A NEW SYNTHESIS OF UNSATURATED NITRILES.
TOTAL SYNTHESIS OF STEPHALIC ACID

by
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B. Sc. (Hons), Massey University (N. Z.), 1986

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We accept this thesis as conforming
to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA
July 1990

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Date 10 July 1990
ABSTRACT

This thesis describes the total synthesis of (±)-stephalic acid (96), the development of methodology for the conversion of ketones into α,β-unsaturated nitriles and exploratory studies aimed at developing a synthetic approach to cis-clerodane diterpenoids.

In the total synthesis of (±)-stephalic acid (96), the ketone 94 (previously synthesized from 3-methyl-2-cyclohexen-1-one (105)) was converted into the enol trifluoromethanesulfonate (triflate) 108. The enol triflate 108 was coupled with lithium cyanide in the presence of a Pd(0) catalyst to provide the α,β-unsaturated nitrile 102. The latter substance was transformed into the α,β-unsaturated aldehyde 104, which was stereoselectively converted into the enol silyl ether 111. A novel triisobutylaluminum-promoted Claisen rearrangement-reduction process converted the enol allyl ether 103, obtained from the enol silyl ether 111, into the diene alcohol 118. The diene alcohol 118 was transformed via a series of reactions into (±)-stephalic acid (96).

Conversion of the ketone 94 into the α,β-unsaturated nitrile 102 required the development of new methodology for the conversion of ketones into the corresponding α,β-unsaturated nitriles. Reaction of the enol triflates 158 and 162-167 with lithium cyanide in benzene (room temperature) in the presence of catalytic amounts of 12-crown-4 and tetrakistriphenylphosphinepalladium(0) provided the α,β-unsaturated nitriles 168 and 170-175, respectively.

Conversion of the ketone 92 (previously synthesized from 2-methyl-2-cyclohexen-1-one (191)) into the enol silyl ether 204 was accomplished via an eight step sequence. Several features of this sequence should prove useful in the development of synthetic routes to the cis-clerodane family of diterpenoids.
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<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>9-BBn</td>
<td>9-borabicyclo[3.3.1.]nonane</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>CSA</td>
<td>10-camphorsulfonic acid</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazobicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-N,N-dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent(s)</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>glc</td>
<td>gas-liquid-chromatography</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HETCOR</td>
<td>heteronuclear correlation spectroscopy</td>
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<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>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonate</td>
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<td>Description</td>
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<tr>
<td>--------------</td>
<td>-------------</td>
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<tr>
<td>nmr</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser enhancement</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>py</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>SINEPT</td>
<td>selective insensitive nuclei enhanced by polarization transfer</td>
</tr>
<tr>
<td>Sia</td>
<td>-CH(CH$_3$)CH(CH$_3$)$_2$</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>tert</td>
<td>tertiary</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>tlc</td>
<td>thin layer chromatography</td>
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<tr>
<td>p-TsOH</td>
<td>para-toluenesulfonic acid</td>
</tr>
<tr>
<td>Ts</td>
<td>para-toluenesulfonyl</td>
</tr>
<tr>
<td>X</td>
<td>chlorine, bromine or iodine</td>
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<tr>
<td>Δ</td>
<td>heat</td>
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INTRODUCTION

General Introduction

The number and structural complexity of natural products being reported attests to the importance of total synthesis within the discipline of synthetic organic chemistry. The concluding decade has seen increasingly larger and more intricate natural products succumb to the efforts of total synthesis. In much of this work, a particular emphasis has been placed on compounds exhibiting biological activities. A pertinent example is the synthesis of palytoxin which contains 129 carbon atoms and 65 chiral centers and exhibits the highest toxicity of any non-peptidal substance known.

The design of such intricate synthetic sequences necessitates a logical method for theoretically disconnecting the target molecule into smaller fragments. A systematic approach, which was developed in the mid 1960s, depends on the perception of structural features in the target and the manipulation of these structures in the reverse-synthetic sense. This method is now known as retrosynthetic or antithetic analysis.

"Retrosynthetic (or antithetic) analysis is a problem-solving technique for transforming the structure of a synthetic target (TGT) molecule to a sequence of progressively simpler structures along a pathway which ultimately leads to simple or commercially available starting materials for a chemical synthesis. The transformation of a molecule to a synthetic precursor is accomplished by the application of a transform, the exact reverse of a synthetic reaction, to a target structure." 2

For example, application of the Diels-Alder transform to cyclohexene (1) leads to the synthetic precursors 1,3-butadiene (2) and ethylene (3) (equation 1).
The minimum substructural element, in a target, which suggests the application of a particular transform is termed a *retron*. Thus, identification of cyclohexene (1) as the retron in equation 1 was guided by recognizing that this unit can be disconnected to simple precursors by the Diels-Alder transform. Identification of the retron cyclohexenone (7) in structure 4 suggests the Robinson annulation transform and the starting materials 5 and 6 (equation 2). Similarly, the δ,γ-unsaturated carbonyl retron 11 that exists in 8 suggests the use of the Claisen rearrangement transform and the precursors 9 and 10 (equation 3).
Identification of retrons is most effective when the corresponding transform is high on the hierarchical scale of importance with regard to simplifying power. For example, a transform which produces two structures of approximately equal size and structural complexity is of high merit.

The retrosynthetic analysis of a target which suggests a particular synthetic sequence may be guided by factors other than the application of simplifying transforms. Identification of a potential intermediate or a potential starting material may suggest a structure-goal strategy. Targets with a high level of molecular complexity may require a different approach. For example, disconnection to a simpler molecular fragment in which the number of stereochemical centers or the number of functional groups are reduced, may suggest stereochemical or functional group-based strategies, respectively.

Synthetic plans may incorporate one or more of these strategies. Syntheses which incorporate two or more of these strategies in a synthetic plan tend to be particularly efficient, especially where this can be achieved via the application of a single transform. Furthermore, by incorporating potential branches at strategic points of the synthetic plan the success of the synthesis can often be ensured when unexpected difficulties are encountered.

Retrosynthetic analysis is not only useful for synthetic planning, but is also a valuable tool for analyzing other syntheses. By applying this technique to syntheses where there is no discussion of the synthetic plan, it is often possible to discern the challenges of a particular synthesis. A partial knowledge of the retrosynthetic plan may also show how key transforms have been used to overcome these challenges. Such knowledge will clearly help synthetic endeavours to related targets.

Clerodane Diterpenoids

Members of a class of natural products known as the clerodanes have been targets in several synthetic endeavours. Thus far there has been no attempt to retrosynthetically
analyze the different synthetic approaches. Following a brief discussion of these rather interesting natural products, an analysis of this type will be presented.

The clerodanes are a group of bicyclic diterpenoids found particularly in plants, although they have also been isolated from microorganisms and marine animals. Initially, interest in the clerodanes was generated because a number of these compounds were active as antifeedants. Some clerodane diterpenoids have also been identified as having antitumor, piscicidal, psychotropic and antibiotic biological activities. There appears to be a correlation between the type of plants producing biologically active clerodanes and the nature of that clerodane's biological activity. For example, the clerodanes isolated from the plant family Verbinaceae are known insect antifeedants. These correlations should be examined carefully, since the crude plant extracts are not always tested for a wide range of activities. Consequently, the correlation may reflect the type of tests that have been performed on a particular plant family rather than being a true indication of the complete spectrum of activity of a particular plant's secondary metabolites.

Clerodane diterpenoids all contain the basic carbon skeleton and are subdivided into two main groups, cis and trans, with respect to the stereochemistry of the ring fusion. The carbon skeleton has been shown to be derived biosynthetically from the labdane skeleton via a prototropism migration followed by rearrangement of the basic skeleton.
Formation of the trans-clerodane series probably occurs via path a which involves a concerted migration of the axial methyl group at C-4 as illustrated in 14 (Scheme 1). The cis-clerodane ring fusion may occur via a "pause" at the carbocation 15 during the skeletal rearrangement, followed by the migration of the pseudoaxial methyl group at C-4 via path b (Scheme 1). These two postulates correlate well with the major structural variations of clerodane diterpenoids: (i) the trans ring fusion is more prevalent than the cis; (ii) the vicinal dimethyl groups at C-8 and C-9 are usually cis but can be trans in rare cases for both the cis and trans series; (iii) an olefinic bond commonly exists between C-3 and C-4.

The clerodanes also show functional group variations. For example: (i) there are variations in the site of oxygenation on the rings, with C-6 oxygenation often being associated with antifeedant properties; (ii) C-17, C-18 and C-19 may have various

* Unless otherwise stated the clerodane numbering system, shown for 12, is referred to throughout.
oxidation levels but C-20 is seldom oxygenated; (iii) the six carbon side chain may incorporate different functionality but often contains 3-furyl, 5(2H)-furanon-2-yl or 3-carboxy-2-propen-2-yl termini.

Previous Synthetic Approaches

Since 1974 several synthetic approaches to clerodane diterpenoids have appeared in the literature. Synthetic efforts were initially directed towards model compounds in order to probe the functionalities responsible for insect antifeedant activity. Several of these exploratory studies have resulted in the delineation of structural and functional group difficulties that must be overcome for a particular synthetic sequence to be successful. Since this early work has been summarized, only the key retrosynthetic disconnections and the more recent syntheses will be discussed.

The principle difficulty encountered in clerodane syntheses is the stereocontrol required for the introduction of the four contiguous chiral centers C-5, C-10, C-9 and C-8. Extensive investigation on the stability of decalin systems has shown that in most cases the trans-ring fusion is thermodynamically favoured over the corresponding cis-ring fusion. Due to this configurational preference for trans-decalones, it is hardly surprising that most research has focused on targets with a trans-ring fusion, where the relative stereochemistry at C-5 and C-10 can be controlled by equilibration. For example, in the synthesis of (±)-isolinaridiol (19), the chloro ketone 16 was cyclized and the resultant product equilibrated in situ with potassium tert-butoxide to yield a 94:6 mixture of the trans- and cis-decalones 17 and 18, respectively (Scheme 2).

The stereochemistry of the secondary methyl group in 17 is also noteworthy. The secondary methyl group prefers to adopt the more stable equatorial orientation and this arrangement corresponds to the relative stereochemistry present in most trans-clerodanes.
However, to date, few syntheses have taken advantage of this fact, but have instead made recourse to topological control elements (for example, hydrogenation of a C-8 exocyclic methylene precursor as illustrated in scheme 4 for the conversion of $39 \rightarrow 40 + 41$, vide infra).\textsuperscript{15}

Methodology for the introduction of the C-9 quarternary chiral center in the clerodanes effectively classifies the clerodane syntheses into four main groups. Each of these approaches, described in the following subsections, are based on the retrosynthetic disconnection of the six carbon side chain to a simpler two or three carbon unit that can later be elaborated into the required functionality. Disconnection of the side chain is followed by identification of the key classifying transform or strategy.
Enolate Alkylation Transform

The application of the enolate alkylation transform has been guided by the recognition of the Robinson annulation retron for assembling the bicyclic framework of clerodane diterpenoids. This structure-goal strategy requires that any functionality present at C-4 or C-5 must already be in place in the starting materials or, at least, latent functionality suitable for future manipulations must be present at this stage. Suitable starting materials for the Robinson annulation must obviously accommodate such functional groups.

The Robinson annulation is illustrated in scheme 3. The reaction is essentially a Michael addition of 1,3-cyclohexanedione (20) to ethyl vinyl ketone (21), followed by an intramolecular aldol reaction. Product 22 was used as the starting material for the synthesis of 23 and 25 (equations 4 and 5 respectively).

\[
\begin{align*}
\text{20} & \quad + \quad \text{21} \\
1. \text{KOH, MeOH} & \quad \rightarrow \quad \text{22} \\
2. & 
\end{align*}
\]

Scheme 3

Dissolving metal reductions of Robinson annulation type products have been studied extensively. Bicyclic enones such as 23, 25 and 27 are usually reduced to the more stable trans-fused enolates, which can be alkylated with appropriate

* The Robinson annulation retron was discussed previously on page 2. The retrosynthetic analysis on page 2 can be contrasted with the synthetic equivalent shown in scheme 3.
electrophiles. The choice of an electrophile seems to be limited to those exhibiting a high reactivity, as can be seen from equations 4, 5 and 6.

\[
\begin{align*}
\text{23} & \quad \text{1. Li, NH}_3 \quad \text{24} \\
\text{OH 25} & \quad \text{1. Li, NH}_3 \quad \text{26} \\
\text{O 27} & \quad \text{1. Li, NH}_3 \quad \text{28}
\end{align*}
\] (4-6)

In each of the products 24, 26 and 28 the ketonic moiety was used to introduce the secondary methyl group and then the vinyl or methoxycarbonyl groups were further elaborated.

The most recent alkylation based strategy for the formation of the quarternary center in a clerodane diterpenoid involves a slightly different approach. Rather than using a ketone enolate where the ketone is part of the ring, the anion derived from a nitrile attached to the ring was employed (see equation 7). Thus, deprotonation of the mixture of nitriles...
29 and 30 (85:15, respectively) with LDA followed by the addition of the alkyl iodide 31 installed the quarternary center in nitrile 32 in high yield.\textsuperscript{14} (The nitriles 29 and 30 were prepared by treatment of the ketone 17 with $(p$-toluenesulfonyl)methyl isocyanide).

\[
\begin{align*}
29 \ R = \text{CN}, \ R' &= \text{H} \\
30 \ R &= \text{H}, \ R' &= \text{CN}
\end{align*}
\]

(7)

Compound 32 was an intermediate in the total synthesis of (±)-isolinaridiol (19) (Scheme 2). A series of steps was required for the conversion of the nitrile moiety in 32 into the requisite methyl group.

**Claisen Rearrangement Transform**

Historically, the Claisen rearrangement was used as a key step in the first successful total synthesis of a clerodane diterpenoid, namely (±)-annonene (42).\textsuperscript{14} Despite this, the Claisen rearrangement approach has neither been repeated nor discussed in reviews. Therefore, a brief discussion will be included here.

The quarternary chiral center at C-9 of (±)- annonene (42) was introduced using a Claisen rearrangement. Conceptually, the application of the Claisen rearrangement to quarternize C-9 is most elegant as it uses structural features inherent in the substrate molecule both to control the stereochemistry and to introduce the somewhat hindered center. Thus, preference for approach of the enol ether from the top face was induced by the angular methyl group, as shown in equations (8) and (9).
In the alternative approach from the lower face (equation 9) an interaction between the olefinic methylene and the angular methyl may cause the transition state to be less favorable. The transformation was accomplished readily in 95% yield. Two isomers were obtained in a ratio of 85:15, with the desired isomer predominating. Unfortunately, stereocontrol and regiocontrol were lacking at other stages of the synthesis,\* and this may partially explain why others have not adopted this strategy.

The synthesis began with the protected Robinson annulation product, the ketone 33\* (Scheme 4). Birch reduction of 33 established the trans-ring junction and yielded the ketone 34. The latter substance was converted into a 1:1 mixture of the unsaturated nitriles 35 and 36 via cyanohydrin formation using potassium cyanide and acetic acid, followed by dehydration with thionyl chloride. Regioisomeric unsaturated nitriles, such as 35 and 36, often result when epimeric mixtures of cyanohydrins are dehydrated.\*20

The nitrile 36 was reduced with diisobutylaluminum hydride, the resulting imine was hydrolyzed to afford the corresponding aldehyde and the aldehyde was reduced with

\* The conversions of 39 \(\rightarrow\) 40 + 41 and 34 \(\rightarrow\) 35 + 36 illustrate examples of poor stereocontrol and regiocontrol respectively (Scheme 4).

\* The ketone 33 was prepared from the ketone 22 (Scheme 3).
sodium borohydride. The resultant alcohol 37 was converted into the allyl vinyl ether 38, using mercuric acetate and ethyl vinyl ether. Claisen rearrangement occurred, as described earlier, upon heating 38 at 200 °C for 6 hours.

Reduction of the aldehyde 39, followed by catalytic hydrogenation of the resultant alkene alcohol provided the alcohols 40 and 41. Unfortunately the ratio of epimers was 1:1, resulting from a complete lack of facial preference in the hydrogenation. The alcohols 40 and 41 were separated and 40 was subsequently converted into (±)-annonene (42) via a series of synthetic transformations.

\[
\begin{align*}
\text{Birch Reduction} & \\
33 & \rightarrow \\
\text{KCN, HOAc} & \\
34 & \rightarrow \\
\text{SOCl}_2, \text{py} & \\
35 & \\
\text{Hg(OAc)}_2 & \\
38 & \rightarrow \\
37 & \\
1. \text{DIBAL; H}^+ & \\
36 & \\
\text{NaBH}_4 & \\
\text{加热} & \\
39 & \rightarrow \\
1. \text{NaBH}_4 & \\
2. \text{H}_2, \text{Pd-C} & \\
40 \ R = \text{CH}_3, \ R' = \text{H} \\
41 \ R = \text{H}, \ R' = \text{CH}_3 & \\
\text{Several steps} & \\
42 & \\
\end{align*}
\]
**Formation of a Bicyclic Precursor Containing Stereocenters 9 and 10**

To date, there has been only one reported synthetic approach to the clerodanes in which the two chiral centers at C-9 and C-10 are introduced concurrent with the formation of the bicyclic framework. Perhaps this is not surprising since, apart from the Diels-Alder reaction, there are few methods by which the stereoselectivity at several asymmetric centers can be secured at the same time. Discovery of this selectivity developed from model studies involving the intramolecular Sakurai reaction (Scheme 5).\(^\text{21}\)

\[\text{43} \xrightarrow{\text{SiMe}_3} \begin{array}{l}
\text{SiMe}_3 \\
\text{SiMe}_3
\end{array}
\]

\[\begin{array}{l}
\text{44} \\
\text{45}
\end{array}\]

\[\begin{array}{l}
\text{TiCl}_4 \\
\text{CH}_2\text{Cl}_2 \\
-78^\circ\text{C}
\end{array}\]

\[\text{46} \quad \text{Trans/Cis} = 3-4:1 \quad \text{after equilibration}\]

Scheme 5

The stereocontrol has been rationalized by considering steric interactions in the possible transition states. Chair-like conformations of the emerging ring in the transition state are presumed to be preferred over the corresponding boat-like conformations. Two possible chair-like conformations of 43 (depicted by 44 and 45) may precede the possible transition states. The Z isomer of 43 should prefer to adopt conformation 44 rather than conformation 45 since the latter conformation is energetically destabilized by the allylic strain between the trimethylsilylmethyl and secondary methyl groups. The E isomer of 43 does not experience a comparable allylic strain in conformation 45 since the allylic strain...
between a hydrogen and a methyl group is less than that between the trimethylsilylmethyl and methyl groups. However, even for the E isomer of 43, the relief of this allylic strain may be sufficient to make conformation 44 energetically more favourable than conformation 45.

An extension of this work has led to the first total synthesis of a cis-clerodane, namely (±)-linaridial (51).22 Entry to the cis-decalin skeleton was achieved by trapping the intermediate titanium enolate 47 with a highly active electrophile from the more sterically accessible face, opposite to the axial tertiary methyl group (Scheme 6). Desulfurization of 48 and subsequent olefination led to the diene 49 which was isomerized to the diene 50. With the installation of the requisite chiral centers, the olefinic side chain present in 50 was further elaborated to complete the synthesis of (±)-linaridial (51).

Scheme 6
Formation of a Monocyclic Precursor Containing Stereocenters 8 and 9

Syntheses which incorporate the two centers that will ultimately become C-8 and C-9 of a clerodane diterpenoid in a monocyclic precursor reduce the steric demands associated with the introduction of these two centers in a bicyclic intermediate.

Ley and co-workers were the first to recognize this approach. A Diels-Alder reaction was used to introduce the correct relative stereochemistry at the two centers that would ultimately become C-8 and C-9. Thus, treatment of the Danishefsky diene 52 with (E)-2-methyl-2-butenal (53) gave, after hydrolysis of the initially formed product, the aldehyde 54 (Scheme 7). Thioacetalization of the aldehyde 54 gave 55. The steric bulk of the thioketal was used to direct the annulation sequence (55 → 57) to the opposite face. Thus, addition of lithium di(3-butenyl)cuprate to 55 gave 56. Compound 56 was converted into the bicyclic enone 57, which was subsequently transformed into (±)-ajugarin (58).
A similar approach, which also begins with a monocyclic precursor that contains the correct stereochemistry at the centers that will become C-8 and C-9 of a clerodane diterpenoid, has allowed an entry into both the cis- and trans-clerodane series.$^{24, 25}$ Explicitly, retrosynthetic disconnection of the clerodane carbon skeleton to two Δ4-octal-3-one retons was central to the synthetic plan since intermediates 59 and 60 allow access to the cis and trans-clerodanes respectively (Scheme 8). Thus, treatment of 59 with lithium dimethylcuprate followed by the addition of formaldehyde gives 61. Compound 61 contains the same relative stereochemistry as the cis-clerodanes. Similarly, treatment of 59 with diethylaluminum cyanide yields 62 which provides an entry to the trans-clerodanes.

![Scheme 8](image)

The bicyclic enones 59 and 60 were synthesized from the enone 63 via a sequence in which the secondary methyl group, present in 63, was used to direct the introduction of all the subsequent chiral centers (Scheme 9).$^{26}$
Thus, conjugate addition of vinylmagnesium bromide-Cu(I)-tri-n-butylphosphine complex to the enone 63, followed by the addition of gaseous formaldehyde, gave the hydroxy ketones 64 and 65 (Scheme 9). The diastereomeric mixture of the hydroxy ketones 64 and 65 (approximately 1:1) gave the mesylates 66 and 67 under standard conditions. Treatment of 66 and 67 with \( RCH_2COCH_2CO_2CH_3 \) (\( R = \text{H or } \text{CH}_3 \)) in the presence of sodium methoxide in methanol, followed by refluxing with acid yielded the bicyclic enones 59 and 60 (\( R = \text{H and } \text{CH}_3 \), respectively).

The most recent application of this divergent strategy to both the *cis* and *trans* clerodanes from the bicyclic enones 59 and 60 illustrates the versatility of this approach.\(^{26}\) The synthetic target was the natural product cascarillone, which was proposed as having the *cis*-clerodane structure 71 (Scheme 10).

Thus, successive treatment of the enone 59 with lithium dimethylcuprate and formaldehyde gave the hydroxy ketone 61. Dehydration of 61 was achieved by mesylation followed by base induced elimination to yield an enone intermediate. This latter
material was smoothly reduced with lithium tri-sec-butylborohydride to afford the cis-ketone 68. Acetalization of 68, followed by a hydroboration-oxidation sequence, secured the aldehyde 69. Addition of 3-furyllithium to 69, acetylation and Birch reduction of the resulting acetate gave the furan 70. Removal of the acetal under acidic conditions led to the expected target 71. Unfortunately, the spectral data for compound 71 did not correlate with that of the natural product cascarillone.

Structural proof for cascarillone was sought by carrying out the total synthesis of the trans-clerodane type compound 73, which is epimeric with 71 at C-4 and C-5 (Scheme 11). Access to the trans-decalone skeleton was achieved by treating the ketone 60 with diethylaluminum cyanide in benzene to provide the trans-cyano ketone 62. In a series of reactions essentially identical with those described for the conversion of 68 into 71.
(Scheme 10), the trans-cyano ketone 62 was converted into the furan 72, which was then transformed into the target 73. Spectral data again showed that the structure of the target, 73, did not correlate with that of the natural product cascarillone.

Scheme 11

At this stage, a sample of the natural product cascarillone was isolated and a series of $^1$H nmr experiments were performed on this sample. On the basis of these experiments the structure of cascarillone was proposed to be as shown in 77 (Scheme 12).

Confirmation of the structural assignment was sought by carrying out the total synthesis of 77.$^{26}$ The starting material for this synthesis was the cyano ketone 62 (Scheme 12). Carbonyl transposition of the ketone moiety of 62 was accomplished by $\alpha$-sulfenylation, ketone reduction, mesylation and elimination to give the vinyl sulfide 74. Treatment of 74 with titanium tetrachloride and acetic acid gave the corresponding ketone, which under standard conditions, was subjected to acetalization to give compound 75. Hydroboration-oxidation of the olefin 75, followed by reduction of the nitrile with diisobutylaluminum hydride gave, after hydrolysis, an intermediate aldehyde. This latter material was deoxygenated using the Wolff-Kishner procedure to give the alcohol 76. Oxidation of the alcohol 76, introduction of the furan side chain as before ($69 \rightarrow 70$, Scheme 10) and removal of the acetal gave the furano ketone 77. Compound 77 exhibited
spectroscopic properties identical to those of cascarrillone, thus confirming the proposed structure and completing the first total synthesis of this natural product.\textsuperscript{26}

\begin{center}
\begin{tikzpicture}
  \node (a) {\begin{tikzcd}
    \text{62} & \text{74} & \text{75} \\
    \text{76} & \text{77}
  \end{tikzcd}};
  \node at (a) [below=1cm] {Scheme 12};
\end{tikzpicture}
\end{center}

Although the merit of these synthetic endeavors to elucidate the structure of cascarrillone is questionable, the versatility of this approach is succinctly illustrated.

**Previous Work**

An interest in clerodane synthesis in our laboratory was stimulated by the development of an efficient annulation method for the assembly of five and six membered rings.\textsuperscript{27, 28} The efficiency of this method results from the incorporation of both a potential nucleophilic and an electrophilic center within the same molecule. The formation of
molecules containing one nucleophilic and one electrophilic center had previously been achieved using organotin methodology.\textsuperscript{29} Thus, reaction of a terminal acetylene 78 with (trimethylstannyl)copper(I)-dimethylsulfide, under suitable conditions, provided the corresponding 2-trimethylstannyl-1-alkenes 79 (equation 10).

\[
\begin{align*}
\text{X} \quad &\quad \text{Me}_3\text{SnCu.SMe}_2 \\
\text{MeOH (60 eq.)} &\quad \rightarrow \quad \text{Me}_3\text{SnMe} \\
\text{78} &\quad \rightarrow \quad \text{79}
\end{align*}
\]

\( n = 1-4 \)

\( X = \text{OH, Cl, OSiBu'Me}_2 \)

O-tetrahydropyryanyl

(10)

The two chloro stannanes 80 and 84 have proven to be synthetically useful bifunctional reagents.\textsuperscript{27, 28} Treatment of 80 or 84 with methyllithium in THF at \(-78^\circ\text{C}\) gives solutions containing the corresponding vinylithium species 81 and 85, respectively (Schemes 13 and 14). These vinylithiums can be converted to organocopper reagents, via the addition of a copper(I) salt, and the resulting species will add to enones in a conjugate sense.\textsuperscript{27, 28} Intramolecular cyclization of the resulting chloro ketones 82 and 86 is accomplished by treatment of these substances with potassium hydride, and the annulated ketones 83 and 87, respectively, are formed cleanly and efficiently.
The sequences shown in schemes 13 and 14 represent methylenecyclopentane and methylenecyclohexane annulation methods respectively. Application of the latter method to cyclohexenones would provide an entry into the bicyclic skeleton of the clerodanes. Thus, formation of the vinyllithium followed by the addition of anhydrous magnesium bromide-etherate, provides the corresponding Grignard reagent (Scheme 15). In the presence of copper(I) bromide-dimethyl sulfide, the Grignard reagent undergoes conjugate addition to a variety of substituted enones. The resulting chloro ketones were cyclized by treatment with potassium hydride in THF.
The cyclized products resulting from intramolecular alkylation were found to contain the cis-ring fusion, although a significant amount of epimerization was observed in those products where cis/trans equilibration could occur. For example, 91 gave only cis-fused 92 while 93 cyclized to a 1:2 mixture of trans and cis-decalones 94 and 95, respectively (equation 11 and scheme 16). The initially formed product mixture was equilibrated to a 3.5:1 ratio of 94 to 95.

The stereochemical difference between the kinetic and thermodynamic products may enable access into both the cis- and trans-clerodanes. For example, 92 may be a
suitable precursor for the cis-clerodanes * while 94 could provide an intermediate suitable for the synthesis of trans-clerodanes. This latter protocol was used previously in the synthesis of the trans-clerodane (±)-isolinaridial (19) (Scheme 2).\textsuperscript{14}

**Research Objectives**

The successful completion of several clerodane syntheses demonstrates that the more common clerodanes can be accessed via previously reported strategies.\textsuperscript{14-16, 21-26} The challenge now would seem to be the successful synthesis of the more unusually functionalized or substituted members of the clerodane family. In particular, the existing strategies seem poorly suited to accommodate a change in the stereochemical orientation of the one-carbon substituent at C-8. Most trans-clerodanes have the one carbon substituent at C-8 in an equatorial, rather than an axial, orientation.

One of the few trans-clerodanes with an axial substituent at C-8 \textsuperscript{30} is stephalic acid (96).\textsuperscript{11c} Stephalic acid was isolated as the polar component of the methanolic extract from *Stevia polycephala*, collected in the state of Tlaxcala, Mexico.\textsuperscript{11c} This particular trans-clerodane is not only structurally novel but is also functionally interesting, being one of the few clerodanes possessing oxygenation at C-20.

\* The relationship between the ketone 92 and the clerodane skeleton 12 is easily seen when 92 is drawn as shown.

\begin{center}
\includegraphics[width=0.2\textwidth]{keto.png}
\end{center}
In a retrosynthetic sense, access to the C-8 substituent of the clerodanes may be possible by using an organocopper reagent to effect the conjugate addition of the requisite methyl group to an activated olefin of part structure 97 (Scheme 17). Furthermore, the previously described methylenecyclohexane annulation method seemed well suited for the formation of the bicyclic framework of (±)-stephalic acid (96). Thus, it was decided to attempt the synthesis of (±)-stephalic acid (96) via a series of reactions in which this annulation method would assume a key role.
DISCUSSION

Retrosynthetic Analysis of (±)-Stephalic Acid (96)

The retrosynthetic analysis of (±)-stephalic acid (96) was based on the recognition of two key transforms for controlling the stereochemistry of the secondary methyl group and for assembling the bicyclic framework. The respective transforms were the previously mentioned organocopper(I) transform and the methylene cyclohexane annulation transform (Schemes 14 and 17). A branch point was incorporated in the strategy to allow for any difficulties that might be encountered during the introduction of the quarternary center at C-9 of (±)-stephalic acid (96).

Disconnection of the carbon-carbon single bond between C-13 and C-16 of (±)-stephalic acid (96), along with appropriate functional group manipulations, would lead to the acetylenic ester 98. Organocuprate additions to acetylenic esters had previously been shown to occur with predictable stereochemistry and should provide access to the requisite cis stereochemistry of the α,β-unsaturated acid moiety in (±)-stephalic acid (96). Identification of the acetylenic ester moiety in 98 as a retron for Corey's dibromoolefin transform leads, retrosynthetically, to the aldehyde 99 and, after several functional group manipulations, to the alcohol 100 (Scheme 18).
The alcohol 100 provided a branch point in the retrosynthetic plan (Scheme 19). Disconnection of the carbon-carbon single bond between C-9 and C-11 in 100, along with appropriate functional group interconversions, would lead to the nitrile 101 and allyl iodide. For steric reasons, alkylation of the nitrile 101 with allyl iodide would be expected to lead to a product with the desired stereochemistry.\textsuperscript{33} Disconnection of the bond between the ring carbon and the secondary methyl group in 101 would lead to the $\alpha,\beta$-unsaturated nitrile 102. The latter retrosynthetic step would be reasonable provided that conjugate addition of the requisite methyl group could be effected.\textsuperscript{34}

Alternatively, identification of the bis-homoallylic alcohol in 100 as a retron for the Claisen rearrangement transform\textsuperscript{35} leads retrosynthetically to the enol vinyl ether 103. A series of functional group manipulations would then allow disconnection of the bond between the ring carbon and the secondary methyl group to give the $\alpha,\beta$-unsaturated
aldehyde 104. The α,β-unsaturated aldehyde 104 was presumed to be available from the α,β-unsaturated nitrile 102.36

Scheme 19

Retrosynthetic conversion of the α,β-unsaturated nitrile 102 to the ketone 94 was made on the basis of reported conversions of ketones to α,β-unsaturated nitriles 37 and a recognition of the presence of a methylenecyclohexane unit. Thus, the ketone 94 would be derived from the vinylstannane 84 and 3-methyl-2-cyclohexen-1-one (105) as described previously (Schemes 16 and 20).28
The Total Synthesis of (±)-Stephalic Acid (96)

The vinylstannane 84 was prepared using a slightly modified version of the reported methodology (Scheme 21).\(^{29}\) Thus, reaction of hexamethylditin with methyllithium in THF (-20 °C, 20 min) provided a pale yellow solution of trimethylstannyl lithium. Formation of (trimethylstannyl)copper(I)-dimethyl sulfide (106) was effected by the addition of solid copper(I) bromide-dimethyl sulfide complex at -78 °C and stirring at -78 °C for 1 h rather than at -63 °C for 20 min as previously reported.\(^{29}\) (Performing the reaction at -78 °C avoids the use of the carcinogenic chloroform/dry ice bath used to maintain a temperature of -63 °C, and also avoids long equilibration times when large volumes are warmed or cooled). Reaction of reagent 106 with 5-chloro-1-pentyne at -78 °C for 6 h, followed by workup and slow column chromatography of the crude product on silica gel, provided 5-chloro-2-trimethylstannyl-1-pentene (84)\(^{29}\) in 82% yield. The \(^1\)H nmr spectrum of 84 shows signals due to the two olefinic protons as a pair of multiplets at \(\delta\) 5.22-5.24 (\(3J_{\text{Sn-H}} = 70\) Hz) and 5.71-5.73 (\(3J_{\text{Sn-H}} = 150\) Hz).
Since it was necessary to use the vinylstannane 84 in relatively large quantities, the stability and reactivity of the corresponding vinyllithium species 85 was briefly examined so that 84 could be used as efficiently as possible. The vinyllithium 85 was previously proposed to suffer intramolecular alkylation on warming to temperatures above -65 °C, to produce methylenecyclobutane (107). In order to verify this assumption a THF solution of the vinylstannane 84 was transmetallated with methyllithium (-78 °C, 20 min) and the resultant solution was warmed to 0 °C for 0.5 h (Scheme 22). Benzyl benzoate was added as an internal standard, and a portion of the resultant solution was removed and analyzed by $^1$H nmr spectroscopy. The $^1$H nmr spectrum (CDCl$_3$ solution) was compared with that previously reported for methylenecyclobutane (107). The three signals due to methylenecyclobutane at $\delta$ 1.99 (quintet, $J = 7$ Hz, homoallylic methylene protons), 2.67 (triplet of triplets, $J = 7$, 2 Hz, allylic methylene protons) and 4.65 (quintet, $J = 2$ Hz, olefinic protons) were readily identified. Comparison of the $^1$H nmr integration of the signals due to the methylene protons of benzyl benzoate ($\delta$ 5.34) and the allylic protons of methylenecyclobutane ($\delta$ 2.67) indicated that methylenecyclobutane (107) had been produced in a yield of approximately 93%. No 5-chloro-2-trimethylstannyl-1-pentene (84) was detected by $^1$H nmr spectroscopy.

