The retro-ene reaction of 2-vinylcyclohexanols occurs readily in the vapor phase at 400-450° producing unsaturated carbonyl compounds in good yields. The starting materials were prepared in general by the carbenoid addition reaction of ethyl diazoacetate, appropriately substituted cyclohexene, and copper catalyst to produce bicyclic esters which were reduced to the alcohols and rearranged with aqueous acid. Stereochemical examination of several examples suggest the reaction is concerted and the products are kinetically determined. The reaction constitutes a useful stereoselective procedure for the synthesis of tri-substituted olefins.

The synthesis of botryococcene, a geochemically important, abundant hydrocarbon of Botryococcus braunii, focused on an appropriate half-molecule which could be asymmetrically coupled. A retro-ene route was examined, but an alternative, more
conventional route provided better results. This reaction scheme was founded on the convergent coupling of an organometallic reagent from the THP derivative of 6-bromo-3-methyl-2-hexen-1-ol and 4,5-dimethyl-5-hexenal. The aldehyde was prepared from ethyl methyl acetoacetate in seven steps with an overall yield of 24%. The second component, 6-bromo-3-methyl-2-hexen-1-ol was prepared from 2,5-hexanediol in five steps with an overall yield of 22%. The correct conditions to generate the organometallic reagent have not yet been discovered.
The Retro-ene Reaction of 2-Vinylcyclohexanols and Approaches to the Synthesis of Botryococcene

by

Ronald Joseph Rusay

A THESIS submitted to Oregon State University

in partial fulfillment of the requirements for the degree of Doctor of Philosophy

June 1977
APPROVED:

Redacted for privacy
Professor of Chemistry
in charge of major

Redacted for privacy
Chairman of Department of Chemistry

Redacted for privacy
Dean of Graduate School

Date thesis is presented September 17, 1976

Typed by A & S Bookkeeping/Typing for Ronald Joseph Rusay
ACKNOWLEDGEMENTS

Sincere appreciation is offered to Dr. Elliot N. Marvell, a dedicated educator and true friend, for his patience, guidance, and assistance throughout the author's graduate career. Further, gratitude is expressed to the faculty and graduate student body of the Organic Chemistry division who have made this research a pleasant experience through their association, professional interest, and cooperative spirit.

The Petroleum Research Fund generously provided the funds to conduct this research and maintained the author as a pre-doctoral research fellow during the period 1974-1976.
# TABLE OF CONTENTS

**INTRODUCTION**

1

**PART 1. THE RETRO-ENE REACTION OF 2-VINYL CYCLOHEXANOLS**

**HISTORICAL**

3

**RESULTS AND DISCUSSION**

16

**EXPERIMENTAL**

30

- 1-Methylcyclohexene (34b) 30
- 1, 2-Dimethylcyclohexene (34d) 31
- Ethyl diazoacetate 31
- Trimethyl phosphite copper (I) chloride 32
- 7-Carbethoxybicyclo[4.1.0] heptane (35a) 32
- 1-Methyl-7-carbethoxybicyclo[4.1.0] heptane (35b) 32
- Copper Catalyst 33
- 1,6-dimethyl-7-carbethoxybicyclo[4.1.0] heptane (35d) 33
- 7-Hydroxymethylbicyclo[4.1.0] heptane (36a) 34
- 1-Methyl-7-hydroxymethylbicyclo[4.1.0] heptane (36b) 34
- 1,6-Dimethyl-7-hydroxymethylbicyclo[4.1.0] heptane (36d) 35

**Trans-2-vinylcyclohexanol (37a-T)**

35

**Trans-1-methyl-2-vinylcyclohexanol (37b-T)**

36

**Trans-1,2-dimethyl-2-vinylcyclohexanol (37d-T)**

36

2-Vinylcyclohexanone (38) 37

**Cis-1-methyl-2-vinylcyclohexanol (37b-C)** 37

2-Methyl-2-vinylcyclohexanone (39) 38

**Cis-2-vinylcyclohexanol (37a-C)** 39

1-Methyl-2-vinylcyclohexanol (37c) 40

**Thermolytic Reactions**

41

**Thermolysis of trans-2-vinylcyclohexanol (37a-T)**

42

**Thermolysis of trans-1-methyl-2-vinylcyclohexanol (37b-T)**

42
Thermolysis of cis-1-methyl-2-vinylcyclohexanol (37b-C) 43
Thermolysis of cis- and trans-1,2-dimethyl-2-vinylcyclohexanol (37d) 43
Thermolysis of cis- and trans-2-methyl-2-vinylcyclohexanol (37c) 44
(E) and (Z) 6-methyl-6-octenol (42) 44
Thermolysis of cis-2-vinylcyclohexanol (37a-C) 45

**PART II. APPROACHES TO THE SYNTHESIS OF BOTRYOCOCCENE**

**HISTORICAL** 46

**RESULTS AND DISCUSSION** 55

**EXPERIMENTAL** 86

<table>
<thead>
<tr>
<th>Compound</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethyl 3-methyl-6-oxo-2-heptenoate (77)</td>
<td>86</td>
</tr>
<tr>
<td>Ethyl 3-methyl-6-hydroxy-2-heptenoate (78)</td>
<td>87</td>
</tr>
<tr>
<td>Ethyl 3-methyl-6-chloro-2-heptenoate (79)</td>
<td>88</td>
</tr>
<tr>
<td>3-Methyl-6-chloro-2-hepten-1-ol (80)</td>
<td>88</td>
</tr>
<tr>
<td>Tetrahydropyranyl derivative of 3-methyl-6-chloro-2-hepten-1-ol (81)</td>
<td>89</td>
</tr>
<tr>
<td>Ethyl 3-methyl-6-bromo-2-heptenoate (82)</td>
<td>90</td>
</tr>
<tr>
<td>3-Methyl-6-bromo-2-hepten-1-ol (83)</td>
<td>91</td>
</tr>
<tr>
<td>Tetrahydropyranyl derivative of 3-methyl-6-bromo-2-hepten-1-ol (84)</td>
<td>91</td>
</tr>
<tr>
<td>Methoxy-3-methyl-6-bromo-2-hepten-1-ol oxymethane (85)</td>
<td>92</td>
</tr>
<tr>
<td>2-Methyl-2-buten-1-ol (94)</td>
<td>92</td>
</tr>
<tr>
<td>Ethyl 3,4-dimethyl-2-pentenoate (98)</td>
<td>94</td>
</tr>
<tr>
<td>3, 4-Dimethyl-4-penten-1-ol (91)</td>
<td>95</td>
</tr>
<tr>
<td>4, 5-Dimethyl-5-hexenonitrile (88)</td>
<td>95</td>
</tr>
<tr>
<td>4, 5-Dimethyl-5-hexenal (87)</td>
<td>96</td>
</tr>
<tr>
<td>3, 4-Dimethyl-4-pentenal (89)</td>
<td>97</td>
</tr>
<tr>
<td>3, 4-Dimethyl-4-pentenoic acid (100)</td>
<td>98</td>
</tr>
<tr>
<td>3, 4-Dimethyl-4-pentenoyl chloride (101)</td>
<td>99</td>
</tr>
<tr>
<td>Methyl 4, 5-dimethyl-5-hexenoate (103)</td>
<td>99</td>
</tr>
<tr>
<td>4, 7-Dimethyl-1, 3-dioxyacycloheptane (71)</td>
<td>100</td>
</tr>
<tr>
<td>(4, 7-dimethyl tetrahydrodioxepin)</td>
<td></td>
</tr>
<tr>
<td>4, 7-Dimethyl-2-phenyl-1, 3-dioxyacycloheptane (72)</td>
<td>101</td>
</tr>
<tr>
<td>(4, 7-dimethyl-2-phenyl tetrahydrodioxepin)</td>
<td></td>
</tr>
</tbody>
</table>
5-Benzyloxy-2-hexanol (73) 102
2-Benzyloxy-5-bromohexane (74) 102
5-Benzyloxy-2-hexanone (75) 103

BIBLIOGRAPHY 105
THE RETRO-ENE REACTION OF 2-VINYLCYCLOHEXANOLS AND APPROACHES TO THE SYNTHESIS OF BOTRYOCOCCENE

INTRODUCTION

Concerted reactions display a high degree of stereoselectivity, and this property makes them important synthetic tools. The ene and retro-ene reactions are concerted in nature, and therefore have stereoselective, synthetic potential. Arnold and Smolinsky have investigated the retro-ene reaction of a trans-2-alkenylcyclohexanol and reported that only a trans-aldehyde resulted from the rearrangement. Their research centered on generation of an aldehyde function from the alcohol, and the stereochemistry of the double bond was incidental.

Carbon-carbon double bonds, particularly trisubstituted entities, have significant importance. There are a number of biologically active natural products which have these substituted double bonds with specific configuration. One good example is cecropia juvenile hormone.

The endeavor of this research was first to re-examine Arnold and Smolinsky's work with compounds similar to their 2-alkenylcyclohexanol and to focus attention on the stereoselectivity of the rearrangement. The next consideration was the
stereoselective generation of trisubstituted double bonds from suitably substituted starting materials.

**Scheme 1**

The retro-ene process was to be applied synthetically in the construction of the half-molecule (48) of botryococcene (44), a naturally occurring hydrocarbon. This compound has been isolated in appreciable amounts from a green algal species, *Botryococcus braunii*. The alga has been the subject of geochemical interest and is suggested to be the petrochemical source for the boghead coals.
PART I. THE RETRO-ENE REACTION OF 2-VINYL CYCLOHEXANOLS

HISTORICAL

The ene reaction is normally a concerted process which involves the transfer of a hydrogen (ene) either allylic or similarly situated to a double bond (enophile) and a bond shift between the unsaturated positions. Although the simplest example of an ene reaction, e.g. the reaction of propylene (1) with ethylene (2) is unknown, it serves to illustrate the reaction.

There are examples of various substrates used as the ene component in the reaction. In addition to aliphatic and alicyclic hydrocarbons containing one double bond, 1,3 and 1,4 dienes, trienes, propynes, and allenes can also serve as the ene component.

The character of the enophile is also quite diverse. Alkenes, alkynes, aryne, azo compounds, carbonyl compounds, and singlet oxygen have been employed as enophiles. 1,2

An extension of the earlier work on the ene reaction has been
its synthetic application in an intramolecular sense. The intramolecular reaction involves the ene and enophile in the same molecule and generates a cyclic product. The commercial process for the preparation of (-) menthol (4) employs the ene reaction of (+)-β-citronella (3).³

Oppolzer⁴,⁵ has imaginatively used the reaction in the synthesis of two spirosesquiterpenes, (+)-β-acorenol (5) and (+) acorenone - B (6).
These two applications serve to demonstrate the stereoselectivity of the process.

The retro-ene reaction is the reversal of the ene reaction. Although propylene does not react with ethylene as previously noted, 1-pentene does pyrolyze at temperatures above 400° to decomposition products which may include propylene and ethylene. Research on the retroene reaction has closely paralleled that on the ene reaction, but fewer systems have been investigated. There are several examples of olefinic retro-ene reactions, but the majority of the work has focused on heteroatom analogs, particularly certain unsaturated ethers and alcohols. These compounds will undergo cleavage to produce carbonyl and olefinic moieties. Two simple examples are the reactions of 3-buten-1-ol (7) and methyl-allyl-ether (8) at approximately 500° C. Both compounds produce propylene (9) and formaldehyde (10).
The principle of microscopic reversibility suggests that the ene and retro-ene reactions should occur within the same system under appropriate conditions and indeed a number of reactions are notably reversible. The reaction of \( \beta \)-pinene (11) with ethyl pyruvate (12) produces an equilibrium mixture which can also be obtained by thermolysis of the corresponding alpha hydroxy ester (13).\(^8\)

\[
\begin{align*}
\text{(11)} & + \text{CH}_3\text{C}=\text{COCH}_3 \\
\text{(12)} & \quad \leftrightarrow \quad \text{CH}_3\text{C}-\text{COOCH}_3 \\
\text{(13)} & \quad \text{CH}_3
\end{align*}
\]

The stereoselectivity noted in the ene reaction is also evident in the retroprocess, where \((-\)-6-hydroxymethyl-\( \Delta^1 \)-p-methene (14) forms \((+\)-\( \Delta^1 \)-p-menthene (15) with 100\% conservation of optical activity.\(^9\)

\[
\begin{align*}
\text{(14)} & \quad \text{OH} \\
\text{(15)} & \quad \text{OH} + \text{CH}_2\text{O}
\end{align*}
\]
The reaction need not result in fragmentation as in the above cases. Arnold and Smolinsky\textsuperscript{10} examined the reaction of a trans-2-alkenylcyclohexanol (16) and observed that an unsaturated aldehyde with solely a trans olefinic bond (17) was produced.

\[
\text{(16)} \quad \text{OH} \quad \text{\xrightarrow{R}} \quad \text{O} \quad \text{H} \quad \text{\xrightarrow{R}} \\
\]

This study also indicated that the reaction was applicable to cyclopentanols and cycloheptanols which also produced only trans double bonds.

The retro-ene reaction displays high stereoselectivity, and this behavior is mainly a result of its concerted nature and conservation of orbital symmetry, conforming to Woodward-Hoffman rules for cycloadditions, but the reaction is also highly sensitive to steric effects.

A number of investigators have shown the pyrolysis of beta hydroxy olefins to occur through a six-membered transition state,\textsuperscript{11,12,13} and although Arnold claimed exclusive formation of the trans isomers, the data were not totally conclusive. Some question about the exact product composition exists and cannot be
satisfactorily answered due to limitations of the analytical method used in the study.

The retro-ene reaction seemed to offer promise for the stereoselective synthesis of highly substituted double bonds. Tri-substituted double bonds of specific geometry are of frequent occurrence in natural products, and the importance of some of these naturally occurring materials has increased dramatically since 1967. In that year, cecropia juvenile hormone was isolated and its structure elucidated by a group of researchers at the University of Wisconsin. The compound is responsible for arresting development at the pupal stage in the *Cecropia* moth. This stirred immediate interest due to the implication that the hormone might provide a potent pesticide without the corollary toxic side effects of most insecticides, and indeed, a synthetic hormonal mimic has been utilized in controlling mosquito populations by retarding their development and keeping them in a larval state. Since 1967 a number of insect pheremones have been characterized and most contain trisubstituted double bonds with specific configurations.

