1969

Studies in Syntheses of Non-Isoprenoid Sesquiterpenes

Raojibhai Javerbhai Patel
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STUDIES IN SYNTHESES OF

NON-ISOPRENOID SESQUITERPENES

(TITLE)

BY

Raojibhai Javerbhai Patel
B.Sc. (1962)
M.Sc. (1964)
The M.S. University of Baroda, India

THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF

Master of Science

IN THE GRADUATE SCHOOL, EASTERN ILLINOIS UNIVERSITY
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I HEREBY RECOMMEND THIS THESIS BE ACCEPTED AS FULFILLING
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DEPARTMENT HEAD

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Submitted to the Faculty of the Graduate
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Thesis Approved:

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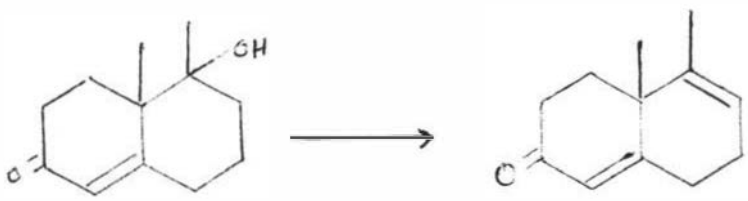
I am deeply grateful to Dr. J. W. Ellis for his valuable guidance, inspirations and patience during my graduate program. I would like to thank Dr. S. R. Steele, for his active interest, and the Department of Chemistry for a Graduate Assistantship. Also, thanks are due to other members of the faculty for their active interest and help.

Also I want to thank my parents for their patience and encouragement during my study.

TABLE OF CONTENTS

ABSTRACT OF A THESIS

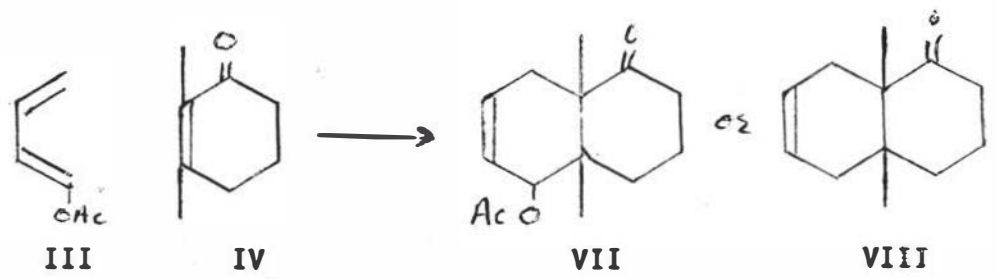
The purpose of this study was to find the shortest route to prepare the 1,9-dimethyl decalone system I, a key intermediate in the synthesis of non-isoprenoid sesquiterpenes. The decalone system I was prepared in good yield by dehydrating the hydroxyketone II with 50% H_2SO_4. The dehydration of hydroxyketone II was also affected by heating in the presence of iodine crystals to yield 80% of the decalone system I.



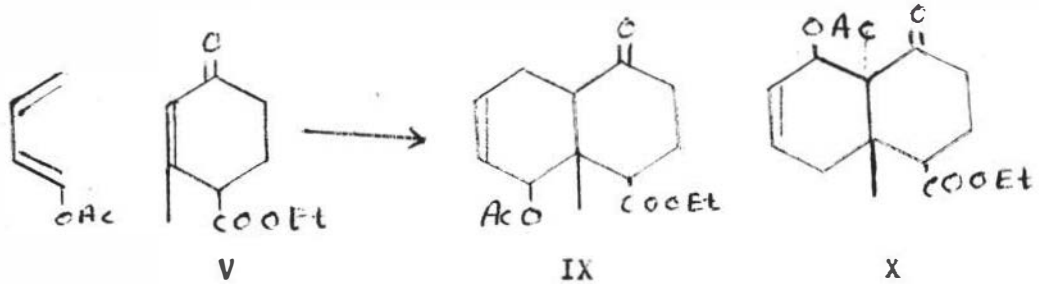
II I

The basic kinds of approaches under investigation were the Diels-Alder reaction and the Robinson annellation. The Diels-Alder reaction between the conjugated diene, 1-acetoxybutadiene (III) and 2,3-dimethylcyclohexenone (IV) under typical conditions as well as in the presence of catalysts such as anhydrous $AlCl_3$, CCl_3COOH and $SnCl_4$ was studied. The mixture of 1-acetoxybutadiene (III) and 2,3-dimethylcyclohexenone (IV) was heated for 15 hours but the formation of the compounds VII or VIII was not accomplished. The same mixture was dissolved in dry benzene and refluxed for 15 hours but found no evidence by vpc the formation of the compounds VII or VIII. Further attempts were made in the presence of the catalysts, such as anhydrous $AlCl_3$, CCl_3COOH and

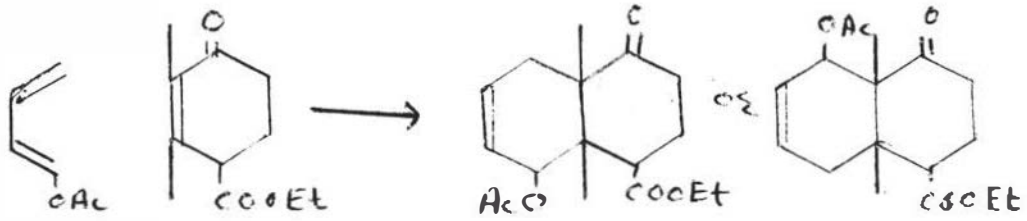
$SnCl_4$ but the results were not satisfactory. Similarly, the reactions between 1-acetoxybutadiene and Hagemann's ester (V) as well as methylated Hagemann's ester (VI) were found unsatisfactory.



III IV VII VIII



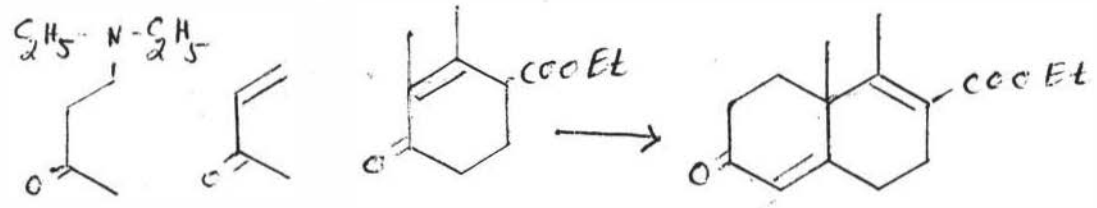
V IX X



VI XI XII

The condensation of methyl vinyl ketone (XIV) or 1-diethylamino-3-butanone (XIII) and methylated Hagemann's ester (VI) gave compound XVII in unsatisfactory yield. Similar condensations with 2-methyl-2-cyclohexenone (XV) and 2,3-dimethyl-2-cyclohexenone (IV) were not accomplished. Other attempts were made to condense 1,3-dichloro-2-butene (XVI) with 2,3-dimethyl-2-cyclohexenone (IV) in presence of NaH in dry benzene as an alternate route to decalone system I through the chloroketone XIX. But the chloroketone was obtained in too poor of a yield to proceed

further. The hydroxymethylene derivative XX was prepared from the hydroxyketone II by the treatment with HCOOEt and NaH in dry benzene. Further reaction of the hydroxymethylene derivative XX with ethyl α-bromopropionate was not accomplished to yield the compound XXI.

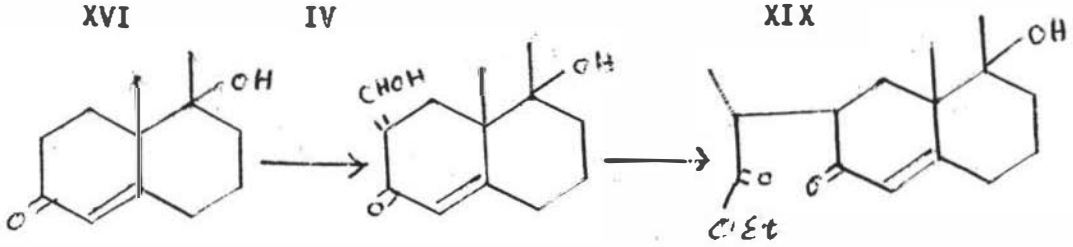


XIII XIV VI XVII

XV XVIII

IV I

XVI IV XIX

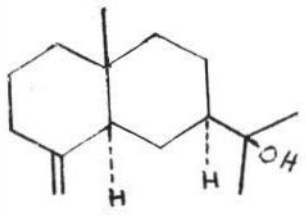


II XX XXI

CHAPTER I

INTRODUCTION

Terpenes are naturally occurring compounds produced by plants. The essential oils, such as peppermint, anise, etc.,[1] derived by the steam distillation of the plant materials, are the main source. Since these terpenes have been found to contain an integral number of C_5 isoprene units (I), the "isoprene rule" was formulated,[2] which states that terpenes are compounds with a carbon skeleton consisting of isoprene units linked in a "head to tail" fashion, as in eudesmol (II).[3] Compounds in which isoprene units are not linked in a "head to tail" fashion, are known as non-isoprenoids, such as eremophilone (III). They may still be classed terpenes since their carbon skeleton may be rationalized by a simple re-arrangement from some isoprenoid. Such a precursor for eremophilone



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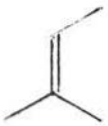

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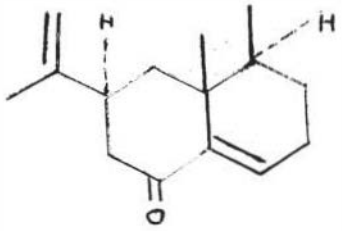

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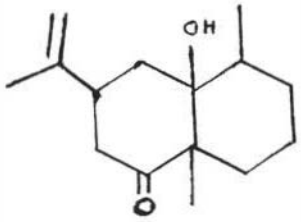
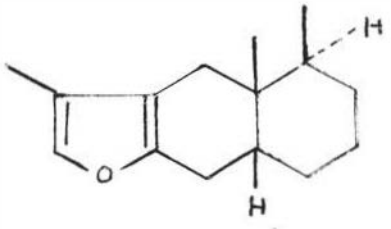


IV



V

might be the eudesmol type IV.

