THE SYNTHESIS OF SESQUITERPENES CONTAINING THE AROMADENDRANE SKELETON

A THESIS

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The Faculty of the Division of Graduate

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by

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THE SYNTHESIS OF SESQUITERPENES

CONTAINING THE AROMADENDRANE SKELETON

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Date approved by Chairman: April 30, 1975

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I would especially like to thank my wife who unselfishly gave me the help and encouragement necessary to complete this work. In addition to typing the rough draft of this thesis, she made numerous sacrifices so that I could give full attention to my research and examinations. Without the help that was given to me by my wife and Dr. Caine, it is likely I would have been considerably less successful.

TABLE OF CONTENTS

TABLE OF CONTENTS (Concluded)

GLOSSARY OF ABBREVIATIONS

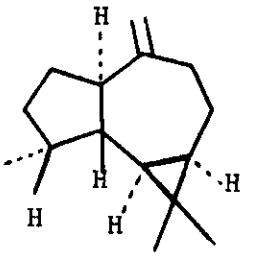
Anal.	C, H analysis
bp	boiling point
cm^{-1}	wave numbers (ir spectrum)
DDHQ	2,3-dichloro-5,6-dicyano-p-hydroquinone
DDQ	2,3-dichloro-5,6-dicyano-p-benzoquinone
1,2-DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
eV	electron volt
glc	gas-liquid chromatography
Hz	Hertz (cycles per second, nmr spectrum)
ir	infrared
J	coupling constant (nmr spectrum)
LAH	lithium aluminum hydride
mm	millimeters of mercury (pressure)
m/e	mass to charge ratio (mass spectrum)
mp	melting point
ms	mass spectrum
nm	nanometers (millimicrons, uv spectrum)
nmr	nuclear magnetic resonance
PNB	p-nitrobenzoyl group
ppm	parts per million (nmr spectrum)

GLOSSARY OF ABBREVIATIONS (Concluded)

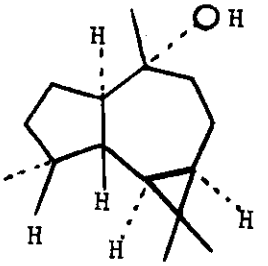
PTSA	p-toluene sulfonic acid
THF	tetrahydrofuran
TMS	tetramethylsilane
Ts	p-toluenesulfonyl group
uv	ultraviolet
$[\alpha]D$	specific rotation at the sodium D line
ϵ	extinction coefficient (uv spectrum)
λ	wavelength
ϕ	phenyl group

SUMMARY

The initial goal of this research was to generate the aromadendrane skeleton by the photochemical rearrangement of an appropriately substituted cross-conjugated cyclohexadienone. The photoproduct would then be converted to (+)-aromadendrene (I) or (-)-globulol (II) which are naturally occurring sesquiterpenes.

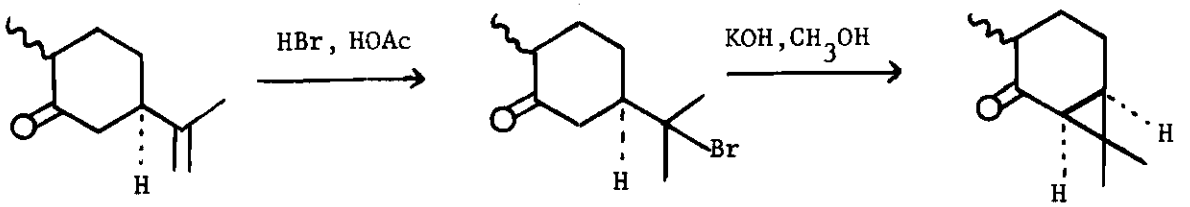


I

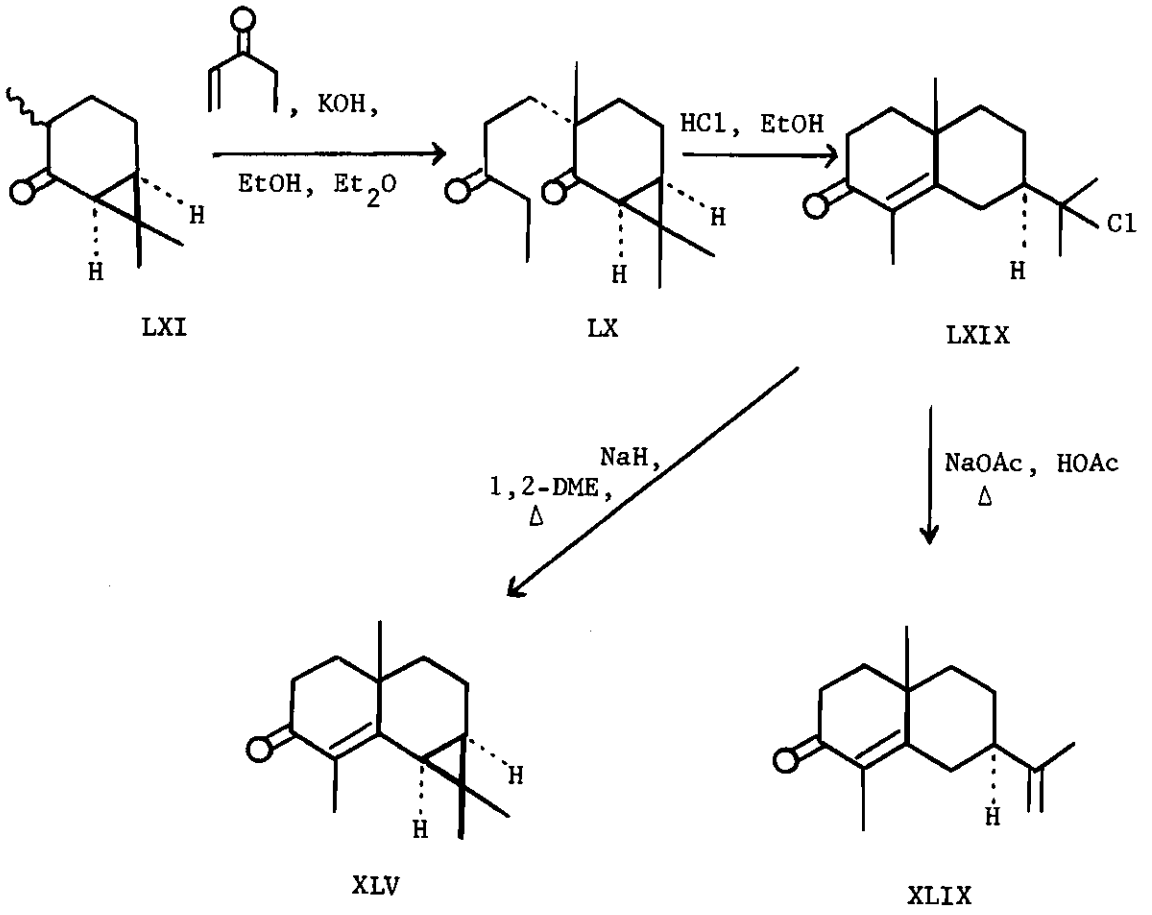


II

The logical precursor to the desired dienone was (-)-epimaalienone (XLV) which had been prepared by Ourisson and co-workers by a somewhat inefficient procedure. A new, more efficient synthesis of (-)-epimaalienone was developed which utilized (+)-dihydrocarvone (LXII) as the starting material.

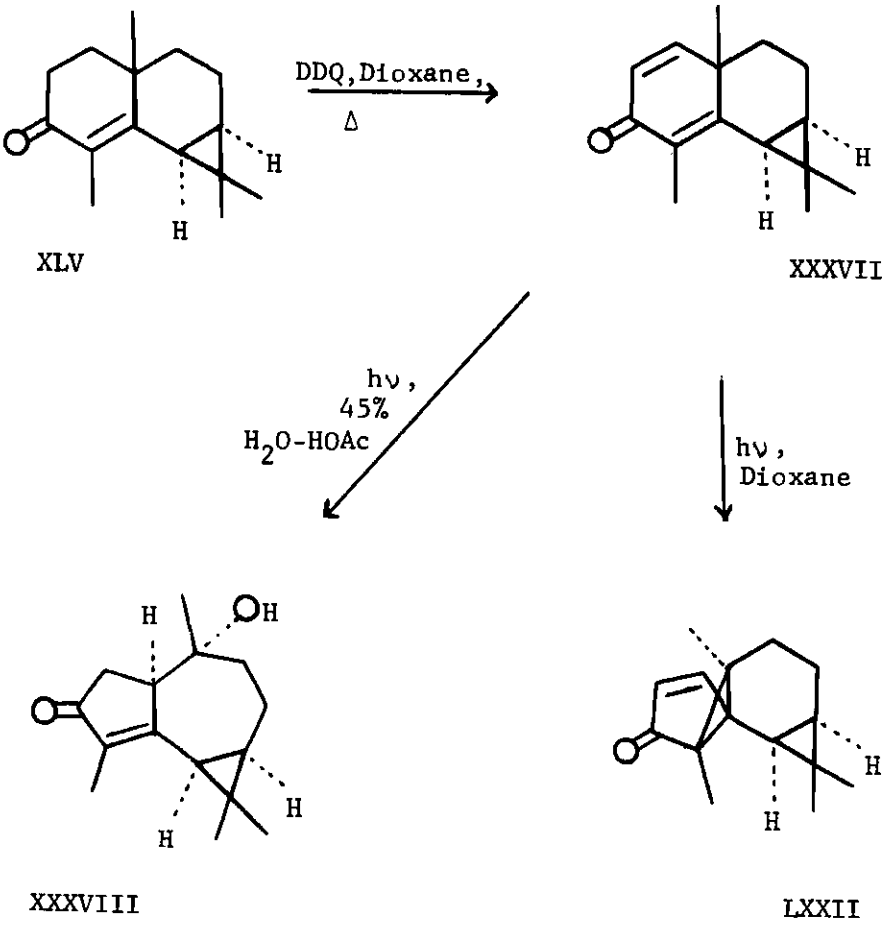


LXII LXIII LXI



(+)-Dihydrocarvone was converted to (-)-2-carone (LXI) by addition of hydrogen bromide to the exocyclic double bond and treatment of the tertiary bromide (LXIII) with potassium hydroxide in methanol. The Michael addition of (-)-2-carone (LXI) to ethyl vinyl ketone occurred in a stereospecific manner to afford a 1,5-diketone (LX) which was cyclized with hydrogen chloride in ethanol to produce an α,β-unsaturated chloro ketone (LXIX). This ketone (LXIX) was treated with sodium hydride in 1,2-dimethoxyethane to produce (-)-epimaalienone (XLV) as the only product in good yield. The chloro enone (LXIX) was also converted to the difficultly obtainable sesquiterpene, (+)-α-cyperone (XLIX), by dehydrochlorination

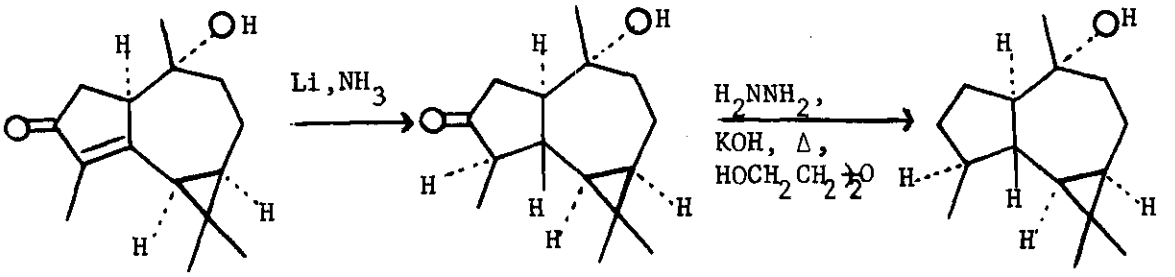
with sodium acetate in acetic acid. (-)-Dehydroepimaalienone (XXXVII) was prepared by oxidation of (-)-epimaalienone (XLV) with DDQ. Irradiation of (-)-dehydroepimaalienone in aqueous acetic acid afforded a 5,7-fused hydroxy ketone (XXXVIII) and irradiation in dioxane afforded a lumiproduct (LXXII).



XLV XXXVII

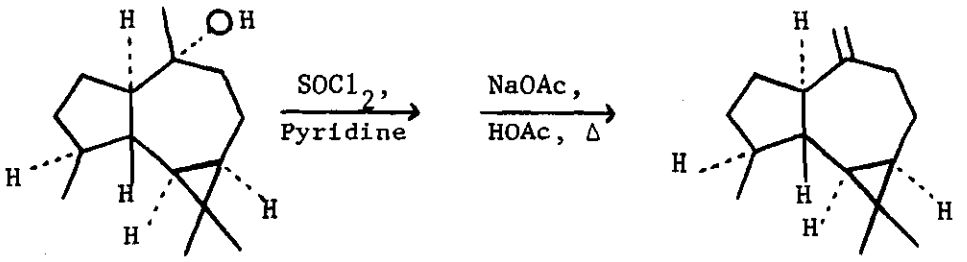
XXXVIII LXXII

Compound XXXVIII was converted to (-)-4-epiglobulol (LXXVIII) by reductions with lithium in liquid ammonia followed by hydrazine and potassium hydroxide in diethylene glycol.



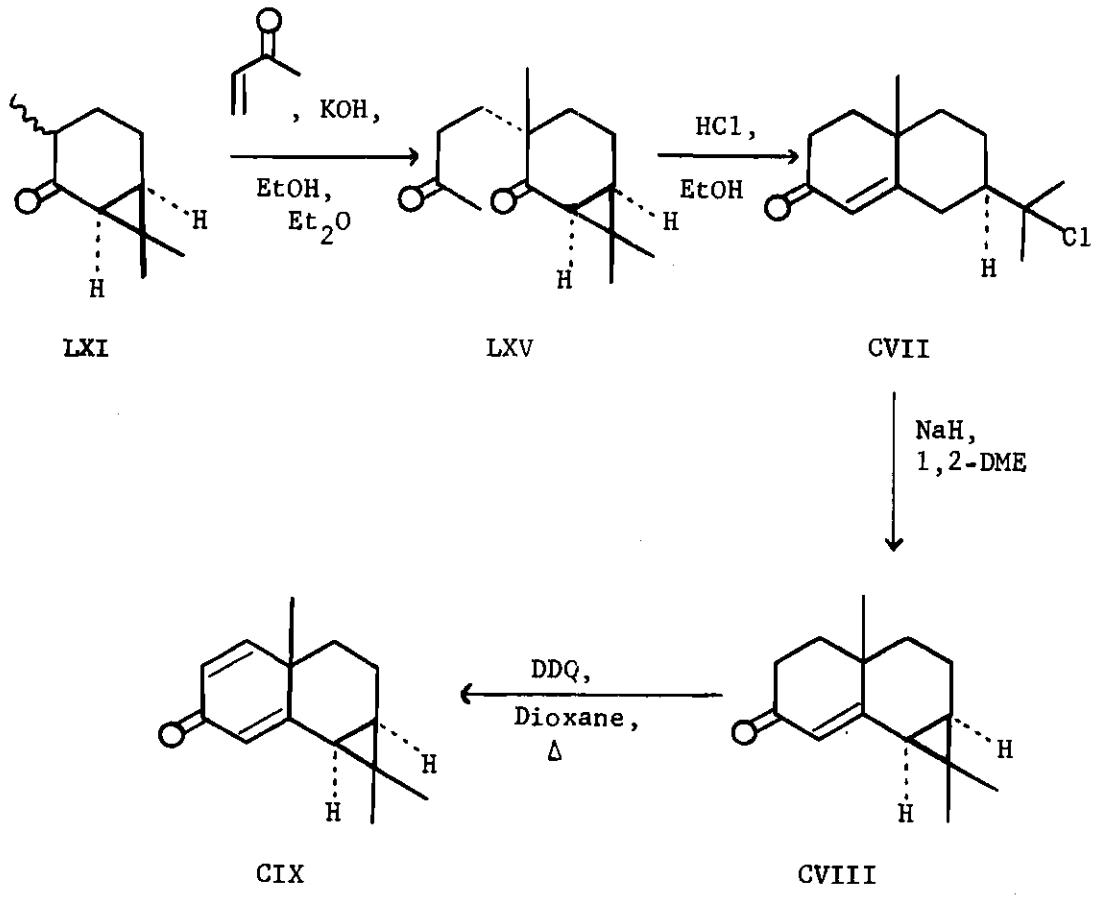
XXXVIII LXXVI LXXVIII

The absolute stereochemistry of (-)-4-epiglobulol (LXXVIII) was determined by its dehydration with thionyl chloride to (+)-4-epiaromadendrene (III) which exhibited identical ir and nmr spectral properties to those of (-)-4-epiaromadendrene that had been prepared by Büchi and co-workers by a different route.



LXXVIII III

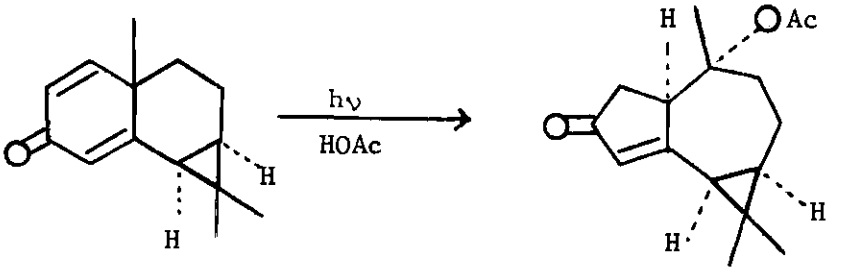
The unsubstituted dienone (CIX) was prepared by a route identical to that used to synthesize (-)-dehydroepimaalienone.



LXI LXV CVII

CIX CVIII

When 4-normethyl-dehydroepimaalienone (CIX) was irradiated in glacial acetic acid, a 5,7-fused acetoxy ketone (CXI) was produced as the only major product.



CIX CXI

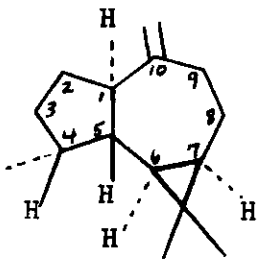
Several unsuccessful attempts were directed at converting either compound XXXVIII, LXXVI, or CXI to naturally occurring (-)-globulol (II).

Although successful preparation of (+)-aromadendrene (I) and (-)-globulol (II) was not realized, efficient syntheses of (+)-α-cyperone (XLIX), (-)-epimaalienone (XLV), (-)-4-epiglobulol (LXXVIII), and (+)-4-epiaromadendrene (III) were developed. Additionally, the photochemistry of (-)-dehydroepimaalienone (XXXVII) and 4-normethyl-dehydroepimaalienone (CIX) was elucidated.

CHAPTER I

INTRODUCTION

The naturally occurring sesquiterpenes (+)-aromadendrene (I) and (-)-globulol (II) have been isolated from numerous species of Eucalyptus as well as other plant sources [1]. The earliest, rational structure (III) proposed for the absolute configuration of (+)-aromadendrene was offered by Birch [2] in 1953. Subsequent degradative work [3] eliminated an alternate structure proposed by the early workers.



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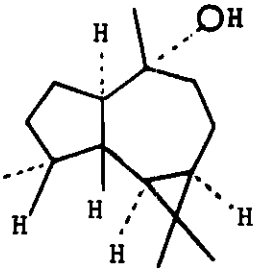
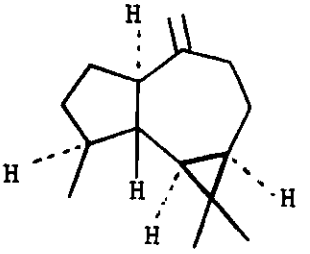


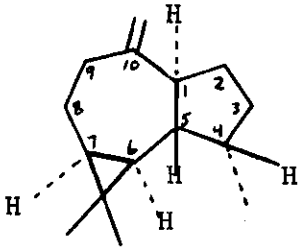
II



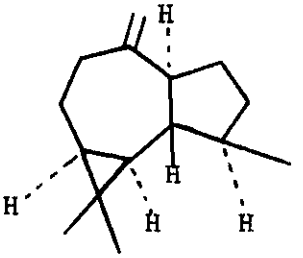
III

The structure of (-)-globulol was established by its partial synthesis [4] from (+)-aromadendrene via epoxidation and subsequent lithium aluminum hydride reduction. The correct structure of naturally occurring (+)-aromadendrene was unambiguously established in 1969 when Büchi and co-workers [5] prepared (-)-aromadendrene (IV) and (-)-4-epi-aromadendrene (V) by total synthesis from (-)-perillaldehyde (VI). Comparison of (IV) and (V) with an authentic sample of naturally occurring (+)-aromadendrene indicated that the assignment of the alpha configuration

of the methyl group at C-4 was correct.

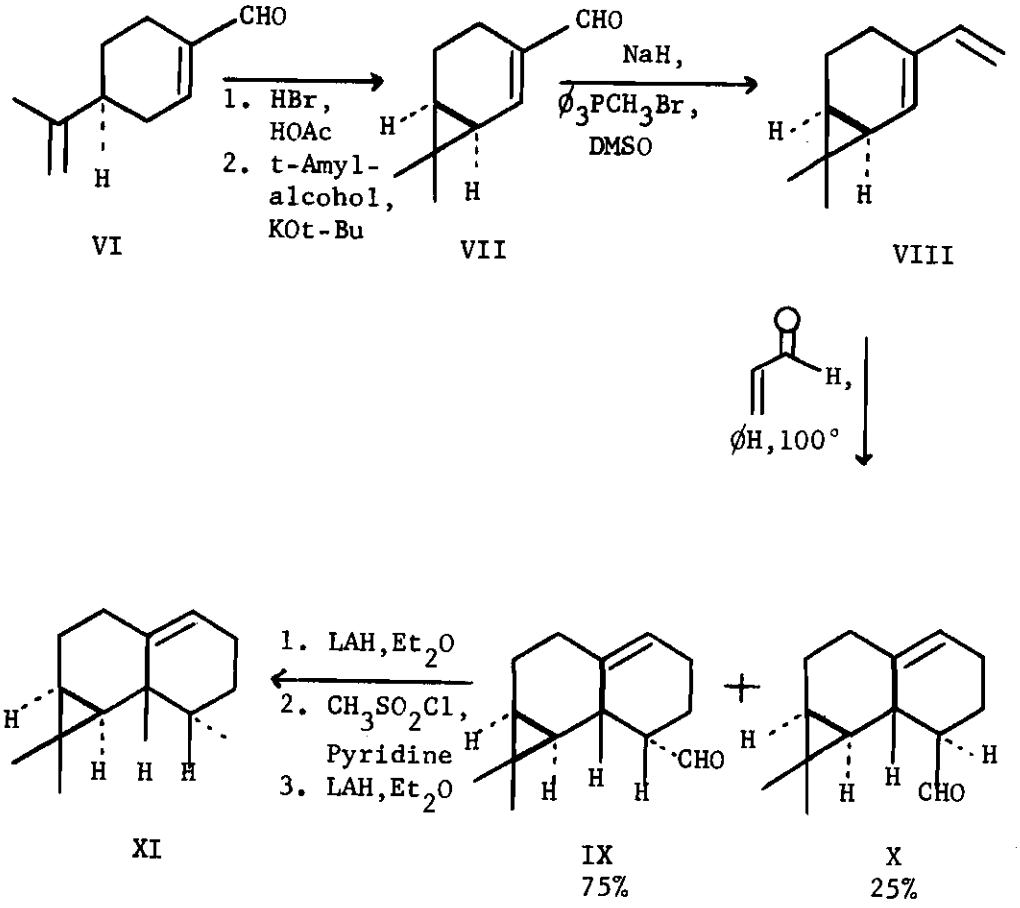


IV

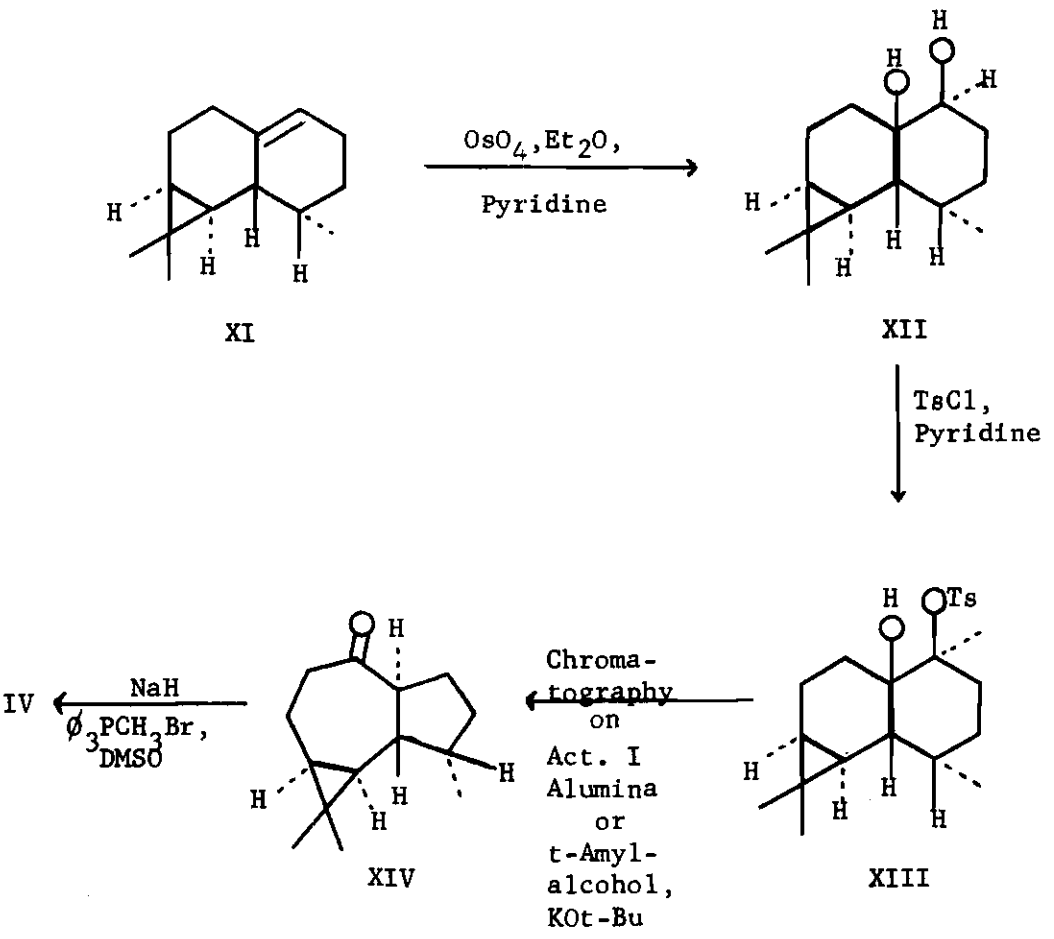


V

Büchi's total synthesis of (-)-aromadendrene (IV) is outlined in Scheme 1.

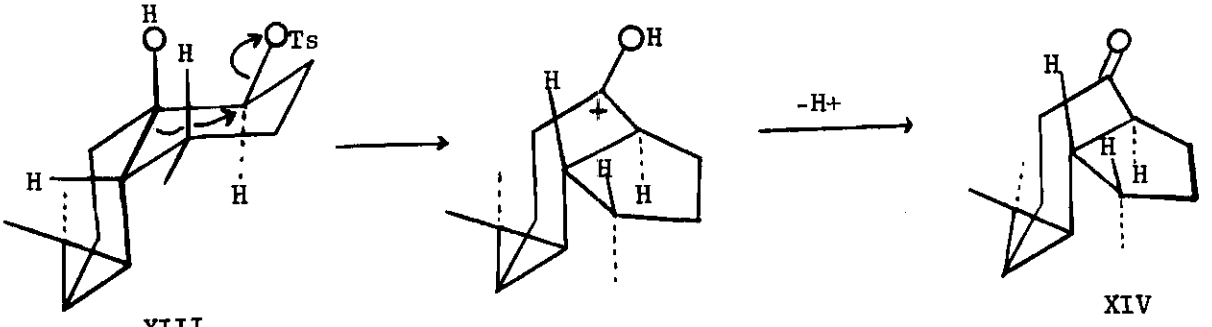


Scheme 1



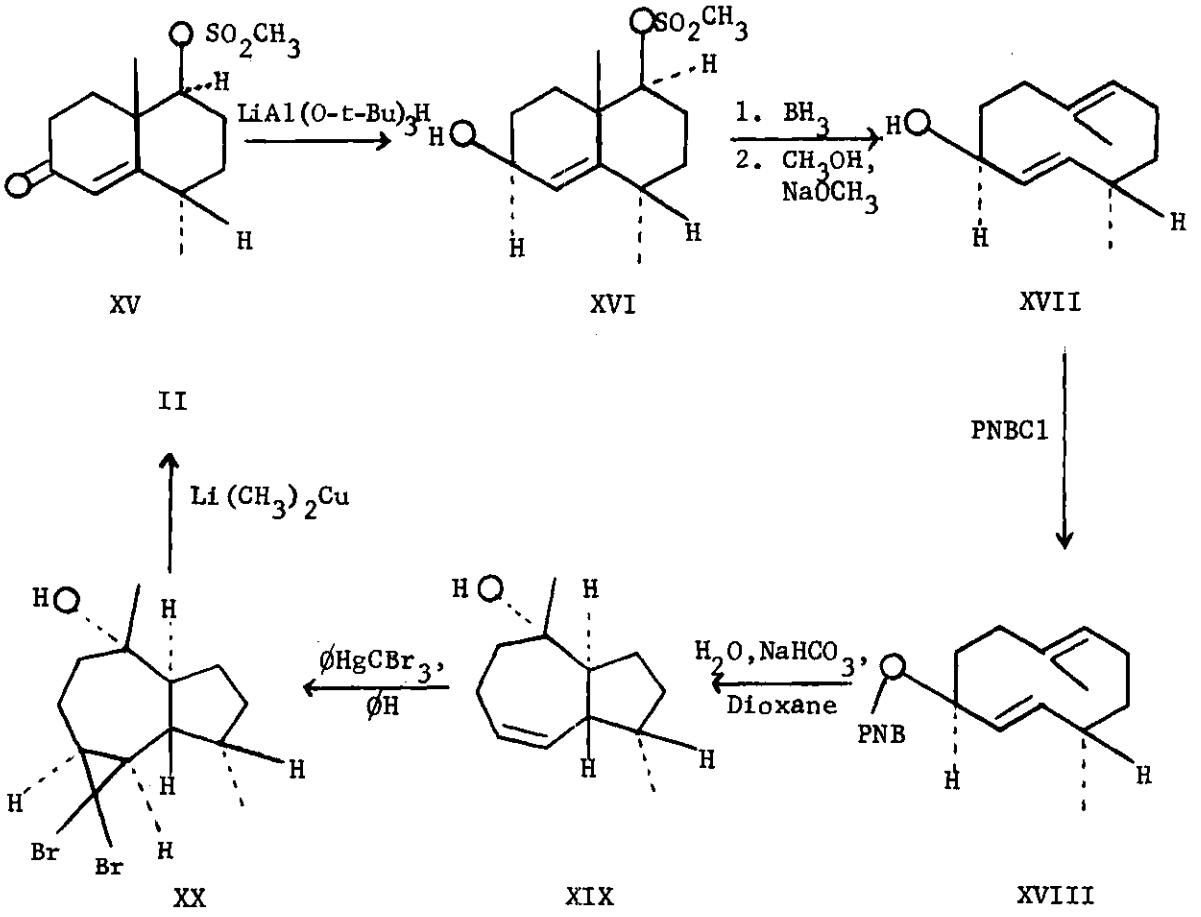
Scheme 1 (Continued)

The key step in Büchi's synthesis involved the rearrangement of monotosylate (XIII). The rearrangement occurs sterospecifically as the result of a trans and coplanar migration as illustrated in Scheme 2.



