BIFUNCTIONAL ORGANOMETALLIC REAGENTS:
PREPARATION AND USE IN ANNULATION SEQUENCES

by

ALAN MATTHEW KALLER

B. Comm., The University of Saskatchewan, 1988
B. Sc. (Hons.), The University of British Columbia, 1991

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
in
THE FACULTY OF GRADUATE STUDIES
(Department of Chemistry)

We accept this thesis as conforming
to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA
October 1997
© Alan Matthew Kaller, 1997
In presenting this thesis in partial fulfilment of the requirements for an advanced
degree at the University of British Columbia, I agree that the Library shall make it
freely available for reference and study. I further agree that permission for extensive
copying of this thesis for scholarly purposes may be granted by the head of my
department or by his or her representatives. It is understood that copying or
publication of this thesis for financial gain shall not be allowed without my written
permission.

Department of Chemistry

The University of British Columbia
Vancouver, Canada

Date October 6, 1997
ABSTRACT

The use of bifunctional organometallic reagents (182, 35, and 271) to afford novel annulation products, such as the trans-fused bicyclo[3.3.0]octane (236) and bicyclo[4.3.0]nonane (83) systems and highly functionalized cyclopentene (273) systems, was investigated.

The bifunctional reagent 132, was obtained in three steps from the bromo alcohol 134 via the alcohol 133 and the tosylate 158. The novel functionalized allylcopper(I) reagents, 162 and 182, were prepared from the corresponding allylstannanes 132 and 183 by treatment with methyllithium followed by CuBr•Me2S. These allylcopper(I) reagents were shown to add in a 1,4-fashion to a variety of α,β-unsaturated cyclic ketones (30) to provide ketones of general structures 191 and 192.

A general annulation method for the preparation of trans-fused bicyclo[3.3.0]octane and bicyclo[4.3.0]nonane systems from a cyclopentanone system 61 was also developed. A palladium(0) catalyzed methoxycarbonylation of the alkenyl triflate 67, obtained from the keto ketal 61, provided the α,β-unsaturated ester 68, which was converted into the corresponding aldehyde 71. Conjugate addition of the allylcopper(I) reagent 182 or the lower order cyanocuprate 35, to the α,β-unsaturated aldehyde 71, were the key transformations to afford the aldehydes 239 and 80, respectively. Treatment of 239 or 80 with N-iodosuccinimide provided the alkenyl iodides 238 and 99 which underwent CrCl2/NiCl2-mediated cyclizations to provide the trans-fused bicyclo[3.3.0]octane and bicyclo[4.3.0]nonane systems, 237 and 102 & 103, respectively. These alcohols were converted into the corresponding ketones 236 and 83 in three additional steps.

A copper(I) chloride-mediated intramolecular coupling reaction of alkenyltrimethylstannane moieties was used to provide highly substituted cyclopentene systems (273). Addition of 271, generated from 183 by treatment with methyllithium, to β-trimethylstanny1 α,β-unsaturated aldehydes of general structure 275, followed by acetylation of the
resultant alcohols provided 274. An intramolecular copper(I) chloride-mediated coupling of the alkenyltrimethylstannanes of general structure 274 gave the highly functionalized cyclopentenes of general structure 273.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>ii</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>iv</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>xi</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>xiii</td>
</tr>
<tr>
<td>LIST OF GENERAL PROCEDURES</td>
<td>xiv</td>
</tr>
<tr>
<td>LIST OF ABBREVIATIONS</td>
<td>xv</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>xix</td>
</tr>
<tr>
<td>I. INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>1. General</td>
<td>1</td>
</tr>
<tr>
<td>2. Background</td>
<td>4</td>
</tr>
<tr>
<td>3. Proposals</td>
<td>10</td>
</tr>
<tr>
<td>II. DISCUSSION</td>
<td>13</td>
</tr>
<tr>
<td>1. Stereocontrolled Annulation Method for the Synthesis of the Trans-Fused Bicyclo[4.3.0]nonane Ring System</td>
<td>13</td>
</tr>
<tr>
<td>1.1 Background</td>
<td>13</td>
</tr>
<tr>
<td>1.2 Introductory remarks</td>
<td>15</td>
</tr>
<tr>
<td>1.3 Preparation of the cyclopent-1-enecarbaldehyde substrate</td>
<td>16</td>
</tr>
<tr>
<td>1.4 Conjugate addition of the cyanocuprate 35 to the (\alpha,\beta)-unsaturated aldehyde 71</td>
<td>20</td>
</tr>
<tr>
<td>1.5 Attempted anionic ring closure</td>
<td>29</td>
</tr>
<tr>
<td>1.6 Transition metal mediated ring closure</td>
<td>33</td>
</tr>
<tr>
<td>1.7 Conclusions</td>
<td>46</td>
</tr>
</tbody>
</table>
2. Functionalized Allylcopper(I) Reagents

2.1 Background

2.2 Introductory remarks

2.3 Synthetic Plan

2.4 Preparation of 2-(trimethylgermyl)-3-(trimethylstannyl)-propene (132)

2.5 Preparation of 2-(trimethylgermyldiallylcopper(I)-dimethyl sulfide (162) and conjugate additions of 162 to α,β-unsaturated ketones

2.6 A new bifunctional reagent: 2-(Trimethylstannyl)diallylcopper(I)-dimethyl sulfide (182)

2.7 Conclusions

3. Stereocontrolled Annulation Method for the Synthesis of the Trans-Fused Bicyclo[3.3.0]octane Ring System

3.1 Background

3.2 Introductory remarks

3.3 Preparation of cyclization precursor iodo aldehyde 238

3.4 Ring closure: Cyclization of iodo aldehyde 238

3.5 Conclusions

4. Copper(I) Chloride-Mediated Intramolecular Coupling of Bis(Alkenyltrimethylstannanes)

4.1 Background

4.2 Introductory remarks

4.3 Preparation of β-trimethylstannyl α,β-unsaturated aldehydes

4.4 Preparation of 2-(trimethylstannyl)allyllithium (271)

4.5 Reaction of 2-(trimethylstannyl)allyllithium (271) with the aldehydes 276, 277, 282, 287, 291, and 292

4.6 Attempted copper(I) chloride-mediated cyclization of alcohols 302 and 303

4.7 Acetylation of the alcohols 299-304

4.8 Copper(I) chloride-mediated cyclization of the acetates 307-312

4.9 Conclusions
### III. CONCLUSIONS

III. CONCLUSIONS

### IV. EXPERIMENTAL

IV. EXPERIMENTAL

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. General</td>
<td>Data acquisition, presentation and techniques</td>
<td>151</td>
</tr>
<tr>
<td>1.2 Solvents and reagents</td>
<td></td>
<td>154</td>
</tr>
<tr>
<td>2. Trans-Fused Bicyclo[4.3.0]nonane Ring Systems</td>
<td>Preparation of the triflate 67</td>
<td>157</td>
</tr>
<tr>
<td></td>
<td>Preparation of the ester 68</td>
<td>158</td>
</tr>
<tr>
<td></td>
<td>Preparation of the allylic alcohol 70</td>
<td>159</td>
</tr>
<tr>
<td></td>
<td>Preparation of the $\alpha,\beta$-unsaturated aldehyde 71</td>
<td>161</td>
</tr>
<tr>
<td></td>
<td>Preparation of lithium (3-trimethylgermylbut-3-en-1-yl)-(cyano)cuprate (35)</td>
<td>164</td>
</tr>
<tr>
<td></td>
<td>Preparation of the aldehyde 80</td>
<td>164</td>
</tr>
<tr>
<td></td>
<td>Equilibration of the aldehyde 80</td>
<td>166</td>
</tr>
<tr>
<td></td>
<td>Preparation of the alkenyl iodide 99</td>
<td>168</td>
</tr>
<tr>
<td></td>
<td>Preparation of the alcohols 102 and 103</td>
<td>169</td>
</tr>
<tr>
<td></td>
<td>Preparation of the $\alpha$-acetate 104</td>
<td>176</td>
</tr>
<tr>
<td></td>
<td>Preparation of the $\beta$-acetate 105</td>
<td>177</td>
</tr>
<tr>
<td></td>
<td>Preparation of the keto $\alpha$-acetate 106</td>
<td>178</td>
</tr>
<tr>
<td></td>
<td>Preparation of the keto $\beta$-acetate 107</td>
<td>179</td>
</tr>
<tr>
<td></td>
<td>Preparation of the tricyclic ketone 83 from the keto acetate 106</td>
<td>181</td>
</tr>
<tr>
<td></td>
<td>Preparation of the tricyclic ketone 83 from the keto acetate 107</td>
<td>182</td>
</tr>
</tbody>
</table>
3. **Substituted Allylcopper(I) Reagents**

- Preparation of 2-bromoprop-2-enol (134) .................. 183
- Preparation of 2-(trimethylgermyl)prop-2-enol (133) ....... 184
- Preparation of 3-bromo-2-(trimethylgermyl)propene (135) .. 185
- Preparation of 3-p-toluenesulfonyloxy-2-(trimethylgermyl)propene (158) .................................................. 186
- Preparation of trimethyltin hydride (160) ..................... 187
- Preparation of 2-(trimethylgermyl)3-(trimethylstannyl)propene (132) ...................................................... 188
- Preparation of a mixture of 2-(trimethylgermyl)-3-(trimethylstannyl)propene (132) and 2,5-bis(trimethylgermyl)hexa-1,5-diene (148) ............. 189
- Preparation of 2,3-bis(trimethylstannyl)propene (183) ...... 191
- Preparation of 2-(trimethylgermyl)allylcopper(I)-dimethyl sulfide (162) ...................................................... 192

**General Procedure A:** Conjugate addition of 2-(trimethylgermyl)allylcopper(I)-dimethyl sulfide (162) to $\alpha,\beta$-unsaturated ketones .................................................. 192

- Preparation of 3-(2-(trimethylgermyl)allyl)cyclohexanone (163) ................................................................. 193
- Preparation of trans-4-isopropyl-3-(2-(trimethylgermyl)allyl)cyclohexanone (164) ...................................................... 194
- Preparation of 3-methyl-3-(2-(trimethylgermyl)allyl)cyclohexanone (165) ....................................................... 195
- Preparation of 3-(2-(trimethylgermyl)allyl)cyclopentanone (166) ................................................................. 196
- Preparation of 3-methyl-3-(2-(trimethylgermyl)allyl)cyclopentanone (167) ....................................................... 197
- Preparation of a mixture of trans- and cis-2-methyl-3-(2-(trimethylgermyl)allyl)cyclopentanone (168) ............. 198
- Preparation of a mixture of (2R, 3S, 5R)- and (2S, 3S, 5R)-2-methyl-5-isopropenyl-3-(2-(trimethylgermyl)allyl)cyclohexanone (169) ...................................................... 199
- Preparation of 2-(trimethylstannyl)allylcopper(I)-dimethyl sulfide (182) ....................................................... 201

**General Procedure B:** Conjugate addition of 2-(trimethylstannyl)allylcopper(I)-dimethyl sulfide (182) to $\alpha,\beta$-unsaturated ketones and aldehydes .................................................. 201

- Preparation of 3-(2-(trimethylstannyl)allyl)cyclohexanone (184) ................................................................. 202
Preparation of trans-4-isopropyl-3-(2-(trimethylstannyl)allyl)-cyclohexanone (185) ................................................................. 203
Preparation of 3-methyl-3-(2-(trimethylstannyl)allyl)-cyclohexanone (186) ................................................................. 204
Preparation of 3-(2-(trimethylstannyl)allyl)-cyclopentanone (187) ................................................................. 205
Preparation of 3-methyl-3-(2-(trimethylstannyl)allyl)-cyclopentanone (188) ................................................................. 206
Preparation of a mixture of trans- and cis-2-methyl-3-(2-(trimethylstannyl)allyl)cyclopentanone (189) ................................................................. 207
Preparation of a mixture of (2R, 3S, 5R)- and (25, 35, 5/?)-2-methyl-5-isopropenyl-3-(2-(trimethylstannyl)allyl)cyclohexanone (190) ................................................................. 209

4. Trans-Fused Bicyclo[3.3.0]octane Ring Systems ....... 210

Preparation of the aldehyde 239 ................................................................. 210
Preparation of the alkenyl iodides 238 and 241 ................................................................. 211
Epimerization of the aldehyde 241 ................................................................. 213
Preparation of the alcohol 237 ................................................................. 214
Preparation of the allylic acetate 249 ................................................................. 216
Preparation of the keto acetate 250 ................................................................. 217
Preparation of the triquinane keto ketal 236 ................................................................. 219

5. Copper(I) Chloride-Mediated Coupling of Bis(alkenyltrimethylstannanes) ................................................................. 220

Preparation of methyl 2-(trifluoromethanesulfonyloxy)-cyclohept-1-enecarboxylate (283) ................................................................. 220
Preparation of methyl 2-(trimethylstannyl)-cyclohept-1-enecarboxylate (285) ................................................................. 221
Preparation of 2-(trimethylstannyl)-cyclohept-1-enecarbaldehyde (282) ................................................................. 223

General Procedure C: Addition of 2-(trimethylstannyl)-allyllithium (271) to β-(trimethylstannyl) α,β-unsaturated aldehydes ................................................................. 224
Preparation of (Z)-9-chloro-2,6-bis(trimethylstannyl)-nona-1,5-dien-4-ol (299) ................................................................. 225
Preparation of (Z)-10-(tert-butylidimethylsilyloxy)-2,6-bis(trimethylstannyl)deca-1,5-dien-4-ol (300) ................................................................. 226
Preparation of (Z)-11-(tert-butyl(dimethyl)silyl)-2,6-bis(trimethylstannyl)undeca-1,5-dien-10-yn-4-ol (301).

Preparation of 1-(1-hydroxy-3-(trimethylstannyl)-but-3-en-1-yl)-2-(trimethylstannyl)cyclopentene (302).

Preparation of 1-(1-hydroxy-3-(trimethylstannyl)-but-3-en-1-yl)-2-(trimethylstannyl)cyclohexene (303).

Preparation of 1-(1-hydroxy-3-(trimethylstannyl)-but-3-en-1-yl)-2-(trimethylstannyl)cycloheptene (304).

General procedure D: Acylation of allylic alcohols.

Preparation of (Z)-4-acetoxy-9-chloro-2,6-bis(trimethylstannyl)nona-1,5-diene (307).

Preparation of (Z)-4-acetoxy-10-(tert-butyl(dimethyl)silyloxy)-2,6-bis(trimethylstannyl)deca-1,5-diene (308).

Preparation of (Z)-4-acetoxy-11-(tert-butyl(dimethyl)silyl)-2,6-bis(trimethylstannyl)undeca-1,5-dien-10-yn (309).

Preparation of 1-(1-acetoxy-3-(trimethylstannyl)-but-3-en-1-yl)-2-(trimethylstannyl)cyclopentene (310).

Preparation of 1-(1-acetoxy-3-(trimethylstannyl)-but-3-en-1-yl)-2-(trimethylstannyl)cyclohexene (311).

Preparation of 1-(1-acetoxy-3-(trimethylstannyl)-but-3-en-1-yl)-2-(trimethylstannyl)cycloheptene (312).

Preparation of 1-(1-acetoxy-3-(trimethylstannyl)-but-3-en-1-yl)-2-(trimethylstannyl)cycloheptene and 1-(1-acetoxy-3-(trimethylstannyl)-but-3-en-1-yl)-cycloheptene (313).

Alternative procedure for the preparation of 1-(1-acetoxy-3-(trimethylstannyl)-but-3-en-1-yl)-2-(trimethylstannyl)-cycloheptene (312).

General Procedure E: Copper(I) chloride-mediated intramolecular coupling of bis(alkenyltrimethylstannanes).

Preparation of 3-acetoxy-1-(3-chloropropyl)-5-methylenecyclopentene (316).

Preparation of 3-acetoxy-1-(4-(tert-butyl(dimethyl)siloxy)butyl)-5-methylenecyclopentene (317).

Preparation of 3-acetoxy-1-(5-(tert-butyl(dimethyl)silyl)pent-4-yn-1-yl)-5-methylenecyclopentene (318).

Preparation of 2-acetoxy-4-methylenebicyclo[3.3.0]oct-1(5)-ene (319).

Preparation of 7-acetoxy-9-methylenebicyclo[4.3.0]non-1(6)-ene (320).

Preparation of 8-acetoxy-10-methylenebicyclo[5.3.0]dec-1(7)-ene (321).

Alternative procedure for the preparation of 8-acetoxy-10-methylenebicyclo[5.3.0]dec-1(7)-ene (321).
Appendix 1: X-Ray Crystallographic Data ................................. 251

Appendix 2: Additional Experimental Procedures ............... 252

Preparation of (Z)-6-chloro-3-(trimethylstannyl)-hex-2-enal (291) .................................................. 252
Preparation of 1-(tert-butyldimethylsilyl)-hepta-1,6-diyne (297) .................................................. 253
Preparation of ethyl 8-(tert-butyldimethylsilyl)-octa-2,7-diynoate (295) .................................................. 255
Preparation of ethyl (Z) 8-tert-butyldimethylsilyl-3-(trimethylstannyl)oct-2-en-7-yonoate (293) .................................................. 256
Preparation of (Z) 8-tert-butyldimethylsilyl-3-(trimethylstannyl)oct-2-en-7-ynal (292) .................................................. 257

VI. REFERENCES AND FOOTNOTES ................................................. 260
### LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 1</td>
<td>Energy Difference Between Substituted <em>Cis</em>- and <em>Trans</em>-Bicyclo[4.3.0]nonan-2-one Systems</td>
<td>14</td>
</tr>
<tr>
<td>Table 2</td>
<td>Addition of the Cuprate 35 to the $\alpha,\beta$-Unsaturated Aldehyde 71</td>
<td>25</td>
</tr>
<tr>
<td>Table 3</td>
<td>Attempted Anionic Ring Closure Reactions</td>
<td>32</td>
</tr>
<tr>
<td>Table 4</td>
<td>Germanium - Iodine Exchange Reactions</td>
<td>37</td>
</tr>
<tr>
<td>Table 5</td>
<td>Acetylation of the Alcohols 102 and 103</td>
<td>42</td>
</tr>
<tr>
<td>Table 6</td>
<td>Ozonolysis of the Exocyclic Methylene Moiety of 104 and 105</td>
<td>44</td>
</tr>
<tr>
<td>Table 7</td>
<td>Reductive Removal of the Acetoxy Moieties from 106 and 107</td>
<td>45</td>
</tr>
<tr>
<td>Table 8</td>
<td>Nucleophilic Displacement Reactions to Prepare the Bifunctional Reagent 132</td>
<td>68</td>
</tr>
<tr>
<td>Table 9</td>
<td>Conjugate Addition of 162 to $\alpha,\beta$-Unsaturated Ketones</td>
<td>75</td>
</tr>
<tr>
<td>Table 10</td>
<td>Conjugate Addition of 182 to $\alpha,\beta$-Unsaturated Ketones</td>
<td>83</td>
</tr>
<tr>
<td>Table 11</td>
<td>Transition Metal-Mediated Cyclization of Iodo Aldehyde 238</td>
<td>106</td>
</tr>
<tr>
<td>Table 12</td>
<td>Intramolecular Coupling Reactions of the Ester 258</td>
<td>118</td>
</tr>
<tr>
<td>Table 13</td>
<td>Lithiodestannylation of 2,3-Bis(trimethylstannyl)propene (183) and Reaction of the Resultant 2-(Trimethylstannyl)-allyllithium (271) with Electrophiles</td>
<td>131</td>
</tr>
<tr>
<td>Table 14</td>
<td>Synthesis of the Alcohols 299-304</td>
<td>132</td>
</tr>
<tr>
<td>Table 15</td>
<td>Synthesis of the Acetates 307-312</td>
<td>136</td>
</tr>
<tr>
<td>Table 16</td>
<td>Copper(I) Chloride-Mediated Cyclization of 307-312</td>
<td>141</td>
</tr>
<tr>
<td>Table 17</td>
<td>$^1$H nmr (400 MHz, CDCl$_3$) Data for the $\alpha,\beta$-Unsaturated Aldehyde 71: COSY Experiment</td>
<td>162</td>
</tr>
</tbody>
</table>
Table 18 \( ^{13}C\) nmr (125.8 MHz, CDCl\(_3\)) and \(^1H\) nmr (500.2 MHz) Data for the \(\alpha,\beta\)- Unsaturated Aldehyde 71: HMQC Experiment..... 163

Table 19 \(^1H\) nmr (400 MHz, CDCl\(_3\)) Data for the Allylic Alcohol 102: COSY Experiment............................................................. 171

Table 20 \( ^{13}C\) nmr (125.8 MHz, CDCl\(_3\)) and \(^1H\) nmr (500.2 MHz) Data for the Allylic Alcohol 102: HMQC Experiment.............. 172

Table 21 \(^1H\) nmr (400 MHz, CDCl\(_3\)) Data for the Allylic Alcohol 103: COSY Experiment............................................................. 174

Table 22 \( ^{13}C\) nmr (125.8 MHz, CDCl\(_3\)) and \(^1H\) nmr (500.2 MHz) Data for the Allylic Alcohol 103: HMQC Experiment.............. 175
LIST OF FIGURES

Figure 1 Bifunctional Conjunctive Reagents ........................................... 4

Figure 2 cis-Bicyclo[3.3.0]octane-3,7-dione  
mono-2,2-Dimethylpropylene Ketal (61) ........................................... 16

Figure 3 Stereoselective Attack of the Cyanocuprate 35 to the Enal 71...... 27

Figure 4 Stereoview of the β-Acetate 105 .............................................. 43

Figure 5 Products from Addition of the Allylcopper(I)  
Reagent 182 to Enal 71 ................................................................. 97

Figure 6 Stereoview of the Tricyclic Keto Ketal 236 ............................. 110

Figure 7 Catalytic Cycle of the Stille Coupling Reaction ....................... 115
LIST OF GENERAL PROCEDURES

General Procedure A: Conjugate addition of 2-(trimethylgermyl)-allylcopper(I)-dimethyl sulfide (162) to \(\alpha,\beta\)-unsaturated ketones........... 192

General Procedure B: Conjugate addition of 2-(trimethylstannyl)-allylcopper(I)-dimethyl sulfide (182) to \(\alpha,\beta\)-unsaturated ketones and aldehydes.................................................. 201

General Procedure C: Addition of 2-(trimethylstannyl)-allyllithium (271) to \(\beta\)-(trimethylstannyl) \(\alpha,\beta\)-unsaturated aldehydes......... 224

General procedure D: Acylation of allylic alcohols......................... 232

General Procedure E: Copper(I) chloride-mediated intramolecular coupling of bis(alkenyltrimethylstannanes)......................... 242
LIST OF ABBREVIATIONS

Å - angstrom(s)
α - below the plane of a ring OR 1,2-relative position
Ac - acetyl
anal. - analysis
APT - attached proton test
aq. - aqueous
β - above the plane of a ring OR 1,3-relative position
bp - boiling point
br - broad
Bu - butyl
calcd - calculated
COSY - (1H,1H) - homonuclear correlation spectroscopy
Cp - cyclopentadienyl
C-x - carbon number x
d - doublet
δ - chemical shift in parts per million from tetramethylsilane
dba - dibenzylideneacetone
DIBAL-H - diisobutylaluminum hydride
DMAP - 4-dimethylaminopyridine
DME - 1,2-dimethoxyethane
DMF - N,N-dimethylformamide
DMS - dimethyl sulfide
DMSO - dimethyl sulfoxide
ed. - edition
Ed., Eds. - editor, editors
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>equiv</td>
<td>equivalent(s)</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Et₂O</td>
<td>diethyl ether = ether</td>
</tr>
<tr>
<td>FT</td>
<td>Fourier transform</td>
</tr>
<tr>
<td>GLC</td>
<td>gas liquid chromatography</td>
</tr>
<tr>
<td>GLCMS</td>
<td>gas - liquid chromatography - mass spectrometry</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HMBC</td>
<td>heteronuclear multiple bond coherence</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HMQC</td>
<td>heteronuclear multiple quantum coherence</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>H-x</td>
<td>hydrogen number x</td>
</tr>
<tr>
<td>i</td>
<td>iso</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant in Hz</td>
</tr>
<tr>
<td>nJ&lt;sub&gt;Sn-H&lt;/sub&gt;</td>
<td>n bonds coupling for tin and proton nuclei (in Hz; n = 2, 3, or 4)</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>lit.</td>
<td>literature</td>
</tr>
<tr>
<td>LRMS</td>
<td>low resolution mass spectrometry</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>m</td>
<td>meta</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>m-chloroperbenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>min</td>
<td>minutes</td>
</tr>
<tr>
<td>mol.</td>
<td>molecular</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl = -CH₂OCH₃</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>n</td>
<td>normal</td>
</tr>
<tr>
<td>NIS</td>
<td>N-iodosuccinimide</td>
</tr>
<tr>
<td>NMO</td>
<td>N-methylmorpholine N-oxide</td>
</tr>
<tr>
<td>NMP</td>
<td>N-methylpyrrolidinone</td>
</tr>
<tr>
<td>nmr</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>OMe</td>
<td>methoxy</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>pH</td>
<td>-log₁₀[H⁺]</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>py</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>t</td>
<td>tertiary</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>TBSO</td>
<td>tert-butyldimethylsilyloxy</td>
</tr>
<tr>
<td>tert</td>
<td>tertiary</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
</tbody>
</table>
TMS - trimethylsilyl
TMEDA - N,N,N',N'-tetramethylethylenediamine
TPAP - tetrapropylammonium perruthenate
Ts - para-toluenesulfonyl, tosyl
-ve - negative
• - coordination or complex
ACKNOWLEDGMENTS

I would like to thank my research supervisor, Dr. Edward Piers, for his guidance and support during the course of my graduate studies at the University of British Columbia. Thanks to all the members of the Piers group (1991-97: Christine, Phil, Serge, Tim, Patricia, Jimmy, Katherine, Wen-Lung, Miguel, Todd, René, Renata, Krystyna, Shawn, Richard, Ernie, Eva, Debra, Ralph, Pat B., Livain, Chantal, Han, Jim, Tommy, Rob, Michael, Sebastien, Francisco, Anthony, Veljko, Jacques, Johanne, and Keith) for advice, helpful suggestions regarding my research project, and the sharing of equipment and chemicals (purified and dried solvents and reagents). I hope that all those who worked in the A-304 lab with me and endured hours of my mindless babble day in, day out enjoyed their time as much as I did.

Special thanks to Dr. Patricia Gladstone and Dr. Christine Rogers, as well as Dr. Dave McConville, for their help in proof-reading my thesis.

The contributions of the support staff of the nmr, mass spectrometry, and elemental analyses laboratories in the Department of Chemistry are gratefully acknowledged.

Finally, I wish to express my deepest thanks to my parents for their encouragement and support throughout all these years, no matter what half-baked schemes I concocted.
I. INTRODUCTION

1. General

The synthetic organic chemist can be classified as a member of either of two groups. Those in the first group are engaged in the total synthesis of a particular substance from simple, readily available, and generally inexpensive starting materials. The goal of these chemists is the synthetic preparation of a known substance, usually a naturally occurring compound or an analogue thereof, which has some desired biological activity. While the methods used to prepare this natural product are important, they are secondary to obtaining the product itself.

The second group of synthetic organic chemists investigates methods to achieve particular transformations, to determine the scope of particular reaction types, and to control reactivity in order to achieve selectivity in product formation. For these chemists, the goals are the methods, reactions, and procedures developed that afford a particular transformation. The products obtained, although they may be structurally novel and interesting, are of secondary importance to their method of preparation. Generally, it is hoped that these methodological studies will find subsequent use in the total synthesis of naturally occurring substances.

Considerable research effort has been spent developing new methods for the preparation of functionalized ring systems. The term *annulation* is used to describe the process of constructing a ring onto a pre-existing cyclic or acyclic system.\(^1\) The two new carbon-carbon bonds can be formed simultaneously, consecutively in a one-pot process, or separately in two reactions. In principle, the newly formed ring may be of any size, but in the vast majority of cases, five- and six-membered rings are formed. In a broad sense, annulation methods include Diels-Alder reactions, acid-catalyzed olefinic cyclizations,
radical cyclizations, photochemical and thermal cyclizations, and most commonly, alkylation or Michael additions followed by ring closure.

The investigations of new annulation sequences has led to the development of numerous bifunctional conjunctive reagents, which possess two potentially reactive sites and can be incorporated in whole or in part into a more complex system. The reactive sites can be either nucleophilic or electrophilic in nature and have been termed donor (d) or acceptor (a) sites, respectively. These bifunctional reagents must be designed in such a manner to both allow the coexistence of the two reactive sites yet facilitate the selective deployment, either sequentially or simultaneously, of the reactive sites (vide infra).

While a review of bifunctional reagents is beyond the scope of this thesis, the following examples demonstrate the application of these types of reagents in organic synthesis. Some of the pioneering work in the field of bifunctional conjunctive reagents was conducted by Trost nearly two decades ago. The use of 2-acetoxymethyl-3-allyltrimethylsilane (1), as the synthetic equivalent of the a^1,d^3 prop-1-ene synthon (2), in a methylenecyclopentane annulation sequence was demonstrated (Scheme 1). In a one-pot reaction, the bifunctional reagent 1 underwent a palladium(0) catalyzed cycloaddition reaction with electron poor alkenes (such as 3) to provide the methylenecyclopentane product 4.

![Scheme 1](image-url)
A notable contribution from Magnus$^6$ outlined the use of a reagent (5) equivalent to the d$^2$,$a^4$ but-1-ene synthon (6) in the total synthesis of (±)-hirsutene (7) (Scheme 2). In the first step, the donor site of 5 was deployed by converting 5 to the corresponding cuprate via a lithium-halogen exchange and addition of a copper(I) salt. Addition of the bicyclic enone 8 to a solution of this cuprate provided the 1,4-addition adduct 9. Conversion of silyl ether moiety to the better leaving group (para-toluenesulfonate ester) gave 10. An intramolecular alkylation provided the tricyclic system 11 which was subsequently converted to the natural product 7.

Scheme 2
2. Background

The discovery of new methods for the construction of usefully functionalized five- and six-membered rings has been a primary research objective of the Piers group. These annulation methods have been effected through the use of novel bifunctional reagents (12-16) containing both nucleophilic (donor) and electrophilic (acceptor) sites (Figure 1).

Annulation of cyclic ketone systems 19 has been effected by first deploying the acceptor sites of 13 or 15 via alkylation of the dimethylhydrazone derivative of 19, followed by hydrolysis of the hydrazone function. Iododestannylation of 20 or 21 provided the alkenyl iodide 22 or 23 (Scheme 3). A lithium-halogen exchange unmasks the latent donor activity of the alkenyl site. The resultant alkenyllithium species 24 or 25 attacks the carbonyl function resulting in ring closure to give the bicyclic product 26 or 27 with an exocyclic methylene moiety adjacent to an angular hydroxyl group. In this manner, a methylenecyclopentane annulation sequence is achieved using 13 as the synthetic equivalent of the \( d^2,a^4 \) but-1-ene synthon 6, while a methylenecyclohexane annulation
sequence is achieved using 15 as the synthetic equivalent of the \( \text{d}^2,\text{a}^5 \) pent-1-ene synthon 17.\(^7\)

![Chemical structure and reaction scheme]

With \( \alpha,\beta \)-unsaturated ketones as substrates, alternative methylenecycloalkane annulation sequences can be employed. The bifunctional conjunctive reagents 12 and 14 (equations 1 and 2) serve as the synthetic equivalents of the \( \text{d}^2,\text{a}^4 \) but-1-ene synthon 6 and the \( \text{d}^2,\text{a}^5 \) pent-1-ene synthon 17, respectively. The donor activity of these reagents is utilized first by transmetalation with methylolithium.
Addition of copper(I) cyanide to the lithio derivative obtained in situ from 12 provides an organocuprate reagent 28 (equation 1), which adds in a conjugate sense to cyclic enone systems (30) to provide 31 (Scheme 4). Alternatively, 14 is converted to the Grignard reagent 29 (equation 2), which can also be added in a conjugate sense to cyclic enones (30) in the presence of catalytic copper(I) to provide 32. The acceptor sites are then deployed in a subsequent intramolecular alkylation to generate the methylenecyclopentane annulated product 33 and the methylenecyclohexane annulated product 34 (Scheme 4).

A methylenecyclopentane annulation sequence, regiochemically complementary to that illustrated in Scheme 4, has also been developed using the bifunctional conjunctive reagent 16 as the synthetic equivalent of the a²,d⁴ but-1-ene synthon 18 (Scheme 5). By converting reagent 16 to the organocopper(I) species 35 (equation 3), the donor site of the bifunctional reagent can be utilized in a conjugate addition to an enone (30) to provide the 1,4-addition adduct 36 (Scheme 5). The carbon-germanium bond is stronger than the carbon-tin bond, causing the alkenyltrimethylgermyl function in 16 to be more resistant to transmetalation with an alkylithium than is the corresponding alkenyltrimethylstanny moiety. Lithium-halogen exchange can be performed chemoselectively on the iodide substituent at carbon-4 of 16 without affecting the trimethylgermyl moiety.
Unmasking of the acceptor site of the bifunctional reagent 16 is achieved by converting the alkenyltrimethylgermane adduct 36 to the corresponding alkenyl iodide 37. A palladium(0) catalyzed intramolecular coupling reaction between an enolate carbon (donor) and the alkenyl iodide (acceptor) generates the regiochemically opposite methylenecyclopentane ring 38\textsuperscript{11} (Scheme 5), compared with 33 (Scheme 4).

The synthetic utility of the annulation sequences outlined in Schemes 4 and 5, employing bifunctional organometallic reagents 12, 14, and 16, has been verified by their application in the total syntheses of several natural products including: (±)-pentalenene,\textsuperscript{12} (±)-Δ\textsuperscript{9(12)}-capnellene,\textsuperscript{8} (±)-axamide-1,\textsuperscript{9} (±)-axisonitrile-1,\textsuperscript{9} (±)-palauolide,\textsuperscript{13} and (±)-crinipellin B.\textsuperscript{14}
The alkenyltrimethylgermane bifunctional reagent 16 has also been employed in a methylenecyclohexane annihilation sequence to provide products similar to 27, described in Scheme 3. In this annihilation method, the organocopper(I) reagent 35, prepared from the bifunctional conjunctive reagent 16, is used as the synthetic equivalent of the \( \text{d}^2,\text{d}^4 \) but-1-ene synthon 39.

\[
\begin{align*}
\text{GeMe}_3 & \quad \equiv \quad \text{d} \quad \text{d} \quad \equiv \quad \text{GeMe}_3 \quad \text{Cu(CN)Li}
\end{align*}
\]

This sequence was employed in the total synthesis of (±)-ambliol B (40) (Scheme 6). A conjugate addition of the organocopper(I) reagent 35, obtained from 16 (equation 3), to the enone 41 deploys the donor site at carbon-4 of 35 to provide the addition adduct 42. The latent donor activity of the alkenyltrimethylgermane is unmasked by an iododegermylation reaction followed by lithium-halogen exchange. The resultant
alkenylithium species attacks the carbonyl carbon in an intramolecular fashion resulting in ring closure to provide the bicyclic product 43. Further synthetic transformations on this compound leads to the synthesis of the target compound (40) (Scheme 6).
3. Proposals

Previous work in the Piers lab has shown the utility of bifunctional organometallic reagents in a variety of annulation sequences to provide bicyclo[x.y.0]alkane (x, y = 4; x = 4, y = 3; x, y = 3) ring systems. In most cases, the annulation sequences provided either exclusively or predominately the cis-fused products. Only when the ring junction contained an epimerizable center and at least one of the rings was a cyclohexyl moiety could the trans-fused product be obtained. Thus the trans-fused bicyclo[4.3.0]nonane system could be prepared via epimerization of the cis-fused isomer, but the trans-fused bicyclo[3.3.0]octane ring system was inaccessible using the established annulation protocols.

A potentially important extension to the aforementioned annulation methods is the development of a general method for the stereocontrolled synthesis of trans-fused bicyclo[4.3.0]nonane and trans-fused bicyclo[3.3.0]octane systems. The use of 16 as the synthetic equivalent of the d2,d4 but-l-ene synthon (39) in the total synthesis of (±)-ambliol B (40) provided the trans-fused bicyclo[4.4.0]decane ring system 43 (vide supra, Scheme 6). It was proposed that if a cyclopent-l-enecarbaldehyde substrate 44 (Scheme 7) was employed as the a1,a3 propane synthon, it could be combined with the organocopper(I) reagent 35, here employed as the synthetic equivalent of the d2,d4 but-l-ene synthon (39), to provide 45 and ultimately the trans-fused bicyclo[4.3.0]nonane ring system 46 (Scheme 7). Thus, extension of synthetic utility of the bifunctional reagent 16 would be demonstrated. In order to ensure formation of the trans ring junction, the last bond to be formed would not be to a ring fusion atom, and thus the stereochemistry of the ring junction would be established prior to the ring closure step.
Provided that the trans-fused bicyclo[4.3.0]nonane ring system could be constructed stereoselectively, it was envisaged that a similar approach could be utilized to form the trans-fused bicyclo[3.3.0]octane ring system 47 (Scheme 8). In this case, the synthesis of a reagent equivalent the to d^2,d^3 prop-1-ene synthon 48 that could be delivered to the β-position of α,β-unsaturated carbonyl compounds would be required. It was thought that the organocopper(I) reagent 49, perhaps the one carbon lower homologue of 35, could function as the d^2,d^3 prop-1-ene synthon 48. Thus, if the organocopper(I) reagent 49 could be added stereoselectively to 44, it would provide 50. Cyclization of 50 would ultimately generate the trans-fused bicyclo[3.3.0]octane ring system 47.
In summary, the development of the annulation methods to prepare stereoselectively trans-fused bicyclo[\(x.3.0\)]alkane (\(x = 3\) or 4) rings using bifunctional organometallic reagents containing two donor sites was the primary goal of this work. If a reagent equivalent to the \(d^2,d^3\) prop-1-ene synthon 48 could be prepared, its utility in other synthetic applications would also be probed.
II. DISCUSSION

1. Stereocontrolled Annulation Method for the Synthesis of the Trans-Fused Bicyclo[4.3.0]nonane Ring System

1.1 Background

Both the trans-fused (51) and cis-fused (52) bicyclo[4.3.0]nonane ring systems are common structural units in many naturally occurring compounds\(^{17}\) including vitamin D derivatives\(^{18}\) and steroids.\(^{19}\) While a plethora of methods have been developed to prepare these ring systems,\(^{20}\) the stereoselective formation of either the cis-fused or trans-fused rings has been problematic,\(^{21}\) especially when they are substituted in any manner.

An examination of the parent hydrocarbons shows that the strain energy of the trans-fused isomer 51 is only 1.0 kcal/mol lower than that of the cis-fused isomer 52.\(^{22}\) Because of the small energy difference between the two isomers, substitution or functionalization at any position of the bicyclo[4.3.0]nonane system can dramatically affect the relative thermodynamic stabilities.\(^{23}\) This point is illustrated by the data summarized in Table 1 pertaining to bicyclo[4.3.0]nonan-2-ones.
Table 1  Energy Difference Between Substituted Cis- and Trans-Bicyclo[4.3.0]-nonan-2-one Systems

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Rα</th>
<th>Rβ</th>
<th>% trans 53</th>
<th>% cis 54</th>
<th>% cis 55</th>
<th>Energy Difference (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>24</td>
<td>76</td>
<td>-</td>
<td>0.7</td>
</tr>
<tr>
<td>2</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>8</td>
<td>92</td>
<td>-</td>
<td>1.4</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>CH₃</td>
<td>H</td>
<td>94</td>
<td>-</td>
<td>6</td>
<td>1.6</td>
</tr>
<tr>
<td>4</td>
<td>CH₃</td>
<td>CH₃</td>
<td>H</td>
<td>69</td>
<td>-</td>
<td>31</td>
<td>0.4</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>0</td>
<td>100</td>
<td>-</td>
<td>&gt;4.5</td>
</tr>
<tr>
<td>6</td>
<td>CH₃</td>
<td>H</td>
<td>CH₃</td>
<td>0</td>
<td>100</td>
<td>-</td>
<td>&gt;4.5</td>
</tr>
</tbody>
</table>

a The conformational equilibria were determined by ¹H and ¹³C nmr spectroscopy.

With the substituted hydrindanone systems shown in Table 1, the trans-fused system exists in a rigid conformation (53), while the cis-isomer can exist in two interconvertible conformers (54 and 55) with the six-membered ring in the chair form. In contrast with nonfunctionalized bicyclo[4.3.0]nonanes, where the trans-fused system is more stable than the cis-fused (cf. 51 and 52), the cis-fused isomer of the substituted bicyclo[4.3.0]nonanone system (54 or 55) is actually more stable than the trans-fused isomer (53) (Table 1, entries 1, 2, 5, and 6) except when Rα = CH₃ (Table 1, entries 3 and 4). Unfavorable steric and 1,3-syn-axial interactions were used to explain these relative stabilities.

The stereoselective formation of the trans-fused bicyclo[4.3.0]nonane ring system is further complicated by the preferential formation of the cis-fused product when cyclizations are conducted in which the last bond formed is a bond to a ring fusion atom. In most cases, such as intramolecular radical cyclizations or intramolecular alkylations.
the kinetic product has the cis-ring junction. Thus, to stereoselectively form the trans-fused bicyclo[4.3.0]nonane ring system, the final bond formed must not be to a ring fusion atom.26

1.2 Introductory remarks

The initial goal of our studies was the development of a general method for the preparation of the trans-fused bicyclo[4.3.0]nonane ring system using the bifunctional reagent 35. We had envisaged that any cyclopentanone system (56) could function as the starting material for this novel annulation procedure. In order to ensure a trans-fused ring junction, it was decided that the stereochemistry of the ring substituents (57) would be fixed as trans early in the sequence. A retrosynthesis of the proposed annulation sequence is shown in Scheme 9.
It was proposed that the trans-fused bicyclo[4.3.0]nonane ring system 58 could be obtained from 59 by the intramolecular nucleophilic displacement of a suitable leaving group X by the alkenyllithium function. Oxidative cleavage of the resultant exocyclic methylene moiety would provide 58. Compound 59, could in turn be prepared from 57 by a series of functional group interconversions. A stereoselective 1,4-addition of the cyanocuprate 35 to the α,β-unsaturated aldehyde 44 should provide 57. The cyclopent-1-enecarbaldehyde 44 could be obtained via reduction of the corresponding methyl ester 60. A palladium(0) catalyzed carbonylation of the alkenyl triflate derived from the cyclopentanone species 56, in the presence of methanol, should provide the ester 60.

1.3 Preparation of the cyclopent-1-enecarbaldehyde substrate

Although in theory any cyclopentanone system could have been used as the starting material for the proposed annulation method, cis-bicyclo[3.3.0]octane-3,7-dione mono-2,2-dimethylpropylene ketal (61) was chosen (Figure 2).

Figure 2 cis-Bicyclo[3.3.0]octane-3,7-dione mono-2,2-Dimethylpropylene Ketal (61)

This keto ketal 61 was prepared previously in our laboratories, and is a nonvolatile, stable crystalline material (mp 48 °C) with characteristic nmr and IR signals due to its ketal function (Figure 2). The resonances in the $^1$H nmr spectrum due to the ketal function generally appear as two 3-proton singlets between δ 0.90 and δ 1.00 (for the methyl
groups), and a 4-proton multiplet between $\delta$ 3.34 and $\delta$ 3.53 (for the methylene groups). The ketal moiety also shows distinctive signals in the $^{13}$C nmr spectra: two signals for the methylene carbons at $\sim\delta$ 72, a signal for the quaternary carbon at $\sim\delta$ 30, and two signals for the methyl carbons at $\sim\delta$ 22. A strong C-O-C stretching absorption at $\sim$1110 cm$^{-1}$ is evident in the IR spectrum of compounds containing the 2,2-dimethylpropylene ketal moiety.

![Chemical structure](image)

**Scheme 10**

Even though cis-bicyclo[3.3.0]octane-3,7-dione (62) is commercially available, it is prepared easily and inexpensively by a base-mediated Weiss-Cook condensation using glyoxal (63) and dimethyl 1,3-acetonedicarboxylate (64), followed by an acid-catalyzed hydrolysis and decarboxylation of the tetraester intermediate (65) (Scheme 10). Protection of one of the carbonyl functions of the dione 62 was accomplished under Dean-Stark conditions by treatment with 2,2-dimethylpropanediol (66) and a catalytic amount of acid. The keto ketal 61 was isolated after chromatographic separation of it from the
The method of Scott and McMurry\textsuperscript{27a} was used to convert the keto ketal 61 into the known alkenyl triflate 67.\textsuperscript{30} Thus, deprotonation of 61 with LDA, followed by treatment with \(N\)-phenyltrifluoromethanesulfonimide, provided the alkenyl triflate 67 in 90\% yield (Scheme 11).

The \(\alpha,\beta\)-unsaturated ester 68 was prepared, in 88\% yield, by a palladium(0) catalyzed carbonylation of 67 with carbon monoxide in the presence of methanol\textsuperscript{31} (Scheme 11). The IR spectrum of 68 exhibited a strong \(\text{C} = \text{O}\) stretching absorption at 1717 \(\text{cm}^{-1}\) and a weak \(\text{C} = \text{C}\) stretching absorption at 1633 \(\text{cm}^{-1}\), both consistent with an \(\alpha,\beta\)-unsaturated ester moiety. The \(^1\text{H}\) nmr spectrum displayed a 3-proton singlet at \(\delta 3.70\), indicating the presence of a methyl ester, and a 1-proton signal for the olefinic proton at \(\delta 6.61\) (dd, \(J = 2, 2\) Hz). The characteristic signals for the 2,2-dimethyl-
propylene ketal, two 3-proton singlets at δ 0.92 and δ 0.94 and a 4-proton multiplet centered at δ 3.44, were also observed in the 1H nmr spectrum of 68.

While it had initially been hoped that the α,β-unsaturated ester 68 would be a suitable Michael acceptor for the cyanocuprate 35, preliminary studies showed that the organocuprate 35 did not undergo 1,4-addition to 68\textsuperscript{32} (Scheme 12). Therefore, we proceeded with the preparation of the aldehyde 71 from the ester 68 by a straightforward reduction - oxidation sequence.

Reduction of the ester 68 in THF with 2.5 equivalents of DIBAL-H\textsuperscript{33} afforded, after appropriate workup and chromatography, the allylic alcohol 70 in 95% yield. Attempts to reduce the ester 68 directly to the aldehyde 71 using 1.0 equivalents of DIBAL-H in THF provided a mixture of the alcohol 70 and recovered ester 68. The IR spectrum of the alcohol 70 exhibited a strong O-H stretching absorption at 3429 cm\textsuperscript{-1}, a weak C=C stretching absorption at 1657 cm\textsuperscript{-1}, and a strong C-O-C stretching absorption at
The $^1$H nmr spectrum of 70 showed the expected signals for the 2,2-dimethylpropylene ketal (two 3-protons singlets at $\delta$ 0.93 and $\delta$ 0.94 and a 4-proton multiplet centered at $\delta$ 3.45), a hydroxyl proton (a broad 1-proton signal at $\delta$ 1.34, which exchanges with D$_2$O), two hydroxymethyl protons (a broad 2-proton signal at $\delta$ 4.12), and an olefinic proton (a broad 1-proton doublet at $\delta$ 5.50).

Oxidation of 70 with pyridinium chlorochromate$^{34}$ in methylene chloride provided, after a non-aqueous workup and chromatography, the cyclopent-l-enecarbaldehyde 71 in 86% yield. The IR spectrum of 71 exhibited the expected signals for an $\alpha,\beta$-unsaturated aldehyde, a strong C=O stretching absorption at 1681 cm$^{-1}$ and a weak C=C stretching absorption at 1617 cm$^{-1}$. The $^1$H nmr spectrum displayed a 1-proton singlet at $\delta$ 9.75 attributed to the aldehyde function and a 1-proton doublet of doublets ($J = 2.5, 2$ Hz) at $\delta$ 6.69 due to the olefinic proton. Characteristic signals for the 2,2-dimethylpropylene ketal were seen in both the $^1$H nmr and IR spectra of 71. The $^{13}$C nmr spectrum of 71 contained all of the expected 14 signals. Complete assignment of the signals in the $^1$H nmr and $^{13}$C nmr spectra of the $\alpha,\beta$-unsaturated aldehyde 71 was achieved through use of two-dimensional nmr spectroscopy, both COSY and HMQC spectra (Tables 17 and 18, experimental section).

1.4 Conjugate addition of the cyanocuprate 35 to the $\alpha,\beta$-unsaturated aldehyde 71

With the $\alpha,\beta$-unsaturated aldehyde 71 in hand, we set out to investigate its reactivity in the conjugate addition reaction with the well known lower order cyanocuprate 35.$^{11}$ The bifunctional reagent 16, the precursor of the cuprate 35, was prepared by two different methods.

\[
\begin{align*}
\text{SnMe}_3 & \rightarrow \text{MeLi}, \text{THF, -78 °C} \\
& \rightarrow \text{Me}_3\text{GeBr} \\
& \rightarrow \text{Nal, acetone reflux} \\
\text{12} & \rightarrow \text{GeMe}_3 \\
\end{align*}
\]
The original preparation\textsuperscript{15} involved the use of 4-chloro-2-(trimethylstannyl)-but-1-ene (12) as the starting material (equation 4). Treatment of 12 in THF with a solution of methyllithium results in a transmetalation to provide an alkenyllithium species, which can be trapped with trimethylgermanium bromide to afford 4-chloro-2-trimethylgermylbut-1-ene. This volatile alkenyltrimethylgermane was immediately converted to the iodide 16 using Finkelstein conditions. Although this sequence is not experimentally complex, it does require the prior preparation of 12, a somewhat laborious and tedious procedure\textsuperscript{8} (equation 5). In addition, the relatively expensive trimethyltin moiety is wasted in this process.

\begin{align*}
\text{Me}_3\text{SnCu} & \xrightarrow{\text{Me}_2\text{S}, \text{THF}, -78 \, ^\circ\text{C}} \text{MeOH, -78 \, ^\circ\text{C}} \\
& \xrightarrow{\text{NH}_4\text{Cl} - \text{NH}_4\text{OH}, \text{H}_2\text{O} (\text{pH} \, 8)} \text{silica gel chromatography} \\
& \xrightarrow{\text{Ph}_3\text{P}, \text{Et}_3\text{N}, \text{CCl}_4, \text{reflux}} \text{SnMe}_3 (5)
\end{align*}

An alternative and more cost and time effective procedure for the preparation of 16 was developed recently by Piers and Lemieux\textsuperscript{35} (equation 6).

\begin{align*}
\text{MeLi, THF, -78 \, ^\circ\text{C}} \\
& \xrightarrow{\text{TMSCl, -78 \, ^\circ\text{C}} \rightarrow 0 \, ^\circ\text{C}} \\
& \xrightarrow{\text{Me}_3\text{GeH}, \text{H}_2\text{PtCl}_6 \cdot \text{xH}_2\text{O, CH}_2\text{Cl}_2, 0 \, ^\circ\text{C} \rightarrow \text{rt}} \\
& \xrightarrow{\text{p-TsOH} \cdot \text{H}_2\text{O, CH}_2\text{Cl}_2, 30 \, ^\circ\text{C}} \text{Ph}_3\text{P} \cdot \text{I}_2, \text{imidazole, Et}_2\text{O} : \text{CH}_3\text{CN (3:1), rt}} \text{GeMe}_3 (6)
\end{align*}

A palladium catalyzed hydrogermylation of 4-trimethylsilyloxy-1-trimethylsilylbut-1-ene (obtained from 72), followed by a protodesilylation reaction under acid conditions, were the key steps in the preparation of 3-trimethylgermylbut-3-en-1-ol. The resultant alcohol was converted to the iodide 16 under mild conditions.\textsuperscript{36,37}
Preparation of the cyanocuprate $35^{11,37}$ was achieved by the treatment of a solution of $16$ in cold (-98°C) THF with two equivalents of tert-butyllithium (73), followed by addition of one equivalent of copper(I) cyanide and brief warming to -35 °C, to give a homogeneous tan solution of the required reagent $35$ (equation 7).

$$16 + 73 \rightarrow 78 + 74$$

$$16 + 78 \rightarrow 79$$

$$73 + 74 \rightarrow 75 + 76 + 77$$

Scheme 13

It was necessary to use two equivalents of tert-butyllithium to ensure success of the lithium - iodine exchange reaction (Scheme 13). Reaction of tert-butyllithium (73) with tert-butyl iodide (74), formed from the metal - halogen exchange with $16$, is competitive with the initial lithium - iodine exchange process (path A), giving 2-methylpropane (75), 2-methylpropene (76), and lithium iodide (77) (path C).$^{38}$ If less than two equivalents of
tert-butyllithium are used, the iodide 16 and the alkyllithium species 78 (produced from 16 by the metal-halogen exchange) are present together in solution and will react to form the coupled product 79 (path B). Furthermore, if tert-butyllithium is added slowly to 16, then both 16 and 78 are present together in solution for sufficient time that the coupling reaction (path B) predominates. It was also found that, at temperatures higher than -95 °C, the coupling process indicated (16 + 78 → 79) becomes the predominate reaction (path B). Thus, to minimize formation of the coupled product 79 and to ensure complete formation of 78, two equivalents of tert-butyllithium must be added rapidly, in one portion, to the cold (-98 °C) reaction mixture.

Previous studies\textsuperscript{11,37} have shown that the 1,4-addition of the cyanocuprate 35 to cold solutions of α,β-unsaturated ketones (30) in THF proceed smoothly in the presence of trimethylsilyl bromide\textsuperscript{39} (equation 8). Reaction times are typically on the order of 4 - 8 hours. The resultant silyl enol ether is generally hydrolyzed with water prior to workup with aqueous NH\textsubscript{4}Cl-NH\textsubscript{4}OH (pH 8) to provide the 1,4-addition adduct 36. When these conditions were applied with the α,β-unsaturated aldehyde 71 (Scheme 14), the desired 1,4-addition product 80 was obtained in low yield (35%), along with recovered 71 (22%), and an unidentified byproduct (Table 2, entry 1). Utilizing essentially the same reaction conditions, but with the addition of two equivalents of HMPA,\textsuperscript{40,41} the 1,4-addition product 80 was obtained in yields as high as 80% (Table 2, entries 2-4). In all cases, 80
was isolated as a 3:1 mixture of epimeric aldehydes. However, these yields were variable and were not reproducible (Table 2, entries 1-4).

Scheme 14
Table 2 Addition of the Cuprate 35 to the α,β-Unsaturated Aldehyde 71 (Scheme 14)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Time&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Silyl Enol Ether Hydrolysis and Reaction Workup Conditions&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Isolated Yield of 80 (%&lt;sup&gt;f&lt;/sup&gt;)</th>
<th>Other Products Isolated (% yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.0 h&lt;sup&gt;c&lt;/sup&gt;</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O&lt;sup&gt;d&lt;/sup&gt; (1 h), Ae (overnight)</td>
<td>35 (45)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>71 (22)</td>
</tr>
<tr>
<td>2</td>
<td>60 min</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O&lt;sup&gt;d&lt;/sup&gt; (2 h), Ae (2 h)</td>
<td>80 (92)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>71 (13)</td>
</tr>
<tr>
<td>3</td>
<td>30 min</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O&lt;sup&gt;d&lt;/sup&gt; (1 h), Ae (2 h)</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>30 min</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;O&lt;sup&gt;d&lt;/sup&gt; (30 min), Ae (3 h)</td>
<td>38</td>
<td>??g</td>
</tr>
<tr>
<td>5</td>
<td>2.0 h</td>
<td>Ae (4 h), TBAF&lt;sup&gt;h&lt;/sup&gt; (1 min)</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>20 min</td>
<td>Ae (2 h), TBAF&lt;sup&gt;h&lt;/sup&gt; (15 min)</td>
<td>46</td>
<td>82 (49)</td>
</tr>
<tr>
<td>7</td>
<td>2.5 h</td>
<td>Ae (2 h), TBAF&lt;sup&gt;h&lt;/sup&gt; (2 min)</td>
<td>0</td>
<td>71 (40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>82 (57)</td>
</tr>
<tr>
<td>8</td>
<td>30 min</td>
<td>Ae (2 h), MeLi&lt;sup&gt;i&lt;/sup&gt; (15 min)</td>
<td>65 (89)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>71 (27)</td>
</tr>
<tr>
<td>9</td>
<td>30 min</td>
<td>Ae (3 h), MeLi&lt;sup&gt;i&lt;/sup&gt; (10 min)</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>15 min&lt;sup&gt;k&lt;/sup&gt;</td>
<td>Ae (3 h), MeLi&lt;sup&gt;i&lt;/sup&gt; (10 min)</td>
<td>66 (84)&lt;sup&gt;j&lt;/sup&gt;</td>
<td>81 (18)</td>
</tr>
<tr>
<td>11</td>
<td>15 min&lt;sup&gt;k&lt;/sup&gt;</td>
<td>Ae (3 h), MeLi&lt;sup&gt;i&lt;/sup&gt; (30 min)</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>15 min&lt;sup&gt;k&lt;/sup&gt;</td>
<td>Ae (3 h), MeLi&lt;sup&gt;i&lt;/sup&gt; (10 min)</td>
<td>84 (95)&lt;sup&gt;j&lt;/sup&gt;</td>
<td>81 (11)</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions were performed by the sequential addition of 3 - 4 equiv Me<sub>3</sub>SiBr, ~2 equiv HMPA, and 71 to a solution of 1.6 - 2.0 equiv 35 unless otherwise noted.

<sup>b</sup> The method of hydrolysis of the silyl enol ether and reaction workup are listed in the order of performance. The time for each step is given in parenthesis. In entries 1-4, the silyl enol ether was hydrolyzed prior to workup while in entries 5-12, the reaction mixture was worked up to provide the crude silyl enol ether, which was subjected to a non-aqueous cleavage.

<sup>c</sup> Reaction run without the addition of HMPA.

<sup>d</sup> Reaction mixture quenched with water, then warmed to room temperature and stirred open to the air for the indicated time.

