(Z)-4-(TRIMETHYLSTANNYL)-1,3-BUTADIENES: PREPARATION AND USES IN ORGANIC SYNTHESIS

By

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We accept this thesis as conforming to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA
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Department of **CHEMISTRY**

The University of British Columbia
Vancouver, Canada

Date  _30 October 1990_
ABSTRACT

This thesis is divided into three parts. Part 1 describes the chemistry of dilithium (trimethylstannyl)(2-thienyl)(cyano) cuprate (61). This higher order cuprate reagent efficiently transfers the trimethylstannyl group, in a conjugate sense, to a variety of α,β-unsaturated carbonyl compounds. Also, it reacts with α,β-acetylenic esters 43 to give, stereoselectively, (Z)-β-trimethylstannyl α,β-unsaturated esters 46.

Part 2 describes the stereoselective preparation of (Z)-β-trimethylstannyl α,β-unsaturated aldehydes/ketones 151 via the Pd(0)-catalyzed reactions of α,β-acetylenic aldehydes and ketones 115 with hexamethylditin. Compounds 151 were converted into stannyldienes 166 via Wittig olefinations. The aldehydes 151 (R^1=H) undergo Wittig-Horner olefination. For example, reaction of 154 with the sodio-phosphonate reagent prepared from diisopropyl tert-butylphosphonoacetate 179, afforded 180. The stannyldienes 166 are synthetic equivalents of the diene donor synthon 183. For example, transmetallation of 169 with methyllithium, followed by alkylation of the resulting alkenyllithium species with ethylene oxide, provided 187.

The third section describes the synthesis of 6-endo-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones 237 (R^1=H) from stannyldienes 250. The stannyldienes 250 were converted into the corresponding iodo dienes 249, which undergo Pd(0)-catalyzed cross coupling with the reagent 246 to give the diene esters 241. Compounds 241 were converted into diene diazoketones 240 which, upon reaction with an appropriate transition metal catalyst, provided, stereospecifically, the ketones 237 (R^1=H).

The ketones 237 (R^1=H) are excellent precursors to functionalized, substituted 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes 215 (R^1=H). The cis divinylcyclopropanes 215 undergo facile, clean and efficient Cope rearrangement to the bicyclo[3.2.1]octa-2,6-dienes 216 (R^1=H). The rates of a number of these Cope rearrangements were measured at
43°C using $^1$H nmr spectroscopy. The effects of different substituents on the rate of Cope rearrangement were rationalized in terms of steric and/or electronic factors.
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<tr>
<td>acac</td>
<td>acetylacetonate</td>
</tr>
<tr>
<td>Ac₂O</td>
<td>acetic anhydride</td>
</tr>
<tr>
<td>ADD</td>
<td>1,1'- (azodicarbonyl) dipiperidine</td>
</tr>
<tr>
<td>approx.</td>
<td>approximately</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>n-Bu</td>
<td>n-butyl</td>
</tr>
<tr>
<td>Bu₃</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>calcd.</td>
<td>calculated</td>
</tr>
<tr>
<td>cims</td>
<td>chemical ionization mass spectrometry</td>
</tr>
<tr>
<td>COSY</td>
<td>(homonuclear) correlation spectroscopy</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMA</td>
<td>N,N-dimethylacetamide</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</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>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HOAc</td>
<td>acetic acid</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>ir</td>
<td>infrared</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
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<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>NMO</td>
<td>N-methylmorpholine N-oxide</td>
</tr>
<tr>
<td>nmr</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser enhancement</td>
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<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>
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<tr>
<td>PhH</td>
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<td>Pr^i</td>
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<td>singlet</td>
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<tr>
<td>t</td>
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<tr>
<td>TBDMS</td>
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<td>Tf</td>
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</tr>
<tr>
<td>2-Th</td>
<td>2-thienyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>tlc</td>
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<tr>
<td>TPAP</td>
<td>tetra-n-propylammonium perruthenate</td>
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Firstly, I would like to thank my research supervisor Dr. Edward Piers for his guidance and support during the course of these studies.

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The development of new reagents and reactions and the improvement of existing synthetic methods are fundamental aspects of synthetic organic chemistry. Despite the vast amount of literature that is concerned with these topics, it is fair to say that efficient, general methodologies are still required in all areas of organic synthesis. One such area is that of carbon-carbon double bond formation. Most, if not all, planned synthetic pathways to a given structurally complex target molecule will involve the construction of one or more carbon-carbon double bonds. Usually, it is required that these units be synthesized with a specific geometry and in a highly stereoselective manner. For example, if the geometry of the carbon-carbon double bond determines the stereochemical outcome of a later synthetic transformation, the alkene of correct geometry (and high isomeric purity) must be available, so that the desired product is obtained stereoselectively. Examples of such reactions include Diels-Alder reactions, Claisen rearrangements, Cope rearrangements and cyclopropanations.

There has been an enormous amount of literature dedicated to the stereoselective synthesis of olefinic compounds, covering a wide range of reaction types. A particularly useful approach is based on the reactions of organometallic reagents with acetylenic compounds. These reactions can be divided into four general categories: a) hydrometallation; b) halometallation; c) carbometallation; and d) bismetallation (Scheme 1).

To be a useful synthetic method the reaction must possess a number of characteristics. It should be efficient. It should be both regioselective (i.e. produce one of the alkenylmetal regioisomers exclusively or predominantly) and stereoselective (i.e. produce one of the alkenylmetal stereoisomers exclusively or predominantly). The reaction should be compatible with a wide range of functionality in the acetylenic starting material. Finally, the alkenylmetal species produced by the reaction must be easily transformed (stereospecifically) into an
alkene by replacement of the metal by other groups, such as H, alkyl, aryl, alkenyl, halogens, acyl, other metals, and so forth.

\[
\begin{align*}
\text{M} & \text{R} \quad \text{M} \quad \text{R}
\end{align*}
\]

Regioisomers

\[
\begin{align*}
\text{M} & \text{X} \quad \text{M} \quad \text{X}
\end{align*}
\]

Stereoisomers

Scheme 1

Numerous successful, general methodologies for the synthesis of stereodefined substituted alkenes have been developed based on hydrometallation, carbometallation, and halometallation of acetylenic compounds and these subjects have been well reviewed. However, there are fewer general methods of alkene synthesis based on bismetallation reactions. Some of the available bismetallation methodology is briefly discussed in this introduction.
The reaction of terminal acetylenes 1 and internal acetylenes 2 with bimetallic reagents (depicted as 3) usually results in the formation of bismetallated alkenes of general structures 4 and 5 respectively (Scheme 2). In order to be a synthetically useful process the reaction must fulfill the requirements mentioned above. Additionally, it is necessary to be able to perform chemistry at one alkenylmetal site in compounds 4 or 5, without affecting the other alkenylmetal site. Successive replacement of the alkenylmetal moieties in 4 or 5 by organic groups results in the stereoselective synthesis of trisubstituted alkenes 6, and tetrasubstituted alkenes 7, respectively.

\[ R \equiv \equiv H \xrightarrow{M^1-M^2} \begin{array}{c} \begin{array}{c} R \equiv \equiv H \\ M^1 \quad M^2 \end{array} \\ R \equiv \equiv R^1 \end{array} \]

1. \( R = \text{alkyl} \)

2. \( R, R^1 = \text{alkyl} \)

3. \( R^2, R^3 = \text{newly introduced organic groups} \)

\[ \begin{array}{c} \begin{array}{c} R \equiv \equiv H \\ M^1 \quad M^2 \end{array} \\ R \equiv \equiv R^1 \end{array} \xrightarrow{M^1-M^2} \begin{array}{c} \begin{array}{c} R \equiv \equiv R^1 \\ M^1 \quad M^2 \end{array} \\ R \equiv \equiv R^1 \end{array} \]

4. \( R = \text{alkyl} \)

5. \( R, R^1 = \text{alkyl} \)

6. \( R = \text{alkyl} \)

7. \( R, R^1 = \text{alkyl} \)

\( R^2, R^3 = \text{newly introduced organic groups} \)

Scheme 2

Most of the bismetallation methodology reported to date involves the regio- and stereoselective preparation of alkenylsilanes or alkenylstannanes. These compounds may subsequently be converted into stereodefined substituted alkenes.
1. **The preparation of alkenylsilanes via bismetallation of acetylenic compounds, and the conversion of these compounds into stereodefined alkenes**

Alkenylsilanes may be converted into stereodefined alkenes in a number of ways. For example, they react with iodine to give alkenyl iodides. These reactions usually proceed stereospecifically, with retention of carbon-carbon double bond geometry. For example, the alkenylsilane 8 reacts with iodine to give the alkenyl iodide 9 (Scheme 3).

Alkenylsilanes also react efficiently with acyl halides, in the presence of Lewis acids, to give $\alpha,\beta$-unsaturated ketones in a highly stereospecific manner. For example, the alkenylsilane 10 reacts with acetyl chloride in the presence of aluminum trichloride, to give the unsaturated ketone 11 (Scheme 3).

![Scheme 3](image)

Regarding the preparation of alkenylsilanes, Fleming *et al.* have reported that terminal acetylenes react with the higher order silylcuprate reagent 12 (Scheme 4) regio- and stereoselectively, to give alkenylsilane/alkenylcopper intermediates of general structure 13. The reaction is also applicable to symmetrical internal acetylenes, but with unsymmetrical internal acetylenes it does not proceed with high regioselectivity. It was shown that the
alkenylcopper moieties of intermediates 13 can be replaced stereospecifically by other groups, without affecting the alkenylsilane sites (Scheme 4). For example, the intermediates 13 react directly with a variety of electrophiles (e.g. I₂, CO₂, acyl chlorides, and MeI) to give alkenylsilanes of general structure 14. They also react with α,β-unsaturated ketones to give the conjugate adducts 15, and with epoxides (in the presence of a lithium acetylide), to give the alkenylsilanes/homoallylic alcohols 16.

![Scheme 4](image)

Oshima and coworkers have developed several reagents that effect silylmetallation of acetylenic compounds. Some of these reagents add to terminal acetylenes regio- and stereoselectively, giving alkenylsilanes similar to those obtained via the silylcupration methodology discussed above. However, the silylzincate reagent 17 reacts with terminal acetylenes to give alkenylsilane/alkenylzincate intermediates of general structure 18 (Scheme 5). The alkenylzincate moiety of intermediates 18 may be reacted with electrophiles (e.g. protons, MeI or PhCHO), to give alkenylsilanes of general structure 19.
The alkenylsilanes 19 obtained via this methodology are regiochemically different from the alkenylsilanes 14 obtained via silylcupration. These processes are, therefore, complementary.

\[
\begin{align*}
R-\equiv-H & \quad \xrightarrow{[\text{Me}_2\text{Bu}^\text{t}\text{SiZnBu}^\text{t}_2\text{]}\text{Li}} \\
17 & \quad \xrightarrow{18} \\
18 & \quad \xrightarrow{E^+} \\
19 &
\end{align*}
\]

\[E = \text{H, Me or CH(OH)Ph}\]

Scheme 5

2. The preparation of alkenylstannanes via bismetallation of acetylenic compounds and the conversion of these compounds into stereodefined alkenes

Alkenylstannanes are extremely versatile synthetic intermediates, as there are many methods available for the conversion of these compounds into substituted alkenes. For example, alkenyltrimethylstannanes depicted generally as 20 usually react cleanly with MeLi\textsuperscript{22a} to give alkenyllithium species of general type 21(Scheme 6), although the efficiency of the transmetallation process is dependant on the substitution pattern of the alkene.\textsuperscript{23} The
alkenyllithium reagents 21 may be reacted with electrophiles directly,23,24 or via the corresponding organocopper (I) reagents23,25 22 to give substituted alkenes 23.

Furthermore, the alkenylstannanes 20 may be cross coupled26 (in the presence of a Pd(0) catalyst) with a wide range of aryl, allyl, alkenyl, benzyl, and acyl halides, as well as with alkenyl triflates27 to give, stereospecifically, alkenes of general structure 24 (Scheme 6). Additionally, alkenylstannanes 20 react with iodine22b to give the corresponding alkenyl iodides 25 in a highly stereospecific manner (Scheme 6).

Scheme 6
Regarding the synthesis of alkenylstannanes, Piers and Chong\textsuperscript{28,29} have shown that the trimethylstannylicopper(I) reagent 26 reacts with terminal acetylenes efficiently and both regio- and stereoselectively, to give alkenylstannane/alkenylcopper intermediates of general structure 27 (equation 1). Several types of functional groups, such as halides, hydroxyls, and ethers are compatible with the reaction conditions. Unfortunately, the alkenylcopper moiety of the intermediates 27 does not react with electrophiles other than proton. In fact, an \textit{in situ} proton source is required in these reactions in order to achieve complete consumption of the acetylene by the organocopper(I) reagent. Therefore, this methodology is limited to the synthesis of alkenylstannanes of general structure 28.

\[
\begin{align*}
R & \equiv H & \quad \text{Me}_3\text{SnCu'SMe}_2 \quad 26 \\
R & \equiv H & \quad \text{Me}_3\text{Sn} \quad 27 \\
R & \equiv H & \quad \text{Me}_3\text{Sn} \quad 28
\end{align*}
\]

Oehlschlager and Sharma\textsuperscript{30} have reported that the stannyloborate reagent 29 reacts with terminal acetylenes (in the presence of a Cu(I) catalyst) to give, regio- and stereoselectively, alkenylstannane/alkenylborate intermediates of general structure 30 (Scheme 7). The alkenylborate moiety of intermediates 30 may be selectively replaced by a proton or by a variety of organic groups. For example, protonation of intermediates 30 gives alkenylstannanes of general structure 31. The intermediates 30 react with 3-bromopropene (in the presence of a Cu(I) salt or a Pd(0) catalyst) to give the substituted alkenylstannanes 32. They also react with iodobenzene (in the presence of a Pd(0) catalyst) to give substituted alkenylstannanes 33 and with 3-buten-2-one (in the presence of a Cu(I) salt) to give the alkenylstannanes 34 (Scheme 7).

A novel approach to the preparation of substituted alkenylstannanes has been reported by Wang \textit{et al.}\textsuperscript{25} It was shown acetylenic triethylborates of general structure 35 (prepared
via reaction of the appropriate lithium acetylides with triethylborane) react with trimethyltin chloride to give alkenylstannanes/alkenylboranes of general structure 36 (Scheme 8). Presumably, these compounds arise via migration of an ethyl group from boron to carbon, induced by electrophilic attack of trimethylstannyl chloride on the carbon-carbon triple bond of borates 35.

Interestingly, treatment of compounds 36 with n-BuLi gives the corresponding alkenylborates 37 (without destruction of the alkenylstannane moiety), which react with copper(I) bromide-dimethyl sulphide complex to give alkenylcopper/alkenylstannane intermediates of general structure 38. These alkenylcopper intermediates may be trapped
with reactive electrophiles such as 3-bromopropene, 2,3-dibromopropene, MeI or MeOH, to give stereodefined alkenylstannanes of general structure 39 (Scheme 8).

Scheme 8
Alkenylstannanes 39 are readily converted into stereodefined alkenylcopper(I) reagents 40. These reagents react with $\alpha,\beta$-unsaturated ketones to give stereodefined tetrastriiminated alkenes 41, or react with alkylating agents to give stereodefined tetrastriiminated alkenes of general structure 42.

The bis metallation methodology described so far has involved the preparation of alkenylstannanes (or alkenylsilanes) from terminal acetylenes. Sometimes, regio- and stereoselective bis metallation reactions can be achieved using $\alpha,\beta$-acetylenic esters as starting materials. For example, Piers et al.\textsuperscript{31-33} have reported that the stannylcopper reagent 26 reacts with $\alpha,\beta$-acetylenic esters 43 to give (upon protonation of the reaction intermediates) alkenylstannanes of general structure 44. On the other hand, the stannylcuprate reagent 45 reacts with acetylenic esters to give, depending on the reaction conditions, alkenylstannanes of general structures 44 or 46 (Scheme 9). A wide range of functional groups, such as halides, ethers and carbon-carbon double bonds, are compatible with the reaction conditions. This stannylcupration methodology is discussed in detail in the introduction to Part 1 of this thesis.

\begin{scheme}
\centering
\begin{align*}
\text{Me}_3\text{SnCu-SMe}_2 \\
\text{26} \\
\text{[Me}_3\text{SnCuSPh]}\text{Li} \\
\text{45}
\end{align*}
\text{R} \equiv \text{CO}_2\text{R}^1 \\
\text{43}
\text{R} \\
\text{Me}_3\text{Sn} \\
\text{44}
\text{CO}_2\text{R}^1
\end{scheme}

\begin{scheme}
\centering
\text{R} \\
\text{Me}_3\text{Sn} \\
\text{H} \\
\text{45}
\text{R} \\
\text{Me}_3\text{Sn} \\
\text{H} \\
\text{46}
\text{CO}_2\text{R}^1
\end{scheme}

Scheme 9

Alkenylstannanes of general structure 44 are exceptionally useful synthetic intermediates. For example, the compound 47 (prepared via stannylcupration of methyl
6-chloro-2-hexynoate) is readily converted into the alkenylstannane 48. This compound was used for the preparation of the bicyclic diene 49, which was a key intermediate in the total synthesis of (±)-8,15-diisocyano-11(20)-amphilectene 50 reported by Piers and Llinas-Brunet34 (Scheme 10). Thus, alkylation of the potassium enolate 51 with compound 48
gave the ketone 52. The desired bicyclic diene 49 was prepared from ketone 52 in a one-pot operation, involving formation of the enol triflate 53, followed by Pd(0)-catalyzed intramolecular cross coupling between the alkenylstannane and alkenyl triflate35,36 moieties of this compound.

It has also been shown that α,β-acetylenic esters 43 react with hexamethylditin in the presence of a Pd(0) catalyst to give (Z)-2,3-bis(trimethylstannyl)-2-alkenoates of general structure 54 (equation 2).37 These bismetallation reactions are both efficient and stereoselective, and a variety of functional groups, including halides, ethers, and carbon-carbon double bonds are compatible with the reaction conditions. The distannyl alkenoates 54 are excellent precursors to stereodefined tetrasubstituted alkenes of general type 55, since it is possible to sequentially replace the alkenylstannyl moieties of these compounds by organic groups.23 This methodology is described in detail in the introduction to Part 2 of this thesis.

\[
\begin{align*}
&\text{Me}_3\text{SnSnMe}_3 \\
&\text{Pd}(0) \quad \text{R} \quad \text{CO}_2\text{R}^1 \quad \text{Me}_3\text{Sn} \quad \text{SnMe}_3 \quad \text{R} \quad \text{E} \quad \text{R}^2 \quad \text{R}^3 \\
&\text{CO}_2\text{R}^1 \quad \text{SnMe}_3 \quad \text{SnMe}_3 \\
&\text{R} \quad \text{E} \quad \text{R} \quad \text{R}^2 \\
&\text{E} = \text{group derived from the ester function} \\
&\text{R}^2,\text{R}^3 = \text{newly introduced organic groups}
\end{align*}
\]

Pd(0)-catalyzed bismetallation reactions similar to those described above have been performed using terminal acetylenes 1 as starting materials. For example Mitchell et al.38 reported that terminal acetylenes 1 react with hexamethylditin (in the presence of a Pd(0) catalyst) to give bis(trimethylstannyl) alkenes of general structure 56 (Scheme 11). Also, Chenard and Van Zyl39 and Mitchell et al.40 have independently reported that trialkylsilyl
trialkylstannanes react with terminal acetylenes (in the presence of a Pd(0) catalyst) to give, highly regio- and stereoselectively, alkenylsilanes/alkenylstannanes of general structure 57 (Scheme 11). It was shown that the alkenylstannane moiety of compounds 57 can sometimes be manipulated without affecting the alkenylsilane moiety. For example,\(^{41}\) compound 58 was coupled efficiently and stereospecifically with the acid chloride 59, in the presence of a Pd(0) catalyst, to give the alkenylsilane 60 (Scheme 11).

The chemistry described in this general introduction has shown that bismetallation of acetylenic compounds is an exceptionally useful approach to the regio- and stereoselective preparation of alkenylsilanes and alkenylstannanes, which are precursors to stereodefined
substituted alkenes. However, at the time that the work described in this thesis was initiated, it appeared that there was certainly room for the development of new methodology in this area.

The work described in the first two sections of this thesis is concerned primarily with the development of new bismetallation methodology for the preparation of stereodefined alkenylstannanes. Each section contains a brief introduction to the existing methodologies as well as an outline of the proposed research.

The first section deals with stannylcupration reactions. In particular, the chemistry of a new, higher order trimethylstannylcuprate reagent, dilithium (trimethylstannyl)(2-thienyl)(cyano)cuprate, is described.

The second section is concerned with the Pd(0)-catalyzed reactions of hexamethylditin with \( \alpha,\beta \)-acetylenic aldehydes and ketones, and the subsequent preparation and general synthetic uses of (Z)-4-(trimethylstannyl)-1,3-butadienes.

The final section involves the use of these stannyldienes in the construction of 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes, and a study of the Cope rearrangements of these compounds to highly substituted bicyclo[3.2.1]octa-2,6-dienes. A brief introduction to these topics is included.
PART 1. The chemistry of dilithium (trimethylstannyl)(2-thienyl)(cyano) cuprate (61).

I. Introduction

Previous work carried out in this laboratory has demonstrated the viability and synthetic utility of several (trimethylstannyl)copper(I) reagents. These reagents are easily prepared and transfer the trimethylstannyl moiety to a variety of organic substrates. For example, both the (trimethylstannyl)copper(I) reagent 26 (prepared from equimolar amounts of trimethylstannyllithium and cuprous bromide-dimethyl sulphide complex) and the phenylthio(trimethylstannyl)cuprate reagent 45 (prepared from equimolar amounts of trimethylstannyllithium and phenylthiocopper) react with $\alpha,\beta$-unsaturated ketones of general structure 62 to give $\beta$-trimethylstannyl $\alpha,\beta$-unsaturated ketones of general structure 63 (Scheme 12). Also, the cuprate reagent 45 reacts with $\alpha,\beta$-unsaturated ketones to give $\beta$-trimethylstannyl ketones of general structure 64, whereas reagent 26 does not effect this transformation efficiently.

Reagents 26 and 45 react efficiently and both regio- and stereoselectively with $\alpha,\beta$-acetylenic esters 43. In particular, the (trimethylstannyl)copper(I) reagent 26 reacts with acetylenic esters either at -78°C or at -48°C to give (after protonation of the reaction intermediates) (E)-$\beta$-trimethylstannyl $\alpha,\beta$-unsaturated esters of general structure 44 (Scheme 12). The (trimethylstannyl)cuprate reagent 45 reacts with acetylenic esters at -78°C in the presence of a proton source to give compounds 44 stereoselectively. Alternatively, 45 reacts with acetylenic esters at -48°C to give (Z)-$\beta$-trimethylstannyl $\alpha,\beta$-unsaturated esters of general structure 46 (Scheme 12). A wide range of functional groups, including ethers, halides, and carbon-carbon double bonds, are compatible with all of the above reaction conditions.
\[
\begin{align*}
\text{CuSPh} & \quad \text{[Me}_3\text{SnCuSPh]Li} \\
\text{(Me}_3\text{Sn)}_2 + \text{MeLi} & \rightarrow \text{Me}_3\text{SnLi} + \text{Me}_4\text{Sn} \\
\text{CuBr-Me}_2\text{S} & \rightarrow \text{Me}_3\text{SnCu-SMe}_2 + \text{LiBr}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{CO}_2R \\
\text{R—CO}_2\text{R} & \quad \text{R—CO}_2\text{R}^1 \\
\text{43} & \quad \text{44} \\
\text{62} & \quad \text{63} \\
\text{63} & \quad \text{64}
\end{align*}
\]

\[
\begin{align*}
\text{R—CO}_2\text{R}^1 & \quad \text{R—CO}_2\text{R}^1 \\
\text{43} & \quad \text{44} \\
\text{45} & \quad \text{46}
\end{align*}
\]

**Scheme 12**
The stereochemical outcomes of these reactions may be rationalized in the following manner (Scheme 13). Reaction of either 26 or 45 with acetylenic esters probably involves reversible cis stannylcupration of the carbon-carbon triple bond to give alkenylcopper intermediates depicted as 65A or 65B, respectively. The alkenylcopper intermediates 65A are, apparently, stable at -78°C or at -48°C and protonation provides, stereoselectively, the (E)-alkenylstannanes 44 (Scheme 13). It is proposed that alkenylcopper intermediates 65B, on the other hand, isomerize to copper allenoate intermediates of general structure 66B. This isomerization occurs quite readily at -48°C and, after 4 hours at this temperature, the allenoates 66B are, apparently, formed predominantly. Protonation of 66B occurs in the plane of the groups attached to the β-carbon, from the side opposite the bulky trimethylstannyl group, to give the (Z)-alkenylstannanes of general structure 46.
The alkenylcopper-copper allenoate isomerization may proceed even at -78°C, but if an *in situ* proton source is used at this temperature, the alkenylcopper intermediates 65B are protonated before any isomerization to the allenoates can occur and the (E)-alkenylstannanes 44 are obtained stereoselectively.

It is not clear why the alkenylcopper intermediates 65B readily isomerize to the corresponding copper allenoates 66B, whereas the alkenylcopper intermediates 65A are stable species. The reasons must be related to the nature of Z and, therefore, to the actual structures of 65A and 65B, which are at present unknown.

It should be emphasized that the above arguments are presented purely on the basis of the observed stereochemical outcomes of these stannylcupration reactions. Very little is known about the actual structures of the reaction intermediates, and it is not even certain that allenoate intermediates are involved. However, other workers have suggested that allenoate species are intermediates in reactions of alkylcuprates with acetylenic esters and some evidence has been presented to support this. For example, Marino and Lindermann have reported that the reaction of the mixed cuprate 67 with ethyl propynoate results in the formation of an allenoate intermediate 68, which can be trapped as the allenic compound 69 by addition of trimethylsilyl chloride to the reaction mixture (equation 3).

\[
\begin{align*}
\text{MeCuYLi} & \quad 67 \\
\text{H—} & \quad \text{CO}_2\text{Et} \\
\rightarrow & \quad \left[ \begin{array}{c}
\text{H} \\
\text{Me} \\
\text{OEt} \\
\text{OCuY}
\end{array} \right] \\
\rightarrow & \quad \text{Li}^+ \\
\text{ClSiMe}_3 & \quad 68 \\
\rightarrow & \quad \text{Me} \\
\text{OEt} \\
\text{OSiMe}_3 & \quad 69
\end{align*}
\]

\(Y = \text{1-hexynyl}\)

Regardless of these mechanistic considerations, the stannylcupration of acetylenic esters with reagents 26 and 45 constitutes a general, efficient, stereoselective method for the synthesis of stereodefined, disubstituted alkenylstannanes. There are, however, some problems associated with this methodology.
The (trimethylstannyl)cuprate reagent 45 reacts anomalously with acetylenic esters which possess an ether function at the γ position. For example, 45 reacts with the acetylenic ester 70 to give compound 71 as the major product, along with a low yield of the expected alkenylstannane 72 (equation 4). Additionally, 45 reacts with the acetylenic ester 73 to give compounds 74 and none of the expected alkenylstannane 75 (equation 5).

In these reactions, the cuprate reagent 45 preferentially transfers the phenylthio group (rather than the trimethylstannyl group) to the substrate. This is somewhat surprising, since phenylthiocuprates are generally reluctant to release the phenylthio moiety from copper (although examples of this have been reported). The reasons for the anomalous behavior of reagent 45 in these reactions are not clear, although they are likely related to the presence of an electron withdrawing group close to the carbon-carbon triple bond in substrates 70 and 73. It is interesting to note that the reagent Me₃SnCu·SMe₂ (26) reacts efficiently with the acetylenic esters 70 and 73 to give the expected γ-alkoxy-(E)-β-trimethylstannyl α,β-unsaturated esters. Therefore, only γ-alkoxy-(Z)-β-trimethylstannyl α,β-unsaturated esters are not available via the existing stannylcupration methodology.
The intermediates formed in the reactions of either reagent 26 or 45 with acetylenic esters do not react efficiently with electrophiles other than proton. In attempted intermolecular conjugate addition/alkylation reactions, the products obtained are those due to protonation of the reaction intermediates (i.e. alkenylstannanes of general structures 44 and 46). Apparently, the reaction intermediates (alkenylcopper species or copper allenoates) are unreactive towards alkylating agents and, therefore, remain unchanged until a proton source is added during workup. In attempts to trap reaction intermediates with iodine, a highly reactive electrophile, only the protonated products 44 and 46 are obtained, along with variable amounts of the acetylenic ester starting material. In these cases, it appears that the iodine reacts preferentially with the (trimethylstannyl)copper(I) or cuprate reagent, driving the reversible stannylcupration reaction to the left and resulting in regeneration of the acetylenic ester.

II. Proposals

Organometallic reagents derived from copper(I) can be broadly classified into three groups:

1) Organocopper(I) reagents.

These are prepared from equimolar amounts of a copper(I) halide and an organolithium or Grignard reagent. Reagent 26 is, therefore, a trimethylstannyl version of an organocopper(I) reagent.

\[
\text{RLi} + \text{CuX} \rightarrow \text{RCu} + \text{LiX}
\]

\[
\text{Me}_3\text{SnLi} + \text{CuBr}\cdot\text{SMe}_2 \rightarrow \text{Me}_3\text{SnCu}\cdot\text{SMe}_2 + \text{LiBr}
\]
2) **Lower order cuprate reagents.**

Lower order cuprates are represented generally by the stoichiometric formula \( R^1R^2CuM \), in which \( R^1 \) and \( R^2 \) are organic ligands and \( M \) is a metal counter ion, usually \( \text{Li}^+ \) (or \( \text{MgBr}^+ \)). Lower order cuprates in which \( R^1 \) and \( R^2 \) are the same are generally referred to as Gilman reagents, and may be prepared via reaction of two equivalents of an organolithium or Grignard reagent with one equivalent of a copper(I) halide. Lower order cuprates in which \( R^1 \) and \( R^2 \) are different are generally termed "mixed" cuprates. In these reagents, one of the organic groups attached to copper is necessarily a non-transferable ligand or "dummy" ligand, meaning that the other group will be transferred preferentially to the substrate by the cuprate reagent. Synthetically useful "mixed" lower order cuprate reagents have been developed using 1-alkynyl, cyano, phenylthio, dicyclohexylamido, and dicyclohexylphosphido groups as non-transferable ligands. These reagents can be derived from the reaction of an alkylolithium reagent (which provides the transferable ligand) with an organocopper(I) reagent (which contains the non-transferable ligand). The phenylthiocuprate reagent 45 is a trimethylstannyl analogue of a "mixed" lower order cuprate.

The use of mixed cuprates (rather than Gilman type reagents) in organic synthesis is preferred if the transferable organic group is available only via multistep synthesis or is derived from an expensive reagent. Gilman type reagents, derived from two equivalents of the transferable group, usually transfer only one of these groups to the organic substrate, resulting in wastage of the other.

\[
\begin{align*}
2RLi + CuX & \rightarrow R_2CuLi + LiX & \text{GILMAN TYPE REAGENTS} \\
RLi + CuR^{NT} & \rightarrow RR^{NT}CuLi & \text{MIXED LOWER ORDER CUPRATES} \\
Me_3SnLi + CuSPh & \rightarrow Me_3SnCuSPhLi \\
\end{align*}
\]

\( R^{NT} = \text{NON-TRANSFERABLE LIGAND} \)
3) **Higher order cuprates.**

The most common higher order cuprate reagents are those represented by the general formula \([R^1R^2CuCN]Li_2\). These higher order cyanocuprates are, therefore, different from lower order reagents in that there are three (rather than two) groups attached to copper, making these complexes formally dianionic. In these reagents, the cyano group is a non-transferable ligand, and the two organic groups attached to copper may either be the same or different ("mixed" cuprates). In higher order "mixed" cyanocuprates, one of the organic groups attached to copper must be a non-transferable ligand so that the remaining organic group may be transferred selectively by the cuprate. Lipshutz *et al.* have shown that the

\[
2RLi + CuCN \rightarrow [R_2CuCN]Li_2 \quad \text{HIGHER ORDER CYANO CUPRATES}
\]

\[
RLi + R^{NT}Li + CuCN \rightarrow [RR^{NT}CuCN]Li_2 \quad \text{MIXED HIGHER ORDER CYANO CUPRATES}
\]

\[R^{NT} = \text{NON-TRANSFERABLE LIGAND}\]

2-thienyl ligand is not usually transferred easily from copper and that higher order mixed cyanocuprates are conveniently prepared via addition of an organolithium reagent (the transferable ligand) to the lower order thienyl cyanocuprate (equation 6).

\[
2-\text{ThLi} + CuCN \rightarrow 2-\text{ThCuCNLi} \quad \text{RLi} \rightarrow R(2-\text{Th})CuCNLi_2 \quad (6)
\]

\[= 2-\text{Th}\]

Alkyl higher order cuprates are generally superior reagents compared with their lower order analogues. For example, the higher order mixed cuprate reagent reacts with the
epoxide 79 (2.5 h at 0°C) to give a 92 % yield of the alcohol 80. The lower order reagent 81 reacts with the epoxide 79 under identical conditions to give an 11% yield of the same alcohol (equation 7).\(^\text{60}\)

![Equation 7](image)

On the basis of previous results reported in the literature regarding alkylcuprate reagents, as summarized above, it was envisaged that a higher order (trimethylstannyl)cuprate reagent should exhibit reactivity somewhat different from that of the lower order cuprates 26 and 45. Thus, it seemed possible that a higher order (trimethylstannyl)cuprate might serve as a useful alternative to these well established reagents.

The aim of this project was, therefore, to investigate the chemistry of a higher order (trimethylstannyl)cuprate reagent. Initially, we wanted to determine the reactivity of such a reagent, relative to 26 and 45, with typical organic substrates, such as \(\alpha,\beta\)-unsaturated carbonyl compounds. However, the main objective was to investigate the reactions of this type of reagent with \(\alpha,\beta\)-acytylenic esters 43. Several questions needed to be addressed regarding these reactions. Firstly, would the reagent transfer the trimethylstannyl group efficiently to these acetylenic esters, and if so, what would be the stereochemical outcome in these reactions? Also, would the reagent react "normally" with \(\alpha,\beta\)-acytylenic esters that have an ether function at the \(\gamma\) position (e.g. compounds 70 and 73)? Finally, would the intermediates formed in the reactions of acetylenic esters with the higher order cuprate reagent
be amenable to trapping with electrophilic reagents (e.g. alkylating reagents) other than proton?

III. Results and discussion

At the outset of this project there were no reports regarding the preparation and reactions of higher order (trimethylstannyl)cuprates, although a number of such reports appeared in the literature during the course of our work and since the publication of our results. Due to the high cost of hexamethylditin (which is used to prepare trimethylstannyllithium), the decision was made to investigate the chemistry of a mixed cuprate reagent rather than a bis(trimethylstannyl) species. Therefore, based on the methodology developed by Lipshutz et al. in connection with alkylcuprate chemistry, we decided to prepare a higher order mixed cyanocuprate reagent composed of 1 equivalent of trimethylstannylithium (the transferable ligand), 1 equivalent of 2-thienyllithium (the non-transferable ligand), and 1 equivalent of copper(I) cyanide.

3.1. Preparation of dilithium (trimethylstannyM2-thienyiycyanokuprate (61)

It was found that a reagent of the required stoichiometry could be conveniently prepared by the following procedure. To a cold (-20°C), stirred solution (argon atmosphere) of Me₆Sn₂ and thiophene (1 equivalent each) in dry THF was added a solution of MeLi (2 equivalents) in ether. After the mixture had been stirred at -20°C for 50 min, it was cooled to -78°C and solid copper(I) cyanide was added, giving a bright yellow solution which contained undissolved CuCN. On warming to -48°C the solids dissolved to give a clear, homogeneous, yellow solution of the cuprate reagent 61 (Scheme 14).
3.2. Reactions of the higher order cuprate 61 with $\alpha,\beta$-unsaturated carbonyl compounds

With a simple, reproducible preparation of reagent 61 in hand, it was now possible to determine its reactivity with simple organic substrates, such as $\alpha,\beta$-unsaturated carbonyl compounds. Of particular concern was the ability of reagent 61 to transfer the trimethylstannyl group to these substrates selectively and efficiently, without competitive transfer of the thienyl residue. In connection with this, it is known that some higher order (alkyl)(thienyl) cyanocuprates preferentially transfer the thienyl group ($in a 1,2 sense$) to sterically hindered $\beta,\beta$-disubstituted $\alpha,\beta$-unsaturated ketones, although this problem may be avoided by the use of Lewis acid additives.

The substrates chosen for this study were sterically hindered $\beta,\beta$-disubstituted $\alpha,\beta$-unsaturated ketones, namely 3-methyl-2-cyclohexen-1-one, 3,5,5-trimethyl-2-cyclohexen-1-one, and pulegone, which are commercially available, and the bicyclic enone 82. The reaction conditions and results are summarized in Table 1. Several important points regarding these reactions should be noted. In all cases, the reactions proceeded smoothly and in reasonable reaction times, using 1.5 equivalents of 61, to give good isolated yields of the products. In no case was any material isolated which was derived from the transfer of the thienyl group to the organic substrate. Therefore, the higher order cuprate 61
Table 1. Reactions of reagent 61 with α,β-unsaturated ketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate Image" /></td>
<td>THF, -78°C, 5 min; -20°C, 4 h</td>
<td><img src="image2" alt="Product Image" /></td>
<td>87 %</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate Image" /></td>
<td>THF, -78°C, 5 min; -20°C, 4 h</td>
<td><img src="image4" alt="Product Image" /></td>
<td>90 %</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Substrate Image" /></td>
<td>THF, -78°C, 5 min; -20°C, 2 h</td>
<td><img src="image6" alt="Product Image" /></td>
<td>69 %</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Substrate Image" /></td>
<td>THF, -78°C, 10 min; -20°C, 3 h</td>
<td><img src="image8" alt="Product Image" /></td>
<td>70 %</td>
</tr>
</tbody>
</table>

<sup>1</sup> Isolated yield of distilled product
appears to be a viable reagent for the selective transfer of the trimethylstannyl group to organic substrates. In fact, the yield (87%) of compound 83 obtained from the reaction of 61 with 3,5,5-trimethyl-2-cyclohexen-1-one (entry 1) compares favorably with that obtained (69%) using the lower order reagent 45.\textsuperscript{42}

The spectral data for the reaction products shown in Table 1 were consistent with the proposed structures. Compound 83 exhibited spectral data identical with those reported for the same compound prepared by previous workers in this laboratory.\textsuperscript{42}

Regarding the reaction of the higher order cuprate 61 with pulegone, a mixture of two products, in a ratio of 3:1 (glc analysis), was obtained. The two products were easily separated by flash chromatography. The stereochemistry of the minor component was confirmed to be \textit{cis} by the treatment of this compound with NaOMe/MeOH at room temperature. The pure \textit{cis} isomer 84 was thus converted into an 88:12 mixture (by glc analysis) of the \textit{trans} isomer 85 and the \textit{cis} isomer 84, respectively.

Regarding the reaction of the cuprate reagent 61 with the bicyclic enone 82, a single product 86 was obtained. The relative stereochemistry at the ring fusion in this compound was assumed to be \textit{cis}, based on the known reactions of enone 82 with alkylcuprates.\textsuperscript{66,67} Despite attempts to confirm this relative stereochemistry by nOe difference experiments, no conclusive evidence was obtained to support our assignment. The lack of an nOe effect between the angular methyl group and the trimethylstannyl group is most likely due to the long carbon-tin bond. As a result of this, the protons of the trimethylstannyl group and the protons of the methyl group at the ring fusion are apparently too far away from each other for an nOe effect to be observed between these groups.

The reactions of the higher order cuprate reagent 61 with other types of \(\alpha,\beta\)-unsaturated carbonyl compounds were investigated next. The substrates chosen for this brief study were (\(E\))-2-hexenal and (\(2E, 6Z\))-2,6-nonadienal, which are commercially available, the aldehyde 88,\textsuperscript{68} and the ester 89.\textsuperscript{69} The conditions employed for these reactions and the results are presented in Table 2.
Table 2. Reactions of reagent 61 with α,β-unsaturated aldehydes and esters

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Substrate 1" /></td>
<td>THF, -78°C, 1 h; -20°C, 30 min</td>
<td><img src="image2.png" alt="Product 1" /></td>
<td>91%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Substrate 2" /></td>
<td>THF, -78°C, 1 h; -20°C, 1 h</td>
<td><img src="image4.png" alt="Product 2" /></td>
<td>61%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Substrate 3" /></td>
<td>THF, -78°C, 1 h; -20°C, 1 h</td>
<td><img src="image6.png" alt="Product 3" /></td>
<td>64%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Substrate 4" /></td>
<td>THF, -78°C, 1 h; -20°C, 1 h</td>
<td><img src="image8.png" alt="Product 4" /></td>
<td>62%</td>
</tr>
</tbody>
</table>

¹ Isolated yield of distilled product
Several comments must be made regarding the reactions summarized in Table 2. Firstly, the reactions of the cuprate reagent 61 (1.5 equivalents) with these substrates were complete within reasonable lengths of time, and gave respectable to very good yields of products. Secondly, it was pleasing to find that 61 reacted efficiently with the \(\beta,\beta\)-disubstituted ester 89 (entry 1) to give the conjugate addition product 90 in high yield. It had been shown previously\(^{42}\) that the lower order phenylthiocuprate reagent 45 does not react with this substrate at all. Additionally, the higher order cuprate reagent 61 reacted with \(\alpha,\beta\)-unsaturated aldehydes to give reasonable yields of the corresponding conjugate addition products, even in the case of the sterically hindered \(\beta,\beta\)-disubstituted aldehyde 88 (entry 4). These results are of particular note since it is known that tri-\(n\)-butylstannyllithium\(^{70}\) reacts with \(\alpha,\beta\)-unsaturated aldehydes, in THF, to give mainly the products of 1,2-addition. Finally, the spectral data for the products shown in Table 2 were in full accord with the assigned structures.

3.3. Reactions of the higher order cuprate 61 with \(\alpha,\beta\)-acetylenic esters

The substrates used in this brief study were the \(\alpha,\beta\)-acetylenic esters 70 and 73. As mentioned earlier, the lower order phenylthiocuprate 45 reacts with these substrates to give, predominantly, products resulting from phenylthio transfer. The reasons for this anomalous behaviour are linked to the presence of an ether function at the \(\gamma\) position of compounds 70 and 73.

The cuprate reagent 61 was allowed to react with the acetylenic ester 70 for 2 hours at -78°C. After appropriate workup, glc analysis of the crude reaction product showed the presence of the \((Z)\) - and \((E)\)-alkenylstannanes 72 and 94 in a ratio of 95:5 respectively (equation 8). The crude reaction mixture was purified by flash chromatography to give a 65% yield (after distillation) of the pure (\(Z\))-alkenylstannane 72, which was spectroscopically identical with the same substance prepared previously.\(^{33}\)
In an identical procedure, the cuprate reagent 61 was allowed to react with the acetylenic ester 73. After appropriate workup, glc analysis of the crude product showed the presence of the (Z)- and (E)-alkenylstannanes 75 and 95, in a ratio of 9:1 respectively, as well as some other minor unidentified products (equation 9). The (Z)-alkenylstannane 75 was isolated in 55 % yield after flash chromatography and distillation.

The isolated yields of compounds 72 and 75 in these reactions are much better than those obtained previously by reaction of the acetylenic esters 70 and 73 with the lower order phenylthiocuprate 45 (65 % and 55 %, respectively, compared with 29 % and 0 %, respectively). However, they are not as high as would have been expected from the very clean glc analyses of the crude reaction mixtures. The presence of baseline material by tlc analyses suggested that some polar, high molecular weight compounds may have been formed, but the nature of this material was not investigated.

The above results show that the higher order cuprate 61 can be used effectively for the stereoselective preparation of (Z)-β-trimethylstannyl α,β-unsaturated esters 46 from acetylenic esters, and is therefore a useful alternative to the lower order reagent 45. The stereochemical outcomes in these reactions may be rationalized using arguments similar to
those presented earlier. Thus, it may be proposed that the higher order reagent 61 reacts with acetylenic esters regio- and stereoselectively to give alkenylcopper intermediates of general structure 65C (Scheme 15). Apparently, the alkenylcopper intermediates 65C undergo isomerization (even at -78°C) to the corresponding copper allenoates 66C. Upon workup, protonation of the allenoates 66C takes place from the less hindered face to give, stereoselectively, (Z)-alkenylstannanes of general structure 46. It is not immediately clear why the alkenylcopper intermediates 65C isomerize so readily to the corresponding allenoates 66C. As suggested earlier for the reactions of the lower order reagents 26 and 45 with acetylenic esters, the nature of Z affects the stability of the alkenylcopper intermediates, and it appears that the intermediate 65C is somewhat more prone to isomerization than 65B (Z=SPh(Li)).

The next objective was to investigate the possibility of trapping the intermediates formed in these stannylicupration reactions with alkylating agents. For this study, it was decided to use the acetylenic ester 70 as the starting material, since the conditions for reaction of 61 with this substrate had been determined and the reaction was known to proceed cleanly.
Interestingly, it was found that the intermediate formed in this reaction could be smoothly alkylated with methyl iodide under the following conditions. A solution of the cuprate reagent 61 (1.5 equivalents) and the acetylenic ester 70 (1 equivalents) in dry THF was stirred at -78°C for 1 hour and at -20°C for 30 min. Hexamethylphosphoramide (excess, 10 equivalents) and MeI (excess) were added successively and the resulting mixture was stirred at -20°C for 30 min and at room temperature for 1 hour. After appropriate workup, glc analysis of the crude product showed one major peak attributable to the alkylated product 96. Flash chromatography of the crude product gave the compound 96 in 65 % yield (after distillation) (Table 3). The ¹H nmr spectrum of this material showed no signal due to an olefinic proton, but did show a 3-proton singlet at δ 1.93 (4JSn-H = 7.1 Hz) due to the vinyl methyl group. The ¹³C nmr spectrum of this compound showed signals at δ 169.47 (-CO₂Et), and at 163.06 and 134.53 (olefinic carbons). The proposed double bond geometry (which is that expected from approach of the alkylating agent to the less hindered face of an allenoate intermediate (66C) in a manner similar to that described earlier) was confirmed by nOe difference experiments. Thus, irradiation of the signal at δ 1.93 (vinyl methyl) resulted in the expected enhancement of the signal at δ 4.40 (-SiOCH₂-) and *vice versa*.

Similar trapping experiments were carried out successfully using other reactive alkylating agents. The conditions for these reactions and the results are summarized in Table 3. Several points should be made in connection with these reactions.

Regarding the reaction using 3-iodopropene as the alkylating agent, glc analysis of the crude product showed one major peak, attributable to the desired alkylated product 97. The crude product was readily purified by flash chromatography (followed by distillation) to give the alkylated product 97 in 60% yield. The ¹H nmr spectrum of this material showed 1-proton multiplets at δ 4.93, 4.98, and 5.77, corresponding to the olefinic protons of the propenyl group, as well as a 2-proton multiplet at δ 3.14 (bis-allylic methylene). The ¹³C
Table 3. Reaction of the acetylenic ester 70 with the reagent 61 and trapping of the intermediate with alkylating reagents.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Alkylation Conditions</th>
<th>Product</th>
<th>Yield¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBDMSO (-\equiv\text{CO}_2\text{Et}) 70</td>
<td>HMPA, MeI, -20°C, 30 min; room temp, 1 h</td>
<td>Me(_3)Sn(-\equiv\text{CO}_2\text{Et})</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>HMPA, 3-iodo-propene, -20°C, 30 min</td>
<td>Me(_3)Sn(-\equiv\text{CO}_2\text{Et})</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>HMPA, 3-bromo-propyne, -78°C, 1 h; -20°C, 1 h</td>
<td>Me(_3)Sn(-\equiv\text{CO}_2\text{Et})</td>
<td>40%</td>
</tr>
</tbody>
</table>

¹ Isolated yield of distilled, stereochemically pure material.

Nmr spectrum showed signals at \(\delta\) 168.92 (-CO\(_2\)Et) and at \(\delta\) 164.93, 136.12, 135.72 and 115.13 (olefinic carbons). The proposed double bond geometry was confirmed by NOE difference experiments. Thus, irradiation of the signal at \(\delta\) 3.14 (bis-allylic methylene) resulted in signal enhancement at \(\delta\) 4.39 (-SiOCH\(_2\)-) and vice versa.

Regarding the reaction using 3-bromopropyne as the electrophile, glc analysis of the crude product showed the presence of the expected alkylated product 98 along with a significant amount (approx. 25 % by glc analysis) of the products 72 and 94, which resulted from protonation of the reaction intermediates. The crude product was purified by careful
flash chromatography (followed by distillation) to give the alkylated product 98 in 40% yield. The infrared spectrum of this material showed signals at 2121 cm\(^{-1}\) and 3312 cm\(^{-1}\) attributable to the carbon-carbon and carbon-hydrogen stretching frequencies, respectively, of the terminal acetylene function. The \(^1\text{H} nmr\) spectrum showed a 1-proton triplet \((J = 2.8 \text{ Hz})\) at \(\delta 1.94\) (acetylenic H) and a 2-proton doublet \((J = 2.8 \text{ Hz})\) at \(\delta 3.31\) (allylic-propargylic methylene). The proposed double bond geometry was confirmed by nOe difference experiments. Thus, irradiation of the signal at \(\delta 3.31\) (allylic-propargylic methylene) caused signal enhancement at \(\delta 4.49\) \((-\text{SiOCH}_2-)\) and vice versa.

Although the (allenoate) intermediate formed by reaction of the acetylenic ester 70 with the higher order cuprate reagent 61 may be trapped using highly reactive alkylating agents, it was found that none of the desired products were obtained when less reactive alkylating agents (e.g. 1-iodobutane or 4-bromo-1-butene) were used. In these cases, glc analyses of the crude reaction products showed the presence of compounds 72 and 94, which result from protonation of the reaction intermediate.

Although these conjugate addition/alkylation reactions appear to be of limited scope, they do constitute the first successful stereoselective intermolecular alkylation reactions of intermediates formed in the reactions of stannylcuprates with acetylenic esters. It appears from the success of these trapping reactions that the allenoate intermediates 66\(\text{C}\) are more reactive than both the allenoate intermediates 66\(\text{B}\) and the alkenylcopper intermediates 65\(\text{A}\) which are obtained from the reactions of the lower order reagents 45 and 26, respectively, with acetylenic esters.
As mentioned earlier, the intermediates formed by reaction of the lower order reagents 26 or 45 with acetylenic esters cannot be trapped by electrophiles (other than proton) in an intermolecular sense. On the other hand, intramolecular alkylations of such intermediates are feasible. For example, reaction of methyl 6-ido-2-hexynoate with the phenylthiocuprate reagent 45 at -48 °C, followed by addition of HMPA and warming of the reaction mixture to room temperature, gives the cyclic alkenylstannane 99 in 78% yield (equation 10).

\[
\text{\חת \hat{\mathbf{CO}}_2 \text{Me}} \quad \begin{array}{c}
\text{i} \quad \text{Me}_3\text{SnCuSPhLi (45)} \\
\text{THF, -48°C, 4 h}
\end{array} \quad \text{Me}_3\text{Sn} \quad \begin{array}{c}
\text{\hat{\mathbf{CO}}_2 \text{Me}}
\end{array} \\
\begin{array}{c}
\text{ii} \quad \text{HMPA,}
\end{array} \quad \text{room temp, 2 h}
\]

(10) 99 78%

In order to test our new higher order reagent 61, a similar reaction was performed using ethyl 6-ido-2-hexynoate (101), which was prepared from commercially available 5-chloro-1-pentyne in two steps (Scheme 16). It was found that the higher order cuprate reagent reacted smoothly with this acetylenic ester in the absence of HMPA to give the cyclized compound 102 in 62% yield (Scheme 16).

\[
\text{\חת \hat{\mathbf{CO}}_2 \text{Et}} \quad \begin{array}{c}
\text{i} \quad \text{MeLi, THF}
\end{array} \quad \text{\hat{\mathbf{CO}}_2 \text{Et}} \quad \begin{array}{c}
\text{NaI, acetone}
\end{array} \quad \text{\hat{\mathbf{CO}}_2 \text{Et}} \\
\text{Cl} \quad \begin{array}{c}
\text{ii} \quad \text{EtOCOCl}
\end{array} \quad \text{Cl} \quad \begin{array}{c}
\text{i} \quad \text{Me}_3\text{Sn(2-Th)CuCNLi_2 (61)}
\end{array} \quad \\
\text{THF, -78°C, 2 h; -48°C, 1 h}
\]

100 88% 101 86% 102 62%

Scheme 16
3.4. Conclusions

It has been shown that the higher order cuprate formulated as 61 is an easily prepared, synthetically useful reagent. It reacts efficiently with α,β-unsaturated ketones, esters, and aldehydes, transferring the trimethylstannyl group to these substrates in a conjugate sense. The cuprate also reacts cleanly with α,β-acetylenic esters 43. In particular, 61 reacts with substrates possessing an ether function at the γ position (e.g. 70 and 73) to give the γ-alkoxy-(Z)-β-trimethylstannyl α,β-unsaturated esters (72 and 75) stereoselectively and in reasonable yields. Furthermore, the intermediates formed in the reaction of the higher order cuprate 61 with the acetylenic ester 70 may be trapped by highly reactive alkylating agents to give the corresponding (Z)-trisubstituted alkenylstannanes (96, 97 and 98) stereoselectively and in reasonable yields.

This brief study of the chemistry of the higher order stannylcuprate reagent 61 has shown that, like alkyl higher order cuprate reagents, it is generally more reactive towards organic substrates than its lower order analogues 26 and 45. Reagent 61 can be used effectively for the preparation of a variety of organotin compounds and is a useful alternative to reagents 26 and 45.

IV. Experimental

4.1. General

Melting points (uncorrected) were determined using a Fisher-Johns melting point apparatus. Distillation temperatures (uncorrected) quoted for the compounds described in the experimental procedures were recorded as air bath temperatures required for bulb-to-bulb (Kugelrohr) distillations. Infrared (ir) spectra were obtained either as liquid films (NaCl plate) or as KBr disks, using a Perkin Elmer model 1710 spectrophotometer (internal
The IR signals quoted for each compound in the experimental procedures are the characteristic absorptions for the compound and/or the most prominent signals. Proton nuclear magnetic resonance (\(^1\)H nmr) spectra were recorded on deuteriochloroform solutions (unless otherwise stated), using a Bruker WH-400 or a Varian XL-300 spectrometer. Carbon nuclear magnetic resonance (\(^{13}\)C nmr) and phosphorus nuclear magnetic resonance (\(^{31}\)P nmr) were recorded on deuteriochloroform solutions (unless otherwise stated), using a Bruker AM-200 or a Varian XL-300 spectrometer. Signal positions for \(^1\)H nmr spectroscopy are given in \(\delta\) units and were measured relative to the chloroform signal (\(\delta 7.25\))\(^{71a}\) (or the pentadeuteriobenzene signal \(\delta 7.20\)).\(^{71a}\) The multiplicity, number of protons, assignments (where possible) and coupling constants are indicated in parenthesis. Tin-hydrogen coupling constants (\(J_{Sn-H}\)) are given as an average of the \(^{117}\)Sn and \(^{119}\)Sn values. In some cases, the proton assignments were supported by decoupling, noe difference, and/or COSY experiments. These experiments were carried out using a Bruker WH-400 spectrometer. Variable temperature studies were carried out on hexadeuteriobenzene solutions using a Varian XL-300 spectrometer. For \(^{13}\)C nmr spectroscopy \(\delta\) was measured relative to the deuteriochloroform signal (\(\delta 77.0\))\(^{71b}\) (or hexadeuteriobenzene \(\delta 128.0\)).\(^{71b}\) Mass spectra were recorded with AEI MS9 (low resolution) or Kratos MS50 (low and high resolution) mass spectrometers. Chemical ionization mass spectra were recorded with a Delsi-Nermag R-10-10 quadrupole mass spectrometer. Molecular mass determinations (high resolution mass spectrometry) in cases of compounds with trimethylstannyl groups were based on \(^{120}\)Sn and were made on the (M\(^+\)-Me) peak.\(^{72}\) Elemental analyses were provided by the UBC microanalytical laboratory.

Gas-liquid chromatography (glc) analyses were performed on Hewlett-Packard models 5880 or 5890 capillary gas chromatographs, using 25 m x 0.21 mm fused silica columns coated with cross-linked SE-54, and equipped with flame ionization detectors.

Thin layer chromatography (tlc) analyses were done on commercial aluminium backed silica gel plates (E. Merck, Type 5554). Visualization was accomplished with ultraviolet
light, iodine, or staining with 5% ammonium molybdate - 10% aqueous sulphuric acid, or phospomolybdic acid. Flash chromatography\textsuperscript{73} was done on 230-400 mesh silica gel. The approximate amounts of silica gel used for chromatography are quoted in each experimental procedure.

All compounds that were subjected to high resolution mass spectrometry and elemental analysis were homogeneous by tlc and glc analyses.

Unless otherwise stated, all reactions were carried out under an atmosphere of dry argon using glassware that had been thoroughly flame dried. Glass syringes and metal syringe needles used for solvents and reagents were oven dried (approx. 140°C). Plastic syringes were dried at room temperature under reduced pressure (0.5 Torr).

Cooling baths used for various reactions were obtained as follows: ice-acetone (-10°C), 27 g CaCl2/100 mL H2O - CO2 (-20°C), 46 g CaCl2/100 mL H2O - CO2 (-48°C), acetone-CO2 (-78°C).

4.2. Solvents and reagents

Solvents and reagents were purified and dried using well known procedures.\textsuperscript{74} Diethyl ether and THF were distilled from sodium benzophenone ketyl. Methylene chloride, triethylamine, diisopropylamine, N,N-diisopropylethylamine, HMPA, DMF, hexane and benzene were distilled from calcium hydride. N,N-dimethylacetamide was distilled from BaO and stored over 4Å molecular sieves. Petroleum ether refers to the fraction boiling between 30-60°C. Acetic acid was fractionally distilled using a Vigreux column. Acetic anhydride was stirred over calcium carbide for several days and then was distilled.

Hexamethylditin was obtained from Organometallics Inc., while tetrakis(triphenylphosphine)palladium(0) was obtained from either Aldrich Chemical Co.,
Inc., or from Morton Thiokol, Inc. (Alfa Products). These materials were used without further purification.

Solutions of methyllithium (lithium bromide complex (this was generally used), or low halide) in diethyl ether, \( n \)-butyllithium in hexane, and diisobutylaluminium hydride in hexane were obtained from Aldrich Chemical Co., Inc. and the former two reagents were standardized using diphenylacetic acid as primary standard.\(^{75}\)

Copper(I) cyanide was available from Aldrich Chemical Co., Inc., and was dried under reduced pressure (room temperature, 0.5 Torr). Copper(I) bromide-dimethyl sulphide complex was prepared by the method of House,\(^{76}\) after washing commercial copper(I) bromide with methanol.\(^{77}\) Copper(II) acetylacetonate (commercial) was recrystallized from absolute ethanol. Rhodium(II) acetate was prepared according to the method of Wilkinson and coworkers.\(^{78}\) Tetra \( n \)-propylammonium perruthenate was available from the Aldrich Chemical Co., Inc., and was used without further purification.