Stereo selective generation of these olefinic units has drawn a great deal of research effort, and a variety of methods have been employed in these investigations. However, the real thrust of the research has been to find totally general methods for the transformation. Two recent reviews of the extensive literature have been
published, one by Faulkner\textsuperscript{18} and another by Reucroft and Sammes.\textsuperscript{19}

In 1960, Julia\textsuperscript{20} introduced the first novel stereoselective method of generating trisubstituted double bonds which utilized methylcyclopropyl ketone. The method was later applied by Johnson\textsuperscript{21} to the synthesis of (\textpm) - nerolidol (18).

\begin{center}
\begin{tikzpicture}
  \node (Br) at (0,0) {Br};
  \node (1) at (1,0) {1. Mg};
  \node (2) at (2,0) {2. \text{\textsuperscript{1}}C\text{\textsuperscript{3}}H\text{\textsuperscript{5}}O\text{\textsuperscript{2}}};
  \node (19) at (3,0) {	extsuperscript{19}};
  \node (18) at (0,-2) (18);
  \node (48\% HBr) at (3,-2) {48\% HBr};
  \node (18) at (0,-4) (18);
  \node (1. Mg) at (0,-5) {1. Mg};
  \node (2. O) at (0,-6) {2. \text{\textsuperscript{1}}C\text{\textsuperscript{3}}H\text{\textsuperscript{5}}O\text{\textsuperscript{2}}};
  \node (18) at (0,-8) (18);

\end{tikzpicture}
\end{center}

The ring opening of the cyclopropylcarbinol (19) provided 75\% of the trans isomer and 25\% of the cis isomer.
Johnson and coworkers\(^{22}\) improved on this method by utilizing the cyclopentylcarbinyl bromide (20) and opened the ring with zinc bromide. They applied this homoallylic rearrangement (20) to (21) in their synthesis of cercropia juvenile hormone (22) and obtained 95% stereoselectivity for the trans double bond.

\[
\begin{align*}
\text{(20)} & \quad \text{CO}_2\text{CH}_3 \\
\text{Br} & \quad \text{Br} \\
\text{(21)} & \quad \text{CO}_2\text{CH}_3
\end{align*}
\]

Corey has devised a general synthesis which employs the stereospecific formation of a trans iodide (23) from a propargylic alcohol and stereospecific alkylation with lithium alkyl cuprate to produce solely the trans isomer (24). He has applied this scheme
to a large number of compounds \(^{23-26}\) including the synthesis of juvenile hormone \(^{22}\). \(^{27}\)

Katzenellenbogen \(^{28}\) further refined this procedure by utilizing the alkynyl ester in lieu of the propargylic alcohol and applied it to the synthesis of 7-methyl-3-propyl-2-(E)\(^6\), (Z)-decadien-1-ol \(^{25}\). By comparison with an authentic sample of a naturally occurring material which was isolated from the codling moth, he discovered that the natural product actually possessed the 2(Z)\(^6\), (Z) configuration \(^{26}\) rather than 2(E)\(^6\), (Z).
With this unexpected result in mind, he undertook to develop a way to obtain double bonds of either configuration. He accomplished this by the conjugate reduction of $\alpha, \beta$-unsaturated epoxides (27). Diisobutyl aluminum hydride in refluxing hexane produced
a 95:5 distribution of the \( \text{Z}(28):\text{E}(29) \) alcohols respectively, whereas dissolving calcium metal in liquid ammonia produced an 8:92 ratio of the \( \text{Z}:\text{E} \) isomers.

\[ \text{(27)} \xrightarrow{} \text{(28)} + \text{(29)} \]

The stereoselectivity of sigmatropic rearrangements is well documented, and Thomas\(^\text{30, 31}\) has ingeniously synthesized the naturally occurring \textit{trans}-\textit{trans} isomer of \( \beta \)-sinensal (30) stereoselectively through what can be viewed as sequential Claisen (I) and Cope (II) rearrangements.
The [3,3] Claisen rearrangement has been extremely popular in its application due to its high degree of stereoselectivity, and constant improvements have been made over the years by manipulating steric factors to further increase the selectivity. In Faulkner and Petersen's publication on the use of the Claisen rearrangement in the synthesis of squalene and juvenile hormone, there is a good historical bibliography of the numerous refinements. One of the latest features has been the use of the bulky trimethylsilyloxy group which led to only the correct isomer of a pheremonal diol (31) of the queen butterfly.

\[ \text{Me}_3\text{SiO} \]

Grieco has shown that allyl-aryl sulfoxides (32) are suitable for the stereoselective generation of double bonds by way of a 2,3-sigmatropic rearrangement.
The sulfoxide approach was successfully used to prepare (E)-nucliferol (33).

There are many additional means to produce trisubstituted double bonds, too numerous to cover completely in this document. These selected examples serve to illustrate some interesting and general cases for the construction of the moiety.
RESULTS AND DISCUSSION

A new method had to be devised to prepare the substituted 2-alkenylcyclohexanols since Arnold's route \(^{10}\), treating cyclohexene oxide with an acetylide followed by catalytic reduction, gave poor yields and the reaction cannot be applied to substituted oxides. Use of a modified form of Julia's method \(^{20}\) appeared feasible, but the required ethyl-7-norcaranecarboxylate (7-carbethoxybicyclo[4.1.0] heptane (35a)), which has been prepared by heating cyclohexene oxide with carbethoxy Wittig reagent, was obtained in poor yield. \(^{35}\) Use of a carbenoid addition procedure to form this ester offered a better approach. Scheme 2 depicts the selected route.

**Scheme 2**

\[
\begin{align*}
\text{(34)} + N_2 - \text{CH} - \text{CO}_2\text{Et} & \rightarrow \text{(35)} \\
\text{Copper} & \text{Cat.} \\
\text{LiAlH}_4 & \downarrow \\
\text{(37)} & \rightarrow \text{(36)}
\end{align*}
\]

(a) \( R = R' = H \)
(b) \( R = \text{Me}; R' = H \)
(d) \( R = R' = \text{Me} \)
This carbenoid addition reaction gave the bicyclic esters in fair to good yields depending on R and R' and the copper catalyst. Use of a treated copper metal catalyst gave better yields than a soluble coordination complex, and unlike the soluble catalyst gave no insertion products. The two catalysts gave comparable results with cyclohexene, but the metal catalyst was markedly superior for the mono- and di- substituted compounds. Reduction of the esters (35) to the alcohols (36) with lithium aluminum hydride was trivial, and the subsequent cyclopropylcarbinyl rearrangements occurred with varying degrees of stereoselectivity.

The rearrangement of 7-hydroxymethylbicyclo [4.1.0] heptane (35a) produced only one discernible isomer of 2-vinylcyclohexanol. Crandall reported that only the trans isomer of the vinyl alcohol was obtained from the reaction of vinyllithium with cyclohexene oxide. He also reported that the lithium aluminum hydride reduction of 2-vinylcyclohexanone (38) produced a mixture of cis- and trans-2-vinylcyclohexanols in a ratio of 3:10, respectively. In this case the hydride, being relatively small, approaches mainly from the axial side (R=H, k_a) (Scheme 3) leading to a preponderance of the trans material.
Our isolated product was oxidized to the ketone and subsequently reduced with lithium aluminum hydride which produced a distribution nearly identical with Crandall's. Gas chromatographic coinjection of the starting 2-vinylcyclohexanol with the mixture confirmed the stereochemistry of the cyclopropylcarbinol rearrangement product as trans. The cis alcohol was produced in greater than 95% purity by reduction of 2-vinylcyclohexanone with lithium tri-s-butylborohydride, an extremely bulky reducing agent. The large steric size of the group results in almost exclusive equatorial hydride attack and provides excellent stereoselectivity.

Rearrangement of 1-methyl-7-hydroxymethylbicyclo[4.1.0]heptane (36b) produced two isomers of 1-methyl-2-vinylcyclohexanol in an 83:17 ratio. By analogy, it was inferred that the major isomer
was trans, but by applying known stereochemical reactions of 2-substituted cyclohexanones, this assignment was further documented. The reaction of 2-vinylcyclohexanone with methyl magnesium iodide produced two products in a 75:25 ratio. Gas chromatographic comparison showed that the major isomer from the rearrangement was identical to the minor product from the Grignard reaction. This indicated that the major isomer was trans since the Grignard reaction is known to produce mainly the cis compound (37b-c). Here the bulky Grignard reagent leads predominantly to equatorial attack, (R=CH₃; kₑ) (Scheme 3).

The last rearrangement, that of 1,6-dimethyl-7-hydroxymethylbicyclo [4.1.0] heptane (37d), led to two isomers in an 86:14 ratio. The major isomer was assigned a trans configuration solely on the basis of the other two rearrangements.

Although formation of a homoallylic product from a cyclopropylcarbinyl substrate is a thermodynamically controlled process, in this case the cation seems to be trapped nearly entirely from the axial side. The major product must therefore come from kinetic control in the trapping step of the homoallylic cation, but it is not evident from this study at what point the cis isomers of the tertiary

---

The geometries will be referred solely to the relationship of the vinyl and hydroxyl groups for the purpose of this dissertation.
alcohols are formed (Scheme 4). Two possibilities exist: the cation could undergo ring inversion prior to being trapped, or equilibrium could occur after the cation has been trapped. Regardless of the mechanism, both the mono and dimethyl alcohols produce nearly identical isomeric distribution.

**Scheme 4**

\[ R = \text{CH}_3; \quad R' = \text{H} \]

\[ R = R' = \text{CH}_3 \]
The final pair of isomers was obtained by alkylation of 2-vinylcyclohexanone (38) and then reduction to the alcohol (37c) (Scheme 5).

Scheme 5

The alkylation step caused considerable difficulty due to the anion's reluctance to act as a nucleophile. The generation of the anion is a low temperature reaction (-78° C) and normal alkylations of this type occur at 0° C. However, numerous attempts were made to cause the anion to react at various temperatures up to room temperature by using mixed solvents including HMPA which enhances nucleophilicity, but in each case the ketone was recovered in rearranged, conjugated form. Attempts to trap the anion as the trimethylsilyloxy derivative were also fruitless. Finally, proper reaction conditions were uncovered, i.e., alkylation proceeds smoothly at an elevated temperature (30° - 40° C) and 90% of 2-methyl-2-vinylcyclohexanone (39c) was obtained. The reduction with the bulky reducing agent, lithium triethoxyaluminum hydride, was not expected to show any degree of selectivity, since the methyl
and vinyl groups are nearly of equal size. Although the reducing agent must approach equatorially, the energies of the transition states with axial methyl or axial vinyl groups should be approximately equal. The observed result was a 53:47 distribution. Separation was not attempted, but the major isomer was assigned the trans configuration. The assignment was based on the chemical shift differences of the two methyl groups; the trans isomer's being farther downfield (1.12 ppm) than the cis isomer's (0.98 ppm).

Thermolyses were carried out in a flow reactor, and the resulting product distributions are given in Table 1. Prior to considering the data, the basis for product assignments needs consideration. The products from compounds (37a) and (37b) have di-substituted double bonds, but the nmr did not fix the configurations of the isomers since the chemical shift difference between the two olefinic hydrogens were too small to permit determination of coupling constants. However, analysis of the infrared out-of-plane C-H bending allowed the determination. The trans isomers showed a band at 970 cm\(^{-1}\) which was absent in the cis isomers. The assignment was reinforced by observable homoallylic, virtual coupling of the allylic methyl groups in the nmr of both trans isomers and its absence in the cis compounds.

The isomeric products from (37c) were inseparable by gas chromatography. However, the nmr did indicate that the product
**Table 1**

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>E</th>
<th>Z</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% Other Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>37a-T</td>
<td>H</td>
<td>H</td>
<td>100</td>
<td>-</td>
<td>95</td>
</tr>
<tr>
<td>37a-C</td>
<td>H</td>
<td>H</td>
<td>62</td>
<td>38</td>
<td>97</td>
</tr>
<tr>
<td>37b-T</td>
<td>CH₃</td>
<td>H</td>
<td>100</td>
<td>-</td>
<td>98</td>
</tr>
<tr>
<td>37b-C</td>
<td>CH₃</td>
<td>H</td>
<td>54</td>
<td>46</td>
<td>93</td>
</tr>
<tr>
<td>37c-T</td>
<td>H</td>
<td>CH₃</td>
<td>85</td>
<td>15</td>
<td>92</td>
</tr>
<tr>
<td>37c-C</td>
<td>H</td>
<td>CH₃</td>
<td>100(-5)</td>
<td>0(+5)</td>
<td>96</td>
</tr>
<tr>
<td>37d-T</td>
<td>CH₃</td>
<td>CH₃</td>
<td>100(-5)</td>
<td>0(+5)</td>
<td>96</td>
</tr>
<tr>
<td>37d-C</td>
<td>CH₃</td>
<td>CH₃</td>
<td>100(-5)</td>
<td>0(+5)</td>
<td>96</td>
</tr>
</tbody>
</table>

<sup>a</sup> Total isolated material including by-products

<sup>b</sup> 53% T and 47% C

<sup>c</sup> 90% T and 10% C
was a mixture, since there were two neatly separated aldehydic resonances in a ratio of approximately 80:20. Reduction of the isomeric aldehydes to alcohols permitted separation. Thus the mixture was shown to contain an 85:15 ratio of isomers by gas chromatography, and although Julia\textsuperscript{48} and others\textsuperscript{17, 33, 49} have utilized the chemical shift and coupling of the internal, allylic methyl group (Figure 1) to assign geometry, the comparison of the spectra of the two alcohols provided only tenuous results.

The separation of the methyl resonances was not appreciable and the doublet of the terminal methyl could not be clearly identified. However, leaning heavily on theory and lightly on the experimental evidence, we have assigned the major component as the E isomer. This result would also conform to the observations for the previous
cases. The final pyrolysis, that of (37d), produced a product which appeared to be uniformly one material within the experimental limits of the gas chromatography. Since the aldehydic protons showed a chemical shift difference of 15 Hz for the other tri-substituted olefins, it seemed reasonable to expect that the carbonyl methyls of the E and Z isomers of the ketone would show a difference though less pronounced. However, the nmr showed a solitary, sharp singlet at 2.02 ppm, and the material appears to us to be entirely one isomer. Structural assignment was made as (E) 7-methyl-7-nonen-2-one based on analogy.

It was shown using mixtures of the cis and trans 6-octenals that 0.1% of cis-6-octenal could be detected, and therefore, at least 99.9% of trans-6-octenal results from pyrolysis of trans-2-vinylcyclohexanol (37a-T). This high degree of stereoselectivity is also observed for the other trans alcohols, and results from kinetic control without stereomutation of the double bond.

Examination of the stereoelectronic requirements for the ene reaction has shown that the O-H and C-C sigma bond orbitals must be parallelly aligned with the p orbitals of the pi bond. Scheme 6 demonstrates that this requirement can easily be satisfied for the di-equatorial chair conforms (I) of the trans reactants, and produces E isomers. A boat-like conformation (II) would produce the Z isomers, but would cause perturbation of the sigma-pi bond.
coplanarity and would not fulfill the stereoelectronic requirements.
It is estimated that the boat-like transition state must lie at least
10 kcal/mole higher in energy than the chair-like transition state.

Scheme 6

The cis reactants pose a more difficult problem. We assume
that the Curtin-Hammett principle applies, i.e., that the product
distribution is determined solely from differences in the transition
states, and that the conformation of the starting material is irrelevant. Considering then the transition state geometries, there exist two possible chair-like transition states, one with the hydroxyl group axial (k_a) and another with it equatorial (k_e). Close examination reveals that the k_e state better satisfies the stereoelectronic requirements than k_a. However, the k_e state will also be burdened by an unfavorable interaction between a vinyl hydrogen and an axial ring hydrogen. Although one cannot predict the outcome in view of this conflict, one can draw the conclusions that the stereoselectivity will be reduced and will be a function of the substituents, R and R'.

A qualitative test of this argument can be obtained from the data, if we assume that the trans reactants are 100% stereoselective and produce only the E isomers, whereas the cis reactants produce the E isomers from the transition state with an equatorial hydroxyl (k_e) and conversely the Z isomers from the transition state with an axial hydroxyl (k_a).

Table 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>k_e/k_a</th>
</tr>
</thead>
<tbody>
<tr>
<td>37 a-C</td>
<td>1.6</td>
</tr>
<tr>
<td>37 b-C</td>
<td>1.2</td>
</tr>
<tr>
<td>37 c-C</td>
<td>2.2</td>
</tr>
<tr>
<td>37 d-C</td>
<td>---</td>
</tr>
</tbody>
</table>
The ratios of $k_e/k_a$ in Table 2 compare favorably with expectations based on the effect of substitution on the transition states. When $R$ is changed from $H$ to $CH_3$, the transition state energy for $k_e$ will increase because of the axial methyl. However, considering that $\Delta G_{\text{conf}} = 1.7$ kcal/mole for the methyl group, it is evident that the full effect of the methyl group is not exerted. There will also be an increase in the transition state energy of $k_a$ as a result of the vinyl-methyl skew interaction. From the data it can be calculated that changing $R=H$ to $R=CH_3$ results in a $\Delta \Delta G^\ddagger$ of about 0.5 kcal/mole favoring $k_a$. Realizing that the effect of the methyl group in (37c-C) where $R'=CH_3$ will have an apposite influence on the transition states with $k_e$ being favored, one can then calculate the ratio $k_e/k_a$ for (37c-C) from the $\Delta \Delta G^\ddagger$ value of 0.5 kcal/mole obtained from comparison of (37b-C) to (37a-C). This computation results in a predicted value of 2.2 which is in excellent agreement with the experimental result.

