TOTAL SYNTHESIS OF (±)-PALAUOLIDE,
(±)-ISOLINARIDIOL AND (±)-ISOLINARIDIOL DIACETATE

By

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B.Sc., University of Hong Kong, 1982
M.Phil., University of Hong Kong, 1984

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
in
THE FACULTY OF GRADUATE STUDIES
DEPARTMENT OF CHEMISTRY

We accept this thesis as conforming
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THE UNIVERSITY OF BRITISH COLUMBIA
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This thesis describes the total syntheses of the sesterterpenoid (±)-palauolide (55) and the diterpenoids (±)-isolinaridiol (64) and (±)-isolinaridiol diacetate (61).

In the total synthesis of (±)-palauolide, the decalin substructure was constructed by a copper(I) bromide-dimethyl sulfide catalyzed addition of the Grignard reagent 40 to 3,6-dimethyl-2-cyclohexen-1-one (115), followed by intramolecular alkylation of the resultant chloro ketone 121. The resultant annulation product 114 was converted into the nitrile 112, which was stereoselectively alkylated with ICH₂CH₂CH₂OCH₂OCH₃ to provide the nitrile 173. The latter substance was transformed via a series of reactions into compound 175 which was converted into the α,β-unsaturated aldehyde 107. Julia olefination of 107 with the lithium salt of the sulfone 223 provided stereoselectively the triene 216, which was photooxygenated to provide (±)-palauolide (55).

In the total syntheses of (±)-isolinaridiol (64) and (±)-isolinaridiol diacetate (61), the bicyclic substance 276 was prepared by following the chemistry developed in the synthesis of (±)-palauolide (55). Conversion of 276 into the aldehyde 234, followed by treatment of this material, under carefully defined conditions, with the anion of the γ-lactone phosphonate 261, provided the Z lactone 279 as the major product. Diisobutylaluminum hydride reduction of 279 yielded (±)-isolinaridiol (64). Bis-acetylation of the latter material provided (±)-isolinaridiol diacetate (61).
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LIST OF ABBREVIATIONS

Ac - acetyl
AIBN - 2,2'-azobisisobutyronitrile
br - broad
Bu - butyl
Bn - benzyl
Bz - benzoyl
d - doublet
DBU - 1,8-diazobicyclo[5.4.0]undec-7-ene
DEG - diethylene glycol
DIBAL-H - diisobutylaluminum hydride
DMAP - 4-N,N-dimethylaminopyridine
DME - 1,2-dimethoxyethane
DMF - N,N-dimethylformamide
DMSO - dimethylsulfoxide
equiv - equivalent(s)
Et - ethyl
glc - gas-liquid chromatography
h - hour(s)
HMPA - hexamethylphosphoramidate
ir - infrared
LAH - lithium aluminum hydride
LDA - lithium diisopropylamide
m - multiplet
<table>
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<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonate</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>nmr</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser enhancement</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium p-toluenesulfonate</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>Py</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
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<td>s</td>
<td>singlet</td>
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<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>tert</td>
<td>tertiary</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyranyl</td>
</tr>
<tr>
<td>tlc</td>
<td>thin layer chromatography</td>
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<tr>
<td>TMEDA</td>
<td>N,N,N',N'-tetramethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TosMIC</td>
<td>(p-toluenesulfonyl) methyl isocyanide</td>
</tr>
<tr>
<td>TPP</td>
<td>tetraphenylporphin</td>
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μ-TsOH - para-toluenesulfonic acid
Ts - para-toluenesulfonyl
v - very
Δ - heat
ACKNOWLEDGEMENTS

This thesis is based on the research work carried out in the Department of Chemistry, University of British Columbia from January, 1985 to November, 1987, under the supervision of Professor Edward Piers.

I would like to express my deepest gratitude to Professor Piers for his invaluable guidance, encouragement and discussion throughout the course of the research work, and for his immense effort in setting up our problem sets to further educate us in the science of organic chemistry. His advice on writing this thesis is greatly appreciated.

I would like to thank all the members of Professor Piers' research group with whom I have shared the pleasure of discussion, the frustration of failure, and the joy of success. Special thanks are due to Dr. Montse Llinas-Brunet, Mr. Fraser Fleming, and Miss Betty-Anne Story for their careful proofreading, and to Professor J.R. Scheffer for showing me how to do MM2 calculations.

Thanks are also extended to the technical staffs of the nuclear magnetic resonance and mass spectroscopy services for their reliable and usually efficient service, and to Mrs. Rani Theeparajah for typing the thesis.

The generosity of the Swire Company (HK) for providing a "free ride" to Vancouver is acknowledged with thanks.
TO MY WIFE

JENNY
INTRODUCTION

I. General

The achievement of the chemical synthesis of a complex organic molecule involves the development and experimental execution of a synthetic plan. When the chemical behaviour of the compounds in the synthetic sequence is different from what was expected, the plan is modified, repeatedly if necessary, until success is accomplished. In planning a synthesis, the complex target molecule is theoretically broken into pieces in such a way that they might be rejoined experimentally to construct the target molecule. Thus, the planning of a synthesis is greatly facilitated by recognizing, within the target molecule, certain fragments which can be synthesized and joined by known or conceivable synthetic operations. Such fragments are referred to as synthons.

The reactions most frequently used in organic synthesis are polar in nature. They usually involve nucleophilic sites interacting with electrophilic sites to form bonds. Thus, most of the chemical reagents used to carry out synthetic operations have either a nucleophilic site or an electrophilic center. However, some chemical reagents possess two reactive sites, e.g. two nucleophilic sites, two electrophilic sites or one nucleophilic and one electrophilic site. These species, if they are incorporated in whole or in part into a substrate molecule to give a more complex system, are commonly referred to as "bifunctional conjunct-
tive reagents". Examples of some simple bifunctional reagents are given below.

Dialkyl malonates and dithianes are well-known, simple examples of conjunctive reagents. They have been used effectively as synthetic equivalents of donor-donor (d,d) synthons.* For example, diethyl malonate (1) has been used in the preparation of the synthetically valuable cyclopropane-1,1-dicarboxylic acid (2)^3 (equation 1), while 1,3-dithiane (3) had been employed in the preparation of dithioketals 4. Hydrolysis of the latter materials provides access to cyclic ketones 5 of different ring sizes^4 (equation 2). In these reactions, reagents 1 and 3 serve as synthetic equivalents of the d,d synthons 6 and 7, respectively.

In organic synthesis, annulation reactions are frequently involved in the construction of a target molecule. Many bifunctional conjunctive reagents have been used to effect annulation reactions. On such occasions, the bifunctional reagents react with a suitable substrate via an intermolecular coupling step, followed by an intramolecular cycliza-

---

* Heteroatoms in an organic molecule impose an alternating acceptor and donor reactivity pattern (as shown) upon the carbon skeleton. Thus, carbons\(^1,3,5\) are acceptors (attack by donors) and carbons\(^2,4,6\) are donors (attack by acceptors); the heteroatom \(X^0\) is a donor center.

\[
\begin{array}{c}
\text{d} \\
\text{a} \\
\text{1} \\
\text{2} \\
\text{3} \\
\text{4} \\
\text{5} \\
\text{6} \\
\text{d} \\
\text{a}
\end{array}
\]

\[X = O, N\]

Condensation of the dianion 8 with ethyl 4-bromobutanoate in THF-HMPA at -60° to -80°C gave the diester 9 in 60% yield. Decarboxylation and saponification of the latter material provided the valuable octalone 10 (equation 3). In this case 8 acts as a synthetic equivalent of the d,d synthon 11. The ketone 10 has been used as an intermediate in sesquiterpene syntheses.
The aryllithium reagent 12 is a synthetic equivalent of the d,a synthon 13. The reagent has been shown to add to vinyl sulfones and the resulting α-lithio sulfones undergo spontaneous intramolecular alkylation. For example, reaction of the aryllithium 12 with the sulfone 14 in diethyl ether (-78°C to room temperature) afforded the annulation product 15 in 78% yield (equation 4). This tetrahydronaphthalene annulation sequence could have considerable application in the synthesis of steroids and other polycyclic systems.

Compounds such as 16 (X = leaving group; M = Si or Sn) were first described by Trost as equivalents of synthetically valuable d,a synthons of the general structure 17. The former substances have been demonstrated to be very effective for the syntheses of five-membered rings. For example, treatment of the acetoxy allylsilane 18 with 2-cyclopenten-1-one (19) in the presence of catalytic amount of tetra-
kis(triphenylphosphine)palladium and bis(diphenylphosphino)ethane [dppe] in refluxing THF for 20 h gave the ketone 20 in 56% yield (equation 5). This reaction was one of the key steps in an elegant synthesis of hirsutene (21).
Mechanistically, the above reaction involves firstly the interaction of the acetoxyallylsilane 18 with palladium(0) complexes to give a \( \pi \)-allylpalladium intermediate 22 and acetate ion. Attack of the latter species on the silyl group results in the formation of the palladium complex 23, which attacks the electron deficient carbon-carbon double bond of the \( \alpha,\beta \)-unsaturated ketone 19 to afford the methylene cyclopropane annulation product 20 (Scheme 1).

\[ \text{Scheme 1} \]
An alternative approach which inverts the electronic sense of the reagents of general structure 16 has also been reported. In these cases, the reagents 16 still function as equivalents to the d,a synthon 17. For example, reaction of the potassium enolate of the ketone 24 with 3-iodo-2-(trimethylsilylmethyl)-1-propene (25) gave the alkylation product 26. Fluoride ion induced cyclization of the latter material afforded the alcohol 27 (equation 6).^8c

\[
\begin{align*}
\text{24} + \text{25} & \xrightarrow{\text{KH, DME}} \text{26} \\
\text{26} & \xrightarrow{\text{n-Bu}_4\text{NF, THF, 1h}} \text{27}
\end{align*}
\]

Recently, Danheiser has described the use of (trimethylsilyl)-allenes 28 as synthetic equivalents of the d,a synthon 29.\textsuperscript{9} For example, reaction of 2-cyclohexen-1-one (30) with the (trimethylsilyl)-allene 31 in the presence of titanium tetrachloride in dichloromethane at -78°C for 1 h gave regioselectively the (trimethylsilyl)cyclopentene annulation product 34 in 85% yield (equation 7).
The reaction is thought to involve firstly complexation of titanium tetrachloride with the enone to generate the alkoxy allylic carbocation 32, which is regioselectively attacked by the (trimethylsilyl)allene 31 to afford the vinyl cation 33. Such a cation is stabilized by interaction with the adjacent carbon-silicon bond. A 1,2-shift of the trimethylsilyl group, followed by interception of the isomeric vinyl cation by the titanium enolate, produces the annulated product 34 (Scheme 2).
II. Previous Work

Previous work in our laboratories had shown that the (trimethylstannyl)copper reagent 35 adds regioselectively to ω-substituted 1-alkynes 36 (X = leaving group or potential leaving group). Thus, treatment of 36 with 35 in THF at -78°C for 6 h provided efficiently the corresponding 2-(trimethylstannyl)-1-alkenes 37 (equation 8).10

The vinylstannanes 37 have been shown to serve as effective precursors of a number of bifunctional conjunctive reagents that are synthetic equivalents to the donor-acceptor synthons 38.11,12 Thus,
transmetalation of 5-chloro-2-(trimethylstannyl)-1-pentene (39) with methyllithium in THF at -78°C, followed by addition of anhydrous magnesium bromide-etherate, provided the corresponding Grignard reagent 40. In the presence of copper(I) bromide-dimethyl sulfide complex, this reagent underwent conjugate addition to enones 41. In some cases, addition of boron trifluoride-etherate significantly improved the yields of the reactions (equation 9). 12
The conjugate addition products 42 were readily cyclized by treatment with potassium hydride in THF (equation 10). As expected,\textsuperscript{12a} under such conditions, the "kinetic" products possessed a cis ring junction and in each case in which subsequent equilibration was not possible, a single, cis-fused annulated product was obtained. For example the adduct 45 cyclized to give only the cis-decalone 46 in 78% yield (equation 11).

In other cases, varying degrees of equilibration occurred under the conditions of cyclization and for the decalones, further equilibration gave the trans-decalones as the major products. For example the conjugate addition product 47 cyclized to give a 3.5:1 mixture of the decalones 48 and 49, respectively on treatment with potassium hydride in THF. After further equilibration with sodium methoxide in boiling methanol, a 1:2.8 mixture of the ketones 48 and 49, respectively was obtained (equation 12).
It can be seen that, in the above reactions, 5-chloro-2-(trimethylstannyl)-1-pentene (39) serves as a synthetic equivalent of the 1-pentene $d^2,a^5$ synthon (50). Use of the former substance as shown in the above examples provided a valuable methylenecyclohexane annulation sequence. The methylenecyclohexane moiety is a fairly common structural feature in the terpenoid family of natural products.

![Diagram](image-url)

Scheme 3
The utility of this methylenecyclohexane annulation process was demonstrated by its application to the synthesis of (±)-axamide-1 (53) and (±)-axisonitrile-1 (54). Thus, CuBrMe₂S-BF₃.Et₂O catalyzed addition of the Grignard reagent (40) to 2-methyl-2-cyclopenten-1-one (51), followed by treatment with potassium hydride in THF, afforded the annulation product 52 in 85% yield. After incorporation of the side chain and appropriate functional group manipulations, (±)-axamide-1 (53) and (±)-axisonitrile (54) were obtained (Scheme 3).

III. Isolation and Structural Elucidation of Palauolide (55)

In 1982 Sullivan and Faulkner isolated a new sesterterpenoid from the methanolic extract of a mixture of at least three different species of sponges collected from Palau, Western Caroline Islands. This new compound, which inhibited the growth of *Bacillus subtilis* and *Staphylococcus aureus* at 10 μg/disc, was named palauolide. It had the molecular formula C₂₅H₃₆O₃. Infrared bands at 3500 and 1740 cm⁻¹ indicated the presence of a γ-hydroxybutenolide moiety and an ultraviolet absorption at 322 nm (ε 17,000) indicated that the butenolide was further conjugated to two carbon-carbon double bonds. Signals at δ 5.95 (d, 1H, J = 11 Hz), 7.16 (dd, 1H, J = 15.5, 11 Hz), 6.28 (d, 1H, J = 15.5 Hz), 5.83 (s, 1H), and 6.26 (s, 1H) in the ¹H nmr spectrum of palauolide and a resonance at δ 15.18 (q) in the ¹³C nmr spectrum indicated the stereochemistry and the substitution pattern of this triene unit.
Comparison of the remaining signals in the $^{13}$C and $^1$H nmr spectra of palauolide (55) with those of illimaquinone (56) indicated that both substances have the same bicyclic ring system. This was further supported by the fact that chemical degradations of both substances led to the same diketone 57. Thus, the structure of palauolide (55) was established.

Although the carbon skeleton that comprises the bicyclic portion of palauolide is relatively common among sponge metabolites, the entire carbon framework of palauolide (55) had not been reported previously in the literature.
IV. Isolation and Structural Elucidation of Isolinaridial (60) and Isolinaridiol diacetate (61)

In 1982, San Feliciano et al.\textsuperscript{16} reported the isolation of a new ent-clerodane type\textsuperscript{*} diterpenoid from the hexane extract of the aerial part of \textit{Linaria saxatilis} (L.), a plant which grows in the northern and central part of Spain and in Portugal. The chemical composition of \textit{Linaria saxatilis} (L.) had not been studied previously.

The new compound showed two strong infrared bands at 1725 and 1675 cm\textsuperscript{-1} indicating the presence of saturated and $\alpha,\beta$-unsaturated carbonyl moieties. The signals at $\delta$ 9.93 (s, 1H), 9.45 (br s, 1H), 6.41 (br s, 1H, sharpened on irradiation at $\delta$ 9.93-9.45 and 6.41), 2.57 (m, 2H) in the $^1$H nmr spectrum indicated the presence of a (Z)-RCH$_2$CH=CH=CHO moiety in the molecule. The remaining signals in the $^1$H nmr spectrum and the ir spectrum of the new compound indicated the presence of clerodane-type bicyclic substructure. This new substance was chemically transformed into solidagolactone (62) (see Scheme 4), an ent-clerodane, the structure and absolute stereochemistry of which had already been established by Okazaki et al.\textsuperscript{17} Thus, structure 60 was proposed for the

\* According to Rowe's nomenclature,\textsuperscript{15} structures 58 and 59 with absolute stereochemistry indicated are referred to as clerodane and ent-clerodane, respectively. For detailed discussion, see F. Piozzi, \textit{Heterocycle}, 15, 1489 (1981).
new compound and it was named isolinaridial, since it is structurally closely related to the diterpenoid linaridial (63), which was isolated earlier by Kitagawa et al.\textsuperscript{18} from \textit{Linaria japonica} (Scheme 4).

In 1985, the same Spanish group reported the isolation from \textit{Linaria
saxatilis (L.) of another *ent*-clerodane-type diterpenoid having a carbon skeleton identical with that of isolinaridial (60). This new compound showed IR absorptions due to acetoxy groups at 1745, 1240, 1030 cm\(^{-1}\). In the \(^1\)H NMR spectrum, signals at \(\delta 1.97, 1.91\) (s, s, 3H each) also indicated the presence of two acetate groups. Saponification of this new diterpene and lithium aluminum hydride reduction of isolinaridial (60) led to the same diol 64 (Scheme 5), which was named isolineridiol. Thus structure 61 was proposed for the new diterpenoid and was named isolinaridiol diacetate.

![Scheme 5](image)

V. Previous Syntheses of Clerodane-type Diterpenoids

The terpenoids, palauolide (55), isolinaridol (64) and isolinaridiol diacetate (61) had not been synthesized prior to the work described in this thesis. However, the syntheses of a number of *trans*-fused clerodane type diterpenoids had been reported. Thus, the total syntheses of (±)-annonene (65), (±)-ajugarin-IV (66), (±)-ajugarin-I (67), (±)-4-epi-ajugarin, (±)-maingayic acid (68), and (-)-methyl kolavenate (69) had been carried out.
In the following discussion, which reviews briefly the above syntheses, the strategies employed for the construction of the decalin substructure of the clerodane diterpenoids will be emphasized.

Kende et al.,21 and de Groot et al.,23 employed basically the same approach for the construction of the decalin moiety. Starting with a suitable derivative of the Wieland-Miescher ketone (70), reductive alkylation provided a trans-ring junction and produced the desired stereochemistry at C-9. A suitable sequence of reactions then introduced the required secondary methyl group at C-8. For example, in the total synthesis of (±)-ajugarin-IV,21 reductive alkylation of the enone 71 with allyl bromide afforded the ketone 72. The latter material was converted into the conjugated ketone 73 in five steps. Lithium-ammonia reduction of 73 in the absence of an alcohol provided ketone 74, which was converted into (±)-ajugarin-IV (66) (Scheme 6).
Kakisawa et al.\textsuperscript{20} also employed the Wieland-Miescher ketone (70) as a starting material for the syntheses of (±)- annonene (65). Furthermore, they also used an alkali metal-ammonia reduction to provide the trans-fused ring junction (Scheme 7). However, they employed a Claisen rearrangement process to introduce the required side chain at C-9. This reaction was found to be less stereoselective than the reductive alkylation mentioned above and provided an 85:15 mixture of the aldehydes 75 and 76, respectively. Subsequent catalytic hydrogenation of the carbon-carbon double bond in 75 provided the aldehyde 77, which was converted into (±)- annonene (65) (Scheme 7).
Ley et al.\textsuperscript{22} employed a very different approach and built up the required decalin system from the keto dithioacetal 78. In this case, the necessary C-8 and C-9 substituents were already present in compound 78 and an annulation sequence was employed to construct the carbon skeleton of ring A. Thus, compound 78 was treated with \((\text{CH}_2=\text{CHCH}_2\text{CH}_2)\text{CuMgBr}\) to provide the olefin 79, which was treated success-
ively with borane-dimethyl sulfide complex and hydrogen peroxide-sodium hydroxide to give the alcohol 80. The latter material was oxidized to the aldehyde 81 which underwent an aldol condensation to provide the enone 82 (Scheme 8). The remaining appendages were added stereoselectively to the annulated product 82 to give 83, which was converted into (±)-ajugarin-I (67) (Scheme 8).

Scheme 8
A slightly different approach was employed by Tokoroyama et al.\textsuperscript{24a} in the total synthesis of (±)-maingayic acid (68). Reaction of \(3,4\)-dimethyl-2-cyclohexen-1-one (84) with \(\text{CH}_2=\text{CHMgBr.}(\text{n-Bu}_3\text{PCuI})_4\) complex, followed by trapping of the resulting enolate anion with formaldehyde provided the alcohol 85. Mesylation of the latter material gave compound 86 which was treated successively with \([\text{RCH}_2\text{COCH}^\text{CO}_2\text{CH}_3]\text{Na}^+\) and methanolic hydrogen chloride, to afford the decalone 87 (Scheme 9). The C-5 substituent was then introduced. By a proper choice of conjugate addition reagent, either the \textit{trans}-fused or \textit{cis}-fused bicyclic product could be obtained selectively. For example, treatment of the enone 87a successively with \(\text{Me}_2\text{CuLi}\), formaldehyde, methanesulfonyl chloride, and 1,8-diazabicyclo[5.4.0]undec-7-ene provided the \textit{cis}-fused decalone 88 (equation 13). On the other hand, treatment of 87b with diethylaluminum
cyanide provided the trans-fused decalone 89 stereoselectively (Scheme 10). Thus, this approach provided access to both the trans- and cis-clerodane systems. The nitrile 89 was converted into (±)-maingayic acid (68) (Scheme 10).

![Scheme 10](image)

Recently, the Japanese group employed the same method to construct the bicyclic substructure of (-)-methyl kolavenate (69). The starting material was the enantiomerically pure (R)-3,4-dimethyl-2-cyclohexen-1-one (90), which was converted into the optically active decalone 91. Hydrocyanation of the latter material provided the nitrile 92, which was converted into (-)-methyl kolavenate (69) (Scheme 11).

In addition to the syntheses of clerodane-type diterpenoids summarized above, Goldsmith et al. and Kato et al. have reported prelimi-
nary studies on the potential application of a Diels-Alder reaction in the construction of the clerodane decalin substructure. Both groups chose the substituted quinone 93 as the starting material and constructed the decalin skeleton in the first step. For example, a Diels-Alder reaction of the diene 94 with the quinone 93, followed by suitable reductions and equilibration, provided the ketone 95. Subsequent successful transformation of 95 into the ketone 96 and the nitrile 97 opened up a new potential route to the total synthesis of clerodanes (Scheme 12).

A distinctly different synthetic approach to the synthesis of clerodanes has been reported by ApSimon et al. Instead of introducing the side chain into the decalin by alkylation, they made use of the
cleavage of the cyclic hemiacetal 98 to prepare 99. The key intermediate 98 was prepared in five steps, which included the condensation of 2-methyl-1,3-cyclohexadione (100) with the hydroxy α,β-unsaturated ketone 101, the catalytic hydrogenation of the condensation product 102, the addition of methyl magnesium bromide to the hydrogenation product 103, dehydration of the resultant alcohol 104, and the hydration of the enol ether function in 105 (see Scheme 13). Provided that the necessary vicinal methyl groups at C-8 and C-9 can be introduced stereoselectively, compound 98 would be a valuable intermediate for the total synthesis of clerodanes.
Scheme 13
VI. Aim

As mentioned previously, a new methylenecyclohexane annihilation sequence had been developed in our laboratory. Furthermore, as also noted earlier, there are a fair number of known naturally occurring terpenoids that possess a methylenecyclohexane moiety as part of their carbon skeleton. In the annihilation reaction between 3-methyl-2-cyclohexen-1-one (106) and the Grignard reagent 40, the decalone 49 is obtained as the major product (Scheme 14). The latter material possesses the same relative stereochemistry at the ring junction and the same methylenecyclohexane moiety as the natural products palauolide (55), isolinaridiol (64) and isolinaridiol diacetate (61). Thus, it was decided to attempt the total syntheses of these natural products via reaction sequences in which the methylenecyclohexane annulation process would play a key role.
DISCUSSION

I. Total Synthesis of (±)-Palauolide (55)

A. Retrosynthetic Analysis

Our retrosynthetic analysis of (±)-palauolide (55) was based on the premise that the decalin substructure of this substance would be prepared readily by use of the methylenecyclohexane annulation method discussed in the Introduction section of this thesis.

Disconnection of the carbon-carbon double bond α to the butenolide moiety, along with suitable functionalization of the resultant fragments, would provide the α,β-unsaturated aldehyde 107 and the stabilized phosphorane 108. It was expected that the phosphorane 108 would couple with the aldehyde 107 to give primarily the desired E olefin. The phosphorane 108 was anticipated to be available from the chloride 109, which, in turn, should be preparable from the 2-trimethylsilylfuran 110. Recently, 2-trimethylsilylfuran derivatives have been successfully photo-oxygenated to afford γ-hydroxy butenolides.²⁸

Suitable retrosynthetic functional group interconversions of the aldehyde 107 would provide the nitrile 111. Disconnection at the carbon-carbon bond joining the side chain and the bicyclic system, along with suitable functionalization of the resultant fragments, would provide the nitrile 112 and the homoallylic iodide 113. Alkylation of the nitrile 112 with the latter substance would, for steric reasons, be
Retrosynthetic Scheme of Palauolide
expected to take place with the desired stereochemistry to form the required nitrile \textit{111}. Disconnection of the nitrile group of \textit{112}, along with introduction of a suitable functional group, would provide the ketone \textit{114}. The latter material was anticipated to be the thermodynamically most stable product derived from a methylenecyclohexane annulation reaction involving the vinylstannane \textit{39} and the enone \textit{115}. Thus, the correct relative stereochemistry of three of the chiral centers in the bicyclic ring system was expected to be installed at the annulation stage of the synthesis.

A retrosynthetic disconnection, along with suitable functional group interconversions involving the homoallylic iodide \textit{113}, would provide the \textit{Z} chloro pentenoate \textit{116}. This ester was expected to be available from the chloro pentynoate \textit{117}. Previous work in our laboratories had shown that the elements of trimethylstannane can be added regioselectively to \textit{\alpha,\beta}-acetylenic esters and that the stereochemistry of such additions may be controlled by a judicious choice of reagents and reaction conditions.\textsuperscript{29}

\textbf{B. Synthesis of the nitrile \textit{112}}

3-Methyl-2-cyclohexen-1-one (\textit{106}) was kinetically deprotonated by treatment with lithium diisopropylamide in THF at -78°C. The resultant enolate anion was allowed to react with iodomethane to afford, on the basis of a glc analysis and \textsuperscript{1}H nmr spectroscopy, exclusively the desired 3,6-dimethyl-2-cyclohexen-1-one (\textit{115}) in 93\% yield (equation 14).\textsuperscript{30} The
ir spectrum of 115 exhibited an absorption at 1672 cm\(^{-1}\), indicating the presence of an \(\alpha,\beta\)-unsaturated six-membered ring ketone. The \(^1\)H nmr spectrum of 115 exhibited a broad singlet at \(\delta 1.96\) due to the vinyl methyl group and a doublet at \(\delta 1.13\) (\(J = 7\) Hz) due to the secondary methyl group.

\[
\text{106} \quad \xrightarrow{1. \text{LDA, THF, } -78^\circ\text{C}} \quad \text{115}
\]

Equation 14

Reaction of the (trimethylstannyl)copper(I) reagent 35\(^{10}\) with 5-chloro-1-pentyne (118)* in THF at \(-78^\circ\text{C}\) for 6 h afforded, on the basis of a glc analysis, a mixture of the desired chloro vinylstannane 39 and its isomer 119\(^{31}\) in a ratio of 85:15, respectively (equation 15). Fortunately, when this mixture was subjected to (slow) column chromatography on silica gel, only the desired vinylstannane 39 was recovered (62% yield).\(^{10}\) However, when the mixture was subjected to flash column chromatography, both isomers could be recovered, but were not cleanly separated. After a solution of a mixture of these two isomeric materials in aqueous acetic acid-THF had been stirred at room temperature for 12 h, only the vinylstannane 39 was recovered (30%). Glc analysis indicated total disappearance of the other isomer. These experiments indicated that while both isomers are susceptible to acid-catalyzed destannylation, the minor isomer 119 is more labile.

* This material is commercially available from Aldrich Chemical Company.
The $^1H$ nmr spectrum of 39 showed signals due to two olefinic protons ($H_A$ and $H_B$) as a pair of doublet of triplets at $\delta$ 5.71 ($J = 2.5, 1.2$ Hz, $J_{Sn-H} = 150$ Hz) and 5.23 ($J = 2.5, 0.8$ Hz, $J_{Sn-H} = 70$ Hz), respectively.

The vinylstannane 39 was transmetalated by addition of an ethereal solution of methyllithium to a THF solution of 39 at $-78^\circ$C. The resultant vinyllithium reagent 120 was converted into the corresponding Grignard reagent 40 by addition of solid magnesium bromide-etherate. Successive addition of copper(I) bromide-dimethyl sulfide complex, boron trifluoride-etherate and the enone 115 gave a bright yellow slurry which was stirred at $-78^\circ$C for 3 h. After appropriate workup, a mixture of two epimeric chloro ketones 121 was obtained in 77% yield (equation 16).

The ir spectrum of 121 exhibited absorptions at 1705 and 905 cm$^{-1}$, indicating the presence of a saturated six-membered cyclic ketone and a terminal double bond, respectively.

Upon exposure to potassium tert-butoxide in tert-butyl alcohol at
30°C for 12 h, the chloro ketones 121 underwent intramolecular alkylation and the initially formed annulation product(s) was (were) equilibrated to produce a 94:6 mixture of the ketones 114 and 122, respectively in 89% yield (equation 17). A pure sample of each isomer was obtained by subjecting a portion of the crude product to column chromatography on silica gel impregnated with 25% silver nitrate.

\[
\text{Cl} \quad \text{O} \quad \text{O} \quad \text{Cl} \quad \text{O} \quad \text{O} \\
\text{121} \quad \text{114} \quad \text{122} \\
+ \quad \text{94:6}
\]

The \(^1\text{H}\) nmr spectrum of the major product 114 showed signals due to the olefinic protons (\(\delta\) 4.70, broad singlet), the secondary methyl group (\(\delta\) 0.99, doublet, \(J = 6\) Hz) and the angular methyl group (\(\delta\) 0.87, singlet). By correlation of the latter value with the chemical shifts of the angular methyl groups in trans- and cis-1-decalones (\(\delta\) 0.75-0.9 and 1.05-1.20, respectively), as reported by Boeckman et al.,\(^{33}\) 114 was tentatively assigned a trans-fused ring junction.

The \(^1\text{H}\) nmr spectrum of 122 exhibited two olefinic signals at \(\delta\) 4.74 and 4.63. The signals due to the angular and the secondary methyl groups appeared at \(\delta\) 1.31 and 0.98 (\(J = 6\) Hz), respectively. By correlation of the former value with Boeckman's data, 122 was tentatively assigned a cis-fused ring junction.

Since there are two epimerizable chiral centres in the annulation product(s), four isomeric products, possessing structures 114, 123, 122, and 124, could have been produced. Based on conformational analysis,
structures 114 and 122 (see conformations 114a and 122a) would be expected to be more stable than structures 123 and 124 (conformations 123a and 124a). Molecular mechanics calculations (MM2)\textsuperscript{34} predicted that structure 114 would be more stable than structure 122 by \(-0.7\) kcal mol\(^{-1}\). Although this energy difference is not large enough to result in an equilibrium ratio of 94:6, the calculation did indicate that the major annulation product should be the \textit{trans} isomer 114.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{structures.png}
\caption{Structures 114, 123, 122, and 124.}
\end{figure}

Lithium aluminum hydride reduction of the ketone 114 (diethylether solution, room temperature, 3 h) afforded exclusively the axial alcohol 125 in 84\% yield (equation 18). The stereoselectivity of this reduction is primarily due to the fact that approach of the hydride reagent to the \(\alpha\)-face of the ketone is hindered by the angular methyl group, whereas \(\beta\) attack is relatively unhindered. On the other hand, dissolving metal reduction (calcium, liquid ammonia) of the ketone 114 at \(-33^\circ C\) for 10 min afforded stereoselectively the thermodynamically more stable equatorial alcohol 126 in 75\% yield (equation 19).
The IR spectrum of 125 showed a broad absorption at 3490 cm\(^{-1}\), indicating the presence of an alcohol group. The \(^1\)H NMR spectrum of 125 exhibited a broad singlet at \(\delta 3.56\) for the \(\text{>CH}_2\text{OH}\) proton. The fact that this proton was only weakly coupled with its vicinal neighboring protons indicated that it was equatorially oriented.\(^{34a}\) The alcohol 126 exhibited a broad IR absorption at 3300 cm\(^{-1}\). The \(^1\)H NMR spectrum showed a triplet at \(\delta 3.04\) (\(J = 9\) Hz) for the \(\text{>CH}_2\text{OH}\) proton. Thus, in this case, it was clear that the carbinol proton was in an axial orientation.\(^{34a}\)

Treatment of the alcohol 126 with p-toluenesulfonyl chloride in the presence of 4-N,N-dimethylaminopyridine in dichloromethane at room temperature for 12 h afforded the p-toluenesulfonate 127 in 83% yield (equation 20). Reaction of the latter material 127 with sodium cyanide in HMPA at 80°C for 3 h provided the axial nitrile 112a in 44% yield (equation 21).
The IR spectrum of 112a exhibited a nitrile absorption at 2225 cm$^{-1}$. In the $^1$H NMR spectrum of 112a the >CH-CN proton appeared as a triplet of doublets at $\delta$ 2.60 ($J = 4.5, 1.3 \text{ Hz}^*$), indicating that this proton is equatorially orientated. The signal due to the angular methyl group was strongly deshielded by the nitrile group (1,3 diaxial relationship) and appeared at $\delta$ 1.24. This chemical shift may be compared with that of the angular methyl group of 126 ($\delta$ 0.98). These observations further supported the assignment of a trans-fused ring junction to ketone 114, since successive metal-ammonia reduction, tosylation, and nitrile formation on the cis-fused 1-decalone 122 would not give a nitrile in which the angular methyl group could be deshielded by the nitrile group (Scheme 15).

The preparation of the desired nitrile 112 from the ketone 114 via

* The origin of the small coupling ($J = 1.3 \text{ Hz}$) is not known.
the route described above was both tedious and low yielding. Therefore, a more direct route was investigated. Treatment of a 94:6 mixture of the ketones 114 and 122, respectively, with p-toluenesulfonylmethyl isocyanide\textsuperscript{35} and potassium tert-butoxide in HMPA at 45°C for 88 h gave, based on a glc analysis, a 15:85 mixture of nitriles 112a and 112b, respectively, in 68% yield (equation 22).

\begin{align*}
\text{114} + \text{122} & \xrightarrow{\text{CH}_3\text{-SO}_2\text{CH}_2\text{NMe}_3^- , \text{tert-BuOK, HMPA}} \text{112a} + \text{112b} \quad (22) \\
15:85
\end{align*}

Column chromatography of a portion of this mixture on silica gel impregnated with 25% silver nitrate afforded a pure sample of each compound. The minor isomer exhibited spectra identical with those of the axial nitrile 112a obtained from the route described earlier. The major isomer exhibited a nitrile absorption at 2225 cm\(^{-1}\) in the ir
spectrum. The $^1$H nmr spectrum showed a triplet at $\delta$ 2.08 ($J = 11.5$ Hz) for the $>\text{CH-CN}$ proton, indicating that this proton was axially orientated, and a singlet at $\delta$ 0.96 for the angular methyl group, indicating that the methyl group was not 1,3 diaxial to the nitrile group (cf. the angular methyl of 112a appeared at $\delta$ 1.24). Since the rest of the $^1$H nmr spectrum was very similar to that of the minor isomer, the major isomer was assigned structure 112b.

The exclusive formation of the trans-fused nitriles 112a and 112b is in accord with reports that trans-1-decalones usually react faster with nucleophiles than the corresponding cis-1-decalones. Therefore, under reaction conditions in which the two ketones are in equilibrium, the products are expected to be derived mainly or even solely from the trans-1-decalone.$^{36}$ For example, Marshall et al.$^{37}$ reported that treatment of a 2:1 mixture of the 1-decalones 128 and 129, respectively, with methylene-triphenylphosphorane in dimethyl sulfoxide afforded an 87:13 mixture of the trans- and cis-fused alkenes 130 and 131, respectively (equation 23). Kato et al.$^{26b}$ reported that treatment of the ketone 96 with $p$-toluenesulfonylmethylisocyanide and potassium tert-butoxide produced only the trans-fused nitrile 97 (equation 24).

$$
\begin{align*}
& \begin{array}{c}
\text{Ketone} \\
128
\end{array} +
\begin{array}{c}
\text{Ketone} \\
129
\end{array} \\
\xrightarrow{\text{Ph$_3$P=CH$_2$}}
\begin{array}{c}
\text{Alkene} \\
130
\end{array} +
\begin{array}{c}
\text{Alkene} \\
131
\end{array} \\
\text{DMSO} \\
\text{2:1} & \text{87:13}
\end{align*}
$$

(23)
When a 15:85 mixture of the nitriles 112a and 112b, respectively, was deprotonated with lithium diisopropylamide in HMPA*-THF at 0°C and the resultant anion was alkylated with n-butyl iodide, only the nitrile 132 was obtained in 92% yield (equation 25). This result further supported the earlier conclusion that the nitriles 112a and 112b are epimeric only at the carbon bearing the nitrile group. The high stereoselectivity of the alkylation is probably due to the fact that alkylation of the nitrile anion from the α face of the molecule is sterically hindered by the angular methyl group whereas the β face is relatively unhindered. Thus, predominant or exclusive formation of the nitrile 132 would be expected.

* Treatment of a THF solution of 15:85 mixture of the axial and equatorial nitriles 112a and 112b, respectively, with lithium diisopropylamide in the absence of HMPA, followed by addition of iodo- methane, provided a 15:85 mixture of the alkylated product and the original equatorial nitrile 112b, respectively. Thus, under these conditions, only the axial nitrile 112a underwent deprotonation.
The $^1$H nmr spectrum of 132 exhibited a singlet at $\delta$ 1.26 due to the angular methyl group, which is deshielded by the axial nitrile (1,3 diaxial relationship). It may be recalled that the angular methyl groups of the axial and equatorial nitriles 112a and 112b appeared at $\delta$ 1.24 and 0.96, respectively. The exclusive formation of 132 demonstrated that a high stereochemical control of the desired relative stereochemistry of the newly formed chiral centre is possible.