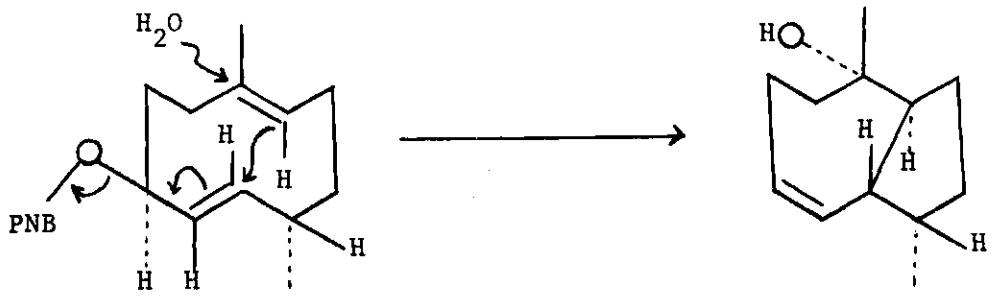
Scheme 2

More recently Marshall [6] has reported the total synthesis of racemic globulol (Scheme 3).



Scheme 3

The key step in Marshall's synthesis utilizes a solvolytic cyclization of XVIII to generate the hydroazulene skeleton. The stereochemistry of the cyclization is determined by the reacting conformation of the ester as depicted in Scheme 4.



XVIII XIX

Scheme 4

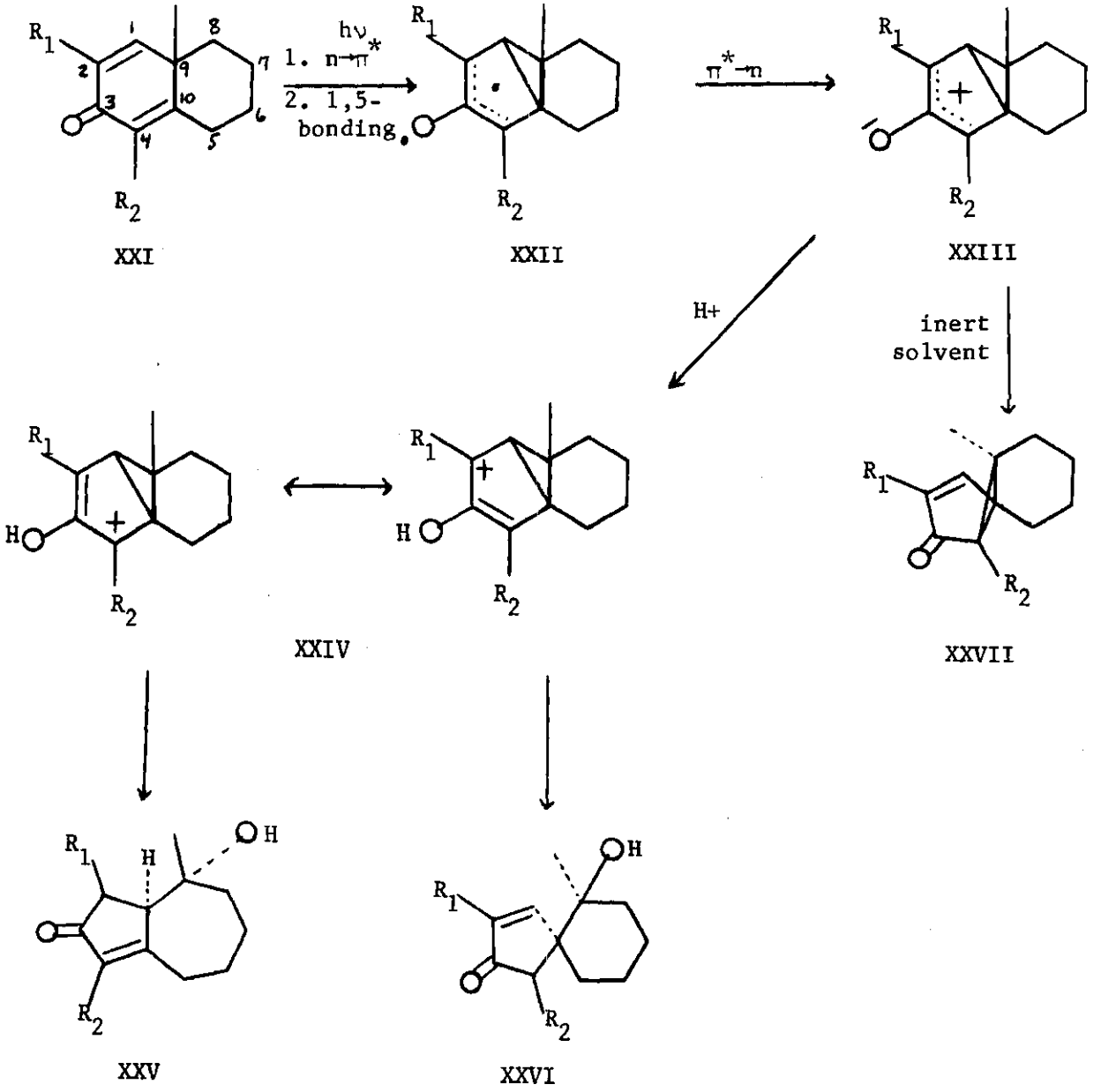
Additionally, the difficulty [7] in obtaining the starting material (XV) for this synthetic scheme appears to be a drawback.

The purpose of this research was to generate the aromadendrene skeleton by the photochemical rearrangement of an appropriately substituted 6/6-fused cross-conjugated cyclohexadienone. The photoproduct would then be converted into (+)-aromadendrene or (-)-globulol by subsequent transformations.

Since Barton and co-workers [8] first observed the photochemical behavior of 6/6-fused cross-conjugated cyclohexadienones in 1957, considerable work has been undertaken in order to understand the nature of these reactions. Consequently, this technology has been applied in many cases [9] to the synthesis of naturally occurring sesquiterpenes.

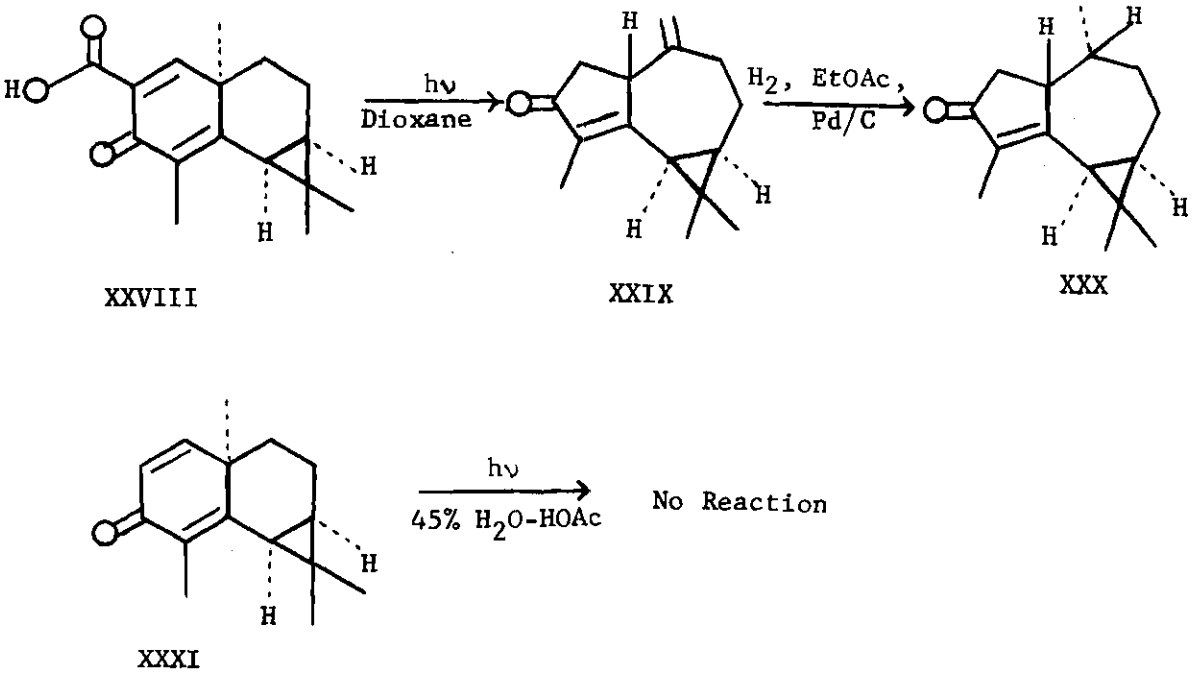
Zimmerman [10] has proposed a mechanism (Scheme 5) that involves an $n \rightarrow \pi^*$ electronic transition to a singlet excited state. The singlet state undergoes intersystem crossing to the triplet state which is followed by 1,5-bonding to give a diradical (XXII). This diradical then undergoes $\pi^* \rightarrow n$ demotion to give a zwitterion (XXIII) which can protonate and cleave to give either 5/7-fused hydroxy ketones (XXV) or [4,5]-spiro

hydroxy ketones (XXVI). The type of product which is formed depends upon the nature of the substituents at C-2 and C-4 and their relative ability in stabilizing intermediate (XXIV). If an inert, aprotic solvent is used, the zwitterion normally undergoes a 1,3 sigmatropic rearrangement to give tricyclic ketones which are referred to as "lumiproducts" (XXVII).



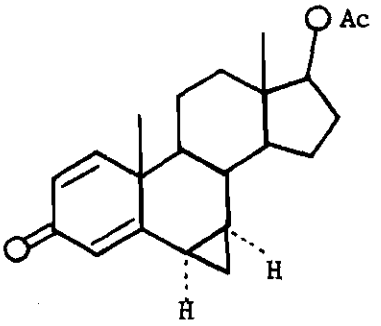
Scheme 5

Caine and Ingwalson [9d] have reported employing dienone XXVIII in the photochemical preparation of (-)-cyclocolorenone (XXX). In this work it was also reported that dehydromaalienone (XXXI) was photochemically stable under standard conditions of irradiation. This result is also consistent with the findings of Kropp [11] and Streith and Blind [12].

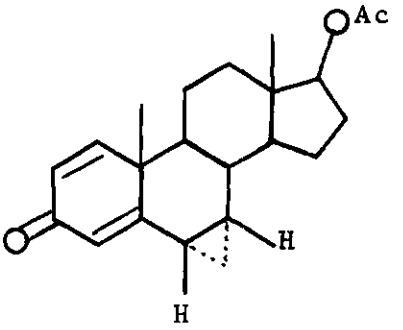


Scheme 6

In an analogous study, Schaffner and co-workers [13] have investigated the photochemical reactivity of steroidal dienones XXXII and XXXIII in dioxane. They observed that XXXII was photochemically labile while XXXIII was not.

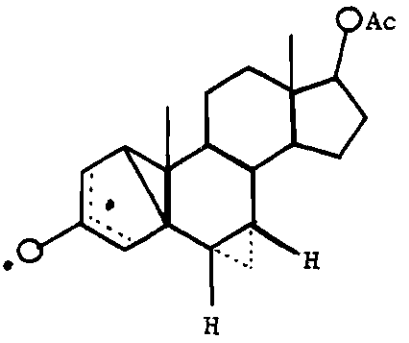


XXXII



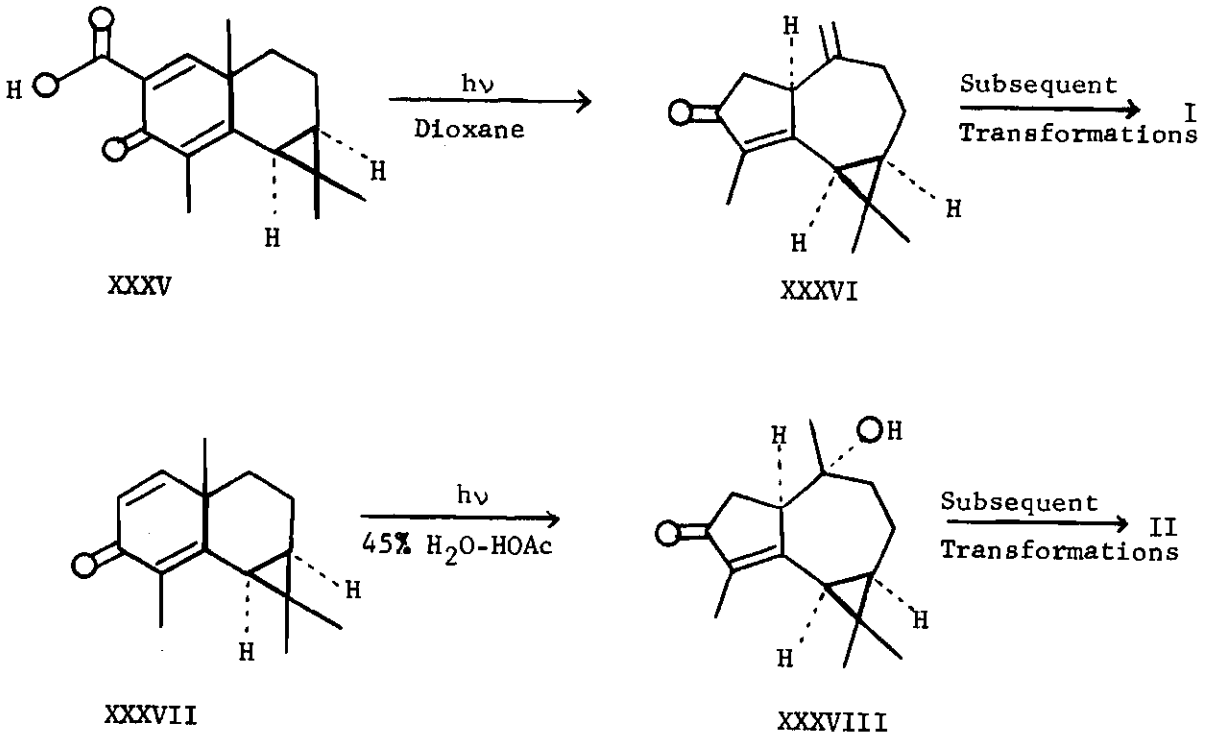
XXXIII

These workers proposed [14] that the stability of XXXIII is due to the fact that a significant amount of strain would be introduced by the two, cis cyclopropane rings in the formation of the diradical intermediate (XXXIV).



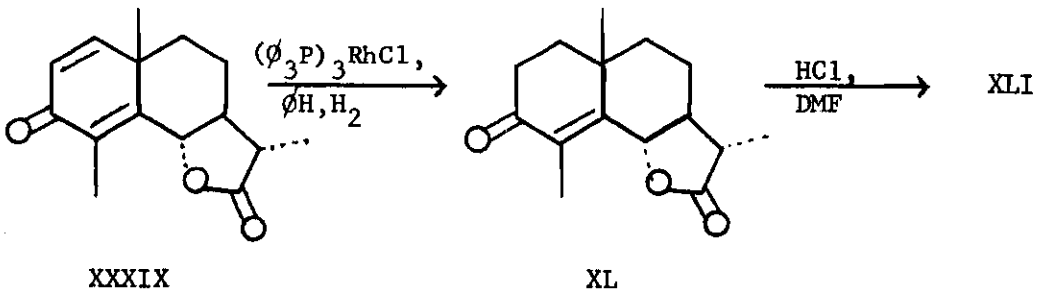
XXXIV

Based on these reports it appeared that either dienone XXXV or XXXVII should be the logical precursor to (+)-aromadendrene or (-)-globulol, respectively.

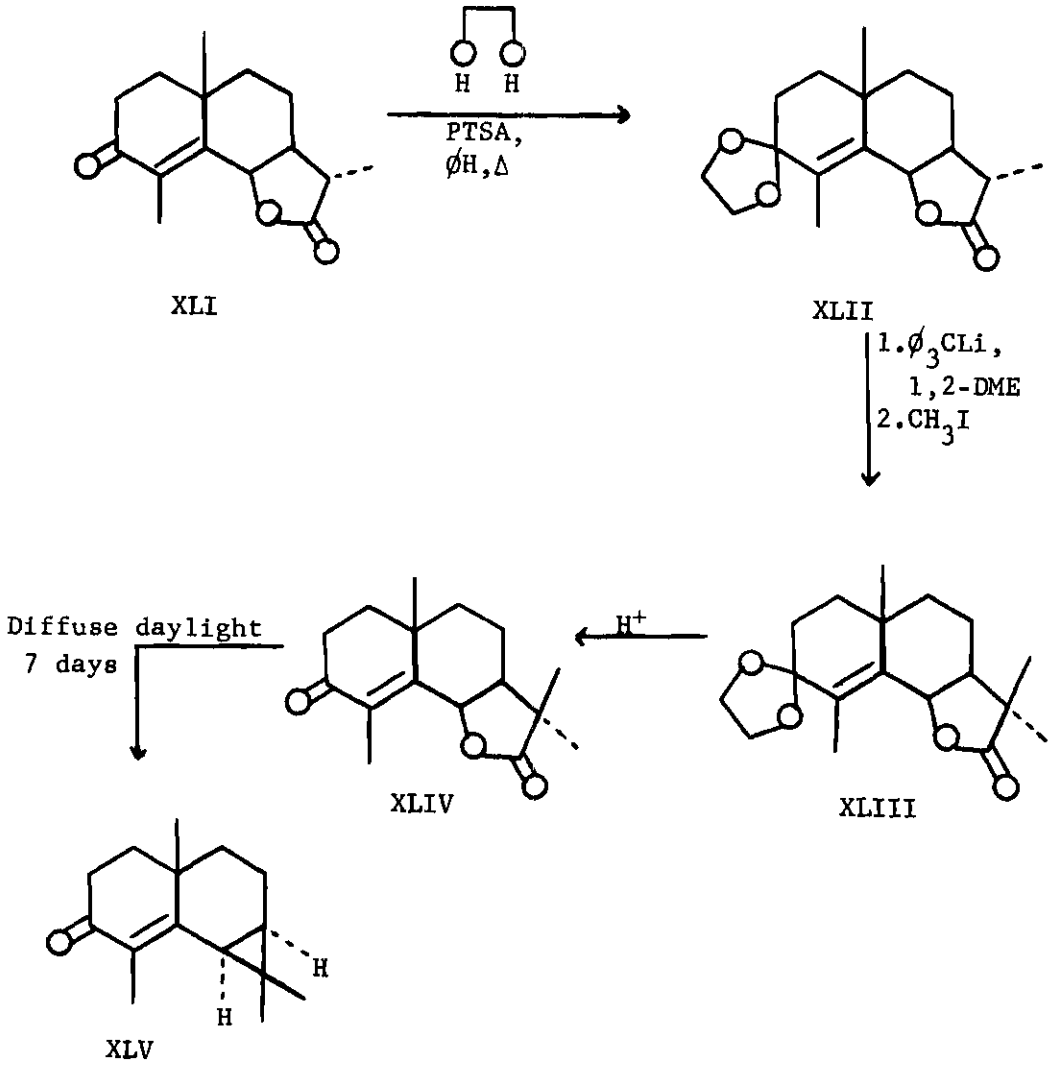


Scheme 7

In order to obtain dienone XXXV or XXXVII, the preparation of (-)-epimaalienone (XLV) would be required. Ourisson [15] has reported a six-step synthesis (Scheme 8) of this compound which employed (-)-α-santonin (XXXIX) as the starting material.

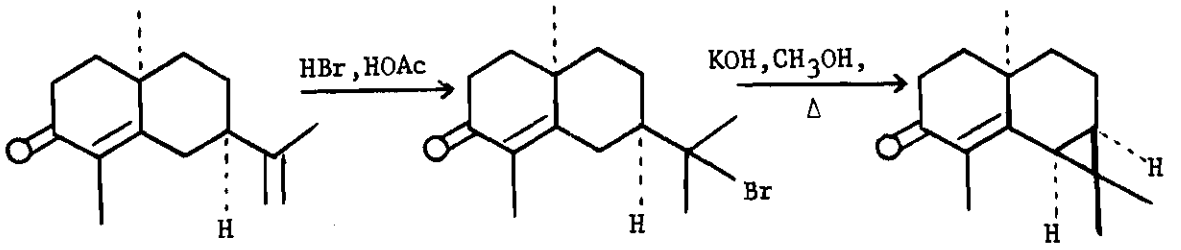


Scheme 8



Scheme 8 (Continued)

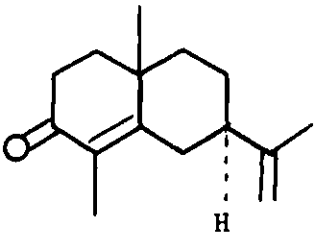
Additionally, Büchi [16] reported the preparation of maalienone (XLVIII) from epi-α-cyperone (XLVI) which utilized an intramolecular displacement of bromide to generate the three-membered ring.



XLVI XLVII XLVIII

Scheme 9

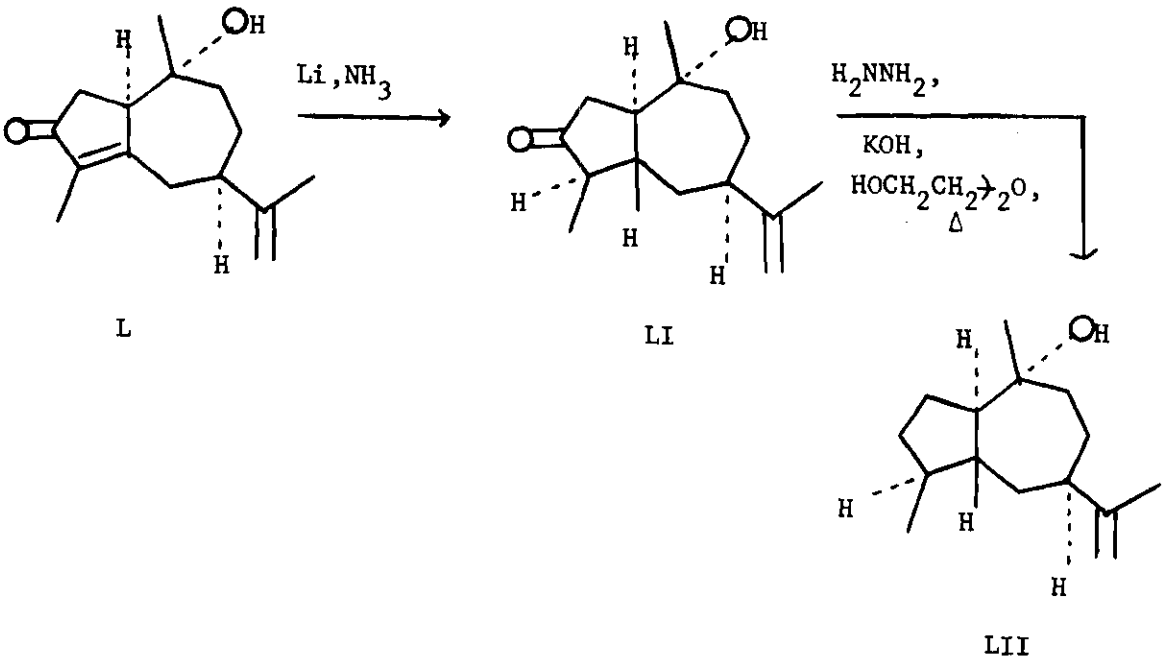
It was, therefore, expected that Ourisson's synthesis or Büchi's procedure, as applied to (+)-α-cyperone (XLIX), would afford (-)-epimaalienone (XLV) in an efficient manner.



XLIX

The transformation of (-)-epimaalienone (XLV) to either XXXV or XXXVII could then be carried out in the standard manner [9d].

Assuming that the photochemical transformations, as depicted in Scheme 7, were successful, compounds XXVI and XXXVIII would have to be reduced stereospecifically at the 4,5 position and the carbonyl group at C-3 would have to be removed. Piers has reported [9b] carrying out a similar set of transformations in his synthesis of the bulnesenes (Scheme 10).



L LI LII

Scheme 10

The stereochemistry of the lithium in liquid ammonia reduction was determined by optical rotatory dispersion data and comparison of subsequent reaction products with natural α-bulnesene. Although Piers reported finding only the more thermodynamically stable, 4β-methyl isomer, it was hoped that lithium in liquid ammonia reduction of XXXVI or XXXVIII would produce a mixture of 4-methyl isomers as a result of possible steric interaction between the dimethylcyclopropane group at C-6 and C-7 and the 4β-methyl group. The carbonyl group at C-3 would then be removed by the Wolf-Kishner procedure and either (+)-aromadendrene or (-)-globulol, as well as their C-4 epimers, would be produced depending on which dienone had been used.

CHAPTER II

INSTRUMENTATION AND EQUIPMENT

A Hanovia 450-watt high pressure mercury lamp in a quartz or a Pyrex apparatus similar to that described by Kropp and Erman [17] was used for the irradiations. A slow stream of nitrogen was bubbled through the solution prior to and during all irradiations for deoxygenation and agitation of the solution. Removal of solvents in vacuo was done using a Büchi Rotavapor rotary evaporator. Column chromatography was carried out using Grace grade 923, 100-200 mesh silica gel or Fisher 100-200 mesh florisil in the ratio of 30 g of adsorbent per gram of mixture.

Nuclear magnetic resonance spectra were obtained at 60 MHz on a Varian Associates Model A-60D or T-60 spectrometer. Chemical shifts are reported in ppm (δ) downfield from tetramethyl silane which was used as an internal standard. The abbreviations s, d, t, q, and m refer, respectively, to singlet, doublet, triplet, quartet, and multiplet, and coupling constants (J) are reported in Hz. Infrared spectra were recorded using a Perkin-Elmer Model 457 spectrophotometer and absorptions are reported in cm^{-1}. For spectra run with a solvent, 0.1 mm sodium chloride cells were used. Ultraviolet spectra were obtained on a Beckman Model DB-GT recording spectrophotometer using one centimeter matched quartz cells and 95% ethanol as the solvent. Mass spectra were obtained using a Hitachi Perkin-Elmer RMV-7 or a Varian Model M-66 spectrometer with a 70 electron volt source. Optical rotations were determined with a Bendix

ETL-NPL automatic polarimeter. The sodium D line was used as the light source and chloroform was the solvent for all determinations. A JASCO ORD/UV/CD-5 spectrophotometer was used for ORD determinations. Quartz cells (1 mm) were employed for these measurements and methanol was used as the solvent. Gas chromatographic analyses were obtained using a Perkin-Elmer Model 881 flame ionization or an Aerograph A-90-P thermal conductivity gas chromatograph. The following columns were used: A (6 ft x 0.125 in., 10% Carbowax K-20M on Chromosorb W); B (6 ft x 0.125 in., 10% SE-30 on Chromosorb W); C (10 ft x 0.25 in., 10% SE-30 on Chromosorb W). Boiling points and melting points are uncorrected and a Fisher-Johns melting point apparatus was used for melting point determinations. Carbon and hydrogen analyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia.

CHAPTER III

EXPERIMENTAL

Attempted Preparation of (-)-Epimaalienone (XLV) via Enolate Ring Closure with Potassium Hydroxide

A mixture (3.00 g, 0.014 mol) of 40% α-cyperone (XLIX) and 60% epi-α-cyperone (XLVI) which had been prepared by the method of Howe and McQuillen [18] was placed in a 50-ml, three-necked, round-bottom flask. The flask was equipped with a magnetic stirrer, dropping funnel and placed under a nitrogen atmosphere. Glacial acetic acid (6.0 ml) was added to the flask and the resulting mixture was cooled to 5° by an ice bath. A 30% solution of hydrogen bromide (2.23 g, 0.028 mol) in acetic acid was added dropwise to the reaction mixture and after the addition was completed the reaction was allowed to warm to room temperature and stirred for 15 minutes. The reaction mixture was poured into ice water and then extracted with several portions of ether. The combined ether extracts were washed with saturated aqueous solutions of sodium bicarbonate and sodium chloride, respectively, and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the crude material was used without further purification. A 100-ml, three-necked, round-bottom flask was equipped with a reflux condenser, magnetic stirrer, and placed under a nitrogen atmosphere. To the flask was added 7.72 g (0.138 mol) of potassium hydroxide and 70 ml of methanol and the mixture was stirred until solution had occurred. The crude material from the previous reaction

was added in one portion to the reaction flask and the resulting mixture was heated at reflux with stirring for 30 minutes. The reaction was cooled to room temperature and the solvent was removed in vacuo. The residue was partitioned between water and ether and the aqueous phase was saturated with sodium chloride and re-extracted with ether. The combined ether extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo afforded 1.90 g of an oil. Examination of the nmr spectrum and glc behavior (Column B) of the oil indicated that the major products of reaction were β-cyperone (LVI) and maalienone (XLVIII) as determined by comparison with authentic samples.

(+)-1,2-Dihydrosantonin (XL)

(-)-α-Santonin (50.3 g, 0.204 mol) was dissolved in 400 ml of reagent grade benzene and a solution of tristriphenylphosphine-rhodium (I) chloride (1.58 g, 1.66 mmol) in 50 ml of reagent grade benzene was added. The solution was hydrogenated at atmospheric pressure until one equivalent of hydrogen had been taken up. The solvent was removed in vacuo and the residue was filtered through a column of 300 g of acetone-washed, neutral alumina. The column was washed with benzene until no further material could be isolated. The pale yellow solid obtained was recrystallized from an ether-pentane mixture yielding a white solid (43.65 g, 86%) which exhibited properties [nmr, ir, and mp (97-99°)] consistent with the reported values [15,19].