The vinylstannane 84 was employed for the methylenecyclohexane annulation of 3-methyl-2-cyclohexen-1-one (105), using a procedure modified slightly from that discussed
previously (Scheme 15). Thus, transmetallation of 84 with methyllithium in THF (-78 °C, 20 min), followed by the addition of solid magnesium bromide-etherate (-78 °C, 20 min), gave the corresponding Grignard reagent 88 (Scheme 23). Successive addition of copper(I) bromide-dimethyl sulfide complex*, boron trifluoride-etherate and 3-methyl-2-cyclohexen-1-one (105) gave a bright yellow slurry which was stirred at -78 °C for 2 hours. After appropriate workup, the chloro ketone 93 was obtained in 91% yield (Scheme 23).

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{SnMe}_3 & \quad \text{MgBr} \\
84 & \quad 88 \\
1. \text{MeLi, THF, -78 °C, 20 min} & \quad 1. \text{CuBr \cdot SMe}_2 \\
2. \text{MgBr}_2 \text{OEt}_2, -78 °C, 20 min & \quad 2. \text{BF}_3 \text{OEt}_2 \\
& \quad 3. 105 \\
& \quad 93
\end{align*}
\]

Scheme 23

The ir spectrum of the chloro ketone 93 exhibits absorptions at 1709 cm\(^{-1}\) and 1636 cm\(^{-1}\), indicating the presence of a saturated six-membered cyclic ketone and a double bond, respectively. The \(^1\)H nmr spectrum shows a triplet at \(\delta 3.51\) (two protons, \(J = 7\) Hz) due to the methylene protons adjacent to a chlorine atom, and two singlets at \(\delta 4.80\) and 4.86, which supported the presence of a disubstituted double bond.

The chloro ketone 93 underwent clean intramolecular alkylation upon exposure to excess potassium hydride in THF to give, after 1 hour, the ketones 94 and 95 in a 1:2 ratio (glc analysis) (Scheme 16). Excess ethanol was added to the reaction mixture and the resultant solution was refluxed for 1 h. Under these conditions the 1:2 mixture of ketones was equilibrated to a 3.5:1 mixture of the trans and cis-ketones 94 and 95, respectively.

* The use of 0.05 equiv of the copper (I) bromide-dimethyl sulfide complex rather than the reported 0.25 equiv gave the chloro ketone 93 in consistently higher yield.
(equation 12). (The glc analysis of a mixture (36:64, \textit{trans}:\textit{cis}) of these ketones showed good correlation with the compound ratios obtained from $^1$H nmr spectroscopy (37:63, \textit{trans}:\textit{cis})). The combined overall yield of the ketones 94 and 95 from 3-methyl-2-cyclohexen-1-one (105) was 82%. The ketones 94 and 95 were separated by preparative liquid chromatography on a Waters Prep LC/System 500 chromatograph, giving 68% and 21% recovery of the respective ketones 94 and 95, in addition to 6% of a mixture of the ketones (76:24, \textit{trans}:\textit{cis}).

\[
\text{Cl} \quad \text{KH, THF} \quad \text{H} \quad \text{O} \\
\text{93} \quad \text{94} \quad + \quad \text{95}
\]

\[
1 : 2 \\
3.5 : 1 \text{ after equilibration with KOEt, EtOH}
\]

(12)

The $^1$H nmr spectrum of the major product 94 shows signals at $\delta$ 0.94 (singlet) for the angular methyl group, and at 4.72-4.77 (multiplet, two protons) due to the olefinic protons. The former value correlated with chemical shifts of angular methyl groups in \textit{trans} and \textit{cis}-1-decalones ($\delta$ 0.75-0.90 and 1.05-1.20, respectively), as reported by Boeckman and co-workers,\textsuperscript{39} and correlated with the $^1$H nmr spectral data previously reported for the \textit{trans}-fused ketone 94.\textsuperscript{28b}

The $^1$H nmr spectrum of 95 exhibits two one-proton olefinic signals at $\delta$ 4.74 and 4.76, both of which were broad singlets. The signal due to the angular methyl group appears at $\delta$ 1.17, in agreement with the assigned \textsuperscript{28b} \textit{cis}-ring fusion and Boeckman's data.\textsuperscript{39}
With ready access to the *trans*-ketone 94, the bicyclic framework of the *trans*-clerodanes could be efficiently assembled. As outlined in the retrosynthetic analysis (Scheme 20), the synthetic plan required that the ketone 94 be converted regioselectively into the α,β-unsaturated nitrile 102. Previous one-carbon homologation methods for the formation of α,β-unsaturated nitriles from ketones 37 often proceed with poor regiocontrol*. In order to overcome the regiochemical problem new methodology was developed for the conversion of ketones into α,β-unsaturated nitriles via a mild two-step one-carbon homologation sequence.

The methodology for synthesizing α,β-unsaturated nitriles, outlined in the second part of the Discussion Section of this thesis, was used to convert the ketone 94 into the α,β-unsaturated nitrile 102. Thus, successive treatment of a THF solution of LDA with a THF solution of the ketone 94 (-78 °C, 2 h) and *N*-phenyltrifluoromethanesulfonimide 40 (-78 °C → 0 °C, overnight) gave, after chromatography of the crude product, the enol triflate 108 in 80% yield (equation 13). The ir spectrum of the enol triflate 108 shows olefinic absorptions at 1681 cm⁻¹ and 1645 cm⁻¹ and a sulfonate symmetric stretch at 1144 cm⁻¹. The ¹H nmr spectrum of 108 exhibits a signal at  δ 1.03 (singlet) due to the angular methyl group, and three signals at 4.64 (broad singlet), 4.72 (broad singlet) and 5.70-5.74 (multiplet) assigned to the two exocyclic and one endocyclic olefinic protons, respectively.

See the conversion of 34 into 35 and 36 in the synthesis of (±)-annonene (42) (Scheme 4, p 12).
Palladium(0)-catalyzed coupling of the enol triflate 108 with lithium cyanide in benzene in the presence of the phase transfer catalyst, 12-Crown-4, proceeded smoothly at room temperature (2 h) to give the α,β-unsaturated nitrile 102. Purification of the crude product by column chromatography on silica gel gave the α,β-unsaturated nitrile 102 in 89% yield (equation 14).

\[
\begin{aligned}
\text{OSO}_2\text{CF}_3 & \quad \text{LiCN, Pd(Ph}_3\text{P})_4, \text{rt} \\
108 & \quad 12\text{-Crown-4, PhH, 2 h} \\
& \quad 102
\end{aligned}
\]

(14)

The presence of the nitrile moiety in 102 was distinctly apparent from the strong absorption at 2213 cm\(^{-1}\) in the ir spectrum. The \(^1\text{H} \) nmr spectrum exhibits the characteristic signal for the angular methyl group at δ 0.95 (three proton singlet), the expected signals for the aliphatic protons at 1.34-2.52 (eleven protons), and resonances for three olefinic protons at 4.61 (one proton singlet), 4.73 (one proton singlet) and 6.61-6.65 (one proton multiplet) (Figure 1). The presence of signals for three olefinic protons in the \(^1\text{H} \) nmr spectrum is consistent with the endocyclic double bond being positioned away from the ring fusion. In addition, the chemical shift (δ 6.61-6.65) of one of the signals is typical of an olefinic proton being oriented cis to a nitrile group,\(^{41}\) and is thus assigned to the proton H\(_c\). Further support for the structure of 102 was obtained from an nOe difference experiment in which irradiation of the signal at δ 6.61-6.65 caused signal enhancement at δ 2.27-2.38 (multiplet). Comparison of the enhanced signals with the \(^1\text{H} \) nmr spectrum of 102 indicates that two protons, assigned as H\(_a\) and H\(_b\), are adjacent to the olefinic proton H\(_c\).
Figure 1: The 400 MHz $^1$H nmr spectrum of the $\alpha,\beta$-unsaturated nitrile 102

The $^{13}$C nmr spectrum of the $\alpha,\beta$-unsaturated nitrile 102 exhibits signals for thirteen unique carbons. Three of these $^{13}$C signals, at $\delta$ 16.6, 44.0 and 144.8, displayed negative amplitudes in an attached proton test (APT) experiment and were consequently assigned to the angular methyl carbon, the ring-fused methine carbon and the olefinic carbon $\beta$- to the nitrile function, respectively. The nitrile carbon was assigned to the resonance at $\delta$ 118.4 on the basis of signals exhibited by comparable systems. The connectivity of 102 was further supported by the results of a SINEPT experiment optimized for a $J_{C,H}$ of 7 Hz. Thus, irradiation of the signal at $\delta$ 6.61-6.65 (H$_c$) gave strong polarization transfer through three-bond coupling to the sp nitrile carbon at 118.4 and to the methine carbon at the ring junction at 44.0.

Having confidently assigned the structure of the $\alpha,\beta$-unsaturated nitrile 102, the conjugate addition of organocopper(I) reagents to the $\alpha,\beta$-unsaturated nitrile moiety present in 102 was examined. Although reports concerning the addition of organocopper(I)
reagents to \( \alpha,\beta \)-unsaturated nitriles are sparse,\(^{34}\) we were optimistic that, with the recent advances in cuprate chemistry\(^{44}\), a reaction of this type could be effected.

Yamamoto and co-workers had reported\(^{34a,34b}\) that \( n \)-butylcopper(I), in the presence of boron trifluoride-etherate, effects the 1,4-addition of a \( n \)-butyl group to acrylonitrile in 40% yield. Unfortunately, treatment of the \( \alpha,\beta \)-unsaturated nitrile \( \text{102} \) with methylcopper(I) and boron trifluoride-etherate under the same conditions led only to recovered starting material. Alexakis and co-workers had also reported conditions for effecting conjugate additions to \( \alpha,\beta \)-unsaturated nitriles, using lithium dimethylcuprate in the presence of chlorotrimethylsilane.\(^{34c}\) Treatment of the \( \alpha,\beta \)-unsaturated nitrile \( \text{102} \) under Alexakis' conditions gave only recovered starting material upon workup.

Attention was next focused on organocopper(I) reagents that had proved to be effective for conjugate additions to \( \alpha,\beta \)-unsaturated carbonyl compounds that are often problematic in this type of reaction. The use of lithium (cyano)(methyl)cuprate with chlorotrimethylsilane under Corey's conditions,\(^{45}\) or with added HMPA as reported by Kuwajima and co-workers,\(^{46}\) had no effect on the \( \alpha,\beta \)-unsaturated nitrile \( \text{102} \). Iodotrimethylsilane-promoted additions of methylcopper(I) to \( \alpha,\beta \)-unsaturated ketones and esters was reported to be very effective for conjugate addition reactions.\(^{47}\) Treatment of the \( \alpha,\beta \)-unsaturated nitrile \( \text{102} \) with methylcopper(I) and iodotrimethylsilane did not give any of the desired compound but rather gave an unstable material that was not fully characterized.

The presence of boron trifluoride-etherate in reactions of higher order mixed cuprates with \( \alpha,\beta \)-unsaturated ketones has been reported to dramatically enhance reaction rates and, in some cases, the product yields.\(^{48}\) Since this reagent combination was effective for conjugate additions in cases that often proved problematic, the \( \alpha,\beta \)-unsaturated nitrile \( \text{102} \) was evaluated as a possible substrate. Treatment of the \( \alpha,\beta \)-unsaturated nitrile \( \text{102} \) with the higher order cuprate \( \text{Me}_2\text{Cu(CN)Li}_2 \) (formed from the addition of 2 equivalents of methyllithium to copper(I) cyanide) in the presence of 1.5
equivalents of boron trifluoride-etherate (0 °C, 2 h) gave only recovered starting material on workup. Interestingly, in the absence of boron trifluoride-etherate, but otherwise under the same conditions, two compounds were formed after two hours at 0 °C. Careful chromatography of the crude product mixture on silica gel provided clean samples of each compound, in yields of 21% and 22%.

The two compounds were identified as the β,γ-unsaturated nitriles 109 and 110 on the basis of their spectral data. The ir spectrum of the β,γ-unsaturated nitrile 109 exhibits signals at 2239 cm\(^{-1}\) and 1637 cm\(^{-1}\) characteristic of nitrile and olefinic functions, respectively. The \(^1\)H nmr spectrum exhibits signals at \(\delta 1.21\) (three proton singlet) for the angular methyl group, 1.30-2.45 (nine protons) for the aliphatic protons, 3.22-3.30 (one proton multiplet) for the allylic methine proton and four olefinic signals at 4.60 (one proton singlet), 4.70 (one proton singlet), 5.62-5.69 (one proton multiplet) and 5.91-6.02 (one proton multiplet). The signals at \(\delta 3.22-3.30\), 5.62-5.69 and 5.91-6.02 were assigned to the protons \(H_a\), \(H_b\) and \(H_c\), respectively, on the basis of decoupling experiments and the chemical shift value 49 for \(H_a\). Thus, irradiation of the signal at \(\delta 3.22-3.30\) (\(H_a\)) simplified the signal at 5.62-5.69 (\(H_b\)) to a doublet of doublets \((J = 9, 3 \text{ Hz})\) and simplified the signal at 5.91-6.02 (\(H_c\)). Irradiation of the signal at \(\delta 5.62-5.69\) (\(H_b\)) simplified the signal at 3.22-3.30 (\(H_a\)) to a narrow multiplet \((w_{1/2} =12 \text{ Hz})\) and simplified the signal at 5.91-6.02 (\(H_c\)) to a broad singlet. Irradiation of the signal at \(\delta 5.91-6.02\) (\(H_c\)) simplified the signal at 3.22-3.30 (\(H_a\)) to a multiplet \((w_{1/2} =16 \text{ Hz})\) and simplified the signal at 5.62-
5.69 (H_b). The high resolution mass spectrum of 109 shows a molecular ion at m/e 187.1360, consistent with the molecular formula C_{13}H_{17}N.

The spectral data of the \( \beta,\gamma \)-unsaturated nitrile 110 was very similar to that of 109. The IR spectrum of 110 exhibits signals at 2234 cm\(^{-1}\) and 1637 cm\(^{-1}\) characteristic of nitrile and olefinic functions, respectively. The \(^1\)H NMR spectrum exhibits signals at \( \delta \) 0.97 (three proton singlet) for the angular methyl group, 1.34-2.39 (nine protons) for the aliphatic protons, 2.93-3.00 (one proton multiplet) for the allylic methine proton and four olefinic signals at 4.62 (one proton singlet), 4.73 (one proton singlet), 5.47-5.53 (broad one proton doublet, \( J = 10 \) Hz) and 5.90-5.97 (one proton multiplet). The signals at \( \delta \) 2.93-3.00, 5.47-5.53 and 5.90-5.97 were assigned to the protons H_a, H_b and H_c on the basis of decoupling experiments and the chemical shift value for H_a. Thus, irradiation of the signal at \( \delta \) 2.93-3.00 (H_a) simplified the signal at 5.47-5.53 (H_b) to a doublet of doublets (\( J = 10, 2 \) Hz) and sharpened the signal at 5.90-5.97 (H_c). Irradiation of the signal at \( \delta \) 5.47-5.53 (H_b) simplified the signal at 2.93-3.00 (H_a) to a multiplet (\( w_{1/2} = 20 \) Hz) and simplified the signal at 5.90-5.97 (H_c). Irradiation of the signal at \( \delta \) 5.90-5.97 (H_c) simplified the signal at 2.93-3.00 (H_a) to a multiplet (\( w_{1/2} = 18 \) Hz) and simplified the signal at 5.47-5.53 (H_b) to a broad singlet. The high resolution mass spectrum of 110 shows a molecular ion at m/e 187.1354, consistent with the molecular formula C_{13}H_{17}N.

The treatment of the \( \alpha,\beta \)-unsaturated nitrile 102 with a variety of organocopper(I) species had failed to afford any trace of the desired product. The difficulty associated with organocopper(I) mediated conjugate additions to \( \alpha,\beta \)-unsaturated nitriles has been noted previously and would appear to remain as a challenge in this area. Therefore, an alternative route was examined (see Scheme 19).

Reduction of the \( \alpha,\beta \)-unsaturated nitrile 102 was smoothly effected by reaction of 102 with diisobutylaluminum hydride in THF at room temperature for 1 h.\(^{36a}\) Hydrolysis of the intermediate imine under acidic conditions gave, after workup, the \( \alpha,\beta \)-unsaturated aldehyde 104 in 89% yield (equation 15).
The IR spectrum of the \( \alpha,\beta \)-unsaturated aldehyde 104 exhibits an aldehydic C-H absorption at 2711 cm\(^{-1}\), a carbonyl absorption at 1688 cm\(^{-1}\) and an olefinic absorption at 1627 cm\(^{-1}\). The \(^1\)H NMR spectrum of 104 shows signals at \( \delta \) 4.61 (one proton singlet), 4.69 (one proton singlet), and 6.73 (one proton multiplet) for the olefinic protons and a signal at 9.45 (one proton singlet) characteristic of an aldehydic proton.

A THF solution of the \( \alpha,\beta \)-unsaturated aldehyde 104 was added to a THF solution of lithium (cyano)(methyl)cuprate in the presence of chlorotrimethylsilane (-78 °C, 2 h) to afford the enol silyl ethers 111 in 86% yield (equation 16).

Analysis of this material by \(^1\)H NMR spectroscopy showed that a 1:1 mixture of isomers had been formed. This result was encouraging, since there are potentially four isomers that could have been formed in this reaction. That is, the process could have produced two isomers epimeric at the newly introduced secondary methyl group, each of which could have consisted of a mixture of geometrically isomeric enol ethers. The \(^1\)H
nmr spectrum of the product shows signals at $\delta$ 0.16 and 0.17 (singlets) for the trimethylsilyl groups, 0.98 and 0.99 (singlets) for the angular methyl groups, 0.97 and 1.05 (doublets, $J = 7$ Hz each) for the secondary methyl groups, and 6.04 and 6.22 (singlets) for the olefinic protons of the enol ether functions.

The fact that the mixture was stereochemically homogeneous at the secondary methyl group was shown as follows. Conversion of 104 into the enol silyl ethers 111 using lithium (cyano)(methyl)cuprate in the presence of chlorotrimethylsilane $^{45}$ (-78 °C, 2 h), as before (equation 15), followed by acid hydrolysis (10% aqueous sulfuric acid, THF, 0.5 h) of the crude product gave the aldehyde 112 in 67% overall yield (Scheme 24).

The ir spectrum of the aldehyde 112 displays absorptions at 2728 cm$^{-1}$ and 1718 cm$^{-1}$ which are characteristic of an aldehyde function. The $^1$H nmr spectrum exhibits signals at $\delta$ 0.90 (three proton singlet) and 1.04 (three proton doublet, $J = 7$ Hz) which were assigned to the angular and secondary methyl groups, respectively. Additionally, a signal at $\delta$ 2.57 (one proton quintet, $J = 6$ Hz) was assigned to the methine proton adjacent to the secondary methyl group. In a decoupling experiment, irradiation of the signal at $\delta$ 1.04 (secondary methyl) simplified the signal at 2.57 (methine proton adjacent to the secondary methyl) to a broad doublet ($J = 6$ Hz) requiring that the proton adjacent to the secondary methyl group have an equatorial orientation and, therefore, that the secondary methyl be axially oriented.
Acid hydrolysis of the enol silyl ethers 111 was expected to yield a product in which the aldehyde function had adopted the equatorial orientation since acid catalyzed enolization of the aldehyde would allow equilibration to the more stable equatorial isomer. Also, the $^1$H nmr spectrum of the aldehyde 112 is significantly different from that of the aldehyde 113, which was readily prepared by reduction-hydrolysis of the known 85:15 mixture of the nitriles 29 and 30 (equation 17).

\[
\begin{align*}
29 & \quad R = \text{CN}, \quad R' = \text{H} \\
30 & \quad R = \text{H}, \quad R' = \text{CN}
\end{align*}
\]

(17)

The axial addition of the secondary methyl group to the $\alpha,\beta$-unsaturated aldehyde 104 can be rationalized on the basis of the preferred transition state having a chair-like conformation in which there is maximal overlap of the electrons of the $\pi$-system with the d-orbitals of copper, as shown for structure 114 (Scheme 25). Migration of the methyl group from copper to carbon then occurs with retention of configuration.
The enol silyl ethers \textbf{111} have the correct relative stereochemistry at three of the four chiral centers present in (±)-stephalic acid (96). The most direct route for the introduction of the final chiral center would be to alkylate the enolate \textbf{115} with a suitable electrophile (Scheme 26). The enolate \textbf{115} should be available from the enol silyl ether \textbf{111} based on work by Stork and Hudrlik, who showed that treatment of enol trimethylsilyl ethers with methyllithium in DME generated the corresponding lithium enolates.\textsuperscript{54} For steric reasons, alkylation of the enolate \textbf{115} was expected to occur from the face opposite the angular methyl group to furnish the aldehyde \textbf{116} rather than the aldehyde \textbf{117} (Scheme 26).
Treatment of a DME solution of the enol silyl ethers 111 with methyllithium (-20 °C, 1 h), followed by the addition of allyl iodide and stirring (-78 °C, 1 h then -78 °C → room temperature, 1 h) of the resultant mixture, gave, after workup, the aldehyde 112, the allyl enol ethers 103, the aldehyde 116 and another component tentatively proposed to be the aldehyde 117.

The allyl enol ethers 103 proved to be difficult to purify. The 1H nmr spectrum of the allyl enol ethers 103 showed doubling of the olefinic protons of the allyl moiety (δ 5.17-5.22, 5.26-5.33 and 5.87-6.00) and indicated that a mixture of geometric isomers had been obtained in a ratio of approximately 1:1. The high resolution mass spectrum of the mixture of allyl enol ethers 103 shows a molecular ion at m/e 246.1981, consistent with the molecular formula C17H26O.

The aldehydes 116 and 117 were not separable by silica gel column chromatography and consequently their identification is based on the 1H nmr spectrum of the mixture (≈ 7:4 of 116:117 by 1H nmr integration). The major component was identified as the aldehyde 116 by comparison of the 1H nmr spectrum of a pure sample of 116 (vide infra) with that of the mixture. The minor component 117 exhibits two signals in the 1H nmr spectrum of the mixture at δ 5.59-5.71 (multiplet) and at 10.02 (singlet) due to the olefinic -CH=CH2 and aldehydic protons, respectively. The presence of both the olefinic -CH=CH2 and aldehydic signals in the 1H nmr spectrum of 117 suggests a structure isomeric to that of 116. Structure 117 should exhibit the observed 1H nmr signals although the alkylation of the enolate 115 from the face syn to the angular methyl group was not predicted from molecular models.

Since alkylation of the enolate 115 appeared to be problematic, the Lewis acid induced alkylation of the enol silyl ethers 111 was examined. Treatment of a dichloromethane solution of the enol silyl ethers 111 with either zinc bromide and allyl
bromide 56 or with zinc iodide and allyl acetate 57 gave product mixtures in which the desired aldehyde 116 was a minor component.

Since neither the enolate alkylation of 115 nor the Lewis acid induced alkylation of 111 had given acceptable results, the formation of the aldehyde 116 via a Claisen rearrangement of the enol ethers 103 was examined (Scheme 27). The formation of the enol ethers 103 exploited the propensity of the enolate 115 to undergo O-alkylation. Thus, treatment of the enol silyl ethers 111 with methyllithium in HMPA (10 min, room temperature) followed by the addition of allyl chloride gave only O-alkylated products. The crude allyl enol ethers 103 (1:1 mixture of geometric isomers as indicated by 1H nmr spectroscopy) were obtained in consistently high yields (= 95%) and were used without purification (Scheme 27).

The Claisen rearrangement has been employed extensively,35 due largely to the stereoselectivity associated with this facile reaction. Because of the facility of the thermal Claisen rearrangement, the reaction has been used to synthesize quaternary centers 58 that are otherwise difficult to access. Indeed, thermolysis (200 °C, 0.5 h) of the allyl enol ethers 103 did afford the desired aldehyde 116 but a considerable number of unidentified compounds were also formed (glc and tlc analysis). Fortunately, an organoaluminum-promoted Claisen rearrangement process,59,60 in which a dichloromethane solution of the allyl enol ethers 103 was added to a solution of triethylaluminum and thiophenol in hexane (1 h, room temperature), gave the aldehyde 116 in 44% overall yield from 111 (Scheme 27). In addition, the diene alcohol 118 was obtained in 21% overall yield from this reaction.
The ir spectrum of the aldehyde 116 displays an aldehydic C-H absorption at 2722 cm\(^{-1}\), a carbonyl absorption at 1719 cm\(^{-1}\) and an olefinic absorption at 1637 cm\(^{-1}\). The \(^1\)H nmr spectrum exhibits four olefinic signals at \(\delta\) 4.59 (one proton singlet), 4.60 (one proton singlet), 4.98-5.07 (two proton multiplet) and 5.47-5.59 (one proton multiplet), and an aldehydic signal at 9.85 (one proton singlet). The high resolution mass spectrum of 116 shows a molecular ion at m/e 246.1988, consistent with the molecular formula C\(_{17}\)H\(_{26}\)O.

The structure of the diene alcohol 118 was assigned on the basis of the following spectral data. The ir spectrum of 118 exhibits hydroxyl and olefinic resonances at 3420 cm\(^{-1}\) and 1637 cm\(^{-1}\), respectively. The \(^1\)H nmr spectrum of 118 (Figure 2) displays two carbinol methylene signals at \(\delta\) 3.76 (one proton doublet, \(J = 12\) Hz) and 3.90 (one proton doublet, \(J = 12\) Hz), and five olefinic signals at \(\delta\) 4.50 (one proton singlet), 4.55 (one proton singlet), 5.07 (one proton doublet, \(J = 10\) Hz), 5.12 (one proton doublet, \(J = 16\) Hz) and 5.98-6.11 (one proton multiplet). The configuration of the newly created quarternary center was confirmed by an NOe difference experiment in which irradiation at \(\delta\) 3.90 (one of the carbinol methylene protons) caused enhancement of the signal due to the angular methyl group at 1.13 and the resonance corresponding to the other carbinol
methylene proton at 3.76. Thus, it is clear that the hydroxymethyl and angular methyl groups have a cis relationship.

Figure 2: The 400 MHz $^1$H nmr spectrum of the diene alcohol 118

The relative stereochemistry of the aldehyde 116 was determined as follows. Reduction of the aldehyde 116 with diisobutylaluminum hydride $^{36b}$ (room temperature, dichloromethane, 30 min), followed by suitable workup and product purification gave a material (97% yield) that was spectrally identical with 118 (equation 18).
Although the organoaluminum-promoted Claisen rearrangement of 103, along with the diisobutylaluminum hydride reduction of 116, gave the diene alcohol 118 efficiently (Scheme 27), it was found that the same transformation could be effected more conveniently in a single step by treatment of a dichloromethane solution of the allyl enol ethers 103 with a solution of triisobutylaluminum in toluene. The resultant mixture was stirred at room temperature for 1 h. After an acidic workup and chromatography of the crude product, the diene alcohol 118 was isolated in 52% overall yield from the enol silyl ethers 111 (Scheme 28).

Scheme 28

Oshima and co-workers suggested \textsuperscript{59b} that the triisobutylaluminum-promoted Claisen rearrangement-reduction process may proceed via a transition state which, in the conversion of 103 into 118, may be represented by 119. Thus, co-ordination of the aluminum atom with the oxygen atom of the enol ether function is followed by a sigmatropic rearrangement, which occurs concomitantly with hydride migration from one of the isobutyl groups to the developing alkoxymethyl carbon atom (Scheme 29). In a recent report by Yamamoto and co-workers, \textsuperscript{60} the suggestion is made that the success of the organoaluminum-promoted Claisen rearrangement reaction is due to the Lewis acidity of the organoaluminum reagent. Other factors may be involved since not all Lewis acids are effective in promoting the Claisen rearrangement reaction.\textsuperscript{59b}
Structural comparison of the diene alcohol 118 with (±)-stephalic acid (96) indicates that 118 contains all of the chiral centers with the same relative stereochemistry as those present in 96. For the conversion of 118 into (±)-stephalic acid (96), the exocyclic double bond must be isomerized to the endocyclic position and the allyl group must be synthetically elaborated in order to introduce the α,β-unsaturated acid moiety (equation 19). Since the exocyclic double bond was to be isomerized under acidic conditions and the elaboration of the allyl group was to involve the use of very nucleophilic reagents, it seemed appropriate to protect the alcohol function of 118 as a tert-butyldimethylsilyl ether.61

Conversion of the diene alcohol 118 into the silyl ether 120 was smoothly effected by treatment of 118 with 2,6-lutidine and tert-butyldimethylsilyl trifluoromethanesulfonate.
in dichloromethane at room temperature for 2 h. Chromatography of the crude product on silica gel furnished the silyl ether 120 in 76% yield (equation 20).

\[
\begin{align*}
\text{118} & \xrightarrow{2,6\text{-lutidine, TBDMSTf, } \text{CH}_2\text{Cl}_2} \text{120} \\
\text{OSiBu}^\text{t}\text{Me}_2
\end{align*}
\]

(20)

The ir spectrum of the silyl ether 120 displays an olefinic absorption at 1637 cm\(^{-1}\) and a siloxyl stretching absorption at 1092 cm\(^{-1}\). The \(^1\text{H} \text{nmr}\) spectrum of 120 exhibits signals at \(\delta 0.02\) (three proton singlet), 0.04 (three proton singlet) and 0.91 (nine proton singlet) due to the methyl and tert-butyl groups of the silyl ether moiety. In an nOe difference experiment, irradiation at \(\delta 3.90\) (one of the carbinol methylene protons) caused enhancement of the signal due to the angular methyl group at 1.13 and the resonance due to the other carbinol methylene proton at 3.51.

Treatment of the silyl ether 120 with \(p\)-toluenesulfonic acid in dichloromethane at room temperature for 2 h gave the silyl ether 121 in 81% yield.

\[
\begin{align*}
\text{120} & \xrightarrow{\text{p-toluenesulfonic acid, } \text{CH}_2\text{Cl}_2, 2\text{ h}} \text{121} \\
\text{OSiBu}^\text{t}\text{Me}_2
\end{align*}
\]

(21)

The ir spectrum of 121 exhibits an olefinic absorption at 1637 cm\(^{-1}\). The \(^1\text{H} \text{nmr}\) spectrum of 121 shows resonances at \(\delta 1.59\) (broad three proton singlet) for the vinylic
methyl group and at 5.01-5.12 (two proton multiplet), 5.19 (broad one proton singlet) and 5.82-5.95 (one proton multiplet) for the olefinic protons. The $^1$H nmr signals due to the vinylic methyl protons at $\delta$ 1.59 and to the olefinic proton at 5.19 confirm the presence of an endocyclic double bond.

Chemoselective hydroboration of 121 was achieved using 9-BBN. Addition of a THF solution of the silyl ether 121 to a THF solution of 9-BBN led to complete consumption of 121 after 3 hours at room temperature. The intermediate trialkylborane was oxidized with alkaline aqueous hydrogen peroxide to give the alcohol 122 in 90% yield, after silica gel chromatography (equation 22).

$$\begin{align*}
\text{121} & \xrightarrow{1. \text{9-BBN, THF}} \text{122} \\
& \xrightarrow{2. \text{H}_2\text{O}_2, \text{NaOH, THF-H}_2\text{O}} \text{122}
\end{align*}$$

The ir spectrum of the alcohol 122 exhibits a broad band centered at 3328 cm$^{-1}$ due to the hydroxyl functions. The $^1$H nmr spectrum of the alcohol 122 shows resonances at $\delta$ 3.57-3.69 (two proton multiplet) for the carbinol methylene protons and one olefinic resonance at 5.19 (broad one proton singlet). The spectral data clearly verifies that hydroboration has occurred chemoselectively at the mono-substituted double bond.

The alcohol 122 was oxidized by allowing a dichloromethane solution of 122 to react with pyridinium chlorochromate and sodium acetate at room temperature for 2 h. Upon workup the aldehyde 123 was obtained in 82% yield (equation 23).
The ir spectrum of the aldehyde 123 shows signals for an aldehydic C-H absorption at 2710 cm\(^{-1}\) and a carbonyl absorption at 1728 cm\(^{-1}\). The \(^1\)H nmr spectrum exhibits a signal at δ 9.77 (one proton triplet, \(J = 2\) Hz) for the aldehydic proton.

As mentioned previously (Scheme 18), the chain extension of the aldehyde 123 to the acetylenic ester 126 was based on methodology developed by Corey and Fuchs.\(^{32}\) The homologation to the acetylenic ester 126 involved a Wittig reaction to form the dibromooolefin 124, followed by treatment of 124 with \(n\)-butyllithium (Scheme 30). The latter step generated the lithium acetylide 125 which was acylated with methyl chloroformate to give 126.
Addition of a dichloromethane solution of the aldehyde 123 to a solution of dibromomethylenetriphenylphosphorane, formed in situ from carbon tetrabromide and triphenylphosphine,\textsuperscript{65} led to the complete consumption of 123 after 1.25 hours at room temperature. Purification of the crude product gave a 96% yield of the dibromide 124.