C. Synthesis of the homoallylic iodide 113

Reaction of 3-butyn-1-ol* (133) with phosphorus trichloride-dimethyl-formamide$^{38}$ at room temperature for 40 min afforded, after two careful fractional distillations of the crude product, the volatile chloro alkyne 134$^{10}$ in 42% yield (equation 26). It was necessary that the reagents and solvent be carefully purified before use, otherwise no desired material was obtained.

\[ \text{HO} \xrightarrow{\text{PCl}_3 \cdot \text{DMF}} \text{Cl} \]

\[ 133 \quad 134 \quad \text{(26)} \]

The ir spectrum of 134 exhibited absorptions at 3000 and 2120 cm$^{-1}$, indicating the presence of a terminal alkyne function. The $^1$H nmr spectrum of 134 showed a triplet at $\delta$ 3.63 ($J = 7$ Hz) for the $-\text{CH}_2\text{Cl}$

* This alcohol is commercially available from Aldrich Chemical Company.
protons, a doublet of triplets at $\delta$ 2.68 ($J = 2.5, 7$ Hz) for the $\text{-CH}_2\text{CH}_2\text{Cl}$ protons and a triplet at $\delta$ 2.11 ($J = 2.5$ Hz) for the acetylenic proton.

A solution of the chloro alkyne 134 in THF was treated with an ethereal solution of methyllithium at -78°C. The resultant acetylenic anion was allowed to react with ethyl chloroformate at -20°C for 1 h and then at room temperature for 1 h. After appropriate workup and column chromatography of the crude product on silica gel, the required acetylenic ester 117 was obtained in 63% yield (equation 27). The ir spectrum of 117 showed the acetylene and carbonyl absorptions at 2235 and 1710 cm$^{-1}$, respectively.

\[
\begin{align*}
\text{Cl} & \equiv \equiv \\
1. \text{MeLi, THF} & \rightarrow \\
\text{Cl} & \equiv \equiv \text{CO}_2\text{Et} \\
2. \text{ClCO}_2\text{Et} & \rightarrow 117
\end{align*}
\]

(27)

Reaction of lithium (trimethylstannyl)(phenylthio)cuprate 135 with the acetylenic ester 117 in THF at -48°C for 4 h afforded a 4:1 mixture of the desired ester 116 and the bis(trimethylstannyl) compound 136, respectively (equation 28). When this mixture was subjected to careful fractional distillation and column chromatography, a pure sample of each compound was obtained. The ir spectrum of 116 showed an absorption at 1704 cm$^{-1}$, indicating the presence of an $\alpha,\beta$-unsaturated ester group. The $^1$H nmr spectrum of 116 exhibited a broad triplet at $\delta$ 3.56 due to the $\text{ClCH}_2$-protons and a triplet at $\delta$ 6.43 ($J = 1.1$ Hz, $J_{\text{Sn-H}} = 114$ Hz) due to the olefinic proton. The coupling constant $J_{\text{Sn-H}}$ of 114 Hz indicated that this product possessed the $Z$ geometry.
The IR spectrum of 136 exhibited a carbonyl absorption at 1702 cm\(^{-1}\) while the \(^1\)H NMR spectrum showed two signals (\(\delta 0.22, 0.12\)) due to the trimethylstannyl groups. Furthermore, a multiplet at \(\delta 0.83\) due to the Me\(_3\)SnCH\(_2\)CH\(_2\)- protons indicated that the chlorine had been replaced by a trimethylstannyl group. This conclusion was supported by the high resolution mass spectrum of 136 which indicated that the M\(^+\)-CH\(_3\) peak had a mass corresponding to C\(_{12}\)H\(_{25}\)O\(_2\)\(^{120}\)Sn\(_2\).

This nucleophilic substitution of a chloride by a trimethylstannyl group had not been observed previously in our laboratories when similar reactions had been carried out on higher homologues of the acetylenic ester 117.\(^4\) In order to eliminate the undesired substitution reaction, the synthetic route for preparing the homoallylic iodide 113 was modified by replacing the chlorine atom by a tert-butyldimethylsilyloxy group (Scheme 16).
Reaction of 3-butyn-1-ol (133) with tert-butyldimethylsilyl chloride in the presence of imidazole in dimethylformamide at room temperature for 12 h afforded the alkyne 137 in 98% yield (equation 29). The ir spectrum of 137 showed absorptions at 3300 and 2100 cm\(^{-1}\), indicating the presence of a terminal alkyne. A solution of the latter material 137 in THF was treated with methyllithium at -78°C. The resultant anion was allowed to react with ethyl chloroformate at -20°C for 1 h and then at room temperature for 1 h. The required pentyonoate 138 was obtained in 90% yield (equation 30). The ir spectrum of 138 showed absorptions at 2230 and 1705 cm\(^{-1}\), indicating the presence of an alkyne and a conjugated ester carbonyl group, respectively.

\[
\begin{align*}
\text{HO} & \quad \text{TBDMSCl, imidazole} \quad \text{DMF} \\
\text{133} & \quad \text{SiO} \quad \text{137}
\end{align*}
\]

Treatment of the pentyonoate 138 with lithium (trimethylstannyl)(phenylthio)cuprate 135 in THF at -40°C for 9 h afforded, after workup, the Z ester 139 in 91% yield (equation 31). The \(^1\)H nmr spectrum of 139 exhibited a singlet at \(\delta 0.18\) (J\(_{\text{Sn-H}}\) = 52/54 Hz), indicating the presence of a trimethylstannyl group. The olefinic proton appeared at
δ 6.40 as a triplet (J = 1 Hz, J_{Sn-H} = 120 Hz). The value of J_{Sn-H} confirmed the Z geometry of the ester.\textsuperscript{32} The \textsuperscript{1}H nmr spectrum also showed singlets at δ 0.90 and 0.04 due to the methyl protons of the tert-butylsilyloxy group, confirming that the ether linkage was intact.

Diisobutylaluminum hydride reduction of the ester 139 in THF at -78°C for 1 h and then at 0°C for 1 h provided the allylic alcohol 140 in 96% yield (equation 32). The ir spectrum of 140 showed a broad absorption at 3350 cm\(^{-1}\), indicating the presence of a hydroxy group. The \textsuperscript{1}H nmr spectrum of 140 showed a triplet at δ 4.08 (J = 6 Hz, collapsed to a doublet on D\(_2\)O exchange), indicating the presence of an allylic alcohol group. Reaction of the alcohol 140 with chloromethyl methyl ether in the presence of diisopropylethylamine in dichloromethane at room temperature for 12 h afforded the ether 141 in 90% yield (equation 33). The \textsuperscript{1}H nmr spectrum of 141 showed a singlet at δ 4.63 for the acetal protons and a singlet at δ 3.38 for the methoxy protons, indicating that the methoxymethoxy group had been installed.
The vinylstannane 141 was transmetalated with methyllithium in THF at -78°C. The resultant vinyllithium reagent was treated with iodomethane to give the E olefin 142 in 90% yield (equation 34). The $^1$H nmr spectrum of 142 exhibited a broad singlet at δ 1.69 due to the vinyl methyl group.

The silyl ether linkage in compound 142 was cleaved by treatment of this material with tetra-$n$-butylammonium fluoride in THF at room temperature for 40 min. The alcohol 143 was produced in 98% yield (Scheme 17). The ir spectrum of 143 exhibited a broad absorption at 3400 cm$^{-1}$ due to the hydroxy group. Reaction of the alcohol 143 with p-toluenesulfonyl chloride in the presence of 4-$N,N$-dimethylaminopyridine in dichloromethane at room temperature for 12 h gave, after appropriate workup and column chromatography of the crude product, the p-toluenesulfonate 144 in 75% yield (Scheme 17). This material decomposed on heating under vacuum and slowly turned brown on storage.
under argon in a freezer. The $^1$H nmr spectrum of 144 showed two doublets at $\delta$ 7.83 ($J = 8$ Hz) and 7.37 ($J = 8$ Hz) and a singlet at $\delta$ 2.48 due to the p-toluenesulfonate group. The p-toluenesulfonate 144 was readily converted into the iodide 113 by treatment with sodium iodide in dimethylformamide at room temperature in the dark for 4 days (91% yield, Scheme 17). The overall yield for the synthesis of the homoallylic iodide 113, based on the starting 3-butyln-1-ol (133), was 42%. The high resolution mass spectrum of 113 showed a molecular ion at m/e 270.0111, consistent with a formula of C$_8$H$_{15}$O$_2$I.

An attempt to by-pass the p-toluenesulfonation step by conversion of the alcohol 143 directly into the iodide 113 using triphenylphosphine diiodide gave the desired material 113 in only 21% yield (equation 35).
D. Alkylation of the nitrile 112 with the iodide 113. Attempts to prepare compound 145

Treatment of a 15:85 mixture of the nitriles 112a and 112b, respectively (1 mmol), in THF at 0°C with lithium diisopropylamide (1.2 mmol) in the presence of HMPA for 15 min, was followed by addition of the homoallylic iodide 113 (1.3 mmol). The resultant solution was gradually warmed to room temperature. Workup gave a mixture of the starting material, 112a and 112b (0.23 mmol), the desired alkylated nitrile 111 (0.69 mmol; 94% yield based on recovery of starting material), and the diene 146 (equation 36).
The presence of the diene 146 indicated that an elimination reaction was in competition with the desired alkylation process. Thus, the nitrile anion functioned not only as a nucleophile (displacement of iodide), but also as a base that effected dehydrohalogenation of the homoallylic iodide 113.

The $^1$H nmr spectrum of the alkylated material 111 showed that it consisted of only one compound (Fig. 1). The signals due to the angular methyl group appeared at $\delta$ 1.27, indicating that the methyl was 1,3 diaxial to the nitrile group and that the product with the expected relative stereochemistry had been obtained. The singlets at $\delta$ 4.62, 3.38 and 1.68 were due to the acetal protons, methoxy protons and vinyl methyl protons, respectively, on the side chain. The ir spectrum of 111 showed absorptions at 1671 and 1638 cm$^{-1}$, indicating the presence of the trisubstituted double bond and the exocyclic double bond, respectively.

The $^1$H nmr spectrum of 146 showed three singlets at $\delta$ 4.65, 3.40 and 1.80 due to the acetal, methoxy and vinyl methyl protons, respectively, and a doublet at $\delta$ 4.22 ($J = 7$ Hz) due to the -CH$_2$OMOM protons. The remaining signals at $\delta$ 6.43 (dd, 1H, $J = 11, 17$ Hz, $H_A$), 5.63 (br t, 1H, $J = 7$ Hz, $H_B$), 5.23 (d, 1H, $J = 17$ Hz, $H_C$), 5.05 (d, 1H, $J = 11$ Hz, $H_D$) indicated the presence of a diene unit with the stereochemistry shown.

It is evident that the synthetic sequence discussed above had produced a product 111 in which the relative stereochemistry of the four chiral centres on the decalin substructure of palauolide (55) had been correctly established. The next required transformation was the conversion of the nitrile group into a methyl group.
Figure 1: The 400MHz $^1$H nmr spectrum of compound 111
When the nitrile 111 was treated with diisobutylaluminum hydride at room temperature in benzene, ether, THF or dimethoxyethane, no reduction occurred and the nitrile 111 was recovered intact. On the other hand, when the reduction was carried out in benzene at 80°C for 8 h, all the starting material was consumed. After aqueous workup and aqueous acid hydrolysis of the crude product, there was obtained, on the basis of $^1$H nmr spectroscopy, a 4:1 mixture of two aldehydes. The $^1$H nmr spectrum of this mixture showed two aldehyde proton signals at δ 9.98 and 9.93. The former signal was due to the major component which was later found to be the desired aldehyde 147. No further work was carried out to determine the structure of the minor component. Fortunately, reduction of the nitrile in dimethoxyethane at 60°C for 6 h gave, after workup and aqueous acid hydrolysis of the crude product, only the desired aldehyde 147 in 87% yield (equation 37). The intermediate imine 148 was rather insensitive to the aqueous acid workup, and the aldehyde 147 was obtained only after the imine had been stirred in an aqueous THF-acetic acid solution at room temperature for 12 h. The ir spectrum of the imine 148 showed a broad absorption at 3254 cm$^{-1}$ due to the N-H group. The ir spectrum of the aldehyde 147 exhibited a strong absorption at 1713 cm$^{-1}$ due to the carbonyl. In the $^1$H nmr spectrum of 147, the
aldehyde proton appeared at $\delta$ 9.98 as a singlet and the angular methyl group gave rise to a singlet at $\delta$ 0.96.

To generate the required methyl substituent, the aldehyde 147 was treated with an excess of anhydrous hydrazine (10 equiv) in methanol under reflux for 24 h. The resultant hydrazone 149, which exhibited a broad absorption at 3250 cm$^{-1}$, was allowed to react with potassium hydroxide in diethylene glycol at 210°C for 3 h. The reaction mixture gradually turned from colorless to dark brown. Workup and column chromatography of the crude product provided two different oils (equation 38).

The more polar component was isolated in 10% yield and its spectra were consistent with those expected for the desired deoxygenated material 145. Thus, the $^1$H nmr spectrum of this material showed singlets at $\delta$ 4.63, 3.37 and 1.66 due to the acetal, methoxy and vinyl methyl protons, respectively, on the side chain. It also exhibited a broad singlet at $\delta$ 4.51 due to the exocyclic olefinic protons and methyl signals at $\delta$ 1.05 (singlet), 0.82 (doublet, $J = 6$ Hz), and 0.74
(singlet). The chemical shifts of these signals associated with the
decaline substructure of 145 were almost exactly the same as those
reported for palauolide (55)\textsuperscript{14} [cf. \( \delta 4.51 \) (s, 2H), 1.05 (s, 3H), 0.82
(d, 3H, \( J = 7 \) Hz), and 0.74 (s, 3H)].

The less polar product from the Wolff-Kishner reduction was isolated
in 45\% yield. It exhibited an ir band at 1594 cm\(^{-1}\), indicating the
presence of a diene moiety.\textsuperscript{42} This conclusion was supported by signals
at \( \delta 6.45 \) (dd, 1H, \( J = 10, 16 \) Hz, \( H_A \)), 5.20 (d, 1H, \( J = 16 \) Hz, \( H_B \)), 5.04
(d, 1H, \( J = 10 \) Hz, \( H_C \)), 4.97 (br t, 1H, \( J = 6 \) Hz, \( H_D \)), 1.70 (br s, 3H,
vinyl methyl) in the \(^{1}\hbox{H} \) nmr spectrum of this material and the
disappearance of the signals due to the methoxymethoxy group. The three methyl groups of the decalin substructure appeared at δ 1.06 (singlet), 0.82 (doublet, J = 6 Hz) and 0.78 (singlet). These chemical shifts were similar to those of the corresponding signals in the 1H nmr spectrum of 145. Thus, structure 150 was assigned to this less polar material.

The Wolff-Kishner reduction of 147 was carried out in diethylene glycol in the presence of anhydrous potassium carbonate, a milder base, and the reaction temperature was slowly raised from 110° to 180°C. Tlc analysis of aliquots of the reaction mixture indicated that there was no reaction until the reaction temperature reached 160°C. Furthermore, both products 145 and 150 appeared simultaneously.

The 3-proton vinyl methyl group signal at δ 1.70 in the 1H nmr spectrum of the diene 150 indicated that the elimination reaction leading to this substance was highly regioselective. This selectivity can be accounted for by postulating an intramolecular reaction mechanism in which the incipient carbanion resulting from decomposition of the hydrazone group abstracts an allylic proton from the side chain via a five-membered cyclic transition state (see Scheme 18). If this postulate is correct, it is apparent that the elimination reaction via the cyclic transition state competes relatively well with the desired
intermolecular protonation of the carbanion by the solvent, diethylene glycol (Scheme 18).

When the hydrazone 149 was treated with potassium tert-butoxide in dimethylsulfoxide at room temperature, only the diene 150 was isolated, in 36% yield (equation 39).

In an attempt to slow down the elimination process, it was decided to convert the methoxymethoxy group on the hydrazone 149 to a hydroxy
group. Thus, the aldehyde 147 was treated with dimethylboron bromide in dichloromethane (-78°C, 1 h) to afford the alcohol 151 in 72% yield (equation 40). The ir spectrum of 151 showed absorptions at 3366 and 1714 cm$^{-1}$ due to the hydroxy group and the carbonyl group, respectively. The $^1$H nmr spectrum of 151 exhibited a singlet at $\delta$ 9.98 due to the aldehyde proton and a doublet at $\delta$ 4.14 ($J = 8$ Hz) due to the $=\text{CCH}_2\text{OH}$ protons.

The aldehyde 151 was allowed to react with anhydrous hydrazine in refluxing methanol for 24 h. However, treatment of the resultant hydrazone with potassium hydroxide or potassium carbonate in diethylene glycol at 170°C for 3 h afforded the diene 150 as the only isolable product (equation 41).

Since all these attempts to convert the aldehyde 147 into the
bicyclic diene 145 using the Wolf-Kishner reduction, failed to give the desired product in synthetically useful yields, other deoxygenation methods were investigated. Thus, the aldehyde 147 was reduced with lithium aluminum hydride (ether solution, room temperature) to the alcohol 152 (93%, equation 42). The ir spectrum of 152 showed a broad absorption at 3469 cm\(^{-1}\) due to the hydroxy group. The \(^1\)H nmr spectrum of 152 exhibited a pair of doublet of doublets at \(\delta\) 3.80 and 3.70 (\(J = 6, 12\) Hz) due to the \(-\text{CH}_2\text{OH}\) protons, and each of them collapsed to a doublet (\(J = 12\) Hz) on D\(_2\)O exchange. These signals also showed a positive enhancement in a nuclear Overhauser enhancement difference experiment in which the signal (\(\delta\) 1.06) due to the angular methyl group was irradiated. This experiment confirmed the expectation that the \(-\text{CH}_2\text{OH}\) and angular methyl groups are in 1,3 diaxial relationship in the alcohol 152.

\[
\begin{align*}
\text{OHC} & \quad \begin{array}{c}
\text{147} \\
\end{array} \\
\text{1. LiAlH}_4, \text{Et}_2\text{O} & \quad \begin{array}{c}
\text{152} \\
\end{array} \\
\text{2. Na}_2\text{SO}_4, 10\text{H}_2\text{O} & \\
\end{align*}
\]

The alcohol 152 was converted into the corresponding xanthate 153 and the latter substance was subjected to Barton's deoxygenation conditions. Thus, successive treatment of a solution of the alcohol 152 in dimethylformamide with 1,8-diazabicyclo[5.4.0]undec-7-ene, carbon disulfide, and iodomethane afforded, after column chromatography of the crude product on silica gel, the xanthate 153 (100%, equation 43).
The $^1$H nmr spectrum of 153 showed a singlet at $\delta$ 2.57 due to the $\text{-SCH}_3$ protons. The high resolution mass spectrum of 153 showed a molecular ion at m/e 440.2410, consistent with a formula of $\text{C}_{24}\text{H}_{40}\text{S}_{2}\text{O}_3$.

Following the conditions normally employed for Barton deoxygenation, a toluene solution of the xanthate 153 and tri-$n$-butyltin hydride in the presence of 2,2'-azobisisobutyronitrile (AIBN) was refluxed for 4 h. However, no deoxygenation occurred and the xanthate 153 was recovered intact. It is pertinent to note that both Barton and Fraser-Reid have reported that xanthates of some primary alcohols failed to undergo the desired deoxygenation.

Recently, Barton et al. have reported that sterically hindered primary alcohols can be deoxygenated efficiently when a $p$-cymene solution of tri-$n$-butyltin hydride is added slowly to a $p$-cymene solution of the corresponding xanthates at 150°C. Under these conditions, the solution contains a very low concentration of tin hydride and in the case of our xanthate 153, it is certainly possible that the neopentyl radical 154 formed would cyclize onto the double bond of the side chain before it would abstract a hydrogen atom from the tin hydride. Nevertheless, the reaction was carried out and a mixture of compounds was obtained. On the basis of $^1$H nmr spectroscopy, the
mixture consisted of at least four compounds which were not separable by column chromatography on silica gel. No further work was carried out to determine the structure of these compounds.

More recently, Robins et al. reported that phenylthionocarbonate esters of alcohols undergo deoxygenation more readily than the corresponding xanthates. Furthermore, the deoxygenation reaction could be carried out in the presence of an excess of tin hydride. Thus, it was felt that, under these conditions, the neopentyl radical 154, if it was formed, might abstract a hydrogen from n-Bu₃SnH rather than cyclize.

Treatment of the alcohol 152 with phenoxythiocarbonyl chloride in acetonitrile in the presence of 4-N,N-dimethylaminopyridine provided the thionocarbonate 155 (40%, equation 44). The ir spectrum of 155 exhibited an absorption at 1729 cm⁻¹. The ¹H nmr spectrum of 155 showed
a 2-proton triplet at $\delta$ 7.40 ($J = 8$ Hz), a 1-proton triplet at $\delta$ 7.27 ($J = 8$ Hz), and a 2-proton doublet at $\delta$ 7.40 ($J = 8$ Hz) due to the phenyl group, indicating that the phenylthionocarbonate functional group had been installed.

Reaction of the thionocarbonate 155 with tri-n-butyltin hydride (10 equiv., 0.41 M solution in toluene) in the presence of AIBN (radical initiator) at 70°C for 3 h afforded cleanly, but rather surprisingly, the methyl ether 156 (75%, equation 45).

The $^1$H nmr spectrum of 156 showed a pair of doublets at $\delta$ 3.39 ($J = 10$ Hz) and 3.21 ($J = 10$ Hz) due to the MeOCH$_2$C protons and two 3-proton singlets at $\delta$ 3.38 and 3.74 due to the two methoxy groups. The mass spectrum of 156 showed a molecular ion consistent with a formula of C$_{23}$H$_{40}$O$_3$.

The formation of 156 can be rationalized on the basis of the postulated reaction mechanism of Barton deoxygenation of alcohols. Recently, Beckwith et al. have gathered evidence that suggests that the deoxygenation proceeds via the following pathway: Reaction of an O-alkyl-S-methyl dithiocarbonate(xanthate) 157 with a trialkyltin radical affords an alkoxythiocarbonyl radical 158 (see Scheme 19). The latter species, which has been detected by electron spin resonance
spectroscopy undergoes slow $\beta$-fission to give an alkyl radical 159 and carbon oxysulfide 160. The alkyl radical 159 reacts with trialkyltin hydride to give the alkane 161 (Scheme 19).

If this mechanism operates in the reaction of our thionocarbonate 155 with $n$-Bu$_3$SnH, the substrate 155 would be converted initially into the alkoxythiocarbonyl radical 162 (see Scheme 20). Since the reaction was carried out in the presence of a relatively high concentration of $n$-Bu$_3$SnH (0.4 M), the radical 162 could abstract a hydrogen atom from $n$-Bu$_3$SnH (to give 163) rather than undergo (slow) $\beta$-fission to the corresponding alkyl radical 164. Further reduction of 163 via the thioacetal radical 165, the thioacetal 166, and the alkoxyalkyl radical 167 would afford the methyl ether 156 (Scheme 20).

Pete et al. have reported that irradiation of acetates of primary, secondary, tertiary and some highly hindered alcohols in a 5% aqueous hexamethylphosphoramide solution with ultraviolet light (254 nm) at room
Scheme 20

(1) \( \text{PhCO} \quad 155 \) \[ \text{n-Bu}_3\text{Sn}^+ \] \( \text{R} \quad \text{S=CO} \) \( \text{R} \quad + \text{n-Bu}_3\text{SnOPh} \)

(2) \( \text{n-Bu}_3\text{SnH} \)

(3) \( \text{n-Bu}_3\text{Sn}^+ \) \( \text{R} \quad \text{S=CO} \) \( \text{R} \quad + \text{n-Bu}_3\text{Sn}^+ \)

(4) \( \text{n-Bu}_3\text{SnH} \)

(5) \( \text{n-Bu}_3\text{Sn}^+ \)

(6) \( \text{n-Bu}_3\text{SnH} \)

\( \text{MeO} \) \( 156 \) \( + \text{n-Bu}_3\text{Sn}^+ \)
temperature gives good to excellent yields of the desired deoxygenated products. The radical mechanism they propose for this process is similar to that of Barton deoxygenation. Treatment of the alcohol 152 with acetic anhydride in pyridine in the presence of 4-\text{N},\text{N}-dimethylamino-pyridine (catalyst) afforded the acetate 168 (95%, equation 46).

\[
\begin{align*}
\text{HO} & \quad \text{Ac}_2\text{O}, \text{pyridine} \\
152 & \quad \rightarrow \\
\text{MeCO} & \quad 168
\end{align*}
\]

The ir spectrum of 168 exhibited a strong absorption at 1741 cm$^{-1}$ due to the carbonyl group. The $^1$H nmr spectrum of 168 showed a 3-proton singlet at $\delta$ 2.06 due to the acetyl protons, indicating that the acetate had been formed.

However, when the acetate 168 was subjected to the photolytic deoxygenation conditions described above for 3 h, no reaction occurred (tlc analysis).

Since all of the above-described attempts to deoxygenate the alcohol 152 failed to give useful yields of the desired material 145, it was decided to investigate the Ireland deoxygenation. Following Ireland's procedure, the alcohol 152 was treated with $n$-butyllithium and bis(dimethylamino)phosphorochloridate in a 4:1 mixture of dimethoxy-ethane and $\text{N},\text{N},\text{N}',\text{N}''$-tetramethylethylenediamine (TMEDA) at room temperature for 12 h. However, no reaction took place and the starting material was recovered. Liu et al. have reported the use of
dimethylaminophosphorodichloridate to prepare phosphorodiamidates of highly hindered alcohols. Thus, a solution of the alcohol 152 in a 4:1 mixture of dimethoxyethane and TMEDA was treated successively with n-butyllithium for 30 min and dimethylaminophosphorodichloridate for 12 h at room temperature, and then with anhydrous dimethylamine at 0°C for 2 h. Column chromatography of the crude product on silica gel provided the phosphorodiamidate 169 (71%, equation 47).

The $^1$H nmr spectrum of 169 exhibited two broad 6-proton singlets at $\delta$ 2.69 and 2.66 due to the $\text{P(\text{NMe}_2)_2}$ protons, indicating that the phosphorodiamidate group had been installed.

Reaction of 169 with a solution of lithium in anhydrous ethylamine in the presence of tert-butyl alcohol at 0°C for 30 min afforded the over-reduction product 170 in 75% yield (equation 48). The $^1$H nmr spectrum of 170 showed a quartet at $\delta$ 5.16 ($J = 7$ Hz) due to the olefinic proton.
in the side chain, a broad doublet at $\delta$ 1.55 ($J = 7$ Hz) and a broad singlet at $\delta$ 1.58 due to the vinyl methyl groups. These signals, along with the fact that resonances due to the methoxymethoxy group were not present, indicated that the allylic ether linkage had been cleaved. However, the chemical shifts of the signals due to the olefinic protons and the methyl groups on the decalin portion of 170 [$\delta$ 4.50 (s, 2H), 1.05 (s, 3H), 0.82 (d, 3H, $J = 6$ Hz), 0.74 (s, 3H)] were almost exactly the same as those reported for palauolide (55) [$\delta$ 4.51 (s, 2H), 1.05 (s, 3H), 0.82 (d, 3H, $J = 7$ Hz), 0.74 (s, 3H)]. These data indicated that the relative stereochemistry of the decalin substructure of 170 was the same as that of palauolide (55).

In an attempt to avoid the reductive cleavage of the methoxymethoxy group, the reaction of the phosphorodiamidate 169 with a solution of lithium in ethylamine in the presence of tert-butyl alcohol was carried out at -48°C and was quenched prematurely after 15 minutes. A mixture of the starting material 161 and a new compound was obtained. The $^1$H nmr spectrum of the latter material showed that the phosphorodiamidate group was intact while the methoxymethoxy group had been cleaved. This suggested that reductive cleavage of the methoxymethoxy group was occurring preferentially to the reductive removal of the phosphoro-
diamidate group.

In an attempt to avoid the loss of the allylic oxygen function on the side chain, the acetal linkage on 169 was cleaved to the corresponding alcohol 171. It was hoped that, during the reduction process, the alcohol function would exist largely as an alkoxide and, therefore, would be less susceptible to reductive cleavage than the methoxymethoxy group. Thus, the phosphorodiamidate 169 was treated with dimethylboron bromide in dichloromethane at -78°C for 1 h to afford the allylic alcohol 171 (65%, equation 49).

\[
\begin{align*}
\text{169} & \xrightarrow{1. \text{Me}_2\text{BBr}, \text{CH}_2\text{Cl}_2, -78^\circ\text{C}} \text{171} \\
\end{align*}
\]

The ir spectrum of 171 exhibited a broad absorption at 3350 cm\(^{-1}\). The \(^1\text{H}\) nmr spectrum of 171 showed a triplet at \(\delta 5.40\) (J = 7 Hz) due to the olefinic proton in the side chain, a doublet at \(\delta 4.13\) (J = 7 Hz) due to the \(-\text{CH}_2\text{OH}\) protons, and two 6-proton doublets at \(\delta 2.66\) (J = 4 Hz) and 2.64 (J = 4 Hz) due to the \(-\text{PO(NMe}_2\text{)}_2\) protons.

Treatment of 171 with a solution of lithium in ethylamine in the presence of tert-butyl alcohol at 0°C also led to an over-reduction product, the ir and \(^1\text{H}\) nmr spectra of which were identical with that of 170 (equation 50).
E. Alkylation of the nitrile 112 with the iodide 172. Preparation of the \( \alpha,\beta \)-unsaturated aldehyde 107

Of the various deoxygenation methods tried (see previous section), it appeared that only the Ireland deoxygenation was capable of reducing the \(-\text{CH}_2\text{OH}\) group to a methyl group in a clean and synthetically useful yield. However, this method also resulted in reductive cleavage of the allylic alkoxy group on the side chain attached to the decalin substructure. Clearly this undesired side reaction could be avoided if the double bond was installed after the deoxygenation. Thus, the synthetic plan to construct the \( \alpha,\beta \)-unsaturated aldehyde 107 from the nitrile 112 was modified according to the following plan (see Scheme 21). It was expected that alkylation of the nitrile 112 with the alkyl iodide 172 would be stereoselective. Conversion of the resultant product 173 into the phosphorodiamidate 174, followed by reduction of the latter substance would be expected to afford cleanly the ether 175. A
Scheme 21
straightforward sequence of reactions would effect the conversion of 175 into the methyl ketone 176. Reaction of the latter material with the anion of a trialkyl phosphonoacetate was expected to give the \( \alpha,\beta \)-unsaturated ester 177 as the major product. Finally, reduction of the ester 177 would give the desired aldehyde 107. Indeed, this plan worked very well and its execution is described in the following paragraphs.

Reaction of 3-chloro-1-propanol (178) with chloromethyl methyl ether in the presence of diisopropylethylamine in dichloromethane gave 3-chloro-1-methoxymethoxypropane 179 (80\%). Treatment of the latter material with sodium iodide in acetone at 60\(^\circ\)C in the dark for 30 h gave 3-iodo-1-methoxymethoxypropane (172) in 70\% yield (equation 51). Vigorous reflux of the reaction mixture led to a low yield of the iodide 172 and the formation of side products.

\[
\begin{align*}
\text{Cl} & \quad \text{CH}_3\text{OCH}_2\text{Cl} \\
\text{178} & \quad \text{i-Pr}_2\text{NET}, \text{CH}_2\text{Cl}_2 \\
\rightarrow & \\
\text{Cl} & \quad \text{CH}_2\text{O} \quad \text{O} \\
\text{179} & \quad \text{NaI, 60}^\circ\text{C} \\
\rightarrow & \\
\text{I} & \quad \text{CH}_2\text{O} \quad \text{O} \\
\text{172} & \quad \text{acetone}
\end{align*}
\]

(51)

The \(^1\text{H} \text{nmr} \) spectrum of 172 exhibited two singlets at \( \delta = 4.63 \) and \( \delta = 3.40 \) due to the acetal and methoxy protons, respectively. The triplets at \( \delta = 3.60 \) (\( J = 6 \text{ Hz} \)) and \( \delta = 3.30 \) (\( J = 6 \text{ Hz} \)) were due to the \( -\text{CH}_2\text{CH}_2\text{O}- \) and \( -\text{CH}_2\text{I} \) protons, respectively, and the quintet at \( \delta = 2.05 \) (\( J = 6 \text{ Hz} \)) was
due to the \(-\text{CH}_2\text{CH}_2\text{CH}_2-\) protons.

A 15:85 mixture of the nitriles 112a and 112b, respectively, was treated with lithium diisopropylamide in THF at 0°C in the presence of hexamethylphosphoramide. Addition of the iodide 172, followed by stirring of the resultant solution at 0°C for 30 min and at room temperature for 1 h, gave the alkylated nitrile 173 in 99% yield (equation 52). Glc analysis and $^1$H nmr spectroscopy showed that only one alkylation product had been formed.

The ir spectrum of 173 showed absorptions at 2228 and 1638 cm$^{-1}$ due to the nitrile group and the exocyclic olefin, respectively. The $^1$H nmr spectrum of 173 exhibited a singlet at $\delta$ 1.27 due to the angular methyl group, indicating that this group was in a 1,3 diaxial relationship to the nitrile function. (Note that the angular methyl protons of 112a and 112b appeared at $\delta$ 1.24 and 0.96, respectively). The signals due to the acetal protons and one of the olefinic protons overlapped and appeared at $\delta$ 4.59.

Following the procedures developed earlier for the transformation of the nitrile 111 into the phosphorodiamidate 169, the nitrile 173 was converted into the corresponding phosphorodiamidate.
Thus, diisobutylaluminum hydride reduction of the nitrile 173 in dimethoxyethane at 60°C for 6 h, followed by acid catalyzed hydrolysis of the resultant product, provided the aldehyde 180 in 85% yield (equation 53).*

\[ \text{173} \xrightarrow{1. 	ext{DIBAL-H, DME, 60°C}} \xrightarrow{2. \text{HOAc-H}_2\text{O-THF}} \text{180} \]

The ir spectrum of 180 exhibited a strong absorption at 1713 cm\(^{-1}\) due to the carbonyl group. The \(^1\text{H nmr}\) spectrum 180 showed a singlet at \(\delta 9.53\) due to the aldehyde proton, a doublet at \(\delta 1.02\) (\(J = 6\) Hz) due to the secondary methyl protons, and a singlet at \(\delta 0.98\) due to the angular methyl protons.

The aldehyde 180 was treated with an ethereal solution-suspension of lithium aluminum hydride at room temperature. After workup, the

* An attempt to deoxygenate the aldehyde 180 using the Wolff-Kishner reduction failed. No desired product was isolated.
alcohol \( \text{181} \) was obtained in 91% yield (equation 54). The IR spectrum of \( \text{181} \) exhibited a broad absorption at 3462 cm\(^{-1}\) due to the hydroxyl group. The \(^1\)H NMR spectrum of \( \text{181} \) showed a pair of doublets at \( \delta 3.78 \) (\( J = 12 \) Hz) and \( \delta 3.70 \) (\( J = 12 \) Hz) due to the -CH\(_2\)OH protons.

A solution of the alcohol \( \text{181} \) in a 4:1 mixture of dimethoxyethane and \( \text{N,N,N',N'}\)-tetramethylethylenediamine, respectively, at room temperature, was treated successively with \( n \)-butyllithium and dimethylaminophosphorodichloridate. The resultant solution was treated with anhydrous dimethylamine at 0°C for 2 h. After workup and column chromatography of the crude product on silica gel, the phosphorodiamidate \( \text{174} \) was obtained in 88% yield (equation 55).

The \(^1\)H NMR spectrum of \( \text{174} \) showed a pair of doublet of doublets at \( \delta 4.00 \) (\( J = 4, 12 \) Hz) and \( \delta 3.95 \) (\( J = 4, 12 \) Hz) due to the -CH\(_2\)OPO-protons. It also showed a pair of doublets at \( \delta 2.66 \) (\( J = 4 \) Hz) and
2.64 (J = 4 Hz) due to the \(-\text{PO(NMe}_2\text{)}_2\) protons, indicating the presence of the phosphorodiamidate group.

The phosphorodiamidate 174 was subjected to Ireland deoxygenation. Reaction of 174 with an anhydrous ethylamine solution of lithium in the presence of \textit{tert}-butyl alcohol at 0°C for 10 min\(^{52}\) gave a 1:1 mixture of the desired deoxygenated material 175 and an over-reduced product 182 in which the carbon-carbon double bond on the bicyclic substructure had also been reduced (equation 56). The ratio of products was improved to 2:1, in favour of 175, when the reaction was carried out at \(-10^\circ\text{C}\) for 5 min. This experiment suggested that the phosphorodiamidate group could be reduced selectively under suitable conditions. When a more dilute ethylamine solution of lithium was employed for the reaction, the selectivity improved to 25:1 in favour of the desired material 175. However, when this reaction was carried out on a larger scale, the selectivity dropped. Fortunately, when the reduction was carried out in
anhydrous methylamine in the absence of tert-butyl alcohol at -20°C for 10 min, the phosphorodiamidate group was reduced selectively and 175 was obtained in 81% yield (equation 57).

The ir spectrum of 175 showed absorptions at 1636 and 891 cm⁻¹ due to the exocyclic double bond. The ¹H nmr spectrum of 175 (Fig. 2) exhibited two singlets at δ 1.04 and 0.73, and a doublet at δ 0.80 (J = 6 Hz) due to the methyl substituents on the bicyclic moiety. That the C-5 angular methyl protons appeared at lower field (δ 1.04) than the C-9 methyl protons (δ 0.73) was probably due to the fact that the former experienced a deshielding anisotropic effect from the adjacent exocyclic olefin. The ¹H nmr spectrum of 175 also showed three distinct signals at δ 2.28 (br dt, 1H, J = 5, 13.5 Hz), 2.09 (br d, 1H, J = 13.5 Hz), and 1.87 (br d, 1H, J = 12 Hz). These signals did not overlap with one another and were well separated from the remaining signals. In a decoupling experiment, irradiation at δ 4.49 (olefinic protons) caused the signal at δ 2.28 to sharpen. This result suggested that the latter signal was due to an allylic proton, and based on its appearance (br dt, J = 5, 13.5 Hz), it was assigned to proton A. On irradiation of proton HA at δ 2.28, the broad doublet at δ 2.09 became a broad singlet and was therefore assigned to proton B. Irradiation of proton HA also caused the broad doublet at δ 1.87 to sharpen and, thus, this resonance was assigned to HC. The ¹H nmr spectra of other compounds in this series exhibited similar signals in the region δ 2.3-1.8 and these signals were assigned on the basis of the decoupling experiments carried out on compound 175, as described above.
Figure 2: The 400 MHz $^1$H nmr spectrum of compound 175
A pure sample of the over-reduction product 182 was obtained by treatment of the phosphorodiamidate 174 with an anhydrous ethylamine solution of lithium in the presence of tert-butyl alcohol at 0°C for 20 min (equation 58).