11-Methyl-1,2-dihydrosantonin (LIX)

A 1-ℓ, one-necked, round-bottom flask was equipped with a Dean-

Stark tube, which contained anhydrous sodium carbonate, reflux condenser, and a magnetic stirrer. To the flask was added 5.672 g (0.0229 mol) of XL, 500 ml of dry benzene, 45 ml of ethylene glycol, and 0.141 g (0.819 mol) of p-toluenesulfonic acid. The resulting mixture was stirred and heated overnight at reflux with removal of water by azeotropic distillation. The solution was cooled to room temperature and 10 ml of pyridine and 20.0 g of sodium bicarbonate were added. The mixture was stirred for several minutes and washed with aqueous sodium bicarbonate, water, and aqueous sodium chloride, respectively. After drying over anhydrous magnesium sulfate the solvent was removed in vacuo leaving an amber oil: nmr δ_{TMS} ($DCCl_3$) 1.12 (s, 3H), 1.17 (d, J=7.0 Hz, 3H), 1.80 (d, J=2.0 Hz, 3H), 4.00 (m, 4H), and 4.57 ppm (d, J=10.0 Hz, 1H); ir (CCl_4) 1790 cm^{-1}; m/e (70 eV) M^+ 292.

This compound (LVII) was used without further purification. A 1-ℓ, three-necked, round-bottom flask was equipped with a magnetic stirrer, reflux condenser, and placed under a nitrogen atmosphere. The apparatus was flame dried and 16.76 g (0.0687 mol) of triphenylmethane and 400 ml of dry 1,2-dimethoxyethane were introduced. The mixture was stirred until the triphenylmethane had dissolved and 152 ml (ca 0.059 mol) of a 0.392 M solution of phenyllithium was added via a syringe and the resulting deep red solution was stirred for 1 hr. The crude ketal (LVII) from the previous reaction, which had been dissolved in 40 ml of dry 1,2-dimethoxyethane, was added dropwise to the reaction mixture via a syringe. After the addition was complete, the solution still maintained its red color and was stirred for 30 min. Methyl iodide (15 ml, ca 0.24 mol) was added

in a thin stream via a syringe and the resulting mixture turned a yellow-brown color. This mixture was stirred for 30 min and water was added slowly. The mixture was extracted with ether and the aqueous phase was saturated with sodium chloride and re-extracted several times. The combined ether extracts were washed with a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo leaving an amber oil which was used without further purification. The crude material was placed in a 500-ml, one-necked, round-bottom flask which had been equipped with a magnetic stirrer and reflux condenser. To the flask was added 0.143 g (0.83 mmol) of p-toluenesulfonic acid and 250 ml of acetone. The resulting mixture was refluxed overnight and cooled to room temperature. Pyridine (5 ml) and sodium bicarbonate (10 g) were added and the resulting mixture was stirred for several min. Solvents were removed in vacuo and the residue was partitioned between water and ether. The aqueous phase was saturated with sodium chloride and re-extracted with ether. The combined ether extracts were washed several times with a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and the residue was placed on a column of 100 g of acetone-washed silica gel. Elution with hexane afforded triphenylmethane and elution with a 40% ether-hexane mixture afforded 4.05 g of a solid (LIX). The solid was recrystallized from an ether-pentane mixture yielding 3.34 g (56%) of a white solid: mp 115-117°; ir (CCl_4) 1792, 1680, and 1620 cm^{-1}; nmr δ_{TMS} ($DCCl_3$) 4.84 (d, J=10.0 Hz, 1H), 1.96 (d, J=2.0 Hz, 3H), 1.34 (s, 3H), 1.22 (s, 3H), and 1.12 ppm (s, 3H); m/e (70 eV) M+ 262.

(-)-11-Methyl-epidihydrosantonin (XLIV)

Compound LIX (7.00 g, 0.027 mol) was placed in a 250-ml, one-necked, round-bottom flask which had been equipped with a magnetic stirrer, reflux condenser, and calcium chloride drying tube. A solution of 2.88 g (0.080 mol) of hydrogen chloride in 70 ml of dry dimethylformamide was added and the resulting solution was heated at 85° for 3.5 hr and stirred at room temperature overnight. Water was added and the mixture was extracted with several portions of chloroform. The combined chloroform extracts were washed with saturated aqueous solutions of sodium bicarbonate and sodium chloride, respectively, and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* leaving a yellow solid (XLIV). Recrystallization of this material from a pentane-ether mixture afforded 3.76 g (54%) of a pale yellow solid (mp 123-125°) which exhibited spectral properties (nmr, ir, and ms) that were consistent with the reported values [15].

(-)-2-Carone (LXI)

This compound was prepared by the procedure of Wagner and v.Bayer [20]. A 1-ℓ, three-necked, round-bottom flask was equipped with a mechanical stirrer, dropping funnel, and condenser. The apparatus was placed under a nitrogen atmosphere and 50.1 g (0.330 mol) of (+)-dihydrocarvone was added to the flask along with 150 ml of glacial acetic acid. The resulting mixture was stirred and cooled to 0° by means of an ice-water bath. To the dropping funnel was added 173.9 g (*ca* 0.64 mol) of a 30-32% solution of hydrogen bromide in acetic acid. This solution was added dropwise over a 170-min period while the bath temperature was maintained below 5°.

The reaction was stirred for 25 min at 5° and 20 min while being warmed to room temperature. The mixture was poured into 500 ml of an ice-water slush and stirred for several minutes. The mixture was then extracted with 200 ml of ether and the aqueous phase was saturated with sodium chloride and re-extracted with three 200-ml portions of ether. The combined ether extracts were washed with six 200-ml portions of a saturated aqueous solution of sodium bicarbonate and then with two 200-ml portions of a saturated aqueous solution of sodium chloride. The ether extracts were dried over anhydrous magnesium sulfate and the solvent was removed in vacuo at room temperature leaving a pale brown oil.

A 3-ℓ, three-necked, round-bottom flask was equipped with a condenser, magnetic stirrer, and placed under a nitrogen atmosphere. To the flask was added 1840 ml of methanol and 184 g of potassium hydroxide. The resulting mixture was stirred until a solution was obtained. The crude material from the previous reaction was added to the flask and the resulting mixture was heated at reflux for 30 min and cooled to room temperature. The solvent was removed in vacuo and the residue was partitioned between 500 ml of water and 200 ml of ether. The phases were separated and the aqueous phase was saturated with sodium chloride and extracted with three 200-ml portions of ether. The combined ether extracts were washed with one 100-ml portion of water and two 200-ml portions of a saturated aqueous solution of sodium chloride. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed in vacuo leaving 44.9 g of a yellow oil. The oil was distilled at reduced pressure (bp 43-47°/0.10 mm) to yield 41.8 g (83%) of (-)-2-carone.

(-)-3-(3-Pentanone-5-yl)-2-carone (LX)

To a solution of 105 g (0.688 mol) of (-)-2-carone in 1045 ml of anhydrous ether was added a solution of 7.70 g (0.138 mol) of potassium hydroxide in 77 ml of anhydrous ethyl alcohol under nitrogen. The mixture was cooled to -5° and a solution of 55.4 g (0.660 mol) of ethyl vinyl ketone in 400 ml of anhydrous ether was added dropwise with stirring. After the addition was complete, stirring was continued for 75 min while the mixture was allowed to warm to room temperature and the mixture was poured into 1 ℓ of an ice-cold solution of 10% hydrochloric acid. The aqueous layer was saturated with sodium chloride and extracted with three 200-ml portions of ether and the combined organic extracts were washed with two 200-ml portions of a saturated aqueous solution of sodium bicarbonate followed by two 200-ml portions of a saturated sodium chloride solution. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo* to give a pale yellow oil. Distillation yielded 35.8 g of (-)-2-carone, bp 45-55° (0.10 mm), and 91.3 g (86%) of LX: bp 109-120° (0.10 mm); uv λ_{max} (95% EtOH) 216 nm (ϵ 2,790); ir (CCl_4) 1721 and 1692 cm^{-1}; nmr δ_{TMS} (CCl_4) 0.83 (s, 3H), 1.02 (s, 3H), 1.10 (s, 3H), 0.98-1.24 (broad absorption, 5H), and 1.33-2.51 ppm (broad absorption, 10H); m/e (70 eV) 236.177 (calcd. 236.177); $[\alpha]^{25°}$D-149° (c 0.57, $CHCl_3$).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.17; H, 10.25.

(+)-Cis-6-(2-chloropropane-2-yl)-4,9-dimethyl-3-keto-Δ^4-octahydronaphthalene (LXIX)

The diketone (LX) (20.0 g, 0.085 mol) was added dropwise with stirring to 200 ml of an anhydrous saturated solution of ethanolic hydrogen chloride at 5°. After the addition was complete the reaction mixture was allowed to warm to room temperature and stirring was continued for 30 min. The reaction mixture was then poured into 200 ml of ice water and extracted with four 100-ml portions of chloroform. The combined chloroform extracts were washed with a saturated aqueous solution of sodium bicarbonate and then with a sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo* to give a yellow solid. Recrystallization of this material from pentane gave 17.8 g (83%) of LXIX: mp 86-87°: uv λ_{max} (95% EtOH) 248 nm (ε 20,100); ir (CCl_4) 1668 and 1612 cm^{-1}; nmr δ_{TMS} (CCl_4) 1.22 (s, 3H), 1.62 (s, 6H), 1.75 (s, 3H), 1.80-3.20 ppm (broad absorption, 11H): $[\alpha]^{25°}D$ + 165° (c 0.40, $CHCl_3$).

Anal. Calcd. for $C_{15}H_{23}ClO$: C, 70.71; H, 9.10. Found: C, 70.57; H, 9.13.

(+)-α-Cyperone (XLIX)

A solution of 4.0 g (0.02 mol) of LXIX and 6.6 g (0.08 mol) of sodium acetate in 50 ml of glacial acetic acid was stirred rapidly and heated at 90-100° for 1 hr. The reaction mixture was then allowed to cool to room temperature and poured into 50 ml of water. The resulting mixture was extracted with four 50-ml portions of carbon tetrachloride and the combined organic extracts were washed with two 50-ml portions of

2 N hydrochloric acid, one 50-ml portion of 5% aqueous sodium bicarbonate, and three 50-ml portions of a saturated aqueous solution of sodium chloride. The organic layer was then dried over anhydrous magnesium sulfate and the solvent was removed to give 3.65 g of a yellow oil. Glc analysis of the crude reaction mixture (Column A) revealed that it contained α- and β-cyperone in ca an 85:15 ratio. Distillation of the crude material gave 2.85 g (82%) of (+)-α-cyperone, bp 109-118° (0.05 mm), which was greater than 94% one component by glc (Column A). This material showed identical optical properties (ir, nmr, and optical rotation) and glc behavior (Columns A and B) with an authentic sample of (+)-α-cyperone prepared by the method of Howe and McQuillin [18].

(-)-Epimaalienone (XLV)

A 1-ℓ, three-necked, round-bottom flask was equipped with a Friedrich condenser and magnetic stirrer. The apparatus was placed under a nitrogen atmosphere and 10.71 g (ca 0.25 mol) of a 57% dispersion of sodium hydride was introduced into the flask. The sodium hydride was washed twice with hexane and a solution of 25.0 g (0.098 mol) of LXIX in 500 ml of dry 1,2-dimethoxyethane was added slowly via a syringe. The resulting mixture was stirred for 20 min at room temperature and was then heated at reflux overnight. The reaction mixture was cooled to room temperature and 25 ml of absolute ethanol was added to decompose any unreacted sodium hydride. After stirring for several minutes, solvents were removed in vacuo and the residue was partitioned between 300 ml of water and 300 ml of ether. The aqueous phase was saturated with sodium chloride and extracted with two 200-ml portions of ether. The combined ether ex-

tracts were washed with five 100-ml portions of a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo leaving 23.8 g of an amber oil. The oil was distilled at reduced pressure (102-118°/0.03 mm) to give 15.9 g (74%) of (-)-epimaalienone. This compound exhibited identical spectral (ir, nmr, ms, and optical rotation) and glc behavior (Column A) to an authentic sample prepared by the procedure of Ourisson and co-workers [15].

(-)-Epimaalienone was also prepared by a modification of Ourisson's procedure. A solution of 1.04 g (3.97 mmol) of (-)-11-methyl-epidihydrosantonin (XLIV) in 300 ml of reagent grade benzene was irradiated with a 450-watt Hanovia high-pressure mercury source in a Pyrex apparatus for 12 hr. The solvent was removed in vacuo and residue was placed on a column of 30 g of acetone-washed silica gel. Elution with a 10% ether-hexane mixture gave 0.200 g (83%) of (-)-epimaalienone. Further elution with 100% ether gave 0.750 g of 11-methyl-epidihydrosantonin. The (-)-epimaalienone prepared in this fashion had identical spectral properties (ir, nmr, and uv) to a sample prepared by Ourisson's procedure.

2-Hydroxymethyleneepimaalienone (LIII)

A 57% oil dispersion of sodium hydride (0.470 g, 0.011 mol) was placed in a 100-ml, three-necked, round-bottom flask which had been equipped with a reflux condenser, magnetic stirrer, and placed under a nitrogen atmosphere. The sodium hydride was washed with several portions of hexane and 15 ml of dry benzene was added. The solution was stirred for several minutes, and 0.265 g (0.0083 mol) of dry methanol was added, the resulting solution was heated to reflux, and cooled to room tempera-

ture. Ethyl formate (0.8417 g, 0.0114 mol), which had been dried over anhydrous phosphorous pentoxide, was added to the flask and the resulting mixture was stirred for 30 min. The reaction mixture was cooled in an ice bath and a dropping funnel was installed. A solution of 1.05 g (4.82 mmol) of epimaalienone (XLV) in 15 ml of dry benzene was added dropwise to the reaction mixture with cooling over a 15-min period. After the addition was complete, the ice bath was removed and the reaction mixture was stirred at room temperature overnight. The reaction mixture was acidified with a cold 5% aqueous solution of sulfuric acid and the aqueous phase was extracted several times with a 50% benzene-ether mixture. The combined benzene-ether extracts were extracted with a cold 2% aqueous potassium hydroxide solution and the base extracts were washed with several portions of ether. The basic extracts were acidified with a 5% aqueous solution of hydrogen chloride and extracted several times with a 50% benzene-ether solution. The benzene-ether extracts were washed with a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo leaving 0.89 g (75%) of an amber oil: ir (CCl_4) 1640, 1600, and 1565 cm^{-1}; nmr δ_{TMS} ($DCCl_3$) 0.98 (s, 3H), 0.99 (s, 3H), 1.23 (s, 3H), 1.88 (s, 3H), 7.40-7.47 (m, 1H), and 14.8 ppm (m, 1H); m/e (70 eV) 246.163 (calcd., 246.161).

2-Formyl-1,2-dehydroepimaalienone (LIV)

A 1-ℓ, three-necked, round-bottom flask was equipped with a magnetic stirrer and placed under a nitrogen atmosphere. Compound LIII (1.655 g, 6.7 mmol) was dissolved in 25 ml of dry dioxane and placed in the flask. A solution of 1.673 g (7.4 mmol) of DDQ in 25 ml of dry dioxane

was added in one portion to the reaction flask and the resulting mixture was stirred for 4 min. The reaction mixture was diluted with 500 ml of methylene chloride and the resulting solution was extracted with three 200-ml portions of a cold 2% aqueous potassium hydroxide solution. The organic phase was washed with several portions of water and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo leaving 1.207 g (74%) of an orange oil which slowly crystallized upon standing: mp 122-124°; ir (CCl_4) 1701, 1650, and 1621 cm^{-1}; nmr δ_{TMS} ($DCCl_3$) 1.11 (s, 3H), 1.13 (s, 3H), 1.20 (s, 3H), 1.92 (s, 3H), 7.58 (s, 1H), and 10.20 ppm (s, 1H); m/e (70 eV) 244.148 (calcd., 244.146).

Attempted Oxidation of 2-Formyl-1,2-dehydroepimaalienone (LIV)

A. With Tollen's Reagent

Compound LIV (0.101 g, 0.4 mmol) was dissolved in 5 ml of distilled 95% ethanol and placed in a 25-ml, three-necked, round-bottom flask which had been equipped with a magnetic stirrer. A solution of 0.153 g (0.9 mmol) of silver nitrate in 1.0 ml of distilled water was added to the reaction flask in one portion. An aqueous solution of sodium hydroxide (0.080 g in 2.0 ml of water) was added dropwise to the reaction mixture via a syringe and a black precipitate began to form. The mixture was stirred for 4 hr and filtered through a fritted glass funnel. The solid was washed with a saturated aqueous solution of sodium bicarbonate and the combined filtrates were acidified with 6 N hydrochloric acid. The filtrate was then made alkaline with a saturated aqueous solution of sodium bicarbonate and filtered. The filtrate was acidified with 4 N hydrochloric acid and extracted with several portions of ether. The ether

extracts were washed with a saturated aqueous solution of sodium chloride until neutral, the phases were separated, and the solvent was removed *in vacuo* from the organic phase. The residue was taken up in benzene and dried over anhydrous magnesium sulfate. The residue from the first filtration was washed with ether and the combined ether extracts were washed with a saturated aqueous solution of sodium chloride until neutral and dried over anhydrous magnesium sulfate. The solvents were removed *in vacuo* from both organic extracts and examination of the nmr spectrum of both residues indicated that no reaction had taken place.

B. With Jones Reagent

A solution of Jones reagent was prepared by dissolving 26.79 g of chromium trioxide in 23 ml of concentrated sulfuric acid and diluting the mixture to a volume of 100 ml with water. Compound LIV (0.101 g, 0.41 mmol) was dissolved in 4 ml of reagent grade acetone and placed in a 50-ml, one-necked, round-bottom flask which had been equipped with a magnetic stirrer. The acetone solution and the Jones reagent were cooled to 0° and the Jones reagent was added dropwise (*ca* 11 drops) to the reaction and stirred for 5 min. The mixture was diluted with 15 ml of a saturated aqueous sodium chloride solution and extracted with four 15-ml portions of ether. The combined ether extracts were washed with several 15-ml portions of a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo*. Examination of the nmr spectrum of the residue (0.06 g) indicated the formation of a phenol (LXX) as the only product; nmr δ_{TMS} ($DCCl_3$) 0.61 (s, 3H), 1.22 (s, 3H), 2.10 (s, 3H), 2.38 (s, 3H), 10.30 (s, 1H), and

12.30 ppm (s, 1H).

C. With Neutral Potassium Permanganate

Compound LIV (0.104 g, 0.41 mmol) was dissolved in 3 ml of reagent-grade acetone and placed in a 25-ml erlenmeyer flask. Potassium permanganate (0.096 g, 0.62 mmol) was dissolved in 3 ml of distilled water and added dropwise to the acetone solution. After the addition was completed, the reaction mixture was stirred for 10 min and filtered to remove the brown precipitate which had formed. The residue was washed with 15 ml of a saturated aqueous solution of sodium bicarbonate and 20 ml of ether. The filtrates were combined and the phases were separated. The aqueous phase was acidified with a 5% aqueous solution of hydrochloric acid and extracted with ether. The combined ether extracts were washed with a saturated aqueous solution of sodium chloride and extracted with a saturated aqueous solution of sodium bicarbonate, respectively. The ether phase was washed with a saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The sodium bicarbonate extract was acidified with a 5% aqueous solution of hydrochloric acid and extracted with ether. The ether extract was washed with a saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was removed from both organic extracts and nmr analysis of the residues (0.07 g) indicated the absence of the desired carboxylic acid (XXXV).

D. With Sarett Reagent

The Sarett reagent was prepared by cautious addition of 1.03 g (10.3 mmol) of chromium trioxide to 10.3 ml of pyridine. To the resulting yellow slurry was added compound LIV (0.100 g, 0.41 mmol) in 1.0-ml of pyridine and five drops of distilled water. The resulting dark mixture

was stirred overnight at room temperature. The reaction mixture was acidified with a cold 5% aqueous hydrochloric acid solution and extracted with ether. The ether extract was filtered through Celite and washed with a saturated sodium chloride solution until neutral. After drying over anhydrous magnesium sulfate, the ether was removed in vacuo and the residue (0.06 g) was subjected to nmr analysis which indicated the absence of the desired carboxylic acid (XXXV).

E. With Argentinic Oxide

Argentinic oxide was prepared by the procedure of Jirsa [21a,b]. Argentinic oxide (0.255 g, 0.021 mol) and sodium cyanide (0.050 g, 1.02 mmol) were placed in a 50-ml, one-necked, round-bottom flask which was equipped with a magnetic stirrer. A solution of 0.052 g (2.1 mmol) of compound LIV in 5 ml of methanol was added and the resulting solution was stirred at room temperature for 5 hr. The solvent was removed in vacuo and the residue was partitioned between water and ether. The aqueous phase was acidified with a 5% aqueous hydrochloric acid solution and extracted with ether. The combined ether extracts were washed with a saturated sodium chloride solution until neutral and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and examination of the nmr spectrum of the residue (0.04 g) indicated the presence of only starting material (LIV).

F. With Palladium and Air

Compound LIV (0.035 g, 0.143 mmol) was dissolved in 15 ml of reagent grade acetone. Palladium supported on carbon (0.037 g) was added and air was bubbled through the solution with stirring for 6 hr. The

solvent was removed in vacuo and nmr examination of the residue indicated the presence of only starting material (LIV).

(-)-1,2-Dehydroepimaalienone (XXXVII)

A 2-ℓ, three-necked, round-bottom flask was equipped with a Friedrich condenser and magnetic stirrer. The apparatus was placed under a nitrogen atmosphere and 11.87 g (0.052 mol) of DDQ was placed in the flask along with 1-ℓ of dry dioxane. The mixture was stirred until solution occurred and 10.00 g (0.046 mol) of (-)-epimaalienone (XLV) was added. The resulting mixture was stirred and heated at reflux for 24 hr. The reaction was cooled to room temperature at which point the DDHQ produced in the reaction precipitated. The solid was filtered off and solvent was removed from the filtrate in vacuo. The residue was taken up in 500 ml of ether and extracted with five 100-ml portions of a cold 2% aqueous solution of potassium hydroxide. The organic phase was washed with three 100-ml portions of a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo leaving 8.88 g of a dark brown oil. The oil was distilled at reduced pressure (105-130°/0.10 mm) to give 5.52 g(56%) of a yellow oil (XXXVII). The yellow oil exhibited the following properties: uv λ_{max} (95% EtOH) 244 (ε 10,400) and 305 nm (ε 8,400); ir (CCl_4) 1654, 1622, and 1585 cm^{-1}; nmr δ_{TMS} (CCl_4) 1.14 (s, 6H), 1.24 (s, 3H), 1.84 (s, 3H), 6.08 (d, J=10 Hz, 1H), and 6.78 ppm (d, J=10 Hz, 1H); m/e (70 eV) 216.153 (calcd., 216.151); $[\alpha]^{25}D$ - 367° (c 0.132, $CHCl_3$).

Anal. Calcd. for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.02; H, 9.39.

Irradiation of (-)-1,2-Dehydroepimaalienone (XXXVII)

A. In 45% Aqueous Acetic Acid

A solution of 2.41 g of (-)-dehydroepimaalienone (XXXVII) in 300 ml of 45% aqueous acetic acid was irradiated in a Pyrex apparatus with a 450-watt Hanovia high pressure mercury source for 30 min. The solution was saturated with sodium chloride and extracted with three 100-ml portions of ether. The combined ether extracts were washed with five 100-ml portions of a saturated aqueous sodium bicarbonate solution and three 100-ml portions of a saturated aqueous sodium chloride solution, respectively. The organic phase was dried over anhydrous magnesium sulfate and concentrated *in vacuo* leaving 2.52 g of a viscous yellow oil which was placed on a column of 75 g of acetone-washed silica gel. Elution with a 40% ether-hexane mixture removed the starting material and other non-hydroxylic substances from the column. Further elution with a 75% ether-hexane mixture afforded 1.25 g (48%) of a viscous oil (XXXVIII) which crystallized upon standing. An analytical sample was recrystallized from an ether-hexane mixture at low temperature: mp 93-95°; uv λ_{max} (95% EtOH) 251 nm (ϵ 11,300); ir (CCl_4) 3420, 1700, and 1628 cm^{-1}; nmr δ_{TMS} (CCl_4) 0.80 (s, 3H), 0.92 (s, 3H), 1.18 (s, 3H), 1.68 (d of d, J=2.0 Hz, 3H), and 4.90 ppm (broad absorption, 1H); m/e (70 eV) 234.162 (calcd., 234.162); $[\alpha]^{25}D$ - 152° (c 0.11, $CHCl_3$).

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.64; H, 9.48.

B. In Dioxane

A solution of 0.516 g (0.0024 mol) of (-)-dehydroepimaalienone (XXXVII) in 100 ml of dry dioxane was irradiated with a Hanau HK 6/20 low-

pressure mercury lamp for 160 minutes. The solvent was removed in vacuo and the residue was placed on a column of 15.0 g of acetone-washed silica gel. Elution with 250 ml of hexane afforded 0.267 g (52%) of an oil (LXXII). An analytical sample was prepared by distillation of the oil at reduced pressure [78-105° (bath temperature)/0.05 mm]; uv λ_{max} (95% EtOH) 220 (ε 5,450) and 280 nm (ε 2,490); ir (CCl_4) 1695 and 1651 cm^{-1}; nmr δ_{TMS} (CCl_4) 0.98 (s, 3H), 1.03 (s, 3H), 1.12 (s, 3H), 1.38 (s, 3H), 5.84 (d, J=6.0 Hz, 1H), and 7.34 ppm (d, J=6.0 Hz, 1H); m/e (70 eV) 216.155 (calcd., 216.151); $[\alpha]^{25}D$ - 153° (c 0.06, $CHCl_3$).

Anal. Calcd. for $C_{15}H_{20}O$: C, 83.29; H, 9.32. Found: C, 83.09; H, 9.40.

(-)-3-Oxo-4-epiglobulol (LXXVI)

A 500-ml, three-necked, round-bottom flask was equipped with a dropping funnel, acetone-dry ice condenser, and magnetic stirrer. The apparatus was placed under a nitrogen atmosphere and flame dried. Dry ammonia (ca 100 ml) was distilled into the flask and 0.094 g (0.014 g-atm) of lithium metal was added. The resulting blue solution was stirred for 30 min and a solution of 1.034 g (0.0044 mol) of hydroxy ketone (XXXVIII) in 40 ml of anhydrous ether was added dropwise to the flask over a 50-min period. The reaction mixture still maintained its blue color after the addition and stirring was continued for 105 min. Solid ammonium chloride (2.52 g, 0.047 mol) was added and the solution became colorless. Stirring was continued for 15 min and the ammonia was allowed to evaporate from the reaction mixture. To the residue was added 50 ml of water and 50 ml of ether and the resulting mixture was stirred vigorously for several minutes.

After separation of the phases the aqueous phase was saturated with sodium chloride and extracted with two 20-ml portions of ether. The combined ether extracts were washed with three 20-ml portions of a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and the residue was dissolved in methanol and filtered to remove silicone grease. The solvent was removed in vacuo leaving 1.011 g (97%) of a viscous oil which crystallized upon standing. Recrystallization of a small amount of this material from an ether-hexane mixture at low temperature afforded a white solid (LXXVI) (mp 68-69°) with the following physical properties: ir (CCl_4) 3600, 3420, and 1740 cm^{-1}; nmr δ_{TMS} ($DCCl_3$) 0.99 (s, 3H), 1.06 (d, J=6.5 Hz, 3H), 1.09 (s, 3H), and 1.12 ppm (s, 3H): m/e (70 eV) 236.175 (calcd., 236.178); $[\alpha]^{25}$ D - 86° (c 0.072, $CHCl_3$).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.11; H, 10.27.

Deuterium Exchange of (-)-3-Oxo-4-epiglobulol (LXXVI)

A solution of sodium deuteroxide (6.41% by wt.) in deuterium oxide was prepared by adding 3.00 g of sodium metal to 80.78 g of deuterium oxide under ether. Compound LXXVI (0.061 g, 0.26 mmol) was placed in a 25-ml, one-necked, round-bottom flask, which had been equipped with a reflux condenser and placed under a nitrogen atmosphere. To the flask was added 4.0 ml of the sodium deuteroxide solution and 1.6 ml of dry dioxane. The resulting mixture was stirred magnetically and refluxed for 1 hr. The reaction was then cooled to room temperature and saturated with sodium chloride. The resulting mixture was extracted with three 10-ml portions of ether and the combined ether extracts were washed with two

10-ml portions of a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and the residue was subjected to deuterium exchange two additional times. Examination of the mass spectrum of the residue remaining (0.046 g) after three successive exchanges indicated 81% of the α-hydrogens had been replaced by deuterium. The nmr spectrum of this material was examined in deuterochloroform with the aid of europium nmr shift reagent. After the addition of twenty-eight drops of a solution of the shift reagent and four drops of deuterochloroform, a doublet (J=11.2 Hz) was observed at 4.10 ppm.

Attempted Isomerization of (-)-3-Oxo-4-epiglobulol (LXXVI) with Base

A 25-ml, three-necked flask was equipped with a magnetic stirrer, reflux condenser, and placed under a nitrogen atmosphere. Sodium metal (0.005 g, 0.217 mmol) was placed in the flask along with 5 ml of reagent grade methanol and the mixture was stirred until no further hydrogen evolution could be noted. Compound LXXVI (0.029 g, 0.124 mmol) was dissolved in 2.0 ml of methanol and added to the flask. The resulting mixture was stirred and heated at reflux for 90 min and cooled to room temperature. The solvent was removed and the residue was partitioned between 10 ml of water and 10 ml of ether. The aqueous phase was saturated with sodium chloride and extracted with two 10-ml portions of ether. The combined ether extracts were washed with three 10-ml portions of a saturated, aqueous solution of sodium chloride and dried. The solvent was removed and the residue (0.02 g) was subjected to nmr analysis. The residue exhibited an identical spectrum with that of the starting material.