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.

A solution of lithium diisopropylamide in THF (0.3 M) was prepared by the addition of a solution of \( n \)-butyllithium in hexane to a solution of diisopropylamine (1 equiv.) in dry THF at \(-78^\circ\text{C}\). The resulting colourless solution was stirred at \(-78^\circ\text{C}\) for 15 min and at 0°C for 10 min before being used.

Activated 4Å molecular sieves were prepared by flame drying powdered 4Å molecular sieves under vacuum (approx 0.5 Torr) for several minutes.
4.3. **Experimental procedures**

**Preparation of Me₃SnCu(2-Th)(CN)Li₂ (61).**

To a cold (-20°C), stirred solution of (Me₃Sn)₂ (164 mg, 0.5 mmol) in 10 mL of dry THF (argon atmosphere) was added, successively, thiophene (42 mg, 0.5 mmol) and a solution of MeLi (1.0 mmol) in Et₂O. After the pale yellow solution had been stirred at -20°C for 50 min, it was cooled to -78°C and CuCN (45 mg, 0.5 mmol) was added. The resulting suspension was stirred for 5 min at -78°C and for 10 min at -48°C to provide a bright yellow solution of the cuprate reagent 61. The solution was cooled to -78°C and used immediately.

**General Procedure A. Reaction of the cuprate reagent 61 with α,β-unsaturated aldehydes, ketones and esters.**

To a cold (-78°C), stirred solution of the cuprate reagent 61 (0.5 mmol) in 10 mL of dry THF (argon atmosphere) was added the α,β-unsaturated carbonyl compound (0.33 mmol). After the solution had been stirred at -78°C (5 min -1 h) and at -20°C (1-4 h), it was treated with saturated aqueous NH₄Cl-NH₄OH (pH 8) (10 mL) and Et₂O (10 mL). The vigorously stirred mixture was exposed to air and allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with Et₂O (3x10 mL). The combined organic extracts were dried (MgSO₄) and concentrated. The resultant oils were purified by flash chromatography, followed by distillation.
Preparation of 3-methyl-3-trimethylstannylcyclohexanone (87).

Following general procedure A, 37 mg (0.33 mmol) of 3-methyl-2-cyclohexen-1-one was allowed to react with the cuprate reagent 61 (0.5 mmol) for 5 min at -78°C and 4 h at -20°C. Flash chromatography (1:4 Et2O - petroleum ether; 24 g of silica gel) of the crude product, followed by distillation of the oil thus obtained (90-100°C/2.0 Torr), gave 83 mg (90%) of the ketone 87, a colourless oil which exhibited ir (neat): 1713, 1452, 1224, 768 cm⁻¹; ¹H nmr (300 MHz) δ: 0.06 (s, 9H, -SnMe₃, 2J Sn-H = 50 Hz), 1.20 (s, 3H, -Me, 3J Sn-H = 60 Hz), 1.55-2.60 (m, 10H). Exact Mass calcd. for C₉H₁₇OSn (M⁺-Me) : 261.0301; found: 261.0306.

Preparation of 3,5,5-trimethyl-3-trimethylstannylcyclohexanone (83).
Following general procedure A, 46 mg (0.33 mmol) of isophorone (3,5,5-trimethyl-2-cyclohexen-1-one) was allowed to react with the cuprate reagent 61 for 5 min at -78°C and 4 h at -20°C. Flash chromatography (1:4 Et2O - petroleum ether; 24 g of silica gel) of the crude product, followed by distillation of the oil thus obtained (90-95°C/2.0 Torr), gave 88 mg (87%) of the ketone 83, a colourless oil that was spectrally identical with the same substance prepared previously.42

Preparation of the ketones 84 and 85.

Following general procedure A, 51 mg (0.33 mmol) of pulegone was allowed to react with the cuprate reagent 61 for 5 min at -78°C and 2 h at -20°C. Flash chromatography (3:97 Et2O - petroleum ether; 24 g of silica gel) of the crude product, followed by distillation of the oils thus obtained (90-100°C/2.0 Torr), gave 74 mg (69%) of the ketone 85 and 21 mg (20%) of the ketone 84. The trans isomer 85 was a colourless oil which exhibited ir (neat): 1705, 1457, 764 cm⁻¹; ¹H nmr (300 MHz) δ: 0.00 (s, 9H, -SnMe₃), ¹J Sn-H = 48 Hz, 1.00 (d, 3H, CHMe, J = 6 Hz), 1.03, 1.07 (s, s, 3H each, CMes, ³J Sn-H = 65 Hz for each signal), 1.32 (br t, 2H), 1.70 - 2.05 (m, 3H), 2.15 (m, 2H), 2.30 (m, 1H); ¹³C nmr
Exact Mass calculated for C_{12}H_{23}O_{Sn} (M^+-Me): 303.0771; found: 303.0763.

The cis isomer 84 was a colourless oil which exhibited \textit{ir} (neat): 1704, 1467, 763 cm\(^{-1}\); \textit{\textsuperscript{1}H} nmr (300 MHz) \(\delta\): 0.00 (s, 9H, -SnMe\(_3\), \(\text{\(\text{\textsuperscript{2}J} \text{Sn-H} = 49\text{ Hz}\))}, 0.90 (d, 3H, CHMe, \(J = 6\text{ Hz}\)), 1.03, 1.06 (s, s 3H each, CMe\(_2\), \(\text{\(\text{\textsuperscript{3}J} \text{Sn-H} = 65\text{ Hz for each signal}\))}, 1.56 - 1.65 (m, 2H), 1.82 - 2.23 (m, 4H), 2.4 - 2.55 (m, 2H). Exact Mass calculated for C_{12}H_{23}O_{Sn} (M^+-Me): 303.0771; found: 303.0765. Treatment of pure 84 with MeONa in MeOH (room temperature, overnight), resulted in an 88:12 mixture of 85 and 84 respectively.

\textbf{Preparation of the ketone 86.}

\begin{center}
\includegraphics[width=0.2\textwidth]{86.png}
\end{center}

Following general procedure A, 55 mg (0.33 mmol) of the bicyclic enone 82 was allowed to react with the cuprate reagent 61 for 10 min at -78°C and 3 h at -20°C. Flash chromatography (1:4 Et\(_2\)O - petroleum ether; 24 g of silica gel) of the crude product, followed by distillation of the oil thus obtained (150-160°C/2.0 Torr), gave 77 mg (70%) of the ketone 86, a colourless oil which exhibited \textit{ir} (neat): 1708, 1158, 765 cm\(^{-1}\); \textit{\textsuperscript{1}H} nmr (300 MHz) \(\delta\): 0.08 (s, 9H, -SnMe\(_3\), \(\text{\(\text{\textsuperscript{2}J} \text{Sn-H} = 48\text{ Hz}\))}, 1.04 (s, 3H, Me), 1.16 - 1.87 (m, 10H), 2.05 - 2.75 (m, 4H); \textit{\textsuperscript{13}C} nmr (75.4 MHz) \(\delta\): -5.94, 15.09, 21.17, 24.66, 33.23,
Preparation of the ester 90.

Following general procedure A, 42 mg of the \(\alpha,\beta\)-unsaturated ester 89 (0.33 mmol) was allowed to react with the cuprate reagent 61 at -78°C for 1 h and -20°C for 30 min. Flash chromatography (3:97 EtO - petroleum ether; 24 g of silica gel) of the crude product, followed by distillation of the oil thus obtained (120-125°C/2.0 Torr), gave 76 mg (91%) of the ester 90, a colourless oil which exhibited IR (neat): 1729, 1186, 1163, 766 cm\(^{-1}\); \(^1\)H nmr (300 MHz) \(\delta:\) 0.04 (s, 9H, SnMe\(^3\)), \(^2\)J \(\text{Sn-H} = 49\) Hz), 1.22 (t, 3H, -OCH\(_2\)CH\(_3\), \(^3\)J \(\text{Sn-H} = 72\) Hz), 1.30 (m, 5H), 1.60 (m, 3H), 1.85 (m, 2H), 2.45 (s, 2H, -CH\(_2\)CO\(_2\)Et, \(^3\)J \(\text{Sn-H} = 72\) Hz), 4.07 (q, 2H, -OCH\(_2\)CH\(_3\), \(^3\)J \(\text{Sn-H} = 8\) Hz); \(^1\)C nmr (75.4 MHz) \(\delta:\) -8.62, 14.27, 23.69, 26.35, 32.41, 36.67, 45.27, 60.13, 173.33. Exact Mass calcd. for C\(_{12}\)H\(_{23}\)O\(_2\)Sn (M\(^+\)-Me): 319.0720; found: 319.0718.
Preparation of 3-trimethylstannylhexanal (91).

Following general procedure A, 33 mg (0.33 mmol) of (E)-2-hexenal was allowed to react with the cuprate reagent 61 for 1 h at -78°C and 1 h at -20°C. Flash chromatography (1:4 Et2O - petroleum ether; 24 g of silica gel) of the crude product, followed by distillation of the oil thus obtained (50-55°C/2.0 Torr), gave 54 mg (61%) of the aldehyde 91, a colourless oil which exhibited ir (neat): 2718, 1723, 1186, 764 cm⁻¹; ¹H nmr (300 MHz) δ: 0.04 (s, 9H, -SnMe₃, 2J Sn-H = 51 Hz), 0.87 (t, 3H, -CH₂CH₃, J = 8 Hz), 1.38 - 1.70 (m, 5H), 2.65 (dd, 2H, -CH₂CHO, J = 6 Hz, J = 1.5 Hz, 3J Sn-H = 62 Hz), 9.74 (t, 1H, -CHO, J = 1.5 Hz); ¹³C nmr (75.4 MHz) δ: -9.86, 14.12, 19.42, 23.14, 35.63, 47.94, 203.34. Exact Mass calcd. for C₈H₁₇OSn (M⁺-Me): 249.0301; found: 249.0304.

Preparation of (Z)-3-trimethylstannyl-6-nonenal (92).
Following general procedure A, 46 mg (0.33 mmol) of \((2E,6Z)-2,6\)-nonadienal was allowed to react with the cuprate reagent 61 for 1 h at -78°C and 1 h at -20°C. Flash chromatography (1:4 Et\(_2\)O - petroleum ether; 24 g of silica gel) of the crude product, followed by distillation of the oil thus obtained (75-80°C/2.0 Torr), gave 65 mg (64%) of the aldehyde 92, a colourless oil which exhibited ir (neat) : 2715, 1724, 1187, 767 cm\(^{-1}\); \(^1\)H nmr (300 MHz) \(\delta\) : 0.05 (s, 9H, -SnMe\(_3\)), \(2J\) Sn-H = 50 Hz), 0.93 (t, 3H, -CH\(_2\)CH\(_3\)), \(J = 7\) Hz), 1.4-1.75 (m, 3H), 1.85-2.15 (m, 4H, both allylic CH\(_2\)), 2.68 (dd, 2H, -CH\(_2\)CHO, \(J = 6.5\) Hz, \(J = 1.3\) Hz), \(3J\) Sn-H = 62 Hz), 5.33 (m, 2H, olefinic H), 9.75 (t, 1H, -CHO, \(J = 1.3\) Hz); \(^{13}\)C nmr (75.4 MHz) \(\delta\) : -9.82, 14.36, 19.18, 20.58, 27.42, 33.39, 47.83, 128.28, 132.06, 203.11. Exact Mass. calcd. for C\(_{11}\)H\(_{21}\)OSn (M\(^+\)-Me): 289.0614 ; found: 289.0617.

Preparation of the aldehyde 93.

Following general procedure A, 41 mg (0.33 mmol) of the \(\alpha,\beta\)-unsaturated aldehyde 88 was allowed to react with the cuprate reagent 61 for 1 h at -78°C and 1 h at -20°C. Flash chromatography of the crude product (1:4 Et\(_2\)O - petroleum ether ; 24 g of silica gel), followed by distillation of the oil thus obtained (120-125°C/2.0 Torr), gave 60 mg (62%) of the aldehyde 93, a colourless oil which exhibited ir (neat) : 2722, 1720, 1450, 896,
767 cm\(^{-1}\); \(\text{\(^1\)H nmr (300 MHz) \(\delta\): 0.05 (s, 9H, }\text{-SnMe}_3\text{, }_2^J \text{Sn-H } = 49 \text{ Hz), 1.15-1.44 (m, 5H), 1.76-2.04 (m, 2H), 2.60 (d, 2H, }\text{-CH}_2\text{CHO, }_J = 1.6 \text{ Hz, }_3^J \text{Sn-H } = 67 \text{ Hz), 9.77 (t, 1H, }\text{-CHO, }_J = 1.6 \text{ Hz); }\text{\(^{13}\)C nmr (75.4 MHz)} \(\delta\): -8.66, 23.95, 26.23, 31.40, 36.85, 55.74, 203.05. \text{Exact Mass calcd. for C}_{10}\text{H}_{19}\text{OSn (M}^+\text{-Me): 275.0458; found: 275.0457.}

**General Procedure B. Reaction of the cuprate reagent 61 with }\alpha,\beta\text{-acytylenic esters.**}

To a cold (-78°C), stirred solution of the cuprate reagent 61 (0.5 mmol) in 10 mL of dry THF (argon atmosphere) was added a solution of the \(\alpha,\beta\text{-acytylenic ester (0.38 mmol) in 0.5 mL of dry THF. After the mixture had been stirred for 2 h at -78°C, saturated aqueous NH}_4\text{Cl-NH}_4\text{OH (pH 8) (10 mL) was added and the vigorously stirred mixture was exposed to air and allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with Et}_2\text{O (3 x 10 mL). The combined organic extracts were dried (MgSO}_4\text{) and concentrated. The crude product thus obtained was purified by flash chromatography, followed by distillation.**

**Preparation of ethyl (Z)-4-\text{\textit{tert}-butyldimethylsilyloxy-3-trimethylstannyl-2-butenoate (72).**}

![Diagram of compounds 72 and 94]
Following general procedure B, 93 mg (0.38 mmol) of the $\alpha,\beta$-acytylenic ester 70 was allowed to react with the cuprate reagent 61. Glc analysis of the crude product showed that it consisted of a 95:5 mixture of compounds 72 and 94, respectively. Flash chromatography (3:97 Et$_2$O - petroleum ether; 30 g of silica gel) of the crude mixture, followed by distillation of the oil thus obtained (110-120°C/2.0 Torr), gave 102 mg (65%) of the ester 72, a colourless oil which exhibited spectra identical with those of the same substance reported previously.  

Preparation of ethyl (Z)-4-(methoxymethoxy)-3-trimethylstanny-2-butenoate (75).

Following general procedure B, 65 mg (0.38 mmol) of the $\alpha,\beta$-acytylenic ester 73 was allowed to react with the cuprate reagent 61. Glc analysis of the crude product showed that it consisted of a 9:1 mixture of compounds 75 and 95, respectively. Flash chromatography (3:97 Et$_2$O - petroleum ether; 30 g of silica gel) of the crude mixture, followed by distillation of the oil thus obtained (130-135°C/2.0 Torr), gave 72 mg (55%) of the ester 75, a colourless oil which exhibited ir (neat): 1703, 1608, 1198, 1040, 775 cm$^{-1}$; $^1$H nmr (300 MHz) δ: 0.2 (s, 9H, -SnMe$_3$, $^2$J$_{Sn-H}$ = 56 Hz), 1.29 (t, 3H, -OCH$_2$CH$_3$, $J = 8$ Hz), 3.40 (s, 3H, -OMe), 4.22 (q, 2H, -OCH$_2$CH$_3$, $J = 8$ Hz), 4.39 (d, 2H, -OCH$_2$-, $J = 3$ Hz, $^3$J$_{Sn-H}$ = 30 Hz), 4.69 (s, 2H, -OCH$_2$O-), 6.69 (t, 1H, vinyl H, $J = 3$ Hz,
$^3J_{\text{Sn-H}} = 108$ Hz.  Exact Mass calcd. for $\text{C}_{10}\text{H}_{19}\text{O}_4\text{Sn}$ (M$^+$-Me): 323.0305; found: 323.0298.

**General Procedure C.** Reaction of the cuprate reagent 61 with the $\alpha,\beta$-acytylenic ester 70, and trapping of the reaction intermediate with alkylating agents.

To a cold (-78°C), stirred solution of the cuprate reagent 61 (0.5 mmol) in 10 mL of dry THF (argon atmosphere) was slowly added a solution of the $\alpha,\beta$-acytylenic ester 70 (81 mg, 0.33 mmol) in 0.5 mL of dry THF. After the mixture had been stirred at -78°C for 1 h and at -20°C for 30 min, HMPA (3.3 mmol) and the appropriate alkylating agent (excess) were added successively. The solution was stirred at -20°C for 30 min and at room temperature (0-1 h). Saturated aqueous NH$_4$Cl-NH$_4$OH (pH 8) (10 mL) and Et$_2$O (10 mL) were added and the vigorously stirred mixture was exposed to air. The phases were separated and the deep blue aqueous phase was extracted with Et$_2$O (4 x 10 mL). The combined organic extracts were washed with saturated aqueous CuSO$_4$ (3 x 10 mL) and brine (2 x 10 mL) and were then dried (MgSO$_4$) and concentrated. The crude product thus obtained was purified by chromatography, followed by distillation.

**Preparation of ethyl (Z)-4-tert-butyldimethylsiloxy-2-methyl-3-trimethylstannyl-2-butenoate (96).**

![Chemical Structure](image-url)
Following general procedure C, the $\alpha,\beta$-acetylenic ester 70 (81 mg, 0.33 mmol) was allowed to react with the cuprate reagent 61. After addition of HMPA (3.3 mmol) and MeI (8 mmol) the mixture was stirred at -20°C for 30 min and at room temperature for 1 h. Flash chromatography (3:97 Et$_2$O - petroleum ether; 30 g of silica gel) of the crude product, followed by distillation of the oil thus obtained (130-135°C/2.0 Torr), gave 91 mg (65%) of the ester 96, a colourless oil which exhibited ir (neat): 1702, 1599, 1176, 838, 776 cm$^{-1}$; $^1$H nmr (300 MHz) $\delta$: 0.04 (s, 6H, -SiMe$_2$), 0.11 (s, 9H, -SnMe$_3$, $^2$J Sn-H = 55 Hz), 0.87 (s, 9H, -SiBu$_3$), 1.28 (t, 3H, -OCH$_2$CH$_3$, $^3$J $\mathrm{Sn-H} = 7.1$ Hz), 1.93 (s, 3H, vinyl Me, $^4$J Sn-H = 7.1 Hz), 4.17 (q, 2H, -OCH$_2$CH$_3$, $^3$JSn-H = 48 Hz). In nOe difference experiments, irradiation at $\delta$ 1.93 (vinyl Me) caused signal enhancement at $\delta$ 4.40 (-SiOCH$_2$-), while irradiation at $\delta$ 4.40 (-SiOCH$_2$-) caused signal enhancement at $\delta$ 1.93 (vinyl Me) and $\delta$ 0.11 (-SnMe$_3$); $^{13}$C nmr (75.4 MHz) $\delta$: -5.99, -5.19, 14.26, 14.60, 18.28, 25.95, 61.04, 64.26, 134.53, 163.06, 169.47. Exact Mass calcd. for C$_{15}$H$_{31}$O$_3$SiSn (M$^+$-Me): 407.1072; found: 407.1064.

Preparation of ethyl (Z-4-tert-butylidimethylsiloxy-2-(2-propenyl)-3-trimethylstannyl-2-butenoate (97).
Following general procedure C, the \( \alpha,\beta \)-acetylenic ester 70 (81 mg, 0.33 mmol) was allowed to react with the cuprate reagent 61. After addition of HMPA (3.3 mmol) and 3-iodopropene (5.5 mmol) the mixture was stirred at -20°C for 30 min. Flash chromatography (3:97 Et\(_2\)O - petroleum ether; 30 g of silica gel) of the crude product, followed by distillation of the oil thus obtained (115-120°C/2.0 Torr), gave 91 mg (60%) of the ester 97, a colourless oil which exhibited ir (neat): 3080, 1703, 1639, 1154, 1073, 776 cm\(^{-1}\); \(^1\)H nmr (300 MHz) \( \delta \): 0.03 (s, 6H, -SiMe\(^3\)), 0.13 (s, 9H, -SnMe\(^3\)), 2\(^J\) Sn-H = 54 Hz), 0.86 (s, 9H, -SiBu\(^t\)), 1.26 (t, 3H, -OCH\(_2\)CH\(_3\), \( J = 8 \) Hz), 3.14 (m, 2H, bis-allylic CH\(_2\)), 4.16 (q, 2H, -OCH\(_2\)CH\(_3\), \( J = 8 \) Hz), 4.39 (s, 2H, -SiOCH\(_2\)), 3\(^J\) Sn-H = 49 Hz), 4.93 (m, 1H), 4.98 (m, 1H), 5.77 (m, 1H, HA). In nOe difference experiments, irradiation of the signal at \( \delta \) 3.14 (bis-allylic CH\(_2\)) caused signal enhancement at \( \delta \) 4.39 (-SiOCH\(_2\)) and \( \delta \) 5.77 (HA), while irradiation of the signal at \( \delta \) 4.39 (-SiOCH\(_2\)) caused signal enhancement at \( \delta \) 3.14 (bis-allylic CH\(_2\)), and \( \delta \) 0.13 (-SnMe\(^3\)); \(^{13}\)C nmr (75.4 MHz) \( \delta \): -5.93, -5.21, 14.21, 18.27, 25.94, 32.91, 61.04, 64.11, 115.13, 135.72, 136.12, 164.93, 168.92. Exact Mass calcd. for C\(_{17}\)H\(_{33}\)O\(_3\)SiSn (M\(^+\)-Me): 433.1221; found: 433.1216.

Preparation of ethyl (Z)-4-\( tert \)-butyldimethylsiloxy-2-(2-propynyl)-3-trimethylstannyl-2-hexenoate (98).
Following a procedure similar to general procedure C, the \( \alpha,\beta \)-acetylenic ester 70 (81 mg, 0.33 mmol) was allowed to react with the cuprate reagent 61 for 2 h at \(-78^\circ \text{C}\). HMPA (3.3 mmol) and 3-bromopropyne (1.67 mmol) were added successively and the mixture was stirred at \(-78^\circ \text{C}\) for 1 h and at \(-20^\circ \text{C}\) for 1 h. The crude product consisted of a 3:1 mixture of compound 98 (glc analysis) and the corresponding protonation products 72 and 94. Flash chromatography (3:97 Et\(_2\)O - petroleum ether; 30 g of silica gel), followed by distillation of the oil thus obtained (140-145°C/2.0 Torr), gave 59 mg (40%) of compound 98, a colourless oil which exhibited ir (neat): 3312, 2121, 1704, 1599, 1206, 1043, 839, 779 cm\(^{-1}\); \(^{1}\)H nmr (300 MHz) \( \delta \): 0.06 (s, 6H, \(-\text{SiMe}_2\)), 0.15 (s, 9H, \(-\text{SnMe}_3\), \( ^{2}J_{\text{Sn-H}} = 56 \text{ Hz}\)), 0.87 (s, 9H, \(-\text{SiBu}_3\)), 1.30 (t, 3H, \(-\text{OCH}_2\text{CH}_3\), \( J = 7 \text{ Hz}\)), 1.94 (t, 1H, acetylenic H, \( J = 2.8 \text{ Hz}\)), 3.31 (d, 2H, allylic-propargylic CH\(_2\), \( J = 2.8 \text{ Hz}\)), 4.22 (q, 2H, \(-\text{OCH}_2\text{CH}_3\), \( J = 7 \text{ Hz}\)), 4.49 (s, 2H, \(-\text{SiOCH}_2\)-, \( ^{3}J_{\text{Sn-H}} = 44 \text{ Hz}\)). In nOe difference experiments, irradiation of the signal at \( \delta 4.49 \) (\(-\text{SiOCH}_2\)-) caused signal enhancement at \( \delta 3.31 \) (allylic-propargylic CH\(_2\)) and \( \delta 0.15 \) (\(-\text{SnMe}_3\)), while irradiation of the signal at \( \delta 3.31 \) (allylic-propargylic CH\(_2\)) caused signal enhancement at \( \delta 4.49 \) (\(-\text{SiOCH}_2\)-). Exact Mass calcd. for C\(_{17}\)H\(_{31}\)O\(_3\)SiSn (M\(^+\)-Me): 431.1064; found: 431.1059.

**Preparation of ethyl 6-chloro-2-hexynoate (100).**
To a cold (-78°C), stirred solution of 5-chloro-1-pentyne (2 g, 19.5 mmol) in 100 mL of dry THF (argon atmosphere) was added a solution of MeLi (19.5 mmol) in Et₂O. After the mixture had been stirred at -78°C for 10 min and at -20°C for 45 min, EtOCOCl (3.15 g, 29 mmol) was added and stirring was continued at -20°C for 1 h and at room temperature for 1 h. Saturated aqueous NaHCO₃ (30 mL) and Et₂O (50 mL) were added and the phases were separated. The aqueous phase was extracted with Et₂O (2 x 20 mL). The combined organic extracts were dried (MgSO₄) and concentrated. Distillation (85-90°C/2.0 Torr) of the crude product gave 3.0 g (88%) of the ester 100, a colourless oil which exhibited ir (neat); 2243, 1717, 1447, 1084 cm⁻¹; ¹H nmr (300 MHz) δ: 1.26 (t, 3H, -OCH₂CH₃, J = 8 Hz), 2.00 (quintet, 2H, -CH₂CH₂CH₂, J = 7 Hz), 2.52 (t, 2H, -CH₂CH₂CH₂Cl, J = 7 Hz), 3.64 (t, 2H, -CH₂CH₂CH₂Cl, J = 7 Hz), 4.18 (q, 2H, -OCH₂CH₃, J = 8 Hz). Exact Mass calcd. for C₈H₁₇ClO₂ (M⁺): 174.0448; found: 174.0456.

Preparation of ethyl 6-iodo-2-hexynoate (101).

\[
\begin{align*}
\text{I} & \quad \text{CO}_2\text{Et} \\
\end{align*}
\]

To a solution of NaI (17.2 g, 115 mmol) in dry acetone (150 mL) (argon atmosphere) was added a solution of the chloro ester 100 (2 g, 11.5 mmol) in 10 ml of dry acetone, and the mixture was refluxed overnight. Most of the solvent was removed and water (50 mL) and Et₂O (50 mL) were added to the residue. The phases were separated and the aqueous phase was extracted with Et₂O (2 x 20 mL). The combined extracts were dried (MgSO₄) and
concentrated. Distillation (100-110°C/2.0 Torr) of the crude product gave 2.62 g (86%) of the iodo ester 101, a colourless oil which exhibited ir (neat): 2237, 1703, 1273, 1078 cm⁻¹; \(^1H\) nmr (300 MHz) \(\delta\): 1.26 (t, 3H, \(-OCH_2CH_3, J = 8\) Hz), 2.02 (quintet, 2H, \(-CH_2CH_2CH_2I, J = 8\) Hz), 2.45 (t, 2H, \(-CH_2CH_2CH_2I, J = 8\) Hz), 3.24 (t, 2H, \(-CH_2CH_2CH_2I, J = 8\) Hz), 4.17 (q, 2H, \(-OCH_2CH_3, J = 8\) Hz). Exact Mass calcd. for \(C_{8}H_{11}IO_2(M^+)\): 265.9804; found: 265.9815.

**Preparation of ethyl 2-trimethylstannyl-1-cyclopentenecarboxylate (102).**

Following a procedure very similar to general procedure B, the iodo ester 101 (102 mg, 0.38 mmol) was allowed to react with the cuprate reagent 61 for 2 h at -78°C and 1 h at -48°C. Flash chromatography (3:97 Et₂O - petroleum ether; 30 g of silica gel) of the crude product, followed by distillation of the oil thus obtained (110-115°C/2.0 Torr), gave 73 mg (62%) of the ester 102, a colourless oil which exhibited ir (neat): 1699, 1592, 1187, 768 cm⁻¹; \(^1H\) nmr (400 MHz) \(\delta\): 0.17 (s, 9H, \(-SnMe_3, 2J Sn-H = 50\) Hz), 1.27 (t, 3H, \(-OCH_2CH_3, J = 6\) Hz), 1.90 (m, 2H, \(-CH_2CH_2CH_2\)), 2.49 (br t, 4H, both allylic CH₂), 4.18 (q, 2H, \(-OCH_2CH_3, J = 6\) Hz). Exact Mass calcd. for \(C_{10}H_{17}O_2Sn (M^+-Me)\): 289.0250; found: 289.0252.
PART 2. The preparation of (Z)-β-trimethylstannyl α,β-unsaturated aldehydes and ketones via the Pd(0)-catalyzed reaction of hexamethylditin with α,β-acetylenic aldehydes and ketones. The preparation and synthetic uses of (Z)-4-(trimethylstannyl)-1,3-butadienes. 

I. Introduction

Recently, it was shown37 that α,β-acetylenic esters of general structure 43 react with equimolar amounts of hexamethylditin (THF, room temperature or reflux) in the presence of a Pd(0) catalyst to give alkyl (Z)-2,3-bis(trimethylstannyl)-2-alkenoates of general structure 54 (equation 11). These bismetallation reactions are both efficient and stereoselective, and a wide range of functional groups in R, including halides, ethers, and carbon-carbon double bonds, are compatible with the reaction conditions.

A possible pathway for the formation of compounds 54 in these reactions is shown in Scheme 17. It is known that, in solution, Pd(PPh3)4 is in equilibrium79,80 with the co-ordinatively unsaturated species Pd(PPh3)3 and Pd(PPh3)2. It is generally accepted that the active catalyst in Pd(0)-catalyzed cross coupling reactions is Pd(PPh3)2. Oxidative addition of the tin-tin bond of hexamethylditin to Pd(PPh3)2 would result in an intermediate square planar bis(trimethylstannyl) Pd(II) species 103. Co-ordination of the acetylenic ester 43 with 103 could give the intermediate Pd(II) complex 104, which could then lead, via stannylpalladation of the carbon-carbon triple bond, to the intermediate 105. If the
Intermediate 105 has cis geometry (as depicted in Scheme 17), reductive elimination\(^\text{81}\) could occur to give the alkyl (Z)-2,3-bis(trimethylstanny1)-2-alkenoate 54, with concomitant regeneration of the Pd(0) catalyst. If, however, the complex 105 has trans geometry, then a trans to cis isomerization is required before reductive elimination can take place.\(^\text{81,82}\)

Although there is as yet no direct evidence to support the participation of this catalytic cycle in these reactions, it is appropriate to consider this proposed pathway as a working model to account for the formation of the observed products 54. Other workers have used similar arguments to explain the Pd(0)-catalyzed reactions of disilanes with acetylenic compounds.\(^\text{83}\)
Interestingly, it was found that the alkyl (Z)-2,3-bis(trimethylstanny1)-2-alkenoates 54 may be thermally rearranged (at 75-95°C) to the corresponding (E)-isomers 106 in a clean, efficient manner. A possible route by which this isomerization could occur is shown in equation 12. Thus, it is proposed that at elevated temperatures the compounds 54 are in equilibrium with their (E)-isomers 106 via trimethylstannyl allenoates of general structure 107. The equilibrium position apparently lies far to the right, favoring the (E)-isomers 106, due primarily to steric interactions between the trimethylstannyl groups in compounds of structure 54.

\[
\begin{align*}
&\text{R} \quad \text{CO}_2\text{R}^1 \\
&\text{Me}_3\text{Sn} \quad \text{SnMe}_3 \\
54 & \iff \quad \text{Me}_3\text{Sn} \quad \text{OSnMe}_3 \\
& \text{R} \quad \text{OR}^1 \\
107 & \iff \quad \text{Me}_3\text{Sn} \quad \text{CO}_2\text{R}^1 \\
&\text{R} \quad \text{SnMe}_3 \\
106
\end{align*}
\]

The synthetic utility of alkyl 2,3-bis(trimethylstanny1)-2-alkenoates was described very briefly in the general introduction of this thesis, where it was stated that they serve as precursors to stereodefined tetrasubstituted alkenes. In fact, both compounds 54 and 106 are synthetic equivalents of the trans (d, d) synthon of general structure 108 (Scheme 18). Thus, reaction of either compounds 54 or 106 with MeLi results in tin-lithium exchange at the trimethylstannyl group adjacent to the ester function to give, presumably, lithium allenolate intermediates of general structure 109. Alkylation of the allenoates 109 occurs from the least hindered face, that is, opposite the bulky trimethylstannyl group, to give the (Z)-β-trimethylstannyl α,β-unsaturated esters of general structure 110 efficiently and stereoselectively. It is important to emphasize that since the isomeric alkyl 2,3-bis(trimethylstanny1)-2-alkenoates (54 and 106) give identical products in these transmetallation/alkylation sequences, this methodology can only be used for the preparation of compounds of structure 110. The isomeric (E)-β-trimethylstannyl α,β-unsaturated esters cannot be prepared in this manner.
Scheme 18
After conversion of the ester function of compounds 110 into a group that is stable to alkyllithium reagents (e.g. alkoxy)methyl, the resulting alkenylstannanes of general structure 111 are readily converted, stereospecifically, into alkenyllithium species of general structure 112. These may be alkylated directly to give stereodefined tetrasubstituted alkenes of general structure 55 (R^3=alkyl). Alternatively, they may be converted into the corresponding alkenylcopper species 113, which react with allylic halides or with α,β-unsaturated ketones to give stereodefined tetrasubstituted alkenes of general structures 55 (R^3=allyl) or 114, respectively.

II. Proposals

Other Pd(0)-catalyzed bis-stannylation reactions similar to those described above have been reported using either α,β-acetylenic amides^37 or terminal acetylenes^38 as starting materials. However, Mitchell et al.^38 have reported that this methodology cannot be applied to internal unactivated acetylenes. We were, therefore, interested in extending the bis-stannylation methodology to other types of acetylenic compounds, especially to activated substrates such as α,β-acetylenic aldehydes and ketones.

Thus, the immediate aims of this project were to examine the reactions of acetylenic aldehydes and ketones of general structure 115 with hexamethylditin under Pd(0) catalysis. The expected products in these reactions were bis(trimethylstannyl) compounds of general structure 116 (equation 13), which were considered to be potentially useful precursors to stereodefined substituted alkenes.

\[
\begin{align*}
\text{115} & \quad \text{Me}_3\text{Sn}_2, \text{Pd}(0) \\
\text{115A} & \quad R^1=\text{H} \\
\text{115B} & \quad R^1=\text{Alkyl} \\
\text{116} & \\
\text{116A} & \quad R^1=\text{H} \\
\text{116B} & \quad R^1=\text{Alkyl}
\end{align*}
\]
III. Results and discussion

A series of diversely functionalized $\alpha,\beta$-acetylenic aldehydes of general structure 115A and $\alpha,\beta$-acetylenic ketones of general structure 115B were required for this study. Two methods were used for the preparation of these materials.

A) The first method involved the reaction of lithium acetylides (derived from the appropriate terminal acetylenes 1) with aldehydes, followed by oxidation of the resulting propargylic alcohols of general structure 117 (equation 14).

\[
\begin{align*}
\text{R} & \equiv \equiv \text{H} \quad \text{i) MeLi} \quad \text{R} \equiv \equiv \text{OH} \quad \text{oxidation} \quad \text{R} \equiv \equiv \text{O} \\
1 & \quad \text{117} & & & \quad \text{115} \\
\text{117A} \quad \text{R}^1=\text{H} & & & & \quad \text{115A} \quad \text{R}^1=\text{H} \\
\text{117B} \quad \text{R}^1=\text{Alkyl} & & & & \quad \text{115B} \quad \text{R}^1=\text{Alkyl}
\end{align*}
\]

B) The second method, leading specifically to acetylenic methyl ketones 115B ($\text{R}^1=\text{Me}$), involved the reaction of lithium acetylides with acetic anhydride (equation 15).

\[
\begin{align*}
\text{R} & \equiv \equiv \text{H} \quad \text{i) MeLi} \quad \text{R} \equiv \equiv \text{O} \\
1 & \quad \text{115B (R}^1=\text{Me)} \\
\text{R} & \equiv \equiv \text{H} \quad \text{ii) (MeCO)}_2\text{O} \\
\end{align*}
\]

3.1. The preparation of terminal acetylenes 1

The terminal acetylenes 4-\text{tert}-butyldimethylsiloxy-1-butyne (118) and 4-methoxymethoxy-1-butyne (119), were prepared from commercially available 3-butyn-1-ol using standard literature methods (equation 16).\textsuperscript{84,85}
The terminal acetylene 6-tert-butyldimethylsiloxy-1-hexyne (120) was prepared from commercially available 5-hexyn-1-ol via a procedure identical with that used for the preparation of 118 (equation 17).

The terminal acetylene 121 was prepared in three steps from 4-pentyn-1-ol, as shown in Scheme 19. Thus, 4-pentyn-1-ol (in dry CH₂Cl₂, argon atmosphere) was allowed to react with pyridinium chlorochromate (1.5 equivalents) and NaOAc (0.3 equivalents) for two hours at room temperature. After appropriate workup, the solvent was removed by atmospheric pressure distillation to give a crude, volatile oil containing 4-pentynal. This oil was dissolved in dry THF and was then treated with excess vinyl magnesium bromide (-78°C, then room temperature). After appropriate workup, the solvent was removed by atmospheric pressure distillation to give a crude, volatile oil containing the alcohol 122. This oil was dissolved in dry DMF and the resulting solution was treated with TBDMSI and imidazole, using a procedure similar to that reported in the literature. After workup, the crude reaction product was purified by flash chromatography and distillation to give the
terminal acetylene 121 in an overall yield of 31%. This material exhibited spectral data which were fully consistent with the proposed structure. For example, the infrared spectrum showed absorbances at 3314 cm\(^{-1}\) and 2121 cm\(^{-1}\) attributable to the carbon-hydrogen and carbon-carbon stretching frequencies, respectively, of the terminal acetylene function. The \(^1\)H nmr spectrum of 121 showed a 6-proton singlet at \(\delta 0.02\) and a 9-proton singlet at \(\delta 0.89\) due to the TBDMS group, as well a 1-proton triplet at \(\delta 1.92\) (\(J = 4\) Hz) due to the acetylenic proton. Also, a 1-proton doublet of doublet of doublets at \(\delta 5.78\) (\(J = 16\) Hz, \(J = 10\) Hz, \(J = 6\) Hz), a 1-proton doublet of doublet of doublets at \(\delta 5.17\) (\(J = 16\) Hz, \(J = 2\) Hz, \(J = 2\) Hz), a 1-proton doublet of doublet of doublets at \(\delta 5.05\) (\(J = 10\) Hz, \(J = 2\) Hz, \(J = 2\) Hz), and a 1-proton multiplet at \(\delta 4.22\) were assigned to HF, HE, HD, and HX, respectively.

3.2. The preparation of propargylic alcohols 117

Lithium acetylides (derived from terminal acetylenes 1) react readily with formaldehyde\(^{87a}\) to give primary propargyl alcohols 117A, and with other aldehydes to give secondary propargyl alcohols 117B (equation 18).\(^{87b}\)
In a typical procedure, ethereal MeLi (1 equivalents) was added to a solution of the terminal acetylene 1 in dry THF at -78°C and the resulting mixture was stirred at -78°C for 10 min and at -20°C for 1 hour. The appropriate aldehyde (excess) was added and the reaction mixture was allowed to warm to room temperature. After appropriate workup, the crude product was purified by flash chromatography, followed by distillation, to give the pure propargyl alcohol 117.

A series of propargyl alcohols 117 were prepared in this manner. The conditions used in these reactions and the results are summarized in Table 4. A few points should be noted regarding the data in Table 4. Firstly, the reactions were generally very clean. In most cases, tlc analysis of the crude reaction product showed the presence of the desired product 117 and very minor amounts of other materials. Secondly, the products obtained in these reactions exhibited spectral data which were in full accord with the assigned structures. For example, the infrared spectrum of compound 123 showed a strong broad absorption at 3394 cm\(^{-1}\) attributable to the oxygen-hydrogen stretching frequency of the hydroxyl group, as well as a weak absorption at 2227 cm\(^{-1}\) attributable to the carbon-carbon stretching frequency of the internal acetylene function. The \(^1\)H nmr spectrum of 123 showed a 1-proton broad multiplet at \(\delta\) 1.8-1.95 (-OH) which disappeared upon addition of D\(_2\)O, and
Table 4. The preparation of propargylic alcohols 117

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Conditions&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Yield&lt;sup&gt;2&lt;/sup&gt; %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>118 CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;TBDMS&lt;/sub&gt;</td>
<td>H</td>
<td>123</td>
<td>A</td>
</tr>
<tr>
<td>2</td>
<td>120 (CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;TBDMS&lt;/sub&gt;</td>
<td>H</td>
<td>124</td>
<td>A</td>
</tr>
<tr>
<td>3</td>
<td>119 CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OMOM</td>
<td>H</td>
<td>125</td>
<td>A</td>
</tr>
<tr>
<td>4</td>
<td>118 CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;TBDMS&lt;/sub&gt;</td>
<td>Me</td>
<td>126</td>
<td>B</td>
</tr>
<tr>
<td>5</td>
<td>120 (CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;TBDMS&lt;/sub&gt;</td>
<td>Me</td>
<td>127</td>
<td>B</td>
</tr>
<tr>
<td>6</td>
<td>(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;CCH</td>
<td>Me</td>
<td>128</td>
<td>C</td>
</tr>
<tr>
<td>7</td>
<td>(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;Cl</td>
<td>Me</td>
<td>129</td>
<td>B</td>
</tr>
<tr>
<td>8</td>
<td>But</td>
<td>C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;</td>
<td>130</td>
<td>D</td>
</tr>
<tr>
<td>9</td>
<td>118 CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;TBDMS&lt;/sub&gt;</td>
<td>Pri</td>
<td>131</td>
<td>E</td>
</tr>
</tbody>
</table>

1 Conditions. A) i) MeLi (1 equiv.), THF, -78°C, 10 min; -20°C, 1 h: ii) HCHO (4 equiv.), warmed to room temp; room temp, 30 min.
B) i) as A: ii) cooled to -78°C, CH<sub>3</sub>CHO added (2 equiv.), -78°C, 10 min; warmed to room temp.
C) as B except 5 equiv. of acetaldehyde was used.
D) i) as A: ii) cooled to -78°C, heptanal (1.5 equiv.) added, -78°C, 10 min; warmed to room temp.
E) i) as A: ii) cooled to -78°C, 2-methylpropanal added (1.5 equiv.), -78°C, 10 min; warmed to room temp.

2 Isolated yield of distilled product.
a 2-proton broad singlet at $\delta$ 4.24 (-CH$_2$OH) which sharpened to a triplet ($J = 2$ Hz) upon addition of D$_2$O.

Regarding the reaction of the lithium acetylide of 1, 6-heptadiyne with acetaldehyde (entry 6), tlc analysis of the crude reaction product showed the presence of two compounds. These compounds were easily separated by flash chromatography. The less polar (and major) product was assigned the structure 128, on the basis of its spectral data. In particular, the infrared spectrum showed an absorption at 2247 cm$^{-1}$ attributable to the carbon-carbon stretching frequency of the internal acetylene function, and an absorption at 3301 cm$^{-1}$, attributable to the oxygen-hydrogen stretching frequency of the hydroxyl group. Also present were absorptions at 2118 cm$^{-1}$ and 3350 cm$^{-1}$ attributable to the carbon-carbon and carbon-hydrogen stretching frequencies, respectively, of the terminal acetylene function. The $^1$H nmr spectrum of this compound showed a 1-proton triplet at $\delta$ 1.95 ($J = 2.5$ Hz) due to the acetylenic proton. The more polar (and minor) compound was not characterized but it was assumed to be the diol arising from reaction at both terminal acetylene functions of the starting material.

3.3. The oxidation of propargylic alcohols 117 to $\alpha,\beta$-acetylenic aldehydes and ketones 115

Pyridinium chlorochromate (PCC), an oxidizing reagent developed by Corey and Suggs, was chosen for our initial studies. Although pyridinium chlorochromate is slightly
acidic, it may be used as a reagent for the oxidation of alcohols containing acid sensitive functional groups (such as TBDMS ethers) to the corresponding aldehydes or ketones, providing that the reactions are buffered by NaOAc.86,88

It was found that PCC reacts with the propargylic alcohols 117 (CH₂Cl₂, room temperature) in the presence of NaOAc to give the corresponding α,β-acetylenic carbonyl compounds 115 in reasonable yield (equation 19).

\[
\begin{array}{c}
\text{OH} \\
\text{PCC, CH₂Cl₂, NaOAc, room temperature} \\
\end{array} \rightarrow \begin{array}{c}
\text{O} \\
\text{R—}—\text{R}^1 \\
\text{115} \\
\end{array}
\]

The conditions used in these reactions and the results are presented in Table 5. Several comments should be made regarding these data. Firstly, the crude reaction products were generally very clean (as judged by glc analysis). The pure compounds 115 were readily obtained by flash chromatography of the crude reaction products, followed by distillation. Secondly, the spectral data derived from the products obtained in these reactions were in full accord with the proposed structures. The spectral data exhibited by compound 133 are typical of those exhibited by the acetylenic aldehydes. The infrared spectrum of 133 showed an absorbance at 2740 cm⁻¹ attributable to the carbon-hydrogen stretching frequency of the aldehyde function, as well as absorbances at 1673 cm⁻¹ and 2207 cm⁻¹ attributable to the carbon-oxygen and carbon-carbon stretching frequencies, respectively, of the conjugated acetylenic aldehyde function. The ¹H nmr spectrum of 133 showed a 1-proton singlet at δ 9.15 (-CHO).
Table 5. The oxidation of propargylic alcohols 117

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>117</th>
<th>R</th>
<th>R¹</th>
<th>115</th>
<th>Conditions¹</th>
<th>Yield² %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>123</td>
<td>CH₂CH₂OTBDMS</td>
<td>H</td>
<td>133</td>
<td>A</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>124</td>
<td>(CH₂)₄OTBDMS</td>
<td>H</td>
<td>134</td>
<td>A</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>125</td>
<td>CH₂CH₂OMOM</td>
<td>H</td>
<td>135</td>
<td>A</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>126</td>
<td>CH₂CH₂OTBDMS</td>
<td>Me</td>
<td>136</td>
<td>B</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>127</td>
<td>(CH₂)₄OTBDMS</td>
<td>Me</td>
<td>137</td>
<td>B</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>128</td>
<td>(CH₂)₃CCH</td>
<td>Me</td>
<td>138</td>
<td>B</td>
<td>55</td>
</tr>
<tr>
<td>7</td>
<td>129</td>
<td>(CH₂)₃Cl</td>
<td>Me</td>
<td>139</td>
<td>B</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td>130</td>
<td>Bu¹</td>
<td>C₆H₁₃</td>
<td>140</td>
<td>B</td>
<td>72</td>
</tr>
<tr>
<td>9</td>
<td>131</td>
<td>CH₂CH₂OTBDMS</td>
<td>Pr¹</td>
<td>141</td>
<td>B</td>
<td>81</td>
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<tr>
<td>10</td>
<td>132</td>
<td>Pr¹</td>
<td>Me</td>
<td>142</td>
<td>C</td>
<td>56</td>
</tr>
</tbody>
</table>

¹Conditions. A) PCC (1.5 equiv.), NaOAc (0.3 equiv.), CH₂Cl₂, room temp, 2 h
B) PCC (2.5 equiv.), NaOAc (0.3 equiv.), CH₂Cl₂, room temp, 2.5 h
C) This compound was prepared from isopropyl acetylene without purification of the propargyl alcohol 132 formed in the first step. See text.

²Isolated yield of distilled product.
The spectral data exhibited by compound 136 are typical of those exhibited by the acetylenic ketones. The infrared spectrum of 136 showed strong absorbances at 1680 cm\(^{-1}\) and 2214 cm\(^{-1}\) attributable to the carbon-oxygen and carbon-carbon stretching frequencies, respectively, of the conjugated acetylenic ketone function. The \(^1\text{H}\) nmr spectrum of 136 showed a 3-proton singlet at \(\delta 2.30\) (-C(O)CH\(_3\)).

![Chemical structure of compound 136]

Finally, the preparation of compound 142 requires special mention, since a slightly different procedure was used in this case. Reaction of the lithium acetylide of isopropyl acetylene with acetaldehyde, in the usual manner, provided the propargyl alcohol 132. Since this material was volatile, attempts were not made to remove all traces of solvent from it. Thus, after appropriate workup, most of the solvent was removed by atmospheric pressure distillation and the residual oil, containing 132, was carried on to the next step. Oxidation of this material, using PCC, proceeded cleanly and efficiently to give the acetylenic ketone 142. After appropriate workup, the solvent was removed by atmospheric pressure distillation to give a crude, volatile oil containing the product. This oil was distilled to give the pure compound 142 in an overall yield of 56%.

The data presented in Table 5 show that pyridinium chlorochromate is a suitable reagent for the oxidation of propargylic alcohols 117 to the corresponding acetylenic aldehydes and ketones 115. The reagent is commercially available and inexpensive. Also, the reactions are convenient and fairly efficient, and the products are readily purified. Nevertheless, the decision was made to investigate some oxidation methods to determine whether better yields could be obtained for the conversion of propargylic alcohols 117 to the acetylenic carbonyl compounds 115.
Pyridinium dichromate (PDC), an oxidizing reagent developed by Corey and Schmidt,\textsuperscript{89} is known to oxidize alcohols to aldehydes or ketones efficiently and under neutral conditions. However, when the propargyl alcohol 123 was allowed to react with PDC according to the reported procedure,\textsuperscript{89} only a 50% yield of the acetylenic aldehyde 133 was obtained (equation 20).

\[
\begin{array}{ccc}
\text{OH} & \text{PDC, CH}_2\text{Cl}_2 & \text{room temperature} \\
\text{OTBDMS} & \text{123} & \text{50\% 133}
\end{array}
\]

Marshall et al.\textsuperscript{90} have recently reported that the propargylic alcohol 143 (equation 21) reacts with 1,1'-(azodicarbonyl)dipiperidine (ADD)\textsuperscript{91} in the presence of tert-butoxymagnesium bromide to give the acetylenic aldehyde 144 in 81% yield. This aldehyde was a key intermediate in a cembranolide total synthesis.

\[
\begin{array}{ccc}
\text{OMOM} & \text{SnBu}_3 & \text{Bu'OMgBr} \\
\text{OMOM} & \text{143} & \text{144}
\end{array}
\]

The propargyl alcohol 125 was readily oxidized to the acetylenic aldehyde 135 using a similar procedure (equation 22). Thus, a solution of the alcohol 125 in dry CH\textsubscript{2}Cl\textsubscript{2} was
added to a solution of *tert*-butoxymagnesium bromide (1.5 equivalents) and ADD (1.5 equivalents) in dry CH$_2$Cl$_2$ at 0°C (argon atmosphere), and the resulting mixture was stirred for 15 min at this temperature. After workup, the crude reaction product was purified by flash chromatography, followed by distillation, to give the aldehyde 135 in 81% yield. This material was spectrally identical with the same substance prepared earlier (using PCC as oxidant). This oxidation method appears to be superior to that employing PCC, at least for the oxidation of alcohol 125 to the aldehyde 135 (81 % compared to 57% with PCC), but suffers from one major disadvantage. Commercially available ADD costs approximately 70 cents per mmol (compared to approximately 2 cents per mmol for PCC), which means that large scale oxidations can be very expensive. However, the cost of ADD is reduced significantly if it is prepared in the laboratory from piperidine and diethyl azodicarboxylate.$^{92}$

The periodinane reagent 145, developed by Dess and Martin,$^{93}$ has been used for the oxidation of highly functionalized and/or sensitive alcohols to the corresponding carbonyl compounds.$^{94}$ It was, therefore, expected that this reagent would be suitable for the oxidation of propargyl alcohols 117 to acetylenic aldehydes/ketones 115.

The reagent 145 was prepared, via the reported procedure, in two steps from commercially available 2-iodobenzoic acid (equation 23). Thus, 2-iodobenzoic acid was allowed to react with acidic potassium perbromate to give the compound 146, which was then treated with a mixture of hot (140°C) acetic anhydride and acetic acid to give 145. The reagent 145 is a white, moisture sensitive solid and was found to contain traces of acetic acid.
even after being stored under high vacuum for several days. Therefore, it was always prewashed with anhydrous ether (under an argon atmosphere) immediately prior to use.

\[
\begin{align*}
\text{I} & \xrightarrow{\text{KBrO}_3, \text{H}_2\text{SO}_4} \text{146} & \xrightarrow{\text{HOAc}, \text{Ac}_2\text{O}} \text{145}
\end{align*}
\]

In a typical oxidation procedure, a solution of the substrate alcohol in dry \(\text{CH}_2\text{Cl}_2\) was added to a solution/suspension of (prewashed) reagent \text{145} (1.3 equivalents) in dry \(\text{CH}_2\text{Cl}_2\) at room temperature (argon atmosphere), and the resulting mixture was stirred for 15 minutes. After appropriate workup, the crude product was distilled to give the pure acetylenic carbonyl compound. In this manner, the alcohols \text{123} and \text{124} were oxidized to the aldehydes \text{133} and \text{134} in 88 and 86% yields, respectively. These materials were spectroscopically identical with the same materials prepared earlier, via PCC oxidation. This oxidation method appears to be superior to the PCC oxidation procedure in terms of yield, ease of workup, and purification of products.

3.4. \textbf{The preparation of \(\alpha,\beta\)-acetylenic methyl ketones \text{115B} (R^1=Me) via direct acylation of lithium acetylides.}

It was found that acetylenic methyl ketones may be prepared in reasonable yield via reaction of lithium acetylides (derived from the appropriate terminal acetylenes \text{1}) with acetic anhydride, using a procedure developed by Brandsma and coworkers.\(^{95}\) Typically, an ethereal solution of the terminal acetylene \text{1} was allowed to react with MeLi (1 equivalents) for 10 min at -78°C and for 1 hour at -20°C. The ethereal solution of the lithium acetylide
thus obtained was added, via cannula, into a cold (-78°C) ethereal solution of acetic anhydride (2 equivalents) and the resulting mixture was stirred at -78°C for 10 min and then at -48°C for 30 min. After appropriate workup, the crude product was purified by flash chromatography, followed by distillation, to give the pure acetylenic methyl ketone 115B. Several terminal acetylenes were converted into acetylenic methyl ketones in this manner and the results are summarized in Table 6.

Table 6. The preparation of α,β-acetylenic methyl ketones 115B (R¹=Me).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>115B</th>
<th>Yield2 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂CH₂OTBDMS</td>
<td>136</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>(CH₂)₃Cl</td>
<td>139</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>(CH₂)₃CCCH</td>
<td>138</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>TBDMSO</td>
<td>148</td>
<td>63</td>
</tr>
</tbody>
</table>

1Conditions. i) MeLi (1 equiv.), Et₂O, -78°C, 10 min; 20°C, 1h: ii) Ac₂O (2 equiv.), Et₂O, -78°C, 10 min; -48°C, 30 min: iii) NH₄Cl-NH₄OH (pH 8).

2 Isolated yield of distilled product.
A few comments should be made regarding these reactions. Firstly, in each case, it was shown (by glc analysis) that significant amounts of terminal acetylene were present after workup. Hence, it is concluded that the lithium acetylide reacts with the product acetylenic ketone 115B (R^1=Me) in competition with the acylation reaction, to give the lithium enolate of general structure 147 and the starting terminal acetylene (equation 24). This type of proton exchange should be thermodynamically favorable since there is a reasonable difference in acidity between a methyl ketone function (pKa approximately 20) and a terminal acetylene function (pKa approximately 25). Upon workup, the enolate 147 is protonated, and the acetylenic ketone 115B (R^1=Me) is obtained, along with unreacted terminal acetylene.

Secondly, when 1,6 heptadiyne was used as the starting material (entry 3), glc analysis of the crude reaction mixture showed the presence of the expected product 138 plus a small amount of a higher molecular weight material. This material was not characterized but was assumed to be the diacylated material, formed via reaction at both terminal acetylene functions of the starting material. Interestingly, the yield (50%) of the mono-acylated material 138 obtained in this reaction is better than that obtained via the two step procedure described earlier (33%).

Finally, the products obtained in these reactions were spectroscopically identical with the same materials prepared by the two step route outlined previously. As well, the acetylenic ketone 148, prepared only via the present method, exhibited spectral data which were in full accord with the assigned structure. For example, the infrared spectrum of this material

![Diagram](image_url)
showed absorbances at 2211 cm\(^{-1}\) and 1681 cm\(^{-1}\), attributable to the carbon-carbon and carbon-oxygen stretching frequencies, respectively, of the conjugated acetylenic ketone function. The \(^1\)H nmr spectrum of 148 showed a 3-proton singlet at \(\delta 2.31\) (\(-\text{C(O)}\text{CH}_3\)).

In summary, the synthesis of acetylenic aldehydes and ketones 115 is readily accomplished via a two step sequence involving the preparation and oxidation of propargyl alcohols 117. In connection with this, PCC is an efficient, convenient oxidizing reagent, although superior yields of \(\alpha,\beta\)-acetylenic aldehydes may be obtained using either ADD or the periodinane reagent 145 as oxidant.

The direct acylation of lithium acetylides with acetic anhydride, as described above, is a useful method for the preparation of \(\alpha,\beta\)-acetylenic methyl ketones. However, although it is more convenient than the two step procedure involving the preparation and PCC oxidation of propargyl alcohols 117B (\(R^1=\text{Me}\)), it is generally less efficient.

3.5. The Pd(0)-catalyzed reaction of \(\alpha,\beta\)-acetylenic aldehydes and ketones with hexamethylditin.\(^{96}\)

With convenient, reliable procedures available for the preparation of functionalized acetylenic aldehydes and ketones 115, it was now possible to examine in detail the reactions of these compounds with hexamethylditin under Pd(0) catalysis. The initial experiment was performed using the acetylenic ketone 142 as substrate. Thus, using a procedure similar to that reported previously in connection with the Pd(0)-catalyzed reaction of hexamethylditin with \(\alpha,\beta\)-acetylenic esters,\(^{37}\) Pd(PPh\(_3\))\(_4\) (5 mol %) was added to a stirred solution of the ketone 142 (1 equivalent) and hexamethylditin (1 equivalent) in dry THF under an argon
atmosphere. The concentration of 142 in THF was approximately 0.6 M. The resulting mixture was refluxed and the progress of the reaction was monitored periodically by tlc analysis. After 5 hours at reflux, tlc analysis of the reaction mixture showed that all of the acetylenic ketone 142 had been consumed. In fact, a major component was present which was less polar than the starting material (by tlc analysis), was uv active, and stained heavily with ammonium molybdate and with iodine. Also present were small amounts of hexamethylditin, triphenylphosphine, and minor amounts of some more polar components.

