STEREOSELECTIVE TOTAL SYNTHESES OF (±)-LONGICYCLENE, (±)-LONGICAMPHOR, AND (±)-LONGIBORNEOL

A Dissertation

Presented to

the Faculty of the Department of Chemistry

College of Arts and Sciences

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

---

by

Roland Lawrence Walters

May 1974

FOR MARIAN, MARGE, AND ED

ACKNOWLEDGMENT

This work would not have been possible without the encouragement of several people. The assistance of Julie Norris, both before and during my graduate career, has been invaluable. The excellent direction and guidance of Dr. Steven C. Welch during the course of this study has provided an incentive for my continuing development as an organic chemist. The patience and help of Marian, my wife, has made this work a pleasant task. To these friends I would like to extend my deepest appreciation.

I also appreciate the assistance of Dr. M. R. Willcott and Bill Bearden for their instruction on the use of shift reagents. The author wishes to acknowledge the Robert A. Welch Foundation for its support of this research and the National Aeronautics and Space Administration for a predoctoral traineeship.

STEREOSELECTIVE TOTAL SYNTHESES OF (±)-LONGICYCLENE, (±)-LONGICAMPHOR, AND (±)-LONGIBORNEOL

An Abstract of

A Dissertation

Presented to

the Faculty of the Department of Chemistry

College of Arts and Sciences

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

---

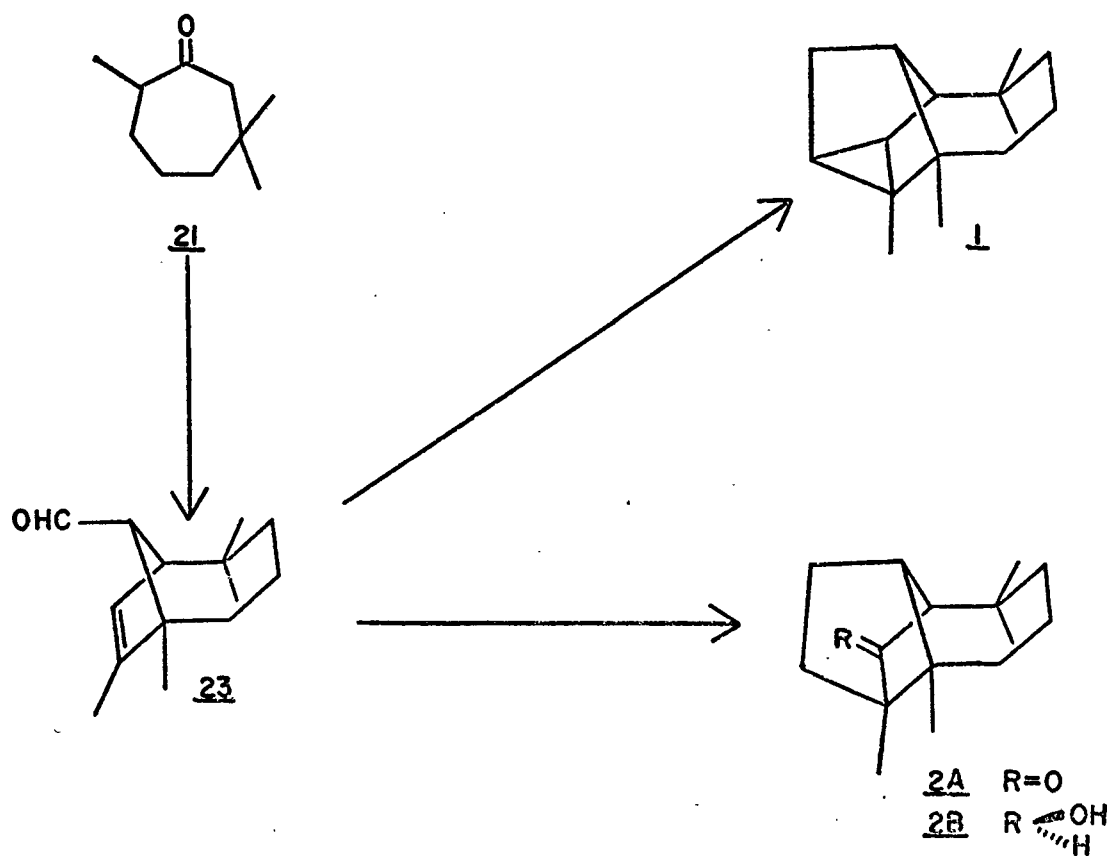
by

Roland Lawrence Walters

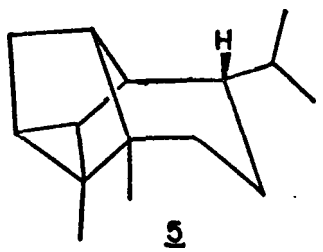
May 1974

ABSTRACT

Stereoselective total syntheses of (±)-longicyclene (1), (±)-longicamphor (2A), and (±)-longiborneol (2B) from tetrahydroeucarvone (21) via intermediate aldehyde 23 are discussed. The synthetic approach contains a reductive-cyclization reaction utilizing diisobutylaluminum hydride to convert an enol-lactone to a bicyclic ketol. A new sequence of reactions is used to convert a cyclopropyl ketone intermediate to (±)-longicyclene (1) without fragmentation.



An attempt to apply a modification of the synthetic scheme used in the (±)-longicyclene synthesis to the synthesis of (+)-cyclosativine (5) is also presented.



5

TABLE OF CONTENTS

TABLE OF CONTENTS

TABLE OF CONTENTS CONTINUED

CHAPTER Page

TABLE OF CONTENTS CONTINUED

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1

INTRODUCTION

INTRODUCTION

The sesquiterpene class of terpenoids contains a fascinating variety of intricately bridged structures. This particular class of natural products is characterized by a fifteen-carbon framework which nearly always can be dissected into isoprene units. Some of the more elaborately bridged members of this class are included in the longibornane and sativene groups (Figures 2-4): namely longicyclene (1), longifolene (3), longicamphor (2A), longiborneol (2B), culmorin (16), sativene (4), and cyclosativene (5).

The biogenetic precursor for these natural products is cis, trans-farnesyl pyrophosphate. This compound is synthesized in living organisms via enzymatic processes from acetyl-coenzyme A and acetoacetyl-coenzyme A.[1-4] An ionization to cation 6 (Figures 1-4) is thought to be the initial step. Cation 6 can then interact with the terminal olefin to give nonclassical cation 7. A 1,3-hydride shift in resonance form 8 to cyclic cation 9 ultimately yields the longibornane system,[5] while a similar shift in resonance form 10 to cyclic cation 11 could lead to the sativene series. Cations 9 and 11 can interact with the isolated double bonds to give the bicyclic cations 12 and 13.[5-7] These bicyclic cations interact with the π system of the olefin to give the nonclassical forms 14 and 15. The stereospecific attack of water on cation 14 gives longiborneol (2B). Longiborneol can then undergo enzymatic oxidation to give either longicamphor (2A) or culmorin (16).

Wagner-Meerwein rearrangements of resonance forms 14 and 15 to the tricyclic cations 17 and 18 yield longifolene (3) and sativene (4),

FIGURE I.

BIOLOGICAL ORIGINS OF THE LONGIBORNANE AND SATIVENE GROUPS

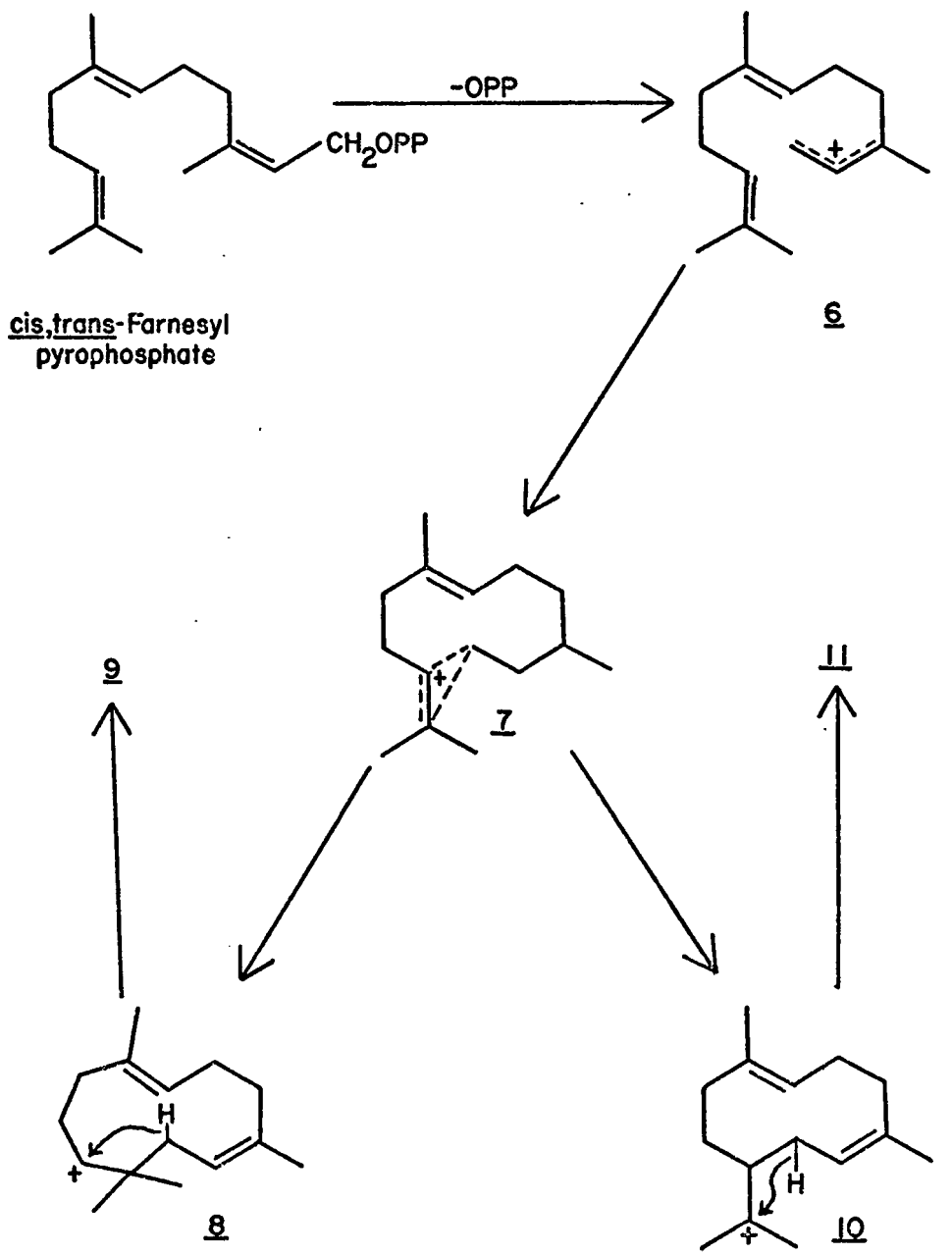


FIGURE 2.

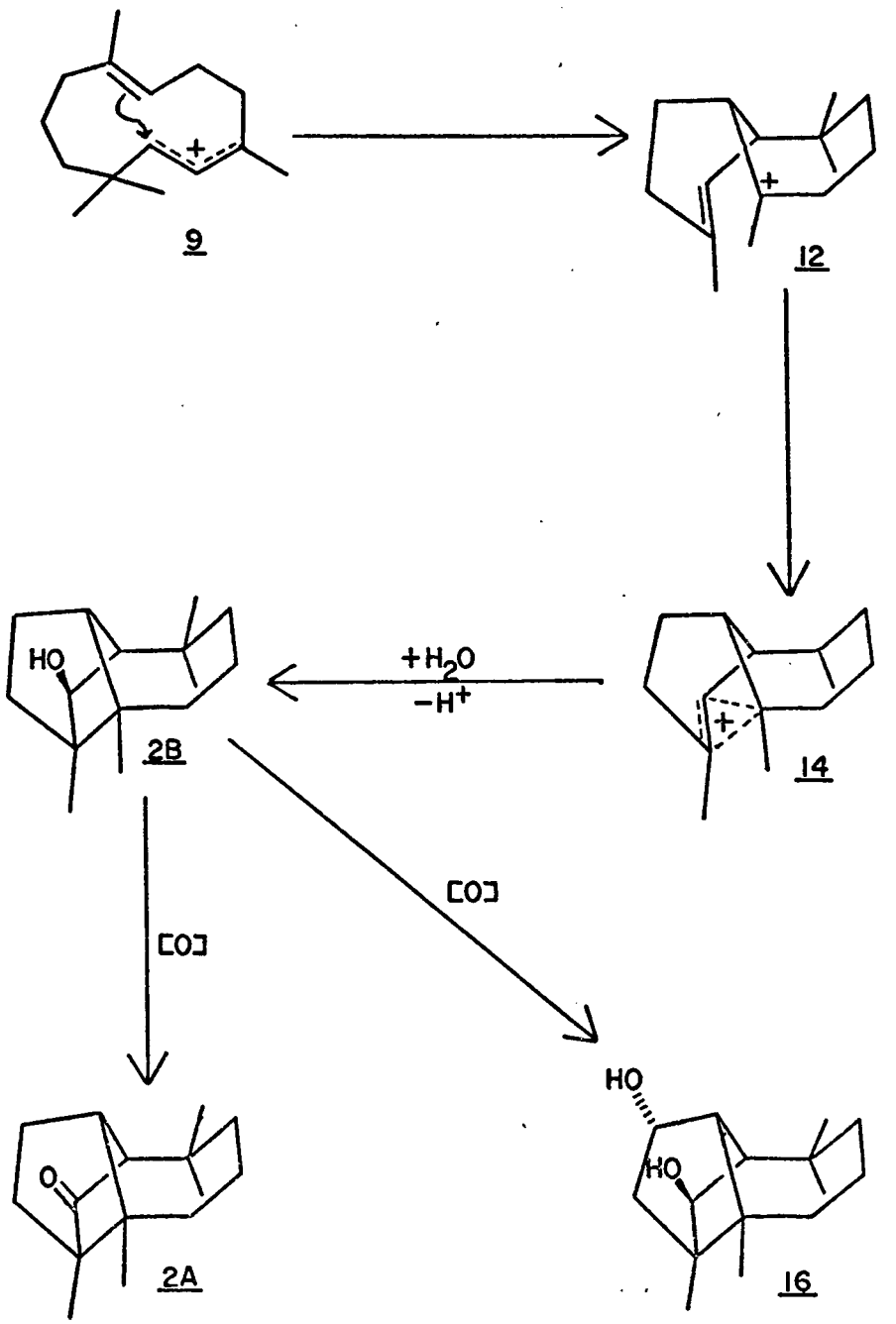


FIGURE 3.

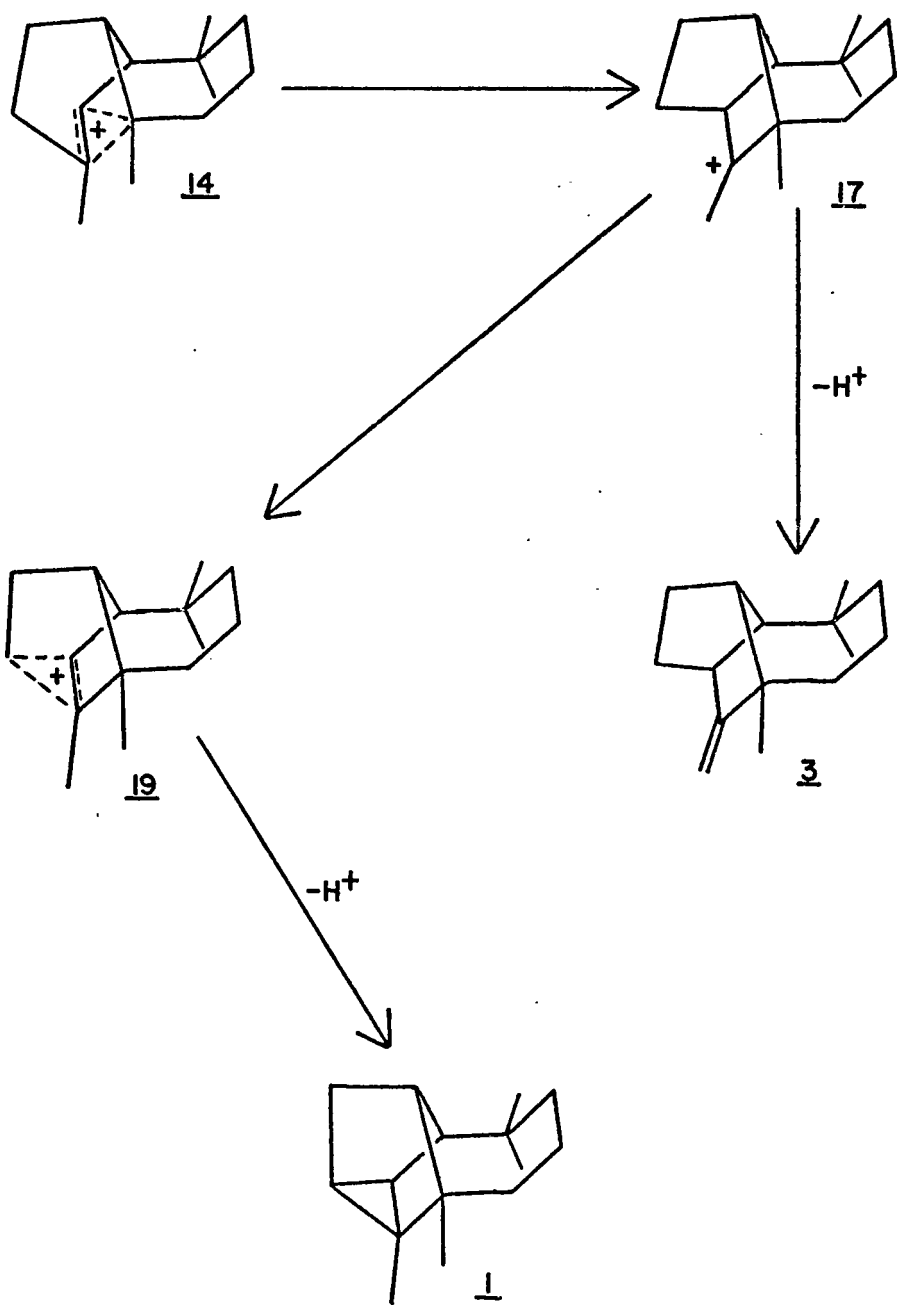
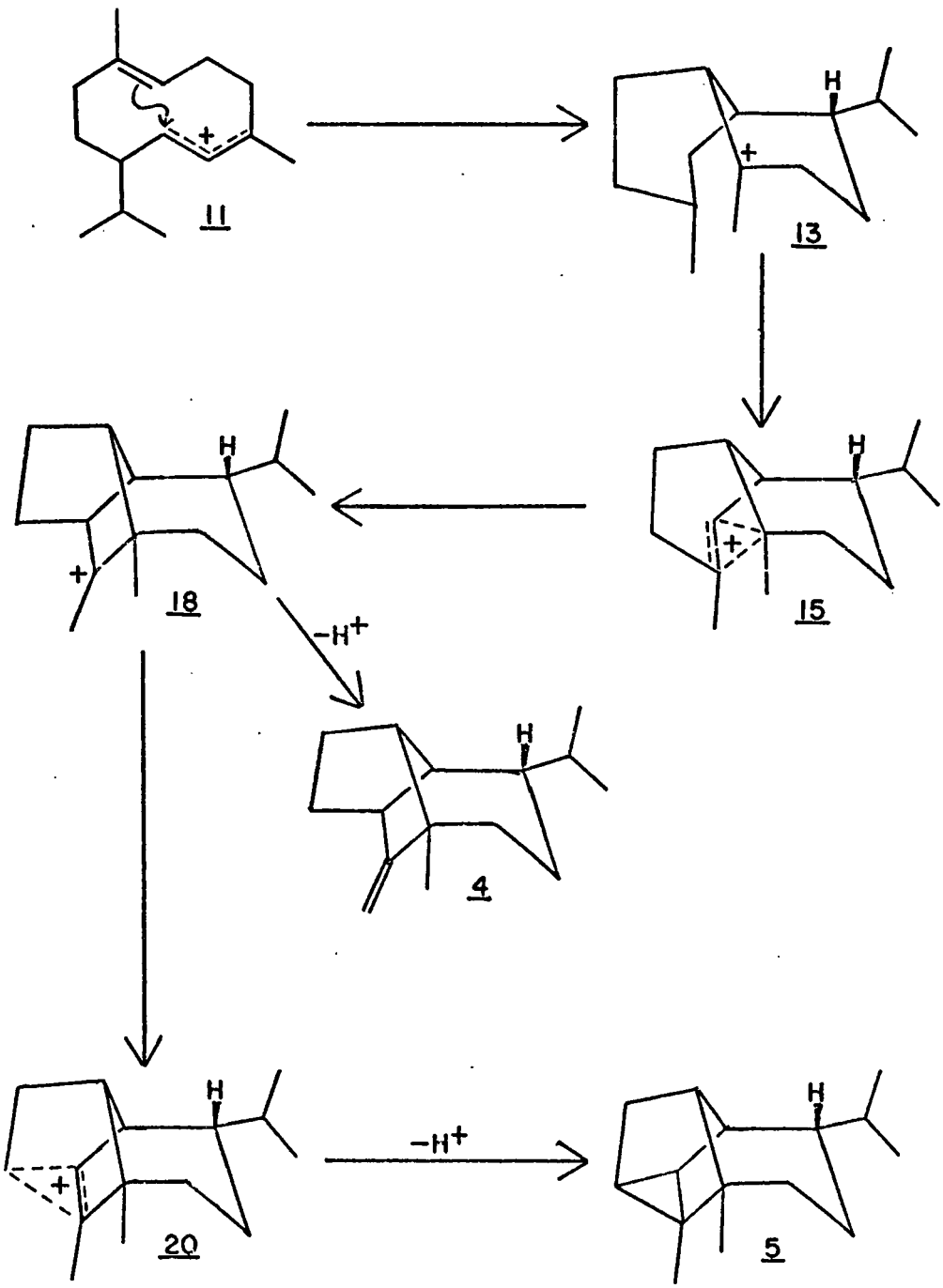


FIGURE 4.



respectively, upon deprotonation. Deprotonation of the nonclassical forms 19 and 20 leads to longicyclene (1) and cyclosativene (5). These suggested transformations allow a broader appreciation for the relationships within and between the sativene and longibornane groups.

Longicyclene, a tetracyclic hydrocarbon, was isolated from the turpentine oil of Pinus longifolia. Structure 1 was assigned from its elemental composition ($C_{15}H_{24}$), its spectral properties, and an acid-catalyzed conversion to longifolene (3).[8,9] Cyclosativene (5), another tetracyclic hydrocarbon, was isolated from Abies magnifica, Murray (the California red fir). Its structure was assigned via spectral and physical properties and the acid-catalyzed conversion to sativene.[10] The unique nature of these two tetracyclic structures provides a significant challenge to the synthetic organic chemist. The resemblance of the two ring systems suggests similar synthetic approaches to the two molecules.

Longiborneol (2B) was isolated from Cupressus macrocarpa (the Monterey cypress).[11,12] Its structure was assigned from physical and chemical characteristics. Longicamphor (2A) is the corresponding oxidation product of longiborneol. Longiborneol (2B) and longifolene (3) were synthesized by Corey and coworkers via an elegant scheme in 1964. They were able to construct both natural products from the Wieland-Meisher diketone via a tricyclic diketone.[13] A synthesis of culmorin has also been reported recently.[14]

The novel structures of longicyclene (1), longicamphor (2A), longiborneol (2B), and cyclosativene (5) together with the stereochemistry of these compounds are significant as synthetic goals. A number of considerations are involved in the stereoselective synthesis of these

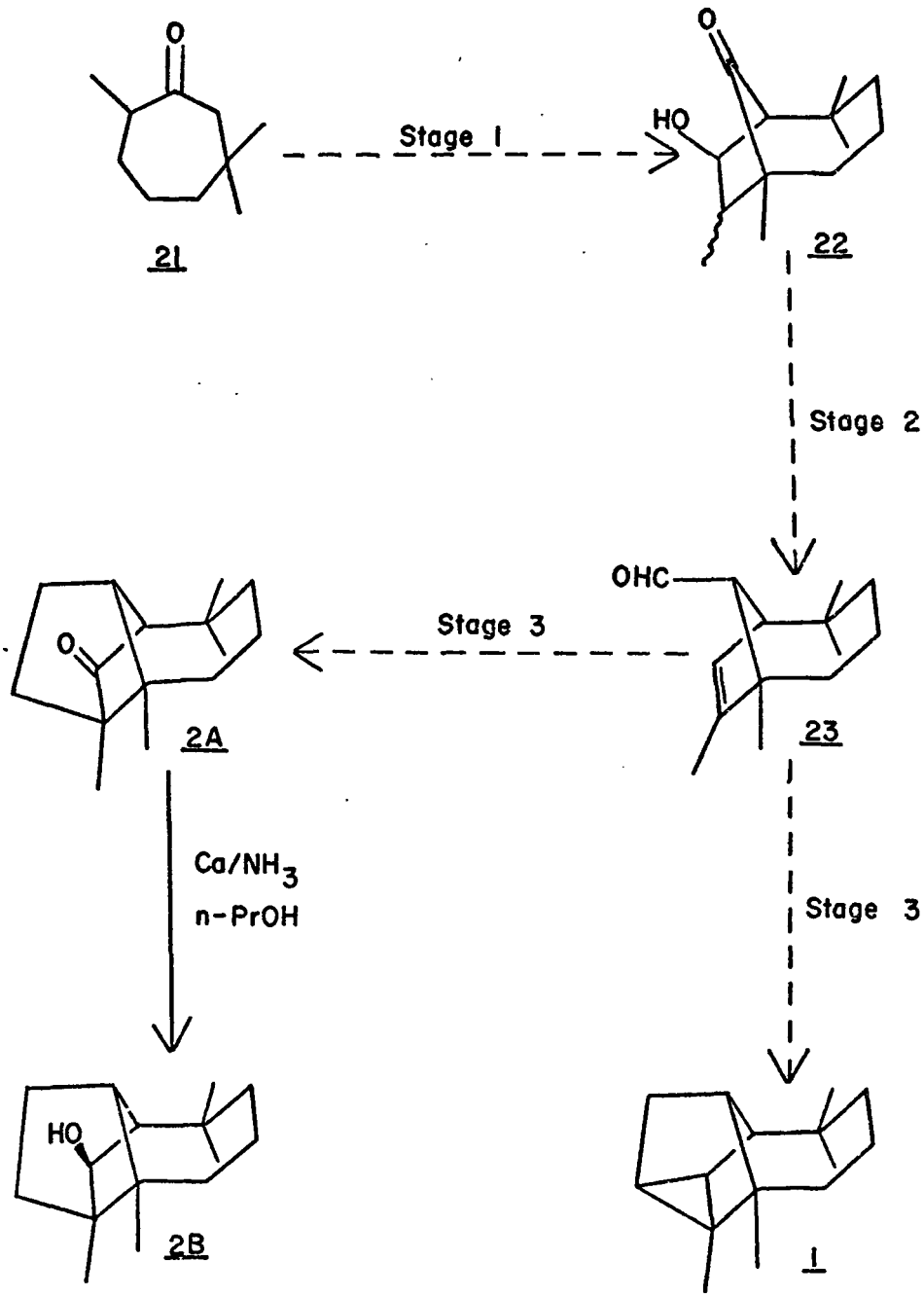
complex sesquiterpenes. First, readily available starting materials must be selected. Second, a general synthetic scheme must be proposed which takes into account such factors as functionality, presence of chiral centers, and the stability of intermediates. Finally, the whole sequence must be accomplished in a limited number of synthetic steps.