(-)-4-Epiglobulol (LXXVIII)

A 250-ml, one-necked, round-bottom flask was equipped with a magnetic stirrer and a variable, take-off condenser. The apparatus was placed under a nitrogen atmosphere and 0.602 g (0.26 mmol) of compound LXXVI were placed in the flask along with 78 ml of diethylene glycol. To this mixture was added 0.817 g (0.015 mol) of powdered potassium hydroxide and 36 ml of an 85% solution of hydrazine hydrate. The resulting mixture was stirred vigorously and heated at 115° for 2 hr and the hydrazine was removed by distillation until the reflux temperature reached 205°. The reaction was refluxed at 205° for 5 hr and cooled to room temperature and 150 ml of water was added. The mixture was extracted with three 75-ml portions of benzene and the combined benzene extracts were washed with three 50-ml portions of water and one 50-ml portion of a saturated aqueous solution of sodium chloride. The benzene extract was dried over anhydrous magnesium sulfate and the solvent was removed in vacuo leaving 0.62 g of a viscous oil. The oil was placed on a column of 15.0 g of acetone-washed silica gel and elution with a 10% ether-hexane mixture afforded 0.309 g (55%) of a colorless, viscous oil (LXXVIII) which crystallized upon standing. A small amount of this material was sublimed at reduced pressure (40°/0.05 mm) yielding a white solid (mp 49-50°): ir (CCl_4) 3600 cm^{-1}; nmr δ_{TMS} ($DCCl_3$) 0.94 (d, J=5.9 Hz, 3H), 0.96 (s, 3H), 1.02 (s, 3H), and 1.09 ppm (s, 3H); m/e (70 eV) 222.196 (calcd., 222.198); $[\alpha]^{25}$ D - 16° (c 0.12, $CHCl_3$).

Anal. Calcd. for $C_{15}H_{26}O$; C, 81.02; H, 11.79. Found: C, 81.04; H, 11.79.

(+)-4-Epiaromadendrene (III)

A 25-ml three-necked, round-bottom blask was equipped with a thermometer, rubber septum, and magnetic stirrer. The apparatus was placed under a nitrogen atmosphere and 0.254 g (1.15 mmol) of compound LXXVIII and 15.3 ml of dry pyridine were added. The solution was cooled to -5° and 0.674 g (5.7 mmol) of freshly distilled thionyl chloride was added dropwise via a syringe at a rate such that the reaction temperature did not rise above 0°. The reaction mixture was stirred for 12 min at 0° and 15 ml of water were added at such a rate that the reaction temperature did not rise above 10°. The mixture was extracted with 10 ml of ether and the aqueous phase was saturated with sodium chloride and extracted with three additional portions of ether. The combined ether extracts were washed with three 10-ml portions of a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo leaving 0.172 g of a dark brown oil. The oil was dissolved in 10 ml of glacial acetic acid and 0.744 g (9.08 mmol) of sodium acetate were added. The resulting mixture was stirred vigorously and heated at 90-100° for 1 hr. The reaction was cooled to room temperature and poured into 10 ml of water. The mixture was extracted with three 10 ml portions of carbon tetrachloride and the combined organic extracts were washed with 10-ml portions of 2% aqueous potassium hydroxide, 2N aqueous hydrochloric acid, and 5% aqueous sodium bicarbonate solutions, respectively. The carbon tetrachloride extracts were then washed with three 10-ml portions of a saturated aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo

leaving 0.218 g of a brown oil. The oil was placed on a column of 5.0 g of acetone washed silica gel. Elution with 30 ml of hexane afforded 0.129 g (55%) of an oil which contained two components in a 75:25 ratio as determined by glc (column A). The two components were collected by preparative glc (column C) and the major component exhibited an ir and nmr spectrum identical to a sample of (-)-4-epiaromadendrene prepared by Büchi and coworkers [5]. This material also exhibited the following properties: m/e (70 eV) 204.186 (calcd., 204.188); $[\alpha]^{25}$ D + 33° (c, 0.049, $CHCl_3$). The minor component (LXXX) exhibited the following nmr absorptions: nmr δ_{TMS} (CCl_4) 1.01 (d, J=6 Hz, 3H), 1.05 (s, 3H), 1.10 (s, 3H), and 1.60 ppm (broad s, 3H).

Attempted Preparation of (-)-Globulol (II) by Catalytic Hydrogenation of 3,4-Dehydroglobulol (LXXXV)

(-)-3-Oxo-4-epiglobulol (LXXVI) (0.075 g, 0.32 mmol) was dissolved in 10 ml of anhydrous ether and added dropwise to a 50-ml, round-bottom flask, which contained 0.018 g (0.47 mmol) of lithium aluminum hydride and was under a nitrogen atmosphere. The resulting mixture was refluxed for 1 hr and stirred for 45 min at room temperature. A saturated aqueous solution of sodium sulfate (15 ml) was added dropwise to the reaction mixture and the phases were separated. The aqueous phase was extracted with two 10-ml portions of ether and the combined ether extracts were washed with two 10-ml portions of a saturated aqueous solution of sodium chloride. The ether extracts were dried over anhydrous magnesium sulfate and the solvent was removed in vacuo leaving 0.063 g (84%) of a white solid: ir (CCl_4) 3600 and 3400 cm^{-1}; nmr δ_{TMS} ($DCCl_3$) 3.65 ppm (q,

J=8.0 Hz, 1H).

A 25-ml, three-necked, round-bottom flask was equipped with a magnetic stirrer, reflux condenser, and placed under a nitrogen atmosphere. To the flask was added the crude product from the previous reaction along with 0.063 g (0.33 mmol) of p-toluenesulfonyl chloride and 2.0 ml of dry pyridine. After stirring overnight at room temperature, 8.0 ml of dry pyridine was added and the mixture was heated at reflux for 4 hr. The reaction was cooled to room temperature and poured into 20 ml of water. The mixture was extracted with three 10-ml portions of benzene and the combined benzene extracts were washed with water, saturated aqueous sodium bicarbonate solution, and a saturated aqueous sodium chloride solution. The benzene extracts were dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo* leaving a dark brown oil: ir (CCl_4) 3600 and 3400 cm^{-1}.

The residue from the previous reaction was dissolved in 25 ml of 95% ethanol and placed in a hydrogenation bottle. To the bottle was added 0.031 g of palladium supported on carbon and the resulting mixture was hydrogenated on a Paar Shaker at 50 psi for 1 hr. The catalyst was then filtered off and the solvent was removed *in vacuo* leaving a brown oil. Analysis of this material by glc (Column A) indicated the major product was (-)-4-epiglobulol (LXXVIII) and the absence of (-)-globulol as determined by comparison with authentic samples.

Attempted Preparation of (-)-Globulol (II) from (-)-3-Oxo-4-epiglobulol (LXXVI) via the Pyrrolidene Enamine

A 25-ml, one-necked, round-bottom flask was equipped with a calcium chloride filled soxhlet extractor, reflux condenser, and magnetic stirrer.

The apparatus was placed under a nitrogen atmosphere and 0.096 g (0.41 mmol) of compound LXXVI, 15 ml of dry toluene, and 0.117 g (1.6 mmol) of freshly distilled pyrrolidene were placed in the flask. The resulting mixture was stirred and heated at reflux overnight. After cooling the reaction to room temperature, the solvent was removed in vacuo leaving a dark brown viscous oil. Examination of the ir spectrum of this residue indicated no significant absorption at 1740 cm^{-1}. This material was then used in a subsequent reaction without further purification or characterization. A 25-ml, three-necked, round-bottom flask was equipped with a magnetic stirrer and placed under a nitrogen atmosphere. The apparatus was flame dried and the material from the previous reaction, which had been dissolved in 10 ml of dry tetrahydrofuran, was syringed into the flask. The solution was cooled to 0° and 2.0 ml (2.8 mmol) of a 1.38 M solution of borane in tetrahydrofuran was added dropwise via a syringe. The reaction was then allowed to warm to room temperature and stirred for 72 hr. The solvent was removed in vacuo leaving an amber oil which was used without any purification or characterization. The oil was dissolved in 10 ml of dry diglyme and placed in a 25-ml, one-necked, round-bottom flask, which was under a nitrogen atmosphere. Propionic acid (0.187 g, 2.5 mmol) was added and the flask was fitted with a reflux condenser and heated at reflux for 4 hr. The reaction mixture was cooled to room temperature and poured into 30 ml of water. The mixture was saturated with sodium chloride and extracted with several portions of ether. The combined ether extracts were washed with a saturated aqueous solution of sodium bicarbonate and water, respectively, and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo leaving a dark brown oil.

The crude product was dissolved in 25 ml of 95% ethanol and 0.036 g of palladium supported on carbon was added and the mixture was hydrogenated at atmospheric pressure overnight. The catalyst was filtered off and the solvent was removed *in vacuo*. The residue was subjected to glc analysis (column A) which indicated a gross mixture of substances, none of which corresponded to (-)-4-epiglobulol (LXXVIII) or (-)-globulol (II).

Attempted Preparation of (-)-Globulol (II) via Kinetic Quenching of the Lithium-Ammonia Reduction of (-)-3-Oxo-4,5-dehydroglobulol (XXXVIII)

A 100-ml, three-necked, round-bottom flask was equipped with a mechanical stirrer, acetone-dry ice condenser and addition funnel. The apparatus was placed under a nitrogen atmosphere and flame dried. Dry ammonia (*ca* 50 ml) was distilled into the flask and 0.015 g (0.0022 g-atm) of lithium metal was added. The resulting blue solution was stirred for 30 min and 0.097 g (0.41 mmol) of XXXVIII in 15 ml of anhydrous ether was added dropwise over a 5-min period. The reaction mixture was stirred for 15 min and the mixture was added in a thin stream to 125 ml of a saturated aqueous solution of ammonium chloride, which contained additional suspended ammonium chloride. The layers were separated and the aqueous phase was extracted with three 50-ml portions of ether and the combined ether extracts were washed with water until neutral. The ether extracts were dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. Examination of the ir spectrum (1740 cm^{-1}) of the residue indicated reduction of the 4,5 double bond had taken place.

Lithium aluminum hydride (0.016 g, 0.43 mmol) was placed in a 50-ml, three-necked, round-bottom flask which had been equipped with a reflux

condenser, magnetic stirrer, and dropping funnel and was under a nitrogen atmosphere. The crude material from the previous reaction was dissolved in 15 ml of anhydrous ether and added dropwise to the reaction flask. After the addition was complete, the reaction was refluxed for 1 hr and stirred at room temperature for 105 min. A saturated aqueous solution of sodium sulfate was added dropwise to decompose any unreacted lithium aluminum hydride and the resulting phases were separated. The aqueous phase was extracted with two 10-ml portions of ether and the combined ether extracts were washed with two 10-ml portions of a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo leaving 0.121 g of material: ir (CCl_4) 3400 and 3600 cm^{-1}; nmr δ_{TMS} ($DCCl_3$) 3.65 ppm (q, J=8.0 Hz, 1H).

The crude material from the lithium aluminum hydride reaction was placed in a 25-ml, three-necked, round-bottom flask which had been placed under a nitrogen atmosphere. p-Toluenesulfonyl chloride (0.085 g, 0.44 mmol) and 2.0 ml of dry pyridine were added to the flask and the resulting mixture was stirred magnetically overnight. The solvent was then removed in vacuo leaving a dark brown residue which was subsequently extracted with ether. The ether was removed in vacuo leaving a brown oil: ir (CCl_4) 3600, 3400, 1380, and 1180 cm^{-1}; nmr δ_{TMS} (CCl_4) 4.20 (q, J=8.0 Hz, 1H), 7.20-8.00 (m, 4H), and 2.41 ppm (s, 3H).

A 25-ml, three-necked, round-bottom flask was equipped with a magnetic stirrer, reflux condenser, and placed under a nitrogen atmosphere. To the flask was added 0.025 g (0.62 mmol) of lithium aluminum hydride and the crude product from the previous reaction, which had been dissolved in 10 ml of dry tetrahydrofuran, was added dropwise. The resulting

mixture was refluxed overnight and then cooled to room temperature. A saturated aqueous solution of sodium sulfate (10 ml) was added dropwise and the mixture was extracted with two 10-ml portions of benzene. The combined benzene extracts were washed with two 10-ml portions of water and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* leaving a yellow oil. Examination of the oil by glc (Column A) indicated the major component of the mixture was (-)-4-epiglobulol and the absence of (-)-globulol, as determined by comparison with authentic samples.

A slightly modified procedure was attempted in the lithium in liquid ammonia reduction. Dry ammonia (*ca* 50 ml) was distilled into a 100-ml, three-necked, round-bottom flask which had been flame dried and equipped with a mechanical stirrer, acetone-dry ice condenser, dropping funnel, and was under a nitrogen atmosphere. Lithium metal (0.009 g, 0.0013 g-atm) was added and the resulting blue solution was stirred for 45 min. A solution of compound XXXVIII (0.054 g, 0.23 mmol) in 20 ml of anhydrous ether was added dropwise over a 5-min period and the blue solution was stirred for 55 min. The ammonia was allowed to evaporate off at room temperature and the last traces were removed *in vacuo* at 5.00 mm of mercury for 20 min. Dry tetrahydrofuran (50 ml) was added and the mixture was stirred for 15 min and cooled with dry ice. The cold solution was added dropwise to a mixture of 100 ml of pentane, 50 ml of glacial acetic acid, and 50 ml of water which was rapidly stirred and cooled in an ice-water bath. The phases were separated and the organic phase was washed with two 20-ml portions of a cold, aqueous solution of sodium bicarbonate and two 30-ml portions of a saturated aqueous solution of sodium chloride,

respectively. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed in vacuo. Examination of the residue by glc (Column A) and nmr indicated (-)-3-oxo-4-epiglobulol (LXXVI) had been produced without any trace of the 4α-methyl isomer.

Lithium Aluminum Hydride Reduction of (-)-3-Oxo-4,5-dehydroglobulol (XXXVIII)

A 50-ml, three-necked, round-bottom flask was equipped with a magnetic stirrer, and reflux condenser. The apparatus was placed under a nitrogen atmosphere and flame dried, and 0.019 g (0.49 mmol) of lithium aluminum hydride was added. Anhydrous ether (15 ml) was added and a solution of compound XXXVIII (0.080 g, 0.34 mmol) in 10 ml of anhydrous ether was added dropwise to the reaction flask via a syringe. The resulting mixture was refluxed for 1 hr and stirred for 45 min at room temperature. A saturated aqueous solution of sodium sulfate was added dropwise and the phases were separated. The aqueous phase was extracted with two 10-ml portions of ether and the combined ether extracts were washed with a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo leaving 0.116 g of a dark brown oil (CV); ir (CCl_4) 3600 and 3420 cm^{-1}; nmr δ_{TMS} ($DCCl_3$) 0.90 (s, 3H), 0.95 (s, 3H), 1.10 (s, 3H), 1.70 (broad s, 3H), and 4.71 ppm (broad m, 1H); m/e (70 eV) 220 (loss of H_2O).

Catalytic Hydrogenation of 3-Hydroxy-4,5-dehydroglobulol (CV)

The crude material (CV) from the previous reaction was dissolved in 5 ml of glacial acetic acid and 0.012 g of platinum oxide was added. The resulting mixture was stirred and hydrogenated at 1 atm pressure for

22 hr. The catalyst was filtered off and the filtrate was diluted with 15 ml of ether and 10 ml of water. The phases were separated and the ether phase was washed with saturated aqueous solutions of sodium bicarbonate and sodium chloride, respectively. After drying over anhydrous magnesium sulfate, the solvent was removed in vacuo leaving a yellow oil. Examination of the mass spectrum and glc behavior (Column A) indicated the absence of any (-)-globulol; m/e (70 eV) 204.

The reaction was repeated and an attempt was made to control the extent of hydrogenation. After one equivalent of hydrogen had been absorbed, the reaction mixture was worked up and glc and ms analysis of the residue indicated the absence of (-)-4-epiglobulol or (-)-globulol and the presence of starting material and the hydrogenolysis product (CVI).

3-(2-Butanone-4-yl)-2-carone (LXV)

This compound (LXV) was prepared by the same procedure used in the preparation of compound LX with the exception that methyl vinyl ketone was used in place of ethyl vinyl ketone. When 81.0 g (0.53 mol) of (-)-2-carone were used, 54.2 g (64%) of a pale yellow oil (LXV) was obtained after distillation (100-135°/0.30 mm) of the crude product (109.6 g); uv λ_{max} (95% EtOH) 220 nm (ϵ 3,540); ir (CCl_4) 1720 and 1690 cm^{-1}; nmr δ_{TMS} (CCl_4) 0.85 (s, 3H), 1.05 (s, 3H), 1.15 (s, 3H), and 2.10 ppm (s, 3H); m/e (70 eV) 222.161 (calcd., 222.162).

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.51; H, 9.96.

Attempted Cyclization of 3-(2-Butanone-4-yl)-2-carone (LXV)

A. With Potassium Hydroxide in Ethanol

Compound LXV (2.78 g, 0.013 mol) was placed in a 50-ml, one-necked, round-bottom flask under a nitrogen atmosphere. Absolute ethanol (50 ml) and potassium hydroxide (0.403 g, 7.2 mmol) were added and the resulting mixture was refluxed with stirring for 75 min. The reaction mixture was cooled to room temperature and neutralized with acetic acid. The solvents were removed *in vacuo* and the residue was partitioned with water and ether. The aqueous phase was extracted with several portions of ether and the combined ether extracts were washed with saturated aqueous solutions of sodium bicarbonate and sodium chloride, respectively. After the ether extracts had been dried over anhydrous sodium sulfate, the solvent was removed *in vacuo* leaving 2.09 g of an oil. Examination of the nmr spectrum of this oil indicated that no reaction had taken place.

B. With Pyrrolidene

Compound LXV (2.09 g, .009 mol) was placed in a 100-ml, one-necked, round-bottom flask along with 1.47 g (0.021 mol) of pyrrolidene and 50 ml of dry benzene. A catalytic amount of *p*-toluenesulfonic acid was added and the reaction flask was equipped with a Dean-Stark trap, reflux condenser, and placed under a nitrogen atmosphere. The solution was refluxed overnight with removal of water by azeotropic distillation. After cooling the reaction mixture to room temperature, the solvent was removed *in vacuo* and the residue was used without purification. This residue was placed in a 50-ml, round-bottom flask along with 0.425 g (5.2 mmol) of sodium acetate, 1.493 g (0.025 mol) of acetic acid, 3 ml

of water and 25 ml of benzene. The flask was equipped with a reflux condenser and placed under a nitrogen atmosphere. The reaction mixture was heated at reflux for 3.5 hr and cooled to room temperature. The mixture was washed with water and aqueous solutions of dilute hydrochloric acid, saturated sodium bicarbonate, and sodium chloride, respectively. After the organic phase had been dried over anhydrous sodium sulfate, the solvent was removed in vacuo leaving 2.14 g of an oil. Examination of the nmr and ir spectrum and glc behavior of the reaction mixture indicated a gross mixture of products.

Cis-6-(2-chloropropane-2-yl)-3-keto-9-methyl-Δ^4-ocatahydronaphthalene (CVII)

This compound (CVII) was prepared by a procedure identical to that used to prepare chloro enone LXIX. When 23.25 g (0.105 mol) of compound LXV were used, 24.00 g (95%) of a pale yellow solid (CVII) were obtained. An analytical sample was prepared by recrystallization of the solid from boiling hexane; mp 106-107°; ir (CCl_4) 1675 and 1620 cm^{-1}; nmr δ_{tms} (CCl_4) 1.25 (s, 3H), 1.60 (s, 6H), and 5.65 ppm (broad s, 1H); m/e (70 eV) 204 (loss of HCl).

Anal. Calcd. for $C_{14}H_{21}OCl$: C, 69.84; H, 8.79. Found: C, 69.72; H, 8.80.

4-Normethyl-epimaalienone (CVIII)

This compound (CVIII) was prepared by a procedure identical to that used to prepare epimaalienone (XLV). When 20.4 g (0.085 mol) of compound CVII was used, 11.8 g (68%) of an amber oil (CVIII) was obtained after distillation (109-119°/0.08 mm); uv λ_{max} (95% EtOH) 277 nm (ϵ 18,200); ir (CCl_4) 1663 and 1592 cm^{-1}; nmr δ_{TMS} (CCl_4) 1.10 (s, 3H), 1.16 (s, 3H),

1.20 (s, 3H), and 5.86 ppm (s, 1H); m/e (70 eV) 204.151 (calcd., 204.151).

Anal. Calcd. for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.10; H, 9.88.

4-Normethyl-1,2-dehydroepimaalienone (CIX)

This compound (CIX) was prepared by a procedure identical to that used to prepare dienone XXXVII. When 9.23 g (0.045 mol) of compound CVIII were used, 7.10 g of crude material were obtained. This material was placed on a column of 213.0 g of hexane washed florisil and elution with a 10% ether-hexane mixture removed starting material. Elution with a 20% ether-hexane mixture afforded 2.748 g (37%) of a yellow oil (CIX); bp 124-129°/0.04 mm; uv λ max (95% EtOH) 243 (ε 10,000) and 303 nm (ε 8,600); ir (CCl_4) 1660, 1622, and 1588 cm^{-1}; nmr δ_{TMS} ($DCCl_3$) 1.14 (s, 6H), 1.23 (s, 3H), 6.15 (m, 2H), and 6.76 ppm (d, J=10.0 Hz, 1H); m/e (70 eV) 202.139 (calcd., 202.136). A small amount of the dienone (CIX) was distilled (bp 124-129°/0.04 mm) in order to obtain an analytical sample for combustion analysis. Although the nmr spectrum of this sample indicated a high degree of purity, the combustion analysis data differed from the calculated values by a factor greater than the experimental error of the determination. The dienone (CIX) was also unstable to glc when various columns and temperatures were employed.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 81.49; H, 8.91.

Irradiation of 4-Normethyl-1,2-dehydroepimaalienone (CIX) in Glacial Acetic Acid

Compound CIX (1.015 g) was dissolved in 275 ml of glacial acetic

acid and the solution was irradiated in a Pyrex apparatus with a 450-watt Hanovia high pressure mercury source for 45 min. The solution was diluted with 500 ml of water and extracted with two 200-ml portions of ether. The combined ether extracts were washed with three 200-ml portions of a saturated aqueous solution of sodium bicarbonate and two 100-ml portions of a saturated aqueous sodium chloride solution, respectively. After drying over anhydrous magnesium sulfate, the solvent was removed in vacuo leaving 1.610 g of an amber oil. This material was placed on a column of 42 g of acetone-washed silica gel. Elution with a 10% ether-hexane mixture removed starting material and further elution with a 15% mixture of ether-hexane afforded 0.668 g (51%) of a viscous oil (CXI); bp 124-130°/0.03 mm; uv λ_{max} (95% EtOH) 241 nm (ϵ 11,800); ir (CCl_4) 1712, 1688, and 1608 cm^{-1}; nmr δ_{TMS} ($DCCl_3$) 1.00 (s, 3H), 1.15 (s, 6H), 1.98 (s, 3H), and 6.08 (m, 1H); m/e (70 eV) 202 (loss of HOAc).

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.95; H, 8.58.

Attempted Reductive-Silylation of Photoproduct CXI

A 100-ml, three-necked, round-bottom flask was equipped with a magnetic stirrer, acetone-dry ice condenser, and dropping funnel. The apparatus was placed under a nitrogen atmosphere, flame dried, and ca 50 ml of dry ammonia were introduced. To the reaction flask was added lithium metal (0.008 g, 0.0012 g-atm) and the resulting blue solution was stirred for 1 hr. A solution of photoproduct CXI (0.008 g, 1.2 mmol) and tert.-butyl alcohol (0.007 g, 0.96 mmol) in 25 ml of anhydrous ether were added dropwise with stirring to the reaction flask over a 15-min period. The resulting blue solution was stirred for 1 hr and sodium benzoate

(0.063 g, 0.44 mmol) was added and the solution became yellow. The ammonia was evaporated off at room temperature and then under vacuum (3.50 mm, 45 min) to remove the final traces of ammonia. Dry tetrahydrofuran (25 ml) was added and the solution was cooled to 0° with an ice-salt bath. A 6.0-ml portion of a solution of chlorotrimethylsilane (0.889 g, 8.2 mmol) and dry triethylamine (0.788 g, 7.8 mmol) in 12.0 ml of dry tetrahydrofuran was added in a thin stream to the reaction flask and the mixture was stirred for 10 min. Pentane (25 ml) and a cold, saturated, aqueous solution of sodium bicarbonate (25 ml) were added and the phases were separated. The organic phase was washed with four 15-ml portions of a saturated, aqueous sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* leaving an amber oil. This material was subjected to glc (Column A), ir and nmr analysis which indicated the absence of any silyl enol ether; ir (CCl_4) 3680, 3360, and 1742 cm^{-1}.

Reductive-Alkyllation of Photoproduct CXI

A 100-ml, three-necked, round-bottom flask was equipped with a magnetic stirrer, acetone-dry ice condenser, and dropping funnel. The apparatus was placed under a nitrogen atmosphere, flame dried, and *ca* 50 ml of dry ammonia were introduced. To the reaction flask was added lithium metal (0.009 g, 0.0014 g-atm) and the resulting blue solution was stirred for 1 hr. A solution of compound CXI (0.040 g, 0.15 mmol) and water (0.002 g, 0.12 mmol) in 25 ml of anhydrous ether was added dropwise to the reaction flask over a 20-min period and the blue solution was stirred for 1 hr. The ammonia was evaporated off and the final traces

were removed under vacuum (4.50 mm/45 min). Dry tetrahydrofuran (25 ml) was added and the solution was stirred and cooled to 0°. A 1.5-ml portion of a solution of 1.228 g of methyl iodide in 10 ml of dry tetrahydrofuran was added in a thin stream to the reaction flask and the resulting solution was stirred for 15 min. Ammonium chloride (0.6463 g) was added in one portion and this was followed by the addition of 25 ml of pentane and 25 ml of water. The phases were separated and the organic phase was washed with four 10-ml portions of a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo leaving an amber oil. This material was subjected to glc (Column A), ir and nmr analysis which indicated that only partial alkylation (ca 30%) had occurred and that the β-methyl isomer had been produced without any significant amount of another isomer; ir (CCl_4) 3680, 3360, and 1742 cm^{-1}.

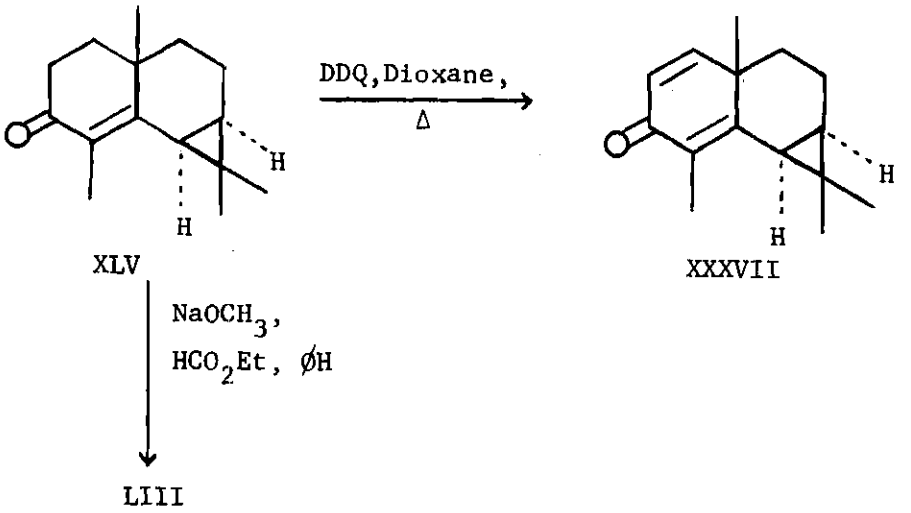
This reaction was also run with ammonia as the solvent for the alkylation step and a reaction time of 5 min. A lower degree of alkylation (< 30% by glc) was observed and only the β-methyl isomer could be observed as determined by glc (Column A), ir, and nmr analysis; ir (CCl_4) 3680, 3360, and 1742 cm^{-1}.

CHAPTER IV

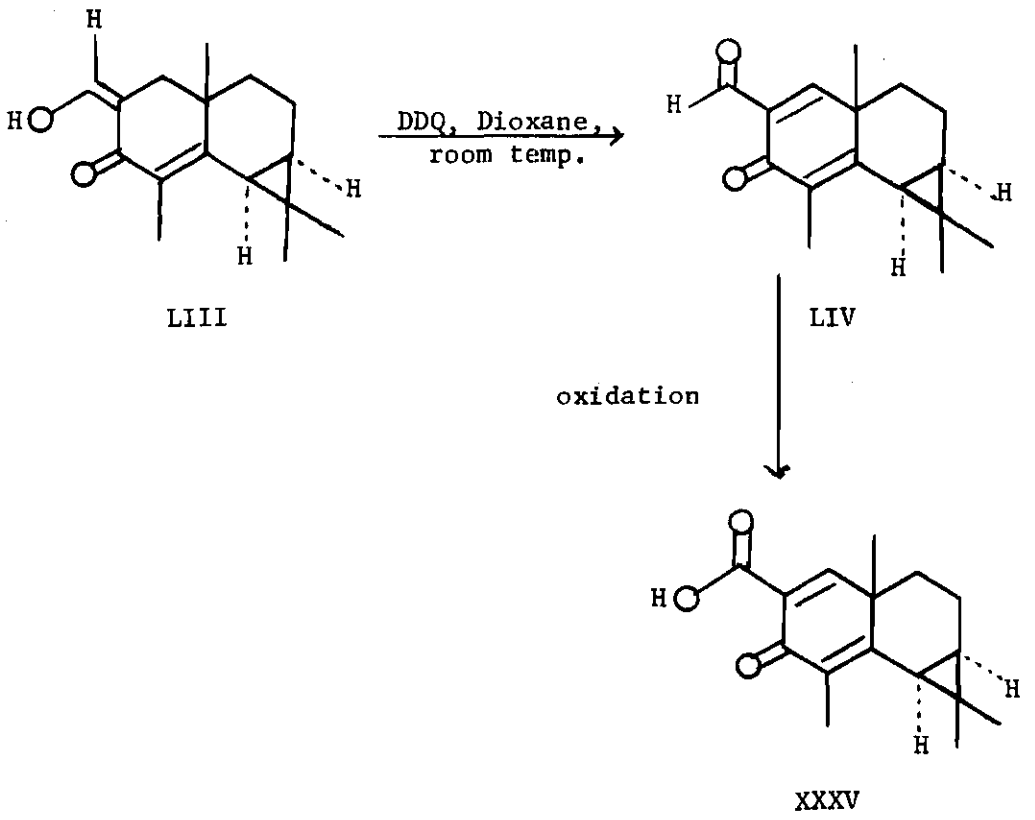
DISCUSSION OF RESULTS

As stated in the introduction, the principal goal of this research was to generate the aromadendrane skeleton by the photochemical rearrangement of an appropriately substituted 6/6-fused cross-conjugated cyclohexadienone (compound XXXV or XXXVII). The photoproduct would then be converted into (+)-aromadendrene (I) or (-)-globulol (II) by subsequent transformations.

