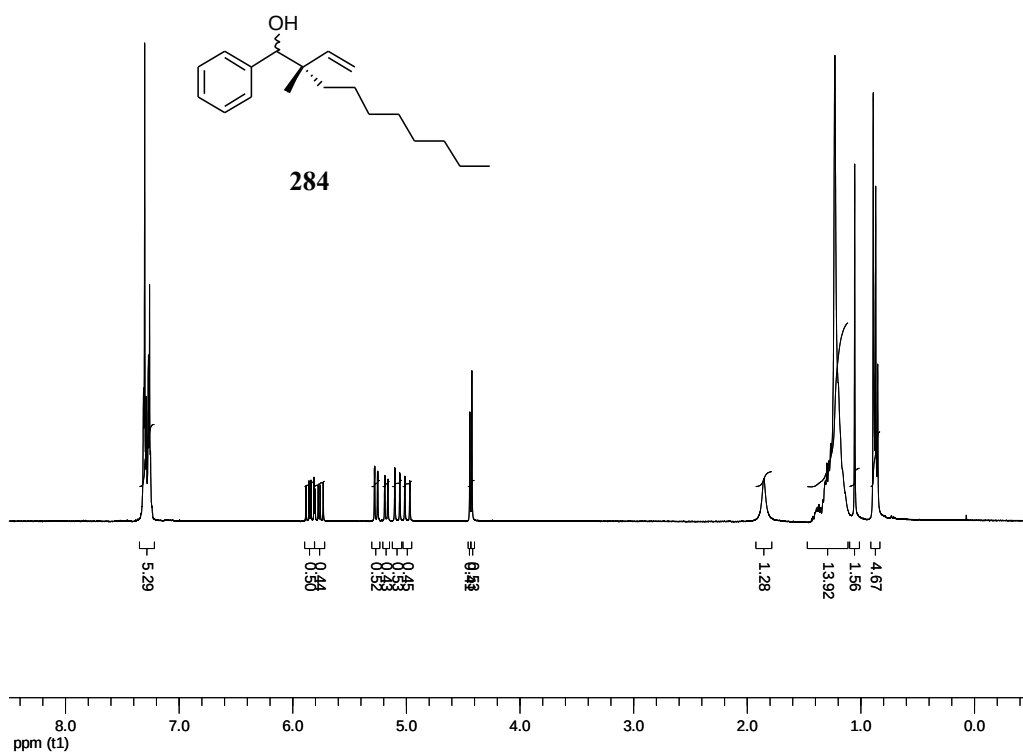


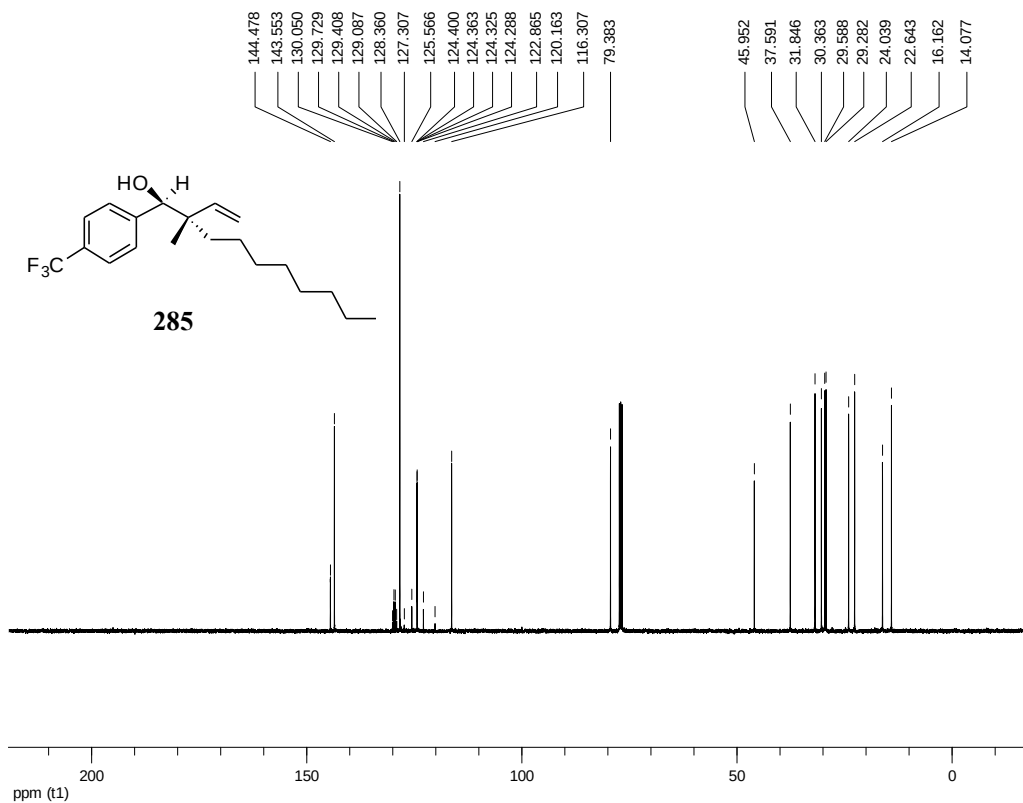
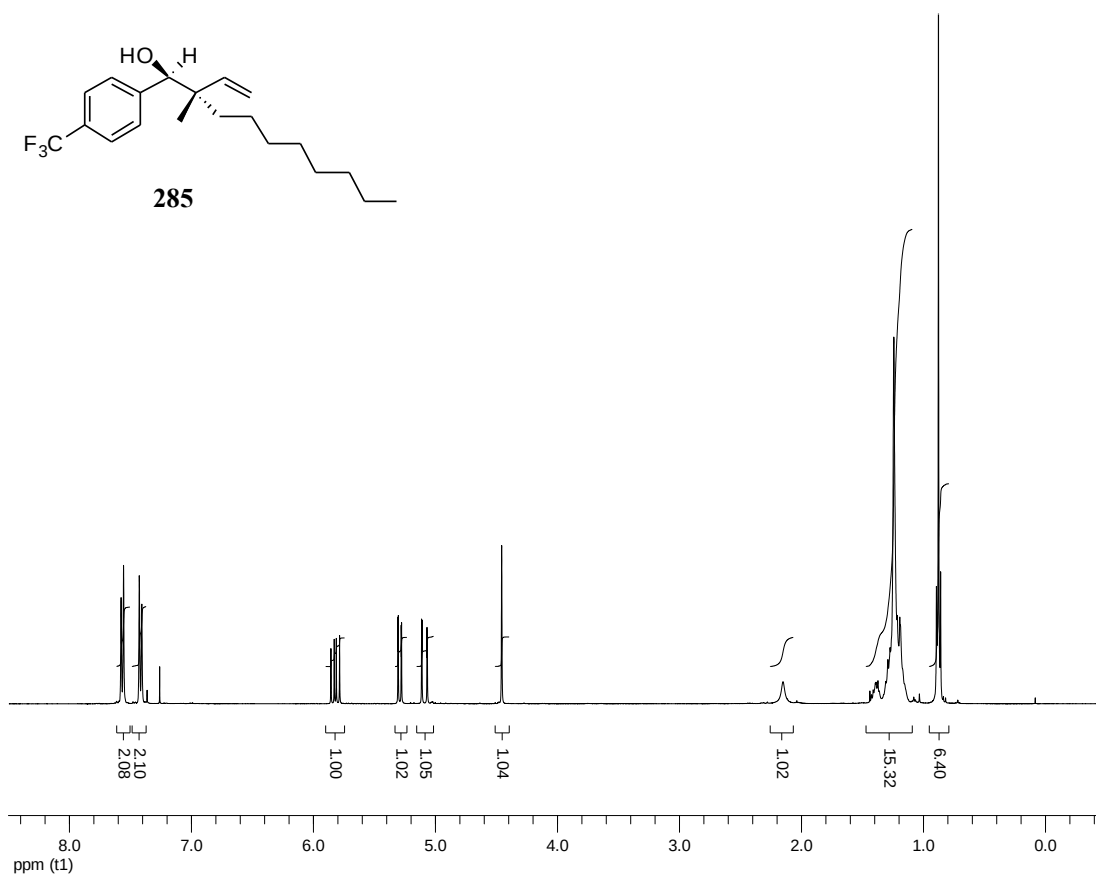


