AN APPROACH TO THE
SYNTHESIS OF NEOCLOVENE

BY

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This thesis describes the investigation of two synthetic approaches to the keto tosylate 90, a key intermediate in a proposed synthesis of neoclovene. The first approach involved an efficient 9-step synthesis of the epoxy acetals 152 and 153 from indan-1-one 142. Dialkylation of 142 with methyl iodide followed by the reaction of the dimethyl ketone 143 with diethyl cyanomethylphosphorane gave the nitriles 144 and 145. Successive subjection of the nitriles to hydrolysis, hydrogenation, and reduction resulted in the formation of the aromatic alcohol 141. Treatment of the latter with lithium in liquid ammonia followed by regioselective hydrogenation of the disubstituted double bond of 149 with the homogeneous catalyst tris(triphenylphosphine)chlororhodium gave the olefin alcohol 150. Epoxidation of the double bond of the olefin acetal 151, corresponding to the alcohol 150, with m-chloroperbenzoic acid gave a mixture of epoxy acetals 152 and 153 in quantitative yield. However, all attempts to obtain the keto tosylate 90 from the epoxy acetals failed to give synthetically useful yields of the desired products. This precluded further use of this approach.

The second approach involved the synthesis of the olefin alcohol 179, a proposed intermediate in the synthesis of the keto tosylate 90. Thus, alkylation of isobutyronitrile 165 with allyl bromide followed by ozonolysis of the alkylation product gave the aldehydic nitrile 167. Successive treatment with cyclopentylidenetriphenylphosphorane, polyphosphoric acid, and alcoholic sodium hydroxide afforded the ketone 170. The ketone 170 was converted into the epoxy ketone 171 and the latter was reacted with methylenetriphenylphosphorane to yield the epoxy olefin 173. The latter
was subjected to hydroboration-oxidation to produce the epoxy alcohols 174 and 175. The alcoholic functionality was protected as the acetate and the epoxide was reduced with tungsten hexachloride-n-butyllithium to give the olefin acetate 178 in 90% yield. Reduction of the olefin acetate with lithium aluminum hydride yielded the olefin alcohol 179. Unfortunately, due to the lack of time and material, this project was concluded at this point. A possible synthetic route to the keto tosylate 90 from the olefin alcohol 179 is given.
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INTRODUCTION

1. Diorganocopper Reagents

The use of a catalytic amount of a copper salt in the reaction of an α,β-unsaturated carbonyl compound with an organometallic reagent to achieve a Michael (1,4) addition has been known since 1941.\(^1\) It was not until twenty-five years later that House, Respess, and Whitesides\(^2\) experimentally showed that the reactive intermediate was in fact an organocopper derivative. This derivative, preformed from Cu(I) and an organometallic reagent or formed from the same reagents in situ gave the same product upon reaction with E-3-penten-2-one.\(^1\)

Since 1966, extensive research\(^3\) has shown that diorganocopper reagents can be used with a wide variety of substrates other than α,β-unsaturated carbonyl compounds. The coupling reaction of organocuprates with alkyl halides\(^4-8\) and tosylates\(^9-11\) has been shown to
6,0%  M  6.5%  0= c  60%  s  9  15%  11

CH₂ = CCH₂OT₅  Ph₂CuLi  89%  CH₂ = CHCH₂φ

(CH₂)₂CuLi + CH₃OT₅  98%  2%
proceed not only in high yield but in some cases\(^9\) with high stereo-
selectivity (see Chart 1). Other leaving groups have also been
displaced by organocuprate reagents. In the case of ethynylcarbinol
acetates, allenes\(^{12}\) are formed. Olefins are formed stereoselectively
from allylic acetates\(^{13}\) and \(\beta\)-alkoxy- and \(\beta\)-alkythio-\(\alpha\),\(\beta\)-unsaturated
carbonyl compounds\(^{14,15}\) (see Chart 2) and ketones are formed from
carboxylic acid chlorides\(^{15}\) (see Chart 3). Epoxide rings can also be
opened in a nucleophilic manner by organocuprates.\(^{17-19}\) Although
organocuprate reagents react with the aforementioned substrates,
organic chemists have found these reagents to be most useful in their
unusually effective conjugate addition to \(\alpha\),\(\beta\)-unsaturated aldehydes,\(^{20}\)
ketones,\(^{3,21}\) esters,\(^{3,22}\) and nitriles\(^{23,24}\) (see Charts 2 and 3).

The proposed mechanism of organocupper conjugation additions\(^2,25\)
involves either partial or complete electron transfer from organo-
cuprate, \([\text{RCu(I)Y}]^-\), to unsaturated substrate forming either a charge-
transfer complex or a radical anion. Subsequent transfer of an organic
radical from a transient organocopper(II) species to the end of the
conjugated anion radical or collapse of the charge transfer complex

\[
\begin{align*}
[\text{R:Cu(I)Y}]^- & \quad \text{R:Cu(II)Y} & \quad \text{Cu(I)Y} \\
\begin{array}{c}
\text{O} \\
\text{C=C-C-} \\
\text{54}
\end{array} & \quad \begin{array}{c}
\text{O}^- \\
\text{C-C=C-} \\
\text{55}
\end{array} & \quad \begin{array}{c}
\text{R} \\
\text{O}^- \\
\text{C-C=C-} \\
\text{56}
\end{array}
\end{align*}
\]

\(Y = \text{R, halogen, CN}\)

would complete the addition sequence and generate enolate 56 which is
CHART 2

- 4 -

[Chemical reactions and structures]
\[ \text{CN} \,(\text{CH}_2)_10 \,\text{CoCl} \quad \text{R} = \text{CH}_3 \,80\% \quad \text{CN} \,(\text{CH}_2)_10 \,\text{CoR} \quad \text{R} = \text{nBu} \,95\% \]

\[ \text{nC}_4\text{H}_9 \,\text{O}_2 \,\text{CCH}_2 \,\text{CH}_2 \,\text{CoCl} \quad \text{R} = \text{CH}_3 \,83\% \quad \text{nC}_4\text{H}_9 \,\text{O}_2 \,\text{CCH}_2 \,\text{CH}_2 \,\text{CoR} \quad \text{R} = \text{nBu} \,93\% \]

\[ \text{I} \,(\text{CH}_2)_10 \,\text{CoCl} \quad \text{R} = \text{CH}_3 \,91\% \quad \text{I} \,(\text{CH}_2)_10 \,\text{CoR} \quad \text{R} = \text{nBu} \,93\% \]

\[ \begin{array}{c}
\text{Me}_2\text{CuLi} \\
88\% \end{array} \quad \begin{array}{c}
\text{Me}_2\text{CuLi} \\
68\% \end{array} \]

\[ \begin{array}{c}
\text{Ph}_2\text{CuLi} \\
84\% \end{array} \quad \begin{array}{c}
\text{Me}_2\text{CuLi} \\
97\% \end{array} \]

\[ \text{Me}_2\text{CuLi} \quad \text{Me}_2\text{CuLi} \]

\[ \text{CH}_3 \,\text{CO}_2 \text{CH}_2 \text{CH}_3 \]

**Chart 3**
quenched on subsequent aqueous workup. The apparent requirements of a net negative charge on the copper complex for efficient conjugate addition has recently been confirmed.\textsuperscript{26,27}

Although enolates such as \textsuperscript{56} have been trapped as enol derivatives with acetyl chloride, acetic anhydride,\textsuperscript{2} and diethyl phosphorochloridate\textsuperscript{28} and have been found to give only one double bond isomer, few researchers have,\textsuperscript{*} until recently, alkylated these enolates \textit{in situ} to further elaborate the carbonyl substrate.

Last year, Boeckman and Coates independently showed that organo-copper enolates can be regioselectively and, in some cases, stereoselectively alkylated to yield \(\alpha\)-disubstituted\textsuperscript{34} and \(\alpha,\beta\)-disubstituted\textsuperscript{34-36} carbonyl compounds.

\* To date, the direct alkylation of the intermediate magnesium enolate formed from the copper-catalyzed conjugate addition of Grignard reagents to \(\alpha,\beta\)-unsaturated ketones has been achieved by Stork\textsuperscript{29,30} and Kretchmer.\textsuperscript{31,32} The alkylation of copper-lithium malonates has been reported by Grieco.\textsuperscript{33}
In his first paper on this subject, Boeckman was able to successfully react some regio-stable copper enolates with various α-trimethylsilyl α,β-unsaturated ketones. It was found that in the case of cyclic α,β-unsaturated ketones, the incoming α-trimethylsilyl vinyl ketones add predominately anti to the previously introduced (from the cuprate addition) alkyl group and therefore the overall annelation reaction produces a highly stereoselective product. In the case of enolate 62, the cyclohexene skeleton assumes a half-chair conformation in which the allylic methyl group is in a pseudoaxial position to relieve A(1,2) strain. In this conformation, the steric requirements favor alkylation on the α face. The resulting ratio (97:3) of the cis octalone 64 to the trans octalone 65 respectively shows the potential of the conjugate addition-annelation sequence in organic synthesis.