The starting material chosen for the synthesis of longicyclene (1), longiborneol (2B), and longicamphor (2A) is 2,6,6-trimethylcycloheptanone (21). This material can be readily prepared from carvone via literature procedures.[15,16] The synthesis of the longibornane group of sesquiterpenes is divided into three stages. The first stage of the synthetic scheme (Figure 5) involves the construction of a bicyclo[4.2.1] nonane derivative (22) by the formation of a two-carbon bridge between positions two and seven of ketone 21. The second stage consists of converting the bicyclic compound 22 to olefinic aldehyde 23, after which the synthesis of longicyclene diverges from that of longicamphor and longiborneol. The third stage consists of conversion of the bicyclic olefinic aldehyde 23 to the respective natural products.

The synthetic scheme for cyclosativene utilizes (+)-carvomenthone as the starting material. The proposed synthetic route is completely analogous to that used in the synthesis of longicyclene.

FIGURE 5.

PLANNED SYNTHETIC SCHEME

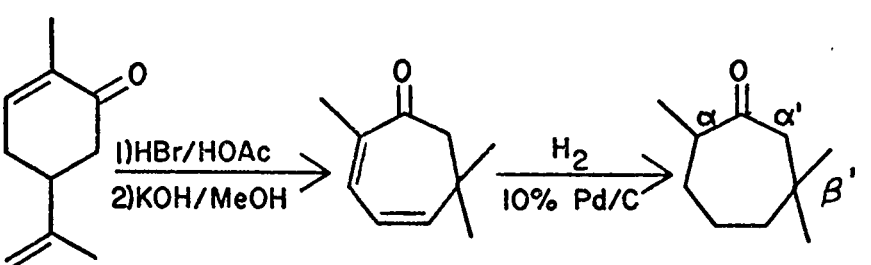


CHAPTER 2

RESULTS AND DISCUSSION

RESULTS AND DISCUSSION

Tetrahydroeucarvone can be prepared from carvone (24) via eucarvone (25) in good yield.[15,16] Treatment of carvone with anhydrous hydrogen bromide in glacial acetic acid affords a monohydrobromide. When this crude monohydrobromide is allowed to react with potassium hydroxide in methanol, eucarvone (25) is formed in 76% yield. The reaction proceeds via an intramolecular alkylation to a carenone intermediate followed by fragmentation of the cyclopropyl ring in the presence of excess base. The mechanism of this reaction is well understood due to the work of van Tamelen and coworkers.[17] Hydrogenation of eucarvone (25) over palladium-on-carbon results in the formation of the desired 2,6,6-trimethylcycloheptanone (21) in an overall yield of about 65% from carvone (24).[18,19]



24 25 21

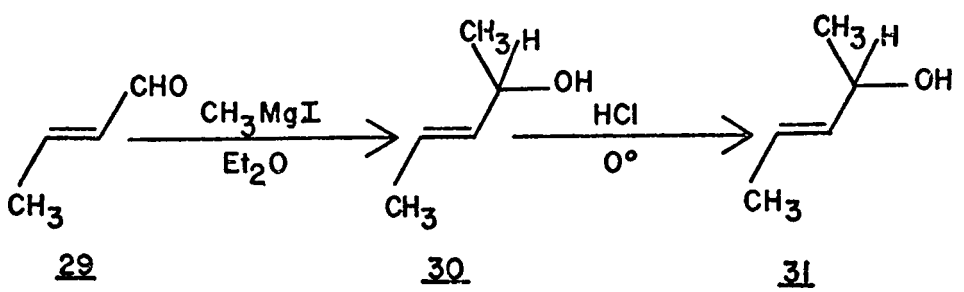
Alkylation of tetrahydroeucarvone (21) was expected to occur predominantly at the α-position for the following reasons. Recent reviews have indicated that the alkylation of an unsymmetrical ketone such as tetrahydroeucarvone is favored at the α-methine position when the corresponding enolate anion is generated under thermodynamically

controlled conditions.[20,21] This selectivity is due to the greater thermodynamic stability of the more substituted enolate. In addition, the presence of substituents at the β'-position also favors alkylation at the α-methine position. The steric hindrance that these groups provide toward proton abstraction by bases at the α'-methylene position is believed responsible for the observed selectivity. Since both effects favor alkylation at position two in tetrahydroeucarvone, it seems reasonable that alkylation should proceed at that position with a high degree of regioselectivity.

The enolate anion of tetrahydroeucarvone (21) was generated by stirring the ketone with sodium hydride in 1,2-dimethoxyethane at 80° for 48 hours. Alkylation (Figure 6) of the enolate anion using allyl bromide or ethyl 2-bromoacetate resulted in an 80% yield of keto-olefin 26 and a 53% yield of keto-ester 27, respectively.[22] Both compounds were found to be greater than 99.6% one single isomer by glc and nmr. Both compounds exhibited an AB quartet in the nmr spectrum corresponding to two protons adjacent to a ketone carbonyl ($-COCH_2-$ centered at 2.38 δ, J_{AB}=11 Hz and 2.73 δ, J_{AB}=14 Hz for compounds 26 and 27, respectively). No isomeric alkylated products at the α'-methylene position were observed spectroscopically (nmr) or detected chromatographically (glc). Tetrahydroeucarvone was similarly alkylated with 4-chloro-2-pentene[22,23] to produce keto-olefin 28 in 86% yield (Figure 8).

The structural assignment for keto-olefin 28 was fully supported by spectral evidence. Bands indicative of a seven-membered ring ketone (1700 cm^{-1}) and an olefin (3025, 1675, and 966 cm^{-1}) were present in the ir. The nmr spectrum showed two olefinic protons (4.6 - 5.16 δ) and two methylene protons alpha to a ketone (2.63, 2.47 δ; two doublets).

4-Chloro-2-pentene was synthesized via the procedure of Coburn.[22,23] The reaction of crotonaldehyde (29) with methyl Grignard reagent gave 3-penten-2-ol (30) in 80% yield. Distillation of the allylic alcohol resulted in its decomposition if the entire system was not kept basic and residual traces of iodine were not removed with a bisulfite wash during the work-up. Bubbling anhydrous hydrogen chloride through the neat allylic alcohol 30 at 0° resulted in the formation of the desired allylic chloride 31 in 77% yield.

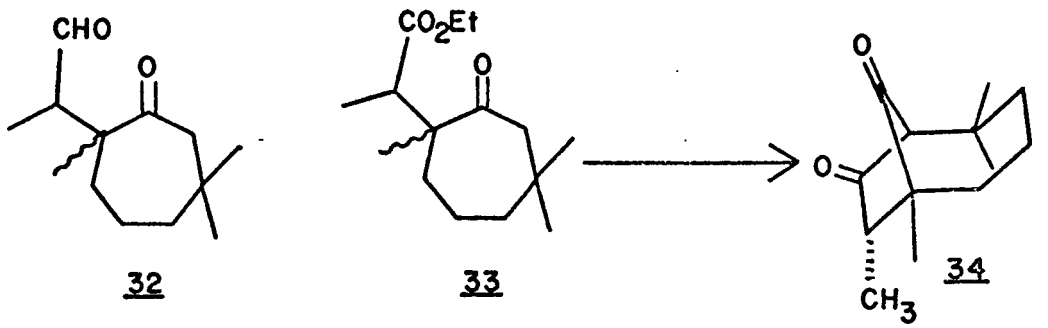


29 30 31

Model Study to Prepare an Appropriately Functionalized Bicyclo[4.2.1]nonane Intermediate

Previous attempts to produce a bicyclo[4.2.1]nonane ring system met with disappointing results.[22] Attempts to close keto-aldehyde 32 to

the bicyclic system via an acid or base catalyzed aldol failed, affording only starting material or unidentified polymeric products. Keto-ester 33, however, was successfully used to form the bicyclo-[4.2.1]nonan-8,9-dione 34.[22] This compound did not prove to be a satisfactory intermediate for the synthesis of longicyclene at that time.



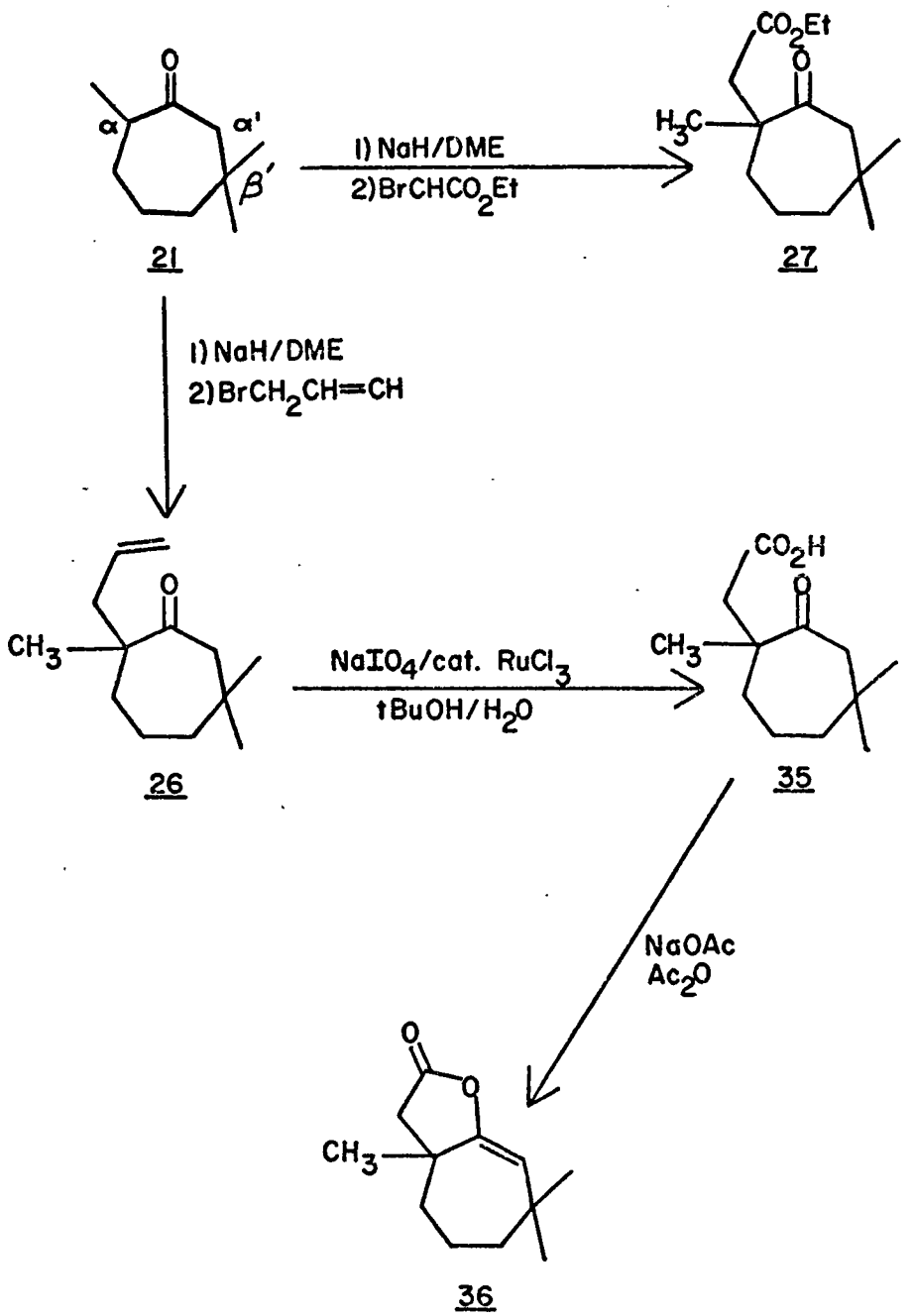
32 33 34

Raphael and coworkers recently produced a bicyclo[3.3.1]nonane ring skeleton via a reductive-cyclization using lithium aluminum tri-tert-butoxyhydride.[24] This successful ring closure prompted a model study to determine if this reductive-cyclization technique could be applied to the bicyclo[4.2.1]nonane system. In order to avoid any possible difficulty in the interpretation of the spectral results that a diastereomeric mixture of products could cause, the preparation of a bicyclo[4.2.1]nonane ring system without the methyl group present at carbon-7 was attempted.

Keto-olefin 26 was cleaved oxidatively (Figure 6) using 5.4 equivalents of sodium metaperiodate with a catalytic amount of ruthenium trichloride in aqueous tert-butanol to give keto-acid 35 in an 87%

FIGURE 6.

MODEL STUDY



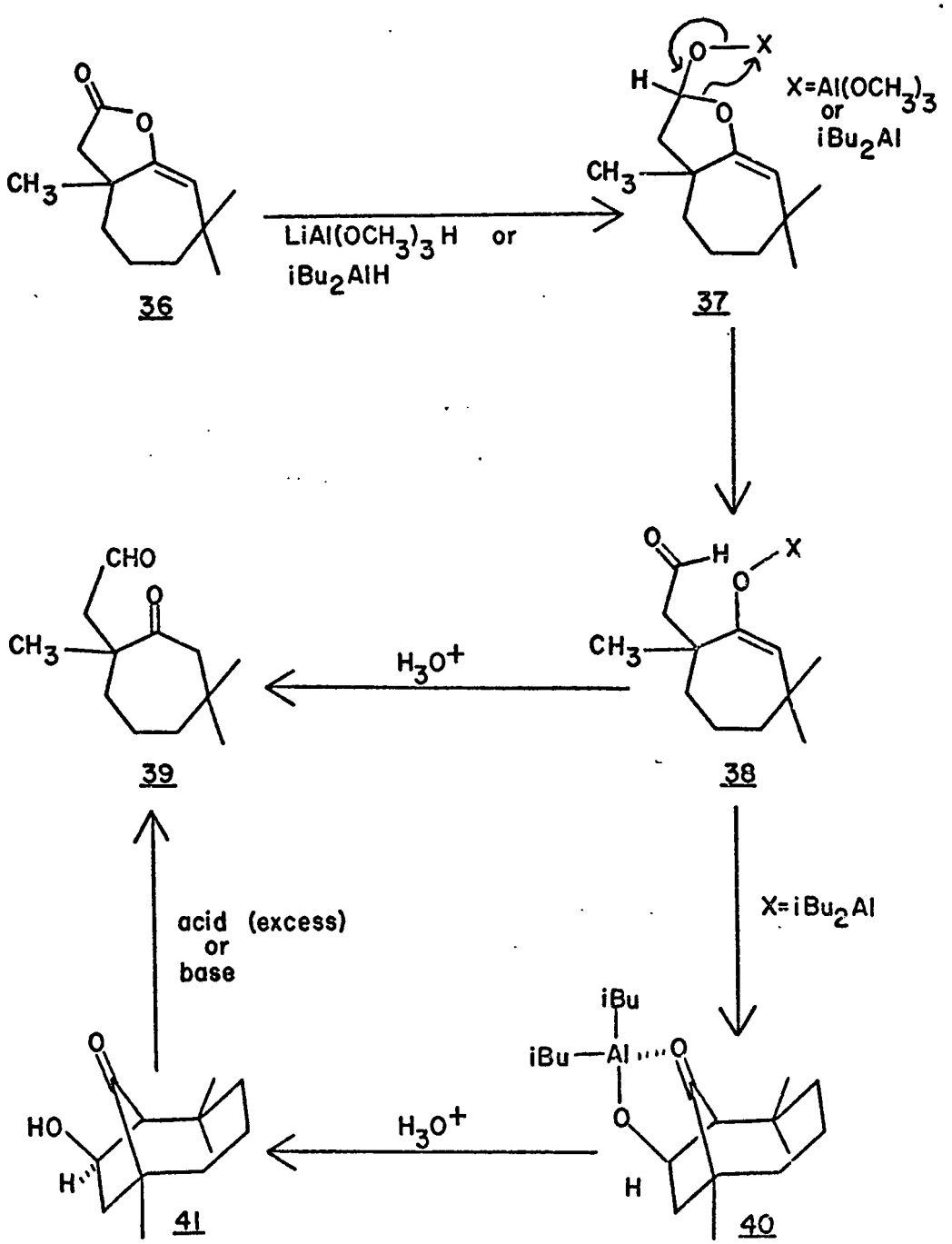
yield.[25] This conversion was confirmed by characteristic acid bands in the ir (2450 - 3650, 1700 cm^{-1}). Keto-acid 35 was heated to reflux with sodium acetate in acetic anhydride for 5 hours to give enol-lactone 36 in 87% yield.[24] Confirmation of this structure was provided by carbonyl ir absorptions (1800, 1790 cm^{-1}) and an oxygenated olefin band (1685 cm^{-1}). The nmr spectrum showed a single olefinic proton peak (5.06 δ).

Attempts to affect reductive-cyclization of the model system using either lithium aluminum tri-tert-butoxyhydride or lithium aluminum trimethoxyhydride failed. The former reagent gave starting material unaltered. With the latter reagent reduction took place, but the product was keto-aldehyde 39 instead of the desired ketol 41. When the reductive-cyclization was attempted using diisobutylaluminum hydride, the course of the reaction was altered considerably. The use of diisobutylaluminum hydride as the reducing agent allowed the isolation of bicyclic ketol 41 in an 82% yield.

The isolation of the two different products from the reductive-cyclization reactions can be understood by consideration of the proposed reaction mechanism. Enol-lactone 36 is reduced by both lithium aluminum trimethoxyhydride and diisobutylaluminum hydride to give intermediate 37 (Figure 7). Intermediate 37 then rearranges to give an aluminum enolate aldehyde 38. For the aluminum trimethoxy group, intermediate 38 (or possibly the aluminum enolate of the aldehyde function) is the thermodynamically most stable product. When intermediate 38 is treated with acid, keto-aldehyde 39 results.

FIGURE 7.

REDUCTIVE CYCLIZATION



When diisobutylaluminum hydride is used, intermediate 38 undergoes one further transformation. The aluminum enolate closes on the aldehyde to give the bicyclic keto-alkoxide 40. This intermediate is stabilized by the coordination of the aluminum via its empty orbital to the ketone oxygen. This coordiation, which was less probable with the other reducing agent, causes the bicyclic intermediate 40 to be favored under kinetically controlled conditions. Careful neutralization with acid and rapid work-up allowed trapping of crystalline bicyclic ketol 41.

Support for this reasoning comes from two observations. First, the bicyclic ketol 41 is a sensitive compound which rearranges to keto-aldehyde 39 in the presence of acid or base. Hence, the keto-aldehyde 39 is thermodynamically more stable than bicyclic ketol 41. Therefore some factor must serve to stabilize intermediate 40 over intermediate 39. Second, the only bicyclic ketol observed is the exo-isomer. This fact was verified by glc (only one product observed) and by nmr. The configuration for the alcohol group was assigned on the basis of the nmr vicinal coupling constant of the hydroxymethine proton at carbon-8 with the bridgehead proton at carbon-1. A coupling constant of $J_{1,8}$=2 Hz was observed. The magnitude of this coupling constant would be expected for a dihedral angle near 130°.[26,27] The same dihedral angle was found for the exo-alcohol 41 in Dreiding models. Examination of a Dreiding model indicates that the endo-alcohol would have a dihedral angle near 15°. The coupling constant for that isomer would have to be $J_{1,8}$=7.7 Hz.

This development of the reductive-cyclization using diisobutylaluminum hydride has overcome the previously noted problem of forming a suitably functionalized bicyclo[4.2.1]nonane system.

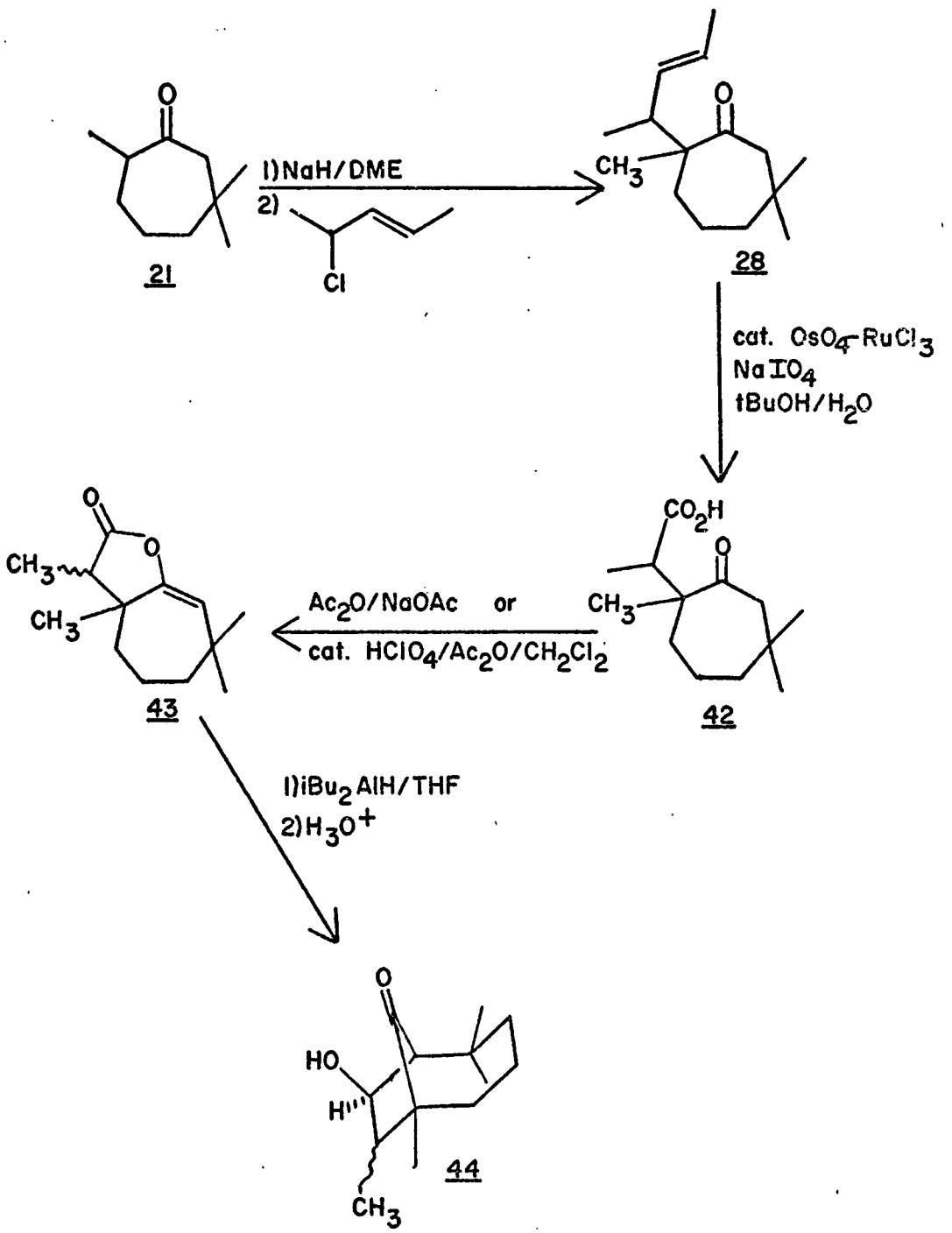
The Synthesis of (±)-Longicyclene (1)

Keto-olefin 28, five equivalents of sodium metaperiodate, water, and enough tert-butanol to form a homogeneous solution were stirred in the presence of a catalytic amount of ruthenium chloride and osmium tetroxide. Keto-acid 42 was produced in 93% yield. When a catalytic amount of ruthenium chloride alone was used keto-acid 42 (Figure 8) was isolated in a much lower yield. If the flask was not completely filled, repeated additions of ruthenium chloride were needed because the ruthenium dioxide plated on the walls of the flask above the liquid. Spectral data, ir bands indicative of an acid (3580 - 2400, and 1710 cm^{-1}) and of a ketone in a seven-membered ring (1700 cm^{-1}) and an acid proton (8.05 δ) in the nmr, support the structure.

Two satisfactory preparations of enol-lactone 43 were devised. The base-catalyzed method[24] involved stirring a solution of keto-acid 42 and sodium acetate in acetic anhydride at reflux for five hours. The resultant enol-lactone 43 was isolated in an 87% yield. An acid-catalyzed method involved stirring a solution of keto-acid 42 and acetic anhydride in dichloromethane with a catalytic amount of 60% perchloric acid at room temperature for four hours. This method gave enol-lactone 43 in a 90% yield.[29] Enol-lactone 43 was isolated as a mixture of

FIGURE 8.

STAGE I.



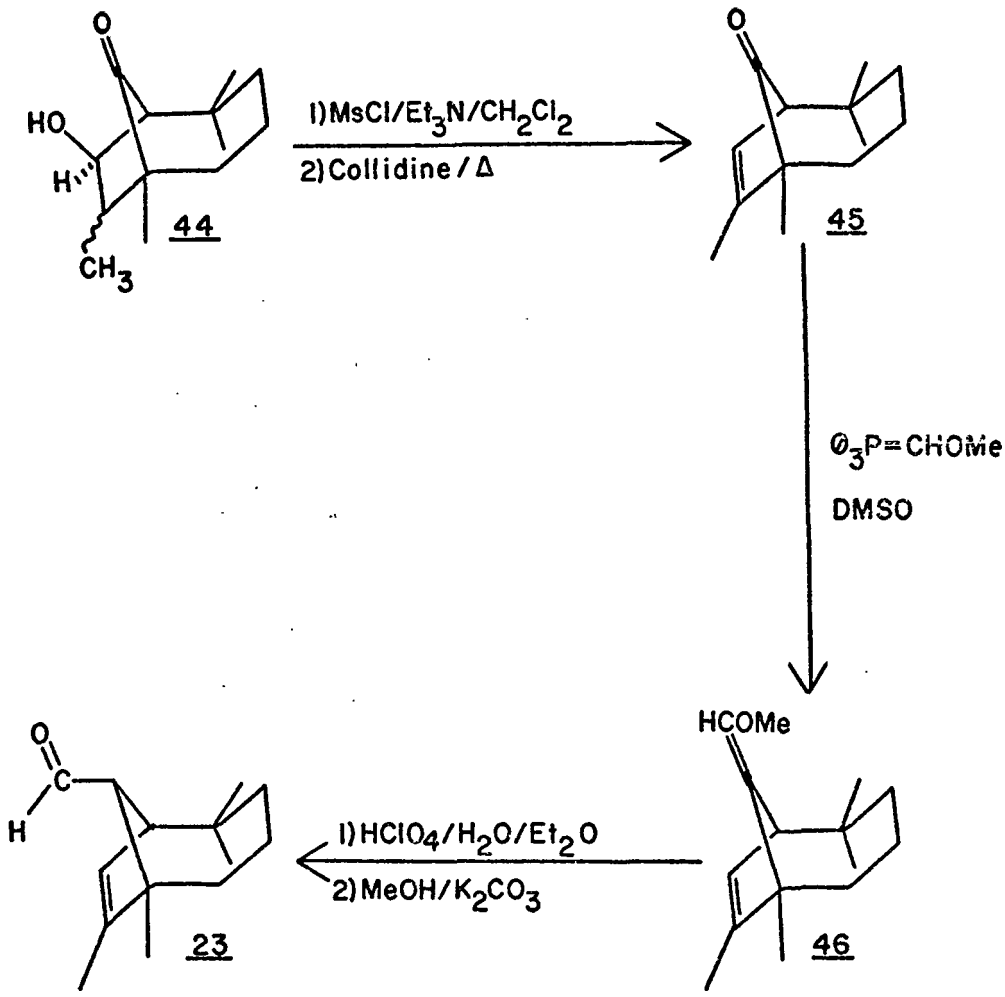
diastereomers. These compounds were characterized by ir bands indicative of a lactone carbonyl (1790 cm^{-1}) and an oxygenated olefin (1685 cm^{-1}), and a nmr signal for one olefinic proton (5.19 δ).