<sup>e</sup> A = Reaction mixture poured into a vigorously stirred solution of aqueous NH<sub>4</sub>Cl-NH<sub>4</sub>OH (pH 8) and stirred open to the air for the indicated time upon which the aqueous layer turned bright blue.

<sup>f</sup> Yield based on recovered starting material.

<sup>g</sup> A spectroscopic analysis of this unidentified byproduct indicated the presence of the following functional groups: 2,2-dimethylpropylene ketal, alkenyltrimethylgermane, and a carbonyl group (1737 cm<sup>-1</sup>).

<sup>h</sup> The crude silyl enol ether 81 was isolated, dissolved in THF and treated with TBAF for the indicated time prior to an aqueous quench.

<sup>i</sup> The crude silyl enol ether 81 was isolated, dissolved in THF, cooled to -78 °C, and treated with a solution of MeLi (in Et<sub>2</sub>O) for the indicated time prior to an aqueous quench.

<sup>j</sup> Total yield of 1,4-addition products (80 + 81).

<sup>k</sup> HMPA added after the addition of 71.
The hydrolysis of the silyl enol ether with water prior to aqueous workup with aqueous NH₄Cl-NH₄OH (pH 8) was believed to be the problematic step. It has been reported⁴²,⁴³ that improved yields of the 1,4-addition product often result if the product aldehyde is isolated by way of the corresponding silyl enol ether rather than by direct hydrolysis of the reaction mixture.⁴⁴ Thus, it was decided to isolate the silyl enol ether and subject it to non-aqueous cleavage conditions. When trimethylsilyl bromide, HMPA, and the α,β-unsaturated aldehyde 71 were added to a cold solution of 35 in THF, after only 15 minutes a TLC analysis showed complete consumption of 71. The reaction mixture was poured into a vigorously stirred solution of aqueous NH₄Cl-NH₄OH (pH 8), and after workup and chromatography, a sample of pure 81 was isolated. The IR spectrum of 81 exhibited a C-O-C stretching absorption at 1113 cm⁻¹, attributed to the ketal, and a germanium - methyl rocking absorption at 841 cm⁻¹. The ¹H nmr spectrum of 81 displayed two 9-proton singlets at δ 0.07 and δ 0.18, indicative of the Me₃Si and Me₃Ge groups, respectively, a 6-proton singlet at δ 0.93 and two 2-proton singlets at δ 3.41 and δ 3.47, characteristic of the 2,2-dimethylpropylene ketal moiety, and three alkenyl protons positioned at δ 5.14, δ 5.38, and δ 5.48. The ¹³C nmr spectrum of 81 contained all the expected signals. In addition to this spectral data, the molecular formula of 81 was confirmed as C₂₂H₄₄GeO₃Si by a high resolution mass spectrometric measurement on the molecular ion.

Use of TBAF⁴⁵ in THF to cleave the silyl enol ether in 81 resulted in low yields of 80 (isolated as a 3:1 mixture of epimeric aldehydes), as well as the formation of significant amounts of the acetal 82 (Table 2, entries 5-7). It seemed likely that the ketal hydrolysis and the concomitant acetal formation was catalyzed by the Lewis acidic trimethylsilyl fluoride. Aldehydes can be protected as acetals chemoselectively in the presence of ketones,⁴⁶ while ketals are generally much more easily hydrolyzed than acetals.⁴⁷ Evidence for the formation of the acetal was obtained by ¹H nmr spectroscopy. The ¹H nmr spectrum of 82 contained a 1-proton doublet (J = 7 Hz) at δ 4.11, characteristic of
an acetal proton, as well as the expected signals for the 2,2-dimethylpropylene acetal, two 3-proton singlets at $\delta$ 0.93 and $\delta$ 0.96 and a 4-proton singlet at $\delta$ 3.47. Also observed in the $^1$H nmr spectrum were signals for two alkenyl protons, at $\delta$ 5.50 and $\delta$ 5.17, and the Me$_3$Ge moiety at $\delta$ 0.19.

Treatment of a solution of the silyl enol ether 81 in THF with methyllithium$^{48,49}$ at low temperature, followed by protonation with the addition of water proved to be a consistent and reproducible method of cleavage of the trimethylsilyl enol ether, providing 80 in high yields (Table 2, entries 8-12). In all cases, 80 was isolated as an chromatographically inseparable mixture (3:1) of epimeric aldehydes. Although at this point the configuration of the major isomer was unknown, it seemed probable that in the major product the substituents would be trans.

![Figure 3 Stereochemical Attack of the Cyanocuprate 35 to the Enal 71](image)

Through an examination of molecular models, the cuprate reagent 35 was predicted to attack stereoselectively from the convex face of the bicyclic system of 71 (Figure 3). Hydrolysis of the resultant silyl enol ether 81 could lead to two epimeric aldehydes. The isomer in which the aldehyde is trans to the butenyl substituent should be the thermodynamically more stable product to minimize torsional strain.$^{50}$ Epimerization of the 3:1 mixture of aldehydes 80 under thermodynamic conditions (sodium methoxide in dry methanol) improved the product ratio to 9:1, as evidenced by integration of the $^1$H nmr
spectrum. Thus, the thermodynamic product ratio for 80 was 9:1.\textsuperscript{51} It was expected that the major isomer was the one in which the substituents bore a \textit{trans} relationship; indeed, this expectation was confirmed by a subsequent X-ray crystallographic study (\textit{vide infra}). Thus, at this stage the stereochemistry of the ring substituents was fixed as \textit{trans}.

The spectral data obtained for the 9:1 epimeric mixture of aldehydes 80 was fully consistent with the assigned structures. The IR spectrum of 80 showed stretching absorptions at 1724 cm\textsuperscript{-1} (aldehyde C=O) and 1116 cm\textsuperscript{-1} (ketal C-O-C), and a germanium-methyl rocking absorption at 825 cm\textsuperscript{-1}. The \textsuperscript{1}H nmr spectrum of 80 displayed two aldehyde resonances in a 9:1 ratio (\(\alpha:\beta\)) at \(\delta 9.50\) (doublet, \(J = 4\) Hz, \(\alpha\) aldehyde) and \(\delta 9.78\) (doublet, \(J = 3\) Hz, \(\beta\) aldehyde), and a 9-proton singlet for the Me\textsubscript{3}Ge group at \(\delta 0.17\). Resonances for two alkenyl protons and the characteristic signals for the ketal were also seen in the nmr spectrum. The \textsuperscript{13}C nmr spectrum of 80 contained all of the expected 19 signals. Lastly, the molecular formula was confirmed by a high resolution mass spectrometric measurement on the molecular ion.

The 1,4-addition of the cuprate reagent 35 to the \(\alpha,\beta\)-unsaturated aldehyde 71, in the presence of trimethylsilyl bromide and HMPA, was extremely fast (15 minutes) and no 1,2-addition products were observed. High yields of 80 were readily obtained, providing that the silyl enol ether 81 was isolated prior to its conversion to 80. Although HMPA may be added to the reaction mixture prior to the \(\alpha,\beta\)-unsaturated aldehyde 71 (Table 2, entries 1-9), higher yields of 81 were generally obtained when the HMPA was added after the addition of 71 (Table 2, entries 10-12). The reaction is conveniently run on scales of \(\sim 1\) mmol of aldehyde 71, but have been successfully performed using 2.5 mmol of 71 with no reduction in the isolated yields (Table 2, entry 12). As for all reactions involving 35, careful temperature control is critical to the successful formation of the cuprate 35 from the iodide 16. Without proper temperature control, the cuprate 35 does not form and the 1,4-addition reaction will fail.
1.5 Attempted anionic ring closure

The initial synthetic plan called for an anionic ring closure in which an alkenyl lithium displaces a leaving group on a primary carbon in an $S_{N2}$ fashion to provide the trans-fused bicyclo[4.3.0]nonane system 83 (Scheme 15). Thus, it was necessary to prepare compounds of general structure 84 to attempt the ring closure that would provide compound 85.

Scheme 15

The initial synthetic plan called for an anionic ring closure in which an alkenyl lithium displaces a leaving group on a primary carbon in an $S_{N2}$ fashion to provide the trans-fused bicyclo[4.3.0]nonane system 83 (Scheme 15). Thus, it was necessary to prepare compounds of general structure 84 to attempt the ring closure that would provide compound 85.
Treatment of a cold solution of the aldehyde 80 (9:1 mixture of epimers) in THF with DIBAL-H\textsuperscript{33} provided a chromatographically inseparable mixture of primary alcohols 86 in nearly quantitative yield (equation 9). The IR spectrum of 86 showed the disappearance of the aldehyde signal and the appearance of a strong O-H stretching absorption at 3383 cm\textsuperscript{-1}. The \textsuperscript{1}H nmr spectrum of 86 displayed a 9-proton signal for the Me\textsubscript{3}Ge at \(\delta 0.18\), a 2-proton multiplet at \(\delta 3.72\) from the hydroxymethyl protons, and two 1-proton multiplets attributed to the alkenyl protons centered at \(\delta 5.15\) and \(\delta 5.49\). The expected signals for the ketal were observed in both the IR and \textsuperscript{1}H nmr spectra of 86.

The desired iododegermylation of 86 did not proceed as planned. The alkenyltrimethylgermane 86 was treated with iodine in methylene chloride,\textsuperscript{52} typical conditions for iododegermylation reactions. After aqueous workup and purification by radial chromatography, the corresponding alkenyl iodide 87 and the deketalized adduct 88 were isolated in 63\% and 22\% yields, respectively (equation 10). Evidence obtained from \textsuperscript{1}H nmr spectroscopy was used to support these structural assignments. The \textsuperscript{1}H nmr spectrum of the alkenyl iodide 87 showed the characteristic signals for the 2,2-dimethylpropylene ketal (two 3-proton singlets at \(\delta 0.90\) and \(\delta 0.96\) and a 4-proton multiplet centered at \(\delta 3.45\)), signals for the hydroxymethyl protons at \(\delta 3.51\) and \(\delta 3.73\), and resonances for...
the alkenyl protons at δ 5.66 and δ 5.99. The 1H nmr spectrum of 88 showed resonances for the alkenyl protons at δ 5.66 and δ 6.00, but did not display the characteristic ketal resonances. The IR spectrum of 88 also exhibited a strong C=O stretching absorption at 1735 cm⁻¹, attributed to a cyclopentanone. The significant downfield shift of the 1H nmr resonances for the alkenyl protons in 87 and 88 from those in 86 supports the replacement of the Me₃Ge group with the more electronegative iodine atom.

The unexpected deketalization which occurred during the iodo-degermylation reaction can be rationalized by the interaction of the oxyphilic Me₃GeI, a byproduct of the exchange reaction, with the ketal. It is well known that Me₃SiI can be used to cleave ketals, and it seemed likely that the Me₃GeI byproduct could react in a similar manner to catalyze deketalization.

The ketone 88 was easily converted into the ketal 87 under Dean-Stark conditions by treatment of the former substance with 2,2-dimethylpropanediol under acid catalysis.¹²

With compound 87 in hand, the remaining task was to convert the alcohol into an appropriate leaving group. It was decided that two different leaving groups would be investigated, a halogen (Br) and a sulfonate ester (p-toluenesulfonyl). Treatment of 87 with p-toluenesulfonyl chloride, triethylamine, and DMAP in methylene chloride provided 89 in 89% yield,⁵⁴ while treatment of 87 with triphenylphosphine - bromide complex⁵⁵ in
methylene chloride provided 90 in 79% yield (Scheme 16). The \( ^1H \) nmr of 89 exhibited two 2-proton doublets \( (J = 8 \text{ Hz}) \) at \( \delta 7.32 \) and \( \delta 7.78 \) attributed to the aromatic protons, two 1-proton multiplets at \( \delta 5.67 \) and \( \delta 5.98 \) attributed to the alkenyl protons, two 1-proton signals at \( \delta 3.89 \) and \( \delta 4.08 \) attributed to the methylene protons of the -CH\(_2\)OTs, a 3-proton singlet at \( \delta 2.45 \) attributed to the methyl group of the tosylate, and the characteristic ketal resonances. The \( ^1H \) nmr spectrum of the bromide 90 displayed resonances for the alkenyl protons at \( \delta 5.68 \) and \( \delta 6.01 \), resonances for the bromomethyl protons centered at \( \delta 3.40 \) and \( \delta 3.58 \), and the characteristic resonances for the 2,2-dimethylpropylene ketal. The mass spectrum of 90 showed the molecular ion peaks at 482 and 484.

**Table 3** Attempted Anionic Ring Closure Reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Reaction Conditions</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>89</td>
<td>( n)-BuLi, THF, -78 °C ( \rightarrow ) rt</td>
<td>91</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
<td>( n)-BuLi, THF, -78 °C ( \rightarrow ) rt</td>
<td>92</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>( n)-BuLi, HMPA, THF, -78 °C ( \rightarrow ) rt</td>
<td>92</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>( n)-BuLi, HMPA, 12-crown-4, THF, -78 °C ( \rightarrow ) rt</td>
<td>92</td>
<td>89</td>
</tr>
</tbody>
</table>

Having synthesized suitable cyclization precursors, the ring closure reaction was attempted (equation 11). Treatment of 89 with \( n\)-butyllithium gave only the protonated alkene 91 in 83% yield (Table 3, entry 1), while treatment of 90 with \( n\)-butyllithium under a variety of conditions gave only the protonated alkene 92 (Table 3, entries 2-4). Even the addition of HMPA, a polar aprotic co-solvent, and the crown ether 57 12-crown-4,
additives known to make nucleophiles much more reactive by forming complexes with the cationic counterions and thereby increasing the negative charge density on the alkenyl carbon, did not provide any of the cyclized products. In the $^1$H nmr spectra of 91 and 92, the alkenyl regions showed signals for three distinct protons, including a complex 1-proton multiplet between $\delta$ 5.70 and $\delta$ 5.90 and two 1-proton signals between $\delta$ 4.90 and $\delta$ 5.00. There was no indication of any displacement of either the bromide or tosylate leaving groups although the nucleophile had formed as evidenced by the disappearance of the iodine moiety. Clearly, the anionic cyclization was unsuccessful and the synthetic plan needed revision.

1.6 Transition metal mediated ring closure

The failure of the anionic cyclization, via the nucleophilic displacement reaction, was believed to be a result of unfavorable orbital overlap. Examination of molecular models indicated that a strained transition state was required in order for this cyclization to attain the correct orientation for a $S_N$2 displacement. Since the direct nucleophilic displacement did not work, it was decided to investigate the corresponding aldehyde system. A literature review showed that alkenyl iodides have been successfully coupled with aldehydes using chromium(II) chloride and nickel(II) chloride salts in DMF.$^{58}$ The pathway for the cyclization is postulated to proceed through the following mechanism (Scheme 17).
Nickel(II) chloride is first reduced to nickel(0) with two equivalents of chromium(II) chloride. Oxidative insertion of nickel(0) into the alkenyl carbon-iodine bond of 93 then takes place. A transmetalation between the alkenynickel species 94 and the chromium(III) salt provides an alkenylchromium species 95 which reacts with the aldehyde to initially yield a chromium alkoxide species 97. The high stability of the oxygen-chromium(III) bond serves as the thermodynamic sink which drives the conversion. Subsequent hydrolysis of this species upon workup provides an allylic alcohol 98.

Thus, the new plan required the preparation of the iodo aldehyde 99 from 80 through a germanium-iodine exchange reaction. Subsequently, ring closure of 99 would be attempted via the chromium(II) chloride and nickel(II) chloride-mediated cyclization protocol. The resultant allylic alcohol 100 would be converted to the ketone 83 (Scheme 18).
Using the standard conditions for germanium-iodine exchange,\textsuperscript{52} the alkenyltrimethylgermane 80 (9:1 epimeric mixture) was treated with iodine in methylene chloride. After aqueous workup and chromatography, none of the desired product 99 was obtained. Instead, the acetal 101 was isolated in 73\% yield (Scheme 19). Not only had germanium-iodine exchange occurred, but also cleavage of the ketal along with concomitant formation of the acetal.
The $^1$H nmr spectrum of 101 showed the disappearance of the 9-proton signal at high field, for the Me$_3$Ge moiety. The downfield shift of the alkenyl protons to $\delta$ 5.68 and $\delta$ 6.00 was characteristic of the replacement of the Me$_3$Ge group with the more electronegative iodine atom. The cleavage of the ketal and formation of an acetal moiety was indicated by a 1-proton doublet ($J = 3.5$ Hz) at $\delta$ 4.37 attributed to the methine proton of the acetal and the disappearance of the aldehyde signal. In addition, the resonances of the 2,2-dimethylpropylene acetal are significantly different from those of the corresponding ketal in the starting material 80. The acetal 101 displays two 3-proton singlets at $\delta$ 0.69 and $\delta$ 1.14, a separation of 0.44 ppm, while the ketal 80 displays two 3-proton singlets at $\delta$ 0.93 and $\delta$ 0.96 for the geminal dimethyl protons. The methylene protons of the ketal and acetal are also different in the $^1$H nmr spectra. The acetal 101 shows two 1-proton doublets at $\delta$ 3.36 ($J = 11$ Hz) and $\delta$ 3.38 ($J = 11$ Hz) and one 2-proton doublet at $\delta$ 3.56 ($J = 11$ Hz), while the ketal 80 exhibits a 4-proton broad signal at $\delta$ 3.45.
The instability of the ketal function to the reaction conditions was not totally unexpected. In the germanium-iodine exchange reaction of 86, partial deketalization had been observed (equation 10). Trimethylgermanium iodide, a byproduct of the iodo-degermylation reaction, was believed to have catalyzed that process. When the silyl enol ether 81 was treated with TBAF, significant transmogrification of the ketal to the more stable acetal 82 was attributed to catalysis by the mildly Lewis acid trimethylsilyl fluoride byproduct (Scheme 14). In the reaction above (Scheme 19), the trimethylgermanium iodide could have played a similar catalytic role in promotion of the undesired side reaction.

In order to test the hypothesis that the Me₃GeI was responsible for the ketal migration, the exchange reaction was repeated with the addition of triethylamine to the solution of iodine in methylene chloride. It was hoped that the rate of ketal cleavage would be retarded by the addition of the Lewis basic triethylamine. After aqueous workup and chromatography, the desired iodo aldehyde 99 was isolated, albeit in low (43%) yield (equation 12, Table 4, entry 2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Isolated Yield (%) of 99</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I₂, CH₂Cl₂, rt</td>
<td>0 (73)ᵃ</td>
</tr>
<tr>
<td>2</td>
<td>I₂, Et₃N, CH₂Cl₂, rt</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>NIS, CH₂Cl₂, rt</td>
<td>84</td>
</tr>
</tbody>
</table>

ᵃ Yield of acetal 101.

It became clear that an alternative source of the halonium ion (I⁺) was required for the germanium-iodine exchange reaction to proceed successfully. While the use of
N-bromosuccinimide, a known source of bromonium ion (Br⁺), has been reported in the literature for bromodegermylation reactions, the use of N-iodosuccinimide to achieve a similar transformation had not, even though the latter is a well known source of iodonium ion. N-Iodosuccinimide has several advantages over iodine as a source of I⁺. The polarized nitrogen-iodine bond makes NIS more electrophilic than iodine. Loss of the iodonium ion from NIS results in a resonance stabilized anion in which the negative charge resides partially on oxygen. In light of the previous experimental results, in which coordination of the germanium containing byproduct with the ketal oxygens led to undesired hydrolysis, the negatively charged succinimide ion should compete effectively to reduce this unwanted side reaction.

Treatment of 80 (9:1 mixture of epimers) with N-iodosuccinimide in methylene chloride gave exclusively the iodo aldehyde 99 in 84% yield with no sign of acetal formation (Table 4, entry 3). Spectroscopic evidence for the conversion of 80 into 99 was seen in the IR spectrum of 99. Notable absorbances include a weak stretching absorption at 1617 cm⁻¹ attributed to the alkenyl iodide, a strong stretching absorption at 1722 cm⁻¹ attributed to the aldehyde, and the characteristic C-O-C stretching absorption of the ketal at 1115 cm⁻¹. The ¹H nmr spectrum of 99 displayed a downfield shift of the alkenyl protons to δ 5.69 and δ 6.01, characteristic of the replacement of the Me₃Ge moiety with the more electronegative iodine atom, as well as the disappearance of the 9-proton singlet at high field due to the Me₃Ge group. The ¹H nmr resonances for the 2,2-dimethylpropylene ketal were also observed in their characteristic positions – two 3-proton singlets at δ 0.93 and δ 0.96 and a 4-proton signal at δ 3.45. In the aldehyde region, two doublets at δ 9.51 (J = 4 Hz, α aldehyde) and δ 9.78 (J = 3 Hz, β aldehyde) in a 9:1 ratio were seen. Thus, the germanium - iodine exchange reaction conditions did not epimerize this mixture. The 9:1 ratio of epimers of 99 was in fact the thermodynamic ratio, as treatment of this mixture with sodium methoxide in methanol for 20 hours did not change the product ratio.
With the alkenyl iodide aldehyde 99 in hand, we were ready to attempt the ring closure to provide the trans-fused bicyclo[4.3.0]nonane ring system.

The alkenyl iodide 99 was added to a slurry of chromium(II) chloride and nickel(II) chloride in dry DMF (equation 13). After one hour, TLC analysis of the reaction mixture indicated that all of 99 had been consumed. Analysis of the crude reaction mixture, after workup, by ¹H nmr spectroscopy revealed that the reaction products lacked both the aldehyde and alkenyl iodide moieties. After purification of the crude material by silica gel chromatography, two major products were isolated and spectroscopic analysis indicated that two epimeric alcohols, 102 and 103, had been formed in yields of 23% and 57%, respectively (equation 13). A minor amount (~9%) of a mixture of allylic alcohols resulting from the ring closure of the cis component of 99 was also produced.

The spectroscopic evidence obtained supported the conclusion that the desired cyclized products (alcohols 102 and 103) had formed. The infrared spectra of both 102 and 103 displayed strong O-H stretching absorptions at 3456 cm⁻¹ and 3436 cm⁻¹, respectively, weak C=C stretching absorptions at 1651 cm⁻¹ in both compounds, and strong C-O-C stretching absorptions for their ketal moieties at 1110 cm⁻¹ and 1117 cm⁻¹, respectively. The ¹H nmr spectrum of 102 exhibited a broad singlet at δ 4.23 attributed to the carbinol proton and two signals attributed to the alkenyl protons at δ 4.74 and δ 4.83, while the ¹H nmr spectrum of 103 exhibited a resonance for the carbinol proton at δ 3.81 (dd, J = 11.5, 6 Hz) and resonances for the alkenyl protons at δ 4.77 and δ 4.94. The
$^{13}$C nmr spectrum of 102 contained all of the expected 18 signals, but the $^{13}$C spectrum of 103 displayed only 17 unique resonances due to coincidental overlap of the signals attributed to the methylene carbons of the ketal.

Two dimensional nmr spectroscopy (COSY and HMQC) was used to assign all of the proton and carbon resonances in 102 and 103 (Tables 19 - 22, experimental section). Through an examination of the coupling constants of the protons at the ring junction, it was hoped that the ring junction could be proven to be trans-fused. The $^1$H nmr spectra of 103 shows that H-1 (δ 1.25) and H-6 (δ 1.39) are coupled by 11.5 Hz. This large coupling constant, although consistent with a trans-diaxial relationship of protons on a six membered ring, did not offer conclusive proof that the trans-fused system had been formed. However, a single crystal X-ray structure determination of a derivative of 103 (vide infra) confirmed the relative trans relationship between H-1 and H-6.

The chromium(II) chloride and nickel(II) chloride mediated cyclization of 99 exhibited a moderate preference for the formation of 103, in which the newly formed hydroxyl function is cis to the adjacent angular proton. An examination of the chair-like transition states, 102* and 103*, leading to the products shows two competing effects (Scheme 20). In the transition state 103* leading to the major product (103), A\textsubscript{1,3} strain between the olefin and the chromium alkoxide is observed.\textsuperscript{63} On the other hand, in the transition state 102* leading to the minor product (102), the A\textsuperscript{1,3} strain is relieved by the newly formed hydroxyl group adopting an axial orientation. However, 102* does experience 1,3-syn-axial interactions due to the chromium alkoxide adopting an axial orientation. These two effects, A\textsuperscript{1,3} strain and 1,3-syn-axial interactions, result in little energy difference between the two possible transition states, as can be seen by the product ratio of ~2.5:1 in favor of 103.
It was decided that the two newly formed alcohols 102 and 103 would be converted to the same product, namely ketone 83 (Scheme 18).

The allylic alcohols 102 and 103 were converted into their corresponding acetates by treatment of each alcohol with acetic anhydride in methylene chloride in the presence of DMAP and triethylamine (equation 14). After workup and purification, the acetates 104 and 105 were isolated in excellent yields (Table 5).
Table 5  Acetylation of the Alcohols 102 and 103

\[
\begin{align*}
\text{102: } & R_1 = H, R_2 = \text{OH} \\
\text{103: } & R_1 = \text{OH}, R_2 = H \\
& \xrightarrow{\text{Ac}_2\text{O}} \text{DMAP} \\
& \text{Et}_3\text{N} \text{, CH}_2\text{Cl}_2, \text{rt} \\
\text{104: } & R_1 = H, R_2 = \text{OAc} \\
\text{105: } & R_1 = \text{OAc}, R_2 = H
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Isolated Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>102</td>
<td>104</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>103</td>
<td>105</td>
<td>95</td>
</tr>
</tbody>
</table>

The spectral data of 104 and 105 were found to be in full accord with their assigned structures. The IR spectrum of 105 exhibited a strong absorption at 1742 cm\(^{-1}\) attributed to the carbonyl stretching absorption of an ester function, a weak absorption at 1652 cm\(^{-1}\) attributed to the C=C stretching absorption, and a strong absorption at 1117 cm\(^{-1}\) attributed to the C-O-C stretching absorption of the ketal. Similar absorptions were found in the IR spectrum of 104 at 1739, 1656, and 1112 cm\(^{-1}\), respectively. The \(^1\)H nmr spectrum of 105 displayed a resonance for the acetoxy methine at \(\delta 5.07\) (d, \(J = 9.5 \text{ Hz}\), a significant downfield shift from the resonance of the carbinol proton (\(\delta 3.81\)) in the starting material 103. This finding supported the assertion that the hydroxyl proton was replaced by the electron withdrawing acetyl group since the methine proton would be deshielded by the acetoxy group. A 3-proton singlet attributed to the acetoxy methyl group at \(\delta 2.10\) was also seen in the \(^1\)H nmr of 105. Similarly, the \(^1\)H nmr spectrum of 104 revealed a resonance for the acetoxy methine at \(\delta 5.40\) and a singlet for the acetoxy methyl group at \(\delta 2.01\). Additionally, the \(^{13}\)C nmr spectra of 104 and 105 each contained the expected 20 signals.
The relative configuration of 105 was confirmed through an X-ray crystallographic analysis. The stereoview of this substance is shown below (Figure 4).

Figure 4 Stereoview of the β-Acetate 105 (note that this structure (105) is drawn as the enantiomer to that which was presented earlier in this thesis and a different numbering system has been used to label the atoms in this stereoview diagram)

Several assumptions were confirmed by the X-ray structure. The angular protons at the A-B ring junction clearly exhibit a trans relationship, with a torsional angle of 175°. The six membered ring has adopted a chair-like conformation with the acetoxy group in an equatorial orientation. The approach of the cuprate 35 to the α,β-unsaturated aldehyde 71 had, as expected, occurred stereoselectively from the convex face of the substrate, and the major product from the 1,4-addition, after cleavage of the enol silyl ether function, did indeed have the ring substituents in a trans relationship.
Oxidative cleavage of the exocyclic methylene groups in 104 and 105 was, in each case, achieved through ozonolysis of the compound in cold methanol, followed by reductive workup with dimethyl sulfide (equation 15). After chromatographic purification, the acetoxy ketones 106 and 107 were isolated in excellent yields (Table 6).

Table 6 Ozonolysis of the Exocyclic Methylene Moiety of 104 and 105

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R₁</th>
<th>R₂</th>
<th>Product</th>
<th>Isolated Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>104</td>
<td>H</td>
<td>OAc</td>
<td>106</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>105</td>
<td>OAc</td>
<td>H</td>
<td>107</td>
<td>90</td>
</tr>
</tbody>
</table>

The structural assignments for 106 and 107 were confirmed by IR and ¹H nmr spectral analysis. The IR spectra of 107 exhibited two strong C=O stretches: one at 1750 cm⁻¹ attributed to the acetate carbonyl, and the second at 1728 cm⁻¹ attributed to the ketone. A strong C-O stretching absorption at 1235 cm⁻¹ attributed to the acetate moiety, and a strong C-O-C stretching absorption at 1116 cm⁻¹ attributed to the ketal were also observed. Similar absorptions were found in the IR spectrum of 106 at 1750, 1730, 1225, and 1108 cm⁻¹, respectively. The ¹H nmr spectra revealed that both 106 and 107 lacked the resonances for the exocyclic methylene protons. The ¹H nmr spectrum of 107 did display a 3-proton singlet at δ 2.12, attributed to the acetoxy methyl group, a 1-proton doublet (J = 12 Hz) at δ 5.03, due to the acetoxy methine proton, and the characteristic signals for the 2,2-dimethylpropylene ketal function. The ¹³C nmr spectrum of 107 contained all of the 19 expected signals. The nmr (¹H and ¹³C) spectra of 106 showed features similar to those for 107.
Reductive removal of the acetoxy function from 106 and 107 was achieved under mild conditions with SmI₂ in the presence of a proton source (equation 16). Addition of a solution of either 106 or 107 in a 3:1 mixture of THF and methanol to a cold solution of SmI₂ in THF provided the tricyclic keto ketal 83 in good yield after workup and silica gel chromatography (Table 7).

Table 7 Reductive Removal of the Acetoxy Moieties from 106 and 107

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R₁</th>
<th>R₂</th>
<th>Product</th>
<th>Isolated Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>106</td>
<td>H</td>
<td>OAc</td>
<td>83</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>107</td>
<td>OAc</td>
<td>H</td>
<td>83</td>
<td>94</td>
</tr>
</tbody>
</table>

The structural assignment of 83 was in agreement with the spectral data obtained. The IR spectrum of 83 exhibited as strong C=O stretching absorption at 1714 cm⁻¹ and a strong C-O-C stretching absorption for the ketal moiety at 1117 cm⁻¹. From the absorption position for the carbonyl, it can be concluded that no transketalization from the cyclopentanone carbonyl to the cyclohexanone carbonyl had occurred. The ¹³C nmr spectrum of 83 displayed distinct resonances for each of the 17 carbons in the compound. Notable resonances were the carbonyl signal at δ 211.7, the quaternary ketal carbon signal at δ 110.8, the two ketal methylene carbon signals at δ 71.8 and δ 72.0, the two ketal methyl signals at δ 22.4 and δ 22.6, and four methine signals at δ 40.5, δ 44.7, δ 47.6, and δ 50.9. The ¹H nmr spectrum of 83 showed the characteristic 2,2-dimethylpropylene ketal resonances, two 3-proton singlets at δ 0.92 and δ 0.98 for the two methyl groups and a 4-proton multiplet centered at δ 3.45 for the methylene protons. In addition, a high
resolution mass spectrometric analysis confirmed that the molecular formula of 83 was indeed C\textsubscript{17}H\textsubscript{26}O\textsubscript{3}.

1.7 Conclusions

A new stereoselective method for the preparation of the trans-fused bicyclo[4.3.0]-nonane ring system 83 starting from a cyclopentanone system 61 has been developed\textsuperscript{69} (Scheme 21). The procedure involves the conversion of the cyclopentanone 61 into the \(\alpha,\beta\)-unsaturated aldehyde 71. A stereoselective 1,4-addition of the known cyanocuprate 35 to 71 provides 80 as a mixture of epimeric aldehydes. Conversion of the alkenyltrimethylgermane to an alkenyl iodide yields 99, which can be efficiently cyclized under mild conditions to produce the alcohols 102 and 103. Suitable functional group conversions provide the ketone 83 from the two alcohols.
The key steps in this annulation sequence were the stereoselective conjugate addition of 35 to the unsaturated aldehyde 71, the iododegermylation of 80, and the chromium(II) chloride-nickel(II) chloride-mediated cyclization of 99. The effectiveness of an alternative reagent for iododegermylations of alkenyltrimethylgermanes was demonstrated in the course of our studies. The use of $N$-iodosuccinimide in methylene chloride provides mild conditions for this conversion, allowing for germanium - iodine exchange in the presence of acid labile groups such as ketals, which are unstable to iododegermylation with iodine in methylene chloride.
2. **Functionalized Allylcopper(I) Reagents**

2.1 **Background**

The ability of organocopper(I) reagents to effect 1,4-additions of organic ligands to \(\alpha,\beta\)-unsaturated carbonyl systems is undoubtedly one of the most valuable transition metal mediated processes available to synthetic organic chemists.\(^{42,70-79}\) While the literature does contain some examples of the successful 1,4-addition of allylic ligands to enones, oftentimes the allylic cuprates react nonselectively giving mixtures of both 1,4- and 1,2-addition products.\(^{80,81}\) Only recently has a consistently reliable method for the delivery of the allyl group to the \(\beta\)-position of \(\alpha,\beta\)-unsaturated carbonyl systems been developed.\(^{82-84}\)

\[
\begin{align*}
2 \text{Li} &\quad + \quad \text{Cu(I) salt} \quad \xrightarrow{\text{Et}_2\text{O}} \quad \underset{-78 \degree \text{C}}{\text{CuLi}} \\
\text{109} &\quad \quad \text{108}
\end{align*}
\]

The tendency of the Gilman-type cuprates, LiCuR\(_2\) (R = alkyl, alkenyl, or aryl), to add in a conjugate sense to \(\alpha,\beta\)-unsaturated carbonyl compounds initially led to investigations of the analogous allyl cuprate. Lithium diallylcuprate (108) is prepared\(^{40,85}\) at low temperature by the addition of a copper(I) salt, such as copper(I)bromide-dimethyl sulfide or copper(I) iodide, to two equivalents of allyllithium (109) (equation 17). Although the reaction of lithium diallylcuprate 108 with cyclohex-2-enone (110) in cold ether did produce the conjugate addition adduct 111 in high (90%) yield (equation 18), with more hindered systems such as the \(\beta,\beta\)-disubstituted enone 112, only the 1,2-addition product 113 was detected\(^{85}\) (equation 19).
The high degree of substrate dependence\(^{40,80,85}\) on the successful 1,4-addition of lithium diallylcuprate has resulted in several negative reports regarding this clan of reagents, and because of their temperamental nature, allylcuprates have found very limited use in synthesis. In fact, many syntheses which require an allyl group to be delivered in a 1,4-fashion to an enone instead employ Sakurai's\(^{86}\) Lewis acid catalyzed addition of allyltrimethylsilane to \(\alpha,\beta\)-unsaturated ketones. For example, reaction of 112 with titanium tetrachloride and allyltrimethylsilane (114) provides the 1,4-addition product 115 in 85% yield\(^{87}\) (equation 20).

Investigations of lithium diallylcuprate (108), prepared in THF via equation 17, by Lipshutz and coworkers\(^{88}\) using low temperature \(^{13}\)C nmr spectroscopic analysis showed 108 to be thermally unstable. Even at temperatures at or below -78 °C, significant decomposition of 108 to give the Wurtz-like coupling product, hexa-1,5-diene, is observed. The \(^{13}\)C nmr spectrum of 108 at -95 °C contained signals for free allyllithium
the decomposition product hexa-1,5-diene, another species presumed to be Li(allyl)₃Cu₂, and the σ-bound allylcuprate reagent 108. The method of preparation of 108 seems to determine its success in 1,4-additions to enones. Formation of 108 by the addition of allyllithium to copper(I) iodide and brief warming to effect dissolution severely compromises cuprate formation, and loss of an allyl ligand from 108 produces other species, which undoubtedly have modified reactivity. The source and purity of the copper(I) salt can also affect the extent of cuprate formation. Impurities in commercially available copper(I) salts, such as other transition metals or copper(II) salts, are known to cause cuprate decomposition. Hence, careful purification of the copper(I) source is oftentimes required.

Further investigations by Lipshutz revealed that, if anything, allylic cuprates are overly reactive and are in need of attenuation if discrimination between 1,2- and 1,4-addition is to be achieved. Attempts at conjugate additions using the lower order cyanocuprate 116, prepared from allyllithium and copper(I) cyanide, were completely unsuccessful. Even the thermally more stable higher order cyanocuprate 117, prepared from two equivalents of allyllithium and one equivalent of copper(I) cyanide, could not effect 1,4-addition of the allyl moiety. Reaction of either 116 or 117 with cyclohex-2-enone resulted only in 1,2-addition, even in the presence of additives such as trimethylsilyl chloride or boron trifluoride-etherate which normally promote 1,4-over 1,2-addition.
Allylcopper(I) (118), prepared by the treatment of allyltributylstannane (119) in THF with methyllithium, followed by the addition of lithium chloride solubilized copper(I) iodide (equation 21), does add to enones such as 110, in the presence of trimethylsilyl chloride, to provide the 1,4-addition product 111 in high (95%) yield (equation 22).

This result was quite surprising as non-ate organocopper(I) reagents (RCu) are generally quite unreactive towards conjugate addition. Subsequent investigations illustrated that allylic groups can be delivered 1,4 to enones using Grignard derived allylcopper reagents, (allyl)Cu•MgBr\(_2\), obtained from allylmagnesium bromide and copper bromide-dimethyl sulfide complex. In this case, the copper(I)-mediated 1,4-addition of the allylic group to the enone 110, in the presence of lithium chloride and trimethylsilyl chloride, proceeded in 86% yield (equation 23).
Using either allylcopper(I) (118) or the copper(I)-mediated Grignard protocol, the allyl group can be delivered efficiently to the β-position of α,β-unsaturated ketones in high yields with relatively short (10 minutes) reaction times. Nevertheless, examples in the literature of the conjugate addition of allyl moieties to α,β-unsaturated carbonyl systems are still quite rare. In general, only simple allyl groups\(^92\) have been added in a conjugate sense to enones. In none of these cases does the allyl group possess a function with potential for facile synthetic manipulations at carbon-2.

Rieke and coworkers\(^93\) have demonstrated that a highly reactive form of zerovalent copper, Cu\(^*\), can be prepared by the reduction of copper cyanide-lithium bromide complex\(^94\) (CuCN\(\cdot\)2LiBr) with lithium naphthalenide. The copper species Cu\(^*\) undergoes direct metalation of allyl halides, resulting in an efficient preparation of allylcopper(I) reagents without any Wurtz-like homocoupling. The allylcopper(I) reagent 120, prepared from 121 by this method, reacted with cyclohex-2-enone (110) in the presence of trimethylsilyl chloride to provide the 1,4-addition product 122 in good (81%) yield\(^93\) (equation 24).

\[
\begin{align*}
\text{Cl} & \quad \text{Cu}^* \quad \text{THF} \quad -95 \; ^\circ\text{C} \\
121 & \quad \text{Cu} \quad 110 \quad \text{Me}_3\text{SiCl, THF} \quad -78 \; ^\circ\text{C} \rightarrow \text{rt} \\
& \quad \text{122} (24)
\end{align*}
\]

Limited cases of the conjugate addition of allylcopper(I) reagents functionalized at carbon-1 have been reported. Corriu\(^95\) prepared the lower order cyanocuprate 123 via the deprotonation of allyltrimethylsilane (114) with n-butyllithium in the presence of TMEDA, followed by the addition of copper(I) cyanide (equation 25).
This allylcuprate reagent 123, substituted at carbon-1, undergoes highly selective conjugate addition reactions with α,β-unsaturated esters and ketones in moderate (65-80%) yields, but only afforded 1,2-addition products when reacted with α,β-unsaturated aldehydes. Interestingly, the reaction of 123 with α,β-unsaturated carbonyls such as 110 proceeded in good yield to provide the 1,4-addition adduct 124 without the addition of trimethylsilyl chloride (equation 26). Presumably the trimethylsilyl group at carbon-1 stabilizes 123 such that its reactivity is modified compared with the unsubstituted lithium (allyl)(cyano)cuprate 116, which is reported to add only in a 1,2-fasion to enones.

Hosomi and coworkers prepared a substituted allylcopper(I) species from a ketene dithioacetal bearing a chlorine atom at the allylic position (125) via a ligand exchange reaction with the higher order methyl(cyano)cuprate, Me₂Cu(CN)Li₂.    

![Chemical reaction diagram](image-url)
This carbon-1 substituted allylcopper reagent, when combined with boron trifluoride etherate, gave exclusive 1,4-addition to cyclohex-1-enone (110), to provide 126 in synthetically poor (37%) yield, but with no reported 1,2-addition products\(^9\) (equation 27).

While the conjugate addition of allylcopper reagents substituted at carbon-2 to \(\alpha,\beta\)-unsaturated carbonyl compounds was, prior to the work described herein, unknown, organocopper reagents containing the allyl moiety functionalized in the 2-position have been prepared, and have been reacted with a variety of electrophiles. Fleming and coworkers prepared the higher order organocopper reagents 127 and 128, containing a carbon-2 substituted allyl ligand, by the silyl-cupration\(^{98}\) and stannyl-cupration\(^{99}\) of allene (equations 28 and 29, respectively).

\[
\begin{align*}
\text{2 Me}_2\text{PhSiCl} & \quad \text{1) Li metal, THF, -10 °C} \\
& \quad \text{2) CuCN, 0 °C} \\
& \quad \text{3) H}_2\text{C}=\text{C}=\text{CH}_2, -78 °C \quad \rightarrow \\
& \quad \text{SiMe}_2\text{Ph} \\
& \quad \text{127}
\end{align*}
\]

\[
\begin{align*}
\text{2 n-Bu}_3\text{SnLi} & \quad \text{1) CuCN, THF, -78 °C} \\
& \quad \text{2) H}_2\text{C}=\text{C}=\text{CH}_2 \quad \rightarrow \\
& \quad \text{Sn(n-Bu)}_3 \\
& \quad \text{128}
\end{align*}
\]

These reagents (127 and 128) can be trapped with a variety of electrophilic species in good yields\(^{98,99}\). However, both of these substituted allylcopper reagents react only in a 1,2-manner with cyclohex-2-enone (110) to provide the tertiary alcohols 129 and 130 (equation 30).
Overman\textsuperscript{100} has also demonstrated that the higher order cuprate 127, prepared by the silyl-cupration of allene according to Fleming's procedure,\textsuperscript{98} efficiently opened a variety of terminal epoxides in moderate to good yields (36-81\%) to provide alcohols of general structure 131 (equation 31). However, Overman did not investigate the reactivity of 127 with $\alpha,\beta$-unsaturated ketones.

2.2 Introductory remarks

The ultimate goal of our studies of allylcopper(I) reagents was the preparation of a bifunctional reagent that would serve as the synthetic equivalent of the $d^2$, $d^3$ prop-1-ene synthon (48) and that could be added in a conjugate sense to a variety of Michael acceptor substrates. To achieve this goal, our initial objective was the preparation of an allylstannane that was usefully functionalized at carbon two. Our second objective was to convert this allylstannane to an allylcopper(I) species and investigate its utility in conjugate addition reactions to $\alpha,\beta$ unsaturated ketones.
It was envisaged that a copper(I) species (49) derived from 2-(trimethylgermyl)-3-(trimethylstannyl)propene (132) could function as the d^2, d^3 prop-1-ene synthon (48). Work by Lipshutz^82 has shown that allylstannanes are useful precursors for allylcopper(I) reagents and that these allylcopper(I) reagents can undergo efficient 1,4-addition to enones. Previous studies^11,14,15,39^ in our laboratories have shown the latent synthetic potential of alkenyltrimethylgermanes, especially as stable precursors to alkenyl iodides.

2.3 Synthetic Plan

We proposed that 2-(trimethylgermyl)-3-(trimethylstannyl)propene (132) could be prepared as outlined in Scheme 22. It seemed reasonable to conclude that 133 could be obtained by treating the readily available bromo alcohol 134 with tert-butyllithium,^102 followed by trapping of the resultant alkenyl anion with trimethylgermanium bromide. Treatment of the alcohol 133 with triphenylphosphine dibromide^55 should provide the allylic bromide 135. The allylstannane 132 could be formed by reaction of 135 with trimethyltin chloride and magnesium in refluxing THF.^103
Scheme 22

2.4 Preparation of 2-(trimethylgermyl)-3-(trimethylstannyl)propene (132)

2-Bromoprop-2-enol (134) was prepared by the method described by Hatch and coworkers. Treatment of commercially available 2,3-dibromopropene (136) with aqueous potassium carbonate at 90 °C provided, after extraction of the aqueous solution and distillation of the derived oil, 2-bromoprop-2-enol in 94% yield (equation 32).

Our yield obtained was significantly higher than that originally reported in the literature (47%). Hatch rationalized the low yield by proposing that the severity of the conditions resulted in the removal of both bromine atoms. However, the low yield was likely a result of an incomplete extraction of the polar, water soluble bromo alcohol 134 from the aqueous solution. In order to efficiently extract 134 from the aqueous solution, we found that 20 extractions with methylene chloride provided good recovery of the alcohol 134 from the aqueous phase.
Spectroscopic evidence obtained was in full accord with the above transformation. The IR spectrum of 134 exhibited a strong O-H stretching absorption at 3311 cm\(^{-1}\) and a strong C=C stretch at 1641 cm\(^{-1}\). The \(^1\)H nmr spectrum of 134 displayed two 1-proton doublets in the alkenyl region at \(\delta \ 5.89\ (J = 1\ \text{Hz})\) and \(\delta \ 5.53\ (J = 1\ \text{Hz})\), and a 2-proton doublet \((J = 6\ \text{Hz})\) at \(\delta \ 4.16\) attributed to the allylic protons. A broad 1-proton signal, due to the hydroxyl proton, at \(\delta \ 2.02\) disappeared with the addition of D\(_2\)O with a concomitant simplification of the signal at \(\delta \ 4.16\) to a singlet. The mass spectrum of 134 showed the molecular ions at 136 and 138, indicative of a single bromine atom present in the molecule.

\[
\begin{align*}
\text{Br} & \quad \text{OH} \\
134 & \quad \xrightarrow{1) \ t-BuLi, \ Et_2O, -78^\circ C \rightarrow 0^\circ C} \quad \text{GeMe}_3 \\
\quad & \quad \xrightarrow{2) \ Me_3GeBr, \ 0^\circ C} \\
\quad & \quad \xrightarrow{3) \ p-TsOH-H_2O, \ CH_2Cl_2, \ rt} \\
\quad & \quad \xrightarrow{4) \ \text{silica gel,} \ CH_2Cl_2, \ rt} \quad \text{OH} \\
133 & 
\end{align*}
\]

(33)

Conversion of bromo alcohol 134 into the trimethylgermyl alcohol 133 was achieved according to equation 33. Using the procedure developed by Corey,\(^{102}\) slow addition of tert-butylthlium to a cold solution of 134 in diethyl ether, followed by addition of trimethylgermanium bromide to the resultant dianion provided, after appropriate workup procedures and distillation, 2-((trimethylgermyl)prop-2-enol (133) in 72% yield. The \(^1\)H nmr spectrum of 133 confirmed the replacement of the alkenyl bromide with the Me\(_3\)Ge group by a 9-proton singlet at \(\delta \ 0.23\). Resonances for the two alkenyl protons at \(\delta \ 5.28\) and \(\delta \ 5.72\) were also present in the \(^1\)H nmr spectrum of 133. In addition, the IR spectrum of 133 exhibited a strong O-H stretching absorption at 3306 cm\(^{-1}\).
Several factors regarding this reaction are noteworthy and deserve further explanation.

\[
\text{LiBr + 75 + H}_3C\equiv\text{C-Br} \xrightarrow{t\text{-BuLi}} \text{H}_3C\equiv\text{C-Br} + \text{H}_3C\equiv\text{CH} + (\text{H}_3\text{C})_2\text{C} = \text{CH}_2 + \text{LiBr}
\] (34)

Scheme 23

Three equivalents of \textit{tert}-butyllithium are required to form the dianion \textit{137} (Scheme 23). The first equivalent of \textit{tert}-butyllithium is used to deprotonate \textit{134}, generating the lithium alkoxide \textit{138}. The second equivalent is consumed in the lithium-bromine exchange reaction, providing \textit{137} from \textit{138} (via path B). The third equivalent of \textit{tert}-butyllithium is required to destroy the \textit{tert}-butyl bromide (\textit{139}) that is formed in the lithium-halogen exchange reaction. Reaction of \textit{139} with \textit{tert}-butyllithium provides the volatile products 2-methylpropane (\textit{75}) and 2-methylpropene (\textit{76}) (equation 34). The rate of addition of \textit{tert}-butyllithium to \textit{134} is of critical importance and must be slow (~1 mL \textit{t}-BuLi solution in pentane/min) to ensure successful generation of the dianion \textit{137} (via path B). As was
suggested by Corey, rapid addition of the tert-butyllithium to a solution of 134 promotes the elimination of HBr from 138 (via path A) to provide 140. Reaction of 140 with another equivalent of tert-butyllithium ultimately generates the dianion of propargyl alcohol (141).

Scheme 24

The generation of the byproduct 141, in addition to the desired 137, upon treatment of 134 with tert-butyllithium initially presented considerable problems. Treatment of this mixture (137 and 141) with trimethylgermanium bromide provided four products, the alcohols 133 and 142 and the trimethylgermyl ethers 143 and 144 (Scheme 24). Fortuitously, the trimethylgermyl ethers 143 and 144 were hydrolyzed to the
corresponding alcohols 133 and 142 during silica gel chromatography. Thus, when the 
mixture of the alcohols 133 and 142 and the trimethylgermyl ethers 143 and 144 was 
applied to a silica gel column, after flash chromatography a single fraction containing 133 
and 142 was collected. Unfortunately, 133 and 142 were neither separable by silica gel 
chromatography nor by a subsequent distillation. Interestingly, an analysis by GLC 
indicated that ratio of 133 : 142 obtained after chromatography was identical with the ratio 
of 133 and 143 : 142 and 144 in the initial mixture. Thus, the trimethylgermyl ethers 
143 and 144 were hydrolyzed to their corresponding alcohols during silica gel 
chromatography, not simply decomposed.

The $^1$H nmr spectrum of the mixture of 142 and 133 displayed unique signals for 
their Me$_3$Ge functions at $\delta$ 0.33 for 142 and $\delta$ 0.24 for 133, unique broad signals for their 
alcohol protons at $\delta$ 1.71 for 142 and $\delta$ 1.35 for 133, but the hydroxymethyl signals of 
142 and 133 overlapped giving a multiplet centered at $\delta$ 4.26. Since separation of 133 
from 142 was not possible by silica gel chromatography nor simple distillation, it was 
hoped that some chemical means could be employed. Other studies on the preparation of 
alkenyltrimethylgermanes in our laboratories$^{35}$ had indicated that 2-(trimethylgermyl)alk-
enes are stable to certain acidic conditions. It was hoped that the alkynyltrimethyl-
germane 142 would be less stable (than 133) to acid and would undergo protio-
degermylation upon treatment with acid. To our delight, treatment of the mixture of 133 
and 142 with p-toluenesulfonic acid monohydrate in methylene chloride at room 
temperature resulted in complete degermylation of 142 while 133 was unaffected. 
Presumably 142 is converted to propargyl alcohol, which is volatile and easily separated 
from 133. Unfortunately, the trimethylgermyl ether moiety is also stable to this acidic 
treatment.
A nagging difficulty in this entire process was the generation of trimethylgermyl ethers (Scheme 24). Trimethylgermyl ethers of both 142 and 133 were generated in the reaction of 134 with tert-butylithium and trimethylgermanium bromide. As mentioned previously, these ethers, 143 and 144, could be hydrolyzed by silica gel chromatography. More annoying, however, was the generation of the trimethylgermyl ether 143 in the protiodegermylation reaction. Treatment of a mixture of the alcohols 142 and 133 under acidic conditions, with p-toluenesulfonic acid monohydrate in methylene chloride, provided the alcohol 133 and the trimethylgermyl ether 143 as well as the volatile propargyl alcohol (Scheme 24). A proposed mechanism for the formation of 143 is given in Scheme 25. Initially, the alkyne 142 is protonated to provide 145, which contains a germanium stabilized cation to the trimethylgermyl moiety. Apparently the trimethylgermyl moiety has a very high affinity for oxygen, and a lone pair from the oxygen of 133 attacks this function resulting in the formation of propargyl alcohol (146) and the trimethylgermyl
ether 143 via the intermediate 147. More interestingly, a GLC analysis indicated that the ratio of 133:142 in the starting mixture (prior to treatment with acid) was identical with the ratio of 133:143 found in the product mixture (after treatment with acid). The trimethylgermyl ether 143 exhibits a singlet in the $^1$H nmr spectrum at $\delta$ 0.37 for the OGeMe$_3$ moiety, slightly downfield from that attributed to the alkenyltrimethylgermane moiety ($\delta$ 0.23). Although trimethylgermyl ethers are unstable to silica gel chromatography, and are hydrolyzed to the corresponding alcohol during this process, it was hoped to avoid this purification step as the reaction was essentially clean, yielding only the desired alcohol 133 and the ether 143. The instability of trimethylgermyl ethers to silica gel chromatography led us to attempt a more convenient hydrolysis of these ethers by employing silica gel as the drying agent rather than MgSO$_4$. Silica gel itself is a marvelous drying agent but has not gained favor, due not only to its expense but also because it is acidic, and can therefore react, usually unfavorably, with desired compounds. Fortunately, in our case, silica gel, when used in excess as a drying agent, effectively hydrolyzed the trimethylgermyl ether 143 to provide 133.

$$\begin{align*}
\text{Br} & \quad \text{1) } t\text{-BuLi, Et}_2\text{O, -78 °C } \rightarrow 0 \text{ °C} \\
& \quad \text{2) Me}_3\text{GeBr, 0 °C} \\
& \quad \text{3) } p\text{-TsOH}+\text{H}_2\text{O, CH}_2\text{Cl}_2, \text{rt} \\
& \quad \text{4) silica gel, CH}_2\text{Cl}_2, \text{rt} \\
\text{134} & \quad \rightarrow \\
& \quad \text{GeMe}_3 \\
\text{133} & \quad (33)
\end{align*}$$

The experimental procedure routinely used to prepare 133 (equation 33) therefore does not require any silica gel chromatography. The bromo alcohol 134 is treated with tert-butyllithium followed by trimethylgermanium bromide. After an aqueous workup, the ethereal solvent is removed. The crude residue is dissolved in methylene chloride and treated with $p$-toluenesulfonic acid monohydrate. After another aqueous workup, the combined organic phases are dried using silica gel. The slurry is filtered and concentrated. Fractional distillation of the derived oil provides 133.
Preparation of the bromide 135 was straightforward and was achieved under standard conditions. Treatment of the alcohol 133 with triphenylphosphine dibromide in methylene chloride provided, after workup and distillation, 135, a volatile oil, in 93% yield (equation 35). The IR spectrum of 135 lacked the O-H stretching absorption which was present in the starting material. The $^1$H nmr spectrum of 135 displayed a 9-proton singlet at $\delta$ 0.29 for the Me$_3$Ge moiety, a 2-proton multiplet at $\delta$ 4.16 attributed to the allylic methylene group, and two alkenyl protons at $\delta$ 5.34 and $\delta$ 5.83. The $^{13}$C nmr spectrum of 135 exhibited a resonance for each of the four types of carbon atoms in the molecule.

The preparation of 2-(trimethylgermyl)-3-(trimethylstannyl)propene (132) was attempted using a modification of Keck's procedure for the preparation of allyltributylstannane from tributyltin chloride and allyl chloride. Reaction of 135 with excess trimethyltin chloride and magnesium metal in refluxing THF provided two products (equation 36). Analysis by GLCMS indicated that the desired allylstannane 132 and the dimer 148 were formed in 87% yield and $^1$H nmr and GLC analysis indicated that 132 and 148 were formed in a 10:1 ratio. These products (132 and 148) proved to be inseparable both by silica gel chromatography as well as by distillation. Although Keck did not report the formation of any dimer (hexa-1,5-diene) in his method, it would have been
much more volatile than allyltributylstannane and would have been readily removed by distillation.

The $^1$H nmr spectrum of this mixture of 132 and 148 exhibited two types of peaks: one set displayed tin-proton coupling while the other set did not display this sort of coupling. This coupling data, along with the integration of the signals, allowed identification of the products and assignment of the $^1$H nmr signals. The resonances attributed to the dimer 148 were a singlet at $\delta$ 0.20 (the Me$_3$Ge moieties), a singlet at $\delta$ 2.26 (the allylic protons), and two doublets in the alkenyl region at $\delta$ 5.18 ($J$ = 2.5 Hz) and $\delta$ 5.52 ($J$ = 2.5 Hz). The following $^1$H nmr signals were attributed to the desired bifunctional reagent 132: $\delta$ 0.07 (9-proton singlet for the Me$_3$Sn moiety with satellite peaks due to tin-proton coupling $^2J_{\text{Sn-H}} = 52$ Hz), $\delta$ 0.17 (9-proton singlet for the Me$_3$Ge moiety), $\delta$ 1.96 (2-proton doublet, $J$ = 1 Hz, for the allylic protons with satellite peaks due to tin-proton coupling $^2J_{\text{Sn-H}} = 69$ Hz), $\delta$ 4.91 (1-proton doublet, $J$ = 2.5 Hz, with satellite peaks due to tin-proton coupling $^4J_{\text{Sn-H}} = 25$ Hz), and $\delta$ 5.28 (1-proton doublet of triplets, $J$ = 2.5, 1 Hz, with satellite peaks due to tin-proton coupling $^4J_{\text{Sn-H}} = 23$ Hz).