The ir spectrum of the overreduction product 182 did not show the characteristic absorptions at 1635 and 890 cm\(^{-1}\) due to the exocyclic olefin. The \(^1\)H nmr spectrum of 182 exhibited two doublets at \(\delta 0.78\) and \(\delta 0.73\) due to the secondary methyl protons, and two singlets at \(\delta 0.77\) and \(\delta 0.70\) due to the tertiary methyl protons. The C-4 methyl group was assumed to be in an equatorial orientation since dissolving metal reduction usually lead to the thermodynamically more stable product. The high resolution mass spectrum of 182 showed a peak at m/e 296.2707, corresponding to the molecular ion with a formula of \(\text{C}_{19}\text{H}_{36}\text{O}_2\).

Treatment of 175 with pyridinium \(p\)-toluenesulfonate in tert-butyl
alcohol \(^5\) at 70°C for 12 h gave the alcohol 183 (91\%, equation 59). Vigorous reflux of the reaction solution led to a significant amount of a side product in which the olefinic double bond had isomerized into the ring. The ir spectrum of 183 showed a broad absorption at 3319 \(\text{cm}^{-1}\) due to the hydroxyl group and absorptions at 1635 and 891 \(\text{cm}^{-1}\) due to the exocyclic olefin.

![Chemical structure image](image)

The alcohol 183, upon oxidation with pyridinium chlorochromate in the presence of anhydrous sodium acetate in dichloromethane (room temperature, 1 h), afforded the aldehyde 184 (99\%, equation 60). The ir spectrum of 184 showed a strong absorption at 1728 \(\text{cm}^{-1}\) due to the carbonyl group. The \(^1\text{H}\) nmr spectrum of 184 exhibited a triplet at 6 9.74 (\(\text{j} = 2 \text{ Hz}\)) due to the aldehyde proton.

![Chemical structure image](image)

Reaction of the aldehyde 184 with methyllithium in ether at 0°C gave a mixture of epimeric alcohols 185 (see equation 61). The ir spectrum
of the latter material showed a broad absorption at 3349 cm\(^{-1}\) due to the hydroxy group. The high resolution mass spectrum of 185 showed a peak at m/e 264.2455, corresponding to a molecular ion with a formula of C\(_{18}\)H\(_{32}\)O. Subsequent oxidation of the mixture of epimeric alcohols 185 with pyridinium chlorochromate in the presence of sodium acetate in dichloromethane provided the methyl ketone 176 in an overall yield of 97\% (from the aldehyde 184) (equation 61). The ir spectrum of 176 exhibited a strong absorption at 1718 cm\(^{-1}\) due to the carbonyl group. The \(^1\)H nmr spectrum of 176 exhibited a singlet at \(\delta\) 2.13 due to the -COCH\(_3\) protons, indicating the presence of a methyl ketone.

It should be noted that the ketone 176 has been prepared by Sharma et al.\(^{56}\) via a route very different from that described above. The \(^1\)H nmr and ir spectroscopic data reported\(^{56}\) for this material were identical with those derived from our material.

It is well-known that under suitable conditions, treatment of an unsymmetrical ketone with the salt of a phosphonoacetate gives the trans ester as the major product.\(^{57}\) Indeed, reaction of the ketone 176 (65 \(\mu\)mol) with [EtO\(_2\)C\(\text{CHPO(OEt)}\)]\(\text{K}^+\) (0.7 mmol) in THF (3 mL) at room temperature for 15 h provided, in nearly quantitative yield, a 10:1 mixture of 177 and its geometric isomer 186. These two products were
readily separable by column chromatography on silica gel (equation 62).

Both the ir spectra of 177 and 186 exhibited an absorption at 1718 cm$^{-1}$ due to the carbonyl group of the ester. In the $^1$H nmr spectrum of 177, the vinyl methyl protons and the -CH$_2$(CH$_3$)C= protons appeared at $\delta$ 2.14 (d, $J = 1.5$ Hz) and $\delta$ 2.02-1.78 (m), respectively. On the other hand, the $^1$H nmr spectrum of 186 showed a doublet at $\delta$ 1.85 ($J = 1.3$ Hz) due to the vinyl methyl protons and a pair of broad doublets of triplets at $\delta$ 2.32 ($J = 5, 12$ Hz) and $\delta$ 2.24 ($J = 5, 12$ Hz) due to the -CH$_2$(CH$_3$)C= protons. Since the allylic protons on the same side of the double bond as the ester group in an $\alpha,\beta$-unsaturated ester would experience an anisotropic magnetic deshielding effect from the carbonyl group, compound 177 was assigned the E stereochemistry, while 186 was assigned the Z stereochemistry.

The $\alpha,\beta$-unsaturated ester 177, upon treatment with diisobutylaluminium hydride in THF at -78°C for 1 h and 0°C for 2 h, afforded the allylic alcohol 187 in 98% yield (equation 63). The ir spectrum of 187 showed a broad absorption at 3327 cm$^{-1}$ indicating the presence of the hydroxyl group. The $^1$H nmr spectrum of 187 exhibited a doublet at $\delta$ 4.12 ($J = 8$ Hz) due to the =CCH$_2$OH protons.
Manganese(IV) oxide oxidation of the alcohol 187 in hexane provided the key intermediate, the $\alpha,\beta$-unsaturated aldehyde 107, in 88% yield (equation 64). The IR spectrum of 107 exhibited an absorption at 1676 cm$^{-1}$ due to the conjugated carbonyl group. The $^1$H nmr spectrum of 107 showed a doublet at $\delta$ 9.97 (J = 8 Hz) due to the aldehyde proton and a broad doublet at $\delta$ 5.86 (J = 8 Hz) due to the olefinic proton on the side chain (Fig. 3).

**F. Synthesis of the phosphonium salt 188**

Recently, Katsumura et al. reported a very efficient synthesis of $\gamma$-hydroxybutenolides by photosensitized oxygenation of substituted
Figure 3: The 270 MHz $^1$H nmr spectrum of compound 107
2-trimethylsilylfurans. For example the silylfuran 189a could be transformed readily into the butenolide 190a in 91% yield (equation 65). It was expected that the phosphonium salt 188 could be synthesized from the chloro butenolide 109, and that the latter material could be prepared from 4-chloromethyl-2-trimethylsilylfuran (110) (Scheme 22).

![Chemical structure of 189a and 190a with reaction conditions](image)

\[ \text{O}_2, \text{iodo-halogen lamp} \]
\[ \mathrm{tetraphenylphosphin} \]
\[ -78^\circ \text{C}, \text{CH}_2\text{Cl}_2, 5 \text{ min} \]

Scheme 22

Following the chemistry reported by Goldsmith et al.\textsuperscript{58} and Tanis et al.\textsuperscript{59}, the furan 110 was prepared from 3-furanmethanol (189) in six steps in an overall yield of 45% (equations 66 to 71). 3-Furanmethanol (189) (6 mmol) was treated with n-butyllithium (13 mmol) in THF at 0°C. The resultant dianion was treated with diphenyldisulfide at 0°C for 12 h to give regioselectively the furan alcohol 190 (81%, equation 66). The \(^1\text{H} \text{nmr spectrum of 190 exhibited two doublets at } \delta 7.59 (J = 2 \text{ Hz})\) and
δ 6.65 (J = 2 Hz) due to the furan protons, a 5-proton multiplet at δ 7.25-7.15 due to the phenylthio group, and a triplet at δ 1.62 (J = 5 Hz) due to the hydroxyl proton. The latter signal underwent D₂O exchange.

The alcohol 190 was treated with tert-butyldimethylsilyl chloride in the presence of imidazole in dimethylformamide at room temperature to give the furan 191 (95%, equation 67). The ¹H nmr spectrum of 191 exhibited a 9-proton singlet and a 6-proton singlet at δ 0.91 and δ 0.07, respectively, due to the silyl protecting group, indicating that the latter had been installed.

An ethereal solution of the furan 191 (4.7 mmol) was treated with n-butyllithium (5.2 mmol). The resultant mixture was treated with trimethylsilyl chloride at 0°C for 48 h to give the silylfuran 192 (83%, equation 68). The ¹H nmr spectrum of 192 exhibited a broad singlet at δ
6.85 due to the furan proton and 9-proton singlet at δ 0.38 due to the trimethylsilyl group.

An ethanolic solution of the phenylthiofuran 192 (2.6 mmol) was refluxed in the presence of Raney nickel (7 g)* for 3 h to provide the furan derivative 193 in 90% yield (equation 69). An excess of Raney nickel led to an over-reduced tetrahydrofuran derivative. The 1H nmr spectrum 193 showed two broad singlets at δ 7.56 and δ 6.60 due to the furan protons.

Treatment of compound 193 with a 3:1:1 mixture of acetic acid, water and THF, respectively, at room temperature for 12 h provided the...

*Raney nickel is commercially available as a 50% slurry in water, pH 10, from Aldrich Chemical Co. The reagent was washed three times with distilled water and six times with distilled absolute ethanol before use. The required quantity (~2.7 g per mmol of the phenylthiofuran 192) of Raney-nickel was obtained by weighing together with a minimum amount of ethanol under an atmosphere of argon.
alcohol 194 (99%, equation 70). The ir spectrum of 194 showed a broad absorption at 3326 cm\(^{-1}\) due to the hydroxy group. The \(^1\)H nmr spectrum of 194 showed two broad singlets at \(\delta 7.60\) and 6.66 due to the furan protons, and a singlet at \(\delta 0.30\) due to the trimethyl silyl group.

\[
\text{HOAc-H}_2\text{O-THF} \quad \text{rt, 12h} \quad \text{Me}_3\text{Si} \quad \text{OH} \quad (70)
\]

The alcohol 194 was treated with a mixture of lithium chloride, \(\sigma\)-collidine and methanesulfonyl chloride in dimethylformamide at 0°C for 2 h to give the chloride 110 in 79% yield (equation 71). The \(^1\)H nmr spectrum of 110 exhibited a singlet at \(\delta 4.45\) due to the \(-\text{CH}_2\text{Cl}\) protons.

\[
\text{LiCl, MeSO}_2\text{Cl}, 0^\circ\text{C} \quad \text{\sigma-collidine, DMF} \quad \text{Me}_3\text{Si} \quad \text{OH} \quad \text{Cl} \quad (71)
\]

With the acquisition of 4-chloromethyl-2-trimethylsilylfuran (110), the stage was set for the critical photosensitized oxygenation. Following the conditions reported by Katsumura \textit{et al.}, a cold (-78°C) dichloromethane solution of 110 (10 mmol), containing a catalytic amount of tetraphenylporphin, was irradiated with a halogen-tungsten lamp (325W) while oxygen was bubbled through the solution. After a reaction
time of 27 min, the solution was concentrated and the residue was dissolved in methanol. The resultant solution was stirred for 12 h at room temperature. After workup and column chromatography of the crude product on silica gel, the (chloromethyl)butenolide 109 was obtained in 78% yield (equation 72). The ir spectrum of 109 showed a broad absorption at 3357 cm⁻¹ due to the hydroxy group and an absorption at 1736 cm⁻¹ due to the carbonyl group. The ¹H nmr spectrum of 109 showed a 2-proton broad singlet at δ 6.21 due to the vinyl and >CH₂OH protons, whose signals overlapped with one another. The signals due to the hydroxy and -CH₂Cl protons appeared at δ 4.80 and δ 4.37, respectively.

\[
\begin{align*}
1. & \text{O}_2, \text{light} \\
& \text{tetraphenylphorphin} \\
& \text{CH}_2\text{Cl}_2, -78^\circ\text{C} \\
\rightarrow & \text{MeOH, rt} \\
\end{align*}
\]

(72)

Recently, Faulkner et al.⁶¹ reported that photosensitized oxygenation of 3-substituted furans 195 in the presence of diisopropylethylamine at 0°C provides regioselectively the corresponding γ-hydroxy butenolides 196 (equation 73). This approach makes the presence of the
trimethylsilyl group on the furan ring unnecessary and thus shortens substantially the route to \(\gamma\)-hydroxybutenolides.

The \(\gamma\)-hydroxybutenolide 109, upon treatment with a methanolic solution of \(p\)-toluenesulfonic acid at room temperature for 12 h, was readily transformed into the methoxybutenolide 197 in 92\% yield (equation 74). The ir spectrum of 197 exhibited absorptions at 1800 and 1768 cm\(^{-1}\) due to the carbonyl group. It is known that the carbonyl absorption of a \(\delta\)-butenolide is split in the presence of an \(\alpha\) vinyl proton.\(^{62}\) The \(\text{^1H nmr}\) spectrum of 197 showed a multiplet at \(\delta\) 6.20 and a broad singlet at \(\delta\) 5.80 due to the vinyl proton and the \(>\text{CHOMe}\) proton, respectively. The spectrum also showed a singlet at \(\delta\) 3.61 due to the methoxy group.

\[
\begin{align*}
109 & \xrightarrow{\text{MeOH, TsOH, rt}} & 197 \\
\end{align*}
\]

Treatment of the chloride 197 with triphenylphosphine in refluxing benzene provided the phosphonium salt 188 in 70\% yield (equation 75).

\[
\begin{align*}
197 & \xrightarrow{\text{Ph\textsubscript{3}P, benzene, reflux}} & 188 \\
\end{align*}
\]
The $^1$H nmr spectrum of 188 exhibited a broad multiplet at $\delta$ 6.00 due to the $\text{-CH}_2\text{PPh}_3$ protons.

With the phosphonium salt 188 now available, it was possible to investigate the reaction of the corresponding phosphorane with some $\alpha,\beta$-unsaturated aldehydes.

G. Conversion of $\gamma$-methoxybutenolides into $\gamma$-hydroxybutenolides

Prior to the investigation of the olefination of $\alpha,\beta$-unsaturated aldehydes with butenolide phosphoranes and phosphonate anions, the conversion of $\gamma$-methoxybutenolides into $\gamma$-hydroxybutenolides was studied. This type of reaction was to be employed in the generation of (±)-palauolide (55) from the product 198 of the reaction between the aldehyde 107 and the phosphorane 108 (Scheme 23).
Recently, Wernuth et al.\textsuperscript{63} reported the preparation of the \(\gamma\)-ethoxybutenolide 199. Their procedure was modified for the preparation of the \(\gamma\)-methoxybutenolide 200, which was employed as a model for studying the transformation of \(\gamma\)-methoxybutenolides into \(\gamma\)-hydroxybutenolides. Thus, reaction of glyoxylic acid 201 with propanal in the presence of morpholine hydrogen chloride in aqueous dioxane at room temperature for 1 h and at reflux temperature for 24 h provided the \(\gamma\)-hydroxybutenolide \textsuperscript{202} in 63\% yield (see equation 76). Treatment of the latter material with methanolic hydrogen chloride (\(-7 \text{ g anhydrous hydrogen chloride gas in 150 mL of dry methanol}\) under reflux for 16 h provided the \(\gamma\)-methoxybutenolide 200 in 47\% yield (equation 76).

\[ \text{HCl-MeOH} \quad \text{(76)} \]

The ir spectrum of 200 exhibited absorptions at 1797 and 1769 cm\(^{-1}\) due to the carbonyl group. The \(^1\text{H nmr}\) spectrum of 200 showed two broad singlets at \(\delta 5.89\) and 5.60 due to the olefinic and >CHOCH\(_3\) protons respectively, a singlet at \(\delta 3.58\) due to the methoxy protons and a doublet at \(\delta 2.06\) (\(J = 2 \text{ Hz}\)) due to the vinyl methyl group.
Wermuth et al.\(^3\) reported that treatment of 199 with refluxing concentrated hydrochloric acid (2 ml per gram of 199) for 15 min regenerated the \(\gamma\)-hydroxybutenolide 202 (equation 77). However, it was thought that under such drastic conditions, the olefinic double bonds present in the palauolide skeleton would undergo rearrangement reactions. Therefore, milder reaction conditions would have to be developed for our synthesis.

\[
\begin{align*}
\text{HC1-EtOH} & \quad \text{conc. HCl} \\
202 & \quad 199 & \quad 202
\end{align*}
\]

Acid hydrolysis of the \(\gamma\)-methoxybutenolide 200 under a variety of conditions failed to provide useful yields of the \(\gamma\)-hydroxybutenolide 202. However, recently, Larcheveque et al.\(^4\) reported that the \(\gamma\)-methoxybutenolide 203 may be converted into the \(\gamma\)-hydroxybutenolide 204 by treatment with hydroxide ion (equation 78). Unfortunately, no information on the experimental conditions was reported.

\[
\begin{align*}
\text{OH}^- & \\
203 & \quad 204
\end{align*}
\]

After some experimentation, it was found that treatment of the \(\gamma\)-methoxybutenolide 200 with sodium hydroxide in aqueous acetonitrile at
room temperature for 30 min produced the acid aldehyde 205 (see equation 79). When dilute hydrochloric acid was added to the above product solution, the $\gamma$-hydroxybutenolide 202 could be obtained directly (70%) without isolation of the intermediate acid aldehyde 205 (equation 79). The IR and $^1$H NMR spectral data of the latter material were identical with those of the $\gamma$-hydroxybutenolide 202 prepared as described earlier in this section of the thesis (see equation 76, p. 89). The IR spectrum of the acid aldehyde 205 showed absorptions at 3034 and 1698 cm$^{-1}$ due to the hydroxy group and the carbonyl groups, respectively. The $^1$H NMR spectrum of 205 showed a singlet at $\delta$ 9.60 due to the aldehyde proton and two broad singlets at $\delta$ 6.53 and $\delta$ 2.21 due to the olefinic and the vinyl methyl protons, respectively.

Thus, a method for the conversion of $\gamma$-methoxybutenolides into $\gamma$-hydroxybutenolides under mild reaction conditions had been developed.

H. Reaction of $\alpha,\beta$-unsaturated aldehydes with phosphoranes and phosphonate anions derived from 4-(halomethyl)butenolides

Recently, Thaller et al.\textsuperscript{65} reported the isolation and total synthesis of a new monoterpene, scobinolide (206). In their synthesis,
the phosphonium salt 207 was treated with an aqueous methanolic solution of sodium hydroxide and the resultant stable phosphorane 208 was isolated as a yellow solid (see equation 80). The phosphorane 208 was then allowed to react with the aldehyde 209 in refluxing dichloromethane for 3 h. Preparative thin layer chromatography of the crude product mixture gave scobinolide (206) and the corresponding Z-isomer 210 in yields of 47% and 11%, respectively (equation 80).

\[
\begin{align*}
\text{NaOH, MeOH-H}_2\text{O} & \quad \overset{\text{CH}_2\text{Cl}_2, \text{reflux}}{\longrightarrow} \\
\text{PPh}_3\text{Br}^- & \quad \overset{\text{OHC}}{\longrightarrow} \\
\end{align*}
\]

\[
\begin{align*}
207 & \quad \rightarrow \\
208 & \quad (209) \\
\end{align*}
\]

\[
\begin{align*}
206 & \quad + \\
210 & \quad \sim \frac{4}{1} \\
\end{align*}
\] (80)

Following the chemistry reported by Boeckman et al. and Thaller et al., the phosphorane 208 was prepared and isolated. When we repeated the above olefination reaction exactly according to the conditions reported, most of the phosphorane 208 was recovered and the olefination product mixture was isolated in only 10% yield. However, when the reaction mixture was refluxed for 24 h, scobinolide (206) was isolated in 48% yield.

Treatment of geranial (211) with the phosphorane 208 in refluxing
dichloromethane (bp 40°C) for 24 h did not give much of the olefination products. However, when the reaction was carried out in boiling 1,2-dichloroethane (bp 80°C) for 16 h, compound 212 was isolated in 46% yield (equation 81). These results suggest that the phosphorane 208 is not very reactive and that the olefination is sensitive to structural changes in the α,β-unsaturated aldehyde.

The ir spectrum of 212 showed absorptions at 1778 and 1747 cm\(^{-1}\) due to the carbonyl group. In the \(^1\)H nmr spectrum of 212, the olefinic protons appeared at δ 6.75 (dd, 1H, \(J = 12, 16\) Hz, HA), 6.35 (d, 1H, \(J = 16\) Hz, HB), 5.97 (d, 1H, \(J = 12\) Hz, HC), 5.84 (br s, 1H, HD), and 5.07 (br s, 1H, HE) and the methyl groups at δ 1.85 (br s), 1.69 (br s) and 1.63 (br s).

In order to by-pass the isolation of the phosphorane, the butenolide phosphonium salt 207 was treated with dimethyl potassium in a minimum amount of dimethyl sulfoxide. The resultant solution was treated with a 1,2-dichloroethane solution of geranial (211) and the mixture was refluxed for 17 h. Workup and column chromatography of the crude product on silica gel provided compound 212 in 47% yield. This result showed that the olefination could be carried out successfully without
isolation of the phosphorane 208.

However, when the reaction of geranial (211) with the γ-methoxybute­
nolide phosphonium salt 188 was attempted under conditions identical
with those just described, geranial (211) was recovered intact and no
olefination product could be detected by glc and tlc analysis (equation
82).

\[
\begin{align*}
\text{188} & \quad \text{1. CH}_3\text{SCH}_2\text{K}^+, \text{DMSO} \\
& \quad \text{2. OHC} \quad \text{ClCH}_2\text{CH}_2\text{Cl, reflux} \\
& \quad \text{no reaction}
\end{align*}
\]

In view of this failure, attention was turned to the use of the
butenolide phosphonate 213, the anion of which was expected to be more
reactive than the corresponding phosphorane. The phosphonate 213 was
prepared in 78% yield by heating a mixture of the β-(chloromethyl)
butenolide 197 and purified triethylphosphite at 150°C for 18 h
(equation 83). The \(^1\)H nmr spectrum of 213 exhibited a broad quintet at
\(\delta 4.15 (J = 7 \text{ Hz})\) due to the \(-\text{P(OCH}_2\text{CH}_3)_2\) protons, a singlet at \(\delta 3.60\)
due to the methoxy protons, and a pair of doublet of doublets at \(\delta 3.01\)
\((J = 16, 21 \text{ Hz})\) and \(\delta 2.89 (J = 16, 21 \text{ Hz})\) due to the \(-\text{CH}_2\text{PO(OEt)}_2\)
protons.
The phosphonate 214 was prepared according to the procedure reported by Boeckman et al., and was employed as a model for studying the olefination of an \(\alpha,\beta\)-unsaturated aldehyde. Under a variety of conditions, as reported by Boeckman et al.,\(^{66}\) Corey et al.,\(^{67}\) and Masamune et al.,\(^{68}\) for coupling of \(\gamma\)-phosphonates of \(\alpha,\beta\)-unsaturated esters with \(\alpha,\beta\)-unsaturated aldehydes, no olefination product could be isolated from the reaction of geranial (211) with the anion of the phosphonate 214 (equation 84). Nevertheless, the reactions were repeated with the \(\gamma\)-methoxybutenolide phosphonate 213, and not surprisingly, no olefination product could be isolated (equation 85).

\[
\begin{align*}
\text{O} & \quad \text{OHC} - \text{C} - \text{C} - \text{C} - \text{H} \quad (211) \\
\text{214} \quad \text{\text{\scriptsize various conditions}} & \quad \text{no olefination product} \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{OHC} - \text{C} - \text{C} - \text{C} - \text{H} \quad (211) \\
\text{213} \quad \text{\text{\scriptsize various conditions}} & \quad \text{no olefination product} \\
\end{align*}
\]

Without any success in olefination of \(\alpha,\beta\)-unsaturated aldehydes using the \(\gamma\)-methoxybutenolide phosphonium salt 188 or the phosphonate 213, other means of olefination were investigated.
I. Reaction of \( \alpha,\beta \)-unsaturated aldehydes with phosphoranes derived from 4-(halomethyl)-2-trimethylsilylfurans

Our attention was turned to the use of the phosphonium salts derived from 4-(halomethyl)-2-trimethylsilylfurans. Deprotonation of such phosphonium salts would provide the stabilized phosphorane 215 (see Scheme 24). The latter material was expected to react with the \( \alpha,\beta \)-unsaturated aldehyde 107 to give the \( E \) olefin 216 as the major product. Selective photosensitized oxygenation of the silylfuran moiety of 216 would provide (±)-palauolide (55) (Scheme 24). The desired chemoselective photosensitized oxygenation was expected since oxygenation of silylfurans proceeds at a rate faster than the allylic oxygenation of alkenes.\(^{28}\) Furthermore, the diene moiety in the side chain of 216 is not likely to undergo a [2+4] cycloaddition with generated singlet oxygen, since this reaction would require the diene moiety to adopt a sterically congested cisoid conformation.
In an attempt to prepare the required phosphonium salt, 4-chloromethyl-2-trimethylsilylfuran (110) was treated with triphenylphosphine in refluxing benzene for 24 h. However, no product was obtained and the starting materials were recovered intact.

Treatment of the furan 110 with a mixture of calcium bromide monohydrate and tetra-n-butylammonium bromide (catalyst)\(^9\) in hexane at 50°C for 2 h provided the corresponding bromo derivative 217 (equation 86). The \(^1\)H nmr spectrum of 217 exhibited two singlets at \(\delta 7.65\) and \(\delta 6.64\) due to the furan protons, a singlet at \(\delta 4.37\) due to the \(-\text{CH}_2\text{Br}\) protons and a singlet at \(\delta 0.28\) due to the trimethylsilyl protons.

\[
\begin{align*}
\text{Me}_3\text{Si} &\quad \text{Cl} \\
\text{110} &\quad \text{n-Bu}_4\text{NBr}, \text{CaBr}.\text{H}_2\text{O} \\
\text{hexane, 50°C} &\quad \rightarrow \\
\text{Me}_3\text{Si} &\quad \text{Br} \\
\text{217}
\end{align*}
\] (86)

Reaction of the bromide 217 with triphenylphosphine in ether\(^70\) under reflux for 24 h provided the phosphonium salt 218 as a white, amorphous solid (77% from the furan 110, equation 87). The \(^1\)H spectrum of 218 exhibited a 2-proton multiplet at \(\delta 5.30\) due to the \(-\text{CH}_2\text{PPh}_3\) protons.

\[
\begin{align*}
\text{Me}_3\text{Si} &\quad \text{Br} \\
\text{217} &\quad \text{Ph}_3\text{P}, \text{ether} \\
\text{reflux} &\quad \rightarrow \\
\text{Me}_3\text{Si} &\quad \text{Br}^+\text{PPh}_3^- \\
\text{218}
\end{align*}
\] (87)
Similarly the phosphonium iodide 219 was prepared as follows. Treatment of the chloride 110 with sodium iodide in acetone at 60°C gave the iodide 220. Reaction of the latter substance with triphenylphosphine in ether afforded the phosphonium salt 219 (equation 88).

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \text{Cl} \quad \text{NaI, acetone} \quad \rightarrow \quad \text{Me}_3\text{Si} & \quad \text{I} \quad \text{Ph}_3\text{P, ether} \quad \rightarrow \quad \text{Me}_3\text{Si} & \quad \text{PPh}_3\text{I} \\
\text{110} & \quad \rightarrow & \quad \text{220} & \quad \rightarrow & \quad \text{219}
\end{align*}
\]

With both phosphonium salts 218 and 219 available, their use in the olefination of geranial (211) was studied. To a solution of the phosphonium bromide 218 in ether was added, successively, an ethereal solution of phenyllithium and a dichloromethane solution of geranial. The resultant mixture was stirred at room temperature for 1 h. Workup provided, on the basis of $^1$H nmr spectroscopy and a glc analysis, a 3:2 mixture of the olefination products 221 and 222, respectively (equation 89). When the phosphonium iodide 219 was subjected to the same reaction conditions, the stereoselectivity of the olefination improved slightly to 2:1 in favour of 221 (equation 90).

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \text{PPh}_3\text{Br}^- \quad \text{1. PhLi, ether} \quad \rightarrow \quad \frac{\text{Me}_3\text{Si}}{} & \quad \text{221} \quad \frac{3}{2} \quad \text{CH}_2\text{Cl}_2 \\
\text{218} & \quad \text{2. OHC} \quad \rightarrow & \quad \text{222}
\end{align*}
\]
The olefination products 221 and 222 were unstable and decomposed on silica gel during chromatography. Attempts to separate them on deactivated neutral alumina were not successful. However, the major product was later confirmed to be the E olefin (see p. 102).

It was expected that refluxing a solution of the mixture of 221 and 222 in n-hexane in the presence of iodine would convert the Z olefin to the E olefin. However, little stereomutation was detected and the mixture underwent slow decomposition.

Since the olefinations with the phosphorane 215 were not very stereoselective, another method that might eventually be used for the (±)-palauolide synthesis was investigated.

J. Reaction of geranial (211) with the sulfone 223. Photosensitized oxidation of the resultant triene 221 to the corresponding butenolide

Our attention turned to the possibility of employing the Julia olefination. In general, the synthesis of 1,2-disubstituted alkenes
using this method provide exclusively the E olefins.\textsuperscript{72} For example, successive treatment of the sulfone 224 with n-butyllithium, benzaldehyde and acetic anhydride provided the α-acetoxy sulfone 225. The latter material underwent smooth reductive elimination with sodium amalgam to give stereoselectively the diene 226 in 93% yield (equation 91).\textsuperscript{72} The stereochemistry of the reaction can be rationalized by proposing that the reductive cleavage of the phenylsulfonyl group generates an anion which assumes the lowest energy conformation (see structure 225a) from which the E-alkene is formed.

![Structure 225a](image)

Recently, in connection with work directed toward the total synthesis of indanomycin,\textsuperscript{73} Ley employed the Julia olefination to couple the structurally complex α,β-unsaturated aldehyde 227 with the highly functionalized sulfone 228. The olefination was totally stereoselective and produced only the E,E-1,3-diene 229 (equation 92).
The sulfone 223 required for our work was prepared by heating a mixture of 4-(chloromethyl)-2-trimethylsilylfuran (110) and sodium benzenesulfinate in dimethylformamide at 80-90°C for 2.5 h (72%, equation 93). The $^1$H nmr spectrum of 223 showed a singlet at $\delta$ 4.15 due to the $-\text{CH}_2\text{SO}_2\text{Ph}$ protons. The high resolution mass spectrum of 223
showed a molecular ion at m/e 294.0744, consistent with a molecular formula of C_{14}H_{18}SO_{3}Si.

The sulfone 223 was treated with n-butyllithium in THF at -78°C. The resultant solution was treated successively with geranial (211) (-78°C, 3 h) and benzoyl chloride (-78°C to rt, 1.5 h) to afford the benzoyloxy phenylsulfone 230. The latter material was treated with sodium amalgam (4%) in methanolic THF at -20°C for 3 h to afford stereoselectively the triene 221 (68% yield from sulfone 223, equation 94). In the 1H nmr spectrum of 221, the olefinic signals appeared at δ 6.65 (dd, 1H, J = 11, 16 Hz, H_A), 6.26 (d, 1H, J = 16 Hz, H_B), 5.90 (d, 1H, J = 11 Hz, H_C) and 5.07 (br s, 1H, H_D), indicating that the newly formed carbon-carbon double bond had the desired E stereochemistry. This material was identical with the major product obtained from the previously described Wittig reaction (see p. 99).
The furan triene 221 was then used as a model to investigate the photosensitized oxygenation reaction. When a cold (-78°C) dichloromethane solution of the furan triene 221, containing a catalytic amount of tetraphenylporphin, was irradiated while oxygen was bubbled through the mixture,* a terrible mixture of products was obtained. Fortunately, when a cold (-78°C) methanolic solution of the furan triene 221, containing a catalytic amount of Rose Bengal, was irradiated with a tungsten-halogen lamp (325W) through an aqueous sodium nitrite filter, while oxygen was bubbled through the methanolic solution, the γ-hydroxybutenolide 231 was obtained in 70% yield (equation 95). The ir spectrum of 231 exhibited a broad absorption at 3343 cm\(^{-1}\) due to the hydroxy group and a strong absorption at 1744 cm\(^{-1}\) due to the carbonyl group. The \(^1\)H nmr spectrum of 231 exhibited signals at \(\delta 7.18\) (dd, 1H, \(J = 11, 16\) Hz, \(H_A\)), 6.30 (d, 1H, \(J = 16\) Hz, \(H_B\)), 6.23 (d, 1H, \(J = 8.5\) Hz, \(H_C\)), 6.00 (d, 1H, \(J = 11\) Hz, \(H_D\)), and 5.87 (s, 1H, \(H_E\)) due to the protons on the diene butenolide moiety of 231. These chemical shifts were almost exactly the same as those reported for the diene butenolide 109.

* These reaction conditions are identical with those used for converting 4-(chloromethyl)-2-trimethylsilylfuran (110) to the corresponding γ-hydroxybutenolide 109.

\[
\text{Me}_3\text{Si} - \begin{array}{c}
\text{Cl} \\
\end{array} \\
110 \\
\]

\[
\text{Cl} - \begin{array}{c}
\text{OH} \\
\end{array} \\
109 \\
]

moiety of palauolide (55) [δ 7.16 (dd, J = 11, 15.5 Hz), 6.28 (d, J = 15.5 Hz), 6.26 (s), 5.95 (d, J = 11 Hz), 5.83 (s)].

K. Reaction of the aldehyde 107 with the sulfone 223. Photosensitized oxidation of the resultant triene 216 to (+)-palauolide (55)

With suitable conditions developed (section J) for the required olefination and photosensitized oxygenation, the stage was set to employ these reactions to effect a total synthesis of (+)-palauolide (55). To a solution of the sulfone 223 in THF at -78°C was added a solution of n-butyllithium. The resultant solution was treated with the α,β-unsaturated aldehyde 107 (-78°C, 3 h) and benzoyl chloride (-78°C to room temperature, 1.5 h). The resultant benzoyloxy phenylsulfone 232 was allowed to react with sodium amalgam (4%) in a 3:1 mixture of THF and methanol, respectively, at -20°C for 3 h. Workup afforded the furan triene 216 (51% from the aldehyde 107, equation 96).
The $^1$H nmr spectrum of 216 exhibited singlets at $\delta$ 7.58 and 6.76 due to the furan protons $H_A$ and $H_B$, respectively, and at $\delta$ 0.27 due to the trimethylsilyl group. The olefinic protons in the side chain appeared at $\delta$ 6.56 (dd, 1H, $J = 10, 16$ Hz, $H_C$), 6.30 (d, 1H, $J = 16$ Hz, $H_D$), 5.89 (d, 1H, $J = 10$ Hz, $H_E$), indicating that the newly introduced carbon-carbon double bond in the diene moiety possesses the desired $E$ stereochemistry. The high resolution mass spectrum of 216 showed the molecular ion at m/e 424.3161, which is consistent with a formula of $C_{28}H_{44}SiO$.

A cold (-78°C) dichloromethane-methanol solution of the furan triene 216, containing a catalytic amount of Rose Bengal, was irradiated for 8 minutes with a halogen-tungsten lamp (325W) through an aqueous sodium nitrite filter, while oxygen was bubbled through the mixture. The resultant solution was purged with argon and kept at room temperature in the dark for 3 h. After workup and column chromatography of the crude
product, (±)-palauolide (55) was obtained as a pale yellow oil in 68% yield (equation 97).

The synthetic material was spectroscopically identical with natural palauolide (Figs. 4 and 5).* For comparison purposes, the $^1$H nmr spectral data reported for the natural material$^{14}$ and those derived from our synthetic material are compiled in Table 1.

Table 1: $^1$H nmr spectral data of natural palauolide and synthetic (±)-palauolide (55)

<table>
<thead>
<tr>
<th>Reported Data</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^1$H nmr (CDCl$_3$) $\delta$: 7.16 (dd, 1H, $J$ = 15.5, 11 Hz, H$_A$), 6.28 (d, 1H, $J$ = 15.5 Hz, H$_B$), 6.26 (s, 1H, H$_C$), 5.95 (d, 1H, $J$ = 11 Hz, H$_D$), 5.83 (s, 1H, H$_E$), 4.51 (s, 2H, H$_F$), 1.86 (s, 3H, vinyl methyl protons), 1.05 (s, 3H, methyl protons), 0.82 (d, 3H, $J$ = 7 Hz, methyl protons), 0.74 (s, 3H, methyl protons).</td>
<td></td>
</tr>
<tr>
<td>Structure (97)</td>
<td></td>
</tr>
</tbody>
</table>

Our data

$^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 7.14 (dd, 1H, $J$ = 15.5, 11 Hz, H$_A$), 6.29 (d, 1H, $J$ = 15.5 Hz, H$_B$), 6.26 (d, $J$ = 8.5 Hz, collapsed to s on D$_2$O exchange, H$_C$), 5.97 (d, 1H, $J$ = 11 Hz, H$_D$), 5.87 (s, 1H, H$_E$), 4.51 (s, 2H, H$_F$), 1.88 (s, 3H, vinyl methyl protons), 1.06 (s, 3H, methyl protons), 0.82 (d, 3H, $J$ = 6 Hz, methyl protons), 0.74 (s, 3H, methyl protons).

* We are grateful to Professor D.J. Faulkner for the $^1$H nmr spectrum of palauolide (55).
Figure 4: The $^1$H nmr spectrum of natural palauolide
Figure 5: The 400 MHz $^1$H nmr spectrum of synthetic (±)-palauolide (55)
The work summarized above constitutes the successful total synthesis of (+)-palauolide in a total of seventeen steps from 3,6-dimethyl-2-cyclohexen-1-one with an overall yield of 5% (see Scheme 25) and represents the first reported total synthesis of this structurally and biologically interesting natural product.