Boeckman has also added an isopropenyl group via the cuprate as shown by his synthesis of hydrindenone 68 (see Chart 4). In his second paper on the alkylation of organocopper enolates, Boeckman turned his attention toward the use of alkyl halides as the alkylation agents (see Chart 4). This work showed that these metal enolates (formed in a regioselective manner), because of the covalent nature of the copper-oxygen bond, may be alkylated regiospecifically in unhindered cases without a significant amount of polyalkylation. If the β position of the carbonyl substrate is sterically hindered, as in ketone 71 (see Chart 4), the metal enolates will undergo equilibration* at a significant

* Boeckman also proposed that reduction in the size of the alkyl halide would increase the ratio of alkylation to equilibration.
rate relative to the rate of alkylation resulting in loss of regio-
specificity.*

In a very similar study, Coates\textsuperscript{34} investigated the conjugate
addition-alkylation of 2-\textit{n}-butylthiomethylene ketones as well as
other \(\alpha,\beta\)-unsaturated ketones. Although the results obtained did not
show as high a degree of stereoselectivity as Boeckman's work, he has
demonstrated a new method of acquiring \(\alpha,\alpha\)-disubstituted ketones. Thus,
double conjugate addition\textsuperscript{37} to 2-\textit{n}-butylthiomethylene ketones (see
for example ketone 74, Chart 4), followed by alkylation of the copper-
lithium enolate resulted in the formation of \(\alpha\)-isopropyl-\(\alpha\)-alkyl-
disubstituted ketones.

2. \textbf{Intramolecular Alkylations}

Intramolecular alkylations play a very important role in synthetic
organic chemistry.\textsuperscript{38} With the advent and refinement of chromato-
graphic techniques, p.m.r. spectrometers, and X-ray crystallographic
techniques chemists are now able to isolate and determine the structure
of many natural products in a relatively short time. Most of these
compounds have complex, polycyclic structures. In order to synthesize
these compounds from simpler mono-, di-, or tri-cyclic precursors,
more and more chemists have used intramolecular cyclizations as an
integral step in their synthetic sequence. This type of alkylation is
attractive because of the facility of intramolecular reactions. Also,
since it is kinetically controlled, this process can lead to very

* It must be remembered that other steric factors in the \textit{cis}-decalin
system also contribute to the rate of alkylation.
strained ring systems (*vide infra*). In the synthesis of sesquiterpenes, the first good examples of intramolecular alkylation are to be found in McMurry's synthesis of (±)-sativene and Heathcock's synthesis of (±)-copaene and (±)-ylangene. Intramolecular cyclizations have been used not only in the synthesis of sesquiterpenes but also in the synthesis of steroids, diterpene alkaloids, triterpenes, and alkaloids.

In Piers' synthesis of (±)-seychellene, the keto tosylate, upon treatment with base, gave in excellent yield (±)-norseychellanone. This ketone was then converted by standard methods into (±)-seychellene. In the field of diterpene alkaloids, Nagata and co-workers, in the synthesis of the pentacyclic compound atisine, employed an intramolecular alkylation of ketone to form the C-D ring system of this complex compound. Piers and co-workers again demonstrated the use of this type of alkylation in the synthesis of (+)-copacamphor by base treatment of the keto-tosylate. The final example is taken from Corey's recent synthesis of (±)-α-copaene. The keto tosylate was converted to the ketone thus establishing the required tricyclic skeleton. The isopropyl substituent was then established to yield (±)-α-copaene.

In view of the potential synthetic utility of the conjugate addition-alkylation reaction and the importance of the intramolecular alkylation in organic synthesis, we were interested in combining these two aspects in one step. That is to say, it was proposed to "trap" an organocopper enolate formed from a cuprate addition via an intramolecular alkylation step. To demonstrate the application of this reaction, we proposed to synthesize neoclovene. The key
CHART 5
reaction for the proposed synthesis was the formation of the tricyclic skelton via the organocopper enolate 91. The expected stereochemistry of the addition product, intermediate 91 will be discussed at a later time (see p. 23).

3. Origin and Structural Elucidation of Neoclovene

Since this thesis is partially concerned with an approach to the synthesis of neoclovene, it is pertinent to discuss the origin and the work which led to the establishment of the structure and stereochemistry of this compound.

Neoclovene was first isolated by Parker, Raphael, and Roberts, when, in an attempt to obtain a pure sample of (±)-clovene by the well-known sulphuric acid-catalyzed rearrangement of caryophyllene,
they discovered a then unknown hydrocarbon as one of the two main products in this reaction. They subsequently characterized this hydrocarbon and showed its structure and absolute stereochemistry to be as depicted in structure 89. This structural determination by Raphael and co-workers will be summarized in the following paragraphs.

Neoclovene \( \text{C}_{15}H_{24} \) was shown to be tricyclic by catalytic hydrogenation over 10% palladium on charcoal to a fully saturated dihydro derivative, neoclovane 93. The p.m.r. spectrum of neoclovene indicated one vinyl proton at \( \tau 4.19 \), three tertiary methyl groups at \( \tau 8.80 (3H) \) and \( \tau 8.99 (6H) \) and a vinylic methyl group at \( \tau 8.41 \) (\( J = 1.5 \) Hz). Hydroboration followed by Jones oxidation gave two epimeric ketones 94 whose carbonyl absorptions at 1712 cm\(^{-1}\) were indicative of cyclohexanones (see Chart 6). Treatment of neoclovene with osmium tetroxide followed by sodium metaperiodate cleavage of the diol resulted in the keto-aldehyde 95, the p.m.r. spectrum of which showed a sharp singlet at \( \tau 7.98 (3H) \) confirming the presence of the vinylic methyl group. Further, the aldehydic proton at \( \tau 0.2 \) appeared as a triplet (\( J = 2.5 \) Hz) thus indicating the presence of a neighbouring methylene group.
When the keto-aldehyde 95 was sequentially treated with chromium trioxide, diazomethane, and trifluoroperacetic acid, the resultant acetoxy-methyl ester 96 was shown to possess a tertiary acetoxy group due to a lack of resonance in the \( \tau \) 5-6 region. In addition, none of the three tertiary methyl groups showed any appreciable downfield shift to be expected if one or two of them were substituted on the carbon bearing the acetoxy-function.

Treatment of the hydroxy-ester 97 corresponding to 96 with excess phenyl magnesium bromide, followed by acetic anhydride dehydration gave the diphenylene acetate 98. The vinylic proton signal at \( \tau \) 3.89 was clearly resolved into a triplet \( (J = 8 \text{ Hz}) \) demonstrating the juxtaposition of a methylene group. Treatment of 98 with a catalytic amount of ruthenium dioxide and an excess of sodium metaperiodate followed by methanolic sodium hydroxide hydrolysis and esterification gave the nor-hydroxy-ester 99.

A second Barbier-Wieland sequence performed on 99 afforded initially the nor-diphenylenecacetate 100 the p.m.r. spectrum of which, revealed the vinylic proton as a sharp singlet at \( \tau \) 3.62 indicative of a neighbouring quaternary center. In addition, one of the tertiary methyl groups had moved downfield in the conversion of 98 to 100 suggesting that one of the substituents at this quaternary center was probably a methyl group. Conversion of this product to the hydroxy-ester 101 was achieved in the same manner as for the higher homologue. Lithium aluminum hydride reduction of 101 led to a 1,3-diol which was transformed to the mono-tosylate 102. Base induced fragmentation of 102 yielded 4-isopropenyl-3,3-dimethylcyclohex-2-enone 103. This
established the tricyclic system of neoclovene.

The assignment of the relative configuration of the tertiary methyl group at C₆ with respect to the gem-dimethyl group at C₈ was proven by the following method. Hydroboration of neoclovene gave two epimeric alcohols 104 and 105 which were shown by p.m.r. to have the structure shown. Jones oxidation of 104 gave ketone 106 the o.r.d. curve of which showed a marked negative Cotton effect which is consistent with the prediction of the octant rule.⁵⁰,⁵¹ If this ketone had possessed a structure in which the C₆ methyl group were anti to the C₈ gem-dimethyl group then the Cotton curve would be expected to show a positive effect.

The mechanism proposed⁴⁶,⁴⁷ for the rearrangement of caryophyllene into neoclovene involves initially the isomerization of the exocyclic double-bond followed by an acid-catalyzed cyclization to the tricyclic cation 109. A Wagner-Meerwein rearrangement of this cation would produce the bridge-head cation 110. A final Wagner-Meerwein rearrangement and subsequent proton loss would then generate neoclovene.
4. Other Synthetic Approaches to Neoclovene

There has been a number of approaches to the total synthesis of neoclovene but, for the sake of brevity, the only successful one will be discussed. Parker and co-workers succeeded in synthesizing neoclovene by utilizing a synthetic scheme which also added support to his proposed mechanism for the rearrangement of caryophyllene into neoclovene (vide supra). Thus, the tri-substituted double bond of
caryophyllene was epoxidized with m-chloroperbenzoic acid followed by oxidative cleavage of the exocyclic double bond with osmium tetroxide-sodium periodate to give the epoxy-ketone (see Chart 7). Treatment of the latter with potassium hydroxide produced the ketol. The carbonate ester, formed from the reaction of the ketol with ethyl chloroformate, was pyrolyzed at 350° to give a 3:1 mixture of ketones and respectively. Hydrogenation of this mixture over 10% palladium on charcoal yielded the saturated ketone. Treatment of the tricyclic ketone with methylmagnesium iodide afforded the tertiary alcohol which, when treated in ether with concentrated sulphuric acid rearranged to neoclovene.
DISCUSSION

1. General

At the onset of this project, we wished to apply the conjugate addition-intramolecular alkylation sequence to the synthesis of neoclovene. Because of the great diversity in the number of theoretical pathways in which this complex molecule could be constructed, a brief discussion of synthetic stratagem and methodology is appropriate. The first order of business in planning a synthesis of a complex molecule must be the reduction of the complex framework to simpler rational precursors. A less complex ring structure may be obtained by the theoretical cleavage of a bond in a complex bridged-ring structure. The cyclization of the appropriately functionalized intermediate would regenerate the desired polycyclic skeleton. This approach is well illustrated by Corey and co-workers,\textsuperscript{54} in the synthesis of longifolene \textsuperscript{118}. The theoretical cleavage of the C\textsubscript{6}-C\textsubscript{10} bond in longifolene \textsuperscript{118} produced a simplified structure \textsuperscript{119} as compared with \textsuperscript{118}. The appropriately functionalized intermediate \textsuperscript{120} underwent an intramolecular Michael cyclization to produce the tricyclic diketone \textsuperscript{121}. 
This same basic approach was used by McMurry in his synthesis of (±)-sativene. The key step in this synthesis involved the intramolecular alkylation of an appropriately functionalized intermediate, the bicyclic keto tosylate, to afford the tricyclic ketone.

\[ \text{121} \]
Following this general outline, the theoretical cleavage of two carbon-carbon bonds in neoclovene 89 were considered (see Chart 8). Cleavage of the C\textsubscript{1}-C\textsubscript{10} and C\textsubscript{7}-C\textsubscript{11} bonds of neoclovene 89 (see numbering below) would lead to the hypothetical intermediates 125 and 126 respectively. Bearing in mind that the conjugate addition-cyclization sequence involves, initially, the addition of a methyl group by an organocuprate reagent, the appropriately functionalized intermediates that might be envisaged for the regeneration of the required tricyclic skeleton were 90, 127, 128, and 129.

