THERMAL REARRANGEMENT OF FUNCTIONALIZED
6-EXO-(1-ALKENYL)BICYCLO[3.1.0]HEX-2-ENES.
APPLICATION TO THE TOTAL SYNTHESIS OF
(+)-SINULARENE

by

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B.Sc., University of British Columbia, 1980

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
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THE FACULTY OF GRADUATE STUDIES
(DEPARTMENT OF CHEMISTRY)

We accept this thesis as conforming
to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA
June 1985
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Date Aug. 12, 1985
This thesis describes firstly, a study involving the thermal rearrangement of substituted 6-exo-(1-alkenyl)bicyclo-[3.1.0]hexenes, and secondly, the application of this type of transformation to a total synthesis of (+)-sinularene (125).

The 6-exo-(1-alkenyl)bicyclo[3.1.0]hexenes (187, 189, 192, 194, 240, 274 and 340) were prepared and thermolyzed in sealed tubes to afford the corresponding bicyclo[3.2.1]octa-2,6-dienes (188, 190, 193, 195, 241, 276 and 341) in generally excellent yields. With the exception of 190, the thermolysis products were subjected to acid-catalyzed hydrolysis to give the respective bicyclo[3.2.1]octenones. From this study, it is clear that a) the Cope rearrangement of substrates, such as 274 and 340, containing even sterically bulky substituents on the 6-alkenyl side chain presents a viable means of generating functionalized bicyclo[3.2.1]octa-2,6-dienes, b) this methodology provides for the placement of synthetically useful functionalities on any of the carbon bridges of the bicyclo-[3.2.1]octane skeleton, and c) the transformations 240→241 and 274→276 provide strong evidence for the stereospecificity of the rearrangement process.

In the total synthesis of (+)-sinularene (125), the key step involved the thermal rearrangement of 322 to afford the bicyclo[3.2.1]octadiene 321. The compound 322 was readily prepared as follows. 1-Lithio-3-methyl-1-butyn was treated with methacrolein to furnish the allylic alcohol 331, which
was transformed into the ester 332 via an orthoester Claisen rearrangement (hot triethyl orthoacetate, propionic acid). Hydrolysis of the ester 332, followed by reaction of the resultant acid with oxalyl chloride in refluxing hexane gave the corresponding acid chloride 334. Treatment of 334 with a cold, ethereal solution of diazomethane afforded the diazo ketone 335, which in the presence of copper (II) acetoacetate in refluxing benzene, underwent an intramolecular carbenoid cyclization to furnish the bicyclic ketone 336. Semihydrogenation of 336 using Lindlar's catalyst gave stereoselectively the cis-alkenyl ketone 337. The enone 338 was obtained by oxidizing the trimethylsilyl enol ether of 337 using palladium (II) acetate in acetonitrile. When the enone 338 was treated with lithium divinylcuprate, the two epimeric products 339 and 346 were obtained in a ratio of 9:1, respectively, and were subsequently separated by column chromatography. Trapping the lithium enolate of 339 with t-butyldimethylsilyl chloride led to the required enol ether 322. Thermolysis (220°C, sealed tube) of 322 in benzene produced exclusively in 86% yield the desired bicyclic triene 321. Subjection of 321 to hydroboration using disiamylborane gave, after oxidative workup, the alcohol 347, which on treatment with p-toluenesulfonyl chloride in the presence of 4-dimethylaminopyridine, afforded the ketone 349. Successive hydrogenation of 349 and Wittig olefination of the resultant ketone 280 completed the total synthesis of (+)-sinularene (125).
TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE PAGE</td>
<td>i</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>ii</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>v</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>vii</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>viii</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>x</td>
</tr>
<tr>
<td>ABBREVIATIONS</td>
<td>xi</td>
</tr>
<tr>
<td>CHAPTER I: THERMAL REARRANGEMENTS OF 6-ALKENYL-BICYCLO[3.1.0]HEX-2-ENES</td>
<td>1</td>
</tr>
<tr>
<td>1.1 Introduction</td>
<td>1</td>
</tr>
<tr>
<td>1.1.1 Previous Work on the Cope Rearrangements of cis-1,2-Divinylcyclopropanes</td>
<td>1</td>
</tr>
<tr>
<td>1.1.2 The Application of Divinylcyclopropane Rearrangements in Synthesis</td>
<td>15</td>
</tr>
<tr>
<td>1.1.3 Previous Work on the Cope Rearrangements of 6-Alkenylbicyclo[3.1.0]-hex-2-enes</td>
<td>26</td>
</tr>
<tr>
<td>1.1.4 The Problem</td>
<td>34</td>
</tr>
<tr>
<td>1.1.5 Methods for the Assembly of Bicyclo[3.1.0]hexanones</td>
<td>36</td>
</tr>
<tr>
<td>1.2 Discussion</td>
<td>50</td>
</tr>
<tr>
<td>1.2.1 The Synthesis and Rearrangement of 2-(tert-Butyldimethylsiloxy)-6-exo-vinylbicyclo[3.1.0]hex-2-ene (187)</td>
<td>50</td>
</tr>
<tr>
<td>1.2.2 The Synthesis and Rearrangement of 6-exo-Vinylbicyclo[3.1.0]hex-3-en-2-one (189) and C-4 Function-alized 6-exo-Vinylbicyclo[3.1.0]-hex-2-enes 192 and 194</td>
<td>60</td>
</tr>
</tbody>
</table>
1.2.3 The Synthesis and Rearrangement of 6-exo-[(E)- and (Z)-1-alkenyl]-bicyclo[3.1.0]hex-2-enes (240) and (274) .................................................. 95

1.2.4 Conclusion .................................................. 138

CHAPTER II: THE TOTAL SYNTHESIS OF (+)-SINULARENE .................. 139

2.1 Introduction .................................................. 139

2.1.1 The Isolation and Characterization of (-)-Sinularene .................. 139

2.1.2 Previous Syntheses of Sinularene .......................... 141

2.2 Discussion .................................................. 150

2.2.1 The Synthetic Plan ........................................ 150

CHAPTER III: EXPERIMENTAL ........................................ 196

3.1 General .................................................. 196

3.2 Solvents and Reagents ....................................... 198

3.3 Model Studies ............................................... 201

3.4 The Total Synthesis of (+)-Sinularene .......................... 258

BIBLIOGRAPHY .................................................. 286
### LIST OF TABLES

<table>
<thead>
<tr>
<th>TABLE I:  $^1H$ nmr Spectral Data for Compounds 278 and 279</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>134</td>
</tr>
<tr>
<td>TABLE II. $^1H$ nmr Spectral Data for Compounds 276 and 341</td>
<td>168</td>
</tr>
<tr>
<td>TABLE III. Drying Agents Used for Solvents and Reagents</td>
<td>199</td>
</tr>
</tbody>
</table>
# LIST OF FIGURES

<table>
<thead>
<tr>
<th>FIGURE</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIGURE 1.</td>
<td>$^1$H nmr spectrum assignments for the vinylcyclopropane moiety of ketone</td>
<td>52</td>
</tr>
<tr>
<td>FIGURE 2.</td>
<td>The homonuclear spin decoupling experiment with $189$</td>
<td>69</td>
</tr>
<tr>
<td>FIGURE 3.</td>
<td>The 400 MHz $^1$H nmr spectrum of $190$</td>
<td>71</td>
</tr>
<tr>
<td>FIGURE 4.</td>
<td>The homonuclear spin decoupling experiment with $190$</td>
<td>73</td>
</tr>
<tr>
<td>FIGURE 5.</td>
<td>The 400 MHz $^1$H nmr spectrum of $237$</td>
<td>78</td>
</tr>
<tr>
<td>FIGURE 6.</td>
<td>The homonuclear spin decoupling experiment with $237$</td>
<td>80</td>
</tr>
<tr>
<td>FIGURE 7.</td>
<td>The 400 MHz $^1$H nmr spectrum of $192$</td>
<td>82</td>
</tr>
<tr>
<td>FIGURE 8.</td>
<td>The 400 MHz $^1$H nmr spectrum of $194$</td>
<td>85</td>
</tr>
<tr>
<td>FIGURE 9.</td>
<td>The homonuclear spin decoupling experiment with $194$</td>
<td>87</td>
</tr>
<tr>
<td>FIGURE 10.</td>
<td>The 400 MHz $^1$H nmr spectrum of $193$</td>
<td>89</td>
</tr>
<tr>
<td>FIGURE 11.</td>
<td>The 400 MHz $^1$H nmr spectrum of $238$</td>
<td>91</td>
</tr>
<tr>
<td>FIGURE 12.</td>
<td>The homonuclear spin decoupling experiment for $238$</td>
<td>93</td>
</tr>
<tr>
<td>FIGURE 13.</td>
<td>The 400 MHz $^1$H nmr spectrum of $258$</td>
<td>102</td>
</tr>
<tr>
<td>FIGURE 14.</td>
<td>The expanded region $\delta$ 5.6-6.3 of the $^1$H nmr spectrum of $259$</td>
<td>104</td>
</tr>
<tr>
<td>FIGURE 15.</td>
<td>The 400 MHz $^1$H nmr spectrum of $274$</td>
<td>121</td>
</tr>
<tr>
<td>FIGURE 16.</td>
<td>The homonuclear spin decoupling experiment with $241$</td>
<td>126</td>
</tr>
<tr>
<td>FIGURE 17.</td>
<td>The 400 MHz $^1$H nmr spectrum of $276$</td>
<td>128</td>
</tr>
<tr>
<td>FIGURE 18.</td>
<td>The homonuclear spin decoupling experiment with $276$</td>
<td>130</td>
</tr>
</tbody>
</table>
LIST OF FIGURES (CONT.'D)

<table>
<thead>
<tr>
<th>FIGURE</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIGURE 19</td>
<td>The 400 MHz $^1$H nmr spectrum of 278</td>
<td>132</td>
</tr>
<tr>
<td>FIGURE 20</td>
<td>The 400 MHz $^1$H nmr spectrum of 279</td>
<td>133</td>
</tr>
<tr>
<td>FIGURE 21</td>
<td>The homonuclear spin decoupling experiment with 278</td>
<td>136</td>
</tr>
<tr>
<td>FIGURE 22</td>
<td>The 400 MHz $^1$H nmr spectrum of 336</td>
<td>159</td>
</tr>
<tr>
<td>FIGURE 23</td>
<td>The 400 MHz $^1$H nmr spectrum of 340</td>
<td>163</td>
</tr>
<tr>
<td>FIGURE 24</td>
<td>The 400 MHz $^1$H nmr spectrum of 341</td>
<td>165</td>
</tr>
<tr>
<td>FIGURE 25</td>
<td>The homonuclear spin decoupling experiment with 341</td>
<td>167</td>
</tr>
<tr>
<td>FIGURE 26</td>
<td>The homonuclear spin decoupling experiment with 343</td>
<td>170</td>
</tr>
<tr>
<td>FIGURE 27</td>
<td>The 400 MHz $^1$H nmr spectrum of 339</td>
<td>176</td>
</tr>
<tr>
<td>FIGURE 28</td>
<td>The nuclear Overhauser enhancement experiment with 339</td>
<td>178</td>
</tr>
<tr>
<td>FIGURE 29</td>
<td>The 400 MHz $^1$H nmr spectrum of 346</td>
<td>180</td>
</tr>
<tr>
<td>FIGURE 30</td>
<td>The 400 MHz $^1$H nmr spectrum of 322</td>
<td>182</td>
</tr>
<tr>
<td>FIGURE 31</td>
<td>The 400 MHz $^1$H nmr spectrum of 321</td>
<td>184</td>
</tr>
<tr>
<td>FIGURE 32</td>
<td>The 400 MHz $^1$H nmr spectrum of 190</td>
<td>190</td>
</tr>
<tr>
<td>FIGURE 33</td>
<td>The 400 MHz $^1$H nmr spectrum of (+)-sinularene</td>
<td>192a</td>
</tr>
<tr>
<td>FIGURE 34</td>
<td>The 100.6 MHz $^{13}$C nmr spectrum of (+)-sinularene</td>
<td>192b</td>
</tr>
</tbody>
</table>
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# ABBREVIATIONS

The following abbreviations have been used throughout this thesis:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>acetylacetonate</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2'-azobisisobutyronitrile</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>mCPBA</td>
<td>meta-chloroperbenzoic acid</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>Dibal</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent(s)</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>glc</td>
<td>gas-liquid chromatography</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramidate</td>
</tr>
<tr>
<td>ir</td>
<td>infrared</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>nmr</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>r.t.</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>sia</td>
<td>siamyel</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
</tbody>
</table>
TMS = trimethylsilyl

tlc = thin-layer chromatography

Ts = para-toluenesulfonyl
TO MY PARENTS,
with affection, gratitude
and respect ...
1.1 Introduction

1.1.1 Previous Work on the Cope Rearrangements of cis-1,2-Divinylcyclopropanes

A well-documented* reaction of cis-1,2-divinylcyclopropane systems is the [3,3]-sigmatropic shift (Cope rearrangement), the facility of which is attributed to the accompanying

* It is not the intention nor is it within the scope of this thesis to provide an exhaustive review of the Cope rearrangement of cis-1,2-divinylcyclopropane systems. For review articles on the subject, the reader is referred to refs. 1-6. For a theoretical treatment of the Cope rearrangement, see refs. 7 and 8.
relief of strain in the cyclopropane ring and the favorable orbital overlap between the double bonds in the transition state.\(^6\) First reported\(^9\) about 25 years ago, cis-1,2-divinylcyclopropane (1) was noted for its extreme lability, as Vogel's attempts to synthesize and isolate this compound were thwarted. Under the conditions of the Hoffmann degradation of the quaternary ammonium hydroxide \(3^{5,10}\) and the elimination of the amine oxide \(4^{10}\) only 1,4-cycloheptadiene (2) was isolated. Doering and Roth\(^11\) obtained similar results; copper (I) chloride catalyzed cyclopropanation of cis-1,3,5-hexatriene at \(-45^\circ C\) (eq. [1]) furnished 1,4-cycloheptadiene rather than cis-1,2-divinylcyclopropane, presumably via intermediate formation of cis-1,2-divinylcyclopropane. Indeed, cis-1,2-divinylcyclopropane eluded isolation and characterization until 1973, when Brown and coworkers\(^12\) found that it rearranged quickly to 1,4-cycloheptadiene at temperatures above \(-20^\circ C\), with a half-life of 90 seconds at \(35^\circ C\). Since then, it has been characterized also, in the form of a complex \(5\), which is stable at ambient temperatures.\(^13\)

There are a number of compounds incorporating a cis-1,2-
divinylcyclopropane system which exhibit facile degenerate Cope rearrangements. This phenomenon gives rise to some interesting features in the temperature-dependent nmr spectra of systems such as bullvalene (6), barbaralane (7), and semibullvalene (8). While the nmr spectra recorded at low temperatures are consistent with the structures shown.

TABLE 1: Rate Constants for the Valence Tautomerization of Bullvalene, Barbaralane and Semibullvalene

<table>
<thead>
<tr>
<th>Compound</th>
<th>First-Order Rate Constant (/sec)</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>3440</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>1.73x10^6</td>
<td>25</td>
</tr>
<tr>
<td>8</td>
<td>2.2x10^5</td>
<td>103</td>
</tr>
</tbody>
</table>

* This type of rearrangement affords a product which is equivalent to the starting material.
(Table 1), those recorded at higher temperatures reveal the coalescence of signals, indicative of a rapid equilibrium between the tautomeric forms. In the case of semibullvalene, this interchange is observed even at -110°C, faster than any other system known to undergo the Cope rearrangement.\textsuperscript{16e}

Simpler, bicyclic derivatives of cis-1,2-divinylcyclopropanes, such as norcaradiene (9), homotropilidene (10) and 11, have been found to undergo thermal isomerizations also with remarkable ease. Doering and Knox\textsuperscript{17} reported that carbene addition to benzene (eq. [3]) led to the exclusive

\[
\begin{align*}
\text{benzene} & \quad \text{+} \quad \text{CH}_2^* \quad \rightarrow \quad \text{[3]} \\
 & \quad \rightarrow \quad \text{[3]} \\
[9] & \quad \rightarrow \quad [3]
\end{align*}
\]

\[
\begin{align*}
\text{10} & \quad \leftrightarrow \quad \text{[4]} \\
[4] & \quad \rightarrow \quad [4]
\end{align*}
\]

\[
\begin{align*}
\text{carbene} & \quad \text{addition,} \quad 20^\circ \text{C} \quad \rightarrow \quad \text{[5]} \\
[11] & \quad \rightarrow \quad [5]
\end{align*}
\]

\[
\begin{align*}
[11] & \quad \rightarrow \quad [12]
\end{align*}
\]
isolation of 1,3,5-cycloheptatriene, rather than norcaradiene. In fact, there is no evidence for the existence of norcaradiene even at $-150\,^\circ C$,\textsuperscript{18} although certain substituted norcaradienes have been isolated.\textsuperscript{19} Homotropilidene (10)$^4,12$ another example of a compound which undergoes the degenerate Cope rearrangement (eq. [4]), exhibits the rapid equilibration characteristic of bullvalene (6). Perhaps the simplest known example of a stable \textit{cis}-1,2-divinylcyclopropane, 11 was isolated and characterized by Baird and Reese,\textsuperscript{20} after its existence was speculated by Roth\textsuperscript{21} over 20 years ago. Roth isolated\textsuperscript{21} only the bicyclic nonadiene 12 after subjection of 1,3,5-cyclooctatriene to carbene addition (eq. [5]), and postulated that the Cope rearrangement of 11 to 12 had occurred rapidly at room temperature. However, Baird and Reese\textsuperscript{20} reported that 11, having a half-life of \textit{ca}. 1 day at 25$^\circ C$, isomerized to give 12 when heated for 1 hour at 60$^\circ C$.

Alkyl substitution at the terminal sites of the vinyl groups, particularly when this substitution is of \textit{cis} orientation, has been shown to have quite a dramatic influence on the rate of rearrangement of \textit{cis}-1,2-divinylcyclopropanes. For example, the \textit{cis},\textit{trans} derivative 13 rearranges at 15$^\circ C$ to give the cycloheptadiene 15 whereas the \textit{cis},\textit{cis} isomer 14 requires heating at 75$^\circ C$ to achieve the same transformation.\textsuperscript{22}

Just as striking are the relative rate differences found in the thermal isomerizations for the \textit{cis}-1,2-divinylcyclopropanes shown in Table 2.\textsuperscript{23} It is noteworthy that 18 with a single
cis methyl group substitution on the vinyl moiety rearranges considerably slower than 17, which has two methyl substituents both of trans orientation on the vinyl groups. Again, the marked contrast in rate of rearrangement is observed between cis- and trans- methyl substitution on a vinyl moiety in 18 and 16, respectively. In addition, the rearrangement rate of these systems appears to be affected in a very similar fashion by the presence of alkyl substituents of syn orientation (relative to vinyl moieties) on the cyclopropane ring. While the anti-9-methyl derivative 19 readily rearranges to 21 at room temperature,21 the syn-9-methyl isomer 20 requires

TABLE 2: Relative Rates of the Cope Rearrangement of cis-1,2-Dialkenylcyclopropanes

<table>
<thead>
<tr>
<th>Compound</th>
<th>k_{rel} (40°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5800</td>
</tr>
<tr>
<td>16</td>
<td>1500</td>
</tr>
<tr>
<td>17</td>
<td>1000</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
</tr>
</tbody>
</table>
heating at 150°C for its transformation into the epimeric product 22.24

These variations in reaction rates may be rationalized by examination of the transition state through which the cis-1,2-dialkenylcyclopropanes undergo the Cope rearrangement. Although two possible transition states can be envisaged as shown in Scheme 1, it is believed that these transformations proceed through a transition state having boat-like geometry (23b) during the course of a [3,3]-sigmatropic shift.25-27 A Cope rearrangement proceeding via a chair-like transition state (23a) would furnish the highly unstable trans,trans-cycloheptadiene 24, whereas the rearrangement involving a boat-like transition state (23b) would afford the relatively more stable cis,cis-cycloheptadiene 25. A comparison of the boat-like transition states 26 and 27 (eqs. [6] and [7]) to 23b reveals the destabilizing steric interactions which would account for the rearrangement rate differences between 16, 18 and cis-1,2-divinylcyclopropane. The [3,3]-sigmatropic rearrangement of 16 would proceed through a transition state (26), which suffers
mainly from a methyl-hydrogen interaction. In addition to this steric interaction, $27$ is further destabilized (relative to $23b$) by a steric repulsion of greater severity between the propenyl methyl and cis-cyclopropyl proton ('methyl-ring interaction'),* as reflected by the relatively slower transformation of $18$ to $32$. Intermediate to these two types of steric

* The deactivation energies ($\Delta\Delta G^+$) of the methyl-ring and methyl-hydrogen interactions have been approximated as 4.55 and 0.84 kcal/mol, respectively.**
repulsions is the methyl-methyl interaction* destabilizing 28 in the Cope rearrangement of 17 to 33 (eq. [8]). The relative ease of the conversion of 19 into 21 (eq. [9]), in contrast to the transformation of 20 into 22 (eq. [10]) may be rationalized by a similar argument. That is, one can envisage that the destabilization of 30 by the steric repulsion between the cis-cyclopropyl methyl and ring residue (−CH₂CH₂−) would necessitate harsher conditions for the rearrangement of 20 to 22.

* The $\Delta \Delta G^+$ value estimated for a methyl-methyl interaction is 1.03 kcal/mol.\textsuperscript{23}
There are cases where such steric interactions present in the transition state of the Cope rearrangement may be so severe that the cis-1,2-dialkenylcyclopropanes fail to undergo [3,3]-sigmatropic shifts and only equilibration between the cis and trans isomers (34 ⇄ 35, 36 ⇄ 37, 38 ⇄ 39) is observed even at elevated temperatures.26,27

Generally, the trans-1,2-divinylcyclopropanes exhibit greater thermal stability than their cis counterparts. Certainly this is the case with trans-1,2-divinylcyclopropane since it was isolated and characterized 13 years before its elusive cis isomer.9 However, the trans compound is known to rearrange at elevated temperatures (ca. 190°C) to afford 1,4-cycloheptadiene, either by epimerizing to the cis isomer (path a), which then suffers a rapid Cope rearrangement, or by way of a biradical species 40 which closes directly (path b) to give the cycloheptadiene (Scheme 2). While there is evidence that the pathway
leading to the transient formation of cis-1,2-divinylcyclopropane may involve one- or two-centre epimerizations,* the role of biradicals mechanistically is still a matter of discussion. Under thermolytic and photo-lytic conditions, there are indications that a biradical species is manifested in the intermediate formation of cis-1,2-divinylcyclopropane (path a), which then spontaneously undergoes the Cope rearrangement. However, there seems to be little evidence supporting the direct closure of a biradical intermediate (path b) to furnish cycloheptadiene.

The rearrangements of a number of trans-1,2-dialkenylcyclopropane systems have been studied. For example, 41 and 42 have been shown to isomerize cleanly to 33 and 43, respectively, upon subjection to a temperature of 178°C for 4.2 hours (eq. [14]). Similarly, the rearrangement products 46 and 47 were obtained by heating 44 and 45, respectively, at 200°C for 5 hours. It has been proposed that these transformations involve a one-centre epimerization to the corresponding cis-dialkenylcyclopropanes in the initial and rate-determining step, followed by a rapid [3,3]-sigmatropic rearrangement of the cis isomers to the observed cycloheptadienes. Particularly noteworthy is the highly stereospecific nature of these thermal rearrangements, in which geometrically isomeric trans-dialkenylcyclopropanes afford exclusively the

* Garin has shown that both modes of epimerization may be competing processes.
epimeric cycloheptadienes.

In fact, the first hint of the stereospecificity exhibited by the Cope rearrangement of these systems, appeared in the work connected to the isolation and study of naturally occurring trans-1,2-dialkenylcyclopropanes* (50 and 52) and cycloheptadienes (51 and 53) found in the brown algaes Dictyopteris\textsuperscript{48-51} and Ectocarpus siliculosus\textsuperscript{52}. Pettus and Moore\textsuperscript{49} investigated the possibility of dictyopterene A (50) and dictyopterene B (52) being the biogenetic precursors of dictyopterene C' (51)
and dictyopterene D' (53) respectively (eqs. [16] and [17]). Interestingly, they discovered that subjection of 50 and 52 to elevated temperatures led to the exclusive isolation of cycloheptadienes which were enantiomeric to 51 and 53. From these findings, they concluded that the formation of 51 and 53 via thermal in vivo rearrangement from trans-1,2-dialkenylcyclopropanes 50 and 52, respectively, was improbable. Another consideration which supported this conclusion is the high activation energy parameters of a thermal pathway. Since then, the plausibility of photochemical in vivo rearrangements of 50 and 52 has been demonstrated and has thus lent support to the role of biradicals in such transformations.

* Few examples of natural products incorporating the trans-1,2-dialkenylcyclopropane system are known. Ambrucitin (48), found in a soil-inhabiting bacteria Polyanthus cellulosum var. fulvum has been shown to exhibit both anti-fungal and antibiotic activity. As well, Epstein et al. have reported the isolation of rothrockene (49) from a species of sagebrush A. tridenta rothrockii.
The studies on these marine natural products soon spurred the interest of synthetic organic chemists and the Cope rearrangement of 1,2-divinylcyclopropanes gradually attracted attention in synthetic applications.

1.1.2 The Application of Divinylcyclopropane Rearrangements in Synthesis

Although the Cope rearrangement of divinylcyclopropane systems has much literature precedent, it saw only sporadic use in the syntheses of natural products in the first fifteen years or so after its discovery. Generally, such syntheses were directed at bridged arachidonic acid analogues and simple monocyclic cycloheptadienes isolated from marine sources. However, as the synthetic potential of divinylcyclopropane rearrangements received more recognition,
synthetic organic chemists began using this interesting transformation with increasing frequency.

In studies aimed at the synthesis of the diterpene plant-growth regulator, portulal (54), Marino and Ferro showed that the rearrangement of the 3-cyclopropyl unsaturated ester 55 to the functionalized cycloheptadiene 56 proceeded smoothly at 210°C and in excellent yield (92%).

Having proven the feasibility of this rearrangement in synthesis, investigators then sought to demonstrate the versatility of the thermal isomerization of increasingly complex divinylcyclopropanes.

In developing synthetic approaches to hydroazulene systems, Marino and Kaneko studied the rearrangement of the 6-cyclopropyl enone 57a to the cycloheptadiene 58a (Scheme 3). Under the conditions of the thermolysis, 58a was not actually isolated, but isomerized to the more stable enone 59 via a
SCHEME 3

[1,3]-hydrogen shift. Similarly, the cyclopropyl enone 57b was found to rearrange to the bicyclo[5.3.0]decadiene 58b at elevated temperatures. However, this methodology was not only lacking in stereoselectivity in the preparation of the key intermediates 57, but demonstrated limited flexibility in substitution patterns on the cyclopropane ring. For example, reaction of the enone sulfoxonium methylide 60a with acrolein led to a mixture of cyclopropyl aldehydes 61a. Subsequent subjection of 61a to carboethoxymethylenetriphenylphosphorane (62) furnished the mixture of dialkenylcyclopropanes 57a.

Later studies done independently by both Marino and Wender demonstrated the use of 1-lithio-2-vinylcyclopropane 63 in the assembly of β-cyclopropyl enones 64 and the thermal
isomerization of the latter substances to the bicyclo[5.3.0]-
decadienone 65 (Scheme 4). Extension of these studies to the

![Scheme 4]

R=Me or Et

\[ \begin{align*}
& \text{a: } R' = \text{CH} = \text{CH}_2, \ R'' = \text{H} \\
& \text{b: } R' = \text{H}, \ R'' = \text{CH} = \text{CH}_2
\end{align*} \]

preparation of functionalized cycloheptanes was exemplified by
Wender's synthesis 61 (Scheme 5) of (+)-karahanaenone (66).
The key intermediate 67 was prepared in three steps from iso-
butyraldehyde and a mixture of 1-lithio-2-methyl-2-vinylcyclo-
propanes 68, and rearranged on heating (ca. 165-175°C) to
afford 69. Subsequent deprotection of 69 provided
(+)-karahanaenone (66) in an overall yield of 54%.

Concurrent studies by Piers and Nagakura 62 investigated
the utilization of lithium phenylthio(2-vinylcyclopropyl)cuprate
70 in the preparation of β-(2-vinylcyclopropyl) enones 71 and
dienones 72 from β-iodo enones 73 (eq. [18]). These studies
SCHEME 5

\[
\text{Me} \quad \text{Li} \quad + \quad \text{Me} - \text{CHO} \quad \rightleftharpoons \quad \text{Me} \quad \text{OSiMe}_3
\]

\[
\text{68} \quad \text{67} \quad \text{66} \quad \text{69}
\]

\[
\text{O} \quad \text{R} \quad \rightleftharpoons \quad \text{O} \quad \text{R} \quad \text{[18]}
\]

\[
\text{73} \quad \text{71} \quad \text{72}
\]

\[
a: \quad n=1, \text{R}=\text{H} \\
b: \quad n=1, \text{R}=\text{Me} \\
c: \quad n=0, \text{R}=\text{H} \\
d: \quad n=0, \text{R}=\text{Me}
\]
led eventually to the highly stereoselective preparation of lithium phenylthio[2,2-dimethyl-cis-(and trans)-3-vinyl-cyclopropyl]cuprates (74 and 75, respectively), which were

**Scheme 6**

\[ \begin{align*}
73 & \xrightarrow{74} 76 \xrightarrow{69^\circ C} 78 \xrightarrow{110^\circ C} 79 \\
75 & \xrightarrow{145^\circ C} 80 + 77b \\
77 & \xrightarrow{220^\circ C} 80 + 81
\end{align*} \]
employed to prepare the 8-cyclopropyl enones 76 and 77 (Scheme 6). Where R=H, both 76 and 77 rearranged smoothly to give the bicyclic enone 79. However, where R=Me, 76 and 77 isomerized to give not only the expected Cope rearrangement product 80, but also the product 77b resulting from epimerization and 81, obtained through a [1,5]-hydrogen shift.

SCHEME 7

\[ a: \text{n}=0 \]
\[ b: \text{n}=1 \]

[a] (i) LDA, THF, -78°C (ii) Me\textsubscript{3}SiCl, Et\textsubscript{3}N  [b] 100-110°C

Reaction of a similar reagent, lithium phenylthio(2-cis-vinylcyclopropyl)cuprate (70a) with various cyclic acyl chlorides 82 provided an entry into spiro systems such as 83a and 83b (Scheme 7).\textsuperscript{65}

The complex cyclopropyl cuprate reagents 84a and 84b, stereoselectively prepared\textsuperscript{66} from the corresponding cyclopropyl bromides, found application in the synthesis of polycyclic systems. Thus, treatment of the 8-iodo enone 73a with the
cuprate 84 led to the isolation of the $\beta,\gamma$-unsaturated ketone 85, presumably formed from the thermal isomerization of the cis-divinylcyclopropane 86 under the reaction conditions (Scheme 8). Interestingly, a degree of stereospecificity was observed in the thermal (240°C) rearrangement of a 1:1
mixture of 87b and 87c (prepared from 89 and lithium propionate), which afforded a 1:1 mixture of the bicyclic enol ethers 88b and 88c (Scheme 9).67

The Cope rearrangement of divinylcyclopropanes continued to find application in the syntheses of naturally-occurring substances, as exemplified by the use of this methodology by Wender and coworkers68 in the synthesis of the pseudoguaianes (+)-damsinic acid (90) and (+)-confertin (91) as indicated in Scheme 10. Initially, efforts to convert the β-cyclopropyl enone 92a into the corresponding ring-fused cycloheptadiene 93 under thermal conditions encountered difficulties since
the desired 93 was obtained only as a minor product. At elevated temperatures approximating 140°C, 92a was found to isomerize predominantly via a [1,5]-sigmatropic hydrogen shift to afford the trienone 94. This obstacle was neatly overcome by simultaneous irradiation (>290 nm) and thermolysis (ca. 98°C) of 92a, resulting in a photo-induced equilibration between 92a and 92b, and the irreversible Cope rearrangement of the latter substance to the key intermediate 93. Subsequent elaboration of 93 furnished both of the pharmocologically interesting natural products 90 and 91.

SCHEME 11
Concurrent investigations by Piers and Ruediger\textsuperscript{69,70} demonstrated again the versatility of a synthetic strategy incorporating the thermal rearrangement of divinylcyclopropanes in the synthesis of racemic $\beta$-himachalene (95) as shown in Scheme 11. The lithium phenylthiobis(vinylcyclopropyl)cuprate, synthesized from acrolein in six steps, was allowed to react with 3-iodo-2-cyclohexen-1-one to afford the $\beta$-cyclopropyl enone 97. Subjection of the intermediate 97 to thermolysis in refluxing xylene provided the desired bicyclo-[5.4.0]undecadienone 98 exclusively, and subsequent appropriate synthetic manipulation of 98 led smoothly to (+)-$\beta$-himachalene (95).

More recently, Wender and coworkers,\textsuperscript{71} while developing a viable synthetic approach to highly functionalized tri- and tetracyclic diterpenes, have prepared and rearranged a complex divinylcyclopropane 99. Treatment of 99 with dilute acid at room temperature provided the tricyclic methoxy ketone 100, which constitutes the basic backbone of the tigliane, daphnane and ingenane families of natural products.
Given the various examples of synthetic strategies incorporating the Cope rearrangement of divinylcyclopropane systems, it would seem that the synthetic potential of this interesting transformation has been well demonstrated. In contrast, the thermal rearrangement of the 6-alkenylbicyclo-[3.1.0]hex-2-enes 101, a type of complex divinylcyclopropane, has attracted relatively little attention from a synthetic point of view, and will be discussed in the next section.

1.1.3 Previous Work on the Cope Rearrangements of 6-Alkenylbicyclo[3.1.0]hex-2-enes

In view of the considerable documentation available on the Cope rearrangement of divinylcyclopropanes, it is somewhat surprising to discover the relative paucity of literature precedents for thermal rearrangements of 6-alkenylbicyclo[3.1.0]-hexenes to the corresponding bicyclo[3.2.1]octadiene systems. Generally, the few studies done have been limited to systems which have very little substitution, and the simplest of these, 6-endo-vinylbicyclo[3.1.0]hex-2-ene (101a) was first reported by Cupas et al. 72 These investigators found that treatment of the bicyclic aldehyde 102 with methylenetriphenylphosphorane
(103) in refluxing THF did not allow isolation of the presumed intermediate 101a, but cleanly provided bicyclo[3.2.1]octa-2,6-diene (104). Milder conditions for the preparation of 101a were sought and in 1965, Brown isolated this dialkenylcyclopropane 101a from low temperature (ca. -15° to 0°C) Wittig conditions and reported its half-life of 1 day at 25°C. 73

In contrast, 6-exo-vinylbicyclo[3.1.0]hex-2-ene (101b) displays the stability typical of trans-divinylcyclopropanes at ambient temperatures and rearranges at 195°C to furnish the same compound 104. 28 Baldwin and Gilbert's investigations have shown 28 that this process proceeds by way of a one-centre epimerization at C-6, presumably to afford the intermediate 101a, which is rapidly transformed into 104 via a Cope
rearrangement.* Thus, both optically active 101a and 101b were thermally isomerized at different temperatures to give the same optically active compound 104, as outlined in Scheme 12. Had a two-centre (C-1 and C-5) epimerization process occurred exclusively, the enantiomer (+)-104 would have been expected.

As in the cases of simple divinylcyclopropanes, substitution seems to impart greater stability to the 6-alkenyl-bicyclo[3.1.0]hexenes. For example, the bicyclic diene 110, which could be stored at room temperature for months without any apparent change,75 exhibits a stability attributed to the repulsive steric interactions of the gem-dimethyl group and

* Klumpp and Schakel74 have recently shown that subjection of 105 to a temperature of 325°C resulted in the isolation of the Cope rearrangement product 107 and a trace of 109. However, the thermolysis of 107 at 500°C afforded exclusively 109, presumably via the biradical 108.
the cyclopropane ring in the boat-like transition state\textsuperscript{25-27} \textbf{111} (eq. [21]). However, at 350°C, \textbf{110} undergoes a [3,3]-

sigmatropic isomerization to afford \textbf{112} exclusively. As well, both methyl enol ethers \textbf{113} and \textbf{114} require elevated temperatures (ca. 220°C) to rearrange into the bicyclic ether \textbf{115}

\textbf{SCHEME 13}
(Scheme 13).\textsuperscript{76} In fact, \textbf{113} does not rearrange to \textbf{115} at a lower temperature, but instead undergoes a geometrical isomerization to yield \textbf{114}. This behaviour, contrasted with the relatively facile rearrangement of 6-endo-(2-trans-methoxy-vinyl)bicyclo[3.1.0]hex-2-ene (\textbf{116}) to \textbf{117}, is ascribed to the severe steric interaction between the cis-methoxy group and the ring methylene in the transition state \textbf{118}. Notably, these transformations (\textbf{113} $\rightarrow \textbf{115}$ and \textbf{116} $\rightarrow \textbf{117}$) also constitute an example of the stereospecificity with which the 6-alkenylbicyclo[3.1.0]hex-2-enes undergo [3,3]-sigmatropic isomerizations.

\textbf{SCHEME 14}

\[\begin{align*}
\textbf{120} & \quad \text{CHO} \\
\textbf{119} & \quad \text{R}_1 \quad \text{R}_2 \quad \text{R}_3 \\
\textbf{121} & \quad \text{R}_1 \quad \text{R}_2 \quad \text{R}_3
\end{align*}\]

\begin{align*}
\text{a:} & \quad \text{R}_1 = \text{R}_2 = \text{H}, \text{R}_3 = \text{CO}_2\text{Me} \\
\text{b:} & \quad \text{R}_1 = \text{R}_3 = \text{H}, \text{R}_2 = \text{CO}_2\text{Me} \\
\text{c:} & \quad \text{R}_1 = \text{OBu}^T, \text{R}_2 = \text{CO}_2\text{H}, \text{R}_3 = \text{H} \\
\text{d:} & \quad \text{R}_1 = \text{OBu}^T, \text{R}_2 = \text{H}, \text{R}_3 = \text{CO}_2\text{H}
\end{align*}

A later study conducted by Cantello and coworkers\textsuperscript{77} gives further testimony to the highly stereospecific nature of these transformations. Thus, both \textbf{119a} and \textbf{119b}, prepared from \textbf{120} under Wittig conditions, rearranged smoothly to the bicyclo-
[3.2.1]octadienes 121a and 121b, respectively (Scheme 14).

Interestingly, investigations regarding the Cope rearrangement of substituted 6-alkenylbicyclo[3.1.0]hex-2-enes have been conspicuously lacking, and the study conducted by Klumpp et al.\textsuperscript{78} constitutes one of the few in this area. Thus, the preparation and rearrangement of systems such as 119c and 119d provide an entry into bicyclo[3.2.1]octadienes substituted at C-4 and C-8. Unfortunately, this case presents a poor example of the stereospecificity of these thermal isomerizations since a mixture of the trans and cis carboxylic acids 119c and 119d, respectively, obtained from a Knoevenagel condensation of the bicyclic aldehyde 120 and malonic acid, was rearranged to afford a mixture of 121c and 121d.

Our own interest in the [3,3]-sigmatropic rearrangement of 6-alkenylbicyclo[3.1.0]hex-2-enes stems from the fact that a number of structurally intriguing natural products incorporate the bicyclo[3.2.1]octane carbon skeleton into their structures. That naturally occurring substances such as 9-isocyanopupukeanane (122),\textsuperscript{79} quadrone (123),\textsuperscript{80} prezizaene (124)\textsuperscript{81} and sinularene (125)\textsuperscript{82} have recently piqued the interest of many organic synthetic chemists, is plainly indicated by the abundance of independent syntheses\textsuperscript{83} of quadrone (123).

Since substituted bicyclo[3.2.1]octadienes are potentially excellent intermediates for the total syntheses of prezizaene (124), quadrone (123) and sinularene (125), we embarked on a
study directed at the syntheses of functionalized bicyclo-
[3.2.1]octadienes through the Cope rearrangement of the
corresponding precursor 6-alkenylbicyclo[3.1.0]hex-2-enes.
In this connection, recent investigations by Piers and
Ruediger\textsuperscript{70,84} have focussed on the preparation and rearrange-
ment of systems 126-129, which possess a variety of substitution
patterns, particularly at C-1, C-2, C-3 and C-5. The synthetic
strategy employed to assemble these divinylcyclopropane
analogue is outlined in Scheme 15. The bicyclic ketones
130a-c were prepared from the allylic bromides 131a-c and the
dianion of methyl acetoacetate (139) in three steps. Using
standard conditions, the ketones 130a-c and 132 were converted
into the desired bicyclo[3.1.0]hexenes 126-129. Subjection
of 126-129 to refluxing xylene afforded the corresponding bi-
cyclo[3.2.1]octadienes 133-135 in quantitative yields while
136 was obtained in an overall yield of 57% from 132. Also
SCHEME 15

\[ R = R_1 = H \]
\[ R = H, R = Me \]
\[ R = R_1 = Me \]

133: R=R_1=R_2=H
134: R=R_2=H, R_1=Me
135: R_2=H, R=R_1=Me
136: R=R_1=H, R_2=Me

[a] (i) LDA, THF, -78°C (ii) MeI  
[b] (i) LDA, THF, -78°C  
(ii) t-BuMe_2SiCl, THF-HMPA
described\textsuperscript{84} was the preparation and thermal isomerization of a compound with a substitution pattern quite different from that of \textsuperscript{126}. Trapping the enolate anion of \textsuperscript{130a} with phenylselenenyl chloride followed by an oxidation-elimination procedure yielded \textsuperscript{137}. Subsequent thermolysis of \textsuperscript{137} produced the interesting bicyclo[3.2.1]octadienone \textsuperscript{138} in modest yield. Clearly, this methodology would appear to hold considerable promise, allowing for the convenient preparation of bicyclo[3.2.1]octane compounds possessing substituents at either bridgehead position and with synthetically useful functionalities on two or all three bridges.

1.1.4 The Problem

The Cope rearrangement of substituted 6-alkenylbicyclo[3.1.0]hex-2-enes presents a synthetic entry into functionalized bicyclo[3.2.1]octadienes. In view of the scarcity with which this methodology has seen exploitation synthetically, it became desirable to demonstrate the versatility of this interesting transformation by its application to the syntheses of naturally occurring substances, namely quadrone (\textsuperscript{123})\textsuperscript{*} and sinularene (\textsuperscript{125}).

