PART I

AN INVESTIGATION OF THE UTILITY OF THE CLAISEN REARRANGEMENT IN ANGULAR METHYLATION AS ILLUSTRATED BY THE SYNTHESIS OF *l*-VALERANONE

PART II

THE TOTAL SYNTHESIS OF THE PENTACYCLIC TRITERPENE *dl*-GERMANICOL

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To Marcia

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ABSTRACT

I. A new method of angular methylation was developed in a synthesis of l-valeranone. This Claisen rearrangement--decarbonylation procedure was further investigated on the substrate cholest-4-en-3β-ol.

II. The synthesis of the pentacyclic triterpene dl-germanicol is described.

TABLE OF CONTENTS

page

LIST OF CHARTS AND TABLES

PART I

PART II

LIST OF FIGURES

PART I

PART II

INTRODUCTION

The results of two independent research projects are presented herein:

Part I: An Investigation of the Utility of the Claisen Rearrangement in Angular Methylation as Illustrated by the Synthesis of _l_-Valeranone.

Part II: The Total Synthesis of the Pentacyclic Triterpene _dl_-Germanicol.

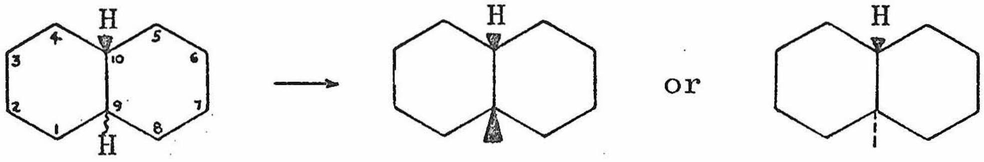
An introduction and a discussion of each project is given separately; a combined experimental section follows.

PART I

THE INVESTIGATION OF THE UTILITY OF THE CLAISEN REARRANGEMENT IN ANGULAR METHYLATION AS ILLUSTRATED BY THE SYNTHESIS OF 1-VALERANONE

INTRODUCTION

Angular methylation has long been one of the most difficult problems encountered in synthetic organic chemistry, especially in the synthesis of natural products. The difficulty in this procedure resides both in the attachment of a methyl group to a ring fusion and in the stereospecific control of this process to give a product with either a *cis* or a *trans* ring fusion, Figure 1.



cis *trans*

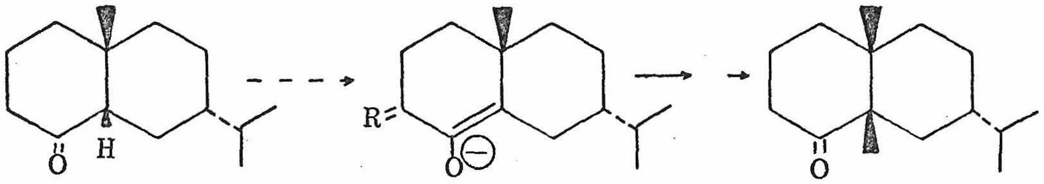
I II III

Figure 1: Angular Methylation

In order to add this methyl group to the carbon atom of a ring fusion, the angular carbon atom must either be adjacent to an activating group (Type A) or be functionalized itself (Type B). Four common methods of angular methylation are described below:

1. Alkylation of a ketone (Type A)

Treatment of the ketone IV with a base such as sodium hydride gave the corresponding sodium enolate V. The C-2 position was blocked with an *n*-butylthiomethylene group to prevent enolization in the wrong direction. The $\Delta^{1(9)}$-enolate was alkylated with methyl iodide to give, after removal of the blocking group, the angularly methylated ketone VI, *d*-valeranone[1,2] (Figure 2).



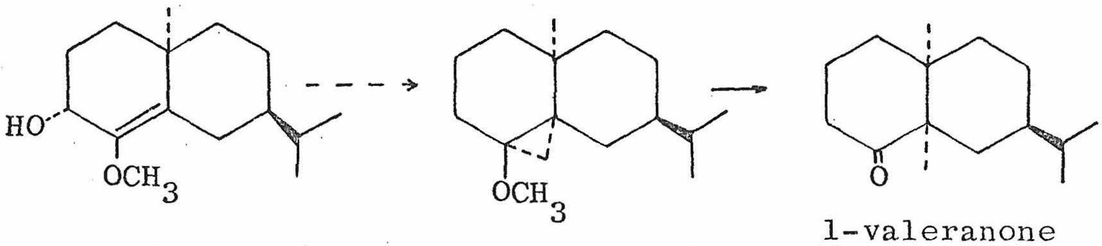
d-valeranone

IV V VI

Figure 2: Angular Methylation by Alkylation of a Ketone

2. Cleavage of a methoxycyclopropane (Type B)

Simmons-Smith cyclopropylation of the allylic alcohol VII, followed by Jones oxidation and Wolff-Kishner reduction of the resulting cyclopropyl alcohol, yielded the methoxy-cyclopropane VIII, the cyclopropyl group of which was in the α-configuration, the same configuration as the hydroxyl group of the starting material. Acid hydrolysis of this methoxy-cyclopropane (VIII) gave *l*-valeranone (IX) directly.[3]



l-valeranone

VII VIII IX

Figure 3: Angular Methylation by Methoxy-cylcopropane Cleavage

3. Conjugate addition of methylcopper complexes (Type B)

In the presence of copper salts, methylmagnesium halides or methyllithium adds 1,4 to an α,β-unsaturated ketone.[4] Thus, reaction of octalone X with methyllithium and cuprous iodide gave the angularly methylated <u>cis</u> decalone XI in one step.[5] Under the same conditions, enone XII did not undergo a 1,4-addition,[2] demonstrating the sensitivity of methylcopper complexes to steric hindrance.

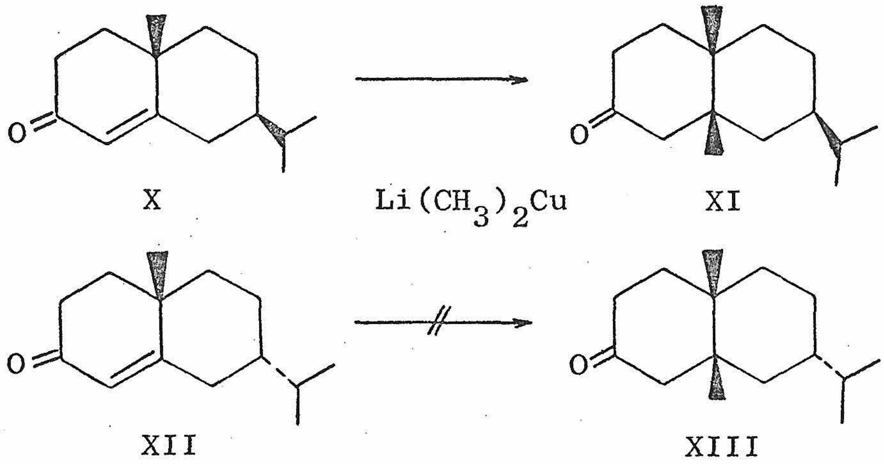


Figure 4: Angular Methylation by the Conjugate Addition of Organocopper Reagents

4. Conjugate addition of cyanide (Type B)

Diethylaluminum cyanide in benzene (thermodynamic conditions) or triethylaluminum and hydrogen cyanide in tetrahydrofuran (kinetic conditions) add cyanide 1,4 to an α,β-unsaturated ketone (XIV). In the former case the <u>cis</u>-fused isomer XV usually predominates, and in the latter it is the <u>trans</u>-fused isomer XVII which is the major product. In each case. the nitrile group can be reduced to the corresponding methyl group to give the angularly methylated ketones XVI and XVIII.[6]

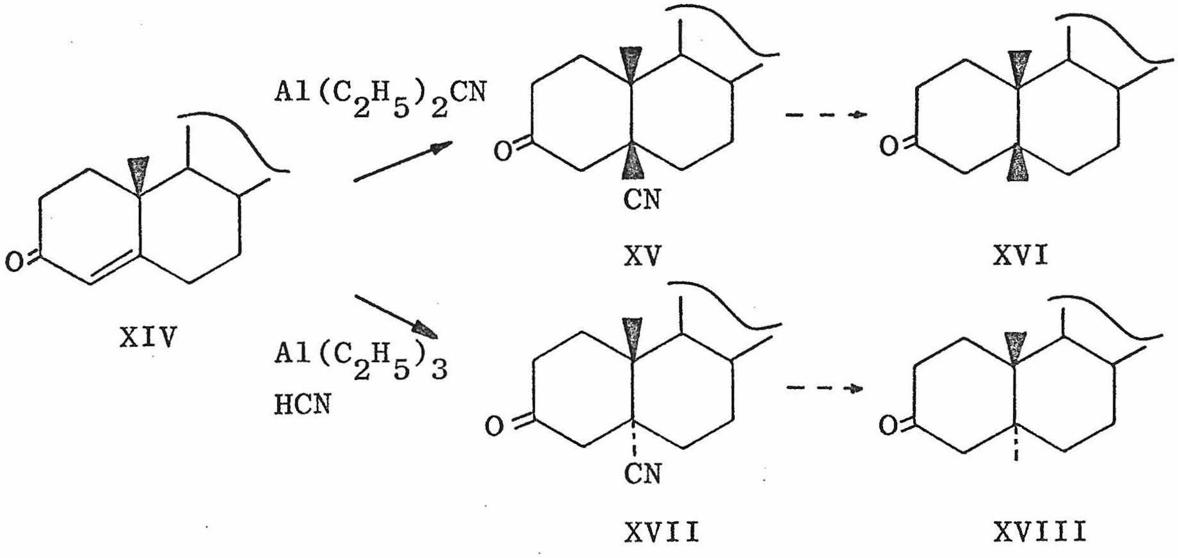
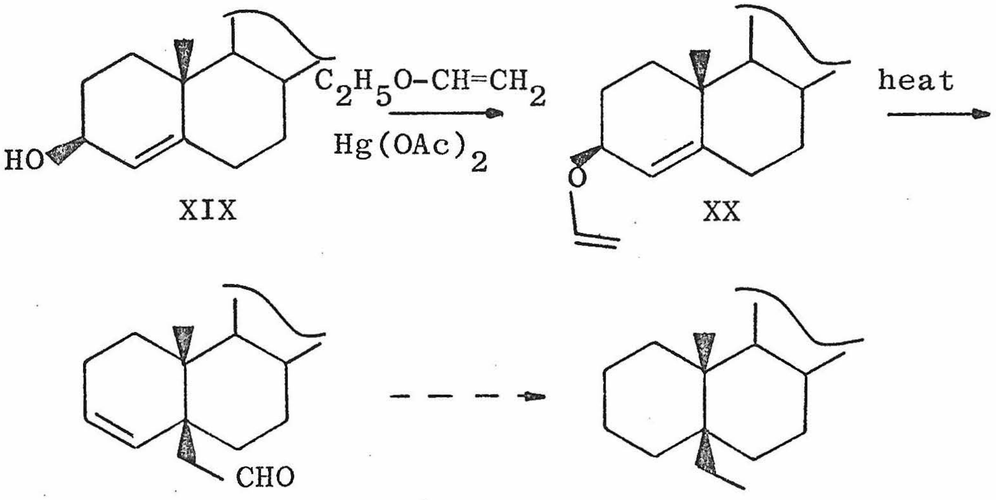


Figure 5: Angular Methylation by Conjugate Addition of Cyanide

Each of the above angular methylation procedures suffers from some deficiency, for example, low yield, harsh reaction conditions, or susceptibility to steric hindrance; no one method is suitable for all applications. Therefore another method of angular methylation was sought to supplement the four methods listed above.

In 1961, Burgstahler and Nordin[7] reported the use of the Claisen rearrangement to effect angular ethylation (Figure 6). The allyl vinyl ether intermediate XX was prepared by a mercury(II)-catalyzed transetherification of the allylic alcohol XIX with ethyl vinyl ether. On heating, the allyl vinyl ether XX underwent a Claisen rearrangement to give the unsaturated aldehyde XXI. Catalytic reduction of the olefinic double bond and thioketalization followed by Raney nickel desulfurization provided the angularly ethylated compound XXII.



XIX XX XXI XXII

Figure 6: Angular Substitution by Claisen Rearrangement

Since then, Ireland and coworkers,[8] Büchi and White,[9] and Mori and Matsui[10] have successfully used this procedure to introduce a quaternary acetaldehyde group.

A similar type of Claisen rearrangement was recently employed by Eschenmoser and coworkers.[11] In this modification, the allylic alcohol XXIV underwent an acetal exchange with N,N-dimethylacetamidedimethylacetal (XXIII) followed by loss of methanol. Claisen rearrangement then occurred to give a compound with a quaternary dimethylacetamide group (Figure 7). Since an angular acetamide can be readily converted to an angular acetaldehyde by reduction with lithium dihydrodiethoxy-

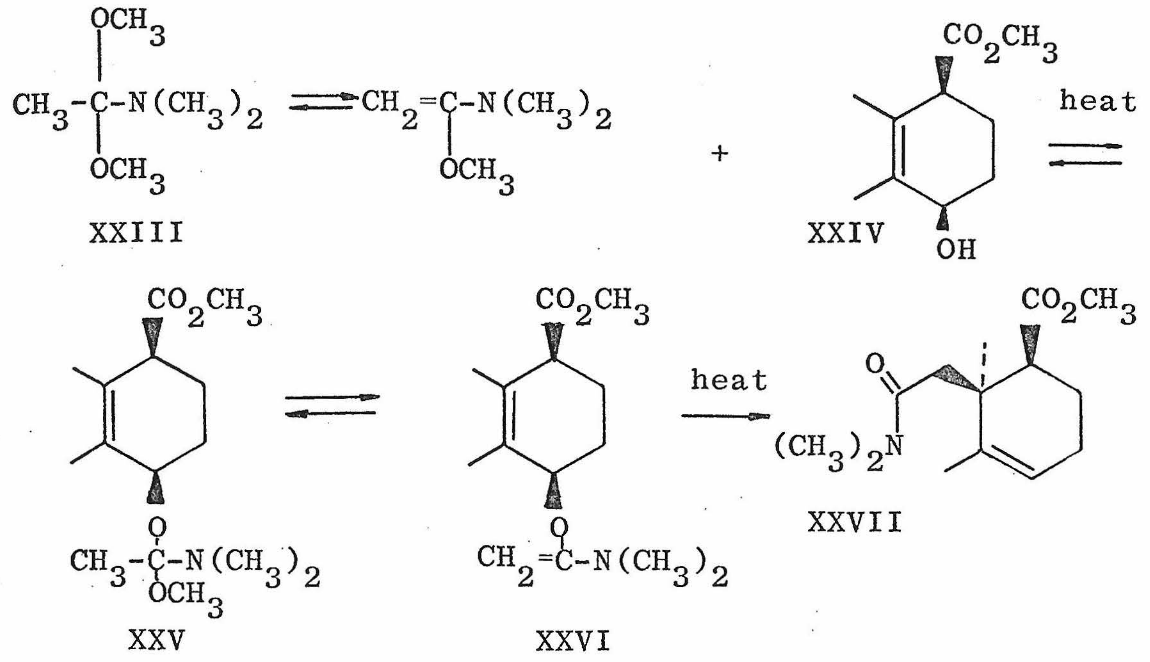


Figure 7: Amide-Acetal Claisen Rearrangement

aluminate[12] or disiamylborane,[13] or electrolytic reduction,[14] the amide-acetal Claisen route could also be used to prepare angular acetaldehydes.

Transformation of the angular acetaldehyde moiety to an angular methyl group would result in a new angular methylation procedure. The decarbonylation reaction reported by Tsuji and Ohno,[15] and Wilkinson and coworkers[16] appeared ideal for a one step conversion of an acetaldehyde to a methyl group. Heating an alkyl aldehyde with an equivalent of tris(triphenylphosphine)-chlororhodium(I) (XXIX) in benzene or acetonitrile effected a high yield decarbonylation to give the hydrocarbon (Figure 8).

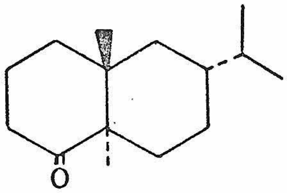
$$\text{R-CHO} + \text{Rh}(\O_3\text{P})_3\text{Cl} \xrightarrow[\text{heat}]{C_6H_6} \text{R-H} + \text{Rh}(\O_3\text{P})_2(\text{CO})\text{Cl} + \O_3\text{P}$$

XXVIII XXIX XXX

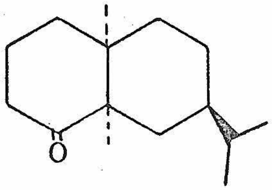
Figure 8: Decarbonylation

Studies on valeranone and cholestenol were undertaken to determine the utility of the proposed angular methylation procedure. The synthesis of valeranone was selected to illustrate the advantage of this procedure in synthetic chemistry. The cholestenol system was chosen as a model on which the reaction conditions could be standardized.

In 1957 *l*-valeranone was discovered in the roots of the garden heliotrope, *Valeriana officinalis*, by Stoll, Seebeck, and Stauffacher.[17] A year later, Govindachari and coworkers[18] isolated a compound, which they named jatamansone, from the oil of *Nardostachys jatamansi* and found that it was therapeutically useful in the treatment of heart seizures caused by electric shock. Šorm and coworkers[19] later showed that jatamansone and valeranone were identical. Govindachari[20,21] and Djerassi[21] proposed the structure XXXI for valeranone,



XXXI



IX

which was later proved incorrect by Šorm,[22] who then determined the correct relative structure (IX).[23] Finally, Klyne and coworkers found that *l*-valeranone had the absolute configuration shown in structure IX.[24]

Valeranone has been successfully synthesized by Marshall and coworkers[1,2] in 1965 and by Wenkert and Berges[3] in 1967. Both synthetic schemes began with carvomenthone. Marshall used l-carvomenthone to synthesize d-valeranone, while Wenkert employed the d form to synthesize the natural isomer, l-valeranone.

Marshall's synthesis,[1,2] outlined in Chart A, is straightforward. l-Carvomenthone (A-1) was annellated with methyl vinyl ketone under basic conditions to give the keto-alcohol A-2 which was readily dehydrated to the octalone A-3. The ketone function was removed by a three step sequence: lithium aluminum hydride reduction of the enone to an allylic alcohol (A-4), acetylation, and cleavage of the acetate group with lithium in ethylamine gave the octalin A-6. Hydroboration--oxidation of the octalin yielded the β-alcohol A-7 which was then oxidized to the decalone A-8. Since enol acetate formation under equilibrating conditions gave a 1:1 mixture of the two possible enol acetates, which could not be readily separated, the C-2 position of decalone A-8 was blocked by an n-butylthiomethylene group. Enolization of this blocked ketone (A-9) gave the desired enolate A-10. Methylation of this enolate in benzene produced a 3:1 mixture of O-methylated and C-methylated (A-11) material. Alkaline hydrolysis of the methylated ketone A-11 yielded d-valeranone (VI).

Wenkert's synthesis[3] of l-valeranone (Chart B) introduced a new and highly successful method for angular methylation. d-Carvomenthone (B-1) was annellated with 1,4-

CHART A

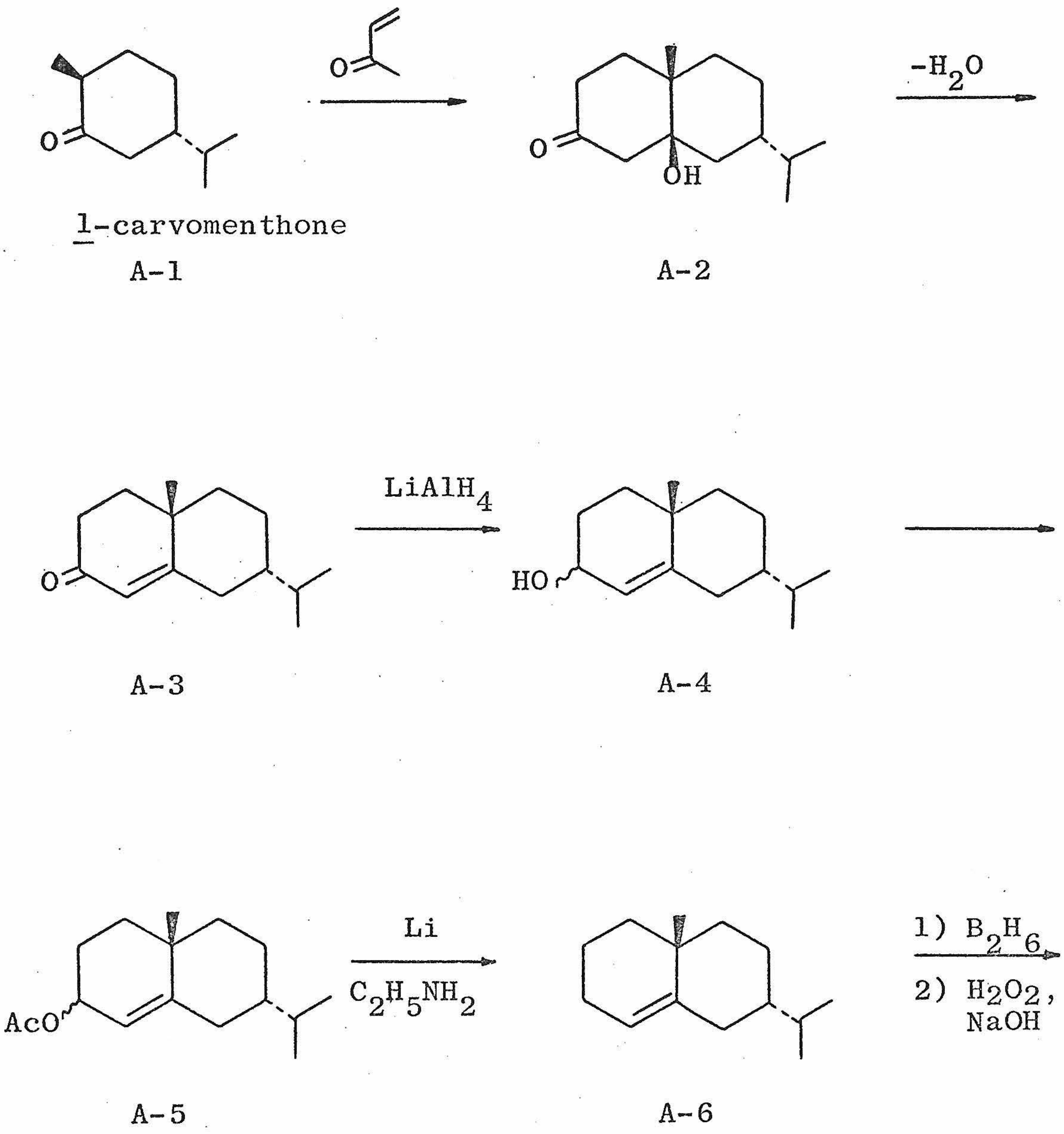
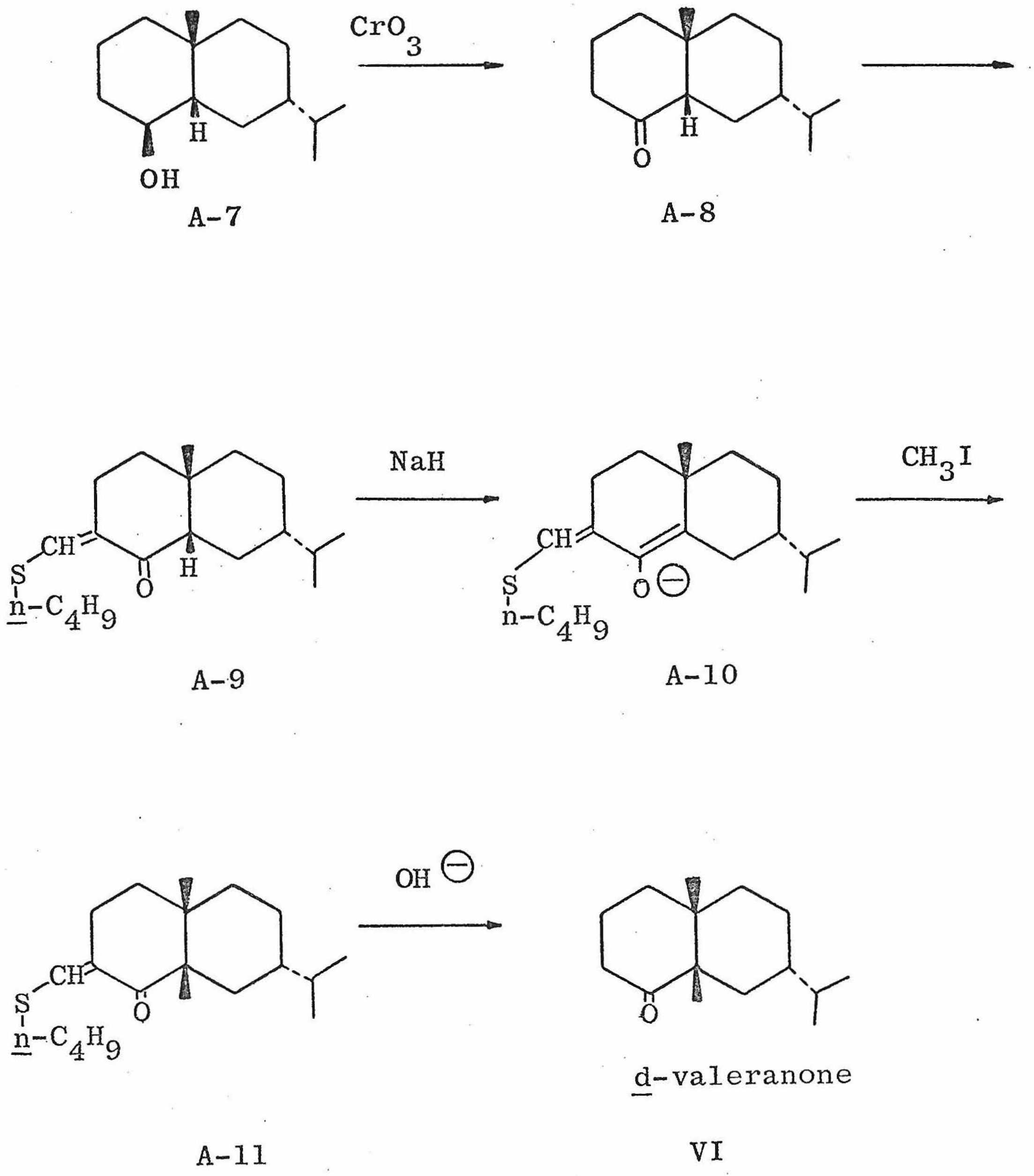

O
1-carvomenthone
A-1
O
O
OH
A-2
$-H_2O$
O
A-3
$LiAlH_4$
HO
A-4
AcO
A-5
Li
$C_2H_5NH_2$
A-6
1) B_2H_6
2) H_2O_2,
NaOH

CHART A (continued)

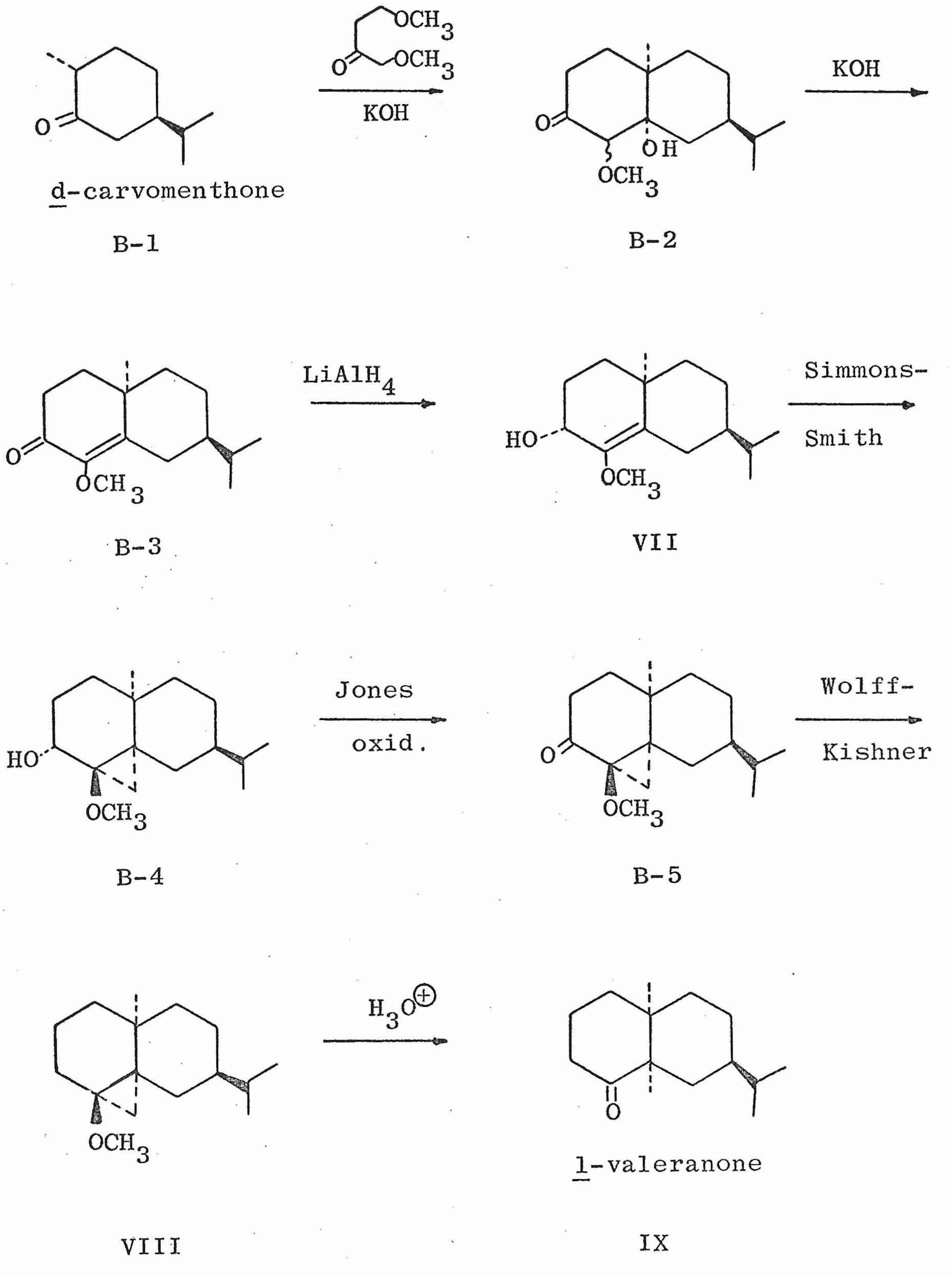


dimethoxy-2-butanone, and the resulting keto-alcohol B-2 was dehydrated with potassium hydroxide to the methoxyoctalone B-3. Lithium aluminum hydride reduction of this octalone gave almost exclusively the α-allylic alcohol VII, which formed the corresponding $1\alpha,9\alpha$-cyclopropane B-4 on treatment with iodomethylzinc iodide (Simmons-Smith reaction). Jones oxidation of alcohol B-4 to the ketone B-5, followed by Wolff-Kishner reduction of this ketone yielded the methoxycyclopropyldecalin VIII, which upon acid hydrolysis yielded l-valeranone in excellent yield.

In each of the above valeranone syntheses, the crucial step was the angular methylation. By employing the Claisen rearrangement--decarbonylation procedure in a synthesis of valeranone, its effectiveness as an angular methylation route could be compared with the methods used in the other two syntheses.

Cholestenol, employed in the second part of this angular methylation study, has long been a popular substrate for investigating new reactions or determining the stereochemical features of well-known reactions because of the rigidity of its ring system and its availability. Ireland and Pfister[25] have performed preliminary work on the Claisen rearrangement--decarbonylation method of angular methylation with cholestenol. The low and variable yields obtained prompted further investigation.

CHART B



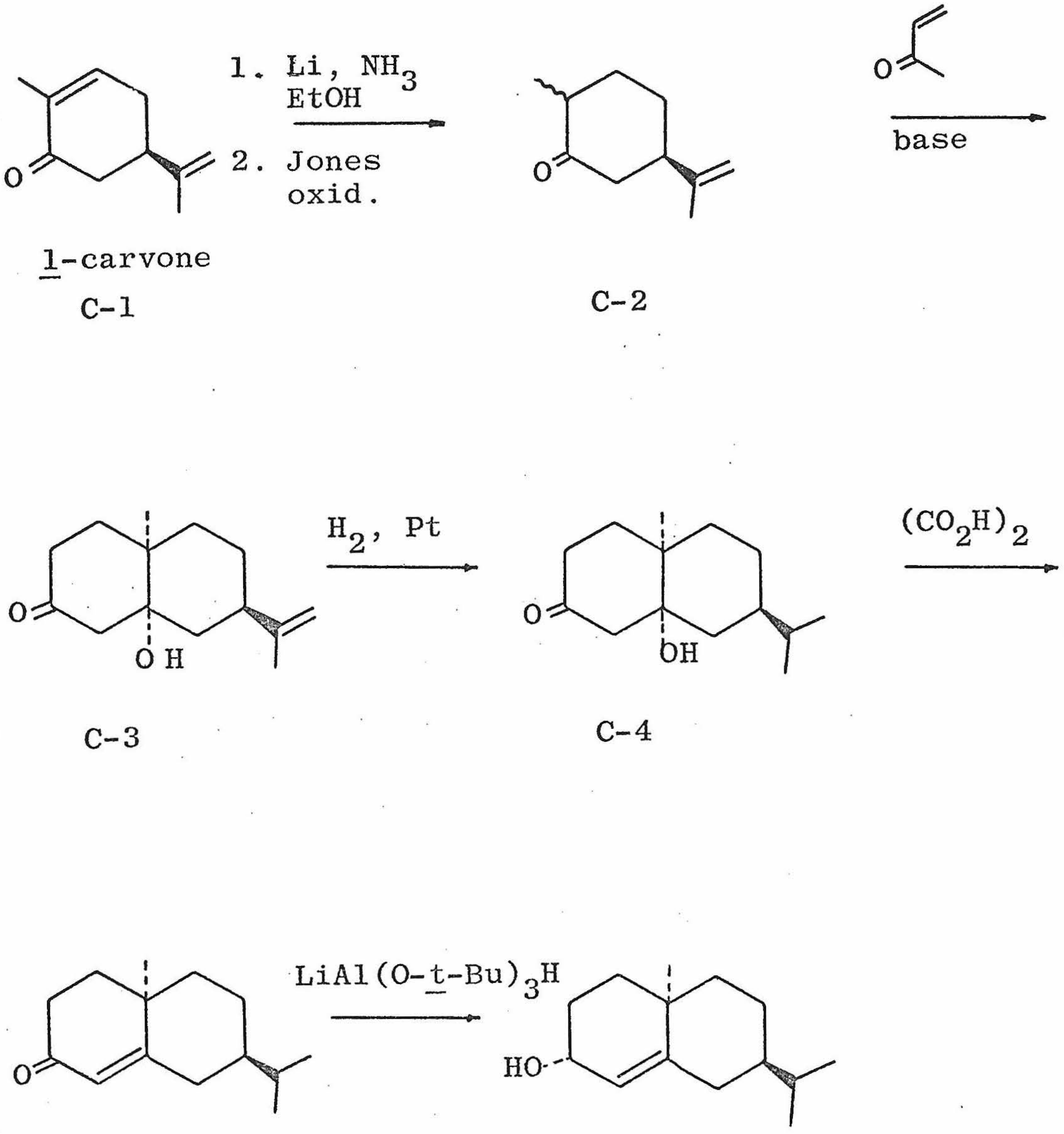
d-carvomenthone
B-1
OCH3
OCH3
O
KOH
O
OH
OCH3
B-2
KOH
O
OCH3
B-3
LiAlH4
HO
OCH3
VII
Simmons-
Smith
HO
OCH3
B-4
Jones
oxid.
O
OCH3
B-5
Wolff-
Kishner
OCH3
VIII
H3O⊕
O
l-valeranone
IX

THE SYNTHESIS OF l-VALERANONE

l-Carvone (C-1 in Chart C) was used as the starting material in the synthesis of l-valeranone since it was both readily available and the proper enantiomer for the conversion. The first four steps in this synthesis were developed by Marshall and coworkers during their studies on the valeranone system.[26] Marshall found that the Birch reduction of carvone gave a higher yield of the desired product when a proton source was present during the reaction. Some over-reduction to the alcohol did occur, but Jones oxidation of this alcohol restored the ketone function. Thus, reduction of l-carvone on a 100-g scale with lithium and ethanol in liquid ammonia followed by Jones oxidation[27] and distillation of the crude product afforded dihydrocarvone (C-2) in 74% yield. Addition of a catalytic amount of sodium ethoxide in ethanol to dihydrocarvone, which had been cooled to -10°, followed by the addition of 0.5 equivalent of methyl vinyl ketone gave the homoannellated keto-alcohol C-3 in low yield, however by recycling the recovered starting material twice a good yield of the keto-alcohol was obtained (38% conversion or 51% based on unrecovered dihydrocarvone).

The unsaturated keto-alcohol C-3 was quantitatively hydrogenated in the presence of a platinum catalyst in ethanol

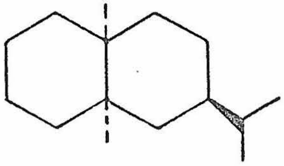
CHART C


1. Li, NH3 EtOH
2. Jones oxid.
l-carvone
C-1
C-2
base
C-3
H2, Pt
C-4
(CO2H)2
C-5
LiAl(O-t-Bu)3H
C-6
O
OH
HO

to afford the saturated keto-alcohol C-4 which, in turn, was dehydrated with hot aqueous oxalic acid to give the octalone C-5 in quantitative yield.

The next step was the reduction of the octalone C-5 to the proper allylic alcohol required for the Claisen rearrangement reaction. Since the synthesis of valeranone necessitated the insertion of an α methyl group at the C-9 position, it was evident that the hydroxyl group of the allylic alcohol also had to have an α configuration (alcohol C-6). One of the best reagents for the reduction of a cyclic ketone to an equatorial alcohol is lithium aluminum tri-t-butoxy hydride.[28] Reduction of the octalone C-5 with this reagent in refluxing tetrahydrofuran afforded an allylic alcohol in 91% yield. Nuclear magnetic resonance (nmr) analysis established that this was the expected quasi-equatorial isomer C-6. This alcohol, obtained in 34% overall yield from l-carvone, was the precursor for all the compounds synthesized in this phase of the project.

The first goal of the project was the conversion of this precursor to the cis-9,10-dimethyldecalin XXXII, which possesses the valeranone skeleton, thereby providing a test of



XXXII

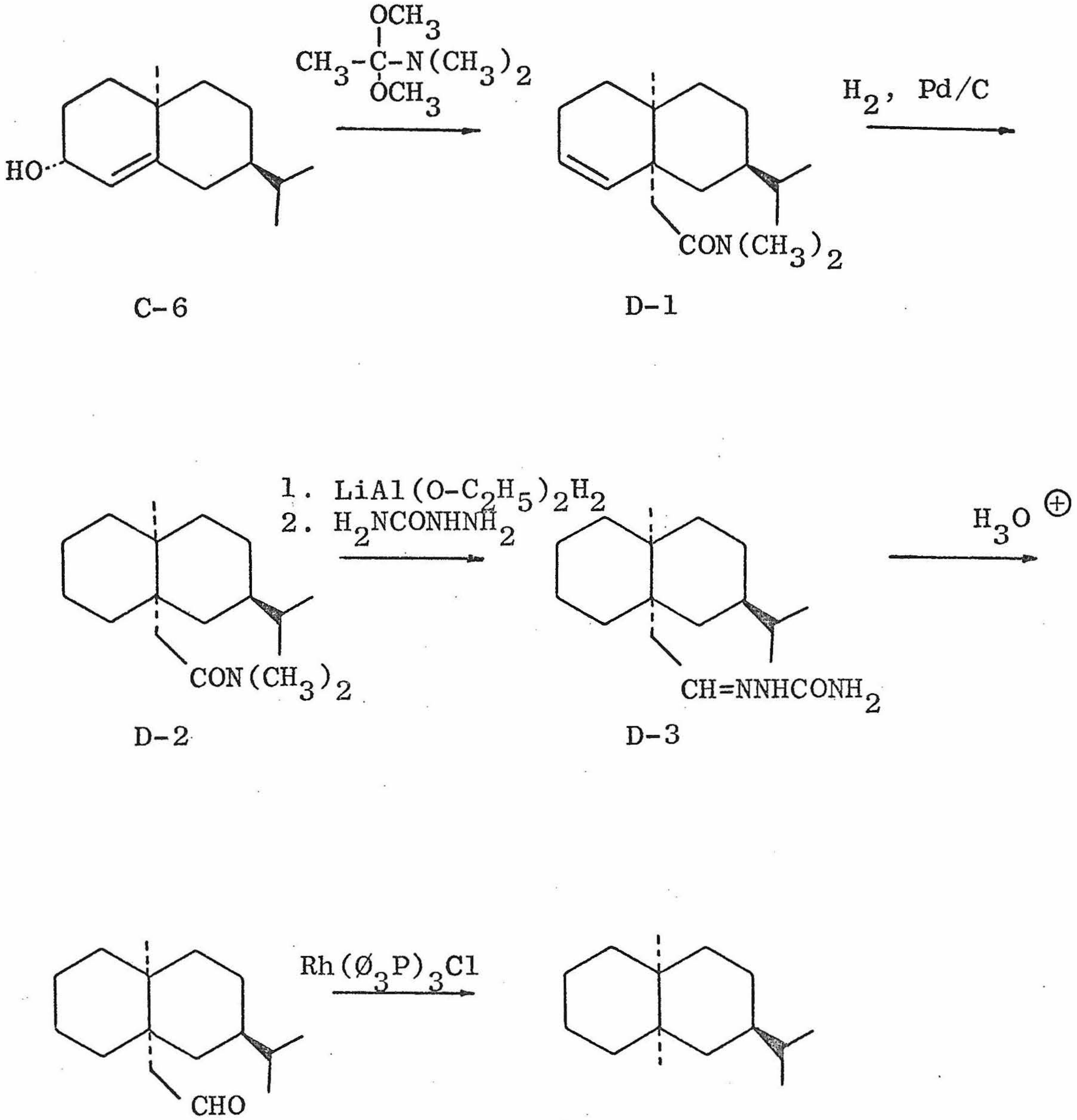
the angular methylation procedure. After this procedure had been developed on the model, the next objective was the modification of the route to include functionality at the C-1 position, ultimately leading to 1-valeranone.

Since the procedure for the Eschenmoser amide-acetal Claisen rearrangement[11] is simpler than that for the vinyl ether Claisen rearrangement used by Burgstahler,[7] the former method was chosen for this model study. Upon heating a solution of the allylic alcohol C-6 with four equivalents of N,N-dimethylacetamidedimethylacetal in p-xylene, the unsaturated amide D-1 was isolated in a rather disappointing yield of 29% (Chart D). Angular methylation studies on the cholestenol system provided an explanation for this low yield, p 43.

The unsaturated amide D-1 was hydrogenated in ethanol in the presence of a 10% palladium-on-carbon catalyst to afford the saturated amide D-2 in quantitative yield. Reduction of this amide with lithium dihydrodiethoxyaluminate[12] in ether gave a product which consisted of 89% aldehyde D-4 and 11% starting material by vapor phase chromatography (vpc). The crude reaction product on treatment with semicarbazide hydrochloride and pyridine in methanol[28] gave pure semicarbazone D-3 in 51% overall yield from the saturated amide D-2. On heating in benzene solution with aqueous hydrochloric acid, the aldehyde D-4 was quantitatively regenerated from the semicarbazone.

Decarbonylation[15,16] of the purified aldehyde was

CHART D

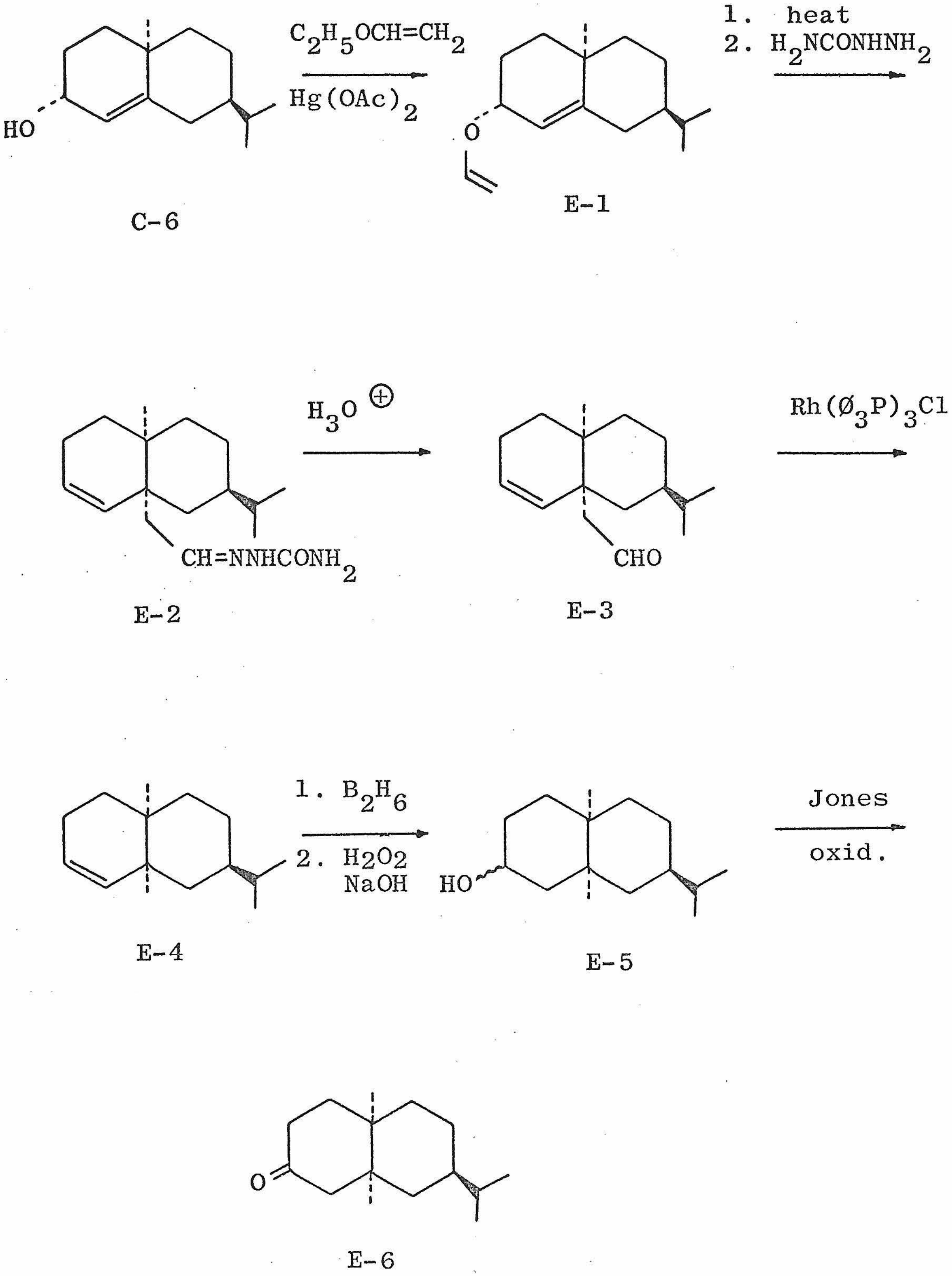

HO
OCH3
CH3-C-N(CH3)2
OCH3
H2, Pd/C
CON(CH3)2
C-6
D-1
1. LiAl(O-C2H5)2H2
2. H2NCONHNH2
H3O ⊕
CON(CH3)2
CH=NNHCONH2
D-2
D-3
Rh(Ø3P)3Cl
CHO
D-4
XXXII

achieved by heating with tris(triphenylphosphine)chlororhodium(I). Evaporative distillation gave a 43% yield of the desired hydrocarbon XXXII,[29] the structural assignment of which was verified by the nmr and infrared (ir) spectra.

Since this new angular methylation procedure worked satisfactorily in the model route, the synthesis of l-valeranone, itself, was undertaken by the scheme outlined in Chart E. This scheme, a modification of the one used above, eliminated the $\Delta^{1(2)}$ double bond hydrogenation; by leaving this double bond intact, provision was made for the eventual production of the C-1 ketone in valeranone. In addition, the vinyl ether Claisen rearrangement was used because of the poor yield observed in the amide-acetal procedure. Accordingly, treatment of the allylic alcohol C-6 with mercuric acetate in ethyl vinyl ether,[7] work-up and filtration through alumina gave the vinyl ether E-1 in greatly variable yields: 0-87% (Chart E). In the nine times that this reaction was done, no relationship between yield and experimental procedures could be deduced. The problem appeared to be in the filtration step; although filtration conditions were varied each time, the original yield of 87% was never again duplicated. This problem was encountered and finally resolved in the cholestenol series (p 44).

On heating at 195° for three hours, the vinyl ether E-1 rearranged to the aldehyde E-3. Vpc analysis of the crude product indicated that the aldehyde comprised 85-90% of the

CHART E


C-6
$C_2H_5OCH=CH_2$
$Hg(OAc)_2$
E-1
1. heat
2. $H_2NCONHNH_2$
E-2
$CH=NNHCONH_2$
$H_3O^{\oplus}$
E-3
CHO
$Rh(Ø_3P)_3Cl$
E-4
1. B_2H_6
2. H_2O_2
NaOH
E-5
Jones
oxid.
E-6
HO
O

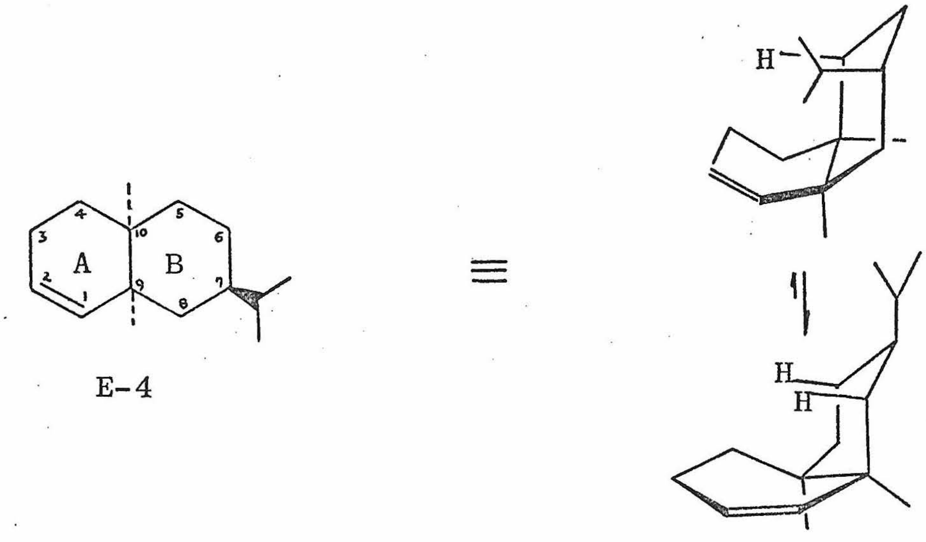
mixture; the remainder was starting material and dienes, which originated from the thermal loss of acetaldehyde from the vinyl ether E-1. The aldehyde was isolated from the crude reaction product as the semicarbazone E-2 in 54% overall yield from the vinyl ether E-1. Hydrolysis of the semicarbazone regenerated the aldehyde E-3 in 93% yield.

Decarbonylation[15,16] of the aldehyde by tris(triphenylphosphine)chlororhodium(I) in refluxing benzene afforded the angularly methylated octalin E-4 in medium to good yield (47-78%). It is interesting to note, in view of later developments, that the $\Delta^{1(2)}$ double bond did not interfere in any way with the decarbonylation reaction.

Now, all that remained was the conversion of the double bond in octalin E-4 to a ketone function at the C-1 position. The first method attempted was hydroboration. Hydroboration--oxidation of the olefin E-4 should afford a mixture of the C-1 and C-2 alcohols, which could be oxidized to the respective C-1 and C-2 ketones. Valeranone and its C-2 keto isomer could then be separated chromatographically.