Upon analyzing the proposed intermediates, keto tosylate 127 was rejected for lack of a "handle" on C\textsubscript{2} for the introduction of the C\textsubscript{12} vinyl methyl group. The ester tosylate 128 was also rejected not only because of the obvious difficulty in synthesizing this complex intermediate but also of the uncertainty in the decarboxylation of the cyclized product. Thus, our attention was focused on intermediates 90 and 129. There was an obvious limitation if 129 were to be the bicyclic precursor to neoclovene, since conjugate addition could produce not only the desired trans hydrindenone 130 but also the cis isomer 131. Therefore, we believed that the keto tosylate 90 should be our objective.

In a search of the current literature, several examples were found which led us to believe that conjugate addition would occur anti to the two carbon chain. In an investigation on some approaches to the synthesis of cadinene sesquiterpenenes, Phillips found that conjugate addition to the dienones 132 and 133 occurred anti to the axial bridgehead substituents\textsuperscript{55} to afford ketones 134 and 135. In a recent
CLEAVAGE OF:

PROPOSED INTERMEDIATE FOR CYCLIZATION

CHART 8
paper, Ziegler and Wender\textsuperscript{56} reported that upon treatment of 3,4-
dimethylcyclohex-2-en-1-one \textsuperscript{136} with lithium divinyl cuprate-tri-n-
butylphosphine complex, the vinyl ketone \textsuperscript{137} was produced in good
yield free of its diastereomer. The cuprate reagent was proposed to
have added \textit{anti} to the axial (due to A\textsuperscript{(1,2)} interaction) C\textsubscript{4} methyl
group.

An examination of molecular models of keto tosylate \textsuperscript{90} clearly
showed that, although the two carbon side chain is in a pseudo-axial
and not a purely axial orientation, approach of the cuprate reagent
from the \( \beta \) face would cause the reagent to be almost eclipsed with the
C\textsubscript{10} methylene group. This steric interaction should be almost
comparable in magnitude to the interaction experienced by the cuprate
reagent in the above examples (see Chart 9) and thus, attack from the
\( \alpha \) face would be predicted. This would produce, after intramolecular
alkylation of the initially formed enolate, the required stereochemistry
in the product, ketone \textsuperscript{97}. The latter could be easily transformed
via the alcohol \textsuperscript{138} to neoclovene.
CHART 9
2. **Attempted Synthesis of Keto Tosylate 90**

At the outset of this work, we had available a sample* of the methoxy alcohol 139 which we attempted to reduce and hydrolyze to the keto alcohol 140. Unfortunately, the lithium-liquid ammonia reduction,\textsuperscript{57,58} when attempted under a variety of conditions (varying temperature, amount of lithium and inverse addition), either gave no reduction products using mild reaction conditions or a complex mixture of saturated and unsaturated products using a greater amount of lithium and a higher reaction temperature. We therefore synthesized the aromatic alcohol 141, the demethoxy analogue of 139 in the hopes

* We thank Dr. F. Kido for a generous sample of this compound.
of introducing an oxygen functionality at the C₄ carbon atom of the indane system at a later stage in the synthesis.

We chose as our starting material, indan-1-one 142 which was alkylated with methyl iodide in the presence of potassium t-butoxide to give an 86% yield of 2,2-dimethylindan-1-one 143 (see Chart 10). The keto group of 143 was then used as a "handle" for the introduction of the two carbon side chain. Initially considered for this purpose was the reaction of 143 with the modified Wittig reagent, triethyl phosphonoacetate. However, this reaction proved very sluggish and even when carried out at elevated temperatures, produced no synthetically useful results. Since it was felt that the failure of this reaction was due, at least in part, to the sterically hindered nature of the carbonyl group in 143, it was decided to attempt the use of a reagent which was sterically less demanding, namely, diethyl cyanomethylphosphonate. This approach proved successful. Thus, reaction of ketone 143 with diethyl cyanomethylphosphonate in the presence of methyl-sulfinyl carbanion in dimethyl sulfoxide at 105° for twenty hours produced a mixture* of Z and E isomers 144 and 145.

* A 65:35 mixture of the Z 144 and E 145 isomers was obtained as judged by g.l.c. analysis and by integration of the signals at τ 4.36 and τ 4.87 in the p.m.r. spectrum.
respectively in 93% yield.

The physical and spectral properties of the nitriles were in agreement with structures 144 and 145. Thus the infrared spectrum showed a nitrile absorption at 2238 cm\(^{-1}\) and olefinic absorptions at 1615 and 1600 cm\(^{-1}\). This mixture of isomers were partially separated by column chromatography to give a fraction that contained the major \(_Z\) isomer in 96% purity. From the p.m.r. spectrum of this fraction, the proton resonances of the \(_E\) isomer could be deduced. Of particular interest was the anisotropic effect\(^64\) of the cyano group shown in the p.m.r. spectrum. The C\(_7\) proton (see Chart 10) of the \(_Z\) isomer was deshielded by the cyano group and appeared as a multiplet at \(\tau\) 1.53-1.83. The gem dimethyl group appeared as a singlet at \(\tau\) 8.73 in the \(_Z\) isomer while it appeared at lower field (\(\tau\) 8.54), due to the deshielding effect of the nitrile group, in the \(_E\) isomer. The vinyl proton of the \(_E\) isomer, deshielded by the aromatic ring, appeared as a singlet at \(\tau\) 4.36 while it appeared at \(\tau\) 4.87 in the \(_Z\) isomer.

The mixture of nitriles 144 and 145 was hydrolyzed\(^65\) to a mixture of unsaturated acids 146 and 147 using a refluxing mixture of ethylene glycol, water, and sodium hydroxide. The white crystalline product exhibited physical properties in accord with those expected for a mixture of compounds 146 and 147. Of particular interest in the infrared spectrum was the absence of the nitrile absorption, the presence of the hydroxyl absorption at 3600-2400 cm\(^{-1}\), and an unsaturated carbonyl absorption at 1690 cm\(^{-1}\). Again, the presence of the \(_Z\) 146 and 147 isomers were evident in the p.m.r. spectrum. The deshielding effect of the acid group and the aromatic ring system caused the resonances of the gem dimethyl group (\(\tau\) 8.45) and the vinyl proton (\(\tau\) 3.62) to appear
at lower field in the E isomer as compared to the corresponding signals (τ 8.72 and 4.15 respectively) of the Z isomer. The C7 proton of the Z isomer was also deshielded by the acid functionality and appeared as a multiplet at τ 1.14-1.42.

Hydrogenation of the mixture of acids (one equivalent of hydrogen) over palladium on charcoal gave a 94% yield of the saturated acid 148. The physical and spectral properties of the acid were in agreement with structure 148. Thus the infrared spectrum showed a hydroxyl absorption at 3500-2400 cm⁻¹, and a saturated carbonyl absorption at 1705 cm⁻¹. The presence of the acidic proton was evidenced in the p.m.r. spectrum by a broad singlet at τ -1.08. The doublet of doublets at τ 6.73 (J = 6 Hz) was assigned to the benzylic methine proton and the unresolved multiplet (AB of ABM system) between τ 7.16 and τ 7.68 was readily attributable to the methylene protons adjacent to the acid functionality. The magnetic nonequivalence of methylene protons found in an asymmetric environment is a well-established phenomenon, and this therefore deserves no further comment. The sharp singlets at τ 9.08 and τ 8.82 were attributed to the tertiary methyl groups.

The reduction of the aromatic acid 148 to the aromatic alcohol 141 was achieved by the reaction of the former with diborane in tetrahydrofuran. The physical and spectral properties of the resulting product (93% yield) were in accord with structure 141. The hydroxyl group was evident due to an absorption at 3360 cm⁻¹ in the infrared spectrum and an exchangeable hydroxyl proton (broad singlet, τ 6.50-6.93) in the p.m.r. spectrum. The aromatic protons appeared as a singlet at τ 2.98. The triplet at τ 6.27 (J = 6 Hz) was assigned to the methylene protons α to the hydroxyl group. The geminal dimethyl
group appeared as singlets at $\tau$ 8.89 and 9.05 while the singlet at $\tau$ 7.38 was attributed to the C$_3$ methylene protons.