The ir spectrum of the dibromide 124 exhibits a strong olefinic absorption at 1656 cm\(^{-1}\). The \(^1\)H nmr spectrum of 124 shows signals at \(\delta 5.18\) (broad one proton singlet) and 6.37 (one proton triplet, \(J = 6\) Hz) for the two olefinic protons.

Conversion of the dibromide 124 into the acetylenic ester 126 was effected by treating a THF solution of 124 with 2 equivalents of \(n\)-butyllithium at -78 °C for 1 h and then at 0 °C for 1 h.\textsuperscript{32} The resultant lithium acetylide 125 was allowed to react with
methyl chloroformate (-78 °C, 1.25 h, then -78 → 0 °C over 0.5 h) to afford the acetylenic ester 126 in 90% yield after chromatography on silica gel.

The ir spectrum of the acetylenic ester 126 exhibits absorptions at 2237 cm\(^{-1}\) and 1718 cm\(^{-1}\) due to the acetylenic and carbonyl functions, respectively. The \(^1\)H nmr spectrum of 126 shows the expected signal for the methoxy methyl group at \(\delta\) 3.77 (three proton singlet).

The conversion of the acetylenic ester 126 into the \(\alpha,\beta\)-unsaturated ester 127 requires the cis addition of a methyl group and a hydrogen atom to the triple bond. Transformations of this type can be accomplished by reaction of acetylenic esters with lithium dialkylcuprates \(^{31}\) or lithium (dialkyl)(cyano)cuprates \(^{66}\) at low temperatures. Siddall and co-workers showed that both the cis and trans \(\alpha,\beta\)-unsaturated esters can be obtained from the reaction of lithium dialkylcuprates with acetylenic esters reaction and that the proportions of the two isomers are dependent on the time and temperature of the reaction and on the method of workup.\(^{31b, 31c}\)

Following the procedural requirements for cis addition to acetylenic esters,\(^{31}\) a THF solution of the acetylenic ester 126 was added, dropwise, to a cold (-78 °C) THF solution of lithium dimethylcuprate formed from methylolithium and copper(I) bromide-dimethyl sulfide complex.\(^{67}\) The resultant mixture was stirred at -78 °C for 2 hours. To prevent the formation of the unwanted trans \(\alpha,\beta\)-unsaturated ester, it was necessary to quench the reaction by cannulating the reaction mixture into a stirred solution of aqueous 5% hydrochloric acid. After chromatography of the crude product on silica gel, the \(\alpha,\beta\)-unsaturated ester 127 was obtained in 87% yield (equation 24).
The IR spectrum of the α,β-unsaturated ester 127 shows strong absorptions at 1723 cm\(^{-1}\) and 1648 cm\(^{-1}\) due to the ester and olefinic functions, respectively. The \(^1\)H nmr spectrum of 127 exhibits signals at \(\delta\) 1.05 (three proton doublet, \(J = 6\) Hz), 1.11 (three proton singlet), 1.60 (broad three proton singlet), 1.91 (broad three proton singlet) and 3.67 (three proton singlet) due to the secondary, angular, two vinylic and methoxy methyl groups, respectively. Additionally, \(^1\)H nmr signals were observed at \(\delta\) 2.25 (one proton triplet of doublets, \(J = 12, 4\) Hz) and 3.03 (one proton triplet of doublets, \(J = 12, 4\) Hz) for the \(-\text{CH}_2\text{C(CH}_3\text{)=CHCO}_2\text{CH}_3\) protons, and at 5.18 (broad one proton singlet) and 5.65 (one proton singlet) for the two olefinic protons. The three-proton and one-proton resonances at \(\delta\) 1.91 and 5.65, respectively, are, in terms of chemical shifts, typical of those exhibited by compounds of part structure \(-\text{C(CH}_3\text)=CHCO}_2\text{CH}_3\) in which the vinylic methyl group and the olefinic proton are in a cis relationship.\(^6\) Confirmation of the configuration of the olefinic double bond in 127 was obtained from an nOe difference experiment in which irradiation of the signal at \(\delta\) 5.65 caused signal enhancement at 1.91. Thus, it is clear that the newly introduced vinylic methyl group and the adjacent olefinic proton have a cis relationship.
A comparison of the structure of the $\alpha,\beta$-unsaturated ester 127 with that of (±)-stephalic acid (96) reveals that two "deprotections" are necessary for completion of the synthesis of 96. The order in which the two functions are deprotected is crucial, since initial cleavage of the silyl ether function can generate an alkoxide that could undergo Michael addition to the $\alpha,\beta$-unsaturated ester function, with the formation of a six-membered ring. The cleavage of the ester function prior to the removal of the silyl ether function therefore appeared to be the more straightforward and less problematic route.*

Conversion of the $\alpha,\beta$-unsaturated ester 127 into the $\alpha,\beta$-unsaturated acid 128 was achieved via a procedure reported by Liotta and co-workers for the $S_N2$ cleavage of esters using sodium benzeneselenenide (equation 25). Thus, treatment of a THF solution of 127 with a solution of sodium benzeneselenenide and HMPA in THF (formed by the addition of benzeneselenenol and HMPA to a slurry of sodium hydride in THF) followed by heating the mixture at the reflux temperature for 4 h gave, after workup and chromatography of the crude product, a 64% yield of the $\alpha,\beta$-unsaturated acid 128.

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* Hydrofluoric acid-induced cleavage of the silyl ether function of the $\alpha,\beta$-unsaturated ester 127, followed by attempts to cleave the ester function of the crude product with sodium benzeneselenenide, did indeed afford an intramolecular Michael addition product as indicated by $^1$H nmr, ir and mass spectral determinations of the crude products thus obtained.
The ir spectrum of the α,β-unsaturated acid **128** shows a broad absorption in the region 3500-2500 cm\(^{-1}\) and a strong signal at 1691 cm\(^{-1}\) due to the carboxylic acid function, and an olefinic absorption at 1637 cm\(^{-1}\). The \(^1\)H nmr spectrum of the α,β-unsaturated acid **128** exhibits signals at δ 1.59 (broad three proton singlet) and 1.94 (three proton singlet) for the vinylic methyl groups, and at 5.18 (broad one proton singlet) and 5.68 (one proton singlet) for the two olefinic protons. The chemical shifts of the methyl and olefinic protons of the α,β-unsaturated acid **128** are very similar to those reported for (±)-stephalic acid (96),\(^{11c}\) as indicated in the following structural formulas.

The transformation of the α,β-unsaturated acid **128** into (±)-stephalic acid (96) requires cleavage of the silyl ether function. The cleavage of tert-butyldimethylsilyl ethers has been reported to occur upon exposure of a dry THF solution of the tert-
butyldimethylsilyl ether to tetra-\(n\)-butylammonium fluoride at room temperature for 40 min.\(^{70a}\) Treatment of a dry THF solution of the \(\alpha,\beta\)-unsaturated acid 128 with tetra-\(n\)-butylammonium fluoride at room temperature for 1 h \(^{70b}\) resulted only in the recovery of unreacted 128, while complete consumption of 128 required that the reaction mixture be heated to reflux for 22 h. Workup and \(^1\)H nmr spectroscopic analysis of the crude product mixture showed that (±)-stephalic acid (96) was present only as a minor component. Similarly, when a pyridine-THF-water solution of 128 was treated with tetra-\(n\)-butylammonium fluoride at room temperature for 0.5 h,\(^{70c}\) only recovered 128 was obtained upon workup.

Lithium tetrafluoroborate has been reported to be an effective reagent for the cleavage of tert-butyldimethylsilyl ethers and in one case good results were obtained where tetra-\(n\)-butylammonium fluoride had been ineffective.\(^{71}\) Unfortunately, treatment of a dichloromethane-acetonitrile solution (3:2) of 128 with lithium tetrafluoroborate gave only trace amounts of (±)-stephalic acid (96) as indicated by \(^1\)H nmr spectroscopy of the crude product mixture. Similar results were obtained when a THF solution of 128 was treated with anhydrous cesium fluoride at room temperature for 16 h.\(^{72}\)

The tert-butyldimethylsilyl protecting group for alcohols had been shown to undergo facile cleavage upon exposure to boron trifluoride-etherate in dichloromethane at room temperature for times ranging from 15 min to 3 h.\(^{73}\) Addition of boron trifluoride-etherate to a dichloromethane solution of the \(\alpha,\beta\)-unsaturated acid 128 led to complete consumption of 128 after 16 h at room temperature. Chromatography of the crude product gave a material which exhibits a broad absorption at 3500-2500 cm\(^{-1}\) in the ir spectrum. The ir spectrum also exhibits absorptions at 1688 cm\(^{-1}\) and 1639 cm\(^{-1}\) characteristic of an \(\alpha,\beta\)-unsaturated carbonyl function. The \(^1\)H nmr spectrum of this material shows signals at \(\delta\) 0.89 (three proton singlet), 0.92 (three proton singlet), 0.98 (three proton doublet, \(J = 8\) Hz) and 1.90 (three proton singlet), 3.80-3.87 (two proton multiplet) and one olefinic signal at 5.67 (one proton singlet). No signals were detected in the \(^1\)H nmr spectrum that
would suggest the presence of the silyl ether function. The three-proton and one-proton resonances at $\delta$ 1.90 and 5.67, respectively, are, in terms of chemical shifts, typical of those exhibited by compounds of part structure $-C(CH_3)=CHCX\text{H}$, which suggests that the latter unit is present in the product obtained from the reaction of 128 with boron trifluoride-etherate. The absence of signals at $\delta \approx 1.6$ and $\approx 5.2$ typical of the vinylic methyl signal and the olefinic signal, respectively, suggest that skeletal rearrangement may have occurred. Skeletal rearrangement of bicyclic decalins have previously been shown to occur in the presence of boron trifluoride-etherate.\(^{74}\)

Aqueous hydrofluoric acid has been shown to be a mild and efficient reagent for the cleavage of tert-butyldimethylsilyl ethers.\(^{75}\) After some experimentation in which the concentration of hydrofluoric acid was varied, it was found that addition of an aqueous 20% solution of hydrofluoric acid to an acetonitrile solution of the $\alpha,\beta$-unsaturated acid 128 cleaved the silyl ether function after 10-30 min at room temperature. \(^1H\) nmr analysis of the crude product showed that (±)-stephalic acid (96) is present as a major component. However, the use of hydrofluoric acid for the cleavage of the silyl ether 128 was, in practice, not satisfactory, since the results derived from this method were found to be erratic and the reason(s) for this inconsistency could not be found. Additionally, efforts to purify the crude product repeatedly returned a material that was equal in purity or, more often, was less pure than the original material.

During these frustrating studies it became necessary to obtain more of the $\alpha,\beta$-unsaturated acid 128. Since, in order to obtain a pure sample of (±)-stephalic acid (96), it appeared essential to remove the alcohol protecting group without the formation of side products, it seemed prudent to re-examine the choice of protecting group.

Results from the hydrofluoric acid-induced cleavage of the silyl ether 128 indicated that the initial cleavage occurred quite cleanly, and that the formation of complex product mixtures resulted from prolonged exposure of (±)-stephalic acid (96) to the acidic reaction conditions. The latter inference was suggested by a comparison of product mixtures
obtained from reactions performed at different hydrofluoric acid concentrations and from reactions analyzed over extended time periods. If (±)-stephalic acid (96) is unstable to the acidic conditions then the protecting group should be removed under neutral or basic conditions. Furthermore, the protecting group must be compatible with the reactions encountered earlier in the sequence.

The stability required of the protecting group seemed best fulfilled by a silyl ether that could be removed more easily than a tert-butyldimethylsilyl ether. In particular, the recently reported tert-butoxydiphenylsilyl ethers were shown to exhibit a stability similar to that of the tert-butyldimethylsilyl ethers but with greatly increased fluoride sensitivity (the half lives for the tetra-\(n\)-butylammonium fluoride-induced silyl ether cleavages of dodecyl tert-butoxydiphenylsilyl ether and dodecyl tert-butyldimethylsilyl ether are 5.8 h and 140 h, respectively, at room temperature). Since the tert-butoxydiphenylsilyl ether function appeared to fulfill the stability requirements and would likely necessitate no major changes to the synthetic pathway, efforts were made to repeat the sequence using this protecting group.

Conversion of the diene alcohol 118 into the silyl ether 129 was smoothly effected by treatment of the diene alcohol 118 with triethylamine, 4-\(N\),\(N\)-dimethylaminopyridine, and tert-butoxydiphenylsilyl chloride in dichloromethane at room temperature for 2 h (equation 26).\(^{76}\) Chromatography of the crude product on silica gel furnished the silyl ether 129 in 91% yield.

\[
\begin{align*}
\text{Ph}_2(\text{Bu'O})\text{SiCl}, \text{Et}_3\text{N}, & \quad \text{DMAP, CH}_2\text{Cl}_2, 2 \text{ h} \\
118 & \quad \rightarrow \\
129 & \quad \text{OSi}(\text{OBu'})\text{Ph}_2
\end{align*}
\]
The IR spectrum of the silyl ether 129 displays a benzene ring absorption at 1592 cm\(^{-1}\) and a siloxyl absorption at 1057 cm\(^{-1}\). The \(^1\)H NMR spectrum of 129 exhibits signals at \(\delta\) 1.29 (nine proton singlet) due to the \(t\)-butyl group, and at 3.82 (one proton doublet, \(J = 10\) Hz) and 3.88 (one proton doublet, \(J = 10\) Hz) due to the \(-\text{CH}_2\text{OSi(OBu})_3\text{)}\text{Ph}_2\) protons. In addition, two aromatic resonances at \(\delta\) 7.32-7.44 (six proton multiplet) and 7.63-7.71 (four proton multiplet) were observed.

Isomerization of the exocyclic double bond of the silyl ether 129 into the endocyclic position using \(p\)-toluenesulfonic acid in dichloromethane at room temperature (2.5 h), as described previously (equation 21), gave two inseparable products. The \(^1\)H NMR spectrum of the product mixture shows that the major component of the mixture (ratio = 3:1) exhibits signals at \(\delta\) 1.55 (broad singlet) and another broad singlet at 5.15 (broad singlet) * which indicated that isomerization had occurred. Efforts to suppress the formation of the unidentified minor component were unsuccessful and therefore the isomerization of the exocyclic double bond was delayed until later in the sequence.

The silyl ether 129 was allowed to react with one equivalent of 9-BBN in THF for 2 h at room temperature.\(^{63}\) After an oxidative workup using alkaline hydrogen peroxide and chromatography of the crude product mixture, unreacted 129 was recovered in a yield of 54\%. In addition three new compounds had been produced. These three substances were identified as the alcohol 130 (32\% based on recovered 129), the diol 131 (29\% based on recovered 129) and the alcohol 132 (5\% based on recovered 129) on the basis of their spectral data (Scheme 31).

* The chemical shift values for the corresponding protons of the silyl ether 121 are \(\delta\) 1.59 and 5.19.
The IR spectrum of the alcohol \(130\) exhibits signals at 3388 cm\(^{-1}\), 1637 cm\(^{-1}\) and 1592 cm\(^{-1}\) due to the alcohol, olefin and benzene ring functions, respectively. The \(^1\)H NMR spectrum of the alcohol \(130\) shows resonances at \(\delta 3.46\) (two proton triplet, \(J = 6\) Hz) for the carbinol methylene protons, and at 4.46 (one proton singlet) and 4.50 (one proton singlet) for the two olefinic protons.

The IR spectrum of the diol \(131\) exhibits signals at 3410 cm\(^{-1}\) and 1592 cm\(^{-1}\) due to the alcohol and benzene ring functions, respectively. The \(^1\)H NMR spectrum of \(131\) shows signals for two methyl groups at \(\delta 0.73\) (three proton singlet) and 0.93 (three proton doublet, \(J = 7\) Hz) and a signal at 1.29 (nine proton singlet) due to the \(t\)-butyl group. The spectrum also exhibits signals at \(\delta 3.26\) (one proton doublet of doublets, \(J = 10, 8\) Hz) and 3.81 (one proton doublet of doublets, \(J = 10, 2\) Hz) due to the protons of the hydroxymethyl function adjacent to the angular methyl group, 3.46 (two proton triplet, \(J =\)
5 Hz) due to protons of the other hydroxymethyl group, 3.69 (one proton doublet, $J = 10$ Hz) and 3.98 (one proton doublet, $J = 10$ Hz) due to the $-\text{CH}_2\text{OSi(OBu}_t\text{)}\text{Ph}_2$ protons, and aromatic signals at 7.33-7.46 (six proton multiplet) and 7.62-7.70 (four proton multiplet). The configuration assigned to the chiral center adjacent to the hydroxymethyl group was made on the basis of an nOe difference experiment in which irradiation at $\delta$ 3.26 (one $-\text{CH}_2\text{OH}$ proton) caused enhancement at 3.81 (the other $-\text{CH}_2\text{OH}$ proton) and at 0.73 (angular methyl group). Thus, the angular methyl and the adjacent hydroxymethyl groups must have a cis relationship. The high resolution mass spectrum of 131 shows a molecular ion at m/e 538.3478, consistent with the molecular formula C$_{33}$H$_{50}$O$_4$Si.

The ir spectrum of the alcohol 132 exhibits signals at 3390 cm$^{-1}$, 1637 cm$^{-1}$ and 1592 cm$^{-1}$ due to the alcohol, olefinic and benzene ring functions, respectively. The $^1$H nmr spectrum of 132 shows signals for two methyl groups at $\delta$ 0.63 (three proton singlet) and 0.99 (three proton doublet, $J = 8$ Hz) and a signal at 1.28 (nine proton singlet) due to the $t$-butyl group. The spectrum also exhibits signals at $\delta$ 3.20-3.27 (one proton multiplet, simplifies to a doublet of doublets on addition of D$_2$O, $J = 12$, 9 Hz) and 3.72-3.86 (three proton multiplet) due to the protons of the hydroxymethyl function adjacent to the angular methyl group and the $-\text{CH}_2\text{OSi(OBu}_t\text{)}\text{Ph}_2$ protons. Three olefinic protons at $\delta$ 4.95 (one proton doublet of doublets, $J = 10$, 2 Hz), 5.01 (one proton doublet of doublets, $J = 16$, 2 Hz) and 5.90-6.02 (one proton multiplet) and aromatic signals at 7.31-7.43 (six proton multiplet) and 7.62-7.68 (four proton multiplet) were also observed in the $^1$H nmr spectrum of 132. The configuration of the chiral center bearing the $-\text{CH}_2\text{OH}$ function was assumed to be as shown in 132, by analogy with the stereochemistry of the diol 131. The high resolution mass spectrum of 132 shows a molecular ion at m/e 520.3375, consistent with the molecular formula C$_{33}$H$_{48}$O$_3$Si.

Chemoselective hydroboration of the silyl ether 129 was achieved by treatment of a THF solution of 129 with disiamylborane (formed in situ from borane-dimethyl sulfide complex and 2-methyl-2-butene) at 0 °C for 20 minutes and at room temperature for 45
After an oxidative workup with alkaline hydrogen peroxide and chromatography of the crude product, the alcohol 130 was obtained in 80% yield (equation 27). Only traces of 131 and 132 were detected in the crude product (tlc analysis). The $^1$H nmr spectrum of 130 exhibits signals for two carbinol methylene protons and two olefinic protons. The chemical shifts of the latter signals are characteristic of exocyclic methylene protons, which is consistent with hydroboration having occurred only at the mono-substituted double bond.

$$\begin{align*}
\text{129} & \xrightarrow{1. \text{(Sia)}_2\text{BH, THF}} \text{130} \\
\text{130} & \xrightarrow{2. \text{H}_2\text{O}_2, \text{NaOH}} \text{130}
\end{align*}$$

(27)

The alcohol 130 was oxidized with pyridinium chlorochromate in the presence of sodium acetate at room temperature for 16 h. Upon workup, the aldehyde 133 was obtained in 85% yield (equation 28).

$$\begin{align*}
\text{130} & \xrightarrow{\text{PCC, NaOAc, CH}_2\text{Cl}_2, 16 \text{ h}} \text{133}
\end{align*}$$

(28)
The ir spectrum of the aldehyde 133 shows an aldehydic C-H absorption at 2714 cm\(^{-1}\) and an absorption at 1727 cm\(^{-1}\) due to the carbonyl moiety. Additionally, the \(^1\)H nmr spectrum of 133 exhibits an aldehydic signal at \(\delta 9.61\) (one proton triplet, \(J = 2\) Hz).

The chain extension of the aldehyde 133 to the acetylenic ester 134 was achieved via a method identical with that employed previously (Scheme 30). Thus, addition of a dichloromethane solution of the aldehyde 133 to a solution of dibromomethylenetriphenylphosphorane, formed \textit{in situ} from carbon tetrabromide and triphenylphosphine,\(^{65}\) led to complete consumption of 133 after 15 min at room temperature. Purification of the crude product gave the dibromide 134 in a yield of 96% (equation 29).

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\begin{array}{c}
\text{Br} \\
\text{Br}
\end{array} & \quad \text{Ph}_3\text{P}=\text{CBr}_2, \\
\text{CH}_2\text{Cl}_2, 15 \text{ min}
\end{align*}
\]

The ir spectrum of the dibromide 134 exhibits a strong olefinic absorption at 1637 cm\(^{-1}\). The \(^1\)H nmr spectrum of 134 shows a signal at \(\delta 6.24\) (one proton triplet, \(J = 6\) Hz) for the olefinic proton adjacent to the two bromine atoms.

A THF solution of the dibromide 134 was treated with two equivalents of \(n\)-butyllithium at -78 °C for 1 h and then at 0 °C for 1 h. The resultant mixture was cooled to -78 °C, methyl chloroformate was added, and the mixture was stirred for 1.25 h at -78 °C and warmed to 0°C over 0.5 h, to give two products. The two products were inseparable by silica gel column chromatography and consequently their identification is
based on the $^1$H nmr spectrum of the mixture (= 5:3 by $^1$H nmr integration). The major component was identified as the acetylenic ester 135 by comparison of the $^1$H nmr spectrum of a pure sample of 135 (vide infra, equation 30) with that of the mixture. The minor component has $^1$H nmr chemical shift values almost identical with those of 135 and is thought to be the corresponding n-butyldiphenylsilyl ether 136. In the presence of n-butyllithium at temperatures above -78 °C tert-butoxydiphenylsilyl ethers have been reported to sustain replacement of the tert-butoxy group with an n-butyl group.76

The formation of the undesired minor component, thought to be the n-butyldiphenylsilyl ether 136, was completely suppressed when a THF solution of the dibromide 134 was treated sequentially with 2 equivalents of n-butyllithium (-78 °C for 3 h) and methyl chloroformate (-78 °C for 0.5 h, room temperature for 1 h).32 The latter procedure afforded the acetylenic ester 135 in 76% yield after silica gel chromatography (equation 30).
The IR spectrum of the acetylenic ester 135 exhibits absorptions at 2236 cm\(^{-1}\), 1718 cm\(^{-1}\) and 1638 cm\(^{-1}\) due to the acetylenic, carbonyl and olefinic functions, respectively. The \(^1\)H NMR spectrum of 135 (Figure 3) shows signals at \(\delta 0.83\) (three proton singlet), 0.94 (three proton doublet, \(J = 8\) Hz) and 3.75 (three proton singlet) for the angular, secondary and methoxy methyl groups, respectively, and at 3.72 (one proton doublet, \(J = 10\) Hz) and 3.85 (one proton doublet, \(J = 10\) Hz) for the \(-\text{CH}_2\text{OSi(OBu\text{)}}\text{Ph}_2\) protons. \(^1\)H NMR resonances were also observed at \(\delta 4.43\) (one proton singlet) and 4.46 (one proton singlet) for the two olefinic protons, and at 7.33-7.45 (six proton multiplet) and 7.60-7.68 (four proton multiplet) for the aromatic protons (Figure 3).
Treatment of the acetylenic ester 135 with $p$-toluenesulfonic acid in dichloromethane at room temperature for 15 h effected the required isomerization of the exocyclic double bond into the endocyclic position (equation 31). Silica gel chromatography of the crude product mixture afforded a 56% yield of the acetylenic ester 137 and a 28% yield of the alcohol 138.

\[
\begin{align*}
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
135 & \quad 137 & \quad 138
\end{align*}
\]

Figure 3: The 400 MHz $^1$H nmr spectrum of the acetylenic ester 135
The IR spectrum of the acetylenic ester 137 exhibits signals due to the olefin function at 1655 cm\(^{-1}\). The \(^1\)H NMR spectrum of 137 has resonances at \(\delta 1.55\) (broad three proton singlet) for the vinylic methyl group and at \(\delta 5.15\) (broad one proton singlet) for the olefinic proton.

The IR spectrum of the alcohol 138 shows a broad hydroxyl absorption at 3421 cm\(^{-1}\). The \(^1\)H NMR spectrum of 138 exhibits signals at \(\delta 1.59\) (broad three proton singlet) for the vinylic methyl group, 3.60 (one proton doublet, \(J = 11\) Hz) and 3.99 (one proton doublet, \(J = 11\) Hz) for the carbinol methylene protons, and at 5.19 (broad one proton singlet) for the olefinic proton.

The alcohol function present in the alcohol 138 was reprotected by allowing 138 to react with tert-butoxydiphenylsilyl chloride in the presence of triethylamine and 4-\(N,N\)-dimethyldiaminopyridine in dichloromethane at room temperature for 2 h.\(^{76}\) Silica gel chromatography of the crude product afforded the acetylenic ester 137 in 57% yield (equation 32).

\[
\text{HO} \quad \text{Ph}_2\text{Bu'O}\text{SiCl, Et}_3\text{N}, \quad \text{DMAP, CH}_2\text{Cl}_2, 2\text{ h} \quad \text{OSi(OBu)}\text{Ph}_2
\]

The conjugate addition of a methyl group to the acetylenic ester 137 was achieved using lithium dimethylcuprate under conditions identical with those employed previously (equation 24). Thus, a THF solution of the acetylenic ester 137 was added, dropwise, to a cold (-78 °C) THF solution of lithium dimethylcuprate formed from methyllithium and
copper(I) bromide-dimethyl sulfide complex. The resultant mixture was stirred at -78 °C for 2 hours and was then cannulated into a stirred solution of aqueous 5% hydrochloric acid. After silica gel chromatography of the crude product, the α,β-unsaturated ester 139 was obtained in 65% yield (equation 33).

The ir spectrum of the α,β-unsaturated ester 139 shows strong absorptions at 1719 cm⁻¹, 1685 cm⁻¹ and 1648 cm⁻¹ due to the ester and two olefinic functions, respectively. The ¹H nmr spectrum of 139 exhibits signals at δ 1.56 (broad three proton singlet) and 1.83 (three proton singlet) for the two vinylic methyl groups, 2.30 (one proton triplet of doublets, J = 12, 4 Hz) and 3.02 (one proton triplet of doublets, J = 12, 4 Hz) for the -CH₂C(CH₃)═CHCO₂CH₃ protons, and 5.14 (broad one proton singlet) and 5.61 (one proton singlet) for the olefinic protons.

Cleavage of the ester function of 139 occurred smoothly using the procedure of Liotta and co-workers, as described previously for the ester cleavage of the α,β-unsaturated ester 128 (equation 25). Treatment of a THF solution of 139 with a solution of sodium benzeneselenide and HMPA in THF (formed by the addition of benzeneselenol and HMPA to a slurry of sodium hydride in THF) followed by heating the mixture at the
reflux temperature for 6.5 h gave, after workup and chromatography * of the crude product, a 64% yield of the α,β-unsaturated acid 140 (equation 34).

\[
\begin{align*}
\text{PhSeNa, HMPA,} \\
\text{THF, Δ, 6.5 h}
\end{align*}
\]

\[
\begin{align*}
\text{139} & \quad \rightarrow \quad \text{140}
\end{align*}
\]

The ir spectrum of the α,β-unsaturated acid 140 shows a broad absorption in the region 3300-2500 cm\(^{-1}\) and a strong signal at 1717 cm\(^{-1}\) due to the carboxylic acid function. The \(^1\)H nmr spectrum of 140 exhibits signals in accordance with the assigned structure.

With access to the α,β-unsaturated acid 140, the cleavage of silyl ether function of 140 was examined. It was gratifying to find that a THF solution of the α,β-unsaturated acid 140 underwent complete silyl ether cleavage after 4 h at room temperature in the presence of tetra-\(n\)-butylammonium fluoride, indicating that the \(t\)-butoxydiphenylsilyl ether moiety of 140 was indeed more fluoride sensitive than the corresponding \(t\)-butyldimethylsilyl ether function of 129 (equation 35). The crude product (= 6 mg) was analyzed by \(^1\)H nmr spectroscopy (CDCl\(_3\) solution) and shows resonances for (±)-stephalic acid (96), tetra-\(n\)-butylammonium fluoride and a small amount of an unknown impurity.

* Purification of the crude α,β-unsaturated acid 140 required both flash chromatography and preparative silica gel thin-layer chromatography.
The crude product obtained from the reaction of the α,β-unsaturated acid 140 with tetra-n-butylammonium fluoride was subjected to column chromatography on Sephadex® LH-20. The latter technique provided two fractions of which the major fraction (= 4 mg) was judged to be of increased purity while the minor fraction (= 2 mg) showed little, if any, change in purity, as indicated by $^1$H nmr spectroscopy.

Although silica gel chromatography appeared to have deleterious effects on (+)-stephalic acid (96), the original isolation of (+)-stephalic acid (96) involved preparative silica gel thin layer chromatography. Therefore, in an attempt to purify the minor fraction, the material was chromatographed by preparative silica gel thin layer chromatography. The latter protocol gave a material of purity similar to that of the major fraction and consequently the two fractions were combined.

Purification of the combined crude sample of (+)-stephalic acid (96) was next examined using preparative reverse phase tlc (Whatman KC18) which provided 3.4 mg of a material judged to be at least 80% pure by $^1$H nmr spectroscopy. A comparison of the latter purification method with others examined deemed the use of preparative reverse phase tlc most efficacious. Slow multiple recrystallization of the solid obtained after preparative reverse phase tlc gave, in 15% yield, (+)-stephalic acid (96), mp 219-221 °C, which showed tlc behaviour, as well as $^1$H nmr and mass spectra, identical with those of an
authentic sample of (+)-stephalic acid *. The 1H nmr spectra of natural and synthetic 96 are shown in Figures 4 and 5.

---

* We are grateful to Professor M. Salmón for providing a sample of natural (+)-stephalic acid.
Figure 4: The 400 MHz $^1$H nmr spectrum of synthetic (±)-stephalic acid (96).
Figure 5: The 400 MHz $^1$H nmr spectrum of natural (+)-stephalic acid (96).
Conclusion

The series of reactions described above have culminated in the first total synthesis of the structurally and stereochemically novel trans-clerodane diterpenoid (±)-stephalic acid (96). (±)-Stephalic acid (96) was obtained from the known ketone 94 via a stereocontrolled 15-step sequence of reactions.

The synthesis of the ketone 94 employed the previously developed methylenecyclohexane annulation method and, as such, represents an application of this methodology to the total synthesis of natural products. The conversion of the ketone 94 into the α,β-unsaturated nitrile 102 constitutes the first use, in natural product synthesis, of methodology developed for the conversion of ketones into the corresponding α,β-unsaturated nitriles.

The secondary methyl group present in (±)-stephalic acid (96) was introduced in a highly stereoselective manner via a chlorotrimethylsilane-promoted conjugate addition of lithium (cyano)(methyl)cuprate to the α,β-unsaturated aldehyde 104. The latter transformation introduced the secondary methyl group in the required axial orientation.

The formation of the chiral quaternary center at C-9 of (±)-stephalic acid (96) was accomplished by employing a novel triisobutylaluminum-promoted Claisen rearrangement-reduction process. The Claisen variant introduces the quaternary center at C-9 in the correct configuration with the requisite hydroxymethyl function and a three carbon unit that is suitable for elaboration into the required diterpenoid side-chain. The use of the triisobutylaluminum-promoted Claisen rearrangement-reduction process appears to constitute the first application of this methodology to natural product synthesis.
The Conversion of Ketones into $\alpha,\beta$-Unsaturated Nitriles

**Previous Methodology**

"The direct conversion of carbonyl compounds into 2-alkenenitriles is of great interest, as the latter compounds serve as versatile intermediates in organic synthesis."\(^{37}\) Several methods have been devised for the two-carbon homologation of ketones into the corresponding $\alpha,\beta$-unsaturated nitriles, mainly through the application of Wittig type methodology.\(^{37,78}\) The formation of $\alpha,\beta$-unsaturated nitriles from acetylenes, acetylenic nitriles and alkenyl halides has also been reported.\(^{37}\)

Fewer methods exist for the one-carbon homologation of ketones into $\alpha,\beta$-unsaturated nitriles than exist for the corresponding two-carbon homologation, and most of these methods are variants of the hydrocyanation-dehydration procedure*.\(^{37,79}\) For example, the addition of trimethylsilyl cyanide to the ketone 141 affords the trimethylsiloxy nitriles 142, which are treated *in situ* with pyridine and phosphoryl chloride to give the $\alpha,\beta$-unsaturated nitriles 143 and 144 (Scheme 32).\(^{80}\) The formation of regioisomers such as 143 and 144 is typical for hydrocyanation-dehydration type procedures \(^{20}\) and remains as one of the major disadvantages of an otherwise very efficient and well developed synthetic method.\(^{37}\)

* For an example of a synthetic application of the hydrocyanation-dehydration procedure see the conversion of the ketone 33 into the unsaturated nitriles 35 and 36 (Scheme 4, p. 12).
It has recently been shown that \( \alpha,\beta \)-unsaturated nitriles can be obtained by coupling vinyl halides with potassium cyanide in the presence of catalytic amounts of various transition metals. Yamamura and Murahashi reported the first coupling of vinyl halides with potassium cyanide and employed tetrakistriphenylphosphine palladium(0) and 18-crown-6 as co-catalysts. The scope of the latter procedure was subsequently investigated by Prochazka and Siroky who examined the use of different cyanide sources, the use of other crown-ether catalysts and the effect of different solvent systems. Under optimized conditions, refluxing a solution containing the vinyl bromide 145, tetrakistriphenylphosphine palladium(0) and 18-crown-6 in benzene at 80 °C for 50 h gave the \( \alpha,\beta \)-unsaturated nitrile 146 in 92% yield (glc analysis) (equation 36).