Most of the solvent was removed and the residual dark brown oil was purified by flash chromatography and distillation, to give the pure major product. The infrared spectrum of this material indicated that it could be the expected bis(trimethylstannyl) adduct 149 (equation 25). For example, there were strong absorbances at 1682 cm\(^{-1}\) and 1568 cm\(^{-1}\) attributable to the carbon-oxygen and carbon-carbon stretching frequencies, respectively, of an \(\alpha,\beta\)-unsaturated ketone function. Also present was an absorbance at 770 cm\(^{-1}\) attributable to the tin-methyl rocking vibration of a trimethylstannyl group. However, upon inspection of the \(^1\)H nmr spectrum of this material it was immediately obvious that the product was not the expected bis(trimethylstannyl) adduct 149, but was actually the (Z)-\(\beta\)-trimethylstannyl \(\alpha,\beta\)-unsaturated ketone 150 (equation 25). The 300 MHz \(^1\)H nmr spectrum for this compound is shown in Figure 1. This spectrum shows a 9-proton singlet at \(\delta\) 0.09 (\(^2J_{\text{Sn-H}} = 54\) Hz) due to the trimethylstannyl group, as well as a 6-proton doublet at \(\delta\) 1.03 (\(J = 6.5\) Hz) and a 1-proton septet of doublets at \(\delta\) 2.75 (\(J = 6.5\) Hz, \(J = 1.5\) Hz) due to the
Figure 1. 300 MHz $^1$H nmr spectrum of compound 150
isopropyl group. Also, there is a 3-proton singlet at $\delta$ 2.20 due to the methyl ketone group and a 1-proton doublet at $\delta$ 6.77 ($J = 1.5$ Hz, $^{3}J_{\text{Sn-H}} = 127$ Hz) due to $H_A$. The magnitude of the tin-hydrogen coupling constant for $H_A$ is characteristic of coupling between tin and a proton that are trans to each other on a carbon-carbon double bond.\(^{97}\) This trans relationship was confirmed by nOe difference experiments, in which irradiation of the signal at $\delta$ 6.77 ($H_A$) caused signal enhancements at $\delta$ 2.75 (-CHMe\(_2\)), 1.03 (-CHMe\(_2\)) and 2.20 (methyl ketone). This last enhancement indicates that compound 150 exists preferentially in the cisoid conformation 150(A) (equation 26). Presumably, 150(A) is the preferred conformation primarily because the transoid conformation 150(B) suffers from steric interactions between the methyl group of the methyl ketone function and the trimethylstannyl group.

There are several important features associated with this reaction. Firstly, the compound 150 was produced in high yield (80%). Additionally, this material was stereochemically homogeneous. If any of the ($E$)-isomer was formed in this reaction, it was present in extremely minor amounts and did not contaminate the product after chromatography. Finally, there was no evidence obtained which indicated the presence of any bis(trimethylstannyl) compounds such as 149 in the reaction mixture. In fact, the only other compounds isolated from the crude reaction mixture were hexamethylditin and triphenylphosphine. Although the expected product 149 was not obtained in this reaction,
the efficient, stereoselective formation of compound 150 was an interesting and potentially useful result. It was, therefore, decided to determine whether this transformation could be achieved using a variety of α,β-acetylenic aldehydes and ketones 115 as substrates.

It was pleasing to find that this reaction is indeed general. Good to excellent yields of (Z)-β-trimethylstannyl α,β-unsaturated ketones 151B and (Z)-β-trimethylstannyl α,β-unsaturated aldehydes 151A were obtained from a variety of α,β-acetylenic ketones 115B and aldehydes 115A, respectively. The conditions used in these reactions and the results are summarized in Table 7.

Several points should be made regarding the data in Table 7. Firstly, the reactions were carried out at concentrations (of the acetylenic carbonyl compound in dry THF) ranging between 0.3M and 0.6M, and were generally complete within reasonable lengths of time. The products were easily isolated by flash chromatography of the crude oil obtained after removal of the solvent from the reaction mixture. Secondly, the products obtained in these reactions exhibited spectral data which were in full accord with the proposed structures. Some of the important infrared and H nmr data for these compounds is presented in Table 8. Thus, the infrared spectrum of each of these compounds showed absorbances attributable to the carbon-carbon and carbon-oxygen stretching frequencies of the α,β-unsaturated carbonyl function. The H nmr spectrum of each of these compounds showed a 1-proton signal due to HA. The magnitude of the three bond tin-hydrogen coupling constant for this signal was, in each case, consistent with the proton and tin being trans to each other on the carbon-carbon double bond. It is interesting to note that the values of 3JSn-H associated with HA are consistently lower for the aldehydes 152-154 than for the ketones 150 and 155-161.

Some of the reactions listed in Table 7 deserve extra comment. Regarding the reaction using the acetylenic ketone 140 as the substrate (entry 8), it was found that starting materials were present even after a reaction time of 24 hours. It was decided to stop the
Table 7. The preparation of \( \beta \)-trimethylstannyl \( \alpha,\beta \)-unsaturated aldehydes and ketones 151.

\[
\begin{align*}
\text{Conditions}^1 & \quad \text{Me}_3\text{Sn}^=\text{O} \\
\text{Entry} & \quad \text{R} & \quad \text{R}^1 & \quad \text{151} & \quad \text{Time/h} & \quad \text{Yield}^2 \% \\
1 & 133 & \text{CH}_2\text{CH}_2\text{OTBDMS} & \text{H} & 152 & 2 & 87 \\
2 & 134 & \text{(CH}_2\text{)}_4\text{OTBDMS} & \text{H} & 153 & 2 & 88 \\
3 & 135 & \text{CH}_2\text{CH}_2\text{OMOM} & \text{H} & 154 & 2 & 76 \\
4 & 136 & \text{CH}_2\text{CH}_2\text{OTBDMS} & \text{Me} & 155 & 2 & 90 \\
5 & 137 & \text{(CH}_2\text{)}_4\text{OTBDMS} & \text{Me} & 156 & 2 & 83 \\
6 & 138 & \text{(CH}_2\text{)}_3\text{CCH} & \text{Me} & 157 & 4 & 69 \\
7 & 139 & \text{(CH}_2\text{)}_3\text{Cl} & \text{Me} & 158 & 3 & 81 \\
8 & 140 & \text{Bu}^t & \text{C}_6\text{H}_{13} & 159 & 24 & 48 \\
9 & 141 & \text{CH}_2\text{CH}_2\text{OTBDMS} & \text{Pr}^i & 160 & 5 & 94 \\
10 & 142 & \text{Pr}^i & \text{Me} & 150 & 5 & 80 \\
11 & 148 & \text{TBDS} & \text{Me} & 161 & 8 & 95 \\
\end{align*}
\]

1. Conditions: \( \text{Me}_3\text{SnSnMe}_3 \) (1 equiv.), \( \text{Pd}(0) \) (5 mol%), THF, reflux.

2. Isolated yield of distilled product.
Table 8. Selected spectral data for (Z)-β-trimethylstannyl α,β-unsaturated aldehydes and ketones 151

<table>
<thead>
<tr>
<th></th>
<th>ν(C=O) (cm⁻¹)</th>
<th>ν(C=C) (cm⁻¹)</th>
<th>δ(Hₐ)</th>
<th>3J.Sn-H(Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>151</td>
<td></td>
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</tr>
<tr>
<td>152</td>
<td>1685</td>
<td>1563</td>
<td>6.68</td>
<td>114</td>
</tr>
<tr>
<td>153</td>
<td>1685</td>
<td>1562</td>
<td>6.62</td>
<td>115</td>
</tr>
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<td>1682</td>
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<td>1568</td>
<td>6.77</td>
<td>127</td>
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<td>161</td>
<td>1682</td>
<td>1571</td>
<td>6.80</td>
<td>124</td>
</tr>
</tbody>
</table>

reaction at this point, since tlc and glc analyses indicated that the reaction mixture was becoming progressively more messy as time went on. The expected product 159 was isolated in 48% yield (Scheme 20). The sluggish nature of the reaction with the substrate 140 is consistent with results obtained by previous workers (Scheme 20). It was shown that neither the acetylenic ester 162 nor 3,3-dimethyl-1-butyne reacts with hexamethylditin in the presence of a Pd(0) catalyst, even after prolonged heating of the reaction mixtures (Scheme 20). Therefore, it is reasonable to conclude that the rates of bis-metallation reactions of this type are sensitive to the size of the groups attached to the carbon-carbon triple bond.
Regarding the reaction using the acetylenic ketone 138 as starting material (Table 7, entry 6), it was found that the (Z)-β-trimethylstannyl α,β-unsaturated ketone 157 was obtained in (an unoptimized) 69% yield (equation 27). The fact that the terminal acetylene functions present in compounds 138 and 157 do not interfere with the "observed" reaction is particularly noteworthy, since it is known that terminal acetylenes may be bis-stannylated under conditions similar to those used here. It is clear, therefore, that the Pd(0)-catalyzed reactions of terminal acetylenes with hexamethylditin are slower than the similar reactions involving α,β-acetylenic aldehydes and ketones.

The observation that α,β-acetylenic aldehydes/ketones 115 react with hexamethylditin in the presence of a Pd(0) catalyst to give (Z)-β-trimethylstannyl
α,β-unsaturated aldehydes/ketones 151, whilst similar reactions involving α,β-acetylenic esters 43 afford the bis(trimethylstannyl) adducts 54 may be rationalized by the following arguments (Scheme 21). It was proposed earlier that the thermal isomerization of alkyl (Z)-2,3-bis(trimethylstannyl)-2-alkenoates 54 to the corresponding (E)-isomers 106 proceeds via trimethylstannyl allenotes of general structure 107. However, in the Pd(0)-catalyzed reactions of acetylenic esters with hexamethylditin, the initially formed products 54 are stable and, apparently, the allenoates 107 are not produced (Scheme 21).

\[
\begin{align*}
&\text{Me}_6\text{Sn}_2 \quad \text{Pd}(0) \\
&\quad \downarrow \\
&\quad R \equiv \quad \equiv \quad \equiv \\
&\quad \text{OR}^1 \\
&\quad \text{Me}_3\text{Sn} \quad \text{SnMe}_3 \\
&\quad \text{54} \\
&\quad \text{Me}_3\text{Sn} \quad \text{SnMe}_3 \\
&\quad \text{OR}^1 \\
&\quad \text{Me}_3\text{Sn} \quad \text{SnMe}_3 \\
&\quad \text{106} \\
&\quad \text{Me}_3\text{Sn} \quad \text{SnMe}_3 \\
&\quad \text{107} \\
&\quad \text{Me}_3\text{Sn} \quad \text{SnMe}_3 \\
&\quad \text{116} \\
&\text{Me}_6\text{Sn}_2 \quad \text{Pd}(0) \\
&\quad \downarrow \\
&\quad R \equiv \quad \equiv \quad \equiv \\
&\quad \text{OR}^1 \\
&\quad \text{Me}_3\text{Sn} \quad \text{SnMe}_3 \\
&\quad \text{151} \\
&\quad \text{Me}_6\text{Sn}_2 \quad \text{Pd}(0) \\
&\quad \downarrow \\
&\quad R \equiv \quad \equiv \quad \equiv \\
&\quad \text{OR}^1 \\
&\quad \text{Me}_3\text{Sn} \quad \text{SnMe}_3 \\
&\quad \text{115} \\
&\quad \text{163} \\
&\quad \text{Me}_3\text{Sn} \quad \text{SnMe}_3 \\
&\quad \text{116} \\
&\quad \text{151} \\
&\quad \text{Scheme 21}
\end{align*}
\]
In a similar fashion, it is proposed that bis(trimethylstannyl) compounds of general structure 116 (which were the expected products in the Pd(0)-catalyzed reactions of $\alpha,\beta$-acetylenic aldehydes/ketones with hexamethylditin) may isomerize to the corresponding allenolates 163 (Scheme 21). Apparently, the tendency to form allenolates 163 from compounds 116 is greater than the tendency to form allenoates 107 from the distannyl alkenoates 54. Thus, it is proposed that the initial products from the Pd(0)-catalyzed reactions of $\alpha,\beta$-acetylenic aldehydes/ketones 115 with hexamethylditin are the expected bis(trimethylstannyl) adducts 116, which, under the conditions of the reaction, readily isomerize to the trimethylstannyl allenolates 163 (Scheme 21). Protonation of 163, presumably during silica gel chromatography, occurs from the face opposite the bulky trimethylstannyl group to give the (Z)-$\beta$-trimethylstannyl $\alpha,\beta$-unsaturated aldehydes/ketones 151 stereoselectively (Scheme 21).

It must be emphasized that this proposed pathway is intended only as a hypothetical rationalization of the results observed from the Pd(0)-catalyzed stannylation reactions of $\alpha,\beta$-acetylenic esters on one hand and $\alpha,\beta$-acetylenic aldehydes/ketones on the other. Nothing as yet is known about the intermediates in these reactions. However, the arguments presented above are supported by some observations made recently by Saegusa and coworkers. It was reported that reaction of $\alpha,\beta$-acetylenic carbonyl compounds with DIBAL produces organoaluminum intermediates which are both thermally stable and identifiable. Interestingly, the structures of these intermediates are dependant on the nature of the carbonyl group in the starting material. For example, methyl propynoate gives rise to the alkenylalane 164, whilst 2-hexyn-3-one gives rise to the aluminum allenolate 165 (Scheme 22). The similarities between these results and those presented above are striking.

In summary, regardless of the pathway by which the products are formed, the Pd(0)-catalyzed reaction of $\alpha,\beta$-acetylenic aldehydes and ketones 115 with hexamethylditin constitutes a general method for the synthesis of (Z)-$\beta$-trimethylstannyl $\alpha,\beta$-unsaturated aldehydes and ketones 151. The reaction proceeds in high yield and with excellent regio-
and stereoselectivity, and a wide variety of functional groups in the substrate, such as halides, ethers, allylic ethers and terminal acetylenes are compatible with the reaction conditions.

3.6. The preparation of (Z)-4-(trimethylstannyI)-1,3-butadienes 166

The readily available (Z)-β-trimethylstannyI α,β-unsaturated aldehydes and ketones 151 are potentially useful intermediates in organic synthesis. For example, these compounds should readily undergo Wittig olefination reactions to give a variety of substituted stannyldienes of general structure 166 (equation 28). A few stannyldienes of type 166A have been prepared by previous workers in this laboratory via Wittig olefination of aldehydes of structure 151A. However, at the time of this study the ketones of general structure 151B were not readily available and therefore the olefination reactions of these compounds had not been investigated.
It was found that the (Z)-β-trimethylstannyl α,β-unsaturated aldehydes 152-154 react with methylenetriphenylphosphorane to give the corresponding stannyldienes in a clean and efficient manner (Scheme 23). Typically, a solution of the aldehyde in dry THF was added to a slight excess of methylenetriphenylphosphorane (prepared from n-BuLi and methyltriphenylphosphonium bromide) in dry THF at room temperature. The resulting mixture was stirred at room temperature until the reaction was complete (as judged by glc analysis). After appropriate workup, the crude product was purified by flash chromatography followed by distillation.

Scheme 23
The products obtained from these reactions exhibited spectral data which were in full accord with the assigned structures. For example, the $^1$H nmr spectrum of compound 167 showed a series of signals due to the diene unit. Thus, a 1-proton doublet of doublets at $\delta$ 5.10 ($J = 11$ Hz, $J = 1.5$ Hz), a 1-proton doublet of doublets at $\delta$ 5.15 ($J = 16$ Hz, $J = 1.5$ Hz), a 1-proton multiplet at $\delta$ 6.30, and a one proton broad doublet at $\delta$ 6.64 ($J = 11$ Hz, $J_{SN-H} = 131$ Hz) were assigned to $H_C$, $H_B$, $H_D$ and $H_A$, respectively. The $^{13}$C nmr spectrum of 167 showed signals at $\delta$ 117.07, 137.67, 142.63, and 147.33 due to the olefinic carbons. The spectral data for the dienes 168 and 169 exhibited similar features (see the Experimental section).

The (Z)-$\beta$-trimethylstannyl $\alpha,\beta$-unsaturated ketones of general structure 151B may also be converted into the corresponding stannyldienes using the procedure described above. However, in these cases complete conversion of the starting materials into products was not achieved, even after reaction times of several hours at room temperature. Also, after long reaction times the reaction mixtures were generally messy and the isolated yields of stannyldienes were low. In fact, only the ketone 150 was converted into the corresponding stannyldiene in satisfactory yield using this method (See Table 9, entry 6).

The unsatisfactory nature of these transformations might be the result of a competition between the olefination process and the (reversible) formation of the enolate of general structure 170 (Scheme 24). Since the olefination reaction is irreversible it should, in principle, be possible to achieve complete conversion of starting material into product. However, side reactions (presumably due to the presence of the enolate 170) apparently
compete with the olefination reaction and low yields of stannyldienes 166B are generally the result.

\[
\begin{align*}
\text{Me}_2\text{Sn} & \quad \text{O} & \quad \text{R}^1 \\
\begin{array}{c}
\text{R} \\
\text{151B}
\end{array} & \quad \text{Ph}_3\text{P} \equiv \text{CH}_2 & \quad \text{Me}_2\text{Sn} \\
\begin{array}{c}
\text{R} \\
\text{166B}
\end{array} & \quad \text{+} & \quad \text{Ph}_3\text{PO} \\
\begin{array}{c}
\text{R} \\
\text{170}
\end{array} & \quad \text{+} & \quad \text{Ph}_3\text{PCl}_3
\end{align*}
\]

Scheme 24

Since most of the \(\beta\)-trimethylstanny1 \(\alpha,\beta\)-unsaturated ketones 151B gave disappointingly low yields of the stannyldienes 166B under these conditions (\(\text{Ph}_3\text{P}=\text{CH}_2\), THF, room temperature) an alternative method was sought which might effect this transformation more efficiently.

It has been reported\textsuperscript{100,101} that reaction of enolizable ketones with a mixture of sodium 2-methyl-2-butoxide and methyltriphenylphosphonium bromide in dry benzene at room temperature, provides the corresponding olefins in a highly efficient manner.

It was found that the \((Z)\)-\(\beta\)-trimethylstanny1 \(\alpha,\beta\)-unsaturated ketones 151B were smoothly converted into the corresponding stannyldienes 166B via this method. Typically, a solution of the ketone 151B in dry benzene was added to a mixture of sodium 2-methyl-2-butoxide (2.5 equivalents) and methyltriphenylphosphonium bromide (2.5 equivalents) in dry benzene, at room temperature under an argon atmosphere. The mixture was stirred at room temperature until the reaction was complete (as judged by glc and tlc analyses). After
appropriate workup, the crude product was purified by flash chromatography, followed by distillation, to give the pure stannyldiene 166B. The conditions used in these reactions and the results are summarized in Table 9.

Table 9. The preparation of \((Z)-4\)-(trimethylstannyl)-1,3-butadienes 166.

<table>
<thead>
<tr>
<th>Entry</th>
<th>151B</th>
<th>R</th>
<th>R¹</th>
<th>166B</th>
<th>Conditions¹</th>
<th>Yield² %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>155</td>
<td>CH₂CH₂OTBDMS</td>
<td>Me</td>
<td>171</td>
<td>B</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>156</td>
<td>(CH₂)₄OTBDMS</td>
<td>Me</td>
<td>172</td>
<td>B</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>157</td>
<td>(CH₂)₃CCH</td>
<td>Me</td>
<td>173</td>
<td>B</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>158</td>
<td>(CH₂)₃Cl</td>
<td>Me</td>
<td>174</td>
<td>B</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>159</td>
<td>Bu¹</td>
<td>C₆H₁₃</td>
<td>175</td>
<td>B</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>150</td>
<td>Pri</td>
<td>Me</td>
<td>176</td>
<td>A</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>160</td>
<td>CH₂CH₂OTBDMS</td>
<td>Pri</td>
<td>177</td>
<td>C</td>
<td>64</td>
</tr>
<tr>
<td>8</td>
<td>161</td>
<td>TBDMSO</td>
<td>Me</td>
<td>178</td>
<td>B</td>
<td>85</td>
</tr>
</tbody>
</table>

¹Conditions. A) Ph₃PCH₂ (1.5 equiv.), THF, room temp, 5 h; B) MePPh₃⁺Br⁻ (2.5 equiv.), Sodium 2-methyl-2-butoxide (2.5 equiv.), benzene, room temp, 30 min; C) as B) except 15 min at room temp.

²Isolated yield of distilled product.
The stannyldienes 166B which were obtained in these reactions exhibited spectral data which were in full accord with the assigned structures. For example, the $^1$H nmr spectrum of compound 171 showed a series of signals due to the substituted 1,3-butadiene unit. Thus, 1-proton broad singlets at $\delta$ 4.75 and 4.79 could be assigned to $H_B$ and $H_C$ (or vice versa) while a 1-proton broad singlet at $\delta$ 6.53 ($^3J_{Sn-H} = 137$ Hz) was attributed to $H_A$. The $^{13}$C nmr spectrum of this compound showed signals at $\delta$ 112.91, 141.78, 144.95 and 146.61 (olefinic carbons).

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me}_3\text{Sn} & \quad \text{H}_A \\
\text{TBDMSO} & \quad 171 \\
\end{align*}
\]

The spectral data derived from the other stannyldienes 166B exhibited features similar to those mentioned above. Some important $^1$H nmr data for these compounds are listed in Table 10. Regarding the data in Table 10, it should be noted that the 3-bond tin hydrogen coupling constants associated with $H_A$ are consistently larger for compounds 166B than for the precursor unsaturated carbonyl compounds 151B (see Table 8).

The results presented in Scheme 23 and in Table 9 show that (Z)-4-(trimethylstannyl)-1,3-butadienes of general structure 166 are readily prepared from the (Z)-$\beta$-trimethylstannyl $\alpha,\beta$-unsaturated aldehydes 151A and ketones 151B via Wittig olefination reactions. It was subsequently shown that the (Z)-$\beta$-trimethylstannyl $\alpha,\beta$-unsaturated aldehydes 151A readily undergo Wittig-Horner olefination reactions. For example, the aldehyde 154 reacted with the sodio-phosphonate reagent, derived from the reaction of tert-butyl diisopropylphosphonacetate 179 with NaH, to give the $\alpha,\beta$-unsaturated ester 180 (equation 29). In a similar manner, the aldehyde 152 reacted with the sodio-phosphonate reagent, derived from the reaction of trimethylphosphonoacetate 181 with NaH,
to give the \( \alpha,\beta \)-unsaturated ester 182 (equation 30). Both of these reactions proceed in high yield and with excellent stereoselectivity.

Table 10. Selected \(^1\)H nmr data for stannyldienes 166B

<table>
<thead>
<tr>
<th>166B</th>
<th>( \delta (H_A) )</th>
<th>( J_{Sn-H}(HA) ) (Hz)</th>
<th>( \delta (H_B/H_C) )</th>
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</thead>
<tbody>
<tr>
<td>171</td>
<td>6.53</td>
<td>137</td>
<td>4.75, 4.79</td>
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<td>6.47</td>
<td>139</td>
<td>4.74, 4.79</td>
</tr>
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<td>173</td>
<td>6.51</td>
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<td>4.75, 4.79</td>
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<tr>
<td>174</td>
<td>6.52</td>
<td>136</td>
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<td>6.49</td>
<td>151</td>
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<td>177</td>
<td>6.60</td>
<td>140</td>
<td>4.71, 4.80</td>
</tr>
<tr>
<td>178</td>
<td>6.50</td>
<td>139</td>
<td>4.76, 4.80</td>
</tr>
</tbody>
</table>

i) \((PrO)_{2}P(O)CH_{2}CO_{2}Bu^+\) (179), NaH, THF

ii) 154, -20°C, 90 min; room temp, 30 min

\[ 154 \xrightarrow{i) \text{ (PrO)}_{2}P(O)CH_{2}CO_{2}Bu^+ (179), NaH, THF} 180 \ (91\%) \]

\[ 152 \xrightarrow{i) (MeO)_{2}P(O)CH_{2}CO_{2}Me (181) \text{ NaH, THF} \quad \text{ii) 152, 0°C, 2 h} 182 \ (92\%) \]
The products obtained from these reactions exhibited spectral data which were in full accord with the assigned structures. For example the infrared spectrum of compound 180 showed an absorbance at 1703 cm\(^{-1}\), attributable to the carbonyl stretching frequency of the \(\alpha,\beta\)-unsaturated ester function. The 400 MHz \(^1\)H nmr spectrum of 180 is shown in Figure 2. This spectrum shows a 9-proton singlet at \(\delta\ 0.25\) (\(^3J_{\text{Sn-H}} = 52\) Hz) due to the trimethylstannyl group, a 9-proton singlet at \(\delta\ 1.48\) (-CO\(_2\)Bu\(^t\)), a 2-proton broad triplet at \(\delta\ 2.64\) (-OCH\(_2\)CH\(_2\)-, \(J = 7\) Hz, \(^3J_{\text{Sn-H}} = 49\) Hz), a 3-proton singlet at \(\delta\ 3.33\) (-OMe), a 2-proton triplet at \(\delta\ 3.54\) (-OCH\(_2\)CH\(_2\)-, \(J = 7\) Hz), and a 2-proton singlet at \(\delta\ 4.58\) (-OCH\(_2\)O-). Also, a 1-proton broad doublet at \(\delta\ 5.72\) (\(J = 15\) Hz), a 1-proton broad doublet at \(\delta\ 6.74\) (\(J = 11\) Hz, \(^3J_{\text{Sn-H}} = 120\) Hz), and a 1-proton doublet of doublets at \(\delta\ 7.21\) (\(J = 15\) Hz, \(J = 11\) Hz, \(^4J_{\text{Sn-H}} = 7\) Hz), were assigned to HB, HA, and HC, respectively. The magnitude of the 3-bond tin-hydrogen coupling constant for HA indicates that HA and the trimethylstannyl group are located trans to each other on the carbon-carbon double bond. This stereochemical configuration, along with that of the \(\alpha,\beta\)-unsaturated ester function, were confirmed by nOe difference experiments. Thus, irradiation of the signal at \(\delta\ 6.74\) (HA) caused signal enhancements at \(\delta\ 5.72\) (HB) and 2.64 (-OCH\(_2\)CH\(_2\)-) whilst irradiation at \(\delta\ 5.72\) (HB) caused signal enhancement at \(\delta\ 6.74\) (HA).

The spectral data derived from compound 182 exhibited similiar features to those exhibited by compound 180 (see Experimental section).
Figure 2. 400 MHz $^1$H nmr spectrum of compound 180
3.7. Synthetic uses of \( (Z)-4-(\text{trimethylstannyl})-1,3\)-butadienes 166

With simple convenient methodology available for the preparation of stannyldienes 166, it was our next objective to demonstrate the synthetic utility of these substances. It was anticipated that these stannyldienes could serve effectively as synthetic equivalents of the donor synthon 183 (Scheme 25). In other words, treatment of compounds 166 with MeLi should result in transmetallation of the alkenylstannane moiety to give alkenyllithium species of general structure 184. These reagents should react with electrophiles, either directly or via the corresponding alkenylcopper(I) species 185, to give substituted 1,3-butadienes of general structure 186 (Scheme 25).

It was found that reaction of the stannyldiene 154 with MeLi (1.1 equivalents) for 45 min at -78°C, in THF, resulted in clean transmetallation of the alkenylstannane moiety (as judged by gc analysis of an aliquot taken from the reaction mixture). Reaction of the dienyllithium so formed with excess ethylene oxide gave, after purification of the crude product by flash chromatography and distillation, the homoallylic alcohol 187 in 71% yield.
This compound exhibited spectral data which were in full accord with the assigned structure (see Experimental section).

Additionally, the stannyldiene 154 was converted into the corresponding alkenyllithium species, as described above, which was then treated with CuBr•SMe2 (1.1 equivalents) to give the corresponding alkenylcopper(I) reagent. This species, upon reaction with 2,3-dibromopropene gave the compound 188 in 83 % yield (equation 32). The 400 MHz $^1$H nmr spectrum for 188 is shown in Figure 3. This spectrum shows a 2-proton triplet at $\delta$ 2.38 (-OCH$_2$CH$_2$-, $J = 6$ Hz), a 5-proton broad singlet at $\delta$ 3.35 (-OMe and the bis-allylic methylene), a 2-proton triplet at $\delta$ 3.62 (-OCH$_2$CH$_2$-) and a 2-proton singlet at $\delta$ 4.60 (-OCH$_2$O-). Also present are broad singlets at $\delta$ 5.48 and 5.62 due to HE and HF (or vice versa). Additionally, a 1-proton doublet of doublets at $\delta$ 5.12 ($J = 11$ Hz, $J = 1.5$ Hz), a 1-proton doublet of doublets at $\delta$ 5.20 ($J = 17$ Hz, $J = 1.5$ Hz), a 1-proton broad doublet at...
Figure 3. 400 MHz $^1$H nmr spectrum of compound 188
\( \delta 6.13 \) \((J = 11 \text{ Hz})\), and a 1-proton doublet of doublets of doublets at \( \delta 6.54 \) \((J = 11 \text{ Hz}, J = 11 \text{ Hz})\), may be assigned to \( \text{H}_C, \text{H}_B, \text{H}_A \) and \( \text{H}_D \), respectively.

Previous workers in this laboratory have shown that the alkenylstannanes \( 189^{103} \) and \( 190^{104} \) are readily transmetallated with \( \text{MeLi} \) in THF at low temperatures to form the corresponding alkenyllithium species \( 191 \) (equation 33) and \( 192 \) (equation 34), respectively. These alkenyllithium species are stable below approximately \(-60^\circ\text{C}\). However, at slightly higher temperatures \( 191 \) reacts, via intramolecular displacement of the chloride by the nucleophilic alkenyllithium moiety, to give methylenecyclopropane \( 193 \). Compound \( 192 \) likewise reacts to give methylenecyclobutane \( 194 \).

\[ 
\begin{align*}
\text{Cl} & \quad \text{MeLi, THF,} & \quad \text{Cl} \\
\text{SnMe}_3 & \quad -78^\circ\text{C} & \quad \text{Li} \\
189 & \quad > -60^\circ\text{C} & \quad \text{Cl} \\
& & \quad \text{Cl} \\
& & \quad \text{Li} \\
& & \quad \text{Cl} \\
193 & & 194 \\
\end{align*}
\]

The stannyldiene \( 174 \) (which is readily prepared from the acetylenic ketone \( 139 \) via the chemistry described earlier in this section of the thesis; see Table 7, entry 7 and Table 9, entry 4) is structurally similar to the alkenylstannane \( 190 \). On the basis of the chemistry of \( 190 \) described above it was anticipated that the alkenyllithium species \( 195 \), derived from reaction of \( 174 \) with \( \text{MeLi} \), would be a stable reagent at low temperature (Scheme 26). However, upon warming, it was expected that \( 195 \) should undergo intramolecular alkylation to give the strained cyclobutyl diene \( 196 \). This diene should, in principle, undergo Diels-
Alder reactions with suitable dienophiles to give interesting, structurally novel spirocyclobutanes of general structure 197 (Scheme 26).

Unfortunately, it was found that the transmetallation/intramolecular alkylation reactions of the stannyldiene 174 did not proceed cleanly under any of the reaction conditions that were employed. Glc analyses of the crude reaction products always showed the presence of two major compounds, which were assumed to be (based on glc retention times) the desired cyclobutyl diene 196 and the transmetallated but uncyclized compound 198 (Scheme 27). The ratio of these materials obtained in these reactions depended on the reaction conditions, and at best was approximately 6:1 in favour of 196. These products could be derived from the dienyllithium 195 via competing intramolecular cyclization and intramolecular proton transfer (Scheme 27). This proton transfer could proceed via a 5-membered ring transition state 199 to give an allyllithium species 200, which cannot undergo intramolecular alkylation due to geometrical constraints. Upon workup, the allyllithium 200 would be protonated to give the compound 198.
On the basis of the above proposed reaction pathway it was expected that the desired cyclobutyl diene 196 would be more readily prepared via transmetallation/intramolecular alkylation reaction using the iodide 201 as starting material (Scheme 28). The alkenyllithium species derived from 201 would be expected to undergo intramolecular alkylation much faster than the alkenyllithium species 195 (derived from the chloride 174). Therefore, it was hoped that the intramolecular proton transfer mode of reaction would be suppressed.

The iodide 201 was prepared from the chloride 174 via reaction with NaI in acetone (see Experimental section). Fortunately, when a solution of compound 201 in dry THF was treated with MeLi at -78°C and the solution was warmed to -48°C, glc analysis of the reaction mixture after workup showed the presence of one compound, which was assumed to be the desired cyclized product 196 (based on its glc retention time). Due to the volatility of this compound attempts to isolate it free of solvent were not carried out. Instead, it was treated,
in situ, with the highly reactive dienophile tetracyanoethylene (Scheme 28). Thus, to the ethereal solution (argon atmosphere, room temperature) of the crude diene 196 obtained after extractive workup, was added, in batches, tetracyanoethylene. Upon addition of each batch, the solution became bright red and then was decolourized immediately. When the reaction was complete, as judged by glc analysis, the crude reaction product was purified by flash chromatography to give (after recrystallization) the compound 202 in 69% yield (Scheme 28).

In a manner similar to that described above, a solution of the crude cyclobutyl diene 196 was treated with excess dimethylacetylene dicarboxylate to give the corresponding Diels-Alder adduct 203 in 70% overall yield (Scheme 28). However, the use of excess dienophile and prolonged heating was required in order for this reaction to proceed to completion.

The success of these Diels-Alder reactions might be attributable primarily to two factors. Firstly, the diene 196 should be able to adopt the required cisoid conformation fairly easily. Comparison of molecular models of 196 and the similar diene 204 indicates that the steric interaction between HA and the protons on the four-membered ring in compound 196...
(cisoid conformation) is less severe than that between HA and the methyl group in compound 204 (cisoid conformation).

Secondly, there is release of some strain in the four-membered ring upon formation of the Diels-Alder adducts from the diene 196. Carbon 1 is sp² hybridized in compound 196 and becomes sp³ hybridized in the products. This release in angle strain should be "felt" by the transition state for the Diels-Alder reaction.

![chemical structures]

The reactions described above constitute a novel method for the preparation of spirocyclic cyclobutanes. It is quite possible that this methodology could be extended to the preparation of a variety of spirocyclic compounds of general structure 205, by appropriate choices of stannyldienes for the transmetallation/intramolecular alkylation reaction, and dienophiles for the Diels-Alder reaction (equation 35).

![chemical reaction]

3.8. Conclusions

It was shown in this section of the thesis that α,β-acetylenic aldehydes and ketones 115 are efficiently and stereoselectively converted into the corresponding
(Z)-β-trimethylstannyl α,β-unsaturated aldehydes and ketones 151, by reaction with hexamethylditin under Pd(0) catalysis (Scheme 29). These unsaturated carbonyl compounds are excellent precursors to a variety of (Z)-4-(trimethylstannyl)-1,3-butadienes 166, by way of Wittig olefination reactions. The synthetic utility of functionalized stannyldienes of general structure 166 was demonstrated by the efficient preparation of compounds 187 and 188 (via the transmetallation/alkylation reactions of compound 154). It was also shown that the stannyldiene 201 may be converted in a simple, efficient manner into the spirocyclic cyclobutanes 202 and 203. The synthetic applications of the stannyldienes 166 are again exemplified in the next section of this thesis, where these compounds are used as the starting materials for the preparation of highly substituted bicyclo[3.2.1]octa-2,6-dienes.

Scheme 29
IV. Experimental

For General experimental details and "Solvents and reagents", see Experimental section for Part 1 of this thesis.

Preparation of the terminal acetylene 121.

To a stirred solution of 4-pentyn-1-ol (3 g, 35.7 mmol) in dry CH₂Cl₂ (100 mL) (argon atmosphere) was added NaOAc (860 mg, 0.3 equiv.) and PCC (11.6 g, 1.5 equiv.). After the mixture had been stirred for 2 h at room temperature, dry Et₂O (approx 100 mL) was added and the mixture was filtered through Florisil® (approx. 100 g), using ether as the eluant. The material remaining in the reaction vessel was rinsed (and sonicated) thoroughly with Et₂O, and the washings were also passed through the Florisil® column. The combined eluate was dried (MgSO₄) and most of the solvent was removed by atmospheric pressure distillation using a long Vigreux column (50 cm x 2 cm). The crude product thus obtained was immediately dissolved in dry THF (100 mL) (argon atmosphere) and the solution was cooled to -78°C. A solution of vinyl magnesium bromide [2 equiv. (based on 35.7 mmol of 4-pentyn-1-ol)] in THF was added at -78°C and then the mixture was allowed to warm to room temperature. Saturated aqueous NH₄Cl (approx. 50 mL) and Et₂O (approx. 50 mL)
were added, and the phases were separated. The aqueous phase was extracted with Et₂O (3 x 50 mL) and the combined organic extracts were dried (MgSO₄) and concentrated by atmospheric pressure distillation, using a long Vigreux column (50 cm x 2 cm). The remaining volatile oil was carried on to the next step without further purification.

To a stirred solution of the crude oil in dry DMF (80 mL) (argon atmosphere) was added imidazole (6.07 g, 2.5 equiv. (based on 35.7 mmol of 4-pentyn-1-ol)) and TBDMSCl (8.07 g, 1.5 equiv.). The mixture was stirred at room temperature overnight. Saturated aqueous NaHCO₃ (approx 50 mL) and Et₂O (approx 50 mL) were added, and the aqueous phase was extracted with Et₂O (3 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL) and then were dried (MgSO₄) and concentrated. Flash chromatography of the crude reaction product (2:98 Et₂O - petroleum ether; 180 g of silica gel), followed by distillation of the oil thus obtained (80-90°C/0.5 Torr), gave 2.5 g (31%) of the acetylene 121, a colourless oil which exhibited ir (neat): 3314, 3081, 2121, 1254, 838 cm⁻¹; ¹H nmr (400 MHz) δ: 0.02 (s, 3H, -SiMe), 0.06 (s, 3H, -SiMe), 0.89 (s, 9H, -SiBuᵗ), 1.68 (m, 2H, methylene Y), 1.92 (t, 1H, acetylenic H, J = 4 Hz), 2.22 (m, 2H, methylene Z), 4.22 (m, 1H, Hₓ), 5.05 (ddd, 1H, Hₓ, J = 10 Hz, J = 2 Hz, J = 2 Hz), 5.17 (ddd, 1H, Hₓ, J = 16 Hz, J = 2 Hz, J = 2 Hz), 5.78 (ddd, 1H, Hₓ, J = 16 Hz, J = 10 Hz, J = 6 Hz). Exact Mass calcd. for C₁₃H₂₄OSi (M⁺): 224.1597; found: 224.1593.

**General Procedure D. The preparation of primary propargyl alcohols 117A.**

To a cold (-78°C) stirred solution of the terminal acetylene (1 equiv.) in dry THF (argon atmosphere) was added a solution of MeLi (1 equiv.) in Et₂O. After the mixture had been stirred at -78°C for 10 min and at -20°C for 1 h, solid paraformaldehyde (4 equiv.) was added and the mixture was allowed to warm to room temperature. After the mixture had been
stirred for 30 min at room temperature, saturated aqueous NaHCO₃ and Et₂O were added. The phases were separated and the aqueous phase was extracted with Et₂O. The combined organic extracts were dried (MgSO₄) and concentrated. The crude product was purified by flash chromatography, followed by distillation.

**Preparation of the alcohol 123.**

Following general procedure D, the terminal acetylene 118 (2.8 g, 15.22 mmol; in 75 mL of dry THF) was converted into the corresponding lithium acetylide, which was allowed to react with paraformaldehyde (1.85 g, 4 equiv.). Flash chromatography of the crude reaction product (3:7 Et₂O - petroleum ether; 130 g of silica gel), followed by distillation of the oil thus obtained (75-80°C/0.5 Torr), gave 2.4 g (74%) of the alcohol 123, a colourless oil which exhibited ir (neat): 3394, 2227, 1473, 1109 cm⁻¹; ¹H nmr (300 MHz) δ: 0.06 (s, 6H, -SiMe₃), 0.89 (s, 9H, -SiBu₄), 1.8-1.95 (br m, 1H, -OH), 2.43 (tt, 2H, -SiOCH₂CH₂-, 1/ = 7 Hz, 1/ = 2 Hz), 3.72 (t, 2H, -SiOCH₂-, 1/ = 1 Hz), 4.24 (br s, 2H, -CH₂OH). On addition of D₂O, the signal at δ 1.8-1.95 (-OH) disappeared, and the signal at δ 4.24 (-CH₂OH) sharpened to a t (1/ = 2 Hz). **Exact Mass** calcd. for C₇H₁₃O₂Si (M⁺-Bu₄): 157.0685; found: 157.0679; cims (negative ion detection, NH₃): 213 (M⁻-H).
Preparation of the alcohol 124.

Following general procedure D, the terminal acetylene 120 (2 g, 9.43 mmol; in 50 mL of dry THF) was converted into the corresponding lithium acetylide, which was allowed to react with paraformaldehyde (1.2 g, 4 equiv.). Flash chromatography of the crude reaction product (3:7 Et₂O - petroleum ether; 85 g of silica gel), followed by distillation of the oil thus obtained (100-110°C/0.5 Torr), gave 1.85 g (81%) of the alcohol 124, a colourless oil which exhibited ir (neat): 3362, 2230, 1256, 1107, 838 cm⁻¹; ¹H nmr (300 MHz) δ: 0.04 (s, 6H, -SiMe₂), 0.86 (s, 9H, -SiBu°), 1.57 (m, 4H, -SiOCH₂CH₂CH₂-), 1.78 (br s, 1H, -OH), 2.23 (m, 2H, -SiOCH₂CH₂CH₂CH₂-), 3.61 (t, 2H, -SiOCH₂-, J = 7 Hz), 4.24 (br t, 2H, -CH₂OH, J = 2 Hz). On addition of D₂O, the signal at δ 1.78 (-OH) disappeared. Exact Mass calcd. for C₉H₂₇O₂Si (M⁺-Bu°): 185.0998; found: 185.0997; cims (negative ion detection, NH₃): 241 (M⁻-H).

Preparation of the alcohol 125.
Following general procedure D, the terminal acetylene 119 (8.46 g, 74.2 mmol; in 200 mL of dry THF) was converted into the corresponding lithium acetylide, which was allowed to react with paraformaldehyde (8.9 g, 4 equiv.). Flash chromatography of the crude reaction product (65:35 Et2O - petroleum ether; 280 g of silica gel), followed by distillation of the oil thus obtained (110-120°C/0.5 Torr), gave 8.60 g (80%) of the alcohol 125, a colourless oil which exhibited ir (neat): 3424, 2227, 1151, 1111, 1029 cm⁻¹; ¹H nmr (400 MHz) δ: 0.75-0.9 (br m, 1H, -OH), 1.52 (tt, 2H, -OCH₂CH₂-,  J = 6.5 Hz, J = 2 Hz), 3.38 (s, 3H, -OMe), 3.65 (t, 2H, -OCH₂CH₂-,  J = 6.5 Hz), 4.24 (dt, 2H, -CH₂OH,  J = 6 Hz, J = 2 Hz), 4.64 (s, 2H, -OCH₂O-). On addition of D₂O, the signal at δ 0.75-0.9 (-OH) disappeared, and the signal at δ 4.24 (-CH₂OH) collapsed to a br s. **Exact Mass** calcd. for C₅H₇O₂ (M⁺-C₂H₅O): 99.0446; found: 99.0446.

**General Procedure E. The preparation of secondary propargyl alcohols 117B.**

To a cold (-78°C), stirred solution of the terminal acetylene (1 equiv.) in dry THF (argon atmosphere) was added a solution of MeLi (1 equiv.) in Et₂O. After the mixture had been stirred at -78°C for 10 min and at -20°C for 1 h, it was re-cooled to -78°C and the aldehyde (1.5-5 equiv.) (freshly distilled) was added. The mixture was stirred at -78°C for 10 min and was then allowed to warm to room temperature. Saturated aqueous NaHCO₃ and Et₂O were added, the phases were separated, and the aqueous phase was extracted with Et₂O. The combined organic extracts were dried (MgSO₄) and concentrated. The crude product was purified by flash chromatography, followed by distillation.
Preparation of the alcohol 126.

Following general procedure E, the terminal acetylene 118 (1.5 g, 8.15 mmol, 1 equiv.; in 50 mL of dry THF) was converted into the corresponding lithium acetylide, which was allowed to react with acetaldehyde (0.72 g, 2 equiv.). Flash chromatography of the crude reaction product (3:7 Et2O - petroleum ether; 80 g of silica gel), followed by distillation of the oil thus obtained (80-90°C/0.5 Torr), gave 1.71 g (92%) of the alcohol 126, a colourless oil which exhibited ir (neat): 3368, 2250, 1256, 818 cm⁻¹; ¹H nmr (300 MHz) δ: 0.04 (s, 6H, -SiMe3), 0.86 (s, 9H, -SiBu+i), 1.39 (d, 3H, -Me, J = 8 Hz), 2.25 (br s, 1H, -OH), 2.38 (td, 2H, -OCH2CH2-, J = 7 Hz, J = 2 Hz), 3.68 (t, 2H, -OCH2CH2-, J = 7 Hz), 4.49 (m, 1H, -CHOH-). On addition of D2O, the signal at δ 2.25 (-OH) disappeared, and the signal at δ 4.49 (-CHOH-) simplified to a br q (J = 8 Hz).

Exact Mass calcd. for C₈H₁₅O₂Si (M⁺-Bu+i): 171.0842; found: 171.0834; cims (negative ion detection, NH₃): 227 (M⁻-H).

Preparation of the alcohol 127.
Following general procedure E, the terminal acetylene 120 (2 g, 9.43 mmol, 1 equiv.; in 50 mL of dry THF) was converted into the corresponding lithium acetylide, which was allowed to react with acetaldehyde (830 mg, 2 equiv.). Flash chromatography of the crude reaction product (3:7 Et₂O - petroleum ether; 80 g of silica gel), followed by distillation of the oil thus obtained (110-120°C/0.5 Torr), gave 2.17 g (90%) of the alcohol 127, a colourless oil which exhibited IR (neat): 3353, 2248, 1256 cm⁻¹; ¹H nmr (300 MHz) δ: 0.03 (s, 6H, -SiMe₂), 0.87 (s, 9H, -SiBu¹), 1.40 (d, 3H, J = 8 Hz), 1.56 (m, 4H, -OCH₂CH₂CH₂CH₂-), 1.74-1.80 (br m, 1H, -OH), 2.22 (m, 2H, -OCH₂CH₂CH₂CH₂-), 3.60 (t, 2H, -OCH₂CH₂CH₂CH₂-, J = 6 Hz), 4.50 (m, 1H, -CHMe-). On addition of D₂O, the signal at δ 1.74-1.80 (-OH) disappeared, and the signal at δ 4.50 (-CHMe-) simplified to a br q (J = 8 Hz). Exact Mass calcd. for C₁₀H₁₉O₂Si (M⁺-Bu⁴): 199.1155; found: 199.1156; cims (negative ion detection, NH₃): 255 (M⁻-H).

Preparation of the alcohol 128.

Following general procedure E, 1,6-heptadiyne (1 g, 10.87 mmol, 1 equiv.; in 50 mL of dry THF) was converted into the corresponding lithium acetylide, which was allowed to react with acetaldehyde (2.39 g, 5 equiv.). Flash chromatography of the crude product (35:65 Et₂O - petroleum ether; 65 g of silica gel), followed by distillation of the oil thus
obtained (80-85°C/0.5 Torr), gave 883 mg (60%) of the alcohol 128, a colourless oil which exhibited ir (neat): 3301, 2247, 2118, 1154, 1013, 882 cm⁻¹; ¹H nmr (400 MHz) δ: 1.41 (d, 3H, -CHMe-, J = 6.5 Hz), 1.65-1.75 (m, 3H, -OH and methylene Y), 1.95 (t, 1H, acetylenic H, J = 2.5 Hz), 2.25-2.40 (m, 4H, methylenes X and Z), 4.49 (m, 1H, -CHMe-). On addition of D₂O, the signal at δ 1.65-1.75 (-OH and H_y) collapsed to a quintet (2H, H_y, J = 7 Hz), and the signal at 4.49 (-CHMe-) simplified to a br q (J = 6.5 Hz). Exact Mass calcd. for C₉H₁₁O (M⁺-H): 135.0810; found: 135.0815.

Preparation of the alcohol 129.

Following general procedure E, 5-chloro-1-pentyne (4 g, 39 mmol, 1 equiv.; in 100 mL of dry THF) was converted into the corresponding lithium acetylide, which was allowed to react with acetaldehyde (3.43 g, 2 equiv.). Flash chromatography of the crude reaction product (3:7 Et₂O - petroleum ether; 150 g of silica gel), followed by distillation of the oil thus obtained (65-70 °C/0.5 Torr), gave 4.85 g (85%) of the alcohol 129, a colourless oil which exhibited ir (neat): 3372, 1089, 1050, 881 cm⁻¹; ¹H nmr (300 MHz) δ: 1.36 (d, 3H, -Me, J = 8 Hz), 1.80 (quintet, 2H, ClCH₂CH₂CH₂-, J = 8 Hz), 2.33 (td, 2H, ClCH₂CH₂CH₂-, J = 8 Hz, J = 2 Hz), 2.75 (br s, 1H, -OH), 3.59 (t, 2H, ClCH₂CH₂CH₂-, J = 8 Hz), 4.46 (m, 1H, -CHMe-). On addition of D₂O, the signal at
\[ \delta 2.75 (-\text{OH}) \text{ disappeared, and the signal at } \delta 4.46 (-\text{CHMe}) \text{ simplified to a br q } (J = 8 \text{ Hz}). \]

*Exact Mass* calcd. for \( \text{C}_7\text{H}_{11}\text{ClO}(\text{M}^+) \): 146.0499; found: 146.0504.

**Preparation of the alcohol 130**

Following general procedure E, \(3,3\text{-dimethyl-1-butyne \ (3.5 g, 42.68 mmol, 1 equiv.; in 120 mL of dry THF)} \) was converted into the corresponding lithium acetylide, which was allowed to react with heptanal (\(7.3 \text{ g, 1.5 equiv.)} \). Flash chromatography of the crude reaction product (3:7 Et\(_2\)O - petroleum ether; 250 g of silica gel), followed by distillation of the oil thus obtained (80-85°C/0.5 mmol), gave 8.05 g (96%) of the alcohol 130, a colourless oil which exhibited ir (neat): 3342, 2238, 1460, 1265 cm\(^{-1}\); \(^1\)H nmr (300 MHz) \(\delta\): 0.87 (m, 3H, -\text{CH}_2\text{CH}_3), 1.20 (s, 9H, -\text{Bu}^t), 1.25-1.70 (m, 10H), 2.85 (br s, 1H, -\text{OH}), 4.33 (br t, 1H, -\text{CHOH}, J = 8 \text{ Hz}). On addition of D\(_2\)O, the signal at \(\delta 2.85 (-\text{OH}) \text{ disappeared. *Exact Mass* calcd. for C}_{13}\text{H}_{24}\text{O (M}^+) \): 196.1828; found: 196.1819.
Preparation of the alcohol 131.

Following general procedure E, the terminal acetylene 118 (8.212 g, 44.6 mmol, 1 equiv.; in 120 mL of dry THF) was converted into the corresponding lithium acetylide, which was allowed to react with 2-methylpropanal (4.82 g, 1.5 equiv.). Flash chromatography of the crude reaction product (3:7 Et2O - petroleum ether; 300 g of silica gel), followed by distillation of the oil thus obtained (110-120°C/0.5 Torr), gave 9.70 g (85%) of the alcohol 131, a colourless oil which exhibited ir (neat): 3368, 2218, 1256, 1113, 836, 777 cm⁻¹; ¹H nmr (400 MHz) δ: 0.06 (s, 6H, -SiMe₂), 0.89 (s, 9H, -SiBu⁴), 0.96, 0.98 (2 doublets, 6H, Me₂CH-, J = 6 Hz, J = 6 Hz), 1.70 (br d, 1H, -OH, J = 4 Hz), 1.82 (m, 1H, -CHMe₂), 2.42 (td, 2H, -OCH₂CH₂-, J = 8 Hz, J = 2 Hz), 3.70 (t, 2H, -OCH₂CH₂-, J = 8 Hz), 4.13 (br m, 1H, -CHOH-). On addition of D₂O, the signal at δ 1.70 (-OH) disappeared, and the signal at δ 4.13 (-CHOH-) simplified to a br d (J = 6 Hz). Exact Mass calcd. for C₁₁H₂₁O₂Si (M⁻-Pr): 213.1311; found: 213.1318; cims (positive ion detection, NH₃): 257 (M⁺+H).

General Procedure F. The oxidation of propargyl alcohols 117 to α,β-acetylenic aldehydes and ketones 115

A mixture of the propargyl alcohol (1 equiv.), NaOAc (0.3 equiv) and PCC (1.5 - 2.5 equiv.) in dry CH₂Cl₂ (argon atmosphere) was stirred (2 - 2.5 h) at room temperature. Dry
Et₂O (approx. the same volume as that of solvent used for the reaction) was added and the mixture was filtered through a column of Florisil® (approx. 30 g of Florisil® per g of propargyl alcohol), using ether as the eluant. The material remaining in the reaction vessel was rinsed (and sonicated) thoroughly with Et₂O, and the washings were also passed through the Florisil® column. The combined eluate was dried (MgSO₄) and concentrated. The crude reaction product was purified by flash chromatography, followed by distillation.

General Procedure G. The oxidation of primary propargyl alcohols 117A to α,β-acetylenic aldehydes 115A

![Chemical Structure](image)

To a stirred suspension of the Dess-Martin periodinane reagent 145⁹³ (1.3 equiv.) (prewashed with dry Et₂O) in dry CH₂Cl₂ (approx. 5 mL per mmol of the periodinane) (argon atmosphere) was added a solution of the propargyl alcohol (1 equiv.) in dry CH₂Cl₂ (approx 3 mL per mmol of the propargyl alcohol). After the mixture had been stirred for 15 min at room temperature, it was diluted with Et₂O (approx. the same volume as that of solvent used in the reaction) and then was poured into saturated aqueous NaHCO₃ (approx. the same volume as the volume of solvent used for the reaction) containing 7 equiv. of Na₂S₂O₃. The mixture was stirred vigorously until all solids had dissolved (approx. 10 min). The phases were separated and the aqueous phase was extracted with Et₂O. The combined organic extracts were washed with saturated aqueous NaHCO₃ and with water,
and were then dried (MgSO₄) and concentrated. The crude reaction product was purified by distillation.

**Preparation of the aldehyde 133.**

Following general procedure F, the propargyl alcohol 123 (3.6 g, 16.82 mmol, 1 equiv.; in 120 mL of dry CH₂Cl₂) was allowed to react with NaOAc (404 mg, 0.3 equiv.) and PCC (5.44 g, 1.5 equiv.) for 2 h at room temperature. Flash chromatography of the crude reaction mixture (15:85 Et₂O - petroleum ether; 140 g of silica gel), followed by distillation of the oil thus obtained (75-85°C/0.5 Torr), gave 2.55 g (72%) of the aldehyde 133, a colourless oil which exhibited ir (neat): 2740, 2207, 1673, 1257 cm⁻¹; ¹H nmr (300 MHz) δ: 0.05 (s, 6H, -SiMe₂), 0.87 (s, 9H, -SiBu¹), 2.60 (t, 2H, -OCH₂CH₂-, J = 8 Hz), 3.77 (t, 2H, -OCH₂CH₂-, J = 8 Hz), 9.15 (s, 1H, -CHO). *Exact Mass* calcd. for C₇H₁₁O₂Si (M⁺-Bu¹): 155.0528; found: 155.0532; cims (negative ion detection, NH₃): 211 (M⁻-H).

Following general procedure G, the propargyl alcohol 123 (2.4 g, 11.2 mmol, 1 equiv.) was allowed to react with the Dess-Martin periodinane reagent (6.2 g, 1.3 equiv.) for 15 min at room temperature. Distillation of the crude reaction product gave 2.1 g (88%) of the aldehyde 133.
Preparation of the aldehyde 134.

Following general procedure F, the propargyl alcohol 124 (1 g, 4.13 mmol, 1 equiv.; in 50 mL of dry CH2Cl2) was allowed to react with NaOAc (100 mg, 0.3 equiv.) and PCC (1.34 g, 1.5 equiv.) for 2 h at room temperature. Flash chromatography of the crude reaction product (15:85 Et2O - petroleum ether; 60 g of silica gel), followed by distillation of the oil thus obtained (95-100°C/0.5 Torr), gave 730 mg (74%) of the aldehyde 134, a colourless oil which exhibited ir (neat): 2742, 2202, 1673, 1107, 838 cm⁻¹; ¹H nmr (300 MHz) δ: 0.05 (s, 6H, -SiMe₂), 0.9 (s, 9H, -SiBu¹), 1.65 (m, 4H, -OCH₂CH₂CH₂CH₂-), 2.46 (t, 2H, -OCH₂CH₂CH₂CH₂-, J = 8 Hz), 3.63 (t, 2H, -OCH₂CH₂CH₂CH₂-, J = 6 Hz), 9.18 (s, 1H, -CHO). Exact Mass calcd. for C₉H₁₅O₂Si (M⁺-Bu¹): 183.0842; found: 183.0834; cims (negative ion detection, NH₃): 239 (M⁻-H).

Following general procedure G, the propargyl alcohol 124 (900 mg, 3.7 mmol, 1 equiv.) was allowed to react with the Dess-Martin periodinane reagent (2.05 g, 1.3 equiv.) for 15 min at room temperature. Distillation of the crude reaction product gave 768 mg (86%) of the aldehyde 134.
Preparation of the aldehyde 135.

Following general procedure F, the propargyl alcohol 125 (3.55 g, 24.65 mmol, 1 equiv.; in 150 mL of dry CH₂Cl₂) was allowed to react with NaOAc (600 mg, 0.3 equiv.) and PCC (8.0 g, 1.5 equiv.) for 2 h at room temperature. Flash chromatography of the crude reaction product (6:4 Et₂O - petroleum ether; 120 g of silica gel), followed by distillation of the oil thus obtained (90-95°C/0.5 Torr), gave 1.90 g (57%) of the aldehyde 135, a colourless oil which exhibited ir (neat): 2827, 2207, 1669, 1151, 1111, 963 cm⁻¹; ¹H nmr (400 MHz) δ: 2.72 (t, 2H, -OCH₂CH₂-, J = 7 Hz), 3.38 (s, 3H, -OMe), 3.72 (t, -OCH₂CH₂-, J = 7 Hz), 4.64 (s, 2H, -OCH₂O-), 9.18 (s, 1H, -CHO). Exact Mass calcd. for C₇H₉O₃ (M⁺-H): 141.0551; found: 141.0546.

Preparation of the ketone 136.

TBDMSO— 136
Following general procedure F, the propargyl alcohol 126 (200 mg, 0.88 mmol, 1 equiv.; in 8 mL of dry CH₂Cl₂) was allowed to react with NaOAc (21 mg, 0.3 equiv.) and PCC (472 mg, 2.5 equiv.) for 2.5 h at room temperature. Flash chromatography of the crude reaction product (1:9 Et₂O - petroleum ether; 45 g of silica gel), followed by distillation of the oil thus obtained (70-80°C/0.5 Torr), gave 146 mg (74%) of the ketone 136, a colourless oil which exhibited ir (neat): 2214, 1680, 1113, 839 cm⁻¹; ¹H nmr (300 MHz) δ: 0.08 (s, 6H, -SiMe₂), 0.89 (s, 9H, -SiBu¹), 2.30 (s, 3H, -Me), 2.56 (t, 2H, -OCH₂CH₂-, / = 8 Hz), 3.76 (t, 2H, -OCH₂CH₂-, J = 8 Hz). Exact Mass calcd. for C₁₀H₁₅O₂Si (M⁺-Bu¹): 169.0685; found: 169.0684.