Scheme 25
Reagents and conditions: i, 2-(5-chloropent-1-enyl)magnesium bromide, CuBr·Me₂S, BF₃·Et₂O, THF, -78°C, 3 h; NH₄Cl, H₂O, 77%; ii, Bu²OK, Bu²OH, 30°C, 10 h, 82%; iii, (p-tolylsulphonyl)methyl isocyanide, Bu²OK, Bu²OH-HMPA, 40-55°C, 3 days, 64%; iv, lithium diisopropylamide, THF-HMPA, 0°C; I[CH₂]₃OCH₂OMe, 0°C → room temp., 99%; v, Bu²AlH, DME, 60°C, 6 h; HOAc·H₂O, THF, room temp., 10 h, 85%; vi, LiAlH₄, Et₂O, room temp., 91%; vii, Bu²Li, DME-TMEDA; Cl₂PONMe₂, room temp., 10 h; Me₂NH, 0°C, 2 h, 88%; viii, Li, MeNH₂, -20°C, 10 min, 81%; ix, pyridinium toluene-p-sulphonate, Bu²OH, 70°C, 91%; x, pyridinium chlorochromate, NaOAc, CH₂Cl₂, 99%; xi, MeLi, Et₂O, 98%; xii, [EtO₂CCHPO(OEt)₂]K, THF, room temp., 18 h, 88%; xiii, Bu²AlH, Et₂O, -78 → 0°C, 98%; xiv, MnO₂, hexane, room temp., 88%; xv, 223a, THF, -78°C, 3 h; PhCOCl, -78°C → room temp.; Na(Hg), MeOH-THF, -20°C, 3 h, 51%; xvi, hν (tungsten halogen lamp, aqueous NaN₂O₂ filter, O₂, Rose Bengal (catalyst), MeOH-CH₂Cl₂, -78°C, 8 min; purge reaction mixture with argon and then keep at room temp. in the dark for 3 h, 68%.
II. Total Synthesis of (±)-Isolinaridiol (64) and (±)-Isolinaridiol Diacetate (61)

A. Retrosynthetic Analysis

Our retrosynthetic analysis of (±)-isolinaridiol (64) and (±)-isolinaridiol diacetate (61) was based on the methodology employed in the construction of the decalin substructure of (±)-palauolide (55), as discussed in a previous section of this thesis.

Suitable retrosynthetic functional group interconversions of the diacetate 61 would provide the diol 64. It may be noted that San Feliciano et al.\(^9\) have reported the reduction of isolinaridial (60) and the saponification of the natural diacetate 61 to isolinaridol 64. Further retrosynthetic functional group interconversions involving 64 would provide the ester 223. Retrosynthetic disconnection of the carbon-carbon double bond in the side chain of the latter substance, along with suitable functionalization of resultant fragments, would provide the aldehyde 234 and the phosphonate 235. Recently, Still et al.\(^74\) have reported the use of the methyl bis(trifluoroethyl)-phosphonoacetate 236 to effect highly stereoselective $Z$ olefination of aldehydes. For example, reaction of the potassium salt of the phosphonate 236 with $n$-heptanal in THF at -78°C in the presence of 18-crown-6 gave a 46:1 mixture of the $Z$ and $E$ esters, 237 and 238, respectively (equation 97). It was expected that the analogous phosphonate 235 should be preparable by monoalkylation of 239 with the iodide 240. Further, it was hoped that the reaction of the anion of 235 with
Retrosynthetic plan for the synthesis of
(±)-isolinaridiol (64) and (±)-isolinaridiol diacetate (61)

\[ \text{61} \rightarrow \text{64} \rightarrow \text{223} \]

\[ \text{234} + \text{235} \rightarrow \text{239} + \text{240} \]

\[ \text{241} \rightarrow \text{112} + \text{240} \]
aldehyde 234 would give primarily the $Z$ olefin 223.

Suitable retrosynthetic functional group interconversions involving the aldehyde 234 would provide the nitrile 241. Disconnection at the carbon-carbon bond joining the side chain and the bicyclic system, along with the suitable functionalization of the fragments, would provide the nitrile 112 and the iodide 240. Alkylation of the nitrile 112 had already been demonstrated to be completely stereoselective and the preparation of the nitrile 112 had been developed for the synthesis of (±)-palauolide (55).

B. **Z Selective Horner-Wittig olefinations**

1. **Olefinations with acyclic bis(trifluoroethyl)phosphonates**

   Treatment of distilled trimethyl phosphonoacetate (242) with phosphorus pentachloride$^{74}$ at room temperature for 1 h and at 75°C for 3 h, provided the dichloride 243 in 99% yield (equation 98). The latter material was treated with 2,2,2-trifluoroethanol in benzene in the presence of diisopropylethylamine at room temperature for 2 h. Column
chromatography of the crude product on silica gel provided the bis(trifluoroethyl)phosphonate 239 (57%, equation 99). The $^1$H nmr spectrum of 239 exhibited a quintet at $\delta$ 4.44 ($J = 8$ Hz) due to the $(\text{CF}_3\text{CH}_2\text{O})_2\text{P}^\text{O}$- protons, a singlet at $\delta$ 3.75 due to the methoxy protons, and a doublet at $\delta$ 3.15 ($J = 20$ Hz) due to the $\text{-PCH}_2$- protons.

Reaction of 2-chloroethanol (244) with chloromethyl methyl ether in the presence of diisopropylethylamine in dichloromethane at room temperature gave 2-chloro-1-methoxymethoxyethane (80%, see equation 100). Treatment of the latter material with an acetone solution of sodium iodide at 60°C in the dark for 30 h afforded 2-iodo-1-methoxymethoxyethane (240) (50%, equation 100). The $^1$H nmr spectrum of 240
exhibited two singlets at $\delta$ 4.68 and 3.40, due to the acetal and methoxy protons, respectively, and two triplets at $\delta$ 3.82 ($\Delta = 6$ Hz) and $\delta$ 3.30 ($\Delta = 6$ Hz) due to the -OCH$_2$CH$_2$- and ICH$_2$- protons, respectively. The high resolution mass spectrum of 240 showed a molecular ion at m/e 215.9649, consistent with a molecular formula of C$_4$H$_9$IO$_2$.

The phosphonate 239 (0.63 mmol) was treated with sodium hydride (0.71 mmol) in dimethylformamide (2 mL) at room temperature for 15 min. The resultant solution was treated with 18-crown-6 ether (47 $\mu$mol)$^{75}$ and 2-iodo-1-methoxymethoxyethane (240) (0.47 mmol). The mixture was heated at 60°C for 4 h. Workup provided a 6:20:1 mixture of the phosphonate 239, the mono-alkylated phosphonate 235, and the di-alkylated phosphonate 245, respectively ($^1$H nmr spectroscopy, equation 101). However, these compounds were not separable by chromatography on either silica gel or alumina.

$$\begin{align*}
\text{(CF}_3\text{CH}_2\text{O})_2\text{PCH}_2\text{CO}_2\text{Me} & \xrightarrow{1. \text{NaH, DMF}} (\text{CF}_3\text{CH}_2\text{O})_2\text{PCRR'CO}_2\text{Me} \quad (101) \\
\text{239} & \xrightarrow{2. \text{ICH}_2\text{CH}_2\text{OCH}_2\text{OCH}_3} \text{18-crown-6 ether} \\
239 & \xrightarrow{239 \; R=R=H} \\
235 & \xrightarrow{235 \; R=H, R'=\text{CH}_2\text{CH}_2\text{OCH}_2\text{OMe}} \\
245 & \xrightarrow{245 \; R=R'=\text{CH}_2\text{CH}_2\text{OCH}_2\text{OMe}}
\end{align*}$$

It was expected that employing 2-iodo-1-benzyloxymethoxyethane (246) as the alkylating reagent would provide a separable mixture of products. Treatment of 2-chloroethanol (244) with freshly distilled benzyl chloromethyl ether in the presence of diisopropylethylamine in dichloromethane at room temperature provided 2-chloro-1-benzyloxymethoxyethane.
(247) in 86% yield (see equation 102). The $^1$H nmr spectrum of 247 exhibited two singlets at $\delta$ 4.81 and $\delta$ 4.63 due to the benzyl and acetal protons, respectively. In the $^1$H nmr spectra of a number of compounds described in this thesis that contain the $\text{-OCH}_2\text{OCH}_3$ group, the chemical shifts of the acetal protons invariably appeared between $\delta$ 4.68 and $\delta$ 4.56. The spectrum of 247 also showed two triplets at $\delta$ 3.83 ($J = 6$ Hz) and $\delta$ 3.63 ($J = 6$ Hz) due to the ClCH$_2$CH$_2$O- and ClCH$_2$CH$_2$O- protons, respectively.

Treatment of 247 with sodium iodide in acetone at 60°C for 40 h provided the iodide 246 in 77% yield (equation 102). The high resolution mass spectrum of 246 showed a molecular ion at m/e 291.9966, corresponding to a molecular formula of C$_{10}$H$_{13}$O$_2$I.

Following conditions identical with those described in the previous page, a dimethylformamide solution of the bis(trifluoroethyl)phosphonate 239 was treated successively with sodium hydride, 18-crown-6 ether, and the iodide 246. After workup and column chromatography of the crude product on silica gel, pure mono-alkylated phosphonate 248 was isolated in 70% yield (equation 103). The $^1$H nmr spectrum of 248 exhibited a 5-proton multiplet at $\delta$ 7.34 due to the aromatic protons, a singlet at
δ 3.75 due to the methoxy protons, and a doublet of doublet of doublets of doublets at δ 3.39 (J = 4, 10, 22 Hz) due to the >CHP(OR)₂ proton.

With the desired substituted bis(trifluoroethyl)phosphonate available, the use of this reagent for the olefination of 3-methylbutanal was investigated. Following Still's procedure, a solution of the phosphonate (0.58 mmol) in THF (10 mL) at 0°C was treated with potassium bis(trimethylsilyl)amide (0.64 mmol), and 18-crown-6·nCH₃CN complex (0.74 g). The resultant solution was cooled to -78°C and treated with 3-methylbutanal (0.46 mmol). The reaction mixture was stirred at -78°C for 4 h. Workup provided a 3:1 mixture of the Z and E esters, 249 and 250, respectively (87%, equation 104). Column
chromatography of this material on silica gel (4 g, 230-400 mesh, elution with petroleum ether-ether, 9:1 v/v) afforded a pure sample of each compound for characterization.

The ir spectrum of the less polar Z ester 249 exhibited absorptions at 1719 and 1644 cm⁻¹ due to the carbonyl and alkene groups, respectively. The ¹H nmr spectrum of 249 showed a triplet at 6 6.01 (J = 7 Hz) due to the olefinic proton, and a triplet at 6 2.35 (J = 7 Hz) due to the i-PrCH₂ protons. The ir spectrum of the more polar E ester 250 exhibited absorptions at 1713 and 1646 cm⁻¹ due to the carbonyl and olefin groups, respectively. The ¹H nmr spectrum of 250 showed a triplet at 6 6.90 (J = 7 Hz) due to the olefinic proton, and a triplet at 6 2.12 (J = 7 Hz) due to the i-PrCH₂ protons. The assignment of stereochemistry was based on comparison of the chemical shifts of the olefinic protons and the i-PrCH₂ protons of the two isomers. The i-PrCH₂ protons of the Z isomer are deshielded by the cis CO₂Me group and thus resonate at lower field than the corresponding protons of the E isomer. On the other hand, as expected, the olefinic proton of the E isomer produces a signal at lower field than the olefinic proton of the Z isomer.

The Z selectivity of the olefination of 3-methylbutanal with the bis(trifluoroethyl)phosphonate 248 (3:1, Z:E) was rather low. In contrast, Still et al. had reported that reaction of the phosphonate 236 with various aldehydes gave high Z selectivity (≥30:1, Z:E). On comparison of the structures of the two phosphonates, 236 and 248, the lower selectivity with 248 must be due to the presence of a more bulky side chain (Me vs CH₂CH₂OCH₂OCH₂Ph). It was thought that reducing the
effective size of this side chain by using the phosphonate 251 might improve the \( Z \) selectivity.

\[
\begin{align*}
&\text{(CF}_3\text{CH}_2\text{O)}_2\text{P}-\text{CHCO}_2\text{Me} & \quad \text{(CF}_3\text{CH}_2\text{O)}_2\text{P}-\text{CHCO}_2\text{Me} \\
&\text{Me} & \quad \text{CH}_2\text{CH}_2\text{OCH}_2\text{OCH}_2\text{Ph} \\
&\text{236} & \quad \text{248} \\
&\text{251} 
\end{align*}
\]

2. Olefinations with \( \gamma \)-lactone \( \alpha \)-phosphonates

It was expected that the \( \gamma \)-lactone phosphonate 251 would be preparable from the reaction of \( \alpha \)-bromo-\( \gamma \)-butyrolactone (252)* with tris(2,2,2-trifluoroethyl)phosphite (253).* However, heating a mixture of these substances at 130°C for 2 days did not give any of the desired product and most of the bromo lactone 252 was recovered intact.

\[
\begin{align*}
&\text{(CF}_3\text{CH}_2\text{O)}_3\text{P} + \text{Br}-\text{C} & \quad 130^\circ\text{C} \\
&\text{253} & \quad \text{252} \\
&\text{no reaction}
\end{align*}
\]

It was thought that 251 might be accessible from \( \alpha \)-diethylphosphono-\( \gamma \)-butyrolactone (254) by substituting the ethoxy groups with

* Both 252 and 253 are commercially available from Aldrich Chemical Co.
trifluoroethoxy groups. Treatment of the bromo lactone 252 with triethylphosphite at 140°C for 5 h provided the phosphonate 254\textsuperscript{77} (equation 105). However, subsequent treatment of the phosphonate 254 with phosphorus pentachloride and trifluoroethanol did not provide any of the desired phosphonate 251.

\[
(EtO)_3P \quad + \quad Br\text-\text{Lactone} \quad \rightarrow \quad (EtO)_2P\text-\text{Lactone}
\]

(105)

Since attempts to prepare the bis(trifluoroethyl)phosphonate 251 were unsuccessful, it was decided to investigate the use of a simpler \(\gamma\)-lactone phosphonate for aldehyde olefinations, in order to determine whether high \(Z\) selectivity could be achieved. Recently, Kishi \textit{et al.}\textsuperscript{78} reported that the ratio of \(Z\) and \(E\) esters obtained from Horner-Wittig reactions of aldehydes is sensitive to the structure of the phosphonate reagents, the nature of the solvent and the reaction temperature. Furthermore, Nagaoka and Kishi\textsuperscript{79} reported that in general, phosphonate reagents 255 with bulky \(R\) groups react with aldehydes to give predominantly \(E\) \(\alpha,\beta\)-unsaturated esters, while phosphonate reagents 255 with small \(R\) groups provide predominantly \(Z\) \(\alpha,\beta\)-unsaturated esters. For example, reaction of the aldehyde 256 with the diisopropylphosphonate 257 provided a 1:9 mixture of 258 and 259, respectively (see equation 106). On the other hand, reaction of 256 with the dimethylphosphonate 260 provided a 9:1 mixture of 258 and 259, respectively (equation 106). Thus, olefination of aldehydes with dimethyl \(\gamma\)-butyrolactone phosphonate
261 was investigated.

\[
\begin{align*}
\text{261} & = \text{255} \\
\text{256} & \rightarrow \text{258} + \text{259} \\
257 \ R=i\text{Pr} & \quad 1 : 9 \\
260 \ R=\text{Me} & \quad 9 : 1
\end{align*}
\]

The phosphonate 261 was prepared by heating a mixture of \(\alpha\)-bromo-\(\gamma\)-butyrolactone (252) with purified trimethyl phosphite 262 at 150°C for 8 h. A bulb to bulb distillation of the resultant oil provided the crude product, which was subjected to column chromatography on silica gel to provide the pure phosphonate 261 (30%, equation 107). The ir spectrum of 261 showed a strong absorption at 1772 cm\(^{-1}\) due to the carbonyl group. The \(^1\)H nmr spectrum of 261 exhibited two doublets at \(\delta 3.77\ (J = 10 \text{ Hz})\) and \(\delta 3.73\ (J = 10 \text{ Hz})\) due to the \(-\text{P(OMe)}_2\) protons, and a triplet of doublets at \(\delta 3.03\ (J = 8, 24 \text{ Hz})\) due to the \(-\text{PCH}_3\).
proton. The high resolution mass spectrum of 261 showed a molecular ion at m/e 194.0352, consistent with a molecular formula of $C_{6}H_{11}PO_{5}$.

The reaction of 3-methylbutanal with the $\gamma$-lactone phosphonate 261 (equation 108), under a variety of experimental conditions, was investigated. The results are summarized in Table 2.

![Chemical structure](image)

Table 2: Reaction of 3-methylbutanal with the $\gamma$-lactone phosphonate 261

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Product ratio$^a$ 263 : 264</th>
<th>Total isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH/benzene/rt$^b$</td>
<td>64 : 36</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>tert-BuOK/THF/-78°C$^c$</td>
<td>73 : 27</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>tert-BuOK/THF-HMPA/-78°C$^c$</td>
<td>77 : 23</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>KN(TMS)$_2$/THF/18-crown-6/-78°C$^d$</td>
<td>&gt;99 : &lt;1</td>
<td>86</td>
</tr>
</tbody>
</table>

$^a$ The product ratios were determined by glc analysis of the crude product mixtures, and were supported by $^1H$ nmr spectroscopy.

$^b$ See reference 80.

$^c$ See reference 79.

$^d$ See reference 74.
Treatment of the phosphonate 261 with sodium hydride in benzene, followed by addition of 3-methylbutanal, gave a 64:36 mixture of the Z and E lactones, 263 and 264, respectively (Table 2, entry 1). The lactones were separated by column chromatography on silica gel. The IR spectrum of the less polar Z lactone 263 exhibited absorptions at 1752 and 1670 cm\(^{-1}\) due to the carbonyl group and the olefinic double bond, respectively. The \(^1\)H NMR spectrum of 263 showed a triplet of triplets at \(\delta 6.27\) (\(J = 4.5, 7\) Hz) due to the olefinic proton and a broad triplet at \(\delta 2.60\) (\(J = 7\) Hz) due to the i-PrCH\(_2\)- protons. The IR spectrum of the more polar E lactone 264 exhibited absorptions at 1757 and 1681 cm\(^{-1}\) due to the carbonyl and alkene functions, respectively. The \(^1\)H NMR spectrum of 264 showed a triplet of triplets at \(\delta 6.78\) (\(J = 3, 7\) Hz) due to the olefinic proton and a broad triplet at \(\delta 2.09\) (\(J = 7\) Hz) due to the i-PrCH\(_2\)- protons.

When the reaction of 3-methylbutanal with the phosphonate 261 was carried out in THF in the presence of potassium tert-butoxide at -78°C, the Z selectivity improved marginally to 73:27 (Table 2, entry 2). Addition of hexamethylphosphoramide to the reaction mixture resulted in a further slight improvement in the Z:E ratio (77:23) (Table 2, entry 3). However, when potassium bis(trimethylsilyl)amide was used as the base and the reaction was carried out in THF in the presence of 18-crown-6 at -78°C for 4 h, only the Z lactone 263 could be detected in the crude product. This material was isolated in 86% yield (Table 2, entry 4).

Employing reaction conditions identical with those summarized in Table 2, entry 4, the olefination of a number of aldehydes with the
γ-lactone phosphonate 261 was investigated (equation 109). The results are summarized in Table 3.

![Equation 109]

Table 3: Reaction of aldehydes with the γ-lactone phosphonate 261

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product ratio&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Total isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>heptanal (267)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>265a : 266a, &gt;99:1</td>
<td>94%</td>
</tr>
<tr>
<td>2</td>
<td>cyclohexanecarboxaldehyde (268)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>265b : 266b, 83:17</td>
<td>68%</td>
</tr>
<tr>
<td>3</td>
<td>(E)-2-hexenal (269)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>265c : 266c, 97:3</td>
<td>78%</td>
</tr>
<tr>
<td>4</td>
<td>benzaldehyde (270)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>265d : 266d, 50:50</td>
<td>91%</td>
</tr>
</tbody>
</table>

<sup>a</sup> The product ratios were determined by glc analysis of the crude product mixture, and were substantiated by <sup>1</sup>H nmr spectroscopy.

<sup>b</sup> These aldehydes were distilled (atmospheric pressure) just prior to use.

<sup>c</sup> This aldehyde was distilled under reduced pressure (bp 40-45°C/15 torr).
In the reactions of the phosphonate 261 with the aliphatic aldehydes 267, 268 and 269 (Table 3, entry 1-3), under the conditions described, the products were formed with good to excellent Z selectivity. However, with benzaldehyde, no selectivity was observed. It is interesting to note that Minami et al.\textsuperscript{80} reported that reaction of the sodium salt of the diethyl phosphonate 254 with benzaldehyde in benzene gave only the E lactone 266d (equation 110).

\[
\begin{align*}
(\text{EtO})_2\text{P} & \quad \xrightarrow{\text{1. NaH, benzene}} \quad \text{Ph} \\
\text{254} & \quad \xrightarrow{\text{2. PhCHO}} \quad \text{266d}
\end{align*}
\]  

The Z selective olefination of aliphatic aldehydes with the \(\gamma\)-lactone phosphonate 261 described above is complimentary to the E selective olefination of the aliphatic aldehyde 271 with the phosphorane 272 reported recently by Secrist et al.\textsuperscript{81} (equation 111).

\[
\begin{align*}
\text{272} + \text{271} & \quad \xrightarrow{\text{MeCN}} \quad \text{271}
\end{align*}
\]
A pure sample of each of the lactones 256b and 266b (Table 3, entry 2) was obtained by column chromatography of the crude product mixture on silica gel (70-230 mesh, elution with petroleum ether-ether, 8:2 v/v). Similarly, the lactones 265d and 266d (Table 3, entry 4) were readily separable by column chromatography of the crude product mixture on silica gel (230-400 mesh, elution with benzene-ether, 30:1 v/v). A pure sample of the E lactone 266a was obtained as follows. Treatment of the phosphonate 261 with a suspension of sodium hydride in benzene, followed by addition of heptanal (267), gave a 1:1 mixture of the Z and E lactones, 265a and 266a. These substances were separated by column chromatography on silica gel. Similarly, reaction of the sodium salt of the phosphonate 261 with (E)-2-hexenal (269) in benzene provided a 1:3 mixture of the Z and E lactones, 265c and 266c. The pure E lactone 266c was obtained by subjection of the crude product mixture to column chromatography on silica gel.

The assignment of stereochemistry of the olefination products listed in Table 3 was, in each case, based on comparison of the chemical shifts of the olefinic protons and/or the allylic γ'-protons (see general structures A and B) of the two possible geometric isomers.

![general structure A](image)

Z-lactone
general structure A

![general structure B](image)

E-lactone
general structure B
The olefinic protons of the E isomers are deshielded by the cis carbonyl group of the lactone moiety and thus resonate at lower field than the corresponding protons of the Z isomers. On the other hand, for the Z isomers, the allylic γ'-protons, if present, resonate at lower field than those of the E isomers.

Some of the spectroscopic data derived from the olefination products obtained from the experiments summarized in Tables 2 and 3 are tabulated in Table 4 (page 127). It is pertinent to note that, in the \(^1\)H nmr spectra of the lactones, the olefinic protons of the E isomers resonate at ~0.50-0.56 ppm lower field than the corresponding protons of the Z isomers. It is also interesting to point out that, in the ir spectra of these materials, the carbon-carbon double bond stretching vibrations of the E lactones appear at higher wavenumbers (~5-11 cm\(^{-1}\)) than those of the Z lactones. On the other hand, the positions of the carbonyl stretching vibrations of the Z and E isomers do not show any well defined differences.

C. Synthesis of the aldehyde 234

A 15:85 mixture of the nitriles 112a and 112b, respectively, was treated with lithium diisopropylamide in THF-HMPA at 0°C for 15 min. 1-Iodo-2-methoxymethoxyethane (240) was added and the resultant solution was stirred at 0°C for 30 min and at room temperature for 1 h. Workup provided the nitrile 241 in 99% yield (equation 112).
Table 4: Partial $^1$H nmr and infrared data for olefination products derived from reactions of aldehydes with the $\gamma$-lactone phosphonate 261

<table>
<thead>
<tr>
<th>Lactone(^a)</th>
<th>Chemical shifts ((\delta))</th>
<th>ir absorptions (cm(^{-1}))(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>olefinic proton</td>
<td>allylic $\gamma'$-proton(s)(^b)</td>
</tr>
<tr>
<td>263</td>
<td>6.35</td>
<td>2.60</td>
</tr>
<tr>
<td>264</td>
<td>6.85</td>
<td>2.09</td>
</tr>
<tr>
<td>265a</td>
<td>6.24</td>
<td>2.70</td>
</tr>
<tr>
<td>266a</td>
<td>6.76</td>
<td>2.20</td>
</tr>
<tr>
<td>265b</td>
<td>6.03</td>
<td>3.45</td>
</tr>
<tr>
<td>266b</td>
<td>6.54</td>
<td>2.11</td>
</tr>
<tr>
<td>265c</td>
<td>6.57</td>
<td>-(^d)</td>
</tr>
<tr>
<td>266c</td>
<td>7.09</td>
<td>-(^d)</td>
</tr>
<tr>
<td>265d</td>
<td>7.02</td>
<td>-(^d)</td>
</tr>
<tr>
<td>266d</td>
<td>7.58</td>
<td>-(^d)</td>
</tr>
</tbody>
</table>

\(^a\) All compounds exhibited one peak on glc analysis and one spot by tlc analysis.

\(^b\) See structures A and B.

\(^c\) All infrared spectra were recorded on a Perkin-Elmer model 1710 spectrophotometer with internal calibration.

\(^d\) This compound contains no allylic $\gamma'$-proton.
1. LDA, THF-HMPA
2. ICH₂CH₂OCH₂OCH₃ (240)

The ir spectrum of 241 exhibited absorptions at 2228 and 1638 cm⁻¹ due to the nitrile and olefinic groups, respectively. The ¹H nmr spectrum of 241 showed a singlet at δ 3.34 due to the methoxy protons, and a pair of broad triplet of doublets at δ 2.15 (J = 7, 15 Hz) and 2.09 (J = 7, 15 Hz) due to the -CH₂CH₂O- protons.

Treatment of the nitrile 241 with diisobutylaluminum hydride in dimethoxyethane at 60°C for 6 h afforded, after workup and acid catalyzed hydrolysis of the crude imine, the aldehyde 273 (92%, equation 113). The ir spectrum of 273 showed a strong absorption at 1713 cm⁻¹ due to the carbonyl group, while the ¹H nmr spectrum exhibited a singlet at δ 9.97 due to the aldehyde proton.
Reduction of the aldehyde 273 with lithium aluminum hydride in ether at room temperature provided the alcohol 274 in 95% yield (equation 114). The IR spectrum of 274 showed a broad absorption at 3443 cm\(^{-1}\) due to the hydroxy group. The \(^1\)H nmr spectrum of 274 showed a pair of doublets at \(\delta 3.77 (J = 11\text{ Hz})\) and \(\delta 3.68 (J = 11\text{ Hz})\) due to the \(-\text{CH}_2\text{OH}\) protons.

Successive treatment of a solution of the alcohol 274 in a 4:1 mixture of dimethoxyethane and \(\text{N,N,N',N'-tetramethylethylene diamine}\) with \(n\)-butyllithium (15 min, room temperature), dimethylaminophosphorodichloridate (12 h, room temperature), and anhydrous dimethylamine (2 h, \(0^\circ\text{C}\)) afforded, after column chromatography of the crude product on silica gel, the phosphorodiamidate 275 (63%, equation 115). The \(^1\)H nmr
spectrum of 275 exhibited a pair of doublets of doublets at \( \delta 4.00 \) (\( J = 4, 11 \) Hz) and \( \delta 3.94 \) (\( J = 4, 11 \) Hz) due to the \( \text{CH}_2\text{OP(NMe}_2\text{)}_2 \) protons, and a pair of doublets at \( \delta 2.67 \) (\( J = 6 \) Hz) and 2.65 (\( J = 6 \) Hz) due to the \( \text{OP(NMe}_2\text{)}_2 \) protons. These spectral data showed that the phosphorodiamidate group had been installed.

Treatment of the phosphorodiamidate 275 with an anhydrous methyamine solution of lithium, in the absence of tert-butyl alcohol, at -20°C for 10 min gave the deoxygenated compound 276 in 80% yield (equation 116). The \( ^1H \) nmr spectrum of 276 exhibited two singlets at \( \delta 1.04 \) and \( \delta 0.75 \), and a doublet at \( \delta 0.85 \) (\( J = 6 \) Hz) due to the methyl groups in the decalin substructure.

The ether 276 was treated with pyridinium p-toluenesulfonate in tert-butylalcohol\(^{55} \) at 70°C for 12 h to give the alcohol 277 (91%, equation 117). The ir spectrum of 277 showed a broad absorption at 3375 cm\(^{-1} \). The \( ^1H \) nmr spectrum of 277 exhibited a broad singlet at \( \delta 4.50 \) due to the exocyclic olefinic protons, and a pair of doublet of triplets at \( \delta 3.61 \) (\( J = 5.5, 10 \) Hz) and \( \delta 3.52 \) (\( J = 5.5, 10 \) Hz) due to the \( \text{CH}_2\text{OH} \) protons.
When the alcohol 277 was oxidized with pyridinium chlorochromate in the presence of anhydrous sodium acetate in dichloromethane at room temperature, a mixture of products was obtained. However, treatment of the alcohol 277 with a dichloromethane solution of dimethylsulfoxide-oxalyl chloride reagent at -78°C, followed by addition of triethylamine, provided the aldehyde 234 cleanly (85%, equation 118). The IR spectrum of 234 exhibited a strong absorption at 1718 cm⁻¹ due to the carbonyl group. The ¹H nmr spectrum of 234 showed a triplet at δ 9.78 (J = 3.5 Hz) due to the aldehyde proton, and a pair of doublet of doublets at δ 2.41 (J = 3.5, 14.5 Hz) and δ 2.29 (J = 3.5, 14.5 Hz) due to the -CH₂CHO protons.
D. Synthesis of (±)-isolinaridiol (64) and its geometric isomer 278

With suitable conditions developed for the required Ζ olefination (Section B) and with the acquisition of the aldehyde 234 (Section C), the stage was set to effect the synthesis of (±)-isolinaridiol (64). A cold (0°C) THF (1.9 mL) solution of the phosphonate 261 (0.11 mmol) was treated with a toluene solution of potassium bis(trimethylsilyl)amide* (0.12 mmol) and then 18-crown-6.nCH₃CN complex (0.16 g) was added. The resultant solution was cooled to -78°C, a THF solution of the aldehyde 234 (85 μmol) was added, and stirring was continued at -78°C for 4 h. Glc analysis of the crude product showed that it consisted of a 3:1 mixture of the olefination products. Subjection of this mixture to column chromatography on silica gel provided both the pure Ζ lactone 279 (58%) and the pure Ε lactone 280 (19%, equation 119).

* This reagent solution is commercially available from Aldrich Chemical Co.
The IR spectrum of the less polar lactone 279 exhibited absorptions at 1753 cm\(^{-1}\) due to the carbonyl group and at 1666 and 1635 cm\(^{-1}\) due to the olefinic linkages. The \(^1H\) NMR spectrum of 279 exhibited a 1-proton triplet of triplets at \(\delta 6.24 (J = 2.8 \text{ Hz})\) due to the olefinic proton on the side chain, and a pair of triplet of doublet of doublets at \(\delta 2.89\) and \(\delta 2.65 (J = 2.5, 8, 17 \text{ Hz})\) due to the \(-\text{CH}_2\text{CH}=\) protons.

The IR spectrum of the more polar lactone 280 showed absorptions at 1758 cm\(^{-1}\) due to the carbonyl group and at 1676 and 1635 cm\(^{-1}\) due to the carbon-carbon double bonds. The \(^1H\) NMR spectrum of 280 exhibited a 1-proton triplet of triplets at \(\delta 6.76 (J = 2.5, 6.5 \text{ Hz})\) due to the olefinic proton on the side chain, and a pair of multiplets at \(\delta 2.30-2.22\) and \(\delta 2.18-2.10\) due to the \(-\text{CH}_2\text{CH}=\) protons.

Since a vicinal olefinic proton on the same side of the double bond as the carbonyl group in an \(\alpha,\beta\)-unsaturated ester would experience an anisotropic magnetic deshielding effect from the carbonyl group, the lactone 279 was assigned the Z stereochemistry, while the lactone 280 was assigned the E stereochemistry.

The Z selectivity (3:1, Z:E) of the olefination of the aldehyde 234 with the potassium salt of the phosphonate 261 was not as high as those observed in the olefination of 3-methylbutanal (>99% Z selectivity, Table 2, entry 4) and heptanal (>99% Z selectivity, Table 2, entry 1). Attempts to improve the Z selectivity by changing the concentration of the potassium salt of the phosphonate 261, and that of the aldehyde 234 proved to be fruitless.

The Z lactone 279, upon treatment with diisobutyaluminum hydride in THF at -78°C for 1 h and 0°C for 2 h, afforded (±)-isolinaridiol (64) in
96% yield (equation 120). The ir spectrum of 64 exhibited a broad absorption at 3328 cm\(^{-1}\) due to the hydroxy groups and absorptions at 1636 and 891 cm\(^{-1}\) due to the exocyclic terminal double bond. The \(^1\)H nmr spectrum of this material was shown to be identical with that of a sample of natural isolinaridiol provided by Professor A. San Feliciano* (see Figs. 7 and 8). However, these \(^1\)H nmr data are slightly different from those reported by San Feliciano et al.\(^{19}\) For comparison purposes, the \(^1\)H nmr spectral data reported for natural isolinaridiol,\(^{19}\) those derived from the authentic sample provided by Professor San Feliciano, and those obtained from our synthetic (±)-isolinaridiol are compiled in Table 5.

![Reduction of the E lactone 280 with diisobutylaluminum hydride in THF afforded the diol 278 (89%, equation 121), which is spectroscopically distinctly different from isolinaridiol 64. The \(^1\)H nmr of the diol 64 (see Fig. 9) exhibited a 1-proton triplet at \(\delta 5.52 (J = 7.5 \text{ Hz})\) due to the olefinic proton, a broad singlet at \(\delta 4.05\) due to the \(-\text{CCH}_2\text{OH}\)](image)

\* We are grateful to Professor A. San Feliciano for a sample of isolinaridiol and for copies of its \(^1\)H nmr, ir, and mass spectra.
Fig. 7: The 400 MHz $^1$H nmr spectrum of natural isolinaridiol
Fig. 8: The 400 MHz $^1$H nmr spectrum of synthetic (±)-isolinaridiol
Table 5: $^1{H}$ nmr spectral data of isolinaridiol (64)

I. Reported Data

$^1{H}$ nmr (200 MHz, CDCl$_3$) δ: 5.32 (t, 1H, J = 7.5 Hz, olefinic proton), 4.49 (d, 2H, J = 1.4 Hz, olefinic protons),$^a$ 3.68 (t, 2H, J = 5.7 Hz, -CH$_2$CH$_2$OH), 2.34 (t, 2H, 5.7 Hz, -CH$_2$CH$_2$OH), 2.10 (m, 2H, -CH$_2$CH=),$^b$ 1.04 (s, 3H, methyl protons), 0.82 (d, 3H, J = 6 Hz, methyl protons), 0.75 (s, 3H, methyl protons).

II. Data derived from the sample provided by Professor San Feliciano

$^1{H}$ nmr (400 MHz, CDCl$_3$) δ: 5.36 (br t, 1H, J = 8 Hz, olefinic proton), 4.50 (br s, 2H, olefinic protons), 4.18, 4.15 (d, d, 1H each, J = 12 Hz, -CCH$_2$OH), 3.74 (br t, 2H, J = 6 Hz, -CH$_2$CH$_2$OH), 2.39 (t, 2H, J = 6 Hz, -CH$_2$CH$_2$OH), 2.09 (m, 2H, -CH$_2$CH=), 1.80 (br s, 2H, D$_2$O exchanged, -OH), 1.05 (s, 3H, methyl protons), 0.83 (d, 3H, J = 7 Hz, methyl protons), 0.77 (s, 3H, methyl protons).

III. Data derived from our synthetic material

$^1{H}$ nmr (400 MHz, CDCl$_3$) δ: 5.36 (br t, 1H, J = 8 Hz, olefinic proton), 4.50 (br s, 2H, olefinic protons), 4.18, 4.15 (d, d, 1H each, J = 12 Hz, -CCH$_2$OH), 3.74 (br t, 2H, J = 6 Hz, -CH$_2$CH$_2$OH), 2.39 (t, 2H, J = 6 Hz, -CH$_2$CH$_2$OH), 2.09 (m, 2H, -CH$_2$CH=), 1.80 (br s, 2H, D$_2$O exchanged, -OH), 1.05 (s, 3H, methyl protons), 0.84 (d, 3H, J = 7 Hz, methyl protons), 0.77 (s, 3H, methyl protons).

$^a$ The signals at δ 4.2-4.1 were not reported, however the $^1{H}$ nmr spectrum of isolinaridiol provided by Professor San Feliciano showed that there is a broad singlet at ~δ 4.12.

$^b$ No hydroxyl protons were reported.
Fig. 9: The 300 MHz $^1$H nmr spectrum of compound 278
protons, a triplet at $\delta$ 3.71 ($J = 6$ Hz) due to the $-\text{CH}_2\text{CH}_2\text{OH}$ protons, and a triplet at $\delta$ 2.43 ($J = 6$ Hz), due to the $-\text{CH}_2\text{CH}_2\text{OH}$ protons.

E. Synthesis of (±)-isolinaridiol diacetate (61)

Treatment of (±)-isolinaridiol (64) with acetic anhydride in pyridine containing a catalytic amount of 4-$N,N$-dimethylaminopyridine provided the diacetate 61 in 90% yield (equation 122). The ir spectrum of 61 exhibited absorptions at 1742 and 1635 cm$^{-1}$ due to the carbonyl groups and the exocyclic olefinic double bond. The $^1$H nmr spectral data (see Fig. 10) of our synthetic (±)-isolinaridiol diacetate (61) were
Fig. 10: The 300 MHz $^1$H nmr spectrum of synthetic isolinaridiol diacetate
found to be somewhat different from those reported\textsuperscript{19} for natural isolinaridiol diacetate (\textit{vide infra}).

Treatment of the diol 278 with acetic anhydride in pyridine in the presence of 4-\textit{N},\textit{N}-dimethylaminopyridine (catalyst) gave the diacetate 281 (78\%, equation 123). This material exhibited IR absorptions at 1747 and 1635 cm\textsuperscript{-1}. The \textsuperscript{1}H nmr spectral data (see Fig. 11) 281 were also different from those reported for natural isolinaridiol diacetate.\textsuperscript{19}

For comparison, the \textsuperscript{1}H nmr spectral data reported for natural isolinaridiol diacetate,\textsuperscript{19} and those derived from our synthetic (\textpm)-isolinaridiol diacetate (61) and the diacetate 281 are compiled in Table 6.