Terpenoids are classified as monoterpenoids, sesquiterpenoids, diterpenoids and triterpenoids containing ten, fifteen, twenty, and thirty carbon atoms respectively. Eremophilone and related compounds are non-isoprenoid sesquiterpenoids and the study of the synthesis of this group of compounds is the subject of this thesis. Terpenoids containing the furan system are referred to as "furanoterpenoids". An example is furanoeremophilane (V), a key compound in this subgroup.

Literature Survey

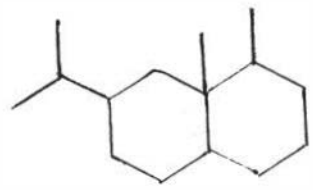
The literature covering recent developments of the naturally occurring eremophilane sesquiterpene group has been reviewed by A. R. Pinder.[4] The review covers the literature to 1968 concerning occurrance, structure elucidation, and stereochemistry. This section of the thesis attempts to bring up to date that review and cover the more recent literature concerning eremophilane and related sesquiterpenoids. The synthesis have not been described by A. R. Pinder[4] but will be discussed in later section. The biosynthes s will not be discussed.

Bicyclic Structures

Eremophilone (VII), $C_{15}H_{22}O$.

The eremophilone group of sesquiterpenes is characterized by a carbon framework VI which does not obey the well known isoprene rule. The members known are eremophilone (VII), hydroxy-

eremophilone (VIII), and hydroxydihydroeremophilone (IX), which are constituents of the essential oil of the Australian shrub, Eremophila mitchelli.[5]



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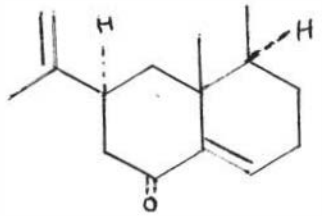

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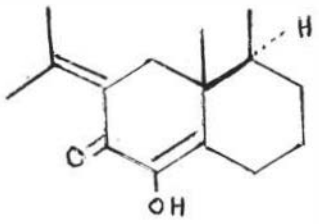

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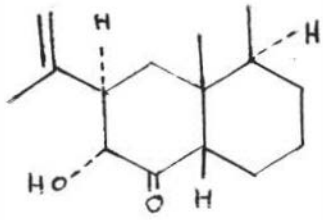
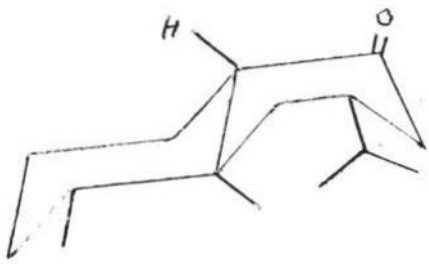
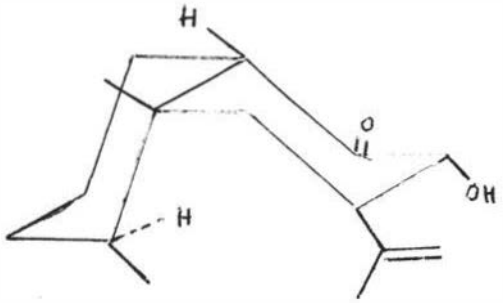


IX

The natural (+)-hydroxydihydroeremophilone has been shown by x-ray diffraction studies to have the relative stereochemistry shown in IX.[5] The structure X represents the shape of the molecule, the two cyclohexane rings being locked in the cis steriodal manner,[6] with all substituents equitorially disposed.



XI

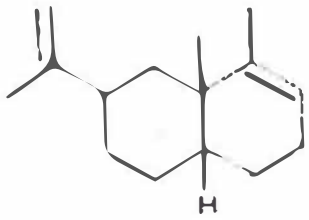


X

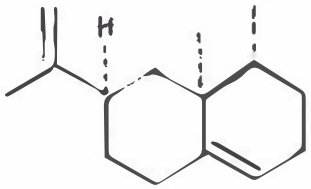
The absolute configeration VII for the (-)-eremophilone (VII) was confirmed by optical studies. The optical rotatory dispersion studies of eremophilone and some of its derivatives indicated the carbonyl containing ring of eremophilone does not exist as a chair but has the twist boat conformation XI. In the latter, the severe 1,3 diaxial interaction between the isopropenyl and angular methyl group, which occurs when the ring is a chair, is avoided.[8]

Eremophilene (XII), $C_{15}H_{24}$.

Eremophilene is a levorotatory hydrocarbon occuring in rhizomes of Petasites officinalis, P. albus, and P. japanocus,[9] while the dextrorotatory form is found in the oil of Valeriana officinalis.[10] On reduction it takes four hydrogen atoms, leading to eremophilane. The reduction to eremophilane proves the absolute configeration of (-)-eremophilene (XII).[9]



XII



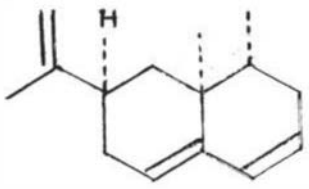
XIII

Valencene (XIII), $C_{15}H_{24}$.

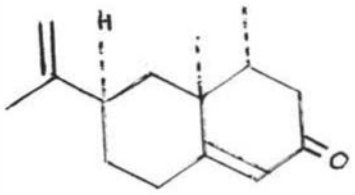
(+)-Valencene is found in orange juice and orange peel oil[11] and has the structure XIII. Its structure follows from its close relation to nootkatone, into which it is converted by tertiary butyl chromate oxidation and, conversely, from which it is formed by Wolf-Kishner reduction.

Nootkatene (XIV), $C_{15}H_{22}$.

Nootkatene is a hydrocarbon constituent of the heart wood of Chamaecyparis nootkatensis[12] (Alaska yellow cedar). It has three double bonds with two of them conjugated. The structure XIV has assigned to (-)-nootkatene.[13]



XIV



XV

Nootkatone (XV), $C_{15}H_{22}O$.

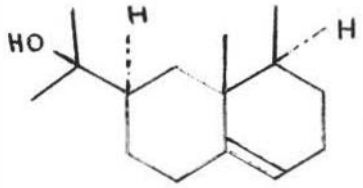
Nootkatone is crystalline, dextrorotatory ketone first isolated from the heart wood of Alaska yellow cedar[14] and later found in grapefruit peel oil and other citrus oil.[14,15] The ketone is valued for its distinctive flavor of grapefruit. The absolute stereochemistry was deduced from optical rotatory dispersion studies[13] after the structural[14] and synthetic studies[16] indicated structure XV to be correct.

Eremoligenol (XVI), $C_{15}H_{26}O$.

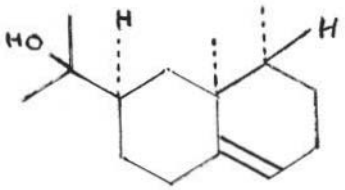
Eremoligenol is a levorotatory alcohol found in Ligularia fischerirurez. It is tertiary alcohol, containing a trisubstituted double bond and has been transformed stepwise into eremophilane, of known absolute stereochemistry. Various chemical transformations have been described which are in complete agreement with the structure and absolute configuration for eremoligenol (XVI).[17] The structure has also been confirmed by synthesis.[18]

Valeriano (XVII), $C_{15}H_{26}O$.

Valerianol occurs in the roots of Valeriana officinalis. It is a tertiary alcohol which on dehydration yields valencene (XIII). (+)-valerianol has been assigned the structure XVII. The absolute stereochemistry was confirmed by optical rotatory dispersion studies.[19]



XVI



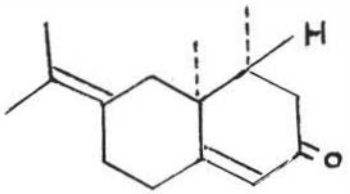
XVII

α-Vativone (XVIII), $C_{15}H_{22}O$.

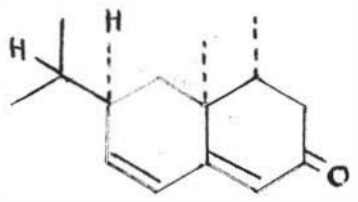
α-Vativone, also known as isonootkatone, is a constituent of vetiver oil and has been assigned the absolute stereochemistry and the structure of XVIII.[20]

Nardostachone (XIX), $C_{15}H_{22}O$.

Nardostachone is a ketonic constituent of Indian spikenard oil from Nardostachys jatamansi. It is a dextrorotatory conjugated dienone, hydrogenation of which affords tetrahydronootkatone. Nardostachone is therefore a double bond isomer of nootkatone. Spectral considerations[21] lead to the formula XIX for nordostachone, which also represents the absolute stereochemistry of the natural dextrorotatory ketone.



XVIII



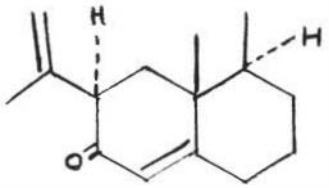
XIX

Alloeremophilone (XX), $C_{15}H_{22}O$.

Alloeremophilone accompanies eremophilone in the essential oil of Eremophila mitchelli. Its formulation as the ketone XX is based on its synthesis from hydroxydihydroeremophilone.[22]

Dehydrofukinone (XXI), $C_{15}H_{22}O$.

