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

by

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We accept this thesis as conforming

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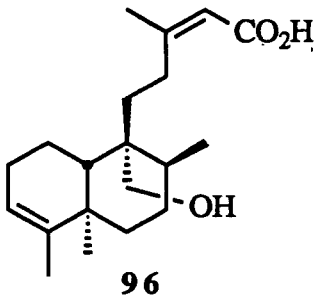
ABSTRACT

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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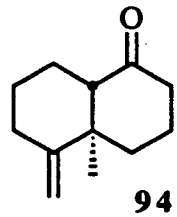

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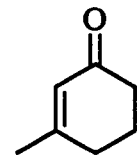

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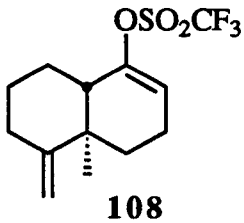

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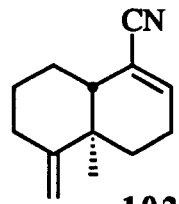

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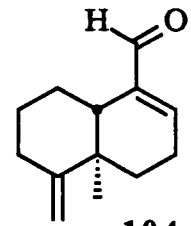

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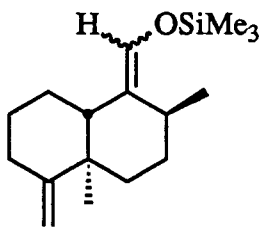

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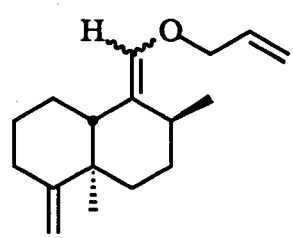

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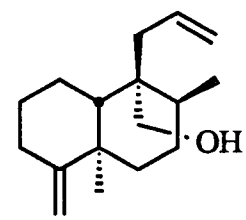

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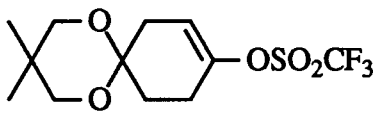

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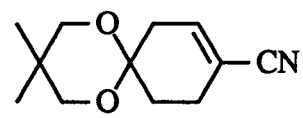

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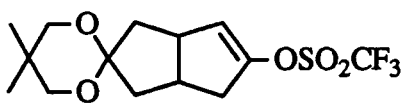

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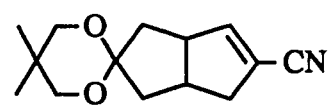

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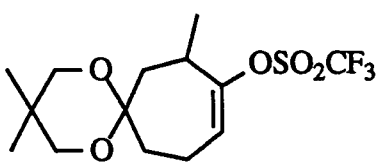

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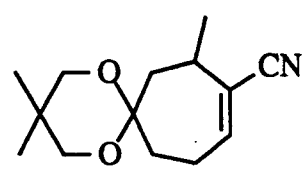

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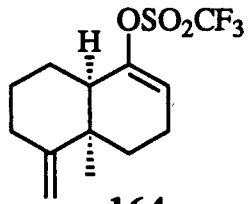

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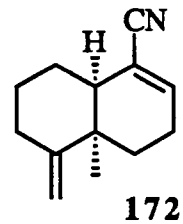

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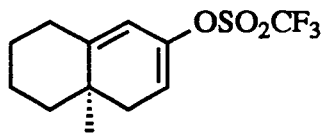

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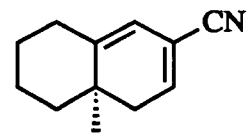

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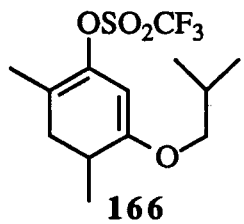

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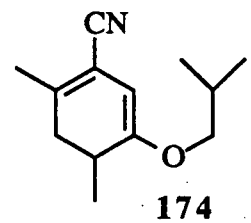

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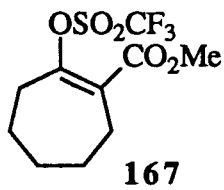

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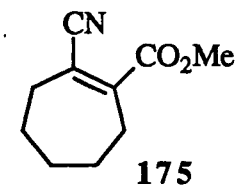

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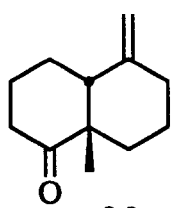

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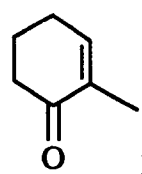

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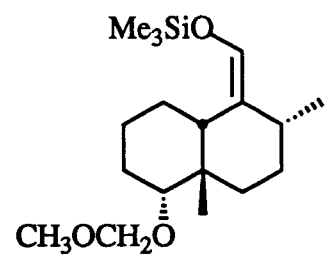

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LIST OF ABBREVIATIONS

Ac	-	acetyl
br	-	broad
9-BBn	-	9-borabicyclo[3.3.1.]nonane
Bu	-	butyl
CSA	-	10-camphorsulfonic acid
d	-	doublet
DBU	-	1,8-diazobicyclo[5.4.0]undec-7-ene
DIBAL	-	diisobutylaluminum hydride
DMAP	-	4-*N*,*N*-dimethylaminopyridine
DME	-	1,2-dimethoxyethane
DMSO	-	dimethylsulfoxide
equiv	-	equivalent(s)
Et	-	ethyl
glc	-	gas-liquid-chromatography
h	-	hour(s)
HETCOR	-	heteronuclear correlation spectroscopy
HMPA	-	hexamethylphosphoramide
ir	-	infrared
LDA	-	lithium diisopropylamide
m	-	multiplet
Me	-	methyl
MOM	-	methoxymethyl
min	-	minute(s)
mp	-	melting point
Ms	-	methanesulfonate

nmr	-	nuclear magnetic resonance
nOe	-	nuclear Overhauser enhancement
PCC	-	pyridinium chlorochromate
Ph	-	phenyl
py	-	pyridine
q	-	quartet
rt	-	room temperature
s	-	singlet
SINEPT	-	selective insensitive nuclei enhanced by polarization transfer
Sia	-	$-CH(CH_3)CH(CH_3)_2$
t	-	triplet
tert	-	tertiary
TBAF	-	tetra-*n*-butylammonium fluoride
THF	-	tetrahydrofuran
tlc	-	thin layer chromatography
p-TsOH	-	*para*-toluenesulfonic acid
Ts	-	*para*-toluenesulfonyl
X	-	chlorine, bromine or iodine
Δ	-	heat

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INTRODUCTION

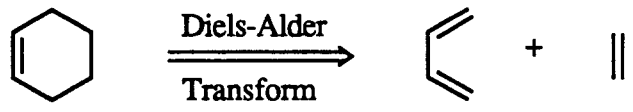
General Introduction

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 [1] 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.

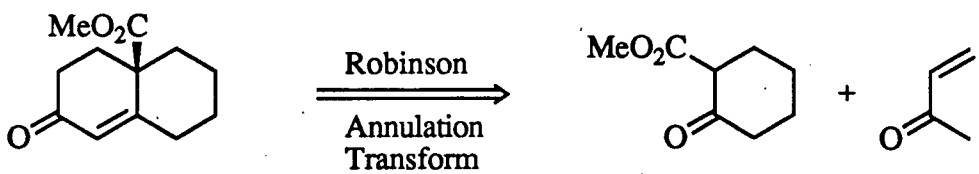
"Retrosynthetic (or antithetic) analysis is a problem-solving technique for transforming the structure of a *synthetic target* (TGT) molecule to a sequence of progressively simpler structures along a pathway which ultimately leads to simple or commercially available starting materials for a chemical 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).

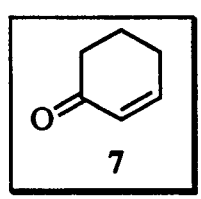


1 **2** **3** (1)

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).



4 **5** **6** (2)



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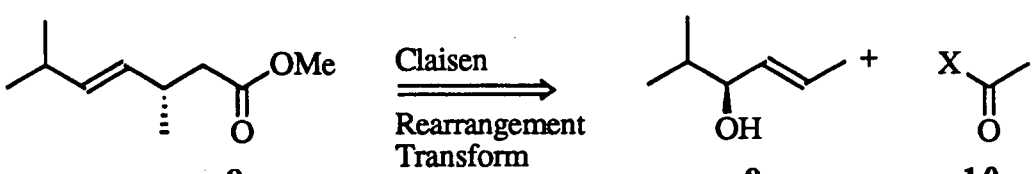
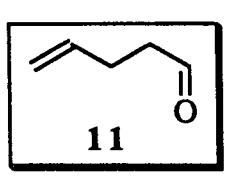


8 **9** **10** (3)



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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.

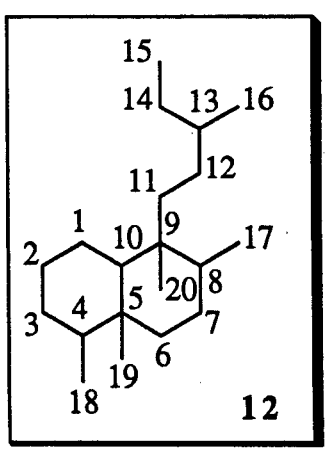
Clerodane Diterpenoids

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 [3] and marine animals.[4] Initially, interest in the clerodanes was generated because a number of these compounds were active as antifeedants.[5] Some clerodane diterpenoids have also been identified as having antitumor [3,6], piscicidal [7], psychotropic [8] and antibiotic [9] 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.[10] 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 **12** 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 **13** via a prototropic migration followed by rearrangement of the basic skeleton.[10]



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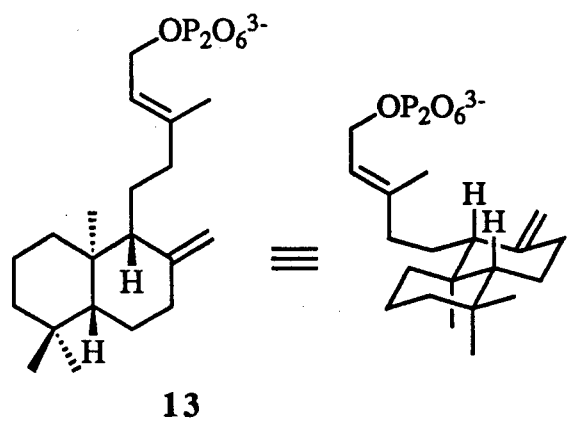

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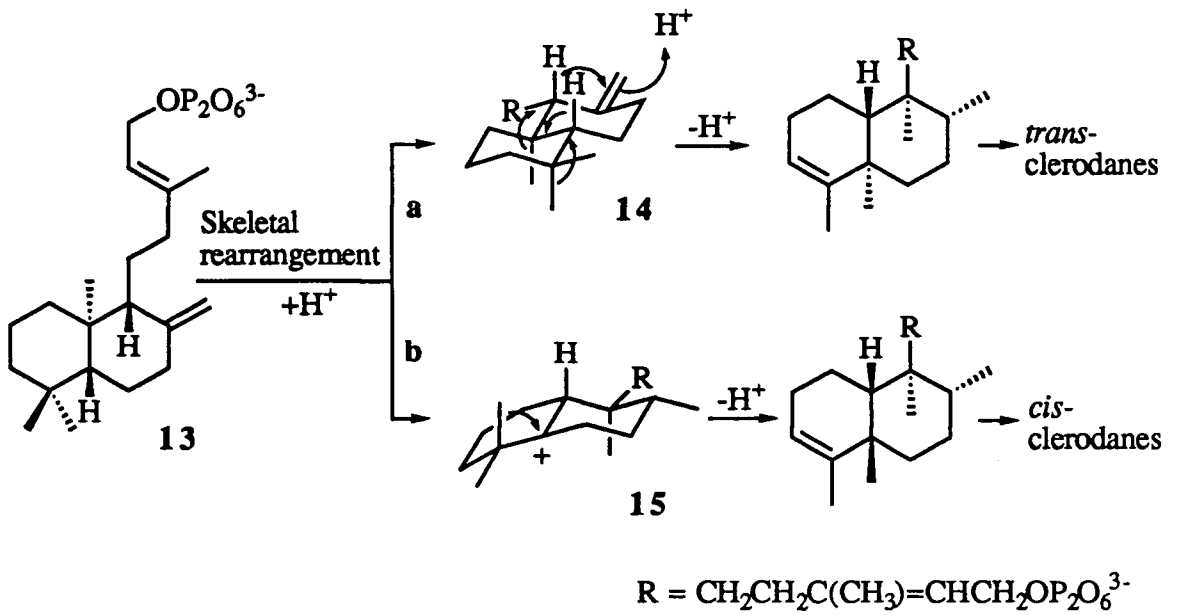

Scheme 1

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).[9] 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).[9] 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; [4] (ii) C-17, C-18 and C-19 may have various

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* Unless otherwise stated the clerodane numbering system, shown for **12**, is referred to throughout.

oxidation levels but C-20 is seldom oxygenated; [11] (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.

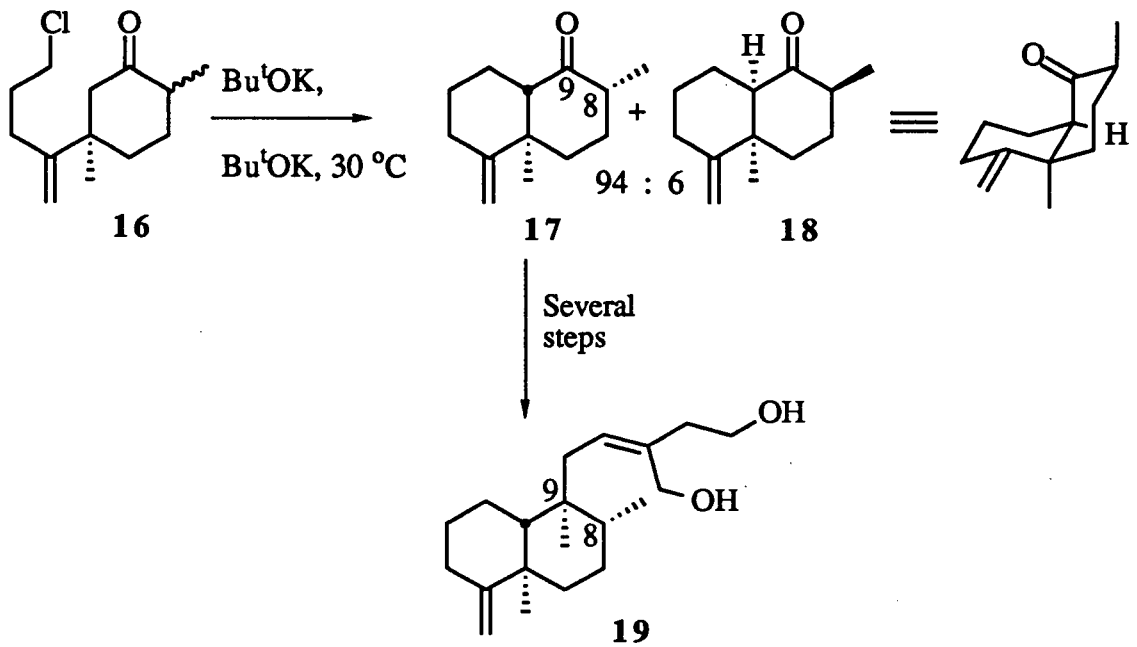
Previous Synthetic Approaches

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, [12] 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.[13] 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).[14]

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** → **40** + **41**, *vide infra*).[15]



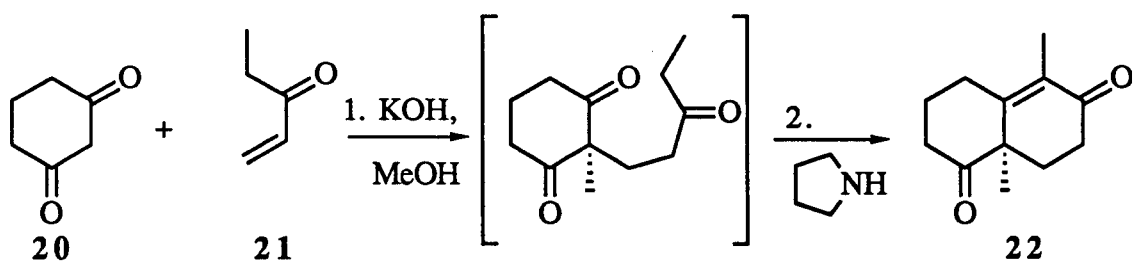
Scheme 2

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.[16] 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** [17] was used as the starting material for the synthesis of **23** and **25** (equations 4 and 5 respectively).



20 **21** **22**

Scheme 3

Dissolving metal reductions of Robinson annulation type products have been studied extensively.[18,19] Bicyclic enones such as **23**, **25** and **27** are usually reduced to the more stable *trans*-fused enolates,[19] which can be alkylated with appropriate

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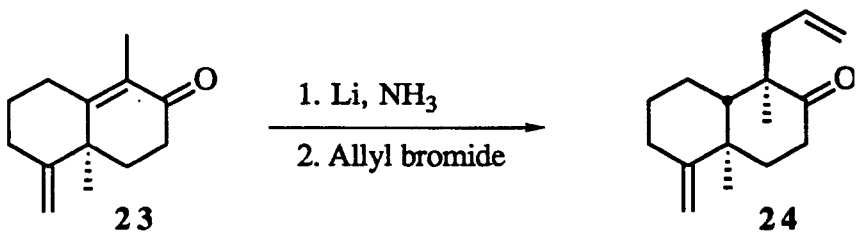
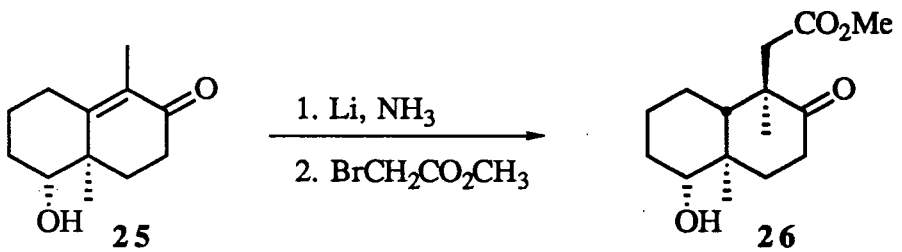
* The Robinson annulation retron was discussed previously on page 2. The retrosynthetic analysis on page 2 can be contrasted with the synthetic equivalent shown in scheme 3.

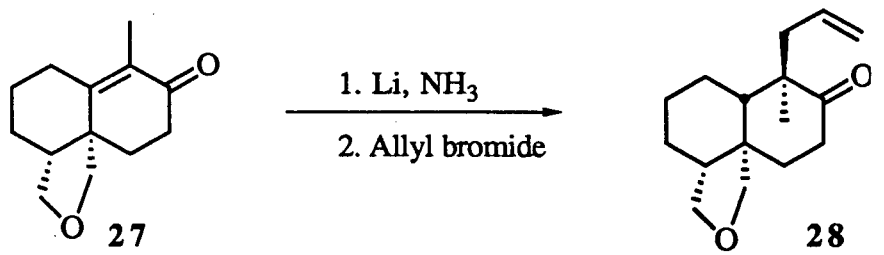
electrophiles. The choice of an electrophile seems to be limited to those exhibiting a high reactivity, as can be seen from equations 4, 5 and 6.



23 **24** (4)



25 **26** (5)

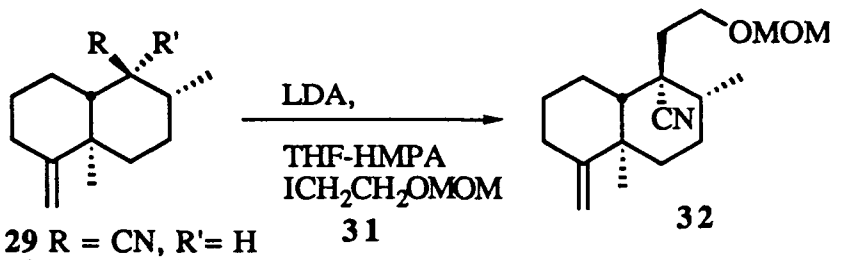


27 **28** (6)

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.[14] (The nitriles **29** and **30** were prepared by treatment of the ketone **17** with (*p*-toluenesulfonyl)methyl isocyanide).



29 R = CN, R'= H
30 R = H, R'= CN

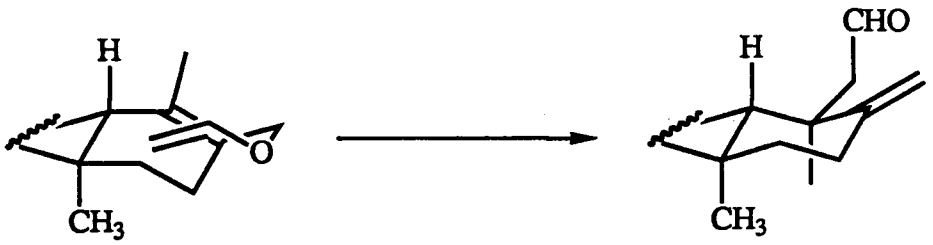
(7)

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.

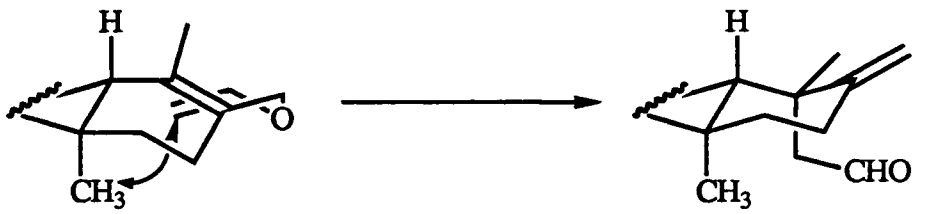
Claisen Rearrangement Transform

Historically, the Claisen rearrangement was used as a key step in the first successful total synthesis of a clerodane diterpenoid, namely (±)-annonene (**42**).[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).



(8)



(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

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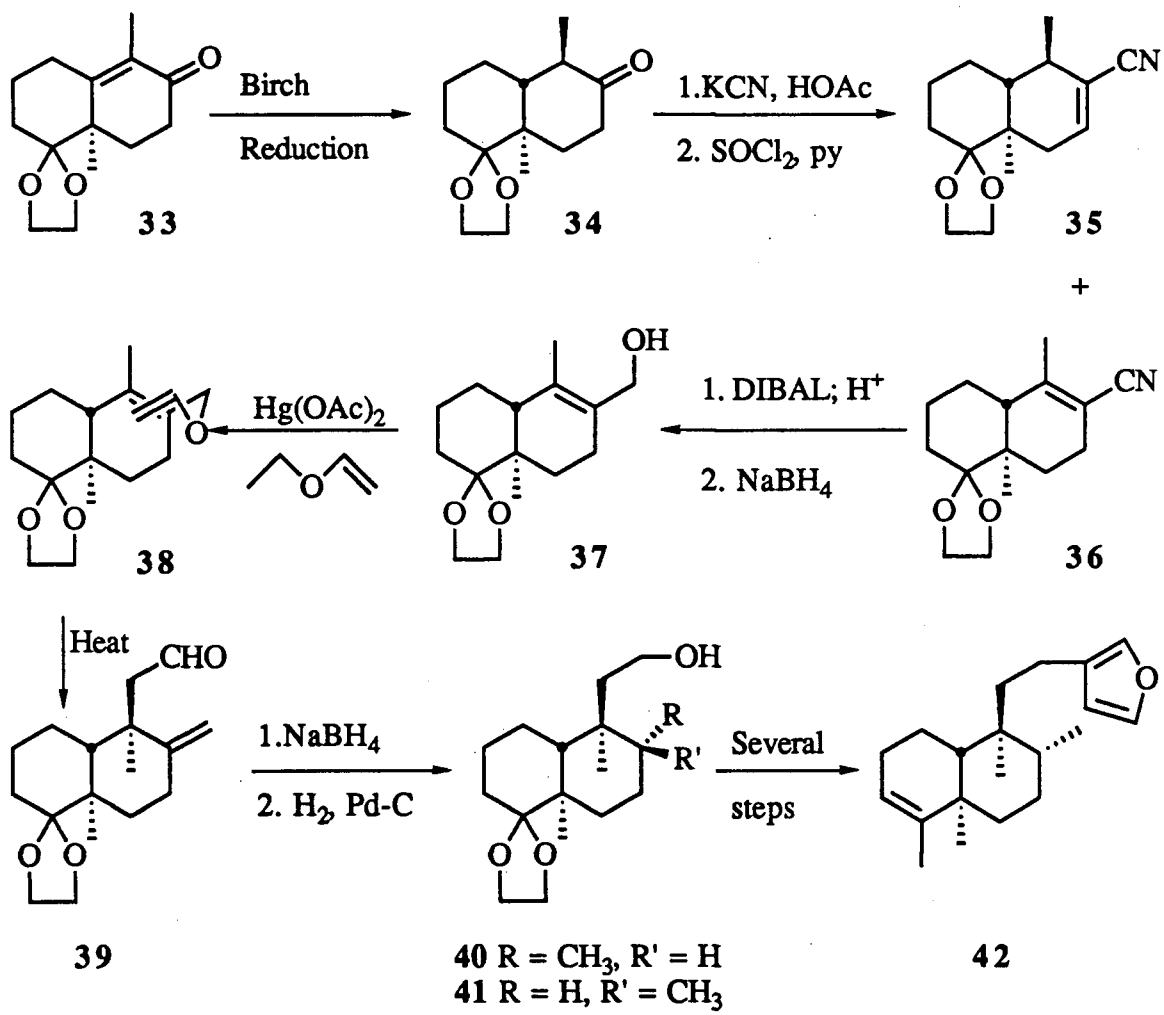
* The conversions of **39** → **40** + **41** and **34** → **35** + **36** illustrate examples of poor stereocontrol and regiocontrol respectively (Scheme 4).

† 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.

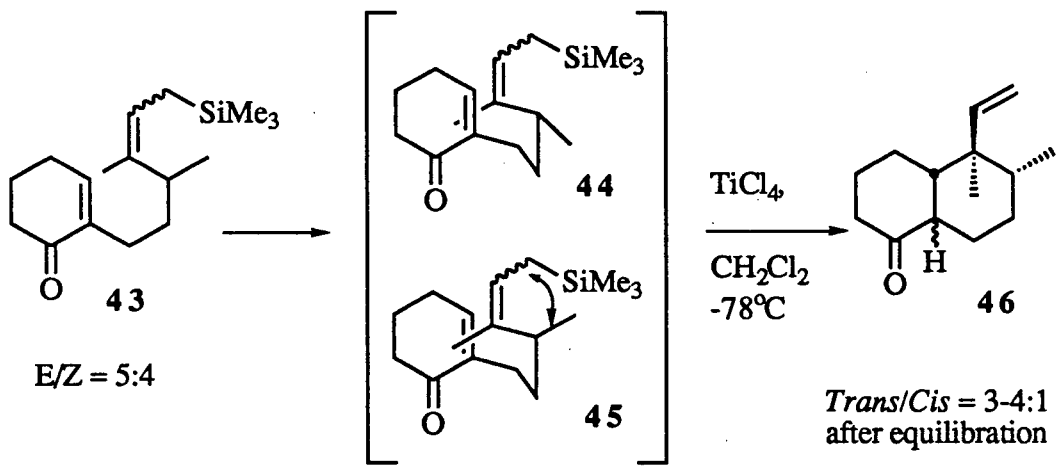
Reduction of the aldehyde **39**, followed by catalytic hydrogenation of the resultant alkene alcohol provided the alcohols **40** and **41**. Unfortunately the ratio of epimers was 1:1, resulting from a complete lack of facial preference in the hydrogenation. The alcohols **40** and **41** were separated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



Scheme 4

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).[21]

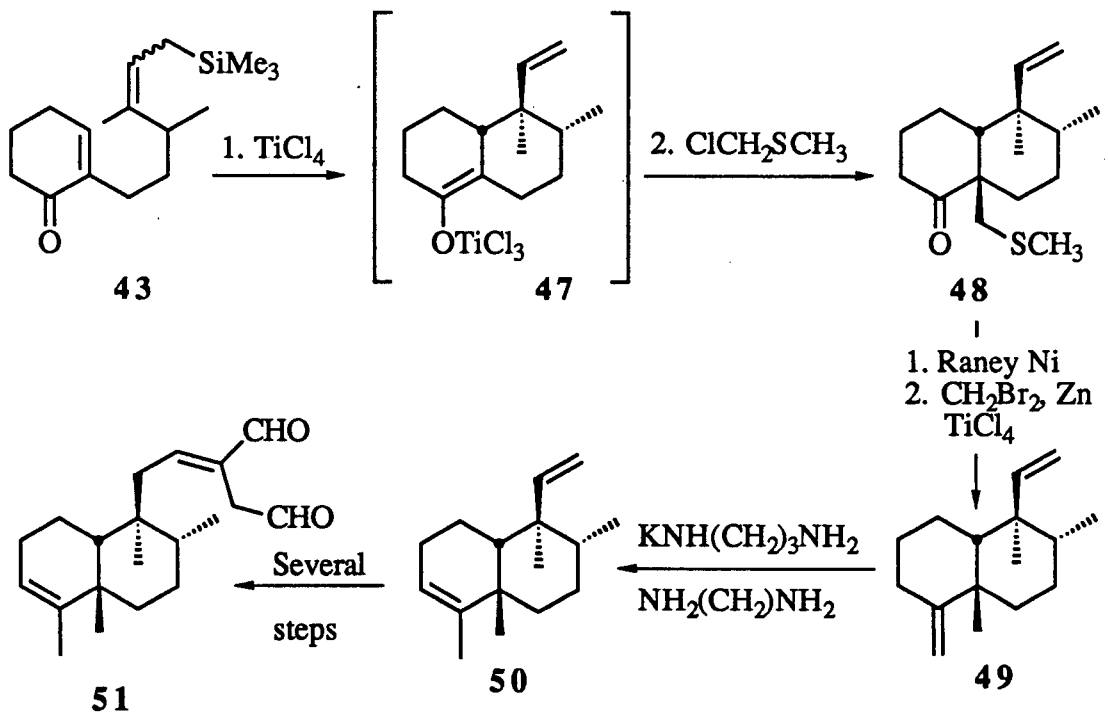


Scheme 5

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**).