Preparation of the ketone 137.

Following general procedure F, the propargyl alcohol 127 (1 g, 3.9 mmol, 1 equiv.; in 40 mL of dry CH₂Cl₂) was allowed to react with NaOAc (96 mg, 0.3 equiv.) and PCC (2.10 g, 2.5 equiv.) for 2.5 h at room temperature. Flash chromatography of the crude reaction product (1:9 Et₂O - petroleum ether; 75 g of silica gel), followed by distillation of the oil thus obtained (95-100°C/0.5 Torr), gave 755 mg (76%) of the ketone 137, a colourless oil which exhibited ir (neat): 2212, 1680, 1360, 1104 cm⁻¹; ¹H nmr (300 MHz) δ: 0.04 (s, 6H, -SiMe₂), 0.88 (s, 9H, -SiBu¹), 1.62 (m, 4H, -OCH₂CH₂CH₂CH₂-), 2.30 (s, 3H, -Me), 2.38 (t, 2H, -OCH₂CH₂CH₂CH₂-, J = 7 Hz), 3.62 (t, 2H, -OCH₂CH₂CH₂CH₂-, J = 7 Hz).
= 6 Hz). *Exact Mass* calcd. for C\textsubscript{10}H\textsubscript{17}O\textsubscript{2}Si (M\textsuperscript{+}-Bu\textsuperscript{i}) : 197.0998; found: 197.1006; cims (negative ion detection, NH\textsubscript{3}): 253 (M\textsuperscript{−}-H).

Preparation of the ketone 138.

\begin{center}
\includegraphics[width=0.2\textwidth]{138}
\end{center}

Following general procedure F, the propargyl alcohol 128 (130 mg, 0.96 mmol, 1 equiv.; in 8 mL of dry CH\textsubscript{2}Cl\textsubscript{2}) was allowed to react with NaOAc (23 mg, 0.3 equiv.) and PCC (515 mg, 2.5 equiv.) for 2.5 h at room temperature. Flash chromatography of the crude reaction mixture (1:9 Et\textsubscript{2}O - petroleum ether; 35 g of silica gel), followed by distillation of the oil thus obtained (120-130°C/6.0 Torr), gave 70 mg (55%) of the ketone 138, a colourless oil which exhibited ir (neat): 2215, 1680, 1231 cm\textsuperscript{-1}; \textsuperscript{1}H nmr (400 MHz) \textdelta: 1.79 (quintet, 2H, methylene Y, J = 7 Hz), 1.98 (t, 1H, acetylenic H, J = 2.5 Hz), 2.31 (s, 3H, -Me), 2.32 (td, 2H, methylene X, J = 7 Hz, J = 2.5 Hz), 2.50 (t, 2H, methylene Z, J = 7 Hz). *Exact Mass* calcd. for C\textsubscript{9}H\textsubscript{9}O (M\textsuperscript{+}-H): 133.0653; found: 133.0651.
Preparation of the ketone 139.

Following general procedure F, the propargyl alcohol 129 (1.5 g, 10.24 mmol, 1 equiv.; in 100 mL of dry CH₂Cl₂) was allowed to react with NaOAc (252 mg, 0.3 equiv.) and PCC (5.52 g, 2.5 equiv.) for 2.5 h at room temperature. Flash chromatography of the crude reaction product (1:9 Et₂O - petroleum ether; 80 g of silica gel), followed by distillation of the oil thus obtained (60-65°C/0.5 Torr), gave 1.09 g (74%) of the ketone 139, a colourless oil which exhibited IR (neat): 2215, 1677, 1232, 734 cm⁻¹; ¹H nmr (300 MHz) δ: 2.0 (quintet, 2H, -CH₂CH₂CH₂-, J = 7 Hz), 2.30 (s, 3H, -Me), 2.54 (t, 2H, -CH₂CH₂CH₂-, J = 7 Hz), 3.51 (t, 2H, -CH₂CH₂CH₂-, J = 7 Hz). Exact Mass calcd. for C₇H₉³⁵ClO (M⁺): 144.0343; found: 144.0343.

Preparation of the ketone 140

119
Following general procedure F, the propargyl alcohol 130 (4.0 g, 20.41 mmol, 1 equiv.; in 130 mL of dry CH₂Cl₂) was allowed to react with NaOAc (500 mg, 0.3 equiv.) and PCC (11 g, 2.5 equiv.) for 2.5 h at room temperature. Flash chromatography of the crude reaction product (1:9 Et₂O - petroleum ether; 150 g of silica gel), followed by distillation of the oil thus obtained (75-80°C/0.5 Torr), gave 2.85 g (72%) of the ketone 140, a colourless oil which exhibited ir (neat): 2213, 1675, 1263, 1142 cm⁻¹; ¹H nmr (300 MHz) δ: 0.87 (m, 3H, -CH₂CH₃), 1.28 (br s, 15H), 1.63 (m, 2H), 2.50 (t, 2H, -C(O)CH₂-, J = 7 Hz). Exact Mass calcd. for C₁₃H₂₂O (M⁺): 194.1672; found 194.1680.

Preparation of the ketone 141.

\[
\begin{aligned}
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\text{141}
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\]

Following general procedure F, the propargyl alcohol 131 (2.92 g, 11.41 mmol, 1 equiv.; in 80 mL of dry CH₂Cl₂) was allowed to react with NaOAc (280 mg, 0.3 equiv.) and PCC (6.15 g, 2.5 equiv.) for 2.5 h at room temperature. Flash chromatography of the crude reaction product (1:9 Et₂O - petroleum ether; 150 g of silica gel), followed by distillation of the oil thus obtained (95-105°C/0.5 Torr), gave 2.35 g (81%) of the ketone 141, a colourless oil which exhibited ir (neat): 1676, 2214, 1118, 779 cm⁻¹; ¹H nmr (400 MHz) δ: 0.08 (s, 6H, -SiMe₂), 0.90 (s, 9H, -SiBu⁴), 1.18 (d, 6H, -CHMe₂, J = 8 Hz), 2.58-2.68 (m, 3H, -CHMe₂ and -OCH₂CH₂-), 3.80 (t, 2H, -OCH₂CH₂-, J = 6 Hz). Exact Mass calcd. for
C_{10}H_{17}O_{2}Si (M^+-Bu): 197.0998; found: 197.1003; cims (positive ion detection, CH_{4}): 255 (M^+H).

Preparation of the ketone 142.

To a cold (−78°C), stirred solution of 3-methyl-1-butyne (3 g, 44 mmol, 1 equiv.) in dry THF (150 mL) (argon atmosphere) was added a solution of MeLi (1 equiv.) in Et_{2}O. After the mixture had been stirred at -78°C for 10 min and at -20° for 1 h, it was re-cooled to -78°C and acetaldehyde (2.52 g, 1.3 equiv.) was added. The mixture was stirred at -78°C for 10 min and then was allowed to warm to room temperature. Saturated aqueous NaHCO_{3} (50 mL) and Et_{2}O (50 mL) were added. The phases were separated and the aqueous layer was extracted with Et_{2}O (3 × 50 mL). The combined organic extracts were dried (MgSO_{4}) and most of the solvent was removed by atmospheric pressure distillation using a long Vigreux column (50 cm x 2 cm). Distillation of the residual oil thus obtained (80-90°C/10 Torr) gave 4.6 g of a crude oil, which was carried on to the next step without further purification.

To a solution of this crude oil in dry CH_{2}Cl_{2} (200 mL) (argon atmosphere), was added NaOAc (1.08 g, 0.3 equiv. (based on 44 mmol of 3-methyl-1-butyne)) and PCC (14.22 g, 1.5 equiv.). After the mixture had been stirred at room temperature for 3 h, dry Et_{2}O (approx 100 mL) was added and the mixture was filtered through a column of Florisil®
(approx 150 g), using Et₂O as the eluant. The material remaining in the reaction vessel was thoroughly rinsed (and sonicated) with Et₂O, and the washings were also passed through the Florisil® column. The combined eluate was dried (MgSO₄) and most of the solvent was removed by atmospheric pressure distillation using a long Vigreux column (50 cm x 2 cm). Distillation of the crude oil thus obtained (80-90°C/10 Torr) gave 2.7 g (56%) of the ketone 142, a colourless oil which exhibited ir (neat): 2208, 1679, 1228 cm⁻¹; ¹H nmr (300 MHz) δ: 1.20 (d, 6H, -CHMe₂, ⁷J = 8 Hz), 2.29 (s, 3H, -Me), 2.68 (septet, 1H, -CHMe₂, ⁷J = 8 Hz). Exact Mass calcd. for C₇H₁₀O (M⁺): 110.0732; found: 110.0726.

**General Procedure H. The preparation of α,β-acetylenic methyl ketones from the corresponding terminal acetylenes**

To a cold (-78°C), stirred solution of the terminal acetylene (1 equiv.) in dry Et₂O (argon atmosphere) was added a solution of MeLi (1 equiv.) in Et₂O. After the reaction mixture had been stirred at -78°C for 10 min and at -20°C for 1 h, it was re-cooled to -78°C and then was transferred slowly (over approx. 10 min, via cannula) into a cold (-78°C), stirred solution of Ac₂O (2 equiv.) in Et₂O. After the mixture had been stirred for 10 min at -78°C and 30 min at -48°C, saturated NH₄Cl-NH₄OH (pH 8) (approx. the same volume as that of solvent used for the reaction) was added and the vigorously stirred mixture was allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with Et₂O. The combined organic extracts were washed with saturated aqueous NH₄Cl, dried (MgSO₄) and concentrated. The crude reaction product was then purified by flash chromatography, followed by distillation.
Preparation of the ketone 136

Following general procedure H, the terminal acetylene 118 (3.26 g, 17.7 mmol, 1 equiv.; in 80 mL of dry Et2O) was converted into the corresponding lithium acetylide, which was added to Ac2O (3.61 g, 2 equiv.; in 30 mL of dry Et2O). Flash chromatography of the crude reaction product (1:9 Et2O - petroleum ether; 130 g of silica gel), followed by distillation of the oil thus obtained (70-80°C/0.5 Torr), gave 2.0 g (50%) of the ketone 136.

Preparation of the ketone 138.

Following general procedure H, 1,6-heptadiyne (3 g, 32.56 mmol, 1 equiv.; in 100 mL of dry Et2O) was converted into the corresponding lithium acetylide, which was added to Ac2O (6.65 g, 2 equiv.; in 50 mL of dry Et2O). Flash chromatography of the crude reaction product (15:85 Et2O - petroleum ether; 150 g of silica gel), followed by distillation of the oil thus obtained (120-130°C/6.0 Torr), gave 2.18 g (50%) of the ketone 138.

Preparation of the ketone 139.

Following general procedure H, 5-chloro-1-pentyne (3 g, 29.27 mmol; in 100 mL of dry Et2O) was converted into the corresponding lithium acetylide, which was added to Ac2O (6 g , 2 equiv.; in 40 mL of dry Et2O). Flash chromatography of the crude reaction product (1:9 Et2O - petroleum ether; 150 g of silica gel), followed by distillation of the oil thus obtained (60-65°C/0.5 Torr), gave 2.31 g (54%) of the ketone 139.
Preparation of the ketone 148.

Following general procedure H, the terminal acetylene 121 (441 mg, 1.97 mmol, 1 equiv.; in 10 mL of dry Et2O) was converted into the corresponding lithium acetylide, which was added to Ac2O (402 mg, 2 equiv.; in 4 mL of dry Et2O). Flash chromatography of the crude reaction product (1:9 Et2O - petroleum ether; 50 g of silica gel), followed by distillation of the oil thus obtained (90-100°C/0.5 Torr), gave 330 mg (63%) of the ketone 148, a colourless oil which exhibited ir (neat): 3082, 2211, 1681, 1228, 838 cm⁻¹;¹H nmr (400 MHz) δ: 0.03 (s, 3H, -SiMe), 0.06 (s, 3H, -SiMe), 0.89 (s, 9H, -SiBu³), 1.74 (m, 2H, methylene Y), 2.31 (s, 3H, -Me), 2.41 (m, 2H, methylene Z), 4.22 (m, 1H, Hx), 5.08 (ddd, 1H, HD, J = 10 Hz, J = 2 Hz, J = 2 Hz), 5.19 (ddd, 1H, HE, J = 17 Hz, J = 2 Hz, J = 2 Hz), 5.77 (ddd, 1H, HF, J = 17 Hz, J = 10 Hz, J = 6 Hz). Exact Mass calcd. for C₁₁H₁₇O₂Si (M⁺-Bu³): 209.0998; found: 209.0995; cims (positive ion detection, CH₄): 267 (M⁺+H).

General Procedure I. The Pd(0)-catalyzed reaction of α,β-acetylenic aldehydes and ketones with hexamethyliditin⁹⁶

To a stirred solution of the α,β-acetylenic aldehyde or ketone (1 equiv.) in dry THF (argon atmosphere) was added (Me₃Sn)₂ (1 equiv.) and Pd(PPh₃)₄ (5 mol%). The mixture
was allowed to reflux (2-24 h), and the progress of the reaction was monitored by tlc. When the reaction was complete, the solvent was removed and the viscous residual oil was purified by chromatography, followed by distillation.

**Preparation of the ketone 150.**

![Chemical structure of ketone 150]

Following general procedure I, a solution of the ketone 142 (200 mg, 1.82 mmol), (Me₃Sn)₂ (600 mg) and Pd(PPh₃)₄ (105 mg, 5 mol %) in dry THF (3 mL) was allowed to reflux for 5 h. Flash chromatography of the crude product (2:98 Et₂O - petroleum ether; 45 g of silica gel) followed by distillation of the oil thus obtained (70-75°C/0.5 Torr), gave 400 mg (80%) of the ketone 150, a colourless oil which exhibited ir (neat): 1682, 1568, 1203, 770 cm⁻¹; ¹H nmr (300 MHz): 0.09 (s, 9H, -SnMe₃, ²J Sn-H = 54 Hz), 1.03 (d, 6H, -CHMe₂, ²J = 6.5 Hz), 2.20 (s, 3H, -Me), 2.75 (septet of d, -CHMe₂, ⁷J = 6.5 Hz, ³J = 1.5 Hz, ³J Sn-H = 54 Hz), 6.77 (d, 1H, HA, ³J = 1.5 Hz, ³J Sn-H = 127 Hz). In nOe difference experiments, irradiation at δ 6.77 (HA) caused signal enhancement at δ 2.75 (-CHMe₂), δ 1.03 (-CHMe₂) and δ 2.20 (-Me), while irradiation at δ 2.75 (-CHMe₂) caused signal enhancement at δ 1.03 (-CHMe₂) and δ 6.77 (HA). ¹³C nmr (75.4 MHz) δ: -6.86,

Preparation of the aldehyde 152.

Following general procedure I, a solution of the aldehyde 133 (1.50 g, 7.08 mmol), (Me₃Sn)₂ (2.33 g) and Pd(PPh₃)₄ (410 mg, 5 mol %) in dry THF (12 mL) was allowed to reflux for 2 h. Flash chromatography of the crude product (5:95 Et₂O - petroleum ether; 100 g of silica gel), followed by distillation of the oil thus obtained (110-120°C/0.5 Torr), gave 2.33 g (87%) of the aldehyde 152, a colourless oil which exhibited ir (neat): 2743, 1685, 1563, 1099, 776 cm⁻¹; ¹H nmr (300 MHz) δ: 0.04 (s, 6H, -SiMe₆), 0.26 (s, 9H, -SnMe₃, ²J Sn-H = 54 Hz), 0.86 (s, 9H, -SiBu³), 2.69 (td, 2H, -OCH₂CH₂-, ³J = 6.5 Hz, ²J Sn-H = 46 Hz), 3.69 (t, 2H, -OCH₂CH₂-, ³J = 6.5 Hz), 6.68 (dt, 1H, HA, ³J = 5.5 Hz, ²J Sn-H = 114 Hz), 9.56 (d, 1H, -CHO, ³J = 5.5 Hz, ⁴J Sn-H = 5.5 Hz). In nOe difference experiments, irradiation at δ 6.68 (HA) caused signal enhancement at δ 2.69 (-OCH₂CH₂-) and δ 9.59 (-CHO); irradiation at δ 9.59 (-CHO) caused signal enhancement at δ 6.68 (HA); irradiation at δ 2.69 (-OCH₂CH₂-) caused signal enhancement at δ 6.68 (HA) and δ 3.69 (-OCH₂CH₂-). ¹³C nmr (75.4 MHz) δ: -7.17,
Exact Mass calcd. for C₁₃H₂₇O₂SnSi (M⁺-Me): 363.0802; found: 363.0806.

Preparation of the aldehyde 153.

Following general procedure I, a solution of the aldehyde 134 (300 mg, 1.25 mmol), (Me₃Sn)₂ (413 mg) and Pd(PPh₃)₄ (72 mg, 5 mol %) in dry THF (2 mL) was allowed to reflux for 2 h. Flash chromatography of the crude product (5:95 Et₂O - petroleum ether; 30 g of silica gel), followed by distillation of the oil thus obtained (120-130°C/0.5 Torr), gave 448 mg (88%) of the aldehyde 153, a colourless oil which exhibited ir (neat): 2742, 1685, 1562, 1256, 1106, 775 cm⁻¹; ¹H nmr (300 MHz) δ: 0.02 (s, 6H, -SiMe₂), 0.25 (s, 9H, -SnMe₂, JₗSn-H = 55 Hz), 0.87 (s, 9H, -SiBu-t), 1.48 (m, 4H, -OCH₂CH₂CH₂CH₂-), 2.49 (br t, 2H, -OCH₂CH₂CH₂CH₂-, J = 6.5 Hz, ³JₗSn-H = 47 Hz), 3.59 (t, 2H, -OCH₂CH₂CH₂CH₂-, J = 6 Hz), 6.62 (dt, 1H, HA, J = 6 Hz, J = 1.3 Hz, ³JₗSn-H = 115 Hz), 9.55 (d, 1H, -CHO, J = 6 Hz, ⁴JₗSn-H = 5.5 Hz). In nOe difference experiments, irradiation at δ 6.62 (HA) caused signal enhancement at δ 9.55 (-CHO) and δ 2.49 (-OCH₂CH₂CH₂CH₂-); irradiation at δ 9.55 (-CHO) caused signal enhancement at δ 6.62 (HA); irradiation at δ 2.49 (-OCH₂CH₂CH₂CH₂-) caused signal enhancement at

Preparation of the aldehyde 154.

Following general procedure I, a solution of the aldehyde 135 (1.897 g, 13.36 mmol), (Me₃Sn)₂ (4.41 g) and Pd(PPh₃)₄ (772 mg, 5 mol %) in dry THF (45 mL) was allowed to reflux for 2 h. Flash chromatography of the crude product (35:65 Et₂O - petroleum ether; 120 g of silica gel), followed by distillation of the oil thus obtained (100 - 105°C/0.5 Torr), gave 3.12 g (76%) of the aldehyde 154, a colourless oil which exhibited ir (neat): 1683, 1562, 1151, 1043, 776 cm⁻¹; ¹H nmr (400 MHz) δ: 0.25 (s, 9H, -SnMe₃, ²J Sn-H = 54 Hz), 2.77 (td, 2H, -OCH₂CH₂-, J = 6.5 Hz, J = 1.3 Hz, ³J Sn-H = 44 Hz), 3.61 (t, 2H, -OCH₂CH₂-, J = 6.5 Hz), 4.58 (s, 2H, -OCH₂O-), 6.72 (dt, 1H, H_A, J = 5.5 Hz, J = 1.3 Hz, ³J Sn-H = 113 Hz), 9.59 (d, 1H, -CHO, J = 5.5 Hz, ⁴J Sn-H = 5.5 Hz). Exact Mass calcd. for C₉H₁₇O₃Sn (M⁺-Me): 293.0199; found: 293.0201.
Preparation of the ketone 155.

Following general procedure I, a solution of the ketone 136 (130 mg, 0.58 mmol, 1 equiv.), (Me3Sn)2 (190 mg) and Pd(PPh3)4 (33 mg, 5 mol %) in dry THF (2 mL), was allowed to reflux for 2 h. Flash chromatography of the crude reaction product (4:96 Et2O - petroleum ether; 30 g of silica gel), followed by distillation of the oil thus obtained (110-120°C/0.5 Torr), gave 204 mg (90%) of the ketone 155, a colourless oil which exhibited ir (neat): 1682, 1573, 1192, 1095, 776 cm⁻¹; ¹H nmr (300 MHz) δ: 0.00 (s, 6H, -SiMe₂), 0.10 (s, 9H, -SnMe₃, 2J Sn-H = 54 Hz), 0.84 (s, 9H, -SiBu₃), 2.19 (s, 3H, -Me), 2.63 (td, 2H, -OCH₂CH₂-, J = 6.5 Hz, J = 1.3 Hz, 3J Sn-H = 49 Hz), 3.62 (t, 2H, -OCH₂CH₂-, J = 6.5 Hz), 6.82 (br s, 1H, HA, 3J Sn-H = 121 Hz). In nOe difference experiments, irradiation at δ 6.82 (HA) caused signal enhancement at δ 2.63 (-OCH₂CH₂-) and δ 2.19 (-Me); irradiation at δ 2.63 (-OCH₂CH₂-) caused signal enhancement at δ 3.62 (-OCH₂CH₂-) and δ 6.82 (HA); irradiation at δ 2.19 (-Me) caused signal enhancement at δ 6.82 (HA). ¹³C nmr (75.4 MHz) δ: -7.42, -5.31, 18.23, 25.88, 30.01, 42.51, 61.97, 136.69, 172.45, 197.29. Exact Mass calcd. for C₁₄H₂₉O₂SiSn (M⁺-Me): 377.0959; found: 377.0966.
Preparation of the ketone 156.

Following general procedure I, a solution of the ketone 137 (160 mg, 0.63 mmol), (Me₃Sn)₂ (208 mg) and Pd(PPh₃)₄ (36 mg, 5 mol %) in dry THF (2 mL) was allowed to reflux for 2 h. Flash chromatography of the crude product (4:96 Et₂O - petroleum ether, 35 g of silica gel), followed by distillation of the oil thus obtained (120-130°C/0.5 Torr), gave 265 mg (83%) of the ketone 156, a colourless oil which exhibited ir (neat): 1682, 1572, 1103, 776 cm⁻¹; ¹H nmr (300 MHz) δ: 0.04 (s, 6H, -SiMe₃), 0.12 (s, 9H, -SnMe₃), 0.88 (s, 9H, -SiBu₃), 1.35-1.55 (m, 4H, -OCH₂CH₂CH₂CH₂-), 2.22 (s, 3H, -Me), 2.44 (br t, 2H, -OCH₂CH₂CH₂CH₂-, J = 6.5 Hz, 3J Sn-H = 49 Hz), 3.60 (t, 2H, -OCH₂CH₂CH₂CH₂-, J = 6.5 Hz), 6.79 (br s, 1H, HA, 3J Sn-H = 122 Hz). In nOe difference experiments, irradiation at δ 6.79 (HA) caused signal enhancement at δ 2.44 (-OCH₂CH₂CH₂CH₂-) and δ 2.22 (-Me); irradiation at δ 2.22 (-Me) caused signal enhancement at δ 6.79 (HA); irradiation at δ 2.44 (-OCH₂CH₂CH₂CH₂-) caused signal enhancement at δ 6.79 (HA). ¹³C nmr (75.4 MHz) δ: -7.48, -5.30, 18.31, 25.55, 25.91, 30.09, 32.46, 39.67, 62.91, 134.68, 176.80, 197.59. Exact Mass calcd. for C₁₆H₃₃O₂SiSn (M⁺-Me): 405.1272; found: 405.1266.
Preparation of the ketone 157.

Following general procedure I, a solution of the ketone 138 (175 mg, 1.31 mmol), (Me₃Sn)₂ (431 mg) and Pd(PPh₃)₄ (75 mg, 5 mol %) in 4 mL of dry THF was allowed to reflux for 4 h. Flash chromatography of the crude product (5:95 Et₂O - petroleum ether; 35 g of silica gel), followed by distillation of the oil thus obtained (70-80°C/0.5 Torr), gave 270 mg (69%) of the ketone 157, a colourless oil which exhibited ir (neat): 3308, 2119, 1681, 1571, 772 cm⁻¹; ^1H nmr (400 MHz) δ: 0.12 (s, 9H, -SnMe₃, J_{Sn-H} = 54 Hz), 1.63 (quintet, 2H, methylene Y, J = 7.5 Hz), 1.97 (t, 1H, acetylenic H, J = 2.5 Hz), 2.19 (td, 2H, methylene X, J = 7.5 Hz, J = 2.5 Hz), 2.22 (s, 3H, -Me), 2.54 (td, 2H, methylene Z, J = 7.5 Hz, J = 1.3 Hz, J_{Sn-H} = 48 Hz), 6.62 (br s, 1H, HA, J_{Sn-H} = 120 Hz). In nOe difference experiments, irradiation at δ 6.62 (HA) caused signal enhancement at δ 2.54 (methylene Z) and δ 2.22 (-Me); irradiation at δ 2.54 (methylene Z) caused signal enhancement at δ 6.62 (HA) and δ 1.63 (methylene Y); irradiation at δ 2.22 (-Me) caused signal enhancement at δ 6.62 (HA). Exact Mass calcd. for C₁₁H₁₁O₂Sn (M⁺-Me): 285.0302; found: 285.0302.
Preparation of the ketone 158

Following general procedure I, a solution of the ketone 139 (800 mg, 5.54 mmol), (Me₃Sn)₂ (1.83 g) and Pd(PPh₃)₄ (320 mg, 5 mol %) in dry THF (9 mL) was allowed to reflux for 3 h. Flash chromatography of the crude product (5:95 Et₂O - petroleum ether; 75 g of silica gel), followed by distillation of the oil thus obtained (100-105°C/0.5 Torr), gave 1.40 g (81%) of the ketone 158, a colourless oil which exhibited ir (neat): 1682, 1572, 1202, 774 cm⁻¹; ¹H nmr (300 MHz) δ: 0.12 (s, 9H, -SnMe₃, 2J Sn-H = 54 Hz), 1.85 (br quintet, 2H, ClCH₂CH₂CH₂-, J = 7 Hz), 2.23 (s, 3H, -Me), 2.59 (br t, 2H, ClCH₂CH₂CH₂-, J = 7 Hz, 3J Sn-H = 48 Hz), 3.50 (t, 2H, ClCH₂CH₂CH₂-, J = 7 Hz), 6.82 (br s, 1H, HA, 3J Sn-H = 120 Hz). In nOe difference experiments, irradiation at δ 6.82 (HA) caused signal enhancement at δ 2.59 (ClCH₂CH₂CH₂-) and δ 2.23 (-Me), while irradiation at δ 2.59 (ClCH₂CH₂CH₂-) caused signal enhancement at δ 1.85 (ClCH₂CH₂CH₂-), δ 3.50 (ClCH₂CH₂CH₂-) and δ 6.82 (HA). ¹³C nmr (75.4 MHz) δ: -7.41, 30.19, 31.60, 36.55, 44.10, 135.59, 174.63, 197.53. Exact Mass calcd. for C₉H₁₆³⁵ClO₅Sn (M⁺-Me): 294.9912; found: 294.9912.
Preparation of the ketone 159.

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\text{Me}_3\text{Sn} \quad \xrightarrow{\text{C}} \quad \text{O}
\]

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Following general procedure I, a solution of the ketone 140 (1g, 5.15 mmol), (Me₃Sn)₂ (1.70 g) and Pd(PPh₃)₄ (300 mg, 5 mol %) in dry THF (8 mL) was allowed to reflux for 24 h. Flash chromatography of the crude product (3:97 Et₂O - petroleum ether; 75 g of silica gel), followed by distillation of the oil thus obtained (120-130°C/0.5 Torr), gave 900 mg (48%) of the ketone 159, a colourless oil which exhibited ir (neat): 1685, 1562, 779, 532 cm⁻¹; ¹H nmr (300 MHz) δ: 0.16 (s, 9H, -SnMe₃, 2J Sn-H = 53 Hz), 0.86 (m, 3H, -Me), 1.13 (s, 9H, -Bu⁻), 1.27 (br s, 6H), 1.5-1.67 (m, 2H, -C(O)CH₂CH₂⁻), 2.49 (t, 2H, -C(O)CH₂⁻, J = 7.5 Hz), 6.75 (s, 1H, HA, 3J Sn-H = 130 Hz). In nOe difference experiments, irradiation at δ 6.75 (HA) caused signal enhancement at δ 1.13 (Bu⁻) and δ 2.49 (-C(O)CH₂⁻); irradiation at δ 2.49 (-C(O)CH₂⁻) caused signal enhancement at δ 6.75 (HA) and δ 1.5-1.67 (-C(O)CH₂CH₂⁻); irradiation at δ 1.13 (-Bu⁻) caused signal enhancement at δ 6.75 (HA). ¹³C nmr (75.4 MHz) δ: -3.61, 14.11, 22.58, 24.29, 28.99, 29.65, 31.62, 39.97, 43.43, 130.30, 184.93, 200.97. Exact Mass calcd. for C₁₅H₂₉OSn (M⁺-Me): 345.1241; found: 345.1237.
Preparation of the ketone 160.

Following general procedure I, a solution of the ketone 141 (2.34 g, 9.23 mmol), (Me₃Sn)₂ (3.04 g) and Pd(PPh₃)₄ (533 mg, 5 mol%) in dry THF (15 mL) was allowed to reflux for 5 h. Flash chromatography of the crude product (5:95 Et₂O - petroleum ether; 140 g of silica gel), followed by distillation of the oil thus obtained (130-135°C/0.5 Torr), gave 3.64 g (94%) of the ketone 160, a colourless oil which exhibited ir (neat): 1678, 1572, 1256, 1098, 777 cm⁻¹; ¹H nmr (400 MHz) δ: 0.04 (s, 6H, -SiMe3), 0.12 (s, 9H, -SnMe3), 2J Sn-H = 55 Hz), 0.87 (s, 9H, -SiBu3), 1.12 (d, 6H, -CHMe2, J = 7 Hz), 2.66 (m, 3H, -CHMe2 and -OCH₂CH₂⁻), 3.66 (t, 2H, -OCH₂CH₂⁻, J = 6.5 Hz), 6.88 (br s, 1H, HA, 3J Sn-H = 127 Hz). In nOe difference experiments, irradiation at δ 6.88 (HA) caused signal enhancement at δ 2.66 (-CHMe2 and -OCH₂CH₂⁻), while irradiation at δ 2.66 (-CHMe2 and -OCH₂CH₂⁻) caused signal enhancement at δ 6.88 (HA). Exact Mass calcd. for C₁₆H₃₃O₂SnSi (M⁺-Me): 405.1272; found: 405.1269.
Preparation of the ketone 161.

Following general procedure I, a solution of the ketone 148 (840 mg, 3.16 mmol), (Me₃Sn)₂ (1.04 g) and Pd(PPh₃)₄ (182 mg, 5 mol %) in dry THF (10 mL) was allowed to reflux for 8 h. Flash chromatography of the crude product (5:95 Et₂O - petroleum ether; 75 g of silica gel), followed by distillation of the oil thus obtained (130-135°C/0.5 Torr), gave 1.29 g (95%) of the ketone 161, a colourless oil which exhibited IR (neat): 1682, 1571, 1537, 776 cm⁻¹; ¹H nmr (400 MHz): 0.02 (s, 3H, -SiMe), 0.05 (s, 3H, -SiMe), 0.12 (s, 9H, -SnMe₃, ²J Sn-H = 54 Hz), 0.89 (s, 9H, -SiBu³), 1.45-1.65 (m, 2H, methylene Y), 2.21 (s, 3H, -Me), 2.35-2.60 (m, 2H, methylene Z), 4.10 (m, 1H, HX), 5.05 (ddd, 1H, HD, J = 10 Hz, J = 2 Hz, J = 2 Hz), 5.14 (ddd, 1H, HF, J = 18 Hz, J = 2 Hz, J = 2 Hz), 5.80 (ddd, 1H, HF, J = 18 Hz, J = 10 Hz, J = 6 Hz), 6.80 (br s, 1H, HA, ³J Sn-H = 124 Hz).

Exact Mass calcd. for C₁₇H₃₃O₂SiSn (M⁺-Me): 417.1272; found: 417.1270.

General Procedure I. The preparation of (Z)-4-(trimethylstannyld)-1,3-butadienes 166

To a cold (0°C), stirred suspension of methyltriphenylphosphonium bromide (1.8-2.0 equiv.) in dry THF (argon atmosphere) was added a solution of n-BuLi in hexane (1.3-1.5
equiv.). After the resulting yellow solution/suspension had been stirred for 10 min at 0°C and for 30 min at room temperature, a solution of the aldehyde (or ketone) (1 equiv.) in dry THF was added. After the reaction mixture had been stirred at room temperature for 30 min-5 h, H2O (approx. 0.5 mL per mL of reaction solution) and Et2O (approx. 0.5 mL per mL of reaction solution) were added and the phases were separated. The aqueous phase was extracted with ether and the combined organic extracts were washed with brine, dried (MgSO4) and concentrated. The crude product was purified by flash chromatography, followed by distillation.

**Preparation of the diene 167.**

![Diagram of diene 167]

Following general procedure J, a solution of the aldehyde 152 (2.72 g, 7.2 mmol, 1 equiv.) in dry THF (15 mL) was added to the Wittig reagent (prepared by the addition of a solution of n- BuLi (1.3 equiv.) in hexane to a suspension of methyltriphenylphosphonium bromide (4.63 g, 1.8 equiv.) in 50 mL of dry THF) and the mixture was stirred at room temperature for 30 min. Flash chromatography of the crude product (2:98 Et2O - petroleum ether; 120 g of silica gel), followed by distillation of the oil thus obtained (105-110°C/0.5 Torr), gave 2.35 g (87 %) of the diene 167, a colourless oil which exhibited ir (neat): 3087, 3049, 1621, 1574, 1100, 774 cm⁻¹; ¹H nmr (300 MHz) δ: 0.04 (s, 6H, -SiMe2),
0.21 (s, 9H, -SnMe$_3$, $^2J$ Sn-H = 53 Hz), 0.88 (s, 9H, -SiBu$_3$), 2.49 (br t, 2H, -OCH$_2$CH$_2$-, $J$ = 7 Hz, $^3J$ Sn-H = 55 Hz), 3.57 (t, 2H, -OCH$_2$CH$_2$-, $J$ = 7 Hz), 5.10 (dd, 1H, H$_C$, $J$ = 11 Hz, $J$ = 1.5 Hz), 5.15 (dd, 1H, H$_B$, $J$ = 16 Hz, $J$ = 1.5 Hz), 6.30 (m, 1H, H$_D$), 6.64 (br d, 1H, H$_A$, $J$ = 11 Hz, $^3J$ Sn-H = 131 Hz). $^{13}$C nmr (75.4 MHz) δ: -8.01, -5.09, 18.44, 26.04, 43.61, 63.60, 117.07, 137.67, 142.63, 147.33. Exact Mass calcd. for C$_{14}$H$_{29}$OSiSn (M+-Me): 361.1010; found: 361.1018. Anal. calcd. for C$_{15}$H$_{32}$OSiSn: C 48.02, H 8.60; found: C 48.00, H 8.70.

Preparation of the diene 168.

Following general procedure J, a solution of the aldehyde 153 (100 mg, 0.25 mmol, 1 equiv.) in dry THF (2 mL) was added to the Wittig reagent (prepared by the addition of a solution of n- BuLi (1.3 equiv.) in hexane to a suspension of methyltriphenylphosphonium bromide (160 mg, 1.8 equiv.) in 3 mL of dry THF) and the mixture was stirred at room temperature for 30 min. Flash chromatography of the crude product (2:98 Et2O - petroleum ether; 30 g of silica gel), followed by distillation of the oil thus obtained (110-115°C/0.5 Torr), gave 81 mg (81 %) of the diene 168, a colourless oil which exhibited ir (neat): 3086, 1622, 1574, 1255, 1105, 775 cm$^{-1}$; $^1$H nmr (300 MHz) δ: 0.04 (s, 6H, -SiMe$_2$), 0.20 (s,
9H, -SnMe₃, ²J Sn-H = 53 Hz), 0.88 (s, 9H, -SiBu₃), 1.30-1.55 (m, 4H, -OCH₂CH₂CH₂CH₂-, 2.28 (br t, 2H, -OCH₂CH₂CH₂CH₂-, J = 7 Hz, ³J Sn-H = 56 Hz), 3.59 (t, 2H, -OCH₂CH₂CH₂CH₂-, J = 6 Hz), 5.06 (dd, 1H, HC, J = 10 Hz, J = 1.5 Hz), 5.13 (dd, 1H, HB, J = 16 Hz, J = 1.5 Hz), 6.31 (m, 1H, HD), 6.59 (br d, 1H, HA, J = 11 Hz, ³J Sn-H = 136 Hz)). ¹³C nmr (75.4 MHz) δ: -8.12, -5.15, 18.43, 26.07, 26.53, 32.51, 40.60, 62.07, 116.52, 137.83, 140.26, 152.05. Exact Mass calcd. for C₁₆H₃₃OSnSi (M+Me): 389.1323; found: 389.1329.

Preparation of the diene 169.

Following general procedure J, a solution of the aldehyde 154 (5.84 g, 18.96 mmol, 1 equiv.) in dry THF (25 mL) was added to the Wittig reagent (prepared by the addition of a solution of n-BuLi (1.3 equiv.) in hexane to a suspension of methyltriphenylphosphonium bromide (10.84 g, 1.6 equiv.) in 120 mL of dry THF) and the mixture was stirred at room temperature for 30 min. Flash chromatography of the crude product (1:9 Et₂O - petroleum ether; 230 g of silica gel), followed by distillation of the oil thus obtained (95-105°C/0.5 Torr), gave 4.76 g (82%) of the diene 169, a colourless oil which exhibited ir (neat): 3086, 1149, 1045, 771 cm⁻¹; ¹H nmr (300 MHz) δ: 0.02 (s, 9H, -SnMe₃, ²J Sn-H = 53 Hz),
2.55 (br t, 2H, -OCH₂CH₂-, J = 6 Hz, ³J Sn-H = 53 Hz), 3.24 (s, 3H, -OMe), 3.50 (t, 2H, -OCH₂CH₂-, J = 6 Hz), 4.60 (s, 2H, -OCH₂O-), 5.10 (br d, 1H, H₃C, J = 10 Hz), 5.15 (br d, 1H, H₃B, J = 17 Hz), 6.30 (m, 1H, H₃D), 6.66 (br d, 1H, H₃A, J = 11 Hz, ³J Sn-H = 125 Hz). ¹³C nmr (75.4 MHz) δ: -8.20, 40.33, 55.01, 67.83, 96.22, 117.28, 137.62, 142.36, 147.68. Exact Mass calcd. for C₁₀H₁₉O₂Sn (M⁺-Me): 291.0407; found: 291.0406.

Preparation of the diene 176.

Following general procedure J, a solution of the ketone 150 (3.6 g, 13.04 mmol, 1 equiv.) in dry THF (20 mL) was added to the Wittig reagent (prepared by the addition of a solution of n-BuLi (1.5 equiv.) in hexane to a suspension of methyltriphenylphosphonium bromide (9.4 g, 2 equiv.) in 100 mL of dry THF) and the mixture was stirred at room temperature for 5 h. Flash chromatography of the crude product (petroleum ether; 150 g of silica gel), followed by distillation of the oil thus obtained (90-105°C/10 Torr), gave 3.10 g (87 %) of the diene 176, a colourless oil which exhibited ir (neat): 3083, 1632, 1602, 1188, 769 cm⁻¹; ¹H nmr (300 MHz) δ: 0.14 (s, 9H, -SnMe₃, ²J Sn-H = 52 Hz), 1.03 (d, 6H, -CHMe₂, J = 7 Hz), 1.77 (s, 3H, -Me), 2.51 (septet of d, 1H, -CHMe₂, J = 7 Hz, J = 1.5 Hz, ³J Sn-H = 60 Hz), 4.74 (br s, 1H), 4.78 (br s, 1H), 6.45 (br s, 1H, H₃A,
$^{3}J_{\text{Sn-H}} = 144 \text{ Hz}$). $^{13}$C nmr (75.4 MHz) δ: -6.34, 22.70, 23.05, 36.88, 112.55, 138.52, 147.21, 152.94. *Exact Mass* calcd. for $\text{C}_{10}\text{H}_{19}\text{Sn} (\text{M}^+\text{-Me})$: 259.0509; found: 259.0512.

The preparation of a solution of sodium 2-methyl-2-butoxide in benzene

To a stirred suspension of sodium wire (41.4 g, 1.8 mol) in dry benzene (750 mL) at room temperature (argon atmosphere) was added, slowly, 2-methyl-2-butanol (132.2 g, 1.5 mol) (freshly distilled from Mg (activated by I$_2$)). The mixture was allowed to gently reflux overnight. The solution was cannulated from the reaction vessel into an airtight container, and was stored in the refrigerator. The solution (2 ml in 5 mL of 95% EtOH) was titrated with 1M HCl, using phenolphthalein as indicator and was found to be 1.75 M.

General Procedure K. The preparation of (Z)-4-(trimethylstannyl)-1,3-butadienes

To a stirred suspension of methyltriphenylphosphonium bromide (2.5 equiv.) in dry benzene (room temperature, argon atmosphere) was added a solution (1.75 M) of sodium 2-methyl-2-butoxide (2.5 equiv.) in dry benzene. After the mixture had been stirred for 20 min at room temperature, a solution of the ketone (1 equiv.) in dry benzene was added, and stirring was continued for 15-30 min. Water (approx. 0.5 mL per mL of reaction solution) and Et$_2$O (approx. 1 mL per mL of reaction solution) were added and the phases were separated. The aqueous phase was extracted with Et$_2$O, and the combined organic extracts were washed with brine, dried (MgSO$_4$) and concentrated. The crude product was purified by flash chromatography, followed by distillation.
Preparation of the diene 171.

Following general procedure K, a solution of the ketone 155 (200 mg, 0.51 mmol, 1 equiv.) in dry benzene (2 mL) was added to the Wittig reagent (prepared by the addition of a solution of sodium 2-methyl-2-butoxide in dry benzene (1.75 M, 0.73 mL, 2.5 equiv.) to a suspension of methyltriphenylphosphonium bromide (456 mg, 2.5 equiv.) in dry benzene (4 mL)) and the mixture was stirred at room temperature for 30 min. Flash chromatography of the crude product (2:98 Et2O - petroleum ether; 35 g of silica gel), followed by distillation of the oil thus obtained (105-110°C/0.5 Torr), gave 172 mg (86%) of the diene 171, a colourless oil which exhibited ir (neat): 3083, 1633, 1604, 1572, 1255, 774 cm⁻¹; ¹H nmr (300 MHz) δ: 0.04 (s, 6H, -SiMe₂), 0.13 (s, 9H, -SnMe₃, 2J Sn-H = 53 Hz), 0.88 (s, 9H, -SiBu₃), 1.76 (s, 3H, -Me), 2.45 (td, 2H, -OCH₂CH₂-, J = 7 Hz, J = 1.3 Hz, 3J Sn-H = 55 Hz), 3.56 (t, 2H, -OCH₂CH₂-, J = 7 Hz), 4.75 (br s, 1H), 4.79 (br s, 1H), 6.53 (br s, 1H, HA, 3J Sn-H = 137 Hz). ¹³C nmr (75.4 MHz) δ: -7.20, -5.20, 18.40, 22.68, 26.02, 43.56, 63.67, 112.91, 141.78, 144.95, 146.61. Exact Mass calcd. for C₁₅H₃₁O₃SiSn (M⁺-Me): 375.1166; found: 375.1161.
Preparation of the diene 172.

Following general procedure K, a solution of the ketone 156 (155 mg, 0.37 mmol, 1 equiv.) in dry benzene (2 mL) was added to the Wittig reagent (prepared by the addition of a solution of sodium 2-methyl-2-butoxide in dry benzene (1.75 M, 0.53 mL, 2.5 equiv.) to a suspension of methyltriphenylphosphonium bromide (330 mg, 2.5 equiv.) in dry benzene (3 mL)) and the mixture was stirred at room temperature for 30 min. Flash chromatography of the crude product (3:97 Et2O - petroleum ether; 30 g of silica gel), followed by distillation of the oil thus obtained (110-115°C/0.5 Torr), gave 116 mg (75%) of the diene 172, a colourless oil which exhibited ir (neat): 3081, 1572, 1562, 1255, 1103, 775 cm⁻¹; ¹H nmr (300 MHz) δ: 0.03 (s, 6H, -SiMe₃), 0.12 (s, 9H, -SnMe₃, 2J Sn-H = 52 Hz), 0.88 (s, 9H, -SiBu¹), 1.29-1.55 (m, 4H, -OCH₂CH₂CH₂CH₂-), 1.76 (s, 3H, -Me), 2.24 (br t, 2H, -OCH₂CH₂CH₂CH₂-, J = 7 Hz, 3J Sn-H = 55 Hz), 3.59 (t, 2H, -OCH₂CH₂CH₂CH₂-, J = 6 Hz), 4.74 (br s, 1H), 4.79 (br s, 1H), 6.47 (br s, 1H, HA, 3J Sn-H = 139 Hz). ¹³C nmr (75.4 MHz) δ: -7.41, -5.27, 18.33, 22.71, 25.98, 26.50, 32.38, 40.40, 60.13, 112.62, 142.48, 146.21, 146.60. Exact Mass calcd. for C₁₇H₃₅OSn (M⁺-Me): 403.1479; found: 403.1472.
Preparation of the diene 173

Following general procedure K, a solution of the ketone 157 (1.22 g, 4.07 mmol, 1 equiv.) in dry benzene (8 mL) was added to the Wittig reagent (prepared by the addition of a solution of sodium 2-methyl-2-butoxide in dry benzene (1.75 M, 5.8 mL, 2.5 equiv.) to a suspension of methyltriphenylphosphonium bromide (3.63 g, 2.5 equiv.) in dry benzene (15 mL)) and the mixture was stirred at room temperature for 30 min. Flash chromatography of the crude product (petroleum ether; 65 g of silica gel), followed by distillation of the oil thus obtained (70-80°C/0.5 Torr), gave 1.01 g (83%) of the diene 173, a colourless oil which exhibited ir (neat): 3312, 3082, 2120, 897, 770 cm⁻¹; ¹H nmr (400 MHz) δ: 0.13 (s, 9H, -SnMe₃), 1.57 (quintet, 2H, methylene Y, J = 7 Hz), 1.76 (s, 3H, Me), 1.94 (t, 1H, acetylenic H, J = 2.6 Hz), 2.16 (td, 2H, methylene X, J = 7 Hz, J = 2.6 Hz), 2.34 (td, 2H, methylene Z, J = 7 Hz, J = 1.3 Hz, 3J Sn-H = 55 Hz), 4.75 (br s, 1H), 4.79 (br s, 1H), 6.51 (br s, 1H, HA, 3J Sn-H = 139 Hz). ¹³C nmr (75.4 MHz) δ: -7.3, 17.77, 22.71, 28.83, 39.38, 68.42, 84.39, 112.86, 143.46, 144.93, 146.55. Exact Mass calcd. for C₁₂H₁₉Sn (M+−Me): 283.0509; found: 283.0510.
Preparation of the diene 174.

Following general procedure K, a solution of the ketone 158 (288 mg, 0.73 mmol, 1 equiv.) in dry benzene (3 mL) was added to the Wittig reagent (prepared by the addition of a solution of sodium 2-methyl-2-butoxide in dry benzene (1.75 M, 1.05 mL, 2.5 equiv.) to a suspension of methyltriphenylphosphonium bromide (656 mg, 2.5 equiv.) in dry benzene (5 mL)) and the mixture was stirred at room temperature for 30 min. Flash chromatography of the crude product (2:98 Et2O - petroleum ether; 35 g of silica gel), followed by distillation of the oil thus obtained (85-90°C/0.5 Torr), gave 128 mg (57%) of the diene 174, a colourless oil which exhibited ir (neat): 3082, 1632, 1605, 897 cm⁻¹; ¹H nmr (300 MHz) δ: 0.14 (s, 9H, -SnMe₃, ²J Sn-H = 53 Hz), 1.77 (s, 3H, -Me), 1.81 (quintet, 2H, ClCH₂CH₂CH₂-, ⁷J = 7 Hz), 2.38 (td, 2H, ClCH₂CH₂CH₂-, ⁷J = 7 Hz, ³J = 1.3 Hz, ⁵J Sn-H = 54 Hz), 3.50 (t, 2H, ClCH₂CH₂CH₂-, ⁷J = 7 Hz), 4.76 (br s, 1H), 4.80 (br s, 1H), 6.52 (br s, 1H, HA, ³J Sn-H =136 Hz). Exact Mass calcd. for C₁₀H₁₈³⁵ClSn (M⁺-Me): 293.0119; found: 293.0114.
Preparation of the diene 175.

Following general procedure K, a solution of the ketone 159 (110 mg, 0.31 mmol, 1 equiv.) in dry benzene (2 mL) was added to the Wittig reagent (prepared by the addition of a solution of sodium 2-methyl-2-butoxide in dry benzene (1.75 M, 0.44 mL, 2.5 equiv.) to a suspension of methyltriphenylphosphonium bromide (273 mg, 2.5 equiv.) in dry benzene (3 mL)) and the mixture was stirred at room temperature for 30 min. Flash chromatography of the crude product (2:98 Et2O - petroleum ether; 35 g of silica gel), followed by distillation of the oil thus obtained (105-110°C/0.5 Torr), gave 89 mg (81%) of the diene 175, a colourless oil which exhibited ir (neat): 3038, 1630, 899, 770 cm⁻¹; ¹H nmr (300 MHz) δ: 0.15 (s, 9H, SnMe₃), 2J Sn-H = 52 Hz), 0.88 (m, 3H, CH₃CH₂CH₂CH₂CH₂CH₂CH₂-), 1.07 (s, 9H, Bu¹), 1.30 (br s, 6H, CH₃CH₂CH₂CH₂CH₂CH₂CH₂-), 1.42 (m, 2H, CH₃CH₂CH₂CH₂CH₂CH₂CH₂-), 2.01 (br t, 2H, CH₃CH₂CH₂CH₂CH₂CH₂CH₂-, J = 8 Hz), 4.72 (br s, 1H), 4.77 (br s, 1H), 6.49 (br s, 1H, HA, J = 151 Hz). ¹³C nmr (75.4 MHz) δ: -3.60, 14.19, 22.77, 27.66, 29.41, 30.74, 31.84, 37.07, 38.91, 111.22, 137.32, 151.34, 156.63. Exact Mass calcd. for C₁₆H₃₁Sn (M⁺-Me): 343.1448; found: 343.1453.
Preparation of the diene 177

Following general procedure K, a solution of the ketone 160 (174 mg, 0.41 mmol, 1 equiv.) in dry benzene (2 mL) was added to the Wittig reagent (prepared by the addition of a solution of sodium 2-methyl-2-butoxide in dry benzene (1.75 M, 0.6 mL, 2.5 equiv.) to a suspension of methyltriphenylphosphonium bromide (370 mg, 2.5 equiv.) in dry benzene (4 mL)) and the mixture was stirred at room temperature for 15 min. Flash chromatography of the crude product (3:97 Et2O - petroleum ether; 35 g of silica gel), followed by distillation of the oil thus obtained (110-115°C/0.5 Torr), gave 111 mg (64%) of the diene 177, a colourless oil which exhibited ir (neat): 3090, 1461, 1255, 1007, 775 cm⁻¹; ¹H nmr (400 MHz) δ: 0.04 (s, 6H, -SiMe₃), 0.12 (s, 9H, -SnMe₃, ²J Sn-H = 53 Hz), 0.87 (s, 9H, -SiBu‴), 1.02 (d, 6H, -CHMe₂, J = 7 Hz), 2.27 (br septet, 1H, -CHMe₂, J = 7 Hz), 2.48 (br t, 2H, -OCH₂CH₂-, J = 7 Hz, ³J Sn-H = 53 Hz), 3.56 (t, 2H, -OCH₂CH₂-, J = 7 Hz), 4.71 (br s, 1H), 4.80 (br s, 1H), 6.60 (br s, 1H, HA, ³J Sn-H = 140 Hz). ¹³C nmr (75.4 MHz) δ: -7.07, -5.17, 18.41, 21.60, 26.03, 34.0, 43.74, 63.77, 108.94, 143.40, 143.44, 156.40. Exact Mass calcd. for C₁₇H₃₅OSn (M⁺-Me): 403.1479; found: 403.1474.
Preparation of the diene 178.

Following general procedure K, a solution of the ketone 161 (92 mg, 0.21 mmol, 1 equiv.) in dry benzene (2 mL) was added to the Wittig reagent (prepared by the addition of a solution of sodium 2-methyl-2-butoxide in dry benzene (1.75 M, 0.3 mL, 2.5 equiv.) to a suspension of methyltriphenylphosphonium bromide (190 mg, 2.5 equiv.) in dry benzene (3 mL)) and the mixture was stirred at room temperature for 30 min. Flash chromatography of the crude product (3:97 Et2O - petroleum ether; 30 g of silica gel), followed by distillation of the oil thus obtained (125-130°C/0.5 Torr), gave 78 mg (85%) of the diene 178, a colourless oil which exhibited ir (neat): 3081, 1253, 1084, 775 cm⁻¹; ¹H nmr (400 MHz) δ: 0.04 (s, 3H, -SiMe), 0.06 (s, 3H, -SiMe₂), 0.14 (s, 9H, -SnMe₃), 2JSn-H = 52 Hz), 0.90 (s, 9H, -SiBu³), 1.40-1.60 (m, 2H, methylene Y), 1.78 (s, 3H, -Me), 2.19-2.40 (m, 2H, methylene Z), 4.10 (br m, 1H, HX), 4.76 (br s, 1H), 4.80 (br s, 1H), 5.03 (ddd, 1H, HD, J = 10 Hz, J = 2 Hz, J = 2 Hz), 5.14 (ddd, 1H, HF, J = 17 Hz, J = 2 Hz, J = 2 Hz), 5.81 (ddd, 1H, HF, J = 17 Hz, J = 10 Hz, J = 6 Hz), 6.50 (br s, 1H, HA), 3JSn-H = 139 Hz). ¹³C nmr (50 MHz) δ: -7.28, -4.76, -4.32, 18.23, 22.72, 25.92, 36.40, 38.86, 73.60, 112.69, 113.72, 141.75, 142.56, 145.89, 146.66. Exact Mass calcd. for C₁₈H₃₅OSn (M⁺-Me): 415.1480; found: 415.1478.
Preparation of the phosphonate reagent 179

A mixture of triisopropyl phosphite (3.2 g, 15.38 mmol, 1 equiv.) and tert-butyl bromoacetate (3 g, 1 equiv.) (argon atmosphere) was heated at 125°C for 1.5 h. Distillation of the oil thus obtained (fraction collected between 110-115°C/0.5 torr) gave 3.50 g (81%) of the phosphonate 179, a colourless oil which exhibited ir (neat): 1730, 1289, 1107, 991 cm⁻¹; ¹H nmr (400 MHz) δ: 1.27 (d, 6H, Me₂CHO-, J = 7 Hz), 1.29 (d, 6H, Me₂CHO, J = 7 Hz), 1.42 (s, 9H, -CO₂Bu), 2.77 (d, 2H, -CH₂CO₂Bu, 2J p-H = 22 Hz), 4.68 (m, 2H, Me₂CHO-). ¹³C nmr (75.4 MHz) δ: 23.76 (d, Me₂CHO-, 3J p-C = 5 Hz), 23.93 (d, Me₂CHO-, 3J p-C = 4 Hz), 27.82, 36.62 (d, -CH₂CO₂Bu, 1J p-C = 134 Hz), 70.88 (d,Me₂CHO-, 2J p-C = 6 Hz), 81.60, 164.94 (d,-CH₂CO₂Bu, 3J p-C = 6 Hz). ³¹P nmr (122 MHz) δ: 16.20 (tt, J = 22 Hz, J = 8 Hz).

Preparation of the diene 180.
A 60% dispersion of NaH (260 mg, 6.4 mmol, 1.7 equiv.) in mineral oil was washed with dry THF (3 x 2 mL) (argon atmosphere), and to the residual oil-free solid was added 25 mL of dry THF. The stirred suspension was cooled to 0°C and a solution of the phosphonate reagent 179 (1.79 g, 6.4 mmol, 1.7 equiv.) in 10 mL of dry THF was added slowly (over a period of approx. 5 min). After the mixture had been stirred at 0°C for 5 min and at room temperature for 20 min it was cooled to -20°C and a solution of the aldehyde 154 (1.17 g, 3.8 mmol, 1 equiv.) in 10 mL of dry THF was added. The mixture was stirred at -20°C for 1.5 h and was then allowed to warm to room temperature (30 min). Water (approx. 20 mL) and Et2O (approx. 40 mL) were added and the phases were separated. The aqueous phase was extracted with Et2O (2 x 20 mL) and the combined organic extracts were washed with brine (20 mL), dried (MgSO4), and concentrated. Flash chromatography of the crude product (1:4 Et2O - petroleum ether; 65 g of silica gel), followed by distillation of the oil thus obtained (190-210°C/0.5 Torr), gave 1.4 g (91%) of the diene 180, a colourless oil which exhibited ir (neat): 1703, 1626, 1368, 1045, 770 cm⁻¹; ¹H nmr (400 MHz) δ: 0.25 (s, 9H, -SnMe₃, 2J Sn-H = 52 Hz), 1.48 (s, 9H, -CO₂Bu), 2.64 (br t, 2H, -OCH₂CH₂-, J = 7 Hz, 3J Sn-H = 49 Hz), 3.33 (s, 3H, -OMe), 3.54 (t, 2H, -OCH₂CH₂-, J = 7 Hz), 4.58 (s, 2H, -OCH₂O-), 5.72 (br d, 1H, HA, J = 15 Hz), 6.74 (br d, 1H, HB, J = 11 Hz, 3J Sn-H = 120 Hz), 7.21 (dd, 1H, HC, J = 15 Hz, J = 11 Hz, 4J Sn-H = 7 Hz). In nOe difference experiments, irradiation at δ 6.74 (HA) caused signal enhancement at δ 5.72 (HB) and δ 2.64 (-OCH₂CH₂-); irradiation at δ 2.64 (-OCH₂CH₂-) caused signal enhancement at δ 3.54 (-OCH₂CH₂-) and δ 6.74 (HA); irradiation at δ 5.72 (HB) caused signal enhancement at δ 6.74 (HA). ¹³C nmr (75.4 MHz) δ: -7.80, 28.21, 40.95, 55.27, 67.45, 80.08, 96.39, 123.22, 139.47, 144.19, 160.52, 166.50. Exact Mass calcd. for C₁₅H₂₇O₄Sn (M⁺-Me): 391.0931; found: 391.0938. Anal. calcd. for C₁₆H₃₀O₄Sn: C 47.42, H 7.47; found: C 47.59, H 7.39.