Funabiki and co-workers showed that \( \alpha,\beta \)-unsaturated nitriles can be obtained by allowing vinyl halides to react with an aqueous solution of cobalt(II) chloride, potassium hydroxide and potassium cyanide under an atmosphere of hydrogen gas. Treatment of the vinyl bromide 147 under the latter conditions at 45 °C for 1 h provided the \( \alpha,\beta \)-unsaturated nitrile 148 in 80% yield (equation 37).
Sakakibara and co-workers reported a similar coupling of vinyl halides with potassium cyanide and a nickel(0) catalyst.\textsuperscript{81c} Typically the catalyst was prepared \textit{in situ} by heating a DMF solution of nickel(II) bis(triphenylphosphine) dibromide, potassium cyanide, zinc powder and triphenylphosphine at 50 °C for 30 min. Addition of the vinyl bromide 149 to a DMF solution containing the nickel(0) catalyst, followed by heating at 50 °C for 8h, afforded the \(\alpha,\beta\)-unsaturated nitrile 150 in 70 % yield based on recovered 149 (equation 38).

\[
\begin{align*}
\text{Br} & \quad \text{CoCl}_2, \text{KOH, KCN}, \quad \text{H}_2\text{O}, \text{H}_2, 1\ h, 45\ ^\circ\text{C} \quad \text{CN} \\
147 & \quad \\
\text{CN} & \quad \\
148 & \\
\end{align*}
\]

The transition metal-catalyzed coupling methodology represents a significant development for the stereoselective formation of \(\alpha,\beta\)-unsaturated nitriles. Application of the latter methodology to organic synthesis has been sparse and may be due to difficulties associated with the formation of substituted and stereochemically defined vinyl bromides.

A readily accessible vinyl halide equivalent is a class of compounds known as enol trifluoromethanesulfonates (enol triflates).\textsuperscript{82} Enol triflates are readily available from both aldehydes \textsuperscript{82} and ketones.\textsuperscript{40} For example, deprotonation of the ketone of part structure 151 with LDA followed by the addition of \(N\)-phenyltrifluoromethanesulfonimide gives good yields of the corresponding enol triflate 152 (Scheme 33).\textsuperscript{40} Furthermore, Stille and co-workers have shown \textsuperscript{83} that enol triflates can be coupled with tetraorganostannanes in
the presence of a suitable palladium(0) catalyst to give substituted olefins 153 (Scheme 33). Thus, the possibility of synthesizing α,β-unsaturated nitriles 154 via the transition metal-catalyzed coupling of enol triflates with a suitable cyanide source became particularly attractive (Scheme 33).

\[
\begin{align*}
151 & \xrightarrow{1. \text{LDA, THF}} 152 & \xrightarrow{2. \text{PhNTf}_2} \xrightarrow{R_3\text{SnR}', (\text{Ph}_3\text{P})_4\text{Pd}, \text{THF}} 153 \\
\end{align*}
\]

Scheme 33

The Development of the Palladium-Catalyzed Coupling of Enol Triflates with Lithium Cyanide

The requisite enol triflates were prepared according to the procedure of McMurry and Scott, who demonstrated that ketone enolates are readily O-sulfonylated with N-phenyltrifluoromethanesulfonimide (see the conversion of 151 into 152, Scheme 33). The enol triflates, shown in Table I, were derived from ketones that were chosen to typify substrates used in synthetic endeavours. It is pertinent to note that the five, six and seven membered ring ketones 155-157 and 159, respectively, were previously used as intermediates in total syntheses.

The conversion of the ketone 156 into the enol trflate 158 is typical of the procedure used for the formation of the enol triflates listed in Table I (equation 39). The
ketone 156 was added to a cold (-78 °C) THF solution of LDA and allowed to react at -78 °C for 2 hours. *N*-Phenyltrifluoromethanesulfonimide was added, the cold bath was removed and the reaction mixture was allowed to warm to room temperature. The reaction mixture was then stirred at room temperature for a further period of time. The total reaction time was 16 h. Chromatography of the crude product gave the enol triflate 158 in 75% yield (equation 39).

\[
\text{156} \xrightarrow{1. \text{LDA}} \text{OSO}_2\text{CF}_3
\]

The ir spectrum of the enol triflate 158 exhibits absorptions at 1695 cm\(^{-1}\) and 1206 cm\(^{-1}\) due to the olefinic and sulfonyl functions, respectively. The \(^1\)H nmr spectrum of 158 shows a signal at \(\delta \) 5.62 (one proton triplet, \(J = 4 \) Hz) for the olefinic proton.
Table I. Conversion of ketones into enol triflates.

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Enol triflate</th>
<th>Reaction time/h</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="#" alt="Image 155" /></td>
<td><img src="#" alt="Image 162" /></td>
<td>2.0</td>
<td>84%</td>
</tr>
<tr>
<td><img src="#" alt="Image 156" /></td>
<td><img src="#" alt="Image 158" /></td>
<td>16.0</td>
<td>75%</td>
</tr>
<tr>
<td><img src="#" alt="Image 157" /></td>
<td><img src="#" alt="Image 163" /></td>
<td>2.5</td>
<td>72%</td>
</tr>
<tr>
<td><img src="#" alt="Image 94" /></td>
<td><img src="#" alt="Image 108" /></td>
<td>2.0</td>
<td>80%</td>
</tr>
<tr>
<td><img src="#" alt="Image 95" /></td>
<td><img src="#" alt="Image 164" /></td>
<td>1.0</td>
<td>76%</td>
</tr>
<tr>
<td><img src="#" alt="Image 159" /></td>
<td><img src="#" alt="Image 165" /></td>
<td>1.0</td>
<td>66%</td>
</tr>
</tbody>
</table>
The following points concerning the synthesis of the enol triflates listed in Table I are noteworthy. The reported workup procedure involves removal of the solvent from the solution containing the crude product, followed by silica gel chromatography. After examining several modifications of the workup procedure an easier and more efficient protocol was found. Thus, direct filtration of the reaction mixture through silica gel or Florisil® and removal of the solvent from the filtrate gave an oil that was chromatographed on silica gel. Use of the latter procedure during the isolation of the enol triflate 158 consistently gave 158 in yields approximately 10% higher than that obtained by the reported workup method.

Formation of the enol triflate 167 was achieved by treatment of the keto ester 161 with potassium hydride in THF at room temperature for 1 h, followed by the addition of N-phenyltrifluoromethanesulfonylimide. After 16 h water was cautiously added. The crude product, obtained after workup, was chromatographed on silica gel to give the enol triflate 167 in 82% yield.

Exploratory studies aimed at coupling enol triflates with cyanide were undertaken using the enol triflate 158, derived from the commercially available ketone 156. Initially, the conversion of the enol triflate 158 into the corresponding α,β-unsaturated nitrile 168
was examined using the conditions employed by Yamamura and Murahashi for the conversion of vinyl halides into nitriles. Treatment of a benzene solution of 158 with potassium cyanide, tetrakistriphenylphosphine palladium(0) and 18-crown-6 at reflux for 8 h gave two inseparable products in a ratio of 5:1 (glc analysis) (equation 40). The two products were identified as the α,β-unsaturated nitriles 168 and 169 by comparing the \( ^1H \) nmr spectra obtained from pure samples of 168 and 169 (vide infra).

\[
\text{OSO}_2\text{CF}_3 \quad \text{KCN, (Ph}_3\text{P)}_4\text{Pd, PhH,} \quad 18\text{-C-6, reflux, 8 h} \quad \begin{array}{c}
158 \\
\text{CN} \\
168 \\
169
\end{array}
\]

(40)

The formation of the α,β-unsaturated nitrile 169 was most unexpected. Attempts to maximize the formation of 169 did not lead to synthetically useful results, but did provide a means of obtaining a small amount of 169 for characterization purposes. Thus, a benzene solution of tetrakis(triphenylphosphine)palladium(0) (0.07 equiv), 12-crown-4 (0.35 equiv) and the enol triflate 158 was heated at reflux temperature for 20 min. To the resultant dark brown solution was added dry lithium cyanide (5.5 equiv), and reflux was continued for another 20 min (equation 41). The reaction mixture was allowed to cool to room temperature and was then passed through a column of Florisil \(^\circledR\). The crude product was chromatographed on silica gel and gave an 85% recovery of the enol triflate 158, and a very low yield (15% based on recovered 158) of the α,β-unsaturated nitrile 169.
The ir spectrum of the α,β-unsaturated nitrile 169 exhibits absorptions at 2217 cm\(^{-1}\), 1638 cm\(^{-1}\) and 1099 cm\(^{-1}\) due to the nitrile, olefinic and acetal functions, respectively. The \(^1\)H nmr spectrum of 169 shows signals at \(\delta\) 0.98 (three proton singlet) and 1.00 (three proton singlet) for the two methyl groups, 1.93 (two proton triplet, \(J = 6\) Hz, \(H_c\) and \(H_d\)), 2.29-2.36 (two proton multiplet, \(H_a\) and \(H_b\)) and 2.55-2.59 (two proton multiplet, \(H_e\) and \(H_f\)) for the aliphatic protons, 3.48-3.56 (four proton multiplet) for the acetal methylene protons, and at 6.59-6.63 (one proton multiplet, \(H_g\)) for the olefinic proton.

The structure of the α,β-unsaturated nitrile 169 was assigned on the basis of decoupling experiments, an nOe difference experiment and two SINEPT experiments.\(^43\) In a decoupling experiment, irradiation of the signal at \(\delta\) 2.29-2.36 (\(H_a\) and \(H_b\)) simplified the triplet at 1.93 (\(H_c\) and \(H_d\)) to a singlet, simplified the multiplet at 2.55-2.59 (\(H_e\) and \(H_f\)) to a narrow signal (\(\omega_{1/2} = 4\) Hz), and simplified the multiplet at 6.59-6.63 (\(H_g\)) to a triplet (\(J = 2\) Hz). Irradiation of the signal at \(\delta\) 2.55-2.59 (\(H_e\) and \(H_f\)) simplified the multiplet at 2.29-2.36 (\(H_a\) and \(H_b\)) and simplified the multiplet at 6.59-6.63 (\(H_g\)) to a triplet (\(J = 4\) Hz). Irradiation of the signal at \(\delta\) 6.59-6.63 (\(H_g\)) simplified the multiplet at 2.29-2.36 (\(H_a\) and \(H_b\)) and simplified the multiplet at 2.55-2.59 (\(H_e\) and \(H_f\)) to a triplet (\(J = 2\) Hz).

In an nOe difference experiment, irradiation of the signal at \(\delta\) 6.59-6.63 (\(H_g\)) caused signal enhancement at \(\delta\) 2.29-2.36 (\(H_a\) and \(H_b\)) but not at 2.55-2.59 (\(H_e\) and \(H_f\)).
In a SINEPT experiment \(^{43}\) optimized for a \(J_{C,H}\) of 7 Hz, irradiation of the signal at \(\delta 3.56\) (both pairs of acetal methylene protons) gave strong polarization transfer through three-bond coupling to the quaternary acetal carbon at \(\delta 95.3\). A second SINEPT experiment,\(^{43}\) utilizing the same \(J_{C,H}\) of 7 Hz, in which an irradiation was centered at \(\delta 6.64\) (H\(_g\)), gave strong polarization transfer through three-bond coupling to the sp nitrile carbon at \(\delta 118.9\) but not to the quaternary acetal carbon. These results are consistent only with the structure 169. The high resolution mass spectrum of 169 shows a molecular ion at m/e 207.1255, consistent with the molecular formula C\(_{12}\)H\(_{17}\)NO\(_2\).

Experiments aimed at suppressing the formation of the undesired \(\alpha,\beta\)-unsaturated nitrile 169 examined the use of a number of different solvents (\(N,N\)-dimethylformamide, hexamethylphosphoramide, tetrahydrofuran, benzene) at different temperatures. Eventually it was found that only the \(\alpha,\beta\)-unsaturated nitrile 168 and the enol triflate 158 were obtained (glc analysis) from reaction mixtures in which potassium cyanide, 18-crown-6 and tetrakistriphenylphosphinepalladium(0) were allowed to react in benzene at room temperature for 4 h. Longer reaction times (47 h) led to almost complete consumption of the enol triflate 158 but both the \(\alpha,\beta\)-unsaturated nitriles 168 and 169 were detected by glc analysis (in a ratio of 17:1, respectively).

The latter results were encouraging and led to the discovery that at room temperature the reaction between the enol triflate 158, lithium cyanide, tetrakistriphenylphosphinepalladium(0) and 12-crown-4 gave only the \(\alpha,\beta\)-unsaturated nitrile 168. After extensive experimentation in which the reaction temperature and the relative concentrations of reagents and catalysts were varied, the conversion of the enol triflate 158 into the \(\alpha,\beta\)-unsaturated nitrile 168 was found to proceed cleanly and efficiently (80% yield) using lithium cyanide (2 equivalents), tetrakistriphenylphosphinepalladium(0) (0.07 equivalents) and 12-crown-4 (0.07 equivalents) in benzene at room temperature (equation 42). Furthermore, complete conversion of 158 into 168 was achieved after 2 h.
The IR spectrum of the α,β-unsaturated nitrile 168 exhibits absorptions at 2211 cm$^{-1}$, 1642 cm$^{-1}$ and 1114 cm$^{-1}$ due to the nitrile, olefinic and acetal functions, respectively. The $^1$H NMR spectrum of 168 shows signals at $\delta$ 0.94 (three proton singlet) and 1.03 (three proton singlet) for the two methyl groups, 2.01 (two proton triplet, $J = 6$ Hz, H$_c$ and H$_d$), 2.32-2.39 (two proton multiplet, H$_a$ and H$_b$) and 2.50-2.55 (two proton multiplet, H$_e$ and H$_f$) for the aliphatic protons, 3.47 (two proton doublet, $J = 11$ Hz) and 3.57 (two proton doublet, $J = 11$ Hz) for the acetal methylene protons, and at 6.44-6.48 (one proton multiplet, H$_g$) for the olefinic proton (Figure 6).

Figure 6: The 400 MHz $^1$H NMR spectrum of the α,β-unsaturated nitrile 168.
The structure of the α,β-unsaturated nitrile 168 was assigned on the basis of decoupling experiments, an nOe difference experiment and two SINEPT experiments. In a decoupling experiment, irradiation of the signal at δ 2.32-2.39 (H\textsubscript{a} and H\textsubscript{b}) simplified the triplet at 2.01 (H\textsubscript{c} and H\textsubscript{d}) to a singlet, simplified the multiplet at 2.50-2.55 (H\textsubscript{e} and H\textsubscript{f}) to a doublet (J = 4 Hz), and simplified the multiplet at 6.44-6.48 (H\textsubscript{g}) to a triplet (J = 4 Hz). Irradiation of the signal at δ 2.50-2.55 (H\textsubscript{e} and H\textsubscript{f}) simplified the multiplet at 2.32-2.39 (H\textsubscript{a} and H\textsubscript{b}) to a broad triplet (J = 6 Hz) and simplified the multiplet at 6.44-6.48 (H\textsubscript{g}) to a broad singlet. Irradiation of the signal at δ 6.44-6.48 (H\textsubscript{g}) simplified the multiplets at 2.32-2.39 (H\textsubscript{a} and H\textsubscript{b}) and at 2.50-2.55 (H\textsubscript{e} and H\textsubscript{f}).

The substitution pattern of the α,β-unsaturated nitrile 168 was assigned on the basis of an nOe difference experiment and two SINEPT experiments. In an nOe difference experiment irradiation of the signal at δ 6.44-6.48 (H\textsubscript{g}) caused signal enhancement at 2.50-2.55 (H\textsubscript{e} and H\textsubscript{f}) but not at 2.32-2.39 (H\textsubscript{a} and H\textsubscript{b}). In a SINEPT experiment optimized for a \( J_{C,H} \) of 7 Hz, irradiation of the signal at δ 3.52 (both pairs of acetal methylene protons) gave strong polarization transfer through three-bond coupling to the quaternary acetal carbon at δ 95.3 and to the acetal methylene carbon at 70.3 (Figure 7). A second SINEPT experiment, utilizing the same \( J_{C,H} \) of 7 Hz, in which an irradiation was centered at δ 6.46 (H\textsubscript{g}), gave strong polarization transfer through three-bond coupling to the quaternary acetal carbon at δ 95.3 and to the sp nitrile carbon at 119.0 (Figure 8). These results are consistent only with the structure 168.
The generality of the coupling reaction was demonstrated by converting the enol triflates listed in Table I into the corresponding α,β-unsaturated nitriles. The enol triflates 108, 158, and 162-167 were allowed to react with lithium cyanide, tetrakistriphenylphosphinepalladium(0) and 12-crown-4 in benzene at room temperature for the times indicated in Table II (equation 38). The results are summarized in Table II.
Table II. Conversion of enol triflates into α, β-unsaturated nitriles.

<table>
<thead>
<tr>
<th>Enol triflate</th>
<th>α, β-Unsaturated nitrile</th>
<th>Reaction time/h</th>
<th>Isolated Yield</th>
</tr>
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<tbody>
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<td><img src="image" alt="162" /></td>
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<tr>
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<tr>
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</tr>
<tr>
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<td><img src="image" alt="102" /></td>
<td>2.0</td>
<td>89%</td>
</tr>
<tr>
<td><img src="image" alt="164" /></td>
<td><img src="image" alt="172" /></td>
<td>1.5</td>
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</tr>
<tr>
<td><img src="image" alt="165" /></td>
<td><img src="image" alt="173" /></td>
<td>1.0</td>
<td>78%</td>
</tr>
</tbody>
</table>
As can be seen from Table II, the coupling of a variety of functionalized enol triflates with lithium cyanide in benzene gives good yields of the corresponding α,β-unsaturated nitriles. The reaction tolerates the presence of acetal, diene, enol ether and ester functions and, for most of the examples listed in Table II, the reaction was complete within 2-3 h. The formation of 170 from 162 was considerably slower. Treatment of the reaction mixture with an additional 0.07 equivalents of tetrakistriphenylphosphinepalladium(0) after a reaction time of 6.5 h was required for an acceptable rate of conversion of 162 into 170. Similarly, formation of the β-methoxycarbonyl α,β-unsaturated nitrile 175 required treatment of the reaction mixture with three additional amounts of tetrakistriphenylphosphinepalladium(0) (0.07 equivalents), added at 1 hour intervals, in order to achieve complete conversion of 167 into 175.

All of the α,β-unsaturated nitriles in Table II exhibit $^1$H nmr spectra in agreement with the assigned structures. Furthermore, a series of nOe difference experiments, in which the olefinic proton β to the nitrile function of the α,β-unsaturated nitriles 168, 170, 171, 102, and 173 were irradiated, gave enhancements that were consistent only with the assigned structures.
The constitution of the $\alpha,\beta$-unsaturated nitrile 172 (as well as of the $\alpha,\beta$-unsaturated nitriles 102 and 168 *) was corroborated by SINEPT experiments.\textsuperscript{43} Thus, in a SINEPT experiment \textsuperscript{43} optimized for a $J_{\text{C,H}}$ of 7 Hz, irradiation of the signal at $\delta$ 6.57 (the olefinic proton $\beta$ to the nitrile function) of 172, gave strong polarization transfer through three-bond coupling to the sp nitrile carbon at $\delta$ 119.5 and to the methine carbon at the ring junction at 44.2.

It is interesting to note that the $\alpha,\beta$-unsaturated nitriles 168, 102 and 170-175 which contain an olefinic proton that is cis to the nitrile function all exhibit resonances between $\delta$ 6.44 and 6.79 for these protons. In contrast, the olefinic proton of the $\alpha,\beta$-unsaturated nitrile 174 has a chemical shift value of $\delta$ 4.85.

By analogy with the proposed course of the reaction involving palladium catalyzed coupling of tetraorganostannanes and enol triflates,\textsuperscript{83} the following pathway is proposed for the catalytic coupling of lithium cyanide with enol triflates (Scheme 34).

\* For a discussion of the results of SINEPT experiments for 102 and 168 see the Discussion Section of this thesis p. 35 and p. 87, respectively.
The zero valent tetrakistriphenylphosphinepalladium(0) is proposed to dissociate to an active 14 electron species 176 which can add oxidatively to the carbon-oxygen bond of the enol triflate 177. The resultant palladium(II) complex 178 can undergo triflate ligand exchange with cyanide to form the trans-vinylpalladate 179, with the concomitant formation of lithium triflate. Isomerization of 179 to give the cis-vinylpalladate 180, followed by reductive elimination from the latter species would regenerate the catalyst and result in the formation the α,β-unsaturated nitrile 181.

The proposed pathway is based, partially, on elegant work recently reported by Stang and co-workers. These researchers have obtained crystal structures of some platinum(II) complexes derived from the reaction of tetrakistriphenylphosphineplatinum(0) with enol triflates. Evidence is presented which suggests that the oxidative addition to an enol triflate (general structure 177) occurs via the slow reversible formation of the
platinocycle 182, followed by the fast collapse of 182 to the trans-vinylplatinate 183 (Scheme 35).

\[
\begin{align*}
\text{OSO}_2\text{CF}_3 + \text{Pt(Ph}_3\text{)}_2 & \quad\text{Slow}\quad\frac{\text{Ph}_3\text{P-Pt}}{\text{Ph}_3\text{P-O}} \quad\text{OSO}_2\text{CF}_3 \\
177 & \quad\rightarrow\quad 182 & \quad\text{Fast}\quad \text{Ph}_3\text{P-}\text{Pt-}\text{PPh}_3 \\
& \quad\rightarrow\quad 183
\end{align*}
\]

Scheme 35

Stang and co-workers have demonstrated that 183 can be converted into 184 by treatment with the lithium acetylide 185, and that the reductive elimination of 184 requires higher temperatures and longer reaction times than for the corresponding cis complex. The conversion of 183 into 184 is similar to the proposed triflate ligand exchange in 178 with cyanide (equation 43).

\[
\begin{align*}
\text{OSO}_2\text{CF}_3 & \quad\text{Ph}_3\text{P-}\text{Pt-}\text{PPh}_3 \quad\text{OSO}_2\text{CF}_3 \\
183 & \quad\text{Li}\quad \text{Ph}_3\text{P-}\text{Pt-}\text{PPh}_3 \\
& \quad\rightarrow\quad 184
\end{align*}
\]

(43)

Since many of the steps proposed for the palladium-catalyzed coupling of enol triflates are made by analogy with the reactions of related metals, such as platinum, the exact pathway by which the coupling reaction occurs remains unknown. The pathway outlined in Scheme 34 for the coupling of enol triflates with lithium cyanide would, however, seem to serve as an acceptable model.
Conclusion

The current section of this thesis describes a method for the palladium(0)-catalyzed coupling of enol triflates with lithium cyanide in the presence of 12-crown-4. This reaction converts enol triflates into the corresponding α,β-unsaturated nitriles in an efficient manner. Since enol triflates can be regioselectively formed from ketone enolates, using a variety of well precededted procedures, the two-step sequence enables methodology for the conversion of ketones into α,β-unsaturated nitriles. Since α,β-unsaturated nitriles are synthetically versatile compounds, the method described in this thesis should prove useful in organic synthesis.*

* Subsequent to this work the nickel-catalyzed coupling of aryl triflates with potassium cyanide was reported.
Synthetic Studies Toward cis-Clerodanes

Retrosynthetic Analysis

From a stereochemical viewpoint, there are two central problems associated with developing a general synthetic route to cis-clerodanes. The problems concern the stereochemical control of the ring junction and the stereochemically controlled introduction of the one carbon substituents at C-8 and C-9 of the cis-clerodane skeleton 186 (Scheme 36).

The first problem associated with the formation of a cis-clerodane skeleton should be surmountable by using cis-decalin intermediates which are not epimerizable at the ring junction. In connection with the development of the methylenecyclohexane annulation method, the non-epimerizable cis-ketone 92 was shown to be formed efficiently from readily available precursors (equation 11, p. 23) and seemed well suited as a precursor for the synthesis of cis-clerodanes. Furthermore, the ketone 92 contains functional groups appropriately positioned for future synthetic manipulations.

\[ \text{Scheme 36} \]
The second problem concerning the stereocontrolled introduction of the one carbon substituents at C-8 and C-9 seemed potentially solvable by employing methods used in the successful synthesis of (±)-stephalic acid (96). For example, the successful, stereocontrolled conjugate addition of lithium (cyano)(methyl)cuprate $^{45}$ to the $\alpha,\beta$-unsaturated aldehyde 104 to produce the enol silyl ether 111 (equation 16, p. 39) suggested that a similar method could be used to effect the stereocontrolled installation of the C-8 substituent of cis-clerodanes. Presumably the one-carbon substituent at C-9 could be introduced via an alkylation or a rearrangement reaction.

The retrosynthetic analysis of the cis-clerodane skeleton 186 was guided by a structure-goal strategy in which the ketone 92 could be used as an intermediate. Disconnection of the bonds between C-4 and C-18 and between C-11 and C-12 of the cis-clerodane skeleton 186, along with appropriate functional group manipulations, would lead to the aldehyde 188 (Scheme 37). The C-11—C-12 disconnection was made by analogy with previous syntheses in which the functionalized six-carbon side chain was elaborated toward the end of the synthetic sequence (see, for example, the Introduction-Enolate Alkylation Transform Section of this thesis, p. 8).

It appears highly likely that the stereochemistry of the alkylation of the aldehyde 187 would be dependant upon the conformation adopted by the corresponding enolate anion. However, the relative stereochemical outcome of the alkylation is of little concern since varying the electrophile would provide access to either configuration (Scheme 37). Thus, if the one-carbon alkylation (methylation) of 187 afforded 188, then the aldehyde function of 188 would be used to introduce the requisite side chain. Alternatively, if the alkylation of 187 afforded 189, then the side chain would be introduced via an alkylation procedure and the aldehyde function of 189 would be transformed into the one carbon C-20 substituent (Scheme 37).
Identification of the aldehyde function of \( \text{187} \) as a retron for the lithium (cyano)(methyl)cuprate transform \(^{45}\) leads, retrosynthetically, to the \( \alpha,\beta \)-unsaturated aldehyde \( \text{190} \) (Scheme 38). Since the stereocontrolled conjugate addition to \( \text{190} \) could be complicated by conformation factors it seemed expedient to use the ether function of \( \text{190} \) to introduce a conformational bias into the molecule. The ether function of \( \text{190} \) was therefore retrosynthetically interconverted to a ketone function, since several methods are available for stereoselectively converting ketones to alcohols \(^{18,88}\) and for converting alcohols to ethers.\(^{70a}\) Thus, a series of functional group manipulations was required in order to retrosynthetically convert \( \text{190} \) into the ketone \( \text{92} \) (Scheme 38).
Synthesis of Potential cis-Clerodane Precursors

The ketone 92 had previously been synthesized from 2-methyl-2-cyclohexen-1-one (191) via the methylenecyclohexane annulation method. Since 2-methyl-2-cyclohexen-1-one (191) is not commercially available, it was prepared from 2-vinylpyridine using the method described by Danishefsky and Cain (Scheme 39). An argon purged ethereal solution of 2-vinylpyridine (192) and ethanol was added to a cold (-78 °C), stirred solution of lithium in ammonia. The resultant solution quickly became transparent. After 20 min, the cooling bath was replaced with a warm water bath. The system was opened to the atmosphere and argon was allowed to pass through the reaction mixture in order to aid in the removal of the ammonia. After most of the ammonia had been removed, an argon purged methanolic solution of aqueous sodium hydroxide was added and the resultant solution was stirred at room temperature for 3 hours. The crude product was distilled to provide 2-methyl-2-cyclohexen-1-one in 60% yield (Scheme 39).

* Solutions were purged by allowing a constant stream of argon gas to diffuse through each solution for approximately 15 min. Failure to purge solutions of the reagents with argon led to the formation of variable amounts of 2-ethylpyridine.
The vinylstannane 84 was employed for the methylenecyclohexane annulation of 2-methyl-2-cyclohexen-1-one (191), using the procedure discussed previously (Scheme 15, p. 22). Transmetallation of 84 with methylthium in THF (-78 °C, 20 min), followed by the addition of solid magnesium bromide-etherate (-78 °C, 20 min), gave the corresponding Grignard reagent 88 (Scheme 40). Successive addition of copper(I) bromide-dimethyl sulfide complex, boron trifluoride-etherate and 2-methyl-2-cyclohexen-1-one (191) gave a bright yellow slurry which was stirred at -78 °C for 3 hours. After appropriate workup, the chloro ketones 91 were obtained (Scheme 40). The crude chloro ketones 91 underwent clean intramolecular alkylation upon exposure to excess potassium hydride in THF for 2 hours, to yield the cis-ketone 92 in 84% yield. The "kinetic" preference for cis fused products in alkylations of this type is well preceded.90
Scheme 40

The ir spectrum of the ketone 92 shows the expected absorptions for the ketone and olefin functions at 1703 cm\(^{-1}\) and 1648 cm\(^{-1}\), respectively. The \(^1\)H nmr spectrum of 92 exhibits signals at δ 1.10 (three proton singlet) for the angular methyl group, and 4.69-4.72 (one proton multiplet) and 4.72-4.75 (one proton multiplet) for the olefinic protons. The \(^1\)H nmr spectral data of 92 is in good agreement with that previously reported.\(^{28b}\)

Additionally, the chemical shift value of the angular methyl group (δ 1.10) correlates with values of cis-1-decalones (δ 1.05-1.20), reported by Boeckman and co-workers.\(^{39}\)

The ketone function of 92 was reduced in order to impart a conformational bias into the resultant alcohol 194. Treatment of the ketone 92 with a cold (-78 °C) solution of calcium in ammonia\(^{91}\) for 1 hour, followed by the addition of anhydrous ethanol (-78 °C, 15 min), gave a single alcohol 194 in 95% yield (equation 44). The configuration of the alcohol 194 was assigned by conversion of 194 into the ether 195, whose stereochemistry was assigned from the results of several \(^1\)H nmr experiments (vide infra).
The ir spectrum of the alcohol 194 shows a broad hydroxyl absorption at 3385 cm\(^{-1}\) and an olefinic absorption at 1646 cm\(^{-1}\). The \(^1\)H nmr spectrum of 194 exhibits signals at \(\delta\) 1.04 (three proton singlet) for the angular methyl group and at 3.32 (one proton doublet of doublets, \(J = 13, 5\) Hz) for the carbinol methine proton.

Protection of the alcohol function of 194 was accomplished by conversion of this substance into the ether 195.\(^{92}\) Treatment of a cold (0 °C) dichloromethane solution of the alcohol 194 and \(N,N\)-diisopropylethylamine with chloromethyl methyl ether gave the ether 195 in 97% yield (equation 45).

The ir spectrum of the ether 195 shows a strong absorption at 1123 cm\(^{-1}\) due to the acetal function. The \(^1\)H nmr spectrum of 195 exhibits signals at \(\delta\) 3.12 (one proton doublet of doublets, \(J = 12, 4\) Hz) for the -\(\text{CH}-\text{OCH}_2\text{OCH}_3\) proton, 3.38 (three proton singlet) for the protons of the methoxyl group, and 4.59 (one proton doublet, \(J = 6\) Hz) and 4.72 (one proton doublet, \(J = 6\) Hz) for the acetal methylene protons. The \(^{13}\)C nmr spectrum of the ether 195 exhibits signals for fourteen unique carbons. Two of these \(^{13}\)C signals, at \(\delta\) 52.1 and 84.9, displayed negative amplitudes in an attached proton test (APT)
experiment and were consequently assigned to the ring-fused methine carbon and to the \(-\text{CH-OCH}_2\text{OCH}_3\) carbon, respectively.

The configuration of the \(-\text{CH-OCH}_2\text{OCH}_3\) carbon of 195 was assigned by assuming that the ether 195 existed primarily in a chair-chair conformation in which the \(-\text{CH-OCH}_2\text{OCH}_3\) proton has an axial orientation.* The ether 195 was therefore predicted to exist in the conformation depicted by structure 195a. Similarly, if the configuration of the \(-\text{CH-OCH}_2\text{OCH}_3\) carbon was epimeric with that of 195, then the epimeric ether 196 should exist in the conformation depicted by structure 196a. The two methine protons \(H_a\) and \(H_b\) are in a 1, 3-diaxial relationship in the structure 195a and therefore an nOe between \(H_a\) and \(H_b\) should be observed. In contrast, the protons \(H_a\) and \(H_b\) in 196a are at a considerable distance from each other and would not be expected to show a mutual nOe. Additionally, the proton \(H_a\) and the angular methyl group of 195a are gauche to one another and, therefore, irradiation of the signal due to \(H_a\) would be expected to enhance the resonance due to the methyl group. In structure 196a the proton \(H_a\) and the angular methyl group are in a 1, 2-diaxial relationship and would not be expected to show a mutual nOe.

\[ \text{H}_b \]
\[ \text{H}_a \]
\[ \text{OCH}_2\text{OCH}_3 \]

\[ 195a \]

\[ \text{CH}_3\text{OCH}_2\text{O} \]
\[ \text{H}_a \]

\[ 196a \]

In an nOe difference experiment, irradiation of the ether methine proton at \(\delta 3.18\) (\(H_a\)) caused enhancement of the signal due to the angular methyl group at 1.02, a multiplet

* The signal for the ether methine proton of 195 is a doublet of doublets, with coupling constants \((J = 12, 4 \text{ Hz})\) consistent with those of an axially oriented proton.
at 1.73-1.80, a multiplet at 1.80-1.87, and the resonances due to the -OCH₂OCH₃ protons at 4.59 and 4.72. It was not obvious whether either of the enhanced multiplets at 1.73-1.80 or 1.80-1.87 corresponded to the signal for the methine proton Hₐ. However, the chemical shift value of the proton Hₐ was readily assigned from the results of a HETCOR experiment since the chemical shift value of the methine carbon attached to the proton Hₐ was readily identified (δ 52.1) from the results of an APT experiment (vide supra). Thus, in a HETCOR experiment a strong correlation between the ¹³C nmr signal at δ 52.1 and the ¹H nmr signal at δ 1.80-1.87 was observed (Figure 9). (The HETCOR results also verify the chemical shift value previously assigned to the ether methine proton Hₐ (δ 3.18)). Thus, the fact that irradiation at δ 3.18 (HA) causes enhancement of both the signals due to the angular methyl group (δ 1.02) and Hb (δ 1.80-1.87) shows clearly that the configuration and conformation of the ether 195 is that depicted by the structure 195a.