Reductive-cyclization[24] of enol-lactone 43 proved to be as facile as the model study had indicated. Enol-lactone 43 was treated with diisobutylaluminum hydride at 0° in tetrahydrofuran followed by heating at 60° for 18 hours. Careful neutralization of the reaction mixture with dilute hydrochloric acid at 0° gave the desired liquid ketol 44 as a mixture of diastereomers in 80% yield. This ketol proved to be as sensitive to fragmentation to a corresponding keto-aldehyde as was ketol 41 in the model study. The structure was confirmed by ir bands indicative of a five-membered ring ketone (1725 cm^{-1}) and an alcohol (3440 cm^{-1}). The construction of this ketol completed the first stage of the planned synthesis.

Due to the sensitivity of bicyclic ketol 44 to fragmentation it was necessary to convert it to a more stable intermediate. After isolation ketol 44 was immediately dissolved in dichloromethane (Figure 9) to which was added methane sulfonyl chloride and triethylamine.[29] After 17 hours at 3° the mesylate ester could be isolated by stirring in collidine at 170° - 175° for 16 hours.[30] The resulting bicyclic enone 45 was isolated in 87% overall yield from ketol 44. The infrared data for bicyclic enone 45 were in good agreement with that reported for the same structure by Barton and Werstiuk as a degradation product of culmorin.[31] In addition, the structure was supported by nmr signals

FIGURE 9.

STAGE 2.



for the olefinic proton (5.8 δ) and three allylic methyl protons (1.66 δ).

Methoxymethylenetriphenylphosphorane was generated in dimethyl sulfoxide by treating methoxymethylenetriphenylphosphonium chloride with the sodium salt of dimethyl sulfoxide. After addition of enone 45 the solution was stirred at 60° for 23.5 hours. Methoxyvinyl ether 46 was then isolated in 88% yield.[32] Initially, the removal of triphenylphosphine oxide, a by-product of the reaction, proved to be a problem. The best procedure devised to alleviate this problem involved concentrating the crude material in vacuo, dissolving the concentrated oil in petroleum ether, and allowing most of the triphenylphosphine oxide to crystallize. The remaining traces of the oxide could then be removed from the product by filtering the concentrated crude product through a column of silica gel followed by distillation. Structural assignment was based on ir bands indicative of an oxygenated olefin (1695 cm^{-1}) and the nmr signals of two olefinic protons (5.64 and 5.4 δ) and a methyl ether (3.5 δ). Although only one isomer was observed (nmr, glc), no effort was made to determine the configuration of the methoxymethylene group.

Stirring enol-ether 46 in a homogeneous solution of 50% perchloric acid and diethyl ether (1:5 v:v respectively) for 1.75 hours at room temperature completely hydrolyzed the enol-ether to a pair of epimeric aldehydes. Attempted hydrolysis in nonhomogeneous solutions resulted in a much slower reaction and poor yields of the aldehyde. The mixture of

aldehydes was epimerized in methanol containing anhydrous potassium carbonate for 1.75 hours at room temperature. A quantitative yield of aldehyde 23 was obtained.[32] The presence of an aldehyde function was confirmed by ir bands (2745, and 1720 cm^{-1}).

The assignment of the stereochemistry for aldehyde 23 was based on two considerations. First, the presence of the aldehyde group on the same side as the four-carbon bridge causes severe steric interactions between the aldehyde and groups attached to the four-carbon bridge. This strain could be relieved by epimerization of the aldehyde group to a position over the less hindered two-carbon bridge. Because there are lessened steric interactions this configuration would be thermodynamically favored. Second, the stereochemistry of the assigned structure 23 is such that the aldehyde proton is within the shielding effect of the olefinic double bond.[33] This shielding effect is not possible in the other epimer. The disappearance of the less shielded aldehyde proton signal (10.05 δ, singlet) and the enhancement of the more shielded aldehyde proton signal (9.32 δ, $J_{9,10}$=5.5 Hz) upon epimerization also supports the assigned structure.

Further evidence for the configurations of the aldehyde isomer is available from the coupling constants. The observed coupling constant is $J_{9,10}$=5.5 Hz for the aldehyde proton to the α-methine proton in the desired isomer. Such a value is consistent with a freely rotating aldehyde group. The aldehyde proton of the other isomer exhibits no coupling. This would indicate a dihedral angle of about 90° between the

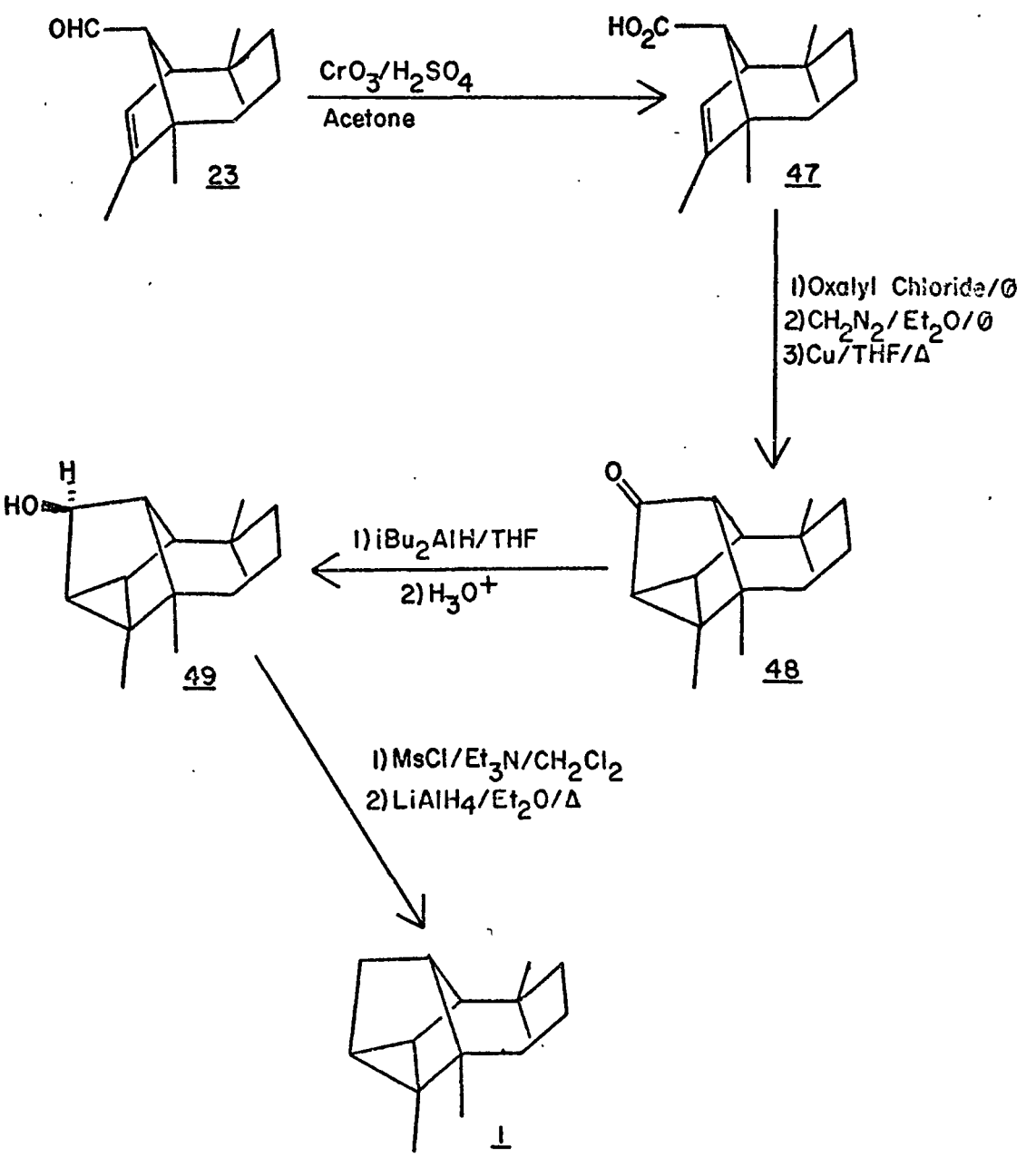
aldehyde proton and the α-methine proton. Examination of Dreiding models reveals that the aldehyde function of the desired isomer can rotate freely. In the undesired isomer, however, the rotation of the aldehyde is restricted due to steric interactions with the four carbon bridge. The most stable conformation for the aldehyde is one in which there is a dihedral angle of about 90° between the aldehyde proton and the α-methine prtoon. These observations further support the structural assignments of the two isomeric aldehydes. The assigned structure 23 was the only isomer observed by nmr or glc after epimerization. The preparation of this compound completed the second stage of the synthetic scheme.

Treatment of aldehyde 23 (Figure 10) with Jones' reagent added dropwise at 0° with rapid stirring at room temperature for 30 minutes gave carboxylic acid 47 in 86% yield.[34,35] The conversion was confirmed by the presence of carboxylic acid bands (3060 and 1760 cm^{-1}) in the ir and an acid proton (11.47 δ) in the nmr.

Oxalyl chloride was added dropwise to a stirred solution of olefinic acid 47 in benzene at 0°. The solution was stirred at room temperature for two hours. The excess reagent and solvent were removed *in vacuo*. Anhydrous diazomethane in ether was added dropwise at 0° to the resulting crude acid chloride in benzene. After stirring at 0° for one hour and at room temperature for one hour the excess reagent and solvent were removed *in vacuo*. The resultant crude diazoketone was then heated to reflux for two hours in the presence of powdered copper metal in tetrahydrofuran. Crystalline cyclopropyl ketone 48 was isolated from

FIGURE 10.

PREPARATION OF LONGICYCLENE



the crude oily product by column chromatography in 33% overall yield.[36] No attempt was made to isolate or purify any of the intermediate compounds due to the sensitivity of these intermediates. Structural assignment was made on the basis of ir bands indicative of a ketone carbonyl (1755 cm^{-1}) and cyclopropyl carbon-hydrogen stretching bands (3095 cm^{-1}) and the presence of four methyl singlets (1.18, 1.03, 0.97, and 0.90 δ) in the nmr spectrum.

Removal of the ketone function from cyclopropyl ketone 48 would complete the synthesis of (±)-longicyclene. The first method attempted to affect this conversion was a Huang-Minlon modification of the Wolff-Kishner reduction.[37] This reduction afforded mostly starting material plus a small amount of unidentified clavage products. Application of the Nagata-Itazaki modification of the Wolff-Kishner reaction[38,39] also proved unsuccessful. This modification gave the same results as previously noted. An attempt to form the tosyl hydrazone derivative of ketone 48 under forcing conditions gave only starting material.

The lack of reactivity of the ketone function in compound 48 toward hydrazine can be explained by examining Dreiding models. First, approach to the ketone carbonyl is severly hindered by the methyl group at carbon-6 and the hydrogen at carbon-1. Attack of hydrazine at the carbonyl carbon forms an intermediate which would force the oxygen of the ketone into the methyl group at carbon-6. Restricted access to the ketone carbonyl atom and the large amount of strain produced in forming this intermediate explains the lack of reactivity of this ketone.

Reduction of ketone 48 using diisobutylaluminum hydride in tetrahydrofuran produced cyclopropyl carbinyl alcohol 49 in a 98% yield. Only one isomer was observed by nmr and glc. The stereochemistry of alcohol 49 was assigned on the basis of "steric approach control."[40] The bulky reducing agent would approach the carbonyl group from the less hindered side, producing an alcohol with the stereochemistry indicated by structure 49.

Treatment of alcohol 49 with methanesulfonyl chloride in dichloromethane at -15° for 72 hours resulted in the formation of the methanesulfonate ester.[29] The reaction was monitored by tlc. Only one product was observed. Due to the probable ease of fragmentation and rearrangement of this cyclopropyl carbinyl mesylate ester no attempt was made to isolate it. The entire reaction mixture was added to a large excess of lithium aluminum hydride in ether. Refluxing this mixture resulted in the formation of (±)-longicyclene (1) in 98% overall yield from alcohol 49. No fragmentation or rearrangement of the cyclopropane ring to give olefinic products was observed by nmr or glc.

The synthetic (±)-longicyclene was compared to an authentic sample of the naturally occurring (+)-longicyclene.[9] There was no detectable spectroscopic difference in the two samples by ir or nmr. Comparisons of glc retention times of separate and coinjected samples on three different packed columns and two different capillary columns showed the compounds to be identical. Completion of this total synthesis of (±)-longicyclene (1) provided unambiguous proof for the structure of (+)-

longicyclene and completed the first objective of this research program.

Synthesis of (±)-Longicamphor (2A) and (±)-Longiborneol (2B)

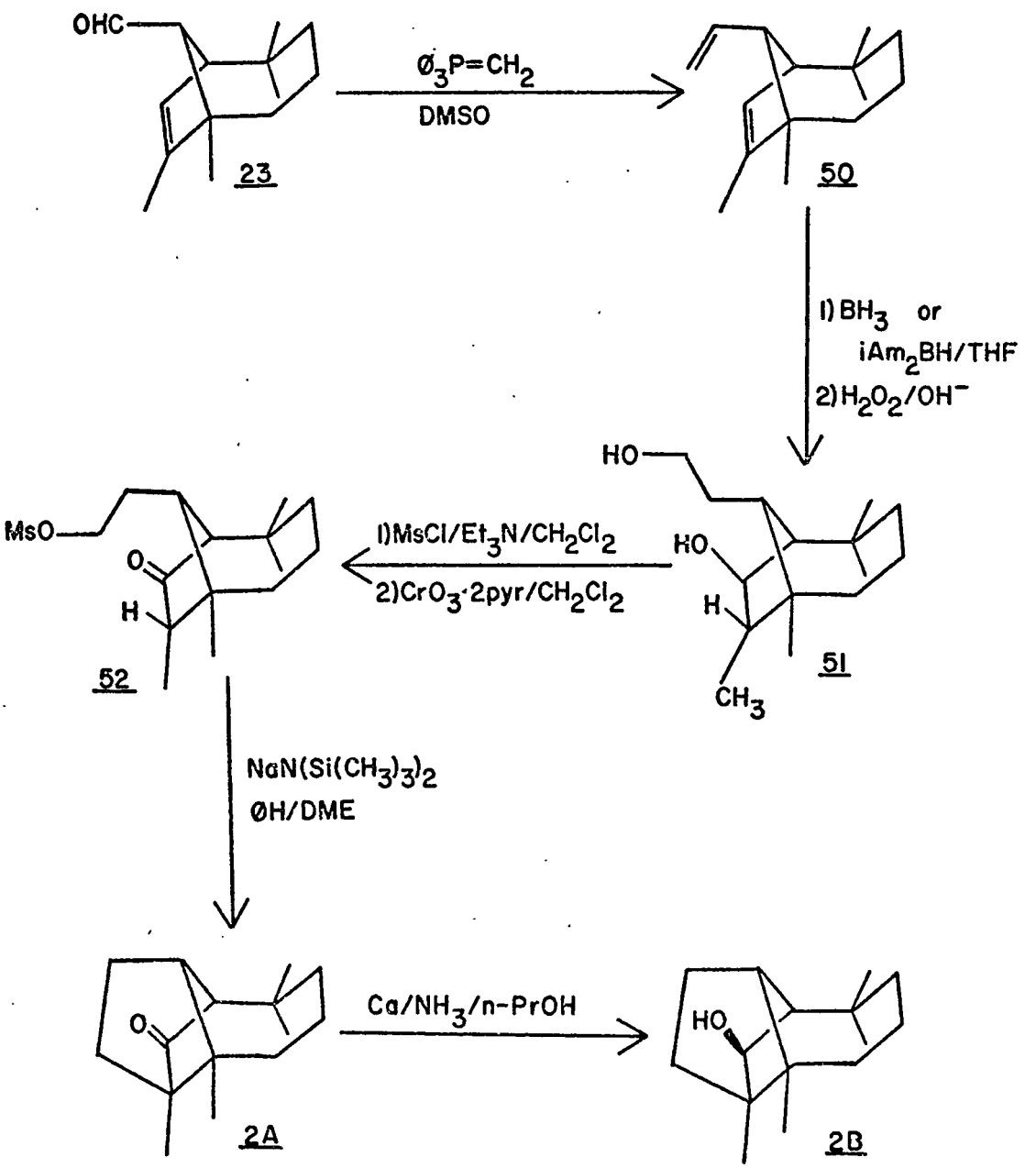
Synthesis of longicamphor (2A) necessitated extending the carbon chain of aldehyde 23 by one carbon atom. This extension was accomplished by treating aldehyde 23 (Figure 11) with methylenetriphenylphosphorane, generated from methyltriphenylphosphonium bromide with the sodium salt of dimethyl sulfoxide, in dimethyl sulfoxide for 13.5 hours at room temperature.[32] The resultant diene 50, isolated in an 83% yield, was characterized by nmr signals corresponding to four olefinic protons (5.3 - 6.0, 4.88, and 4.67 δ).

The conversion of diene 50 to diol 51 proved to be less successful than anticipated. In the initial attempt, diborane in tetrahydrofuran was added dropwise to a solution of diene 50 in tetrahydrofuran at 0°. The resultant solution was stirred at room temperature for 3 hours. After cooling the reaction to 0°, a solution of 30% hydrogen peroxide and 10% sodium hydroxide (1:1, v:v) was added dropwise. The solution was then stirred at 0° for 1 hour and at room temperature for one hour.[41] The desired diol 51 was isolated in 49% yield by column chromatography.

A systematic study was undertaken in an attempt to improve the yield of diol 51. The reagents and conditions used are listed in Table I. In no case was the yield of the desired diol 51 greater than

FIGURE II.

PREPARATION OF LONGICAMPHOR AND LONGIBORNEOL



in the initial attempt. In addition, a variety of unidentified products was formed in each reaction.

TABLE I

HYDROBORATION CONDITIONS

Reagent	Reaction Time (Hr.)	Reaction Temp.	Oxidation Time 0 (Hr.)	Oxidation Time R. T. (Hr.)	Yield
BH_3	3	r. t.	1	1	49%
BH_3	6.5	r. t.	1	1.5	26%
BH_3	9	r. t.	1	2	27%
iAm_2BH	2	r. t.	1	1	47%
iAm_2BH	11.3	r. t.	3	3	49%

The structure of diol 51 was confirmed by ir bands indicative of an alcohol (3625 and 3400 cm^{-1}). The configuration of carbon-8 was established from a nmr study. First-order analysis of the coupling constants for the hydroxymethine proton at carbon-8 (the X part of an AMX system) showed coupling constants of $\underline{J}$ = 2.6 Hz and $\underline{J}$ = 7.8 Hz. Routine use of europium $(DPM)_3$[42] dispersed the nmr spectrum so that the bridgehead proton on carbon-1 was clearly observable. This dispersal of the spectrum allowed the coupling constant $\underline{J}_{1,8}$=2.6 Hz to be established. This coupling constant is in agreement with the value predicted

for exo-alcohol 51 based on a dihedral angle near 120° (derived from a Dreiding model of the compound). Examination of the Dreiding model for the endo-isomer of structure 51 shows a dihedral angle near 0°, leading to a predicted coupling constant near 8 Hz.[26,27]

The construction of the tricyclic carbon framework of longicamphor (2A) from diol 51 utilized an intramolecular alkylation similar to that employed by Johnson and coworkers in their synthesis of aldosterone.[43] Selective esterification of diol 51 at the primary alcohol was accomplished by treatment with 1.1 equivalents of methanesulfonyl chloride at 3° in dichloromethane in the presence of triethylamine for 36 hours.[29] The crude liquid hydroxymesylate ester was then oxidized using a chromium trioxide-dipyridine complex in dry dichloromethane.[44,45,46] The crystalline ketomesylate 52 was isolated in 92% overall yield from diol 51. The structure was supported by ir band indicative of a ketone (1725 cm^{-1}) and a mesylate ester (1370 and 1180 cm^{-1}) and a nmr absorption indicative of a mesylate methyl group (3.0 δ).

Sodium bis(trimethylsilyl)amide in benzene[47] was added dropwise to a solution of ketomesylate 52 in 1,2-dimethoxyethane at 0°. After stirring for forty minutes at room temperature (±)-longicamphor (2A) was obtained in 98% yield.[48] The ir and nmr spectra of synthetic (±)-longicamphor and natural (+)-longicamphor were identical. Glc retention times of separate and coinjected samples of the natural and synthetic compounds on three packed columns and two capillary columns showed no differences in the two samples.

The addition of (±)-longicamphor (2A) to a solution of calcium metal in liquid ammonia followed immediately by the addition of n-propyl alcohol produced (±)-longiborneol (2B) in 97% yield.[31,48] This compound was identical to a sample of (+)-longiborneol with respect to ir, nmr, and glc retention times on five columns. The (+)-longiborneol was prepared *via* a literature procedure from (+)-longicamphor for comparison purposes.

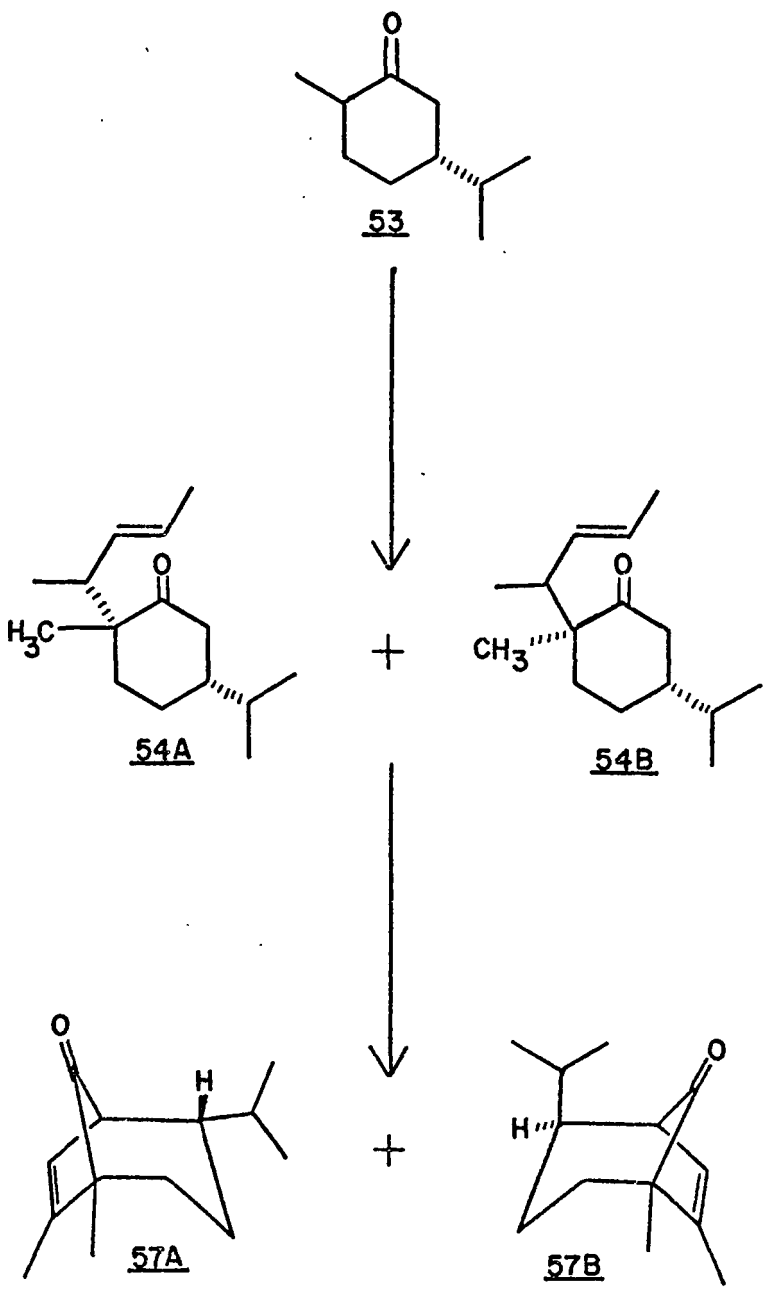
An Attempted Synthesis of (+)-Cyclosativene (5)

Due to the structural similarities of cyclosativene (5) and longicyclene (1) an attempt was made to apply the synthetic scheme utilized in the longicyclene synthesis to a total synthesis of (+)-cyclosativene. The starting material chosen for the synthesis was the readily available (+)-carvomenthone (53).[49] Alkylation of ketone 53 (Figure 12) was expected to give a mixture of isomeric keto-olefins in which isomer 54A would predominate significantly over isomer 54B.[50] Subsequent closure of the two-carbon bridge would result in the isopropyl group of isomer 57B being axial while that of isomer 57A would be equatorial. At that point separation of the two isomers would be possible by chromatography. The desired isomer could then be converted to (+)-cyclosativene *via* the same sequence of reactions employed in the synthesis of (±)-longicyclene (1).

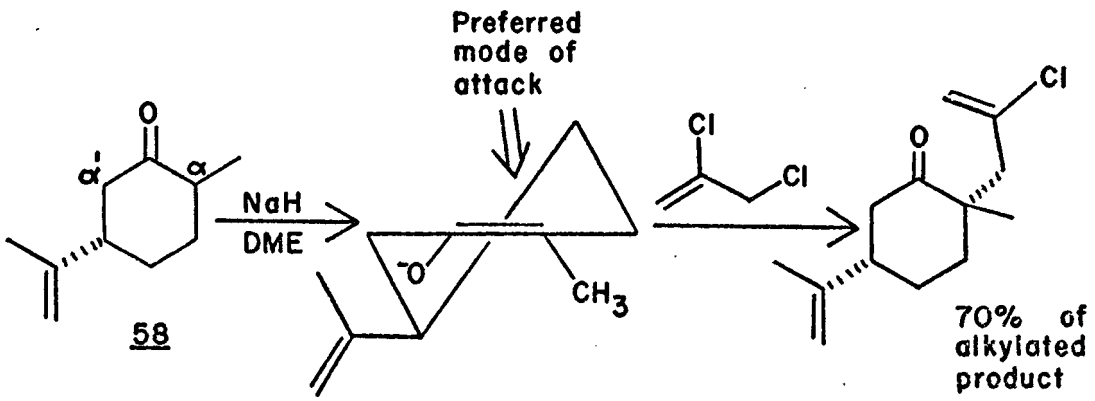
Carvomenthone (53) should alkylate at the α-methine carbon rather than at the α'-methylene carbon for the same reasons that were previously

FIGURE 12.