Hydroboration[30] of the octalin E-4 with the least hindered hydroboration reagent, diborane, followed by oxidation with alkaline hydrogen peroxide afforded a 1:1 mixture of two alcohols by vpc analysis. Jones oxidation[27] of the crude alcohol mixture gave a single ketone which was obtained in 62% yield from the octalin E-4. The nmr spectrum of this ketone indicated the presence of four α-keto protons. Therefore, the oxidation product had a keto function at the C-2 position (E-6), and the two alcohols (E-5) must have been epimeric at C-2.

Such stereospecifity in the hydroboration of a 1,2-disubstituted double bond was impressive as well as unexpected. A consideration of the steric environment about this double bond may offer an explanation for the results of this reaction.



E-4

E-4a

E-4b

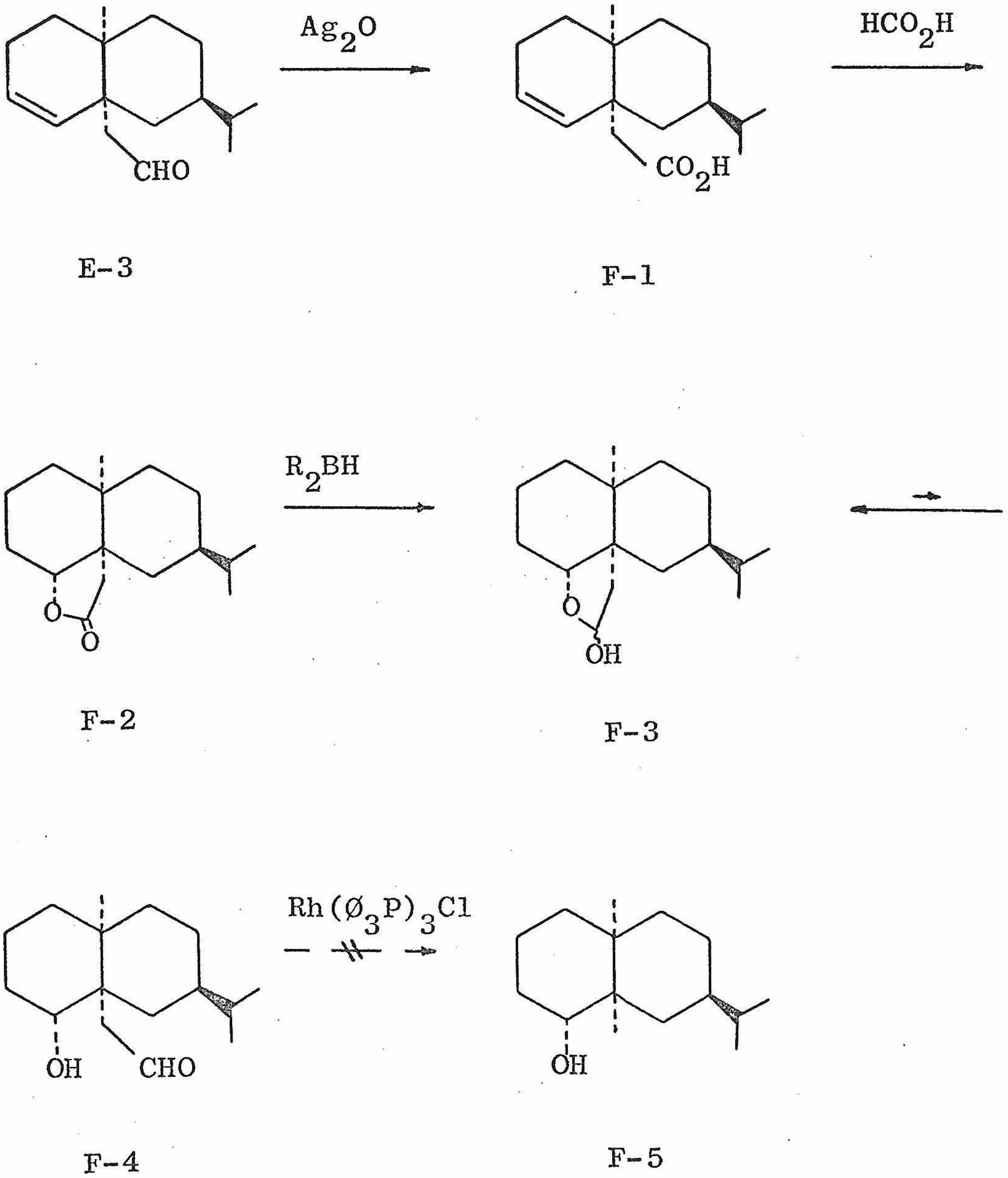
Figure 9: Conformers of Octalin E-4

The cis ring fusion in the octalin E-4 allows two chair-chair conformers (Figure 9), one with the isopropyl group axial (E-4a) and one with it equatorial (E-4b). The conformer with the axial isopropyl group should be less stable because of 1,3-diaxial nonbonded interactions between the isopropyl group and the C-1 carbon atom and the C-5 hydrogen, and, therefore, the conformer with the isopropyl group equatorial

(E-4b) should predominate and control the course of the reaction. Attack by diborane on the β-face of the cup-shaped conformer E-4b is hindered by the C-6β and C-8β protons on the B ring. The hindrance is greater at the C-1 position than at the C-2 because of the proximity of the C-1 position to the B ring. Any β-face attack by diborane would thus be directed to the C-2 end of the double bond to give, after oxidation, the C-2β alcohol. Attack on the α-face is hindered by the C-10 methyl group which is axial to the A ring. Again, the hindrance is greater at the C-1 carbon because of its 1,3-diaxial interaction with the C-10 methyl. As a result, any α-face attack by diborane would lead to the formation of the C-2α alcohol.

In an attempt to exploit the proximity of the C-9 angular substitutent to the olefinic double bond and thereby obviate the problem of steric hindrance, the scheme outlined in Chart F was tried. The lactol F-3, which could be easily obtained from the aldehyde E-3, should be in equilibrium with the hydroxy-aldehyde F-4, which, in turn, should undergo decarbonylation to the C-1 alcohol F-5, which is one oxidation step from valeranone. The crude aldehyde E-3, obtained by Claisen rearrangement of vinyl ether E-1, was oxidized with silver oxide[8] to the carboxylic acid F-1. Treatment of this γ,δ-unsaturated acid with refluxing formic acid[31] afforded the γ-lactone F-2 in 58% yield from the vinyl ether E-1. Reduction of the lactone with disiamylborane[32,33] in tetrahydrofuran

CHART F


Ag$_2$O
HCO$_2$H
CHO
CO$_2$H
E-3
F-1
R$_2$BH
O
O
O
OH
F-2
F-3
Rh(Ø$_3$P)$_3$Cl
OH
CHO
OH
F-4
F-5

gave a 64% yield of the lactol F-3. The decarbonylation of the lactol was unsuccessful. Apparently the equilibrium between the lactol F-3 and the hydroxy-aldehyde F-4 greatly favors the lactol. The only volatile material isolated from the reaction mixture was the lactone F-2, which was obtained in 22% yield and was probably produced by a catalytic dehydrogenation of the lactol.

Since reagents such as N-bromosuccinimide and peracids are not as sensitive as diborane to steric hindrance, such an oxidation of the double bond in octalin E-4 should lead to a mixture of C-1 and C-2 functionalized compounds, thereby circumventing the steric hindrance problem. The bromohydrin route is shown in Chart G. Treatment of olefin E-4 with N-bromosuccinimide in aqueous dimethylsulfoxide[34] afforded a mixture of bromohydrins in 66% yield. The crude product was oxidized with Jones reagent[27] in 83% yield to give one bromo-ketone. Reduction of the bromo-ketone with zinc dust in an acetic acid--sodium acetate buffer[35] resulted in an excellent yield of the undesired isomeric ketone E-6, the same isomer as that produced by the hydroboration route (Chart E). Therefore, the only bromohydrin formed was the 1-bromo-2-hydroxydecalin G-1, which on oxidation produced the 1-bromo-2-decalone G-2.

The final functionalization scheme employed epoxidation of the double bond of the octalin E-4 followed by hydride reduction of the resultant epoxide (Chart H). In this route steric hindrance should preclude attack by hydride at the C-1

CHART G

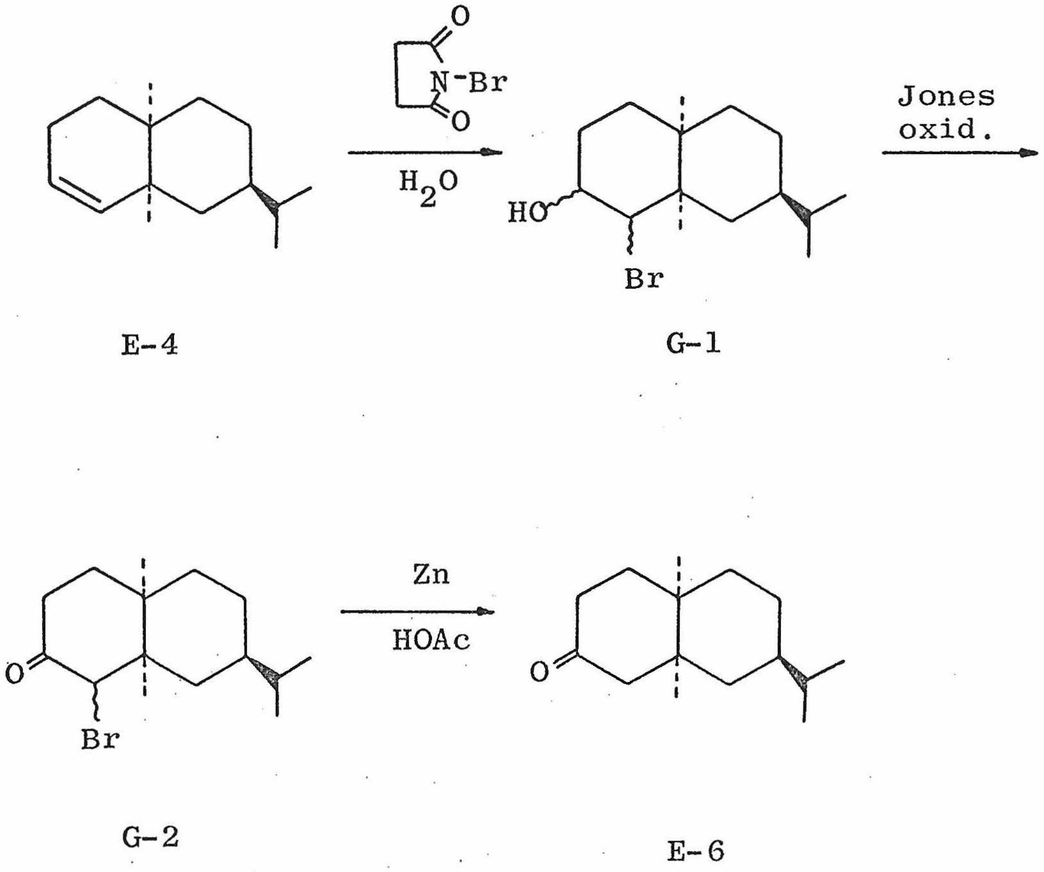
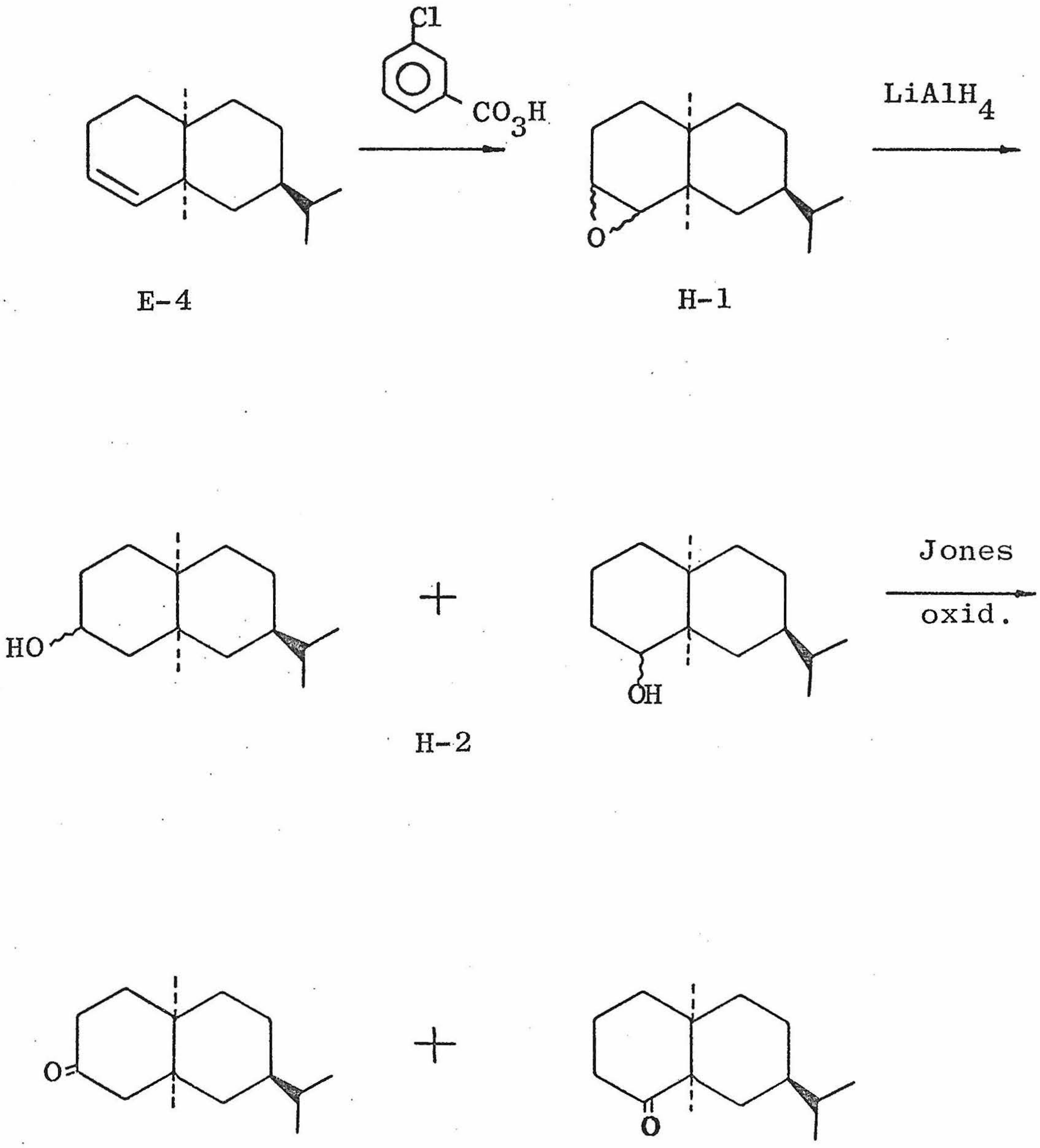


CHART H



E-4

H-1

H-2

E-6

l-valeranone

IX

position of the intermediate epoxide. The resulting alcohol with a C-1 hydroxyl group could then be oxidized to valeranone.

Octalin E-4 was epoxidized with *m*-chloroperoxybenzoic acid in dichloromethane.[28] The product, isolated in 55% yield, was a mixture of two compounds by analytical thin-layer chromatography (tlc) and nmr spectroscopy, which indicated that both α and β epoxides were present in about a 1:2 ratio. Since both epoxides were expected to give C-1 alcohol upon reduction, the mixture was treated with the hindered reducing agent, lithium tri-*t*-butoxy aluminum hydride,[28] in refluxing tetrahydrofuran, however no reduction occurred. The epoxides were then reduced with less selective but more reactive reducing agents, lithium aluminum hydride[28] (74% yield) and aluminum hydride[36] (69% yield) to a mixture of two alcohols (H-2) in a 30:70 ratio. Jones oxidation[27] of the alcohol mixture gave a mixture of two ketones, *1*-valeranone (IX) and the 2-keto isomer E-6, again, by vpc analysis, in a 30:70 ratio.

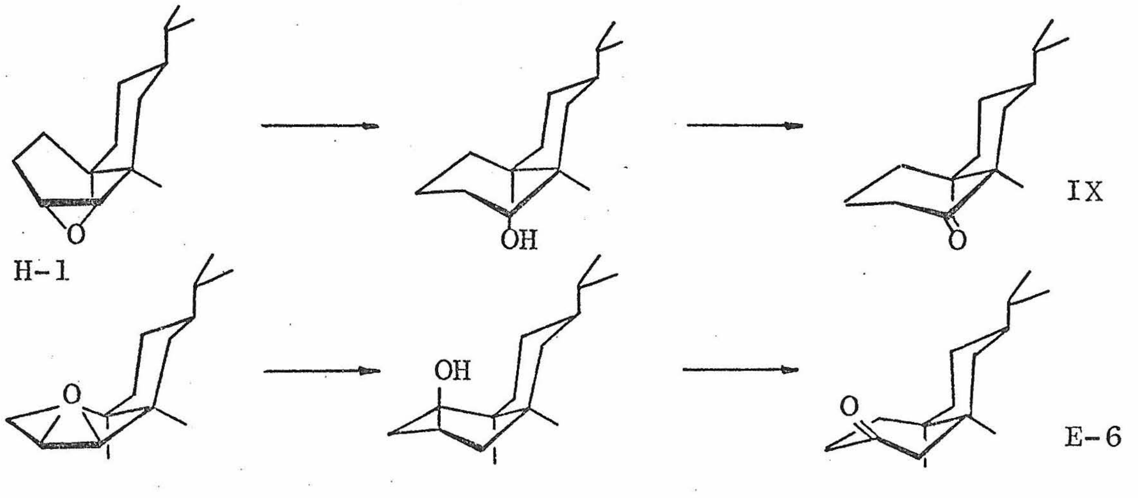


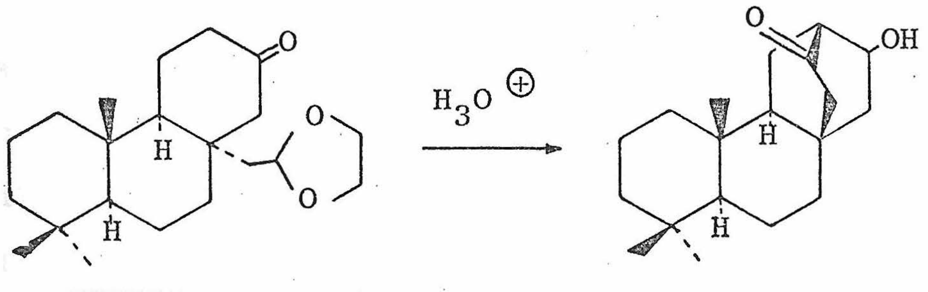
Figure 10: Reduction of the Epoxide Mixture H-1

It appears that steric hindrance had a negligible effect in the reduction of the epoxides. As shown in Figure 10, trans-diaxial opening of the 1:2 epoxide mixture would, after oxidation, yield the 30:70 ketone mixture. Therefore, it must be assumed that the reduction proceeded under stereoelectronic control rather than steric control.

The isomeric ketones IX and E-6 were separated by preparative thin layer chromatography to give ketone E-6 in 35% yield and pure l-valeranone in 23% yield. The l-valeranone was identified by comparison of its optical rotation and infrared spectrum, and the melting point of its 2,4-dinitrophenylhydrazone derivative with those of the natural l-valeranone.[17,18]

The above work demonstrated that it is possible to insert an angular methyl group to give a compound having a cis ring fusion. To illustrate the flexibility of this synthetic procedure, the insertion of an angular methyl group to give a compound (I-10) having a trans ring fusion was undertaken.

Conversion of a cis-fused δ-keto-acetal to a bicyclo-[2.2.2] octane ring system has been accomplished by Ireland

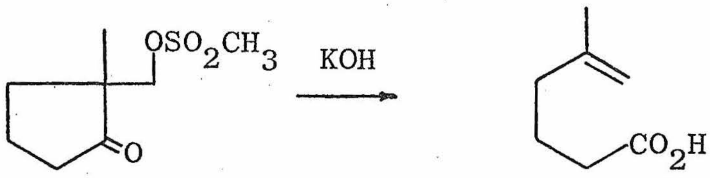


XXXIII

XXXIV

Figure 11: Conversion of a δ-Keto-acetal to a Bicyclo[2.2.2] octane

and coworkers[30] on the system illustrated in Figure 11. A similar transformation in the valeranone system can be effected by the conversion of the 2-decalone I-2 to the bicyclo [2.2.2]octane I-3 (Chart I). Eschenmoser and coworkers have found that a β-keto-sulfonate cleaves under basic conditions to the corresponding unsaturated carbonyl compound[37] (Figure 12). On the basis of this precedent, the success of the conversion of the bicyclo[2.2.2]octane I-3 to the trans-octalin I-5 was assured. Manipulation of the functionality in this octalin would then afford the trans-di(angular methyl) decalin I-10.



XXXV XXXVI

Figure 12: β-Keto-sulfonate Cleavage

The unsaturated acetal I-1 was prepared in 93% yield by reaction of the unsaturated aldehyde E-3 with ethylene glycol and sulfuric acid.[38] Hydroboration--oxidation[30] of the unsaturated acetal followed by Jones oxidation of the resulting alcohol mixture afforded the decalone I-2 in 88% overall yield. The structural assignment of this ketone was confirmed by the nmr spectrum. Hydrolysis of the keto-acetal I-2 occurred in

CHART I

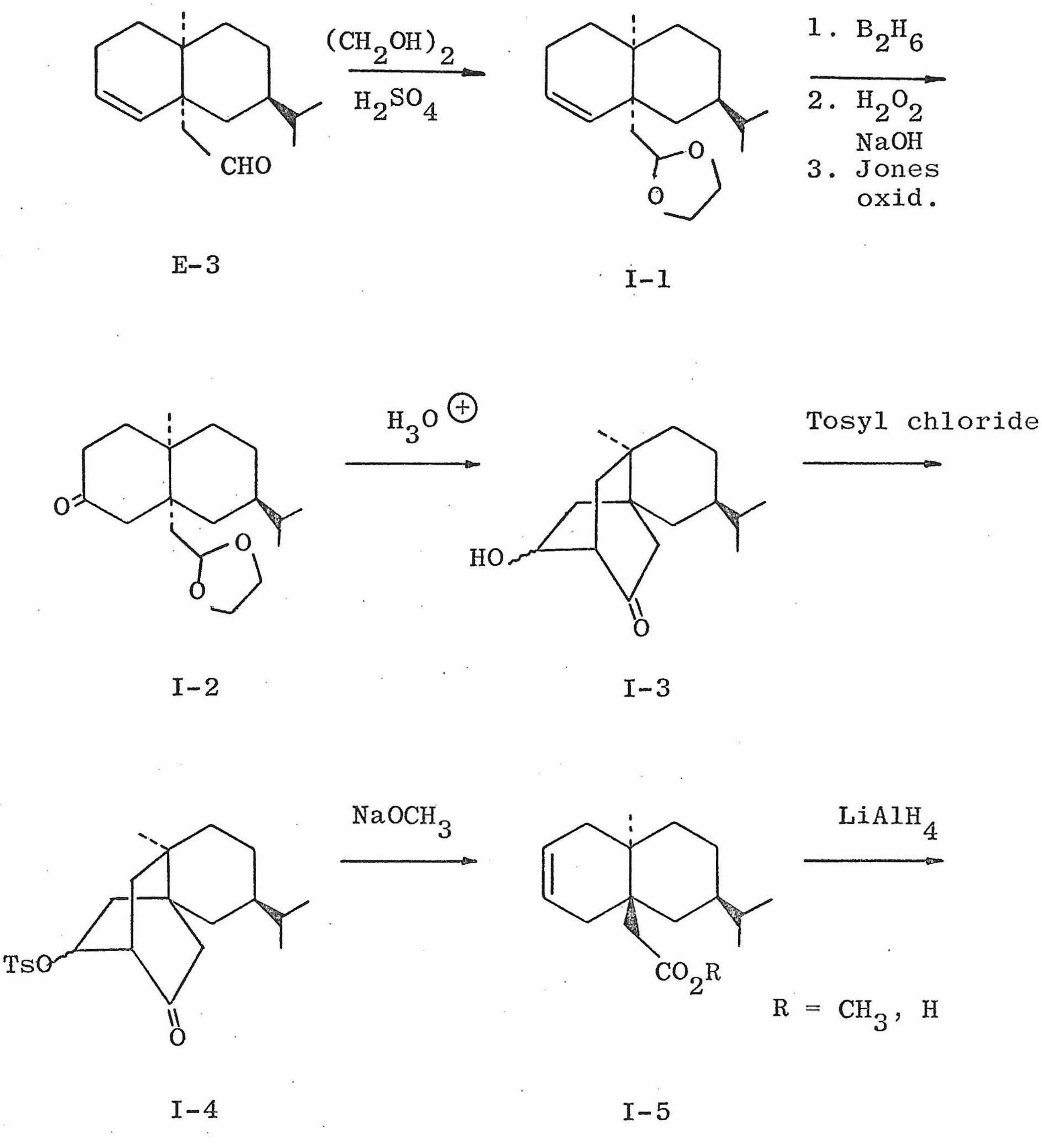
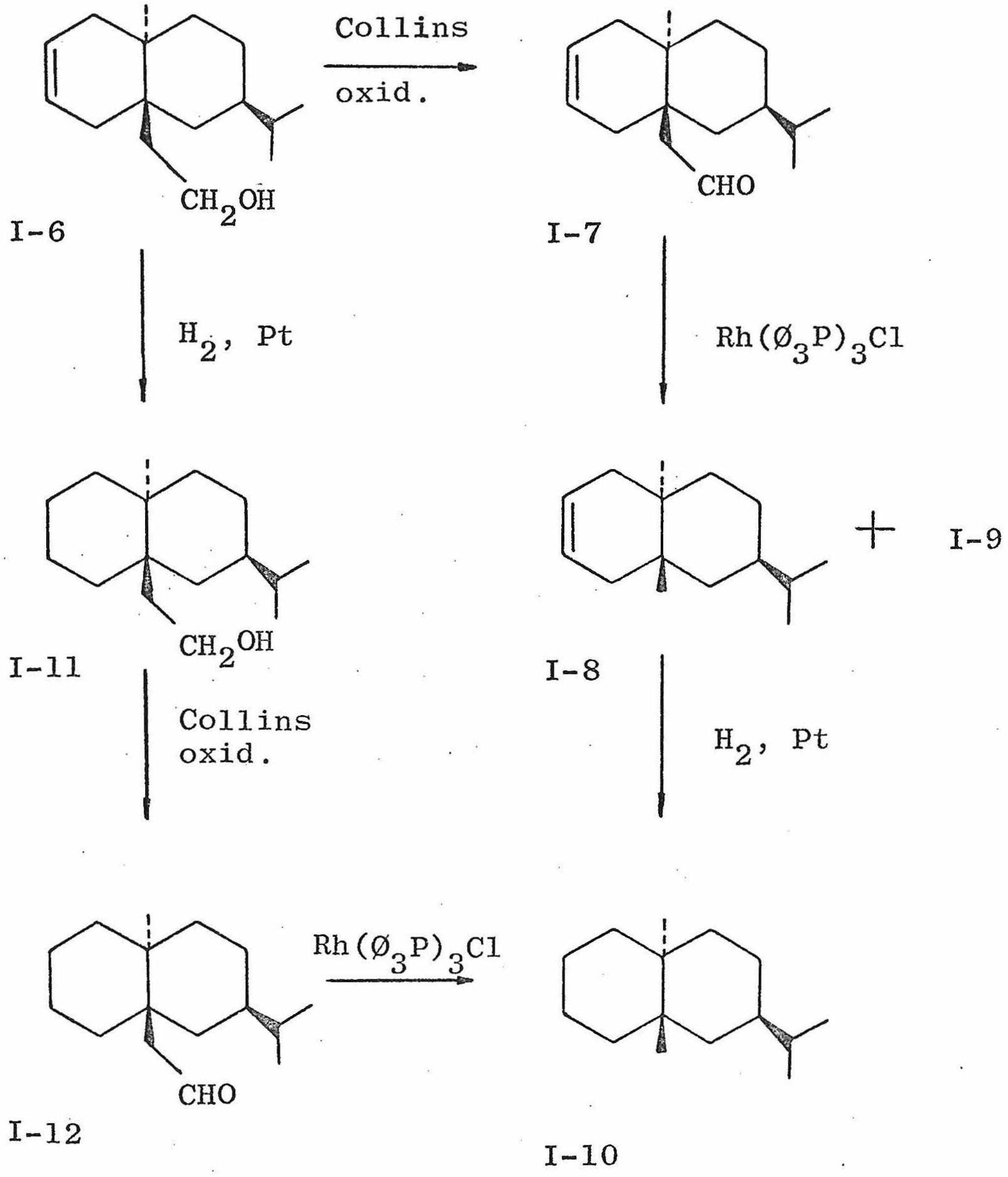

CHO
$(CH_2OH)_2$
H_2SO_4
E-3
1. B_2H_6
2. H_2O_2 NaOH
3. Jones oxid.
I-1
$H_3O^{\oplus}$
HO
I-2
Tosyl chloride
I-3
TsO
NaOCH$_3$
I-4
CO_2R
$LiAlH_4$
R = CH_3, H
I-5

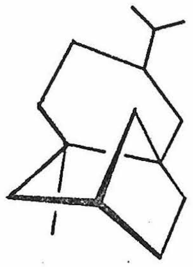
CHART I (continued)



aqueous hydrochloric acid in acetone[30] with concomitant cyclization to the substituted bicyclo [2.2.2] octane I-3 in 77% yield.

Treatment[28] of the keto-alcohol I-3 with _p_-toluenesulfonyl chloride in pyridine led to the tosylate I-4. The yield based on unrecovered starting material was 94% or a 74% conversion. Treatment of the tosylate with sodium methoxide in methanol[37] gave in 50-60% yield a variable mixture of methyl ester I-5 ($R = CH_3$) and acid I-5 ($R = H$). The ester--acid mixture was reduced by lithium aluminum hydride in refluxing tetrahydrofuran to the unsaturated alcohol I-6 in 96% yield, thereby obviating the need for separation of the ester from the acid.

Collins oxidation (chromium trioxide--dipyridine complex in dichloromethane)[39] of the unsaturated alcohol I-6 proceeded in 84% yield to give the air-stable unsaturated aldehyde I-7. Decarbonylation[15,16] of this aldehyde with tris(triphenylphosphine)chlororhodium(I) in refluxing benzene gave in 74% yield a 1:1 mixture of two compounds. The nmr spectrum of this mixture indicated that one of these compounds was the _trans_-di(angular methyl) octalin I-8. The other product (I-9), a saturated hydrocarbon, was not identified. It is thought that this hydrocarbon was a bicyclo [2.2.1] heptane, originating from addition of an organorhodium decarbonylation intermediate across the double bond. The mixture of olefin I-8 and hydrocarbon I-9 was quantitatively hydrogenated



A Possible Structure for Hydrocarbon I-9

in the presence of platinum in ethanol to a 1:1 mixture of the desired trans-di(angular methyl) decalin I-10 and the unchanged hydrocarbon I-9.

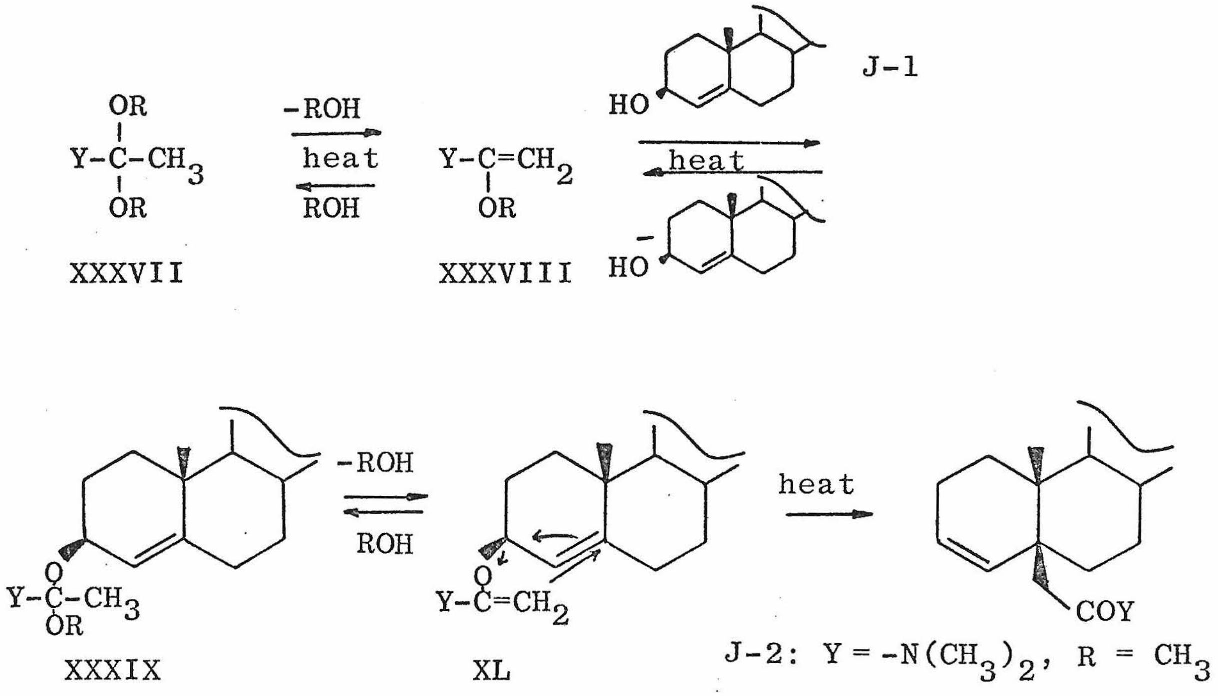
The difficulty encountered in the decarbonylation reaction originated in the olefinic double bond; therefore, this bond was reduced prior to decarbonylation. Since catalytic hydrogenation of the unsaturated aldehyde with platinum in ethanol resulted in partial reduction of the aldehyde moiety, the double bond of the unsaturated alcohol I-6 was quantitatively hydrogenated giving the saturated alcohol I-11, which was oxidized with Collins reagent[39] to the aldehyde I-12. This aldehyde was very air-sensitive and decomposed to several products after exposure to air for only an hour. The other three aldehydes prepared in this study: D-4 (cis, saturated), E-3 (cis, unsaturated), and I-7 (trans, unsaturated) were all stable in air. Because of this sensitivity, the saturated aldehyde I-12 was immediately decarbonylated[15,16] to the desired angularly dimethylated trans-decalin I-10 in 64% yield.

The above work demonstrates that it is possible to insert an angular methyl group to give a compound with either a *cis* or a *trans* ring fusion with complete stereospecificity. The three main problems with this new procedure were the low yield of the amide-acetal Claisen reaction, the variable yield in the vinyl ether preparaton, and the side product possible from the decarbonylation of an unsaturated aldehyde. These problems were subsequently studied on the cholestenol system.

ANGULAR SUBSTITUTION STUDIES ON THE CHOLESTENOL SYSTEM

Five reactions were studied in the cholestenol series (Chart J): (a) the reaction of cholest-4-en-3β-ol (J-1) with N,N-dimethylacetamidedimethylacetal to give the amide J-2, (b) the reaction of this cholestenol with triethyl orthoacetate to give the ester J-3, a procedure used by Johnson and coworkers with great success,[40] (c) the synthesis of cholest-4-en-3β-yl vinyl ether (J-4) from the alcohol J-1, (d) the Claisen rearrangement of this vinyl ether to the aldehyde J-5, and (e) the decarbonylation of the unsaturated aldehyde J-5. The objectives of this study also included the determination of reaction conditions leading to the highest yields and the identification of any side products in these reactions.

The three products of angular substitution: (a) amide, (b) ester, and (c) aldehyde originate by similar mechanisms. The mechanism for the first two, amide [$Y = -N(CH_3)_2$] and ester [$Y = -OC_2H_5$], is shown in Figure 13. In each case the high reaction temperatures used cause rapid equilibration of the acetal XXXVII and vinyl XXXVIII forms of the reagent (N,N-dimethylacetamidedimethylacetal or triethyl orthoacetate). Cholestenol J-1 adds to the vinyl form XXXVIII to give the acetal XXXIX, which, upon loss of methanol or ethanol,



XXXVII XXXVIII J-1

XXXIX XL

J-2: Y = $-N(CH_3)_2$, R = CH_3

J-3: Y = $-OC_2H_5$, R = C_2H_5

Figure 13: Mechanism for Amide and Ester Formation

yields the substituted allyl vinyl ether XL.

All the reactions so far have been reversible. Now, with the formation of the cholestenyl vinyl ether XL an essentially irreversible pathway out of the equilibrium occurs; the allyl vinyl ether undergoes a Claisen rearrangement to an angular acetamide (J-2) or acetic ester (J-3). If the equilibrium mixture contains enough of the allyl vinyl ether XL and if the temperature is high enough to effect the Claisen rearrangement, all the allylic alcohol is eventually converted to the Claisen product. At the high temperature necessary for the Claisen rearrangement, the methanol or ethanol is driven from the reaction mixture. The loss of one of the reaction

CHART J

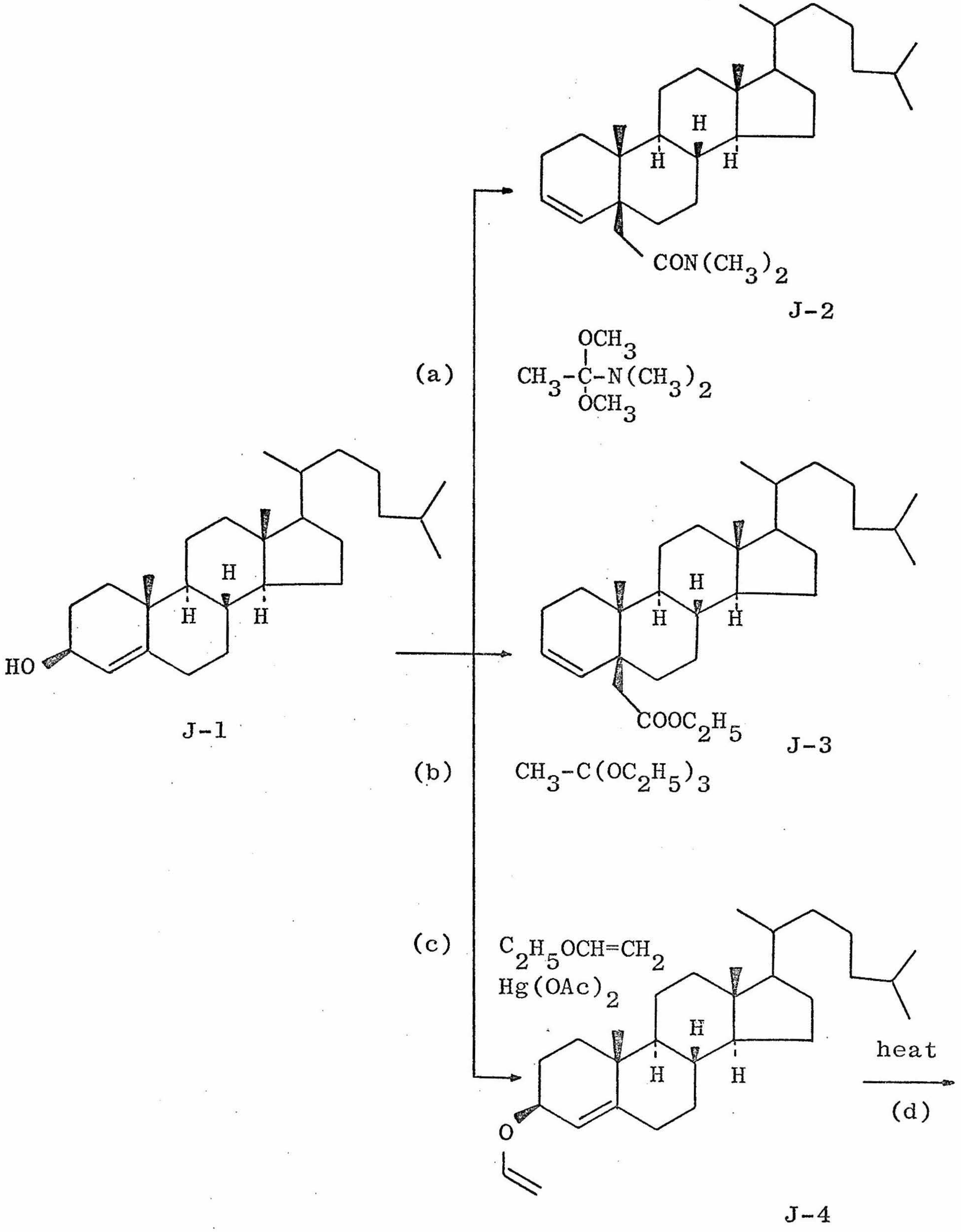
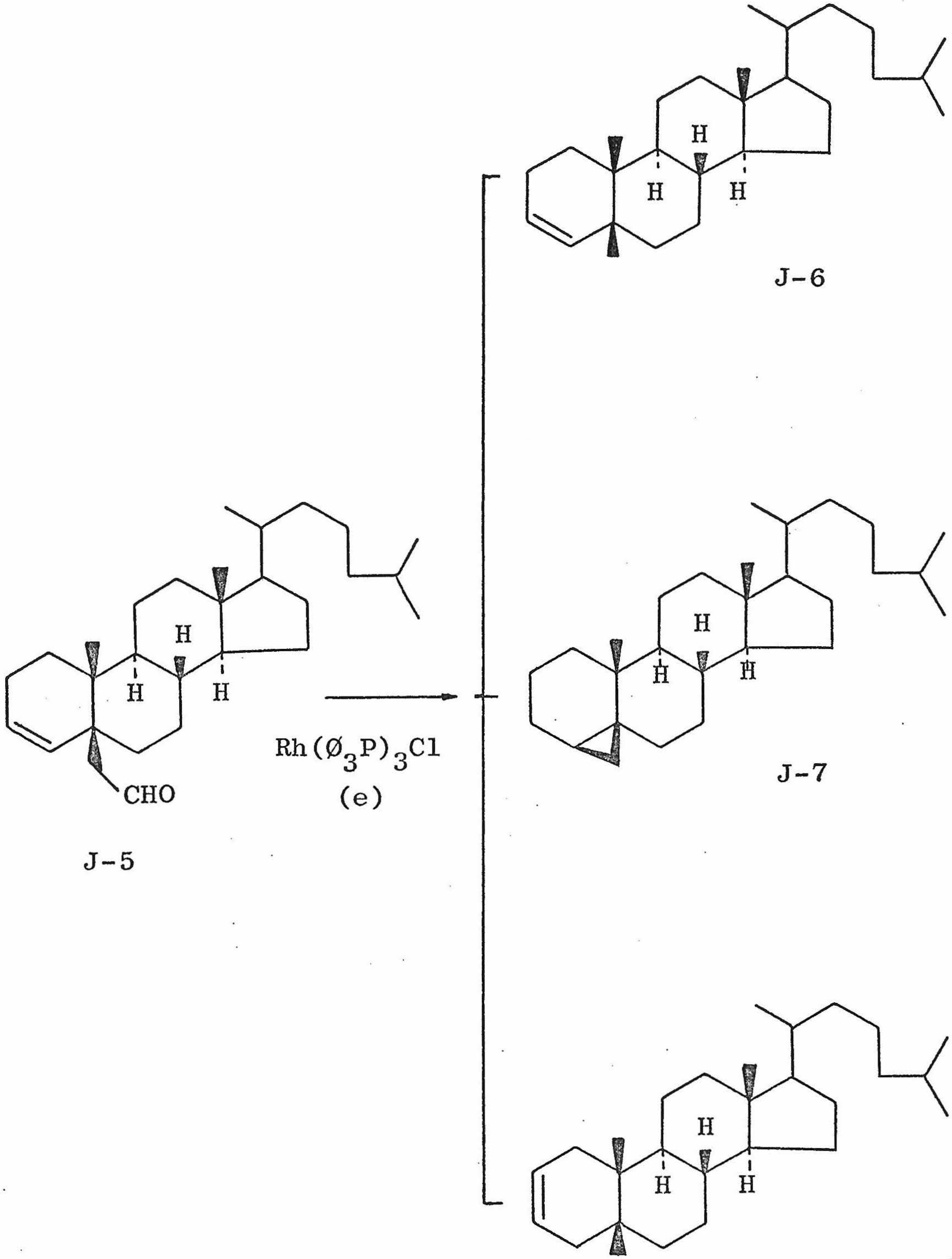

CON(CH3)2
J-2
(a)
CH3-C(OCH3)2-N(CH3)2
HO
J-1
COOC2H5
J-3
(b)
CH3-C(OC2H5)3
(c)
C2H5OCH=CH2
Hg(OAc)2
heat
(d)
O
J-4
H

CHART J (continued)



J-5

J-6

J-7

J-8

products also favors the formation of the allyl vinyl ether.

The mechanism for the formation[41] and Claisen rearrangement of the vinyl ether J-4 is almost identical to that shown above. Because ethyl vinyl ether is volatile (bp 36°), the reaction must be done at a low temperature. At this low temperature a catalyst is necessary for the addition of an alcohol to the ethyl vinyl ether; the catalyst used is mercuric acetate, and so the equilibration between the vinyl species XLI or XLIII and the acetal XLII actually becomes a reversible alkoxy-mercuration (Figure 14). Since the reaction

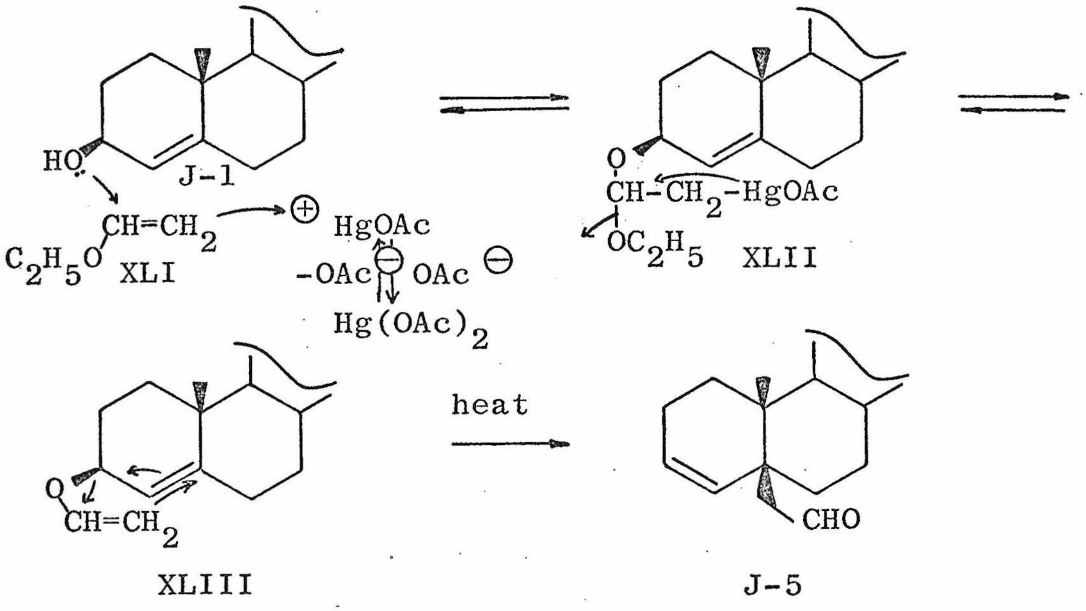
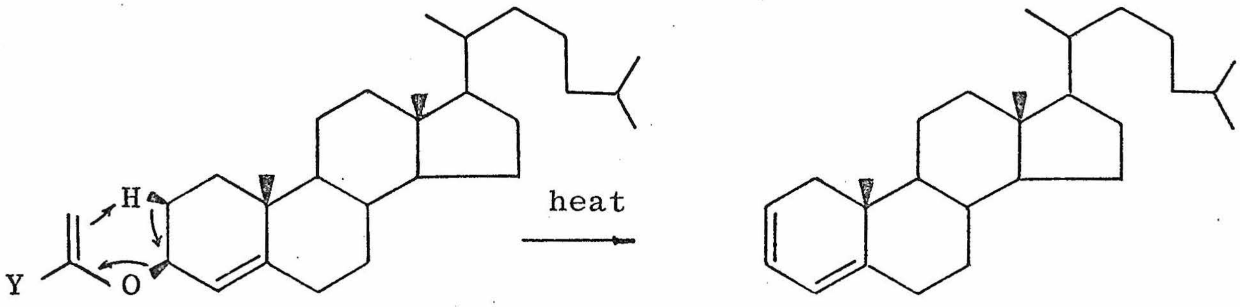


Figure 14: Mechanism of Vinyl Ether Formation

temperature is too low for the Claisen rearrangement and distillative removal of ethanol, product formation is not favored. The equilibrium mixture must therefore be forced toward product by the use of a large excess of one of the reactants, namely ethyl vinyl ether, which becomes the reaction solvent. The vinyl ether XLIII is then isolated and rearranged at a higher temperature.

A major side reaction of these Claisen rearrangements is diene formation, resulting from loss of dimethylacetamide, ethyl acetate, or acetaldehyde from the vinyl ether XL (Figure 15). Abstraction of a proton from the C-2 position of the vinyl ether by the terminal methylene group gives the



XL

XLIV

+

CH_3COY

Y = $-N(CH_3)_2$, $-OC_2H_5$, H

Figure 15: Mechanism for Diene Formation

diene, identified in one reaction as $\Delta^{2,4}$-cholestadiene (XLIV). Since vpc usually indicated the presence of two dienes, it is likely that the $\Delta^{2,4}$-diene slowly isomerized to the more stable $\Delta^{3,5}$-diene during the reaction. The elimination occurred to a greater extent in the amide and ester product mixtures than in the aldehyde product, presumably because the electron-donating properties of the nitrogen and oxygen atoms in the vinyl ether XL [Y = $-N(CH_3)_2$ and $-OC_2H_5$] are greater than that of hydrogen and increase the nucleophilicity of the terminal methylene.

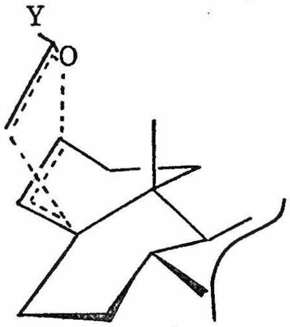
The best conditions found for the preparation of the amide J-2 were heating a solution of cholestenol and N,N-dimethylacetamidedimethylacetal in refluxing o-xylene (bp 140°) for about 65 hours. At this time vpc analysis indicated that the reaction was complete: 70% amide J-2 and 30% dienes. Removal of the volatile material at reduced pressure and chromatography of the residue on silica gel afforded the amide in 65% yield, a much better yield than that obtained in the valeranone synthesis. The higher temperature used in this later study probably accounted for the higher yield.

The optimum conditions for the preparation of the ester J-3 were similar to those used above. A solution of cholestenol J-1 in freshly distilled triethyl orthoacetate was heated at reflux (142°) for eight days with distillative removal of ethanol. Vpc analysis indicated that the reaction mixture contained 70% ester product J-3 and 30% dienes. Removal of the volatile material and chromatography of the residue gave a 60% yield of the ester J-3. Use of propionic acid as a catalyst[40] increased the reaction rate at the expense of yield and is therefore not recommended.

The vinyl ether--aldehyde preparation was far more difficult to optimize. The best procedure found was heating a solution of the cholestenol and mercuric acetate in ethyl vinyl ether at reflux for 17 hours, followed by the addition of acetic acid to decompose the alkyl mercury complex. The crude product was chromatographed on silica gel to give a 78% yield of the vinyl ether J-4, which was thermally rearranged at 220-225° for five hours and then chromatographed to afford the aldehyde J-5 in an overall yield of 53%.