With the achievement of our first synthetic objective, the next step involved the reduction of the aromatic system and hopefully the introduction of an oxygen functionality at the C$_4$ carbon atom \textit{(vide supra)}. Since previous work$^{69}$ in this laboratory showed that the allylic oxidation$^{70}$ of the alcohol 154, under a variety of conditions, yielded a number of $\alpha,\beta$-unsaturated carbonyl products, we decided to synthesize the epoxy ethers 152 and 153 (see Chart 10) and introduce

\begin{center}
\begin{align*}
\text{154} & \quad \text{155} \\
\end{align*}
\begin{align*}
\text{+ OTHER PRODUCTS}
\end{align*}
\end{center}

the oxygen functionality \textit{via} an allylic alcohol \textit{(vide infra)}.

Reaction of the aromatic alcohol 141 with lithium in liquid ammonia$^{72}$ afforded the diene alcohol 149 in 90% yield. This compound showed the expected spectral properties. The infrared spectrum showed a hydroxyl absorption at 3365 cm$^{-1}$ and an olefinic absorption at 1645 cm$^{-1}$. In the p.m.r. spectrum the vinyl protons were evident as a singlet at $\tau$ 4.25. The C$_3$ methylene protons appeared as a singlet at $\tau$ 7.38 while the triplet at $\tau$ 6.33 ($J = 7$ Hz) was assigned to the methylene protons adjacent to the hydroxyl group. The exchangeable hydroxyl proton appeared as a singlet at $\tau$ 7.05, and the geminal methyl group as singlets at $\tau$ 8.92 and 9.03.
Regioselective hydrogenation of diene 149 was achieved by the use of the homogeneous catalyst tris(triphenylphosphine)chlororodium. After the uptake of one equivalent of hydrogen, the olefinic alcohol 150 was isolated in 95% yield. The spectral properties of this compound were in complete agreement with the assigned structure. There was an absence of olefinic absorptions due to the disubstituted double bond in the infrared spectrum. The hydroxyl absorption appeared at 3370 cm\(^{-1}\). In the p.m.r. spectrum, the complete reduction of the disubstituted double bond was evident due to the lack of resonances in the vinyl proton region. The triplet at \(\tau 6.45\) (\(J = 7\) Hz) was assigned to the methylene protons adjacent to the hydroxyl group while the singlets at \(\tau 8.95\) and \(\tau 9.08\) were attributed to the geminal methyl group. The exchangeable hydroxyl proton appeared as a broad singlet at \(\tau 6.05\) to \(\tau 6.28\).

The hydroxy functionality of 150 was protected as an acetal. Thus treatment of the olefinic alcohol 150 with chloromethyl methyl ether\(^{73,74}\) in the presence of excess potassium \(\text{t-butoxide}\) afforded, in 92% yield, the olefinic acetal. The physical and spectral properties of this product were in agreement with structure 151. Of interest was the absence of hydroxyl absorptions in the infrared spectrum. The p.m.r. spectrum showed the methoxy group as a singlet at \(\tau 6.73\) while the methylene protons adjacent to the methoxy group appeared as a singlet at \(\tau 5.48\). The multiplet at \(\tau 6.20\) to \(\tau 6.66\) was attributed to the \(C_9\) methylene protons. The two singlets at \(\tau 8.95\) and \(\tau 9.07\) are due to the geminal methyl group.

The epoxy acetals 152 and 153 were formed by treatment of the
olefinic acetal 151 with m-chloroperbenzoic acid.\textsuperscript{76,77} This mixture had spectral properties that were almost identical with those of the corresponding olefinic acetal 151, except for the presence of the epoxy absorption at 740 cm\textsuperscript{-1} in the infrared spectrum. Gas-liquid chromatographic analysis of the product revealed an 80:20 mixture of the epimeric epoxy acetals 152 and 153 respectively. This assignment was based on the steric approach control principle. The epoxidizing reagent was assumed to have attacked from the less hindered side of the double bond, anti to the two carbon chain, thus forming the major isomer 152.

\[ \text{R-CH}_2\text{OCH}_3 \]
With the achievement of our second objective, we now wished to introduce an oxygen substituent at the C₄ position. We therefore reacted the epoxy acetals 152 and 153 with lithium diethylamide⁷⁷-⁷⁹ in tetrahydrofuran to produce a mixture of allylic alcohols 156 (two diastereomers) and 157 (two diastereomers). The above tentative assignment was supported by a hydroxyl absorption at 3480 cm⁻¹ in the infrared spectrum and a broad singlet, assigned to the vinyl proton, at ℏ 4.62 in the p.m.r. spectrum. Although the four products, evidenced by gas-liquid chromatographic analysis, showed that this sequence would probably be synthetically unproductive, we nevertheless decided to continue with the sequence.

Upon treatment of this mixture with aqueous hydrochloric acid,⁸⁰ a diastereomeric mixture of the rearranged allylic alcohols 158 (two diastereomers) and 159 (two diastereomers) were formed. This tentative assignment was based on the disappearance of the vinyl proton resonance in the p.m.r. spectrum and the presence of a multiplet at ℏ 5.84-6.17 which was assigned to the proton adjacent to the hydroxyl group. When the alcohols 158 and 159 were oxidized with Collins reagent,⁸¹,⁸² a mixture of ketones 160 and 161 were formed. This tentative assignment was sustained by the presence of an α,β-unsaturated ketone absorption at 1665 and 1630 cm⁻¹ in the infrared spectrum. The presence of two major products were evident by gas-liquid chromatographic analysis.

Although this sequence produced the desired ketone 160, it was not synthetically useful due to the poor overall yield and the expectation that the desired ketone 160 was the minor component. The
above expectation was due to the fact, established by Rickborn,\textsuperscript{77} that the base induced rearrangement of epoxides occurs with the abstraction of a proton that is $\alpha$ and \textit{syn} to the epoxide. Abstraction of a proton at C\textsubscript{7} by the base would be sterically hindered by the two carbon side chain but, since this steric interaction is more pronounced in the minor epoxide, that is epoxy acetal \textit{153}, the attack by the base at the C\textsubscript{4} position is highly favored for only this compound. Therefore, the desired ketone \textit{160} should be the minor isomer. Thus, we attempted to synthesize the keto tosylate \textit{90} by another synthetic sequence.

2. Second Attempted Synthesis of Keto Tosylate \textit{90}

The difficulties encountered in the reduction of the methoxy alcohol \textit{139} and in the introduction of an oxygen-containing functional group at the C\textsubscript{4} position of the epoxy acetals \textit{152} and \textit{153} led us to investigate a synthetic sequence in which the introduction of the oxygen containing substituent at C\textsubscript{4} and the formation of the desired bicyclic system was realized in the same reaction. This could be achieved through the base-catalyzed Aldol cyclization of the diketone \textit{162}. Upon examination of the possible cyclized intermediates of the diketone \textit{162}, there are initially four possible cyclization products. Two of these products have a four membered ring incorporated in their skeleton and the third product cannot be dehydrated to give an $\alpha,\beta$-unsaturated ketone. Since only the ketol \textit{163} can be dehydrated to the $\alpha,\beta$-unsaturated ketone \textit{164}, the thermodynamically favored product, ketone \textit{164}, would be realized if the cyclization were carried out under the proper conditions.
We chose, as our first objective, the ketone 170, which would be an intermediate to the diketone 162. The starting material chosen was isobutyronitrile 165 which was alkylated with allyl bromide in the presence of lithium diisopropylamide to give a 83% yield of 2,2-dimethyl-4-pentenenitrile 166 (see Chart 11). The physical and spectral properties of the olefinic nitrile were in agreement with structure 166, and with the data reported in the literature \textsuperscript{83,84} for this compound. Thus the infrared spectrum showed the presence of the terminal olefinic functionality as bands at 3090, 1640, and 920 cm\textsuperscript{-1} and a nitrile absorption at 2245 cm\textsuperscript{-1}. In the p.m.r. spectrum of 166, the vinyl group exhibited a multiplet at \( \tau \) 3.75-4.45 for the \( C_4 \) proton and a multiplet at \( \tau \) 4.63-5.06 for the \( C_5 \) protons. The doublet (\( J = 7 \) Hz) at \( \tau \) 7.72 was assigned to the allylic \( C_3 \) protons.
while the singlet at $\tau$ 8.67 was assigned to the tertiary methyl groups.

Cleavage of the double bond of compound 166 was effected by ozonolysis in 1% pyridine-dichloromethane solution at -78°, followed by decomposition of the resulting ozonide with zinc and acetic acid. The resulting crude aldehyde nitrile 167 was somewhat unstable and prone to autoxidation and was therefore used in the next reaction without further purification. However, the spectral data obtained from the crude product supported the assigned structure 167. The infrared spectrum showed the presence of the aldehydic carbonyl functionality with absorptions at 2750 and 1720 cm$^{-1}$ while the absorption band at 2250 cm$^{-1}$ indicated the presence of the nitrile group. A multiplet at $\tau$ 0.10 in the p.m.r. spectrum confirmed the presence of the aldehyde functionality. The tertiary methyl groups appeared as a sharp singlet at $\tau$ 8.50 while the methylene protons were evident as a multiplet at $\tau$ 7.26.

The crude aldehyde nitrile was then reacted with the Wittig reagent cyclopentylidenetriphenylphosphorane in dimethoxyethane to give, in 87% yield, the olefinic nitrile 168.* This compound showed

* We attempted to synthesize compound 168 by an alternate route. Unfortunately, even at low temperatures, the Wittig reagent acted as a base causing the formation of the Aldol condensation product 1-cyclopentylidenecyclopentanone.
the expected spectral properties. The nitrile group was evidenced by the absorption at 2255 cm\(^{-1}\) in the infrared spectrum while the olefinic absorption appeared at 1680 cm\(^{-1}\). The p.m.r. spectrum showed a sharp singlet at \(\tau\) 8.65 for the tertiary methyl groups while the vinyl proton appeared as a multiplet at \(\tau\) 4.37-4.90.