Although disheartened by our continuing chromatographic difficulties, we were encouraged that the reagent (132) could be prepared, and presumably under the appropriate reaction conditions, it could be obtained in a pure form. The dimer byproduct 148 presumably was formed by a Wurtz type coupling reaction, a reaction for which allylic Grignard reagents are notorious$^{106}$ (Scheme 26).
Initially, 2-(trimethylgermyl)allylmagnesium bromide (149) is formed by reaction of 135 with magnesium, but it can react with another molecule of the allylic bromide 135, providing the Wurtz type coupling product 148, instead of reacting with trimethyltin chloride, which would give 132. It was hoped that the use of a nucleophilic displacement reaction would suppress the formation of 148. In this case, the allylic bromide would be displaced with an appropriate nucleophilic tin species (Scheme 26). The nucleophilic reagent that was chosen was (trimethylstannyl)lithium (150), which can be generated easily by the treatment of hexamethylditin (151) with methylolithium \(^{107}\) (equation 37).

\[
\text{(Me}_3\text{Sn)}_2 \xrightarrow{\text{MeLi}} \text{Me}_3\text{SnLi} \quad \text{(37)}
\]

In practice, when 135 was treated with an excess of (trimethylstannyl)lithium (150), a GLC analysis (Table 8, entry 1) of the crude reaction mixture showed the formation of three products: the desired product 132, the dimer 148, and hexamethylditin (151) (Scheme 27). It was thought that the formation of the dimer was the result of lithium-bromine exchange with (trimethylstannyl)lithium (150) and the allyl bromide 135 giving 2-(trimethylgermyl)-allyllithium (152), which could react with another molecule of...
135, giving the dimerized product 148 (Scheme 27). The formation of hexamethylditin (151) in the product mixture was thought to occur either from reaction of 150 with 153 (formed as a byproduct in the dimerization of 135), or from incomplete initial cleavage of the Sn-Sn bond in hexamethylditin by methyllithium (equation 37 and Scheme 27). Separation of these three products (132, 148, and 151) by silica gel chromatography proved to be impossible as all three products are very non-polar and run with the solvent front, even in 100% petroleum ether. The use of silver nitrate impregnated silica gel, useful in the separation of alkene mixtures, was completely unsuccessful as not only was no separation possible, but the silver nitrate impregnated silica gel actually catalyzed the dimerization of 132 so that only hexamethylditin (151) and the dimer 148 were obtained after chromatography.

\[
\begin{align*}
\text{GeMe}_3 & \quad \text{Br} \\
135 & \quad \xrightarrow{\text{Me}_3\text{SnLi} (150)} \\
& \quad \text{GeMe}_3 \text{SnMe}_3 + \text{LiBr} \\
\text{GeMe}_3 & \quad \text{Li} \\
152 & \quad \xrightarrow{\text{Me}_3\text{SnLi} (150)} \\
& \quad \text{GeMe}_3 \quad \text{Br} \\
135 & \quad \xrightarrow{\text{Me}_3\text{SnLi} (150)} \\
& \quad \text{GeMe}_3 \\
153 & \quad \xrightarrow{\text{Me}_3\text{SnLi} (150)} \\
& \quad \text{LiBr} \\
& \quad \text{GeMe}_3 \\
& \quad \text{Me}_3\text{Sn}_2 \\
151 &
\end{align*}
\]

**Scheme 27**

In an attempt to suppress the proposed lithium-halogen exchange between 150 and 135, and to moderate the activity of the trimethylstannyl nucleophile, a (trimethylstannyl)-copper(I) species was used for the nucleophilic displacement reaction. Organocopper(I) reagents are well known to effect this type of displacement. While treatment of 135
with Me$_3$SnCu•Me$_2$S (154)\textsuperscript{111} provided the same three products 132, 148, and 151 (equation 38, Table 8, entry 2), the amount of the dimer 148 formed was reduced.

**Table 8** Nucleophilic Displacement Reactions to Prepare the Bifunctional Reagent 132

![Chemical Reaction Diagram](image)

\[
\text{GeMe}_3 \xrightarrow{\text{Nuc, THF, } -78 \, ^\circ\text{C}} \text{GeMe}_3 \xrightarrow{\text{SnMe, + + (Me}}_3\text{Sn)}_2 (38)
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Leaving Group</th>
<th>132 (tole)</th>
<th>148 (tole)</th>
<th>151 (Me$_3$Sn)$_2$</th>
<th>Recovered Starting Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Me$_3$SnLi (150)</td>
<td>Br</td>
<td>76</td>
<td>6</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>2b</td>
<td>Me$_3$SnCu•Me$_2$S (154)</td>
<td>Br</td>
<td>88</td>
<td>2</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>3c</td>
<td>Me$_3$SnLi (150)</td>
<td>OTs</td>
<td>93</td>
<td>0</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>4d</td>
<td>Me$_3$SnCu(CN)Li (155)</td>
<td>OTs</td>
<td>58</td>
<td>0</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>5e</td>
<td>Me$_3$SnLi (150)</td>
<td>OTs</td>
<td>75</td>
<td>0</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>6f</td>
<td>Me$_3$SnLi (150)</td>
<td>OTs</td>
<td>99</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

\[^a\] 1.3 equiv Me$_3$SnLi generated from the interaction of MeLi with (Me$_3$Sn)$_2$.
\[^b\] 1.5 equiv Me$_3$SnCu•Me$_2$S generated from the interaction of MeLi with (Me$_3$Sn)$_2$ followed by addition of CuBr•Me$_2$S.
\[^c\] 0.9 equiv Me$_3$SnLi generated from the interaction of MeLi with (Me$_3$Sn)$_2$.
\[^d\] 0.9 equiv Me$_3$SnCu(CN)Li generated from the interaction of MeLi with (Me$_3$Sn)$_2$ followed by addition of CuCN.
\[^e\] 0.8 equiv Me$_3$SnLi generated from Me$_3$SnH.
\[^f\] 0.97 equiv Me$_3$SnLi generated from Me$_3$SnH.

At this juncture, we re-evaluated the situation. It appeared that the formation of the dimer could not be eliminated and that a different leaving group, particularly one that was not prone to this dimerization, was required. In addition, this leaving group should possess some polar functionality such that it would be suitable for chromatographic separation on silica gel. Overman\textsuperscript{100} reported a one pot procedure for the conversion of 2-(trimethylsilyl)prop-2-enol (156) into its corresponding allylstannane 157 via an *in situ*
displacement of the mesylate derived from 156 with the tributylstannyl anion (equation 39).

\[
\begin{align*}
\text{SiMe}_3 \quad & \quad 1) \text{n-BuLi, THF, -50 °C; MsCl} \\
\text{OH} \quad & \quad 2) \text{n-Bu}_3\text{SnLi, -78 °C \to rt}
\end{align*}
\]

It was decided that a similar procedure involving the p-toluenesulfonyl group would be employed to prepare the bifunctional reagent 132. After some experimentation, the preparation of the tosylate 158 was achieved in 86% isolated yield through the treatment of 133 in diethyl ether with halide-free methylithium followed the addition of by p-toluene-sulfonyl chloride (Scheme 28). These atypical conditions\textsuperscript{112} were needed since the use of other conditions (p-TsCl, DMAP, Et\textsubscript{3}N in CH\textsubscript{2}Cl\textsubscript{2}) resulted in the formation of a mixture of the expected product 158, as well as the allylic chloride 159 through an \textit{in situ} displacement of the tosylate group\textsuperscript{54}. Deprotonation of 133 with methylithium-lithium bromide complex followed by addition of p-toluenesulfonyl chloride gave rise to a mixture of 158 and the allylic bromide 135, the latter product being produced via a similar \textit{in situ} displacement of the tosylate group with the bromide anion.
The structural assignment of the tosylate 158 was supported by spectral data. The IR spectrum of 158 displayed a stretching absorption at 1599 cm\(^{-1}\) (C=C), and two strong absorptions at 1368 and 1176 cm\(^{-1}\) (SO\(_2\)). The \(^1\)H nmr spectrum of 158 exhibited a 9-proton singlet at \(\delta\) 0.19 for the Me\(_3\)Ge group, a 3-proton singlet at \(\delta\) 2.43 for the aromatic methyl group, a 2-proton singlet at \(\delta\) 4.64 attributed to the allylic protons, two 1-proton singlets at \(\delta\) 5.33 and \(\delta\) 5.72 indicative of the two alkenyl protons, and two 2-proton doublets at \(\delta\) 7.32 (\(J=8\) Hz) and \(\delta\) 7.78 (\(J=8\) Hz) for the aromatic protons.

Our hypothesis about the effect of the leaving group on the success of the reaction proved to be correct. Treatment of an excess of 158 with (trimethylstannyl)lithium (150)\(^{107}\) (Table 8, entry 3) or the corresponding lithium(trimethylstannyl)(cyano)cuprate (155)\(^{111}\) (Table 8, entry 4) still provided a chromatographically inseparable mixture of hexamethylditin (151) and the desired 132, but none of the dimer 148 was evident through GLC and \(^1\)H nmr spectroscopic analyses of the crude reaction mixture. The remaining starting material 158 was easily separated from the product mixture by silica gel chromatography.
Despite completely suppressing the formation of the dimer 148, the significant problem of contamination from hexamethylditin (151) remained. Whereas the presence of 148 would not affect the further use of 132, the same could not be said for hexamethylditin (151). In order for 132 to be synthetically useful, it needed to be isolated free from hexamethylditin.

It was proposed that the presence of hexamethylditin in product mixture was a result of incomplete cleavage of the Sn-Sn bond by methyllithium (equation 37), and studies by Oehlschlager and coworkers\textsuperscript{108} support this hypothesis. An alternative method for the generation of (trimethylstannyl)lithium which did not require the use of hexamethylditin or an alkylolithium was needed. The generation of (trimethylstannyl)lithium using Still’s method,\textsuperscript{113} by treatment of trimethyltin hydride (160) with LDA, has been reported,\textsuperscript{114} but the prospect of using the volatile and highly toxic trimethyltin hydride was not overly appealing. However, Lipshutz has reported\textsuperscript{115} a convenient preparation of this volatile material (160) in triglyme, using conditions similar to those shown in equation 40.

\[
\begin{align*}
\text{Me}_3\text{SnCl} & \xrightarrow{\text{LiAlH}_4, \text{diglyme, } 65 \, ^\circ\text{C}} \text{Me}_3\text{SnH} \\
\text{161} & \xrightarrow{} \text{160}
\end{align*}
\]

Employing a modification of the procedure described by Lipshutz, reduction of trimethyltin chloride (161) was achieved in warm diglyme using lithium aluminum hydride (equation 40) to provide the volatile trimethyltin hydride (160), which was distilled directly from the reaction mixture. After a subsequent distillation to remove trace amounts of solvent, the resonances observed in the \textsuperscript{1}H nmr spectrum of trimethyltin hydride agreed with the reported literature values.\textsuperscript{115}

\[
\begin{align*}
\text{Me}_3\text{SnH} & \xrightarrow{\text{LDA, THF, } 0 \, ^\circ\text{C}} \text{Me}_3\text{SnLi} \\
\text{160} & \xrightarrow{} \text{150}
\end{align*}
\]
We now were ready to see if the source from which (trimethylstannyl)lithium (150) was generated had any effect on the product mixture in the reaction to prepare 132 (equation 38, Table 8). (Trimethylstannyl)lithium (150) was generated by the treatment of trimethyltin hydride (160) with LDA (equation 41) and to this mixture was added excess 158 (Table 8, entry 5). After aqueous workup, an analysis of the crude reaction mixture by GLC and $^1$H nmr spectroscopy showed the presence of 132 and unreacted starting material but there was neither dimer (148) nor hexamethylditin (151) in the product mixture. With the addition of only a slight excess of 158 to a solution of (trimethylstannyl)lithium (150) (Table 8, entry 6), the bifunctional reagent 132 was isolated, after workup and silica gel chromatography, in 90% yield (equation 42).

The structural assignment for 132 was in complete agreement with its spectral data. The $^1$H nmr spectrum of 132 displayed two 9-proton singlets, one at $\delta$ 0.07 (Me$_3$Sn) and the other at $\delta$ 0.17 (Me$_3$Ge). The assignment of these peaks was facilitated by the presence of satellite peaks due to tin-proton coupling ($^2$J$_{Sn-H}$ = 52 Hz) for the signal at $\delta$ 0.07. The allylic protons appeared as a 2-proton doublet ($J$ = 1 Hz) at $\delta$ 1.96 and also exhibited tin-proton coupling ($^2$J$_{Sn-H}$ = 69 Hz). Resonances for the alkenyl protons appeared at $\delta$ 4.91 (a 1-proton doublet, $J$ = 2.5 Hz) and $\delta$ 5.28 (a 1-proton doublet of triplets, $J$ = 2.5, 1 Hz), and both displayed long range tin-proton coupling ($^4$J$_{Sn-H}$, 25 Hz and 23 Hz, respectively). Resonances for each of the 5 different carbon atoms were seen in the $^{13}$C nmr spectrum of 132. In addition to this spectral data, the molecular formula of 132 was confirmed by a high resolution mass spectrometric measurement on the molecular ion.
2.5 Preparation of 2-(trimethylgermyl)allylcopper(I)-dimethyl sulfide (162) and conjugate additions of 162 to α,β-unsaturated ketones

The crucial transmetalation required for the formation of the allylcopper(I) species could now be investigated. It has been reported that allylcopper(I) reagents can be prepared by combining allyllithium (obtained by the treatment of allyltributylstannane with an alkylthiium) and a copper(I) source such as copper(I) iodide.

\[ \text{GeMe}_3 \text{SnMe}_3 \xrightarrow{1) \text{MeLi-LiBr, THF, -78 °C}} \text{CuBr}\cdot\text{Me}_2\text{S, -78 °C} \]

After much experimentation, it was found that treatment of 132 in cold THF with methyllithium-lithium bromide complex, followed by copper(I) bromide-dimethylsulfide complex, provided 2-(trimethylgermyl)allylcopper(I)-dimethylsulfide (162) (Scheme 29).

Evidence for the successful preparation of 162 came from the conjugate addition reaction of this reagent with cyclohex-2-enone in the presence of trimethylsilyl bromide. After appropriate workup and purification, 163 was isolated in 91% yield. The IR spectrum of 163 indicated that a ketone was present and that it was no longer conjugated (1713 cm\(^{-1}\)).
and the $^1$H nmr spectrum of 163 exhibited a 9-proton singlet at $\delta$ 0.18 for the methyl substituents on germanium and two 1-proton signals in the alkenyl region at $\delta$ 5.24 and $\delta$ 5.48.

Several $\alpha,\beta$-unsaturated ketones were used as substrates to test the generality and the viability of the conjugate addition process. Thus, addition of a variety of $\alpha,\beta$-unsaturated ketones (110, 170-175) and trimethylsilyl bromide to a solution of the allylcopper(I) reagent (162) in cold (-78 °C) THF (equation 43, Table 9) provided, after workup and purification, fair to excellent yields of the conjugate addition products 163-169 (Table 9). In each case, the conjugate addition reaction was complete (by TLC analysis) in less than 15 minutes. The conjugate addition reactions have been routinely performed using ~0.5 mmol of the enone although no reduction in yields were observed when the reactions were performed on larger scale (~3 mmol of enone).

\[
\begin{align*}
110 & \quad R = H \\
171 & \quad R = Me \\
170 & \\
175 & \\
172 & \quad R_1 = H, \quad R_2 = H \\
173 & \quad R_1 = H, \quad R_2 = Me \\
174 & \quad R_1 = Me, \quad R_2 = H
\end{align*}
\]
Table 9 Conjugate Addition of 162 to α,β-Unsaturated Ketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enone Substrate</th>
<th>Product</th>
<th>Yield(%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>cyclohex-2-enone (110)</td>
<td>163</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>4-isopropylcyclohex-2-enone (170)</td>
<td>164</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>3-methylcyclohex-2-enone (171)</td>
<td>165</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>cyclopent-2-enone (172)</td>
<td>166</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>3-methylcyclopent-2-enone (173)</td>
<td>167</td>
<td>56</td>
</tr>
<tr>
<td>6</td>
<td>2-methylcyclopent-2-enone (174)</td>
<td>168</td>
<td>89b</td>
</tr>
<tr>
<td>7</td>
<td>(R)-(-)-carvone (175)</td>
<td>169</td>
<td>86c</td>
</tr>
</tbody>
</table>

a Yield of purified, distilled product.
b Consisted of a mixture of C-2 epimers (ratio ~8:1).
c Consisted primarily of a mixture of C-2 epimers (ratio ~2:1). Also present was a small amount (2-3%) of a corresponding C-3 epimer.

The structural assignments for 163 through 169 were based on the spectral data obtained. For example, the IR spectrum of 166 indicated the presence of a cyclopentanone carbonyl group (1746 cm⁻¹). Similar C=O stretching absorptions were seen in the IR
spectra of the remaining products, confirming that chemoselective 1,4-addition (and not 1,2-addition) had occurred. Also observed in the fingerprint region of the IR spectra of 163 - 169 was a characteristic germanium - methyl rocking absorption at ~825 cm\(^{-1}\). The \(^1\)H nmr spectrum of 166 exhibited a 9-proton singlet at \(\delta 0.20\) for the methyl substituents on germanium and two 1-proton signals in the alkenyl region at \(\delta 5.23\) and \(\delta 5.50\). Similar resonances were seen in the \(^1\)H nmr spectra of the remaining products. The \(^{13}\)C nmr spectra of 163 - 169 were also consistent with the assigned structures. Resonances for each of the different carbon atoms in compounds 163 - 169 were seen in their \(^{13}\)C nmr spectra. Finally, the molecular formulae of 163 - 169 were confirmed by high resolution mass spectrometric measurements on either the molecular ion or the \((M^+ - Me)\) fragment.

The stereochemistry of the conjugate addition products 164 and 169 deserves further comment. It has been suggested that the preferred mode of attack of organometallic reagents to \(\alpha,\beta\)-unsaturated ketones is antiparallel to the \(\pi\) system of the enone so that continuous overlap of the developing sigma bond with \(\pi\) system is possible through the transition state.\(^{116}\) As conjugate addition reactions are typically under kinetic control,\(^{117}\) the stereochemical outcome has often been explained on the basis of attack of the nucleophile perpendicular to the \(\pi\) system of the enone (stereoelectronic control), and from the least hindered side of the molecule (steric control).\(^{118}\)
The addition of 162 to 4-isopropylcyclohex-2-enone (170) gave the product 164, as a single diastereomer with exclusively trans relative stereochemistry of the ring substituents. There is ample literature precedent for the stereoselective addition of organocopper reagents to 4-alkylcyclohex-2-enones (Scheme 30). Two possible half-chair conformations that the enone can adopt are 176 (the more stable conformer due to the pseudo equatorial orientation of the C-4 alkyl group) and 177. Attack of an organocopper nucleophile (Y\textsuperscript{-}), perpendicular to the π system of the enone, from the top face (path A) of 176 proceeds through a chair-like transition state to give the enolate 178. Approach of the nucleophile, in a perpendicular fashion to the enone, from the bottom face (path B) of 176 proceeds through a boat-like transition state to provide the enolate 179. On the other hand, approach of the nucleophile (Y\textsuperscript{-}) from the bottom face of the less stable conformer (177) gives the chair-like enolate 180 (path C) while a perpendicular attack on the top face results in 181 (path D). The boat-like intermediate 181 is clearly energetically less favorable than the chair-like 180. The preferential formation of the trans isomer is attributed to steric hindrance in the transition state leading to 178, between the incoming nucleophile and the
substituent at carbon four. This steric factor disfavors the formation of the \textit{cis} isomer. Both the boat-like 179 and the chair-like 180 lead to the formation of the \textit{trans} isomer without steric interference from the C-4 substituent. As the size of the C-4 alkyl substituent (R) and the incoming nucleophile (Y-) increase, the stereoselectivity of the addition was found to increase.\textsuperscript{120b}

The addition of the organocopper(I) reagent 162 to (R)-(\texttextit{-})-carvone (175) proceeded in the precedented\textsuperscript{121} stereoselective manner, predominantly \textit{trans} to the substituent at carbon five (ratio of \textit{trans}:\textit{cis} addition -97:3). The $^1$H nmr spectrum of the product indicated that 169 was actually a 65:32:3 mixture of three diastereomers,\textsuperscript{122} with the two major diastereomers being epimeric at carbon two. Signals for the C-2 methyl substituent appeared at $\delta$ 1.03 (d, $J = 7$ Hz), $\delta$ 1.08 (d, $J = 7$ Hz), and $\delta$ 1.14 (d, $J = 7$ Hz) in a ratio of 11:1:22.

The addition of the allylcopper(I) reagent 162 to 3-methylcyclohex-2-enone (171) and 3-methylcyclopent-2-enone (173) proceeded only in moderate yields (Table 9, entries 3 and 5, respectively). Both of these enones are disubstituted in the \textit{\beta}-position and therefore are sterically crowded. In many cases, 1,4-addition to \textit{\beta},\textit{\beta}-disubstituted enones proceeds only reluctantly without the addition of HMPA or Lewis acids.\textsuperscript{123} In this respect, the yields of 165 and 167 (46\% and 56\%, respectively) are quite reasonable.

There are several noteworthy results from this conjugate addition that require comment. Although either solutions of halide-free methyllithium or the methyllithium-lithium bromide complex in diethyl ether may be used for the initial transmetalation of 132, use of the latter reagent results in the much more rapid dissolution of the copper(I) salt in THF, and hence a more rapid formation of the required allylcopper(I) reagent. Under the reaction conditions employed, none of the trimethylsilyl enol ether intermediates were isolated. A $^1$H nmr analysis of the crude reaction products indicated that complete hydrolysis of the trimethylsilyl enol ether intermediates had been effected during the workup with aqueous NH$_4$Cl-NH$_4$OH (pH 8). The use of recrystallized copper(I)
bromide-dimethyl sulfide provides consistently high yields of the 1,4-addition adduct. Although copper(I) iodide can be used as the copper(I) source, the yields using copper(I) iodide are vastly inferior and poor regioselectivity is observed. This competition between 1,2- and 1,4-addition has been rationalized\(^{81}\) as the result of incomplete formation of the allylcopper(I) reagents due to the high sensitivity of the reaction to impurities in the copper(I) salt used to generate the organocopper species. As copper(I) iodide is difficult to prepare in a pure form,\(^{124}\) it is likely that impurities in copper(I) iodide prevent complete formation of the allylcopper(I) reagents. However, since copper(I)bromide-dimethyl sulfide can readily be obtained in high purity by recrystallization,\(^{89,125}\) complete formation of 162 is assured with the use of this salt.

\[
\begin{align*}
\text{GeMe}_3\text{SnMe}_3 & \xrightarrow{1\text{) MeLi\cdotLiBr, THF, -78 °C}} \text{GeMe}_3\text{Cu\cdotMe}_2\text{S} \\
\text{132} & \xrightarrow{2\text{) CuBr\cdotMe}_2\text{S, -78 °C}} \text{162} \\
n & + \\
\text{GeMe}_3\text{SnMe}_3 & \xrightarrow{1\text{) MeLi\cdotLiBr, THF, -78 °C}} \text{GeMe}_3\text{Cu\cdotMe}_2\text{S} \\
\text{132} & \xrightarrow{2\text{) CuBr\cdotMe}_2\text{S, -78 °C}} \text{162} \\
\text{GeMe}_3 & + \\
\text{GeMe}_3\text{SnMe}_3 & \xrightarrow{1\text{) MeLi\cdotLiBr, THF, -78 °C}} \text{GeMe}_3\text{Cu\cdotMe}_2\text{S} \\
\text{132} & \xrightarrow{2\text{) CuBr\cdotMe}_2\text{S, -78 °C}} \text{162} \\
\text{148} & + \\
\text{GeMe}_3\text{SnMe}_3 & \xrightarrow{1\text{) MeLi\cdotLiBr, THF, -78 °C}} \text{GeMe}_3\text{Cu\cdotMe}_2\text{S} \\
\text{132} & \xrightarrow{2\text{) CuBr\cdotMe}_2\text{S, -78 °C}} \text{162} \\
\text{148} & + \\
\text{GeMe}_3\text{SnMe}_3 & \xrightarrow{1\text{) MeLi\cdotLiBr, THF, -78 °C}} \text{GeMe}_3\text{Cu\cdotMe}_2\text{S} \\
\text{132} & \xrightarrow{2\text{) CuBr\cdotMe}_2\text{S, -78 °C}} \text{162} \\
\text{148} & + \\
\text{GeMe}_3\text{SnMe}_3 & \xrightarrow{1\text{) MeLi\cdotLiBr, THF, -78 °C}} \text{GeMe}_3\text{Cu\cdotMe}_2\text{S} \\
\text{132} & \xrightarrow{2\text{) CuBr\cdotMe}_2\text{S, -78 °C}} \text{162} \\
\text{148} & + \\
\end{align*}
\]

Both pure 132 (equation 44) and the mixture of 132 and the dimer 148 (equation 45) can be used to prepare 162. The dimer 148 is unreactive towards alkyllithiums and does not interfere in the preparation of 162. Since the procedure which produces the mixture of 132 and 148 is experimentally more convenient than the protocol used to prepare pure 132, especially on a large scale, and does not require the use of the volatile
and toxic trimethyltin hydride, it is the preferred method for the generation of the bifunctional reagent 162. In a typical experiment, treatment of 0.30 g of an 10:1 mixture of 132:148 (−0.86 mmol 132, −0.09 mmol 148) in cold THF with 0.65 mL of MeLi•LiBr (1.31 M solution in Et2O, 0.85 mmol) and 0.18 g of CuBr•Me2S (0.88 mmol) provided the organocopper(I) reagent 162 along with unreacted dimer 148. Reaction of this mixture with 70 μL of 4-isopropylcyclohex-2-enone (170) provided 0.13 g of the 1,4-addition product 164 (90% yield).

2.6 A new bifunctional reagent: 2-(Trimethylstannyldiallylcopper(I))-dimethyl sulfide (182)

\[
\begin{align*}
\text{d} & \quad \text{d} \\
48 & \quad 182 & \quad 183
\end{align*}
\]

Given the success in the preparation of 162 and its conjugate addition to α,β-unsaturated ketones, it was decided to investigate the reactivity of another functionalized allylic reagent, 2,3-bis(trimethylstannyl)propene (183). We were intrigued with the possibility of preparing another functionalized allylcopper(I) reagent 182, which would also be equivalent to the d2, d3 prop-1-ene synthon, and we wished to see if it too could be added in a conjugate sense to α,β-unsaturated ketones. Alkenyltrimethylstannanes are well known for their synthetic utility in coupling reactions and as precursors to alkenyl iodides and alkenyllithium reagents.126,127

The preparation of 183 was achieved, according to a literature procedure,128 by the palladium(0) catalyzed addition of hexamethylditin (151) to allene (equation 46).

\[
\text{Me}_3\text{Sn} - \text{SnMe}_3 \quad \xrightarrow{\text{H}_2\text{C} = \text{C} = \text{CH}_2, \quad \text{Pd}(\text{PPh}_3)_4, \quad 75^\circ\text{C}} \quad \text{SnMe}_3 \\
151 & \quad 183
\]
While one would expect different reactivities of the allylic and vinylic tin moieties in 183, it was reported\textsuperscript{128} that when 183 was treated with methyllithium followed by a variety of electrophiles, only low yields of products were isolated. Undaunted, we proceeded with our plans and attempted the formation of an allylcopper species (182) and its conjugate addition to cyclic enones. In our hands, treatment of 183 with 1 equivalent of methyllithium gave cleanly the corresponding allyllithium species, which could be successfully trapped in high yields with a variety of electrophiles (\textit{vide infra}, Chapter 4). Analysis of these products by $^1$H nmr spectroscopy indicated that no transmetalation of the alkenyl(trimethylstannyl) function had occurred.

![Scheme 31](image)

Following a procedure essentially identical with that used for the successful preparation of 2-(trimethylgermyl)allylcopper(I)-dimethyl sulfide (162), treatment of a solution of 183 in cold THF with methyllithium-lithium bromide complex, followed by copper(I) bromide-dimethyl sulfide, provided 2-(trimethylstannyl)allylcopper(I)-dimethyl...
sulfide (182) (Scheme 31). Evidence for the successful formation of this species came from its conjugate addition reaction with cyclohex-2-enone (110) in the presence of trimethylsilyl bromide. After suitable workup and purification by silica gel chromatography and distillation, 184 was isolated in 93% yield. The IR spectrum of 184 indicated the presence of a ketone function (1714 cm\(^{-1}\)) and the \(^1\)H nmr spectrum exhibited a 9-proton singlet at \(\delta 0.10\) for the methyl substituents on tin, along with satellite peaks due to tin-proton coupling (\(^2J_{\text{Sn-H}} = 53\) Hz), and two 1-proton signals in the alkenyl region at \(\delta 5.19\) and \(\delta 5.61\), along with satellite peaks due to tin-proton coupling (\(^3J_{\text{Sn-H}}, 70\) Hz and 150 Hz, respectively).

The generality of this conjugate addition reaction was demonstrated with a variety of \(\alpha,\beta\)-unsaturated ketones. Treatment of a cold (-78 °C) solution of 182 in THF with the enones 110 and 170-175 in the presence of trimethylsilyl bromide (equation 47, Table 10) provided, after workup and purification, the 1,4-addition products 184-190, all isolated in fair to excellent yields (Table 10).

\[
\begin{align*}
110 & \quad R = H \\
171 & \quad R = \text{Me} \\
170 & \\
175 & \\
172 & \quad R_1 = H, R_2 = \text{H} \\
173 & \quad R_1 = H, R_2 = \text{Me} \\
174 & \quad R_1 = \text{Me}, R_2 = \text{H}
\end{align*}
\]
Table 10 Conjugate Addition of 182 to $\alpha,\beta$-Unsaturated Ketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enone Substrate</th>
<th>Product</th>
<th>Yield(%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>cyclohex-2-enone (110)</td>
<td>184</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>4-isopropylcyclohex-2-enone (170)</td>
<td>185</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>3-methylcyclohex-2-enone (171)</td>
<td>186</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>cyclopent-2-enone (172)</td>
<td>187</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>3-methylcyclopent-2-enone (173)</td>
<td>188</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>2-methylcyclopent-2-enone (174)</td>
<td>189</td>
<td>82$^b$</td>
</tr>
<tr>
<td>7</td>
<td>(R)-(-)-carvone (175)</td>
<td>190</td>
<td>85$^c$</td>
</tr>
</tbody>
</table>

$^a$ Yield of purified, distilled product.

$^b$ Consisted of a mixture of C-2 epimers (ratio ~8:1).

$^c$ Consisted primarily of a mixture of C-2 epimers (ratio ~2:1). Also present was a small amount (2-3%) of a corresponding C-3 epimer.

The structural assignments for 184-190 were based on the spectral data. For example, the IR spectrum of 187 indicated the presence of a cyclopentanone carbonyl function (1746 cm$^{-1}$). Similar C=O stretching absorptions were seen in the IR spectra of...
the other products, confirming that 1,4-addition had occurred. Also observed in the
fingerprint region of the IR spectra of 184-190 was a characteristic tin - methyl rocking
absorption at ~769 cm\(^{-1}\). The \(^{1}\)H nmr spectrum of 187 exhibited a 9-proton singlet at
\(\delta 0.13\) for the methyl substituents on tin, along with satellite peaks due to tin-proton
coupling (\(^{2}J_{\text{Sn-H}} = 53 \text{ Hz}\)) and two 1-proton signals in the alkenyl region at \(\delta 5.19\) and
\(\delta 5.64\), along with satellite peaks due to tin-proton coupling (\(^{3}J_{\text{Sn-H}} 70 \text{ Hz and 150 Hz,}
\) respectively). Similar resonances were seen in the \(^{1}\)H nmr spectra of the other products.
The \(^{13}\)C nmr spectra of 184-190 were also consistent with the assigned structures.
Resonances for each of the different carbon atoms in 184-190 were seen in their \(^{13}\)C nmr
spectra. Finally, the molecular formulae of 184-190 were confirmed by high resolution
mass spectrometric measurements on either the molecular ion or the (M\(^{+}\) - Me) fragment.

The reactivity of 182 with enones was similar to that of 2-(trimethylgermyl)-allylcopper(I)-dimethylsulfide (162) with enones. The addition of 182 to 4-isopropyl-
cyclohex-2-enone (170) and (R)-(-)-carvone (175) proceeded in the precedented
stereoselective manner described for the addition of 162 to those enones.\(^{119-122}\) Not
unexpectedly, moderate yields were obtained from the reaction of the allylcopper(I) reagent
182 with enones disubstituted in the \(\beta\)-position\(^{123}\) (Table 10, entries 3 and 5, respectively).

A number of factors are worthy of further comment in this general procedure. The
reaction time is short. The allylcopper reagent 182 adds to enones giving the products in
less than 15 minutes. While the conjugate addition reactions have been routinely performed
using ~0.5 mmol of the enone, no reduction in yields were observed when the reactions
were performed on larger scale (2.0 mmol of enone). Only the 1,4-addition products were
isolated; no 1,2-addition was observed. In the formation of 182, only transmetalation at
the allylic trimethylstannyl group of 183 was observed, with no transmetalation at the
alkenyl site. Under the reaction conditions employed, none of the trimethylsilyl enol ether
intermediates were isolated. A \(^{1}\)H nmr analysis of the crude reaction products indicated
complete hydrolysis of the trimethylsilyl enol ether intermediates by the workup with aqueous NH₄Cl-NH₄OH (pH 8). It is important that, in this workup protocol, the mixture be stirred for the minimum amount of time required to oxidize the copper(I) species. Longer times for this aqueous workup result in significant destannylation of the conjugate addition products.

2.7 Conclusions

The preparation of two novel, usefully functionalized allylcopper(I) reagents, 2-(trimethylgermyl)allylcopper(I)-dimethylsulfide (162) and 2-(trimethylstannyl)allylcopper(I)-dimethylsulfide (182) has been accomplished. These species efficiently transfer, in a 1,4-manner, the 2-(trimethylgermyl)allyl and 2-(trimethylstannyl)allyl groups, respectively, to α,β-unsaturated ketones (30) (Scheme 32). The conjugate addition products 191 and 192 are structurally novel, containing an allyl group functionalized at carbon two, which should have great potential in organic synthesis. The synthetic utility of these allylcopper(I) reagents, 162 and 182, in natural product synthesis, remains to be investigated, but looks promising since all of the conversions can be accomplished on relatively large scale.

\[
\begin{align*}
162 & \quad M = \text{GeMe}_3 \\
182 & \quad M = \text{SnMe}_3 \\
\end{align*}
\]

\[
\begin{align*}
\text{Me}_3\text{SiBr, THF, -78 °C;} \\
\text{H}_2\text{O (pH 8)} \\
\end{align*}
\]

\[
\begin{align*}
\text{NH}_4\text{Cl-NH}_4\text{OH} \\
\end{align*}
\]

\[
\begin{align*}
191 & \quad M = \text{GeMe}_3 \\
192 & \quad M = \text{SnMe}_3 \\
\end{align*}
\]

Scheme 32
The conjugate addition reactions of either 162 or 182 to enones are experimentally facile. These allylcopper(I) reagents are extremely reactive and transfer of the substituted allyl group to the β-position of α,β-unsaturated ketones (30) proceeds generally in high yields in less than 15 minutes. However, as with many organocopper reactions, in cases where the enone substrate is sterically congested or disubstituted in the β-position (R₂ = alkyl, Scheme 32), lower product yields are obtained.¹²³
3. Stereocontrolled Annulation Method for the Synthesis of the \textit{Trans}-Fused \textit{Bicyclo}[3.3.0]octane Ring System

3.1 Background

The bicyclo[3.3.0]octane ring system is a common structural unit found in many naturally occurring compounds.\textsuperscript{130,131} While in most of the latter compounds the ring fusion is \textit{cis},\textsuperscript{130,131} the \textit{trans} ring fusion is also known.\textsuperscript{132} The abundance of annulation methods that have been developed to produce fused cyclopentyl rings attest to the importance of this structural unit.\textsuperscript{133}

\begin{center}
\begin{tikzpicture}
\draw (-1,0) circle [radius=1cm];
\draw (0,-1) circle [radius=1cm];
\filldraw[fill=white] (0,0) circle [radius=0.1cm];
\filldraw[fill=white] (-1,0) circle [radius=0.1cm];
\filldraw[fill=white] (0,-1) circle [radius=0.1cm];
\end{tikzpicture}
\end{center}

\begin{center}
\begin{tikzpicture}
\draw (-1,0) circle [radius=1cm];
\draw (0,-1) circle [radius=1cm];
\filldraw[fill=white] (0,0) circle [radius=0.1cm];
\filldraw[fill=white] (-1,0) circle [radius=0.1cm];
\filldraw[fill=white] (0,-1) circle [radius=0.1cm];
\end{tikzpicture}
\end{center}

The strain energy of the \textit{trans}-fused bicyclo[3.3.0]octane (193) is 6.4 kcal/mol greater than that for the \textit{cis}-fused system (194).\textsuperscript{22} Oftentimes researchers engaged in the construction of polyquinanes have operated with the basic assumption that the ring junction formed between two fused cyclopentyl rings is necessarily \textit{cis}, because the transition state producing the \textit{cis}-fused ring junction should be much less strained, and consequently lower in energy, than that leading to the \textit{trans}-fused product. However, under the appropriate conditions (\textit{vide infra}), the \textit{trans}-fused bicyclo[3.3.0]octane ring systems can be formed,\textsuperscript{134-149} and thus, due caution is required when assigning ring junction stereochemistry in polyquinane molecules.

The major impetus for investigations into the preparation of the \textit{trans}-fused bicyclo[3.3.0]octane ring system have been studies of the physical properties of this conformationally rigid, strained system and methodological studies of annulation methods
for the construction of fused ring systems. A brief outline of the methods that have been reported to synthesize such systems will follow.

In the course of investigating the strain energy of the cis- and trans-fused bicyclo[3.3.0]octane ring system, Linstead and Meade\textsuperscript{140} prepared trans-bicyclo[3.3.0]octan-3-one (195) in low (5\%) yield from the diester 196 by a Dieckmann condensation, followed by hydrolysis of the ester and decarboxylation of the resulting carboxylic acid (equation 48).

\begin{center}
\begin{align*}
\text{H} & \text{CO}_2\text{Et} & \text{1) Dieckmann condensation} & \text{H} \\
\text{196} & \text{CO}_2\text{Et} & \text{2) ester hydrolysis} & \text{195} \\
& & \text{3) decarboxylation} & \\
\end{align*}
\end{center}

Subsequent modifications\textsuperscript{141} of this procedure using the diacid provided 195 in significantly higher (50\%) yields.

Investigations by the research groups of Negishi\textsuperscript{142} and Whitby\textsuperscript{143} showed that dibutylzirconocene [Cp\textsubscript{2}Zr(n-Bu)\textsubscript{2}] mediated cyclizations of 1,6-dienes proceed stereoselectively to produce trans-fused zirconabicyclo[3.3.0]octanes. Carbonylation of the resultant zirconabicycle intermediate provides trans-fused bicyclo[3.3.0]octan-3-ones. Negishi\textsuperscript{142} reported that the zirconocene-mediated cyclization of the geometrically isomeric dienes 197 and 198 provided exclusively the trans-fused zirconabicycles 199 and 200, respectively, which were subsequently converted into the ketones 201 and 202 (equations 49 and 50). Interestingly, the thermodynamically less stable zirconacyclopentane derivative 200 slowly isomerized to the more stable stereoisomer 199.
Yamamoto and coworkers\textsuperscript{144} achieved the formation of a \textit{trans}-fused bicyclo[3.3.0]octane ring system by a novel palladium(0) catalyzed cyclization of a 6-substituted octa-2,7-dienyl acetates. For example, the cyclization of 203 under palladium(0) catalysis provided the bicyclic system 204 in 56\% yield with exclusive \textit{trans} diastereoselectivity at the ring junction, along with the monocyclic system 205 in 11\% yield (equation 51).

However, when 203 was further functionalized (with R=CO\textsubscript{2}Et or R=CH\textsubscript{2}OMOM), only the monocyclic system 205 was produced under these conditions. The failure of the latter intramolecular Heck reactions to form the bicyclic systems was attributed to steric factors.

Investigations by Bailey and coworkers\textsuperscript{145} provide an example of tandem anionic ring closure of bis(olefinic) alkyllithiums to provide the \textit{trans}-fused bicyclo[3.3.0]octane
system. Treatment of 4-ethenyl-7-iodohexene (206) with t-butyllithium, followed by addition of TMEDA and an electrophile to the cyclized intermediate 207, provides a general method for the synthesis of 3-substituted trans-bicyclo[3.3.0]octanes 208 in good (65 - 87%) synthetic yields (equation 52).

Cooke and Gopal\textsuperscript{146} conducted similar research into stereoselective tandem anionic cyclizations to provide trans-fused ring systems. Carbanion stabilizing groups (esters) at the terminal positions of the alkenes moieties (see 209, equation 53) were investigated to alleviate the need for reaction accelerating additives such as TMEDA. When the carbon-5 alkenyl moiety had an \textit{E} geometry, a mixture of the trans- and cis-fused bicyclo[3.3.0]octane ring systems 210 and 211, respectively, was obtained in low yield. Incorporation of the \textit{Z} alkene geometry increased the stereoselectively such that only the trans-fused system 210 was produced in 63% yield. The authors proposed that the stereoselectivity of the reaction originated from destabilization of the transition state leading to the cis-fused product 211, through increased A\textsubscript{1,3} strain in the \textit{Z}-olefin substrate.
In the course of their studies of annulating agents for the construction of five-membered carbocycles, Trost and coworkers\textsuperscript{147} prepared the bifunctional reagent 2-bromo-3-(trimethylsilyl)propene (212). Reagent 212 was added in a Michael fashion to 1-acetylcyclopentene (213) under Lewis acid catalysis to provide an \textasciitilde{}1:1 mixture of 214 and 215 in 75\% yield (equation 54).

An intramolecular Barbier reaction of the trans-isomer 215 produced the highly functionalized trans-bicyclo[3.3.0]octane system 216 in 44\% yield, along with the protiodebrominated byproduct 217 in 48\% yield\textsuperscript{147} (equation 55). This annulation method relies on fixing the stereochemistry of the ring substituents prior to cyclization to ensure that the stereochemistry of the ring substituents in the precursor was retained in the cyclized product. It is notable that under the reaction conditions, no epimerization occurred prior to cyclization.
In the process of carrying out the total syntheses of two linearly fused triquinane natural products, hypnophilin and coriolin, Little and coworkers\textsuperscript{148} discovered that the trans-fused bicyclo[3.3.0]octane ring system was easily accessible depending on the identity of R in compound 218-221 (equation 56). Epoxidation of the hydroxyalkene 218 provided a 4:1 mixture of the cis- and trans-fused systems 222 and 223 respectively, in 90% combined yield. Epoxidation of the benzoate protected system 219 provided the trans-fused 225 in preference to the cis-fused 224. Interestingly, epoxidation of the bulky silyl ether 220 provided exclusively the trans-fused 227. More surprisingly, epoxidation of 221, where the hydroxyl moiety had been replaced by hydrogen, provided an ~2:1 preference for the trans-fused 229 over the cis-fused isomer 228. Clearly steric factors play a major role in the stereochemical outcome of these epoxidations, but are not the sole factor determining the product ratios.
Paquette and coworkers\textsuperscript{149} have recently reported that complex polyquinanes can be constructed rapidly by the addition of two alkenyllithium species to a squarate ester (Scheme 33). Sequential addition of 2-propenyllithium and cyclopentenyllithium to the squarate ester 230 would provide an intermediate such as 231. The bridging lithium counterion is believed to play an important role in directing the second nucleophilic attack to the opposite face after the first addition. Cleavage of the cyclobutane ring in 231, followed by an 8\pi electrolyclization of 232, provides the bis(enolate) 233. After protonation of 233, a transannular aldol condensation gives the angularly-fused 234 as well as the linearly-fused triquinane 235 containing the trans-bicyclo[3.3.0]octane moiety.\textsuperscript{149b}

\[\text{Scheme 33}\]
3.2 Introductory remarks

Given the previously described success in developing a useful annulation method for the preparation of the trans-fused bicyclo[4.3.0]nonane ring system, as well as the successful preparation of the substituted allylcopper(I) reagents, we embarked on our goal of developing a general method for the preparation of the trans-fused bicyclo[3.3.0]octane ring system. It was hoped that the annulation sequence used to prepare the trans-fused bicyclo[4.3.0]nonane ring system could be adapted for the preparation of the trans-fused bicyclo[3.3.0]octane ring system. The use of 2-(trimethylstannyl)allylcopper(I)-dimethyl sulfide (182), as the synthetic equivalent of the d\textsuperscript{2},d\textsuperscript{3} prop-1-ene synthon 48, would be an integral part of the proposed cyclization method. A retrosynthetic plan for the annulation sequence is shown in Scheme 34.

![Scheme 34](image-url)
Ketone 236, containing the trans-fused bicyclo[3.3.0]octane ring system, could be obtained from the allylic alcohol 237 by simple functional group interconversions. The key step in this new annulation sequence would be the CrCl2/NiCl2-mediated coupling of the alkenyl iodide and aldehyde functions of 238 to provide 237. The iodide 238 could be obtained from the corresponding alkenyltrimethylstannane, which would be prepared by the 1,4-addition of the newly developed, functionalized allylcopper(I) reagent 182 to the enal 71. It was expected that the addition would occur stereoselectively, cis to the adjacent angular proton in 71. The α,β-unsaturated aldehyde 71 is readily available from the keto ketal 61 (vide supra, Chapter 1).

3.3 Preparation of cyclization precursor iodo aldehyde 238

Scheme 35
Using the allylcopper(I) reagent 182, the preparation of compound 239 was achieved. This was accomplished by the addition of the aldehyde 71 to a cold solution of 182 and trimethylsilyl bromide in THF, followed by aqueous workup and silica gel chromatography, to provide 239 in 75% yield (Scheme 35). An analysis of this material by $^1$H nmr spectroscopy showed that 239 was in fact a 2.2:1 mixture of epimeric aldehydes. The addition of 182 had occurred stereoselectively, exclusively from the more open convex (top) face of the enal 71, while hydrolysis of the enol silyl ether intermediate during the aqueous workup gave rise to two epimers at the center adjacent to the aldehyde moiety. To minimize torsional strain, it was expected that the major isomer was the one in which the substituents bore a trans relationship. This expectation was confirmed by a subsequent X-ray crystallographic study (vide infra). When the epimeric mixture of aldehydes 239 was treated with sodium methoxide in dry methanol, the ratio of major to minor epimer could be improved from ~2.2:1 to ~8:1.

Spectroscopic evidence fully supported the formation of the 1,4-addition product 239. The IR spectrum of 239 exhibited a strong C=O stretching absorption at 1723 cm\(^{-1}\), characteristic of an unconjugated aldehyde, a C-O-C stretching absorption at 1116 cm\(^{-1}\), attributed to the ketal, and a tin-methyl rocking absorption at 769 cm\(^{-1}\). The $^1$H nmr spectrum of 239 displayed two aldehyde resonances in an ~2.2:1 ratio ($\alpha:\beta$) at $\delta$ 9.48 (doublet, $J = 3.5$ Hz, $\alpha$ aldehyde) and $\delta$ 9.80 (doublet, $J = 2$ Hz, $\beta$ aldehyde), and a 9-proton singlet for the Me\(_3\)Sn group at $\delta$ 0.13, along with satellite peaks due to tin-proton coupling ($^{2}J_{\text{Sn-H}} = 53$ Hz). Two alkenyl protons were observed and these protons also showed satellite peaks due to tin-proton coupling. The characteristic resonances for the 2,2-dimethylpropylene ketal were also seen in the $^1$H nmr spectrum of 239.
A small amount of a byproduct (approximately 7%) thought to be the 1,2-addition product 240 (1:1 mixture of epimeric alcohols), on the basis of IR and nmr ($^1$H and $^{13}$C) spectroscopic analysis, was also detected (Figure 5). The IR spectrum of this epimeric mixture possessed a strong O-H stretching absorption at 3456 cm$^{-1}$, a ketal C-O-C stretching absorption at 1111 cm$^{-1}$, and a tin-methyl rocking absorption at 769 cm$^{-1}$, but no strong absorption in the carbonyl region. The $^1$H nmr spectrum 240 showed three alkenyl protons at $\delta$ 5.74, $\delta$ 5.48, $\delta$ 5.29, the first and last exhibiting tin-proton coupling, while the other showed no such coupling. A 9-proton singlet for the Me$_3$Sn group at $\delta$ 0.14 along with satellite peaks due to tin-proton coupling ($^2$J$_{Sn-H}$ = 54 Hz), a 1-proton signal at $\delta$ 4.16 attributed to the allylic carbinol proton, and the characteristic ketal resonances were also observed.

A further complication in the preparation of 239 occurred during the workup with aqueous NH$_4$Cl-NH$_4$OH (pH 8). Prolonged treatment of the crude reaction mixture with this solution resulted in undesired destannylation, in addition to hydrolysis of the silyl enol ether intermediate. Thus, it was necessary for the aqueous workup to be conducted rapidly to ensure consistently high yields of the 1,4-addition product 239.

The conversion of the alkenyltrimethylstannanes 239 into the corresponding alkenyl iodides was accomplished by treating the 2.2:1 epimeric mixture 239 in methylene chloride with $N$-iodosuccinimide.$^{61}$ The conversion was fast (10 minutes) and facile. After workup, a TLC analysis showed that two distinct, separable products had been
formed. Purification of this material by radial chromatography on silica gel provided two crystalline products 238 and 241 in 64% and 27% yields, respectively (Scheme 35). The ring substituents in the major product 238 bore a *trans* relationship. Treatment of 241 with sodium methoxide in dry methanol provided two products. After purification, 238 was isolated in 79% yield along with recovered 241 (11%). Thus, the thermodynamic product ratio was ~7:1 and the overall yield of 238 from 239, after equilibration of the alkenyl iodides, was 85%.

The structural assignments of the alkenyl iodides were in full accord with their spectral data. The major product 238 showed stretching absorptions, in its IR spectrum, at 1723 cm⁻¹ (aldehyde C=O), 1615 cm⁻¹ (alkenyl iodide C=C), and 1115 cm⁻¹ (ketal C-O-C). The ¹H nmr spectrum of 238 exhibited a 1-proton doublet (*J* = 3.5 Hz) at δ 9.55 for the aldehyde proton and two 1-proton doublets (*J* = 1.5 Hz each) at δ 5.70 and δ 6.07 for the alkenyl protons. These alkenyl resonances did not display any satellite peaks due to tin-proton coupling and were shifted downfield from those of the starting material, consistent with the replacement of the Me₃Sn group with the more electronegative iodine atom. The absence of a 9-proton singlet at high field in the ¹H nmr spectrum of 238 also supported that the conversion of the alkenyltrimethylstannyl moiety to an alkenyl iodide had proceeded. It was extremely gratifying to find that the ketal function was unmolested during this exchange reaction. Two 3-proton singlets at δ 0.91 and δ 0.98 for the gem-dimethyl group of the ketal and the signals at δ 3.41-3.48 (multiplet for three of the methylene protons) and δ 3.57 (doublet, *J* = 11.5 Hz, for one of the methylene protons) in the proton nmr spectrum indicated that the ketal was still intact. The ¹³C nmr spectrum of 238 contained only 16 of the expected 17 signals. The "missing" signal was attributed to one of the methylene carbons of the ketal. Only one very intense resonance at δ 72.0 appeared for the two methylene carbons of the ketal. Other characteristic resonances in the ¹³C nmr spectrum of 238 included two methyl signals at δ 22.4 and δ 22.6, and an
aldehyde signal at δ 203.2. In addition to this spectral data, the molecular formula of 238 was confirmed by a high resolution mass spectrometric measurement on the molecular ion.

The spectral data obtained for the minor product 241 were similar to those of the major epimer. The IR spectrum of 241 exhibited the following stretching absorptions: 1719 cm\(^{-1}\) (aldehyde C=O), 1615 cm\(^{-1}\) (alkenyl iodide C=C), and 1112 cm\(^{-1}\) (ketal C-O-C). The \(^1\)H nmr spectrum of 241 displayed resonances similar to those in the spectrum of its epimer 238. The doublet (\(J = 2\) Hz) for the aldehyde proton in 241 at δ 9.76 was downfield from that in 238, similar to the relative shifts observed in the alkenyltrimethylstannane starting materials. The two alkenyl protons appeared as mutually coupled doublets (\(J = 1.5\) Hz each) at δ 5.73 and δ 6.04. The \(^{13}\)C nmr spectrum of 241 contained all of the expected 17 signals. In this case, the methylene carbons of the ketal displayed unique resonances at δ 72.0 and δ 72.2. In addition to the spectral data, the molecular formula of 241 was confirmed by a high resolution mass spectrometric measurement on the molecular ion.

While it was gratifying to obtain the iodo aldehyde required to attempt the cyclization, an alternative route was also investigated. Thus, the possibility of using the allylcopper(I) reagent 162 to prepare the trimethylgermyl aldehyde 242, followed by a germanium-iodine exchange to give 238, was studied (Scheme 36).
Addition of 71 to a solution of 2-(trimethylgermyl)allylcopper(I)-dimethyl sulfide (162) and trimethylsilyl bromide in cold THF provided the 1,4-addition adduct 242 in 70% yield (~2:1 α:β mixture of epimeric aldehydes, inseparable by chromatography on silica gel) and the 1,2-addition product 243 in 16% yield (1:1 mixture of epimeric alcohols, inseparable on silica gel). The IR spectrum of 242 exhibited a strong C=O stretching absorption at 1723 cm⁻¹, indicative of an unconjugated aldehyde, a C-O-C stretching absorption at 1114 cm⁻¹, attributed to the ketal, and a germanium-methyl rocking absorption at 826 cm⁻¹. The ¹H nmr spectrum of 242 displayed two aldehyde resonances in an ~2:1 ratio at δ 9.47 (doublet, J = 3.5 Hz, α aldehyde) and δ 9.79 (doublet, J = 2 Hz, β aldehyde) and a 9-proton singlet for the Me₃Ge group at δ 0.19. The characteristic resonances for the 2,2-dimethylpropylene ketal, as well as two signals in the alkenyl region, were also seen in the ¹H nmr spectrum of 242. Finally, a low resolution mass
spectrometric analysis confirmed the presence of a compound with the molecular formula C$_{20}$H$_{34}$O$_3$Ge$^{74}$ (M$^+$ = 396).

It was concluded that the minor byproduct 243 was the 1,2-addition product based on the spectra data obtained. The IR spectrum of this compound (243) displayed a strong O-H stretching absorption at 3455 cm$^{-1}$, a ketal C-O-C stretching absorption at 1111 cm$^{-1}$, a germanium-methyl rocking absorption at 825 cm$^{-1}$, but no strong absorptions in the carbonyl region. The $^1$H nmr spectrum of this compound showed three alkenyl protons at $\delta$ 5.33, $\delta$ 5.11, $\delta$ 5.35 and an allylic carbinol proton at $\delta$ 4.20. A 9-proton singlet for the Me$_3$Ge group at $\delta$ 0.21 and the characteristic ketal resonances were also present in the proton nmr spectrum of this compound. Finally, a low resolution mass spectrometric analysis confirmed the presence of a compound with the molecular formula C$_{20}$H$_{34}$O$_3$Ge$^{74}$ (M$^+$ = 396).

When 242 was treated with either N-iodosuccinimide or iodine in methylene chloride, a complex mixture of unidentified products was obtained. A GLC analysis of the reaction mixture showed a plethora of products, including a small amount (less than 5%) of 238. It was thought that the close proximity of the carbonyl oxygen of the aldehyde function was interfering with the germanium-iodine exchange through a germanium-oxygen coordination species. While isolated cases of germanium-oxygen coordination have been reported in the literature, studies on organostannanes, where an alkenyltrimethylstannane and electron donating group (oxygen or nitrogen) are held in close proximity, have shown that intramolecular coordination does occur resulting in a pentacoordinate tin species. More interestingly, this intramolecular coordination affects the normal reactivity of the alkenyltrimethylstannane in halodestannylation reactions such that tin-methyl cleavage occurs in preference to tin-alkene cleavage. To test the hypothesis that germanium-oxygen coordination was interfering with the halodegermylation reaction, it was proposed to reduce the aldehyde moiety to the primary
alcohol, and then to protect the alcohol as a silyl ether and attempt the exchange reaction using this protected substrate (Scheme 37).

Overall Yields:
242 → 247 = 54%
242 → 248 = 22%
242 → 238 = 45%

Scheme 37
When the 2:1 epimeric mixture of aldehyde 242 in THF was treated with DIBAL-H,\textsuperscript{33} for 30 minutes at low temperature, the alcohol 244 was obtained in nearly quantitative yield (Scheme 37). The IR spectrum of 244 displayed a strong O-H stretching absorption at 3427 cm\textsuperscript{-1}, a ketal C-O-C stretching absorption at 1115 cm\textsuperscript{-1}, a germanium-methyl rocking absorption at 825 cm\textsuperscript{-1}, but no absorption in the carbonyl region for an aldehyde. The \textsuperscript{1}H nmr spectrum of 244 showed the appearance of two hydroxymethyl protons with a multiplet centered at δ 3.70.

Treatment of the alcohol 244 with N-iodosuccinimide in methylene chloride also provided a complex mixture of unidentified products. Consistent with the previous proposal, the failure of the halodegermylation reaction with 244 was thought to be a result of germanium-oxygen coordination involving the primary hydroxyl group. To reduce the possibility of intramolecular germanium-oxygen coordination, the alcohol 244 was converted into the silyl ether 245. \textit{tert}-Butyldimethylsilyl ethers are sterically bulky and are known to be non-coordinating.\textsuperscript{155} The reduced Lewis basicity of silyl ethers, when compared with the corresponding alcohols, is due to back donation of nonbonding electrons from oxygen into the low lying empty d orbitals of silicon. Thus, silyl ethers are poorer donor ligands than free alcohols. Using Corey's conditions,\textsuperscript{156} the alcohol 244 was converted into 245 by treatment with \textit{tert}-butyldimethylsilyl chloride and imidazole in DMF for one hour. The silyl ether 245 was obtained in 97% yield (Scheme 37). The IR spectrum of 245 displayed a broad, strong stretching absorption at 1116 cm\textsuperscript{-1} (ketal C-O-C and silyl ether C-O-Si), and a germanium-methyl rocking absorption at 835 cm\textsuperscript{-1}, but no absorption in the O-H stretching region. The \textsuperscript{1}H nmr spectrum of the diastereomeric mixture 245 displayed the expected signals for a \textit{tert}-butyldimethylsilyl group (a 6-proton signal at δ 0.01 and a 9-proton signal at δ 0.86), a trimethylgermyl group (a 9-proton signal at δ 0.19), and a 2,2-dimethylpropylene ketal function (two 3-proton signals at δ 0.91 and δ 0.94 and a 4-proton multiplet centered at δ 3.44). Finally, a low resolution
mass spectrometric analysis confirmed the presence of a compound with the molecular formula $C_{26}H_{50}O_{37}GeSi$ ($M^+ = 512$).