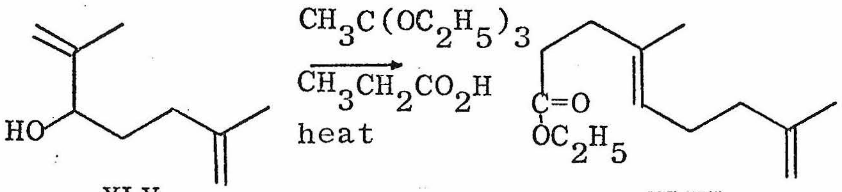
Unfortunately, this procedure is sensitive to a great many factors. The mercuric acetate had to be recrystallized.[8] The ethyl vinyl ether had to be purified with great care. The vinyl ether J-4 had been successfully chromatographed on alumina by Burgstahler,[7] and Ireland and Pfister.[25] However, when alumina chromatography was attempted, the yield of product was low and variable. In contrast, silica gel chromatography was quite successful. All glassware had to be base-washed; an attempt to rearrange the vinyl ether in a new flask, which had not been washed with base, resulted predominately in diene formation.

Incomplete rearrangement occurred when the vinyl ether was heated under the conditions used in the valeranone study, 195° for three hours. Increasing the temperature (220°) and time (five hours) led to a better yield, although not as high as that found in the valeranone system. Apparently the unfavorable geometry of the steroid ring system necessitates the higher rearrangement temperature (Figure 16), which, in turn, produces more elimination products. Ring rigidity may explain why the rearrangements at 140° in the amide and ester preparations were so slow, 65 hours and 8 days respectively. A higher reaction temperature in a pressure vessel may decrease the reaction time but also increase the extent of side reactions. In acyclic systems the unfavorable geometry is eliminated, and far shorter reaction times are needed. For example, Johnson and coworkers[40] converted the acyclic alcohol XLV to the ester XLVI in 92% yield in one hour.



XLa

Figure 16: Transition State for Claisen Rearrangement



XLV XLVI

Figure 17: Conversion of an Acyclic Alcohol to a Rearranged Ester

TABLE I

CLAISEN REARRANGEMENT REACTIONS OF CHOLEST-4-EN-3β-OL

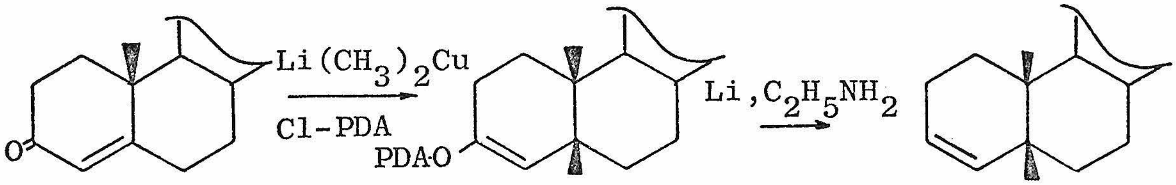
Reagent	Time	Temperature	Yield of Isolated Product
N,N-Dimethylacetamide-dimethylacetal	65 hr	140°	65%
Triethyl orthoacetate	8 days	140°	60%
Triethyl orthoacetate, propionic acid	32 hr	140°	55%[a]
Ethyl vinyl ether, mercuric acetate	17 hr	36°	78%,[b] 53%[c]

[a] vpc yield; [b] yield of vinyl ether; [c] overall yield to aldehyde

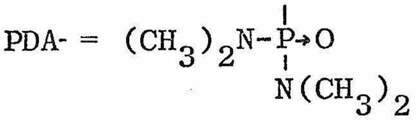
A comparison of the three routes to angular substitution is presented in Table I. Although the vinyl ether--aldehyde route affords the lowest yield, the aldehyde can be directly decarbonylated, while the amide or ester must first be transformed to the aldehyde.

The decarbonylation[15,16] of the unsaturated aldehyde J-5 with 1.0-1.5 equivalents of tris(triphenylphosphine)chlororhodium(I) proceeded in very high yield (98 - 99% mass recovery), and the ir spectrum of the product showed no aldehyde absorption. However, the nmr spectrum, vpc, and preparative silver nitrate chromatography demonstrated the presence of three compounds: the desired material, 5β-methylcholest-3-ene (J-6); the cyclopropane J-7; and an olefin, probably 5β-methylcholest-

2-ene (J-8). These compounds were present in an approximate ratio of 65:15:20. The desired decarbonylation product J-6 was identified by comparison (vpc and nmr) with authetic material prepared in these laboratories by Ireland and Pfister,[25] and Muchmore[42] by the sequence outlined in Figure 18.



XLVII XLVIII J-6



$$\text{PDA-} = (CH_3)_2N-\overset{|}{\underset{N(CH_3)_2}{P}}\rightarrow O$$

Figure 18: Preparation of 5β-Methylcholest-3-ene by the Lithium Dimethylcopper--Phosphodiamidate Cleavage Route

The identity of the cyclopropane was confirmed by an independent synthesis,* which is outlined in Chart K. Simmons-Smith[43] cyclopropylation of cholest-4-en-3β-ol (J-1), followed by

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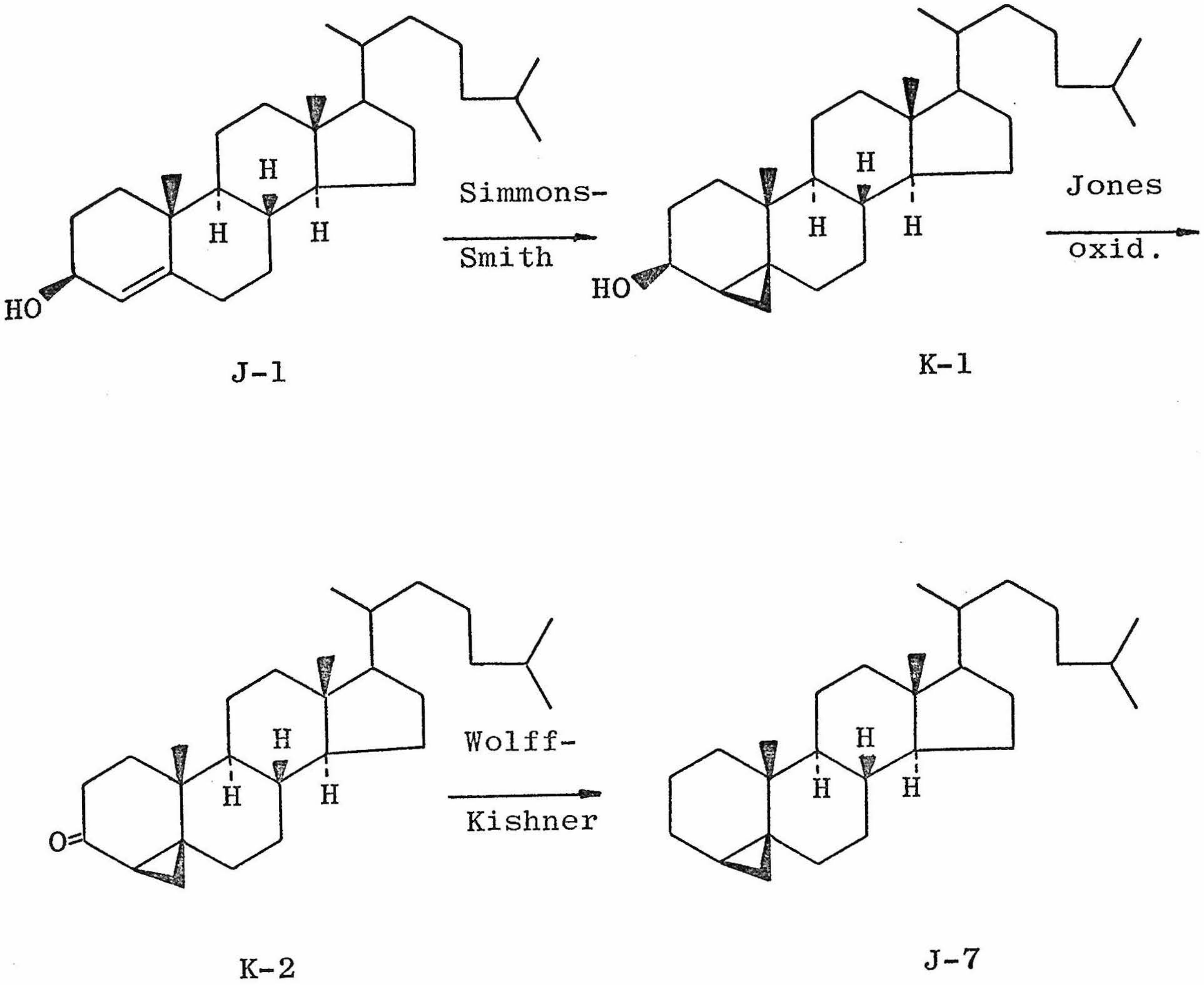
*The first two steps of this synthesis were performed by J. Tilley in the Ireland laboratories.

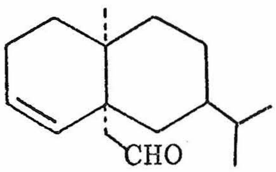
CHART K


HO
H
H
H
J-1
Simmons-
Smith
HO
H
H
H
K-1
Jones
oxid.
O
H
H
H
K-2
Wolff-
Kishner
H
H
H
J-7

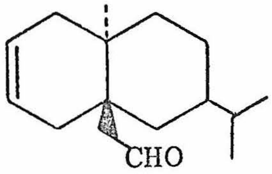
Jones oxidation[27] gave the cyclopropyl ketone K-2, which, after Wolff-Kishner reduction,[44] afforded the cyclopropane J-7. This cyclopropane was identical by ir, nmr, vpc, and tlc analysis with the decarbonylation side product.

The assignment of the side product J-8 as 5β-methylcholest-2-ene was made from the nmr and ir spectra, and the vpc and silver nitrate thin layer chromatographic behavior of this compound.

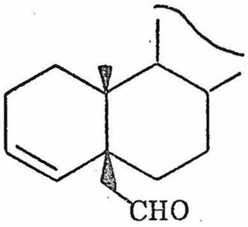
The mechanism for the formation of the two side products remains elusive. Although 1-butene is partially isomerized to 2-butene by tris(triphenylphosphine)chlororhodium(I) and 1-pentene is isomerized to 2-pentene by bis(triphenylphosphine)carbonylchlororhodium(I),[45] treatment of the Δ^3 olefin J-6 with either of these rhodium compounds in benzene (decarbonylation conditions) resulted in no isomerization to the Δ^2 olefin J-8. Evidently, isomerization must occur before or during the decarbonylation step itself. Another unexplained fact is the selectivity with which the decarbonylation intermediates attacked the double bond. Unsaturated aldehyde E-3 underwent decarbonylation with no side product formation, whereas the unsaturated aldehydes I-7 and J-5 experienced attack on the double bond.



E-3



I-7



J-5

The three-component mixture obtained by decarbonylation of aldehyde J-5 cannot be readily separated. The cyclopropane J-7 was isolated by chromatography on silica gel impregnated with silver nitrate, but the isomeric olefins J-6 and J-8 were incompletely separated by this method. Preparative gas chromatography would provide a means of separating these isomers, but this method is not suitable for a large scale manipulation. Alteration of the reaction conditions (using acetonitrile as the solvent, or reducing the temperature) did not eliminate the two side products. It must therefore be concluded that, in this case, the olefinic double bond would have to be reduced or converted to another functional group before decarbonylation to one angularly methylated product could occur.

CONCLUSION

The work reported above demonstrated that the Claisen rearrangement--decarbonylation method of angular methylation can be quite useful, especially in cases where more direct routes fail. Moreover, this route provides for the insertion of a functionalized angular substituent, a process which could be applied to the synthesis of natural product analogs. Reaction conditions have been optimized to the point where the yields are competitive with those of other methods, and so a facile application of this procedure to other systems is foreseen.

PART II

THE TOTAL SYNTHESIS
OF THE PENTACYCLIC TRITERPENE
dl-GERMANICOL

INTRODUCTION

Triterpenes are a large diverse group of C_{30} isoprenoid natural products. Most triterpenes, especially the pentacyclic triterpenes, are only found in plants, but a few, for example squalene, ambrein, and lanosterol, do occur in animals. Although the first of the triterpenes was isolated in 1788,[46] the size, complexity, and lack of functionality of members of this class of compounds prevented any structural elucidation until 1949.[47] Ruzicka and coworkers[48] did much of the work on the structure determination of the triterpenes and also promulgated a theory on their biosynthetic orgin.

This theory, now established for the triterpenes lanosterol[49] and β-amyrin[50] proposed that the cyclic triterpenes originate from a concerted enzymatic cyclization of the polyene squalene (L-1), followed by a series of rearrangements (Chart L). The cyclization product is dependent upon the configuration which the squalene molecule assumes on a particular enzyme. A chair-chair-chair-boat-boat conformation is necessary in the biosynthesis of most pentacyclic triterpenes; the two known exceptions are hydroxyhopenone and davallic acid, which are produced from an all-chair conformation of squalene.[48b]

The proposed biosynthetic pathway[48b] for lupeol (L-5), germanicol (L-7), and several other pentacyclic triterpenes

CHART L

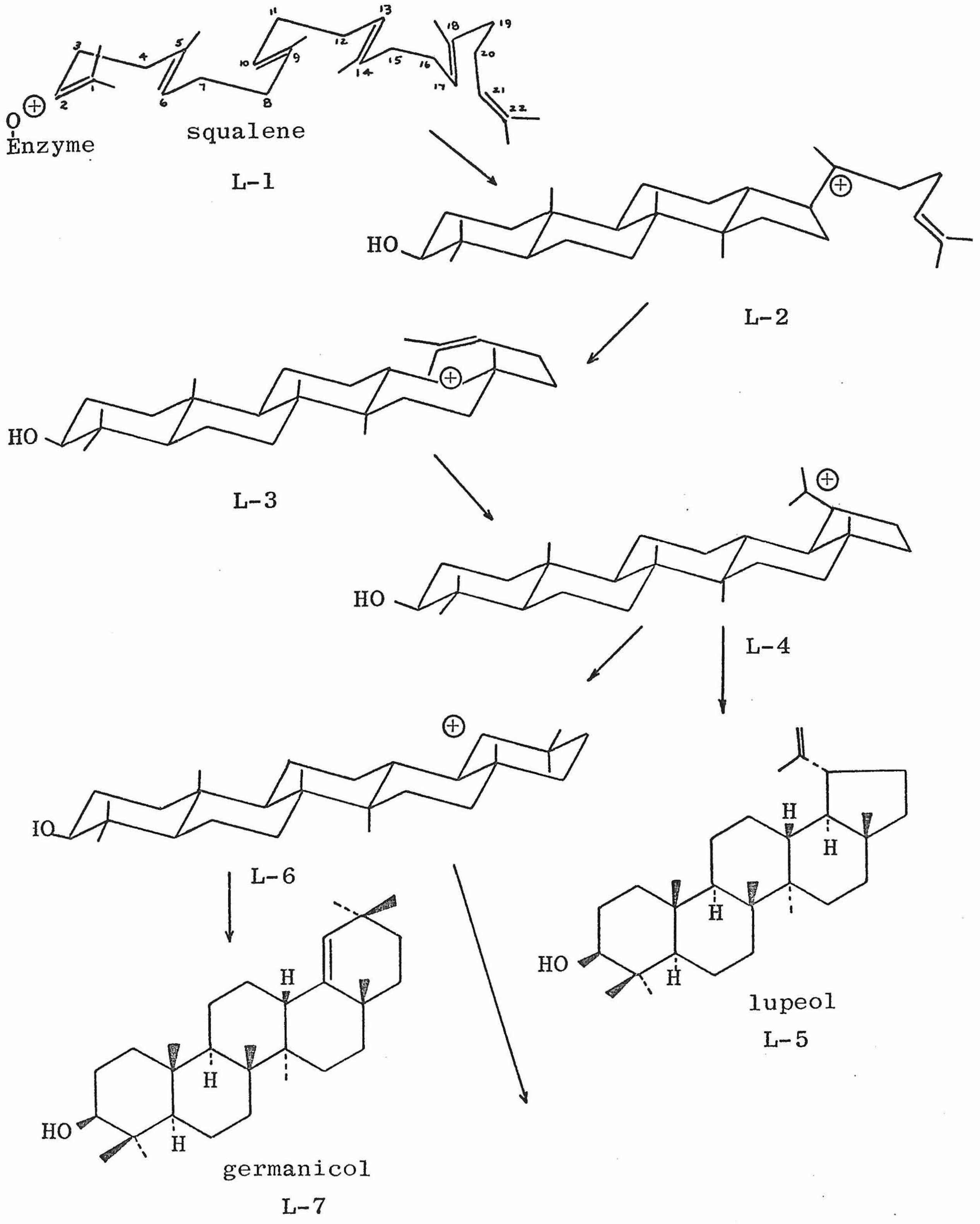
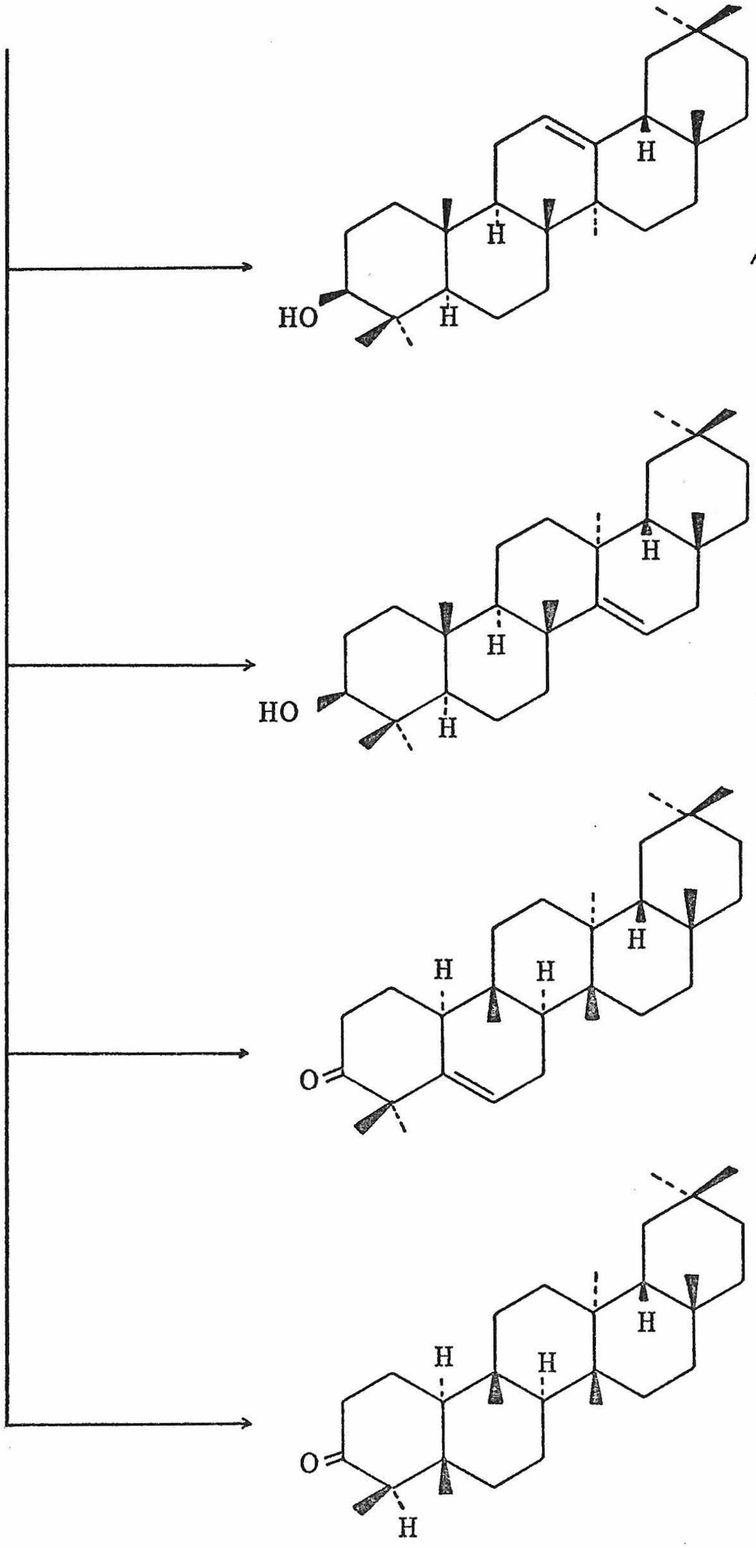

O
Enzyme
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
squalene
L-1
HO
L-2
HO
L-3
HO
L-4
IO
L-6
H
H
H
H
H
lupeol
L-5
HO
H
H
H
germanicol
L-7

CHART L (continued)



β-amyrin
L-8

taraxerol
L-9

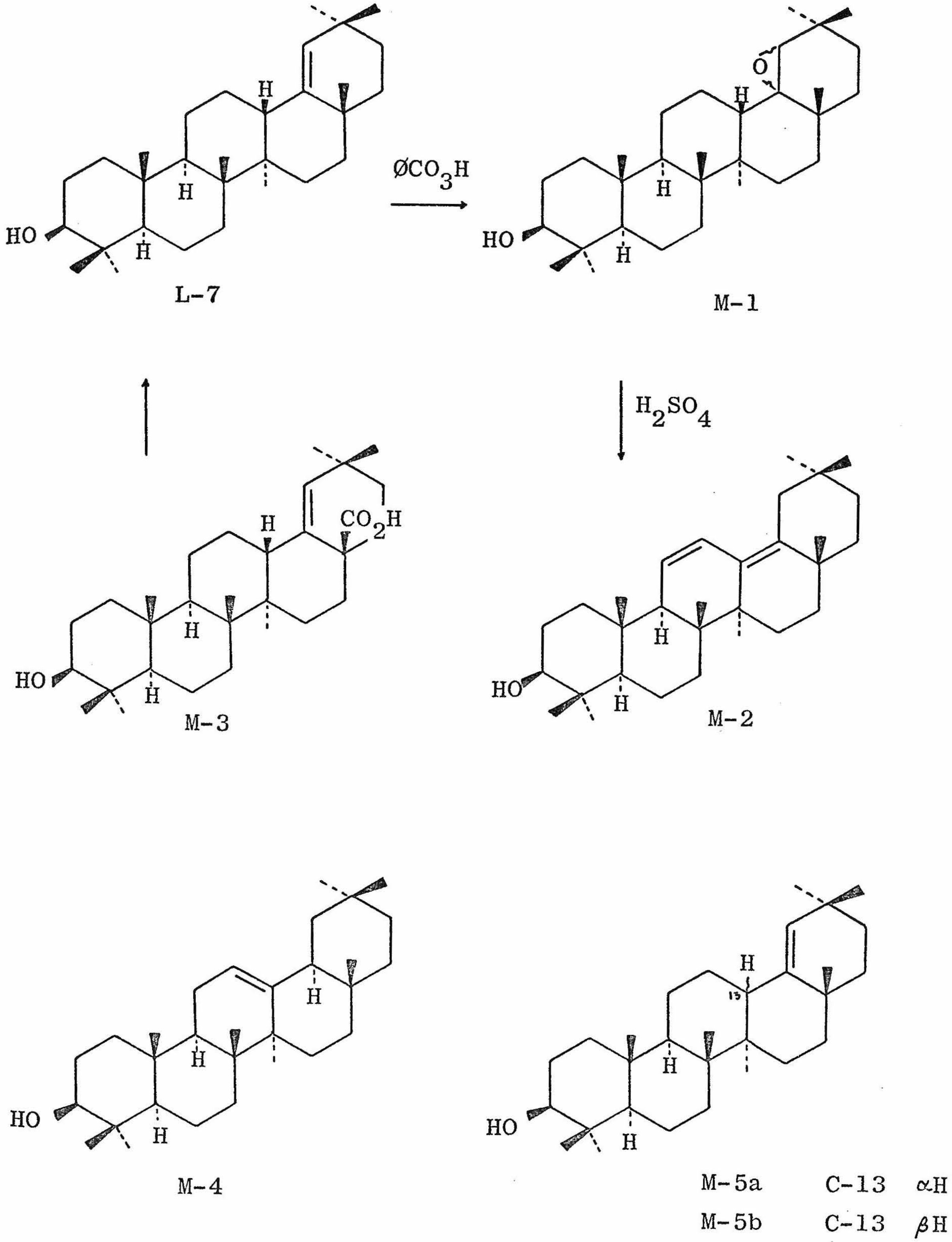
alnusenone
L-10

friedelin
L-11

is illustrated in Chart L. In this pathway, the polyolefin squalene cyclizes to give a carbonium ion (L-2). A "pause"[48b] then occurs while the C-16 group undergoes a Wagner-Meerwein shift to the C-18 position giving "intermediate" L-3. Intramolecular attack of the terminal double bond on the C-17 position of the carbonium ion affords a new bridged ion with a completed E ring. Either a proton from one of the terminal methyl groups of the ion L-4 can be lost to give lupeol (L-5), or the C-20 group can undergo a 1,2-shift to the C-22 position to give a new ion L-6. Loss of the C-17 proton by the ion L-6 affords germanicol (L-7). The ion L-6 can also produce the triterpenes β-amyrin (L-8), taraxerol (L-9), alnusenone (L-10), and friedelin (L-11) by a succession of 1,2-shifts, followed by loss of a proton.

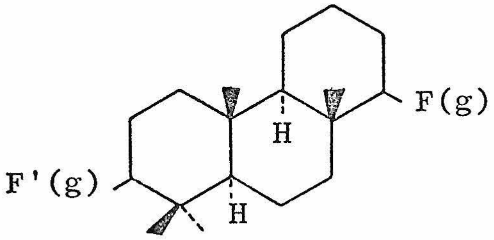
The second of these triterpenes and the object of the work reported herein, germanicol (L-7),[51] was first isolated by Simpson in 1944 from Lactucarium germanicum, the dried latex of Lactuca virosa.[52] David,[53] who undertook the first structural study of germanicol (Chart M), found that the double bond in this compound would not undergo a catalytic hydrogenation but did form an epoxide (M-1) with perbenzoic acid. The epoxide yielded the known compound oleana-11,13-dienol (M-2) on treatment with ethanolic sulfuric acid. This discovery, together with the determination of the germanicol empirical formula as $C_{30}H_{50}O$, established that germanicol was an isomer

CHART M



of β-amyrin (L-8). The infrared spectrum supported two structural assignments M-4 and M-5. Definite proof that germanicol had the structure L-7 (M-5b) was obtained in 1950 by its synthesis from morolic acid (M-3).[54] This result was verified by the conversion of both lupeol (L-5)[55] and β-amyrin (L-8)[56] to germanicol.

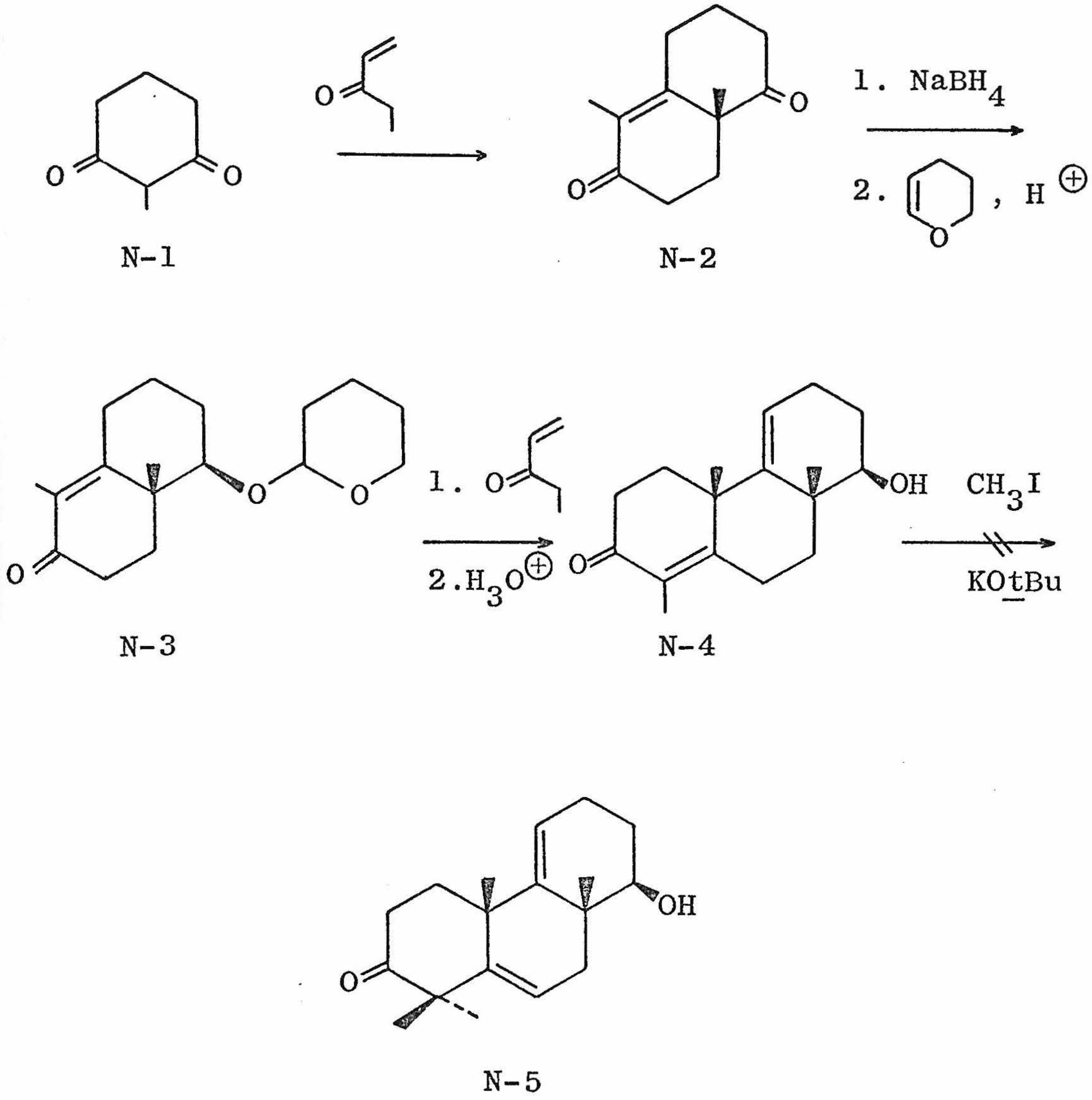
The synthesis of germanicol was undertaken as the first part of a program to establish an efficacious general route to several of the pentacyclic triterpenes. The first synthetic objective in this program was the functionalized tricyclic intermediate with the general structure XLIX, which was then to be converted to pentacyclic compounds.



XLIX

The original workers in this ten year long synthetic project, Dolfini and Ireland, synthesized the intermediate tricyclic keto-alcohol N-4 (Chart N).[57] Homoannelation of methyldihydroresorcinol (N-1) with ethyl vinyl ketone yielded the bicyclic dione N-2, which was then selectively protected

CHART N



to give the tetrahydropyranyl ether N-3. Another homoannelation with ethyl vinyl ketone, followed by acid hydrolysis of the tetrahydropyranyl ether, yielded the tricyclic enone N-4 in 19% yield. This compound lacked a methyl group at the C-1[*] position. All attempts at methylation with base and methyl iodide failed.

At about the same time the above work was done, Johnson, Brown,[58] and Schmiegel[59] developed another synthesis of the tricyclic system that eliminated the difficulties encountered in the methylation of enone N-4. They found that direct homoannelation of the dione N-2 with ethyl vinyl ketone, without protection of the saturated ketone function, resulted in a 15% yield of the tricyclic dione O-1. The dione was then selectively ketalized to the keto-ketal O-2, which underwent

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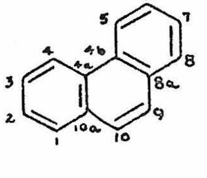
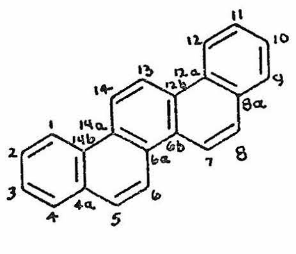
[*] The tricyclic compounds discussed herein are named as derivatives of phenanthrene, and the pentacyclic compounds are named as picene derivatives. The numbering system used is that found in the Ring Index (A. M. Patterson, L. T. Capell, and D. F. Walker, "The Ring Index," American Chemical Society, Washington, D. C., 1960.).

Although only one enantiomer is drawn, all compounds synthesized from methyldihydroresorcinol are racemic.

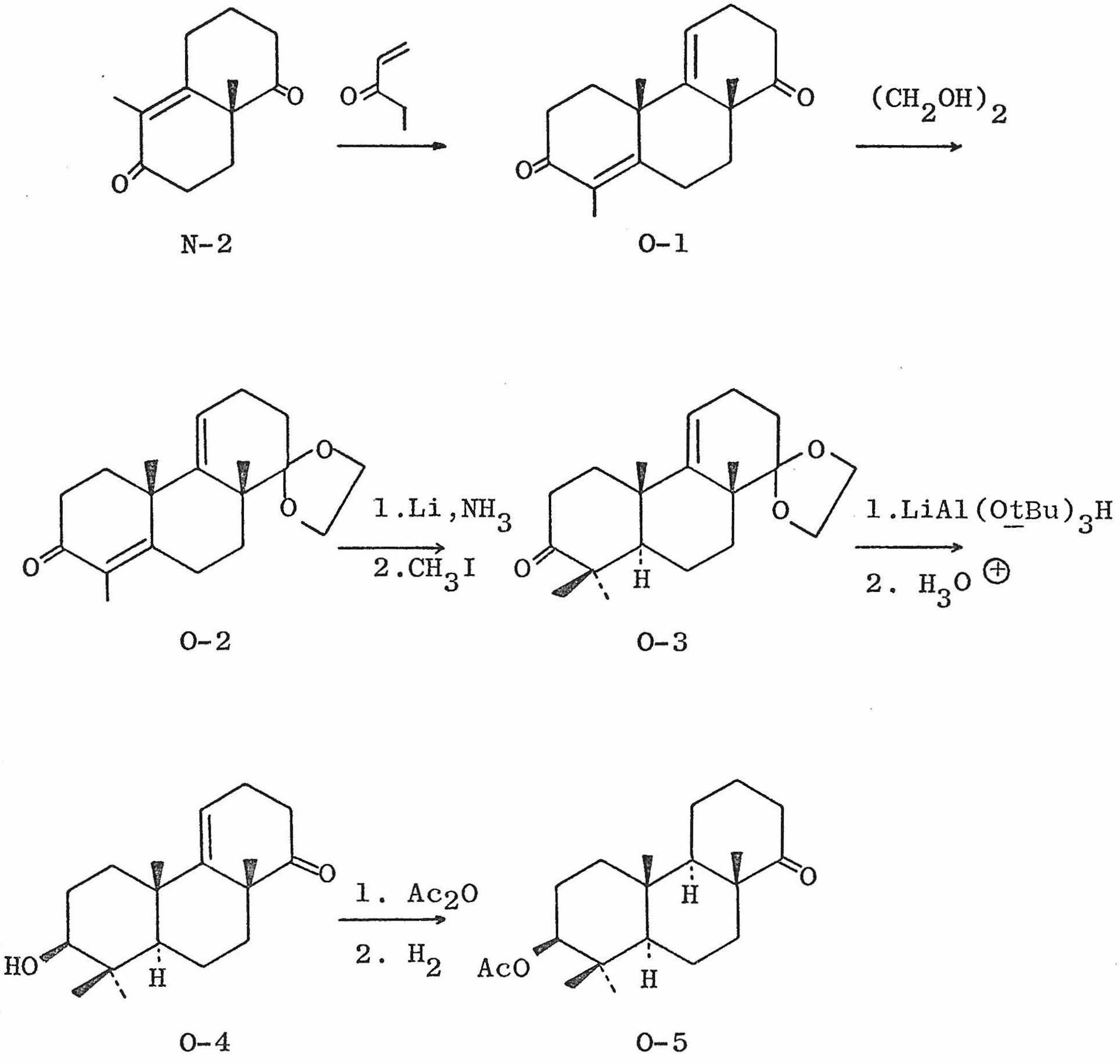


phenanthrene



picene

CHART O


N-2
O-1
(CH$_2$OH)$_2$
O-2
1.Li,NH$_3$
2.CH$_3$I
O-3
1.LiAl(O$\underline{t}$Bu)$_3$H
2. H$_3$O ⊕
O-4
1. Ac$_2$O
2. H$_2$
O-5
O
HO
AcO
H

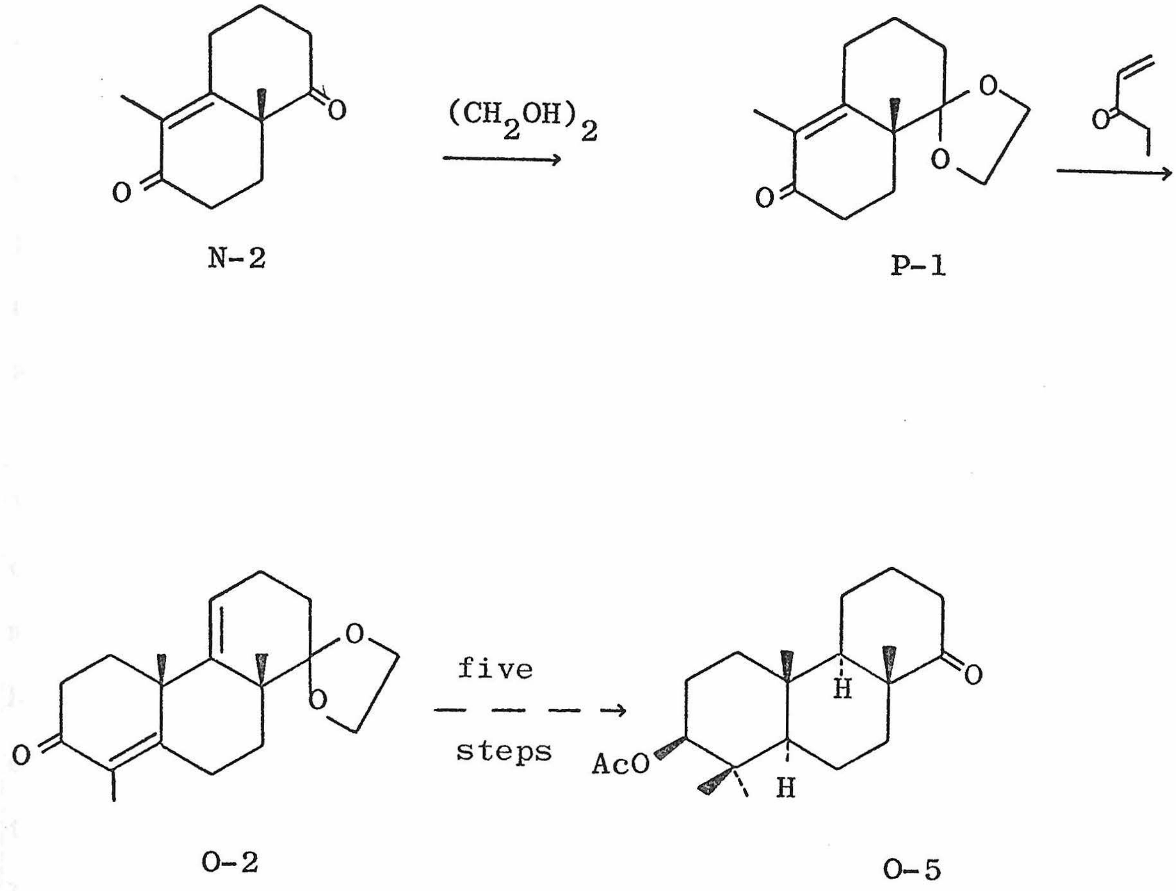
reductive methylation to afford the keto-ketal O-3. Hydrolysis of the C-8 ketal and protection of the C-2 oxygen function as an acetate, followed by catalytic hydrogenation of the $\Delta^{4b(5)}$ double bond, gave the tricyclic acetoxy-ketone O-5 with the desired stereochemistry (Chart O).

The most discouraging step in the sequence shown in Chart O was the second homoannelation, conversion of the bicyclic diketone N-2 to the tricyclic O-1. A competitive base-induced cleavage of the vinylogous β-diketone reduced the yield of homoannelated product to 15%. The following step, a selective ketalization of diketone O-1, proceeded in only 50% yield.

Baldwin and Ireland were able to improve the yield considerably by interchanging these two steps.[60] Selective ketalization of the bicyclic diketone N-2 afforded the keto-ketal P-1 in 94% yield (Chart P). Homoannelation of this enone (P-1) with ethyl vinyl ketone gave a 25% yield of the tricyclic enone O-2 along with a 52% recovery of starting material. Recycling the recovered starting material twice resulted in an overall homoannelation yield of 46%. The yield for the conversion of the bicyclic diketone to the tricyclic keto-ketal was therefore raised from 7.5 to 43%, a nearly five-fold increase. This improvement permitted the synthesis of the tricyclic acetoxy-ketone O-5 in an overall yield of 22% from methyldihydroresorcinol.

Since the acetoxy-ketone was available in reasonable quantities, the project was then directed toward the synthesis

CHART P



of germanicol. The next important synthetic objectives were the construction of the remaining rings (D and E) and the insertion of the C-6bα angular methyl group. The synthetic scheme selected to attain these objectives involved conversion of the acetoxy-ketone to an exocyclic methylene ketone, followed by a 1,4-addition of a benzyl Grignard reagent to this enone and then methylation of the resulting enolate at the C-8 position. By following this route, Baldwin and Ireland were able to synthesize the diketone Q-11, one step removed from a pentacyclic germanicol intermediate (Chart Q).

The exocyclic methylene ketone Q-7 was obtained from the acetoxy-ketone O-5 through the intermediacy of the endocyclic olefin Q-5. Treatment of the acetoxy-ketone O-5 with methyllithium afforded the diol mixture Q-1. The secondary hydroxyl group of the diol, arising from methyllithium cleavage of the acetate group, was oxidized with Jones reagent[27] to the ketone, and the tertiary hydroxyl, the result of methyllithium addition to the C-8 carbonyl, was dehydrated with thionyl chloride in pyridine to give the isomeric keto-olefins Q-3. This olefin mixture was equilibrated with p-toluenesulfonic acid in benzene to give the thermodynamically more stable endo isomer Q-4, which upon treatment with ethylene glycol and p-toluenesulfonic acid gave the ketal olefin Q-5. The five step synthetic sequence from the acetoxy-ketone O-5 to the ketal olefin Q-5 was accomplished in 86% yield.

CHART Q

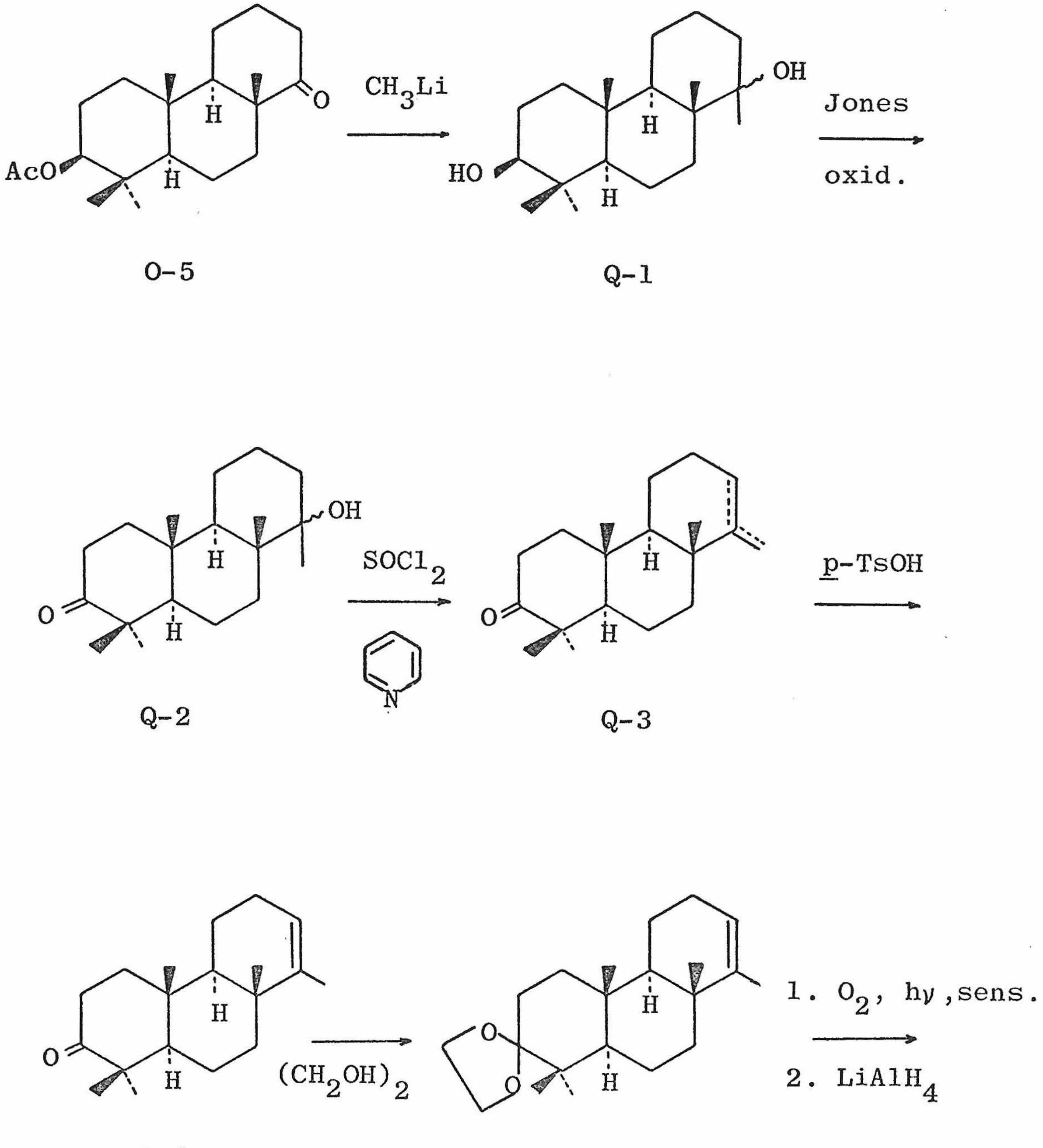

AcO
H
H
O
CH$_3$Li
O-5
HO
H
H
OH
Q-1
Jones
oxid.
O
H
H
OH
Q-2
SOCl$_2$
N
O
H
H
Q-3
p-TsOH
O
H
H
Q-4
(CH$_2$OH)$_2$
O
O
H
H
Q-5
1. O$_2$, hν, sens.
2. LiAlH$_4$

CHART Q (continued)

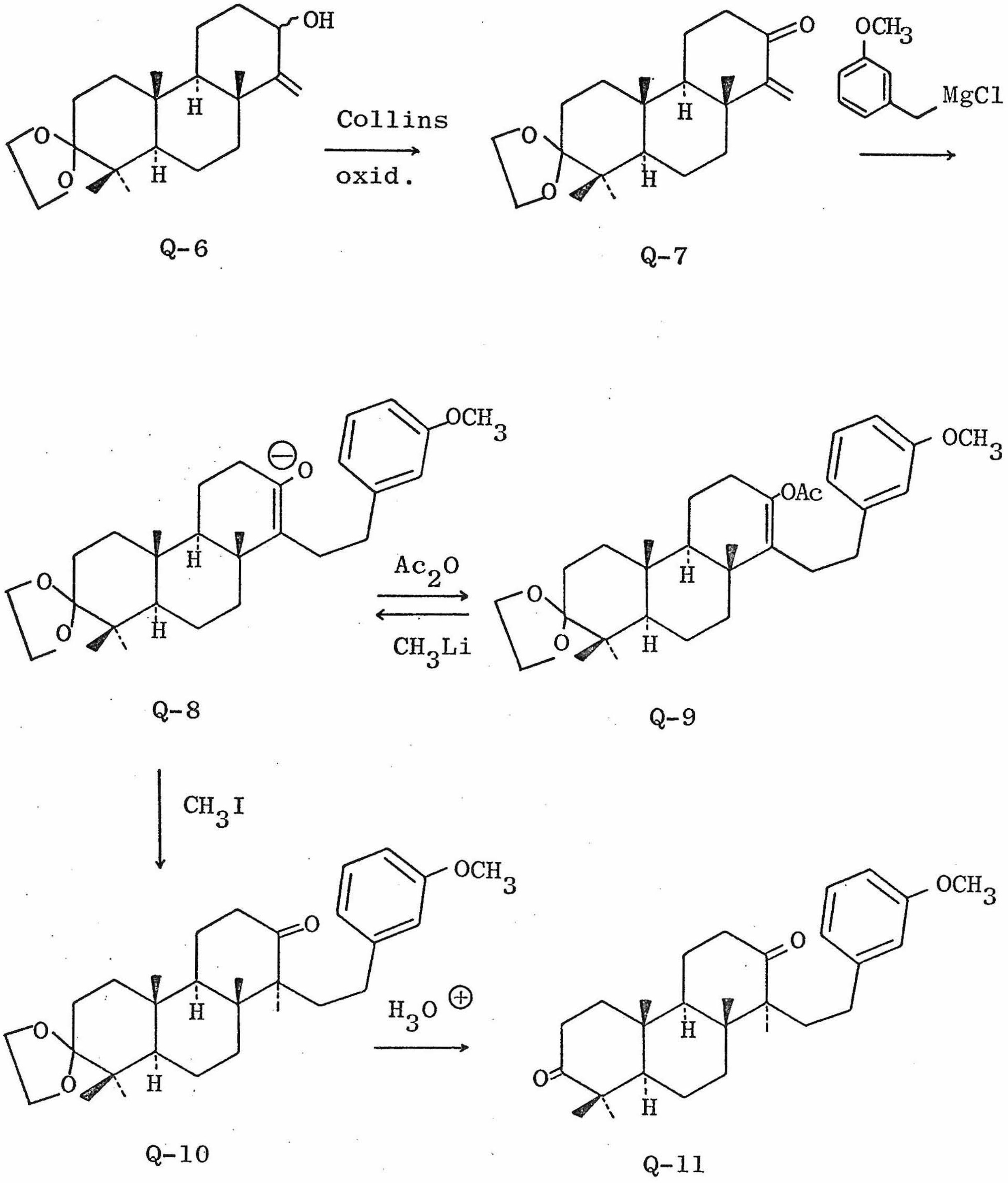


Photo-oxygenation[61] of the ketal olefin Q-5 in pyridine solution in the presence of hematoporphyrin as the sensitizer, followed by reduction of the intermediate hydroperoxide with lithium aluminum hydride, afforded the allylic alcohol Q-6 in variable yields (45-67%).[60]

Oxidation of the allylic alcohol with Collins reagent[39] gave the desired exocyclic methylene ketone Q-7 in 91% yield. The methylene ketone was then treated with *m*-methoxybenzylmagnesium chloride in ether. The *m*-methoxy group was used to introduce oxygen functionality in the E ring, which was necessary for the modification of this ring at a later stage in the synthesis. With or without cupric acetate catalysis, 1,4-addition of the Grignard reagent to the enone predominated over 1,2-addition.

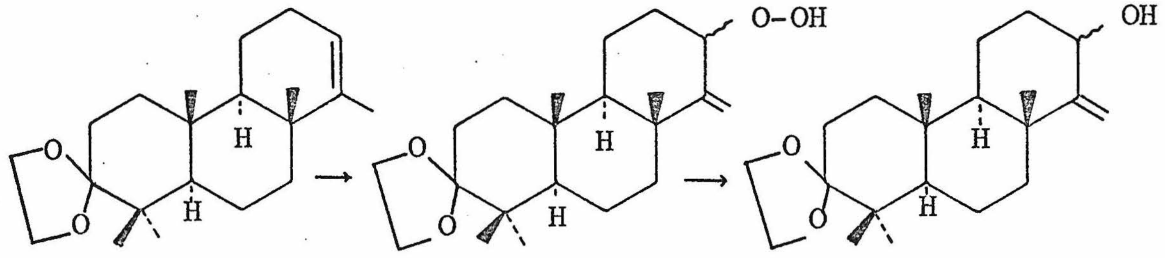
Since direct methylation of the enolate produced by Grignard addition (Q-8) was unsuccessful, the enolate was quenched with acetic anhydride to afford the 1,4-adduct, enol acetate Q-9, in 71-74% yield. The enolate Q-8 was then regenerated from the purified enol acetate Q-9 with methyllithium in dimethoxyethane. Methylation of the enolate with methyl iodide produced the keto-ketal Q-10, which was hydrolyzed to the diketone Q-11. The yield reported for this conversion from the enol acetate was 68%.