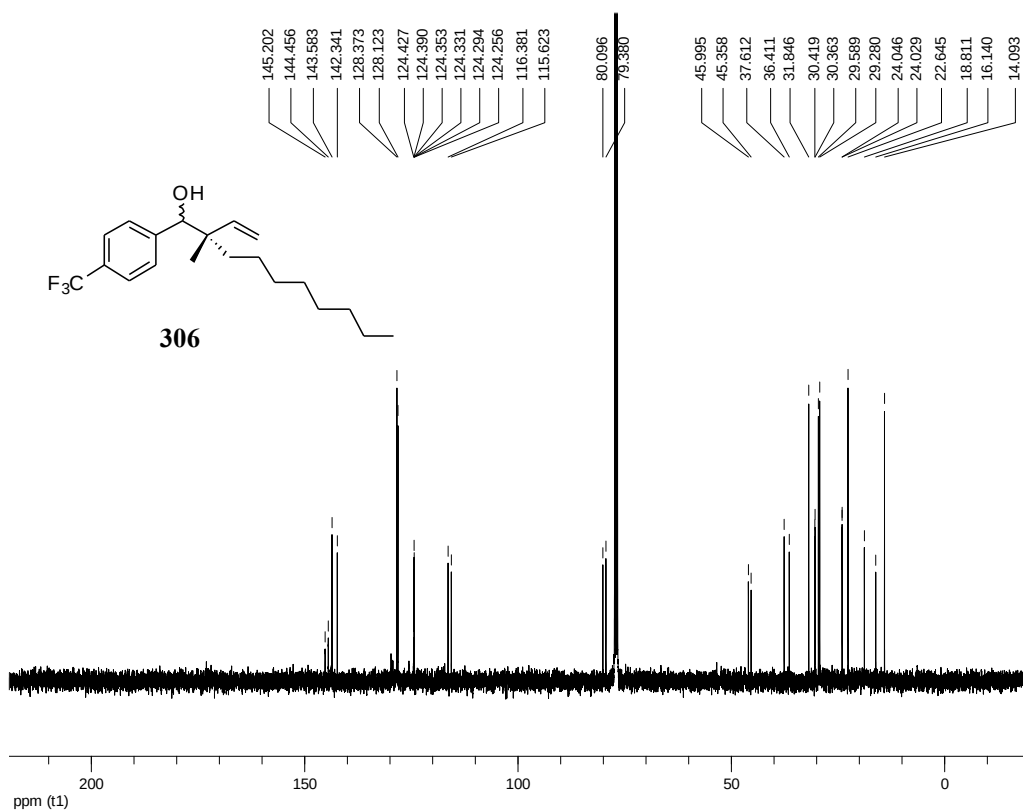
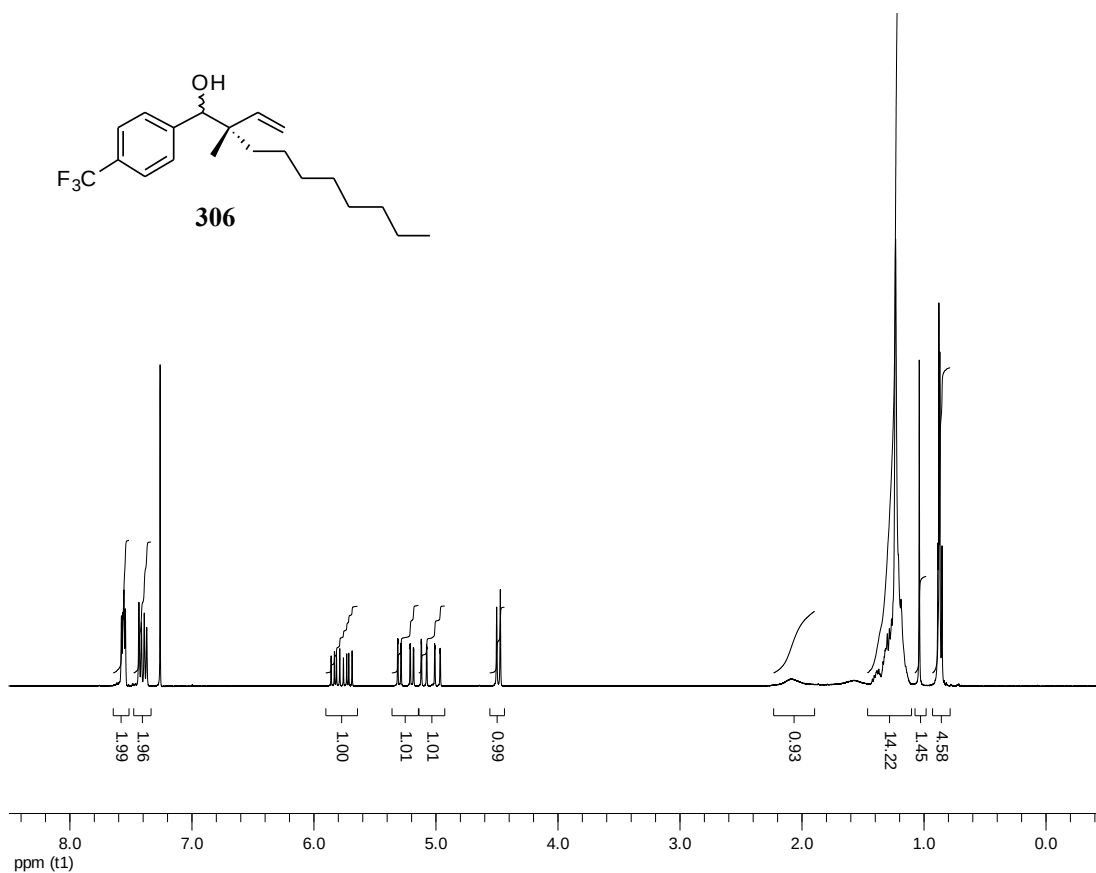


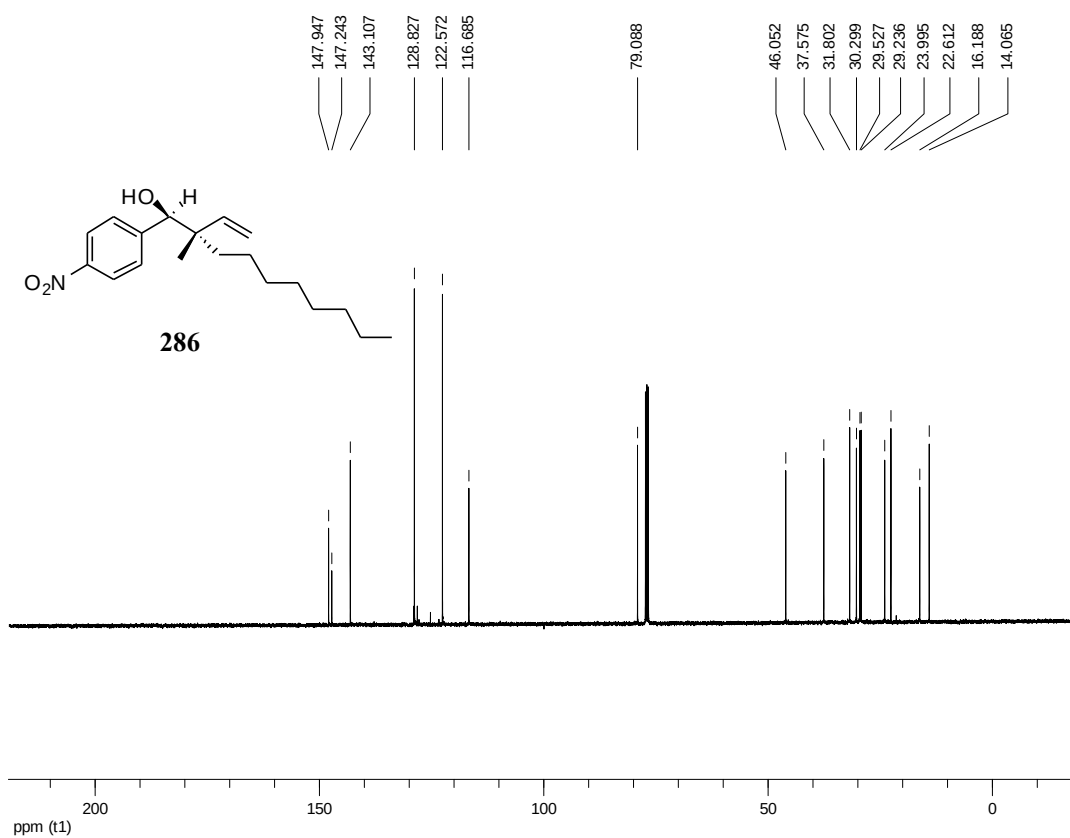
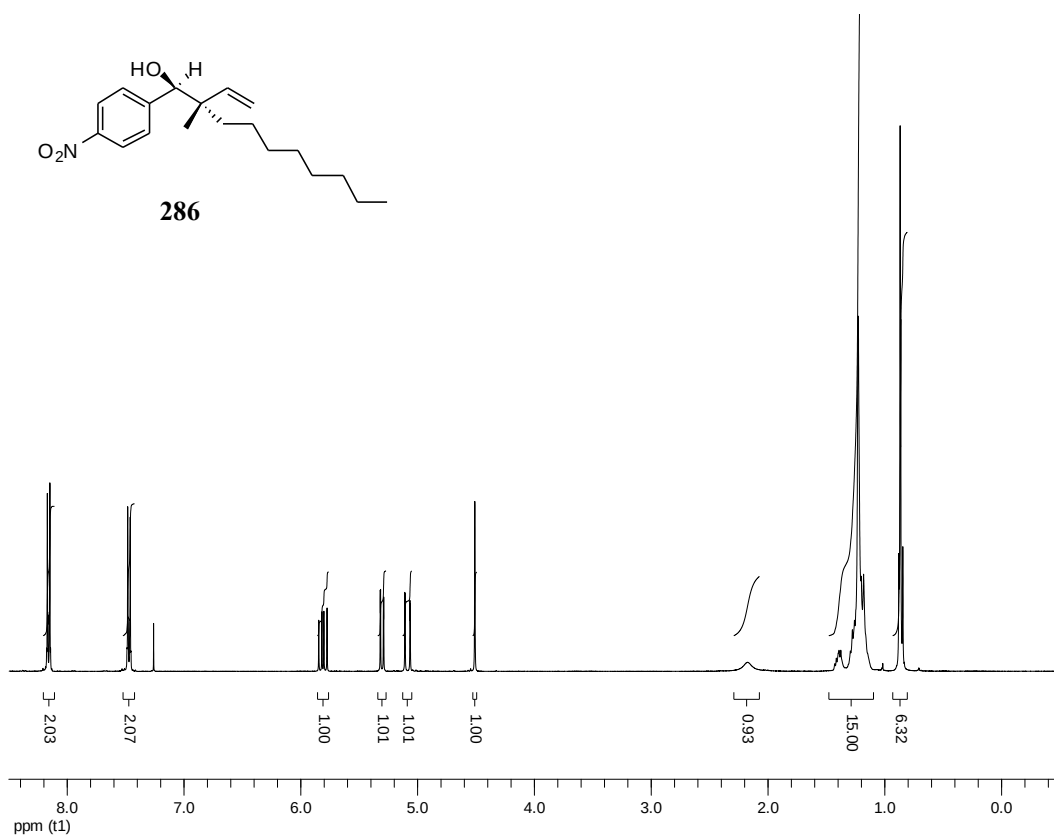