The generation of trisubstituted double bonds by this approach shows excellent stereoselectivity with trans-2-vinylcyclohexanols but only moderate to good stereoselectivity with the cis isomers. However, the overall prognosis for the method is good. In most cases the synthesis of the starting materials is heavily weighted in favor of the trans isomers, and even in the case were this is not
so, i.e. 37c, the mixture gives a high proportion of one isomer in the product.
EXPERIMENTAL

1-Methylcyclohexene (34b)

A solution of 142.5 g (1.5 moles) of chilled methyl bromide in 500 ml of cold, anhydrous ether was slowly added to 36.5 g (1.5 g atoms) of magnesium turnings in 150 ml of dry ether which had been cooled in an ice bath. The mixture was stirred at room temperature for two hours and 147 g (1.5 moles) of cyclohexanone in 100 ml of dry ether was added dropwise. The reaction mixture was stirred overnight and hydrolyzed with 200 ml of a saturated solution of ammonium chloride. The layers were separated, and the aqueous layer was extracted with ether. The ether solution was dried over magnesium sulfate, filtered, and the ether evaporated. The resulting oil was stirred with 100 ml of 10% sulfuric acid at 75°C overnight, and then distilled. The organic material was separated, and the aqueous layer extracted with ether. The ethereal solution was dried over magnesium sulfate, filtered, and the solvent evaporated. The resulting liquid was distilled producing 126.3 g (88%) of 1-methylcyclohexene: bp 106-108°C (lit. bp 110°C)40; nmr (CCl₄) δ 1.54 (s, 3H), 1.82 (m, 8H), 5.25 (m, 1H).
1,2-Dimethylcyclohexene (34d)

A solution of 112 g (1.0 mole) of 2-methylcyclohexanone in 500 ml of dry ether was treated with one mole of methylmagnesium bromide as described above to give 100 g (78%) of 1,2-dimethylcyclohexanol, bp 83°/50 mm (lit. bp 166°). A portion, 48.8 g (0.38 mole), of this alcohol was distilled with 0.1 g of iodine. The layers were separated and the aqueous layer extracted with ether. The ether solution was dried over magnesium sulfate, filtered and the ether evaporated. The resulting liquid was fractionally distilled on a spinning band column at a reflux ratio of 20:1. Refractionation produced 16 g (38%) of 1,2-dimethylcyclohexene, bp 136° (lit. bp 135.5-136.5°) of greater than 95% purity as determined by gas chromatographic analysis. Nmr (CCl₄) δ 1.56(s, 6H), (overlapping broad m, 4H), 1.82(broad m, 4H).

Ethyl diazoacetate

The reaction of 140 g (one mole) of glycine ethyl ester hydrochloride with 80 g (1.15 moles) of sodium nitrite and 10% sulfuric acid according to the procedure of Womach and Nelson produced 69 g of ethyl diazoacetate (60%).
Trimethyl phosphite copper (I) chloride

The procedure of Peace et. al. was followed. The reaction of 4.95 g (0.05 mole) of copper (I) chloride and 7.2 g (0.05 mole) of trimethyl phosphite yielded 6.15 g (85%) of trimethyl phosphite copper (I) chloride, mp 191-193° (lit. mp 192-193°).

7-Carbethoxybicyclo[4.1.0]heptane (35a)

A mixture of 82 g (1.0 mole) of cyclohexene, 2.9 mg of benzoyl peroxide and 222 mg of trimethyl phosphite copper (I) chloride was heated to reflux to form a green solution. To the solution was added 82 g of cyclohexene and 23 g (0.2 mole) of ethyl diazoacetate. The solution was refluxed overnight, cooled to room temperature, filtered, and the cyclohexene distilled. The residue was distilled and the fraction which distilled at 100-140°/25 mm was collected. This fraction was redistilled on a spinning band column to yield 26 g (77%) of 7-carbethoxybicyclo[4.1.0]heptane: bp 41°/1.9 mm (lit. bp 110°/18 mm); ^4^1 nmr (CCl$_4$) 1.13(t, 3H, J=7Hz), 1.82(broad m, 4H), 4.04(q, 2H, J=7Hz).

1-Methyl-7-carbethoxybicyclo[4.1.0]heptane (35b)

The reaction was conducted as described above: 13 g (0.14 mole) of 1-methylcyclohexene, 5.5 mg of benzoyl peroxide and
260 mg of trimethyl phosphite copper (I) chloride were heated to reflux, and 6.9 g (0.06 mole) of ethyl diazoacetate in 13 g of 1-methylcyclohexene was added dropwise. The solution was refluxed overnight, the 1-methylcyclohexene distilled and 4.4 g (40%) of 1-methyl-7-carbethoxybicyclo[4.1.0]heptane, bp 125-130°C/25 mm was obtained. Nmr (CCl₄) δ 1.05(s, 3H), 1.15(t, 3H, J=7Hz), overlapping m, 5H), 1.62(broad m, 4H), 4.04(q, 2H, J=7Hz).

Copper Catalyst

A solution of 60 g of copper (II) sulfate pentahydrate in 400 ml of water was added to 10 g of 20 mesh zinc powder and stirred for two hours at 120°C. The copper was separated by filtration and was treated with 100 ml of a 2% (wt:vol) iodine-acetone solution. The mixture was stirred for 30 minutes and the catalyst isolated on a filter. The catalyst was washed with 2 x 10 ml portions of a 1:1 hydrochloric acid-acetone solution and dried at 66°C and 0.01 mm for two hours. A total of 6.6 g of catalyst was obtained.

1,6-Dimethyl-7-carbethoxybicyclo[4.1.0]heptane (35d)

A mixture of 6.0 g (55 mmoles) of 1,2-dimethylcyclohexene and 300 mg of copper catalyst was heated to reflux, and 6.3 g (55 mmoles) of ethyl diazoacetate was added dropwise. The reaction
mixture was refluxed overnight, cooled to room temperature, filtered and distilled on a spinning band column. The fraction with bp 133-135⁰/13 mm was identified as 1,6-dimethyl-7-carbethoxybicyclo[4.1.0]heptane ¹⁰¹ and 3.6 g (51%) was obtained. Nmr (CCl₄) δ 1.17 (t, 3H, J=7Hz), 1.23(s, 6H), (overlapping m, 4H), 1.63(broad m, 4H), 4.02(q, 2H, J=7Hz).

7-Hydroxymethylbicyclo[4.1.0]heptane (36a)

A solution of 5.6 g (33 mmoles) of 7-carbethoxybicyclo[4.1.0]heptane in 25 ml of dry ether was added dropwise to 1.30 g (31 mmoles) of lithium aluminum hydride in 25 ml of dry ether. After the addition had been completed, the mixture was hydrolyzed with 1.0 ml of water followed by 50 ml of 10% sulfuric acid. The layers were separated, and the aqueous layer extracted with ether. The ether layers were combined and dried over magnesium sulfate, and the ether evaporated producing 3.8 g (90%) of 7-hydroxymethylbicyclo[4.1.0]heptane. Nmr (CCl₄) δ 0.70(broad s, 2H), 1.1 to 1.2 (broad m, 5H), 1.73(broad s, 4H), 3.33(d, 3/2H, J=6Hz), 3.59(d, 1/2H, J=6Hz), 4.43(broad s, 1H), exchanged in D₂O. This spectrum matched that of an authentic sample. ⁴⁵

1-Methyl-7-hydroxymethylbicyclo[4.1.0]heptane (36b)

A solution of 4.4 g (24 mmoles) of 1-methyl-7-
carbethoxybicyclo [4.1.0] heptane in ether was reacted with 0.95 g (25 moles) of lithium aluminum hydride as above, producing 3.3 g (97%) of 1-methyl-7-hydroxymethyl-bicyclo[4.1.0] heptane. Nmr (CCl₄) δ 0.70 (m, 1H), 1.11 (s, 3H), 1.1 to 1.3 (broad m, 5H), 1.72 (broad m, 4H), 3.59 (m, 2H), 3.97 (broad s, 1H) (exchanged with D₂O).

1,6-Dimethyl-7-hydroxymethylbicyclo [4.1.0] heptane (36d)

A solution of 3.2 g (16 mmoles) of 1,6-dimethyl-7-carbethoxybicyclo [4.1.0] heptane in ether was treated as described above with 0.64 g of lithium aluminum hydride (16 mmoles) producing 1.2 g (85%) of 1,6-dimethyl-7-hydroxymethylbicyclo [4.1.0] heptane. Nmr (CCl₄) δ 1.04 (s, 3H), 1.16 (s, 3H), 1.1 to 1.3 (broad m, 5H), 1.60 (broad m, 4H), 3.54 and 3.68 (two d, 2H, J=7Hz), 4.08 (broad s, 1H) (exchanged with D₂O).

Note: The stereochemistry refers to the relationship of the vinyl and hydroxyl groups in the entire vinyl-cyclohexanol series.

Trans-2-vinylcyclohexanol (37a-T)

A two phase reaction mixture of 3.4 g (26 mmoles) of 7-hydroxymethylbicyclo [4.1.0] heptane and 25 ml of 10% sulfuric acid was stirred overnight. The layers were separated and the aqueous layer extracted with ether. The ether extracts were combined with the organic layer and washed with 25 ml of a saturated sodium bicarbonate solution followed by 25 ml of a saturated sodium chloride. The ether solution was dried with anhydrous sodium sulfate, and the ether was evaporated, producing 3.2 g (94% of crude trans-2-
vinylcyclohexanol. Gas chromatographic analysis on a 5% FFAP column at 150° showed the material to be nearly 100% pure. Nmr (CCl\textsubscript{4})\textsubscript{6} 1.22(m, 4H), 1.78(m, 5H), 2.42(broad s, 1H)(exchanged with D\textsubscript{2}O), 3.18 (apparent sextet, spacing 4Hz, probable d of t, 1H, J\textsubscript{a,a} 8, J\textsubscript{a,e} 4Hz), 5.05, 5.75 (ABM of ABMX pattern, 3H, J\textsubscript{AM} = 2J\textsubscript{BM}, J\textsubscript{BM} = 28, J\textsubscript{MX} = 6Hz); ir (neat) 3400, 1640, 995, 910 cm\textsuperscript{-1}.

**Trans-1-methyl-2-vinylcyclohexanol (37b-T)**

A 3.1 g (22 mmoles) sample of 1-methyl-7-hydroxymethyl-bicyclo[4.1.0] hexane was treated with 25 ml of 10% sulfuric acid as above. The reaction produced 1 g (32%) of a mixture of 83% trans- and 17% cis-1-methyl-2-vinylcyclohexanol plus several by-products after distillation. Preparative gas chromatography on a 5% FFAP column, with chromosorb W and an operating temperature of 155° C and a flow rate of 60 ml/min. produced 300 mg of the trans isomer. Nmr (CCl\textsubscript{4})\textsubscript{6} 1.02(s, 3H), 1.0-2.2(broad m, 9H), 2.30(s, 1H)(exchanged with D\textsubscript{2}O), 5.05 5.88(ABM of ABMX, 3H, J\textsubscript{MX} = 7.5, J\textsubscript{AM} + J\textsubscript{BM} = 27Hz); ir (neat) 3500, 1640, 970, 910 cm\textsuperscript{-1}. Anal. Calcd for C\textsubscript{9}H\textsubscript{16}O; C, 77.09; H, 11.50. Found: C, 76.82; H, 11.49.

**Trans-1,2-dimethyl-2-vinylcyclohexanol (37d-T)**

A 2.1 g (13 mmoles) sample of 1,6-dimethyl-7-hydroxymethyl-bicyclo[4.1.0] heptane was treated with 25 ml of 10% H\textsubscript{2}SO\textsubscript{4} as before producing 1.6 g (76%) of an 86:14 mixture of trans:cis-1,2 dimethyl-2-vinylcyclohexanols, respectively. Nmr (CCl\textsubscript{4})\textsubscript{6} 1.08(s, 3H), 1.08(s, 3H), 1.2 to 1.9(m, 9H), 4.92, 5.04, 6.12(ABX pattern,
\[ J_{AB} = 1.8, J_{AX} = 18, J_{BX} = 10 \text{Hz}; \text{ir (neat)} 3550, 1640, 950, 910 \text{ cm}^{-1}. \] Anal. Calcd for C_{10}H_{18}O: C, 77.87; H, 11.76. Found: C, 77.97; H, 11.83.

2-Vinylcyclohexanone (38)

A solution of 1.5 g (16 mmoles) of 2-vinylcyclohexanol in 50 ml of dry dichloromethane was added at once to 24 g (103 mmoles) of Collins reagent in 315 ml of dry dichloromethane. The reaction mixture was stirred for two hours and the solution was decanted. The gummy residue was washed with dichloromethane and combined with the decanted portion. The dichloromethane solution was extracted with 5% sodium hydroxide solution and then with 0.6 N hydrochloric acid. The solution was concentrated to approximately 50 ml, dried over magnesium sulfate, and the solvent was evaporated, yielding 1.82 (92%) of crude material. The crude product was distilled to produce 1.67 g (85%) of 1-vinylcyclohexanone, bp 95-96°/35 mm (lit. bp 35°/0.3 mm); \[ \text{nmr (CCl}_4) \delta 1.77 \text{ (m, 6H), 2.33 (m, 2H), 2.94 (m, 1H), 5.04 and 6.00 (ABM of ABMX pattern,} \]

Cis-1-methyl-2-vinylcyclohexanol (37b-C)

A weighed amount of magnesium turnings, 0.3806 g (15.6 mg
atoms), was placed in 20 ml of anhydrous ether and 2.22 g (15.6 mmoles) of methyl iodide was added in 20 ml of dry ether. A solution of 1.8 g (14 mmoles) of 2-vinylcyclohexanone in 20 ml of dry ether was added. The reaction was hydrolyzed with the dropwise addition of a saturated ammonium chloride solution. The ether layer was filtered and dried over magnesium sulfate. The ether was evaporated and 2.0 g (93%) of crude product distilled to yield 0.8 g (39%) of a mixture of 75% cis- and 25% trans-1-methyl-2-vinylcyclohexanols. The mixture was separated by preparative gas chromatography on 5% FFAP on chromosorb W and an operating temperature of 135°, injector temperature 135°, and detector 160° with a flow rate of 60 ml/minute. At higher injector and detector temperatures the trans compound tended to eliminate water.

Nmr (CCl₄) δ 1.13(s, 3H), 1.20-2.00(m, 10H), 5.00 and 5.94 (ABM of ABMX pattern, 3H, JAB =2, JM =8, JAM +JBM =27Hz); ir 3500, 1640, 1000, 910 cm⁻¹.

2-Methyl-2-vinylcyclohexanone (39)

A solution of 0.15 ml (1.0 mmole) of diisopropylamine in 25 ml of dry THF was cooled to -55° C under nitrogen. A 2N solution of n-butyllithium in hexane, 0.5 ml (1.0 mmole), was added at -55° C with stirring. The solution was stirred at -60° C for 30 minutes and 0.1109 g (0.89 mmoles) of 2-vinylcyclohexanone in 2 ml
of dry THF was added dropwise. The solution was allowed to warm to room temperature and then heated to 30° C in an oil bath for 30 minutes, at which time 0.20 ml (1.2 mmoles) of hexamethylphosphoramide was added followed by 0.3 g (2.1 mmoles) of methyl iodide. The solution was then heated to 40° C for two hours, cooled to room temperature, filtered and 25 ml of ether was added. The solution was extracted with saturated ammonium chloride solution, water, and saturated sodium chloride solution. The ether layer was dried with magnesium sulfate, and the solvent was evaporated, producing 0.110 g (90%) of 2-methyl-2-vinylcyclohexanone. Nmr \( (\text{CCl}_4) \delta 1.09(\text{s, } 3\text{H}), 1.5-2.1(\text{broad m, } 6\text{H}), 2.32(\text{m, } 2\text{H}), 5.05 \text{ and } 5.94(\text{ABX pattern, } 3\text{H}, J_{AB} = 1.5, J_{AX} + J_{BX} = 2.7); \text{ ir } (\text{CCl}_4) 1725, 1000, 910 \text{ cm}^{-1}. \\

\text{Cis-2-vinylcyclohexanol (37a-C)}

A solution of 1.0844 g (8.74 mmoles) of 2-vinylcyclohexanone in 25 ml of dry THF was cooled in an ice bath under nitrogen. A 1 M solution of L-selectride (lithium tri-sec-butyl borohydride) in THF, 8.9 ml (8.9 mmoles), was added dropwise and the solution was stirred in an ice bath for six hours. Then 1 ml of water was added followed by ether, and the reaction mixture extracted with 25 ml of a saturated ammonium chloride solution. The ether layer was extracted with water, saturated sodium chloride solution, and dried.
over magnesium sulfate. The solvent was evaporated and the residue was treated with 5 ml of glacial acetic acid. The acid was neutralized and the organic layer was taken up in 10 ml of ether. After 10 ml of a 1.5 N sodium hydroxide solution had been added, the mixture was cooled in an ice bath and 4 ml of a 50% hydrogen peroxide solution was added dropwise. The reaction mixture was stirred for 12 hrs at room temperature, the layers were separated, and the aqueous layer was extracted with ether. The ether solution was dried over magnesium sulfate and the ether was evaporated. The residue was distilled, yielding 0.660 g (60%) of greater than 95% cis-2-vinylcyclohexanol, bp 68-70°C/4 mm. A 200 mg sample was collected from a 3% DEGS column with an operating temperature of 165°C and a flow rate of 80 ml/minute: nmr (CCl₄) 1.05-2.04 (broad m, 9H), 2.18 (broad s, 1H) (exchanged with D₂O), 3.80 (m, 1H), 5.17 and 5.95 (ABM of ABMX pattern, 3H, J₆,5 = 6.5, J₆,7 = 28, J₇,8 = 1 Hz); ir (CCl₄) 3650, 3100, 1640, 1010, 920 cm⁻¹.