The remaining work entailed the development of a large-scale preparation of diketone Q-11 and its transformation into *dl*-germanicol.

DISCUSSION

Before the synthesis of germanicol could be continued, it was necessary to prepare the diketone Q-11 in larger quantity. Both the aforementioned route and a new, epoxide cleavage route were used for this preparation.

The photo-oxygenation procedure[60,61] used for the conversion of olefin Q-5 to the allylic alcohol (Figure 19) had the disadvantages of moderate yield, experimental difficulties on other than a small scale, and long reaction times. In an effort to avoid these problems an alternate route was investigated. In this route the olefin R-1 was epoxidized, and the product rearranged with base to the allylic alcohol R-3 (Chart R). This route has precedence in the work of Crandall



Q-5 L Q-6

Figure 19: Photo-oxygenation of the Ketal Olefin Q-5

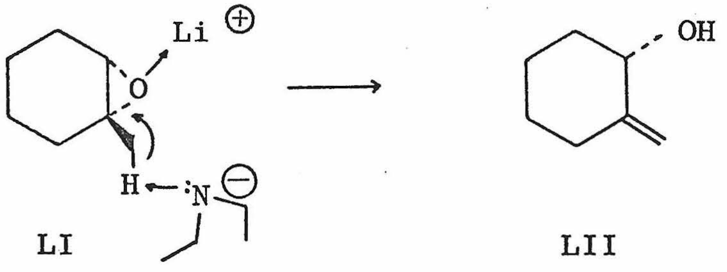


Figure 20: Epoxide Cleavage by Lithium Diethylamide

and Lin,[62] who cleaved the epoxide LI with lithium diethylamide to obtain the exo-methylene allylic alcohol LII (Figure 20).

Since the carbonyl group of keto-olefin Q-4[*] was sensitive to the basic reaction conditions used, it required protection. The protecting group selected was the 2,2-dimethylpropylene ketal, for Heathcock[63] has reported that an ethylene ketal is not stable to the extremely basic conditions used in the epoxide cleavage reaction. Apparently, an ethylene ketal can undergo a β-elimination reaction with a strong base (Figure 21). The dimethyl propylene ketal, lacking β protons, is stable.

In contrast to the formation of the ethylene ketal Q-5 in 84% yield with ethylene glycol, the six-membered ring ketal

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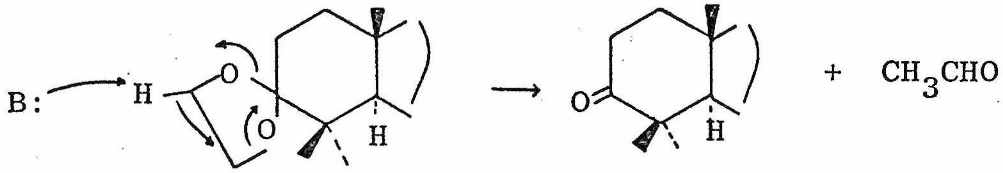
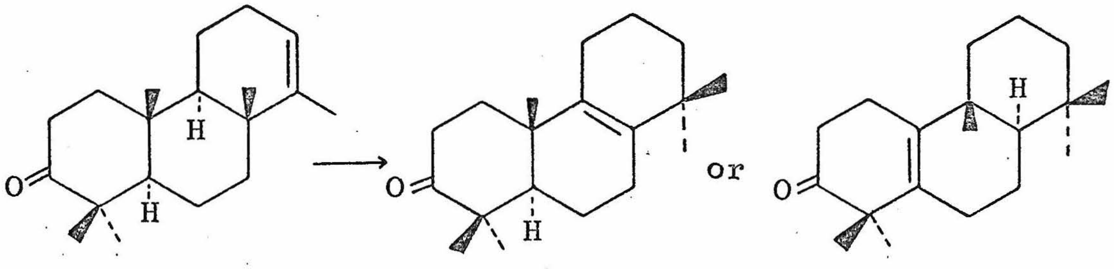
[*] All racemic materials in this part of the germanicol project were prepared from 20 g of keto-alcohol O-4 left by S.W. Baldwin and 30 g of keto-ketal O-3 prepared by J.H. Ham in the Ireland laboratories.



LIII LIV

Figure 21: β-Elimination of an Ethylene Ketal

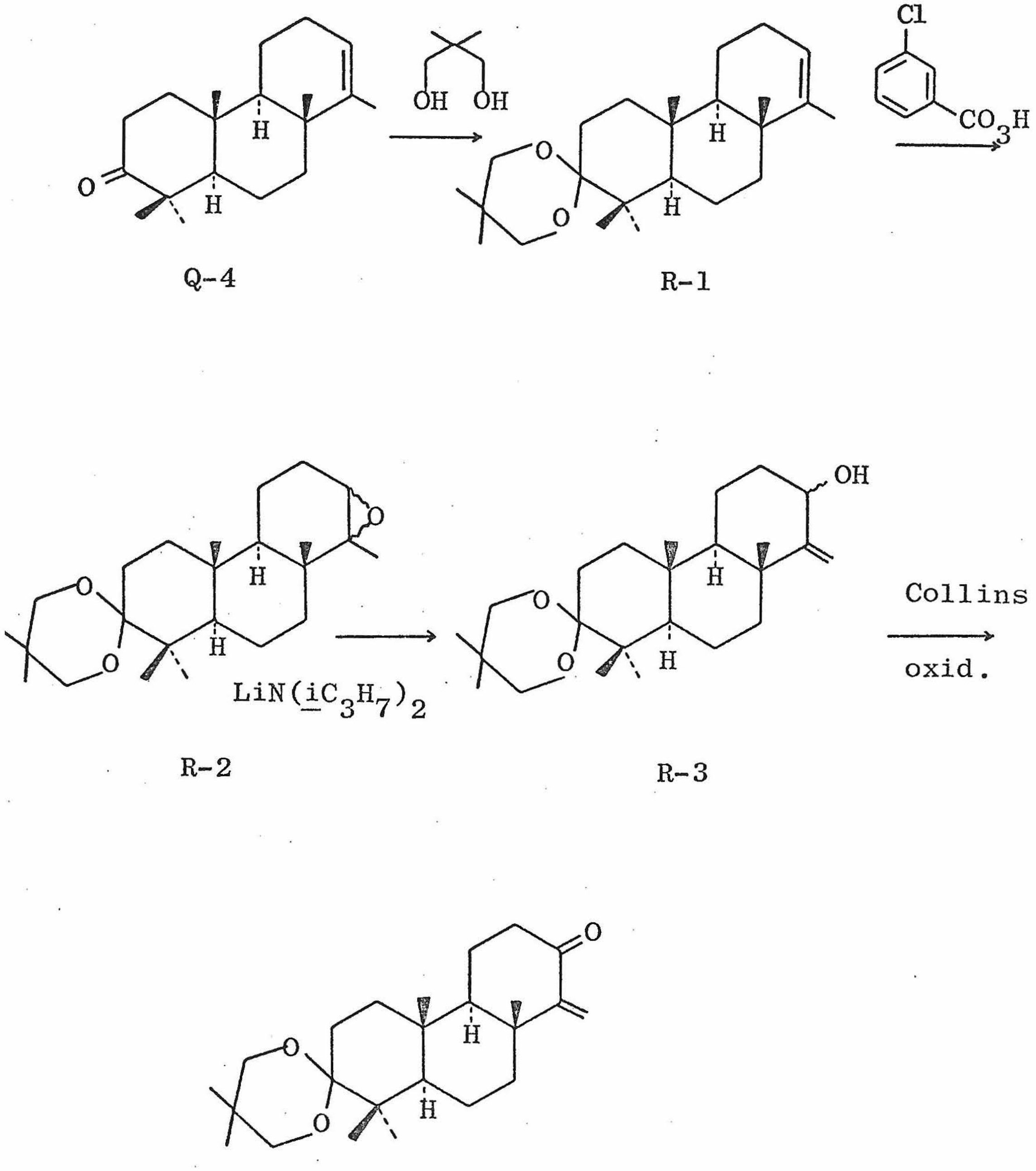
R-1 was obtained in only 58% yield with 2,2-dimethyl-1,3-propanediol. The cause of this low yield is not immediately apparent, however vpc analysis of the crude reaction product indicated numerous side products. It is possible that the acid catalyst induced methyl group migrations. A similar rearrangement was proposed by Baldwin to rationalize the isomerization of the keto-olefin Q-4 during silica gel chromatography[60] (Figure 22).



Q-4 LV LVI

Figure 22: Acid-Catalyzed Rearrangement of Keto-Olefin Q-4

CHART R


OH OH
Cl
CO_3H
Q-4
R-1
$LiN(\underline{i}C_3H_7)_2$
Collins
oxid.
R-2
R-3
R-4
H
O
OH

Treatment of the ketal olefin R-1 with *m*-chloroperoxybenzoic acid resulted in the formation of the epimeric mixture of epoxides R-2 in 99% yield (Chart R). On exposure to lithium diisopropylamide in refluxing ether, the epoxide mixture rearranged to a mixture of allylic alcohols. Collins oxidation[39] of the mixture gave both endo- and exo-cyclic enones, from which the desired methylene ketone R-4 was separated by silica gel column chromatography. The yield for the epoxide formation, cleavage, and oxidation steps was 52%.

The infrared spectrum of the crude oxidation product exhibited two carbonyl bands of equal intensity (1685 and 1655 cm^{-1}). The absorption at 1685 cm^{-1} originated from the desired exocyclic enone R-4, and that at 1655 cm^{-1} was due to the endocyclic enone LVIII. This major side product, isolated in 35% yield in one reaction, was apparently the result of an oxidative rearrangement of the tertiary allylic alcohol LVII, which, in turn, was a side product of the epoxide cleavage reaction (Figure 23). Evidence for the origin of this side product was supported by the results of an epoxide cleavage with lithium diethylamide. Since lithium diethylamide is less sterically hindered than lithium diisopropylamide, it was expected to exhibit less preference for the primary protons of the C-8 methyl group and therefore to also abstract a C-6 proton. The nmr spectrum of the alcohol mixture obtained by using this base indicated that the pre-

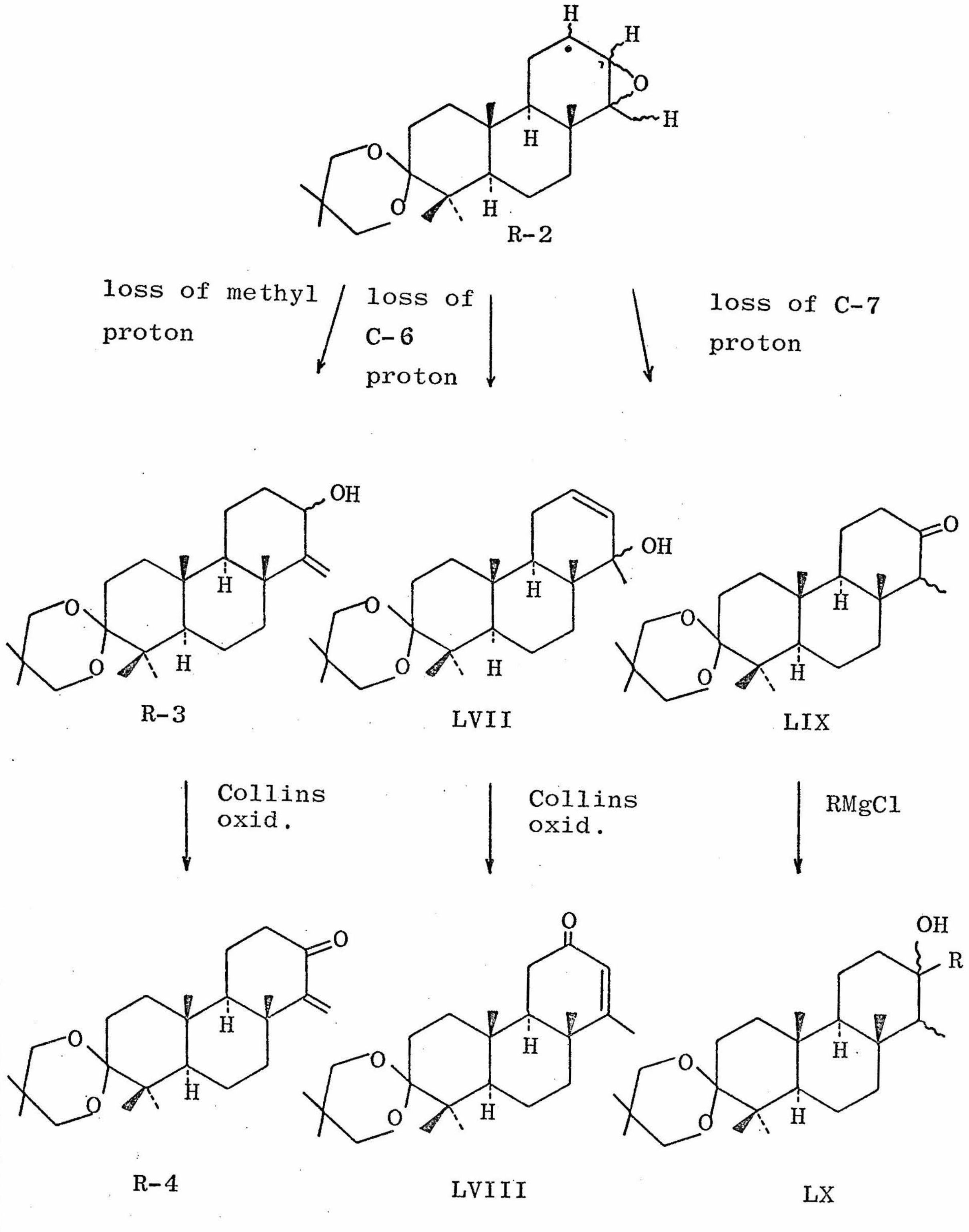


Figure 23: Base Cleavage Products of Epoxide R-2

dominant isomer was, indeed, the tertiary allylic alcohol LVII. Moreover, Collins oxidation of this mixture produced an enone mixture in which the endocyclic enone LVIII was the main isomer. The infrared spectrum of this mixture had the two carbonyl absorptions corresponding to the enones LVIII and R-4 in a ratio of 3:1.

A second side product of the epoxide cleavage was the saturated ketone LIX (Figure 23), which probably resulted from a C-7 proton abstraction. Although this saturated ketone was a minor side product in the small scale epoxide cleavage, a large scale cleavage resulted in a 20% yield of this ketone, which was isolated as the Grignard addition product LX (R = m-methoxybenzyl). It is possible that the formation of this side product was caused by the presence of a 25% excess of diisopropylamine in the large scale cleavage reaction mixture.

The yield for the epoxidation, base cleavage, and Collins oxidation (52%) is comparable to that of the photo-oxygenation--Collins oxidation synthon (41-61%). However, if the olefin equilibration and ketal formation steps (84% yield for the five-membered ring ketal and 58% for the six-membered) are considered, the photo-oxygenation route is definitely superior. Improvement of the dimethylpropylene ketal formation or the suppression of the side products of epoxide cleavage would enhance the desirability of the epoxide route.

The 1,4-addition of m-methoxybenzylmagnesium chloride to the methylene ketone R-4 in ether, followed by quenching of the enolate with acetic anhydride, formed the enol acetate S-1 in 56% yield, which was the same yield as that obtained using the ethylene ketal ketone Q-7. Treatment of the enol acetate S-1 (Chart S) with methyllithium in dimethoxyethane regenerated the enolate, which was alkylated with methyl iodide to give a mixture of keto-ketal S-2 (60%), dimethylated ketone LXI (16%), and another compound (20%), which was considered to be the methyl enol ether LXII, since hydrolysis of this material yielded the unmethylated ketone LXIII. No unmethylated ketone, however, was found in the crude product mixture. Hydrolysis of ketal S-2 gave a 64% yield of dione Q-11.

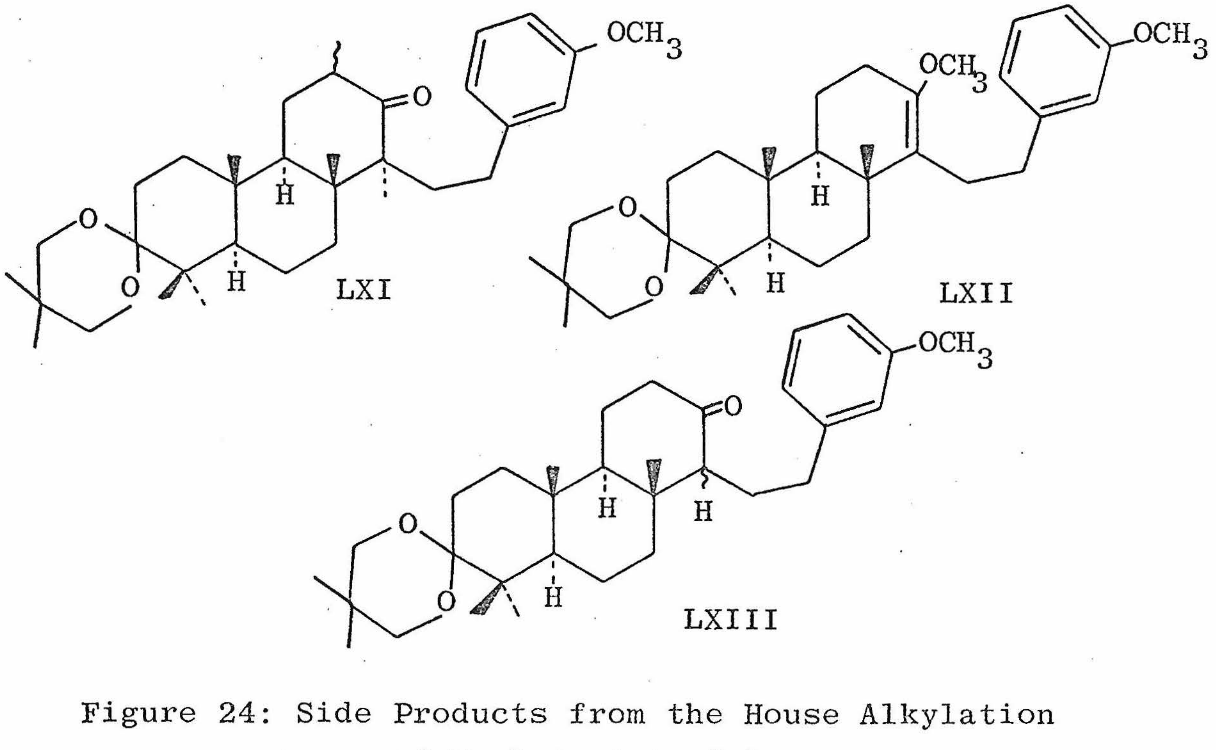
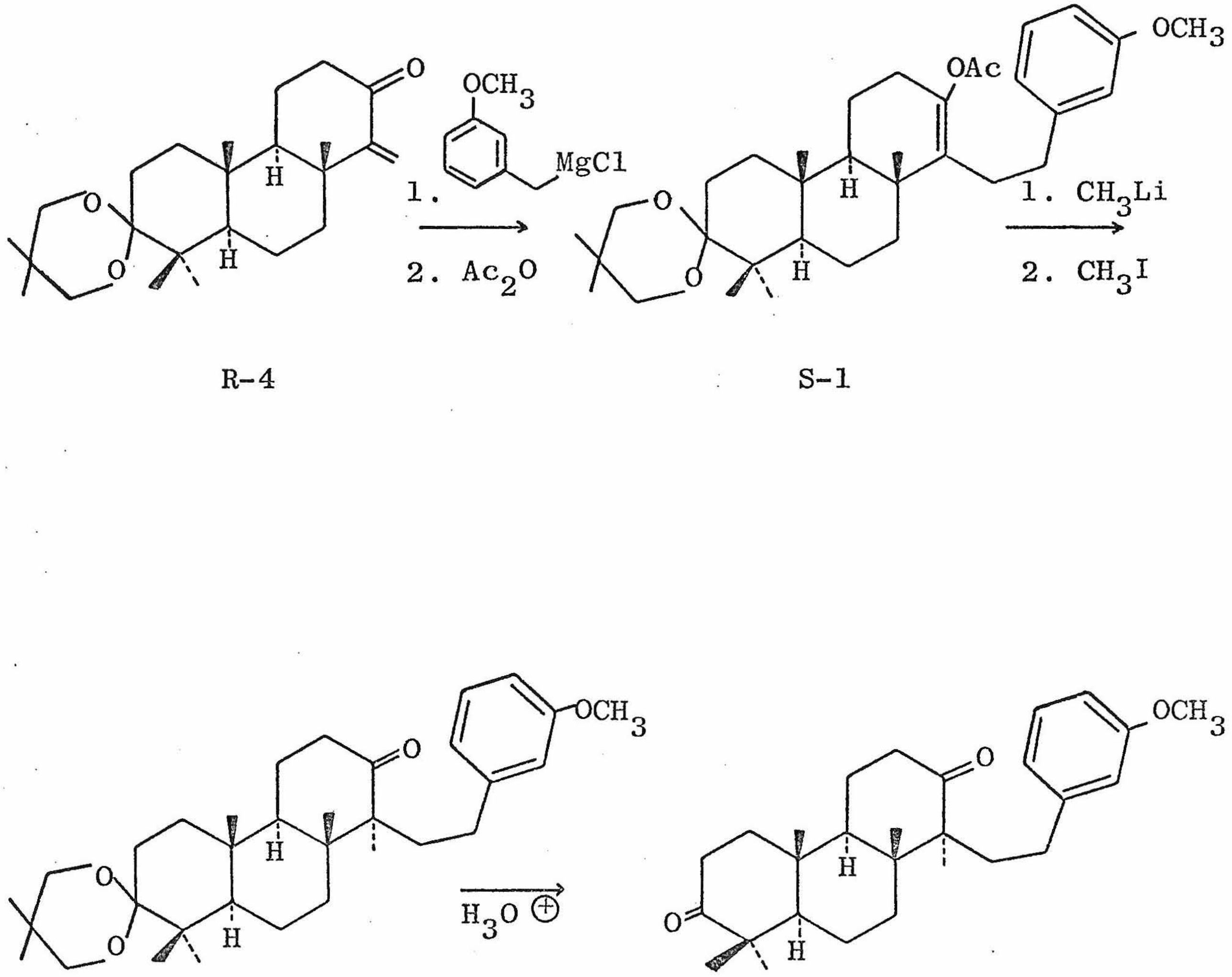


Figure 24: Side Products from the House Alkylation of Enol Acetate S-1

CHART S



R-4

S-1

S-2

Q-11

The next problem was the verification of the structure of the diketone Q-11. Preliminary aromatic solvent induced shift measurements by Baldwin and Ireland indicated that the C-8 methyl group of the keto-ketal Q-10 did have the anticipated α configuration. The collision complex of a ketone with benzene causes the nmr absorption of an axial methyl group adjacent to this ketone to experience a large upfield shift (20-30 Hz) relative to its position in pure deuteriochloroform. The absorption of an equatorial methyl group exhibits only a small upfield or downfield shift.[64] The observed shift of the C-8 methyl group signal of keto-ketal Q-10 was 17 Hz upfield, which is consistent with the axial assignment.[60]

This result was confirmed by a direct comparison of the racemic diketone Q-11 with the optically active diketone obtained by degradation of the tetracyclic triterpene euphol. Johnson, Crawford,[65] and Hudrlik[66] isolated euphol (T-1) from euphorbium gum and degraded it to the lactone acetate T-8 (Chart T) by a modification of the procedures developed by Arigoni and coworkers.[67]

The lactone acetate was then converted to the optically active diketone Q-11 by M. Dawson [68] by the sequence of reactions outlined in Chart U. Saponification of the lactone acetate T-8, followed by acidification, yielded the hydroxylactone U-1, which was oxidized with Collins reagent[39] to the

CHART T

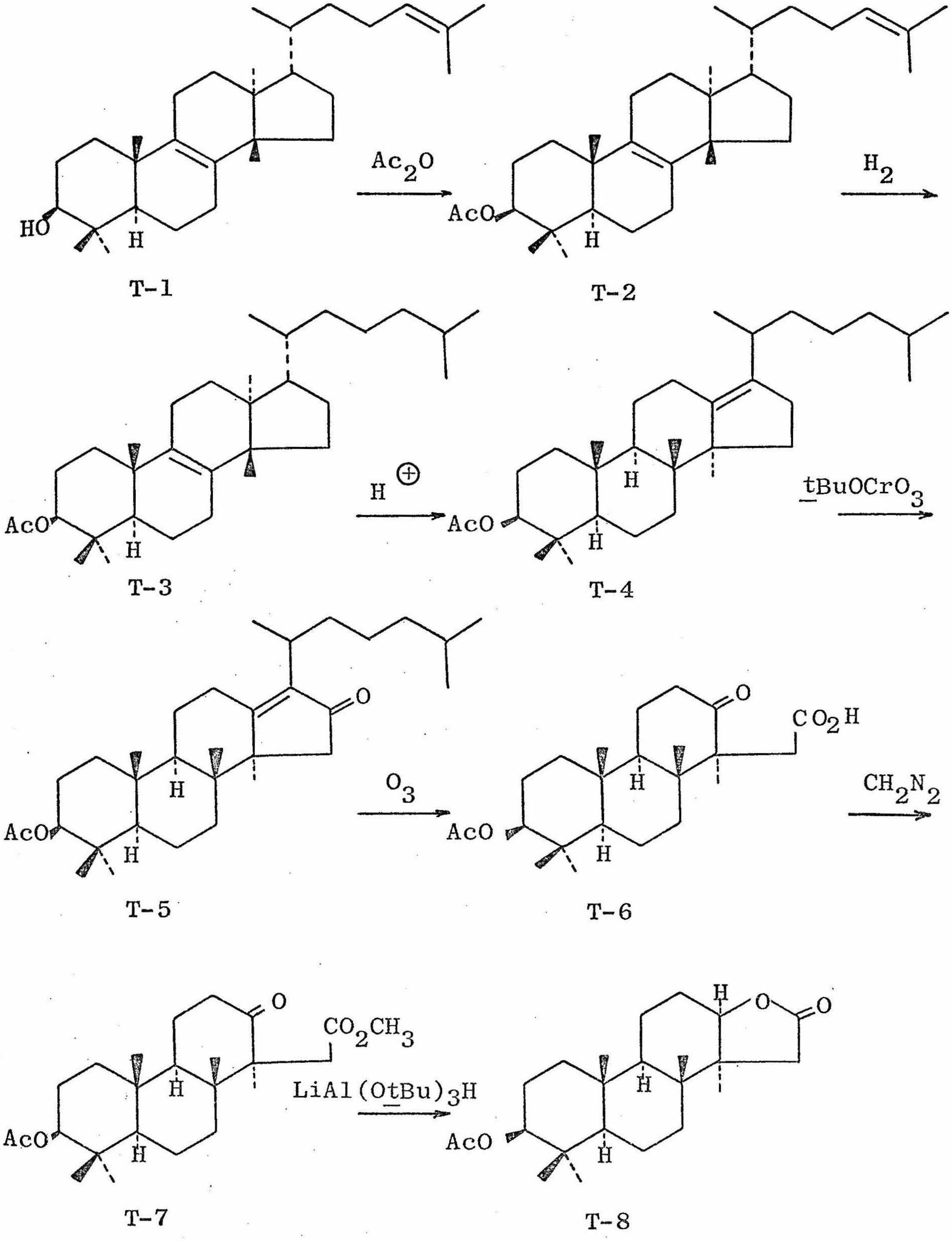
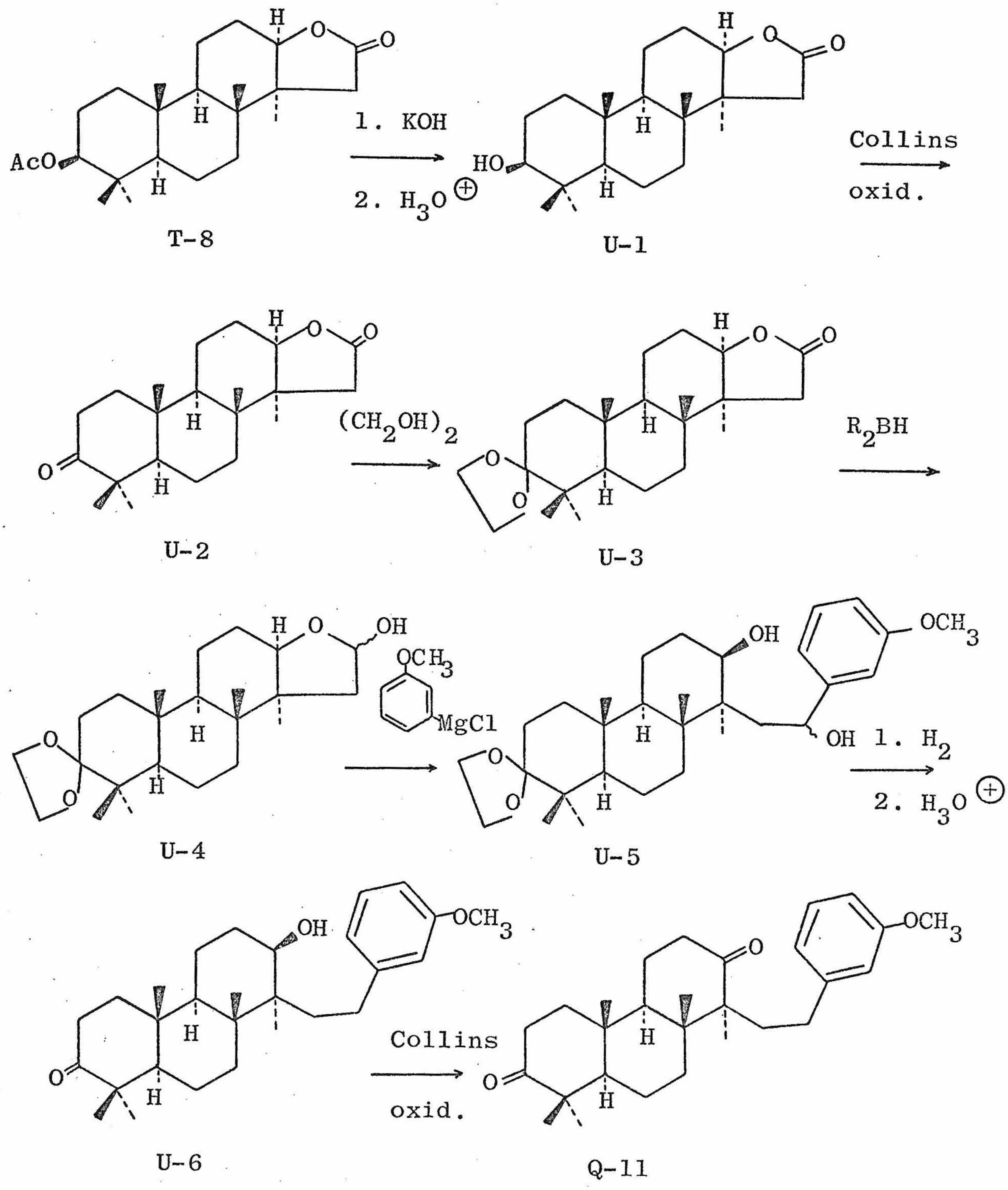

HO
H
T-1
Ac2O
AcO
H
T-2
H2
AcO
H
T-3
H⊕
AcO
H
H
T-4
tBuOCrO3
O
AcO
H
H
T-5
O3
O
CO2H
AcO
H
H
T-6
CH2N2
O
CO2CH3
AcO
H
H
T-7
LiAl(OtBu)3H
H
O
O
AcO
H
H
T-8

CHART U


T-8
1. KOH
2. $H_3O^{\oplus}$
U-1
Collins
oxid.
U-2
$(CH_2OH)_2$
U-3
R_2BH
U-4
OCH_3
MgCl
U-5
1. H_2
2. $H_3O^{\oplus}$
U-6
Collins
oxid.
Q-11

keto-lactone U-2. Protection of the ketone function as a ketal and reduction of the lactone moiety by disiamylborane[69] afforded the ketal lactol U-4, which reacted with m-methoxyphenylmagnesium bromide[69] to give the diol U-5. This diol, upon hydrogenolysis of the benzyl hydroxyl group,[69] hydrolysis of the C-2 ketal, and oxidation of the C-7 hydroxyl group afforded the optically active diketone Q-11 in an overall yield of 57% for the eight steps. The racemic and optically active diketones were identical by vpc, tlc, and ir and nmr (60 and 220 MHz) spectroscopy.

The structure of the intermediate diketone Q-11 having been established, the synthesis of germanicol was continued. The next two synthetic objectives were the construction of the D and E rings by the acid-catalyzed cyclodehydration of the diketone and the insertion of the C-8aβ angular methyl group (picene numbering).

In a model study, Baldwin and Ireland[60] found that treatment of the keto-ketal LXIV with polyphosphoric acid (PPA) did not afford the cyclodehydration product LXV but decomposed instead (Figure 25). In contrast, the related diketone LXVI cyclized smoothly in PPA to give an excellent yield of the tetracyclic ketone LXVII. When they applied this procedure in a preliminary cyclodehydration of ketone Q-11, only decomposition occurred.

Therefore, the synthesis of the diketone Q-11 through the ethylene ketal--photo-oxygenation route was repeated. As in the

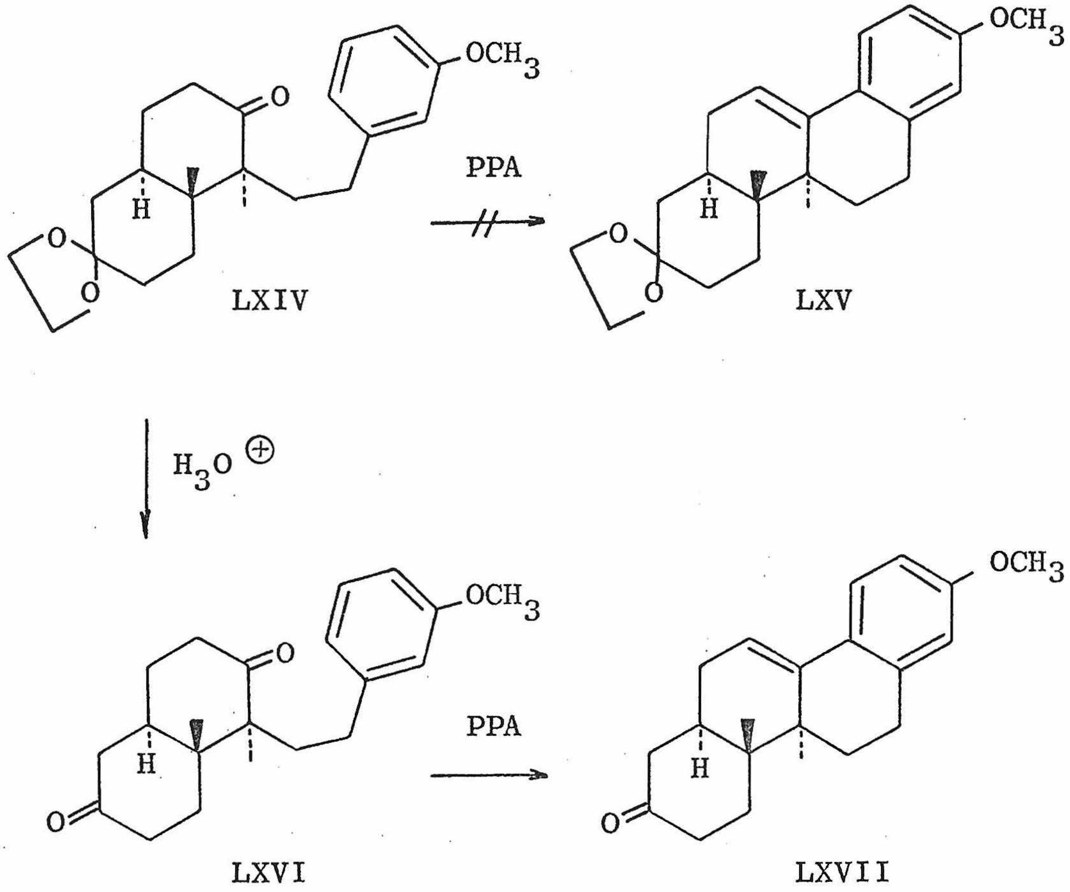
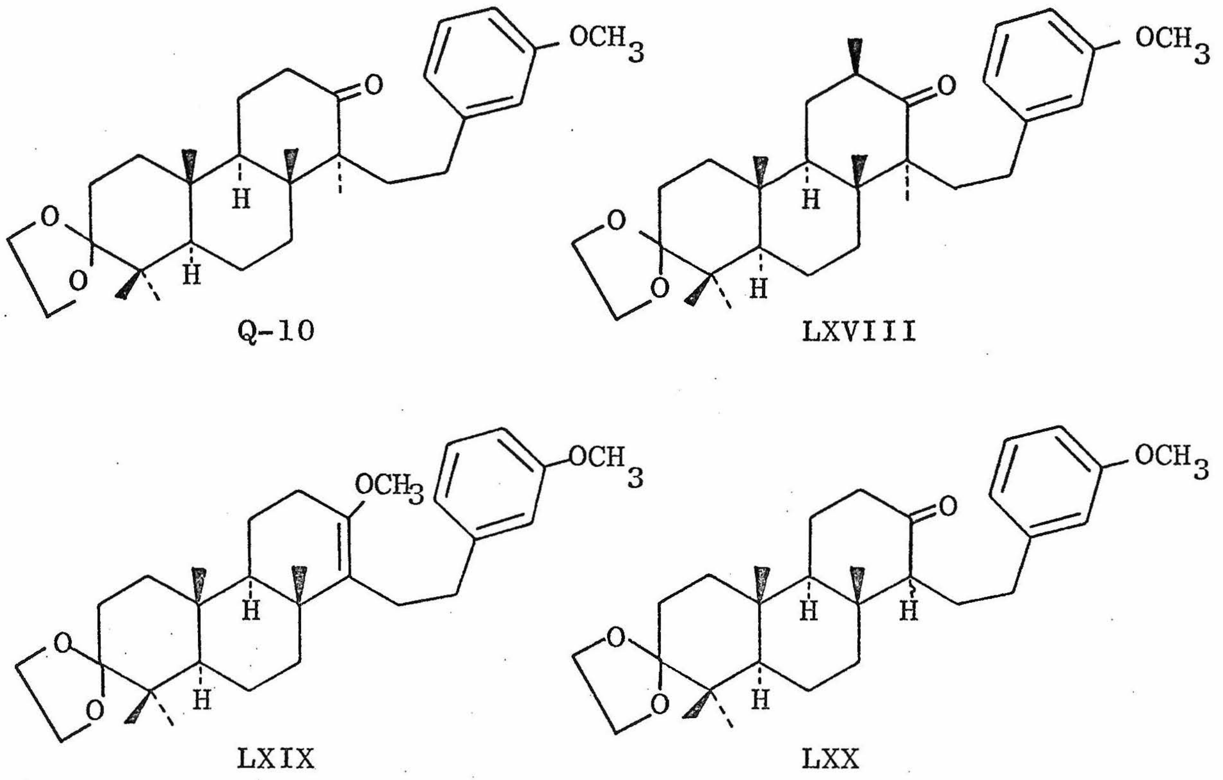


Figure 25: Cyclodehydration in the Model System

case of the methylation of the dimethylpropylene ketal enol acetate S-1 (Chart S), several products were observed in the conversion of the enol acetate Q-9 to the ketone Q-10. In addition to the desired monomethylated ketone Q-10, the crude product always contained some dimethylated (LXVIII), O-methylated (LXIX), and unmethylated (LXX) material (Figure 26). The last two contaminants were observable in the vapor phase


Q-10 LXVIII

LXIX LXX

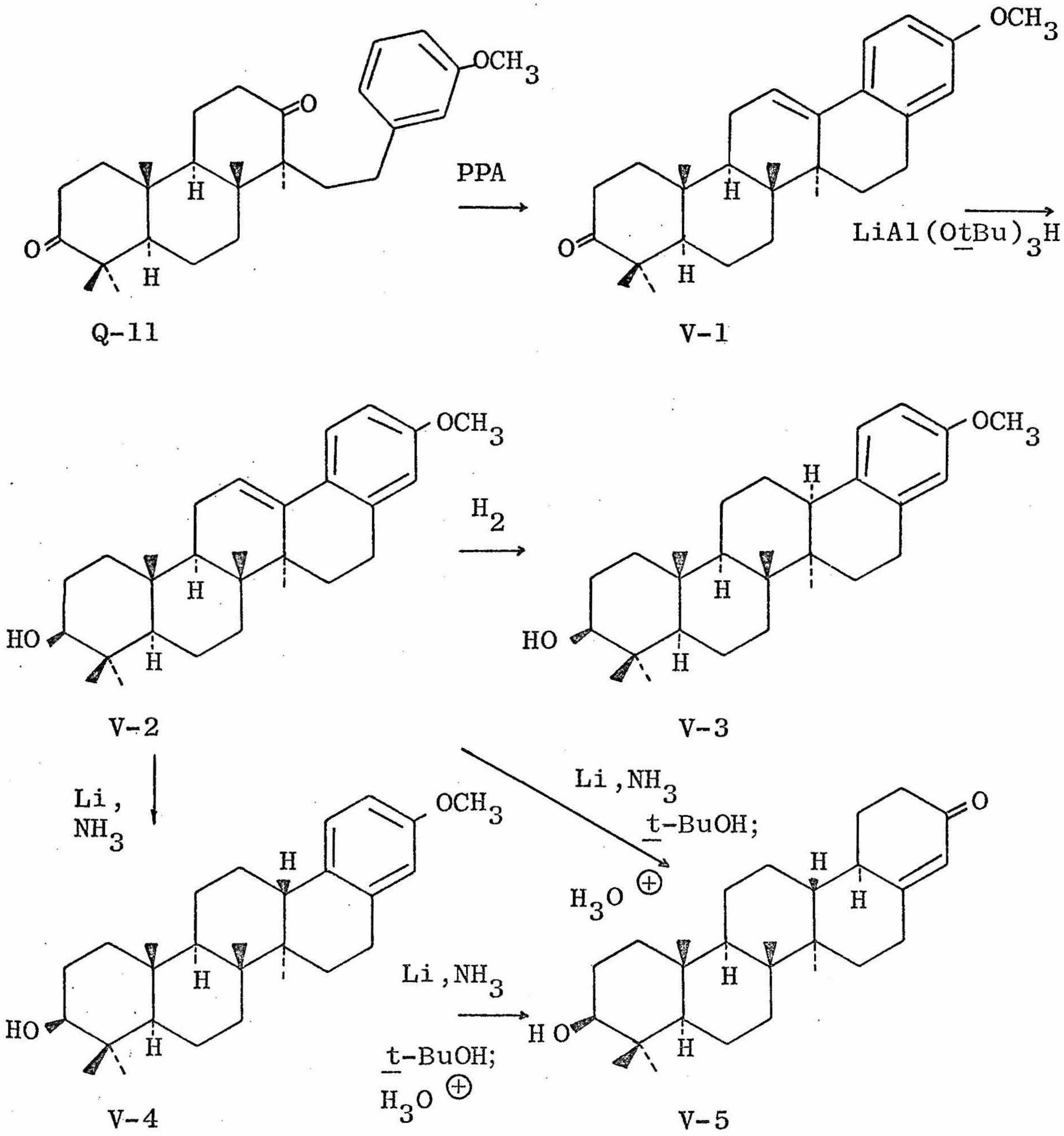
Figure 26: Products from the House Methylation of the Enol Acetate Q-9

chromatogram of the mixture and easily removed by preparative thin layer chromatography. The dimethylated ketone LXVIII had the same vpc retention time as the ketone Q-10, and a chromatographic separation of these two compounds was difficult. Hydrolysis of the purified keto-ketal Q-10 afforded the diketone Q-11 in 41% overall yield from the enol acetate. Treatment of the pure diketone with PPA gave a 90% yield of the pentacyclic ketone V-1 (Chart V). Because of these results, it appears likely that the sample of diketone Q-11 isolated by Baldwin [60] was very impure, since it gave numerous products on an attempted cyclodehydration.

The pentacyclic ketone V-1 was reduced with lithium tri-_t_-butoxy aluminum hydride to the pentacyclic alcohol V-2. The styrene double bond (Δ^{12b}) of this alcohol could then be reduced by either a Birch reduction or a hydrogenation to afford a mixture of the pentacyclic alcohols V-3 (_cis_ C/D ring fusion) and V-4 (_trans_ C/D ring fusion). The stereochemical assignment for these two structures was made from a comparison of the nmr spectra. One of the C/D ring-fused isomers had a quaternary methyl absorption at $0.40\ \delta$. The position of this signal was very much farther upfield than the other four methyl resonances of this isomer and the five methyl signals of the other isomer. The upfield position of the methyl signal would be expected for the _cis_-fused compound V-3 since models reveal that only in the _cis_ isomer does a methyl group (C-6aβ CH_3) lie in the shielding cone of an aromatic ring (ring E).[70]

The _trans_:_cis_ product ratios differed for the reduction methods. Vapor phase chromatographic analysis indicated that the _trans_:_cis_ hydrogenation product ratio was 25:75, while that for the Birch reduction was 55:45. Since the _trans_ isomer was the desired one, a Birch reduction in the absence of a proton source was used to saturate the styrene double bond. After

CHART V


OCH3
O
O
H
H
Q-11
PPA
OCH3
O
H
H
V-1
LiAl(OtBu)3H
OCH3
HO
H
H
V-2
H2
OCH3
H
HO
H
H
V-3
Li, NH3
Li, NH3
t-BuOH;
H3O ⊕
OCH3
H
HO
H
H
V-4
Li, NH3
t-BuOH;
H3O ⊕
O
H
H
H O
H
H
V-5

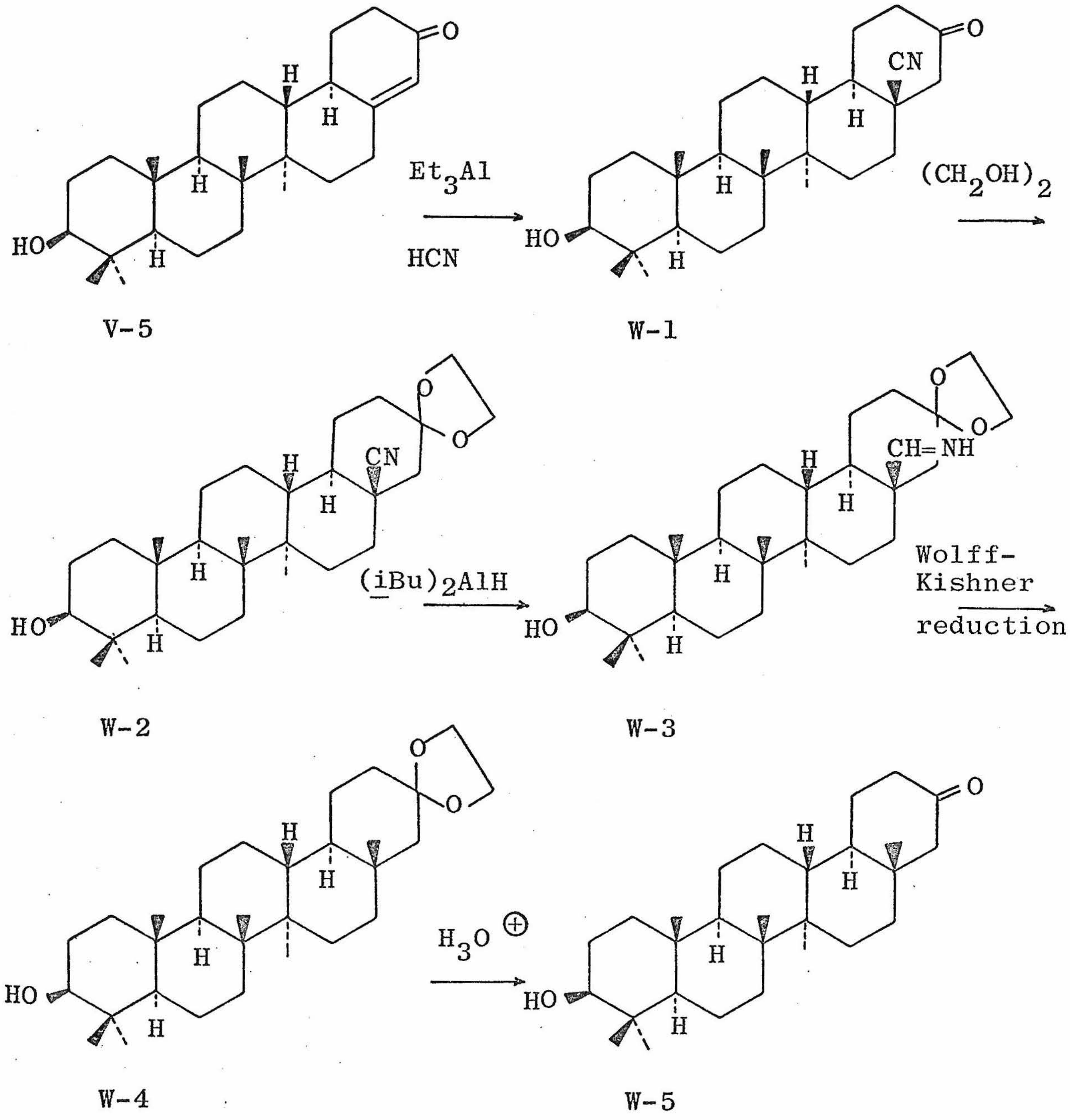
purification, the trans-fused product, pentacyclic alcohol V-4, was converted to the hydroxy-enone V-5 by a Birch reduction in the presence of a proton source, followed by acid hydrolysis and equilibration of the dihydroanisole intermediate.

The preparation of the enone could be more conveniently accomplished by concurrent reduction of both the styrene double bond and the aromatic ring of the alcohol V-2. The overall yield for the hydride reduction of the ketone and this Birch reduction of the alcohol product was 45%.

The angular methylation of the enone V-5 was performed according to procedures developed by Nagata and coworkers[6] and modified by Welch and Ireland.[44] Treatment of the enone with triethylaluminum and hydrogen cyanide in tetrahydrofuran (kinetic conditions) afforded the cyano-ketone W-1 as the only isolated product in a quantitative crude yield (Chart W). Nagata[6] and Welch[44] have found that kinetic hydrocyanation conditions, such as those used to prepare compound W-1, generally give a preponderance of trans-fused material in similar systems. Therefore, the D/E ring juncture of the cyano-ketone W-1 was assumed to be trans.

The conversion of the cyano-ketone W-1 to the corresponding methyl ketone W-5 was accomplished by a four-step synthon. The ketone function was protected by ketalization. The resulting cyano-ketal W-2, which was obtained in 77% yield from the enone V-5, was then treated with diisobutylaluminum hydride to form

CHART W


V-5
Et_3Al
HCN
W-1
$(CH_2OH)_2$
W-2
$(\underline{i}Bu)_2AlH$
W-3
Wolff-
Kishner
reduction
W-4
$H_3O^{\oplus}$
W-5
HO
H
CN
CH=NH
O

the imine W-3, which was immediately reduced to the methyl ketal W-4 under Wolff-Kishner conditions. Finally, removal of the ketal protecting group by acid hydrolysis gave the hexamethyl ketone W-5 in 93% yield from the cyano-ketal W-2.

All that remained in the synthesis of germanicol was the addition of the gem-dimethyl grouping at the C-11 position, the formation of the Δ^{12} double bond, and the removal of the C-10 carbonyl function. The first two transformations were to be accomplished by conversion of the saturated ketone W-5 to the α,β-unsaturated ketone X-2 and then dimethylation.