![Figure 9: HETCOR plot for the ether 195.](image)

In an attempt to prepare the methoxymethyl ether 196 epimeric with 195, the ketone 92 was reduced with lithium tri-sec-butylborohydride in THF at -78 °C. After an
oxidative workup, a mixture of the alcohols 197 and 194 was obtained in 85% yield (equation 46). Glc analysis of the mixture indicated that the two alcohols 197 and 194 were present in a ratio of 1.8:1, respectively. The two alcohols 197 and 194 proved difficult to separate, but eventually pure samples were obtained after careful silica gel chromatography.

\[
\begin{align*}
\text{1. Bu}^3\text{BHLi, THF,} & \quad \text{-78°C, 3 h then 0°C, 45 min} \\
\text{2. H}_2\text{O}_2, \text{NaOH} & \quad \text{+} \\
\end{align*}
\]

(46)

The ir spectrum of the alcohol 197 shows a broad hydroxyl absorption at 3389 cm\(^{-1}\) and an olefinic absorption at 1646 cm\(^{-1}\). The \(^1\)H nmr spectrum of 197 exhibits a signal at \(\delta\) 3.50 (one proton multiplet) for the carbinol methine proton.

Treatment of a cold (0 °C) dichloromethane solution of the alcohol 197 and \(N, N\)-diisopropylethylamine with chloromethyl methyl ether 92 gave the ether 196 in 74% yield (equation 47).

\[
\begin{align*}
\text{Pr}^2\text{NEt, CH}_3\text{OCH}_2\text{Cl,} & \quad \text{CH}_2\text{Cl}_2 \\
\text{197} & \quad \text{+} \\
\text{CH}_3\text{OCH}_2\text{O} & \quad \text{196} \\
\end{align*}
\]

(47)

The ir spectrum of the ether 196 shows an absorption at 1148 cm\(^{-1}\) due to the acetal function. The \(^1\)H nmr spectrum of 196 exhibits signals at \(\delta\) 1.02 (three proton singlet) for
the angular methyl group, 3.34 (one proton multiplet) for the -CH$_2$OCH$_2$OCH$_3$ proton, 3.40 (three proton singlet) for the protons of the methoxy group, and 4.59 (one proton doublet, $J = 6$ Hz) and 4.72 (one proton doublet, $J = 6$ Hz) for the acetal methylene protons.

In the $^1$H nmr spectrum of 196, the signal due to the -CH$_2$OCH$_2$OCH$_3$ proton has a width-at-half-height of 12 Hz, consistent with the $w_{1/2}$ values of equatorially oriented protons.$^{95}$ For comparison, the signal for the -CH$_2$OCH$_2$OCH$_3$ proton of 195 is a doublet of doublets, with coupling constants consistent with that of an axially oriented proton. Thus, it is clear that 196 exists primarily in the chair-chair conformation 196b and that the epimeric ethers 195 and 196 adopt similar conformations.

![196b]

Conversion of the ether 195 into the $\alpha,\beta$-unsaturated aldehyde 202 (see Scheme 38, p. 98, and Scheme 41, p. 109, *vide infra*) would involve the conversion of the exocyclic olefin into an aldehyde function and the introduction of a double bond. After some experimentation it was found that the aldehyde function was most effectively introduced via hydroboration-oxidation $^{96}$ of 195 followed by oxidation of the resultant alcohol.

Treatment of the ether 195 with a THF solution of borane-THF $^{96}$ at room temperature for 3 h, followed by oxidation of the resultant alkylborane species with an alkaline solution of hydrogen peroxide gave the alcohol 199 in 88% yield (equation 48).
The i.r. spectrum of the alcohol 199 shows a broad hydroxyl absorption at 3412 cm\(^{-1}\). The \(^1\)H nmr spectrum of 199 exhibits signals at \(\delta 3.63-3.75\) (two proton multiplet) for the carbinol methylene protons. An examination of molecular models suggested that the hydroborating reagent should approach the double bond from the face opposite to the angular methyl group, and hence the configuration of the hydroxymethyl group was assigned as being \textit{cis} to the angular methyl group. The configuration assigned to the hydroxymethyl function of 199 was confirmed by conversion of 199 into the aldehyde 198, whose stereochemistry was assigned from the results of epimerization experiments (\textit{vide infra}).

The alcohol 199 was oxidized by allowing a dichloromethane solution of 199 to react with pyridinium chlorochromate and sodium acetate at room temperature for 2 h.\(^{64}\) Upon workup, the aldehyde 198 was obtained in 92% yield (equation 49).

The i.r. spectrum of the aldehyde 198 shows absorptions at 2704 cm\(^{-1}\) and 1722 cm\(^{-1}\) for the aldehyde function. The \(^1\)H nmr spectrum of 198 exhibits signals at \(\delta 0.93\)
(three proton singlet) for the angular methyl group, 2.21 (one proton multiplet, $\omega_{1/2} = 12$ Hz) for the proton adjacent to the aldehyde function, 3.22 (one proton doublet of doublets, $J = 11, 4$ Hz) for the -CH-OCH$_2$OCH$_3$ proton and at 9.71 (one proton singlet) for the aldehydic proton.

The coupling constants of the -CH-OCH$_2$OCH$_3$ proton ($J = 11, 4$ Hz) are consistent with the methine proton having an axial orientation. Thus, the preferred chair-chair conformation of the aldehyde 198 should be that depicted by 198a. Structure 198a clearly shows that the aldehyde function and the angular methyl group are in a 1, 3-diaxial relationship. In order to relieve the steric interaction between these two groups, equilibration of the aldehyde function of 198 would be expected to lead to structure 200a in which the aldehyde moiety is equatorially oriented.

\[
\begin{align*}
\text{O} & \text{H} \\
\text{OCH$_2$OCH$_3$} & \text{O} \text{H} \\
\text{198a} & \text{200a}
\end{align*}
\]

Treatment of the aldehyde 198 with sodium methoxide in methanol at room temperature for 18 h afforded the aldehyde 200 in 70% yield (equation 50). The formation of an aldehyde different from 198 confirmed the stereochemistry assigned to the aldehyde 198.

\[
\begin{align*}
\text{CH$_3$OCH$_2$O} & \text{198} \quad \text{NaOMe, MeOH,} \quad \text{rt, 18 h} \\
\text{CH$_3$OCH$_2$O} & \text{200}
\end{align*}
\]

(50)
The ir spectrum of the aldehyde 200 shows absorptions at 2711 cm\(^{-1}\) and 1721 cm\(^{-1}\) for the aldehyde function. The \(^1\text{H}\) nmr spectrum of 200 exhibits signals at \(\delta 1.07\) (three proton singlet) for the angular methyl group, 2.67 (one proton doublet of triplets, \(J = 12, 3\) Hz) for the proton adjacent to the aldehyde function, and 9.64 (one proton singlet) for the aldehydic proton.

Several points concerning the \(^1\text{H}\) nmr spectrum of the aldehyde 200 are noteworthy. The coupling pattern of the proton adjacent to the aldehyde function (\(\delta 2.67\)) is consistent with that of an axially oriented proton having a large axial-axial and two small equatorial-equatorial couplings. The chemical shift value of the angular methyl group changes from 0.93 for 198 to 1.07 for 200. The latter value is similar to the values of the angular methyl group of the structurally related alcohol 199 and the ether 195. The chemical shift difference between the angular methyl groups of 198 and 200 can be explained as the result of the axial aldehyde moiety of 198 (see conformation 198a) having a conformational orientation such that the carbonyl \(\pi\)-electrons shield the angular methyl protons.

Treatment of a dichloromethane solution of the aldehyde 198 with triethylamine and iodotrimethylsilane at -20 °C for 10 min and at room temperature for 5 min gave the enol trimethylsilyl ethers 201 (Scheme 41). The \(^1\text{H}\) nmr spectrum of the enol silyl ethers 201 exhibits signals at \(\delta 0.15\) and 0.16 (singlets) for the silyl methyl protons and at 6.02 and 6.05 (doublets, \(J = 2\) Hz, 1:2 ratio, respectively) for the olefinic protons. The crude product was not stable to silica gel chromatography and was therefore used without purification.

Addition of palladium acetate to a solution of the enol trimethylsilyl ethers 201 in acetonitrile led to the complete consumption of 201 after 4 hours at room temperature (glc and tlc analysis). Silica gel chromatography of the crude product gave the \(\alpha,\beta\)-unsaturated aldehyde 202 in 48% overall yield from the aldehyde 198 (Scheme 41).
The ir spectrum of the α,β-unsaturated aldehyde 202 shows absorptions at 1684 cm\(^{-1}\) and 1640 cm\(^{-1}\) for the carbonyl and olefin functions, respectively. The \(^1\)H nmr spectrum of 202 exhibits signals at \(\delta 2.47\) (one proton doublet of triplets, \(J = 15, 4\) Hz) for one of the \(-CH-CH_2-\) protons, \(6.70\) (one proton triplet, \(J = 4\) Hz) for the olefinic proton, and at \(9.40\) (one proton singlet) for the aldehydic proton.

The regiochemical outcome of the Saegusa reaction \(^98\) is particularly interesting since the enol trimethylsilyl ethers 201 could undergo dehydrogenation either toward or away from the ring junction. The mechanism of the Saegusa reaction \(^98\) has not been investigated but probably involves an initial complexation between the enol ether double bond and palladium acetate. The palladium acetate should prefer to approach the enol ether double bond from the face opposite the angular methyl group to form the \(\pi\)-complex 203 (Scheme 42). Elimination of the proton \(H_a\) \(cis\) to palladium seems most likely since the \(\sigma\) bond between the proton \(H_a\) and the adjacent carbon atom is aligned with the \(\pi\)-orbitals of the olefin. Comparable alignment of the \(\pi\)-orbitals of the olefin and the \(\sigma\)-bond between the proton \(H_b\) and the adjacent carbon atom (or between \(H_c\) and the adjacent carbon atom) is not possible in the structure 203.
The conjugate addition of a methyl group to the α,β-unsaturated aldehyde 202 proceeded smoothly. A THF solution of 202 was added to a THF solution of lithium (cyano)(methyl)cuprate and chlorotrimethylsilane 45 and the reaction mixture was stirred at -78 °C for 8 h. After workup the enol silyl ether 204 was obtained in 92% yield (equation 51).

The ir spectrum of the enol silyl ether 204 shows an absorption at 1654 cm⁻¹ for the olefin function. The ¹H nmr spectrum of 204 exhibits signals at δ 0.08 (nine proton singlet) for the silyl methyl protons, 1.06 (three proton doublet, J = 7 Hz) for the secondary methyl group, 2.23 (broad one proton quintet, J = 7 Hz) for the proton adjacent to the secondary methyl group, and 6.09 (one proton singlet) for the olefinic proton.
The stereochemistry of the enol silyl ether 204 was assigned on the basis of results obtained from $^1$H nmr decoupling and nOe difference experiments. In a decoupling experiment, irradiation of the signal at $\delta$ 1.06 (secondary methyl group) simplified the signal at 2.23 ($H_a$) to a broad doublet ($J = 7$ Hz). Irradiation of the signal at $\delta$ 2.23 ($H_a$) simplified the doublet at 1.06 (secondary methyl group) to a singlet and simplified the multiplet at 1.10-1.85. The decoupling experiments established that the quintet at $\delta$ 2.23 ($H_a$) was indeed due to the proton adjacent to the secondary methyl group, although the coupling pattern was not that predicted a priori. The multiplicity and coupling constant associated with the $H_a$ resonance can be rationalized by proposing that the cyclohexane ring containing the secondary methyl group adopts a slightly twisted chair conformation, 204a, in which the secondary methyl group moves away from the 1, 3-diaxial methylene group (see * in 204a). This twist results in the coupling between the protons $H_c$ and $H_a$ and between $H_a$ and the secondary methyl protons being of approximately the same magnitude. Concomitantly, the coupling between $H_a$ and $H_d$ is very weak. The slightly distorted chair conformation 204a alleviates steric interaction between the secondary methyl and the $^*CH_2$ moiety, and therefore would be of lower energy than the conformation in which the secondary methyl group is truly axially oriented.

In an nOe difference experiment, irradiation of the signal at $\delta$ 2.23 ($H_a$) caused enhancement of the signals at 1.06 (secondary methyl group) and 6.09 ($H_b$). Similarly, in another nOe difference experiment, irradiation of the olefinic signal at $\delta$ 6.09 ($H_b$) caused
enhancement of the signal at 2.23 (H$_a$). The nOe difference results require the proton H$_a$ and the olefinic proton H$_b$ to be in close proximity to each other. This requirement appears to be possible only if the proton H$_a$ has an equatorial orientation. It is clear that if the proton H$_a$ is in the equatorial orientation then the secondary methyl group must be axially oriented.

The formation of only one enol silyl ether was particularly gratifying since there are potentially four isomers that could have been formed in this reaction. That is, the process could have produced two isomers epimeric at the carbon containing the newly introduced secondary methyl group, each of which could have consisted of a mixture of geometrically isomeric enol ethers. The formation of only one geometric isomer must be due to the $\alpha,\beta$-unsaturated aldehyde function adopting an $s$-trans geometry which is maintained during the conjugate addition process (Scheme 43). The results suggest that the conjugate addition process occurs via a chair-like transition state in which the copper(I) species adds in an axial manner via a transition state which, in the conversion of 202 into 204, can be represented by 205.\textsuperscript{53} Rearrangement of resultant copper(III) intermediate affords the enol silyl ether 204. The stereochemistry of the reaction would therefore seem to be controlled by stereoelectronic rather than steric factors.

![Scheme 43](image)

On the basis of an examination of molecular models and by analogy with the organoaluminum-promoted Claisen rearrangement \textsuperscript{59} of 103 (Scheme 29, p. 48), the
Claisen rearrangement\(^{35}\) of the enol allyl ether \(\text{206}\) would be predicted to occur from the face opposite to the angular methyl group to give the aldehyde \(\text{207}\) (equation \(52\)). Since we are unaware of \(\text{cis}\)-clerodanes in which the side chain and the angular methyl group have a \textit{trans} relationship (see the \(\text{cis}\)-clerodane skeleton \(\text{186}\), Scheme \(36\)) the Claisen rearrangement could not be used to introduce the final quaternary center.

\[
\begin{align*}
\text{CH}_3\text{OCH}_2\text{O} \quad \Delta \quad \text{H} & \quad \text{O} \\
\text{CH}_3\text{OCH}_2\text{O} \\
206 & \quad 207 \\
\end{align*}
\]

In order to obtain the required configuration of the quaternary center at C-9 of the \(\text{cis}\)-clerodanes, the one-carbon substituent had to be introduced from the face opposite the angular methyl group. The axial aldehyde function at C-9 would then be used to introduce the required side chain.

Treatment of the enol trimethylsilyl ether \(\text{204}\) with methyllithium in DME at 0 °C for 15 min and at room temperature for 15 min according to the procedure of Stork and Hudrlik,\(^{54}\) followed by the addition of methyl iodide at 0 °C and stirring of the resultant solution at 0 °C for 4 h, gave a mixture of products (equation \(53\)). The major component was isolated in 41% yield by silica gel chromatography and was shown to be the methyl enol ether \(\text{208}\).
The ir spectrum of the methyl enol ether 208 exhibits a strong olefinic absorption at 1665 cm\(^{-1}\). The \(^1\)H nmr spectrum of 208 shows signals at \(\delta\) 1.00 (three proton singlet), 1.14 (three proton doublet, \(J = 8\) Hz), 3.37 (three proton singlet) and 3.51 (three proton singlet) for four methyl groups and a signal at 5.84 (one proton singlet) for the olefinic proton. The high resolution mass spectrum of the methyl enol ether 208 shows a molecular ion at m/e 268.2033, consistent with the molecular formula C\(_{16}\)H\(_{28}\)O\(_{3}\).

Further attempts to quaternize the enol trimethylsilyl ether 204 by treatment with methyl lithium in DME or THF at various temperatures, followed by the addition of methyl iodide, gave variable amounts of the methyl enol ether 208 and the aldehyde 209 (equation 54). Similar results were obtained when the enol trimethylsilyl ether 204 was treated sequentially with lithium amide in ammonia-THF and methyl iodide, a procedure which is reported \(^99\) to suppress the formation of O-alkylated products.
The aldehyde 209 exhibits a strong ir absorption at 1722 cm$^{-1}$ and shows a $^1$H nmr resonance at $\delta$ 9.31 (one proton doublet, $J = 5$ Hz), both of which are diagnostic of an aldehyde function. The high resolution mass spectrum of the aldehyde 209 shows a molecular ion at m/e 254.1877, consistent with the molecular formula C$_{15}$H$_{26}$O$_3$.

Indirect alkylation procedures such as the cyclopropanation of the enol trimethylsilyl ether 204 with diiodomethane and diethylzinc 100 or zinc-copper couple 101 did not lead to acceptable yields of cyclopropanated products. Disappointing results were also obtained when the enol trimethylsilyl ether 204 was treated with diisoproxy titanium dichloride and chloromethyl phenyl sulfide.102 Results from the attempted quaternization of C-9 indicated that such a transformation would not be trivial. Due to time constraints, further attempts to quaternize C-9 were not undertaken.

Conclusion

The series of reactions described here illustrate methods by which three of the four chiral centers of cis-clerodanes can be introduced in a stereocontrolled manner. The stereocontrol relies on the formation of non-epimerizable cis-decalin intermediates with a conformational preference for the non-steroidal conformation.103 Access to the latter conformation is readily achieved by reduction of the ketone 92 with calcium in ammonia.

A regioselective Saegusa reaction 98 was used to convert the aldehyde 198 into the $\alpha,\beta$-unsaturated aldehyde 202. The secondary methyl group present in the enol trimethylsilyl ether 204 was introduced in a highly stereoselective manner via a chlorotrimethylsilane-promoted conjugate addition of lithium (cyano)(methyl)cuprate 45 to the $\alpha,\beta$-unsaturated aldehyde 202. The preference of the resultant product 204 to exist in a twisted chair-like conformation suggests that a conformation flip may occur if the CH$_3$OCH$_2$O group did not exert such a large conformational preference. The enol
trimethylsilyl ether 204 was synthesized in seven synthetic steps in 33% overall yield from the previously reported ketone 92.

Further work aimed at the synthesis of cis-clerodanes could exploit the stereocontrolled route developed here by carrying out a series of reactions similar to that used to convert 195 into 204. Thus, the conversion of 196 into the α,β-unsaturated aldehyde 210 would presumably be possible by employing the sequence used to convert 195 into 202. Reaction of 210 with lithium (cyano)(methyl)cuprate in the presence of chlorotrimethylsilane should afford 211 in which the secondary methyl group has added in an axial manner. In contrast to the enol trimethylsilyl ether 204, 211 would be expected to undergo a conformational flip from 211a to 211b (Scheme 44). Alkylation of the enol trimethylsilyl ether 211, from the conformation 211b, should be considerably easier than for 204. The resultant aldehyde 212 has the same relative stereochemistry as that of the cis-clerodanes. In addition, the Claisen rearrangement reaction of the enol allyl ether 213, which would presumably be preparable from 211, would also be expected to afford 212.
MeCu(CN)Li (5.0 eq.),
TMSCl (5.3 eq.),
THF, -78 °C

Scheme 44
EXPERIMENTAL

General

Proton nuclear magnetic resonance ($^1$H nmr) spectra were recorded on Varian model XL-300 or Bruker model WH 400 spectrometers using deuteriochloroform as the solvent. Signal positions are given in parts per million (δ) from tetramethylsilane (TMS) as the internal standard. For those compounds containing trimethylstannyl or trialkylsilyl groups, the resonance positions were determined relative to the chloroform signal (δ 7.25).\textsuperscript{104} Coupling constants (J-values) are given in Hz. Spectral content is listed in the following order: chemical shift (δ), multiplicity, number of protons, coupling constants (Hz), assignment (where possible).

Carbon nuclear magnetic resonance ($^{13}$C nmr) spectra were recorded on a Varian model XL-300 spectrometer at 75.3 MHz using deuteriochloroform as the solvent. Signal positions are given in parts per million (δ) from TMS. Signals with negative intensities in an attached proton test (APT) are so indicated in brackets (-ve) following the chemical shift.

Infrared (ir) spectra were recorded on a Perkin-Elmer model 1710 Fourier transform spectrophotometer with internal calibration. The ir spectra of liquids were recorded as films on sodium chloride plates and the ir spectra of solids were obtained from potassium bromide discs.

Low resolution mass spectra (LRMS) were recorded on an AEI MS9/DS55SM (1964, In-House 1980) or on a KRATOS MS50/DS55SM (1974) spectrometer. High resolution mass spectra were recorded on a KRATOS MS50/DS55SM (1974) spectrometer.

Analytical gas-liquid chromatography (glc) was performed on either a Hewlett-Packard model 5890 or model 5880 capillary gas chromatograph, employing 20 m x 0.21
mm fused silica columns coated with cross-linked SE-54, both using a flame ionization detector.

Preparative silica gel thin layer chromatography was performed on commercially available, glass backed plates (25 x 25 cm), precoated with silica gel 60 to a thickness of 0.5 mm (Kieselgel, type F-254). Preparative reverse phase thin layer chromatography was performed on commercially available, glass backed plates (25 x 25 cm, Whatman, type KC18/KC18F). Thin-layer chromatography (tlc) was performed on commercially available, aluminum backed sheets, precoated with silica gel 60 to a thickness of 0.2 mm (E. Merck, type 5554). Visualization of the chromatograms was accomplished with an ultraviolet light (254 nm) tube, iodine stain or heating the chromatogram after staining with either a 5% aqueous solution of ammonium molybdate in 10% aqueous sulfuric acid (w/v) or in commercially available (Aldrich Chemical Co., Inc.) phosphomolybdic acid. Conventional column chromatography (drip) as well as medium pressure and flash chromatography were performed using 230-400 mesh silica gel (E. Merck, Silica gel 60).

Preparative liquid chromatography was performed on a Waters Prep LC/System 500. A flow rate of 100 mL/min and a chart speed of 5 min/cm was used. Typically, the detector response was set at 50 and doubled each time the material was recycled.

Sononation was performed with either a Branson ® Ultrasonic Cleaner B-220 or a Bransonic ® Ultrasonic Cleaner B-3200R-1.

Distillation temperatures (uncorrected) were recorded as air-bath temperatures required for short path bulb-to-bulb (Kugelrhor) distillation. Melting points were measured on a Fisher-Johns melting point apparatus and are uncorrected.

All dry solvents used were obtained by refluxing over an appropriate drying agent. Distilled solvents were used immediately or stored over molecular sieves where appropriate. Dimethoxyethane, diethyl ether and tetrahydrofuran were dried over sodium benzophenone ketyl. Dichloromethane was dried over phosphorous pentoxide or calcium hydride. Diisopropylamine, hexamethylphosphoramide, benzene, chlorotrimethylsilane,
2,6-lutidine and triethylamine were dried over calcium hydride. Ethanol was distilled from magnesium turnings activated with iodine when necessary. The petroleum ether used was a hydrocarbon mixture with a b.p. 35-60 °C. Methyl chloroformate was distilled and stored over activated 4Å molecular sieves and basic alumina activity 1.

*p*-Toluenesulfonic acid monohydrate was dried at ≈ 105 °C (at which temperature a melt was obtained) under vacuum (vacuum pump) for 0.5 h and stored under an atmosphere of argon. Lithium cyanide obtained from Morton Thiokol Inc. (Alfa Products) was dried at 40-50 °C under vacuum (vacuum pump) for 2 h. Sodium acetate was dried at ≈ 120 °C under vacuum (vacuum pump) for 1-2 h.

Solutions of methyllithium-lithium bromide complex (subsequently referred to as methyllithium) in diethyl ether and n-butyllithium in hexanes were obtained from the Aldrich Chemical Co., Inc. and were standardized using the method of Kafron and Baclawski.107

Copper(I) bromide-dimethyl sulfide complex was prepared in the manner described by House and co-workers,108 after washing commercially available copper(I) bromide with methanol. Magnesium bromide-etherate was prepared by the reaction of 1,2-dibromoethane (in excess) with magnesium metal in diethyl ether, followed by removal of diethyl ether under reduced pressure (0.3 torr) at room temperature. tert-Butoxydiphenylsilyl chloride was prepared according to the procedure reported by Gillard and co-workers.76 Saturated aqueous ammonium chloride (pH 8) was prepared by the addition of ≈50 mL of aqueous ammonium hydroxide (58%) to ≈1L of saturated aqueous ammonium chloride.

Lithium diisopropylamide (LDA) was prepared by the addition of a solution of methyllithium in diethyl ether to a solution of diisopropylamine in dry THF at 0 °C. The resulting solution was then stirred at this temperature for 5 min before use.109
Cold bath temperatures were maintained by the use of the following baths: 27 g CaCl$_2$/100 mL H$_2$O/dry ice (-20 °C), chloroform-dry ice (-63 °C), acetone-dry ice (-78 °C).

Unless stated otherwise, all reactions were carried out under an atmosphere of dry argon using glassware that had been thoroughly oven or flame-dried.
Procedures for the Total Synthesis of (±)-Stephalic Acid

Preparation of 5-Chloro-2-trimethylstanny1-1-pentene (84)

To a cold (-20 °C) stirred solution of hexamethylditin (33.5 mL, 1.3 equiv) in dry THF (1.0 L) was added methyllithium (130 mL, 1.3 equiv) as a solution in diethyl ether. The resulting pale yellow solution was stirred at -20 °C for 20 min and was then cooled to -78 °C. Solid copper(I) bromide-dimethyl sulfide complex (33.0 g, 1.3 equiv) was added in one portion and the mixture stirred at -78 °C for 1 h. To the resulting reddish brown solution was added neat 5-chloro-l-pentyne (13.1 mL, 123 mmol) and the reaction mixture was stirred at -78 °C for 6 h. Saturated aqueous ammonium chloride (pH 8, ≈ 200 mL) was added and the mixture was stirred at -78 °C for 15 min. The cooling bath was removed and petroleum ether (≈ 200 mL) was added. The mixture was allowed to warm to room temperature and was stirred vigorously with exposure to air until the aqueous phase became a deep blue colour (most conveniently overnight). The blue aqueous layer was separated and extracted three times with petroleum ether. The combined organic solution was washed with saturated aqueous ammonium chloride (pH 8) until the washings were colourless and then was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure (rotary evaporator) afforded a pale yellow oil that was subjected to column chromatography on silica gel (8.5 x 50 cm column, elution with petroleum ether). Distillation (air-bath temperature 100-105 °C/30 torr) of the oil obtained from the
appropriate fractions provided 25.6 g (82%) of 5-chloro-2-trimethylstannyl-1-pentene (84) 29 as a colourless oil. This material exhibits ir (film): 3040, 920, 772 cm⁻¹; ¹H nmr (400 MHz) δ: 0.16 (s, 9H, -Sn(CH₃)₃, ²J_Sn-H = 54 Hz), 1.85 (quintet, 2H, J = 7 Hz, -CH₂CH₂CH₂Cl), 2.40 (br t, 2H, J = 7 Hz, -CSn(CH₃)₃CH₂-), 3.50 (t, 2H, J = 7 Hz, -CH₂Cl), 5.22-5.24 (m, 1H, ³J_Sn-H = 70 Hz, olefinic proton cis to -Sn(CH₃)₃), 5.71-5.73 (m, 1H, ³J_Sn-H = 152 Hz, olefinic proton trans to -Sn(CH₃)₃).

**Preparation of Methylene cyclobutane (107)**

To a cold (-78 °C) solution of 5-chloro-2-trimethylstannyl-1-pentene (84) (115 mg, 0.431 mmol) in dry THF (4.3 mL) was added a solution of methyllithium in diethyl ether (0.344 mL, 1.2 equiv). The resulting solution was stirred at -78 °C for 20 min and then was warmed to 0 °C for 0.5 h. Benzyl benzoate (80 μL, 0.419 mmol) was added to the cold (0 °C) solution to provide an internal standard and the mixture was stirred briefly. A portion of the resulting solution (50 μL) was removed, deuteriochloroform was added and the resultant solution was analyzed by ¹H nmr spectroscopy. The latter material exhibits signals due to tetramethyltin (δ 0.04, s, ²J_Sn-H = 54), diethyl ether (δ 1.17, t and 3.45, q), THF (δ 1.83 and 4.72), benzyl benzoate (δ 5.34, s; 7.29-7.56, m and 8.02-8.07, m) and methylene cyclobutane (δ 1.99, quintet, J = 7 Hz; 2.67, tt, J = 7 Hz, 2; 4.65, quintet, J = 2 Hz). Comparison of the ¹H nmr integration of the signals due to the methylene protons of benzyl benzoate (δ 5.34) and the allylic protons of methylene cyclobutane (δ 2.67) indicated that methylene cyclobutane (107) had been produced in a yield of approximately 93%.
Preparation of the Chloro Ketone 93

To a cold (-78 °C) stirred solution of 5-chloro-2-trimethylstannyl-1-pentene (84) (1.13 g, 1.24 equiv) in dry THF (40 mL) was added a solution of methyllithium (3.6 mL, 1.42 equiv) in diethyl ether. After the mixture had been stirred at -78 °C for 20 min, solid magnesium bromide-etherate (1.12 g, 1.28 equiv) was added in one portion and the resulting milky solution was stirred for an additional 40 min. Solid copper(I) bromide-dimethyl sulfide complex (35 mg, 0.05 equiv), boron trifluoride-etherate (0.46 mL, 1.1 equiv) and 3-methyl-2-cyclohexen-1-one (0.39 mL, 3.4 mmol) were added sequentially. The resulting bright yellow slurry was stirred at -78 °C for 2 h and then saturated aqueous ammonium chloride (pH 8, 20 mL) was added. Petroleum ether (= 20 mL) was added and the mixture was stirred vigorously with exposure to air until the aqueous phase became a deep blue colour (usually after 1-2 h). The aqueous layer was separated and extracted twice with diethyl ether. The combined organic extract was washed once with aqueous ammonium chloride (pH 8) and repeatedly with brine until the aqueous phase was neutral as indicated by pH paper. The organic phase was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded a pale yellow oil that was subjected to column chromatography on silica gel (4.5 x 15 cm column, elution with petroleum ether-diethyl ether, 4:1). Distillation (air-bath temperature 85-90 °C/0.2 torr) of the oil obtained from the appropriate fractions provided 660 mg (91%) of the chloro ketone 93 as a colourless oil. This material exhibits ir (film) : 3040, 1709, 1636, 904 cm⁻¹; ¹H nmr (400 MHz) δ: 1.03 (s, 3H, tertiary methyl), 1.51-1.93 (m, 6H), 2.05-2.28 (m, 5H),
2.54 (dt, 1H, J = 16, 2 Hz), 3.51 (t, 2H, J = 7 Hz, -CH₂Cl), 4.80 (s, 1H, one of =CH₂), 4.86 (s, 1H, one of =CH₂). Exact Mass calcd. for C₁₂H₁₉₃₅ClO: 214.1124; found: 214.1128.

Preparation of the Ketones 94 and 95

To a well stirred suspension of potassium hydride (5.17 g, 2.0 equiv) in dry THF (150 mL) at room temperature was added a solution of the chloro ketone 93 (4.84 g, 22.6 mmol) in dry THF (25 mL). The resulting mixture was stirred at room temperature for 1 h and then dry ethanol (13.3 mL, 10 equiv) was added in a dropwise manner. The mixture was refluxed for 1 h and then was allowed to cool to room temperature. Brine was added, the layers were separated, and the organic phase was extracted repeatedly with brine until the aqueous phase was neutral as indicated by pH paper. The organic phase was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded an oil which was subjected to column chromatography on silica gel (4.5 x 15 cm column, elution with petroleum ether-diethyl ether, 9:1). Glc analysis of the oil thus obtained showed that it consisted of a mixture of two compounds in a ratio of 78:22*. Distillation (air-bath temperature 72-78 °C/0.3 torr) of this material yielded 3.28 g (82%) of a colourless oil.

* Ratios are quoted as trans : cis ratios of ketones 94 and 95 respectively.
The two compounds were separated using a Waters preparative liquid chromatograph. Optimum conditions, in terms of recovery and resolution, were achieved when the sample load was limited to = 1.5 g. The following example is typical. Thus, preparative liquid chromatography of the mixture (78:22, 1.47 g) on silica gel (1 PrepPak ® 500 column, elution with hexanes-ethyl acetate, 9:1) in which the mixed fractions were recycled internally (recycling to a total of 4 times), followed by concentration of the appropriate fractions gave 1.00 g (68%, recovery) of the trans-ketone 94 29 (air-bath temperature 80-85 °C/0.35 torr), 0.307 g (21%, recovery) of the cis-ketone 95 29 (air-bath temperature 72-78 °C/0.3 torr) and 0.090 g (6%, recovery) of a mixture (in a ratio of 76:24 by glc, air-bath temperature 72-78 °C/0.3 torr)).

The trans-ketone 94 exhibits ir (film): 3086, 1713, 1640 cm⁻¹; ¹H nmr (400 MHz) δ: 0.94 (s, 3H, angular methyl), 1.19-1.33 (m, 1H), 1.53-1.75 (m, 3H), 1.84-2.40 (m, 9H), 4.72-4.77 (m, 2H, =CH₂). Exact Mass calcd. for C₁₂H₁₈O: 178.1358; found: 178.1355.