Since dienones XXXV or XXXVII would be required for the photochemical step, an efficient synthesis of these compounds would be necessary. The logical precursor to both dienones should be (-)-epimaalienone (XLV) since conversions as depicted in Scheme 11 are standard [9d].

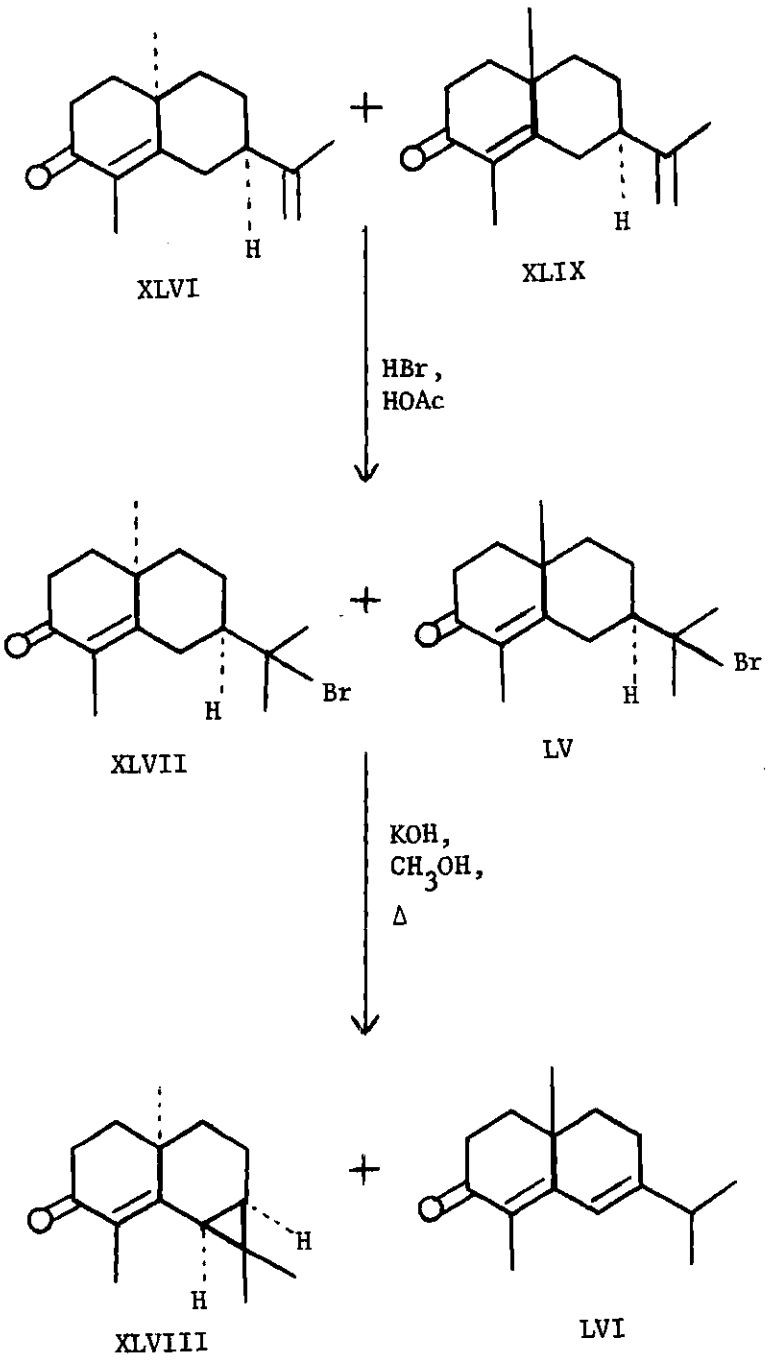


Scheme 11



Scheme 11 (Continued)

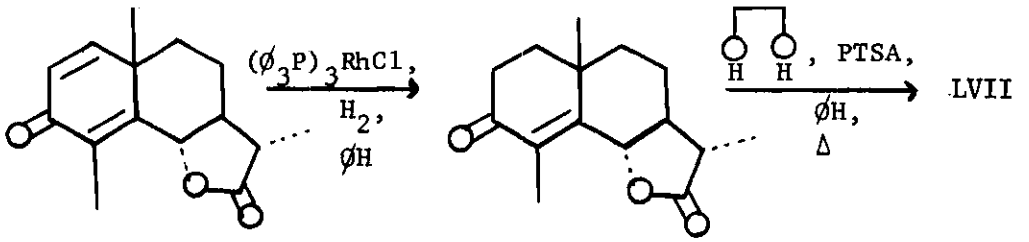
A sequence of reactions which were analogous to that carried out by Büchi (Scheme 9) on epi-α-cyperone (XLVI) was attempted on a mixture of 60% epi-α-cyperone and 40% (+)-α-cyperone (XLIX), which had been prepared by the method of Howe and McQuillin [18]. A mixture of maalienone (XLVIII) and β-cyperone (LVI) was produced (Scheme 12) as the only products of the reaction as determined by glc and nmr comparison with authentic samples.


H
XLVI
H
XLIX
HBr,
HOAc
H
Br
XLVII
H
Br
LV
KOH,
CH_3OH,
Δ
H
H
XLVIII
LVI

Scheme 12

Examination of a model of (-)-epimaalienone indicated that there is strong steric interaction between the endocyclic methyl group on the cyclopropane ring and the angular methyl group, whereas in maalienone (XLVIII) the angular methyl group and the three-membered ring are trans and no such interaction can take place. Therefore, it seemed reasonable that elimination of hydrogen bromide, which would lead to the formation of an α, β, δ, ε dienone which could isomerize to β-cyperone (LVI), might become the major path and not the desired intramolecular substitution reaction.

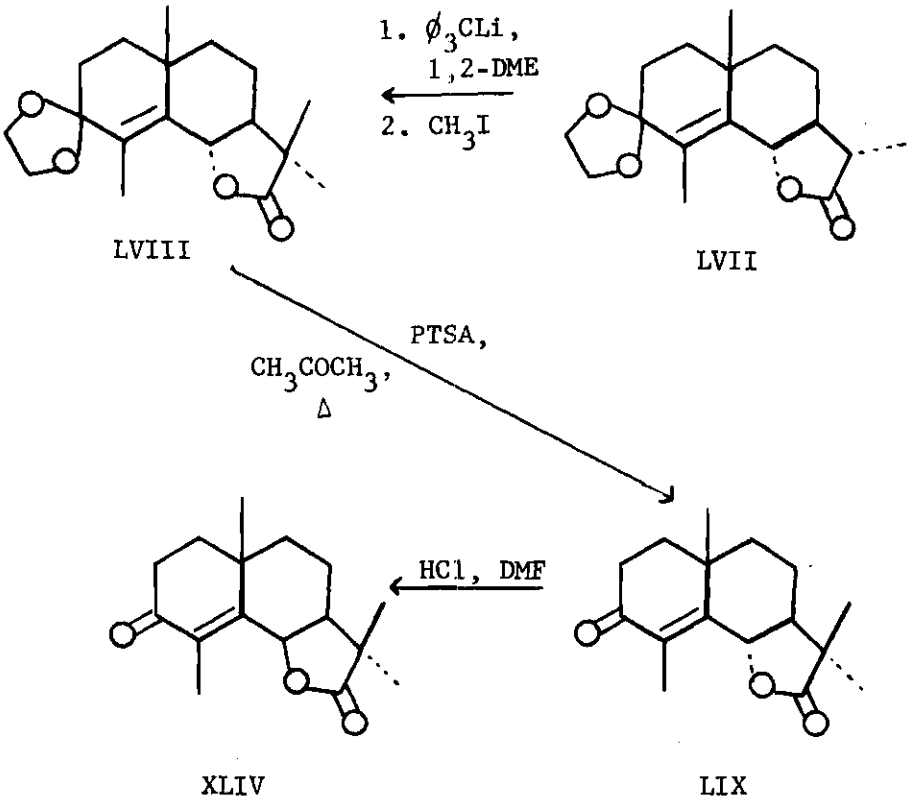
The only reported synthesis of (-)-epimaalienone (XLV) was developed by Ourisson (Scheme 8) and utilized (-)-α-santonin (XXXIX) as the starting material. Upon repeating this work, considerable difficulty* was encountered in preparing ethylene ketal XLII on a synthetically useful scale. This problem was circumvented by modifying Ourisson's sequence of reactions (Scheme 13).



XXXIX XL

Scheme 13

*Professor Ourisson was contacted and he indicated he was unable to carry out this transformation successfully on any scale larger than 500 mg.

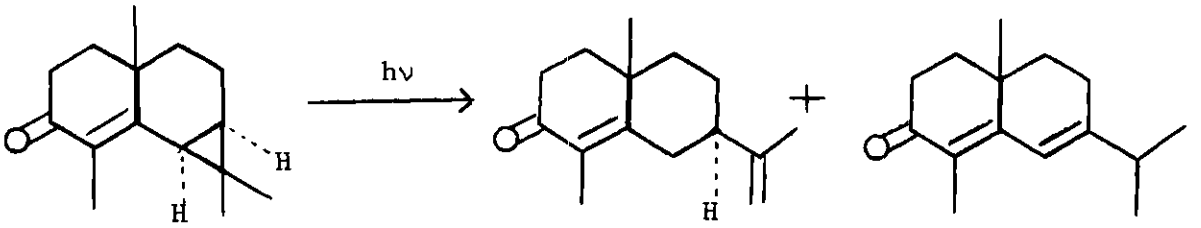


Scheme 13 (Continued)

The structure of ketal LVII was established by the absence of an absorption at 1680 cm^{-1} in the ir, an nmr absorption at 4.00 ppm (m, 4H), and a molecular ion at 292 m/e in the mass spectrum.

Since exposure of 11-methyl-epidihydrosantonin (XLIV) to diffuse daylight proved to an an inefficient and time consuming preparation of (-)-epimaalienone, a more efficient procedure was desired. Irradiation of this compound in a Pyrex vessel with a 450-watt Hanovia source in benzene for 12 hr produced the same result as was obtained by exposure to diffuse daylight. Although this latter method was significantly more efficient, a low conversion (ca 30%) had to be tolerated in order to

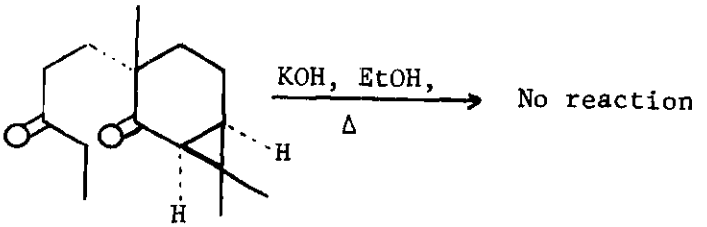
realize a high yield (ca 90%) as a result of the known photochemical instability of (-)-epimaalienone [15].



XLV XLIX LVI

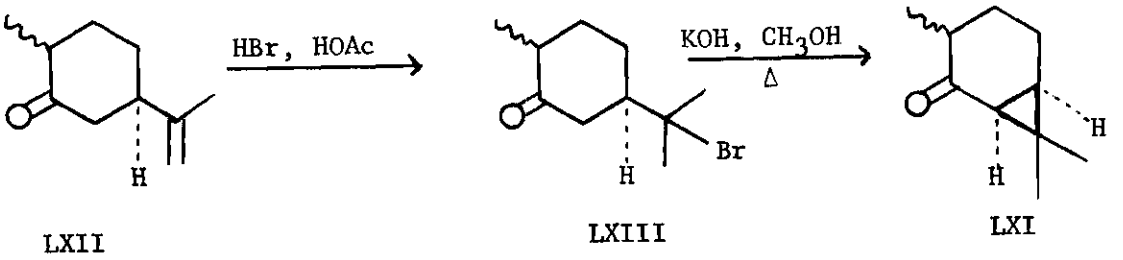
Since the preparation of (-)-epimaalienone was approximately the midway point in a multistep synthesis, a more efficient synthesis of this compound was desirable.

Büchi and co-workers [16] had reported the preparation of a 1,5-diketone (LX) and had attempted to cyclize it under basic conditions to (-)-epimaalienone.



LX

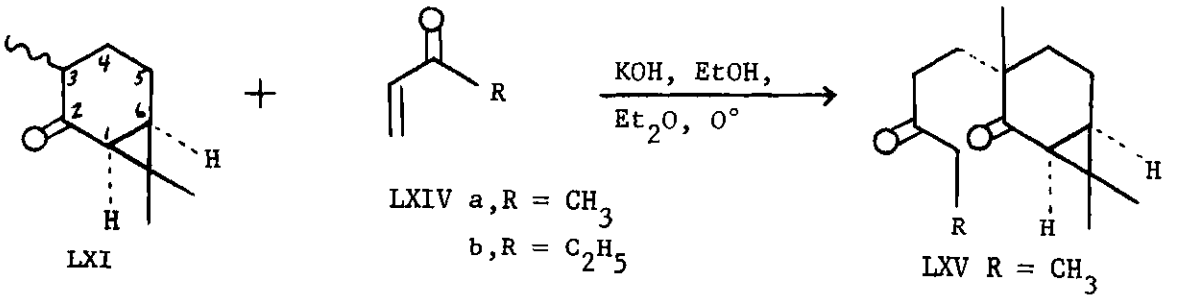
In reporting the preparation of LX, only partial spectral data (ir and uv) and no experimental details were given. In order to prepare LX, it was necessary to synthesize (-)-2-carone (LXI) which was readily available [20] from (+)-dihydrocarvone (LXII) (Scheme 14).



LXII LXIII LXI

Scheme 14

The preparation of (-)-2-carone in this fashion was achieved in an overall yield of 83%. It was now desired to prepare not only compound LX but also compound LXV under the conditions of the Michael reaction, since LXV might afford less steric interference in a base catalyzed cyclization as a result of possessing one less carbon atom on the side chain.



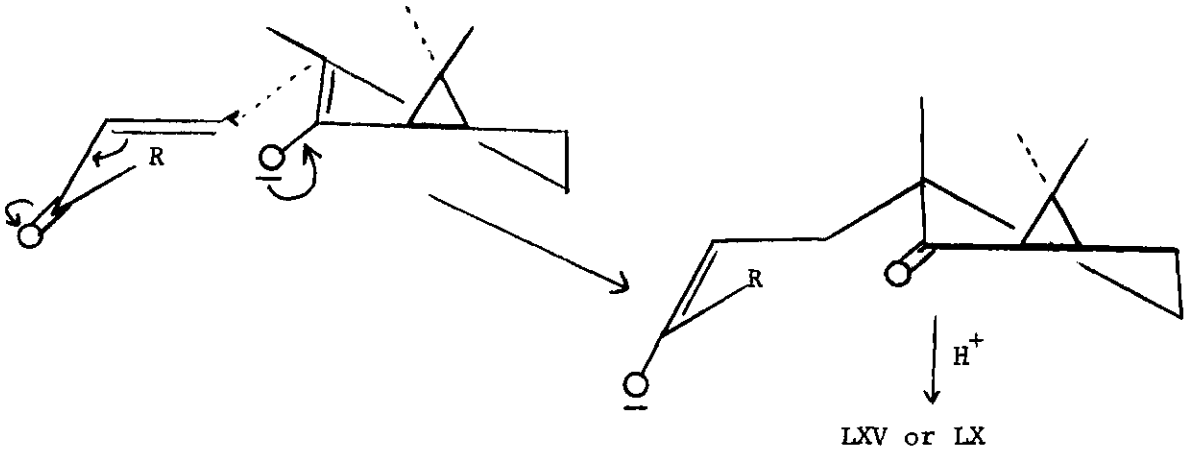
LXI

LXIV a, R = CH_3
b, R = C_2H_5

LXV R = CH_3
LX R = C_2H_5

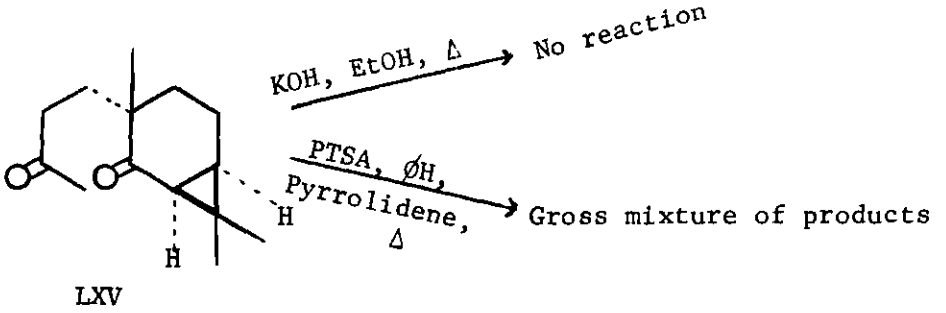
Both 1,5-diketones (LXV and LX) were obtained in good yield (64% and 86%, respectively) as the only products of this reaction. Compound LX exhibited the same ir (1721 and 1692 cm^{-1}) and uv spectrum (216 nm, ϵ 2,790) as reported by Büchi and showed no methyl doublet in the nmr which would have resulted from bond formation occurring at C-1 instead

of C-3. Subsequent transformations unambiguously established LX as the correct structural assignment. It is important to note in these reactions that the presence of the dimethylcyclopropane group results in a stereospecific attack from the bottom side of the 2,3-enolate of (-)-2-carone on the Michael acceptor.



Therefore, these stereochemical results allow for the stereospecific preparation of the isomer having the α-methyl group and the dimethylcyclopropane group cis to each other.

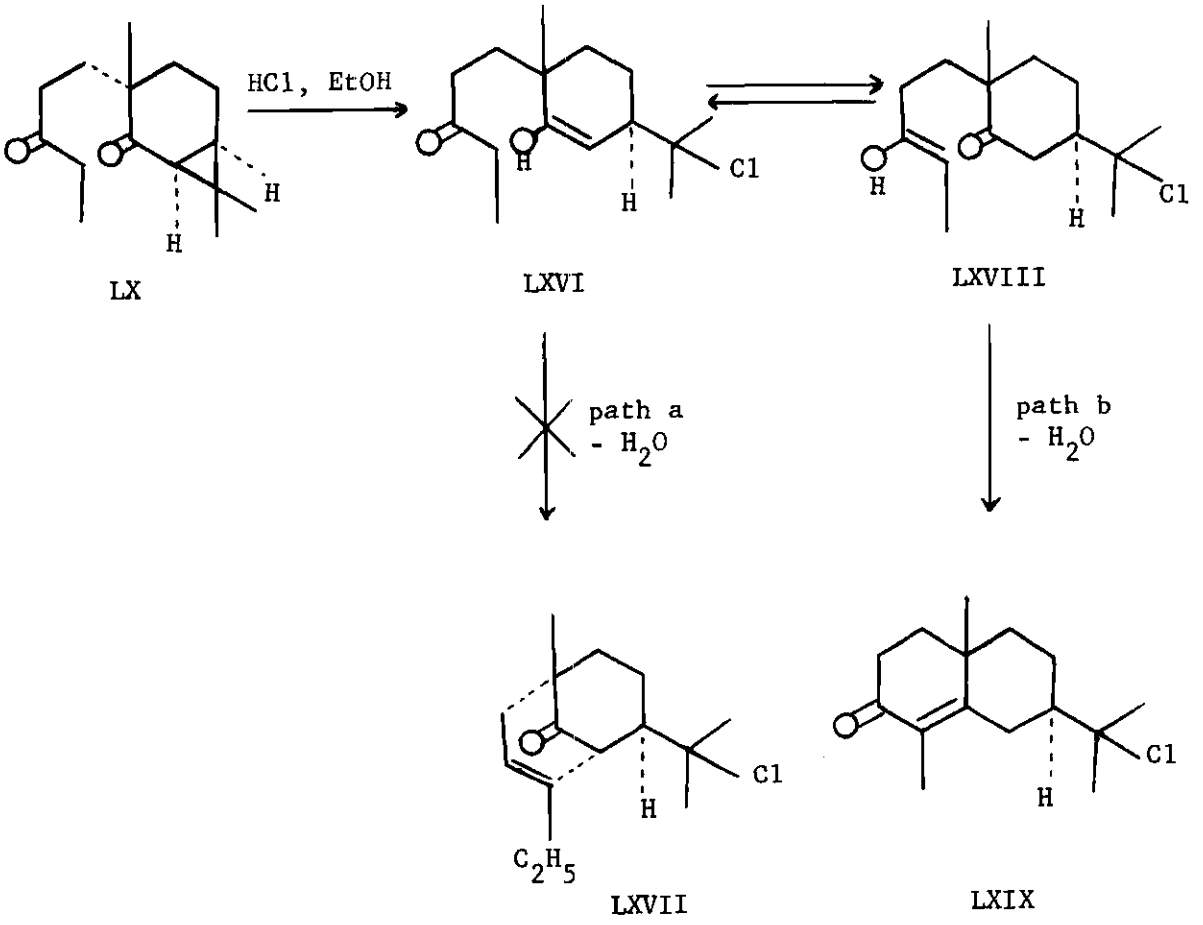
Attempts to cyclize LXV with potassium hydroxide in ethanol or pyrrolidene in benzene were unsuccessful (Scheme 15).



Scheme 15

Van der Gen [22] and co-workers have reported an acid catalyzed opening of a cyclopropyl ketone in a successful synthesis of (-)-α-vetivone and (-)-nootkatone and it was therefore decided to investigate such a reaction as applied to the cyclopropyl enones LXV and LX.

Treatment of LX with an anhydrous, saturated solution of hydrogen chloride in absolute ethanol afforded chloro enone LXIX as the only product in 83% yield.



LX LXVI LXVIII

LXVII LXIX

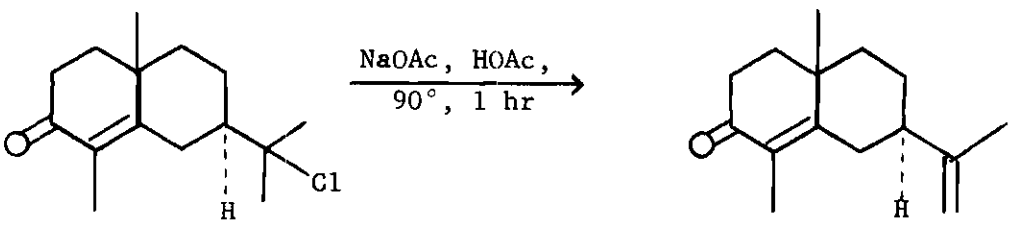
Scheme 16

Aldol cyclization of the enolized, monocyclic, chloro ketone (LXVI or LXVIII), obtained from opening of the three-membered ring, occurs by

path b only. This is a consequence of it being necessary for LXVI to adopt a boat conformation or a chair conformation with the 5-substituent axial in order to cyclize via path a. Both of these structures should be of relatively high energy with respect to LXVIII with the cyclohexanone ring in a chair conformation and therefore unfavorable as compared with path b.

Chloro enone LXIX exhibited a uv absorption at 248 nm (ε 20,100) and ir absorptions at 1668 and 1612 cm^{-1} which are both characteristic of α,β-unsaturated cyclohexenones. Additionally, an nmr absorption at 1.62 ppm (s, 6H) indicated two methyl groups alpha to a halogen and the absorption at 1.75 ppm (s, 3H) was indicative of a methyl group on a double bond.

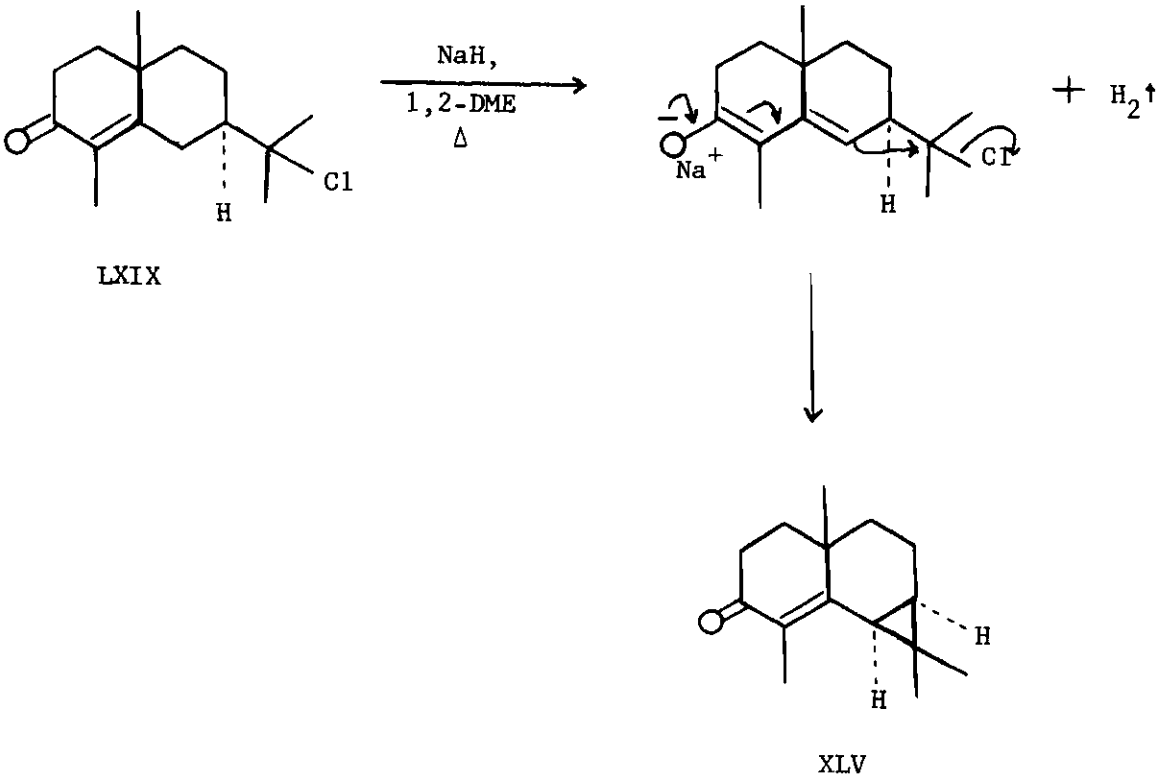
At this point it appeared useful to investigate the possible dehydrochlorination of LXIX to (+)-α-cyperone (XLIX), since a convenient, stereospecific synthesis of this compound was unavailable [18,23] and XLIX had been utilized as an intermediate in many sesquiterpene syntheses [24,9b]. When LXIX was heated at 90° for 1 hr with sodium acetate in acetic acid, (+)-α-cyperone was obtained in 82% yield and the product was greater than 95% one component by glc. The structure of this material was determined by comparison of its properties [nmr, ir, optical rotation, and glc (Columns A and B)] with an authentic sample.



LXIX XLIX

Since it was known that the bromo enone related to LXIX underwent elimination of hydrogen bromide to give β-cyperone when refluxed with potassium hydroxide in methanol, more selective conditions for the conversion of LXIX to (-)-epimaalienone were needed.

When LXIX was heated with sodium hydride in 1,2-dimethoxyethane overnight, (-)-epimaalienone was isolated as the only component in 74% yield (Scheme 17). Apparently sodium hydride leads selectively to the formation of the conjugate enolate of LXIX which undergoes cyclization as shown.



LXIX

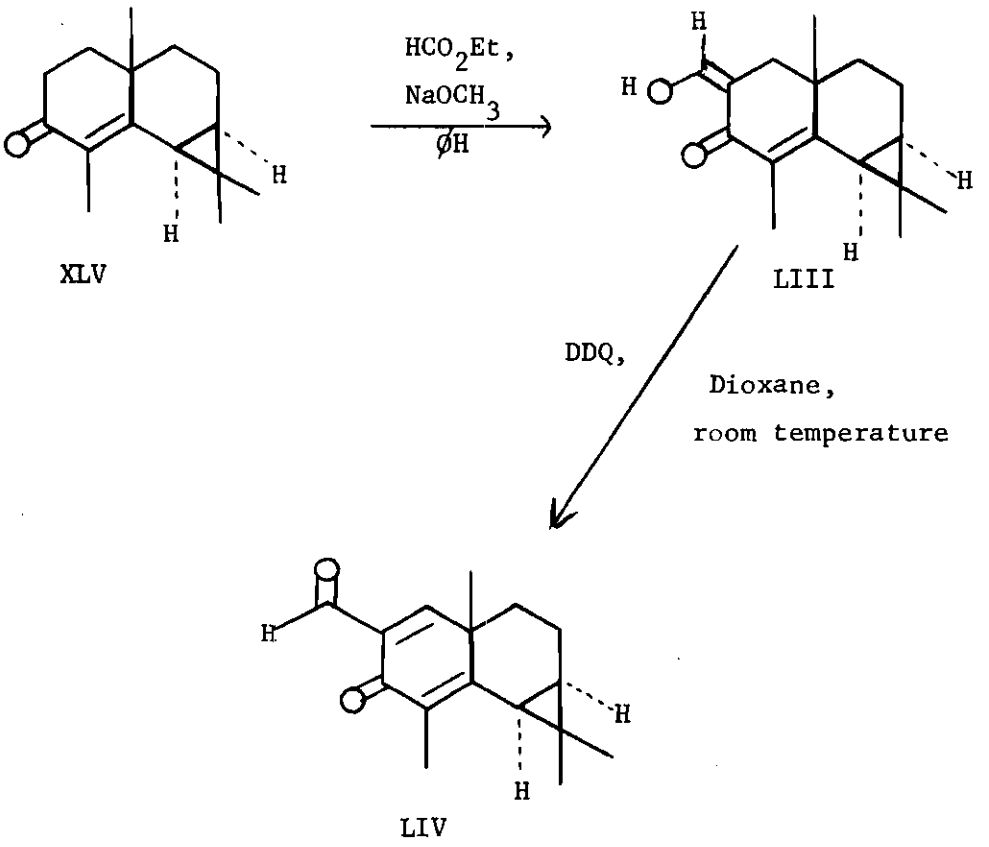
XLV

Scheme 17

The structural assignment of XLV was based on a comparison of its properties [ir, nmr, ms, optical rotation, and glc behavior (Column A)]

with a sample of (-)-epimaalienone prepared by the method of Ourisson [15].

The next step to be attempted was the preparation of the carboxy dienone (XXXV), since its epimer (XXVIII) (Scheme 6) was known to be photochemically labile. The 2-formyl dienone (LIV) was prepared (Scheme 18) in a straightforward manner by formylation of (-)-epimaalienone and oxidation with DDQ in dioxane.