We were now prepared to test our hypothesis that the failure of 242 to undergo iododegermylation cleanly was an electronic effect, the result of germanium-oxygen coordination, and not due to steric crowding. Our vilification of germanium-oxygen coordination was not unfounded. Treatment of 245 with N-iodosuccinimide in methylene chloride for 2.5 days provided the alkenyl iodide 246 in 87% yield (Scheme 37). The long reaction time required is indicative of steric crowding. The $^1H$ nmr spectrum of 246 exhibited two 1-proton signals at $\delta$ 5.65 and $\delta$ 6.05 for the alkenyl protons and the expected signals for a tert-butyldimethylsilyl group and the 2,2-dimethylpropylene ketal. The alkenyl resonances were shifted downfield from those of the starting material ($\delta$ 5.18 and $\delta$ 5.53 in 245), consistent with the replacement of the Me$_3$Ge group with the more electronegative iodine atom. The absence of a 9-proton singlet at high field in the $^1H$ nmr spectrum of 246 also supported the conversion of the alkenyltrimethylgermyl moiety into an alkenyl iodide.

After much experimentation, conditions were found to deprotect the hydroxyl moiety of 246 without disturbing the ketal or alkenyl iodide functions. Treatment of 246 in cool THF with hydrofluoric acid-pyridine complex for 90 minutes provided two alcohols (Scheme 37). At this point, chromatographic separation on silica gel was possible, providing pure 247 in 71% yield (54% overall from 242) and the isomeric alcohol 248 in 29% yield (22% overall from 242). The IR spectrum of 247 displayed a strong O-H stretching absorption at 3418 cm$^{-1}$, an alkenyl iodide C$=$C stretching absorption at 1615 cm$^{-1}$, and a ketal C-O-C stretching absorption at 1112 cm$^{-1}$. The $^1H$ nmr spectra of 247 gave further evidence of the successful, clean hydrolysis of the silyl ether. Both the 9-proton and 6-proton signals at high field, characteristic of a tert-butyldimethylsilyl group, had disappeared. The $^1H$ nmr spectrum of 247 did show two 1-proton signals for the alkenyl protons at $\delta$ 5.68 and $\delta$ 6.07, and two 3-proton singlets at
δ 0.91 and δ 0.95 for the gem-dimethyl groups of the ketal. The $^{13}$C nmr spectrum of 247 contained all the expected 17 signals. In addition to this spectral data, the molecular formula of 247 was confirmed by a high resolution mass spectrometric measurement on the molecular ion. The structure of 248 was assigned by a similar analysis of the IR and $^1$H nmr spectral data obtained.

The aldehyde 238 was obtained by oxidation of the alcohol 247. Treatment of a solution of 247 in methylene chloride with pyridinium chlorochromate$^{34}$ for 60 minutes provided 238 in 84% isolated yield (Scheme 37). The structure of this product was confirmed by comparison of the spectral data obtained to the spectral data of 238 obtained by the previously described route.

![Scheme 38](image-url)
In summary, either of the substituted allylcopper(I) reagents 182 or 162 can be added efficiently, in a 1,4-manner, to the α,β-unsaturated aldehyde 71 providing 239 or 242 in good yield (Scheme 38). While the corresponding alkenyl iodide 238 can easily be prepared from 239 by an iododestannylation reaction, 242 does not undergo clean iododegermylation when treated with N-iodosuccinimide. This difficulty is proposed to be due to intramolecular coordination between the alkenyltrimethylgermane and aldehyde functions. Nonetheless, 242 can function as a precursor to the alkenyl iodide 238. The use of 242 requires a multistep protection - deprotection sequence to inhibit the undesired germanium-oxygen coordination which interferes in the iododegermylation reaction necessary to generate 238. Thus, the more efficient method to prepare 238 is through the use of the organocopper(I) reagent 182.

3.4 Ring closure: Cyclization of iodo aldehyde 238

The cyclization of the iodo aldehyde 238 was attempted using conditions essentially identical with those developed for the preparation of trans-fused bicyclo[4.3.0]nonane ring systems (vide supra, Chapter 1). Thus, addition of 238 to a slurry of CrCl₂ and NiCl₂ in DMF⁵⁸ (equation 57) provided the trans-fused bicyclo-[3.3.0]octane system (237) in 65% yield (Table 11, entry 1).

Table 11 Transition Metal-Mediated Cyclization of Iodo Aldehyde 238

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Reaction Time</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>60 minutes</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>4:1 DMF-DMSO</td>
<td>30 minutes</td>
<td>92</td>
</tr>
</tbody>
</table>
Other solvents and solvent pairs, including DMF-DME, DMSO-DMS, DMSO, and THF have been used in the CrCl2/NiCl2 mediated coupling reaction. The use of DMSO as the solvent has been reported to give a much cleaner, albeit slower, reaction for the coupling of iodo olefins with aldehydes. Changing the solvent for the cyclization to a 4:1 mixture of DMF and DMSO (equation 57), provided immediate rewards (Table 11, entry 2). After only 30 minutes, a TLC analysis showed complete consumption of the starting material. After workup and silica gel chromatography, 237 was obtained in 92% yield. The cyclized product was isolated as a 1:1 mixture of alcohols, epimeric at the carbinol carbon, which were inseparable by silica gel chromatography. The IR spectrum of this mixture displayed stretching absorptions at 3436 cm⁻¹ (O-H), 1656 cm⁻¹ (C=C), and 1110 cm⁻¹ (ketal C-O-C). The ¹H nmr spectrum of 237 exhibited broad resonances, in a 1:1 ratio, for the carbinol protons at δ 4.09 and δ 4.20. The two exocyclic methylene protons were observed at δ 4.98 and δ 5.06 (1:1 ratio) and δ 5.08 and δ 5.21 (1:1 ratio).

\[
\begin{align*}
\text{Ac}_2\text{O} & \quad \text{DMAP, Et}_3\text{N} & \quad \text{CH}_2\text{Cl}_2, \text{rt} \\
\end{align*}
\]

\[
\begin{align*}
\text{Sml}_2 & \quad \text{MeOH} & \quad \text{THF, -78 °C} \\
\end{align*}
\]

Scheme 39
At this point, rather than spending excessive amounts of time trying to separate the mixture of allylic alcohols by other chromatographic methods, it was decided to use the mixture directly in the next step, since both of the alcohols are precursors to the desired ketone 236 (Scheme 39). The acetate 249 was prepared under standard conditions by treatment of the alcohol 237 in methylene chloride with acetic anhydride in the presence of DMAP and triethylamine (Scheme 39). As expected, the acetate 249 was obtained (96% yield) as a 1:1 mixture of epimers, which again proved to be inseparable by chromatography on silica gel. Evidence for the conversion of the hydroxyl group to an acetate was obtained from the IR spectrum of 249. The O-H stretching absorption at 3436 cm\(^{-1}\) had disappeared and new stretching absorptions at 1737 cm\(^{-1}\) (acetate C=O) and 1239 cm\(^{-1}\) (acetate C-O) appeared. Absorptions at 1657 cm\(^{-1}\) (C=C) and 1112 cm\(^{-1}\) (ketal C-O-C) were also observed in the IR spectrum of 249. In addition, the \(^1\)H nmr spectrum of 249 displayed resonances for the acetoxy methine proton at \(\delta\) 4.98 and \(\delta\) 5.06 (1:1 ratio), shifted significantly downfield from those in the alcohol 237, as would be expected for the conversion of an alcohol to an acetate. Resonances for the methyl protons of the acetate were seen at \(\delta\) 2.03 and \(\delta\) 2.09 (1:1 ratio). The two exocyclic methylene protons of 249 were observed at \(\delta\) 4.96 and \(\delta\) 4.99 (1:1 ratio) and \(\delta\) 5.11 and \(\delta\) 5.25 (1:1 ratio).

The efficient preparation of the keto acetate 250 was not as straightforward as might be expected. Treatment of a cold (-78 °C) solution of 249 in methanol with ozone, followed by reductive workup with dimethyl sulfide provided 250 in 71% yield along with a polar byproduct. It has been suggested that, in polar hydroxylic solvents such as methanol, the intermediate methoxy hydroperoxide can undergo further oxidations before reduction with dimethyl sulfide can occur. In less polar, non-hydroxylic solvents such as methylene chloride, the ozonide intermediate is quite stable, and is only slowly reduced by dimethyl sulfide. In a mixed solvent system of methanol and methylene chloride, secondary reactions (such as over-oxidation) are inhibited yet the reduction of the ozonide
is still quite rapid. When a solution of 249 in cold methylene chloride containing 1.5 equivalents of methanol\textsuperscript{160} was treated with ozone followed by reductive workup with dimethyl sulfide, the keto acetate 250 was obtained in 90\% yield (Scheme 39). An analysis of the product by \textsuperscript{1}H nmr spectroscopy indicated a 1:1 mixture of epimers had been isolated. The spectral data obtained from 250 fully supported oxidative cleavage of the exocyclic methylene group. The IR spectrum of 250 showed that the C=C absorption at 1657 cm\textsuperscript{-1} had disappeared and was replaced by a broad absorption at 1757 cm\textsuperscript{-1} (C=O cyclopentanone and C=O acetate), in addition to the stretching absorptions at 1230 cm\textsuperscript{-1} (C-O acetate) and 1110 cm\textsuperscript{-1} (C-O-C ketal). The \textsuperscript{1}H nmr spectrum of 250 offered further proof for the conversion of the exocyclic methylene to a ketone. There were resonances for the acetoxy methine proton at \( \delta \) 4.88 and \( \delta \) 4.92 (1:1 ratio), but the resonances of the alkenyl resonances of the exocyclic methylene had disappeared.

Reductive removal of the \( \alpha \)-acetoxy function was achieved smoothly by addition of a solution of 250 in THF and methanol to a cold solution of SmI\textsubscript{2} in THF (Scheme 39).\textsuperscript{68} After workup and silica gel chromatography, a single compound, the triquinane keto ketal 236, was obtained in 89\% yield. The IR spectrum of 236 exhibited strong stretching absorptions at 1745 cm\textsuperscript{-1} (C=O) and 1113 cm\textsuperscript{-1} (ketal C-O-C). The \textsuperscript{1}H nmr spectrum of 236 displayed two 3-proton singlets at \( \delta \) 0.93 and \( \delta \) 0.94 and a 4-proton multiplet centered at \( \delta \) 3.45, which confirmed that the ketal had remained intact. Further proof of the successful reductive cleavage of the acetoxy moiety was seen by the absence of the resonances attributed to the methyl protons of the acetate group in the \textsuperscript{1}H nmr spectrum. The \textsuperscript{13}C nmr spectrum of 236 contained the expected 16 signals. Characteristic resonances were the carbonyl signal at \( \delta \) 220.2, the quaternary ketal carbon signal at \( \delta \) 110.9, the two ketal methylene carbon signals at \( \delta \) 71.9 and 72.0, the two ketal methyl signals at \( \delta \) 22.48 and 22.53, and four methine carbon signals at \( \delta \) 42.3, 44.80, 49.2, and 54.6. In addition to this spectral data, the molecular formula of 236 was confirmed by a high resolution mass spectrometric measurement on the molecular ion.
Despite good evidence that the proposed cyclization had indeed been successful, none of the recorded data provided conclusive evidence for the assigned relative stereochemistry at the ring junction of 236 (or 237, 249, or 250). As 236 is a single diastereomer (as opposed to the epimeric mixtures 237, 249, and 250) and is a crystalline solid (mp 74 - 75 °C) which could be recrystallized from n-heptane, an X-ray crystallographic study was undertaken. As expected, a single crystal X-ray analysis of 236 (Appendix 2) showed conclusively that the protons at the ring fusion, in the newly formed ring (A-B rings), are in a trans relationship (Figure 6). The reason for difference in

Figure 6 Stereoview of the Tricyclic Keto Ketal 236
the strain energy of the *trans*- and *cis*-fused bicyclo[3.3.0] systems can be seen from their respective torsional angles. The *trans*-fused system (rings A and B) has a torsional angle going from C-a to C-d (via C-b and C-c) of 44.5°, while the *cis*-fused system (rings B and C) has a torsional angle going from C-e to C-h (via C-f and C-g) of -4.8°.

Several key assumptions made early in our synthesis were confirmed by this X-ray structure. The approach of the allylcopper(I) reagent 182 to the α,β-unsaturated aldehyde 71 was stereoselective, occurring exclusively from the convex face of the molecule. The major product obtained from this 1,4-addition, after hydrolysis of the silyl enol ether intermediate, did indeed have the ring substituents in a *trans* relationship. Thus, the annulation strategy developed does provide an efficient method for the construction of the *trans*-fused bicyclo[3.3.0]octane ring system.

3.5 Conclusions

A new method for the stereocontrolled synthesis of the *trans*-fused bicyclo-[3.3.0]octane ring system has been developed.69 Starting with the bicyclic cyclopentanone system (61), the *trans*-fused bicyclo[3.3.0]octane ring system (236) can easily be produced. The annulation method employs the substituted allylcopper(I) reagent 2-(trimethylstannyl)allylcopper(I) (182) as the synthetic equivalent of the d2,d3 prop-1-ene synthon (48), sequentially deploying the donor sites at carbon three then carbon two (Scheme 40). Thus, 182 could be combined with the α,β-unsaturated aldehyde 71, obtained from the keto ketal 61, to provide the bicyclo[3.3.0]octane ring system (237). On the basis of molecular model analysis and an X-ray crystallographic study on 236, the stereochemistry of the newly formed ring junction was established as being *trans*-fused.
Concurrently, during our studies to develop the aforementioned annulation method, evidence was obtained in support of germanium-oxygen coordination. It was found that alkenyltrimethylgermanium species can form a chelate species with an electron donating oxygen which is held in close proximity. Furthermore, this chelate species, when subjected to iododegermylation conditions, does not react in the expected manner. Several side reactions, presumably including germanium-methyl cleavage, compete with the expected germanium-alkene cleavage reaction.
4. Copper(I) Chloride - Mediated Intramolecular Coupling of Bis(Alkenyltrimethylstannanes)

4.1 Background

The use of transition metal salts, particularly palladium, to mediate carbon-carbon bond formation is a powerful tool for the synthetic organic chemist. One of the most well known reactions of this type is the palladium(0)-catalyzed cross coupling reaction of organostannanes (R'SnR"3) with organic halides and related electrophiles (R-X) (equation 58). This reaction is widely known as the Stille coupling reaction to acknowledge the seminal contributions of the late J. K. Stille to the development of this important method. Some of the merits of this catalytic reaction are the mild conditions required to effect coupling, the wide variety of functional groups that can be tolerated on either of the coupling partners, excellent control of the configuration of the final products, and the high yields routinely obtained.

\[
R-X + R'SnR"_3 \xrightarrow{\text{Pd(0) catalyst}} R-R' + XSnR"_3 \quad (58)
\]

The Stille coupling reaction provides the coupled product (R-R') by the selective transfer of an organic group (R') from the organostannane to the organic group (R) which is originally bonded to the leaving group (X). The rate of transfer of different organic groups from the tin atom varies with the ability of the group to stabilize a negative charge, with simple alkyl group having the slowest transfer rates. Since both organo-(trimethylstannanes) and organo(tri(n-butylstannanes)) are readily available compounds, the nontransferable group (R") has generally been chosen as either methyl or n-butyl, while moieties such as alkenyl, alkynyl, allyl, aryl or benzyl have been used for the transferable ligand (R'). The electrophilic coupling partner (R-X) oftentimes is an alkenyl halide or a
alkenyl triflate, but other activated electrophiles such as acid chlorides, allyl halides, aryl halides, benzyl halides, and aryl triflates have also been used successfully.

In addition to the variety of substrates available for coupling, the reaction may be fine-tuned by adjusting the palladium source and the solvent. A number of palladium catalysts\textsuperscript{127} have been used for the Stille coupling reaction, including tetrakis-(triphenylphosphine)palladium(0) \([\text{Pd}(\text{PPh}_3)_4]\), tris(dibenzylideneacetone)dipalladium(0) \([\text{Pd}_2(\text{dba})_3]\), bis(triphenylphosphine)palladium(II) chloride \([\text{Pd}(\text{PPh}_3)_2\text{Cl}_2]\), and bis(acetonitrile)palladium(II) chloride \([\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2]\). The palladium-dibenzylideneacetone complexes are generally used in conjunction with donor ligands such as \text{PPh}_3 or \text{AsPh}_3. Since the active catalyst in the coupling reaction is palladium(0), prior to entering the catalytic cycle, palladium(II) catalysts must first be reduced to palladium(0), typically \textit{in situ}, through the homocoupling of two equivalents of the stannane.

Stille coupling reactions have been performed in almost all conceivable solvents at temperatures ranging from ambient to reflux conditions.\textsuperscript{127} While many couplings have been carried out in ethereal solvents, such as THF or dioxane, polar solvents such as DMF and NMP have become the solvents of choice.\textsuperscript{127} The use of other solvents, including acetone, acetonitrile, benzene, chloroform, 1,2-dichloroethane, DMSO, HMPA, and even water\textsuperscript{165} have been reported in the literature.\textsuperscript{127}

The overall reaction pathway for the palladium catalyzed coupling process is shown in Figure 7.\textsuperscript{162} The catalytic process is widely accepted as involving loss of ligands from the palladium(0) catalyst to form a coordinatively unsaturated palladium(0) species (PdL\textsubscript{2}), an oxidative insertion of the coordinatively unsaturated palladium(0) catalyst into the carbon-halogen bond of the organic halide (R-X), a transmetalation of the resulting organopalladium(II) species with the organostannane (\(\text{R'}\text{SnR''}_3\)), a \textit{trans - cis} isomerization of the bis(organo)palladium(II) complex, and a subsequent reductive elimination to provide the coupled product (R-R'), accompanied by regeneration of the palladium(0) catalyst. The
transmetalation of the organopalladium(II) species with the organostannane (R'SnR''\textsubscript{3}) is considered to be the rate determining step.

Copper(I) iodide has been employed as a co-catalyst to accelerate the reaction rate.\textsuperscript{166} The copper(I) salt is thought to have a dual role. In ethereal solvents and in conjunction with highly coordinating ligands (PPh\textsubscript{3}), the copper(I) co-catalyst acts as a ligand scavenger to facilitate the formation of the coordinatively unsaturated palladium(0) catalyst. In polar solvents (DMF or NMP), it is proposed that the copper(I) salt causes a reversible tin - copper transmetalation (equation 59). The resulting organocopper species (R'Cu) transmetalates with the organopalladium(II) species (R-PdL\textsubscript{2}-X, Figure 7) at a rate higher than that of the organostannane itself.

\textbf{Figure 7} Catalytic Cycle of the Stille Coupling Reaction

Copper(I) iodide has been employed as a co-catalyst to accelerate the reaction rate.\textsuperscript{166} The copper(I) salt is thought to have a dual role. In ethereal solvents and in conjunction with highly coordinating ligands (PPh\textsubscript{3}), the copper(I) co-catalyst acts as a ligand scavenger to facilitate the formation of the coordinatively unsaturated palladium(0) catalyst. In polar solvents (DMF or NMP), it is proposed that the copper(I) salt causes a reversible tin - copper transmetalation (equation 59). The resulting organocopper species (R'Cu) transmetalates with the organopalladium(II) species (R-PdL\textsubscript{2}-X, Figure 7) at a rate higher than that of the organostannane itself.
Inorganic salts, usually lithium chloride (LiCl), have also been added to the reaction mixture, especially for intermolecular Stille cross couplings employing alkenyl triflates. It has been postulated that substitution of the triflate ligand for a chloride ligand in the initial oxidative addition product (Figure 7, R-PdL$_2$-X, X = OTf $\rightarrow$ X = Cl) results in a more reactive species.$^{167}$ More recently, it has been found that the addition of LiCl is often not necessary if the reaction is performed in highly polar solvents (NMP or DMF).$^{168}$

The synthetic utility of the Stille reaction has been demonstrated by numerous publications involving the synthesis of natural products. Piers and Friesen implemented the palladium(0) catalyzed intramolecular coupling as a key bond forming step in the preparation of (±)-amijitrienol (251) from the intermediate 252 (equation 60).$^{169}$

The palladium catalyzed coupling reaction has also been applied successfully in an intermolecular fashion in the convergent synthesis of pleraplysilllin-1 (253), from the alkenyl triflate 254 and the organostannane 255 (equation 61).$^{170}$
Investigations into the stereocontrolled synthesis of alkyl 2,3-bis(alkylidene)-cyclopentanecarboxylates (256) by Piers and Wong revealed an important discovery about the use of a copper(I) salt as a catalyst in the Stille coupling reaction. Under the standard Stille coupling conditions, treatment of a variety of esters of general structure 257, each containing an alkenyl(trimethylstannane) moiety and an alkenyl halide moiety, with Pd(PPh)$_3$$_4$ (5 mol %) and lithium chloride (2 equiv) in dry DMF at 80 °C for 1 hour provided the alkyl 2,3-bis(alkylidene)cyclopentanecarboxylates of general structure 256 in good yields with excellent stereoselectivity (equation 62).

\[
\begin{align*}
\text{257} & \quad \xrightarrow{\text{Pd(PPh$_3$)$_4$, LiCl}} \quad \text{256} \\
\begin{array}{c}
\text{R}^3 \text{C} = \text{C} \text{R}^1 \\
\text{X} \text{SnMe}_3
\end{array} & \quad \text{DMF, 80 °C} & \quad \begin{array}{c}
\text{R}^3 \text{C} = \text{C} \text{R}^1 \\
\text{CO}_2\text{R}^2
\end{array}
\end{align*}
\]

In the case of the ester 258, however, poor stereocontrol and a low yield was obtained (equation 63, Table 12, entry 1). Using standard palladium(0) coupling conditions, the ester 258, provided three products (259-261). It has been reported that the reaction rate of palladium(0) catalyzed coupling reactions are accelerated by the inclusion of copper(I) salt co-catalysts. When the above reaction was repeated with added copper(I) chloride, a dramatic improvement in yield and stereocontrol was observed (Table 12, entry 2).
Table 12 Intramolecular Coupling Reactions of the Ester 258

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Product Ratio 259:260:261 (Combined Yield of 259+260+261)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh₃)₄, LiCl, DMF, 80 °C</td>
<td>27:11:7 (39%)</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh₃)₄, CuCl, DMSO, 60 °C</td>
<td>11:1:0 (67%)</td>
</tr>
<tr>
<td>3</td>
<td>CuCl, DMF, 60 °C</td>
<td>13:1:0 (86%)</td>
</tr>
<tr>
<td>4</td>
<td>CuCl, DMF, 23 °C</td>
<td>31:1:0 (94%)</td>
</tr>
</tbody>
</table>

After further experimentation, Piers and Wong discovered that the intramolecular coupling of compounds of general structure 257 could be achieved by the use of copper(I) chloride in warm DMF, in the absence of any palladium catalyst (equation 64).¹⁷¹ Most remarkably, with the ester 258 better stereocontrol and yields were obtained by treatment with copper(I) chloride alone in DMF than with traditional Stille coupling conditions (Table 12, entries 3 and 4). In addition, the copper(I) chloride-mediated coupling of 258 proceeded in better yield with greater selectivity when a lower reaction temperature was employed. In this case, the copper(I) chloride protocol is clearly superior to the palladium(0) catalyzed process.
The use of 2 - 2.5 equivalents of copper(I) chloride was required for the coupling reaction to go to completion in a short (less than 5 minutes) time and with high yields. Preliminary investigations on the mechanism of the reaction revealed that the alkenyl(trimethylstannane) moiety initially undergoes a reversible transmetalation with copper(I) chloride to afford an alkenylcopper species, along with trimethyltin chloride. Studies by Liebeskind using $^{119}$Sn nmr have shown that in polar solvents, copper(I) iodide undergoes a reversible transmetalation with unsaturated stannanes to provide an organocopper species.$^{166}$a The excess copper(I) salt helps drive the equilibrium towards the tin-copper transmetalation product. Subsequently, the alkenylcopper species reacts with the alkenyl halide to provide the coupled product. The mechanistic details of this step are uncertain.

This novel copper(I) chloride mediated intramolecular coupling reaction of an alkenyl halide and an alkenyl(trimethylstannane) has shown utility in the stereospecific synthesis of bicyclic conjugated diene systems such as 263 (equation 65).$^{171}$ By altering the ring size in 262 and changing the chain length attached to the alkenyl halide, bicyclic ring systems other than 263 have been prepared containing the conjugated diene moiety.$^{171}$

Subsequent investigations$^{172}$ to examine the scope of this novel copper(I) chloride coupling reaction revealed that alkenyl(trimethylstannanes) can be efficiently coupled using a solution of copper(I) chloride in DMF. The intermolecular coupling of two
alkenyl(trimethylstannanes) provides an efficient method for the construction of structurally diverse conjugate dienes (equations 66 and 67).

\[
\begin{align*}
&\text{Cl} \quad \text{Me}_3\text{Sn} \quad \text{CO}_2\text{Me} \\
&\quad \text{CuCl} \quad \text{DMF, rt} \\
&\text{Cl} \quad \text{Me}_3\text{Sn} \quad \text{CO}_2\text{Me} \\
\end{align*}
\]

A variety of β-trimethylstanny-α,β-unsaturated esters have been coupled in high yields using 2.5 equivalents of copper(I) chloride in DMF at room temperature. For example, the ester 264 provided the diene 265 in 90% yield (equation 66).\(^{172}\) The geometric isomer of 264 also underwent efficient coupling when treated with copper(I) chloride. The coupling of a stannane alcohol (266) as well as the corresponding ether (267) were also successful providing 268 and 269,\(^{172b}\) but proceeded in lower (51% and 53%, respectively) yields (equation 67).\(^{173}\)

\[
\begin{align*}
&\text{CH} = \text{CH} \quad \text{OR} \\
&\quad \text{SnMe}_3 \\
&\quad \text{CuCl} \quad \text{DMF, rt} \\
&\text{CH} = \text{CH} \quad \text{OR} \\
\end{align*}
\]

The synthetic utility of the copper(I) chloride mediated coupling reaction has been extended to the preparation of a variety of bicyclic systems via an intramolecular copper(I) chloride mediated coupling of two different alkenyl(trimethylstannane) moieties in the same molecule.\(^{174}\)
The bis(alkenyltrimethylstannane) 270 was successfully cyclized in 15 minutes to provide the bicyclo[4.3.0]nonane system 263 in high yield (equation 68). The intramolecular coupling of two different alkenyl(trimethylstannane) moieties in the same molecule has provided an efficient process for the closure of 4-, 5-, 6-, 7-, and 8-membered rings containing a conjugated diene function. Interestingly, the intramolecular coupling process requires 5 equivalents of copper(I) chloride in warm (60 °C) DMF to ensure complete conversion of starting material to product within a relatively short period of time. The mechanistic details of the copper(I) chloride mediated coupling of two alkenyl(trimethylstannanes) remain obscure. Based on previous studies, a tentative proposal suggests an initial reversible transmetalation between one of the trimethylstannyl moieties and copper(I) chloride to provide an alkenylcopper species and Me₃SnCl. A subsequent step involving coupling of the alkenylcopper moiety with the other alkenyl(trimethylstannane) provides the cyclized product.

4.2 Introductory remarks

The successful use of 2,3-bis(trimethylstannyl)propene (183) (Scheme 41) to prepare the functionalized allylcopper(I) reagent 2-(trimethylstannyl)allylcopper(I)-dimethyl sulfide (182) and the conjugate addition of 182 to enones (to provide compounds of general structure 192) were described in Chapter 2 of this thesis. The use of 182 as the synthetic equivalent of the d²,d³ prop-1-ene synthon, suitable for conjugate addition to α,β-unsaturated carbonyl compounds, in an annulation method for the preparation of trans-fused bicyclo[3.3.0]octane ring systems was described in Chapter 3. It was also
thought that 183 itself might be a synthetically useful reagent. 2-(Trimethylstannyl)-allyllithium (271) is prepared from 183 by treatment with methyllithium. While 271 would not be expected to undergo 1,4-addition to α,β-unsaturated carbonyl compounds, it was hoped that 271 would react, in synthetically useful yields, with electrophilic species to provide compounds of general structure 272 (Scheme 41).

It was envisaged that the synthetic utility of 271 could be demonstrated in a new cyclization method to provide highly functionalized cyclopentenyl systems of general structure 273. A retrosynthetic analysis of the proposed annulation procedure is shown in Scheme 42.
It was proposed that 273 could be prepared from compounds such as 274. The key step in this annulation sequence would be a copper(I) chloride mediated intramolecular coupling\(^{172,174}\) of the alkenyltrimethylstannane moieties in 274. Previous work in our laboratories has provided general methods for the preparation of configurationally defined \(\beta\)-trimethylstannyl \(\alpha,\beta\)-unsaturated carbonyl compounds.\(^{175-177}\) A suitable precursor (274) for the intramolecular copper(I) chloride cyclization could be obtained from addition of 271 to \(\beta\)-trimethylstannyl \(\alpha,\beta\)-unsaturated aldehydes (general structure 275), followed by a functional group interconversion, namely conversion of the alcohol into an acetate.

**4.3 Preparation of \(\beta\)-trimethylstannyl \(\alpha,\beta\)-unsaturated aldehydes**

A number of \(\beta\)-trimethylstannyl \(\alpha,\beta\)-unsaturated aldehydes of general structure 275 were required as starting materials for this study and these compounds were prepared using methods previously developed in our laboratories.
The cyclic $\beta$-trimethylstannyl $\alpha,\beta$-unsaturated aldehydes\textsuperscript{178} 276 and 277, prepared by reduction of the esters\textsuperscript{172,177} 278 and 279 followed by oxidation of the resultant alcohols 280 and 281, have been reported previously. The spectral data obtained from the purified aldehydes 276 and 277 were in accordance with the reported values.\textsuperscript{178} The previously unreported aldehyde 282, containing the cycloheptenyl moiety, was prepared by a procedure similar to that used for the preparation 276 and 277 (Scheme 43).

The alkenyl triflate 283 was prepared\textsuperscript{177} by treatment of the commercially available methyl 2-oxo-1-cycloheptanecarboxylate (284) with potassium hydride and $N$-phenyl-
trifluoromethanesulfonimide (Scheme 43).172a After appropriate workup and purification of the crude material by flash chromatography, followed by distillation of the resultant oil, compound 283 was isolated in 89% yield. The IR spectrum of 283 displayed a strong C=O stretching absorption at 1728 cm\(^{-1}\) and a C=C stretching absorption at 1659 cm\(^{-1}\). The \(^1\)H nmr spectrum of 283 exhibited a 3-proton singlet at \(\delta\) 3.78 attributed to the methoxy protons. The successful incorporation of the trifluoromethanesulfonyl group was confirmed by the presence of a quartet \(J_{C-F} = 4\) Hz) at \(\delta\) 118.3, attributed to the CF\(_3\) carbon, in the proton decoupled \(^{13}\)C nmr spectrum of 283.

Reaction of the alkenyl triflate 283 with lithium (phenylthio)(trimethylstannyI)-cuprate\(^\text{111}\) provided, after aqueous workup and purification of the crude material by chromatography on silica gel, the ester 285 in 82% yield (Scheme 43).172a The IR spectrum of 285 showed a strong C=O stretching absorption at 1694 cm\(^{-1}\) for the conjugated ester carbonyl. The \(^1\)H nmr spectrum of 285 confirmed incorporation of the Me\(_3\)Sn group by a 9-proton singlet at \(\delta\) 0.09 with satellite peaks due to tin-proton coupling \(\(2J_{\text{Sn-H}} = 53\) Hz) and a methyl ester by a 3-proton singlet at \(\delta\) 3.70.

Conversion of the ester 285 into the aldehyde 282 was accomplished through a simple reduction - oxidation sequence (Scheme 43). Treatment of a solution of 285 in THF with DIBAL-H\(^\text{33}\) provided the corresponding allylic alcohol (286). This material was extremely unstable and rapidly decomposed, especially when neat. Due to the instability of 286, the crude material was immediately oxidized under mild conditions using tetra-n-propylammonium perruthenate (TPAP)\(^\text{179}\) to provide the aldehyde 282 in 77% yield from the ester 285, after workup and purification. The spectral data obtained for 282 were in full accord with the above transformation. The IR spectrum of 282 showed, for the conjugated aldehyde, a strong C=O stretching absorption at 1680 cm\(^{-1}\) and a tin-methyl rocking absorption at 772 cm\(^{-1}\). The \(^1\)H nmr spectrum of 282 indicated the presence of a Me\(_3\)Sn group (a 9-proton singlet with satellite peaks due to tin-proton coupling at \(\delta\) 0.23, \(2J_{\text{Sn-H}} = 53\) Hz) and an aldehyde (a 1-proton singlet at \(\delta\) 9.43, with
satellite peaks due to long range tin proton coupling $^4J_{\text{Sn-H}} = 6$ Hz). The $^{13}$C nmr spectrum of 282 contained the expected 9 signals. Characteristic resonances were the two alkenyl signals at $\delta$ 153.4 and 179.6, the aldehyde signal at $\delta$ 193.8, and the signal for the Me$_3$Sn group at $\delta$ -7.2.

The close proximity of the alcohol and trimethylstannyl moieties in 286 was thought to be the cause of its instability. An analysis of molecular models of 286, 281, and 280 showed that the distance between the trimethylstannyl moiety and the hydroxyl group increases with decreasing ring size. The geometric constraints of the cyclopentenyl (280) and cyclohexenyl (281) systems keep the alkenyl substituents rather far apart, but the larger ring size of the cycloheptenyl system (286) allows for their close proximity. In systems with a rigid skeleton, where a coordinating heteroatom substituent such as oxygen is at the $\gamma$-position relative to the tin atom of an alkenyltrialkylstannane, tin-oxygen coordination via a five membered ring is known.$^{180}$ It was thought that this tin-oxygen coordination causes the decomposition of 286. However, the stable and isolable alcohols 280 and 281 cannot have intramolecular tin - oxygen coordination without imparting a high degree of angle strain to the molecule. Interestingly, this is also true of the aldehydes 276, 277, and 282 and the corresponding esters 278, 279, and 285.
The preparation of aldehyde 287 has been described previously by Piers and Tillyer (Scheme 44). Treatment of 288 in THF with methyllithium and paraformaldehyde gave the primary alcohol 289, which, upon oxidation with pyridinium chlorochromate in the presence of sodium acetate, provided the aldehyde 290. A palladium catalyzed addition of hexamethylditin to the α,β-alkynic aldehyde 290 provided the requisite β-trimethylstannyl α,β-unsaturated aldehyde 287. The spectral data derived from 287 were in full accord with the values reported in the literature.

The aldehydes 291 and 292 were prepared from esters 264 and 293 (previously unreported), respectively, by a straightforward sequence using DIBAL-H reduction followed immediately by oxidation with TPAP (Scheme 45). Spectral data obtained for 291 and 292 were fully consistent with the assigned structures. The esters 264 and 293 were prepared by the addition of lithium (trimethylstannyl)(cyano)cuprate to the appropriate acetylenic esters 294 and 295 using the general procedure developed by Piers, Wong, and Ellis (Scheme 45).
The α,β-alkynic esters 294 and 295 were obtained by treatment of the terminal alkynes 296 and 297 with methyllithium followed addition of either ethyl or methyl chloroformate to the resultant lithium acetylide\textsuperscript{175} (Scheme 46). While 296 is commercially available, the monoprotected alkyne 297 can be prepared from hepta-1,6-diyne (298) by the addition of one equivalent of methyllithium followed by tert-butyl-dimethylsilyl chloride.
The acyclic aldehydes 287, 291, and 292 contain a range of functional groups including a primary chloride (291), a silyl protected alcohol (287) and a silyl protected terminal alkyne (292), while the cyclic aldehydes 276, 277 and 282 are of varying ring size (5 to 7 membered rings).

These substrates provide a diverse collection of interestingly substituted β-trimethylstannyl α,β-unsaturated aldehydes of general structure 275 on which to test the scope and limitations of the proposed annulation method.
4.4 Preparation of 2-(trimethylstannyl)allyllithium (271)

\[ \text{SnMe}_3 \quad \text{MeLi} \cdot \text{LiBr, THF, } -78 \, ^\circ \text{C} \rightarrow \text{SnMe}_3 \quad \text{Li} \]

The generation of 2-(trimethylstannyl)allyllithium (271) from 2,3-bis(trimethylstannyl)propene (183) was achieved by the method previously described in connection with the preparation of 2-(trimethylstannyl)allylcopper(I)-dimethyl sulfide. Thus, treatment of 183 with a solution of methyllithium-lithium bromide complex (1 equiv) in THF at low temperature provided 2-(trimethylstannyl)allyllithium (271) (equation 69). Evidence for the successful generation of 271 came from the reaction of this reagent with aldehydes 276, 277, 282, 287, 291, and 292 (vide infra).

A report by Mitchell\textsuperscript{128} indicated that transmetalation of the allylic Me\textsubscript{3}Sn group in 183 using methyllithium and subsequent reaction of 271 with a variety of electrophiles gave synthetically poor yields of products (equation 70, Table 13). However, in our studies on the preparation of 2-(trimethylstannyl)allylcopper(I)-dimethyl sulfide (182) and its conjugate addition reaction with \( \alpha,\beta \)-unsaturated ketones and aldehydes, excellent yields were obtained (vide supra, chapter 2 and 3).
Table 13  Lithiodestannylation of 2,3-Bis(trimethylstannyl)propene (183) and Reaction of the Resultant 2-(Trimethylstannyl)allyllithium (271) with Electrophiles

\[
\begin{align*}
\text{SnMe}_3 & \quad \text{1) MeLi, THF, -78^\circ C} & \quad \text{SnMe}_3 \\
\text{SnMe}_3 & \quad \text{2) electrophile, -78^\circ C \rightarrow rt} & \quad \text{(70)}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>E</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H2O</td>
<td>H</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>Me2SO4</td>
<td>Me</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>Me3SiCl</td>
<td>Me3Si</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>Me2CO</td>
<td>Me2C(OH)</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>PhCOMe</td>
<td>PhC(OH)Me</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>MeCHO</td>
<td>MeCH(OH)</td>
<td>44</td>
</tr>
<tr>
<td>7</td>
<td>EtCHO</td>
<td>EtCH(OH)</td>
<td>47</td>
</tr>
<tr>
<td>8</td>
<td>PhCHO</td>
<td>PhCH(OH)</td>
<td>48</td>
</tr>
</tbody>
</table>

4.5 Reaction of 2-(trimethylstannyl)allyllithium (271) with the aldehydes 276, 277, 282, 287, 291, and 292

Addition of the aldehyde substrates 291, 287, 292, 276, 277, and 282 to cold solutions of 2-(trimethylstannyl)allyllithium (271) in dry THF provided the alcohols, 299-304 respectively, in excellent yields (equation 71). The results are summarized in Table 14.
For example, when (Z)-6-chloro-3-trimethylstannylhex-2-enal (291) was added to a cold (-78 °C) solution of 271 in THF, after only 20 minutes TLC analysis of the reaction mixture indicated complete consumption of the aldehyde. Upon aqueous workup and purification by silica gel chromatography, the alcohol 299 was isolated in 93% yield (Table 14, entry 1).

All of the product alcohols 299-304 were acid sensitive, but the cyclic substrates were especially so due to their reduced conformational mobility with respect to their acyclic counterparts. Monodestannylation was observed during silica gel chromatography; the cyclic substrates selectively lose the trimethylstannyl group bound to the ring alkene while the acyclic substrates preferentially lose the trimethylstannyl group bound to carbon-6. Interestingly, the terminal alkenyltrimethylstannyl moiety was quite stable and no destannylation at this position was observed. Destannylation could be minimized through deactivation of the silica gel by adding triethylamine (1%) to the solvent system.
The structures assigned to the alcohols 299-304 were confirmed by spectroscopic data. For instance, the IR spectrum of 299 showed a strong O-H stretching absorption at 3558 cm\(^{-1}\) and a tin-methyl rocking absorption at 770 cm\(^{-1}\). The \(^1\)H nmr spectrum of 299 indicated the presence of two Me\(_3\)Sn groups (two 9-proton singlets with satellite peaks due to tin-proton coupling at \(\delta\ 0.15, 2J_{\text{Sn}-\text{H}} = 54 \text{ Hz}, \) and \(\delta\ 0.16, 2J_{\text{Sn}-\text{H}} = 54 \text{ Hz}\)), an hydroxyl group (a 1-proton doublet at \(\delta\ 1.63, J = 2.5 \text{ Hz}, \) which exchanges with D\(_2\)O), two methylene groups (a 2-proton triplet at \(\delta\ 3.49, J = 6.5 \text{ Hz,} \) and a 2-proton multiplet centered at \(\delta\ 1.78\)), four allylic protons (a 3-proton multiplet centered at \(\delta\ 2.35\) and a 1-proton doublet of doublets, with satellite peaks due to tin - proton coupling at \(\delta\ 2.57, J = 14, 4 \text{ Hz,} 3J_{\text{Sn}-\text{H}} = 54 \text{ Hz}\)), an hydroxymethine proton (a 1-proton multiplet centered at \(\delta\ 4.05\)), and three alkenyl protons (two mutually coupled 1-proton doublets with satellite peaks due to tin - proton coupling at \(\delta\ 5.35, J = 2.5 \text{ Hz,} 3J_{\text{Sn}-\text{H}} = 68 \text{ Hz,} \) and \(\delta\ 5.77, J = 2.5 \text{ Hz,} 3J_{\text{Sn}-\text{H}} = 146 \text{ Hz,} \) and a 1-proton doublet with satellite peaks due to tin - proton coupling at \(\delta\ 6.06, J = 6.5 \text{ Hz,} 3J_{\text{Sn}-\text{H}} = 137 \text{ Hz}\)). The geometry of the internal alkene was unaffected in the reaction and was established as Z by the magnitude of the tin-proton coupling constant\(^{182}\) \((3J_{\text{Sn}-\text{H}} = 137 \text{ Hz})\) between the alkenyl proton (H-5) and the tin atom attached to carbon six. The \(^{13}\)C nmr spectrum of 299 contained the expected 11 signals. The characteristic resonances displayed include the four alkenyl signals at \(\delta\ 129.0, 142.5, 145.1, \) and 151.9, the carbinol signal at \(\delta\ 71.5, \) and the signals for the two Me\(_3\)Sn groups at \(\delta\ 7.2\) and \(\delta\ -9.0\). In addition to this spectral data, the molecular formula of 299 was confirmed by the high resolution mass spectrometric measurement on the (M\(^+\) - Me) fragment.

The structural assignments of the remaining alcohols 300-304 were based on spectral data (\(^1\)H nmr, \(^{13}\)C nmr, and IR) and their molecular formulae also were confirmed by high resolution mass spectrometric measurements on the (M\(^+\) - Me) fragment. While the acyclic alcohols 300 and 301 contained three alkenyl protons, the cyclic alcohols 302-
304 contained two, and the ¹H nmr spectra of these compounds reflected this structural
difference.

In summary, 2-(trimethylstannyl)allyllithium (271) can be prepared efficiently from
2,3-bis(trimethylstannyl)propene (183) by treatment with methyllithium. Furthermore,
271 reacts with electrophilic species, such as the aldehydes 291, 287, 292, 276, 277,
and 282, and provides the corresponding products (299-304) in excellent synthetic yields
(equation 71).

4.6 Attempted copper(I) chloride-mediated cyclizations of alcohols 302 and 303

Attempts to effect the intramolecular copper(I) chloride-mediate coupling¹⁷⁴ of the
alkenyltrimethylstannane moieties in the alcohols 302 and 303 were unsuccessful
(equation 72). When 302 was treated with 5 equivalents of copper(I) chloride in warm
(60 °C) DMF, after appropriate workup, not only was none of the cyclized adduct 305
detected, a poor mass balance was obtained. Similarly, treatment of 303 with
5 equivalents of copper(I) chloride DMF, at room temperature, did not provide any of the
cyclized adduct 306. Apparently, the presence of an allylic alcohol not only inhibits the
coupling reaction, but also promotes decomposition of the substrate. Previous studies¹⁷²b
on the intermolecular copper(I) chloride coupling of alkenyltrialkylstannane substrates
containing an hydroxyl moiety at the allylic position were reported to proceed in only
moderate yield (~50%). Since it was the presence of the hydroxyl moiety in the alcohols
302 and 303 that was thought to inhibit the copper(I) chloride-mediate coupling reaction
of the alkenyltrimethylstannane functions, it was decided to convert the alcohols to the corresponding acetates, before repeating the copper(I) chloride-mediated coupling reactions.

4.7 Acetylation of the alcohols 299 - 304

Conversion of the alcohols 299-303 into the corresponding acetates 307-311 was achieved under standard conditions\textsuperscript{64} in nearly quantitative yields (equation 73). Only in the case of the alcohol 304 (Table 15, entries 6 and 7), which contains a seven membered ring, was the acetate 312 obtained in lower yield. The results of the acetylation reactions are summarized in Table 15.

For example, treatment of a solution of the alcohol 299 in methylene chloride with acetic anhydride in the presence of DMAP and triethylamine provided, after workup and silica gel chromatography, the acetate 307 in 99% yield (Table 15, entry 1). With the acyclic substrates 299-301, only short reaction times (2-4 hours) were needed to effect the conversion to the corresponding acetates 307-309; however, with the cyclic substrates 302-304, complete protection of the alcohols required a prolonged (overnight) treatment with acetic anhydride to afford the acetates 310-312.
Table 15  Synthesis of the Acetates 307-312

\[
\begin{align*}
\begin{array}{cccccc}
\text{Entry} & \text{Substrate} & R_1 & R_2 & \text{Product} & \% \text{ Yield}^a \\
1^b & 299 & H & \text{Cl-(CH}_2\text{)}_3^- & \text{307} & 99 \\
2^b & 300 & H & \text{TBSO-(CH}_2\text{)}_4^- & \text{308} & 100 \\
3^b & 301 & H & \text{TBS-C=C-(CH}_2\text{)}_3^- & \text{309} & 98 \\
4^b & 302 & -(\text{CH}_2)_3^- & \text{310} & 99 \\
5^b & 303 & -(\text{CH}_2)_4^- & \text{311} & 97 \\
6^b & 304 & -(\text{CH}_2)_5^- & \text{312} & 54^c \\
& & & (313) & (44)^d \\
7^e & 304 & -(\text{CH}_2)_5^- & \text{312} & 62 (77)^f \\
\end{array}
\end{align*}
\]

\(^a\) Isolated yield of purified products.
\(^b\) General Procedure D (Ac\(_2\)O, DMAP, Et\(_3\)N, CH\(_2\)Cl\(_2\), rt) was employed.
\(^c\) Yield of 312.
\(^d\) Yield of destannylated material 313.
\(^e\) Alternative reaction conditions (LDA, THF, 0 \(^\circ\)C; Ac\(_2\)O, rt) were employed.
\(^f\) Yield based on recovered starting material 304.

While the acetates 307-311 were prepared easily and in high yields from the corresponding alcohols, preparation of the acetate 312 in good yield was not as straightforward. Treatment of a solution of the alcohol 304 in methylene chloride with acetic anhydride in the presence of DMAP and triethylamine provided the expected acetate 312 in 54\% yield, as well as the monodestannylated acetate 313 in 44\% yield (Table 15, entry 6). The difference in reactivity of 304, as compared with the other cyclic substrates (302 and 303), deserves comment.
An examination of molecular models indicates that in the 5 and 6 membered ring systems (alcohols 302 and 303), the stabilizing influence of tin-oxygen coordination would be offset by the angle strain that would result, but in the 7 membered ring case (alcohol 304) tin-oxygen coordination gives a relatively strain free system (Scheme 47). A proposed mechanism for the protiodestannylation-acetylation of 304 is shown in Scheme 47. Protonation of the internal alkene provides a tertiary cation (314) which is stabilized by the β-tin atom. By contrast, protonation of the terminal carbon-carbon double bond in the same manner would result in the formation of a primary cation and is not observed. The tin-oxygen coordination could aid in the protiodestannylation of 304, to provide the trimethylstannyl ether 315, which is then subsequently acylated to provide 313 (Scheme 47). Thus, it is the distance between the alcohol oxygen and the tin atom of the alkenyltrimethylstannyl moiety on the ring that is believed to be responsible for this reactivity. A similar mechanism could rationalize the destannylation of the alcohols 299-304 which occurred during silica gel chromatography.
Other reaction conditions to effect acetylation of 304, while suppressing the unwanted destannylation reaction, were investigated. After much experimentation, it was found that generation of the lithium alkoxide of 304 using a strong base (LDA) followed by addition of acetic anhydride, prevented the destannylation reaction and gave only 312. Unfortunately, conditions could not be found such that the reaction would go to completion with high yields of 312. When short reaction times (2 hours) were allowed for trapping the alkoxide with acetic anhydride, some of the starting alcohol 304 was always recovered (20%) along with the acetate 312 in 62% isolated yield (Table 15, entry 7). Prolonged reaction times (overnight), resulted in a poor mass balance and low yield (~50%), although no starting material was then recovered.

The acetates 307-312 were found to be more stable to acidic conditions than the corresponding alcohols. While the alcohols 299-304 monodestannylated when chromatographed on silica gel without the addition of triethylamine to the solvent system, the acetates destannylated only upon prolonged exposure to silica gel during chromatography. The acyclic acetates 307-309 could easily be purified by silica gel chromatography without the addition of triethylamine to the solvent system. The cyclic acetatea 310-312, however, were slightly more acid sensitive than the acyclic acetates (307-309) and their purification by silica gel chromatography required the addition of triethylamine (1%) to the solvent system to prevent destannylation.

The structural assignments for compounds 307-313 were supported by their spectral data. For instance, the IR spectrum of 307 indicated the presence of an acetoxy moiety by strong stretching absorptions at 1740 cm\(^{-1}\) (C=O) and 1240 cm\(^{-1}\) (C-O), and the presence of the Me\(_3\)Sn group by a tin-methyl rocking absorption at 774 cm\(^{-1}\). The \(^1\)H nmr spectrum of 307 displayed the expected signals for two trimethylstannyl groups (two 9-proton singlets, with satellite peaks due to tin-proton coupling, at \(\delta 0.13, \, 2J_{\text{Sn-H}} = 53\) Hz, and \(\delta 0.21, \, 2J_{\text{Sn-H}} = 53\) Hz) and an acetate moiety (a 3-proton singlet at \(\delta 1.98\)). Other notable features in the \(^1\)H nmr spectrum of 307 include resonances for three alkenyl
protons with satellite peaks due to tin-proton coupling at δ 5.92 (a 1-proton doublet, J = 9 Hz, 3J_{Sn-H} = 134 Hz), δ 5.70 (a 1-proton doublet, J = 2.5 Hz, 3J_{Sn-H} = 147 Hz), and δ 5.28 (a 1-proton doublet, J = 2.5 Hz, 3J_{Sn-H} = 71 Hz), a methine proton at δ 5.16 (a 1-proton signal with coupling to three other protons, J = 9, 7, 5 Hz), four allylic protons at δ 2.57 (a 1-proton doublet of doublets, J = 14, 7 Hz), δ 2.53 (a 1-proton doublet of doublets, J = 14, 5 Hz), and δ 2.35 (a 2-proton triplet, J = 7 Hz, 3J_{Sn-H} = 50 Hz), and two other methylene groups at δ 3.46 (a 2-proton triplet, J = 6.5 Hz) and δ 1.77 (a 2-proton multiplet). The $^{13}$C nmr spectrum of 307 contained the expected 13 signals. Characteristic resonances exhibited were the four alkenyl carbon signals at δ 128.8, 139.6, 147.6, and 150.0, the methine carbon signal at δ 76.0, the acetoxy methyl and carbonyl signals at δ 21.5 and δ 170.0, respectively, and the signals for the two Me$_3$Sn groups at δ -7.9 and δ -8.9. In addition to this spectral data, the molecular formula of 307 was confirmed by the high resolution mass spectrometric measurement on the (M$^+$ - Me) fragment.

A similar analysis of the spectral data ($^1$H nmr, $^{13}$C nmr, and IR) was performed to assign the structures of 308-313, and their molecular formulae also were confirmed by high resolution mass spectrometric measurement on the (M$^+$ - Me) fragment. While the $^1$H nmr spectra of the acetates 308-312 displayed two signals for the Me$_3$Sn moieties, the monodestannyalted acetate 313 exhibited only one 9-proton singlet. Upon examination of the alkenyl regions of the $^1$H nmr spectra of 312 and 313, compound 312 was seen to possess two mutually coupled alkenyl protons, while compound 313 showed two mutually coupled alkenyl protons along with an additional alkenyl proton.
4.8 Copper(I) chloride-mediated cyclization of the acetates 307-312

Having prepared a variety of bis(alkenyltrimethylstannanes) containing diverse functionality, we were ready to attempt the intramolecular copper(I) chloride-mediated coupling of the two alkenyltrimethylstannane functions. Our hypothesis as to the deleterious effect of the hydroxyl function in the coupling reaction of alcohols 302 and 303 proved to be correct. Treatment of the acetates 307-312 with ~5 equivalents copper(I) chloride in warm DMF for 15 minutes provided the cyclized adducts 316-321 in moderate to good yields (Table 16, equation 74). For example, a solution of 307 in DMF was added to a warm (60 °C) slurry of copper(I) chloride in DMF. After 15 minutes, an analysis by TLC showed the disappearance of the starting material and the formation of a new product. Following aqueous workup and silica gel chromatography, the cyclized adduct 316 was isolated in 86% yield (Table 16, entry 1). In the cases where the products are relatively unstrained (Table 16, entries 1, 2, 3, and 5), good yields were obtained. However, in the cyclization of 310 (Table 16, entry 4), angle and torsional strain in the cyclized adduct 319 is thought to result in a lower product yield. With the conformationally less rigid seven membered ring system 312 (Table 16, entries 6 and 7), lower yields of the cyclized system 321 were also obtained.
Table 16 Copper(I) Chloride-Mediated Cyclization of 307-312

\[
\begin{align*}
R_1 & \quad R_2 & & \text{Product} & \text{% Yield}^a \\
1^b & 307 & H & Cl-(CH_2)_3- & 316 & 86 \\
2^b & 308 & H & TBSO-(CH_2)_4- & 317 & 79 \\
3^b & 309 & H & TBS-C≡C-(CH_2)_3- & 318 & 86 \\
4^b & 310 & -(CH_2)_3- & & 319 & 67 \\
5^b & 311 & -(CH_2)_4- & & 320 & 82 \\
6^b & 312 & -(CH_2)_5- & & 321 & 42 \\
7^c & 312 & -(CH_2)_5- & & 321 & 66 \\
\end{align*}
\]

\(^a\) Isolated yield of purified products.
\(^b\) General Procedure E (~5 equivalents CuCl, DMF, 60 °C) was employed.
\(^c\) Alternative reaction conditions (~5 equivalents CuCl, DMF, 0 °C) were employed.

The structures of the cyclized products 316-321 were assigned by analysis of the spectroscopic data. For instance, the IR spectrum of 316 showed the presence of an acetoxy moiety by strong stretching absorptions at 1729 cm\(^{-1}\) (C=O) and 1240 cm\(^{-1}\) (C-O), and two alkenyl moieties by stretching absorptions at 1639 cm\(^{-1}\) and 1618 cm\(^{-1}\). Further evidence for the success of the cyclization by the coupling of the two alkenyltrimethylstannyl functions was seen in the \(^1\)H nmr spectrum of 316. The two 9-proton singlets (attributed to the trimethylstannyl moieties) at high field had disappeared and there was no evidence of tin-proton coupling in any of the signals in the spectrum. The \(^1\)H nmr spectrum displayed resonances for the three alkenyl protons at \(\delta 5.91\) (a 1-proton singlet), \(\delta 4.98\) (a 1-proton doublet of doublets \(J = 2, 2\) Hz), and \(\delta 4.90\) (a 1-proton doublet, \(J = 2\) Hz), an allylic methine proton at \(\delta 5.63\) (a 1-proton doublet, \(J = 7\) Hz), four allylic methylene protons at \(\delta 3.00\) (a 1-proton doublet of doublet of triplets, \(J = 17\),
7, 2 Hz), δ 2.50 (a 1-proton doublet of doublets, J = 17, 2 Hz), and δ 2.36 (a 2-proton triplet, J = 8 Hz), two other methylene groups at δ 2.00 (a 2-proton multiplet) and δ 3.55 (a 2-proton triplet, J = 6.5 Hz), and an acetoxy methyl group at δ 2.01 (a 3-proton singlet). The 13C nmr spectrum of 316 contained the expected 11 signals. Characteristic resonances displayed were the four alkenyl carbon signals at δ 103.7, 131.3, 148.5, and 149.7, the methine carbon signal at δ 76.2, and the acetoxy methyl and carbonyl signals at δ 21.2 and δ 170.9, respectively. In addition to these spectral data, the molecular formula of 316 was confirmed by high resolution mass spectrometric measurement on the molecular ion.

The structures of the other cyclized adducts 317-321 were assigned by a similar analysis of their respective nmr (1H and 13C) and IR spectra, and their molecular formulae also were confirmed by their high resolution mass spectra.

Examination of the yields for the copper(I) chloride-mediated coupling reactions (Table 16) reveals that the cyclization proceeded in lower yield for substrate 310 than for 307-309 and 311. Cyclization of 312 under standard conditions also proceeded in poor yield (42%) and gave a poor mass balance (Table 16, entry 6). When the latter cyclization was attempted at a lower temperature (0 °C), conditions which have been employed in the intermolecular homocoupling of alkenyltrimethylstannanes,183 a superior, although still modest yield (66%), was obtained (Table 16, entry 7).