Dehydrofukinone, a naturally occurring sesquiterpene, was assigned the structure XXI and confirmed by synthesis.[23]



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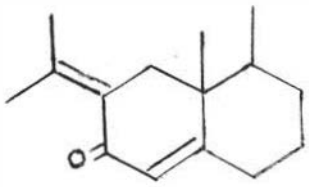
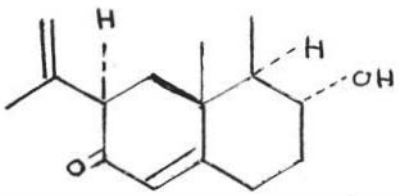


XXI

Petasol (XXII), $C_{15}H_{22}O$, and Petasin.

Petasin is the angelate ester of the sesquiterpene alcohol petasol (XXII). It occurs in the rhizomes of Petasites hybridus and P. officinalis, and is in part responsible for the spasmolytic



XXII

action of the extracts thereof.

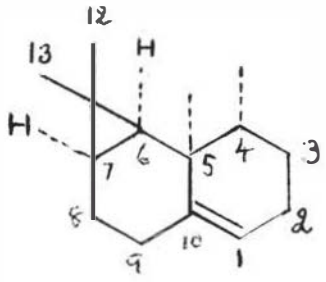
Tricyclic Structures

Calarene (XXIII), $C_{15}H_{24}$.

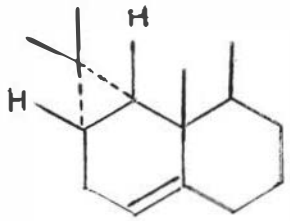
Calarene is found in oil of sweet flag, in Chinese spikenard oil,[24] and in the Indian valerian root oil.[25] The structure and configuration were confirmed by optical rotatory dispersion studies to be the eremophilane carbon skeleton fused via position 6 and 7 with a cyclopropane ring, as represented by XXIII.

α-Ferulene (XXIV), $C_{15}H_{24}$.

α-Ferulene, or (+)-aristolene, isomeric with calarene, is a destrorotatory hydrocarbon present in the latex of Ferula communis L.[26] α-Ferulene has been assigned the structure XXIV.



XXIII



XXIV

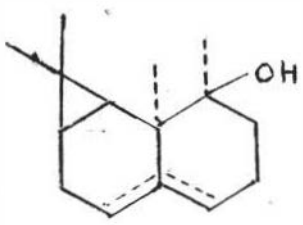
Calarenol (XXV), $C_{15}H_{24}O$.

Calarenol is a dextrorotatory tertiary alcohol, occuring in the roots of Nardo stachys jatamansi, an Indian medicinal plant.[27] Calarenol is regarded as the mixture of double bond isomers

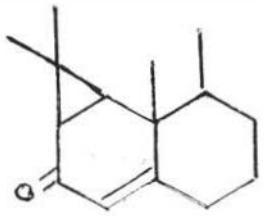
represented by XXV.[27]

Aristolone (XXVI), $C_{15}H_{22}O$.

Aristolone is a crystalline levorotatory ketonic constituent of Aristolochia debilis.[28] Catalytic hydrogenation afforded a saturated dihydroketone, $C_{15}H_{24}O$, indicating that aristolone is tricyclic. Spectral studies on aristolone, dihydroaristolone, deoxyaristolone, and aristolol suggested that aristolone contained a keto group cross conjugated with a double bond and a cyclopropane ring. The stereochemistry of aristolone has been settled by a correlation with calarene and assigned the structure XXVI.[29]



XXV

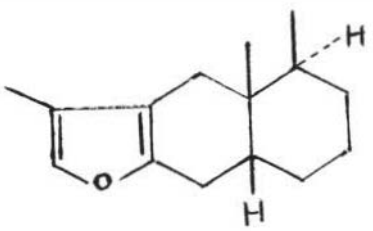


XXVI

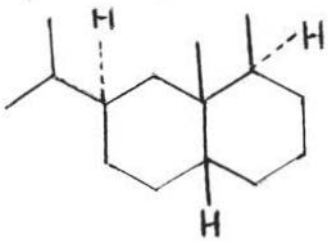
The Furanoeremophilanes

Several members of the eremophilane group of sesquiterpenes related to furanoeremophilane (XXVII) have been isolated from botanically related plants, especially the Petasites species. The key compound in this subgroup is (-)-furanoeremophilane, into which many of the members have been converted by simple steps. It has

been isolated from rhizomes of Petasites albus,[9] P. officinalis,[9] P. spurius,[29] and Ligularia Fischeri.[17] The presence of a furan ring was inferred from its infrared and ultraviolet spectra and from its positive Ehrlich reaction. Hydrogenation led to a saturated tetrahydro derivative, and ultimately to eremophilane (XXVIII).



XXVII



XXVIII

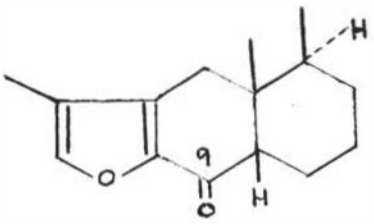
Furanoeremophilone (XXIX), $C_{15}H_{20}O_2$.

Furanoeremophilone is an optically inactive ketone occuring in the rhizomes of Petasites officinallis.[9] The presence of a furan ring conjugated with a ketonic carbonyl group was established by infrared spectroscopy, and the structure XXIX has been proposed for the compound.[30]

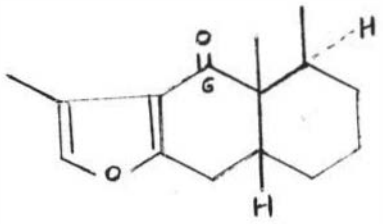
Ligularone (XXX) $C_{15}H_{20}O_2$.

Ligularone, is a ketonic constituent of aerial parts of Ligularia sibirica.[31] The structure of ligularone is intimately bound up with that of petasalbin, which on oxidation affords ligularone (XXX). Conversely, ligularone on lithium aluminua

hydride reduction yields epipetasalbin or epiligularol.



XXIX



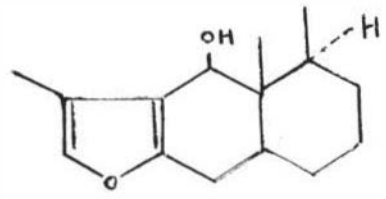
XXX

Petasalbin (XXXI), $C_{15}H_{22}O_2$.

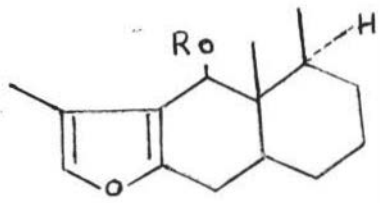
Petasalbin or ligularol, is found in the rhizomes of several petasites. It is crystalline levorotatory alcohol, containing a furan ring.[32] The structure XXXI has been assigned to Petasalbin.

Albopetasin (XXXII), $C_{20}H_{28}O_3$.

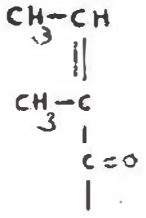
Albopetasin (XXXII), is also present in C. albus rhizomes and is the angelate ester of petasalbin.



XXXI



XXXII

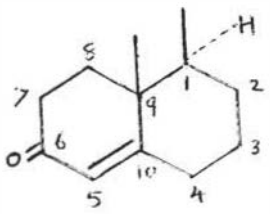


R =

Review of the Synthesis Reported.

A review of the literature indicates that few of the non-isoprenoid, naturally occuring terpenes of the eremophilone (VII)

type have been synthesized. The preparation of the cis-1,9-dimethyl decalin system XXXIII via various approaches has been studied extensively.[33] The reported syntheses of naturally occurring non-isoprenoids are summarized in this section, to bring the nature of the work published up to date.

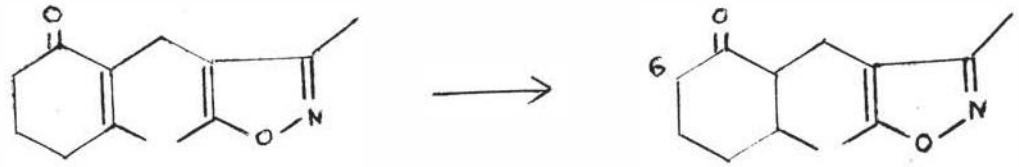


XXXIII

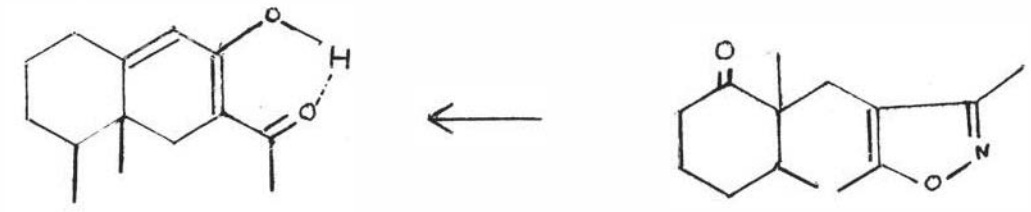
Synthesis of Dehydrofukinone[23]

Dehydrofukinone has been synthesized in good yield via isoxazole annelation[23] and consists of two steps, alkylation and ring formation. The isoxazole XXXIV was hydrogenated with Pd/C to give XXXV in 66% yield. After protecting the methylene group at C-6, methylation with methyl iodide and sodium hydride in dimethyl formamide followed by removal of the protecting group gave XXXVI in 40% yield. The treatment of XXXVI with triethyloxonium fluoborate followed by heating under reflux with 1 N sodium hydroxide in 20% ethanol for one hour gave XXXVII in 38% yield. The annelation product XXXVII was converted into its enol ether XXXVIII by heating under reflux with isopropyl iodide and potassium carbonate in ethyl

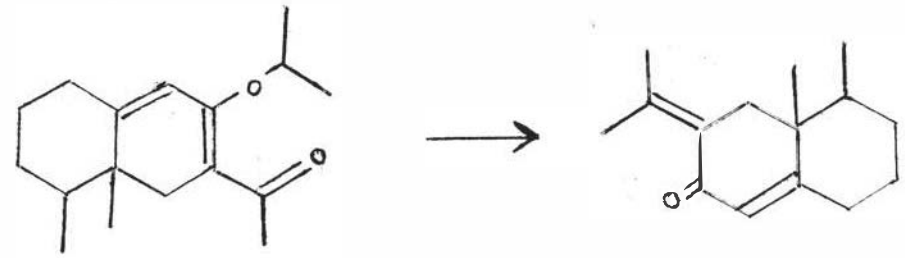
methyl ketone for 48 hours. The successive treatment of XXXVIII with methyl lithium, dilute hydrochloric acid and phosphorus oxychloride in pyridine gave (±)-dehydrofukinone (XXI) whose spectral properties were identical with those of natural fukinone.