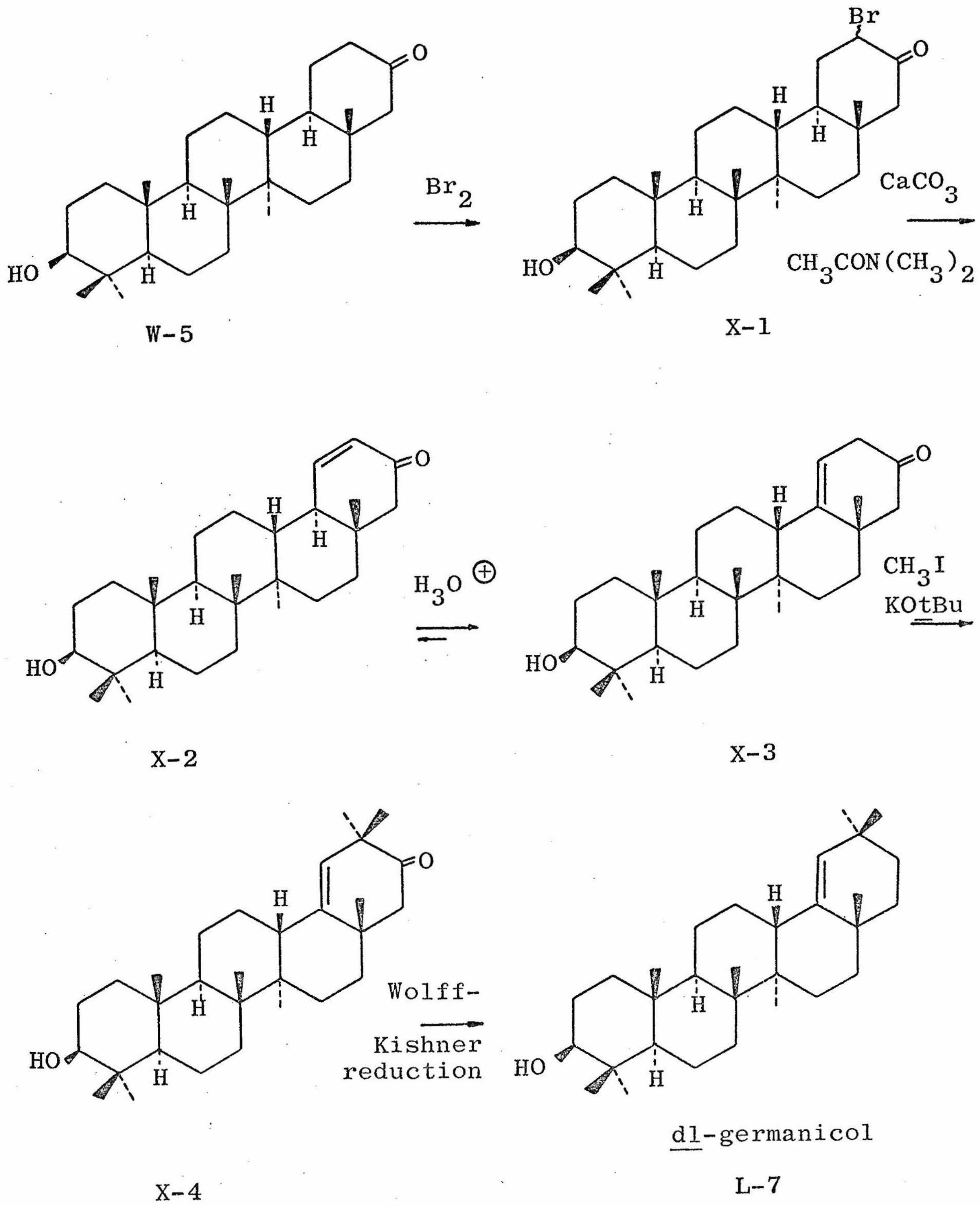
The double bond of ketone X-2 was introduced by a bromination--dehydrobromination procedure used by Marshall and coworkers,[2] and Long and Green.[71] This procedure (bromination with bromine in acetic acid, followed by dehydrobromination with calcium carbonate in refluxing dimethylacetamide) gave high yields in cis decalin and steroid systems,[2,71] however application of this method to the ketone W-5 resulted in only a fair yield of the α,β-unsaturated ketone X-2. Bromination of the ketone [ir ($CHCl_3$) 1700 cm^{-1} (C=O)] led to a mixture of bromoketones X-1 [ir ($CHCl_3$) 1715 cm^{-1} (broad C=O)] (Chart X). Treatment of this mixture with calcium carbonate in dimethylacetamide gave, after purification, the enone X-2. The yield for these two steps was 32%. The reason for this low yield is uncertain; perhaps only one of the bromoketone isomers eliminated to give the enone X-2 and the others did not.

The original plan for the conversion of the hexamethyl ketone X-2 to the octamethyl ketone X-4 called for a simple dimethylation step, however three attempts at gem-dimethylation of this unsaturated ketone with methyl iodide and potassium t-butoxide only resulted in recovery of starting material. Forcing conditions led to the destruction of the enone. Evidently the C-12aα proton of the enone is too hindered to be abstracted by the base.

This problem was solved by deconjugation of the enone prior to methylation. A ketalization--deketalization experiment indicated that the Δ^{11} double bond could be deconjugated to the Δ^{12} position. The double bond of the enone X-2 was equilibrated with hydrochloric acid in refluxing methanol. From an inspection of the infrared spectrum (1715 and 1675 cm^{-1}) of the product, it appears that at equilibrium the β,γ- and α,β-enones were present in a 2:1 ratio. After re-equilibration of the α,β-enone fraction, obtained from the first acid treatment, a 67% yield of the β,γ-unsaturated ketone X-3 was obtained.

Alkylation of this ketone with potassium t-butoxide and methyl iodide gave the dimethylated ketone X-4 in 42% yield after purification. The oxygen function at the C-10 position was removed by a Wolff-Kishner reduction[44] to afford a 57% yield of dl-germanicol.

CHART X


W-5
Br$_2$
X-1
CaCO$_3$
CH$_3$CON(CH$_3$)$_2$
X-2
H$_3$O$^+$
X-3
CH$_3$I
KOtBu
X-4
Wolff-Kishner reduction
dl-germanicol
L-7

CONCLUSION

The synthetic germanicol was identified by comparison with a sample of natural d-germanicol.* Both the natural and the synthetic compounds exhibited a single spot ($R_f = 0.65$) on analytical thin layer chromatography (3.3% methanol in chloroform). The vapor phase chromatograms (270°, 4% SE-30) of both exhibited one major peak at a retention time of 4.9 min. Co-injection produced a chromatogram with a peak at the same retention time. As Figures 27 and 28 illustrate, the infrared and nmr (220 MHz) spectra for the dl and d forms of germanicol were the same.

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*The natural triterpene was prepared by reduction of germanicyl acetate, which had been kindly provided by Professor C. Djerassi, Stanford University.

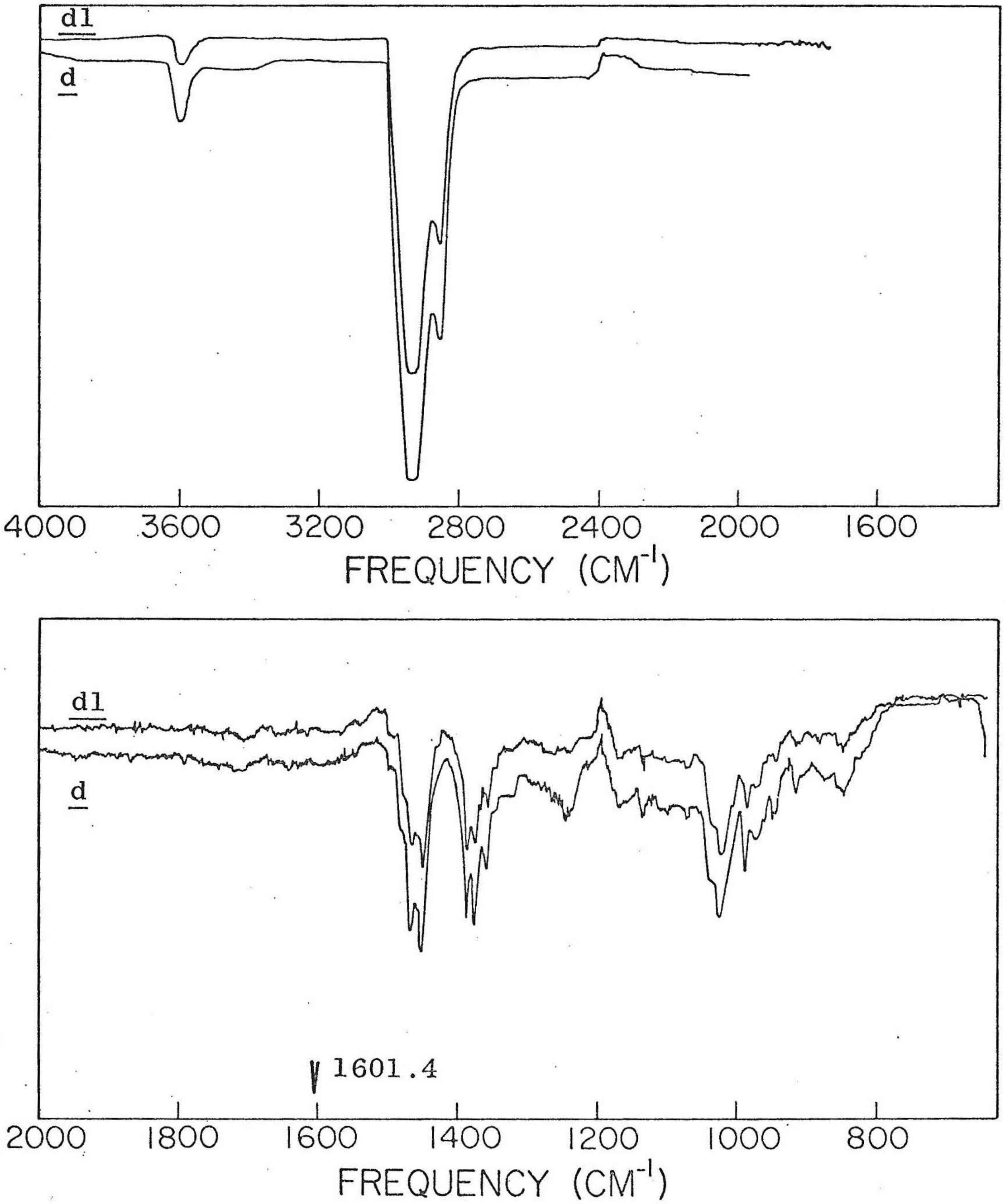

Figure 27: Infrared Spectra ($CHCl_3$) of Natural (d) and Synthetic (dl) Germanicol

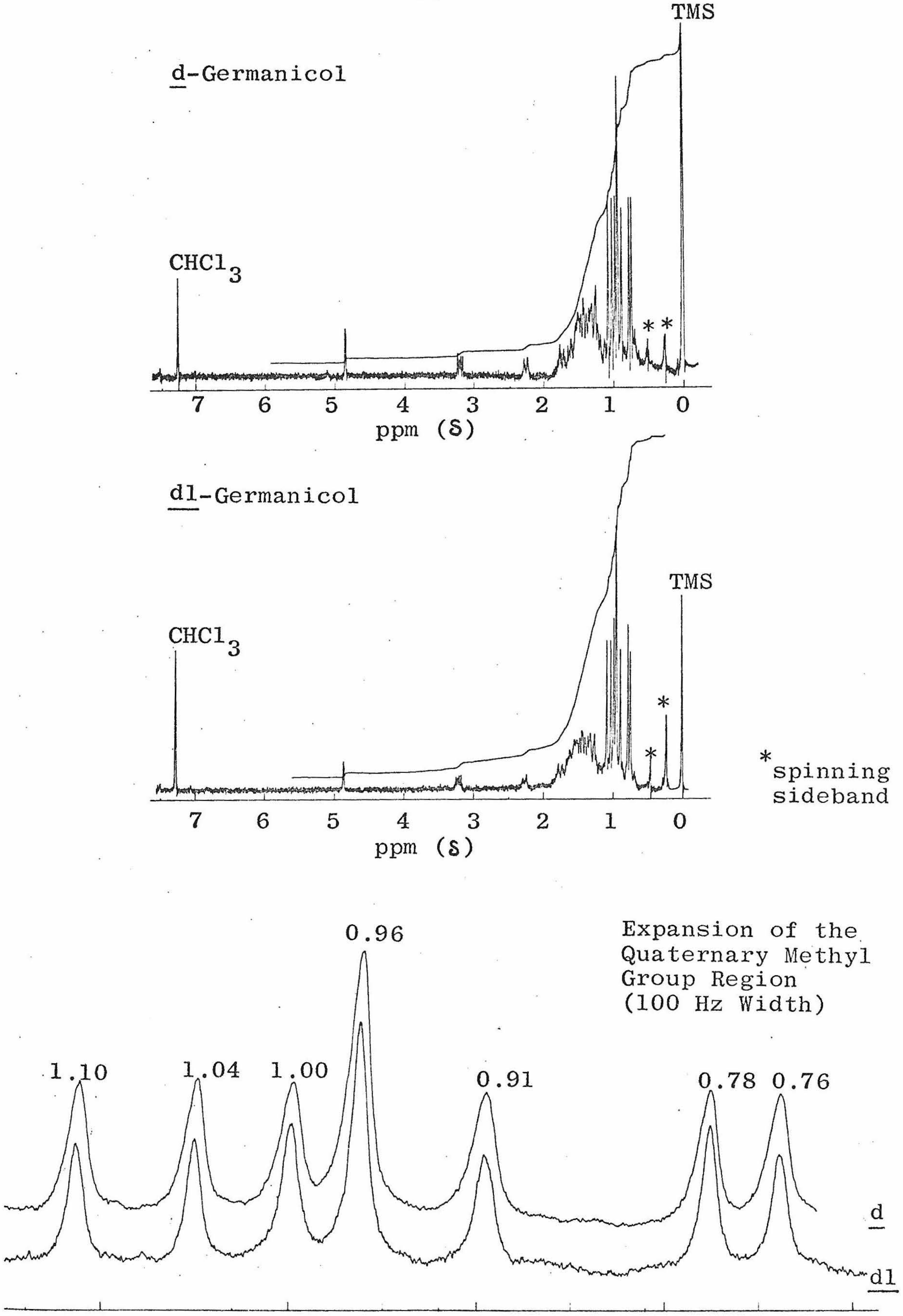

Figure 28: HR-220 NMR Spectra of Natural (d) and Synthetic (dl) Germanicol

EXPERIMENTAL SECTION
FOR
PARTS I AND II

EXPERIMENTAL SECTION*

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*(a) The compounds containing an asymmetric carbon atom, which are mentioned in Part I of this thesis and are described herein, are optically active; the "*d*" or "*l*" prefix has been omitted.

The compounds of Part II, which possess an asymmetric carbon atom, with the exception of *d*-germanicol, are racemic. The "dl" prefix has been omitted.

(b) Melting points (mp) were determined on a Kofler Micro Hot Stage or a Thomas Hoover capillary melting point apparatus and are uncorrected.

(c) Infrared (ir) spectra were determined on a Perkin-Elmer 237B grating infrared spectrophotometer. Solution spectra were observed in 0.1 or 0.2 mm cavity cells using chloroform or carbon tetrachloride as the solvent and a polystyrene calibration band at 1601.4 cm^{-1}.

(d) Ultraviolet (uv) spectral determinations were taken on a Cary spectrophotometer (Model 11).

(e) Optical rotation $[\alpha]_D^{T^\circ}$ measurements were performed on a Perkin-Elmer polarimeter (Model 141).

(f) Nuclear magnetic resonance (nmr) spectra were determined on Varian A-60A, T-60, and HR-220 spectrometers. Silanor C [Merck, Sharp and Dohme deuteriochloroform containing 1% tetramethylsilane (TMS) as the internal reference], unless otherwise mentioned, was used as the solvent. The chemical shifts are reported as δ values in ppm relative to TMS = 0.

(g) Vapor phase chromatographic (vpc) analyses were performed on a F and M gas chromatograph (Model 810),equipped with hydrogen flame detectors. Helium was used as the carrier gas at a flow rate of 50-75 ml/min. Analyses were carried out on 6-ft x 0.125-in columns packed with 1) 5% SE-30 on Diatoport S, 60/80 mesh, referred to as a 5% SE-30 column; 2) 10% SE-30 on Chromosorb P, 60/80 mesh, referred to as a 10% SE-30 column; 3) 4% SE-30 on Chromosorb WAWDMCS, 80/100 mesh, referred to as a 4% SE-30 column; and 4) 10% SE-52 on Chromosorb P, 60/80 mesh, referred to as a 10% SE-52 column. Relative peak areas were determined by a disc chart integrator.

(h) Analytical thin layer chromatography (tlc) was performed according to Stahl. (E. Stahl, "Dünnschicht-Chromatographie Ein Laboratoriumshandbuch," Springer-Verlag, Berlin, 1962.) Silica Gel G (E. Merck AG) on 1x3-in microscope slides was employed as the adsorbent. Components were detected with iodine vapor or spraying with a 5% solution of phosphomolybdic acid in ethanol followed by heating at 100-150° for a few min.

Preparative thin layer chromatography (source of adsorbent, plate size, development solvent) was performed on plates coated with a 0.1-cm layer of silica gel PF$_{254+366}$ (Brinkman Instrument Co.) or commercially prepared plates coated with a 0.25-cm layer of silica gel (Analtech). Unless otherwise mentioned, the dimensions of the plates were 20x20 cm. Bands were observed with the aid of ultraviolet light.

Merck silica gel (0.05-0.2 mm, 70/325 mesh) was used for column chromatography.

(i) Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Michigan, and Elek Microanalytical Laboratories, Torrance, California.

(j) Reactions were run under an inert gas. For the preparation of the compounds of Part I up to the cholestenol study, nitrogen was used; thereafter, argon was used.

(k) As reaction solvents, dimethoxyethane, ether, tetrahydrofuran, benzene, pyridine, and dichloromethane were dried by distillation immediately prior to use. The first three were distilled from lithium aluminum hydride. Dimethoxyethane was distilled in an argon atmosphere. Benzene and pyridine were distilled from calcium hydride, dichloromethane from phosphorous pentoxide.

Petroleum ether refers to the fraction with a boiling point (bp) range of 30-60°, which is supplied by J. T. Baker Chemical Co.

The solvents used for extraction in the work-up procedures were reagent grade quality. In addition, benzene was distilled from calcium hydride before use.

(l) The brine referred to in the work-up procedure is an aqueous saturated sodium chloride solution. Dilute brine is a saturated sodium chloride solution diluted with an equal part of water.

(m) Concentration at reduced pressure refers to evaporation on a rotary evaporator connected to an aspirator system (20 mm) followed by additional evaporation on a vacuum line (0.05-0.1 mm). The latter step was omitted in the preparation of volatile compounds.

(n) The chloroform used for crystallization and chromatography was reagent grade, which was stabilized with 0.75% ethanol.

Dihydrocarvone (C-2) was prepared by the procedure of Marshall.[26] To a solution of 18.7 g (2.69 moles) of lithium wire (cut in small pieces and washed with dry petroleum ether) in 3.0 l of liquid ammonia (distilled) was added 101.2 g (0.674 mole) of l-carvone (Calbiochem.) in 830 ml of anhydrous ether over a period of 3 hr. Then, 200 ml of absolute ethanol were added over a 3.5-hr period. The reaction mixture was quenched with 170 g (3.2 moles) of ammonium chloride, and the ammonia was allowed to evaporate overnight. Dilute brine (1000 ml) was added to the residue, and the resulting mixture was extracted with five 200-ml portions of ether. The combined extracts were washed with 200 ml of brine and dried (Na_2SO_4). Benzene (200 ml) was added, and the solvents were removed at reduced pressure to give 107 g of a yellow oil, which was dissolved in 700 ml of acetone, cooled to 2^o, and treated with 150 ml of 8 N chromium trioxide in sulfuric acid (Jones reagent[27]). The excess Jones reagent was destroyed by the dropwise addition of isopropyl alcohol, and the color of the reaction mixture changed from brown to green. The mixture was neutralized with solid sodium bicarbonate and filtered. Distillation of the filtrate at atmospheric pressure removed most of the solvent. The residue was poured into 500 ml of brine and extracted with five 100-ml portions of ether. The combined extracts were washed with two 100-ml portions of brine. These washings were re-extracted with 200 ml of ether. Benzene (5 ml) was added to the combined ethereal extracts, and this pale yellow oil was distilled. After removal of the solvents, the pressure was reduced to 22 mm. The product, dihydrocarvone, was obtained as a clear, colorless oil, weighing 75.5 g (74% yield), bp 106-109° (22 mm); ir (film) 3080 (vinylic C-H), 1715 (C=O), 1645 (C=C), and 890 cm^{-1} ($C=CH_2$).

7β-Isopropenyl-9α-hydroxy-10α-methyldecal-2-one (C-3)[26] was prepared by the procedure of Marshall. To 68.4 g (448 mmoles) of dihydrocarvone (prepared by the above method), which was cooled to -10° and mechanically stirred, was added 2.7 ml of 3 N (8.1 mmoles) ethanolic sodium ethoxide. To this yellow reaction mixture was added 18.75 ml (231 mmoles) of methyl vinyl ketone (Aldrich) over a period of 1.25 hr. The resulting emerald green solution was stirred at -10° for 15 min and at room temperature for 18 hr. It was then poured into 200 ml of brine and extracted with five 100-ml portions of ether. The combined extracts were washed with 50 ml of brine and dried (Na_2SO_4). On distillation, first at atmospheric pressure and then at reduced pressure, 40.6 g of dihydrocarvone (bp 38-42°, 0.1 mm) was recovered. The crude product (C-3) was left in the distillation pot.

The recovered starting material (40.6 g, 263 mmoles) was treated as above with 1.6 ml of 3 N (4.8 mmoles) ethanolic sodium ethoxide and 11.1 ml (137 mmoles) of methyl vinyl ketone. The reaction mixture was distilled from the same flask, which was used above and still contained the crude ketol C-3. The recovered dihydrocarvone (bp 41-43°,0.12 mm), which weighed 22.9 g (150 mmoles), was homoannelated a third time with 0.9 ml of 3 N (2.7 mmoles) ethanolic sodium ethoxide and 6.3 ml (77.6 mmoles) of methyl vinyl ketone. Distillation of this product mixture from the flask used above afforded 17.1 g (25% recovery) of dihydrocarvone (bp 36-42°, 0.12 mm) and 56.4 g of crude ketol C-3 (bp 95°, 0.06 mm, to 170°, 0.15 mm), which crystallized upon seeding with a previously purified sample. Recrystallization of this material from ether--petroleum ether gave two crops of crystalline ketol C-3: 21.5 g, mp 105-107°, and 9.4 g, mp 103-106°. The mother liquors were chromatographed on 1 kg of activity III Woelm alumina. Elution with 7.0 l of 10% ether in petroleum ether and 1.0 l of 30% ether in petroleum ether gave only unidentified side products. Continued elution with 30% (1.5 l) and 50% (4.0 l) ether in petroleum ether afforded 9.7 g of ketol, which was recrystallized from ether--petroleum ether to give a third crop of ketol C-3: 7.2 g, mp 103-106°. The total yield of 38.1 g represented a 38% conversion or a 51% yield based on unrecovered dihydrocarvone.

ir (film) 3460 (O-H), 3080 (vinylic C-H), 1705 (C=O),
    1645 (C=C), and 890 cm^{-1} (C=CH_2).

nmr ($CDCl_3$) δ 1.22 (s, 1, C-10 CH_3), 1.70 (d, 3, J=1, vinylic
    CH_3), 2.2-3.0 (m, 4, CH_2COCH_2), 4.70 (m, 2, =CH_2).

7β-Isopropyl-10α-methyl-1(9)-octal-2-one (C-5)[26] was synthesized by the method of Marshall. Platinum oxide (2.5 g) was added to a solution of 38.0 g (171 mmoles) of ketol C-3 (prepared above) in 400 ml of absolute ethanol. This mixture was stirred under a hydrogen atmosphere for 18 hr and then filtered through Celite and 5 g of Merck silica gel to remove the colloidal platinum. The solvent was evaporated at reduced pressure to give 40.8 g of a very viscous oil, containing the saturated ketol C-4 and some solvent.

ir (film) 3445 (O-H), 1700 (C=O), and 1360 and 1380 cm^{-1} (gem-dimethyl).

To the crude ketol C-4 was added 400 ml of 10% aqueous oxalic acid; the resulting biphasic mixture was boiled vigorously for 9 hr, cooled and extracted with five 100-ml portions of a 2:1 ether-benzene solution. The combined extracts were washed with two 50-ml portions of saturated aqueous sodium bicarbonate and 50 ml of brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure and evaporative distillation (60-120°, 0.1 mm) of the residue afforded 35.4 g (100% yield from the unsaturated ketol C-3) of the octalone C-5 as a colorless oil:

ir (film) 1675 (C=O), 1620 (C=C), and 1365 and 1380 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.88 (m, 6, $-CH(C\underline{H}_3)_2$), 1.27 (s, 3, C-10 CH_3), 5.73 (s, 1, vinylic H).

Lithium Aluminum Tri-*t*-butoxy Hydride.[28] To approximately 38 g (1.0 mole) of lithium aluminum hydride (obtained from 45 g of Ventron lithium aluminum hydride by a Soxhlet extraction) in 2.0 l of anhydrous ether was added over a period of 4 hr with stirring 253 g (3.41 moles) of t-butanol (purified by distillation from calcium hydride). During the addition, heat was evolved. A reflux condenser was used to prevent excessive loss of ether. The product precipitated as a white powder, which was washed thoroughly with ether and dried under vacuum to afford 266 g of lithium aluminum tri-*t*-butoxy hydride.

7β-Isopropyl-10α-methyl-1(9)-octal-2α-ol (C-6). A procedure used by Bell[72] was modified for this reduction. A solution of 9.0 g (43.6 mmoles) of octalone C-5 (obtained in the manner described above) in 450 ml of tetrahydrofuran was added to a solution of 50.2 g (197 mmoles) of lithium aluminum tri-*t*-butoxy hydride in 750 ml of tetrahydrofuran. The cloudy solution was heated at a vigorous reflux for 2 hr and then cooled. Next, 20-ml portions of 10% aqueous sodium hydroxide and saturated aqueous sodium sulfate were added slowly. After the resulting paste had been stirred at room temperature for 18 hr, the solvent was removed at reduced pressure and the white residue was dissolved in a mixture of 1.0 l of saturated aqueous ammonium chloride, 500 ml of a 2:1 ether-benzene solution, and just enough 10% aqueous hydrochloric acid to effect solution of the aluminum salts. This mixture was extracted with five 200-ml portions of a 2:1 ether-benzene solution. The combined extracts were washed with saturated aqueous sodium bicarbonate and brine. The washings were back-extracted with 100 ml of the ether-benzene solution. The combined organic extracts were dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded the allylic alcohol C-6 as white crystals weighing 8.96 g (99% crude yield). In the same manner, another 14.75 g (71.5 mmoles) of octalone C-5 was reduced with 64.0 g (252 mmoles) of lithium aluminum tri-*t*-butoxy hydride in 2.0 l of tetrahydrofuran, and then quenched with 25.5-ml portions of 10% aqueous sodium hydroxide and saturated aqueous sodium sulfate. Upon work-up, 14.87 g (quantitative crude yield) of the allylic alcohol C-6 was obtained. The combined products were sublimed (70^{o}, 0.07 mm) to afford 22.0 g (91% yield) of white solid, the allylic alcohol C-6:

ir ($CHCl_3$) 3595 and 3410 (O-H), 1655 (C=C), and 1365 and 1380 cm^{-1} (*gem*-dimethyl).

A portion of the allylic alcohol obtained from another experiment was recrystallized from petroleum ether for the analytical sample: mp 83-84^{o};

nmr ($CDCl_3$) δ 0.84 (m, 6, $CH(C\underline{H}_3)_2$), 1.14 (s, 3, C-10 CH_3), 4.22 (m, 1, $C\underline{H}OH$), 5.29 (s, 1, vinylic H);

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.77; H, 11.48.

9α-(N,N-Dimethylcarboxamidomethyl)-7β-isopropyl-10α-methyl-1-octalin (D-1). The procedure of Ning[73] was modified. A mixture of 5.0 g (24.0 mmoles) of allylic alcohol C-6 (mp 73-80° after sublimation, prepared by the method described in the preceding experiment) and 6.35 g (47.7 mmoles) of N,N-dimethylacetamidedimethylacetal (Fluka) in 48 ml of p-xylene was heated in a sealed flask at 114° for 8 hr. After cooling, another 6.35 g (47.7 mmoles) of N,N-dimethylacetamidedimethylacetal was added and heating (114°) was continued for 16 hr. After removal of the volatile materials at reduced pressure, the residue was chromatographed on 240 g of activity I Woelm alumina. Elution with ether and 10% methanol in ether gave 4.27 g of crude amide D-1. Recrystallization from petroleum ether afforded a small amount of purer material. The mother liquors were chromatographed on 100 g of activity III Woelm alumina; elution with petroleum ether and then ether gave 1.94 g of purer amide. The combined purified fractions were crystallized from petroleum ether and gave 1.96 g (29% yield) of analytically pure unsaturated amide D-1 as white crystals: mp <37°;

ir (film) 3000 (vinylic C-H), 1645 (C=O), and 1385 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.87 (m, 9, all CH_3), 2.44 and 2.49 (s, 1 each, $C\underline{H}_2$-CO), 2.95 and 3.04 (s, 3 each, N-$C\underline{H}_3$), 5.63 (m, 2, vinylic H);

Anal. Calcd for $C_{18}H_{31}NO$: C, 77.92; H, 11.26; N, 5.05.

Found: C, 78.06; H, 11.31; N, 4.99.

9α-(N,N-Dimethylcarboxamidomethyl)-7β-isopropyl-10α-methyldecalin (D-2). To a solution of 228 mg (0.83 mmole) of unsaturated amide D-1 (obtained by a procedure similar to the one described above) in 20 ml of absolute ethanol was added 50 mg of 10% palladium on charcoal. This mixture was stirred under a hydrogen atmosphere for 4.5 hr and then filtered. The solvent was removed at reduced pressure to give 228 mg (99% crude yield) of saturated amide D-2 as a pale yellow oil: ir (film) 1645 (C=O) and 1385 cm^{-1} (gem-dimethyl); nmr ($CDCl_3$) δ 0.87 (m, 9, all CH_3), 2.12 and 2.66 (d, 1 each, J=14, CH_2-CO), 2.92 and 3.07 (s, 3 each, N-CH_3). This material was used in the next reaction without further purification.

A sample prepared by an identical procedure was purified for analysis by evaporative distillation at 133° (0.1 mm). The infrared spectrum of this distilled material was identical to that of the crude material.obtained above.

Anal. Calcd for $C_{18}H_{33}NO$: C, 77.36; H, 11.90; N, 5.01. Found: C, 77.45; H, 11.99; N, 5.04.

9α-Carboxaldehydomethyl-7β-isopropyl-10α-methyldecalin Semicarbazone (D-3). The procedure of Brown and Tsukamoto[12] was modified. A solution of 224 mg (0.80 mmole) of amide D-2 (prepared in the previous reaction) in 2 ml of dry ether was cooled to 0^{o}, while 0.89 ml of 0.523 M (0.46 mmole) lithium dihydrodiethoxyaluminate in ether was added over a period of 1.5 hr. The cloudy solution was stirred at 0^{o} for another 30 min, and then 4.5 ml of 2 N (9.0 mmoles) aqueous hydrochloric acid was slowly added. The reaction mixture was extracted with four 50-ml portions of a 2:1 ether-benzene solution, and the combined extracts were washed with 50 ml portions of saturated aqueous sodium bicarbonate and brine. The washings were re-extracted with 50 ml of the ether-benzene solution. The combined organic phases were dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 194 mg of an oil:

ir (film) 3410 (O-H), 2720 (aldehyde C-H), 1720 (aldehyde C=O), 1640 (amide C=O), and 1365 and 1380 cm^{-1} (gem-dimethyl).

The aldehyde D-4 was isolated and purified as the semicarbazone D-3 by the procedure of Fieser and Fieser.[28] A solution of the crude aldehyde in the minimum amount of methanol necessary to effect solution was treated with 0.5 ml of 2 M (1.0 mmole) aqueous semicarbazide hydrochloride and 0.14 ml of pyridine. Two crops of crystalline semicarbazone were obtained: 86 mg of white crystals, mp 171-173^{o}, and 34 mg of cream-colored crystals, mp 164-168^{o}, a total yield of 120 mg (51%):

ir ($CHCl_3$) 3150, 3475, and 3540 (N-H), and 1690 cm^{-1} (C=O).

A sample of the semicarbazone prepared in a similar manner was recrystallized from benzene to give the analytical sample as a white powder, mp 170-173°, the infrared spectrum of which was identical to that described above.

Anal. Calcd for $C_{17}H_{31}N_3O$: C, 69.58; H, 10.65; N, 14.32.

Found: C, 69.76; H, 10.67; N, 14.39.

9α-Carboxaldehydomethyl-7β-isopropyl-10α-methyldecalin (D-4). The semicarbazone D-3 (122 mg, 0.42 mmole), which was obtained by a procedure similar to that described above, was dissolved in 25 ml of benzene. After the additon of 25 ml of 3 N aqueous hydrochloric acid, the mixture was heated at reflux for 3 hr, cooled, and then extracted with four 50-ml portions of a 2:1 ether-benzene solution. The combined extracts were washed with 50-ml portions of saturated aqueous sodium bicarbonate and brine. The washings were re-extracted with two 50-ml portions of the ether-benzene solution. The combined organic phases were dried (Na_2SO_4). Removal of the solvent at reduced pressure left 101 mg (103% crude yield) of the aldehyde D-4 as a pale yellow oil:

ir (film) 2710 (aldehyde C-H), 1720 (C=O), 1365 and 1385 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.85 (m, 9, CH_3), 2.11 (d of d, 1, J_{AX}=3, J_{AB}=14, $C\underline{H}_2$-CHO), 2.74 (d of d, 1, J_{BX}=4, J_{AB}=14, $C\underline{H}_2$-CHO), 9.87 (d of d, 1, J_{AX}=3, J_{BX}=4, -CHO).

This material was decarbonylated immediately without further purification.

Tris(triphenylphosphine)chlororhodium(I) (XXIX) was prepared by the procedure of Wilkinson.[16] A solution of 3.0 g (11.4 mmoles) of rhodium trichloride trihydrate (Alfa) in 105 ml of hot absolute ethanol was added to a warm solution of 18.0 g (68.6 mmoles) of triphenylphosphine in 525 ml of absolute ethanol. A brown solid immediately precipitated. On heating the stirred mixture at reflux for 1.5 hr in a nitrogen atmosphere, the brown precipitate was replaced by reddish-purple crystals. The suspension was cooled, and the solid was washed twice with ethanol and twice with ether, and dried at reduced pressure to afford 8.84 g (84% yield) of tris(triphenylphosphine)chlororhodium(I) as reddish-purple crystals.

$9\alpha,10\alpha$-Dimethyl-7β-isopropyldecalin (XXXII). A reported procedure[15] was modified. To a solution of 101 mg (about 0.42 mmole) of crude aldehyde D-4 (synthesized by the above procedure) in 10 ml of benzene was added 444 mg (0.48 mmole) of tris(triphenylphosphine)chlororhodium(I) (prepared by the procedure of Wilkinson[16]), and the resulting red suspension was heated at reflux for 22 hr. The solvent was removed at reduced pressure, and the residue was evaporatively distilled at 130-155° (10-12 mm) over a period of 6 hr to give 37.3 mg (43% yield from the semicarbazone D-3) of analytically pure hydrocarbon XXXII as a clear, colorless oil:

ir (film) 1365 and 1380 cm^{-1} (*gem*-dimethyl);

nmr ($CDCl_3$) δ 0.88 (m, 12, all CH_3);

Anal. Calcd for $C_{15}H_{28}$: C, 86.46; H, 13.54. Found: C, 86.38; H, 13.59.

7β-Isopropyl-10α-methyl-1(9)-octal-2α-yl Vinyl Ether (E-1). A procedure used by Ireland and coworkers[8] was modified. Ethyl vinyl ether (Eastman) was purified by heating at reflux over sodium for 3 hr and then distilling into a flask, which had been cleaned with hot chromic acid solution, rinsed with distilled water, and dried in an oven. To 400 ml of the purified ethyl vinyl ether was added 6.89 g (33.1 mmoles) of allylic alcohol C-6 (obtained by the procedure described above) and 3.32 g (10.4 mmoles) of mercuric acetate (MCB, recrystallized from ethanol containing 0.02% acetic acid, and dried and stored at reduced pressure). The clear, colorless solution was heated at reflux for 17 hr; then 0.25 ml (4.4 mmoles) of acetic acid was added, and the solution was stirred for 3.5 hr at room temperature, before it was poured into a mixture of 600 ml of petroleum ether and 90 ml of 5% aqueous potassium hydroxide. The organic layer was washed with three 90-ml portions of water and dried (Na_2SO_4 and Na_2CO_3). Removal of the solvent at reduced pressure afforded 8.3 g of a colorless oil, which was filtered through 240 g of neutral Merck alumina to remove the mercuric salts and starting material. Petroleum ether eluted 6.71 g (87% yield) of the vinyl ether E-1, as a clear, colorless oil:

ir (film) 3110 (vinylic C-H), 1605 and 1630 (C=C), and 1365 and 1385 cm^{-1} (*gem*-dimethyl);

nmr ($CDCl_3$) δ 0.87 (m, 6, $CH(C\underline{H}_3)_2$), 1.15 (s, 3, angular CH_3), 4.00 (d of d, 1, J_{AX}=7, J_{AB}=1.5, $-CH=C\underline{H}_2$), 4.32 (d of d, 1, J_{BX}=14, J_{AB}=1.5, $-CH=C\underline{H}_2$), 4.0-4.6 (m, 1, $C\underline{H}OH$), 5.37 (m, 1, C-1 H), 6.39 (d of d, 1, J_{AX}=7, J_{BX}=14, $-C\underline{H}=CH_2$).

A portion of this material was evaporatively distilled at 80° (0.1 mm) to give the analytical sample, the infrared spectrum of which was identical to that of the undistilled material.

Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 82.04; H, 11.26.

Repetition of this experimental procedure gave low and variable yields.

9α-Carboxaldehydomethyl-7β-isopropyl-10α-methyl-1-octalin Semicarbazone (E-2). A procedure of Ireland and coworkers[8] was modified. A sample (523 mg, 2.2 mmoles) of vinyl ether E-1 (prepared in the preceding reaction) was sealed in a Carius tube under a reduced nitrogen pressure. The tube was suspended in refluxing ethylene glycol (bp 196-198°) for 3 hr, cooled, and opened carefully. Vapor phase chromatography (200°, 5% SE-30) of the contents showed one major peak with a retention time of 3.9 min (85%)

ir (film) 3010 (vinylic C-H), and 1365, 1375, and 1385 (*gem*-dimethyl), 2725 (aldehyde C-H), and 1720 cm^{-1} (C=O).

A mixture of this material, 1.1 ml of 2 M (2.2 mmoles) aqueous semicarbazide hydrochloride, and 0.28 ml of pyridine was dissolved in enough methanol and ether to effect solution (total volume: 30 ml). After warming on a steam bath, the solution was filtered and boiled to dryness. The residue was crystallized from benzene, and crystalline semicarbazone E-2 was obtained in two crops: 105 mg, mp 181°, which was used for the analytical sample, and 248 mg, mp 178-180° (a total yield of 54%).

Anal. Calcd for $C_{17}H_{29}N_3O$: C, 70.06; H, 10.03; N, 14.42.
Found: C, 70.17; H, 10.10; N, 14.36.

9α-Carboxaldehydomethyl-7β-isopropyl-10α-methyl-1-octalin (E-3). The saturated semicarbazone D-3 cleavage procedure was used. A mixture of 248 mg (0.85 mmole) of semicarbazone E-2 (mp 178-180°), 50 ml of benzene, and 50 ml of 3N aqueous hydrochloric acid was stirred and heated at reflux for 3 hr, cooled, and extracted with four 100-ml portions of a 2:1 ether-benzene solution. The extracts were washed with 100-ml portions of saturated aqueous sodium bicarbonate and brine. The combined washings were re-extracted with 100 ml of ether-benzene. The combined extracts were dried (Na_2SO_4) and then concentrated at reduced pressure to afford 186 mg (93% crude yield) of the unsaturated aldehyde E-3 as a pale yellow oil, which was used in the next reaction without further purification:

ir (film) 3010 (vinylic C-H), 2725 (aldehyde C-H), 1720 (C=O), 1650 (C=C), and 1370 and 1380 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.85 (m, 9, all CH_3), 2.46 (d, 2, J=3, $-C\underline{H}_2-CHO$), 5.72 (s, 2, vinylic H), 9.91 (t, 1, J=3, $-C\underline{H}O$).

9α,10α-Dimethyl-7β-isopropyl-1-octalin (E-4). The procedure used for the decarbonylation of the saturated aldehyde D-4 was followed. To a solution of 1.52 g (6.5 mmoles) of unsaturated aldehyde E-3 (prepared by the above procedure) in 150 ml of benzene was added 6.64 g (7.2 mmoles) of tris-(triphenylphosphine)chlororhodium(I). After the red suspension had been heated at reflux for 39 hr, the solvent was removed by distillation first at atmospheric and then at reduced pressure. The residue was filtered through 45 g of Merck silica gel; ether was used as the eluant. After removal of the solvent, the residual oil was evaporatively distilled at 85° (0.03 mm) to give 1.04 g (78% yield) of olefin E-4 as a clear, colorless oil:

ir (film) 3010 (vinylic C-H), 1650 (C=C), and 1370, 1375, and 1385 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.88 (m, 12, all CH_3), 5.42 (m, 2, vinylic H).

A similarly prepared sample had the same infrared spectrum and was submitted for analysis.

Anal. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.22; H, 12.60.

9α,10α-Dimethyl-7β-isopropyl-2-decalone (E-6). The hydroboration--oxidation and Jones oxidation procedures used by Ireland and coworkers[30] were modified. To a solution of 207 mg (1.00 mmole) of octalin E-4 (prepared in the preceding reaction) in 6.6 ml of ether was added 4.9 ml of 0.213 M (1.04 mmoles) diborane in tetrahydrofuran.[74] After the reaction mixture had been stirred at room temperature for 1.5 hr, 1.6 ml of 10% aqueous sodium hydroxide and 1.6 ml of 30% aqueous hydrogen peroxide were slowly added. The solution was heated at reflux for 30 min, cooled, poured into 100 ml of brine, and extracted with five 25-ml portions of ether. The combined extracts were washed with 50-ml portions of water and brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 225 mg (quantitative crude yield) of alcohol mixture E-5 as a clear oil.

The crude hydroboration--oxidation product was dissolved in 14 ml of acetone and cooled in an ice bath, while 0.29 ml of 8 N chromic acid (Jones reagent)[27] was slowly added with stirring. After 3 min, the excess oxidant was reduced with isopropanol, and 7.2 ml of 5% aqueous potassium carbonate was added to neutralize the acid. This reaction mixture was worked-up the same way as the alcohol mixture E-5 was and afforded 203 mg of a clear oil, the vapor phase chromatogram (200°, 10% SE-30) of which showed two peaks with retention times of 2.1 (12%) and 4.5 min (88%). Under the same conditions, the chromatogram of the starting material (olefin E-4)

had one peak with a retention time of 2.1 min. The crude oxidation product was purified by preparative thin layer chromatography (Merck silica gel, 25% petroleum ether in benzene) to give 150 mg of ketone E-6 as a clear oil:
ir (film) 1720 (C=O), and 1375 and 1385 cm^{-1} (*gem*-dimethyl);
nmr ($CDCl_3$) δ 0.83 (m, 6, $CH(C\underline{H}_3)_2$), 0.98 (s, 3, C-9 CH_3), 1.12 (s, 3, C-10 CH_3), 1.9-2.6 (m, 4, $-CH_2COCH_2-$).
The assignment of the nmr signals for the C-9 and C-10 methyl groups was based on a comparison of this spectrum with that of the keto-acetal I-2.

Evaporative distillation at 75° (0.02 mm) of the clear oil gave 138 mg (62% yield from the olefin E-4) of analytically pure ketone E-6.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.06; H, 11.75.

9α-Carboxymethyl-7β-isopropyl-10α-methyl-1-octalin (F-1). An oxidation procedure used by Ireland and coworkers[8] was modified. The crude aldehyde E-3 (1.75 g, 7.5 mmoles) from Claisen rearrangement of vinyl ether E-1, was dissolved in 75 ml of absolute ethanol. To this solution was added 1.2 g (7.1 mmoles) of silver nitrate dissolved in 13 ml of water and 1.2 g (30 mmoles) of sodium hydroxide in 49 ml of water. The black reaction mixture was stirred at room temperature for 2.5 hr, poured into 150 ml of water, and extracted with three 50-ml portions of ether, which were then discarded. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with four 50-ml portions of ether. The combined extracts were washed with 50 ml of brine and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 1.12 g (70% yield) of the acid F-1 as white crystals: mp 95-98.5°; *ir* ($CHCl_3$) 1700 (C=O), and 1370 and 1385 cm^{-1} (*gem*-dimethyl); *nmr* ($CDCl_3$) δ 0.85 (m, 9, all CH_3), 2.22 and 2.67 (d, 1 each, J=13, $-\underline{H}_2CO_2H$), 5.3-6.1 (m, 2, vinylic H), 11.19 (broad s, 1, CO_2H).

A portion of this material was chromatographed on Merck silica gel. The petroleum ether eluant was discarded. Ether eluted the analytically pure, white crystalline carboxylic acid F-1, mp 97-99°.

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.77; H, 10.43.

The Lactonization of Octalin F-1 was accomplished with the procedure of Dietrich and Lederer.[75] A solution of 500 mg (2.00 mmoles) of the carboxylic acid F-1 (prepared by the above procedure) in 120 ml of formic acid (98-100%, B and A) was heated at reflux for 1.25 hr, cooled, poured into 500 ml of water, and extracted with four 50-ml portions of a 2:1 ether-benzene solution. The combined extracts were washed with two 50-ml portions of saturated aqueous sodium bicarbonate and two 50-ml portions of brine, and dried (Na_2SO_4). The solvent was removed at reduced pressure. The residue, a golden oil, was evaporatively distilled at 115° (0.02 mm) to give 486 mg (97% yield) of the lactone F-2 as a clear, colorless oil, which solidified upon seeding. The infrared spectrum of this material was identical to that of the analytical sample, mp 40-45^o, obtained earlier using this procedure:

ir ($CHCl_3$) 1770 (C=O), and 1370 and 1385 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.87 (m, 6, $CH(C\underline{H}_3)_2$), 1.00 (s, 3, angular CH_3), 2.07 and 2.72 (d, 1 each, J=17, $-C\underline{H}_2CO-$), 4.10 (m, 1, $>C\underline{H}O-CO-$);

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.88; H, 10.42.

The Reduction of the Lactone F-2 to the Lactol F-3 was carried out by an adaptation of a procedure of Brown and Moerikofer[33] which was modified by Ireland and Evans.[32] A solution of 0.59 g (8.5 mmoles) of 2-methyl-2-butene in 0.34 ml of dry tetrahydrofuran was cooled to -20^o while 4.05 ml of 0.48 M (1.94 mmoles) diborane[74] in tetrahydrofuran was added over a period of 1 hr. The solution was stirred at 0^o for 4 hr and then diluted with 3.0 ml of dry tetrahydrofuran. A solution of 251 mg (1.00 mmole) of the lactone F-2 (prepared in the preceding experiment) in 2.2 ml of dry tetrahydrofuran was added dropwise over a period of 15 min to this disiamylborane solution, and the resulting reaction mixture was stirred at 0^o for two hr and at room temperature for 10.5 hr. The reaction mixture was again cooled to 0^o while 0.74 ml of water and 1.76 ml of 30% aqueous hydrogen peroxide, which had been made basic (pH=8) with 10% aqueous sodium hydroxide, were slowly added. This mixture was stirred at room temperature for 1 hr. The solvent was removed at reduced pressure. To the residue was added 100 ml of benzene, and this mixture was washed with 50 ml of 5% aqueous potassium hydroxide and three 50-ml portions of brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure gave 227 mg of a cloudy oil, which was evaporatively distilled at 115° (0.03 mm) to afford 163 mg of analytically pure lactol F-3 as a clear, colorless oil (64% yield):

ir (film) 3385 (O-H), and 1365 and 1380 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.85 (m, 6, $CH(C\underline{H}_3)_2$), 0.93 (s, 3, angular CH_3), 3.82 (m, 1, $>C\underline{H}O\text{-}CHOH\text{-}$), 5.47 (m, 1, $>CHO\text{-}C\underline{H}OH\text{-}$);

Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14; H, 11.18. Found: C, 76.26; H, 11.15.

The Attempted Decarbonylation of Lactol F-3. The aldehyde E-3 decarbonylation procedure was used. A mixture of 151 mg (0.60 mmole) of lactol F-3 (prepared in the above procedure) dissolved in 14 ml of benzene and 0.62 g (0.67 mmole) of tris-(triphenylphosphine)chlororhodium(I) was heated at reflux for 45 hr. The vapor phase chromatograms (260°, 10% SE-30) of aliquots of the reaction mixture, which were taken during this time period, indicated that the three peaks corresponding to the vpc pattern of the starting material (retention times 1.3, 2.2, and 3.1 min) were not decreasing. Therefore, 1.0 ml of concentrated hydrochloric acid was added to the reaction mixture to shift the position of the lactol--hydroxy-aldehyde equilibrium. The reaction mixture first turned clear and then a yellow precipitate formed. After being heated at reflux

for 26 hr, the mixture was poured into ether, washed with saturated aqueous sodium bicarbonate and brine, and dried (Na_2SO_4). The residue left after removal of the solvent at reduced pressure was chromatographed on 15 g of activity I Woelm alumina. Elution with petroleum ether and 5% ether in petroleum ether produced only unidentifiable material; elution with 50% ether in petroleum ether afforded 32 mg (22% yield) of the lactone F-2 as a yellow oil:
ir ($CHCl_3$) 1770 (C=O), and 1365 and 1385 cm^{-1} (*gem*-dimethyl). The infrared spectrum of this material was the same as that obtained in the lactonization of octalin F-1 experiment.

1-Bromo-9α,10α-dimethyl-2-hydroxy-7β-isopropyldecalin (G-1). The procedure of Dalton and coworkers[34] was modified. To a solution of 206 mg (1.00 mmole) of octalin E-4 (prepared above) and 45 μl (2.50 mmoles) of water in 5 ml of dimethylsulfoxide (dried over Linde 4A molecular sieves) was added 356 mg (2.00 mmoles) of N-bromosuccinimide. The resulting yellow solution was stirred at room temperature for 1 hr, poured into 50 ml of brine, and extracted with five 25-ml portions of ether. The combined organic extracts were washed with two 50-ml portions of water and 50 ml of brine, and dried (Na_2SO_4). Removal of the solvent afforded 292 mg of yellow crystals. Two recrystallizations from petroleum ether produced 25 mg of pure bromohydrin G-1 as white needles:
mp 88.5-91.5°;

Anal. Calcd for $C_{15}H_{27}BrO$: C, 59.40; H, 8.97; Br, 26.35.
Found: C, 59.17; H, 8.94; Br, 26.29.

The mother liquors were chromatographed on 30 g of Merck silica gel. Elution with petroleum ether gave only unidentifiable material; elution with 20% ether in petroleum ether produced 175 mg of bromohydrin G-1 as pale yellow needles:
mp 85-89.5°;
ir ($CHCl_3$) 3550-3600 (O-H), and 1365 and 1385 cm^{-1} (*gem*-dimethyl);
nmr ($CDCl_3$) δ 0.82-1.07 (m, 12, all CH_3), 3.9-4.4 (m, 1, C*H*OH), 4.45 (d, 1, J=7, C*H*Br).
The total yield was 200 mg (66%).