Hence, with the eventual goal of synthesizing (+)-sinularene (\textsuperscript{125}), we extended the investigation initiated

\textsuperscript{*} At the present time, the investigation of this methodology in the syntheses of (+)-quadrone is ongoing in our laboratory.
in our laboratory\textsuperscript{70,84} to accommodate a number of features pertinent to the assembly of this natural product:

1. Since these previous studies in our laboratory were made on the rearrangement of substrates with a carbomethoxy group at C-1 (see Scheme 15, \textsuperscript{126-129}), we wished to investigate the rearrangement of substrates which lack a C-1 substituent.

2. It would be necessary to provide a synthetic "handle" on the one-carbon bridge (C-8) of the bicyclo-octadiene product \textsuperscript{141} thereby requiring the preparation and rearrangement of a 6-alkenylbicyclo[3.1.0]hex-2-ene \textsuperscript{140} with a suitable functionality at C-4.

\[ \text{140} \rightarrow \text{141} \]
3. It was important to determine whether the rearrangement of these systems was stereospecific with respect to the substituents on the 6-alkenyl side chain in 140. That is, would rearrangement of geometrically isomeric substrates [R group (E) or (Z) on the 6-alkenyl side chain] afford products (cf. 141) epimeric at C-4? Indeed, where R₅ is a sterically bulky group (e.g. isopropyl), the viability of the Cope rearrangement of 140 is in question.*

This thesis will discuss the preparation and rearrangement of various substituted 6-(1-alkenyl)bicyclo[3.1.0]hex-2-enes to the corresponding functionalized bicyclo[3.2.1]octadienes, and the application of this methodology to the total synthesis of (+)-sinularene (125) will be discussed.

1.1.5 Methods for the Assembly of Bicyclo[3.1.0]hexanones

Although the [3,3]-sigmatropic rearrangement of 6-alkenyl-bicyclo[3.1.0]hex-2-enes provides a potentially useful synthetic entry into bicyclo[3.2.1]octadienes, it is clear that a viable method for the preparation of the substrate systems is requisite to the application of this transformation in synthesis. In principle, this methodology should not only utilize established synthetic routes but just as importantly,

* For a discussion concerning steric factors involved in divinylcyclopropane rearrangements, see ref. 64 and references cited therein.
demonstrate versatility in terms of substitution patterns in the desired bicyclo[3.1.0]hexenes.

\[\text{[23]}\]

Fortunately, the methods to assemble bicyclo[3.1.0]hexan-2-ones 142, which can be converted easily to the corresponding bicyclo[3.1.0]hex-2-enes 140 (eq. [23]), have been well investigated. A proven route used for the synthesis of polycycles incorporating the bicyclo[x.1.0] moiety is the intramolecular reaction* of olefinic diazocarbonyl compounds, as first demonstrated by Stork and Ficini\(^86\) (eq. [24]). Thus, in the presence of copper-bronze in refluxing cyclohexane, the diazoketone 143 was converted into bicyclo[4.1.0]heptan-2-one (144). In a similar fashion, the bicyclo[3.1.0]hexan-2-one 145 was prepared by means of a copper (II) mediated

\[\text{[24]}\]

* A survey of intramolecular cyclizations of diazocarbonyl compounds has been compiled by Burke and Grieco.\(^85\)
cyclization of the diazo ketone 146 (eq. [25]). Indeed, the numerous examples (eqs. [26]-[28]) of bicyclo[3.1.0]-hexanones such as 149-153, synthesized exploiting the carbenoid cyclization of diazocarbonyl precursors gives testimony to the flexibility of this methodology to substitution patterns. Particularly noteworthy is the stereospecificity of this process as exemplified by eqs. [27] and [28].
Investigations connected to the stereocontrolled generation of acyclic side chains of some natural products led Trost and coworkers\textsuperscript{92} to the preparation and copper-induced cyclization of the diazo keto ester \textit{154} to furnish the more complex bicyclic keto ester \textit{155} as shown in Scheme 16. Carbenoid cyclization of \textit{154} provided stereoselectively \textit{155},

\textbf{SCHEME 16}

\begin{center}
\begin{tikzpicture}[scale=0.8]
\node (a) at (0,0) {\textit{154}};
\node (b) at (0,3) {\textit{155}};
\node (c) at (3,0) {\textit{156}};
\node (d) at (3,3) {\textit{157}};
\node (e) at (6,3) {\textit{158}};
\draw[->] (a) -- (b) node [midway, above] {a};
\draw[->] (a) -- (c) node [midway, above] {b};
\draw[->] (b) -- (d) node [midway, right] {\text{[a] copper-bronze, refluxing MeC}_6H_5 (73-80%) \hspace{1cm} \text{[b] LiMe}_2Cu,\text{ Et}_2O, \text{0}^\circ\text{C} (86\%)};
\end{tikzpicture}
\end{center}

which, upon subjection to lithium dimethylcuprate, was transformed into the ketone \textit{156} with the desired stereochemistry for the acyclic side chain of the steroidal D ring (see \textit{157}) and vitamin D metabolites \textit{158}.

In a particularly intriguing example of these carbenoid cyclizations, Nozaki \textit{et al.}\textsuperscript{93} employed an optically active
copper (II) complex 159 to induce asymmetry in the product 160 obtained from the diazo ketone 161. This case constitutes strong evidence for a carbene-copper-olefin complex as an intermediate despite the slightly differing interpretations on the exact nature of these intermediate complexes.

Of carbenoid additions to conjugated olefins, there seem to be fewer examples, but of a sufficient number to demonstrate the expedience of this synthetic route to 6-alkenylbicyclo-[3.1.0]hexan-2-ones. Such systems drew particular attention as the key intermediates in syntheses directed at the biologically important prostaglandins. Concurrent but independent studies by Taber$^{94}$ and Kondo et al.$^{95,96}$ yielded a means of generating with high stereoselectivity the 6-exo-(E-1-alkenyl)-bicyclo[3.1.0]hexanones 162 from the trans,trans dienic diazo
esters 163 (eq. [30]). This transformation was put to prompt use by Kondo et al.97 in a synthesis of (+)-prostaglandin F$_2$α (164) as shown in Scheme 17.

SCHEME 17

[a] Cu(acac)$_2$, refluxing benzene (61%)  [b] i-ProOH-H$_2$O, p-MeC$_6$H$_4$SO$_3$H$^-$ (86%)  

More recently, Hudlicky and coworkers$^{98,99}$ completed a total synthesis of (+)-hirsutene (168), starting from the cyclic aldehyde 169. Thus, the dienic diazo ketone 170 was prepared via a five step sequence from 169 and the intramolecular cyclopropanation of the former produced
Scheme 18

[\text{169}] \xrightarrow{\text{CHO}} \xrightarrow{\text{d,e}} \xrightarrow{\text{168}} \xrightarrow{\text{c}} \xrightarrow{\text{172}} \xrightarrow{\text{b}} \xrightarrow{\text{a}} \xrightarrow{\text{171}} \xrightarrow{\text{170}}

\begin{align*}
[a] \text{Cu(acac)}_2, \text{refluxing benzene, 8 h (94\%)} & \quad [b] \text{Vycor (pretreated with PbCO}_3\text{), 580°C (68\%)} \\
[c] \text{RhCl}_3, \text{H}_2\text{O-EtOH, reflux, 30 min (\%)} & \quad [d] \text{PtO}_2, \text{H}_2, 40 \text{ psi, 8 h} \\
[e] \text{Ph}_3\text{P=CH}_2, \text{DMSO (\%)} & \\
\end{align*}

Stereoselectively the key intermediate 171. Thermal bond reorganization of 171 provided the cyclopentene annulation product 172, which was converted into the naturally occurring substance 168 after three steps.

Hudlicky \textit{et al.}^{100-102} have applied this intramolecular carbenoid cyclization to generate the tricyclic skeletons of a number of natural products such as coriolin, the isocomenes and pentalenic acid.
It is clear that the thermal rearrangements exhibited by several bicyclo[3.1.0]hexanones (e.g. 171 → 172) must be considered potentially competing processes in the Cope rearrangements of the structurally similar 6-alkenylbicyclo[3.1.0]hex-2-enes. Indeed, at elevated temperatures, there are a number of avenues available to bicyclo[3.1.0]hexanones. For example, Trost and Vladuchick\textsuperscript{103} discovered that thermolysis (350°C) of the bicyclic ketone 173 proceeded via a concerted proton
migration and concomitant cyclopropane ring cleavage to yield smoothly the β-keto ester 174.

Elsewhere, Hudlicky and coworkers\textsuperscript{98,104} found that flash thermolysis of the vinylcyclopropane 175 through a Pyrex\textsuperscript{R}

\textbf{SCHEME 19}
column heated at 400°C gave exclusively the 1,4-diene 176 through a [1,5]-hydrogen shift* (Scheme 19). However, when the thermolysis of 175 was done at 600°C using a Vycor column pretreated with lead carbonate, a 3:1 mixture of 177 and 178 was obtained. It is interesting to note that subjection of 176 to a temperature of 600°C also afforded a mixture of 177 and 178 in similar proportions. It was proposed that the latter reaction entailed the reformation of the ketone 175, which subsequently underwent bond reorganization to give 177 and 178.

\[ 179 \xrightarrow{\Delta} 180 \]  

Both Corey\textsuperscript{106} and Hudlicky\textsuperscript{98,107,108} found that the simpler 6-exo-vinylbicyclo[3.1.0]hexan-2-one (179) rearranged smoothly at elevated temperatures (ca. 500°-600°C) to furnish the bicyclo[3.3.0]octenone 180. In fact, this transformation was pivotal in a synthesis of 11-deoxyprostaglandin E\textsubscript{2} (181) by Corey and Wollenberg\textsuperscript{104} as outlined in Scheme 20. It is noteworthy that the application of the organotin reagent 182 to the preparation of the key intermediate 179 constitutes yet

* For a review on [1,5]-sigmatropic hydrogen shifts, see Ref. 105, and the references cited therein.
SCHEME 20

\[
\begin{align*}
\text{M} & \equiv \text{OTHP} \\
\text{182: M} & = \text{nBu}_3\text{Sn} \\
\text{183: M} & = \text{Li} \\
\text{184: M} & = \text{Cu-C≡C-C}_3\text{H}_7
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \rightarrow \text{f} \\
\text{186} & \rightarrow \text{180} \\
\text{e} & \rightarrow \text{179}
\end{align*}
\]

\[
\begin{align*}
\text{g, h} & \rightarrow \text{several steps} \\
\text{OMe} & \rightarrow \text{181}
\end{align*}
\]

[a] (i) nBuLi, THF, \(-78^\circ\text{C}\), 1 h (ii) 1-pentylnylcopper, THF, \(-78^\circ\text{C}\), 1 h (iii) \(-50^\circ\text{C}\), 10 min (iv) 2-cyclopentenone, \(-78^\circ\text{C}\), \(-50^\circ\text{C}\), 2 h (80%) [b] hydrolysis [c] mesylation [d] KOBu\(^-\), THF, 0°C, 5 min (quant.) [e] 600°C [f] NaBH\(_4\), MeOH, \(-40^\circ\text{C}\) [g] OsO\(_4\), NaIO\(_4\) [h] BF\(_3\)·Et\(_2\)O, MeOH (65% from 186)

another means of assembling a bicyclo[3.1.0]hexanone system.

Thus, the (tri-n-butylstannyl)alkene 182 was transformed into the mixed Gilman (cuprate) reagent 184, which added conjugately
to 2-cyclopentenone to provide 185. Subsequent hydrolysis of the tetrahydropyranyl ether and mesylation of the resultant alcohol, followed by base-mediated ring closure afforded the vinylcyclopropane 179. Flash thermolysis of this latter material at 600°C furnished the bicyclo[3.3.0]octenone 180, which, upon suitable elaboration, led to the biologically interesting prostaglandin 181.

Although these thermal rearrangements generally require higher temperatures than those reported for the Cope rearrangement of 6-alkenylbicyclo[3.1.0]hex-2-enes, such processes may warrant consideration especially in those cases where the transition state for the Cope rearrangement suffers from destabilization.

It seemed appropriate to extend the previously initiated investigations regarding the Cope rearrangements of these bicyclic divinylcyclopropane systems by first turning to 6-exo-vinylbicyclo[3.1.0]hexan-2-one (179), the synthesis of which has been described by Corey\textsuperscript{106} and Hudlicky.\textsuperscript{98,107,108} In principle, 179 could serve as a cornerstone from which a number of the desired substituted 6-vinylbicyclo[3.1.0]hexene systems (cf. 187, 189, 192 and 194) can be derived. Such systems embody a 1,2-trans-divinylcyclopropane moiety and should be capable of undergoing Cope rearrangement to the corresponding bicyclo[3.2.1]octadienes (cf. 188, 190, 193 and 195). In light of the reported\textsuperscript{84} rearrangement of 126 to 133 (eq. [32]), it became desirable to prepare and rearrange
the analogue 187 for the sake of a comparison, i.e. to determine the effect (if any) of the carbomethoxy moiety at C-1 (cf. 126) on the thermal bond reorganization.
\[ \text{SiO} \rightarrow \text{CO}_2\text{Me} \xrightarrow{\Delta} \text{MeO}_2\text{C} \]
1.2 Discussion

1.2.1 The Synthesis and Rearrangement of 2-tert-Butyldimethylsiloxy-6-exo-vinylbicyclo[3.1.0]hex-2-ene (187)

The first task at hand was the preparation of 6-exo-vinylbicyclo[3.1.0]hexan-2-one (179). This was accomplished in an overall yield of 32%, starting from divinylcarbinol (196) and using a synthetic route described by Hudlicky et al.98,107-108 (Scheme 21; in our hands, the intermediates were obtained in the yields shown). Divinylcarbinol (196)109-110 was readily prepared by reaction of acrolein with vinyl magnesium bromide in THF (27%). Treatment of 196 with triethyl orthoacetate and
a catalytic amount of acid provided the trans-dienoate 197 via an orthoester Claisen rearrangement.

The high stereoselectivity of this rearrangement is well documented\textsuperscript{111} and can be rationalized by a comparison of the non-covalent interactions present in the two possible chair-like transition states (represented by 201 and 202) for the Claisen rearrangement (Scheme 22). It is clear that of the two transition states, 201 is more destabilized owing to the 1,3-diaxial interaction between the vinyl and ethoxy substituents. Consequently, the reaction proceeds by way of the thermodynamically preferred transition state 202, which affords the ester 197 with a trans-disubstituted γ,δ-olefinic bond.

The ester 197 was transformed smoothly into the desired bicyclic ketone 179 via a sequence of standard reactions. Thus,
the acid 198 obtained from 197, was converted into the corresponding acyl chloride 199, which provided, upon treatment with ethereal diazomethane, the diazo ketone 200 in excellent yield. Subsequent intramolecular cyclopropanation of the latter material in the presence of Cu(acac)$_2$ furnished the ketone 179, which exhibited a carbonyl absorption ($\nu_{\text{max}}$ 1725 cm$^{-1}$; lit. $\nu_{\text{max}}$ 1723 cm$^{-1}$) and absorptions expected for a vinyl group ($\nu_{\text{max}}$ 3085, 1640, 990, 910 cm$^{-1}$) in the ir spectrum. Although it revealed more fine structure, the 400 MHz $^1$H nmr spectrum of this material compared favourably with that reported by Hudlicky et al., and displayed the vinyl group clearly as an AMX system (Fig. 1). The assignment of

\[ \begin{align*}
\delta & 1.93 \\
\delta & 5.14 \\
\delta & 4.99 \\
\delta & 5.35 \\
\end{align*} \]

\[ \begin{align*}
J_{BC} &= 1.5 \text{ Hz} \\
J_{BD} &= 17 \text{ Hz} \\
J_{CD} &= 10 \text{ Hz} \\
J_{DE} &= 8.5 \text{ Hz} \\
J_{EG} &= J_{EF} = 2.5 \text{ Hz} \\
J_{FG} &= 5 \text{ Hz} \\
\end{align*} \]

Fig. 1. $^1$H nmr spectrum assignments for the vinylcyclopropane moiety of ketone 179.

the signal at $\delta$ 1.93 to the cyclopropyl proton $H_E$ was based on a decoupling study, in which irradiation at $\delta$ 5.35 ($H_D$) caused not only the expected signal simplifications at $\delta$ 5.14 ($H_B$) and $\delta$ 5.35 ($H_C$), but the collapse of the resonance at $\delta$ 1.93 to an overlapping doublet of doublets ($J_{EG} = J_{EF} = 2.5$ Hz).
With the bicyclic ketone 179 in hand, attention was directed to the preparation of the 6-vinylbicyclo[3.1.0]hexene systems 187 and 189. Thus, treatment of the ketone 179 with 1.1 equivalents of lithium diisopropylamide at -78°C, followed by trapping of the resultant enolate anion with tert-butyldimethylsilyl chloride* in the presence of hexamethylphosphoramide provided the silyl enol ether 187 in 95% yield.

* Initially, trimethylsilyl chloride was employed to trap the lithium enolates. However, the resultant silyl enol ethers proved to be unstable, unlike their tert-butyldimethylsilyl counterparts, which posed few problems to handling and purification.
The ir spectrum of this compound lacked a carbonyl absorption and exhibited the absorptions ($\nu_{\text{max}}$ 3060, 3020, 1622, 840 cm$^{-1}$) typical of the olefinic moieties in the assigned structure. On the other hand, the $^1$H nmr spectrum of 187, in which there were few overlapping signals, provided a relative wealth of information. As expected, the proton resonances, attributed to the t-butyl and methyl groups bonded to silicon, were found at $\delta$ 0.93 and 0.15, respectively. Markedly upfield from the set of signals due to the vinyl group, the broad singlet at $\delta$ 4.30 was indicative of the olefinic proton $H_I$ adjacent to the siloxy substituent. The neighbouring methylene protons ($H_J$ and $H_Z$) gave rise to two sets of overlapping doublet of doublet of doublets ($\delta$ 2.29 and 2.52) in which the telltale large coupling ($J = 17$ Hz) characteristic of geminal protons, was quite obvious. From models, it appeared that the $H_G-H_J$ dihedral angle approximated 90° whereas that of $H_G-H_Z$ was $\approx$20°. In accordance with the Karplus equation,\textsuperscript{112} one would expect a stronger coupling between $H_G$ and $H_Z$ than that between $H_G$ and $H_J$, and the resonances at $\delta$ 2.29 ($J_{GJ} = 0$) and 2.52 ($J_{GZ} = 8$ Hz) were consequently assigned to $H_J$ and $H_Z$, respectively. Both of these protons exhibited a small coupling to the vinyl proton $H_I$ ($J_{IJ} = 3$ Hz, $J_{IZ} = 2$ Hz). The cyclopropyl protons $H_E$, $H_F$ and $H_G$ appeared as complex multiplets at $\delta$ 1.14, 1.57-1.63 and 1.67-1.72. However, the resonance at $\delta$ 1.14 displayed a large coupling ($J_{DE} = 9$ Hz) and was consequently attributed to $H_E$.\textsuperscript{112}
The stage was now set for the Cope rearrangement of the 6-vinylbicyclo[3.1.0]hex-2-ene 187. Thus, the silyl enol ether 187 was sealed in vacuo in a silylated pyrolysis tube and subjected to a temperature of 200°C for 2 hours, after which time glc analysis indicated the presence of a new single component. This material, identified as the bicyclo[3.2.1]-octadiene 188, was obtained in almost quantitative yield (eq. [34]).

Although the ir spectrum ($\nu_{\text{max}}$ 3040, 3000, 1615 cm$^{-1}$) of this compound did not differ dramatically from that of its precursor 187, the $^1$H nmr spectrum was quite complicated in comparison, and did not lend itself readily to analysis.
However, the signals at $\delta$ 0.14, 0.16, 0.93 and 5.11 indicated that the tert-butyldimethylsilyl enol ether moiety had remained intact, and more significantly, the signals due to a vinyl substituent were clearly absent, being supplanted by resonances attributable to environmentally different olefinic protons ($\delta$ 5.11, 5.27-5.32 and 6.16-6.22). By means of decoupling studies, it was possible to show that the methylene proton $H_I$ exhibits a long-range coupling to $H_J$. These two protons are in an orientation approaching the planar zig-zag or W arrangement which maximizes long-range interactions of this type. Interestingly, this proton ($H_I$) couples with neither bridgehead protons ($H_F$ and $H_K$) since both $H_F$-$H_I$ and $H_I$-$H_K$ dihedral angles approximate 90°. Therefore, $H_I$ appears as a broad doublet with the geminal coupling ($J = 9.5$ Hz) to $H_Z$, and weak long-range coupling to $H_J$.

\[ \text{[32]} \]

Compared with the reported rearrangement of 126 to 133 (eq. [32]) under the conditions of refluxing xylene (b.p. 138°C) for 2.5 hours, the Cope rearrangement of 187 to the bicyclo-[3.2.1]octadiene 188 (eq. [34]) necessitated a higher thermolysis temperature (200°C, 2 hours) for the reaction to complete in
a reasonable length of time. Indeed, in an early attempt, a solution of $^{187}$ in xylene was heated under reflux to yield, after 17.5 hours, mainly the starting material. This observed difference in reaction rates of $^{126}$ and $^{187}$, although it is by no means quantified, may be rationalized in terms of the relative stabilization imparted by the C-1 carbomethoxy moiety in $^{126}$ to the transition state involved in the rate-determining epimerization step ($^{126} \rightarrow^{205}$) as outlined in Scheme 23.

Prior to Cope rearrangement, the 6-exo-vinylbicyclo[3.1.0]-hex-2-ene $^{187}$ is believed to undergo a one-center thermal epimerization$^{28}$ at C-6 to furnish the endo isomer $^{206}$, presumably via formation of an intermediary biradical species.$^{25,35-39}$ By a similar mechanism, the carbomethoxy analogue $^{126}$ epimerizes to $^{205}$, but at a rate faster than that involving the conversion of $^{187}$ into $^{206}$. The facilitation of the epimerization process ($^{126} + ^{205}$) may be attributed to the stabilization of the biradical intermediate arising from $^{126}$ by means of delocalization involving the carbomethoxy substituent.

On the other hand, the biradical intermediate arising from $^{187}$ clearly lacks this extra stabilization and is thus formed from $^{187}$ at a much slower rate. Nevertheless, once the epimerization has occurred, both $^{205}$ and $^{206}$ undergo Cope rearrangement quite readily, owing to the concomitant relief of strain in the cyclopropane ring as well as the favourable $\pi$-orbital overlap between the double bonds in the quasi-boat
transition state.\(^6\)

Hydrolysis of the enol ether 188 was accomplished smoothly in THF at room temperature by treatment of this substance with aqueous hydrochloric acid. Bicyclo[3.2.1]oct-2-en-6-one (207) was thus obtained in 88\% yield (eq. [35]), and exhibited an ir spectrum which indicated the presence of a ketone (\(v_{\text{max}} 1730\ \text{cm}^{-1}\)) and a cis-disubstituted alkene (\(v_{\text{max}} 3025, 1640, 735\ \text{cm}^{-1}\)). Examination of the \(1^H\) nmr spectrum of 207 showed that

the resonance of the enol ether olefinic proton was absent. The upfield region was complicated by the presence of three pairs of methylene protons, two of these pairs appearing as AB systems. While \(H_I\) and \(H_Z\) appeared at \(\delta 2.03\) and 2.08, respectively with a geminal coupling of 11 Hz, \(H_J\) and \(H_Y\)
resonated at $\delta$ 2.34 and 2.29, respectively with a geminal coupling of 17.5 Hz. Lastly, the methylene protons $H_C$ and $H_X$, constituting an AX system, were also coupled strongly ($J_{CX} = 18$ Hz) to each other and appeared at $\delta$ 2.43 and 2.20, respectively.

Having demonstrated that the Cope rearrangement of 2-tert-butylidimethylsiloxy-6-exo-vinylbicyclo[3.1.0]hex-2-ene (187) occurs very efficiently, we were encouraged to investigate similar rearrangements of more highly substituted substrates.

1.2.2 The Synthesis and Rearrangement of 6-exo-Vinylbicyclo-[3.1.0]hex-3-en-2-one (189) and C-4 Functionalized 6-exo-Vinylbicyclo[3.1.0]hex-2-enes 192 and 194

On the basis of the reactions shown in general terms in Scheme 24, one can envisage that an enone such as 189 could serve as a suitable precursor for the synthesis of
bicyclo[3.2.1]octadienes substituted at C-8. That is, nucleophilic attack at C-4 of 189 should occur predominantly from the convex side of the molecule, giving an intermediate enolate anion with the newly introduced substituent in an exo orientation. The intermediate, upon trapping with a suitable electrophile, would provide the enol ether 208, which should, upon thermolysis, rearrange to the bicyclic diene 209.

For the placement of a two-carbon "handle" with exo orientation at C-8 of the bicyclo[3.2.1]octane skeleton, it was felt that the stereoselective preparation (with respect to C-4) and rearrangement of the systems 192 and 194 would be instructive. Conceivably, the functionalization at C-4 in these systems could be accomplished via known methods, i.e. the conjugate addition to the enone 189 using either vinyl cuprate or Grignard reagents (eq. [36]) or a silyl ketene
Moreover, the enone 189 is itself a vinylbicyclo[3.1.0]-hexene and successful Cope rearrangement of this compound would provide a bicyclo[3.2.1]octadiene 190 functionalized at C-8, as shown in equation [38]. The α,β-unsaturated ketone 189 may be derived from the bicyclic ketone 179, the synthesis of which was discussed earlier (vide supra).

For the preparation of α,β-enones from the parent saturated ketones, a number of methods are known. For example, bicyclo[3.1.0]hex-3-en-2-one (211) was generated from the ketone 145 using a three-step sequence involving initially the synthesis of the α-bromoacetal 212, which subsequently was dehydrohalogenated and deprotected (Scheme 25). However, for the conversion of the ketone 179 into the desired enone 189 (eq.
(39)), this method was not considered suitable since the use of bromine could present the problem of competing side reactions.
Alternatively, there have been recent reports of oxidizing trimethylsilyl enol ethers to $\alpha,\beta$-enones. Fleming and Patterson$^{115}$ described the use of dichlorodicyanobenzoquinone (DDQ) to oxidize the enol ether 213 to 2-cyclopenten-1-one (eq. [40]) in a yield of 20%. In an earlier paper, Saegusa et al.$^{116}$ reported that palladium (II) acetate supplemented by 1,2-benzoquinone constituted an efficient oxidant system to effect the same transformation in a yield of 98% (eq. [40]). Indeed, the palladium (II) catalyzed dehydrosilylation of silyl enol ethers has been applied to a number of natural product syntheses in the past six years, as exemplified in Schlessinger's synthesis$^{117}$ (Scheme 26) of the pseudougaianolide helenalin (214), and very recently, in a synthesis of the sesquiterpenoid

SCHEME 26

![SCHEME 26](image)

[a] (i) LiN(SiMe$_3$)$_2$ (ii) Me$_3$SiCl  [b] Pd(OAc)$_2$, MeCN (73% from 215)
capnellene (216) by Piers and Karunaratne (Scheme 27). Despite the offer of good yields, this method was not particularly appealing as a means to prepare the bicyclic enone in view of the instability observed in our previous experience with 2-trimethylsiloxy-6-exo-vinylbicyclo[3.1.0]hex-2-ene (218). However, we found (vide infra) that this method was a good alternative to the well established selenoxide fragmentation to generate \( \alpha,\beta \)-enones from the saturated ketones.

Undeniably, there exists a considerable volume of documentation dedicated to the procedure for the conversion of ketones to their \( \alpha,\beta \)-unsaturated derivatives via the sequence of
reactions shown in Scheme 28. This conversion is implemented formally in three steps: (a) introduction of a seleno group alpha to the carbonyl, (b) oxidation of the resultant selenide 219 to the selenoxide level, and (c) fragmentation of the selenoxide 220 to give the α,β-enone. However, from a practical point of view, this procedure is usually a "two-pot" process, since the selenoxide normally fragments under the conditions of its formation. For example, Reich et al.121 have reported the preparation of the cyclopentenone 221 from the ketone 222. The intermediary α-phenylselenenyl ketone 223 was obtained by treating the lithium enolate of ketone 222 with phenylselenenyl

* For reviews on the use of organoselenium reagents in organic synthesis, the reader is referred to Refs. 119 and 120, and the references cited therein.
bromide. Oxidation of 223 with hydrogen peroxide, followed by elimination,* gave 221 in an overall yield of 66%.

In a similar manner, the lithium enolate of the bicyclic ketone 179 was formed using 1.1 equivalents of lithium diisopropylamide in THF at -78°C, and was subsequently quenched by the addition of a solution of phenylseleneny1 chloride in HMPA. The resultant selenides 224, which were obtained in 79% yield, were subjected to oxidative elimination using hydrogen peroxide and pyridine in dichloromethane at room temperature to furnish the enone 189 in a mediocre overall yield of 50%. Initial attempts to improve the yield of the oxidation by using sodium metaperiodate in methanol led to much lower yields, but our efforts were rewarded when the entire sequence of reactions was performed in "one-pot" as described by Reich et al.123

* Toshimitsu et al.122 have recently reported that α-pyridyl-seleno derivatives undergo oxidative elimination more readily than α-phenylseleneny1 ketones.
Thus, the lithium enolate of ketone 179 generated by the method described above, was quenched by the addition of a solution of phenylselenenyl chloride in THF. Oxidation of the α-phenylselenenides to the selenoxides was induced by the introduction of acetic acid and hydrogen peroxide to the resultant reaction mixture at 0°C. Under these conditions, selenoxide fragmentation ensued and the bicyclic enone 189 was isolated in 88% yield.

The ir spectrum of 189 exhibited the expected absorptions ($\nu_{\text{max}}$ 3050, 1690, 1640 cm$^{-1}$) for an α,β-unsaturated ketone. In the $^1$H nmr spectrum, the vinyl protons of the conjugated system were clearly visible. While the α-proton ($H_I$) resonated as a doublet at $\delta$ 5.70, the β-proton ($H_J$) appeared characteristically downfield at $\delta$ 7.64 as a doublet of doublet of doublets. The splitting pattern shown by $H_J$ arose from dissimilar coupling to $H_I$ ($J_{IJ} = 5.5$ Hz), $H_G$ ($J_{GJ} = 2.5$ Hz) and $H_F$ ($J_{FJ} = 1$ Hz). That the vinyl group had retained its integrity was evidenced by the AMX pattern in the olefinic region. In the higher field portion of the spectrum, the resonances of the three cyclopropyl protons were well resolved and were assigned on the basis of a decoupling experiment (Fig. 2). By irradiating at $\delta$ 7.64
Fig. 2. The homonuclear spin decoupling experiment with 189: (a) the normal 400 MHz $^1$H nmr spectrum, and (b) the spectrum with irradiation at δ 7.64 ($H_7$).
(\(H_J\)), the signal at \(\delta\ 2.59\) collapsed to a doublet of doublets
(\(J_{FG} = 4\) Hz, \(J_{EG} = 3\) Hz) and was attributed to \(H_G\). The
assignment of the complex resonance at \(\delta\ 2.17\) to \(H_E\) was made
without difficulty since the strong coupling between \(H_D\) and
\(H_E\) (\(J = 9\) Hz) was quite evident. Furthermore, the similar
coupling between \(H_E\) and the other cyclopropyl protons (\(J_{EF} =
J_{EG} = 3.0\) Hz) were apparent. By the process of elimination,
the multiplet at \(\delta\ 2.27-2.32\) was attributed to the remaining
cyclopropyl proton \(H_F\).

For the rearrangement of the bicyclic enone \(189\) to the
ketone \(190\) (eq. [38]), the conditions were chosen to minimize
the decomposition of the substrate \(189\), which darkened on
standing at \(4^\circ\)C under argon and in the absence of light. Thus,
\(189\) was thermolyzed in solution (dry benzene) at \(160^\circ\)C for 4
hours (sealed tube) to give, after distillation, a material
which was shown to be the bicyclo[3.2.1]octa-2,6-dien-8-one
(\(190\)). In light of the instability exhibited by the substrate
\(189\), it was perhaps not entirely surprising to isolate the
product \(190\) in a modest yield of 68% while the remaining
balance of mass was recovered in the form of a tar.
Fig. 3. The 400 MHz $^1$H nmr spectrum of 190.
Nevertheless, spectral analysis of the distilled product verified that the desired compound 190 had been obtained. Examination of the ir spectrum of this material indicated the presence of a saturated ketone \((\nu_{\text{max}} 1755 \text{ cm}^{-1})\) as well as the olefinic moieties \((\nu_{\text{max}} 3050, 1622, 680 \text{ cm}^{-1})\). Close scrutiny of the \(^1H\) nmr spectrum of 190 (Fig. 3) revealed the presence of four olefinic protons, which were environmentally different \((\delta 5.46-5.53, 6.04, 6.21 \text{ and } 6.69)\) from those in 189. It was possible to distinguish between \(H_J\) and \(H_Y\) by decoupling \(H_J\) \((\delta 6.69)\), which clearly revealed \(J_{KE} (7 \text{ Hz})\) while the multiplet at \(\delta 2.73-2.82\), attributed in part to \(H_F\) and \(H_K\), simplified (Fig. 4).

With the desired \(\alpha,\beta\)-enone 189 in hand and the successful
Fig. 4. The homonuclear spin decoupling experiment with $^{190}$: (a) the normal 400 MHz $^1$H nmr spectrum expanded for the region between $\delta$ 2.4-6.7, and (b) the spectrum with irradiation at $\delta$ 6.69 ($H_J$).
demonstration of a route for the preparation of bicyclo[3.2.1]-octadienes functionalized at C-8, attention was directed to the task of synthesizing and rearranging the silyl enol ethers 192 and 194 substituted at C-4 with exo geometry.

In principle, the desired enol ether 192 could be obtained from the copper (I)-catalyzed conjugate addition of vinyl magnesium bromide to the enone 189, followed by derivatization using tert-butyldimethylsilyl chloride. However, under the conditions of conjugate addition, there are indications that cyclopropane ring cleavage could be a competing process. For instance, Marshall and Ruden\textsuperscript{125} observed that reaction of the conjugated cyclopropyl enone 225 with lithium dimethylcuprate yielded the 1,4-adduct 226 (43%) and cyclopropane ring cleaved adduct 227 (49%) as shown in eq. [41]. Reaction of the same
cuprate reagent with the α,β-enone 228 furnished a 48:52 mixture of the normal conjugate addition product 229 and the cyclopropane ring opened product 230 (eq. [42]).

An example which perhaps resembles the bicyclic ketone 189 more closely is shown in eq. [43]. Treatment of the bicyclo[3.1.0]hexenone 231 with lithium dimethylcuprate gave a mixture of the 1,4-adduct 232 (92%), and the ring-cleaved products 233 (2%) and 234 (6%).

Although the examples cited above bear some resemblance to the bicyclic enone 189 of interest, they may not serve appropriately as models for the behaviour of 189 under similar reaction conditions. Due to the presence of the C-6 vinyl substituent, the reduction potential and therefore the reactivity pattern of 189 may be quite different from those of the cyclopropyl ketones shown in eqs. [41]-[43]. However, cyclopropane ring-cleavage should not be entirely dismissed as a possible
side reaction in the conjugate addition of a Grignard reagent to the cyclopropyl enone 189.

Assuming that the addition of vinyl magnesium bromide to the enone 189 proceeds in a conjugate sense, the silyl enol ether 192 could conceivably be obtained by the direct trapping of the resultant metalated enolate 235 with tert-butyldimethylsilyl chloride in a "one-pot" procedure. However, in practice, only trimethylsilyl enol ethers have been prepared* in this manner.

In an initial attempt to prepare the trimethylsilyl enol ether 236 using this method, the procedure described by House et al.133 was employed to form the metalated enolate 235 by the addition of vinyl magnesium bromide to the enone 189 in the

* For more information concerning the preparation of silyl enol ethers from enolates, the reader should consult refs. 116, 129 and 130. The trapping of enolates generated from copper (I)-catalyzed Grignard additions to enones, using trimethylsilyl chloride, has been described.80e,131,132
presence of a catalytic amount of cuprous bromide-dimethyl sulfide complex. Direct quenching of the enolate with a mixture of trimethylsilyl chloride, triethylamine and hexamethylphosphoramde gave a 7:1 mixture of the divinyl ketone and the enol ether in an unenviable yield of 48%.

Because was quite susceptible to hydrolysis and consequently did not lend itself readily to handling or purification, the alternative "two-pot" method of preparing the tert-butyldimethylsilyl enol ether was investigated and proved to be more successful. Thus, using the procedure of House et al. the enone was added to a mixture of vinyl magnesium bromide and a catalytic amount of cuprous bromide-dimethyl sulfide complex in THF to give, after quenching with aqueous ammonium chloride, the ketone in an isolated yield of 80%. Since none of the products resulting from cyclopropane cleavage were detected, our initial misgivings about such competing processes proved, in fact, to be unfounded.

Not surprisingly, the ir spectrum of resembled that of the simple bicyclic ketone and indicated the presence of a ketone carbonyl (νmax 1718 cm⁻¹) and the vinyl moieties (νmax 3050, 1635, 990, 915 cm⁻¹). Due to the presence of the vinyl substituent on the cyclopentane ring, the ¹H nmr spectrum of not only differed from that exhibited by, but displayed

* Cuprous bromide-dimethyl sulfide complex was prepared and purified in accordance with refs. 134-136.
Fig. 5. The 400 MHz $^1$H nmr spectrum of 237.
well resolved signals, which offered themselves readily to analysis (Fig. 5). The presence of two vinyl groups was quite apparent in the olefinic portion of the spectrum. Upfield from this area was the resonance at δ 3.02 attributed to H_J, whose overlapping doublet of doublets arose from similar couplings to H_I and the vinyl proton H_K (J_{JK} = J_{IJ} = 8 Hz). Most interestingly, H_J appears to couple neither with H_Z nor the bridgehead proton H_G, thereby suggesting that both H_J-H_Z and H_G-H_J dihedral angles approximate 90°. Indeed, a model of easily assumes a conformation which accommodates these observations, as did subsequent decoupling experiments. Thus, irradiation at δ 3.02 (H_J) led to no change at the resonances at δ 1.87-1.94 (H_Z) and 2.04 (H_G), while the anticipated signal simplifications occurred at δ 2.36 (H_I) and 5.84 (H_K) as shown in Fig. 6. More importantly, this decoupling study provided grounds for the stereochemical assignment of H_J in the form of a 22% signal intensity increase or nuclear Overhauser enhancement (n.O.e.)\textsuperscript{137} at δ 2.36 (H_I). If the orientation of H_J was exo, the resonance due to H_Z rather than H_I would be expected to shown a n.O.e. To dismiss this
Fig. 6. The homonuclear spin decoupling experiment with 237: (a) the normal 400 MHz $^1$H nmr spectrum expanded for the region between $\delta$ 1.5-3.3, and (b) the spectrum with irradiation at $\delta$ 3.02 ($H_J$).
possibility and to confirm the endo stereochemistry of \( H_J \), an experiment wherein \( H_Z \) was decoupled might have proven useful. However, such an experiment was not possible since the signal of interest was obscured by that of \( H_F \) at \( \delta 1.87-1.94 \).

With the stereochemistry of the C-4 vinyl substituent established, the divinyl ketone 237 was smoothly converted into the requisite silyl enol ether 192 in >97% yield (eq. [44]).

As expected, a carbonyl absorption was absent in the ir spectrum of 192, but the olefinic absorptions (\( \nu_{\text{max}} \) 3060, 3015, 1618 cm\(^{-1} \)) were clearly visible. The uncomplicated \( ^1H \) nmr spectrum of this material as shown in Fig. 7 presented itself readily to analysis. Immediately evident were the singlets at \( \delta 0.18 \) and 0.95 due to the tert-butyldimethylsiloxy substituent
Fig. 7. The 400 MHz $^1$H nmr spectrum of 192.
and the broad singlet at $\delta$ 4.31, which was attributed to the vinyl proton adjacent to the siloxy substituent. With the introduction of another sp$^2$ centre in the cyclopentane ring, the $H_I$-$H_J$ dihedral angle apparently approaches $90^\circ$. Consequently, $H_J$ appeared as an unresolved doublet at $\delta$ 3.13 with the largest coupling to $H_K$ ($J_{JK} = 7.5$ Hz).

The other silyl enol ether 194 of interest could be prepared from the bicyclic enone 189 via Michael addition of tert-butyldimethylsilyl ketene acetal 210 with concomitant trapping of the resultant enolate (eq. [37]). To date, conjugate additions of 210 to $\alpha,\beta$-unsaturated carbonyl systems have been effected using Lewis acids (e.g. TiCl$_4$)\textsuperscript{138} in

\begin{equation}
\begin{array}{c}
\text{189} \\
\end{array}
\begin{array}{c}
\text{210} \\
\end{array}
\begin{array}{c}
\text{194} \\
\end{array}
\end{equation}

dichloromethane and a (rather exotic) Lewis base [i.e. tris-(dimethylamino)sulfonium difluorotrimethylsiliconate]\textsuperscript{139} in THF, under high pressure (10-15 kbar)\textsuperscript{140,141} and thermally in acetonitrile.\textsuperscript{142} However, the silyl enol ethers cannot be isolated using Lewis acid catalysts, and only the trimethylsilyl derivatives have been prepared via Lewis base catalysis. The high pressure method seems to be effective in inducing ketene acetal additions to enones having steric and conformational constraints, and has been used to prepare both
trialkyl- and tert-butyldimethylsilyl enol ethers. Due purely to technical reasons, this method was not attempted in our efforts to transform 189 into 194. Instead, the alternative thermally-induced addition, which is conducted in acetonitrile, was investigated.

Thus, in accordance with the procedure described by Tamura et al.\textsuperscript{142} a mixture of the enone 189 and 1.5 equivalents of the silyl ketene acetal 210\textsuperscript{*} in acetonitrile was warmed at 55°C. Small amounts of 210 were added every 30 minutes for 12 hours, after which time the silyl enol ether 194 was obtained in only 33% yield. The remaining unreacted enone 189 was recovered almost quantitatively, thereby indicating that 194 was isolated in >95% yield based on unrecovered enone 189. These results were not entirely discouraging since yields as high as 60% were obtained but after long reaction times. Considering the reaction times of 12 hours reported by Tamura\textsuperscript{142} for the addition of 210 to the relatively unhindered 2-cyclohexen-1-one, the sluggish nature of the reaction using the enone 189 as substrate was not unexpected.