When the olefinic nitrile was treated with polyphosphoric acid,\(^{88,89}\) it underwent cyclization and formed the bicyclic imine \(^{169}\). The crude imine was immediately hydrolyzed using a methanolic sodium hydroxide solution to afford a 70% (overall) yield of the desired product. The physical and spectral properties of this compound were in complete accord with structure \(^{170}\). The ultraviolet spectrum exhibited an absorption at 248 m\(\mu\) (\(\varepsilon = 14,500\)) which is typical of a fully substituted \(\alpha,\beta\)-unsaturated ketone. This was supported by the infrared spectrum with absorptions at 1660 and 1640 cm\(^{-1}\). In the p.m.r. spectrum, the tertiary methyl groups appeared as a singlet at \(\tau\) 8.90.

Having accomplished our first objective, we next wished to introduce a two carbon chain at the carbonyl carbon. The solution to this problem seemed to be the use of the modified Wittig reagent triethyl phosphonoacetate. Unfortunately, all attempts at the reaction of the ketone \(^{170}\) with this reagent or the less sterically demanding reagent diethyl cyanomethylphosphonate failed due to the enolization

\* In our hands, it was found that the use of 10% phosphorous pentoxide-methanesulfonic acid\(^{90}\) was superior to that of polyphosphoric acid due to the difficulty in stirring a solution of the latter. The yields of ketone \(^{170}\) was approximately the same in both cases.
of the ketone. Various other attempts at the introduction of only one carbon atom at the carbonyl carbon also failed. We, therefore, decided to prevent the enolization of the ketone 170 by "blocking" the double bond. The blocking group chosen had to prohibit enolization and had to be susceptible to removal to reform the double bond. The epoxide moiety seemed to meet both requirements. Thus treatment of the ketone 170 with a mixture of hydrogen peroxide and sodium hydroxide gave, in 76% yield, the epoxy ketone 171. An analytical sample of this material was obtained by preparative g.l.c. and exhibited spectral data in agreement with the assigned structure. Most notable in the infrared spectrum was the carbonyl absorption at 1700 cm\(^{-1}\). In the p.m.r. spectrum, the tertiary methyl groups now appeared as two singlets at \(\tau 9.07\) and \(\tau 5.92\). One of the methyl groups was apparently shielded by the oxygen atom of the epoxide ring thus causing it to resonate at a higher field.

With the establishment of the blocking group, we again attempted to introduce the two carbon chain via the Wittig reaction. Although the reaction of the epoxy ketone with triethyl phosphonoacetate was unsuccessful, we were able to react the former with diethyl cyano- methylphosphonate at an elevated temperature (see page 27). However, when we tried to hydrogenate the double bond of the epoxy nitrile 172 (see Chart 11) with a variety of catalysts, hydrogenolysis of the allylic C-O bond occurred concurrently with the reduction of the double bond. We therefore decided to insert the two carbon chain via two one-carbon homologations.

The first carbon atom was introduced by means of the Wittig
reaction. Thus, reaction of the epoxy ketone 171 with methylenetriphenylphosphorane resulted in an 88% yield of the epoxy olefin 173. The spectral properties of this product were consistent with the assigned structure. Of interest was the complete disappearance of the carbonyl absorption and the presence of olefinic absorptions at 3120, 1635, and 890 cm$^{-1}$ in the infrared spectrum. The vinyl protons in the p.m.r. spectrum were evident as a singlet at $\tau$ 4.73. The signals at $\tau$ 9.05 and 8.87 were assigned to the tertiary methyl groups.

In accord with our plans to convert this compound into the next higher homologue, it was necessary at this stage of the synthesis to functionalize the terminal double bond into a primary alcohol functionality. This was achieved by subjecting the epoxy olefin 173 to hydroboration with diborane in tetrahydrofuran followed by decomposition of the intermediate alkylborane with alkaline hydrogen peroxide. The resultant ratio of the products (epoxy alcohols 174 and 175) varied somewhat from reaction to reaction but the mixture of products, as judged by gas-liquid chromatographic analysis, never contained less than 75% of the major isomer,* epoxy alcohol 175. An analytical sample of this major isomer, collected by preparative g.l.c., exhibited spectral properties in accord with structure 175. Thus, the infrared spectrum showed a hydroxyl absorption at 3460 cm$^{-1}$. In the p.m.r. spectrum, the tertiary methyl groups were evident as sharp singlets at $\tau$ 9.30 and 9.00.

* The assignment of the stereochemistry of the two epimeric epoxy alcohols 174 and 175 is tentative and was based on examination of molecular models and the application of the steric approach control principle.
The protons adjacent to the hydroxyl group appeared as a multiplet at \( \tau \) 5.84 to \( \tau \) 6.57.

The alcohol functionality was protected as an ester by treatment of the epoxy alcohols 174 and 175 with acetic anhydride in dry pyridine to give, in 92\% yield, a mixture of epoxy acetates 176 and 177. The ratio of the epimeric acetates was dependent on the ratio of the mixture of epoxy alcohols 174 and 175 used. An analytical sample of the major isomer 177, obtained by preparative g.l.c., exhibited spectral properties in accord with the assigned structure. The presence of the acetate group was apparent with absorptions at 1740 and 1230 cm\(^{-1}\) in the infrared spectrum. In the p.m.r. spectrum, the multiplet at \( \tau \) 5.47-6.40 was assigned to the protons adjacent to the acetate functionality. The tertiary methyl groups appeared as singlets at \( \tau \) 9.27 and \( \tau \) 8.97 while the acetoxy group appeared as a singlet at \( \tau \) 7.97.

At this time, we felt that it would be appropriate to reintroduce the double bond by the reduction of the epoxide functionality. Although there were many examples of the reduction of epoxides to olefins in the literature, there was, apparently, no example of the reduction of a tetrasubstituted epoxide. The attempted reduction of the epoxy acetate 176 and 177 with chromium(II) ethylenediamine complex in dimethylformamide\(^{94}\) yielded only starting material. The reduction of the epoxide with zinc-copper\(^{95}\) or zinc-silver\(^{96}\) couple at elevated temperatures also failed to produce any reduction product. We were finally able to effect the reduction by the treatment of the epoxy acetates 176 and 177 with tungsten hexachloride and n-butyl-
lithium in refluxing tetrahydrofuran. The desired olefinic acetate was thus obtained in 90% yield. The physical and spectral properties were in agreement with the assigned structure. Thus, the infrared spectrum showed carbonyl absorptions at 1740 and 1230 cm\(^{-1}\). Of particular interest was the p.m.r. spectrum in which, due to the removal of the shielding effect of the oxygen atom of the epoxide ring, the tertiary methyl groups appeared as singlets at \(\tau\) 9.07 and 9.03. The acetoxy group was evident as a singlet at \(\tau\) 8.04 while the multiplet at \(\tau\) 5.66-6.31 was assigned to the protons adjacent to acetate functionality.

In order to add another carbon atom to the side chain, the acetate protecting group was removed by the reaction of the olefinic acetate with lithium aluminium hydride. The product, obtained in 97% yield, exhibited spectral properties in agreement with structure. Thus, the infrared spectrum showed a hydroxyl absorption at 3410 cm\(^{-1}\). In the p.m.r. spectrum, the singlets at \(\tau\) 9.14 and \(\tau\) 9.08 were assigned to the tertiary methyl groups while the doublet (\(J = 4\) Hz) at \(\tau\) 6.40 was attributed to the methylene protons adjacent to the hydroxyl group.

At this point in the synthesis, we wished to homologate the olefinic alcohol according to the scheme shown in Chart 12. The proposed synthesis of the keto tosylate involved reaction of the olefinic tosylate, corresponding to the olefinic alcohol, with sodium cyanide in dimethyl sulfoxide to give the olefinic nitrile. Base hydrolysis of the latter would afford the olefinic acid. Subjection of to ozonolysis and base-catalyzed cyclization
would produce the keto acid 184. Selective reduction of the acid functionality with diborane followed by tosylation of the resultant alcohol would then give the desired product, keto tosylate 90. Unfortunately due to the lack of time and starting material, the olefin alcohol 179, the synthesis of the keto tosylate 90, as proposed on Chart 12, was not carried out.

Thus, in conclusion, an attractive and quite feasible approach to the synthesis of neoclovene has been developed which included the application of some recent synthetic methods. The second and most successful approach described offers the possibility that further development of the synthetic sequence could lead to the syntheses of neoclovene in the near future.
CHART 12
EXPERIMENTAL

General

Melting points, which were determined on a Kofler block, and boiling points are uncorrected. Ultraviolet spectra were measured in methanol solution on either a Cary, model 14, or a Unicam, model SP 800, spectrophotometer. Refractive indices were taken on an Officine Galileo Refractometer. Routine infrared spectra were recorded on a Perkin-Elmer model 710 spectrophotometer while comparison spectra were recorded on a Perkin-Elmer model 457 spectrophotometer. The p.m.r. spectra were taken in deuterochloroform or carbon tetrachloride solution on Varian Associates spectrometers models T-60 and/or HA-100, XL-100. Line positions are given in the Tiers $T$ scale, with tetramethylsilane as internal standard; the multiplicity, integrated peak areas, and proton assignments are indicated in parentheses. Gas-liquid chromatography (g.l.c.) was carried out on either an Aerograph Autoprep model 700 or a Varian Aerograph, model 90-P. The following columns were employed:
The specific column used along with column temperature and carrier gas (helium) flow-rate (in ml/min), are indicated in parentheses. Column chromatography was performed using florisil (Fisher Scientific Co.), neutral silica gel (Camag or Macheray, Nagel and Co.) or neutral alumina (Camag or Macheray, Nagel and Co.). The alumina was deactivated as required by addition of the correct amount of water. High resolution mass spectra were recorded on an AEI type MS-9 mass spectrometer. Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia, Vancouver.