Examination of molecular models revealed possible reasons for the lower yields of 319 and 321 compared with 320. The cyclized adduct 319, 2-acetoxy-4-methylene-bicyclo[3.3.0]oct-1(5)-ene, has greater angle strain than compounds 316-318 and 320. In addition, the conformational rigidity of 319 precludes relief of torsional strain by ring puckering.184 In contrast, cyclization of 312 may be hindered by an intramolecular tin-oxygen coordination. Coordination of the two tin atoms to the carbinol oxygen provides a tricyclic chelate system in 312, containing a seven member ring and two five member rings with a low degree of angle strain. This relatively unstrained system appears not only to
disfavor the intramolecular copper(I) chloride-mediated coupling reaction, but may also promote the decomposition of 312, leading to the poor product yields and low mass balance observed for this conversion.

![Image of compound 312]

Tin-oxygen chelation of this type, between an alkenyltrimethylstannane and an oxygen held in close proximity, has been shown\textsuperscript{154} to affect the normal reactivity of these compounds, particularly in halodestannylation reactions. In these cases, alkyl groups are cleaved from the tin atom in preference to the alkenyl moiety. A similar mechanism may be affecting the tin-copper transmetalation in compound 312.

The fused bicyclic compounds 319 and 321 may be particularly susceptible to further reactions once formed. The reaction of a diene system containing an allylic leaving group (acetate) with potential nucleophiles such as chloride ion (from CuCl), could produce the reactive cyclopentadienyl system by a 1,5 addition. Cyclopentadienes are known substrates for reactions such as polymerization and Diels-Alder cycloadditions.\textsuperscript{185} Thus, further reaction or decomposition of the products (319 and 321) cannot be discounted as an explanation of the low mass balance.
4.9 Conclusions

The reaction of methyllithium with 2,3-bis(trimethylstannyl)propene (183) provides 2-(trimethylstannyl)allyllithium (271),\textsuperscript{128} which was shown to react with electrophilic species in high yields. The synthetic usefulness of 271 was shown in the development of a new methylenecyclopentene annulation sequence. This method involves addition of 271 to β-trimethylstannyl α,β-unsaturated aldehydes (275), followed by protection of the resultant alcohols as the corresponding acetates 274. The key reaction in the cyclization is a copper(I) chloride mediated intramolecular coupling of the two alkenyltrimethylstannane moieties in 274 to provide 273 (Scheme 48).

\[ \text{SnMe}_3 \text{SnMe}_3 \xrightarrow{\text{MeLiLiBr, THF, -78 °C}} \text{SnMe}_3 \text{Li} \]

\[ \begin{array}{c}
\text{R}_1 \text{CHO} \\
\text{R}_2 \text{SnMe}_3
\end{array} \xrightarrow{1) \text{271, THF, -78 °C}} \begin{array}{c}
\text{R}_2 \text{SnMe}_3 \\
\text{OAc}
\end{array} \xrightarrow{2) \text{Ac}_2\text{O, DMAP, Et}_3\text{N, CH}_2\text{Cl}_2, \text{rt}} \begin{array}{c}
\text{R}_2 \text{Me}_3\text{Sn} \\
\text{SnMe}_3
\end{array} \]

\[ \text{CuCl} \xrightarrow{\text{DMF, 60 °C}} \]

\[ \text{R}_1 \text{C}=\text{C}=\text{C} \quad \text{OAc} \]

Scheme 48
The annulation method makes use of procedures previously developed in our laboratories for the preparation of configurationally defined β-trimethylstannyl α,β-unsaturated aldehydes and esters, and shows an interesting synthetic use of 2,3-bis(trimethylstannyl)propene (183) and the corresponding 2-(trimethylstannyl)-allyllithium (271). Also illustrated is a further extension of the copper(I) chloride mediated intramolecular coupling reactions of two alkenyltrimethylstannane functions,\textsuperscript{174} effecting the closure of 5-membered rings. A variety of functional groups are tolerated in this cyclization procedure, providing novel monocyclic and bicyclic products of general structure 273, containing highly substituted cyclopentenyl systems.
III. CONCLUSIONS

The use of four bifunctional organometallic reagents in annulation sequences has been described in this thesis. Two of these reagents, 2-(trimethylgermyl)allylcopper(I)-dimethyl sulfide\(^{129}\) (162) and 2-(trimethylstannyl)allylcopper(I)-dimethyl sulfide\(^{129}\) (182) are novel, and were prepared for the first time during our studies of annulation sequences, while the other two reagents, 35\(^{11}\) and 271\(^{128}\) had been prepared previously.

![Structural formulas of GeMe\(_3\), Cu(CN)Li, M = GeMe\(_3\), M = SnMe\(_3\), and Li](image)

Michael addition of a functionalized allylic group to a variety of \(\alpha,\beta\)-unsaturated ketones of general structure 30 can be effected in synthetically useful yields using the allylcopper(I) reagents 162 and 182 in the presence of trimethylsilyl bromide (equation 75).\(^{129}\) The conjugate addition products 191 and 192 contain the structurally interesting \(\delta,\varepsilon\)-unsaturated carbonyl moiety, functionalized with a synthetically useful group in the \(\delta\)-position.
Several potential uses of the conjugate addition products 191 and 192 can be envisaged (Scheme 49). Both 191 and 192 could be converted into the corresponding iodide 322 by treatment with either iodine or N-iodosuccinimide. The alkenyl iodides 322, as well as the alkenyl(trimethylstannane) 192, could also be ready sources of the corresponding alkenyllithium 323 via metalation with an alkyl lithium (RLi). If the carbonyl function were protected prior to the lithiation, the alkenyllithium 323 could be reacted with a variety of electrophilic species. If the carbonyl of 323 were not
protected, the alkenyllithium would likely react in either an inter- or intramolecular fashion with the carbonyl function. The alkenyl iodide 322 and the alkenyl(trimethylstannane) 192 could also be used in transition metal catalyzed coupling reactions, such as the Stille cross coupling reaction,\textsuperscript{127} to provide 324.

A new method for the stereoselective synthesis of functionalized \textit{trans}-fused bicyclo[\textit{x}.3.0]alkanes (\textit{x} = 3, 4) was developed (Scheme 50).\textsuperscript{69} Reagents 162 and 182 are the synthetic equivalent of the d\textsuperscript{2},d\textsuperscript{3} prop-1-ene synthon (48), and reagent 35 is the synthetic equivalent of the d\textsuperscript{2},d\textsuperscript{4} but-1-ene synthon (39). In this capacity, these reagents have been used in annulation reactions with cyclopent-1-enecarbaldehydes (44) to yield products with the angular hydrogens at the newly formed ring junction bearing a \textit{trans}-relationship. The use of either 162 or 182 yields the \textit{trans}-fused bicyclo[3.3.0]octane ring.
system 325 while use of 35 yields the trans-fused bicyclo[4.3.0]nonane ring system 326. Thus, starting with a cyclopentanone system (56), the trans-fused bicyclic products 327 and 58 can be produced stereoselectively.

Clearly, this new methodology could be employed in a wide variety of synthetic contexts which required the stereocontrolled construction of trans-fused bicyclic systems. In principle, similar strategies could be developed to prepare trans-fused bicyclic systems other than the bicyclo[3.3.0]octane and bicyclo[4.3.0]nonane systems by varying the size of the cyclic ketone starting material, or by using a higher homologue of the bifunctional reagent 35. These changes would generalize the annulation method so that any trans-fused bicyclo[x.y.0]alkane system (x ≥ y ≥ 3) could be constructed.

The synthetic utility of 2-(trimethylstannyl)allyllithium (271) was also demonstrated in a method for the preparation of highly functionalized cyclopentenyl systems (equation 76). Suitable β-trimethylstannyl α,β-unsaturated aldehydes of general structure 275 were combined with 271 in excellent yields. The key step in this annulation sequence utilized a novel intramolecular copper(I) chloride-mediated coupling of two alkenyltrimethylstannane moieties under mild conditions to give the cyclopentenyl systems 273. A variety of functional groups can be tolerated in this annulation procedure, providing usefully functionalized cyclopentenyl systems 273.
The aforementioned annulation method could conceivably be used in the total synthesis of naturally occurring products. Several prostaglandins, such as PGE$_1$, have a carbocyclic framework similar to that of 273. Thus, this annulation sequence could allow rapid access into the prostaglandin family of compounds.
IV. EXPERIMENTAL

1. General

1.1 Data acquisition, presentation and techniques

Proton nuclear magnetic resonance ($^1$H nmr) spectra were recorded on a Bruker model WH-400 (400 MHz) or AMX-500 (500.2 MHz) spectrometer using deuteriochloroform (CDCl$_3$) or hexadeuteriobenzene (C$_6$D$_6$) as the solvent. CDCl$_3$ and C$_6$D$_6$ were passed through a short column of dry activated basic aluminum oxide, which had been dried in an oven (~140 °C) overnight and then allowed to cool in a desiccator prior to use. Signal positions (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of chloroform (δ 7.24) or benzene (δ 7.15). Coupling constants (J values) are given in Hertz (Hz) and are reported to the nearest 0.5 Hz. The tin-proton coupling constants ($J_{\text{Sn-H}}$) are given as an average of the $^{117}$Sn and $^{119}$Sn values. The multiplicity, number of protons, coupling constants and assignments (where known) are given in parentheses following the chemical shift. Abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. In the $^1$H nmr spectra, H-x and H-x' have been used to designate protons on the same carbon, with H-x' being the proton resonating at lower field. In some cases, the proton assignments were supported by two-dimensional ($^1$H,$^1$H) - homonuclear correlation spectroscopy (COSY), which was carried out using a Bruker WH-400 spectrometer.

Carbon nuclear magnetic resonance ($^{13}$C nmr) spectra were recorded on a Varian model XL-300 (75.3 MHz) spectrometer or on Bruker models AC-200E (50.3 MHz) or AMX-500 (125.8 MHz) spectrometers using deuteriochloroform (CDCl$_3$) or hexadeuteriochloroform (C$_6$D$_6$) as the solvent. Signal positions (δ) are given in parts per million from tetramethylsilane and were measured relative to the signal of deuteriochloroform (δ 77.0)
or hexadeuteriobenzene (δ 128.0). Attached proton tests (APTs), used to differentiate methyl and methine carbons (negative phase signals) from methylene and quaternary carbons (positive phase signals), were recorded on a Varian XL-300 or Bruker AC-200E spectrometers. Where APT data is given, signals with negative phases are so indicated in brackets (-ve) following the $^{13}$C nmr chemical shifts. In some cases, the proton and carbon assignments were supported by two-dimensional ($^1$H,$^{13}$C) heteronuclear multiple quantum coherence experiments (HMQC) and heteronuclear multiple bond correlation experiments (HMBC), which were carried out using a Bruker AMX-500 spectrometer.

Infrared (IR) spectra were recorded on a Perkin Elmer 1710 Fourier transform spectrophotometer with internal calibration as films between sodium chloride plates (liquid samples) or as potassium bromide pellets (solid samples). Only selected characteristic absorption data are provided for each compound.

Low and high resolution mass spectra were recorded on a Kratos MS 80 or on a Kratos Concept II HQ mass spectrometer using an electron impact source. The molecular ion (M$^+$) masses are given unless otherwise noted. For some of the compounds containing the trimethylstannyl (Me$_3$Sn), trimethylgermyl (Me$_3$Ge), trimethylsilyl (Me$_3$Si), or tert-butyldimethylsilyl (t-BuMe$_2$Si) moiety, the high resolution mass spectrometry molecular mass determinations were based on the (M$^+$ - Me) peak. Gas-liquid chromatography-mass spectrometry (GLCMS) was performed on a Carlo Erba model 4160 capillary gas chromatograph (15 m x 0.25 m fused silica column coated with DB-5) and a Kratos/RFA MS 80 mass spectrometer. All compounds subjected to high resolution mass measurements were homogeneous by GLC and/or TLC analyses.

Elemental analyses were performed on a Carlo Erba CHN model 1106 or on a Fisons EA model 1108 elemental analyzer, by the UBC Microanalytical Laboratory.

Melting points (mp) were measured on a Fisher-Johns melting point apparatus and are uncorrected. Distillation temperatures (air baths), which refer to bulb-to-bulb (Kugelrohr) distillations, are uncorrected.
Unless otherwise stated, all reactions were carried out under an atmosphere of dry argon using glassware that had been oven (~140 °C) dried and/or flame dried. Glass syringes, stainless steel needles, and Teflon® cannulae used to handle various anhydrous solvents and reagents were oven dried and flushed with argon prior to use. Plastic syringes were flushed with argon prior to use. Gas-tight microliter syringes (Hamilton series 1700) were dried under reduced pressure (vacuum pump), stored in a desiccator and flushed with argon prior to use. The small and large bore Teflon® cannulae were purchased from Canlab and have the following dimensions: the small cannulae has an inner diameter of 0.38 mm and a wall thickness of 0.23 mm; the large cannulae has an inner diameter of 0.97 mm and a wall thickness of 0.30 mm.

Thin layer chromatography (TLC) was performed using commercial aluminum-backed silica gel 60 F254 plates (E. Merck, type 5554, thickness 0.2 mm). Visualization of the chromatograms was accomplished using ultraviolet light (254 nm) and/or iodine (iodine which had been adsorbed onto unbound silica gel) followed by heating the plate after staining with one of the following solutions: (a) vanillin in a sulfuric acid-EtOH mixture (6% vanillin w/v, 4% sulfuric acid v/v, and 10% water v/v in EtOH), (b) phosphomolybdic acid in EtOH (20% phosphomolybdic acid w/v, Aldrich), (c) anisaldehyde in a sulfuric acid-EtOH mixture (5% anisaldehyde v/v and 5% sulfuric acid v/v in EtOH). Flash chromatography was performed using 230-400 mesh silica gel (E. Merck, Silica Gel 60), following the technique describe by Still. Short column chromatography, using TLC grade silica gel, was performed using Sigma type H silica gel 10-40 μm, no binder, following the technique described by Taber. Radial chromatography was carried out on a Chromatotron® Model 7924 using 1, 2, or 4 mm thick radial plates coated with silica gel (silica gel 60, PF254, with Gypsum, E. Merck #7749).

Gas-liquid chromatography (GLC) was performed on Hewlett-Packard models 5880A and 5890 gas chromatographs, both equipped with flame ionization detectors and
fused silica columns (Hewlett-Packard HP-5), ~25 m x 0.20 mm coated with 5% phenylmethylsilicone.

Concentration, evaporation or removal of solvent under reduced pressure (water aspirator) refers to solvent removal via a Büchi rotary evaporator at ~ 15 Torr.

Cold temperatures were maintained by the use of the following baths: 0 °C, ice-water; -20 °C, -35 °C, -48 °C, aqueous calcium chloride-dry ice (27, 39, and 47 g CaCl₂/100 mL H₂O, respectively);193 -78 °C, acetone-dry ice; -98 °C, methanol-liquid nitrogen.

1.2 Solvents and reagents

All solvents and reagents were purified, dried, and/or distilled using standard procedures.194 Benzene and dichloromethane were distilled from calcium hydride. Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl. The four aforementioned solvents were distilled under an atmosphere of dry argon and used immediately.

Diglyme was distilled from sodium benzophenone ketyl and stored over sodium borohydride. Triethylamine, diisopropylamine, dimethylsulfoxide (DMSO), and hexamethylphosphoramide (HMPA) were distilled from calcium hydride. Magnesium was added to methanol and, after refluxing the mixture, the methanol was distilled from the resulting solution of magnesium methoxide. Acetic anhydride was refluxed over and then distilled from phosphorous pentoxide. N,N-Dimethylformamide (DMF) was sequentially dried over 3 Å molecular sieves.195 The aforementioned reagents were stored under an atmosphere of argon in bottles sealed with a Sure/Seal (Aldrich Chemical Co., Inc.).

Petroleum ether refers to a hydrocarbon mixture with a boiling range of 35-60 °C.

Solutions of methyllithium (both as a complex with lithium bromide (MeLi•LiBr) and halide free (MeLi) forms) in diethyl ether, n-butyllithium in hexanes, and
 tert-butyllithium in pentane were obtained from Aldrich Chemical Co., Inc. and standardized using the procedure of Kofron and Baclawski.\textsuperscript{196}

\textit{p}-Toluenesulfonyl chloride was purified by the method described by Pelletier,\textsuperscript{197} dried (vacuum pump), and stored under an atmosphere of dry argon.

Copper(I) bromide-dimethyl sulfide complex was prepared by the method described by Wuts\textsuperscript{125} (by René Lemieux of Dr. Piers’ research group at UBC) and was stored in a desiccator under an atmosphere of dry argon. Copper(I) chloride (99.995%+ or 99%+), copper(I) cyanide, and phenylthiocopper(I) were purchased from Aldrich Chemical Co., Inc., and were used without further purification.

Trimethylsilyl bromide (Me\textsubscript{3}SiBr) and trimethylgermanium bromide (Me\textsubscript{3}GeBr) (obtained from Organometallics Inc.) were distilled, bulb-to-bulb, from calcium hydride using a Kugelrohr distillation apparatus and were used immediately.

Hexamethylditin and trimethyltin chloride were obtained from Organometallics Inc. and Aldrich Chemical Co., Inc., respectively, and were used without further purification.

Tetrakis(triphenylphosphine)palladium(0) was obtained from Aldrich Chemical Co., Inc. and was used without further purification. Chromium(II) chloride was obtained from Alfa Products and was used without further purification. Nickel(II) chloride was prepared from nickel(II) chloride hexahydrate (NiCl\textsubscript{2}•6H\textsubscript{2}O) using the procedure described by Pray.\textsuperscript{198} Samarium(II) iodide (0.1 M solution in THF) was prepared by the procedure described by Kagan\textsuperscript{199} (by Todd Schindeler of Dr. Piers’ research group at UBC) from samarium powder (obtained from Cerac Incorporated) and diiodomethane.

Lithium diisopropylamide (LDA) was prepared by the addition of a solution of \textit{n}-butyllithium (1 equiv) in hexanes to a solution of dry diisopropylamine (1.1 equiv) in dry tetrahydrofuran at 0 °C. The resulting colorless solution was then stirred at 0 °C for 15 minutes prior to use.
Potassium hydride was obtained as a 35% suspension in mineral oil from Aldrich Chemical Co., Inc. and was rinsed free of oil with dry diethyl ether under a stream of dry argon and dried (vacuum pump) prior to use.

A solution of sodium methoxide (NaO Me) in dry methanol (MeOH) was prepared in the following manner: to a cold (-78 °C) flask containing dry sodium hydride (NaH) was added the appropriate amount of dry methanol. The flask was warmed to room temperature and the solution was used immediately.

All other reagents are commercially available and were used without further purification.

Aqueous ammonium chloride-ammonium hydroxide (NH₄Cl-NH₄OH) (pH 8) was prepared by the addition of ~50 mL of concentrated aqueous ammonium hydroxide to 950 mL of a saturated aqueous ammonium chloride solution. Aqueous ammonium chloride-ammonium hydroxide (NH₄Cl-NH₄OH) (pH 7) was prepared by the addition of ~5 mL of concentrated aqueous ammonium hydroxide to ~1 L of a saturated aqueous ammonium chloride solution.
2. *Trans*-Fused Bicyclo[4.3.0]nonane Ring Systems

**Preparation of the triflate 67**

To a cold (-78 °C), stirred solution of LDA (42.5 mmol, 1.1 equiv) in dry THF (130 mL) was added cis-bicyclo[3.3.0]octane-3,7-dione mono-2,2-dimethylpropylene ketal 61 (8.47 g, 37.8 mmol) as a solution in THF (20 mL). After 2 hours, *N*-phenyltrifluoromethanesulphonimide (14.9 g, 41.6 mmol) was added as a solid and the reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction mixture was treated with saturated aqueous NaHCO₃ (150 mL) and diluted with Et₂O (150 mL). The phases were separated, the aqueous phase was extracted with Et₂O (4 x 50 mL), and the combined organic phases were washed sequentially with water (3 x 50 mL) and brine (3 x 50 mL), dried (MgSO₄), and concentrated. The crude product was purified by flash chromatography (400 g silica gel, 5:1 petroleum ether - Et₂O) to provide 12.2 g (90%) of the triflate 67 as a white solid. Recrystallization from hexanes - Et₂O afforded the triflate as colorless crystals (mp 80 - 82 °C).

**¹H nmr** (400 MHz, CDCl₃) δ: 0.93 (s, 3H, -CH₃), 0.95 (s, 3H, -CH₃), 1.64-1.71 (m, 2H), 2.22-2.39 (m, 3H), 2.77-2.87 (m, 2H), 3.15-3.23 (m, 1H, allylic methine), 3.42 (s, 2H, -CH₂O-), 3.44 (s, 2H, -CH₂O-), 5.45 (dd, 1H, olefinic proton, J = 2, 2 Hz).

**¹³C nmr** (75.3 MHz, CDCl₃) δ: 22.5 (-ve, 2 signals, -CH₃), 30.1, 35.5 (-ve), 37.7, 38.0, 40.8, 42.6 (-ve), 71.8, 72.6, 108.1, 118.5 (q, -CF₃, J = 4 Hz), 121.1 (-ve), 147.6.
IR (KBr): 1662, 1416, 1206, 1143, 1110 cm⁻¹.

Exact mass calcd for C₁₄H₁₉F₃O₅S: 356.0905; found: 356.0908.

Anal. calcd for C₁₄H₁₉F₃O₅S: C 47.19, H 5.37, S 9.00; found: C 47.13, H 5.39, S 9.21.

**Preparation of the ester 68**

![Chemical Structure](image)

To a stirred solution of Pd(OAc)₂ (0.244 g, 1.09 mmol), Ph₃P (0.606 g, 2.31 mmol), Et₃N (10 mL, 72 mmol), and MeOH (55 mL, 1.4 mol) in dry DMF (125 mL), at room temperature, was added the triflate 67 (11.9 g, 33.3 mmol). Carbon monoxide was bubbled through the solution for 30 minutes and a static atmosphere of carbon monoxide was maintained in the flask, over the reaction mixture, using a balloon filled with carbon monoxide. After 5 hours, the mixture was diluted with water (125 mL) and Et₂O (250 mL) and the phases were separated. The aqueous phase was extracted with Et₂O (3 x 50 mL) and the combined organic phases were washed with brine (4 x 30 mL), dried (MgSO₄) and concentrated. The crude product was purified by flash chromatography (155 g silica gel, 4:1 petroleum ether - Et₂O) to provide 7.77 g (88%) of the ester 68 as a white solid. Recrystallization from hexanes - Et₂O afforded the ester as colorless needles (mp 93 - 94 °C).
$^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.92 (s, 3H, -CH$_3$), 0.94 (s, 3H, -CH$_3$), 1.55 (dd, 1H, $J = 13.5, 8.5$ Hz), 1.66 (dd, 1H, $J = 13.5, 6.5$ Hz), 2.28-2.39 (m, 3H), 2.73-2.83 (m, 2H), 3.24-3.33 (m, 1H, allylic methine), 3.38-3.50 (m, 4H, -CH$_2$O-), 3.70 (s, 3H, -OCH$_3$), 6.61 (dd, 1H, olefinic proton, $J = 2, 2$ Hz).

$^{13}$C nmr (75.3 MHz, CDCl$_3$) $\delta$: 22.4 (-ve), 22.5 (-ve), 30.0, 37.9 (2 signals), 38.2, 40.4, 47.8 (-ve), 51.4 (-ve), 71.6, 72.7, 108.6, 134.1, 146.2 (-ve), 165.8.

$^{13}$C nmr (75.3 MHz, C$_6$D$_6$) $\delta$: 22.4 (-ve), 22.5 (-ve), 29.9, 38.3 (-ve), 38.6 (2 signals), 40.7, 48.2 (-ve), 50.9 (-ve), 71.6, 72.4, 108.9, 134.7, 146.1 (-ve), 165.4.

IR (KBr): 1717, 1633, 1278, 1100 cm$^{-1}$.

Exact mass calcd for C$_{15}$H$_{22}$O$_4$: 266.1518; found: 266.1526.

Anal. calcd for C$_{15}$H$_{22}$O$_4$: C 67.65, H 8.33; found: C 67.43, H 8.43.

Preparation of the allylic alcohol 70

![Chemical Structure]

To a cold (-78 °C), stirred solution of the ester 68 (4.86 g, 18.2 mmol) in dry THF (180 mL) was added DIBAL-H (1.0 M in hexanes, 45.0 mL, 45.0 mmol). After 15 minutes, the reaction mixture was warmed to 0 °C for an additional 15 minutes. The
reaction mixture was treated with solid ground Na₂SO₄·10H₂O (4.5 g, ~0.1 g/mmol DIBAL-H), warmed to room temperature, diluted with Et₂O (180 mL), and stirred open to the air for 30 minutes. The mixture was suction filtered through Celite® (45 g) and the cake was washed with Et₂O (~ 1.5 L). The solvent was removed from the filtrate under reduced pressure and the oil thus obtained was purified by flash chromatography (73 g silica gel, 2:1 petroleum ether - Et₂O) to provide 4.12 g (95%) of the allylic alcohol 70 as a white solid. Recrystallization from petroleum ether - Et₂O afforded the allylic alcohol as colorless crystals (mp 49 - 50 °C).

¹H nmr (400 MHz, CDCl₃) δ: 0.93 (s, 3H, -CH₃), 0.94 (s, 3H, -CH₃), 1.34 (br s, 1H, exchanges with D₂O, -OH), 1.53 (dd, 1H, J = 13, 9 Hz), 1.58 (dd, 1H, J = 13, 6 Hz), 2.08 (d, 1H, J = 16.5 Hz), 2.26-2.35 (m, 2H), 2.57 (dd, 1H, J = 16.5, 9 Hz), 2.76 (ddddd, 1H, J = 9, 9, 9, 9, 2.5 Hz), 3.11-3.18 (m, 1H), 3.39-3.50 (m, 4H, -CH₂O-), 4.12 (br s, 2H, -CH₂OH), 5.50 (br d, 1H, olefinic proton, J = 1.5 Hz).

¹³C nmr (75.3 MHz, CDCl₃) δ: 22.4 (-ve), 22.5 (-ve), 30.0, 38.1 (-ve), 39.0 (2 signals), 40.6, 47.0 (-ve), 61.9, 71.5, 72.7, 109.2, 129.0 (-ve), 142.2.

¹³C nmr (75.3 MHz, C₆D₆) δ: 22.48 (-ve), 22.53 (-ve), 30.0, 38.7 (-ve), 39.2, 39.5, 41.2, 47.6 (-ve), 61.9, 71.4, 72.7, 109.5, 128.8 (-ve), 142.9.

IR (KBr): 3429, 1657, 1112 cm⁻¹.

Exact mass calcd for C₁₄H₂₂O₃: 238.1569; found: 238.1561.

Anal. calcd for C₁₄H₂₂O₃: C 70.56, H 9.30; found: C 70.93, H 9.36.
Preparation of the \( \alpha, \beta \)-unsaturated aldehyde 71

To a stirred slurry of PCC (6.83 g, 31.7 mmol) and Celite® (6.8 g, ~1 g/g PCC) in dry CH\(_2\)Cl\(_2\) (65 mL), at room temperature, was added the allylic alcohol 70 (3.73 g, 15.7 mmol) in CH\(_2\)Cl\(_2\) (15 mL). The initially bright orange slurry turned dark brown. After 1 hour, the mixture was diluted with dry Et\(_2\)O (200 mL) and then was stirred for an additional hour. The mixture was suction filtered through Florisil (88 g) and the cake was washed with Et\(_2\)O (~1 L). The solvent was removed from the filtrate under reduced pressure and the solid thus obtained was purified by flash chromatography (75 g silica gel, 2:1 petroleum ether - Et\(_2\)O) to provide 3.17 g (86%) of the unsaturated aldehyde 71 as a white solid. Recrystallization from hexanes - Et\(_2\)O afforded the unsaturated aldehyde as colorless crystals (mp 64 - 65 °C).

\(^1\)H nmr (500.2 MHz, CDCl\(_3\)) \( \delta \): 0.90 (s, 3H, -CH\(_3\)), 0.97 (s, 3H, -CH\(_3\)), 1.58 (dd, 1H, H-2, \( J = 13.5, 8.5 \) Hz), 1.75 (dd, 1H, H-4, \( J = 13.5, 6 \) Hz), 2.29-2.37 (m, 3H, H-2', H-4' and H-8), 2.70 (dddd, 1H, H-8', \( J = 16.5, 8.5, 2, 2 \) Hz), 2.86 (ddddd, 1H, H-1, \( J = 8.5, 8.5, 8.5, 8.5, 2.5 \) Hz), 3.34-3.47 (m, 5H, four from -CH\(_2\)O- and H-5), 6.69 (dd, 1H, H-6, \( J = 2.5, 2 \) Hz), 9.75 (s, 1H, -CHO).

\(^1^3\)C nmr (125.8 MHz, CDCl\(_3\)) \( \delta \): 22.4 (-ve, -CH\(_3\)), 22.6 (-ve -CH\(_3\)), 30.1 (C-11), 35.0 (C-8), 38.0 (-ve, C-1), 38.7 (C-4), 40.0 (C-2), 48.1 (-ve, C-5), 71.8 (-CH\(_2\)O-), 72.6 (-CH\(_2\)O-), 108.6 (C-3), 145.6 (C-7), 155.0 (-ve, C-6), 190.4 (-ve, -CHO).
IR (KBr): 1681, 1617, 1111 cm\(^{-1}\).

Exact mass calcd for C\(_{14}H_{20}O_3\): 236.1412; found: 236.1406.

Anal. calcd for C\(_{14}H_{20}O_3\): C 71.16, H 8.53; found: C 71.33, H 8.69.

**Table 17** \(^1\)H nmr (400 MHz, CDCl\(_3\)) Data for the \(\alpha,\beta\)-Unsaturated Aldehyde 71:

COSY Experiment

![Chemical Structure](image)

### Table

<table>
<thead>
<tr>
<th>Assignment H-x</th>
<th>(^1)H nmr (\delta) (multiplicity, (J) (Hz))</th>
<th>COSY Correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-1</td>
<td>2.86 (ddddd, (J = 8.5, 8.5, 8.5, 8.5, 2.5))</td>
<td>H-2, H-2', H-8, H-8', H-5</td>
</tr>
<tr>
<td>H-2</td>
<td>1.58 (dd, (J = 13.5, 8.5))</td>
<td>H-2', H-1</td>
</tr>
<tr>
<td>H-2'</td>
<td>part of the m at 2.29-2.37</td>
<td>H-2, H-1</td>
</tr>
<tr>
<td>H-4</td>
<td>1.75 (dd, (J = 13.5, 6))</td>
<td>H-4', H-5</td>
</tr>
<tr>
<td>H-4'</td>
<td>part of the m at 2.29-2.37</td>
<td>H-4, H-5</td>
</tr>
<tr>
<td>H-5</td>
<td>part of the m at 3.34-3.47</td>
<td>H-1, H-4, H-4', H-6 ,H-8'</td>
</tr>
<tr>
<td>H-6</td>
<td>6.69 (dd, (J = 2.5, 2))</td>
<td>H-5, H-8'</td>
</tr>
<tr>
<td>H-8</td>
<td>part of the m at 2.29-2.37</td>
<td>H-1, H-8'</td>
</tr>
<tr>
<td>H-8'</td>
<td>2.70 (dddd, (J = 16.5, 8.5, 2, 2))</td>
<td>H-1, H-5, H-6, H-8</td>
</tr>
<tr>
<td>H-9</td>
<td>9.75 (s)</td>
<td></td>
</tr>
<tr>
<td>H-10, H-10'</td>
<td>part of the m at 3.34-3.47</td>
<td></td>
</tr>
<tr>
<td>H-12, H-12'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me-13</td>
<td>0.90 (s)</td>
<td></td>
</tr>
<tr>
<td>Me-14</td>
<td>0.97 (s)</td>
<td></td>
</tr>
</tbody>
</table>
Table 18 \(^{13}\text{C} \text{nmr} \ (125.8 \ MHz, \text{CDCl}_3) \) and \(^1\text{H} \text{nmr} \ (500.2 \ MHz) \) Data for the \(\alpha,\beta\)-Unsaturated Aldehyde \(\text{71}\): HMQC Experiment

<table>
<thead>
<tr>
<th>Assignment</th>
<th>(^{13}\text{C} \text{nmr} ) (\delta ) ppm</th>
<th>APT</th>
<th>HMQC (^1\text{H} \text{nmr} ) Correlations ((\delta ) ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-x</td>
<td>(\delta ) ppm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me-14</td>
<td>22.4</td>
<td>CH or CH(_3)</td>
<td>Me-14 (0.90)</td>
</tr>
<tr>
<td>Me-13</td>
<td>22.6</td>
<td>CH or CH(_3)</td>
<td>Me-13 (0.97)</td>
</tr>
<tr>
<td>C-11</td>
<td>30.1</td>
<td>C or CH(_2)</td>
<td></td>
</tr>
<tr>
<td>C-8</td>
<td>35.0</td>
<td>C or CH(_2)</td>
<td>H-8 (2.29-2.37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-8' (2.70)</td>
</tr>
<tr>
<td>C-1</td>
<td>38.0</td>
<td>CH or CH(_3)</td>
<td>H-1 (2.86)</td>
</tr>
<tr>
<td>C-4</td>
<td>38.7</td>
<td>C or CH(_2)</td>
<td>H-4 (1.75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-4' (2.29-2.37)</td>
</tr>
<tr>
<td>C-2</td>
<td>40.0</td>
<td>C or CH(_2)</td>
<td>H-2 (1.58)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-2' (2.29-2.37)</td>
</tr>
<tr>
<td>C-5</td>
<td>48.1</td>
<td>CH or CH(_3)</td>
<td>H-5 (3.34-3.47)</td>
</tr>
<tr>
<td>C-10</td>
<td>71.8</td>
<td>C or CH(_2)</td>
<td>H-10 (3.34-3.47)</td>
</tr>
<tr>
<td>C-12</td>
<td>72.6</td>
<td>C or CH(_2)</td>
<td>H-12 (3.34-3.47)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-12' (3.34-3.47)</td>
</tr>
<tr>
<td>C-3</td>
<td>108.6</td>
<td>C or CH(_2)</td>
<td></td>
</tr>
<tr>
<td>C-7</td>
<td>145.6</td>
<td>C or CH(_2)</td>
<td></td>
</tr>
<tr>
<td>C-6</td>
<td>155.5</td>
<td>CH or CH(_3)</td>
<td>H-6 (6.69)</td>
</tr>
<tr>
<td>C-9</td>
<td>190.4</td>
<td>CH or CH(_3)</td>
<td>H-9 (9.75)</td>
</tr>
</tbody>
</table>
Preparation of lithium (3-trimethylgermylbut-3-en-1-yI)(cyano)cuprate \(35^{11,37}\)

\[
\text{GeMe}_3 \quad \longrightarrow \quad \text{Cu(CN)Li}
\]

\(35\)

To a cold (\(-98^\circ\text{C}\)), stirred solution of freshly distilled 4-iodo-2-trimethylgermyl-1-butene (16) (0.684 g, 2.29 mmol) in dry THF (25 mL) was added rapidly a solution of \textit{tert}-butyllithium (2.11 M in pentane, 2.10 mL, 4.43 mmol). (CAUTION: Careful control of the temperature of the cooling bath is critical for the lithium iodine exchange reaction. At temperatures higher than -98 \(^\circ\text{C}\), dimerization of 16 is the predominant reaction.) The resultant clear yellow solution was stirred at -98 \(^\circ\text{C}\) for 10 minutes and was warmed to -78 \(^\circ\text{C}\). Copper(I) cyanide (0.230 g, 2.56 mmol) was added in one portion and the suspension became colorless. The reaction mixture was warmed briefly (~5 minutes) to -35 \(^\circ\text{C}\) to provide a light tan homogeneous solution of the cuprate reagent 35, which was cooled to -78 \(^\circ\text{C}\) and used immediately. (CAUTION: While it is necessary to warm the reaction mixture for the copper(I) cyanide to dissolve, prolonged warming will result in the decomposition of the cuprate reagent.)

Preparation of the aldehyde 80

To a cold (-78 \(^\circ\text{C}\)), stirred solution of the cuprate reagent 35 (2.22 mmol) in dry THF (25 mL) was added neat trimethylsilyl bromide (0.818 g, 5.24 mmol). After
2 minutes, a solution of the unsaturated aldehyde 71 (0.346 g, 1.46 mmol) in dry THF (3 mL) was added dropwise (over 5 minutes), using a small bore cannula, followed by dropwise addition of HMPA (0.51 mL, 2.9 mmol). The reaction mixture was stirred at -78 °C for 15 minutes, then was poured into aqueous NH₄Cl-NH₄OH (pH 8) (30 mL). The mixture was diluted with Et₂O (60 mL) and vigorously stirred open to the air for 3 hours, upon which the aqueous layer turned bright blue. The phases were separated and the aqueous phase was extracted with Et₂O (3 x 25 mL). The combined organic phases were washed sequentially with aqueous 10% CuSO₄ (2 x 25 mL) and brine (2 x 25 mL), dried (MgSO₄), and concentrated. A small sample was purified by radial chromatography (1 mm plate, 19:1 petroleum ether - Et₂O) to provide the silyl enol ether 81 as a low melting white solid (mp 25 - 26 °C).

¹H nmr (400 MHz, CDCl₃) δ: 0.07 (s, 9H, -Si Me₃), 0.18 (s, 9H, -Ge Me₃), 0.93 (s, 6H, -CH₃), 1.41-1.61 (m, 4H), 2.04-2.12 (m, 2H), 2.17-2.25 (m, 1H), 2.28-2.37 (m, 2H), 2.47 (dd, 1H, J = 16, 8.5 Hz), 2.71 (dddd, 1H, J = 8.5, 8.5, 8.5, 8.5, 2.5 Hz), 3.08-3.12 (m, 1H), 3.41 (s, 2H, -CH₂O-), 3.47 (s, 2H, -CH₂O-), 4.16 (dd, 1H, J = 6, 6 Hz), 5.14 (m, 1H), 5.38 (br s, 1H), 5.48 (m, 1H).

¹³C nmr (75.3 MHz, CDCl₃) δ: -1.9 (-ve), 0.3 (-ve), 22.5 (-ve, 2 signals, CH₃), 30.1, 33.2, 35.4, 37.1, 37.9 (-ve), 38.9, 40.8, 46.7 (-ve), 71.2 (-ve), 71.4, 72.8, 109.1, 121.2, 128.6 (-ve), 144.8, 153.9.

IR (neat): 1250, 1113, 1009, 841, 599 cm⁻¹.

Exact mass calcd for C₂₄H₄₄⁷⁴GeO₃Si: 482.2271; found: 482.2275.

The crude oil (compound 81) was dissolved in dry THF (25 mL) and the solution was cooled to -78 °C and treated with MeLi (1.40 M in Et2O, 1.25 mL, 1.75 mmol). After 30 minutes, the reaction mixture was poured into water (10 mL). The phases were separated and the aqueous phase was extracted with Et2O (3 x 10 mL). The combined organic phases were washed with brine (2 x 10 mL), dried (MgSO4), and concentrated. Purification of the crude product by radial chromatography (2 mm plate, 5:1 petroleum ether - Et2O) and removal of trace amounts of solvent (vacuum pump) from the resulting liquid provided 0.541 g (90%) of the aldehyde 80 as a colorless oil. 1H nmr spectroscopic analysis of the oil indicated a 3:1 mixture (α:β) of epimeric aldehydes.

1H nmr (400 MHz, CDCl3) δ: 0.17 (s, 9H, -GeMe3), 0.93 (s, 3H, -CH3), 0.96 (s, 3H, -CH3), 1.37-1.82 (m, 5H), 1.96-2.25 (m, 7H), 2.33-2.40 (m, 1H), 2.55-2.70 (m, 1H), 3.45 (br s, 4H, -CH2O-), 5.14-5.16 (m, 1H), 5.46-5.48 (m, 1H), 9.50, 9.78 (d, J = 4 Hz, d, J = 3 Hz, α:β ratio ~3:1, 1H total, -CHO).

Equilibration of the aldehyde 80

To a stirred solution of the aldehyde 80 (0.822 g, 2.01 mmol, 3:1 mixture of epimers), at room temperature, in dry MeOH (20 mL) was added NaOMe (0.5 M in MeOH, 8 mL, 4 mmol). After 4 hours, the MeOH was removed under reduced pressure and Et2O (100 mL) and water (10 mL) were added to the residue. The organic phase was
washed with water (3 x 15 mL) and brine (2 x 15 mL), dried (MgSO₄), and concentrated. Purification of the crude product by radial chromatography (4 mm plate, 5:1 petroleum ether - Et₂O) and removal of trace amounts of solvent (vacuum pump) from the resulting liquid provided 0.751 g (91%) of the aldehyde 80 as a colorless oil. ¹H nmr spectroscopic analysis of the oil indicated a 9:1 mixture (α:β) of epimeric aldehydes.

¹H nmr (400 MHz, CDCl₃) δ: 0.17 (s, 9H, -GeMe₃), 0.93 (s, 3H, -CH₃), 0.96 (s, 3H, -CH₃), 1.37-1.82 (m, 5H), 1.96-2.25 (m, 7H), 2.33-2.40 (m, 1H), 2.55-2.70 (m, 1H), 3.45 (br s, 4H, -CH₂O-), 5.14-5.16 (m, 1H), 5.46-5.48 (m, 1H), 9.50, 9.78 (d, J = 4 Hz, d, J = 3 Hz, α:β ratio ~9:1, 1H total, -CHO).

Signals attributed to the major epimer:
¹³C nmr (75.3 MHz, CDCl₃) δ: -1.9 (-ve, -GeMe₃), 22.4 (-ve, -CH₃), 22.5 (-ve, -CH₃), 30.0, 33.9, 34.4, 35.6, 39.4, 40.2, 40.4 (-ve, CH), 47.6 (-ve, CH), 48.2 (-ve, CH), 60.8 (-ve, CH), 71.9 (-CH₂O-), 72.0 (-CH₂O-), 110.3 (O-C=O), 121.5 (C=CH₂), 153.5 (C=CH₂), 203.8 (-ve, -CHO).

IR (neat): 2704, 1724, 1237, 1116, 825, 600 cm⁻¹.

Exact mass calcd for C₂₁H₃₆⁷⁴GeO₃: 410.1876; found: 410.1883.

Anal. calcd for C₂₁H₃₆GeO₃: C 61.65, H 8.87; found: C 61.70, H 8.91.
Preparation of the alkenyl iodide 99

To a stirred solution of the alkenyltrimethylgermane 80 (0.503 g, 1.23 mmol, 9:1 mixture of epimers) in dry CH₂Cl₂ (25 mL), at room temperature, was added N-iodo-succinimide (0.573 g, 2.55 mmol). The pink slurry was stirred, in the dark, for 20 hours. The reaction mixture was poured into a vigorously stirred solution of saturated aqueous Na₂S₂O₃ (25 mL). The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 x 15 mL). The combined organic phases were washed with saturated aqueous Na₂S₂O₃ (10 mL), dried (MgSO₄), and concentrated. The crude product was purified by radial chromatography (4 mm plate, 4:1 petroleum ether - Et₂O) and removal of trace amounts of solvent (vacuum pump) from the resulting liquid provided 0.430 g (84%) of the alkenyl iodide 99 as a colorless oil. ¹H nmr spectroscopic analysis of the oil indicated a 9:1 mixture (α:β) of epimeric aldehydes.

¹H nmr (400 MHz, CDCl₃) δ: 0.93 (s, 3H, -CH₃), 0.96 (s, 3H, -CH₃), 1.51-1.76 (m, 5H), 1.79-1.83 (m, 1H), 1.97-2.27 (m, 5H), 2.33-2.45 (m, 2H), 2.58-2.72 (m, 1H), 3.45 (br s, 4H, -CH₂O-), 5.69 (m, 1H), 6.01 (m, 1H), 9.51, 9.78 (d, J = 4 Hz, d, J = 3 Hz, α:β ratio ~9:1, 1H total, -CHO).

Signals attributed to the major epimer:

¹³C nmr (75.3 MHz, CDCl₃) δ: 22.4 (-ve, -CH₃), 22.5 (-ve, -CH₃), 30.0, 34.3, 34.5, 39.4, 39.8, 40.3 (-ve, CH), 43.4, 46.7 (-ve, CH), 47.5 (-ve, CH), 60.6 (-ve, CH), 71.9 (2 signals, -CH₂O-), 110.2, 111.6, 125.8 (C=CH₂), 203.6 (-ve, -CHO).
IR (neat): 2707, 1722, 1617, 1115 cm⁻¹.

Exact mass calcd for C₁₈H₂₇I₂O₃: 418.1005; found: 418.1000.


**Preparation of the alcohols 102 and 103**

![Chemical Structures](image1)

To a stirred suspension of CrCl₂ (0.825 g, 6.72 mmol) and NiCl₂ (0.067 g, 0.52 mmol) in dry DMF (20 mL), at room temperature, was added the iodo aldehyde 99 (0.506 g, 1.21 mmol, 9:1 mixture of epimers) as a solution in dry DMF (5 mL). After 1 hour, the reaction mixture was diluted with Et₂O (50 mL) and brine (25 mL) and the phases were separated. The organic phase was washed with brine (5 x 10 mL), dried (MgSO₄), and concentrated. The crude product was purified by radial chromatography (2 mm plate, 2:1 petroleum ether - Et₂O) and the appropriate fractions were concentrated to provide 0.082 g (23%) of 102 and 0.200 g (57%) of 103, both as white solids. Recrystallization of 102 from pentane afforded the α-alcohol 102 as colorless needles (mp 130 -131 °C) while recrystallization of 103 from petroleum ether - Et₂O afforded the β-alcohol 103 as colorless needles (mp 97 - 98 °C).
α-alcohol 102

$^1$H nmr (400 MHz, CDCl$_3$) δ: 0.92 (s, 3H, -CH$_3$), 0.95 (s, 3H, -CH$_3$), 0.99 (dddd, 1H, H-5$_{axial}$, $J = 12, 12, 12, 4$ Hz), 1.32-1.41 (m, 2H, H-12 and -OH; after D$_2$O exchange: m, 1H), 1.47 (dddd, 1H, H-1, $J = 12, 12, 5.5, 2.5$ Hz), 1.62-1.73 (m, 3H, H-6, H-8 and H-10), 1.79-1.85 (m, 1H, H-12'), 1.88-1.96 (m, 2H, H-5$_{equatorial}$ and H-7), 2.10-2.22 (m, 3H, H-4$_{equatorial}$, H-8' and H-10'), 2.34 (br dd, 1H, H-4$_{axial}$, $J = 13.5, 12$ Hz), 2.46-2.55 (m, 1H, H-11), 3.45 (s, 4H, -CH$_2$O-), 4.23 (br s, 1H, -CH(OH)-), 4.74 (dd, 1H, H-13, $J = 2, 2$ Hz), 4.83 (dd, 1H, H-13', $J = 2, 2$ Hz).

$^{13}$C nmr (75.3 MHz, CDCl$_3$) δ: 22.5 (-ve, -CH$_3$), 22.6 (-ve, -CH$_3$), 29.9 (C-4), 30.0 (C-15), 31.6 (C-5), 33.5 (C-12), 38.3 (C-8 or C-10), 39.2 (-ve, C-11), 40.0 (C-8 or C-10), 43.9 (-ve, C-6), 45.3 (-ve, C-7), 53.0 (-ve, C-1), 71.8 (-CH$_2$O-), 72.2 (-CH$_2$O-), 73.6 (-ve, -CH(OH)-), 110.8 (C=CH$_2$), 111.1 (O-C-O), 150.6 (C=CH$_2$).

IR (KBr): 3456, 1651, 1110 cm$^{-1}$.

Exact mass caled for C$_{18}$H$_{28}$O$_3$: 292.2038; found: 292.2036.

Anal. caled for C$_{18}$H$_{28}$O$_3$: C 73.93, H 9.65; found: C 73.81, H 9.75.
Table 19 \(^1\)H nmr (400 MHz, CDCl\(_3\)) Data for the Allylic Alcohol 102: COSY Experiment

<table>
<thead>
<tr>
<th>Assignment</th>
<th>(\Delta) (multiplicity, (J) (Hz))</th>
<th>COSY Correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-1</td>
<td>1.47 (dddd, (J = 12, 12, 5.5, 2.5))</td>
<td>H-2, H-6, H-12, H-12'</td>
</tr>
<tr>
<td>H-2</td>
<td>4.23 (br s)</td>
<td>H-1, O-H</td>
</tr>
<tr>
<td>H-4(_{ax})</td>
<td>2.34 (br dd, (J = 13.5, 12))</td>
<td>H-4(<em>{eq}), H-5(</em>{ax}), H-5(_{eq}), H-13, H-13'</td>
</tr>
<tr>
<td>H-4(_{eq})</td>
<td>part of the m at 2.10-2.22</td>
<td>H-4(<em>{ax}), H-5(</em>{ax}), H-5(_{eq})</td>
</tr>
<tr>
<td>H-5(_{ax})</td>
<td>0.99 (dddd, (J = 12, 12, 12, 4))</td>
<td>H-4(<em>{ax}), H-4(</em>{eq}), H-5(_{eq}), H-6</td>
</tr>
<tr>
<td>H-5(_{eq})</td>
<td>part of the m at 1.88-1.96</td>
<td>H-4(<em>{ax}), H-4(</em>{eq}), H-5(_{ax}), H-6</td>
</tr>
<tr>
<td>H-6</td>
<td>part of the m at 1.62-1.73</td>
<td>H-1, H-5(<em>{ax}), H-5(</em>{eq}), H-7</td>
</tr>
<tr>
<td>H-7</td>
<td>part of the m at 1.88-1.96</td>
<td>H-6, H-8, H-8', H-11</td>
</tr>
<tr>
<td>H-8</td>
<td>part of the m at 1.62-1.73</td>
<td>H-7, H-8'</td>
</tr>
<tr>
<td>H-8'</td>
<td>part of the m at 2.10-2.22</td>
<td>H-7, H-8</td>
</tr>
<tr>
<td>H-10</td>
<td>part of the m at 1.62-1.73</td>
<td>H-10', H-11</td>
</tr>
<tr>
<td>H-10'</td>
<td>part of the m at 2.10-2.22</td>
<td>H-10, H-11</td>
</tr>
<tr>
<td>H-11</td>
<td>2.46-2.55 (m)</td>
<td>H-7, H-10, H-10', H-12, H-12'</td>
</tr>
<tr>
<td>H-12</td>
<td>part of the m at 1.32-1.41</td>
<td>H-1, H-11, H-12'</td>
</tr>
<tr>
<td>H-12'</td>
<td>1.79-1.85 (m)</td>
<td>H-1, H-11, H-12</td>
</tr>
<tr>
<td>H-13</td>
<td>4.74 (dd, (J = 2, 2))</td>
<td>H-4(_{ax}), H-13'</td>
</tr>
<tr>
<td>H-13'</td>
<td>4.83 (dd, (J = 2, 2))</td>
<td>H-4(_{ax}), H-13</td>
</tr>
<tr>
<td>H-14, H-14'</td>
<td>part of the signal at 3.45 (s)</td>
<td></td>
</tr>
<tr>
<td>H-16, H-16'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me-17</td>
<td>0.92 (s)</td>
<td></td>
</tr>
<tr>
<td>Me-18</td>
<td>0.95 (s)</td>
<td></td>
</tr>
<tr>
<td>O-H</td>
<td>part of the m at 1.32-1.41</td>
<td>H-2</td>
</tr>
</tbody>
</table>
Table 20 $^{13}\text{C} \text{nmr}$ (125.8 MHz, CDCl$_3$) and $^1\text{H} \text{nmr}$ (500.2 MHz) Data for the Allylic Alcohol 102: HMQC Experiment

<table>
<thead>
<tr>
<th>Assignment C-x</th>
<th>$^{13}\text{C} \text{nmr}$ $\delta$ ppm</th>
<th>APT</th>
<th>HMQC $^1\text{H} \text{nmr}$ Correlations ($\delta$ ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-17</td>
<td>22.5</td>
<td>CH or CH$_3$</td>
<td>Me-17 (0.92)</td>
</tr>
<tr>
<td>C-18</td>
<td>22.6</td>
<td>CH or CH$_3$</td>
<td>Me-18 (0.95)</td>
</tr>
<tr>
<td>C-4</td>
<td>29.9</td>
<td>C or CH$_2$</td>
<td>H-4$_{eq}$ (2.10-2.22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-4$_{ax}$ (2.34)</td>
</tr>
<tr>
<td>C-15</td>
<td>30.0</td>
<td>C or CH$_2$</td>
<td></td>
</tr>
<tr>
<td>C-5</td>
<td>31.6</td>
<td>C or CH$_2$</td>
<td>H-5$_{eq}$ (1.88-1.96)</td>
</tr>
<tr>
<td>C-12</td>
<td>33.5</td>
<td>C or CH$_2$</td>
<td>H-12 (1.32-1.41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-12' (1.79-1.85)</td>
</tr>
<tr>
<td>C-8 or C-10</td>
<td>38.3</td>
<td>C or CH$_2$</td>
<td>H-8 or H-10 (1.62-1.73)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-8' or H-10' (2.10-2.22)</td>
</tr>
<tr>
<td>C-11</td>
<td>39.2</td>
<td>CH or CH$_3$</td>
<td>H-11 (2.46-2.55)</td>
</tr>
<tr>
<td>C-8 or C-10</td>
<td>40.0</td>
<td>C or CH$_2$</td>
<td>H-8 or H-10 (1.62-1.73)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-8' or H-10' (2.10-2.22)</td>
</tr>
<tr>
<td>C-6</td>
<td>43.9</td>
<td>CH or CH$_3$</td>
<td>H-6 (1.62-1.73)</td>
</tr>
<tr>
<td>C-7</td>
<td>45.3</td>
<td>CH or CH$_3$</td>
<td>H-7 (1.88-1.96)</td>
</tr>
<tr>
<td>C-1</td>
<td>53.0</td>
<td>CH or CH$_3$</td>
<td>H-1 (1.47)</td>
</tr>
<tr>
<td>C-14</td>
<td>71.8</td>
<td>C or CH$_2$</td>
<td>H-14 (3.45)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-14' (3.45)</td>
</tr>
<tr>
<td>C-16</td>
<td>72.2</td>
<td>C or CH$_2$</td>
<td>H-16 (3.45)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-16' (3.45)</td>
</tr>
<tr>
<td>C-2</td>
<td>73.6</td>
<td>CH or CH$_3$</td>
<td>H-2 (4.74)</td>
</tr>
<tr>
<td>C-13</td>
<td>110.8</td>
<td>C or CH$_2$</td>
<td>H-13 (4.74)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-13' (4.83)</td>
</tr>
<tr>
<td>C-9</td>
<td>111.1</td>
<td>C or CH$_2$</td>
<td></td>
</tr>
<tr>
<td>C-3</td>
<td>150.6</td>
<td>C or CH$_2$</td>
<td></td>
</tr>
</tbody>
</table>
β-alcohol 103

$^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.91 (s, 3H, -CH$_3$), 0.97 (s, 3H, -CH$_3$), 0.99 (dddd, 1H, H-5$_{axial}$, $J = 11.5$, 11.5, 11.5, 4 Hz), 1.15 (ddd, 1H, H-12, $J = 8.5$, 11.5, 11.5 Hz), 1.25 (ddddd, 1H, H-1, $J = 11.5$, 11.5, 11.5, 5.5 Hz), 1.39 (ddddd, 1H, H-6, $J = 11.5$, 11.5, 11.5, 3.5 Hz), 1.56 (d, 1H, -OH, exchanges with D$_2$O, $J = 6$ Hz), 1.71-1.76 (m, 2H, H-8 and H-10), 1.81-1.87 (m, 1H, H-5$_{equatorial}$), 1.98-2.15 (m, 4H, H-4$_{axial}$, H-7, H-8' and H-10'), 2.22 (ddd, 1H, H-12', $J = 11.5$, 8, 5.5 Hz), 2.42 (ddd, 1H, H-4$_{equatorial}$, $J = 14$, 4, 2 Hz), 2.46-2.56 (m, 1H, H-11), 3.41-3.50 (m, 4H, -CH$_2$O-), 3.81 (dd, 1H, -CH(OH)-, $J = 11.5$, 6 Hz; after D$_2$O exchange: d, $J = 11.5$ Hz), 4.77 (br d, 1H, H-13, $J = 2$ Hz), 4.94 (br d, 1H, H-13', $J = 2$ Hz).

$^{13}$C nmr (125.8 MHz, CDCl$_3$) $\delta$: 22.5 (-ve, -CH$_3$), 22.6 (-ve, -CH$_3$), 30.1 (C-15), 31.1 (C-5), 34.7 (C-4), 37.1 (C-12), 38.5 (C-8 or C-10), 39.7 (C-8 or C-10), 39.8 (-ve, C-11), 45.6 (-ve, C-7), 51.3 (-ve, C-6), 56.2 (-ve, C-1), 72.0 (2 signals, -CH$_2$O-), 76.9 (-ve, -CH(OH)-), 104.8 (C=CH$_2$), 111.0 (O-C=O), 151.3 (C=CH$_2$).

IR (KBr): 3436, 1651, 1117 cm$^{-1}$.

Exact mass calcd for C$_{18}$H$_{28}$O$_3$: 292.2038; found: 292.2038.