\footnote{The silyl ketene acetal 210 was prepared from ethyl acetate.\textsuperscript{143}}
Fig. 8. The 400 MHz $^1$H nmr spectrum of 194.
Nevertheless, spectral analysis of the product indicated that these efforts were fruitful in providing the desired 194. The ir spectrum of this material was consistent with the proposed structure and exhibited the expected absorptions of an ester ($\nu_{\text{max}} 1730, 1255 \text{ cm}^{-1}$) as well as those of the olefinic residues ($\nu_{\text{max}} 3050, 787 \text{ cm}^{-1}$). Immediately evident in the $^1$H nmr spectrum (Fig. 8) were the presence of the tert-butyl-dimethylsiloxy group (singlets at $\delta$ 0.16 and 0.94), the ethyl ester and the vinyl moiety. Interestingly, decoupling of H$_G$ (Fig. 9) revealed a small coupling ($J = 3$ Hz) between H$_G$ and H$_J$ despite the approximation of the H$_G$-H$_J$ dihedral angle to 90°. It is pertinent to point out that the similarity between the coupling ($J_{GJ} = 3$ Hz) and the corresponding $J_{GJ}$ (2.5 Hz) in 192, provided the basis on which the endo stereochemistry of H$_J$ in 194 was assigned.

With the two desired vinylbicyclo[3.1.0]hex-2-enes 192 and 194 in hand, attention was directed to their thermal
Fig. 9. The homonuclear spin decoupling experiment with 194: (a) the normal 400 MHz $^1$H nmr spectrum expanded for the region $\delta$ 1.2-3.0, and (b) the spectrum with irradiation at $\delta$ 1.73 ($H_G$).
rearrangement. It was gratifying to discover that heating the silyl enol ethers in sealed tubes at 200°C afforded cleanly in each case a new single product, as indicated by glc analysis (eqs. [45] and [46]). The rearranged silyl enol ethers 193 and 195 were isolated in yields of 89% and 98% respectively.

Olefinic absorptions were clearly visible in the ir spectra of 193 ($\nu_{\text{max}}$ 3050, 3010, 1624 cm$^{-1}$) and 195 ($\nu_{\text{max}}$ 3050, 3010, 1620 cm$^{-1}$) in addition to the ester carbonyl stretch ($\nu_{\text{max}}$ 1725 cm$^{-1}$) in the latter compound. In the $^1$H nmr spectra, the resonances of the tert-butyl group ($\delta$ 0.92), the silyl methyls ($\delta$ 0.14-0.16) and the $H_J$ vinyl proton (193: $\delta$ 4.95-5.01; 195: $\delta$ 4.97) bore testimony to the fact that the silyl enol ether moieties had survived the thermolyses. Also evident were the now-familiar splitting patterns of the vinyl protons $H_D$ and $H_E$, each occurring at almost identical chemical shifts in the spectra of 193 and 195.

In the $^1$H nmr spectrum of 193 (Fig. 10), the proton $H_I$ appeared as a doublet at $\delta$ 2.65, due to coupling only with the vinyl proton $H_Z$ ($J = 7.5$ Hz). Indeed, the apparent lack of coupling implies that both $H_F$-$H_I$ and $H_I$-$H_K$ dihedral angles must be close to 90°, thereby verifying the endo stereochemistry
Fig. 10. The 400 MHz $^1$H nmr spectrum of 193.
of \( H_I \). It was possible to distinguish between the two bridgehead protons \( H_F \) and \( H_K \) by decoupling \( H_E \), which led to the collapse of the resonance at \( \delta 2.38 \) (\( H_K \)) to an unresolved doublet (\( J_{JK} = 2.5 \) Hz).

The low field region of the \( ^1H \) nmr spectrum of 195 was, in contrast, much simpler owing to the lack of a C-8 vinyl substituent, while the higher field portion consisting of overlapping resonances was quite difficult to interpret even with the aid of decoupling studies. Disappointingly, not a clue regarding the stereochemistry at C-8 could be gleaned from this spectrum. It was therefore gratifying to find that analysis of the \( ^1H \) nmr spectrum of the hydrolyzed product 239 provided grounds for the stereochemical assignment at C-8.

Acid-catalyzed hydrolysis (THF-5% HCl, r.t.) of the rearranged silyl enol ethers 193 and 195 to the corresponding bicyclo[3.2.1]octenones 238 and 239 proceeded smoothly in yields of 93% and 94%, respectively (eqs. [47] and [48]).
Fig. 11. The 400 MHz $^1$H nmr spectrum of 238.
The anticipated ketone absorptions ($v_{\text{max}}$ 1730 cm$^{-1}$) were clearly visible in the ir spectra of 238 and 239 and in the latter, the ester carbonyl absorption appeared at 1740 cm$^{-1}$. These spectra also exhibited the absorptions typical of alkenes (238: $v_{\text{max}}$ 3052, 3010, 1630 cm$^{-1}$; 239: $v_{\text{max}}$ 3000, 1625 cm$^{-1}$).

A cursory examination of the $^1$H nmr spectrum of the ketone 238 (Fig. 11) showed that the silyl enol ether moiety was absent. Due to the presence of two pairs of methylene protons, the high-field region presented a challenging exercise for a detailed analysis. The resonance at $\delta$ 2.91, which was the furthest downfield in this region, was assigned to $H_1$ with the aid of an experiment in which $H_2$ was decoupled. $H_1$ is coupled not only to $H_2$ ($J = 5.5$ Hz), but also quite weakly to the bridgehead protons $H_F$ ($\delta$ 2.59-2.63) and $H_K$ ($\delta$ 2.66), whose resonances sharpened when $H_1$ was decoupled (Fig. 12). This same decoupling experiment revealed the long-range coupling ($J = 2$ Hz) between $H_1$ and $H_J$, which are oriented in a planar zig-zag or W arrangement. This finding provided further substantiation of the stereochemistry at C-8. The experiment in which $H_D$ was decoupled proved very informative for the
Fig. 12. The homonuclear spin decoupling experiment for 238: (a) the normal 400 MHz $^1$H nmr spectrum expanded for $\delta$ 2.2-3.0, and (b) the spectrum with irradiation at $\delta$ 2.91 ($H_I$).
assignment of the complex resonances at δ 2.52 and δ 2.30 to H_C and H_X, respectively. Other than coupling geminally to H_X (J = 18 Hz), H_C couples to H_F (J = 5.5 Hz), and similarly to H_D and H_E (J_CD = J_CE = 2 Hz). Compared to H_C, H_X differs in its coupling to H_F (J = 2 Hz) and H_D (J = 3.5 Hz). The other methylene protons H_J and H_Y appeared at δ 2.20 and 2.43 respectively, the former of which forms a dihedral angle of ≈90° with the bridgehead proton H_K. Consequently, H_J apparently couples with H_I (J = 2 Hz) and H_Y (J = 17.5 Hz), but not with H_K. In contrast, H_Y exhibits a strong coupling to H_K (J = 6 Hz).

It was obvious from the 1H nmr spectrum of 239 that the silyl enol ether moiety was absent. The complexity of the high field portion of the spectrum was undoubtedly attributed to the presence of three pairs of methylene protons. Nevertheless, H_I resonated as an overlapping doublet of doublets at δ 2.70 due to similar couplings to the protons alpha to the ester group. H_I was coupled weakly to one bridgehead proton H_K, the resonance (δ 2.60) of which sharpened when the signal at δ 2.70 was irradiated. These data seemed to be consistent with the endo stereochemical assignment of H_I in 239.
Although the "compression" of resonances in the region of $\delta$ 2.22-2.45 did not permit a detailed interpretation, the available data indicated the successful preparation of the desired keto ester 239.

Even though the reactions described to this point provide access to bicyclo[3.2.1]octa-2,6-dienes which bear substituents on the one- and two-carbon bridges, examples of these systems which are substituted on the three-carbon bridge were scarce. It was thought that this problem could be approached in conjunction with a study regarding the stereospecificity with which 6-(1-alkenyl)bicyclo[3.1.0]hex-2-ene systems undergo [3,3]-sigmatropic rearrangements.

1.2.3 The Synthesis and Rearrangement of 6-exo-[\((E)\)- and 
\((Z)\)-1-alkenyl]bicyclo[3.1.0]hex-2-enes (240) and (274)

An unquestionably appealing feature of the Cope rearrangement as the key step in a synthesis of sinularene (125) using this methodology would be its capacity to situate stereospecifically the sterically bulky isopropyl substituent with exo geometry at C-4 of the bicyclo[3.2.1]octane skeleton. This feature would be suitably demonstrated by the stereospecific rearrangement of the geometric isomers 240 and 242.

\[ \text{SiO} \quad \text{CO}_2\text{Me} \quad \Delta \quad \text{MeO}_2\text{C} \]

[49]

240 241
to the 4-endo- and 4-exo-isopropylbicyclo[3.2.1]octadienes 241 and 243, respectively (eqs. [49] and [50]).

In principle, the preparation of the trans isomer 240 could be patterned after the reported\(^8^4\) syntheses of similar compounds (cf. Scheme 15) and could therefore be accessed by utilizing the allylic bromide 244 to alkylate the dianion of methyl acetoacetate. This synthetic sequence is shown in Scheme 29.

**SCHEME 29**
The initial task at hand then entailed the preparation of the allylic bromide 244, in which the two trans double bonds could be generated by means of Wittig-type olefination processes (Scheme 30). A report by Isler and coworkers described the use of the Wittig reaction between the α,β-unsaturated aldehyde 248 and the stabilized phosphorane* 249 in the synthesis of the carotenoid 250 (eq. [51]). The high stereoselectivity of this olefination was exemplified again when acetaldehyde was treated with the stabilized phosphorane 251 to give an ester mixture composed of 96.5% methyl tiglate 252 and 3.5% of the geometric isomer 253.146

* A review article on the Wittig reaction is available and provides a survey of stabilized phosphoranes which have been prepared.
In a similar manner, carbethoxymethylenetriphenylphosphorane (254), prepared from triphenylphosphine and ethyl bromoacetate according to the procedure of Denney and Ross, was allowed to react with isobutyraldehyde in refluxing dichloromethane to give the $\alpha,\beta$-unsaturated ester 255 in 92% yield (eq. [53]). Quite evident in the IR spectrum of this material
were the absorptions typical of an \( \alpha, \beta \)-unsaturated ester
\( (\nu_{\text{max}} \, 1715, \, 1648 \, \text{cm}^{-1}) \). The \( ^1\text{H} \) nmr spectrum clearly indicated
the presence of the ester and isopropyl groups and, as
expected for a conjugated system, the \( \alpha \)- and \( \beta \)-protons resonated at \( \delta \, 5.76 \) and \( 6.95 \), respectively. Importantly, these
olefinic signals exhibited the large (\( J = 16 \) Hz) coupling
typical of protons having a trans relationship.

The possibility of reducing the ester 255 directly to
the \( \alpha, \beta \)-unsaturated aldehyde at low temperatures (ca. \(-127^\circ \text{C})
using one equivalent of diisobutylaluminum hydride (DIBAL)
in pentane was investigated.* This reaction was abandoned

\[
\text{CO}_2\text{Et} \quad \begin{array}{c} \text{DIBAL} \\ \text{pentane} \end{array} \rightarrow \quad \text{OH}
\]

[54] 255 \quad \quad \quad \quad \quad 256

after several trials led to mixtures of the desired \( \alpha, \beta \)-unsaturated aldehyde 257 and the allylic alcohol 256. Con-
sequently, a two-step sequence was used to effect the same
transformation.

Using a slight excess over the required 2 equivalents of
diisobutylaluminum hydride in pentane, the unsaturated ester

* A review on the applications of DIBAL as a reducing agent
has been published\(^{148} \). For examples of reductions of esters
to aldehydes using DIBAL, the reader should consult ref. 148
and the references cited therein.
255 was reduced smoothly to the allylic alcohol 256 ($\nu_{\text{max}}$ 3300, 1660 cm$^{-1}$) in a yield of 95% (eq. [54]). In the $^1$H nmr spectrum of 256, the resonances at $\delta$ 5.38-5.87, which integrated for two protons, testified to the fact that the double bond had remained intact throughout the reduction, and the two-proton multiplet at $\delta$ 4.04-4.17 were undoubtedly due to the protons which were adjacent to the OH group.

A number of methods to oxidize the allylic alcohol 256 to the $\alpha,\beta$-unsaturated aldehyde 257 were attempted. These attempts included the use of pyridinium chlorochromate (PCC)$^{149}$ in dichloromethane and the oxidative combination of dimethyl sulfoxide-oxalyl chloride-trimethylamine in dichloromethane (Swern oxidation)$^{150}$ However, the best yields were obtained using pyridinium chlorochromate adsorbed on alumina,$^{151}$ and were likely due, in part, to the ease of workup.

Thus, reaction of the allylic alcohol 256 with an excess of pyridinium chlorochromate adsorbed on alumina in dichloromethane gave, after 3 hours at ambient temperatures, the desired aldehyde 257 in a quantitative yield (eq. [55]). In the ir spectrum of this material, there was no sign of an O-H
absorption, but the presence of an α,β-unsaturated aldehyde function (ν\text{max} \, 2780, 2700, 1675, 1622 \, \text{cm}^{-1}) was evident. In the \textsuperscript{1}H nmr spectrum of 257, the aldehyde proton appeared at δ 9.55 as a doublet with a coupling of 8 Hz to the adjacent olefinic proton.

![Chemical structure diagram]

To obtain the doubly unsaturated ester 258\textsuperscript{152} (eq. [56]), the aldehyde 257 was subjected to the same Wittig olefination conditions as described earlier for the transformation\textsuperscript{144,145} of isobutyraldehyde to 255. Unfortunately, the yield of this reaction was disappointingly and inexplicably low (44%). However, due to time constraints, the investigation of alternative reagents which may have provided better results was not pursued.

![Chemical structure diagram]

Nevertheless, the ir spectrum of 258 was consistent with
Fig. 13. The 400 MHz $^1$H nmr spectrum of 258.
the shown structure ($\nu_{\text{max}}$ 3010, 1700, 1635, 1612 cm$^{-1}$), and in the $^1$H nmr spectrum of this material, the isopropyl and ethyl ester groups were evident (Fig. 13). The trans stereochemistry of the $\alpha,\beta$-unsaturation was clearly visible in the form of a 14 Hz coupling exhibited by $H_F$ (doublet at $\delta$ 5.80). Appearing typically downfield at $\delta$ 7.26 was a doublet of doublets due to $H_E$. The remaining olefinic protons, $H_C$ and $H_D$ resonated as a pair of doublet of doublets at $\delta$ 6.09 and 6.13, respectively, with AB symmetry. By decoupling $H_E$, the large trans coupling of 15 Hz ($J_{CD}$) was observed in the collapsed doublet at $\delta$ 6.13 ($H_D$).

\[
\text{CO}_2\text{Et} \quad \text{DIBAL} \quad \text{pentane} \quad \text{OH} \quad \text{[57]}
\]

\[
\text{258} \quad \text{259}
\]

Again using diisobutylaluminum hydride in pentane, the doubly unsaturated ester 258 was reduced cleanly to the allylic alcohol 259 ($\nu_{\text{max}}$ 3300, 1650 cm$^{-1}$) as shown in eq. [57]. In the $^1$H nmr spectrum of 259, the two protons adjacent to the OH moiety appeared as a doublet ($J = 6$ Hz) at $\delta$ 4.15. A detailed analysis of the olefinic region of the $^1$H nmr spectrum of 259 is provided in Fig. 14.

Initial efforts to convert the alcohol 259 into the corresponding allylic bromide using triphenylphosphine dibromide
Fig. 14. The expanded region 6 5.6-6.3 of the $^1$H nmr spectrum of 259.
in acetonitrile containing an equivalent of triethylamine did not prove fruitful. An alternative method which was described by Miller\textsuperscript{154} fortunately met with more success. Thus, treatment of \textsuperscript{259} with phosphorus tribromide in the presence of pyridine furnished, after 4 hours at 0°C, the allylic bromide \textsuperscript{244} as a volatile liquid in a yield of 78\% (eq. [58]). Because this material had a tendency to darken on standing even at 0°C, it was distilled immediately prior to use. The ir spectrum of \textsuperscript{244} showed no O-H absorption and in the \textsuperscript{1}H nmr spectrum, the resonances of the protons adjacent to the bromine appeared as a doublet (J = 8 Hz) at \textit{\delta} 4.04. The isopropyl group and the four olefinic protons were clearly visible, as was the almost 1:1 ratio of bromine-isotopic molecular ions in the mass spectrum.

With the desired alkylating material \textsuperscript{244} in hand, the assembly of the bicyclo[3.1.0]hexane skeleton was initiated according to Scheme 29 (\textit{vide supra}).

The dianion of methyl acetoacetate, which was generated in the manner reported by Huckin and Weiler,\textsuperscript{155} reacted with the allylic bromide \textsuperscript{244} at 0°C in THF to afford the desired
β-keto ester 245 in a modest yield of 53% (eq. [59]). It is possible that the mediocre yield reflected the instability of the alkylating material 244 and perhaps, the efficiency of the reaction could be improved by shortening the reaction times. However, this was not investigated further.

The ir spectrum of the alkylated product 245 exhibited the anticipated absorptions of an unsaturated keto ester ($v_{\text{max}}$ 1740, 1710, 1650, 1620 cm$^{-1}$). In the $^1$H nmr spectrum of this compound, the resonances which were attributed to the isopropyl and methyl ester groups were quite visible. The two protons alpha to both the ketone and ester moieties appeared as a singlet at $\delta$ 3.46 while the two which were alpha to only the ketone function resonated at $\delta$ 2.65 as a triplet ($J = 7$ Hz). Although the olefinic signals were partially overlapped, it was possible to discern the two large couplings of 14.5 and 15 Hz which indicated the trans,trans geometry of the two conjugated double bonds.

Treatment of the β-keto ester 245 with p-toluenesulfonyl azide* in acetonitrile containing triethylamine 162 led to the
essentially quantitative formation of a yellow viscous oil, which was identified as the diazo keto ester 246 (eq. [60]). The strong characteristic absorption ($v_{\text{max}} 2120 \text{ cm}^{-1}$) of diazo-containing compounds was clearly in evidence in the ir spectrum of 246, as were the carbonyl bands at $v_{\text{max}} 1710$ and $1650 \text{ cm}^{-1}$. With the exception of the missing singlet ($\delta 3.46$) which was due to the $\alpha$-methylene protons of 245, the $^1\text{H nmr}$ spectrum of the diazo ester 246 resembled that of the precursor 245.

---

* Tosyl azide ($p$-toluenesulfonyl azide) was prepared in accordance with Doering and DePuy. A comparison of a number of diazo transfer agents has been reported. Diazo transfer has been effected from tosyl azide and phase-transfer conditons, as well as from 2,4,6-tri-isopropylbenzene-sulfonyl azide and $p$-carboxybenzene-sulfonyl azide.
The intramolecular carbenoid cyclization of the diazo ester 246 was induced by a catalytic amount of copper (II) acetoacetonate * in refluxing benzene and furnished the 6-vinylbicyclo[3.1.0]hexanone 247 in 78% yield (eq. [61]). In view of the stereospecificity with which copper-induced carbenoid additions have been known to occur, 91,92 the assignment of exo stereochemistry to the C-6 alkenyl side chain did not seem presumptuous. Spectral confirmation of this stereochemical assignment was not available until after the next step.

The carbonyl groups in compound 247 gave rise to ir absorptions at \( \nu_{\text{max}} \) 1750 and 1720 cm\(^{-1}\). In the high field region of the \( ^1H \) nmr spectrum of this material, the only discernible resonances were the pair of doublets at \( \delta \) 0.95 and 0.96, which were assigned to the isopropyl methyl groups, and the overlapping doublet of doublets at \( \delta \) 2.67, which were due to the C-5 cyclopropyl proton. This proton is apparently coupled similarly to the other cyclopropyl proton at C-6 (J = 5.5 Hz) and to the C-4 exo proton. The C-5 and C-4 endo protons form a dihedral angle which is near to 90° and these protons would therefore be expected to couple weakly (if at all) with each other. Further downfield, the three-proton singlet at \( \delta \) 3.76 easily established the presence of the methyl ester. More importantly, the large coupling (J = 15.5 Hz)

---

* Copper (II) acetoacetonate [Cu(acac)\(_2\)] was prepared from acetylacetone and cupric acetate in accordance with ref. 163.
which was observed in the olefinic resonances at $\delta$ 5.21 and 5.71, attested to the E stereochemistry of the 3-methyl-1-butyl side chain.

Conversion of the bicyclic keto ester 247 to the desired silyl enol ether 240 was routinely accomplished in 87% yield. Not surprisingly, the IR spectrum of 240 showed a strong olefinic band at 1620 cm$^{-1}$. An examination of the $^1$H NMR spectrum of 240 clearly revealed the presence of the tert-butyl and silyl methyl groups by the singlets at $\delta$ 0.95 and 0.16, respectively. The diagnostically important broad singlet at $\delta$ 4.38 was assigned to the shielded vinyl proton which is adjacent to the silyloxy substituent. The cyclopropyl proton $H_E$ resonated at $\delta$ 1.73, at slightly higher field than the corresponding proton in the precursor ketone 247 ($\delta$ 2.00-
2.34). This phenomenon was observed also in the cases of other analogous silyl enol ethers (vide supra) and is probably due to the position of $H_E$ within the shielding cone of the cyclopentene double bond. It is pertinent to point out that $H_E$ must necessarily be endo to experience this shielding effect, but the most convincing grounds for the stereochemical assignment of $H_E$ lies in the observed thermal stability of 240. If the butenyl side chain was endo, 240 would probably be quite susceptible to Cope rearrangement at ambient temperatures. 72, 73, 76

Two sets of signals which exhibited the conspicuously large geminal coupling of 16 Hz, were situated at $\delta$ 2.58 and 2.23. The former was assigned to $H_z$, which coupled to the bridgehead proton $H_G$ ($J = 7$ Hz) and to the vinyl proton $H_I$ ($J = 2$ Hz), while the latter was attributed to $H_J$. Again, the $H_G$-$H_J$ dihedral angle appears to be almost 90° and consequently no coupling was observed between these two protons. $H_J$, however, exhibited a coupling of 3 Hz to $H_I$. The olefinic protons $H_B$ and $H_D$, both of which occurred as doublet of doublets at $\delta$ 5.59 and 5.48, respectively, exhibited their trans relationship in the form of a 15 Hz coupling.

Having successfully prepared the requisite silyl enol ether 240 with the (E)-3-methyl-1-butenyl substituent, we directed our efforts at the synthesis of the corresponding (Z) isomer 242. Scheme 31 shows a possible means of preparing 242 from the bicyclic keto ester 130a. That is, one can envisage
an oxidative cleavage of the alkene moiety in 130a to furnish the cyclopropyl aldehyde 260 which, upon suitable olefination and appropriate derivatization, would give the desired compound 242.

The starting material 130a was synthesized* in accordance with the route described by Piers and Ruediger81 (Scheme 32).

* We are thankful to Pam Murch who prepared a sufficient quantity of 130a as part of a summer project in our laboratory.
SCHEME 32

[a] 131a, THF-HMPA, 0°C (70%)  [b] p-MeC₆H₄SO₂N₃, Et₃N, MeCN  
[c] Cu-bronze, refluxing toluene (50% from 262)

Ozonolysis (O₃, MeOH, CH₂Cl₂, -78°C) of the keto ester 130a followed by reductive workup with dimethyl sulfide proceeded smoothly to afford the cyclopropyl aldehyde 260* in 87% yield (eq. [63]).

* This material exhibited spectra in accord with structural assignments and gave satisfactory high resolution mass spectrometric measurements.
Unfortunately, treatment\textsuperscript{164} of the aldehyde \textsuperscript{260} with the phosphorane \textsuperscript{264}, which was prepared\textsuperscript{165} from triphenylphosphine and isobutyl bromide, yielded little if any of the desired alkene \textsuperscript{261} (eq. [64]). This failure might be attributed at least partly to the steric congestion provided by the ester group, thereby rendering the aldehyde less accessible to nucleophilic attack. To remedy this problem, another aldehyde such as \textsuperscript{265}, which was deemed suitable\footnote{It was assumed that the lack of a C-1 carbomethoxy group would be of no consequence to the stereospecificity of the Cope rearrangement of these vinylbicyclo[3.1.0]hexenes.} for the investigation at hand, was sought.

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) \textsuperscript{179};
  \node (b) at (2,0) \textsuperscript{265};
  \draw (a) edge[->] node[above] {\textbf{a)} $O_3$} (b);
  \draw (a) edge[->] node[below] {\textbf{b)} $Me_2S$} (b);
\end{tikzpicture}
\end{center}

Subjection of the bicyclic ketone \textsuperscript{179} to ozonolytic conditions ($O_3$, MeOH, CH$_2$Cl$_2$, -78°C) gave, after workup with dimethyl sulfide, the aldehyde \textsuperscript{265}\footnote{This material exhibited spectra in accord with structural assignments and gave satisfactory high resolution mass spectrometric determinations.} in 86% yield (eq. [65]).

Using inverse addition of the phosphorane \textsuperscript{264} to the aldehyde \textsuperscript{265}, the Wittig olefination gave the alkene \textsuperscript{266} and its \textit{trans} isomer in an unenviable yield of 35% (eq. [66]).
Moreover, the **cis** and **trans** isomers were obtained in a ratio of no higher than 7:2 (as judged by glc analysis). Efforts to separate these geometric isomers by column and gas-liquid chromatography proved fruitless. Due to the unacceptably low yields and poor stereoselectivity of this reaction, this synthetic approach to prepare a bicyclo[3.1.0]hex-2-ene with a C-6 (Z)-3-methyl-1-butenyl substituent was abandoned.

An alternative means of generating **cis**-olefins is provided by the partial hydrogenation of acetylenic bonds, and by using this strategy it should be possible to obtain 266 from the acetylenic compound 267 (eq. [67]). The task at hand then was to prepare 267 and this could be accomplished employing a
synthetic approach which is analogous to that used in the preparation of the simple bicyclic ketone 179. Scheme 33 outlines the sequence for the preparation of 267, starting from the acetylenic alcohol 268.

The acetylenic alcohol 268 was readily prepared from 3-methyl-1-butyne and acrolein in one step (eq. [68]). Thus, 3-methyl-1-butyne was treated with 1.1 equivalents of n-butyllithium in THF at -78°C and the resultant lithium acetylide was treated with acrolein to afford the alcohol 268 (ν max
as a volatile oil in 86% yield. The ir spectrum of this material featured bands which are characteristic of triple ($\nu_{\text{max}}$ 2215 cm$^{-1}$) and double ($\nu_{\text{max}}$ 1630 cm$^{-1}$) bonds. The $^1$H nmr spectrum of the alcohol 268 clearly indicated the presence of the isopropyl and vinyl groups and was consistent with the given structure 268.

\[
\text{CH}_3\text{C(OEt)}_3 \xrightarrow{\text{H}^+, \Delta} \text{EtO} \]

268

269

The transformation of the alcohol 268 to the $\gamma,\delta$-unsaturated ester 269 via an orthoester Claisen rearrangement, presumably involving the transition state 273, proceeded smoothly and with high stereoselectivity. Thus, reaction of 268 with hot triethyl orthoacetate in the presence of a catalytic amount of propionic acid afforded the trans-olefin 269 in a yield of 66%. The ir spectrum of 269 clearly showed the carbonyl band ($\nu_{\text{max}}$ 1730 cm$^{-1}$) of the ester function along with the acetylenic absorption ($\nu_{\text{max}}$ 2190 cm$^{-1}$), while the $^1$H
nmr spectrum confirmed the trans stereochemistry of the double bond. That is, a large trans coupling of 15.5 Hz was discernible in the olefinic resonances at δ 5.49 and 6.00.

\[
\text{EtO} \quad \text{KOH} \quad \text{H}_2\text{O-MeOH,} \quad \Delta \quad \text{HO} \\
\text{269} \quad \rightarrow \quad \text{270}
\]

Routine hydrolysis (KOH, H\textsubscript{2}O-MeOH) of the ethyl ester 269 furnished the corresponding acid 270 as colourless crystals, which were purified by low-temperature recrystallization from heptane (eq. [70]). Obtained in 78% yield, the acid 270 \( (\nu_{\text{max}} 3200-2500, 1701 \text{ cm}^{-1}) \) exhibited a \(^1\text{H} \) nmr spectrum which lacked the ethoxy resonances, but otherwise resembled that of the starting material 269.

\[
\text{HO} \quad \text{(COCl)}_2 \quad \text{hexane, } \Delta \quad \text{Cl} \\
\text{270} \quad \rightarrow \quad \text{271}
\]

In accordance with a procedure described by Hudlicky et al.,\textsuperscript{98} the acid 270 was refluxed with oxalyl chloride in hexane to provide, after one hour, the acid chloride 271 in 83% yield (eq. [71]). The ir spectrum of this material exhibited the
carbonyl absorption typical of acyl chlorides ($v_{\text{max}}$ 1790 cm$^{-1}$) and the weak but unmistakable acetylenic band ($v_{\text{max}}$ 2190 cm$^{-1}$). The $^1$H nmr spectrum was consistent with the structure 271.

$$
\begin{align*}
\text{CH}_2\text{N}_2 & \quad \text{Et}_2\text{O}, 0^\circ\text{C} \\
\text{271} & \text{272}
\end{align*}
$$

[72]

Treatment of the acyl chloride 271 with ethereal diazomethane* at 0°C led smoothly to the almost quantative formation of the diazo ketone 272 (eq. [72]). In the ir spectrum of 272, the strong bands at $v_{\text{max}}$ 2085 and 1634 cm$^{-1}$, which are characteristic of $\alpha$-diazo ketones, were clearly visible. With the exception of the singlet at $\delta$ 5.21 which was assigned to the proton adjacent to the diazo moiety, the $^1$H nmr spectrum was quite similar to those of the acid 270 and the acyl chloride 271.

In the presence of a catalytic amount of copper (II) acetoacetonate, the diazo ketone 272 underwent a carbenoid cyclization in refluxing benzene to afford stereoselectively in 77% yield, the desired bicyclo[3.1.0]hexanone 267 (eq.

* Scott and Minton $^{166}$ have circumvented the problem of using an excess of diazomethane to scavenge HCl by developing a procedure which calls for 1 equivalent of diazomethane in the presence of triethylamine.
As in the case of 247, the stereochemistry of the C-6 alkenyl substituent was assigned as exo in light of the well documented stereospecificity of the carbenoid cyclization. In the ir spectrum of this compound, the carbonyl band appeared at $\nu_{\text{max}}$ 1725 cm$^{-1}$. No olefinic resonances were observed in the $^1$H nmr spectrum of 267, which provided little information other than evidence for an isopropyl group.

To generate the cis-alkene, the acetylenic ketone 267 was partially hydrogenated using Lindlar's catalyst (5% Pd/CaCO$_3$)* and a trace of quinoline to temper the activity of the catalyst. Marvell and Li* have made a survey of various catalysts used for the semihydrogenation of triple bonds. Lindlar's catalyst was prepared and used in accordance with procedures given in ref. 169.
catalyst (eq. [67]). No further hydrogenation of the resultant alkene was observed since the reaction simply stopped after the uptake of one equivalent of hydrogen. A 95:2 mixture (judged by glc analysis) of the cis-alkene 266 and its trans isomer were obtained and these substances were readily separated by column chromatography. In this manner, 266 was isolated in 94% yield.

![Chemical Structure](image)

Little information was gleaned from the ir spectrum of 266, which was similar to that of the starting material 267. The $^1$H nmr spectrum of this material was more helpful, and indicated the presence of two olefinic protons in the form of a pair of overlapping doublet of doublets, one at $\delta$ 4.65 and the other at $\delta$ 5.24. Both sets of resonances revealed a coupling of 10.5 Hz, which is typical of cis disubstituted double bonds. Other than the isopropyl resonances, the doublet of doublets at $\delta$ 1.75 which was assigned to $H_F$ was clearly visible. This cyclopropyl proton couples to $H_G$ ($J = 5$ Hz) and to $H_E$ ($J = 2.5$ Hz).

Transformation of the ketone 266 into the silyl enol ether 274 was effected smoothly in the usual way and in 98%
Fig. 15. The 400 MHz $^1$H nmr spectrum of 274.
yield (eq. [74]).

As expected, the ir spectrum of 274 exhibited a strong olefinic band at $\nu_{\text{max}}$ 1625 cm$^{-1}$. The $^1$H nmr spectrum of this compound (Fig. 15), having well resolved signals which were revealing in fine structure, presented a veritable challenge to spectral interpretation. As in the spectrum of the ketone 266, the cis geometry of the (Z)-3-methyl-1-butenyl double bond was shown by a coupling constant of 10.5 Hz in the olefinic resonances at $\delta$ 4.64 and 5.14. By decoupling $H_B$, it was possible to assign the overlapping doublet of doublets at $\delta$ 4.64 to $H_D$ and the signal at $\delta$ 5.14 (similar splitting pattern) to $H_C$. Expectedly, $H_I$ appeared as a broad singlet at
δ 4.31 and is the most shielded of the olefinic protons owing to the electron-rich nature of the enol ether double bond. By decoupling H_I, which eliminated a small allylic coupling, the multiplet at δ 1.60 sharpened and was consequently assigned to H_F. To distinguish between the other cyclopropyl protons, H_D was decoupled. As a result, the unresolved doublet at δ 1.28 collapsed to a broad singlet and was therefore assigned to H_E, which couples quite strongly to H_D (J = 10 Hz). By a process of elimination, the final cyclopropyl proton H_G was assigned to the multiplet at δ 1.50-1.55. As in similar systems, H_J resonated at higher field (δ 2.30) than H_Z (δ 2.52), and exhibited a very small coupling to the bridgehead proton H_G (J < 1 Hz), presumably due to the fact that the H_G-H_J dihedral angle is close to 90°. As reflected by the overlapping doublet of doublet of doublets, H_J is coupled to H_I (J = 3 Hz), geminally to H_Z (J = 16.5 Hz) and surprisingly to H_F (J = 3 Hz!). Indeed, when H_J was decoupled, the signal at δ 1.60 (H_F) collapsed to a doublet of doublets (J_{FG} = 6 Hz, J_{EF} = 2 Hz). The proton H_Z, which resonated as a doublet of doublet of doublets at δ 2.52, couples to H_J (J = 16.5 Hz), to H_G (J = 7 Hz) and to H_I (J = 2 Hz).

Having successfully synthesized the E and Z olefins 240 and 274, we turned our attention to the thermal rearrangement of these systems. A potential problem attends the Cope rearrangement of 274, which possesses a Z isopropyl group on the 6-alkenyl side chain. Bond reorganization of 274 in a
Cope sense would be presumed to proceed via the transition state 275. However, this transition state suffers from a notable steric interaction between the isopropyl group and the cyclopentenyl ring residue. It is possible that this steric strain could so destabilize the transition state that, upon thermolysis, an alternative lower energy rearrangement takes place.
Compounds 240 and 274 were dissolved in benzene and the solutions were heated in sealed pyrolysis tubes. Thus, thermolysis of 240 at 200°C for 2 hours afforded, in 95% yield, the bicyclo[3.2.1]octadiene 241 with an endo isopropyl substituent at C-4 (eq. [49]). On the other hand, 274 rearranged smoothly at 240°C to provide, after 4.5 hours, a single product in 93% yield. It was gratifying to identify this thermolysis product as the desired bicyclo[3.2.1]octadiene 276 with an exo C-4 isopropyl group (eq. [75]), and to find that our misgivings concerning the viability of this transformation (274 \rightarrow 276) were in fact unfounded.

The IR spectrum of the enol ether 241 was much like that of the starting material 240 in general appearance. However, the ester carbonyl band occurred at $\nu_{\text{max}}$ 1700 cm$^{-1}$ as expected for an $\alpha,\beta$-unsaturated ester, and an olefinic absorption was found at 1610 cm$^{-1}$. In the $^1$H nmr spectrum of 241, the doublet displaying a geminal coupling ($J_{HF} = 9.5$ Hz) at $\delta$ 1.78 was assigned to $H_I$. In view of both $H_I-H_F$ and $H_I-H_K$ dihedral angles being $\approx 90^\circ$, it was not surprising to find that $H_I$ couples with neither bridgehead protons. Decoupling $H_I$ led
Fig. 16. The homonuclear spin decoupling experiment with 241: (a) the normal 400 MHz $^1$H nmr spectrum for the region $\delta$ 2.0-6.4, and (b) the spectrum with irradiation at $\delta$ 5.44 ($H_D$).
to the assignment of the complex resonance at $\delta$ 2.20 to $H_2^\prime$, which couples to the two bridgehead protons ($J_{FZ} = 4$ Hz, $J_{KZ} = 5$ Hz) and long-range to $H_E$ ($J = 1$ Hz). To verify the assignment of $H_K$, $H_E$ was decoupled, leading to the collapse of the splitting pattern at $\delta$ 2.92 ($H_K^\prime$) to a doublet ($J_{KZ} = 5$ Hz). The 5 Hz coupling between $H_C$ and $H_F$ is of diagnostic importance in the endo stereochemical assignment of the C-4 isopropyl substituent. Had this substituent been exo, a smaller coupling between $H_C$ and $H_F$ would be anticipated in view of the $H_C-H_F$ dihedral angle being, in such a case, almost 90°. By decoupling $H_D$, the collapsed signal due to $H_C$ at $\delta$ 2.06 clearly exhibited the 5 Hz coupling ($J_{CF}$) as shown in detail by Fig. 16b.

The ir spectrum of the silyl enol ether 276, other than displaying an olefinic band at $\nu_{\text{max}}$ 1620 cm$^{-1}$, offered little information of diagnostic value. The $^1H$ nmr spectrum of 276 (Fig. 17) in many ways resembled that of the endo isomer 241, but on closer examination the subtle differences proved enlightening. At $\delta$ 5.11, the doublet exhibiting a 3 Hz coupling ($J_{JK}$), was assigned to $H_J$, which is relatively shielded by the
Fig. 17. The 400 MHz $^1$H nmr spectrum of 276.
electron-rich enol ether double bond. The proton $H_I$, being coupled only to $H_Z$ ($J = 9.5$ Hz), appeared as a doublet at $\delta 1.75$. This geminal coupling ($J = 9.5$ Hz) was found in the complex signal assigned to $H_Z$ at $\delta 1.97$. It was possible to distinguish between the bridgehead protons $H_F$ and $H_K$ by decoupling $H_J$. Apparently $H_F$ exhibits a 5 Hz coupling with $H_Z$ as shown by the collapse of the complex signal ($H_Z$) at $\delta 1.97$ to a doublet of doublets ($J_{IZ} = 9.5$ Hz, $J_{KZ} = 3$ Hz) when $H_F$ was decoupled (Fig. 18). Significantly, this decoupling experiment caused only a slight sharpening of the signal assigned to $H_C$ at $\delta 1.88-1.94$. That is, the coupling between $H_C$ and $H_F$ is $< 1$ Hz, as would be anticipated if $H_C$ was endo, an orientation in which $H_C$ forms, with $H_F$, a dihedral angle approximating 90°.

The $\beta$-siloxy $\alpha,\beta$-unsaturated ester 241 was converted to a mixture of the $\beta$-keto esters 277 via fluoride-mediated cleavage of the silyl enol ether moiety. Tlc analysis clearly indicated the presence of two components. Subsequent decarboxylation was accomplished by refluxing the mixture 277 in THF in the presence of hydrochloric acid. A single
Fig. 18. The homonuclear spin decoupling experiment with 276: (a) the normal 400 MHz $^1$H nmr spectrum expanded for the region $\delta$ 1.6-2.0, and (b) the spectrum with irradiation at $\delta$ 2.38 ($H_F$).
compound was obtained in 50% yield over the two steps, and was shown to have the structure 278.

![Chemical Structure](image)

Acid-catalyzed hydrolysis (THF-5% HCl, r.t.) of the silyl enol ether 276 provided the ketone 279 in 57% yield.

Ketones 278 and 279 were shown to be two distinctly different compounds by glc analysis. The ir spectra of these epimeric ketones were expectedly similar. In the spectrum of 278, the carbonyl absorption occurred at $v_{\text{max}}$ 1730 cm$^{-1}$, whereas in the spectrum of 279, the corresponding band was at 1735 cm$^{-1}$.

In contrast, the $^1$H nmr spectra of 278 and 279 as shown in Figs. 19 and 20, are remarkably different, particularly in the high field region. In fact, the only similarity lies in the splitting patterns and chemical shifts of the olefinic protons in 278 and 279. Table I shows a comparison of the $^1$H nmr spectral data for the ketones 278 and 279.

It is interesting to note that the resonances of the non-equivalent isopropyl methyl groups in the $^1$H nmr spectrum of 278 appeared almost 0.1 ppm apart, at $\delta$ 0.95 and 1.06. In the high field region of the normal spectrum, the only signal
Fig. 19. The 400 MHz $^1$H nmr spectrum of 278.
Fig. 20. The 400 MHz $^1$H nmr spectrum of 279.
TABLE I. $^1$H nmr Data for Compounds 278 and 279.**

![Diagram of compounds 278 and 279]

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\delta$ H C</th>
<th>$\delta$ H D</th>
<th>$\delta$ H E</th>
<th>$\delta$ H F</th>
<th>$\delta$ H I</th>
<th>$\delta$ H J</th>
<th>$\delta$ H K</th>
<th>$\delta$ H Y</th>
<th>$\delta$ H Z</th>
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<tr>
<td>278</td>
<td>2.12 OL dddd</td>
<td>5.63 dddd</td>
<td>6.05 dddd</td>
<td>2.69- 2.77 m</td>
<td>2.00 dd</td>
<td>2.22 dd</td>
<td>2.69- 2.77 m</td>
<td>2.28 ddd</td>
<td>2.09 ddd</td>
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<td>OL dddd</td>
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<td>J_{DE} = 10</td>
<td>J_{DE} = 10</td>
<td>J_{DE} = 10</td>
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<tr>
<td>279</td>
<td>1.85- 1.93 m</td>
<td>5.55 ddd</td>
<td>6.07 * OL dddd</td>
<td>2.59 d</td>
<td>2.06 d</td>
<td>2.28 OL ddd</td>
<td>2.73- 2.79 m</td>
<td>2.23 dd</td>
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* OL=overlapping  ** All coupling constants given in Hertz (Hz)
which was well resolved was a doublet of doublets at $\delta$ 2.00, assigned to $H_I$. This proton exhibits a 11.5 Hz geminal coupling with $H_Z$ and a long-range coupling of 3 Hz with $H_J$. Protons $H_J$ and $H_Y$ appeared as a pair of doublet of doublets with AB symmetry at $\delta$ 2.22 and 2.28, respectively. Other than coupling geminally with $H_Y$ ($J = 17.5$ Hz), $H_J$ couples only with $H_I$. Upon consideration of the dihedral angles involved, it is not surprising that the bridgehead proton $H_K$ couples with $H_Y$ ($J = 5.5$ Hz), but not with $H_J$. Without the aid of decoupling experiments, it was not possible to make any further assignments due to the complexity of the remaining resonances in the region $\delta$ 2.05-2.15. However, the elimination of small couplings in this region by decoupling $H_E$ revealed a number of details which proved helpful in completing the assignments (Fig. 21b). That is, the 11.5 Hz geminal coupling between $H_I$ and $H_Z$ was discernible in the collapsed splitting pattern at $\delta$ 2.09 which was consequently assigned to $H_Z$. The proton $H_Z$ also exhibits 5.5 and 4 Hz couplings with the neighbouring bridgehead protons $H_F$ and $H_K$. The other signal partially uncovered by decoupling $H_E$ was attributed to $H_C$. As
Fig. 21. The homonuclear spin decoupling experiment with 278: (a) the normal 400 MHz $^1\text{H}$ nmr spectrum expanded for the region $\delta$ 1.9-2.8, and (b) the spectrum with irradiation at $\delta$ 6.05 ($H_E$).
in the precursor silyl enol ether 241, H_C displays a 5 Hz coupling with H_F, reaffirming the endo stereochemistry of the isopropyl substituent at C-4.