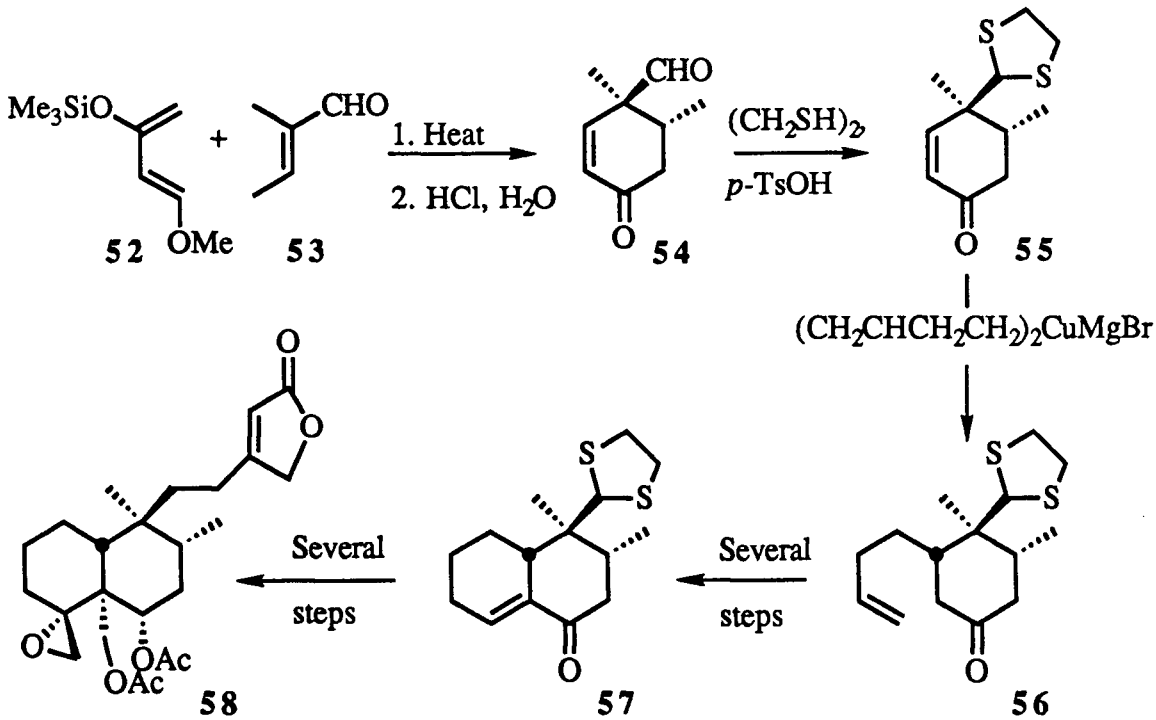
43 **47** **48** **49** **50** **51**

Scheme 6

Formation of a Monocyclic Precursor Containing Stereocenters 8 and 9

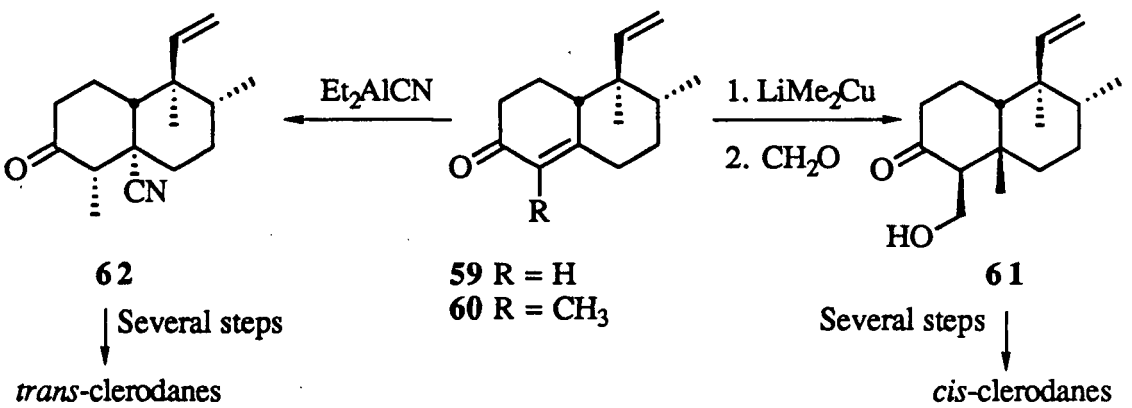
Syntheses which incorporate the two centers that will ultimately become C-8 and C-9 of a clerodane diterpenoid in a monocyclic precursor reduce the steric demands associated with the introduction of these two centers in a bicyclic intermediate.

Ley and co-workers were the first to recognize this approach.[23] 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**).



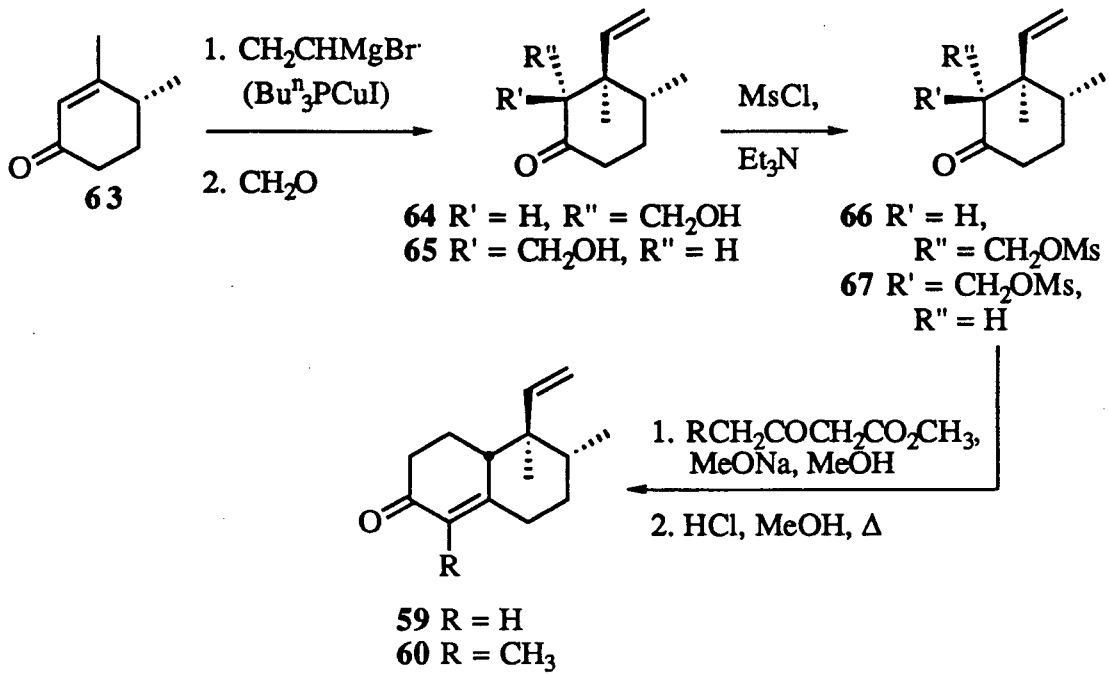
Scheme 7

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 Δ^4-octal-3-one retrons 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

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]



63

64 R' = H, R" = CH_2OH
65 R' = CH_2OH, R" = H

66 R' = H, R" = CH_2OMs
67 R' = CH_2OMs, R" = H

59 R = H
60 R = CH_3

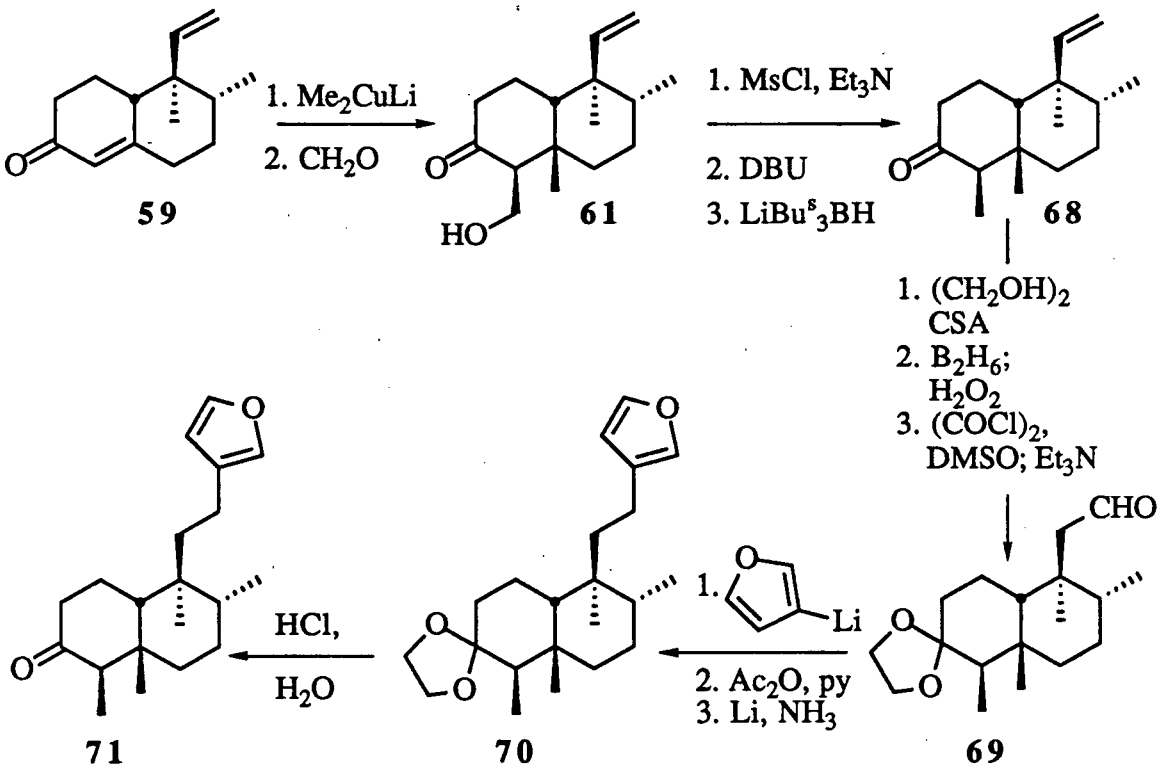
Scheme 9

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 = H or R = CH_3) in the presence of sodium methoxide in methanol, followed by refluxing with acid yielded the bicyclic enones **59** and **60** (R = H and R = 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

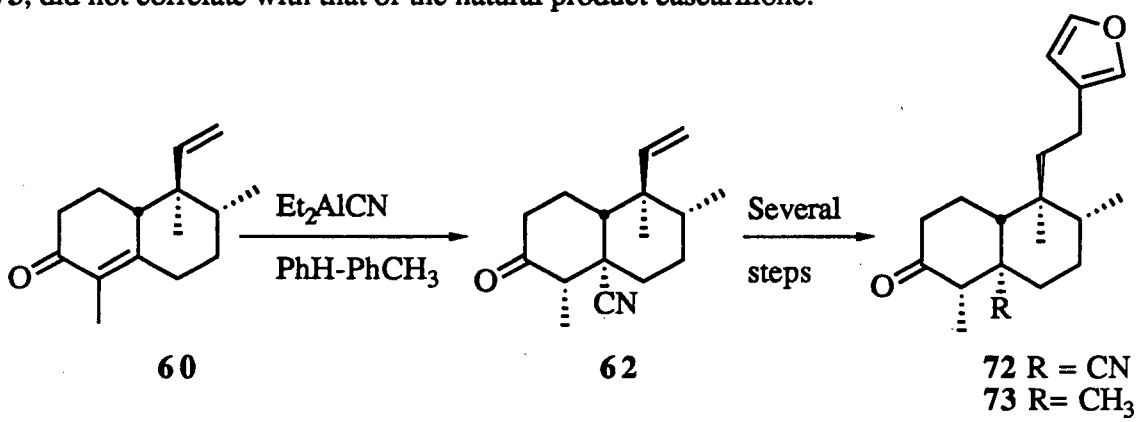
material was smoothly reduced with lithium tri-*sec*-butylborohydide to afford the *cis*-ketone **68**. Acetalization of **68**, followed by a hydroboration-oxidation sequence, secured the aldehyde **69**. Addition of 3-furyllithium to **69**, acetylation and Birch reduction of the resulting acetate gave the furan **70**. Removal of the acetal under acidic conditions led to the expected target **71**.[26] Unfortunately, the spectral data for compound **71** did not correlate with that of the natural product cascarillone.



Scheme 10

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).[26] 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.

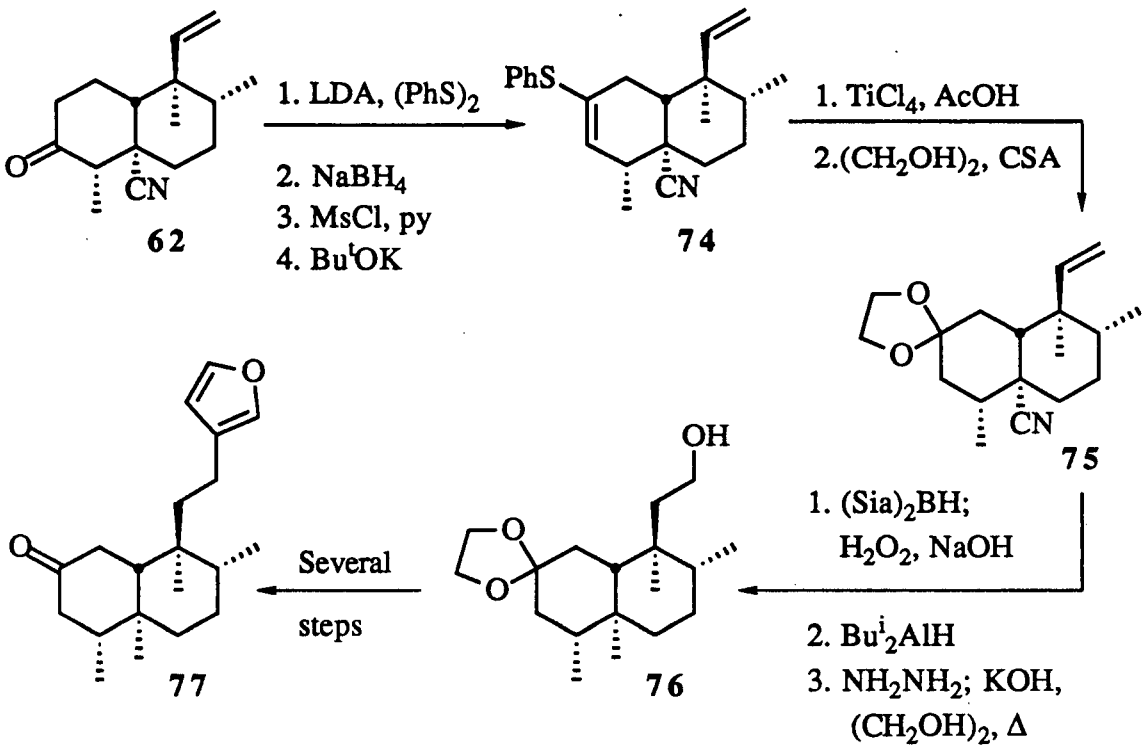


Scheme 11

At this stage, a sample of the natural product cascarillone was isolated and a series of ^1H 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 α-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** → **70**, Scheme 10) and removal of the acetal gave the furano ketone **77**. Compound **77** exhibited

spectroscopic properties identical to those of cascarillone, thus confirming the proposed structure and completing the first total synthesis of this natural product.[26]



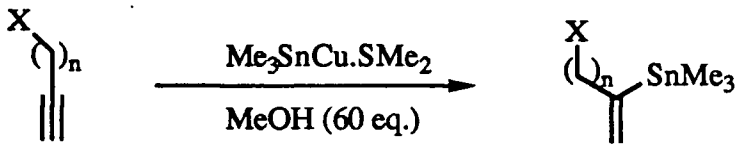
Scheme 12

Although the merit of these synthetic endeavors to elucidate the structure of cascarillone 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.[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

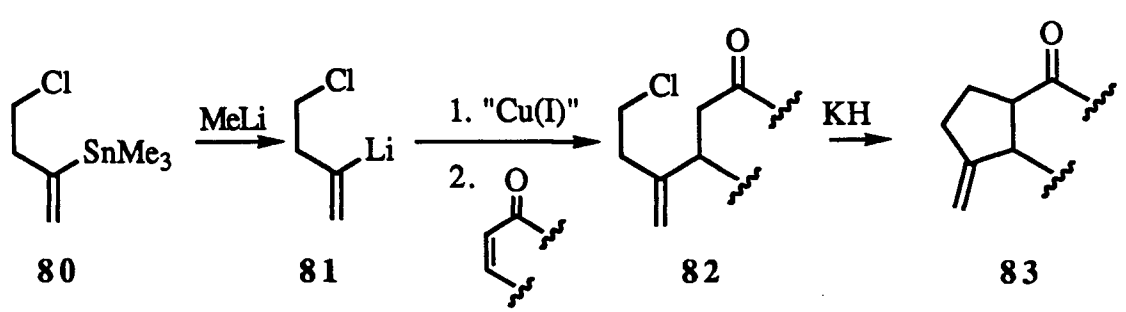
molecules containing one nucleophilic and one electrophilic center had previously been achieved using organotin methodology.[29] Thus, reaction of a terminal acetylene **78** with (trimethylstannyl)copper(I)-dimethylsulfide, under suitable conditions, provided the corresponding 2-trimethylstannyl-1-alkenes **79** (equation 10).



78 **79**

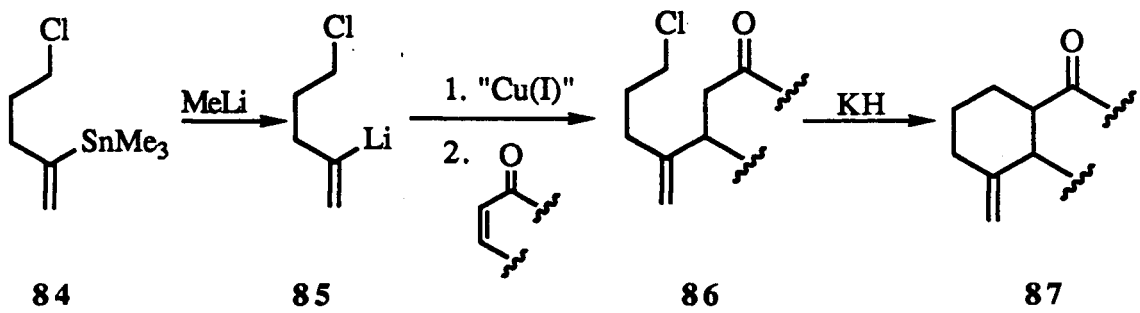
n = 1-4
X = OH, Cl, OSiBu^{t}Me$_2$
O-tetrahydropyranyl (10)

The two chloro stannanes **80** and **84** have proven to be synthetically useful bifunctional reagents.[27, 28] Treatment of **80** or **84** with methyllithium in THF at -78 °C gives solutions containing the corresponding vinyllithium species **81** and **85**, respectively (Schemes 13 and 14). These vinyllithiums 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.[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.



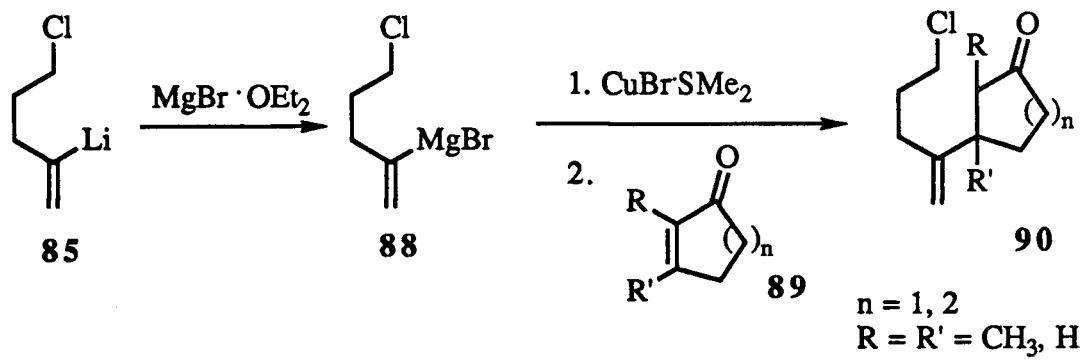
80 **81** **82** **83**

Scheme 13



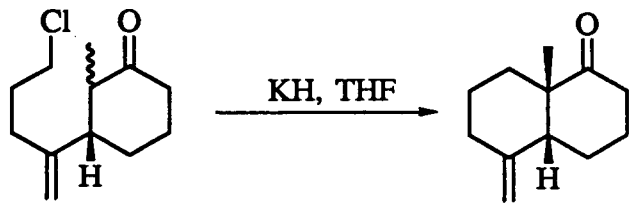
Scheme 14

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.[28] Thus, formation of the vinyllithium **85**, as in scheme 14, followed by the addition of anhydrous magnesium bromide-etherate, provides the corresponding Grignard reagent **88** (Scheme 15). In the presence of copper(I) bromide-dimethyl sulfide, the Grignard reagent **88** undergoes conjugate addition to a variety of substituted enones **89**.[28] The resulting chloro ketones **90** were cyclized by treatment with potassium hydride in THF.

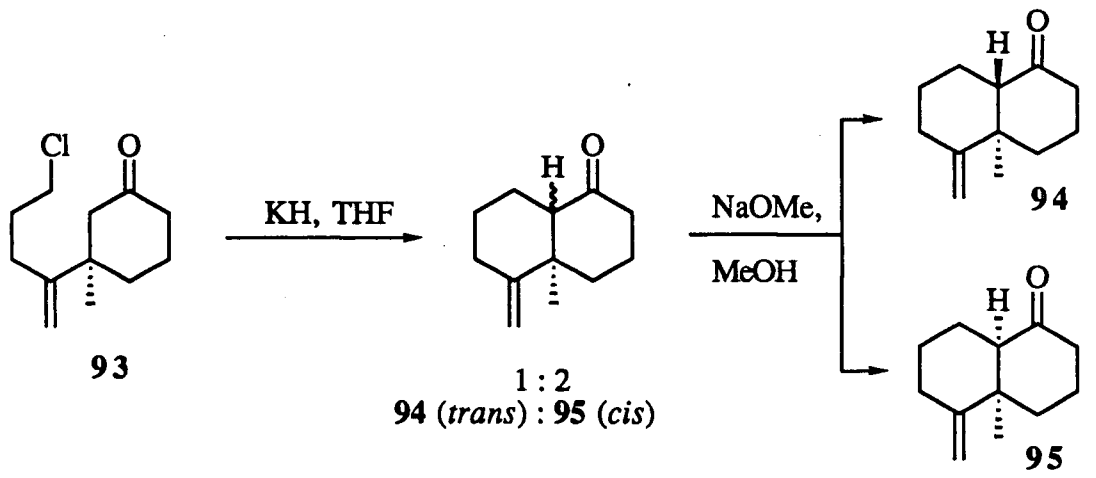


Scheme 15

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**.



91 **92** (11)



93

1 : 2
94 (*trans*) : **95** (*cis*)

94

95

3.5 : 1
94 (*trans*) : **95** (*cis*)

Scheme 16

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).[14]

Research Objectives

The successful completion of several clerodane syntheses demonstrates that the more common clerodanes can be accessed via previously reported strategies.[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 [30] is stephalic acid (**96**).[11c] Stephalic acid was isolated as the polar component of the methanolic extract from *Stevia polycephala*, collected in the state of Tlaxcala, Mexico.[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.

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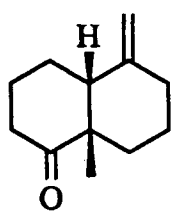
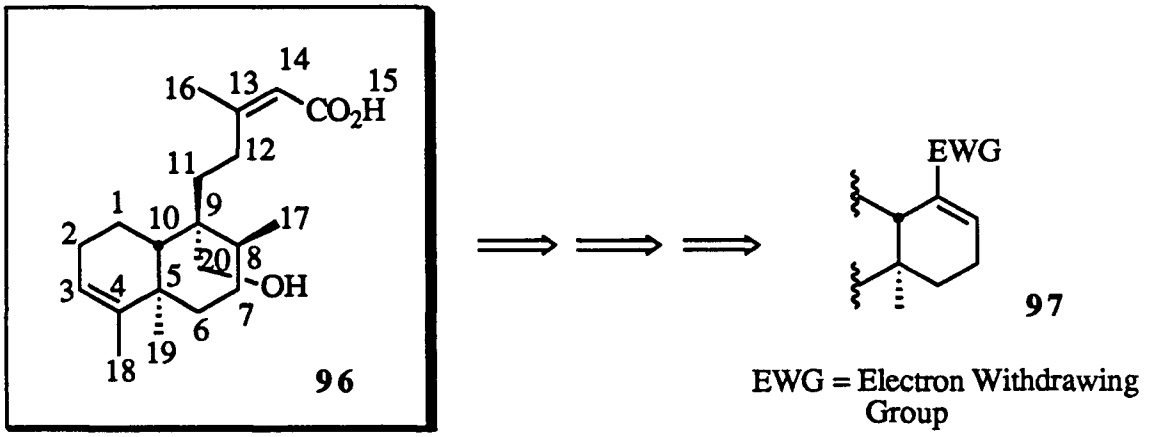
* The relationship between the ketone **92** and the clerodane skeleton **12** is easily seen when **92** is drawn as shown.





Scheme 17

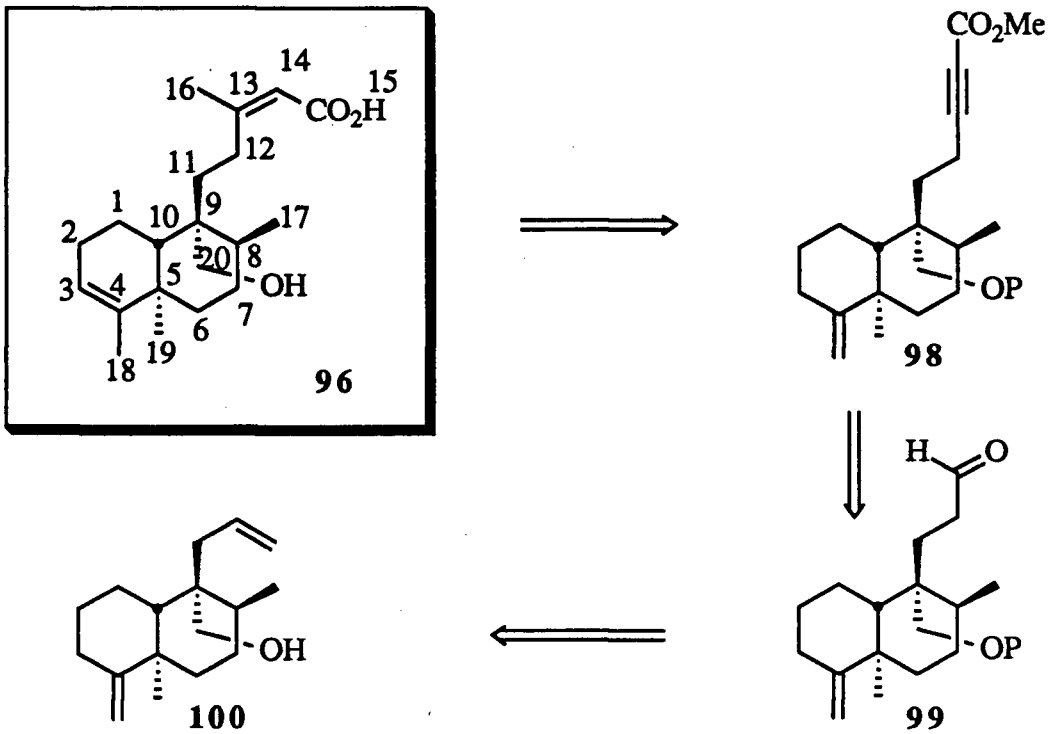
In a retrosynthetic sense, access to the C-8 substituent of the clerodanes may be possible by using an organocopper reagent to effect the conjugate addition of the requisite methyl group to an activated olefin of part structure **97** (Scheme 17). Furthermore, the previously described methylenecyclohexane 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 [31] 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 [32] leads, retrosynthetically, to the aldehyde **99** and, after several functional group manipulations, to the alcohol **100** (Scheme 18).

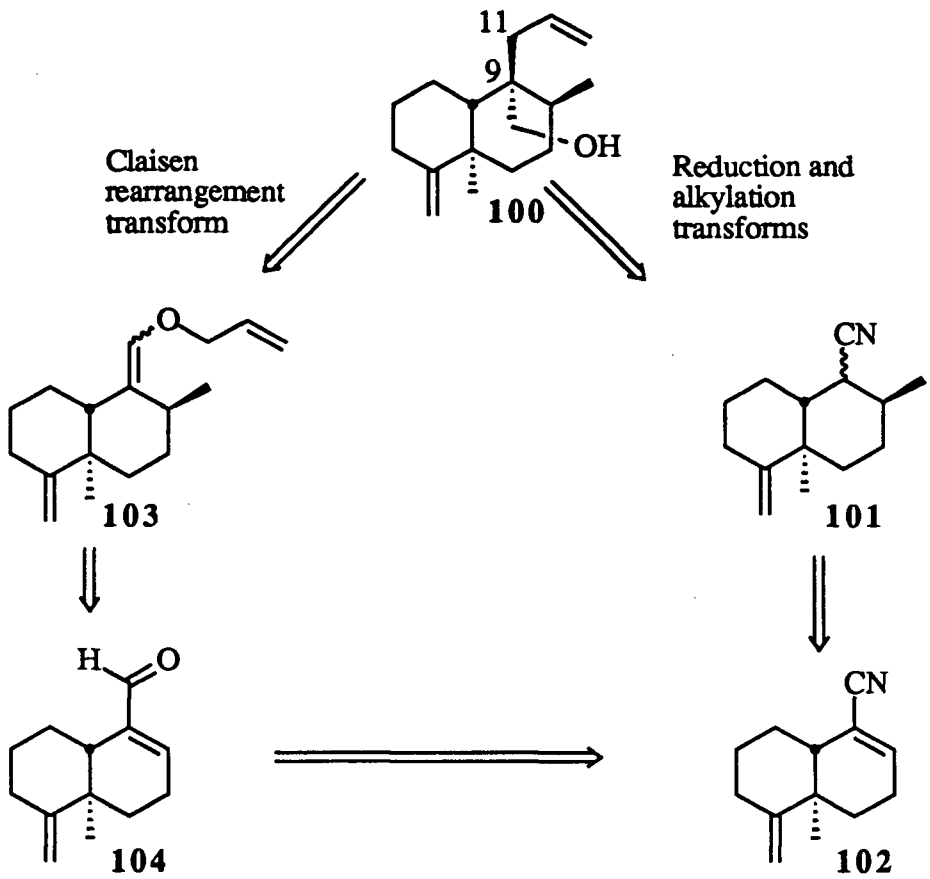


Scheme 18

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.[33] Disconnection of the bond between the ring carbon and the secondary methyl group in **101** would lead to the α,β-unsaturated nitrile **102**. The latter retrosynthetic step would be reasonable provided that conjugate addition of the requisite methyl group could be effected.[34]

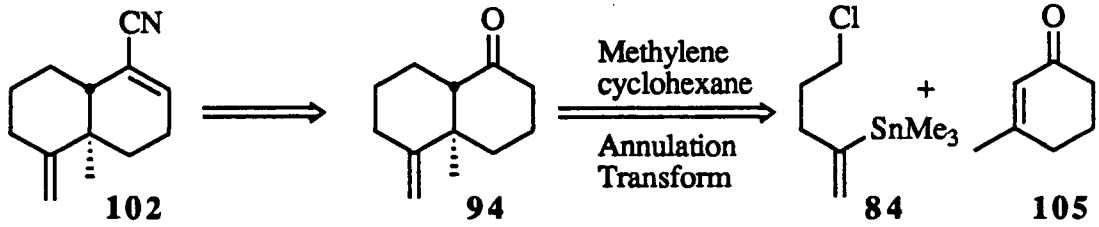
Alternatively, identification of the bis-homoallylic alcohol in **100** as a retron for the Claisen rearrangement transform [35] leads retrosynthetically to the enol vinyl ether **103**. A series of functional group manipulations would then allow disconnection of the bond between the ring carbon and the secondary methyl group to give the α,β-unsaturated

aldehyde **104**. The α,β-unsaturated aldehyde **104** was presumed to be available from the α,β-unsaturated nitrile **102**.[36]



Scheme 19

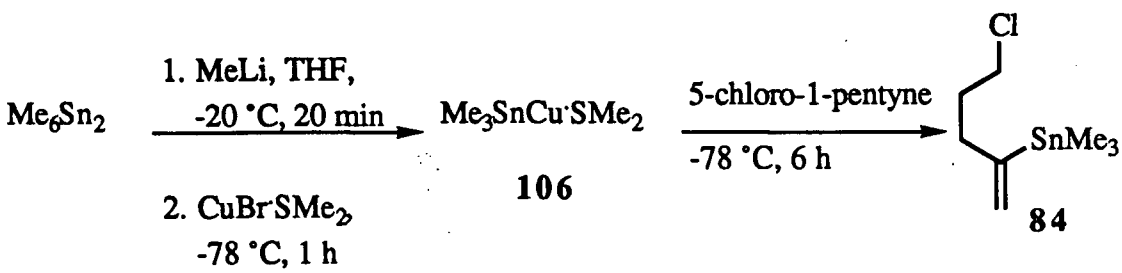
Retrosynthetic conversion of the α,β-unsaturated nitrile **102** to the ketone **94** was made on the basis of reported conversions of ketones to α,β-unsaturated nitriles [37] and a recognition of the presence of a methylenecyclohexane unit. Thus, the ketone **94** would be derived from the vinylstannane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



Scheme 20

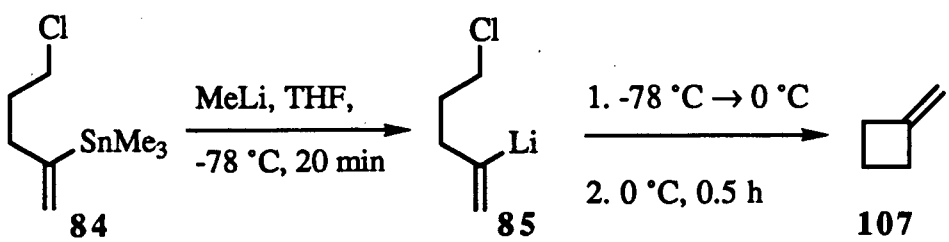
The Total Synthesis of (±)-Stephalic Acid (96)

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 trimethylstannyllithium. Formation of (trimethylstannyl)copper(I)-dimethylsulfide (**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 δ 5.22-5.24 ($^3J_{Sn-H}$ = 70 Hz) and 5.71-5.73 ($^3J_{Sn-H}$ = 150 Hz).