Comparison of the \textsuperscript{1}H nmr spectral data reported for natural isolinaridiol diacetate with those derived from our synthetic (\textpm)-isolinaridiol diacetate (61) and the racemic diacetate 281 does not show conclusively that one of our synthetic materials is identical with the natural product. Thus far, we have not been successful in our attempts to obtain a sample of natural isolinaridiol diacetate. However, we hope that Professor San Feliciano will be able to send us a small amount of this material so that a proper comparison can be carried out. In any case, there seems to be little doubt that the structural assignments of our synthetic materials are correct.
Fig. 11: The 300 MHz $^1$H nmr spectrum of compound 281.
Table 6: $^1$H nmr spectral data reported for natural isolinaridiol diacetate, and those derived from our synthetic (±)-isolinaridiol diacetate (61) and the diacetate 281

I. Spectral data reported for natural isolinaridiol diacetate

$^1$H nmr (50 MHz, CDCl$_3$) $\delta$: 5.45 (m, 1H, olefinic proton), 4.47 (s, 2H, =CH$_2$0Ac), 4.43 (br s, 2H, olefinic protons), 4.04 (t, 2H, $J = 6$ Hz, -CH$_2$CH$_2$0Ac), 2.38 (t, 2H, $J = 6$ Hz, -CH$_2$CH$_2$0Ac), 1.97, 1.91 (s, s, 3H each, acetyl protons), 1.03 (s, 3H, methyl protons), 0.81 (br d, 3H, methyl protons), 0.75 (s, 3H, methyl protons).

II. Data derived from our synthetic (±)-isolinaridiol diacetate (61)

$^1$H nmr (300 MHz, CDCl$_3$) $\delta$: 5.44 (t, 1H, $J = 7.5$ Hz, olefinic proton), 4.61 (br s, 2H, =CH$_2$0Ac), 4.49 (br s, 2H, olefinic protons), 4.13 (m, 2H, -CH$_2$CH$_2$0Ac), 2.40 (t, 2H, $J = 7$ Hz, -CH$_2$CH$_2$0Ac), 2.06, 2.03 (s, s, 3H each, acetyl protons), 1.04 (s, 3H, methyl protons), 0.81 (d, 3H, $J = 6$ Hz, methyl protons), 0.75 (s, 3H, methyl protons).

III. Data derived from the synthetic diacetate 281

$^1$H nmr (300 MHz, CDCl$_3$) $\delta$: 5.57 (t, 1H, $J = 7.5$ Hz, olefinic proton), 4.50 (br s, 4H, =CH$_2$0Ac and olefinic protons), 4.10 (t, 2H, $J = 7.5$ Hz, -CH$_2$CH$_2$0Ac), 2.43 (t, 2H, $J = 7.5$ Hz, -CH$_2$CH$_2$0Ac), 2.06, 2.04 (s, s, 3H each, acetyl protons), 1.04 (s, 3H, methyl protons), 0.82 (d, 3H, $J = 6$ Hz, methyl protons), 0.77 (s, 3H, methyl protons).

a No coupling constant was given.

b The assignment is based on the fact that the olefinic protons of compounds described in this thesis bearing the general structure C invariably appear at $\delta$ 4.49 to 4.52 in the $^1$H nmr spectra and the =CH$_2$0Ac protons of compound 282 (prepared by reduction of the lactone 263, Table 2, followed by bis-acetylation of the product) appears at $\delta$ 4.63 (s).
F. Attempts to oxidize (±)-isolinaridiol (64) to (±)-isolinaridial (60)

Recently, in connection with work directed toward the total synthesis of polygodial (284), Lallemand et al. employed the Swern oxidation to oxidize the diol 283 to the dialdehyde 284 (75%, equation 124). It was expected that this method could be employed to oxidize (±)-isolinaridiol (64) to (±)-isolinaridial (60).

![Chemical structures](image)

Diisobutylaluminum hydride reduction of the lactone 263 provided the diol 285 (85%, equation 125), which was employed for a model study of the oxidation of the diol 64 to the dialdehyde 60. The IR spectrum of 285 showed a broad absorption at 3336 cm\(^{-1}\) due to the hydroxy groups and a weak absorption at 1656 cm\(^{-1}\) due to the olefinic linkage. The \(^1\)H NMR spectrum of 285 exhibited a triplet at \(\delta 5.42 (J = 6 \text{ Hz})\) due to the

* The preparation of the lactone 263 was described in p. 116 of this thesis.
olefinic proton, a singlet at $\delta$ 4.15 due to the $-\text{CCH}_2\text{OH}$ protons, and two triplets at $\delta$ 3.73 ($J = 6$ Hz) and $\delta$ 2.39 ($J = 6$ Hz) due to the $-\text{CH}_2\text{CH}_2\text{OH}$ and $-\text{CH}_2\text{CH}_2\text{OH}$ protons, respectively.

Treatment of the diol 285 with a dichloromethane solution of the Swern dimethylsulfoxide-oxalyl chloride reagent at $-78^\circ$C, followed by addition of triethylamine$^{82}$ and column chromatography of the crude product mixture on silica gel, provided the aldehyde 286 in 58% yield (equation 126). The ir spectrum of 286 showed absorptions at 1728 and 1674 cm$^{-1}$ due to the saturated aldehyde and the $\alpha,\beta$-unsaturated aldehyde carbonyl groups, respectively. The $^1$H nmr spectrum of 286 exhibited a triplet at $\delta$ 9.60 ($J = 2$ Hz) due to the $-\text{CH}_2\text{CHO}$ proton, a singlet at $\delta$ 9.48 due to the $-\text{CCH}_2\text{O}$ proton, and a triplet at $\delta$ 6.83 ($J = 8$ Hz) due to the olefinic proton.
However, attempts to oxidize (±)-isolinaridiol (64) under the conditions described above persistently provided a terrible mixture of products. The ir spectrum of the crude product mixture showed absorptions at 1727 and 1673 cm⁻¹, suggesting that the desired dialdehyde had been generated. However, all attempts to purify the dialdehyde were not successful. Since, at this stage of the work, all of the available diol 64 had been used, further attempts to prepare (±)-isolinaridial (60) were not possible.

The work summarized above constitutes the successful total synthesis of (±)-isolinaridiol (64) in a total of nine steps from the nitrile 112 with an overall yield of 19% (see Scheme 26). Bis-acetylation of (±)-isolinaridiol (64) provided (±)-isolinaridiol diacetate (61). The identity of this material with natural 61 has not yet been established (see page 141).
Reagents and conditions: i, lithium diisopropylamide, THF-HMPA, 0°C; I(CH₂)₂OCH₂OMe, 0°C → room temp., 99%; ii, Bu₂AlH, DME, 60°C, 6 h; HOAc-H₂O, THF, room temp., 10 h, 92%; iii, LiAlH₄, Et₂O, room temp., 95%; iv, Bu₃Li, DME-TMEDA; Cl₂PONMe₂, room temp., 10 h; Me₂NH, 0°C, 2 h, 63%; v, Li, MeNH₂, -20°C, 10 min, 80%; vi, pyridinium p-toluenesulfonate, BuOH, 70°C, 91%; vii, DMSO-(COCl)₂, CH₂Cl₂, -78°C; Et₃N, -78°C to room temp., 85%; viii, dimethyl γ-butyrolactone phosphonate (261), lithium bis(trimethylsilyl)amide, THF, 0°C; 18-crown-6·nCH₃CN complex, -78°C, 4 h, 58%; ix, Bu₂AlH, THF, -78 → 0°C, 96%; x, Ac₂O, DMAP, pyridine, 90%.
III. Miscellaneous

In the chemical literature, there are a fairly large number of reported diterpenoid natural products bearing a general structure in which the decalin substructure has an endocyclic olefinic function instead of an exocyclic double bond as in palauolide (55) and isolinaridiol (64). Examples include kolavenic acid (287), kolavenol (288), the acid 289, the furano-olefin 290, junceic acid (291), kolav-3-en-15-oic acid (292), and kolavelool (293).
In order to employ the methylenecyclohexane annulation sequence used in our total synthesis of (±)-palauolide (55) and (±)-isolinaridiol (64) for the construction of the decalin substructure of this category of natural products, conditions would have to be developed to isomerize the double bond into the ring (Scheme 28).

Scheme 28
In connection with work directed toward the total synthesis of avarol, Sarma et al. reported that rhodium (III) chloride catalyzed isomerization of a 2:1 mixture of 294 and 295 furnished exclusively the dimethyl ether 294 (equation 127).

Attempts were made to isomerize the exocyclic double bond of a number of intermediates prepared during the course of the synthesis of palauolide (55) and isolinaridiol (64). When a solution of the decalone 114 in ethanol was refluxed in the presence of rhodium (III) chloride or of p-toluenesulfonic acid, a complicated mixture of products was obtained in each case (equation 128).

Treatment of the alcohol 126 with potassium 3-aminopropylamide (KAPA) in 3-aminopropylamine (APA), or with rhodium (III) chloride
in ethanol, gave, in each case, only recovered starting material. The same result was observed when the nitrile 112 was subjected to similar reaction conditions.

During the investigation of the use of dimethylboron bromide\textsuperscript{44} to cleave the methoxymethyl group of compound 276, a 3:1 mixture of the desired material 277 and the isomerized material 296 was obtained (\textsuperscript{1}H nmr spectroscopy, equation 129). Thus, it appeared that this reaction could be used to effect the desired double bond isomerization. Indeed, when a solution of the ether 276 in dichloromethane was treated with dimethylboron bromide (6 equiv.) at -78°C for a prolonged period of time (6 h), the alcohol 296 was obtained in 84% yield (equation 130).

The alcohol 296 exhibited an ir absorption at 3304 cm\textsuperscript{-1} due to the hydroxy group. The \textsuperscript{1}H nmr spectrum of 296 showed a very broad singlet at \( \delta 5.18 \) due to the endocyclic olefinic proton, and a broad singlet at \( \delta 1.57 \) due to the vinyl methyl protons. The \textsuperscript{1}H nmr spectra also exhibited two singlets at \( \delta 1.00 \) and 0.73, and a doublet at \( \delta 0.87 \) (J = 6 Hz) due to the methyl substituents on the bicyclic moiety. These chemical shifts are very similar to those reported for the corresponding protons in the furano-olefin 290.\textsuperscript{87}
\[
\text{Me}_2\text{BBr, CH}_2\text{Cl}_2 \\
-78^\circ\text{C, 1h}
\]

276 → 277

296

290
EXPERIMENTAL

General

Proton nuclear magnetic resonance ($^1$H nmr) spectra were recorded on either a Bruker model WP 80, Bruker model HXS 270, Varian model XL 300 or Bruker model WH 400 spectrometers using deuterochloroform as the solvent and tetramethyilsilane (TMS) as the internal or external standard. Signal positions are given in parts per million ($\delta$) from TMS. Coupling constants ($J$-values) are given in Hz. The multiplicity, number of protons, assignments (if possible), and coupling constants are given in parentheses. Abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; v, very.

Carbon nuclear magnetic resonance ($^{13}$C nmr) spectra were recorded on a Bruker model WH 400 spectrometer at 100.6 Hz or on a Varian model XL 300 spectrometer at 75.3 Hz using deuterochloroform as the solvent and TMS as the internal standard. Signal positions are given in parts per million ($\delta$) from TMS.

Infrared (ir) spectra were recorded either on a Perkin-Elmer model 1710 Fourier transform spectrophotometer with internal calibration or on a Perkin-Elmer model 710B spectrophotometer using the 1601 cm$^{-1}$ band of polystyrene film for calibration.

Low resolution mass spectra (LRMS) were recorded on a Varian/MAT CH4B spectrometer. High resolution mass spectra (HRMS) were recorded on a Kratos/AEI MS 50 or MS 902 spectrometer. In cases of compounds with
trimethylstannyl groups the molecular weight determinations (HRMS) were based on $^{120}$Sn and were made on the ($M^+ - 15$) peak.

Gas-liquid chromatography (glc) was performed on either a Hewlett-Packard model 5880 or model 5890 capillary gas chromatograph, both using a flame ionization detector and a 25 m x 0.21 mm fused silica column coated with cross-linked SE-54.

Thin layer chromatography (tlc) was performed on commercially available aluminum backed silica gel plates (E. Merck, type 5554). Visualization was accomplished with iodine vapor, ultraviolet light or a 5% solution of ammonium molybdate in 10% aqueous sulfuric acid (w/v). Conventional column chromatography was done on 70-230 mesh silica (E. Merck, Silica Gel 60) while flash chromatography was done on 230-400 mesh silica gel (E. Merck, Silica Gel 60). Silica gel impregnated with silver nitrate was prepared according to the following procedure. A solution of 12.5 g of silver nitrate in 100 mL of distilled water was added to 50 g of 70-230 mesh silica gel with stirring until the slurry was homogeneous. Most of the water was removed under reduced pressure (20 torr) and the silica gel was dried under reduced pressure (0.02 torr) over Drierite overnight at room temperature with protection from light.

Melting points (uncorrected) were measured on a Fischer-Johns melting point apparatus. Distillation temperatures (uncorrected) are indicated as air-bath temperatures of Kugelrohr distillations.

Unless otherwise stated, all reactions were carried out under an atmosphere of dry argon, with dry solvents in flame dried glassware.

Cold temperatures were maintained by the use of the following baths:
aqueous calcium chloride/CO$_2$ (-20°C, -30°C, -40°C), acetonitrile/CO$_2$ (-48°C), chloroform/CO$_2$ (-63°C), acetone/CO$_2$ (-78°C).

All temperatures recorded were in degrees Celsius.

Solvents and Reagents

Petroleum ether refers to a hydrocarbon mixture with b.p. 30-60°C. Ether refers to diethyl ether. Tetrahydrofuran, ether, dimethoxyethane and benzene were distilled from sodium benzophenone ketyl. Dichloromethane and carbon tetrachloride were distilled from phosphorus pentoxide. Iodomethane was passed through a short column of basic alumina (activity I) before use.

Diisopropylamine, triethylamine, pyridine, collidine, lutidine, hexamethylphosphoramide, dimethyl sulfoxide, and acetonitrile were distilled from calcium hydride and stored over activated 4Å molecular sieves. N,N,N',N'-Tetramethylethylene diamine, toluene and dimethylamine were distilled from sodium. Ethylamine was distilled from lithium.

Ethanol and methanol were distilled from magnesium. tert-Butyl alcohol was dried over activated powdered 3Å molecular sieves. Dimethylformamide was dried over activated 4Å molecular sieves and distilled before use.

p-Toluenesulfonyl chloride was purified by recrystallization from chloroform-petroleum ether. Phosphorus trichloride and trimethylsilyl chloride were freshly distilled before use. Boron trifluoride-etherate was distilled under reduced pressure (~55°C/16 torr). Benzyl chloro-
methyl ether was distilled under reduced pressure (-120°C/16 torr).

Triethylphosphite and trimethylphosphite were dried over sodium, decanted and distilled before use. Hexamethylditin was distilled and stored under argon.

Copper(I) bromide-dimethyl sulfide complex was prepared by the method described by Wats\textsuperscript{96} and phenylthiocopper was prepared by the method described by Posner.\textsuperscript{97} Magnesium bromide-etherate was prepared by the reaction of 1,2-dibromoethane with magnesium metal in ether, followed by removal of ether under reduced pressure (0.02 torr) at room temperature.

Triphenylphosphine was purified by recrystallization from methanol-ethyl acetate. N-Bromosuccinimide was recrystallized from hot water. 18-Crown-6 ether was recrystallized from dry acetonitrile and dried under reduced pressure (0.02 torr).\textsuperscript{76}

Tetra-n-butylammonium fluoride, prepared by the titration of hydrofluoric acid with tetra-n-butylammonium hydroxide, was crystallized at -0°C and freeze dried under reduced pressure (0.02 torr). Dimethylaminophosphorodichloridate was prepared by the method described by Walsh et al.\textsuperscript{98} Phenoxythiocarbonyl chloride was prepared by the method described by Miyazaki.\textsuperscript{99} Pyridinium p-toluenesulfonate was prepared by the method described by Miyashita et al.\textsuperscript{100} Methyl bis(trifluoroethyl)-phosphonoacetate was prepared by the method described by Still et al.\textsuperscript{74}

Manganese(IV) oxide was prepared by the reaction between potassium permanganate and manganese sulfate.\textsuperscript{101} Sodium amalgam (4%) was prepared by mixing sodium and mercury.\textsuperscript{102}
Solutions of methyllithium in ether and n-butyllithium in hexanes were obtained from Aldrich Chemical Co., Inc. and were standardized using the procedure of Kofron et al. Potassium hydride and sodium hydride were washed free of oil with dry ether, dried under a stream of argon and weighed before use.

All other reagents were commercially available and were utilized without further purification.

Preparation of 3,6-dimethyl-2-cyclohexen-1-one (115)

\[
\text{To a cold (-78°C) solution of diisopropylamine (8.4 mL, 60 mmol) in THF (50 mL) was added n-butyllithium (42 mmol) as a solution in hexanes. The resulting solution was stirred at 0°C for 15 min and recooled to -78°C. 3-Methyl-2-cyclohexen-1-one (4.5 mL, 40 mmol) was added dropwise and the mixture was stirred for 30 min at -78°C. To the resultant white slurry was added iodomethane (5 mL, 80 mmol), the reaction mixture was allowed to warm gradually to room temperature, and then was stirred overnight. The reaction mixture was diluted with pentane, and washed with water. The organic layer was separated and the aqueous layer was extracted twice with pentane. The organic extracts were combined, washed once with 2N hydrochloric acid and three times with brine, and} \]
then were dried (MgSO<sub>4</sub>), filtered and concentrated.

Distillation [bp 40-42°C/0.02 torr (lit. 30 bp 95-100°C/22 torr)], of
the remaining oil yielded 4.6 g (93%) of the cyclohexenone 115. This
material was homogeneous by glc analysis and exhibited ir (film): 3031,
1672, 1635 cm<sup>-1</sup>; <sup>1</sup>H nmr (80 MHz) δ: 5.83 (m, 1H, olefinic proton), 3.72
(m, 1H, H<sub>A</sub>), 2.50-1.40 (m, 4H, methylene protons), 1.96 (br s, 3H, vinyl
methyl protons), 1.13 (d, 3H, J = 7 Hz, methyl protons).

Preparation of 5-chloro-2-trimethylstannyl-1-pentene (39)

![Diagram of 5-chloro-2-trimethylstannyl-1-pentene](image)

To a cold (-20°C) solution of hexamethylditin (16 mL, 70 mmol) in
THF (500 mL) was added methyllithium (80 mmol) as a solution in ether.
The resulting pale yellow solution was stirred at -20°C for 20 min and
then was cooled to -78°C. Solid copper(I) bromide-dimethylsulfide
complex (14.8 g, 60 mmol) was added in one portion and the mixture was
stirred at -78°C for 5 min and then at -63°C for 30 min. The resulting
reddish brown solution was recooled to -78°C. 5-Chloro-1-pentyne (6.4
ml, 60 mmol) was added and the reaction mixture was stirred at -78°C for
6 h. Acetic acid (3.4 mL, 60 mmol) was added and the mixture was
stirred for 10 min. Saturated aqueous ammonium chloride (pH 8) and
petroleum ether were added. The mixture was allowed to warm to room
temperature and was stirred vigorously with exposure to air. The blue aqueous layer was separated and extracted twice with petroleum ether. The combined extract was washed once with saturated aqueous ammonium chloride (pH 8) and twice with brine, and then was dried (MgSO₄), filtered and concentrated. The residual material was subjected to column chromatography on silica gel (450 g, elution with petroleum ether). Distillation [bp 95-100°C/15 torr (lit. °C/25 torr)] of the oil obtained from the appropriate fractions provided 9.6 g (62%) of the chloride 39 as a colorless oil. This material was homogeneous by glc analysis and exhibited ir (film): 3040, 930 cm⁻¹; ¹H nmr (80 MHz) δ: 5.71 (dt, 1H, J = 2.5, 1.2 Hz, J_Sn-H = 150 Hz, Hₐ), 5.23 (dt, 1H, J = 2.5, 0.8 Hz, J_Sn-H = 70 Hz, Hₐ), 3.51 (t, 2H, J = 7 Hz, -CH₂Cl), 2.43 (br t, 2H, J = 7 Hz, allylic CH₂), 1.89 (quintet, 2H, J = 7 Hz, -CH₂CH₂CH₂Cl), 0.15 (s, 9H, J_Sn-H = 52/54 Hz, -SnMe₃).

Preparation of 5-[2-(5-Chloro-1-pentenyl)]-2,5-dimethylcyclohexanone (121)

To a cold (-78°C) solution of 5-chloro-2-trimethylstannyl-1-pentene (39) (1.7 g, 6.4 mmol) in THF (50 mL) was added a solution of methyllithium in ether (7.1 mmol). After the mixture had been stirred
at -78°C for 20 min, solid magnesium bromide-etherate (1.7 g, 6.6 mmol) was added in one portion and the resulting milky solution was stirred for an additional 20 min. Solid copper(I) bromide-dimethyl sulfide complex (0.28 g, 1.4 mmol), boron trifluoride-etherate (0.71 mL, 5.8 mmol) and the ketone 115 (0.75 mL, 5.3 mmol) were added successively. After the resulting bright yellow mixture had been stirred at -78°C for 3 h, saturated aqueous ammonium chloride (pH 8) was added. The mixture was warmed to room temperature and stirred vigorously with exposure to air. The blue aqueous layer was separated and extracted twice with petroleum ether. The combined organic extract was washed once with aqueous ammonium chloride (pH 8) and three times with brine, and then was dried (MgSO₄) and concentrated. Distillation (air-bath temperature 88-89°C/0.02 torr) of the remaining oil provided 0.93 g (77%) of a colorless oil. Analysis of this material by glc and ¹H nmr spectroscopy showed that it consisted of a mixture of epimers of 121 in the ratio of ~2:1. This material exhibited ir (film): 3098, 1705, 1640, 905 cm⁻¹; ¹H nmr (80 MHz) δ: 4.93 (br s, ~1.3H, olefinic protons of the major isomer), 4.80 (m, ~0.7 H, olefinic protons of the minor isomer), 3.59 (br t, 2H, -CH₂Cl), 2.9-1.2 (m, 11H), 1.15 (s, ~1H, tertiary methyl of minor isomer), 1.05 (d, ~2H, J = 7 Hz, -CHCH₃ of major isomer), 1.03 (s, ~2H, tertiary methyl of major isomer), 1.00 (d, ~1H, J = 7 Hz, -CHCH₃ of minor isomer). Exact Mass calcd. for C₁₃H₂₁ClO: 228.1281; found: 228.1276.
Preparation of the ketones 114 and 122

![Ketone Structures](image)

To a solution of potassium tert-butoxide (6.2 g, 55 mmol) in tert-butyl alcohol (40 mL) was added a solution of the chloro ketone 121 (6.3 g, 27 mmol) in tert-butanol (10 mL) and the solution was stirred at 30°C for 12 h. The reaction mixture was neutralized with 2N hydrochloric acid with cooling and the resultant mixture was extracted three times with petroleum ether. The combined extract was washed three times with brine and then was dried (MgSO\(_4\)) and concentrated. Distillation (air-bath temperature 80-85°C/0.02 torr) of the remaining oil yielded 4.6 g (89%) of a colorless oil. Glc analysis of this oil showed that it consisted of a mixture of two compounds in a ratio of 94:6. A portion of this material was subjected to column chromatography, so that a pure sample of each compound was available for characterization. Thus column chromatography of this material (0.22 g) on silica gel impregnated with 25% silver nitrate (25 g, elution with petroleum ether-ether, 25:1, v/v) followed by concentration of the appropriate fractions provided 0.17 g of the trans ketone 114 and trace amounts of the less polar cis ketone 122. The trans ketone 114 exhibited ir (film): 3086, 1713, 1638, 895, 876 cm\(^{-1}\); \(^1\)H nmr (400 MHz) \(\delta\): 4.70 (br s, 2H, olefinic protons), 2.40-2.04 (m, 5H), 1.96 (dt, 1H, \(J = 4\) Hz, 13 Hz), 1.90-1.78 (m, 2H), 1.69-1.50 (m, 3H), 1.32-1.15 (m, 1H), 0.99 (d, 3H, \(J = 6.0\) Hz, methyl protons),
0.87 (s, 3H, angular methyl protons). $^{13}$C nmr (100.6 MHz) δ: 204.46 (carbonyl carbon), 155.85 (quaternary olefinic carbon), 105.54 (secondary olefinic carbon), 58.01, 44.51 (tertiary carbons), 35.92 (quaternary carbon), 35.92, 32.19, 31.75, 26.61, 21.05 (secondary carbons), 18.91, 14.36 (methyl carbons). Exact Mass calcd. for C$_{13}$H$_{20}$O: 192.1514; found: 192.1515.

The cis ketone 122 exhibited ir (film): 3084, 1708, 1639, 894, 874 cm$^{-1}$; $^1$H nmr (400 MHz) δ: 4.74, 4.63 (br s, br s, 1H each, olefinic protons), 2.39-2.25 (m, 4H), 2.17-2.08 (m, 2H), 1.92-1.55 (m, 6H), 1.31 (s, 3H, angular methyl protons), 0.98 (d, 3H, $J$ = 6 Hz, methyl protons). Exact Mass calcd. for C$_{13}$H$_{20}$O: 192.1514; found: 192.1517.

Preparation of the alcohol 125

To a solution-suspension of lithium aluminum hydride (22 mg, 0.57 mmol) in ether (2 mL) was added dropwise a solution of the trans ketone 114 (91 mg, 0.47 mmol) in dry ether (0.5 mL). The reaction mixture was stirred for 3 h and then was treated with solid sodium sulfate decahydrate until the evolution of gas ceased. The mixture was filtered and the residue was washed three times with ether. The filtrate was concentrated and the residual oil was distilled (air-bath temperature
110-115°C/0.5 torr) to yield 76 mg (84%) of the alcohol 125. This material was homogeneous by gc analysis and exhibited ir (film): 3490 (br), 3075, 1637, 895 cm⁻¹; ¹H nmr (400 MHz) δ: 4.55 (t, 1H, J = 1.5 Hz, olefinic proton), 4.53 (br s, 1H, olefinic proton), 3.56 (br s, 1H, Hₐ), 2.40 (br dt, 1H J = 4, 12 Hz, Hₜ), 2.14 (br d, 1H, J 12 Hz, Hₜ), 1.95-1.80 (m, 2H), 1.70-1.30 (m, 7H), 1.20 (br s, 2H), 1.17 (s, 3H, angular methyl protons), 0.98 (d, 3H, J = 6 Hz, methyl protons). Exact Mass calcd. for C₁₃H₂₂O: 194.1670; found: 194.1670.

Preparation of the alcohol 126

Liquid ammonia (15 mL) was condensed into a cold (-78°C) dried flask containing calcium (55 mg, 14 mmol) and the mixture was stirred under reflux (dry ice-acetone condenser) for 10 min. An ethereal solution of the trans ketone 114 (50 mg, 1.3 mmol) was added and the mixture was refluxed for 45 min. The reaction mixture was quenched with ethanol (150 μL) and water (2 mL) and then was extracted three times with ether. The combined organic extract was washed three times with brine, dried (MgSO₄) and concentrated. Distillation (air-bath temperature 80-82°C/0.5 torr) yielded 38 mg (75%) of the alcohol 126 which solidified on cooling. Recrystallization from ether afforded colorless
prisms, m.p. 129-130°C. This material was homogeneous by glc analysis and exhibited ir (CHCl$_3$): 3300 (br), 3080, 1642, 1035, 895 cm$^{-1}$; $^1$H nmr (400 MHz) δ: 4.62 (t, 1H, J = 1.7 Hz, olefinic proton), 4.59 (t, 1H, J = 1.4 Hz, olefinic proton), 3.04 (t, 1H, J = 9 Hz, HA), 2.35 (br dt, 1H, J = 4, 12 Hz, HB), 2.14 (br d, 1H, J = 12 Hz, HC), 1.99 (m, 1H), 1.88 (m, 1H), 1.71-1.14 (m, 9H), 1.05 (d, 3H, J = 6 Hz, methyl protons), 0.98 (s, 3H, angular methyl protons). Exact Mass calcd. for C$_{13}$H$_{22}$O: 194.1670; found: 194.1670.

Preparation of the tosylate 127

A solution of the alcohol 126 (22 mg, 0.11 mmol), p-toluenesulfonyl chloride (26 mg, 0.13 mmol) and 4-N,N-dimethylaminopyridine (16 mg, 0.13 mmol) in dichloromethane (2 mL) was stirred at room temperature for 12 h. The solution was diluted with ether, washed with saturated aqueous sodium bicarbonate and brine, and then was dried (MgSO$_4$) and concentrated. The residual material was subjected to column chromatography on silica gel (4 g, elution with petroleum ether-ether, 8:1 v/v). Concentration of the appropriate fractions provided the tosylate 127 (32 mg, 83%) which exhibited one spot on tlc; ir (CHCl$_3$): 3089, 3032, 1638, 1600, 1496, 898 cm$^{-1}$; $^1$H nmr (80 MHz) δ: 7.75, 7.31 (d, d, 2H each, J =
8 Hz, aromatic protons), 4.60 (m, 2H, olefinic protons), 4.38 (m, 1H, CHOTs), 2.44 (s, 3H, aromatic methyl protons), 2.5-1.0 (m, 12H), 1.00 (s, 3H, angular methyl protons), 0.82 (d, 3H, J = 7.5 Hz, methyl protons). Exact Mass calcd. for C20H28O3S: 348.1759; found: 348.1756.

Preparation of nitrile 112a

A solution of the tosylate 127 (9 mg, 25 µmol) and sodium cyanide (2.5 mg, 52 µmol) in dry HMPA (1 mL) was heated at 80°C for 3 h. The reaction mixture was diluted with petroleum ether and washed once with water, twice with aqueous copper(II) sulfate and twice with brine. The organic layer was dried (MgSO4) and concentrated and the residue was subjected to column chromatography on silica gel (1 g, elution with petroleum ether-ether, 19:1 v/v). The appropriate fractions were collected and concentrated. Distillation (air-bath temperature 65-68°C/0.02 torr) of the remaining oil yielded 2.3 mg (44%) of the nitrile 112a as a colorless oil which was homogeneous by glc analysis and exhibited ir (film): 3070, 2225, 1638, 998, 895 cm⁻¹; ¹H nmr (400 MHz) δ: 4.61 (t, 1H, J = 1.5 Hz, olefinic proton), 4.56 (br s, 1H, olefinic proton), 2.60 (dt, 1H, J = 1.3, 4.5 Hz, HA), 2.41 (tdt, 1H, J = 1.5, 5, 14 Hz, HB), 2.16 (br d, 1H, J = 14 Hz, HC), 2.00-1.87 (m, 2H), 1.75-1.30
(m, 8H), 1.24 (s, 3H, angular methyl protons), 1.14 (d, 3H, J = 6.4 Hz, methyl protons). **Exact Mass** calcd. for C\textsubscript{14}H\textsubscript{21}N: 203.1674; found: 203.1676.

**Preparation of the nitriles 112a and 112b**

To a cold (0°C) solution of (p-toluenesulfonyl) methyl isocyanide\textsuperscript{35} (2.9 g, 15 mmol) in dry HMPA (17 mL) was added potassium tert-butoxide (4.0 g, 36 mmol) and the solution was stirred for 15 min. tert-Butyl alcohol (0.47 mL, 5 mmol) and the ketones 114 and 122 (0.96 g, 5 mmol; 94:6 respectively), were added and the resultant mixture was stirred at room temperature for 1 h and at 45°C for 88 h. The reaction mixture was poured into cool 1N hydrochloric acid and the mixture was extracted three times with petroleum ether. The combined extract was washed once with water, twice with aqueous copper(II) sulfate and twice with brine and then was dried (MgSO\textsubscript{4}) and concentrated. The residual oil was subjected to flash chromatography on silica gel (40 g, elution with petroleum ether-ether, 19:1 v/v). The appropriate fractions were collected and concentrated. Distillation (air-bath temperature 65-68°C/0.02 torr) of the remaining oil yielded 0.69 g (68%) of a colorless oil. Glc analysis of this oil showed that it consisted of a
mixture of two compounds, 112a and 112b, in a ratio of 15:85, respectively. Column chromatography of a portion (0.1 g) of this material on silica gel impregnated with 25% silver nitrate (55 g, elution with petroleum ether-ether, 25:1, v/v) afforded pure samples of each compound for characterization.

The less polar minor component exhibited spectra identical with those of the axial nitrile 112a prepared previously (see above). The more polar component 112b exhibited ir (film): 3070, 2225, 1638, 998, 895 cm⁻¹; ¹H nmr (400 MHz) δ: 4.68 (t, 1H, J = 1.7 Hz, olefinic proton), 4.62 (br s, 1H, olefinic proton), 2.36 (br t, 1H, J = 12 Hz, H₈), 2.17 (br d, 1H, J = 12 Hz, H₆), 2.08 (t, 1H, J = 11.5 Hz, H₄), 2.0-1.85 (m, 2H), 1.78-1.25 (m, 8H), 1.17 (d, 3H, J = 6.2 Hz, methyl protons), 0.96 (s, 3H, angular methyl protons). Exact Mass calcd. for C₁₄H₂₁N: 203.1674; found: 203.1676.

Preparation of 4-chloro-1-butyne (134)

\[ \text{Cl} \quad \equiv \quad \equiv \]

To dimethylformamide (50 mL) at room temperature was added, dropwise, phosphorus trichloride (2.5 mL, 69 µmol) and the mixture was stirred for 90 min. To the resultant yellow slurry was added 3-butyn-1-ol (6.7 mL, 0.2 mol) and stirring was continued for 40 min. The crude product was distilled (70-110°C) from the reaction mixture and collected
as a colorless oil, which was then fractional distilled (bp 80-85°C/760 torr) to afford 7 g (42%) of the chloride 134. \( \text{IR (CH}_2\text{Cl}_2): 3300, 2120, 650 \text{ cm}^{-1}; \text{^1H nmr (80 MHz) } \delta: 3.63 (t, 2H, J = 7 Hz, -CH}_2\text{Cl), 2.68 (dt, 2H, J = 2.5, 7 Hz, -CH}_2\text{CH}_2\text{Cl), 2.11 (t, 1H, J = 2.5 Hz, acetylenic proton). Exact Mass} \) calcd. for \( \text{C}_9\text{H}_8\text{Cl}: 88.0079; \text{found: 88.0074.} \\

**Preparation of ethyl 5-chloro-2-pentynoate (117)**

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

To a cold (-78°C) solution of 4-chloro-1-butyne (134) (4.4 g, 50 mmol) in THF (100 mL) was added methyllithium (55 mmol) as a solution in diethyl ether. After the mixture had been stirred at -78°C for 10 min and at -20°C for 1 h, ethyl chloroformate (5.7 mL, 60 mmol) was added and the resultant mixture was stirred at -20°C for 1 h, and then at room temperature for an additional hour. The reaction mixture was diluted with ether, washed twice with aqueous sodium bicarbonate and twice with brine, and then was dried (MgSO\(_4\)) and concentrated. The residue was subjected to flash column chromatography on silica gel (300 g, elution with petroleum ether-ether, 9:1 v/v) and the appropriate fractions were collected and concentrated. Distillation (air-bath temperature 80-82°C/0.02 torr) of the remaining oil yielded 5.0 g (63%) of the pentynoate 117 as a colorless oil which was homogeneous by glc analysis and
exhibited ir (film): 2235, 1710, 1258, 1090, 760 cm\(^{-1}\); \(^1\)H nmr (80 MHz) \(\delta\): 4.20 (q, 2H, \(J = 7\) Hz, -OCH\(_2\)-), 3.65 (t, 2H, \(J = 7\) Hz, ClCH\(_2\)-), 2.83 (t, 2H, \(J = 7\) Hz, ClCH\(_2\)CH\(_2\)-), 1.32 (t, 3H, \(J = 7\) Hz, CH\(_3\)-). Exact Mass calcd. for C\(_5\)H\(_4\)O\(^{35}\)ClO (M\(^+\)-OEt): 114.9950; found: 114.9950.

**Preparation of ethyl (Z)-5-chloro-3-trimethylstannyl-2-pentenoate (116)**

![Structural diagram]

To a cold (-20°C) solution of hexamethylditin (1.1 mL, 4.9 mmol) in THF (50 mL) was added methyllithium (4.9 mmol) as a solution in ether. The resulting pale yellow solution was stirred at -20°C for 20 min and then solid phenylthiocopper (0.84 g, 4.9 mmol) was added. The resulting red solution was stirred at -20°C for an additional 15 min and then was cooled to -78°C. The chloro pentynoate 117 (0.74 g, 4.6 mmol) was added and the mixture was stirred at -78°C for 15 min and at -48°C for 4 h. Saturated aqueous ammonium chloride (pH 8) and petroleum ether (300 mL) were added, and the mixture was warmed to room temperature. The organic layer was separated, washed twice with brine and the dried (MgSO\(_4\)), filtered through a short pad of Florisil and concentrated. G lc analysis of the residue showed that it consisted of a mixture of two compounds. Careful fractional distillation (air-bath temperature 60-62°C/0.02 torr) of this material afforded 0.39 g (26%) of the more volatile desired
ester 116. This material exhibited ir (film): 1704, 1603, 1207, 774 cm\(^{-1}\); \(^1\)H nmr (80 MHz) \(\delta\): 6.43 (t, 1H, \(J = 1.1\) Hz, \(J_{Sn-H} = 114\) Hz, olefinic proton), 4.19 (q, 2H, \(J = 7\) Hz, -OCH\(_2\)-), 3.56 (br t, 2H, \(J = 7\) Hz, ClCH\(_2\)-), 2.86 (t, 2H, \(J = 7\) Hz, ClCH\(_2\)CH\(_2\)-), 1.29 (t, 3H, \(J = 7\) Hz, CH\(_3\)-), 0.21 (s, 9H, \(J_{Sn-H} = 52/54\) Hz, -SnMe\(_3\)). **Exact Mass** calcd. for \(C_9H_{16}^{35}ClO_2^{120}Sn\) (\(M^+\)-CH\(_3\)): 310.9859; found: 310.9866.