ORIGIN OF ENONE ISOMERS



discussed for the alkylation of tetrahydroeucarvone. It was noted previously in the alkylation of dihydrocarvone (58) that the alkylating

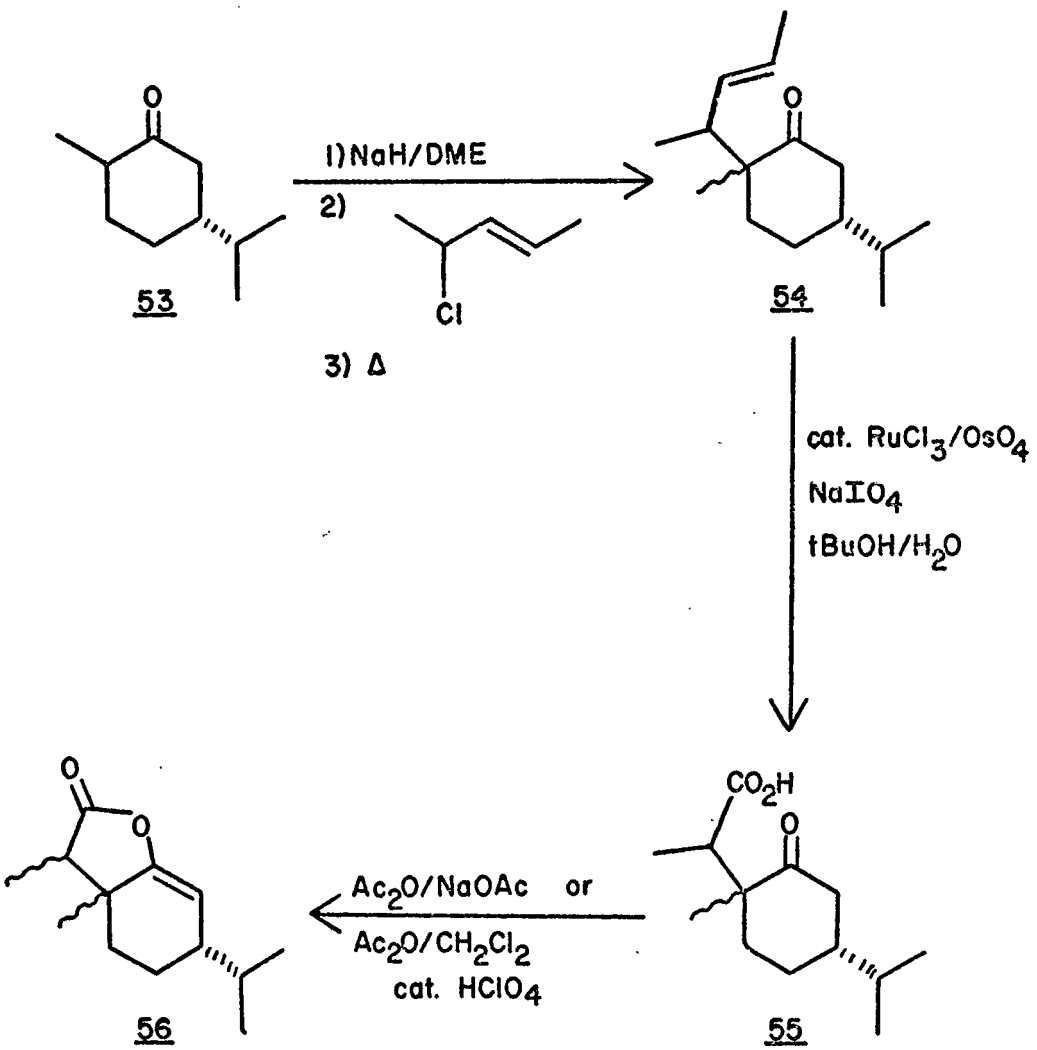


reagent approached the enolate to form the cis-product preferentially.[50] The stereoselectivity is due to alkylation of the thermodynamically favored enolate through a conformation in which the isopropenyl group occupies an equatorial position via the prechair transition state. Since the isopropyl group of carvomenthone is no less bulky than the isopropenyl group, the alkylation of carvomenthone should exhibit nearly the same stereoselective preference.

A mixture of sodium hydride and (+)-carvomenthone (53) in 1,2-dimethoxyethane (Figure 13) was stirred at 76° for 46 hours to generate the enolate anion. Next 4-chloro-2-pentene was added to the solution at -78°. Stirring the solution at -78° for two hours, then 0° for two hours, followed by room temperature for 19 hours, and finally at reflux for one hour gave a mixture of keto-olefins in a 64% yield. Confirmation of the structure was based on the presence of ir bands indicative of a

FIGURE 13.

PREPARATION OF ENCL-LACTONE



ketone (1710 cm^{-1}) and an olefin (980 cm^{-1}) and nmr peaks indicative of two olefinic protons (5.27 δ). No material alkylated at the α'-methylene carbon could be detected by glc or nmr. It was not possible to determine the ratio of the two isomers at this point.

Evidence indicates that alkylation at oxygen predominates in this reaction.[51] This observation is based on the fact that failure to reflux the reaction before isolation of the product resulted in very poor yields of the desired keto-olefin, even though all the starting material was consumed (glc) in the reaction flask. Instead most starting material was isolated. Heating would cause the O-alkylated material to undergo a thermal Claisen rearrangement[52] to give a mixture of the desired keto-olefins 54.

The oxidation of keto-olefin 54 was accomplished by the same procedure used in the synthesis of longicyclene.[26] Stirring a solution of keto-olefin 54, five equivalents of sodium metaperiodate, and catalytic amounts of ruthenium trichloride and osmium tetroxide in tert-butanol-water gave an epimeric mixture of keto-acids 55 in 95% yield. The structure was confirmed by ir bands indicative of a ketone (1700 cm^{-1}) and an acid (3400 and 1770 cm^{-1}).

At this point the analogous behavior of the two systems was found to diverge. Although enol-lactone 43 was easily formed in high yields by both acid and base catalyzed methods,[24,28] this was not true for enol-lactone 56. The base catalyzed conversion of keto-acid 55 to enol-lactone 56 gave poor results. The desired enol-lactone 56 was

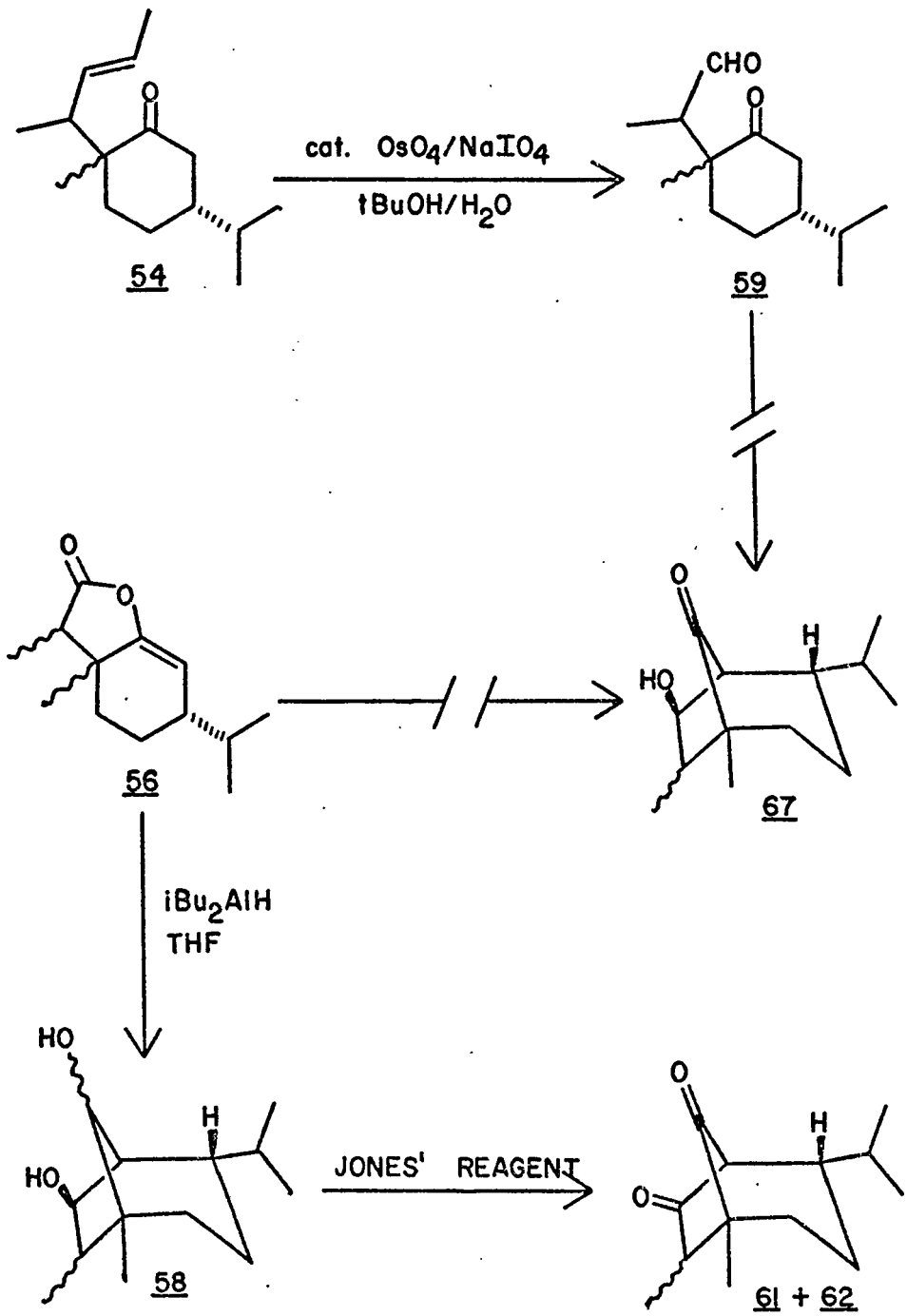
obtained in about 20% yield. In both cases a variety of unidentified side products was also formed. The structure of enol-lactone 56 was confirmed by ir bands indicative of a lactone carbonyl (1800 cm^{-1}) and an oxygenated olefin (1700 cm^{-1}) and a nmr absorption due to a single olefinic proton (5.4 δ).

Again the analogous behavior expected for the two systems was found to differ. The reductive-cyclization[24] which had proved so successful in forming ketol 44 failed to give ketol 67 from enol-lactone 56 at all. Instead of the desired ketol 67, the reductive-cyclization of enol-lactone 56 (Figure 14) using 1.1 equivalents of diisobutylaluminum hydride in tetrahydrofuran yielded a mixture of starting material and diol 58. At no time was any of the desired ketol 67 detected.

The conversion of enol-lactone 56 to diol 58 proved to be a very efficient reaction. The reductive-cyclization reaction using excess diisobutylaluminum hydride in tetrahydrofuran gave diol 58 in 97% yield. The structure of diol 58 was confirmed by its conversion to dione 61,62, which was prepared by an alternate synthetic route. Because of the low yield for enol-lactone formation and failure of the selective reductive-cyclization route, an attempt was made to cyclize keto-aldehyde 59. Keto-aldehyde 59 was prepared by stirring a solution of keto-olefin 54, three equivalents of sodium metaperiodate, and a catalytic amount of osmium tetroxide in a water-tert-butanol mixture for 48 hours. The keto-aldehyde was isolated in 72% yield.[58] The structure was confirmed

FIGURE 14.

FORMATION OF A BICYCLO[3.2.1] INTERMEDIATE



by a proton signal (9.4 δ) corresponding to the aldehyde proton and ir bands indicative of a ketone and aldehyde (1720, 1710, and 2745 cm^{-1}).

Four different procedures were utilized in attempting to affect the ring closure of keto-aldehyde 59.[53] The reagents and reaction conditions are summarized in Table II. In all cases either starting material or a complex mixture of products resulted.

TABLE II

CYCLIZATION CONDITIONS

	Conditions		Result
	°C	Hours	
HCl/MeOH	r. t.	28	Complex mixture
HCl/Acetone	r. t.	28	Mostly starting material
KOH/MeOH	r. t.	25	Complex misture
$HClO_4/CH_2Cl_2$	r. t.	21	Mostly starting material

Due to these failures to prepare a satisfactory bicyclo[3.2.1]octane intermediate for the synthesis of (+)-cyclosativene, a different approach was explored. It should be possible to produce diketone 61 from keto-ester 60 via an intramolecular Claisen condensation previously used to prepare diketone 34.

A mixture of keto-acid 55, six equivalents of ethyl iodide, and potassium carbonate in anhydrous acetone was stirred at reflux for three

hours (Figure 15).[54] Distillation at reduced pressure afforded a mixture of the four keto-ester isomers (glc) in 89% yield. This conversion was confirmed by ir bands indicative of an ester (1730 cm^{-1}) and a ketone (1705 cm^{-1}) and nmr signals corresponding to two protons alpha to the oxygen in an ethyl ester (4.05 δ).

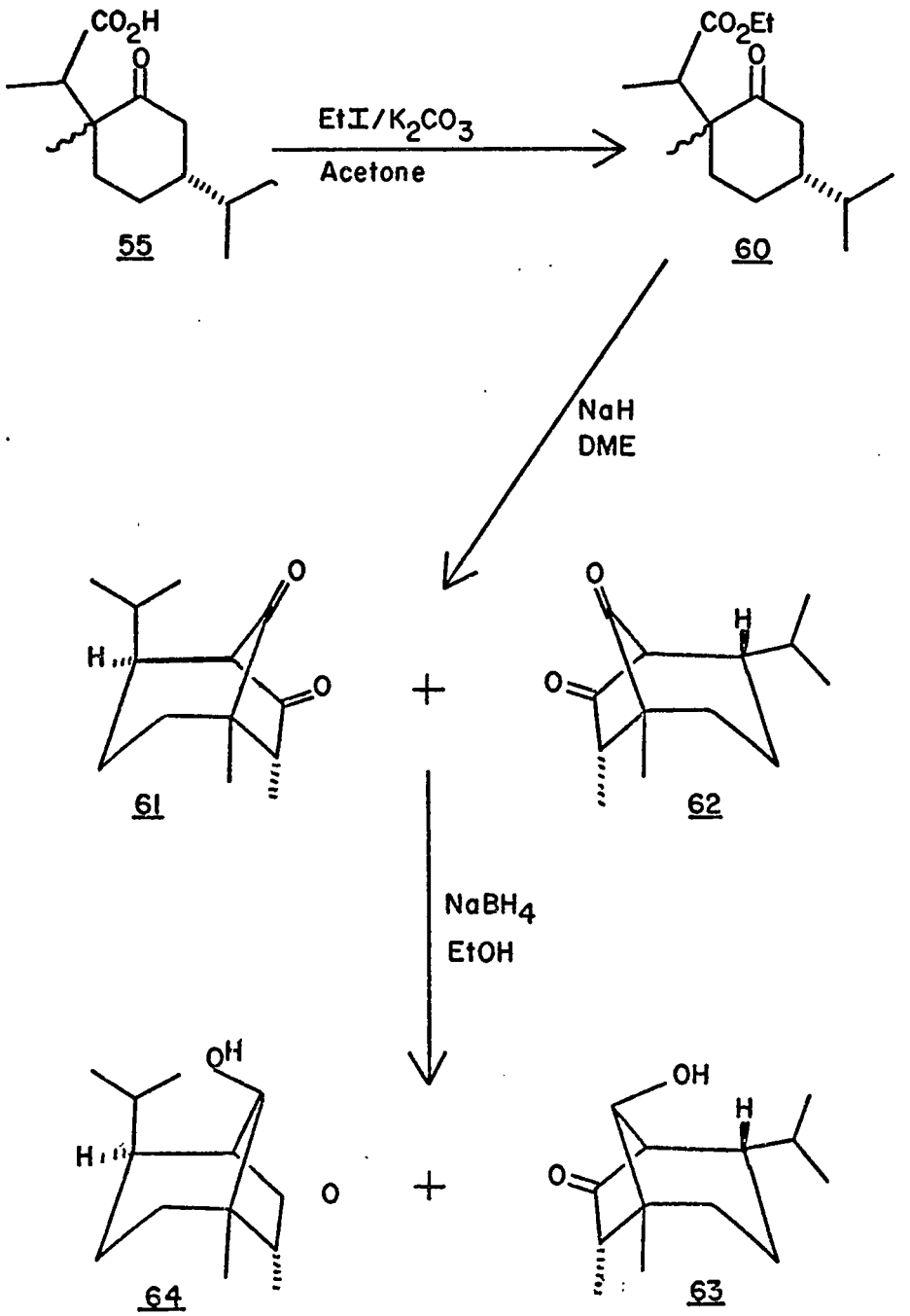
A mixture of three equivalents of sodium hydride and keto-ester 60 were stirred at 68° in 1,2-dimethoxyethane with monitoring by glc.[22,51] The reaction was quenched after ten hours--there was some decomposition of the desired product--even though all the keto-ester had not completely reacted. A crystalline mixture of diketones 61 and 62 was isolated in a 65% yield. The conversion was confirmed by ir bands indicative of a β-diketone (1765 and 1725 cm^{-1}) and a nmr signal of one proton corresponding to the bridgehead hydrogen (2.7 δ). Separation of the two isomers was not possible at this stage.

This crude mixture of diketones 61 and 62[22,51] was dissolved in anhydrous ethanol. A solution of excess sodium borohydride in ethanol at 0° was added. The resulting solution was stirred at 0°. After 30 minutes the reaction was quenched with glacial acetic acid.[55] A careful chromatography allowed the isolation of ketol 64 in 24% yield and ketol 63 in 35% yield.

The structures of ketols 63 and 64 were confirmed by ir bands indicative of a ketone (1725 cm^{-1}) and an alcohol (3475, 3490 cm^{-1}, respectively) and a nmr signal of one hydroxymethine proton (3.8 δ). These compounds were subsequently converted to olefinic alcohols for further confirmation of their structures.

FIGURE 15.

FORMATION OF BICYCLO[3.2.1] KETOLS



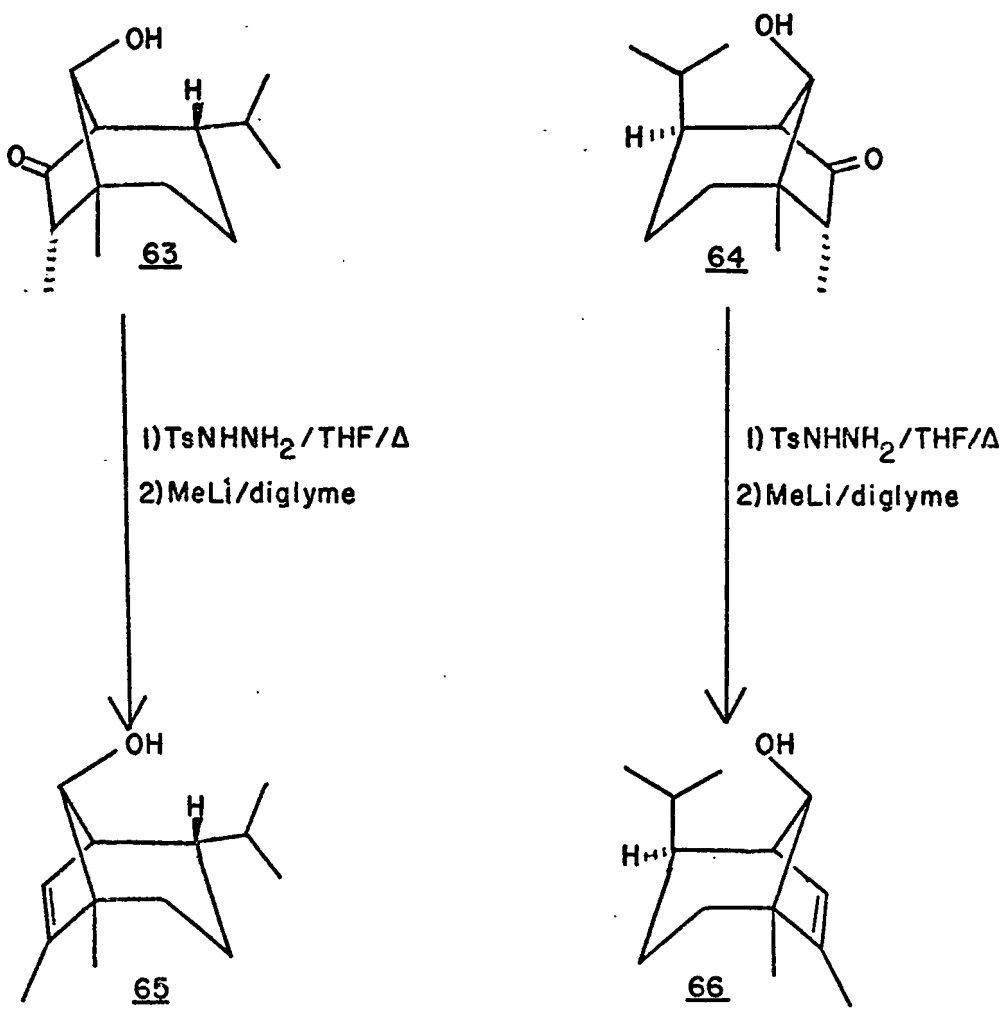
A solution of toluenesulfonyl hydrazine, one drop of concentrated hydrochloric acid, and ketol 64 in tetrahydrofuran (Figure 16) was stirred at 45° for 16.5 hours. The solvent was removed *in vacuo* and diglyme was added. Excess methyl lithium was added at 0°. The solution was stirred at room temperature for 11 hours.[56] Chromatography of the crude material after work-up afforded olefinic alcohol 66 in 63% yield. The spectral data supported the structure: ir bands indicative of an alcohol (3490 cm^{-1}) and an olefin (3055, 1630, and 820 cm^{-1}) and an olefinic proton signal (5.35 δ) in the nmr.

A solution of toluenesulfonyl hydrazine, one drop of concentrated hydrochloric acid, and ketol 63 in tetrahydrofuran was stirred at 45° for 24 hours and 55° for 37.5 hours. The solvent was removed *in vacuo* and diglyme was added. Excess methyl lithium was added at 0°. The solution was stirred at room temperature 1.5 hours.[56] Chromatography of the crude material resulted in 65% yield of olefinic alcohol 65. The spectral data, ir bands indicative of an alcohol (3400 cm^{-1}) and an olefin (3060, 1635, and 820 cm^{-1}) and an olefinic proton signal (5.35 δ) in the nmr, supported the structure.

In order to assign the proper stereochemistry to the isopropyl groups of olefinic alcohols 65 and 66, a nmr study using europium $(DPM)_3$[42] was performed. Previous studies using europium $(DPM)_3$ have shown that the rate of change of the chemical shifts of signals in the nmr spectrum is dependent on the distance of the protons producing the signal from the bonding site of the europium atom to a first approximation.[59] The

FIGURE 16.