Scheme 21

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**).[28a] 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**).[38] The three signals due to methylenecyclobutane at δ 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 (δ 5.34) and the allylic protons of methylenecyclobutane (δ 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.

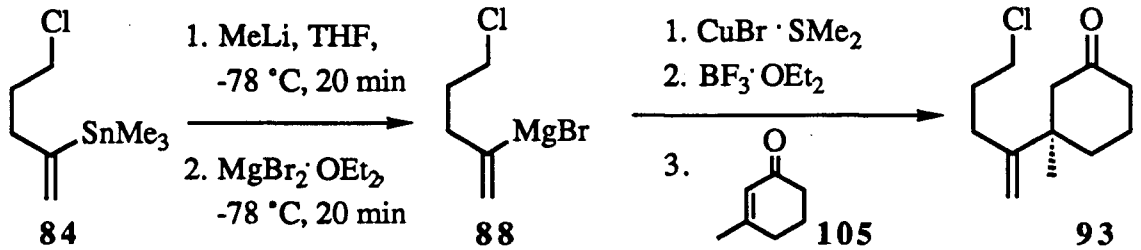


84 **85** **107**

Scheme 22

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).[28] 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** [28] was obtained in 91% yield (Scheme 23).



84 **88** **105** **93**

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 ^1H nmr spectrum shows a triplet at δ 3.51 (two protons, J = 7 Hz) due to the methylene protons adjacent to a chlorine atom, and two singlets at δ 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).[28] 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

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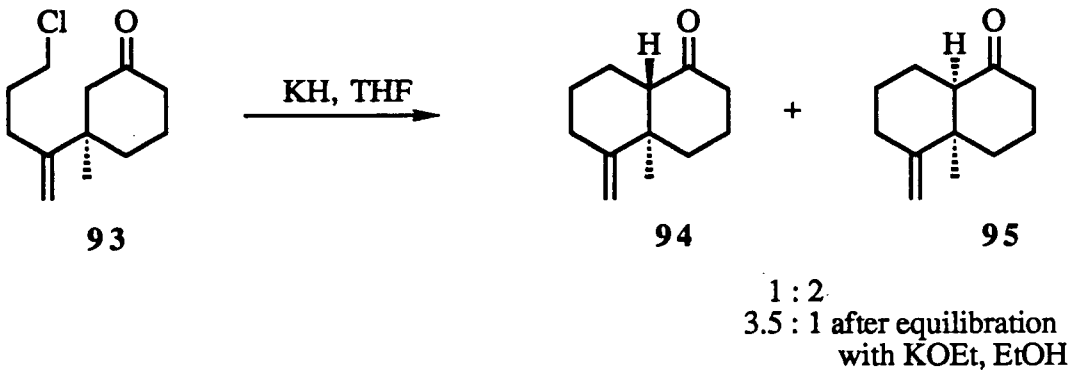
* The use of 0.05 equiv of the copper (I) bromide-dimethyl sulfide complex rather than the reported [28] 0.25 equiv gave the chloro ketone **93** in consistently higher yield.

(equation 12). (The glc analysis of a mixture (36:64, *trans*:*cis*) of these ketones showed good correlation with the compound ratios obtained from ^{1}H nmr spectroscopy (37:63, *trans*:*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, *trans*:*cis*).



93 **94** **95**

1 : 2
3.5 : 1 after equilibration with KOEt, EtOH

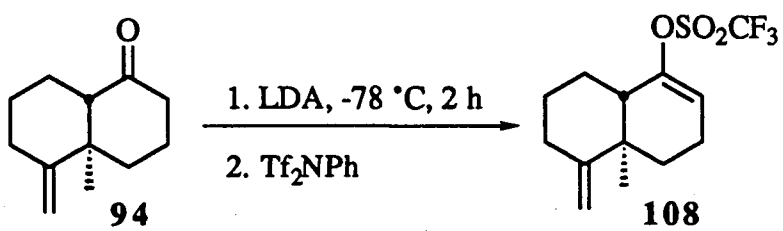
(12)

The ^{1}H nmr spectrum of the major product **94** shows signals at δ 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 *trans* and *cis*-1-decalones (δ 0.75-0.90 and 1.05-1.20, respectively), as reported by Boeckman and co-workers,[39] and correlated with the ^{1}H nmr spectral data previously reported for the *trans*-fused ketone **94**.[28b]

The ^{1}H nmr spectrum of **95** exhibits two one-proton olefinic signals at δ 4.74 and 4.76, both of which were broad singlets. The signal due to the angular methyl group appears at δ 1.17, in agreement with the assigned [28b] *cis*-ring fusion and Boeckman's data.[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.



(13)

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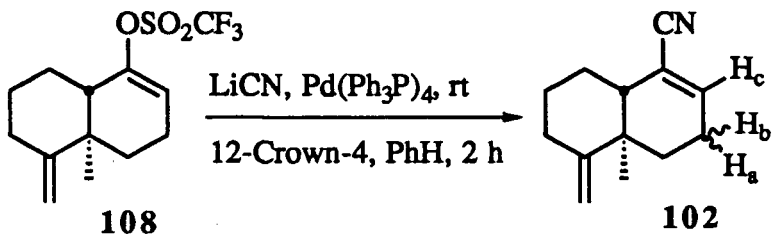
* See the conversion of **34** into **35** and **36** in the synthesis of (±)-annonene (**42**) (Scheme 4, p 12).

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).



108 **102**

(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 ^1H 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 ^1H 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 ^1H nmr spectrum of **102** indicates that two protons, assigned as H_a and H_b, are adjacent to the olefinic proton H_c.

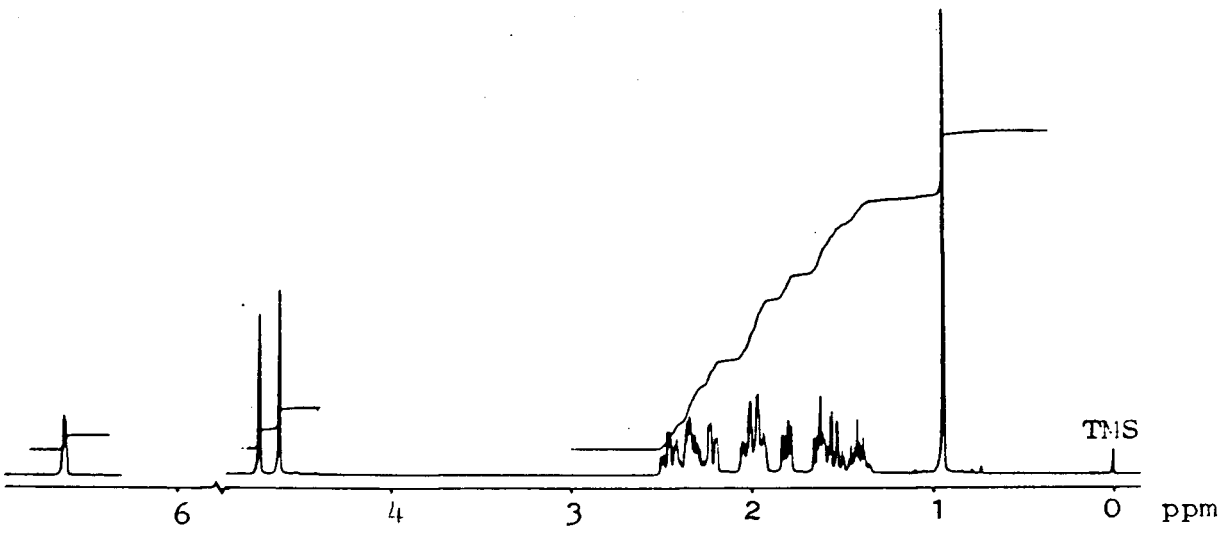


Figure 1 : The 400 MHz ^{1}H nmr spectrum of the α,β-unsaturated nitrile **102**

The ^{13}C nmr spectrum of the α,β-unsaturated nitrile **102** exhibits signals for thirteen unique carbons. Three of these ^{13}C signals, at δ 16.6, 44.0 and 144.8, displayed negative amplitudes in an attached proton test (APT) experiment [42] and were consequently assigned to the angular methyl carbon, the ring-fused methine carbon and the olefinic carbon β- to the nitrile function, respectively. The nitrile carbon was assigned to the resonance at δ 118.4 on the basis of signals exhibited by comparable systems.[41] The connectivity of **102** was further supported by the results of a SINEPT experiment [43] optimized for a $J_{C,H}$ of 7 Hz. Thus, irradiation of the signal at δ 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 α,β-unsaturated nitrile **102**, the conjugate addition of organocopper(I) reagents to the α,β-unsaturated nitrile moiety present in **102** was examined. Although reports concerning the addition of organocopper(I)

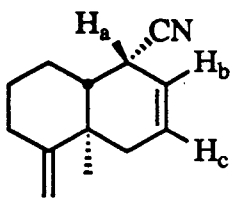
reagents to α,β-unsaturated nitriles are sparse, [34] we were optimistic that, with the recent advances in cuprate chemistry [44], a reaction of this type could be effected.

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 α,β-unsaturated nitrile **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 α,β-unsaturated nitriles, using lithium dimethylcuprate in the presence of chlorotrimethylsilane.[34c] Treatment of the α,β-unsaturated nitrile **102** under Alexakis' conditions gave only recovered starting material upon workup.

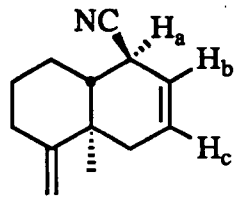
Attention was next focused on organocopper(I) reagents that had proved to be effective for conjugate additions to α,β-unsaturated carbonyl compounds that are often problematic in this type of reaction. The use of lithium (cyano)(methyl)cuprate with chlorotrimethylsilane under Corey's conditions,[45] or with added HMPA as reported by Kuwajima and co-workers,[46] had no effect on the α,β-unsaturated nitrile **102**. Iodotrimethylsilane-promoted additions of methylcopper(I) to α,β-unsaturated ketones and esters was reported to be very effective for conjugate addition reactions.[47] Treatment of the α,β-unsaturated nitrile **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 α,β-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 α,β-unsaturated nitrile **102** was evaluated as a possible substrate. Treatment of the α,β-unsaturated nitrile **102** with the higher order cuprate $Me_2Cu(CN)Li_2$ (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%.



109



110

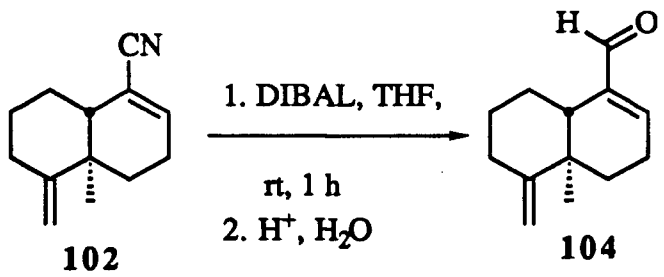
The two compounds were identified as the β,γ-unsaturated nitriles **109** and **110** on the basis of their spectral data. The ir spectrum of the β,γ-unsaturated nitrile **109** exhibits signals at 2239 cm^{-1} and 1637 cm^{-1} characteristic of nitrile and olefinic functions, respectively. The ^1H nmr spectrum exhibits signals at δ 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 δ 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 δ 3.22-3.30 (H_a) simplified the signal at 5.62-5.69 (H_b) to a doublet of doublets (J = 9, 3 Hz) and simplified the signal at 5.91-6.02 (H_c). Irradiation of the signal at δ 5.62-5.69 (H_b) simplified the signal at 3.22-3.30 (H_a) to a narrow multiplet ($w_{1/2}$ =12 Hz) and simplified the signal at 5.91-6.02 (H_c) to a broad singlet. Irradiation of the signal at δ 5.91-6.02 (H_c) simplified the signal at 3.22-3.30 (H_a) to a multiplet ($w_{1/2}$ =16 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 β,γ-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 ^1H nmr spectrum exhibits signals at δ 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 δ 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 [49] for H_a. Thus, irradiation of the signal at δ 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 δ 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 δ 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 α,β-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 α,β-unsaturated nitriles has been noted previously [50] and would appear to remain as a challenge in this area. Therefore, an alternative route was examined (see Scheme 19).

Reduction of the α,β-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 α,β-unsaturated aldehyde **104** in 89% yield (equation 15).

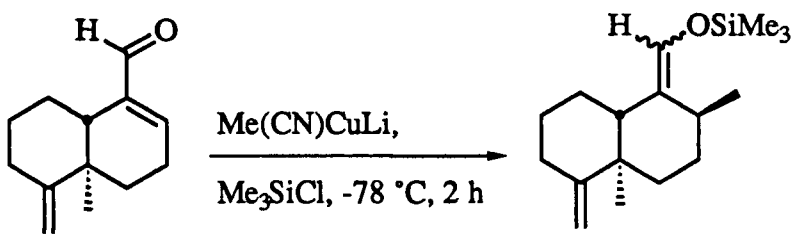


102 **104**

(15)

The ir spectrum of the α,β-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 ^1H nmr spectrum of **104** shows signals at δ 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 α,β-unsaturated aldehyde **104** was added to a THF solution of lithium (cyano)(methyl)cuprate in the presence of chlorotrimethylsilane (-78 °C, 2 h) [45] to afford the enol silyl ethers **111** in 86% yield (equation 16).



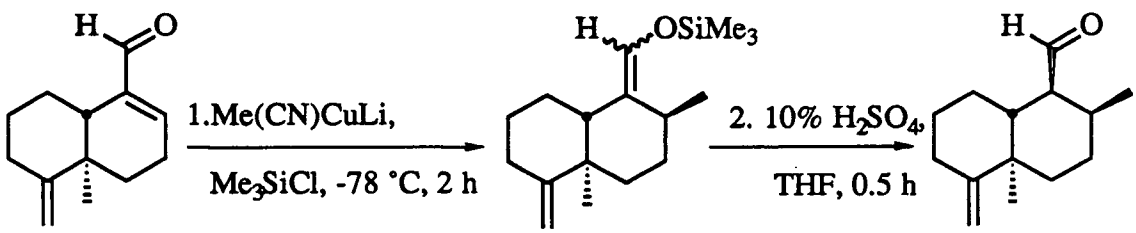
104 **111**

(16)

Analysis of this material by ^1H 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 ^1H

nmr spectrum of the product shows signals at δ 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.

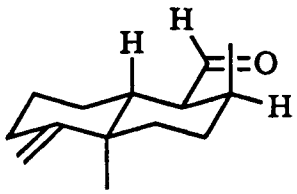
The fact that the mixture was stereochemically homogeneous at the secondary methyl group was shown as follows. Conversion of **104** into the enol silyl ethers **111** using lithium (cyano)(methyl)cuprate in the presence of chlorotrimethylsilane [45] (-78 °C, 2 h), as before (equation 15), followed by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



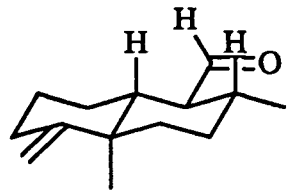
104 **111** **112**

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 ^1H nmr spectrum exhibits signals at δ 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 δ 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 δ 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.

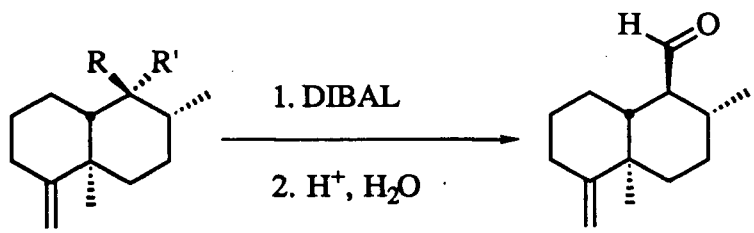


112



113

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 ^1H nmr spectrum of the aldehyde **112** is significantly different from that of the aldehyde **113**, which was readily prepared by reduction-hydrolysis [51] of the known [52] 85:15 mixture of the nitriles **29** and **30** (equation 17).

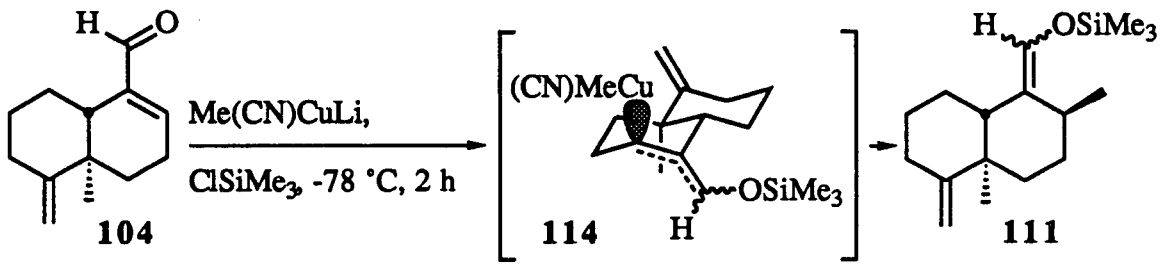


29 R = CN, R'= H
30 R = H, R'= CN

113

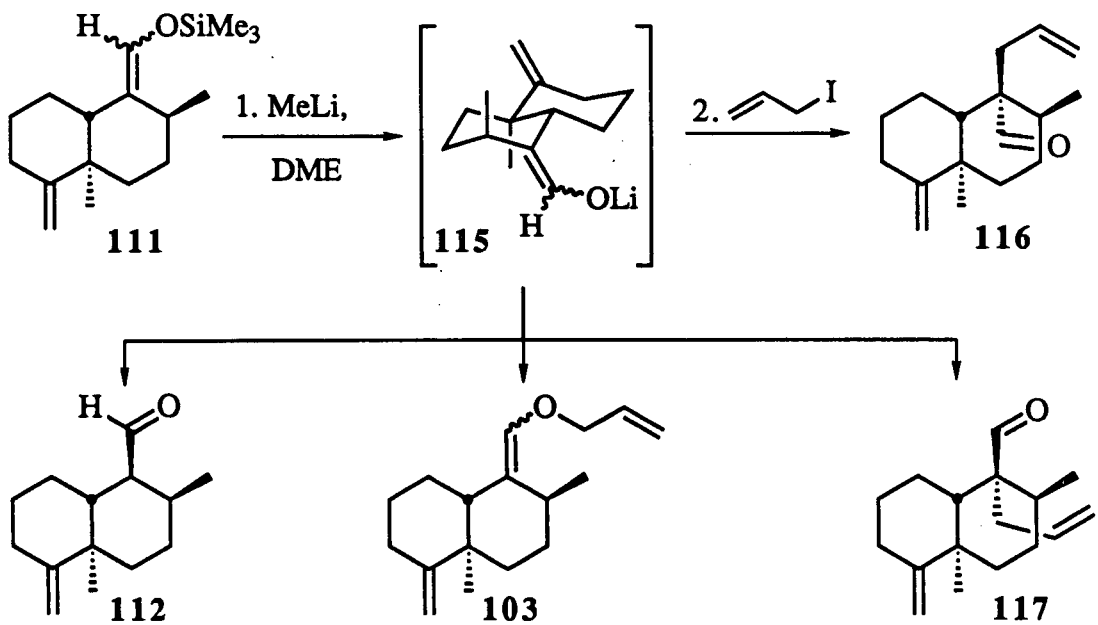
(17)

The axial addition of the secondary methyl group to the α,β-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 π-system with the d-orbitals of copper,[53] as shown for structure **114** (Scheme 25). Migration of the methyl group from copper to carbon then occurs with retention of configuration.



Scheme 25

The enol silyl ethers **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 **115** with a suitable electrophile (Scheme 26). The enolate **115** should be available from the enol silyl ether **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.[54] For steric reasons, alkylation of the enolate **115** was expected to occur from the face opposite the angular methyl group to furnish the aldehyde **116** rather than the aldehyde **117** (Scheme 26).



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 ^{1}H 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 $C_{17}H_{26}O$.

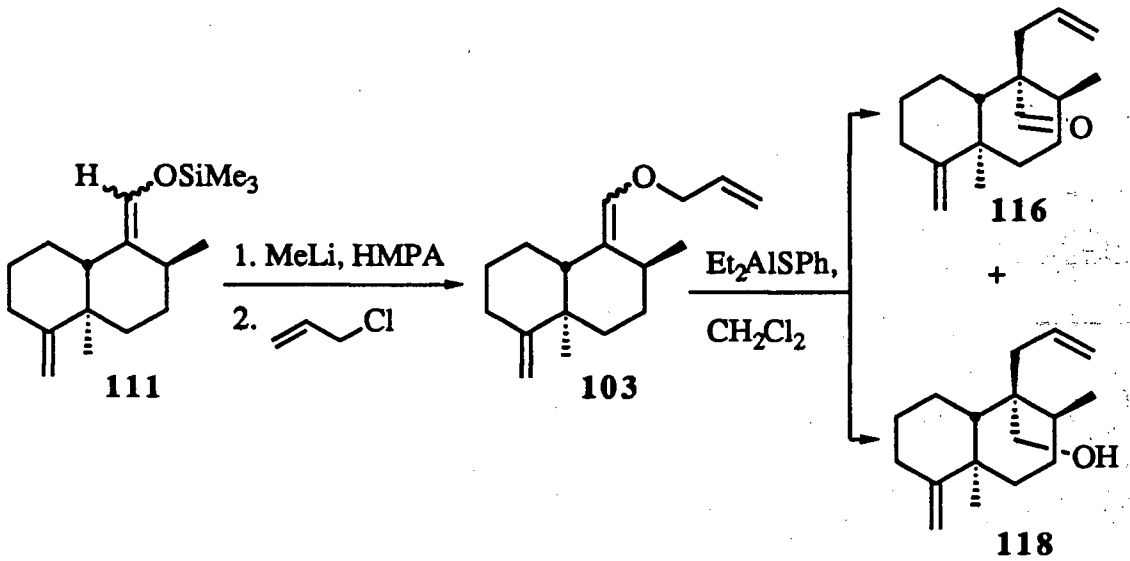
The aldehydes **116** and **117** were not separable by silica gel column chromatography and consequently their identification is based on the ^{1}H nmr spectrum of the mixture (≈ 7:4 of **116**:**117** by ^{1}H nmr integration). The major component was identified as the aldehyde **116** by comparison of the ^{1}H nmr spectrum of a pure sample of **116** (*vide infra*) with that of the mixture. The minor component **117** exhibits two signals in the ^{1}H nmr spectrum of the mixture at δ 5.59-5.71 (multiplet) and at 10.02 (singlet) due to the olefinic -C<u>H</u>=CH_2 and aldehydic protons, respectively. The presence of both the olefinic -CH=CH_2 and aldehydic signals in the ^{1}H nmr spectrum of **117** suggests a structure isomeric to that of **116**. Structure **117** should exhibit the observed ^{1}H 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 [55] 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 ^{1}H 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 quarternary 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.



Scheme 27

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 ^1H nmr spectrum exhibits four olefinic signals at δ 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 ^1H nmr spectrum of **118** (Figure 2) displays two carbinol methylene signals at δ 3.76 (one proton doublet, J = 12 Hz) and 3.90 (one proton doublet, J = 12 Hz), and five olefinic signals at δ 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 δ 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.

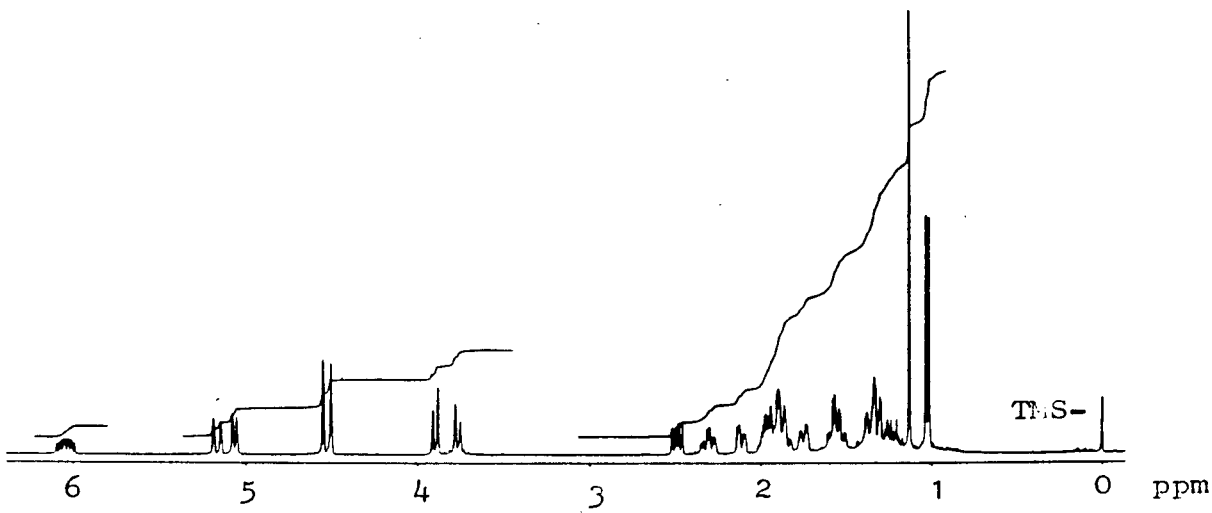
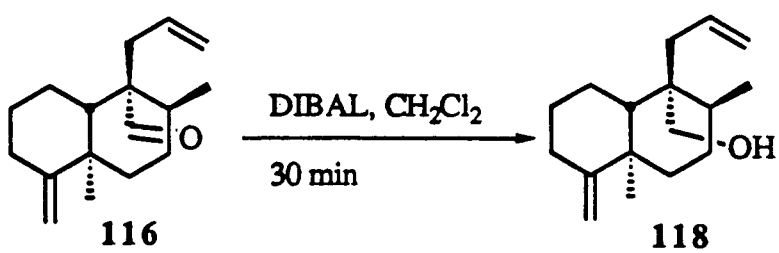


Figure 2 : The 400 MHz ^1H nmr spectrum of the diene alcohol **118**

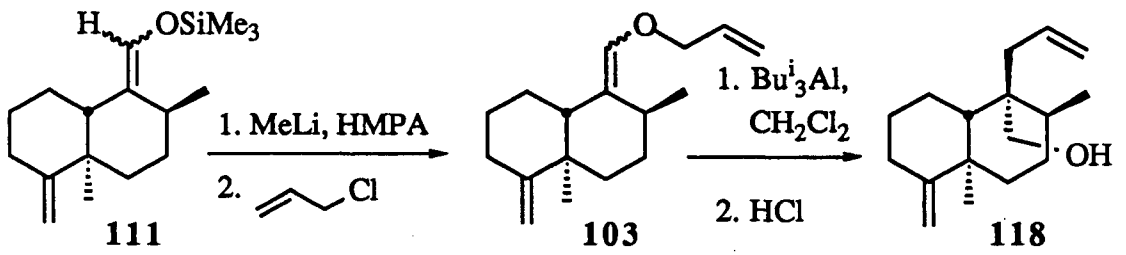
The relative stereochemistry of the aldehyde **116** was determined as follows. Reduction of the aldehyde **116** with diisobutylaluminum hydride [36b] (room temperature, dichloromethane, 30 min), followed by suitable workup and product purification gave a material (97% yield) that was spectrally identical with **118** (equation 18).



116 **118**

(18)

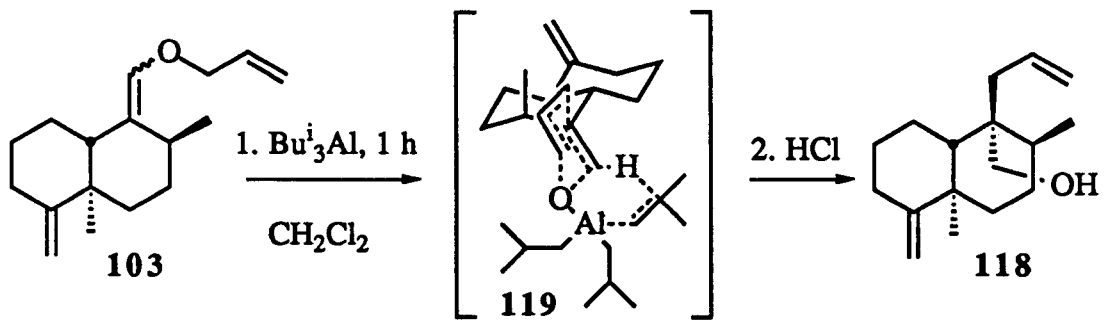
Although the organoaluminum-promoted Claisen rearrangement of **103**, along with the diisobutylaluminum hydride reduction of **116**, gave the diene alcohol **118** efficiently (Scheme 27), it was found that the same transformation could be effected more conveniently in a single step by treatment of a dichloromethane solution of the allyl enol ethers **103** with a solution of triisobutylaluminum in toluene.[59] 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).



111 **103** **118**

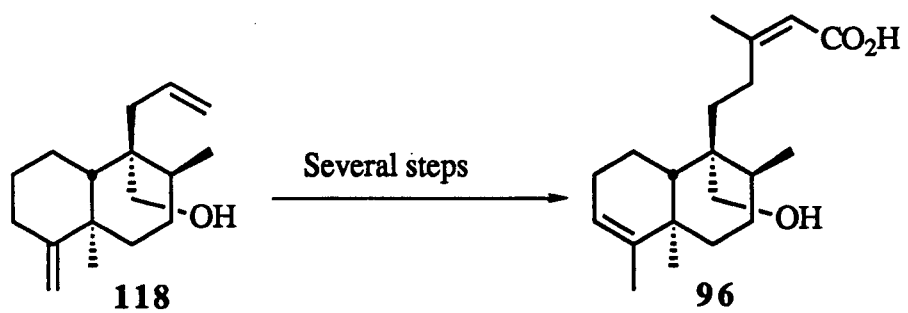
Scheme 28

Oshima and co-workers suggested [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, [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.[59b]



Scheme 29

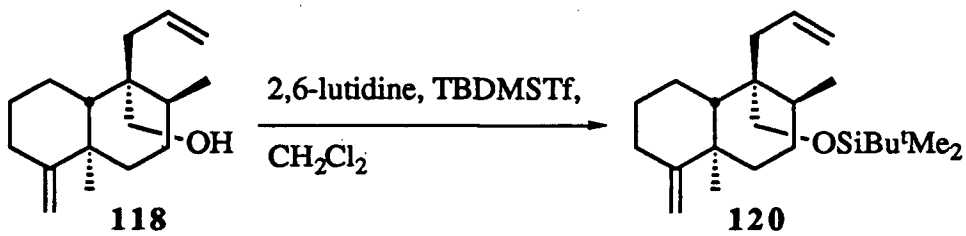
Structural comparison of the diene alcohol **118** with (±)-stephalic acid (**96**) indicates that **118** contains all of the chiral centers with the same relative stereochemistry as those present in **96**. For the conversion of **118** into (±)-stephalic acid (**96**), the exocyclic double bond must 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]



(19)

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.[61] Chromatography of the crude product on silica gel furnished the silyl ether **120** in 76% yield (equation 20).