The Oxidation and Debromination of Bromohydrin G-1. The bromohydrin was oxidized by a procedure used by Ireland and coworkers.[30] A solution of 173 mg (0.57 mmole) of bromohydrin G-1 (prepared in the preceding reaction) in 8 ml of acetone was stirred at 0° while 0.23 ml of 8 *N* chromic acid[27] was added dropwise. The yellow solution was stirred at 0° for 2 min, quenched with excess isopropanol (the mixture became green) and 6.1 ml of 5% aqueous potassium carbonate, poured into 50 ml of brine, and extracted with four 25-ml portions of a 2:1 ether-benzene solution. The combined extracts were washed with 50 ml of brine and dried (Na_2SO_4). The residue left after removal of the solvent at reduced pressure was evaporatively distilled at 95° (0.01 mm) to afford 143 mg (83% yield) of the bromoketone G-2 as a pale yellow oil:

ir (film) 1720 (C=O), and 1375 and 1385 cm^{-1} (gem-dimethyl); nmr ($CDCl_3$) δ 0.84 (m, 6, $CH(C\underline{H}_3)_2$), 1.23 and 1.33 (s, 3 each, angular CH_3), 3.78 (m, 1, $C\underline{H}Br$).

The debromination step was perfomed according to a modified published procedure.[35] A solution of 82 mg (0.27 mmole) of the bromoketone and 44 mg (0.53 mmole) of sodium acetate in 0.44 ml of acetic acid was stirred at 100° while 52 mg (0.81 mmole) of zinc dust was added. Stirring at 100° was continued for 25 min, and then the reaction mixture was cooled, diluted with ether, and filtered. The solvent was removed from the filtrate at reduced pressure. The residue was added to 100 ml of ether, washed with 50-ml portions of 10% aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, and brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 60 mg (99% crude yield) of ketone E-6 as an oil, the infrared and nmr spectra of which were identical to those of decalone E-6 prepared by the hydroboration--oxidation route.

The Epoxidation of the Octalin E-4 was done according to a standard procedure.[28] A solution of 206 mg (1.00 mmole) of octalin E-4 (prepared by a previously described procedure) and 244 mg (1.20 mmoles) of m-chloroperoxybenzoic acid (85%, Aldrich) in 10 ml of methylene chloride was stirred at -20° for 2 hr and at room temperature for 15.5 hr, then 120 mg (0.60 mmole) more of m-chloroperoxybenzoic acid was added, and stirring was continued for 4.5 hr. A 10% aqueous sodium sulfite solution was added until a negative starch-iodide test was obtained. The reaction mixture was diluted with 50 ml of ether and washed with two 50-ml portions of 5% aqueous sodium bicarbonate and 50 ml of brine, and dried (Na_2SO_4). After removal of the solvents at reduced pressure, the residue (232 mg of an oil) was purified to remove the starting material (octalin E-4). Preparative thin layer chromatography (Merck silica gel, petroleum ether) afforded 151 mg of epoxide, which was evaporatively distilled at 65° (0.03 mm) to give 121 mg (55% yield) of the purified epoxide mixture H-1 as a clear, colorless oil:

ir (film) 1365 and 1380 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.78 (m, 6, $CH(C\underline{H}_3)_2$), 0.91 (s, 2, angular CH_3), 0.95 (s, 1, angular CH_3), 1.02 (s, 2, angular CH_3), 1.13 (s, 1, angular CH_3), 2.61 and 3.22 (m, 1 each, C-1 and C-2 H);

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.13; H, 11.94.

Marshall and coworkers[2] have synthesized the optical isomer of the α epoxide, the nmr spectrum of which had angular methyl signals at 0.93 and 1.12 δ. Therefore, it appears that the epoxide mixture prepared above contains the α and β epoxides in a ratio of 1:2.

1-Valeranone (IX). A 114-mg portion (0.51 mmole) of the epoxide mixture H-1 from the preceding reaction was dissolved in 14.5 ml of tetrahydrofuran, and then 22.4 mg (0.59 mmoles) of lithium aluminum hydride (Ventron) was added. This mixture was heated at reflux for 21 hr. The vapor phase chromatogram (220^{o}, 10% SE-52) of the mixture exhibited two peaks with retention times of 2.3 (70%) and 2.6 min (30%). The retention time of the starting material was 2.3 min. Another portion of lithium aluminum hydride (0.50 g, 13.2 mmoles) was added, and heating at reflux was continued for 1.25 hr. At the end of this period, the vapor phase chromatogram of the reaction mixture had no 2.3 min retention time peak. The reaction mixture was diluted with 50 ml of ether, quenched by the addition of excess ethyl acetate, 10% aqueous sodium hydroxide, and saturated sodium sulfate, and poured into 100 ml of ether. This mixture was washed with two 50-ml portions of brine, and dried (Na_2SO_4). The residue obtained by removal of the solvent at reduced pressure was evaporatively distilled at 75^{o} (0.03 mm) to afford 86 mg (74% yield) of a mixture of alcohols as a colorless oil:

ir (film) 3350 (O-H), and 1370 and 1380 cm^{-1} (gem-dimethyl).

nmr ($CDCl_3$) δ 0.81-1.03 (m, 12, CH_3), 3.33 (m, 0.3, C-1 C$\underline{H}$OH),
4.10 (m, 0.7, C-2 C$\underline{H}$OH).

By a similar procedure,[36] reduction of 194 mg (0.87 mmole) of the epoxide mixture H-1 with aluminum hydride, which was prepared from 380 mg (10.0 mmoles) of lithium aluminum hydride and 441 mg (3.30 mmoles) of aluminum chloride, in 5 ml of refluxing tetrahydrofuran afforded a 69% yield of an alcohol mixture after 18 hr. This mixture was identical to that produced in the lithium aluminum hydride reduction by an ir and nmr spectral comparison.

The attempted reduction of the epoxide mixture with lithium aluminum tri-*t*-butoxy hydride in refluxing tetrahydrofuran for a period of 18 hr resulted in a 97% recovery of starting material.

A portion of the alcohol mixture, which was obtained from the lithium aluminum hydride reduction of the epoxides, was oxidized with Jones reagent by the procedure used above. To a stirred solution of 83 mg (0.37 mmole) of the alcohol mixture H-2 in 5 ml of acetone at 0° was added 0.15 ml of 8 *N* chromic acid solution. The orange solution was stirred at 0° for 2 min and then quenched by the sequential addition of excess isopropanol and 3.9 ml of 5% aqueous potassium carbonate. The mixture was poured into 50 ml of brine and extracted with four 25-ml portions of a 2:1 ether-benzene solution. The combined extracts were washed with 50 ml of brine and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 75 mg (91% crude yield) of a mixture of ketones:

ir (film) 1700-1715 (C=O), and 1370 and 1380 cm^{-1} (*gem*-dimethyl).

The vapor phase chromatogram (200°, 10% SE-52) of this oil showed two partially separated peaks with retention times of 4.1 (30%) and 4.3 min (70%).

A similar ketone mixture (123 mg) was obtained by a

Jones oxidation of 126 mg of the alcohol mixture from the aluminum hydride reduction of the epoxides.

These two oxidation products were combined. A 162-mg portion of this mixture was separated by preparative thin layer chromatography (Merck silica gel, 5x20x0.1 cm plate, 8% ether in petroleum ether, extended development). The component with the lower R_f was the 2-decalone E-6, which weighed 71.5 mg (35% yield) and which was identified by comparison of its infrared spectrum with that of the 2-decalone prepared in a previous experiment. The 2,4-dinitrophenylhydrazone derivative melted at 118-122^o with decomposition.

The faster moving component was evaporatively distilled at 65^o (0.02 mm) to give 47 mg (23% yield) of 1-valeranone as a colorless oil. The 2,4-dinitrophenylhydrazone, which was prepared by the method of Shriner and Fuson[76] and crystallized from ethanol, melted at 100-104.5^o (literature:[2] 104-105^o). The infrared spectrum of the synthetic <u>l</u>-valeranone was identical to the published infrared spectrum[17] of the natural <u>l</u>-valeranone.

<u>ir</u> (film) 1700 (C=O), and 1370 and 1380 cm^{-1} (<u>gem</u>-dimethyl);
<u>nmr</u> ($CDCl_3$) δ 0.86 (m, 9, $CH(C\underline{H}_3)_2$ and one angular CH_3),
1.05 (s, 3, angular CH_3).
<u>Anal</u>. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.11;
H, 11.88.

The specific rotation ($[\alpha]_D^{35^o}$) of the synthesized _l_-valeranone in ethanol was $-42.1^{o} \pm 2.8^{o}$, which is in good agreement with the published value of -40.1^{o}.[18]

9α-(2',2'-Ethylenedioxyethyl)—7β-isopropyl-10α-methyl-1-octalin (I-1). A procedure developed in the Johnson laboratories[38] was followed. To a solution of 2.01 g (8.6 mmoles) of the crude unsaturated aldehyde E-3 (obtained by the Claisen rearrangement of vinyl ether E-1) and 7.8 ml (113 mmoles) of ethylene glycol (redistilled) in 78 ml of dry tetrahydrofuran, which was cooled in a Dry Ice--isopropanol bath, were added 26 g of anhydrous calcium sulfate (Drierite) and 0.18 ml (2.6 mmoles) of concentrated sulfuric acid. This mixture was kept at 3^{o} for 13 hr, and then the acid was neutralized by the addition of 7.8 g (93 mmoles) of sodium bicarbonate. After 15 min the mixture was filtered and poured into 150 ml of 3% aqueous sodium bicarbonate and 400 ml of petroleum ether. The organic phase was washed with 100 ml of brine and dried (Na_2SO_4). Removal of the solvent afforded 2.24 g of crude acetal I-1 as a clear oil. In another experiment, 1.29 g (4.7 mmoles) of crude aldehyde was treated with 5 ml (89.5 mmoles) of ethylene glycol, 17 g of calcium sulfate, and 0.11 ml of concentrated sulfuric acid in 50 ml of tetrahydrofuran to give 1.35 g of crude acetal.

The combined products (3.59 g) were chromatographed on 200 g of activity III Woelm alumina. Elution with 300 ml of petroleum ether afforded 0.19 g of the vinyl ether E-1, which was identified by its infrared spectrum. Continued elution with petroleum ether gave 3.2 g of acetal, which was evaporatively distilled at 140° (0.09 mm) to afford 3.13 g (93% yield) of the analytically pure acetal I-1 as a clear, colorless oil:

ir (film) 3010 (vinylic C-H), 1650 (C=C), and 1365 and 1380 cm^{-1} (*gem*-dimethyl);

nmr ($CDCl_3$) δ 0.86 (m, 9, CH_3), 1.70 (d, 1, J=5.5, $-C\underline{H}_2-CH{<}^{O}_{O}$), 1.90 (d, 1, J=4.5, $-C\underline{H}_2-CH{<}^{O}_{O}$), 3.90 (m, 4, OCH_2CH_2O), 4.98 (d of d, 1, J=4.5 and 5.5, $-CH_2-C\underline{H}{<}^{O}_{O}$), 5.3-6.0 (m, 2, vinylic H);

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.76; H, 10.77.

9α-(2',2'-Ethylenedioxyethyl)-7β-isopropyl-10α-methyl-2-decalone (I-2). The procedure employed for the conversion of octalin E-4 to the decalone E-6 was modified. To a solution of 3.00 g (10.8 mmoles) of acetal I-1 from the preceding reaction in 71 ml of ether was added 23.7 ml of 0.48 *M* (11.4 mmoles) diborane in tetrahyrdofuran.[74] After this solution was stirred at room temperature for 2.5 hr, 11.4 ml of 10% aqueous sodium hydroxide and 11.4 ml of 30% aqueous hydrogen peroxide were added slowly and sequentially. This solution was heated at reflux for 1 hr, cooled, poured into 100 ml of brine, and extracted with five 100-ml portions of ether. The combined extracts were washed with 100-ml portions of water and brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure left 3.39 g of a viscous, colorless oil:

ir (film) 3400 (O-H),and 1365 and 1380 cm^{-1} (*gem*-dimethyl).

This oil was dissolved in 150 ml of acetone, and the solution was cooled in ice while 3.4 ml of 8 *N* chromic acid solution [27] were added dropwise. The orange mixture, which resulted, was stirred at 0° for 2 min more. Then excess isopropanol and 114 ml of 5% aqueous potassium carbonate were added, and this greenish mixture was poured into 100 ml of brine and extracted with four 100-ml portions of a 2:1 ether-benzene solution. The combined extracts were washed with 100 ml of brine and dried (Na_2SO_4). After removal of the solvent at reduced pressure, the oily residue was evaporatively distilled at 155° (0.05 mm) to afford 2.79 g (88% yield from the octalin I-1) of analytically pure decalone I-2 as a clear, colorless oil:

ir (film) 1710 (C=O), and 1365 and 1380 cm^{-1} (*gem*-dimethyl);

nmr ($CDCl_3$) δ 0.84 (m, 6, $CH(C\underline{H}_3)_2$), 1.13 (s, 3, angular CH_3), 1.71 (d, 1, J=5.5, $-C\underline{H}_2-CH{<}^{O}_{O}$), 2.07 (d, 1, J=4,$-C\underline{H}_2-CH{<}^{O}_{O}$), 2.42 (m, 4, CH_2COCH_2), 3.88 (m, 4, OCH_2CH_2O), 4.83 (d of d, 1, J=4 and 5.5, $-CH_2-C\underline{H}{<}^{O}_{O}$);

Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.31; H, 10.23.

Tricyclic Keto-alcohol I-3. The decalone I-2 was rearranged by a modification of a procedure of Ireland and coworkers.[30] A mixture of 1.65 g (5.6 mmoles) of decalone I-2 from the preceding reaction, 75 ml of acetone, and 15 ml of 10% aqueous hydrochloric acid was heated at reflux for 45 min, cooled, and poured into 200 ml of water. The reaction mixture from another deketalization--rearrangement [80 mg (0.27 mmole) of decalone in 3.5 ml of acetone and 0.7 ml of 10% aqueous hydrochloric acid] was added. The combined mixture was extracted with four 100-ml portions of a 1:1 ether-benzene solution. The combined extracts were washed with 100 ml of brine and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 1.43 g of white crystals, mp 163-175°, which were recrystallized from benzene--heptane to give 1.13 g (77% yield) of keto-alcohol I-3 as white crystals, mp 175-179.5°, the infrared spectrum of which was identical to that of the analytical sample, mp 178-178.5°, which was obtained in an earlier experiment:

ir ($CHCl_3$) 3595 and 3400 (O-H), 1710-1725 (C=O), and 1360 and 1380 cm^{-1} (*gem*-dimethyl);

nmr ($CDCl_3$) δ 0.90 (m, 6, CH($\underline{C}H_3)_2$), 1.12 (s, 3, angular CH_3), 4.2-4.6 (m, 1, C$\underline{H}$OH);

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found, C, 76.51; H, 10.30.

The Tosylation of the Tricyclic Keto-alcohol I-3 was done by a standard procedure.[28] A solution of 1.13 g (4.5 mmoles) of the keto-alcohol I-3 (prepared in the preceding reaction) in 23 ml of pyridine (dried by distillation from calcium hydride) was cooled to 0° while 1.72 g (8.8 mmoles) of p-toluenesulfonyl chloride was added. This mixture was kept at 3° for 4 days, and then it was poured into 280 ml of ice-water and 50 ml of ether. The aqueous phase was extracted with four 100-ml portions of a 2:1 ether-benzene solution. The combined organic phases were washed with 100 ml of water, two 100-ml portions of saturated aqueous cupric sulfate, and 100-ml portions of saturated aqueous sodium bicarbonate, water, and brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure left 2.01 g of a yellow oily solid, which was chromatographed on 140 g of Merck silica gel. Elution with 300 ml of ether afforded 1.59 g of crude tosylate; further elution with ether (1100 ml) gave 248 mg (22% recovery) of starting material, the white crystalline keto-alcohol I-3, mp 165-167°.

The crude tosylate was recrystallized from ether--petroleum ether to give the keto-tosylate I-4 in two crops of white crystals: 1.07 g, mp 91-93.5°, and 0.27 g, mp 92.5-94°, for a total yield of 1.34 g (74% conversion or 94% yield based on unrecovered starting material). The analytical sample, which was prepared by this procedure, melted at 78.5-79°; however, the ir and nmr spectra of this reaction product and the analytical sample were the same:

ir ($CHCl_3$) 1730 (C=O), 1595 (aromatic), and 1175 cm^{-1} (tosylate);

nmr ($CDCl_3$) δ 0.88 (m, 6, $CH(CH_3)_2$), 1.08 (s, 3, angular CH_3), 2.44 (s, 3, aromatic CH_3), 4.9-5.3 (m, 1, $CHOSO_2$), 7.2-7.9 (m, 4, aromatic H);

Anal. Calcd for $C_{23}H_{32}O_4S$: C, 68.28; H, 7.97; S, 7.93.
Found: C, 68.26; H, 8.00; S, 8.04.

9β-Carboxymethyl-7β-isopropyl-10α-methyl-2-octalin and Its Methyl Ester (I-5, R = H, CH_3). A variation of the method of Eschenmoser and coworkers[37] was used. To 35.0 g (1,500 mmoles) of sodium dissolved in 700 ml of methanol (dried by two distillations from magnesium) was added 1.11 g (2.8 mmoles) of the keto-tosylate I-4 (prepared by the above procedure). This solution was heated at reflux for 22 hr and then cooled in a Dry Ice--isopropanol bath while hydrogen chloride gas was bubbled in at such a rate that an internal temperature of -20° to -30° was maintained. After the solution was acidic to litmus, the solvent was removed at reduced pressure. To the residue was added 300 ml of water and 200 ml of ether. The resulting aqueous phase was extracted with four 100-ml portions of a 2:1 ether-benzene solution. The combined organic phases were washed with 100-ml portions of water and brine, and dried (Na_2SO_4). The 0.69 g of a cloudy yellow oil, which was left after the removal of the solvent at reduced pressure, was chromatographed on 70 g of Merck silica gel with 20% ether in petroleum ether. A 75-ml portion of this solvent mixture eluted 0.3 g of the ester, which was evaporatively distilled at 85° (0.03 mm) to give 244 mg (34% yield) of pure ester I-5 (R = CH_3) as a clear, colorless oil:

ir (film) 3005 (vinylic C-H), 1735 (C=O), 1640 (C=C), and 1370 and 1385 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.86 (m, 6, $CH(C\underline{H}_3)_2$), 1.00 (s, 3, angular CH_3), 2.52 (s, 2, $C\underline{H}_2CO_2CH_3$), 3.62 (s, 3, CO_2CH_3), 5.60 (m, 2, vinylic H);

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.16; H, 10.53.

Further elution of the column with 175 ml of 20% ether in petroleum ether afforded 165 mg (24% yield) of the carboxylic acid I-5 (R = H) as a white solid:

ir ($CHCl_3$) 1705 (C=O), 1640 (C=C), and 1380 and 1400 cm^{-1} (gem-dimethyl).

nmr ($CDCl_3$) δ 0.83, 0.92, and 1.01 (s, 3 each, CH_3), 2.57 (s, 2, $C\underline{H}_2CO_2H$), 5.62 (m, 2, vinylic H), 9.0-9.7 (broad s, 1, $CO_2\underline{H}$).

The analytical sample, which was prepared by a similar procedure and recrystallized from pentane, melted at 116-118.5°. The infrared spectrum of this sample was identical to that of the material isolated above.

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.79;

H, 10.53.

9β-(2'-Hydroxyethyl)-7β-isopropyl-10α-methyl-2-octalin (I-6). To a solution of 10.9 mg (0.041 mmole) of ester I-5 (R = CH_3) (prepared in the previous reaction) and 5.2 mg (0.021 mmole) of carboxylic acid I-5 (R = H) (prepared by the above procedure) in 4.0 ml of tetrahydrofuran was added 40 mg (1.06 mmoles) of lithium aluminum hydride (Ventron). This cloudy solution was heated at reflux for 2 hr and then cooled to 0^{o} while the excess hydride was destroyed by the addition of 1.0 ml of 10% aqueous sodium hydroxide. The tetrahydrofuran was removed at reduced pressure, and the residue was dissolved in dilute hydrochloric acid and extracted with four 25-ml portions of ether. The combined extracts were washed with 25-ml portions of water and brine, and dried (Na_2SO_4). The residue obtained by removal of the solvent at reduced pressure was evaporatively distilled at 105^{o} (0.04 mm) to give 15.8 mg (108% yield) of the alcohol I-6 as a clear, colorless oil, which solidified on standing.

When the reduction of the ester I-5 (R = CH_3) was performed separately on a larger scale and under similar conditions, a 98% yield of the alcohol I-6 was obtained; when the acid was reduced, a 96% yield of alcohol was obtained.

The analytical sample, which was prepared by reduction of the ester and evaporative distillation at 110^{o} (0.1 mm) was a white solid, which melted at $52-59^{o}$:

ir (film) 3310 (O-H), 3015 (vinylic C-H), 1640 (C=C), and

1365 and 1380 cm^{-1} (gem-dimethyl).

nmr (CDCl$_3$) δ 0.83-0.98 (m, 9, CH$_3$), 3.71 (t, 2, J=7.5, -CH$_2$C$\underline{H}_2$OH), 5.62 (m, 2, vinylic H);

Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.46; H, 11.94.

The Preparation and Decarbonylation of 9β-Carboxaldehydomethyl-7β-isopropyl-10α-methyl-2-octalin (I-7). The alcohol I-6 was oxidized to the aldehyde by a modification of the procedure of Collins and coworkers.[39] A solution of 116 mg (0.49 mmole) of the unsaturated alcohol I-6, which was a portion of the analytically pure material prepared by the above procedure, in 5.3 ml of methylene chloride was added to a stirred solution of 1.1 g (2.99 mmoles) of the chromium trioxide-dipyridine complex in 5.3 ml of methylene chloride. The dark brown mixture was stirred for 15 min, diluted with 10 ml of ether, and filtered through 9g of acid-washed Merck alumina with 150 ml of methylene chloride. After removal of the solvent at reduced pressure, the residue was evaporatively distilled at 95° (0.08 mm) to give 97.1 mg (84% yield) of the unsaturated aldehyde I-7 as a clear, colorless oil:

ir (film) 3010 (vinylic C-H), 2715 (aldehyde C-H), 1715 (C=O), 1640 (C=C), and 1365, 1370, and 1385 cm^{-1} (gem-dimethyl);

nmr (CDCl$_3$) δ 0.88 (m, 6, CH(C$\underline{H}_3$)$_2$), 1.01 (s, 3, angular CH$_3$), 2.53 (d, 2, J=2.5, -C$\underline{H}_2$CHO), 5.63 (m, 2, vinylic H), 9.88 (t, 1, J=2.5, C$\underline{H}$O).

The procedure used for the preparation of the octalin E-4 was modified for the decarbonylation of the aldehyde I-7. A mixture of 97 mg (0.41 mmole) of the unsaturated aldehyde and 425 mg (0.46 mmole) of tris(triphenylphosphine)chlororhodium(I) in 9.6 ml of benzene was heated at reflux for 23 hr. Heptane was added to the boiling reaction mixture while the benzene was removed by distillation. The rhodium compounds precipitated as a yellow solid. The yellow supernatant solution was filtered through 3 g of Merck silica gel with 75 ml of petroleum ether. The solvent was removed at reduced pressure, and the residue obtained was evaporatively distilled at 60° (0.04 mm) to give 64 mg (74% yield) of a clear, colorless oil:

ir (film) 3010 (vinylic C-H), 1640 (C=C), and 1370 and 1380 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.78-1.00 (m, 11, CH_3), 5.57 (m, 1, vinylic H). The vapor phase chromatogram (160°, 5% SE-30) exhibited only one peak with a retention time of 6.0 min. However, the nmr spectrum had only one proton in the vinylic region, where two were expected, thereby indicating that more than one compound was present.

A portion of the decarbonylation product (39 mg, 0.19 mmole) and 39 mg of platinum oxide in 20 ml of 95% ethanol was stirred under an atmosphere of hydrogen for 18 hr. After filtration, the solvent was removed by distillation at atmospheric pressure. The residue on evaporative distillation (60°, 0.05 mm) afforded 39 mg (quantitative yield) of a clear, colorless oil:

ir (film) 1370 and 1380 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.78-0.88 (m, 6, $CH(C\underline{H}_3)_2$), 1.02 and 1.04 (s, total of 6).

The vapor phase chromatogram of this oil showed two peaks with retention times of 6.0 (50%) and 6.7 min (50%).

9β-(2'-Hydroxyethyl)-7β-isopropyl-10α-methyldecalin (I-11). To a solution of 231 mg (0.98 mmole) of the unsaturated alcohol I-6 (prepared by a previously described procedure) in 180 ml of 95% ethanol was added 0.20 g of platinum oxide. This mixture was stirred under a hydrogen atmosphere for 48 hr, filtered, and concentrated at reduced pressure. The residue obtained was evaporatively distilled at 100° (0.03 mm) to afford 236 mg (quantitative yield) of the saturated alcohol I-11 as a clear, colorless oil.

A sample was prepared for analysis by an identical procedure:

ir (film) 3300 (O-H), and 1360 and 1380 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.87 (m, 6, $CH(C\underline{H}_3)_2$), 1.05 (s, 3, angular CH_3), 3.68 (t, 2, J=8, $-CH_2C\underline{H}_2OH$);

Anal. Calcd for $C_{16}H_{30}O$: C, 80.61; H, 12.68. Found: C, 80.77; H, 12.74.

9β-Carboxaldehydomethyl-7β-isopropyl-10α-methyldecalin (I-12). Because of the sensitivity of the aldehyde I-12 to air, the Collins oxidation procedure used for the preparation of the unsaturated aldehyde I-7 was modified. To a solution of 145 mg (0.61 mmole) of the alcohol I-11 in 2.9 ml of methylene chloride (freshly distilled from phosphorous pentoxide) was added under nitrogen a solution of 1.00 g (3.87 mmoles) of the chromium trioxide--dipyridine complex[39] in 10 ml of dry methylene chloride. This mixture was stirred under nitrogen for 30 min and then filtered through 10 g of acid-washed Merck alumina with 75 ml of methylene chloride. The solvent was evaporated under a stream of nitrogen to give an oily residue, which was evaporatively distilled at 95° (0.03 mm) to afford 128 mg (89% yield) of the saturated aldehyde I-12 as a clear, colorless oil.

The analytical sample was prepared by this procedure in an earlier experiment:

ir (film) 2710 (aldehyde C-H), 1715 (C=O), 1360 and 1375 cm^{-1} (*gem*-dimethyl);

nmr (CCl_4) δ 0.88 (m, 6, $CH(C\underline{H}_3)_2$), 1.10 (s, 3, angular CH_3), 2.33 (d of d, 1, J_{AX}=2.5, J_{AB}=14, $-C\underline{H}_2CHO$), 2.83 (d of d, 1, J_{BX}=2.5, J_{AB}=14, $-C\underline{H}_2CHO$), 9.79 (two superimposed doublets, 1, J_{AX}=J_{BX}=2.5, CHO);

Anal. Calcd for $C_{16}H_{28}O$: C, 80.61; H, 12.68. Found: C, 80.77; H, 12.74.

9β,10α-Dimethyl-7β-isopropyldecalin (I-10). A red suspension of 583 mg (0.63 mmole) of tris(triphenylphosphine)-chlororhodium in a solution of 128 mg (0.54 mmole) of the aldehyde I-12 (obtained in the preceding reaction) in 20 ml of benzene was heated at reflux for 66 hr. The benzene was displaced with heptane, and the red mixture was filtered through 5 g of activity III Woelm alumina and 5 g of Merck silica gel with 50 ml of petroleum ether. Removal of the solvent by distillation and evaporative distillation of the residue at 65° (0.03 mm) afforded 71.7 mg (64% yield) of the decalin I-10 as a clear colorless oil:

ir (film) 1370 and 1380 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.87 (m, 6, $CH(C\underline{H}_3)_2$), 1.04 (s, 6, angular CH_3);

Anal. Calcd for $C_{15}H_{28}$: C, 86.46; H, 13.54; Found: C, 86.45; H, 13.54.

Cholest-4-en-3β-ol (J-1). A solution of 12.3 g (32.0 mmoles) of cholest-4-en-3-one (mp 77-80°, prepared in the Ireland laboratories by D. Muchmore) in 320 ml of tetrahydrofuran was added to 32.6 g (128 mmoles) of lithium tri-t-butoxy aluminum hydride dissolved in 500 ml of tetrahydrofuran. This cloudy solution was heated at reflux for a period of 4 hr, cooled, and quenched by the addition of 52 ml of 10% aqueous sodium hydroxide. The white mixture was stirred at room temperature for 18 hr and then filtered. The filtrate was concentrated at reduced pressure. Ether was added, and the mixture was filtered again. Concentration of this filtrate gave 10.5 g of white crystalline cholest-4-en-3β-ol, mp 122-126°. This material was chromatographed on 1.0 kg of Merck silica gel with 10% ether in reagent grade chloroform. Material eluted with the first 3 l of this solvent mixture was discarded; further elution with 1.7 l of solvent gave 9.1 g of white crystals, which were recrystallized from 100 ml of ethanol to afford cholest-4-en-3β-ol in two crops: 5.94 g, mp 130.5-131°, and 3.01 g, mp 128-130°, for a total yield of 73%.

ir ($CHCl_3$) 3605, 3450 (O-H), 1660 cm^{-1} (C=C);

nmr ($CDCl_3$) δ 0.68, 0.80, 0.90, and 1.05 (all CH_3), 4.2 (m, 1, C$\underline{H}$OH), 5.28 (s, 1, vinylic H).

5β-(N,N-Dimethylcarboxamidomethyl)-3-cholestene (J-2). The procedure of Eschenmoser and coworkers[11] was modified. A solution of 0.97 g (2.5 mmoles) of cholest-4-en-3β-ol (mp 130.5-131°, prepared in the previous reaction) and 1.67 g (12.5 mmoles) of dimethylacetamidedimethylacetal (Fluka) in 30 ml of o-xylene was heated at reflux (140°) for 65 hr. The volatile material was removed at reduced pressure, and the residue (1.19 g of a yellow oil) was chromatographed on 60 g of Merck silica gel with ether. The material, which was eluted with 275 ml of ether, was discarded; further elution with 425 ml of ether afforded 0.74 g of a clear, colorless oil, which crystallized upon trituration with acetone to give 0.74 g (65% yield) of the amide J-2 as white prisms: mp 128-129.5°, the infrared spectrum of which was identical to that of the analytical sample, mp 126-128°, prepared by a similar procedure:

ir ($CHCl_3$) 1620 cm^{-1} (C=O);

nmr ($CDCl_3$) δ 0.65, 0.80, 0.86, and 0.90 (all CH_3), 2.05 (d, 1, J=13, $-C\underline{H_2}CO-$), 2.73 (d, 1, J=13, $-C\underline{H_2}CO-$), 2.89 and 2.96

(s, 3 each, N-CH_3), 5.3-5.8 (m, 2, vinylic H);

Anal. Calcd for $C_{31}H_{53}NO$: C, 81.70; H, 11.72; N, 3.07.

Found: C, 81.52; H, 11.81; N, 3.13.

5β-Carboethoxymethyl-3-cholestene (J-3) was prepared by a modification of the procedure of Johnson and coworkers.[40] A solution of 0.97 g (2.5 mmoles) of cholest-4-en-3β-ol (mp 130.5-131°, prepared above) in 40 ml of triethyl orthoacetate (MCB, distilled at 142-147°) was heated at reflux (142°) for 8 days with concomitant slow distillative removal of ethanol. The volatile materials were then removed at reduced pressure, and the residue (1.27 g of a thick pale yellow oil) was chromatographed on 120 g of silica gel with 10% ether in petroleum ether. The material obtained by elution with 240 ml of this solvent was discarded. Further elution with 120 ml of solvent afforded 0.69 g of a clear, colorless oil, which, upon trituration with acetone, gave 0.69 g (60% yield) of the ester J-3 as white crystals, mp 89-92.5°. The infrared spectrum of this material was identical to that of the analytical sample, mp 90.5-94°, which was prepared by a similar procedure:

ir ($CHCl_3$) 1720 (C=O), and 1370 and 1380 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.65, 0.80, 0.86, and 0.92 (all CH_3), 2.20 (d, 1, J=13, -CH_2CO), 2.48 (d, 1, J=13, -CH_2CO), 4.10 (q, 2, J=7, -$CO_2\underline{CH_2}CH_3$), 5.2-5.9 (m, 2, vinylic H);

Anal. Calcd for $C_{31}H_{52}O_2$: C, 81.52; H, 11.48. Found: C, 81.71; H, 11.60.

Cholest-4-en-3β-yl Vinyl Ether (J-4). The procedures of Burgstahler and Nordin,[7] and Ireland and coworkers[8] were modified. Ethyl vinyl ether (Eastman) was purified by drying (Na_2CO_3), distillation from sodium wire (bp 36°), and then distillation from calcium hydride (bp 36°). Mercuric acetate (MCB) was dissolved in ethanol containing 0.02% acetic acid, and the solution was filtered and cooled. The crystalline plates of mercuric acetate which formed were isolated by filtration and dried at reduced pressure. The reaction flask was cleaned with hot chromic acid solution, and then, with all the other glassware used in this procedure, washed with base, rinsed with distilled water, and dried in an oven.

Ethyl vinyl ether (20 ml) was distilled into a 50-ml flask containing 0.97 g (2.5 mmoles) of cholest-4-en-3β-ol (mp 130.5-131°, prepared above). To this solution was added 0.82 g (2.55 mmoles) of recrystallized mercuric acetate. The slightly cloudy mixture was heated at reflux for 17 hr and then cooled. Acetic acid (62 μl, 1.09 mmoles) was added, and the resulting clear solution was stirred at room temperature for 3 hr, and poured into 150 ml of petroleum ether and 50 ml of 5% aqueous potassium hydroxide. The aqueous layer was extracted with 50 ml of petroleum ether, and the combined organic extracts were washed with three 50-ml portions of 20% aqueous sodium chloride and dried (Na_2CO_3). Removal of the solvent at reduced pressure afforded 1.11 g of a clear, colorless oil, which was filtered through 5 g of Merck silica gel with 200 ml of petroleum ether. The 0.81 g of an oil, which was obtained on removal of the solvent at reduced pressure, was used in the next step without further purification.

In another experiment on twice this scale, the crude product was crystallized from acetone to give a 76% yield of the vinyl ether J-4 as needles: mp 55-56.5° (literature:[7] mp 56-57°);

ir (film) 3120 (vinylic C-H), 1605 and 1635 (C=C), and 1365 and 1380 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.70, 0.83, 0.93, and 1.08 (all CH_3), 3.97 (d of d, 1, J_{AB}=1.5, J_{AX}=7, $-OCH{=}C\underline{H}_2$), 4.27 (d of d, 1, J_{AB}=1.5, J_{BX}=14, $-OCH{=}C\underline{H}_2$), 4.32 (m, 1, C-3 H), 5.30 (s, 1, C-4 H), 6.32 (d of d, 1, J_{AX}=7, J_{BX}=14, $-OC\underline{H}{=}CH_2$).

5β-Carboxaldehydomethyl-3-cholestene (J-5) was prepared by modifying a procedure of Ireland and coworkers.[8] The crude vinyl ether (0.81 g, 1.96 mmoles), which was obtained in the preceding reaction in 78% yield, was transferred to a 50-ml flask, which had been washed with chromic acid, base, and distilled water, and oven-dried. The flask was then filled with argon and heated in an air bath at 220-225° for a period of 5 hr. The residue, which weighed 0.78 g, was chromatographed on 75 g of Merck silica gel with 10% ether in petroleum ether. The material which was eluted with 175 ml of this solvent was discarded; elution with another 175-ml portion of solvent afforded 0.55 g (53% yield from the allylic alcohol

J-1) of the aldehyde J-5 as white crystals: mp 66.5-68° (literature:[7] mp 66-69°);

ir ($CHCl_3$) 2760 (aldehyde C-H), 1715 (C=O), and 1380 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.67, 0.82, 0.88, and 0.92 (all CH_3), 2.18 (d of d, 1, J_{AB}=14, J_{AX}=3.5, -$C\underline{H}_2$CHO), 2.55 (d of d, 1, J_{AB}=14, J_{BX}=3.5, -$C\underline{H}_2$CHO), 5.2-6.0 (m, 2, vinylic H), 9.83 (two superimposed doublets, 1, J_{AX}=J_{BX}=3.5, CHO).

The Decarbonylation of 5β-Carboxaldehydomethyl-3-cholestene (J-5). The previously used decarbonylation procedure was modified. To a solution of 206 mg (0.50 mmole) of the aldehyde J-5 (mp 64-67°, prepared by the above procedure) in 20 ml of dry benzene was added 0.69 g (0.75 mmole) of tris-(triphenylphosphine)chlororhodium(I) (Alfa Inorganics). On heating at reflux for 20 hr, the red solution changed to a red suspension. The benzene was removed at reduced pressure and was replaced with heptane. This mixture was filtered through a column, which was layered with 5 g of Merck silica gel and then with 5 g of Merck alumina, with 40 ml of petroleum ether. Removal of the solvent afforded 188 mg (98% crude yield) of a clear, colorless oil:

ir (film) 3060 (cyclopropyl C-H), 3015 (vinylic C-H), 1650 and 1665 (C=C), and 1370, 1375, and 1380 cm^{-1} (gem-dimethyl);

nmr (CCl_4) δ 0.67, 0.87, 0.88, and 0.95 (all CH_3), 5.1-5.7 (m, 1.3, vinylic H).

The vapor phase chromatogram (220°, 4% SE-30) of this oil had two peaks with retention times of 9.0 and 9.8 min in a ratio of 2:1. Injection of a known sample of the desired olefin J-6, which was prepared by G. Pfister in the Ireland laboratories by an alternate route,[25] produced a chromatogram with one peak at a retention time of 9.0 min. A comparison of the nmr spectrum of the decarbonylation product with that of the pure olefin J-6 [($CDCl_3$) δ 0.67, 0.83, 0.87, 0.88, 0.93 (all CH_3), 5.1-5.7 (m, 2, vinylic H)] indicated that the decarbonylation product did, indeed, contain the olefin J-6.

An 85-mg portion of the crude decarbonylation product was separated by preparative thin layer chromatography (Analtech silica gel impregnated with a 10% silver nitrate solution in 1:3.28 water-methanol and then air-dried in the dark, 20x10x0.1 cm plate, hexane). One component (R_f= 0.4-1.0) was obtained in pure form from this plate. This colorless oil (8.1 mg, 10% yield) had a vpc (220°, 4% SE-30) retention time of 9.8 min. Analytical tlc under the same conditions that were used for the preparative work showed a single spot at R_f= 0.65. This oil was identified as the cyclopropane J-7 by comparison with an authentic sample prepared by an alternate route, which is presented below. The ir and nmr spectra of these two samples were identical. Co-injection of these samples produced a vapor phase chromatogram (250°, 4% SE-30) with a single peak at a retention time of 3.1 min.

Extraction of the remainder of the preparative tlc plate (R_f= 0-0.4) produced 74.6 mg (88% yield) of a colorless oil, which on vpc analysis (220°, 4% SE-30) gave two peaks with retention times of 9.0 and 9.8 min in a ratio of 3.5:1. Analytical tlc (silver nitrate impregnated silica gel, hexane) showed two spots (R_f= 0.25 and 0.35).

nmr ($CDCl_3$) δ 0.67, 0.83, 0.87, 0.88, and 0.93 (all CH_3), 5.1-5.7 (m, 1.7, vinylic H).

4β,5-Methanocholestane (J-7) was prepared by a modification of the Wolff-Kishner reduction procedure used by Ireland and Welch.[44] To a solution of 49.8 mg (0.13 mmole) of the cyclopropyl ketone K-2 (prepared by J. Tilley in the Ireland laboratories according to a published procedure[43]) in 8.5 ml of triethylene glycol (MCB) was added 0.85 ml (15 mmoles) of 85% aqueous hydrazine hydrate (MCB) and 0.22 g (2.1 mmoles) of hydrazine dihydrochloride (Eastman). This solution was heated at 130-135° for 3.5 hr, and then cooled to 100° while 1.40 g (about 25 mmoles) of potassium hydroxide pellets (B and A, 85%) were added. The temperature was then raised to 170° over a period of 20 min, while the volatile material was removed by distillation under a stream of argon. The internal temperature of the reaction mixture was kept at 170-175° for a period of 6 hr while a slow stream of argon was allowed to pass over the surface of the mixture. After cooling, this mixture was added to 150 ml of brine and extracted with four 50-ml portions of ether. The combined extracts were washed with ten 50-ml portions of water and 50 ml of brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 49.2 mg of the cyclopropane as a pale yellow oil, the vapor phase chromatogram (250°, 4% SE-30) of which had a single peak with a retention time of 3.1 min.

ir ($CHCl_3$) 3060 (cyclopropyl C-H), and 1375 and 1385 cm^{-1} (gem-dimethyl).

nmr ($CDCl_3$) δ 0.20 (m, cyclopropyl H), 0.67, 0.80, 0.90, and 0.95 (all CH_3).

This oil was evaporatively distilled at 190° (1.0 mm) to give 45 mg (94% yield) of the analytically pure cyclopropane J-7 as a clear, colorless oil;

Anal. Calcd for $C_{28}H_{48}$: C, 87.42; H, 12.58. Found: C, 87.54; H, 12.62.

2,2-(2',2'-Dimethylpropylenedioxy)-1,1 4aβ,8,8aβ-pentamethyl-1,2,3,4,4a,4bα,5,6,8a,9,10,10aα-dodecahydrophenanthrene (R-1). A solution of 0.5 g (1.82 mmoles) of the keto-olefin mixture Q-3 (prepared by the procedure of Baldwin and Ireland[60]) and 48 mg of p-toluenesulfonic acid monohydrate in 65 ml of benzene was heated at reflux for 2.75 hr. After cooling and the addition of 28.5 g (274 mmoles) of 2,2-dimethyl-1,3-propanediol (MCB), the solution was again heated at reflux for 37 hr. Then 1.0 g of sodium bicarbonate and 10 ml of water were added. This mixture was poured into 150 ml of dilute brine and extracted with three 50-ml portions of ether. The combined organic phases were washed with five 50-ml portions of water and 50 ml of brine, and dried (Na_2CO_3). Removal of the solvent at reduced pressure yielded 0.95 g of pale yellow oily crystals. Trituration with acetone gave 406 mg (58% yield) of white crystalline ketal olefin R-1, mp 165-168.5°, the vapor phase chromatogram (220°, 4% SE-30) of which exhibited one main peak with a retention time of 4.6 min (85%).

The analytical sample, which was obtained by an acetone recrystallization of identically prepared material, melted at 169-172°:

ir ($CHCl_3$) 1660 (C=C), 1390 (*gem*-dimethyl group), and 1110 cm^{-1} (C-O of ketal);

nmr ($CDCl_3$) δ 0.70, 1.00, 1.02, and 1.18 (s, 3 each, CH_3), 0.88 (s, 6, CH_3), 1.57 (d, 3, J=2, vinylic CH_3), 3.1-3.9 (m, 4, $-OCH_2-$), 5.18 (m, 1, vinylic H);

Anal. Calcd for $C_{24}H_{40}O_2$: C, 79.94; H, 11.18. Found: C, 79.92; H, 11.27.

The Epoxidation of the Ketal Olefin R-1 was done according to a published procedure.[28] A solution of 406 mg (1.13 mmoles) of the ketal olefin R-1 from the preceding reaction in 7.8 ml of dry methylene chloride was cooled to 0° while 273 mg (1.34 mmoles) of *m*-chloroperoxybenzoic acid (Aldrich, 85%) dissolved in 7.8 ml of dry methylene chloride was added over a period of 4 min. After stirring at room temperature for 1 hr, the reaction mixture was neutralized by the addition of 4 ml of 5% aqueous sodium bicarbonate. A

10% sodium sulfite solution was then added dropwise until a negative starch-potassium iodide test was obtained, indicating complete decomposition of the excess peroxide. The reaction mixture was diluted with 150 ml of ether, washed with two 50-ml portions of 5% aqueous sodium bicarbonate, 50 ml of water, and 50 ml of brine, and then dried (Na_2CO_3). Removal of the solvent at reduced pressure afforded 0.42 g (99% yield) of the epoxide mixture R-2 as a white foam.

The analytical sample, which was obtained by acetone crystallization of identically prepared material, was an epimeric mixture: mp 138-158°;

ir ($CHCl_3$) 1390 (gem-dimethyl), and 1110 cm^{-1} (C-O of ketal);

nmr ($CDCl_3$) δ 0.70, 1.00, and 1.05 (s, 3 each, CH_3), 0.83 and 1.18 (s, 6 each, CH_3), 2.85 (m, 1, epoxide H), 3.1-3.9 (m, 4, $-OCH_2-$);

Anal. Calcd for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71. Found: C, 76.40; H, 10.72.

2,2-(2',2'-Dimethylpropylenedioxy)-7-hydroxy-8-methylene-1,1,4aβ,8aβ-tetramethyl-1,2,3,4,4a,4bα,5,6,7,8,8a,9,10,10aα-tetradecahydrophenanthrene (R-3) was prepared from the epoxide mixture R-2 by a procedure of Crandall and Lin,[62] which was modified by U. Hengartner in the Ireland laboratories.[77] A 1.67-ml portion of 2.66 M (4.44 mmoles) n-butyllithium in hexane (Alfa Inorganics) was added at room temperature to a stirred solution of 0.64 ml (4.56 mmoles) of distilled diisopropylamine (bp 83-84°) in 8 ml of dry ether. A solution of 0.42 g (1.12 mmoles) of the epoxide mixture R-2 (prepared as described above) in 8 ml of dry ether was added 5 min later. The pale yellow reaction mixture was heated at reflux for 17.5 hr, cooled, poured into 150 ml of dilute brine, and extracted with four 50-ml portions of ether. The combined extracts were washed with 50 ml of 1 N hydrochloric acid, followed very quickly by 50-ml portions of saturated sodium bicarbonate solution, water, and brine. Drying (Na_2CO_3) and removal of the solvent at reduced pressure afforded 0.40 g (95% crude yield) of a mixture of allylic alcohols as a white foam:

ir ($CHCl_3$) 3605 and 3460 (O-H), 1705 (very weak C=O), 1635-1640 (C=C), 1390 (*gem*-dimethyl), and 1110 cm^{-1} (C-O of ketal);

nmr ($CDCl_3$) δ 0.72 and 1.20 (s, 3 each, CH_3), 0.88 and 1.05 (s, 6 each, CH_3), 0.93, 1.00, 1.15, and 1.27 (s, weak, CH_3), 3.1-3.9 (m, 4, $-OCH_2-$), 4.3 (m, 0.7, $\geq C\underline{H}OH$), 4.7-4.9 (m, 1.3, $\geq C=CH_2$), 5.6 (m, 0.6, -CH=CH-).

This material was used in the next step (Collins oxidation) without further purification.

2,2-(2',2'-Dimethylpropylenedioxy)-8-methylene-1,1,4aβ,-8aβ-tetramethyl-1,2,3,4,4a,4bα,5,6,8a,9,10,10aα-dodecahydro-7(8H)-phenanthrone (R-4) was prepared by a Collins oxidation of the allylic alcohol mixture obtained in the preceding reaction. A solution of 156 mg (0.414 mmole) of the crude allylic alcohol mixture in 6.2 ml of dry methylene chloride was added at room temperature to a stirred solution of 644 mg (2.49 mmoles, 6 equivalents) of the chromium trioxide--dipyridine complex[39] in 14.5 ml of dry methylene chloride. After stirring for 5 min, the brown suspension was filtered through 8 g of Woelm alumina (activity III) with 30 ml of methylene chloride. Removal of the methylene chloride and pyridine at reduced pressure left 130 mg of white crystalline solid, the ir spectrum ($CHCl_3$) of which exhibited equal intensity absorptions at 1655 and 1685 cm^{-1}, indicating both endo- and exocyclic unsaturated ketones.

The white solid was chromatographed on 20 g of Merck silica gel. Elution with 65 ml of 1% ether in reagent grade chloroform gave 70 mg (52% yield from the epoxide mixture R-2) of white crystalline exocyclic enone R-4, mp 160-168°.

The analytical sample was recrystallized from hexane: prisms, mp 166-170.5°;

ir ($CHCl_3$) 1685 (C=O), 1610 (C=C), 1390 (*gem*-dimethyl), and 1110 cm^{-1} (C-O of ketal);

nmr ($CDCl_3$) δ 0.70, 0.90, 0.97, 1.06, 1.08, and 1.22 (s, 3 each, CH_3), 3.1-3.9 (m, 4, $-OCH_2-$), 5.02 (d, 1, J=1.5, $>C=CH_2$), 5.54 (d, 1, J=1.5, $>C=CH_2$);

Anal. Calcd for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 76.92; H, 10.32.

Further elution of the column with the same solvent gave an approximately 20% yield of the endocyclic enone LVIII as white needles, mp 176.5-183°.

A comparable sample from an earlier experiment was crystallized from methylene chloride--ether to give the analytical sample: needles, mp 175-180°;

ir ($CHCl_3$) 1655 (C=O), 1615 (C=C), 1390 (*gem*-dimethyl), and 1110 cm^{-1} (C-O of ketal);

nmr ($CDCl_3$) δ 0.73, 0.90, 0.98, 1.05, 1.13, and 1.20 (s, 3 each, CH_3), 1.85 (d, 3, J=1, vinylic CH_3), 3.1-3.9 (m, 4, $-OCH_2-$), 5.70 (d, 1, J=1, vinylic H);

Anal. Calcd for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 76.91; H, 10.22.

When the epoxide cleavage reaction was done on a large scale [8.02 g (21.3 mmoles) of the epoxide mixture R-2 and lithium diisopropylamide, which was prepared from 14.9 ml (106 mmoles) of diisopropylamine and 31.8 ml of 2.67 *M* (85 mmoles) *n*-butyllithium in hexane, in 300 ml of ether], the product mixture contained a saturated ketone [*ir* ($CHCl_3$) 1705 cm^{-1} (C=O)], which was assumed to be the ketone LIX on the basis of further reactions. This impurity was carried through the Collins oxidation reaction with the allylic alcohols. On purification of the oxidation product, the ketone LIX was found to co-crystallize (hexane) and to co-chromatograph (reagent chloroform) with the desired exocyclic methylene ketone R-4.

2,2-(2',2'-Dimethylpropylenedioxy)-8-(2'-*m*-methoxyphenylethyl)-1,1,4aβ,8aβ-tetramethyl-1,2,3,4,4a,4bα,5,6,8a,9,10,10aα-dodecahydro-7-phenanthryl Acetate (S-1) was synthesized by the conjugate addition procedure of Baldwin and Ireland.[60] A solution of 1.0 ml (7.42 mmoles) of *m*-methoxybenzyl chloride [prepared by J. Tilley and C. Lipinski in the Ireland laboratories according to a published procedure,[78] bp 132-134° (20 mm)] in 23 ml of dry ether was added dropwise over a period of 40 min to 180 mg (7.4 mmoles) of freshly cut magnesium shavings covered with 45 ml of dry ether. The Grignard reagent was stirred at room temperature for 2 hr and then cooled to 0° (internal temperature) while a solution of 923 mg (2.46 mmoles) of a 4:1 mixture of the unsaturated ketone R-4 and the ketone impurity LIX (obtained from the Collins oxidation of the large scale epoxide cleavage product mixture) in 12 ml of dry benzene and 60 ml of dry ether was added dropwise over a 1.25 hr period. Each drop produced a transient amber color. After the addition was complete, the cooling bath was replaced by a water bath at room temperature, and the reaction mixture was stirred at room temperature for 1 hr. After quenching the enolate by the rapid addition of 2.3 ml (24.4 mmoles) of acetic anhydride (twice distilled, bp 139-140°), the resulting suspension was stirred for 19 hr, poured into 200 ml of dilute brine and 100 g of ice, and extracted with four 100-ml portions of ether. The combined extracts were washed with 100-ml portions of water and brine, and dried ($MgSO_4$). Removal of the solvent at reduced pressure afforded 2.00 g of a pale yellow oil.

In an identical experiment, the reaction of 1.86 g (4.96 mmoles) of the same enone-ketone mixture with the Grignard reagent produced from 363 mg (14.9 mmoles) of magnesium shavings and 2.0 ml (14.9 mmoles) of m-methoxybenzyl chloride and then reaction of the enolate with 4.6 ml (48.8 mmoles) of acetic anhydride produced 4.28 g of oil.