Anal. calcd for C$_{18}$H$_{28}$O$_3$: C 73.93, H 9.65; found: C 74.12, H 9.68.
Table 21 $^1$H nmr (400 MHz, CDCl$_3$) Data for the Allylic Alcohol 103:
COSY Experiment

<table>
<thead>
<tr>
<th>Assignment</th>
<th>$^1$H nmr $\delta$ (multiplicity, $J$ (Hz))</th>
<th>COSY Correlations</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-1</td>
<td>1.25 (ddddd, $J = 11.5, 11.5, 11.5, 5.5$)</td>
<td>H-2, H-6, H-12, H-12'</td>
</tr>
<tr>
<td>H-2</td>
<td>3.81 (dd, $J = 11.5, 6$)</td>
<td>H-1, O-H</td>
</tr>
<tr>
<td>H-4$_{ax}$</td>
<td>part of the m at 1.98-2.15</td>
<td>H-4$<em>{eq}$, H-5$</em>{ax}$, H-5$_{eq}$, H-13, H-13'</td>
</tr>
<tr>
<td>H-4$_{eq}$</td>
<td>2.42 (ddd, $J = 2, 4, 14$)</td>
<td>H-4$<em>{ax}$, H-5$</em>{ax}$, H-5$_{eq}$</td>
</tr>
<tr>
<td>H-5$_{ax}$</td>
<td>0.99 (ddddd, $J = 11.5, 11.5, 11.5, 4$)</td>
<td>H-4$<em>{ax}$, H-4$</em>{eq}$, H-5$_{eq}$, H-6</td>
</tr>
<tr>
<td>H-5$_{eq}$</td>
<td>1.81-1.87 (m)</td>
<td>H-4$<em>{ax}$, H-4$</em>{eq}$, H-5$_{ax}$, H-6</td>
</tr>
<tr>
<td>H-6</td>
<td>1.39 (ddddd, $J = 11.5, 11.5, 11.5, 3.5$)</td>
<td>H-1, H-5$<em>{ax}$, H-5$</em>{eq}$, H-7</td>
</tr>
<tr>
<td>H-7</td>
<td>part of the m at 1.98-2.15</td>
<td>H-6, H-8, H-8', H-11</td>
</tr>
<tr>
<td>H-8</td>
<td>part of the m a 1.71-1.76</td>
<td>H-7, H-8'</td>
</tr>
<tr>
<td>H-8'</td>
<td>part of the m at 1.98-2.15</td>
<td>H-8</td>
</tr>
<tr>
<td>H-10</td>
<td>part of the m at 1.71-1.76</td>
<td>H-10', H-11</td>
</tr>
<tr>
<td>H-10'</td>
<td>part of the m at 1.98-2.15</td>
<td>H-10, H-11</td>
</tr>
<tr>
<td>H-11</td>
<td>2.46-2.56 (m)</td>
<td>H-7, H-10, H-10', H-12, H-12'</td>
</tr>
<tr>
<td>H-12</td>
<td>1.15 (ddddd, $J = 8.5, 11.5, 11.5$)</td>
<td>H-1, H-11, H-12'</td>
</tr>
<tr>
<td>H-12'</td>
<td>2.22 (ddddd, $J = 5.5, 8.5, 11.5$)</td>
<td>H-1, H-11, H-12</td>
</tr>
<tr>
<td>H-13</td>
<td>4.77 (br d, $J = 2$)</td>
<td>H-2, H-4$_{ax}$, H-13'</td>
</tr>
<tr>
<td>H-13'</td>
<td>4.94 (br d, $J = 2$)</td>
<td>H-2, H-4$_{ax}$, H-13</td>
</tr>
<tr>
<td>H-14, H-14'</td>
<td>3.41-3.50 (m)</td>
<td></td>
</tr>
<tr>
<td>H-16, H-16'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me-17</td>
<td>0.91 (s)</td>
<td></td>
</tr>
<tr>
<td>Me-18</td>
<td>0.97 (s)</td>
<td></td>
</tr>
<tr>
<td>O-H</td>
<td>1.56 (d, $J = 6$)</td>
<td>H-2</td>
</tr>
</tbody>
</table>
Table 22  $^{13}$C nmr (125.8 MHz, CDCl$_3$) and $^1$H nmr (500.2 MHz) Data for the Allylic Alcohol 103: HMQC Experiment

103

<table>
<thead>
<tr>
<th>Assignment C-x</th>
<th>$^{13}$C nmr $\delta$ ppm</th>
<th>APT</th>
<th>HMQC $^1$H nmr Correlations ($\delta$ ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-17</td>
<td>22.5</td>
<td>CH or CH$_3$</td>
<td>Me-17 (0.92)</td>
</tr>
<tr>
<td>C-18</td>
<td>22.6</td>
<td></td>
<td>Me-18 (0.95)</td>
</tr>
<tr>
<td>C-15</td>
<td>30.1</td>
<td>C or CH$_2$</td>
<td>H-5$_{eq}$ (1.81-1.87)</td>
</tr>
<tr>
<td>C-5</td>
<td>31.1</td>
<td>C or CH$_2$</td>
<td>H-5$_{ax}$ (0.99)</td>
</tr>
<tr>
<td>C-4</td>
<td>34.7</td>
<td>C or CH$_2$</td>
<td>H-4$_{eq}$ (2.42)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-4$_{ax}$ (1.98-2.15)</td>
</tr>
<tr>
<td>C-12</td>
<td>37.1</td>
<td>C or CH$_2$</td>
<td>H-12 (1.15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-12' (2.22)</td>
</tr>
<tr>
<td>C-8 or C-10</td>
<td>38.5</td>
<td>C or CH$_2$</td>
<td>H-8 or H-10 (1.71-1.76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-8' or H-10' (1.98-2.15)</td>
</tr>
<tr>
<td>C-8 or C-10</td>
<td>39.7</td>
<td>C or CH$_2$</td>
<td>H-8 or H-10 (1.71-1.76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-8' or H-10' (1.98-2.15)</td>
</tr>
<tr>
<td>C-11</td>
<td>39.8</td>
<td>CH or CH$_3$</td>
<td>H-11 (2.46-2.56)</td>
</tr>
<tr>
<td>C-7</td>
<td>45.6</td>
<td>CH or CH$_3$</td>
<td>H-7 (1.98-2.15)</td>
</tr>
<tr>
<td>C-6</td>
<td>51.3</td>
<td>CH or CH$_3$</td>
<td>H-6 (1.39)</td>
</tr>
<tr>
<td>C-1</td>
<td>56.2</td>
<td>CH or CH$_3$</td>
<td>H-1 (1.25)</td>
</tr>
<tr>
<td>C-14</td>
<td>72.0</td>
<td>C or CH$_2$</td>
<td>H-14 (3.41-3.50)</td>
</tr>
<tr>
<td>C-16</td>
<td></td>
<td></td>
<td>H-14' (3.41-3.50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-16 (3.41-3.50)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>H-16' (3.41-3.50)</td>
</tr>
<tr>
<td>C-2</td>
<td>76.9</td>
<td>CH or CH$_3$</td>
<td>H-2 (3.81)</td>
</tr>
<tr>
<td>C-13</td>
<td>104.8</td>
<td>C or CH$_2$</td>
<td>H-13 (4.77)</td>
</tr>
<tr>
<td>C-9</td>
<td>111.0</td>
<td>C or CH$_2$</td>
<td>H-13' (4.94)</td>
</tr>
<tr>
<td>C-3</td>
<td>151.3</td>
<td>C or CH$_2$</td>
<td></td>
</tr>
</tbody>
</table>
Preparation of the α-acetate 104

To a stirred solution of the allylic alcohol 102 (0.080 g, 0.28 mmol) in dry CH₂Cl₂ (3 mL), at room temperature, were added sequentially Et₃N (57 µL, 0.41 mmol), Ac₂O (39 µL, 0.41 mmol) and DMAP (0.050 g, 0.41 mmol). After 2 hours, water (10 mL) and CH₂Cl₂ (10 mL) were added and the phases were separated. The organic phase was washed with brine (2 x 5 mL), dried (Na₂SO₄), and concentrated. Purification of the crude product by radial chromatography (1 mm plate, 6:1 petroleum ether - Et₂O) provided 0.091 g (98%) of the α-acetate 104 as a white solid. Recrystallization from pentane afforded the acetate as colorless crystals (mp 85 - 86 °C).

$^1$H nmr (400 MHz, CDCl₃) δ: 0.91 (s, 3H, -CH₃), 0.98 (s, 3H, -CH₃), 0.96-1.13 (m, 2H), 1.51 (dddd, 1H, $J = 12, 12, 6, 2.5$ Hz), 1.63-1.73 (m, 3H), 1.79-1.97 (m, 3H), 2.01 (s, 3H, -C(=O)CH₃), 2.07-2.29 (m, 4H), 2.43-2.54 (m, 1H), 3.42-3.50 (m, 4H, -CH₂O-), 4.84 (m, 1H), 4.96 (m, 1H), 5.40 (d, 1H, -CH(OAc)-, $J = 2.5$ Hz).

$^{13}$C nmr (75.3 MHz, CDCl₃) δ: 21.2 (-ve), 22.5 (-ve), 22.7 (-ve), 30.1, 30.7, 31.3, 33.9, 38.5, 39.2 (-ve), 39.5, 44.9 (-ve), 45.0 (-ve), 51.5 (-ve), 71.8, 72.1, 75.1 (-ve), 110.9, 113.4, 146.1, 170.4.

IR (KBr): 1739, 1656, 1234, 1112 cm$^{-1}$. 

Exact mass calcd for C_{20}H_{30}O_{4}: 334.2144; found: 334.2136.

Anal. calcd for C_{20}H_{30}O_{4}: C 71.82, H 9.04; found: C 71.68, H 8.95.

**Preparation of the β-acetate 105**

To a stirred solution of the allylic alcohol 103 (0.112 g, 0.381 mmol) in dry CH_{2}Cl_{2} (4 mL), at room temperature, were added sequentially Et_{3}N (80 µL, 0.57 mmol), Ac_{2}O (55 µL, 0.58 mmol) and DMAP (0.070 g, 0.57 mmol). After 1 hour, water (10 mL) and CH_{2}Cl_{2} (10 mL) were added and the phases were separated. The organic phase was washed with brine (2 x 5 mL), dried (Na_{2}SO_{4}), and concentrated. Purification of the crude product by radial chromatography (1 mm plate, 6:1 petroleum ether - Et_{2}O) provided 0.121 g (95%) of the β-acetate 105 as a white solid. Recrystallization from heptane afforded the acetate as colorless needles (mp 92 - 93 °C).

{\textsuperscript{1}H} nmr (400 MHz, CDCl_{3}) δ: 0.91 (s, 3H, -CH_{3}), 0.96 (s, 3H, -CH_{3}), 0.88-1.05 (m, 1H), 1.09-1.18 (m, 1H), 1.39-1.49 (m, 2H), 1.70-1.75 (m, 2H), 1.87 (br d, 1H, J = 12 Hz), 1.99-2.16 (m, 5H), 2.10 (s, 3H, -C(=O)CH_{3}), 2.44 (ddd, 1H, J = 14, 4, 2 Hz), 2.46-2.53 (m, 1H), 3.40-3.51 (m, 4H, -CH_{2}O-), 4.67 (d, 1H, J = 1.5 Hz), 4.73 (d, 1H, J = 1.5 Hz), 5.07 (d, 1H, -CH(OAc)-, J = 9.5 Hz).
$^{13}$C nmr (75.3 MHz, CDCl$_3$) $\delta$: 20.8 (-ve), 22.4 (-ve), 22.5 (-ve), 30.0, 30.8, 34.6, 36.7, 38.2, 39.4, 39.5 (-ve), 45.4 (-ve), 51.0 (-ve), 53.2 (-ve), 71.8, 71.9, 77.6 (-ve), 105.4, 110.7, 146.3, 170.1.

IR (KBr): 1742, 1652, 1239, 1117 cm$^{-1}$.

Exact mass calcd for C$_{20}$H$_{30}$O$_4$: 334.2144; found: 334.2146.

Anal. calcd for C$_{20}$H$_{30}$O$_4$: C 71.82, H 9.04; found: C 71.84, H 8.97.

Preparation of the keto $\alpha$-acetate 106

Ozone was bubbled through a cold (-78 °C), stirred solution of the allylic acetate 104 (0.082 g, 0.25 mmol) in dry MeOH (5 mL) until a blue - grey color persisted (~5 minutes). Dimethyl sulfide (~1 mL) was added and the mixture was stirred at -78 °C for 10 minutes and then was warmed to room temperature. The solution was purged with argon and the solvent was removed under reduced pressure. The crude oil was purified by flash chromatography (8 g silica gel, 1:1 petroleum ether - Et$_2$O) to provide 0.081 g (98%) of 106 as a white solid. Recrystallization from heptane afforded the keto acetate 106 as colorless crystals (mp 100 - 101 °C).
$^1$H nmr (400 MHz, CDCl$_3$) δ: 0.91 (s, 3H, -CH$_3$), 1.00 (s, 3H, -CH$_3$), 1.24-1.40 (m, 2H), 1.73-1.89 (m, 4H), 1.92-2.16 (m, 5H), 2.09 (s, 3H, -C(=O)CH$_3$), 2.22 (br d, 1H, J = 14 Hz), 2.55-2.66 (m, 2H), 3.42-3.52 (m, 4H, -CH$_2$O-), 4.93 (d, 1H, -CH(OAc)-, J = 1 Hz).

$^{13}$C nmr (75.3 MHz, CDCl$_3$) δ: 20.6 (-ve), 22.4 (-ve), 22.6 (-ve), 30.0, 30.1, 33.5, 37.0, 38.6, 39.2, 40.1 (-ve), 43.9 (-ve), 44.0 (-ve), 52.2 (-ve), 71.9, 72.0, 77.7 (-ve), 110.6, 169.7, 207.9.

IR (KBr): 1750, 1730, 1225, 1108 cm$^{-1}$.

Exact mass calcd for C$_{19}$H$_{28}$O$_5$: 336.1937; found: 336.1930.

Anal. calcd for C$_{19}$H$_{28}$O$_5$: C 67.83, H 8.39; found: C 67.84, H 8.50.

Preparation of the keto β-acetate 107

Ozone was bubbled through a cold (-78 °C), stirred solution of the allylic acetate 105 (0.112 g, 0.344 mmol) in dry MeOH (7 mL) until a blue - grey color persisted (~5 minutes). Dimethyl sulfide (~1 mL) was added and the mixture was stirred at -78 °C for 10 minutes and then was warmed to room temperature. The solution was purged with argon and the solvent was removed under reduced pressure. The crude oil
was purified by flash chromatography (8 g silica gel, 2:1 petroleum ether - Et₂O) to provide 0.104 g (90%) of 107 as a white solid. Recrystallization from pentane afforded the keto acetate 107 as colorless needles (mp 144 - 145 °C).

\(^1\)H nmr (400 MHz, CDCl₃) \(\delta\): 0.91 (s, 3H, -CH₃), 0.99 (s, 3H, -CH₃), 1.20-1.27 (m, 1H), 1.35 (dddd, 1H, \(J = 13, 13, 13, 5\) Hz), 1.72-1.96 (m, 4H), 2.00-2.16 (m, 5H), 2.12 (s, 3H, -C(=O)CH₃), 2.42 (ddddd, 1H, \(J = 13.5, 13.5, 13.5, 6.5\) Hz), 2.47 (ddddd, 1H, \(J = 13.5, 13.5, 5, 2.5\) Hz), 2.59-2.69 (m, 1H), 3.41-3.52 (m, 4H, -CH₂O-), 5.03 (d, 1H, -CH(OAc)-, \(J = 12\) Hz).

\(^{13}\)C nmr (75.3 MHz, CDCl₃) \(\delta\): 20.6 (-ve), 22.4 (-ve), 22.6 (-ve), 29.1, 30.0, 37.4, 38.4, 39.0, 39.8, 40.5 (-ve), 44.8 (-ve), 49.7 (-ve), 51.8 (-ve), 71.7, 72.2, 80.7 (-ve), 110.5, 170.1, 204.2.

IR (KBr): 1750, 1728, 1235, 1116 cm\(^{-1}\).

Exact mass calcd for C₁₉H₂₈O₅: 336.1937; found: 336.1940.

Preparation of the tricyclic ketone 83 from the keto acetate 106

To a cold (-78 °C), stirred solution of SmI₂ (0.1 M in THF, 5.4 mL, 0.54 mmol) was added the keto acetate 106 (0.072 g, 0.21 mmol) as a solution in a mixture of dry THF (3 mL) and dry MeOH (1 mL). The initially deep blue solution turned dark green. After 10 minutes, the reaction mixture was warmed to room temperature for 15 minutes.

The mixture was poured into saturated aqueous K₂CO₃ (10 mL) and the resultant mixture was diluted with saturated aqueous Na₂S₂O₃ (5 mL) and Et₂O (10 mL). The phases were separated and the aqueous phase was extracted with Et₂O (5 x 10 mL). The combined organic extracts were dried (MgSO₄) and concentrated. The acquired material was purified by radial chromatography (1 mm plate, 2:1 petroleum ether - Et₂O) to provide 0.050 g (85%) of the ketone 83 as a white solid. Recrystallization from pentane afforded the ketone 83 as colorless plates (mp 72 - 74 °C).

¹H nmr (400 MHz, CDCl₃) δ: 0.92 (s, 3H, -CH₃), 0.98 (s, 3H, -CH₃), 1.11 (ddd, 1H, J = 10, 10, 10 Hz), 1.34 (dddd, 1H, J = 12.5, 12.5, 12.5, 5 Hz), 1.52-1.68 (m, 2H), 1.77-1.82 (m, 2H), 1.99-2.17 (m, 6H), 2.22-2.40 (m, 2H), 2.48 (br d, 1H, J = 14 Hz), 2.55-2.65 (m, 1H), 3.41-3.50 (m, 4H, -CH₂O-).

¹³C nmr (75.3 MHz, CDCl₃) δ: 22.4 (-ve), 22.6 (-ve), 29.1, 30.0, 38.3, 39.5, 39.7, 40.5 (-ve), 40.8, 44.7 (-ve), 47.2, 47.6 (-ve), 50.9 (-ve), 71.8, 72.0, 110.8, 211.7.

IR (KBr): 1714, 1117 cm⁻¹.
Exact mass calcd for C_{17}H_{26}O_{3}: 278.1882; found: 278.1876.

Anal. calcd for C_{17}H_{26}O_{3}: C 73.35, H 9.41; found: C 73.40, H 9.51.

**Preparation of the tricyclic ketone 83 from the keto acetate 107**

To a cold (-78 °C), stirred solution of SmI\textsubscript{2} (0.1 M in THF, 6 mL, 0.6 mmol) was added the keto acetate 107 (0.080 g, 0.24 mmol) as a solution in a mixture of dry THF (3 mL) and dry MeOH (1 mL). The initially deep blue solution turned dark green. After 10 minutes, the reaction mixture was warmed to room temperature for 15 minutes. The mixture was poured into saturated aqueous K_{2}CO\textsubscript{3} (10 mL) and the resultant mixture was diluted with saturated aqueous Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} (5 mL) and Et\textsubscript{2}O (10 mL). The phases were separated and the aqueous phase was extracted with Et\textsubscript{2}O (5 x 10 mL). The combined organic extracts were dried (MgSO\textsubscript{4}) and concentrated. The acquired material was purified by radial chromatography (1 mm plate, 2:1 petroleum ether - Et\textsubscript{2}O) to provide 0.062 g (94%) of the ketone 83 as a white solid, which exhibited spectroscopic data identical with those reported above.
3. Substituted Allylcopper(I) Reagents

**Preparation of 2-bromoprop-2-enol (134)**

![Structural formula of 134]

To a stirred solution of 10% aqueous K$_2$CO$_3$ (1100 mL) at room temperature was added 2,3-dibromopropene (136) (Aldrich 80% pure, 145 g, 580 mmol). The two phase mixture was heated at 90 °C for 9 hours and then was cooled to room temperature. The now single phase solution was extracted with CH$_2$Cl$_2$ (20 x 50 mL) and the combined organic extracts were dried (MgSO$_4$). Removal of the solvent under reduced pressure followed by fractional distillation (bp 88 °C/70 Torr) of the remaining liquid through a Vigreaux column (1.5 x 15 cm) provided 74.3 g (94%) of the allylic alcohol 134 as a colorless oil.

$^1$H nmr (400 MHz, CDCl$_3$) δ: 2.02 (br s, 1H, -OH, exchanges with D$_2$O), 4.16 (d, 2H, -CH$_2$OH, $J = 6$ Hz; after D$_2$O exchange: s), 5.53 (d, 1H, $J = 1$ Hz), 5.89 (d, 1H, $J = 1$ Hz).

$^{13}$C nmr (50.3 MHz, CDCl$_3$) δ: 67.6, 116.3, 132.4.

IR (neat): 3311, 1641, 1235, 1044, 893 cm$^{-1}$.

Exact mass calcd for C$_3$H$_5$$^{79}$BrO: 135.9524; found: 135.9521.

Preparation of 2-(trimethylgermyl)prop-2-enol (133)

![Chemical Structure](image)

To a cold (-78 °C), stirred solution of freshly distilled 2-bromoprop-2-enol (134) (15.6 g, 113 mmol) in dry Et₂O (320 mL) was added slowly (1 mL/min) a solution of t-BuLi (1.7 M in pentane, 200 mL, 340 mmol). The pale yellow, cloudy mixture was warmed to 0 °C and stirred for 3 hours. Freshly distilled Me₃GeBr (24.7 g, 125 mmol) was added and the solution was stirred at 0 °C for an additional 1 hour. Saturated aqueous NH₄Cl (100 mL) was added and the phases were separated. The aqueous phase was extracted with Et₂O (3 x 50 mL) and the combined organic extracts were washed once with brine (50 mL), dried (MgSO₄), and concentrated. The crude oil was dissolved in CH₂Cl₂ (115 mL) and p-TsOH·H₂O (21.7 g, 114 mmol) was added. After the resultant solution had been stirred at room temperature for 3 hours, saturated aqueous NaHCO₃ (115 mL) was added. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (4 x 25 mL). Silica gel (230 - 400 mesh, 125 g) was added to the combined organic phases and the slurry was stirred for 15 minutes. The slurry was filtered and the filtrate was concentrated under reduced pressure to provide an orange oil which was fractionally distilled (bp 81 °C/25 Torr) through a Vigreux column (1.5 x 15 cm) to provide 14.3 g (72%) of the alkenylgermane 133 as a colorless oil.

¹H nmr (400 MHz, CDCl₃) δ: 0.23 (s, 9H, -GeMe₃), 1.35 (br s, 1H, -OH, exchanges with D₂O), 4.26 (br d, 2H, -CH₂OH, J = 5.5 Hz; after D₂O exchange: s), 5.28 (m, 1H), 5.72 (dt, 1H, J = 2, 2 Hz).
$^{13}$C nmr (75.3 MHz, CDCl$_3$) $\delta$: -2.2, 66.7, 120.1, 153.1.

IR (neat): 3306, 1237, 1031, 924, 827, 601 cm$^{-1}$.

Exact mass calcd for C$_5$H$_{11}^{74}$GeO (M$^+$ - Me): 161.0022; found: 161.0028.

Anal. calcd for C$_6$H$_{14}$GeO: C 41.23, H 8.07; found: C 41.30, H 8.13.

Preparation of 3-bromo-2-((trimethylgermyl)propene (135)

To a cold (-20 $^\circ$C), stirred solution of Ph$_3$P (21.9 g, 83.5 mmol) in dry CH$_2$Cl$_2$ (725 mL) was added a solution of bromine (13.4 g, 83.8 mmol) in dry CH$_2$Cl$_2$ (25 mL). The resulting pale yellow solution was warmed to room temperature and a few crystals of Ph$_3$P were added until the solution turned colorless. A solution of freshly distilled 2-((trimethylgermyl)prop-2-enol (133) (13.2 g, 75.5 mmol) in dry CH$_2$Cl$_2$ (10 mL) was added and the resulting mixture was stirred at room temperature for 30 minutes. The majority of the solvent was removed under reduced pressure and the resulting slurry was filtered through a column (7 x 15 cm) of Florisil® (300g) and the column was eluted with $n$-pentane (~2 L). The appropriate fractions were combined and concentrated under reduced pressure and the remaining oil was distilled bulb-to-bulb (70 - 90 $^\circ$C/13 Torr) to provide 16.7 g (93%) of the allylic bromide 135 as a colorless oil.
\^1H nmr (400 MHz, CDCl\textsubscript{3}) \( \delta \): 0.29 (s, 9H, -GeMe\textsubscript{3}), 4.16 (m, 2H, -CH\textsubscript{2}Br), 5.34 (m, 1H), 5.83 (dt, 1H, \( J = 1.5, 1.5 \) Hz).

\^13C nmr (75.3 MHz, CDCl\textsubscript{3}) \( \delta \): -1.6, 38.5, 126.3, 149.2.

IR (neat): 1239, 1206, 930, 828, 604 cm\textsuperscript{-1}.

Exact mass calcd for C\textsubscript{5}H\textsubscript{10}Br\textsuperscript{74}Ge (M\textsuperscript{+} - Me): 222.9178; found: 222.9169.

Anal. calcd for C\textsubscript{6}H\textsubscript{13}BrGe: C 30.32, H 5.51; found: C 30.52, H 5.58.

Preparation of 3-\textit{p}-toluenesulfonyloxy-2-(trimethylgermyl)propene (158)

\begin{center}
\textbf{158}
\end{center}

To a cold (-48 °C), stirred solution of freshly distilled 2-(trimethylgermyl)prop-2-enol (133) (1.07 g, 6.14 mmol) in dry Et\textsubscript{2}O (55 mL) was added dropwise, over a period of 5 minutes, a solution of MeLi (1.20 M in Et\textsubscript{2}O, 5.70 mL, 6.84 mmol). After the solution had been stirred at -48 °C for 1.5 hours, a solution of \textit{p}-toluenesulfonyl chloride (1.39 g, 7.27 mmol) in dry Et\textsubscript{2}O (5 mL) was added. The mixture was stirred at 0 °C for 1 hour and at room temperature for 2 hours. Water (20 mL) was added and the phases were separated. The aqueous phase was extracted with Et\textsubscript{2}O (3 x 10 mL). The combined organic phases were dried (MgSO\textsubscript{4}) and concentrated under reduced pressure. Purification of the crude product by radial chromatography (4 mm plate, 15:1 petroleum ether - Et\textsubscript{2}O) provided 1.74 g (86%) of the tosylate 158 as a pale yellow oil. Upon standing in the
freezer, the oil solidified to provide a low melting (less than room temperature), white, waxy solid.

$^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.19 (s, 9H, -GeMe$_3$), 2.43 (s, 3H, -Ar-CH$_3$), 4.64 (s, 2H, -CH$_2$O-), 5.33 (s, 1H), 5.72 (s, 1H), 7.32 (d, 2H, $J = 8$ Hz), 7.78 (d, 2H, $J = 8$ Hz).

$^{13}$C nmr (75.3 MHz, CDCl$_3$) $\delta$: -2.1 (-ve), 21.6 (-ve), 74.3, 125.1, 127.9 (-ve), 129.8 (-ve), 133.3, 144.7, 146.1.

IR (neat): 1599, 1368, 1239, 1176, 1098, 937, 829, 604, 557 cm$^{-1}$.

Exact mass calcd for $C_{12}H_{17}^{74}$GeO$_3$S (M$^+$ - Me): 315.0110; found: 315.0110.

Anal. calcd for $C_{13}H_{20}$GeO$_3$S: C 47.47, H 6.13, S 9.75; found: C 47.59, H 6.05, S 9.75.

Preparation of trimethyltin hydride (160)$^{115}$

Me$_3$SnH

160

To a warm (65 $^\circ$C), stirred solution of LiAlH$_4$ (0.624 g, 16.5 mmol) in dry diglyme (8 mL) was added slowly by syringe pump a solution of Me$_3$SnCl (3.11 g, 15.6 mmol) in dry diglyme (3 mL), over a period of 2.5 hours. The reaction mixture was stirred for an additional 1 hour while the product was distilled directly from the reaction mixture through a short path distillation apparatus connected to a receiving flask cooled
to -78 °C. Bulb-to-bulb distillation (65 - 75 °C/760 Torr) of the acquired liquid provided 2.22 g (86%) of trimethyltin hydride 160 as a colorless oil which was stored in a Schlenk flask in a freezer.

\[ \text{H nmr (400 MHz, C}_6\text{D}_6) \delta: \ 0.04 (d, 9H, Me}_3\text{Sn-}, J = 2.5 \text{ Hz, } ^2J_{\text{Sn-H}} = 56 \text{ Hz}, 4.75 (m, 1H, -SnH). \]

Preparation of 2-(trimethylgermyl)-3-(trimethylstanny1)propene (132)

To a cold (0 °C), stirred solution of diisopropylamine (0.35 mL, 2.5 mmol) in dry THF (10 mL) was added a solution of n-BuLi (1.67 M in hexanes, 1.42 mL, 2.37 mmol). After the solution had been stirred for 20 minutes, neat Me\(_3\)SnH (160) (0.274 g, 200 µL, 1.66 mmol) was added by syringe and stirring was continued at 0 °C for 30 minutes. The mixture was cooled to -78 °C and a solution of 3-p-toluenesulfonyloxy-2-(trimethylgermyl)propene (158) (0.561 g, 1.71 mmol) in dry THF (1 mL) was added dropwise. The solution was stirred for 30 minutes, was quenched with aqueous NH\(_4\)OH-NH\(_4\)Cl (pH 8) (12 mL) and then was warmed to room temperature. The phases were separated and the aqueous phase was extracted with Et\(_2\)O (3 x 10 mL). The combined organic phases were washed with brine (2 x 10 mL), dried (MgSO\(_4\)) and concentrated. Purification of the crude product by radial chromatography (2 mm plate, petroleum ether followed by 15:1 petroleum ether - Et\(_2\)O), followed by bulb-to-bulb distillation (95 - 105 °C/15 Torr) of the derived oil, provided 0.480 g (90%) of the allylstannane 132 as a colorless oil.
$^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.07 (s, 9H, -SnMe$_3$), $^2$J$_{Sn-H}$ = 52 Hz, 0.17 (s, 9H, -GeMe$_3$), 1.96 (d, 2H, -CH$_2$-SnMe$_3$, $J$ = 1 Hz, $^2$J$_{Sn-H}$ = 69 Hz), 4.91 (d, 1H, $J$ = 2.5 Hz, $^4$J$_{Sn-H}$ = 25 Hz), 5.28 (dt, 1H, $J$ = 2.5, 1 Hz, $^4$J$_{Sn-H}$ = 23 Hz).

$^{13}$C nmr (75.3 MHz, CDCl$_3$) $\delta$: -9.3, -2.0, 21.1, 117.0, 153.4.

IR (neat): 1235, 1213, 824, 764, 599, 526 cm$^{-1}$.

Exact mass calcd for C$_9$H$_{22}$Ge$_{12}$Sn: 323.9955; found: 323.9960.

Anal. calcd for C$_9$H$_{22}$GeSn: C 33.62, H 6.90; found: C 33.65, H 6.90.

Preparation of a mixture of 2-(trimethylgermyl)-3-(trimethylstannyl)propene (132) and 2,5-bis(trimethylgermyl)hexa-1,5-diene (148)

To a cold (0 °C), stirred slurry of magnesium turnings (4.48 g, 184 mmol) in dry THF (20 mL) was added slowly (0.5 mL/min) by syringe pump a solution of Me$_3$SnCl (24.4 g, 142 mmol) and freshly distilled 3-bromo-2-(trimethylgermyl)propene (135) (15.9 g, 67.0 mmol) in dry THF (45 mL). (CAUTION: the solution reflexes spontaneously and quite vigorously, especially if the rate of addition is too rapid). After the addition was complete, the solution was heated to reflux for 2 hours. The solution was
cooled in an ice water bath and water (10 mL) was added dropwise. The slurry was
diluted with Et₂O (100 mL), filtered through a sintered glass funnel and the collected
material was washed with Et₂O (200 mL). Saturated aqueous NH₄Cl (50 mL) was added
to the filtrate and the phases were separated. The aqueous phase was extracted with
Et₂O (2 x 25 mL) and the combined organic phases were washed with brine (2 x 25 mL),
dried (MgSO₄) and concentrated. Bulb-to-bulb distillation (95 - 120 °C/15 Torr) of the
acquired liquid provided 17.2 g (87%) of a colorless oil. ¹H nmr analysis of the oil
indicated an ~10:1 mixture of 2-(trimethylgermyl)-3-(trimethylstannyl)propene (132) and
2,5-bis(trimethylgermyl)hexa-1,5-diene (148), which was found to be inseparable from
132 by silica gel chromatography.

Signals attributed to 2-(trimethylgermyl)-3-(trimethylstannyl)propene (132):
¹H nmr (400 MHz, CDCl₃) δ: 0.07 (s, 9H, -SnMe₃, ²Jₘₜₚ-H = 52 Hz), 0.17 (s, 9H,
-GeMe₃), 1.96 (d, 2H, -CH₂-SnMe₃, J = 1 Hz, ²Jₘₜₚ-H = 69 Hz), 4.91 (d, 1H, J =
2.5 Hz, ⁴Jₘₜₚ-H = 25 Hz), 5.28 (dt, 1H, J = 2.5, 1 Hz, ⁴Jₘₜₚ-H = 23 Hz).

Signals attributed to 2,5-bis(trimethylgermyl)hexa-1,5-diene (148):
¹H nmr (400 MHz, CDCl₃) δ: 0.20 (s, 18H, -GeMe₃), 2.26 (s, 4H, -CH₂-), 5.18 (d, 2H,
olefinic proton, J = 2.5 Hz), 5.52 (d, 2H, olefinic proton, J = 2.5 Hz).

Analysis of the mixture by GLCMS showed: 324 (M⁺ (132)) and 303 (M⁺ - Me (148)).
Exact mass calcd for C₉H₁₂⁷⁴Ge₁²⁰Sn (M⁺ (132)): 323.9955; found: 323.9955.
Exact mass calcd for C₁₁H₂₃⁷⁴Ge₂ (M⁺ - Me (148)): 303.0223; found: 303.0232.
Preparation of 2,3-bis(trimethylstannyl)propene (183)\textsuperscript{128}

\[
\text{SnMe}_3 \quad \text{SnMe}_3
\]

Allene was bubbled through a warm (75 °C), stirred solution of 0.1 mol\% tetrakis-(triphenylphosphine)palladium(0) (0.10 g, 0.087 mmol) in neat hexamethylditin (151) (25.0 g, 76.4 mmol). After 2.5 hours, the solution was cooled to room temperature, filtered through a cake of Celite\textsuperscript{®} (10 g), and the cake was washed with n-pentane (150 mL). The filtrate was concentrated under reduced pressure. Bulb-to-bulb distillation (54 - 70 °C/0.3 Torr) of the residual oil provided 27.2 g (97\%) of the bis(trimethylstannane) 183 as a colorless oil.

\[^1\text{H} \text{nmr (400 MHz, CDCl}_3\] \(\delta:\) 0.07 (s, 9H, \(^2\text{J}_{\text{Sn-H}} = 52 \text{ Hz})\), 0.10 (s, 9H, \(^2\text{J}_{\text{Sn-H}} = 52 \text{ Hz})\), 2.07 (d, 2H, \(-\text{CH}_2\text{-}, J = 1 \text{ Hz}, \(^2\text{J}_{\text{Sn-H}} = 67 \text{ Hz})\)), 4.85 (d, 1H, \(J = 2.5 \text{ Hz}, \(^3\text{J}_{\text{Sn-H}} = 71 \text{ Hz}, \(^4\text{J}_{\text{Sn-H}} = 26 \text{ Hz})\)), 5.41 (dt, 1H, \(J = 2.5 \text{ Hz}, 1 \text{ Hz}, \(^3\text{J}_{\text{Sn-H}} = 155 \text{ Hz}, \(^4\text{J}_{\text{Sn-H}} = 23 \text{ Hz})\)).

\[^{13}\text{C} \text{nmr (50.3 MHz, CDCl}_3\] \(\delta:\) -9.6, -9.4, 24.7, 119.8, 154.3.

IR (neat): 764, 525 cm\(^{-1}\).

Exact mass calcd for C\(_9\)H\(_{22}\)\(^{120}\)Sn\(_2\): 369.9766; found: 369.9770.

Anal. calcd for C\(_9\)H\(_{22}\)Sn\(_2\): C 29.40, H 6.03; found: C 29.76, H 5.95.
Preparation of 2-(trimethylgermyl)allylcopper(I)-dimethyl sulfide (162)

To a cold (-78 °C), stirred solution of freshly distilled 2-(trimethylgermyl)-3-(trimethylstannyl)propene (132) (1 equiv) in dry THF (~7 mL/mmol of allylstannane) was added Me$_2$Li·LiBr (1 equiv, 1.5 M solution in Et$_2$O). After the pale yellow solution had been stirred for 30 minutes, solid CuBr·Me$_2$S (1.05 equiv) was added in one portion. The solution turned cloudy, but then after 20 minutes, a homogeneous yellow solution of 2-(trimethylgermyl)allylcopper(I)-dimethyl sulfide (162) was obtained.

**General Procedure A: Conjugate addition of 2-(trimethylgermyl)allylcopper(I)-dimethyl sulfide (162) to α,β-unsaturated ketones**

To a cold (-78 °C), stirred solution of 2-(trimethylgermyl)allylcopper(I)-dimethyl sulfide (162) (~1.75 equiv) in dry THF (~7 mL/mmol of allylstannane) were added freshly distilled, neat trimethylsilyl bromide (5 to 9 equiv), followed by the appropriate, freshly distilled α,β-unsaturated ketone (1.0 equiv). After 15 minutes, the reaction mixture was poured into aqueous NH$_4$Cl-NH$_4$OH (pH 8) (~1 mL/mL THF) and the resultant mixture was diluted with Et$_2$O (~4 mL/mL THF). The mixture was stirred open to the air for 15 minutes before the phases were separated. The aqueous phase was extracted with Et$_2$O (3 x ~1 mL/mL THF) and the combined organic phases were washed with brine (2 x ~1 mL/mL THF), dried (MgSO$_4$) and concentrated. The crude product was purified by radial chromatography and the acquired liquid was distilled.
Preparation of 3-(2-(trimethylgermyl)allyl)cyclohexanone (163)

Following general procedure A, 3-(2-(trimethylgermyl)allyl)cyclohexanone (163) was prepared by treating a solution of 2-(trimethylgermyl)allylcopper(I)-dimethyl sulfide (162) (1.74 equiv, 0.90 mmol) in dry THF (6 mL) with trimethylsilyl bromide (0.618 g, 4.03 mmol) and cyclohex-2-enone (110) (50 µL, 0.52 mmol). Purification of the crude product by radial chromatography (2 mm plate, 10:1 petroleum ether - Et₂O), followed by bulb-to-bulb distillation (160 - 170 °C/8 Torr) of the acquired liquid, provided 0.119 g (91%) of the ketone 163 as a colorless oil.

\[ ^1H \text{ nmr} \quad (400 \text{ MHz, CDCl}_3) \delta: 0.18 \text{ (s, 9H, -GeMe}_3\text{)}, 1.21-1.32 \text{ (m, 1H), 1.54-1.67 \text{ (m, 1H), 1.81-2.06 \text{ (m, 4H), 2.15-2.28 \text{ (m, 3H), 2.31-2.42 \text{ (m, 2H), 5.24 \text{ (d, 1H, } J = 2.5 \text{ Hz)}, 5.48 \text{ (dt, 1H, } J = 2.5, 1.5 \text{ Hz).}}}} \]

\[ ^13C \text{ nmr} \quad (75.3 \text{ MHz, CDCl}_3) \delta: -1.8 \text{ (-ve), 25.0, 31.1, 37.9 \text{ (-ve), 41.4, 45.1, 48.1, 124.0, 151.2, 211.7.}} \]

IR (neat): 1713, 1237, 919, 826, 599 cm⁻¹.

Exact mass calcd for C₁₁H₁₉⁻⁷⁴GeO (M⁺ - Me): 241.0648; found: 241.0656.

Anal. calcd for C₁₂H₂₂GeO: C 56.55, H 8.70; found: C 56.70, H 8.90.
Preparation of *trans*-4-isopropyl-3-(2-((trimethylgermyl)allyl)cyclohexanone (164)

Following general procedure A, *trans*-4-isopropyl-3-(2-((trimethylgermyl)allyl)cyclohexanone (164) was prepared by treating a solution of 2-((trimethylgermyl)allyl)copper(I)-dimethyl sulfide (162) (1.71 equiv, 0.885 mmol) in dry THF (6 mL) with trimethylsilyl bromide (0.658 g, 4.30 mmol) and 4-isopropylcyclohex-2-enone (170) (76 μL, 0.52 mmol). Purification of the crude product by radial chromatography (2 mm plate, 10:1 petroleum ether - Et2O), followed by bulb-to-bulb distillation (120 - 128 °C/0.3 Torr) of the acquired liquid, provided 0.142 g (92%) of the ketone 164 as a colorless oil.

$^1$H nmr (400 MHz, CDCl$_3$) δ: 0.18 (s, 9H, -GeMe$_3$), 0.84 (d, 3H, $J$ = 7 Hz), 0.98 (d, 3H, $J$ = 7 Hz), 1.28-1.35 (m, 1H), 1.50-1.60 (m, 1H), 1.85-1.97 (m, 4H), 2.00-2.08 (m, 1H), 2.18-2.26 (ddd, 1H, $J$ = 16, 10.5, 5.5 Hz), 2.33-2.42 (m, 2H), 2.57-2.64 (m, 1H), 5.24 (dd, 1H, $J$ = 2.5, 1 Hz), 5.46 (m, 1H).

$^{13}$C nmr (75.3 MHz, CDCl$_3$) δ: -1.6 (-ve), 16.8 (-ve), 21.5 (-ve), 23.9, 27.0 (-ve), 37.9 (-ve), 40.1, 42.8, 44.9, 46.3 (-ve), 124.5, 151.2, 212.3.

IR (neat): 1718, 1236, 920, 825, 599 cm$^{-1}$. 
Exact mass calcd for C_{15}H_{28}^{74}\text{GeO}: 298.1352; found: 298.1349.

Anal. calcd for C_{15}H_{28}GeO: C 60.67, H 9.50; found: C 60.87, H 9.57.

**Preparation of 3-methyl-3-(2-(trimethylgermyl)allyl)cyclohexanone (165)**

Following general procedure A, 3-methyl-3-(2-(trimethylgermyl)allyl)cyclohexanone (165) was prepared by treating a solution of 2-(trimethylgermyl)allylcopper(I)-dimethyl sulfide (162) (1.73 equiv, 0.79 mmol) in dry THF (5 mL) with trimethylsilyl bromide (0.416 g, 2.72 mmol) and 3-methylcyclohex-2-enone (171) (52 µL, 0.46 mmol). Purification of the crude product by radial chromatography (1 mm plate, 9:1 petroleum ether - Et_2O), followed by bulb-to-bulb distillation (160 - 178 °C/11 Torr) of the acquired liquid, provided 0.057 g (46%) of the ketone 165 as a colorless oil.

$^1$H nmr (400 MHz, CDCl_3) δ: 0.20 (s, 9H, -GeMe_3), 0.87 (s, 3H, -CH_3), 1.48-1.55 (m, 1H), 1.60-1.67 (m, 1H), 1.75-1.96 (m, 2H), 2.03 (d, 1H, $J = 12.5$ Hz), 2.17 (s, 2H), 2.21-2.30 (m, 3H), 5.41 (d, 1H, $J = 2$ Hz), 5.55 (br s, 1H).

$^{13}$C nmr (75.3 MHz, CDCl_3) δ: -0.8 (-ve), 22.1, 24.9 (-ve), 36.1, 39.6, 41.0, 48.8, 53.5, 128.2, 150.2, 212.3.
IR (neat): 1713, 1235, 923, 826, 598 cm\(^{-1}\).

Exact mass calcd for C\(_{12}\)H\(_{21}\)\(^{74}\)GeO (M\(^{+}\) - Me): 255.0804; found: 255.0806.

Anal. calcd for C\(_{13}\)H\(_{24}\)GeO: C 58.06, H 9.00; found: C 58.03, H 9.15.

Preparation of 3-(2-(trimethylgermyl)allyl)cyclopentanone (166)

Following general procedure A, 3-(2-(trimethylgermyl)allyl)cyclopentanone (166) was prepared by treating a solution of 2-(trimethylgermyl)allylcopper(I)-dimethyl sulfide (162) (1.74 equiv, 0.90 mmol) in dry THF (6 mL) with trimethylsilyl bromide (0.657 g, 4.23 mmol) and cyclopent-2-enone (172) (43 μL, 0.51 mmol). Purification of the crude product by radial chromatography (1 mm plate, 10:1 petroleum ether - Et\(_2\)O), followed by bulb-to-bulb distillation (153 - 164 °C/8 Torr) of the acquired liquid, provided 0.105 g (85%) of the ketone 166 as a colorless oil.

\(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 0.20 (s, 9H, -GeMe\(_3\)), 1.48-1.58 (m, 1H), 1.76-1.84 (m, 1H), 2.06-2.18 (m, 2H), 2.23-2.36 (m, 5H), 5.23 (d, 1H, \(J = 2.5\) Hz), 5.50 (m, 1H).

\(^{13}\)C nmr (75.3 MHz, CDCl\(_3\)) \(\delta\): -1.9 (-ve), 29.1, 35.7 (-ve), 38.1, 43.6, 45.0, 123.2, 151.8, 219.5.
IR (neat): 1746, 1236, 919, 826, 599 cm⁻¹.

Exact mass calcd for C₁₀H₁₇⁷⁴GeO (M⁺ - Me): 227.0491; found: 227.0486.

Anal. calcd for C₁₁H₂₀GeO:  C 54.85, H 8.37; found:  C 54.97, H 8.60.

Preparation of 3-methyl-3-(2-(trimethylgermyl)allyl)cyclopentanone (167)

Following general procedure A, 3-methyl-3-(2-(trimethylgermyl)allyl)cyclopentanone (167) was prepared by treating a solution of 2-(trimethylgermyl)allylcopper(I)-dimethyl sulfide (162) (1.72 equiv, 0.83 mmol) in dry THF (5.5 mL) with trimethylsilyl bromide (0.466 g, 3.04 mmol) and 3-methylcyclopent-2-enone (173) (48 µL, 0.49 mmol). Purification of the crude product by radial chromatography (1 mm plate, 10:1 petroleum ether - Et₂O), followed by bulb-to-bulb distillation (128 - 139 °C/9 Torr) of the acquired liquid, provided 0.069 g (56%) of the ketone 167 as a colorless oil.

¹H nmr (400 MHz, CDCl₃) δ: 0.21 (s, 9H, -GeMe₃), 1.02 (s, 3H, -CH₃), 1.68-1.75 (m, 1H), 1.82-1.90 (m, 1H), 1.96 (dd, 1H, J = 17.5, 1 Hz), 2.15 (d, 1H, J = 17.5 Hz), 2.24-2.30 (m, 4H), 5.39 (d, 1H, J = 2.5 Hz), 5.56 (m, 1H).

¹³C nmr (75.3 MHz, CDCl₃) δ: -1.0 (-ve), 25.7 (-ve), 35.2, 36.5, 40.1, 47.5, 52.1, 127.3, 150.8, 219.7.
IR (neat): 1746, 1236, 923, 826, 598 cm⁻¹.

Exact mass calcd for C₁₁H₁⁹⁷⁴GeO (M⁺ - Me): 241.0648; found: 241.0653.

Anal. calcd for C₁₂H₂₂GeO: C 56.55, H 8.70; found: C 56.80, H 8.62.

Preparation of a mixture of trans- and cis-2-methyl-3-(2-(trimethylgermyl)allyl)cyclopentanone (168)

Following general procedure A, a mixture of trans- and cis-2-methyl-3-(2-(trimethylgermyl)allyl)cyclopentanone (168) was prepared by treating a solution of 2-(trimethylgermyl)allylcopper(I)-dimethyl sulfide (162) (1.70 equiv, 0.87 mmol) in dry THF (6 mL) with trimethylsilyl bromide (0.454 g, 2.96 mmol) and 2-methylcyclopent-2-enone (174) (50 µL, 0.51 mmol). Purification of the crude product by radial chromatography (1 mm plate, 10:1 petroleum ether - Et₂O), followed by bulb-to-bulb distillation (103 - 110 °C/0.3 Torr) of the acquired liquid, provided 0.116 g (89%) of the ketone 168 as a colorless oil. ¹H nmr analysis of the oil indicated an ~8:1 mixture of C-2 epimers.

¹H nmr (400 MHz, CDCl₃) δ: 0.21 (s, 9H, -GeMe₃), 0.98, 1.07 (d, J = 7 Hz, d, J = 7 Hz, ratio 1:8, 3H total), 1.23-1.36 (m, 1H), 1.67-1.92 (m, 2H), 2.01-2.20 (m, 3H),
2.27-2.39 (m, 1H), 2.62-2.67 (m, 1H), 5.25 (d, 1H, J = 2.5 Hz), 5.50, 5.55 (m, m, ratio 1:8, 1H total).

Signals attributed to the major epimer:

$^{13}$C nmr (75.3 MHz, CDCl$_3$) $\delta$: -1.7 (-ve), 12.7 (-ve), 27.3, 37.2, 43.1, 43.7 (-ve), 50.4 (-ve), 123.5, 151.7, 221.0.

IR (neat): 1744, 1236, 918, 825, 599 cm$^{-1}$.

Exact mass calcd for C$_{11}$H$_{19}^{74}$GeO (M$^+$ - Me): 241.0648; found: 241.0652.

Anal. calcd for C$_{12}$H$_{22}$GeO: C 56.55, H 8.70; found: C 56.80, H 8.50.

**Preparation of a mixture of (2R, 3S, 5R) and (2S, 3S, 5R)-2-methyl-5-isopropenyl-3-(2-(trimethylgermyl)allyl)cyclohexanone (169)**

Following general procedure A, a mixture of (2R, 3S, 5R)- and (2S, 3S, 5R)-2-methyl-5-isopropenyl-3-(2-(trimethylgermyl)allyl)cyclohexanone (169) was prepared by treating a solution of 2-(trimethylgermyl)allylcopper(I)-dimethyl sulfide (162) (1.73 equiv, 0.62 mmol) in dry THF (5 mL) with trimethylsilyl bromide (0.402 g, 2.63 mmol) and (R)-(−)-carvone (175) (56 µL, 0.36 mmol). Purification of the crude product by radial
chromatography (1 mm plate, 20:1 petroleum ether - Et2O), followed by bulb-to-bulb distillation (132 - 138 °C/0.3 Torr) of the acquired liquid, provided 0.095 g (86%) of the ketone 169 as a colorless oil. ¹H nmr analysis of the oil indicated an ~2:1 mixture of C-2 epimers containing a small amount (2-3%) of a corresponding C-3 epimer.

¹H nmr (400 MHz, CDCl₃) δ: 0.176, 0.184, 0.194 (s, s, s, ratio undetermined, 9H total, -GeMe₃), 1.03, 1.08, 1.14 (d, J = 7 Hz, d, J = 7 Hz, d, J = 7 Hz, ratio 11:1:22, 3H total), 1.47-2.79 (m, 12H), 4.66, 4.68 (s, s, ratio 1:2, 1H total), 4.74, 4.78 (s, s, ratio 2:1, 1H total), 5.23, 5.26 (m, m, ratio 2:1, 1H total), 5.48 (m, 1H).

Signals attributed to the major epimer:

¹³C nmr (75.3 MHz, CDCl₃) δ: -1.6 (-ve), 11.7 (-ve), 20.7 (-ve), 32.5, 35.6, 39.6 (-ve), 40.4 (-ve), 46.1, 48.1 (-ve), 109.7, 124.0, 147.5, 151.8, 212.8.

IR (neat): 1713, 1646, 1447, 1236, 918, 825, 599 cm⁻¹.

Exact mass calcd for C₁₆H₂₈GeO: 310.1352; found: 310.1345.

Preparation of 2-(trimethylstannyldiallylcopper(I))-dimethyl sulfide (182)

\[
\text{SnMe}_3 \quad \text{Cu} \quad \text{Me}_2\text{S}
\]

(182)

To a cold (-78 °C), stirred solution of freshly distilled 2,3-bis(trimethylstannyl)propene (183) (1 equiv) in dry THF (~7 mL/mmol of allylstannane) was added MeLi\text{LiBr} (1 equiv, 1.5 M solution in Et\text{2}O). After the pale yellow solution had been stirred for 30 minutes, solid CuBr\text{Me}_2\text{S} (1.05 equiv) was added in one portion. The solution turned cloudy, but then after 15 minutes, a homogeneous yellow solution of 2-(trimethylstannyl)-allylcopper(I)-dimethyl sulfide (182) was obtained.

**General Procedure B:** Conjugate addition of 2-(trimethylstannyldiallylcopper(I))-dimethyl sulfide (182) to α,β-unsaturated ketones and aldehydes

To a cold (-78 °C), stirred solution of 2-(trimethylstannyl)allylcopper(I)-dimethyl sulfide (182) (~1.75 equiv) in dry THF (~7 mL/mmol of allylstannane) were added freshly distilled, neat trimethylsilyl bromide (5 to 9 equiv), followed by the appropriate, freshly distilled α,β-unsaturated carbonyl compound (1.0 equiv). After 15 minutes, the reaction mixture was poured into aqueous NH\text{4}Cl-NH\text{4}OH (pH 8) (~1 mL/mL THF) and the resultant mixture was diluted with Et\text{2}O (~4 mL/mL THF). The mixture was stirred open to the air for 15 minutes before the phases were separated. The aqueous phase was extracted with Et\text{2}O (3 x ~1 mL/mL THF) and the combined organic phases were washed with brine (2 x ~1 mL/mL THF), dried (MgSO\text{4}) and concentrated. The crude product was purified by radial chromatography and the acquired liquid was distilled.
Preparation of 3-(2-(trimethylstannyl)ally)cyclohexanone (184)

Following general procedure B, 3-(2-(trimethylstannyl)ally)cyclohexanone (184) was prepared by treating a solution of 2-(trimethylstannyl)allylcopper(I)-dimethyl sulfide (182) (1.76 equiv, 1.09 mmol) in dry THF (7 mL) with trimethylsilyl bromide (0.691 g, 4.52 mmol) and cyclohex-2-enone (110) (60 µL, 0.62 mmol). Purification of the crude product by radial chromatography (2 mm plate, 10:1 petroleum ether - Et₂O), followed by bulb-to-bulb distillation (108 - 126 °C/0.3 Torr) of the acquired liquid, provided 0.173 g (93%) of the ketone 184 as a colorless oil.

\[ \text{IR (neat): 1714, 917, 769, 527 cm}^{-1} \]

\[ \text{Exact mass calcd for C}_{11}\text{H}_{19}\text{O}^{120}\text{Sn} (M^+ - Me): 287.0458; found: 287.0460.} \]

\[ \text{Anal. calcd for C}_{12}\text{H}_{22}\text{OSn: C 47.89, H 7.37; found: C 48.09, H 7.55.} \]
Preparation of trans-4-isopropyl-3-(2-(trimethylstannyl)allyl)cyclohexanone (185)

Following general procedure B, trans-4-isopropyl-3-(2-(trimethylstannyl)allyl)-cyclohexanone (185) was prepared by treating a solution of 2-(trimethylstannyl)-allylcopper(I)-dimethyl sulfide (182) (1.75 equiv, 0.884 mmol) in dry THF (6 mL) with trimethylsilyl bromide (0.511 g, 3.34 mmol) and 4-isopropylcyclohex-2-enone (170) (74 µL, 0.50 mmol). Purification of the crude product by radial chromatography (2 mm plate, 10:1 petroleum ether - Et2O), followed by bulb-to-bulb distillation (138 - 154 °C/0.3 Torr) of the acquired liquid, provided 0.156 g (90%) of the ketone 185 as a colorless oil.

$^1$H nmr (400 MHz, CDCl$_3$) δ: 0.12 (s, 9H, -SnMe$_3$), $^2$J$_{Sn-H}$ = 53 Hz), 0.83 (d, 3H, $J = 7$ Hz), 0.98 (d, 3H, $J = 7$ Hz), 1.30-1.37 (m, 1H), 1.49-1.59 (m, 1H), 1.77-2.10 (m, 5H), 2.18-2.26 (m, 1H), 2.32-2.39 (m, 2H), 2.66 (ddt, 1H, $J = 13$, 4, 2 Hz, $^3$J$_{Sn-H}$ = 41 Hz), 5.20 (m, 1H, $^3$J$_{Sn-H}$ = 70 Hz), 5.60 (m, 1H, $^3$J$_{Sn-H}$ = 150 Hz).

$^{13}$C nmr (75.3 MHz, CDCl$_3$) δ: -9.3 (-ve), 16.7 (-ve), 21.5 (-ve), 24.0, 27.0 (-ve), 38.7 (-ve), 40.2, 45.0, 45.8, 46.1 (-ve), 127.1, 153.1, 212.2.

IR (neat): 1718, 918, 769, 527 cm$^{-1}$.
Exact mass calcd for $\text{C}_{15}\text{H}_{28}\text{O}^{120}\text{Sn}$: 344.1162; found: 344.1169.

Anal. calcd for $\text{C}_{15}\text{H}_{28}\text{O}\text{Sn}$: C 52.51, H 8.23; found: C 52.46, H 8.29.

**Preparation of 3-methyl-3-(2-(trimethylstannyl)allyl)cyclohexanone (186)**

![Structural formula of 186]

Following general procedure B, 3-methyl-3-(2-(trimethylstannyl)allyl)cyclohexanone (186) was prepared by treating a solution of 2-(trimethylstannyl)allylcopper(I)-dimethyl sulfide (182) (1.99 equiv, 1.14 mmol) in dry THF (7.5 mL) with trimethylsilyl bromide (0.512 g, 3.35 mmol) and 3-methylcyclohex-2-enone (171) (65 µL, 0.57 mmol). Purification of the crude product by radial chromatography (2 mm plate, 10:1 petroleum ether - Et₂O), followed by bulb-to-bulb distillation (135 - 140 °C/0.3 Torr) of the acquired liquid, provided 0.110 g (61%) of the ketone 186 as a colorless oil.