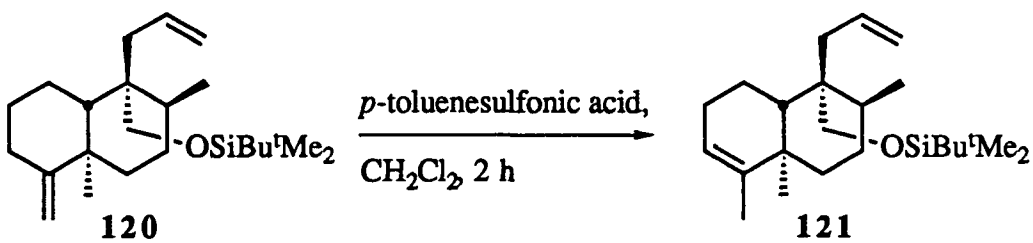


118 **120**

(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 ^1H nmr spectrum of **120** exhibits signals at δ 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 δ 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 [62] at room temperature for 2 h gave the silyl ether **121** in 81% yield.



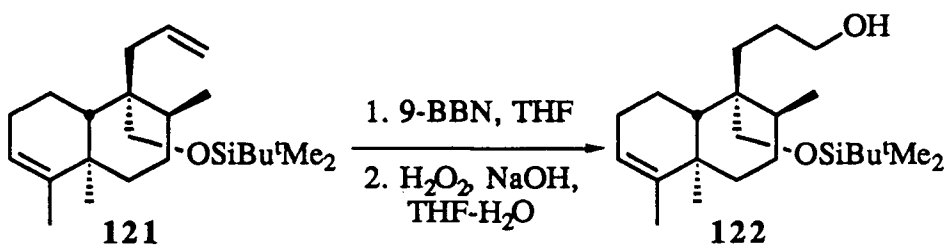
120 **121**

(21)

The ir spectrum of **121** exhibits an olefinic absorption at 1637 cm^{-1}. The ^1H nmr spectrum of **121** shows resonances at δ 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 ^1H nmr signals due to the vinylic methyl protons at δ 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.[63] 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).

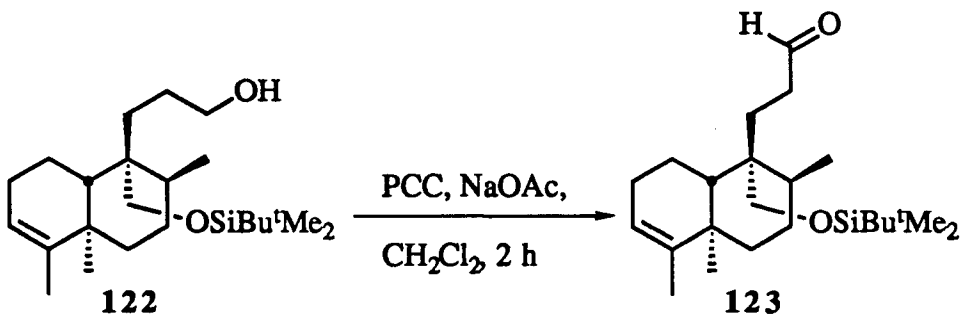


121 **122**

(22)

The ir spectrum of the alcohol **122** exhibits a broad band centered at 3328 cm^{-1} due to the hydroxyl functions. The ^1H nmr spectrum of the alcohol **122** shows resonances at δ 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.[64] Upon workup the aldehyde **123** was obtained in 82% yield (equation 23).

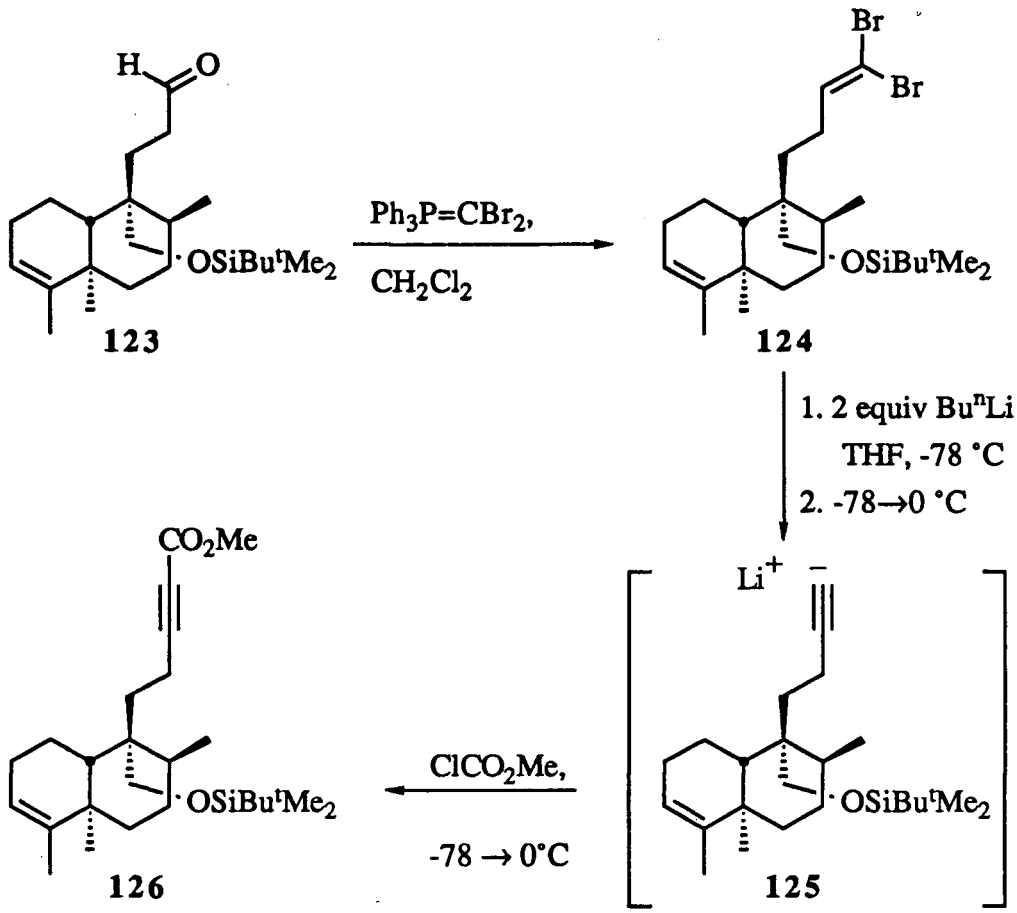


122 **123**

(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 ^1H 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 dibromoolefin **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**.



Scheme 30

Addition of a dichloromethane solution of the aldehyde **123** to a solution of dibromomethylenetriphenylphosphorane, formed *in situ* from carbon tetrabromide and triphenylphosphine,[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 ^1H nmr spectrum of **124** shows signals at δ 5.18 (broad one proton singlet) and 6.37 (one proton triplet, J = 6 Hz) for the two olefinic protons.

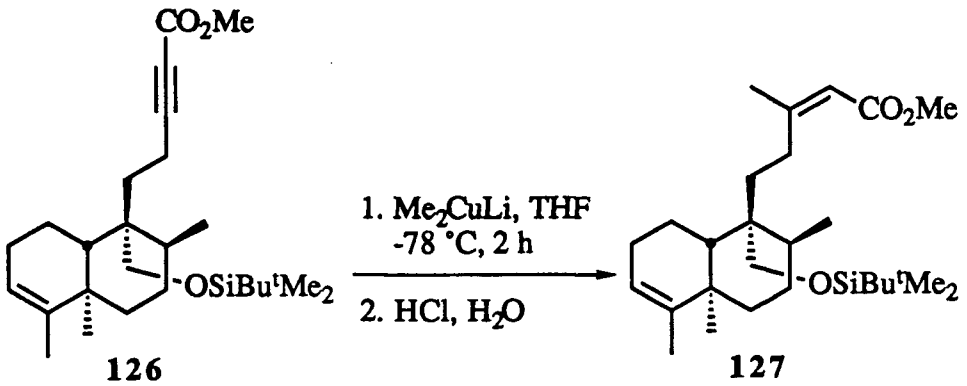
Conversion of the dibromide **124** into the acetylenic ester **126** was effected by treating a THF solution of **124** with 2 equivalents of *n*-butyllithium at -78 °C for 1 h and then at 0 °C for 1 h.[32] The resultant lithium acetylide **125** was allowed to react with

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 ^1H nmr spectrum of **126** shows the expected signal for the methoxy methyl group at δ 3.77 (three proton singlet).

The conversion of the acetylenic ester **126** into the α,β-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* α,β-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]

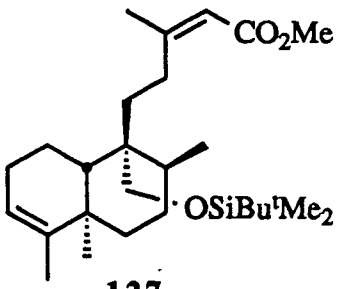
Following the procedural requirements for *cis* addition to acetylenic esters,[31] a THF solution of the actylenic ester **126** was added, dropwise, to a cold (-78 °C) THF solution of lithium dimethylcuprate formed from methyllithium and copper(I) bromide-dimethyl sulfide complex.[67] The resultant mixture was stirred at -78 °C for 2 hours. To prevent the formation of the unwanted *trans* α,β-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 α,β-unsaturated ester **127** was obtained in 87% yield (equation 24).



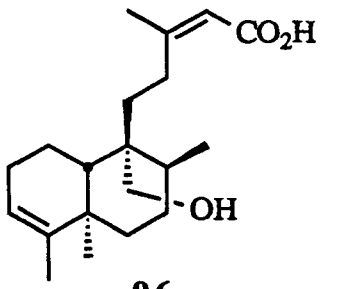
126 **127**

(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 ^1H nmr spectrum of **127** exhibits signals at δ 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, ^1H nmr signals were observed at δ 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 -$C\underline{H}_2C(CH_3)$=$CHCO_2CH_3$ 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 δ 1.91 and 5.65, respectively, are, in terms of chemical shifts, typical of those exhibited by compounds of part structure -$C(CH_3)$=$CHCO_2CH_3$ in which the vinylic methyl group and the olefinic proton are in a *cis* relationship.[68] 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 δ 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.



127



96

A comparison of the structure of the α,β-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 α,β-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 α,β-unsaturated ester **127** into the α,β-unsaturated acid **128** was achieved via a procedure reported by Liotta and co-workers for the S_N2 cleavage of esters using sodium benzeneselenide (equation 25).[69] Thus, treatment of a THF solution of **127** 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 4 h gave, after workup and chromatography of the crude product, a 64% yield of the α,β-unsaturated acid **128**.

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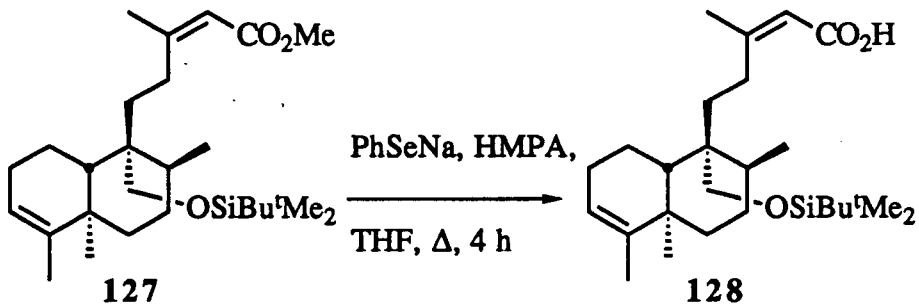
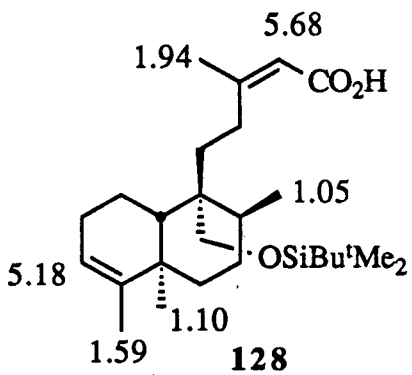
* Hydrofluoric acid-induced cleavage of the silyl ether function of the α,β-unsaturated ester **127**, followed by attempts to cleave the ester function of the crude product with sodium benzeneselenide,[69] did indeed afford an intramolecular Michael addition product as indicated by ^1H nmr, ir and mass spectral determinations of the crude products thus obtained.



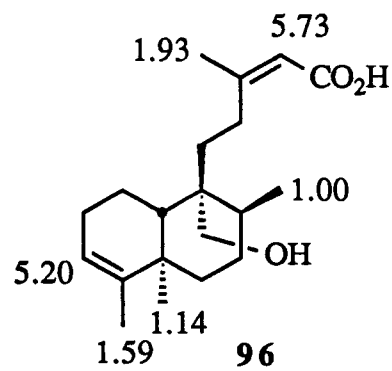
127 **128**

(25)

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 ^1H 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.



128



96

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 α,β-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 α,β-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 α,β-unsaturated carbonyl function. The ^{1}H nmr spectrum of this material shows signals at δ 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 δ 1.90 and 5.67, respectively, are, in terms of chemical shifts, typical of those exhibited by compounds of part structure -$C(CH_3)$=$CHCO_2H$,[68] 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 δ ≈1.6 and ≈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 α,β-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.

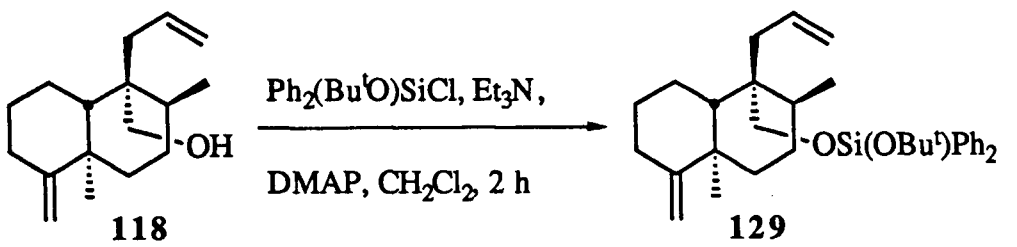
During these frustrating studies it became necessary to obtain more of the α,β-unsaturated acid **128**. Since, in order to obtain a pure sample of (±)-stephalic acid (**96**), it appeared essential to remove the alcohol protecting group without the formation of side products, it seemed prudent to re-examine 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 [76] (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.



118 **129**

(26)

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 ^1H nmr spectrum of **129** exhibits signals at δ 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 -CH_2OSi(OBu^t)Ph_2 protons. In addition, two aromatic resonances at δ 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 ^1H nmr spectrum of the product mixture shows that the major component of the mixture (ratio ≈ 3:1) exhibits signals at δ 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).

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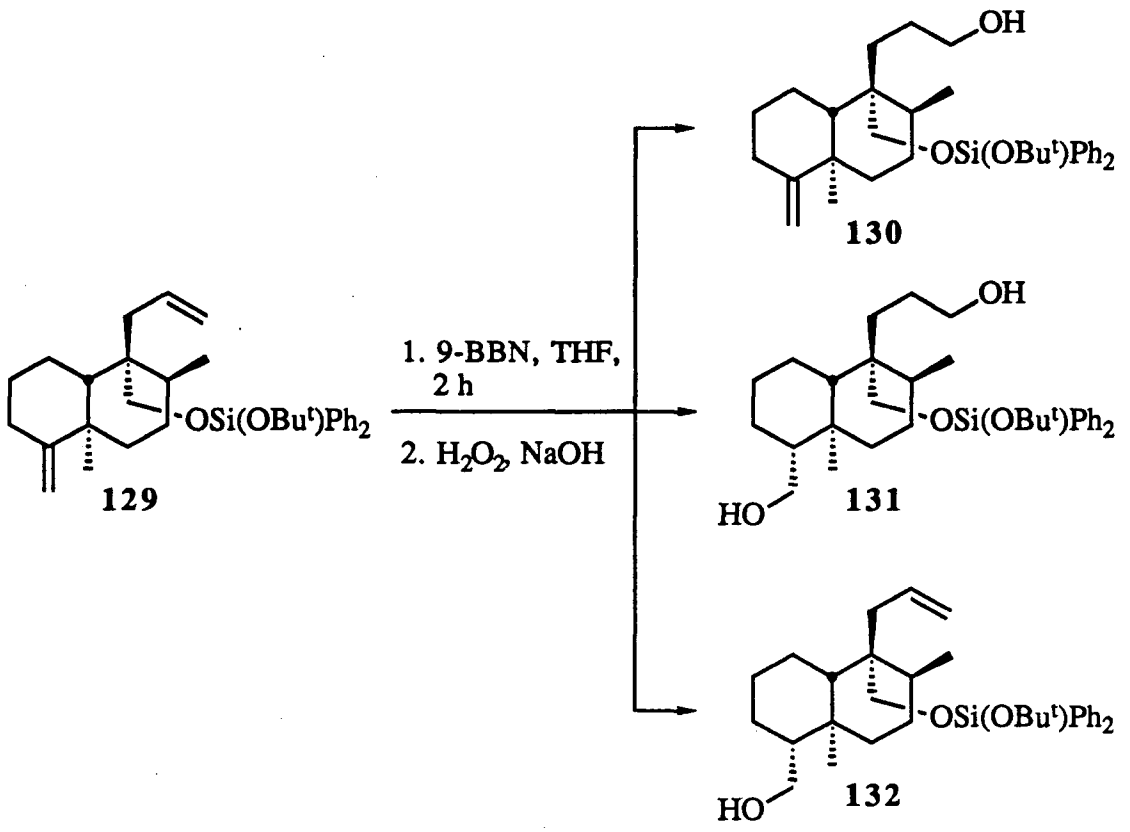
* The chemical shift values for the corresponding protons of the silyl ether **121** are δ 1.59 and 5.19.



Scheme 31

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 δ 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.

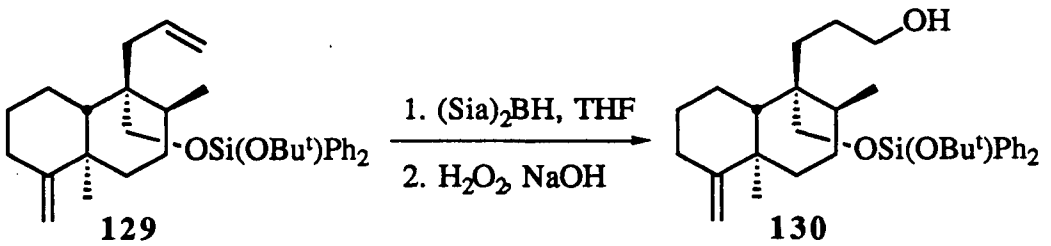
The ir spectrum of the diol **131** exhibits signals at 3410 cm^{-1} and 1592 cm^{-1} due to the alcohol and benzene ring functions, respectively. The ^{1}H nmr spectrum of **131** shows signals for two methyl groups at δ 0.73 (three proton singlet) and 0.93 (three proton doublet, J = 7 Hz) and a signal at 1.29 (nine proton singlet) due to the *t*-butyl group. The spectrum also exhibits signals at δ 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 -$\underline{CH_2}$OSi(OBu^t)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 δ 3.26 (one -$\underline{CH_2}$OH proton) caused enhancement at 3.81 (the other -$\underline{CH_2}$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 $C_{33}H_{50}O_4Si$.

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 δ 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 δ 3.20-3.27 (one proton multiplet, simplifies to a doublet of doublets on addition of D_2O, 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 -$\underline{CH_2}$OSi(OBu^t)Ph$_2$ protons. Three olefinic protons at δ 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 -CH$_2$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 $C_{33}H_{48}O_3Si$.

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

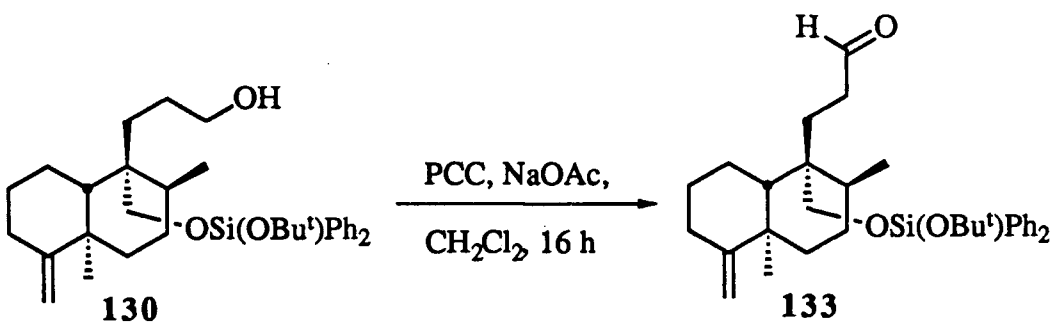
minutes.[77] After an oxidative workup with alkaline hydrogen peroxide and chromatography of the crude product, the alcohol **130** was obtained in 80 % yield (equation 27). Only traces of **131** and **132** were detected in the crude product (tlc analysis). The ^1H nmr spectrum of **130** exhibits 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.



129 **130**

(27)

The alcohol **130** was oxidized with pyridinium chlorochromate in the presence of sodium acetate at room temperature for 16 h.[64] Upon workup, the aldehyde **133** was obtained in 85% yield (equation 28).

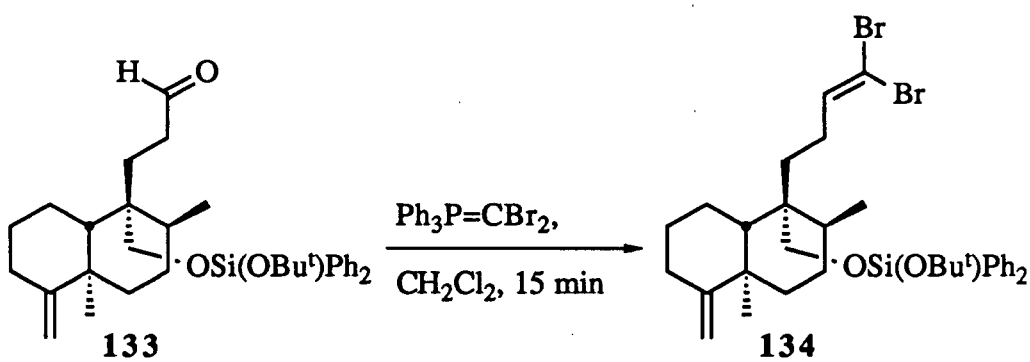


130 **133**

(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 ^1H nmr spectrum of **133** exhibits an aldehydic signal at δ 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 *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).



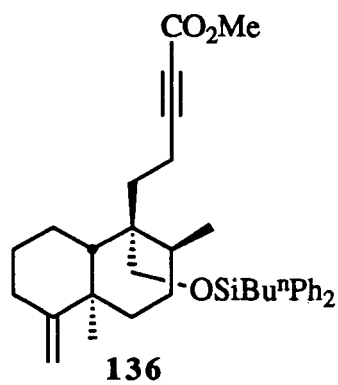
133 **134**

(29)

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

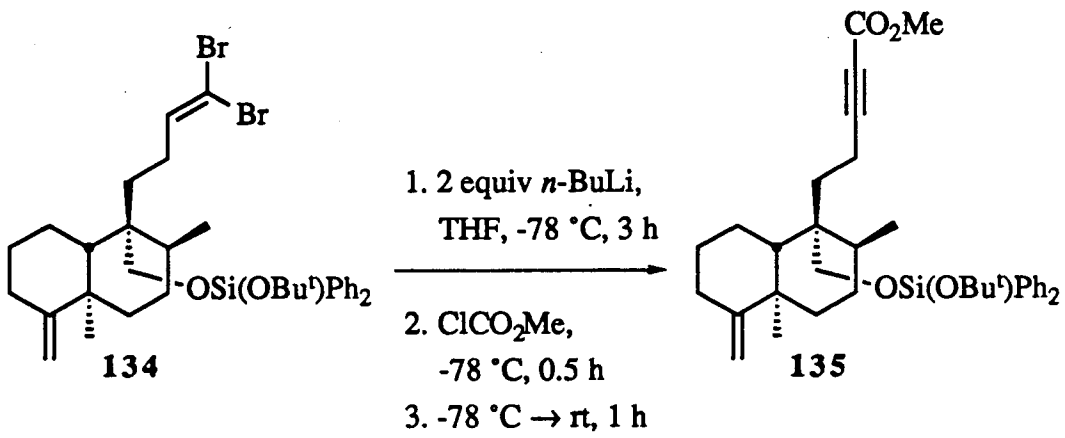
A THF solution of the dibromide **134** was treated with two equivalents of *n*-butyllithium at -78 °C for 1 h and then at 0 °C for 1 h. The resultant mixture was cooled to -78 °C, methyl chloroformate was added, and the mixture was stirred for 1.25 h at -78 °C and warmed to 0°C over 0.5 h, to give two 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]



136

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).



(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 ^1H nmr spectrum of **135** (Figure 3) shows signals at δ 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 -C$\underline{H}_2$OSi(OBu^t)Ph$_2$ protons. ^1H nmr resonances were also observed at δ 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).

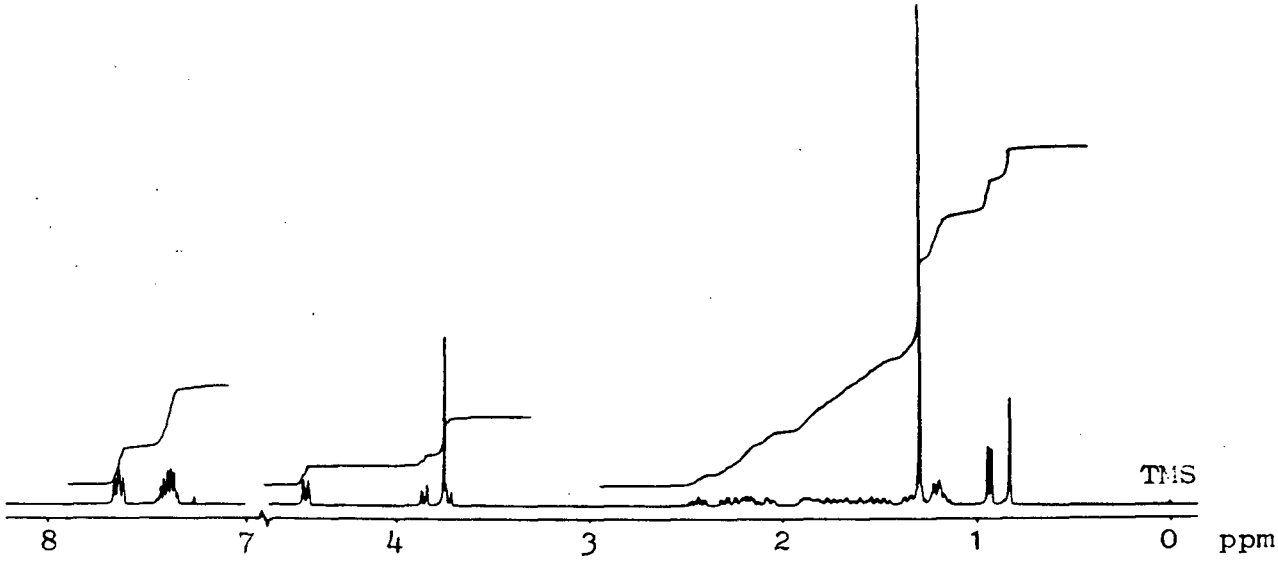
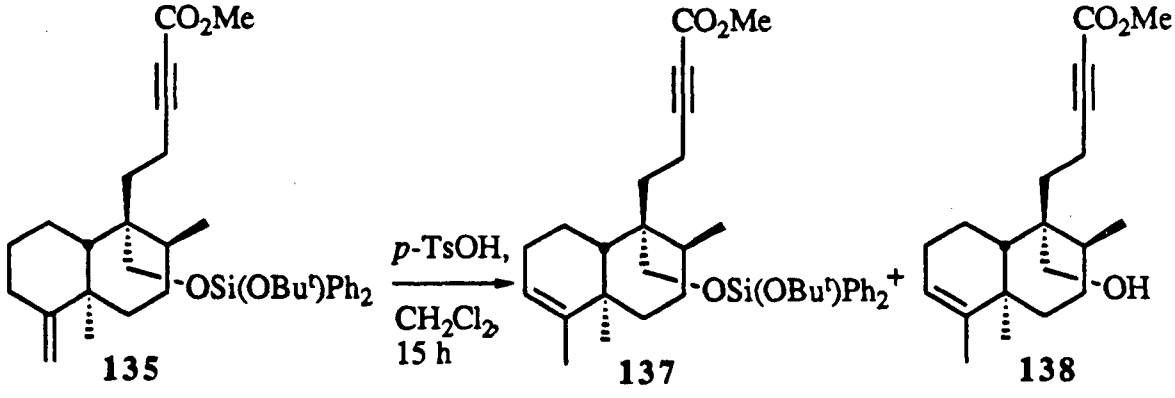


Figure 3 : The 400 MHz ^1H nmr spectrum of the acetylenic ester **135**

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**.

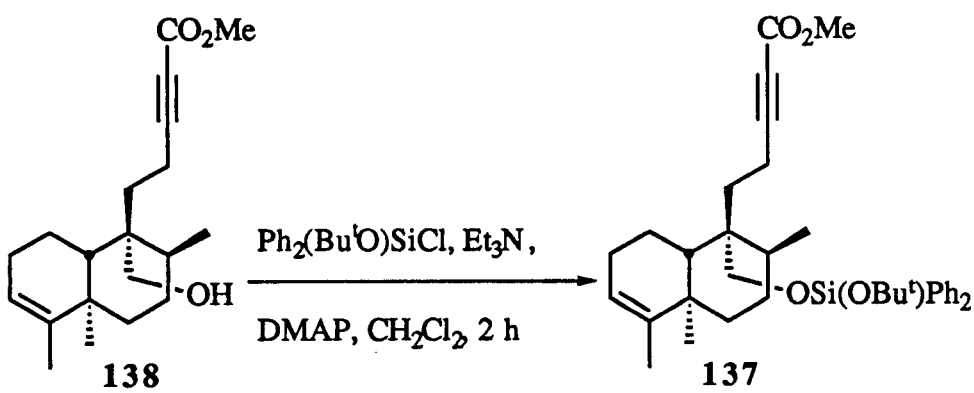


(31)

The ir spectrum of the acetylenic ester **137** exhibits signals due to the olefin function at 1655 cm^{-1}. The ^1H nmr spectrum of **137** has resonances at δ 1.55 (broad three proton singlet) for the vinylic methyl group and at δ 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 ^1H nmr spectrum of **138** exhibits signals at δ 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*-dimethylaminopyridine 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).

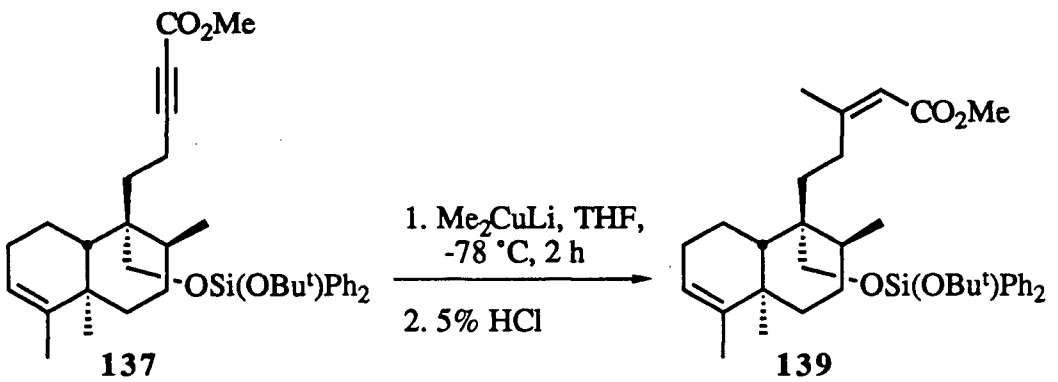


138 **137**

(32)

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.[67] 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).