XXXIV XXXV



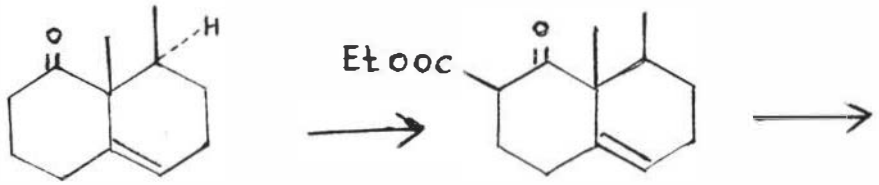
XXXVII XXXVI



XXXIII XXI

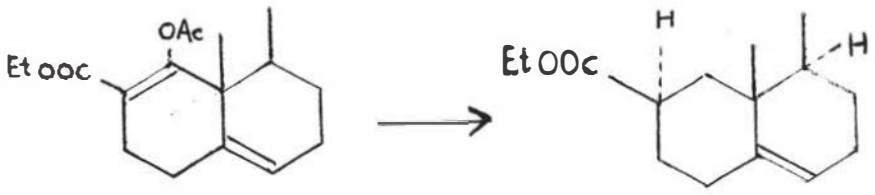
Synthesis of (±)-Eremophilene and Eremoligenol

Eremophilene (XII) was synthesized starting with cis-1,9-dimethyloctalone (XXXIX).[18] The ester XL was obtained from XXXIX by treatment with diethyl carbonate[34] and sodium hydride in dry benzene. The ester enol acetate XLI was obtained from the reaction of the sodium salt of XL with acetyl chloride in dimethoxyethane. The key step in the reaction sequence was the double reduction of XLI, which serves to remove both the conjugated double bond and the extraneous oxygen function to generate the required axial configuration in the product ester XLII. The reduction of unpurified XLI with lithium in liquid ammonia followed by quenching with ammonium chloride, gave XLII in 34% yield. The axial configuration of the carbethoxy grouping in XLII follws from the upfield shift of nmr signal (τ, 9.18) due to the angular methyl group. The reaction of XLII with excess methyl lithium in ether afforded eremoligenol (XVI) in 81% yield. The infrared spectrum was superimposable on the corresponding spectrum of natural eremoligenol. The dehydration of XVI with thionyl chloride in pyridine furnished

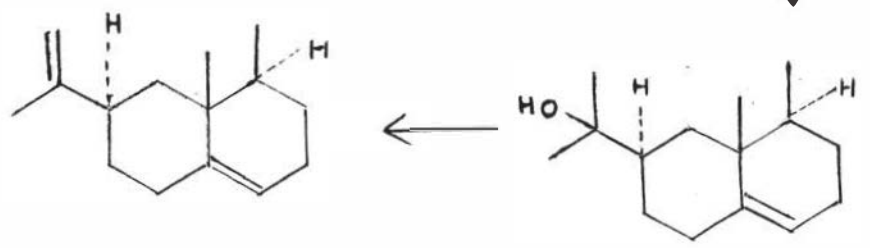


XXXIX XL

(±)-eremophilene (XII) in 28% yield.



XLI XLII

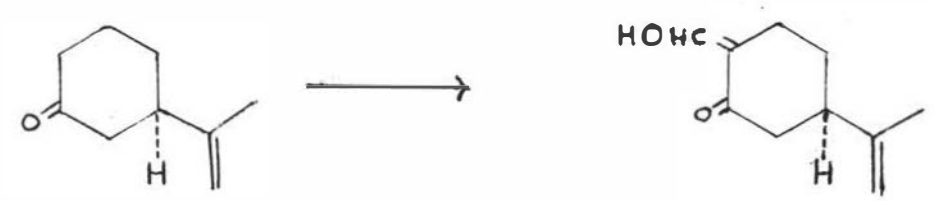


XII XV

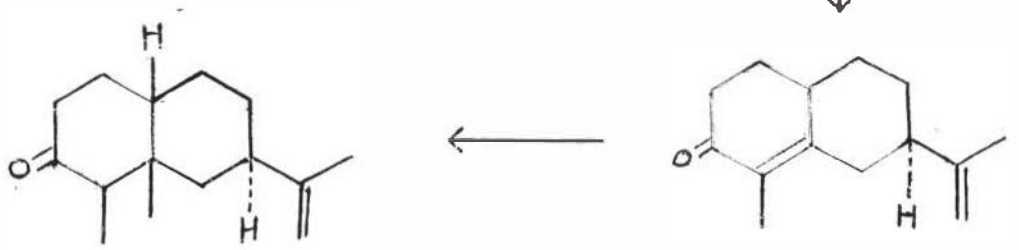
Synthesis of (±)-Eremophil-3,11-diene

Eremophil-3,11-diene was synthesized starting with 3-isopropenylcyclohexanone (XLIII).[35] The hydroxymethylene derivative XLIV was prepared by treatment of XLIII with ethyl formate and sodium hydride in benzene. The reaction of XLIV with 1-diethylamino-3-pentanone methiodide in sodium methoxide/methanol gave, after deformylation and ring closure, a 64% yield of the substituted octalone XLV. The stereoselective introduction of the angular methyl group at C_5 was successful using the reagent lithium

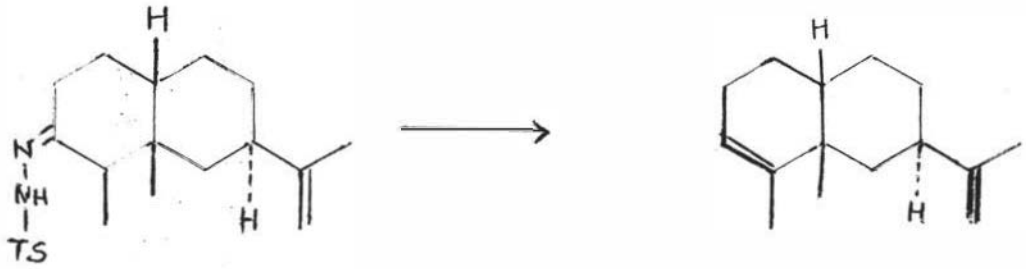
dimethyl cuprate in ether and resulted in the formation of (±)-eremophil-11-en-3-one (XLVI). The ketone XLVI was converted into the corresponding tosyl hydrazone XLVII which, on treatment with sodium borohydride in dioxane afforded, in 73% yield, (±)-eremophil-3,11-diene (XLVIII).



XLIII XLIV



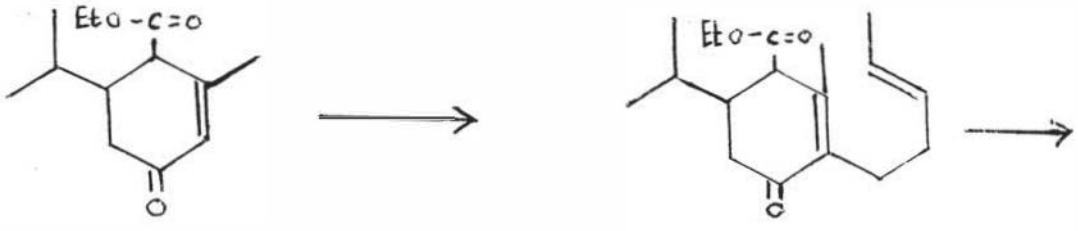
XLVI XLV



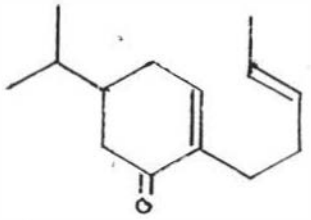
XLVII XLVIII

Synthesis of (dl)-Tetrahydroeremophilone

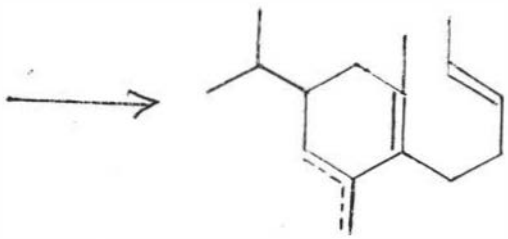
The starting material for the synthesis[36] was the keto ester XLIX, which was alkylated with trans-1-bromo-3-pentene to give the keto ester L. Hydrolysis and decarboxylation of ester L gave the unsaturated ketone LI. Addition of CH_3Li to the ketone LI, followed by phosphorus oxychloride in pyridine dehydration, gave a mixture of trienes LII. The triene mixture was cyclized by treatment with anhydrous formic acid and reduced with lithium aluminum hydride to give LIII. The oxidation of the alcohol LIII with Jones reagent gave LIV which, on Wolf-Kishner reduction gave the olefin LV. Photo-oxygenation of LV, followed by lithium aluminum hydride reduction, gave the mixture of allylic alcohols LVI, which was added to one equivalent of ozone in methylene chloride at -70°C. Immediate reduction of the ozonide with zinc dust and acetic acid gave the ketol LVII. Acetylation of the ketol with acetic anhydride and phosphoric acid, followed by calcium and liquid ammonia reduction, gave dl-cis-tetrahydroeremophilone (LVIII).