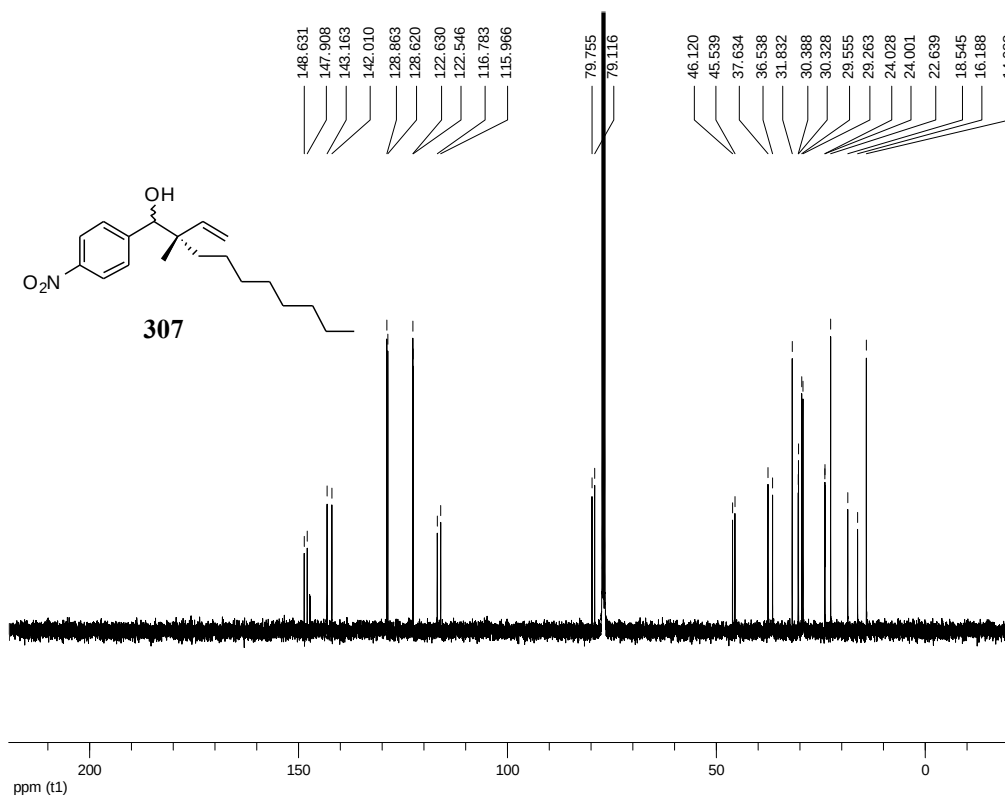
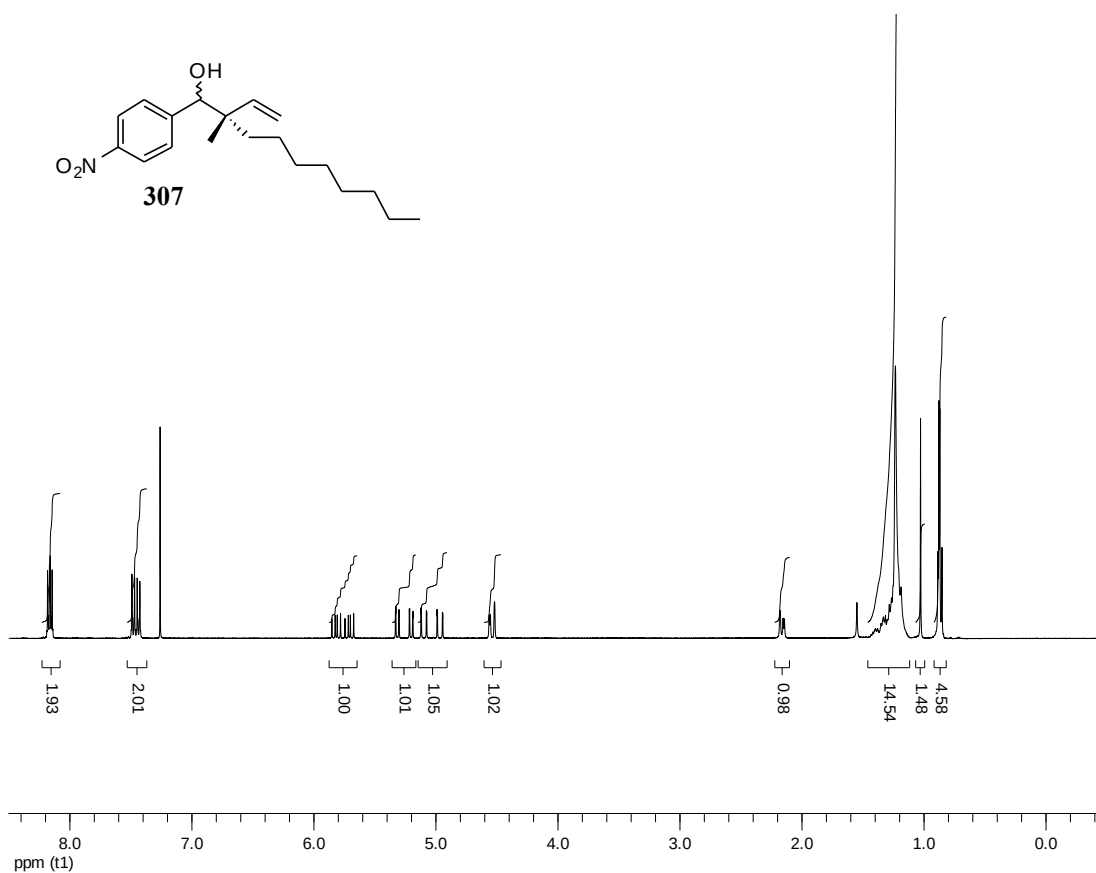