1-Methyl-2-vinylcyclohexanol (37c)

Lithium tri-t-butoxyaluminum hydride was prepared by the method of Brown and Hess. Lithium aluminum hydride, 1.22 g (32.6 mmoles), reacted with 7.26 g (98 mmoles) of t-butanol in dry THF under nitrogen. A solution of 0.946 g (6.85 mmoles) of 2-methyl-2-vinylcyclohexanol in 6 ml of dry THF was added dropwise
at 0\degree. The mixture was warmed to room temperature and stirred for 22 hrs. The reaction mixture was hydrolyzed with 10 ml of a 1:1, THF-water solution, and 30 ml of 10% sulfuric acid was added followed by 50 ml of ether. The organic layer was extracted with water, saturated sodium bicarbonate solution and saturated salt solution. The ether layer was dried over magnesium sulfate, and the solvent was evaporated, yielding 0.7825 g (75%) of 2-methyl-2-vinylcyclohexanol. Gas chromatographic analysis showed the presence of two isomers in a 53:47 distribution: nmr (CDCl₃) δ 0.98 and 1.13(2s, 3H), 1.13 to 2.0(broad m, 9H), 3.24(broad m, 1H), 5.1 and 5.9(two overlapping ABX patterns, 3H, Jₓₓ+Jₓₓ =28Hz); ir (neat) 3400, 1640, 990, 915 cm⁻¹.

**Thermolytic Reactions**

The following thermolyses were conducted on a vertical quartz column packed with pieces of quartz tubing, encased in an insulated heating jacket. The top of the column was extended with a second column, wrapped with heating tape, and equipped with a nitrogen inlet and septum. The samples were injected through the spectum to the pre-heated, upper column (temperature 200-215\degree) and carried through the upper and main column (temperature 440\degree) with a flow of nitrogen generally between 50-75 ml/min, which equated to contact times between 1.5 and 2.2 minutes. The products were
collected in a series of three dry ice-acetone cooled traps. The column was flushed with small fractions of n-hexane after several minutes following injection and the hexane was evaporated.

**Thermolysis of trans-2-vinylcyclohexanol (37a-T)**

A sample of 78 mg (0.62 mmole) of trans-2-vinylcyclohexanol was injected onto the column and had a contact time of 1.46 min. Collection of 74.2 mg (95%) of material from a 5% FFAP column showed a composition of 95.5% trans-6-octenal (40T). Nmr (CCl₄) δ 1.65(m, 3H), 1.20-1.87(broad m, 4H), 2.0(m, 2H), 2.36(d of t, 2H, J=6.8, J=1.8Hz), 5.38(m, 2H), 9.13(t, 1H, J=1.8Hz); ir (neat) 2725, 1725(s), 965 cm⁻¹. Anal. Calcd for C₈H₁₄O: C, 76.14; H, 11.18. Found: C, 75.72; H, 11.23.

**Thermolysis of trans-1-methyl-2-vinylcyclohexanol (37b-T)**

A 71.1 mg (0.515 mmole) sample of trans-1-methyl-2-vinylcyclohexanol was injected onto the column and had a contact time of 1.50 min. In the traps was 70.0 mg (98%) of material which consisted of 90% 2-trans-non-8-one (41T). Nmr (CCl₄) δ 1.65 (m, 3H), 1.20-1.85(broad m, 4H), 1.95(broad m, 2H), 2.04(s, 3H), 2.33(t, 2H, J=7Hz), 5.38 (m, 2H); ir (neat) 1730(s), 1360, 970(s) cm⁻¹.
Thermolysis of cis-1-methyl-2-vinylcyclohexanol (37b-C)

A 45 mg (0.325 mmole) sample of cis-1-methyl-2-vinylcyclohexanol was injected onto the column with a contact time of 1.98 min. and 42 mg (93%) of material was collected. This consisted of 96% of a 54:46 mixture of 2-trans-nonen-8-one to 2-cis-nonen-8-one (41C) as determined by gas chromatographic coinjection. The compounds were separated on a 3% DEGS column on chromosorb G with an operating temperature of 150° and flow rate of 10 ml/7.5 seconds. The cis ketone 41C showed an nmr (CCl₄) 6 1.62(d, 3H, J=5Hz), 1.20-1.85(m, 4H), 1.98(broad m, 2H), 2.05(s, 3H), 2.35(t, 2H, J=7Hz), 5.38(m, 2H); ir (CCl₄) 1730(s), 1340, 860 cm⁻¹.

Thermolysis of cis- and trans-1,2-dimethyl-2-vinylcyclohexanol (37d)

A 75.3 mg (0.50 mmole) sample of 86% trans- and 14% cis-1,2-dimethyl-2-vinylcyclohexanol was injected onto the column with a contact time of 2.20 min. The traps yielded 72.1 mg (95.7%) of product composed of 5% elimination products and 93% of 3-methyl-2-E-nonen-8-one. Two other distributions were run: 88:12 and 90:10 trans:cis respectively and produced 94% and 95% 3-methyl-2-E-nonen-8-one (42). Nmr (CCl₄) 6 1.56(s, 3H), 1.20-1.76(broad m, 5H), 1.96(broad m, 2H), 2.05(s, 3H), 2.36(t, 2H, J=6.5Hz), 5.17
(broad m, 1H); ir 1730(s), 1380, 1372, 1360, 805 cm\(^{-1}\). **Anal.**

Calcd for C\(_{10}\)H\(_{18}\)O: C, 77.87; H, 11.76. Found: C, 77.65; H, 11.80.

**Thermolysis of cis- and trans-2-methyl-2-vinylcyclohexanol (37c)**

A 300 µl (224 mg) sample of the crude product, 53% trans- and 47% cis-2-methyl-2-vinylcyclohexanol produced 250 µl (205 mg 92% contact time 2.00 minutes). The material was not separable on 5% FFAP, 3% DEGS and 5% OV-17 columns. Nmr (CCl\(_4\)) 6 1.55 (m) and 1.60(s) 3H, 1.15-1.76(broadened H), 1.98(apparent t, 2H, J=7Hz), 2.48 (d of t, 2H, J=7, J=1Hz), 5.2(m, 1H, 9.56 and 9.70 (2t, 1H, J=1Hz); ir (CCl\(_4\)) 1730, 1370 cm\(^{-1}\). **Anal.** Calcd for C\(_9\)H\(_{16}\)O: C, 77.09; H, 11.50. Found: C, 77.20; H, 11.49.

**(E) and (Z) 6-methyl-6-octenol (42)**

A solution of 66.8 mg (0.48 mmole) of 6-methyl-6-octenal in ether was added dropwise to 20 mg (0.52 mmole) of lithium aluminum hydride in 20 ml of anhydrous ether. The reaction mixture was stirred at room temperature for 2 hrs., then was hydrolyzed with 0.2 ml of water, followed by 10 ml of 10% sulfuric acid. The layers were separated and the aqueous layer was extracted with ether. The ether fractions were combined, dried with
magnesium sulfate, and the ether evaporated yielding 65.5 mg (97%) of an 85:15 mixture of (E) and (Z) 6-methyl-6-octenol (42). These were separated on a 3% DEGS column with an operating temperature of 140° and flow rate of 10 m./sec. The E isomer had an nmr (CCl₄) δ 1.2-1.8(broad m), 1.55(partly resolved d, J=1Hz), 1.8-2.2(m), 3.50(m), 5.0-5.3(broad m). Z isomer nmr (CCl₄) δ 1.2-1.8(broad m), 1.56(s), 1.8-2.2(m), 2.85(s, OH), 3.2-3.9(broad m), 5.0-5.3(broad m).

**Thermolysis of cis-2-vinylcyclohexanol (37a-C)**

An 80 mg sample of cis-2-vinylcyclohexanol (greater than 99% purity) was pyrolyzed with a contact time of 5.1 minutes. Collection gave 78 mg (97%) of material which proved to be 61.5% 6-trans-octenal and 38.5% 6-cis-octenal (40-C). The isomers were separated on a 5% OV-17 column with an operating temperature of 150°. The cis isomer showed an nmr (CCl₄) δ 1.62(d, 3H, J=5Hz), 1.20-1.86(broad m, 4H), 2.0(broad m, 2H), 2.35(m, 2H), 5.38(m, 2H), 9.15(t, 1H, J=1.8Hz); ir (CCl₄) 1715, 905, 670 cm⁻¹.
PART II: APPROACHES TO THE SYNTHESIS OF BOTRYOCOCCENE

HISTORICAL

Botryococcene was isolated and its structure determined as a result of geochemical interest in the genesis of certain hydrocarbons in nature and the relationship between these hydrocarbons and the formation of continental shale, petroleum crude oil, and other petrochemical deposits.

In the mid-nineteenth century, examination of boghead coals revealed the ubiquitous presence of minute yellow globules. Several sources were suggested for these globules, and nearly a century later an algal species, *Botryococcus braunii* of the order Chlorophyceae, was considered as a possible progenitor. This hypothesis was based on the morphology, behavior, and composition of the algal species. The alga forms nearly spherical colonies which can attach to one another by threads to form aggregate colonies of various sizes which are either green or orange depending on the availability of nutrients. Each cell is embedded in a cup of oil. When a cell divides, the product cells secrete oil while remaining within the cup of the mother cell, and in this manner, the colony's matrix is constructed. Traverse \(^51, 52, 53\) asserted that *Botryococcus* contributed to the oil content of certain Paleozoic and
perhaps Cenozoic rocks since he found evidence of the remains of this species in lignites and other Tertiary sediments. Chemical analysis of the algal hydrocarbon fraction was undertaken in order further to characterize any direct relation with the oils in these oil bearing rocks.

A typical preparative method began with freeze drying of a cultured stock of *Botryococcus braunii*, followed by ultrasonic extraction with acetone, centrifugal separation, and finally evaporation of the solvent. The hydrocarbon fraction was then obtained by column chromatography. Gelpi and coworkers used gas chromatography and mass spectroscopy to show that there was a correlation with oils present in rocks of the Tertiary period. Although this method failed to identify conclusively any particular compound, it did establish that hydrocarbons of relatively high carbon number (C\(_{29}\) and C\(_{31}\)) were present in the algae, and that there were a number of degrees of unsaturation in these compounds.

Eglinton and coworkers obtained from the hydrocarbon fraction two isomeric compounds in a ratio of 9:1 by preparative thin layer chromatography. Surprisingly, the hydrocarbon fraction constituted 76% of the dry weight of the non-cultured algae, and consisted almost entirely of these two compounds. The major hydrocarbon was named botryococcene and the other isomer was called isobotryococcene. They attempted to elucidate the complete
structure of botryococcene through normal spectroscopic and chemical techniques, but were able only to ascertain the presence of certain structural units and could not provide a definitive structure.

Their investigation provided a molecular formula of $C_{34}H_{58}$ from the molecular ion peak of 466 in the mass spectrum and the absence of functional peaks in the infrared region. Quantitative analysis of the infrared data indicated the presence of four methylene groups ($v = 891 \text{ cm}^{-1}$), one trans double bond ($v = 979 \text{ cm}^{-1}$) and one vinylic double bond ($v = 916 \text{ cm}^{-1}$ and 1002 $\text{ cm}^{-1}$). The ultraviolet spectrum showed only end absorption, and thereby indicated complete lack of conjugation. The proton magnetic resonance spectrum had a sharp singlet at 4.6, which integrated to eight protons and was assigned to the methylene hydrogens. The vinyl group was assigned to an (ABX) pattern with two doublets and a singlet at the 4.66 to 4.9 region corresponding to the AB portion, and a grouping composed of a singlet, two doublets plus an additional singlet in the 5.52 to 5.8 range corresponding to the X portion. The splitting of the X portion also indicated that the vinyl group was bonded to a tetrasubstituted carbon atom. The trans double bond was identified by an AB quartet with a coupling constant of sixteen Herz; the A portion was further coupled to an allylic proton which was confirmed by upfield irradiation causing collapse to a doublet. A singlet at 1.62 integrating to six hydrogens was assigned
to two methyl groups attached to double bonds. Finally, the saturated C-methyl region integrated for five or six methyl groups.

Hydrogenation of botryococcene to botryococccane was carried out, and although the mass spectrum did not show a molecular ion, the fragmentation pattern did point to two possible structures for botryococccane. Interpretation of the fingerprint region of the infrared spectrum further elaborated the proposed structures and finally (42a) and (42b) were considered as possibilities.
Selective reduction of the vinyl double bond was accomplished with P-2 nickel boride, and produced dihydro botryococcene. The presence of a vinyl group in botryococcene was confirmed by the reduced material's infrared and nuclear magnetic spectra which showed no indication of a vinyl group, and a parent peak of 468 in the mass spectrum.

Application of $^{13}$C nuclear magnetic resonance helped to develop a complete structure for the unique hydrocarbon. Cox and coworkers$^{57}$ identified 2, 5, 9-trimethyl-6, 9-dioxoundecanoic acid (43) as the major product of the permangateperiodate oxidation of botryococcene. This proved vital in the assignment of a structure, since it was to fix the asymmetric nature of the molecule, although this had not been immediately apparent. However, this information coupled with the $^{13}$C nmr data eventually led to structure (44).

The spectra of botryococcene and dihydrobotryococcene were compared and the appropriate assignments made (Table 3). The carbons are numbered so that the basic chain includes the two terminal double bonds from C$_1$ to C$_{22}$, and the remaining substituents are then numbered sequentially from left to right. Some assignments
were uncertain, such as the resonances of the methyl groups 23, 34 and 24, 33 respectively, which in fact might be the reverse of those indicated. Off-resonance decoupling was employed to identify primary, secondary, tertiary and quaternary carbons, and pulsed decoupling was used to avoid nuclear Overhauser effects which cleared any ambiguity caused by overlap.

The oxidative cleavage of the double bonds can be viewed as leading to two products, (43) and (45), one of which is a diketodiacid (43) which easily decarboxylates to the diketo-monoacid (45).

\[ \begin{align*}
    &\text{(43)} \\
    &\text{(45)}
\end{align*} \]

It appears that only the proposed structure can accommodate this result.

There seems to be little data available in which to base a biosynthetic pathway to the hydrocarbon, but Cox\textsuperscript{57} has suggested there exists a precedent in isodigeranyl (46) for what he terms a tail-to-tail linkage of dimethylated C\textsubscript{15} units.

\[ \text{(46)} \]
Table 3. $^{13}$C chemical shifts (relative to CS$_2$) and assignments for botryococcene and dihydrobotryococcene.