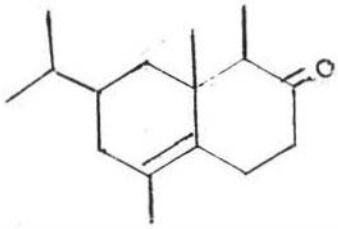
XLIX L



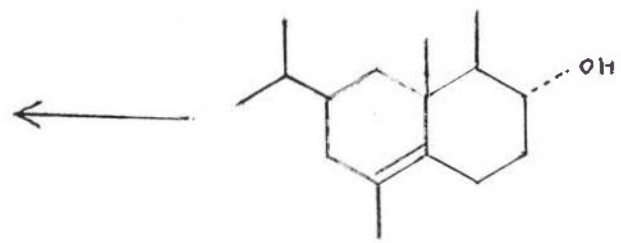
LI



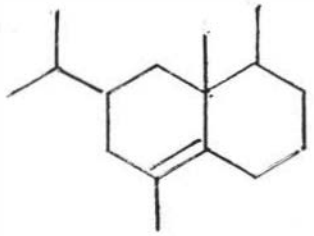
LII



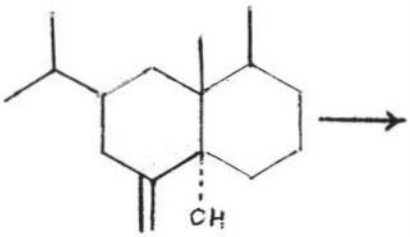
LIV



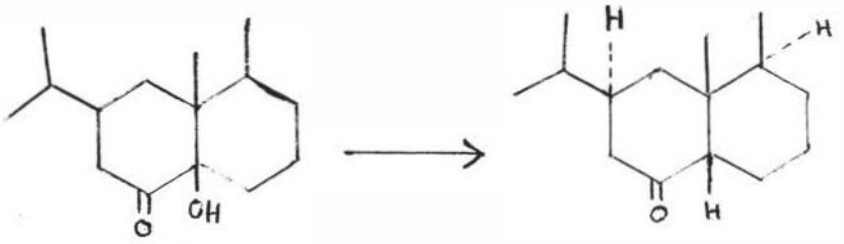
LIII



LV



LVI

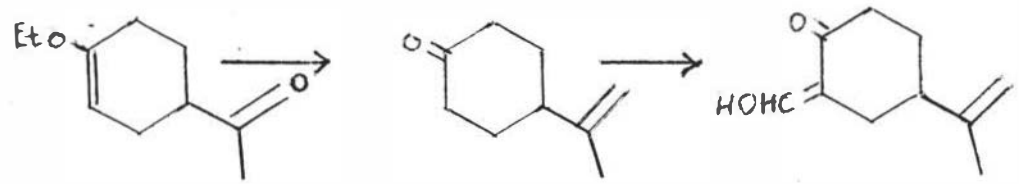


LVII LVIII

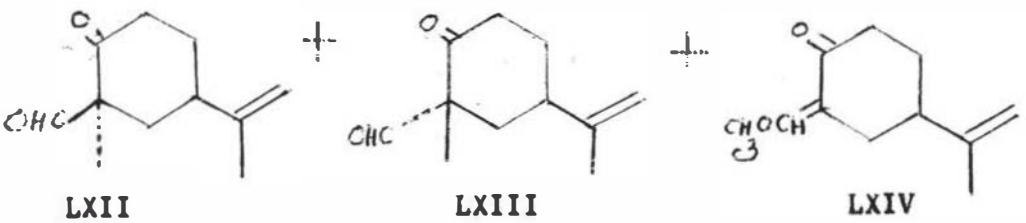
Synthesis of (±)-Nootkatone

The total synthesis[16] of racemic nootkatone started with 4-acetyl-1-ethoxycyclohexene[37] (LIX). The reaction of LIX with triphenylmethylphosphonium iodide, in tetrahydrofuran, in the presence of n-butyl lithium, followed by mild acid hydrolysis yielded 4-isopropenyl cyclohexanone (LX). The sodium methoxide catalyzed condensation of LX with ethyl formate[38] lead to the hydroxymethylene derivative LXI, which was treated with methyl iodide in acetone to give a mixture of the keto aldehydes LXII and LXIII and the enol ether LXIV. The keto aldehydes were separated from the enol ether by preparative gas chromatography. The condensation of LXII and LXIII with acetone in the presence of piperidine, followed by subsequent treatment of the reaction product with methanolic potassium hydroxide yielded the dienones LXV and LXVI. The reductive methylation of LXV with lithium dimethyl cuprate in absolute ether gave 4-nootkatone (LXVII) and

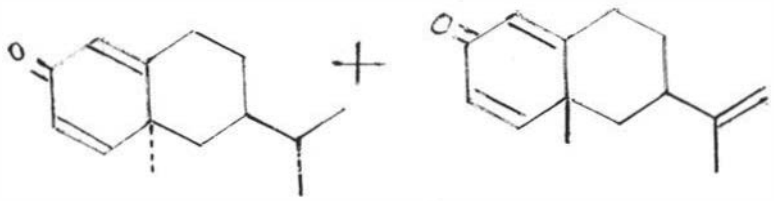
only traces of the desired nootkatone (LXVIII). However, a successful attempt was made by the condensation of LXII, LXIII, and LXIV with methyl acetoacetate in the presence of piperidine[39], followed by treatment with potassium hydroxide and re-esterification with diazomethane to give the dienone LXIX. The methylation of LXIX with methyl iodide gave the keto ester LXX. Dehydrogenation of LXX with 2,3-dichloro-5,6-dicyanobenzoquinone in toluene[40] gave the dienone ester LXXI, which was reduced easily to the keto ester LXXII with sodium borohydride in pyridine.[41] The subsequent saponification and decarboxylation gave racemic nootkatone (LXVIII).



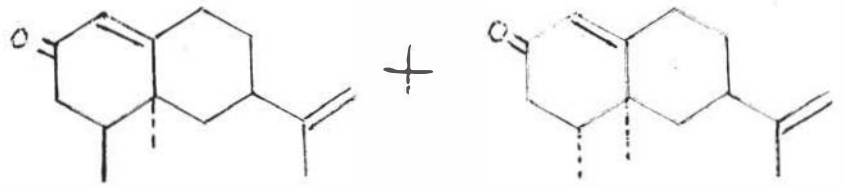
LIX LX LXI



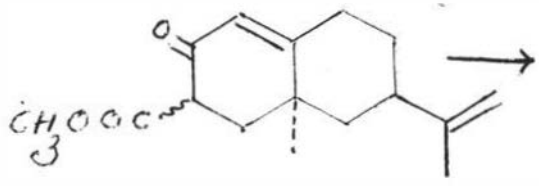
LXII LXIII LXIV

LXII + LXIII ⟶ 

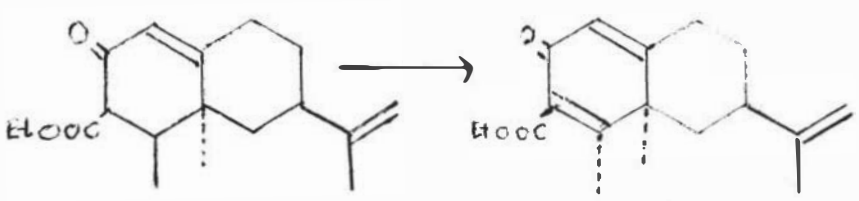
LXV LXVI

LXV ⟶ 

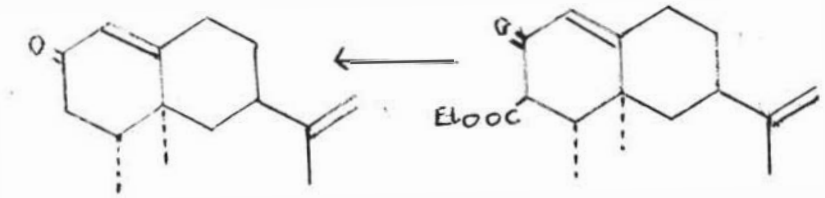
LXVII LXVIII

LXII + LXIII + LXIV ⟶ 

LXIX



LXX LXXI



LXVIII LXXII

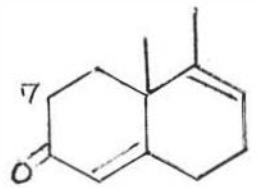
Chapter II

Results and Discussion

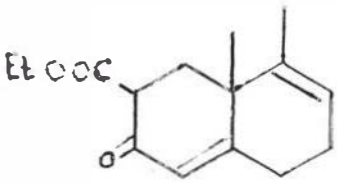
The purpose of this study was to find the shortest route to prepare the 1,9-dimethyl decalone system LXXIII, which would further allow the isopropenyl functional group to be introduced at position 7, as in LXXVII, via alkylation.

One proposed route was to prepare the compound LXXIV by cathylation of LXXIII. The cathylated product would be treated with methyl magnesium iodide, after protecting the 6-keto group by ketalization to give compound LXXV. Removing the ketal group by hydrolysis would yield the compound LXXVI which could be dehydrated to give LXXVII. Compound LXXVII is closely related to allo-eremophilone, petasol, and dehydrofukinone. Further, LXXIII is also an important starting material for the synthesis of furano-eremophilane system (LXXX).