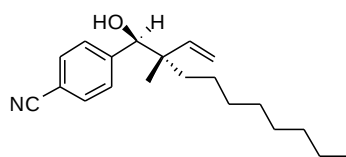




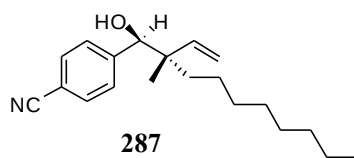
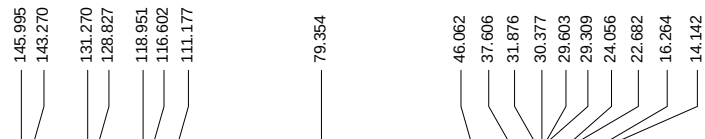
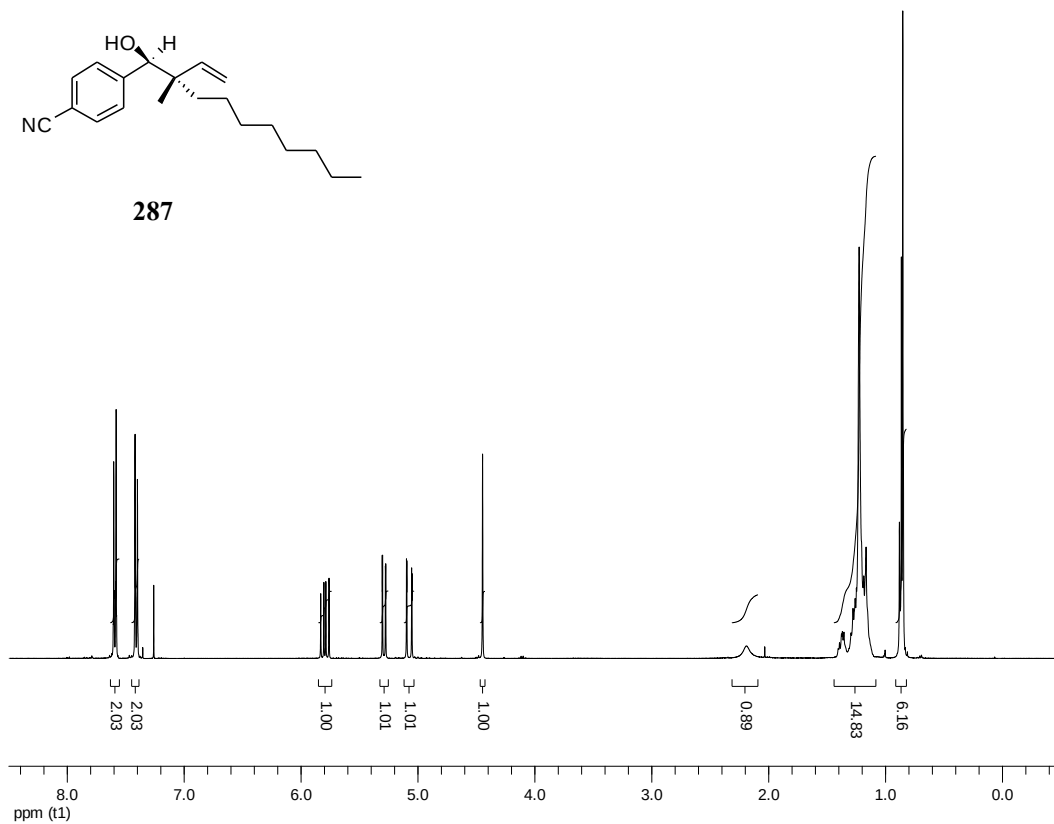




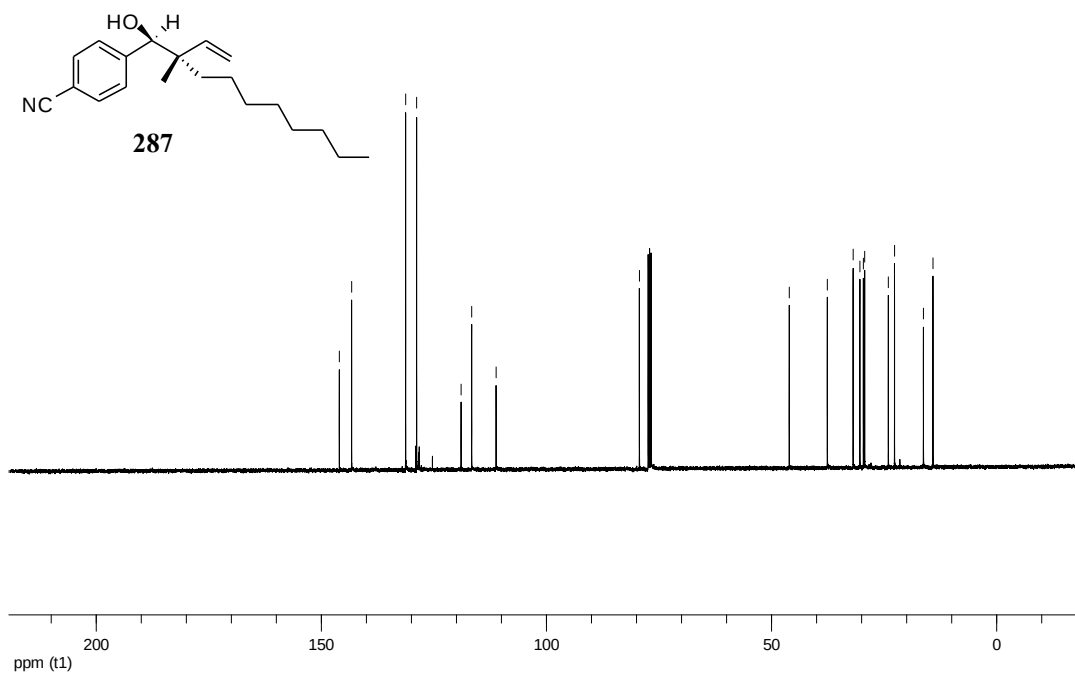


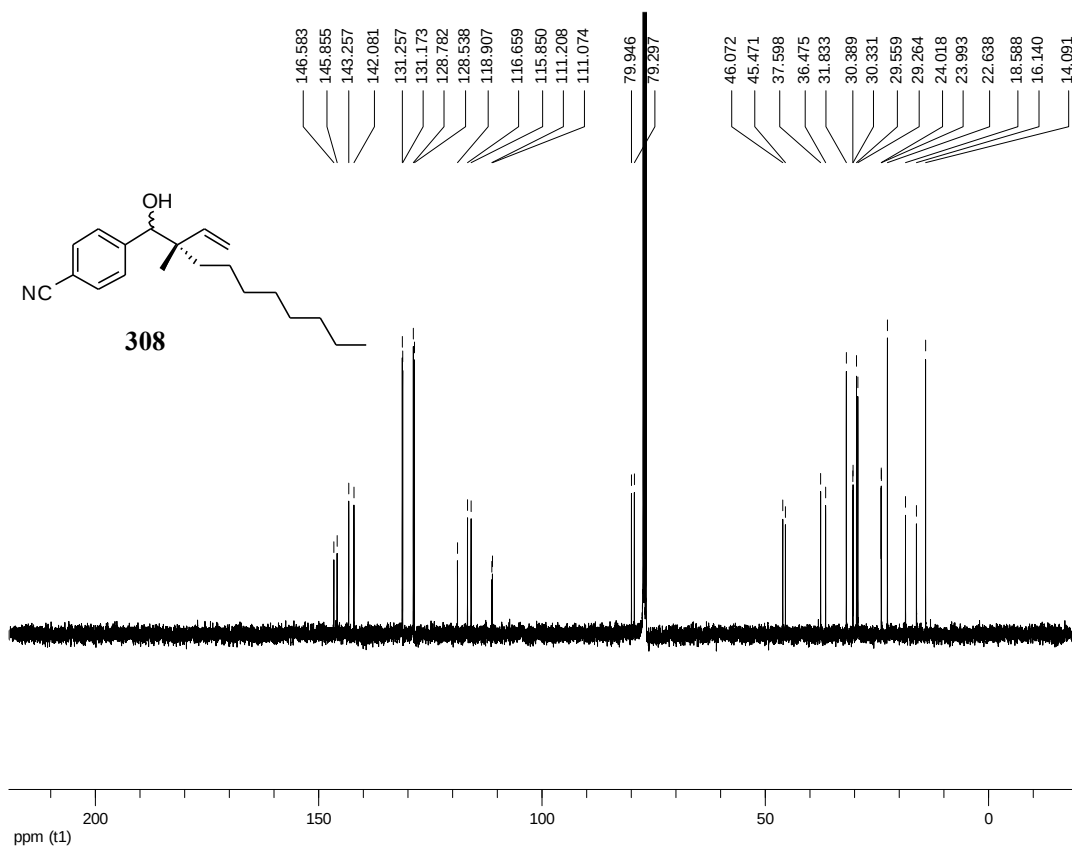
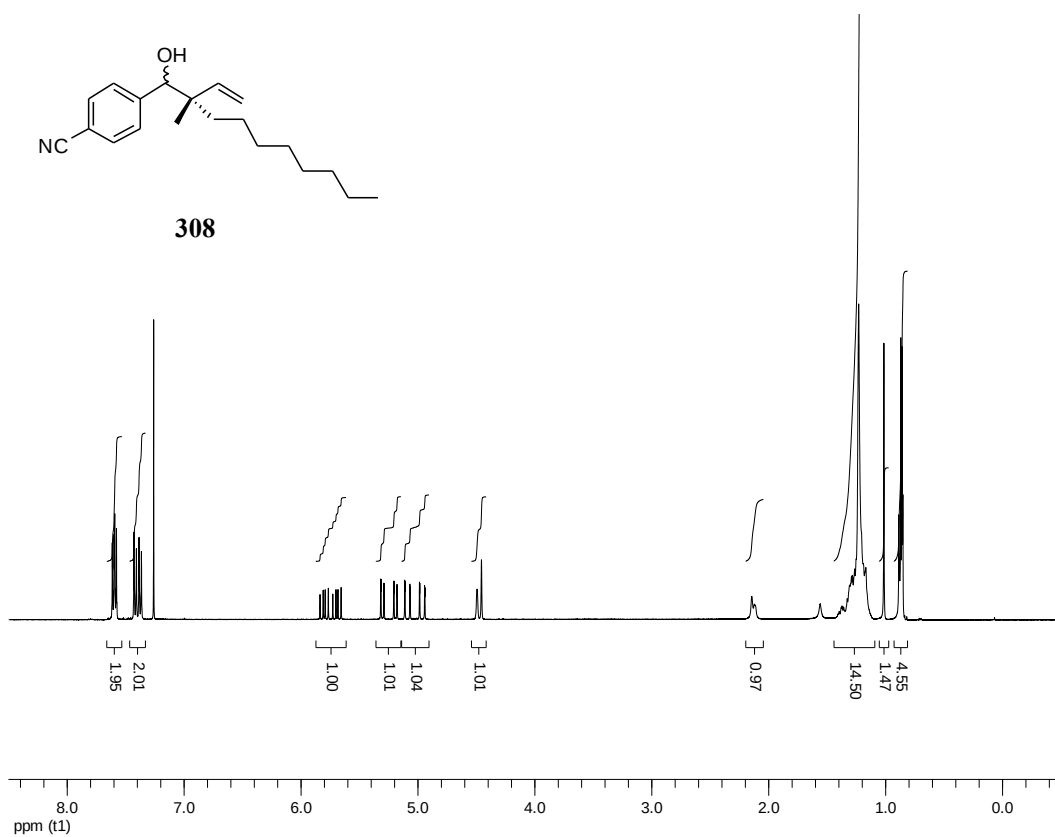