<table>
<thead>
<tr>
<th>Carbon No.</th>
<th>Botryococcene</th>
<th>Dihydrobotryococcene</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 22</td>
<td>83.0</td>
<td>83.0</td>
</tr>
<tr>
<td>2, 21</td>
<td>42.9</td>
<td>42.7</td>
</tr>
<tr>
<td>3, 20</td>
<td>151.6</td>
<td>151.5</td>
</tr>
<tr>
<td>4, 19</td>
<td>159.1</td>
<td>159.1</td>
</tr>
<tr>
<td>5, 18</td>
<td>160.9</td>
<td>160.9</td>
</tr>
<tr>
<td>6, 17</td>
<td>37.9, 38.1</td>
<td>37.7</td>
</tr>
<tr>
<td>7</td>
<td>152.0</td>
<td>151.9</td>
</tr>
<tr>
<td>8</td>
<td>159.2</td>
<td>159.1</td>
</tr>
<tr>
<td>9</td>
<td>157.6</td>
<td>157.4</td>
</tr>
<tr>
<td>10</td>
<td>155.4</td>
<td>155.1</td>
</tr>
<tr>
<td>11</td>
<td>58.8</td>
<td>59.1</td>
</tr>
<tr>
<td>12</td>
<td>56.7</td>
<td>55.4</td>
</tr>
<tr>
<td>13</td>
<td>150.8</td>
<td>154.2</td>
</tr>
<tr>
<td>14</td>
<td>153.5</td>
<td>153.8</td>
</tr>
<tr>
<td>15</td>
<td>162.4</td>
<td>162.6</td>
</tr>
<tr>
<td>16</td>
<td>152.5</td>
<td>152.4</td>
</tr>
<tr>
<td>23, 34</td>
<td>172.8</td>
<td>172.8</td>
</tr>
<tr>
<td>24, 33</td>
<td>173.7</td>
<td>173.7</td>
</tr>
<tr>
<td>25, 32</td>
<td>85.1, 85.3</td>
<td>85.3</td>
</tr>
<tr>
<td>26, 31</td>
<td>172.2, 172.4</td>
<td>172.1, 172.3</td>
</tr>
<tr>
<td>27</td>
<td>171.5</td>
<td>171.1</td>
</tr>
<tr>
<td>28</td>
<td>45.8</td>
<td>158.9</td>
</tr>
<tr>
<td>29</td>
<td>81.6</td>
<td>184.1</td>
</tr>
<tr>
<td>30</td>
<td>168.9</td>
<td>169.8</td>
</tr>
</tbody>
</table>
He compared the methylation pattern to the methylated side chains of plant sterols but in particular to cyclolaudenol (47).

From these analogies he suggests the olefin is isoprenoid in nature.

An interesting feature of the biosynthesis of botryococcene is that it is highly dependent upon the physiological state of the colony. Brown and Knights (58) had discerned that there were three phases in the life cycle of the species and each exhibits a characteristic hydrocarbon content and composition. A green active colony was associated with an exponential growth phase and the total hydrocarbons accounted for 17% of the dry weight. Three hydrocarbons, heptacosa-1,18-diene(C$_{27}$H$_{52}$), nonacosa-1,20-diene(C$_{29}$H$_{56}$) and hentriaconta-1,22-diene(C$_{31}$H$_{60}$) were identified as the principal components of this fraction. (59) The second state was the senescent or resting phase of a brown colored colony in which up to 85% of the dry weight was composed of hydrocarbons and 90% of the hydrocarbon fraction was botryococcene. A third state was composed of
large green cells with very little hydrocarbon content, only about 6% of the dry weight.  

Several hypotheses have been offered to explain the presence of algal hydrocarbons; among them are the provision of a food store, a flotation sack to control the colony's position in the water column, and a toxicity effect on herbivores. There is little available evidence to discount any particular theory, but considering Brown and Knights' observations, it seems evident that botryococcene is related to some nebulous way to the cell's ability or inability to undergo rapid photosynthesis.
RESULTS AND DISCUSSION

The synthesis of botryococcene was intended originally to confirm the structure assigned to the compound and also to illustrate one synthetic value of the retro-ene process discussed in Part I of this manuscript.

The basic strategy for the synthesis was patterned after Cox's conjecture that the hydrocarbon resulted biochemically from the asymmetric coupling of two identical units. The basic $C_{17}$ half molecule (48) would contain the appropriate carbon skeleton and the appropriate functionality to be used in the coupling step.

![Molecule diagram](48)

The vinyl group would be formed directly in the dimerization, but the \textit{trans} disubstituted double bond would have to be elaborated after the dimerization step.

This approach was predicated on Baldwin and Hackler's elegant application of a 2, 3-sigmatropic rearrangement to produce asymmetrically coupled dimers of exactly this type with 99\% specificity. They studied a number of examples, and their work
provided a sound basis for planning. The key step is portrayed in Scheme 4.

**Scheme 4.**

Elaboration of the trans double bond from (50) was not considered to be a trivial matter, but there existed enough evidence to suggest that this transformation could be accomplished through protonation of an allylic Grignard reagent. The method (Scheme 5) would involve oxidation of the sulfide (50) to a sulfoxide (51) and capture of the 2,3-sigmatropic shift product. \(^{61, 62, 63}\) The resulting allylic alcohol (52) would be converted to the chloride (53) via an \(S_N^{i'}\) reaction and then formation of a Grignard reagent (54). Roberts et. al. \(^{64}\) had found that allylic Grignard reagents interconvert rapidly
and the equilibrium strongly favors the primary over a secondary or tertiary position. In the present case, the question involves a secondary (54s) versus a tertiary position (54t) and it would appear that the secondary site should predominate.

Roberts and coworkers had also shown previously that protonation of allylic Grignard reagents with aqueous acid resulted in mixtures of olefins which favored the thermodynamically less stable isomer, i.e., the less substituted double bond. Furthermore, use of phenylacetylene (55) in lieu of aqueous acid resulted in almost exclusive formation of the less stable form. The mechanism of protonation is unknown and the case of a secondary versus a tertiary reagent has not been explored. It is not certain whether the outcome of protonation is dependent on the intrinsic nature of the reagent or is merely a function of competitive rates of protonation. These questions are being explored through model compounds in our laboratory.

The half molecule was the primary objective and the initial route to that end employed the retro-ene process, Scheme 6. Perhaps the greatest uncertainty in the scheme lies in the necessity that the group, X, be a halide or some functionality which could be converted to a halide. There is no precedent in the literature of the retro-ene process that vinyl halides can act as enophiles, and there is some indication that vinyl halides are not particularly stable
though thermal stability has not been studied. In the event that the halide should prove inapplicable, the possibility of employing a vinyl benzloxy grouping could be considered, but this too is without precedent.

The synthesis of (56) appeared to be easily accessible, Scheme 7, since a reasonable precursor (59) had been reported by Chuche and Wiemann \(^{66}\) to result from the thermolysis of the dienediol (58). This process can be viewed as a Cope rearrangement followed by an intramolecular ene reaction. The dienediol (58) was readily prepared by the reductive coupling of methacrolein (57) with
zinc and acetic acid. The thermolysis of this diol was studied carefully and we found that the diastereomeric hydroxy-aldehydes were indeed present, as determined from the NMR and IR spectra, in agreement with the results of Chuche and Wiemann. However, there were also a number of additional unidentified products indicated by gas chromatography, and we were unable to find conditions to eliminate these. The aldehydes were extremely unstable and separation by fractional distillation proved impractical. Thus an alternate route to 59 was sought.

Scheme 7

\[
\begin{align*}
\text{CHO} & \xrightarrow{\text{Zn, HOAc}} \text{HOAc} \\
\text{(57)} & \xrightarrow{\Delta} \text{(58)} \\
\text{RMgX,} & \xrightarrow{\left(\begin{array}{c}
\text{CHO} \\
\text{Ph}_3\text{P} = \text{CHX}
\end{array}\right)} \text{CHO} \\
\text{(59)} & \xrightarrow{\text{H}_3\text{O}^+} \text{CHO} \\
\text{Ph}_3\text{P} = \text{CHX}
\end{align*}
\]
There are a number of possible routes to (56) which begin with cyclopentanone (59a) or some simple derivative of it. Although alkylations and condensations of cyclopentanone have been widely reported, in general they proceed in modest yield because of cyclopentanone's propensity for self-condensation. This limitation is unfortunate but it is balanced by the availability of cyclopentanone. Therefore the route shown in Scheme 8 seemed quite feasible.

Scheme 8

The first step in Scheme 8 caused unexpected difficulty. Although 2-hydroxymethylene cyclopentanone (60) had been prepared by this same condensation, in our hands the method provided much lower yields than were reported, and rather surprisingly, the product proved extremely air sensitive. To expedite study of the question of whether vinyl halides would tolerate the conditions of the retro-ene reaction, we decided to explore use of the more
readily available cyclohexanone analogs as models.

**Scheme 9**

Following preparation of the well known (61), we attempted direct formation of 2-methyl-2-vinylcyclohexanone via a selective Wittig reaction. The Wittig reagent apparently did react faster with the aldehyde but the betaine (63) decomposed via a retroaldol process, Scheme 10, to produce 2-methylcyclohexanone (64) as the major product. We were unable to find conditions which would overcome this difficulty. One attempt to prepare selectively an acetal (62), in order to permit reduction of the ketone, was totally
unsatisfactory. On this unproductive note, the route via a retro-ene reaction was abandoned. With time becoming a limiting feature, we decided to by-pass some rather more elegant but apparently more uncertain routes to concentrate on a more conventional scheme.

The new strategy involved a convergent approach with attention focused upon construction of the carbon-carbon bond at $C_6-C_7$ (65), using two non-identical halves, (66) and (67).
Formation of the ultimate bond was proposed via Grignard reaction. Therefore Y must be a halide and Z must be a function which will not interfere with formation of the reagent. The requirement for W is that addition of a Grignard reagent will result in an adduct which will ultimately generate a methine group. Since (67) is difunctional it will be considered first as opposed to the simpler (66).

Two readily available materials, 2,5-hexanediol and 2,5-hexanedione can serve as starting materials. Both compounds are symmetrically difunctional and a means of mono-modification is required. Our initial efforts centered on the diol, with attention directed mainly to formation of a monoether to act as a protective group. For convenience in the eventual hydrolysis step, use of an acetal was indicated. The derivative decided upon to satisfy this objective was the methoxymethyl ether, formed from chloromethyl methyl ether (68), an extremely reactive compound with nucleophiles (Scheme 11). The resulting hydroxyacetal (69) was expected to be easily separated from the diacetal (70).

The experimental result was most unexpected in that only the seven-membered cyclic acetal (71) was obtained. The yield was quantitative despite variations in conditions such as concentration, amount of excess diol, temperature, and nature of the base. Considering this behavior coupled with knowledge that cyclic acetals can undergo ring opening by hydrogenolysis to produce alcohol and
ether functionalities, the cyclic acetal seemed an attractive intermediate. The cyclic acetal of benzaldehyde (72) was prepared by conventional procedures and (72) was treated with diisobutyl-aluminum hydride, DIBAL, to produce (73) which was converted to the bromide (74). The hydrogenolysis step proceeded in poor yield,
though subsequent work with this batch of DIBAL suggested it might have a lowered activity as a result of prolonged storage. An alternative reagent, dichloroaluminum hydride, was examined. The reagent was generated in situ by the reaction of aluminum chloride with lithium aluminum hydride. Application to (72) gave instead of the expected (73) the keto-ether (75) in low yield. Though certainly unusual, this product could be as the result of an internal oxidation catalyzed by aluminum chloride, Scheme 12.

Scheme 12
However, attempts to reproduce the oxidation by using only aluminum chloride proved unsuccessful.

While the above work was in progress we discovered that the dione (76) would react nicely with triethyl phosphonoacetate (86) to
produce the keto-α,β-unsaturated ester (77) in quite acceptable yield. The keto moiety was reduced with sodium borohydride to the alcohol (78) which was converted to the chloride (79) and also to the bromide (82). The ester function in both halides was reduced with lithium aluminum hydride to produce the allylic alcohols (80) and (83). This reduction was carried out by adding an ethereal solution of the ester to a cold ethereal lithium aluminum hydride reaction mixture and hydrolyzing in the cold after approximately five minutes. This method was necessitated because concomittant reduction of the carbon-carbon double bond in addition to the ester occurred very readily. Inverse addition had little effect on the outcome nor did the amount of lithium aluminum hydride (an excess was actually used), but the critical features were reaction time and temperature. The halo-alcohols were then protected as the tetrahydropyranyl (THP) derivatives (81) and (84). The bromo-alcohol (83) was also converted to the methoxymethyl derivative (85) as an alternative means of protection for the hydroxyl function. In addition, the acid catalyzed reaction of the bromo-alcohol with ethyl vinyl ether was examined, but this reaction was unacceptable since the ethyl vinyl ether condensation products gave mixtures which were difficult to separate.

Successful preparation of compounds, (81), (84), and (85) provided three substrates to generate the half-molecule from the
corresponding Grignard reagents. Two compounds were considered for reaction with these reagents, an aldehyde (87) and a nitrile (88).

\[
\text{CHO} \\ (87) \\
\text{CN} \\ (88)
\]

Although the use of the nitrile would reduce the number of steps, since the resulting imine would lead directly to a ketone after hydrolysis (Scheme 14), Grignard reactions with nitriles are generally sluggish and the yields are often lower than those from reactions of aldehydes. Therefore, the aldehyde was also studied even though there would be an additional oxidation step, Scheme 15.

Scheme 14

\[
\begin{align*}
\text{MgX} & \quad \text{OR} \\
\text{OR} & \quad \text{CN} \\
\text{OR} & \quad \text{CN} \\
\end{align*}
\]
The route devised to both the nitrile and the aldehyde has a common precursor (89). Homologation via a methoxy Wittig would complete the elaboration of the aldehyde (90). The nitrile (88) would be derived from the corresponding tosylate (92), Scheme 16.
Finally, the aldehyde (89) was to be prepared by a Claisen rearrangement of the allyl vinyl ether (93), Scheme 17.

The 2-methyl-2-butanol (94) can be obtained by the reduction of tigaldehyde, tiglic acid, or alkyl tiglates which are commercially available. However, these compounds are relatively expensive and a more economical route from ethyl acetoacetate (95) (Scheme 18)
was employed in our work. The overall yield was nearly 50%, and the sole feature worthy of note was the acid-catalyzed elimination of (96) which was done by azeotropic removal of water to avoid saponification of the ester (97).

Scheme 18

\[
\begin{align*}
\text{CH}_3\text{C-CH}_2\text{CO}_2\text{Et} & \xrightarrow{1. \text{NaOEt}} \text{CH}_3\text{C-CHCO}_2\text{Et} & \xrightarrow{\text{NaBH}_4} \text{CH}_3\text{CH-CHCO}_2\text{Et} \\
\text{(95)} & & \text{(96)} \\
\text{CH}_3\text{CH} & \xrightarrow{2. \text{CH}_3\text{Br}} \text{CH}_3\text{C-CH}_2\text{CO}_2\text{Et} & \text{CH}_3\text{CH}-\text{CHCO}_2\text{Et} & \text{CH}_3 \\
\text{(94)} & & \text{(97)} \\
\text{LiAlH}_4 & & \\
p = \text{TsOH} \\
\end{align*}
\]

The Claisen rearrangement of 93 goes smoothly in good yield, but the generation\(^{72}\) of the ether (93) gave only a 30% yield. The unreacted alcohol (94) can be recycled, but an appreciable amount of alcohol was lost during fractionation. The ortho-ester Claisen rearrangement\(^{73}\) proved superior and gave a high yield of ester (98).
The ester was reduced with lithium aluminum hydride to the alcohol (91), Scheme 20, which was converted to the tosylate and then the nitrile (see Scheme 16). The alcohol was also oxidized with Collin's reagent to the aldehyde (89), but the Wittig homologation was unsuccessful. The desired aldehyde was obtained (Scheme 21) by reduction of the nitrile with lithium triethoxy aluminum hydride (99). The aldehyde (87) was also obtained via the Arndt-Eistert chain extension route, but was not satisfactory because of the number of steps and a poor yield in rearrangement of the diazoketone (102).
The final step, formation of the C₆-C₇ bond, was undertaken. The first attempts to prepare a Grignard reagent from 81 proved abortive. No reaction with magnesium dry ether at room temperature or in refluxing ether was apparent. In THF after several hours at reflux, the magnesium metal had disappeared and some white solid was present in the reaction flask. This material gave the proper color test with Michler's ketone which was interpreted as confirming the presence of the Grignard reagent. 77 No reaction,
however, occurred with the nitrile, and the nitrile was recovered, but the fate of the chloro compound was not ascertained. Similar results were obtained with the bromo analog, even though it should have been a better substrate for preparation of the Grignard reagent.

Since Grignard reactions are often difficult to initiate, this behavior was viewed initially as merely a technical problem.

Secondary bromides are known to form Grignard reagents and THP protecting groups have also been used in the reactions. To overcome this problem we turned to "super magnesium" metal, formed by reducing magnesium chloride with potassium. The resulting magnesium is a finely dispersed material and the reaction conditions call for a large excess of the metal relative to the halide. The presence of the excess metal consequently does not permit
monitoring of the reaction by disappearance of the metal. The reaction was run with the bromo and chloro compounds using the nitrile and also butyraldehyde as acceptors, but all cases produced negative results.