![structure]

136

The residual material from the above distillation was subjected to flash chromatography on silica gel (300 g, elution with petroleum ether-ether, 100:1 v/v). Concentration of the appropriate fractions and distillation (air-bath temperature 75-78°C/0.02 torr) of the remaining material gave a small sample of the less volatile product 136, which exhibited ir (film): 1702, 1601, 1200, 770 cm\(^{-1}\); \(^1\)H (80 MHz) \(\delta\): 6.34 (t, 1H, \(J = 1.1\) Hz, \(J_{Sn-H} = 120\) Hz, olefinic proton), 4.18 (q, 2H, \(J = 7\) Hz, -OCH\(_2\)), 2.55 (br t, 2H, \(J = 7\) Hz, allylic protons), 1.28 (t, 3H, \(J = 7\) Hz, -OCH\(_2\)CH\(_3\)), 0.83 (m, 2H, -SnCH\(_2\)-), 0.22 (s, 9H, \(J_{Sn-H} = 52/54\) Hz, -SnMe\(_3\)), 0.12 (s, 9H, \(J_{Sn-H} = 50/52\) Hz, -SnMe\(_3\)). **Exact Mass** calcd. for \(C_{12}H_{25}O_2^{120}Sn_2\) (\(M^+\)-CH\(_3\)): 440.9897; found: 440.9900.
Preparation of 1-tert-butyldimethylsilyloxy-3-butyne (137)

\[
\text{SiO}\quad=\quad=\quad=\quad\text{CO}_2\text{Et}
\]

A solution of 3-butyne-1-ol (3.8 mL, 50 mmol), tert-butyldimethylsilyl chloride (9 g, 60 mmol) and imidazole (8.5 g, 125 mmol) in dimethylformamide (17 mL) was stirred at room temperature for 12 h. Aqueous sodium bicarbonate was added and the mixture was extracted three times with petroleum ether. The combined extract was washed twice with brine, dried (MgSO\textsubscript{4}) and concentrated. Distillation [bp 55-60°C/15 torr (lit.\textsuperscript{41} bp 45-46°C/2.5 torr)] of the remaining oil yielded 9 g (98%) of the silyl ether 137 which exhibited ir (film): 3300, 2100, 1110, 632 cm\textsuperscript{-1}; \textsuperscript{1}H nmr (80 MHz) \delta: 3.72 (t, 2H, J = 7 Hz, -OCH\textsubscript{2}-), 2.37 (dt, 2H, J = 2.5, 7 Hz, -CH\textsubscript{2}C=), 1.92 (t, 1H, J = 2.5 Hz, acetylenic proton), 0.90 (s, 9H, tert-butyl protons), 0.07 (s, 6H, methyl protons).

Preparation of ethyl 5-tert-butyldimethylsilyloxy-2-pentynoate (138)

To a cold (-78°C) solution of the alkyne (137) (9.2 g, 50 mmol) in
THF (180 mL) was added methyl lithium (55 mmol) as a solution in ether. After the solution had been stirred at -78°C for 10 min and at -20°C for 1 h, ethyl chloroformate (5.7 mL, 60 mmol) was added and the mixture was stirred at -20°C for 1 h, and at room temperature for 1 h. The reaction mixture was diluted with ether, washed twice with aqueous sodium bicarbonate and twice with brine, and then was dried (MgSO₄) and concentrated. Distillation (air-bath temperature 75-78°C/0.02 torr) of the remaining oil yielded 11.5 g (90%) of the pentynoate 138 as a colorless oil which exhibited IR (film): 2230, 1705, 1250, 1110, 1080 cm⁻¹; H NMR (80 MHz) δ: 4.20 (q, 2H, J = 7 Hz, -OCH₂CH₃), 3.76 (t, 2H, J = 7 Hz, SiOCH₂⁻), 2.52 (t, 2H, J = 7 Hz, -CH₂CH₃), 1.28 (t, 3H, J = 7 Hz, -OCH₂CH₃), 0.90 (s, 9H, tert-butyl protons), 0.07 (s, 6H, silyl methyl protons). Exact Mass calcd. for C₁₂H₂₁O₃Si (M⁺·CH₃): 241.1260; found: 241.1256.

Preparation of ethyl (Z)-5-tert-butyldimethylsilyloxy-3-trimethylstannyl-2-pentenoate (139)

\[
\begin{align*}
\text{SnMe}_3 & \\
\text{SiO} & \\
\text{CO}_2\text{Et} & \\
\end{align*}
\]

To a cold (-20°C) solution of hexamethylditin (2.6 mL, 12 mmol) in THF (120 mL) was added methyl lithium (13 mmol) as a solution in ether. The resulting pale yellow solution was stirred at -20°C for 20 min and then solid phenylthiocopper (2.1 g, 12 mmol) was added. The red solu-
tion was stirred at -20°C for an additional 15 min and then was cooled to -78°C. The pentynoate 138 (2.6 g, 10 mmol) was added and the mixture was stirred at -78°C for 15 min and at -40°C for 9 h. To the reaction mixture, saturated aqueous ammonium chloride (pH 8) and petroleum ether were added, and the mixture was warmed to room temperature. More petroleum ether was added until most of the phenylthiocopper had precipitated and the organic layer became nearly colorless. The organic layer was separated, washed twice with brine, dried (MgSO₄), filtered through a short pad of Florisil and concentrated. Distillation (air-bath temperature 91-95°C/0.02 torr) of the remaining oil yielded 3.8 g (91%) of the ester 139, which exhibited ir (film): 1700, 1600, 1110, 1052 cm⁻¹; ¹H nmr (80 MHz) δ: 6.40 (t, 1H, J = 1 Hz, J_Sn-H = 120 Hz, olefinic proton), 4.18 (q, 2H, J = 7 Hz, -OCH₂CH₃), 3.63 (t, 2H, J = 6.5 Hz, SiOCH₂-), 2.63 (br t, 2H, J = 6.5 Hz, SiOCH₂CH₂-), 1.28 (t, 3H, J = 7 Hz, -OCH₂CH₃-), 0.90 (s, 9H, tert-butyl protons), 0.18 (s, 9H, J_Sn-H = 52/54 Hz, -SnMe₃), 0.04 (s, 6H, silyl methyl protons). Exact Mass calcd. for C₁₅H₃₁O₃Si₁₂₀Sn (M⁺-CH₃): 407.1063; found: 407.1058.

Preparation of (Z)-5-tert-butyl(dimethyl)silyloxy-3-trimethylstannyl-2-penten-1-ol (140)
To a cold (-78°C) solution of the pentynoate 138 (3.8 g, 9 mmol) in THF (90 mL) was added a solution of diisobutylaluminum hydride (27 mmol) in hexanes. After the mixture had been stirred at -78°C for 1 h and at 0°C for 1 h, it was treated with aqueous ammonium chloride (1.6 mL) and diluted with ether. The mixture was stirred at room temperature for 5 min, dried (MgSO₄), filtered through Florisil and concentrated. Distillation (air-bath temperature 104-105°C/0.02 torr) of the residual oil yielded 3.3 g (96%) of the alcohol 140 which exhibited IR (film): 3350 (br), 1621, 1090, 1010 cm⁻¹; ¹H nmr (80 MHz) δ: 6.26 (br t, 1H, J = 6 Hz, olefinic H), 4.08 (t, 2H, J = 6 Hz, collapsed to a d on D₂O exchange, -CH₂OH), 3.57 (t, 2H, J = 7 Hz, SiOCH₂⁻), 2.43 (t, 2H, J = 7 Hz, SiOCH₂CH₂⁻), 1.18 (t, 1H, J = 6 Hz, exchanged with D₂O, -OH), 0.89 (s, 9H, tert-butyl protons), 0.19 (s, 9H, J_{Sn-H} = 52/54 Hz, -SnMe₃), 0.05 (s, 6H, silyl methyl protons). Exact Mass calcd. for C₁₃H₂₉O₂Si₂₁₂0Sn (M⁺-CH₃): 365.0958; found: 365.0959.

Preparation of (Z)-5-tert-butyldimethylsilyloxy-3-trimethylstannyl-1-methoxymethoxy-2-pentene (141)

\[
\begin{align*}
\text{SiO} & \quad \text{SnMe}_3 \\
\end{align*}
\]

To a cold (-20°C) solution of the alcohol 140 (3.3 g, 8.7 mmol) and diisopropylethylamine (2.3 mL, 13 mmol) in dichloromethane (25 mL) was
added chloromethyl methyl ether (1 mL, 13 mmol) and the mixture was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced pressure and the residual oil was triturated with petroleum ether. The organic solution was decanted and the remaining solid was washed three more times (decantation) with petroleum ether. The combined extract was concentrated and the residue was filtered through a short column of silica gel (75 g, elution with petroleum ether-ether, 9:1 v/v). The filtrate was concentrated and distillation (air-bath temperature 90-93°C/0.02 torr) of the remaining oil yielded 3.3 g (90%) of the diether 141, which exhibited \( \text{IR (film): } 1100, 1040 \text{ cm}^{-1}; \text{H} \text{nmr (80 MHz)} \delta: 6.21 (t, 1H, } J = 6 \text{ Hz, olefinic proton), 4.63 (s, 2H, acetal protons), 4.01 (d, 2H, } J = 6 \text{ Hz, } -\text{CCH}_2\text{O}-), 3.58 (t, 2H, } J = 7 \text{ Hz, } -\text{SiOCH}_2\text{-), 3.38 (s, 3H, } -\text{OCH}_3\text{), 2.45 (t, 2H, } J = 7 \text{ Hz, } -\text{CH}_2\text{CH}_2\text{C=), 0.91 (s, 9H, tert-butyl protons), 0.20 (s, 9H, } J_{\text{Sn-H}} = 52/54 \text{ Hz, } -\text{SnMe}_3\text{), 0.06 (s, 6H, silyl methyl protons). Exact Mass calcd. for } C_{15}H_{33}O_{3}Si_{12}O_{3}Sn (M^+CH_3): 409.1220; \text{ found: } 409.1228. \)

Preparation of (E)-5-tert-butyldimethylsilyloxy-3-methyl-1-methoxy-methoxy-2-pentene (142)
To a cold (-78°C) solution of the vinylstannane 141 (3.3 g, 8 mmol) in THF (65 mL) was added methyllithium (9 mmol) as a solution in diethyl ether. After the solution had been stirred at -78°C for 30 min, iodomethane (1.2 mL, 20 mmol) was added and the mixture was stirred for a further 90 min. The resultant solution was diluted with petroleum ether, washed three times with brine, dried (MgSO₄) and concentrated. Distillation (air-bath temperature 81-83°C/0.02 torr) of the remaining oil yielded 2 g (90%) of the alkene 142. This material was homogeneous by glc analysis and exhibited ir (film): 2725, 1100, 1050 cm⁻¹; ¹H nmr (80 MHz) δ: 5.36 (br t, 1H, J = 7 Hz, olefinic proton), 4.61 (s, 2H, acetal protons), 4.04 (d, 2H, J = 7 Hz, =CCH₂O⁻), 3.68 (t, 2H, J = 7 Hz, -SiOCH₂⁻), 3.35 (s, 3H, -OCH₃), 2.23 (t, 2H, J = 7 Hz, =CCH₂CH₂⁻), 1.69 (br s, 3H, vinyl methyl protons), 0.88 (s, 9H, tert-butyl protons), 0.03 (s, 6H, silyl methyl protons). Exact Mass calcd. for C₁₂H₂₅OSi (M⁺-OCH₂OCH₃): 213.1674; found: 213.1671.

Preparation of (E)-3-methyl-5-methoxymethoxy-3-penten-1-ol (143)

To a solution of tetra-n-butylammonium fluoride (5.6 g, 20 mmol) in THF (35 mL) at room temperature was added a solution of the silyl ether 142 (2 g, 7.2 mmol) in THF. After the solution had been stirred for 40
min, it was diluted with ether, washed three times with brine, dried
(MgSO₄) and concentrated. Distillation (air-bath temperature 81-83°C/
0.02 torr) of the remaining oil yielded 1.1 g (98%) of the homoallylic
alcohol 143 which exhibited IR (film): 3400 (br), 2760, 1040, 922 cm⁻¹;
¹H NMR (80 MHz) δ:  5.48 (br t, 1H, J = 7 Hz, olefinic proton), 4.65 (s,
2H, acetal protons),  4.11 (d, 2H, J = 7 Hz, −CH₂O), 3.73 (t, 2H, J =
6.5 Hz, HOCH₂⁻),  3.40 (s, 3H, −OCH₃), 2.30 (t, 2H, J = 6.5 Hz,
−CH₂CH₂⁻),  1.72 (br s, 4H, vinyl methyl and hydroxyl protons). Exact
Mass calcd. for C₆H₁₁O₂ (M⁺−CH₂OCH₃): 115.0759; found: 115.0762.

Preparation of (E)-3-methyl-5-methoxymethoxy-3-penten-1-yl tosylate
(144)

A solution of the alcohol 143 (0.84 g, 5.3 mmol), p-toluenesulfonyl
chloride (1.2 g, 6.3 mmol) and 4-N,N-dimethylaminopyridine (0.77 g, 6.3
mmol) in dichloromethane (15 mL) was stirred at room temperature for 12
h. The solution was diluted with ether, washed with saturated aqueous
sodium bicarbonate and brine, dried (MgSO₄) and concentrated. The
residual material was subjected to flash column chromatography on silica
gel (75 g, elution with petroleum ether-ether, 1:1 v/v). Collection and
concentration of the appropriate fractions provided the tosylate 144
(1.2 g, 75%) as a colorless oil which exhibited IR (film): 1600, 1360, 1180, 1100 cm⁻¹; ¹H nmr (80 MHz) δ: 7.83, 7.37 (d, d, 2H each, J = 8 Hz, aromatic protons), 5.38 (t, 1H, J = 6.5 Hz, olefinic proton), 4.64 (s, 2H, acetal protons), 4.14 (t, 2H, J = 7 Hz, -OCH₂CH₂-), 4.03 (d, 2H, J = 6.5 Hz, -CCH₂O-), 3.40 (s, 3H, -OCH₃), 2.48 (s, 3H, benzylic protons), 2.39 (t, 2H, J = 7 Hz, -OCH₂CH₂-), 1.65 (s, 3H, vinyl methyl protons). Exact Mass calcd. for C₁₄H₁₈O₄S (M⁺-CH₄O): 282.0926; found: 282.0930.

This tosylate decomposed on heating under vacuum and slowly turned brown on storage under argon in a freezer.

Preparation of (E)-5-iodo-1-methoxymethoxy-3-methyl-2-pentene (113)

![Structure](image)

To a solution of the tosylate 144 (1.27 g, 4.04 mmol) in dimethylformamide (8 mL) was added sodium iodide (1 g, 6.6 mmol) and the resultant mixture was stirred at room temperature for 4 days with protection from light. Water was added and the mixture was extracted three times with pentane. The combined extract was washed twice with brine, dried (MgSO₄) and concentrated. Distillation (air-bath temperature 48-51°C/0.02 torr) of the remaining oil yielded 1 g (91%) of the iodide 113 as a colorless oil which was stored over copper dust in a freezer. This material was homogeneous by glc analysis and exhibited IR (film): 2770,
1040 cm<sup>-1</sup>; <sup>1</sup>H nmr (80 MHz) δ: 5.41 (br t, 1H, J = 7 Hz, olefinic proton), 4.63 (s, 2H, acetal protons), 4.07 (d, 2H, J = 7 Hz, -CCH<sub>2</sub>O), 3.38 (s, 3H, -OCH<sub>3</sub>), 3.23 (t, 2H, J = 8 Hz, -CH<sub>2</sub>I), 2.58 (t, 2H, J = 8 Hz, -CH<sub>2</sub>CH<sub>2</sub>I), 1.68 (br s, 3H, vinyl methyl protons). <strong>Exact Mass</strong> calcd. for C<sub>8</sub>H<sub>15</sub>IO<sub>2</sub>: 270.0116; found: 270.0111.

**Preparation of the nitrile III**

![Chemical structure](image)

To a cold (-78°C) solution of diisopropylamine (0.17 mL, 1.2 mmol) in THF (10 mL) was added n-butyllithium (1.2 mmol) as a solution in hexanes and the mixture was stirred at 0°C for 15 min. HMPA (0.34 mL, 2 mmol) and a solution of a mixture of the nitriles 112a and 112b (0.2 g, 1 mmol; 15:85, respectively) in THF were added and the solution was stirred at 0°C for 15 min. To the resultant yellow solution at 0°C was added the iodide 113 (0.35 g, 1.3 mmol). The solution was allowed to warm gradually to room temperature and was stirred overnight. The solution was diluted with petroleum ether, washed with water, aqueous copper(II) sulfate, twice with brine, dried (MgSO<sub>4</sub>) and concentrated. The residual oil was subjected to flash column chromatography on silica
gel (35 g, elution with petroleum ether-ether, 3:1 v/v) and collection of the appropriate fractions afforded 0.24 g [94% based on recovery of 47 mg of the starting material and the nitriles, 112a and 112b, (60:40 (respectively))] of the nitrile 111 which exhibited ir (film): 3086, 2780, 2227, 1671, 1638, 1150, 1103, 1045, 2045, 895 cm⁻¹; ¹H nmr (400 MHz) δ: 5.35 (t, 1H, J = 6.5 Hz, Hₐ), 4.62 (s, 2H, acetal protons), 4.60, 4.55 (s, s, 1H each, exocyclic olefinic protons), 4.05 (d, 2H, J = 6.5 Hz, =CCH₂O⁻), 3.38 (s, 3H, -OCH₃), 2.40 (br dt, 1H, J = 5, 13.5 Hz, Hₜ), 2.14 (br dd, 1H, J = 4, 13.5 Hz, Hₖ), 2.0-1.82 (m, 5H), 1.8-1.5 (m, 9H), 1.68 (s, 3H, vinyl methyl protons), 1.27 (s, 3H, angular methyl protons), 1.11 (d, 3H, J = 6 Hz, methyl protons). Exact Mass calcd. for C₂₂H₃₅NO₂: 345.2668; found: 345.2668.

Preparation of the aldehyde 147

To a solution of the nitrile 111 (0.17 g, 0.5 mmol) in dimethoxyethane (7 mL) was added diisobutylaluminum hydride (2 mmol) as a solution in hexanes and the mixture was heated at 60°C for 6 h. The reaction mixture was cautiously poured into water, and the resultant
mixture was neutralized with 1N hydrochloric acid and extracted three times with ether. The extracts were combined, washed with brine, dried (Na$_2$SO$_4$) and concentrated. The residual oil was dissolved in a mixture of THF-acetic acid-water (4 mL, 3:1:0.16 by volume) and stirred at room temperature for 12 h. After removal of the solvents under reduced pressure (0.02 torr), the residue was dissolved in ether. The solution was washed with aqueous sodium bicarbonate and brine, then dried (MgSO$_4$) and concentrated to afford 0.15 g (87%) of the aldehyde 147. This material was homogeneous by tlc analysis and exhibited ir (film): 3086, 2776, 2736, 1713, 1671, 1637, 1149, 893 cm$^{-1}$; $^1$H nmr (400 MHz) $\delta$: 9.98 (s, 1H, aldehyde proton), 5.36 (t, 1H, $J = 7$ Hz, H$_A$), 4.62 (s, 2H, acetal protons), 4.58 (br s, 2H, olefinic protons), 4.06 (d, 2H, $J = 7$ Hz, =CCH$_2$O-), 3.37 (s, 3H, -OCH$_3$), 2.27 (br dt, 1H, $J = 5$, 13 Hz, H$_B$), 2.12 (br d, 1H, $J = 13$ Hz, H$_C$), 2.0-1.1 (m, 14H), 1.69 (s, 3H, vinyl methyl protons), 1.03 (d, 3H, $J = 7$ Hz, methyl protons), 0.96 (s, 3H, angular methyl protons). Exact Mass calcd. for C$_{22}$H$_{36}$O$_3$: 348.2664; found: 348.2658.

Preparation of the alcohol 152

![Diagram of the alcohol 152]
To a solution-suspension of lithium aluminum hydride (16 mg, 0.42 mmol) in ether (3 mL) was added an ethereal solution of the aldehyde 147 (99 mg, 0.28 mmol) and the mixture was stirred at room temperature for 1 h. Sodium sulfate decahydrate was added in small portions to the stirred mixture until evolution of gas ceased. The mixture was filtered and the residue was washed three times with ether. The combined filtrate was concentrated to afford 92 mg (93%) of the alcohol 152 which exhibited IR (film): 3469 (br), 3085, 1669, 1635, 1150, 1103, 1043, 892 cm\(^{-1}\); \(^{1}\)H NMR (400 MHz) \(\delta\): 5.47 (t, 1H, \(J = 7\) Hz, \(H_A\)), 4.63 (s, 2H, acetal protons), 4.52 (br s, 2H, exocyclic olefinic protons), 4.06 (d, 2H, \(J = 7\) Hz, =CCH\(\text{H}_2\)O), 3.80, 3.70 (dd, dd, 1H each, \(J = 6, 12\) Hz; each collapses to d, \(J = 12\) Hz on D\(_2\)O exchange, -CH\(\text{H}_2\)OH), 3.38 (s, 3H, -OCH\(_3\)), 2.27 (br dt, 1H, \(J = 4, 14\) Hz, \(H_B\)), 2.11 (br d, 1H, \(J = 14\) Hz, \(H_C\)), 1.93-1.40 (m, 12H), 1.71 (s, 3H, vinyl methyl protons), 1.27-1.11 (m, 2H), 1.06 (s, 3H, angular methyl protons), 1.02 (t, 1H, \(J = 6\) Hz, D\(_2\)O exchanged, -CH\(\text{H}_2\)OH), 0.94 (d, 3H, \(J = 6.5\) Hz, methyl protons); NMR difference spectrum showed positive signal enhancement at \(\delta\) 3.80 and 3.70 (-CH\(\text{H}_2\)OH) on irradiation at \(\delta\) 1.06 (angular methyl protons). Exact Mass calcd for C\(_{21}\)H\(_{35}\)O\(_2\) (M\(^+\)-OCH\(_3\)): 319.2637; found: 319.2636.
Preparation of the xanthate 153

To a solution of the alcohol 152 (67 mg, 0.2 mmol) in dimethylformamide (1 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.17 mL, 1.3 mmol) and the solution was stirred at room temperature for 5 min. Carbon disulphide (0.93 mL, 15 mmol) was added and stirring was continued at room temperature for 1 h. The resultant red solution turned yellow on addition of iodomethane (1.8 mL, 29 mmol). The solution was stirred for three more hours at room temperature. Excess reagents and solvent were removed under reduced pressure (0.02 torr), and the residue was subjected to column chromatography on silica gel (3 g, elution with petroleum ether-ether, 6:4 v/v). Collection and concentration of the appropriate fractions afforded 86 mg (100%) of the xanthate 153 as a viscous yellow oil which exhibited IR (film): 3085, 1669, 1635, 1219, 894 cm\(^{-1}\); \(^1\)H NMR (400 MHz) \(\delta\): 5.36 (t, 1H, \(J = 7\) Hz, \(H_A\)), 4.69, 4.64 (d, d, 1H each, \(J = 12\) Hz, -CH\(_2\)OCS\(_2\)-), 4.63 (s, 2H, acetal protons), 4.54 (br s, 2H, exocyclic olefinic protons), 4.07 (d, 2H, \(J = 7\) Hz, -CCH\(_2\)O-), 3.39 (s, 3H, -OCH\(_3\)), 2.57 (s, 3H, -SCH\(_3\)), 2.29 (br dt, 1H, \(J = 5\), 13.5 Hz, \(H_B\)), 2.13 (br d, 1H, \(J = 13.5\) Hz, \(H_C\)), 1.97-1.48 (m, 11H), 1.71 (s, 3H, vinyl methyl protons), 1.35-1.15 (m, 3H), 1.17 (s, 3H, angular
methyl protons), 0.93 (d, 3H, J = 6 Hz, methyl protons). Exact Mass calcd. for C_{24}H_{40}O_{3}S_{2}: 440.2419; found: 440.2410.

Preparation of the thionocarbonate 155

A solution of the alcohol 152 (20 mg, 57 µmol), phenoxythiocarbonyl chloride (10 µL, 68 µmol) and 4-N,N-dimethylaminopyridine (15 mg, 0.13 mmol) in acetonitrile (1 mL) was stirred at room temperature for 48 h. The solution was diluted with ethyl acetate, washed twice with brine, dried (MgSO₄) and concentrated. The residue was subjected to column chromatography on silica gel (2 g, elution with petroleum ether-ether, 9:1 v/v). Collection and concentration of the appropriate fractions afforded 11 mg (40%) of the thionocarbonate 155 which exhibited ir (film): 3085, 1729, 1635, 1592, 1491, 894 cm⁻¹; ¹H nmr (400 MHz) δ: 7.40 (t, 2H, J = 8 Hz, aromatic protons), 7.27 (t, 1H, J = 8 Hz, aromatic proton), 7.10 (d, 2H, J = 8 Hz, aromatic protons), 5.35 (t, 1H, J = 7 Hz, Hₐ), 4.65 (s, 2H, acetal protons), 4.63, 4.52 (d, d, 1H each, J = 10 Hz, -CH₂OCOS-), 4.54 (br s, 2H, exocyclic olefinic protons), 4.07 (d, 2H, J = 7 Hz, -CH₂O-), 3.40 (s, 3H, -OCH₃), 2.28 (br dt, 1H, J = 4,
14 Hz, H_B), 2.13 (br d, 1H, J = 14 Hz, H_C), 1.95-1.49 (m, 11H), 1.69 (s, 3H, vinyl methyl protons), 1.35-1.18 (m, 3H), 1.09 (s, 3H, angular methyl protons), 0.89 (s, 3H, methyl protons).

Preparation of the acetate 168

\[
\begin{align*}
\text{AcO} & \quad \text{CH}_2\text{CH}_2\text{OAc} \\
\text{H}_A & \quad \text{H}_B \quad \text{H}_C \\
\end{align*}
\]

A solution of the alcohol 152 (10 mg, 29 \(\mu\)mol), acetic anhydride (0.1 mL, 1 mmol) and 4-N,N-dimethylaminopyridine (2 mg, 16 \(\mu\)mol) in pyridine (0.4 mL) was stirred at room temperature for 90 min. Solvent and excess reagents were removed under reduced pressure (0.02 torr) and the residue was dissolved in ether. The ethereal solution was washed twice with brine, dried (MgSO_4) and concentrated. The residue showed one spot on tlc and exhibited ir (film): 3086, 1741, 1669, 1635, 1240, 1150, 1104, 1044, 893 cm\(^{-1}\); \(^1\)H nmr (270 MHz) \(\delta\): 5.35 (t, 1H, J = 6.8 Hz, H_A), 4.65 (s, 2H, acetal protons), 4.54 (br s, 2H, exocyclic olefinic protons), 4.16 (s, 2H, -CH_2OAc), 4.07 (d, 2H, J = 6.8 Hz, -CCH_2O-), 3.40 (s, 3H, -OCH_3), 2.4-1.1 (m, 16H), 2.06 (s, 3H, acetyl methyl protons), 1.70 (s, 3H, vinyl methyl protons), 1.09 (s, 3H, angular methyl protons), 0.90 (br s, 3H, methyl protons).
Preparation of the phosphorodiamidate 174

To a solution of the alcohol 152 (23 mg, 66 \( \mu \)mol) in a mixture of dimethoxyethane (1 mL) and \( N,N,N',N' \)-tetramethylethylenediamine (0.25 mL) at 0°C was added a solution of \( n \)-butyllithium (73 \( \mu \)mol) in hexanes. After the mixture had been stirred at room temperature for 30 min, dimethylaminophosphorodichloridate (40 \( \mu \)L, 0.32 mmol) was added and the mixture was stirred at room temperature for 12 h. The reaction mixture was cooled to 0°C, and anhydrous dimethylamine (1 mL) was added. After the resultant mixture had been stirred at 0°C for 2 h, it was diluted with ether, and then was washed twice with brine, dried (MgSO\(_4\)) and concentrated. The residue was subjected to column chromatography on silica gel (2 g, elution with ether-acetone 10:1 v/v). Collection and concentration of the appropriate fractions gave the phosphorodiamidate 174 which exhibited ir (film): 3085, 1667, 1634, 1224, 1041, 994, 891 cm\(^{-1}\); \(^1\)H nmr (270 MHz) \( \delta \): 5.34 (t, 1H, \( J = 6.8 \) Hz, \( H_A \)), 4.63 (s, 2H, acetal protons), 4.53 (s, 2H, exocyclic olefinic protons), 4.06 (d, 2H, \( J = 6.8 \) Hz, -CCH\(_2\)O-), 4.00 (br m, 2H, -PO\(_2\)CH\(_2\)-), 3.39 (s, 3H, -OCH\(_3\)), 2.69, 2.66 (br s, br s, 6H each, -N(CH\(_3\))\(_2\)), 2.30-1.10 (m, 16H), 1.70 (s, 3H, vinyl methyl protons), 1.08 (s, 3H, angular methyl protons), 0.93 (br s, 3H, methyl protons).
Preparation of 3-iodo-1-methoxymethoxypropane (172)

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To a cold (-20°C) solution of 3-chloro-1-propanol (8.4 mL, 0.10 mol) and diisopropylethylamine (28 mL, 0.16 mol) in dichloromethane (200 mL) was added chloromethyl methyl ether (11.4 mL, 0.15 mol). After the solution had been stirred at room temperature for 12 h, it was diluted with dichloromethane and washed three times with 1N hydrochloric acid, once with saturated aqueous sodium bicarbonate, twice with brine, and then was dried (MgSO₄). The solution was concentrated at atmospheric pressure via a Vigreux column (10 cm). Distillation (bp 73-80°C/15 torr) of the remaining oil afforded 11 g (80%) of 3-chloro-1-methoxymethoxypropane.

A solution of 3-chloro-1-methoxymethoxypropane (11 g, 80 mmol) and sodium iodide (47 g, 0.32 mol) in acetone (150 mL) was stirred at 60°C for 30 h. The solution was diluted with petroleum ether, filtered and concentrated at atmospheric pressure via a Vigreux column (10 cm). Distillation [bp 80-85°C/15 torr (lit.⁵⁴ bp 87-85°C/1.87 kPa)] of the remaining oil yielded 13 g (70%) of the iodide 172 as a colorless oil which was stored over copper dust under argon in a freezer. This material was homogeneous by glc analysis and exhibited ¹H nmr (80 MHz) δ: 4.63 (s, 2H, acetal protons), 3.60 (t, 2H, J = 6 Hz, -CH₂O-), 3.40 (s, 3H, methoxy protons), 3.30 (t, 2H, J = 6 Hz, -CH₂I), 2.05 (quintet,
Preparation of the nitrile 173

To a cold (-78°C) solution of diisopropylamine (0.24 mL, 1.7 mmol) in THF (11 mL) was added n-butyllithium (1.5 mmol) as a solution in hexanes and the solution was stirred at 0°C for 15 min. HMPA (0.4 mL, 2.2 mmol) and a solution of a mixture of the nitriles 112a and 112b (0.23 g, 1.1 mmol; 15:85, respectively) in THF were added and the solution was stirred at 0°C for 15 min. To the resultant yellow solution was added the iodide 172 (0.35 g, 1.5 mmol) and the solution was stirred at 0°C for 30 min and at room temperature for 1 h. The solution was diluted with petroleum ether, washed with 1N hydrochloric acid, twice with aqueous copper sulfate and twice with brine and then was dried (MgSO₄), filtered through a small pad of Florisil and concentrated under reduced pressure (0.02 torr) to afford 0.34 g (99%) of the desired nitrile 173. This material was homogeneous by glc analysis and exhibited ir (film): 3086, 2766, 2228, 1638, 1153, 1112, 1039, 921, 894 cm⁻¹; ¹H nmr (400 MHz) δ: 4.59 (br s, 3H, olefinic and
acetal protons), 4.55 (br s, 1H, olefinic proton), 3.43 (t, 2H, J = 6 Hz, -CH₂CH₂O-), 3.35 (s, 3H, -OCH₃), 2.34 (br dt, 1H, J = 5, 12 Hz, Hₐ),
2.14 (br d, 1H, J = 12 Hz, Hₜ), 2.00-1.20 (m, 14H), 1.27 (s, 3H, angular methyl protons), 1.11 (d, 3H, J = 6 Hz, methyl protons). Exact Mass calcd. for C₁₉H₃₁N₂O: 305.2355; found: 305.2356.

Preparation of the aldehyde 180

To a solution of the nitrile 173 (0.34 g, 1.1 mmol) in dimethoxyethane (11 mL) was added diisobutylaluminum hydride (4.4 mmol) as a solution in hexanes and the solution was warmed at 60°C for 6 h. The reaction mixture was cautiously poured into water, and the resultant mixture was neutralized with 1N hydrochloric acid, and then was extracted three times with ether. The extracts were combined, washed with brine, dried (Na₂SO₄) and concentrated. The residual oil was dissolved in a mixture of THF-acetic acid-water (8 mL, 1:1:0.16 by volume) and the solution was stirred at room temperature for 12 h. After removal of the solvent under reduced pressure (0.02 torr), the residue was dissolved in ether and the resultant solution was washed
with aqueous sodium bicarbonate and brine, and then was dried (MgSO₄) and concentrated to afford 0.29 g (85%) of the aldehyde 180, which exhibited ir (film): 3086, 2766, 2740, 1713, 1636, 1153, 1112, 1039, 921, 893 cm⁻¹; H nmr (400 MHz) δ: 9.52 (s, 1H, aldehyde proton), 4.60 (s, 2H, acetal protons), 4.58 (br s, 2H, olefinic protons), 3.50 (t, 2H, J = 6 Hz, -CH₂O-), 3.35 (s, 3H, -OCH₃), 2.26 (br dt, 1H, J = 5, 12 Hz, Hₐ), 2.11 (br d, 1H, J = 12 Hz, Hₐ), 1.95-1.10 (m, 14H), 1.02 (d, 3H, J = 6 Hz, methyl protons), 0.98 (s, 3H, angular methyl protons). Exact Mass calcd. for C₁₉H₃₂O₃: 308.2351; found: 308.2359.

Preparation of the alcohol 181

To a solution-suspension of lithium aluminum hydride (70 mg, 1.8 mmol) in ether (10 mL) was added an ethereal solution of the aldehyde 180 (0.28 g, 0.9 mmol) and the mixture was stirred at room temperature for 1 h. Sodium sulfate decahydrate was added in small portions to the stirred mixture until evolution of gas ceased. The mixture was filtered and the collected material was washed three times with ether. The combined filtrate was concentrated to yield 0.25 g (91%) of the alcohol
which exhibited ir (film): 3462 (br), 3085, 1635, 1152, 1111, 1039, 921, 891 cm\(^{-1}\); \(^1\)H nmr (400 MHz) \(\delta\): 4.62 (s, 2H, acetal protons), 4.51 (br s, 2H, olefinic protons), 3.78, 3.70 (d, d, 1H each, \(J = 12\) Hz, \(-\text{CH}_2\text{OH}\)), 3.51 (t, 2H, \(J = 6.5\) Hz, \(-\text{CH}_2\text{CH}_2\text{O}^-\)), 3.37 (s, 3H, -OCH\(_3\)), 2.26 (br dt, 1H, \(J = 5, 12\) Hz, \(H_A\)), 2.10 (br d, 1H, \(J = 12\) Hz, \(H_B\)), 1.87 (br d, 1H, \(J = 12\) Hz, \(H_C\)), 1.70-1.10 (m, 14H), 1.06 (s, 3H, angular methyl protons), 0.94 (d, 3H, \(J = 6\) Hz, methyl protons). Exact Mass calcd. for C\(_{19}\)H\(_{34}\)O\(_3\): 310.2508; found: 310.2509.

Preparation of the phosphorodiamidate 174

To a solution of the alcohol 181 (0.22 g, 0.7 mmol) in a mixture of dimethoxyethane (6 mL) and N,N,N',N'-tetramethylethylenediamine (1.5 mL) at 0°C was added n-butyllithium (0.77 mmol) as a solution in hexanes. After the mixture had been stirred for 15 min, dimethylaminophosphorodichloridate (0.45 mL, 3.6 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was cooled to 0°C, anhydrous dimethylamine (10 mL) was added, and stirring was continued at 0°C for 2 h. The solution was diluted with ether, washed
twice with brine, dried (MgSO₄) and concentrated. The residue was subjected to column chromatography on silica gel (10 g, elution with ether-acetone 10:1 v/v). The appropriate fractions were combined and concentrated under reduced pressure (16 torr, then 0.02 torr) to yield 0.27 g (88%) of the phosphorodiamidate 174 as a colorless viscous oil which exhibited ir (film): 3084, 1635, 1305, 1215, 1152, 1111, 1037, 920, 888 cm⁻¹; ¹H nmr (400 MHz) δ: 4.60 (s, 2H, acetal protons), 4.51 (s, 2H, olefinic protons), 4.00, 3.95 (dd, dd, 1H each, J = 4, 12 Hz, -CH₂OP), 3.48 (t, 2H, J = 6 Hz, -CH₂CH₂O⁻), 3.35 (s, 3H, -OCH₃), 2.66, 2.64 (d, d, 6H each, J = 4 Hz, -PNMe₂), 2.26 (br dt, 1H, J = 5, 12 Hz, Hₐ), 2.11 (br d, 1H, J = 12 Hz, Hₐ), 1.9–1.1 (m, 14H), 1.06 (s, 3H, angular methyl protons), 0.93 (d, 3H, J = 6 Hz, methyl protons). Exact Mass calcd. for C₂₃H₄₅N₂O₄P: 444.3117; found: 444.3119.