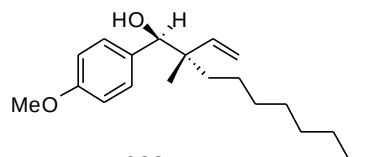
287



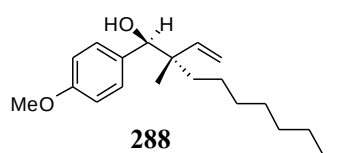
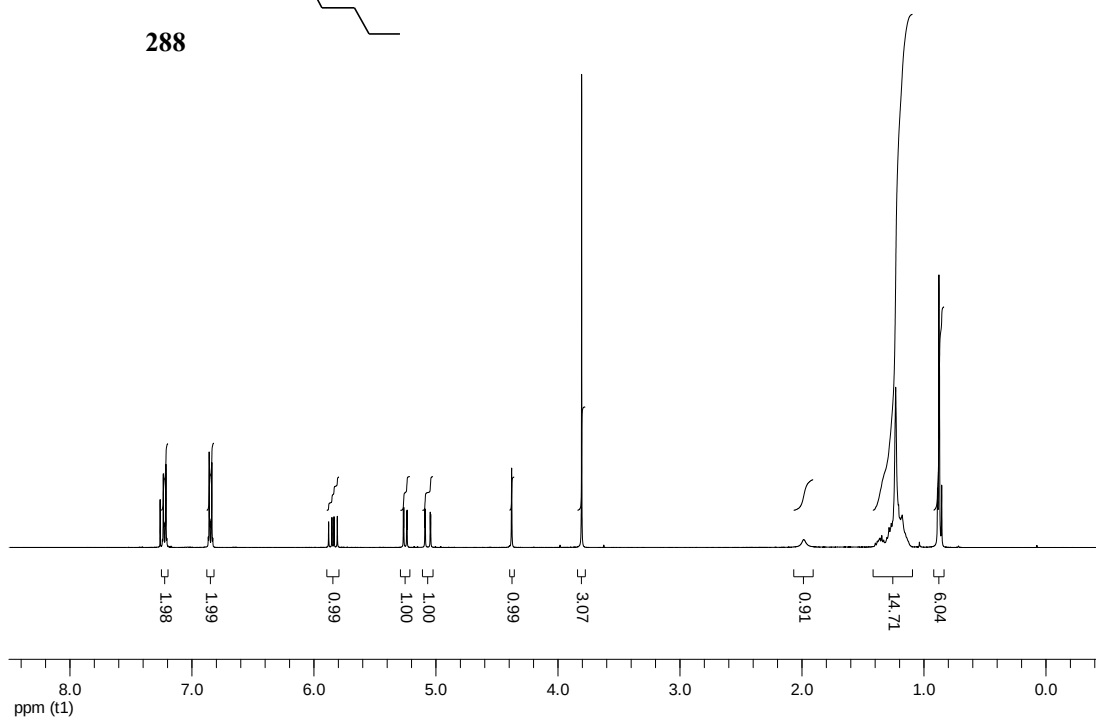
287