$^1\text{H nmr (400 MHz, CDCl}_3\text{)} \delta$: 0.13 (s, 9H, -SnMe₃), $^2J_{\text{Sn-H}} = 52 \text{ Hz}$, 0.88 (s, 3H, -CH₃), 1.47-1.53 (m, 1H), 1.58-1.65 (m, 1H), 1.76-1.96 (m, 2H), 2.03 (dt, 1H, $J = 13.5$, 1.5 Hz), 2.16-2.32 (m, 5H), 5.35 (br d, 1H, $J = 2.5 \text{ Hz}$, $^3J_{\text{Sn-H}} = 70 \text{ Hz}$), 5.65 (m, 1H, $^3J_{\text{Sn-H}} = 151 \text{ Hz}$).

$^{13}\text{C nmr (75.3 MHz, CDCl}_3\text{)} \delta$: -8.4 (-ve), 22.0, 25.0 (-ve), 36.0, 39.5, 40.9, 52.2, 53.5, 130.8, 150.8, 212.1.
IR (neat): 1713, 922, 770, 526 cm⁻¹.

Exact mass calcd for C₁₂H₂₁O¹²⁰Sn (M⁺ - Me): 301.0614; found: 301.0606.

Anal. calcd for C₁₃H₂₄OSn:  C 49.57, H 7.68; found: C 49.70, H 7.86.

**Preparation of 3-(2-(trimethylstannyDally)allyl)cyclopentanone (187)**

Following general procedure B, 3-(2-(trimethylstannyDally)allyl)cyclopentanone (187) was prepared by treating a solution of 2-(trimethylstannyDally)allylcopper(I)-dimethyl sulfide (182) (1.71 equiv, 0.980 mmol) in dry THF (6.5 mL) with trimethylsilyl bromide (0.444 g, 2.90 mmol) and cyclopent-2-enone (172) (48 μL, 0.57 mmol). Purification of the crude product by radial chromatography (2 mm plate, 10:1 petroleum ether - Et₂O), followed by bulb-to-bulb distillation (185 - 195 °C/16 Torr) of the acquired liquid, provided 0.145 g (88%) of the ketone 187 as a colorless oil.

¹H nmr (400 MHz, CDCl₃) δ: 0.13 (s, 9H, -SnMe₃, ²JSn-H = 53 Hz), 1.48-1.59 (m, 1H), 1.81 (dd, 1H, J = 17, 7.5 Hz), 2.03-2.45 (m, 7H), 5.19 (m, 1H, ³JSn-H = 70 Hz), 5.64 (m, 1H, ³JSn-H = 150 Hz).
$^{13}$C nmr (75.3 MHz, CDCl$_3$) δ: -9.4 (-ve), 29.0, 36.5 (-ve), 38.1, 44.9, 46.8, 126.2, 153.4, 219.5.

IR (neat): 1746, 918, 770, 526 cm$^{-1}$.

Exact mass calcd for C$_{10}$H$_{17}$O$_{120}$Sn (M$^+$ - Me): 273.0302; found: 273.0302.

Anal. calcd for C$_{11}$H$_{20}$O$_{120}$Sn: C 46.04, H 7.02; found: C 46.34, H 7.27.

**Preparation of 3-methyl-3-(2-(trimethylstannyl)allyl)cyclopentanone (188)**

Following general procedure B, 3-methyl-3-(2-(trimethylstannyl)allyl)cyclopentanone (188) was prepared by treating a solution of 2-(trimethylstannyl)allylcopper(I)-dimethyl sulfide (182) (1.72 equiv, 0.955 mmol) in dry THF (7 mL) with trimethylsilyl bromide (0.470 g, 3.07 mmol) and 3-methylcyclopent-2-enone (173) (55 µL, 0.56 mmol). Purification of the crude product by radial chromatography (1 mm plate, 10:1 petroleum ether - Et$_2$O), followed by bulb-to-bulb distillation (115 - 121 °C/0.3 Torr) of the acquired liquid, provided 0.090 g (54%) of the ketone 188 as a colorless oil.
$^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.14 (s, 9H, $-$SnMe$_3$), $^{2}J_{\text{Sn-H}} = 52$ Hz), 1.01 (s, 3H), 1.67-1.74 (m, 1H), 1.80-1.88 (m, 1H), 1.95 (d, 1H, $J = 17$ Hz), 2.13 (d, 1H, $J = 17$ Hz), 2.24-2.29 (m, 2H), 2.36 (s, 2H, $^{3}J_{\text{Sn-H}} = 58$ Hz), 5.34 (d, 1H, $J = 2.5$ Hz, $^{3}J_{\text{Sn-H}} = 69$ Hz), 5.67 (m, 1H, $^{3}J_{\text{Sn-H}} = 150$ Hz).

$^{13}$C nmr (75.3 MHz, CDCl$_3$) $\delta$: -8.5 (-ve), 25.7 (-ve), 35.1, 36.5, 40.0, 51.3, 52.1, 130.2, 151.6, 219.6.

IR (neat): 1745, 921, 770, 526 cm$^{-1}$.

Exact mass calcd for C$_{11}$H$_{19}$O$^{120}$Sn (M$^+$ - Me): 287.0458; found: 287.0459.

Anal. calcd for C$_{12}$H$_{22}$OSn: C 47.89, H 7.37; found: C 47.97, H 7.35.

Preparation of a mixture of trans- and cis-2-methyl-3-(2-(trimethylstannyl)allyl)cyclopentanone (189)

Following general procedure B, a mixture of trans- and cis-2-methyl-3-(2-(trimethylstannyl)allyl)cyclopentanone (189) was prepared by treating a solution of 2-(trimethylstannyl)allylcopper(I)-dimethyl sulfide (182) (1.72 equiv, 0.979 mmol) in dry THF (7 mL) with trimethylsilyl bromide (0.524 g, 3.42 mmol) and 2-methyl-cyclopent-2-enone (174) (56 $\mu$L, 0.57 mmol). Purification of the crude product by radial
chromatography (2 mm plate, 10:1 petroleum ether - Et2O), followed by bulb-to-bulb distillation (94 - 99 °C/0.3 Torr) of the acquired liquid, provided 0.140 g (82%) of the ketone 189 as a colorless oil. 1H nmr analysis of the oil indicated an ~8:1 mixture of C-2 epimers.

1H nmr (400 MHz, CDCl3) δ: 0.13 (s, 9H, -SnMe3, $^2J_{Sn-H} = 53$ Hz), 0.98, 1.07 (d, $J = 6.5$ Hz, d, $J = 6.5$ Hz, ratio 1:8, 3H total), 1.22-1.38 (m, 1H), 1.62-1.78 (m, 2H), 1.92-2.19 (m, 3H), 2.27-2.37 (m, 1H), 2.67-2.74 (m, 1H), 5.20 (m, 1H, $^3J_{Sn-H} = 70$ Hz), 5.64, 5.69 (m, m, ratio 1:8, 1H total, $^3J_{Sn-H} = 150$ Hz).

Signals attributed to the major epimer:

13C nmr (75.3 MHz, CDCl3) δ: -9.4 (-ve), 12.8 (-ve), 27.3, 37.2, 44.5 (-ve), 46.2, 50.2 (-ve), 126.3, 153.4, 221.0.

IR (neat): 1743, 916, 768, 527 cm⁻¹.

Exact mass calcld for C11H19O120Sn (M⁺ - Me): 287.0458; found: 287.0463.

Anal. calcld for C12H22OSn: C 47.89, H 7.37; found: C 48.02, H 7.21.
Preparation of a mixture of (2R, 3S, 5R)- and (2S, 3S, 5R)-2-methyl-5-isopropenyl-3-(2-(trimethylstannyl)allyl)cyclohexanone (190)

Following general procedure B, a mixture of (2R, 3S, 5R)- and (2S, 3S, 5R)-2-methyl-5-isopropenyl-3-(2-(trimethylstannyl)allyl)cyclohexanone (190) was prepared by treating a solution of 2-(trimethylstannyl)allylcopper(I)-dimethyl sulfide (182) (1.75 equiv, 0.85 mmol) in dry THF (6 mL) with trimethylsilyl bromide (0.508 g, 3.32 mmol) and (7R)-(-)-carvone (175) (76 μL, 0.49 mmol). Purification of the crude product by radial chromatography (2 mm plate, 20:1 petroleum ether - Et2O), followed by bulb-to-bulb distillation (136 - 144 °C/0.3 Torr) of the acquired liquid, provided 0.146 g (85%) of the ketone 190 as a colorless oil. ¹H nmr analysis of the oil indicated an ~2:1 mixture of C-2 epimers containing a small amount (2-3%) of a corresponding C-3 epimer.

¹H nmr (400 MHz, CDCl₃) δ: 0.10, 0.12 (s, s, ratio 1:2, 9H total, -SnMe₃, ²J_{Sn-H} = 53 Hz), 1.02, 1.07, 1.14 (d, J = 7 Hz, d, J = 7 Hz, d, J = 7 Hz, ratio 20:1:10, 3H total), 1.50-1.78 (m, 4H), 1.84-2.05 (m, 2H), 2.08-2.80 (m, 6H), 4.65, 4.68 (s, s, ratio 1:2, 1H total), 4.74, 4.78 (m, s, ratio 2:1, 1H total), 5.19, 5.22 (m, d, J= 2.5 Hz, ratio 2:1, 1H total, ³J_{Sn-H} = 69 Hz), 5.62 (m, 1H, ³J_{Sn-H} = 149 Hz).

Signals attributed to the major C-2 epimer:

¹³C nmr (75.3 MHz, CDCl₃) δ: -9.4 (-ve), 11.7 (-ve), 20.8 (-ve), 32.6, 38.4 (-ve), 40.1 (-ve), 43.6, 46.1, 48.0 (-ve), 109.7, 126.5, 147.5, 153.5, 212.6.
IR (neat): 1713, 1646, 917, 892, 769, 529 cm\(^{-1}\).

Exact mass calcd for C\(_{16}\)H\(_{28}\)O\(_{120}\)Sn: 356.1162; found: 356.1171.

Anal. calcd for C\(_{16}\)H\(_{28}\)O\(_{120}\)Sn: C 54.12, H 7.95; found: C 54.27, H 7.93.

4. *Trans*-Fused Bicyclo[3.3.0]octane Ring Systems

Preparation of the aldehyde 239

Following general procedure B, the aldehyde 239 was prepared by treating a solution of 2-(trimethylstanny)allylcopper(I)-dimethyl sulfide (182) (1.79 equiv, 1.05 mmol) in dry THF (7 mL) with trimethylsilyl bromide (0.550 g, 3.59 mmol), followed by the dropwise addition of a solution of the unsaturated aldehyde 71 (0.139 g, 0.588 mmol) in dry THF (1 mL). Purification of the crude product by radial chromatography (2 mm plate, 7:1 petroleum ether - Et\(_2\)O) and removal of trace amounts of solvent (vacuum pump) from the resulting liquid provided 0.195 g (75%) of the aldehyde 239 as a colorless oil. \(^1\)H nmr spectroscopic analysis of the oil indicated an \(\sim2.2:1\) mixture (\(\alpha:\beta\)) of epimeric aldehydes.

\(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 0.13 (s, 9H, -SnMe\(_3\), \(^2\)J\(_{Sn-H}\) = 53 Hz), 0.909, 0.913 (s, s, ratio \(\sim1:2\), 3H total, -CH\(_3\)), 0.950, 0.956 (s, s, ratio \(\sim2:1\), 3H total, -CH\(_3\)), 1.42-1.78 (m,
3H), 1.99-2.43 (m, 8H), 2.54-2.72, 2.89-2.94 (m, m, 1H total), 3.40-3.47 (m, 4H, -CH2O-), 5.18, 5.20 (d, J = 2.5 Hz, m, ratio -2:1, 1H total, J = 69 Hz), 5.63-5.65 (m, 1H, J = 151 Hz), 9.48, 9.80 (d, J = 3.5 Hz, d, J = 2 Hz, α:β ratio -2:2:1, 1H total, -CHO).

13C nmr (75.3 MHz, CDCl3) δ: -9.5 (-ve, -SnMe3), -9.3 (-ve, -SnMe3), 22.4 (-ve, -CH3), 22.5 (-ve, -CH3), 30.0, 32.6, 34.4, 38.5 (-ve, CH), 39.4, 39.7, 39.8, 39.9, 40.0 (-ve, CH), 41.8, 45.1 (-ve, CH), 46.2, 47.5 (-ve, CH), 47.9 (-ve, CH), 49.0 (-ve, CH), 55.1 (-ve, CH), 60.5 (-ve, CH), 72.0 (-CH2O-), 72.1 (-CH2O-), 109.6 (O-C-O), 110.1 (O-C-O), 126.4 (C=CH2), 127.2 (C=CH2), 153.9 (C=CH2), 203.7 (-ve, CHO), 204.8 (-ve, CHO).

IR (neat): 2710, 1723, 1116, 917, 769, 528 cm⁻¹.

Exact mass calcd for C20H34O3120Sn: 442.1530; found: 442.1535.

Anal. calcd for C20H34O3Sn: C 54.45, H 7.77; found: C 54.26, H 8.00.

Preparation of the alkenyl iodides 238 and 241

To a stirred solution of the alkenyltrimethylstannane 239 (0.556 g, 1.26 mmol, 2.2:1 mixture of epimers) in dry CH2Cl2 (25 mL), at room temperature, was added N-iodo-
succinimide (0.425 g, 1.89 mmol). The mixture turned pink immediately and was stirred at room temperature for 10 minutes. Saturated aqueous Na$_2$S$_2$O$_3$ (25 mL) was added and the phases were separated. The aqueous phase was extracted with CH$_2$Cl$_2$ (3 x 25 mL). The combined organic extracts were washed with saturated aqueous Na$_2$S$_2$O$_3$ (10 mL), dried (Na$_2$SO$_4$), and concentrated. The crude product was purified by radial chromatography (4 mm plate, 5:1 petroleum ether - Et$_2$O) to yield two compounds, 0.137 g (27%) of the cis-alkenyl iodide 241 and 0.325 g (64%) of the trans-alkenyl iodide 238, both as white solids. Recrystallization of 241 from pentane - Et$_2$O afforded colorless crystals (mp 80 -81 °C), while recrystallization of 238 from pentane afforded colorless plates (mp 55 -56 °C).

trans-alkenyl iodide 238

$^1$H nmr (400 MHz, CDCl$_3$) δ: 0.91 (s, 3H, -CH$_3$), 0.98 (s, 3H, -CH$_3$), 1.69-1.78 (m, 2H), 1.94-2.09 (m, 3H), 2.14 (ddd, 1H, $J = 13.5, 9, 1$ Hz), 2.19-2.27 (m, 1H), 2.34-2.50 (m, 4H), 2.56-2.66 (m, 1H), 3.41-3.48 (m, 3H, three from -CH$_2$O-), 3.57 (d, 1H, one from -CH$_2$O-, $J = 11.5$ Hz), 5.70 (d, 1H, $J = 1.5$ Hz), 6.07 (d, 1H, $J = 1.5$ Hz), 9.55 (d, 1H, -CHO, $J = 3.5$ Hz).

$^{13}$C nmr (75.3 MHz, CDCl$_3$) δ: 22.4 (-ve), 22.6 (-ve), 30.0, 34.3, 38.2, 39.8 (-ve), 40.6, 46.7 (-ve), 47.1 (-ve), 50.3, 59.8 (-ve), 72.0 (2 signals, -OC$_2$H$_5$), 110.06, 110.12, 127.3, 203.2 (-ve).

IR (KBr): 2709, 1723, 1615, 1115 cm$^{-1}$.

Exact mass calcd for C$_{17}$H$_{25}$O$_3$I: 404.0848; found: 404.0850.

Anal. calcd for C$_{17}$H$_{25}$O$_3$I: C 50.51, H 6.23, I 31.39; found: C 50.70, H 6.40, I 31.25.
cis-alkenyl iodide 241

$^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.91 (s, 3H, -CH$_3$), 0.97 (s, 3H, -CH$_3$), 1.59-1.66 (m, 2H), 1.79 (dd, 1H, $J = 13.5$, 5.5 Hz), 2.07-2.24 (m, 3H), 2.30-2.44 (m, 3H), 2.50-2.55 (m, 1H), 2.59-2.67 (m, 1H), 2.98-3.03 (m, 1H), 3.41-3.48 (m, 3H, three from -CH$_2$O-), 3.53 (d, 1H, one from -CH$_2$O-, $J = 11.5$ Hz), 5.73 (d, 1H, $J = 1.5$ Hz), 6.04 (d, 1H, $J = 1.5$ Hz), 9.76 (d, 1H, -CHO, $J = 2$ Hz).

$^{13}$C nmr (50.3 MHz, CDCl$_3$) $\delta$: 22.5 (-ve), 22.6 (-ve), 30.1, 32.8, 38.4, 38.5 (-ve), 41.0, 45.0 (-ve), 46.1, 48.2 (-ve), 55.0 (-ve), 72.0, 72.2, 109.8, 110.9, 127.2, 203.9 (-ve).

IR (KBr): 2720, 1719, 1615, 1112 cm$^{-1}$.

Exact mass calcd for C$_{17}$H$_{25}$O$_3$I: 404.0848; found: 404.0851.

Anal. calcd for C$_{17}$H$_{25}$O$_3$I: C 50.51, H 6.23, I 31.39; found: C 50.70, H 6.48, I 31.20.

Epimerization of the aldehyde 241
To a stirred solution of 241 (0.097 g, 0.24 mmol) in dry MeOH (2.5 mL), at room temperature, was added NaOMe (0.5 M in MeOH, 1.0 mL, 0.5 mmol). After 4 hours, the MeOH was removed under reduced pressure and Et₂O (10 mL) and water (5 mL) were added to the residue and the phases were separated. The organic phase was washed with water (3 x 5 mL) and brine (2 x 5 mL), dried (MgSO₄), and concentrated. Purification of the crude product by radial chromatography (1 mm plate, 5:1 petroleum ether - Et₂O) provided two compounds, 0.011 g (11%) of 241 and 0.077 g (79%) of 238, both as white solids. Thus the total yield of 238 from the alkenyltrimethylstannane 239 was 85%.

Preparation of the alcohol 237

To a stirred suspension of CrCl₂ (0.580 g, 4.72 mmol) and NiCl₂ (0.060 g, 0.46 mmol) in a mixture of dry DMF (12 mL) and dry DMSO (4 mL), at room temperature, was added the iodo aldehyde 238 (0.316 g, 0.783 mmol) as a solution in dry DMF (4 mL). After 30 minutes, the reaction mixture was diluted with Et₂O (40 mL) and brine (20 mL) and the phases were separated. The organic phase was washed with brine (5 x 10 mL), dried (MgSO₄), and concentrated. The crude product was purified by short column chromatography (20 g TLC grade silica gel, 2:1 petroleum ether - Et₂O). Removal of trace amounts of solvent (vacuum pump) from the acquired material provided 0.200 g (92%) of 237 as a white solid. ¹H nmr spectroscopic analysis of the solid indicated a 1:1 mixture of epimeric alcohols.
\textsuperscript{1}H nmr (400 MHz, CDCl\textsubscript{3}) \(\delta\): 0.919, 0.923 (s, s, 3H total, -CH\textsubscript{3}), 0.950, 0.952 (s, s, 3H total, -CH\textsubscript{3}), 1.00-1.10 (m, 1H), 1.18-1.31 (m, 1H), 1.48 (d, 1H, -OH, exchanges with D\textsubscript{2}O, \(J = 7.5\) Hz), 1.64-1.86 (m, 4H), 1.98-2.26 (m, 4H), 2.40-2.47 (m, 1H), 2.81-2.93 (m, 1H), 3.41-3.49 (m, 4H, -CH\textsubscript{2}O-), 4.09, 4.20 (br signal, br signal, ratio \(-1:1\), 1H total, -CH(OH)-), 4.98, 5.06 (ddd, \(J = 2.5, 2.5, 2.5\) Hz, m, 1H total), 5.08, 5.21 (ddd, \(J = 2.5, 2.5, 2.5\) Hz, m, 1H total).

\textsuperscript{13}C nmr (75.3 MHz, CDCl\textsubscript{3}) \(\delta\): 22.37 (-ve, -CH\textsubscript{3}), 22.44 (-ve, -CH\textsubscript{3}), 29.0, 29.9, 33.3, 33.4, 33.7, 37.9, 38.2, 39.6, 39.7, 40.9 (-ve, CH), 41.1 (-ve, CH), 45.7 (-ve, CH), 46.0 (-ve, CH), 51.6 (-ve, CH), 52.8 (-ve, CH), 59.1 (-ve, CH), 60.4 (-ve, CH), 70.9 (-ve, -CH(OH)-), 71.5 (-CH\textsubscript{2}O-), 71.7 (-CH\textsubscript{2}O-), 71.9 (-CH\textsubscript{2}O-), 72.1 (-CH\textsubscript{2}O-), 75.9 (-ve, -CH(OH)-), 108.4, 110.9, 111.0, 111.8, 158.9 (C=CH\textsubscript{2}), 160.3 (C=CH\textsubscript{2}).

IR (KBr): 3436, 1656, 1110 cm\textsuperscript{-1}.

Exact mass calcd for C\textsubscript{17}H\textsubscript{26}O\textsubscript{3}: 278.1882; found: 278.1879.

Anal. calcd for C\textsubscript{17}H\textsubscript{26}O\textsubscript{3}: C 73.35, H 9.41; found: C 73.10, H 9.40.
Preparation of the allylic acetate 249

To a stirred solution of the allylic alcohol 237 (0.260 g, 0.935 mmol, 1:1 mixture of epimers) in dry CH₂Cl₂ (10 mL), at room temperature, were added sequentially Et₃N (260 µL, 1.86 mmol), Ac₂O (175 µL, 1.85 mmol) and DMAP (0.227 g, 1.86 mmol). After 1 hour, water (10 mL) and CH₂Cl₂ (20 mL) were added and the phases were separated. The organic phases was washed with brine (2 x 10 mL), dried (Na₂SO₄), and concentrated. Purification of the crude product by short column chromatography (15 g TLC grade silica gel, 1:1 petroleum ether - Et₂O) and removal of trace amounts of solvent (vacuum pump) from the acquired liquid provided 0.288 g (96%) of the allylic acetate 249 as a colorless oil. ¹H nmr spectroscopic analysis of the oil indicated a 1:1 mixture of epimeric acetates.

¹H nmr (400 MHz, CDCl₃) δ: 0.90, 0.92 (s, s, 3H total, -CH₃), 0.95, 0.96 (s, s, 3H total, -CH₃), 0.98-1.08, 1.14-1.22 (m, m, 1H total), 1.64-1.91 (m, 5H), 2.01, 2.06 (s, s, 3H total, -C(=O)CH₃), 1.93-2.23 (m, 4H), 2.41-2.48 (m, 1H), 2.79-2.89 (m, 1H), 3.41-3.49 (m, 4H, -CH₂O-), 4.96, 4.99 (m, m, 1H total), 5.11, 5.25 (m, m, 1H total), 5.20, 5.29 (br d, J = 9.5 Hz, d, J = 4 Hz, ratio ~1:1, 1H total, -CH(OAc)-).

¹³C nmr (75.3 MHz, CDCl₃) δ: 21.1 (-ve, -C(=O)-CH₃), 21.2 (-ve, -C(=O)-CH₃), 22.41 (-ve, -CH₃), 22.46 (-ve, -CH₃), 22.54 (-ve, 2 signals, -CH₃), 30.0, 30.1, 33.65, 33.75, 33.79, 38.19, 38.25, 39.2, 39.7, 40.7 (-ve, CH), 41.0 (-ve, CH), 45.6 (-ve, CH), 45.9 (-ve, CH), 52.2 (-ve, CH), 53.6 (-ve, CH), 57.5 (-ve, CH), 57.8 (-ve, CH),
71.65 (-CH$_2$O-), 71.86 (-CH$_2$O-), 71.93 (-CH$_2$O-), 72.14 (-CH$_2$O-), 73.2 (-ve, -CH(OAc)-), 76.7 (-ve, -CH(OAc)-), 110.0, 110.8, 110.9, 114.4, 153.9 (C=CH$_2$), 155.4 (C=CH$_2$), 170.7 (C=O), 171.1 (C=O).

IR (neat): 1737, 1657, 1239, 1112 cm$^{-1}$.


Anal. calcd for C$_{19}$H$_{28}$O$_4$: C 71.22, H 8.81; found: C 70.82, H 8.87.

**Preparation of the keto acetate 250**

![Chemical structure of 250](image)

Ozone was bubbled through a cold (-78 °C), stirred solution of the allylic acetate 249 (0.243 g, 0.758 mmol, 1:1 mixture of epimers) and dry MeOH (48 µL, 1.2 mmol, 1.5 equiv) in dry CH$_2$Cl$_2$ (15 mL) until a blue - grey color persisted (~5 minutes). Dimethyl sulfide (~2 mL) was added and the mixture was stirred at -78 °C for 10 minutes and then was warmed to room temperature. The solution was purged with argon and the solvent was removed under reduced pressure. The crude oil was purified by radial chromatography (2 mm plate, 2:1 petroleum ether - Et$_2$O). Removal of trace amounts of solvent (vacuum pump) from the acquired liquid provided 0.220 g (90%) of 250 as a colorless oil. $^1$H nmr spectroscopic analysis of the oil indicated a 1:1 ratio of epimeric acetates.
$^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.90, 0.91 (s, s, 3H total, -CH$_3$), 0.95, 0.96 (s, s, 3H total, -CH$_3$), 0.99-1.14, 1.19-1.32 (m, m, 1H total), 1.71-1.94 (m, 5H), 2.03, 2.09 (s, s, 3H total, -C(=O)CH$_3$), 1.95-2.21 (m, 4H), 2.48-2.53 (m, 1H), 2.75-2.87 (m, 1H), 3.40-3.49 (m, 4H, -CH$_2$O-), 4.88, 4.92 (d, $J = 5.5$ Hz, d, $J = 11$ Hz, ratio $\sim$1:1, 1H total, -CH(OAc)-).

$^{13}$C nmr (75.3 MHz, CDCl$_3$) $\delta$: 20.4 (-ve, -C(=O)-CH$_3$), 20.6 (-ve, -C(=O)-CH$_3$), 22.31 (-ve, -CH$_3$), 22.35 (-ve, -CH$_3$), 22.44 (-ve, 2 signals, -CH$_3$), 29.9, 30.6, 34.5, 37.9, 38.7, 39.0, 40.8, 42.1 (-ve, CH), 42.4 (-ve, CH), 42.5, 43.0 (-ve, CH), 43.4 (-ve, CH), 46.5 (-ve, CH), 49.5 (-ve, CH), 52.7 (-ve, CH), 53.8 (-ve, CH), 71.64 (-CH$_2$O-), 71.79 (-CH$_2$O-), 71.82 (-CH$_2$O-), 72.01 (-CH$_2$O-), 72.6 (-ve, -CH(OAc)-), 80.1 (-ve, -CH(OAc)-), 110.5 (O-C=O), 110.6 (O-C=O), 169.6 (OC(=O)CH$_3$), 170.1 (OC(=O)CH$_3$), 212.4 (C=O), 214.3 (C=O).

IR (neat): 1757, 1230, 1110 cm$^{-1}$.

Exact mass calcd for C$_{18}$H$_{26}$O$_5$: 322.1780; found: 322.1777.
Preparation of the triquinane keto ketal 236

To a cold (-78 °C), stirred solution of SmI₂ (0.1 M in THF, 20 mL, 2.0 mmol) was added the keto acetate 250 (0.250 g, 0.775 mmol, 1:1 mixture of epimers) as a solution in a mixture of dry THF (12 mL) and dry MeOH (4 mL). The initially deep blue solution turned dark green. After 10 minutes, the reaction mixture was warmed to room temperature for 15 minutes. The mixture was poured into saturated aqueous K₂CO₃ (25 mL) and the mixture was diluted with saturated aqueous Na₂S₂O₃ (10 mL) and Et₂O (35 mL). The phases were separated and the aqueous phase was extracted with Et₂O (5 x 10 mL). The combined organic extracts were dried (MgSO₄) and concentrated. Purification of the crude product by radial chromatography (2 mm plate, 2:1 petroleum ether - Et₂O) provided 0.234 g (89%) of the ketone 236 as a white solid. Recrystallization from heptane afforded ketone 236 as colorless crystals (mp 74 - 75 °C).

¹H nmr (400 MHz, CDCl₃) δ: 0.93 (s, 3H, -CH₃), 0.94 (s, 3H, -CH₃), 1.06-1.14 (m, 1H), 1.69-1.89 (m, 6H), 2.07-2.22 (m, 4H), 2.31 (dd, 1H, J = 16, 5.5 Hz), 2.37 (dd, 1H, J = 16, 4 Hz), 2.76-2.87 (m, 1H), 3.44-3.45 (m, 4H, -CH₂O-).

¹³C nmr (75.3 MHz, CDCl₃) δ: 22.48 (-ve), 22.53 (-ve), 30.0, 36.0, 37.8, 39.6, 42.3 (-ve), 43.4, 43.77, 44.80 (-ve), 49.2 (-ve), 54.6 (-ve), 71.9, 72.0, 110.9, 220.2.

IR (KBr): 1745, 1113 cm⁻¹.
Exact mass calcd for $\text{C}_{16}\text{H}_{24}\text{O}_{3}$: 264.1726; found: 264.1725.

Anal. calcd for $\text{C}_{16}\text{H}_{24}\text{O}_{3}$: C 72.69, H 9.15; found: C 73.00, H 9.15.

5. Copper(I) Chloride-Mediated Coupling of Bis(alkenyltrimethyl-stannanes)

Preparation of methyl 2-(trifluoromethanesulfonyloxy)cyclohept-1-ene-carboxylate (283)$^{172a}$

![283](image)

To a cold (0 °C), stirred suspension of KH (0.518, 12.9 mmol) in dry THF (40 mL) was added, dropwise, a solution of freshly distilled methyl 2-oxo-1-cycloheptanecarboxylate (284) (1.71 g, 10.0 mmol) in THF (10 mL). After 30 minutes, $N$-phenyltrifluoromethanesulphonimide (4.35 g, 12.2 mmol) was added as a solid. After an additional 30 minutes, the reaction mixture was warmed to room temperature for 90 minutes. The mixture was suction filtered through Florisil® (20 g) and the cake was washed with Et$_2$O (400 mL). The filtrate was concentrated under reduced pressure and the crude oil was purified by flash chromatography (170 g silica gel, 19:1 petroleum ether - Et$_2$O). Bulb-to-bulb distillation (130 - 150 °C/0.3 Torr) of the acquired liquid provided 2.71 g (89%) of methyl 2-(trifluoromethanesulfonyloxy)cyclohept-1-ene-carboxylate (283) as a colorless oil.
\[ \text{^{1}H nmr (400 MHz, CDCl}_3 \delta: 1.60-1.71 (m, 4H), 1.73-1.79 (m, 2H), 2.49-2.52 (m, 2H), 2.56-2.59 (m, 2H), 3.78 (s, 3H, -CO}_2\text{Me).} \]

\[ \text{^{13}C nmr (75.3 MHz, CDCl}_3 \delta: 23.7, 25.2, 28.0, 30.7, 34.0, 52.3 (-ve), 118.3 (q, -CF}_3, J_{C-F} = 4 \text{ Hz), 127.8, 155.0, 166.1.} \]

IR (neat): 1728, 1659, 1423, 1212, 1141, 1003, 867 cm\(^{-1}\).

Exact mass calcd for C\(_{10}\)H\(_{13}\)F\(_3\)O\(_5\)S: 302.0436; found: 302.0431.

Anal. calcd for C\(_{10}\)H\(_{13}\)F\(_3\)O\(_5\)S: C 39.74, H 4.33, S 10.61; found: C 39.97, H 4.41, S 10.57.

**Preparation of methyl 2-(trimethylstannyl)cyclohept-1-enecarboxylate (285)\(^{172a} \)**

\[ \text{\begin{figure}
\begin{center}
\includegraphics[width=0.5\textwidth]{285.png}
\end{center}
\end{figure}} \]  

285

To a cold (-20°C), stirred solution of (Me\(_3\)Sn)\(_2\) (4.21 g, 12.9 mmol) in dry THF (65 mL) was added MeLi (1.40 M in Et\(_2\)O, 9.30 mL, 13.0 mmol). After 30 minutes, CuSPh (2.29 g, 13.2 mmol) was added as a solid to the now pale yellow solution. After an additional 30 minutes, methyl 2-(trifluoromethanesulfonyloxy)cyclohept-1-ene-carboxylate (283) (2.52 g, 8.33 mmol) was added as a solution in THF (10 mL) to the red-brown solution of the cuprate. Sixty minutes later, HMPA (4.60 mL, 26.4 mmol) was added and the reaction mixture was warmed to 0 °C for 90 minutes. The reaction mixture was poured into aqueous NH\(_4\)Cl-NH\(_4\)OH (pH 8) (100 mL), the resultant mixture
was diluted with 7:3 petroleum ether-Et₂O (200 mL), and then was stirred open to the air for 30 minutes, during which time the aqueous layer turned bright blue. The mixture was filtered through a glass wool plug to remove insoluble byproducts. The phases of the filtrate were separated and the aqueous phase was extracted with Et₂O (3 x 30 mL) and the combined organic phases were washed sequentially with aqueous 10% CuSO₄ (3 x 40 mL), water (40 mL), and brine (2 x 40 mL). The organic phase was dried (MgSO₄) and concentrated under reduced pressure. Purification of the crude product by short column chromatography (53 g TLC grade silica gel, petroleum ether (200 mL) then 30:1 petroleum ether - Et₂O (400 mL)), followed by bulb-to-bulb distillation (114 - 124 °C/0.3 Torr) of the acquired liquid, provided 2.16 g (82%) of methyl 2-(trimethylstannyl)cyclohept-1-ene carboxylate (285) as a colorless oil.

¹H nmr (400 MHz, CDCl₃) δ: 0.09 (s, 9H, -SnMe₃, ²J_{Sn-H} = 53 Hz), 1.38-1.45 (m, 4H), 1.75-1.81 (m, 2H), 2.53-2.56 (m, 2H), 2.61-2.63 (m, 2H), 3.70 (s, 3H, -CO₂Me).

¹³C nmr (75.3 MHz, CDCl₃) δ: -6.8 (-ve), 24.8, 26.0, 28.3, 32.6, 34.8, 51.9 (-ve), 143.5, 169.7, 170.0.

IR (neat): 1694, 1583, 1281, 1259, 1205, 1156, 769 cm⁻¹.

Exact mass calcd for C₁₁H₁₉O₂¹²⁰Sn (M⁺ - Me): 303.0407; found: 303.0407.

Anal. calcd for C₁₂H₂₂O₂Sn: C 45.47, H 7.00; found: C 45.35, H 6.97.
Preparation of 2-(trimethylstannyl)cyclohept-1-enecarbaldehyde (282)

\[
\begin{align*}
\text{CH}_2\text{OH} & \quad \text{SnMe}_3 \\
\text{CHO} & \quad \text{SnMe}_3
\end{align*}
\]

286  
282

To a cold (-78 °C), stirred solution of freshly distilled methyl 2-(trimethylstannyl)cyclohept-1-enecarboxylate (285) (1.01 g, 3.18 mmol) in dry THF (32 mL) was added DIBAL-H (1.0 M in hexanes, 9.60 mL, 9.60 mmol). After 30 minutes, the reaction mixture was warmed to room temperature and stirred for an additional 60 minutes. The reaction mixture was treated with solid ground Na\(_2\)SO\(_4\)•10H\(_2\)O (~ 0.1 g/mmol DIBAL-H), diluted with Et\(_2\)O (40 mL) and stirred open to the air for 30 minutes. The solution was suction filtered through Celite® (20 g) and the cake was washed with Et\(_2\)O (200 mL). The filtrate was concentrated under reduced pressure to yield the allylic alcohol 286, an unstable colorless oil, which was used without further purification.

To a cold (0 °C), stirred solution of the crude allylic alcohol 286 in CH\(_2\)Cl\(_2\) (8 mL) was added sequentially 3 Å molecular sieves (1.55 g), NMO (0.565 g, 4.82 mmol), and TPAP (0.115 g, 0.33 mmol). The solution turned green-black immediately. After 30 minutes, the reaction mixture was warmed to room temperature for 60 minutes. The mixture was filtered through silica gel (20 g) and the cake was washed with Et\(_2\)O (150 mL). The solvent was removed from the filtrate under reduced pressure and the oil thus obtained was distilled bulb-to-bulb (96 - 104 °C/0.3 Torr) to yield 0.699 g (77% from the ester 285) of 2-(trimethylstannyl)cyclohept-1-enecarbaldehyde (282) as a colorless oil.

\(^1\)H nmr (400 MHz, CDC\(_3\)) \(\delta\): 0.23 (s, 9H, -SnMe\(_3\)), \(2J_{\text{Sn-H}} = 53\) Hz), 1.37-1.49 (m, 4H), 1.77-1.82 (m, 2H), 2.53-2.56 (m, 2H), 2.63-2.66 (m, 2H, =C(SnMe\(_3\))=CH\(_2\)), \(3J_{\text{Sn-H}} = 47\) Hz), 9.43 (s, 1H, -CHO), \(4J_{\text{Sn-H}} = 6\) Hz).
\(^{13}\)C nmr (75.3 MHz, CDCl\(_3\)) \(\delta\): -7.2 (-ve), 25.0, 26.0, 26.3, 32.5, 36.4, 153.4, 179.6, 193.8 (-ve).

IR (neat): 2720, 1680, 1562, 772 cm\(^{-1}\).

Exact mass calcd for C\(_{10}\)H\(_{17}\)O\(^{120}\)Sn (M+ - Me): 273.0302; found: 273.0301.

Anal. calcd for C\(_{11}\)H\(_{20}\)OSn: C 46.04, H 7.02; found: C 46.28, H 7.24.

**General Procedure C: Addition of 2-(trimethylstannyl)allyllithium (271) to \(\beta\)-(trimethylstannyl)-\(\alpha\),\(\beta\)-unsaturated aldehydes**

To a cold (-78 °C), stirred solution of freshly distilled 2,3-bis(trimethylstannyl)propene (183) (1.25 equiv) in dry THF (10 mL/mmol of allylstannane) was added MeLi\(\cdot\)LiBr (1.10 equiv, 1.5 M in Et\(_2\)O). After the pale yellow solution had been stirred for 30 minutes, the appropriate freshly distilled \(\beta\)-(trimethylstannyl)-\(\alpha\),\(\beta\)-unsaturated aldehyde (1 equiv) was added as a solution in THF (1 mL/mmol of unsaturated aldehyde). After 20 minutes, the reaction mixture was poured into aqueous NH\(_4\)Cl-NH\(_4\)OH (pH 8) (\(~1\ mL/mL\ THF\) and the mixture was diluted with Et\(_2\)O (\(~2\ mL/mL\ THF\)). The mixture was stirred open to the air for 15 minutes before the phases were separated. The aqueous phase was extracted with Et\(_2\)O (3 x \(~1\ mL/mL\ THF\)) and the combined organic phases were washed with brine (2 x \(~1\ mL/mL\ THF\)), dried (MgSO\(_4\)), and concentrated. The crude product was purified and dried in vacuo.
Preparation of (Z)-9-chloro-2,6-bis(trimethylstannyl)nona-1,5-dien-4-ol (299)

Following general procedure C, the alcohol 299 was prepared by treating 2,3-bis(trimethylstannyl)propene (183) (0.750 g, 2.04 mmol) in dry THF (20 mL) with MeLi·LiBr (1.5 M in Et₂O, 1.24 mL, 1.86 mmol), followed by addition of (Z)-6-chloro-3-(trimethylstannyl)hex-2-enal (291) (0.460 g, 1.56 mmol) in dry THF (1.5 mL). Purification of the crude product by short column chromatography (50 g TLC grade silica gel, 10:1 petroleum ether - Et₂O containing 1% Et₃N) and removal of trace amounts of solvent (vacuum pump) from the resulting liquid provided 0.728 g (93%) of the alcohol 299 as a colorless oil.

$^1$H nmr (400 MHz, CDCl₃) δ: 0.15 (s, 9H, -SnMe₃, $^2$J$^\text{Sn-H} = 54$ Hz), 0.16 (s, 9H, -SnMe₃, $^2$J$^\text{Sn-H} = 53$ Hz), 1.63 (d, 1H, -OH, exchanges with D₂O, $J = 2.5$ Hz), 1.74-1.82 (m, 2H, H-8 and H-8'), 2.25-2.45 (m, 3H, allylic protons H-3, H-7, and H-7'), 2.57 (dd, 1H, allylic proton H-3', $J = 14$, 4 Hz, $^3$J$^\text{Sn-H} = 54$ Hz), 3.49 (t, 2H, H-9 and H-9', $J = 6.5$ Hz), 4.02-4.07 (m, 1H, -CH(OH)-), 5.35 (d, 1H, H-1, $J = 2.5$ Hz, $^3$J$^\text{Sn-H} = 68$ Hz), 5.77 (d, 1H, H-1', $J = 2.5$ Hz, $^3$J$^\text{Sn-H} = 146$ Hz), 6.06 (d, 1H, H-5, $J = 6.5$ Hz, $^3$J$^\text{Sn-H} = 137$ Hz).

$^{13}$C nmr (75.3 MHz, CDCl₃) δ: -9.0 (-ve), -7.2 (-ve), 32.7, 37.1, 44.2, 49.1, 71.5 (-ve), 129.0, 142.5 (-ve), 145.1, 151.9.

IR (neat): 3558, 921, 770, 526 cm⁻¹.
Exact mass calcd for $\text{C}_{14}\text{H}_{28}\text{ClO} \text{Sn}^{118} \text{Sn}^{120} \text{Sn} (\text{M}^+ - \text{Me})$: 484.9867; found: 484.9859.

Anal. calcd for $\text{C}_{15}\text{H}_{31}\text{ClOSn}_2$: C 36.02, H 6.25; found: C 36.36, H 6.33.

Preparation of (Z)-10-(tert-butyldimethylsilyloxy)-2,6-bis(trimethylstannyl)-deca-1,5-dien-4-ol (300)

Following general procedure C, the alcohol 300 was prepared by treating 2,3 bis(trimethylstannyl)propene (183) (1.187 g, 3.23 mmol) in dry THF (32 mL) with MeLi•LiBr (1.5 M in Et$_2$O, 1.90 mL, 2.85 mmol), followed by addition of (Z)-7-(tert-butyldimethylsilyloxy)-3-(trimethylstannyl)hept-2-enal (287)\textsuperscript{201} (0.982 g, 2.42 mmol) in dry THF (2.5 mL). Purification of the crude product by short column chromatography (50 g TLC grade silica gel, 20:1 petroleum ether - Et$_2$O containing 1% Et$_3$N) and removal of trace amounts of solvent (vacuum pump) from the resulting liquid provided 1.385 g (94%) of the alcohol 300 as a colorless oil.

$^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.02 (s, 6H, -SiMe$_2$-), 0.14 (s, 9H, -SnMe$_3$, $^2$J$_{\text{Sn-H}}$ = 53 Hz), 0.15 (s, 9H, -SnMe$_3$, $^2$J$_{\text{Sn-H}}$ = 53 Hz), 0.87 (s, 9H, -SiBu-), 1.31-1.39 (m, 2H), 1.43-1.52 (m, 2H), 1.57 (d, 1H, -OH, exchanges with D$_2$O, $J = 2.5$ Hz), 2.20 (t, 2H, allylic protons H-7 and H-7', $J = 7$ Hz, $^3$J$_{\text{Sn-H}}$ = 55 Hz), 2.37 (dd, 1H, allylic proton H-3, $J = 13.5$, 9 Hz), 2.55 (dd, 1H, allylic proton H-3', $J = 13.5$, 3 Hz), 3.58 (t, 2H,
H-10 and H-10', \( J = 6.5 \text{ Hz} \), 3.99-4.05 (m, 1H, -CH(OH)-), 5.34 (d, 1H, H-1, \( J = 2.5 \text{ Hz} \), \( 3J_{\text{Sn-H}} = 68.5 \text{ Hz} \)), 5.76 (br s, 1H, H-1', \( 3J_{\text{Sn-H}} = 147 \text{ Hz} \)), 5.99 (d, 1H, H-5, \( J = 7 \text{ Hz} \), \( 3J_{\text{Sn-H}} = 140 \text{ Hz} \)).

\( ^{13}\text{C} \) nmr (75.3 MHz, CDCl\(_3\)) \( \delta \): -8.8 (-ve), -7.3 (-ve), -5.2 (-ve), 18.4, 26.1 (-ve), 26.6, 32.5, 40.2, 49.1, 63.1, 72.0 (-ve), 128.8, 141.5 (-ve), 147.5, 152.1.

IR (neat): 3450, 1103, 919, 837, 775, 527 cm\(^{-1}\).

Exact mass calcd for \( \text{C}_{21}\text{H}_{45}\text{O}_{2}\text{Si}_{120}\text{Sn}_{2} (M^+ - \text{Me}) \): 597.1233; found: 597.1243.

Anal. calcd for \( \text{C}_{22}\text{H}_{48}\text{O}_{2}\text{SiSn}_{2} \): C 43.31, H 7.93; found: C 43.68, H 8.00.

Preparation of (Z)-11-(tert-butyldimethylsilyl)-2,6-bis(trimethylstannyl)-undeca-1,5-dien-10-yn-4-ol (301)

\[
\begin{array}{c}
\text{TBS} \\
\text{Me}_3\text{Sn} \\
\text{OH} \\
\text{SnMe}_3
\end{array}
\]

Following general procedure C, the alcohol 301 was prepared by treating 2,3-bis(trimethylstannyl)propene (183) (0.491 g, 1.33 mmol) in dry THF (13 mL) with MeLi•LiBr (1.46 M in Et\(_2\)O, 0.84 mL, 1.22 mmol), followed by addition of (Z)-8-(tert-butyldimethylsilyl)-3-(trimethylstannyl)oct-2-en-7-ynal (292)\(^{202}\) (0.413 g, 1.03 mmol) in dry THF (1.0 mL). Purification of the crude product by short column chromatography (51 g TLC grade silica gel, 25:1 petroleum ether - Et\(_2\)O containing
1% Et₃N) and removal of trace amounts of solvent (vacuum pump) from the resulting liquid provided 0.565 g (91%) of the alcohol 301 as a colorless oil.

¹H nmr (400 MHz, CDCl₃) δ: 0.06 (s, 6H, -SiMe₂-), 0.14 (s, 9H, -SnMe₃, ²J₃₇Sn-H = 54 Hz), 0.16 (s, 9H, -SnMe₃, ²J₃₇Sn-H = 53 Hz), 0.91 (s, 9H, -Si'Bu-), 1.47-1.55 (m, 2H, H-8 and H-8'), 1.59 (d, 1H, -OH, exchanges with D₂O, J = 2.5 Hz), 2.20 (t, 2H, H-9 and H-9', J = 7 Hz), 2.33 (t, 2H, allylic protons H-7 and H-7', J = 7.5 Hz), 2.37 (dd, 1H, allylic proton H-3, J = 13.5, 9 Hz), 2.56 (dd, 1H, allylic proton H-3', J = 13.5, 3 Hz), 4.01-4.05 (m, 1H, -CH(OH)-), 5.35 (d, 1H, H-1, J = 2.5 Hz, ³J₃₇Sn-H = 68 Hz), 5.77 (br s, 1H, H-1', ³J₃₇Sn-H = 147 Hz), 6.04 (d, 1H, H-5, J = 7 Hz, ³J₃₇Sn-H = 137 Hz).

¹³C nmr (75.3 MHz, CDCl₃) δ: -8.9 (-ve), -7.3 (-ve), -4.4 (-ve), 16.5, 19.2, 26.1 (-ve), 28.9, 39.1, 49.1, 71.8 (-ve), 82.9, 107.6, 128.9, 142.1 (-ve), 146.3, 151.9.

IR (neat): 3558, 2174, 921, 838, 775, 528 cm⁻¹.

Exact mass calcd for C₂₂H₄₃OSi¹²⁰Sn₂ (M⁺ - Me): 591.1127; found: 591.1147.

Anal. calcd for C₂₃H₄₆OSiSn₂: C 45.73, H 7.68; found: C 46.00, H 7.84.
Preparation of 1-(1-hydroxy-3-(trimethylstannyl)but-3-en-1-yl)-2-(trimethylstannyl)cyclopentene (302)

Following general procedure C, the alcohol 302 was prepared by treating 2,3-bis(trimethylstannyl)propene (183) (0.823 g, 2.24 mmol) in dry THF (23 mL) with MeLi·LiBr (1.26 M in Et2O, 1.65 mL, 2.08 mmol), followed by addition of 2-(trimethylstannyl)cyclopent-1-enecarbaldehyde (276) (0.478 g, 1.85 mmol) in dry THF (2.0 mL). Purification of the crude product by short column chromatography (50 g TLC grade silica gel, 20:1 petroleum ether - Et2O containing 1% Et3N) and removal of trace amounts of solvent (vacuum pump) from the resulting liquid provided 0.805 g (94%) of the alcohol 302 as a colorless oil.

1H nmr (400 MHz, CDCl3) δ: 0.11 (s, 9H, -SnMe3, 2J_{Sn-H} = 54 Hz), 0.16 (s, 9H, -SnMe3, 2J_{Sn-H} = 53 Hz), 1.79 (d, 1H, -OH, exchanges with D2O, J = 2 Hz), 1.84 (quintet, 2H, -CH2-CH2-CH2-, J = 7.5 Hz), 2.27-2.34 (m, 2H), 2.38-2.47 (m, 3H) 2.64 (br d, 1H, allylic proton -CH(OH)-CH2-, J = 14 Hz, 3J_{Sn-H} = 35 Hz), 4.22 (br d, 1H, -CH(OH)-, J = 10.5 Hz), 5.36 (d, 1H, H_a, J = 2.5 Hz, 3J_{Sn-H} = 67 Hz), 5.79 (br s, 1H, Hb, 3J_{Sn-H} = 146 Hz).

13C nmr (75.3 MHz, CDCl3) δ: -9.1 (-ve), -7.9 (-ve), 24.1, 33.8, 39.6, 48.1, 71.0 (-ve), 128.8, 138.1, 152.9, 153.9.

IR (neat): 3559, 1617, 926, 770, 529 cm⁻¹.

Anal. calcd for C₁₅H₃₀OSn₂: C 38.85, H 6.52; found: C 39.08, H 6.82.

**Preparation of 1-(1-hydroxy-3-(trimethylstannyl)but-3-en-1-yl)-2-(trimethylstannyl)cyclohexene (303)**

Following general procedure C, the alcohol 303 was prepared by treating 2,3-bis(trimethylstannyl)propene (183) (0.369 g, 1.00 mmol) in dry THF (10 mL) with MeLi•LiBr (1.48 M in Et₂O, 0.61 mL, 0.90 mmol), followed by addition of 2-(trimethylstannyl)cyclohex-1-enecarbaldehyde (277)²⁰⁴ (0.214 g, 0.78 mmol) in dry THF (1.0 mL). Purification of the crude product by short column chromatography (33 g TLC grade silica gel, 30:1 petroleum ether - Et₂O containing 1% Et₃N) and removal of trace amounts of solvent (vacuum pump) from the resulting liquid provided 0.352 g (94%) of the alcohol 303 as a colorless oil.

¹H nmr (400 MHz, CDCl₃) δ: 0.08 (s, 9H, -SnMe₃, ²J_Sn-H = 52 Hz), 0.15 (s, 9H, -SnMe₃, ²J_Sn-H = 53 Hz), 1.52-1.69 (m, 4H), 1.72 (d, 1H, -OH, exchanges with D₂O, J = 1.5 Hz), 1.91-2.00 (m, 1H), 2.09-2.22 (m, 3H), 2.33 (dd, 1H, allylic proton -CH(OH)-CH₂-, J = 14, 10.5 Hz, ³J_Sn-H = 64 Hz), 2.59 (d, 1H, allylic proton -CH(OH)-
CH₂, J = 14 Hz, ³J_{Sn-H} = 40 Hz), 3.89 (br d, 1H, -CH(OH)-, J = 10.5 Hz), 5.34 (d, 1H, Hₐ, J = 2.5 Hz, ³J_{Sn-H} = 68 Hz), 5.79 (d, 1H, Hₐ, J = 2.5 Hz, ³J_{Sn-H} = 146 Hz).

¹³C nmr (75.3 MHz, CDCl₃) δ: -9.0 (-ve), -6.8 (-ve), 22.7, 24.0, 27.2, 32.6, 47.5, 75.8 (-ve), 128.5, 134.9, 145.9, 153.3.

IR (neat): 3552, 919, 769, 526 cm⁻¹.


Anal. calcd for C₁₆H₃₂OSn₂: C 40.22, H 6.75; found: C 40.41, H 6.82.

**Preparation of 1-(1-hydroxy-3-(trimethylstannyl)but-3-en-1-yl)-2-(trimethylstannyl)cycloheptene (304)**

Following general procedure C, the alcohol 304 was prepared by treating 2,3-bis(trimethylstannyl)propene (183) (0.785 g, 2.13 mmol) in dry THF (21 mL) with MeLi•LiBr (1.44 M in Et₂O, 1.37 mL, 1.97 mmol), followed by addition of 2-(trimethylstannyl)cyclo-hept-1-enecarbaldehyde (282) (0.467 g, 1.63 mmol) in dry THF (2.0 mL). Purification of the crude product by short column chromatography (50 g TLC grade silica gel, 25:1 petroleum ether - Et₂O containing 1% Et₃N) and removal of
trace amounts of solvent (vacuum pump) from the resulting liquid provided 0.709 g (89%) of the alcohol 304 as a colorless oil.

$^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.08 (s, 9H, -SnMe$_3$, $^2$J$_{Sn-H}$ = 53 Hz), 0.15 (s, 9H, -SnMe$_3$, $^2$J$_{Sn-H}$ = 54 Hz), 1.29-1.50 (m, 4H), 1.68-1.82 (m, 2H), 1.72 (d, 1H, -OH, exchanges with D$_2$O, $J$ = 1.5 Hz), 2.15 (ddd, 1H, $J$ = 14, 8.5, 2 Hz), 2.25-2.42 (m, 4H), 2.56 (br d, 1H, allylic proton -CH(OH)-CH$_2$-, $J$ = 14 Hz, $^3$J$_{Sn-H}$ = 54 Hz), 3.97 (br d, 1H, -CH(OH)-, $J$ = 10.5 Hz), 5.35 (d, 1H, $H_a$, $J$ = 2.5 Hz, $^3$J$_{Sn-H}$ = 67 Hz), 5.80 (d, 1H, $H_b$, $J$ = 2.5 Hz, $^3$J$_{Sn-H}$ = 146.5 Hz).

$^{13}$C nmr (75.3 MHz, CDCl$_3$) $\delta$: -8.9 (-ve), -6.4 (-ve), 26.3, 27.1, 30.5, 32.8, 33.9, 47.3, 76.7 (-ve), 128.5, 140.6, 153.0, 153.9.

IR (neat): 3550, 918, 767, 525 cm$^{-1}$.

Exact mass calcd for C$_{18}$H$_{31}$O$_{120}$Sn$_2$ (M$^+$ - Me): 479.0419; found: 479.0407.

Anal. calcd for C$_{17}$H$_{34}$OSn$_2$: C 41.52, H 6.97; found: C 41.83, H 7.00.

**General procedure D: Acylation of allylic alcohols**

To a stirred solution of the alcohol (1 equiv) in dry CH$_2$Cl$_2$ (10 mL/mmol of alcohol), at room temperature, were added sequentially Et$_3$N (2 equiv), Ac$_2$O (2 equiv) and DMAP (2 equiv). The mixture was stirred at room temperature for the indicated period of time. The reaction mixture was poured into water (~10 mL/mmol of alcohol) and the phases were separated. The aqueous phase was extracted with CH$_2$Cl$_2$ (3 x ~10 mL/mmol of
alcohol) and the combined organic phases were washed once with brine (~10 mL/mmol of alcohol), dried (Na$_2$SO$_4$), and concentrated. The crude product was purified by chromatography and dried in vacuo.

**Preparation of (Z)-4-acetoxy-9-chloro-2,6-bis(trimethylstannyl)nona-1,5-diene (307)**

Following general procedure D, the acetate 307 was prepared by treating the alcohol 299 (0.506 g, 1.01 mmol) in dry CH$_2$Cl$_2$ (10 mL) with Et$_3$N (0.30 mL, 2.15 mmol), Ac$_2$O (190 µL, 2.01 mmol), and DMAP (0.248 g, 2.03 mmol) for 2 hours. Purification of the crude product by short column chromatography (52 g TLC grade silica gel, 20:1 petroleum ether - Et$_2$O) and removal of trace amounts of solvent (vacuum pump) from the resulting liquid provided 0.545 g (99%) of the acetate 307 as a colorless oil.

$^1$H nmr (400 MHz, CDCl$_3$) δ: 0.13 (s, 9H, -SnMe$_3$, $^2J_{Sn-H} = 53$ Hz), 0.21 (s, 9H, -SnMe$_3$, $^2J_{Sn-H} = 53$ Hz), 1.72-1.82 (m, 2H, H-8 and H-8'), 1.98 (s, 3H, -C(=O)CH$_3$), 2.35 (t, 2H, allylic protons H-7 and H-7', $J = 7$ Hz, $^3J_{Sn-H} = 50$ Hz), 2.53 (dd, 1H, allylic proton H-3, $J = 14$, 5 Hz), 2.57 (dd, 1H, allylic proton H-3', $J = 14$, 7 Hz), 3.46 (t, 2H, H-9 and H-9', $J = 6.5$ Hz), 5.16 (ddd, 1H, -CH(OAc)-, $J = 9$, 7, 5 Hz), 5.28 (d, 1H, H-1, $J = 2.5$ Hz, $^3J_{Sn-H} = 71$ Hz), 5.70 (d, 1H, H-1', $J = 2.5$ Hz, $^3J_{Sn-H} = 147$ Hz), 5.92 (d, 1H, H-5, $J = 9$ Hz, $^3J_{Sn-H} = 134$ Hz).
$^{13}$C nmr (75.3 MHz, CDCl$_3$) $\delta$: -8.9 (-ve), -7.9 (-ve), 21.5 (-ve), 32.2, 37.2, 44.0, 45.7, 76.0 (-ve), 128.8, 139.6 (-ve), 147.6, 150.0, 170.0.