A recent development permits generation of lithium reagents in 70%-80% yield from a 2% sodium-lithium dispersion with various primary and secondary halides. This method was employed with both halides, but again there was no indication of any reaction. As far as we can ascertain there appears to be no precedent for such astounding inactivity of a secondary halide. Considering these improbable results, we were led to make a careful examination of the structural assignments for the halides to insure that the halogen atoms were in fact present.

Although analyses were not obtained for the THP derivatives, the chloroalcohol (80) precursor was analyzed and the results were in excellent agreement with the calculated composition.

\[
\begin{align*}
\text{CH}_3 & \quad \text{Cl} \\
\text{H}_3 & \quad \text{OR} \\
\end{align*}
\]

\[ R = \text{H} \quad (80) \]
\[ R = \text{THP} \quad (81) \]
The nmr spectrum of 81 showed a one hydrogen sextet at 3.97 ppm with a coupling constant of seven Herz which was assigned to $H_a$ and a three hydrogen doublet at 1.50 ppm with a coupling of seven Herz which was assigned to the adjacent methyl group. The nmr of the corresponding tetrahydropyranyl derivative (81) showed a three hydrogen doublet at 1.51 ppm with a coupling of seven Herz, and while the $H_a$ resonance was buried beneath the resonances of other protons, the integration showed it was still present.

The nmr spectrum of the bromo-alcohol (83) displayed a three hydrogen doublet at 1.74 ppm with a coupling of seven Herz which was assigned to the methyl group. The multiplet of proton $H_a$ was shifted downfield further than the CHCl and overlapped the allylic methylene protons $H_b$ and $H_c$ at approximately 4.1 ppm. The spectrum of the tetrahydropyranyl derivative (84) had a three hydrogen doublet at 1.71 ppm with a coupling of seven Herz, but again, the resonance of $H_a$ could not be assigned due to overlap.

Neither compound showed a molecular ion peak in its spectrum, Tables 4 and 5, but in both cases the base peak at 85 and the next two more intense peaks at 109 and 101 appear with
equivalent intensities in both compounds. The base peak at 85 can be attributed to loss of the tetrahydropyranyl ion, and the peak at 101 to the oxytetrahydropyranyl ion. This confirms the presence of the THP group in both compounds. The 109 peak probably has the composition $C_8H_{13}$ and may arise via loss of $HX$ from the allylic ion below. Aside from the three sets of peaks to be discussed
Table 4. Mass Spectrum of (81).

<table>
<thead>
<tr>
<th>m/e</th>
<th>rel. intens.</th>
<th>m/e</th>
<th>rel. intens.</th>
<th>m/e</th>
<th>rel. intens.</th>
<th>m/e</th>
<th>rel. intens.</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>2.3</td>
<td>71</td>
<td>4.1</td>
<td>102</td>
<td>1.9</td>
<td>133</td>
<td>0.5</td>
</tr>
<tr>
<td>--</td>
<td>---</td>
<td>72</td>
<td>0.3</td>
<td>103</td>
<td>3.9</td>
<td>134</td>
<td>0.4</td>
</tr>
<tr>
<td>38</td>
<td>0.1</td>
<td>73</td>
<td>0.5</td>
<td>104</td>
<td>0.7</td>
<td>135</td>
<td>0.8</td>
</tr>
<tr>
<td>39</td>
<td>5.2</td>
<td>74</td>
<td>0.3</td>
<td>105</td>
<td>1.4</td>
<td>136</td>
<td>0.4</td>
</tr>
<tr>
<td>40</td>
<td>0.9</td>
<td>75</td>
<td>2.1</td>
<td>106</td>
<td>0.1</td>
<td>137</td>
<td>1.6</td>
</tr>
<tr>
<td>41</td>
<td>26.0</td>
<td>--</td>
<td>---</td>
<td>107</td>
<td>1.5</td>
<td>138</td>
<td>0.2</td>
</tr>
<tr>
<td>42</td>
<td>2.6</td>
<td>77</td>
<td>2.2</td>
<td>108</td>
<td>3.4</td>
<td>139</td>
<td>0.2</td>
</tr>
<tr>
<td>43</td>
<td>19.6</td>
<td>78</td>
<td>0.4</td>
<td>109</td>
<td>43.9</td>
<td>140</td>
<td>0.2</td>
</tr>
<tr>
<td>44</td>
<td>1.4</td>
<td>79</td>
<td>3.1</td>
<td>110</td>
<td>4.7</td>
<td>141</td>
<td>0.2</td>
</tr>
<tr>
<td>45</td>
<td>0.9</td>
<td>80</td>
<td>0.7</td>
<td>111</td>
<td>4.5</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>--</td>
<td>---</td>
<td>81</td>
<td>8.2</td>
<td>112</td>
<td>0.6</td>
<td>143</td>
<td>0.1</td>
</tr>
<tr>
<td>47</td>
<td>0.1</td>
<td>82</td>
<td>1.6</td>
<td>113</td>
<td>0.3</td>
<td>144</td>
<td>2.0</td>
</tr>
<tr>
<td>--</td>
<td>---</td>
<td>83</td>
<td>4.8</td>
<td>---</td>
<td>---</td>
<td>145</td>
<td>9.1</td>
</tr>
<tr>
<td>51</td>
<td>0.5</td>
<td>84</td>
<td>8.0</td>
<td>115</td>
<td>0.7</td>
<td>146</td>
<td>2.1</td>
</tr>
<tr>
<td>52</td>
<td>0.4</td>
<td>85</td>
<td>100.0</td>
<td>116</td>
<td>0.2</td>
<td>147</td>
<td>3.4</td>
</tr>
<tr>
<td>53</td>
<td>5.6</td>
<td>86</td>
<td>9.4</td>
<td>117</td>
<td>0.3</td>
<td>148</td>
<td>0.6</td>
</tr>
<tr>
<td>54</td>
<td>1.6</td>
<td>87</td>
<td>0.8</td>
<td>118</td>
<td>0.3</td>
<td>149</td>
<td>0.2</td>
</tr>
<tr>
<td>55</td>
<td>22.2</td>
<td>--</td>
<td>---</td>
<td>119</td>
<td>0.7</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>56</td>
<td>8.1</td>
<td>89</td>
<td>2.0</td>
<td>120</td>
<td>0.6</td>
<td>151</td>
<td>0.4</td>
</tr>
<tr>
<td>57</td>
<td>19.1</td>
<td>90</td>
<td>0.2</td>
<td>121</td>
<td>0.6</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>58</td>
<td>1.8</td>
<td>91</td>
<td>2.0</td>
<td>122</td>
<td>0.4</td>
<td>153</td>
<td>0.1</td>
</tr>
<tr>
<td>59</td>
<td>2.2</td>
<td>92</td>
<td>0.3</td>
<td>123</td>
<td>0.7</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>--</td>
<td>---</td>
<td>93</td>
<td>2.3</td>
<td>124</td>
<td>0.5</td>
<td>155</td>
<td>1.8</td>
</tr>
<tr>
<td>63</td>
<td>1.4</td>
<td>94</td>
<td>0.7</td>
<td>125</td>
<td>1.1</td>
<td>156</td>
<td>0.4</td>
</tr>
<tr>
<td>--</td>
<td>---</td>
<td>95</td>
<td>3.7</td>
<td>126</td>
<td>0.2</td>
<td>157</td>
<td>0.2</td>
</tr>
<tr>
<td>65</td>
<td>1.5</td>
<td>96</td>
<td>0.5</td>
<td>127</td>
<td>0.2</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>66</td>
<td>0.9</td>
<td>97</td>
<td>3.9</td>
<td>---</td>
<td>---</td>
<td>159</td>
<td>0.3</td>
</tr>
<tr>
<td>67</td>
<td>29.0</td>
<td>98</td>
<td>1.2</td>
<td>129</td>
<td>0.3</td>
<td>160</td>
<td>0.7</td>
</tr>
<tr>
<td>68</td>
<td>7.2</td>
<td>99</td>
<td>1.6</td>
<td>---</td>
<td>---</td>
<td>161</td>
<td>1.7</td>
</tr>
<tr>
<td>69</td>
<td>13.0</td>
<td>100</td>
<td>0.4</td>
<td>131</td>
<td>0.6</td>
<td>162</td>
<td>0.5</td>
</tr>
<tr>
<td>70</td>
<td>3.3</td>
<td>101</td>
<td>12.4</td>
<td>132</td>
<td>0.1</td>
<td>163</td>
<td>0.6</td>
</tr>
</tbody>
</table>
Table 5. Mass Spectrum of (84).

<table>
<thead>
<tr>
<th>m/e</th>
<th>rel. intens.</th>
<th>m/e</th>
<th>rel. intens.</th>
<th>m/e</th>
<th>rel. intens.</th>
<th>m/e</th>
<th>rel. intens.</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>0.7</td>
<td>78</td>
<td>0.2</td>
<td>109</td>
<td>42.1</td>
<td>150</td>
<td>0.2</td>
</tr>
<tr>
<td>--</td>
<td>---</td>
<td>79</td>
<td>1.9</td>
<td>110</td>
<td>4.7</td>
<td>151</td>
<td>0.3</td>
</tr>
<tr>
<td>39</td>
<td>2.0</td>
<td>80</td>
<td>0.5</td>
<td>111</td>
<td>2.7</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>40</td>
<td>0.7</td>
<td>81</td>
<td>6.2</td>
<td>112</td>
<td>0.4</td>
<td>155</td>
<td>2.0</td>
</tr>
<tr>
<td>41</td>
<td>14.5</td>
<td>82</td>
<td>0.9</td>
<td>---</td>
<td>---</td>
<td>156</td>
<td>0.1</td>
</tr>
<tr>
<td>42</td>
<td>1.2</td>
<td>83</td>
<td>3.1</td>
<td>115</td>
<td>0.1</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>43</td>
<td>8.7</td>
<td>84</td>
<td>4.3</td>
<td>---</td>
<td>---</td>
<td>163</td>
<td>0.1</td>
</tr>
<tr>
<td>44</td>
<td>0.5</td>
<td>85</td>
<td>100.0</td>
<td>119</td>
<td>0.2</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>45</td>
<td>0.2</td>
<td>86</td>
<td>6.3</td>
<td>---</td>
<td>---</td>
<td>165</td>
<td>0.3</td>
</tr>
<tr>
<td>--</td>
<td>---</td>
<td>87</td>
<td>0.5</td>
<td>121</td>
<td>0.8</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>51</td>
<td>0.1</td>
<td>--</td>
<td>---</td>
<td>122</td>
<td>0.2</td>
<td>188</td>
<td>1.6</td>
</tr>
<tr>
<td>52</td>
<td>0.1</td>
<td>91</td>
<td>0.7</td>
<td>123</td>
<td>0.7</td>
<td>189</td>
<td>8.5</td>
</tr>
<tr>
<td>53</td>
<td>3.0</td>
<td>--</td>
<td>---</td>
<td>124</td>
<td>0.4</td>
<td>190</td>
<td>3.1</td>
</tr>
<tr>
<td>54</td>
<td>0.6</td>
<td>93</td>
<td>1.6</td>
<td>125</td>
<td>0.8</td>
<td>191</td>
<td>8.7</td>
</tr>
<tr>
<td>55</td>
<td>14.9</td>
<td>94</td>
<td>0.6</td>
<td>---</td>
<td>---</td>
<td>192</td>
<td>1.6</td>
</tr>
<tr>
<td>56</td>
<td>3.1</td>
<td>95</td>
<td>3.1</td>
<td>127</td>
<td>0.3</td>
<td>193</td>
<td>0.2</td>
</tr>
<tr>
<td>57</td>
<td>12.2</td>
<td>96</td>
<td>0.7</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>58</td>
<td>0.6</td>
<td>97</td>
<td>1.9</td>
<td>133</td>
<td>0.7</td>
<td>204</td>
<td>0.4</td>
</tr>
<tr>
<td>59</td>
<td>0.4</td>
<td>98</td>
<td>0.3</td>
<td>134</td>
<td>0.2</td>
<td>205</td>
<td>1.1</td>
</tr>
<tr>
<td>--</td>
<td>---</td>
<td>99</td>
<td>0.7</td>
<td>135</td>
<td>0.8</td>
<td>206</td>
<td>0.4</td>
</tr>
<tr>
<td>65</td>
<td>0.7</td>
<td>--</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>207</td>
<td>1.0</td>
</tr>
<tr>
<td>66</td>
<td>0.6</td>
<td>101</td>
<td>9.4</td>
<td>137</td>
<td>1.2</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>67</td>
<td>22.4</td>
<td>102</td>
<td>0.6</td>
<td>138</td>
<td>0.1</td>
<td>210</td>
<td>1.0</td>
</tr>
<tr>
<td>68</td>
<td>7.1</td>
<td>103</td>
<td>0.4</td>
<td>139</td>
<td>0.1</td>
<td>211</td>
<td>0.5</td>
</tr>
<tr>
<td>69</td>
<td>9.1</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>70</td>
<td>2.2</td>
<td>105</td>
<td>0.3</td>
<td>146</td>
<td>0.6</td>
<td>291</td>
<td>0.2</td>
</tr>
<tr>
<td>71</td>
<td>2.1</td>
<td>---</td>
<td>---</td>
<td>147</td>
<td>2.6</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>--</td>
<td>---</td>
<td>107</td>
<td>1.3</td>
<td>148</td>
<td>0.8</td>
<td>293</td>
<td>0.1</td>
</tr>
<tr>
<td>77</td>
<td>0.9</td>
<td>108</td>
<td>1.8</td>
<td>149</td>
<td>2.4</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
below, there appear only two peaks with m/e > 130 with intensity greater than 1%, i.e., at m/e 137 and 155 and these appear with equivalent intensities in both spectra. The most significant information about the presence of the halogen atom is derived from three sets of peaks which are shown in Table 6. In each set the intensity ratio is ca. 3:1 for the chloro compound and 1:1 for the bromo, and it is also very striking that the difference m/e(Br) - m/e(Cl) = 44 in every case. Thus, in each case the same organic skeleton has a chlorine present in one and a bromine in the other. These peaks can be at least formally accounted for in the following way. In view of all of the spectral information, we are convinced that the halogen atoms must be present in these compounds.
Table 6. Significant Pairs of Peaks in the Mass Spectra of 81 and 84.

<table>
<thead>
<tr>
<th>Chloride(81)</th>
<th>Bromide(84)</th>
<th>Possible composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>m/e</td>
<td>rel. intens.</td>
<td>m/e</td>
</tr>
<tr>
<td>103</td>
<td>3.9</td>
<td>147</td>
</tr>
<tr>
<td>105</td>
<td>1.4</td>
<td>149</td>
</tr>
<tr>
<td>145</td>
<td>9.1</td>
<td>189</td>
</tr>
<tr>
<td>147</td>
<td>3.4</td>
<td>191</td>
</tr>
<tr>
<td>161</td>
<td>1.7</td>
<td>205</td>
</tr>
<tr>
<td>163</td>
<td>0.6</td>
<td>207</td>
</tr>
</tbody>
</table>

The problem was therefore inferred to be in the formation of the organometallic reagent, and attempts were made to circumvent this difficulty through a modified scheme, which utilized the halide as substrate in a displacement reaction, Scheme 23. Corey and Seebach developed the use of lithium dithianes as reagents for addition of one carbon atom leading directly to an aldehyde. The reagent is also capable of being used as a connecting link joining two halide units with the addition of a carbonyl unit. Seebach has made a disubstituted dithiane from a secondary bromide in 66% yield which appeared to provide a sound basis for the reactions of Scheme 23.

However, in our case reaction of (84) with lithium, dithiane gave what was thought on the basis of nmr to be about 10% of the mono substituted dithiane (104) plus approximately 75% of recovered starting material and additional, unidentified products. This
Scheme 23

\[ R - Br + \text{(84)} \rightarrow \text{(104)} \]

\[ \text{(104)} \rightarrow \text{(83)} \]
conclusion was tenuous, and further experimentation with different reaction conditions including elevation of the reaction temperature and increase of the reaction's duration did not improve on this result. Since formation of (104) was uncertain, and if in fact (104) was present, it was in small amounts, Scheme 23 was not further pursued.