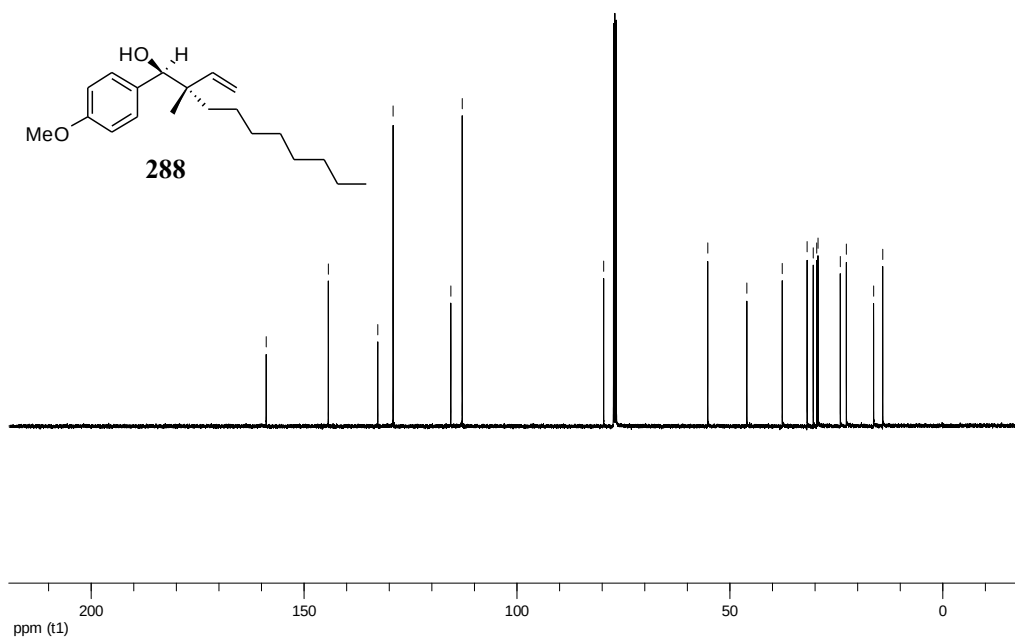


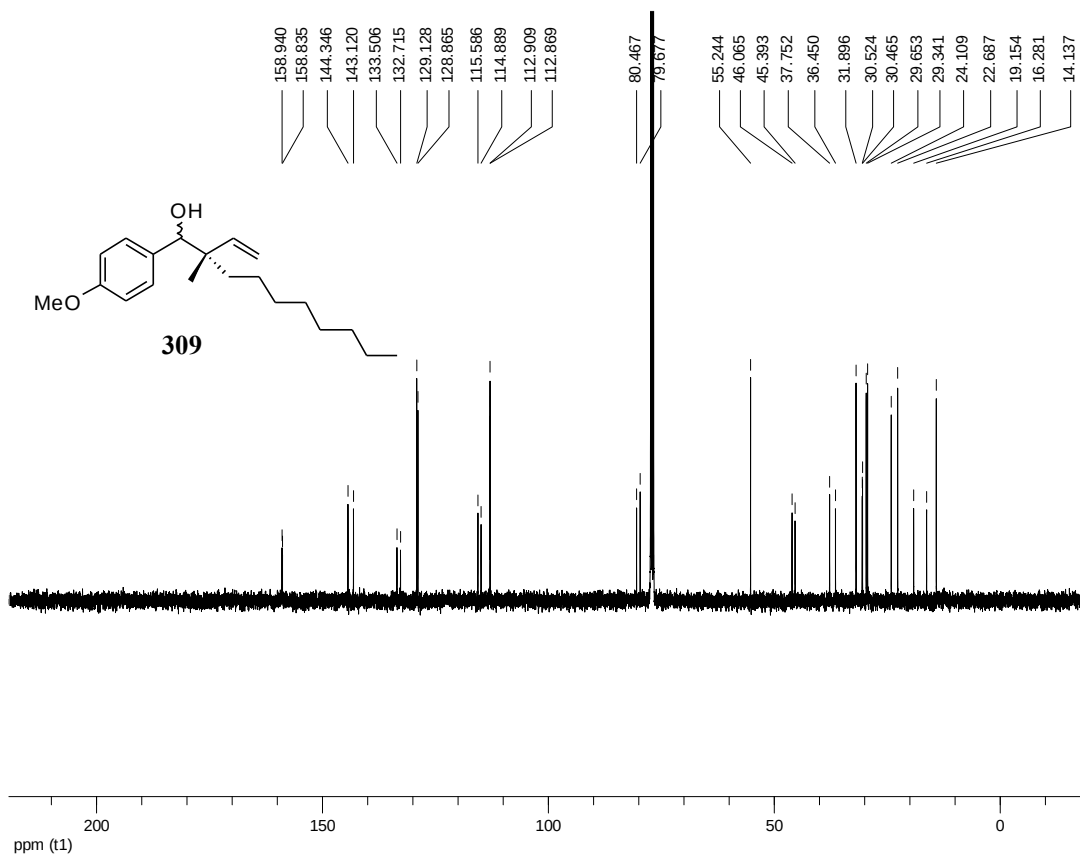
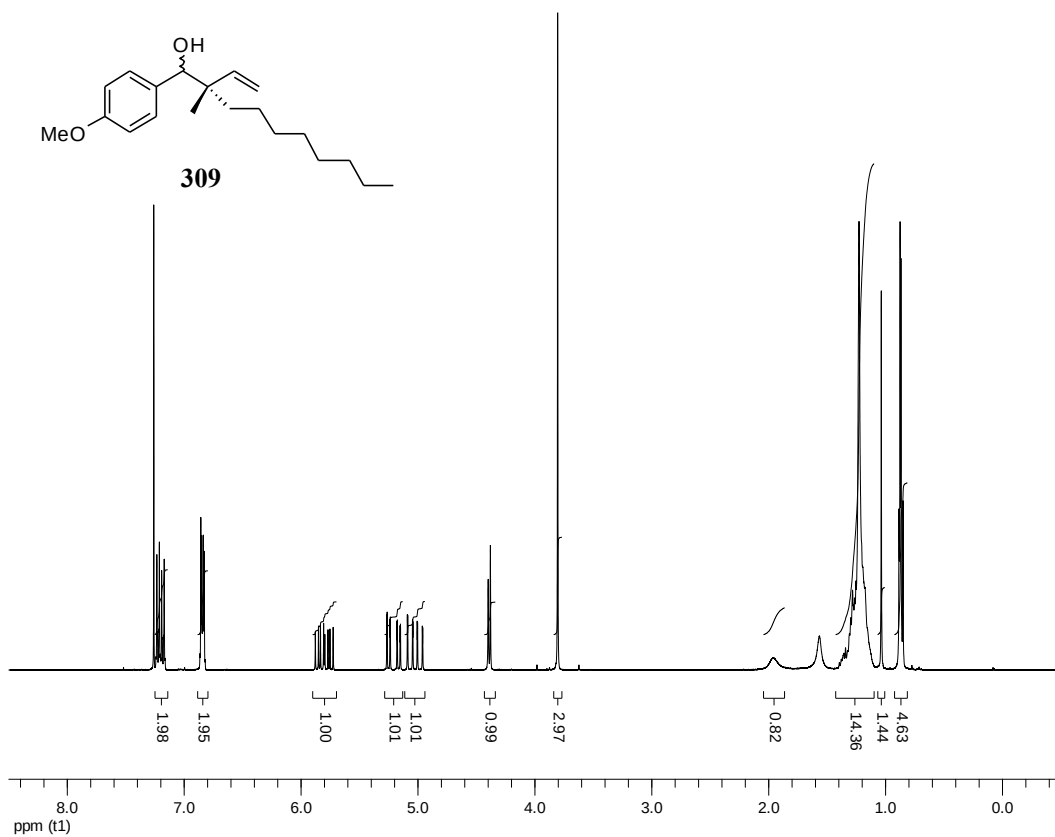