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Preparation of the diene 182.

\[
\begin{align*}
\text{Me}_3\text{Sn} & \quad \text{H} \\
& \quad \text{CO}_2\text{Me} \\
\text{TBDMSO} & \quad 182
\end{align*}
\]

A 50% dispersion of NaH (1.02 g, 21.25 mmol, 1.5 equiv.) in mineral oil was washed with dry THF (3 x 5 mL) (argon atmosphere), and to the residual oil-free solid was added 100 mL of dry THF. The stirred suspension was cooled to 0°C and trimethylphosphonoacetate (181) (3.87 g, 21.25 mmol, 1.5 equiv.) was added dropwise (over a period of approx. 5 min). The resultant slurry was stirred at 0°C for 5 min and at room temperature for 20 min. The mixture was then re-cooled to 0°C and a solution of the aldehyde 152 (5.35 g, 14.15 mmol, 1 equiv.) in 25 mL of dry THF was added. The resulting suspension was stirred at 0°C for 2 h. Water (approx. 50 mL) and Et\textsubscript{2}O (approx. 50 mL) were added and the phases were separated. The aqueous phase was extracted with Et\textsubscript{2}O (2 x 40 mL) and the combined organic extracts were washed with brine (40 mL), dried (MgSO\textsubscript{4}) and concentrated. Flash chromatography of the crude product (6:94 Et\textsubscript{2}O - petroleum ether; 250 g of silica gel), followed by distillation of the oil thus obtained (140-150°C/0.5 Torr), gave 5.65 g (92%) of the diene 182, a colourless oil which exhibited ir (neat): 1723, 1626, 1268, 1100, 776 cm\textsuperscript{-1}; \textsuperscript{1}H nmr (400 MHz) \(\delta\): 0.03 (s, 6H, -SiMe\textsubscript{2}), 0.27 (s, 9H, -SnMe\textsubscript{3}), 2\(J\) Sn-H = 54 Hz), 0.87 (s, 9H, -SiBu\textsubscript{1}), 2.57 (br t, 2H, -OCH\textsubscript{2}CH\textsubscript{2}-, \(J\) = 7 Hz, 3\(J\) Sn-H = 50 Hz), 3.62 (t, 2H, -OCH\textsubscript{2}CH\textsubscript{2}-, \(J\) = 7 Hz), 3.73 (s, 3H, -OMe), 5.80 (br d, 1H, HB, \(J\) = 15 Hz), 6.73 (br d, 1H, HA, \(J\) = 11 Hz, 3\(J\) Sn-H = 122 Hz), 7.30 (dd, 1H, HC, \(J\) = 15 Hz, \(J\) = 11 Hz, 4\(J\) Sn-H = 7 Hz). In nOe difference experiments, irradiation at \(\delta\) 2.57 (-OCH\textsubscript{2}CH\textsubscript{2}-) caused signal enhancement at \(\delta\) 6.73 (HA).
and \( \delta 3.62 \) (-OCH\textsubscript{2}CH\textsubscript{2}-); irradiation at \( \delta 5.80 \) (H\textsubscript{B}) caused signal enhancement at \( \delta 6.73 \) (H\textsubscript{A}); irradiation at \( \delta 6.73 \) (H\textsubscript{A}) caused signal enhancement at \( \delta 5.80 \) (H\textsubscript{B}) and \( \delta 2.57 \) (-OCH\textsubscript{2}CH\textsubscript{2}-). *Exact Mass* calcd. for C\textsubscript{16}H\textsubscript{31}O\textsubscript{3}SnSi (M\textsuperscript{+}-Me): 419.1065; found: 419.1070.

**Preparation of the alcohol 187**

![Chemical Structure](image)

To a cold (-78°C), stirred solution of the stannyldiene 169 (870 mg, 2.84 mmol) in dry THF (50 mL) (argon atmosphere) was added a solution of MeLi (1.1 equiv.) in Et\textsubscript{2}O. After the mixture had been stirred for 45 min at -78°C, ethylene oxide (excess, approx. 2.5 g, 20 equiv.) was added via syringe (the barrel of the syringe was cooled, using a piece of dry ice, in order to facilitate the transfer of the volatile liquid). The resulting mixture was stirred at -78°C for 5 min and at -20°C for 20 min and was then allowed to warm to room temperature (30 min). Saturated aqueous NaHCO\textsubscript{3} (10 mL) and Et\textsubscript{2}O (30 mL) were added, the phases were separated and the aqueous phase was extracted with Et\textsubscript{2}O (3 x 20 mL). The combined organic extracts were washed with brine (20 mL) and then dried and concentrated. Flash chromatography of the crude product (6:4 Et\textsubscript{2}O - petroleum ether; 40 g of silica gel), followed by distillation of the oil thus obtained (110 -120°C/0.5 Torr), gave 375 mg (71%)
of the alcohol 187, a colourless oil which exhibited IR (neat): 3401, 3085, 1150, 1109, 1039 cm\(^{-1}\); \(^1\)H NMR (400 MHz) \(\delta\): 1.74 (br s, 1H, -OH), 2.39 (br t, 2H, -OCH\(_2\)CH\(_2\)-, \(J = 6.5\) Hz), 2.49 (t, 2H, -CH\(_2\)CH\(_2\)OH, \(J = 6.5\) Hz), 3.34 (s, 3H, -OMe), 3.67 (t, 2H, -OCH\(_2\)CH\(_2\)-, \(J = 6.5\) Hz), 3.70 (br m, 2H, -CH₂OH), 4.01 (s, 2H, -OCH\(_2\)O-), 5.05 (dd, 1H, H\(_C\), \(J = 10\) Hz, \(J = 1.5\) Hz), 5.15 (dd, 1H, H\(_B\), \(J = 17\) Hz, \(J = 1.5\) Hz), 6.06 (br d, 1H, H\(_A\), \(J = 11\) Hz), 6.60 (ddd, 1H, H\(_D\), \(J = 17\) Hz, \(J = 11\) Hz, \(J = 10\) Hz). On addition of D\(_2\)O the signal at \(\delta\) 3.70 (-CH\(_2\)OH) sharpened to a t \((J = 6.5\) Hz) and the signal at \(\delta\) 1.74 disappeared. \(^1\)C NMR (75.4 MHz) \(\delta\): 34.44, 37.06, 55.34, 61.16, 66.53, 96.37, 116.80, 129.91, 132.54, 136.27. *Exact Mass* calcd. for C\(_{10}\)H\(_{16}\)O\(_2\) (M\(^+-\)H\(_2\)O): 168.1151; found: 168.1152. *Anal.* calcd. for C\(_{10}\)H\(_{18}\)O\(_3\): C 64.49, H 9.74; found: 64.49, H 9.88.

**Preparation of the triene 188**

![Triene 188](image)

To a cold (-78°C), stirred solution of the stannyldiene 169 (346 mg, 1.13 mmol) in dry THF (5 mL) (argon atmosphere) was added a solution of MeLi (1.1 equiv.) in Et\(_2\)O. After the mixture had been stirred for 45 min at -78°C, CuBr.Me\(_2\)S (256 mg, 1.1 equiv.) was added. The resulting bright pink solution/suspension was stirred at -78°C for 5 min and
at -48°C for 15 min. To the resulting bright orange-red solution was added 2,3-dibromopropene (excess, 1.5 g, 6.7 equiv.) and the resulting colourless solution was stirred at -48°C for 45 min. Saturated NH₄Cl-NH₄OH (pH 8) (5 mL) and Et₂O (10 mL) were added and the vigorously stirred mixture was allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with Et₂O (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried (MgSO₄), and concentrated. Flash chromatography of the crude product (1:9 Et₂O - petroleum ether, 40 g of silica gel), followed by distillation (100-110°C/0.5 Torr) of the oil thus obtained, gave 244 mg (83%) of the triene 188, a colourless oil which exhibited ir (neat): 3086, 1150, 1072, 917 cm⁻¹; ¹H nmr (400 MHz) δ: 2.38 (br t, 2H, -OCH₂CH₂-, J = 6 Hz), 3.35 (br s, 5H, -OMe and bis-allylic CH₂), 3.62 (t, 2H, -OCH₂CH₂-, J = 6 Hz), 4.60 (s, 2H, -OCH₂O-), 5.12 (dd, 1H, HA, J = 11 Hz, J = 1.5 Hz), 5.20 (dd, 1H, HB, J = 17 Hz, J = 1.5 Hz), 5.48 (br s, 1H, HF or HF), 5.62 (br s, 1H, HE or HE), 6.13 (br d, 1H, HA, J = 11 Hz), 6.54 (ddd, 1H, HD, J = 17 Hz, J = 11 Hz, J = 11 Hz). ¹³C nmr (75.4 MHz) δ: 36.55, 42.76, 55.23, 66.1, 96.34, 117.53, 117.82, 130.43, 130.89, 132.35, 134.56. 


**Preparation of the diene 201**
To a stirred solution of NaI (1.80 g, 11.8 mmol) in dry acetone (7 mL) (room temperature, argon atmosphere) was added a solution of the stannyldiene 174 (364 mg, 1.18 mmol) in dry acetone (3 mL). The mixture was allowed to reflux overnight. Most of the acetone was removed, Et2O (20 mL) and H2O (10 mL) were added to the residue, and the aqueous phase was extracted with Et2O (3 x 10 mL). The combined organic extracts were washed with H2O (10 mL) and then dried (MgSO4) and concentrated. Flash chromatography of the crude product (5:95 Et2O - petroleum ether; 35 g of silica gel), followed by distillation of the oil thus obtained (100-110°C/0.5 Torr), gave 406 mg (86%) of the diene 201, a colourless oil which exhibited ir (neat): 3080, 1215, 769 cm⁻¹; ¹H nmr (400 MHz) δ: 0.16 (s, 9H, -SnMe₃, ²J Sn-H = 56 Hz), 1.78 (s, 3H, -Me), 1.87 (quintet, 2H, ICH₂CH₂CH₂⁻, ⁴J Sn-H = 7 Hz, ³J Sn-H = 54 Hz), 3.15 (t, 2H, ICH₂CH₂CH₂⁻, ⁴J Sn-H = 7 Hz, ³J Sn-H = 7 Hz), 4.76 (br s, 1H), 4.80 (br s, 1H), 6.54 (s, 1H, Hₐ, ³J Sn-H = 132 Hz). ¹³C nmr (50 MHz) δ: -7.28, 6.15, 22.66, 33.62, 40.82, 113.015, 143.77, 143.99, 146.45. Exact Mass calcd. for C₁₀H₁₈Sn (M⁺-Me): 384.9477; found: 384.9476.

Preparation of the spirocyclic compound 202
To a cold (-78°C), stirred solution of the stannyliene 201 (186 mg, 0.47 mmol) in dry THF (2 mL) (argon atmosphere) was added a solution of MeLi (1.1 equiv) in Et₂O. After the mixture had been stirred for 10 min at -78°C and 20 min at -48 °C, H₂O (0.5 mL) and Et₂O (2 mL) were added, and the mixture was allowed to warm to room temperature. The phases were separated, the aqueous phase was extracted with Et₂O (2 x 2 mL), and the combined organic extracts were dried (MgSO₄). The ethereal solution of the crude reaction product exhibited essentially one (non-solvent) peak by glc analysis and was used immediately in the next step. To the ethereal solution of the crude reaction product (argon atmosphere) was added (in portions of 5 mg) tetracyanoethylene (50 mg), until the reaction was shown to be complete (by glc analysis). The solvent was removed and the white solid thus obtained was dissolved in a minimum amount of Et₂O. Flash chromatography of this solution (1:1 Et₂O - petroleum ether; 25 g of silica gel) and recrystallization of the white solid thus obtained (petroleum ether), gave 75 mg (69%) of the spirocyclic compound 202, a white solid which exhibited, mp 166-167°C; ir (KBr disk): 2253, 1440, 883, 696 cm⁻¹; ¹H nmr (400 MHz) δ: 1.88 (br s, 3H, -Me), 2.08-2.10 (m, 1H), 2.17-2.24 (m, 3H), 2.73-2.75 (m, 2H), 2.95 (br s, 2H, HA), 5.99 (br s, 1H, HB). Exact Mass calcd. for C₁₄H₁₂N₄ (M⁺): 236.1062; found: 236.1056.

Preparation of the spirocyclic compound 203

![Diagram of 203](image-url)
To a cold (-78°C), stirred solution of the stannyldiene 201 (170 mg, 0.43 mmol) in dry THF (2 mL) (argon atmosphere) was added a solution of MeLi (1.1 equiv.) in Et₂O. After the mixture had been stirred for 10 min at -78°C and 20 min at -48°C, H₂O (0.5 mL) and benzene (2 mL) were added, and the mixture was allowed to warm to room temperature. The phases were separated, the aqueous phase was extracted with benzene (3 x 1 mL), and the combined organic extracts were dried (MgSO₄). To the solution of the crude product (in a sealable reaction vessel, argon atmosphere) was added dimethylacetylene dicarboxylate (360 mg, 6 equiv.). The vessel was sealed and the mixture was heated at 70°C for 36 h. After the solvent had been removed the residual oil was purified by flash chromatography (1:1 Et₂O - petroleum ether; 30 g of silica gel), followed by distillation (100-110°C/0.5 Torr), to give 74 mg (70%) of the spirocyclic compound 203, a colourless oil which crystallized on standing. Recrystallization of this material from pentane produced white crystals, which exhibited mp 55-56 °C; ir (KBr disk): 1724, 1635, 1440, 1267, 1051, 754 cm⁻¹; ¹H nmr (400 MHz) δ: 1.72 (br s, 3H, -Me), 1.72-1.80 (m, 1H), 1.92-1.96 (m, 3H), 2.58-2.59 (m, 2H), 2.82 (br s, 2H, HA), 3.73 (s, 3H, -OMe), 3.88 (s, 3H, -OMe), 5.73 (br s, 1H, HB). Exact Mass calcd. for C₁₄H₁₈O₄ (M⁺): 250.1205; found: 250.1203.
PART 3. The preparation of 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes and the thermal Cope rearrangement of these compounds into substituted bicyclo[3.2.1]octa-2,6-dienes.

I. Introduction

Cis divinylcyclopropanes of general structure 206 can undergo thermal [3,3]-sigmatropic (Cope) rearrangement to give 1,4-cycloheptadienes of general structure 207.105-108 There are several important features associated with this type of rearrangement. Firstly, it is usually a facile process since it is accompanied by opening of the highly strained cyclopropane ring (the strain energy of a cyclopropane is approximately 27.5 kcal mol⁻¹).107 Also, the rearrangement is completely stereospecific, in that the geometries of the carbon-carbon double bonds in the divinylcyclopropane 206 determine the relative stereochemistry of the substituents in the product 207. Thus, the substituents R³ and R⁶ in the divinylcyclopropane 206 end up cis to each other in the product 207, as do R² and R⁵.
(Scheme 30). Finally, the mechanism of the reaction is generally described as a concerted bond reorganization via a boat-like transition state \(208A\), in which the two vinyl groups hang over the cyclopropyl ring (Scheme 30).\(^{105}\) The alternative, chair-like, transition state of type \(208B\) is assumed to be much higher in energy than \(208A\) since it would lead to highly strained 1,4-cycloheptadienes \(209\) which have two \(trans\) carbon-carbon double bonds.

**Trans** divinylcyclopropanes of general structure \(210\) cannot attain the transition state \(208A\) for Cope rearrangement due to geometric reasons (Scheme 31). However, at high temperatures \(trans\) divinylcyclopropanes \(210\) often rearrange, cleanly and efficiently, to give the 1,4-cycloheptadienes \(207\).\(^{106,109-112}\) In these cases, it is generally accepted that the \(trans\) divinylcyclopropane \(210\) is first isomerized, via a diradical intermediate \(211\), to the \(cis\) isomer \(206\), which then undergoes the Cope rearrangement.\(^{106,113}\) This \(trans\) to \(cis\) isomerization is generally (but not always) rate determining and, therefore, once formed, the \(cis\) divinylcyclopropane \(206\) usually rearranges rapidly, via the transition state \(208A\), to the 1,4-cycloheptadiene \(207\) (Scheme 31). The Cope rearrangements of \(trans\) divinylcyclopropanes are completely stereospecific. Therefore, if the \(trans\) to \(cis\) isomerization involves a diradical intermediate \(211\), it apparently re-closes to either the \(cis\) divinylcyclopropane \(206\) or the \(trans\) isomer \(210\) without allowing for bond rotation within either allyl unit.

The effects of substituents on the rate of Cope rearrangement of \(cis\) divinylcyclopropanes of general structure \(206\) have not been thoroughly investigated. However, it has been shown that \(cis\) divinylcyclopropanes \(206\) which have alkyl groups attached to the termini of the vinyl groups undergo Cope rearrangement more slowly than those which are unsubstituted at these positions.\(^{114}\) These effects are readily rationalized in terms of steric interactions between substituents in the transition state \(208A\), as shown in Scheme 32. For example, \(trans\) substituents (i.e. \(R^2\) and/or \(R^5\)=alkyl) cause moderate rate
retardation, presumably due to eclipsing interactions between these groups in the boat-like transition state 208A (Scheme 32). On the other hand, cis substituents (R³ and/or R⁶=alkyl) cause drastic reductions in the rate of Cope rearrangement. In these cases, the transition states 208A are destabilized by eclipsing interactions involving R³ and/or R⁶ as well as by
severe steric interactions between \( R^3 \) and/or \( R^6 \) and the cyclopropyl ring, as shown in Scheme 32. In fact, Schneider and Rau\(^{114} \), and Baldwin and Ullenius\(^{113} \) have reported that, upon thermolysis, the \textit{cis} divinylcyclopropane 212 (which has a \textit{cis} methyl group attached to the terminus of each vinyl group) equilibrates with the \textit{trans} divinylcyclopropane 213 faster than it undergoes Cope rearrangement. Only minor amounts of the 1,4-cycloheptadiene 214 are produced even after prolonged heating. Apparently, the transition state for this Cope rearrangement is sufficiently congested to be of higher energy than the transition states associated with interconversion of the \textit{trans} isomer 213 and the \textit{cis} isomer 212 (via a diradical intermediate).

The thermal [3,3]-sigmatropic (Cope) rearrangement of \textit{cis} divinylcyclopropanes of general structure 215 (i.e. 6-\textit{endo}-(1-alkenyl)bicyclo[3.1.0]hex-2-enes) provides substituted bicyclo[3.2.1]octa-2,6-dienes of general structure 216 (Scheme 33).\(^{115}-117 \) The rearrangement is stereospecific and presumably proceeds via a transition state of general
structure 217. The corresponding \textit{trans} divinylcyclopropanes 218 (i.e. 6-\textit{exo}-(1-alkenyl)bicyclo[3.1.0]hex-2-enes) may also undergo Cope rearrangement to give the bicyclic products 216.\textsuperscript{118-120} However, high temperatures are required to effect this transformation, since the 6-\textit{exo}-(1-alkenyl)bicyclo[3.1.0]hex-2-enes 218 must first be isomerized to the \textit{endo} isomers 215, before the Cope rearrangement can take place (Scheme 33).\textsuperscript{121} This \textit{exo-endo} isomerization is usually rate limiting and probably involves a diradical intermediate of general structure 219 (Scheme 33).

Since, in principle, either the \textit{endo}-(1-alkenyl)bicyclo[3.1.0]hex-2-enes 215 or the \textit{exo} isomers 218 can undergo the Cope rearrangement, it should be possible to prepare the desired bicyclo[3.2.1]octa-2,6-dienes 216 from either isomer or a mixture of both isomers.
In practice, however, the high temperatures required to effect Cope rearrangement of the \textit{exo} isomers 218 may result in alternative modes of reaction and/or substrate decomposition. In these cases, the desired products are available only via Cope rearrangement of the \textit{endo} isomers 215 which, therefore, must be synthesized stereoselectively. These points are well illustrated by the following examples.

In a recent synthesis of sinularene 220 (Scheme 34),\textsuperscript{122} the key bicyclic intermediate 221 was prepared in 86\% yield via thermolysis (220°C, 4.5 hours) of the \textit{exo}-(1-alkenyl)bicyclo[3.1.0]hex-2-ene 222, which was derived from the \(\alpha,\beta\)-unsaturated ketone 223. The reaction probably proceeds via rate limiting isomerization of 222 to the \textit{endo} isomer 224 which then undergoes Cope rearrangement. Apparently, alternative modes of reaction which could be available to 222, such as a [1,5] sigmatropic hydrogen shift, do not compete with \textit{exo} to \textit{endo} isomerization or Cope rearrangement under these conditions.

In the total syntheses of (±)-prezizaene 225 and (±)-prezizanol 226 recently carried out in this laboratory,\textsuperscript{123} the key intermediate 227 was expected to be available via Cope

\begin{center}
\begin{tikzpicture}
\node (222) at (0,0) {\includegraphics[width=0.2\textwidth]{222.png}};
\node (224) at (2,0) {\includegraphics[width=0.2\textwidth]{224.png}};
\node (221) at (4,0) {\includegraphics[width=0.2\textwidth]{221.png}};
\node (223) at (0,-2) {\includegraphics[width=0.2\textwidth]{223.png}};
\node (220) at (4,-2) {\includegraphics[width=0.2\textwidth]{220.png}};
\node [align=center] at (2,-0.5) {\textbf{Scheme 34}};
\node (220C) at (1,0) {220°C};
\node (TBDMSO) at (-0.5,-1) {TBDMSO};
\node (OTBDMS) at (3.5,-1) {OTBDMS};
\end{tikzpicture}
\end{center}
rearrangement of the exo-(1-alkenyl)bicyclo[3.1.0]hex-2-ene 228. However, it was found that thermolysis of 228 produced a mixture of many products and only minor amounts of 227. Evidently, the high temperature required for isomerization of 228 to the endo isomer 229, which must precede the Cope rearrangement, results in substrate decomposition. In fact, it was shown that the \(\beta,\gamma\)-unsaturated ester function present in 228 is responsible for its thermal instability, since thermolysis of the structurally similar compound 230 gives the expected Cope rearrangement product 231 cleanly and efficiently (Scheme 35).¹²⁴

![Scheme 35](image)
intermediate 227 was subsequently prepared via stereoselective synthesis and facile Cope rearrangement of the \textit{endo}-(1-alkenyl)bicyclo[3.1.0]hex-2-ene 229 (Scheme 35). Compound 227 was readily converted into the target molecules 225 and 226.

There is very little quantitative data available regarding the effects of substituents on the rates of Cope rearrangement of 6-\textit{endo}-(1-alkenyl)bicyclo[3.1.0]hex-2-enes of general structure 215. Generally, it appears that substituents attached to the termini of the vinyl groups in 215 cause rate retardation in a manner similar to that described earlier (Scheme 32) for the "simple" \textit{cis} divinylcyclopropanes 206. For example,\textsuperscript{125} compound 232 (Scheme 36) rearranges to bicyclo[3.2.1]octa-2,6-diene (233) with a half life of approximately 1 day at 25°C, whereas the diene 234 is stable at room temperature. However, upon flash vacuum pyrolysis at 350°C, 234 rearranges to the bicyclo[3.2.1]octa-2,6-diene 235.\textsuperscript{126} Presumably, this Cope rearrangement proceeds via a boat-like transition state 236 in which there is an eclipsing interaction between the \textit{trans} vinyl methyl group and the hydrogen attached to C3, as well as a severe interaction between the \textit{cis} vinyl methyl group and the hydrogen attached to C4 (Scheme 36).
II. Proposals

Although bicyclo[3.2.1]octa-2,6-dienes 216 may often be prepared efficiently via Cope rearrangement of 6-exo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes 218, the high temperatures that are required to effect this transformation may limit its utility as a general synthetic method. The Cope rearrangement of the corresponding 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes 215 is a more reliable process, yet has not been greatly exploited primarily due to the lack of general methods available for the stereoselective preparation of these compounds. The main objective of this project was, therefore, to develop a general synthesis of functionalized, substituted 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes 215 and to convert these compounds (via Cope rearrangement) into the corresponding bicyclo[3.2.1]octa-2,6-dienes. It was envisaged that the availability of a wide range of functionalized compounds of general structure 215 would provide an excellent opportunity to observe the effects of different substituents and substitution patterns on the rate of Cope rearrangement.

It was anticipated that 6-endo-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones of general structure 237 would be excellent precursors to a variety of 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes 215 (equation 36).\textsuperscript{118,119,122} The ketone function in compounds 237 was expected to serve as a "handle" for incorporation of a number of different alkyl substituents or functional groups at C3 as well as for introduction of the C2-C3 double bond (equation 36). The ketones 237 were, therefore, our initial synthetic targets.

\begin{equation}
\begin{array}{c}
\text{237} \\
\begin{array}{c}
R^8 \\
R^9 \\
R^7 \\
R^6 \\
R^5 \\
R^2 \\
R^1 \\
R^3 \\
R^4 \\
R^5 \\
R^1 \\
R^2 \\
R^7 \\
R^3 \\
R^9 \\
R^8 \\
R^9
\end{array}
\end{array}
\rightarrow
\begin{array}{c}
\text{215} \\
\begin{array}{c}
R^8 \\
R^9 \\
R^7 \\
R^6 \\
R^5 \\
R^2 \\
R^1 \\
R^3 \\
R^4 \\
R^5 \\
R^1 \\
R^2 \\
R^7 \\
R^3 \\
R^9 \\
R^8 \\
R^9
\end{array}
\end{array}
\end{equation}
Workers in this group\textsuperscript{118,119,122} and in others\textsuperscript{127,128} have shown that compounds related to \ref{fig:237} may be prepared via intramolecular transition metal-catalyzed cyclopropanation reactions of molecules containing a diene unit and a diazoketone function. For example,\textsuperscript{118} it was shown that diene diazoketones of general structure \ref{fig:238} undergo chemoselective and stereoselective intramolecular cyclopropanation in the presence of a copper(II) or copper(0) catalyst to give 6-\textit{exo}-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones of general structure \ref{fig:239} (equation 37). The geometry of the diene unit determines the relative stereochemistry of the cyclopropane ring, as indicated by the bold lines in structures \ref{fig:238} and \ref{fig:239}.

![Diagram](https://via.placeholder.com/150)

\textsuperscript{R}_{1}
\begin{align*}
\text{MeO}_{2}\text{C} & \quad \text{N}_{2} \\
\text{C} & \quad \text{O} \\
\text{R'} & \quad \text{R} \\
\end{align*}

\begin{align*}
\text{Cu(acac})_{2} & \quad \text{Cu bronze, heat} \quad \text{PhH or PhMe, heat} \\
\text{O} & \quad \text{CO}_{2}\text{Me} \\
\end{align*}

\begin{align*}
\text{R'} & \quad \text{R} \\
\end{align*}

\textsuperscript{238}

\textsuperscript{239}

It was envisaged that 6-\textit{endo}-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones \ref{fig:237} (in which R\textsuperscript{1}=H) would be available via intramolecular transition metal-catalyzed cyclopropanation reactions involving diene diazoketones of appropriate geometry (i.e. compounds of general structure \ref{fig:240}) (Scheme 37). Retrosynthetically, the diene diazoketones \ref{fig:240} could be derived from the diene esters of general structure \ref{fig:241} via functional group manipulation.\textsuperscript{122,128} In particular, it was expected that the esters \ref{fig:241} could be hydrolyzed to give the corresponding carboxylic acids \ref{fig:242}, which could then be converted into the corresponding acid chlorides \ref{fig:243}. Reaction of the acid chlorides \ref{fig:243} with diazomethane should provide the desired diene diazoketones \ref{fig:240}.

Although there are many ways of dissecting the diene esters \ref{fig:241} retrosynthetically, disconnection of the C4-C5 bond to give a substituted diene acceptor synthon \ref{fig:244} and a

166
three carbon donor synthon 245 (Scheme 37) seemed particularly attractive, for the

Scheme 37

following reasons. Firstly, Yoshida and coworkers\textsuperscript{129} recently reported that the organozinc reagent 246 (which is actually a zinc homoenolate reagent) undergoes Pd(0)-catalyzed cross coupling reactions with alkenyl iodides or enol triflates. For example, the reagent 246 reacts with the alkenyl iodide 247 in the presence of a catalytic amount of Pd(PPh\textsubscript{3})\textsubscript{4} to give, stereoselectively, the cross coupled product 248 (Scheme 38). It was, therefore, expected that 246 would react with iodo dienes of general structure 249, in the presence of a Pd(0) catalyst, to give the desired diene esters 241 (Scheme 38). In this type of reaction the organozinc reagent 246 would be a synthetic equivalent of the donor synthon 245, whilst the iodo dienes 249 would be synthetic equivalents of the diene acceptor synthon 244.
Secondly, iodo dienes 249 should be readily available via reaction of the corresponding stannyldienes 250 with iodine (equation 38).22b Stannyldienes similar to those of general structure 250 can be prepared from α,β-acetylenic aldehydes or ketones 251 in a highly efficient and stereoselective manner, via the methodology described in the part 2 of this thesis.96
III. Results and discussion

3.1. The preparation of the stannyldienes

The starting materials used in this project were the stannyldienes 167, 171, 177, 180 and 182, which were prepared efficiently and stereoselectively as described in Part 2 of this thesis.

The stannyldiene 252 was prepared from 182 in two steps, as shown in equation 39. Thus, reaction of 182 with DIBAL provided the alcohol 253 in 95% yield. The alcohol 253 was then converted into compound 252 in 90% yield via reaction with chloromethyl methyl ether and N,N-diisopropylethylamine, following a standard literature procedure (equation 39).85
3.2. The preparation of the iodo dienes 249

Alkenylstannanes may be converted into the corresponding alkenyl iodides via reaction with iodine.\textsuperscript{22b} This transformation is usually both highly efficient and stereospecific, and generally proceeds with retention of carbon-carbon double bond geometry.

It was found that stannyldienes 250 were readily converted into the corresponding iodo dienes 249 by reaction with iodine in CH\(_2\)Cl\(_2\) (equation 40). These reactions were carried out either at -78°C or at 0°C, and essentially involved titration of a solution of the stannyldiene 250 in CH\(_2\)Cl\(_2\) with a solution of I\(_2\) in CH\(_2\)Cl\(_2\). The end point was reached when the reaction mixture maintained a permanent yellow-orange colour, due to the presence of excess iodine. After appropriate workup, the iodo dienes 249 were readily obtained in high yield and stereochemical purity by flash chromatography of the crude reaction product, followed by distillation. The iodo dienes obtained from these reactions and the yields are shown in Chart 1.

These compounds exhibited spectral data which were in full accord with the proposed structures. For example, the \(^1\)H nmr spectrum of 254 showed a 1-proton doublet of doublets at \(\delta 5.30\) (\(J = 10\) Hz, \(J = 1.5\) Hz), a 1-proton doublet of doublets at \(\delta 5.41\) (\(J = 17\) Hz, \(J = 1.5\) Hz), a 1-proton broad doublet at \(\delta 6.23\) (\(J = 10\) Hz), and a 1-proton doublet of doublets of doublets at \(\delta 6.44\) (\(J = 17\) Hz, \(J = 10\) Hz, \(J = 10\) Hz), which were assigned to
HC, HB, HA, and HD respectively. The low resolution chemical ionization mass spectrum of 254 showed a molecular ion (M+H) at m/z 339 corresponding to C12H24OISi.

The diene esters 241 were prepared via Pd(0)-catalyzed cross coupling reactions between the iodo dienes 249 and the organozinc reagent 246 (equation 41). The cross coupling reactions were carried out in a manner similar to that reported in the literature. Typically, a mixture of ethyl 3-iodopropanoate (259) (1.5 equivalents) and zinc-copper couple (2.3 equivalents) in dry benzene-DMA (15:1)(argon atmosphere) was stirred at room temperature for 1 hour and at 60°C for 4 hours (equation 41). Tetrakis(triphenylphosphine)palladium(0) (5 mol%) was added and the mixture was stirred at 60°C for 5 minutes. Then, a solution of the iodo diene 249 in dry benzene was added quickly and the resulting mixture was stirred at 60°C for 15 minutes. The reaction mixture was cooled and diluted with diethyl ether, and the resulting mixture was filtered through a
plug of Florisil®, using ether as eluant. The crude reaction product thus obtained was purified by flash chromatography, followed by distillation, to give the diene ester 241.

\[
\begin{align*}
R^8 & \quad R^9 \\
R^7 & \quad R^5
\end{align*}
\]

\[
Pd(PPh_3)_4, 60°C
\]

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{ZnI} \\
\text{EtO}_2\text{C} & \quad \text{I}
\end{align*}
\]

The amounts of reagents used in these reactions and the results are summarized in Table 11. There are several points which should be mentioned regarding the data in Table 11. Firstly, in some cases it was found that more than 1.5 equivalents of the organozinc reagent 246 was required in order to achieve clean and complete consumption of the iodo diene substrate (entries 1, 4, 5).

Secondly, the workup procedure described above was adopted for all of the reactions listed in Table 11. The reported workup procedure,\textsuperscript{129} which involves addition of hydrochloric acid to the reaction mixture, was avoided since most of the substrates used in these reactions have acid sensitive functional groups (such as TBDMS ethers). In most cases, glc analysis of the crude reaction mixture showed the presence of one major peak, which was attributable to the diene ester product. Flash chromatography of the crude reaction product followed by distillation, provided the desired, stereochemically homogeneous diene ester in high purity.
Table 11. The preparation of the diene esters 241

<table>
<thead>
<tr>
<th>Entry</th>
<th>249</th>
<th>Reagent quantities¹</th>
<th>241</th>
<th>Yield²%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>TBDMSO</td>
<td>254</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>TBDMSO</td>
<td>255</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>TBDMSO</td>
<td>256</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>TBDMSO</td>
<td>257</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>MOMO CO₂Bu¹</td>
<td>258</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TBDMSO</td>
<td>259</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TBDMSO</td>
<td>260</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TBDMSO</td>
<td>261</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TBDMSO</td>
<td>262</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TBDMSO</td>
<td>263</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>TBDMSO</td>
<td>264</td>
<td></td>
</tr>
</tbody>
</table>

¹ Reagent quantities:  
A) 1.5 equiv. 259, 2.3 equiv. Zn-Cu;  
B) 1.9 equiv. 259, 2.9 equiv. Zn-Cu;  
C) 1.7 equiv. 259, 2.7 equiv. Zn-Cu.

² Isolated yield of distilled product.
Finally, the spectral data for these compounds were in full accord with the assigned structures, and are exemplified by those derived from compound 261. Thus, the infrared spectrum of 261 showed an absorbance at 1736 cm\(^{-1}\) attributable to the carbonyl stretching frequency of the ester function. The 400 MHz \(^1\)H nmr spectrum (C\(_6\)D\(_6\)) of this compound is shown in Figure 4. This spectrum shows a 6-proton singlet at \(\delta 0.09\) and a 9-proton singlet at 1.00 due to the TBDMS ether group, a 3-proton triplet at \(\delta 0.99\) \((J = 8\) Hz\) and a 2-proton quartet at \(\delta 3.99\) \((J = 8\) Hz\) due to the ethyl ester group, and a 3-proton singlet at \(\delta 1.81\) (vinyl methyl). A 2-proton broad triplet at \(\delta 2.24\) \((J = 7\) Hz\), a 2-proton triplet at \(\delta 3.66\) \((J = 7\) Hz\), a 2-proton multiplet at \(\delta 2.41\), and a 2-proton triplet at \(\delta 2.75\) \((J = 7\) Hz\) were assigned to the methylene groups A, D, B, and C, respectively. Also, a 1-proton broad singlet at \(\delta 4.95\), a 1-proton broad singlet at \(\delta 4.97\), and a 1-proton broad singlet at \(\delta 5.80\) were assigned to H\(_F\), H\(_G\) and H\(_E\), respectively. The stereochemistry of the diene unit of 261 was confirmed by nOe difference experiments. Thus, irradiation of the signal at \(\delta 5.80\) (H\(_E\)) caused signal enhancements at \(\delta 2.24\) (methylene A) and 1.81 (vinyl Me), whilst irradiation at \(\delta 2.24\) (methylene A) caused signal enhancement at \(\delta 5.80\) (H\(_E\)) and 3.66 (methylene D). Also, irradiation at \(\delta 1.81\) (vinyl methyl) caused signal enhancement at \(\delta 5.80\) (H\(_E\)) and 4.97 (H\(_F\)). The observed nOe enhancements also confirm the signal assignments, and indicate that the diene is in the cisoid conformation, as shown below.

![Diagram of compound 261 with signal assignments and nOe enhancements](image-url)
Figure 4  400 MHz $^1$H nmr spectrum (C$_6$D$_6$) of compound 261
A possible pathway for the formation of diene esters 241 in these cross coupling reactions is summarized in Scheme 39. Firstly, oxidative addition of the iodo diene 249 to the active Pd(0) catalyst would provide a trans Pd(II) square planar complex of general structure 265. Reaction of 265 with the organozinc reagent 246 would result in transmetallation, to give a di-organopalladium(II) complex of general structure 266. The intermediate 266 could then isomerize to the cis complex 267 which may then undergo reductive elimination to give the diene ester 241, with concomitant regeneration of the Pd(0) catalyst.
3.4. The preparation of the diene acids 242.

The diene esters of general structure 241 were hydrolyzed to the corresponding carboxylic acids 242 via reaction with a mixture of aqueous K$_2$CO$_3$ and methanol at room temperature (equation 42). It was found that the hydrolysis reactions proceeded at a reasonable rate only if the reaction mixtures were completely homogeneous. Thus, the hydrolysis solution was prepared via dropwise addition of water to a 1:1 mixture of saturated aqueous K$_2$CO$_3$ and MeOH, until the mixture was homogeneous. Upon addition of the hydrolysis solution to the diene ester 241 a two phase mixture was formed, so MeOH was added dropwise, while stirring, until the droplets of substrate dissolved in the reaction medium. If the addition of MeOH resulted in precipitation of K$_2$CO$_3$, a few drops of water were added to redissolve it. The mixture was stirred at room temperature until the reaction was complete (as judged by tlc analysis). After appropriate workup, all traces of solvent were removed from the product to give the carboxylic acid 242 in a highly pure state. The carboxylic acids 242 which were obtained in these reactions, along with their yields, are listed in Chart 2. These compounds exhibited spectral data which were in full accord with the assigned structures. For example, the infrared spectrum of compound 269 showed a broad intense absorption at 2400-3400 cm$^{-1}$ attributable to the oxygen-hydrogen stretching frequency of the carboxylic acid function, and an absorption at 1713 cm$^{-1}$ attributable to the carbonyl stretching frequency of the carboxylic acid function. The $^1$H nmr spectrum of 269
showed very similar features to those already discussed for the precursor ester 261 except that the resonances due to the ethyl ester function were not present. Also, the signal due to the carboxylic acid proton was not visible. The low resolution chemical ionization mass spectrum of 269 showed a peak at m/z 299 (M⁺+H) corresponding to the molecular formula C₁₆H₃₁O₃Si.

3.5. The preparation of the diene diazoketones 240

The requisite diene diazoketones of general structure 240 were prepared from the appropriate carboxylic acids 242 using a procedure similar to that reported by previous workers. Thus, the carboxylic acids 242 were converted into the corresponding acid chlorides 243 via reaction with oxalyl chloride in refluxing hexane. Reaction of the crude acid chlorides 243 with diazomethane provided the diazoketones 240 (equation 43).
In a typical procedure, a mixture of the carboxylic acid 242 and oxalyl chloride (3 equivalents) in dry hexane (argon atmosphere) was refluxed for 2 hours. Removal of solvent and volatile material from the crude reaction mixture, under reduced pressure (0.5 Torr, room temperature), provided the crude acid chloride 243. A solution of the crude acid chloride 243 in anhydrous ether was added slowly, via cannula, to an ethereal solution of diazomethane in dry ether at 0°C. Immediate and rapid effervescence was observed. The mixture was stirred at 0°C for 30 min and at room temperature for 45 min. Then, excess diazomethane was removed from the reaction mixture by bubbling argon through the solution for approximately 30 min. The crude reaction product was purified by flash chromatography to give the essentially pure (as judged by tlc analysis) diazoketone 240, a bright yellow viscous oil. These compounds were committed to the next step without further purification or characterization. However, it was found that the diazoketones 240 are stable in a freezer in the dark for several months. The diazoketones which were prepared in this manner, along with their yields, are listed in Chart 3.

![Chart 3](image)

The initial experiments were carried out using the diazoketone 273 as substrate. It was found that 273 was smoothly converted into the desired 6-endo-vinylbicyclo[3.1.0]hexan-2-one 278, via reaction with a mixture of copper(II) sulphate and copper(II) acetylacetonate in refluxing benzene (equation 44). Thus, a 0.1M (approximately) solution of the diazoketone 273 in dry benzene was added slowly (over approximately 30 min), via syringe pump, to a suspension of copper(II) sulphate (1 equivalent) and copper(II) acetylacetonate (10 weight percent relative to copper(II) sulphate) in the same volume of refluxing anhydrous benzene. The resulting mixture was refluxed for a further 15 min and was then cooled to room temperature. Glc analysis of the crude reaction mixture showed the presence of only one compound, which was assumed to be the desired ketone 278. Tlc analysis of the crude reaction mixture showed that all of the diazoketone 273 had been consumed and that one major product was formed. The crude product was passed through a short column of Florisil® and was then purified by flash chromatography followed by distillation, to give 278 in 87% yield, an overall yield of 70% from the carboxylic acid 268.
Compound 278 exhibited spectral data which were entirely consistent with the proposed structure. Thus, the infrared spectrum of 278 showed a strong absorbance at 1719 cm\(^{-1}\), attributable to the carbon-oxygen stretching frequency of the ketone function. The \(^1\)H nmr spectrum (400 MHz, C\(_6\)D\(_6\)) of 278 is shown in Figure 5. Although this spectrum contains many overlapping multiplets, several characteristic features can be readily identified. Thus, there is a 6-proton singlet at \(\delta 0.06\) and a 9-proton singlet at \(\delta 0.99\) due to the TBDMS group. There is a 2-proton triplet at \(\delta 3.48 (J = 6\) Hz, -CH\(_2\)CH\(_2\)O-), as well as a doublet of triplets at \(\delta 1.22 (J = 14\) Hz, \(J = 6\) Hz) and a doublet of triplets at \(\delta 1.59 (J = 14\) Hz, \(J = 6\) Hz) due to \(\text{H}_A\) and \(\text{H}_A'\). Also, a 1-proton doublet of doublets of doublets at \(\delta 5.08 (J = 10\) Hz, \(J = 2\) Hz, \(J = 1\) Hz), a 1-proton doublet of doublets of doublets at \(\delta 5.24 (J = 16\) Hz, \(J = 2\) Hz, \(J = 1\) Hz) and a 1-proton doublet of doublets of doublets at \(\delta 5.51 (J = 16\) Hz, \(J = 10\) Hz, \(J = 6\) Hz) were assigned to \(\text{H}_B\), \(\text{H}_C\) and \(\text{H}_D\) respectively.

The relative stereochemistry of compound 278 was not proven spectroscopically, but the vinyl group was assumed to be in the endo orientation on the basis of the known stereospecificity\(^{118,119,122,127,128}\) of transition metal catalyzed cyclopropanation reactions involving \(\alpha\)-diazocarbonyl compounds. This relative stereochemistry was later confirmed since divinylcyclopropanes derived from 278 were found to undergo extremely facile Cope rearrangement. This would not be the case if the vinyl group was in the exo orientation.

Reaction of the diazoketone 276 with CuSO\(_4\)-Cu(acac)\(_2\) in refluxing benzene, using a procedure very similar to that described above, afforded the ketone 279 in 90% yield, an overall yield of 78% from the carboxylic acid 271 (equation 45).
Figure 5  400 MHz $^1$H nmr spectrum ($C_6D_6$) of compound 278
The diazoketone 277 was converted into the ketone 280 via reaction with CuSO₄-Cu(acac)₂ in refluxing benzene (equation 46), using a procedure similar to that described above. However, this reaction was neither as clean nor as efficient as those involving the diazoketones 273 and 276. Glc analysis of the crude reaction mixture showed the presence of several compounds, the major component being the desired product 280. Flash chromatography of the crude product followed by distillation provided the ketone 280 in 56% yield (42% from the carboxylic acid 272) (equation 46).

It was found that the cyclopropanation reaction proceeded much more cleanly when Rh₂(OAc)₄ was used as the catalyst (equation 47). Thus, reaction of the diazoketone 277
with Rh$_2$(OAc)$_4$ (3 mol%) in dry CH$_2$Cl$_2$ at room temperature, for 30 min, provided 280 in 75% yield, an overall yield of 56% from the carboxylic acid 272.

Reaction of the diazoketone 274 with CuSO$_4$-Cu(acac)$_2$ in refluxing benzene via a procedure similar to that described earlier, provided a 1:1 mixture of two compounds, which were inseparable by silica gel flash chromatography. One of the compounds was the expected product 281 (equation 48). This was confirmed later by comparison of the $^1$H nmr spectrum of the mixture of products with that of a pure sample of compound 281. The other product was assigned the structure 282 based on the $^1$H nmr spectrum of the mixture.
Thus, the $^1$H nmr spectrum of the mixture showed, as well as peaks due to the desired product 281, a 1-proton broad singlet at $\delta$ 5.41, a 1-proton doublet of doublets at $\delta$ 0.74 ($J = 8$ Hz, $J = 4$ Hz), and a 3-proton singlet at $\delta$ 0.98, which were assigned to HA, HB (or HC) and the angular methyl group, respectively, of compound 282.

The ketones 281 and 282 are derived from the diazoketone 274 by cyclopropanation taking place at different carbon-carbon double bonds of the diene unit. The lack of chemoselectivity in this cyclopropanation reaction was an interesting but undesirable result. Therefore it was decided to investigate different cyclopropanation conditions to determine whether the chemoselectivity could be improved. Fortunately, it was found that reaction of the diazoketone 274 with Rh$_2$(OAc)$_4$ (5 mol%) in dry CH$_2$Cl$_2$ (-78°C to room temperature, 4 hours) provided a 4:1 mixture of the ketones 281 and 282, respectively, in 78% yield (an overall yield of 59% from the carboxylic acid 269) (equation 49).

Since 281 and 282 were inseparable by silica gel chromatography, later synthetic transformations were carried out on mixtures of the two compounds. However, a pure sample of 281 was required for full characterization and was obtained in the following manner (Scheme 40). Reaction of a 4:1 mixture of ketones 281 and 282 (respectively) with
DIBAL in THF afforded a mixture of products, consisting of the alcohol 283 and the alcohols 284. Flash chromatography of this mixture provided the alcohol 283 in 66% yield and the alcohols 284 in 20% yield. The $^1$H nmr spectrum of 283 indicated that it was stereochemically homogeneous. Although the orientation of the hydroxyl group was not determined, it was assumed to be endo (as shown in Scheme 40) since the bulky reducing agent (DIBAL) would be expected to react with the ketone 281 from the less hindered, convex face of the molecule.

Scheme 40

The pure alcohol 283 was oxidized to the ketone 281 using a procedure developed by Griffith and Ley. Thus, to a solution of the alcohol 283 in dry CH$_2$Cl$_2$ was added freshly activated molecular sieves and N-methylmorpholine N-oxide (NMO) (2.5
equivalents). After the resulting mixture had been stirred for 10 min at room temperature, tetra-\(n\)-propylammonium perruthenate (TPAP) (5 mol\%) was added, and stirring was continued until the reaction was complete (as judged by tlc analysis). After appropriate workup, the crude reaction product was purified by flash chromatography, followed by distillation, to give the pure ketone 281 in 84\% yield. This compound exhibited spectral data which were in full accord with the assigned structure. For example, the infrared spectrum of 281 showed an absorbance at 1723 cm\(^{-1}\), attributable to the carbon-oxygen stretching frequency of the ketone function. The 400 MHz \(^1\)H nmr spectrum of this compound is shown in Figure 6. Several features are readily discernible from this spectrum. There is a 6-proton singlet at \(\delta 0.06\) and a 9-proton singlet at \(\delta 1.00\) due to the TBDMS ether function, a 1-proton doublet of triplets at \(\delta 1.18\) (\(J = 13\) Hz, \(J = 6\) Hz) due to either \(\text{H}_A\) or \(\text{H}_A^1\) and a 2-proton triplet at \(\delta 3.52\) (\(J = 6\) Hz, -CH\(_2\)CH\(_2\)O-). Also, there are 1-proton broad singlets at \(\delta 4.85\) and 4.98 due to the olefinic protons.

Reaction of the diazoketone 275 with CuSO\(_4\)-Cu(acac)\(_2\) in refluxing benzene afforded two products in a 1:1 ratio, which were inseparable by silica gel chromatography. One of the products was readily identified as the ketone 285 (equation 50) by comparison of
the $^1$H nmr spectrum of the crude reaction mixture with that of a pure sample of 285 (the preparation of which is described later). The presence of a 1-proton broad singlet at $\delta$ 5.49 (H$_A$) in the $^1$H nmr spectrum of the crude reaction mixture indicated that the other product was compound 286 (equation 50).

It was found that the chemoselectivity of the intramolecular cyclopropanation reaction could be improved by using Rh$_2$(OAc)$_4$ as catalyst. Thus, reaction of the diazoketone 275 with Rh$_2$(OAc)$_4$ (3 mol%) in CH$_2$Cl$_2$ (-78°C to room temperature, 4 hours) gave a 4:1 ratio of 285 and 286, respectively, in 63% yield (an overall yield of 49% from the carboxylic acid 270) (equation 51).

Since these compounds were inseparable by silica gel chromatography, later synthetic transformations were carried out using mixtures containing both compounds. However, a pure sample of 285 was required for spectral characterization and was prepared from the mixture of ketones 285 and 286 (Scheme 41) via a reduction-separation-oxidation sequence very similar to that described earlier, in connection with preparation of pure compound 281. Thus, DIBAL reduction of a 4:1 mixture of 285 and 286 (respectively) provided, after chromatographic separation of the products, the pure alcohol 287 in 66% yield and the
alcohols 288 (in 17% yield). Oxidation of 287 using TPAP and NMO proceeded cleanly, to give the pure ketone 285 in 83% yield. This material exhibited spectral data entirely consistent with the proposed structure.

There are several general comments that should be made regarding the transition metal-catalyzed intramolecular cyclopropanation reactions of diene diazoketones of general structure 240. Firstly, with the correct choice of catalyst, these reactions proceed cleanly and efficiently to give good overall yields of the cyclopropyl ketones 237 (R^1=H) and/or 289 from the corresponding carboxylic acids 242 (equation 52).

Secondly, the reactions are completely stereospecific, providing the 6-endo-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones of general structure 237 (R^1=H) and none of the corresponding exo isomers. However, the chemoselectivity of this process appears to be dependant on the substitution pattern of the diene unit of diazoketones 240. In particular, the reactions are completely chemoselective when R^7=H, but when R^7=alkyl both five and seven
membered ring ketones [237 (R\(^1\)=H) and 289] are formed. These results may be rationalized using the following arguments (Scheme 42). It is likely that the first step in this process involves reaction of the diazoketone function in compounds 240 with the transition metal catalyst to give a transition metal carbene complex, represented by 290.\(^{134,135}\) Presumably, the carbenoid site of intermediates 290 interacts with one of the carbon-carbon double bonds of the diene unit, resulting in cyclopropanation with concomitant regeneration of the catalyst. How readily either carbon-carbon double bond of the diene unit in 290 is cyclopropanated should depend primarily on how accessible it is to the metal carbenoid site. Examination of a molecular model representing 290 indicates that the carbenoid site can readily approach the C5-C6 double bond when the diene unit is either in the transoid conformation or the cisoid conformation, but can approach the C7-C8 double bond only when the diene unit is cisoid. Therefore, it is proposed that formation of five membered ring ketones 237 (R\(^1\)=H) may take place either via a transition state [TS1]\(^*\) derived from a conformer of general structure 290A (diene unit transoid) or via a transition state [TS2]\(^*\) derived from a conformer of general structure 290B (diene unit cisoid). Additionally, formation of the seven membered ring ketones 289 is possible only via a transition state [TS3]\(^*\) derived from a conformer of general structure 290C (diene unit cisoid) (Scheme 42). The differences in free energy between these transition states should determine the chemoselectivity of the cyclopropanation reaction.
It would be expected that formation of five membered ring products 237 (R^1=H) (via either [TS1]^# or [TS2]^#) is inherently favoured over formation of seven membered ring products 289 (via [TS3]^#), primarily due to entropy effects. However, steric effects might also be important in these reactions. The transition state [TS1]^# would experience a steric
interaction between HA and R7, whereas the transition states [TS2]# and [TS3]# would experience a steric interaction between HA and R9. The substituent R8 should not cause unfavourable steric interactions in any of the possible transition states.

For each of the diene diazoketones 273, 276 and 277, R9=H and R7=H. Regarding the cyclopropanation reactions involving these substrates, the steric interaction in the transition state [TS1]# appears to be less severe than the steric interaction in the transition states [TS2]# and [TS3]#. It is, therefore, proposed that these reactions proceed preferentially via [TS1]# to give five membered ring products 237 (R1=H)

For the diene diazoketones 274 and 275, R9=H and R7=alkyl. Regarding the cyclopropanation reactions involving these substrates, the steric interaction in the transition state [TS1]# appears to be more severe than the steric interaction in the transition states [TS2]# and [TS3]#. Therefore, it is proposed that these reactions proceed primarily via [TS2]# and [TS3]# to give both the five and seven membered ring products 237 (R1=H) and 289, respectively. Although the ketones 237 (R1=H) would still be expected to be formed more readily than the seven membered ring products 289, the low (or lack of) chemoselectivity in these reactions must be a result of a subtle balance between steric and entropic effects. The ratio of 237 (R1=H) to 289 formed in these reactions is somewhat dependant on the reaction conditions (e.g. the nature of the catalyst) which suggests that other factors may also be involved in determining the chemoselectivity.

In summary, an efficient, stereoselective synthesis of functionalized 6-endo-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones of general structure 237 (R1=H) has been developed, employing stannyldienes of general structure 250 as starting materials (equation 53). The compounds which were prepared via this general synthetic route, and the overall yields, are presented in Table 12. In principle, it should be possible to prepare many other ketones 237 (R1=H) via this methodology.

The 6-endo-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones 237 (R¹=H) were readily converted, via simple manipulation of the ketone function, into functionalized 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes of general structure 215 (R¹=H) (equation 54). These cis divinylcyclopropanes were found to undergo facile Cope rearrangement, to give the corresponding bicyclo[3.2.1]octa-2,6-dienes 216 (R¹=H) cleanly and efficiently (equation 54). It was found that the overall transformation of the ketones 237 into the bicyclic compounds 216 could be achieved conveniently without full purification of the intermediate cis divinylcyclopropanes 215. The Cope rearrangements were effected either by distillation of the crude cis divinylcyclopropane 215, or by warming a solution of (crude) 215 in benzene (in which case the products were purified by flash chromatography).
<table>
<thead>
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<th>Entry</th>
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Table 12. The preparation of 6-endo-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones 237

1 Notes. A) Product contaminated by approx. 20% of the corresponding seven membered ring ketone 289.

2 Overall yield of product from the appropriate stannyldiene
It was found that the 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes 215 are readily available from the ketones 237 via formation of the corresponding enol silyl ethers. For example, the ketone 278 was converted into the silyl enol ether 291 via reaction with KH and TBDMSCl, using a procedure very similar to that reported in the literature (equation 55). Thus, a suspension of KH (approximately 5 equivalents) in dry THF was added to a mixture of 278 and TBDMSCl (1.5 equivalents) in dry THF at -78°C. The resulting mixture was allowed to warm to room temperature and was stirred until the reaction was complete. After appropriate workup, glc analysis of the crude reaction mixture showed the presence of one major product. Distillation of this material under reduced pressure (140°C/0.2 Torr) afforded the pure bicyclo[3.2.1]octa-2,6-diene 292 in 82% yield (equation 55).

\[ \text{KH, TBDMSCl, THF, -78°C to room temp} \rightarrow \text{TKBDMOS} \]  
\[ \text{140°C, 0.2 Torr} \rightarrow \text{TKBDMOS} \]  
\[ \text{292} 82\% \]

The ketone 279 was converted into the enol silyl ether 293 via reaction with KH and TBDMSCl using a procedure identical with that described above (equation 56). Distillation of the crude reaction product under reduced pressure (170-175°C/0.2 Torr) afforded the pure bicyclo[3.2.1]octa-2,6-diene 294 in 88% yield (equation 56).

The \(^1\)H nmr spectrum for 294 is shown in Figure 7. This spectrum shows 6-proton singlets at δ 0.11 and 0.17 as well as 9-proton singlets at δ 1.00 and 1.03, due to the TBDMS ether functions. There is a 3-proton singlet at δ 3.25 (-OMe), a 2-proton multiplet at δ 3.57-3.72 (-CHOOMOM), a 2-proton triplet at δ 3.76 (J = 6 Hz, -OCH\(_2\)CH\(_2\)-), 1-proton

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doublets at $\delta$ 4.59 and 4.66 ($J = 7$ Hz for each signal, -OCH$_2$O-), and a 1-proton singlet at $\delta$ 5.12, due to $H_F$. The remaining signals were assigned using a combination of decoupling and COSY experiments (see Experimental section). Thus, the 1-proton doublet of doublets of doublets at $\delta$ 2.11 ($J = 10$ Hz, $J = 5$ Hz, $J = 1.5$ Hz), the 1-proton doublet of doublets of doublets at $\delta$ 5.58 ($J = 10$ Hz, $J = 2$ Hz, $J = 2$ Hz), and the 1-proton broad doublet at $\delta$ 6.24 ($J = 10$ Hz) were assigned to $H_B$, $H_F$, and $H_G$, respectively. Also, the 2-proton multiplet at $\delta$ 2.70-2.80 was assigned to $H_C$ and $H_D$ whilst the 3-proton multiplet at $\delta$ 1.70-1.90 was assigned to $H_A$ and -OCH$_2$CH$_2$-. Several points should be made regarding these assignments. Firstly, $H_G$ and $H_F$ were readily distinguished since there is a long range ("W") coupling between $H_B$ and $H_G$ ($J = 1.5$ Hz) but no observable coupling between $H_B$ and $H_F$. Secondly, $H_B$ and $H_A$ were readily distinguished on the basis of multiplicity and coupling constants. Thus, the signal due to $H_B$ appears as a doublet of doublets of doublets (at $\delta$ 2.11) due to coupling to $H_A$ ($J_{BA} = 10$ Hz), $H_C$ ($J_{BC} = 5$ Hz) and $H_G$ ($J_{BG} = 1.5$ Hz). Irradiation at $\delta$ 3.76 (-CH$_2$CH$_2$O-) enabled identification the signal due to $H_A$ as a
Figure 7
400 MHz $^1$H nmr spectrum (C$_6$D$_6$) of compound 294

$H_A$, $H_B$, $H_C$, $H_D$, $H_E$, $H_F$, $H_G$, TBDMS, OMOM
doublet at $\delta$ 1.81 ($J_{AB} = 10$ Hz). The observation that $H_A$ couples weakly, if at all, to $H_C$ is fully consistent with the 90° dihedral angle which exists between these protons (as indicated by molecular models).

The ketone 280 could not be converted into its enol silyl ether using the procedure described above. In fact, it was found that reaction of 280 with KH and TBDMSCl provided, after aqueous workup, a single product which was assigned the structure 295 (equation 57). Reaction of the ketone 280 with KH in THF (without TBDMSCl) also provided 295 (in 87% yield) (equation 57). This compound is the product of an intramolecular Michael reaction involving the potassium enolate derived from the ketone 280.