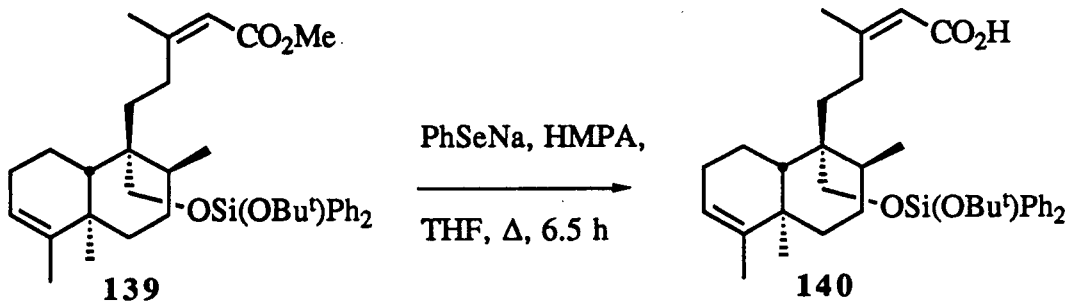
137 **139**

(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 -$C\underline{H}_2C(CH_3)$=$CHCO_2CH_3$ 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,[69] 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).



139 **140**

(34)

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 ^1H 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 ^1H nmr spectroscopy ($CDCl_3$ solution) and shows resonances for (±)-stephalic acid (**96**), tetra-*n*-butylammonium fluoride and a small amount of an unknown impurity.

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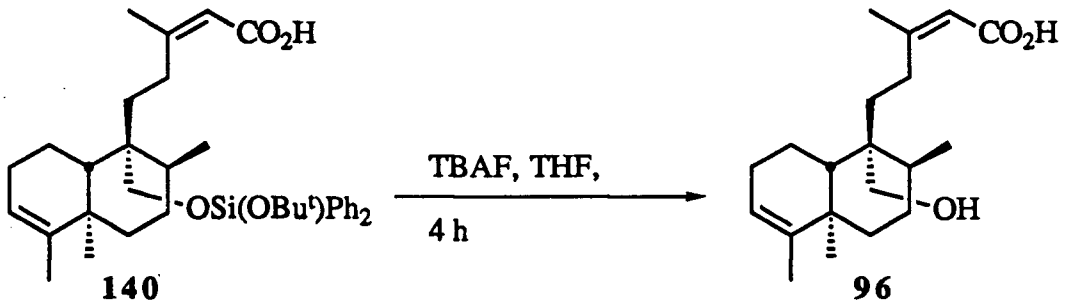
* Purification of the crude α,β-unsaturated acid **140** required both flash chromatography and preparative silica gel thin-layer chromatography.



140 **96**

(35)

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.[11c] 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 KC_{18}) 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 * .[11c] The ^1H nmr spectra of natural and synthetic **96** are shown in Figures 4 and 5.

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* We are grateful to Professor M. Salmón for providing a sample of natural (+)-stephalic acid.

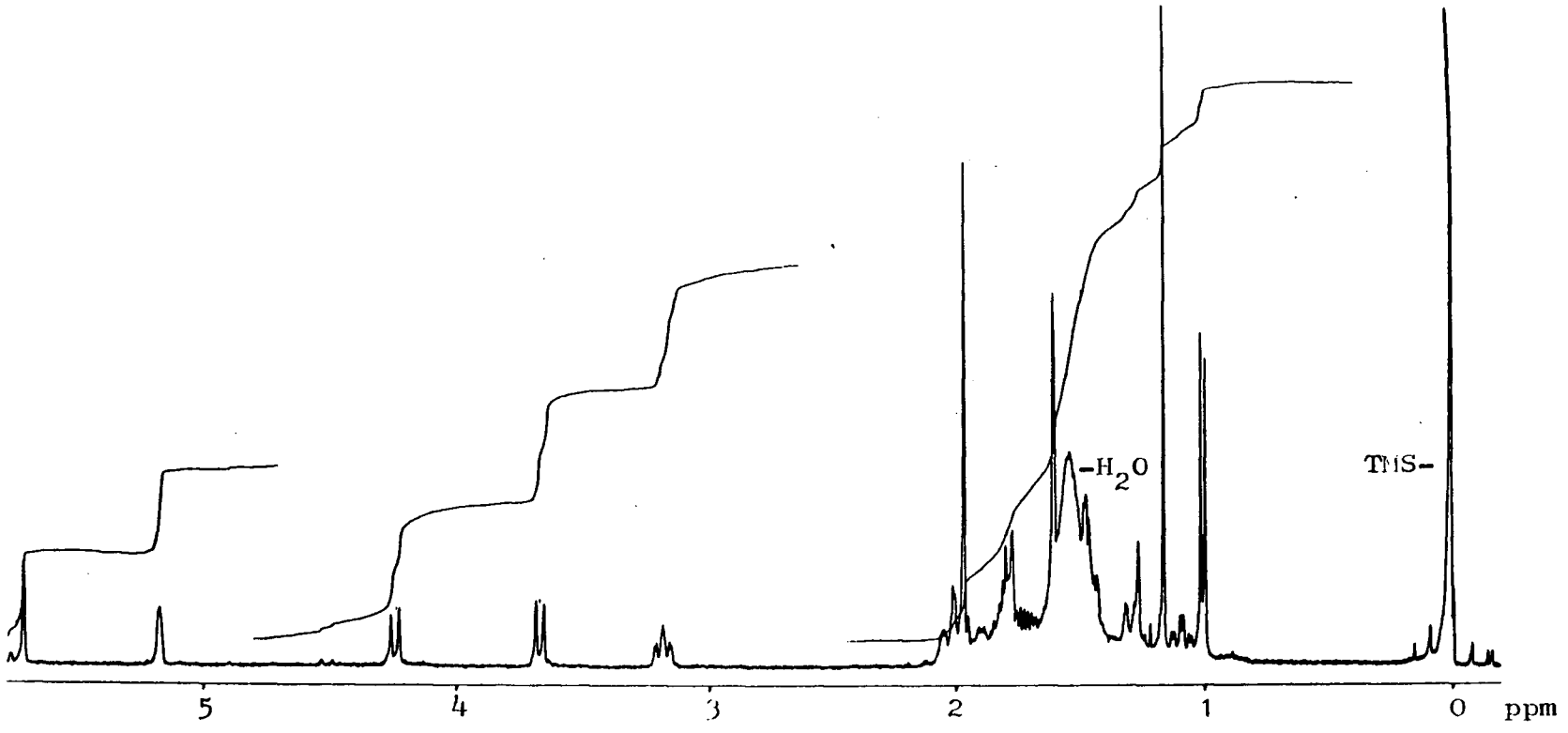

Figure 4 : The 400 MHz ^{1}H nmr spectrum of synthetic (±)-stephalic acid (96).

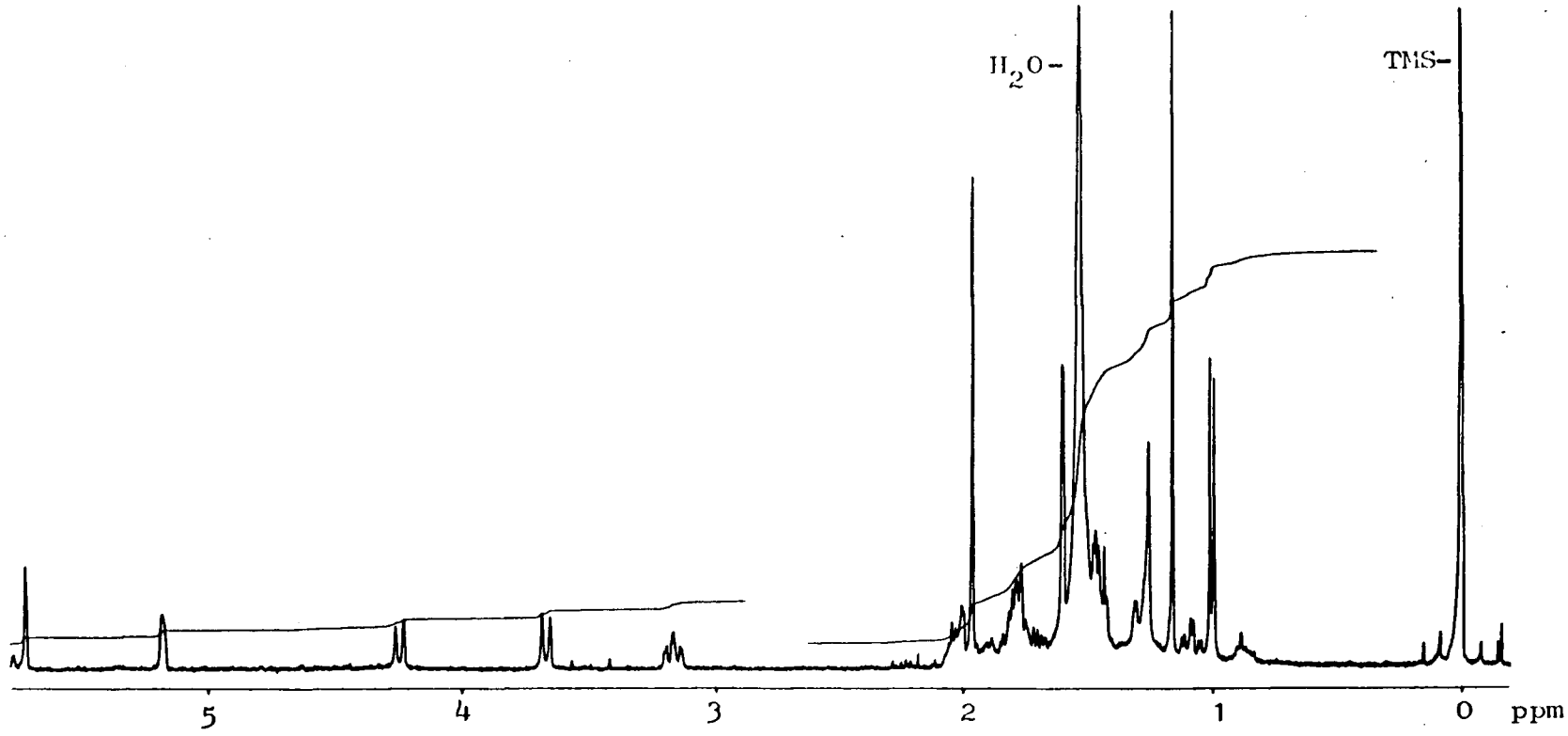

Figure 5 : The 400 MHz ^{1}H nmr spectrum of natural (+)-stephalic acid (96).

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 α,β-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 α,β-unsaturated nitriles, mainly through the application of Wittig type methodology.[37, 78] The formation of α,β-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 α,β-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 α,β-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]

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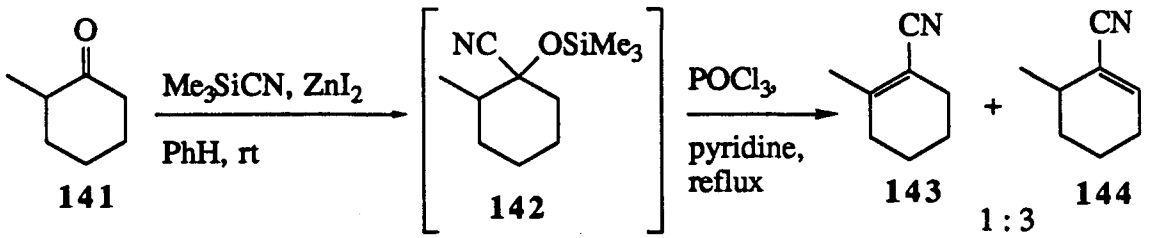
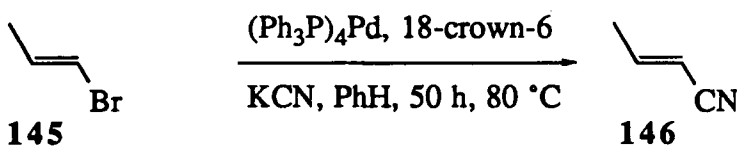
* For an example of a synthetic application of the hydrocyanation-dehydration procedure see the conversion of the ketone **33** into the unsaturated nitriles **35** and **36** (Scheme 4, p. 12).



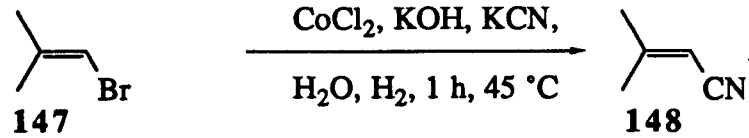
Scheme 32

It has recently been shown [81, 41] that α,β-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.[81a] 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.[81b] 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 α,β-unsaturated nitrile **146** in 92% yield (glc analysis) (equation 36).[81b]



(36)

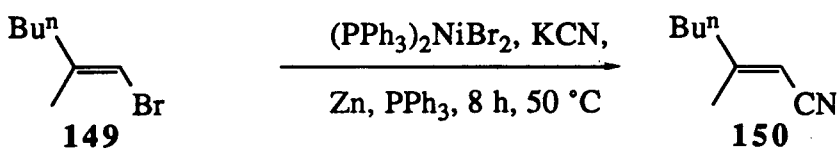
Funabiki and co-workers showed that α,β-unsaturated nitriles can be obtained by allowing vinyl halides to react with an aqueous solution of cobalt(II) chloride, potassium hydroxide and potassium cyanide under an atmosphere of hydrogen gas.[41] Treatment of the vinyl bromide **147** under the latter conditions at 45 °C for 1 h provided the α,β-unsaturated nitrile **148** in 80% yield (equation 37).



147 **148**

(37)

Sakakibara and co-workers reported a similar coupling of vinyl halides with potassium cyanide and a nickel(0) catalyst.[81c] Typically the catalyst was prepared *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 α,β-unsaturated nitrile **150** in 70 % yield based on recovered **149** (equation 38).



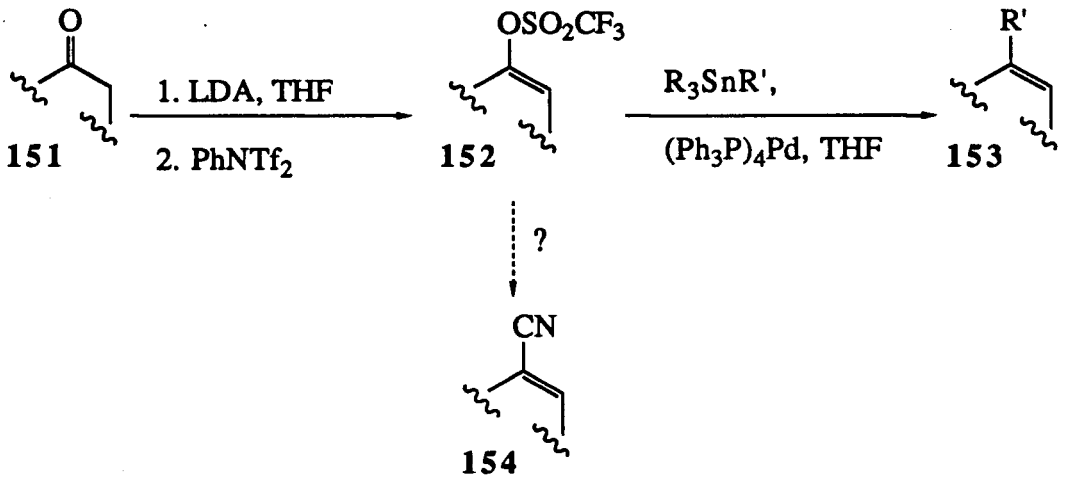
149 **150**

(38)

The transition metal-catalyzed coupling methodology represents a significant development for the stereoselective formation of α,β-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).[82] Enol triflates are readily available from both aldehydes [82] and ketones.[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).[40] Furthermore, Stille and co-workers have shown [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).



151 **152** **153** **154**

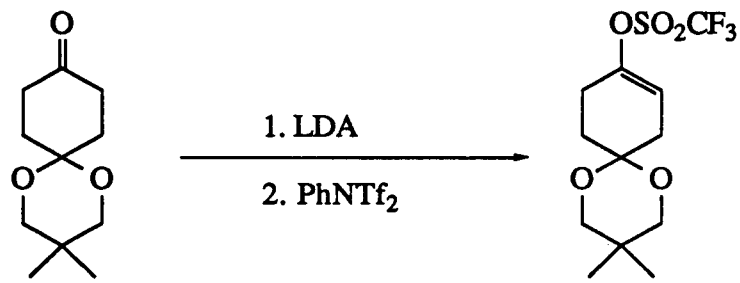
Scheme 33

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,[40] 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.[84]

The conversion of the ketone **156** into the enol triflate **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).

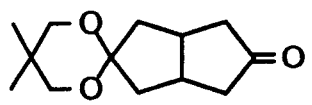
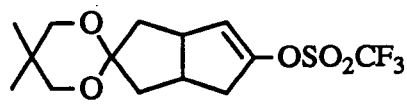
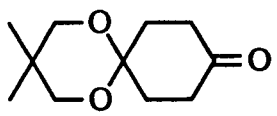
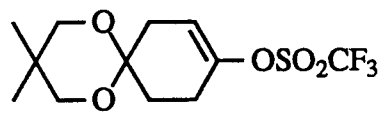
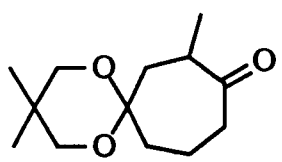
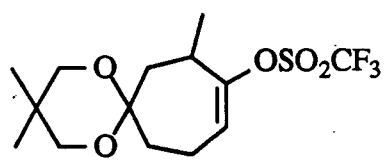
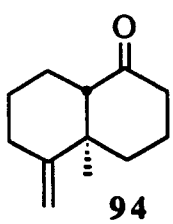
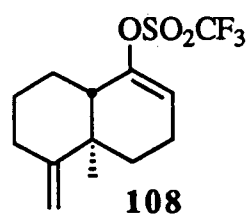
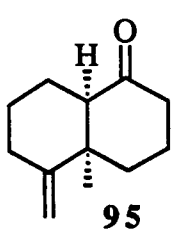
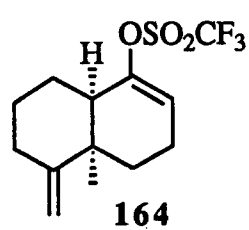
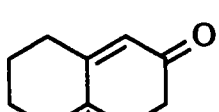
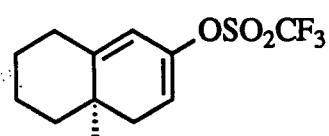


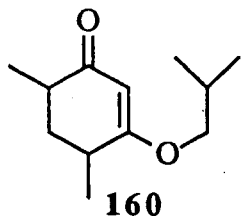
156 **158**

(39)

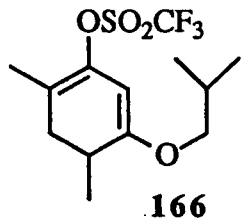
The ir spectrum of the enol triflate **158** exhibits absorptions at 1695 cm^{-1} and 1206 cm^{-1} due to the olefinic and sulfonyl functions, respectively. The ^1H nmr spectrum of **158** shows a signal at δ 5.62 (one proton triplet, J = 4 Hz) for the olefinic proton.

Table I. Conversion of ketones into enol triflates.

Ketone	Enol triflate	Reaction time/h	Isolated Yield
 **155**	 **162**	2.0	84%
 **156**	 **158**	16.0	75%
 **157**	 **163**	2.5	72%
 **94**	 **108**	2.0	80%
 **95**	 **164**	1.0	76%
 **159**	 **165**	1.0	66%

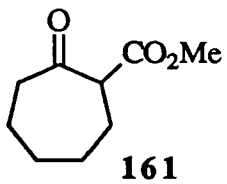


160

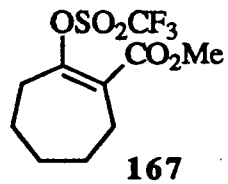


166

16.0 73%



161



167

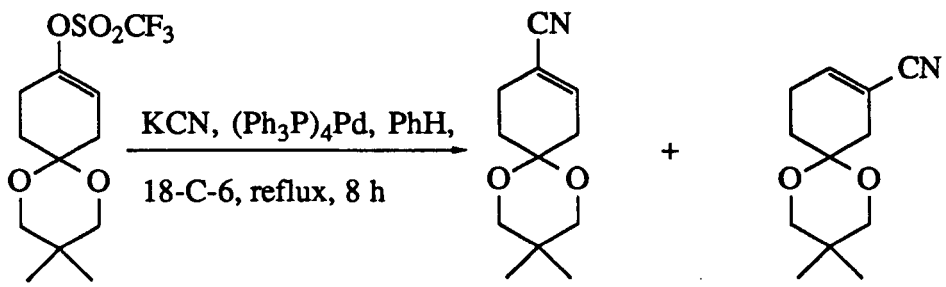
16.0 82%

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.[40] 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.[40]

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*-phenyltrifluoromethanesulfonimide. 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**

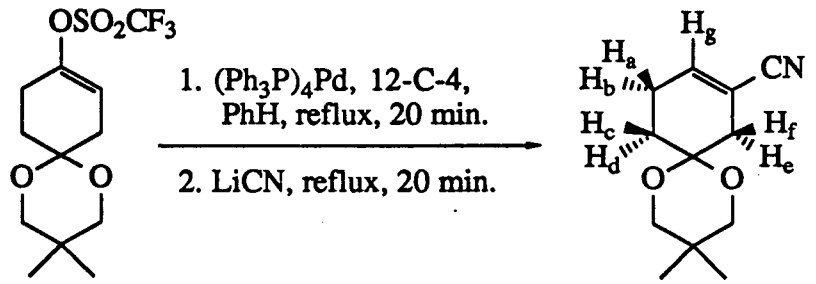
was examined using the conditions employed by Yamamura and Murahashi for the conversion of vinyl halides into nitriles.[81a] Treatment of a benzene solution of **158** with potassium cyanide, tetrakistriphenylphosphine palladium(0) and 18-crown-6 at reflux for 8 h gave two inseparable products in a ratio 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 spectrum of the mixture with ^1H nmr spectra obtained from pure samples of **168** and **169** (*vide infra*).



158 **168** **169**

(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 ®. 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**.



158 **169**

(41)

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 ^1H nmr spectrum of **169** shows signals at δ 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.

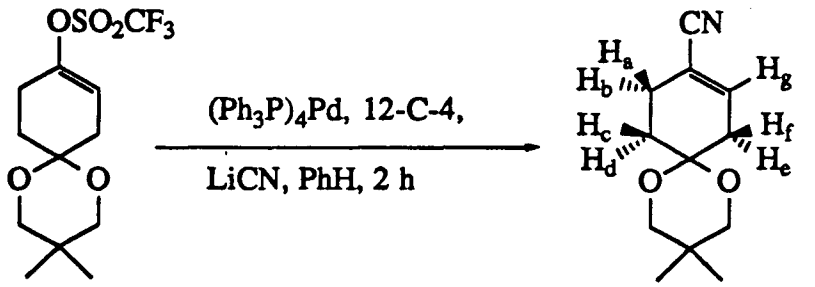
The structure of the α,β-unsaturated nitrile **169** was assigned on the basis of decoupling experiments, an nOe difference experiment and two SINEPT experiments.[43] In a decoupling experiment, irradiation of the signal at δ 2.29-2.36 (H_a and H_b) simplified the triplet at 1.93 (H_c and H_d) to a singlet, simplified the multiplet at 2.55-2.59 (H_e and H_f) to a narrow signal ($w_{1/2}$ = 4 Hz), and simplified the multiplet at 6.59-6.63 (H_g) to a triplet (J = 2 Hz). Irradiation of the signal at δ 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 δ 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 δ 6.59-6.63 (H_g) caused signal enhancement at δ 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 δ 3.56 (both pairs of acetal methylene protons) gave strong polarization transfer through three-bond coupling to the quaternary acetal carbon at δ 95.3. A second SINEPT experiment,[43] utilizing the same $J_{C,H}$ of 7 Hz, in which an irradiation was centered at δ 6.64 (H_g), gave strong polarization transfer through three-bond coupling to the sp nitrile carbon at δ 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 α,β-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 α,β-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 α,β-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 α,β-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 α,β-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.



158 **168**

(42)

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 ^1H nmr spectrum of **168** shows signals at δ 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).

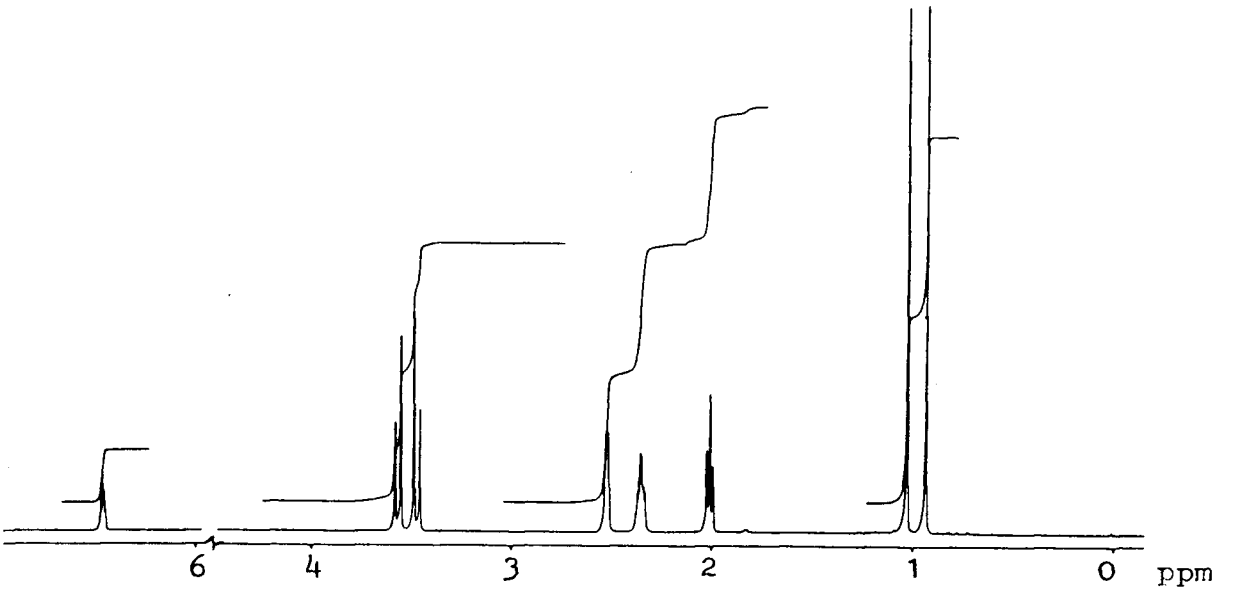


Figure 6 : The 400 MHz ^1H nmr spectrum of the α,β-unsaturated nitrile **168**.

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.[43] In a decoupling experiment, irradiation of the signal at δ 2.32-2.39 (H_a and H_b) simplified the triplet at 2.01 (H_c and H_d) to a singlet, simplified the multiplet at 2.50-2.55 (H_e and H_f) to a doublet (J = 4 Hz), and simplified the multiplet at 6.44-6.48 (H_g)to a triplet (J = 4 Hz). Irradiation of the signal at δ 2.50-2.55 (H_e and H_f) simplified the multiplet at 2.32-2.39 (H_a and H_b) to a broad triplet (J = 6 Hz) and simplified the multiplet at 6.44-6.48 (H_g) to a broad singlet. Irradiation of the signal at δ 6.44-6.48 (H_g) simplified the multiplets at 2.32-2.39 (H_a and H_b) and at 2.50-2.55 (H_e and H_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.[43] In an nOe difference experiment irradiation of the signal at δ 6.44-6.48 (H_g) caused signal enhancement at 2.50-2.55 (H_e and H_f) but not at 2.32-2.39 (H_a and H_b). In a SINEPT experiment [43] 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,[43] utilizing the same $J_{C,H}$ of 7 Hz, in which an irradiation was centered at δ 6.46 (H_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.**

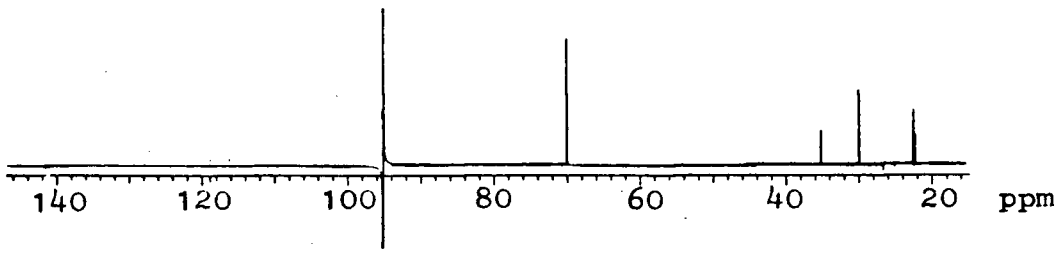


Figure 7 : SINEPT ^{13}C nmr spectrum of the α,β-unsaturated nitrile **168** decoupled at δ 3.52

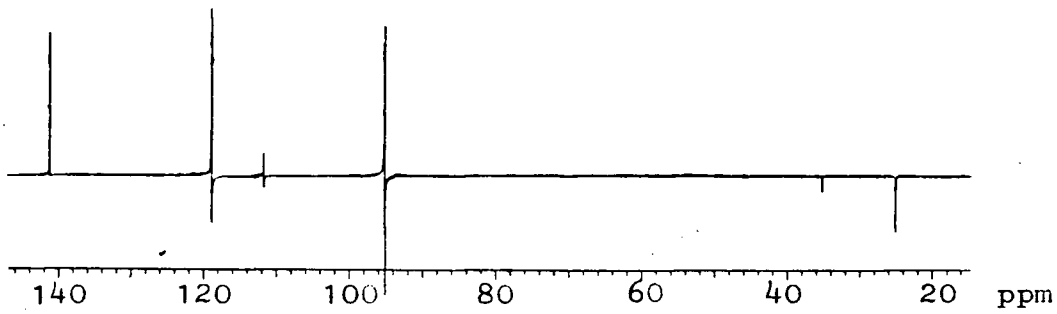
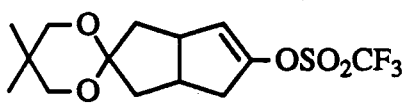
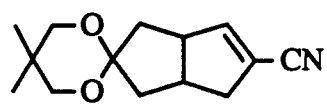
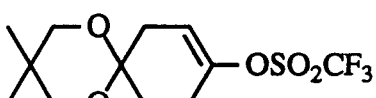
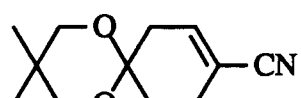
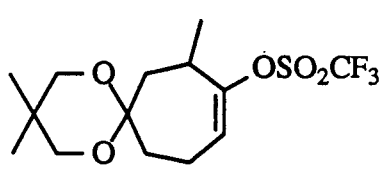
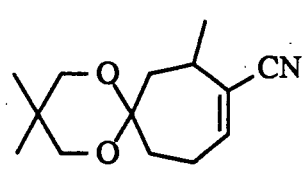
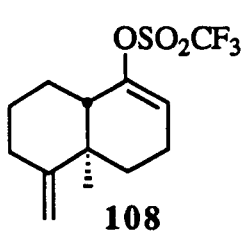
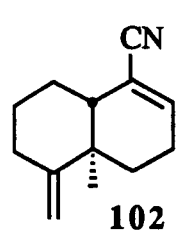
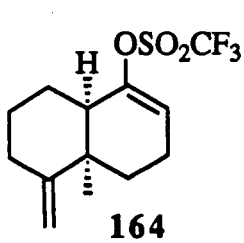
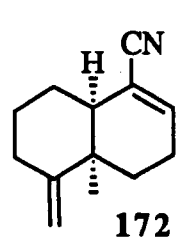
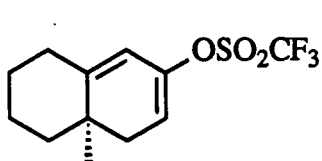
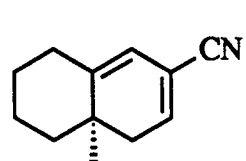
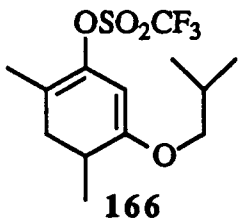


Figure 8 : SINEPT ^{13}C nmr spectrum of the α,β-unsaturated nitrile **168** decoupled at δ 6.46

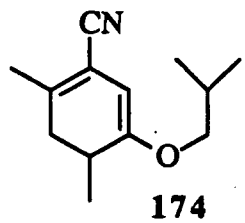
The generality of the coupling reaction was demonstrated by converting the enol triflates listed in Table I into the corresponding α,β-unsaturated nitriles. The enol triflates **108, 158,** and **162-167** were allowed to react with lithium cyanide, tetrakistriphenylphosphinepalladium(0) and 12-crown-4 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.