![Chemical structure 279]

In contrast with that of 278, the ^1H nmr spectrum of 279 exhibited fewer overlapping resonances in the high field region. The resonances of the isopropyl methyl groups, unlike those of 278, occurred as an almost overlapping pair of doublets. Decoupling the isopropyl methine proton showed that the signal due to H_C was obscured by the multiplet at δ 1.85-1.93. The protons H_J and H_Y appeared as an AB system, and were assigned with the aid of an experiment in which H_I was decoupled. The long-range coupling (J_{IJ} = 2.5 Hz) constant was eliminated from the splitting pattern of H_J. The proton H_K appeared as a complex multiplet at δ 2.73-2.79, while H_F resonated as an unresolved doublet at δ 2.59, exhibiting a 5.5 Hz coupling with H_Z. As in the precursor silyl enol ether 276, the coupling between H_C and H_F was ≤ 1 Hz, thereby supporting the exo stereochemical assignment of the isopropyl substituent at C-4.

Clearly, compounds 278 and 279 are epimeric at C-4.
Thus, for bicyclo[3.1.0]hex-2-enes which contain bulky substituents on the 6-(1-alkenyl) side chain, this study not only demonstrates the viability of the Cope rearrangement, but also provides strong evidence for the stereospecificity of this process.*

1.2.4 Conclusion

It is clear from the synthetic studies described thus far in this thesis that the Cope rearrangement of 6-(1-alkenyl)bicyclo[3.1.0]hex-2-enes containing even sterically bulky substituents on the 6-alkenyl side chain presents a viable means of generating functionalized bicyclo[3.2.1]octa-2,6-dienes. Moreover, this methodology provides for the placement of synthetically useful functionalities on any of the carbon bridges of the bicyclo[3.2.1]octane skeleton. Finally, the stereospecificity of the rearrangement process would lend a measure of elegance to a natural product synthesis using this methodology to access the key intermediate.

For any newly developed synthetic approach, the ultimate test of its potential lies in its application to the synthesis of target molecules, and in our work, the naturally occurring sesquiterpenoid sinularene (125) was such a target molecule.

* These results were recently reported in a communication.
Chapter II
THE TOTAL SYNTHESIS OF (+)-SINULARENE

2.1 Introduction

2.1.1 The Isolation and Characterization of (-)-Sinularene

In 1977, Djerassi and coworkers\textsuperscript{82} isolated a new sesquiterpene hydrocarbon, named sinularene, as a major component from the hexane extract of dried colonies of a soft coral *Sinularia mayi* (Coelenterata, Anthozoa, Alcyonaria, Alcyonacea). Obtained in 0.01\% yield (based on dried animal material), sinularene was deduced to possess a tricyclic skeleton and empirical formula \( \text{C}_{15}\text{H}_{24}\).

From the infrared, \(^1\text{H}\) and \(^{13}\text{C}\) nmr spectra\textsuperscript{82b} of sinularene, a number of structural features were immediately apparent. First, bands \((\nu_{\text{max}} 3076, 1660, 870 \text{ cm}^{-1})\) in the infrared spectrum, as well as the resonances of two vinylic protons \((^{1}\text{H nmr})\), an olefinic methylene carbon and an olefinic quaternary carbon \((^{13}\text{C nmr})\) indicated the presence of an exocyclic methylene. Second, both infrared \((\nu_{\text{max}} 1382, 1365 \text{ cm}^{-1})\) and \(^{1}\text{H nmr} [\delta 0.90, 0.92 (\text{d, d, 3H each, J=6.4 Hz})]\) spectra supported the presence of an isopropyl group. And third, based on the \(^{1}\text{H nmr} \) spectrum, sinularene also contained a tertiary methyl group.

Ozonolysis of sinularene provided a compound (later
assigned as \(280\), which was found to have an empirical formula \(\text{C}_{14}\text{H}_{22}\text{O}\) and displayed an infrared band at \(1740\ \text{cm}^{-1}\) \((\nu_{\text{max}})\), indicative of a cyclopentanone. Subjection of sinularene to osmium tetroxide oxidation afforded a diol (later assigned as \(281\)) with empirical formula \(\text{C}_{15}\text{H}_{26}\text{O}_2\) and which exhibited resonances \(^1\text{H}\ \text{nmr} \delta 3.68, 3.91 \text{ (d, d, 1H each, J=11.0 Hz)}\) attributed to two isolated methylene protons adjacent to the hydroxyl moiety. In addition, sinularene was subjected to hydroboration-oxidation conditions to yield
the primary alcohol \(282\), and reaction of \(281\) with \(p\)-bromo-
benzoyl chloride led to the crystalline benzoate \(283\), but the
spectra of \(282\) and \(283\) provided few structural clues of use.

On the basis of these experimental and spectral data, it was
determined that the exocyclic methylene was on a five-
membered ring in sinularene. In fact, the exact structure
of sinularene was not established until an x-ray determination
of \(283\) was made. Consequently, a purified sample of
sinularene \(\{[\alpha]_D^{20} -142^\circ (c 0.55 \text{ in } \text{CCl}_4)\}\) was accorded the
structure \(125\).

Two sesquiterpenes, 12-acetoxysinularene \(284\) and
12-acetoxycyclosinularene \(285\), which are related to
sinularene structurally, have been isolated recently from
the dichloromethane extract of a coral \textit{Clavularia inflata}
and characterized.\(^{170}\)

2.1.2 Previous Syntheses of Sinularene

Up until the present time, three total syntheses of
\((\pm)\)-sinularene have been reported, and it seems relevant to
briefly outline them here.

Collins and Wege\(^{171}\) completed the total synthesis of
sinularene \(125\) in a fifteen step sequence starting with the
lactone \(286\)\(^{172}\) (Scheme 34). Thus, treatment of \(286\) with
lithium aluminum hydride followed by conversion of the result-
ant material to an intermediate hydroxy tosylate and oxidation
provided the bicyclic ketone \(287\). Transformation of the latter
material to the iodide and protection of the ketone moiety
SCHEME 34

[a] LiAlH₄, Et₂O, reflux, 1 h (88%)  [b] p-MeC₆H₄SO₂Cl, pyridine, 0°C, 5 h  [c] PCC, CH₂Cl₂, r.t., 2 h (45% over two steps)  [d] NaI, DMF, 80°C, 4.5 h (74%)  [e] HOCH₂CH₂OH, H⁺ (75%)  [f] 289, DMF, 55°C, 20 h (77%)  [g] H₃O⁺  [h] m-ClC₆H₄CO₃H, benzene, 0°C, 2 h (91%)  [i] KOBu⁺, HOBu⁺, reflux, 4 h (292: 22%; 296: 31%)  [j] AcCl, Me₂NPh  [k] 450°C  [l] H₂, Pt, 0°C, 20 min  [m] MeLi, Et₂O, reflux, 2 h; H₂O
gave the iodo acetal 288, which, when treated with the
\[ \text{Ni} \quad \begin{array}{c}
\text{Br} \\
\text{Ni} \\
\text{Br}
\end{array} \]
\[ 289 \]
\[ \text{Ni} \quad \begin{array}{c}
\text{Br} \\
\text{Br}
\end{array} \]
n-allyl nickel complex 289, was converted into 290. Acetal 290 was hydrolyzed to the corresponding ketone, which was subsequently treated with m-chloroperbenzoic acid to give a diastereomeric mixture of the epoxy ketones 291. When 291 was subjected to basic conditions, a mixture of the alcohols 292 and 296 was obtained in a 1:1 ratio (as judged by glc analysis). These epimeric alcohols 292 and 296 were separated by column chromatography, and each were transformed into the corresponding acetates and thermolyzed. Thus, from 296 was obtained a mixture of 294 and 297 in a ratio of 4:6 respectively, while from 292, a mixture of 293 and 294 was recovered in a ratio of 95:5, respectively. Hydrogenation of the terminal alkene 293 furnished the intermediate bicyclic ketone 280, which exhibited a $^1$H nmr spectrum quite different from that of the epimer 298, obtained via hydrogenation of 294. Subsequent treatment of the ketone 280 with methylthium gave the alcohol 295, which, upon acetylation followed by pyrolytic elimination of acetic acid, was transformed into racemic sinularene (125). Unfortunately, this total synthesis of (+)-sinularene was marred by the lack of stereoselectivity in the epoxidation leading to the formation of 291.

In the key step of their reported synthesis of (+)-sinularene (125), Oppolzer and coworkers demonstrated
the use of a highly regio- and stereoselective intramolecular "magnesium-ene" reaction (Scheme 35). Thus, the bicyclic tosylate 299 was converted into the corresponding iodide 300, which was treated with the dianion 301 of tiglic acid to provide, with high regioselectivity, the γ-alkylated acid 302. Reduction of the acid 302 followed by tosylation and subjection of the resultant tosylate to nucleophilic displacement by chloride ion furnished 303. In the critical cyclization step, the Grignard reagent formed from 303 was heated to give the cyclized alkenylmagnesium chloride, which was subsequently carboxylated to afford the bicyclic acid 304 regio- and stereoselectively. The relative stereochemistry resulting from this reaction was evidenced by the smooth iodolactonization of 304 as well as by trapping the cyclized Grignard species with O₂ followed by Jones' oxidation to afford the ketone 298, the ¹H nmr and infrared spectra of which was identical to those of an authentic sample of 298. Subsequently, reduction of 304 led to the intermediate alcohol 305, from which both sinularene (125) and 5-epi-sinularene (308) were obtained via different synthetic paths. Thus, hydrogenation of 305 followed by acetylation and pyrolytic elimination of acetic acid afforded (+)-5-epi-sinularene (308). To obtain the desired exo configuration of the isopropenyl moiety, 305 was subjected to a sequence of synthetic transformations which had the overall effect of epimerizing the isopropenyl group to the
SCHEME 35

[a] NaI, acetone, reflux, 9 h (87%) [b] 301, HMPA, -78°-0°C→r.t., 16 h (78%) [c] LiAlH₄ [d] MeSO₂Cl, pyridine, 0°C, 3 h
[e] 1N aq. HCl, 0°C, 10 min (55% from 302) [f] (i) act. Mg, THF, -78°C→r.t., 2 h (ii) 50°C, 16 h (iii) CO₂, -10°C (iv)
80°C, 2 h (47% from 303) [g] H₂, Pt, MeOH (99%) [h] AcCl, NEt₃, DMAP, CH₂Cl₂, 0°C, 2 h [i] 500°C [j] (i) NaH, DMF, r.t. (ii) HMPA, MeI, r.t., 16 h (89%) [k] (i) O₃, MeOH,
-78°C (ii) Me₂S, -78°C→r.t., 2 h (quant.) [l] KOH, EtOH,
H₂O, reflux, 7 h (90%) [m] Ph₃P=CH₂, THF, r.t., 16 h (69%)
[n] Me₃SiI, NaI, MeCN, r.t., 2 h (78%)
thermodynamically preferred orientation. Hence, ozonolysis of the methyl ether 306 followed by base-mediated epimerization and Wittig olefination of the resultant ketone afforded the exo-isopropenyl isomer 307. Subsequently, 307 was hydrogenated and deprotection of the methyl ether gave an intermediate alcohol, which, when subjected to acetylation and then flash pyrolysis, was converted to (+)-sinularene (125). In light of the stereochemistry obtained as a result of the key cyclization step, this work constitutes an interesting application of the unusual "magnesium-ene" reaction, but more so with respect to the synthesis of 5-epi-sinularene (308) than to that of sinularene (125).

\[ \text{OAc} \]
\[ \text{284} \]
\[ \text{OAc} \]
\[ \text{309} \]

This same methodology was recently applied to the total syntheses\(^{174}\) of (+)-12-acetoxysinularene (284) and (+)-5-epi-12-acetoxysinularene (309).

The synthetic approach\(^{175,176}\) developed by Fallis and coworkers, to the total synthesis\(^{177}\) of (+)-sinularene (125) was quite different from those used in the two previously reported syntheses of sinularene. Central to this fourteen step synthesis (Scheme 36), was an intramolecular Diels-Alder
Scheme 36

310: R = CH₂OH
311: R = CHO

312: R = Ac

[a] MnO₂ (83%)  [b] LDA, THF, -78°C, 312 (93%)  [c] NaH, PhCH₂Br, DME (80%)  [d] LiAlH₄ (95%)  [e] PDC (65%)  [f] Ph₃P=CHCO₂Me, THF, reflux (72%)  [g] H₂, Pd/C (85%)  [h] Ph₃P, CCl₄, MeCN (97%)  [i] H₂, Pd/C, MeOH (99%)  [j] LiAlH₄ (99%)  [k] Ac₂O, pyridine (99%)  [l] 550°C (77%)
reaction, which, in addition to generating the required tricyclic skeleton of sinularene, provides for incorporation of the tertiary methyl group. Thus, oxidation of the bicyclic alcohol 310 provided the corresponding aldehyde 311, which was treated with the anion of methyl 3-methylbutyrate 312 to give a 2:14:30:47 mixture of diastereomeric β-hydroxy esters. Subsequently this mixture was separated and the major diastereomer was protected as a benzyl ether and reduced to the alcohol 313. Oxidation of the alcohol 313 and Wittig olefination furnished the intermediate α,β-unsaturated ester 314, which underwent cycloaddition under the conditions of the latter reaction to give the tetracyclic ester 315. Under the conditions for hydrogenolytic deprotection of the benzyl ether in 315, cyclopropane ring cleavage and hydrogenation of the double bond occurred concomitantly. Treatment of the resultant hydroxy ester 316 with triphenylphosphine and carbon tetrachloride in acetonitrile led to the formation of the olefin 317, which, when hydrogenated and reduced, was converted to the alcohol 318. Acetylation of 318 followed by pyrolytic elimination afforded (+)-sinularene (125). Although this work embodies a novel means of assembling the bicyclo[3.2.1]octane framework of sinularene and was executed generally with good yields, it is unfortunate that there was a lapse in stereoselectivity in the preparation of the Diels-Alder cycloaddition substrate.

With respect to these previous syntheses, the novelty and stereoselectivity featured by our synthetic methodology
(vide infra) seemed to warrant the application of this methodology to a new total synthesis of (+)-sinularene.
2.2 Discussion

2.2.1 The Synthetic Plan

In principle, any complex organic molecule (target molecule) may be broken down by a series of (bond-breaking) disconnections and/or functional group interconversions (FGI) to generate successively simpler intermediates until an easily accessible starting material is obtained.* Using this "retro-synthetic analysis",\textsuperscript{179} one can envisage sinularene (125) being derived from the bicyclic ketone 280 via a possible first disconnection which corresponds to a Wittig-type olefination. The two-carbon bridge indicated as the site of the second disconnection could be put into place by the formation of a bond between C-7 and the terminal

\begin{scheme}

\begin{center}
\begin{tikzpicture}
  \node (a) {125};
  \node (b) [right of=a] {280};
  \node (c) [right of=b] {320};
  \node (d) [below of=a] {322};
  \node (e) [below of=b] {321};
  \draw[->] (a) -- node[above] {$D$} (b);
  \draw[->] (b) -- node[above] {FGI,D} (c);
  \draw[->] (b) -- node[below] {FGI} (e);
  \draw[->] (a) -- node[below] {SiO} (d);
  \draw[->] (d) -- node[above] {$\text{SiO}$} (e);
\end{tikzpicture}
\end{center}
\end{scheme}

* An excellent introduction to the strategy and tactics of designing organic syntheses is provided by ref. 178.
carbon of the vinyl group at C-8. This could be accomplished by an intramolecular reaction between the ketone enolate and a primary halide or tosylate elaborated from the vinyl "handle" in 320. At this stage, it is clear that the bicyclo[3.1.0]-hex-2-ene 322 and the bicyclo[3.2.1]octadiene 321 would constitute potentially excellent key intermediates in this retro-synthetic sequence. The Cope rearrangement of the silyl enol ether 322 might be expected to occur under conditions which are similar to those required for the transformation (274 $\rightarrow$ 276).

![Chemical Structure](image)

However, there is a potential problem attending the thermal rearrangement of 322. The presence of a methyl substituent at C-5 in this substance provides for the possibility of a [1,5]-sigmatropic hydrogen shift,\textsuperscript{105} which would afford, at least initially, the tetraene 323 (eq. [77]).

For trans-divinylcyclopropane systems, there are not only examples in which the [1,5]-hydrogen shift was a competing thermal process, but cases in which this reaction was the only one observed. Upon thermolysis at 220°C, the $\beta$-cyclopropyl
enone 77 afforded a 1:4 mixture of 80 and 81, respectively, the latter compound arising from a [1,5]-hydrogen shift (eq. [78]).

Indeed, the sigmatropic hydrogen migration has been observed at reaction temperatures as low as 100°C. Sarel et al.\textsuperscript{180} have found that subjection of the divinylcyclopropane 324 to a temperature of 130°C gave, after 6 hours, the triene 325 in 83% yield (eq. [79]). Under similar conditions, 326 was obtained in 81% yield from 327.\textsuperscript{180} Both Marino\textsuperscript{60} and Wender\textsuperscript{68} showed that thermolysis of 92a produces almost exclusively the trienone 94 (eq. [80]).

For the \textit{trans}-divinylcyclopropane of interest (322), thermal bond reorganization proceeding via the Cope rearrangement would presumably involve isomerization of 322 to its
epimer 328 which would undergo the [3,3]-sigmatropic rearrangement to give the bicyclo[3.2.1]octadiene 321 as shown in Scheme 38. In the anticipated transition state 330 for this process, there is a severe steric repulsion between the isopropyl group and H. On the other hand, a similar steric interaction involving the isopropyl substituent and H would destabilize the presumed transition state 329 for the [1,5]-sigmatropic hydrogen shift. It was therefore difficult to predict the preferred mode of rearrangement in the case of the vinylbicyclo[3.1.0]hex-2-ene 322. Indeed, it seemed the answer would be provided only upon thermolysis of this material.

The preparation of the silyl enol ether 322 could be accomplished employing a synthetic route similar to that
described previously for the synthesis of compound 274. This entire sequence is outlined in Scheme 39, starting with the acetylenic alcohol 331.

The acetylenic alcohol 331 was conveniently prepared from 3-methyl-1-butyne and methacrolein. Thus, 1.1 equivalents of methacrolein were added to a THF solution of 1-lithio-3-methyl-1-butyne, which was generated by treating 3-methyl-1-butyne

\[ \text{SCHEME 39} \]

![Chemical structure diagram](attachment:image.png)
with n-butyllithium (eq. [81]). A single compound was obtained in quantitative yield and was identified as the desired alcohol \[331\] \(v_{\text{max}}\ 3350, 2220, 1650 \text{ cm}^{-1}\).

An examination of the \(^1\text{H} \text{nmr spectrum}\) of this material showed clearly the presence of the isopropyl group, the two olefinic protons and the carbinol proton. The vinyl methyl group appeared as a broad singlet at \(\delta 1.85\) while the carbinol (adjacent to the hydroxyl group) resonated as a broad singlet at \(\delta 4.77\).

This alcohol \[331\], when treated with triethyl orthoacetate in the presence of propionic acid, provided stereoselectively the \(\gamma,\delta\)-unsaturated ester \[332\] \(v_{\text{max}}\ 1730 \text{ cm}^{-1}\) in 58\% yield
via the orthoester Claisen rearrangement (eq. [82]).

The $^1$H nmr spectrum of the ester 332 was not complex and the resonances of the isopropyl, ethoxy and vinyl methyl groups were easily identified. The sole olefinic proton occurred as a broad singlet at $\delta$ 5.29. Although spectral substantiation of the trans geometry of the trisubstituted olefin was not available, it did not seem presumptuous to assign the given structure to the ester in light of the literature documentation on the predominance of trans-substituted olefins generated by the Claisen rearrangement.

\[
\begin{align*}
\text{EtO} & \xrightarrow{\text{KOH}} \xrightarrow{\text{MeOH-H}_2\text{O}} \\
\text{332} & \xrightarrow{\Delta} \text{333}
\end{align*}
\]

The ester 332 was routinely hydrolyzed (KOH, MeOH-H$_2$O) to furnish the corresponding acid 333 in a moderate yield of 68%. In the ir spectrum of this compound, the broad O-H ($\nu_{\text{max}}$ 3300-2500 cm$^{-1}$) and carbonyl ($\nu_{\text{max}}$ 1705 cm$^{-1}$) absorptions typical of a saturated carboxylic acid were evident, while in the $^1$H nmr spectrum of 333, a very broad singlet at $\delta$ 10.85 was attributed to the carboxyl proton.

In the manner described by Hudlicky and coworkers, treatment of the acid 333 with oxalyl chloride in refluxing
hexane smoothly afforded in quantitative yield the acyl chloride 334 (eq. [84]). The characteristic carbonyl absorption of an acid chloride at high wavenumbers ($\nu_{\text{max}}$ 1790 cm$^{-1}$) was clearly visible in the ir spectrum, as were the unsaturated bands at $\nu_{\text{max}}$ 2200 and 1623 cm$^{-1}$. The $^1$H nmr spectrum of this compound was consistent with the assigned structure.

Upon reaction of the acyl chloride 334 with ethereal diazomethane, the diazo ketone 335 was readily and quantitatively obtained as a viscous yellow oil (eq. [85]). This material, which tended to darken on standing even at 5°C and in the absence of light, was used shortly after its preparation.
Fig. 22. The 400 MHz $^1\text{H}$ nmr spectrum of 336.
The diazo ketone 335 was identified by the strong diazo absorption at \( v_{\text{max}} = 2085 \text{ cm}^{-1} \) and the carbonyl band at 1633 cm\(^{-1}\) in the ir spectrum. Also in evidence was the weaker, but distinct acetylenic absorption at 2200 cm\(^{-1}\). The \(^1\)H nmr spectrum of 335 resembled that of its precursor acid 333 with the exception of a singlet at \( \delta = 5.21 \) due to the proton flanked by the ketone and diazo moieties.

![Copper-catalyzed intramolecular cyclization of the diazo ketone](image)

Copper-catalyzed intramolecular cyclization of the diazo ketone 335 proceeded smoothly and stereoselectively in refluxing benzene to furnish the bicyclic ketone 336 in 81\% yield.

A cursory examination of the ir spectrum of this material showed the presence of a ketone carbonyl group (\( v_{\text{max}} = 1725 \text{ cm}^{-1} \)).

As shown in Fig. 22, the isopropyl methyl resonances were clearly visible in the \(^1\)H nmr spectrum of 336, as was the singlet due to the bridgehead methyl group at \( \delta = 1.44 \). Whereas most of the remaining protons occurred as a cluster of resonances at \( \delta = 1.94-2.14 \), the two cyclopropyl protons appeared as well isolated signals at \( \delta = 1.69 \) and 1.87. The doublet at \( \delta = 1.69 \) was easily assigned to the cyclopropyl
proton alpha to the ketone. Apparently, this proton couples (\( J = 3 \) Hz) only with the other cyclopropyl proton.

\[
\begin{array}{c}
\text{H}_2 \\
Pd/CaCO_3 \\
\text{quinoline}
\end{array}
\rightarrow
\begin{array}{c}
\text{336} \\
\text{337}
\end{array}
\]

Semihydrogenation of the alkyne 336 using Lindlar's catalyst (Pd/CaCO_3) and a trace of quinoline in pentane gave stereoselectively, after 3 hours, the desired cis-alkene 337 in a yield of 91% (eq. [87]).

Besides the appearance of the olefinic absorption (\( \nu_{\text{max}} 1650 \text{ cm}^{-1} \)) as a shoulder on the carbonyl absorption (\( \nu_{\text{max}} 1719 \text{ cm}^{-1} \)), the ir spectrum of this compound did not seem much different from that of the starting material 336. On the other hand, the \(^1\text{H}\) nmr spectrum was more informative and clearly exhibited two olefinic signals at \( \delta 4.91 \) and \( 5.36 \), both of which displayed the 11.5 Hz coupling consistent with a cis-disubstituted olefinic bond. Compared with that of the precursor alkyne 336, the allylic cyclopropyl proton appeared further downfield as part of a multiplet which integrated for 5 protons at \( \delta 1.90-2.25 \). The bridgehead proton occurred as an unresolved doublet at \( \delta 1.57 \), exhibiting a 2 Hz coupling to the neighboring cyclopropyl proton.

With the cis-olefinic ketone 337 in hand, we felt that
the thermal rearrangement of its silyl enol ether 340 would prove a worthy exercise to provide some insight into the rearrangement of the key intermediate 322. That is, would the Cope rearrangement of 322 be plagued by a competing [1,5]-hydrogen shift?

Using standard conditions, the ketone 337 was smoothly and almost quantitatively transformed into the silyl enol ether 340 (eq. [88]).

The ir spectrum of this compound exhibited a strong olefinic absorption at \( v_{\text{max}} \) 1627 cm\(^{-1}\). The presence of the bridgehead methyl group rendered the \(^1\)H nmr spectrum of 340 (Fig. 23) somewhat less complex than that of the analogue 274, which lacked a methyl substituent at C-5. In the
Fig. 23. The 400 MHz $^1$H nmr spectrum of 340.
olefinic region of the spectrum, $H_1$ appeared as a broad singlet at $\delta 4.27$ and exhibited small couplings to the neighbouring methylene protons ($J_{IZ} = J_{IJ} = 2.5$ Hz). Indeed, when $H_1$ was decoupled, the signals at $\delta 2.37$ and $2.30$ collapsed to a doublet of doublets ($J_{JZ} = 16.5$ Hz, $J = 2.5$ Hz) and a doublet ($J_{JZ} = 16.5$ Hz) respectively. Unfortunately, it was not possible to make unequivocal assignments for $H_J$ and $H_Z$. Decoupling the isopropyl methine proton provided a means to distinguish between the olefinic protons. In the event, the signal at $\delta 5.27$ collapsed to a doublet ($J_{CD} = 11$ Hz) and was assigned to $H_C$, while the overlapping doublet of doublet of doublets at $\delta 4.92$ was accorded to $H_D$ ($J_{CD} = 11$ Hz, $J_{DE} = 9$ Hz, $J_{BD} = 1$ Hz). In turn, the decoupling of $H_D$ was used to assign the doublet of doublets at $\delta 1.34$ to $H_E$ ($J_{DE} = 9$ Hz, $J_{EF} = 2.5$ Hz) and the signal at $\delta 1.32$ to $H_F$.
Fig. 24. The 400 MHz $^1$H nmr spectrum of 341.
With a measure of anticipation, a benzene solution of the silyl enol ether $340$ was sealed in a pyrolysis tube and heated at 240°C for 4.5 hours. Gratifyingly, the sole product isolated in 86% yield was identified as the bicyclo[3.2.1]-octa-2,6-diene $341$ (eq. [89]), and no sign of the triene $342$ anticipated from a [1,5]-hydrogen migration was observed.

As expected, the ir spectrum of compound $341$ was not very helpful from a diagnostic point of view. On the other hand, the $^1H$ nmr spectrum of $341$ (Fig. 24) indicated that the silyl enol ether moiety was intact. A cis coupling of 10 Hz ($J_{DE}$) can be detected in the olefinic resonances at $\delta$ 5.29 and 5.96 ($H_D$ and $H_E$, respectively). Decoupling $H_D$ (Fig. 25b) showed that $H_F$ ($\delta$ 2.46) coupled strongly with $H_Z$ ($J_{FZ} = 5$ Hz) but only weakly with $H_C$ ($J_{CF} < 1$ Hz). This latter observation is noteworthy since it supports the exo assignment of the isopropyl group at C-4. When $H_F$ was decoupled (Fig. 25c), the complex pattern due to $H_C$ simplified and exhibited a 7 Hz coupling between $H_C$ and the isopropyl methine proton, as well as two similar couplings ($J_{CD} \approx J_{CE} \approx 3$ Hz). Decoupling $H_F$
Fig. 25. The homonuclear spin decoupling experiment with 341: (a) the normal 400 MHz $^1$H nmr spectrum expanded for region $\delta$ 1.6-2.5, (b) the spectrum with irradiation at $\delta$ 5.29 ($H_D$), and (c) the spectrum with irradiation at $\delta$ 2.46 ($H_F$).
TABLE II. $^1$H nmr Data for Compounds 276 and 341.**

<table>
<thead>
<tr>
<th></th>
<th>$\delta$ H_C</th>
<th>$\delta$ H_D</th>
<th>$\delta$ H_E</th>
<th>$\delta$ H_F</th>
<th>$\delta$ H_I</th>
<th>$\delta$ H_J</th>
<th>$\delta$ H_K</th>
<th>$\delta$ H_K</th>
</tr>
</thead>
<tbody>
<tr>
<td>276</td>
<td>1.88-1.94 m</td>
<td>5.33 OL ddd</td>
<td>6.21 OL dddd</td>
<td>2.38 d</td>
<td>1.75 d</td>
<td>5.11 d</td>
<td>2.52-2.57 m</td>
<td>1.97 OL dddd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$J_{DE}=9.5$</td>
<td>$J_{DE}=9.5$</td>
<td>$J_{FZ}=5$</td>
<td>$J_{IZ}=9.5$</td>
<td>$J_{JK}=3$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$J_{CD}=3$</td>
<td>$J_{CD}=3$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$J_{DF}=2$</td>
<td>$J_{DF}=2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>341</td>
<td>1.83-1.88 m</td>
<td>5.29 ddd</td>
<td>5.96 ddd</td>
<td>2.46 d</td>
<td>1.62-1.72 m</td>
<td>4.87 s</td>
<td></td>
<td>1.75 ddd</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$J_{DE}=10$</td>
<td>$J_{DE}=10$</td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td></td>
<td>$J_{CD}=3$</td>
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<td>$J_{DF}=2$</td>
<td>$J_{DF}=2$</td>
<td></td>
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</tr>
</tbody>
</table>

* OL=overlapping  ** All coupling constants given in Hertz (Hz)
also made it possible to assign the complex signal at $\delta$ 1.75 to $\text{H}_Z$, which is coupled geminally to $\text{H}_I$ ($J_{IZ} = 9$ Hz). This large 9 Hz coupling was also discernible in the multiplet at $\delta$ 1.62-1.72, which was consequently attributed to $\text{H}_I$ and the isopropyl methine proton.

Table II compares the $^1\text{H}$ nmr spectral data of compounds 276 and 341. These compounds differ only in the presence of a bridgehead methyl substituent at C-1 of 341 but their spectra show subtle differences in chemical shifts, particularly for $\text{H}_E$ and $\text{H}_Z$, which are in closer proximity to this substituent.

Hydrolysis of the silyl enol ether was accomplished efficiently by treating 341 with 5% aqueous hydrochloric acid in THF. The bicyclo[3.2.1]octenone 343 ($\nu_{\text{max}}$ 1735 cm$^{-1}$) was thus obtained in 93% yield.

In the $^1\text{H}$ nmr spectrum of the bicyclic ketone 343, a 9.5 Hz cis coupling can be seen in the resonances assigned to $\text{H}_D$ and $\text{H}_E$ at $\delta$ 5.51 and 5.75, respectively. As in compound 341, $\text{H}_F$, which resonated as an unresolved doublet at $\delta$ 2.60,
Fig. 26. The homonuclear spin decoupling experiment with 343: (a) the normal 400 MHz $^1$H nmr spectrum expanded for the region $\delta$ 1.5-2.3, and (b) the spectrum with irradiation at $\delta$ 2.60 ($H_F$).
couples strongly to \( H_Z \) (\( J = 5.5 \) Hz) and weakly to \( H_C \) (\( J \leq 1 \) Hz). Indeed, when \( H_F \) was decoupled (Fig. 26c), only a very small coupling was eliminated from the splitting pattern of \( H_C \) at \( \delta 1.77-1.84 \). Again, the lack of coupling between \( H_F \) and \( H_I \) was not surprising, considering the dihedral angle involved (\( \approx 90^\circ \)). Consequently in the same decoupling experiment, the doublet of doublet accorded to \( H_I \) at \( \delta 1.86 \) showed no change whereas the signal of the geminal proton \( H_Z \) at 1.69 collapsed to a doublet (\( J_{IZ} = 11.5 \) Hz). The assignments of the doublet of doublets at \( \delta 2.24 \) to \( H_J \) and the doublet (\( J_{JX} = 17 \) Hz) at \( \delta 1.95 \) to \( H_X \) were made without difficulty. Of these two protons, only \( H_J \) exhibits a long-range coupling of 3.5 Hz with \( H_I \). Presumably, this arises from the planar zig-zag orientation of \( H_I \) and \( H_J \).113

Certainly the successful Cope rearrangement of 340 to 341 seemed to bode well for the key step (322 + 321) in assembling the bicyclo[3.2.1]octane frame of sinularene. Without further ado, efforts were directed at the placement of an exo vinyl substituent at C-4, which could be accomplished by
the conjugate addition of an appropriate nucleophile to the enone 338.

The preparation of the latter compound proved to be problematic, plagued either by poor yields or by the production of inseparable mixtures consisting of the desired enone 338 and small amounts of the saturated ketone 337. For example,

![Chemical structure](image)

after some experimentation, the best yield for the transformation of 337 into 338 via selenoxide fragmentation was obtained using Reich's "one-pot" procedure of forming and oxidizing the α-selenide, followed by elimination of the resultant selenoxide. Thus, the lithium enolate of 337 which was generated by treating 337 with 1.5 equivalents of lithium diisopropylamide, was quenched with phenylselenenyl chloride to afford the α-phenylselenides 344. To the resultant reaction mixture was added acetic acid and hydrogen peroxide for the conversion of the selenides into selenoxides, which conveniently fragmented under the conditions of the reaction to furnish the bicyclic enone 338 in an unenviable yield of 50%. In an
attempt to better this yield, an alternative method was sought. Using the method of Tamura, the trimethylsilyl enol ether \textsuperscript{345} was readily prepared from the reaction of the ketone \textsuperscript{337} and trimethylsilyl iodide in the presence of triethylamine in dichloromethane. Unfortunately, due to the instability of the product \textsuperscript{345}, a small amount of the starting material \textsuperscript{337} was always obtained after workup. Consequently, the crude enol ether was not purified but was used immediately in the subsequent step. Subjection of this material to a two-fold excess of palladium (II) acetate invariably produced a mixture of the desired enone \textsuperscript{338} and the saturated ketone \textsuperscript{337}, with the best ratio obtained under these conditions being 5:1 (as judged by glc analysis), respectively. The overall material balance of this two-step sequence was 78%. Although efforts to resolve the mixture by tlc and preparative glc were fruitless, this mixture was used in the next step since it was possible to recover and recycle the ketone \textsuperscript{337} at that stage.
The IR spectrum of the enone 338 was consistent for an α,β-unsaturated enone ($v_{\text{max}}$ 1690 cm$^{-1}$). In the $^1$H NMR spectrum of 338, the olefinic protons $H_J$ and $H_I$ appeared at $\delta$ 5.66 and 7.52, respectively. By decoupling $H_D$, it was possible to assign the doublet of doublets at $\delta$ 2.36 to $H_E$. The cyclopropyl proton $H_E$ exhibits a 9.5 Hz coupling with $H_D$ and a 3 Hz coupling to the other cyclopropyl proton $H_F$. This latter proton resonated as an unresolved doublet ($J_{EF} = 3$ Hz) at $\delta$ 1.99.

![Chemical structure](image)

Although conjugate addition of a nucleophile at C-4 would be expected to occur predominantly from the convex face of 338 to provide a vinyl substituent with an exo orientation, it was possible that the presence of the bridgehead methyl group would reduce the stereoselectivity of 1,4-addition, as compared to that observed for the enone 189. In an attempt to prepare the ketone 339, the enone 338 was added to a mixture of vinyl magnesium bromide$^{109,110}$ and a catalytic quantity of copper (I) bromide-dimethyl sulfide complex$^*$.
in THF at -30°C in accordance with a procedure described by House et al.\textsuperscript{133} After workup with aqueous ammonium chloride, a 9:4 mixture consisting of the desired alkylated ketone 339 and its epimer 346 was obtained in an isolated yield of 63% (eq. [92]).

Alternatively, conjugate addition to the enone 338 using lithium divinylcuprate was found to provide better stereoselectivity than the copper (I)-catalyzed Grignard reaction described above. Thus, using another method reported by House et al.,\textsuperscript{134} lithium divinylcuprate was prepared from tetraethylene and added to an 85:15 mixture of the enone 338 and the saturated ketone 337 at -63°C. The product thus obtained consisted of a 9:1:0.8 mixture of the desired ketone 339, the epimer 346 and the ketone 337, respectively (eq. [93]). This mixture was conveniently resolved by column chromatography and the ketone 339 was recovered in 69% yield.

\* It was found that yields of these copper (I)-catalyzed conjugate additions were affected dramatically by the purity of the copper (I) catalyst. Hence copper (I) bromide-dimethyl sulfide was purified using the methods indicated in refs. 134-136.
Fig. 27. The 400 MHz $^1$H nmr spectrum of 339.
The ir spectrum of the ketone 339 exhibited the expected carbonyl ($v_{max}$ 1722 cm$^{-1}$) and olefinic ($v_{max}$ 3070, 3000, 1635 cm$^{-1}$) absorptions. Fig. 27 shows the 400 MHz $^1H$ nmr spectrum of 339, in which the two olefinic protons $H_C$ and $H_D$ appeared at $\delta$ 5.39 and 4.91, respectively, and exhibited a 10.5 Hz coupling typical of a cis-disubstituted alkene. Interestingly, $H_J$, which appeared at $\delta$ 2.91, couples to $H_I$ ($J = 8$ Hz) but not to $H_Z$. These observations were not unexpected upon examination of models, which showed that the $H_J$-$H_Z$ dihedral angle approximated 90° while the $H_I$-$H_J$ dihedral angle was $\approx$30°. Indeed, decoupling $H_J$ caused the signal due to $H_I$ at $\delta$ 2.55 to collapse to a doublet ($J_{IZ} = 18.5$ Hz) but caused no change to the doublet ($J_{IZ} = 18.5$ Hz) assigned to $H_Z$ at $\delta$ 1.89. To distinguish between the cyclopropyl protons, $H_D$ was decoupled, eliminating a 8.5 Hz coupling from the signal at $\delta$ 2.15, which was consequently accorded to $H_E$. Using a nuclear Overhauser enhancement experiment in which the signal at $\delta$ 2.15 ($H_E$) was irradiated, it was possible to assign unequivocally the endo configuration to $H_J$ (Fig. 28). As well, the signal at $\delta$ 2.55
Fig. 28. The nuclear Overhauser enhancement experiment with 339: (a) the normal 400 MHz $^1$H nmr spectrum for the region $\delta$ 0.9-3.0, and (b) the spectrum with irradiation at $\delta$ 2.15 ($H_E$).
exhibited a n.O.e. effect, thereby verifying its assignment to H_I.

![Chemical structure](image)

The $^1$H nmr spectrum of the epimer 346 as shown in Fig. 29, is expectedly similar to that of 339, particularly in the olefinic region. A comparison of these two spectra brings to light a number of noteworthy differences in the high field area. Firstly, the resonance of the tertiary methyl substituent in 339 is 0.11 ppm upfield from the resonance of the same group in 346. This observation may be rationalized by the shielding provided to the methyl substituent by the syn vinyl group in 339. A similar argument may be applied to explain the second phenomenon: the apparent reversal of shielding experienced by the two methylene protons alpha to the ketone; in 339, H_Z appeared further upfield than H_I, whereas in 346, the situation was reversed. That is to say, the vinyl group seems to shield the neighbouring syn proton, which happens to be H_Z in 339 but H_I in 346. Thirdly, other than coupling to H_K, H_J couples to both H_I and H_Z ($J_{IJ} = 9.5$ Hz, $J_{JZ} = 9$ Hz) in 346 as anticipated if its configuration was exo.
Fig. 29. The 400 MHz $^1$H nmr spectrum of 346.
In anticipation of the crucial Cope rearrangement, the ketone 339 was transformed routinely into the trans-divinylcyclopropane 322 in 96% yield (eq. [94]).

The ir spectrum of 322 exhibited strong olefinic absorptions at $\nu_{\text{max}}$ 1635 and 1620 cm$^{-1}$. Moreover, the singlets at $\delta$ 0.17 and 0.94 in the $^1$H nmr spectrum of 322 (Fig. 30) testified to the presence of the silyl methyl and t-butyl groups. The large ($J_{DE} = 9$ Hz) coupling easily qualified the signal at $\delta$ 1.40 to be attributable to $H_E$. The other cyclopropyl proton $H_F$, which resonated at $\delta$ 1.34, couples to $H_E$ ($J = 2.5$ Hz) and allylically to $H_I$ ($J = 1$ Hz). Being doubly allylic, $H_J$ is quite deshielded and appeared at $\delta$ 3.10 as a unresolved doublet ($J = 9$ Hz) due to the coupling with $H_K$. The proton $H_I$,
Fig. 30. The 400 MHz $^1$H nmr spectrum of 322.
the most shielded of the olefinic protons, resonated at δ 4.20 while the remaining olefinic protons assumed splitting patterns almost identical with those observed for the ketone 339.