The spectral data derived from 295 were in full accord with the proposed structure. For example, the infrared spectrum of 295 showed strong absorbances at 1752 cm$^{-1}$ and 1729 cm$^{-1}$ attributable to the carbonyl stretching frequencies of the ketone and ester functions, respectively. The $^1$H nmr spectrum (400 MHz, C$_6$D$_6$) of 295 is shown in Figure 8. This spectrum shows a 9-proton singlet at $\delta$ 1.39 (\(-\text{CO}_2\text{Bu}^t\)), a 3-proton singlet at $\delta$ 3.19 (\(-\text{OMe}\)), a 2-proton triplet at $\delta$ 3.32 ($J = 6$ Hz, \(-\text{OCH}_2\text{CH}_2\)-), a 2-proton multiplet at $\delta$ 2.00 (\(-\text{CH}_2\text{CO}_2\text{Bu}^t\)) and 1-proton doublets at $\delta$ 4.41 and 4.42 ($J = 6$ Hz for each signal, \(-\text{OCH}_2\text{O}\)-). The remaining signals were assigned using a COSY experiment (see Experimental section). Thus, the 1-proton broad doublet at $\delta$ 1.18 ($J = 6$ Hz), the 1-proton
broad doublet at δ 1.67 (J = 6 Hz), the 1-proton broad singlet at δ 1.84, and the 1-proton broad triplet at δ 2.49 (J = 6 Hz), were assigned to HB, HA, HC, and HD, respectively. Also, the 1-proton multiplet at δ 1.41-1.51 was assigned to HG or HG' and the 3-proton multiplet at δ 1.52-1.62 was assigned to HG or HG', HE and HF.

The relative stereochemistry of 295 was confirmed by nOe difference experiments. In particular, irradiation at δ 2.00 (-CH2CO2Bu') resulted in signal enhancement at δ 1.58 (which was assigned to HF), 2.49 (HD), 1.67 (HA), and δ 1.84 (HC).

It was found that the ketone 280 could be converted into the corresponding enol silyl ether 296 via reaction with TBDMSOTf and Et3N, using a procedure very similar to that reported by Mander and Sethi (equation 58).137 Thus, TBDMSOTf (1.5 equivalents) was
added to a mixture of 280 and Et3N (3 equivalents) in dry CH2Cl2 at -78 °C, and the resulting mixture was stirred at -78 °C for 30 min. After appropriate workup, glc analysis of the crude reaction product showed the presence of a single compound. The crude product was dissolved in dry benzene and the resulting solution was warmed to 50°C overnight. Flash chromatography of the material thus obtained provided the bicyclo[3.2.1]octa-2,6-diene 297 in 82% yield (equation 58).

The ketone 281 (which was contaminated with approximately 20% of the seven membered ring ketone 282) was converted into the silyl enol ether 298 via reaction with TBDMSOTf and Et3N, following a procedure very similar to that which was described above (Scheme 43). After appropriate workup, glc analysis of the crude product showed the
presence of two products, in a ratio of approximately 4:1. The crude material was dissolved in dry benzene and the resulting solution was warmed to 50°C overnight. The crude mixture of enol silyl ethers (containing the bicyclo[3.2.1]octa-2,6-diene 299) thus obtained was treated with HOAc in THF at room temperature to give a readily separable mixture of products containing the bicyclo[3.2.1]oct-2-en-6-one 300 (Scheme 43). Flash chromatography of this mixture, followed by distillation, afforded the pure bicyclo[3.2.1]oct-2-en-6-one 300 in 55% yield.

The spectral data derived from the ketone 300 were fully consistent with the assigned structure. For example, the infrared spectrum of 300 showed a strong absorbance at 1747 cm\(^{-1}\) attributable to the carbon-oxygen stretching frequency of the ketone function. The \(^1\)H nmr spectrum of 300 (400 MHz, C\(_6\)D\(_6\)) is shown in Figure 9. This spectrum shows a 6-proton singlet at \(\delta 0.07\) and a 9-proton singlet at \(\delta 1.01\) due to the TBDMS group, a 3-proton singlet at \(\delta 1.41\) (vinyl methyl group), a 2-proton multiplet at \(\delta 3.61\) (-OCH\(_2\)CH\(_2\)-) and a 1-proton broad singlet at \(\delta 5.44\), due to H\(_H\). The remaining signals were assigned using decoupling experiments (see Experimental section). Thus, the 3-proton broad multiplet at \(\delta 1.53\)\(-\)1.67 was assigned to H\(_A\) and -CH\(_2\)CH\(_2\)O-, whilst the 1-proton broad doublet of doublets at \(\delta 1.51\) (\(J = 11\) Hz, \(J = 5.5\) Hz), the 1-proton doublet of doublets at \(\delta 2.27\) (\(J = 17\) Hz, \(J = 3\) Hz), and the 1-proton doublet at \(\delta 1.87\) (\(J = 17\) Hz) were assigned to H\(_B\), H\(_G\), and H\(_F\), respectively. Also, the 1-proton multiplet at \(\delta 2.42\), the 1-proton broad doublet of doublets at \(\delta 1.97\) (\(J = 17\) Hz, \(J = 5\) Hz), and the 1-proton broad doublet at \(\delta 2.05\) (\(J = 17\) Hz) were assigned to H\(_C\), H\(_D\) and H\(_E\), respectively. Two points should be made regarding these data. Firstly, H\(_B\) shows coupling to H\(_C\) (\(J_{BC} = 5.5\) Hz) whereas H\(_A\) couples weakly, if at all to H\(_C\). This observation is fully consistent with the 90° dihedral angle which exists between H\(_A\) and H\(_C\) (as indicated by molecular models). Similarly, H\(_E\) couples weakly (if at all) to H\(_C\), which is consistent with the 90° dihedral angle which exists between these protons, whereas H\(_D\) does show coupling to H\(_C\) (\(J_{DC} = 5\) Hz). Secondly,
Figure 9  400 MHz $^1$H nmr spectrum ($C_6D_6$) of compound 300
HQ and HP are readily distinguished since HA shows a long range ('W') coupling to HG (J = 3 Hz) but does not show coupling to HP.

The ketone 285 (which was contaminated with approximately 20% of the ketone 286) was converted into the silyl enol ether 301 via reaction with TBDMSOTf and Et3N (Scheme 44). Using a procedure similar to that described earlier, a benzene solution of crude 301 was warmed to 50°C overnight and the resulting mixture of products (containing the bicyclo[3.2.1]octa-2,6-diene 302) was treated with HOAc in THF (Scheme 44). Flash chromatography of the crude reaction product thus obtained, followed by distillation, provided the bicyclo[3.2.1]oct-2-en-6-one 303 in 65% yield.

The 6-endo-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones of general structure 237 were converted into functionalized 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes 215 in several other ways, as described below.
Thus, reaction of the ketone 279 with lithium diisopropylamide (LDA) in THF provided the corresponding lithium enolate 304 (Scheme 45). Reaction of the enolate 304 with N-phenyltrifluoromethanesulfonimide138 (excess) at -20°C for 1 hour, provided the enol triflate 305. After appropriate workup, the crude product was partially purified by flash chromatography. The material thus obtained was dissolved in dry benzene and the resulting solution was warmed to 50°C overnight. Flash chromatography of the resulting mixture afforded the bicyclo[3.2.1]octa-2,6-diene 306 in 73% overall yield.

\[
\begin{align*}
\text{MOMO} & \quad \text{LDA, THF,} \ -78^\circ\text{C,} \\
279 \quad & \quad 20 \text{ min;} \ -20^\circ\text{C,} \ 30 \text{ min} \\
\text{OTBDMS} & \\
\end{align*}
\]

\[
\begin{align*}
\text{MOMO} & \quad \text{Li}^+ \quad \text{PhN(SO}_2\text{CF}_3\text{)}_2 \\
304 \quad & \quad -20^\circ\text{C,} \ 1 \text{ hour} \\
\text{OTBDMS} & \end{align*}
\]

\[
\begin{align*}
\text{MOMO} & \quad \text{CF}_3\text{SO}_2\text{O} \\
305 \quad & \quad \text{PhH,} \ 50^\circ\text{C} \\
\text{OTBDMS} & \end{align*}
\]

\[
\begin{align*}
\text{TDBMSO} & \quad \text{OMOM} \\
306 \quad & \quad \text{PhH,} \ 50^\circ\text{C} \\
\end{align*}
\]

\[
\begin{align*}
\text{MOMO} & \quad \text{LDA, THF,} \ -78^\circ\text{C,} \\
279 \quad & \quad 20 \text{ min;} \ -20^\circ\text{C,} \ 30 \text{ min} \\
\text{OTBDMS} & \\
\end{align*}
\]

\[
\begin{align*}
\text{MOMO} & \quad \text{Li}^+ \quad \text{PhN(SO}_2\text{CF}_3\text{)}_2 \\
304 \quad & \quad -20^\circ\text{C,} \ 1 \text{ hour} \\
\text{OTBDMS} & \end{align*}
\]

\[
\begin{align*}
\text{MOMO} & \quad \text{CF}_3\text{SO}_2\text{O} \\
305 \quad & \quad \text{PhH,} \ 50^\circ\text{C} \\
\text{OTBDMS} & \end{align*}
\]

\[
\begin{align*}
\text{TDBMSO} & \quad \text{OMOM} \\
306 \quad & \quad \text{PhH,} \ 50^\circ\text{C} \\
\end{align*}
\]

Scheme 45

Also, reaction of the lithium enolate 304 with excess diphenyldisulphide139 (PhSSPh) at room temperature (1.5 hours) afforded the α-phenylthio ketones 307 in 77% yield (after flash chromatography) (Scheme 46). Compounds 307 were converted into the silyl enol ether 308 via reaction with KH and TBDMSCl in THF, following a procedure
which was very similar to that described earlier. After appropriate workup, the crude silyl enol ether was dissolved in dry benzene and the resulting solution was warmed to 60°C overnight. Flash chromatography of the mixture thus obtained provided the bicyclo[3.2.1]octa-2,6-diene 309 in 44% overall yield from the ketone 279 (Scheme 46).

Additionally, reaction of the lithium enolate 304 with methyl cyanoformate (MeOOCOCN)\textsuperscript{140} at -78°C, in the presence of hexamethylphosporamide (HMPA), afforded the \( \beta \)-ketoesters 310 (Scheme 46). Reaction of the crude product (containing 310) with TBDMSCl and KH, in THF, provided the silyl enol ether 311. After appropriate workup, the crude oil containing 311 was dissolved in dry benzene and the resulting solution was warmed to 50°C overnight. Flash chromatography of the reaction mixture afforded the bicyclo[3.2.1]octa-2,6-diene 312 in 74% yield from the ketone 279 (Scheme 46).

The spectral data derived from the bicyclo[3.2.1]octa-2,6-dienes 309 and 312 were in full accord with the assigned structures. For example, the infrared spectrum of 312 showed a strong absorbance at 1737 cm\textsuperscript{-1}, attributable to the carbonyl stretching frequency of the ester function, and an absorbance at 1627 cm\textsuperscript{-1}, attributable to the carbon-carbon stretching frequency of the enol ether function. The \(^1\)H nmr spectrum (400 MHz, CD\textsubscript{6}D\textsubscript{6}) of 312 is shown in Figure 10. This spectrum shows a 6-proton singlet at \( \delta \) 0.11, a 3-proton singlet at \( \delta \) 0.18, a 3-proton singlet at \( \delta \) 0.21, a 9-proton singlet at \( \delta \) 0.97 and a 9-proton singlet at \( \delta \) 1.02, which are attributable to the TBDMS ether functions. Also, there is a 2-proton multiplet at \( \delta \) 1.68-1.85 (-OCH\textsubscript{2}CH\textsubscript{2}-), a 3-proton singlet at \( \delta \) 3.24 (-OMe), a 3-proton singlet at \( \delta \) 3.50 (-OMe), a 2-proton multiplet at \( \delta \) 3.71 (-OCH\textsubscript{2}CH\textsubscript{2}-) and 1-proton doublets at \( \delta \) 4.61 and 4.67 (\( J = 6 \) Hz, -OCH\textsubscript{2}O-). The remaining signals were assigned using decoupling and COSY experiments (see Experimental section). Thus, the 1-proton doublet at \( \delta \) 1.93 (\( J = 9 \) Hz) and the 1-proton broad doublet at \( \delta \) 2.50 (\( J = 9 \) Hz) were assigned to \( H_A \) and \( H_B \), respectively. The 1-proton singlet at \( \delta \) 5.08, the 1-proton doublet of doublets at \( \delta \) 5.97 (\( J = 10 \) Hz, \( J = 2 \) Hz), and the 1-proton broad doublet at \( \delta \) 6.18 (\( J = \)
LDA, -78°C, 20 min; -20°C, 30 min

MOMO-PhSSPh

MeOCOCN, HMPA, -78°C

KH, TBDMSCl, THF, 78°C to room temp

MOMO-MeOCOCN, HMPA, -78°C

KH, TBDMSCl, THF, 78°C to room temp

PhH, 60°C

PhH, 50°C

Scheme 46
10 Hz) were assigned to H_E, H_F, and H_G, respectively. Finally, the 2-proton multiplet at \( \delta \) 3.50-3.58 was assigned to H_C plus H_D or H_D', whilst the 1-proton multiplet at \( \delta \) 4.22 was assigned to H_D or H_D'. Two points should be made regarding these data. Firstly, the signals due to H_A and H_B could easily be assigned, since irradiation at \( \delta \) 2.50 (H_B) caused the signal at \( \delta \) 6.18 (H_G) to sharpen to a doublet of doublets \((J_{GF} = 10 \text{ Hz}, J_{GC} = 1.5 \text{ Hz})\), whereas irradiation at \( \delta \) 1.93 (H_A) did not affect the signal at \( \delta \) 6.18 (H_G). The long range coupling between H_B and H_G is fully consistent with the "W" relationship which exists between these protons (as indicated by molecular models). Secondly, the assignment of the 2-proton multiplet at \( \delta \) 3.50-3.58 to H_C plus H_D or H_D', was confirmed by decoupling. Thus, irradiation at \( \delta \) 3.50-3.58 caused the signal at \( \delta \) 4.22 (H_D or H_D') to collapse to a singlet, whilst the signal at \( \delta \) 5.97(H_F) collapsed to a doublet \((J_{FG} = 10 \text{ Hz})\).

The ketone 279 was converted into the 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-ene 313 in two steps, as shown in Scheme 47. Thus, a mixture of 279 and an excess of the lithio phosphonate reagent (which was prepared via reaction of trimethylphosponoacetate (181) with MeLi) in THF was stirred overnight at room temperature. After appropriate workup, flash chromatography of the crude reaction mixture provided the \( \alpha,\beta \)-unsaturated esters 314 (a 1:1 ratio of geometrical isomers, by gc analysis). A solution of this material in dry THF was cooled to -78°C, LDA was added, and the resulting mixture was stirred at -78°C for 45 min and at 0°C for 10 min. The mixture was then transferred, via cannula, into a cold (-78°C) mixture of HOAc and THF (1:1), and the resulting mixture was stirred for 10 min at -78°C. After appropriate workup, gc analysis of the crude reaction product showed the presence of one compound. The crude product was dissolved in dry benzene and the resulting solution was warmed to 50°C overnight. Flash chromatography of the crude product afforded the bicyclo[3.2.1]octa-2,6-diene 315 in 59% overall yield from the ketone 279 (Scheme 47).
Another approach to the synthesis of 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes involves reduction of the carbonyl group in the ketones of general structure followed by dehydration. For example, the ketone was converted into the 6-endo-vinylbicyclo[3.1.0]hex-2-ene via the reaction sequence shown in Scheme 48. Thus, the carbonyl group of was reduced with DIBAL to give the alcohol in 93% yield. The $^1$H nmr spectrum of this compound indicated that it was stereochemically homogeneous. Although the orientation of the hydroxyl group in was not proven, it was assumed to be endo (as shown) since the bulky reducing agent (DIBAL) would be expected to react with from its more open, convex face. The alcohol was converted into the selenide via reaction with $n$-Bu$_3$P and o-nitrophenylselenocyanate (THF, room temp), according to the procedure reported by Grieco (Scheme 48). The crude reaction product was purified by flash chromatography, to give, which was contaminated by a small amount.
of $n$-Bu$_3$P. The relative stereochemistry of this material was assumed to be that shown in Scheme 48, since this substitution reaction would be expected to proceed with inversion of configuration.

The selenide 318 was subjected to an oxidation-selenoxide elimination procedure. Thus, a solution of 318 in CH$_2$Cl$_2$ was treated with 30% aqueous H$_2$O$_2$ (excess) at room temperature. The two-phase mixture was stirred vigorously, until the reaction was complete. After appropriate workup, the crude reaction product was purified by flash chromatography to give the 6-endo-vinylbicyclo[3.1.0]hex-2-ene 316. Distillation (160-170°C/6 Torr) of this material afforded the bicyclo[3.2.1]octa-2,6-diene 320 in 48% overall yield from the ketone 278 (Scheme 48).

Scheme 48
The $^1$H nmr spectrum (400 MHz, C$_6$D$_6$) of 320 is shown in Figure 11. This spectrum shows a 6-proton singlet at $\delta$ 0.1 and a 9-proton singlet at $\delta$ 1.02, due to the TBDMS ether group, and a 2-proton multiplet at $\delta$ 3.73 (-OCH$_2$CH$_2$-). The remaining signals were assigned using a combination of decoupling and COSY experiments (see Experimental section). Thus, the 1-proton doublet of doublets of doublets of doublets at $\delta$ 5.25 ($J = 10$ Hz, $J = 3$ Hz, $J = 2.5$ Hz, $J = 1.5$ Hz), the 1-proton doublet of doublets at $\delta$ 5.61 ($J = 6$ Hz, $J = 3$ Hz), the 1-proton multiplet at $\delta$ 5.98 and the 1-proton doublet at $\delta$ 6.09 ($J = 6$ Hz) were assigned to H$_F$, H$_I$, H$_G$, and H$_H$, respectively. Also, the 1-proton multiplet at $\delta$ 2.61 and the 1-proton doublet of doublets of doublets of doublets at $\delta$ 2.17 ($J = 18$ Hz, $J = 5$ Hz, $J = 3$ Hz, $J = 2.5$ Hz) were assigned to H$_C$ and H$_D$, respectively. Finally, the 5-proton multiplet at $\delta$ 1.65-1.95 was assigned to H$_A$, H$_B$, H$_E$ and -OCH$_2$CH$_2$-. A few points should be made regarding these assignments. Firstly, the signal at $\delta$ 2.17 was assigned to H$_D$ (and not H$_E$), since irradiation at $\delta$ 2.61 (H$_C$) caused the signal at $\delta$ 2.17 (H$_D$) to collapse to a doublet of doublets of doublets ($J = 18$ Hz, $J = 5$ Hz, $J = 3$ Hz, $J = 2.5$ Hz), removing a 5 Hz coupling constant. Therefore, H$_D$ couples to H$_C$ fairly strongly ($J_{CD} = 5$ Hz), whereas H$_E$ would be expected to couple with H$_C$ very weakly (if at all) due to the 90°C dihedral angle which exists between these protons.

Secondly, H$_F$ and H$_G$ were readily distinguished since H$_C$ couples to H$_F$ ($J_{FC} = 1.5$ Hz) but not to H$_G$. This is shown by irradiation at $\delta$ 2.61 (H$_C$), which caused the signal at $\delta$ 5.25 (H$_F$) to collapse to a doublet of doublets of doublets ($J = 10$ Hz, $J = 3$ Hz, $J = 2.5$ Hz), whereas the signal at $\delta$ 5.98 (H$_G$) was unaffected.

The ketone 281 (which was contaminated with approximately 20% of the ketone 282) was converted into the 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-ene 321 via a sequence identical with that described above (Scheme 49). Reduction of a mixture of 281 and 282 with DIBAL, as described earlier gave, after separation of the products by flash chromatography, the alcohol 283 in 66% yield. The alcohol was then converted into the
Figure 11
400 MHz 1H nmr spectrum (CD$_3$OD) of compound 320
selenide 322 via reaction with $n$-Bu$_3$P and o-nitrophenylselenocyanate (319). Reaction of the selenide 322 with H$_2$O$_2$ provided, after flash chromatography of the crude reaction product, the 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-ene 321. Distillation of this material (160-175°C, 6 Torr) afforded the bicyclo[3.2.1]octa-2,6-diene 323 in 29% overall yield from the mixture of ketones 281 and 282 (Scheme 49).

Finally, it was shown that 6-endo-(1-alkenyl)bicyclo[3.1.]hexan-2-ones 237 may be converted into cis divinylcyclopropanes by conversion of the ketone function to an $\alpha,\beta$-unsaturated ketone function. Thus, the ketone 278 was converted into the $\alpha,\beta$-unsaturated ketone 324 via the selenylation-oxidation-selenoxide elimination sequence shown in Scheme 50.143 To a solution of the ketone 278 in THF was added a solution of
LDA (2 equivalents) in THF and the resulting mixture was stirred for 30 min at -78°C and for 20 min at -20°C. Excess PhSeBr (prepared by reaction of PhSeSePh with Br2) was added to the reaction mixture at -78°C, via cannula, and the resulting mixture was stirred at -78°C for 20 min. After appropriate workup, the crude reaction product was purified by flash chromatography, to give the selenides 325 in 75% yield (Scheme 50). This material was carried on to the next step without further purification. The selenides 325 were subjected to an oxidation-selenoxide elimination procedure similar to that reported by Clive. Thus, a mixture of 325 and NaIO4 (excess) in aqueous dimethoxyethane (DME) was stirred at room temperature overnight. After appropriate workup, the crude reaction product was purified by flash chromatography, to give the bicyclo[3.2.1]octa-2,6-diene 326 in 80% yield (60% from 278).
the ketone 278). Apparently, the cis divinylcyclopropane 324, formed in this manner, undergoes Cope rearrangement at room temperature to give the observed product 326 (Scheme 50).

This compound exhibited spectral data which were in full accord with the assigned structure. For example, the infrared spectrum of 326 showed a strong absorbance at 1770 cm\(^{-1}\) attributable to the carbon-oxygen stretching frequency of the ketone function. The \(^1\)H nmr spectrum (400 MHz, C\(_6\)D\(_6\)) of 326 is shown in Figure 12. This spectrum shows a 6-proton singlet at \(\delta 0.05\) and a 9-proton singlet at \(\delta 0.99\), due to the TBDMS group, as well as a 2-proton triplet of doublets at \(\delta 2.03\) (\(J = 6\) Hz, \(J = 1.5\) Hz, -OCH\(_2\)CH\(_2\)-), a 2-proton multiplet at \(\delta 3.43\) (-OCH\(_2\)CH\(_2\)-), and 1-proton multiplets at \(\delta 1.62\) and \(2.27\), attributable to HB and HC (although these signals were not individually assigned). The 1-proton multiplet at \(\delta 2.98\) and the 1-proton broad doublet at \(\delta 4.44\) (\(J = 6.5\) Hz) were assigned to HA and HD, respectively. Finally, the 1-proton multiplet at \(\delta 5.15\), the 1-proton doublet of multiplets at \(\delta 5.32\) (\(J = 6.5\) Hz) and the 1-proton multiplet at \(\delta 5.82\), were assigned to HF, HE, and HG, respectively. These signal assignments were supported by decoupling experiments (see Experimental section). For example, irradiation at \(\delta 2.98\) (HA) caused the signal at \(\delta 5.32\) (HE) to collapse to a multiplet, whilst the signal at \(\delta 5.15\) (HF) sharpened to a doublet of doublets of doublets of doublets of doublets (\(J = 11\) Hz, \(J = 3.5\) Hz, \(J = 3.5\) Hz, \(J = 1\) Hz). Also, irradiation at \(\delta 4.44\) (HD) caused the signal at \(\delta 5.82\) (HG) to sharpen to a doublet of doublets of doublets of doublets of doublets (\(J = 11\) Hz, \(J = 2\) Hz, \(J = 2\) Hz), whilst the signal at \(\delta 5.15\) (HF) sharpened to a doublet of doublets of doublets of doublets of doublets (\(J = 11\) Hz, \(J = 3.5\) Hz, \(J = 3.5\) Hz, \(J = 1.5\) Hz), and the signal at \(\delta 5.32\) (HE) sharpened to a doublet of triplets (\(J = 6.5\) Hz, \(J = 1.5\) Hz). Finally, irradiation at \(\delta 2.03\) (-OCH\(_2\)CH\(_2\)-) caused the signal at \(\delta 5.32\) (HE) to sharpen to a doublet of doublets (\(J = 6.5\) Hz, \(J = 1.5\) Hz), whilst the signal at \(\delta 3.43\) (-OCH\(_2\)CH\(_2\)-) collapsed to a singlet.
Figure 12  400 MHz $^1$H nmr spectrum (C$_6$D$_6$) of compound 326
3.8. The preparation of 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes 215 and the Cope rearrangement of these compounds into bicyclo[3.2.1]octa-2,6-dienes 216. The effects of substituents on the rates of these Cope rearrangements.

Although the 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes 215, which were prepared as described in the previous section, were found to undergo facile Cope rearrangement to the corresponding bicyclo[3.2.1]octa-2,6-dienes 216, these rearrangements generally proceed slowly at room temperature. Since the compounds 215 were prepared from the appropriate precursors under mild conditions (i.e. at or below room temperature), it was usually possible to isolate these materials before significant Cope rearrangement had occurred. As a result, we had the opportunity to observe and, therefore, measure the rates of the Cope rearrangement of these compounds by $^1$H nmr spectroscopy. The general procedure which was used for the kinetic studies is described below for the preparation and Cope rearrangement of compound 291 (equation 59). Thus, the ketone 278 was converted into the 6-endo-vinylbicyclo[3.1.0]hex-2-ene 291 via reaction with KH and TBDMS as described earlier. After appropriate workup, the solvent was removed by rotary evaporation at room temperature. Any remaining volatile material was removed under vacuum.

\[
292 \quad k = 3.7 \times 10^5 \text{ s}^{-1}
\]
0.5 Torr) to provide the essentially pure compound 291, approximately 15 mg (38 μmol) of which was dissolved in enough dry benzene-d₆ (approximately 0.8 mL) to fill a 5mm (base washed) nmr tube to 3 cm. The solution was transferred to the nmr tube, which was then placed in the nmr spectrometer probe (Varian XL-300 spectrometer) at room temperature, and a spectrum was recorded. The olefinic region of this spectrum is shown in Figure 13a. There is a 1-proton singlet at δ 4.48, a 1-proton doublet of doublets at δ 5.20 (J = 10 Hz, J = 2 Hz), a 1-proton doublet of doublets at δ 5.40 (J = 16 Hz, J = 2 Hz) and a 1-proton doublet of doublets of doublets at δ 5.88 (J = 16 Hz, J = 10 Hz, J = 10 Hz), which are assigned as Hw, HB, HC, and HD, respectively. There are no signals present which are due to the rearranged product 292. This spectrum represented the situation at t = 0. The probe temperature was set at 40°C (although this actually achieves a temperature of 43°C, as determined by calibration using ethylene glycol as standard) and the time was noted. Although the required temperature (43°C) was reached after a few seconds, thermal equilibration of the solution in the nmr tube probably takes several minutes. The time taken for thermal equilibration of the solution was neglected since it is small in comparison to the time taken for the overall experiment. Spectra were then recorded at time intervals.

The rearrangement of 291 to 292 proved to be fairly slow at 43°C. After 1.5 hours (at 43°C), some signals due to the rearranged product 292 were readily discernible. The olefinic region of this spectrum is shown in Figure 13b. Thus, as well as signals due to 291, there is a 1-proton broad doublet at δ 6.17 (J = 10 Hz) and a 1-proton singlet at δ 5.14, attributable to HG (292) and HH (292), respectively. The signal due to HF (292) is at approximately δ 5.30, but is overlapped by the signal due to HC (291).

The progress of the Cope rearrangement was measured by observation of the growth of the signal at δ 6.17 (HG, 292) and the decay of the signal at δ 5.86 (HD, 291) (see Figures 13a-f) since these appear to be the most well dispersed signals in this region. Integration of these signals (using Varian XL-300 software, keeping the vertical scale of the
Figure 13  The rearrangement of compound 291 to 292 at 43°C in C₆D₆. Spectra recorded at 300 MHz.
Figure 13, continued. The rearrangement of compound 291 to 292 at 43°C in C₆D₆. Spectra recorded at 300 MHz.
spectrum constant and the integral scale constant) provided the ratios of 291 to 292 which existed after periods of time (measured in seconds) at 43°C. The fractions of 291 remaining after time t seconds were calculated from the integral number for HD (291) divided by the sum of the integral numbers for HD(291) and HG(292). These data are listed in Table 13. A plot of \( \ln([291]/[291]+[292]) \) versus time [where [291] = integration number for HD(291), and [292] = integration number for HG(292)], using the data in Table 13, produces series of points which best fit a straight line of slope \(-3.7 \times 10^{-5} \text{s}^{-1}\) (Figure 14). This corresponds to a rate constant for rearrangement of 291 to 292 of \(3.7 \times 10^{-5} \text{s}^{-1}\).

When this rearrangement reaction was repeated, a similar plot generated a rate constant of \(3.4 \times 10^{-5} \text{s}^{-1}\). The difference in size between these rate constants suggests that an error of approximately 10% is associated with these experiments.

<table>
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Figure 14. Plot of the kinetic data for the Cope rearrangement of 291 to 292.

\[ \ln \left( \frac{[291]}{[291]+[292]} \right) \]

\[ \text{Time (s)} \]

\[ [291] = \text{integration number for } H_D \text{ (291)} \]

\[ [292] = \text{integration number for } H_G \text{ (292)} \]

Slope = $-3.7 \times 10^{-5}$ s$^{-1}$
The rates of Cope rearrangement for other *cis* divinylcyclopropanes 215 were determined in a similar manner. Each compound was prepared from the appropriate precursor, as described in the previous section of this thesis, and the Cope rearrangement was observed by $^1$H nmr spectroscopy at 43°C. The progress of the rearrangement was monitored by integration of well dispersed signals due to the unrearranged and rearranged products. These experiments and the kinetic data are presented in the Experimental section, and the log plots corresponding to these data are shown in Figures 15 and 16. The rate constants for these Cope rearrangements are summarized in Table 14.

Several points should be made regarding the data given in Table 14. Firstly, each kinetic run was repeated, and the rate constant obtained was, in each case, very similar (within ± 10%) to that obtained originally. There are several potential sources of experimental error associated with these kinetic experiments. For example, there is a time period in which the sample warms to 43°C in the nmr probe and equilibrates at this temperature, so the sample does not initially experience a uniform temperature. The major source of error in the data, however, arises from the integration of the $^1$H nmr signals. Firstly, it must be decided where the integration curve for a particular signal begins and finishes. Therefore, in each case the integration limits were kept constant throughout the experiment. Secondly, any signals due to minor (unknown) impurities could be a source of error in the integration if these signals were to be very close to or underneath those due to the divinylcyclopropane and/or the rearranged product. It was felt that this problem was minimized by integration of well defined, well dispersed signals for these measurements.

The data in Table 14 show some general trends with respect to the effect of substituents on the rates of Cope rearrangement of 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes 215. For example, increasing the size of the substituent $R^7$ increases the rate of Cope rearrangement. This is exemplified by comparison of entries 3, 4 and 5, in which replacement of $R^7=\text{H}$ by $R^7=\text{Me}$ causes a three-fold rate increase and replacing $R^7=\text{H}$ by $R^7=\text{Pr}^i$ causes a 12.5 fold rate increase. This effect is also shown by comparison of entries
[215] = integration number for signal representing 215 (1 proton)
[216] = integration number for signal representing 216 (1 proton)

× Rearrangement of 293 to 294. See entry 7, Table 14. Slope = -2.6 \times 10^{-5} \text{ s}^{-1}.
□ Rearrangement of 296 to 297. See entry 6, Table 14. Slope = -2.3 \times 10^{-4} \text{ s}^{-1}.
▲ Rearrangement of 298 to 299. See entry 4, Table 14. Slope = -1.1 \times 10^{-4} \text{ s}^{-1}.
● Rearrangement of 301 to 302. See entry 5, Table 14. Slope = -4.5 \times 10^{-4} \text{ s}^{-1}.
〇 Rearrangement of 308 to 309. See entry 9, Table 14. Slope = -1.5 \times 10^{-5} \text{ s}^{-1}.
△ Rearrangement of 311 to 312. See entry 8, Table 14. Slope = -6.2 \times 10^{-5} \text{ s}^{-1}.

\[a\] The progress of the rearrangement was measured by integration of 2-proton signals corresponding to the starting material and product. See Experimental section.

Figure 15. Plots of kinetic data for Cope rearrangements of the 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes 293, 296, 298, 301, 308 and 311.
\[ \text{[215]} = \text{integration number for signal representing 215 (1 proton)} \]

\[ \text{[216]} = \text{integration number for signal representing 216 (1 proton)} \]

- \( \times \) Rearrangement of 305 to 306. See entry 10, Table 14. Slope = -2.9 \( \times 10^{-4} \) s\(^{-1}\).
- \( \circ \) Rearrangement of 313 to 315. See entry 11, Table 14. Slope = -1.5 \( \times 10^{-4} \) s\(^{-1}\).
- \( \blacktriangle \) Rearrangement of 316 to 320. See entry 1, Table 14. Slope = -9.0 \( \times 10^{-5} \) s\(^{-1}\).
- \( \circ \) Rearrangement of 321 to 323. See entry 2, Table 14. Slope = -6.8 \( \times 10^{-4} \) s\(^{-1}\).

**Figure 16.** Plots of kinetic data for Cope rearrangements of the 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes 305, 313, 316 and 321.
Table 14. The rates of Cope rearrangement of functionalized 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes 215 (R^1=H) into bicyclo[3.2.1]octa-2,6-dienes 216 (R^1=H).

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<tr>
<td>7</td>
<td>TBDMSO</td>
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- **299** \( k = 1.1 \times 10^{-4} \text{ s}^{-1} \)
- **302** \( k = 4.5 \times 10^{-4} \text{ s}^{-1} \)
- **297** \( k = 2.3 \times 10^{-4} \text{ s}^{-1} \)
- **294** \( 2.6 \times 10^{-5} \text{ s}^{-1} \)
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<th>8</th>
<th>MOMO — (-) — MeO₂C — TBDMSO</th>
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<th>MeO₂C — TBDMSO — OMOM</th>
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- 312
- \( k = 6.2 \times 10^{-5} \text{ s}^{-1} \)

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<th>9</th>
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<th>PhS — TBDMSO — OMOM</th>
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- 309
- \( k = 1.5 \times 10^{-5} \text{ s}^{-1} \)

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- 306
- \( 2.9 \times 10^{-4} \text{ s}^{-1} \)

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<th>11</th>
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- 315
- \( k = 1.5 \times 10^{-4} \text{ s}^{-1} \)

230
1 and 2, in which replacing $R^7=H$ by $R^7=\text{Me}$ causes a 7.6 fold increase in rate of Cope rearrangement. Very similar effects have been observed in other types of Cope rearrangement. In particular, Miller and Gadwood reported that the cis divinylcyclobutane 327 rearranges to the cycloocteneone 328 approximately six times faster than 329 rearranges to 330 (Scheme 51). These results were attributed to the greater electron donating nature of the methyl substituent in compound 327 relative to $H$ in compound 329. In our cases, the observed rate enhancements might be related to an increase in $+I$ inductive effect associated with the substituent $R^7$, on going from $R^7=H$ to $\text{-Me}$ to $\text{-Pr}^t$.

Replacement of $R^2=H$ by $R^2=\text{OTBDMS}$ causes a reduction in rate of Cope rearrangement. This is shown by comparison of entry 3 and entry 1, in which there is a 2.5 fold reduction in rate upon replacement of $R^2=H$ by $R^2=\text{OTBDMS}$, and by comparison of entry 4 and entry 2, in which there is a 6.3 fold reduction in rate upon replacement of $R^2=H$ by $R^2=\text{OTBDMS}$. Since, in the former case ($R^2=H$ or OTBDMS, $R^7=H$), only minor steric interactions would exist between $R^2$ and $R^7$ in the transition states 331 for Cope rearrangement, the observed rate reduction might be the result of an electronic effect. However, in the latter case, the steric interaction between $R^2=\text{OTBDMS}$ and $R^7=\text{Me}$ in the
transition state 331 for Cope rearrangement would be significantly larger than the steric
interaction in 331 between R²=H and R⁷=Me. The observed rate reduction could,
therefore, be due to a combination of electronic and steric factors.

![Diagram](image)

A comparison of entry 3 with entry 6 shows that there is a 6.5 fold increase in the rate
of Cope rearrangement upon replacement of R⁸=H by R⁸=CO₂Bu⁺. This effect is most
likely electronic in nature and, apparently, outweighs the eclipsing interaction that would exist
in the transition state 332 for Cope rearrangement, between R⁸=CO₂Bu⁺ and the proton at
C3 (Scheme 52). In light of this observation, it is interesting to note that replacement of
R⁸=H by R⁸=CH₂OMOM causes a 1.3 fold reduction in the rate of rearrangement (a
comparison of entries 3 and 7). This result may be rationalized by the presence of an
eclipsing interaction in the transition state 332 for Cope rearrangement, between
R⁸=CH₂OMOM and the proton at C3 (Scheme 52). However, such an eclipsing interaction
would be expected to cause a larger rate retardation than is actually observed. In a related
study, Schneider and Rau¹¹⁴ reported that the cis divinylcyclopropane 333 rearranges, via a
transition state 334, to the 1,4-cyclohexadiene 335 approximately four times slower than cis
divinylcyclopropane (336) rearranges to 1,4-cyclohexadiene (337) (Scheme 52). Therefore,
in our case it appears that the eclipsing interaction in the transition state 332 is partially
balanced by the electron withdrawing nature of the substituent (CH₂OMOM).
A comparison of entries 7 and 10 shows that replacement of $R^2=\text{OTBDMS}$ by $R^2=\text{OSO}_2\text{CF}_3$ causes a 10.7 fold increase in the rate of Cope rearrangement, whilst a comparison of entries 7 and 11 shows that replacement of $R^2=\text{OTBDMS}$ by $R^2=\text{CH}_2\text{CO}_2\text{Me}$ causes a 5.7 fold increase in rate. These effects are most likely due to the greater electron withdrawing ability of both $R^2=\text{OSO}_2\text{CF}_3$ and $R^2=\text{CH}_2\text{CO}_2\text{Me}$, compared
to \(R^2=\text{OTBDMS}\) since, in each case, the steric interactions involving \(R^2\) in the transition state 338 for Cope rearrangement should be of similar magnitude.

A comparison of entries 7 and 8 shows that replacement of \(R^3=\text{H}\) by \(R^3=\text{CO}_2\text{Me}\) causes a 2.3 fold increase in the rate of Cope rearrangement. It is concluded that this effect is electronic in nature and is large enough to outweigh the significant eclipsing interaction that would exist in the transition state 339 for Cope rearrangement, as shown below.

Finally, a comparison of entries 7 and 9 shows that replacement of \(R^3=\text{H}\) by \(R^3=\text{SPh}\) causes a 1.5 fold reduction in rate of Cope rearrangement. This could be a result of the eclipsing interaction that would exist in the transition state 340 for Cope rearrangement.
However, since the SPh group is potentially electron donating (via a resonance effect), an electronic contribution to this rate reduction cannot be ruled out.

In summary, it has been shown that the rate of Cope rearrangement of 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes 215 depends on the nature of the substituents and the substitution pattern. Although previous workers\textsuperscript{113,114} have rationalized substituent effects in terms steric interactions in the transition state for Cope rearrangement, this study has shown that the electron donating or withdrawing nature of the substituent is also important. In fact, in some cases it appears that the electronic effects outweigh the steric effects. The results presented in Table 14 and discussed above certainly indicate that the transition state for Cope rearrangement of 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes has some polar character. However, no further conclusions can be made regarding the exact nature of the transition state.

3.9. Conclusions

A general, efficient, stereoselective synthesis of 6-endo-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones of general structure 237 (R\textsuperscript{1}=H) was developed, using the readily available stannyldienes of general structure 250 as starting materials
(Scheme 53). The key steps of this synthesis involve the preparation of diene esters 241 via Pd(0)-catalyzed cross coupling reaction between iodo dienes of general structure 249 and the organozinc reagent 246, and the transition metal-catalyzed intramolecular cyclopropanation reactions of diene diazoketones 240 (Scheme 53).

Scheme 53
The ketones 237 (R₁=H) were readily converted into a variety of functionalized 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes of general structure 215 (R₁=H) via simple synthetic manipulation of the carbonyl group. Distillation, or warming benzene solutions of the cis divinylcyclopropanes 215 (R₁=H) provided the bicyclo[3.2.1]octa-2,6-dienes 216 (R₁=H) cleanly and efficiently. This overall synthetic sequence, therefore, constitutes a general, reliable methodology for the preparation of functionalized bicyclo[3.2.1]octanes.

The rates of Cope rearrangement of a number of the cis divinylcyclopropanes 215 (R₁=R₉=H) were measured by ¹H nmr spectroscopy (43°C, C₆D₆). The effects of substituents on the rate of Cope rearrangement of these cis divinylcyclopropanes were attributed to either steric or electronic effects. In some cases, the electronic effects appear to outweigh the steric interactions between substituents in the transition state for Cope rearrangement 217.

IV. Experimental

For General experimental details and "Solvents and reagents", see Experimental section for Part 1 of this thesis.

Preparation of the alcohol 253.
To a cold (-78°C), stirred solution of the ester 182 (5.65 g, 13.02 mmol) in dry Et₂O (100 mL) was added a solution of diisobutylaluminium hydride (2.5 equiv.) in hexane. After the mixture had been stirred at -78°C for 1h and at 0°C for 1 h, saturated aqueous NH₄Cl (5 mL) was added and the mixture was exposed to air and allowed to warm to room temperature. After approx. 30 min at room temperature a heavy gelatinous white precipitate had formed. Et₂O (50 mL) and MgSO₄ were added and the mixture was suction filtered through a short pad of Florisil® (7 cm x 7 cm), using Et₂O as eluant. The eluate was concentrated and the crude reaction product was purified by flash chromatography (1:3 Et₂O - petroleum ether; 180 g of silica gel). Distillation (145-150°C/0.5 Torr) of the oil thus obtained gave 5.02 g (95%) of the alcohol 253, a colourless oil which exhibited ir (neat): 3332, 1472, 1098, 775 cm⁻¹; ¹H nmr (400 MHz, C₆D₆) δ: 0.11 (s, 6H, -SiMe₂), 0.31 (s, 9H, -SnMe₃, ²J Sn-H = 53 Hz), 0.64 (t, 1H, -OH, J = 5.5 Hz), 1.02 (s, 9H, -SiBu₁), 2.64 (br t, 2H, -OCH₂CH₂-, J = 7 Hz, ³J Sn-H = 55 Hz), 3.69 (t, 2H, -OCH₂CH₂-, J = 7 Hz), 3.90 (ddd, 2H, -CH₂OH, J = 5.5 Hz, J = 5.5 Hz, J = 1.5 Hz), 5.66 (dt, 1H, Hₐ, J = 15 Hz, J = 5.5 Hz), 6.45 (ddt, 1H, H₉, J = 15 Hz, J = 11 Hz, J = 1.5 Hz), 6.80 (br d, 1H, Hₐ, J = 11 Hz, ³J Sn-H = 130 Hz). On addition of D₂O the signal at δ 0.64 (-OH) disappeared and the signal at 3.90 (-CH₂OH) collapsed to a br d (J = 5.5 Hz). Exact Mass calcd. for C₁₅H₃₁O₂SiSn (M⁺-Me): 391.1115; found: 391.1114.

Preparation of the diene 252.
To a cold (0°C), stirred solution of the alcohol 253 (5.30 g, 13.05 mmol) in dry 
CH2Cl2 (80 mL) (argon atmosphere) was added, successively, dry 
N,N-diisopropylethylamine (freshly distilled) (3.37 g, 2 equiv.) and chloromethyl methyl 
ether (1.98 g, 1.9 equiv.). After the mixture had been stirred overnight at room temperature, 
saturated aqueous NaHCO3 (30 mL) and Et2O (50 mL) were added. The phases were 
separated and the aqueous phase was extracted with Et2O (3 x 30 mL). The combined 
organic extracts were washed with H2O (30 mL) and brine (30 mL) and were then dried 
(MgSO4) and concentrated. Flash chromatography of the residual oil (7:93 Et2O - petroleum 
ether; 200 g of silica gel), followed by distillation of the oil thus obtained (130-140°C/0.5 
Torr), gave 5.29 g (90%) of the stannyldiene 252, a colourless oil which exhibited ir (neat): 
1472, 1255, 1103, 838, 776 cm⁻¹; ¹H nmr (400 MHz, C6D₆) δ: 0.1 (s, 6H, -SiMe₂), 0.30 
(s, 9H, -SnMe₃, ²J Sn-H = 53 Hz), 1.01 (s, 9H, -SiBu³), 2.62 (br t, 2H, -OCH₂CH₂-, J = 
7 Hz, ³J Sn-H = 55 Hz), 3.21 (s, 3H, -OMe), 3.67 (t, 2H, -OCH₂CH₂-, J = 7 Hz), 4.08 
(dd, 2H, -CH₂O-, J = 5.5 Hz, J = 1.5 Hz), 4.55 (s, 2H, -OCH₂O-), 5.72 (dt, 1H, ḤB, J = 
15 Hz, J = 5.5 Hz), 6.53 (ddt, 1H, ḤC, J = 15 Hz, J = 11 Hz, J = 1.5 Hz), 6.80 (br d, 
1H, ḤA, J = 11 Hz, ³J Sn-H = 130 Hz). In nOe difference experiments, irradiation at 
δ 6.80 (ḤA) caused signal enhancement at δ 5.72 (ḤB) and at δ 2.62 (-OCH₂CH₂-); 
irradiation at δ 2.62 (-OCH₂CH₂-) caused signal enhancement at δ 3.67 (-OCH₂CH₂-) and 
at δ 6.80 (ḤA); irradiation at δ 6.53 (ḤC) caused signal enhancement at δ 4.08 (-CH₂O-); 
irradiation at δ 5.72 (ḤB) caused signal enhancement at δ 6.80 (ḤA) and at δ 4.08 
(-CH₂O-). ¹³C nmr (75.4 MHz, C₆D₆) δ: 8.13, -5.07, 18.55, 26.14, 44.08, 55.88, 
64.00, 67.20, 95.59, 130.15, 133.01, 142.10, 146.92. Exact Mass calcd. for 
C₁₇H₃₅O₃SiSn (M⁺-Me): 435.1378; found: 435.1377.
**General Procedure L. The preparation of the iodo dienes 249.**

To a cold (0°C or -78°C), stirred solution of the stannyldiene in dry CH₂Cl₂ (argon atmosphere), was added, via syringe, a solution of I₂ in CH₂Cl₂ (prepared by dissolving 1.05 equiv. of solid I₂ in a minimum amount of dry CH₂Cl₂). When enough of the solution had been added (as shown by the persistent yellow orange colour of the solution, as well as by glc analysis), 10% aqueous Na₂S₂O₃ (approx. 0.5 mL per mL of reaction solvent) and Et₂O (approx. 0.5 mL per mL of reaction solvent) were added, and the vigorously stirred mixture was allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with Et₂O. The combined organic extracts were washed with 10% aqueous Na₂S₂O₃ and with brine and were then dried (MgSO₄) and concentrated. The crude reaction product was purified by flash chromatography, followed by distillation.

**Preparation of the iodo diene 254**

Following general procedure L, the stannyldiene 167 (2.94 g, 7.82 mmol; in 50 mL of dry CH₂Cl₂), was allowed to react with a solution of I₂ in dry CH₂Cl₂, at -78°C. Flash chromatography of the crude product (3:97 Et₂O - petroleum ether; 70 g of silica gel),
followed by distillation of the oil thus obtained (85-90°C/0.5 Torr), gave 2.43 g (92%) of the iodo diene 254, a pale yellow oil which exhibited ir (neat): 3089, 1632, 1413, 836 cm⁻¹; ¹H nmr (300 MHz) δ: 0.08 (s, 6H, -SiMe²), 0.92 (s, 9H, -SiBu¹), 2.79 (br t, 2H, -OCH₂CH₂-, J = 6.5 Hz), 3.77 (t, 2H, -OCH₂CH₂-, J = 6.5 Hz), 5.30 (dd, 1H, H₈, J = 10 Hz, J = 1.5 Hz), 5.41 (dd, 1H, HB, J = 17 Hz, J = 1.5 Hz), 6.23 (br d, 1H, HA, J = 10 Hz), 6.44 (ddd, 1H, HD, J = 17 Hz, J = 10 Hz, J = 10 Hz). Exact Mass calcd. for C₁₁H₂₀I₂O₅Si (M⁺-Me): 323.0329; found: 323.0333; cims (positive ion detection, NH₃): 339 (M⁺+H). Anal. calcd. for C₁₂H₂₃I₂O₅Si: C 42.60, H 6.85; found: 42.40, H 6.77.

Preparation of the iodo diene 255.

Following general procedure L, the stannyldiene 171 (2.96 g, 7.59 mmol; in 60 mL of dry CH₂Cl₂), was allowed to react with a solution of I₂ in dry CH₂Cl₂, at -78°C. Flash chromatography of the crude product (2:98 Et₂O - petroleum ether; 70 g of silica gel), followed by distillation of the oil thus obtained (95-100°C/0.5 Torr), gave 2.47 g (92%) of the iodo diene 255, a pale yellow oil which exhibited ir (neat): 3086, 1256, 1107, 837 cm⁻¹; ¹H nmr (400 MHz) δ: 0.06 (s, 6H, -SiMe²), 0.88 (s, 9H, -SiBu¹), 1.88 (s, 3H, -Me), 2.75 (br t, 2H, -OCH₂CH₂-, J = 6.5 Hz), 3.74 (t, 2H, -OCH₂CH₂-, J = 6.5 Hz), 5.06 (br s,
1H), 5.07 (br s, 1H), 6.14 (br s, 1H, H\text{A}). \textit{Exact Mass} calcd. for C\textsubscript{11}H\textsubscript{16}OSi (M\textsuperscript{+}-Bu\textsuperscript{t}): 295.0017; found: 295.0018; cims (positive ion detection, NH\textsubscript{3}): 353 (M\textsuperscript{++H}).

\textbf{Preparation of the iodo diene 256.}

\begin{center}
\begin{tikzpicture}
\node[yshift=-0.5cm] (256) {256};
\node[anchor=west, yshift=-0.5cm] at (256.-0.5cm) {\text{H\text{A}}};
\node[anchor=west, yshift=-0.5cm] at (256.-0.25cm) {\text{I}};
\node[anchor=west, yshift=-0.5cm] at (256.-0.1cm) {\text{TBDMOSO}};
\end{tikzpicture}
\end{center}

Following general procedure L, the stannyldiene 177 (1.376 g, 3.29 mmol; in 30 mL of dry CH\textsubscript{2}Cl\textsubscript{2}), was allowed to react with a solution of I\textsubscript{2} in dry CH\textsubscript{2}Cl\textsubscript{2}, at -78\textdegree C. Flash chromatography of the crude product (3:97 Et\textsubscript{2}O - petroleum ether; 40 g of silica gel), followed by distillation of the oil thus obtained (105-110\textdegree C/0.5 Torr), gave 1.102 g (88\%) of the iodo diene 256, a pale yellow oil which exhibited ir (neat): 1472, 1256, 1109, 837, 776 cm\textsuperscript{-1}; \textsuperscript{1}H nmr (300 MHz) \textdelta: 0.05 (s, 6H, SiMe\textsubscript{2}), 0.88 (s, 9H, -SiBu\textsuperscript{t}), 1.02 (d, 6H, -CHMe\textsubscript{2}, \textit{J} = 6 Hz), 1.35 (br septet, 1H, -CHMe\textsubscript{2}, \textit{J} = 6 Hz), 2.74 (br t, 2H, -OCH\textsubscript{2}CH\textsubscript{2}-, \textit{J} = 6 Hz), 3.75 (t, 2H, -OCH\textsubscript{2}CH\textsubscript{2}-, \textit{J} = 6 Hz), 5.01 (br s, 1H), 5.03 (br s, 1H), 6.01 (br s, 1H, H\text{A}). \textit{Exact Mass} calcd. for C\textsubscript{15}H\textsubscript{29}OSi (M\textsuperscript{+}): 380.1034; found: 380.1046.
Preparation of the iodo diene 257.

Following general procedure L, the stannyldiene 252 (2.80 g, 6.2 mmol; in 40 mL of dry CH₂Cl₂), was allowed to react with a solution of I₂ in dry CH₂Cl₂, at -78°C. Flash chromatography of the crude product (8:92 Et₂O - petroleum ether; 70 g of silica gel), followed by distillation of the oil thus obtained (120-130°C/0.5 Torr), gave 2.28 g (92%) of the iodo diene 257, a pale yellow oil which exhibited ir (neat): 1461, 1105, 1043, 837 cm⁻¹; ¹H nmr (400 MHz, C₆D₆) δ: 0.08 (s, 6H, -SiMe₂), 0.98 (s, 9H, -SiBu₁), 2.64 (br t, 2H, -OCH₂CH₂-, J = 7 Hz), 3.19 (s, 3H, -OMe), 3.67 (t, 2H, -OCH₂CH₂-, J = 7 Hz), 3.95 (dd, 2H, -CH₂O-, J = 5 Hz, J = 1.5 Hz), 4.50 (s, 2H, -OCH₂CH₂O-), 5.82 (dt, 1H, HB, J = 16 Hz, J = 5 Hz), 6.08 (br d, 1H, HA, J = 10 Hz), 6.63 (ddt, 1H, HC, J = 16 Hz, J = 10 Hz, J = 1.5 Hz). Exact Mass calcd. for C₁₅H₂₉I₃O₃Si (M⁺): 412.0932; found: 412.0937.

Preparation of the iodo diene 258.

Exact Mass calcd. for C₁₅H₂₉I₃O₃Si (M⁺): 412.0932; found: 412.0937.
Following general procedure L, the stannyldiene 180 (1.80 g, 4.43 mmol; in 30 mL of dry CH₂Cl₂), was allowed to react with a solution of I₂ in dry CH₂Cl₂, at 0°C. Flash chromatography of the crude product (1:4 Et₂O - petroleum ether; 50 g of silica gel), followed by distillation of the oil thus obtained (190-200°C/0.5 Torr), gave 1.39 g (85%) of the iodo diene 258, a pale yellow oil which exhibited ir (neat): 1708, 1260, 1137, 1063; ¹H nmr (400 MHz) δ: 1.50 (s, 9H, -C₆H₄Bu¹), 2.88 (br t, 2H, -OCH₂CH₂-, J = 7 Hz), 3.33 (s, 3H, -OMe), 3.70 (t, 2H, -OCH₂CH₂-, J = 7 Hz), 4.60 (s, 2H, -OCH₂O-), 5.96 (br d, 1H, ḻb, J = 16 Hz), 6.36 (br d, 1H, ḻa, J = 11 Hz), 7.28 (dd, 1H, ḻc, J = 16 Hz, J = 11 Hz). Exact Mass calcd. for C₁₃H₂₁IO₄ (M⁺): 368.0486; found: 368.0483. Anal. calcd. for C₁₃H₂₁IO₄: C 42.41, H 5.75; found: C 42.26, H 5.67.

Preparation of ethyl 3-iodopropanoate (259)

![Chemical structure](image)

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To a stirred solution of NaI (26 g, 8 equiv.) in dry acetone (150 mL) (argon atmosphere) was added ethyl 3-chloropropanoate (3g, 1 equiv.) and the mixture was allowed to reflux overnight. Most of the solvent was removed and Et₂O (50 mL) and H₂O (50 mL) were added to the residue. The phases were separated and the aqueous phase was extracted with Et₂O (3 x 30 mL). The combined organic extracts were washed with H₂O (2 x 20 mL) and then dried (MgSO₄) and concentrated. Flash chromatography (3:7 Et₂O - petroleum ether; 130 g of silica gel), followed by distillation of the oil thus obtained (100-110°C/6.0
Torr), gave 4.38 g (87%) of ethyl 3-iodopropanoate (259), a colourless oil which exhibited
\( \text{ir (neat): } 1736, 1214, 1019 \text{ cm}^{-1}; \ 1^H \text{ nmr (400 MHz) } \delta: \ 1.27 (t, 3H, -OCH}_2\text{CH}_3, J = 8 \text{ Hz}), 1.96 (t, 2H, -CH}_2\text{CO}_2\text{Et, } J = 8 \text{ Hz}), 3.32 (t, 2H, ICH}_2-, J = 8 \text{ Hz}), 4.18 (q, 2H, -OCH}_2\text{CH}_3, J = 8 \text{ Hz}).  \text{Exact Mass calcd. for C}_5\text{H}_9\text{IO}_2 (M^+): } 227.9649; \ \text{found: } 227.9647. \ \text{This reagent decomposes slowly at room temperature and is also light sensitive. It can be stored for several months in a freezer, in the dark. The reagent was always purified immediately before use, by passing it through a short plug of silica gel (in a Pasteur pipette), followed by distillation.}

\text{General Procedure M. The preparation of the diene esters 241}^{129}

\text{A mixture of Zn-Cu couple (2.3-2.9 equiv.) and ethyl 3-iodopropanoate (1.5-1.9
equiv.) in dry benzene (2 mL per mmol of ethyl 3-iodopropanoate) and dry
N,N-dimethylacetamide (0.133 mL per mmol of ethyl 3-iodopropanoate) (argon atmosphere)
was stirred at room temperature for 1 h and at 60°C for 4 h. Pd(PPh}_3)_4 (5 mol%) was added
and stirring was continued for 5 min at 60°C. A solution of the iodo diene (1 equiv.) (freshly
distilled) in dry benzene was added quickly, via syringe (the material remaining in the syringe
was washed in to the reaction mixture with a small amount of dry benzene), and the resulting
mixture was stirred at 60°C for 15 min. The mixture was cooled to room temperature and
Et}_2\text{O (approx. 1 mL per mL of reaction solvent) was added. The mixture was filtered
through a short column of Florisil® (approx. 20 g per g of iodo diene) using Et}_2\text{O as eluant.
The eluate was concentrated and the residual crude oil was purified by flash chromatography,
followed by distillation.}
Preparation of the ester 260.