The cis-ketone 95 exhibits ir (film): 3085, 1708, 1638 cm⁻¹; ¹H nmr (400 MHz) δ: 1.17 (s, 3H, angular methyl), 1.23-1.50 (m, 3H), 1.62-1.71 (m, 1H), 1.76-2.39 (m, 8H), 2.42-2.53 (m, 1H), 4.74 (br s, 1H, one of =CH₂), 4.76 (br s, 1H, one of =CH₂). Exact Mass calcd. for C₁₂H₁₈O: 178.1358; found: 178.1351.

Preparation of the Aldehyde 104
To a stirred solution of the α,β-unsaturated nitrile 102 * (483 mg, 2.58 mmol) in dry THF (2.6 mL) at room temperature was added a solution of diisobutylaluminum hydride (3.2 mL, 1.25 equiv) in hexanes. The resulting solution was stirred at room temperature for 1 h and then an aqueous solution of 10% sulfuric acid (1 mL) was added. The organic phase was removed and the aqueous phase was extracted with diethyl ether (3 x 5 mL). The combined organic phase was washed with brine until the aqueous phase was neutral as indicated by pH paper. The organic solution was filtered through a short pad of Florisil ® (5.0 x 5.5 cm column, elution with diethyl ether (3 x 20 mL)) and was then dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure (rotary evaporator, then vacuum pump, 0.3 torr/15 hr) provided 437 mg (89%) of the α,β-unsaturated aldehyde 104 as a colourless oil. (Distillation of this material (air-bath temperature 131-134 °C/0.3 torr) resulted in a considerable amount of decomposition). This material exhibits ir (film): 3085, 2711, 1688, 1627 cm⁻¹; ¹H nmr (400 MHz) δ: 0.96 (s, 3H, angular methyl), 1.24-1.63 (m, 5H), 1.82 (dt, 1H, J = 12, 3 Hz), 1.86-1.94 (m, 1H), 2.17-2.25 (m, 1H), 2.42-2.53 (m, 2H), 2.71-2.79 (m, 1H), 4.61 (s, 1H, one of =CH₂), 4.69 (s, 1H, one of =CH₂), 6.73 (m, 1H, olefinic proton), 9.45 (s, 1H, aldehydic proton). *Exact Mass calcd. for C₁₃H₁₈O: 190.1358; found: 190.1358.

* The preparation of the α,β-unsaturated nitrile 102 from the ketone 94 is described in the Experimental section of this thesis entitled Procedures for the Conversion of Ketones into α,β- Unsaturated Nitriles.
Preparation of the Enol Silyl Ether 111

To a cold (-78 °C) stirred suspension of copper(I) cyanide (4.69 g, 2 equiv) in dry THF (200 mL) was added methyllithium (37.5 mL, 2.0 equiv) as a solution in diethyl ether. The reaction mixture was stirred at -78 °C for 10 min and then chlorotrimethylsilane (16.6 mL, 5.0 equiv) was added. The solution was stirred at -78 °C for 5 min and then a dry THF solution (5.0 mL, followed by the addition of a 5.0 mL washing) of the α,β-unsaturated aldehyde 104 (4.95 g, 26.1 mmol) was added in a dropwise manner. The reaction mixture was stirred at -78 °C for 2 h and then saturated aqueous ammonium chloride (pH 8, 40 mL) was added. The organic phase was separated and washed repeatedly with brine until the aqueous phase was neutral as indicated by pH paper. The organic solution was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Distillation (air-bath temperature 112-118 °C/0.3 torr) of the oil thus obtained provided 6.26 g (86%) of the enol silyl ether 111 as a colourless oil. Analysis of this material by 1H nmr and glc showed that a mixture of two components was present (1:1 ratio), in addition to a small amount of an impurity (less than 5% by glc analysis). This material proved to be quite unstable with respect to silica gel chromatography (elution with petroleum ether) and resulted in poor recovery of the enol silyl ethers (10:3 ratio by 1H nmr integration) but did provide a pure sample for characterization purposes. This material exhibits ir (film): 3086, 1657, 1637 cm⁻¹; 1H nmr (400 MHz) δ: 0.16, 0.17 (two s, -Si(CH₃)₃), 0.98, 0.99 (two s, angular methyls), 0.97, 1.05 (two d, J = 7 Hz each, secondary methyls, 3:1 ratio by integration), 1.12-1.30
Preparation of the Aldehyde 112

Following the procedure for the conversion of 104 into 111, a sample of the α,β-unsaturated aldehyde 104 (129 mg, 0.679 mmol) was converted into the enol silyl ether 111. A solution of the crude product (undistilled) in THF (2.0 mL) was added to an aqueous solution of 10% sulfuric acid (2.0 mL) and the mixture stirred at room temperature for 0.5 h. Petroleum ether (= 20 mL) was added and the aqueous phase was separated. The organic solution was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the crude product on silica gel (0.7 x 15 cm column, elution with petroleum ether-diethyl ether, 9:1), concentration of the appropriate fractions, and distillation (air-bath temperature 125-132 °C/0.3 torr) of the oil thus obtained provided 94.0 mg (67%) of the aldehyde 112 as a colourless oil. This material exhibits ir (film): 3085, 2728, 1718, 1637 cm⁻¹; ¹H nmr (400 MHz) δ: 0.90 (s, 3H, angular methyl), 1.04 (d, 3H, J = 7 Hz, secondary methyl), 1.35-1.46 (m, 3H), 1.56-1.64 (m, 2H), 1.71 (td, 1H, J = 16, 4 Hz), 1.77-2.09 (m, 4H), 2.15-2.22 (m, 1H), 2.36 (td, 1H, J = 14, 4 Hz), 2.57 (quintet, 1H, J = 6 Hz, methine proton α to the secondary methyl), 4.60 (s, 1H, one of =CH₂), 4.63 (s, 1H, one of =CH₂), 10.01 (s, 1H, aldehydic proton). The following decoupling experiments were carried out. Irradiation of the signal
at $\delta$ 1.04 (secondary methyl): quintet at 2.57 (methylene proton $\alpha$ to the secondary methyl) simplified to a broad doublet ($J = 6$ Hz); irradiation of the signal at $\delta$ 2.57 (methylene proton $\alpha$ to the secondary methyl): doublet at 1.04 (secondary methyl) simplified to a singlet, multiplet at 1.56-1.64 simplified, multiplet at 1.77-1.91 simplified.  

Exact Mass calcd. for $C_{14}H_{22}O$: 206.1670; found: 206.1673.

Preparation of the Diene Alcohol 118

![Diagram of molecules 103 and 118]

To a stirred solution of the enol silyl ether 111 (73.5 mg, 0.264 mmol) in dry HMPA (11.5 mL) at room temperature was added methyllithium (0.228 μL, 1.2 equiv) as a solution in diethyl ether. The mixture was stirred at room temperature for 10 min and then neat allyl chloride (43 μL, 2.0 equiv) that had been passed through a plug of flame-dried basic alumina (activity 1) was added. The resulting solution was stirred at room temperature for 0.5 h. Water (≈ 2 mL) and diethyl ether (≈ 5 mL) were added, the organic phase was removed and the aqueous phase was extracted with diethyl ether (3 x 5 mL). The combined organic phase was washed with water (3 x 5 mL) and dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Analysis of the residual material by $^1H$ nmr, ir, and high resolution mass spectroscopy indicated that the desired allyl enol ether 103 (as a 1:1 mixture of double bond isomers) was the major component. Since this material proved to be quite unstable with respect to silica gel chromatography, the crude product (72.5 mg) was distilled (air-bath temperature 100-110 °C/0.3 torr) and the distillate was used without further purification.
To a solution of the distilled crude allyl enol ether 103 in dry dichloromethane (1.5 mL) at room temperature was added triisobutylaluminum (0.850 mL, 2.5 equiv) as a solution in toluene. The reaction mixture was stirred at room temperature for 1 h and then dry diethyl ether (= 10 mL) was added. The resultant mixture was slowly added to a vigorously stirred aqueous solution of 5% sulfuric acid (= 10 mL). (Treatment of the reaction mixture in this manner results in an extremely vigorous reaction. Care should be exercised during this step, especially when large quantities of reagent are involved.) The organic phase was removed and the aqueous phase was extracted with diethyl ether (3 x 5 mL). The combined organic extract was washed repeatedly with brine until the aqueous phase was neutral as indicated by pH paper. The organic solution was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the crude product on silica gel (0.7 x 15 cm column, elution with petroleum ether-diethyl ether, 4:1), concentration of the appropriate fractions and distillation (air-bath temperature 165-171 °C/0.3 torr) of the oil thus obtained provided 33.6 mg (52%) of the diene alcohol 118 as a colourless oil. This material exhibits ir (film): 3420, 3082, 1637 cm⁻¹; ¹H nmr (400 MHz) δ: 1.02 (d, 3H, J = 8 Hz, secondary methyl), 1.13 (s, 3H, angular methyl), 1.15-1.41 (m, 5H), 1.49-1.62 (m, 2H, simplifies to a one-proton qd on addition of D₂O, J = 13, 3 Hz), 1.71-1.78 (m, 1H), 1.81-2.02 (m, 4H), 2.08-2.15 (m, 1H), 2.30 (td, 1H, J = 12, 4 Hz), 2.48 (dd, 1H, J = 15, 8 Hz), 3.76 (d, 1H, J = 12 Hz, one of -CH₂OH), 3.90 (d, 1H, J = 12 Hz, one of -CH₂OH) 4.50 (s, 1H, one of the exocyclic =CH₂), 4.55 (s, 1H, one of the exocyclic =CH₂), 5.07 (d, 1H, J = 10 Hz, one of -CH=CH₂), 5.12 (d, 1H, J = 16 Hz, one of -CH=CH₂), 5.98-6.11 (m, 1H, -CH=CH₂). In a nuclear Overhauser enhancement (nOe) difference experiment, irradiation at δ 3.90 (one of -CH₂OH) caused signal enhancement at 3.76 (one of -CH₂OH) and at 1.13 (angular methyl). Exact Mass calcd. for C₁₇H₂₈O: 248.2140; found: 248.2141.
Preparation of the Silyl Ether 120

To a stirred solution of the diene alcohol 118 (709 mg, 2.86 mmol) in dry dichloromethane (14 mL) at room temperature were added sequentially 2,6-lutidine (0.831 mL, 2.5 equiv) and tert-butyldimethylsilyl trifluoromethanesulfonate (0.984 mL, 1.5 equiv). The resulting solution was stirred at room temperature for 0.5 h. The mixture was washed with an aqueous solution (= 5 mL) of saturated sodium hydrogen carbonate and the organic phase was separated and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded an oil that was subjected to column chromatography on silica gel (3.5 x 15 cm column, elution with petroleum ether). Distillation (air-bath temperature 140-150 °C/0.2 torr) of the oil obtained from the appropriate fractions provided 784 mg (76%) of the silyl ether 120 as a colourless oil. This material exhibits ir (film): 3076, 1637, 1092 cm⁻¹; ¹H nmr (400 MHz) δ: 0.02 (s, 3H, one of (CH₃)₂Bu’Si-), 0.04 (s, 3H, one of (CH₃)₂Bu’Si-), 0.91 (s, 9H, Bu’), 0.99 (d, 3H, J = 7 Hz, secondary methyl), 1.13 (s, 3H, angular methyl), 1.24-1.34 (m, 3H), 1.60-1.94 (m, 8H), 2.07-2.14 (m, 1H), 2.24 (td, 1H, J = 12, 4 Hz), 2.54 (dd, 1H, J = 14, 8 Hz), 3.51 (d, 1H, J = 10 Hz, one of -CH₂OSiBu’(CH₃)₂), 3.90 (d, 1H, J = 10 Hz, one of -CH₂OSiBu’(CH₃)₂), 4.48 (s, 1H, one of the exocyclic =CH₂), 4.53 (s, 1H, one of the exocyclic =CH₂), 4.98-5.08 (m, 2H, -CH=CH₂), 5.82-5.95 (m, 1H, -CH=CH₂). In a nOe difference experiment, irradiation at δ 3.90 (one of -CH₂OSiBu’Me₂) caused signal enhancement at 3.51 (one of -CH₂OSiBu’Me₂) and at 1.13 (angular methyl). Exact Mass calcd. for C₂₃H₄₂O Si: 362.3005; found: 362.2997.
Preparation of the Silyl Ether 121

To a stirred solution of the silyl ether 120 (40.7 mg, 0.112 mmol) in dry dichloromethane (1.0 mL) at room temperature was added dry p-toluenesulfonic acid (2.1 mg, 0.11 equiv). The reaction mixture was stirred at room temperature for 2 h. A saturated aqueous solution (= 2 mL) of sodium hydrogen carbonate was added and the organic phase was separated and dried over anhydrous magnesium sulfate. The organic solution was passed through a short column of Florisil ® (0.5 x 2 cm column, elution with petroleum ether) and then the solvent was removed from the eluate under reduced pressure. Distillation (air-bath temperature 140-144 °C/0.2 torr) of the oil thus obtained provided 33.1 mg (81%) of the silyl ether 121 as a colourless oil. This material exhibits ir (film): 3075, 1637, 1090 cm⁻¹; ¹H nmr (400 MHz) δ: 0.01 (s, 3H, one of (CH₃)₂Bu¹Si⁻), 0.02 (s, 3H, one of (CH₃)₂Bu¹Si⁻), 0.90 (s, 9H, Bu¹), 1.00 (d, 3H, J = 7 Hz, secondary methyl), 1.09 (s, 3H, angular methyl), 1.22-1.30 (m, 3H), 1.42-1.64 (m, 3H), 1.59 (br s, 3H, vinylic methyl), 1.74-2.03 (m, 5H), 2.67 (dd, 1H, J = 14, 8 Hz), 3.47 (d, 1H, J = 10 Hz, one of -CH₂OSiBu¹(CH₃)₂), 3.91 (d, 1H, J = 10 Hz, one of -CH₂OSiBu¹(CH₃)₂), 5.01-5.12 (m, 2H, -CH=CH₂), 5.19 (br s, 1H, -CH₂CH=C(CH₃)⁻), 5.82-5.95 (m, 1H, -CH=CH₂). Exact Mass calcd. for C₂₃H₄₂OSi: 362.3005; found: 362.2999.
Preparation of the Alcohol 122

\[
\begin{align*}
\text{OH} \\
\text{OSiBu}^t\text{Me}_2
\end{align*}
\]

To a stirred solution of 9-BBN (221 mg, 2.0 equiv) in dry THF (8.2 mL) at room temperature was added the silyl ether \( \text{121} \) (327 mg, 0.904 mmol) as a solution in dry THF (1.0 mL). The resultant mixture was stirred at room temperature for 3 h. Aqueous solutions of sodium hydroxide (0.202 mL, 0.7 equiv) and hydrogen peroxide (0.256 mL, 2.5 equiv) were then added simultaneously in a dropwise manner. The resultant mixture was stirred for 15 min and then brine (\( \approx 5 \) mL) and diethyl ether (\( \approx 5 \) mL) were added. The organic phase was separated and the aqueous phase was extracted with diethyl ether (2 x 5 mL). The combined organic solution was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the crude product on silica gel (2.7 x 15 cm column, elution with petroleum ether-diethyl ether, 4:1), concentration of the appropriate fractions and distillation (air-bath temperature 205-212 °C/0.3 torr) of the oil thus obtained, provided 311 mg (90%) of the alcohol 122. This material exhibits IR (film): 3328, 3088, 1636 cm\(^{-1}\); \(^1\)H NMR (400 MHz) \( \delta \): 0.02 (s, 3H, one of \((\text{CH}_3)^2\text{Bu}^t\text{Si}^-\)), 0.03 (s, 3H, one of \((\text{CH}_3)^2\text{Bu}^t\text{Si}^-\)), 0.90 (s, 9H, \text{Bu}^t\)), 0.94 (d, 3H, \( J = 7 \) Hz, secondary methyl), 1.09 (s, 3H, angular methyl), 1.19-1.32 (m, 3H), 1.42-2.06 (diffuse m, 12H), 1.59 (br s, 3H, vinylic methyl), 3.45 (d, 1H, \( J = 10 \) Hz, one of \(-\text{CH}_2\text{OSiBu}^t(\text{CH}_3)\)), 3.57-3.69 (m, 2H, -\text{CH}_2\text{OH}), 3.97 (d, 1H, \( J = 10 \) Hz, one of \(-\text{CH}_2\text{OSiBu}^t(\text{CH}_3)\)), 5.19 (br s, 1H, -\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)-\). Exact Mass calcd. for \( \text{C}_{19}\text{H}_{35}\text{O}_2\text{Si} \) (M\(^+\) - \text{Bu}^t\): 323.2406; found: 323.2401.
Preparation of the Aldehyde 123

To a stirred solution of the alcohol 122 (11.1 mg, 29.2 μmol) in dry dichloromethane (1.0 mL) were added dry sodium acetate (0.7 mg, 0.3 equiv) and pyridinium chlorochromate (9.5 mg, 1.5 equiv). The dark brown solution was stirred at room temperature for 2 h and then dry diethyl ether (= 2 mL) was added. The heterogeneous mixture was sonicated for 1 min and then was passed through a plug of Florisil® (elution with dry diethyl ether). Removal of the solvent under reduced pressure and distillation (air-bath temperature 165-170 °C/0.17 torr) of the oil thus obtained, provided 9.1 mg (82%) of the aldehyde 123. This material exhibits ir (film): 2710, 1728 cm⁻¹; ¹H nmr (400 MHz) δ: 0.03 (s, 3H, one of (CH₃)₂Bu'Si-), 0.04 (s, 3H, one of (CH₃)₂Bu'Si-), 0.89 (s, 9H, Bu'), 0.93 (d, 3H, J = 7 Hz, secondary methyl), 1.08 (s, 3H, angular methyl), 1.22-1.34 (m, 3H), 1.42-1.62 (m, 2H), 1.59 (br s, 3H, vinylic methyl), 1.67-2.08 (m, 6H), 2.19-2.28 (m, 1H), 2.31-2.41 (m, 1H), 2.46-2.56 (m, 1H), 3.50 (d, 1H, J = 10 Hz, one of -CH₂OSiBu'(CH₃)₂), 3.89 (d, 1H, J = 10 Hz, one of -CH₂OSiBu'(CH₃)₂), 5.19 (br s, 1H, -CH₂=CH=C(CH₃)-), 9.77 (t, 1H, J = 2 Hz, aldehydic proton). Exact Mass calcd. for C₁₉H₃₃O₂Si (M⁺ - Bu'): 321.2250; found: 321.2253.
Preparation of the Dibromide 124

To a dry mixture of carbon tetrabromide (39.0 mg, 2.0 equiv) and triphenylphosphine (61.5 mg, 4.0 equiv) at room temperature was added dry dichloromethane (1.5 mL). The resulting deep red solution was stirred for 5 min and then the aldehyde 123 (22.2 mg, 58.7 µmol) was added as a solution in dry dichloromethane (1.0 mL). After the mixture had been stirred for 1.25 h, hexane (= 10 mL) was added and the resulting precipitate was allowed to settle. The liquid phase was decanted and filtered through a plug of glass wool. The solid residue that remained after the liquid had been decanted was dissolved in a minimum amount of dichloromethane and then pentane (= 10 mL) was added. The resulting precipitate was allowed to settle and the liquid phase was decanted and filtered as before. Removal of the solvent from the combined filtrate gave a viscous oil containing a small amount of a solid residue. The oil was dissolved in pentane (= 10 mL) and the mixture was filtered through a plug (0.5 x 2.0 cm) of anhydrous magnesium sulfate (elution with pentane). The solvent was removed from the filtrate and again the small amount of solid material present was removed by selectively extracting the oil into pentane and filtering as before. Removal of the solvent under reduced pressure (rotary evaporator and then vacuum pump, 0.3 torr/40-50 °C/15-30 min) provided 30.0 mg (96%) of the dibromide 124. This material exhibits ir (film): 1656 cm⁻¹; ¹H nmr (400 MHz) δ: 0.04 (s, 6H, (CH₃)₂Si⁻), 0.90 (s, 9H, Bu°), 0.96 (d, 3H, J = 7 Hz, secondary
methyl), 1.08 (s, 3H, angular methyl), 1.26-1.33 (m, 1H), 1.42-1.63 (m, 4H), 1.59 (br s, 3H, vinylic methyl), 1.66-2.12 (m, 9H), 3.48 (d, 1H, J = 10 Hz, one of -CH2OSiBu4(CH3)2), 3.93 (d, 1H, J = 10 Hz, one of -CH2OSiBu4(CH3)2), 5.18 (br s, 1H, -CH2CH=C(CH3)-), 6.37 (t, 1H, J = 6 Hz, -CH=CBr2). Exact Mass calcd. for C24H42Br2O2Si: 534.1353; found: 534.1360.

Preparation of the Acetylenic Ester 126

\[
\text{CO}_2\text{Me}
\]

To a cold (-78 °C) stirred solution of the dibromide 124 (86.4 mg, 0.162 mmol) in dry THF (3.0 mL) was added a solution of n-butyllithium (0.487 mL, 4.0 equiv) in hexanes. The reaction mixture was stirred at -78 °C for 1 h, warmed to room temperature and stirred for 1 h. The reaction mixture was recooled to -78 °C and then neat methyl chloroformate (50 μL, 4.0 equiv) was added. The resultant solution was stirred at -78 °C for 1.25 h and then was warmed to room temperature and stirred for 0.5 h. Brine (= 2 mL) was added, the organic phase was separated and washed with brine (3 x 2 mL). The organic solution was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the crude product on silica gel (0.7 x 15 cm column, elution with petroleum ether-diethyl ether, 39:1) and removal of the solvent from the appropriate fractions (rotary evaporator and then vacuum pump, 15 min/0.3 torr), provided 62.9 mg (90%) of the acetylenic ester 126 as a white solid (mp
75-77 °C, recrystallized from hexanes). This material exhibits ir (KBr): 2237, 1718, 1646 cm⁻¹; ¹H nmr (400 MHz) δ: 0.04 (s, 6H, (CH₃)₂Si-), 0.90 (s, 9H, Bu¹), 0.95 (d, 3H, J = 7 Hz, secondary methyl), 1.05 (s, 3H, angular methyl), 1.25-1.34 (m, 1H), 1.41-1.66 (m, 4H), 1.59 (br s, 3H, vinylic methyl), 1.69-2.08 (m, 6H), 2.17-2.33 (m, 2H), 2.37-2.48 (m, 1H), 3.52 (d, 1H, J = 10 Hz, one of -CH₂OSiBu¹(CH₃)₂), 3.77 (s, 3H, -OCH₃), 3.82 (d, 1H, J = 10 Hz, one of -CH₂OSiBu¹(CH₃)₂), 5.18 (br s, 1H, -CH₂CH=CH(CH₃)-). Exact Mass calcd. for C₂₆H₄₄O₃Si: 432.3060; found: 432.3057.

Preparation of the α,β-Unsaturated Ester 127

![Image of the α,β-Unsaturated Ester 127]

To a cold (0 °C) stirred suspension of copper(I) bromide-dimethyl sulfide (69.5 mg, 1.0 equiv) in dry THF (5.0 mL) was added a solution of methyllithium (0.435 mL, 2.0 equiv) in diethyl ether. The resulting mixture was stirred at 0 °C for 10 min and then was cooled to -78 °C. A dry THF solution (0.5 mL, followed by the addition of two 0.5 mL washings) of the acetylenic ester 126 (146 mg, 0.337 mmol) was then added in a dropwise manner. The solution was stirred at -78 °C for 2 h and then was cannulated into a stirred solution of aqueous 5% hydrochloric acid (5.0 mL), through which argon had been passed for 10 min. Diethyl ether (5 mL) was added to the mixture. The organic phase was separated and the aqueous phase was extracted with diethyl ether (2 x 5 mL). The combined organic solution was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the crude product
on silica gel (1.7 x 15 cm column, elution with petroleum ether-diethyl ether, 49:1) and removal of the solvent from the appropriate fractions (rotary evaporator and then vacuum pump, 0.3 torr/40-50 °C/15-30 min) of the oil thus obtained, provided 132 mg (87%) of the α,β-unsaturated ester 127. This material exhibits ir (film): 1723, 1648 cm⁻¹; ¹H nmr (400 MHz) δ: 0.05 (s, 6H, (CH₃)₂Si-), 0.90 (s, 9H, Bu⁻), 1.00 (dd, 1H, J = 12, 4 Hz), 1.05 (d, 3H, J = 6 Hz, secondary methyl), 1.11 (s, 3H, angular methyl), 1.25-1.33 (m, 1H), 1.44-2.02 (diffuse m, 9H), 1.60 (br s, 3H, vinylic methyl), 1.91 (s, 3H, -C(CH₃)=CH-CO₂CH₃), 2.07 (td, 1H, J = 12, 4 Hz), 2.25 (td, 1H, J = 12, 4 Hz), 3.03 (td, 1H, J = 12, 4 Hz), 3.51 (d, 1H, J = 10 Hz, one of -CH₂OSiBu⁺(CH₃)₂), 3.67 (s, 3H, -OCH₃), 5.18 (br s, 1H, -CH₂CH=C(CH₃)-), 5.65 (s, 1H, -C=CH-CO₂CH₃). In an nOe difference experiment, irradiation of the signal at δ 3.98 (one of -CH₂OSiBu⁺(CH₃)₂) caused signal enhancement at 3.51 (one of -CH₂OSiBu⁺(CH₃)₂) and at 1.11 (angular methyl). In another nOe difference experiment, irradiation of the signal at δ 5.65 (C=CH-CO₂CH₃) caused signal enhancement at 1.91 ( -C(CH₃)=CH-CO₂CH₃). Exact Mass calcd. for C₂₇H₄₈O₃Si: 448.3372; found: 448.3363.

Preparation of the α,β-Unsaturated Acid 128

![Chemical Structure]

To a sample of sodium hydride (83 mg, 2.08 mmol) in paraffin oil at room temperature was added dry THF (1.0 mL) and the resultant mixture was stirred briefly (≈ 2
min). Stirring was stopped and the solid was allowed to settle. The solvent was removed via syringe, and then dry THF (1.0 mL) was added. The resultant mixture was stirred briefly, the solid was allowed to settle, and the solvent was removed as before. Dry THF (1.9 mL) was then added. To the resultant stirred slurry were added sequentially benzeneselenol (221 μL, 1.0 equiv) and HMPA (434 μL, 1.2 equiv) to give a deep red homogeneous solution containing sodium benzeneselenide.

To a sample of the α,β-unsaturated ester 127 (13.8 mg, 30.8 μmol) in dry THF (1.0 mL) at room temperature was added a portion of the sodium benzeneselenide solution (140 μL, 5.0 equiv). The mixture was refluxed for 4 h and then was allowed to cool to room temperature. Diethyl ether (5.0 mL) and an aqueous solution of 10% hydrochloric acid (2.0 mL) were added to the mixture. The organic phase was separated and the aqueous phase was extracted with diethyl ether (4 x 5 mL). The combined organic solution was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the crude product on silica gel (0.7 x 7 cm column, elution with petroleum ether-diethyl ether, 7:3) and removal of the solvent from the appropriate fractions (rotary evaporator and then vacuum pump, 0.3 torr/2 h) gave 8.6 mg (64%) of the unsaturated acid 128 as a white solid. Recrystallization of this solid from diethyl ether-hexanes gave a white powder (mp 163-164.5 °C). This material exhibits ir (KBr) : 3500-2500, 1691, 1637 cm⁻¹; ¹H nmr (400 MHz) δ: 0.04 (s, 3H, one of (CH₃)₂Bu¹Si⁻), 0.05 (s, 3H, one of (CH₃)₂Bu¹Si⁻), 0.90 (s, 9H, Bu¹), 1.05 (d, 3H, J = 7 Hz, secondary methyl), 1.10 (s, 3H, angular methyl), 1.25-1.33 (m, 1H), 1.42-2.10 (diffuse m, 11H), 1.59 (br s, 3H, vinylic methyl), 1.94 (s, 3H, -C(CH₃)=CH-CO₂H), 2.28 (td, 1H, J = 12, 4 Hz), 3.02 (td, 1H, J = 12, 4 Hz), 3.52 (d, 1H, J = 10 Hz, one of -CH₂OSiBu¹(CH₃)₂), 3.95 (d, 1H, J = 10 Hz, one of -CH₂OSiBu¹(CH₃)₂), 5.18 (br s, 1H, -CH₂CH=C(CH₃)-), 5.68 (s, 1H, -C=CH-CO₂H). Exact Mass calcd. for C₂₆H₄₆O₃Si: 434.3216; found: 434.3209.
Preparation of the Alcohol 130

To a stirred solution of the diene alcohol 118 (703 mg, 2.84 mmol) in dry dichloromethane (14 mL) at room temperature were added, sequentially, triethylamine (0.513 mL, 1.3 equiv), tert-butoxydiphenylsilyl chloride (0.845 mL, 1.1 equiv) and 4-N,N-dimethylaminopyridine (34.6 mg, 0.1 equiv). The resulting solution was stirred at room temperature for 2 h. The mixture was washed with an aqueous solution (= 5 mL) of saturated sodium hydrogen carbonate and the organic phase was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. Flash chromatography of the crude product on silica gel (3.5 x 15 cm column, elution with petroleum ether-diethyl ether, 50:1) and removal of the solvent from the appropriate fractions (rotary evaporator and then vacuum pump, 0.3 torr/40-50 °C/15-30 min) provided 1.30 g (91%) of the silyl ether 129 as an oil. This material exhibits ir (film) : 3070, 1636, 1592, 1057 cm⁻¹; ¹H nmr (400 MHz) δ: 0.83 (s, 3H, angular methyl), 0.99 (d, 3H, J = 7 Hz, secondary methyl), 1.12-1.35 (m, 3H), 1.29 (s, 9H, Buᵗ), 1.44-1.85 (m, 6H), 1.90-2.11 (m, 3H), 2.23 (td, 1H, J = 15, 5 Hz), 2.63 (dd, 1H, J = 15, 6 Hz), 3.82 (d, 1H, J = 10 Hz, one of -CH₂OSi(OBuᵗ)Ph₂), 4.45 (s, 1H, one of =CH₂), 4.48 (s, 1H, one of =CH₂), 4.94 (br d, 1H, J = 10 Hz, one of -CH=CH₂), 5.01 (br d, 1H, J = 17 Hz, one of -CH=CH₂), 5.91-6.03 (m, 1H, -CH=CH₂), 7.32-7.44 (m, 6H), 7.63-7.71 (m, 4H).

A solution of borane-dimethyl sulfide complex (27 μL, 1.3 equiv) was added to a cold (0 °C) sample of 2-methyl-2-butene (74 μL, 3.9 equiv) and the resulting mixture
stirred at 0 °C for 20 min. The silyl ether 129 (90.0 mg, 0.179 mmol) was added as a solution in dry THF (0.448 mL). The reaction mixture was stirred at 0 °C for 20 min and then was warmed to room temperature and stirred for a further 45 min. The reaction mixture was cooled to 0 °C and aqueous solutions of sodium hydroxide (0.155 mL, 2.6 equiv) and hydrogen peroxide (0.235 mL, 2.1 equiv) were added simultaneously in a dropwise manner. The resultant mixture was stirred for 10 min and then brine (= 2 mL) and diethyl ether (= 5 mL) were added. The organic phase was separated and the aqueous phase was extracted with diethyl ether (2 x 5 mL). The combined organic solution was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the crude product on silica gel (1.8 x 15 cm column, elution with petroleum ether-diethyl ether, 4:1) and removal of the solvent from the appropriate fractions (rotary evaporator and then vacuum pump, 0.3 torr/40-50 °C/15-30 min) provided 74.8 mg (80%) of the alcohol 130 as a viscous oil. This material exhibits ir (film): 3388, 3070, 1637, 1592 cm⁻¹; ¹H nmr (400 MHz) δ: 0.91-1.05 (m, 2H), 0.93 (s, 3H, angular methyl), 0.93 (d, 3H, J = 7 Hz), 1.13-1.47 (m, 5H), 1.30 (s, 9H, Bu¹), 1.56-1.89 (m, 8H), 2.05-2.13 (m, 1H), 2.26 (td, 1H, J = 14, 4 Hz), 3.46 (t, 2H, J = 6 Hz, -CH₂OH), 3.73 (d, 1H, J = 10 Hz, one of -CH₂OSi(OBu¹)Ph₂), 4.01 (d, 1H, J = 10 Hz, one of -CH₂OSi(OBu¹)Ph₂), 4.46 (s, 1H, one of =CH₂), 4.50 (s, 1H, one of =CH₂), 7.32-7.44 (m, 6H), 7.63-7.70 (m, 4H). Exact Mass calcd. for C₃₃H₄₈O₃Si: 520.3373; found: 520.3367.
Preparation of the Aldehyde 133

To a stirred solution of the alcohol 130 (34.8 mg, 66.9 μmol) in dry dichloromethane (0.670 mL) at room temperature were added dry sodium acetate (1.6 mg, 0.3 equiv) and pyridinium chlorochromate (21.7 mg, 1.5 equiv). The dark brown solution was stirred at room temperature for 16 h and then dry diethyl ether (= 2 mL) was added. The heterogeneous mixture was sonicated for 1 min and passed through a plug of Florisil® (elution with dry diethyl ether). Removal of the solvent from the eluate under reduced pressure (rotary evaporator and then vacuum pump, 0.3 torr/40-50 °C/15-30 min) provided 29.5 mg (85%) of the aldehyde 133 as a colourless oil. This material exhibits ir (film): 3070, 2714, 1727, 1637, 1592 cm⁻¹; ¹H nmr (400 MHz) δ: 0.89 (d, 3H, J = 7 Hz, secondary methyl), 0.89 (s, 3H, angular methyl), 1.17-1.28 (m, 4H), 1.29 (s, 9H, Bu¹), 1.58-1.89 (m, 7H), 2.05-2.45 (m, 5H), 3.73 (d, 1H, J = 10 Hz, one of -CH₂OSi(OBu¹)Ph₂), 3.94 (d, 1H, J = 10 Hz, one of -CH₂OSi(OBu¹)Ph₂), 4.46 (s, 1H, one of =CH₂), 4.49 (s, 1H, one of =CH₂), 7.33-7.47 (m, 6H), 7.61-7.69 (m, 4H), 9.61 (t, 1H, J = 2 Hz, aldehydic proton). Exact Mass calcd. for C₃₃H₄₆O₃Si: 518.3216; found: 518.3216.
Preparation of the Dibromide 134

To a dry mixture of carbon tetrabromide (62.7 mg, 2.0 equiv) and triphenylphosphine (98.9 mg, 4.0 equiv) at room temperature was added dry dichloromethane (1.0 mL). The resulting deep red solution was stirred for 5 min and then the aldehyde 133 (48.9 mg, 94.4 µmol) was added as a solution in dry dichloromethane (3.7 mL). After the mixture had been stirred for 15 min, pentane (= 10 mL) was added and the resulting precipitate was allowed to settle. The liquid phase was decanted and filtered through a plug of glass wool. The solid residue that remained after the liquid had been decanted, was dissolved in a minimum amount of dichloromethane and then pentane (= 10 mL) was added. The resulting precipitate was allowed to settle and the liquid phase was decanted and filtered as before. The combined filtrate was concentrated, whereupon a viscous oil containing a small amount of a solid residue was obtained. The oil was dissolved in pentane (= 10 mL) and filtered through a plug (0.5 x 2.0 cm) of anhydrous magnesium sulfate (elution with pentane). The filtrate was concentrated and again the small amount of solid material present was removed by selectively extracting the oil into pentane and filtering as before. Removal of the solvent under reduced pressure (rotary evaporator and then vacuum pump, 0.3 torr/40-50 °C/15-30 min) provided 61.1 mg (96%) of the dibromide 134 as an extremely viscous oil. This material exhibits ir (film): 3069, 1637, 1592 cm⁻¹; ¹H nmr (400 MHz) δ: 0.84 (s, 3H, angular methyl), 0.97 (d, 3H, J = 7 Hz,
secondary methyl), 1.01-1.27 (m, 5H), 1.29 (s, 9H, Bu), 1.48-1.97 (m, 9H), 2.04-2.13 (m, 2H), 2.23 (td, 1H, J = 14, 4 Hz), 3.77 (d, 1H, J = 10 Hz, one of -CH2OSi(OBu)Ph2), 3.91 (d, 1H, J = 10 Hz, one of -CH2OSi(OBu)Ph2), 4.45 (s, 1H, one of =CH2), 4.48 (s, 1H, one of =CH2), 6.24 (t, 1H, J = 6 Hz, -CH=CBr2), 7.33-7.44 (m, 6H), 7.62-7.69 (m, 4H). *Exact Mass* calcd. for C34H46Br2O2Si: 674.1615; found: 674.1607.