An attempt to use the procedure of Stork and Maldonado\textsuperscript{84} in the modified form developed by Hunig\textsuperscript{87} to use trimethylsiloxy cyanides, which are readily available via the synthesis of Evans,\textsuperscript{85,86} also proved unproductive. Use of the reagent from butyraldehyde as a model (Scheme 24) with (84) gave no reaction, and the bromide was recovered nearly quantitatively.

\textbf{Scheme 24}

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{CHO} + (\text{CH}_3)_3\text{Si} - \text{CN} & \xrightarrow{\text{ZnI}_2} \text{CH}_3\text{CH}_2\text{CH}_2 - \text{CHCN} \\
& \xrightarrow{\text{1. Li N - (i-propyl)_2}} \\
& \xrightarrow{\text{2. Br}} \\
& \text{OTHP}
\end{align*}
\]
Speculation that the inert nature of both 81 and 84 stemmed from the THP protecting group in some unknown fashion, brought us to prepare the methoxymethyl ether (85). Unfortunately it also proved thoroughly reluctant to form any organometallic reagent and on this note we have terminated our attempts to use this route to the desired half molecule (48).

Further deliberation on the problem led to consideration of the inherent nature of the hydroxyl protecting group as the cause of the unusual chemical behavior. It was thought that some group other than the THP ether might improve the bromides reactivity. The acetal (85) was used in an attempt to form a Grignard reagent, but it acted similarly to the THP derivative.

On this unfortunate note, this research was interrupted. It is the author's opinion that selection of the right protecting group and reaction conditions will result in successful completion of the proposed reaction scheme.
EXPERIMENTAL

Ethyl 3-methyl-6-oxo-2-heptenoate (77)

Triethoxyphosphonoacetate was prepared by heating 150 g (0.9 mole) of triethyl phosphite and 150 g (0.9 mole) of ethyl bromoacetate at 80° for 1 hr. A yield of 199.2 g (98%) of the Wittig reagent was obtained after distillation on a spinning band column, bp 80-80.5°/0.2 mm (lit. b p 140°/10 mm). A 50% sodium hydride-mineral oil suspension, 2.4 g (0.05 mole), was washed with pentane and dried under nitrogen. Anhydrous glyme (100 ml) was added and 11.2 g (0.05 mole) of triethoxyphosphonoacetate was dripped into the slurry. After being stirred for 1 hr., the dark red solution was transferred under nitrogen to an addition funnel. The reagent was then added dropwise to a solution of 5.7 g (0.05 mole) of 2,5-hexanedione in 100 ml of dry glyme. The reaction mixture was stirred an additional hour, 100 ml of ether was added followed by a large excess of water. The layers were separated and the aqueous layer extracted with ether. The ether extracts were combined, washed with a saturated salt solution, dried over magnesium sulfate and the solvent evaporated, giving 5.6 g (60%) of crude oil. Gas chromatographic analyses on 5% FFAP and 2% SE-30 columns showed one material made up 95% of the oil. A sample collected
from the glc had spectral properties identical with those of the distilled sample. The crude oil was fractionally distilled on a spinning band column producing 3.4 g (37%) of ethyl 3-methyl-6-oxo-2-heptenoate: bp 84-86⁰/0.5 mm.; nmr (CCl₄) 5 1.24(t, 3H, J=7Hz), 2.00(s, 3H), 2.13(d, 3H, J=1-2Hz), 2.51(m, 4H), 4.12(q, 2H, J=7Hz), 4.47(m, 1H); ir (neat) 1730, 1725, 1645, 1220, 1135, 860 cm⁻¹;

Anal. Calcd for C₁₀H₁₆O₃: C, 65.09; H, 8.75. Found: C, 64.96; H, 8.88.

Ethyl 3-methyl-6-hydroxy-2-heptenoate (78)

Sodium borohydride, 0.413 g (10.8 mmole), was added at 0° to a stirred solution of 4.0 g (21.7 mmole) of ethyl 3-methyl-6-oxo-2-heptenoate in 50 ml of absolute ethanol. The reaction mixture was hydrolyzed with 6 M hydrochloric acid and 20 ml of water. After addition of 100 ml of ether, the layers were separated and the ether solution was washed with sodium bicarbonate and salt solutions, dried over magnesium sulfate, and distilled on a spinning band column, producing 3.2 g (79%) of ethyl 3-methyl-6-hydroxy-2-heptenoate: bp 88-90⁰/0.05 mm; nmr (CCl₄) 5 1.22(t, 3H, J=7Hz), 1.32(d, 3H, J=7Hz), 1.56(q, broad 2H, J=7Hz), 2.17(d, 3H, J=1-2Hz), 2.86(s, broad 1H), 3.83(sextet, 1H, J=7Hz), 4.12(q, 2H, J=7Hz), 5.56(m, 1H); ir 3500, 1725, 1645, 1220, 1140, 1040, 860 cm⁻¹;
Anal. Calcd for C₁₀H₁₈O₃: C, 64.48; H, 9.74. Found: C, 64.28; H, 9.65.

**Ethyl 3-methyl-6-chloro-2-heptenoate (79)**

A solution of 3.2 g (17 mmoles) of ethyl 3-methyl-6-hydroxy-2-heptenoate, 4.5 g (17 mmoles) of triphenylphosphine and 10 ml of carbon tetrachloride was allowed to stand for 3 days. The carbon tetrachloride was removed under reduced pressure and 3.0 g (85%) of ethyl 3-methyl-6-chloro-2-heptenoate was obtained by distillation under reduced pressure in a kugel-rohr apparatus. Nmr (CCl₄)

δ 1.26(t, 3H, J=7Hz), 1.56(d, 3H, J=7Hz), 1.93(t, 2H, J=7Hz), 2.16(d, 3H, J=1-2Hz), 2.31(m, 2H), 4.04(sextet, 1H, J=7Hz), overlapping 4.13(q, 2H, J=7Hz), 5.64(m, 1H); ir (neat) 1725, 1640, 1220, 1150, 1040, 860 cm⁻¹. This material was used directly in the next step without additional purification.

**3-Methyl-6-chloro-2-hepten-1-ol (80)**

A solution of 3.00 g (14.7 mmoles) of ethyl 3-methyl-6-chloro-2-heptenoate in 20 ml of dry ether was added at 0° with stirring to 0.558 g (14.7 mmoles) of lithium aluminum hydride in 25 ml of ether. The reaction mixture was stirred 5 minutes after the addition had been completed, and was then hydrolyzed in the cold with the calculated amount of a saturated ammonium chloride
solution. The liquid was separated by filtration, and the filter cake was dissolved in 10% sulfuric acid and extracted with ether. All ether solutions were combined, washed with a saturated sodium bicarbonate solution then a saturated salt solution, dried over magnesium sulfate and the ether was evaporated. The crude oil was chromatographed on a 10 cm x 3 cm silica column using a 9:1 hexane: ether solution as the eluant, producing 1.8 g (76%) of 3-methyl-6-chloro-2-hepten-1-ol: nmr (CCl₄) 61.50(d, 3H, J=7Hz), 1.65(s, 3H), 1.84(t, 2H, J=7Hz), 2.13(m, 2H), 2.74(broad s, 1H), 3.97(sextet, 1H, J=7Hz), 4.04(d, 2H, J=8Hz), 5.41(broad t, 1H, J=8Hz); ir (neat) 3500, 1640, 1375, 1000, 900, 860 cm⁻¹; Anal. Calcd for C₈H₁₅OCl: C, 59.07; H, 9.29. Found: C, 58.93; H, 9.41.

Tetrahydropyranyl derivative of 3-methyl-6-chloro-2-hepten-1-ol (81)

A sample, 0.5 g (3 mmoles), of 3-methyl-6-chloro-2-hepten-1-ol was dissolved in 7 ml of anhydrous dioxane, and 8 mg (0.04 m mole) of p-toluenesulfonic acid was added followed by 1.0 ml (11 mmoles) of dihydropyran. The reaction mixture was stirred for 3 hrs. and a methanolic ammonia solution was added until the reaction mixture was slightly basic. The solvent was removed under reduced pressure, and the residue was taken up in chloroform. The solution was washed with a saturated sodium bicarbonate
solution, dried over magnesium sulfate and the solvent evaporated. The resulting oil was chromatographed on a 10 cm x 1.5 cm silica column with a 90:10 solution of hexane:ether producing 0.60 g (79%) of the pyranyl derivative. Nmr (CCl₄) δ 1.51(d, 3H, J=7Hz), 1.65(s, 3H), 1.43-2.06(broad m, 8H), 2.21(m, 2H), 3.46-4.08(m, 5H), 4.56 and 4.87(broad singlets, 1H), 5.38(broad t, 1H, J=8Hz); ir (neat) 1650, 1440, 1370, 1340, 1250, 1200, 1120, 1070, 1020, 910, 870, 820 cm⁻¹; mass spectrum: see Table 4.

**Ethyl 3-methyl-6-bromo-2-heptenoate (82)**

A solution of 2.51 g (7.6 mmoles) of carbon tetrabromide in 10 ml of dry benzene was added to a solution of 1.4 g (7.5 mmoles) of ethyl 3-methyl-6-hydroxy-2-heptenoate, 1.99 g (7.6 mmoles) of triphenylphosphine, and 25 ml of dry benzene. The reaction was exothermic and a white salt was produced almost immediately. The reaction mixture was allowed to stand at room temperature for 18 hrs., the benzene was removed under reduced pressure, and the residue was titurated with n-pentane. The pentane solution was filtered and the solvent evaporated, producing 1.5 g (80%) of ethyl 3-methyl-6-bromo-2-heptenoate. Nmr (CCl₄) δ 1.26(t, 3H, J=7Hz), 1.74(d, 3H, J=7Hz), 2.00(m, 2H), 2.16(d, 3H, J=1-2Hz), 2.31(m, 2H), 4.13(q, 2H, J=7Hz), (overlapping broad m, 1H), 5.64(m, 1H); ir (neat) 1725, 1640, 1220, 1150, 1040, 860 cm⁻¹.
3-Methyl-6-bromo-2-hepten-1-ol (83)

A solution of 5.0 g (20 mmoles) of ethyl 3-methyl-6-bromo-2-heptenoate in 50 ml of dry ether was added at 0° to 0.76 g (20 mmoles) of lithium aluminum hydride in 50 ml of ether. The reaction mixture was hydrolyzed with a saturated ammonium chloride solution and worked up in the same manner as the corresponding chloro compound yielding 3.4 g (83%) of 3-methyl-6-bromo-2-hepten-1-ol. Nmr (CCl₄) δ 1.69(d, 3H, J=1-2Hz), 1.74(d, 3H, J=7Hz), 1.95(m, 2H), 2.18(m, 2H), 2.94(broad s, 1H), 4.06(d, 2H, J=6-8Hz), (overlapping m, 1H), 5.41(broad t, 1H, J=6-8); ir 3500, 1640, 1375, 1000, 900, 860 cm⁻¹.

Tetrahydropyranyl derivative of 3-methyl-6-bromo-2-hepten-1-ol (84)

To a solution of 1.0 g (4.8 mmoles) of 3-methyl-6-bromo-1-hepten-1-ol in 2.0 ml of dry dioxane and 10 mg (0.06 mmole) of p-toluenesulfonic acid was added 1.5 ml (17 mmoles) of dihydropyran. The reaction was worked up in the same way as the chloro compound yielding 1.2 g (86%) of the pyranyl derivative. Nmr (CCl₄) δ 1.45-2.05 (broad m, 8H), 1.68(d, 3H, J=1-2Hz), 1.71(d, 3H, J=7Hz), 2.21(m, 2H), 3.46-4.08(m, 5H), 4.54(broad s, 1H), 5.36(broad t, 1H, J=8Hz); ir (neat) 1650, 1440, 1370, 1340, 1250,
1200, 1120, 1070, 1020, 910, 870, 820 cm\(^{-1}\); mass spectrum; see Table 5.

**Methoxy-3-methyl-6-bromo-2-heptynyloxymethane (85)**

A weighed amount of a 50% sodium hydride-mineral oil dispersion, 65 mg (2.7 mmoles), was washed twice with dry ether and suspended in 25 ml of dry ether. The mixture was stirred under nitrogen and 500 mg (2.7 mmoles) of 3-methyl-6-bromo-2-hepten-1-ol was added. The stirring was continued for 5 min. after cessation of gas evolution and 215 mg (2.7 mmoles) of chloromethyl methyl ether was added. The reaction mixture was stirred for 30 min., the precipitate was separated by filtration, and the ether was evaporated, producing 560 mg (90%) of methoxy-3-methyl-6-bromo-2-heptynyloxymethane. NMR (CCl\(_4\)) \(6\ 1.69(d, 3H, J=1.2\text{Hz})\), 1.74(d, 3H, \(J=7\text{Hz}\)), 1.95(m, 2H), 2.18(m, 2H), 3.29(s, 3H), 4.03(m, 3H), 4.52(s, 2H), 5.34(broad t, 1H, \(J=6-8\text{Hz}\)); IR (neat) 1650, 1440, 1340, 1240, 1130, 1040, 910, 860.

**2-Methyl-2-buten-1-ol (94)**

Sodium metal, 46 g (2.0 moles), was added to 1 l of absolute ethanol and 260 g (2.0 moles) of ethyl acetoacetate was then added dropwise. Then 200 g (2.1 moles) of bromomethane was bubbled into the solution. The reaction mixture was separated by filtration.
and the solid was treated with 600 ml of water and 10 ml of concentrated hydrochloric acid. The filtrate was distilled until most of the ethanol had been removed, dilute hydrochloric acid was added to the residue, and the aqueous layer was extracted with ether. The ether solution was dried over calcium chloride, and the solvent was evaporated. Distillation on a spinning band column produced 234 g (82%) of ethyl 2-methyl-3-oxobutanoate, bp 175-176° (lit. 89 bp 176-180°).

A solution of 71 g (0.5 mole) of the keto-ester in 500 ml of absolute ethanol was stirred in an ice bath while 9.4 g (0.25 mole) of sodium borohydride was added. The reaction mixture was stirred at room temperature for 1 hr., and the mixture was then hydrolyzed with 100 ml of 10% hydrochloric acid. The ethanol was removed by distillation, and the residue was extracted with ether. The ether solution was dried with calcium chloride, and the ether evaporated. Distillation on a spinning band column yielded 57 g (79%) of ethyl 2-methyl-3-hydroxybutanoate, bp 185-186° (lit. 90 bp 186.8).

A solution of 40.8 g (0.28 mole) of the hydroxy ester, 25 ml of benzene and 4.0 g of p-toluene sulfonic acid was heated to reflux for 18 hrs. with azeotropic removal of water. The benzene was distilled and fractionation produced 30 g (84%) of ethyl 2-methyl-2-butenoate, bp 150-152° (lit. 91 bp 152°).
A solution containing 27.1 g (0.215 mole) of the unsaturated ester in 100 ml of anhydrous ether was added to 8.5 g (0.215 mole) of lithium aluminum hydride in 200 ml of ether, which was cooled in an ice bath. Addition of a saturated ammonium chloride solution produced a solid which was removed by filtration. The ether was evaporated and 13.2 g (73%), (40% overall), of 2-methyl-2-butenol, bp 134-136° (lit. 92 bp 138°), was obtained by distillation on a spinning band column.