Preparation of 2,2-Dimethylindan-1-one 143

To an ice-cooled, stirred suspension of powdered potassium t-butoxide (156.8 g, 1.4 moles) in 1 l of dry dimethoxyethane, kept under an atmosphere of dry nitrogen, was added a solution of 79.2 g (0.60 mole) of 1-indanone 142 in 200 ml of dry dimethoxyethane. The resulting mixture was stirred for 10 min, and then a solution of 426 g (3 moles) of methyl iodide in 300 ml of dry dimethoxyethane was added. The mixture was warmed to room temperature and allowed to stir for 3 h. The resulting mixture was diluted with water and thoroughly extracted

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<td>20% SE 30</td>
<td>Chromosorb W</td>
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<td>B</td>
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with ether. The ethereal extracts were combined, washed with brine, and dried over anhydrous magnesium sulfate. Removal of the solvent gave an oil which, upon distillation under reduced pressure, afforded 78.2 g (86%) of the desired alkylated product \textit{143}, b.p. 47-49° at 0.2 mm [lit. \textit{98} b.p. 87-89° at 0.6 mm; \nD \textit{22} 1.5383]; m.p. 37-38°; \nD \textit{20} 1.5442; ultraviolet, \lambda_{\text{max}} 246 \text{m}\mu (\varepsilon = 12,800); infrared (film), \nu_{\text{max}} 1706, 1610 \text{cm}^{-1}; p.m.r., \tau 8.80 (singlet, 6H, tertiary methyls), 7.05 (singlets, 2H, methylene protons), 2.17-2.85 (multiplet, 4H, aromatic protons).


\textbf{Preparation of Nitriles \textit{144} and \textit{145}}

A stirred suspension of sodium hydride (16.8 g, 0.35 mole) in 400 ml of dry dimethyl sulfoxide was slowly heated, under an atmosphere of dry nitrogen, to 75° and kept at this temperature until frothing had ceased (approximately 30 min). The solution was cooled to room temperature and a solution of diethyl cyanomethylphosphonate (67.5 g, 0.38 mole) in 100 ml of dry dimethyl sulfoxide was added. The resulting solution was stirred for 15 min, and then a solution of the ketone \textit{143} (11.2 g, 70 mmole) in 50 ml of dimethyl sulfoxide was added. The reaction mixture was heated (bath temperature 105°) for 20 h, then cooled, diluted with water and thoroughly extracted with ether. The combined extracts were washed with water, saturated brine, and then dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residual oil under reduced
pressure afforded 11.75 g (93%) of a 65:35 mixture of \( Z \) and \( E \) isomers respectively as judged by p.m.r. and gas-liquid chromatographic analysis (column E, 125°, 100). This mixture exhibited b.p. 96-98° at 0.25 mm; infrared (film) \( \nu_{\text{max}} \) 2238, 1615, 1600 cm\(^{-1}\). A sample was subjected to column chromatography using Camag Kieselgel for TLC (without binder) and 98:2 petroleum ether (b.p. 68°)-ether as eluting solvent. A positive pressure (air) was required to maintain a reasonable flow rate. The ratio of compound to silica gel was 1:100. The major \( Z \) isomer was thus obtained in 96% purity. It exhibited p.m.r., \( \tau \) 8.73 (singlet, 6H, tertiary methyls), 7.13 (singlet, 2H, methylene protons), 4.87 (singlet, 1H, vinyl proton), 2.49-2.91 (multiplet, 3H, aromatic protons), 1.53-1.83 (multiplet, 1H, C\(_7\) proton). From the above, the p.m.r. spectrum of the minor \( E \) isomer could be deduced. It showed p.m.r., \( \tau \) 8.54 (singlet, 6H, tertiary methyls), 7.08 (singlet, 2H, methylene protons), 4.36 (singlet, 1H, vinyl proton), 2.43-2.90 (multiplet, 4H, aromatic protons).

Anal. Calcd. for C\(_{13}\)H\(_{17}\)N: C, 85.21; H, 7.15; N, 7.64. Found: C, 84.90; H, 7.08; N, 7.51.

Preparation of Acids 146 and 147

A mixture of nitriles 144 and 145 (24 g, 135 mmoles) was dissolved in 540 ml of 5:1 ethylene glycol-water containing 100 g (2.5 mole) of sodium hydroxide. The resulting solution was refluxed (bath temperature 140°) under an atmosphere of nitrogen for 20 h and then cooled to room temperature. This mixture was diluted with 600 ml of saturated brine and extracted with ether. The aqueous residue was acidified to pH 2
with 6 N hydrochloric acid and the resulting mixture was thoroughly extracted with 600 ml of 1:1 petroleum ether (b.p. 68°)-ether. The combined extracts were washed twice with brine and then dried over anhydrous magnesium sulfate. Removal of the solvent gave 19 g (95%) of white crystals. An analytical sample, obtained by recrystallization from hexane, exhibited m.p. 114-115°; infrared (CHCl₃), ν_max 3600-2400, 1960, 1625 cm⁻¹; ultraviolet, λ_max 276 μ (ε = 12,150), 286 (ε = 11,660), 302 (ε = 10,400). The p.m.r. spectrum showed a 81:19 ratio of Z to E isomers. The major Z isomer exhibited p.m.r., τ 8.72 (singlet, 6H, tertiary methyls), 7.12 (singlet, 2H, methylene protons), 4.15 (singlet, 1H, vinyl proton), 2.35-2.85 (multiplet, 3H, aromatic protons), 1.14-1.42 (multiplet, 1H, C₇ proton). The E isomer had p.m.r., τ 8.45 (singlet, 6H, tertiary methyls), 7.01 (singlet, 2H, methylene protons), 3.62 (singlet, 1H, vinyl proton), 2.46-2.96 (multiplet, 4H, aromatic protons).


Hydrogenation of Acids 146 and 147

The acids 146 and 147 (16 g, 0.89 mole) in 350 ml of ethyl acetate were hydrogenated over 2.0 g of 10% palladium on charcoal at room temperature until the uptake of hydrogen was complete (approximately 10 h). The reaction mixture was filtered through celite and the filtrate was evaporated to dryness to give a yellow oil which was distilled under reduced pressure (b.p. 140-142° at 0.05 mm). The resulting pale yellow oil (17.0 g, 94%) crystallized upon standing.
An analytical sample, obtained by recrystallization from hexane, exhibited m.p. 74.5-75.5°; infrared (film) $\nu_{\text{max}}$ 3500-2400, 1705 cm$^{-1}$; ultraviolet $\lambda_{\text{max}}$ 260 m$\mu$ ($\varepsilon = 615$), 267 m$\mu$ ($\varepsilon = 992$), 273 m$\mu$ ($\varepsilon = 1145$); p.m.r., $\tau$ 9.08 (singlet, 3H, tertiary methyl), 8.82 (singlet, 3H, tertiary methyl), 7.32 (singlet, 2H, C$_3$ protons), 7.16-7.68 (multiplet, 2H, -CH$_2$CO$_2$H), 6.73 (doublet of doublets, 1H, methine proton, J = 6.0 Hz), 2.88 (singlet, 4H, aromatic protons), -1.08 (broad singlet, 1H, -COOH).

Anal. Calcd. for C$_{13}$H$_{16}$O$_2$: C, 76.44; H, 7.90. Found: C, 76.70; H, 8.10.

Preparation of Aromatic Alcohol 141

To a stirred solution of acid 145 (16.2 g, 79 mmoles) in 30 ml of dry tetrahydrofuran, cooled to 0°, was added 75 ml (100 mmoles) of borane in tetrahydrofuran. The ice bath was removed and the resulting solution was stirred under nitrogen for 1 h. The excess hydride was destroyed by careful addition of 50 ml of 1:1 tetrahydrofuran-water and the aqueous phase was saturated with 15 g of anhydrous potassium carbonate. The layers were separated and the aqueous phase was extracted four times with 50 ml portions of ether. The combined organic extracts were dried over anhydrous magnesium sulfate. The concentrated yellow oil was distilled under reduced pressure to afford 14.0 g (93%) of the desired alcohol b.p. 106-108° at 0.55 mm; $n_D^{20}$ 1.5318; ultraviolet $\lambda_{\text{max}}$ 261 m$\mu$ ($\varepsilon = 668$), 267 m$\mu$ ($\varepsilon = 1055$), 274 m$\mu$ ($\varepsilon = 1270$); infrared (film) $\nu_{\text{max}}$ 3360, 3110, 3060, 1040, 1010 cm$^{-1}$; p.m.r., $\tau$ 9.05 (singlet, 3H, tertiary methyl), 8.89 (singlet, 3H,
tertiary methyl), 7.38 (singlet, 2H, C₂ methylene protons), 6.50-6.93 (broad singlet, 1H, exchangeable, -OH), 6.27 (triplet, 2H, -CH₂OH, J = 6.0 Hz), 2.98 (singlet, 4H, aromatic protons).