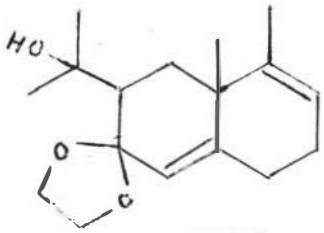
Another proposed route was to prepare the hydroxymethylene derivative, LXXVIII, from LXXIII by treatment with ethyl formate and sodium hydride in dry benzene. Compound LXXIX should be obtained from LXXVIII by treating with ethyl α-bromo propionate with subsequent deformylation. Further, furanoeremophil-3-9-diene (LXXX) should be obtained from LXXIX.



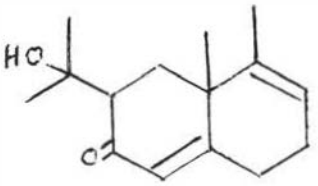
LXXIII



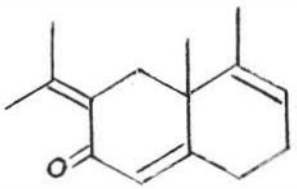
LXXIV



LXXV

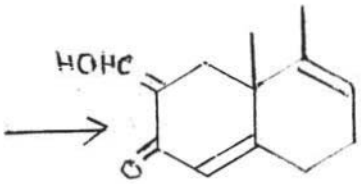


LXXVI

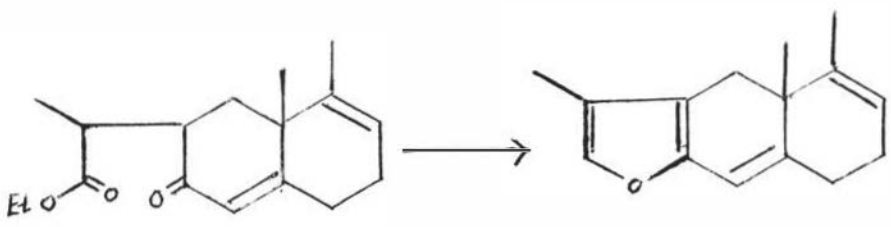


LXXVII

LXXIII



LXXVIII



LXXIX LXXX

The key intermediate LXXIII could be prepared by dehydrating the hydroxyketone LXXXI.

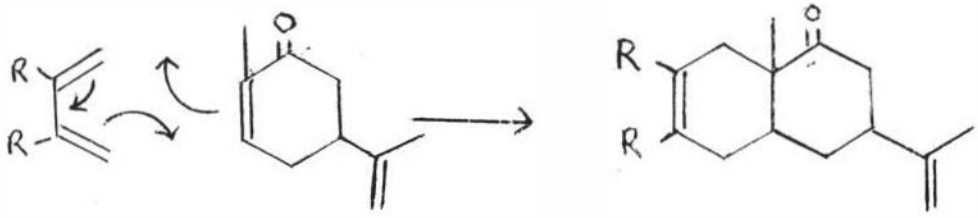
LXXXI LXXIII

The two basic approaches under investigation were the Diels-Alder reaction and the Robinson annellation.

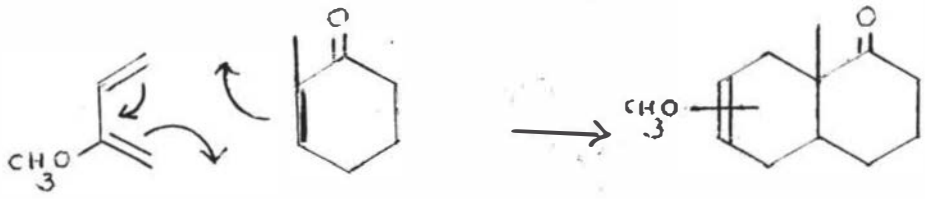
The Diels-Alder Reaction[42]

The Diels-Alder reaction between conjugated dienes like LXXXII, LXXXIII, LXXXIV, and cyclohexenone derivatives LXXXV, LXXXVI, and LXXXVII, respectively, were reported to give the decalin derivatives LXXXVIII, LXXXIX and XC in good yield.[43] Further the introduction of the angular methyl group to obtain the cis-1,9-dimethyl decalin

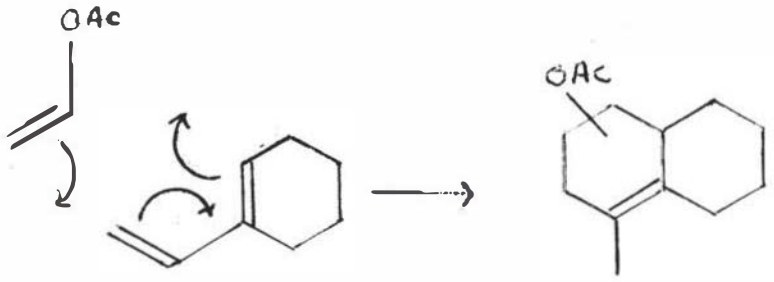
system was found to be difficult.[43]



LXXXII LXXXV LXXXVIII



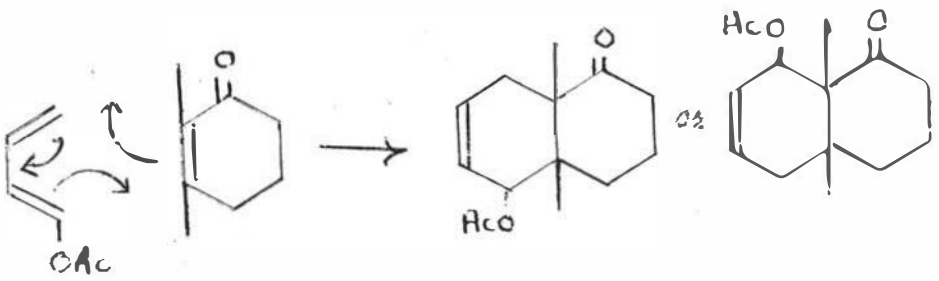
LXXXIII LXXXVI LXXXIX



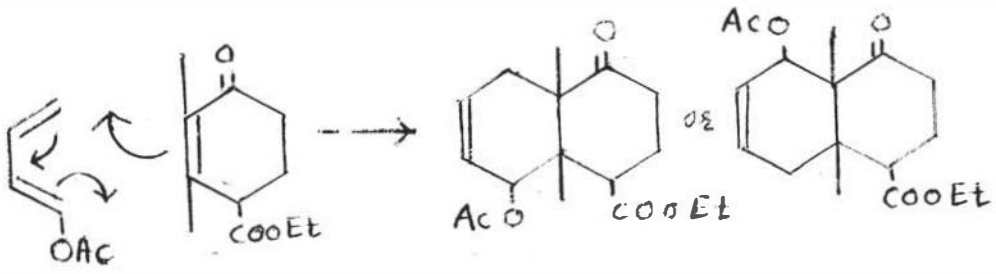
LXXXIV LXXXVII XC

A similar approach was studied with 1-acetoxybutadiene[44] (XCL) and 2,3-dimethyl-2-cyclohexenone (XCII) under typical conditions, as well as in the presence of catalysts such as anhydrous aluminum chloride,[45]

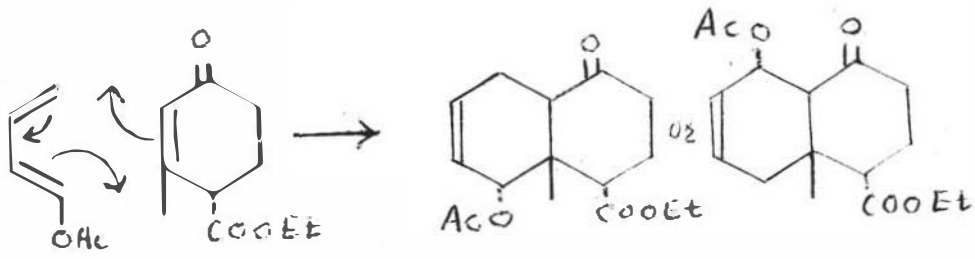
trichloroacetic acid, and anhydrous stannic chloride. The mixture of 1-acetoxy-butadiene and 2,3-dimethyl-2-cyclohexenone[46] was heated for 15 hours without solvent, but the formation of XCV or XCVI was not realized. The same mixture when dissolved in dry benzene and refluxed for 15 hours showed no evidence by gas chromatography for the formation of XCV or XCVI. Further, a mixture of 1-acetoxybutadiene and 2,3-dimethyl-2-cyclohexenone dissolved in dry benzene was cooled in an ice bath and a solution of anhydrous stannic chloride in dry benzene was added dropwise. The mixture turned black and the resulting gummy mass was found to be insoluble in ether. Similarly, anhydrous aluminum chloride and trichloroacetic acid were employed as catalysts but found to be unsatisfactory. Also, the reactions between 1-acetoxybutadiene and methylated Hagemann's ester[46] (XCIII) and Hagemann's ester (XCIV) were studied under the typical conditions but no evidence was found by gas chromatography for the expected products. The mixture of XCIV and 1-acetoxybutadiene when dissolved in a mixture of dry carbon tetrachloride and isopropyl ether and refluxed for 30 hours showed no evidence for the expected product by gas chromatography.