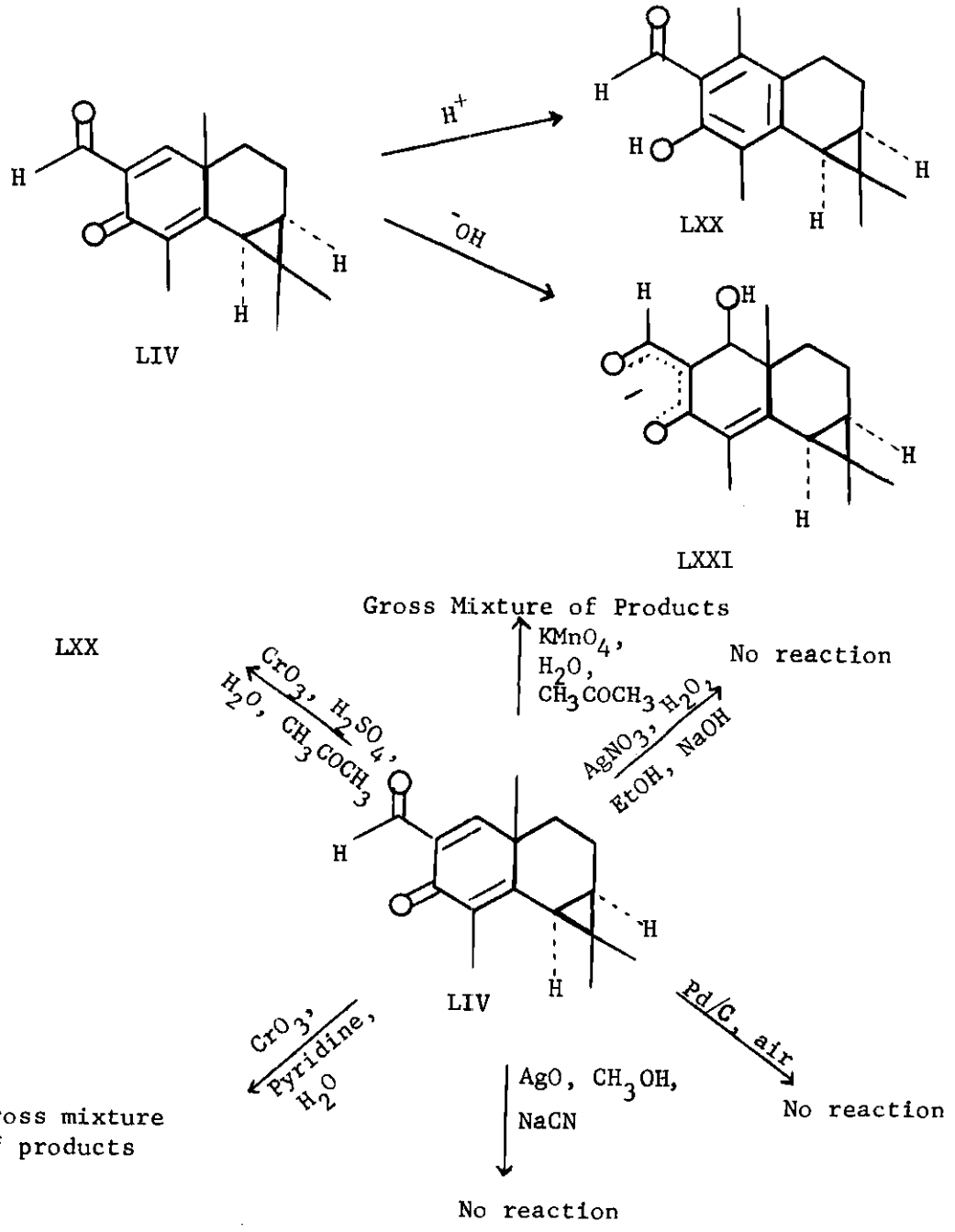


Scheme 18

Compound LIV exhibited nmr absorptions at 1.11 (s, 3H), 1.13 (s, 3H), 1.20 (s, 3H), 1.92 (s, 3H), 7.58 (s, 1H), and 10.20 ppm (s, 1H), and ir absorptions at 1701, 1650, and 1621 cm^{-1}.

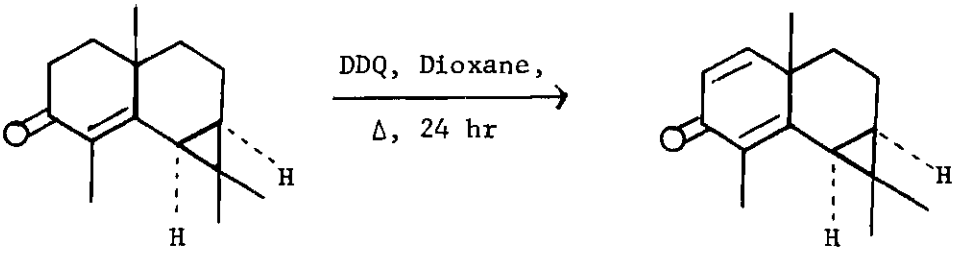
Attempts to oxidize LIV to the acid (XXXV), by a number of differ-

ent procedures (see 21a through g and Scheme 19), proved unsuccessful. This was primarily due to the fact that basic conditions rendered the formyl dienone inactive and acidic conditions caused the dienone-phenol rearrangement to proceed instead of the desired oxidation.



Scheme 19

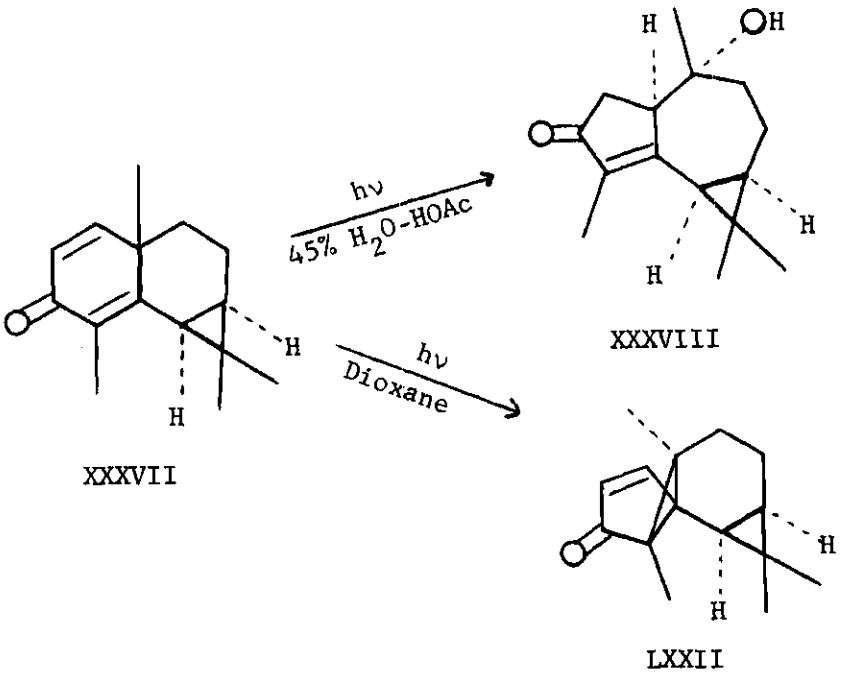
Due to the difficulty encountered in this aldehyde oxidation, it was decided to prepare the unsubstituted dienone (XXXVII) by DDQ oxidation of (-)-epimaalienone. When this was attempted dienone XXXVII was isolated as the only product in 56% yield.



XLV XXXVII

Dienone XXXVII exhibited uv absorptions at 244 (ε 10,400) and 305 nm (ε 8,400). The unusually long wavelength absorption at 305 nm is due to the dimethylcyclopropane group extending the conjugation of the dienone and making the $\pi \rightarrow \pi^*$ transition a more favorable process. Dienone XXXVII also exhibited nmr absorptions at 1.14 (s, 6H), 1.24 (s, 3H), 1.84 (s, 3H), 6.08 (d, J=10.0 Hz, 1H), and 6.78 ppm (d, J=10 Hz, 1H). The doublets at 6.08 and 6.78 ppm can be attributed to the hydrogens at C-2 and C-1, respectively. This compound also exhibited ir absorptions at 1654, 1622, and 1585 cm^{-1}.

When (-)-dehydroepimaalienone was irradiated in 45% aqueous acetic acid, hydroazulene XXXVIII was isolated in 48% yield. Irradiation of the dienone in dioxane with a low pressure lamp afforded lumiproduct LXXII in 52% yield.



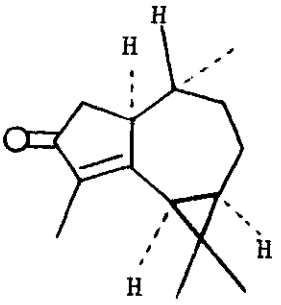
XXXVII

XXXVIII

LXXII

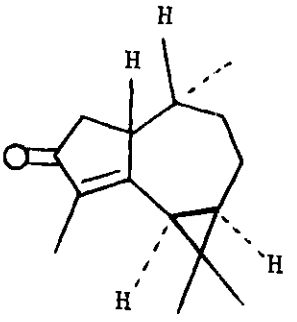
Scheme 20

The hydroazulene (XXXVIII) exhibited a single uv absorption at 251 nm (ε 11,300). This value is consistent with the alpha orientation of the hydrogen at C-1, which Büchi [25] points out in his synthesis of epi-cyclocolorenone (LXXIII).



LXXIII

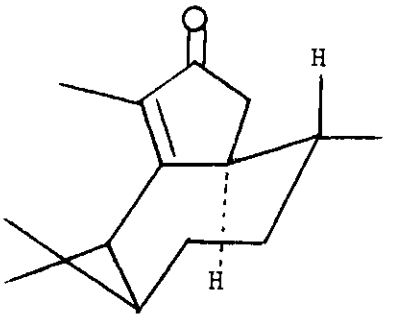
uv λ_{max} 253 nm



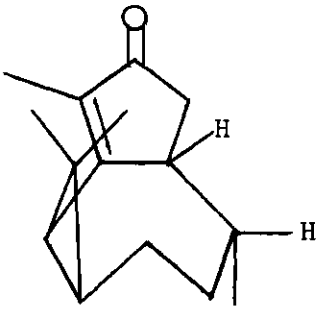
XXX

uv λ_{max} 262 nm

In the case of cyclocolorenone (XXX) the seven-membered B ring assumes a boatlike conformation which allows for good overlap of the cyclopropane ring with the π system due to the fact that the hydrogen at C-1 is beta. This is not the case in epi-cyclocolorenone (LXXIII) and therefore the shorter wavelength absorption is present.

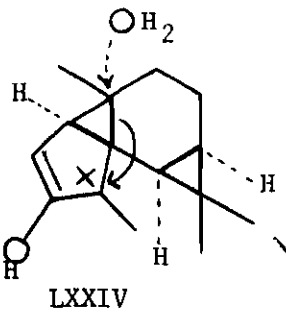


LXXIII

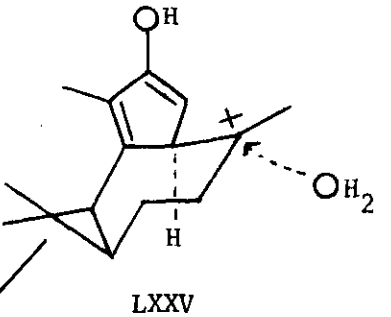


XXX

The assignment of the beta configuration of the methyl group at C-10 in the photoproduct was based upon the premise that concerted attack by water on the protonated mesoionic intermediate (LXXIV) would occur with inversion of configuration or that attack of water would take place from the less sterically hindered equitorial position of the carbonium ion (LXXV) resulting from cleavage of the cyclopropyl intermediate.

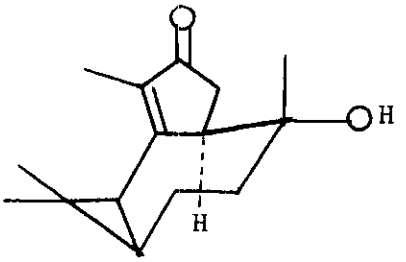


LXXIV



LXXV

XXXVIII

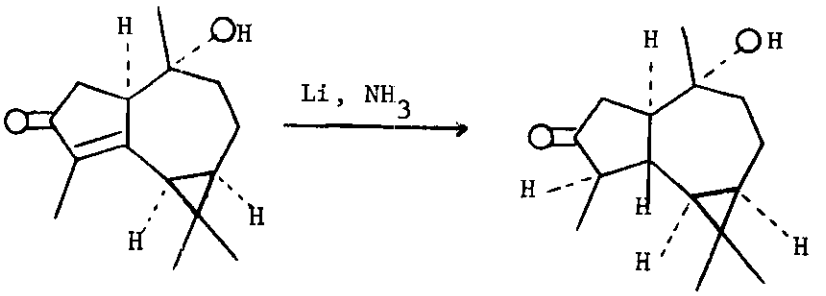


XXXVIII

Compound XXXVIII exhibited nmr absorptions at 0.80 (s, 3H), 0.92 (s, 3H), 1.18 (s, 3H), 1.68 (d of d, J=2.0 Hz, 3H), and 4.90 ppm (broad absorption, 1H) and ir absorptions at 3420, 1700, and 1628 cm^{-1}.

The lumiproduct (LXXII) generated by photolysis in dioxane exhibited uv absorptions at 220 (ε 5,450) and 280 nm (ε 2,490). This compound also showed nmr absorptions at 0.98 (s, 3H), 1.03 (s, 3H), 1.12 (s, 3H), 1.38 (s, 3H), 5.84 (d, J=6.0 Hz, 1H), and 7.34 ppm (d, J=6.0 Hz, 1H) and ir absorptions at 1695 and 1651 cm^{-1}.

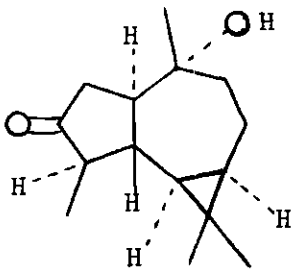
In order to convert photoproduct XXXVIII to (-)-globulol, a stereospecific reduction of the 4,5 double bond was required. When XXXVIII was reduced with lithium in liquid ammonia, hydroxy ketone LXXVI was produced in 97% yield.



XXXVIII LXXVI

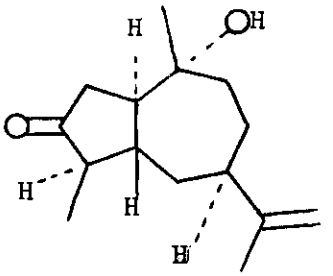
Compound LXXVI exhibited nmr absorptions at 0.99 (s, 3H), 1.06 (d, J=6.5 Hz, 3H), 1.09 (s, 3H), and 1.12 ppm (s, 3H) and ir absorptions at 3600, 3420, and 1740 cm^{-1}.

At this stage it appeared desirable to investigate the configuration of the bridgehead hydrogen at C-5. Piers [9b] had reported that compound LI exhibited a large (16,000) negative cotton curve which was indicative of a trans ring juncture. Examination of the ord curve of compound LXXVI also indicated a large (12,600) negative cotton curve.



LXXVI

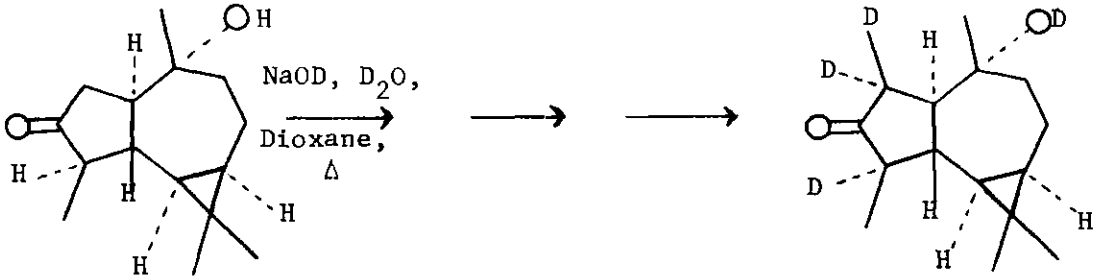
Amplitude = - 12,600



LI

Amplitude = - 16,000

Additionally, compound LXXVI was subjected to three deuterium exchanges. Examination of the mass spectrum of the exchanged material indicated 81% of the material had four hydrogens replaced by deuterium.

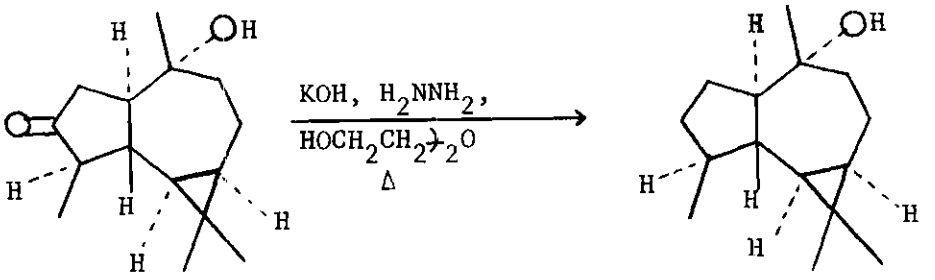


LXXVI

LXXVII

Examination of the nmr spectrum of LXXVII with the aid of europium nmr shift reagent [26] indicated the hydrogen at C-1 was split into a doublet with J=11.2 Hz. This large coupling constant should be indicative of a trans ring juncture [27] since the dihedral angle between the hydrogen at C-1 and C-5 would be between 150 and 170°. If the ring juncture were cis, the dihedral angle would be between 30 and 60° and this would lead to a coupling constant of 4-6 Hz. The stereochemistry of the methyl group at C-4 was unambiguously determined through subsequent transformations. However, the failure of this compound to form a mixture of C-4 isomers on heating with base indicated the more thermodynamically stable β-methyl isomer had been produced. Additionally, the presence of only fifteen absorptions in the C^{13} nmr spectrum of LXXVI indicated the absence of any α-methyl isomer which might have been produced in the lithium ammonia reaction. This result is consistent with the findings of Piers (Scheme 10) in a similar case [9b].

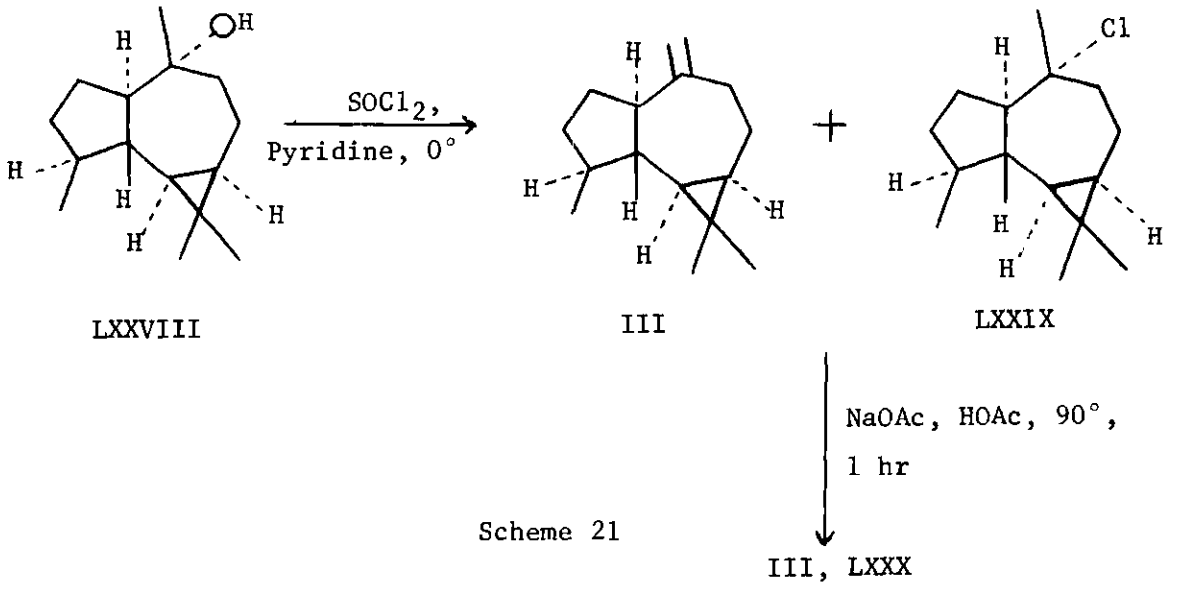
Treatment of hydroxy ketone LXXVI with potassium hydroxide and hydrazine in diethylene glycol cleanly converted this material into (-)-4-epiglobulol (LXXVIII) in 55% yield.



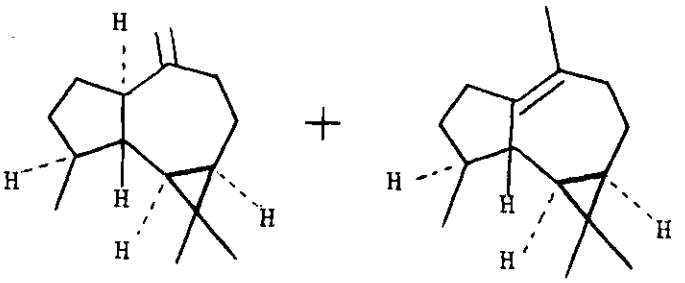
LXXVI LXXVIII

Comparison of the spectral properties (nmr and ir) and glc behavior (Column A) of LXXVIII with an authentic sample of naturally occurring (-)-globulol (II) indicated small but distinct differences. Compound LXXVIII exhibited nmr absorptions at 0.94 (d, J=5.9 Hz, 3H), 0.96 (s, 3H), 1.02 (s, 3H), and 1.09 ppm (s, 3H) and an ir absorption at 3600 cm^{-1}.

Treatment of (-)-4-epiglobulol (LXXVIII) with thionyl chloride in pyridine at 0°, followed by refluxing the crude reaction mixture with sodium acetate in acetic acid in order to dehydrochlorinate the tertiary halide which had formed, afforded an oil in 55% yield which contained a 75:25 mixture of two olefins. The major component was collected by preparative glc (Column C) and exhibited spectral properties (ir and nmr) and an optical rotation (opposite sign) which were identical to (-)-4-epiaromadendrene (III) that was prepared by Büchi [5] by a different route (Scheme 1). The minor component of the reaction exhibited nmr abosrptions at 1.01 (d, J= 6 Hz, 3H), 1.05 (s, 3H), 1.10 (s, 3H), and 1.60 ppm (broad s, 3H) which were consistent with the proposed structure (LXXX).



Scheme 21

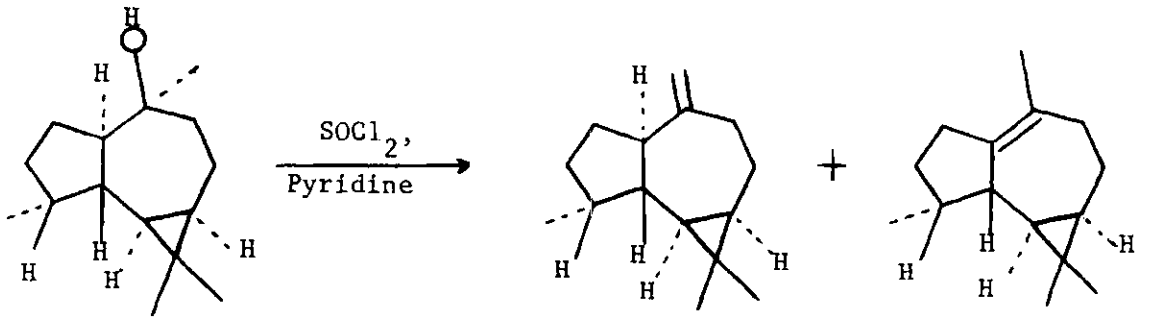


III : LXXX

75 : 25

Scheme 21 (Continued)

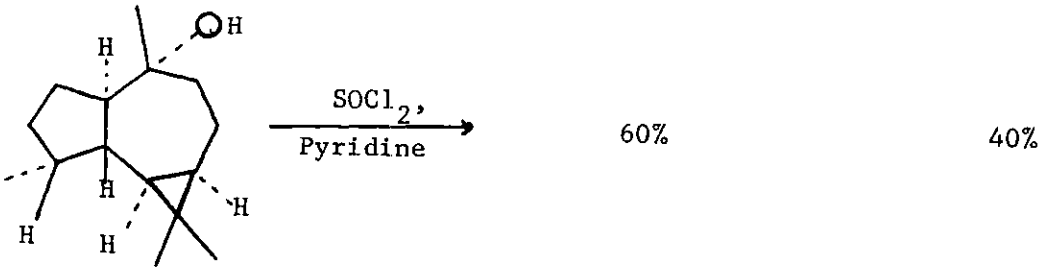
Sorm and co-workers [28] investigated the dehydration of ledol (LXXXI) and (-)-globulol (II) and found that ledol gives 20% aromadendrene (I) while (-)-globulol gives 60% aromadendrene.



LXXXI

I 20%

LXXXII 80%



II

60%

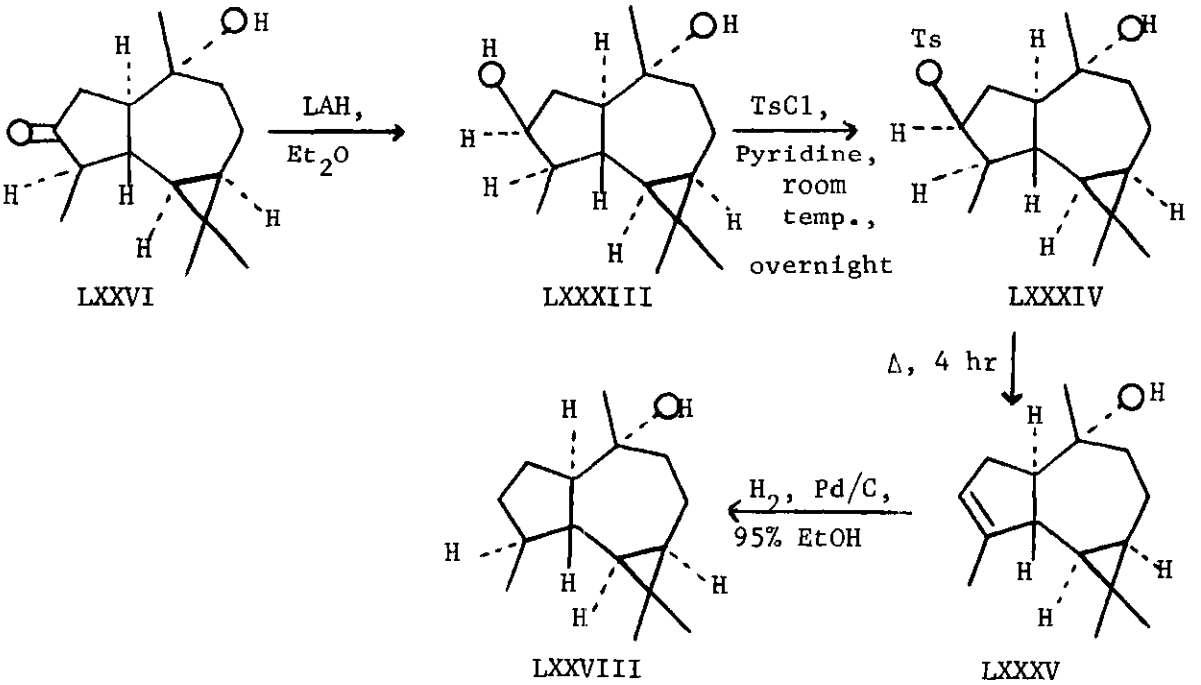
40%

Scheme 22

Based on these dehydration studies and the conversion of LXXVIII into (+)-4-epiaromadendrene (III), compound LXXVIII must have the absolute stereochemistry at assymetric centers C-1, C-4, C-5, C-6, C-7, and C-10 as postulated.

It was now decided to attempt the conversion of XXXVIII or LXXVI to naturally occurring (-)-globulol (II) by controlling the orientation of the methyl group at C-4 in some manner.

The first attempt involved reducing the hydroxy ketone LXXVI to the diol LXXXIII with lithium aluminum hydride. The diol was reacted with p-toluenesulfonyl chloride to produce the monotosylate LXXXIV which underwent elimination in situ to the olefin LXXXV. Hydrogenation of this olefin gave only 4-epiglobulol (LXXVIII) as determined by glc comparison with authentic samples of (-)-4-epiglobulol and (-)-globulol.

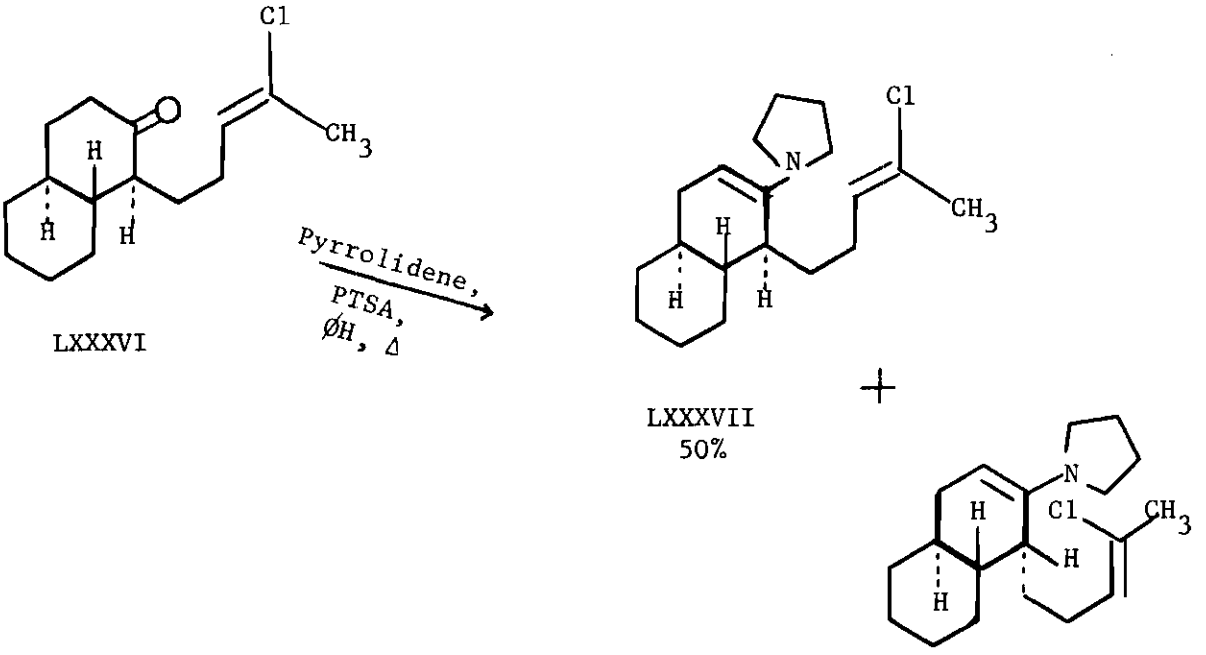


Scheme 23

Compound LXXXIII exhibited ir absorptions at 3600 and 3400 cm^{-1} and an nmr absorption at 3.65 ppm (q, J=8.0 Hz, 1H) which was characteristic of the carbinyl hydrogen at C-3. Compound LXXXV exhibited ir absorptions at 3600 and 3400 cm^{-1} and no absorptions (ir and nmr) were noted which could be attributed to a sulfonate ester.