Ethyl 3, 4-dimethyl-4-pentenoate (98)

The procedure for the Claisen rearrangement of Johnson was followed. A 5.74 g (66.8 mmoles) sample of 2-methyl-2-butenol was added to 75.8 g (0.47 mole) of triethyl orthoacetate and 0.296 g (4.0 mmoles) of propionic acid. The reaction mixture was heated at 140° for 1 hr. and the ethanol was distilled during this period. The unreacted triethyl orthoacetate was recovered by fractional distillation on a spinning band column, and 10.0 g (96%) of ethyl 3, 4-dimethyl-4-pentenoate, bp 44-45°/4.5 mm, was isolated. Nmr (CCl₄) δ 1.05(d, 3H, J=7Hz), 1.23(t, 3H, J=8Hz), 1.62(d, 3H, J=1Hz), 2.27(m, 2H), 2.60(m, 1H), 4.09(q, 2H, J=8Hz), 4.71(m, 2H); ir (neat) 1740, 1640, 1275, 1170, 890 cm⁻¹; Anal. Calcd for C₉H₁₆O₂: C, 69.19; H, 10.32. Found: C, 68.98; H, 10.18.
3, 4-Dimethyl-4-penten-1-ol (91)

A solution of 3.45 g (22.1 mmole) of ethyl 3, 4-dimethyl-4-pentenoate in 20 ml of ether was added to 0.84 g (22.1 mmole) of lithium aluminum hydride in 25 ml of ether which was cooled in an ice bath. The reaction mixture was hydrolyzed with 2 ml of water and 10% sulfuric acid was added until all of the inorganic salts dissolved. The layers were separated and the aqueous layer extracted with ether. The ethereal solution was washed with a saturated sodium bicarbonate solution, then a saturated salt solution, and dried over magnesium sulfate. The ether was evaporated, giving 4.1 g (91%) of 3, 4-dimethyl-4-pentenol. Nmr (CCl₄) δ

1.03(d, 3H, J=7Hz), 1.57(m, 2H), 1.65(d, 3H, J=1Hz), 2.31(sextet, 1H, J=7Hz), 3.52(t, 2H, J=7Hz), 3.66(broad s, 1H), 4.71(m, 2H);

ir (neat) 3450, 1640, 1050, 890 cm⁻¹; Anal. Calcd for C₇H₁₄O:
C, 74.95; H, 10.78. Found: C, 74.86; H, 10.87.

4, 5-Dimethyl-5-hexenonitrile (88)

A 2.0 g (18 mmole) sample of 3, 4-dimetyl-4-penten-1-ol was added to 55 ml of pyridine and 6.1 g (32 mmole) of p-toluenesulfonyl chloride. The reaction mixture was stirred at room temperature for 20 hrs., then was poured into 100 ml of ice water. The organic products were taken up in benzene, and the combined
benzene extracts were washed with 1 M hydrochloric acid and a saturated salt solution. The benzene solution was dried over magnesium sulfate and the benzene removed at room temperature under reduced pressure. Nmr (CCl₄) δ 1.02 (d, 3H, J=7Hz), 1.60 (d, 3H, J=1Hz), 1.68 (t, 2H, J=7Hz), 2.22 (m, 1H), 2.46 (s, 3H), 3.92 (t, 2H, J=7), 4.64 (m, 2H), 7.52 (q, 4H); ir (neat) 1640, 1460, 1190, 970, 890, 830 cm⁻¹.

A solution containing 4.7 g (17.5 mmoles) of the tosylate in 60 ml of anhydrous dimethyl sulfoxide was added to 1.47 g (30 mmoles) of sodium cyanide. The reaction mixture was stirred at 90° under nitrogen for 5 hrs., then was poured into 100 ml of a 50% ammonium chloride solution. The mixture was extracted with methylene chloride, and the extracts were washed with water. The solution was dried over magnesium sulfate and the solvent evaporated to yield 2.0 g of 4,5-dimethyl-5-hexenonitrile. The crude material was distilled in a kugelrohr apparatus to produce 1.6 g (74% overall). Nmr (CCl₄) δ 1.07 (d, 3H, J=7Hz), 1.66 (d, 3H, J=1Hz), 1.72 (t, 2H, J=7), 2.32 (m, 3H), 4.82 (m, 2H); ir (neat) 2260, 1640, 890 cm⁻¹; Anal. Calcd for C₈H₁₃N: C, 77.99; H, 10.64. Found: C, 77.82; H, 10.56.

4,5-Dimethyl-5-hexenal (87)

Lithium triethoxyaluminum hydride⁷⁴ was prepared by adding
290 mg (3.29 mmol) of ethyl acetate under nitrogen to a stirred solution of 83 mg (2.2 mmol) of lithium aluminum hydride in 10 ml of dry ether at 0°C. A sample of 4, 5-dimethyl-5-hexenonitrile, 270 mg (2.19 mmol), was added at 0°C and the solution was stirred for 30 min. The reaction mixture was hydrolyzed with 5% sulfuric acid, and the aqueous layer was extracted with ether. The ether extracts were combined, washed with a saturated sodium bicarbonate solution, and dried over magnesium sulfate. The solvent was evaporated producing 230 mg of a 9:1 mixture of 4, 5-dimethyl-5-hexenal to starting nitrile; adjusted yield 82%. NMR (CDCl₃) δ 1.07 (d, 3H, J=7Hz), 1.65 (s, 3H), (overlapping m, 2H), 2.6 (broad s, 2H), 9.68 (t, 1H, J=1-2Hz); IR (neat) 1730, 1640, 890 cm⁻¹; Anal. Calcd for C₈H₁₄O: C, 76.14; H, 11.18. Found: C, 76.11; H, 11.21.

The aldehyde, 4, 5-dimethyl-5-hexenal, was also prepared by lithium aluminum hydride reduction of methyl 4, 5-dimethyl-5-hexenoate (103) followed by oxidation with Collin's reagent. The general procedures for these reactions followed those used in preparation of (91) and (38) respectively.

3, 4-Dimethyl-4-pentenal (89)

A solution of 2.28 g (20 mmol) of 3, 4-dimethyl-4-penten-1-ol in 10 ml of methylene chloride was added to 25 g (0.11 mole) of
Collin's reagent\textsuperscript{47} in 300 ml of methylene chloride. The reaction mixture was stirred for 1 hr, and the methylene chloride was decanted. The residue was washed with ether which was then combined with the methylene chloride. The combined solution was washed with 5\% sodium hydroxide followed by 10\% hydrochloric acid, saturated sodium bicarbonate solution, and a saturated salt solution. The organic solution was dried over magnesium sulfate and the solvent was evaporated. The crude aldehyde was distilled in a kugelrohr apparatus to produce 1.7 g (79\%) of 3, 4-dimethyl-4-pentenal. Nmr (CCl\textsubscript{4}) \delta 1.07(d, 3H, J=7Hz), 1.72(d, 3H, J=1Hz), 2.42 (m, 2H), 2.73(sextet, 1H, J=7Hz), 4.72(broad s, 2H), 9.63(t, 1H, J=1-2Hz); ir (neat) 1730, 1640, 1390, 895 cm\textsuperscript{-1}; Anal. Calcd for C\textsubscript{7}H\textsubscript{12}O: C, 74.95; H, 10.78. Found: C, 74.86; H, 10.87

3, 4-Dimethyl-4-pentenoic acid (100)

A mixture of 1.21 g (7.7 mmoles) of ethyl 3, 4-dimethyl-4-pentenoate, 12 ml of 95\% ethanol and 0.925 g (16 mmoles) of potassium hydroxide was refluxed for 3 hrs.\textsuperscript{93} Approximately 9 ml of ethanol was distilled and 50 ml of water was added. The reaction mixture was titrated with 5 N sulfuric acid to the end point of Congo red, and then was extracted with n-hexane. The hexane extracts were dried over anhydrous sodium sulfate and the solvent flash distilled, yielding 0.86 g (89\%) of 3, 4-dimethyl-4-pentenoic acid.
Nmr (CCl₄) δ 1.09(d, 3H, J=7Hz), 1.72(d, 3H, J=1Hz), 2.36(m, 2H), 2.64(m, 1H), 4.73(m, 2H), 11.44(s, 1H); ir (CCl₄) 1750, 1400, 1340, 890 cm⁻¹.

3,4-Dimethyl-4-pentenoyl Chloride (101)

A solution of 0.86 g (6.9 mmoles) of 3,4-dimethyl-4-pentenoic acid in 5 ml of anhydrous benzene was added to 1.8 g (13.8 mmoles) of oxalyl chloride and evolution of gas was noted. The reaction mixture was then heated to 60° for 2 hrs. and the benzene and excess oxalyl chloride removed at reduced pressure. The remaining oil was evaporatively distilled in a kugelrohr apparatus, producing 0.51 g (52%) of 3, 4-dimethyl-4-pentenoyl chloride. Nmr (CCl₄) δ 1.09(d, 3H, J=7Hz), 1.75(d, 3H, J=1Hz), 2.64(m, 1H), 2.83(m, 2H), 4.74(m, 2H); ir (neat) 1775, 890 cm⁻¹.

Methyl 4,5-dimethyl-5-hexenoate (103)

The diazomethyl ketone was prepared by the addition of 0.51 g (3.59 mmoles) of 3,4-dimethyl-4-pentenoyl chloride in 3 ml of anhydrous ether to an ethereal diazomethane solution, which was prepared from 1.54 g (9.0 mmoles) of N-nitrosomethylurea and potassium hydroxide. The ether was removed under reduced pressure and the vapor was passed through a propionic acid trap. The pot residue was treated with 0.2 ml of a solution of 0.91 g
(4 mmoles) of silver benzoate, 12 ml of triethylamine, and the mixture was heated to reflux for 1 hr. Activated charcoal was added, the reaction mixture was filtered, and the product was distilled, yielding 0.22 g (40%) of methyl 4,5-dimethyl-5-hexenoate.

Nmr (CCl₄) δ 1.06(d, 3H, J=7Hz), 1.66(d, 3H, J=1Hz), overlapping 1.72(m, 2H), 2.18(m, 3H), 3.60(s, 3H), 4.62(m, 2H); ir (neat) 1740, 1640, 1275, 1180, 890 cm⁻¹.

4,7-Dimethyl-1,3-dioxacycloheptane (71) (4,7-dimethyl-tetrahydrodioxepin)

Method A: A solution of 1.2 g (10 mmoles) of 2,5-hexanediol in 25 ml of anhydrous ether was stirred in a dry-ice acetone bath under nitrogen. A 2 M solution of n-butyl lithium in hexane, (5 mmoles), was added dropwise and the reaction mixture was allowed to warm to room temperature, stirred for 30 min., and then recooled in the bath. Chloromethyl methyl ether (0.4 g, 5 mmoles) was added and the reaction mixture was again warmed to room temperature. After 10 min, the solution was treated with 10 ml of water, the layers were separated, and the ether layer washed with 5 ml of a saturated salt solution, dried over magnesium sulfate and evaporated yielding 0.40 g (61%) of 4,7-dimethyl-1,3-dioxacycloheptane. Similar results were obtained when tetrahydrofuran: hexamethylphosphoramide was used as the solvent, and in
Method B: A solution containing 1.2 g (10 mmoles) of 2,5-hexanediol in 25 ml dry ether was stirred at room temperature with 0.5 g (5 mmoles) of triethylamine under nitrogen. To this was added 0.4 g (5 mmoles) of chloromethyl methyl ether and the mixture was stirred 30 min. The reaction mixture was hydrolyzed with water, washed with 5% sodium hydroxide, dried over magnesium sulfate, and the solvent was evaporated to yield 0.48 g (74%) of 4,7-dimethyl-1,3-dioxacycloheptane, \(\text{nmr (CDCl}_3\} \delta 1.22(\text{d, 6H, J=Hz}), 1.64(\text{m, 4H}), 3.88(\text{broad m, 2H}), 4.82(\text{s, 2H}); \text{ir (neat) 1450, 1370, 1280, 1150, 1110, 1070, 1020 cm}^{-1}\).

4,7-Dimethyl-2-phenyl-1,3-dioxacycloheptane (72) (4,7-dimethyl-2-phenyl tetrahydrodioxe pin)

A solution of 11.8 g (0.1 mole) of 2,5-hexanediol and 10.6 g (0.1 mole) of benzaldehyde in 100 ml of benzene was added to 0.1 g (0.5 mmole) of p-toluenesulfonic acid and the solution was heated at reflux for 20 hrs. with azeotropic removal of water. The benzene was distilled and 10.2 g (71% adjusted) of 4,7-dimethyl-2-phenyl-1,3-dioxacycloheptane, bp 84-86\(^\circ\)/0.8 mm, distilled on a spinning band column. In addition, 4.0 g of starting diol was recovered. \(\text{nmr (CDCl}_3\} \delta 1.36(\text{d, 6H, J=7Hz}), 1.87(\text{m, 4H}), 4.20(\text{broad m, 2H}), 5.57, 5.78, 5.92(\text{s, 1H}), 7.42(\text{m, 5H}); \text{ir (neat)\)
1690, 1450, 1370, 1280, 1200, 1140, 1100, 1060, 1010, 945, 930, 900, 880, 855, 835, 755, 710 cm$^{-1}$.

5-Benzyl peroxy-2-hexanol (73)

A solution of 3.5 g (16.2 mmole) of 4,7-dimethyl-2-phenyl-1,3-dioxacycloheptane, 30 ml of anhydrous benzene, and 11.5 g (16.2 mmole) of a 20% solution of diisobutylaluminum hydride in n-hexane was heated to reflux under nitrogen for four days. The reaction mixture was cooled to room temperature and hydrolyzed with 5% sulfuric acid. The aqueous layer was extracted with ether. The organic solution was washed with a saturated sodium bicarbonate solution, dried over magnesium sulfate, and the solvent was evaporated. Fractional distillation gave 0.5 g of 4-benzyloxy-2-hexanol and 2.1 g of starting material. Nmr (CDCl$_3$) δ 1.17 (d, 3H, J=7Hz), 1.26 (d, 3H, J=7Hz), 1.55 (m, 4H), 2.26 (s, 1H), 3.65 (sextet-broadened, 2H, J=7Hz), 4.42 and 4.62 (AB pattern, J=11Hz), 7.38 (broadened s, 5H); ir (neat) 3500, 1470, 1360, 1200, 1060, 935, 735, 700 cm$^{-1}$.

2-Benzyl peroxy-5-bromohexane (74)

A solution of 700 mg (2.7 mmole) of triphenylphosphine in 5 ml of dry benzene was added to 540 mg (2.6 mmole) of 5-benzyloxyhexan-2-ol in 20 ml of benzene. Immediately after the
addition, a solution of 890 mg (2.7 mmoles) of carbon tetrabromide in 5 ml of benzene was added, and the reaction mixture was allowed to stand at room temperature for 48 hrs. The benzene was removed under reduced pressure and the remaining material was titurated twice with 50 ml portions of pentane. The pentane was removed, producing 610 mg (86%) of 2-benzyloxy-5-bromo-hexane, nmr 

$\text{CCl}_4$: $1.10 (d, 3\text{H}, J=7\text{Hz})$, $1.59 (d, 3\text{H}, J=7\text{Hz})$, (m, overlapping 4H), $4.30$ and $4.50 (AB\text{ pattern}, 2\text{H}, J=11\text{Hz})$, $7.26$ (broadened s, 5H); ir (neat) 1470, 1360, 1270, 1100, 730, 680 cm$^{-1}$.

5-Benzyloxy-2-hexanone (75)

As aluminum chloride, 2.54 g (19 mmoles), in 25 ml of dry ether was being stirred in an ice-salt bath under nitrogen, a solution of 0.175 g (4.63 mmoles) of lithium aluminum hydride in 10 ml of dry ether was added dropwise and the solution was stirred an additional 30 min. A solution of 2.0 g (9.26 mmoles) of 4,7-dimethyl-2-phenyl-1,3-dioxacycloheptane in 10 ml of ether was then added and the reaction mixture was heated to reflux for 1.5 hrs. The solution was cooled and was then treated with 1 ml of water followed by 30 ml of 10% sulfuric acid and finally an additional 30 ml of water. The layers were separated, and the aqueous layer was extracted with ether. The ether extracts were combined, washed with saturated sodium bicarbonate solution, saturated salt solution,
and dried over potassium carbonate. Fractional distillation produced
0.5 g of 4-benzyloxy-2-hexanone and 0.3 g of starting material. Nmr
(CDC13) δ 1.22(d, 3H, J=7Hz), 1.83(q, 2H, J=7Hz), 2.09(s, 3H), 2.54
(t, 2H, J=7Hz), 3.56(sextet, 1H, J=7Hz), 4.42 and 4.62(AB pattern,
2H, J=11Hz), 7.38(broadened s, 5H); ir (neat) 1730, 1450, 1360,
1100, 1060, 790, 700 cm⁻¹.
BIBLIOGRAPHY


15. D. Baker, personal communication, Stauffer Chemical Co., Richmond, California.
42. N. Zelinsky and A. Gorsky, ibid., 41, 2630 (1908).
45. Authentic sample provided by Mr. William Whalley.
54. A. Traverse, Micropaleontology, 1, 343 (1955).
65. K. W. Wilson, J. D. Roberts, and W. G. Young, ibid., 72, 215 (1950) and earlier papers in this series.


80. S. E. Wilson, personal communication, Oregon State University, Corvallis, Oregon.


95. F. Arndt, *ibid.*, pp. 165-166.