Enol triflate	α,β-Unsaturated nitrile	Reaction time/h	Isolated Yield
 **162**	 **170**	20.0	76%
 **158**	 **168**	2.0	80%
 **163**	 **171**	2.0	78%
 **108**	 **102**	2.0	89%
 **164**	 **172**	1.5	87%
 **165**	 **173**	1.0	78%

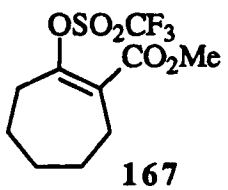


166

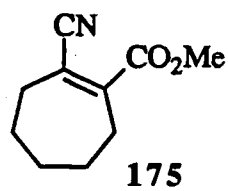


174

3.0 85%



167



175

4.0 59%

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 α,β-unsaturated nitrile **172** (as well as of the α,β-unsaturated nitriles **102** and **168** *) was corroborated by SINEPT experiments.[43] Thus, in a SINEPT experiment [43] optimized for a $J_{C,H}$ of 7 Hz, irradiation of the signal at δ 6.57 (the olefinic proton β to the nitrile function) of **172**, gave strong polarization transfer through three-bond coupling to the sp nitrile carbon at δ 119.5 and to the methine carbon at the ring junction at 44.2.

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

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

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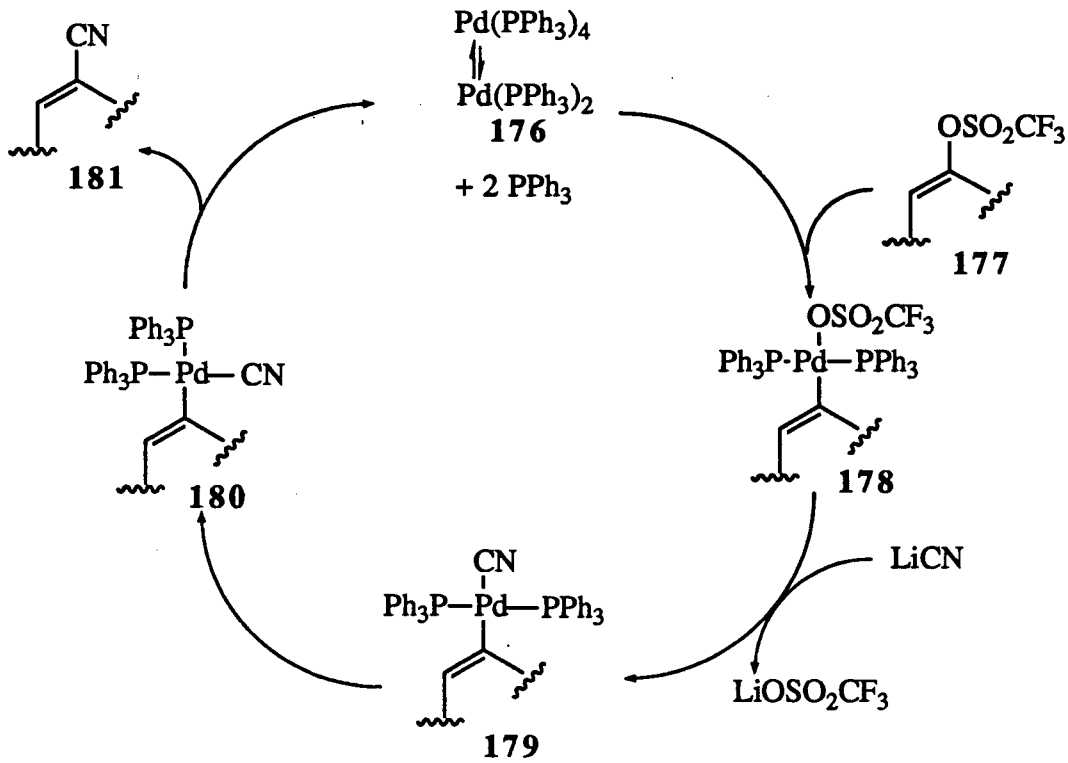
* For a discussion of the results of SINEPT experiments for **102** and **168** see the Discussion Section of this thesis p. 35 and p. 87, respectively.

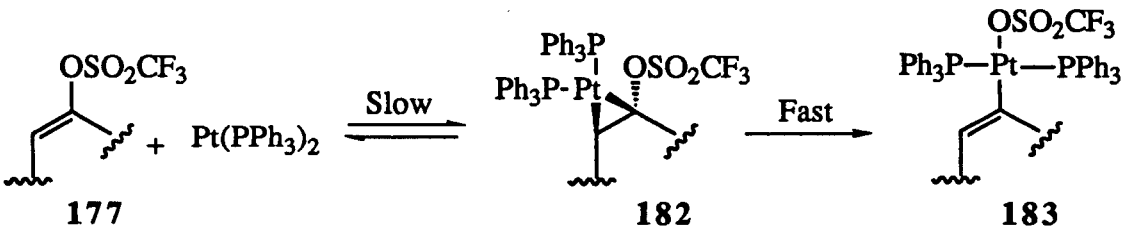


Scheme 34

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**.

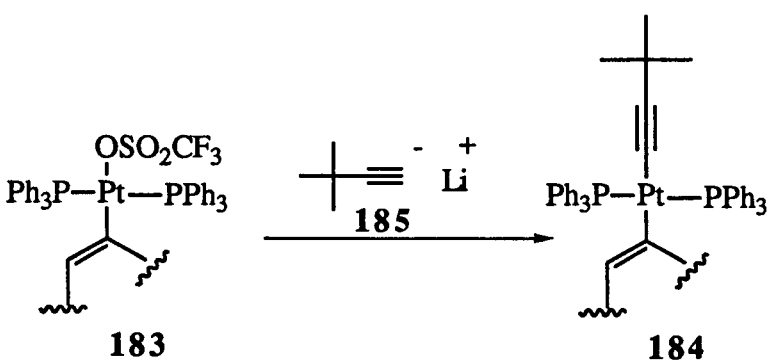
The proposed pathway is based, partially, on elegant work recently reported by Stang and co-workers.[85] These researchers have obtained crystal structures of some platinum(II) complexes derived from the reaction of tetrakistriphenylphosphineplatinum(0) with enol triflates. Evidence is presented [85] 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).



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).



(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 precedented procedures,[86] the two-step sequence enables methodology for the convesion 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.*

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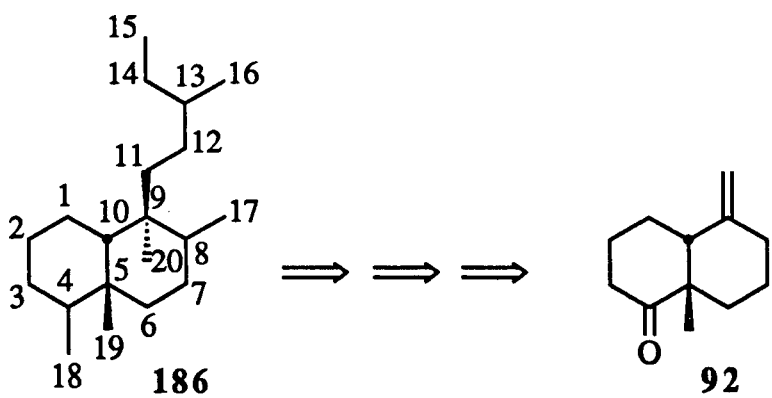
* Subsequent to this work the nickel-catalyzed coupling of aryl triflates with potassium cyanide was reported.[87]

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, [28] 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.



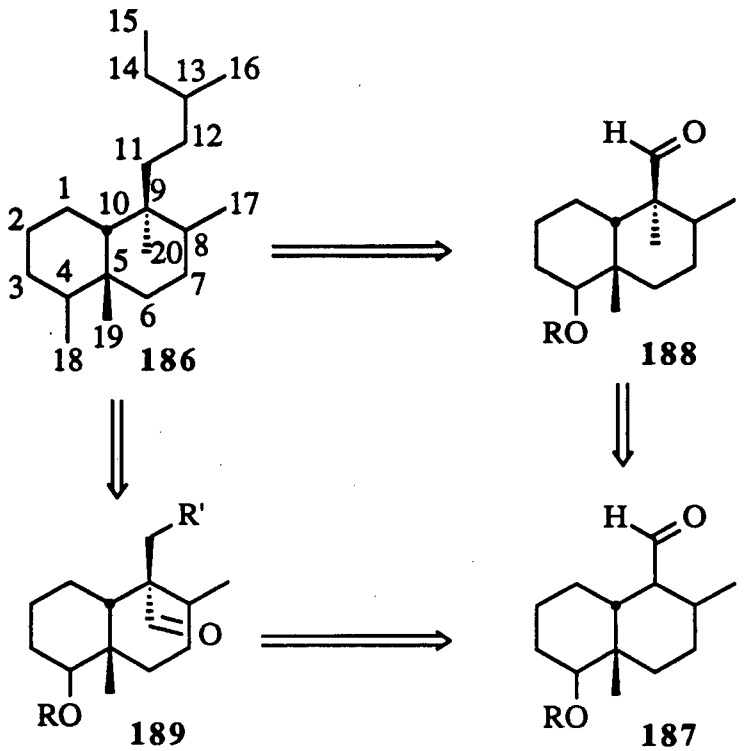
186 **92**

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 α,β-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.

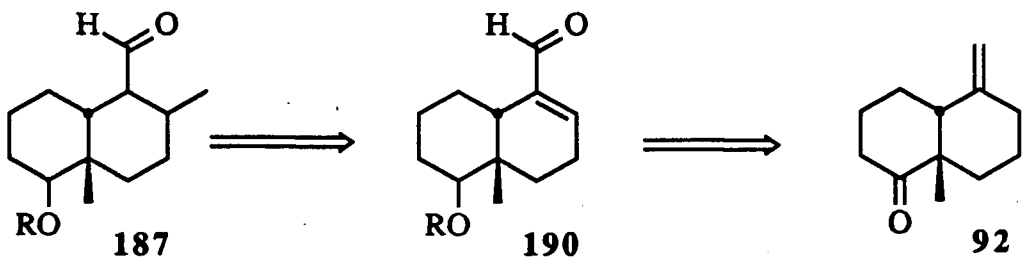
The retrosynthetic analysis of the *cis*-clerodane skeleton **186** was guided by a structure-goal strategy in which the ketone **92** could be used as an intermediate. Disconnection of the bonds between C-4 and C-18 and between C-11 and C-12 of the *cis*-clerodane skeleton **186**, along with appropriate 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).



Scheme 37

Identification of the aldehyde function of **187** as a retron for the lithium (cyano)(methyl)cuprate transform [45] leads, retrosynthetically, to the α,β-unsaturated aldehyde **190** (Scheme 38). Since the stereocontrolled conjugate addition to **190** could be complicated by conformation factors it seemed expedient to use the ether function of **190** to introduce a conformational bias into the molecule. The ether function of **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 **190** into the ketone **92** (Scheme 38).



Scheme 38

Synthesis of Potential *cis*-Clerodane Precursors

The ketone **92** had previously been synthesized [28] 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).[89] 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).

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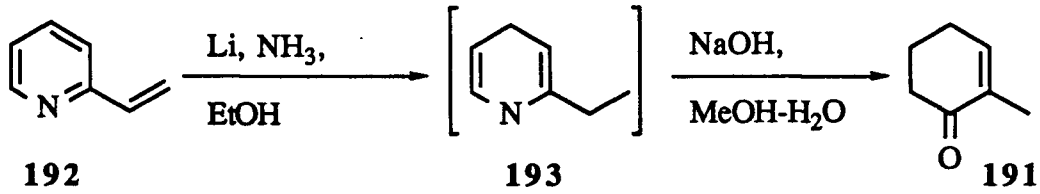
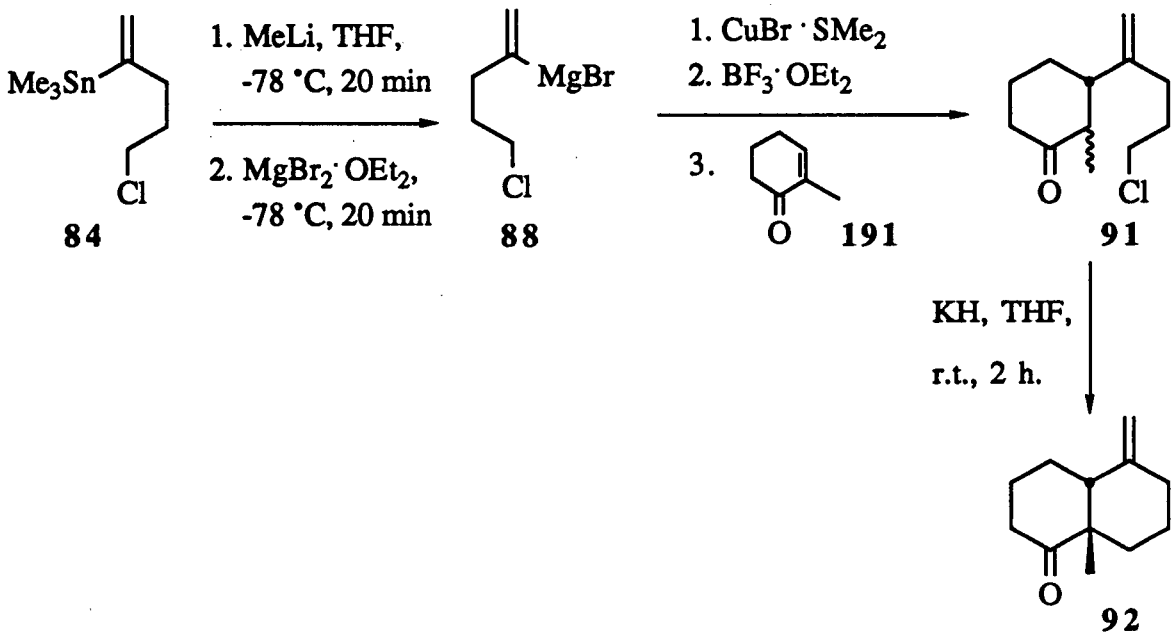
* Solutions were purged by allowing a constant stream of argon gas to diffuse through each solution for approximately 15 min. Failure to purge solutions of the reagents with argon led to the formation of variable amounts of 2-ethylpyridine.



192 **193** **191**

Scheme 39

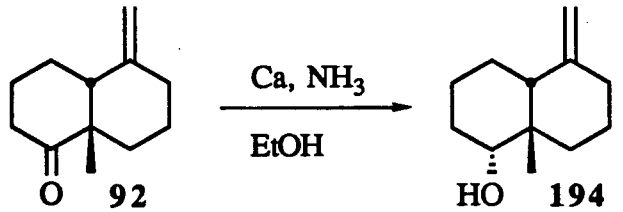
The vinylstannane **84** was employed for the methylenecyclohexane annulation of 2-methyl-2-cyclohexen-1-one (**191**), using the procedure discussed previously (Scheme 15, p. 22).[28] Transmetallation of **84** with methyllithium in THF (-78 °C, 20 min), followed by the addition of solid magnesium bromide-etherate (-78 °C, 20 min), gave the corresponding Grignard reagent **88** (Scheme 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 precedented.[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 ^1H 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 ^1H 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]

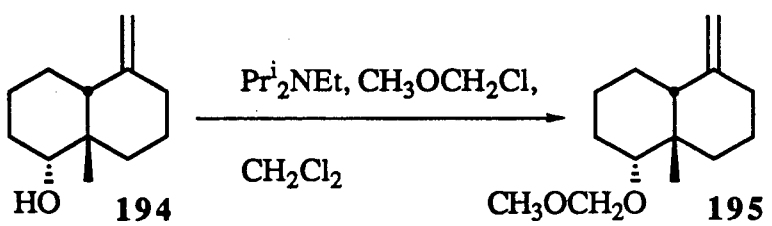
The ketone function of **92** was reduced in order to impart a conformational bias into the resultant alcohol **194**. Treatment of the ketone **92** with a cold (-78 °C) solution of calcium in ammonia [91] for 1 hour, followed by the addition of anhydrous ethanol (-78 °C, 15 min), gave a single alcohol **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 ^1H nmr experiments (*vide infra*).



(44)

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 ^1H nmr spectrum of **194** exhibits signals at δ 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).

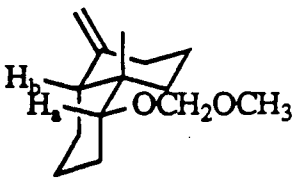


(45)

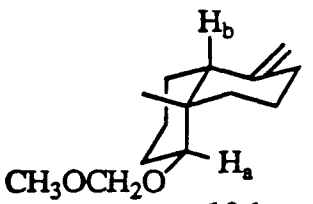
The ir spectrum of the ether **195** shows a strong absorption at 1123 cm^{-1} due to the acetal function. The ^1H nmr spectrum of **195** exhibits signals at δ 3.12 (one proton doublet of doublets, J = 12, 4 Hz) for the -C<u>H</u>-OCH_2OCH_3 proton, 3.38 (three proton singlet) for the protons of the 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 δ 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 -CH-OCH_2OCH_3 carbon, respectively.

The configuration of the -CH-OCH_2OCH_3 carbon of **195** was assigned by assuming that the ether **195** existed primarily in a chair-chair conformation in which the -CH-OCH_2OCH_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 -CH-OCH_2OCH_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.



195a



196a

In an nOe difference experiment, irradiation of the ether methine proton at δ 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 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 -OCH_2OCH_3 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 H_b. However, the chemical shift value of the proton H_b was readily assigned from the results of a HETCOR experiment [93] since the chemical shift value of the methine carbon attached to the proton H_b was readily identified (δ 52.1) from the results of an APT experiment [42] (*vide supra*). Thus, in a HETCOR experiment [93] a strong correlation between the ^{13}C 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 H_a (δ 3.18)). Thus, the fact that irradiation at δ 3.18 (H_a) causes enhancement of both the signals due to the angular methyl group (δ 1.02) and H_b (δ 1.80-1.87) shows clearly that the configuration and conformation of the ether **195** is that depicted by the structure **195a**.

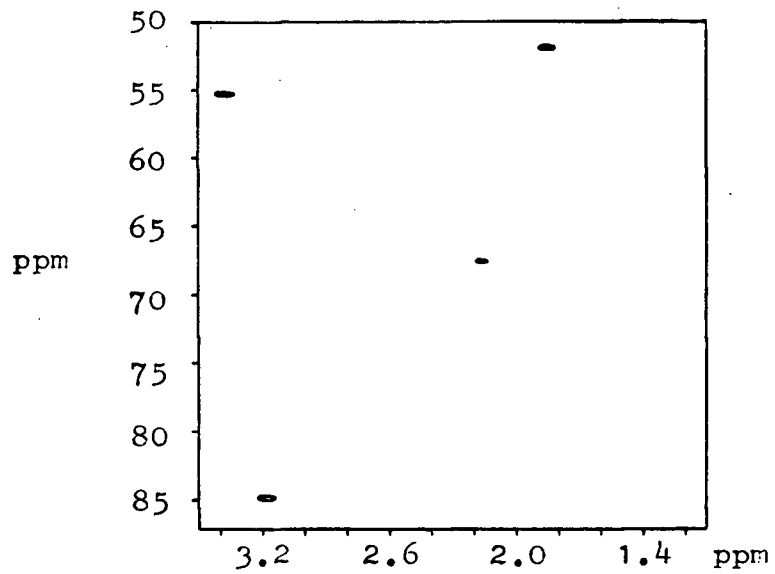
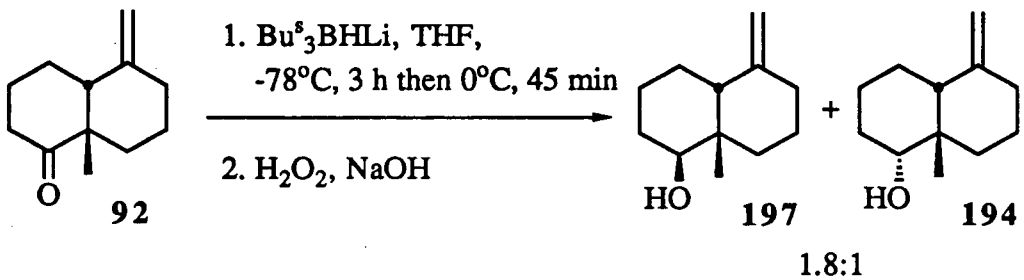


Figure 9 : HETCOR plot for the ether **195**.

In an attempt to prepare the methoxymethyl ether **196** epimeric with **195**, the ketone **92** was reduced with lithium tri-*sec*-butylborohydride [94] in THF at -78 °C. After an

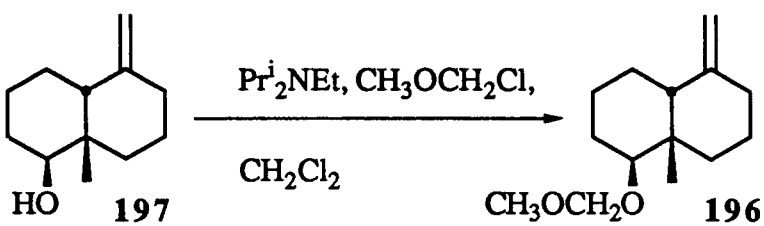
oxidative workup, a mixture of the alcohols **197** and **194** was obtained in 85% yield (equation 46). Glc analysis of the mixture indicated that the two alcohols **197** and **194** were present in a ratio of 1.8:1, respectively. The two alcohols **197** and **194** proved difficult to separate, but eventually pure samples were obtained after careful silica gel chromatography.



(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 ^1H nmr spectrum of **197** exhibits a signal at δ 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).

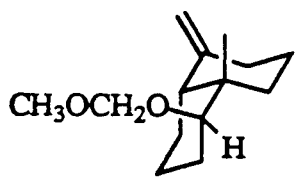


(47)

The ir spectrum of the ether **196** shows an absorption at 1148 cm^{-1} due to the acetal function. The ^1H nmr spectrum of **196** exhibits signals at δ 1.02 (three proton singlet) for

the angular methyl group, 3.34 (one proton multiplet) for the -C<u>H</u>-OCH_2OCH_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.

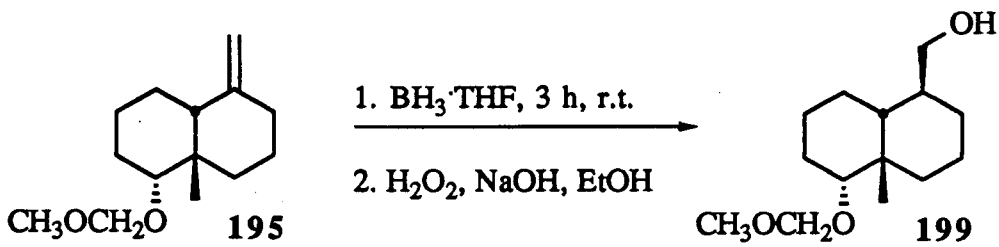
In the ^1H nmr spectrum of **196**, the signal due to the -C<u>H</u>-OCH_2OCH_3 proton has a width-at-half-height of 12 Hz, consistent with the $w_{1/2}$ values of equatorially oriented protons.[95] For comparison, the signal for the -C<u>H</u>-OCH_2OCH_3 proton of **195** is a doublet of doublets, with 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 α,β-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.

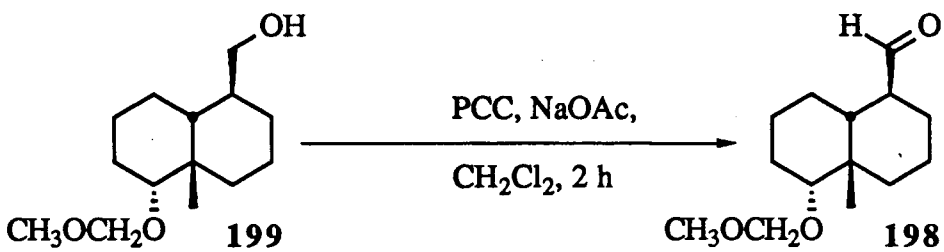
Treatment of the ether **195** with a THF solution of borane-THF [96] at room temperature for 3 h, followed by oxidation of the resultant alkylborane species with an alkaline solution of hydrogen peroxide gave the alcohol **199** in 88% yield (equation 48).



(48)

The ir spectrum of the alcohol **199** shows a broad hydroxyl absorption at 3412 cm^{-1}. The ^1H nmr spectrum of **199** exhibits signals at δ 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 *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 (*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).

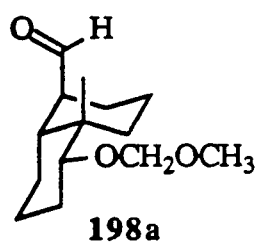


(49)

The ir spectrum of the aldehyde **198** shows absorptions at 2704 cm^{-1} and 1722 cm^{-1} for the aldehyde function. The ^1H nmr spectrum of **198** exhibits signals at δ 0.93

(three proton singlet) for the angular methyl group, 2.21 (one proton multiplet, $w_{1/2}$ = 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_2OCH_3 proton and at 9.71 (one proton singlet) for the aldehydic proton.

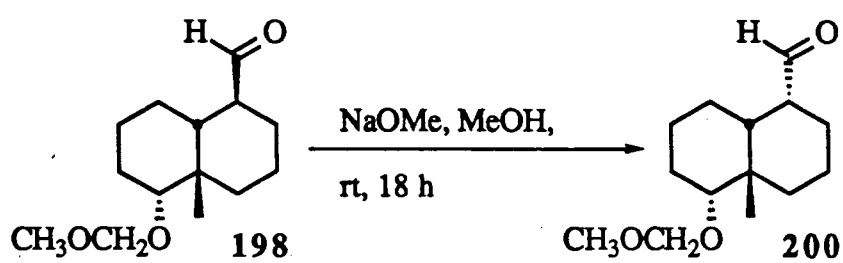
The coupling constants of the -CH-OCH_2OCH_3 proton (J = 11, 4 Hz) are consistent with the methine proton having an axial orientation.[95] Thus, the preferred chair-chair conformation of the aldehyde **198** should be that depicted by **198a**. Structure **198a** clearly shows that the aldehyde function 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.



198a

200a

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** .



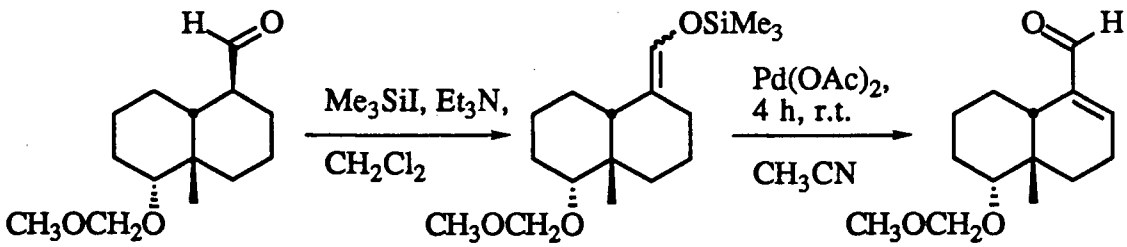
(50)

The ir spectrum of the aldehyde **200** shows absorptions at 2711 cm^{-1} and 1721 cm^{-1} for the aldehyde function. The ^1H nmr spectrum of **200** exhibits signals at δ 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 ^1H nmr spectrum of the aldehyde **200** are noteworthy. The coupling pattern of the proton adjacent to the aldehyde function (δ 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 π-electrons shield the angular methyl protons.

Treatment of a dichloromethane solution of the aldehyde **198** with triethylamine and iodotrimethylsilane [97] at -20 °C for 10 min and at room temperature for 5 min gave the enol trimethylsilyl ethers **201** (Scheme 41). The ^1H nmr spectrum of the enol silyl ethers **201** exhibits signals at δ 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 [98] 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 α,β-unsaturated aldehyde **202** in 48% overall yield from the aldehyde **198** (Scheme 41).

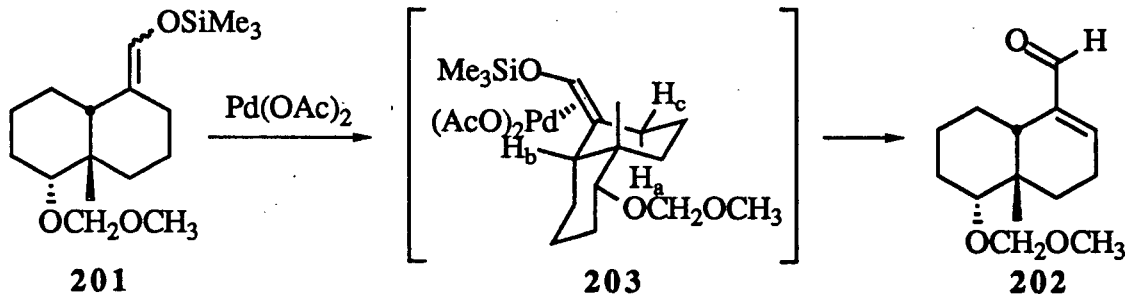


198 **201** **202**

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 ^1H nmr spectrum of **202** exhibits signals at δ 2.47 (one proton doublet of triplets, J = 15, 4 Hz) for one of the =CH-C<u>H</u>$_2$- protons, 6.70 (one proton triplet, J = 4 Hz) for the olefinic proton, and at 9.40 (one proton singlet) for the aldehydic proton.

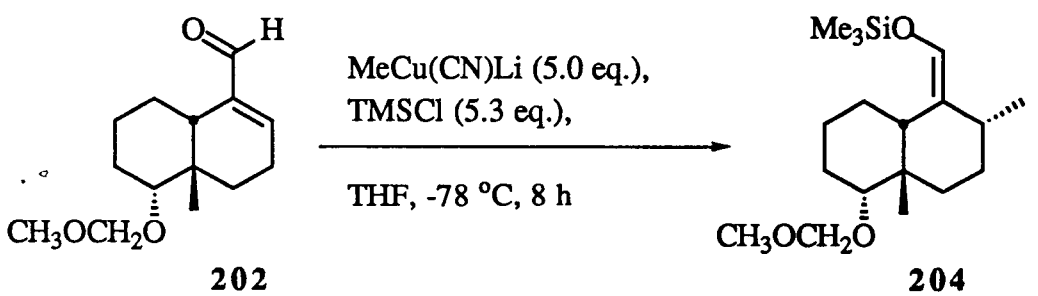
The regiochemical outcome of the Saegusa reaction [98] is particularly interesting since the enol trimethylsilyl ethers **201** could undergo dehydrogenation either toward or away from the ring junction. The mechanism of the Saegusa reaction [98] has not been investigated but probably involves an initial 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 π-complex **203** (Scheme 42). Elimination of the proton H_a *cis* to palladium seems most likely since the σ bond between the proton H_a and the adjacent carbon atom is aligned with the π-orbitals of the olefin. Comparable alignment of the π-orbitals of the olefin and the σ-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**.