With the stereocontrolled synthesis of the key intermediate 322 accomplished successfully, the stage was set for its thermal rearrangement. Thus, a benzene solution of the silyl enol ether 322 was sealed in a pyrolysis tube and heated at 220°C for 4.5 hours to give a single product, which to our delight was identified as the desired bicyclo[3.2.1]octa-2,6-diene 321 (eq. [95]). There was no evidence for the formation of the triene 323 from a possible competing [1,5]-hydrogen shift, thereby proving that our initial misgivings were (happily) unfounded. Indeed, the successful thermolysis of the analogous vinylbicyclo[3.1.0]hex-2-ene 340 forecasted accurately the outcome for the rearrangement of 322.

Produced in 86% yield, the enol ether 321 exhibited an ir spectrum which predictably resembled that of its precursor 322.
Fig. 31. The 400 MHz $^1$H nmr spectrum of 321.
At a glance, the $^1$H nmr spectrum of 321 (Fig. 31) did not seem complicated, its simplicity undoubtedly due to the presence of a bridgehead methyl group and a C-8 vinyl substituent. The t-butyldimethylsilyl enol ether had evidently stayed intact. The proton $H_D$, resonating at $\delta$ 5.35, displayed a cis coupling ($J = 9.5$ Hz) with $H_E$. Decoupling $H_D$ aided in the assignment of the doublet of doublets at $\delta$ 6.00 to $H_E$ and the multiplet at $\delta$ 1.92-1.97 to $H_C$. The proton $H_I$ resonated as a doublet at $\delta$ 2.46 ($J_{IK} = 9$ Hz) and did not exhibit any coupling with the neighbouring $H_F$. Appearing as a broad singlet at $\delta$ 2.26, $H_F$ displays only a small coupling with $H_C$, thereby attesting to the endo configuration of the latter.

These data would seem to indicate the successful assembly of the requisite bicyclo[3.2.1]octane skeleton with the stereospecific placement of an exo isopropyl substituent at C-4. At this stage, the remaining synthetic sequence (Scheme 40) required the elaboration of the vinyl moiety into a primary alcohol which could be converted into its tosylate or some other suitable leaving group. Hydroboration of the vinyl...
substituent should provide the desired primary alcohol, but the question here concerns chemoselectivity. That is, would it be possible to hydroborate the vinyl moiety selectively in the presence of two other double bonds? The double bond on the three-carbon bridge is flanked by a quaternary centre on one side and by a sterically bulky isopropyl substituent on the other, and should therefore be the least likely of the three sites of unsaturation to be attacked by a hydroborating agent. By steric argument alone, the vinyl moiety should be the most reactive alkene. However, it is known that polar substituents have a directive effect on hydroboration\textsuperscript{183a} and that the rate of this reaction is increased by increasing the electron density of the double bond.\textsuperscript{183b} By considering only electronic factors, the silyl enol ether, which consists of an
electron-rich double bond, would be the most susceptible to hydroboration. On the other hand, this moiety is somewhat sterically hindered. Ideally, the hydroborating reagent required under the circumstances, should be both sterically demanding and less sensitive to electronic influences. A candidate which meets these criteria is disiamylborane.\textsuperscript{184,185}

Thus, reaction of the silyl enol ether \textsuperscript{321} with slightly over 2 equivalents of disiamylborane\textsuperscript{186,187} at 0°C, followed by oxidation of the resultant trialkylborane with alkaline hydrogen peroxide gave in 86% yield, the alcohol \textsuperscript{347} ($v_{\text{max}}$ 3300 cm\textsuperscript{-1}, eq. [96]).

In the $^1$H nmr spectrum of \textsuperscript{347}, a 2-proton multiplet corresponding to the methylene protons adjacent to the hydroxyl group, appeared at $\delta$ 3.63-3.79. The singlets at $\delta$ 0.11 and 0.13, integrating for a total of 6 protons, the 9-proton singlet at $\delta$ 0.90 and the singlet at $\delta$ 4.69 collectively indicated that the silyl enol ether moiety had survived the hydroboration. As well, the cis-disubstituted alkene had remained intact as evidenced by the signals due to $H_D$ and $H_E$ at $\delta$ 5.30 and 5.98, respectively. The 9.5 Hz cis coupling was discernible in both
of these olefinic resonances. As expected the upfield region of the spectrum had become more complex and many of the signals now occurred together as multiplets. The resonance of $H_1$ occurred at $\delta 1.94$ and was a doublet of doublets due to dissimilar couplings to the neighbouring methylene protons ($J = 10 \text{ Hz}, J = 3.5 \text{ Hz}$).

To anticipate the formation of the two-carbon bridge in the ketone 349 (see Scheme 40) by fluoride-induced cleavage of the silyl enol ether and a concomitant intramolecular alkylation, it was desirable to convert the primary alcohol into a leaving group such as a tosylate.

After some experimentation, it was discovered that the addition of the alcohol 347 to a mixture of $p$-toluenesulfonyl
chloride and 4-dimethylaminopyridine in dichloromethane, offered the best results. However, none of the anticipated tosylate was isolated. Instead, it was a pleasant surprise to find that the single product isolated could be identified as the cyclized ketone \textbf{349} (eq. [97]). Thus, under the reaction conditions, the initially formed tosylate was unstable and, apparently, underwent an alkene-assisted solvolytic ring closure with accompanying cleavage of the silyl ether.

A similar transformation was observed by Piers and co-workers in work leading to the synthesis of (-)-copacamphene \textbf{350} as shown in eq. [98]. Subjection of the tosylate \textbf{351} to silica gel column chromatography gave, in 89% yield, \textbf{(-)-copacamphene} \textbf{350}.

In our case, this fortuitous transformation (\textbf{347} + \textbf{349}) afforded the ketone \textbf{349} in 79% yield and shortened the remaining synthetic sequence by one step. Examination of the ir spectrum of this material revealed a ketone carbonyl absorption ($v_{\text{max}}$ 1745 cm$^{-1}$) and olefinic bands ($v_{\text{max}}$ 3005, 1630 cm$^{-1}$).

Figure 32 shows the $^1$H nmr spectrum of \textbf{349}, in which the olefinic protons $H_D$ and $H_E$ have converged to an AB system. The
Fig. 32. The 400 MHz $^1$H nmr spectrum of 349.
proton $H_E$ appeared as a doublet at $\delta$ 5.59 due to the cis coupling ($J = 10$ Hz) with $H_D$. The doublet of doublet of doublets displayed by $H_D$ at $\delta$ 5.63 also exhibits smaller couplings with $H_C$ ($J = 3.5$ Hz) and with $H_F$ ($J = 1.5$ Hz). Decoupling both $H_D$ and $H_E$ led to the collapse of the signal due to $H_F$ at $\delta$ 2.28 to a doublet, and the complex multiplet due to $H_C$ at $\delta$ 1.90-1.96 to a doublet of doublets. This decoupling experiment uncovered the small coupling ($J = 2.5$ Hz) between $H_C$ and $H_F$ and that ($J = 9.5$ Hz) between $H_C$ and the isopropyl methine proton.

The reduction of the double bond in 349 was attempted initially using diimide. Thus, reaction of the alkene 349 with diimide generated in situ from p-toluenesulfonylhydrazide
and sodium acetate\textsuperscript{189,190} in a refluxing mixture of THF and water, proceeded sluggishly to give after 54 hours, the ketone \textsuperscript{280} in a yield of 43\% (eq. \[99\]). It was clear that this yield was unacceptable, and as a consequence, catalytic hydrogenation of the bond was attempted. Thus, the alkene \textsuperscript{349} was subjected to hydrogenation catalyzed by palladium supported on carbon in methanol to give after 26.5 hours, a \textsuperscript{43:7} mixture consisting of \textsuperscript{280} and starting material \textsuperscript{349}. The reaction became quite sluggish near the end and despite the addition of more catalyst, would not consume the remaining starting material. Although efforts to resolve this mixture were fruitless, the mixture was used in the next step.

The major component of this mixture was shown by glc analysis to have a retention time identical with that of the product from the diimide reduction of \textsuperscript{349}. The ir spectrum of \textsuperscript{280} was consistent with a ketone (\(\nu_{\text{max}} 1740 \text{ cm}^{-1}\)), and the \(\textsuperscript{1}H\) nmr spectrum of this material exhibited no signals due to olefinic protons. Not surprisingly, most of the signals now occurred as overlapping multiplets between \(\delta 1.38-2.11\), and the only intelligible resonances were those of the isopropyl methyl groups as a 6-proton pair of doublets at \(\delta 0.89\) and \(0.92\), and the tertiary methyl group as a 3-proton singlet at \(\delta 1.00\). The \(\textsuperscript{1}H\) nmr and ir spectra of the ketone \textsuperscript{280}, nevertheless, were identical with those of an authentic sample of \((\pm)-\textsuperscript{280}\).* Since this ketone was used as an intermediate in a

* We are grateful to Professor Wege for copies of \(\textsuperscript{1}H\) nmr and ir spectra of \((\pm)-\textsuperscript{280}\).
FIGURE 33. The 400 MHz $^1$H nmr spectrum of (±)-sinularene (125)
FIGURE 34. The 100.6 MHz $^{13}$C nmr spectrum of (+)-sinularene (125).
reported synthesis of (+)-sinularene by Collins and Wege, the work described to this point constituted a formal synthesis of (+)-sinularene (125).

Previously, the conversion of the ketone 280 into 125 was accomplished in a three-step sequence (see Scheme 34). We were, however, able to effect this transformation in one step by means of a Wittig olefination (eq. [100]).

Thus, treatment of a 93:7 mixture consisting of the ketone and 349 with methylenetriphenylphosphorane (generated by treating methyltriphenylphosphonium bromide with n-butyl-lithium) in refluxing THF gave, after purification (column chromatography) of the crude product, a pure sample of (+)-sinularene in 78% yield. This material exhibited ir, $^1$H nmr, $^{13}$C nmr and mass spectra identical with those of an authentic sample of (+)-sinularene* and the naturally occurring sesquiterpene (-)-sinularene.82

This constitutes the successful total synthesis of (+)-sinularene in a total of sixteen steps (from methacrolein

* We are grateful to Professor Oppolzer for $^1$H nmr, ir and mass spectra of (+)-sinularene.
SCHEME 41

194

[\text{c]} \ 332

R=\text{OEt}

c-f

[a] (i) \text{nBuLi, THF, -30°C} (ii) \text{methacrolein} (iii) \text{NH}_4\text{Cl}  

[b] \text{MeC(OEt)}_3, \text{EtCO}_2\text{H, 130°C}  

c] \text{KOH, H}_2\text{O, MeOH, reflux}  

d] \text{(COCl)}_2,  

ewhane, reflux  

e] \text{CH}_2\text{N}_2, \text{Et}_2\text{O, 0°C}  

[f] \text{Cu(acac)}_2, \text{benzene, reflux}  

g] \text{Pd/CaCO}_3, \text{Pb(OAc)}_2, \text{quinoline, pentane}  

[h] \text{Me}_3\text{SiI} \text{Et}_3\text{N, CH}_2\text{Cl}_2, -78°C  

[i] \text{Pd(OAc)}_2, \text{MeCN, r.t.}  

[j] (i) \text{(CH}_2=\text{CH})_2\text{CuLi, Et}_2\text{O, -63°-30°C} (ii) \text{NH}_4\text{Cl-H}_2\text{O}  

[k] (i) \text{LDA, THF, -78°C} (ii) \text{t-BuMe}_2\text{SiCl, THF-HMPA -78°C-r.t.}  

[l] 220°C, \text{benzene, sealed tube}  

[m] (i) \text{Sia}_2\text{BH, THF} (ii) \text{H}_2\text{O}_2, \text{NaOH}  

[n] \text{P-MeC}_6\text{H}_4\text{SO}_2\text{Cl, DMAP, CH}_2\text{Cl}_2, \text{r.t.}  

[o] \text{H}_2, \text{Pd/C, MeOH, r.t.}  

[p] \text{Ph}_3\text{P=CH}_2, \text{THF, reflux}
and 3-methyl-1-butyne) with an overall yield of 3.9% (see Scheme 41) and represents the first reported application of the stereospecific Cope rearrangement of a 6-exo-[(Z)-1-alkenyl)]bicyclo[3.1.0]hex-2-ene (i.e. 322 → 321) to the total synthesis of a naturally occurring substance.
3.1 General

Melting points were determined using a Fisher-Johns melting point apparatus and are corrected. Boiling points are uncorrected and those designated as air-bath temperatures refer to short-path (Kugelrohr) distillations. Infrared (ir) spectra were recorded on a Perkin-Elmer model 710B infrared spectrophotometer and were calibrated using the 1601 cm$^{-1}$ band of polystyrene film. Proton ($^1$H) and carbon ($^{13}$C) nuclear magnetic resonance spectra were taken in deuteriochloroform using tetramethysilane (TMS) as internal standard. These spectra were recorded using Bruker WP-80 or WH-400 spectrometers. The 270 MHz spectra were recorded on a unit comprised of an Oxford Instruments 63.4 KG superconducting magnet and a Nicolet 32K Model 1180 computer attached to a Bruker WP-60 console. Signal positions are given in parts per million ($\delta$) from TMS and the multiplicity, integrated peak areas, coupling constants (where possible) and proton assignments are indicated in parentheses. In cases of compounds with tert-butyldimethylsilyl groups, the resonance positions were determined relative to the chloroform signal ($\delta$ 7.27). Low resolution mass spectra (ms) were recorded with a
Varian/MAT CH4B mass spectrometer while high resolution mass spectra were recorded with a Kratos/AEI MS 50 mass spectrometer. Glc-mass spectrometric analysis was done using a Carlo ERBA 4100 gas chromatograph equipped with a 15 m x 0.26 mm fused silica column coated with crosslinked and bonded DB-5 [(95%)-dimethyl-(5%)-diphenylpolysiloxane] and coupled with a Kratos MS 80 RFA mass spectrometer. High resolution mass spectra were recorded with a Kratos/AEI MS 50 mass spectrometer. Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia.

Analytical gas liquid chromatography (glc) was performed on a Hewlett-Packard model 5832A gas chromatograph using a 6 ft x 0.125 in stainless steel column packed with 5% OV-17 on 80-100 mesh Chromosorb W (HP) and a thermal conductivity detector or on a Hewlett-Packard model 5880 gas chromatograph using a 25 m x 0.21 mm fused silica column coated with crosslinked SE-54 [(94%)-dimethyl-(5%)-diphenyl-(1%)-vinylpolysiloxane] and a flame-ionization detector. The column used and the initial oven temperature are indicated in parentheses. All analyses were done using a temperature program (20°C per min, final temperature 200°C) after the first 2 min at the initial temperature. Preparative glc was done using a Varian Aerograph 90-F gas chromatograph and a 10 ft x 0.25 in stainless steel column packed with 5% OV-17 on Supelco WHP (100-120 mesh).
Thin layer chromatography (tlc) was accomplished on commercial aluminum-backed silica gel plates (E. Merck, Type 5539). Preparative thin layer chromatography was done on 20 x 20 cm glass plates coated with 0.9 mm of silica gel (E. Merck, Silica gel 60). Conventional column chromatography was performed using 70-230 mesh silica gel (E. Merck) or 80-200 mesh neutral alumina (Fisher-Scientific), while flash column chromatography was done using 230-400 mesh silica gel (E. Merck) according to the procedure developed by Still et al. 194

All reactions requiring anhydrous conditions were done using glassware which was flame-dried under an argon flow. Cold temperatures were maintained by use of the following baths: aqueous calcium chloride/CO₂ (-30°C), 195 chloroform/CO₂ (-63°C) 196 and acetone/CO₂ (-78°C). 196

3.2 Solvents and Reagents

Solvents and reagents were purified and dried using established procedures 197-201 in which the drying agents used are summarized in Table III. All solvents were distilled prior to use. The petroleum ether used was the fractions with a boiling range ca. 30-60°C.

Solutions of n-butyllithium and phenyllithium were obtained from Aldrich Chemical Co., Inc. and were standardized using the procedures described by Gilman and Cartledge, 202
### TABLE III. DRYING AGENTS USED FOR SOLVENTS & REAGENTS

<table>
<thead>
<tr>
<th>Material</th>
<th>Drying Agent</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetonitrile</td>
<td>$P_2O_5$</td>
<td>198</td>
</tr>
<tr>
<td>benzene</td>
<td>$CaH_2$</td>
<td>197</td>
</tr>
<tr>
<td>dichloromethane</td>
<td>$P_2O_5$</td>
<td>197</td>
</tr>
<tr>
<td>diethyl ether</td>
<td>$Na/Ph_2CO$</td>
<td>198</td>
</tr>
<tr>
<td>diisopropylamine</td>
<td>$CaH_2$</td>
<td>199</td>
</tr>
<tr>
<td>hexamethylphosphoramid*</td>
<td>$CaH_2$</td>
<td>200</td>
</tr>
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<td>$CaH_2$</td>
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<td>$CaH_2$</td>
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<tr>
<td>tin (IV) chloride</td>
<td>$P_2O_5$</td>
<td>197</td>
</tr>
<tr>
<td>triethylamine</td>
<td>$CaH_2$</td>
<td>199</td>
</tr>
</tbody>
</table>

* distilled under reduced pressure (0.1 Torr)
Ronald et al.\textsuperscript{203} or Kofron and Baclawski.\textsuperscript{204} Also obtained from Aldrich were tetra-n-butylammonium fluoride (1.0 M) solution in THF, diisobutylaluminum hydride (DIBAL, 1.0 M) solution in hexane, and borane-dimethyl sulfide complex.

3-Methyl-1-butyne was purchased from Farchan Labs.

p-Toluenesulfonyl chloride was purified by continuous extraction with petroleum ether,\textsuperscript{197} triphenylphosphine was recrystallized from ethyl acetate and methanol\textsuperscript{197} and p-toluenesulfonylhydrazide was recrystallized from THF and petroleum ether.

Lithium diisopropylamide (LDA) was prepared by the addition of a hexane solution of n-butyllithium (1.0 equiv) to a solution of diisopropylamine (1.1 equiv) in dry THF at -78°C under argon. The resulting solution was stirred at 0°C for 20 min prior to use.\textsuperscript{205}

Saturated basic aqueous ammonium chloride (pH 8) was prepared by the addition of 50 mL of aqueous ammonium hydroxide (58%) to 1 L of saturated aqueous ammonium chloride.
3.3 Model Studies

3.3.1 General Procedure A: The Preparation of 6-exo-(1-Alkenyl)bicyclo[3.1.0]hex-2-enes

To a cold (-78°C), stirred solution of LDA (1.1 equiv) in anhydrous THF (5 mL/mmol of LDA), under argon, was added a solution of the parent ketone (1.0 equiv) in THF. After the resulting mixture had been stirred at -78°C for 0.5 h, a THF solution of HMPA (2.0 equiv) and freshly sublimed tert-butyldimethylsilyl chloride (1.5 equiv) was added. The reaction mixture was stirred at -78°C for another 0.5 h and then at room temperature for 2 h. The resulting mixture was poured into saturated aqueous sodium bicarbonate and the layers were separated. After extraction of the aqueous layer with ether, the organic extracts were combined, washed thrice with brine and dried (anhydrous magnesium sulfate). Evaporation of the solvent under reduced pressure (water aspirator) afforded a yellow residue, which was subjected to chromatography on a short column of neutral alumina (80-200 mesh, elution with petroleum ether). Subsequent concentration of the appropriate fractions, followed by distillation of the residual material furnished the silyl enol ethers as clear, colourless oils.

3.3.2 General Procedure B: Preparation of Bicyclo[3.2.1]-octa-2,6-dienes

Prior to use, all glass pyrolysis tubes (2 mm wall thickness) were silylated in the following manner. The tubes
were washed thoroughly with detergent and water, and were soaked in 1% aqueous potassium hydroxide for 15 minutes. They were washed successively with spectrograde methanol (4X's) and spectrograde toluene (2X's), and then were soaked in a 5% solution of N,N-bis(trimethylsilyl)acetamide in toluene for 15 minutes. After successive rinses with toluene and methanol, the tubes were oven-dried, cooled to room temperature and stored either in a dessicator or sealed with a rubber septum.

The solutions of substrate silyl enol ethers in dry benzene were degassed in the glass pyrolysis tubes by alternately freezing (in liquid nitrogen) and thawing the solutions thrice. These glass tubes were sealed in vacuo (0.1 Torr) at -196°C (liquid nitrogen), packed with sand in a steel container and heated at the appropriate temperature in an oven. Reaction progress was monitored by glc* and the thermolyses were terminated when starting material was no longer apparent. The tubes were cooled to room temperature and unsealed. Subsequent solvent removal gave light yellow oils which were distilled under reduced pressure to afford the desired silyl enol ethers generally in excellent yields.

* A number of sealed tubes containing the solutions were heated simultaneously, but each tube was opened and its contents analyzed by glc at different times. The reaction was stopped when starting material was no longer apparent by glc.
3.3.3 Preparation of 6-exo-Vinylbicyclo[3.1.0]hexan-2-one

The bicyclic ketone 179 was prepared in accordance with the procedures reported by Hudlicky et al.\(^98\) In our hands, this material was obtained in an overall yield of 36\% from divinylcarbinol,\(^109,110\) and exhibited air-bath distillation temperature 70-75°C/15 Torr; ir (film): 3085, 1725, 1640, 1180, 990, 910, 887 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\) 1.83 (d of d, 1H, H\(_F\), \(J_{FG} = 5\) Hz, \(J_{EF} = 2.5\) Hz), 1.93 (overlapping d of d of d, 1H, H\(_E\), \(J_{DE} = 8.5\) Hz, \(J_{EG} = J_{EF} = 2.5\) Hz), 2.03-2.25 (m, 5H), 4.99 (d of d, 1H, H\(_C\), \(J_{CD} = 10\) Hz, \(J_{BC} = 1.5\) Hz), 5.14 (d of d of d, 1H, H\(_B\), \(J_{BD} = 17\) Hz, \(J_{BC} = 1.5\) Hz), 5.35 (d of d of d, 1H, H\(_D\), \(J_{BD} = 17\) Hz, \(J_{CD} = 10\) Hz, \(J_{DE} = 8.5\) Hz). Irradiation at \(\delta\) 5.35 (H\(_D\)) caused the signal at \(\delta\) 1.93 to collapse to an overlapping d of d (\(J = 2.5\) Hz), the signal at \(\delta\) 4.99 to collapse to a d (\(J = 1.5\) Hz), and the signal at \(\delta\) 5.14 to collapse to a d (\(J = 1.5\) Hz).

**Exact mass** calcd. for C\(_8\)H\(_{10}\)O: 122.0732; found: 122.0730.
3.3.4 Preparation of 2-(tert-Butyldimethylsiloxy)-6-exo-vinylbicyclo[3.1.0]hex-2-ene

Following general procedure A, the ketone 179 (0.122 g, 1.0 mmol) was converted into the silyl enol ether 187 (0.224 g, 95%, air-bath distillation temperature 50-54°C/0.2 Torr), which was shown by glc analysis (OV-17, 80°C) to consist of one component and exhibited ir (film): 3060, 3020, 1627, 1250, 1210, 840 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ 0.15 (s, 6H, CH₃-Si-CH₃), 0.93 (s, 9H, (CH₃)₃C-Si-O⁻), 1.14 (overlapping d of d of d, 1H, Hₓ, JₓE = 9 Hz, JₓF = JₓG = 2 Hz), 1.57-1.63 (m, 1H, Hₓ or Hᵧ), 1.67-1.72 (m, 1H, Hₓ or Hᵧ), 2.29 (overlapping d of d of d, 1H, Hₓ, JₓJₓ = 17 Hz, JₓIₓ = JₓFₓ = 3 Hz), 2.52 (d of d of d, 1H, Hₓ, JₓJₓ = 17 Hz, JₓGₓ = 8 Hz, JₓIₓ = 2 Hz), 4.30 (broad s, 1H, Hₓ, w₁/₂ = 6 Hz), 4.86 (d of d, 1H, Hₓ, JₓCₓ = 10 Hz, JₓBₓ = 2 Hz), 5.01 (d of d, 1H, Hₓ, JₓBₓ = 16 Hz, JₓCₓ = 2 Hz), 5.41 (d of d of d, 1H, Hₓ, JₓDₓ = 16 Hz, JₓCₓ = 10 Hz, JₓDE = 9 Hz).

Exact mass calcd. for C₁₄H₂₄O₃Si: 236.1596; found: 236.1592.
3.3.5 Preparation of 6-([tert-Butyldimethylsiloxy])bicyclo-[3.2.1]octa-2,6-diene

In accordance with general procedure B, the silyl enol ether 187 (0.112 g, 0.474 mmol) was thermolyzed at 200°C for 2 h, but without solvent. Distillation (air-bath temperature 79-82°C/0.1 Torr) of the thermolysate furnished the silyl enol ether 188 (0.110 g, >97%) as a colourless oil, which consisted of a single peak by glc analysis (OV-17, 80°C) and exhibited ir (film): 3040, 3000, 1615, 1245, 880 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\) 0.14, 0.16 (s, s, 3H each, CH\(_3\)-Si-CH\(_3\)), 0.93 (s, 9H, (CH\(_3\))\(_3\)Si-O-), 1.77 (d, 1H, H\(_I\), \(J_{IZ} = 9.5\) Hz), 2.06-2.23 (m, 3H, H\(_C\), H\(_X\), H\(_Z\)), 2.46-2.54 (m, 2H, H\(_K\), H\(_F\)), 5.11 (d, 1H, H\(_J\), \(J_{JK} = 2.5\) Hz), 5.27-5.32 (m, 1H, H\(_D\)), 6.16-6.22 (m, 1H, H\(_E\)). Irradiation at \(\delta\) 6.16-6.22 (H\(_E\)) caused the signals at \(\delta\) 1.77 and \(\delta\) 2.46-2.54 to sharpen, the signals at \(\delta\) 2.06-2.23 and \(\delta\) 5.27-5.32 to simplify; irradiation at \(\delta\) 5.27-5.32 (H\(_D\)) caused the signals at \(\delta\) 2.46-2.54 to sharpen, and the signals at \(\delta\) 2.06-2.23 and \(\delta\) 6.16-6.22 to simplify; and irradiation at \(\delta\) 5.11 (H\(_J\)) caused the signals at \(\delta\) 1.77 and \(\delta\) 2.46-2.54 to sharpen.

Exact mass calcd. for C\(_{14}\)H\(_{24}\)OSi: 236.1596; found:
3.3.6 Preparation of Bicyclo[3.2.1]oct-2-en-6-one

A mixture of the silyl enol ether 188 (0.179 g, 0.757 mmol), 5% aqueous hydrochloric acid (3 mL) and THF (3 mL) was stirred at room temperature for 6 h. Subsequently, the reaction mixture was diluted with ether and poured carefully into saturated aqueous sodium bicarbonate. The layers were separated, the aqueous phase was extracted twice with ether, and the combined organic extracts were washed with brine and dried (anhydrous magnesium sulfate). Careful removal of solvent under reduced pressure (water aspirator) and Kugelrohr distillation (air-bath temperature 40-45°C/0.1 Torr) of the resultant residue afforded 0.081 g (88%) of the desired ketone 207. This material, consisting of one component by glc (OV-17, 80°C) and tlc (petroleum ether-ether, 5:1) analyses, and exhibited ir (film): 3025, 1730, 1640, 735 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ 2.03 (d, 1H, H₁, J₁₂ = 11 Hz), 2.08 (overlapping d of d of d, 1H, H₂, J₂₃ ≈ J₂₅ ≈ 4.5 Hz), 2.20 (unresolved d, 1H, H₃, J₃₄ = 18 Hz), 2.29 (d of d, 1H, H₅, J₅₆ = 17.5 Hz, J₅₇ = 5 Hz),
2.34 (overlapping d of d of d, 1H, H_J, J_{JY} = 17.5 Hz, J_{IJ} = 3 Hz, J_{JK} = 1.5 Hz), 2.43 (overlapping d of d of d of d, 1H, H_C, J_{CX} = 18 Hz, J_{CF} = 5 Hz, J_{CD} = J_{CE} = 2.5 Hz), 2.57-2.62 (m, 1H, H_F), 2.73-2.80 (m, 1H, H_K), 5.47 (overlapping d of d of d, 1H, H_D, J_{DE} = 9.5 Hz, J_{CD} = J_{DX} ≈ 3 Hz), 6.01-6.09 (m, 1H, H_E).

Exact mass calcd. for C_8H_{10}O: 122.0732; found: 122.0732.

3.3.7 Preparation of 6-exo-Vinylbicyclo[3.1.0]hex-3-en-2-one

Following the procedure reported by Reich et al.\textsuperscript{123} the bicyclic ketone 179 was transformed into the enone 189 via a one-pot selenoxide elimination. Thus, to a cold (-78°C), stirred solution of LDA (4.91 mmol) in anhydrous THF (10 mL), under an atmosphere of argon, was added a solution of the ketone 179 (0.500 g, 4.09 mmol) in THF (7 mL). The resultant mixture was stirred at -78°C for 0.5 h, after which time a solution of phenylselenenyi chloride (0.941 g, 4.91 mmol) in THF (6 mL) was added dropwise via a syringe. After the mixture had been stirred at 0°C for 0.5 h, a solution of acetic acid (0.469 mL, 8.18 mmol) in water (0.5 mL) was added.
Subsequently, 30% aqueous hydrogen peroxide (2.32 g, 20.5 mmol) was added dropwise to the cold (0°C) reaction mixture and the mixture was stirred at 0°C for 1 h. The reaction mixture was diluted with petroleum ether-ether (1:1) and then was poured into saturated aqueous sodium bicarbonate. The layers were separated, the aqueous phase was extracted thoroughly with ether, and the combined organic extracts were washed with brine and dried (anhydrous magnesium sulfate). After solvent removal by atmospheric distillation and Kugelrohr distillation (air-bath temperature 78-83°C/0.1 Torr) of the resultant pale yellow residue, 0.431 g (88%) of the enone \[189\] was obtained as a clear, colourless oil. This material tended to decompose on standing even at 4°C under argon and in the absence of light, and therefore was distilled just prior to use. The enone \[189\] exhibited ir (film): 3070, 3050, 1690, 1640 cm\(^{-1}\); \(^{1}\)H nmr (400 MHz, CDC\(_3\)) \(\delta\) 2.17 (overlapping d of d of d, 1H, \(H_E\), \(J_{DE} = 9\) Hz, \(J_{EG} = J_{EF} = 2.5\) Hz), 2.27-2.32 (m, 1H, \(H_F\)), 2.59 (overlapping d of d of d, 1H, \(H_G\), \(J_{FG} = 4\) Hz, \(J_{GJ} = 2.5\) Hz, \(J_{EG} = 3\) Hz), 5.06 (d of d, 1H, \(H_C\), \(J_{CD} = 10\) Hz, \(J_{BC} = 1\) Hz), 5.20 (d of d, 1H, \(H_B\), \(J_{BD} = 17\) Hz, \(J_{BC} = 1\) Hz), 5.45 (d of d of d, 1H, \(H_D\), \(J_{BD} = 17\) Hz, \(J_{CD} = 10\) Hz, \(J_{DE} = 9\) Hz), 5.70 (d, 1H, \(H_I\), \(J_{IJ} = 5.5\) Hz), 7.64 (d of d of d, 1H, \(H_J\), \(J_{IJ} = 5.5\) Hz, \(J_{GJ} = 2.5\) Hz, \(J_{FJ} = 1\) Hz). Irradiation at \(\delta\) 7.64 (\(H_J\)) caused the signal at \(\delta\) 2.27-2.32 to sharpen, the signal at \(\delta\) 2.59 to collapse to a d of d (\(J = 4\) Hz, \(J = 3\) Hz) and the signal at \(\delta\) 5.70 to collapse to a s; and irradiation at
δ 2.59 (H_G) caused the signal at δ 2.17 to collapse to a d of d (J = 9 Hz, J = 2.5 Hz), the signal at δ 2.27-2.32 to collapse to a d of d (J = 2.5 Hz, J = 1 Hz), and the signal at δ 7.64 to collapse to a d of d (J = 5.5 Hz, J = 1 Hz).

**Exact mass** calcd. for C_8H_8O: 120.0575; found: 120.0574.

### 3.3.8 Preparation of Bicyclo[3.2.1]octa-2,6-dien-8-one

![Chemical Structure](image)

According to general procedure B, a solution of the enone 189 (39.7 mg, 0.331 mmol) in anhydrous benzene (3 mL) was heated at 160°C for 4 h to afford, after solvent removal, a pale yellow residue. Distillation (air-bath temperature 47-51°C/0.1 Torr) of this material provided the ketone 190 (27.0 mg, 68%), which exhibited a single spot by tlc (petroleum ether-ether, 1:1) and single peak by glc analysis (OV-17, 80°C); ir (film): 3050, 1755, 1622, 680 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ 2.45-2.53 (m, 1H, H_C or H_X), 2.73-2.82 (m, 3H, H_F, H_K, and H_C or H_X), 5.46-5.53 (m, 1H, H_D), 6.04 (overlapping d of d of d of d, 1H, H_E, J_{DE} = 9 Hz, J_{KE} = 7 Hz, J_{EX} = 3 Hz, J_{CE} = 2 Hz), 6.21 (d of d, 1H, H_Y, J_{JY} = 7 Hz, J_{FY} = 3 Hz), 6.69 (d of d, 1H, H_J, J_{JY} = 7 Hz, J_{JK} = 3 Hz).

Irradiation at δ 2.45-2.53 (H_C or H_X) caused the signals at
δ 2.73-2.82, δ 5.46-5.53 and δ 6.04 to sharpen; and irradiation at δ 6.69 (H*) caused the signal at δ 2.73-2.82 to sharpen and the signal at δ 6.21 to collapse to a d (J = 3 Hz).

**Exact mass** calcd. for C₆H₆O: 120.0575; found: 120.0563.

3.3.9 Preparation of 4-exo-6-exo-Divinylbicyclo[3.1.0]hexan-2-one

In accordance with a procedure reported by House et al., copper (I) catalyzed addition of vinyl magnesium bromide to the enone 189 afforded the ketone 191. To a flame-dried, three-necked flask equipped with a pressure-equalizing addition funnel, dry-ice condenser and argon gas inlet adaptor, was added magnesium turnings (0.0690 g, 2.84 mmol), anhydrous THF (4 mL) and a few crystals of iodine. A solution of vinyl bromide (0.212 mL, 3.00 mmol) in THF (2 mL) was added dropwise until the reaction had initiated, and thereafter at a rate to maintain mild reflux. The resulting mixture was refluxed for 0.3 h and cooled to room temperature to give a clear, yellow solution of vinyl magnesium bromide. Half of this solution was transferred via a syringe to another flask and cooled to -30°C. To the cold (-30°C), efficiently stirred solution of vinyl magnesium bromide, was added copper (I)
bromide-dimethyl sulfide complex (3.0 mg, 0.0134 mmol) and the resultant mixture was stirred at -30°C for 10 min, affording a green suspension. A solution of the enone (0.0947 g, 0.789 mmol) in THF (3 mL) was added dropwise to the reaction mixture over a period of 10 min. Subsequently, the mixture was allowed to warm to 0°C over a period of 40 min, diluted with ether and poured into saturated aqueous ammonium chloride. The aqueous phase was extracted thoroughly with ether and the combined organic extracts were washed successively with saturated aqueous sodium bicarbonate, twice with brine and dried (anhydrous magnesium sulfate). Concentration under reduced pressure (water aspirator) and Kugelrohr distillation (air-bath temperature ≈85°C/0.1 Torr) of the yellow residue thus obtained furnished the desired ketone (0.0932 g, 80%) as a clear, colourless oil, which was essentially pure by glc (OV-17, 80°C) and tlc (petroleum ether-ether, 5:1) analyses. This material exhibited ir (film): 3050, 1718, 1635, 990, 915 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ 1.87-1.94 (m, 2H, H₂, H₃), 1.97 (overlapping d of d of d, 1H, H₄, J₁₂ = 8.5 Hz, J₁₃ ≈ J₁₄ = 4 Hz), 2.04 (overlapping d of d, 1H, H₅, J₁₃ = 5 Hz, J₁₄ ≈ J₁₅ = 4 Hz), 2.36 (d of d, 1H, H₆, J₁₅ = 18.5 Hz, J₂₃ = 8 Hz), 3.02 (overlapping d of d, 1H, H₇, J₁₈ = J₁₉ = 8 Hz), 5.01 (d of d, 1H, H₈, J₈₉ = 10.5 Hz, J₈₁₀ = 1 Hz), 5.04 (overlapping d of d of d, 1H, H₉, J₉₁₀ = 10 Hz, J₉₁₁ = J₉₁₂ = 1 Hz), 5.12 (overlapping d of d of d, 1H, H₁₀, J₁₀₁₁ = 17.5 Hz, J₁₀₁₂ = J₁₀₁₃ = 1 Hz), 5.15 (d of d of d, 1H, H₁₁, J₁₁₁₂ = 17 Hz, J₁₁₁₃ = J₁₁₁₄ = 1 Hz), 5.36 (d of d of d, 1H, H₁₂, J₁₂₁₃ = 17 Hz, J₁₂₁₄ < 1 Hz).
Hz, $J_{CD} = 10.5$ Hz, $J_{DE} = 8.5$ Hz), 5.84 (d of d of d, 1H, $H_K$, $J_{KN} = 17.5$ Hz, $J_{KM} = 10$ Hz, $J_{JK} = 8$ Hz). Irradiation at $\delta$ 3.02 ($H_J$) caused a signal intensity increase of 22% (nuclear Overhauser enhancement) at $\delta$ 2.36, the signal at $\delta$ 5.04 to collapse to a d of d ($J = 10$ Hz, $J = 1$ Hz), the signal at $\delta$ 5.12 to collapse to a d of d ($J = 17.5$ Hz, $J = 1$ Hz), and the signal at $\delta$ 5.84 to collapse to a d of d ($J = 17.5$ Hz, $J = 10$ Hz); irradiation at $\delta$ 5.84 ($H_K$) caused the signal at $\delta$ 3.02 to collapse to a d ($J = 8$ Hz), the signals at $\delta$ 5.04 and $\delta$ 5.12 to simplify; and irradiation at $\delta$ 5.36 ($H_D$) caused the signals at $\delta$ 1.97, $\delta$ 5.01 and $\delta$ 5.15 to simplify.

**Exact mass** calcd. for C$_{10}$H$_{12}$O: 148.0888; found: 148.086.

### 3.3.10 Preparation of 2-((tert-Butyldimethylsiloxy)-4-exo-6-exo-divinylbicyclo[3.1.0]hex-2-ene

In accordance with general procedure A, the ketone 191 (0.140 g, 0.945 mmol) was transformed into the silyl enol ether 192 (0.240 g, >97%, air-bath distillation temperature 130-135°C/0.1 Torr). This material proved to be essentially pure by glc analysis (SE-54, 80°C) and exhibited ir (film): 3060, 3015, 1618 cm$^{-1}$; $^1$H nmr (400 MHz, CDCl$_3$) $\delta$ 0.18 (s, 6H,
CH$_3$-Si-CH$_3$), 0.95 (s, 9H, (CH$_3$)$_3$C-Si-O-), 1.23 (overlapping d of d of d, 1H, H$_E$, J$_{DE}$ = 8.5 Hz, J$_{EF}$ = 3.5 Hz, J$_{EG}$ = 2.5 Hz), 1.51 (d of d of d, 1H, H$_F$, J$_{FG}$ = 6.5 Hz, J$_{EF}$ = 3.5 Hz, J$_{IF}$ = 1.5 Hz), 1.75 (overlapping d of d of d, 1H, H$_G$, J$_{FG}$ = 6.5 Hz, J$_{EG}$ = J$_{GJ}$ = 2.5 Hz), 3.13 (unresolved d, 1H, H$_J$, J$_{JK}$ = 7.5 Hz), 4.31 (broad s, 1H, H$_I$, w$_{1/2}$ = 5 Hz), 4.88 (d of d, 1H, H$_C$, J$_{CD}$ = 10.5 Hz, J$_{BC}$ = 1.5 Hz), 4.94 (d of d of d, 1H, H$_M$, J$_{KM}$ = 10 Hz, J$_{MN}$ = 2 Hz, J$_{JM}$ = 1 Hz), 5.03 (d of d, 1H, H$_B$, J$_{BD}$ = 17 Hz, J$_{BC}$ = 1.5 Hz), 5.05 (d of d of d, 1H, H$_N$, J$_{KN}$ = 17 Hz, J$_{MN}$ = 2 Hz, J$_{JN}$ = 1 Hz), 5.41 (d of d of d, 1H, H$_D$, J$_{BD}$ = 17 Hz, J$_{CD}$ = 10.5 Hz, J$_{DE}$ = 8.5 Hz), 5.75 (d of d of d, 1H, H$_K$, J$_{KN}$ = 17 Hz, J$_{KM}$ = 10 Hz, J$_{JK}$ = 7.5 Hz).

Irradiation at δ 4.31 (H$_I$) caused the signal at δ 1.51 to collapse to a d of d (J = 6.5 Hz, J = 3.5 Hz), the signal at δ 1.75 to sharpen and the signal at δ 3.13 to sharpen to a d of d (J = 7.5 Hz, J = 2.5 Hz); irradiation at δ 3.13 (H$_J$) caused the signal at δ 1.51 to sharpen, the signal at δ 1.75 to collapse to a d of d (J = 6.5 Hz, J = 2.5 Hz), the signal at δ 4.94 to collapse to a d of d (J = 10 Hz, J = 2 Hz), the signal at δ 5.05 to collapse to a d of d (J = 17 Hz, J = 2 Hz), and the signal at δ 5.75 to collapse to a d of d (J = 17 Hz, J = 10 Hz); and irradiation at δ 5.41 (H$_D$) caused the signal at δ 1.23 to collapse to a broad s, and the signals at δ 4.88 and δ 5.03 to simplify.