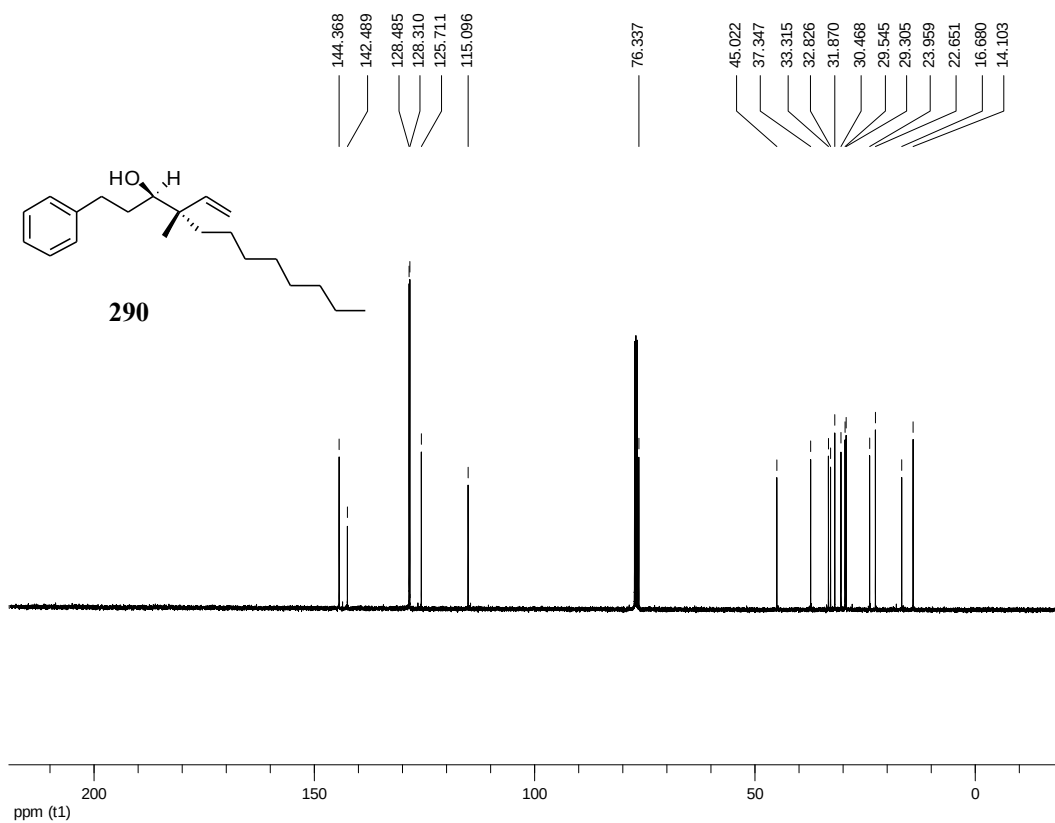
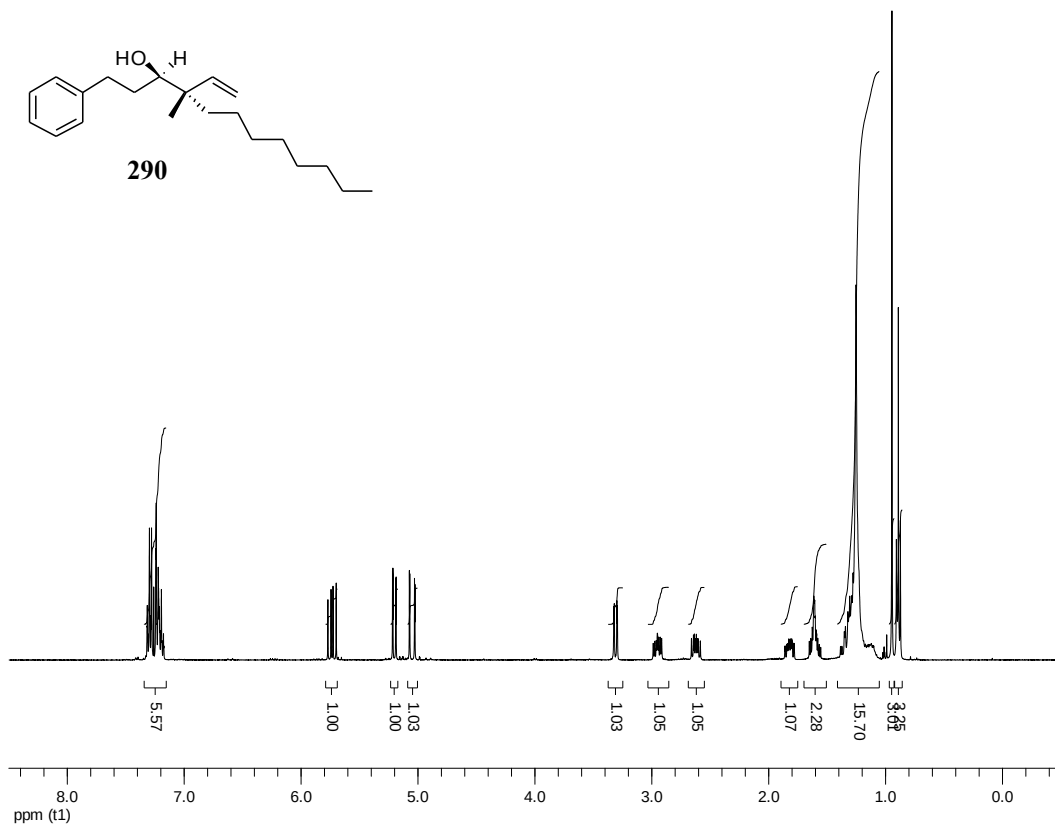
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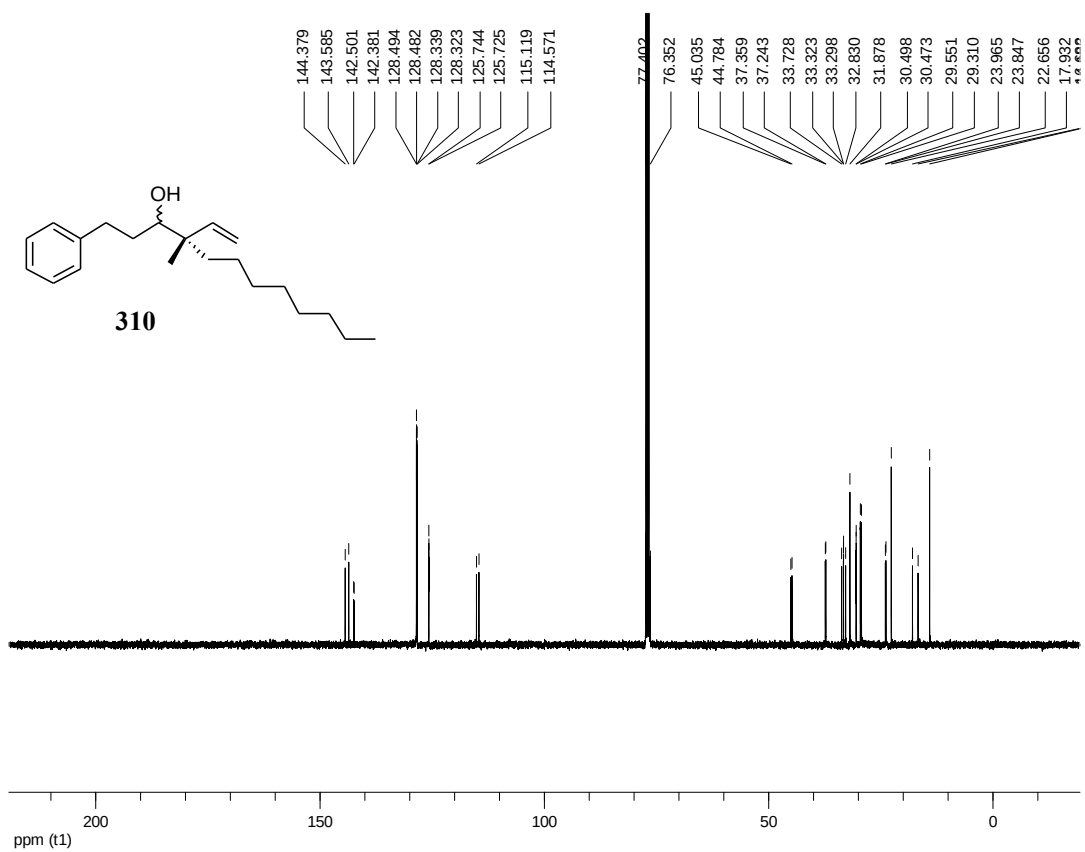
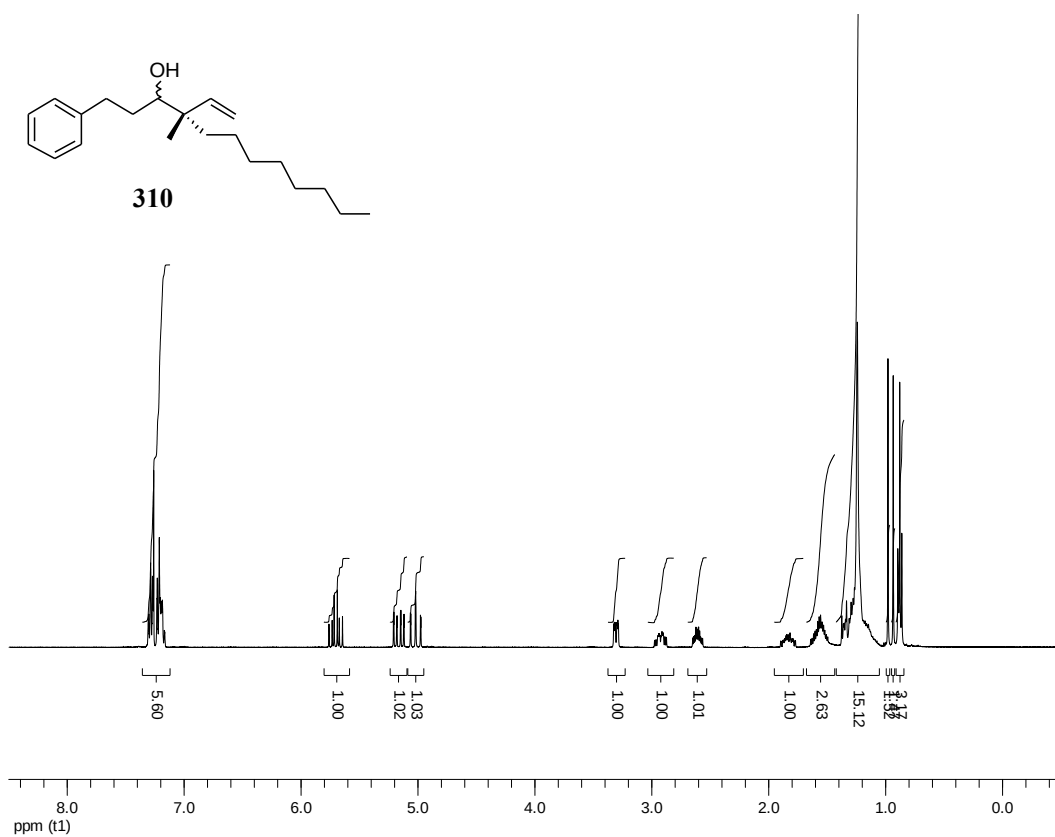