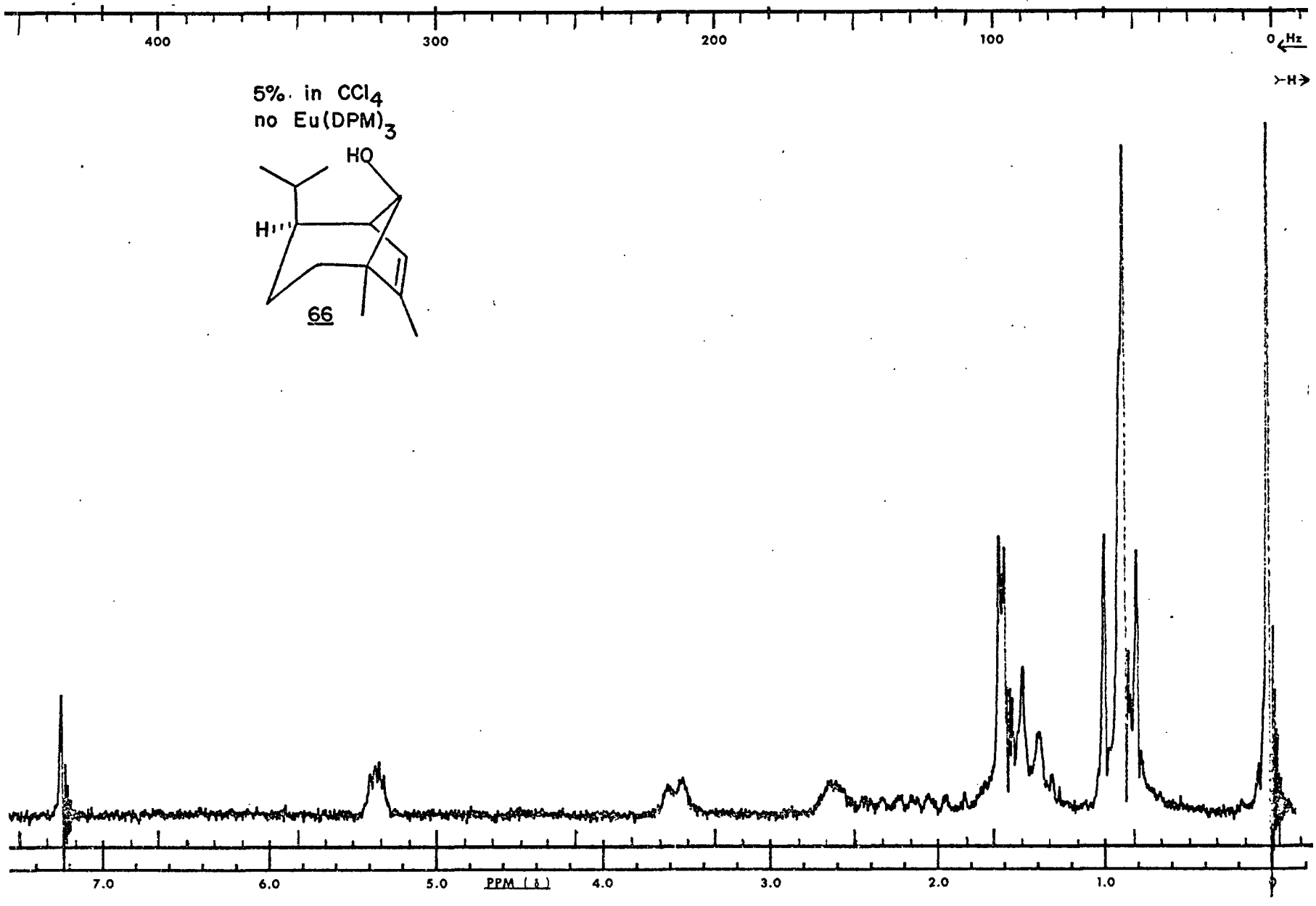
PREPARATION OF THE OLEFINIC ALCOHOLS

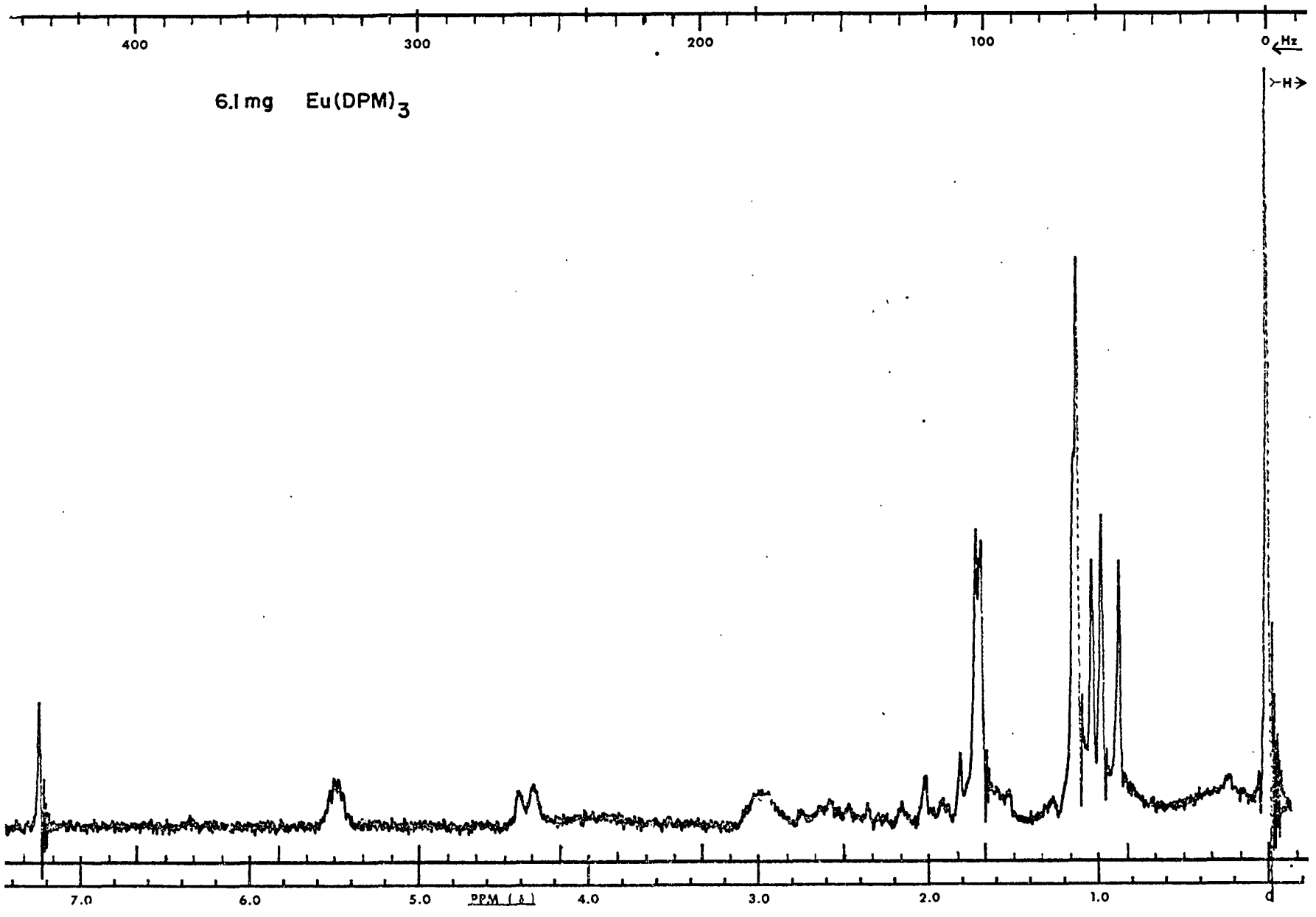


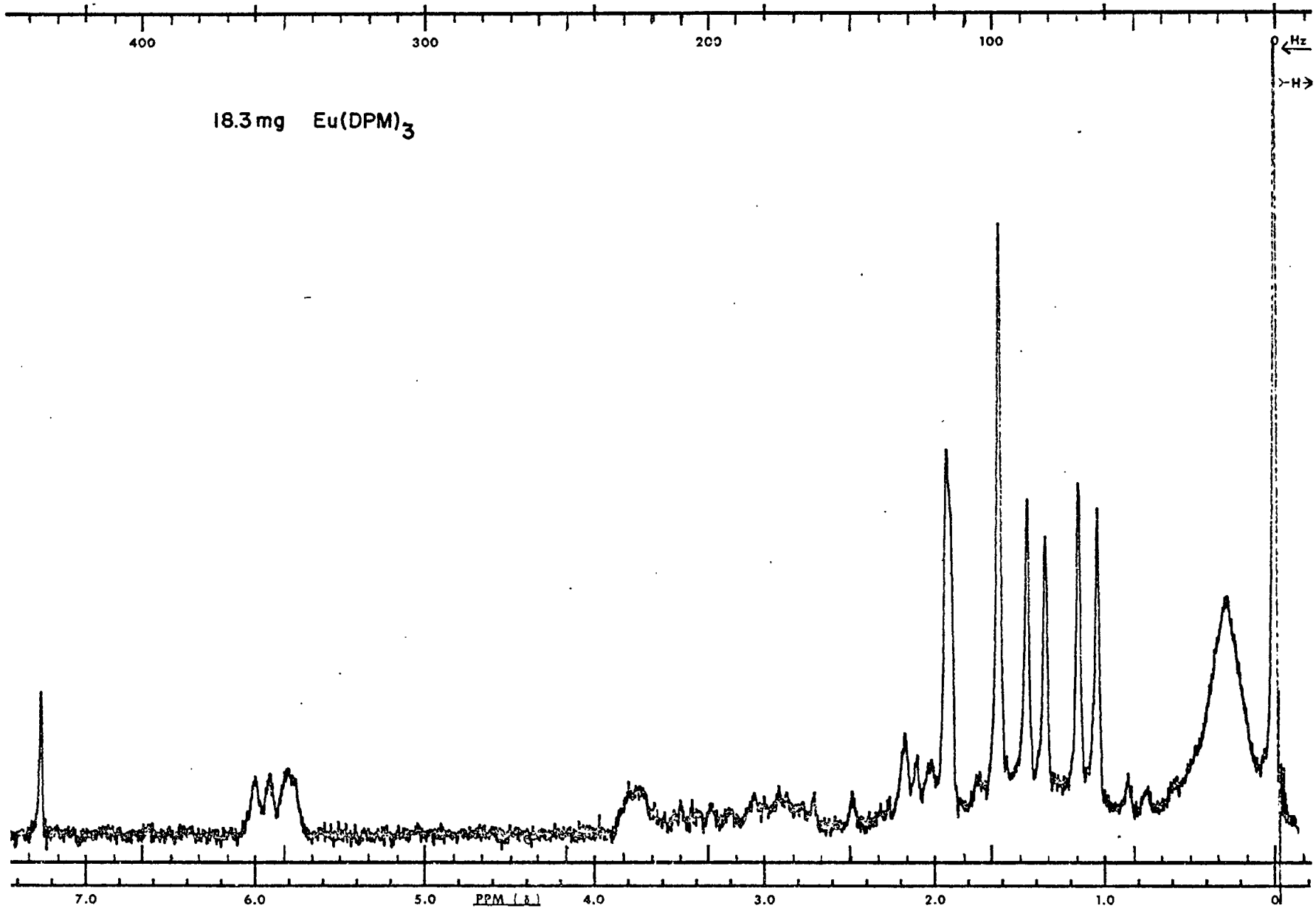
two olefinic alcohols are diastereomers and the isopropyl groups are at different distances from the europium atom bonded to the oxygen atom of the hydroxyl group. The isopropyl group in olefinic alcohol 66, being closer to the europium bonding site, would exhibit a nmr signal which would change chemical shifts at a faster rate than the isopropyl group of olefinic alcohol 65. The results of the experiment, which are shown in the following pages, support fully the assigned stereochemistry.

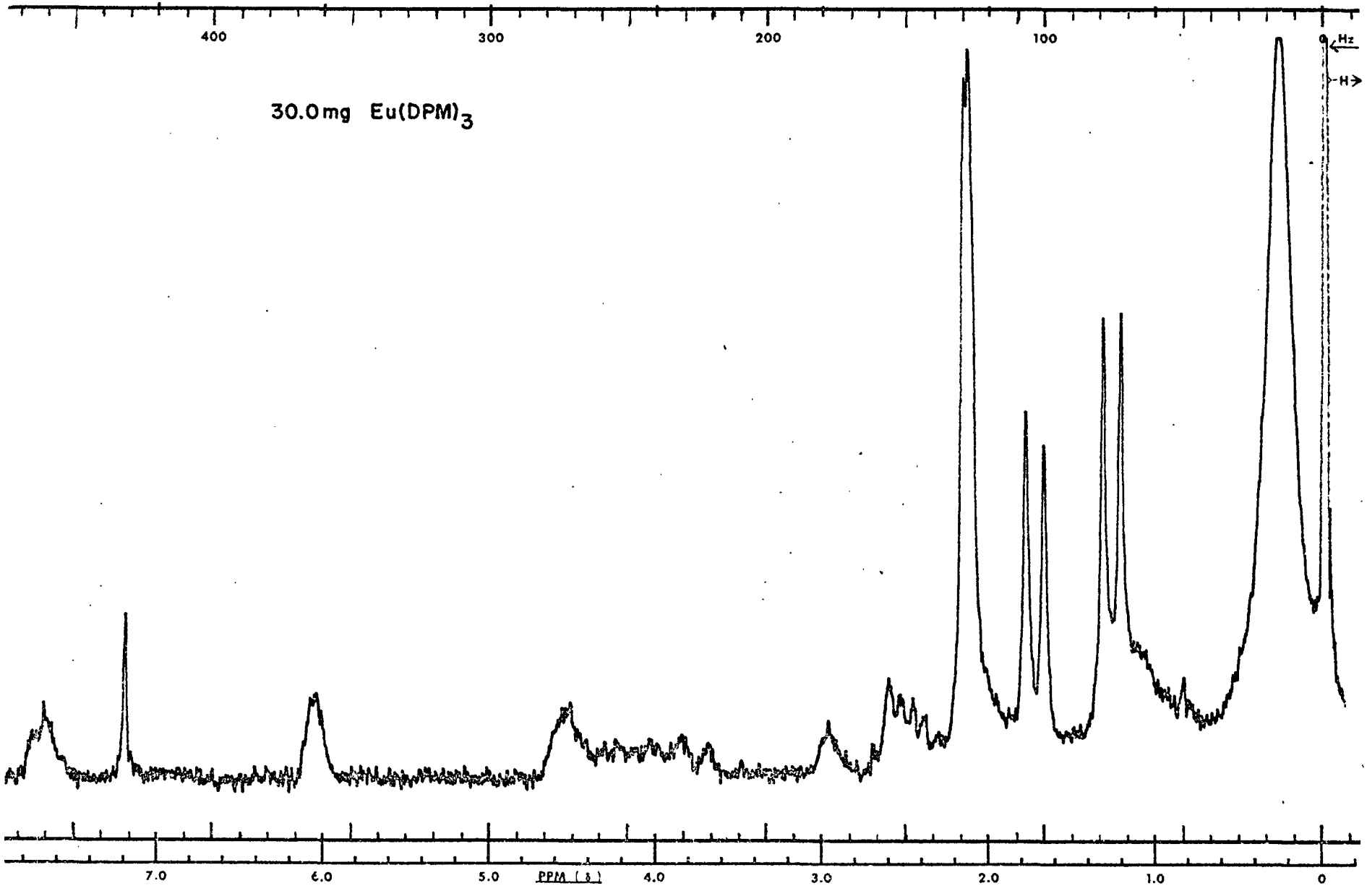
NMR STUDY ON

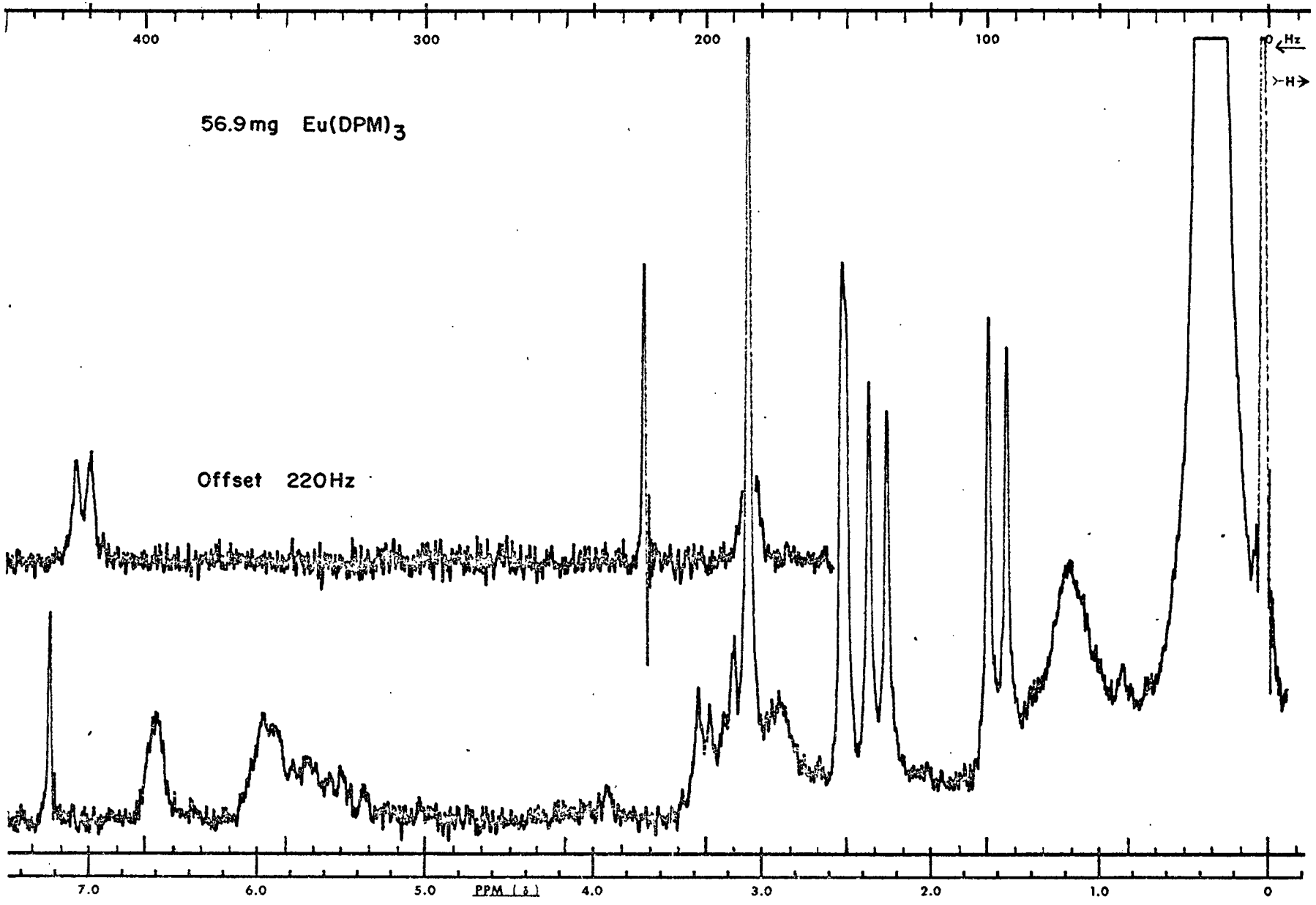
OLEFINIC ALCOHOLS 65 and 66

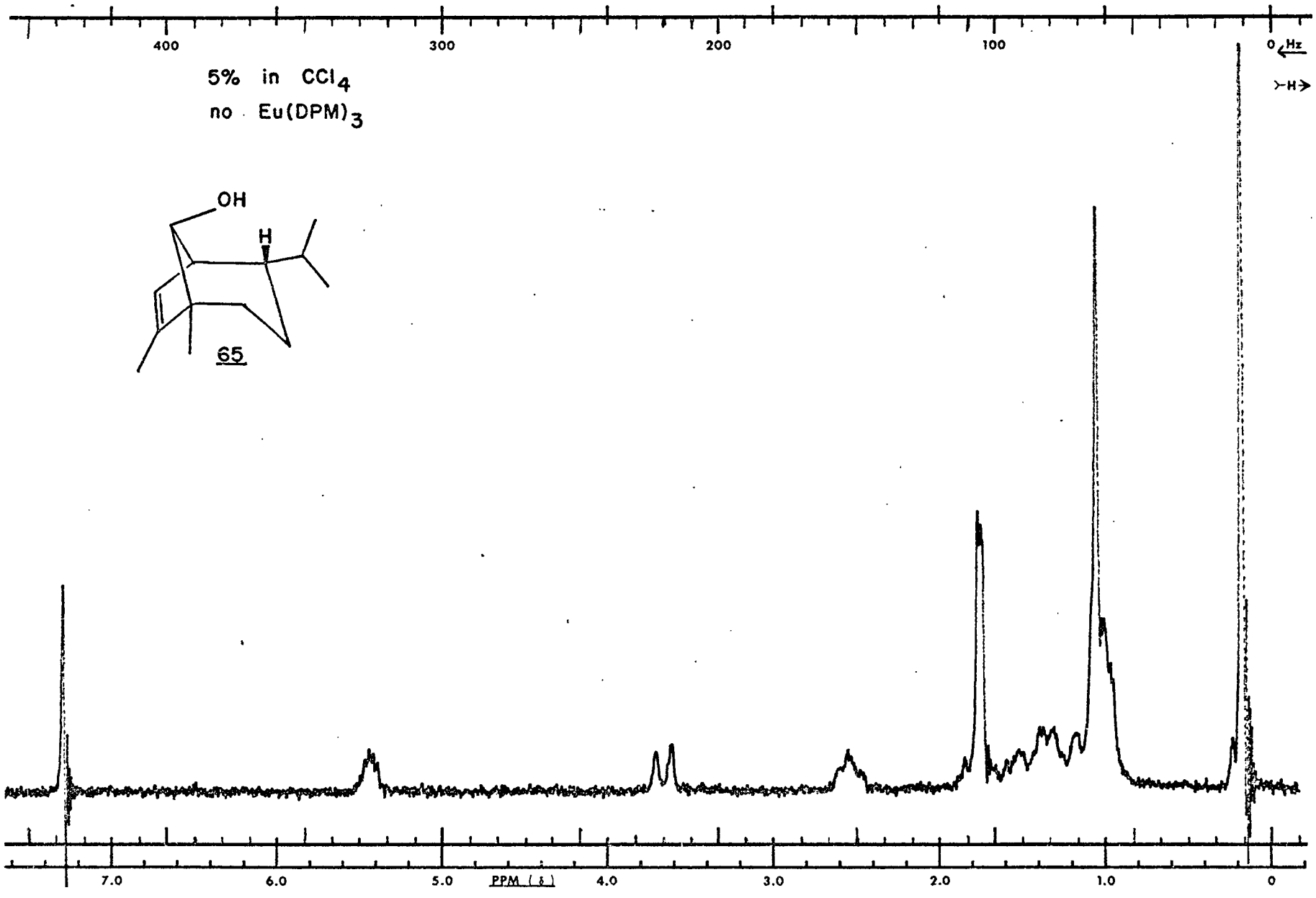

400
300
200
100
0 Hz
H
5% in CCl_4
no $Eu(DPM)_3$
HO
H'''
66
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

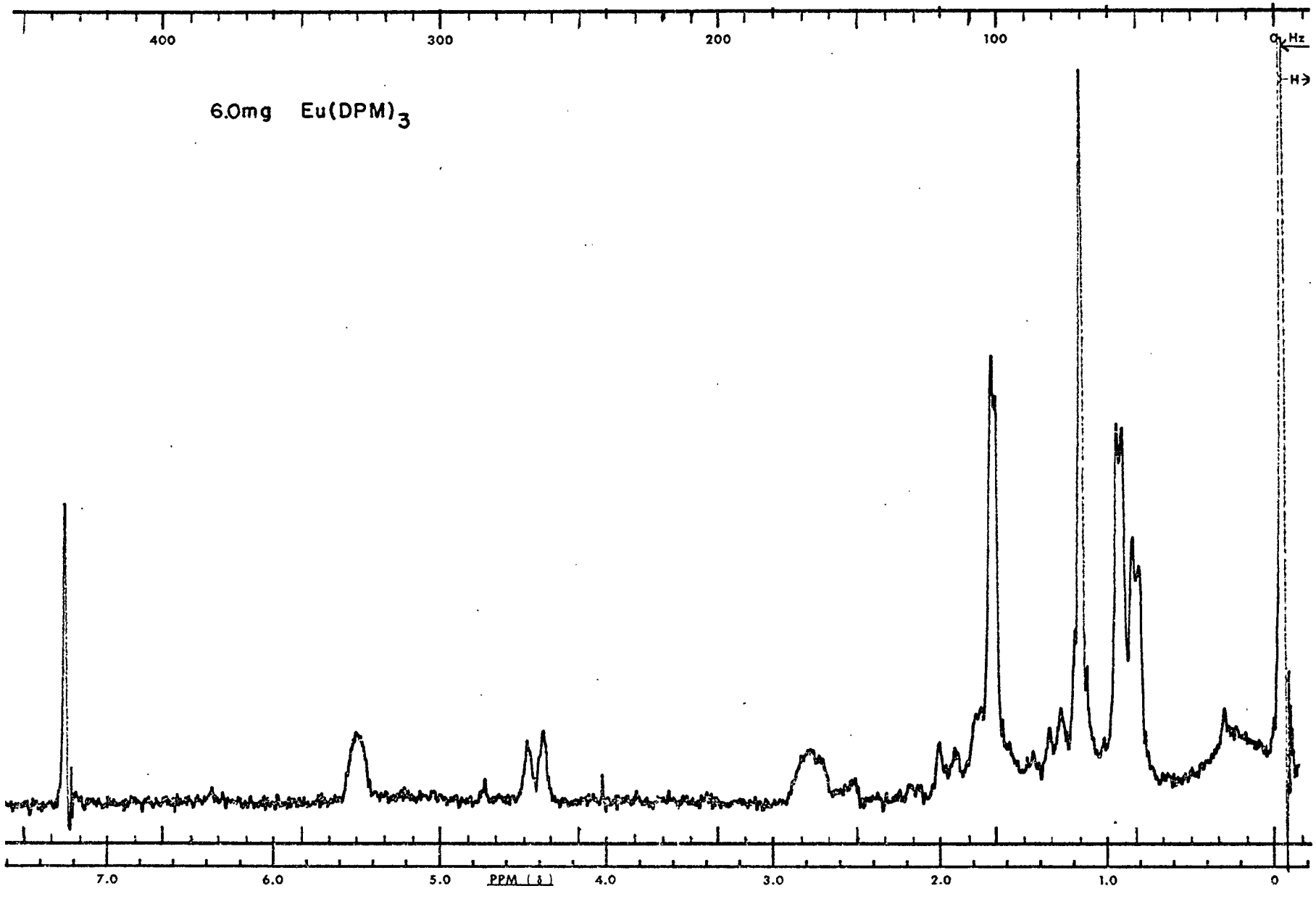

400
300
200
100
0 Hz
6.1 mg Eu(DPM)3
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

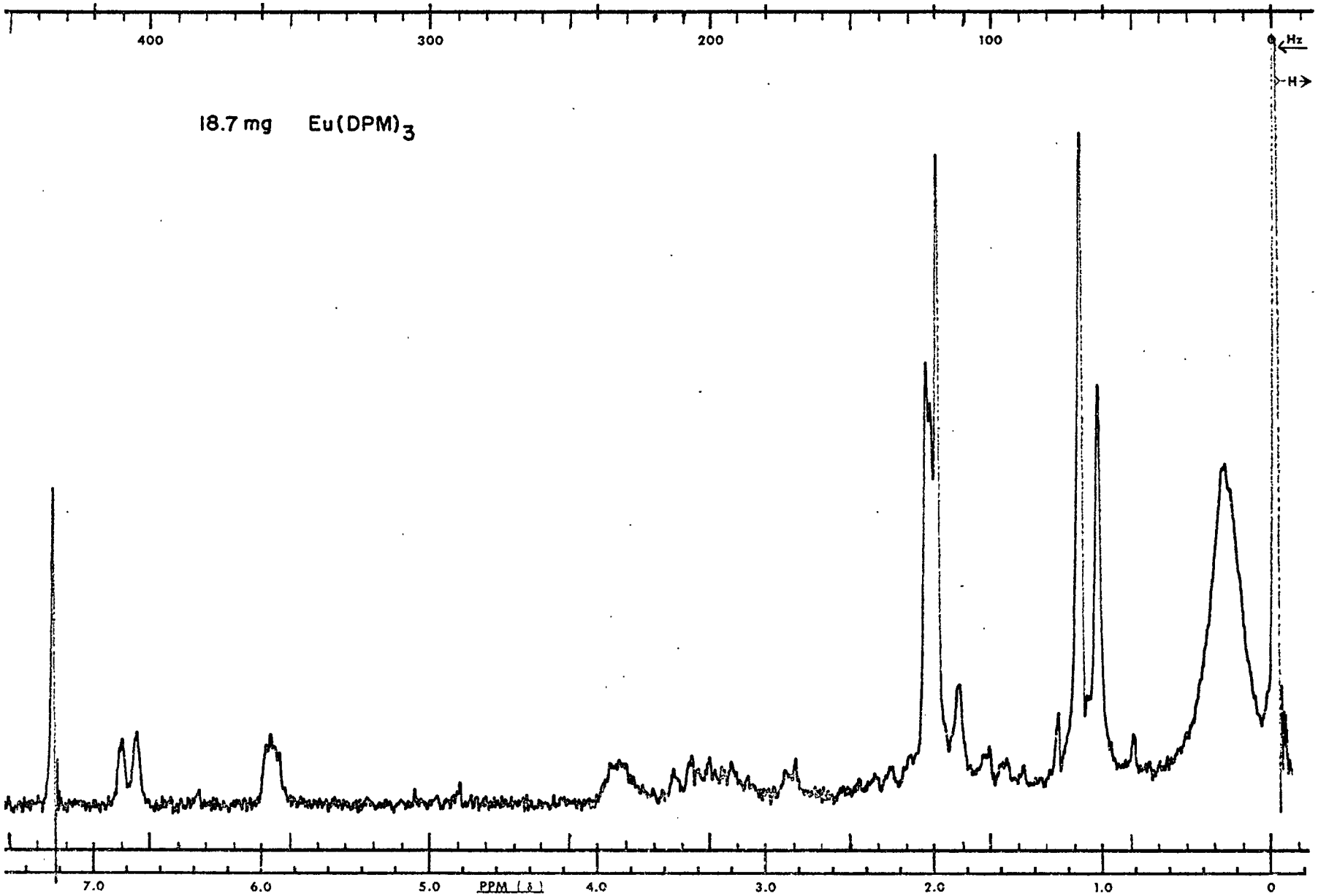

400
300
200
100
Hz
H
18.3 mg Eu(DPM)3
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

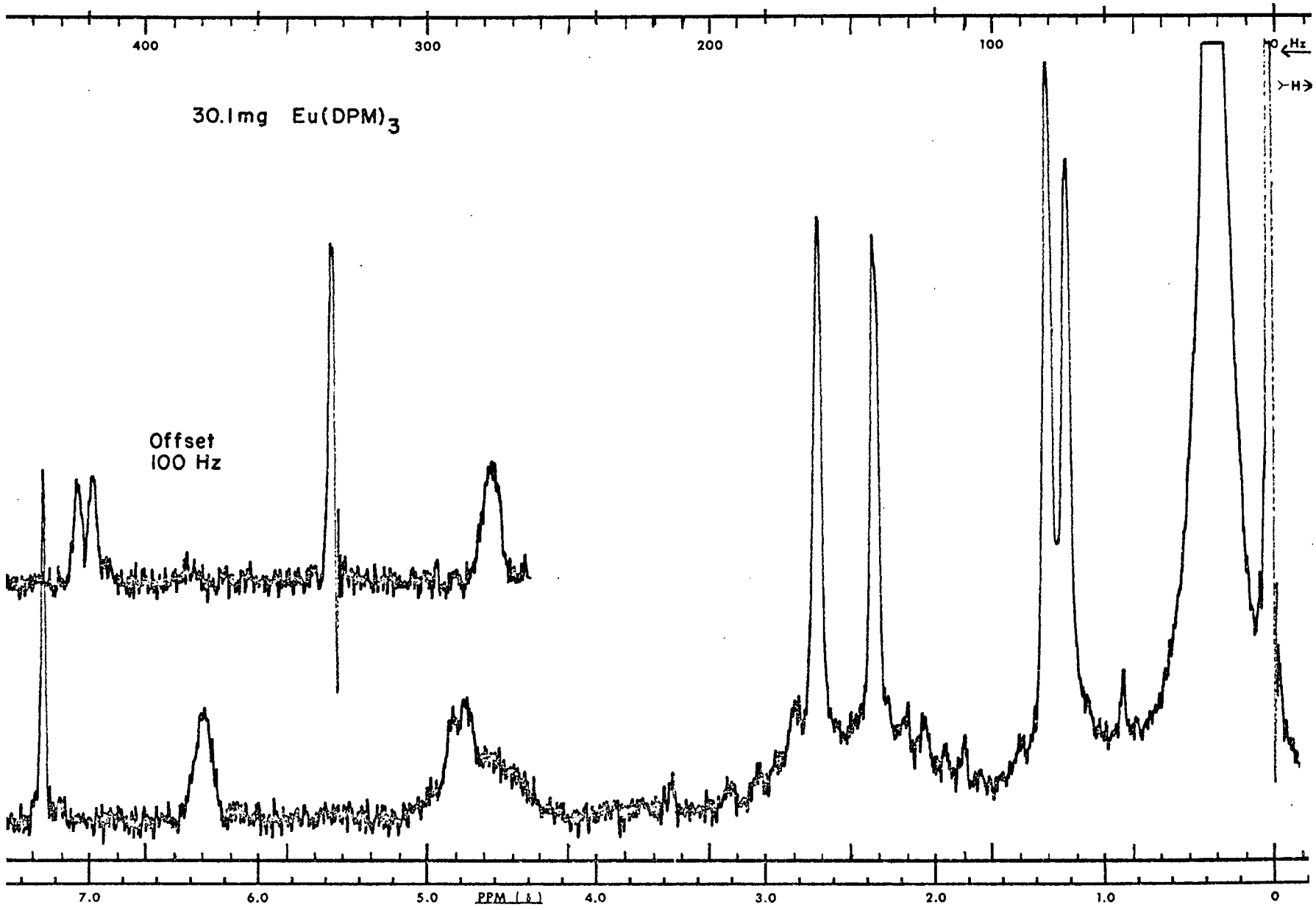

400
300
200
100
0
Hz
H
30.0mg Eu(DPM)3
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