Exact mass calcd. for C$_{16}$H$_{26}$OSi: 262.1753; found: 262.1759.
3.3.11 Preparation of 6-(tert-Butyldimethylsiloxy)-8-exo-vinylbicyclo[3.2.1]octa-2,6-diene

Following general procedure B, a solution of the silyl enol ether 192 (0.118 g, 0.450 mmol) in dry benzene (2.5 mL) was heated at 200°C for 5 h. After solvent removal, distillation (air-bath temperature 80-85°C/0.1 Torr) of the resultant residue provided the desired material 193 (0.105 g, 89%), which exhibited a single peak by glc analysis (SE-54, 80°C) and ir (film): 3050, 3010, 1624, 1245, 790 cm⁻¹; ¹H nmr (400MHz, CDCl₃) δ 0.14, 0.15 (s, s, 3H each, CH₃-Si-CH₃), 0.92 (s, 9H, (CH₃)₃C-Si-O-), 2.14-2.28 (m, 2H, Hᵦ, Hᵦ'), 2.31-2.35 (m, 1H, Hᵦ''), 2.38 (d of d, 1H, Hᵦ'', J_EK = 6 Hz, J_JK = 2.5 Hz), 2.65 (d, 1H, Hᵦ, J_IZ = 7.5 Hz), 4.95-5.01 (m, 2H, Hᵦ, Hᵦ'''), 5.08 (d of d of d, 1H, Hᵦ''', J_NZ = 17.5 Hz, J_MN = 2 Hz, J_IN = 1 Hz), 5.33 (unresolved d, 1H, H_D, J_DE = 9.5 Hz), 6.03 (d of d of d, 1H, Hₚ, J_NZ = 17.5 Hz, J_MZ = 10 Hz, J_IZ = 7.5 Hz), 6.25 (d of d of d of d, 1H, Hₚ, J_DE = 9.5 Hz, J_EK = 6 Hz, J_CE = J_EX = 2 Hz). Irradiation at δ 6.03 (Hₚ) caused the signal at δ 2.65 to collapse to a s, the signals at δ 4.95-5.01 and δ 5.08 to simplify; irradiation at δ 6.25 (Hₚ) caused the signal at δ 2.14-2.28 to simplify, the signal at
δ 2.38 to collapse to an unresolved d (J = 2.5 Hz), and the signal at δ 5.33 to simplify; and irradiation at δ 5.33 (H_D) caused the signal at δ 2.14-2.28 to simplify, the signal at δ 2.31-2.35 to collapse to an unresolved d (J = 4.5 Hz), the signal at δ 2.38 to sharpen and the signal at δ 6.25 to simplify.

Exact mass calcd. for C_{16}H_{26}OSi: 262.1753; found: 262.1752.

3.3.12 Preparation of 8-exo-Vinylbicyclo[3.2.1]oct-2-en-6-one

A mixture of the silyl enol ether 193 (0.0955 g, 0.364 mmol), 5% aqueous hydrochloric acid (9 mL) and THF (5 mL) was stirred at room temperature for 5.5 h. Subsequently, the resultant mixture was diluted with petroleum ether-ether (1:1) and poured carefully into saturated aqueous sodium bicarbonate. The aqueous phase was extracted thoroughly with ether, and the combined organic extracts were washed with brine and dried (anhydrous magnesium sulfate). Concentration and Kugelrohr distillation (air-bath temperature 63-67°C/0.1 Torr) of the resultant pale yellow residue afforded 50 mg (93%) of a clear, colourless oil. This material, identified as the desired
ketone 238, was essentially pure by glc analysis (SE-54, 80°C). An analytical sample, obtained by preparative glc (OV-17), exhibited ir (film): 3052, 3010, 1730, 1630, 998, 920, 730 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDC1\(_3\)) \(\delta\) 2.20 (d of d, 1H, H\(_J\), \(J_{JY} = 17.5\) Hz, \(J_{IJ} = 2\) Hz), 2.30 (overlapping d of d of d of d, 1H, H\(_Y\), \(J_{CX} = 18\) Hz, \(J_{DX} = 3.5\) Hz, \(J_{EX} = J_{FX} = 2\) Hz), 2.43 (d of d, 1H, H\(_Y\), \(J_{JY} = 17.5\) Hz, \(J_{KY} = 6\) Hz), 2.52 (overlapping d of d of d of d, 1H, H\(_C\), \(J_{CX} = 18\) Hz, \(J_{CF} = 5.5\) Hz, \(J_{CD} = J_{CE} = 2\) Hz), 2.59-2.63 (m, 1H, H\(_F\)), 2.66 (overlapping d of d, 1H, H\(_K\), \(J_{KE} = 6.5\) Hz, \(J_{KY} = 6\) Hz), 2.91 (unresolved d of d, 1H, H\(_I\)' \(J_{IZ} = 5.5\) Hz, \(J_{IJ} = 2\) Hz), 5.08 (overlapping d of d of d, 1H, H\(_N\), \(J_{NZ} = 17.5\) Hz, \(J_{MN} = 1.5\) Hz, \(J_{IN} = 1\) Hz), 5.14 (overlapping d of d of d, 1H, H\(_M\)' \(J_{MZ} = 10.5\) Hz, \(J_{MN} = 1.5\) Hz, \(J_{IM} = 1.5\) Hz), 5.53 (overlapping d of d of d, 1H, H\(_D\)' \(J_{DE} = 9.5\) Hz, \(J_{DX} = 3.5\) Hz), 5.90 (d of d of d, 1H, H\(_Z\)' \(J_{NZ} = 17.5\) Hz, \(J_{MZ} = 10.5\) Hz, \(J_{IZ} = 5.5\) Hz), 6.14 (d of d of d of d, 1H, H\(_E\)' \(J_{DE} = 9.5\) Hz, \(J_{KE} = 6.5\) Hz, \(J_{CE} = J_{EX} = 2\) Hz).

Irradiation at \(\delta\) 5.90 (H\(_Z\)) caused the signal at \(\delta\) 2.91 to collapse to a broad s (\(\omega_{1/2} = 5\) Hz), the signal at \(\delta\) 5.08 to collapse to an overlapping d of d (\(J = 1.5\) Hz, \(J = 1\) Hz), and the signal at \(\delta\) 5.14 to collapse to an overlapping d of d (\(J = 1.5\) Hz, \(J = 1\) Hz); irradiation at \(\delta\) 2.91 (H\(_I\)) caused the signal at \(\delta\) 2.66 to sharpen, the signal at \(\delta\) 5.08 to collapse to a d of d (\(J = 17.5\) Hz, \(J = 1.5\) Hz), the signal at \(\delta\) 5.14 to collapse to a d of d (\(J = 10.5\) Hz, \(J = 1.5\) Hz), and the signal at \(\delta\) 5.90 to collapse to a d of d (\(J = 17.5\) Hz, \(J = 10.5\) Hz); irradiation at \(\delta\) 6.14 (H\(_E\)) caused the signal at
δ 2.30 to collapse to a d of d of d (\(J = 18\) Hz, \(J = 3.5\) Hz, \(J = 2\) Hz), the signal at δ 2.52 to collapse to a d of d of d (\(J = 18\) Hz, \(J = 5.5\) Hz, \(J = 2\) Hz), the signal at δ 2.66 to collapse to a d (\(J = 6\) Hz), the signal at δ 2.91 to sharpen and the signal at δ 5.53 to collapse to an overlapping d of d (\(J = 3.5\) Hz, \(J = 2\) Hz); and irradiation at δ 5.53 (\(H_D\)) caused the signal at δ 2.30 to collapse to an unresolved d (\(J = 18\) Hz), the signal at δ 2.52 to collapse to a d of d of d (\(J = 18\) Hz, \(J = 5.5\) Hz, \(J = 2\) Hz), and the signal at δ 6.14 to collapse to an unresolved d (\(J = 6.5\) Hz).

Exact mass calcd. for \(\text{C}_{10}\text{H}_{12}\text{O}\): 148.0888; found: 148.0887.

3.3.13 Preparation of 2-(tert-Butyldimethylsiloxy)-4-exocarbethoxymethyl-6-exo-vinylbicyclo[3.1.0]hex-2-ene

According to a procedure reported by Tamura et al.,\(^{142}\) the enone 189 was transformed into the silyl enol ether 194. Thus, a mixture of the enone 189 (0.157 g, 1.31 mmol), the silyl ketene acetal\(^{143}\) 210 (0.397 g, 1.96 mmol) and anhydrous acetonitrile (3 mL) was stirred at 55°C for 12 h. The reaction mixture was concentrated and the resultant residue was distilled (air-bath temperature 103-106°C/0.1 Torr) to
furnish 0.140 g (33%) of a clear, colourless oil which exhibited ir (film): 3050, 1730, 1620, 1255, 787 cm$^{-1}$; $^1$H nmr (400 MHz, CDCl$_3$) $\delta$ 0.16 (s, 6H, CH$_3$-Si-CH$_3$), 0.94 (s, 9H, (CH$_3$)$_3$C-Si-O-), 1.21 (overlapping d of d of d, 1H, H$_E$, $J_{DE}$ = 9 Hz, $J_{EF}$ = 3.5 Hz, $J_{EG}$ = 2.5 Hz), 1.26 (t, 3H, CH$_3$CH$_2$O-, $J$ = 7.5 Hz), 1.49 (overlapping d of d of d, 1H, H$_F$, $J_{FG}$ = 6.5 Hz, $J_{EF}$ = 3.5 Hz, $J_{FI}$ = 1.5 Hz), 1.73 (overlapping d of d of d, 1H, H$_G$, $J_{FG}$ = 6.5 Hz, $J_{EG}$ = $J_{GJ}$ = 2.5 Hz), 2.29 (d of d, 1H, H$_X$, $J_{XY}$ = 15 Hz, $J_{JX}$ = 8 Hz), 2.34 (d of d, 1H, H$_Y$, $J_{XY}$ = 15 Hz, $J_{JY}$ = 7 Hz), 2.88-2.94 (m, 1H, H$_J$), 4.14 (q, 2H, CH$_3$CH$_2$O-, $J$ = 7 Hz), 4.35 (broad s, 1H, H$_I$, $w_{1/2}$ = 5 Hz), 4.87 (d of d, 1H, H$_C$, $J_{CD}$ = 10 Hz, $J_{BC}$ = 1.5 Hz), 5.20 (d of d, 1H, H$_B$, $J_{BD}$ = 17 Hz, $J_{BC}$ = 1.5 Hz), 5.40 (d of d of d, 1H, H$_D$, $J_{BD}$ = 17 Hz, $J_{CD}$ = 10 Hz, $J_{DE}$ = 9 Hz). Irradiation at $\delta$ 4.35 (H$_I$) caused the signal at $\delta$ 1.49 to sharpen to a d of d ($J$ = 6.5 Hz, $J$ = 3.5 Hz), and the signal at $\delta$ 2.88-2.94 to sharpen to an overlapping d of d of d ($J$ = 8 Hz, $J$ = 7 Hz, $J$ = 3 Hz); irradiation at $\delta$ 2.88-2.94 (H$_J$) caused the signal at $\delta$ 1.73 to collapse to a d of d ($J$ = 6.5 Hz, $J$ = 2.5 Hz), the signal at $\delta$ 2.29 to collapse to a d ($J$ = 15 Hz), the signal at $\delta$ 2.34 to collapse to a d ($J$ = 15 Hz) and the signal at $\delta$ 4.35 to sharpen; irradiation at $\delta$ 5.40 (H$_D$) caused the signal at $\delta$ 1.21 to collapse to a broad s ($w_{1/2}$ = 7 Hz), and the signals at $\delta$ 4.87 and $\delta$ 5.20 to simplify; and irradiation at $\delta$ 1.73 (H$_G$) caused the signal at $\delta$ 1.21 to collapse to a d of d ($J$ = 9 Hz, $J$ = 3.5 Hz), the signal at $\delta$ 1.49 to collapse to a
d of d (J = 3.5 Hz, J = 1.5 Hz), the signal at δ 2.88-2.94 to collapse to an overlapping d of d of d (J = 7 Hz, J = 8 Hz, J = 2.5 Hz), and the signal at δ 4.35 to sharpen.

Exact mass calcd. for C_{18}H_{30}O_{3}Si: 322.1964; found: 322.1957.

3.3.14 Preparation of 6-(tert-Butyldimethylsiloxy)-8-exo-(carbethoxymethyl)bicyclo[3.2.1]octa-2,6-diene

Following general procedure B, a solution of the silyl enol ether 194 (68.0 mg, 0.211 mmol) in dry benzene (3 mL) was thermolyzed at 200°C for 2.5 h. Solvent removal and distillation (air-bath temperature 131-135°C/0.1 Torr) of the residue thus obtained afforded the desired enol ether 195 (66.7 mg, 98%), which exhibited a single peak by glc analysis (SE-54, 80°C) and ir (film): 3050, 3010, 1725, 1620, 790 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) δ 0.14, 0.16 (s, s, 3H each, CH\(_3\)-Si-CH\(_3\)), 0.92 (s, 9H, (CH\(_3\))\(_3\)C-Si-O-), 1.26 (t, 3H, CH\(_3\)CH\(_2\)O-, J = 7 Hz), 2.15 (unresolved d, 1H, H\(_C\) or H\(_X\), J\(_{CX}\) = 17 Hz), 2.20-2.31 (m, 3H), 2.31-2.35 (unresolved d of d, 1H, H\(_K\), J\(_{EK}\) = 5.5 Hz, J\(_{JK}\) = 2.5 Hz), 2.43-2.52 (m, 3H, H\(_M\), H\(_N\)), 4.13 (q, 2H, CH\(_3\)CH\(_2\)O-, J = 7 Hz), 4.97 (d, 1H, H\(_J\), J\(_{JK}\) = 2.5 Hz), 5.28-5.33 (unresolved d, 1H, H\(_D\), J\(_{DE}\) = 10 Hz), 6.20-6.26 (m, 1H, H\(_E\)).
Irradiation at δ 6.20-6.26 (H_E) caused the signal at δ 2.15 to collapse to a d of d (J = 17 Hz, J = 3 Hz), the signal at δ 2.20-2.31 to simplify, the signal at δ 2.31-2.35 to collapse to a broad s, and the signal at δ 5.28-5.33 to collapse to a broad s; and irradiation at δ 5.28-5.33 (H_D) caused the signal at δ 2.15 to sharpen to a d (J = 17 Hz), the signal at δ 2.20-2.31 to simplify and the signal at δ 6.20-6.26 to collapse to an unresolved d (J = 5.5 Hz).

Exact mass calcd. for C_{18}H_{30}O_{3}Si: 322.1964; found: 322.1963.

3.3.15 Preparation of 8-exo-Carbethoxymethylbicyclo[3.2.1]-oct-2-en-6-one

A mixture of the silyl enol ether 195 (54.2 mg, 0.168 mmol), 5% aqueous hydrochloric acid (2 mL) and THF (2 mL) was stirred at room temperature for 5.5 h. Subsequently, the reaction mixture was diluted with ether and poured into saturated aqueous sodium bicarbonate. The aqueous layer was extracted thrice with ether, and the combined ethereal extracts were washed twice with brine and dried over anhydrous magnesium sulfate. Concentration afforded the desired ketone 239 (33 mg, 94%) as a clear, colourless oil, which was homogeneous by
analyses. This material exhibited ir (film): 3000, 1740, 1730, 1625 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\) 1.27 (t, 3H, \(\text{CH}_3\text{CH}_2\text{O}^\text{−}\), \(\text{J} = 7\) Hz), 2.22-2.45 (m, 6H, \(\text{H}_\text{X}, \text{H}_\text{J}, \text{H}_\text{M}, \text{H}_\text{N}, \text{H}_\text{Y}, \text{H}_\text{F}\)), 2.54 (overlapping d of d of d of d, 1H, \(\text{H}_\text{C}\), \(\text{J}_{\text{CX}} = 18\) Hz, \(\text{J}_{\text{CF}} = 5.5\) Hz, \(\text{J}_{\text{CD}} = 2.5\) Hz, \(\text{J}_{\text{CE}} = 2\) Hz), 2.60 (overlapping d of d, 1H, \(\text{H}_\text{K}\), \(\text{J}_{\text{EK}} = 7\) Hz, \(\text{J}_{\text{KY}} = 6\) Hz, \(\text{J}_{\text{JK}} = 1\) Hz), 2.70 (overlapping d of d, 1H, \(\text{H}_\text{I}\), \(\text{J}_{\text{IM}} = 7.5\) Hz, \(\text{J}_{\text{IN}} = 8\) Hz), 4.15 (q, 2H, \(\text{CH}_3\text{CH}_2\text{O}^\text{−}\), \(\text{J} = 7\) Hz), 5.51 (overlapping d of d of d, 1H, \(\text{H}_\text{D}\), \(\text{J}_{\text{DE}} = 9.5\) Hz, \(\text{J}_{\text{CD}} = 2.5\) Hz, \(\text{J}_{\text{DX}} = 3.5\) Hz), 6.11 (overlapping d of d of d of d, 1H, \(\text{H}_\text{E}\), \(\text{J}_{\text{DE}} = 9.5\) Hz, \(\text{J}_{\text{EK}} = 7\) Hz, \(\text{J}_{\text{CE}} = \text{J}_{\text{EX}} = 2\) Hz). Irradiation at \(\delta\) 5.51 (\(\text{H}_\text{D}\)) caused the signal at \(\delta\) 2.22-2.45 to simplify, the signal at \(\delta\) 2.54 to collapse to a d of d of d (\(\text{J} = 18\) Hz, \(\text{J} = 5.5\) Hz, \(\text{J} = 2\) Hz) and the signal at \(\delta\) 6.11 to collapse to a d of d (\(\text{J} = 7\) Hz, \(\text{J} = 2\) Hz); irradiation at \(\delta\) 6.11 (\(\text{H}_\text{E}\)) caused the signal at \(\delta\) 2.22-2.45 to simplify, the signal at \(\delta\) 2.54 to collapse to a d of d of d (\(\text{J} = 18\) Hz, \(\text{J} = 5.5\) Hz, \(\text{J} = 2.5\) Hz), the signal at \(\delta\) 2.60 to collapse to an unresolved d (\(\text{J} = 6\) Hz), and the signal at \(\delta\) 5.51 to collapse to a broad s; and irradiation at \(\delta\) 2.70 (\(\text{H}_\text{I}\)) caused the signal at \(\delta\) 2.22-2.45 to simplify, and the signals at \(\delta\) 2.60 and \(\delta\) 6.11 to sharpen.

**Exact mass** calcd. for \(\text{C}_{12}\text{H}_{16}\text{O}_3\): 208.1099; found: 208.1096.
3.3.16 Preparation of Ethyl (E)-4-methyl-2-pentenoate

The procedure described by Isler et al., and later by House and Rasmussen was followed. Thus, to a stirred solution of carbethoxymethylene triphenylphosphorane (40.0 g, 114.9 mmol) in anhydrous dichloromethane (100 mL), under an atmosphere of argon, was added dropwise, via a syringe, isobutyraldehyde (10.4 mL, 114.9 mmol), and the resultant mixture was refluxed for 4 h. Most of the solvent was removed by distillation at atmospheric pressure leaving a white residue, which was triturated with pentane and the resultant mixture was filtered through a short column of silica gel. Careful concentration of the eluate and distillation (air-bath temperature 45-50°C/0.1 Torr) of the yellow residue thus obtained, furnished the ester (15.0 g, 92%) as an odoriferous, colourless oil. This material, which consisted of one component by glc (OV-17, 80°C) and tlc (petroleum ether-ether, 9:1) analyses, exhibited ir (film): 3050, 1715, 1648, 1308, 995 cm⁻¹; \(^1\)H nmr (80 MHz, CDCl₃) δ 1.06 (d, 6H, CH₃-CH-CH₃, J = 7 Hz), 1.30 (t, 3H, CH₃CH₂O-, J = 7 Hz), 2.46 (overlapping d of d of septet, 1H, H_B, J_{BC} = 7 Hz, J_{BD} = 1 Hz, J = 7 Hz), 4.20 (q, 2H, CH₃CH₂O-, J = 7 Hz), 5.76 (d of d, 1H, H_D, J_{CD} = 16 Hz, \(\text{CO}_2\text{Et} \))
Exact mass calcd. for C_{\text{H}_{14}}O_{2}: 142.0994; found: 142.0991.

3.3.17 Preparation of (E)-4-Methyl-2-penten-1-ol

To a cold (-78°C), stirred solution of the ester 255 (1.00 g, 7.04 mmol) in anhydrous pentane (15 mL), under an atmosphere of argon, was added dropwise via a syringe, a hexane solution of diisobutylaluminum hydride (17.6 mmol). The resultant mixture was stirred at -78°C for 1 h and then at 0°C for an additional hour. Subsequently, saturated aqueous ammonium chloride (1 mL) was added to the cold (0°C) reaction mixture, which was allowed to warm to room temperature and then was poured into 5% aqueous hydrochloric acid. The aqueous phase was washed twice with 5% aqueous hydrochloric acid, brine, saturated aqueous sodium bicarbonate and brine, and dried over anhydrous magnesium sulfate. Solvent removal by distillation at atmospheric pressure furnished the allylic alcohol 256 (0.668 g, 95%) as a clear, colourless oil. This material exhibited a single peak by glc analysis (OV-17, 60°C) and ir (film): 3300 (broad), 3010, 1660, 970 cm$^{-1}$; $^1$H nmr (80 MHz, CDCl$_3$) $\delta$ 1.00 (d, 6H, CH$_3$-CH-CH$_3$, J = 7 Hz),
1.47 (broad s, 1H, -OH, D\textsubscript{2}O exchangeable), 2.10-2.60 (m, 1H, CH\textsubscript{3}-CH-CH\textsubscript{3}), 4.04-4.17 (m, 2H, -CH\textsubscript{2}-OH), 5.38-5.87 (m, 2H, H-C=C-H).

Exact mass calcd. for C\textsubscript{6}H\textsubscript{12}O: 100.0888; found: 100.0887.

3.3.18 Preparation of (E)-4-Methyl-2-pentenal

To an efficiently stirred solution of the allylic alcohol 256 (0.200 g, 2.00 mmol) in anhydrous dichloromethane (10 mL), under an atmosphere of argon, was added pyridinium chlorochromate (3.20 mmol) supported on alumina.\textsuperscript{151} The initially orange suspension became black almost immediately on addition of the oxidizing agent. Subsequently, the resultant mixture was stirred at room temperature for 3 h and then was filtered through a short column of silica gel (70-230 mesh). The brown residue at the head of the column was rinsed thoroughly with anhydrous ether and the solvent was removed from the filtrate by distillation at atmospheric pressure, leaving a brown oil. This material was subjected to flash distillation (air-bath temperature \textasciitilde30°C/0.1 Torr), which afforded the allylic aldehyde 257 (0.194 g, >98%) as a clear, colourless oil. The oil was essentially pure by glc.
analysis (OV-17, 80°C) and exhibited IR (film): 3010, 2780, 2700, 1675, 1622, 980 cm\(^{-1}\); \(^1\)H NMR (80 MHz, CDCl\(_3\)) \(\delta\) 1.13 (d, 6H, CH\(_3\)-CH-CH\(_3\), \(J = 7\) Hz), 2.37-2.85 (m, 1H, H\(_B\)), 6.10 (d of d of d, 1H, H\(_D\), \(J_{CD} = 16\) Hz, \(J_{DE} = 8\) Hz, \(J_{BD} = 1\) Hz), 6.86 (d of d, 1H, H\(_C\), \(J_{CD} = 16\) Hz, \(J_{BC} = 7\) Hz), 9.55 (d, 1H, H\(_E\), \(J_{DE} = 8\) Hz).

Exact mass calcd. for C\(_6\)H\(_{10}\)O: 98.0732; found: 98.0732.

3.3.19 Preparation of Ethyl (2E),(4E)-6-methyl-2,4-heptadienoate\(^{152}\)

![Chemical Structure](image)

The procedure by Isler et al.\(^{144}\) and later by House and Rasmussen\(^{146}\) was followed. Thus, to a stirred solution of 1-carbethoxymethylenetriphenylphosphorane\(^{147}\) (6.32 g, 18.1 mmol) in anhydrous dichloromethane (15 mL), under an atmosphere of argon, was added a solution of the allylic aldehyde 257 (1.78 g, 18.1 mmol) in dichloromethane (4 mL), and the resultant mixture was refluxed for 5 h. Subsequently, the solvent was removed by distillation at atmospheric pressure, and the still-pot residue was triturated with pentane and then was filtered through a layer of silica gel (70-230 mesh). After the filtrate was concentrated, Kugelrohr distillation (air-bath
temperature 68-75°C/0.1 Torr) of the yellow oil thus obtained, gave 1.34 g (44%) of a clear, colourless oil, which was of >99% purity by glc analysis (OV-17, 80°C) and consisted of a single component by tlc analysis (petroleum ether-ether, 1:1). This material, identified as the ester 258, exhibited ir (film): 3010, 1700, 1635, 1612, 1005 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\) 1.05 (d, 6H, CH\(_3\)-CH-CH\(_3\), J = 7 Hz), 1.30 (t, 3H, CH\(_3\)CH\(_2\)O-, J = 7 Hz), 2.43 (overlapping d of septet, 1H, H\(_B\), J\(_{BC}\) = 6 Hz, J = 7 Hz), 4.22 (q, 2H, CH\(_3\)CH\(_2\)O-, J = 7 Hz), 5.80 (d, 1H, H\(_F\), J\(_{EF}\) = 14 Hz), 6.09 (d of d, 1H, H\(_C\), J\(_{CD}\) = 15 Hz, J\(_{BC}\) = 6 Hz), 6.13 (d of d, 1H, H\(_D\), J\(_{CD}\) = 15 Hz, J\(_{DE}\) = 9 Hz), 7.26 (d of d, 1H, H\(_E\), J\(_{EF}\) = 14 Hz, J\(_{DE}\) = 9 Hz). In the following decoupling experiments, the region \(\delta\) 5.5-7.5 was observed: irradiation at \(\delta\) 2.43 (H\(_B\)) caused the signal at \(\delta\) 6.09 to collapse to a d (J = 15 Hz); irradiation at \(\delta\) 7.26 (H\(_E\)) caused the signal at \(\delta\) 5.80 to collapse to a s, and the signal at \(\delta\) 6.13 to collapse to a d (J = 15 Hz); and irradiation at \(\delta\) 5.80 (H\(_F\)) caused the signal at \(\delta\) 7.26 to collapse to a d (J = 9 Hz).

**Exact mass calcd. for C\(_{10}\)H\(_{16}\)O\(_2\): 168.1150; found: 168.1151.**
3.3.20 Preparation of (2E), (4E)-6-Methyl-2,4-heptadien-1-ol

To a cold (-78°C), stirred solution of the ester 258 (0.386 g, 2.30 mmol) in anhydrous pentane (7 mL), under an atmosphere of argon, was added dropwise via a syringe, a hexane solution of diisobutylaluminum hydride (5.05 mmol). The resultant mixture was stirred at -78°C for 1 h and then at 0°C for another 3 h. Subsequently, saturated aqueous ammonium chloride (1 mL) was added to the cold (0°C) reaction mixture, which was allowed to warm to room temperature over a period of 0.5 h. The reaction mixture was diluted with ether, poured into 5% aqueous hydrochloric acid and the layers were separated. The organic layer was washed twice with 5% aqueous hydrochloric acid, brine, saturated aqueous sodium bicarbonate and brine, and dried (anhydrous magnesium sulfate). After solvent removal by distillation at atmospheric pressure, Kugelrohr distillation (air-bath temperature 60-65°C/0.1 Torr) of the residual oil afforded the alcohol 259 (0.280 g, >96%) as a clear, colourless liquid. This material was shown to consist of one component by glc analysis (OV-17, 80°C) and exhibited ir (film): 3300 (broad), 3050, 1650, 990 cm⁻¹; ¹H
nmr (270 MHz, CDCl₃) δ 1.00 (d, 6H, CH₃-CH-CH₃, J = 7 Hz), 1.57 (broad s, 1H, -OH), 2.34 (d of septet, 1H, Hₐ, Jₐ₋c = 7 Hz, J = 7 Hz), 4.15 (d, 2H, H₋c, J₋c₋d = 6 Hz), 5.68 (d of d, 1H, H₋c, J₋c₋d = 15 Hz, J₋b₋c = 7 Hz), 5.74 (d of t, 1H, H₋f, J₋f₋e = 15 Hz, J₋f₋g = 6 Hz), 6.02 (d of d, 1H, H₋d, J₋c₋d = 15 Hz, J₋d₋e = 10 Hz), 6.22 (d of d, 1H, H₋e, J₋e₋f = 15 Hz, J₋d₋e = 10 Hz).

For the following decoupling experiment, the region δ 5.5-6.5 was observed: irradiation at δ 2.34 (H₋a) caused the signal at δ 5.68 to collapse to a d (J = 15 Hz), and the signal at δ 6.02 to sharpen.

Exact mass calcd. for C₁₀H₁₆O: 126.1045; found: 126.1043.

3.3.21 Preparation of (2E),(4E)-1-Bromo-6-methyl-2,4-heptadiene

Following the procedure described by Miller,¹⁵⁴ the allylic alcohol 2₅⁹ was converted into the corresponding allylic bromide 2₄₄. Thus, to a cold (0°C), stirred solution of the alcohol 2₅⁹ (1.00 g, 7.93 mmol) and pyridine (32 μL, 0.40 mmol) in anhydrous ether (2 mL), under an atmosphere of argon, was added dropwise a solution of phosphorus tribromide (0.23 mL, 3.2 mmol) in ether (1 mL). The resultant mixture was stirred at 0°C for 4 h and then was poured into ice-water. The organic phase was washed successively with brine,
5% aqueous sodium bicarbonate and brine, and dried over anhydrous magnesium sulfate. After careful concentration under reduced pressure (water aspirator) and flash distillation (air-bath temperature \( =30^\circ C / 0.1 \) Torr), 1.17 g (78%) of a pale yellow oil was obtained. This material, identified as the bromide 244, darkened rapidly on standing at room temperature. It was therefore distilled immediately prior to use. A sample of the bromide 244 exhibited ir (film): 3010, 1643, 990 cm\(^{-1}\); \(^1\)H nmr (80 MHz, CDCl\(_3\)) \( \delta 1.00 \) (d, 6H, CH\(_3\)-CH-CH\(_3\), \( J = 7 \) Hz), 2.10-2.60 (m, 1H, CH\(_3\)-CH-CH\(_3\)), 4.04 (d, 2H, -CH\(_2\)Br, \( J = 8 \) Hz), 5.55-6.50 (m, 4H, vinylic protons).

Exact mass calcd. for C\(_{8}H_{13}\)^{79}Br: 188.0200; found: 188.0200.

3.3.22 Preparation of Methyl (6E),(8E)-10-methyldodeca-6,8-dien-3-one

In accordance with the procedure reported by Huckin and Weiler,\(^{155}\) the dianion of methyl acetoacetate was alkylated with the allylic bromide 244. To a cold (-78°C), stirred suspension of sodium hydride (0.15 g, 6.8 mmol) in anhydrous THF (30 mL), under an atmosphere of argon, was added a solution of methyl acetoacetate (0.719 g, 6.19 mmol) in THF
(2 mL). The resultant mixture was stirred at 0°C for 10 min to furnish a pale grey suspension, to which was added a hexane solution of n-butyllithium (6.81 mmol). Efficient stirring at 0°C was maintained for another 15 min, after which time a green mixture was obtained. Subsequently, a solution of the allylic bromide 244 (1.17 g, 6.19 mmol) in THF (3 mL) was added and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with ether and then was poured carefully into 5% aqueous hydrochloric acid, more of which was added until the aqueous layer was no longer basic to litmus paper. After the layers were separated and the aqueous phase was extracted thoroughly with ether, the combined organic extracts were washed thrice with brine and dried over anhydrous magnesium sulfate. Solvent removal under reduced pressure (water aspirator) and subjection of the resultant residue to flash column chromatography (100 g of 230-400 mesh silica gel in a 45x150 mm column, elution with petroleum ether-ethyl acetate, 5:1) afforded, after concentration of the appropriate fractions, the β-keto ester 245 (0.743 g, 53%) as a clear, colourless oil. This material exhibited ir (film): 3000, 1740, 1710, 1650, 1620, 993 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ 1.00 (d, 6H, CH₃-CH-CH₃, J = 7 Hz), 2.31 (overlapping d of septet, 1H, Hₙ, J = 7 Hz, Jₕ₋ₓ = 7 Hz), 2.37 (overlapping d of t, 2H, H₂, J = 7 Hz), 2.65 (t, 2H, O=CH₂-CH₂⁻, J = 7 Hz), 3.46 (s, 2H, O=CH₂-CH₂⁻-CO₂CH₃), 3.76 (s, 3H, -CO₂CH₃), 5.57
(overlapping d of t, 1H, H_F, J_{EF} = 14.5 Hz, J_{FG} = 7 Hz), 5.61 (d of d, 1H, H_C, J_{CD} = 15 Hz, J_{BC} = 7 Hz), 5.98 (d of d, 1H, H_D, J_{CD} = 15 Hz, J_{DE} = 10 Hz), 6.06 (d of d, 1H, H_E, J_{EF} = 14.5 Hz, J_{DE} = 10 Hz). Irradiation at δ 2.65 caused the signal at δ 2.37 to collapse to a d (J = 7 Hz).

**Exact mass calcd. for C_{13}H_{20}O_{3}:** 224.1412; found: 224.1411.

### 3.3.23 Preparation of Methyl (6E),(8E)-2-diazo-10-methyl-dodeca-6,8-dien-3-one

![Methyl (6E),(8E)-2-diazo-10-methyl-dodeca-6,8-dien-3-one](image)

In accordance with the procedure reported by Regitz, the β-keto ester 245 was transformed into the diazo keto ester 246. To a stirred solution of the β-keto ester 245 (0.200 g, 0.892 mmol) and p-toluenesulfonyl azide (0.176 g, 0.892 mmol) in anhydrous acetonitrile (4 mL), under an atmosphere of argon, was added triethylamine (0.124 mL, 0.892 mmol), and the resultant mixture was stirred at room temperature. Reaction progress was monitored by tlc (pentane-ether, 4:1), which indicated that all of the starting material had been consumed after 24 h. Removal of solvent under reduced pressure (water aspirator) furnished a yellow residue, which was dissolved in a minimum amount of ether. Pentane was added to this solution
until no further solid material precipitated. The slurry thus obtained was filtered through a layer of Celite\textsuperscript{R} and the filtrate was concentrated to give a yellow oil. Dissolution of the oil in pentane and filtration of the pentane solution was repeated until no further solid precipitated. The viscous, yellow syrup obtained after concentration of the filtrate, displayed a single spot by tlc analysis (petroleum ether-ether, 5:1) and was identified as the desired diazo keto ester 246 (0.216 g, 97%). This material exhibited \textit{ir} (film): 3000, 2120, 1715, 1650, 1310, 995 cm\textsuperscript{-1}; \textit{\textsuperscript{1H} nmr} (80 MHz, CDCl\textsubscript{3}) \delta 1.00 (d, 6H, CH\textsubscript{3}-CH-CH\textsubscript{3}, J = 7 Hz), 2.10-2.65 (m, 3H, CH\textsubscript{3}-CH-CH\textsubscript{3}, -CH\textsubscript{2}-C=C-), 2.94 (t, 2H, \textit{O}=CH-CH\textsubscript{2}-, J = 7 Hz), 3.85 (s, 3H, -CO\textsubscript{2}CH\textsubscript{3}), 5.30-6.30 (m, 4H, olefinic protons).

ms m/e: 250 (M\textsuperscript{+}), 222 (M-N\textsubscript{2})\textsuperscript{+}

3.3.24 Preparation of 1-Carbomethoxy-6-exo-[(E)-3-methyl-1-butenyl]bicyclo[3.1.0]hexan-2-one

![Diagram](http://example.com/diagram.png)

The procedure described by Hudlicky et al.\textsuperscript{98} was followed for the conversion of the diazo keto ester 246 to the bicyclic \textit{\textbeta} keto ester. Thus, to a stirred suspension of Cu(acac)\textsubscript{2}·H\textsubscript{2}O\textsubscript{163} (27 mg, 0.10 mmol) in refluxing, anhydrous benzene (16 mL),
under an atmosphere of argon, was added dropwise a solution of the diazo keto ester 246 (0.180 g, 0.724 mmol) in benzene (3 mL). The resulting mixture was refluxed for 6 h, cooled to room temperature and filtered through a layer of Celite™. Concentration of the clear, green filtrate under reduced pressure (water aspirator) furnished a dark yellow oil, which was subjected to preparative tlc (silica gel, elution with petroleum ether-ethyl acetate, 5:1). Concentration of the appropriate fraction and Kugelrohr distillation (air-bath temperature 90-95°C/0.1 Torr) of the yellow residue thus obtained, afforded 0.125 g (78%) of a clear, colourless oil, which was of >98% purity by glc analysis (OV-17, 80°C). This material, identified as the bicyclic β-keto ester 247, exhibited ir (film): 3010, 1750, 1720 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ 0.95, 0.96 (d, d, 3H each, CH₃-CH-CH₃, J = 7 Hz), 2.00-2.34 (m, 6H), 2.67 (overlapping d of d, 1H, H_G, J_EG = J_G2 = 5.5 Hz), 3.76 (s, 3H, -CO₂CH₃), 5.21 (d of d of d, 1H, H_D, J_BD = 15.5 Hz, J_DE = 8.5 Hz, J_CD = 1 Hz), 5.71 (d of d, 1H, H_B, J_BD = 15.5 Hz, J_BC = 7 Hz).

Exact mass calcd. for C₁₃H₁₈O₃: 222.1256; found: 222.1251.
3.3.25 Preparation of 2-(tert-Butyldimethylsiloxy)-1-carbomethoxy-6-exo-[(E)-3-methyl-1-butene]bicyclo[3.1.0]hex-2-ene

Following general procedure A, the keto ester (0.100 g, 0.450 mmol) was transformed into the silyl enol ether (0.131 g, 87%, air-bath temperature 149-152°C/0.1 Torr).

This material consisted of a single component by glc analysis (SE-54, 110°C) and exhibited ir (film): 1720, 1620 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ 0.16 (s, 6H, CH₃-Si-CH₃), 0.95 (s, 9H, (CH₃)₃-Si-O⁻), 0.97, 0.98 (d, d, 3H each, CH₃-CH-CH₃, J = 7 Hz), 1.73 (d of d, 1H, Hₓ, Jₓₓ = 9 Hz, Jₓᵧ = 5 Hz), 2.11 (overlapping d of d, 1H, Hᵧ, Jᵧᵧ = 5 Hz, Jᵧₓ = 7 Hz), 2.23 (d of d, 1H, Hₓ, Jₓᵧ = 16 Hz, Jₓₓ = 3 Hz), 2.22-2.34 (m, 1H, Hₓ), 2.58 (d of d of d, 1H, Hₓ, Jₓₓ = 16 Hz, Jₓᵧ = 7 Hz, Jₓᵧ = 2 Hz), 3.69 (s, 3H, -CO₂CH₃), 4.38 (broad s, 1H, H₁, w₁/2 = 6 Hz), 5.48 (d of d, 1H, Hₓ, Jₓₓ = 15 Hz, Jₓᵧ = 9 Hz), 5.59 (d of d, 1H, Hₓ, Jₓₓ = 15 Hz, Jₓᵧ = 6 Hz).

Exact mass calcd. for C₁₉H₃₂O₃Si: 336.2121; found: 336.2122.
3.3.26 Preparation of 6-(tert-Butyldimethylsiloxy)-7-carbomethoxy-4-endo-isopropylbicyclo[3.2.1]octa-2,6-diene

According to general procedure B, a solution of the silyl enol ether 240 (0.123 g, 0.366 mmol) in benzene (2.5 mL) was heated at 200°C for 2 h. Removal of solvent and subsequent distillation (air-bath temperature 131-136°C/0.1 Torr) of the residue provided the desired compound 241 (0.117 g, 95%) which consisted of a single component by glc analysis (OV-17, 80°C). This material exhibited ir (film): 3012, 1700, 1610, 1215, 850 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ 0.19, 0.21 (s, s, 3H each, CH₃-Si-CH₃), 0.91, 1.00 (d, d, 3H each, CH₃-CH-CH₃, J = 7 Hz), 0.97 (s, 9H, (CH₃)₃C-Si-O⁻), 1.64 (d of septet, 1H, H₆, J_BC = 8.5 Hz, J = 6.5 Hz), 1.78 (d, 1H, H₄, J_I₂ = 9.5 Hz), 2.06 (overlapping d of d of d of d, 1H, H₂, J_BC = 8.5 Hz, J_CF = 5 Hz, J_CD = J_CE = 2.5 Hz), 2.20 (overlapping d of d of d of d, 1H, H₂, J_I₂ = 9.5 Hz, J_FZ = 4 Hz, J_KZ = 5 Hz, J_EZ = 1 Hz), 2.73 (overlapping d of d, 1H, H₆, J_FZ = 4 Hz, J_CF = 5 Hz), 2.92 (overlapping d of d, 1H, H₆, J_EK = 6 Hz, J_KZ = 5 Hz), 3.66 (s, 3H, -CO₂CH₃), 5.44 (unresolved d, 1H, H₄, J.DE = 9.5 Hz), 6.30 (overlapping d of d of d of d, 1H, H₄, J.DE = 9.5 Hz, J_EK = 6 Hz, J_CE = 2.5 Hz, J_EZ = 1 Hz). Irradiation at δ 5.44
(H<sub>D</sub>) caused the signal at δ 2.06 to collapse to a d of d of d (J = 8.5 Hz, J = 5 Hz, J = 2.5 Hz), the signal at δ 2.73 to sharpen, and the signal at δ 6.30 to collapse to an unresolved d of d (J = 6 Hz, J = 2.5 Hz); irradiation at δ 6.30 (H<sub>E</sub>) caused the signal at δ 2.06 to collapse to a d of d of d (J = 8.5 Hz, J = 5 Hz, J = 2.5 Hz), the signal at δ 2.92 to collapse to a d (J = 5 Hz), and the signal at δ 5.44 to collapse to an overlapping d of d (J = 2 Hz); and irradiation at δ 1.78 (H<sub>I</sub>) caused the signal at δ 2.20 to collapse to an overlapping d of d of d (J = 5 Hz, J = 4 Hz, J = 1 Hz).

Exact mass calcd. for C<sub>19</sub>H<sub>32</sub>O<sub>3</sub>Si: 336.2121; found: 336.2128.

3.3.27 Preparation of 4-endo-Isopropylbicyclo[3.2.1]oct-2-en-6-one

![Diagram of the molecule]

To a stirred solution of the silyl enol ether 241 (0.150 g, 0.446 mmol) in anhydrous THF (5 mL), under an atmosphere of argon, was added a THF solution of tetra-n-butylammonium fluoride (1.34 mmol). Reaction progress was monitored by glc (SE-54, 110°C), which indicated the absence of starting material after the reaction mixture had been stirred at room temperature for 1 h. Subsequently, the mixture was diluted with petroleum
ether-ether (1:1) and was poured into saturated aqueous sodium bicarbonate. The aqueous layer was extracted thoroughly with ether, the combined organic extracts were washed twice with brine and dried over anhydrous magnesium sulfate. Removal of solvent from the solution thus obtained yielded 0.100 g of a pale, yellow oil, which exhibited two spots by tlc analysis (petroleum ether-ether, 2:1).