Preparation of the ether 175

Liquid methylamine (7 mL) was condensed into a cold (-78°C) flask containing lithium metal (9 mg, 1.3 mmol) and the mixture was stirred at -30°C for 30 min. To the resultant dark blue solution was added an
ethereal solution of the phosphorodiamidate 174 (99 mg, 0.2 mmol) and the mixture stirred at -20°C for exactly 10 min. The reaction mixture was cautiously but quickly treated with aqueous ammonium chloride and the resultant mixture was extracted three times with ether. The ethereal extracts were combined, washed with brine, dried (MgSO₄) and concentrated. The residue was subjected to column chromatography on silica gel (4 g, elution with petroleum ether-ether, 20:1 v/v). Collection and concentration of the appropriate fractions afforded 48 mg (81%) of the ether 175 as a colorless oil which exhibited ir (film): 3085, 2767, 1636, 1147, 1112, 1078, 1039, 922, 891 cm⁻¹; ¹H nmr (400 MHz) δ: 4.60 (s, 2H, acetal protons), 4.49 (br s, 2H, olefinic protons), 3.44 (t, 2H, J = 6 Hz, -CH₂CH₂O-), 3.36 (s, 3H, -OCH₃), 2.28 (br dt, 1H, J = 5, 13.5 Hz, Hₐ), 2.09 (br d, 1H, J = 13.5 Hz, Hₐ), 1.87 (br d, 1H, J = 12 Hz, Hₔ), 1.63-1.00 (m, 13H), 1.04 (s, 3H, angular methyl protons), 0.80 (d, 3H, J = 6 Hz, methyl protons), 0.73 (s, 3H, methyl protons). Irradiation at δ 4.49 (olefinic protons) caused the signal at δ 2.34-2.23 to sharpen; irradiation at δ 2.28 (Hₐ) caused the signal at δ 2.14-2.06 to collapse to a broad singlet and the signal at δ 1.91-1.82 to sharpen; irradiation at δ 2.09 (Hₐ) caused the signal at δ 2.34-2.23 to collapse to a broad doublet (J = 13.5 Hz) and the signal at δ 1.91-1.82 to sharpen to a q of d (J = 3.5 Hz, J = 12 Hz); irradiation at δ 1.87 (Hₔ) caused the signal at δ 2.34-2.23 to collapse to a broad triplet (J = 13.5 Hz) and the signal at δ 2.14-2.06 to sharpen to a d of d (J = 4, 13.5 Hz). **Exact Mass** calcd. for C₁₉H₃₄O₂: 294.2559; found: 294.2557.
Preparation of the ether 182

Dry liquid ethylamine (1 mL) was condensed into a cold (-78°C) flask containing lithium metal (11 mg, 0.29 mmol) and the mixture was stirred at 0°C for 20 min. To the resultant dark blue solution was added a THF solution of the phosphorodiamidate 174 (13 mg, 29 µmol) and tert-butyl alcohol (0.11 mmol) and the mixture was stirred at 0°C for 20 min. The reaction mixture was treated with aqueous ammonium chloride and the resultant mixture was extracted three times with ether. The ethereal extracts were combined, washed with brine, dried (MgSO₄) and concentrated. The residue was subjected to column chromatography on silica gel (1 g, elution with petroleum ether-ether, 30:2 v/v). Collection and concentration of the appropriate fractions afforded 6.8 mg (80%) of the ether 182 as a colourless oil which exhibited ir (film): 1463, 1383, 1151, 1112, 1039 cm⁻¹; ¹H nmr (400 MHz) δ: 4.62 (s, 2H, acetal protons), 3.46 (t, 2H, J = 7 Hz, -CH₂CH₂O⁻), 1.8-0.8 (m, 20H), 0.78 (d, 3H, J = 7 Hz, methyl protons), 0.77 (s, 3H, methyl proton), 0.73 (d, 3H, J = 7 Hz, methyl protons), 0.70 (s, 3H, methyl proton). Exact Mass calcd. for C₁₉H₃₆O₂: 296.2715; found: 296.2707.
Preparation of the alcohol 183

A mixture of the ether 175 (65 mg, 0.22 mmol) and pyridinium p-toluenesulfonate (0.55 g, 2.2 mmol) in tert-butyl alcohol (5 mL) was heated at 70°C for 12 h. After removal of solvent under reduced pressure (0.02 torr) the residue was triturated three times with dry ether. The ethereal solution was filtered and concentrated, and the residue was subjected to column chromatography on silica gel (1 g, elution with petroleum ether-ether, 7:3 v/v). Collection and concentration of the appropriate fractions provided 50 mg (91%) of the alcohol 183 as a colorless oil which exhibited IR (film): 3319 (br), 3085, 1635, 1055, 891 cm\(^{-1}\); \(^1\)H NMR (400 MHz) \(\delta\): 4.50 (br s, 2H, olefinic protons), 3.57 (t, 2H, \(J = 6\) Hz, \(-\text{CH}_2\text{CH}_2\text{OH}\)), 2.29 (br dt, 1H, \(J = 5, 12\) Hz, \(H_A\)), 2.10 (br d, 1H, \(J = 12\) Hz, \(H_B\)), 1.87 (br d, 1H, \(J = 12\) Hz, \(H_C\)), 1.65-1.00 (m, 14H), 1.05 (s, 3H, angular methyl protons), 0.80 (d, 3H, \(J = 6\) Hz, methyl protons), 0.75 (s, 3H, methyl protons). \textbf{Exact Mass} calcd. for C\(_{17}\)H\(_{30}\)O: 250.2296; found: 250.2295.
Preparation of the aldehyde 184

To a stirred solution-suspension of pyridinium chlorochromate (70 mg, 0.32 mmol) and anhydrous sodium acetate (5 mg, 61 µmol) in dichloromethane (5 mL) was added a solution of the alcohol 183 (60 mg, 0.24 mmol). After the mixture had been stirred at room temperature for 1 h, it was diluted with dry ether, and then was filtered through a short pad of Florisil. The filtrate was concentrated to afford 58 mg (99%) of the aldehyde 184 as a colorless oil which exhibited ir (film): 3085, 2714, 1728, 1635, 892 cm⁻¹; ¹H nmr (400 MHz) δ: 9.74 (t, 1H, J = 2 Hz, aldehyde proton), 4.50 (br s, 2H, olefinic protons), 2.30-2.16 (m, 3H, Hₐ and -CH₂CHO), 2.10 (br d, 1H, J = 12 Hz, Hₐ), 1.88 (br d, 1H, J = 12 Hz, Hₐ), 1.70-1.15 (m, 11H), 1.05 (s, 3H, angular methyl protons), 0.81 (d, 3H, J = 6 Hz, methyl protons), 0.79 (s, 3H, methyl protons). Exact Mass calcd. for C₁₇H₂₈O: 248.2140; found: 248.2145.
Preparation of the ketone 176

![Chemical structure of ketone 176](image)

To a cold (0°C) stirred solution of the aldehyde 184 (22 mg, 88 μmol) in ether (1 mL) was added methyllithium (0.28 mmol) as a solution in ether. After the mixture had been stirred at room temperature for 3 h, sodium sulfate decahydrate was added in small portions until evolution of gas ceased. The solution was diluted with ether, filtered and concentrated to give a mixture of epimeric alcohols, which showed ir (film): 3349 (br), 3085, 1635, 891 cm⁻¹. *Exact Mass* calcd. for C₁₈H₃₂O: 264.2453; found: 264.2455.

The mixture of alcohols obtained as described above was added to a solution-suspension of pyridinium chlorochromate (31 mg, 14 mmol) and sodium acetate (3 mg, 36 μmol) in dichloromethane (1 mL) at 0°C and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with dry ether and then was filtered through a short pad of Florisil. Concentration of the filtrate gave 22 mg (97%) of the ketone 176 which exhibited ir (film): 3085, 1718, 1635, 891 cm⁻¹; *¹H NMR* (400 MHz) δ: 4.51 (br s, 2H, olefinic protons), 2.28 (br dt, 1H, J = 5, 12 Hz, Hₐ), 2.13 (s, 3H, -COCH₃), 2.21-2.05 (m, 1H), 1.88 (br d, 1H, J = 12 Hz, Hₐ), 1.65-1.10 (m, 13H), 1.05 (s, 3H, angular methyl protons), 0.80 (d, 3H, J = 7 Hz, methyl protons), 0.78 (s, 3H, methyl protons). *Exact Mass* calcd. for C₁₈H₃₀O: 262.2297; found: 262.2298.
Preparation of the esters 186 and 177

To a suspension of potassium hydride (30 mg, 0.75 mmol; washed with ether and dried under a stream of argon) in THF (3 mL) at room temperature was added triethyl phosphonoacetate (140 μL, 0.7 mmol) and the mixture was stirred for 30 min. A solution of the ketone 176 (17 mg, 65 μmol) in THF was added and the mixture was stirred at room temperature for 15 h. The reaction mixture was treated with sodium sulfate decahydrate, diluted with ether, and filtered through Celite. The filtrate was concentrated. Glc analysis of the residual oil showed that it consisted of a mixture of two compounds in a ratio of 1:10. The two products were readily separable by column chromatography on silica gel (2 g, elution with petroleum ether-ether, 50:1 v/v). Collection and concentration of the appropriate fractions afforded both the pure (Z) ester 186, 2.5 mg (11.6%) and the pure (Z) ester 177, 19 mg (88.3%).

The less polar (Z) ester 186 exhibited ir (film): 3085, 1718, 1648, 1151, 890 cm⁻¹; ¹H nmr (400 MHz) δ: 5.60 (br s, 1H, olefinic proton), 4.50 (br s, 2H, terminal olefinic protons), 4.12 (q, 2H, J = 7.5 Hz, -OCH₂CH₃), 2.55 (br dt, 1H, J = 4, 12 Hz, Hₐ), 2.32, 2.24 (br ddd, br ddd, 2H, J = 5, 12, 12 Hz, -CH₂(CH₃)C=), 2.11 (br d, 1H, J = 12 Hz, Hₐ),
1.90 (m, 1H, H<sub>C</sub>), 1.85 (d, 3H, J = 1.5 Hz, vinyl methyl protons), 1.74-1.22 (m, 11H), 1.25 (t, 3H, J = 7.5 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.05 (s, 3H, angular methyl protons), 0.85 (d, 3H, J = 6 Hz, methyl protons), 0.73 (s, 3H, methyl protons). 

**Exact Mass** calcd. for C<sub>22</sub>H<sub>36</sub>O<sub>2</sub>: 332.2715; found: 332.2721.

The more polar (E) ester 177 exhibited ir (film): 3085, 1718, 1646, 1224, 1148, 892, 871 cm<sup>-1</sup>; <sup>1</sup>H nmr (400 MHz) δ: 5.63 (br s, 1H, olefinic proton), 4.51 (br s, 2H, terminal olefinic protons), 4.14 (q, 2H, J = 7.5 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 2.29 (br dt, 1H, J = 5, 13.5 Hz, H<sub>A</sub>), 2.14 (d, 3H, J = 1.5 Hz, vinyl methyl protons), 2.15-2.07 (m, 1H, H<sub>B</sub>), 2.02-1.78 (m, 3H, -CH<sub>2</sub>(CH<sub>3</sub>)= and H<sub>C</sub>), 1.66-1.22 (m, 11H), 1.28 (t, 3H, J = 7.5 Hz, -OCH<sub>2</sub>CH<sub>3</sub>), 1.05 (s, 3H, angular methyl protons), 0.81 (d, 3H, J = 6 Hz, methyl protons), 0.74 (s, 3H, methyl protons). 

**Exact Mass** calcd. for C<sub>22</sub>H<sub>36</sub>O<sub>2</sub>: 332.2715; found: 332.2715.

**Preparation of the allylic alcohol 187**

To a cold (-78°C) stirred solution of the (E) ester 177 (19 mg, 57 µmol) in ether (1 mL) was added diisobutylaluminum hydride (0.25 mmol) as a solution in hexanes. After the solution had been stirred for 1 h
at -78°C and 2 h at 0°C, it was treated with saturated aqueous ammonium chloride (0.1 mL) and then diluted with ether. The resulting mixture was stirred for 5 min at room temperature, dried (MgSO₄) and filtered through a pad of Florisil. Concentration of the filtrate gave 16 mg (98%) of the allylic alcohol 187 which exhibited IR (film): 3327 (br), 3085, 1668, 1636, 1000, 891 cm⁻¹; ¹H NMR (400 MHz) δ: 5.37 (t, 1H, J = 8 Hz, olefinic proton), 4.50 (br s, 2H, terminal olefinic protons), 4.12 (d, 2H, J = 8 Hz, =CH₂OH), 2.29 (br dt, 1H, J = 5, 13.5 Hz, HA), 2.10 (br d, 1H, J = 13.5 Hz, HB), 1.93-1.18 (m, 15H), 1.65 (br s, 3H, vinyl methyl protons), 1.03 (s, 3H, angular methyl protons), 0.81 (d, 3H, J = 8 Hz, methyl protons), 0.72 (s, 3H, methyl protons). Exact Mass calcd. for C₂₀H₃₄O: 290.2610; found: 290.2614.

Preparation of the aldehyde 107

A solution of the allylic alcohol 187 (15.8 mg, 55 µmol) in n-hexane (1.5 mL) was stirred at room temperature with manganese(IV) oxide (70 mg) for 3 h. The mixture was filtered through a pad of Celite. The collected material was washed four more times with diethyl ether. The
combined filtrate was concentrated to afford 14 mg (88%) of the aldehyde 107 as a colorless oil which exhibited ir (film): 3084, 1676, 1633, 1611, 1195, 891 cm⁻¹; ¹H nmr (270 MHz) δ: 9.97 (d, 1H, J = 8 Hz, aldehyde proton), 5.86 (br d, 1H, J = 8 Hz, olefinic proton), 4.51 (br s, 2H, terminal olefinic protons), 2.16 (d, 3H, J = 0.8 Hz, vinyl methyl protons), 2.4-1.1 (m, 16H), 1.06 (s, 3H, angular methyl protons), 0.81 (d, 3H, J = 8 Hz, methyl protons), 0.77 (s, 3H, methyl protons). Exact Mass calcd. for C₂₀H₃₂O: 288.2453; found: 288.2446.

Preparation of 2-trimethylsilyl-4-(chloromethyl)furan (110)

2-Trimethylsilyl-4-(chloromethyl)furan (110) was prepared from 3-furanmethanol as described by Goldsmith et al.⁵⁸ and Tanis et al.⁵⁹ via 190, 191, 192, 193, and 194.

Compound 190 exhibited ¹H nmr (80 MHz) δ: 7.59 (d, 1H, J = 2 Hz, furan α-proton), 7.25-7.15 (m, 5H, phenyl protons), 6.65 (d, 1H, J = 2 Hz, furan β-proton), 4.66 (d, 2H, J = 5 Hz, -CH₂OH), 1.62 (t, 1H, J = 5 Hz, exchanged with D₂O, -OH).

Compound 191 exhibited ¹H nmr (80 MHz) δ: 7.55 (d, 1H, J = 2 Hz,
furan α-proton), 7.23-7.13 (m, 5H, phenyl protons), 6.61 (d, 1H, J = 2 Hz, furan β-proton), 4.66 (s, 2H, -CH₂O), 0.91 (s, 9H, tert-butyl protons), 0.07 (s, 6H, silyl methyl protons).

Compound 192 exhibited ¹H nmr (80 MHz) δ: 7.35-7.15 (m, 5H, phenyl protons), 6.85 (br s, 1H, furan proton), 4.70 (s, 2H, -CH₂O), 0.99 (s, 9H, tert-butyl protons), 0.38 (s, 9H, silyl trimethyl protons), 0.13 (s, 6H, silyl methyl protons).

Compound 193 exhibited ¹H nmr (80 MHz) δ: 7.56 (br s, 1H, furan α-proton), 6.60 (br s, 1H, furan β-proton), 4.63 (br s, 2H, -CH₂O-), 0.97 (s, 9H, tert-butyl protons), 0.30 (s, 9H, silyl trimethyl protons), 0.13 (s, 6H, silyl methyl protons).

Compound 194 exhibited ¹H nmr (80 MHz) δ: 7.60 (br s, 1H, furan α-proton), 6.66 (br s, 1H, furan β-proton), 4.55 (br s, 2H, -CH₂OH), 1.58 (br s, 1H, D₂O exchange, -OH), 0.30 (s, 9H, silyl methyl protons).

Compound 110 exhibited ¹H nmr (270 MHz) δ: 7.61 (br s, 1H, furan α-proton), 6.62 (s, 1H, furan β-proton), 4.45 (s, 2H, -CH₂Cl), 0.25 (s, 9H, silyl methyl protons).

Preparation of the chloro butenolide 109
While oxygen was bubbled through a cold (-78°C) solution of the furan derivative 110 (2 g, 10 mmol) and a catalytic amount of tetraphenylporphin (1 mmol) in dichloromethane (120 mL), it was irradiated with a halogen-tungsten lamp (650 W, 110 V operated at 50 V) for 27 min. The disappearance of starting material was monitored by glc. The solution was allowed to warm to room temperature and then was concentrated. The residue was dissolved in methanol and the solution stirred at room temperature for 12 h. After removal of the solvent, the residue was subjected to flash column chromatography on silica gel (250 g, elution with petroleum ether-ethyl acetate, 6:5 v/v). Collection and concentration of the appropriate fractions afforded 1.27 g (78%) of the butenolide 109, which exhibited ir (film): 3357 (br), 1763, 1660, 1139 cm⁻¹; ¹H nmr (80 MHz) δ: 6.21 (br s, 2H, Hₐ and Hₖ), 4.80 (br s, 1H, exchanged with D₂O, -OH), 4.37 (s, 2H, -CH₂Cl). Exact Mass calcd. for C₅H₄Cl₃O₃ (M⁺-1): 146.9849; found: 146.9843.

Preparation of the methoxy butenolide 197

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   OMe
  /    /
 /     /
 HA    Cl
   /  \
  /   \
     HB
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A solution of the butenolide 109 (0.1 g, 0.67 mmol) and p-toluenesulfonic acid monohydrate (30 mg, 0.16 mmol) in dry methanol (10 mL) was
stirred at room temperature for 2 days. The solution was concentrated and the residue was subjected to column chromatography on silica gel (5 g, elution with petroleum ether-ethyl acetate 3:1 v/v). Collection and concentration of the appropriate fractions afforded 0.1 g (92%) of the methoxy butenolide 197 which exhibited ir (film): 3113, 2845, 1800, 1768, 1662, 1120 cm\(^{-1}\). \(^1\)H nmr (80 MHz) \(\delta\): 6.20 (m, 1H, H\(_A\)), 5.80 (br s, 1H, H\(_B\)), 4.31 (br s, 2H, -CH\(_2\)Cl), 3.61 (s, 3H, -OCH\(_3\)). Exact Mass calcd. for C\(_6\)H\(_6\)\(^{35}\)ClO\(_3\) (M\(^+\)-1): 161.0005; found: 160.9999.

Preparation of the phosphonium salt 188

A solution of the butenolide 197 (0.4 g, 2.5 mmol) and triphenylphosphine (1 g, 3.9 mmol) in benzene (8 mL) was refluxed for 2 days. The resultant slurry was centrifuged and the supernatant solution was decanted. The residue was washed three times with benzene and then was dried under reduced pressure (0.02 torr) to afford 0.74 g (70%) of the phosphonium salt 188. This white fine solid exhibited \(^1\)H nmr (80 MHz, CD\(_2\)Cl\(_2\)) \(\delta\): 8.2-7.5 (m, 15H, aromatic protons), 6.00, 5.98 (br s, br s, 1H each, H\(_A\) and H\(_B\)), 5.80 (d, 2H, \(J = 16\) Hz, -CH\(_2\)P), 3.30 (s, 3H, -OCH\(_3\)).
Hydrolysis of the methoxy butenolide 200 to the hydroxy butenolide 202

To a mixture of the butenolide 200 (0.13 g, 1 mmol) and aqueous sodium hydroxide (4 M, 1.1 mmol) was added acetonitrile until the solution was clear (~7 ml). The solution, which was stirred at room temperature for 0.5 h, gradually turned yellow. The resultant solution was treated with dilute hydrochloric acid (2 M, 1.2 mmol) and the solution turned colorless. After removal of solvents, the residue was triturated with ether. The ethereal solution was filtered, dried (MgSO₄) and concentrated to provide 68 mg (60%) of the hydroxybutenolide 202 which exhibited ir (film): 3350, 1730 cm⁻¹; ¹H nmr (80 MHz) δ: 5.94 (br s, 1H, OCHOH), 5.79 (m, 1H, olefinic proton), 5.48 (v br s, 1H, D₂O exchanged, -OH), 2.06 (d, 3H, J = 2H, methyl protons).
Preparation of the phosphonate 213

\[
\text{\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{phosphonate_213}
\end{figure}}
\]

A mixture of the butenolide (197) (0.11 g, 0.68 mmol) and purified triethylphosphite (5 mL) was heated at \(-150^\circ\text{C}\) for 18 h. Excess triethylphosphite was removed under reduced pressure (0.02 torr) and the residual oil was subjected to column chromatography on silica gel (10 g, elution with ether). Collection and concentration of the appropriate fractions afforded 0.14 g (78\%) of the phosphonate 213 as a colorless oil which exhibited ir (film): 3107, 2846, 1796, 1767, 1651, 1250 cm\(^{-1}\); \(^1\text{H}\) nmr (400 MHz) \(\delta\): 6.11 (br d, 1H, \(J = 4.5\) Hz, HA or HB), 5.82 (br d, 1H, \(J = 3\) Hz, HB or HA), 4.15 (br quintet, 4H, \(J = 7\) Hz, -OCH\(_2\)CH\(_3\)), 3.60 (s, 3H, -OCH\(_3\)), 3.01, 2.89 (dd, dd, 1H each, \(J = 16, 21\) Hz, -CH\(_2\)P), 1.35 (dt, 6H, \(J = 2.7, 7\) Hz, -OCH\(_2\)CH\(_3\)). \text{Exact Mass} calcd. for C\(_{10}\)H\(_{17}\)O\(_6\)P: 264.0762; found: 264.0756.

Preparation of the sulfone 223

\[
\text{\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{sulfone_223}
\end{figure}}
\]
A stirred mixture of the furan 110 (0.56 g, 2.95 mmol), sodium benzenesulfinate (0.58 g, 3.5 mmol) and dimethylformamide (2.5 mL) was heated at 80-90°C for 2.5 h. The resultant solution was diluted with ether, washed twice with brine, dried (MgSO₄), filtered and concentrated. The residue was subjected to column chromatography on neutral alumina (activity III, 20 g, elution with petroleum ether-diethyl ether, 2:8 v/v). Collection and concentration of the appropriate fractions afforded 0.62 g (72%) of the sulfone (223) which exhibited IR (film): 3065, 1681, 1587, 1479, 1448, 1310, 1251, 1152 cm⁻¹; ¹H NMR (80 MHz) δ: 7.8-7.3 (m, 6H, aromatic protons), 6.45 (s, 1H, Hₐ), 4.15 (s, 2H, -CH₂SO₂⁻), 0.25 (s, 9H, silyl methyl protons). **Exact Mass** calcd. for C₁₄H₁₈O₃Si: 294.0746; found: 294.0744.

**Preparation of the triene 216**

![Triene 216](image)

To a cold (-78°C) solution of the sulfone 223 (25.5 mg, 87 μmol) in THF (0.9 mL) was added a solution of n-butyllithium (77 μmol) in hexanes and the solution was stirred for 20 min. A solution of the aldehyde 107 (10 mg, 35 μmol) in THF was added and the solution was stirred at -78°C
for 3 h. Benzoyl chloride (10 μL, 87 μmol) was added and the reaction mixture was allowed to warm to room temperature over a period of 1.5 h. The solution was diluted with ether, washed once with saturated sodium bicarbonate and twice with brine and then was dried (MgSO₄) and concentrated. The residual oil was dissolved in a mixture of THF-methanol (1 mL, 3:1 v/v) and the solution was cooled to -20°C. Sodium amalgam (4%, 23 mg) was added and the mixture was stirred at -20°C for 2 h. Additional amalgam (13 mg) was added and stirring was continued for 1 h. The mixture was diluted with pentane, washed twice with brine, dried (MgSO₄) and concentrated. The residue was subjected to column chromatography on neutral alumina (2 g, activity III, elution with pentane-ether, 50:1 v/v). Collection of the appropriate fractions afforded 7.5 mg (51%) of the desired triene 216, which exhibited IR (film): 3085, 3034, 1635, 1250, 891, 844 cm⁻¹; ¹H NMR (400 MHz) δ: 7.58 (s, 1H, Hₐ), 6.76 (s, 1H, H₇), 6.56 (dd, 1H, J = 10, 16 Hz, Hₐ), 6.30 (d, 1H, J = 16 Hz, Hₙ), 5.89 (d, 1H, J = 10 Hz, Hₜ), 4.50 (br s, 2H, terminal olefinic protons), 2.30 (br dt, 1H, J = 5, 13.5 Hz, Hₕ), 2.12 (br d, 1H, J = 13.5 Hz, H₉), 1.97-1.20 (m, 14H), 1.80 (s, 3H, vinyl methyl protons), 1.05 (s, 3H, angular methyl protons), 0.82 (d, 3H, J = 6 Hz, methyl protons), 0.74 (s, 3H, methyl protons), 0.27 (s, 9H, -SiMe₃). **Exact Mass** calcd. for C₂₈H₄₄SiO: 424.3161; found: 424.3161.
Preparation of (±)-Palauolide (55)

A solution of the triene 216 (7.5 mg, 17 μmol) and a catalytic amount of Rose Bengal (1.7 μmol) in a mixture of methanol-dichloromethane (1 mL, 10:3 v/v) was cooled to -78°C. While a stream of oxygen was bubbled through the solution, it was irradiated for 8 min with a halogen-tungsten lamp (650 W, 110 V operated at 50 V) through an aqueous sodium nitrite filter (74 g per litre). The resultant solution was purged with argon and then was allowed to stand at room temperature in the dark for 3 h. Removal of solvent provided a crude product which was subjected to column chromatography on silica gel (1.5 g, elution with hexane-ethyl acetate, 7:3 v/v). Collection of the appropriate fractions provided (±)-palauolide (4.4 mg, 68%) which exhibited \textit{IR} (film): 3340 (br), 3083, 1757, 1634, 1614, 890 cm\(^{-1}\); \textit{\textit{H NMR}} (400 MHz) \(\delta\): 7.14 (dd, 1H, \(J = 11, 15.5 \text{ Hz}, H_A\)), 6.29 (d, 1H, \(J = 15.5 \text{ Hz}, H_B\)), 6.23 (d, 1H, \(J = 8.5 \text{ Hz}; \text{collapsed to s on D}_2O\text{ exchange}, H_C\)), 5.97 (d, 1H, \(J = 11 \text{ Hz}, H_D\)), 5.87 (s, 1H, \(H_E\)), 4.51 (br s, 2H, terminal olefinic protons), 2.30 (br dt, 1H, \(J = 5, 13.5 \text{ Hz}, H_F\)), 2.12 (br d, 1H, \(J = 13.5 \text{ Hz}, H_G\)), 2.07-1.10 (m, 15H), 1.88 (s, 3H, vinyl methyl protons), 1.06 (s, 3H, angular methyl protons), 0.82 (d, 3H, \(J = 6 \text{ Hz}, \text{methyl protons}\)), 0.75 (s, 3H, methyl protons). The \textit{\textit{H NMR}} spectrum of this material was identical to
that of the naturally occurring sesterterpene (+)-palauolide.*  

**Exact Mass** calcd. for C\textsubscript{25}H\textsubscript{36}O\textsubscript{3}: 384.2664; found: 384.2660.

**Preparation of 2-iodo-1-benzyloxymethoxyethane (246)**

![Chemical Structure](image)

To a cold (0°C) solution of 2-chloroethanol (1.0 mL, 15 mmol) and diisopropylethylamine (5.2 mL, 30 mmol) in dichloromethane (33 mL) was added benzyl chloromethyl ether (3.8 mL, 27 mmol) and the solution was stirred at room temperature for 12 h. The reaction mixture was diluted with ether, washed once with saturated aqueous sodium bicarbonate, twice with 2N hydrochloric acid, twice with saturated aqueous sodium bicarbonate and three times with brine, and then was dried (MgSO\textsubscript{4}) and concentrated. Distillation (air-bath temperature 90-95°C/0.02 torr) of the remaining oil yielded 2.6 g (86%) of 2-chloro-1-benzyloxymethoxyethane (247).

The chloride 247 exhibited ir (film): 3095, 3064, 3032, 1498, 1161, 1118, 1075, 1041, 1002 cm\textsuperscript{-1}; \textsuperscript{1}H nmr (270 MHz) \(\delta\): 7.35-7.20 (m, 5H, aromatic protons), 4.81 (s, 2H, benzyl protons), 4.63 (s, 2H, acetal

* We are grateful to Professor D. John Faulkner for the \textsuperscript{1}H nmr spectrum of palauolide.
protons), 3.83 (t, 2H, J = 6 Hz, -CH₂O⁻), 3.63 (t, 2H, J = 6 Hz, -CH₂Cl).

Exact Mass calcd. for C₁₀H₁₃₃₅ClO₂: 200.0604; found: 200.0600.

A stirred solution of the chloride 247 (2.0 g, 10 mmol) and sodium iodide (6 g, 40 mmol) in acetone (20 mL) was heated at 60°C in the dark for 40 h. The resultant solution was concentrated and the residual material was triturated three times with petroleum ether. The organic solutions were combined, filtered and concentrated. Distillation (air-bath temperature 105-110°C/0.02 torr) of the remaining oil yielded 2.5 g (77%) of 2-iodo-1-benzyloxymethoxyethane (246).

The iodide 246 exhibited ir (film): 3095, 3064, 3030, 1497, 1455, 1152, 1114, 1066, 1027 cm⁻¹; ¹H nmr (270 MHz) δ 7.35-7.20 (m, 5H, aromatic protons), 4.78 (s, 2H, benzyl protons), 4.63 (s, 2H, acetal protons), 3.83 (t, 2H, J = 6 Hz, -CH₂O⁻), 3.26 (t, 2H, J = 6 Hz, -CH₂I).

Exact Mass calcd. for C₁₀H₁₃I₂O: 291.9959; found: 291.9966.

Preparation of the phosphonate 248

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\begin{align*}
\text{O} &
\begin{align*}
&\text{(CF₃CH₂O)}₂\text{PCHCO₂Me} \\
&\text{CH₂CH₂OCH₂OCH₂Ph}
\end{align*}
\end{align*}
\]

To a stirred suspension of sodium hydride (35 mg, 1.46 mmol; washed with diethyl ether and dried) in dimethylformamide (4.4 mL) was added methyl bis(2,2,2-trifluoroethyl)phosphonoacetate (0.42 g, 1.32 mmol) and
the mixture was stirred at room temperature for 15 min. Then 18-crown-6 (25 mg, 95 µmol) and 2-iodo-1-benzyloxyethane (246) (0.28 g, 0.98 mmol) were added. After the reaction mixture had been heated at 60 °C for 4 h, it was diluted with anhydrous ether and filtered through a small pad of Florisil. The filtrate was concentrated under reduced pressure (16 torr, then 0.02 torr). The residue was subjected to flash column chromatography on silica gel (160 g, elution with petroleum ether-ether, 4:6 v/v). Collection and concentration of the appropriate fractions provided 0.45 g (70%) of the phosphonate 248 which exhibited ir (film): 1743, 1499, 1299, 1264, 1174, 1068, 964 cm⁻¹; ¹H nmr (400 MHz) δ: 7.34 (m, 5H, aromatic protons), 4.71, 4.70 (d, d, 1H each, J = 7 Hz, benzyl protons), 4.58, 4.57 (d, d, 1H each, J = 11.5 Hz, acetal protons), 4.40 (m, 4H, CF₃CH₂O-), 3.75 (s, 3H, -OCH₃), 3.64 (m, 2H, -CH₂CH₂O-), 3.39 (ddd, 1H, J = 4, 10, 22 Hz, -PCH-), 2.25 (m, 2H, PCHCH₂-). Exact Mass calcd. for C₁₀H₁₄F₆O₆P (M⁺-OCH₂): 375.0432; found: 375.0425.

Preparation of the phosphonate 261

![Diagram of phosphonate 261]

A mixture of the commercially available α-bromo-γ-butyrolactone (7.4 g, 45 mmol) and purified trimethylphosphite (8.3 g, 67 mmol) was heated
at 150°C for 8 h. Excess trimethylphosphite was removed under reduced pressure (0.02 torr) and the crude product was obtained via a short path distillation (air-bath temperature 120-160°C/0.02 torr) of the residual material. The crude product was subjected to flash column chromatography on silica gel (150 g, elution with ether-acetone, 7:3, v/v). The appropriate fractions were collected and concentrated. Distillation (air-bath temperature 120-130°C/0.02 torr) of the remaining oil yielded 2.6 g (30%) of the phosphonate 261 which exhibited IR (film): 1772, 1236, 1034 cm\(^{-1}\); \(^1\)H NMR (270 MHz) \(\delta\): 4.30 (m, 2H, \(-\text{CH}_2\text{O}\)), 3.77, 3.73 (d, d, 3H each, J = 10 Hz, \(-\text{P(0CH}_3\text{)}_2\)), 3.03 (td, 1H, J = 8, 24 Hz, \(-\text{PCH}\)), 2.50 (m, 2H, \(-\text{CH}_2\text{CH}_2\text{O}\)). **Exact Mass calcd. for C\(_6\)H\(_{11}\)O\(_5\)P:** 194.0344; found: 194.0352.

**General procedure A: reaction of the phosphonate salts 248a and 261a with aldehydes**

To a cold (0°C) stirred solution of the required phosphonate 248 or 261 (0.57 mmol) in THF (10 mL) was added a solution of potassium bis(trimethylsilyl)amide (0.63 mmol) in toluene and 18-crown-6.nCH\(_3\)CN complex (0.85 g). After the solution had been stirred for 15 min, it
was cooled to -78°C and the required aldehyde (0.45 mmol) was added. Stirring was continued at -78°C for 4 h. The resultant solution was treated with brine and then was extracted three times with ether. The combined extract was washed twice with brine, dried (MgSO$_4$) and concentrated. The residue was subjected to column chromatography on silica gel (2 g, elution with either petroleum ether-ether, 8:2 v/v or benzene-ether, 30:1 v/v). Collection and concentration of the appropriate fractions yielded pure sample(s) of the olefination product(s).

General procedure B: reaction of the phosphonate salt 261b with aldehyde

![Phosphonate salt structure](image)

To a suspension of sodium hydride (14 mg, 0.58 mmol; washed with ether and dried under a stream of argon) in benzene (2.7 mL) at room temperature was added the phosphonate 261 (0.1 g, 0.53 mmol) and the solution was stirred at 50°C for 30 min. The appropriate aldehyde (0.42 mmol) was added and the solution was stirred at room temperature for 15 h. The reaction mixture was diluted with petroleum ether, washed three times with brine, and was dried (MgSO$_4$) and concentrated. The residue was subjected to column chromatography on silica gel (2 g, elution with
either petroleum ether-ether, 8:2, v/v or benzene-ether, 30:1 v/v). Collection and concentration of the appropriate fractions yielded pure sample(s) of olefination product(s).

Preparation of the Z and E esters 249 and 250

Following the general procedure A, reaction of the potassium salt of the phosphonate 248 with isovaleraldehyde afforded a 3:1 mixture of the Z ester 249 and the E ester 250, respectively. The following amounts of reagents were used: the phosphonate 248 (0.58 mmol) in THF (10 mL); potassium bis(trimethylsilyl)amide (0.64 mmol); 18-crown-6.nCH3CN complex (0.74 g); isovaleraldehyde (49 µL, 0.46 mmol). Workup, followed by column chromatography of the crude product on silica gel (2 g, elution with petroleum ether-ether, 8:2 v/v) and collection, concentration of the appropriate fractions afforded 122 mg (87%) of a colorless oil. Both glc analysis and $^1$H nmr spectroscopy showed that this material consisted of a mixture of the Z ester 249 and the E ester 250 in a ratio of 3:1. Further column chromatography on silica gel (4 g, 230-400 mesh, elution with petroleum ether-ether, 9:1 v/v) provided pure samples of each isomers.
The less polar $Z$ ester 249 exhibited IR (film): 1719, 1644, 1498 cm$^{-1}$; $^1$H NMR (300 MHz) $\delta$: 7.35 (m, 5H, aromatic protons), 6.01 (t, 1H, $J = 7$ Hz, olefinic proton), 4.73 (s, 2H, benzylic protons), 4.58 (s, 2H, acetal protons), 3.72 (s, 3H, methoxy protons), 3.68 (t, 2H, $J = 7$ Hz, -CH$_2$CH$_2$O-), 2.57 (t, 2H, $J = 7$ Hz, collapsed to s on irradiation at $\delta$ 3.68, -CH$_2$CH$_2$O-), 2.35 (t, 2H, $J = 7$ Hz, Me$_2$CHCH$_2$C=), 1.69 (m, 1H, isopropyl proton), 0.92 (d, 6H, $J = 7$ Hz, methyl protons). *Exact Mass* calcd. for C$_{18}$H$_{26}$O$_4$: 306.1831; found: 306.1826.

The more polar $E$ ester 250 exhibited IR (film): 1713, 1646, 1498 cm$^{-1}$; $^1$H NMR (300 MHz) $\delta$: 7.35 (m, 5H, aromatic protons), 6.90 (t, 1H, $J = 7$ Hz, olefinic proton), 4.75 (s, 2H, benzylic protons), 4.58 (s, 2H, acetal protons), 3.73 (s, 3H, methoxy protons), 3.62 (t, 2H, $J = 7$ Hz, -CH$_2$CH$_2$O-), 2.64 (t, 2H, $J = 7$ Hz, collapsed to a singlet on irradiation at $\delta$ 3.62, -CH$_2$CH$_2$O-), 2.12 (t, 2H, $J = 7$ Hz, Me$_2$CHCH$_2$C=), 1.75 (m, 1H, isopropyl proton), 0.93 (d, 6H, $J = 7$ Hz, methyl protons). *Exact Mass* calcd. for C$_{18}$H$_{26}$O$_4$: 306.1831; found: 306.1835.

Preparation of the $Z$ and $E$ lactones 263 and 264

![Lactone 263](image1.png) ![Lactone 264](image2.png)
Procedure I

Following the general procedure B, reaction of the sodium salt of the phosphonate 261 with isovaleraldehyde afforded, by glc analysis and $^1$H nmr spectroscopy of the crude product, a 2:1 mixture of the Z lactone 263 and the E lactone 264, respectively. The following amounts of reagents were used: the phosphonate 261 (0.1 g, 0.53 mmol) in benzene (2.7 mL); sodium hydride (14 mg, 0.58 mmol); isovaleraldehyde (45 μL, 0.42 mmol). Workup followed by column chromatography of the crude product on silica gel (2 g, elution with petroleum ether-ether, 8:2 v/v), and collection and concentration of the appropriate fractions afforded 30 mg (46%) of the Z lactone 263 and 15 mg (23%) of the E lactone 264.

Procedure II

To a cold (0°C) solution of the phosphonate 261 (0.11 g, 0.57 mmol) in THF (3.8 mL) was added solid potassium tert-butoxide (57 mg, 0.51 mmol) and the mixture was stirred at room temperature for 1 h. The resultant solution was cooled to -78°C and isovaleraldehyde (30 μL, 0.28 mmol) was added and stirring was continued at -78°C for 4 h. The reaction mixture was diluted with petroleum ether, washed three times with brine, dried (MgSO$_4$) and concentrated. Glc analysis of the residue showed that it consisted of a mixture of the Z lactone 263 and the E lactone 264 in a ratio of 73:27. This material was subjected to column chromatography on silica gel (2 g, elution with petroleum ether-ether,
Collection and concentration of the appropriate fractions afforded 26 mg (61%) of the Z lactone 263 and 8.6 mg (20%) of the E lactone 264.