XCI XCII XCV XCVI



XCIII XCVII XCVIII

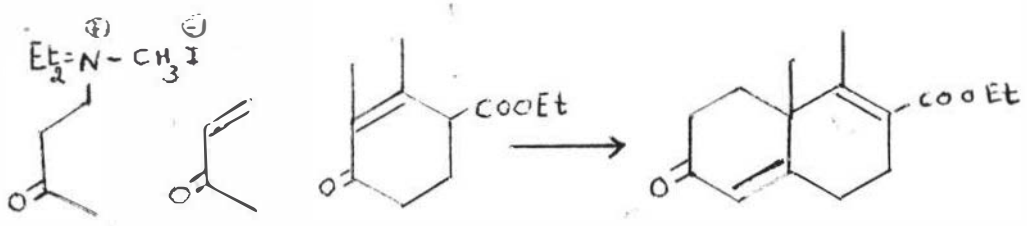


XCIV XCIX C

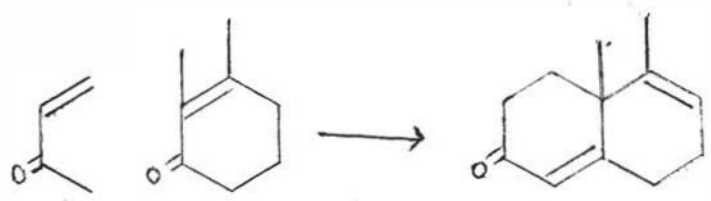
Robinson Annellation[47]

The reactions of methyl vinyl ketone and cyclohexenone derivatives have been studied extensively.[48] The condensations

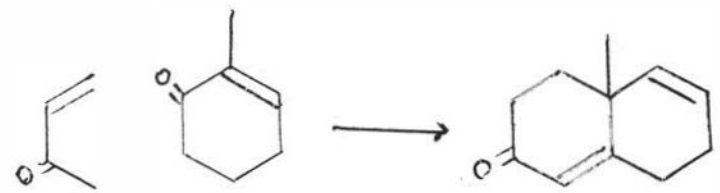
between methyl vinyl ketone (CII) or the methiodide salt of 1-diethyl amine-3-butanone[49] (CI) and methylated Hagemann's ester (XCIII)were studied under standard conditions but the yield of compound CIII was unsatisfactory. One of the primary difficulties was polymerization of methyl vinyl ketone. To avoid this, CI was substituted. Further, condensations with 2,3-dimethyl-2-cyclohexenone and 2-methyl-2-cyclohexenone gave similar unsatisfactory results. After a careful study of the preparation of the decalone system, the hydroxy ketone[50] LXXXI was prepared from the diketone[51] CVII and further dehydrated to give the 1,9-dimethyl decalone system LXXIII. The hydroxymethylene derivative CX of the hydroxy ketone LXXXI was prepared by treatment with ethyl formate and sodium hydride in dry benzene. Many attempts to condense ethyl α-bromo propionate with the hydroxymethylene derivative CX did not produce the desired alkylated compound CXI.



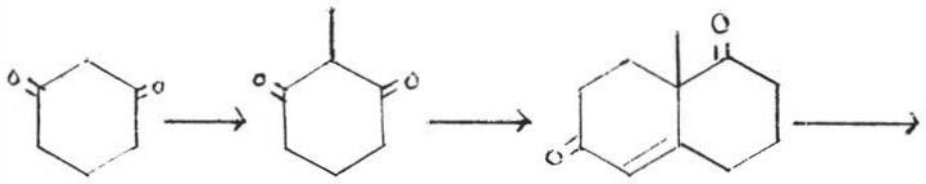
CI CII XCIII CIII



XCII LXXIII

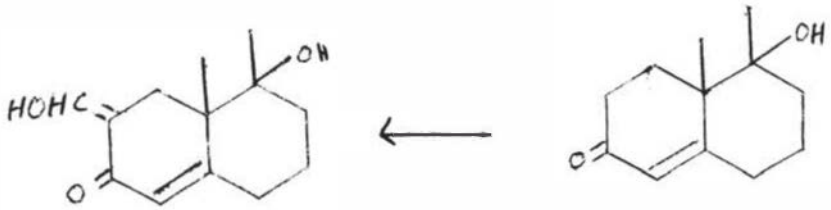


CII LXXXVI CIV

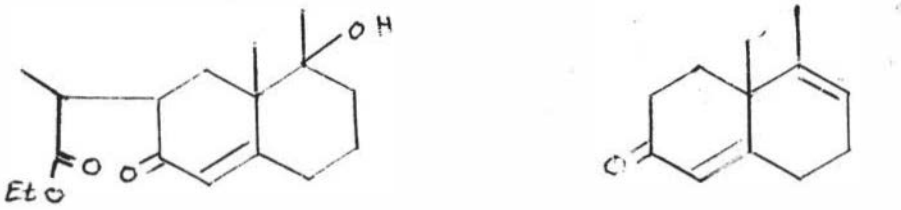


CV CVI CVII

CVIII CIX



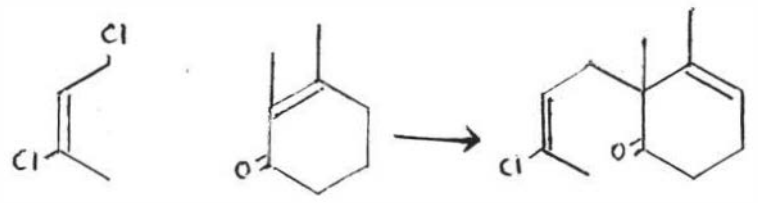
CX LXXXI



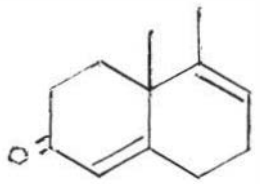
CXI LXXIII

Other attempts were made to condense 1,3-dichloro-2-butene with 2,3-dimethyl-2-cyclohexenone in the presence of sodium hydride in dry benzene as an alternate route to LXXIII through

chloroketone CXIII. The chloroketone was not obtained in high enough yield to proceed further.



CXII XCII CXIII



LXXIII

Chapter III

Experimental

Melting points were taken on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared (i r) spectra were recorded on a Perkin-Elmer 337 infrared spectrophotometer; nuclear magnetic resonance (n m r) spectra were determined with a Varian HA-60 spectrophotometer, using $CDCl_3$ as solvent and tetramethylsilane as an internal standard. Vapor phase chromatograms (vpc), unless otherwise indicated, were obtained with a Perkin-Elmer Model 154L gas chromatograph using a Sargent SR recorder and ¼ inch x 5 ft. column of 5% neopentylglycol sebacate on 60 to 90 mesh non-acid washed Chromosorb W with the helium flowrate at 60 ml/min. Thin layer chromatograms were run on silica gel G with $CHCl_3$ as a solvent and detection was with iodine vapor.

The Diels-Alder Reactions

The Attempted Condensation of 1-Acetoxybutadiene and Methylated Hagemann's ester.

A mixture of methylated Hagemann's ester (XCIII) (1.96 g) and 1-acetoxybutadiene (XCI) (1.12 g) was heated under reflux for 15 hours. The mixture was then cooled, diluted with 15 ml water and the resulting mixture extracted with three 30 ml portions of ether. The combined ether extract was washed with water and saturated NaCl solution, dried over $MgSO_4$, and the solvent removed under reduced

pressure. The brown viscus liquid obtained was starting material, identified by vpc at 240°. Similar results were obtained when the reaction was carried out using 10 ml of dry benzene as a solvent.

The Attempted Condensation of 1-Acetoxybutadiene and Hagemann's ester.

A mixture of Hagemann's ester (XCIV) (1.82 g) and 1-acetoxybutadiene (1.12 g) was heated under reflux for 15 hours. The mixture was cooled, diluted with 15 ml of benzene and 15 ml of water. The resulting mixture was extracted with three 30 ml portions of ether. The combined ether extracts were washed with water and saturated NaCl solution, dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude reaction product was starting material, identified by vpc at 220°.

A similar reaction was not achieved when 2,3-dimethyl-2-cyclohexenone was used in place of Hagemann's ester.

The Attempted Condensation of 1-Acetoxybutadiene and Hagemann's ester in the presence of Anhydrous $AlCl_3$.

A mixture of 1-acetoxybutadiene (1.12 g), Hagemann's ester (XCIV), (1.82 g) and a solution of 1.33 g of anhydrous $AlCl_3$ in 60 ml of dry benzene was refluxed for 30 min. The reaction mixture turned black, and the gummy mass which separated was found to be insoluble in ether. The black residue dissolved in acetone was analyzed by vpc at 220°. Neither product nor starting material was eluted. Similar results were obtained using trichloroacetic acid or $SnCl_4$ as catalysts in place of anhydrous $AlCl_3$.

2-(γ-chlorocrotonyl)-2,3-dimethyl-3-cyclohexenone (CXIII).

A mixture of 2,3-dimethyl-2-cyclohexanone (XCII) (1.24 g) and NaH (0.24 g) in 10 ml dry benzene was cooled in an ice bath for 30 min. Then a solution of 1,3-dichloro-2-butene (CXII) (1.14 g) in 5 ml of dry benzene was added dropwise. The reaction mixture was kept at room temperature for 3 hours and then refluxed for 3½ hours. At the end of that time the reaction mixture was cooled, diluted with 30 ml ether, washed with water, dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude reaction product gave chloroketone CXIII on distillation at 120° to 155° (bath temp) (0.50 mm Hg). The chloroketone CXIII was characterized by vpc at 194° exhibiting retention time 1.50 min. The ir spectrum showed absorption at 1612, 1650 (two double bonds), and 1750 cm^{-1} (unconjugated carbonyl group).

Cyclization of 2-(γ-chlorocrotonyl)-2,3-dimethyl-3-cyclohexenone.

A mixture of the chloroketone CXIII and conc. H_2SO_4 (2 ml) was stirred at room temperature for two hours. During the reaction the evolution of HCl was observed. At the end of this time the mixture was cooled, diluted with 15 ml water, and extracted with three 50 ml portions of ether. The combined ether extracts were washed with water, dried over $MgSO_4$, and the solvent removed under pressure. The crude residue was a black gummy mass insoluble in water.