These two products were combined, and the volatile material (acetic anhydride and m-methoxyphenylacetone) was removed by evaporative distillation at 100° (5μ) to afford, after two recrystallizations from ether--benzene, 0.62 g (16% yield) of the side product, hydroxy-ketal LX as white plates, mp 172.5-177°. The nmr spectrum of this material was the same as that of the analytical sample isolated as a side product of a later experiment.

The mother liquors, which weighed 4.05 g, were chromatographed on 400 g of Merck silica gel. Elution with 30% ether in petroleum ether gave 2.66 g of the impure enol acetate S-1 as oily white crystals and 0.22 g of cruder material. The larger fraction upon trituration with petroleum ether afforded 1.78 g (51% yield) of the enol acetate S-1. The mother liquors from the trituration and the 0.22 g of crude enol acetate from the column chromatography were purified by preparative tlc (two Analtech silica gel 20x20x0.25 cm plates, reagent chloroform) to afford 0.35 g of impure enol acetate (R_f= 0.4-0.55). Trituration with petroleum ether gave 0.16 g of white crystals. The combined product, which weighed 1.94 g (a 56% yield corrected for the presence of 10% ketal alcohol LX, which was isolated from the product mixture of the next experiment), melted at 140-142°.

The analytical sample, which was prepared by the same procedure, was crystallized from petroleum ether: prisms, mp 137-141°;

ir ($CHCl_3$) 1740 (C=O), 1585-1600 (aromatic), 1390 (*gem*-dimethyl), and 1105 cm^{-1} (C-O of ketal);

nmr ($CDCl_3$) δ 0.73 and 1.23 (s, 3 each, CH_3), 0.90 and 1.07 (s, 6 each, CH_3), 2.17 (s, 3, acetate CH_3), 3.1-3.9 (m, 4, $-OCH_2-$), 3.84 (s, 3, $-OCH_3$), 6.6-7.4 (m, 4, aromatic);

Anal. Calcd for $C_{34}H_{50}O_5$: C, 75.80; H, 9.35. Found: C, 75.96; H, 9.42.

2,2-(2',2'-Dimethylpropylenedioxy)-8β-(2'-*m*-methoxyphenylethyl)-1,1,4aβ,8α,8aβ-pentamethyl-1,2,3,4,4a,4bα,5,6,8a,9,10,-10aα-dodecahydro-7(8H)-phenanthrone (S-2). The procedure of Baldwin and Ireland[60] was modified. To the residue left by the evaporation of the solvent from 2.4 ml of 1.67 *M* (4.0 mmoles) ethereal methyllithium (Alfa Inorganics) was added 12 ml of dry dimethoxyethane. To the resulting cloudy solution was added dropwise over a period of 13 min 895 mg (1.66 mmoles) of enol acetate S-1 (prepared in the preceding experiment) dissolved in 12.5 ml of dry dimethoxyethane. After stirring at room temperature for 1.3 hr, the pale yellow solution of the lithium enolate was quenched by the addition of 12 ml (27.4 g, 194 mmoles) of methyl iodide (purified by two distillations from phosphorous pentoxide). After stirring for 5 min, the solution was poured into 100 ml of dilute brine and 50 g of ice, and extracted with four 50-ml portions of ether. The combined extracts were washed with 50 ml of water and 50 ml of brine, and dried (Na_2CO_3). Removal of the solvent at reduced pressure afforded 0.87 g of the crude methylated ketone S-2 as a clear, colorless oil.

In another experiment, 0.99 g (1.84 mmoles) of the enol acetate was treated with 4.4 mmoles of methyllithium in 27 ml of dimethoxyethane and then with 13 ml (209 mmoles) of methyl iodide. After stirring for 10 min, the reaction mixture was worked up as above to give 1.07 g of crude ketone S-2 as an oil.

The combined products were triturated with petroleum ether, which precipitated 0.20 g of the hydroxy ketal LX, mp 178.5-181°. Crystallization from benzene--ether afforded the analytical sample: plates, mp 181.5-183°;

ir ($CHCl_3$) 3580-3610 (O-H), 1585-1600 (aromatic), 1390 (*gem*-dimethyl), and 1110 cm^{-1} (C-O of ketal);

nmr ($CDCl_3$) δ 0.70, 0.98, 1.02, 1.05, and 1.22 (s, 3 each, CH_3), 3.1-3.9 (m, 4, $-OCH_2-$), 3.80 (s, 3, $-OCH_3$), 6.6-7.4 (m, 4, aromatic), 0.88 (s, 6, CH_3);

Anal. Calcd for $C_{32}H_{50}O_4$: C, 77.06; H, 10.10. Found: C, 77.00; H, 10.09.

The amount of this side product isolated from this experiment and the preceding one was 0.82 g or 21% of the Grignard reaction product mixture.

The 1.74 g of mother liquors obtained from the trituration was chromatographed on 200 g of Merck silica gel. Elution with 750 ml of 5% acetone in petroleum ether gave 0.33 g (20% yield) of O-methylated material LXII as a viscous oil: ir ($CHCl_3$) 1670 (C=C), 1585 and 1600 (aromatic), and 1390 cm^{-1} (gem-dimethyl).

The attempted crystallization of this compound resulted in the hydrolysis of the enol ether group, yielding the unmethylated ketone LXIII. Recrystallization of this ketone from methylene chloride--ether--petroleum ether afforded analytically pure material as a microcrystalline solid: mp 153-157°;

ir ($CHCl_3$) 1705 (C=O), 1585-1600 (aromatic), 1390 (gem-dimethyl), and 1115 cm^{-1} (C-O of ketal);

nmr ($CDCl_3$) δ 0.73 and 0.87 (s, 6 each, CH_3), 1.05 and 1.25 (s, 3 each, CH_3), 3.1-3.9 (m, 4, $-OCH_2-$), 3.79 (s, 3, $-OCH_3$), 6.6-7.4 (m, 4, aromatic H);

Anal. Calcd for $C_{32}H_{48}O_4$: C, 77.38; H, 9.74. Found: C, 77.45; H, 9.73.

Further elution of the column with 150 ml of the same solvent gave 0.26 g (15% yield) of the dimethylated ketone

LXI as an oil, which formed white crystals on trituration with petroleum ether, yielding the analytical sample: mp 130-131.5°;

ir ($CHCl_3$) 1690 (C=O), 1585-1600 (aromatic), 1390 (*gem*-dimethyl), and 1115 cm^{-1} (C-O of ketal);

nmr ($CDCl_3$) δ 0.73, 0.87, 0.93, 0.97, 1.07, and 1.23 (s, 3 each, CH_3), 1.23 (d, 3, J=7, C-6 CH_3), 1.28 (s, 3, C-8α CH_3), 3.1-3.9 (m, 4, $-OCH_2-$), 3.82 (s, 3, $-OCH_3$), 6.6-7.4 (m, 4, aromatic);

Anal. Calcd for $C_{34}H_{52}O_4$: C, 77.82; H, 9.99. Found: C, 77.97; H, 10.10.

Elution with 450 ml of the same solvent gave 1.00 g (60% crude yield) of the desired monomethylated ketone S-2, which on trituration with petroleum ether afforded 0.89 g (53% yield) of white crystals, the nmr spectrum of which was identical to that of the analytical sample prepared by two recrystallizations from methylene chloride--ether: microcrystalline solid, mp 168-172°;

ir ($CHCl_3$) 1700 (C=O), 1585-1600 (aromatic), 1390 (*gem*-dimethyl), and 1110 cm^{-1} (C-O of ketal);

nmr ($CDCl_3$) δ 0.73, 0.92, 1.07, and 1.22 (s, 3 each, CH_3), 0.85 (s, 6, CH_3), 1.31 (s, 3, C-8α CH_3), 3.1-3.9 (m, 4, $-OCH_2-$), 3.80 (s, 3, $-OCH_3$), 6.6-7.4 (m, 4, aromatic);

Anal. Calcd for $C_{33}H_{50}O_4$: C, 77.60; H, 9.87. Found: C, 77.64; H, 9.76.

8β-(2'-m-Methoxyphenylethyl)-1,1,4aβ,8α,8aβ-pentamethyl-3,4,4a,4bα,5,6,8a,9,10,10aα-decahydro-2,7(1H,8H)-phenanthrenedione (Q-11) was prepared by the deketalization method used by Baldwin and Ireland.[60] To 0.85 g (1.67 mmoles) of the keto-ketal S-2 (prepared in the above reaction) dissolved in 80 ml of acetone was added 21.4 ml of 10% aqueous hydrochloric acid. After standing for 1 hr, the clear, colorless solution was poured into 800 ml of water and extracted with five 100-ml portions of ether. The combined extracts were washed with 100 ml of water and 100 ml of brine, and dried ($MgSO_4$). Removal of the solvent at reduced pressure afforded 0.71 g of white crystalline diketone Q-11, mp 141-151°, which was purified by recrystallizations from chloroform--ether and hexane. Two crops of white prisms were obtained: 0.39 g, mp 160-166°, and 0.09 g, mp 158-165°, the vapor phase chromatograms (300°, 4% SE-30) of which exhibited one major peak with a retention time of 3.5 min (97% for the first crop, and 86% for the second). The total yield was 64%. The ir and nmr spectra of this diketone were the same as those of the diketone Q-11, which was prepared by the hydrolysis of the ethylene ketal-ketone Q-10. This hydrolysis procedure is presented below.

2,2-Ethylenedioxy-8β-(2'-m-methoxyphenylethyl)-1,1,4aβ,-8α,8aβ-pentamethyl-1,2,3,4,4a,4bα,5,6,8a,9,10,10aα-dodecahydro-7(8H)-phenanthrone (Q-10) was prepared by a procedure of Baldwin and Ireland.[60] To the residue left by the removal of the solvent from 1.66 ml of 1.75 M (2.91 mmoles) ethereal methyllithium (Alfa Inorganics) was added 8.6 ml of dry dimethoxyethane. To the resulting cloudy solution was added dropwise over a period of 8 min 603 mg (1.21 mmoles) of enol acetate Q-9 (obtained from the hydroxy ketone O-4 by the method of Baldwin and Ireland[60]) dissolved in 9 ml of dry dimethoxyethane. After stirring at room temperature for 45 min, the enolate solution was quenched by the addition of 8.6 ml (19.6 g, 139 mmoles) of methyl iodide (purified by distillations from phosphorous pentoxide and from magnesium sulfate). After stirring for 5 min, the solution was poured into 100 ml of brine and 50 g of ice, and extracted with four 50-ml portions of ether. The combined extracts were washed with 50 ml of water and 50 ml of brine, and dried ($MgSO_4$). Removal of the solvent at reduced pressure gave 537 mg of a pale yellow oil.

In another experiment, 625 mg (1.26 mmoles) of enol acetate Q-9 was treated with 3.01 mmoles of methyllithium and 8.9 ml (144 mmoles) of methyl iodide in 18.4 ml of dimethoxyethane, and worked up as above to produce 585 mg of a pale yellow oil.

The combined products were triturated with hexane. The 873 mg of solid obtained was crystallized twice from ethyl acetate--heptane to afford 430 mg (35% yield) of the keto-ketal Q-10 as white crystals, mp 151.5-154°. The vpc chromatogram (300°, 4% SE-30) of this material exhibited one main peak at a retention time of 4.7 min (92%).

Preparative tlc (Merck silica gel, 20x40x0.1 cm plate, 50% ether in petroleum ether) was used to separate the mother liquors into three fractions: keto-ketal Q-10 (R_f=0.25-0.35), dimethylated ketone LXVIII (R_f= 0.35-0.45), and the O-methylated compound LXIX (R_f= 0.45-0.55).

The dimethylated ketone LXVIII was identified by ir and nmr spectral data:

ir ($CHCl_3$) 1685 (C=O), 1585-1600 (aromatic), and 1385 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.88, 0.90, 0.93, and 0.97 (s, 3 each, CH_3), 1.21 (d, 3, J=7, C-6 CH_3), 1.27 (s, 3, C-8α CH_3), 3.78 (s, 3, $-OCH_3$), 3.95 (s, 4, $-OCH_2-$), 6.6-7.4 (m, 4, aromatic H);

nmr (benzene) δ 0.75, 0.78, and 1.00 (s, 3 each, CH_3), 1.05 (s, 6, CH_3), 1.07 (d, 3, J=7.5, C-6 CH_3), 3.40 (s, 3, $-OCH_3$), 3.58 (s, 4, $-OCH_2-$).

The enol ether LXIX was identified from its ir spectrum:

ir ($CHCl_3$) 1660 (C=C), 1580-1600 (aromatic), and 1385 cm^{-1} (gem-dimethyl).

The fraction containing the keto-ketal Q-10 was triturated with hexane, and the solid obtained was crystallized from ethyl acetate--heptane to give an additional 71 mg (6% yield) of white crystals, mp 150.5-153°. The vpc chromatogram (300°, 4% SE-30) had one main peak with a retention time of 4.5 min (93%).

The combined keto-ketal Q-10 product weighed 501 mg (41%

yield): white crystals, mp 151-154°;

ir ($CHCl_3$) 1695 (C=O), 1580-1600 (aromatic), and 1390 cm^{-1}
(gem-dimethyl);

nmr ($CDCl_3$) δ 0.83 and 0.87 (s, 3 each, CH_3), 0.92 (s, 6, CH_3), 1.28 (s, 3, C-8α CH_3), 3.79 (s, 3, $-OCH_3$), 3.96 (s, 4, $-OCH_2-$), 6.6-7.4 (m, 4, aromatic H);

nmr (benzene) δ 0.72 and 1.03 (s, 6 each, CH_3), 0.93 (s, 3, CH_3), 3.42 (s, 3, $-OCH_3$), 3.60 (s, 4, $-OCH_2-$).

A Deketalization of 2,2-Ethylenedioxy-8β-(2'-m-methoxyphenylethyl)-1,1,4aβ,8α,8aβ-pentamethyl-1,2,3,4,4a,4bα,5,6,8a,-9,10,10aα-dodecahydro-7(8H)-phenanthrone (Q-10) was done according to the procedure of Baldwin and Ireland.[60] To a solution of 402 mg (0.86 mmoles) of keto-ketal Q-10 (prepared in the preceding experiment) in 40 ml of acetone was added 10.8 ml of 10% aqueous hydrochloric acid. After 45 min, the clear solution was poured into 700 ml of water and extracted with four 100-ml portions of ether. The combined extracts were washed with 100 ml of water and 100 ml of brine, and dried ($MgSO_4$). Removal of the solvent at reduced pressure gave 354 mg (100% yield) of the diketone Q-11: white crystals, mp 161-165°;

ir ($CHCl_3$) 1700 (C=O), 1580-1600 (aromatic), and 1385-1390 cm^{-1}
(gem-dimethyl)

nmr (60 and 220 MHz, $CDCl_3$) δ 0.87, 0.98, 1.05, 1.12, and 1.30 (s, 3 each, CH_3), 3.80 (s, 3, $-OCH_3$), 6.6-7.4 (m, 4, aromatic H).

The vpc chromatogram (300°, 4% SE-30) of these crystals had only one peak with a retention time of 2.7 min. The optically active diketone Q-11, which was obtained from the degradation of euphol, exhibited a single peak with an identical retention time. Co-injection of the two samples gave a single peak. Analytical tlc (Merck silica gel, 50% benzene in ether) of the racemic and optically active diketones gave a single spot at $R_f = 0.50$. The ir and nmr (60 and 220 MHz) spectra of the optically active material were identical to those of the racemic material (above).

The Preparation of Polyphosphoric Acid (PPA).[28] To 100 ml of 85% phosphoric acid was slowly added 113 g of phosphorous pentoxide with mechanical stirring and occasional cooling in an ice bath to prevent overheating. The resulting clear, colorless liquid was heated at 130° for 1 hr, then cooled to room temperature, and used directly in the cyclodehydration reaction.

10-Methoxy-4,4,6aβ,6bα,14bβ-pentamethyl-1,2,4aα,5,6,6a,-6b,7,8,14,14aα,14b-dodecahydro-3(4H)-picenone (V-1). The cyclodehydration procedure of Baldwin and Ireland[60] was modified. To a saturated solution of 327 mg (0.77 mmole) of pure diketone Q-11 (prepared above, mp 161-165°) in 2 ml of benzene was added 53 ml of polyphosphoric acid. The yellow viscous mixture was rapidly stirred at 50° (internal temperature) with a mechanically driven teflon stirring paddle for a period of 30 min, then poured into 350 g of an ice--water mixture, and extracted with four 50-ml portions of benzene. The combined extracts were washed with 100 ml of saturated aqueous sodium bicarbonate and 100 ml of brine, and dried ($MgSO_4$). On removal of the solvent at reduced pressure, 308.5 mg of oily white crystalline pentacyclic ketone V-1 was obtained. Two crops of crystals, 167.5 and 53.5 mg, of ketone V-1 were produced on crystallization of the crude product from ethyl acetate--heptane. Preparative tlc (Merck silica gel, benzene) of the mother liquors gave another 60 mg of the ketone (R_f= 0.1-0.2). The combined product weighed 281 mg (90% yield), mp 150-151.5^o.

The analytical sample was prepared in the same manner as the above material: mp 147.5-150^o;

<u>ir</u> ($CHCl_3$) 1695 (C=O), 1645 (styrene C=C), 1610 and 1570 (aromatic), and 1375 and 1385 cm^{-1} (<u>gem</u>-dimethyl);

<u>nmr</u> ($CDCl_3$) δ 0.97, and 1.03 (s, 3 each, CH_3), 1.10 (broad s, 9, CH_3), 3.76 (s, 3, $-OCH_3$), 6.15 (two superimposed doublets, 1, J_{AX}=J_{BX}=2, vinylic H), 6.5-7.6 (m, 3, aromatic);

<u>Anal</u>. Calcd for $C_{28}H_{38}O_2$: C, 82.71; H, 9.42. Found: C, 82.86; H, 9.36.

<u>3β-Hydroxy-10-methoxy-4,4,6aβ,6bα,14bβ-pentamethyl-1,2,-3,4,4aα,5,6,6a,6b,7,8,14,14aα,14b-tetradecahydropicene (V-2)</u>. Lithium aluminum tri-<u>t</u>-butoxy hydride (2.24 g, 8.8 mmoles), which was prepared according to a reported procedure,[28] was

added to a solution of 0.38 g (0.93 mmole) of the pentacyclic ketone V-1 in 60 ml of tetrahydrofuran, and the resulting suspension was first heated at reflux for 3 hr and then cooled. Water was added to destroy the unreacted hydride. The resulting mixture was poured into 600 ml of 1% aqueous hydrochloric acid and extracted with four 100-ml portions of benzene. The combined extracts were washed with 100 ml of 1% aqueous hydrochloric acid and then 100-ml portions of 10% aqueous sodium bicarbonate, water, and brine, and dried (Na_2CO_3). Removal of the solvent at reduced pressure afforded 0.39 g (quantitative crude yield) of a white micro-crystalline solid, the pentacyclic alcohol V-2, mp 176-184°.

The analytical sample, which was obtained by recrystallization from benzene of material prepared in an earlier experiment, melted at 185-188.5°:

ir ($CHCl_3$) 3610 (O-H), 1640 (styrene C=C), 1570 and 1605 (aromatic), and 1370 and 1385 cm^{-1} (*gem*-dimethyl);

nmr ($CDCl_3$) δ 0.82 and 0.93 (s, 3 each, CH_3), 1.02 (s, 9, CH_3), 3.2 (m, 1, C<u>H</u>OH), 3.77 (s, 3, $-OCH_3$), 6.15 (two superimposed doublets, 1, $J_{AX}=J_{BX}=2$, vinylic H), 6.5-7.6 (m, 3, aromatic H);

Anal. Calcd for $C_{28}H_{40}O_2$: C, 82.30; H, 9.87. Found: C, 82.14; H, 9.87.

The 3β-Hydroxy-10-methoxy-4,4,6aβ,6bα,14bβ-pentamethyl-1,2,3,4,4aα,5,6,6a,6b,7,8,12b,13,14,14aα,14b-hexadecahydro-

picenes (V-3 and V-4). A mixture of 31.8 mg (0.08 mmole) of the alcohol V-2 (mp 185-188.5°) and 32 mg of 10% palladium on carbon (Engelhard) in 30 ml of absolute ethanol was stirred under a hydrogen atmosphere for 3 days. Removal of the catalyst by filtration, and evaporation of the filtrate at reduced pressure afforded an oily mixture of the *cis* and *trans* pentacyclic alcohols V-3 and V-4, weighing 29.6 mg (93% crude yield), the vapor phase chromatogram (300°, 4% SE-30) of which exhibited two peaks with an area ratio of 3:1 at retention times of 2.8 and 3.3 min.

ir ($CHCl_3$) 3600 (O-H), 1580 and 1610 (aromatic), and 1375 and 1390 cm^{-1} (*gem*-dimethyl);

nmr ($CDCl_3$) δ 0.40 (s, 2, C-6a CH_3), 0.73, 0.97, and 1.27 (s, 3 each, CH_3), 0.80 (s, 4, CH_3), 0.92, 1.07, 1.12, and 1.23 (s, weak, CH_3), 3.2 (m, 1, C*H*OH), 3.77 (s, 3, $-OCH_3$), 6.6-7.3 (m, 3, aromatic H).

The nmr spectrum established that the predominant hydrogenation isomer was the *cis* C/D ring-fused alcohol V-3.

The Birch Reduction of the Styrene Bond of the Pentacyclic Alcohol V-2 was performed using a modification of a published procedure.[79] To a solution of 85 mg (0.21 mmole) of the pentacyclic alcohol V-2 (prepared as described above) in 40 ml of dimethoxyethane and 40 ml of tetrahydrofuran was added 250 ml of liquid ammonia (distilled from lithium and sodium). The solution became slightly cloudy, however the addition of 20 ml of tetrahydrofuran did not clarify it. Sodium (0.24 g, 10.4 mmoles) was added, and the blue mixture was stirred at reflux for 1 hr and then quenched by the slow addition of 1.1 g (20.7 mmoles) of ammonium chloride. The ammonia was allowed to evaporate under a slow stream of argon. The liquid in the flask was decanted and concentrated at reduced pressure. The concentrated material and the residue in the flask were mixed with 150 ml of dilute brine and extracted with four 50-ml portions of benzene. The combined extracts were washed with 50-ml portions of water and brine, and dried (Na_2CO_3). Removal of the solvent left 87 mg of a clear colorless oil, the vapor phase chromatogram (300^o, 4% SE-30) of which had two major peaks with retention times of 2.8 (45%) and 3.3 min (55%). Trituration with ether gave 12.4 mg of the trans isomer V-4: white plates, mp $158-159.5^o$, and 36.7 mg of slightly cruder material. The purer material, the vapor phase chromatogram (300^o, 4% SE-30) of which had one peak with a retention time of 3.3 min (97%), was recrystallized from benzene--methanol to give the analytical sample: prisms, mp $148-151^o$;

ir ($CHCl_3$) 3620 (O-H), 1585 and 1615 (aromatic), and 1385 and 1395 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.80 (s, 6, CH_3), 0.92, 1.01, and 1.08 (s, 3 each, CH_3), 3.2 (m, 1, $C\underline{H}OH$), 3.76 (s, 3, $-OCH_3$), 6.6-7.3 (m, 3, aromatic H);

Anal. Calcd for $C_{28}H_{42}O_2$: C, 81.90; H, 10.31. Found: C, 81.94; H, 10.20.

The 31 mg of mother liquors from the triturations afforded 15.1 mg of *cis* isomer as a micro-crystalline solid, mp 139-144°, on crystallization from ether--petroleum ether. The vapor phase chromatogram (300°, 4% SE-30) of this material had one major peak at a retention time of 2.8 min (91%).

ir ($CHCl_3$) 3615 (O-H), 1580 and 1610 (aromatic), and 1365, 1385, and 1390 cm^{-1} (*gem*-dimethyl);

nmr ($CDCl_3$) δ 0.40, 0.77, 0.81, 1.00, and 1.29 (s, 3 each, CH_3), 3.2 (m, 1, $C\underline{H}OH$), 3.80 (s, 3, $-OCH_3$), 6.6-7.3 (m, 3, aromatic H).

3β-Hydroxy-4,4,6aβ,6bα,14bβ-pentamethyl-1,2,3,4,4aα,5,-6,6a,6b,7,8,12,12aα,12bβ,13,14,14aα,14b-octadecahydro-10(11H)-picenone (V-5). Because of the insolubility of the starting material, a reported Birch reduction procedure[80] was modified. A 10.2-mg (0.25 mmole) portion of the *trans* C/D ring fused pentacyclic alcohol V-4 (prepared in the preceding reaction) was dissolved in 15 ml of dimethoxyethane. Then 40 ml of liquid ammonia (distilled from sodium and lithium) was added. A total of 47 mg (6.7 mmoles) of lithium was added over a period of 23 min to maintain the deep blue color of the reaction mixture. Next, 0.72 ml (7.6 mmoles) of *t*-butanol (dried by distillation from calcium hydride) was added. After the blue color had disappeared, another 38-mg (5.5 mmoles) portion of lithium and 0.48 ml (5.0 mmoles) of *t*-butanol were added. After 45 min, the blue reaction mixture was quenched by the addition of 0.99 g (18.7 mmoles) of ammonium chloride. After the ammonia had evaporated under a slow stream of argon, the residue was diluted with 150 ml of dilute brine and extracted with four 50-ml portions of benzene. The combined extracts were washed with 50-ml portions of water and brine, and dried (Na_2CO_3).

The residue left after the removal of the solvent at reduced pressure was dissolved in 15 ml of methanol with heating. To this solution was added 5 ml of 5 *N* aqueous hydrochloric acid and this mixture was heated at reflux for 30 min, cooled, poured into 150 ml of dilute brine, and extracted with four 50-ml portions of benzene. The combined extracts were washed with 50-ml portions of saturated aqueous sodium carbonate, water, and brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 11.5 mg of a white solid. The vapor phase chromatogram (300^o, 4% SE-30) of this material had two major peaks with retention times of 3.3 (45%) and 3.8 min (40%). The chromatogram of the starting material showed one peak with a retention time of 3.3 min. The nmr spectrum of the crude Birch reduction product exhibited a signal at 3.77 δ (s, 1, $-OCH_3$). Therefore, this crude product contained a large amount of starting material.

Recrystallization of the product mixture from chloroform--ether afforded 5.5 mg of pure pentacyclic enone V-5 as a white microcrystalline solid, vacuum mp 253-256°. The vapor phase chromatogram of this material had one peak at a retention time of 3.8 min. The ir and nmr spectra of this enone were the same as that of the analytical sample, which was prepared by ether--benzene recrystallization of material prepared by a similar route: vacuum mp 263.5-268.5°;

<u>ir</u> ($CHCl_3$) 3605 (O-H), 1660 (C=O), 1615 (C=C), and 1375 and 1390 cm^{-1} (<u>gem</u>-dimethyl);

<u>nmr</u> ($CDCl_3$) δ 0.76, 0.83, and 1.05 (s, 3 each, CH_3), 0.93 (s, 6, CH_3), 3.2 (m, 1, C<u>H</u>OH), 5.80 (broad s, 1, vinylic H);

<u>Anal</u>. Calcd for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.44; H, 10.60.

<u>The Birch Reduction of the Pentacyclic Alcohol V-2</u> was done according to the procedure given above. A 1090-ml portion of liquid ammonia was distilled from sodium and lithium into a solution of 0.31 g (0.76 mmoles) of the pentacyclic alcohol V-2 (prepared by a procedure described above) in 465 ml of dimethoxyethane. To this slightly cloudy solution was added 2.62 g (380 mmoles) of lithium wire, which had been cut into 2-cm pieces and washed with dry hexane. After this blue mixture had stirred at reflux for 1 hr, 43.4 ml (455 mmoles) of <u>t</u>-butanol was added. The blue solution was stirred for 3.5 hr and then quenched by the slow addition of 28.4 g (530 mmoles) of ammonium chloride. The ammonia was allowed to

evaporate under a slow stream of argon. The liquid in the reaction flask was concentrated at reduced pressure. The concentrated material and the white solid in the reaction flask were diluted with 500 ml of water and extracted with four 100-ml portions of benzene. The combined extracts were washed with 100-ml portions of water and brine, and dried (Na_2SO_4). After removal of the solvent at reduced pressure, the white crystalline residue was dissolved in 465 ml of methanol by heating. To this solution was added 155 ml of 5$\underline{N}$ aqueous hydrochloric acid, and the resulting mixture was heated at reflux for 30 min, and cooled. The solution was concentrated at reduced pressure to give an aqueous residue, which was poured into 500 ml of water and extracted with four 100-ml portions of benzene. The combined extracts were washed with 100-ml portions of saturated aqueous sodium bicarbonate, water, and brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure left 0.31 g of a clear, colorless oil, which was triturated with ether to give 0.16 g of crude pentacyclic enone V-5 as white crystals. The mother liquors (157 mg) were chromatographed on 20 g of Merck silica gel with ether. Elution with 75 ml of ether gave two unidentified side products; further elution with 70 ml of ether afforded 44.3 mg of crude enone V-5 as a white solid, which was combined with 0.16 g obtained by trituration.

The crude enone was recrystallized from dichloromethane--ether to give two crops of purified pentacyclic enone V-5 as a white micro-crystalline solid: 103 mg, vacuum mp 258-261°, and 33 mg, vacuum mp 242.5-247° (45% yield). The ir and nmr spectra of the combined product were identical to those of the analytical sample, which are reported in the preceding experiment.

<u>8aβ-Cyano-3β-hydroxy-4,4,6aβ,6bα,14bβ-pentamethyl-1,2,3,-4,4aα,5,6,6a,6b,7,8,8a,11,12,12aα,12bβ,13,14,14aα,14b-eicosahydro-10(9H)-picenone (W-1)</u> was prepared according to the procedure of Nagata and coworkers,[6] as modified by Welch and Ireland.[44] To a solution of 136 mg (0.34 mmole) of enone V-5 (prepared in the preceding reaction) in 15 ml of tetrahydrofuran at 0° was added 1.92 ml of a tetrahydrofuran solution, which was cooled to 0° and which was 0.736 <u>M</u> in triethylaluminum (1.41 mmoles, Texas Alkyls) and 0.540 <u>M</u> in hydrogen cyanide[44] (1.04 mmoles, prepared by R. Farr in the Ireland laboratories). After stirring at 0° for 45 min and at room temperature for 37 hr, the pale yellow reaction mixture was poured into 150 ml of cold 5% aqueous sodium hydroxide and extracted with four 50-ml portions of benzene. The combined extracts were washed with 50-ml portions of 5% aqueous sodium hydroxide, water, and brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure left 148 mg (quantitative crude yield) of the cyano-ketone W-1 as a white micro-crystalline

solid, vacuum mp 294-298°. The ir and nmr spectra of this material were identical to those of the analytical sample, which was prepared by a similar procedure and then recrystallized from ethanol to give a white, micro-crystalline solid: vacuum mp 316-318.5°;

ir ($CHCl_3$) 3600 (O-H), 2220 (-CN), 1720 (C=O), and 1390 cm^{-1} (*gem*-dimethyl);

nmr ($CDCl_3$) δ 0.78, 0.88, and 1.08 (s, 3 each, CH_3), 1.00 (s, 6, CH_3), 3.2 (m, 1, C*H*OH);

Anal. Calcd for $C_{28}H_{43}NO_2$: C, 79.01; H, 10.18; N, 3.29.
Found: C, 78.88; H, 10.14; N, 3.26.

8aβ-Cyano-10,10-ethylenedioxy-3β-hydroxy-4,4,6aβ,6bα,-14bβ-pentamethyl-1,2,3,4,4aα,5,6,6a,6b,7,8,8a,9,10,11,12,12aα,-12bβ,13,14,14aα,14b-docosahydropicene (W-2). A ketalization procedure of Baldwin and Ireland[60] was modified. Distilled ethylene glycol (38 ml) and *p*-toluenesulfonic acid monohydrate (100 mg, 0.53 mmole) were added to a solution of 189 mg (0.44 mmole) of cyano-ketone W-1 (prepared by the above procedure) in 190 ml of benzene. This mixture was heated at reflux for 10 hr in a flask fitted with a Dean-Stark trap, the receiver end of which was filled with benzene-washed Drierite to bind the azeotroped water. After cooling, the reaction mixture was poured into 400 g of ice-water and 200 ml of saturated sodium bicarbonate. The aqueous phase was extracted with two 100-ml portions of benzene. The combined benzene solutions were washed with 100 ml of saturated aqueous sodium bicarbonate, five 100-ml portions of water, and 100 ml of brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure gave 0.20 g of a pale yellow solid, which was identified as the cyano-ketal W-2 from the ir and nmr spectra. Recrystallization of this material from chloroform--ether afforded 158 mg (77% yield from the enone V-5) of cyano-ketal W-2 as a white, micro-crystalline solid, vacuum mp 313-317.5°.

A sample prepared in an earlier experiment was recrystallized from ethanol to give a white micro-crystalline solid: vacuum mp 335-336.5°;

ir ($CHCl_3$) 3605 (O-H), 2220 (-CN), and 1375 and 1390 cm^{-1}
(gem-dimethyl);

nmr ($CDCl_3$) δ 0.78, 0.87, 0.95, 0.98, and 1.08 (s, 3 each,
CH_3), 3.2 (m, 1, C$\underline{H}$OH), 4.00 (m, 4, $-OCH_2CH_2O-$);

Anal. Calcd for $C_{30}H_{47}NO_3$: C, 76.71; H, 10.09; N, 2.98.
Found: C, 76.83; H, 10.15; N, 2.98.

4,4,6aβ,6bα,8aβ,14bβ-Hexamethyl-3β-hydroxy-1,2,3,4,4aα,5,6,6a,6b,7,8,8a,11,12,12aα,12bβ,13,14,14aα,14b-eicosahydro-10(9H)-picenone (W-5) was prepared by a modification of the procedure of Welch and Ireland,[44] followed by removal of the ketal protecting group.

To a solution of 158 mg (0.34 mmole) of cyano-ketal W-2 (prepared in the preceding experiment) in 60 ml of benzene was added at room temperature 1.36 ml of 0.567 M (0.77 mmoles) diisobutylaluminum hydride (K and K) in benzene.

After stirring for 1 hr, the reaction mixture was poured into 150 ml of cold 3.3% aqueous sodium hydroxide and extracted with three 50-ml portions of benzene. The combined extracts were washed with 50-ml portions of water and brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure gave 0.16 g of the crude imine W-3 as a white solid:

<u>ir</u> ($CHCl_3$) 3625 (O-H), 1630 (C=NH), and 1380 and 1390 cm^{-1} (<u>gem</u>-dimethyl).

The crude imine was heated in 22 ml of triethylene glycol (distilled) to effect solution. The solution was cooled to room temperature, and 2.2 ml (38.6 mmoles) of 85% aqueous hydrazine hydrate and 0.56 g (4.96 mmoles) of hydrazine dihydrochloride were added. This mixture was then heated at 130-135° (internal temperature) for 3.5 hr, and cooled to 110° while 3.56 g (54 mmoles) of potassium hydroxide pellets (B and A, 85%) were slowly added. The temperature of the reaction mixture was raised to 175-180° over a period of 10 min to allow for distillation of the volatile material under a rapid stream of argon. The argon flow was decreased, and heating (175-180°) was continued for 6 hr. After cooling, the cloudy reaction mixture was diluted with 500 ml of dilute brine and extracted with six 100-ml portions of benzene. The combined extracts were washed with ten 50-ml portions of water, and one 50-ml portion of brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 0.16 g of a white solid: vacuum mp 245.5-248^{o};

ir (CHCl$_3$) 3600 (O-H), and 1375 and 1385 cm^{-1} (gem-dimethyl);

nmr(CDCl$_3$) δ 0.77, 0.86, 0.98, and 1.04 (s, 3 each, CH$_3$), 0.95 (s, 6, CH$_3$), 3.2 (m, 1, CHOH), 3.88 (m, 4, -OCH$_2$-).

Because of the insolubility of this ketal (W-4), the standard deketalization procedure[60] had to be modified. A solution of 0.16 g of the crude ketal in 80 ml of acetone and 40 ml of methanol was cooled to 10^{o} while 33 ml of 10% aqueous hydrochloric acid was added. The resulting solution was allowed to stand at room temperature for 1 hr, poured into 700 ml of dilute brine, and extracted with five 100-ml portions of benzene. The combined extracts were washed with 100-ml portions of saturated aqueous sodium bicarbonate, water, and brine, and dried (Na$_2$SO$_4$). The solvent was removed at reduced pressure to afford 156 mg of the crude ketone W-5 as a white solid, which was recrystallized from dichloromethane--ether--petroleum ether to give 142 mg of ketone W-5 as a white micro-crystalline solid, vacuum mp 282-292^{o}. The vapor phase chromatogram (300^{o}, 4% SE-30) showed one major peak at a retention time of 3.1 min (91%). The overall yield for the three step conversion of the cyano-ketal W-2 to the ketone W-5 was 93%.

The analytical sample was prepared by an aqueous ethanol crystallization of comparable material: vacuum mp 300-303.5^{o}; ir (CHCl$_3$) 3600 (O-H), 1700 (C=O), and 1385 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.78 (s, 6, CH_3), 0.87, 0.99, 1.02, and 1.03 (s, 3 each, CH_3), 3.2 (m, 1, CHOH);

Anal. Calcd for $C_{28}H_{46}O_2$: C, 81.10; H, 11.18. Found: C, 81.00; H, 11.07.

4,4,6aβ,6bα,8aβ,14bβ-Hexamethyl-3β-hydroxy-1,2,3,4,4aα,-5,6,6a,6b,7,8,8a,12aα,12bβ,13,14,14aα,14b-octadecahydro-10(9H)-picenone (X-2) was prepared by bromination of the ketone W-5, followed by dehydrobromination. A procedure of Marshall and coworkers[2] was modified for the first step. A stirred solution of 132 mg (0.32 mmole) of the pentacyclic hexamethyl ketone W-5 (prepared in the preceding reaction) in 13 ml of glacial acetic acid was cooled to 10-15° while 1.2 ml of 0.313 M (0.37 mmole) bromine in acetic acid, which was also 0.0075 M in hydrobromic acid, was added dropwise over a period of 14 min. The orange solution was immediately poured into 150 ml of dilute brine containing 1.0 g (7.9 mmoles) of sodium sulfite and extracted with four 50-ml portions of benzene. The combined extracts were washed with two 50-ml portions of saturated aqueous sodium bicarbonate, 50 ml of water, and 50 ml of brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure left 151 mg of a yellow solid, which was purified by precipitation from dichloromethane--ether--petroleum ether, treatment with activated charcoal in chloroform and filtration, and reprecipitation from the aforementioned solvent mixture to give 123 mg of the bromoketone X-1 as a pale yellow solid:

vacuum mp 177-181° (decomposition);

ir ($CHCl_3$) 3620 (O-H), 1715 (C=O), and 1390 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.78 (s, 6, CH_3), 0.87, 1.00, 1.03, and 1.06 (s, 3 each, CH_3), 3.2 (m, 1, C$\underline{H}$OH), 4.30 (m, 1, CHBr).

The bromoketone X-1 (123 mg, 0.25 mmole) was dehydrobrominated by the procedures of Marshall and coworkers,[2] and Green and Long.[71] To a solution of the bromoketone in 10 ml of dimethylacetamide (MCB, distilled, bp 166°) was added 0.50 g (5.0 mmoles) of calcium carbonate (Merck). This slurry was stirred and heated at reflux for 30 min, cooled, poured into 150 ml of dilute brine, and extracted with four 50-ml portions of benzene. The combined extracts were washed with two 50-ml portions of 10% aqueous hydrochloric acid, and 50-ml portions of saturated aqueous sodium bicarbonate, water, and brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 148 mg of a yellow oil, which was chromatographed on 20 g of Merck silica gel with 50% ether in benzene. The first 45 ml of eluant were discarded; the next 15 ml of eluant contained 46.3 mg of an unidentified mixture, a white solid:

ir ($CHCl_3$) 3620 (O-H), 1725 (C=O), 1685 (C=O), and 1385 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.78, 0.87, 0.95, 1.00, 1.03, and 1.05 (s, CH_3), 3.2 (m, 1, C$\underline{H}$OH).

This material decomposed at 160° when a vacuum melting point was attempted.

Further elution of the column with the same solvent afforded 39.3 mg (32% yield from the saturated ketone W-5) of the α,β-unsaturated ketone X-2 as a white solid: vacuum mp 235-242°; <u>ir</u> ($CHCl_3$) 3620 (O-H), 1670 (C=O), and 1385 and 1390 cm^{-1}

(gem-dimethyl);

<u>uv</u> max (CH_3OH) 236 nm (ϵ = 7300), calcd[81] 227 nm.

<u>nmr</u> ($CDCl_3$) δ 0.81, 0.88, and 0.91 (s, 3 each, CH_3), 1.03 (m, 9, CH_3), 2.23 (s, 2, CH_2CO), 3.2 (m, 1, $C\underline{H}OH$), 5.99 (d of d, 1, J = 3 and 11, C-11 H), 6.98 (broad d, 1, J = 11, C-12 H).

This material was recrystallized from dichloromethane--ether to give the analytical sample as a white solid: vacuum mp 245-247.5°;

<u>Anal</u>. Calcd for $C_{28}H_{44}O_2$: C, 81.50; H, 10.75. Found: C, 81.30; H, 10.61.

<u>Attempted Dimethylation of the Enone X-2</u>. The procedure employed was a modification of one successfully used by Ireland and Mander.[80] To 0.39 ml of 1.12 <u>M</u> (0.44 mmole) potassium <u>t</u>-butoxide in <u>t</u>-butyl alcohol was added a solution of 36.2 mg (0.09 mmole) of the enone X-2 (prepared as described above) in 0.7 ml of <u>t</u>-butyl alcohol and 0.35 ml of benzene. After stirring for 1 hr, 55 μl (0.88 mmole) of methyl iodide (purified by distillation from phosphorous pentoxide) was added and stirring was continued for 18 hr, during which time a precipitate formed. The reaction mixture was poured into 150 ml of

dilute brine and extracted with four 50-ml portions of benzene. The combined extracts were washed with 50-ml portions of water and brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure left 35.2 mg of an oily solid. The ir spectrum of this material indicated that little of no reaction had occurred:

ir ($CHCl_3$) 3620 (O-H), 1670 (C=O), and 1385 and 1390 cm^{-1} (gem-dimethyl).

4,4,6aβ,6bα,8aβ,14bβ-Hexamethyl-3β-hydroxy-1,2,3,4,4aα,-5,6,6a,6b,7,8,8a,9,12bβ,13,14,14aα,14b-octadecahydro-10(11H)-picenone (X-3) was prepared by acid equilibration of the enone X-2. The hydrolysis and equilibration procedure used for the preparation of the enone V-5 was employed. To 30.5 mg (0.074 mmole) of the α,β-unsaturated ketone X-2 (prepared as described above) dissolved in 45 ml of methanol was added 15 ml of 5 N aqueous hydrochloric acid. This solution was heated at reflux for 5 hr, cooled, and concentrated at reduced pressure. The aqueous residue was poured into 150 ml of dilute brine and extracted with four 25-ml portions of benzene. The combined extracts were washed with 25-ml portions of saturated aqueous sodium bicarbonate, water, and brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 29.7 mg of a yellow solid, which contained a 2:1 mixture of enones X-3 and X-2 according to the strengths of the carbonyl absorptions in the infrared spectrum:

ir ($CHCl_3$) 1715 (β,γ-enone) and 1675 cm^{-1} (α,β-enone). The infrared spectra, which were taken after 30-min and 1-hr periods of reflux, showed these two carbonyl bands in ratios of 1:2 and 1:1, respectively.

The crude mixture was crystallized from dichloromethane--ether to give 15.4 mg of a white solid: vacuum mp 258-261°;

ir ($CHCl_3$) 3615 (O-H), 1715 (strong β,γ-enone C=O), 1675 (very weak α,β-enone C=O), and 1385 and 1395 cm^{-1} (*gem*-dimethyl);

nmr ($CDCl_3$) δ 0.79, 0.86, 0.91, 1.00, 1.06, and 1.11 (s, 3 each, CH_3), 3.2 (m, 1, CHOH), 5.20 (m, 1, vinylic H).

Anal. Calcd for $C_{28}H_{44}O_2$: C, 81.50; H, 10.75. Found: C, 81.31; H, 10.03.

The mother liquors from this crystallization (14.3 mg, 0.035 mmole) were re-equilibrated as above with 7 ml of 5 *N* aqueous hydrochloric acid in 21 ml of refluxing methanol for 2.7 hr. After an identical work-up, 14.1 mg of a yellow oil was recovered, which was crystallized from chloroform--ether to afford 5.2 mg of the β,γ-unsaturated ketone X-3 as a white solid, the infrared spectrum of which was the same as that given above. The total yield was 20.6 mg (67%) of β,γ-enone X-3.

3β-Hydroxy-4,4,6aβ,6bα,8aβ,11,11,14bβ-octamethyl-1,2,3,-4,4aα,5,6,6a,6b,7,8,8a,9,12bβ,13,14,14aα,14b-octadecahydro-10(11H)-picenone (X-4) was prepared by a modification of a procedure used by Ireland and Mander.[80] A mixture of 0.82 g (21 mmoles) of potassium and 25 ml of t-butanol (distilled from calcium hydride) was heated at reflux until the metal had completely reacted (2 hr), affording a 0.84 M solution of potassium t-butoxide. To 0.24 ml of this solution (0.20 mmole of potassium t-butoxide) was added over a period of 6 min a solution of 16.7 mg (0.04 mmole) of the β,γ-unsaturated ketone X-3 (prepared as described above) in 0.5 ml of benzene and 1.3 ml of t-butanol. The resulting clear yellow solution was stirred at room temperature for 10 min before 25 μl (0.40 mmole) of methyl iodide (purified by two distillations from phosphorous pentoxide) was added. A precipitate formed within 2 min. The reaction mixture was allowed to stir at room temperature for 10.5 hr, poured into 100 ml of dilute brine, and extracted with four 25-ml portions of benzene. The combined extracts were washed with 25-ml portions of water and brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure left 17.7 mg of crude dimethylated enone X-4 as a yellow oil, the nmr spectrum of which exhibited methyl signals at 0.79, 0.85, 0.91, 1.01, 1.03, 1.10 (strong), 1.22, and 1.28 δ (weak). The nmr spectrum remained the same after this product was resubjected to potassium t-butoxide and methyl iodide according to the above procedure.

The crude product was purified by chromatography on 5 g of silica gel. Elution with 11 ml of 50% ether in benzene gave no identifiable material; continued elution (4 ml) produced

7.5 mg (42% yield, 28% overall yield from the α,β-unsaturated ketone X-2) of the dimethylated ketone X-4 as a white solid: mp 211-223°, needles;

ir ($CHCl_3$) 3615 (O-H), 1705 (C=O), and 1360, 1380, and 1390 cm^{-1} (gem-dimethyl);

nmr ($CDCl_3$) δ 0.79, 0.85, 0.91, 1.01, 1.03, and 1.22 (s, 3 each, CH_3), 1.10 (s, 6, CH_3), 3.2 (m, 1, C$\underline{H}$OH), 4.99 (m,1, C=CH);

The analytical sample was recrystallized from benzene--ether: mp 229-232°;

Anal. Calcd for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98. Found: C, 81.57; H, 10.83.

dl-Germanicol (L-7). Because of the small scale in this reaction, the previously described Wolff-Kishner procedure was modified. To a solution of 5.9 mg (0.013 mmole) of the octamethyl ketone X-4 (prepared in the preceding reaction) in 3.8 ml of triethylene glycol (redistilled) was added 0.38 ml (6.6 mmoles) of 85% aqueous hydrazine hydrate and 97 mg (0.92 mmole) of hydrazine dihydrochloride. This mixture was stirred at 135-140° (bath temperature) for 3.5 hr, and cooled to 110° while 0.62 g (9.4 mmoles, 85% pure) of potassium hydroxide pellets were added. The bath temperature was increased to 180-185° over a period of 20 min, while a rapid stream of argon was used to remove volatile material from the reaction mixture. After 30 min, the argon flow was reduced. The bath temperature was maintained at 180-185° for 6 hr. The reaction mixture was then cooled, poured into 150 ml of dilute brine, and extracted with four 25-ml portions of benzene. The combined extracts were washed with ten 10-ml portions of water and 10 ml of brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 6.0 mg (quantitative crude yield) of a white solid, mp 214-218°, the nmr spectrum of which was identical to that of the natural d-germanicol. The vapor phase chromatogram (300°, 4% SE-30) showed one major peak with a retention time of 1.7 min (82%). Recrystallization of a 4.9-mg portion of this material from chloroform--methanol afforded 2.8 mg (57% yield) of pure germanicol: needles, mp 224-229°; vpc (300°, 4% SE-30): one peak at 1.7min (98%). Material prepared in an earlier experiment, mp 219-223°, had ir and nmr spectra identical to those of a sample of natural d-germanicol, mp 175-177°, prepared below.

ir ($CHCl_3$) 3600 (O-H), 1355, 1375, and 1390 cm^{-1} (gem-dimethyl);

nmr (60 and 220 MHz, $CDCl_3$) δ 0.76, 0.78, 0.91, 1.00, 1.04, and 1.10 (s, 3 each, CH_3), 0.96 (s, 6, CH_3), 3.2 (m, 1, C$\underline{H}$OH), 4.88 (m, 1, vinylic H).

The spectra are illustrated in Figures 27 and 28.

The vapor phase chromatograms (270°, 4% SE-30) of synthetic and natural germanicol showed one major peak at a retention time of 4.9 min (96% and 99%, respectively). Co-injection produced a chromatogram with one major peak at this retention time.

Analytical thin layer chromatography (Merck silica gel, 3.3% methanol in reagent grade chloroform) of each sample gave one major spot (R_f = 0.65).

A sample of synthetic germanicol, which was prepared for analysis by recrystallization from chloroform--methanol, melted at 220-223°, white needles.

Anal. Calcd for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.35; H, 11.71.

d-Germanicol. A solution of 7.8 mg (0.02 mmoles) of natural germanicyl acetate (mp 267-269°, provided by Professor C. Djerassi of Stanford University) in 5 ml of dry tetrahydrofuran was treated with 26.1 mg (0.69 mmole) of lithium aluminum hydride (Ventron). The mixture was heated at reflux for 30 min, cooled in an ice bath during the addition of excess ethyl acetate, poured into 100 ml of dilute brine, and extracted with 25 ml of benzene. The aqueous phase was acidified with 10% aqueous hydrochloric acid and then extracted with three 25-ml portions of benzene. The combined extracts were washed with 25-ml portions of 2% aqueous hydrochloric acid, water, and brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 7.7 mg (a quantitative yield) of pure d-germanicol as white needles: mp 175-177°, literature[53] mp 180-181°;

ir ($CHCl_3$) 3600 (O-H), and 1355, 1375, and 1390 cm^{-1} (gem-dimethyl);

nmr (60 and 220 MHz, $CDCl_3$) δ 0.76, 0.78, 0.91, 1.00, 1.04, and 1.10 (s, 3 each, CH_3), 0.96 (s, 6, CH_3), 3.2 (m, 1, CHOH), 4.88 (m, 1, vinylic H).

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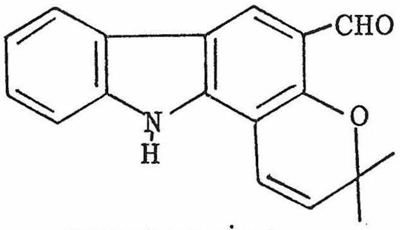
PROPOSITIONS

PROPOSITION I

A synthesis of the alkaloid murrayacine is proposed.