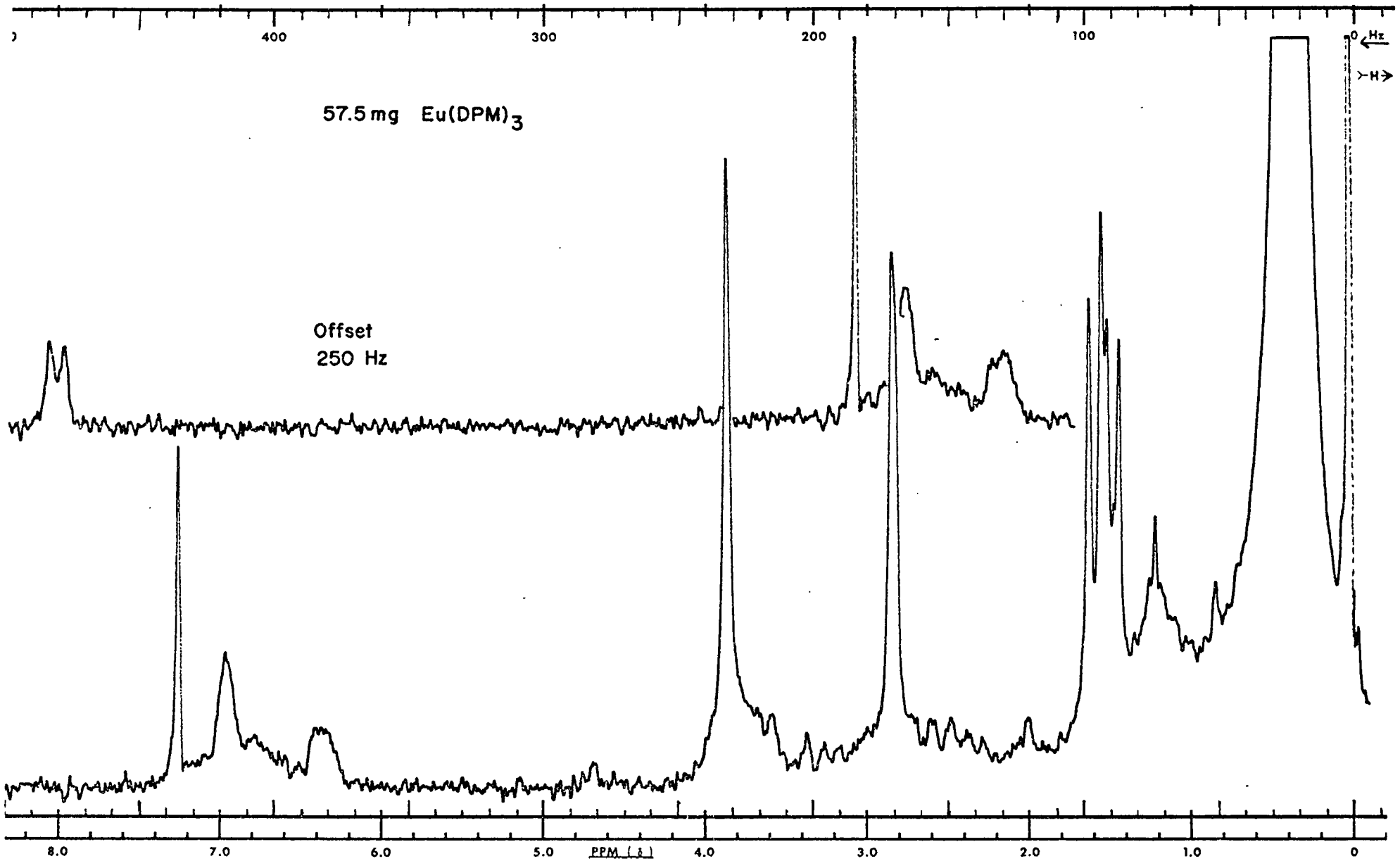

400
300
200
100
0 Hz
H
56.9mg Eu(DPM)3
Offset 220Hz
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


400
300
200
100
0 Hz
H
5% in CCl_4
no $Eu(DPM)_3$
OH
H
65
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


400
300
200
100
0 Hz
H
6.0mg Eu(DPM)3
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


400
300
200
100
0
Hz
H
18.7 mg Eu(DPM)3
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


400
300
200
100
0 Hz
H
30.1mg Eu(DPM)3
Offset
100 Hz
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0


400
300
200
100
0 Hz
H
57.5 mg Eu(DPM)3
Offset
250 Hz
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

CHAPTER 3

CONCLUSIONS

CONCLUSIONS

(±)-Longicyclene has been stereoselectively synthesized in a limited number of specific steps. This synthesis provides additional proof for the structure of (+)-longicyclene. An alternate synthetic route to (±)-longicamphor and (±)-longiborneol also was developed. Two new synthetic reactions, a reductive-cyclization utilizing diisobutylaluminum hydride and a method of deoxygenating cyclopropyl carbinols, have been developed during the course of this study.

The attempt to extend the synthetic scheme utilized in the preparation of (±)-longicyclene to a synthesis of (+)-cyclosativene failed. This failure can best be understood by examining two points. Although the natural products--(+)-longicyclene and (+)-cyclosativene--have a great deal of structural similarity, the respective starting materials--tetrahydroeucarvone and carvomenthone--are quite different in chemical reactivity.

While the alkylation of tetrahydroeucarvone with allyl bromide produced a pair of enantiomers, the alkylation of carvomethone with the same reagent would produce a diastereomeric pair due to the previously established configuration at carbon-4. Under the reaction conditions subsequently utilized, no difference in the chemical properties would be apparent between the two enantiomers resulting from this alkylation of tetrahydroeucarvone. Diastereomeric isomers, however, frequently exhibit quite different chemical properties, such as rates of reactivity or the production of different products under identical conditions.

Such differences provide a host of potential problems to a chemist when working with such a mixture. Such differences, which were exhibited at the enol-lactone stage, caused the failure of the initially planned synthetic scheme.

Two areas of study have been indicated as a direct result of this work. A systematic study of the reductive-cyclization reaction utilizing diisobutylaluminum hydride to determine if the reaction has general synthetic utility is indicated. The deoxygenation of cyclopropyl carbinols without fragmentation is a potentially useful synthetic process. A study should be made to determine the applicability of this reaction to compounds other than the one utilized in this dissertation.

CHAPTER 4

EXPERIMENTAL

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. All boiling points are uncorrected. Analyses were performed by Elek Microanalytical Laboratories, Torrance, California and Spang Microanalytical Laboratory, Ann Arbor, Michigan.

Analytical gas phase chromatography (glc) was performed using the following types of columns and flow rates:

A. 50-foot, stainless steel, 0.02 inch capillary column coated with Carbowax 6000; flow rate 5 ml/min. at ambient temperature.

B. 300-foot, stainless steel, 0.02 inch capillary column coated with OV-17 (Varian); flow rate 5 ml/min. at ambient temperature.

C. 300-foot, stainless steel, 0.02 inch capillary column coated with FFAP (Varian); flow rate 5 ml/min at ambient temperature.

D. 5-foot, stainless steel, 1/8 inch column, packed with 3% SE-30 on Varaport 30, 100/120 mesh (Varian); flow rate 15 ml/min at ambient temperature.

E. 6-foot, stainless steel, 1/8 inch column, packed with 5% FFAP on Varaport-30, 80/100 mesh (Varian); flow rate 15 ml/min at ambient temperature.

F. 6-foot, stainless steel, 1/8 inch column, packed with 5% OV-17 on Varaport-30, 80/100 mesh (Varian); flow rate 15 ml/min at ambient temperature.

Silica gel PF 254+366 (E. Merck No. 7748) and silica gel 60 (E. Merck No. 7734, 70-230 mesh or 75-325 mesh) available from Brinkmann Instruments was used for thin layer and column chromatography, respectively.

Infrared (ir) spectra were recorded on a Perkin-Elmer Model 337 or 700 spectrophotometer. Solid samples were recorded in spectroquality carbon tetrachloride or chloroform using 0.10 mm sodium chloride cells. Liquid samples were taken as thin films between sodium chloride plates.

Nuclear magnetic resonance (nmr) spectra were measured on a Varian Associates Model T-60 or HA-100 spectrometer. The following abbreviations are used to describe nmr spectral bands reported in the experiment section: broad (b), singlet (s), doublet (d), triplet (t), quartet (q), AB quartet (AB), multiplet (m), and δ (parts per million, ppm) downfield from tetramethylsilane.

Finally for all reactions performed under an atmosphere of dry nitrogen, the equipment was dried in an oven at 120° for several hours, then allowed to cool in an atmosphere of dry nitrogen using an apparatus designed by Johnson and Schneider.[57] All liquid transfers were made with nitrogen filled syringes. The term "pet-ether" refers to Baker "Analyzed Reagent" bp 30-60°.

Eucarvone (25)[15,16] - Freshly distilled carvone (24; 200 g, 1.33 mole) was slowly added to a solution of anhydrous hydrogen bromide (295 g, 3.66 mole) in glacial acetic acid (1.0 l) at 5 to 10° with rapid stirring and efficient cooling. The cooling bath was removed and stirring continued for 15 minutes.

The resulting orange solution was poured into water (2 l), the lower layer separated and the aqueous layer extracted with ether (3X). The combined ethereal extracts were washed with water (3X), saturated potassium bicarbonate solution until basic to litmus paper and finally with water until neutral. The organic solution was dried (Na_2SO_4), then added dropwise to a well-stirred and cooled solution of potassium hydroxide (145 g) and anhydrous methanol (550 ml).

After completion of the addition, the resulting suspension was stirred at reflux for 15 minutes, then poured into ice-sulfuric acid. The yellow liquid was separated and the aqueous layer was extracted with ether (3X). The combined ethereal extracts were washed with 10% sodium hydroxide (3X) to remove the carvacrol, then with water until neutral, dried (Na_2SO_4), concentrated *in vacuo*, and distilled to give 130 g (65%) of eucarvone (25): bp 46-49° (1.5 mm) [lit.[16] 81.5 - 84.0° (8mm)]; ir (film) 3010 (CH=CH), 1660 (CO), 1385, 1365 (gem-CH_3), and 728 cm^{-1} (CH=CH); nmr (CCl_4) δ 5.5 - 6.54 (m, 3, CH=CH), δ 2.57 (s, 2, $COCH_2$), δ 1.85 (d, 3, J = 1.8 Hz, CH_3CH=), and δ 1.06 ppm (s, 6, gem-CH_3).

Tetrahydroeucarvone (21)[18,19] - Eucarvone (25, 223 g, 1.49 mole) was carefully mixed with 10% palladium on charcoal (8.5 g) in a Parr Shaker bottle. The unsaturated ketone was hydrogenated on a Parr Shaker at 15 to 50 psi until no further hydrogen uptake was observed. The product was filtered through Celite and distilled to give 215 g (94%) of tetrahydroeucarvone (21): bp 47-50° (1.5 mm) (lit.[18,19] 46-49° 1.5 mm)); ir (film) 1700 (CO), 1385, and 1370 cm^{-1} (gem-CH_3); nmr (CCl_4)

δ 2.34 (distorted AB, 3, J_{AB} = 12 Hz, CHCO and $COCH_2$), δ 1.02 (d, 3, J = 7 Hz, CH_3CH), δ 0.95 and 0.91 ppm (s, s, 6, gem-CH_3); nmr (100 Hz, CCl_4) δ 2.21 (distorted AB, 3, J_{AB} = 12 Hz, CHCO and $COCH_2$), δ 0.88 (d, 3, J = 7 Hz, CH_3CH), δ 0.83 and 0.78 ppm (s, s, 6, gem-CH_3).

2-[3'-Propene]-2,6,6-trimethylcycloheptanone (26)[22] - Sodium hydride (1.63 g, 40 mg-at of a 59% dispersion) was transferred to the reaction flask and washed with anhydrous 1,2-dimethoxyethane (DME, 5 x 10 ml freshly distilled from lithium aluminum hydride). Dry DME (10 ml) was added and the apparatus sealed under dry nitrogen. Tetrahydroeucarvone (21), (6.00 g, 38.9 mmole) dissolved in dry DME (10 ml) was added. The mixture was allowed to stir at 80 ± 2° for 48 hours.

The resulting light yellow slurry of sodium enolate was cooled to room temperature and allyl bromide (7.0 ml, 80 mmole, freshly distilled) dissolved in dry DME (5 ml) was added over a period of one hour. The pale yellow slurry was allowed to stir at room temperature for 24 hours; then poured into a mixture of acetic acid, ice, and ether. The ether layer was separated and washed with 10% sodium bicarbonate solution (3X), with water (3X), then dried (Na_2SO_4), and concentrated in vacuo. Distillation gave 6.05 g (80%) of colorless alkylated ketone 26: bp 49.5-50.5° (0.17 mm); ir (film) 3075 ($CH=CH_2$), 1695 (CO), 1640 ($CH-CH_2$), 1460 (CH), 1390, 1370, 1365 (gem-CH_3), 993 and 912 cm^{-1} ($CH-CH_2$); nmr (CCl_4) δ 4.8-6.1 (m, 3, $CH=CH_2$), δ 2.38 (AB, 2, J_{AB} = 11 Hz, $COCH_2$), δ 2.14 (d, 2, J = 8 Hz, $CH_2-CH=CH_2$) δ 0.99, 0.95, and 0.89 ppm (s, s, s, 9, CH_3);

glc analysis on column A (column temp. 120°, retention time 12.1 min) shows the product to be greater than 99.6% of a single product.

Anal. Calcd for $C_{13}H_{22}O$: C, 80.36; H, 11.41; Found: C, 80.39; H, 11.46.

2-[Ethyl-2'-acetate]-2,6,6-trimethylcycloheptanone (27)[22] - Sodium hydride (1.79 g, 44 mg-at of a 59% dispersion) was transferred to the reaction flask and washed with anhydrous 1,2-dimethoxyethane (DME, 3 x 10 ml, freshly distilled from lithium aluminum hydride). Dry DME (35 ml) was added and the flask sealed under dry nitrogen. Tetrahydroeucarvone (21, 6.00 g, 38.9 mmole dissolved in dry DME, 5 ml) was added to the stirred sodium hydride in refluxing DME. The mixture was allowed to stir at 82 ± 3° for 46 hours.

The resulting light yellow slurry of enolate anion was cooled to 15° and ethyl 2-bromoacetate (4.9 ml, 44 mmole, freshly distilled) dissolved in dry DME (5 ml) was added over a period of 5 minutes. The reaction was allowed to warm to 25° over a period of 90 minutes, then poured into acetic acid-ice and extracted with ether. The combined ethereal extracts were washed with saturated sodium bicarbonate solution (3X), with saturated sodium chloride solution until neutral, then dried ($MgSO_4$), and concentrated in vacuo. Distillation gave 4.80 g (53%) of colorless keto ester 27: bp 76.5-79° (0.08 mm); ir (film) 1735 (CO_2Et), 1700 (CO), 1395, 1380, 1365 (gem-CH_3), 1228, 1200, 1161 (asymmetric COC), 1118, 1066, and 1033 cm^{-1} (symmetric COC); nmr (CCl_4) δ 4.06 (q, J = 7 Hz, OCH_2CH_3). δ 2.43 (bs, 2, CH_2CO_2Et), δ 1.10 (s, 3, CH_3), and δ 0.91 ppm

(s, 6, gem-CH_3O); glc analysis on column A (column temp. 120°, retention time 20.5 min) shows the keto ester to be greater than 99.6% of a single product.

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.06; Found: C, 70.25; H, 10.03.

3-Penten-2-ol (30)[22,23] - Approximately 3.0 l of anhydrous ether and 122 g (5.0 gram-atoms) of magnesium turnings was placed in a 5-l. three-necked flask. Methyl iodide (324 ml, 5.2 mmoles) was placed in a pressure compensating dropping funnel.

After the first 50 ml of methyl iodide had been added, the flask was gently warmed to initiate the reaction. The remainder of the methyl iodide was added at a rate which would maintain the reaction at gentle reflux.

When most of the magnesium had reacted, crotonaldehyde 29 (284 g, 4.04 mole, dissolved in anhydrous ether, 300 ml) was added dropwise with vigorous stirring and cooling (ice-bath). The mixture was then allowed to stir at room temperature for 30 minutes, quenched with saturated sodium chloride solution (500 ml) with cooling (ice-bath), the ether layer decanted, washed with 10% sodium sulfite solution (3X), dried (K_2CO_3 - Na_2SO_4), filtered and concentrated in vacuo at room temperature. A trace of anhydrous calcium oxide was added and the crude product distilled to give 286 g (82%) of colorless 3-pentene-2-ol (30); bp 119-122°; ir (film) 3650-3050 (OH), 3025 (CH=CH), 1675 (trans CH=CH), 1450, 1375, 1360 (CH_3), 1060, 1021 (OH), 962 (trans CH=CH), 909, and 858 cm^{-1};

(CCl_4) δ 5.17-5.97 (m, 2, CH=CH), δ 4.36 (bm, 1, CHOH), δ 4.13 (bm, 1, CHOH), δ 1.67 (doublet of doublets, 3, J_1 = 1 Hz, J_2 = 4.2 Hz, CH_3CH=CH), and δ 1.14 ppm (d, 3, J_3 = 6.5 Hz, CH_3CH).

4-Chloro-2-pentene (31)[22] - 3-Penten-2-ol (30) (73.1 g, 849 mmole) was placed in a 100-ml round-bottomed flask and cooled to 0° (ice-bath). Anhydrous hydrogen chloride gas was slowly bubbled through the alcohol for 3 hours. The mixture was then transferred to a separatory funnel and the aqueous layer separated. The crude chloride was dried ($CaCl_2$) and distilled to give 68.8 g (77%) of 4-chloro-2-pentene (31): bp 99-102°; ir (film) 3040 (w, CH=CH), 1670 (transCH=CH), 1450, 1375 (CH_3), 961 (transCH=CH), and 643 cm^{-1}.(CHCl); nmr (CCl_4) δ 5.28-6.06 (m, 2, CH=CH), δ 4.22-5.0 (m, 1, CHCl), δ 1.63 (doublet of doublets, 3, J_1 = 1 Hz, J_2 = 5 Hz, CH_3CH=CH), and δ 1.49 ppm (d, 3, J_3 = 6.3 Hz, CH_3CHCl).

2-[4'Pent-2'ene]-2,6,6-trimethylcycloheptanone (28)[14,22] - Sodium hydride (17.9 g, 440 mg-at, of a 59% dispersion) was transferred to the flask and washed with anhydrous 1,2-dimethoxyethane (DME, 3 x 25 ml, freshly distilled from lithium aluminum hydride). Dry DME (250 ml) was added and the apparatus sealed under dry nitrogen. Tetrahydroeucarvone (21, 60.0 g, 389 mmole, dissolved in dry DME, 50 ml) was added rapidly. The reaction mixture was allowed to stir at 80 ± 5° for 72 hours.

To the resulting light yellow slurry of sodium enolate at 5° (ice-bath) was added 4-chloro-2-pentene (46.5 g, 440 mmole, dissolved in dry DME, 50 ml). The reaction mixture was allowed to stir at room temperature for 72 hours.

The resulting milky-white slurry was heated to reflux (2 hr.), cooled, and poured into ice-water and extracted with ether. The combined ethereal extracts were washed with saturated sodium chloride solution until neutral, dried ($MgSO_4$), and concentrated in vacuo. Distillation gave 74 g (86%) of colorless alkylated ketone 28: bp 70-71° (0.16 mm); ir (film) 3025 (CH=CH), 1695 (CO), 1675 (trans CH=CH), 1390, 1380, 1370 (gem-CH_3), and 966 cm^{-1} (trans CH=CH); nmr (CCl_4) δ 4.67-5.16 (m, 2, CH=CH), δ 2.63, 2.47 (two doublets, 1, J = 2.2 Hz, J_2 = 1.7 Hz, J_4 = 1.7 Hz, CH_3CHCH=CH), δ 0.92, 0.85, 0.77 (s, s, s, 9, CH_3), and δ 0.74 ppm (d, 3, J_5 = 6.6 Hz, CH_3CH).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79; Found: C, 81.14; H, 11.73.

2-[2'Ethanoic acid]-2,6,6-trimethylcycloheptanone (35)[25] - A solution of sodium metaperiodate (45 g, 210 mg-at), keto-olefin 26 (6.94 g, 38.9 mmole), aqueous ruthenium trichloride solution (0.6 ml, 0.038g/ml, 0.0231 g) in distilled water (1600 ml) and t-butanol (500 ml) was stirred at room temperature for 72 hours. The solution was transferred to a separatory funnel and extracted with dichloromethane (6 x 150 ml). The combined organic extracts were washed with 10% sodium hydroxide solution (5 x 100 ml). The combined basic extracts were washed with dichloromethane (1 x 50 ml). The aqueous layer was acidified with concentrated hydrochloric acid and extracted with dichloromethane (5 x 100 ml). The combined latter organic extracts were washed with saturated sodium chloride solution, dried ($MgSO_4$), and concentrated

in vacuo to 7.52 g of a yellow viscous oil. Distillation gave 7.16 g (87%) of a slightly yellow viscous keto-acid 35: bp 100° (bath temperature, 0.30 mm); ir (film) 2450-3650 (CO_2H), 1735, 1700 (CO_2H), 1380, 1360 (gem-CH_3), 1291, 1224, 1200 cm^{-1} (C-O); nmr (CCl_4) δ 10.0 (s, 1, CO_2H), δ 2.40 (m, .4, CH_2CO), δ 1.19, 0.95, 0.92 ppm (s, s, s, 9, CH_3).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50; Found: C, 67.65; H, 9.41

3,3,7-Trimethyl-9-oxo-10-oxabicyclo[5.3.0] dec-1-ene (36)[24] - A solution of keto-acid 35 (9.10 g, 42.9 mmole) and anhydrous sodium acetate (0.5 g) in acetic anhydride was allowed to stir at 140 ± 2° (bath temp.) for 5 hours.

The resulting orange-brown solution was cooled to room temperature, poured into ice-saturated sodium bicarbonate solution (300 g - 150 ml), and extracted with ether (5 x 50 ml). The combined ethereal extracts were washed with water (3 x 50 ml), saturated socium chloride solution (50 ml), dried (Na_2SO_4), and concentrated in vacuo. The remaining traces of acetic anhydride were removed by codistillation in vacuo with toluene (3 x 50 ml) and with methanol (3 x 50 ml containing a trace of pyridine). The orange oil was dissolved in hexane (50 ml) and concentrated to approximately 25 ml and cooled in the freezer overnight. The crude slightly yellow crystals were purified by sublimation (40 ± 2°, 0.5 mm) to give 7.26 g (87%) of pure white crystalline enol-lactone 36: mp 68.7-69.2°; ir ($CHCl_3$) 1800, 1790 (CO), 1685 (OC=CH), 1390, 1380, 1365 (gem-CH_3, 857 and 848 cm^{-1} (C=CH); nmr (CCl_4), δ 5.06 (s, 1, OC=CH), δ 2.36

(AB, 2, J_{AB} = 17 Hz, CH_2CO), δ 1.28 (s, 3, CH_3), and δ 1.05 ppm (bs, 6, gem-CH_3).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34; Found: C, 74.38; H, 9.35.

2,2,6-Trimethyl-8-exo-hydroxybicyclo[4.2.1]nonan-9-one (41)[24] - Enol-lactone 36 (0.120 g, 0.619 mmole) was stirred in anhydrous tetrahydrofuran (10.0 ml, freshly distilled from lithium aluminum hydride) at -78° (Dry-Ice) under Ar while a solution of diisobutylaluminum hydride in benzene (0.45 ml, 1.50 M, 0.68 mmole) was added dropwise. After 10 minutes the cooling bath was removed and the clear solution was allowed to stir at room temperature for 22 hours. The reaction was quenched at 0° (ice-bath) with 10% hydrochloric acid (1.0 ml), poured into water (50 ml) and extracted with ether (4 x 25 ml). The combined ethereal extracts were washed with water (3 x 50 ml), saturated sodium chloride solution (50 ml), dried (Na_2SO_4), and concentrated in vacuo to give 0.117 g of a colorless oil. Preparative thin layer chromatography on a 20 x 20 cm silica gel plate using 50% ether/50% pet-ether eluent gave 0.099 g (82%) of white crystalline ketol 41 (R_f 0.16-0.34): mp 65-66° ir ($CHCl_3$) 3600, 3460 (OH), 1725 (CO), 1395, 1389, 1375 cm^{-1} (gem-CH_3); nmr ($CDCl_3$) δ 4.37-4.67 (symmetrical multiplet, coupled ABX, 1, $J_{C-1,C-8}$ = 2 Hz, J_{AB} = 14 Hz, CHOH), δ 2.95 (s, 1, -OH), δ 2.50 and 2.27, δ 1.80 and 1.60 (two doublets, 2, J = 8 Hz and two doublets, J = 5 Hz, CH_2 at C-7), δ 1.97 (d, 1, J = 2 Hz bridgehead at C-1; dihedral angle between protons on C-1 and C-7 must be near 130°); δ 1.15 (s, 9, -CH_3).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43, H, 10.27; Found: C, 73.31; H, 10.14.

2-[2'Propanoic acid]-2,6,6-trimethylcycloheptanone (42)[14,22,25]

A mixture of keto-olefin 28 (10.0 g 45.0 mmole), sodium metaperiodate (48.0 g, 225 mg-at) and distilled water (1.0 l) was stirred until all the sodium metaperiodate dissolved. Tert-butanol (525 ml) was added with stirring and the solution became homogeneous. Catalytic amounts of ruthenium trichloride solution (2 ml, 0.0385 g/ml) and osmium tetroxide solution (10 ml, 0.0025 g/ml) were added. The flask was then filled completely with distilled water, carefully stoppered and allowed to stir for 188 hours at room temperature. The reaction mixture was poured into water (2 l) and extracted with ether (10 x 200 ml). The combined ethereal extracts were washed with 10% sodium hydroxide solution (5 x 100 ml). These combined aqueous extracts were washed with ether (100 ml). The aqueous layer was then carefully acidified with cooling (ice-bath) with concentrated hydrochloric acid. The slightly acidic aqueous mixture was extracted with ether (5 x 100 ml) and the combined ethereal extracts were washed with water (50 ml), saturated sodium chloride solution (50 ml), dried ($MgSO_4$), and concentrated in vacuo to give 9.46 g (93%) of pale yellow crystalline keto-acid 42: mp 125-125.5°; ir ($CHCl_3$) 2400-3580 (CO_2H), 1710, 1700 (CO_2H,CO), 1380, 1370 cm^{-1} (gem-CH_3); nmr (CCl_4) δ 8.05 (bs, 1, CO_2H), δ 3.49 (distorted AB, 3, J_{AB} = 7 Hz, CHCO and $COCH_2$), δ 1.18 (s, 3, CH_3), δ 1.04 (bs, 6, gem-CH_3), and δ 0.90 ppm (d, 3, J = 5.6 Hz, CH_3CH).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80; Found: C, 68.81; H, 9.70.

3,3,7,8-Tetramethyl-9-oxo-10- xabicyclo[5.3.0]dec-1-ene (43)[24]

Method A - A solution of keto-acid 42 (13.3 g, 58.9 mmole) and anhydrous sodium acetate (0.274 g) in acetic anhydride (50 ml) was stirred at reflux for 5 hours. After cooling to room temperature the orange-brown mixture was poured into ether (250 ml). This ethereal solution was washed with water (3 x 50 ml), 5% disodium hydrogen phosphate solution (3 x 25 ml), saturated sodium chloride solution (3 x 50 ml), dried overnight (Na_2SO_4) containing methanol (150 ml) and pyridine (0.5 ml). The resulting mixture was filtered and concentrated in vacuo to give 11.6 g (95%) of a red oil. Distillation gave 10.6 g (87%) of colorless liquid enol-lactone 43: bp 86-89° (0.4 mm).