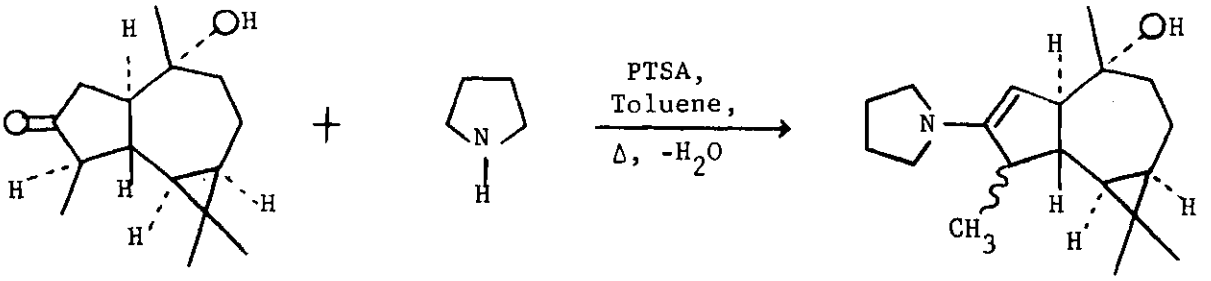
The second approach to the synthesis of (-)-globulol from the hydroxy ketone (LXXVI) involved the preparation of the pyrrolidene enamine (LXXXIX).

It has been reported [29] that the more thermodynamically stable, alpha substituted ketone can often be converted to its less stable epimer by preparing the pyrrolidene enamine. This is the result of the present steric interactions between the alpha substituent and the pyrrolidene ring in the enamine derivative. Lansbury [29a] has reported applying such a technique in the equilibration of alpha substituted decalones (Scheme 24).



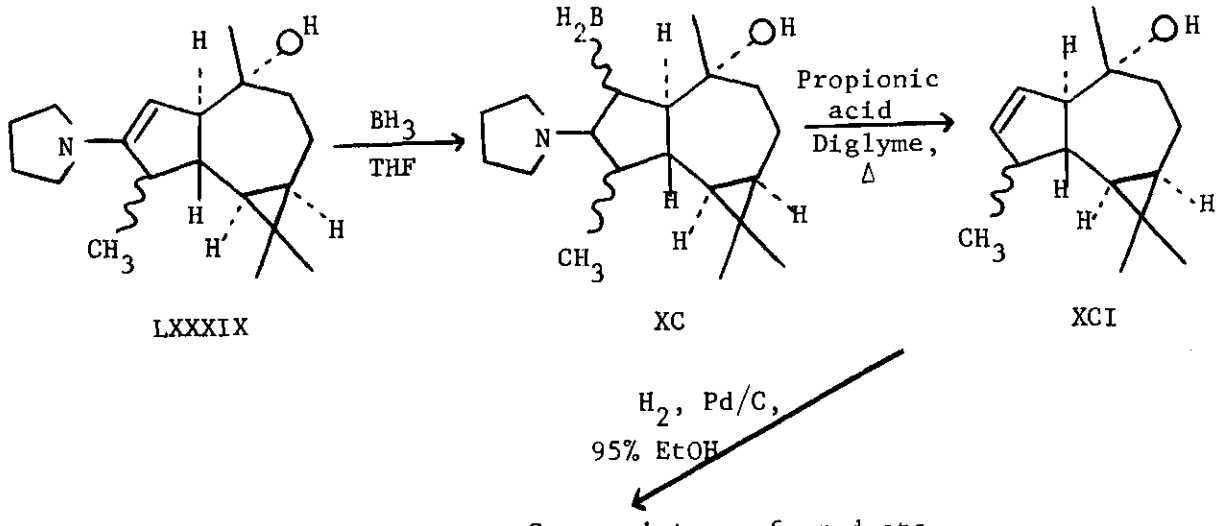
Scheme 24

Compound LXXVI was heated with pyrrolidene, toluene, and p-toluenesulfonic acid overnight with the azeotropic removal of water. Examination of the ir spectrum of the crude product indicated no significant absorption at 1740 cm^{-1}.



LXXVI LXXXIX

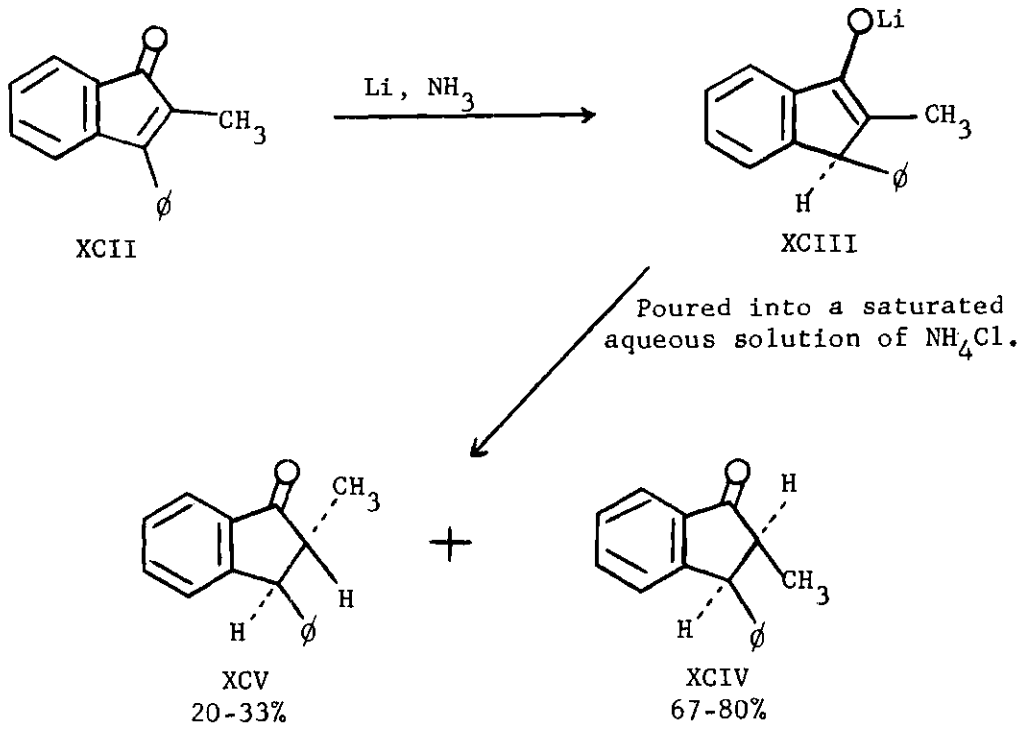
The crude enamine LXXXIX was treated with borane in tetrahydrofuran [30] to reduce the 2,3 double bond and the crude 3-amino, 2-borane (XC) was refluxed with propionic acid in diglyme. The crude material (XCI) from this reaction was hydrogenated and the product was subjected to glc analysis which indicated the absence of (-)-4-epiglobulol or (-)-globulol as determined by comparison with authentic samples.



LXXXIX XC XCI

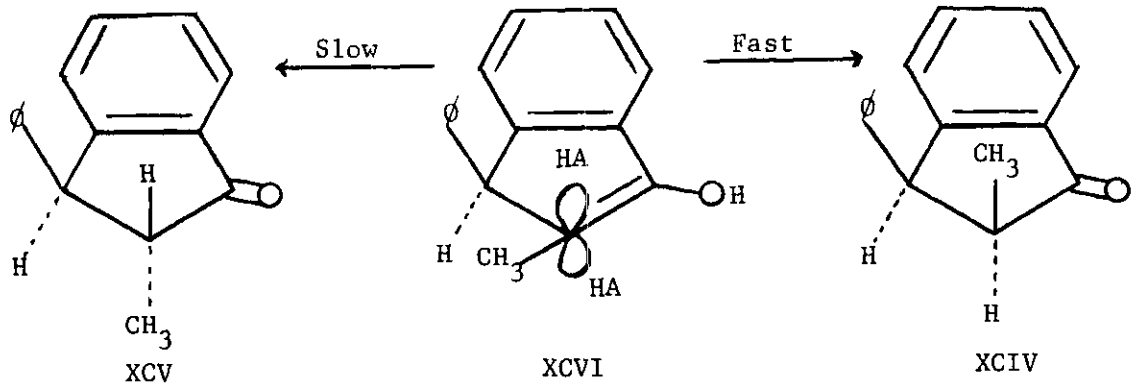
Scheme 25

Zimmerman [31] has reported obtaining the less stable cis-2-methyl-3-phenylindanone (XCIV) by a kinetic quenching of the enolate obtained by the lithium in liquid ammonia reduction of the corresponding α,β-unsaturated ketone (XCII).



Scheme 26

Zimmerman's explanation of this ratio of isomers is based upon ketonization of the enol (XCVI) taking place faster from the less sterically hindered side of the molecule.

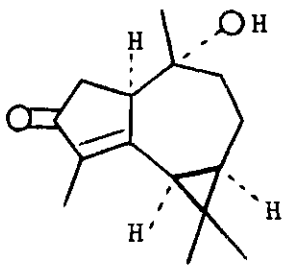


It was therefore expected that applying such a technique to the lithium in liquid ammonia reduction of XXXVIII would afford the less stable cis isomer.

After carrying out this reaction, the product (XCVIII) was reduced with lithium aluminum hydride to prevent possible isomerization to the more stable trans isomer. The crude product (XCIX) of this reaction exhibited ir absorptions at 3400 and 3600 cm^{-1} and an nmr absorption at 3.65 ppm (q, J=8.0 Hz, 1H), which was characteristic of the carbinyl hydrogen at C-3. This diol (XCIX) was treated with p-toluenesulfonyl chloride in pyridine and the monotosylate (C) was obtained. This material exhibited ir absorptions at 3600, 3400, 1380, and 1180 cm^{-1} and nmr absorptions at 4.20 (q, J=8.0 Hz, 1H), 7.20-8.00 (m, 4H), and 2.41 ppm (s, 3H). This material was refluxed overnight with lithium aluminum hydride in tetrahydrofuran and the crude product was subjected to glc analysis. The result of this analysis was that (-)-4-epiglobulol had been produced as the major product without any detection of (-)-globulol as determined by comparison with authentic samples.

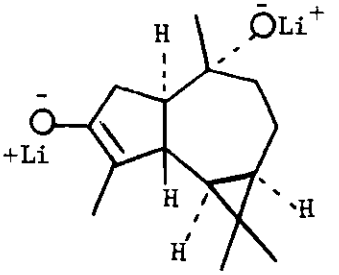
The lithium in liquid ammonia reaction was repeated on compound XXXVIII by a modified procedure. After the reduction was completed, the ammonia was removed and the residue was dissolved in tetrahydrofuran and added dropwise to a mixture of acetic acid, water, and pentane. After work up of the reaction mixture and analysis of the crude product by glc (Column A) and nmr spectroscopy, the presence of the 4β-methyl isomer was established and none of the 4α-methyl isomer was observed.

Herout [32] has reported the conversion of cyclocolorenone (XXX) to aromadendrane (CI) by catalytic hydrogenation with platinum oxide in acetic acid.



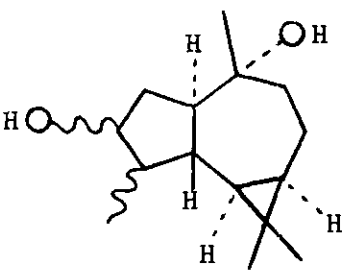
XXXVIII

Li, NH_3



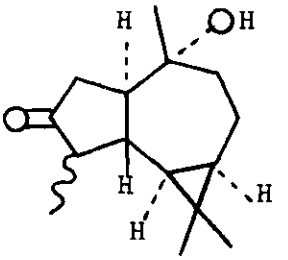
XCVII

poured into a saturated aqueous solution of NH_4Cl



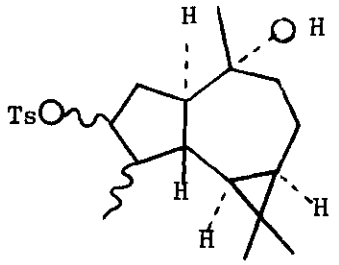
XCIX

LAH, Et_2O



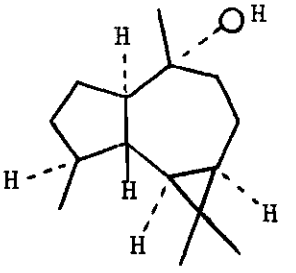
XCVIII

TsCl, Pyridine



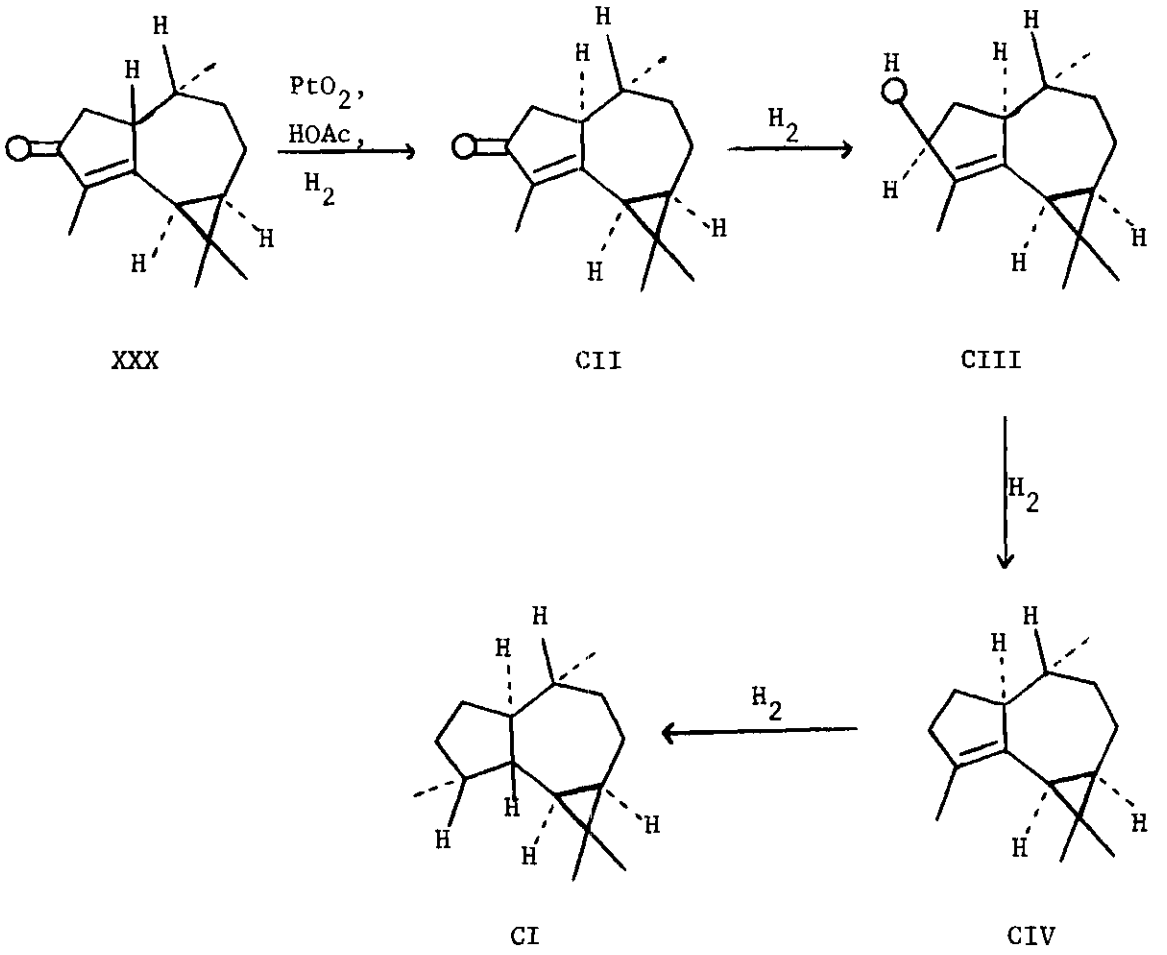
C

LAH, THF, Δ



LXXVIII

Scheme 27

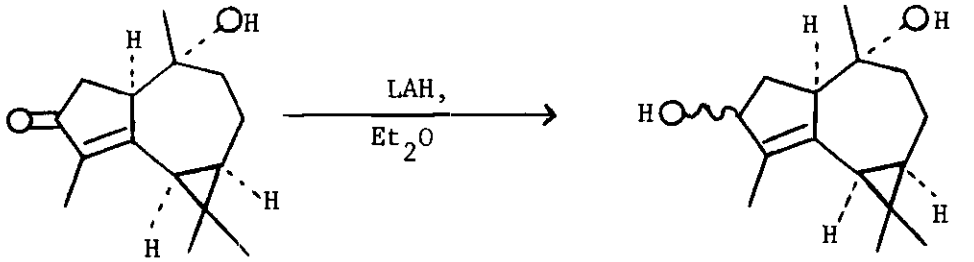


XXX CII CIII

CIV CI

Scheme 28

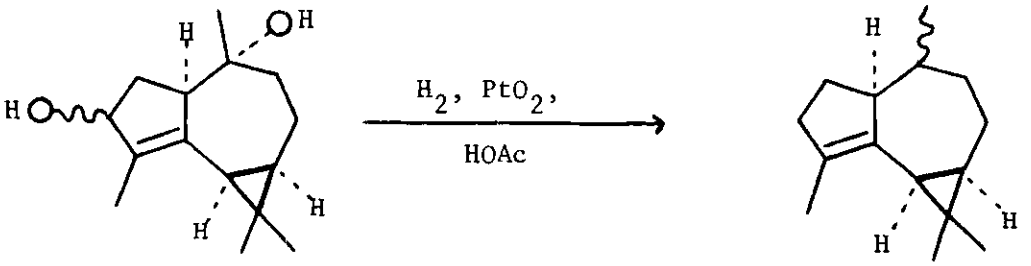
It was hoped that by applying such a procedure to photoproduct XXXVIII, (-)-globulol would be produced. When compound XXXVIII was hydrogenated under these conditions at 40 psi for 3 hr, no reaction was observed. Since an allylic alcohol (CIII) was presumed to be an intermediate in the hydrogenation of cyclocolorenone, compound XXXVIII was reduced with lithium aluminum hydride.



XXXVIII CV

Compound CV exhibited ir absorptions at 3600 and 3420 cm^{-1} and nmr absorptions at 0.90 (s, 3H), 0.95 (s, 3H), 1.10 (s, 3H), 1.70 (broad s, 3H), and 4.71 ppm (broad m, 1H).

When compound CV was hydrogenated with platinum oxide in acetic acid, compound CVI was produced as the major product without any trace of (-)-globulol or (-)-4-epiglobulol as determined by glc and ms analyses.



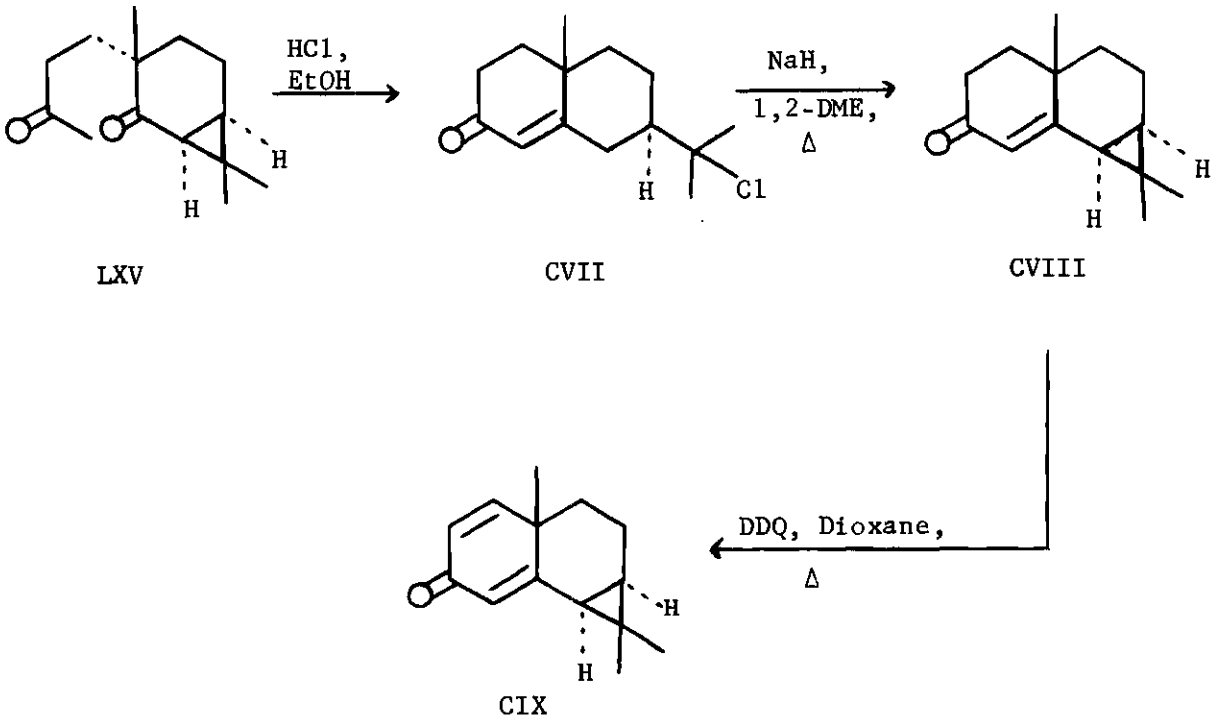
CV CVI

The formation of CVI as the major product indicated that hydrogenolysis of the allylic alcohol and the homoallylic alcohol groups was occurring faster than the reduction of the 4,5 double bond. These conclusions established this procedure as unsuitable for the preparation of (-)-globulol.

Since the preceding experiments were unsuccessful in converting either XXXVIII or LXXVI to (-)-globulol, the synthesis and photolysis of 4-normethyl-1,2-dehydroepimaalienone was undertaken so that the C-4 methyl

group in (-)-globulol might be added in the proper orientation at a later stage in the synthesis.

The synthesis of 4-normethyl-1,2-dehydroepimaalienone was carried out in a sequence of reactions identical to that employed in the synthesis of (-)-1,2-dehydroepimaalienone with the exception that methyl vinyl was substituted for ethyl vinyl ketone in the Michael reaction.



LXV CVII CVIII CIX

Scheme 29

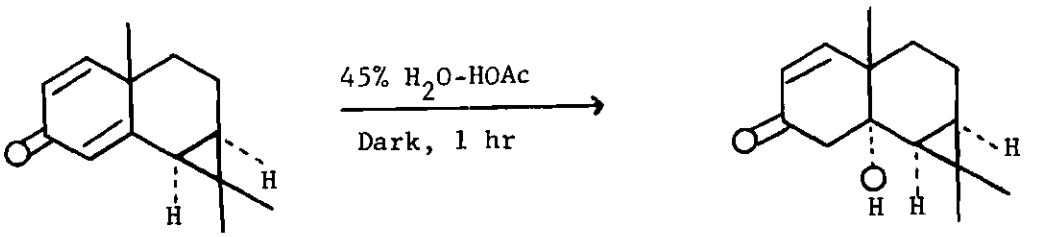
Compound CVII exhibited a uv absorption at 239 nm (ε 20,600) and nmr absorptions at 1.25 (s, 3H), 1.60 (s, 6H), and 5.65 ppm (broad s, 1H). Absorptions in the ir were observed at 1675 and 1620 cm^{-1}.

Compound CVIII exhibited a uv absorption at 277 nm (ε 18,200) which is characteristic of the enone group conjugated with a cyclopropane ring. Absorptions in the nmr were observed at 1.10 (s, 3H), 1.16 (s, 3H),

1.20 (s, 3H), and 5.86 ppm (s, 1H), and in the ir at 1663 and 1592 cm^{-1}.

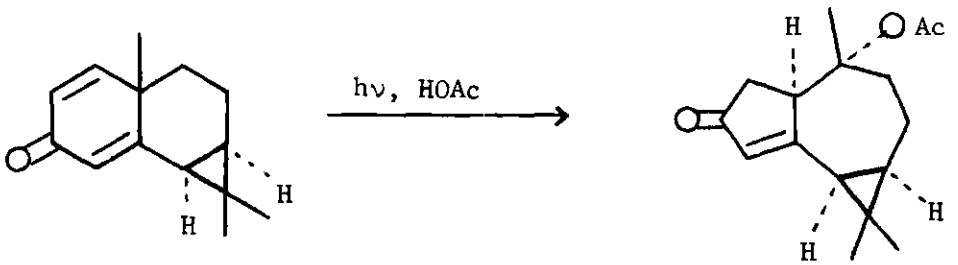
Compound CIX exhibited uv absorptions at 243 (ε 10,000) and 303 nm (ε 8,600) and nmr absorptions at 1.14 (s, 6H), 1.23 (s, 3H), 6.15 (m, 2H), and 6.76 ppm (d, J=10.0 Hz, 1H). Absorptions in the ir were observed at 1660, 1622, and 1588 cm^{-1}.

When 4-normethyl-1,2-dehydroepimaalienone (CIX) was dissolved in 45% aqueous-acetic acid, it was found that addition of water to the 4,5 double bond occurred and this solvent medium was ruled out for subsequent irradiations. The product of this hydration reaction exhibited nmr absorptions at 1.17 (s, 3H), 1.22 (s, 3H), 1.28 (s, 3H), 5.88 (d, J=10.0 Hz, 1H), and 6.68 ppm (d, J=10.0 Hz, 1H), and ir absorptions at 3460, 1670, and 1620 cm^{-1}.



CIX CX

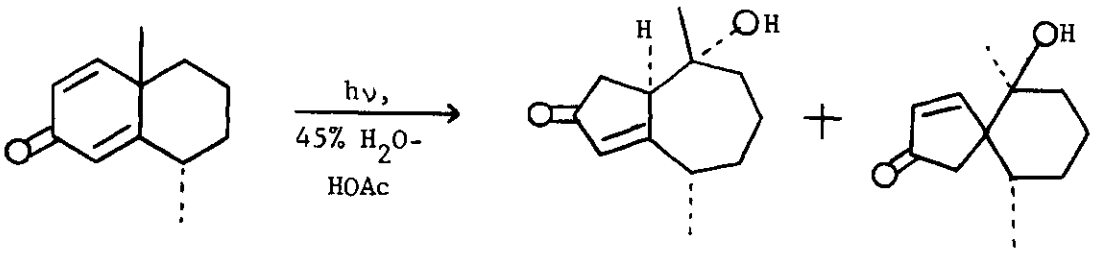
Compound CIX was irradiated in glacial acetic acid for 45 min and the 5,7-fused hydroxy acetate (CXI) was produced in 51% yield.



CIX CXI

Compound CXI exhibited a uv absorption at 241 nm (ε 11,800) and nmr absorptions at 1.00 (s, 3H), 1.15 (s, 6H), 1.98 (s, 3H), and 6.08 ppm (m, 1H). Absorptions in the ir were observed at 1712, 1688, and 1608 cm^{-1}.

The formation of CXI as the only major product of this reaction is noteworthy since Kropp and Erman [33] have reported finding equal amounts of spiro ketones (CXIV) and 5,7-fused ketones (CXIII) upon irradiation of C-4 unsubstituted dienones (CXII) in protic solvents.



CXII CXIII CXIV

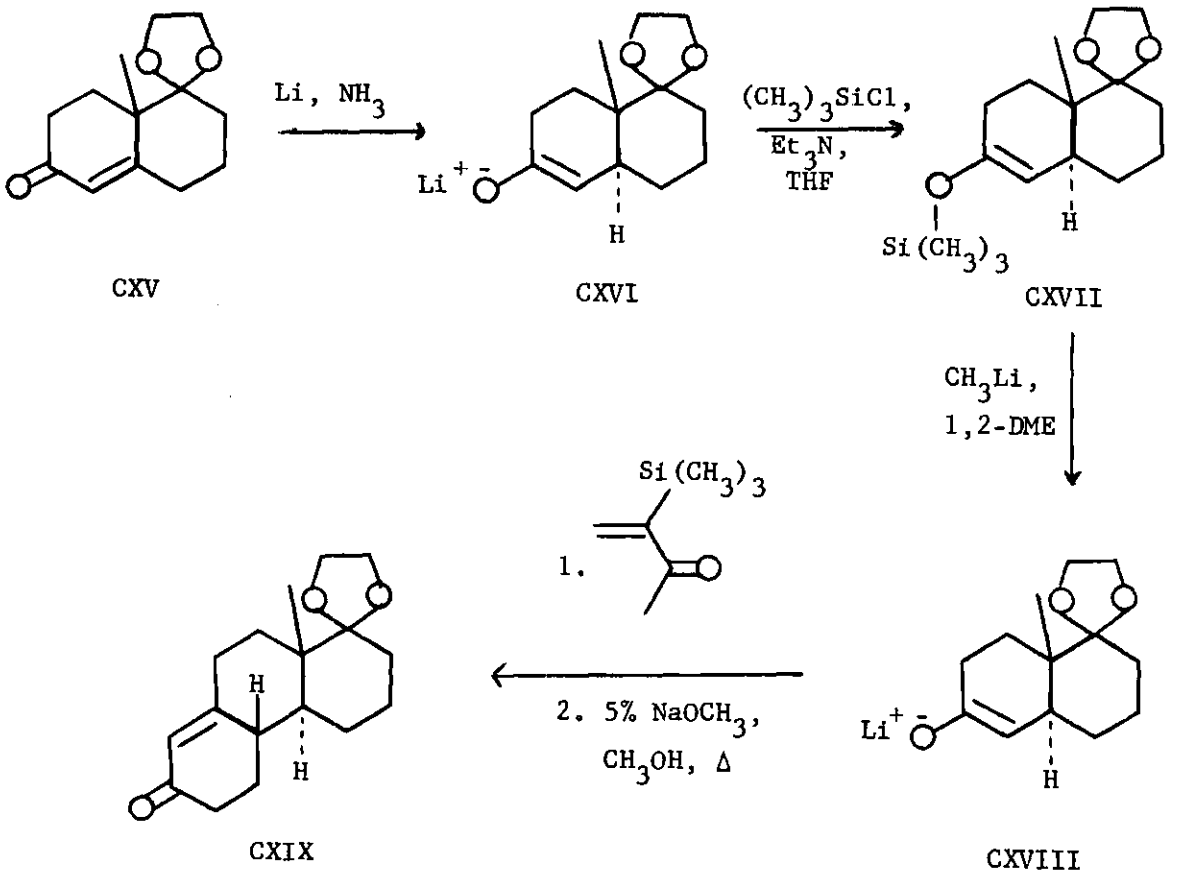
Apparently in the photochemically produced intermediate analogous to LXXIV, attack of acetic acid occurs exclusively from the backside of C-10 because of the presence of the dimethylcyclopropane ring.