Following general procedure M, ethyl 3-iodopropanoate (2.1 g, 9.2 mmol, 1.9 equiv.; in 18.5 mL of dry benzene and 1.25 mL of dry N,N-dimethylacetamide) was allowed to react with Zn-Cu couple (921 mg, 2.9 equiv.). To the reagent thus formed was added, successively, Pd(PPh3)4 (280 mg, 5 mol%) and a solution of the iodo diene 254 (1.63 g, 4.82 mmol, 1 equiv.) in dry benzene (4 mL initially, plus 3 mL for washings). Flash chromatography of the crude reaction product (6:94 Et2O - petroleum ether; 70 g of silica gel), followed by distillation of the oil thus obtained (115-125°C/0.5 Torr), gave 1.313 g (87%) of the ester 260, a colourless oil which exhibited ir (neat): 3085, 1737, 1473, 1256, 1098, 837 cm⁻¹; ¹H nmr (400 MHz, C₆D₆) δ: 0.09 (s, 6H, -SiMe₂), 1.02 (s, 9H, -SiBuᵗ), 1.02 (t, 3H, -OCH₂CH₃, J = 8 Hz), 2.24 (br t, 2H, methylene A, J = 7 Hz), 2.34 (m, 2H, methylene B), 2.58 (br t, 2H, methylene C, J = 7 Hz), 3.63 (t, 2H, methylene D, J = 7 Hz), 4.01 (q, 2H, -OCH₂CH₃, J = 8 Hz), 5.03 (dd, 1H, H₆, J = 10 Hz, J = 2 Hz), 5.16 (dd, 1H, H₅, J = 16 Hz, J = 2 Hz), 5.98 (br d, 1H, H₄, J = 10 Hz), 6.65 (ddd, 1H, J = 16 Hz, J = 10 Hz, J = 10 Hz). Exact Mass calcd. for C₁₇H₃₂O₃Si (M⁺): 312.2121; found: 312.2115. Anal. calcd. for C₁₇H₃₂O₃Si: C 65.33, H 10.32; found: C 65.50, H 10.50.
Preparation of the ester 261.

Following general procedure M, ethyl 3-iodopropanoate (1.65 g, 7.24 mmol, 1.5 equiv.; in 14.5 mL of dry benzene and 1 mL of dry N,N-dimethylacetamide) was allowed to react with Zn-Cu couple (720 mg, 2.3 equiv.). To the reagent thus formed was added, successively, Pd(PPh₃)₄ (280 mg, 5 mol%) and a solution of the iodo diene 255 (1.70 g, 4.83 mmol, 1 equiv.) in dry benzene (4 mL initially, plus 3 mL for washings). Flash chromatography of the crude reaction product (8:92 Et₂O - petroleum ether, 70 g of silica gel), followed by distillation of the oil thus obtained (125-135°C/0.5 Torr), gave 1.22 g (77%) of the ester 261, a colourless oil which exhibited IR (neat): 3083, 1736, 1473, 1095, 838 cm⁻¹; ¹H nmr (400 MHz, C₆D₆) δ: 0.09 (s, 6H, -SiMe₂), 0.99 (t, 3H, -OCH₂CH₃, J = 7 Hz), 1.00 (s, 9H, -SiBu¹), 1.81 (s, 3H, -Me), 2.24 (br t, 2H, methylene A, J = 6.5 Hz), 2.41 (m, 2H, methylene B), 2.75 (br t, 2H, methylene C, J = 8 Hz), 3.66 (t, 2H, methylene D, J = 6.5 Hz), 3.99 (q, 2H, -OCH₂CH₃, J = 7 Hz), 4.95 (br s, 1H, H₂G), 4.97 (br s, 1H, H₂F), 5.80 (br s, 1H, H₂F). In nOe difference experiments, irradiation at δ 5.80 (H₂F) caused signal enhancement at δ 2.24 (methylene A) and at δ 1.81 (vinyl Me); irradiation at δ 2.24 (methylene A) caused signal enhancement at δ 5.80 (H₂F) and at δ 3.66 (methylene D); irradiation at δ 1.81 (vinyl Me) caused signal enhancement at δ 5.80 (H₂F) and at δ 4.97 (H₂F). Exact Mass calcd. for C₁₈H₃₄O₃Si (M⁺): 326.2277; found: 326.2277.
Preparation of the ester 262.

Following general procedure M, ethyl 3-iodopropanoate (1.04 g, 4.56 mmol, 1.5 equiv.; in 9 mL of dry benzene and 0.6 mL of dry N,N-dimethylacetamide) was allowed to react with Zn-Cu couple (457 mg, 2.3 equiv.). To the reagent thus formed was added, successively, Pd(PPh3)4 (176 mg, 5 mol%) and a solution of the iodo diene 256 (1.16 g 3.05 mmol, 1 equiv.) in dry benzene (3 mL initially, plus 2 mL for washings). Flash chromatography of the crude reaction product (6:94 Et2O - petroleum ether; 60 g of silica gel), followed by distillation of the oil thus obtained (140-150°C/0.5 Torr), gave 800 mg (74%) of the ester 262, a colourless oil which exhibited ir (neat): 3088, 1737, 1099, 837 cm$^{-1}$; $^1$H nmr (400 MHz, C$_6$D$_6$) δ: 0.10 (s, 6H, -SiMe$_2$), 1.00 (t, 3H, -OCH$_2$CH$_3$, $J$ = 7 Hz), 1.01 (s, 9H, -SiBu$_3$), 1.04 (d, 6H, -CHMe$_2$, $J$ = 7 Hz), 2.26-2.30 (m, 3H, -CHMe$_2$ and methylene A), 2.44 (m, 2H, methylene B), 2.77 (br t, 2H, methylene C, $J$ = 8 Hz), 3.70 (t, 2H, methylene D, $J$ = 6.5 Hz), 3.99 (q, 2H, -OCH$_2$CH$_3$, $J$ = 7 Hz), 4.91 (br s, 1H), 5.02 (br s, 1H), 5.84 (br s, 1H, H$_E$). Exact Mass calcd. for C$_{20}$H$_{38}$O$_3$Si (M$^+$): 354.2590; found: 354.2597. Anal. calcd. for C$_{20}$H$_{38}$O$_3$Si: C 67.74, H 10.80; found: C 67.99, H 10.79.
Preparation of the ester 263.

Following general procedure M, ethyl 3-iodopropanoate (1.452 g, 6.37 mmol, 1.9 equiv.; in 13 mL of dry benzene and 0.9 mL of dry N,N-dimethylacetamide) was allowed to react with Zn-Cu couple (640 mg, 2.9 equiv.). To the reagent thus formed was added, successively, Pd(PPh3)4 (200 mg, 5 mol%) and a solution of the iodo diene 257 (1.40 g, 3.40 mmol, 1 equiv.) in dry benzene (3 mL initially, plus 3 mL for washings). Flash chromatography of the crude reaction product (1:4 Et2O - petroleum ether; 60 g of silica gel), followed by distillation of the oil thus obtained (140-150°C/0.5 Torr), gave 860 mg (65%) of the ester 263, a colourless oil which exhibited ir (neat): 1737, 1150, 1103, 838 cm⁻¹; ¹H nmr (400 MHz, C₆D₆) δ: 0.08 (s, 6H, -SiMe₂), 1.01 (t, 3H, -OCH₂CH₃, J = 8 Hz), 1.10 (s, 9H, -SiBu¹), 2.25 (br t, 2H, methylene A, J = 7 Hz), 2.35 (br t, 2H, methylene B, J = 8 Hz), 2.60 (br t, 2H, methylene C, J = 8 Hz), 3.23 (s, 3H, -OMe), 3.65 (t, 2H, methylene D, J = 7 Hz), 4.00 (q, 2H, -OCH₂CH₃, J = 8 Hz), 4.09 (br d, 2H, -CH₂O-, J = 6 Hz), 4.57 (s, 2H, -OCH₂O-), 5.75 (dt, 1H, H₅, J = 16 Hz, J = 6 Hz), 5.98 (br d, 1H, H₆, J = 10 Hz), 6.67 (ddt, 1H, H₇, J = 16 Hz, J = 10 Hz, J = 1.5 Hz). Exact Mass calcd. for C₁₉H₃₅O₅Si (M⁺-Me): 371.2254; found: 371.2248; cims (positive ion detection, NH₃): 387 (M⁺+H).
Preparation of the ester 264.

Following general procedure M, ethyl 3-iodopropanoate (631 mg, 2.76 mmol, 1.75 equiv.; in 5.5 mL of dry benzene and 0.4 mL of dry \(N,N\)-dimethylacetamide) was allowed to react with Zn-Cu couple (277 mg, 2.7 equiv.). To the reagent thus formed was added, successively, Pd(PPh\(_\text{3}\))\(_\text{4}\) (91 mg, 5 mol\%) and a solution of the iodo diene 258 (580 mg, 1.58 mmol, 1 equiv.) in dry benzene (2 mL initially, plus 1.5 mL for washings). Flash chromatography of the crude reaction product (3:7 Et\(_2\)O - petroleum ether; 40 g of silica gel), followed by distillation of the oil thus obtained (190-200\(^\circ\)C/0.5 Torr), gave 470 mg (87\%) of the ester 264, a colourless oil which exhibited IR (neat): 1736, 1708, 1636, 1110 cm\(^{-1}\); \(^1\)H nmr (400 MHz, C\(_6\)D\(_6\)) \(\delta\): 1.02 (t, 3H, \(-\text{OCH}_2\text{CH}_3\), \(J = 7\) Hz), 1.49 (s, 9H, \(-\text{CC}^\text{Bu}\)), 2.18 (br t, 2H, methylene A, \(J = 7\) Hz), 2.21 (br t, 2H, methylene B, \(J = 7\) Hz), 2.50 (br t, 2H, methylene C, \(J = 7\) Hz), 3.14 (s, 3H, \(-\text{OMe}\)), 3.42 (t, 2H, methylene D, \(J = 7\) Hz), 3.96 (q, 2H, \(-\text{OCH}_2\text{CH}_3\), \(J = 7\) Hz), 4.43 (s, 2H, \(-\text{OCH}_2\text{O}\)), 5.93 (br d, 1H, \(\text{H}_\text{E}\), \(J = 11\) Hz), 5.95 (d, 1H, \(\text{H}_\text{F}\), \(J = 16\) Hz), 7.89 (dd, 1H, \(\text{H}_\text{G}\), \(J = 16\) Hz, \(J = 11\) Hz). Exact Mass calcd. for C\(_{18}\)H\(_{30}\)O\(_6\) (M\(^+\)): 342.2042; found: 342.2040. Anal. calcd. for C\(_{18}\)H\(_{30}\)O\(_6\): C 63.14, H 8.83; found: C 63.34, H 8.80.
General Procedure N. The preparation of the diene acids 242

A mixture of saturated aqueous K₂CO₃ and MeOH (1:1 v:v) was made homogeneous by dropwise addition of H₂O. Addition of this solution to the ester (approx. 8 mL per mmol of the ester) at room temperature, gave a heterogeneous mixture, which was made homogeneous by the addition of MeOH (and H₂O, to re-dissolve any K₂CO₃ which may precipitate). The solution thus obtained was stirred at room temperature until the reaction was complete (by tlc analysis). Et₂O and H₂O were added, until a two-phase mixture was obtained. The phases were separated and the ethereal layer was extracted with H₂O. The combined aqueous extracts were washed with Et₂O and were then cooled (using a -20°C cooling bath). Aqueous HCl (10%) was added, dropwise, to the cold, stirred solution, until it was neutral. The aqueous solution was then extracted exhaustively with Et₂O. The combined organic extracts were washed with H₂O and then dried and concentrated. The residual oil thus obtained contained some MeOH, which was removed at reduced pressure (0.5 Torr, room temperature), to give the essentially pure carboxylic acid.

Preparation of the acid 268.

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Following general procedure N, a mixture of aqueous K$_2$CO$_3$ and MeOH (30 mL) was added to the ester 260 (1.313 g, 4.21 mmol) and the resulting heterogeneous mixture was made homogeneous by the addition of MeOH and H$_2$O. The mixture was stirred overnight at room temperature to give, after workup, 1.015 g (85%) of the carboxylic acid 268, a colourless oil which exhibited ir (neat): 2400-3700, 1713, 1099, 837, 777 cm$^{-1}$; $^1$H nmr (400 MHz, C$_6$D$_6$) $\delta$: 0.07 (s, 6H, -SiMe$_2$), 0.99 (s, 9H, -SiBu$_3$), 2.17 (br t, 2H, methylene A, $J$ = 6.5 Hz), 2.28 (m, 2H, methylene B), 2.48 (br t, 2H, methylene C, $J$ = 8 Hz), 3.59 (t, 2H, methylene D, $J$ = 6.5 Hz), 5.02 (dd, 1H, $H_G$, $J$ = 10 Hz, $J$ = 2 Hz), 5.14 (dd, 1H, $H_F$, $J$ = 17 Hz, $J$ = 2 Hz), 5.94 (br d, 1H, $H_E$, $J$ = 11 Hz), 6.58 (ddd, 1H, $H_H$, $J$ = 17 Hz, $J$ = 11 Hz, $J$ = 10 Hz). Exact Mass calcd. for C$_{15}$H$_{28}$O$_3$Si (M$^+$): 284.1808; found: 284.1800. Anal. calcd. for C$_{15}$H$_{28}$O$_3$Si: C 63.33, H 9.92; found: C 63.28, H 9.87.

Preparation of the acid 269

Following general procedure N, a mixture of aqueous K$_2$CO$_3$ and MeOH (5 mL) was added to the ester 261 (200 mg, 0.61 mmol) and the resulting heterogeneous mixture was made homogeneous by the addition of MeOH and H$_2$O. The mixture was stirred
overnight at room temperature to give, after workup, 150 mg (82%) of the carboxylic acid 269, a colourless oil which exhibited ir (neat): 2400-3400, 1713, 1099, 837 cm\(^{-1}\); \(^1\)H nmr (400 MHz, C\(_6\)D\(_6\)) \(\delta\): 0.08 (s, 6H, -SiMe\(_2\)), 1.00 (s, 9H, -SiBu\(_t\)), 1.78 (br s, 3H, -Me), 2.18 (br t, 2H, methylene A, \(J = 6.5\) Hz), 2.35 (br t, 2H, methylene B, \(J = 8\) Hz), 2.67 (br t, 2H, methylene C, \(J = 8\) Hz), 3.63 (t, 2H, methylene D, \(J = 6.5\) Hz), 4.90 (br s, 1H), 4.96 (br s, 1H), 5.78 (br s, 1H, H\(_E\)). Exact Mass calcd for C\(_{12}\)H\(_{21}\)O\(_3\)Si (M\(^{+}\)-Bu\(_t\)): 241.1260; found: 241.1258; cims (positive ion detection, CH\(_4\)): 299 (M\(^{+}\)+H). Anal. calcd. for C\(_{16}\)H\(_{30}\)O\(_3\)Si: C 64.38, H 10.13; found: C 64.50, H 10.18.

Preparation of the acid 270

Following general procedure N, a mixture of aqueous K\(_2\)CO\(_3\) and MeOH (10 mL) was added to the ester 262 (433 mg, 1.22 mmol) and the resulting heterogeneous mixture was made homogeneous by the addition of MeOH and H\(_2\)O. The mixture was stirred overnight at room temperature to give, after workup, 318 mg (80%) of the carboxylic acid 270, a colourless oil which exhibited ir (neat): 2400-3600, 1713, 1463, 1288, 899, 777 cm\(^{-1}\); \(^1\)H nmr (400 MHz, C\(_6\)D\(_6\)) \(\delta\): 0.10 (s, 6H, -SiMe\(_2\)), 1.02 (s, 9H, -SiBu\(_t\)), 1.04 (d, 6H, -CHMe\(_2\), \(J = 7\) Hz), 2.20 -2.35 (m, 3H, -CHMe\(_2\) and methylene A), 2.38 (m, 2H,
methylene B), 2.70 (br t, 2H, methylene C, J = 8 Hz), 3.68 (t, 2H, methylene D, J = 6.5 Hz), 4.85 (br s, 1H), 5.01 (br s, 1H), 5.82 (br s, 1H, HE). Exact Mass calcd. for C_{18}H_{34}O_{3}S_{1} (M^{+}): 326.2277; found: 326.2272. Anal. calcd. for C_{18}H_{34}O_{3}Si: C 66.21, H 10.50; found: C 66.20, H 10.61.

Preparation of the acid 271.

Following general procedure N, a mixture of aqueous K_{2}CO_{3} and MeOH (5 mL) was added to the ester 263 (250 mg, 0.65 mmol) and the resulting heterogeneous mixture was made homogeneous by the addition of MeOH and H_{2}O. The mixture was stirred overnight at room temperature to give, after workup, 196 mg (84%) of the carboxylic acid 271, a colourless oil which exhibited ir (neat): 2400-3400, 1708, 1256, 1150, 778 cm^{-1}; \textsuperscript{1}H nmr (400 MHz, C_{6}D_{6}) δ: 0.08 (s, 6H, -SiMe_{3}), 1.00 (s, 9H, -SiBu_{3}), 2.19 (br t, 2H, methylene A, J = 6.5 Hz), 2.26 (br t, 2H, methylene B, J = 8 Hz), 2.50 (br t, 2H, methylene C, J = 8 Hz), 3.21 (s, 3H, -OMe), 3.61 (t, 2H, methylene D, J = 6.5 Hz), 4.07 (dd, 2H, -CH_{2}O-, J = 6 Hz, J = 1.5 Hz), 4.58 (s, 2H, -OCH_{2}O-), 5.71 (dt, 1H, HF, J = 16 Hz, J = 6 Hz), 5.96 (br d, 1H, HE, J = 11 Hz), 6.64 (ddd, HG, J = 16 Hz, J = 11 Hz, J = 1.5 Hz). Exact Mass calcd. for C_{16}H_{29}O_{3}Si (M^{+}-C_{2}H_{5}O_{2}): 297.1886; found:
297.1891; cims (positive ion detection, NH3): 395 (M+H). Anal. calcd. for C18H34O5Si: C 60.30, H 9.56; found: C 60.18, H 9.70.

Preparation of the acid 272

Following general procedure N, a mixture of aqueous K$_2$CO$_3$ and MeOH (5 mL) was added to the ester 264 (210 mg, 0.61 mmol) and the resulting heterogeneous mixture was made homogeneous by the addition of MeOH and H$_2$O. The mixture was stirred overnight at room temperature to give, after workup, 158 mg (82%) of the carboxylic acid 272, a colourless oil which exhibited ir (neat): 2500-3600, 1708, 1636, 1146, 1038 cm$^{-1}$; $^1$H nmr (400 MHz, C$_6$D$_6$) $\delta$: 1.49 (s, 9H, -CO$_2$Bu$^t$), 2.15 (br t, 2H, methylene A, $J = 6$ Hz), 2.23 (br t, 2H, methylene B, $J = 8$ Hz), 2.51 (br t, 2H, methylene C, $J = 8$ Hz), 3.18 (s, 3H, -OMe), 3.43 (t, 2H, methylene D, $J = 6$ Hz), 4.44 (s, 2H, -OCH$_2$O-), 5.94 (br d, 1H, $^6$H, $J = 11$ Hz), 5.97 (br d, 1H, $^6$F, $J = 16$ Hz), 7.91 (dd, 1H, $^6$G, $J = 16$ Hz, $J = 11$ Hz). Exact Mass calcd. for C$_{11}$H$_{14}$O$_5$ (M$^+$-C$_5$H$_{12}$O): 226.0841; found: 226.0846; cims (positive ion detection, CH$_4$): 315 (M$^+$+H).
**Preparation of an ethereal solution of diazomethane**

This preparation was carried out in a specially designed apparatus (available from Aldrich Chemical Co.), that has no ground glass joints. The reaction was performed in a fume hood and the apparatus was set up behind a blast shield. To a stirred mixture of Et₂O (5 mL), diethylene glycol monomethyl ether (17 mL) and a solution of KOH (3 g) in H₂O (5 mL) at 70°C (using a water bath as heat source) was added slowly (over approx. 30 min), via dropping funnel, a solution of Diazald® (10.7 g) in Et₂O (65 mL). During this period, a yellow ethereal solution of diazomethane distilled into a cooled (0°C) round-bottom flask. Diethyl ether (approx. 20 mL) was added to the stillpot mixture (via dropping funnel), until no more diazomethane was generated (at this point the distillate was colourless). The yellow distillate was dried (Na₂SO₄ - this is the only drying agent that should be used) and was used immediately. The amount of diazomethane generated by this procedure was approx. 1.5 g (i.e. approx. 33 mmol in approx. 85 mL of Et₂O).

**General Procedure O. The preparation of the diene diazoketones**

To a stirred solution of the carboxylic acid (1 equiv.) in dry, freshly distilled hexane (argon atmosphere, room temperature) was added oxalyl chloride (3 equiv.). After the mixture had been refluxed for 2 h, it was allowed to cool to room temperature and the solvent was removed. Any remaining volatile material was removed under reduced pressure (0.5 Torr, room temperature), and then dry Et₂O was added to the residue (argon atmosphere). The solution of the acid chloride thus obtained was used immediately. To a
cold (0°C), stirred solution of diazomethane (excess) in Et₂O (argon atmosphere) was added a small amount of drying agent (Na₂SO₄). To this solution was added slowly, via cannula, the solution of the acid chloride in Et₂O, resulting in rapid effervescence. Stirring was continued at 0°C for 30 min and at room temperature for 45 min. Excess diazomethane was removed from the mixture by bubbling argon through the solution for approx. 30 min (using a flame polished pasteur pipette as gas inlet). The solution was dried (MgSO₄) and concentrated, to give the crude diazoketone, a viscous bright yellow oil. The diazoketone was purified by rapid chromatography (silica gel). The diazoketones were stable in a freezer (in the dark) for several weeks, although they were generally used immediately.

Preparation of the diazoketone 273. The conversion of 273 into the ketone 278.

Following general procedure O, the carboxylic acid 268 (700 mg, 1 equiv., 2.46 mmol) in dry hexane (14 mL) was allowed to react with oxalyl chloride (0.94 g, 3 equiv.). A solution of the resulting crude acid chloride in dry Et₂O (approx. 15 mL, including washings) was added to a solution of diazomethane in Et₂O (approx. 50 mL,
approx. 8 equiv.). The crude product thus obtained was purified by rapid chromatography (35:65 Et₂O - petroleum ether; 35 g of silica gel), to give 611 mg (81%) of essentially pure (tlc analysis) diazoketone 273. This compound was used immediately.

A solution of the diazoketone 273 (611 mg, 1.98 mmol, 1 equiv.) in dry benzene (15 mL) was added slowly (over approx. 30 min) via syringe pump to a refluxing suspension of CuSO₄ (1 equiv., 317 mg) and Cu(acac)₂ (32 mg) in dry benzene (15 mL) (argon atmosphere). After the mixture had been refluxed for 15 min, it was allowed to cool to room temperature and then most of the benzene was removed. The residue was passed through a short column of Florisil® (15 g), using Et₂O as eluant. The combined eluate was concentrated and the crude oil thus obtained was purified by flash chromatography (3:7 Et₂O - petroleum ether; 40 g of silica gel). Distillation of the oil thus obtained (115-120°C/0.5 Torr) gave 481 mg (87%; 70% from the acid 268) of the ketone 278, a colourless oil which exhibited ir (neat): 3084, 3045, 1719, 1099, 776 cm⁻¹; ¹H nmr (400 MHz, C₆D₆) δ: 0.06 (s, 6H, -SiMe₂), 0.99 (s, 9H, -SiBu¹), 1.22 (dt, 1H, HA or HA', J = 14 Hz, J = 6 Hz), 1.59 (dt, 1H, HA or HA', J = 14 Hz, J = 6 Hz), 1.64-1.84 (overlapping m, 5H), 2.07 (m, 1H), 3.48 (t, 2H, -OCH₂CH₂-, J = 6 Hz), 5.08 (ddd, 1H, HB, J = 10 Hz, J = 2 Hz, J = 1 Hz), 5.24 (ddd, 1H, HC, J = 16 Hz, J = 2 Hz, J = 1 Hz), 5.51 (ddd, 1H, HD, J = 16 Hz, J = 10 Hz, J = 6 Hz). Exact Mass calcd. for C₁₈H₂₈O₂Si (M⁺): 280.1858; found: 280.1859. Anal. calcd. for C₁₆H₂₈O₂Si: C 68.53, H 10.07; found: C 68.80, H 9.93.
Preparation of the diazoketone 276. The conversion of 276 into the ketone 279.

Following general procedure O, the carboxylic acid 271 (194 mg, 1 equiv., 0.54 mmol) in dry hexane (5 mL) was allowed to react with oxalyl chloride (207 mg, 3 equiv.). A solution of the resulting crude acid chloride in dry Et2O (approx. 5 mL, including washings) was added to a solution of diazomethane in Et2O (approx. 12 mL, approx. 8 equiv.). The crude product thus obtained was purified by rapid chromatography (1:1 Et2O - petroleum ether; 30 g of silica gel), to give 179 mg (86%) of essentially pure (tlc analysis) diazoketone 276. This compound was used immediately.

A solution of the diazoketone 276 (179 mg, 0.47 mmol, 1 equiv.) in dry benzene (4 mL) was added slowly (over approx. 30 min) via syringe pump, to a refluxing suspension of CuSO4 (1 equiv., 75 mg) and Cu(acac)2 (8 mg) in dry benzene (4 mL) (argon atmosphere). After the mixture had been refluxed for 15 min it was allowed to cool to room temperature, and most of the benzene was removed. The mixture was passed through a plug of Florisil® (5 g), using Et2O as eluant. The combined eluate was concentrated and the crude oil thus obtained was purified by flash chromatography (35:65 Et2O - petroleum ether;
30 g of silica gel. Distillation of the oil thus obtained (160-170°C/0.5 Torr) gave 150 mg (90%; 78% from the acid 271) of the ketone 279, a colourless oil which exhibited ir (neat): 1719, 1472, 1256, 1151, 837, 778 cm\(^{-1}\); \(^1\)H nmr (400 MHz, C\(_6\)D\(_6\)) \(\delta\): 0.07 (s, 6H, -SiMe\(_2\)), 1.00 (s, 9H, -SiBu\(_t\)), 1.27 (dt, 1H, HA or HA', \(J = 14\) Hz, \(J = 6\) Hz), 1.62 (dt, 1H, HA or HA', \(J = 14\) Hz, \(J = 6\) Hz), 1.66-1.93 (m, 5H), 2.09 (m, 1H), 3.21 (s, 3H, -OMe), 3.51 (t, 2H, -OCH\(_2\)CH\(_2\), \(J = 6\) Hz), 3.96 (br d, 2H, -CH\(_2\)O-, \(J = 6\) Hz), 4.52 (s, 2H, -OCH\(_2\)O-), 5.58 (br dd, 1H, HB, \(J = 16\) Hz, \(J = 6\) Hz), 5.84 (dtd, 1H, HC, \(J = 16\) Hz, \(J = 6\) Hz, \(J = 1\) Hz). Exact Mass calcd. for C\(_{19}\)H\(_{34}\)C\(_4\)Si (M\(^+\)): 354.2227; found: 354.2231. Anal. calcd. for C\(_{19}\)H\(_{34}\)C\(_4\)Si: C 64.36, H 9.67; found: C 64.42, H 9.76.

Preparation of the diazoketone 277. The conversion of 277 into the ketone 280.

Following general procedure O, the carboxylic acid 272 (257 mg, 1 equiv., 0.82 mmol) in dry hexane (8 mL) was allowed to react with oxalyl chloride (312 mg, 3 equiv.). A solution of the resulting crude acid chloride in dry Et\(_2\)O (approx. 8 mL,
including washings) was added to a solution of diazomethane in Et₂O (approx. 15 mL, approx. 8 equiv.). The crude product thus obtained was purified by rapid chromatography (3:1 Et₂O - petroleum ether; 30 g of silica gel), to give 207 mg (75%) of essentially pure (tlc analysis) diazoketone 277. This compound was used immediately.

To a cold (0°C), stirred solution of the diazoketone 277 (100 mg, 0.30 mmol) in dry CH₂Cl₂ (8 mL) (argon atmosphere) was added Rh₂(OAc)₄ (4 mg, 3 mol%). After the mixture had been stirred at 0°C for 5 min and at room temperature for 30 min, the solvent was removed and the residual oil was purified by flash chromatography (3:7 Et₂O - petroleum ether; 25 g of silica gel). Distillation of the oil thus obtained (190-200°C/0.5 Torr), gave 69 mg (75%, 56% from the acid 272) of the ketone 280, a colourless oil which exhibited ir (neat): 1718, 1640, 1148, 1109 cm⁻¹; ¹H nmr (400 MHz, C₆D₆) δ: 1.20 (m, 1H), 1.43 (s, 9H, -CO₂Bu¹), 1.45-1.57 (m, 2H), 1.58-1.70 (m, 2H), 1.78-1.88 (m, 2H), 1.97 (m, 1H), 3.15 (s, 3H, -OMe), 3.28 (t, 2H, -OCH₂CH₂-, J = 6 Hz), 4.38 (s, 2H, -OCH₂O-, 6.08 (d, 1H, HA, J = 15 Hz), 6.87 (dd, 1H, HB, J = 15 Hz, J = 8 Hz). Anal. calcd. for C₁₇H₂₆O₅: C 65.78, H 8.44; found: C 65.58, H 8.60.

**Preparation of the diazoketone 274.** The conversion of 274 into the ketones 281 and 282.

![Diagram of 274](image)

![Diagram of 281](image)

![Diagram of 282](image)
Following general procedure O, the carboxylic acid 269 (198 mg, 1 equiv., 0.66 mmol) in dry hexane (4 mL) was allowed to react with oxalyl chloride (253 mg, 3 equiv.). A solution of the resulting crude acid chloride in dry Et₂O (approx. 5 mL, including washings) was added to a solution of diazomethane in Et₂O (approx. 15 mL, approx. 8 equiv.). The crude product thus obtained was purified by rapid chromatography (35:65 Et₂O - petroleum ether; 30 g of silica gel), to give 160 mg (75%) of essentially pure (tlc analysis) diazoketone 274. This compound was used immediately.

(a) A solution of the diazoketone 274 (160 mg, 0.50 mmol, 1 equiv.) in dry benzene (4 mL) was added slowly (over approx. 30 min) via syringe pump, to a refluxing suspension of CuSO₄ (1 equiv., 80 mg) and Cu(acac)₂ (8 mg) in dry benzene (4 mL) (argon atmosphere). After the mixture had been refluxed for 15 min, it was allowed to cool to room temperature, and then most of the benzene was removed. The mixture was passed through a plug of Florisil® (5 g), using Et₂O as eluant. The combined eluate was concentrated and the residual oil was purified by flash chromatography (3:7 Et₂O - petroleum ether; 30 g of silica gel). Distillation of the oil thus obtained (130-135°C/0.5 Torr) gave 93 mg (64% ; 48% from the acid 269) of a mixture (1:1 by glc analysis) of the ketones 281 and 282, which was inseparable by column chromatography.

(b) To a cold (-78°C), stirred solution of the diazoketone 274 (62 mg, 0.19 mmol) in dry CH₂Cl₂ (3 mL) (argon atmosphere) was added Rh₂(OAc)₄ (4 mg, 5 mol%). After the mixture had been stirred at -78°C for 10 min it was allowed to warm to room temperature, over 4 h. The solvent was removed and the residual oil was purified by flash chromatography (3:7 Et₂O - petroleum ether; 25 g of silica gel). Distillation of the oil thus obtained gave 44 mg (78%, 59 % from the acid 269) of a mixture of the ketones 281 and 282 (4:1 respectively, by glc analysis).
Characterization of the ketone 281

To a cold (-78°C), stirred solution of the mixture of ketones 281 and 282 (45 mg, 0.15 mmol, 4:1 by glc analysis) in dry THF (2 mL) (argon atmosphere) was added a solution of diisobutylaluminium hydride (2 equiv.) in hexane. After the mixture had been stirred for 1 h at -78°C and for 10 min at 0°C, saturated aqueous NH₄Cl (approx. 0.2 mL) was added and the vigorously stirred mixture was exposed to air and was allowed to warm to room temperature. To the resulting suspension was added diethyl ether (approx. 1 mL) and drying agent (MgSO₄) and the mixture was suction filtered through a short pad (3 g) of Florisil®, using Et₂O as eluant. The combined eluate was concentrated and the resulting oil was purified by flash chromatography (3:7 Et₂O - petroleum ether; 25 g of silica gel), to give 32 mg (66%) of the alcohol 283 (traces of solvent were removed under reduced pressure; 0.5 Torr/25°C), and 9 mg (20%) of the alcohols 284 (traces of solvent were removed under reduced pressure; 0.5 Torr/25°C). The alcohol 283 was a colourless oil which exhibited ir (neat): 3389, 1255, 1064, 837 cm⁻¹; ¹H nmr (400 MHz, C₆D₆), 0.11 (s, 6H, -SiMe₂), 1.04 (s, 9H, -SiBu³), 1.21 (m, 1H), 1.30-1.48 (m, 3H), 1.59-1.79 (m, 2H), 1.80-1.88 (m, 1H), 2.01 (m, 1H), 2.08 (br s, 3H, -Me), 3.70 (m, 2H, -OCH₂CH₂-), 4.48 (m, 1H, -CHOH), 4.98 (br s, 1H), 5.24 (br s, 1H). Exact mass calcd. for C₁₇H₃₀O₂Si (M⁺): 296.2171; found: 296.2165.
To a stirred solution of the alcohol 283 (30 mg, 0.1 mmol) in dry CH₂Cl₂ (2 mL) (argon atmosphere, room temperature) was added N-methylmorpholine N-oxide (30 mg, 2.5 equiv.) and activated 4Å molecular sieves. The resulting suspension was stirred for 10 min at room temperature and then TPAP⁺ (4 mg, 5 mol%) was added. After the mixture had been stirred for 45 min at room temperature it was filtered through a short column of Florisil® (approx. 5 g) using Et₂O as eluant. The combined eluate was concentrated and the resulting oil was purified by flash chromatography (1:4 Et₂O - petroleum ether; 20 g of silica gel). Distillation (130-135°C/0.5 Torr) of the oil thus obtained gave 25 mg (84%) of the ketone 281, a colourless oil which exhibited ir (neat): 1723, 1100, 837, 777 cm⁻¹; ¹H nmr (400 MHz, C₆D₆) δ: 0.06 (s, 6H, -SiMe₂), 1.00 (s, 9H, -SiBu¹), 1.18 (dt, 1H, HA or HA', J = 13 Hz, J = 6 Hz), 1.60-1.72 (m, 6H), 1.75-1.93 (m, 3H), 2.23 (m, 1H), 3.52 (t, 2H, -OCH₂CH₂-, J = 6 Hz), 4.85 (br s, 1H), 4.98 (br s, 1H). Anal. calcd. for C₁₇H₃₀O₂Si: C 69.34, H 10.28; found: C 69.72, H 10.41.

Preparation of the diazoketone 275. The conversion of 275 into the ketones 285 and 286
Following general procedure O, the carboxylic acid 270 (314 mg, 1 equiv., 0.93 mmol) in dry hexane (7 mL) was allowed to react with oxalyl chloride (356 mg, 3 equiv.). A solution of the resulting crude acid chloride in dry Et2O (approx. 8 mL, including washings) was added to a solution of diazomethane in Et2O (approx. 20 mL, approx. 8 equiv.). The crude product thus obtained was purified by rapid chromatography (35:65 Et2O - petroleum ether; 30 g of silica gel), to give 264 mg (78%) of essentially pure (tlc analysis) diazoketone 275. This compound was used immediately.

To a cold (-78°C), stirred solution of the diazoketone 275 (173 mg, 0.48 mmol) in dry CH2Cl2 (10 mL) (argon atmosphere) was added Rh2(OAc)4 (6 mg, 3 mol%). After the mixture had been stirred at -78°C for 10 min it was allowed to warm to room temperature, over 4 h. The solvent was removed and the residual oil was purified by flash chromatography (3:7 Et2O - petroleum ether; 35 g of silica gel). Distillation of the oil thus obtained (140-150°C/0.5 Torr), gave 100 mg (63%, 49% from the acid 270) of a mixture of the ketones 285 and 286 (4:1 respectively, by glc analysis).

Characterization of the ketone 285

[Diagram of 285 and 287]
To a cold (-78°C), stirred solution of the mixture of ketones 285 and 286 (60 mg, 0.19 mmol, 4:1 by glc analysis) in dry THF (3 mL) (argon atmosphere) was added a solution of diisobutylaluminium hydride (2 equiv.) in hexane. After the mixture had been stirred for 1 h at -78°C and for 10 min at 0°C, saturated aqueous NH₄Cl (approx. 0.2 mL) was added and the vigorously stirred mixture was exposed to air and was allowed to warm to room temperature. Diethyl ether (approx. 1 mL) and drying agent (MgSO₄) were added to the suspension thus formed, and the mixture was suction filtered through a short pad (3 g) of Florisil®, using Et₂O as eluant. The combined eluate was concentrated and the resulting oil was purified by flash chromatography (3:7 Et₂O - petroleum ether; 30 g of silica gel), to give 40 mg (66%) of the alcohol 287 (traces of solvent were removed at reduced pressure; 0.5 Torr/25°C), and 10 mg (17%) of the alcohols 288 (traces of solvent were removed at reduced pressure; 0.5 Torr/25°C). The alcohol 287 was a colourless oil which exhibited ir (neat): 3406, 1254, 1067, 836 cm⁻¹; ¹H nmr (400 MHz, C₆D₆), 0.11 (s, 6H, -SiMe₂), 1.03 (s, 9H, -SiBu³), 1.19 (d, 3H, -CHMe₂, J = 6 Hz), 1.22 (d, 3H, -CHMe₂, J = 6 Hz), 1.21-1.35 (m, 2H), 1.44 (dt, 1H, HA or HA', J = 13 Hz, J = 6 Hz), 1.56 (br d, 1H, J = 8 Hz), 1.60-1.73 (m, 2H), 1.83 (dt, 1H, HA or HA', J = 13 Hz, J = 6 Hz), 1.96 (m, 1H), 2.88 (br septet, 1H, -CHMe₂, J = 6 Hz), 3.70 (t, 2H, -OCH₂CH₂-, J = 6 Hz), 4.46 (m, 1H, -CHOH), 5.02 (br s, 1H), 5.27 (br s, 1H). Exact Mass calcd. for C₁₉H₃₆O₂Si (M⁺): 324.2484; found: 324.2477.

To a stirred solution of the alcohol 287 (35 mg, 0.11 mmol) in dry CH₂Cl₂ (2 mL) (argon atmosphere, room temperature) was added N-methylmorpholine-N-oxide (32 mg, 2.5 equiv.) and activated 4Å molecular sieves. The resulting suspension was stirred for 10 min at room temperature and then TPAP¹³³ (4 mg, 5 mol%) was added. After the mixture had been stirred for 45 min at room temperature it was filtered through a short column of Florisil® (approx. 5 g) using Et₂O as eluant. The combined eluate was concentrated and the resulting oil was purified by flash chromatography (1:4 Et₂O - petroleum ether; 20 g of silica gel). Distillation (140-150°C/0.5 Torr) of the oil thus obtained gave 29 mg (83%) of the
ketone 285, a colourless oil which exhibited ir (neat): 1719, 1256, 1099, 837, 777 cm\(^{-1}\);
\(^1\)H nmr (400 MHz, C\(_6\)D\(_6\)) \(\delta\): 0.06 (s, 6H, -SiMe\(_2\)), 0.98 (d, 3H, -CHMe-, \(J = 8\) Hz),
1.00 (s, 9H, -SiBu\(_t\)), 1.02 (d, 3H, -CHMe-, \(J = 8\) Hz), 1.25 (dt, 1H, \(H_A\) or \(H_A'\), \(J = 13\) Hz, \(J = 6\) Hz), 1.63-1.79 (m, 3H), 1.80-1.95 (m, 3H), 2.04 (m, 1H), 2.18 (br septet, 1H, -CHMe\(_2\), \(J = 8\) Hz), 3.55 (t, 2H, -OCH\(_2\)CH\(_2\)-, \(J = 6\) Hz), 4.92 (br s, 1H), 5.05 (br s, 1H). Exact Mass calcd. for C\(_{19}\)H\(_{34}\)O\(_2\)Si (M\(^+\)): 322.2328; found: 232.2330. Anal. calcd.
for C\(_{19}\)H\(_{34}\)O\(_2\)Si: C 70.76, H 10.63; found: C 70.62, H 10.49.

The preparation of compound 291 and the thermal rearrangement of this compound into the
bicyclo[3.2.1]octa-2,6-diene 292.

![Diagram 291](image1)

![Diagram 292](image2)

To a cold (-78°C), stirred solution of the ketone 278 (70 mg, 0.25 mmol) and
TBDMSCl (57 mg, 1.5 equiv.) in dry THF (2 mL) (argon atmosphere) was added quickly,
via Pasteur pipette, a suspension of KH (approx. 150 mg of a 35% dispersion of KH in
mineral oil, 5 equiv.; pre-washed with dry THF) in dry THF (approx. 1 mL). The mixture
was stirred for 5 min at -78°C and was then allowed to warm to room temperature. The
progress of the reaction was monitored by tlc. When all of the ketone had reacted (after
45 min at room temperature) the mixture was cooled to -78°C and saturated aqueous NaHCO₃ (2 mL) and Et₂O (5 mL) were added. The vigorously stirred mixture was exposed to air and was allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with Et₂O (2 x 5 mL). The combined organic extracts were washed with brine (5 mL) and were then dried (MgSO₄) and concentrated, to give the crude compound 291. Distillation of this crude oil (140-145°C/0.2 Torr) gave 81 mg (82%) of the compound 292, a colourless oil which exhibited IR (neat): 3020, 1627, 1255, 871, 779 cm⁻¹; ¹H nmr (400 MHz, C₆D₆) δ: 0.11 (s, 6H, -SiMe₂), 0.17 (s, 3H, -SiMe), 0.19 (s, 3H, -SiMe), 1.00 (s, 9H, -SiBu³), 1.03 (s, 9H, -SiBu³), 1.73-1.90 (m, 3H, -OCH₂CH₂- and Hₐ), 2.04-2.18 (m, 3H, Hₐ, HD, and HE), 2.64 (m, 1H, HC), 3.78 (t, 2H, -OCH₂CH₂-, J = 6 Hz), 5.14 (br s, 1H, Hₐ), 5.33 (dddd, 1H, HF, J = 10 Hz, J = 3 Hz, J = 3 Hz, J = 1.5 Hz), 6.17 br d, 1H, HG, J = 10 Hz). Exact Mass calcd. for C₂₂H₄₂O₂Si₂ (M⁺): 394.2723; found: 394.2717. Anal. calcd. for C₂₂H₄₂O₂Si₂: C 66.94, H 10.72; found: C 67.10, H 10.87.

Preparation of compound 293 and the thermal rearrangement of this compound into the bicyclo[3.2.1]octa-2,6-diene 294
To a cold (-78°C), stirred solution of the ketone 279 (30 mg, 85 μmol) and TBDMSCl (19 mg, 1.5 equiv.) in dry THF (2 mL) (argon atmosphere) was added, quickly, via pasteur pipette, a suspension of KH (approx. 50 mg of a 35% dispersion of KH in mineral oil, 5 equiv.; prewashed with dry THF) in dry THF (approx. 1 mL). The mixture was stirred for 5 min at -78°C and was then allowed to warm to room temperature. The progress of the reaction was monitored by tlc. When all of the ketone had reacted (after 45 min at room temperature) the mixture was cooled to -78°C and saturated aqueous NaHCO₃ (2 mL) and Et₂O (5 mL) were added. The vigorously stirred mixture was exposed to air and allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with Et₂O (2 x 5 mL). The combined organic extracts were washed with brine (5 mL) and were then dried (MgSO₄) and concentrated, to give the crude compound 293. Distillation of this crude oil (170-175°C/0.2 Torr) gave 35 mg (88%) of the compound 294, a colourless oil which exhibited ir (neat): 1625, 1255, 1112, 869, 779 cm⁻¹; ¹H nmr (400 MHz, C₆D₆) δ: 0.11 (s, 6H, -SiMe₂), 0.17 (s, 6H, -SiMe₂), 1.00 (s, 9H, -SiBu₃), 1.03 (s, 9H, -SiBu₃), 1.70-1.90 (m, 3H, -OCH₂CH₂- and HA), 2.11 (ddd, 1H, HB, J = 10 Hz, J = 5 Hz, J = 1.5 Hz), 2.70-2.80 (m, 2H, HC and HD), 3.25 (s, 3H, -OMe), 3.57-3.72 (m, 2H, -CH₂OMOM), 3.76 (t, 2H, -OCH₂CH₂-, J = 6 Hz), 4.59, 4.66 (d, d, 2H, -OCH₂O-, J = 7 Hz), 5.12 (s, 1H, HF), 5.58 (ddd, 1H, HF, J = 10 Hz, J = 2 Hz, J = 2 Hz), 6.24 (br d, 1H, HG, J = 10 Hz). In decoupling experiments, irradiation at δ 6.24 (HG) caused the signal at δ 5.58 (HF) to collapse to a dd (J = 2 Hz, J = 2 Hz), whilst the signal at δ 2.11 (HB) sharpened to a dd (J = 10 Hz, J = 5 Hz); irradiation at δ 5.58 (HF) caused the signal at δ 6.24 (HG) to collapse to a br s; irradiation at δ 3.76 (-OCH₂CH₂-) caused the signal at 1.70-1.90 (-OCH₂CH₂- and HA) to simplify to signals at δ 1.76 and δ 1.85 (d, d, 1H each, -OCH₂CH₂-, J = 14 Hz, J = 14 Hz), plus a signal at 1.81 (d, HA, J = 10 Hz); irradiation at δ 2.70-2.80 (HC and HD) caused the signal at δ 6.24 (HG) to sharpen to a dd (J = 10 Hz, J = 1.5 Hz) whilst the signal at δ 5.58 (HF) sharpened to a d (J = 10 Hz), and the signal at δ 3.57-3.72 (-CH₂O-) collapsed to signals at δ 3.51 (d,
$J = 9 \text{ Hz})$ and $\delta 3.68 \text{ (d, } J = 9 \text{ Hz)}$; irradiation at $\delta 2.11 \text{ (HB)}$ caused the signal at $\delta 6.24 \text{ (HG)}$ to sharpen to a dd ($J = 10 \text{ Hz, } J = 2 \text{ Hz})$ whilst the signal at $\delta 1.69-1.89 \text{ (-OCH}_2\text{CH}_2- \text{ and HA)}$ simplified to a signal at $\delta 1.69-1.89 \text{ (m, -OCH}_2\text{CH}_2- \text{)}$ plus a signal at $\delta 1.81 \text{ (s, HA)}$. In a COSY experiment (400 MHz, C$_6$D$_6$): $\text{HG}$ showed correlations into $\text{HD}$, and $\text{HF}$; $\text{HF}$ showed correlations into $\text{HG}$, and/or $\text{HC/HD}$; $\text{HF}$ showed a correlation into $\text{HA}$; $\text{-CH}_2\text{OMOM}$ showed a correlation into $\text{HD}$; $\text{HB}$ showed a correlation into $\text{HA}$ and $\text{HC}$. 

_Exact Mass_ calcd. for C$_{25}$H$_{48}$O$_4$Si$_2$ (M$^+$): 468.3091; found: 468.3090. _Anal._ calcd. for C$_{25}$H$_{48}$O$_4$Si$_2$: C 64.05, H 10.32; found: C 64.20, H 10.40.

Preparation of compound 296 and the thermal rearrangement of this compound into the 

bicyclo[3.2.1]octa-2,6-diene 297

![Structural formula of compounds 296 and 297](image)

To a cold (-78°C), stirred solution of the ketone 280 (9 mg, 29 μmol) in dry CH$_2$Cl$_2$ (1.5 mL) (argon atmosphere) was added, successively, dry Et$_3$N (3 equiv., 13 μL) and TBDMSOTf (1.5 equiv., 11 μL). After the mixture had been stirred for 30 min at -78°C,
saturated aqueous NaHCO₃ (1 mL) and Et₂O (3 mL) were added, and the mixture was allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with Et₂O (2 x 3 mL). The combined organic extracts were washed with brine (2 mL) and were then dried (MgSO₄) and concentrated, to give the crude compound 296. Dry benzene (3 mL) was added to this crude oil, in a base washed round bottom flask, and the solution was warmed to 50°C overnight (argon atmosphere). The solvent was removed and the residual oil was purified by rapid flash chromatography (15:85 Et₂O - petroleum ether; 10 g of silica gel), to give, after removal of traces of solvent under reduced pressure (room temperature/0.5 Torr), 10 mg (82%) of the compound 297, a colourless oil which exhibited ir (neat): 1733, 1621, 1152, 868, 784 cm⁻¹; ¹H nmr (400 MHz, C₆D₆) δ: 0.20 (s, 3H, -SiMe), 0.22 (s, 3H, -SiMe), 1.03 (s, 9H, -SiBu₃), 1.47 (s, 9H, -CO₂Bu₃), 1.68 (br d, 1H, Hₐ, J = 10 Hz), 1.65-1.82 (m, 2H, -OCH₂CH₂-), 2.06 (br dd, Hₐ, J = 10 Hz, J = 5 Hz), 3.13 (m, 2H, H₉C and H₉D), 3.21 (s, 3H, -OMe), 3.57 (m, 2H, -OCH₂CH₂-), 4.51 (s, 2H, -OCH₂O-), 5.11 (br s, 1H, H₉F), 5.68 (ddd, 1H, H₉F, J = 10 Hz, J = 2 Hz, J = 2 Hz), 6.15 (br d, 1H, H₉G, J = 10 Hz). In a COSY experiment (400 MHz, C₆D₆): H₉G showed correlations into H₉F and H₉D; H₉F showed correlations into H₉G and H₉D/H₉C; H₉E showed a correlation into H₉A; H₉B showed correlations into H₉A and H₉C; H₉A showed correlations into H₉B and H₉E. Exact Mass calcd. for C₂₃H₄₀O₅Si (M⁺): 424.2600; found: 424.2650. Anal. calcd. for C₂₃H₄₀O₅Si: C 65.05, H 9.49; found: C 65.32, H 9.63.
Preparation of the compound 295

To a cold, (-78°C), stirred solution of the ketone 280 (15 mg, 48 μmol) in dry THF (1 mL) (argon atmosphere) was added a suspension of KH (28 mg of a 35% dispersion of KH in mineral oil, approx. 5 equiv., prewashed with dry THF) in dry THF (0.5 mL), via Pasteur pipette. The mixture was warmed to room temperature and stirred for a further 30 min. Then it was re-cooled to -78°C and saturated aqueous NaHCO₃ (1 mL) and Et₂O (3 mL) were added. The vigorously stirred mixture was allowed to warm to room temperature, the phases were separated and the aqueous phase was extracted with Et₂O (2 x 3 mL). The combined organic extracts were washed with brine (3 mL) and were then dried (MgSO₄) and concentrated. Flash chromatography of the crude product (1:1 Et₂O - petroleum ether; 15 g of silica gel) gave (after traces of solvent were removed under reduced pressure; room temperature/0.5 Torr) 13 mg (87%) of the compound 295, a colourless oil which exhibited ir (neat): 1752, 1729, 1151, 1042 cm⁻¹; ¹H nmr (400 MHz, C₆D₆) δ: 1.18 (d, 1H, H₂, J = 6 Hz), 1.39 (s, 9H, -C₆H₅Bu⁴), 1.41-1.51 (m, 1H, -OCH₂CH₂), 1.52-1.62 (m, 3H, OCH₂CH₂ and H₁ and H₂), 1.67 (br d, 1H, J = 6 Hz), 1.84 (br s, 1H, H₃), 2.0 (m, 2H, -CH₂CO₂Bu⁴), 2.49 (br t, 1H, J = 7 Hz), 3.19 (s, 3H, -OMe), 3.32 (t, 2H, -OCH₂CH₂, J = 6 Hz), 4.41, 4.42 (d, d, 2H, -OCH₂O-, J = 6 Hz, J = 6 Hz). In a COSY experiment (400 MHz, C₆D₆): δ 1.18 (H₂B) showed correlations into δ 1.67 (H₃A)
and δ 1.84 (HC); δ 1.67 (HA) showed correlations into δ 1.18 (HB), δ 1.84 (HC) and δ 2.49 (HD); δ 1.84 (HC) showed correlations into δ 1.67 (HA), δ 1.18 (HB), δ 2.49 (HD) and 1.55-1.65 (HF/HF); δ 2.49 (HD) showed correlations to δ 2.00 (-CH$_2$CO$_2$Bu$^t$), δ 1.84 (HC), and δ 1.67 (HA); δ 3.32 (-OCH$_2$CH$_2$-) showed correlations to δ 1.41-1.51 and δ 1.52-1.62 (-OCH$_2$CH$_2$-). In a long range COSY experiment (400 MHz, C$_6$D$_6$): HB showed correlations into HE/HF, HA and HC; HA showed correlations into HB, HC and HD; HC showed correlations into HD, HE/HF, HA and HB; HD showed correlations into -CH$_2$CO$_2$Bu$^t$, HC, HA and HF/HF. In nOe difference experiments; irradiation of the signal at δ 1.84 (HC) caused signal enhancements at δ 1.58 (HF or HF or both) and at δ 2.49 (HD); irradiation of the signal at δ 2.00 (-CH$_2$CO$_2$Bu$^t$) caused signal enhancements at δ 2.49 (HD), δ 1.67 (HA), δ 1.84 (HC) and δ 1.58 (HF); irradiation of the signal at δ 2.49 (HD) caused signal enhancement at δ 2.00 (-CH$_2$CO$_2$Bu$^t$), δ 1.84 (HC) and δ 1.67 (HA). $^{13}$C nmr (50 MHz, C$_6$D$_6$) δ: 27.22, 28.03, 30.26, 31.07, 31.52, 36.10, 40.25, 44.89, 54.99, 65.82, 79.98, 96.54, 170.61, 209.00. Exact Mass calcd. for C$_{13}$H$_{18}$O$_5$ (M$^+$-C$_4$H$_8$): 254.1153; found: 254.1153. Cims (positive ion detection, CH$_4$): 311 (M$^+$+H).
Preparation of compound 298 and the thermal rearrangement of this compound into the bicyclo[3.2.1]octa-2,6-diene 299. Preparation of the bicyclo[3.2.1]oct-2-en-6-one 300.

To a cold (-78°C), stirred solution of the mixture of ketones 281 and 282 (10 mg, 34 µmol, 4:1 by glc analysis, respectively) in dry CH₂Cl₂ (1 mL) (argon atmosphere) was added, successively, dry Et₃N (10 mg, 14 µL, 3 equiv.) and TBDMSOTf (13 mg, 12 µL, 1.5 equiv.). After the mixture had been stirred for 20 min at -78°C, saturated aqueous NaHCO₃ (1 mL) and Et₂O (3 mL) were added and the mixture was allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with Et₂O (2 x 3 mL). The combined organic extracts were dried (MgSO₄) and concentrated. Dry benzene (3 mL) was added to the residue in a base washed round bottom flask and the solution was warmed to 50°C overnight (argon atmosphere). Solvent was removed and the residue was dissolved in THF (0.75 mL). Glacial HOAc (0.25 mL) was added to the solution and the mixture was stirred at room temperature for 1.5 h. Water (2 mL) and Et₂O (3 mL) were
added and the vigorously stirred mixture was neutralized by the addition of solid NaHCO₃.
The phases were separated and the aqueous phase was extracted with Et₂O (3 x 2 mL). The
combined organic extracts were dried (MgSO₄) and concentrated. Flash chromatography of
the crude product (1:4 Et₂O - petroleum ether; 10 g of silica gel) followed by distillation of
the oil thus obtained (130-135°C/0.5 Torr), gave 5.5 mg (55%) of the ketone 300, a
colourless oil which exhibited ir (neat): 1747, 1094, 837, 776 cm⁻¹; ¹H nmr (400 MHz,
C₆D₆) δ: 0.07 (s, 6H, -SiMe₂), 1.01 (s, 9H, -SiBu³), 1.41 (s, 3H, -Me), 1.51 (br dd, 1H,
H₆, J = 11 Hz, J = 5.5 Hz), 1.53-1.67 (m, 3H, -OCH₂CH₂- and H₄), 1.87 (d, 1H, H₇,
J = 17 Hz), 1.97 (br dd, 1H, H₅, J = 17 Hz, J = 5 Hz), 2.05 (br d, 1H, H₆, J = 17 Hz),
2.27 (dd, 1H, H₆, J = 17 Hz, J = 3 Hz), 2.42 (m, 1H, H₅), 3.61 (m, 2H, -OCH₂CH₂-),
5.44 (br s, 1H, HH). In decoupling experiments, irradiation at δ 2.42 (Hc) caused the
signal at δ 1.51 (Hb) to collapse to a br d (J = 11 Hz), whilst the signal at δ 1.97 (Hd)
collapsed to a br d (J = 17 Hz); irradiation at δ 3.61 (-OCH₂CH₂-) caused the signal at 1.53-
1.67 (-OCH₂CH₂- and H₄) to simplify to a signal at δ 1.65 (dd, H₄, J = 11 Hz, J = 3 Hz)
and signals at δ 1.62 (d, J = 13 Hz) and δ 1.56 (d, J = 13 Hz); irradiation at δ 2.27 (Hg)
cause the signal at 1.87 (Hf) to collapse to a s; irradiation at δ 1.87 (Hf) caused the signal
at δ 2.27 (Hg) to collapse to a br d (J = 3 Hz). Exact Mass calcd. for C₁₇H₃₀O₂Si (M⁺):
294.2015; found: 294.2024. Anal. calcd. for C₁₇H₃₀O₂Si: C 69.33, H 10.27; found:
C 69.50, H 10.29.
Preparation of compound 301 and the thermal rearrangement of this compound into the bicyclo[3.2.1]octa-2,6-diene 302. Preparation of the bicyclo[3.2.1]oct-2-en-6-one 303.

To a cold (-78°C), stirred solution of the mixture of ketones 285 and 286 (17 mg, 53 μmol, 4:1 by glc analysis, respectively) in dry CH2Cl2 (2 mL) (argon atmosphere) was added, successively, dry Et3N (16 mg, 22 μL, 3 equiv.) and TBDMSOTf (21 mg, 18 μL, 1.5 equiv.). After the mixture had been stirred for 20 min at -78°C, saturated aqueous NaHCO3 (1 mL) and Et2O (3 mL) were added and the mixture was allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with Et2O (2 x 3 mL). The combined organic extracts were dried (MgSO4) and concentrated. Dry benzene (3 mL) was added to the residue in a base washed round bottom flask and the solution was warmed to 50°C overnight (argon atmosphere). The solvent was removed and the residue was dissolved in THF (1 mL). Glacial HOAc (0.3 mL) was added to the solution and the mixture was stirred at room temperature for 1.5 h. Water (2 mL) and Et2O (3 mL) were
added and the vigorously stirred mixture was neutralized by the addition of solid NaHCO₃. The phases were separated and the aqueous phase was extracted with Et₂O (3 x 2 mL). The combined organic extracts were dried (MgSO₄) and concentrated. Flash chromatography of the crude product (1:4 Et₂O - petroleum ether; 10 g of silica gel) followed by distillation of the oil thus obtained (140-150/0.5 Torr), gave 11 mg (65%) of the ketone 303, a colourless oil which exhibited ir (neat): 1747, 1255, 838, 776 cm⁻¹; ¹H nmr (400 MHz, C₆D₆) δ: 0.10 (s, 6H, -SiMe₂), 0.88 (d, 3H, -CHMe, J = 8 Hz), 0.89 (d, 3H, -CHMe, J = 8 Hz), 1.01 (s, 9H, -SiBu¹), 1.54 (br dd, 1H, HB, J = 11 Hz, J = 5.5 Hz), 1.58-1.68 (m, 3H, -OCH₂CH₂- and HA), 1.91 (dd, 1H, HF, J = 17 Hz, J = 1 Hz), 1.96 (m, 1H, Hl), 2.04 (ddd, 1H, HD, J = 17 Hz, J = 5 Hz, J = 2 Hz), 2.13 (br d, HE, J = 17 Hz), 2.27 (dd, 1H, HG, J = 17 Hz, J = 3 Hz), 2.47 (m, 1H, HC), 3.54 (m, 2H, -OCH₂CH₂-), 5.54 (br s, 1H, HH). In decoupling experiments, irradiation at δ 5.54 (HH) caused the signal at δ 2.13 (HF) to sharpen to a dd (J = 17 Hz, J = 2 Hz), whilst the signal at δ 2.04 (HD) collapsed to a dd (J = 17 Hz, J = 5 Hz), and the signal at δ 1.54 (HB) sharpened to a dd (J = 11 Hz, J = 5.5 Hz); irradiation at δ 3.54 (-OCH₂CH₂-) caused the signal at δ 1.58-1.68 (-OCH₂CH₂- and HA) to simplify to signals at δ 1.60, δ 1.64 (d, d, 1H each, -OCH₂CH₂-, J = 14 Hz, J = 14 Hz) and a signal at δ 1.66 (dd, HA, J = 11 Hz, J = 3 Hz); irradiation at δ 2.47 (HC) caused the signal at 1.54 (HB) to collapse to a br d (J = 11 Hz), whilst the signal at 1.91 (HF) collapsed to a d (J = 17 Hz), and the signal at δ 2.04 (HD) collapsed to a dd (J = 17 Hz, J = 2 Hz); irradiation at δ 2.27 (HG) caused the signal at δ 1.91 (HF) to collapse to a br s, whilst the signal at δ 1.58-1.68 (-OCH₂CH₂- and HA) collapsed to signals at δ 1.58-1.68 (m, -OCH₂CH₂-) and δ 1.66 (s, HA). Exact Mass calcd. for C₁₉H₃₄O₂Si (M⁺): 322.2328; found: 322.2329. Anal. calcd. for C₁₉H₃₄O₂Si: C 70.75, H 10.62; found: C 70.76, H 10.80.
Preparation of compound 305 and the thermal rearrangement of this compound into the bicyclo[3.2.1]octa-2,6-diene 306.