Method B[28] - A solution of keto-acid 42 (16.5 g, 72.9 mmole) and acetic anhydride (20.0 ml, 212 mmole, freshly distilled), in anhydrous dichloromethane (400 ml, freshly distilled from phosphorous pentoxide) containing 60% perchloric acid (20 µl) was allowed to stir at room temperature for 4 hours. The reaction mixture was washed with water (3 x 100 ml), saturated sodium bicarbonate solution (100 ml), water (100 ml), dried ($MgSO_4$), and concentrated in vacuo. The last traces of acetic anhydride were removed with methanol (50 ml) containing a trace of pyridine (0.2 ml) and again concentrated in vacuo to give 14.8 g (97.4%) of an orange oil. Distillation gave 13.7 g (90%) of colorless liquid enol-lactone 43: bp 86-89° (0.4 mm); ir (film) 3040 (OC=CH),

1790 (CO), 1685 (OC=CH), 1390, 1375 (gem-CH_3), 855 and 841 cm^{-1} (OC=CH); nmr (CCl_4), δ 5.19 (m, 1, OC=CH), δ 1.30 (s; 3, CH_3), and δ 1.10 ppm (s, 6, gem-CH_3); glc analysis on column D shows the product to be 70/30 mixture of diastereomers (column temp. 145°, retention times 7.2 min. and 9.1 min.).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68; Found: C, 74.91; H, 9.72.

2,2,6,7-Tetramethyl-8-exo-hydroxybicyclo[4.2.1]nonan-9-one (44)[24]- A solution of enol-lactone 43 (1.796 g, 8.62 mmole) in anhydrous tetrahydrofuran (80 ml, freshly distilled from lithium aluminum hydride) was stirred under nitrogen at -78° (Dry-Ice) while a benzene solution of diisobutylaluminum hydride (6.00 ml, 1.50 M, 9.0 mmole) was added dropwise. After 30 minutes the cooling bath was removed and the clear solution was allowed to stir at 60° (bath temp.) for 18 hours. The reaction mixture was cooled to room temperature and poured into an ice-water mixture (200 ml) containing 10% hydrochloric acid (6 ml). The mixture was extracted with ether (6 x 50 ml). The combined ethereal extracts were washed with water (4 x 100 ml), saturated sodium chloride solution (100 ml), dried (Na_2SO_4), and concentrated in vacuo to give 1.90 g of crude oil. The crude product was immediately chromatographed on silica gel (190 g, 75-325 mesh, E. Merck) in a 2.5 cm diameter column. A 50:50 mixture of ether and pet-ether was used to develop the column taking 80-ml sized fractions. Fractions 7-11 gave 1.45 g (80%) of pure ketol 44 as a colorless liquid. Analysis by glc on column D shows the ketol

44 to be a 66:34 mixture of diastereomers: bp 105° (0.2 mm, bulb to bulb, external temperature); ir (film) 3440 (-OH), 1725 cm^{-1} (CO). This compound was found to be very sensitive to acid or base catalyzed fragmentation and was immediately carried on to the next reaction.

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54; Found: C, 74.25; H, 10.65.

2,2,6,7-Tetramethylbicyclo[4.2.1]non-7-en-9-one (45)[29,30] - A solution of ketol 44 (1.835 g, 8.72 mmole) in anhydrous dichloromethane (60 ml, freshly distilled from phosphorous pentoxide) was stirred at 0° (ice-bath) while triethyl amine (1,337 g, 13.2 mmole, freshly distilled from calcium hydride) and methanesulfonyl chloride (1.105 g, 9.05 mmole, freshly distilled) were added sequentially. The resulting pale yellow solution was stored in a refrigerator at 3° for 17 hours. The solution was transferred to a separatory funnel with dichloromethane (600ml) and water (150 ml). The organic layer was separated and washed with water (150 ml)., 5% hydrochloric acid (150 ml), saturated sodium chloride solution (150 ml), dried (Na_2SO_4), and concentrated in vacuo to give 2.52 g of a crude oil. This oil was dissolved in collidine (55 ml, dried over barium oxide). After stirring under nitrogen at 170-175° (bath-temp.) for 16 hours, the dark brown solution was cooled to room temperature and diluted with ether (500 ml) and water (150 ml). The ether layer was separated and washed with 5% hydrochloric acid (6 x 150 ml), water (150 ml), saturated sodium bicarbonate solution (150 ml), water (150 ml), saturated sodium chloride solution (150 ml), dried (Na_2SO_4), and

concentrated *in vacuo* to give 1.66 g of crude ketone **45**. Distillation gave 1.46 g (87%) of pure ketone **45**: bp 46° (0.2 mm, external temperature); [lit.[34] ir ($CHCl_3$) 1738, 1650, 850 cm^{-1}] ir ($CHCl_3$) 1735 (CO), 1645, 850 cm^{-1} (C=CH); nmr (CCl_4) δ 5.80 (q, 1, *J* = 2 Hz, CH=C), δ 2.35 (q, 1, *J* = 2 Hz, bridgehead at C-1), δ 1.66 (t, 3, *J* = 2 Hz, CH_3C=CH), δ 1.02 (s, 6, CH_3), δ 0.97 ppm (s, 3, CH_3)

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48; Found: C, 80.97; H, 10.52.

2,2,6,7-Tetramethyl-9-methoxymethylenebicyclo[4.2.1]non-7-ene (46)[32]

Sodium hydride (1.288 g of a 57% dispersion in oil, 30.6 mg-at) was washed with anhydrous ether (3 x 20 ml freshly distilled from lithium aluminum hydride) under nitrogen. The remaining traces of ether were removed by warming the sodium hydride in a stream of dry nitrogen. After cooling to room temperature dimethyl sulfoxide (85 ml, freshly vacuum distilled from calcium hydride) was added. The mixture was stirred under nitrogen at 50-60° (bath temp.) for 2.75 hours. After cooling the solution to room temperature methoxymethyltriphenylphosphonium chloride (10.42 g, 30.42 mmole) was added. The resulting deep red solution was stirred 15 minutes, then enone **45** (2.94 g, 15.6 mmole) dissolved in dry dimethyl sulfoxide (3 x 5.0 ml, freshly vacuum distilled from calcium hydride) was added. The resulting reaction mixture was stirred at 59° ± 2° (bath temp.) for 23.5 hours. The orange solution was cooled to room temperature and poured into water (500 ml) and ether (500 ml). The aqueous layer was separated and extracted further with ether

(3 x 250 ml). The combined ethereal extracts were washed with 10% hydrochloric acid (200 ml), water (10 x 200 ml), saturated sodium chloride solution (200 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The resulting concentrate (7.45 g) was dissolved in pet-ether (10 ml) and allowed to stand overnight. The liquid was separated from the crystalline triphenylphosphine oxide and concentrated *in vacuo* to give 4.10 g of crude product. This crude liquid was chromatographed on silica gel (400 g, 75-325 mesh) in a 4.0-cm diameter column using a 2.5% ether 97.5% pet-ether solution to develop the column taking 200-ml sized fractions. Fractions 4-6 were concentrated and distilled to give 2.97 g (88%) of pure methoxyvinyl ether 46: bp 45 ± 2° (0.2 mm, external temperature); ir (film) 3070 (C=CH), 1695 (C=C-O), 1385 and 1365 cm^{-1} (gem-CH_3); nmr (CCl_4) δ 5.64 (m, 1, C=CH-O), δ 5.4 (m, 1, CH=C), δ 3.5 (s, 3, CH_3O), δ 2.92 (m, 1, bridgehead -H), δ 1.57 (m, 3, CH_3C=C), δ 1.01 (s, 3, CH_3), δ 0.92 (s, 3, CH_3), and δ 0.82 ppm (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98; Found: C, 81.79; H, 10.82.

2,2,6,7-Tetramethylbicyclo[4.2.1]non-7-en-9-*exo*-carboxaldehyde (23)[32]- Perchloric acid (20 ml, 50%) was slowly added to a solution of methoxyvinyl ether 46 (1.477 g, 6.7 mmole) in ether (100 ml) under nitrogen. The resulting homogeneous solution was stirred for 1.75 hours at room temperature, then poured into pentane (100 ml) and water (100 ml). The aqueous layer was separated and extracted with pentane (4 x 50 ml). The combined organic extracts were washed with water (50 ml), saturated

sodium chloride solution (50 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The crude aldehyde was dissolved in dry methanol (100 ml) containing anhydrous potassium carbonate (1.0 g). The slurry was stirred at room temperature for 1.75 hours under nitrogen, then poured into water (100 ml). This aqueous solution was extracted with pentane (6 x 40 ml). The combined pentane extracts were washed with water (40 ml), saturated sodium chloride solution (40 ml), dried (Na_2SO_4), and concentrated *in vacuo*. Distillation gave 1.40 g (100%) of pure aldehyde 23: bp 45 ± 2° (0.2 mm, external temperature); ir (CCl_4), 3060 (C=CH), 2745 (-CHO), 1720 (CO), 1385, and 1365 cm^{-1} (gem-CH_3); nmr (CCl_4) δ 9.32 (d, 1, J = 7 Hz, -CHO), δ 5.42 (m, 1, C=CH), δ 2.35 (d, 1, J = 7 Hz, OC-CH), δ 2.11 (m, 1, bridgehead -H), δ 1.55 (m, 3, CH_3C=C), δ 1.03 (s, 3, CH_3), and δ 0.93 ppm (s, 6, CH_3).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75; Found: C, 81.38; H, 10.70.

2,2,6,7-Tetramethylbicyclo[4.2.1]non-7-en-9-*exo*-carboxylic acid (47)[34,35]

Jones' reagent (2.5 ml, 2.67 M, 6.67 mmole) was added dropwise to a solution of aldehyde 23 (1.25 g, 6.06 mmole) dissolved in anhydrous acetone (50 ml, dried over magnesium sulfate) at 0° (ice-bath) with vigorous stirring. The ice-bath was removed after the addition and after 30 minutes the reaction was quenched with reagent isopropanol (enough to remove the orange color). The reaction mixture was dissolved in water (150 ml) and extracted with ether (10 x 25 ml). The combined

ethereal extracts were washed with water (25 ml), then with 10% sodium hydroxide solution (5 x 50 ml). The basic extracts were carefully acidified with concentrated hydrochloric acid while cooling in an ice-bath. This acidified solution was extracted with ether (5 x 50 ml). The combined ethereal extracts were washed with water (25 ml), saturated sodium chloride solution (25 ml), dried (Na_2SO_4), and concentrated *in vacuo* to give 1.15 g (86%) of acid **47**: A small sample of this acid was recrystallized from pentane (3X) to give pure acid **47**: mp 127.5-128°; ir (CCl_4) 3060 ($-CO_2H$), and 1700 (CO); nmr (CCl_4) δ 11.47 (s, 1, $-CO_2\underline{H}$), δ 5.43 (m, 1, C=CH), δ 2.68 (s, 1, $\underline{CH}-CO_2H$), δ 2.37 (m, 1, bridgehead -H), δ 1.52 (m, 3, $CH_3C=C$), δ 1.12 (s, 3, CH_3), δ 0.93 (s, 3, CH_3), and 0.88 ppm (s, 3, CH_3).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97; Found: C, 75.62; H, 9.91.

2,2,6,10-Tetramethyltetracyclo[5.4.0.$0^{6,10}$.$0^{9,11}$]undecan-8-one (**48**)[36]

A solution of the olefinic acid **47** (0.499 g, 2.25 mmole) dissolved in benzene (20 ml, freshly distilled from calcium hydride) was stirred at 0° (ice-bath) under nitrogen while oxalyl chloride (1.35 ml, 2.0 g 15.75 mmole) was added dropwise. The ice-bath was removed and the solution was stirred at room temperature for two hours. The solvent and excess reagent were removed *in vacuo*. The resulting orange oil was dissolved in benzene (2 x 5.0 ml, freshly distilled from calcium hydride) under nitrogen. This solution was added dropwise at 0° (ice-

bath) to an anhydrous ethereal solution of diazomethane (50 ml, ~ 20 mmoles, predried over sodium metal) with vigorous stirring under nitrogen. The resulting solution was stirred at 0° for one hour, then at room temperature for 1.5 hours. The solvents and excess reagent were removed in vacuo. Tetrahydrofuran (40 ml, freshly distilled from lithium aluminum hydride) and finely divided metallic copper powder (0.67 g, Fischer C-434) were added to the crude diazoketone, sequentially. This suspension was vigorously stirred at reflux under nitrogen for 2 hours. The resulting suspension was allowed to stir at room temperature for an additional 14 hours. The solution was filtered into water (100 ml). The mixture was shaken vigorously for five minutes, then extracted with ether (3 x 50 ml). The combined ethereal extracts were washed with saturated sodium bicarbonate solution (4 x 40 ml), water (40 ml), saturated sodium chloride solution (40 ml), dried (Na_2SO_4), and concentrated in vacuo to give 0.673 g of a crude brown oil. This crude oil was chromatographed on silica gel (67 g, 75-325 mesh, E. Merck) in a 2-cm diameter column using 10% ether - 90% pet-ether to develop the column, taking 37-ml sized fractions. Fractions 11-16 gave 0.164 g (33%) of pure ketone 48: mp 64-64.5° (from pentane); ir (CCl_4) 3095 (cyclopropyl C-H) and 1755 cm^{-1} (CO); nmr (CCl_4) δ 1.18 (s, 3 CH_3), δ 1.03 (s, 3, CH_3), δ 0.97 (s, 3, CH_3), and δ 0.90 ppm (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16; Found: C, 82.61; H, 10.01.

2,2,6,10-Tetramethyltetracyclo[5.4.0.$0^{6,10}$.$0^{9,11}$]undecan-8β-ol (49)

Diisobutylaluminum hydride in benzene (0.65 ml, 1.26 M, 0.82 mmole) was added to a stirred solution of tetracyclic ketone 48 (0.164 g, 0.75 mmole) in anhydrous tetrahydrofuran (15 ml, freshly distilled from lithium aluminum hydride) at -78° (Dry-Ice) under nitrogen. The resulting solution was stirred at -78° for 30 minutes, at 0° for 30 minutes, and at room temperature for 3 hours. The solution was then poured into a mixture of ice and 10% sodium hydroxide solution (25 g : 25 ml). The mixture was extracted with ether (6 x 30 ml). The combined ethereal extracts were washed with water (3 x 30 ml), saturated sodium chloride solution (30 ml), dried (Na_2SO_4), and concentrated in vacuo to give 0.169 g of crude crystalline alcohol 49. Recrystallization from pentane (IX) gave 0.162 g (98%) of pure alcohol 49: mp 114-115°; ir (CCl_4) 3650 (free-OH), 3325 (H-bonded-OH), 3075 (cyclopropyl C-H), 1380 and 1365 cm^{-1} (gem-CH_3); nmr (CCl_4) δ 3.63 (s, 1, CH-O), δ 1.73 (s, 1, OH), δ 1.20 (s, 3, CH_3), δ 1.05 (s, 3, CH_3), δ 0.92 (s, 3, CH_3), and δ 0.87 ppm (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98; Found: C, 81.80; H, 10.93.

(±)-Longicyclene (1)[9] - To a stirred solution of tetracyclic alcohol 49 (0.1375 g, 0.625 mmole) in anhydrous dichloromethane (5.0 ml, freshly distilled from phosphorus pentoxide) at 0° (ice-bath) under nitrogen were added sequentially triethyl amine (0.13 g, 0.180 ml, 1.29

mmole, freshly distilled from calcium hydride) and methanesulfonyl chloride (0.147 g, 0.097 ml, 1.28 mmole, freshly distilled). The solution was stored in a freezer at -15° for 72 hours.[29] The reaction mixture was then poured into a mixture of lithium aluminum hydride (0.2033 g, 5.35 mg-at) and ether (20 ml, freshly distilled from lithium aluminum hydride). This mixture was stirred at reflux for 7.5 hours and left to stir at room temperature for 9.5 hours. The reaction mixture was poured into ice-10% sodium hydroxide solution (30 g:30 ml) and extracted with ether (5 x 30 ml). The combined ethereal extracts were washed with 10% hydrochloric acid (30 ml), saturated sodium bicarbonate solution (30 ml), water (2 x 30 ml), saturated sodium chloride solution, dried (Na_2SO_4) and concentrated carefully in vacuo at room temperature to give 0.136 g of crude (±)-longicyclene (1). The crude product was chromatographed on silica gel (10 g, 75-325 mesh, E. Merck) in a 1-cm diameter column using pentane to develop the column, taking 5-ml sized fractions. Fractions 3-5 gave after distillation 0.125 g (98%) of pure (±)-longicyclene (1): bp 82° (2.0 mm, external temperature); ir (CCl_4) 3085 (cyclopropyl -H), 1385, and 1370 cm^{-1} (gem-CH_3); nmr (CCl_4) δ 1.04 (s, 3, CH_3), δ 0.98 (s, 3, CH_3), δ 0.92 (s, 3, CH_3), and δ 0.88 ppm (s, 3, CH_3). The spectral data are identical to those for natural (+)-longicyclene.[9]

Synthetic (±)-longicyclene was found to have identical retention times to natural (+)-longicyclene[9] on glc both in separate and coinjected samples using columns B through F. Glc data on separate and coinjected

samples of longicyclene are listed below:

Column	Column Temperature	Retention time in minutes
B	100°	17.1
C	110°	15.4
D	100°	12.9
E	100°	11.3
F	110°	18.7

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84; Found: C, 88.28; H, 11.78.

2,2,6,7-Tetramethyl-9-exo-vinylbicyclo[4.2.1]non-7-ene (50)[41] - Sodium hydride (0.0840 g 2.00 mg-at) of a 57% dispersion in oil was washed under nitrogen with anhydrous ether (3 x 2 ml freshly distilled from lithium aluminum hydride) and the last traces of ether were removed by warming the sodium hydride in a stream of nitrogen. After cooling to room temperature dry dimethyl sulfoxide (11 ml, freshly distilled from calcium hydride) was added and the mixture was stirred under nitrogen at 60 ± 2° until the evolution of hydrogen ceased. The resulting clear solution was cooled to room temperature and methyltriphenylphosphonium bromide (0.715 g, 2.00 mmole) was added. The yellow solution was stirred at room temperature for 15 minutes, then aldehyde 23 (0.1961 g, 0.95 mmole) was added. The reaction mixture was allowed to stir at room temperature for 13.5 hours. The orange solution was poured into water (60 ml) and extracted with pentane (5 x 30 ml). The combined pentane extracts were washed with 10% hydrochloric acid solution (20 ml), saturated sodium bicarbonate solution (20 ml), water (20 ml), saturated

sodium chloride solution, dried (Na_2SO_4), and concentrated to approximately 10 ml *in vacuo* at room temperature. This solution was chromatographed on silica gel (20 g, 75-325 mesh, E. Merck) in a 1.5 cm diameter column using pentane to develop the column, taking 10-ml sized fractions. Fractions 5 and 6 gave after concentration and distillation 0.1603 g (83%) of pure diene 50: bp 125° (30 mm, external temperature); ir (CCl_4) 3060 (C=CH, H_2C=CH), 1660 (C=CH), 1635 (H_2C=CH), 1385, 1375 (gem-CH_3), and 905 cm^{-1} (H_2C=CH); nmr (CCl_4) δ 5.3-6.0 (m, 2, H_2C=CH and C=CH), δ 4.88 (doublet of doublets, 1, J = 11 Hz and J - 2.5 Hz, cis-proton to R in H_2C=CHR), δ 4.67 (overlapping doublet of doublets, 1, trans-proton to R in H_2C=CHR), δ 2.38 (d, 1, J = 9.5 Hz, H_2C=CH-CH, δ 1.85 (m, 1, bridgehead-H), δ 1.57 (t, 3, CH_3-C=CH), δ 0.97 (s, 3, CH_3), δ 0.95 (s, 3, CH_3), and δ 0.93 ppm (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84; Found: C, 88.22; H, 11.85.

2,2,6,endo-7-Tetramethyl-9-exo-(2'hydroxyethyl)-bicyclo[4.2.1]nonan-exo-8-ol (51)

Method A[41] - Diborane-Tetrahydrofuran solution (2.3 ml, 0.75 M, 1.73 mmole, Alfa-Inorganics) was added to a stirred solution of diene 50 (88.3 mg, 0.432 mmole) in anhydrous tetrahydrofuran (4.0 ml, freshly distilled from lithium aluminum hydride) at 0° (ice-bath) under nitrogen. The resulting solution was allowed to stir at room temperature for 3 hours. The solution was cooled to 0° (ice-bath) and a mixture of 30% hydrogen peroxide and 10% sodium hydroxide solution (5 ml:5 ml) was

added dropwise. The reaction mixture was stirred vigorously at 0° (ice-bath) for one hour, then stirred at room temperature for one hour. The solution was poured into water (50 ml) and extracted with ether (5 x 20 ml). The combined ethereal extracts were washed with 10% sodium hydroxide solution (10 ml), saturated sodium chloride solution (2 x 10 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was chromatographed on silica gel (10 g, 70-230 mesh, E. Merck) in a 1-cm. diameter column using 25% acetone- 75% pet-ether to develop the column, taking 5-ml sized fractions. Fractions 13-17 gave 0.0509 g (49%) of pure diol 51: mp 130.5-131°.

Method B[41] - Diborane-Tetrahydrofuran solution (30 ml, 0.75 M, 20.4 mmole, Alfa-Inorganics) was added to a stirred solution of 2-methyl-2-butene (3.14 g, 44.8 mmole, distilled from sodium metal) in anhydrous tetrahydrofuran (30 ml, freshly distilled from lithium aluminum hydride) at 0° (ice-bath) under nitrogen. The ice-bath was removed and the solution was allowed to stir at room temperature for 3 hours, then recooled to 0° (ice-bath). A solution of diene 50 (0.8324 g, 4.07 mmole) in dry tetrahydrofuran (5.0 ml, freshly distilled from lithium aluminum hydride) was added. The resulting solution was allowed to stir at room temperature for 11.3 hours, then cooled to 0° (ice-bath), and carefully quenched with distilled water (3 ml). This was immediately followed by a mixture of 30% hydrogen peroxide and 10% sodium hydroxide solution, (50 ml:50 ml). The resulting reaction mixture was stirred vigorously at 0° (ice-bath) for 3 hours, then stirred at room temperature for 3 hours.

The mixture was poured into water (400 ml) and extracted with ether (6 x 75 ml). The combined ethereal extracts were washed with 10% sodium hydroxide solution (50 ml), water (3 x 50 ml), saturated sodium chloride solution (50 ml), dried (Na_2SO_4), and concentrated in vacuo. Excess isoamyl alcohol was removed in high vacuum. The crude product (1.58 g) was chromatographed on silica gel (158 g, 70-230 mesh) in a 2.5-cm. diameter column using 25% acetone- 75% pet-ether solution to develop the column taking 75-ml sized fractions. Fractions 14-18 gave 0.478 (49%) of diol 51: mp 130-131°. Recrystallization of a small sample from ether-hexane (IX) gave analytically pure diol 51: mp 130.5-131°; ir ($CHCl_3$) 3625 (free-OH), 3400 (H-bonded-OH), 1385, and 1370 cm^{-1} (gem-CH_3); nmr ($CDCl_3$) δ 4.04 (doublet of doublets an X part of an AMX system, 1, 1st order analysis $J_{7,8}$ = 7.8 Hz and $J_{1,8}$ = 2.6 Hz, RCHOHR;), δ 3.9-3.5 (m, 2, CH_2OH), δ 2.03 (s, 2, OH), δ 1.03 (s, 3, CH_3), δ 0.93 (s, 3, CH_3), and δ 0.90 ppm (s, 6, CH_3).

Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74; Found: C, 74.84; H, 11.71.

2,2,6,endo-7-Tetramethyl-9-exo-(2'-ethyl methanesulfonate)-bicyclo[4.2.1]nonan-8-one (52)[29,44,46] - Triethylamine (0.046 g, 0.454 mmole, freshly distilled from calcium hydride) and methanesulfonyl chloride (0.0596 g, 0.433 mmole) were sequentially added to a stirred solution of diol 51 (0.0994 g, 0.413 mmole) in anhydrous dichloromethane (6.0 ml, freshly distilled from phosphorous pentoxide) at 0° (ice-bath) under nitrogen. The reaction was monitored by tlc (silica gel) using

50% acetone- 50% pet-ether to develop the plates [R_f (product) = 0.66, R_f (starting material) = 0.59]. After 36 hours at 3° (refrigerator) the solution was diluted with dichloromethane (40 ml) and washed with water (2 x 10 ml), 5% hydrochloric acid (10 ml), saturated sodium bicarbonate solution (10 ml), water (10 ml), dried (Na_2SO_4), and concentrated in vacuo to give 0.1286 g (97.4%) of a crude liquid hydroxymesylate; ir (CCl_4) 3400 (OH), 1370, and 1180 cm^{-1} (CH_3SO_2OR); nmr (CCl_4) δ 4.37-3.77 (m, 3, CHOH and CH_2OMS), δ 2.93 (s, 3, CH_3SO_3-), δ 2.50 (s, 1, OH), δ 1.03 (s, 3, CH_3), δ 0.94 (s, 3, CH_3), and δ 0.90 (s, 6, CH_3). This material was used immediately in the next step without further purification.

To a solution of dry pyridine (0.4465 g, 5.65 mmole, freshly distilled from calcium hydride) in anhydrous dichloromethane (5.0 ml, freshly distilled from phosphorus pentoxide) at 0° (ice-bath) under nitrogen was added chromium trioxide (0.282 g, 2.82 mg-at, Alfa-Inorganics No. 87844, dried in a desiccator over phosphorus pentoxide). The burgundy solution was stirred at 0° for 5 minutes then at room temperature for 10 minutes. A solution of the crude hydroxymesylate (0.1286 g, 0.403 mmole) in dry dichloromethane (1.0 ml) was added quickly. A heavy, black, tarry residue separated immediately. After stirring for 15 minutes the brown-black solution was filtered through a column of Woelm neutral alumina (10 g, in a 1-cm. diameter column, activity III) using dichloromethane (4 x 25 ml) to elute. The combined colorless eleunt was concentrated in vacuo to give 0.121 g (92% overall)

of ketomesylate 52: mp 126-127°, tlc (silica gel) using 20% ether- 80% pet-ether to develop the plate shows only one spot. A small sample was recrystallized from pentane to give analytically pure ketomesylate 52: mp 126-127°; ir ($CHCl_3$) 1725 (CO), 1370 and 1180 cm^{-1} (CH_3SO_2-OR: nmr ($CDCl_3$) δ 4.5-4.1 (m, 2, $\underline{CH_2}OMS$), δ 3.0 (s, 3, $\underline{CH_3}SO_3$), δ 1.10 (s, 3, CH_3), δ 1.06 (s, 3, CH_3), δ 1.00 (s, 3, CH_3), and δ 0.97 ppm (d, 3, $\underline{J}$ = 7 Hz, $\underline{CH_3}$-CH).

Anal. Calcd for $C_{16}H_{28}O_4S$: C, 60.65; H, 8.92; S, 10.22; Found: C, 60.72; H, 8.92; S, 10.13.