**Preparation of the Acetylenic Ester 135**

![Chemical Structure](image)

To a cold (-78 °C) stirred solution of the dibromide 134 (207 mg, 0.307 mmol) in dry THF (6.1 mL) was added a solution of *n*-butyllithium (0.427 mL, 2.1 equiv) in hexanes. The reaction mixture was stirred at -78 °C for 3 h and then neat methyl chloroformate (50 µL, 2.1 equiv) was added. The solution was stirred at -78 °C for 0.5 h and then was warmed to room temperature and stirred for 1 h. Brine (~2 mL) was added, the organic phase was separated and the aqueous phase was extracted with diethyl ether (2 x 5 mL). The combined organic solution was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the crude product on silica gel (2.7 x 15 cm column, elution with petroleum ether-diethyl ether, 19:1) and removal of the solvent from the appropriate fractions (rotary evaporator and then vacuum pump, 0.3 torr/40-50 °C/15-30 min) provided 133 mg (76%) of the acetylenic
ester 135 as a colourless oil. This material exhibits ir (film): 3070, 2236, 1718, 1638, 1592 cm$^{-1}$; $^1$H nmr (400 MHz) $\delta$: 0.83 (s, 3H, angular methyl), 0.94 (d, 3H, $J = 8$ Hz, secondary methyl), 1.12-1.25 (m, 3H), 1.29 (s, 9H, Bu$^t$), 1.32-1.39 (m, 1H), 1.43-1.93 (m, 7H), 2.03-2.33 (m, 4H), 2.38-2.49 (m, 1H), 3.72 (d, 1H, $J = 10$ Hz, one of $\text{-CH}_2\text{OSi(OBu}^t\text{)Ph}_2$), 3.75 (s, 3H, -OCH$_3$), 3.85 (d, 1H, $J = 10$ Hz, one of $\text{-CH}_2\text{OSi(OBu}^t\text{)Ph}_2$), 4.43 (s, 1H, one of =CH$_2$), 4.46 (s, 1H, one of =CH$_2$), 7.33-7.45 (m, 6H), 7.60-7.68 (m, 4H). Exact Mass calcd. for C$_{36}$H$_{48}$O$_4$Si: 572.3322; found: 572.3319.

Preparation of the Acetylenic Ester 137 and the Alcohol 138

To a stirred solution of the acetylenic ester 135 (62.8 mg, 0.110 mmol) in dry dichloromethane (1.1 mL) at room temperature was added dry p-toluenesulfonic acid (2.8 mg, 0.14 equiv). The reaction mixture was stirred at room temperature for 15 h and then the solvent was removed under reduced pressure. Flash chromatography of the crude product on silica gel (0.8 x 15 cm column, elution with petroleum ether-diethyl ether, 19:1) and removal of the solvent from the appropriate fractions (rotary evaporator and then vacuum pump, 0.3 torr/40-50 °C/15-30 min) provided 35.0 mg (56%) of the acetylenic ester 137 as a colourless oil. Further elution (with diethyl ether) provided the crude alcohol 138. Flash chromatography of this material on silica gel (0.5 x 7 cm column,
elution with petroleum ether-diethyl ether, 7:3) and removal of the solvent from the appropriate fractions (rotary evaporator and then vacuum pump, 0.3 torr/40-50 °C/15-30 min) provided 9.8 mg (28%) of the alcohol 138 as a colourless oil.

The acetylenic ester 137 exhibits ir (film): 3049, 2237, 1718, 1665, 1592 cm⁻¹; ¹H nmr (400 MHz) δ: 0.86 (s, 3H, angular methyl), 0.92 (d, 3H, J = 8 Hz, secondary methyl), 1.02-1.08 (m, 1H), 1.12-1.16 (m, 2H), 1.29 (s, 9H, Bu⁢⁻), 1.32-1.65 (m, 5H), 1.55 (br s, 3H, vinylic methyl), 1.70-1.80 (m, 1H), 1.87-2.09 (m, 2H), 2.18-2.34 (m, 3H), 3.66 (d, 1H, J = 11 Hz, one of -CH₂OSi(OBu⁻)Ph₂), 3.76 (s, 3H, -OCH₃), 3.89 (d, 1H, J = 11 Hz, one of -CH₂OSi(OBu⁻)Ph₂), 5.15 (br s, 1H, olefinic proton), 7.30-7.45 (m, 6H), 7.59-7.68 (m, 4H). Exact Mass calcd. for C₃₆H₄₈O₄Si: 572.3322; found: 572.3323.

The alcohol 138 exhibits ir (film): 3421, 2236, 1716 cm⁻¹; ¹H nmr (400 MHz) δ: 0.96 (d, 3H, J = 7 Hz, secondary methyl), 1.09 (s, 3H, angular methyl), 1.25-1.63 (m, 7H), 1.59 (br s, 3H, vinylic methyl), 1.65-2.00 (m, 4H), 2.01-2.10 (m, 1H), 2.19-2.36 (m, 2H), 2.42-2.53 (m, 1H), 3.60 (d, 1H, J = 11 Hz, one of -CH₆OH), 3.77 (s, 3H, -OCH₃), 3.99 (d, 1H, J = 11 Hz, one of -CH₂OH), 5.19 (br s, 1H, olefinic proton). Exact Mass calcd. for C₂₀H₃₀O₃: 318.2195; found: 318.2197.

Conversion of the Alcohol 138 into the Acetylenic Ester 137

To a stirred solution of the alcohol 138 (5.1 mg, 16.0 μmol) in dry dichloromethane (0.32 mL) at room temperature were added, sequentially, triethylamine (5.8 μL, 2.6 equiv), tert-butoxydiphenylsilyl chloride (9.6 μL, 2.2 equiv) and 4-N,N-dimethylaminopyridine (0.4 mg, 0.2 equiv). The resulting solution was stirred at room temperature for 2 h and then dichloromethane (= 5 mL) was added. The mixture was washed with an aqueous solution (= 2 mL) of saturated sodium hydrogen carbonate and the organic phase was dried over anhydrous magnesium sulfate. The solvent was removed
under reduced pressure. Flash chromatography of the crude product on silica gel (0.5 x 2 cm column, elution with petroleum ether-diethyl ether, 50:1) and removal of the solvent from the appropriate fractions (rotary evaporator and then vacuum pump, 0.3 torr/40-50 °C/15-30 min) provided 5.2 mg (57%) of the acetylenic ester 137 as an oil. This material exhibits spectral data identical with that of the acetylenic ester 137 prepared previously.

**Preparation of the \( \alpha, \beta \)-Unsaturated Ester 139**

![Chemical Structure](attachment:structure.png)

To a cold (0 °C) stirred suspension of copper(I) bromide-dimethyl sulfide (16.8 mg, 1.0 equiv) in dry THF (0.5 mL) was added a solution of methyllithium (0.10 mL, 2.0 equiv) in diethyl ether. The resulting mixture was stirred at 0 °C for 10 min and then was cooled to -78 °C. A dry THF solution (0.5 mL, followed by the addition of two 0.45 mL washings) of the acetylenic ester 137 (46.6 mg, 81.5 μmol) was then added in a dropwise manner. The solution was stirred at -78 °C for 2 h and was then cannulated into a stirred solution of aqueous 5% hydrochloric acid (5.0 mL), through which argon had been passed for 10 min. Diethyl ether (5 mL) was added to the mixture. The organic phase was separated and the aqueous phase was extracted with diethyl ether (2 x 5 mL). The combined organic solution was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Multiple development preparative silica gel tlc (4 developments, elution with petroleum ether-diethyl ether, 50:1) gave one major uv active band. The silica gel containing this band was removed and sonicated (= 5 min) with
diethyl ether (20 mL). Filtration of the mixture, removal of the solvent from the filtrate under reduced pressure (rotary evaporator then vacuum pump, 0.3 torr/40-50 °C/15-30 min) gave 31.2 mg (65%) of the unsaturated ester 139 as a colourless, viscous oil. This material exhibits ir (film): 3069, 1719, 1685, 1648, 1592 cm⁻¹; ¹H nmr (400 MHz) δ: 0.82 (s, 3H, angular methyl), 1.06 (d, 3H, J = 8 Hz, secondary methyl), 1.14-1.46 (m, 4H), 1.28 (s, 9H, Bu¹), 1.50-1.68 (m, 4H), 1.56 (br s, 3H, vinylic methyl), 1.83 (s, 3H, -C(CH₃)=CHCO₂Me), 1.89-2.08 (m, 4H), 2.30 (td, 1H, J = 12, 4 Hz), 3.02 (td, 1H, J = 12, 4 Hz), 3.65 (s, 3H, -OCH₃), 3.80 (d, 1H, J = 11 Hz, one of -CH₂OSi(OBu¹)Ph₂), 3.93 (d, 1H, J = 11 Hz, one of -CH₂OSi(OBu¹)Ph₂), 5.14 (br s, 1H, -CH₂CH=), 5.61 (s, 1H, =CH-CO₂CH₃), 7.31-7.43 (m, 6H), 7.64-7.68 (m, 4H). Exact Mass calcd. for C₃₇H₅₂O₄Si: 588.3635; found: 588.3627.

**Preparation of the α,β-Unsaturated Acid 140**

![Chemical Structure](image)

To a sample of sodium hydride (83 mg, 2.08 mmol) in paraffin oil at room temperature was added dry THF (1.0 mL) and the resultant mixture was stirred briefly (≈ 2 min). Stirring was stopped and the solid was allowed to settle. The solvent was removed via syringe, and then dry THF (1.0 mL) was added. The resultant mixture was stirred briefly, the solid was allowed to settle, and the solvent was removed as before. Dry THF (1.9 mL) was then added. To the resultant stirred slurry were added sequentially, neat
benzeneselenol (0.221 mL, 1.0 equiv) and HMPA (0.434 mL, 1.2 equiv) to give a deep red homogeneous solution containing sodium benzeneselenide.

To a dry sample of the α,β-unsaturated ester 139 (24.9 mg, 42.3 μmol) was added a portion of the sodium benzeneselenide solution (0.192 mL, 5.0 equiv). The mixture was refluxed for 6.5 h and then was allowed to cool to room temperature. Diethyl ether (5.0 mL) and an aqueous solution of 10% hydrochloric acid (2.0 mL) were added to the mixture. The organic phase was separated and the aqueous phase was extracted with diethyl ether (2 x 5 mL). The combined organic solution was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the crude product on silica gel (0.7 x 7 cm column, elution with petroleum ether-diethyl ether, 7:3), concentration of the appropriate fractions and preparative silica gel tlc (1 development, elution with petroleum ether-diethyl ether, 7:3) of the residual material gave one major uv active band. The silica gel containing this band was removed and sonicated (~ 5 min) with diethyl ether (20 mL). Filtration of the mixture, removal of the solvent from the filtrate under reduced pressure (rotary evaporator then vacuum pump, 0.3 torr/40-50 °C/15-30 min) gave 15.6 mg (64%) of the unsaturated acid 140 as a colourless, viscous oil. This material exhibits ir (film) : 3300-2500, 3069, 1717, 1686, 1637 cm⁻¹; ¹H nmr (400 MHz) δ: 0.80 (s, 3H, angular methyl), 1.03 (d, 3H, J = 7 Hz, secondary methyl), 1.12-1.26 (m, 3H), 1.28 (s, 9H, Bu¹), 1.30-1.45 (m, 2H), 1.48-1.66 (m, 2H), 1.54 (br s, 3H, vinylic methyl), 1.76-2.05 (m, 5H), 1.87 (s, 3H, C(CH₃)=CHCO₂H), 2.30 (td, 1H, J = 12, 4 Hz), 3.04 (td, 1H, J = 12, 4 Hz), 3.80 (d, 1H, J = 12 Hz, one of -CH₂OSi(Obu¹)Ph₂), 3.90 (d, 1H, J = 12 Hz, one of CH₂OSi(Obu¹)Ph₂), 5.13 (br s, 1H, -CH₂CH=C), 5.63 (s, 1H, -C=CH-CO₂CH₃), 7.31-7.43 (m, 6H), 7.63-7.68 (m, 4H). Exact Mass calcd. for C₃₆H₅₀O₄Si: 574.3478; found: 574.3477.
Preparation of (±)-Stephalic Acid (96)

\[
\text{\[CH_2\text{CO}_2\text{H}\]}
\]

To a dry sample of the α,β-unsaturated acid 140 (12.1 mg, 21.1 μmol) was added a THF solution of tetra-n-butylammonium fluoride (0.5 mL, 23.7 equiv). The mixture was stirred at room temperature for 4 h and then diethyl ether (7 mL) and an aqueous solution of 5% hydrochloric acid (1 mL) were added. The organic phase was separated and the aqueous phase was extracted with diethyl ether (2 x 5 mL). The combined organic solution was extracted once with an aqueous solution of 5% hydrochloric acid and then was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to obtain the crude product. Flash chromatography of the crude product on a column of Sephadex® LH-20 (0.5 x 4.0 cm column, elution with dichloromethane followed by methanol-dichloromethane, 1:1) gave two fractions, A (~ 2 mg) and B (~ 4 mg). The smaller fraction, A, was chromatographed on a column of Sephadex® LH-20 (0.5 x 4.0 cm column, elution with methanol-dichloromethane, 1:1). The latter procedure did not produce a pure sample of (±)-stephalic acid (96). Preparative silica gel tlc (1 development, 12.5 x 25.0 cm plate, elution with petroleum ether-diethyl ether, 1:1) of this material gave a wide, diffuse, major band when viewed under uv light. The silica gel containing this band was removed and sonicated (~ 5 min) with diethyl ether (20 mL). Filtration of the mixture and removal of the solvent from the filtrate under reduced pressure gave a material of purity similar to that of fraction B. The partially purified sample A and fraction B were combined
and subjected to preparative reverse phase tlc using a Whatman KC\textsubscript{18} tlc plate (1 development, elution with methanol-water, 7:3). The material (3.4 mg) thus obtained was judged to be at least 80% pure by \textsuperscript{1}H nmr spectroscopy. Slow multiple recrystallization of this solid from hot ethyl acetate gave 1.0 mg (15%) of (±)-stephalic acid as a white powder (mp 219-221 °C). This material exhibits ir (KBr): 3431, 3300-2500, 1694, 1637 cm\textsuperscript{-1}; \textsuperscript{1}H nmr (400 MHz) δ: 1.01 (d, 3H, $J = 7$ Hz, secondary methyl), 1.09 (td, 1H, $J = 12$, 4 Hz), 1.15 (s, 3H, angular methyl), 1.21-1.34 (m, 2H), 1.39-2.08 (diffuse m, 12H), 1.60 (br s, 3H, vinylic methyl), 1.96 (br s, 3H, -C(CH\textsubscript{3})=CHCO\textsubscript{2}H), 3.14-3.23 (m, 1H), 3.68 (d, 1H, $J = 12$ Hz, one of -CH\textsubscript{2}OH), 4.24 (d, 1H, $J = 12$ Hz, one of -CH\textsubscript{2}OH), 5.18 (br s, 1H, -CH\textsubscript{2}CH=C), 5.72 (br s, 1H, C=CH-CO\textsubscript{2}H). The \textsuperscript{1}H nmr spectrum of this material was identical to that of the naturally occurring diterpenoid (+)-stephalic acid.*

*We are grateful to Professor M. Salmón for providing a sample of natural (+)-stephalic acid.*
Procedures for the Conversion of Ketones into α,β-Unsaturated Nitriles

General Procedure 1: Preparation of Enol Triflates

To a cold (−78 °C), well stirred solution of LDA (1.15 equiv) in dry THF (3.4 mL per 1.0 mmol of ketone) was added, dropwise, a solution of the appropriate ketone (1.0 equiv) in dry THF (0.45 mL per 1.0 mmol). The resulting solution was stirred at −78 °C for 2 h. N-Phenyltrifluoromethanesulfonimide (Tf$_2$NPh) (1.10 equiv) was added as a finely powdered solid and the resulting yellow solution was allowed to warm to room temperature and then was stirred for a further period of time. The total reaction time is noted for each individual experiment.

Preparation of the Enol Triflate 162

Following general procedure 1, the ketone 155$^{84a}$ (624 mg, 2.79 mmol) was converted into the enol triflate 162 in 2 h. The entire reaction mixture was filtered through a short pad of silica gel (5.0 x 4.0 cm column) and then the pad was washed with diethyl ether (~250 mL). The solvent was removed from the filtrate under reduced pressure. Flash chromatography of the residual oil on silica gel (3.8 x 15 cm column, elution with petroleum ether-diethyl ether, 17:3) provided 835 mg (84%) of the enol triflate 162 as a
white solid. Recrystallization from hexane-diethyl ether afforded the enol triflate 162 as white crystals (mp 80.0-81.5 °C). This material exhibits ir (KBr): 3092, 1662, 1206, 1143 cm⁻¹; ¹H nmr (400 MHz) δ: 0.95 (s, 3H, tertiary methyl), 0.98 (s, 3H, tertiary methyl), 1.65-1.75 (m, 2H), 2.24-2.42 (m, 3H), 2.77-2.90 (m, 2H), 3.17-3.26 (br m, 1H, allylic methine proton), 3.46 (s, 2H, -CH₂O-), 3.48 (s, 2H, -CH₂O-), 5.59 (br s, 1H, olefinic proton). Exact Mass calcd. for C₁₄H₁₉F₃O₅S: 356.0905; found: 356.0912.

**Preparation of the Enol Triflate 158**

Following general procedure 1, the ketone 156 ⁸⁴ᵇ (5.00 g, 25.3 mmol) was converted into the enol triflate 158 in 16 h. The entire reaction mixture was filtered through a short pad of Florisil ® (5.0 x 5.5 cm column) and then the pad was washed with petroleum ether (≈ 250 mL). The solvent was removed from the combined filtrate under reduced pressure. Flash chromatography of the residual oil on silica gel (5.5 x 15 cm column, elution with petroleum ether-diethyl ether, 9:1) provided 6.22 g (75%) of the enol triflate 158 as a white solid. Recrystallization from hexane-diethyl ether afforded the enol triflate 158 as white, plate-like crystals (mp 24-25 °C). This material exhibits ir (KBr): 3076, 1695, 1206, 1142 cm⁻¹; ¹H nmr (400 MHz) δ: 0.96 (s, 3H, tertiary methyl), 1.02 (s, 3H, tertiary methyl), 2.11 (t, 2H, J = 6 Hz, homoallylic methylene protons), 2.40-2.47 (m, 2H), 2.50-2.56 (m, 2H), 3.50 (d, 2H, J = 10 Hz, -CH₂O-), 3.56 (d, 2H, J = 10 Hz, -
CEbO-), 5.62 (t, 1H, J = 4 Hz, olefinic proton). *Exact Mass* calcd. for C_{12}H_{17}F_{3}O_{5}S: 330.0749; found: 330.0740.

**Preparation of the Enol Triflate 163**

Following general procedure 1, the ketone 157 \(^{84b}\) (1.00 g, 4.42 mmol) was converted into the enol triflate 163 in 2.5 h. Removal of the solvent from the reaction mixture (reduced pressure) gave the crude product as an oil. Flash chromatography of the crude product on silica gel (4.5 x 15 cm column, elution with petroleum ether-diethyl ether, 9:1) and distillation (air-bath temperature 90-94 °C/0.3 torr) of the oil obtained from the appropriate fractions provided 1.15 g (72%) of the enol triflate 163 as a colourless oil. This material exhibits ir (film): 1674, 1210, 1144 cm\(^{-1}\); \(^1\)H nmr (400 MHz) δ: 0.95 (s, 3H, tertiary methyl), 0.99 (s, 3H, tertiary methyl), 1.22 (d, 3H, J = 7 Hz, secondary methyl), 1.92-2.22 (m, 6H), 2.81-2.91 (m, 1H, allylic methine proton), 3.45-3.52 (m, 4H, 2 each of -CH_2O-), 5.88 (br t, 1H, J = 6 Hz, olefinic proton). *Exact Mass* calcd. for C_{14}H_{21}F_{3}O_{5}S: 358.1061; found: 358.1065.
Preparation of the Enol Triflate 108

Following general procedure 1, the ketone 94 (2.47 g, 13.9 mmol) was converted into the enol triflate 108 in 2 h. Removal of the solvent from the reaction mixture (reduced pressure) gave the crude product as an oil. Flash chromatography of the crude product on silica gel (4.5 x 15 cm column, elution with petroleum ether-diethyl ether, 9:1) and distillation (air-bath temperature 81-86 °C/0.3 torr) of the oil obtained from the appropriate fractions provided 3.44 g (80%) of the enol triflate 108 as a colourless oil. This material exhibits ir (film): 3088, 1681, 1645, 1208, 1144 cm⁻¹; ¹H nmr (400 MHz) δ: 1.03 (s, 3H, angular methyl), 1.29-1.67 (m, 4H), 1.73-1.80 (m, 1H), 1.84-1.98 (m, 2H), 2.17-2.24 (dd, 1H, J = 14, 4 Hz), 2.26-2.36 (m, 2H), 2.46 (td, 1H, J = 14, 4 Hz), 4.64 (br s, 1H, one of =CH₂), 4.72 (br s, 1H, one of =CH₂), 5.70-5.74 (m, 1H, =CH-CH₂-). Exact Mass calcd. for C₁₃H₁₇F₃O₃S: 310.0850; found: 310.0845.

Preparation of the Enol Triflate 164

Following general procedure 1, the ketone 95 (719 mg, 4.04 mmol) was converted into the enol triflate 164 in 1 h. Saturated aqueous ammonium chloride (pH 8) was added
to the reaction mixture, the aqueous phase was separated and then was extracted three times with diethyl ether. The combined organic extracts were washed repeatedly with brine until the aqueous phase was neutral as indicated by pH paper and then was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded an oil which was subjected to flash chromatography on silica gel (4.5 x 15 cm column, elution with petroleum ether). Distillation (air-bath temperature 128-134 °C/0.3 torr) of the oil obtained from the appropriate fractions provided 950 mg (76%) of the enol triflate 164 as a colourless oil. This material exhibits ir (film): 3092, 1687, 1638, 1208, 1145 cm⁻¹; ¹H nmr (400 MHz) δ: 1.12-1.18 (m, 1H), 1.20 (s, 3H, angular methyl), 1.28-1.40 (m, 1H), 1.46-1.57 (m, 1H), 1.68-1.77 (m, 1H), 1.93-2.09 (m, 3H), 2.16-2.33 (m, 4H), 4.79 (s, 1H, one of =CH₂), 4.82 (s, 1H, one of =CH₂), 5.57 (t, 1H, J = 4 Hz, =CH-CH₂-).

Exact Mass calcd. for C₁₃H₁₇F₃O₃S: 310.0850; found: 310.0843.

Preparation of the Enol Triflate 165

Following general procedure 1, the ketone 159⁸⁴c (300 mg, 1.83 mmol) was converted into the enol triflate 165 in 1 h. Removal of the solvent from the reaction mixture (reduced pressure) gave the crude product as an oil. Flash chromatography of the crude product on silica gel (2.7 x 15 cm column, elution with petroleum ether) and distillation (air-bath temperature 90-95 °C/0.3 torr) of the oil obtained from the appropriate fractions provided 356 mg (66%) of the enol triflate 165 as a colourless oil. This material exhibits ir (film): 1658, 1612, 1210, 1143 cm⁻¹; ¹H nmr (400 MHz) δ: 1.04 (s, 3H, angular methyl), 1.25-1.37 (m, 2H), 1.47-1.60 (m, 1H), 1.63-1.74 (m, 2H), 1.77-1.85
(m, 1H), 2.14 (dd, 1H, J = 16, 8 Hz, =CH-CH2-), 2.23-2.30 (m, 2H), 2.35 (br d, 1H, J = 16 Hz, =CH-CH2-), 5.48 (s, 1H, Hb), 5.52-5.57 (m, 1H, Ha). Exact Mass calcd. for C\textsubscript{12}H\textsubscript{15}F\textsubscript{3}O\textsubscript{3}S: 296.0694; found: 296.0686.

**Preparation of the Enol Triflate 166**

Following general procedure 1, the ketone 160 (1.00 g, 5.10 mmol) was converted into the enol triflate 166 in 16 h. Removal of the solvent from the reaction mixture (reduced pressure) gave the crude product as an oil. Flash chromatography of the crude product on silica gel (4.5 x 15 cm column, elution with petroleum ether) provided the enol triflate 166 as an oil. Distillation (air-bath temperature 84-88 °C/0.3 torr) provided 1.21 g (73%) of the enol triflate 166 as a colourless oil. This material exhibits ir (film): 1681, 1624, 1208, 1143 cm\textsuperscript{-1}; \textsuperscript{1}H nmr (400 MHz) δ: 0.97 (d, 6H, J = 6 Hz, isopropyl methyls), 1.08 (d, 3H, J = 7 Hz, secondary methyl), 1.80 (s, 3H, vinylic methyl), 1.96-2.05 (m, 2H), 2.53 (dd, 1H, J = 16, 7, allylic methylene proton), 2.40 (br sextet, 1H, J = 7 Hz, allylic methine proton), 3.39-3.54 (m, 2H, -OCH\textsubscript{2}-), 4.78 (s, 1H, olefinic proton). Exact Mass calcd. for C\textsubscript{13}H\textsubscript{19}F\textsubscript{3}O\textsubscript{4}S: 328.0956; found: 328.0949.
Preparation of the Enol Triflate 167

To a well stirred suspension of potassium hydride (1.08 g, 2.0 equiv) in dry THF (16 mL) was added a solution of the keto ester 161 (800 mg, 4.71 mmol) in dry THF (2 mL). The resulting mixture was stirred at room temperature for 1 h and then powdered N-phenyltrifluoromethanesulfonimide (2.02 g, 1.2 equiv) was added in one portion. After 16 h water was added and the aqueous phase was separated and extracted three times with diethyl ether. The combined organic solution was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded an oil which was subjected to column chromatography on silica gel (3.8 x 15 cm column, elution with petroleum ether-diethyl ether, 4:1). Distillation (air-bath temperature 75-78 °C/0.3 torr) of the oil obtained from the appropriate fractions provided 1.17 g (82%) of the enol triflate 167 as a colourless oil. This material exhibits ir (film): 1733, 1655, 1211, 1145 cm⁻¹; \(^1\)H nmr (400 MHz) δ: 1.63-1.83 (m, 6H), 2.51-2.56 (m, 2H, allylic methylene protons), 2.58-2.63 (m, 2H, allylic methylene protons), 3.81 (s, 3H, -OCH₃). Exact Mass calcd. for C₁₀H₁₃F₃O₅S: 302.0436; found: 302.0440.
General Procedure 2: Preparation of $\alpha,\beta$-Unsaturated Nitriles

To a dry sample of lithium cyanide* (2.0 equiv) were added tetrakis(triphenylphosphine)palladium(0) (0.07 equiv) and neat 12-Crown-4 (0.07 equiv). The enol triflate (1.0 equiv) was added as a solution in dry benzene and additional dry benzene was added where required (to give a concentration of 0.1 mmol of enol triflate per 5.6 mL of benzene). The resulting heterogeneous solution was stirred at room temperature until the reaction was determined to have reached completion (as indicated by glc and/or tlc analyses). In those cases where the reaction did not proceed to completion, additional amounts of tetrakis(triphenylphosphine)palladium(0) (0.07 equiv) were added until complete, or nearly complete, starting material conversion was achieved. Water (= 1.5 mL per mmol of enol triflate) was added and the solution was stirred vigorously until no further effervescence occurred. The aqueous layer was separated and extracted three times with diethyl ether. The combined organic solution was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure (rotary evaporator). Column chromatography of the crude product on silica gel, followed by concentration of the suitable fractions and bulb-to-bulb distillation (where appropriate) of the resultant material provided the corresponding $\alpha,\beta$-unsaturated nitrile.

* Lithium cyanide must be dried (as outlined in the Experimental General Introduction section) under carefully controlled conditions for the reaction to be successful.
Preparation of the $\alpha,\beta$-Unsaturated Nitrile 170

Following general procedure 2, the enol triflate 162 (160 mg, 0.453 mmol) was converted into the $\alpha,\beta$-unsaturated nitrile 170 in 20 h. An additional amount of tetrakis(triphenylphosphine)palladium(0) (0.07 equiv) was added after a reaction time of 6.5 h. Flash chromatography of the crude product on silica gel (1.8 x 15 cm column, elution with petroleum ether-diethyl ether, 4:1) provided 79.9 mg (76%) of the nitrile 170 as a white solid. This solid was recrystallized from petroleum ether to provide white flakes (mp 58-59 °C). This material exhibits ir (KBr): 3064, 2216, 1615, 1116 cm$^{-1}$; $^1$H nmr (400 MHz) $\delta$: 0.97 (s, 6H, tertiary methyls), 1.65 (dd, 1H, $J = 13, 8$ Hz), 1.76 (dd, 1H, $J = 13, 6$ Hz), 2.24-2.45 (m, 3H), 2.80-2.93 (m, 2H), 3.30-3.38 (m, 1H, allylic methine proton), 3.41-3.52 (m, 4H, -CH$_2$O-), 6.49-6.53 (m, 1H, olefinic proton). In a nOe difference experiment, irradiation of the signal at $\delta$ 6.49-6.53 (olefinic proton) caused signal enhancement at $\delta$ 3.30-3.38 (m, allylic methine proton). Exact Mass calcd. for C$_{14}$H$_{19}$NO$_2$: 233.1416; found: 233.1415.
Preparation of the \( \alpha, \beta \)-Unsaturated Nitrile 168

Following general procedure 2, the enol triflate 158 (4.81 g, 14.5 mmol) was converted into the \( \alpha, \beta \)-unsaturated nitrile 168 in 2 h. Flash chromatography of the crude product on silica gel (7.5 x 15 cm column, elution with petroleum ether-diethyl ether, 7:3) provided 2.40 g (80%) of the nitrile 168 as a white solid. This solid was recrystallized from petroleum ether to provide white flakes (mp 72-73 °C). This material exhibits IR (KBr): 2211, 1642, 1114 cm\(^{-1}\); \(^1\)H nmr (400 MHz) \( \delta \): 0.94 (s, 3H, tertiary methyl), 1.03 (s, 3H, tertiary methyl), 2.01 (t, 2H, \( J = 6 \) Hz, \( H_c \) and \( H_d \)), 2.32-2.39 (m, 2H, \( H_a \) and \( H_b \)), 2.50-2.55 (m, 2H, \( H_e \) and \( H_f \)), 3.47 (d, 2H, \( J = 11 \) Hz, -CH\(_2\)O-), 3.57 (d, 2H, \( J = 11 \) Hz, -CH\(_2\)O-), 6.44-6.48 (m, 1H, \( H_g \)). The following decoupling experiments were carried out. Irradiation of the signal at \( \delta \) 2.32-2.39 (\( H_a \) and \( H_b \)): triplet at 2.01 (\( H_c \) and \( H_d \)) simplified to a singlet, multiplet at 2.50-2.55 (\( H_e \) and \( H_f \)) simplified to a doublet (\( J = 4 \) Hz), signal at 6.44-6.48 (\( H_g \)) simplified to a triplet (\( J = 4 \) Hz). Irradiation of the signal at \( \delta \) 2.50-2.55 (\( H_e \) and \( H_f \)): multiplet at 2.32-2.39 (\( H_a \) and \( H_b \)) simplified to a broad triplet (\( J = 6 \) Hz), signal at 6.44-6.48 (\( H_g \)) simplified to a broad singlet. Irradiation of the signal at \( \delta \) 6.44-6.48 (\( H_g \)): multiplet at 2.32-2.39 (\( H_a \) and \( H_b \)) simplified, multiplet at 2.50-2.55 (\( H_e \) and \( H_f \)) simplified. In a nOe difference experiment, irradiation of the signal at \( \delta \) 6.44-6.48 (\( H_g \)) caused signal enhancement at \( \delta \) 2.50-2.55 (\( H_e \) and \( H_f \)). \(^{13}\)C nmr (75.3 MHz) \( \delta \): 22.5 (-ve), 22.7 (-ve), 25.3, 26.8, 30.2, 35.4, 70.3, 95.3, 111.9, 119.0, 141.3(-ve). In a SINEPT experiment optimized for a \( J_{C,H} \) of 7 Hz, irradiation at \( \delta \) 3.52 (both pairs of acetal
methylene protons) gave strong polarization transfer through three-bond coupling to the quaternary acetal carbon at $\delta$ 95.3 and to the acetal methylene carbon at $\delta$ 70.3. A second SINEPT experiment, utilizing the same $J_{C,H}$ of 7 Hz, in which an irradiation was centered at $\delta$ 6.46 (H$_g$), gave strong polarization transfer through three-bond coupling to the quaternary acetal carbon at $\delta$ 95.3 and to the sp nitrile carbon at $\delta$ 119.0. Exact Mass calcd. for C$_{12}$H$_{17}$NO$_2$: 207.1260; found: 207.1258.