Consequently, the dimethylcyclopropane group attached to ring B of the dienone (CIX) must be the determining factor in this selective behavior.

In order to convert compound CXI to (-)-globulol it would be necessary to reduce the 4,5 double bond and add a methyl group at C-4 in a stereospecific manner.

Stork [34] and co-workers have reported the reductive-silylation of α,β-unsaturated cyclohexenones and the subsequent use of these silyl-enol ethers in carbon-carbon bond forming reactions at the alpha carbon

atom.

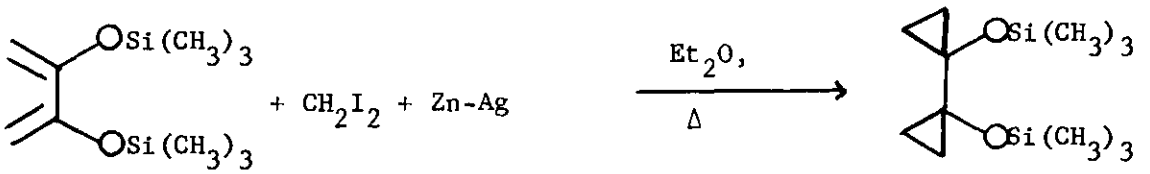


CXV CXVI CXVII

CXIX CXVIII

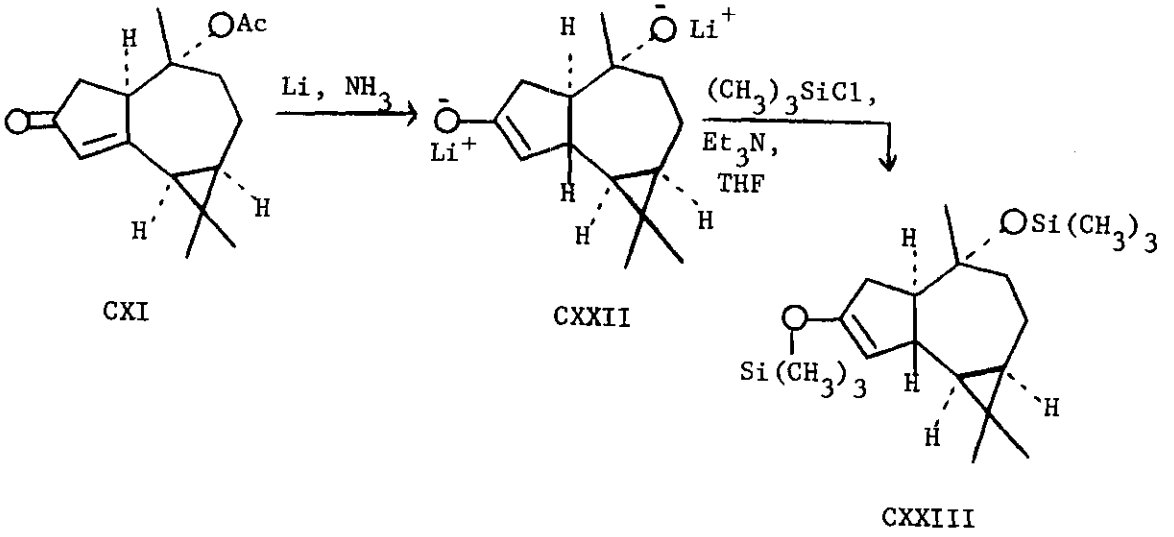
Scheme 30

It was hoped that such a procedure would be an efficient means of trapping the enolate anion (CXXII) which would be produced in the lithium ammonia reduction of compound CXI. The resulting silyl-enol ether (CXXIII) could then be used in a methylation step or a cyclopropanation step as Conia [35] has carried out.

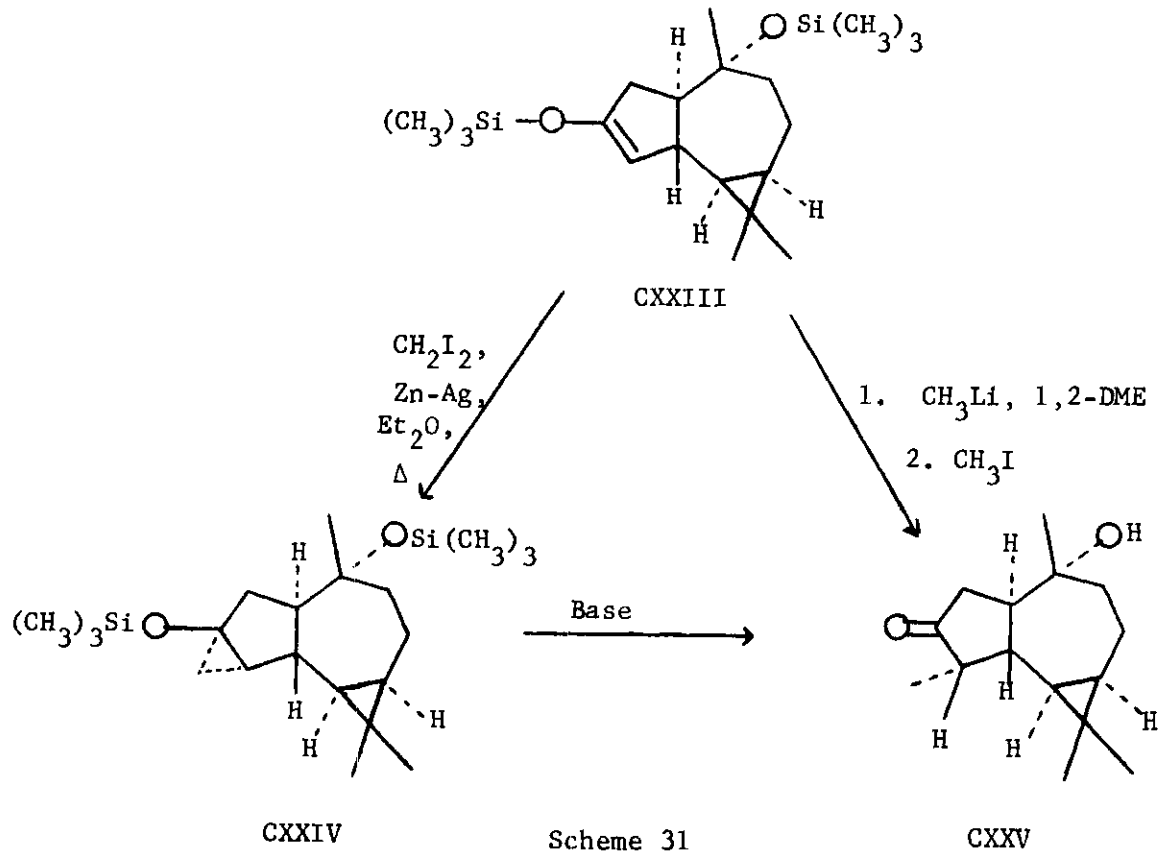


CXX CXXI

The resulting cyclopropyl-silyl ether could then be opened with base to generate a methyl group at the alpha position. Scheme 31 represents the proposed sequence of reactions as applied to keto acetate CXI.



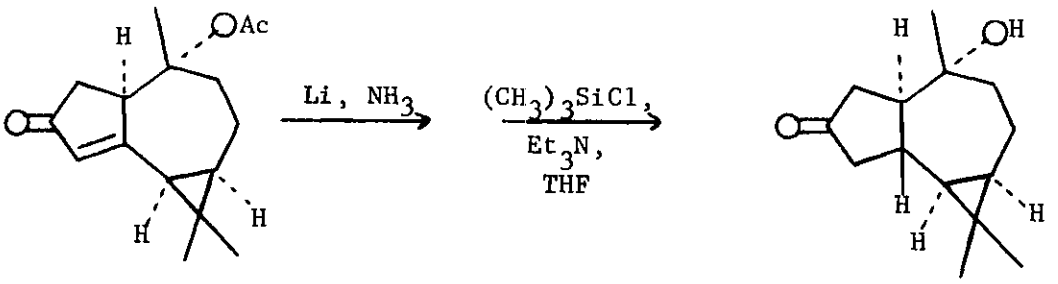
CXI CXXII CXXIII



CXXIII

CXXIV Scheme 31 CXXV

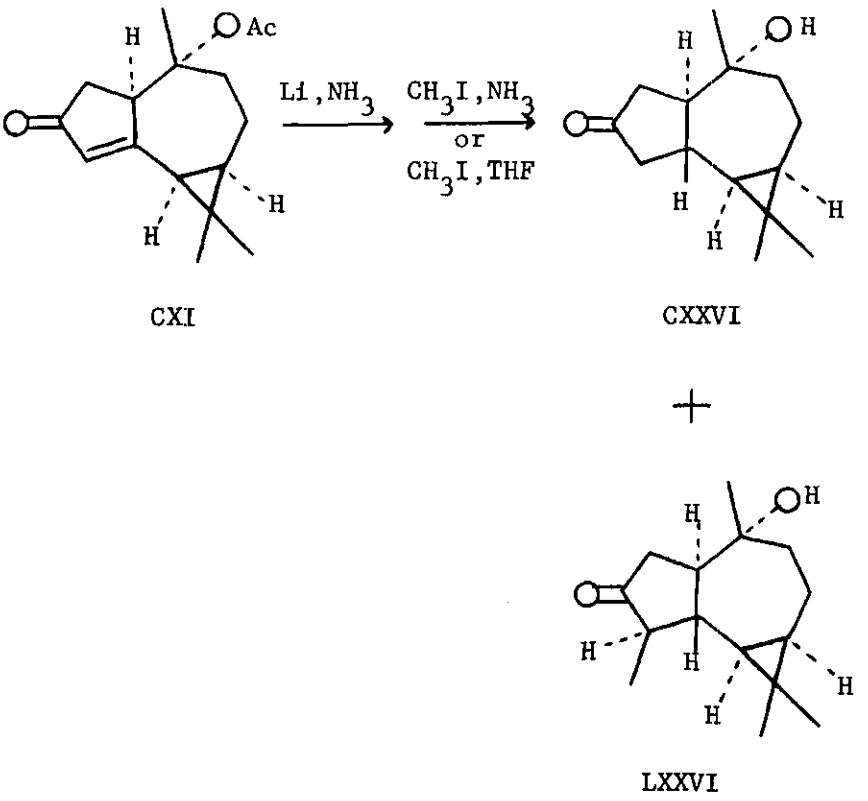
When such a sequence was attempted on compound CXI only the saturated ketone could be detected as determined by its intense absorption at 1742 cm^{-1} in the ir.



CXI CXXVI

The inability to obtain the silyl-enol ether in this case was probably due to the combination of a small scale reaction (< 50 mg of compound CXI was used) and small amounts of residual ammonia reacting with the silyl halide. In addition, although the successful application of such a trapping procedure has been demonstrated in the case of octalones (CXV), the nature of such a reaction as applied to hydroazulenones has not been determined.

Since the enolate anion CXXII produced in the lithium-ammonia reduction of compound CXI could not be trapped as the silyl ether, it was hoped that it could be alkylated *in situ* [36,34a] to give the α-methyl ketone. When this was attempted only partial alkylation (*ca* 30%) was observed and the β-methyl ketone was obtained with no significant amount of the α-methyl isomer being produced.



CXI

CXXVI

+

LXXVI

The crude reaction mixture exhibited ir absorptions at 3680, 3360, and 1742 cm^{-1}. The presence of compound LXXVI was determined by glc comparison with an authentic sample.

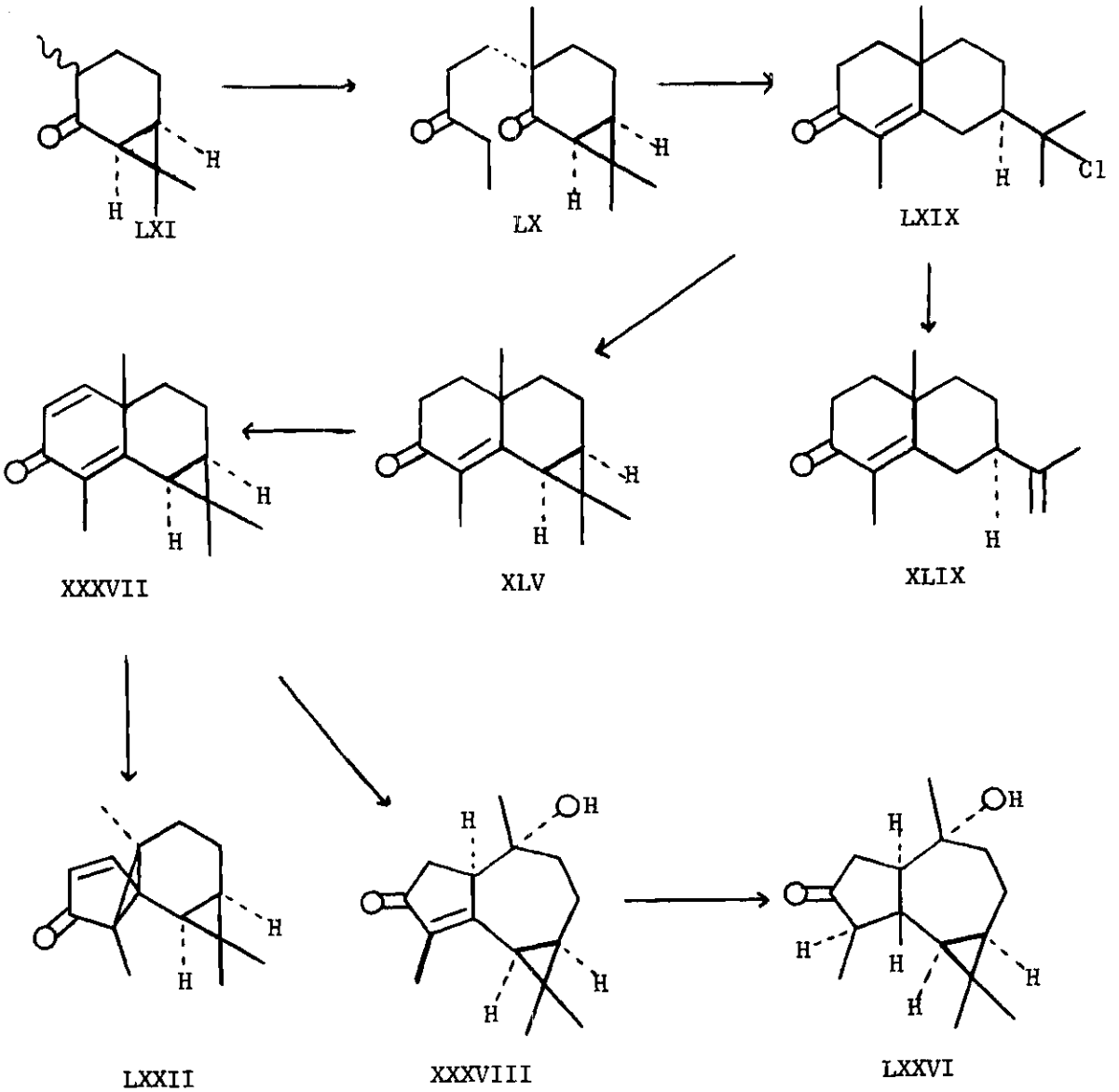
CHAPTER V

CONCLUSIONS

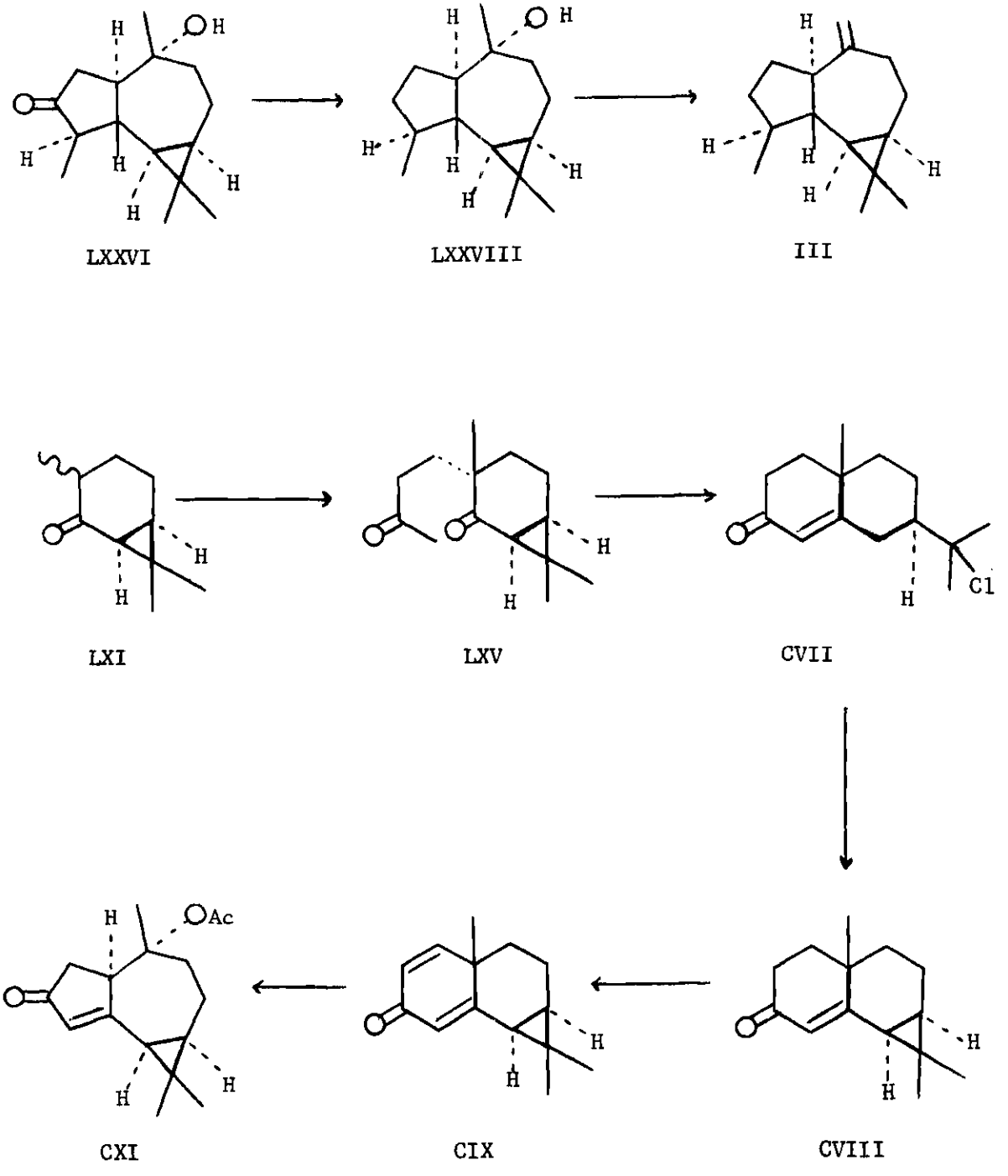
In attempting to prepare (+)-aromadendrene (I) and (-)-globulol (II), convenient stereospecific syntheses of (+)-α-cyperone (XLIX), (-)-epimaalienone (XLV), and 4-normethyl-epimaalienone (CVIII) were developed. The key step in their preparation involved the acid catalyzed cyclization of the appropriate 1,5-diketone (LX or LXV), which was prepared by the stereospecific Michael addition of (-)-2-carone (LXI) to methyl vinyl or ethyl vinyl ketone. The appropriate chloroenone (LXIX or CVII) obtained by this cyclization was either dehydrohalogenated to (+)-α-cyperone (XLIX) or cyclized with sodium hydride in 1,2-dimethoxyethane to the tricyclic α,β-unsaturated ketone (XLV or CVIII). The cross-conjugated dienones (XXXVII or CIX) were prepared by oxidation with DDQ and the photochemistry of (-)-dehydroepimaalienone (XXXVII) was studied in dioxane and aqueous acetic acid. The photoproduct (XXXVIII) from the aqueous acetic acid irradiation was converted to (-)-4-epiglobulol (LXXVIII) by lithium in liquid ammonia reduction and Wolf-Kishner reduction, respectively. The absolute stereochemistry of (-)-4-epiglobulol was determined by its dehydration with thionyl chloride to (+)-4-epiaromadendrane which was identical (nmr, ir, and optical rotation) with (-)-4-epiaromadendrene that had been prepared by Büchi and co-workers by a different route. The unsubstituted dienone (CIX) was successfully rearranged photochemically to the 5,7-fused acetoxy ketone (CXI) and several unsuccessful attempts

were made to convert either photoproduct XXXVIII or CXI to naturally occurring (-)-globulol.

The knowledge gained in this research should be useful in future syntheses of sesquiterpenes containing the aromadendrane or eudesmane skeletons.



Scheme 32

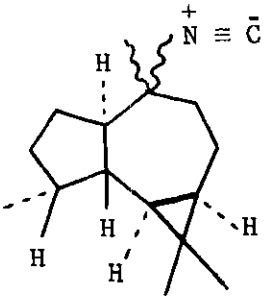


Scheme 32 (Continued)

CHAPTER VI

RECOMMENDATIONS

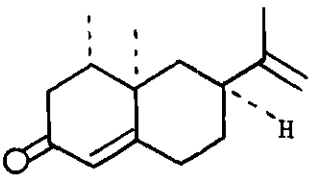
Since (+)-aromadendrene (I) and (-)-globulol (II) were not successfully prepared, additional methods should be explored for the conversion of compound XXXVII or CXI to these natural products. The information gained in this research should also be applied to a photochemical synthesis of axisonitrile-2 (CXXVII) which has been recently isolated [37] from the marine sponge Axinella cannabina.



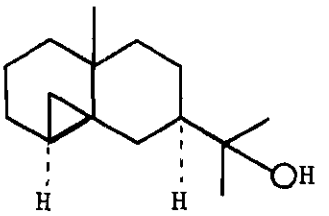
CXXVII

This would require the investigation of various solvent mediums for the irradiation of (-)-dehydroepimaalienone (XXXVII) in order that a group which was readily convertible to the isonitrile function could be attached during the photolysis step.

The information gained in this research may be applicable to syntheses of naturally occurring nootkatone (CXXVIII) and the recently isolated antibiotic [38], cycloeudesmol (CXXIX).

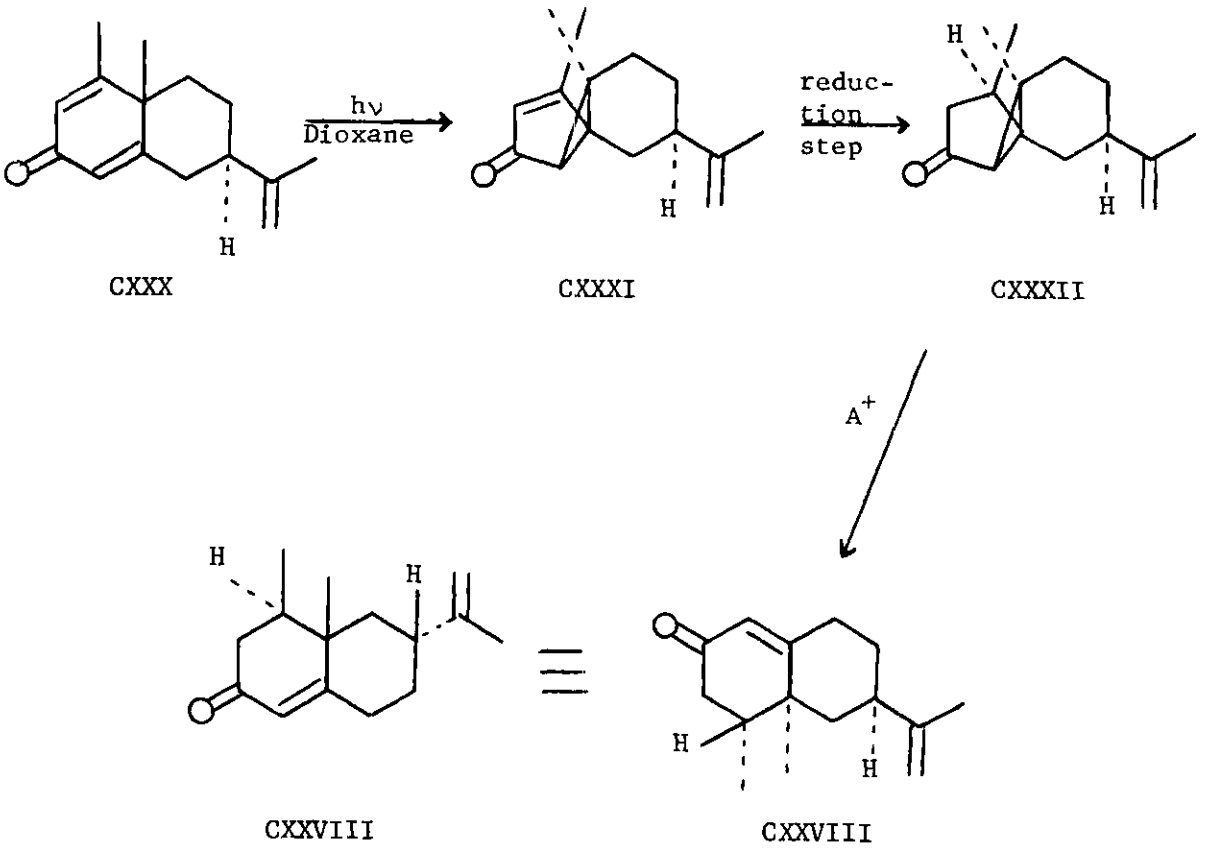


CXXVIII



CXXIX

The preparation of nootkatone (CXXVIII) by a sequence such as that illustrated in Scheme 33 may be possible. The synthesis of the dienone CXXX would be carried out along the lines described for the synthesis of (+)-α-cyperone.

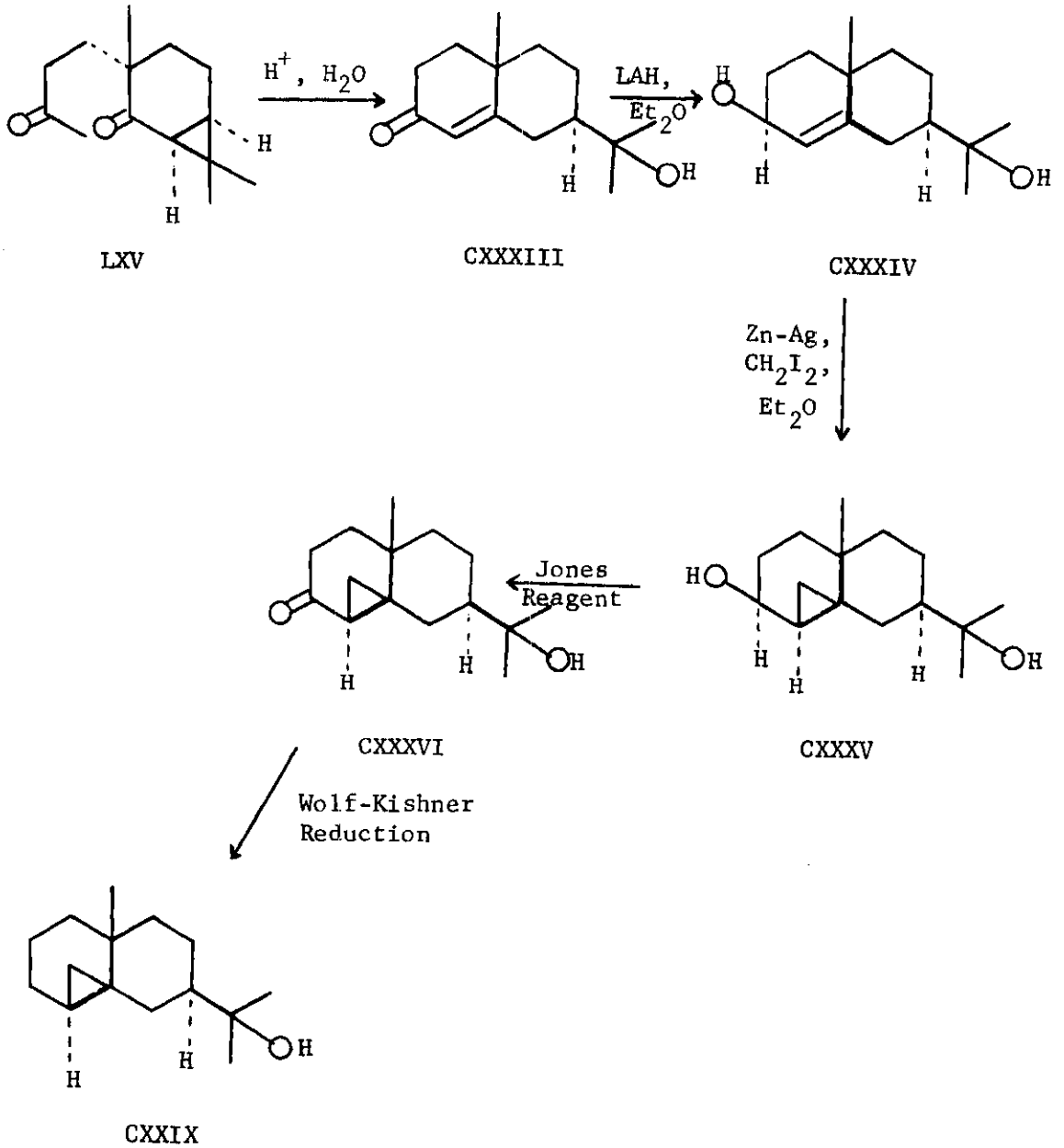


CXXX CXXXI CXXXII

CXXVIII CXXVIII

Scheme 33

The preparation of cycloeudesmol would be accomplished by a sequence of reactions such as those illustrated in Scheme 34. The last four reactions in this sequence are analogous to those carried out by Wenkert [39] in his synthesis of valeranone.



Scheme 34

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