(±)-Longicamphor (2A)[47] - A solution of sodium bis(trimethylsilyl) amide in benzene (0.33 ml, 0.97 M, 0.32 mmole) was added dropwise to a stirred solution of ketomesylate 52 (99.4 mg, 0.314 mmole) dissolved in anhydrous 1,2-dimethoxyethane (5.0 ml freshly distilled from lithium aluminum hydride) under nitrogen at 0° (ice-bath). The solution turned yellow, the ice-bath was removed, and the solution was stirred at room temperature for 40 minutes. The yellow solution was diluted with ether (50 ml), washed with water (10 ml), 10% hydrochloric acid (2 x 10 ml), saturated sodium bicarbonate solution (2 x 10 ml), water (10 ml), saturated sodium chloride solution (10 ml), dried (Na_2SO_4), concentrated in vacuo, and distilled to give 68.0 mg (98%) of pure (±)-longicamphor 2A: bp 50° (20 mm, external temperature); ir (CCl_4) 1735 (CO), 1390, and 1375 cm^{-1} (gem-CH_3); nmr (CCl_4) δ 1.60 (s, 1, bridgehead-H), δ 1.13 (s, 3, CH_3C-CO), δ 0.92 (s, 3, CH_3), and δ 0.87 ppm (s, 6, -CH_3). The spectral data are identical to those observed for natural (+)-longicamphor.

Synthetic (±)-longicamphor was found to have identical retention times to natural (+)-longicamphor[11,12] on glc both in separate and coinjected samples using columns B through F. Glc data on separate and coinjected samples of longicamphor are listed below:

Column	Column Temperature	Retention time in minutes
B	220°	12.3
C	170°	15.0
D	120°	12.0
E	170°	13.2
F	190°	11.2

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76, H, 10.98; Found: C, 81.84; H, 11.08.

(±)-Longiborneol (2B)[31,48] - Racemic longicamphor (1) (67 mg, 0.304 mmole) was added to a blue solution of calcium metal (120 mg) in liquid ammonia (30 ml, distilled through potassium hydroxide towers). Normal-propanol was immediately added dropwise until the blue color was dispelled. The ammonia was evaporated and the residue was taken up in water (100 ml) and ether (100 ml). The aqueous layer was separated and extracted with ether (3 x 25 ml). The combined ethereal extracts were washed with water (5 x 10 ml), saturated sodium chloride solution (20 ml), dried (Na_2SO_4), and concentrated in vacuo. The excess n-propanol was removed under high vacuum. The crude product was recrystallized from pentane (IX) to give 65.5 g (97%) of pure (±)-longiborneol (2B): mp 100-102°; ir (CCl_4) 3640 (free-OHO, 3450 (H-bonded-OH), 1370, 1385 (gem-CH_3), and 1050 cm^{-1} (C-OH); nmr (CCl_4) δ 3.68 (d, 1, J = 6 Hz, CHOH), δ 0.93 (s, 6,

$-CH_3$), and δ 0.85 ppm (s, 6, CH_3). The spectral data are identical to those observed for natural (+)-longiborneol.

Synthetic (±)-longiborneol was found to have identical retention times to natural (+)-longiborneol[11,12] on glc both in separate and coinjected samples using column B through F. Glc data on separate and coinjected samples of longiborneol are listed below:

Column	Column Temperature	Retention time in minutes
B	200°	14.2
C	190°	17.6
D	120°	13.5
E	170°	13.0
F	170°	13.5

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79; Found: C, 81.01; H, 11.77.

2-(4'-Pent-2'-ene)-2-methyl-5-isopropylcyclohexanone (54)[50] - Sodium hydride (9.9 g, 235 mg-at of a 57% dispersion) was transferred to the reaction flask and washed with anhydrous 1,2-dimethoxyethane (DME, 3 x 25 ml freshly distilled from lithium aluminum hydride). Dry DME (500 ml) was added and the apparatus was sealed under dry nitrogen. Carvomenthone (53), (32.28 g, 0.21 mmole) dissolved in dry DME (50 ml) was added. The mixture was allowed to stir at 76 ± 2° for 46 hours.

The resultant light yellow slurry of sodium enolate was cooled to -78° and 4-chloro-2-pentene (24.14 g, 0.231 mmole) was added. The pale yellow slurry was allowed to stir at -78° for two hours, then at 0° for two hours, followed by room temperature for 19 hours, and finally at

reflux for one hour. The resultant white slurry was cooled to room temperature and poured into a mixture of ice (100 g) and water (100 ml). Ether (200 ml) was added and the layers separated. The aqueous layer was extracted with ether (10 x 50 ml). The combined organics were washed with saturated sodium chloride solution (2 x 100 ml). The organics were dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated *in vacuo*. Distillation gave 29.7 g (63.5%) of colorless alkylated ketone 54: bp 77-70° (0.3 mm); ir (film) 2975, 2950, 2890 (h-C), 1710 (C=O), 1395, 1380 (gem-dimethyl), and 980 cm^{-1} (h-C=C); nmr (CCl_4) δ 5.27 (m, 2, H-C=C-H) and δ 1.00 ppm (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79; Found: C, 81.17; H, 11.85.

2-(2'-Propionic acid)-2-methyl-5-isopropylcyclohexanone (55)[25] - A solution of sodium metaperiodate (35.25 g, 165 mg-at), keto-olefin 54 (7.2836 g, 32.7 mmole), osmium tetroxide (7 ml, 0.0025 g/ml), and ruthenium trichloride (1.5 ml, 0.0385 g/ml) was stirred in a flask filled with water (625 ml) and *tert*-butanol (325 ml) for 96 hours. Ruthenium trichloride solution (1 ml, 0.0385 g/ml) was added and the solution stirred for 72 hours longer. The reaction solution was poured into water (2 l) and extracted with ether (10 x 200 ml). The combined ethereal extracts were extracted with 10% sodium hydroxide (5 x 100 ml). The basic solution was washed with ethyl ether (100 ml), cooled to 0° (ice-bath), acidified carefully with concentrated hydrochloric acid, and extracted with ethyl ether (5 x 100 ml). The slightly acidic mixture

was extracted with ether (5 x 100 ml). The combined ethereal extracts were washed with water (50 ml) and saturated sodium chloride solution (50 ml), dried ($MgSO_4$), filtered ($MgSO_4$) and concentrated *in vacuo* to give 6.9 g (94.6%) of viscous liquid keto-acid **55**: bp 120° (external temperature, 0.4 mm); ir (CCl_4) 3400 (O-H), 2925, 2900, 2875 (C-H), 1770 (acid C=O), 1700 (C=O), 1390, 1375 cm^{-1} (gem-CH_3); nmr (CCl_4) δ 7.4-7.8 ppm (bs, 1, CO_2H).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80; Found: C, 69.20; H, 9.80.

6,7-Dimethyl-3-isopropyl-8-oxo-9-oxabicyclo[4.3.0]non-1-ene (56)[24]

Method A - A solution of keto-acid **55** (3.5448 g, 15.69 mmole) and anhydrous sodium acetate (0.2044 g) in acetic anhydride (25 ml) was stirred at reflux for four hours. After cooling to room temperature the mixture was poured into ether (200 ml). The ethereal solution was washed with water (3 x 50 ml), 5% disodium hydrogen phosphate solution (3 x 50 ml), saturated sodium bicarbonate solution (3 x 50 ml), water (2 x 50 ml), and saturated sodium chloride solution (50 ml), dried ($MgSO_4$), filtered ($MgSO_4$), and concentrated *in vacuo*. The crude mixture (3.26 g) was chromatographed on silica gel (400 g, 75-325 mesh, E. Merck) in a 4 cm diameter column. A 15:85 mixture of ether and pet-ether was used to develop the column taking 200 ml fractions. Fractions 6 - 10 gave 0.8099 g (25%) of pure enol-lactone **56**: bp 90° (external temperature, 0.5 mm).

Method B - A solution of keto-acid **55** (1.5976 g, 7.06 mmole) and acetic anhydride (3.5 g, 34.28 mmole, freshly distilled) in anhydrous

dichloromethane (20 ml, freshly distilled from phosphorous pentoxide) containing 60% perchloric acid (3 l) was allowed to stir at room temperature for 35 minutes. The reaction mixture was poured into dichloromethane (250 ml), washed with saturated sodium bicarbonate solution (50 ml), water (2 x 50 ml), and saturated sodium chloride solution (50 ml), dried ($MgSO_4$), filtered ($MgSO_4$), and concentrated *in vacuo*. The last traces of acetic anhydride were removed with methanol (5 ml) containing a trace of pyridine (0.1 ml) and again concentrated *in vacuo* to give 1.75 g of a crude oil. Chromatography on silica gel (175 g, 75-325 mesh, E. Merck) in a 4 cm diameter column using a 15:85 mixture of ether and pet-ether to elute 100 ml fractions gave 0.2773 g (18.9%) of enol-lactone 56 in fractions 6 - 10: bp 90° (external temperature, 0.5 mm); ir (film) 2970, 2890 (C-H), 1800 (C=O), 1695 (C=C), 1390, and 1380 cm^{-1} (gem-CH_3); nmr (CCl_4) δ 5.4 (m, 1, C=C-H) and δ 1.3 ppm (s, 3, CH_3).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68; Found: C, 74.93; H, 9.61.

2-(2'-Propanal)-2-methyl-5-isopropylcyclohexanone (59)[58] - A solution of sodium metaperiodate (13.37 g, 62.5 mmole), keto-olefin 54 (4.6528 g, 20.9 mmole), and osmium tetroxide (5 ml, 0.0025 g/ml) in a mixture of water (425 ml) and tert-butanol (200 ml) was stirred at room temperature for 24 hours. Water (100 ml) was added to dissolve the precipitant. The solution was stirred for an additional 24 hours. The solution was extracted with ether (5 x 175 ml). The combined ethereal

extracts were washed with saturated sodium chloride solution (2 x 100 ml), dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo. Distillation gave 3.2277 g (72.1%) of pure semisolid keto-aldehyde 59: bp 91-94° (0.3 mm); ir (film) 2975, 2900 (h-C), 2745 (aldehyde C-H), 1715 (C=O, broad), 1395, and 1380 cm^{-1} (gem-CH_3); nmr (CCl_4) δ 9.5 ppm (m, 1, CHO).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54; Found: C, 74.32; H, 10.50.

2-(Ethyl 2'-propionate)-2-methyl-5-isopropylcyclohexanone (60)[54] - A mixture of keto-acid 55 (6.9 g, 30.45 mmole), ethyl iodide (28.6 g, 183.5 mmole), and potassium carbonate (6.34 g, 45.75 mmole) was stirred at reflux in anhydrous acetone (250 ml) for three hours. The reaction mixture was cooled to 0° (ice-bath) and poured into a mixture of ice (150 g) and water (150 ml). The solution was extracted with ether (7 x 75 ml). The combined ethereal extracts were washed with saturated sodium carbonate solution (3 x 25 ml), water (25 ml), and saturated sodium chloride solution (50 ml), dried ($MgSO_4$), filtered ($MgSO_4$) and concentrated in vacuo. Distillation gave 6.9783 g (89.6%) of pure keto-ester 60: bp 112° (external temperature, 0.3 mm); ir (film) 2960, 2930, 2870 (C-H), 1730 (C=O) 1705 (C=O), 1395, 1375 (gem-CH_3), and 1200 cm^{-1} (C-O); nmr (CCl_4) δ 4.1 (m, 2, O-CH_2-) and δ 2.0 ppm (m, 1, O_2C-CH).

Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.30; H, 10.30; Found: C, 70.67; H, 10.32.

5,6-Dimethyl-2-isopropylbicyclo[3.2.1]octan-7,8-dione (61) and (62)[22,51]

Method A - Diisobutylaluminum hydride (2.75 ml, 1.445 M/l in benzene) was added dropwise to a stirred solution of enol-lactone 56 (0.8099 g, 3.888 mmole) in tetrahydrofuran (30 ml, freshly distilled from lithium aluminum hydride) at -78°. The solution was stirred at -78° for 40 minutes and at room temperature for 22 hours. The reaction was quenched at 0° with 10% hydrochloric acid (3 ml), poured into water (100 ml), and extracted with ether (1 x 50 ml, 4 x 25 ml). The combined ethereal extracts were washed with water (4 x 25 ml) and saturated sodium chloride solution (2 x 25 ml), dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo. The crude material was recycled twice using diisobutylaluminum hydride (3 ml, 1.445 M/l in benzene) and the same conditions each time. The same workup gave 0.7970 g (97.4%) of diol 58: ir (film) 3370 (O-H), 2960, 2880 (C-H), 1390, and 1375 cm^{-1} (gem-CH_3).

Excess Jones' reagent (0.5 ml) was added dropwise to a solution of diol 58 (0.0501 g, 0.236 mmole) in anhydrous acetone (1 ml). After 30 minutes the excess Jones' reagent was destroyed with isopropanol. The mixture was poured into water (10 ml) and extracted with ether (10 x 5 ml). The ethereal extracts were washed with saturated sodium bicarbonate solution (2 x 5 ml), water (5 ml), and saturated sodium chloride solution (5 ml), dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 0.0470 g (95.5%) of diketones 61 and 62: ir (CCl_4) 2975,

2940, 2880 (C-H), 1765, 1725 (C=O, coupled), 1395, and 1380 cm^{-1} (gem-CH_3).

Method B - Sodium hydride (1.32 g, 31.3 mg-at of a 57% dispersion) was transferred to a flask and washed with anhydrous 1,2-dimethoxyethane (DME, 3 x 20 ml freshly distilled from lithium aluminum hydride). Dry DME (250 ml) was added and the apparatus sealed under dry nitrogen. Keto-ester 60 (2.52 g, 9.9 mmole) and anhydrous ethanol (1 drop) was added. The stirred solution was heated at 68 ± 2° for ten hours. The reaction was quenched at 0° with glacial acetic acid (2 ml), poured into ice water (100 ml), and extracted with ether (10 x 50 ml). The combined ethereal extracts were washed with saturated sodium carbonate solution (2 x 50 ml) and saturated sodium chloride solution (2 x 50 ml), dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo. The crude crystalline material was recrystallized from pentane to give 0.8345 g of the diketones. An additional 0.5084 g was recovered from the mother liquors by column chromatography on silica gel (140 g, 70-325 mesh, E. Merck) in a 2.5 cm diameter column using a 15:85 mixture of ether and pet-ether to elute 75 ml fractions from fractions 10 - 12. The material was combined to give 1.3429 g (64.5%) of diketones 61 and 62: mp 91-92°; ir (CCl_4) 2975, 2940, 2885 (C-H), 1765, 1725 (C=O), 1395, and 1385 cm^{-1} (gem-CH_3); nmr (CCl_4) δ 2.7 ppm (s, 1, bridgehead H).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68; Found: C, 74.74; H, 9.87.

5,6-Dimethyl-2-isopropylbicyclo[3.2.1]octan-7-on-8-ol 63 and 64[22,51] - Sodium hydroxide (1.32 g, 31.3 mg-at of a 57% dispersion) was transferred

to a flask and washed with anhydrous 1,2-dimethoxyethane (DME, 3 x 20 ml freshly distilled from lithium aluminum hydride). Dry DME (250 ml) was added and the apparatus sealed under dry nitrogen. Keto-ester 60 (2.5480 g, 10 mmole) and anhydrous ethanol (1 drop) were added. The mixture was stirred at 65 ± 2° for 11.75 hours. The reaction was quenched at 0° (ice-bath) with glacial acetic acid (2 ml), poured into ice water (500 ml), and extracted with ether (10 x 50 ml). The combined ethereal extracts were washed with saturated sodium carbonate solution (2 x 50 ml) and saturated sodium chloride solution (2 x 50 ml), dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 2.1041 g of crystalline crude material. The crude diketone was dissolved in anhydrous ethanol (55 ml). Sodium borohydride (0.4163 g, 11 mmole) dissolved in anhydrous ethanol (35 ml) at 0° was added dropwise to the solution of the diketone in ethanol at 0°. The reaction was quenched with glacial acetic acid (3.5 ml) after stirring for 30 minutes at 0° (ice-bath). The solution was poured into water (250 ml) and extracted with ether (8 x 50 ml). The combined ethereal extracts were washed with saturated sodium carbonate solution (2 x 50 ml) and saturated sodium chloride solution (2 x 50 ml), dried ($MgSO_4$), filtered ($MgSO_4$), and concentrated in vacuo to give 2.1679 g of a viscous oil. The crude material was chromatographed on silica gel (375 g, 70-325 mesh, E. Merck) in a 3 cm diameter column collecting 200 ml fractions. The eluting solvent ratios were: fractions 1 -26, 20% ether - 80% pet-ether; fractions 27 -34, 25% ether - 75% pet-ether; and fractions 35 - 60,

35% ether - 65% pet-ether. Fractions 27 - 33 gave 0.5145 g (24.4%) of ketol 64: bp 89° (external temperature, 0.3 mm); ir (film) 3475 (O-H), 2960, 2890 (C-H), 1725 (C=O), 1385, and 1370 cm^{-1} (gem-CH_3); nmr (CCl_4) δ 3.78 (d, 1, J = 5 Hz, O-CH) and δ 2.6 ppm (m, 1, bridgehead H). Fractions 36 - 41 gave 0.7267 (34.5%) of ketol 63: bp 89° (external temperature, 0.3 mm); ir (film) 3490 (O-H), 2975, 2895 (C-H), 1725 (C=O), 1385, and 1375 cm^{-1} (gem-CH_3); nmr (CCl_4) δ 3.58 (d, 1, J = 6 Hz, O-CH), δ 2.6 (s, 1, O-H), and δ 2.5 ppm (m, 1, bridgehead H).

Anal. Ketol 63 Calcd for $C_{13}H_{20}O_2$: C, 74.24; H, 10.54; Found: C, 74.02; H, 10.56.

Anal. Ketol 64 Calcd for $C_{13}H_{20}O_2$: C, 74.24; H, 10.54; Found: C, 74.38; H, 10.41.

5,6-Dimethyl-2-isopropylbicyclo[3.2.1]oct-6-en-8-ol (65)[56] - A solution of ketol 63 (0.6570 g, 3.1 mmole), toluenesulfonyl hydrazine (0.6420 g, 3.45 mmole), and concentrated hydrochloric acid (1 drop) in dry tetrahydrofuran (20 ml, freshly distilled from lithium aluminum hydride) was heated at 45° for 24 hours and 55° for 37.5 hours with stirring. The clear solution was cooled to room temperature. The solvent was removed in vacuo to give a yellow solid. The crude material was dissolved in diglyme (20 ml, freshly distilled from lithium aluminum hydride). Methyl lithium (12 ml, 1.744 M in ether) was added dropwise at 0°. The bubbling deep orange solution was stirred at room temperature for 1.5 hours. The reaction was quenched at 0° with water (25 ml). The mixture was poured into water (50 ml) and ether (150 ml). The aqueous

layer was removed. The ethereal solution was washed with water (8 x 50 ml, until neutral to litmus) and saturated sodium chloride solution (2 x 40 ml), dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 0.7231 g of a crude yellow liquid. The crude material was chromatographed on silica gel (72 g, 70-325 mesh, E. Merck) in a 2 cm diameter column using a 1:9 mixture of ether and pet-ether to elute 50 ml fractions. Fractions 8 - 12 gave 0.3900 g (64.8%) of the pure olefinic alcohol 65: bp 72° (external temperature, 0.3 mm); ir (film) 3400 (O-H) 3060 (H-C=C), 2970, 2900 (C-H), 1635 (C=C), 1390, 1380 (gem-CH_3), and 820 cm^{-1} (H-C=C); nmr (CCl_4) δ 5.35 (m, 1, H-C=C), δ 3.72 (d, 1, J = 6 Hz, O-CH), δ 2.41 (m, 1, bridgehead hydrogen), and δ 1.6 ppm (d, 3, J = 2 Hz, C=C-CH_3).

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41; Found: C, 80.20; H, 11.26.

5,6-Dimethyl-2-isopropylbicyclo[3.2.1]oct-6-en-8-ol (66)[56] - A solution of ketol 64 (0.5145 g, w.41 mmole), toluenesulfonyl hydrazine (0.5020 g, w.69 mmole), and concentrated hydrochloric acid (1 drop) in dry tetrahydrofuran (15 ml, freshly distilled from lithium aluminum hydride) was stirred at 45° for 16.5 hours. The clear solution was cooled to room temperature. The solvent was removed in vacuo. The resultant yellow solid was dissolved in diglyme (10 ml, freshly distilled from lithium aluminum hydride). Methyl lithium (8 ml, 1.744 M in ether) was added to the solution at 0°. The bubbling deep orange solution was stirred at room temperature for 11 hours. The reaction

was quenched at 0° with water (25 ml) and poured into water (50 ml) and ether (150 ml). The aqueous layer was discarded. The ethereal layer was washed with water (5 x 50 ml, until neutral to litmus) and saturated sodium chloride solution (2 x 40 ml), dried (Na_2SO_4), filtered ($MgSO_4$), and concentrated in vacuo to give 0.5210 g of a crude yellow oil. The crude material was chromatographed on silica gel (52 g, 70-325 mesh, E. Merck) in a 2 cm diameter column using a 1:9 mixture of ether and pet-ether to elute 30 ml fractions. Fractions 5 - 7 gave 0.2946 g (62.9%) of the olefinic alcohol 66: bp 65° (external temperature, 0.3 mm); ir (film) 3490 (O-H), 3055 (H-C=C), 2955, 2890 (C-H), 1630 (C=C), 1395, 1380 (gem-CH_3), and 820 cm^{-1} (H-C=C); nmr (CCl_4) δ 5.35 (m, 1, H-C=C), δ 3.55 (d, 1, J = 5 Hz, O-CH), and δ 2.6 ppm (m, 1. bridgehead H).

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41; Found: C, 80.25; H, 11.48.

REFERENCES

1. R. B. Clayton, Quart. Rev., 19, 168 (1965).
2. W. Parker and J. S. Roberts, Quart. Rev., 21, 331 (1967).
3. G. Rucker, Angew. Chem. Inter. Ed., 12, 793 (1973).
4. J. W. Cornforth, Chem. in Britain, 102 (1968).
5. J. B. Hendrickson, Tetrahedron, 7, 82 (1959).
6. W. S. Johnson and K. E. Harding, J. Org. Chem., 32, 478 (1967).
7. W. S. Johnson, Accounts of Chem. Research, 1, 1 (1968).
8. P. R. Bai, S. Y. Kamat, B. B. Ghatge, K. K. Chakravati, and S. C. Battacharyya, Tetrahedron, 21, 629 (1965).
9. U. R. Nayak and S. Dev, Tetrahedron Letters, 243 (1963).
10. L. Smedman and E. Zavarin, Tetrahedron Letters, 3833 (1968).
11. L. H. Briggs and M. D. Sutherland, J. Org. Chem., 7, 397 (1942).
12. S. Skiyoshi, H. Erdtman, and T. Kubota, Tetrahedron, 9, 239 (1960).
13. E. J. Corey, M. Ohno, R. B. Mitra, and P. A. Vatakencherry, J. Amer. Chem. Soc., 86, 478 (1964).
14. B. W. Roberts, M. S. Poonian, and S. C. Welch, J. Amer. Chem. Soc., 91, 3400 (1969).
15. A. Baeyer, Ber., 27, 810 (1894).
16. E. J. Corey and H. J. Burke, J. Amer. Chem. Soc., 78, 174 (1956).
17. E. E. van Tamlen, J. McNary, and F. A. Lornitzo, J. Amer. Chem. Soc., 79, 1231 (1957).
18. Y. Naves and P. Ardizio, Helv. Chem. Acta, 32, 329 (1949).
19. J. R. B. Campbell, A. M. Islam, and R. A. Raphael, J. Chem. Soc., 4096 (1956).
20. J. M. Conita, Rec. of Chem. Prog., 24, 43 (1963).

21. H. O. House, Rec. of Chem. Prog., 28, 99 (1967).

22. S. C. Welch, Ph.D. Thesis, University of Southern California, Los Angeles, Calif., 1968.

23. E. R. Coburn, Org. Syn. Coll. Vol. 3, 696 (1955).

24. J. Martin, W. Parker, and R. A. Raphael, J. Chem. Soc., 289 (1964).

25. G. Stork, A. Meisels, and J. E. Davies, J. Amer. Chem. Soc., 85, 3419 (1963).

26. M. Karplus, J. Chem. Phys., 30, 11 (1959).

27. E. W. Garbisch, Jr., J. Chem. Educ., 45, 311, 402, 480 (1968).

28. H. O. House and B. M. Trost, J. Org. Chem., 30, 1341, 2502 (1965).

29. R. K. Crossland and K. L. Servis, J. Org. Chem., 35, 3195 (1970).

30. H. O. House and J. K. Larson, J. Org. Chem., 33, 61 (1968).

31. D. H. R. Barton and N. H. Werstiuk, Chem. Commun., 30 (1967); J. Chem. Soc., C, 148 (1968).

32. A. Maercker, Org. Reactions, 14, 270 (1965).

33. F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, pp. 72-75.

34. K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, J. Chem. Soc., 39 (1946).

35. C. Djerassi, R. R. Engle, and A. Bowers, J. Org. Chem., 21, 1547 (1956).

36. R. M. Coates and J. L. Kirkpatrick, J. Amer. Chem. Soc., 92, 4883 (1970).

37. Huang-Minlon, J. Amer. Chem. Soc., 68 (2487 (1946); 71, 3301 (1949).

38. W. Nagata and H. Itazaki, Chem. Ind., 1194 (1964).

39. R. L. Augustine, "Reduction," Marcel Dekker, Inc., New York, N. Y., 1968, pp. 171-185.

40. H. O. House, "Modern Synthetic Reactions," 2nd ed., W. A. Benjamin, Inc., Menlo Park, Calif., 1972, p. 61; and references cited therein.

41. G. Zweifel and H. C. Brown, Org. Reactions, 13, 1 (1963).

42. C. C. Hinckley, J. Amer. Chem. Soc., 91, 5160 (1969).

43. W. S. Johnson, J. C. Collins, Jr., R. Pappo, M. B. Rubin, P. J. Kropp, W. F. Johns, J. E. Pike, and W. Bartman, J. Amer. Chem. Soc., 85, 1409 (1963).

44. J. C. Collins, W. W. Hess, and F. J. Frank, Tetrahedron Letters, 3363 (1968).

45. J. C. Collins and W. W. Hess, Org. Synthesis, 52, 5 (1972).

46. R. Ratcliffe and R. Rodehorst, J. Org. Chem., 35, 4000 (1970).

47. M. Tanabe and D. F. Crowe, Chem. Commun., 1498 (1969).

48. E. Piers, M. B. Geraghty, F. Kido, and M. Soucy, Syn. Commun., 3, 39 (1973).

49. E. S. Rothman and A. R. Day, J. Amer. Chem. Soc., 76, 111 (1954).

50. R. Howe and F. J. McQuillin, J. Chem. Soc., 1194 (1958).

51. E. Piers, R. W. Britton, R. J. Keziere, and R. D. Smille, Can. J. Chem., 49, 2620 (1971).

52. L. Claisen, Ber., 45, 3157 (1912).

53. R. B. Turner, G. D. Diana, G. E. Fodor, K. Kebert, D. L. Simmons, A. S. Rau, O. Ross, and W. Wirth, J. Amer. Chem. Soc., 88, 1786 (1966).

54. R. E. Ireland, D. A. Evans, D. Glover, G. M. Rubottom, and H. Young, J. Org. Chem., 34, 3717 (1969).

55. H. C. Brown and J. Muzzio, J. Amer. Chem. Soc., 88, 2811 (1966).

56. R. H. Shapiro and M. J. Heath, J. Amer. Chem. Soc., 89, 5735 (1967).

57. W. S. Johnson and W. P. Sneider, Org. Syn. Coll. Vol. IV, 132 (1963).

58. R. Pappo, D. S. Allen, R. U. Lemieux, and W. S. Johnson, J. Org. Chem., 21, 478 (1956).

59. I. H. Sadler, Annual Reports, 68, 18 (1971).

APPENDIX

INDEX OF COMPOUNDS

INDEX OF COMPOUNDS CONTINUED

INDEX OF COMPOUNDS CONTINUED

INDEX OF COMPOUNDS CONTINUED