Preparation of Diene Alcohol 149

To a stirred solution of lithium (2.15 g, 310 mmoles) in 350 ml of liquid ammonia (distilled from sodium metal) cooled to -78° was added a solution of 11.8 g (62 mmoles) aromatic alcohol in 20 ml of dry dimethoxyethane and 8 ml of 95% ethanol. This solution was stirred at -78° for 45 min and then at -33° for 30 min. The blue color was discharged by the addition of 10 ml of 95% ethanol. The ammonia was allowed to evaporate and 360 ml of water was added. This mixture was thrice extracted with ether. The combined organic extracts were washed with saturated brine and dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residue, gave 10.5 g (90%) of the diene alcohol 149 as a colorless oil, b.p. 92-94° at 0.2 mm. An analytical sample, obtained by preparative g.l.c. (column A, 160°, 100) exhibited infrared (film) νmax 3365, 3055, 1645, 1045, 1015 cm⁻¹; p.m.r., τ 9.03 (singlet, 3H, tertiary methyl), 8.92 (singlet, 3H, tertiary methyl), 7.38 (singlet, 2H, C₃ methylene protons), 7.05 (singlet, 1H, exchangeable, -OH), 6.33 (triplet, 2H, -CH₂OH, J = 7.0 Hz), 4.25 (singlet, 2H, vinyl protons).

Hydrogenation of Diene Alcohol 149

The hydrogenation of diene alcohol 149 (10.0 g, 52 mmoles) was carried out in benzene (200 ml) at room temperature and atmospheric pressure using tris(triphenylphosphine)chlororhodium (2.0 g) as catalyst. One equivalent of hydrogen was consumed after 11 h. The reaction mixture was filtered through a column of Camag Kieselgel activity III neutral alumina (360 g) and eluted with 1 L of ether. Removal of the solvent and distillation under reduced pressure afforded 9.5 g (95%) of the olefinic alcohol as a colorless oil, b.p. 94-96° at 0.5 mm. An analytical sample obtained by preparative g.l.c. (column B, 200°, 100) exhibited infrared (film) \( \nu_{\text{max}} \) 3370, 1040, 1005 cm\(^{-1}\); p.m.r., 9.08 (singlet, 3H, tertiary methyl), 8.95 (singlet, 3H, tertiary methyl), 6.45 (triplet, 2H, \(-\text{CH}_2\text{OH}, J = 7.0\) Hz), 6.05-6.28 (broad singlet, 1H, exchangeable, \(-\text{OH}\)).


Preparation of Olefinic Acetal 151

To an ice bath cooled stirred slurry of 8.27 g (72 mmoles) of powdered potassium t-butoxide in 200 ml of anhydrous ether was added a solution of 7.4 g (38 mmoles) of olefinic alcohol 150 in 50 ml of anhydrous ether. After stirring in the cold for 15 min, a solution of 6.45 g (80 mmoles) of chloromethyl methyl ether in 30 ml of anhydrous ether was added. The ice water bath was removed and the reaction mixture was stirred under nitrogen for a further 15 min. Water was then added and this mixture was thoroughly extracted with ether. The
combined ethereal extracts were washed with saturated brine and dried over anhydrous magnesium sulfate. The ether was removed in vacuo and the residue distilled to yield 8.3 g (92%) of the olefinic acetal 151 as a colorless oil, b.p. 92-94° at 0.4 mm. An analytical sample, obtained by preparative g.l.c. (column D, 130°, 100) exhibited $n_D^{20}$ 1.4820; infrared (film) $\nu_{\text{max}}$ 3060, 1140, 1100, 1025 cm$^{-1}$; p.m.r., $\tau$ 9.07 (singlet, 3H, tertiary methyl), 8.95 (singlet, 3H, tertiary methyl), 6.73 (singlet, 3H, -CH$_2$OCH$_3$), 6.29-6.66 (multiplet, 2H, -CH$_2$OCH$_2$OCH$_3$), 5.48 (singlet, 2H, -OCH$_2$OCH$_3$).

Anal. Calcd. for C$_{15}$H$_{26}$O$_2$: C, 75.58; H, 10.99. Found: C, 75.62; H, 10.91.

Preparation of Epoxy Acetals 152 and 153

To a cooled (0°) stirred solution of 500 mg (2.10 mmoles) olefinic acetal 151 in 5 ml of methylene chloride was added a solution of 905 mg (5.25 mmoles) m-chloroperbenzoic acid in 10 ml of methylene chloride. This mixture was stirred under dry nitrogen at 0° for 0.5 h and then at room temperature for 2.5 h. The solution was poured onto 10 ml of 20% sodium hydroxide solution and the layers were separated. The organic extract was washed with a 10% sodium sulfite solution, saturated brine and dried over anhydrous magnesium sulfate. Distillation of the concentrated oil afforded a quantitative yield of the desired compounds as a colorless oil b.p. (hot box) 130-135° at 0.4 mm. Gas-liquid chromatographic analysis (column E, 125°, 100) showed the product to be an 80:20 mixture of epimeric epoxy acetics 152 and 153 respectively. An analytical sample of this mixture, obtained by
preparative g.l.c. (column G, 160°, 200), exhibited infrared (film)

\[ \nu_{\text{max}} \] 2990, 1140, 1100, 1030, 740 cm\(^{-1}\); p.m.r., \( \tau \) 9.02, 9.07 (singlet, singlet, 6H, tertiary methyls), 6.70 (singlet, 3H, -CH\(_2\)OCH\(_3\)), 6.17-6.59 (multiplet, 2H, -CH\(_2\)OCH\(_2\)OCH\(_3\)), 5.47 (singlets, 2H, -OCH\(_2\)OCH\(_3\)).


Preparation of 2,2-Dimethyl-4-pentenenitrile 166

To an ice water bath cooled, stirred solution of diisopropylamine (45.5 g, 0.45 moles) in 75 ml of dry benzene was added 150 ml (0.375 moles) \( \text{n-} \)butyllithium in hexane. After stirring in an inert atmosphere for 5 min, a solution of 20.7 g (0.30 moles) of isobutyronitrile 165 in 45 ml of dry benzene was added dropwise. The cooling bath was removed and this mixture was stirred at room temperature for 5 min. The reaction was again cooled to 0° and a solution of allyl bromide (72.6 g, 0.6 mole) in 75 ml dry benzene was added. The resulting mixture was refluxed for 1.5 h and then cooled to room temperature.

Water was added and the layers were separated. The aqueous layer was thoroughly extracted with ether. The organic extracts were combined, washed with water, saturated brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue distilled to give 27.0 g (83%) of the desired product b.p. 147-148°; \( n_D^{21.3} \) 1.4191 [lit. \( n_D^{20} \) 1.4180]; infrared (film) \[ \nu_{\text{max}} \] 3090, 2245, 1640, 920 cm\(^{-1}\); p.m.r., \( \tau \) 8.67 (singlet, 6H, tertiary methyls), 7.72 (doublet, 2H, methylene protons, \( J = 7 \) Hz), 4.63-5.06 (multiplet, 2H, \( C_5 \) protons), 3.75-4.45 (multiplet, 1H, \( C_4 \) proton).
Preparation of 3-Cyano-3,3-dimethyl propanal 167

A solution of 5 g (46 mmoles) of olefinic nitrile 166 in 80 ml of a 1% pyridine-dichloromethane solution was treated with ozone at -78° until the solution turned blue. The excess ozone was removed by bubbling dry nitrogen through the solution. This mixture was poured onto 24 g (370 mmoles) of zinc dust. Acetic acid (46 ml, 810 mmoles) was immediately added and the resulting slurry was slowly warmed to room temperature. After the solution had been stirred for 1 h, it was filtered, diluted with brine and extracted with methylene chloride. The organic phase was washed with water, saturated sodium bicarbonate solution, saturated brine, and dried over anhydrous magnesium sulfate. The solvent was removed to afford 3.5 g (70%) of the crude aldehyde nitrile 167. Due to the instability of this compound, it was used immediately in the next reaction without further purification. A small sample of the aldehyde nitrile 167 was distilled and exhibited b.p. 90-91° at 19 mm; infrared (film) νmax 2750, 2250, 1720 cm⁻¹; p.m.r., τ 8.50 (singlet, 6H, tertiary methyls), 7.26 (multiplet, 2H, methylene protons), 0.10 (multiplet, 1H, -CHO).

This compound was characterized as its 2,4-dinitrophenylhydrazone derivative, recrystallized from ethanol, m.p. 153-154°.

Anal. Calcd. for C₁₂H₁₅N₅O₄: C, 49.48; H, 4.50; N, 24.04.
Found: C, 49.66; H, 4.47; N, 23.85.
Preparation of Cyclopentyltriphenylphosphonium Iodide

To a solution of 13.6 g (70 mmoles) of cyclopentyl iodide in 50 ml of xylene was added 39.3 g (150 mmole) of triphenylphosphine. This mixture was refluxed for 17 h and then cooled to room temperature. The precipitated salt was filtered, washed with benzene, and dried under vacuum overnight to afford 28.6 g (90%) of the desired compound as a pale yellow crystal. It exhibited m.p. 238-240°; infrared (CHCl₃) \( \nu_{\text{max}} \) 1590, 1440, 1110 cm\(^{-1}\).

Anal. Calcd. for \( \text{C}_{23}\text{H}_{24}\text{IP} \): C, 60.28; H, 5.28; I, 27.68. Found: C, 60.46; H, 5.55; I, 27.32.