**Preparation of the $\alpha,\beta$-Unsaturated Nitrile 171**

![Image of the nitrile structure](image)

Following general procedure 2, the enol triflate 163 (206 mg, 0.574 mmol) was converted into the $\alpha,\beta$-unsaturated nitrile 171 in 2 h. Flash chromatography of the crude product on silica gel (1.8 x 15 cm column, elution with petroleum ether-diethyl ether, 7:3) provided the nitrile 171 as an oil. Distillation (air-bath temperature 75-78 °C/0.3 torr) of this oil provided 105 mg (78%) of the nitrile 171 as a colourless oil. This material exhibits ir (film) : 3035, 2213, 1625, 1120 cm$^{-1}$; $^1$H nmr (400 MHz) $\delta$: 0.95 (s, 3H, tertiary methyl), 0.98 (s, 3H, tertiary methyl), 1.26 (d, 3H, $J = 7$ Hz, secondary methyl), 1.47-1.60 (m, 2H), 2.11-2.35 (m, 4H), 2.58-2.69 (m, 1H, allylic methine proton), 3.41-3.48 (m, 4H, -CH$_2$O-), 6.72-6.79 (m, 1H, olefinic proton). In a nOe difference
experiment, irradiation of the signal at δ 6.72-6.79 caused signal enhancement at δ 2.20-2.35 (m). Exact Mass calcd. for C_{14}H_{21}NO_{2}: 235.1572; found: 235.1572.

Preparation of the α,β-Unsaturated Nitrile 102

Following general procedure 2, the enol triflate 108 (805 mg, 2.60 mmol) was converted into the α,β-unsaturated nitrile 102 in 2 h. Flash chromatography of the crude product on silica gel (3.5 x 15 cm column, elution with petroleum ether-diethyl ether, 9:1) provided the nitrile 102 as an oil. Distillation (air-bath temperature 120-126 °C/0.3 torr) of this material provided 432 mg (89%) of the nitrile 102 as a colourless oil. This material exhibits ir (film) : 3086, 3035, 2213, 1641 cm⁻¹; ¹H nmr (400 MHz) δ: 0.95 (s, 3H, angular methyl), 1.34-1.67 (m, 3H), 1.80 (dd, 1H, J = 12, 4 Hz), 1.91-2.07 (m, 3H), 2.18-2.52 (m, 4H), 4.61 (s, 1H, one of =CH₂), 4.73 (s, 1H, one of =CH₂), 6.61-6.65 (m, 1H, Hc). In a nOe difference experiment, irradiation of the signal at δ 6.61-6.65 (Hc) caused signal enhancement at δ 2.27-2.38 (m, 2H, Ha and Hb). ¹³C nmr (75.3 MHz) δ: 16.6 (-ve), 24.2, 25.2, 27.2, 31.5, 32.0, 37.4, 44.0 (-ve), 105.7, 115.7, 118.4, 144.8(-ve), 154.8. Irradiation of the signal at δ 6.61-6.65 (Hc) in a SINEPT experiment optimized for a J_{C,H} of 7 Hz, gave strong polarization transfer through three-bond coupling to the sp nitrile carbon at δ 118.4 and to the tertiary ring junction carbon at δ 44.0. Exact Mass calcd. for C_{13}H_{17}N: 187.1361; found: 187.1362.
Preparation of the $\alpha,\beta$-Unsaturated Nitrile 172

Following general procedure 2, the enol triflate 164 (35.0 mg, 0.113 mmol) was converted into the $\alpha,\beta$-unsaturated nitrile 172 in 1.5 h. Flash chromatography of the crude product on silica gel (0.7 x 8 cm column, elution with petroleum ether-diethyl ether, 9:1) provided the nitrile 172 as an oil. Distillation (air-bath temperature 103-110 °C/0.3 torr) of this material provided 18.4 mg (87%) of the nitrile 172 as a colourless oil. This material exhibits ir (film): 3088, 3034, 2216, 1636 cm$^{-1}$; $^1$H nmr (400 MHz) $\delta$: 1.14 (s, 3H, angular methyl), 1.18-1.26 (m, 1H), 1.36-1.73 (m, 3H), 1.98-2.11 (m, 3H), 2.16-2.39 (m, 4H), 4.79 (s, 1H, one of =CH$_2$), 4.81 (s, 1H, one of =CH$_2$), 6.57 (t, 1H, $J = 4$ Hz, =CH-CH$_2$). $^{13}$C nmr (75.3 MHz) $\delta$: 23.9, 24.3 (-ve), 25.6, 28.5, 29.3, 32.9, 37.3, 44.2 (-ve), 108.3, 117.2, 119.5, 143.8(-ve). Irradiation of the signal at $\delta$ 6.57 (H$_c$) in a SINEPT experiment optimized for a $J_{C,H}$ of 7 Hz, gave strong polarization transfer through three-bond coupling to the sp nitrile carbon at $\delta$ 119.5 and to the tertiary ring junction carbon at $\delta$ 44.2. Exact Mass calcd. for C$_{13}$H$_{17}$N: 187.1361; found: 187.1355.

Preparation of the $\alpha,\beta$-Unsaturated Nitrile 173
Following general procedure 2, the enol triflate 165 (183 mg, 0.620 mmol) was converted into the α,β-unsaturated nitrile 173 in 3 h. Flash chromatography of the crude product on silica gel (1.8 x 15 cm column, elution with petroleum ether-diethyl ether, 19:1) provided the nitrile 173 as an oil. Distillation (air-bath temperature 100-103 °C/0.3 torr) of this oil provided 83.6 mg (78%) of the nitrile 173 as a colourless oil. This material exhibits ir (film): 3047, 2221, 1640 cm⁻¹; ¹H nmr (400 MHz) δ: 0.98 (s, 3H, angular methyl), 1.22-1.36 (m, 1H), 1.46-1.75 (m, 4H), 1.78-1.86 (m, 1H), 2.15-2.28 (m, 4H), 5.57 (s, 1H, Hb), 6.48 (t, 1H, J = 5 Hz, Ha). In a nOe difference experiment, irradiation at δ 6.48 (Ha) caused signal enhancement at δ 2.19-2.25. Exact Mass calcd. for C₁₂H₁₅N: 173.1204; found: 173.1205.

Preparation of the α,β-Unsaturated Nitrile 174

Following general procedure 2, the enol triflate 166 (197 mg, 0.600 mmol) was converted into the α,β-unsaturated nitrile 174 in 2 h. Flash chromatography of the crude product on silica gel (1.8 x 15 cm column, elution with petroleum ether-diethyl ether, 19:1) provided the nitrile 174 as an oil. Distillation (air-bath temperature 113-118 °C/0.3 torr) of this oil provided 105 mg (85%) of the nitrile 174 as a colourless oil. This material exhibits ir (film): 3082, 2217, 1641, 1604 cm⁻¹; ¹H nmr (400 MHz) δ: 0.97 (d, 6H, J = 6 Hz, isopropyl methyls), 1.03 (d, 3H, J = 7 Hz, secondary methyl), 1.95-2.11 (m, 2H), 2.07 (s, 3H, vinylic methyl), 2.40 (sextet, 1H, J = 7 Hz, allylic methine proton), 2.54 (dd,
$1H, J = 20, 7 \text{ Hz}$), 3.40-3.55 (m, 2H, -CH$_2$O-), 4.85 (s, 1H, olefinic proton). *Exact Mass* calcd. for C$_{13}$H$_{19}$NO: 205.1467; found: 205.1467.

**Preparation of the $\alpha,\beta$-Unsaturated Nitrile 175**

![Chemical Structure](image)

Following general procedure 2, the enol triflate 167 (55.4 mg, 0.183 mmol) was converted into the $\alpha,\beta$-unsaturated nitrile 175 in 4 h. (Additional amounts of tetrakis(triphenylphosphine)palladium(0) (0.07 equiv) were added after reaction times of 1, 2 and 3 h). Flash chromatography of the crude product on silica gel (0.7 x 15 cm column, elution with petroleum ether-diethyl ether, 7:3) provided the nitrile 175 as an oil. Distillation (air-bath temperature 125-131 °C/0.3 torr) of this oil provided 19.2 mg (59%) of the nitrile 175 as a colourless oil. This material exhibits IR (film): 2216, 1722, 1107 cm$^{-1}$; $^1$H NMR (400 MHz) δ: 1.54-1.69 (m, 4H), 1.80-1.88 (m, 2H), 2.59-2.69 (m, 4H), 3.85 (s, 3H, -OCH$_3$). *Exact Mass* calcd. for C$_{10}$H$_{13}$NO$_2$: 179.0946; found: 179.0945.
Procedures for the Synthesis of cis-Decalins

Preparation of 2-Methyl-2-cyclohexen-1-one (191) 89

To a cold (-78 °C) stirred solution of lithium (3.45 g, 5.0 equiv) in ammonia (= 250 mL) was added a solution of 2-vinylpyridine (192) (10.8 mL, 0.10 mol) and ethanol (46.8 mL, 8.0 equiv) in dry diethyl ether (100 mL), through which argon had been passed for 15 min. The solution quickly became transparent and was stirred for 20 min at -78 °C. The cooling bath was replaced with a warm (= 50 °C) water bath and the reflux condenser was removed. Removal of the ammonia in this manner required 2 h. Methanol (100 mL) and an aqueous solution of sodium hydroxide (60 mL, 3 equiv), through which argon had been passed for 15 min were added. The resulting solution was stirred at room temperature for 3 h. Aqueous 10% hydrochloric acid was added until the solution was acidic to pH paper. The aqueous layer was separated and extracted with diethyl ether (3 x 150 mL). The combined organic extract was washed once with aqueous saturated sodium hydrogen carbonate and repeatedly with brine until the aqueous phase was neutral as indicated by pH paper. The organic solution was dried over anhydrous magnesium sulfate. Removal of the solvent by distillation at atmospheric pressure, followed by short path distillation (170-174 °C) of the remaining oil, provided 6.58 g (60%) of 2-methyl-2-cyclohexen-1-one (191) as a colourless oil. This material exhibits ir (film): 1675, 1640 cm⁻¹; ¹H nmr (270 MHz) δ: 1.78 (d, 3H, J = 2 Hz), 1.99 (quintet, 2H, J = 7 Hz), 2.27-2.36 (m, 2H), 2.44 (t, 2H, J = 7 Hz), 6.75 (br s, 1H, olefinic proton). Exact Mass calcd. for C₇H₁₀O: 110.0732; found: 110.0732.
Preparation of the Ketone 92  

\[ \text{To a cold (-78 °C) stirred solution of 5-chloro-2-trimethylstannyl-1-pentene (84)} \]

(6.96 g, 1.24 equiv) in dry THF (250 mL) was added a solution of methyllithium in diethyl ether (24.0 mL, 1.42 equiv). After the mixture had been stirred at -78 °C for 20 min, solid magnesium bromide-etherate (6.94 g, 1.28 equiv) was added in one portion and the resulting milky solution was stirred for an additional 20 min at -78 °C. Solid copper(I) bromide-dimethyl sulfide complex (1.12 g, 0.26 equiv), boron trifluoride-etherate (2.84 mL, 1.1 equiv) and 2-methyl-2-cyclohexen-1-one (191) (2.40 mL, 21.0 mmol) were added sequentially. The resulting bright yellow solution was stirred at -78 °C for 3 h and then saturated aqueous ammonium chloride (pH 8, ≈ 100 mL) was added. Petroleum ether (≈ 50 mL) was added and the mixture was stirred vigorously with exposure to air until the aqueous phase became a deep blue colour (usually after 1-2 h). The aqueous layer was separated and extracted twice with diethyl ether. The combined organic extract was washed once with saturated aqueous ammonium chloride (pH 8) and repeatedly with brine until the aqueous phase was neutral as indicated by pH paper. The organic solution was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure (rotary evaporator and then vacuum pump, 15 min/0.3 torr) afforded a pale yellow oil. The crude chloro ketones 91 exhibit \(^1\)H nmr and mass spectra in accordance with those previously reported.  

\[ \text{91} \quad \text{92} \]
To a well stirred suspension of potassium hydride (1.68 g, 2.0 equiv) in dry THF (42 mL) was added a solution of the crude chloro ketones 91 in dry THF (20 mL). The resulting mixture was stirred at room temperature for 2 h and then saturated aqueous ammonium chloride (pH 8, 100 mL) was added. The aqueous layer was separated and extracted with diethyl ether (3 x 20 mL). The combined organic solution was extracted repeatedly with brine until the aqueous phase was neutral as indicated by pH paper. The organic solution was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded an oil that was distilled (air-bath temperature 108-113 °C/30 torr) to provide 3.13 g (84%) of the ketone 92 as a colourless oil. This material exhibits IR (film): 3069, 1703, 1648 cm⁻¹; ¹H NMR (400 MHz) δ: 1.10 (s, 3H, angular methyl), 1.18-1.27 (m, 1H), 1.52-1.77 (m, 5H), 2.00-2.37 (m, 6H), 2.65-2.77 (m, 1H), 4.69-4.72 (m, 1H, one of =CH₂), 4.72-4.75 (m, 1H, one of =CH₂). The spectral data exhibited by the ketone 92 is in agreement with that previously reported.²⁸

Preparation of the Alcohol 194

To a cold (-78 °C) stirred solution of calcium (1.45 g, 4.8 equiv) in ammonia (~250 mL) was added a solution of the ketone 92 (1.34 g, 7.51 mmol) in dry diethyl ether (35 mL). The solution was stirred at -78 °C for 1 h. Ethanol (8.6 mL, 19.9 equiv) was added and the resultant mixture stirred at -78 °C for 15 min. The mixture was carefully poured into water contained in an Erlenmeyer flask and the resultant mixture was allowed to warm to room temperature. The aqueous phase was separated and extracted with diethyl
ether (3 x 100 mL). The combined organic extract was washed once with aqueous saturated sodium hydrogen carbonate and repeatedly with brine until the aqueous phase was neutral as indicated by pH paper. The organic solution was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded an oil that was distilled (air-bath temperature 74-78 °C/0.08 torr) to provide 1.29 g (95%) of the alcohol 194 as a colourless oil. This material exhibits ir (film): 3385, 3067, 1646, 1082 cm⁻¹; ¹H nmr (400 MHz) δ: 1.04 (s, 3H, angular methyl), 1.22-1.83 (m, 11H, simplifies upon addition of D₂O), 1.87 (dd, 1H, J = 13, 4 Hz), 2.10 (dd, 1H, J = 13, 5 Hz), 2.22 (td, 1H, J = 13, 5 Hz), 3.32 (dd, 1H, J = 13, 5 Hz, -CH₂OH), 4.63-4.66 (m, 1H, one of =CH₂), 4.66-4.69 (m, 1H, one of =CH₂). Exact Mass calcd. for C₁₂H₂₀O: 180.1514; found: 180.1512.

Preparation of the Ether 195

\[ \text{CH}_3\text{OCH}_2\text{O} \]

To a stirred solution of the alcohol 194 (1.15 g, 6.39 mmol) in dry dichloromethane (20 mL) was added N,N-diisopropylethylamine (1.67 mL, 1.5 equiv) and the resultant solution was cooled to 0 °C. Chloromethyl methyl ether (1.67 mL, 1.5 equiv) was added in a dropwise manner over 5 min. The resulting solution was allowed to warm to room temperature and then was stirred for 16 h. The mixture was washed with an aqueous solution (= 5 mL) of 5% hydrochloric acid and repeatedly with brine until the aqueous phase was neutral as indicated by pH paper. The organic phase was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded an
oil that was distilled (air-bath temperature 74-80 °C/0.08 torr) to provide 1.38 g (97%) of the ether 195 as a colourless oil. This material exhibits ir (film): 3067, 1646, 1123 cm⁻¹; ¹H nmr (400 MHz) δ: 1.02 (s, 3H, angular methyl), 1.26-1.90 (m, 11H), 2.08 (dd, 1H, J = 13, 4 Hz), 2.21 (td, 1H, J = 13, 5 Hz), 3.18 (dd, 1H, J = 12, 4 Hz, -CHOCH₂OCH₃), 3.38 (s, 3H, -OCH₃), 4.59 (d, 1H, J = 6 Hz, one of -OCH₂OCH₃), 4.61-4.67 (m, 2H, =CH₂), 4.72 (d, 1H, J = 6 Hz, one of -OCH₂OCH₃). ¹³C nmr (75.3 MHz) δ: 22.5, 23.9, 24.2, 24.2 (-ve), 27.1, 28.0, 30.7, 39.2 (C), 52.1 (-ve, CH), 55.4 (-ve, CH₃), 84.9 (-ve, CH), 95.8 (CH₂), 108.4 (CH₂), 150.3 (C). In a nOe difference experiment, irradiation at δ 3.18 (-CHOCH₂OCH₃) caused signal enhancement at δ 1.02 (s, angular methyl), 1.73-1.80 (m), 1.80-1.87 (m), 4.59 (d, one of -OCH₂OCH₃) and 4.72 (d, one of -OCH₂OCH₃). In a HETCOR nmr experiment the ¹³C signals at δ 52.1 and 84.9 showed strong correlations to the ¹H signals at 1.80-1.87 and 3.18, respectively. Exact Mass calcd. for C₁₄H₂₄O₂:224.1777; found:224.1772.

Preparation of the Alcohol 197

![Chemical structure of 197](image)

To a cold (-78 °C) stirred solution of lithium tri-sec-butylborohydride (1.87 mL, 3 equiv) in THF (5 mL) was added a solution of the ketone 92 (111 mg, 62.3 mmol) in dry THF (2 mL followed by 2 x 1 mL washings). The resultant solution was stirred at -78 °C for 3 h and 0 °C for 0.75 h. Methanol (3.0 mL), aqueous solutions of 2% sodium hydroxide (10 mL) and 30% hydrogen peroxide (5 mL) were added sequentially, the mixture was allowed to warm to room temperature and then was stirred for 16 h. The
organic phase was separated and washed repeatedly with brine until the aqueous phase was neutral as indicated by pH paper. The organic solution was dried over anhydrous magnesium sulfate. Analysis of this solution by glc indicated that two compounds were present in a ratio of 1:1.8 (the minor component had the same retention time on glc as that of the alcohol 194). Removal of the solvent under reduced pressure afforded an oil that was distilled (air-bath temperature 74-78 °C/0.08 torr) to provide 95.5 mg (85%) of a mixture of the alcohols 197 and 194 as a colourless oil. Flash chromatography of a sample (33.7 mg) of this material on silica gel (1.0 x 22 cm column, elution with petroleum ether-ethyl acetate, 4:1), concentration of the appropriate fractions and distillation of each component (air-bath temperature 78-85 °C/0.08 torr for the major component) provided 5.1 mg of the alcohol 197 and 5.9 mg of the alcohol 194 as colourless oils.

The alcohol 197 exhibits ir (film): 3389, 3067, 1646, 1050 cm⁻¹; ¹H nmr (400 MHz) δ: 0.95-1.05 (m, 1H), 0.99 (s, 3H, angular methyl), 1.34-1.92 (m, 10H), 2.07 (dt, 1H, J = 13, 5 Hz), 2.16-2.31 (m, 2H), 3.50 (br s, 1H, -CHOH), 4.66 (s, 1H, one of =CH₂), 4.68 (s, 1H, one of =CH₂). Exact Mass calcd. for C₁₂H₂₀O: 180.1514; found: 180.1507.

Preparation of the Ether 196

\[
\begin{align*}
\text{CH₃OCH₂O} & \\
\end{align*}
\]

To a stirred solution of the alcohol 197 (25.5 mg, 0.141 mmol) in dry dichloromethane (20 mL) was added N,N-diisopropylethylamine (37 µL, 1.5 equiv) and the resultant solution was cooled to 0 °C. Chloromethyl methyl ether (16 µL, 1.5 equiv)
was added. The resulting solution was allowed to warm to room temperature and then was stirred for 16 h. The mixture was washed with an aqueous solution (= 5 mL) of 5% hydrochloric acid and repeatedly with brine until the aqueous phase was neutral as indicated by pH paper. The organic phase was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded an oil that was distilled (air-bath temperature 75-80 °C/0.03 torr) to provide 23.3 mg (74%) of the ether 196 as a colourless oil. This material exhibits ir (film): 3067, 1647, 1148 cm⁻¹; ¹H nmr (400 MHz) δ: 0.96-1.05 (m, 1H), 1.02 (s, 3H, angular methyl), 1.40-1.95 (m, 9H), 2.06 (dt, 1H, J = 13, 5 Hz), 2.16-2.31 (m, 2H), 3.34 (br s, 1H, -CH₂OCH₂OCH₃), 3.40 (s, 3H, -OCH₃), 4.59 (d, 1H, J = 6 Hz, one of -OCH₂OCH₃), 4.66 (s, 1H, one of =CH₂), 4.68 (s, 1H, one of =CH₂), 4.72 (d, 1H, J = 6 Hz, one of -OCH₂OCH₃). Exact Mass calcd. for C₁₄H₂₄O₂: 224.1777; found:224.1780.

Preparation of the Alcohol 199

\[
\text{CH}_3\text{OCH}_2\text{O} \quad \text{OH}
\]

To a cold (0 °C) stirred solution of the ether 195 (522 mg, 2.33 mmol) in dry THF (4.7 mL) was added a THF solution (2.63 mL, 0.7 equiv) of borane-THF complex over 20 min. The solution was warmed to room temperature and stirred for 3 h. Water (0.294 mL, 7 equiv) and ethanol (18.8 mL) were added and the resultant solution was stirred at room temperature for 10 min. The reaction mixture was cooled to 0 °C and aqueous solutions of sodium hydroxide (0.564 mL, 0.7 equiv) and hydrogen peroxide (0.666 mL, 2.5 equiv) were added simultaneously in a dropwise manner. The resultant cloudy solution was
stirred at room temperature for 2 h. The aqueous layer was separated and extracted with petroleum ether (3 x 5 mL). The combined organic solution was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded an oil that was distilled (air-bath temperature 140-150 °C/1.5 torr) to provide 497 mg (88%) of the alcohol 199 as a colourless oil. This material exhibits ir (film): 3412, 1148 cm⁻¹; ¹H nmr (400 MHz) δ: 1.02 (s, 3H, angular methyl), 1.23-1.78 (m, 14H, simplifies on addition of D₂O), 1.83-1.91 (m, 1H), 3.24 (dd, 1H, J = 9, 3 Hz, -CHOCH₂OCH₃), 3.38 (s, 3H, -OCH₃), 3.63-3.75 (m, 2H, -CH₂OH), 4.58 (d, 1H, J = 6 Hz, one of -OCH₂OCH₃), 4.71 (d, 1H, J = 6 Hz, one of -OCH₂OCH₃). Exact Mass calcd. for C₁₃H₂₂O₂ (M⁺-CH₄O): 210.1619; found:210.1616.

Preparation of the Aldehyde 198

![Graphical representation of the aldehyde structure](image)

To a stirred solution of the alcohol 199 (136 mg, 0.560 mmol) in dry dichloromethane (21 mL) were added dry sodium acetate (13.7 mg, 0.3 equiv) and pyridinium chlorochromate (181 mg, 1.5 equiv). The dark brown solution was stirred at room temperature for 2 h and then dry diethyl ether (≈ 2 mL) was added. The heterogeneous mixture was sonicated for 1 min and passed through a plug of Florisil ® (elution with dry diethyl ether). Removal of the solvent from the eluate under reduced pressure and distillation (air-bath temperature 165-170 °C/0.17 torr) of the oil thus obtained, provided 124 mg (92%) of the aldehyde 198. This material exhibits ir (film): 2704, 1722, 1148 cm⁻¹; ¹H nmr (400 MHz) δ: 0.93 (s, 3H, angular methyl), 1.24-1.83
(m, 11H), 1.91-2.07 (m, 2H), 2.21 (br s, 1H, \( \omega_{1/2} = 12 \text{ Hz} \), \(-\text{CHCHO}\)), 3.22 (dd, 1H, \( J = 11, 4 \text{ Hz} \), \(-\text{CHOCH}_2\text{OCH}_3\)), 3.37 (s, 3H, \(-\text{OCH}_3\)), 4.58 (d, 1H, \( J = 6 \text{ Hz} \), one of \(-\text{OCH}_2\text{OCH}_3\)), 4.71 (d, 1H, \( J = 6 \text{ Hz} \), one of \(-\text{OCH}_2\text{OCH}_3\)), 9.76 (s, 1H, aldehydic proton).  *Exact Mass* calcd. for \( \text{C}_{14}\text{H}_{24}\text{O}_3 \): 240.1726; found:240.1731.

**Preparation of the Aldehyde 200**

![Structure of the aldehyde 200](image)

To a stirred solution of the aldehyde 198 (12.0 mg, 50.0 \( \mu \text{mol} \)) in spectral grade methanol (4 mL) was added solid sodium methoxide (11.0 mg, 4.0 equiv) in one portion. The solution was stirred at room temperature for 18 h and then a saturated aqueous solution of ammonium chloride (pH 8, \( \approx 2 \text{ mL} \)) was added. Diethyl ether (= 5 mL) was added, the aqueous phase was separated and extracted with diethyl ether (3 x 2 mL). The combined organic solution was washed with brine (3 x 5 mL), dried over anhydrous magnesium sulfate and passed through a plug of Florisil \(^\circledR\) (elution with dry diethyl ether). Removal of the solvent from the eluate under reduced pressure and distillation (air-bath temperature 105-110 °C/0.03 torr) of the oil thus obtained, provided 8.4 mg (70\%) of the aldehyde 200. This material exhibits \( \text{ir} \) (film) : 2711, 1721, 1148 \( \text{cm} \)^{-1}; \( ^1\text{H nmr} \) (400 MHz) \( \delta \): 1.07-1.88 (diffuse m, 13H), 1.07 (s, 3H, angular methyl), 2.67 (dt, 1H, \( J = 12, 3 \text{ Hz} \), -CHCHO), 3.23 (dd, 1H, \( J = 11, 4 \text{ Hz} \), -CHOCH\(_2\)OCH\(_3\)), 3.39 (s, 3H, -OCH\(_3\)), 4.60 (d, 1H, \( J = 6 \text{ Hz} \), one of -OCH\(_2\)OCH\(_3\)), 4.72 (d, 1H, \( J = 6 \text{ Hz} \), one of -OCH\(_2\)OCH\(_3\)), 9.64 (s, 1H, aldehydic proton).  *Exact Mass* calcd. for \( \text{C}_{14}\text{H}_{24}\text{O}_3 \): 240.1726; found:240.1731.
Preparation of the α,β-Unsaturated Aldehyde 202

To a cold (-20 °C) stirred solution of the aldehyde 198 (47.6 mg, 0.198 mmol) in dry dichloromethane (4 mL) were added dry triethylamine (55 μL, 2.0 equiv) and iodosiltrimethylsilane (42 μL, 1.5 equiv). The resultant solution was stirred at -20 °C for 10 min and at room temperature for 5 min and then petroleum ether (= 5 mL) was added. The resultant solution was washed with a saturated aqueous solution of sodium hydrogen carbonate (2 mL), an aqueous solution of 1% hydrochloric acid (2 mL) and again with aqueous saturated sodium hydrogen carbonate (2 mL). The organic solution was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded an oil that was distilled (air-bath temperature 127-134 °C/1.5 torr) to provide 60.6 mg of the crude enol trimethylsilyl ethers 201 as a pale yellow oil. This material exhibits

1H nmr (400 MHz) δ: 0.15, 0.16 (two s, -Si(CH3)3), 1.00, 1.01 (two s, angular methyls), 1.16-1.84 (m), 2.01-2.11 (m), 2.48 (dd, J = 12, 3 Hz), 2.58-2.65 (m), 3.16, 3.22 (dd, J = 11, 4 Hz each, -CHOCH2CH3), 3.36, 3.37 (two s, CH3O-), 4.56-4.61 (m), 4.69-4.74 (m), 6.02, 6.05 (two d, J = 7 and 8 Hz, respectively, olefinic proton, 1:2 ratio)

To a stirred solution of the crude enol trimethylsilyl ethers 201 (60.6 mg) in dry acetonitrile (10 mL) at room temperature was added solid palladium (II) acetate (47.9 mg, 1.08 equiv). The resultant deep red solution was stirred at room temperature for 4 h. The mixture was passed through a plug of Celite ® (elution with diethyl ether and dichloromethane). The organic solution was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Flash chromatography of the crude
product on silica gel (0.7 x 15 cm column, elution with dichloromethane), concentration of the appropriate fractions and distillation (air-bath temperature 140-150 °C/1.5 torr) of the oil thus obtained provided 22.6 mg (48%) of the α,β-unsaturated aldehyde 202 as a colourless oil. This material exhibits ir (film): 1684, 1640, 1145 cm⁻¹; ¹H nmr (400 MHz) δ: 0.93-1.04 (m, 1H), 0.95 (s, 3H, angular methyl), 1.25-1.90 (m, 8H), 2.20-2.39 (m, 2H), 2.47 (dt, 1H, J = 15, 4 Hz, one of -CH-CH₂⁻), 3.35 (dd, 1H, J = 11, 4 Hz, -CHOCH₂OCH₃), 3.40 (s, 3H, -OCH₃), 4.62 (d, 1H, J = 6 Hz, one of -OCH₂OCH₃), 4.75 (d, 1H, J = 6 Hz, one of -OCH₂OCH₃), 6.70 (t, 1H, J = 4 Hz, =CH⁻) 9.40 (s, 1H, aldehydic proton). Exact Mass calcd. for C₁₄H₂₂O₃: 238.1569; found:238.1570.

Preparation of the Enol Trimethylsilyl Ether 204

To a cold (-78 °C) stirred slurry of copper(I) cyanide (207 mg, 5.0 equiv) in dry THF (26 mL) was added methyllithium (1.45 mL, 5.0 equiv) as a solution in diethyl ether. The reaction mixture was stirred at -78 °C for 10 min and then chlorotrimethylsilane (0.311 mL, 5.3 equiv) was added. The solution was stirred at -78 °C for 5 min and then a dry THF solution (3.6 mL) of the α,β-unsaturated aldehyde 202 (110 mg, 0.462 mmol) was added in a dropwise manner. The reaction mixture was stirred at -78 °C for 8 h and then a saturated aqueous solution of ammonium chloride (pH 8, ~ 5 mL) was added. The organic phase was separated and washed repeatedly with brine until the aqueous phase was neutral as indicated by pH paper. The organic solution was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Distillation (air-bath
temperature 135-140 °C/1.5 torr) of the oil thus obtained provided 138 mg (92%) of the enol trimethylsilyl ether 204 as a colourless oil. This material exhibits ir (film): 1654, 1148 cm⁻¹; ¹H nmr (400 MHz) δ: 0.08 (s, 9H, (CH₃)₃Si), 0.91 (s, 3H, angular methyl), 1.06 (d, 3H, J = 7 Hz, secondary methyl), 1.10-1.85 (m, 10H), 2.23 (br quintet, 1H, J = 7 Hz, methine proton α to the secondary methyl), 2.41 (dd, 1H, J = 11, 4 Hz, angular proton), 3.18 (dd, 1H, J = 11, 4 Hz, -CHOCH₂OCH₃), 3.32 (s, 3H, -OCH₃), 4.54 (d, 1H, J = 6 Hz, one of -OCH₂OCH₃), 4.67 (d, 1H, J = 6 Hz, one of -OCH₂OCH₃), 6.09 (s, 1H, olefinic proton). The following decoupling experiments were carried out. Irradiation at δ 1.06 (secondary methyl): quintet at 2.23 (methine proton α to the secondary methyl) simplified to a broad doublet (J = 7 Hz). Irradiation at δ 2.23 (methine proton α to the secondary methyl): doublet at 1.06 (secondary methyl) simplified to a singlet, multiplet at 1.45-1.56 simplified, multiplet at 1.77-1.85 simplified. In a nOe difference experiment, irradiation at δ 2.23 (proton α to the secondary methyl) caused signal enhancement at 1.06 (d, secondary methyl) and 6.09 (s, olefinic proton). In another nOe difference experiment, irradiation at δ 6.09 (olefinic proton) caused signal enhancement at 2.23 (methine proton α to the secondary methyl). Exact Mass calcd. for C₁₈H₃₄O₃Si: 326.2278; found: 326.2275.
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