A mixture of the pale yellow oil, 5% aqueous hydrochloric acid (11 mL) and THF (7 mL) was refluxed for 23 h, after which time the reaction mixture was cooled to room temperature and was poured carefully into saturated aqueous sodium bicarbonate. The aqueous layer was extracted twice with ether, the organic extracts were combined, washed twice with brine and dried (anhydrous magnesium sulfate). Concentration and subjection of the resultant pale yellow oil to flash column chromatography (18 g of 230-400 mesh silica gel in a 14x150 mm column, elution with petroleum ether-ether, 12:1) afforded the bicyclic ketone \(278\) (36.8 mg, 50%) as a clear, colourless oil. This material, consisting of a single component by glc analysis (OV-17, 80°C), exhibited ir (film): 3020, 1730, 735 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\) 0.95, 1.06 (d, d, 3H each, CH\(_3\)-CH-CH\(_3\), \(J = 7\) Hz), 1.43 (d of septet, 1H, H\(_B\), \(J_{BC} = 10\) Hz, \(J = 6.5\) Hz), 2.00 (d of d, 1H, H\(_I\), \(J_{IZ} = 11.5\) Hz, \(J_{IJ} = 3\) Hz), 2.09 (d of d of d of d, 1H, H\(_Z\), \(J_{IZ} = 11.5\) Hz, \(J = 5.5\) Hz, \(J = 4\) Hz, \(J_{EZ} = 1.5\) Hz), 2.12 (overlapping d of d of d of d, 1H, H\(_C\), \(J_{BC} = 10\) Hz, \(J_{CF} = 5\) Hz, \(J_{CD} = J_{CE} = 2.5\) Hz).
Hz), 2.22 (d of d, 1H, J, J_{XY} = 17.5 Hz, J_{IJ} = 3 Hz), 2.28
(d of d, 1H, H, J_{XY} = 17.5 Hz, J_{KX} = 5.5 Hz), 2.69-2.77 (m,
2H, H, H), 5.63 (d of d of d, 1H, H, J_{DE} = 10 Hz, J_{CD} =
2.5 Hz, J_{DK} = 1.5 Hz), 6.05 (d of d of d of d, 1H, H, J_{DE} =
10 Hz, J_{EK} = 6 Hz, J_{CE} = 2.5 Hz, J_{EZ} = 1.5 Hz). Irradiation
at δ 1.43 (H) caused the signals at δ 0.95 and δ 1.06 to
collapse to a s, and the signal at δ 2.12 to simplify; irra-
diation at δ 5.63 (H) caused the signal at δ 2.12 to
collapse to a d of d of d (J = 10 Hz, J = 5 Hz, J = 2.5 Hz),
and the signal at δ 6.05 to collapse to an unresolved d (J =
6 Hz); irradiation at δ 6.05 (H) caused the signal at δ 2.09
to collapse to a d of d of d (J = 11.5 Hz, J = 5.5 Hz, J =
4 Hz), the signal at δ 2.12 to collapse to a d of d of d (J =
10 Hz, J = 5 Hz, J = 2.5 Hz), the signal at δ 2.69-2.77 to
sharpen, and the signal at δ 5.63 to collapse to a broad s.

Exact mass calcd. for C_{11}H_{16}O: 164.1201; found:
164.1197.

3.3.28 Preparation of 6-Methyl-1-hepten-4-yn-3-ol

To a cold (−78°C), stirred solution of 3-methyl-1-butyne
(1.50 mL, 14.7 mmol) in anhydrous THF (25 mL), under an
atmosphere of argon, was added a hexane solution of n-butyl-lithium (16.1 mmol). The reaction temperature was maintained at -30°C for 1 h and then a solution of acrolein (1.08 mL, 16.1 mmol) in anhydrous THF (5 mL) was added dropwise to the resulting mixture. The reaction mixture was allowed to warm to room temperature over a period of 1 h with stirring, diluted with ether, and was poured into saturated aqueous ammonium chloride. The layers were separated and the organic phase was washed successively with saturated aqueous sodium bicarbonate, twice with brine and dried (anhydrous magnesium sulfate). Careful solvent removal on a rotary evaporator afforded a pale yellow liquid, which was distilled (air-bath temperature 65-68°C/0.1 Torr) to give the alcohol \( \text{268} \) (1.57 g, 86%) as a volatile, colourless oil. This material was >99% pure by glc analysis (OV-17, 80°C) and exhibited ir (film): 3350 (broad), 3050, 2215, 1630, 992, 930 cm\(^{-1} \); \(^1\)H nmr (80 MHz, \( \text{CDCl}_3 \)) \( \delta \) 1.18 (d, 6H, \( \text{CH}_3-\text{CH-CH}_3 \), \( J = 7 \text{ Hz} \)), 1.95 (broad s, 1H, \(-\text{OH}, \text{D}_2\text{O exchangeable}) , 2.62 (septet, 1H, \( \text{Me}_2\text{C-H}, J = 7 \text{ Hz} \)), 4.87 (broad s, 1H, \( \text{H}_C \), \( \text{w}_{1/2} = 6 \text{ Hz} \)), 5.20 (overlapping d of d of d, 1H, \( \text{H}_A \), \( J_{\text{AM}} = 10 \text{ Hz} \), \( J_{\text{AB}} = J_{\text{AC}} = 1.5 \text{ Hz} \)) , 5.43 (overlapping d of d of d, 1H, \( \text{H}_B \), \( J_{\text{BM}} = 17 \text{ Hz} \), \( J_{\text{AB}} = J_{\text{BC}} = 1.5 \text{ Hz} \)), 6.00 (d of d of d, 1H, \( \text{H}_M \), \( J_{\text{BM}} = 17 \text{ Hz} \), \( J_{\text{AM}} = 10 \text{ Hz} \), \( J_{\text{CM}} = 5 \text{ Hz} \))

Exact mass calcd. for \( \text{C}_8\text{H}_{12}\text{O} : 124.0888 \); found: 124.0881.
3.3.29 Preparation of Ethyl (E)-8-methyl-4-nonen-6-ynoate

In accordance with the procedure described by Johnson et al. and later by Parker and Kosley, the alcohol was converted into the ester. A mixture of the vinyl-carbinol (1.82 g, 14.7 mmol), propionic acid (0.066 mL, 0.881 mmol) and triethyl orthoacetate (13.4 mL, 73.3 mmol) was stirred at 130-135°C. The reaction progress was monitored by TLC (petroleum ether-ether, 3:1), which indicated the absence of starting material after 40.5 h. Subsequently, most of the triethyl orthoacetate was removed by fractional distillation at atmospheric pressure of the crude reaction mixture and the stillpot residue was subjected to flash column chromatography (125 g of 230-400 mesh silica gel in a 45x150 mm column, elution with petroleum ether-ether, 9:1). After concentration of the appropriate fractions and Kugelrohr distillation (air-bath temperature 91-104°C/0.1 Torr) of the resultant oil, the ester (1.88 g, 66%) was obtained as an odoriferous, colourless oil of >98% purity by GLC analysis (OV-17, 80°C). This material exhibited IR (film): 3000, 2190, 1730, 960 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.17 (d, 6H, CH₃-CH₂-CH₃, J = 7 Hz),
1.25 (t, 3H, CH$_3$CH$_2$O-, J = 7 Hz), 2.35-2.44 (m, 4H, O=C-CH$_2$-CH$_2$-C=), 2.64 (septet, 1H, Me$_2$C-H, J = 7 Hz), 4.12 (q, 2H, CH$_3$CH$_2$O-, J = 7 Hz), 5.49 (unresolved d, 1H, H$_B$, J$_{AB}$ = 15.5 Hz), 5.95-6.04 (m, 1H, H$_A$).

Exact mass calcd. for C$_{12}$H$_{18}$O$_2$: 194.1307; found: 194.1316.

3.3.30 Preparation of (E)-8-Methyl-4-nonen-6-ynoic acid

![Chemical Structure](image)

A mixture of potassium hydroxide (0.40 g, 7.1 mmol), the ester 269 (1.15 g, 5.94 mmol), water (0.5 mL) and methanol (20 mL) was refluxed for 3.5 h. The reaction mixture was initially checked for basicity and then was extracted with petroleum ether to remove any nonpolar impurities. The aqueous phase was stirred at 0°C and acidified by dropwise addition of a 10% aqueous solution of hydrochloric acid until the solution was strongly acidic to litmus paper. The resulting mixture was extracted thoroughly with ether and the organic extracts were combined and dried (anhydrous magnesium sulfate). Solvent removal under reduced pressure provided a viscous yellow oil, which was distilled (air-bath temperature 139-143°C/0.1 Torr) to give the acid 270 (0.770 g, 78%) as a
colourless oil. On cooling to room temperature, this oil solidified and the acid was recrystallized from heptane to afford a white solid, which consisted of one component by glc analysis (SE-54, 80°C) and exhibited m.p. 65.5-67.5°C; ir (CHCl₃): 3200-2500, 1701, 960 cm⁻¹; ¹H nmr (80 MHz, CDCl₃) δ: 1.17 (d, 6H, CH₃-CH-CH₃, J = 7 Hz), 2.32-2.52 (m, 4H, O=C-CH₂-CH₂-C=), 2.65 (septet, 1H, Me₂C-H, J = 7 Hz), 5.53 (unresolved d, 1H, H_B, J_AB = 15.5 Hz), 5.85-6.30 (m, 1H, H_A).

Exact mass calcd. for C₁₀H₁₄O₂: 166.0994; found: 166.0988.

Anal. calcd. for C₁₀H₁₄O₂: C 72.25, H 8.49; found: C 72.09, H 8.40.

3.3.31 Preparation of (E)-8-methyl-4-nonen-6-ynoyl chloride

In accordance with a procedure reported by Hudlicky et al.⁹⁸ a solution of the acid 270 (0.648 g, 3.90 mmol) and oxalyl chloride (1.02 mL, 11.7 mmol) in dry hexane (17 mL) was refluxed for 1 h. Solvent and excess oxalyl chloride were removed under reduced pressure to afford a dark yellow residue. Kugelrohr distillation (air-bath temperature 70-75°C/0.1 Torr) of this material gave a pungent-smelling,
colourless oil, which was identified as the acid chloride (0.600 g, 83\%). This material exhibited ir (film): 3000, 2190, 1790, 960 cm\(^{-1}\); \(^1\)H nmr (80 MHz, CDCl\(_3\)) \(\delta\): 1.17 (d, 6H, \(\text{CH}_3\)-CH-CH\(_3\), \(J = 7\) Hz), 2.30-3.09 (m, 5H), 5.54 (unresolved d, 1H, \(H_B\), \(J_{AB} = 16\) Hz), 5.99 (d of t, 1H, \(H_A\), \(J_{AB} = 16\) Hz, \(J = 6.5\) Hz).

Exact mass calcd. for C\(_{10}\)H\(_{13}\)O\(_{35}\)Cl: 184.0655; found: 184.0663.

3.3.32 Preparation of (E)-1-Diazo-9-methyl-5-decen-7-yn-2-one

According to a procedure reported by De Boer and Backer, a solution of diazomethane in ether was prepared from Diazald\(^R\) (N-methyl-N-nitroso-p-toluenesulfonamide), which is available from Aldrich.

To a cold (0°C), stirred solution of diazomethane (0.811 g, 19.3 mmol) in ether (30 mL) was added dropwise, via a flame-polished pipette, a solution of the acyl chloride (0.600 g, 3.25 mmol) in ether (4 mL). Gas evolution was immediately evident during addition. The resulting yellow solution was maintained at 0°C for 0.5 h and then warmed to room temperature over a period of 1 h with stirring. Excess
diazomethane was removed by bubbling argon, via a flame-polished pipette, through the solution over a period of 0.5 h. The yellow solution was dried (anhydrous magnesium sulfate) and concentrated to afford the diazo ketone 272 as a viscous yellow oil (0.600 g, 97%), which tended to decompose on standing even at 4°C and in the absence of light. Hence the crude diazo ketone was not purified but was used immediately in the next reaction. A sample of 272 exhibited ir (film): 3070, 2085, 1634, 960 cm⁻¹; ¹H nmr (80 MHz, CDCl₃) δ: 1.18 (d, 6H, CH₃-CH-CH₃, J = 7 Hz), 2.32-2.52 (m, 4H), 2.65 (septet, 1H, Me₂C-H, J = 7 Hz), 5.21 (s, 1H, N₂CH-C=O), 5.50 (unresolved d, 1H, H_B, J_AB = 16 Hz), 5.85-6.20 (m, 1H, H_A).

ms m/e: 162 (M-N₂)⁺

3.3.33 Preparation of 6-exo-(3-Methyl-1-butynyl)bicyclo-[3.1.0]hexan-2-one

Following a procedure reported by Hudlicky et al.,⁹⁸ the diazo ketone 272 was transformed into the bicyclic ketone 267. Thus, to a refluxing suspension of Cu(acac)₂·H₂O¹⁶³ (0.0637 g, 0.226 mmol) in anhydrous benzene (16 mL), under an atmosphere of argon, was added via a pressure-equalizing addition funnel a solution of the yellow diazo ketone 272 (0.618 g, 3.25 mmol)
in benzene (8 mL). After the reaction mixture was refluxed for a period of 1 h and was cooled to room temperature, the benzene was removed carefully under reduced pressure. Subjection of the residue to flash column chromatography (70 g of 230-400 mesh silica gel in a 35x150 mm column, elution with petroleum ether-ether, 5:1) afforded, after concentration of the desired fractions and Kugelrohr distillation (air-bath temperature 74-80°C/0.1 Torr) of the material thus obtained, the ketone 267 as a clear, colourless oil (0.407 g, 77%).

Glc analysis (OV-17, 80°C) showed this material to be pure and tlc analysis (petroleum ether-ether, 5:1) indicated only one spot. The ketone 267 exhibited ir (film): 3030, 1725, 1180, 882 cm$^{-1}$; $^1$H nmr (400 MHz, CDCl$_3$) δ: 1.12 (d, 6H, CH$_3$-CH-CH$_3$, J = 6.5 Hz), 1.70-1.75 (m, 1H), 1.94-2.18 (m, 5H), 2.24 (d of d, 1H, J = 10.5 Hz, J = 4.5 Hz), 2.49 (d of septet, 1H, Me$_2$C-H, J = 1.5 Hz, J = 6.5 Hz).

Exact mass calcd. for C$_{11}$H$_{14}$O: 162.1045; found: 164.1044.
3.3.34 Preparation of 6-exo-[(Z)-3-Methyl-1-butenyl]bicyclo-[3.1.0]hexan-2-one

To a prehydrogenated suspension of Lindlar's catalyst (5% Pd/CaCO₃, 10 mg) and quinoline (4 μL, 0.0309 mmol) in dry pentane (15 mL), was added a solution of the alkyne (0.200 g, 1.23 mmol) in pentane (2 mL), and the mixture was stirred at room temperature under hydrogen. Reaction progress was monitored by glc (SE-54, 120°C), which indicated the absence of starting material after 2.5 h. Removal of palladium catalyst by filtration through a short column of Celite and concentration of the eluate afforded a pale yellow oil which was shown to consist of the cis- and trans-isomers in a ratio of 95:2 respectively, by glc (SE-54, 120°C). These isomers were separated on a AgNO₃-impregnated silica gel (207,208) (20 g of 70-230 mesh impregnated with 5 g of AgNO₃ in a 17x160 mm column, elution with petroleum ether-ether, 12:1) column. After concentration of the appropriate fractions, approximately 3.5 mg of the trans-isomer and 195 mg of the cis-isomer were recovered. Kugelrohr distillation (air-bath temperature 75-80°C/0.1 Torr) of the cis-alkene furnished a colourless oil (190 mg, 94%) which exhibited one peak by glc (SE-54,
120°C) and one spot by tlc; ir (film): 3000, 1722 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.99, 1.01 (d, d, 3H each, CH₃-CH-CH₃, J = 6.5 Hz), 1.75 (d of d, 1H, Hₓ, JₓFG = 5 Hz, JₓEF = 2.5 Hz), 2.00-2.21 (m, 6H), 2.70 (d of d of septet, 1H, Hₙ, JₙEₕ = 9 Hz, JₙBD = 1 Hz), 4.65 (overlapping d of d of d, 1H, Hₓ, JₓCD = 10.5 Hz, JₓDE = 9.5 Hz, JₓBD = 1 Hz), 5.24 (overlapping d of d of d, 1H, Hₙ, JₙCD = 10.5 Hz, JₙBC = 9 Hz, JₙCE < 1 Hz).

Exact mass calcd. for C₁₁H₁₆O: 164.1201; found: 164.1203.

3.3.35 Preparation of 2-(tert-Butyldimethylsiloxy)-6-exo-[(Z)-3-methyl-1-butenyl]bicyclo[3.1.0]hex-2-ene

In accordance with general procedure A, the ketone (0.160 g, 0.975 mmol) was converted into the silyl enol ether (0.266 g, 98%, air-bath distillation temperature 110-115°C/0.1 Torr), which was shown to consist of one component by glc analysis (OV-17, 110°C), and exhibited ir (film): 3030, 1625, 1255, 960, 787 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.17, 0.18 (s, s, 3H each, CH₃-Si-CH₃), 0.94 (s, 9H, (CH₃)₂C-Si-O-), 0.99 (d, 6H, CH₃-CH-CH₃, J = 6.5 Hz), 1.28 (unresolved d, 1H, Hₓ, JₓDE = 10 Hz), 1.50-1.55 (m, 1H, Hₙ), 1.59-1.64 (m, 1H, Hₜ), 2.30 (overlapping d of d of d, 1H, Hₓ, JₓJₓ = 16.5 Hz, JₓIJ =
$J_{FJ} = 3 \text{ Hz}$), 2.52 (d of d of d, 1H, $H_Z$, $J_{JZ} = 16.5 \text{ Hz}$, $J_{GZ} = 7 \text{ Hz}$, $J_{IZ} = 2 \text{ Hz}$), 2.73 (d of d of septet, 1H, $H_B$, $J_{BC} = 9.5 \text{ Hz}$, $J = 6.5 \text{ Hz}$, $J_{BD} < 1 \text{ Hz}$), 4.31 (broad s, 1H, $H_I$, $\omega_{1/2} = 5.5 \text{ Hz}$), 4.64 (overlapping d of d, 1H, $H_D$, $J_{CD} = 10.5 \text{ Hz}$, $J_{DE} = 10 \text{ Hz}$), 5.14 (overlapping d of d, 1H, $H_C$, $J_{CD} = 10.5 \text{ Hz}$, $J_{BC} = 9.5 \text{ Hz}$). Irradiation at $\delta 2.73 (H_B)$ caused the signal at $\delta 0.99$ to collapse to a s, the signal at $\delta 4.64$ to sharpen, and the signal at $\delta 5.14$ to collapse to a d ($J = 10.5 \text{ Hz}$); irradiation at $\delta 5.14 (H_C)$ caused the signal at $\delta 1.28$ to sharpen, the signal at $\delta 2.73$ to collapse to an unresolved septet ($J = 6.5 \text{ Hz}$), and the signal at $\delta 4.64$ to collapse to a d ($J = 10 \text{ Hz}$); irradiation at $\delta 4.64 (H_D)$ caused the signal at $\delta 1.28$ to collapse to a broad s, the signal at $\delta 2.73$ to sharpen, and the signal at $\delta 5.14$ to collapse to a d ($J = 9.5 \text{ Hz}$); irradiation at $\delta 1.28 (H_E)$ caused the signal at $\delta 1.50-1.55$ to collapse to an overlapping d of d ($J = 6 \text{ Hz}$, $J = 7 \text{ Hz}$), the signal at $\delta 1.60$ to collapse to a d of d ($J = 6 \text{ Hz}$, $J = 3 \text{ Hz}$), and the signal at $\delta 4.64$ to collapse to a d ($J = 10.5 \text{ Hz}$); irradiation at $\delta 4.31 (H_I)$ caused the signal at $\delta 1.50-1.55$ to collapse to a d of d of d ($J = 7 \text{ Hz}$, $J = 6 \text{ Hz}$, $J = 3.5 \text{ Hz}$), the signal at $\delta 1.60$ to collapse to an overlapping d of d of d ($J = 6 \text{ Hz}$, $J = 3 \text{ Hz}$), the signal at $\delta 2.30$ to collapse to a d of d ($J = 16.5 \text{ Hz}$, $J = 3 \text{ Hz}$), and the signal at $\delta 2.52$ to collapse to a d of d ($J = 16.5 \text{ Hz}$, $J = 7 \text{ Hz}$); and irradiation at $\delta 2.30 (H_J)$ caused the signal at $\delta 1.50-1.55$ to sharpen, the signal at $\delta 1.60$ to collapse to a d of d ($J = 6$
Hz, \( \bar{J} = 2 \text{ Hz} \), the signal at \( \delta 2.52 \) to collapse to an unresolved d (\( J = 7 \text{ Hz} \)), and the signal at \( \delta 4.31 \) to sharpen.

Exact mass calcd. for \( C_{17}H_{30}OSi \): 278.2066; found: 278.2073.

3.3.36 Preparation of 6-(tert-Butyldimethylsiloxo)-4-exo-isopropylbicyclo[3.2.1]octa-2,6-diene

As outlined in general procedure B, a solution of silyl enol ether 274 (0.101 g, 0.363 mmol) in benzene (2.5 mL) was heated at 240°C for 4.5 h. The crude material obtained after solvent removal was distilled (air-bath temperature 89-93°C/0.1 Torr) to afford the isomerized silyl enol ether 276 (94.2 mg, 93%), which was shown to consist of one component by glc analysis (SE-54, 110°C). This material exhibited ir (film): 3050, 3010, 1620, 841, 785 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \( \delta: \)

0.13, 0.15 (s, s, 3H each, CH\(_3\)-Si-CH\(_3\)), 0.92 (s, 9H, (CH\(_3\))\(_3\)C-Si-O-), 0.96, 0.99 (d, d, 3H each, CH\(_3\)-CH-CH\(_3\), \( \bar{J} = 7 \text{ Hz} \)), 1.68 (d of septet, 1H, \( H_B \), \( \bar{J} = \bar{J}_{BC} = 7 \text{ Hz} \)), 1.75 (d, 1H, \( H_I \), \( \bar{J}_{IZ} = 9.5 \text{ Hz} \)), 1.88-1.94 (m, 1H, \( H_C \)), 1.97 (overlapping d of d of d of d, 1H, \( H_J \), \( \bar{J}_{IZ} = 9.5 \text{ Hz} \), \( \bar{J}_{FZ} = 5 \text{ Hz} \), \( \bar{J}_{KZ} = 3 \text{ Hz} \), \( \bar{J}_{EZ} = 1 \text{ Hz} \)), 2.38 (unresolved d, 1H, \( H_F \), \( \bar{J}_{FZ} = 5 \text{ Hz} \), \( \bar{J}_{KZ} = 3 \text{ Hz} \), \( \bar{J}_{EZ} = 1 \text{ Hz} \)), 2.52-2.57 (m, 1H, \( H_K \)), 5.11 (d, 1H, \( H_J \), \( \bar{J}_{JK} = 3 \text{ Hz} \),
5.33 (overlapping d of d of d, 1H, H_D, J_{DE} = 9.5 Hz, J_{CD} = 3 Hz, J_{DF} = 2 Hz), 6.21 (overlapping d of d of d of d, 1H, H_E, J_{DE} = 9.5 Hz, J_{EK} = 6 Hz, J_{CE} = 2 Hz, J_{EZ} = 1 Hz). Irradiation at δ 5.11 (H_J) caused the signal at δ 2.52-2.57 to collapse to overlapping d of d (J = 6 Hz, J = 3 Hz); irradiation at δ 2.52-2.57 (H_K) caused the signal at δ 1.97 to collapse to a d of d of d (J = 9.5 Hz, J = 5 Hz, J = 1 Hz), the signal at δ 5.11 to collapse to a s, the signal at δ 5.33 to sharpen, and the signal at δ 6.21 to collapse to an unresolved d of d (J = 9.5 Hz, J = 2 Hz); irradiation at δ 6.21 (H_E) caused the signal at δ 1.88-1.94 to collapse to a d of d (J = 7 Hz, J = 3 Hz), the signal at δ 1.97 to sharpen, the signal at δ 2.52-2.57 to collapse to an overlapping d of d (J = 3 Hz), and the signal at δ 5.33 to collapse to an unresolved d of d (J = 3 Hz, J = 2 Hz); irradiation at δ 5.33 (H_D) caused the signal at δ 1.88-1.94 to collapse to an unresolved d (J = 7 Hz), the signals at δ 2.38 and δ 2.52-2.57 to sharpen, and the signal at δ 6.21 to collapse to an unresolved d (J = 6 Hz); and irradiation at δ 2.38 (H_F) caused the signal at δ 1.88-1.94 to collapse to an overlapping d of d of d (J = 7 Hz, J = 3 Hz, J = 2 Hz), the signal at δ 1.97 to collapse to a d of d (J = 9.5 Hz, J = 3 Hz), the signal at δ 5.33 to collapse to a d of d (J = 9.5 Hz, J = 3 Hz), and the signal at δ 6.21 to sharpen.

**Exact mass** calcd. for C_{17}H_{30}OSi: 278.2066; found: 278.2067.
3.3.37 Preparation of 4-exo-Isopropylbicyclo[3.2.1]oct-2-en-6-one

A mixture of the silyl enol ether 276 (0.158 g, 0.568 mmol), 5% aqueous hydrochloric acid (14 mL) and THF (6 mL) was stirred under an atmosphere of argon for 3 h at room temperature. The resulting reaction mixture was diluted with ether and was poured into saturated aqueous sodium bicarbonate and the layers were separated. The aqueous layer was extracted thoroughly with ether, and the combined organic extracts were dried (anhydrous magnesium sulfate). After removal of solvent under reduced pressure (water aspirator), the resulting pale yellow oil was subjected to flash column chromatography (18 g of 230-400 mesh silica gel in a 14x150 mm column, elution with petroleum ether-ether, 9:1). Evaporation of solvent from the appropriate fractions and Kugelrohr distillation (air-bath temperature 98-101°C/0.1 Torr) of the resultant material gave the ketone 279 (53.0 mg, 57%) as a colourless oil. Glc analysis (SE-54, 80°C) of this material indicated the presence of a single component and tlc analysis (petroleum ether-ether, 9:1) showed a single spot. The ketone 279 exhibited ir (film): 3013, 1735, 741 cm⁻¹; $^1$H
nmr (400 MHz, CDCl₃) δ: 0.97, 0.98 (d, d, 3H each, CH₃–CH–CH₃, 
J = 6.5 Hz), 1.68 (d of septet, 1H, Hᵦ, JxBC = 8 Hz, J = 6.5 
Hz), 1.85-1.93 (m, 2H, Hᵧ, Hz), 2.06 (unresolved d, 1H, Hᵢ, 
JᴵZ = 11.5 Hz), 2.23 (d of d, 1H, Hᵧ, Jᵢᵧ = 16.5 Hz, Jₓᵧ = 5 
Hz), 2.28 (overlapping d of d of d, 1H, Hᵦ, Jᵦᵧ = 16.5 Hz, 
Jᵦᵦ = 2.5 Hz, Jᵦᵢ = 1.5 Hz), 2.59 (unresolved d, 1H, Hᵦ, Jᵦᵦ = 5.5 Hz), 2.73–2.79 (m, 1H, Hᵦ), 5.55 (d of d of d, 1H, Hᵦ, 
Jᵦᵦ = 9.5 Hz, Jᵦᵦ = 3.5 Hz, Jᵦᵦ = 1.5 Hz), 6.07 (overlapping 
d of d of d of d, 1H, Hᵦ, Jᵦᵦ = 9.5 Hz, Jᵦᵦ = 6.5 Hz, Jᵦᵦ = 2 
Hz, Jᵦᵦ = 1.5 Hz). Irradiation at δ 0.98 (isopropyl methyl 
protons) caused the signal at δ 1.68 to collapse to a d (J = 
8 Hz); irradiation at δ 1.68 (Hᵦ) caused the signal at δ 1.85– 
1.93 to simplify; irradiation at δ 6.07 (Hᵦ) caused the signals 
at δ 1.85–1.93 and δ 2.73–2.79 to sharpen, and the signal at 
δ 5.55 to collapse to a d of d (J = 3.5 Hz, J = 1.5 Hz); 
irradiation at δ 2.73–2.79 (Hᵦ) caused the signal at δ 1.85– 
1.93 to simplify, the signal at δ 2.06 to sharpen, the signal 
at δ 2.23 to collapse to a d (J = 16.5 Hz), the signal at δ 
2.28 to collapse to a d of d (J = 16.5 Hz, J = 2.5 Hz), and 
the signal at δ 6.07 to collapse to an unresolved d (J = 9.5 
Hz); irradiation at δ 5.55 (Hᵦ) caused the signal at δ 1.85– 
1.93 to simplify, and the signal at δ 6.07 to collapse to an 
unresolved d (J = 6.5 Hz); irradiation at δ 2.59 (Hᵦ) caused 
the signal at δ 1.85–1.93 to simplify, the signal at δ 2.06 
to sharpen, the signal at δ 5.55 to collapse to a d of d (J = 
9.5 Hz, J = 3.5 Hz), and the signal at δ 6.07 to sharpen; and
irradiation at 𝛿 2.06 (H₁) caused the signal at 𝛿 1.85-1.93 to simplify, and the signal at 𝛿 2.28 to sharpen.

Exact mass calcd. for C₁₁H₁₆O: 164.1201; found: 164.1205.

3.3.38 Preparation of 2-(tert-Butyldimethylsiloxy)-5-methyl-6-exo-[(E)-3-methyl-1-butenyl]bicyclo[3.1.0]hex-2-ene

Following general procedure A, the ketone 337 (42.5 mg, 0.239 mmol) was transformed into the silyl enol ether 340 (62.0 mg, 89%, air-bath distillation temperature 112-115°C/0.1 Torr). This material proved to be essentially pure by glc analysis (OV-17, 120°C) and exhibited ir (film): 3060, 3000, 1627, 1258, 960 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ:

0.16 (s, 6H, CH₃-Si-CH₃), 0.93 (s, 9H, (CH₃)₃C-Si-O⁻), 0.98, 0.99 (d, d, 3H each, CH₃-CH=CH₃, J = 7 Hz), 1.24 (s, 3H, tertiary -CH₃), 1.32 (overlapping d of d, H₄, JₕF = JₕZ = 2.5 Hz), 1.34 (d of d, H₅, JₖE = 9 Hz, JₖF = 2.5 Hz), 2.30 (d of d, H₆ or H₇, J₇Z = 16.5 Hz, J = 2.5 Hz), 2.37 (d of d of d, H₆ or H₇, J₆Z = 16.5 Hz, J = 2.5 Hz), 2.70 (m, 1H, H₈), 4.27 (broad s, 1H, H₁, w₁/₂ = 5 Hz), 4.92 (d of d of d, 1H, H₉, J₉CD = 11 Hz, J₉DE = 9 Hz, J₉BD = 1 Hz), 5.27 (d of d of d, 1H, H₀, J₈CD = 11 Hz, J₈BC = 9 Hz, J₈CE = 1 Hz). In the following decoupling experiments, the region δ 1.20-6.00 was observed:
irradiation at δ 2.70 (H_B) caused the signal at δ 4.92 to collapse to a d of d (J = 11 Hz, J = 9 Hz), and the signal at δ 5.27 to collapse to an unresolved d (J = 11 Hz); irradiation at δ 4.27 (H_I) caused the signal at δ 1.32 to sharpen, the signal at δ 2.30 to collapse to a d (J = 16.5 Hz), and the signal at δ 2.37 to collapse to a d of d (J = 16.5 Hz, J = 2.5 Hz); and irradiation at δ 4.92 (H_D) caused the signal at δ 1.34 to collapse to an unresolved d (J = 2.5 Hz), the signal at δ 2.70 to sharpen, and the signal at δ 5.27 to collapse to a d (J = 9 Hz).

Exact mass calcd. for C_{18}H_{32}OSi: 292.2222; found: 292.2219.

3.3.39 Preparation of 1-Methyl-4-exo-isopropyl-6-(tert-butyl-dimethylsiloxy)bicyclo[3.2.1]octa-2,6-diene

Following general procedure B, a solution of the silyl enol ether 340 (48.3 mg, 0.165 mmol) in benzene (3 mL) was thermolyzed at 220°C for 4.5 h. Removal of solvent and subsequent distillation (air-bath temperature 91-96°C/0.1 Torr) furnished the desired material 341 (41.6 mg, 86%), which exhibited a single peak by glc analysis (SE-54, 120°C), and ir (film): 3070, 3020, 1628, 1265, 945, 798 cm⁻¹;¹H nmr (400 MHz,
CDCl\(_3\) δ: 0.12, 0.15 (s, s, 3H each, CH\(_3\)-Si-CH\(_3\)), 0.91 (s, 9H, (CH\(_3\))\(_3\)C-SiO-), 0.96, 0.99 (d, d, 3H each, CH\(_3\)-CH-CH\(_3\), J = 7 Hz), 1.09 (s, 3H, tertiary -CH\(_3\)), 1.62-1.72 (m, 2H, H\(_I\), H\(_B\)), 1.75 (d of d of d, H\(_Z\), J\(_Z\) = 9 Hz, J\(_PZ\) = 5 Hz, J\(_EZ\) = 1 Hz), 1.83-1.88 (m, 1H, H\(_C\)), 2.46 (unresolved d, 1H, H\(_F\), J\(_FZ\) = 5 Hz), 4.87 (s, 1H, H-C=C-0-Si), 5.29 (d of d of d, H\(_D\), J\(_DE\) = 10 Hz, J\(_CD\) = 3 Hz, J\(_DF\) = 2 Hz), 5.96 (d of d of d, H\(_E\), J\(_DE\) = 10 Hz, J\(_CE\) = 2.5 Hz, J\(_EZ\) = 1 Hz). Irradiation at δ 5.29 (H\(_D\)) caused the signal at δ 1.83-1.88 to collapse to an unresolved d (J = 7 Hz), the signal at δ 2.46 to sharpen, and the signal at δ 5.96 to collapse to a broad s; and irradiation at δ 2.46 (H\(_F\)) caused the signal at δ 1.75 to collapse to a d of d (J = 9 Hz, J = 1 Hz), the signal at δ 1.83-1.88 to collapse to an overlapping d of d of d (J = 7 Hz, J = 3 Hz, J = 2.5 Hz), and the signal at δ 5.29 to collapse to a d of d (J = 10 Hz, J = 3 Hz).

**Exact mass** calcd. for C\(_{18}\)H\(_{32}\)OSi: 292.2222; found: 292.2214.

**3.3.40 Preparation of 1-Methyl-4-exo-isopropylbicyclo[3.2.1]-oct-2-en-6-one**
A mixture of the silyl enol ether 341 (0.0587 g, 0.201 mmol), 5% aqueous hydrochloric acid (2 mL) and THF (4 mL) was stirred under an atmosphere of argon at room temperature for 3 h. The resulting reaction mixture was diluted with ether and was poured into saturated aqueous sodium bicarbonate, and the layers were separated. Subsequently, the aqueous layer was extracted thoroughly with ether, the organic extracts were combined and dried (anhydrous magnesium sulfate). After removal of solvent under reduced pressure (water aspirator), the residue thus obtained was subjected to flash column chromatography (48 g of 230-400 mesh silica gel in a 26x150 mm column, elution with petroleum ether-ether, 4:1). Concentration of the desired fractions and Kugelrohr distillation (air-bath temperature 69-73°C/0.1 Torr) of the material thus obtained, afforded the ketone 343 (0.0334 g, 93%) as a clear, colourless liquid. The ketone 343, a single component by glc (SE-54, 120°C) and tlc (petroleum ether-ether, 9:1) analyses exhibited ir (film): 3025, 1735, 1635, 725 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.91, 0.92 (d, d, 3H each, CH₃CH-CH₃, J = 7 Hz), 1.19 (s, 3H, tertiary -CH₃), 1.53-1.65 (m, 1H, H_B), 1.69 (d of d, 1H, H_Z, J_IZ = 11.5 Hz, J_FZ = 5.5 Hz), 1.77-1.84 (m, 1H, H_C), 1.86 (d of d, 1H, H_T, J_IZ = 11.5 Hz, J_IJ = 3.5 Hz), 1.95 (d, 1H, H_X, J_JX = 17 Hz), 2.24 (d of d, 1H, H_J, J_JX = 17 Hz, J_IJ = 3.5 Hz), 2.60 (unresolved d, 1H, H_P, J_FZ = 5.5 Hz), 5.51 (d of d, 1H, H_D, J_DE = 9.5 Hz, J_CD = 3.5 Hz), 5.75 (d, 1H, H_E, J_DE = 9.5 Hz). In the following decoupling experiments,
the region δ 1.00-3.00 was observed: irradiation at δ 5.51 (H_D) caused the signal at δ 1.77-1.84 to collapse to an unresolved d (J = 8 Hz); and irradiation at δ 2.60 (H_P) caused the signal at δ 1.69 to collapse to a d (J = 11.5 Hz), and the signal at δ 1.77-1.84 to sharpen.

Exact mass calcd. for C_{12}H_{18}O: 178.1358; found: 178.1357.
3.4 The Total Synthesis of (+)-Sinularene

3.4.1 Preparation of 2,6-Dimethyl-1-hepten-4-yn-3-ol

To a stirred, cold (-78°C) solution of 3-methyl-1-butyne (0.375 mL, 3.67 mmol) in anhydrous THF (5 mL) was added a hexane solution of n-butyllithium (4.04 mmol), and the resulting mixture was stirred at -30°C for 1 h. Subsequently, methacrolein (0.334 mL, 4.04 mmol) was added dropwise to the yellow reaction mixture, which was then stirred efficiently at -30°C for another hour and then was poured into saturated aqueous ammonium chloride. Ether was added to the resultant mixture and the layers were separated. The aqueous phase was extracted thoroughly with ether and the combined ether extracts were washed successively with saturated aqueous ammonium chloride, saturated sodium bicarbonate, twice with brine and dried (anhydrous magnesium sulfate). Careful solvent removal under reduced pressure (water aspirator) left a volatile, yellow residue, which was distilled (air-bath temperature 67-72°C/0.1 Torr) to furnish the allylic alcohol \[\text{331}\] (0.506 g, >98%) as a clear, colourless oil. Analysis by glc (SE-54, 80°C) indicated that this material was of >98% purity.
The alcohol \[331\] exhibited ir (film): 3350 (broad), 3065, 2220 (disubstituted alkyne), 1650 \(cm^{-1}\); \(^1\)H nmr (80 MHz, \(CDCl_3\)) \(\delta\): 1.17 (d, 6H, \(CH_3-CH-CH_3\), \(J = 7\) Hz), 1.77 (broad s, 1H, -OH, \(D_2O\) exchangeable), 1.85 (broad s, 3H, \(CH_3-C=\)), 2.61 (d of septet, 1H, \(H_B\), \(J = 6.5\) Hz, \(J_{BC} = 2\) Hz), 4.77 (broad s, 1H, \(H-C-OH\)), 4.90, 5.15 (broad s, broad s, 1H each, \(H_2C=C\)).

**Exact mass calcd. for \(C_9H_{14}O\): 138.1045; found: 138.1044.**

3.4.2 Preparation of Ethyl (E)-4,8-dimethyl-4-non-6-ynoate

\[
\begin{align*}
&\text{EtO} \\
&\text{\(\rightarrow\)} \\
&\text{H}_2C=C
\end{align*}
\]

\[332\]

Following the procedure reported by Johnson et al.\(^{111c}\) and later, by Parker and Kosley,\(^{111d}\) the alcohol \[331\] was transformed into the ester \[332\] via the orthoester Claisen rearrangement. Thus, a mixture of the alcohol \[331\] (0.459 g, 3.32 mmol), triethyl orthoacetate (3.05 mL, 16.6 mmol) and propionic acid (0.0149 mL, 0.200 mmol) was stirred at 130°C for 20 h, by which time tlc analysis (petroleum ether-ether, 7:1) indicated the absence of starting material. Most of the triethyl orthoacetate was removed by fractional distillation at atmospheric pressure and the stillpot residue was subjected to flash column chromatography (125 g of 230-400 mesh silica gel in a 45x150 mm column, elution with petroleum ether-ether,
After removal of solvent from the appropriate fractions and Kugelrohr distillation (air-bath temperature 81-86°C/0.1 Torr) of the oil thus obtained, the ester 332 (0.402 g, 58%) was isolated as an odoriferous, colourless liquid, which was shown to consist of one component by glc (SE-54, 80°C) and tlc analyses. This material exhibited ir (film): 1730 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) 6: 1.19 (d, 6H, CH₃-CH-CH₃, J = 7 Hz), 1.25 (t, 3H, CH₃CH₂-O-, J = 7 Hz), 1.87 (s, 3H, CH₃-C=), 2.36-2.45 (m, 4H, O=C-CH₂-CH₂-C=), 2.70 (septet, 1H, Me₂C-H, J = 7 Hz), 4.13 (q, 2H, CH₃CH₂-O-, J = 7 Hz), 5.29 (broad s, 1H, H-C=).

Exact mass calcd. for C₁₃H₂₀O₂: 208.1463; found: 208.1453.

3.4.3 Preparation of (E)-4,8-Dimethyl-4-nonenoic acid

A mixture of the ester 332 (0.500 g, 2.40 mmol), potassium hydroxide (0.276 g, 2.88 mmol), water (1 mL) and methanol (10 mL) was refluxed for 4 h. The reaction mixture was allowed to cool to room temperature, checked for basicity to litmus paper, and extracted twice with petroleum ether to remove nonpolar impurities. The aqueous layer was filtered
through a layer of Celite and cooled to 0°C. To the cold, efficiently stirred solution, was added 10% aqueous hydrochloric acid until the solution was acidic to litmus paper. The aqueous layer was extracted thoroughly with ether and the organic extracts were combined and dried (anhydrous magnesium sulfate). Evaporation of solvent and low-temperature (-78°C) recrystallization of the residual material from hexane furnished the acid 333 (0.294 g, 68%) as a colourless oil, which gave a single peak by glc (OV-17, 100°C) and exhibited ir (film): 3300-2500, 1705 cm⁻¹; ¹H nmr (80 MHz, CDCl₃) 6: 1.22 (d, 6H, CH₃-CH-CH₃, J = 7 Hz), 1.90 (s, 3H, CH₃-C=), 2.30-3.00 (m, 5H, Me₂C-H, O=C-CH₂-CH₂-C=), 5.30 (broad s, 1H, H-C=), 10.85 (broad s, 1H, HO₂C-).

Exact mass calcd. for C₁₁H₁₆O₂: 180.1150; found: 180.1151.