Preparation of Olefinic Nitrile 168

To a cooled (0°), stirred slurry of 45.8 g (100 mmoles) of cyclopentyltriphenylphosphonium iodide in 250 ml of dry dimethoxyethane was added 48.2 ml (92 mmoles) of a 1.9 M solution of \( \text{n-butyllithium} \) in hexane. The resulting blood red solution was stirred, under dry nitrogen, at room temperature for 15 min. A solution of 3.0 g (27 mmole) of crude aldehyde nitrile 167 in 20 ml of dimethoxyethane was added. After stirring for 30 min, the mixture was poured into 300 ml of water and thoroughly extracted with petroleum ether (b.p. 30-60°). The organic extracts were combined, washed with saturated brine, and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation of the residue gave 3.8 g (87%) of the desired compound. An analytical sample, obtained by preparative g.l.c. (column H, 135°, 100) exhibited b.p. 52-54° at 0.35 mm; \( n_D^{21.3} \) 1.4699; infrared (film) \( \nu_{\text{max}} \) 2255, 1680 cm\(^{-1}\); p.m.r., \( \tau \) 8.65 (singlet,
6H, tertiary methyls), 4.37-4.90 (multiplet, 1H, vinyl proton).

Anal. Calcd. for C_{11}H_{17}N: C, 80.93; H, 10.50. Found: C, 80.95; H, 10.72.

**Preparation of Ketone 170**

A stirred solution of 5.0 g (30.5 mmoles) of the olefinic nitrile and 75 g of polyphosphoric acid was heated, in an inert atmosphere, at 125-130° for 30 min. This mixture was poured onto ice, basified with a 20% sodium hydroxide solution, and extracted with chloroform. The organic extract was washed with saturated brine and concentrated to yield the crude imine 169 which exhibited infrared (film) $\nu_{\text{max}}$ 1650, 1600 cm$^{-1}$. The imine 169 was immediately added to a solution of 184 ml of 20% sodium hydroxide solution and 180 ml of methanol and refluxed, under a nitrogen atmosphere, for 2.5 h. The reaction mixture was cooled and the methanol was removed at aspirator pressure. The residue was diluted with water and acidified with 6 N hydrochloric acid. This mixture was thoroughly extracted with ether, the ether layer was washed with saturated brine and dried over anhydrous magnesium sulfate. Removal of the solvent, filtration through a column of Camag Kieselgel activity III neutral alumina (15 g), and elution with ether gave a yellow oil. Distillation of this material under aspirator pressure gave 3.5 g (70%) of the ketone 170, b.p. 108-109° at 10 mm. An analytical sample was obtained by preparative g.l.c. (column A, 155°, 120), and it exhibited $n_D^{19.5}1.5079$; ultraviolet $\lambda_{\text{max}}$ 248 m$\mu$ ($\varepsilon = 14,300$); infrared (film) $\nu_{\text{max}}$ 1660, 1640, 1390 cm$^{-1}$; p.m.r., 8.90 (singlet, 6H, tertiary methyls).
Preparation of Epoxy Ketone 171

To a stirred solution of 2.5 g (15.3 mmoles) of ketone 170 and 5 ml (45.8 mmoles) of 30% hydrogen peroxide solution in 50 ml of methanol was added 15.3 ml (76.3 mmoles) of 20% sodium hydroxide solution. The resulting mixture was stirred at room temperature for 2 h. Water was then added and the mixture was thoroughly extracted with ether. The organic layer was washed twice with saturated brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. Distillation of the residue under reduced pressure afforded 2.1 g (76%) of the epoxy ketone 171, b.p. 65-67° at 1.2 mm. An analytical sample obtained by preparative g.l.c. (column G, 130°, 200) exhibited infrared (film) ν max 1700 cm⁻¹; p.m.r., τ 9.07 (singlet, 3H, tertiary methyl), 8.92 (singlet, 3H, tertiary methyl).


Preparation of Epoxy Olefin 173

To a cooled (0°), stirred slurry of 19.1 g (53.5 mmoles) of methyltriphenylphosphonium bromide in 200 ml of anhydrous ether was added 20.8 ml (50 mmoles) of a 2.4 M solution of n-butyllithium in hexane. After the solution was stirred at room temperature, under an atmosphere of dry nitrogen, for 10 min, a solution of epoxy ketone 171 (3.0 g, 16.7 mmoles) in 20 ml of dry ether was added. This mixture
was refluxed for 4 h, cooled, poured into water, and thoroughly extracted with ether. The ethereal extracts were combined, washed with saturated brine, and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation of the residue gave 2.6 g (88%) of the epoxy olefin 173. This sample was shown to be pure by g.l.c. analysis (column E, 115°, 110). It exhibited b.p. 105-108° (hot box) at 10 mm; infrared (film) ν_max 3120, 1635, 890 cm⁻¹; p.m.r., τ 9.05 (singlet, 3H, tertiary methyl), 8.87 (singlet, 3H, tertiary methyl), 4.73 (singlet, 2H, vinyl protons).

Anal. Calcd. for C_{12}H_{18}O: C, 80.85; H, 10.18. Found: C, 80.68; H, 10.33.

Preparation of Epoxy Alcohols 174 and 175

To a solution of 2.3 g (12.9 mmoles) of epoxy olefin 173 in 80 ml of dry tetrahydrofuran at 0° and under an atmosphere of dry nitrogen was added 5.6 ml (7.4 mmoles) of 1.33 M borane in tetrahydrofuran. This solution was then stirred at room temperature for 1.5 h. The reaction mixture was again cooled to ice temperature, and 16 ml of 20% sodium hydroxide solution was added slowly, followed by addition of 26.6 ml of 30% hydrogen peroxide. The reaction mixture was warmed to room temperature and stirred for 1 h, then concentrated. The resulting material was diluted with water then thoroughly extracted with ether. The combined ether extracts were washed with a saturated brine solution, and dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residual material under reduced pressure (b.p. 105-107° at 0.4 mm) afforded
2.6 g (93%) of the desired epoxy alcohols \textit{174} and \textit{175} as a colorless oil. An analytical sample of the major isomer was obtained by preparative g.l.c. (column G, 165°, 200) and exhibited infrared (film), $\nu_{\text{max}}$ 3460, 1035 cm$^{-1}$; p.m.r., $\tau$ 9.30 (singlet, 3H, tertiary methyl), 9.00 (singlet, 3H, tertiary methyl), 5.84-6.57 (multiplet, 2H, \textit{-CH$_2$OH}).

Mol. Wt. Calcd. for C$_{12}$H$_{20}$O$_2$: 196.1463. Found (high resolution mass spectrometry): 196.1459.

**Preparation of Epoxy Acetates 176 and 177**

To a solution of 2.1 g (10.7 mmoles) of epoxy alcohols \textit{174} and \textit{175} in 14 ml dry pyridine was added 5.6 g (56 mmoles) of acetic anhydride. This solution was stirred at room temperature for 8 h and then diluted with water. The ethereal extracts of this mixture were combined, washed with saturated brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue was distilled at 99-101° at 0.5 mm to give 2.3 g (92%) of the desired products. An analytical sample of the major isomer obtained by preparative g.l.c. (column G, 180°, 200) exhibited infrared (film) $\nu_{\text{max}}$ 1740, 1230, 1030 cm$^{-1}$; p.m.r., $\tau$ 9.27 (singlet, 3H, tertiary methyl), 8.97 (singlet, 3H, tertiary methyl), 7.97 (singlet, 3H, \textit{-OCOCH$_3$}), 5.47-6.40 (multiplet, 2H, \textit{-CH$_2$OAc}).

Anal. Calcd. for C$_{14}$H$_{22}$O$_3$: C, 70.56; H, 9.30. Found: C, 70.43; H, 9.50.
Preparation of Olefinic Acetate 178

To a stirred solution of 12.0 g (30 mmoles) of tungsten hexachloride in 40 ml of dry tetrahydrofuran, cooled to -78°, and under an atmosphere of nitrogen was added 25 ml (60 mmoles) of 2.4 M n-butyl-lithium in hexane. The solution was then warmed to room temperature over a 20 min period. A solution of 1.9 g (8 mmoles) of epoxy acetates 176 and 177 in 5 ml of dry tetrahydrofuran was then added. This green solution was refluxed for 7 h, cooled to room temperature, and poured into 350 ml of a solution that was 1.5 M in sodium tartrate and 2 M in sodium hydroxide. This mixture was thoroughly extracted with ether and the ethereal extracts were combined. This organic extract was washed with saturated brine, dried over anhydrous magnesium sulfate, and then concentrated. The residue was distilled to afford 1.6 g (90%) of the olefinic acetate 178, b.p. 87-90° at 0.5 mm. An analytical sample, obtained by preparative g.l.c. (column F, 180°, 200) exhibited infrared (film) ν max 1740, 1230, 1025 cm⁻¹; p.m.r., δ 9.07 and 9.03 (singlets, 6H, tertiary methyls), 8.04 (singlet, 3H, -COCH₃), 5.66-6.31 (multiplet, 2H, -CH₂OAc).


Preparation of the Olefinic Alcohol 179

To a stirred solution of 1.2 g (5.4 mmole) of olefinic acetate 178 in 10 ml of dry ether was added 100 mg (2.6 mmole) lithium aluminum hydride. This mixture was refluxed, under an atmosphere of dry nitrogen, for 1 h then cooled to room temperature. The excess
hydride was destroyed by the addition of powdered sodium sulfate decahydrate and the reaction mixture was filtered through celite. The filtrate was concentrated and distilled at reduced pressure to afford 900 mg (97%) of the olefin alcohol \( \text{179} \), b.p. (hot-box) 82-85° at 0.3 mm. An analytical sample, obtained by preparative g.l.c. (column G, 160°, 200) exhibited infrared (film) \( \nu_{\text{max}} \) 3410, 1025 cm\(^{-1}\); p.m.r., \( \tau \) 9.14 and 9.08 (triplets, 6H, tertiary methyls), 6.40 (doublet, 2H, -CH\(_2\)OH, \( J = 4 \) Hz).

Mol. Wt. calcd. for \( \text{C}_{14}\text{H}_{20}\text{O} \): 180.1514. Found (high resolution mass spectrometry): 180.1511.
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