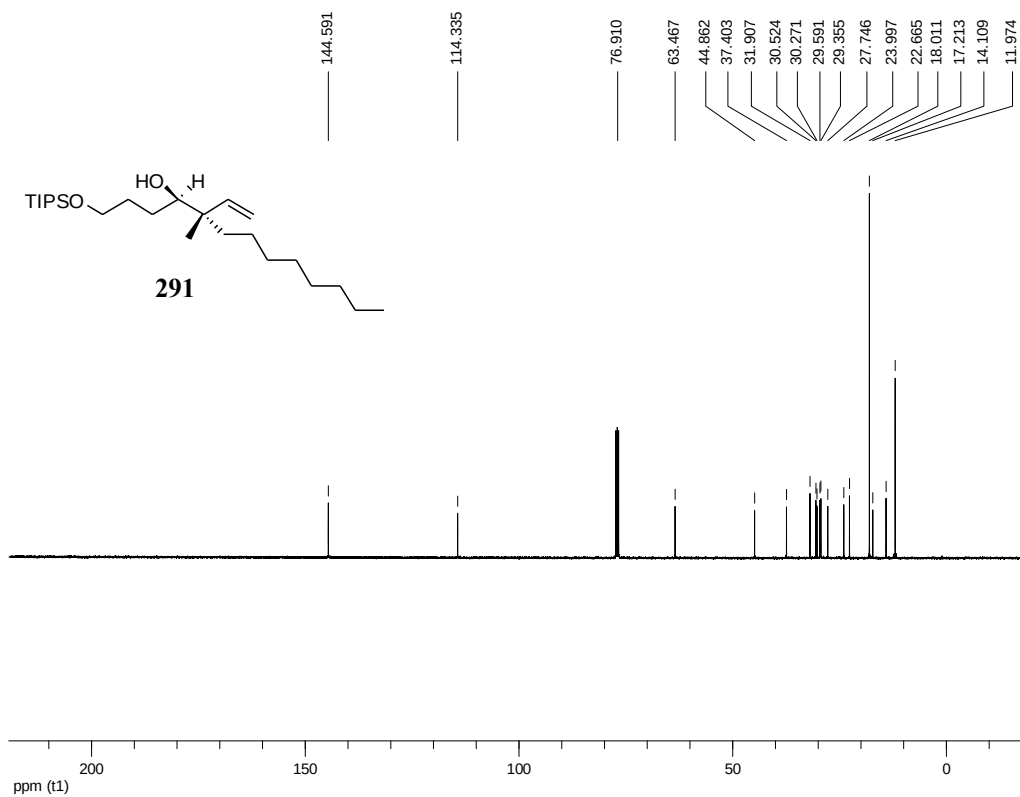
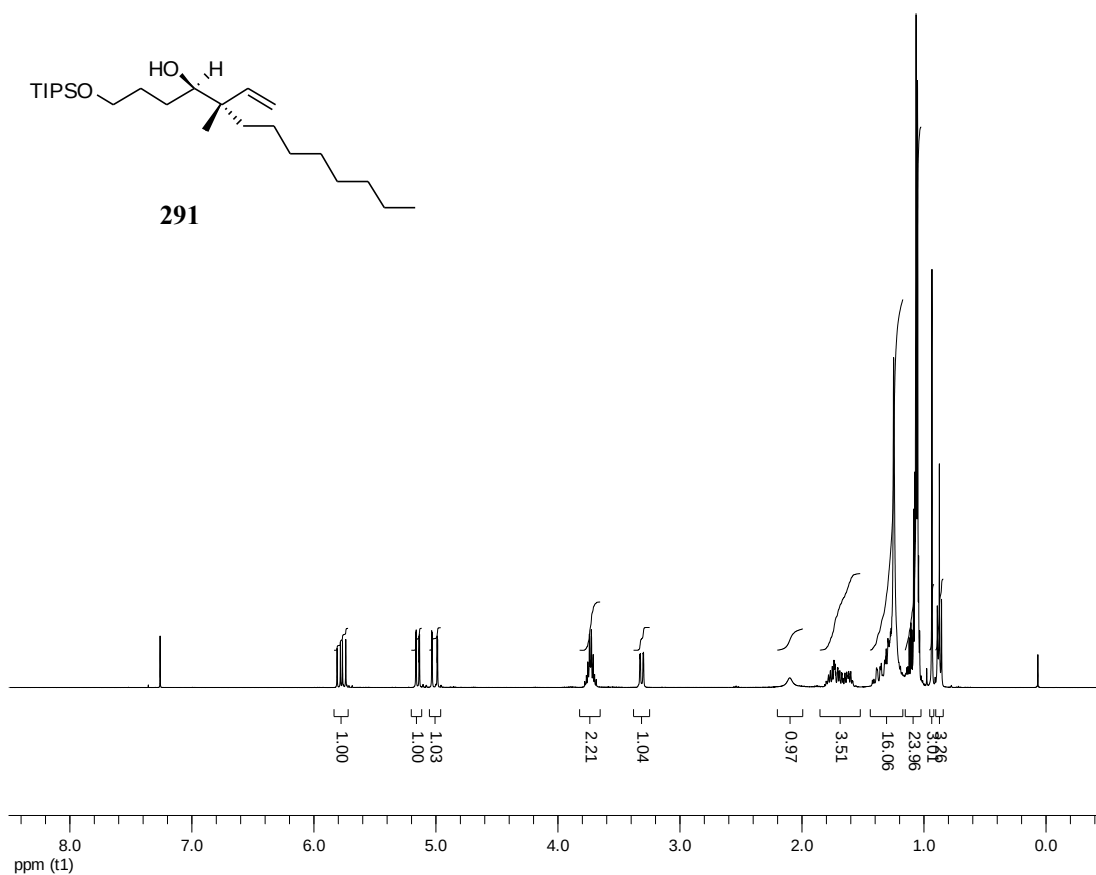
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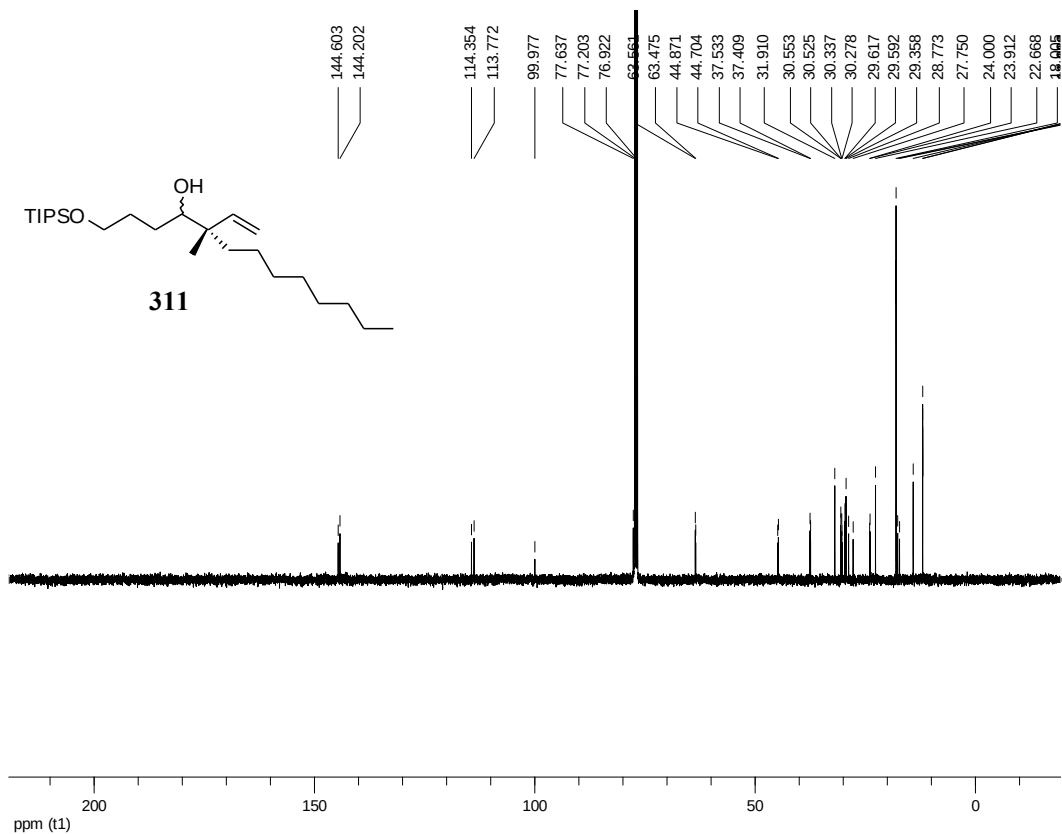
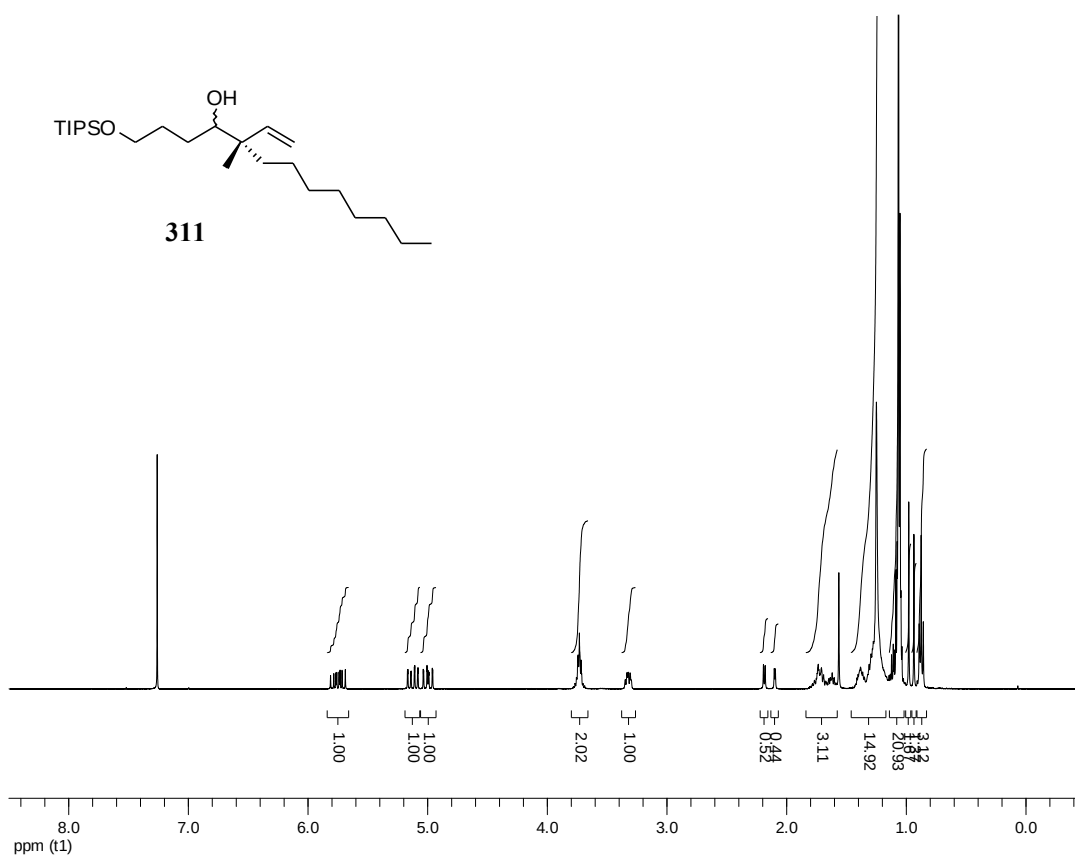


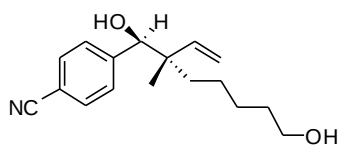












302