To a cold (-78°C), stirred solution of the ketone 279 (18 mg, 51 μmol) in dry THF (1.5 mL) (argon atmosphere) was added a solution of lithium diisopropylamide (0.3 M, 3 equiv.) in THF. After the mixture had been stirred for 20 min at -78°C and for 30 min at -20°C, solid N-phenyltrifluoromethanesulphonimide (66 mg, 4 equiv.) was added and the mixture was stirred for a further 1 h at -20°C. The reaction mixture was passed through a short column of silica gel (in a Pasteur pipette) using Et2O as eluant. The eluate was concentrated and the crude oil thus obtained was purified by flash chromatography (1:9 Et2O - petroleum ether; 15 g of silica gel), to give the compound 305. To this oil, in a base washed round bottom flask was added dry benzene (3 mL). The solution was warmed to 50°C overnight (argon atmosphere). Solvent was removed and the residual oil was purified by flash chromatography (1:9 Et2O - petroleum ether; 15 g of silica gel) to give (after removal of traces of solvent under reduced pressure; 0.5 Torr/room temperature) 18 mg (73%) of the compound 306, a colourless oil which exhibited ir (neat): 1645, 1426, 1213, 1104, 778 cm⁻¹; ¹H nmr (400 MHz, C₆D₆) δ: 0.07 (s, 6H, -SiMe₂), 0.94 (s, 9H, -SiBu⁴), 1.41-1.62 (m, 2H, -OCH₂CH₂-), 1.58 (br d, 1H, HA, J = 10 Hz), 2.07 (ddd, 1H, HB, J =
10 Hz, J = 5.5 Hz, J = 1.5 Hz), 2.49 (m, 1H, HD), 3.12 (ddd, 1H, HC, J = 5.5 Hz, J = 5.5 Hz, J = 1.5 Hz), 3.25 (s, 3H, -OMe), 3.25-3.31 (m, 1H, HH or H'H'), 3.45 (dd, 1H, HH or H'H', J = 10 Hz, J = 6 Hz), 3.52 (m, 2H, -OCH2CH2-), 4.55, 4.58 (d, d, 2H, -OCH2O-, J = 6.5 Hz, J = 6.5 Hz), 5.16 (ddd, 1H, HF, J = 10 Hz, J = 1.5 Hz, J = 1.5 Hz), 5.81 (br s, 1H, HE), 5.89 (ddd, 1H, HG, J = 10 Hz, J = 2 Hz, J = 1.5 Hz). In decoupling experiments, irradiation at δ 5.89 (HG) caused the signal at δ 5.16 (HF) to collapse to a dd (J = 1.5 Hz, J = 1.5 Hz), whilst the signal at δ 2.07 (HB) sharpened to a dd (J = 10 Hz, J = 5.5 Hz); irradiation at δ 5.16 (HF) caused the signal at δ 5.89 (HG) to collapse to a dd (J = 2 Hz, J = 1.5 Hz), whilst the signal at δ 3.12 (HC) sharpened to a dd (J = 5.5 Hz, J = 5.5 Hz); irradiation at δ 3.52 (-OCH2CH2-) caused the signal at 1.41-1.62 (-OCH2CH2-) to simplify to signals at δ 1.45 (d, J = 12 Hz) and δ 1.55 (d, J = 12 Hz); irradiation at δ 2.49 (HD) caused the signal at δ 3.25-3.31 (HH or H'H') to collapse to a d (J = 10 Hz), whilst the signal at δ 3.45 (HH or H'H') collapsed to a d (J = 10 Hz), the signal at δ 3.12 (HC) collapsed to a br d (J = 5.5 Hz), the signal at δ 5.16 (HF) sharpened to a dd (J = 10 Hz, J = 1.5 Hz) and the signal at δ 5.89 (HG) sharpened to a dd (J = 10 Hz, J = 1.5 Hz); irradiation at δ 2.07 (HB) caused the signal at 5.89 (HG) to sharpen to a dd (J = 10 Hz, J = 2 Hz), whilst the signal at δ 1.58 (HA) collapsed to a s, and the signal at δ 3.12 (HC) collapsed to a br d (J = 5.5 Hz); irradiation at δ 3.12 (HC) caused the signal at δ 2.07 (HB) to collapse to a br d (J = 5.5 Hz), whilst the signal at δ 5.14 sharpened to a dd (J = 10 Hz, J = 1.5 Hz). Exact Mass calcd. for C_{16}H_{24}F_{3}O_{6}S (M^{+}-Bu): 429.1015; found: 429.1015 ; cims (positive ion detection, NH3): 505 (M^{+}+NH4).
Preparation of compound 308 via the α-phenylthio ketones 307, and the thermal rearrangement of this compound into the bicyclo[3.2.1]octa-2,6-diene 309.

To a cold (-78°C), stirred solution of the ketone 279 (46 mg, 0.13 mmol) in dry THF (3 mL) (argon atmosphere) was added a solution of lithium diisopropylamide (0.3 M, 3 equiv.) in THF. After the mixture had been stirred for 20 min at -78°C and 30 min at -20°C, it was transferred via cannula into a stirred solution of diphenyl disulphide (4.5 equiv., 156 mg) in dry THF (2 mL) at room temperature (argon atmosphere). After the mixture had been stirred for 1.5 h at room temperature, saturated aqueous NaHCO3 (3 mL) and Et2O (5 mL) were added. The phases were separated and the aqueous phase was extracted with Et2O (3 x 3 mL). The combined organic extracts were washed with brine (5 mL), dried (MgSO4) and concentrated. Flash chromatography (3:7 Et2O - petroleum
ether; 25 g of silica gel) of the residual oil afforded 46 mg (77%) of the \( \alpha \)-phenylthio ketone
307, a pale yellow oil, which was used without further purification.

To a cold (-78°C), stirred solution of the reaction product (46 mg, 0.1 mmol) and
TBDMSCl (22 mg, 1.5 equiv.) in dry THF (3 mL) (argon atmosphere) was added a
suspension of KH (5 equiv., approx. 56 mg of a 35% dispersion of KH in mineral oil,
prewashed with dry THF) in dry THF (approx. 1 mL). After the mixture had been stirred at
-78°C for 5 min and at room temperature for 45 min it was re-cooled to -78°C and saturated
aqueous NaHCO\(_3\) (2 mL) and Et\(_2\)O (5 mL) were added. The vigorously stirred mixture was
allowed to warm to room temperature and the phases were separated. The aqueous phase
was extracted with Et\(_2\)O (2 x 5 mL) and the combined organic extracts were washed with
brine (3 mL), dried (MgSO\(_4\)) and concentrated, to give the crude compound 308. To this
 crude oil (in a base washed round bottom flask) was added dry benzene (4 mL), and the
solution (argon atmosphere) was warmed to 60°C overnight. Solvent was removed, and the
residue was purified by flash chromatography (7:93 Et\(_2\)O - petroleum ether; 20 g of silica
gel) to give (after removal of traces of solvent under reduced pressure; 0.5 Torr/room
temperature) 33 mg (44% from the ketone 279) of the compound 309, a colourless oil
which exhibited ir (neat): 3060, 1620, 1254, 840 cm\(^{-1}\); 1H nmr (400 MHz, C\(_6\)D\(_6\)) \( \delta \): 0.07
(s, 6H, -SiMe\(_2\)), 0.24 (s, 3H, -SiMe), 0.28 (s, 3H, -SiMe), 1.0 (s, 9H, -SiBu\(_t\)), 1.08 (s, 9H, -SiBu\(_t\)),
1.62-1.78 (m, 2H, -OCH\(_2\)CH\(_2\)-), 1.93 (dd, 1H, \( \text{HA}, J = 9\) Hz, \( J = 1\) Hz),
2.43 (dd, 1H, \( \text{HB}, J = 9\) Hz, \( J = 1.5\) Hz), 3.04 (m, 1H, \( \text{HC}\)), 3.26 (s, 3H, -OMe),
3.60-3.70 (m, 3H, -OCH\(_2\)CH\(_2\)- and \( \text{HD} \) or \( \text{HD}'\)), 4.62 (d, 1H, \( \text{HH} \) or \( \text{HH}'\), \( J = 6\) Hz),
4.65-4.72 (m, 2H, \( \text{HD} \) or \( \text{HD}' \) plus \( \text{HH} \) or \( \text{HH}'\)), 5.13 (d, 1H, \( \text{HE}, J = 1\) Hz), 5.94 (dd, 1H, \( \text{HF}, J = 10\) Hz, \( J = 2.5\) Hz),
6.13 (br d, 1H, \( \text{HG}, J = 10\) Hz), 7.01-7.11 (m, 3H), 7.55 (m, 2H). In decoupling experiments, irradiation at \( \delta \) 6.13 (\( \text{HG}\)) caused the signal at \( \delta \) 5.94
(\( \text{HF}\)) to collapse to a d (\( J = 2.5\) Hz), whilst the signal at \( \delta \) 3.04 (\( \text{HC}\)) sharpened to a ddd
(\( J = 11\) Hz, \( J = 3\) Hz, \( J = 2.5\) Hz), and the signal at \( \delta \) 2.43 (\( \text{HB}\)) sharpened to a d (\( J = 9\) Hz);
irradiation at \( \delta \) 5.94 (\( \text{HF}\)) caused the signal at \( \delta \) 6.13 (\( \text{HG}\)) to collapse to a br s, whilst the
signal at δ 3.04 (HC) sharpened to a ddd (J = 11 Hz, J = 3 Hz, J = 2 Hz); irradiation at δ 5.13 (HE) caused the signal at 1.93 (HA) to sharpen to a d (J = 9 Hz); irradiation at δ 4.65-4.72 (HD or HD' plus HH or HH') caused the signal at δ 3.04 (HC) to sharpen to a ddd (J = 11 Hz, J = 2.5 Hz, J = 2 Hz); irradiation at δ 3.04 (HC) caused the signal at δ 6.13 (HG) to sharpen to a dd (J = 10 Hz, J = 1.5 Hz), whilst the signal at δ 5.94 (HF) sharpened to a d (J = 10 Hz), and the signal at δ 4.65-4.72 (HD or HD' plus HH or HH') simplified to doublets at δ 4.67 (HH or HH', J = 6 Hz) and δ 4.69 (HD or HD', J = 9 Hz); irradiation at δ 2.43 (HB) caused the signal at δ 6.13 (HG) to sharpen to a dd (J = 10 Hz, J = 2 Hz), whilst the signal at 1.93 (HA) collapsed to a br s; irradiation of the signal at δ 1.93 (HA) caused the signal at δ 2.43 (HB) to collapse to a br s. Exact Mass calcd. for C_{31}H_{52}O_{4}Si_{2}S (M^+): 576.3124; found: 576.3128. Anal. calcd. for C_{31}H_{52}O_{4}Si_{2}S: C 64.53, H 9.08; found: C 64.36, H 9.20.
Preparation of compound 311, via the \( \beta \)-keto ester 310, and the thermal rearrangement of this compound into the bicyclo[3.2.1]octa-2,6-diene 312.

To a cold (-78\(^\circ\)C), stirred solution of the ketone 279 (21 mg, 59 \( \mu \)mol) in dry THF (1.5 mL) (argon atmosphere) was added a solution of lithium diisopropylamide (0.3 M, 3 equiv.) in THF. After the mixture had been stirred for 20 min at -78\(^\circ\)C and for 30 min at -20\(^\circ\)C, it was re-cooled to -78\(^\circ\)C and HMPA (30 \( \mu \)L, 3 equiv.) and methyl cyanoformate (41 \( \mu \)L, 3 equiv.) were added. After the mixture had been stirred for 15 min at -78\(^\circ\)C it was poured into H\(_2\)O (5 mL). Diethyl ether (5 mL) was added and the vigorously stirred mixture was allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with Et\(_2\)O (2 x 5 mL). The combined organic extracts were washed with H\(_2\)O (3 x 3 mL) and brine (3 mL) and were then dried (MgSO\(_4\)) and concentrated, to give 30 mg of the crude \( \beta \)-keto ester 310 (after removal of traces of solvent under reduced pressure; room temperature/0.5 Torr). This oil was immediately dissolved in dry THF (2 mL), and
TBDMSCl (17 mg, 1.5 equiv.) was added to the solution. The solution was cooled to -78°C (argon atmosphere) and a suspension of KH (5 equiv. approx. 42 mg of a 35% dispersion of KH in mineral oil, prewashed with dry THF) in dry THF (approx. 0.5 mL) was added. After the mixture had been stirred at -78°C for 5 min and at room temperature for 45 min it was re-cooled to -78°C and saturated aqueous NaHCO₃ (2 mL) and Et₂O (5 mL) were added. The vigorously stirred mixture was allowed to warm to room temperature and the phases were separated. The aqueous phase was extracted with Et₂O (2 x 5 mL) and the combined organic extracts were washed with brine (3 mL), dried (MgSO₄) and concentrated, to give the crude compound 311. To this crude oil (in a base washed round bottom flask) was added dry benzene (3 mL), and the solution (argon atmosphere) was warmed to 50°C overnight. Solvent was removed, and the residue was purified by flash chromatography (1:4 Et₂O - petroleum ether; 20 g of silica gel) to give (after removal of traces of solvent at reduced pressure; 0.5 Torr/room temperature) 24 mg (74%) of the compound 312, a colourless oil which exhibited ir (neat): 1737, 1627, 1253, 841, 780 cm⁻¹; ¹H nmr (400 MHz, C₆D₆) δ: 0.11 (s, 6H, -SiMe₂), 0.18 (s, 3H, -SiMe), 0.21 (s, 3H, -SiMe), 0.97 (s, 9H, -SiBu¹), 1.02 (s, 9H, -SiBu¹), 1.68-1.85 (m, 2H, -OCH₂CH₂-), 1.93 (d, 1H, HA, J = 9 Hz), 2.50 (br d, 1H, HB, J = 9 Hz), 3.24 (s, 3H, -OMe), 3.50 (s, 3H, -OMe), 3.50-3.58 (m, 2H, H₁ and H₂ or H₃ and H₄), 3.71 (m, 2H, -OCH₂CH₂-), 4.22 (m, 1H, HD or HD'), 4.61, 4.67 (d, d, 2H, -OCH₂O-, J = 6 Hz, J = 6 Hz), 5.08 (s, 1H, HF), 5.97 (dd, 1H, HF, J = 10 Hz, J = 2 Hz), 6.18 (br d, 1H, HG, J = 10 Hz). In decoupling experiments, irradiation at δ 6.18 (HG) caused the signal at δ 5.97 (HF) to collapse to a d (J = 2 Hz); irradiation at δ 5.97 (HF) caused the signal at δ 6.18 (HG) to collapse to a br s; irradiation at δ 3.71 (-OCH₂CH₂-) caused the signal at δ 1.68-1.85 (-OCH₂CH₂-) to simplify to signals at δ 1.72 (d, J = 13 Hz) and δ 1.83 (d, J = 13 Hz); irradiation at δ 3.50-3.58 (HC plus HD or HD') caused the signal at δ 5.97 (HF) to collapse to a d (J = 10 Hz), whilst the signal at δ 4.22 (HD or HD') collapsed to br s; irradiation at δ 2.50 (HB) caused the signal at δ 1.93 (HA) to collapse to a s, whilst the signal at δ 6.18 (HG) sharpened to a dd (J = 10 Hz, J =
1.5 Hz); irradiation at δ 1.93 (HA) caused the signal at δ 2.50 (HB) to collapse to a br s. In a COSY experiment (400 MHz, C₆D₆): HG showed correlations into HF and HC; HF showed correlations into HG and HC; HF showed a correlation into HA; HD/HD' (δ 4.22) showed a correlation into HD/HD' and HC (both at δ 3.50-3.58); HB showed a correlation into HA; HA showed correlations into HB and HF. Exact Mass: calcd. for C₂₇H₅₀O₆Si₂ (M⁺): 526.3146; found: 526.3142. Anal. calcd. for C₂₇H₅₀O₆Si₂: C 61.55, H 9.57; found: C 61.38, H 9.60.

Preparation of compound 313, via the esters 314, and the thermal rearrangement of this compound into the bicyclo[3.2.1]octa-2,6-diene 315
To a cold (0°C), stirred solution of trimethylphosphonoacetate (1.59 mmol, 10 equiv.) in dry THF (3 mL) (argon atmosphere) was added a solution of MeLi (10 equiv.) in Et₂O. After the mixture had been stirred at 0°C for 10 min and at room temperature for 10 min, a solution of the ketone 279 (56 mg, 0.159 mmol, 1 equiv.) in dry THF (2 mL) was added, and the resulting mixture was stirred at room temperature overnight. Water (2 mL) and Et₂O (5 mL) were added and the phases were separated. The aqueous phase was extracted with Et₂O (3 x 5 mL), and the combined organic extracts were washed with H₂O (3 mL), dried (MgSO₄) and concentrated. Flash chromatography of the crude reaction product (35:65 Et₂O - petroleum ether; 25 g of silica gel), gave (after removal of traces of solvent under reduced pressure; room temperature/0.5 Torr) 55 mg (85%) of the esters 314 (a 1:1 mixture of E and Z isomers by glc analysis), a colourless oil which was used without further purification. To a cold (-78°C), stirred solution of the reaction product (55 mg, 0.13 mmol) in dry THF (2.5 mL) (argon atmosphere) was added a solution of lithium diisopropylamide (0.3 M, 3.5 equiv.) in THF. After the solution had been stirred at -78°C for 45 min and at 0°C for 10 min it was transferred via cannula into a cold (-78°C) stirred mixture of glacial HOAc (0.5 mL) and THF (0.5 mL). After the resulting mixture had been stirred at -78°C for 10 min it was poured into H₂O (5 mL). Ether (5 mL) was added and then solid NaHCO₃ was added to the vigorously stirred mixture until all of the HOAc was neutralized. The layers were separated and the aqueous layer was extracted with Et₂O (3 x 5 mL). The combined organic extracts were washed with H₂O (3 mL), dried (MgSO₄) and concentrated, to give the crude compound 313. Dry benzene (3 mL) was added to this crude oil and the solution thus obtained was warmed to 50°C overnight (argon atmosphere). The solvent was removed and the residue was purified by flash chromatography (1:4 Et₂O - petroleum ether; 25 g of silica gel) to give (after removal of traces of solvent under reduced pressure; 0.5 Torr/room temperature) 38 mg (59% from the ketone 279) of the compound 315, a colourless oil which exhibited IR (neat): 3017, 1745, 1256, 1112, 838 cm⁻¹; ¹H nmr (400 MHz, C₆D₆) δ: 0.1 (s, 6H, -SiMe₂), 1.03 (s, 9H, -SiBu⁴), 1.69-1.82 (m, 2H, 286
-OCH$_2$CH$_2$-, 1.84 (d, 1H, HA, $J = 9$ Hz), 2.22 (ddd, 1H, HB, $J = 9$ Hz, $J = 5$ Hz, $J = 1.5$ Hz), 2.74 (m, 1H, HD), 3.08 (m, 3H, HC and -CH$_2$CO$_2$Me), 3.21 (s, 3H, -OMe), 3.30-3.40 (m, 5H, -OMe and -CH$_2$O-), 3.71 (t, 2H, -OCH$_2$CH$_2$-, $J = 7$ Hz), 4.48, 4.50 (d, d, 2H, -OCH$_2$O-, $J = 7$ Hz, $J = 7$ Hz), 5.24 (ddd, 1H, HF, $J = 10$ Hz, $J = 2$ Hz, $J = 2$ Hz), 6.05 (br s, 1H, HE), 6.10 (ddd, 1H, HG, $J = 10$ Hz, $J = 2.5$ Hz, $J = 1.5$ Hz). In decoupling experiments, irradiation at $\delta$ 6.10 (HG) caused the signal at $\delta$ 5.24 (HF) to collapse to a dd ($J = 2$ Hz, $J = 2$ Hz), whilst the signal at $\delta$ 2.22 (HB) sharpened to a dd ($J = 9$ Hz, $J = 5$ Hz); irradiation at $\delta$ 5.24 (HF) caused the signal at $\delta$ 6.10 (HG) to collapse to a dd ($J = 2.5$ Hz, $J = 1.5$ Hz); irradiation at $\delta$ 3.71 (-OCH$_2$CH$_2$-) caused the signal at 1.69-1.82 (-OCH$_2$CH$_2$-) to simplify to signals at $\delta$ 1.72 (d, $J = 13$ Hz) and $\delta$ 1.80 (d, $J = 13$ Hz); irradiation at $\delta$ 3.08 (-CH$_2$CO$_2$Me and HC) caused the signal at $\delta$ 5.24 (HF) to sharpen to a dd ($J = 10$ Hz, $J = 2$ Hz), whilst the signal at $\delta$ 2.22 (HB) collapsed to a dd ($J = 9$ Hz, $J = 1.5$ Hz); irradiation at $\delta$ 2.74 (HD) caused the signal at $\delta$ 6.10 (HG) to sharpen to a dd ($J = 10$ Hz, $J = 1.5$ Hz), whilst the signal at $\delta$ 5.24 (HF) sharpened to a dd ($J = 10$ Hz, $J = 2$ Hz); irradiation at $\delta$ 2.22 (HB) caused the signal at $\delta$ 6.10 (HG) to sharpen to a dd ($J = 10$ Hz, $J = 2.5$ Hz), whilst the signal at $\delta$ 1.84 (HA) collapsed to a s; irradiation of the signal at $\delta$ 1.84 (HA) caused the signal at $\delta$ 2.22 (HB) to collapse to a dd ($J = 5$ Hz, $J = 1.5$ Hz). 

Exact Mass calcd. for C$_{22}$H$_{38}$O$_5$Si (M$^+$): 410.2489; found: 410.2498. Anal. calcd. for C$_{22}$H$_{38}$O$_5$Si: C 64.35, H 9.33; found: C 64.57, H 9.46.
Preparation of the alcohol 317

To a cold (-78°C), stirred solution of the ketone 278 (152 mg, 0.5 mmol) in dry THF (3 mL) (argon atmosphere) was added a solution of diisobutylaluminium hydride (1.5 equiv.) in hexane. After the mixture had been stirred at -78°C for 1 h and at 0°C for 20 min, saturated aqueous NH₄Cl (approx. 0.2 mL) was added and the vigorously stirred mixture was exposed to air and was allowed to warm to room temperature. To the white suspension thus obtained was added Et₂O (5 mL) and drying agent (MgSO₄). The mixture was suction filtered through a short plug of Florisil® (3 cm x 2 cm) using Et₂O as eluant. The combined eluate was concentrated and the residue was purified by flash chromatography (35:65 Et₂O - petroleum ether; 35 g of silica gel). Distillation (155-165°C/0.5 Torr) of the oil thus obtained gave 142 mg (93%) of the alcohol 317, a colourless oil which exhibited ir (neat): 3356, 1256, 1099, 836, 776 cm⁻¹; ¹H nmr (400 MHz, C₆D₆) δ: 0.08 (s, 6H, -SiMe₃), 0.99 (s, 9H, -SiBu₃), 1.16 (br s, 1H, -OH), 1.25-1.40 (m, 3H, -OCH₂CH₂ and H₅ and H₆ or H₆'), 1.48 (br dd, 1H, H₆, J = 8 Hz, J = 8 Hz), 1.60-1.75 (m, 2H, -OCH₂CH₂ and H₇ or H₇'), 1.85 (ddd, 1H, H₁ or H₁, J = 9 Hz, J = 8 Hz, J = 1.5 Hz), 2.04 (dddd, 1H, H₆ or H₆', J = 13 Hz, J = 9 Hz, J = 9 Hz, J = 1.5 Hz), 4.56 (m, 1H, H₁), 5.12 (ddd, 1H, HA, J = 10 Hz, J = 2 Hz, J = 1 Hz), 5.31 (ddd, 1H, HB, J = 16 Hz, J = 2 Hz, J = 1 Hz),
6.12 (ddd, 1H, J = 16 Hz, J = 10 Hz, J = 8 Hz). On addition of D$_2$O the signal at $\delta$ 1.16 (-OH) disappeared. *Exact Mass* calcd. for C$_{16}$H$_{30}$O$_2$Si (M$^+$): 282.2015; found: 282.2011.

Preparation of compound 316, via the alcohol 317 and the selenide 318. The thermal rearrangement of compound 316 to the bicyclo[3.2.1]octa-2,6-diene 320.

To a stirred solution of the alcohol 317 (98 mg, 0.35 mmol) in dry THF (5 mL) at room temperature (argon atmosphere) was added successively, o-nitrophenylselenocyanate (1.3 equiv., 104 mg) and Bu$_3$P (1.3 equiv., 91 mg). After the mixture had been stirred for 20 min at room temperature, the solvent was removed and the residue was purified by flash chromatography (5:95 Et$_2$O - petroleum ether; 30 g of silica gel), to give 115 mg of the
selenide 318. This yellow solid was not completely pure, but was carried on to the next step without further purification.

To a stirred solution of the selenide 318 (115 mg) in CH₂Cl₂ (4 mL) at room temperature was added 30% aqueous H₂O₂ (3 mL). The mixture was stirred vigorously for 45 min (the solution became decolourized after approx. 10 min) at room temperature, and then saturated aqueous NaHCO₃ (5 mL) and Et₂O (10 mL) were added to the mixture. The phases were separated and the aqueous layer was extracted with Et₂O (3 x 5 mL). The combined organic extracts were washed with brine (3 mL), dried and concentrated. Flash chromatography of the residual oil (3:97 Et₂O - petroleum ether; 20 g of silica gel), followed by distillation of the oil thus obtained (160-170°C/6 Torr) gave 48 mg (52% from the alcohol 317, 48% from the ketone 278) of the compound 320, a colourless oil which exhibited ir (neat): 3020, 1473, 1255, 1095, 837, 776 cm⁻¹; ¹H nmr (400 MHz, C₆D₆) δ: 0.10 (s, 6H, -SiMe₂), 1.02 (s, 9H, -SiBut), 1.65-1.95 (m, 5H, -OCH₂CH₂- and HA, HB and HF), 2.17 (dddd, HD, J = 18 Hz, J = 5 Hz, J = 3 Hz, J = 2.5 Hz), 2.61 (m, 1H, HC), 3.73 (m, 2H, OCH₂CH₂-), 5.25 (dddd, HF, J = 10 Hz, J = 3 Hz, J = 2.5 Hz, J = 1.5 Hz), 5.61 (dd, 1H, HI, J = 6 Hz, J = 3 Hz), 5.98 (m, 1H, HG), 6.09 (d, 1H, HH, J = 6 Hz). In decoupling experiments, irradiation at δ 6.09 (HH) caused the signal at δ 5.61 (HI) to collapse to a d (J = 3 Hz); irradiation at δ 5.98 (HG) caused the signal at δ 5.25 (HF) to collapse to a ddd (J = 3 Hz, J = 2.5 Hz, J = 1.5 Hz), whilst the signal at δ 2.17 (HD) sharpened to a ddd (J = 18 Hz, J = 5 Hz, J = 3 Hz); irradiation at δ 5.61 (HI) caused the signal at δ 6.09 (HH) to collapse to a s, whilst the signal at δ 2.61 (HC) simplified to a br dd (J = 5 Hz, J = 5 Hz); irradiation at δ 5.25 (HF) caused the signal at δ 5.98 (HG) to collapse to a br s, whilst the signal at δ 2.17 (HD) sharpened to a ddd (J = 18 Hz, J = 5 Hz, J = 2.5 Hz); irradiation at δ 2.61 (HC) caused the signal at δ 5.61 (HI) to collapse to a d (J = 6 Hz), whilst the signal at δ 5.25 (HF) sharpened to a ddd (J = 10 Hz, J = 3 Hz, J = 2.5 Hz), and the signal at δ 2.17 (HD) sharpened to a ddd (J = 18 Hz, J = 3 Hz, J = 2.5 Hz); irradiation at δ 2.17 (HD) caused the signal at δ 5.98 (HG) to collapse to a br d (J =
10 Hz), whilst the signal at 5.25 (HF) sharpened to a ddd ($J = 10$ Hz, $J = 2.5$ Hz, $J = 1.5$ Hz). In a COSY experiment (400 MHz, C$_6$D$_6$): HH showed a correlation into HI; HG showed correlations into HF, HD, and HE; HI showed correlations into HH and HC; HF showed correlations into HG, HD and HE; HC showed correlations into HD, HE, HI and HB; HD showed correlations into HF, HG, HC and HE; HB showed correlations into HC and HA. *Exact Mass* calcd. for C$_{12}$H$_{19}$OSi (M$^+$-Bu$^+$): 207.1205; found: 207.1204. *Anal.* calcd. for C$_{16}$H$_{28}$OSi: C 72.66, H 10.67; found: C 72.56, H 10.58.

**Preparation of compound 321 via the alcohol 283 and the selenide 322.** The thermal rearrangement of compound 321 into the bicyclo[3.2.1]octa-2,6-diene 323.

The alcohol 283 was prepared from a mixture of the ketones 281 and 282 as previously described. To a stirred solution of the alcohol 283 (35 mg, 0.12 mmol) in dry
THF (2 mL) at room temperature (argon atmosphere) was added successively, o-nitrophenylselenocyanate (1.3 equiv., 35 mg) and Bu₃P (1.3 equiv., 31 mg). After the mixture had been stirred for 20 min at room temperature, the solvent was removed and the residue was purified by flash chromatography (5:95 Et₂O - petroleum ether; 20 g of silica gel), to give 25 mg of the selenide 322. This yellow solid was not completely pure, but was carried on to the next step without further purification.

To a stirred solution of the reaction product (25 mg) in CH₂Cl₂ (1 mL) at room temperature was added 30% aqueous H₂O₂ (1 mL). The mixture was stirred vigorously for 45 min (the solution became decolourized after approx. 10 min) at room temperature, and then saturated aqueous NaHCO₃ (2 mL) and Et₂O (5 mL) were added to the mixture. The phases were separated and the aqueous layer was extracted with Et₂O (3 x 3 mL). The combined organic extracts were washed with brine (2 mL), dried and concentrated. Flash chromatography of the residual oil (3:97 Et₂O - petroleum ether; 12 g of silica gel), followed by distillation of the oil thus obtained (160-175°C/6 Torr) gave 14.5 mg (44% from the alcohol 283, 29 % from the mixture of the ketones 281 and 282) of the compound 323, a colourless oil which exhibited ir (neat): 3051, 1256, 1093, 775 cm⁻¹; ¹H nmr (400 MHz, C₆D₆) δ: 0.12 (s, 6H, -SiMe₂), 1.04 (s, 9H, -SiBu₃), 1.53 (s, 3H, -Me), 1.60 (br d, 1H, HE, J = 17 Hz), 1.63 (d, 1H, HA, J = 9 Hz), 1.82-1.96 (m, 3H, -OCH₂CH₂- and HB), 2.08 (br dd, 1H, HD, J = 17 Hz, J = 5 Hz), 2.66 (m, 1H, HC), 5.64 (dd, 1H, HG, J = 5.5 Hz, J = 2.5 Hz), 5.71 (m, 1H, HF), 6.08 (d, 1H, HH, J = 5.5 Hz). In decoupling experiments irradiation at δ 6.08 (HH) caused the signal at δ 5.64 (HG) to collapse to a d (J = 2.5 Hz); irradiation at δ 5.64 (HG) caused the signal at δ 6.08 (HH) to collapse to a s, whilst the signal at δ 2.66 (HC) sharpened to a dd (J = 5.5 Hz, J = 5 Hz); irradiation at δ 3.80 (-OCH₂CH₂-) caused the signal at δ 1.82-1.96 (-OCH₂CH₂- and HB) to simplify to signals at δ 1.85 (d, J = 13 Hz), δ 1.93 (d, J = 13 Hz) and δ 1.88 (dd, HB, J = 9 Hz, J = 5 Hz); irradiation at δ 2.66 (HC) caused the signal at δ 5.64 (HG) to collapse to a d (J = 5.5 Hz), whilst the signal at δ 2.08 (HD) collapsed to a br d (J = 17 Hz); irradiation at
δ 2.08 (H_D) caused the signal at δ 1.60 (H_E) to collapse to a br. Exact Mass calcd. for C_{13}H_{21}O_{5}Si (M^{+}-Bu): 221.1363; found: 221.1352; cims (positive ion detection, NH_3): 279 (M^{+}+H).

Preparation of compound 324 via the α-phenylselenoketones 325, and the rearrangement of this compound into the bicyclo[3.2.1]octa-2,6-diene 326

![Chemical Structures](image)

To a cold (-78°C) stirred solution of the ketone 278 (104 mg, 0.37 mmol) in dry THF (3 mL) (argon atmosphere) was added a solution of lithium diisopropylamide (2 equiv., 0.5 M) in THF. After the mixture had been stirred for 30 min at -78°C and 20 min at -20°C, it was re-cooled to -78°C and a solution of PhSeBr (prepared from PhSeSePh (150 mg,
2.6 equiv.) and Br\(_2\) (48 mg, 2.5 equiv., in 2 mL of dry THF) was added, via cannula. After the mixture had been stirred at -78°C for 20 min, saturated aqueous NaHCO\(_3\) (3 mL) and Et\(_2\)O (5 mL) were added and the vigorously stirred mixture was allowed to warm to room temperature. The phases were separated, the aqueous phase was extracted with Et\(_2\)O (2 x 5 mL), and the combined organic extracts were washed with brine (3 mL), dried (MgSO\(_4\)) and concentrated. Flash chromatography of the residual oil (15:85 Et\(_2\)O - petroleum ether; 30 g of silica gel) gave 121 mg (75%) of the selenides 325 (after removal of traces of solvent under reduced pressure; room temperature/0.5 Torr). This yellow oil was carried on to the next step without further purification.

To a stirred solution of the selenides 325 (50 mg, 0.11 mmol) in DME (2 mL) at room temperature, was added solid NaIO\(_4\) (3 equiv. 66 mg). A few drops of water were added, and the mixture was stirred at room temperature overnight. Saturated aqueous NaHCO\(_3\) (2 mL) and Et\(_2\)O (5 mL) were added, the phases were separated and the aqueous phase was extracted with Et\(_2\)O (2 x 3 mL). The combined organic extracts were dried (MgSO\(_4\)) and concentrated. Flash chromatography of the residual oil (35:65 Et\(_2\)O - petroleum ether; 25 g of silica gel) followed by distillation of oil thus obtained (120°C/0.2 Torr), gave 26 mg (80%) of the compound 326, a colourless oil which exhibited IR (neat): 3033, 1770, 1256, 837 cm\(^{-1}\); \(^1\)H nmr (400 MHz, C\(_6\)D\(_6\)) \(\delta\): 0.05 (s, 6H, -SiMe\(_2\)), 0.99 (s, 9H, -SiBu\(_t\)), 1.62 (m, 1H, HC or HB), 2.03 (td, 2H, -OCH\(_2\)CH\(_2\)-, \(J = 6\) Hz, \(J = 1.5\) Hz), 2.27 (m, 1H, HB or HC), 2.88 (m, 1H, HA), 3.43 (m, 2H, -OCH\(_2\)CH\(_2\)-), 4.44 (br d, HD, \(J = 6.5\) Hz), 5.15 (m, 1H, HF), 5.32 (dm, 1H, HE, \(J = 6.5\) Hz), 5.82 (m, 1H, HG). In decoupling experiments, irradiation at \(\delta\) 2.03 (-OCH\(_2\)CH\(_2\)-) caused the signal at \(\delta\) 5.32 (HF) to sharpen to a dd (\(J = 6.5\) Hz, \(J = 1.5\) Hz), whilst the signal at \(\delta\) 3.43 (-OCH\(_2\)CH\(_2\)-) collapsed to a s; irradiation at \(\delta\) 2.88 (HA) caused the signal at \(\delta\) 5.32 (HF) to collapse to a m, whilst the signal at \(\delta\) 5.15 (HF) sharpened to a dddd (\(J = 11\) Hz, \(J = 3.5\) Hz, \(J = 3.5\) Hz, \(J = 1\) Hz); irradiation at \(\delta\) 3.43 (-OCH\(_2\)CH\(_2\)-) caused the signal at \(\delta\) 2.03 (-OCH\(_2\)CH\(_2\)-) to collapse to a d (\(J = 1.5\) Hz); irradiation at \(\delta\) 4.44 (HD) caused the signal at \(\delta\) 5.82 (HG) to
sharpen to a ddd ($J = 11$ Hz, $J = 2$ Hz, $J = 2$ Hz), whilst the signal at $\delta 5.15$ ($HF$) sharpened to a dddd ($J = 11$ Hz, $J = 3.5$ Hz, $J = 3.5$ Hz, $J = 1.5$ Hz), and the signal at $\delta 5.32$ ($HF$) sharpened to a dt ($J = 6.5$ Hz, $J = 1.5$ Hz); irradiation at $\delta 5.32$ ($HF$) caused the signal at $\delta 2.03$ ($-OCH_2CH_2$-) to collapse to a t ($J = 6.5$ Hz); irradiation at $\delta 5.82$ ($HG$) caused the signal at $\delta 4.44$ ($HD$) to collapse to a br s. *Exact Mass* calcd. for $C_{16}H_{26}O_2Si$ ($M^+$): 278.1702; found: 278.1698.

**General Procedure P.** Determination of the rate constants for the Cope rearrangements of the 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes 215 into the corresponding bicyclo[3.2.1]octa-2,6-dienes 216.

The general procedure which was used to determine the rate of Cope rearrangement of 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes is exemplified by that used to determine the rate of rearrangement of compound 291 into compound 292. Thus, the ketone 278 (50 mg, 0.18 mmol) was converted to the silyl enol ether 291 as described previously. After extractive workup, the solvent was removed by rotary evaporation at room temperature
(heating was avoided in order to prevent the Cope rearrangement from occurring before beginning the kinetic measurements). All remaining volatile material was removed from the crude reaction product under reduced pressure (room temperature, 0.5 Torr) to give 67 mg of the crude compound 291. A sample of this oil (15 mg, 38 µmol) was dissolved in enough benzene-d₆ (0.8 mL) to fill a 5 mm nmr tube to 3 cm. The solution was carefully transferred to a dry, base washed 5 mm nmr tube, which was then placed in the probe of the nmr spectrometer (Varian XL-300). A spectrum was recorded (see text). This spectrum represented the situation at t = 0, at which time no Cope rearrangement had occurred. The variable temperature unit was activated and was set at 40°C. This setting actually achieves a temperature of 43°C, as shown by a calibration experiment using ethylene glycol as the standard. The required temperature (43°C) was reached after only a few seconds (as indicated by the digital temperature gauge of the spectrometer). Spectra were then recorded at time intervals (see text), and the relative amounts of 291 compared to the rearrangement product 292 were determined by integration of the signals at δ 5.88 (H_D for 291) and 6.17 (H_G for 292). The fraction of 291 remaining after time t (seconds) is listed below in Table 13. A plot of time (s) versus ln([291]/[291]+[292]) was carried out using "Cricketgraph" software on a Macintosh SE computer. The plot produces a set of points of which the line of best fit (as calculated by the "Cricket Graph" software) has a slope -3.7 x 10⁻⁵ s⁻¹.

The Cope rearrangements of other 6-endo-(1-alkenyl)bicyclo[3.1.0]hex-2-enes were observed in a similar manner. In each case, the ratios of rearranged to unrearranged substrate were determined by integration of well dispersed, diagnostic peaks for these compounds (usually the olefinic peaks). For substrates which undergo rapid Cope rearrangement, the experiment was usually continued until 3 half lives had been observed (after 3 half lives the integration becomes less accurate). For substrates which undergo relatively slow Cope rearrangement, the experiment was usually stopped after two half lives. The probe temperature calibration was performed immediately after each experiment.
Table 13. Kinetic data for the rearrangement of 291 into 292 at 43°C.

<table>
<thead>
<tr>
<th>Time, s</th>
<th>([291]/[291]+[292])</th>
<th>(\ln([291]/[291]+[292]))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>5400</td>
<td>0.83</td>
<td>-0.19</td>
</tr>
<tr>
<td>10,800</td>
<td>0.68</td>
<td>-0.38</td>
</tr>
<tr>
<td>16,200</td>
<td>0.56</td>
<td>-0.57</td>
</tr>
<tr>
<td>18,000</td>
<td>0.53</td>
<td>-0.63</td>
</tr>
<tr>
<td>19,800</td>
<td>0.50</td>
<td>-0.69</td>
</tr>
<tr>
<td>32,400</td>
<td>0.31</td>
<td>-1.18</td>
</tr>
<tr>
<td>36,000</td>
<td>0.27</td>
<td>-1.32</td>
</tr>
<tr>
<td>37,800</td>
<td>0.25</td>
<td>-1.39</td>
</tr>
</tbody>
</table>

The rearrangement of compound 293 to compound 294

![Chemical Structures](293.png) ![Chemical Structures](294.png)
The ketone 279 (10 mg, 28 µmol) was converted into the enol silyl ether 293 as described previously. All volatile material was removed from the crude reaction product under reduced pressure (room temperature, 0.5 Torr), to give 13 mg of the crude compound 293. This oil (13 mg, 28 mmol) was dissolved in benzene-d₆ (0.8 mL), the solution was carefully transferred to a dry, base washed nmr tube and the rearrangement was carried out as described in general procedure P. The relative amounts of 293 and the rearrangement product 294 which were present after time t seconds were measured by integration of the signals at δ 5.80 (Hₓ 293) and 5.58 (Hᶠ 294). The fraction of 293 remaining after time t seconds is listed below (Table 15).

A plot of time (s) versus ln([293]/[293]+[294]) produces a set of points which best fit a straight line (see text) of slope \(-2.6 \times 10^{-5} \text{ s}^{-1}\).

| Table 15. Kinetic data for the rearrangement of 293 into 294 at 43°C. |
|-----------------|-----------------|-----------------|
| **Time, s**     | **[293]/[293]+[294]** | **ln([293]/[293]+[294])** |
| 0               | 1               | 0               |
| 14400           | 0.67            | -0.40           |
| 21600           | 0.54            | -0.61           |
| 25200           | 0.52            | -0.66           |
| 48600           | 0.28            | -1.27           |
The rearrangement of compound 296 into compound 297

The ketone 280 (10 mg, 32 μmol) was converted to the silyl enol ether 296 as described previously. All volatile material was removed from the crude reaction product under reduced pressure (room temperature, 0.5 Torr), to give 12 mg (28 μmol) of the crude compound 296. This oil was dissolved in benzene-d₆ (0.8 mL), the solution was carefully transferred to a dry, base washed nmr tube and the rearrangement was carried out as described in general procedure P. The relative amounts of 296 and the rearrangement product 297 which were present after time t seconds were measured by integration of the 2-proton signals at δ 3.45 (-OCH₂CH₂-, 296) and 3.57 (-OCH₂CH₂-, 297). The fraction of 296 remaining after time t seconds is listed below (Table 16).

A plot of time (s) versus ln([296]/[296]+[297]) produces a set of points which best fit a straight line (see text) of slope \(-2.3 \times 10^{-4} \text{ s}^{-1}\).
Table 16. Kinetic data for the rearrangement of 296 into 297 at 43°C.

<table>
<thead>
<tr>
<th>Time, s</th>
<th>[296]/[296]+[297]</th>
<th>\ln([296]/[296]+[297])</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.92</td>
<td>-0.08</td>
</tr>
<tr>
<td>1800</td>
<td>0.55</td>
<td>-0.60</td>
</tr>
<tr>
<td>2100</td>
<td>0.53</td>
<td>-0.63</td>
</tr>
<tr>
<td>2400</td>
<td>0.49</td>
<td>-0.71</td>
</tr>
<tr>
<td>4200</td>
<td>0.32</td>
<td>-1.14</td>
</tr>
<tr>
<td>4800</td>
<td>0.28</td>
<td>-1.27</td>
</tr>
<tr>
<td>7200</td>
<td>0.18</td>
<td>-1.71</td>
</tr>
</tbody>
</table>

The rearrangement of compound 298 into compound 299

The cis divinylcyclopropane 298 was prepared from a mixture of the ketones 281 and 282 (10 mg, 34 \(\mu\)mol, 4:1 respectively, by glc analysis) as described previously. All volatile material was removed from the crude reaction product under reduced pressure (room
temperature, 0.5 Torr), and the residual oil (12 mg, 29 mmol) was dissolved in benzene-d$_6$
(0.8 mL). The solution was carefully transferred to a dry, base washed nmr tube and the
rearrangement was carried out at 43°C as described in general procedure P. The relative
amounts of 298 and the rearrangement product 299 present after time $t$ seconds was
measured by integration of the signals at $\delta$ 4.32 (H$_X$ 298) and 5.86 (H$_Y$ 299). The fraction
of 298 remaining after time $t$ seconds is listed below (Table 17).

A plot of time (s) versus $\ln([298]/[298]+[299])$ produces a set of points which best
fit a straight line (see text) of slope -$1.1 \times 10^{-4}$ s$^{-1}$.

Table 17. Kinetic data for the rearrangement of 298 into 299 at
43°C.

<table>
<thead>
<tr>
<th>Time, s</th>
<th>$[298]/([298]+[299])$</th>
<th>$\ln([298]/([298]+[299])$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2400</td>
<td>0.72</td>
<td>-0.33</td>
</tr>
<tr>
<td>5400</td>
<td>0.58</td>
<td>-0.55</td>
</tr>
<tr>
<td>6300</td>
<td>0.51</td>
<td>-0.67</td>
</tr>
<tr>
<td>7200</td>
<td>0.46</td>
<td>-0.77</td>
</tr>
<tr>
<td>8100</td>
<td>0.42</td>
<td>-0.87</td>
</tr>
<tr>
<td>12000</td>
<td>0.27</td>
<td>-1.32</td>
</tr>
<tr>
<td>14400</td>
<td>0.20</td>
<td>-1.61</td>
</tr>
</tbody>
</table>
The rearrangement of compound 301 into compound 302

The compound 301 was prepared from a mixture of the ketones 285 and 286 (18 mg, 56 µmol, 4:1 respectively, by glc analysis) as described previously. All volatile material was removed from the crude reaction product under reduced pressure (room temperature, 0.5 Torr) to give 22 mg of the crude silyl enol ether 301. A sample of this oil (16 mg, 37 µmol) was dissolved in benzene-d6 (0.8 mL). The solution was carefully transferred to a dry, base washed nmr tube and the kinetic measurements were carried out as described in general procedure P. The relative amounts of 301 and the rearrangement product 302 which were present after time t seconds were measured by integration of the signals at δ 4.25 (HX 301) and 5.93 (HY 302). The fraction of 301 remaining after time t seconds is listed below (Table 18).

A plot of time (s) versus ln[([301]/[301]+[302])] produces a set of points which best fit a straight line (see text) of slope $-4.5 \times 10^{-4}$ s$^{-1}$. 
Table 18. Kinetic data for the rearrangement of 301 into 302 at 43°C.

<table>
<thead>
<tr>
<th>Time, s</th>
<th>[301]/[301]+[302]</th>
<th>ln([301]/[301]+[302])</th>
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<tr>
<td>0</td>
<td>0.94</td>
<td>-0.06</td>
</tr>
<tr>
<td>600</td>
<td>0.67</td>
<td>-0.40</td>
</tr>
<tr>
<td>1200</td>
<td>0.49</td>
<td>-0.71</td>
</tr>
<tr>
<td>1500</td>
<td>0.45</td>
<td>-0.80</td>
</tr>
<tr>
<td>2400</td>
<td>0.32</td>
<td>-1.14</td>
</tr>
<tr>
<td>2700</td>
<td>0.28</td>
<td>-1.28</td>
</tr>
<tr>
<td>3000</td>
<td>0.24</td>
<td>-1.44</td>
</tr>
<tr>
<td>4500</td>
<td>0.11</td>
<td>-2.17</td>
</tr>
</tbody>
</table>

The rearrangement of compound 305 into the compound 306

The ketone 279 (30 mg, 85 μmol) was converted into the enol triflate 305 as described previously. Flash chromatography (1:9 Et2O - petroleum ether; 25 g of silica gel)
of the crude reaction product gave 30 mg of the compound 305 (after removal of traces of solvent under reduced pressure; room temperature, 0.5 Torr). A sample of this oil (16 mg, 33 mmol) was dissolved in benzene-d6 (0.8 mL), the solution was carefully transferred to a dry, base washed nmr tube and the rearrangement was carried out as described in general procedure P. The relative amounts of 305 and the rearrangement product 306 which were present after time t seconds were measured by integration of the signals at δ 5.49 (Hx, 305) and 5.16 (Hp, 306). The fraction of 305 remaining after time t seconds is listed below (Table 19).

A plot of time (s) versus ln([305]/[305]+[306]) produces a set of points which best fit a straight line (see text) of slope -2.9 x 10⁻⁴ s⁻¹.

Table 19. Kinetic data for the rearrangement of 305 into 306 at 43°C.

<table>
<thead>
<tr>
<th>Time, s</th>
<th>[305]/[305]+[306]</th>
<th>ln([305]/[305]+[306])</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1200</td>
<td>0.68</td>
<td>-0.39</td>
</tr>
<tr>
<td>2400</td>
<td>0.48</td>
<td>-0.73</td>
</tr>
<tr>
<td>3000</td>
<td>0.42</td>
<td>-0.88</td>
</tr>
<tr>
<td>5100</td>
<td>0.25</td>
<td>-1.38</td>
</tr>
<tr>
<td>6000</td>
<td>0.16</td>
<td>-1.85</td>
</tr>
</tbody>
</table>
The rearrangement of compound 308 into compound 309.

The α-phenylthio ketone 307 (27 mg, 58 µmol) was converted to the silyl enol ether 308 as described previously. All volatile material was removed from the crude reaction product under reduced pressure (room temperature, 0.5 Torr), to give 20 mg (35 µmol) of the crude compound 308. This oil was dissolved in benzene-d₆ (0.8 mL), the solution was carefully transferred to a dry, base washed nmr tube and the rearrangement was carried out as described in general procedure P. The relative amounts of 308 and the rearrangement product 309 which were present after time t seconds were measured by integration of the signals at δ 5.75 (Hₓ, 308) and 6.13 (Hₓ, 309). The fraction of 308 remaining after time t seconds is listed below (Table 20).

A plot of time (s) versus ln([308]/[308]+[309]) produces a set of points which best fit a straight line (see text) of slope \(-1.5 \times 10^{-5}\) s\(^{-1}\).
Table 20. Kinetic data for the rearrangement of 308 into 309 at 43°C.

<table>
<thead>
<tr>
<th>Time, s</th>
<th>$[308]/[308]+[309]$</th>
<th>$\ln([308]/[308]+[309])$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>14400</td>
<td>0.81</td>
<td>-0.21</td>
</tr>
<tr>
<td>28800</td>
<td>0.67</td>
<td>-0.40</td>
</tr>
<tr>
<td>50400</td>
<td>0.47</td>
<td>-0.75</td>
</tr>
</tbody>
</table>

The rearrangement of compound 311 into compound 312

The crude $\beta$-keto ester 310 (17 mg, 42 μmol) was converted into the silyl enol ether 311 as described previously. All volatile material was removed from the crude reaction product under reduced pressure (room temperature, 0.5 Torr), to give 18 mg (30 μmol) of the crude compound 311. This oil was dissolved in benzene-$d_6$ (0.8 mL), the solution was carefully transferred to a dry, base washed nmr tube and the rearrangement was carried out as
described in general procedure P. The relative amounts of 311 and the rearrangement product 312 which were present after time t seconds were measured by integration of the signals at δ 5.67 (Hx, 311) and 6.18 (HG, 312). The fraction of 311 remaining after time t seconds is listed below (Table 21).

A plot of time (s) versus ln([311]/[311]+[312]) produces a set of points which best fit a straight line (see text) of slope -6.2 x 10^{-5} s^{-1}.

<table>
<thead>
<tr>
<th>Time, s</th>
<th>[311]/[311]+[312]</th>
<th>ln([311]/[311]+[312])</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>11400</td>
<td>0.53</td>
<td>-0.63</td>
</tr>
<tr>
<td>12600</td>
<td>0.49</td>
<td>-0.70</td>
</tr>
<tr>
<td>22800</td>
<td>0.24</td>
<td>-1.41</td>
</tr>
<tr>
<td>24000</td>
<td>0.23</td>
<td>-1.46</td>
</tr>
</tbody>
</table>

The rearrangement of compound 313 into compound 315
The unsaturated esters 314 (15.5 mg, 38 µmol) were converted into the deconjugated ester 313 as described previously. All volatile material was removed from the crude reaction product under reduced pressure (room temperature, 0.5 Torr), to give 14 mg (34 µmol) of the crude compound 313. This oil was dissolved in benzene-d6 (0.8 mL), the solution was carefully transferred to a dry, base washed nmr tube and the rearrangement was carried out as described in general procedure P. The relative amounts of 313 and the rearrangement product 315 which were present after time t seconds were measured by integration of the signals at δ 5.53 (Hx, 313) and 6.10 (HG, 315). The fraction of 313 remaining after time t seconds is listed below (Table 22).

A plot of time (s) versus ln([313]/[313]+[315]) produces a set of points which best fit a straight line (see text) of slope $-1.5 \times 10^{-4}$ s$^{-1}$.

<table>
<thead>
<tr>
<th>Time, s</th>
<th>[313]/[313]+[315]</th>
<th>ln([313]/[313]+[315])</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1800</td>
<td>0.69</td>
<td>-0.37</td>
</tr>
<tr>
<td>3600</td>
<td>0.60</td>
<td>-0.51</td>
</tr>
<tr>
<td>3900</td>
<td>0.53</td>
<td>-0.63</td>
</tr>
<tr>
<td>8100</td>
<td>0.28</td>
<td>-1.27</td>
</tr>
</tbody>
</table>
The rearrangement of compound 316 into compound 320

The crude selenide 318 (17 mg, 36 μmol) was converted to the alkene 316 as described previously. Flash chromatography (3:97 Et₂O - petroleum ether; 10 g of silica gel) of the crude reaction product, gave 7 mg (27 μmol) of the alkene 316 [after removal of traces of solvent under reduced pressure (room temperature, 6 Torr)]. This oil was dissolved in benzene-d₆ (0.8 mL), the solution was carefully transferred to a dry, base washed nmr tube and the rearrangement was carried out as described in general procedure P. The relative amounts of 316 and the rearrangement product 320 which were present after time t seconds were measured by integration of the signals at δ 5.33 (Hₓ, 316) and 6.09 (HH, 320). The fraction of 316 remaining after time t seconds is listed below (Table 23).

A plot of time (s) versus ln([316]/[316]+[320]) produces a set of points which best fit a straight line (see text) of slope -9 x 10⁻⁵ s⁻¹.
Table 23. Kinetic data for the rearrangement of 316 into 320 at 43°C.

<table>
<thead>
<tr>
<th>Time, s</th>
<th>[316]/[316]+[320]</th>
<th>ln{[316]/[316]+[320]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>3600</td>
<td>0.67</td>
<td>-0.40</td>
</tr>
<tr>
<td>6000</td>
<td>0.57</td>
<td>-0.56</td>
</tr>
<tr>
<td>6600</td>
<td>0.53</td>
<td>-0.62</td>
</tr>
<tr>
<td>13200</td>
<td>0.30</td>
<td>-1.21</td>
</tr>
</tbody>
</table>

The rearrangement of compound 321 into compound 323

\[
\begin{align*}
\text{H}_Y & \quad \text{H}_X \\
\text{OTBDMS} & & \\
\text{321} & & \\
\text{TDBMSO} & & \\
\text{HH} & & \text{323}
\end{align*}
\]

The crude selenide 322 (25 mg, 52 µmol) was converted into the alkene 321 as described previously. Flash chromatography (3:97 Et2O - petroleum ether, 12 g of silica gel) of the crude reaction product, gave 10 mg (35 µmol) of the alkene 321 [after removal of traces of solvent under reduced pressure (room temperature, 6 Torr)]. This oil was dissolved in benzene-d6 (0.8 mL), the solution was carefully transferred to a dry, base washed nmr tube and the rearrangement was carried out as described in general procedure P. It was found
that significant rearrangement had occurred during preparation of this substrate. The relative amounts of 321 and the rearrangement product 323 which were present after time t seconds were measured by integration of the signals at δ 5.16 (H₇, 321) and 6.08 (H₈, 323). The fraction of 321 remaining after time t seconds is listed below (Table 24).

A plot of time (s) versus ln([321]/[321]+[323]) produces a set of points which best fit a straight line (see text) of slope $-6.8 \times 10^{-4}$ s⁻¹.

<table>
<thead>
<tr>
<th>Time, s</th>
<th>[321]/[321]+[323]</th>
<th>ln([321]/[321]+[323])</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.73</td>
<td>-0.31</td>
</tr>
<tr>
<td>900</td>
<td>0.37</td>
<td>-0.99</td>
</tr>
<tr>
<td>1800</td>
<td>0.21</td>
<td>-1.56</td>
</tr>
<tr>
<td>3000</td>
<td>0.10</td>
<td>-2.30</td>
</tr>
<tr>
<td>3900</td>
<td>0.05</td>
<td>-3.0</td>
</tr>
</tbody>
</table>

Table 24. Kinetic data for the rearrangement of 321 into 323 at 43°C.


36. This intramolecular cross coupling reaction is based on the intermolecular cross coupling methodology developed by Stille. See reference 27.


130. Ethyl 3-iodopropanoate was prepared from commercially available ethyl 3-chloropropanoate via reaction with NaI. See Experimental section for Part 3 of this thesis.


145. The lines of best fit were calculated from the kinetic data using Cricket Graph software on a Macintosh computer.