2-Carbethoxy-1-9-dimethyl-6-keto-Δ^{1-5}-hexahydronaphthelene (CIII).

Preparation of the methiodide salt: 1-Diethylamino-3-butanone (1.42 g) and methyl iodide (1.42 g) were mixed in a small flask and the exothermic reaction was controlled by occasionally cooling in ice cold water bath. The viscus, transparent, light yellow liquid was dissolved in 15 ml absolute ethanol for further use.

A solution of sodium ethoxide (5 ml.), (from 1.13 g Na in 25 ml absolute ethanol) was added to a well cooled solution of methylated Hagemann's ester (XCIII) (1.42 g) in absolute ethanol (10 ml). After 40 min. the solution of methiodide salt was added dropwise under a nitrogen atmosphere. The reaction mixture was kept in an ice bath for 3 hrs. and then refluxed for 3½ hours. The reaction mixture was then cooled, diluted with 15 ml of water, and extracted with three 25 ml portions of ether. The combined ether extracts were washed with water and saturated NaCl solution, and dried over anhydrous MgSO4. The solvent was removed under vacuum. The crude reaction product afforded 0.300 g of compound CIII on distillation at 160° to 180° (bath temp.), (0.50 mm Hg). Compound CIII was characterized by vpc at 220°, exhibiting a retention time of 6.0 min. The ir spectrum showed bands at 1675 cm^{-1} (α,β unsaturated carbonyl group), 1625 cm^{-1} (conjugated double bond), 1750 cm^{-1} (ester carbonyl group), and 1250 cm^{-1} (ester group).

1,9-Dimethyl-6-keto-$\Delta^{1,5}$-3,4,6,7,8,9-hexahydronaphthalene (LXXIII).

A mixture of 2,3-dimethyl-2-cyclohexenone (XCII) (1.25 g), NaH (0.6 g) and 15 ml of dry benzene was stirred at room temperature for 12 hours. Then the reaction mixture was cooled to 0° and a solution of the methiodide salt of 1-diethylamino-3-butanone (4.26 g) in pyridine (15 ml) was added dropwise over a period of two hours under a nitrogen atmosphere. The resulting mixture was then neutralized with dil HCl and extracted with three 50 ml portions of ether. The combined ether extracts were washed with water, dried over $MgSO_4$, and the solvent evaporated. The crude residue, characterized by vpc at 194°, showed a single peak with a retention time of 1.5 min. and was identified as starting material.

6-Keto-9-methyl-$\Delta^{1,5}$-3,4,6,7,8,9-hexahydro naphthalene (CIV).

A mixture of 2-methyl-2-cyclohexenone (1.1 g) and 3 N NaOMe (0.10 ml) was cooled to -5° in an ice salt bath. Methyl vinyl ketone (0.70 g) was added dropwise and the reaction mixture was kept at -5° for six hours. It was then diluted with water (15 ml) and extracted with four 25 ml portions of ether. The combined ether extracts were washed with water, saturated NaCl solution, dried over anhydrous $MgSO_4$, and the solvent removed under reduced pressure. The residue was starting material, identified by vpc at 150°.

6-Ethoxy-1-keto-9-methyl-$\Delta^{4,5}$-1,2,3,7,8,9-hexahydronaphthalene (CVIII).

(a) A mixture of diketone CVII (4 g), dry benzene (40 ml) ethyl orthoformate (5 g) and ethanolic HCl solution (3 ml, equivalent to

21.6 mg of HCl) was refluxed for 3 hours. The reaction mixture was cooled and a solution of $NaHCO_3$ (2 g) in water (15 ml) was added. The resulting mixture was extracted with three 30 ml portions of ether. The combined ether extracts were washed with water, saturated NaCl solution, and dried over $MgSO_4$. After removal of solvent under reduced pressure the yellow liquid weighed 4.3 g. Tlc indicated a major spot (R_f 0.72); vpc at 204° showed a major peak, retention time 2.5 min; ir spectrum, 1612 cm^{-1} (two conjugated double bonds), and 1712 cm^{-1} (unconjugated carbonyl group).

(b) A mixture of diketone CVII (10 g), dry benzene (106 ml), ethylorthoformate (8.65 g), and p-toluenesulphonic acid monohydrate (0.142 g) was stirred at room temperature. The reaction was monitored by tlc. After about 50 min., the reaction was quenched with 10 ml of 15% KOH solution. The solvent layer was separated and washed with water, saturated NaCl solution, and dried over $MgSO_4$. The solvent was removed under reduced pressure. The enol ether CVIII was identified and similar analytical data were obtained as in method (a).

1-9-Dimethyl-6-ethoxy-1-hydroxy-$\Delta^{4,5}$-1,2,3,7,8,9-hexahydronaphthalene (CIX).

A mixture of magnesium turnings (2.4 g) and dry ether (10 ml) was placed in one liter round bottom flask equipped with reflux condenser fitted with drying tube, and a separatory funnel. A solution of methyl iodide (14.2 g) in dry ether (40 ml) was added

dropwise and the vigorous reaction was controlled by a cold water bath. When the addition of CH_3I was complete the reaction mixture was refluxed for two hours. After cooling the reaction mixture to room temperature, a solution of the enol ether CVIII in dry ether (30 ml) was added dropwise, and the mixture refluxed for 3 hours. The reaction mixture was cooled and the excess Grignard reagent destroyed by adding a saturated solution of NH_4Cl (60 ml). The resulting mixture was extracted with three 50 ml portions of ether. The combined ether extracts were washed with water, dried over $MgSO_4$, and the solvent was removed under reduced pressure. The brownish yellow liquid (4.2 g) was characterized by its ir spectrum; 3450 cm^{-1} (hydroxyl group) and absence of a carbonyl group at 1712 cm^{-1}.

1-9-Dimethyl-1-hydroxy-6-keto-$\Delta^{5\ (10)}$-1,2,3,4,6,7,8,9-octahydro-naphthalene (LXXXI).

A mixture of compound CIX, oxalic acid (2.0 g), water (10 ml), and ethanol (30 ml) was stirred at room temperature for 3 hours. The reaction mixture was neutralized with $NaHCO_3$ and the ethanol was removed under reduced pressure. The resulting mixture was extracted with three 50 ml portions of ether. The combined ether extracts were washed with water, saturated solution of NaCl, dried over $MgSO_4$, and the solvent removed under reduced pressure. The viscous yellow liquid was diluted with 3 ml of ether, and crystallized after standing several hours in a refrigerator. The yellow crystals of

hydroxyketone weighed 2.1 g and the overall yield from the diketone CVII was 50%.

The analytical data obtained was identical to that reported[50] in the literature. Tlc indicated a single spot (R_f 0.393); m.p. 100°, vpc at 220° showed a single peak, retention time 3.5 min; ir spectrum indicated 3540 cm^{-1} (hydroxyl group), 1650 cm^{-1} (α,β-unsaturated ketone), 1603 cm^{-1} (double bond); λ_{max}^{EtOH} 243 mμ, ε 14,790. The nmr spectrum showed characteristic peaks at τ 8.77 (s,3), 8.67 (s,3) and 4.23 ppm (s,1).

1-9-Dimethyl-6-keto-Δ^{1-5}-3,4,6,7,8,9-hexahydronaphthalene (LXXIII).

A mixture of the hydroxyketone LXXXI (100 mg) and iodine (50 mg) was heated to 115° for 1½ hour. Then the mixture was cooled and dissolved in 30 ml ether. The ether solution was washed with three 10 ml portions of 10% NaOH solution, distilled water, 10% H_2SO_4, distilled water, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude reaction product afforded LXXIII (72 mg), (80% yield) on distillation at 120° to 160° (bath temp) (0.5 mm Hg). The product was identified by vpc at 210°, retention time 4.3 min; tlc showed a major component (R_f 0.625) for the product; ir spectrum showed absence of the broad peak for hydroxyl group, 1602 cm^{-1} (double bond), 1675 cm^{-1} (conjugated carbonyl group); λ_{max}^{EtOH} 243 ε 7850.

1,9-Dimethyl-1-hydroxy-7-hydroxymethylene-6-keto-$\Delta^{5\ (10)}$-1,2,3,4,6,7,8,9-octahydronaphthalene.

A mixture of the hydroxyketone LXXXI (194 mg), dry benzene

(20 ml), NaH (3 g, 55% dispersed in oil) and ethyl formate (300 mg) was stirred at room temperature for two days. The excess of NaH was destroyed by adding 3 ml of CH_3OH and the mixture was acidified with dilute HCl. The resulting mixture was extracted with three 50 ml portions of ether. The combined ether extracts were washed with water, dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude residue (150 mg) was characterized by tlc and showed a major spot of the product (Rf 0.83) and a light spot of the starting material (R_f 0.53). It gave a strong violet color with neutral $FeCl_3$ solution and the ir spectrum showed a broad band 3600 to 3300 cm^{-1} (hydroxyl group), 1650 cm^{-1} (carbonyl group), and 1610 cm^{-1} (double bond). The crude reaction product was used without purification for further steps.

The Attempted Condensation between ethyl α-bromo propionate and the hydroxymethylene derivative CX.

A mixture of the hydroxymethylene derivative CX and ethyl α-bromopropionate (300 mg) was stirred for 16 hours at room temperature then refluxed for one hour with NaOEt solution from (0.200 g Na in 5 ml EtOH). The mixture was cooled, acidified with dilute HCl, and extracted with three 30 ml portions of ether. The combined ether extracts were washed with water and dried over $MgSO_4$, and the solvent removed under reduced pressure. The crude residue was characterized as starting material by vpc at 210°; tlc showed a spot for the hydroxymethylene derivative (R_f 0.81) and gave a violet coloration with neutral $FeCl_3$.

Chapter IV

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