3.4.4 Preparation of (E)-4,8-Dimethyl-4-nonen-6-ynoyl chloride

![Chemical Structure](image)

The procedure described by Hudlicky et al.⁹⁸ was followed to convert the acid 333 into the corresponding acyl chloride 334. Accordingly, a solution of the acid 333 (9.75 g, 54.1 mmol) and oxalyl chloride (14.2 mL, 162.4 mmol) in anhydrous hexane (235 mL) was refluxed under argon for 1 h. Removal of solvent and excess oxalyl chloride was effected under reduced
pressure (water aspirator). The brown, oily stillpot residue
was distilled (air-bath temperature 94-99°C/0.1 Torr) to
afford 10.3 g (>98%) of a pale yellow liquid. This material,
which was identified as the acyl chloride 334, exhibited ir
(film): 2200 (disubstituted alkyne), 1790, 1623 cm⁻¹; ¹H nmr
(80 MHz, CDCl₃) δ 1.20 (d, 6H, CH₃-CH-CH₃, J = 7 Hz), 1.88 (s,
3H, CH₃-C=), 2.32-3.13 (m, 5H, Me₂C-H, O=CH₂-CH₂-C=), 5.31
(broad s, 1H, H-C=).

Exact mass calcd. for C₁₁H₁₅O³⁷Cl: 200.0782; found:
200.0783.

3.4.5 Preparation of (E)-1-Diazo-5,9-dimethyl-5-decen-7-yn-2-one

\[
\begin{align*}
\text{N}_2\text{CH} \\
\text{O} \\
\text{CH} = \text{C} \\
\end{align*}
\]

335

An ethereal solution of diazomethane was prepared as
described by De Boer and Backer. 206

To a cold (0°C), stirred solution of diazomethane (0.24
g, 5.67 mmol) in ether (15 mL) was added dropwise, via a
flame-polished pipette, a solution of the acyl chloride 334
(0.250 g, 1.26 mmol) in ether (3 mL). Evolution of nitrogen
gas was apparent almost immediately. The resulting mixture
was stirred at 0°C for 0.5 h, and at room temperature for 1
The residual diazomethane was dispelled by bubbling argon through the yellow solution via a flame-polished pipette for 0.5 h. Drying (anhydrous magnesium sulfate) and concentration of the yellow ethereal solution yielded the diazo ketone 335 (0.250 g, >97%) as a viscous yellow syrup. The crude diazo ketone was not purified but was used immediately in the next reaction. A sample of this material exhibited ir (film): 3070, 2200, 2085, 1633 cm\(^{-1}\); \(^1\)H nmr (80 MHz, CDC\(_3\)) \(\delta\): 1.18 (d, 6H, CH\(_3\)-CH-CH\(_3\), \(J = 7\) Hz), 1.88 (s, 3H, CH\(_3\)-C=), 2.40 (s, 4H, O=C-CH\(_2\)-CH\(_2\)-C=), 2.70 (septet, 1H, Me\(_2\)C-H, \(J = 7\) Hz), 5.21 (s, 1H, N=N=C-H), 5.28 (broad s, 1H, H-C=).

\[
\text{ms m/e: 204 (M\(^+\)), 176 (M-N}_2\)\(^+\)}
\]

3.4.6 Preparation of 5-Methyl-6-exo-(3-methyl-1-butynyl)-bicyclo[3.1.0]hexan-2-one

In accordance with a procedure described by Hudlicky et al., \(^98\) the diazo ketone 335 was converted into the bicyclic ketone 336. To a stirred suspension of Cu(acac)\(_2\)\(\cdot\)H\(_2\)O\(^{163}\) (0.022 g, 0.084 mmol) in refluxing anhydrous benzene (6 mL), under an atmosphere of argon, was added dropwise, via an addition funnel, a solution of the diazo ketone 335 (0.228 g, 1.12 mmol)
in anhydrous benzene (3 mL). When the addition was complete, the resulting dark brown mixture was refluxed for an hour and then was cooled to room temperature. Most of the benzene was carefully removed under reduced pressure (water aspirator) and the residue was subjected to flash column chromatography (70 g of 230-400 mesh silica gel in a 35x150 mm column, elution with petroleum ether-ether, 3:1). The desired fractions were concentrated to give a yellow oil, which was distilled (air-bath temperature 85-88°C/0.1 Torr) to afford 0.16 g (81%) of a clear, colourless oil. This material, shown to be the desired ketone \(336\), consisted of a single component by glc (SE-54, 120°C) and tlc (petroleum ether-ether, 3:1) analyses, and exhibited ir (film): 1725, 1172 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 1.14 (d, 6H, CH\(_3\)-CH-CH\(_3\), \(J = 7\) Hz), 1.44 (s, 3H, tertiary -CH\(_3\)), 1.69 (d, 1H, \(H_E\), \(J_{EF} = 3\) Hz), 1.87 (overlapping d of d, 1H, \(H_E\), \(J_{EF} = 3\) Hz, \(J_{BE} = 1.7\) Hz), 1.94-2.14 (m, 4H, O=C-CH\(_2\)-CH\(_2\)-), 2.53 (d of septet, 1H, \(H_B\), \(J = 7\) Hz, \(J_{BE} = 1.7\) Hz). Irradiation at \(\delta 1.87 (H_E)\) caused the signal at \(\delta 1.69\) to collapse to a s, and the signal at \(\delta 2.53\) to collapse to a septet (\(J = 7\) Hz).

**Exact mass** calcd. for \(C_{12}H_{16}O\): 176.1201; found: 176.1196.

**Anal. calcd.** for \(C_{12}H_{16}O\): C 81.76, H 9.16; found: C 81.69, H 9.20.
3.4.7 Preparation of 5-Methyl-6-exo-[(Z)-3-methyl-1-butenyl]-bicyclo[3.1.0]hexan-2-one

A suspension of 5% palladium supported on calcium carbonate (0.0487 g, prepared with lead acetate as described by Lindlar and Dubois)\(^{169}\) in anhydrous pentane (7 mL) was pre-hydrogenated. To the resulting mixture was added dropwise, via a syringe, a solution of the alkyne 336 (0.973 g, 5.53 mmol) in pentane (3 mL), and the reaction mixture was stirred efficiently under hydrogen. The progress of the reaction was easily monitored by glc (SE-54, 120°C) and after 3 h, all but a trace of starting material had been consumed. Filtration of the reaction mixture through a layer of Celite\(^R\) and concentration of the filtrate yielded a colourless oil, which was subjected to flash column chromatography (125 g of 230-400 mesh silica gel in a 45x150 mm column, elution with petroleum ether-ether, 5:1). After concentration of the appropriate fractions, Kugelrohr distillation (air-bath temperature 78-80°C/0.1 Torr) of the resultant oil furnished the alkene 337 (0.900 g, 91%) as a clear, colourless oil. Glc analysis (SE-54, 120°C) of this material revealed the presence of only one component and tlc analysis (petroleum ether-ether, 5:1) showed
a single spot. The alkene \textit{exhibited ir (film)}: 3001, 1719, 1650 cm\textsuperscript{-1}; \textit{H nmr (400 MHz, CDC\textsubscript{13})} \(\delta\): 0.98, 1.00 (d, d, 3H each, \textit{CH\textsubscript{3}}-\textit{CH}-\textit{CH\textsubscript{3}}, \(J = 7\) Hz), 1.32 (s, 3H, tertiary \textit{-CH\textsubscript{3}}), 1.57 (unresolved d, 1H, \textit{H\textsubscript{F}}, \(J = 2\) Hz), 1.90-2.25 (m, 5H, \textit{O=C-CH\textsubscript{2}-CH\textsubscript{2}-, H\textsubscript{E}}), 2.60-2.73 (m, 1H, \textit{H\textsubscript{B}}), 4.91 (overlapping d of d, 1H, \textit{H\textsubscript{D}}, \(J\textsubscript{CD} = 11.5\) Hz, \(J\textsubscript{DE} = 10\) Hz), 5.36 (overlapping d of d, 1H, \textit{H\textsubscript{C}}, \(J\textsubscript{CD} = 11.5\) Hz, \(J\textsubscript{BC} = 10\) Hz).

Exact mass calcd. for \(\text{C}_{12}\text{H}_{18}O\): 178.1358; found: 178.1357.

3.4.8 Preparation of 5-Methyl-6-\textit{exo-}[\(Z\)-3-methyl-1-butenyl]-bicyclo[3.1.0]hex-3-en-2-one

![Chemical structure](image)

\textbf{a) Via palladium (II) mediated oxidation\textsuperscript{116} of the trimethylsilyl enol ether 345}

According to the procedure outlined by Seitz and Ferreria\textsuperscript{209} trimethylsilyl iodide was prepared in the following manner. A mixture of iodine (3.55 g, 14.0 mmol) and hexamethyldisilane (2.87 mL, 14.0 mmol) was warmed under argon for 0.5 h at 50°C. The trimethylsilyl iodide was cooled to room temperature, taken up in a syringe, and added dropwise to a cold (\(-78^\circ\)C), stirred solution of the ketone 337 (0.713 g, 4.00 mmol) and triethylamine (4.46 mL, 32.0 mmol) in anhydrous dichloromethane (40 mL). The resulting dark orange suspension was
stirred at -78°C. After 0.5 h, glc analysis (SE-54, 120°C) indicated that all of the starting material had been consumed. The reaction mixture was diluted with ether and poured into a 1:1 mixture of 5% aqueous sodium thiosulfate and saturated aqueous sodium bicarbonate. The layers were separated, and the organic layer was dried over magnesium sulfate and concentrated. The residual material, which was shown by glc analysis to consist of a 12:1 mixture of the silyl enol ether and the starting material, was oxidized immediately in the next reaction.

The crude enol ether was taken up in acetonitrile (3 mL) and the solution was added dropwise, via a syringe, to a stirred suspension of palladium (II) acetate (1.80 g, 8.00 mmol) in anhydrous acetonitrile (3 mL). The initially orange suspension became black immediately on addition of the enol ether solution. Stirring of the resulting mixture was continued for 1 h. The reaction mixture was filtered, washed twice with saturated aqueous sodium bicarbonate, dried (anhydrous magnesium sulfate) and concentrated to give a dark brown oil. Subjection of the residue to flash column chromatography (70 g of 230-400 mesh silica gel in a 45x150 mm column, elution with petroleum ether-ether, 7:1) and concentration of the appropriate fractions afforded 0.554 g of a clear, colourless oil. According to glc analysis (SE-54, 120°C), this material was a 5:1 mixture of the enone and the ketone, respectively. The retention time of the major component was identical
with that of the enone 338 prepared via selenoxide elimination. Attempts to resolve the mixture of 338 and 337 by glc or tlc were not successful. Consequently, the mixture was used in the next reaction.

b) Via selenoxide elimination

To a cold (-78°C), stirred solution of lithium diiso-propylamide (2.30 mmol) in anhydrous THF (15 mL), under an atmosphere of argon, was added dropwise a solution of the ketone 337 (0.273 g, 1.53 mmol) in THF (3 mL), and the resulting mixture was stirred at -78°C for 0.5 h. A solution of phenylselenenyl chloride (0.440 g, 2.30 mmol) in THF (4 mL) was added dropwise and the reaction mixture was stirred at 0°C for 0.5 h. Subsequently, acetic acid (0.175 mL, 3.06 mmol) and a solution of 30% aqueous hydrogen peroxide (0.868 g) diluted with water (2 mL) were added, the latter dropwise. The reaction mixture was maintained at 0°C with efficient stirring for another 0.5 h, diluted with petroleum ether-ether (1:1) and poured into saturated aqueous sodium bicarbonate. The layers were separated and the aqueous phase was extracted thoroughly with ether. The combined organic extracts were washed twice with brine, dried (anhydrous magnesium sulfate) and concentrated. Subjection of the resulting residue to flash column chromatography (70 g of 230-400 mesh silica gel in a 33x150 mm column, elution with petroleum ether-ether, 7:1), concentration of the desired fractions, and Kugelrohr distillation (air-bath temperature 76-80°C/0.1 Torr) furnished the
enone \(338\) (0.136 g, 50%). Analysis by tlc (petroleum ether-ether, 7:1) indicated that this material consisted of only one component. The enone \(338\) exhibited ir (film): 3025, 3000, 1690, 1460, 1175, 767 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\) 0.97, 0.98 (d, d, 3H each, CH\(_3\)-CH-CH\(_3\), \(J = 7\) Hz), 1.45 (s, 3H, tertiary -CH\(_3\)), 1.99 (unresolved d, lH, H\(_F\), \(J\)\(_{EF}\) = 3 Hz), 2.36 (d of d, lH, H\(_E\), \(J\)\(_{DE}\) = 9.5 Hz, \(J\)\(_{EF}\) = 3 Hz), 2.60-2.73 (m, 1H, H\(_B\)), 4.91 (overlapping d of d of d, lH, H\(_D\), \(J\)\(_{CD}\) = 12 Hz, \(J\)\(_{DE}\) = 9.5 Hz, \(J\)\(_{BD}\) = 1 Hz), 5.40 (overlapping d of d of d, lH, H\(_C\), \(J\)\(_{CD}\) = 12 Hz, \(J\)\(_{BC}\) = 9 Hz, \(J\)\(_{CE}\) < 1 Hz), 5.66 (d of d, lH, H\(_J\), \(J\)\(_{IJ}\) = 5.5 Hz, \(J\)\(_{FJ}\) = 1 Hz), 7.52 (d of d, lH, H\(_I\), \(J\)\(_{IJ}\) = 5.5 Hz, \(J\)\(_{FI}\) = 1 Hz). Irradiation at \(\delta\) 4.91 (H\(_D\)) caused the signal at \(\delta\) 2.36 to simplify, the signal at \(\delta\) 2.60-2.73 to sharpen, and the signal at \(\delta\) 5.40 to collapse to a d (\(J = 9\) Hz); irradiation at \(\delta\) 7.52 (H\(_I\)) caused the signal at \(\delta\) 1.99 to collapse to a d of d (\(J = 3\) Hz, \(J = 1\) Hz), and the signal at \(\delta\) 5.66 to collapse to a d (\(J = 1\) Hz).

Exact mass calcd. for C\(_{12}\)H\(_{16}\)O: 176.1201; found: 176.1203.

3.4.9 Preparation of 5-Methyl-6-exo-[(Z)-3-methyl-1-butenyl]-4-exo-vinylbicyclo[3.1.0]hexan-2-one
a) Via copper-catalyzed Grignard reaction with the enone 338

As previously reported by Miginiac,109,110 vinyl magnesium bromide was prepared in the following manner. To a flame-dried three-necked flask fitted with a dry-ice condenser and argon gas inlet adaptor, was added magnesium turnings (0.0203 g, 0.835 mmol), anhydrous THF (3 mL) and a few crystals of iodine. A solution of vinyl bromide (0.060 mL, 0.835 mmol) in THF (1 mL) was added dropwise via a syringe until the reaction had initiated and thereafter, at a rate to maintain mild reflux. After the addition was complete, the mixture was refluxed for 0.3 h to give a clear, yellow solution, half of which was transferred via a syringe to another flask and cooled to -30°C.

To the cold (-30°C), efficiently stirred THF solution of vinyl magnesium bromide, was added copper (I) bromide-dimethyl sulfide complex134-136 (14.3 mg, 0.0696 mmol) and the mixture was stirred at -30°C for 10 min, affording a green suspension. A solution of the enone 338 (0.0490 g, 0.278 mmol) in THF (3 mL) was introduced dropwise to the reaction mixture over a period of 10 min, after which time, a brownish-green mixture was obtained. The resulting mixture was allowed to warm to 0°C over a period of 40 min, diluted with ether and poured into saturated aqueous ammonium chloride. The layers were separated and the aqueous layer was extracted thoroughly with ether. After the combined organic layers were washed successively
with saturated aqueous sodium bicarbonate and twice with brine, dried (anhydrous magnesium sulfate) and concentrated, 36 mg of a pale yellow oil was obtained. This material displayed two spots by tlc (petroleum ether-ether, 7:1) and was shown by glc analysis (SE-54, 120°C) to consist of a 9:4 mixture of the desired ketone 339 and the epimer 346.

b) Via conjugate addition of lithium divinylcuprate\textsuperscript{134} to the enone 338

Tetravinyltin was prepared from tin (IV) chloride and vinyl magnesium bromide as outlined by Seyferth et al.\textsuperscript{181,182} To a stirred solution of tetravinyltin (0.258 g, 1.14 mmol) in anhydrous ether (5 mL), under an atmosphere of argon, was added dropwise a solution of phenyllithium (4.54 mmol) in a mixture of cyclohexane and ethyl ether. A white precipitate formed almost immediately and the resulting reaction mixture was stirred for 0.5 h. The stirring was stopped and the white precipitate was allowed to settle to the bottom of the flask. Via a syringe, the pale yellow supernatant was transferred to another flask and cooled to -63°C with efficient stirring. Cuprous bromide-dimethyl sulfide complex\textsuperscript{134-136} (0.467 g, 2.27 mmol) was added and the resulting mixture was stirred at -63°C for 0.3 h to furnish a dark grey suspension. Subsequently, 0.200 g of a 85:15 (glc analysis: SE-54, 120°C) mixture of the enone 338 and the ketone 337, respectively, was dissolved in ether (3 mL) and this solution was added dropwise via a syringe to the cuprate mixture. During addition of the substrate, the
reaction mixture became dark purple. The resulting mixture was stirred efficiently at -30°C for 0.25 h and then at room temperature for 1 h. Saturated aqueous basic (pH 8) ammonium chloride (6 mL) and ether (5 mL) were added and the resulting mixture was stirred vigorously until the aqueous layer became deep blue. The layers were separated and the aqueous phase was extracted twice with ether. The ethereal layers were combined, washed successively with saturated aqueous pH 8 ammonium chloride and brine, and dried over magnesium sulfate. Solvent removal yielded a pale yellow oil which was subjected to column chromatography (50 g of 70-230 mesh silica gel in a 19x384 mm column, elution with petroleum ether-ether, 5:1). Concentration of the appropriate fractions afforded the desired product 339 (0.136 g, 69%, air-bath distillation temperature 93-97°C/0.1 Torr), the epimer 346 (0.015 g, 8%, air-bath distillation temperature 91-95°C/0.1 Torr) and the ketone 337 (0.0116 g). The ketone 339 exhibited IR (film): 3070, 3000, 1722, 1635, 920 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 1.00, 1.01 (d, d, 3H, CH₃-CH-CH₃, J = 6.5 Hz), 1.20 (s, 3H, tertiary -CH₃), 1.63 (broad s, 1H, Hₚ, w. ∆ν = 5.5 Hz), 1.89 (d, 1H, H_z, ∆ν = 18.5 Hz), 2.15 (d of d of d, 1H, H_p, J_de = 8.5 Hz, J_ef = 3 Hz, J_ce = 1 Hz), 2.55 (d of d, 1H, H_i, J_iz = 18.5 Hz, J_ij = 8 Hz), 2.67 (d of d of septet, 1H, H_d, J_bc = 9.5 Hz, J = 6.5 Hz, J_bd < 1 Hz), 2.91 (overlapping d of d, 1H, H_j, J_jk = 10 Hz, J_ij = 8 Hz), 4.91 (overlapping d of d of d, 1H, H_d, J_cd = 10.5 Hz, J_de = 8.5 Hz, J_bd < 1 Hz), 5.04-5.12 (m, 2H, H_M, H_N),
5.39 (overlapping d of d of d, 1H, H_C, J_CD = 10.5 Hz, J_BC = 9.5 Hz, J_CE = 1 Hz), 5.72 (overlapping d of d of d, 1H, H_K, J_KN = 17 Hz, J_KM = 10 Hz, J_JK = 10 Hz). Irradiation at δ 2.15 (H_E) caused a nuclear Overhauser enhancement (n.O.e.) at δ 2.55, δ 2.67 and δ 2.91; irradiation at δ 5.39 (H_C) caused the signal at δ 2.15 to collapse to a d of d (J = 8.5 Hz, J = 3 Hz), the signal at δ 2.67 to collapse to an unresolved septet (J = 6.5 Hz), and the signal at δ 4.91 to collapse to an unresolved d (J = 8.5 Hz); irradiation at δ 4.91 (H_D) caused the signal at δ 2.15 to collapse to an overlapping d of d (J = 3 Hz, J = 1 Hz), the signal at δ 2.67 to collapse to a d of septet (J = 9.5 Hz, J = 6.5 Hz), and the signal at δ 5.39 to collapse to an unresolved d (J = 9.5 Hz); irradiation at δ 2.15 (H_E) caused the signal at δ 1.63 to sharpen, the signal at δ 4.91 to collapse to an unresolved d (J = 10.5 Hz), and the signal at δ 5.39 to collapse to a d of d (J = 10.5 Hz, J = 9.5 Hz); and irradiation at δ 2.91 (H_J) caused the signal at δ 2.55 to collapse to a d (J = 18.5 Hz), the signal at δ 5.04-5.12 to collapse to an overlapping pair of d of d (J = 17 Hz, J = 10 Hz, J = 1.5 Hz), and the signal at δ 5.72 to collapse to a d of d (J = 17 Hz, J = 10 Hz).

Exact mass calcd. for C_{14}H_{20}O: 204.1514; found: 204.1517.

The epimer 346 exhibited {^1}H nmr (400 MHz, CDCl_3) δ: 1.00 (d, 6H, CH_3-CH-CH_3, J = 6.5 Hz), 1.31 (s, 3H, tertiary -CH_3), 1.63 (broad s, 1H, H_F, w_1/2 = 5.5 Hz), 2.08 (d of d, 1H, H_I,
$J_{IZ} = 18 \text{ Hz}, \ J_{IJ} = 9.5 \text{ Hz}$, 2.20-2.29 (m, 2H, $H_E$, $H_Z$), 2.68 (d of d of septet, 1H, $H_B$, $J_{BC} = 9.5 \text{ Hz}, \ J = 6.5 \text{ Hz}, \ J_{BD} < 1 \text{ Hz}$), 2.91 (overlapping d of d of d, 1H, $H_J$, $J_{IJ} = 9.5 \text{ Hz}, \ J_{JZ} = 9 \text{ Hz}, \ J_{JK} = 7 \text{ Hz}$), 4.89 (overlapping d of d of d, 1H, $H_D$, $J_{CD} = 10.5 \text{ Hz}, \ J_{DE} = 9 \text{ Hz}, \ J_{BD} < 1 \text{ Hz}$), 5.10-5.17 (m, 2H, $H_M$, $H_N$), 5.38 (overlapping d of d of d, 1H, $H_C$, $J_{CD} = 10.5 \text{ Hz}$, $J_{BC} = 9.5 \text{ Hz}, \ J_{CE} = 1 \text{ Hz}$), 5.83 (d of d of d, 1H, $H_K$, $J_{KN} = 17.5 \text{ Hz}, \ J_{KM} = 10 \text{ Hz}, \ J_{JK} = 7 \text{ Hz}$). Irradiation at $\delta$ 4.89 ($H_D$) caused the signal at $\delta$ 2.20-2.29 to simplify, the signal at $\delta$ 2.68 to collapse to a d of d ($J = 9.5 \text{ Hz}, \ J = 6.5 \text{ Hz}$), and the signal at $\delta$ 5.38 to collapse to an unresolved d ($J = 9.5 \text{ Hz}$); irradiation at $\delta$ 1.63 ($H_F$) caused the signal at $\delta$ 2.20-2.29 to collapse to a pair of d ($J = 18 \text{ Hz}, \ J = 9 \text{ Hz}$); irradiation at $\delta$ 2.91 ($H_J$) caused the signal at $\delta$ 2.08 to collapse to a d ($J = 18 \text{ Hz}$), the signal at $\delta$ 2.20-2.29 to simplify, the signal at $\delta$ 5.10-5.17 to collapse to a pair of d ($J = 17.5 \text{ Hz}, \ J = 10 \text{ Hz}, \ J = 1.5 \text{ Hz}$), and the signal at $\delta$ 5.83 to collapse to a d of d ($J = 17.5 \text{ Hz}, \ J = 10 \text{ Hz}$); and irradiation at $\delta$ 5.10-5.17 ($H_M$, $H_N$) caused the signal at $\delta$ 2.91 to sharpen, and the signal at $\delta$ 5.83 to collapse to a d ($J = 7 \text{ Hz}$).

ms m/e: 204 ($M^+$), 189, 162 (100%)
3.4.10 Preparation of 2-(tert-Butyldimethylsiloxy)-5-methyl-6-exo-[(Z)-3-methyl-1-buteny]-4-exo-vinylbicyclo[3.1.0]hex-2-ene

In accordance with general procedure A, the ketone (0.623 g, 3.05 mmol) was converted smoothly into the silyl enol ether (0.933 g, 96%, air-bath distillation temperature 118-123°C/0.1 Torr). This material was essentially pure by glc analysis (SE-54, 120°C) and exhibited ir (film): 3055, 1635, 1620, 960, 920, 790 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ:

0.17 (s, 6H, CH₃-Si-CH₃), 0.94 (s, 9H, (CH₃)₃C-Si-O⁻), 0.99 (d, 6H, CH₃-CH-CH₃), J = 7 Hz), 1.13 (s, 3H, tertiary -CH₃), 1.34 (overlapping d of d, 1H, Hᵢ, Jₑᵢ = 2.5 Hz, Jᶠᵢ = 1 Hz), 1.40 (unresolved d of d, 1H, Hₑ, Jᵈₑ = 9 Hz, Jₑᵢ = 2.5 Hz), 2.71 (d of d of septet, 1H, Hᵣ, Jᵇᵣ = 9 Hz, J = 7 Hz, Jᵢᵣ = 1 Hz), 3.10 (unresolved d, 1H, Hᵣ, Jᵢᵣ = 9 Hz), 4.20 (d of d, 1H, Hᵢ, Jᵢᵣ = 2.5 Hz, Jᵣᵢ = 1 Hz), 4.92 (overlapping d of d of d, 1H, Hᵣ, Jᵣᵣ = 11 Hz, Jᵣᵢ = 9 Hz, Jᵢᵢ = 1 Hz), 4.98 (d of d, 1H, Hᵢ, Jᵢᵢ = 10 Hz, Jᵣᵢ = 2 Hz), 5.04 (d of d of d, 1H, Hᵢ, Jᵢᵢ = 17 Hz, Jᵢᵢ = 2 Hz, Jᵢᵣ = 1 Hz), 5.29 (overlapping d of d of d, 1H, Hᵢ, Jᵢᵢ = 11 Hz, Jᵣᵢ = 9 Hz, Jᵢᵣ = 1 Hz), 5.74 (d of d of d, 1H, Hᵢ, Jᵢᵢ = 17 Hz, Jᵢᵢ = 10 Hz, Jᵣᵢ = 9 Hz).
3.4.11 Preparation of 6-(tert-Butyldimethylsiloxy)-1-methyl-4-exo-isopropyl-8-exo-vinylbicyclo[3.2.1]octa-2,6-diene

Following general procedure B, a solution of the silyl enol ether 322 (0.170 g, 0.534 mmol) in benzene (3 mL) was thermolyzed at 220°C for 4.5 h to afford, after purification of the crude product by column chromatography (70-230 mesh neutral alumina pretreated with triethylamine, elution with petroleum ether) and Kugelrohr distillation (air-bath temperature 88-95°C/0.1 Torr) the enol ether 321 (0.146 g, 86%). This material was >99% pure by glc (SE-54, 120°C) and exhibited ir (film): 3050, 2990, 1630, 1620, 1460, 940, 915, 784 cm⁻¹; 

1H nmr (400 MHz, CDCl₃) δ: 0.13, 0.15 (s, s, 3H each, CH₃-Si-CH₃), 0.92 (s, 9H, (CH₃)₃C-Si-O⁻), 0.95 (s, 3H, tertiary -CH₃), 0.97, 1.00 (d, d, 3H each, CH₃-CH-CH₃, J = 7 Hz), 1.67-1.79 (m, 1H, H_B), 1.92-1.97 (m, 1H, H_C), 2.26 (broad s, 1H, H_F, w₁/₂ = 4 Hz), 2.46 (d, 1H, H_I, J IK = 9 Hz), 4.74 (s, 1H, H-C=CH-O-Si), 5.01 (d of d, 1H, H_M, J KM = 10 Hz, J MN = 2.5 Hz), 5.08 (d of d of d, 1H, H_N, J KN = 17 Hz, J MN = 2.5 Hz, J IN < 1 Hz), 5.35 (d of d of d, 1H, H_D, J DE = 9.5 Hz, J CD = 3 Hz, J DF
= 2 Hz), 5.96 (d of d of d, 1H, H_K, J_{KN} = 17 Hz, J_{KM} = 10 Hz, J_{IK} = 9 Hz), 6.00 (d of d, 1H, H_E, J_{DE} = 9.5 Hz, J_{CE} = 2 Hz). Irradiation at δ 5.35 (H_D) caused the signal at δ 1.97 to collapse to an unresolved d (J = 7 Hz), the signal at δ 2.26 to sharpen, and the signal at δ 6.00 to collapse to a d (J = 2 Hz); irradiation at δ 1.92-1.97 (H_C) caused the signal at δ 1.67-1.79 to collapse to a septet (J = 7 Hz), the signal at δ 2.26 to sharpen, the signal at δ 5.35 to collapse to a d of d (J = 9.5 Hz, J = 2 Hz), and the signal at δ 6.00 to collapse to a d (J = 9.5 Hz); and irradiation at δ 2.26 (H_F) caused the signal at δ 1.92-1.97 to collapse to an overlapping d of d of d (J = 7 Hz, J = 3 Hz, J = 2 Hz), and the signal at δ 5.35 to collapse to a d of d (J = 9.5 Hz, J = 3 Hz).

Exact mass calcd. for C_{20}H_{34}OSi: 318.2379; found: 318.2365.

3.4.12 Preparation of 6-(tert-Butyldimethylsiloxy)-8-exo-(2-hydroxyethyl)-4-exo-Isopropyl-1-methylbicyclo[3.2.1]-octa-2,6-diene

Disiamylborane was generated in situ according to Brown's procedure^{186,187} in the following manner. To a cold (0°C), stirred solution of borane-dimethyl sulfide complex (0.346
mmol) in THF (2 mL), under argon, was added 2-methyl-2-butene (0.110 mL, 1.04 mmol) dropwise via a syringe. Stirring of the mixture was maintained for 2 h at 0°C.

A solution of the alkene 321 (0.050 g, 0.157 mmol) in THF (2 mL) was introduced dropwise to the cold (0°C) disiamylborane solution. The resulting mixture was allowed to warm to room temperature over a period of 1.5 h, by which time glc analysis (SE-54, 120°C) indicated the absence of starting material. A solution of sodium hydroxide (0.0138 g, 0.346 mmol) in water (1 mL) and a 30% aqueous solution of hydrogen peroxide (0.106 mL, 1.04 mmol) were added to the recooled (0°C) reaction mixture. This stirred mixture was allowed to warm to room temperature over a period of 1 h. The reaction mixture was diluted with a 1:1 mixture of petroleum ether and ether, and poured into saturated aqueous ammonium chloride. After the layers had been separated, the aqueous layer was extracted thoroughly with ether, and the organic extracts were combined, washed with brine and dried (anhydrous magnesium sulfate). Solvent removal under reduced pressure (water aspirator) gave a light yellow oil, which was subjected to column chromatography (18 g of 80-200 mesh neutral alumina in a 10x225 mm column). Elution of the column with petroleum ether (30 mL), petroleum ether-ether (5:1, 30 mL), and ether (30 mL), followed by concentration of the appropriate fractions, afforded the alcohol 347 (0.045 g, 86%) as an odoriferous, colourless oil, shown by glc (SE-54, 120°C) and tlc (petroleum
ether-ether, 5:1) analyses to consist of a single component. This material exhibited ir (film): 3300 (broad), 3000, 1622 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.11, 0.13 (s, s, 3H each, CH₃-Si-CH₃), 0.90 (s, 9H, (CH₃)₃C-Si-O⁻), 0.95, 0.97 (d, d, 3H, CH₃-CH-CH₃, J = 6.5 Hz), 0.99 (s, 3H, tertiary -CH₃), 1.49-1.70 (m, 3H, H_B, H_K or H_Z, -OH), 1.73-1.82 (m, 1H, H_K or H_Z), 1.85-1.91 (m, 1H, H_C), 1.94 (d of d, 1H, H_I, J_IK = 10 Hz, J_IZ = 3.5 Hz), 2.28 (broad s, 1H, H_F, w₁/₂ = 4.5 Hz), 3.63-3.79 (m, 2H, HO-CH₂⁻), 4.69 (s, 1H, H-C=C-O-Si), 5.30 (d of d of d, 1H, H_D, J_DE = 9.5 Hz, J_CD = 3 Hz, J_DF = 2 Hz), 5.98 (d of d, 1H, H_F, J_DE = 9.5 Hz, J_CE = 2 Hz). Irradiation at δ 5.30 (H_D) caused the signal at δ 1.85-1.91 to collapse to an unresolved d (J = 7 Hz), the signal at δ 2.28 to sharpen, and the signal at δ 5.98 to collapse to an unresolved s; irradiation at δ 2.28 (H_F) caused the signal at δ 1.85-1.91 to collapse to an overlapping d of d of d (J = 7 Hz, J = 3 Hz, J = 2 Hz), and the signal at δ 5.30 to collapse to a d of d (J = 9.5 Hz, J = 3 Hz); and irradiation at δ 3.63-3.79 (HO-CH₂⁻) caused the signals at δ 1.49-1.70 and δ 1.73-1.82 to simplify.

Exact mass calcd. for C₂₀H₃₆O₂Si: 336.2485; found: 336.2486.
3.4.12 Preparation of 10-exo-Isopropyl-7-methyltricyclo-
[4.4.0.0^3,7]dec-8-en-2-one

A solution of p-toluenesulfonyl chloride (0.184 g, 0.964 mmol) in anhydrous dichloromethane (2 mL) was added dropwise to a cold (0°C), stirred solution of 4-dimethylaminopyridine (0.236 g, 1.93 mmol) in dichloromethane (5 mL), and the resulting mixture was stirred at room temperature for 20-30 min. To this solution was added dropwise a solution of the alcohol (0.216 g, 0.643 mmol) in dichloromethane (3 mL). After the reaction mixture had been stirred for 1.3 h at room temperature, glc analysis (SE-54, 120°C) indicated the absence of starting material and the appearance of a new component. The reaction mixture was diluted with ether and poured into a saturated aqueous solution of sodium bicarbonate. The layers were separated and the aqueous layer was extracted thoroughly with ether. The combined organic extracts were washed successively with brine, 5% aqueous hydrochloric acid, saturated aqueous sodium bicarbonate and brine, and dried (anhydrous magnesium sulfate). Solvent removal under reduced pressure (water aspirator) afforded a pale, yellow oil, which was distilled
(air-bath temperature 83-87°C/0.1 Torr) to furnish 0.103 g (79%) of a clear, colourless oil. This material was identified as the ketone 349 and exhibited a single component by glc (SE-54, 120°C) and tlc (petroleum ether-ether, 9:1) ir (film): 3005, 1743, 1630, 727 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.95, 0.98 (d, d, 3H each, CH₃-CH-CH₃, J = 7 Hz), 1.09 (s, 3H, tertiary -CH₃), 1.35-1.43 (m, 1H), 1.52-1.66 (m, 2H, H₄), 1.90-1.96 (m, 1H, H₅), 1.98-2.07 (m, 3H), 2.28 (broad s, 1H, H₆, \( \omega_{1/2} = 5.5 \) Hz), 2.35 (unresolved d, 1H, H₇, J = 3 Hz), 5.59 (d, 1H, H₈, JDE = 10 Hz), 5.63 (d of d of d, 1H, H₉, JDE = 10 Hz, JCD = 3.5 Hz, JDF = 1.5 Hz). Irradiation at δ 5.61 (H₉, H₈) caused the signal at δ 1.90-1.96 to collapse to a d of d (J = 9.5 Hz, J = 2.5 Hz) and the signal at δ 2.28 to collapse to a d (J = 2.5 Hz).

Exact mass calcd. for C¹⁴H₂₀O: 204.1514; found: 204.1526.

3.4.14 Preparation of 10-exo-Isopropyl-7-methyltricyclo-[4.4.0.0³,⁷]decan-2-one

\[
\text{\begin{center}
\includegraphics[width=0.2\textwidth]{structure.png}
\end{center}}
\]

a) Via palladium-catalyzed hydrogenation of the alkene 349

To a vigorously stirred, prehydrogenated suspension of 10% palladium supported on carbon 210 (4 mg) in methanol (2
mL), under an atmosphere of hydrogen, was added a solution of the unsaturated ketone 349 (43.3 mg, 0.212 mmol) in methanol (2 mL). Efficient stirring of the resulting mixture at room temperature was maintained and reaction progress was monitored employing glc (SE-54, 120°C). After 24.5 h, the hydrogenation had become quite sluggish, and another 3 mg of the palladium catalyst was introduced. The reaction mixture was stirred for another 2 h, filtered through a layer of Celite and concentrated under reduced pressure (water aspirator). Distillation (air-bath temperature 93-98°C/0.1 Torr) of the residue gave 43.1 mg of a clear, colourless oil which was composed of a 93:7 mixture of the desired material (280) and starting material (349), respectively, based on glc analysis. Attempts to resolve the mixture by tlc were fruitless. From glc analysis (SE-54, 120°C), the retention time of the major component proved to be identical with that of the desired ketone 280 prepared via diimide reduction. Subsequently, the ketone mixture was subjected to Wittig olefination.

b) Via diimide reduction of the alkene 349

In accordance with the procedure described by Magnus et al., 189 and Hart and Kanai, 190 a solution of sodium acetate (0.247 g, 3.01 mmol) in water (5 mL) was added dropwise, over a period of 4 h, to a stirred, refluxing mixture of the ketone 349 (30.0 mg, 0.147 mmol), p-toluenesulfonylhydrazide (340 mg, 1.82 mmol), THF (3 mL) and water (3 mL). The resulting mixture was refluxed and reaction progress was monitored by
glc (SE-54, 120°C). After 15 h, the reaction had become sluggish. Consequently, more p-toluenesulfonylhydrazide (340 mg) and aqueous sodium acetate (0.247 g) were added, the latter in a dropwise manner via a syringe. These additions were repeated twice more, after 23 h and 39 h of reaction time. Only a trace of starting material remained unconsumed after 54 h. The reaction mixture was diluted with dichloromethane, poured into saturated aqueous ammonium chloride and the layers were separated. The aqueous layer was extracted thrice with dichloromethane and the combined organic extracts were washed twice with 5% aqueous sodium hydroxide, twice with brine, dried over anhydrous magnesium sulfate and concentrated to furnish a pale yellow, viscous oil. Subjection of this residue to flash column chromatography (18 g of 230-400 mesh silica gel in a 14x150 mm column, elution with petroleum ether-ether, 3:1) provided, after concentration of the desired fractions, the ketone 280 (13.1 mg, 43%) as a clear, colourless oil. This material was essentially pure, based on glc analysis (SE-54, 120°C), and exhibited $^1$H nmr and ir spectra which were identical with those of an authentic sample of (+)-280. The ketone 280 exhibited ir (film): 1740, 1467, 740 cm$^{-1}$; $^1$H nmr (400 MHz, CDCl$_3$) δ: 0.89, 0.92 (d, d, 3H each, CH$_3$-CH-CH$_3$, J = 6.5 Hz), 1.00 (s, 3H, tertiary -CH$_3$), 1.38-1.64 (m, 6H), 1.66-1.77 (m, 2H), 1.91-2.00 (m, 2H), 2.02-2.11 (m, 2H), 2.14 (unresolved

* We are grateful to Professor Wege for copies of $^1$H nmr and ir spectra of (+)-280.
Exact mass calcd. for C_{14}H_{22}O: 206.1671; found: 206.1671.

3.4.15 Preparation of (±)-Sinularene

To a stirred suspension of methyltriphenylphosphonium bromide (0.376 g, 1.05 mmol) in THF (10 mL) was added dropwise, via a syringe, a hexane solution of n-butyllithium (1.05 mmol) and the resulting yellow phosphorane solution was stirred at room temperature for 20 minutes. The ketone 280 (21.7 mg, 0.105 mmol) in THF (2 mL) was added, and the resulting mixture was refluxed. Reaction progress was monitored by glc (SE-54, 120°C), which indicated that after 46.5 h of refluxing, starting material was still present and the reaction had become quite sluggish. Consequently, more methyltriphenylphosphorane (1.05 mmol) was prepared in the manner outlined above, and added to the reaction mixture via a syringe. After the reaction mixture had been refluxed for another 22.5 h, glc revealed that all of the starting material had been consumed. Addition of a few drops of water resulted in immediate decolourization and the formation of a white precipitate. Evaporation of most of the solvent under reduced pressure
(water aspirator) left a white residue, which was taken up in petroleum ether, dried by the addition of anhydrous magnesium sulfate and filtered through a column of silica gel (2.5 g of 70-230 mesh silica gel in a 6x160 mm column, elution with petroleum ether). After concentration of the eluate, 16.8 mg (78%) of a clear, colourless oil was obtained. This material, shown to be 100% pure by glc (SE-54, 120°C) and to exhibit only one spot by tlc (petroleum ether), displayed ir, $^1$H nmr, $^{13}$C nmr and mass spectra identical with those of an authentic sample of (+)-sinularene* and the naturally occurring sesquiterpene (-)-sinularene. The oil exhibited ir (film): 3060, 1661, 1462, 1385, 1382, 1370, 878 cm$^{-1}$; $^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.90, 0.92 (d, d, 3H each, CH$_3$-CH-CH$_3$, $J = 6.5$ Hz), 0.91 (s, 3H, tertiary -CH$_3$), 1.05-1.32 (m, 5H), 1.46-1.51 (m, 2H), 1.56-1.81 (m, 3H), 1.85-1.95 (m, 1H), 2.14 (unresolved d, 1H, H-C-C=C, $J = 3.5$ Hz), 2.20 (broad s, 1H, H-C-C=C, $J = 7$ Hz), 4.58 (broad s, 1H, H-C=C, $J = 3$ Hz), 4.78 (broad s, 1H, H-C=C, $J = 4$ Hz); $^{13}$C nmr (100.6 MHz, CDCl$_3$): three CH$_3$ (20.7, 20.8, 21.4), five CH$_2$ (22.4, 26.0, 30.2, 31.7, 101.2), five CH (29.1, 42.9, 49.2, 50.2, 53.5), two C (46.9, 163.3). Exact mass calcd. for C$_{15}$H$_{24}$: 204.1878; found: 204.1880.

* We are grateful to Professor Oppolzer for $^1$H nmr, ir and mass spectra of (+)-sinularene.
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