IR (neat): 1740, 1240, 923, 774, 526 cm$^{-1}$.

Exact mass calcd for $\text{C}_{16}\text{H}_{30}\text{ClO}_2\text{Sn}^{118}\text{Sn}^{120}$ (M$^+$ - Me): 526.9973; found: 526.9972.

Anal. calcd for $\text{C}_{17}\text{H}_{33}\text{ClO}_2\text{Sn}_2$: C 37.65, H 6.13; found: C 37.99, H 6.22.

**Preparation of (Z)-4-acetoxy-10-(tert-butyldimethylsilyloxy)-2,6-bis(trimethylstannyl)deca-1,5-diene (308)**

Following general procedure D, the acetate 308 was prepared by treating the alcohol 300 (1.09 g, 1.78 mmol) in dry CH$_2$Cl$_2$ (18 mL) with Et$_3$N (0.50 mL, 3.59 mmol), Ac$_2$O (340 $\mu$L, 3.60 mmol), and DMAP (0.437 g, 3.58 mmol) for 2 hours. Purification of the crude product by short column chromatography (53 g TLC grade silica gel, 30:1 petroleum ether - Et$_2$O) and removal of trace amounts of solvent (vacuum pump) from the resulting liquid provided 1.161 g (100%) of the acetate 308 as a colorless oil.

$^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.02 (s, 6H, -SiMe$_2$-), 0.13 (s, 9H, -SnMe$_3$), $^2J_{\text{Sn-H}} = 52$ Hz), 0.20 (s, 9H, -SnMe$_3$), $^2J_{\text{Sn-H}} = 52$ Hz), 0.87 (s, 9H, -Si$^{\text{Bu}}$-), 1.30-1.38 (m, 2H), 1.41-1.49 (m, 2H), 1.98 (s, 3H, -C(=O)CH$_3$), 2.20 (t, 2H, allylic protons H-7 and
H-7', $J = 7$ Hz, $^3J_{Sn-H} = 49$ Hz), 2.53 (dd, 1H, allylic proton H-3, $J = 14$, 5 Hz),
2.56 (dd, 1H, allylic proton H-3', $J = 14$, 7 Hz), 3.57 (t, 2H, H-10 and H-10',
$J = 6$ Hz), 5.18 (ddd, 1H, -CH(OAc)-, $J = 9$, 7, 5 Hz), 5.28 (d, 1H, H-1, $J = 1.5$ Hz,
$^3J_{Sn-H} = 70$ Hz), 5.70 (d, 1H, H-1', $J = 1.5$ Hz, $^3J_{Sn-H} = 148$ Hz), 5.88 (d, 1H, H-5,
$J = 9$ Hz, $^3J_{Sn-H} = 138$ Hz).

$^{13}$C nmr (75.3 MHz, CDCl$_3$) $\delta$: -8.9 (-ve), -7.8 (-ve), -5.3 (-ve), 18.3, 21.6 (-ve),
26.0 (-ve), 26.2, 32.3, 40.4, 45.8, 63.0, 76.1 (-ve), 128.8, 138.2 (-ve), 149.8, 150.1,
169.9.

IR (neat): 1739, 1239, 1103, 1017, 922, 837, 775, 527 cm$^{-1}$.

Exact mass calcd for C$_{23}$H$_{47}$O$_3$Si$_{120}$Sn$_2$ (M$^+$ - Me): 639.1339; found: 639.1339.

Anal. calcd for C$_{24}$H$_{50}$O$_3$SiSn$_2$: C 44.20, H 7.73; found: C 44.56, H 7.96.

Preparation of (Z)-4-acetoxyl-11-(tert-butyl(dimethyl)silyl)-2,6-bis(trimethylstanny1)-
undeca-1,5-dien-10-yne (309)

Following general procedure D, the acetate 309 was prepared by treating the alcohol
301 (0.481 g, 0.80 mmol) in dry CH$_2$Cl$_2$ (8 mL) with Et$_3$N (225 μL, 1.61 mmol),
Ac$_2$O (150 μL, 1.59 mmol), and DMAP (0.194 g, 1.59 mmol) for 4 hours. Purification
of the crude product by short column chromatography (30 g TLC grade silica gel, 20:1 petroleum ether - Et2O) and removal of trace amounts of solvent (vacuum pump) from the resulting liquid provided 0.506 g (98%) of the acetate 309 as a colorless oil.

\(^1\)H nmr (400 MHz, CDCl\textsubscript{3}) \(\delta\): 0.06 (s, 6H, -SiMe\textsubscript{2}-), 0.13 (s, 9H, -SnMe\textsubscript{3}, \(^2\)J\textsubscript{Sn-H} = 53 Hz), 0.21 (s, 9H, -SnMe\textsubscript{3}, \(^2\)J\textsubscript{Sn-H} = 53 Hz), 0.91 (s, 9H, -SiBu-), 1.47-1.55 (m, 2H, H-8 and H-8'), 1.98 (s, 3H, -C(=O)CH\textsubscript{3}), 2.17 (t, 2H, H-9 and H-9', \(J = 7\) Hz), 2.32 (t, 2H, allylic protons H-7 and H-7', \(J = 7.5\) Hz, \(^3\)J\textsubscript{Sn-H} = 51 Hz), 2.53 (dd, 1H, allylic proton H-3, \(J = 14, 5\) Hz), 2.56 (dd, 1H, allylic proton H-3', \(J = 14, 7\) Hz), 5.18 (ddd, 1H, -CH(OAc)-, \(J = 9, 7, 5\) Hz), 5.28 (d, 1H, H-1, \(J = 1\) Hz, \(^3\)J\textsubscript{Sn-H} = 70 Hz), 5.71 (d, 1H, H-1', \(J = 1\) Hz, \(^3\)J\textsubscript{Sn-H} = 147 Hz), 5.92 (d, 1H, H-5, \(J = 9\) Hz, \(^3\)J\textsubscript{Sn-H} = 135 Hz).

\(^{13}\)C nmr (75.3 MHz, CDCl\textsubscript{3}) \(\delta\): -8.9 (-ve), -7.8 (-ve), -4.3 (-ve), 16.6, 19.1, 21.6 (-ve), 26.2 (-ve), 28.6, 39.3, 45.8, 76.1 (-ve), 83.0, 107.5, 128.9, 139.1 (-ve), 148.8, 150.1, 170.0.

IR (neat): 2174, 1739, 1370, 1237, 1017, 923, 838, 776, 527 cm\(^{-1}\).

Exact mass calcd for C\textsubscript{24}H\textsubscript{45}O\textsubscript{2}Si\textsuperscript{120}Sn\textsubscript{2} (M\textsuperscript{+} - Me): 633.1233; found: 633.1224.

Anal. calcd for C\textsubscript{25}H\textsubscript{48}O\textsubscript{2}SiSn\textsubscript{2}: C 46.47, H 7.49; found: C 46.80, H 7.59.
Preparation of 1-(1-acetoxy-3-(trimethylstannyl)but-3-en-1-yl)-2-(trimethylstannyl)-cyclopentene (310)

Following general procedure D, the acetate 310 was prepared by treating the alcohol 302 (0.591 g, 1.27 mmol) in dry CH₂Cl₂ (13 mL) with Et₃N (0.40 mL, 2.87 mmol), Ac₂O (240 μL, 2.54 mmol), and DMAP (0.318 g, 2.60 mmol) for 16 hours. Purification of the crude product by short column chromatography (22 g TLC grade silica gel, 20:1 petroleum ether - Et₂O containing 1% Et₃N) and removal of trace amounts of solvent (vacuum pump) from the resulting liquid provided 0.638 g (99%) of the acetate 310 as a colorless oil.

¹H nmr (400 MHz, CDCl₃) δ: 0.13 (s, 9H, -SnMe₃, ²JSn-H = 53 Hz), 0.17 (s, 9H, -SnMe₃, ²JSn-H = 54 Hz), 1.73-1.83 (m, 2H, -CH₂-C₆H₄-CH₂-), 1.98 (s, 3H, -C(=O)CH₃), 2.32-2.48 (m, 5H), 2.65 (dd, 1H, allylic proton -CH(OAc)-CH₂-, J = 14, 9.5 Hz), 5.24 (d, 1H, Ha, J = 2.5 Hz, ³JSn-H = 70 Hz), 5.44 (dd, 1H, -CH(OAc)-, J = 9.5, 4 Hz), 5.70 (d, 1H, Hb, J = 2.5 Hz, ³JSn-H = 147 Hz).

¹³C nmr (75.3 MHz, CDCl₃) δ: -9.1 (-ve), -8.9 (-ve), 21.4 (-ve), 23.5, 33.0, 39.7, 44.5, 74.8 (-ve), 127.9, 140.8, 150.7, 150.9, 170.0.

IR (neat): 1740, 1616, 1369, 1235, 1020, 920, 770, 530 cm⁻¹.

Exact mass calcd for C₁₆H₂₉O₂¹²⁰Sn₂ (M⁺ - Me): 493.0212; found: 493.0217.
Anal. calcd for C\textsubscript{17}H\textsubscript{32}O\textsubscript{2}Sn\textsubscript{2}: C 40.37, H 6.38; found: C 40.70, H 6.58.

**Preparation of 1-(1-acetoxy-3-(trimethylstannyl)but-3-en-1-yl)-2-(trimethylstannyl)cyclohexene (311)**

Following general procedure D, the acetate 311 was prepared by treating the alcohol 303 (0.265 g, 0.55 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (5.5 mL) with Et\textsubscript{3}N (0.155 \mu L, 1.11 mmol), Ac\textsubscript{2}O (105 \mu L, 1.11 mmol), and DMAP (0.135 g, 1.11 mmol) for 18 hours. Purification of the crude product by short column chromatography (33 g TLC grade silica gel, 30:1 petroleum ether - Et\textsubscript{2}O containing 1% Et\textsubscript{3}N) and removal of trace amounts of solvent (vacuum pump) from the resulting liquid provided 0.278 g (97%) of the acetate 311 as a colorless oil.

\(^1\text{H}\) nmr (400 MHz, CDCl\textsubscript{3}) \(\delta\): 0.13 (s, 9H, -SnMe\textsubscript{3}), \(^2\text{J}_{\text{Sn-H}} = 53\) Hz, 0.16 (s, 9H, -SnMe\textsubscript{3}), \(^2\text{J}_{\text{Sn-H}} = 53\) Hz, 1.46-1.64 (m, 4H), 1.99 (s, 3H, -C(=O)-CH\textsubscript{3}), 2.00-2.07 (m, 2H), 2.15-2.21 (m, 2H), 2.38 (dd, 1H, allylic proton -CH(OAc)-CH\textsubscript{2}, \(J = 15, 3.5\) Hz, \(^3\text{J}_{\text{Sn-H}} = 52\) Hz), 2.72 (dd, 1H, allylic proton -CH(OAc)-CH\textsubscript{2}, \(J = 15, 9.5\) Hz, \(^3\text{J}_{\text{Sn-H}} = 43\) Hz), 5.13 (dd, 1H, -CH(OAc)-, \(J = 9.5, 3.5\) Hz), 5.26 (d, 1H, H\textsubscript{a}, \(J = 2\) Hz, \(^3\text{J}_{\text{Sn-H}} = 71\) Hz), 5.72 (d, 1H, H\textsubscript{b}, \(J = 2\) Hz, \(^3\text{J}_{\text{Sn-H}} = 149\) Hz).
$^1$C nmr (75.3 MHz, CDCl$_3$) $\delta$: -9.1 (-ve), -8.0 (-ve), 21.4 (-ve), 22.5, 23.6, 25.5, 32.3, 43.8, 80.7 (-ve), 127.5, 138.2, 143.8, 151.0, 170.0.

IR (neat): 1739, 1619, 1231, 1017, 921, 769, 526 cm$^{-1}$.

Exact mass calcd for C$_{17}$H$_{31}$O$_2$Sn$_2$ (M$^+$ - Me): 507.0368; found: 507.0359.

Anal. calcd for C$_{18}$H$_{34}$O$_2$Sn$_2$: C 41.59, H 6.59; found: C 41.95, H 6.83.

**Preparation of l-(l-acetoxy-3-(trimethylstannyl)but-3-en-l-yl)-2-(trimethylstannyl)cycloheptene (312) and l-(l-acetoxy-3-(trimethylstannyl)but-3-en-l-yl)cycloheptene (313)**

Following general procedure D, the alcohol 304 (0.511 g, 1.04 mmol) in dry CH$_2$Cl$_2$ (11 mL) was treated with Et$_3$N (0.30 mL, 2.25 mmol), Ac$_2$O (0.20 mL, 2.12 mmol), and DMAP (0.256 g, 2.09 mmol) for 24 hours. Purification of the crude product by short column chromatography (35 g TLC grade silica gel, 40:1 petroleum ether - Et$_2$O containing 1% Et$_3$N), concentration of the appropriate fractions, and removal of trace amounts of solvent (vacuum pump) from the resulting liquids provided 0.302 g (54%) of the desired acetate 312, and 0.170 g (44%) of the destannylated acetate 313, both as colorless oils.
1-(1-acetoxy-3-(trimethylstannyl)but-3-en-1-yl)-2-(trimethylstannyl)cycloheptene (312):

$^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.12 (s, 9H, -SnMe$_3$, $^2$J$_{Sn-H}$ = 53 Hz), 0.17 (s, 9H, -SnMe$_3$, $^2$J$_{Sn-H}$ = 52 Hz), 1.21-1.50 (m, 4H), 1.64-1.81 (m, 2H), 1.97 (s, 3H, -C(=O)CH$_3$), 2.23-2.39 (m, 5H), 2.69 (dd, 1H, allylic proton -CH(OAc)-CH$_2$-, $J$ = 14.5, 10 Hz), 5.15 (dd, 1H, -CH(OAc)-, $J$ = 10, 4.5 Hz), 5.26 (d, 1H, $H_a$, $J$ = 2 Hz, $^3$J$_{Sn-H}$ = 69 Hz), 5.72 (d, 1H, H$_b$, $J$ = 2 Hz, $^3$J$_{Sn-H}$ = 149 Hz).

$^{13}$C nmr (75.3 MHz, CDCl$_3$) $\delta$: -9.0 (-ve), -7.7 (-ve), 21.4 (-ve), 26.1, 27.0, 28.5, 32.9, 34.4, 43.5, 81.6 (-ve), 127.8, 144.9, 150.85, 150.90, 170.0.

IR (neat): 1741, 1615, 1234, 1016, 921, 767, 526 cm$^{-1}$.

Exact mass calcd for C$_{18}$H$_{33}$O$_2$Sn$_2$ (M$^+$ - Me): 521.0524; found: 521.0536.

Anal. calcd for C$_{19}$H$_{36}$O$_2$Sn$_2$: C 42.75, H 6.80; found: C 43.11, H 6.79.

1-(1-acetoxy-3-(trimethylstannyl)but-3-en-1-yl)cycloheptene (313):

$^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.14 (s, 9H, -SnMe$_3$, $^2$J$_{Sn-H}$ = 53 Hz), 1.35-1.56 (m, 4H), 1.62-1.78 (m, 2H), 1.98 (s, 3H, -C(=O)CH$_3$), 2.05-2.13 (m, 4 H), 2.49 (br dd, 1H, allylic proton -CH(OAc)-CH$_2$-, $J$ = 14, 5.5 Hz), 2.52 (br dd, 1H, allylic proton -CH(OAc)-CH$_2$-, $J$ = 14, 8 Hz), 5.11 (dd, 1H, -CH(OAc)-, $J$ = 8, 5.5 Hz), 5.20 (d, 1H, $H_a$, $J$ = 2.5 Hz, $^3$J$_{Sn-H}$ = 69 Hz), 5.65 (dt, 1H, H$_b$, $J$ = 2.5, 1 Hz, $^3$J$_{Sn-H}$ = 147 Hz), 5.77 (t, 1H, H$_c$, $J$ = 6.5 Hz).

$^{13}$C nmr (75.3 MHz, CDCl$_3$) $\delta$: -9.2 (-ve), 21.3 (-ve), 26.7, 26.8, 28.0, 28.5, 32.5, 44.2, 78.7 (-ve), 127.7, 129.7 (-ve), 141.9, 151.1, 170.0.
IR (neat): 1741, 1240, 1019, 919, 769, 528 cm$^{-1}$.

Exact mass calcd for C$_{15}$H$_{25}$O$_2$Sn (M$^+$ - Me): 357.0877; found: 357.0879.

Anal. calcd for C$_{16}$H$_{28}$O$_2$Sn: C 51.79, H 7.61; found: C 52.17, H 7.73.

**Alternative procedure for the preparation of 1-(1-acetoxy-3-(trimethylstannyl)-but-3-en-1-yl)-2-(trimethylstannyl)cycloheptene (312)**

![Diagram of 312]

To a cold (0 °C), stirred solution of LDA (0.994 mmol, 1.3 equiv) in dry THF (6 mL) was added the alcohol 304 (0.376 g, 0.764 mmol) as a solution in dry THF (1.5 mL). After 2 hours, Ac$_2$O (144 µL, 1.53 mmol) was added and the mixture was warmed to room temperature. After an additional hour, the mixture was poured into aqueous NH$_4$Cl-NH$_4$OH (pH 7) (8 mL) and the mixture was diluted with Et$_2$O (8 mL). The phases were separated and the aqueous phase was extracted with Et$_2$O (3 x 8 mL). The combined organic phases were washed with brine (2 x 8 mL), dried (MgSO$_4$), and concentrated. Purification of the crude product by short column chromatography (20 g TLC grade silica gel, 40:1 petroleum ether - Et$_2$O containing 1% Et$_3$N), concentration of the appropriate fractions, and removal of trace amounts of solvent (vacuum pump) from the resulting liquids provided 0.253 g (62%, 77% based on recovered 304) of the desired acetate 312.
and 0.077 g (20%) of recovered starting material, alcohol 304, both as colorless oils. The spectral data for 312 and 304 were identical with those reported above.

**General Procedure E: Copper(I) chloride-mediated intramolecular coupling of bis(alkenyltrimethylstannanes)**

A stirred solution of CuCl (~5 equiv) in dry DMF (3.3 mL/mmol CuCl) was heated at 60 °C with an oil bath (preheated) for 5 minutes. A solution of the bis(alkenyltrimethylstannane) (1 equiv) in dry DMF (5 mL/mmol of bis(alkenyltrimethylstannane)) was added dropwise, using a small bore cannula. The mixture became rust colored. After 15 minutes, the flask was cooled to room temperature and saturated aqueous NH₄Cl (1 mL/mmol CuCl) was added. The resultant solution was diluted with Et₂O (~10 mL/mmol CuCl) and stirred open to the air for 15 minutes. The mixture was poured into an additional quantity of saturated aqueous NH₄Cl (~10 mL/mmol CuCl) and the layers were separated. The aqueous phase was extracted with Et₂O (3 x ~10 mL/mmol CuCl) and the combined organic phases were washed with 2 portions of brine (2 x ~10 mL/mmol CuCl), dried (MgSO₄), and concentrated. The crude product was purified by chromatography and the acquired liquid was distilled.
Preparation of 3-acetoxy-1-(3-chloropropyl)-5-methylene cyclopentene (316)

Following general procedure E, 3-acetoxy-1-(3-chloropropyl)-5-methylene cyclopentene (316) was prepared by the dropwise addition of the bis(alkenyltrimethylstannane) 307 (0.385 g, 0.71 mmol) in dry DMF (3 mL) to a warm (60 °C) solution of CuCl (0.356 g, 3.59 mmol) in dry DMF (11 mL). Purification of the crude product by short column chromatography (30 g TLC grade silica gel, 10:1 petroleum ether - Et2O), followed by bulb-to-bulb distillation (132 - 136 °C/0.3 Torr) of the acquired liquid, provided 0.130 g (86%) of 316 as a colorless oil.

$^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 1.96-2.03 (m, 2H, Cl-CH$_2$-CH$_2$-CH$_2$-), 2.01 (s, 3H, -C(=O)CH$_3$), 2.36 (t, 2H, Cl-CH$_2$-CH$_2$-CH$_2$-, J = 8 Hz), 2.50 (dd, 1H, H$_c$, J = 17, 2 Hz), 3.00 (dddd, 1H, H$_d$, J = 17, 7, 2, 2 Hz), 3.55 (t, 2H, Cl-CH$_2$-CH$_2$-CH$_2$-, J = 6.5 Hz), 4.90 (d, 1H, J = 2 Hz), 4.98 (dd, 1H, J = 2, 2 Hz), 5.63 (d, 1H, H$_b$, J = 7 Hz), 5.91 (s, 1H, H$_a$).

$^{13}$C nmr (75.3 MHz, CDCl$_3$) $\delta$: 21.2 (-ve), 23.9, 30.3, 37.3, 44.5, 76.2 (-ve), 103.7, 131.3 (-ve), 148.5, 149.7, 170.9.

IR (neat): 1729, 1639, 1618, 1372, 1240, 1023, 985 cm$^{-1}$.

Exact mass calcd for $^{35}$ClO$_2$: 214.0761; found: 214.0752.
Anal. calcd for C\textsubscript{11}H\textsubscript{15}ClO\textsubscript{2}: C 61.54, H 7.04; found: C 61.86, H 7.07.

**Preparation of 3-acetoxy-1-(4-(\textit{tert}-butyldimethylsiloxy)butyl)-5-methylene-cyclopentene (317)**

Following general procedure E, 3-acetoxy-1-(4-(\textit{tert}-butyldimethylsiloxy)butyl)-5-methylene-cyclopentene (317) was prepared by the dropwise addition of the bis(alkenyltrimethylstannane) 308 (0.660 g, 1.01 mmol) in dry DMF (5 mL) to a warm (60 °C) solution of CuCl (0.508 g, 5.13 mmol) in dry DMF (17 mL). Purification of the crude product by short column chromatography (50 g TLC grade silica gel, 15:1 petroleum ether - Et\textsubscript{2}O), followed by bulb-to-bulb distillation (161 - 171 °C/0.3 Torr) of the acquired liquid, provided 0.258 g (79%) of 317 as a colorless oil.

\(^1\)H nmr (400 MHz, CDCl\textsubscript{3}) \(\delta\): 0.03 (s, 6H, -SiMe\textsubscript{2}-), 0.87 (s, 9H, -Si'\textit{Bu}-), 1.50-1.62 (m, 4H), 2.01 (s, 3H, -C(=O)CH\textsubscript{3}), 2.19 (t, 2H, TBSO-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-, \(J = 8\) Hz), 2.48 (dd, 1H, \(H_c\), \(J = 17, 2\) Hz), 2.99 (dddd, 1H, \(H_d\), \(J = 17, 7, 2, 2\) Hz), 3.61 (t, 2H, TBSO-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-, \(J = 6\) Hz), 4.86 (d, 1H, \(J = 2\) Hz), 4.95 (dd, 1H, \(J = 2, 2\) Hz), 5.63 (d, 1H, \(H_b\) \(J = 7\) Hz), 5.87 (s, 1H, \(H_a\)).
$^{13}$C nmr (75.3 MHz, CDCl$_3$) $\delta$: -5.4 (-ve), 18.2, 21.1 (-ve), 23.7, 25.9 (-ve), 26.5, 32.6, 37.3, 62.8, 76.4 (-ve), 103.2, 130.6 (-ve), 150.0 (2 quaternary carbons), 170.9.

$^{13}$C nmr (75.3 MHz, C$_6$D$_6$) $\delta$: -5.1 (-ve), 18.5, 20.8 (-ve), 24.3, 26.2 (-ve), 26.9, 33.0, 37.9, 63.0, 76.5 (-ve), 103.3, 131.7 (-ve), 150.0, 150.8, 170.1.

IR (neat): 1739, 1639, 1617, 1241, 1103, 1021, 838 cm$^{-1}$.

Exact mass calcd for C$_{18}$H$_{32}$O$_3$Si: 324.2121; found: 324.2118.

Anal. calcd for C$_{18}$H$_{32}$O$_3$Si: C 66.62, H 9.94; found: C 66.27, H 9.98.

**Preparation of 3-acetoxy-1-(5-(tert-butyldimethylsilyl)pent-4-yn-1-yl)-5-methylene-cyclopentene (318)**

![Diagram of molecule](image)

Following general procedure E, 3-acetoxy-1-(5-(tert-butyldimethylsilyl)pent-4-yn-1-yl)-5-methylene-cyclopentene (318) was prepared by the dropwise addition of the bis(alkenyltrimethylstannane) 309 (0.290 g, 0.45 mmol) in dry DMF (2 mL) to a warm (60 °C) solution of CuCl (0.243 g, 2.45 mmol) in dry DMF (7 mL). Purification of the crude product by short column chromatography (30 g TLC grade silica gel, 10:1 petroleum ether - Et$_2$O), followed by bulb-to-bulb distillation (172 - 179 °C/0.3 Torr) of the acquired liquid, provided 0.123 g (86%) of 318 as a colorless oil.
$^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.06 (s, 6H, -SiMe$_2$), 0.91 (s, 9H, -Si$^i$Bu$^i$), 1.70-1.77 (m, 2H, TBS-C≡C-CH$_2$-CH$_2$-CH$_2$-), 2.01 (s, 3H, -C(=O)CH$_3$), 2.26 (t, 2H, TBS-C≡C-CH$_2$-CH$_2$-CH$_2$-, $J = 7$ Hz), 2.32 (br t, 2H, TBS-C≡C-CH$_2$-CH$_2$-CH$_2$-, $J = 8$ Hz), 2.49 (dd, 1H, H$_c$, $J = 17$, 2 Hz), 3.00 (dddd, 1H, H$_d$, $J = 17$, 7, 2, 2 Hz), 4.88 (d, 1H, $J = 2$ Hz), 4.98 (dd, 1H, $J = 2$, 2 Hz), 5.63 (d, 1H, H$_b$, $J = 7$ Hz), 5.89 (s, 1H, H$_a$).

$^{13}$C nmr (75.3 MHz, CDCl$_3$) $\delta$: -4.5 (-ve), 16.4, 19.6, 21.1 (-ve), 25.7, 26.0 (-ve), 26.6, 37.3, 76.3 (-ve), 83.1, 103.5, 107.1, 131.0 (-ve), 149.3, 149.8, 170.8.

IR (neat): 2173, 1735, 1639, 1618, 1251, 1022, 839 cm$^{-1}$.

Exact mass calcd for C$_{19}$H$_{30}$O$_2$Si: 318.2015; found: 318.2014.

Anal. calcd for C$_{19}$H$_{30}$O$_2$Si: C 71.64, H 9.49; found: C 71.79, H 9.40.

Preparation of 2-acetoxy-4-methylenebicyclo[3.3.0]oct-1(5)-ene (319)

Following general procedure E, 2-acetoxy-4-methylenebicyclo[3.3.0]oct-1(5)-ene (319) was prepared by the dropwise addition of the bis(alkenyltrimethylstannane) 310 (0.209 g,
0.41 mmol) in dry DMF (2 mL) to a warm (60 °C) solution of CuCl (0.223 g, 2.25 mmol) in dry DMF (6 mL). Purification of the crude product by short column chromatography (22 g TLC grade silica gel, 20:1 petroleum ether - Et2O), followed by bulb-to-bulb distillation (162 - 166 °C/12 Torr) of the acquired liquid, provided 0.049 g (67%) of 319 as a colorless oil.

\[ ^1H\text{ nmr (400 MHz, CDCl}_3\text{)} \delta: \ 2.02 \text{ (s, 3 H, -C(=O)CH}_3\text{), 2.25-2.40 \text{ (m, 6 H)}, 2.74 \text{ (dd, 1H, H}_b\text{, J = 17, 2 Hz)}, \ 3.30 \text{ (dddd, 1 H, H}_c\text{, J = 17, 7, 2, 2 Hz)}, \ 4.71 \text{ (br s, 1H), 4.72 (br s, 1H), 5.60 (d, 1H, H}_a\text{, J = 7 Hz).} \]

\[ ^{13}C\text{ nmr (75.3 MHz, CDCl}_3\text{)} \delta: \ 21.0 \text{ (-ve), 25.8, 27.6, 28.4, 42.7, 73.7 (-ve), 102.2, 144.9, 153.5, 153.9, 171.0.} \]

IR (neat): 1741, 1644, 1372, 1255, 1029 cm\(^{-1}\).

Exact mass calcd for C\(_{11}\)H\(_{14}\)O\(_2\): 178.0994; found: 178.0993.

Anal. calcd for C\(_{11}\)H\(_{14}\)O\(_2\): C 74.13, H 7.92; found: C 74.03, H 7.82.
Preparation of 7-acetoxy-9-methylenebicyclo[4.3.0]non-1(6)-ene (320)

Following general procedure E, 7-acetoxy-9-methylenebicyclo[4.3.0]non-1(6)-ene (320) was prepared by the dropwise addition of the bis(alkenyltrimethylstannane) 311 (0.273 g, 0.52 mmol) in dry DMF (2.5 mL) to a warm (60 °C) solution of CuCl (0.285 g, 2.88 mmol) in dry DMF (7.5 mL). Purification of the crude product by short column chromatography (20 g TLC grade silica gel, 20:1 petroleum ether - Et₂O), followed by bulb-to-bulb distillation (96 - 104 °C/0.3 Torr) of the acquired liquid, provided 0.082 g (82%) of 320 as a colorless oil.

\[ \text{320} \]

\[ ^1H \text{ nmr (400 MHz, CDCl}_3) \delta: 1.58-1.74 \text{ (m, 4H), 2.03 (s, 3H, } -\text{C}(=\text{O})\text{CH}_3\text{), 2.00-2.21 \text{ (m, 4H), 2.37 (dd, 1H, } H_b, J = 17, 2 \text{ Hz), 2.99 (dddd, 1H, } H_c, J = 17, 7, 2, 2 \text{ Hz), 4.72 (br s, 1H), 4.77 (br s, 1H), 5.61 (d, 1H, } H_a, J = 7 \text{ Hz).} \]

\[ ^{13}C \text{ nmr (75.3 MHz, CDCl}_3) \delta: 21.1 \text{ (-ve), 21.6, 21.9, 22.3, 23.8, 37.1, 78.3 (-ve), 100.3, 141.5, 142.9, 150.2, 171.1.} \]

IR (neat): 1734, 1635, 1371, 1251, 1025 cm\(^{-1}\).

Exact mass calcd for C\(_{12}\)H\(_{16}\)O\(_2\): 192.1150; found: 192.1149.

Anal. calcd for C\(_{12}\)H\(_{16}\)O\(_2\): C 74.97, H 8.39; found: C 75.22, H 8.32.
Preparation of 8-acetoxy-10-methylenebicyclo[5.3.0]dec-1(7)-ene (321)

Following general procedure E, 8-acetoxy-10-methylenebicyclo[5.3.0]dec-1(7)-ene (321) was prepared by the dropwise addition of the bis(alkenyltrimethylstannane) 312 (0.250 g, 0.47 mmol) in dry DMF (2 mL) to a warm (60 °C) solution of CuCl (0.286 g, 2.89 mmol) in dry DMF (7.5 mL). Purification of the crude product by short column chromatography (30 g TLC grade silica gel, 20:1 petroleum ether - Et₂O) and removal of trace amounts of solvent (vacuum pump) from the resulting liquid provided 0.041 g (42%) of 321 as a colorless oil.

¹H nmr (400 MHz, CDCl₃) δ: 1.54-1.64 (m, 4H), 1.71-1.79 (m, 2H), 2.03 (s, 3H, -C(=O)CH₃), 2.16-2.32 (m, 4H), 2.36 (dd, 1H, Hb, J = 17, 2 Hz), 2.99 (dddd, 1H, Hc, J = 17, 7, 2, 2 Hz), 4.72 (br s, 1H), 4.81 (br s, 1H), 5.58 (d, 1H, Ha, J = 7 Hz).

¹³C nmr (75.3 MHz, CDCl₃) δ: 21.2 (-ve), 25.2, 26.4, 26.8, 28.0, 31.1, 37.5, 79.4 (-ve), 100.5, 145.3, 146.3, 151.3, 171.3.

IR (neat): 1741, 1631, 1371, 1245, 1029 cm⁻¹.

Exact mass calcd for C₁₃H₁₈O₂: 206.1307; found: 206.1301.
Anal. calcd for C$_{13}$H$_{18}$O$_2$: C 75.69, H 8.79; found: C 76.00, H 8.92.

Alternative Procedure for the preparation of 8-acetoxy-10-methylenebicyclo[5.3.0]-dec-1(7)-ene (321)

![321](image)

To a cold (0 °C), stirred solution of CuCl (0.124 g, 1.25 mmol) in dry DMF (4 mL) was added the bis(alkenyltrimethylstannane) 312 (0.130 g, 0.244 mmol) dropwise using a small bore cannula as a solution in dry DMF (1 mL). The solution turned orange immediately. After 15 minutes, the reaction mixture was treated with saturated aqueous NH$_4$Cl (1 mL), diluted with Et$_2$O (10 mL) and stirred open to the air for 15 minutes. The mixture was poured into an additional quantity of saturated aqueous NH$_4$Cl (10 mL) and the layers were separated. The aqueous phase was extracted with Et$_2$O (3 x 10 mL) and the combined organic extracts were washed with brine (2 x 10 mL), dried (MgSO$_4$), and concentrated. Purification of the crude product by short column chromatography (12 g TLC grade silica gel, 15:1 petroleum ether - Et$_2$O) and removal of trace amounts of solvent (vacuum pump) from the resulting liquid provided 0.033 g (66%) of 321 as a colorless oil. The spectral data for 321 were identical with those reported above.
## V. APPENDICES

### Appendix 1: X-Ray Crystallographic Data\(^{65}\)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formula</th>
<th>Formula Weight</th>
<th>Crystal Habit</th>
<th>Crystal System</th>
<th>Space Group</th>
<th>Lattice Parameters</th>
<th>Z Value</th>
<th>Dcalc (g/cm(^3))</th>
<th>Number of Reflections</th>
<th>Residuals R; Rw</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C(<em>{20})H(</em>{30})O(_{4})</td>
<td>334.45</td>
<td>Needle</td>
<td>Monoclinic</td>
<td>P2(_1)/n (#14)</td>
<td>a (Å) 6.189 (1)</td>
<td>b (Å) 9.608 (1)</td>
<td>c (Å) 31.190 (1)</td>
<td>α (°) 92.675 (10)</td>
<td>4048</td>
</tr>
<tr>
<td></td>
<td>C(<em>{16})H(</em>{24})O(_{3})</td>
<td>264.36</td>
<td>Prism</td>
<td>Triclinic</td>
<td>P(\overline{1}) (#2)</td>
<td>a (Å) 10.618 (1)</td>
<td>b (Å) 11.350 (1)</td>
<td>c (Å) 6.2220 (7)</td>
<td>α (°) 91.23</td>
<td>3330</td>
</tr>
</tbody>
</table>

\(^{65}\) Reference number or citation for the crystallographic data.
Appendix 2: Additional Experimental Procedures

The following compounds were prepared by other members of the Piers research group in connection with ongoing synthetic studies. These procedures and spectral data, thus far, have not been reported elsewhere and are included here only for completeness of the experimental details presented in this thesis.

Preparation of (Z)-6-chloro-3-(trimethylstannyl)hex-2-enal (291)\textsuperscript{205}

\[
\begin{align*}
\text{Cl} & \quad \text{Me}_3\text{Sn} \\
& \quad \text{OH} \\
\text{Me}_3\text{Sn} & \quad \text{CHO}
\end{align*}
\]

To a cold (-78 °C), stirred solution of freshly distilled methyl (Z)-6-chloro-3-(trimethylstannyl)hex-2-enoate (264)\textsuperscript{206} (2.02 g, 6.20 mmol) in dry THF (70 mL) was added DIBAL-H (1.0 M in hexanes, 18.6 mL, 18.6 mmol). After 45 minutes, the reaction mixture was warmed to room temperature and stirred for an additional 50 minutes. Saturated aqueous NH\textsubscript{4}Cl (6 mL) was added and the white slurry was stirred at room temperature for 30 minutes. Solid MgSO\textsubscript{4} (~1 g) was added and the mixture was stirred for an additional 30 minutes. The mixture was diluted with Et\textsubscript{2}O (~250 mL) and filtered through Florisil\textsuperscript{®} (20 g). The column was washed with Et\textsubscript{2}O (~80 mL). The combined eluate was concentrated under reduced pressure to yield the allylic alcohol 328, a colorless oil, which was used without further purification.

To a cold (0 °C), stirred solution of the crude allylic alcohol 328 in CH\textsubscript{2}Cl\textsubscript{2} (16 mL) was added sequentially 3 Å molecular sieves (3.67 g), NMO (1.16 g, 9.92 mmol), and TPAP (0.319 g, 0.907 mmol). The solution turned green-black immediately. After 30 minutes, the reaction mixture was warmed to room temperature for 60 minutes. The mixture was filtered through silica gel and the cake was washed with Et\textsubscript{2}O (~400 mL).
The solvent was removed from the filtrate under reduced pressure and the oil thus obtained was distilled bulb-to-bulb (120-132 °C/0.1 Torr) to yield 1.356 g (75% from the ester 264) of (Z)-6-chloro-3-(trimethylstannyl)hex-2-enal (291) as a colorless oil.

\[\begin{array}{l}
^1H \text{ nmr (400 MHz, CDCl}_3) \delta: 0.25 (s, 9H, -SnMe}_3, J_\text{Sn-H} = 54 \text{ Hz}, 1.84-1.91 (m, 2H, Cl-CH}_2-\text{CH}_2-\text{CH}_2-), 2.63 (td, 2H, Cl-CH}_2-\text{CH}_2-\text{CH}_2-), J = 7.5, 1.5 \text{ Hz, } J_\text{Sn-H} = 44 \text{ Hz}, 3.51 (t, 2H, Cl-CH}_2-\text{CH}_2-\text{CH}_2-), J = 7.5 \text{ Hz}, 6.69 (dt, 1H, olefinic proton, } J = 5, 1.5 \text{ Hz, } J_\text{Sn-H} = 116 \text{ Hz}, 9.57 (d, 1H, -CHO, } J = 5 \text{ Hz, } J_\text{Sn-H} = 5 \text{ Hz}. \\
^{13}C \text{ nmr (75.3 MHz, CDCl}_3) \delta: -7.4 (-ve), 31.5, 37.8, 43.9, 139.2 (-ve), 179.4, 192.3 (-ve). \\
\end{array}\]

IR (neat): 2746, 1679, 1563, 779, 532 cm\(^{-1}\).

Exact mass calcd for C\(_8\)H\(_{14}\)O\(^{35}\)Cl\(^{120}\)Sn (M\(^+\) - Me): 280.9755; found: 280.9757.

Anal. calcd for C\(_9\)H\(_{17}\)OClSn: C 36.60, H 5.80; found: C 36.78, H 5.72.

Preparation of 1-(tert-butyldimethylsilyl)hepta-1,6-diyne (297)\(^{207}\)

\[\begin{array}{c}
\text{TBS} \\
297
\end{array}\]

To a cold (-78 °C), stirred solution of hepta-1,6-diyne (298) (2.70 mL, 2.17 g, 23.6 mmol) in dry THF (100 mL) was added a solution of MeLi (1.56 M in Et\(_2\)O, 20.0 mL, 31.2 mmol). After 10 minutes, the reaction mixture was warmed to -20 °C and
stirred for 60 minutes. \textit{tert}-Butyldimethylsilyl chloride (4.95 g, 32.8 mmol) was added in one portion, as a solid, and the resultant solution was stirred at -20 °C for 15 minutes and then warmed to room temperature for 60 minutes. Saturated aqueous NaHCO$_3$ (50 mL) was added and the phases were separated. The aqueous phase was extracted with Et$_2$O (3 x 50 mL) and the combined organic extracts were washed once with brine (50 mL), dried (MgSO$_4$), and concentrated. Purification of the crude product by flash chromatography (150 g silica gel, petroleum ether), followed by bulb-to-bulb distillation (50 °C/0.1 Torr) of the acquired liquid, provided 4.07 g (83%) of 1-(\textit{tert}-butyl-dimethylsilyl)hepta-1,6-diyne (297) as a colorless oil.

$^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.06 (s, 6H, -SiMe$_2$-), 0.90 (s, 9H, -SiBu-), 1.69-1.76 (m, 2H, -CH$_2$-CH$_2$-CH$_2$-), 1.93 (t, 1H, -C≡C-H, $J = 2.5$ Hz), 2.29 (td, 2H, -CH$_2$-C≡C-H, $J = 7$, 2.5 Hz), 2.34 (t, 2H, TBS-C≡C-CH$_2$-, $J = 7$ Hz).

$^{13}$C nmr (125.8 MHz, CDCl$_3$) $\delta$: -4.5 (-ve), 16.5, 17.5, 18.9, 26.1 (-ve), 27.7, 68.7, 83.4, 83.5, 106.6.

IR (neat): 3313, 2175, 1251, 839, 776 cm$^{-1}$.

Exact mass calcd for C$_{13}$H$_{22}$Si: 206.1491; found: 206.1495.

Anal. calcd for C$_{13}$H$_{22}$Si: C 75.65, H 10.74; found: C 75.58, H 10.71.
Preparation of ethyl 8-\((\text{tert-butyldimethylsilyl})\text{octa-2,7-diynato}\) (295)

\[
\text{TBS} \quad \equiv \quad \equiv \quad \text{CO}_2\text{Et}
\]

To a cold (-78 °C), stirred solution of 1-\((\text{tert-butyldimethylsilyl})\text{hepta-1,6-diynie}\) (297) (3.67 g, 17.8 mmol) in dry THF (220 mL) was added a solution of MeLi (1.47 M in Et\(_2\)O, 13.0 mL, 19.1 mmol). After 15 minutes, the reaction mixture was warmed to -20 °C and stirred for 60 minutes. Ethyl chloroformate (1.90 mL, 21.5 mmol) was added, by syringe, and the resultant mixture was stirred at -20 °C for 60 minutes, then warmed to room temperature for an additional 60 minutes. Saturated aqueous NaHCO\(_3\) (200 mL) was added and the phases were separated. The aqueous phase was extracted with Et\(_2\)O (2 x 200 mL) and the combined organic extracts were dried (MgSO\(_4\)), and concentrated. Purification of the crude product by flash chromatography (150 g silica gel, 19:1 petroleum ether - Et\(_2\)O), followed by bulb-to-bulb distillation (130 °C/0.1 Torr) of the acquired liquid, provided 2.75 g (55%) of ethyl 8-\((\text{tert-butyldimethylsilyl})\text{octa-2,7-diynato}\) (295) as a colorless oil.

\(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 0.06 \(\text{(s, 6H, -SiMe}_2\)\(-)}, 0.90 \(\text{(s, 9H, -SiBu}_3\)\(-)}, 1.28 \(\text{(t, 3H, -CO}_2\text{CH}_2\text{CH}_3, J = 7 \text{Hz})\), 1.74-1.81 \(\text{(m, 2H, -CH}_2\text{-CH}_2\text{-CH}_2\)\(-)}, 2.34 \(\text{(t, 2H, J = 7 \text{Hz})\), 2.45 \(\text{(t, 2H, J = 7 \text{Hz})\), 4.20 \(\text{(q, 2H, -CO}_2\text{CH}_2\text{CH}_3, J = 7 \text{Hz})\).

\(^1\)C nmr (75.3 MHz, CDCl\(_3\)) \(\delta\): -4.6 \(\text{(-ve), 14.0 \text{(-ve), 16.4, 17.6, 19.0, 26.0 \text{(-ve), 26.7, 61.8, 73.5, 83.9, 88.1, 105.8, 153.6.}}\)

IR (neat): 2239, 2175, 1713, 1472, 1251, 839, 776 cm\(^{-1}\).
Exact mass calcd for C₁₅H₂₃O₂Si (M⁺ - Me): 263.1467; found: 263.1463.

Anal. calcd for C₁₆H₂₆O₂Si: C 69.01, H 9.41; found: C 69.04, H 9.60.

Preparation of ethyl (Z) 8-tert-butyldimethylsilyl-3-(trimethylstannyl)oct-2-en-7-ynoate (293)

To a cold (-48 °C), stirred solution of hexamethylditin (3.27 g, 9.97 mmol) in dry THF (45 mL) was added a solution of MeLi (1.56 M in Et₂O, 6.30 mL, 9.83 mmol). After the pale yellow solution of (trimethylstannyl)lithium had been stirred for 20 minutes, solid CuCN (0.912 g, 10.2 mmol) was added in one portion. The mixture was stirred at -48 °C for 25 minutes to provide a pale yellow solution of lithium (trimethylstannyl)-(cyano)cuprate. To this solution was added, dropwise, a solution of ethyl 8-(tert-butyldimethylsilyl)octa-2,7-diynoate (295) (2.47 g, 8.88 mmol) in dry THF (5 mL). The mixture was stirred at -48 °C for 2 hours and at 0 °C for 2 hours. Aqueous NH₄Cl-NH₄OH (pH 8) (40 mL) was added and the mixture was warmed to room temperature and stirred open to the air until the aqueous phase became deep blue. The phases were separated and the aqueous phase was extracted with Et₂O (3 x 50 mL). The combined organic extracts were washed with brine (150 mL), dried (MgSO₄), and concentrated. Purification of the crude product by flash chromatography (200 g silica gel, 40:1 petroleum ether - Et₂O), followed by bulb-to-bulb distillation (150 °C/0.1 Torr) of the acquired liquid, provided 3.34 g (85%) of ethyl (Z) 8-tert-butyldimethylsilyl-3-(trimethylstannyl)oct-2-en-7-ynoate (293) as a colorless oil.
$^1$H nmr (400 MHz, CDCl₃) δ: 0.07 (s, 6H, -SiMe₂-), 0.16 (s, 9H, -SnMe₃, $^2$J$_{Sn-H}$ = 55 Hz), 0.91 (s, 9H, -SiBu-), 1.27 (t, 3H, -CO₂CH₂CH₃, $J = 7$ Hz), 1.55-1.62 (m, 2H, -CH₂-CH₂-CH₂-), 2.23 (t, 2H, TBS-C=C-CH₂-, $J = 7$ Hz), 2.53 (td, 2H, -CH₂-C(SnMe₃)=CH-, $J = 7.5$, 1 Hz, $^3$J$_{Sn-H}$ = 47 Hz), 4.16 (q, 2H, -CO₂CH₂CH₃, $J = 7$ Hz), 6.36 (br s, 1H, olefinic proton, $^3$J$_{Sn-H}$ = 118 Hz).

$^{13}$C nmr (75.3 MHz, CDCl₃) δ: -7.4 (-ve), -4.4 (-ve), 14.3 (-ve), 16.5, 19.3, 26.1 (-ve), 27.9, 38.7, 60.4, 83.4, 107.0, 128.6 (-ve), 167.9, 174.5.

IR (neat): 2174, 1703, 1600, 1251, 924, 838, 775, 534 cm$^{-1}$.

Exact mass calcd for C$_{18}$H$_{33}$O$_2$Si$^{120}$Sn (M$^+$ - Me): 429.1272; found: 429.1269.

Anal. calcd for C$_{19}$H$_{36}$O$_2$SiSn: C 51.48, H 8.19; found: C 51.49, H 8.38.

**Preparation of (Z) 8-tert-butyldimethylsilyl-3-(trimethylstannyl)oct-2-en-7-ynal (292)**

To a cold (-78 °C), stirred solution of freshly distilled ethyl (Z) 8-tert-butyldimethylsilyl-3-(trimethylstannyl)oct-2-en-7-ynoate (293) (2.97 g, 6.70 mmol) in dry THF (70 mL) was added DIBAL-H (1.0 M in hexanes, 27.0 mL, 27.0 mmol). After 45 minutes, the reaction mixture was warmed to room temperature and stirred for an additional 60 minutes. Saturated aqueous NH₄Cl (10 mL) was added and the white slurry was stirred at room
temperature for 30 minutes. Solid MgSO\(_4\) (~2 g) was added and the mixture was stirred for an additional 30 minutes. The mixture was diluted with Et\(_2\)O (~300 mL) and filtered through Florisil\(^\text{®}\) (30 g). The column was washed with Et\(_2\)O (~100 mL). The combined eluate was concentrated under reduced pressure to yield the allylic alcohol 329, a colorless oil, which was used without further purification.

To a cold (0 °C), stirred solution of the crude allylic alcohol 329 in CH\(_2\)Cl\(_2\) (18 mL) was added sequentially 3 Å molecular sieves (3.55 g), NMO (1.36 g, 11.6 mmol), and TPAP (0.275 g, 0.780 mmol). The solution turned green-black immediately. After 30 minutes, the reaction mixture was warmed to room temperature for 90 minutes. The mixture was filtered through silica gel (30 g) and the cake was washed with Et\(_2\)O (400 mL). The solvent was removed from the filtrate under reduced pressure. Purification of the crude product by flash chromatography (80 g silica gel, 25:1 petroleum ether - Et\(_2\)O), followed by bulb-to-bulb distillation (140 °C/0.1 Torr) of the acquired liquid, provided 2.142 g (80% from the ester 293) of (Z) 8-tert-butyldimethylsilyl-3-(trimethylstannyl)oct-2-en-7-ynal (292) as a colorless oil.

\(^{1}\text{H}\) nmr (400 MHz, CDCl\(_3\)) \(\delta\): 0.06 (s, 6H, -SiMe\(_2\)-), 0.25 (s, 9H, -SnMe\(_3\)), \(^2\)J\(_{\text{Sn-H}}\) = 54 Hz), 0.90 (s, 9H, -SiBu\(_3\)-), 1.56-1.64 (m, 2H, -CH\(_2\)-CH\(_2\)-CH\(_2\)-), 2.25 (t, 2H, TBS-C≡CH\(_2\)-, \(\text{J} = 7\) Hz), 2.59 (td, 2H, -CH\(_2\)-C(SnMe\(_3\))=CH-, \(\text{J} = 7.5, 1.5\) Hz, \(^3\)J\(_{\text{Sn-H}}\) = 44 Hz), 6.65 (dt, 1H, olefinic proton, \(\text{J} = 5.5, 1.5\) Hz, \(^3\)J\(_{\text{Sn-H}}\) = 115 Hz), 9.56 (d, 1H, -CHO, \(\text{J} = 5.5\) Hz, \(^4\)J\(_{\text{Sn-H}}\) = 5 Hz).

\(^{13}\text{C}\) nmr (75.3 MHz, CDCl\(_3\)) \(\delta\): -7.4 (-ve), -4.5 (-ve), 16.5, 19.3, 26.1 (-ve), 27.6, 39.8, 83.7, 106.6, 139.1 (-ve), 180.7, 192.6 (-ve).

IR (neat): 2744, 2174, 1685, 1564, 1251, 924, 838, 776, 533 cm\(^{-1}\).
Exact mass calcd for $\text{C}_{16}\text{H}_{29}\text{OSi}^{120}\text{Sn} (\text{M}^+ - \text{Me})$: 385.1010; found: 385.1010.

Anal. calcd for $\text{C}_{17}\text{H}_{32}\text{OSiSn}$: C 51.15, H 8.08; found: C 51.37, H 8.06.
VI. REFERENCES AND FOOTNOTES


4. For examples of the uses of bifunctional reagents in organic synthesis, see:


19. (a) Hanson, J. R. *Natural Products Reports* 1996, 227.
   (b) Zeelen, F. J. *Natural Products Reports* 1994, 607.
   (c) Cerny, V. *Natural Products Reports* 1994, 419.
   (d) Hanson, J. R. *Natural Products Reports* 1993, 313.

20. For examples of methods used to prepare the bicyclo[4.3.0]nonane ring system, see:
   (d) Thebtaranonth, C; Thebtaranonth, Y. *Tetrahedron* 1990, 46, 1385.


26. For an excellent recent report on a method of preparing trans-fused bicyclic systems and a comprehensive list of references regarding earlier work in this general area, see: Reference 20(a).

27. (a) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* 1988, 21, 47.

28. (a) See Reference 12.


32. \(\alpha,\beta\)-Unsaturated esters are reported to be less reactive than the corresponding aldehydes or ketones towards organocopper(I) reagents. For a discussion of the relative reactivities of substrates in organocopper(I) reactions, see: Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980; Chapter 1.


39. For the use of trimethylsilyl bromide as an additive in conjugate addition reactions see:


42. Taylor, R. J. K. *Synthesis* 1985, 364.

44. Direct hydrolysis of the reaction mixture from the conjugate addition reaction of cuprates to α,β-unsaturated aldehydes is believed to promote aldol reactions and, in some circumstances, decarbonylation. For examples and mechanistic considerations, see:
   (f) See Reference 43.


51. (a) We wish to thank Bill Goldring of the University of British Columbia for carrying out a molecular modelling study using the MACROMODEL 4.5 program (© Columbia University, 1986-94) and the MM3* Force Field. There was an energy difference of 1.2 kcal/mol between the epimers of 80 which corresponds to an ~7.4:1 product ratio. In the modelling exercise, silicon was substituted for germanium.


65. We thank Dr. Steven J. Rettig (of the X-ray Crystallographic Laboratory in the Department of Chemistry at UBC) for performing the X-ray structure determinations. All X-ray structure determinations were performed on racemic materials.


73. See Reference 41, pp 169-198.


80. For examples, see:


86. (a) Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC: Boca Raton, 1996; Chapter 5.
   (c) Yamamoto, Y.; Asao, N. *Chem. Rev.* 1993, 93, 2207.


91. Pure stoichiometric organocopper(I) reagents (RCu) are reported to be less reactive than the corresponding cuprate species (R₂CuLi). For a discussion of the relative reactivities of organocopper reagents, see:
(a) See Reference 71, pp 11-13.
(b) See Reference 72, pp 1-3.

92. For some examples of the conjugate addition of simple allyl groups to enones, see:
(a) Ref. 39(a).
(b) See Reference 80.
(c) See Reference 81.
(d) See Reference 82.
(e) See Reference 84.


(b) See Reference 74.


(b) Colvin, R. E. Silicon In Organic Synthesis; Krieger: Malabar, FL, 1985; Chapter 3.


(b) Benkeser, R. A. Synthesis 1971, 347.


(b) For the use of AgNO₃ impregnated silica gel in a chromatographic separation of isomeric alkenes, see Reference 13.


(b) Westmijze, H.; Vermeer, P. Synthesis 1979, 390.


119. Lipshutz reported that the addition of allylcopper to 4-isopropylcyclohex-2-enone was completely stereoselective providing exclusively trans-3-allyl-4-isopropylcyclohexanone; see Reference 82.

(b) See Reference 118.  

122. Lipshutz reported that the addition of methallylcopper(I) to (R)-(–)-carvone provided a 95:5 mixture of *trans-cis* isomers, epimeric at C-2 (60:40 and 53:47, respectively); see Reference 82.

(d) See Reference 71.  
(e) See Reference 74.  
(f) See Reference 83.  
(g) See Reference 85.  
(h) See Reference 90(a).

124. Although pure copper(I) iodide is reported to be a white powder, all attempts to recrystallize commercially available CuI resulted in the isolation of a greyish powder.


132. For examples of naturally occurring compounds and derivatives containing the *trans*-fused bicyclo[3.3.0] ring system, see:  
133. For reviews of cyclopentaannulations, see:
   (b) Ramaiah, M. Synthesis 1984, 529.
   (c) See Reference 130.
   (d) See Reference 131.


150. The stereoselective addition of the organocopper(I) reagent 182 to the α,β-unsaturated aldehyde 71 was based on the precedent stereoselective addition of the cyanocuprate 35 to the enal 71 (see Chapter 1).

151. (a) For halodegermylation studies, see Reference 52.
     (b) For similar iododesilylation reactions of alkenyltrimethylsilanes using NIS, see Reference 60.
     (c) For similar iododestannylation reactions of alkenyltrimethylstannanes using NIS, see Reference 61.


     (b) Piers, E.; Coish, P. D. Synthesis 1995, 47.

155. See Reference 104(b), pp 10-12.


(c) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73.


173. For other examples of copper(I) promoted coupling reactions see:


180. For a review of intramolecular coordination in organotin chemistry, see


183. Unpublished results from Dr. Piers' research group at the University of British Columbia.

184. See Reference 50, pp 758-762.

185. For examples of typical reactions of cyclopentadienes, see:

186. (a) Ref. 52.
     (b) See Reference 126, pp 136-140.

187. (a) Ref. 38.
     (b) See Reference 126, pp 151-160.


197. Pelletier, S. W. Chemistry and Industry 1953, 1034.


(Z)-6-Chloro-3-(trimethylstannyl)hex-2-enal (291) was generously supplied by Dr. P. L. Gladstone (of Dr. Piers' research group at UBC). For the experimental procedure used to prepare 291, refer to appendix 2.

(a) See Reference 176.
(b) Mr. James G. K. Yee (of Dr. Piers' research group at UBC) is gratefully acknowledged for this preparation of this compound (287).

(Z)-8-tert-Butyldimethylsilyl-3-(trimethylstannyl)oct-2-en-7-ynal (292) was generously supplied by Mr. James G. K. Yee (of Dr. Piers' research group at UBC). For the experimental procedure used to prepare 292, refer to appendix 2.

(a) See Reference 178.
(b) 1-Hydroxymethyl-2-(trimethylstannyl)cyclopentene (280) was generously supplied by Dr. M. A. Romero (of Dr. Piers' research group at UBC), and was converted to 2-(trimethylstannyl)cyclopent-1-ene-carbaldehyde (276) via TPAP oxidation.

(a) See Reference 178.
(b) Ethyl 2-(trimethylstannyl)cyclohex-1-ene-carboxylate (279) was generously supplied by Dr. P. L. Gladstone (of Dr. Piers' research group at UBC), and was converted to 2-(trimethylstannyl)cyclohex-1-ene-carbaldehyde (277) via DIBAL-H reduction followed by TPAP oxidation.

Dr. P. L. Gladstone (of Dr. Piers' research group at UBC) is gratefully acknowledged for this preparation.

Methyl (Z)-6-chloro-3-(trimethylstannyl)hex-2-enoate (264) was generously supplied by Mr. Todd Schindeler (of Dr. Piers' research group at UBC).

Mr. James G. K. Yee (of Dr. Piers' research group at UBC) is gratefully acknowledged for this preparation.