Procedure III

To a cold (0°C) solution of the phosphonate 261 (0.11 g, 0.57 mmol) in THF (3.3 mL) was added solid potassium tert-butoxide (57 mg, 0.51 mmol) and the mixture was stirred at room temperature for 1 h. HMPA (0.6 mL) was added and the resultant solution was cooled to -78°C. Isovaleraldehyde (30 μL, 0.28 mmol) was added and the reaction mixture was stirred at -78°C for 4 h, and then was diluted with petroleum ether. The resultant mixture was washed once with brine, three times with aqueous copper(II) sulfate, and twice with brine and then was dried (MgSO₄) and concentrated. Glc analysis of the residue showed that it consisted of a 77:23 mixture of the Z lactone 263 and the E lactone 264, respectively. This material was subjected to column chromatography on silica gel (2 g, elution with petroleum ether-ether, 8:2 v/v). Collection and concentration of the appropriate fractions afforded 27 mg (62%) of the Z lactone 263 and 7.7 mg (18%) of the E lactone 264.

Procedure IV

Following the general procedure A, reaction of the potassium salt of the phosphonate 261 with isovaleraldehyde afforded practically pure Z lactone 263. The following amounts of reagents were used: the phospho-
nate 261 (0.57 mmol) in THF (10 mL); potassium bis(trimethylsilyl)amide (0.62 mmol); 18-crown-6·nCH₃CN complex (0.85 g); isovaleraldehyde (49 \(\mu\)L, 0.45 mmol). Glc analysis of the crude product after workup showed only the Z lactone 263. The crude product was then passed through a short pad of silica gel (1 g, elution with petroleum ether-ether, 8:2 v/v). Concentration of the eluant afforded 60 mg (86%) of the Z lactone 263.

The less polar Z lactone 263 exhibited ir (film): 1752, 1670 cm\(^{-1}\); \(^1\)H nmr (270 MHz) \(\delta\): 6.27 (tt, 1H, \(J = 4.5\) Hz, olefinic proton), 4.29 (t, 2H, \(J = 7\) Hz, -CH₂O-), 2.90 (br t, 2H, \(J = 7\) Hz, -CH₂CH₂O-), 2.60 (br t, 2H, \(J = 7\) Hz, -CH₂C=), 1.71 (quintet, 1H, \(J = 7\) Hz, Me₂CH-), 0.95 (d, 6H, \(J = 7\) Hz, methyl protons). Exact Mass calcd. for C₉H₁₄O₂: 154.0994; found: 154.0995.

The more polar E lactone 264 exhibited ir (film): 1757, 1681 cm\(^{-1}\); \(^1\)H nmr (270 MHz) \(\delta\): 6.78 (tt, 1H, \(J = 3, 7\) Hz, olefinic proton), 4.36 (t, 2H, \(J = 7\) Hz, -CH₂O-), 2.85 (br t, 2H, \(J = 7\) Hz, -CH₂CH₂O-), 2.09 (br t, 2H, \(J = 7\) Hz, -CH₂C=), 1.71 (quintet, 1H, \(J = 7\) Hz, Me₂CH-), 0.95 (d, 6H, \(J = 7\) Hz, methyl protons). Exact Mass calcd. for C₉H₁₄O₂: 154.0994; found: 154.0993.
Preparation of the Z and E lactones 265a and 266a

![Structures of 265a and 266a](image)

**Procedure I**

Following the general procedure A, reaction of the potassium salt of the phosphonate 261 with n-heptanal afforded practically pure Z lactone 265a. The following amounts of reagents were used: the phosphonate 261 (0.57 mmol) in THF (10 mL); potassium bis(trimethylsilyl)amide (0.62 mmol); 18-crown-6·nCH₃CN complex (0.85 g); n-heptanal (61 μL, 0.45 mmol). Glc analysis of the crude product after workup showed only the Z lactone 265a. The crude product was passed through a short pad of silica gel (1 g, elution with petroleum ether-ether, 8:2 v/v). Concentration of the eluant afforded 78 mg (94%) of the Z lactone 265a.

**Procedure II**

Following the general procedure B, reaction of the sodium salt of the phosphonate 261 with n-heptanal afforded, by glc analysis of the crude product, a 1:1 mixture of the Z lactone 265a and E lactone 266a. The following amounts of reagents were used: the phosphonate 261 (0.1 g, 0.53 mmol) in benzene (2.7 mL); sodium hydride (14 mg, 0.58 mmol);
n-heptanal (57 µL, 0.42 mmol). Workup, followed by column chromatography of the crude product (2 g, elution with petroleum ether-ether, 8:2 v/v), gave, after collection and concentration of the appropriate fractions, 30 mg (39%) of the Z lactone 265a and 289 mg (36%) of the E lactone 266a.

The less polar Z lactone 265a exhibited IR (film): 1757, 1672 cm⁻¹; \(^1^H\) NMR (300 MHz) δ: 6.24 (tt, 1H, J = 2.5, 7 Hz, olefinic proton), 4.30 (t, 2H, J = 7 Hz, -CH₂O⁻), 2.90 (br t, 2H, J = 7 Hz, -CH₂CH₂O⁻), 2.70 (br q, 2H, J = 7 Hz, -CH₂C=), 1.50-1.20 (m, 8H), 0.90 (t, 3H, J = 6 Hz, methyl protons). Exact Mass calcd. for \(\text{C}_{11}\text{H}_{18}\text{O}_2\): 182.1307; found: 182.1308.

The more polar E lactone 266a exhibited IR (film): 1757, 1681 cm⁻¹; \(^1^H\) NMR (300 MHz) δ: 6.76 (tt, 1H, J = 2.5, 7 Hz, olefinic proton), 4.38 (t, 2H, J = 7 Hz, -CH₂O⁻), 2.88 (br t, 2H, J = 7 Hz, -CH₂CH₂O⁻), 2.20 (br q, 2H, J = 7 Hz, -CH₂C=), 1.70-1.20 (m, 8H), 0.90 (t, 3H, J = 6 Hz, methyl protons). Exact Mass calcd. for \(\text{C}_{11}\text{H}_{18}\text{O}_2\): 182.1307; found: 182.1307.

Preparation of the Z and E lactones 265b and 266b

![265b](image1)

![266b](image2)
Following the general procedure A, reaction of the potassium salt of the phosphonate 261 with cyclohexanecarboxaldehyde afforded, by glc analysis and $^1$H nmr spectroscopy of the crude product, a 5:1 mixture of the $\mathcal{Z}$ lactone 265b and the $\mathcal{E}$ lactone 266b, respectively. The following amounts of reagents were used: the phosphonate (261) (0.11 g, 0.57 mmol) in THF (10 mL); potassium bis(trimethylsilyl)amide (0.62 mmol), 18-crown-6·nCH$_3$CN complex (0.85 g); cyclohexanecarboxyaldehyde (56 µL, 0.45 mmol). After workup, the crude product was subjected to column chromatography on silica gel (2 g, elution with petroleum ether-ether, 8:2 v/v). Concentration of the appropriate fractions afforded 45 mg (56%) of the $\mathcal{Z}$ lactone 265b and 10 mg (12%) of the $\mathcal{E}$ lactone 266b.

The less polar $\mathcal{Z}$ lactone 265b exhibited ir (film): 1756, 1669 cm$^{-1}$; $^1$H nmr (270 MHz) δ: 6.03 (td, 1H, $\mathcal{J}$ = 2.5, 10 Hz, olefinic proton), 4.29 (t, 2H, $\mathcal{J}$ = 8 Hz, -CH$_2$-)O-), 3.45 (br m, 1H, allylic proton), 2.87 (dt, 2H, $\mathcal{J}$ = 2.5, 8 Hz, -CH$_2$CH$_2$O-), 1.9-0.9 (m, 10H). Exact Mass calcd. for C$_{11}$H$_{16}$O$_2$: 180.1150; found: 180.1150.

The less polar $\mathcal{E}$ lactone 266b exhibited ir (film): 1757, 1678 cm$^{-1}$; $^1$H nmr (270 MHz) δ: 6.54 (td, 1H, $\mathcal{J}$ = 3, 10 Hz, olefinic proton), 4.29 (t, 2H, $\mathcal{J}$ = 7 Hz, -CH$_2$-)O-), 2.80 (dt, 2H, $\mathcal{J}$ = 3, 7 Hz, -CH$_2$CH$_2$O-), 2.11 (br m, 1H, allylic proton), 1.9-0.9 (m, 10H). Exact Mass calcd. for C$_{11}$H$_{16}$O$_2$: 180.1150; found: 180.1150.
Preparation of the Z and E lactones 265c and 266c

Procedure I

Following the general procedure A, reaction of the potassium salt of the phosphonate 261 with (E)-2-hexenal afforded, by glc analysis of the crude product, a 97:3 mixture of the Z lactone 265c and the E lactone 266c, respectively. The following amounts of reagents were used: the phosphonate 261 (0.11 g, 0.57 mmol) in THF (10 mL); potassium bis(tri-trimethylsilyl)amide (0.62 mmol); 18-crown-6·nCH3CN complex (0.85 g); (E)-2-hexanal (52 µL, 0.45 mmol). After workup, the crude product was subjected to column chromatography on silica gel (2 g, elution with petroleum ether-ether 8:2 v/v). Concentration of the appropriate fractions afforded 52 mg (78%) of the Z lactone 265c.

Procedure II

Following the general procedure B, reaction of the sodium salt of the phosphonate 261 with (E)-2-hexenal afforded, by glc analysis of the crude product, a 1:3 mixture of the Z lactone 265c and the E lactone 266c. The following amounts of reagents were used: the phosphonate 261...
(0.1 g, 0.53 mmol) in benzene (2.7 mL); sodium hydride (14 mg, 0.58 mmol); (E)-2-hexenal (49 μL, 0.42 mmol). Workup, followed by column chromatography of the crude product on silica gel (2 g, elution with petroleum ether-ether, 8:2 v/v), gave, after collection and concentration of the appropriate fractions, 15 mg (21%) of the Z lactone 265c and 42 mg (60%) of the E lactone 266c.

The less polar Z lactone 265c exhibited ir (film): 1747, 1647 cm⁻¹; ¹H nmr (270 MHz) δ: 7.42 (dd, 1H, J = 10, 16 Hz, Hₐ), 6.57 (td, 1H, J = 2, 10 Hz, Hₐ), 6.00 (td, 1H, J = 7, 16 Hz, Hₗ), 4.33 (t, 2H, J = 7 Hz, -CH₂CH₂O⁻), 2.95 (t, 2H, J = 7 Hz, -CH₂CH₂O⁻), 2.18 (q, 2H, J = 7 Hz, allylic protons), 1.47 (m, 2H, J = 7 Hz, CH₃(CH₂CH₂)O⁻), 0.93 (t, 3H, J = 7 Hz, CH₃⁻). Exact Mass calcd. for C₁₀H₁₄O₂: 166.0994; found: 166.0994.

The more polar E lactone 266c exhibited ir (film): 1751, 1652 cm⁻¹; ¹H nmr (270 MHz) δ: 7.09 (td, 1H, J = 2.5, 10 Hz, Hₐ), 6.3-6.0 (m, 2H, Hₐ and Hₗ), 4.39 (t, 2H, J = 7 Hz, -CH₂CH₂O⁻), 2.96 (dt, 2H, J = 2.5, 7 Hz, -CH₂CH₂O⁻), 2.19 (q, 2H, J = 7 Hz, allylic protons), 1.48 (m, 2H, J = 7 Hz, CH₃(CH₂CH₂)O⁻), 0.93 (t, 3H, J = 7 Hz, CH₃⁻). Exact Mass calcd. for C₁₀H₁₄O₂: 166.0994; found: 166.0992.
Preparation of the Z and E lactones 265d and 266d

Following the general procedure A, reaction of the potassium salt of the phosphonate 261 with benzaldehyde afforded by glc analysis and $^1$H nmr spectroscopy of the crude product, a 1:1 mixture of the Z lactone 265d and the E lactone 266d. The following amounts of reagents were used: the phosphonate 261 (0.11 g, 0.57 mmol) in THF (10 mL); potassium bis(tri-methylsilyl)amide (0.62 mmol); 18-crown-6-nC$_3$CN complex (0.85 g); benzaldehyde (46 µL, 0.45 mmol). After workup, the crude product was subjected to column chromatography on silica gel (2 g, 230-400 mesh, elution with benzene-ether, 30:1 v/v). Concentration of the appropriate fractions afforded 38 mg (48%) of the Z lactone 265d and 34 mg (43%) of the E lactone 266d.

The less polar Z lactone 265d exhibited ir (film): 1747, 1641 cm$^{-1}$; $^1$H nmr (300 MHz) $\delta$: 7.82 (dd, 2H, $\beta = 2$, 7.5 Hz, $H_A$), 7.42-7.32 (m, 3H, aromatic protons), 7.02 (t, 1H, $\beta = 2.5$ Hz, olefinic proton), 4.41 (t, 2H, $\beta = 7$ Hz, $-CH_2CH_2O$), 3.15 (dt, 2H, $\beta = 2.5$, 7 Hz, $-CH_2CH_2O$).

**Exact Mass** calcd. for C$_{11}$H$_{10}$O$_2$: 174.0681; found: 174.0683.

The more polar E lactone 266d exhibited ir (film): 1742, 1651 cm$^{-1}$; $^1$H nmr (300 MHz) $\delta$: 7.58 (t, 1H, $\beta = 3$ Hz, olefinic proton), 7.54-7.38 (m, 5H, aromatic protons), 4.48 (t, 2H, $\beta = 7$ Hz, $-CH_2CH_2O$), 3.26 (dt,
2H, J = 3, 7 Hz, -CH₂CH₂O-). *Exact Mass* calcd. for C₁₁H₁₀O₂: 174.0681; found: 174.0680.

**Preparation of 2-iodo-1-methoxymethoxyethane (240)**

![I-O-O](image)

To a cold (-20°C) solution of 2-chloroethanol (7.35 mL, 0.113 mol) and diisopropylethylamine (31.4 mL, 0.18 mol) in dichloromethane (250 mL) was added chloromethyl methyl ether (12.8 mL, 0.168 mol). After the solution had been stirred at room temperature for 12 h, it was diluted with dichloromethane washed three times with 1N hydrochloric acid, once with saturated aqueous sodium bicarbonate, twice with brine, and then was dried (MgSO₄). The solution was concentrated under atmospheric pressure via a Vigreux column (10 cm). Distillation (bp 50-54°C/15 torr) of the remaining oil afforded 11.2 g (80%) of 2-chloro-1-methoxymethoxyethane.

A solution of 2-chloro-1-methoxymethoxyethane (4.0 g, 32 mmol) and sodium iodide (20 g, 0.13 mol) in acetone (64 mL) was stirred at 60°C for 30 h with protection from light. The solution was diluted with pentane and filtered. The filtrate was concentrated under atmospheric pressure via a Vigreux column (10 cm). Distillation (bp 58-60°C/15 torr) of the remaining oil yielded 3.5 g (50%) of the iodide 240 as a
colorless oil which was stored over copper dust under argon in a freezer. This material was homogeneous by glc analysis and exhibited ir (film): 1144, 1115, 1065, 1030 cm\(^{-1}\); \(^1H\) nmr (270 MHz) \(\delta\): 4.68 (s, 2H, acetal protons), 3.82 (t, 2H, \(J = 6\) Hz, -OCH\(_2\)CH\(_2\)-), 3.40 (s, 3H, -OCH\(_3\)), 3.30 (t, 2H, \(J = 6\) Hz, -CH\(_2\)I). **Exact Mass** calcd. for C\(_4\)H\(_9\)I0: 215.9646; found: 215.9649.

**Preparation of the nitrile 241**

To a cold (-78°C) solution of diisopropylamine (0.83 mL, 5.9 mmol) in THF (40 mL) was added n-butyllithium (5.7 mmol) as a solution in hexanes and the solution was stirred at 0°C for 15 min. HMPA (1.37 mL, 7.9 mmol) and a solution of a mixture of the nitriles 112a and 112b (0.89 g, 3.9 mmol; 15:85, respectively) in THF were added and the solution was stirred at 0°C for 15 min. To the resulting yellow solution was added the iodide 240 (1.15 g, 5.5 mmol) and the solution was stirred at 0°C for 30 min and at room temperature for 1 h. The solution was diluted with petroleum ether, washed once with 1N hydrochloric acid, twice with aqueous copper sulfate and twice with brine and then was dried (MgSO\(_4\)), and filtered through a small pad of Florisil.
The filtrate was concentrated under reduced pressure (16 torr, then 0.02 torr) to afford 1.12 g (99%) of the desired nitrile 241. This material was homogeneous by glc analysis and exhibited ir (film): 3086, 2228, 1638, 1153, 1110, 1070, 1041, 895 cm⁻¹; ¹H nmr (400 MHz) δ: 4.59 (br s, 1H, olefinic proton), 4.57 (s, 2H, acetal protons), 4.55 (br s, 1H, olefinic proton), 3.50 (m, 2H, -CH₂CH₂O⁻), 3.34 (s, 3H, -OCH₃), 2.40 (br dt, 1H, J = 5.5, 13.5 Hz, ḳA), 2.15, 2.09 (br td, br td, 1H each, J = 7, 15 Hz, -CH₂CH₂O⁻), 2.13-1.10 (m, 11H), 1.27 (s, 3H, angular methyl protons), 1.15 (d, 3H, J = 6 Hz, methyl protons). Exact Mass calcd. for C₁₈H₂₉N₀₂: 291.2198; found: 291.2205.

Preparation of the aldehyde 273

To a solution of the nitrile 241 (1.12 g, 3.86 mmol) in dimethoxy-ethane (40 mL) was added diisobutylaluminum hydride (15.4 mmol) as a solution in hexanes and the solution was warmed at 60°C for 6 h. The reaction mixture was cautiously poured into water under a blanket of argon, and the resultant mixture was neutralized with 1N hydrochloric acid, and then was extracted three times with ether. The extracts were combined, washed with brine, dried (Na₂SO₄) and concentrated. The
residual oil was dissolved in a mixture of THF-acetic acid-water (100 mL, 1:1:0.16 by volume) and the solution was stirred at room temperature for 12 h. After removal of the solvent under reduced pressure (0.02 torr), the residue was dissolved in ether and the resultant solution was washed with aqueous sodium bicarbonate and brine, and then was dried (MgSO₄) and concentrated to afford 1.04 g (92%) of the aldehyde 273 which exhibited ir (film): 3086, 2767, 2737, 1713, 1637, 1153, 1109, 1044, 893 cm⁻¹; ¹H nmr (400 MHz) δ: 9.97 (s, 1H, aldehyde proton), 4.56 (s, 2H, acetal protons), 4.55 (br s, 2H, olefinic protons), 3.46 (m, 2H, -CH₂CH₂O-), 3.32 (s, 3H, -OCH₃), 2.30-1.1 (m, 14H), 1.04 (d, 3H, J = 7 Hz, methyl protons), 0.99 (s, 3H, angular methyl protons). Exact Mass. calcd. for C₁₈H₃₀O₃: 294.2195; found: 294.2200.

Preparation of the alcohol 274

To a solution-suspension of lithium aluminum hydride (0.26 g, 6.8 mmol) in ether (40 mL) was added an ethereal solution of the aldehyde 273 (1.04 g, 3.54 mmol) and the mixture was stirred at room temperature for 1 h. Sodium sulfate decahydrate was added in small portions to the stirred mixture until evolution of gas ceased. The mixture was filtered
and the collected material was washed three times with ether. The combined filtrate was concentrated to afford 1.0 g (95%) of the alcohol 274 which exhibited ir (film): 3443 (br), 3085, 2775, 1635, 1152, 1108, 1039, 892 cm\(^{-1}\); \(^1\)H nmr (400 MHz) \(\delta\): 4.59 (s, 2H, acetal protons), 4.50 (br s, 2H, olefinic protons), 3.77, 3.68 (d, d, 1H each, \(J = 11\) Hz, -CH\(_2\)OH), 3.50 (m, 2H, -CH\(_2\)CH\(_2\)O-), 3.34 (s, 3H, -OCH\(_3\)), 2.27 (br dt, 1H, \(J = 5, 13.5\) Hz, on irradiation at \(\delta 4.50\), sharpened to a d of t, \(J = 5, 13.5\) Hz, HA), 2.10 (br d, 1H, \(J = 12\) Hz, HB), 1.95-1.00 (m, 13H), 1.05 (s, 3H, angular methyl protons), 0.99 (d, 3H, \(J = 6\) Hz, methyl protons).

Exact Mass calcd. for C\(_{18}\)H\(_{32}\)O\(_3\): 296.2351; found: 296.2355.

**Preparation of the phosphorodiamidate 275**

To a solution of the alcohol 274 (0.31 g, 1 mmol) in a mixture of dimethoxyethane (4 mL) and N,N,N',N'-tetramethylethylene diamine (1 mL) at 0°C was added n-butyllithium (1.26 mmol) as a solution in hexanes. After the mixture had been stirred for 15 min, dimethylaminophosphorodichloridate (0.4 mL, 3.2 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was cooled to 0°C, anhydrous dimethylamine (5 mL) was added, and stirring was
continued at 0°C for 2 h. The solution was diluted with ether, washed with water, twice with brine, dried (MgSO₄) and concentrated. The residue was subjected to flash column chromatography on silica gel (30 g, elution with ether-acetone, 10:1 v/v). The appropriate fractions were combined and concentrated under reduced pressure (16 torr, then 0.02 torr) to yield 0.27 g (63%) of the phosphorodimmitate as a colorless viscous oil which exhibited IR (film): 3085, 1635, 1213, 895 cm⁻¹; ¹H NMR (400 MHz) δ: 4.58 (s, 2H, acetal protons), 4.51 (br s, 2H, olefinic protons), 4.00, 3.94 (dd, dd, 1H each, J = 4, 11 Hz, -CH₂OP), 3.53, 3.45 (td, td, 1H each, J = 8, 10 Hz, -CH₂CH₂O⁻), 3.33 (3H, s, -OCH₃), 2.67, 2.65 (d, d, 6H each, J = 6 Hz, -PNMe₂), 2.27 (br dt, 1H, J = 5, 14 Hz, HA), 2.11 (br d, 1H, J = 14 Hz, HB), 1.93 (t, 2H, J = 8 Hz, -CH₂CH₂O⁻), 2.04-1.40 (m, 10H), 1.06 (s, 3H, angular methyl protons), 0.99 (d, 3H, J = 6 Hz, methyl protons). Exact Mass calcld. for C₂₂H₄₃N₂O₄P: 430.2960; found: 430.2966.

Preparation of the ether

Liquid methylamine (10 mL) was condensed into a cold (-78°C) flask containing lithium metal (12 mg, 1.7 mmol) and the mixture was stirred
at -30°C for 30 min. To the resultant dark blue solution was added an ethereal solution of the phosphorodiamidate 275 (0.13 g, 0.3 mmol) and the mixture was stirred at -20°C for exactly 10 min. The reaction mixture was cautiously but quickly treated with aqueous ammonium chloride and the resultant mixture was extracted three times with ether. The ethereal extracts were combined, washed with brine, dried (MgSO₄) and concentrated. The residue was subjected to column chromatography on silica gel (4 g, elution with petroleum ether-ether, 100:8 v/v). Collection and concentration of the appropriate fractions afforded 67 mg (80%) of the ether 276 as a colorless oil which exhibited ir (film): 3085, 1636, 1149, 1109, 1078, 1040, 891 cm⁻¹; ¹H nmr (400 MHz) δ: 4.57 (s, 2H, acetal protons), 4.49 (br s, 2H, olefinic protons), 3.47, 3.38 (dt, dt, 1H each, J = 6, 10 Hz, -CH₂CH₂O-), 3.34 (s, 3H, -OCH₃), 2.29 (br tdt, 1H, J = 1.3, 5, 13.5 Hz, HA), 2.10 (br dd, 1H, J = 4, 13.5 Hz, HB), 1.88 (br d, 1H, J = 12 Hz, HC), 1.72-1.20 (m, 11H), 1.04 (s, 3H, angular methyl protons), 0.85 (d, 3H, J = 6 Hz, methyl protons), 0.75 (s, 3H, methyl protons). Irradiation at δ 4.49 (olefinic protons) caused the signal at δ 2.34-2.25 to sharpen to a d of t (J = 5, 13.5 Hz); irradiation at δ 2.29 (HA) caused the signal at δ 2.14-2.06 to collapse to a broad singlet and the signal at δ 1.93-1.83 to sharpen; irradiation at δ 2.10 (HB) caused the signal at δ 2.34-2.25 to collapse to a broad doublet (J = 13 Hz) and signal at δ 1.93-1.83 to sharpen to a q of d (J = 3, 12 Hz); irradiation at δ 1.88 (HC) caused the signal at δ 2.34-2.25 to collapse to a broad triplet (J = 13 Hz) and signal at δ 2.14-2.06 to sharpen to a d of d (J = 4, 13 Hz). Exact Mass calcd. for C₁₈H₃₂O₂: 280.2402; found: 280.2412.
Preparation of the alcohol 277

A solution of the ether 276 (37 mg, 0.13 mmol) and pyridinium p-toluenesulfonate (0.33 g, 1.3 mmol) in tert-butyl alcohol (6 mL) was heated at 70°C for 12 h. After removal of solvent under reduced pressure (0.02 torr), the residue was triturated three times with dry ether. The ethereal solutions were combined, filtered, and concentrated. The residue was subjected to column chromatography on silica gel (4 g, elution with petroleum ether-ether, 7:3 v/v). Collection and concentration of the appropriate fractions afforded 25 mg (91%, based on recovery of 5 mg of starting material) of the alcohol 277 which exhibited ir (film): 3375 (br), 3085, 1636, 892 cm\(^{-1}\); \(^1\)H nmr (300 MHz) \(\delta:\) 4.50 (br s, 2H, olefinic protons), 3.61, 3.52 (dt, dt, 1H each, \(J = 5.5, 10\) Hz, \(-CH_2OH\)), 2.29 (tdt, 1H, \(J = 2, 5.5, 14\) Hz, \(H_A\)), 2.10 (tdd, 1H, \(J = 4.5, 4.5, 14\) Hz, \(H_B\)), 1.88 (br d, 1H, \(J = 13\) Hz, \(H_C\)), 1.72-1.18 (m, 12H), 1.04 (s, 3H, angular methyl protons), 0.86 (d, 3H, \(J = 6\) Hz, methyl protons), 0.75 (s, 3H, methyl protons). Exact Mass calcd. for \(C_{16}H_{28}O\): 236.2140; found: 236.2144.
Preparation of the aldehyde 234

To a cold (-78°C) solution of dimethyl sulfoxide (5.6 mg, 71 μmol) in dichloromethane (0.6 mL) was added oxalyl chloride (9 mg, 66 μmol) and the mixture was stirred at -78°C for 20 min. The alcohol 277 (13 mg, 55 μmol) was added and the mixture was stirred at -78°C for 30 min. Triethylamine (35 μL, 0.25 mmol) was added and the reaction mixture was allowed to warm slowly to room temperature and then was concentrated under reduced pressure (0.02 torr). The residue was triturated three times with pentane and the pentane solution were combined, filtered and concentrated to afford 11 mg (85%) of the aldehyde 234 which exhibited

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\text{ir (film): } 3085, 2724, 1718, 1636, 892 \text{ cm}^{-1}; \text{ }^1\text{H nmr (300 MHz) } \delta: 9.78 (t, 1H, J = 3.5 Hz, aldehyde proton), 4.52 (br s, 2H, olefinic protons), 2.41, 2.29 (dd, dd, 1H each, J = 3.5, 14.5 Hz, -CH}_2\text{CHO}, 2.29 (br dt, 1H, J = 5, 13 Hz, HA), 2.11 (br d, 1H, J = 13 Hz, HB), 1.89 (br d, 1H, J = 13 Hz, HC), 1.80-1.18 (m, 9H), 1.06 (s, 3H, angular methyl protons), 0.96 (d, 3H, J = 6.6 Hz, methyl protons), 0.83 (s, 3H, methyl protons).
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Preparation of the Z and E lactones 279 and 280

To a cold (-0°C) solution of the phosphonate 261 (0.11 mmol) in THF (1.9 mL) was added potassium bis(trimethylsilyl)amide (0.12 mmol) as a solution in toluene and 18-crown-6-nCH3CN complex (0.16 g). After the mixture had been stirred for 15 min, it was cooled to -78°C, a THF solution of the aldehyde 234 (85 μmol) was added and the mixture was stirred at -78°C for 4 h. The resultant solution was treated with brine and then was extracted three times with petroleum ether. The combined extract was washed twice with brine, dried (MgSO4) and concentrated. Glc analysis of the crude material showed that it consisted of two compounds in a ratio of 3:1. The crude material was subjected to column chromatography on silica gel (2 g, elution with petroleum ether-ether, 8:2 v/v). Collection and concentration of the appropriate fractions afforded both the pure Z lactone 279, 15 mg (58%) and the pure E lactone 280, 5 mg (19%).

The less polar Z lactone 279 exhibited ir (film): 3084, 1753, 1666, 1635, 891 cm⁻¹; ¹H nmr (400 MHz) δ: 6.24 (tt, 1H, J = 2, 8 Hz, olefinic proton), 4.52 (br s, 2H, olefinic protons), 4.28 (br t, 2H, J = 7.5 Hz, -CH2O-), 2.91 (br t, 2H, J = 7.5 Hz, -CH2CH2O-), 2.89, 2.65 (tdd, tdd, 1H each, J = 2.5, 8, 17 Hz, -CH2C=), 2.30 (br dt, 1H, J = 5, 13.5 Hz,
H$_A$), 2.10 (br d, 1H, $J = 13.5$ Hz, H$_B$), 1.87 (br d, 1H, $J = 12.5$ Hz, H$_C$), 1.7-1.1 (m, 9H), 1.05 (s, 3H, angular methyl protons), 0.87 (d, 3H, $J = 6.5$ Hz, methyl protons), 0.82 (s, 3H, methyl protons). **Exact Mass calcd. for C$_{20}$H$_{30}$O$_2$: 302.2246; found: 302.2239.**

The more polar $E$ lactone 280 exhibited ir (film): 3084, 1758, 1676, 1635, 892 cm$^{-1}$; $^1$H nmr (400 MHz) $\delta$: 6.76 (tt, 1H, $J = 2.5$, 6.5 Hz, olefinic proton), 4.51 (br s, 2H, olefinic protons), 4.36 (t, 2H, $J = 6$ Hz, $-\text{CH}_2\text{O}$-$)$, 2.85 (br t, 2H, $J = 6$ Hz, $-\text{CH}_2\text{CH}_2\text{O}$-$)$, 2.27 (br dt, 1H, $J = 5$, 13 Hz, H$_A$), 2.30-2.22, 2.18-2.10 (m, 1H each, $-\text{CH}_2\text{C}$-$)$, 2.11 (br d, 1H, $J = 13$ Hz, H$_B$), 1.87 (br d, 1H, $J = 13$ Hz, H$_C$), 1.65-1.10 (m, 9H), 1.05 (s, 3H, angular methyl protons), 0.86 (d, 3H, $J = 6.5$ Hz, methyl protons), 0.82 (s, 3H, methyl protons). **Exact Mass calcd. for C$_{20}$H$_{30}$O$_2$: 302.2246; found: 302.2238.**

Preparation of (±)-isolinaridiol (64) and the diol 278

To a cold (-78°C) solution of the Z lactone 279 (15 mg, 50 µmol) in ether (1 mL) was added diisobutylaluminum hydride (0.2 mmol) as a solution in hexanes. After the mixture had been stirred at -78°C for 1 h and at 0°C for 1 h, it was treated with saturated aqueous ammonium...
chloride (10 μL) and then was diluted with ether. The mixture was stirred at room temperature for 5 min, dried (MgSO₄), filtered through Florisil and concentrated to afford 14.5 mg (96%) of (±)-isolinaridiol (64) which exhibited IR (film): 3328 (br), 3086, 1636, 891 cm⁻¹; ¹H nmr (400 MHz) δ 5.36 (br t, 1H, J = 8 Hz, olefinic proton), 4.50 (br s, 2H, olefinic protons), 4.19, 4.15 (d, d, 2H, J = 12 Hz, -CH₂OH), 3.74 (br t, 2H, J = 6 Hz, -CH₂CH₂OH), 2.39 (t, 2H, J = 6 Hz, -CH₂CH₂OH), 2.30 (br dt, 1H, J = 6, 14 Hz, HA), 2.09 (m, 2H, -CH₂C=), 1.9-1.0 (m, 7H), 1.78 (br s, 2H, D₂O exchanged, -OH), 1.05 (s, 3H, angular methyl protons), 0.83 (d, 3H, J = 7 Hz, methyl protons), 0.76 (s, 3H, methyl protons). The ¹H nmr spectrum of this material was identical to that of natural isolinaridiol (64).* Exact Mass calcd. for C₂₀H₃₂O (H⁺-H₂O): 288.2453; found: 288.2451.

Similarly, the E lactone 280 (10 mg, 33 μmol) was reduced to the diol 278 (9 mg, 89%), which exhibited IR (film): 3309 (br), 3085, 1636, 891 cm⁻¹; ¹H nmr (300 MHz) δ 5.52 (t, 1H, J = 7.5 Hz, olefinic proton), 4.51 (br s, 1H, olefinic protons), 4.05 (br s, 2H, -CH₂OH), 3.71 (t, 2H, J = 6 Hz, -CH₂CH₂O-), 2.43 (t, 2H, J = 6 Hz, -CH₂CH₂O-), 2.30 (br dt, 1H, J = 5, 14 Hz, HA), 2.14-1.10 (m, 11H), 1.04 (s, 3H, angular methyl protons), 0.82 (d, 3H, J = 6 Hz, methyl protons), 0.76 (s, 3H, methyl protons). The ¹H nmr spectrum of this material was very different from that of isolinaridiol (64).* Exact Mass calcd. for C₂₀H₃₂O (H⁺-H₂O): 288.2453; found: 288.2448.

* We are grateful to Professor A. San Feliciano for a sample of natural isolinaridiol.
Preparation of the diacetate 61 and 281

A solution of isolinaridiol (64) (4 mg, 13 μmol), acetic anhydride (5 μL, 52 μmol) and 4-N,N-dimethylaminopyridine (catalyst) in pyridine (0.5 mL) was stirred at room temperature for 1.5 h. The resultant solution was diluted with ethyl acetate and then was washed three times with brine, dried (MgSO₄) and concentrated. The residue was subjected to column chromatography on silica gel (1 g, elution with petroleum ether-ethyl acetate, 8:2 v/v). Collection and concentration of appropriate fractions afforded 4.5 mg (90%) of the diacetate (61) which exhibited ir (film): 3083, 1742, 1635, 1234, 892 cm⁻¹; ¹H nmr (300 MHz) δ: 5.44 (t, 1H, J = 7.5 Hz, olefinic proton), 4.61 (br s, 2H, =CCH₂OAc), 4.49 (br s, 2H, olefinic protons), 4.13 (m, 2H, -CH₂CH₂OAc), 2.40 (t, 2H, J = 7 Hz, -CH₂CH₂OAc), 2.29 (br dt, 1H, J = 5, 13.5 Hz, HA), 2.16-1.96 (m, 3H), 2.06, 2.03 (s, s, 3H each, acetyl protons), 1.84 (br d, 1H, J = 13.5 Hz, HC), 1.54-1.0 (m, 9H), 1.04 (s, 3H, angular methyl protons), 0.81 (d, 3H, J = 6 Hz, methyl protons), 0.75 (s, 3H, methyl protons). The ¹H nmr spectral data of this material is different from those reported by San Feliciano et al19 for isolinaridiol diacetate. Exact Mass calcd. for C₂₂H₃₄O₂ (M⁺-HOAc): 330.2559; found: 330.2560.

Similarly, the diol 278 (4 mg, 14 μmol) was converted into the
diacetate 281 (4 mg, 78%) which exhibited ir (film): 3085, 1747, 1635, 1230, 892 cm⁻¹; ¹H nmr (300 MHz) δ: 5.57 (t, 1H, J = 7.5 Hz, olefinic proton), 4.50 (br s, 4H, =CCH₂OAc and olefinic protons), 4.10 (t, 2H, J = 7.5 Hz, -CH₂CH₂OAc), 2.43 (t, 2H, J = 7.5 Hz, -CH₂CH₂OAc), 2.29 (br dt, 1H, J = 5, 13.5 Hz, HA), 2.15-2.02 (m, 3H), 2.06, 2.04 (s, s, 3H each, acetyl protons), 1.85 (br d, 1H, J = 13.5 Hz, HC), 1.56-1.1 (m, 9H), 1.04 (s, 3H, angular methyl protons), 0.82 (d, 3H, J = 6 Hz, methyl protons), 0.77 (s, 3H, methyl protons). The ¹H nmr spectral data of this material is different from those reported for isolinaridiol diacetate.¹⁹ Exact Mass calcd. for C₂₂H₃₄O₂ (M⁺-HOAc): 330.2559; found: 330.2557.

Preparation of the endocyclic alkene 296

![Endocyclic Alkene](image)

To a cold (-78°C) solution of the exocyclic alkene 276 (20 mg, 71 μmol) in dichloromethane (1 mL) was added dimethylboron bromide (0.43 mmol) as a solution in dichloromethane. After the solution had been stirred at -78°C for 6 h, it was cannulated into a vigorously stirred mixture of THF and saturated aqueous sodium bicarbonate. The mixture was extracted three times with ether. The combined extracts was washed...
with brine, dried (MgSO₄) and concentrated. The residue was subjected to column chromatography on silica gel (1 g, elution with petroleum ether-ether, 7:3 v/v). Collection and concentration of the appropriate fractions afforded 14 mg (84%) of the endocyclic alkene 296 which exhibited ir (film): 3304 (br) cm⁻¹; ¹H nmr (400 MHz) δ: 5.18 (v br s, 1H, olefinic proton), 3.62 (m, 2H, -CH₂OH), 1.57 (br s, 3H, vinyl methyl protons), 2.1-1.1 (m, 13H), 1.00 (s, 3H, angular methyl protons), 0.87 (d, 3H, J = 6 Hz, methyl protons), 0.73 (s, 3H, methyl protons). Exact Mass calcd. for C₁₆H₂₈O: 236.2140; found: 236.2143.
REFERENCES


102. Ref. 95, pp. 1030.