201 **203** **202**

Scheme 42

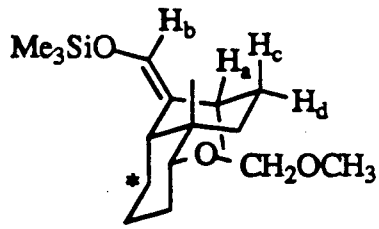
The conjugate addition of a methyl group to the α,β-unsaturated aldehyde **202** proceeded smoothly. A THF solution of **202** was added to a THF solution of lithium (cyano)(methyl)cuprate and chlorotrimethylsilane [45] and the reaction mixture was stirred at -78 °C for 8 h. After workup the enol silyl ether **204** was obtained in 92% yield (equation 51).



202 **204**

(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.



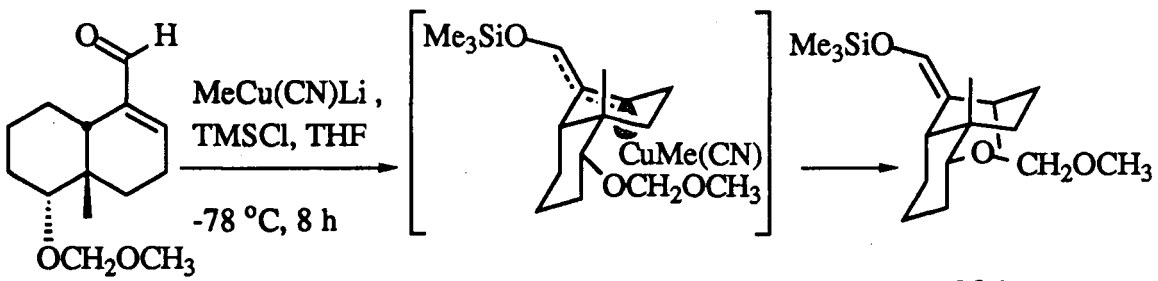
204a

The stereochemistry of the enol silyl ether **204** was assigned on the basis of results obtained from ^1H nmr decoupling and nOe difference experiments. In a decoupling experiment, irradiation of the signal at δ 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 δ 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 δ 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 δ 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 δ 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 α,β-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**.[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.

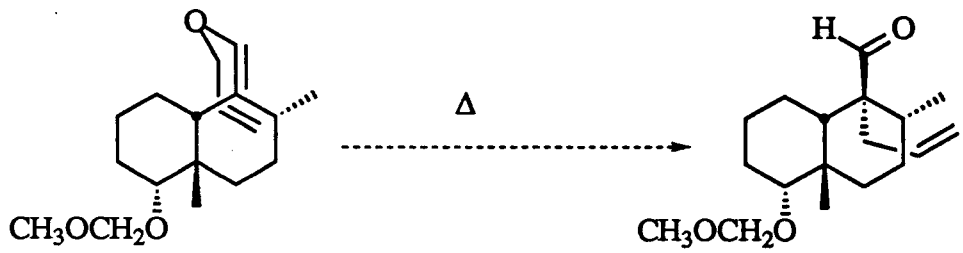


202 **205** **204a**

Scheme 43

On the basis of an examination of molecular models and by analogy with the organoaluminum-promoted Claisen rearrangement [59] of **103** (Scheme 29, p. 48), the

Claisen rearrangement [35] of the enol allyl ether **206** would be predicted to occur from the face opposite to the angular methyl group to give the aldehyde **207** (equation 52). Since we are unaware of *cis*-clerodanes in which the side chain and the angular methyl group have a *trans* relationship (see the *cis*-clerodane skeleton **186**, Scheme 36) the Claisen rearrangement could not be used to introduce the final quaternary center.

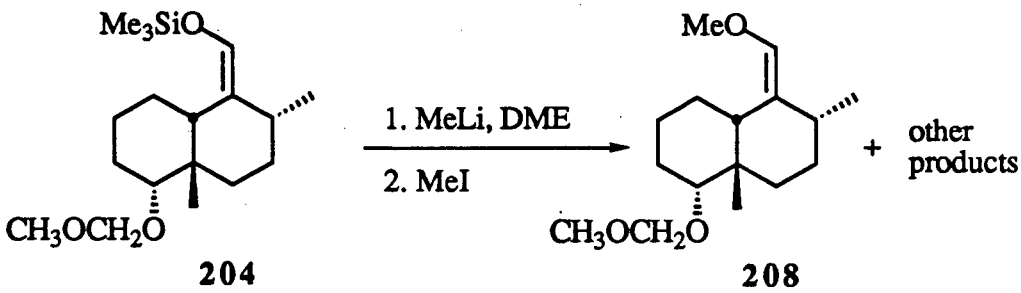


206 **207**

(52)

In order to obtain the required configuration of the quaternary center at C-9 of the *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 **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 **208**.

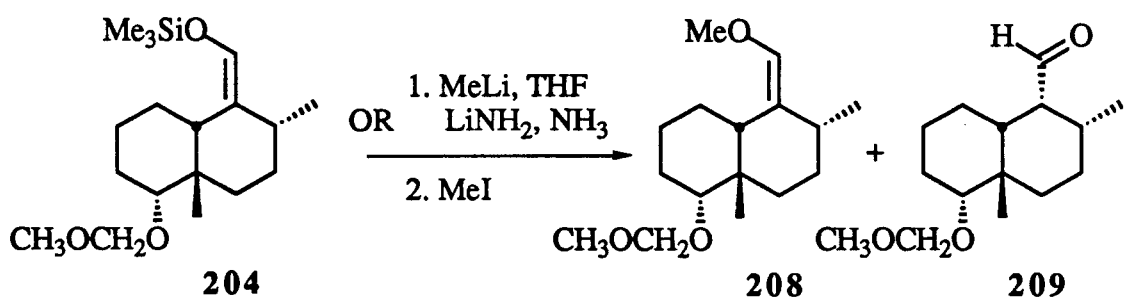


204 **208**

(53)

The ir spectrum of the methyl enol ether **208** exhibits a strong olefinic absorption at 1665 cm^{-1}. The ^1H nmr spectrum of **208** shows signals at δ 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 methyllithium 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.



204 **208** **209**

(54)

The aldehyde **209** exhibits a strong ir absorption at 1722 cm^{-1} and shows a ^1H nmr resonance at δ 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 diisopropoxy 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.

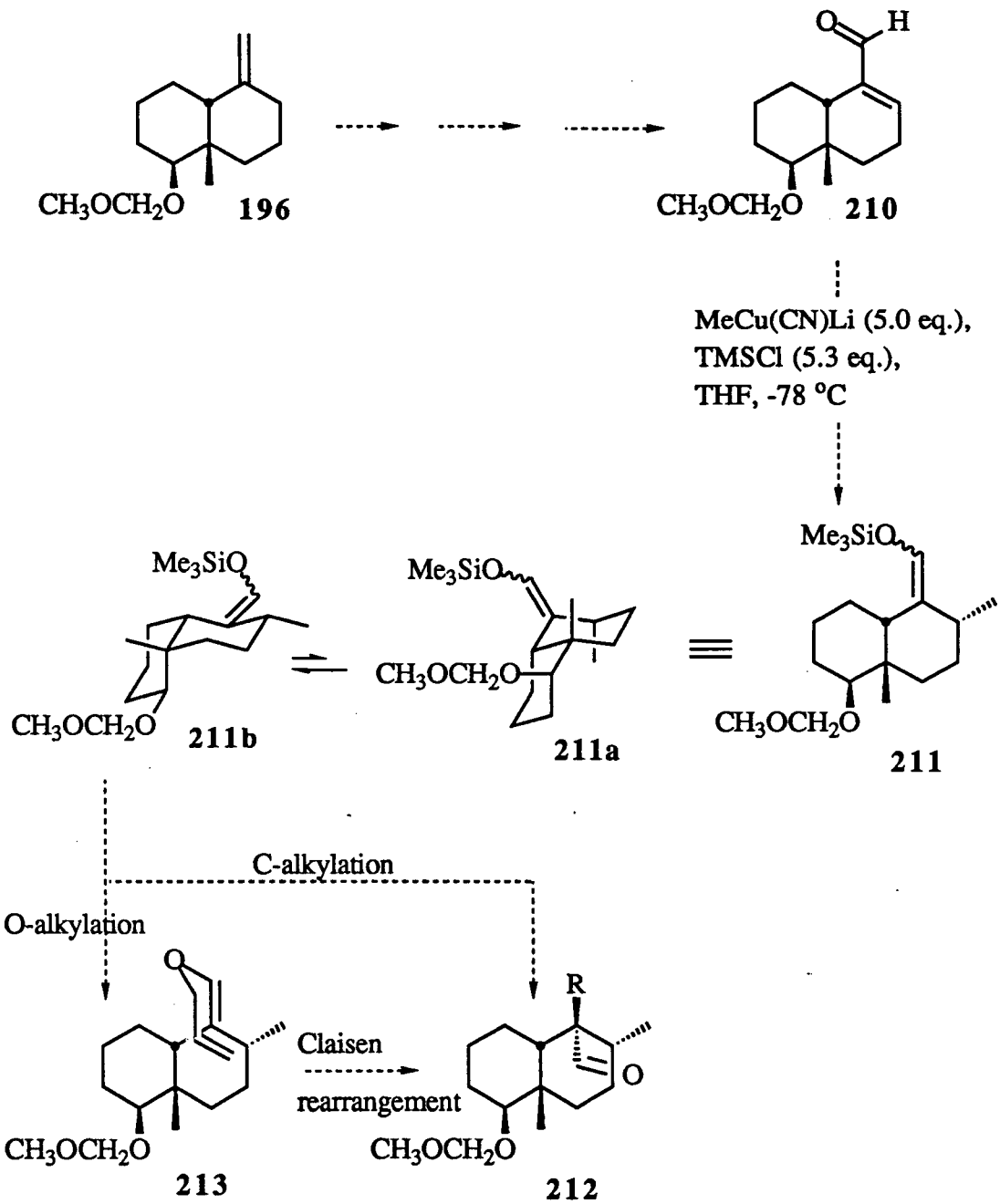
Conclusion

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 α,β-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 α,β-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_3OCH_2O 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**.


CH3OCH2O
196
O
H
CH3OCH2O
210
MeCu(CN)Li (5.0 eq.),
TMSCl (5.3 eq.),
THF, -78 °C
Me3SiO
CH3OCH2O
211b
Me3SiO
CH3OCH2O
211a
Me3SiO
CH3OCH2O
211
C-alkylation
O-alkylation
O
CH3OCH2O
213
Claisen
rearrangement
R
O
CH3OCH2O
212

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).[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 $KC_{18}/KC_{18}F$). 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 [105] 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.

Sonication 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 [106]. 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.

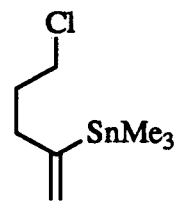
Lithium diisopropylamide (LDA) was prepared by the addition of a solution of methyllithium in diethyl ether to a solution of diisopropylamine in dry THF at 0 °C. The resulting solution was then stirred at this temperature for 5 min before use.[109]

Cold bath temperatures were maintained by the use of the following baths: [110] 27 g $CaCl_2$/100 mL H_2O/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-trimethylstannyl-1-pentene (84)



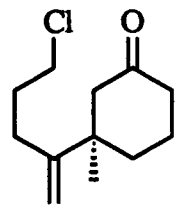
To a cold (-20 °C) stirred solution of hexamethylditin (33.5 mL, 1.3 equiv) in dry THF (1.0 L) was added methyllithium (130 mL, 1.3 equiv) as a solution in diethyl ether. The resulting pale yellow solution was stirred at -20 °C for 20 min and was then cooled to -78 °C. Solid copper(I) bromide-dimethyl 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-1-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 $^{-1}$; ^{1}H nmr (400 MHz) δ: 0.16 (s, 9H, -Sn(C<u>H</u>$_3$)$_3$, $^{2}J_{Sn-H}$ = 54 Hz), 1.85 (quintet, 2H, J = 7 Hz, -CH$_2$C<u>H</u>$_2$CH$_2$Cl), 2.40 (br t, 2H, J = 7 Hz, =CSn(CH$_3$)$_3$C<u>H</u>$_2$-), 3.50 (t, 2H, J = 7 Hz, -C<u>H</u>$_2$Cl), 5.22-5.24 (m, 1H, $^{3}J_{Sn-H}$ = 70 Hz, olefinic proton *cis* to -Sn(CH$_3$)$_3$), 5.71-5.73 (m, 1H, $^{3}J_{Sn-H}$ = 152 Hz, olefinic proton *trans* to -Sn(CH$_3$)$_3$).

Preparation of Methylenecyclobutane (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 ^{1}H nmr spectroscopy. The latter material exhibits signals due to tetramethyltin (δ 0.04, s, $^{2}J_{Sn-H}$ = 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 methylenecyclobutane (δ 1.99, quintet, J = 7 Hz; 2.67, tt, J = 7 Hz, 2; 4.65, quintet, J = 2 Hz). Comparison of the ^{1}H nmr integration of the signals due to the methylene protons of benzyl benzoate (δ 5.34) and the allylic protons of methylenecyclobutane (δ 2.67) indicated that methylenecyclobutane (**107**) had been produced in a yield of approximately 93%.

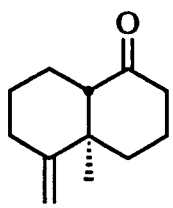
Preparation of the Chloro Ketone 93

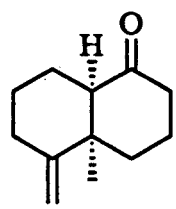


To a cold (-78 °C) stirred solution of 5-chloro-2-trimethylstannyl-1-pentene (**84**) (1.13 g, 1.24 equiv) in dry THF (40 mL) was added a solution of methyllithium (3.6 mL, 1.42 equiv) in diethyl ether. After the mixture had been stirred at -78 °C for 20 min, solid magnesium bromide-etherate (1.12 g, 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, -C$\underline{H_2}$Cl), 4.80 (s, 1H, one of =C$\underline{H_2}$), 4.86 (s, 1H, one of =C$\underline{H_2}$). *Exact Mass* calcd. for $C_{12}H_{19}{}^{35}ClO$: 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.

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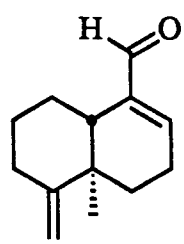
* Ratios are quoted as *trans* : *cis* ratios of ketones **94** and **95** respectively.

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 $^{-1}$; ^{1}H 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, =C$\underline{H_2}$). *Exact Mass* calcd. for $C_{12}H_{18}O$: 178.1358; found: 178.1355.

The *cis*-ketone **95** exhibits ir (film) : 3085, 1708, 1638 cm $^{-1}$; ^{1}H 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 =C$\underline{H_2}$), 4.76 (br s, 1H, one of =C$\underline{H_2}$). *Exact Mass* calcd. for $C_{12}H_{18}O$: 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 $=CH_2$), 4.69 (s, 1H, one of $=CH_2$), 6.73 (m, 1H, olefinic proton), 9.45 (s, 1H, aldehydic proton). *Exact Mass* calcd. for $C_{13}H_{18}O$: 190.1358; found: 190.1358.

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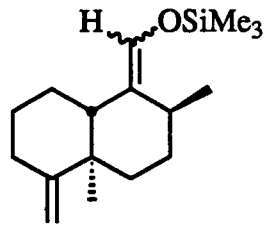
* The preparation of the α,β-unsaturated nitrile **102** from the ketone **94** is described in the Experimental section of this thesis entitled Procedures for the Conversion of Ketones into α,β-Unsaturated Nitriles.

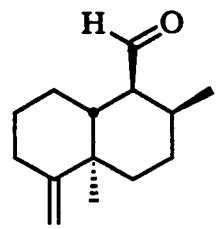
Preparation of the Enol Silyl Ether 111



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 ^{1}H 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 ^{1}H nmr integration) but did provide a pure sample for characterization purposes. This material exhibits ir (film) : 3086, 1657, 1637 cm $^{-1}$; ^{1}H nmr (400 MHz) δ: 0.16, 0.17 (two s, -Si($\underline{CH_3}$)$_3$), 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

(m), 1.41-1.51 (m), 1.58-1.96 (m), 2.05 (qd, J = 12, 3 Hz), 2.11-2.26 (m), 2.30-2.41 (m), 4.63, 4.65 (two br s, =C$\underline{H}_2$), 6.04, 6.22 (two s, olefinic proton of the enol ether, 10:3 ratio by integration). *Exact Mass* calcd. for $C_{17}H_{30}OSi$: 278.2065; found: 278.2068

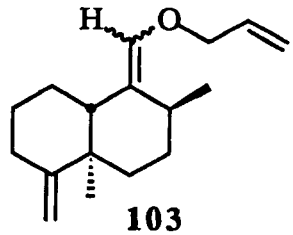
Preparation of the Aldehyde 112



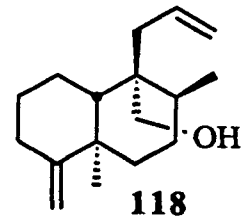
Following the procedure for the conversion of **104** into **111**, a sample of the α,β-unsaturated aldehyde **104** (129 mg, 0.679 mmol) was converted into the enol silyl ether **111**. A solution of the crude product (undistilled) in THF (2.0 mL) was added to an aqueous solution of 10% sulfuric acid (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 $^{-1}$; ^{1}H 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 =C$\underline{H}_2$), 4.63 (s, 1H, one of =C$\underline{H}_2$), 10.01 (s, 1H, aldehydic proton). The following decoupling experiments were carried out. Irradiation of the signal

at δ 1.04 (secondary methyl): quintet at 2.57 (methine proton α to the secondary methyl) simplified to a broad doublet (J = 6 Hz); irradiation of the signal at δ 2.57 (methine proton α 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



103

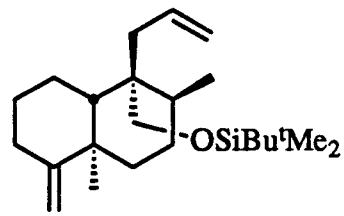


118

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 ^{1}H 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.

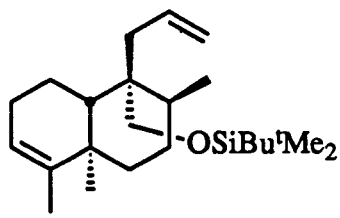
To a solution of the distilled crude allyl enol ether **103** in dry dichloromethane (1.5 mL) at room temperature was added triisobutylaluminum (0.850 mL, 2.5 equiv) as a solution in toluene. The reaction mixture was stirred at room temperature for 1 h and then dry diethyl ether (≈ 10 mL) was added. 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 D_2O, *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 -$C\underline{H}_2$OH), 3.90 (d, 1H, *J* = 12 Hz, one of -$C\underline{H}_2$OH) 4.50 (s, 1H, one of the exocyclic =$C\underline{H}_2$), 4.55 (s, 1H, one of the exocyclic =$C\underline{H}_2$), 5.07 (d, 1H, *J* = 10 Hz, one of -CH=$C\underline{H}_2$), 5.12 (d, 1H, *J* = 16 Hz, one of -CH=$C\underline{H}_2$), 5.98-6.11 (m, 1H, -$C\underline{H}$=CH_2). In a nuclear Overhauser enhancement (nOe) difference experiment, irradiation at δ 3.90 (one of -$C\underline{H}_2$OH) caused signal enhancement at 3.76 (one of -$C\underline{H}_2$OH) and at 1.13 (angular methyl). *Exact Mass* calcd. for $C_{17}H_{28}O$: 248.2140; found: 248.2141.

Preparation of the Silyl Ether 120



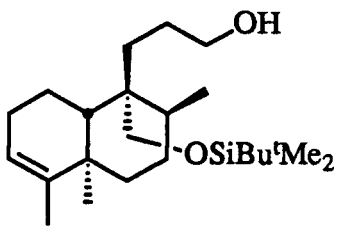
To a stirred solution of the diene alcohol **118** (709 mg, 2.86 mmol) in dry dichloromethane (14 mL) at room temperature were added sequentially 2,6-lutidine (0.831 mL, 2.5 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.984 mL, 1.5 equiv). The resulting solution was stirred at room 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 $^{-1}$; ^{1}H nmr (400 MHz) δ: 0.02 (s, 3H, one of (C$\underline{H}_3$)$_2$Bu^{t}Si-), 0.04 (s, 3H, one of (C$\underline{H}_3$)$_2$Bu^{t}Si-), 0.91 (s, 9H, Bu^t), 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 -C$\underline{H}_2$OSiBu^t(CH$_3$)$_2$), 3.90 (d, 1H, J = 10 Hz, one of -C$\underline{H}_2$OSiBu^t(CH$_3$)$_2$), 4.48 (s, 1H, one of the exocyclic =C$\underline{H}_2$), 4.53 (s, 1H, one of the exocyclic =C$\underline{H}_2$), 4.98-5.08 (m, 2H, -CH=C$\underline{H}_2$), 5.82-5.95 (m, 1H, -C$\underline{H}$=CH$_2$). In a nOe difference experiment, irradiation at δ 3.90 (one of -C$\underline{H}_2$OSiBu^{t}Me$_2$) caused signal enhancement at 3.51 (one of -C$\underline{H}_2$OSiBu^{t}Me$_2$) and at 1.13 (angular methyl). *Exact Mass* calcd. for $C_{23}H_{42}OSi$: 362.3005; found: 362.2997.

Preparation of the Silyl Ether 121



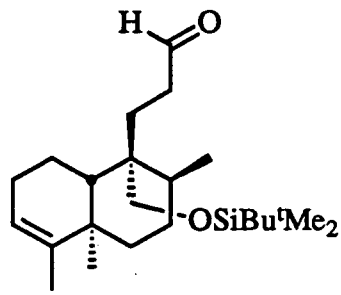
To a stirred solution of the silyl ether **120** (40.7 mg, 0.112 mmol) in dry dichloromethane (1.0 mL) at room temperature was added dry *p*-toluenesulfonic acid (2.1 mg, 0.11 equiv). The reaction mixture was stirred at room temperature for 2 h. A saturated aqueous solution (≈ 2 mL) of sodium hydrogen 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 $^{-1}$; ^{1}H nmr (400 MHz) δ: 0.01 (s, 3H, one of $(C\underline{H}_3)_2Bu^tSi$-), 0.02 (s, 3H, one of $(C\underline{H}_3)_2Bu^tSi$-), 0.90 (s, 9H, Bu^t), 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 $-C\underline{H}_2OSiBu^t(CH_3)_2$), 3.91 (d, 1H, J = 10 Hz, one of $-C\underline{H}_2OSiBu^t(CH_3)_2$), 5.01-5.12 (m, 2H, $-CH=C\underline{H}_2$), 5.19 (br s, 1H, $-CH_2C\underline{H}=C(CH_3)$-), 5.82-5.95 (m, 1H, $-C\underline{H}=CH_2$). *Exact Mass* calcd. for $C_{23}H_{42}OSi$: 362.3005; found: 362.2999.

Preparation of the Alcohol 122



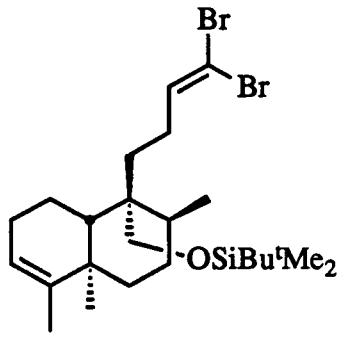
To a stirred solution of 9-BBN (221 mg, 2.0 equiv) in dry THF (8.2 mL) at room temperature was added the silyl ether **121** (327 mg, 0.904 mmol) as a solution in dry THF (1.0 mL). The resultant mixture was stirred at room temperature for 3 h. Aqueous solutions of sodium hydroxide (0.202 mL, 0.7 equiv) 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 (≈ 5 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 (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) δ: 0.02 (s, 3H, one of (C$\underline{H}_3$)$_2$Bu^{t}Si-), 0.03 (s, 3H, one of (C$\underline{H}_3$)$_2$Bu^{t}Si-), 0.90 (s, 9H, 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 -C$\underline{H}_2$OSiBu^t(CH$_3$)$_2$), 3.57-3.69 (m, 2H, -C$\underline{H}_2$OH), 3.97 (d, 1H, *J* = 10 Hz, one of -C$\underline{H}_2$OSiBu^t(CH$_3$)$_2$), 5.19 (br s, 1H, -CH$_2$C$\underline{H}$=C(CH$_3$)-). *Exact Mass* calcd. for C$_{19}$H$_{35}$O$_2$Si (M$^+$ - 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 $^{-1}$; ^{1}H nmr (400 MHz) δ: 0.03 (s, 3H, one of (C$\underline{H}_3$)$_2$Bu^{t}Si-), 0.04 (s, 3H, one of (C$\underline{H}_3$)$_2$Bu^{t}Si-), 0.89 (s, 9H, Bu^t), 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 -C$\underline{H}_2$OSiBu^t(CH$_3$)$_2$), 3.89 (d, 1H, J = 10 Hz, one of -C$\underline{H}_2$OSiBu^t(CH$_3$)$_2$), 5.19 (br s, 1H, -CH$_2$C$\underline{H}$=C(CH$_3$)-), 9.77 (t, 1H, J = 2 Hz, aldehydic proton). *Exact Mass* calcd. for $C_{19}H_{33}O_2Si$ (M^+ - Bu^t): 321.2250; found: 321.2253.

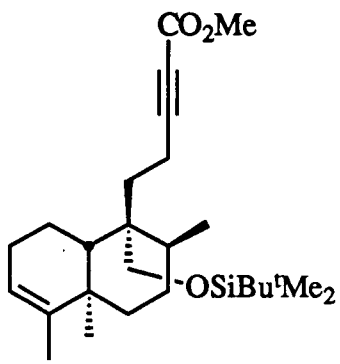
Preparation of the Dibromide 124



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 $^{-1}$; ^{1}H nmr (400 MHz) δ: 0.04 (s, 6H, (C<u>H</u>$_3$)$_2$Si-), 0.90 (s, 9H, Bu^t), 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 -CH_2OSiBu^t$(CH_3)_2$), 3.93 (d, 1H, J = 10 Hz, one of -CH_2OSiBu^t$(CH_3)_2$), 5.18 (br s, 1H, -CH_2CH=$C(CH_3)$-), 6.37 (t, 1H, J = 6 Hz, -CH=CBr_2). *Exact Mass* calcd. for $C_{24}H_{42}Br_2OSi$: 534.1353; found: 534.1360.

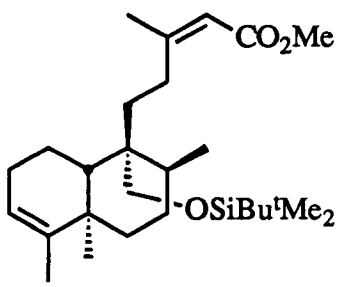
Preparation of the Acetylenic Ester 126



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, $(C\underline{H}_3)_2Si$-), 0.90 (s, 9H, Bu^t), 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 $-C\underline{H}_2OSiBu^t(CH_3)_2$), 3.77 (s, 3H, $-OC\underline{H}_3$), 3.82 (d, 1H, J = 10 Hz, one of $-C\underline{H}_2OSiBu^t(CH_3)_2$), 5.18 (br s, 1H, $-CH_2C\underline{H}=C(CH_3)-$). *Exact Mass* calcd. for $C_{26}H_{44}O_3Si$: 432.3060; found: 432.3057.

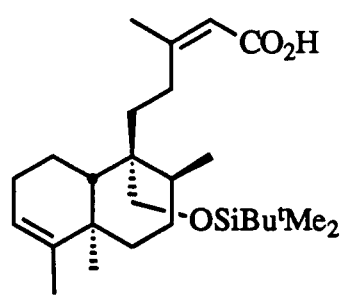
Preparation of the α,β-Unsaturated Ester 127



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, $(C\underline{H}_3)_2Si$-), 0.90 (s, 9H, Bu^t), 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, -$C(C\underline{H}_3)$=CH-CO_2CH_3), 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 -$C\underline{H}_2OSiBu^t(CH_3)_2$), 3.67 (s, 3H, -$OC\underline{H}_3$), 3.98 (d, 1H, *J* = 10 Hz, one of -$C\underline{H}_2OSiBu^t(CH_3)_2$), 5.18 (br s, 1H, -$CH_2C\underline{H}$=$C(CH_3)$-), 5.65 (s, 1H, -C=$C\underline{H}$-$CO_2CH_3$). In an nOe difference experiment, irradiation of the signal at δ 3.98 (one of -$C\underline{H}_2OSiBu^t(CH_3)_2$) caused signal enhancement at 3.51 (one of -$C\underline{H}_2OSiBu^t(CH_3)_2$) and at 1.11 (angular methyl). In another nOe difference experiment, irradiation of the signal at δ 5.65 (C=$C\underline{H}$-CO_2CH_3) caused signal enhancement at 1.91 (-$C(C\underline{H}_3)$=CH-CO_2CH_3). *Exact Mass* calcd. for $C_{27}H_{48}O_3Si$: 448.3372; found: 448.3363.

Preparation of the α,β-Unsaturated Acid 128

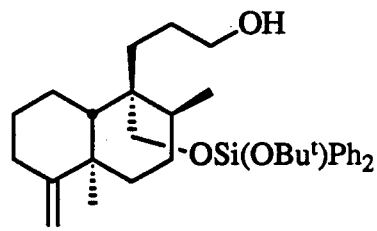


To a sample of sodium hydride (83 mg, 2.08 mmol) in paraffin oil at room temperature was added dry THF (1.0 mL) and the resultant mixture was stirred briefly (≈ 2

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 $(C\underline{H}_3)_2Bu^tSi$-), 0.05 (s, 3H, one of $(C\underline{H}_3)_2Bu^tSi$-), 0.90 (s, 9H, Bu^t), 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, $-C(C\underline{H}_3)=CH-CO_2H$), 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 $-C\underline{H}_2OSiBu^t(CH_3)_2$), 3.95 (d, 1H, J = 10 Hz, one of $-C\underline{H}_2OSiBu^t(CH_3)_2$), 5.18 (br s, 1H, $-CH_2C\underline{H}=C(CH_3)$-), 5.68 (s, 1H, $-C=C\underline{H}-CO_2H$). *Exact Mass* calcd. for $C_{26}H_{46}O_3Si$: 434.3216; found: 434.3209.

Preparation of the Alcohol 130

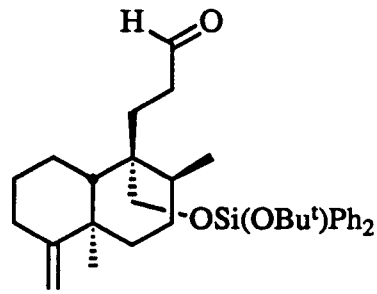


To a stirred solution of the diene alcohol **118** (703 mg, 2.84 mmol) in dry dichloromethane (14 mL) at room temperature were added, sequentially, triethylamine (0.513 mL, 1.3 equiv), *tert*-butoxydiphenylsilyl chloride (0.845 mL, 1.1 equiv) and 4-*N*,*N*-dimethylaminopyridine (34.6 mg, 0.1 equiv). 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 $^{-1}$; ^{1}H 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, Bu^t), 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 -C$\underline{H}_2$OSi(OBu^t)Ph$_2$), 3.88 (d, 1H, J = 10 Hz, one of -C$\underline{H}_2$OSi(OBu^t)Ph$_2$), 4.45 (s, 1H, one of =C$\underline{H}_2$), 4.48 (s, 1H, one of =C$\underline{H}_2$), 4.94 (br d, 1H, J = 10 Hz, one of -CH=C$\underline{H}_2$), 5.01 (br d, 1H, J = 17 Hz, one of -CH=C$\underline{H}_2$), 5.91-6.03 (m, 1H, -C$\underline{H}$=CH$_2$), 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

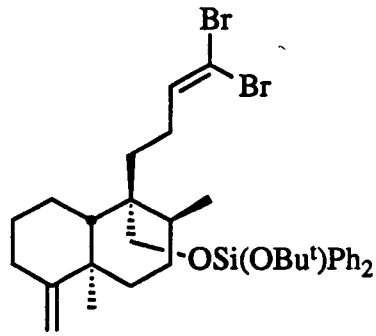
stirred at 0 °C for 20 min. The silyl ether **129** (90.0 mg, 0.179 mmol) was added as a solution in dry THF (0.448 mL). The reaction mixture was stirred at 0 °C for 20 min and then was warmed to room temperature and stirred for a further 45 min. The reaction mixture was cooled to 0 °C and aqueous solutions 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, Bu^t), 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, -$C\underline{H}_2OH$), 3.73 (d, 1H, J = 10 Hz, one of -$C\underline{H}_2OSi(OBu^t)Ph_2$), 4.01 (d, 1H, J = 10 Hz, one of -$C\underline{H}_2OSi(OBu^t)Ph_2$), 4.46 (s, 1H, one of =$C\underline{H}_2$), 4.50 (s, 1H, one of =$C\underline{H}_2$), 7.32-7.44 (m, 6H), 7.63-7.70 (m, 4H). *Exact Mass* calcd. for $C_{33}H_{48}O_3Si$: 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 $^{-1}$; ^{1}H 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, Bu^t), 1.58-1.89 (m, 7H), 2.05-2.45 (m, 5H), 3.73 (d, 1H, J = 10 Hz, one of -C$\underline{H}_2$OSi(OBu^t)Ph$_2$), 3.94 (d, 1H, J = 10 Hz, one of -C$\underline{H}_2$OSi(OBu^t)Ph$_2$), 4.46 (s, 1H, one of =C$\underline{H}_2$), 4.49 (s, 1H, one of =C$\underline{H}_2$), 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 $C_{33}H_{46}O_3Si$: 518.3216; found: 518.3216.

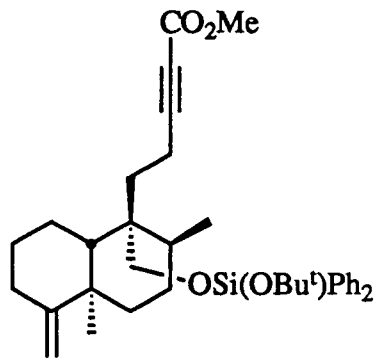
Preparation of the Dibromide 134



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 $^{-1}$; ^{1}H 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^t), 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 -$C\underline{H}_2OSi(OBu^t)Ph_2$), 3.91 (d, 1H, J = 10 Hz, one of -$C\underline{H}_2OSi(OBu^t)Ph_2$), 4.45 (s, 1H, one of =$C\underline{H}_2$), 4.48 (s, 1H, one of =$C\underline{H}_2$), 6.24 (t, 1H, J = 6 Hz, -$C\underline{H}$=CBr_2), 7.33-7.44 (m, 6H), 7.62-7.69 (m, 4H). *Exact Mass* calcd. for $C_{34}H_{46}Br_2O_2Si$: 674.1615; found: 674.1607.

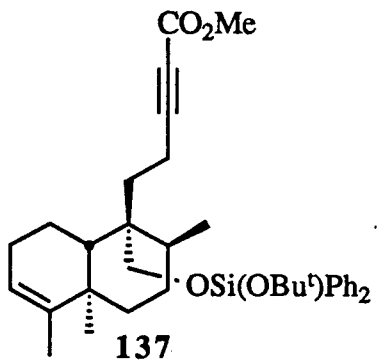
Preparation of the Acetylenic Ester 135



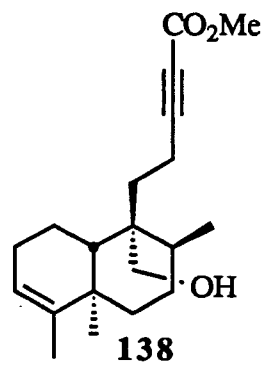
To a cold (-78 °C) stirred solution of the dibromide **134** (207 mg, 0.307 mmol) in dry THF (6.1 mL) was added a solution of *n*-butyllithium (0.427 mL, 2.1 equiv) in hexanes. The reaction mixture was stirred at -78 °C for 3 h and then neat methyl chloroformate (50 μL, 2.1 equiv) was added. The solution 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) δ: 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 -C$\underline{H}_2$OSi(OBu^{t})Ph$_2$), 3.75 (s, 3H, -OC$\underline{H}_3$), 3.85 (d, 1H, J = 10 Hz, one of -C$\underline{H}_2$OSi(OBu^{t})Ph$_2$), 4.43 (s, 1H, one of =C$\underline{H}_2$), 4.46 (s, 1H, one of =C$\underline{H}_2$), 7.33-7.45 (m, 6H), 7.60-7.68 (m, 4H). *Exact Mass* calcd. for $C_{36}H_{48}O_4Si$: 572.3322; found: 572.3319.

Preparation of the Acetylenic Ester 137 and the Alcohol 138



137



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^t), 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 $-C\underline{H}_2OSi(OBu^t)Ph_2$), 3.76 (s, 3H, $-OC\underline{H}_3$), 3.89 (d, 1H, J = 11 Hz, one of $-C\underline{H}_2OSi(OBu^t)Ph_2$), 5.15 (br s, 1H, olefinic proton), 7.30-7.45 (m, 6H), 7.59-7.68 (m, 4H). *Exact Mass* calcd. for $C_{36}H_{48}O_4Si$: 572.3322; found: 572.3323.

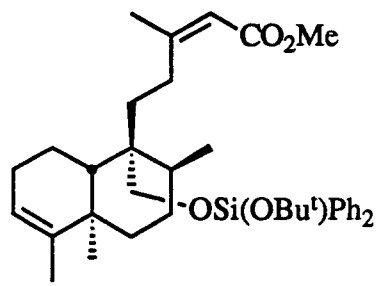
The alcohol **138** exhibits ir (film) : 3421, 2236, 1716 cm^{-1}; ^1H nmr (400 MHz) δ: 0.96 (d, 3H, J = 7 Hz, secondary methyl), 1.09 (s, 3H, angular methyl), 1.25-1.63 (m, 7H), 1.59 (br s, 3H, vinylic methyl), 1.65-2.00 (m, 4H), 2.01-2.10 (m, 1H), 2.19-2.36 (m, 2H), 2.42-2.53 (m, 1H), 3.60 (d, 1H, J = 11 Hz, one of $-C\underline{H}_2OH$), 3.77 (s, 3H, $-OC\underline{H}_3$), 3.99 (d, 1H, J = 11 Hz, one of $-C\underline{H}_2OH$), 5.19 (br s, 1H, olefinic proton). *Exact Mass* calcd. for $C_{20}H_{30}O_3$: 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.

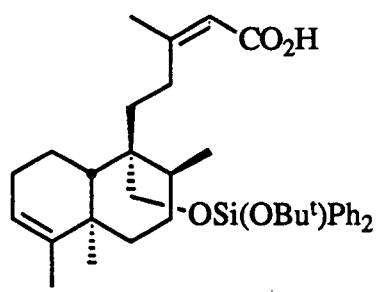
Preparation of the α,β-Unsaturated Ester 139



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 evaoporator 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 $^{-1}$; ^{1}H 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, Bu^{t}), 1.50-1.68 (m, 4H), 1.56 (br s, 3H, vinylic methyl), 1.83 (s, 3H, -C(C$\underline{H}_3$)=CHCO$_2$Me), 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, -OC$\underline{H}_3$), 3.80 (d, 1H, J = 11 Hz, one of -C$\underline{H}_2$OSi(OBu^{t})Ph$_2$), 3.93 (d, 1H, J = 11 Hz, one of -C$\underline{H}_2$OSi(OBu^{t})Ph$_2$), 5.14 (br s, 1H, -CH$_2$C$\underline{H}$=), 5.61 (s, 1H, =C$\underline{H}$-CO$_2$CH$_3$), 7.31-7.43 (m, 6H), 7.64-7.68 (m, 4H). *Exact Mass* calcd. for $C_{37}H_{52}O_4Si$: 588.3635; found: 588.3627.

Preparation of the α,β-Unsaturated Acid 140

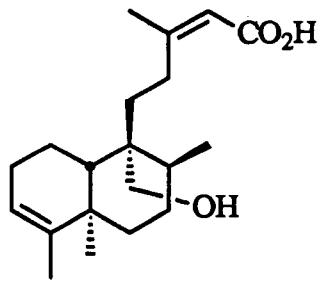


To a sample of sodium hydride (83 mg, 2.08 mmol) in paraffin oil at room temperature was added dry THF (1.0 mL) and the resultant mixture was stirred briefly (≈ 2 min). Stirring was stopped and the solid was allowed to settle. The solvent was removed via syringe, and then dry THF (1.0 mL) was added. 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 evaoporator 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, Bu^t), 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, -$C(C\underline{H}_3)$=$CHCO_2H$), 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 -$C\underline{H}_2OSi(OBu^t)Ph_2$), 3.90 (d, 1H, J = 12 Hz, one of -$C\underline{H}_2OSi(OBu^t)Ph_2$), 5.13 (br s, 1H, -$CH_2C\underline{H}$=C), 5.63 (s, 1H, -C=$C\underline{H}$-$CO_2CH_3$), 7.31-7.43 (m, 6H), 7.63-7.68 (m, 4H). *Exact Mass* calcd. for $C_{36}H_{50}O_4Si$: 574.3478; found: 574.3477.

Preparation of (±)-Stephalic Acid (96)



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_{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 ^1H 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^{-1}; ^1H 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), 121-1.34 (m, 2H), 1.39-2.08 (diffuse m, 12H), 1.60 (br s, 3H, vinylic methyl), 1.96 (br s, 3H, $-C(C\underline{H}_3)=CHCO_2H$), 3.14-3.23 (m, 1H), 3.68 (d, 1H, J = 12 Hz, one of $-C\underline{H}_2OH$), 4.24 (d, 1H, J = 12 Hz, one of $-C\underline{H}_2OH$), 5.18 (br s, 1H, $-CH_2C\underline{H}=C$), 5.72 (br s, 1H, $C=C\underline{H}-CO_2H$). The ^1H nmr spectrum of this material was identical to that of the naturally occurring diterpenoid (+)-stephalic acid.* *Exact Mass* calcd. for $C_{20}H_{32}O_3$: 320.2351; found: 320.2346.

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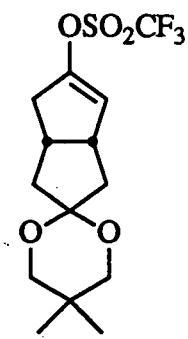
* We are grateful to Professor M. Salmón for providing a sample of natural (+)-stephalic acid.

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_2NPh) (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.

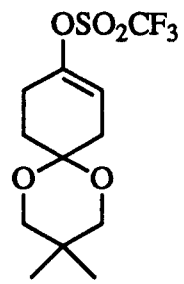
Preparation of the Enol Triflate 162



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 $^{-1}$; ^{1}H 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, -C<u>H</u>$_2$O-), 3.48 (s, 2H, -C<u>H</u>$_2$O-), 5.59 (br s, 1H, olefinic proton). *Exact Mass* calcd. for $C_{14}H_{19}F_3O_5S$: 356.0905; found: 356.0912.

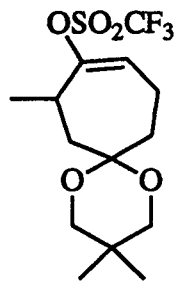
Preparation of the Enol Triflate 158



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 $^{-1}$; ^{1}H 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, -C<u>H</u>$_2$O-), 3.56 (d, 2H, J = 10 Hz, -

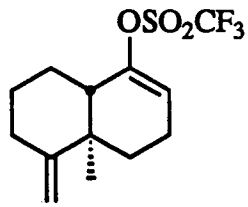
$C\underline{H}_2O$-), 5.62 (t, 1H, J = 4 Hz, olefinic proton). *Exact Mass* calcd. for $C_{12}H_{17}F_3O_5S$: 330.0749; found:330.0740 .

Preparation of the Enol Triflate 163



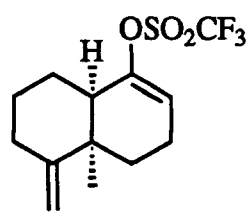
Following general procedure 1, the ketone **157** [84b] (1.00 g, 4.42 mmol) was converted into the enol triflate **163** in 2.5 h. Removal of the solvent from the reaction mixture (reduced pressure) gave the crude product as an oil. Flash chromatography of the crude product on silica gel (4.5 x 15 cm 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}; ^1H 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 -$C\underline{H}_2O$-), 5.88 (br t, 1H, J = 6 Hz, olefinic proton). *Exact Mass* calcd. for $C_{14}H_{21}F_3O_5S$: 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 $=C\underline{H}_2$), 4.72 (br s, 1H, one of $=C\underline{H}_2$), 5.70-5.74 (m, 1H, $=C\underline{H}-CH_2-$). *Exact Mass* calcd. for $C_{13}H_{17}F_3O_3S$: 310.0850; found: 310.0845.

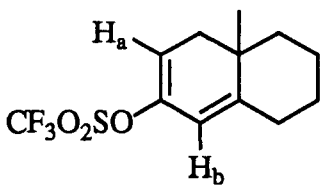
Preparation of the Enol Triflate 164



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 $^{-1}$; ^{1}H 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 =C$\underline{H}_2$), 4.82 (s, 1H, one of =C$\underline{H}_2$), 5.57 (t, 1H, J = 4 Hz, =C$\underline{H}$-CH_2-). *Exact Mass* calcd. for $C_{13}H_{17}F_3O_3S$: 310.0850; found: 310.0843.

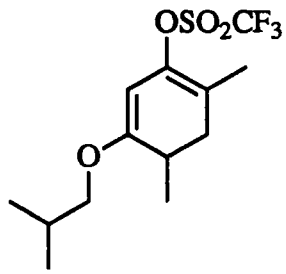
Preparation of the Enol Triflate 165



Following general procedure 1, the ketone **159** [84c] (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 $^{-1}$; ^{1}H 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

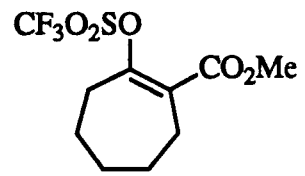
(m, 1H), 2.14 (dd, 1H, J = 16, 8 Hz, =CH-C<u>H</u>$_2$-), 2.23-2.30 (m, 2H), 2.35 (br d, 1H, J = 16 Hz, =CH-C<u>H</u>$_2$-), 5.48 (s, 1H, H_b), 5.52-5.57 (m, 1H, H_a). *Exact Mass* calcd. for $C_{12}H_{15}F_3O_3S$: 296.0694; found: 296.0686.

Preparation of the Enol Triflate 166



Following general procedure 1, the ketone **160** [111] (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 $^{-1}$; ^{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, -OC<u>H</u>$_2$-), 4.78 (s, 1H, olefinic proton). *Exact Mass* calcd. for $C_{13}H_{19}F_3O_4S$: 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** [112] (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}; ^1H 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, -OC<u>H</u>$_3$). *Exact Mass* calcd. for $C_{10}H_{13}F_3O_5S$: 302.0436; found: 302.0440.

General Procedure 2: Preparation of α,β–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 α,β-unsaturated nitrile.

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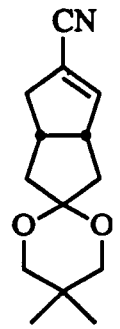
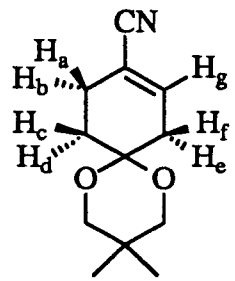
* Lithium cyanide must be dried (as outlined in the Experimental General Introduction section) under carefully controlled conditions for the reaction to be successful.

Preparation of the α,β-Unsaturated Nitrile 170



Following general procedure 2, the enol triflate **162** (160 mg, 0.453 mmol) was converted into the α,β-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}; ^1H nmr (400 MHz) δ: 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, -C<u>H</u>$_2$O-), 6.49-6.53 (m, 1H, olefinic proton). In a nOe difference experiment, irradiation of the signal at δ 6.49-6.53 (olefinic proton) caused signal enhancement at δ 3.30-3.38 (m, allylic methine proton). *Exact Mass* calcd. for $C_{14}H_{19}NO_2$: 233.1416; found: 233.1415.

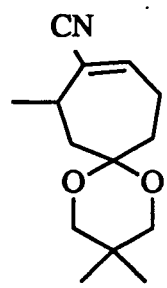
Preparation of the α,β-Unsaturated Nitrile 168



Following general procedure 2, the enol triflate **158** (4.81 g, 14.5 mmol) was converted into the α,β-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}; ^1H nmr (400 MHz) δ: 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, -C<u>H</u>$_2$O-), 3.57 (d, 2H, J = 11 Hz, -C<u>H</u>$_2$O-), 6.44-6.48 (m, 1H, H_g). The following decoupling experiments were carried out. Irradiation of the signal at δ 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 δ 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 δ 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 δ 6.44-6.48 (H_g) caused signal enhancement at δ 2.50-2.55 (H_e and H_f). ^{13}C nmr (75.3 MHz) δ: 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 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 δ 70.3. A second SINEPT experiment, utilizing the same $J_{C,H}$ of 7 Hz, in which an irradiation was centered at δ 6.46 (H_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 δ 119.0. *Exact Mass* calcd. for $C_{12}H_{17}NO_2$: 207.1260; found: 207.1258.

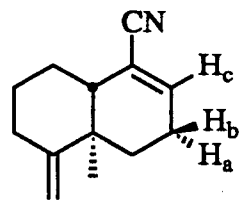
Preparation of the α,β-Unsaturated Nitrile 171



Following general procedure 2, the enol triflate **163** (206 mg, 0.574 mmol) was converted into the α,β-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) δ: 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, -C<u>H</u>$_2$O-), 6.72-6.79 (m, 1H, olefinic proton). In a nOe difference

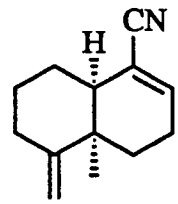
experiment, irradiation of the signal at δ 6.72-6.79 caused signal enhancement at δ 2.20-2.35 (m). *Exact Mass* calcd. for $C_{14}H_{21}NO_2$: 235.1572; found: 235.1572.

Preparation of the α,β-Unsaturated Nitrile 102



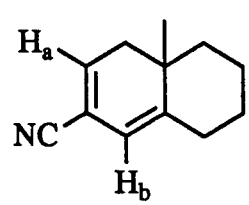
Following general procedure 2, the enol triflate **108** (805 mg, 2.60 mmol) was converted into the α,β-unsaturated nitrile **102** in 2 h. Flash chromatography of the crude product on silica gel (3.5 x 15 cm column, elution with petroleum ether-diethyl ether, 9:1) provided the nitrile **102** as an 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 =C$\underline{H_2}$), 4.73 (s, 1H, one of =C$\underline{H_2}$), 6.61-6.65 (m, 1H, H_c). In a nOe difference experiment, irradiation of the signal at δ 6.61-6.65 (H_c) caused signal enhancement at δ 2.27-2.38 (m, 2H, H_a and H_b). ^{13}C 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 (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 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 α,β-Unsaturated Nitrile 172



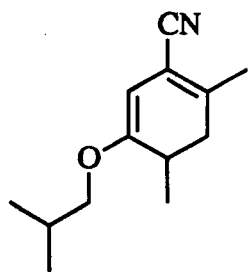
Following general procedure 2, the enol triflate **164** (35.0 mg, 0.113 mmol) was converted into the α,β-unsaturated nitrile **172** in 1.5 h. Flash chromatography of the crude product on silica gel (0.7 x 8 cm column, elution with petroleum ether-diethyl ether, 9:1) provided the nitrile **172** as 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}; ^1H nmr (400 MHz) δ: 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 $=C\underline{H}_2$), 4.81 (s, 1H, one of $=C\underline{H}_2$), 6.57 (t, 1H, J = 4 Hz, $=C\underline{H}\text{-}CH_2$-). ^{13}C nmr (75.3 MHz) δ: 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 δ 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 δ 119.5 and to the tertiary ring junction carbon at δ 44.2. *Exact Mass* calcd. for $C_{13}H_{17}N$: 187.1361; found: 187.1355.

Preparation of the α,β-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 $^{-1}$; ^{1}H 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, H_b), 6.48 (t, 1H, J = 5 Hz, H_a). In a nOe difference experiment, irradiation at δ 6.48 (H_a) caused signal enhancement at δ 2.19-2.25. *Exact Mass* calcd. for $C_{12}H_{15}N$: 173.1204; found: 173.1205.

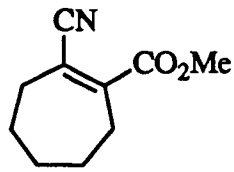
Preparation of the α,β-Unsaturated Nitrile 174



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 $^{-1}$; ^{1}H 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 Hz), 3.40-3.55 (m, 2H, -C<u>H</u>$_2$O-), 4.85 (s, 1H, olefinic proton). *Exact Mass* calcd. for $C_{13}H_{19}NO$: 205.1467; found: 205.1467.

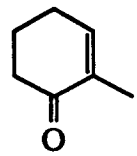
Preparation of the α,β-Unsaturated Nitrile 175



Following general procedure 2, the enol triflate **167** (55.4 mg, 0.183 mmol) was converted into the α,β-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, -OC<u>H</u>$_3$). *Exact Mass* calcd. for $C_{10}H_{13}NO_2$:179.0946; found: 179.0945.

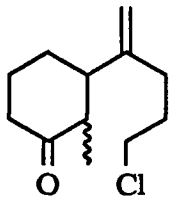
Procedures for the Synthesis of *cis*-Decalins

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

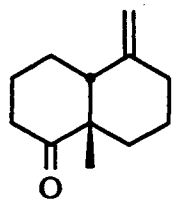


To a cold (-78 °C) stirred solution of lithium (3.45 g, 5.0 equiv) in ammonia (≈ 250 mL) was added a solution of 2-vinylpyridine (**192**) (10.8 mL, 0.10 mol) and ethanol (46.8 mL, 8.0 equiv) in dry diethyl ether (100 mL), through which argon had been passed for 15 min. The solution quickly became transparent 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 $C_7H_{10}O$: 110.0732; found: 110.0732.

Preparation of the Ketone 92 [28]



91

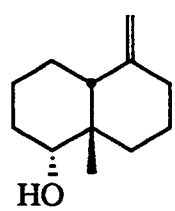


92

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 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.[28]

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 $=CH_2$), 4.72-4.75 (m, 1H, one of $=CH_2$). The spectral data exhibited by the ketone **92** is in agreement with that previously reported.[28]

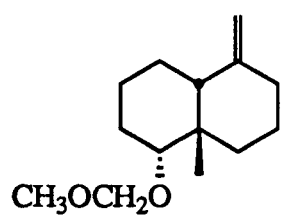
Preparation of the Alcohol 194



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 D_2O), 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, -C<u>H</u>OH), 4.63-4.66 (m, 1H, one of =C<u>H</u>$_2$), 4.66-4.69 (m, 1H, one of =C<u>H</u>$_2$). *Exact Mass* calcd. for $C_{12}H_{20}O$: 180.1514; found:180.1512.

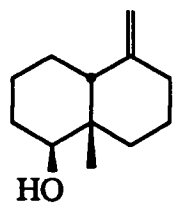
Preparation of the Ether 195



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, -C<u>H</u>OCH_2OCH_3), 3.38 (s, 3H, -$OC\underline{H}_3$), 4.59 (d, 1H, *J* = 6 Hz, one of -$OC\underline{H}_2OCH_3$), 4.61-4.67 (m, 2H, =$C\underline{H}_2$), 4.72 (d, 1H, *J* = 6 Hz, one of -$OC\underline{H}_2OCH_3$). ^{13}C 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, CH_3), 84.9 (-ve, CH), 95.8 (CH_2), 108.4 (CH_2), 150.3 (C). In a nOe difference experiment, irradiation at δ 3.18 (-C<u>H</u>OCH_2OCH_3) 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 -$OC\underline{H}_2OCH_3$) and 4.72 (d, one of -$OC\underline{H}_2OCH_3$). In a HETCOR nmr experiment the ^{13}C 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 $C_{14}H_{24}O_2$:224.1777; found:224.1772.

Preparation of the Alcohol 197

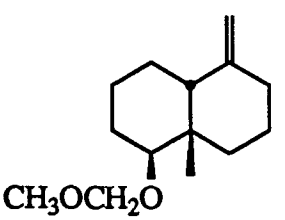


To a cold (-78 °C) stirred solution of lithium tri-*sec*-butylborohydride (1.87 mL, 3 equiv) in THF (5 mL) was added a solution of the ketone **92** (111 mg, 62.3 mmol) in dry THF (2 mL followed by 2 x 1 mL washings). The resultant solution was stirred at -78 °C for 3 h and 0 °C for 0.75 h. Methanol (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, -C<u>H</u>OH), 4.66 (s, 1H, one of =C<u>H</u>$_2$), 4.68 (s, 1H, one of =C<u>H</u>$_2$). *Exact Mass* calcd. for $C_{12}H_{20}O$: 180.1514; found:180.1507.

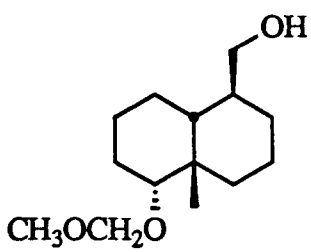
Preparation of the Ether 196



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, -C<u>H</u>OCH_2OCH_3), 3.40 (s, 3H, -$OC\underline{H}_3$), 4.59 (d, 1H, J = 6 Hz, one of -$OC\underline{H}_2OCH_3$), 4.66 (s, 1H, one of =$C\underline{H}_2$), 4.68 (s, 1H, one of =$C\underline{H}_2$), 4.72 (d, 1H, J = 6 Hz, one of -$OC\underline{H}_2OCH_3$). *Exact Mass* calcd. for $C_{14}H_{24}O_2$: 224.1777; found:224.1780.

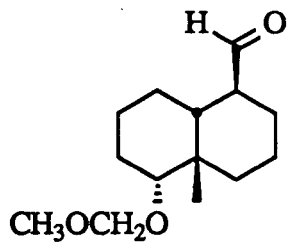
Preparation of the Alcohol 199



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 D_2O), 1.83-1.91 (m, 1H), 3.24 (dd, 1H, J = 9, 3 Hz, -C<u>H</u>OCH_2OCH_3), 3.38 (s, 3H, -$OC\underline{H}_3$), 3.63-3.75 (m, 2H, -$C\underline{H}_2OH$), 4.58 (d, 1H, J = 6 Hz, one of -$OC\underline{H}_2OCH_3$), 4.71 (d, 1H, J = 6 Hz, one of -$OC\underline{H}_2OCH_3$). *Exact Mass* calcd. for $C_{13}H_{22}O_2$ (M^+-CH_4O): 210.1619; found:210.1616.

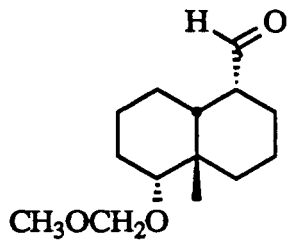
Preparation of the Aldehyde 198



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

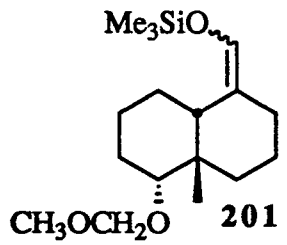
(m, 11H), 1.91-2.07 (m, 2H), 2.21 (br s, 1H, $w_{1/2}$ = 12 Hz, -C<u>H</u>CHO), 3.22 (dd, 1H, *J* = 11, 4 Hz, -C<u>H</u>OCH$_2$OCH$_3$), 3.37 (s, 3H, -OC<u>H</u>$_3$), 4.58 (d, 1H, *J* = 6 Hz, one of -OC<u>H</u>$_2$OCH$_3$), 4.71 (d, 1H, *J* = 6 Hz, one of -OC<u>H</u>$_2$OCH$_3$), 9.76 (s, 1H, aldehydic proton). *Exact Mass* calcd. for $C_{14}H_{24}O_3$: 240.1726; found:240.1731.

Preparation of the Aldehyde 200

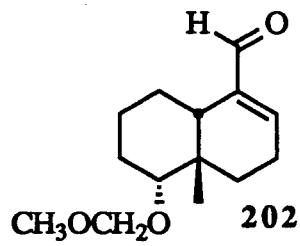


To a stirred solution of the aldehyde **198** (12.0 mg, 50.0 μmol) in spectral grade methanol (4 mL) was added solid sodium methoxide (11.0 mg, 4.0 equiv) in one portion. The solution was stirred at room temperature for 18 h and then a saturated aqueous solution of ammonium chloride (pH 8, ≈ 2 mL) was 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 ® (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 ir (film) : 2711, 1721, 1148 cm $^{-1}$; ^{1}H nmr (400 MHz) δ: 1.07-1.88 (diffuse m, 13H), 1.07 (s, 3H, angular methyl), 2.67 (dt, 1H, *J* = 12, 3 Hz, -C<u>H</u>CHO), 3.23 (dd, 1H, *J* = 11, 4 Hz, -C<u>H</u>OCH$_2$OCH$_3$), 3.39 (s, 3H, -OC<u>H</u>$_3$), 4.60 (d, 1H, *J* = 6 Hz, one of -OC<u>H</u>$_2$OCH$_3$), 4.72 (d, 1H, *J* = 6 Hz, one of -OC<u>H</u>$_2$OCH$_3$), 9.64 (s, 1H, aldehydic proton). *Exact Mass* calcd. for $C_{14}H_{24}O_3$: 240.1726; found:240.1731.

Preparation of the α,β-Unsaturated Aldehyde 202



201



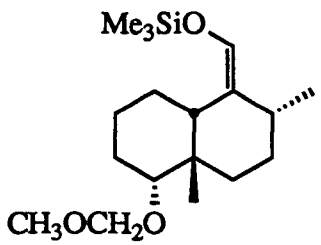
202

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 iodotrimethylsilane (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 ^{1}H nmr (400 MHz) δ: 0.15, 0.16 (two s, -Si(C$\underline{H}_3$)$_3$), 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, -C$\underline{H}$OCH$_2$CH$_3$), 3.36, 3.37 (two s, C$\underline{H}_3$O-), 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-C<u>H</u>$_2$-), 3.35 (dd, 1H, *J* = 11, 4 Hz, -C<u>H</u>OCH$_2$OCH$_3$), 3.40 (s, 3H, -OC<u>H</u>$_3$), 4.62 (d, 1H, *J* = 6 Hz, one of -OC<u>H</u>$_2$OCH$_3$), 4.75 (d, 1H, *J* = 6 Hz, one of -OC<u>H</u>$_2$OCH$_3$), 6.70 (t, 1H, *J* = 4 Hz, =C<u>H</u>-) 9.40 (s, 1H, aldehydic proton). *Exact Mass* calcd. for $C_{14}H_{22}O_3$: 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, $(C\underline{H}_3)_3Si$), 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, $-C\underline{H}OCH_2OCH_3$), 3.32 (s, 3H, $-OC\underline{H}_3$), 4.54 (d, 1H, J = 6 Hz, one of $-OC\underline{H}_2OCH_3$), 4.67 (d, 1H, J = 6 Hz, one of $-OC\underline{H}_2OCH_3$), 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 $C_{18}H_{34}O_3Si$: 326.2278; found: 326.2275.

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