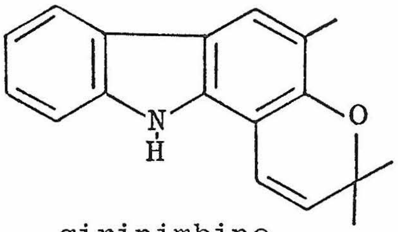
Murrayacine, a newly discovered alkaloid,[1] is found in the plant <u>Murraya</u> <u>koenigii</u> Spreng. The carbazole skeleton of this alkaloid is the same as that of several other alkaloids from the same source. Three of these related alkaloids, murrayanine, girinimbine, and mahanimbine, are active against some human pathogenic fungi.[2] Murrayacine may also exhibit this property.

In addition to isolating murrayacine, Chakraborty[1] has succeeded in determining its structure (1). The structure of girinimbine[1,3] (2) is so similar that a synthesis of murrayacine would serve as a synthesis for both, because



murrayacine

1



girinimbine

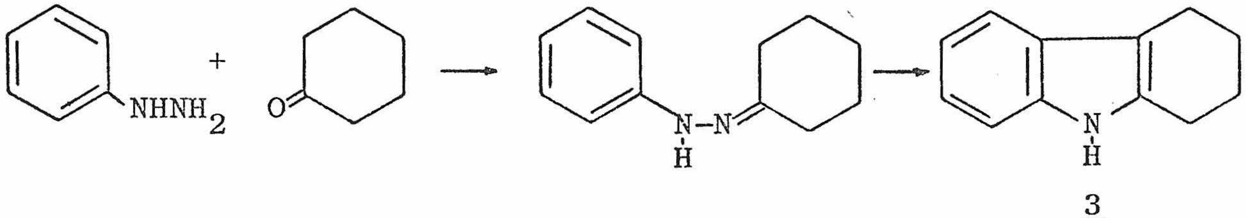
2

girinimbine can probably be prepared from murrayacine by reduction of the aldehyde group. Lithium aluminum hydride reduction of dihydromurrayacine (alkaloid 1 with a reduced pyran ring) produces dihydrogirinimbine.[1]

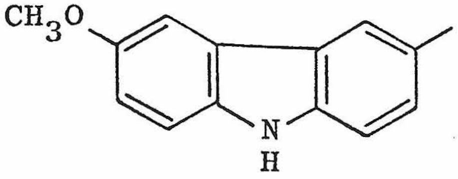
Pyranocarbazole ring systems are virtually unknown, and so no standard syntheses of this ring system are available. An attempt to attach the pyran ring to a finished carbazole or tetrahydrocarbazole would probably result in the formation of undesired isomers or mixtures. The two synthetic schemes proposed avoid this problem. The first, Route A, employs the Borsche--Fischer tetrahydrocarbazole synthesis with a possible Japp--Klingemann modification. The second, Route B, uses an oxidative photochemical coupling reaction, which has been successfully used on diphenylamines, to prepare the required carbazole.

Route A

The Borsche--Fischer tetrahydrocarbazole synthesis was originally a condensation of phenylhydrazine with cyclohexanone to give 1,2,3,4-tetrahydrocarbazole (3).[4] This method has also been used in the synthesis of glycozoline (4),[5] which was prepared by a condensation of p-methoxyphenylhydrazine hydrochloride with 4-methylcyclohexanone followed by a chloranil oxidation. The synthesis of murrayacine by this procedure



3



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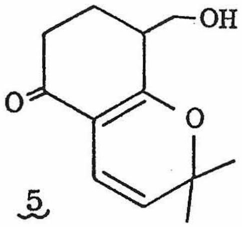
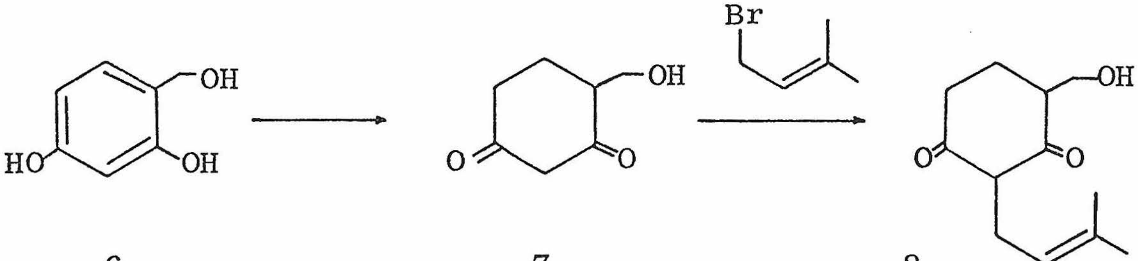


5

would require phenylhydrazine and the dimethylpyranocyclohexanone 5.

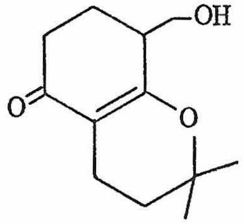
The starting material selected for the synthesis of the dimethylpyranocyclohexanone 5 is 2,4-dihydroxybenzyl alcohol (6), which has been prepared by the reaction of resorcinol with formaldehyde.[6] Reduction of this triol under the same conditions used for the reduction of resorcinol to dihydroresorcinol (hydrogenation in alkaline solution over a 5% rhodium on alumina catalyst)[7] should afford 4-hydroxymethyl-1,3-cyclohexadione (7).



6 7 8

Although the next step, C-alkylation of a 1,3-cyclohexadione, is usually a low-yield reaction, Lukeš and Hofman[8] have obtained 2-allyldimedon in a crude yield of 53% by alkylating dimedon with allyl bromide in the presence of aqueous potassium hydroxide and copper powder, thereby establishing that such a 1,3-dione system could be alkylated. Application of this procedure to the cyclohexadione 7 and 1-bromo-3-methyl-2-butene should result in the alkylated product 8.

The cyclization of the dione 8 to the enone 9 could be readily accomplished by acid treatment.[9,10] This cyclization could give two products (enones 9 and 10). Through hydrogen-bonding, the hydroxymethyl group of the dione may have an influence on the ratio of the products. If this directive effect does not favor the formation of the enone 9, acetylation of the hydroxymethyl group or its transformation to an aldehyde may reverse this situation. After the cyclization step, the acetate group could be removed or the aldehyde reduced with sodium borohydride to the alcohol.



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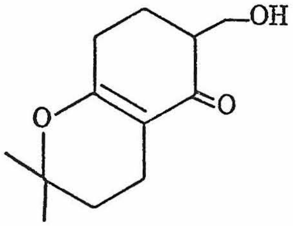

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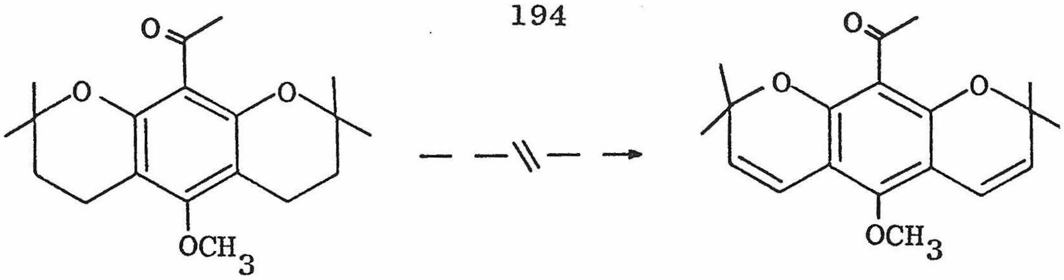
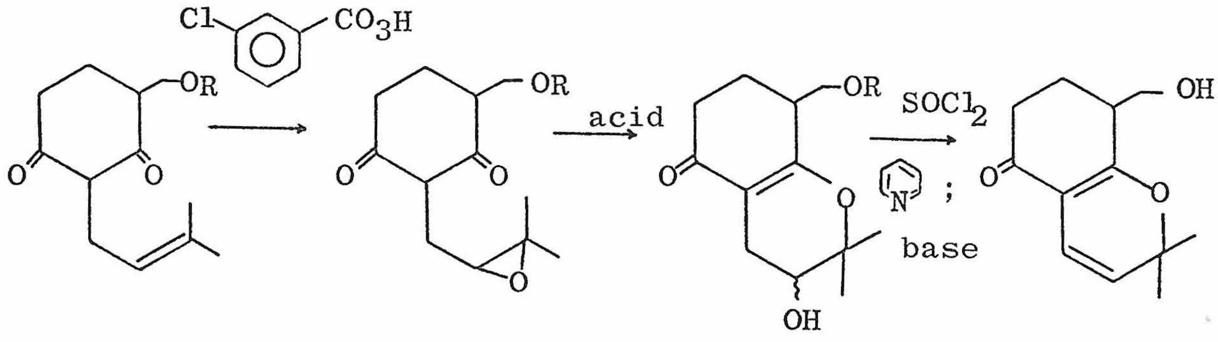
Since enone 9 is a dihydropyran, it may not be easily oxidized to the corresponding pyran. Brown, Burton, and Stevens[10] found that tetrafranklinone (11) could not be oxidized to franklinone by bromination--dehydrobromination.



11

franklinone

This problem may be circumvented by protection of the hydroxymethyl group of the olefin 8, for example as an acetate, followed by epoxidation of the double bond and an acid-catalyzed cyclization. The acetylated hydroxymethyl group may exert a favorable directive influence on the cyclization. Dehydration of the cyclization product, the alcohol 12, would give the desired pyranocyclohexanone 5 after cleavage of the protecting group. If the dione 8 is too reactive and cyclizes



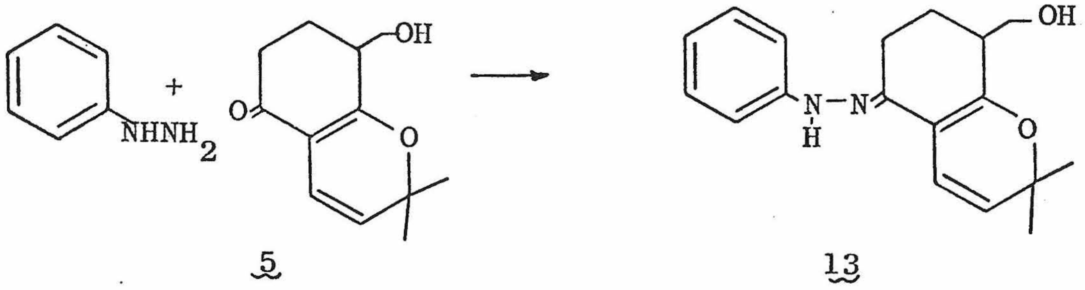
8

12

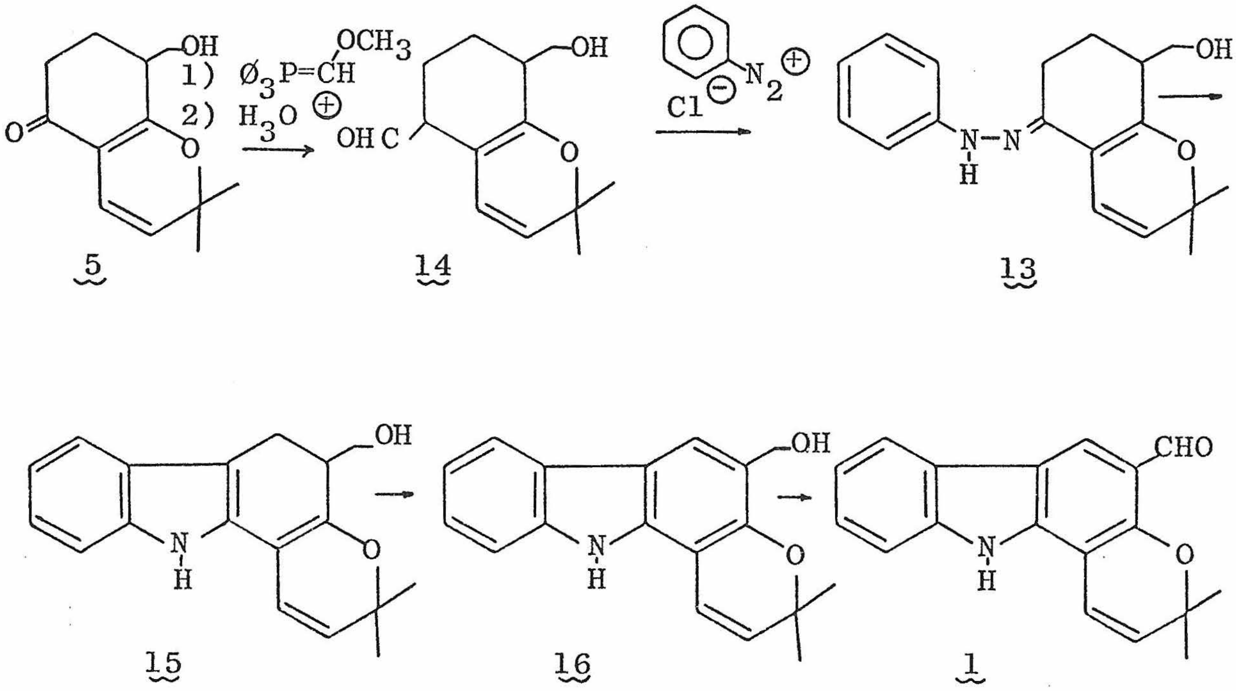
5

to the dihydropyranocyclohexanone 9 prior to the epoxidation step, the dihydropyranocyclohexanone could be carried through the synthetic sequence presented in the next paragraph to give dihydromurrayacine, which on oxidation with chloranil[5,11-13] or selenium dioxide[13] should yield murrayacine.

Heat treatment of a mixture of dimethylpyranocyclohex-



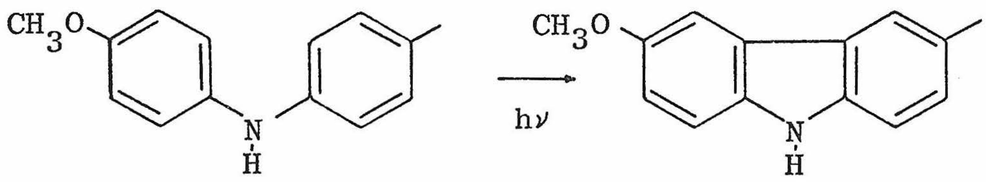
anone 5 with phenylhydrazine (possibly as the hydrochloride)[14] should give the hydrazone 13. Since formation of hydrazones by this procedure can occasionally be a low yield process, the Japp--Klingemann[11,12,15] reaction could also be used to prepare this hydrazone. Before this reaction could be employed, the homologous aldehyde 14 of pyranocyclohexanone 5 must be prepared. Treatment of pyranocyclohexanone 5 with methoxymethylene Wittig reagent (excess), followed by acid cleavage



should yield the corresponding aldehyde **14**; reaction of this aldehyde with phenyldiazonium chloride would give the hydrazone **13**. Heat treatment (100-200°) with an acid catalyst (zinc chloride, aqueous hydrochloric acid, sulfuric acid)[4,11,12] should rearrange this hydrazone to the pyranodihydrocarbazole **15**. Treatment of compound **15** with chloranil, selenium dioxide, or palladium-on-carbon[11] would result in aromatization to the pyranocarbazole **16**. Oxidation of the alcohol function to an aldehyde by Collins reagent,[16] or manganese dioxide in carbon tetrachloride[11] should give the alkaloid, murrayacine.

Route B

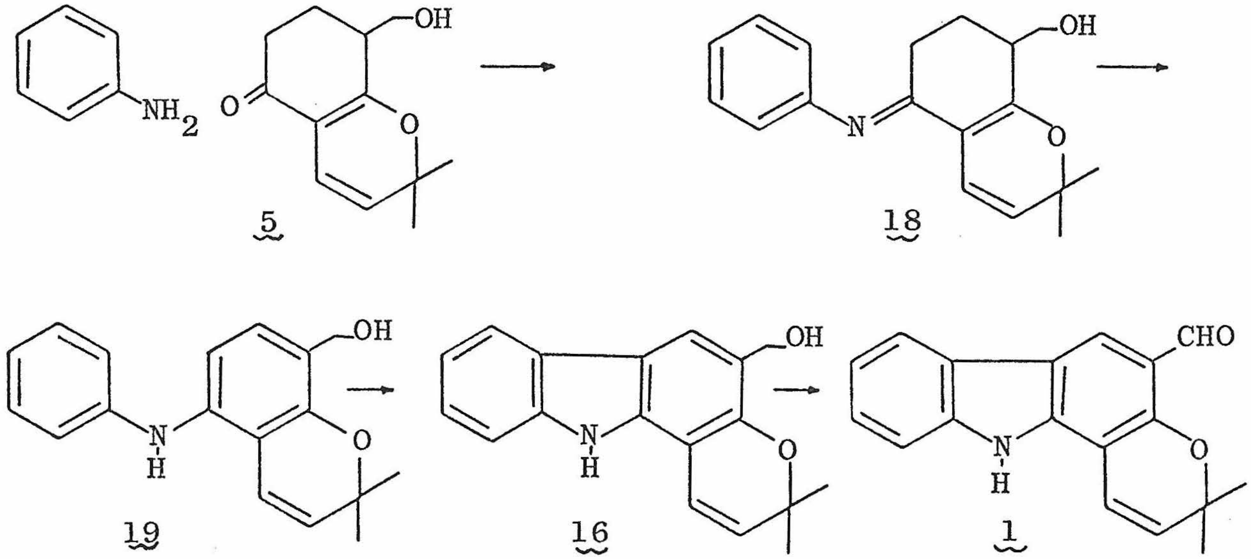
In 1966, Carruthers[17] synthesized glycozoline (**17**) by a convenient high-yield photochemical process. This reaction is synthetically useful as long as the ring substituents



17

either direct the coupling by blocking one of the *ortho* positions or are placed symmetrically on the benzene rings so that isomer formation is precluded. This reaction appears ideal for the preparation of murrayacine, since the left-hand ring of this alkaloid (1) has no substituents and the right-hand ring has one of the *ortho* positions blocked.

The reaction of aniline with the pyranocyclohexanone 5 should produce the Shiff base 18, the cyclohexanimine ring of which on aromatization with selenium dioxide or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[13] should lead to the aryl amine 19. Photochemical coupling of the two aromatic rings of amine 19 by Carruther's procedure (irradiation by a mercury vapor lamp), followed by a Collins or manganese dioxide oxidation of the product, should again yield murrayacine (1).



The availability of the starting materials in these two syntheses and the advantages inherent in convergent syntheses should allow the two aforementioned routes to murrayacine to be competitive with that of the naturally isolated material.

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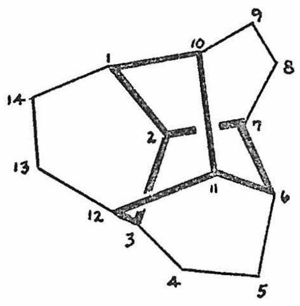
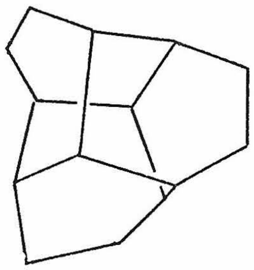
PROPOSITION II

A synthesis of the pentacyclo$[8.4.0.0^{2,7}.0^{3,12}.0^{6,11}]$tetradecane ring system is proposed.

The pentacyclo$[8.4.0.0^{2,7}.0^{3,12}.0^{6,11}]$tetradecane ring system is apparently yet unknown. This is understandable both because of the complexity of this ring system and because numerous bi-, tri-, and tetracyclo ring systems, some of greater general interest, have not yet been synthesized or thoroughly studied.



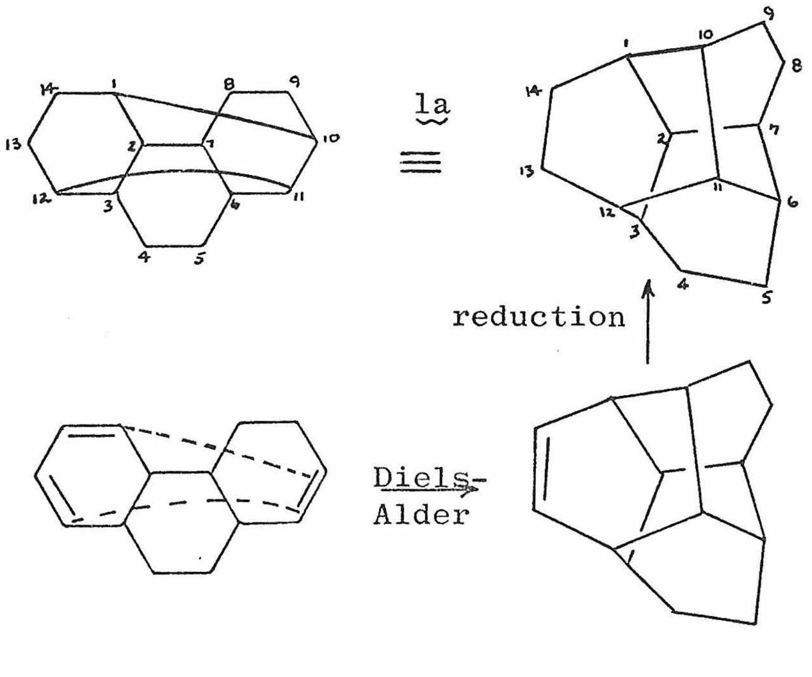
1a



1b

Hydrocarbon 1, the parent compound in this ring system, has several interesting features. Unlike most bridged systems, there is little or no strain in the molecule, which is constructed of nine six-membered rings in a twisted boat conformation. Models demonstrate that even the triene derivative of hydrocarbon 1, the 4,8,13-triene 24, is not very strained. As the figure above illustrates, hydrocarbon 1 is based on a twisted bicyclo[2.2.2]octane ring system (atoms 2, 3, 12, 11, 6, 7, 1, and 10) on which three ethano groups are placed diagonally. The resulting molecule has a pleasing degree of symmetry (a C_3 axis is present, passing through atoms 2 and 11) but is also optically active. Compound **1a** is the right-handed isomer and compound **1b** is the left-handed one. The hydrocarbon twistane (tricyclo[4.4.0.0^{3,8}]decane) is related to structure **1** for it can be considered a bicyclo[2.2.2]octane system with only one ethano bridge added.

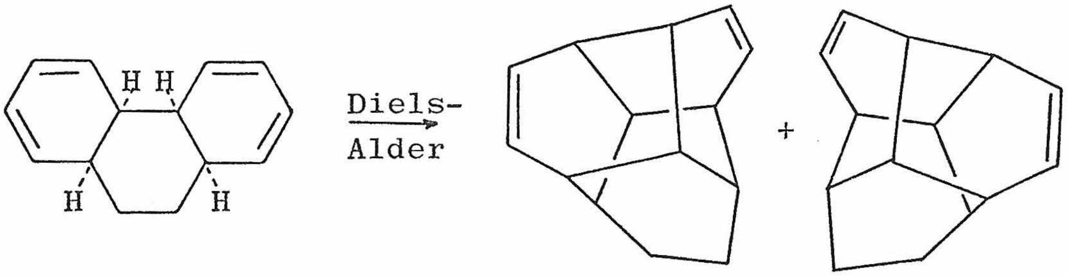
Compound **1a** could also be considered a bridged perhydrophenanthrene, which could be prepared by an intramolecular Diels--Alder reaction, followed by reduction, as illustrated below. Intramolecular Diels--Alder reactions are known to be



2 **3**

facile, high yield reactions in both acyclic[1] and cyclopentadienyl[2] systems. Therefore, this intramolecular reaction, although unusual, appears to have a good chance of success. The *cis*-syn-*cis* nature of the ring fusions allows but does not force the molecule to assume a cup-shaped conformation, bringing the diene and dienophile into close contact. Since intramolecular reactions are much faster than intermolecular reactions, this transformation should be accomplished in good yield even without the presence of activating substituents.

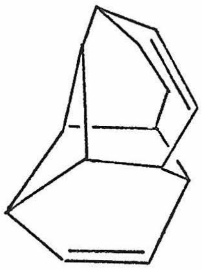
The synthesis of the unsymmetrical triene **2** would pose many problems; therefore it would be more practical to prepare the symmetrical tetraene **4**, which should just as readily undergo an intramolecular Diels--Alder reaction to give two dienes **5a** and **5b**, which, in turn, could be reduced to hydrocarbon **1**. The Diels--Alder reaction of tetraene **4** could occur in two



4 **5a** **5b**

different ways: condensation of the 5,7-diene with the 1-ene would give diene **5a** (the right-handed isomer) and condensation of the 1,3-diene system with the 7-ene would yield diene **5b** (the left-handed isomer). The other two possibilities for condensation (reaction between the 1,3-diene and the 5-ene and between the 5,7-diene and the 3-ene) are not favorable since the products would contain a four-membered ring (diene 6 and its enantiomer).

The tetraene 4 could not be prepared by a direct hydrogenation of phenanthrene. 9-Phenanthrol (7)[3] has been hydrogenated to the corresponding *cis*-syn-*cis* perhydrophenanthrol in only 8% yield. Partial hydrogenation of phenanthrenes usually saturates the rings one by one with the Δ^1, Δ^3, Δ^5, and Δ^7 double bonds being reduced first.



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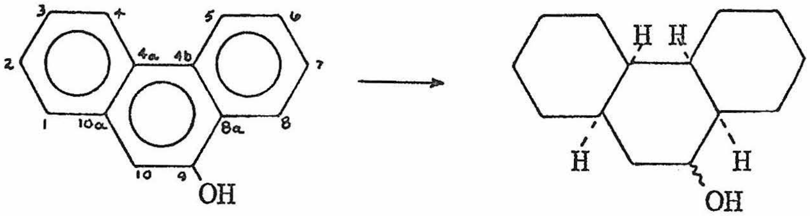

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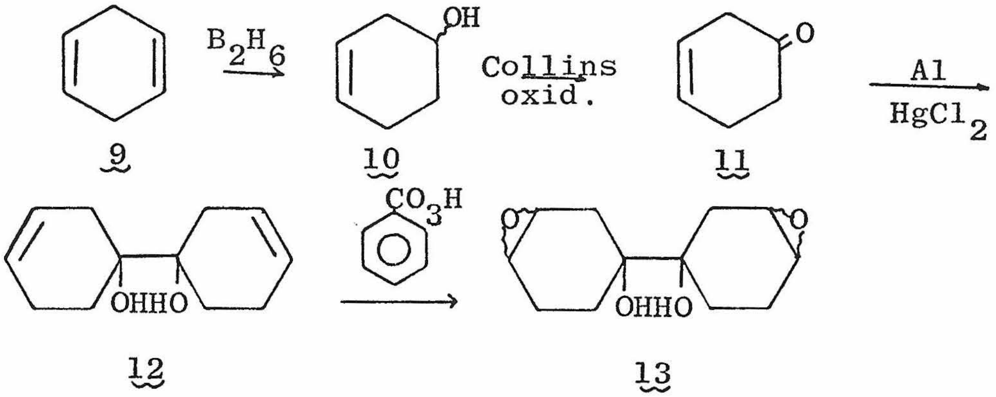
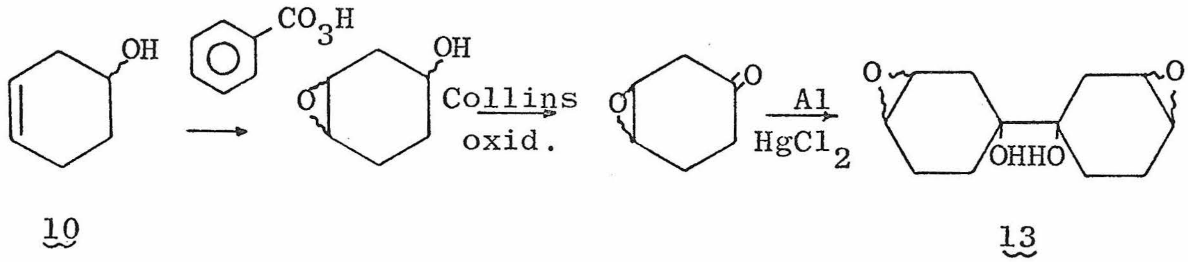
The starting material selected for the synthesis of the tetraene 4 is *dl*-cyclohexen-4-ol (10), which has previously been prepared by hydroboration--oxidation of the commercially available 1,4-cyclohexadiene (9).[4] Collins oxidation[5] of alcohol 10 should afford the β,γ-unsaturated ketone 11.

The reductive coupling of cyclohexanones to form pinacols is a well known reaction.[6,7,8] Application of the pinacol formation procedure of Elagina and Kazanskii[8] to the ketone 11 should produce the dienic pinacol 12. Epoxidation of the pinacol



with peroxybenzoic acid[9] should provide the diepoxy-pinacol 13.

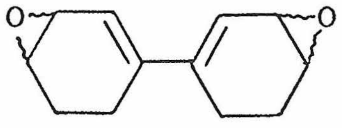
If a rearrangement of the double bond should occur during the pinacol formation, the procedure given below could be used.



Epoxidation of the cyclohexenol 10 with peroxybenzoic acid has been reported to give 1,2-epoxycyclohexan-4-ol.[9] Collins oxidation of this epoxy-alcohol, followed by pinacol formation, should again afford the diepoxy-pinacol 13.

The next step is the dehydration of pinacol 13 to the diene 16. Acid catalyzed dehydration of pinacols occurs in competition with pinacol rearrangements,[10,11] but (bicyclohexyl)-1,1'-diol has been successfully dehydrated to bicyclohexylidene with phosphorous oxychloride in pyridine (95% yield, no rearrangement)[12] and with dimethyl sulfoxide (85% yield, 4% rearrangement).[13] Therefore dehydration should occur on treatment of the diepoxy-pinacol 13 with these reagents to give a statistical mixture of dienes 14, 15, and 16.

Now the diene 16 must be converted to the olefin 17. Bicyclohexylidene has often been used as a diene in Diels--Alder reactions. Among the dienophiles which have been used with this diene are ethylene,[14] nitroethylene,[15] trans-dichloroethylene,[16] acrolein,[11] benzoquinone,[6,7] α-naphthaquinone,[6] and maleic anhydride.[11,13,17] The yields of products range from 30% to 90%. Barring an unlikely thermal decomposition of the



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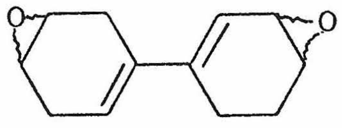

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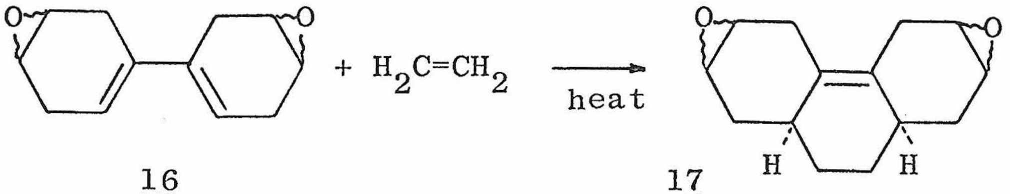

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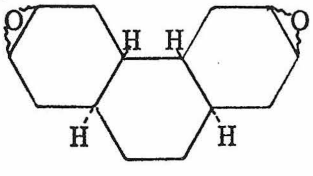
epoxy groups, the diepoxy-diene 16 should undergo a Diels--Alder condensation with any of these dienophiles just as easily as bicyclohexylidene does. Condensation with ethylene should give a precursor for the basic ring system 1. Derivatives could be prepared by condensation of diene 16 with the other dienophiles.

The Diels--Alder product, diepoxydodecahydrophenanthrene 17, could be converted to the tetraene 4 by two routes. In the first route the dodecahydrophenanthrene must be hydrogenated to the perhydrophenanthrene 18. There exist two possible hydrogenation products 18 and 19, however an inspection of a model of the starting material 17 indicates that the desired diepoxide 18 would be the favored product. The two α protons at the C-8a and C-10a positions tend to either force the C-9, C-10 ethano bridge up (β) in some conformations or to force the two end rings up into a cup shape in other conformations. Because of this effect and irrespective of the stereochemistry of the epoxides, there is somewhat more steric hindrance on the β side of the molecule than on the α side. Therefore, hydrogenation should take place on the α side to give predominately the *cis*-syn-*cis* isomer 18. Strong conditions may be necessary to effect this reduction for the hydrogenation of the Diels--Alder adduct of bicyclohexylidene and nitroethylene with a 10% palladium-on-charcoal catalyst in 95% ethanol (Parr shaker) failed.[15] In contrast, the Diels--Alder adduct of bicyclohexylidene and ethylene was epoxidized in 97% yield with peroxybenzoic acid;[11] this success implies that there is no extreme steric hindrance about the double bond.

The two epoxy groups in compound 18 could be transformed to the four double bonds of tetraene 4 by a three step sequence.



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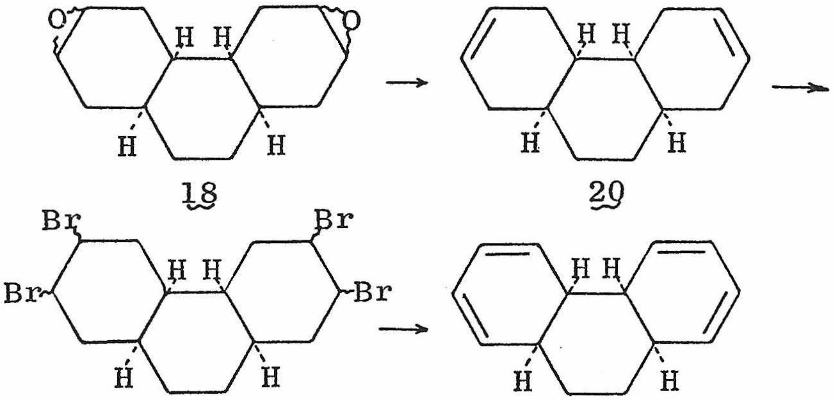
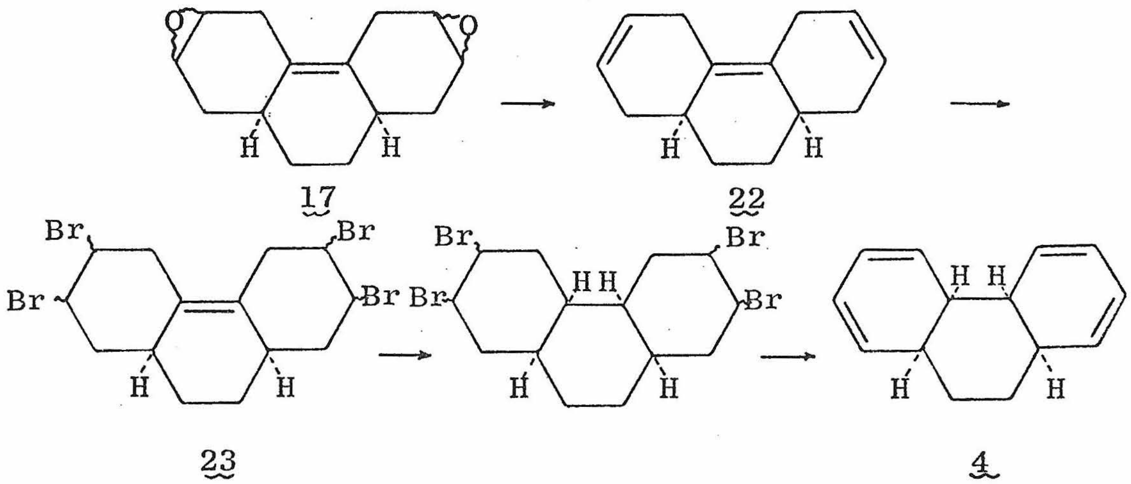


18 20

21 4

On treatment with a mixture of zinc powder, sodium iodide, acetic acid, and sodium acetate the diepoxide 18 would undergo the Cornforth reaction[18] to give the diene 20. Bromination of the diene should yield the epimeric tetrabromide mixture 21. The bromines at the C-2 and C-3 positions would be *trans* to each other, and the bromines at the C-6 and C-7 positions would also be *trans*, therefore dehydrohalogenation would be facilitated and should lead to the desired tetraene 4 rather than vinyl bromides.[19] Another factor influencing this dehydrohalogenation is the *cis* ring fusions. Elimination in a six-membered ring with a *cis* fusion usually produces a Δ^1 or a Δ^3 olefin, while elimination in a *trans*-fused six-membered ring yields a Δ^2 olefin.[20,21,22] Thus, it could be predicted that dehydrobromination would indeed give the tetraene 4. Heating the tetrabromide mixture in collidine or treating it with ethanolic potassium hydroxide should effect this transformation.

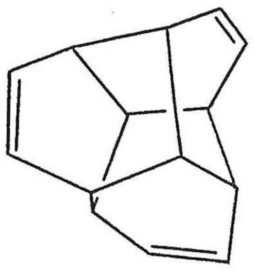
The cupped shape of the cis-syn-cis perhydrophenanthrene ring system may prevent the above scheme from working. Should this difficulty occur, then the second pathway would be followed. The reduction of the Diels--Alder adduct is postponed, and, therefore, most of the reactions are to be performed on a less sterically hindered system, which is flattened by the Δ^{4a} double bond. The diepoxyolefin 17 could be transformed by the Cornforth reaction[18] into the triene 22. Careful bromination of triene 22 with two equivalents of bromine should give the tetrabromide mixture 23, which, upon hydrogenation in a neutral medium with a palladium catalyst,[23] should afford the saturated tetrabromide mixture. As before, dehydrobromination should give the tetraene 4.



17 22 23 4

Next the tetraene 4 must be converted to the racemic dienes 5a and 5b. Heating in a sealed tube should effect this Diels--Alder condensation. Hydrogenation of the dienes should yield the synthetic objective, hydrocarbon 1.

If other derivatives of the hydrocarbon 1 are desired, they could be synthesized from the double bonds of diene 5 or, as mentioned above, by the use of different dienophiles in the Diels--Alder condensation with the diepoxydiene 16, for example, nitroethylene would eventually give the amino derivative of hydrocarbon 1, which could be converted to the triene 24 by standard procedures.



24

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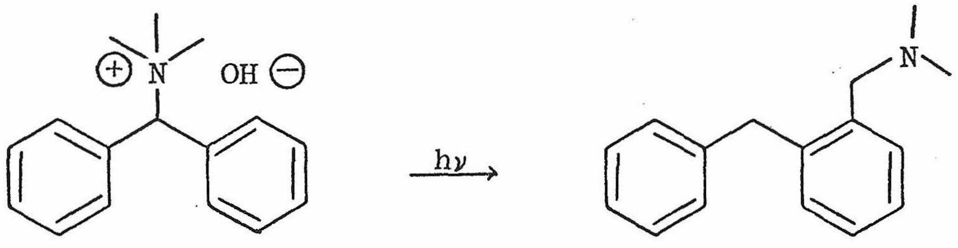
PROPOSITION III

A study of the products from Sommelet--Hauser rearrangement of benzyl-*cyclic*ammonium quarternary halides is proposed.

In 1937, Sommelet[1] discovered a novel rearrangement by allowing sunlight to fall on a dried sample of benzhydriltrimethylammonium hydroxide (**1**). The unexpected product was



1 **2**

o-benzylbenzyldimethylamine (**2**). This rearrangement was also achieved by Wittig, Mangold, and Felletschin[2] in 1948, using phenyllithium in ether. Later, Kantor and Hauser[3], were able to effect numerous similar transformations using sodamide in liquid ammonia. For example, dibenzyldimethylammonium chloride (**3**) rearranged under these conditions to form *o*-dimethylaminobenzyltoluene (**6**) in 95% yield. This rearrangement (first called simply the *ortho* rearrangement and later the Sommelet--Hauser rearrangement) is generally thought to have the mechanism given in Figure 1.[4,5] Since the quaternary ammonium compound **3** has no β-hydrogens, a Hofmann elimination reaction is impossible. The most acidic protons are those in the benzyl posi-

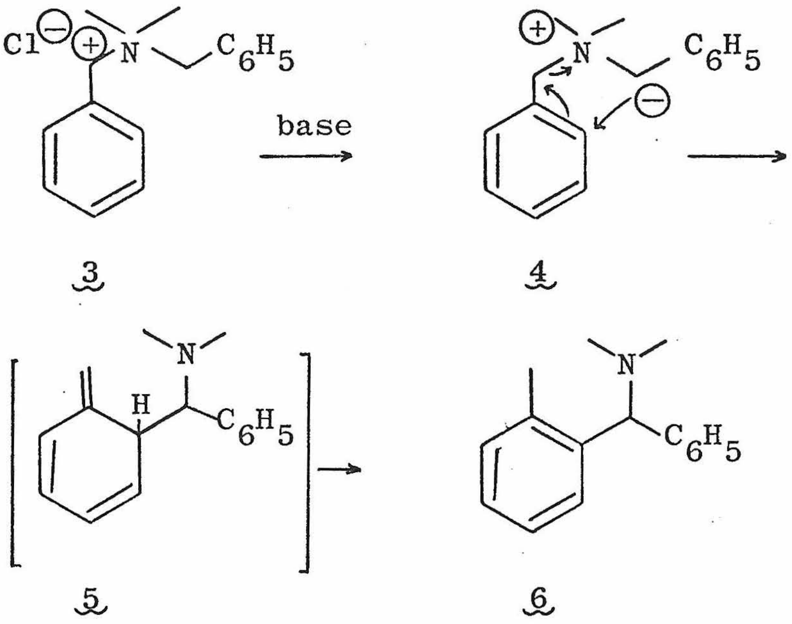


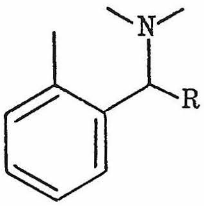
Figure 1: Mechanism of Sommelet--Hauser Rearrangement

tion; abstraction of one of these protons by the base results in a benzyl carbanion (**4**), which attacks the <u>ortho</u> position of the other benzene ring to give, after tautaumerization, the amine **6**.

Although Hauser has mentioned that this <u>ortho</u> rearrangement had great synthetic potential,[6] this potential has not been fully realized. Hauser and coworkers, however, have used this rearrangement to synthesize hexamethylbenzene[3] and several benzene derivatives with ethyl, isopropyl, methoxy, chloro, hydroxy, and amide substituents on the ring.[6,7,8]

Attempts[3] were made to rearrange benzyltri-<u>n</u>-propylammonium and benzyltri-<u>n</u>-butylammonium salts to the corresponding amines but both compounds underwent Hofmann elimination to give only unrearranged tertiary amine and olefin.

In 1963, Bumgardner[9] succeeded in synthesizing three amines 7 (R = cyclopropyl, benzyl, and vinyl) from the corresponding quaternary ammonium compounds. All three rearrangements involved a carbanion other than methyl or benzyl and apparently represent the only successful rearrangements with a different carbanion.



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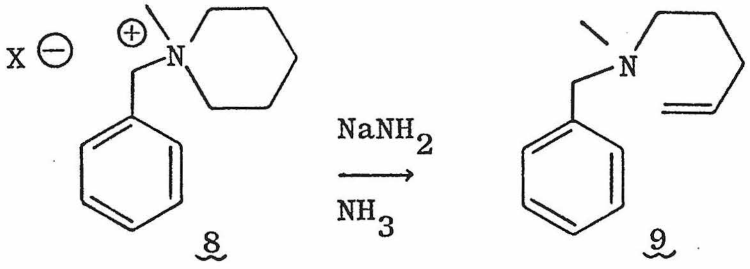
So far, none of the workers in this field have attempted a rearrangement of any cyclic quaternary ammonium compound. It is felt that such an attempt may shed light not only on the electronic effects of the N-substituents but also on the steric effects of rigidly held and large substituents. To this end, it is proposed that the Sommelet-Hauser rearrangement be tried on a variety of cyclic quaternary ammonium salts, both aliphatic and aromatic.

A. Aliphatic

The immediate difficulty that would be encountered in the attempted rearrangement of most aliphatic amines (cyclic or not) is β-elimination. Benzylmethylpiperidinium halide would eliminate to form the unsaturated amine 9 and no rearrangement



would occur. Similarly, a quaternary salt based on pyrollidine should give no ortho rearrangement product.

An obvious choice for a study of this rearrangement is isoindoline for this compound has no β-hydrogens and, of the α-hydrogens, those on the benzylic carbon are more acidic than those on the methyl group. On treatment with sodamide in liquid ammonia, benzylmethylisoindolium halide should undergo the rearrangement shown in Figure 2. The product 11 would give the quaternary salt 12 on reaction with methyl iodide. This salt could rearrange by two different pathways, only one of

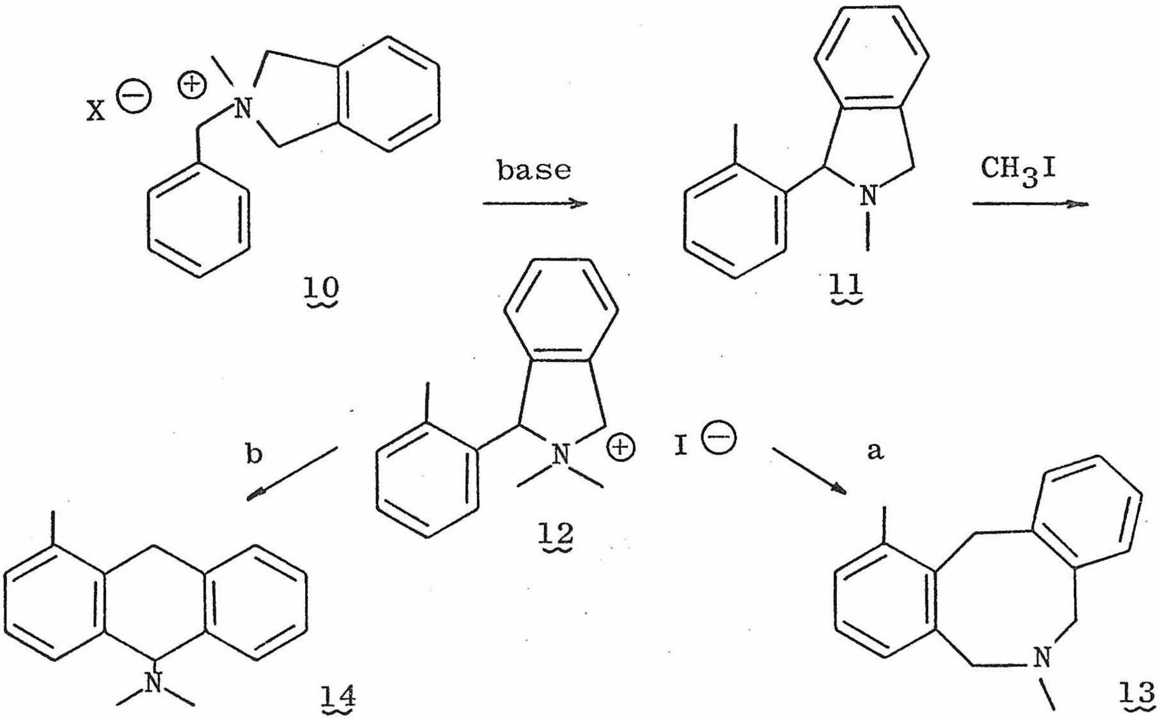


Figure 2: Rearrangement on an Isoindoline System

which (path a) is favored. In the favored path, a compound with a 5,6,7,12-tetrahydrobenz[c,f]azocine ring system (**13**) would be formed. Although the benzylic protons are more acidic than the methyl protons, steric effects should hinder attack by the benzylic carbanion in path b. However, if such an attack occurs, a 9,10-dihydroanthracene (**14**) would be formed. Further rearrangement of amine **13** after methylation appears to be geometrically impossible, however amine **14** after methylation should undergo further rearrangement, in which a series of methyl groups are placed on one of the aromatic rings.

Another cyclic amine worthy of investigation is 2-azabicyclo[2.2.2]octane (**15**). Although β-hydrogens are present in its benzyl methyl derivative (**16**), their loss by a Hofmann elimination would be forbidden by Bredt's rule.[10] A carbanion could be formed by loss of either a C-1 or C-3 proton and would attack the benzene ring to give amine **17** or **18**, respectively. Amine **17** should predominate since the C-1 proton is more acidic (Figure 3). Amines **17** and **18** could be methylated and then treated with base to give two new ring systems **19** and **20**. It should be mentioned that the N-methyl protons of the derivative **16** would be as acidic as the C-3 protons and their loss would also lead to rearranged material. The product, the *ortho* methyl derivative of the starting material, is uninteresting and, therefore, not included in Figure 3.

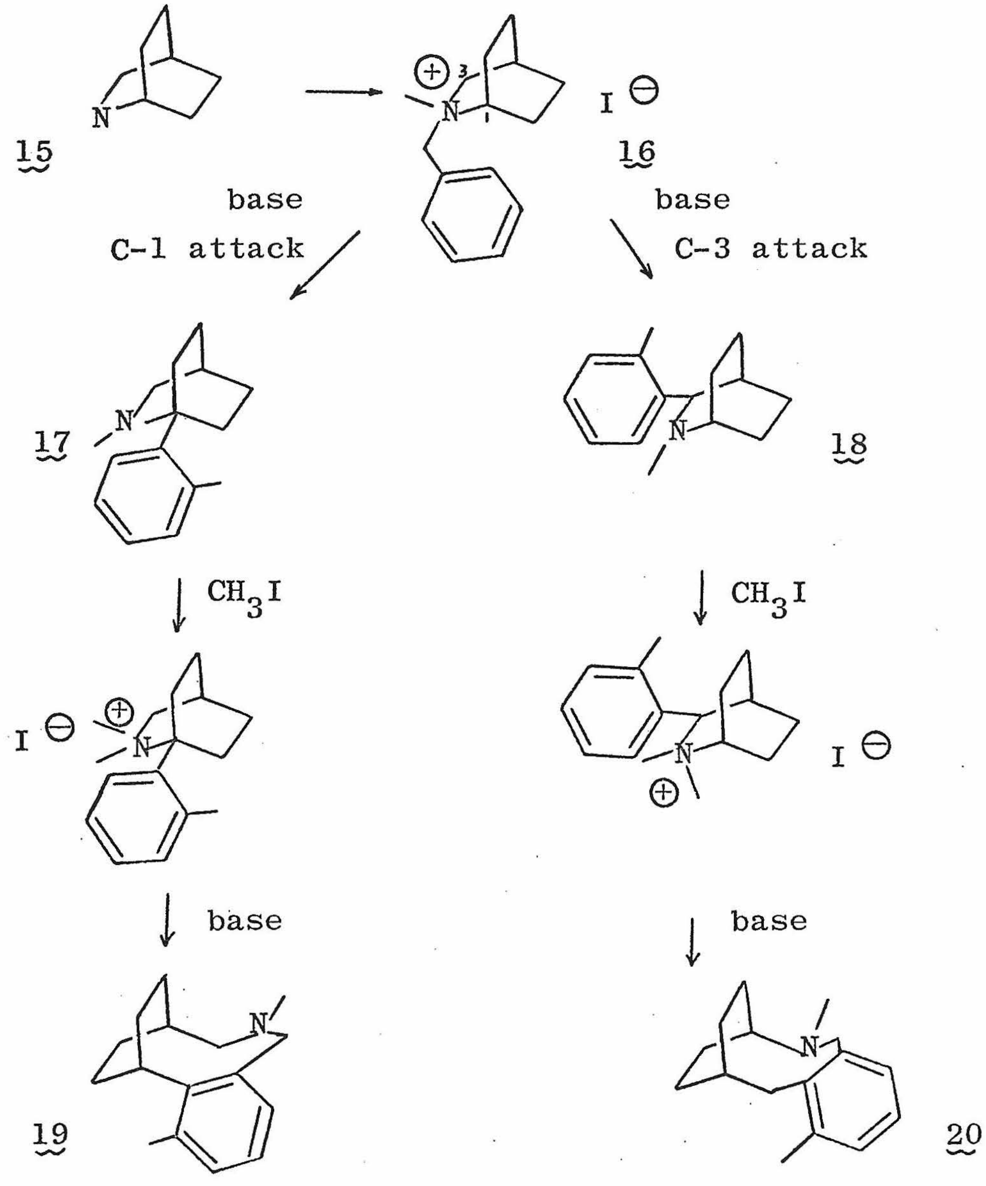


Figure 3: Rearrangement of an Azabicyclo[2.2.2]octane

A third aliphatic amine, quinuclidine (1-azabicyclo-[2.2.2]octane) (21), would also be a likely choice for this rearrangement. This amine does possess β-hydrogens, and Hofmann elimination is not forbidden by Bredt's rule. However,

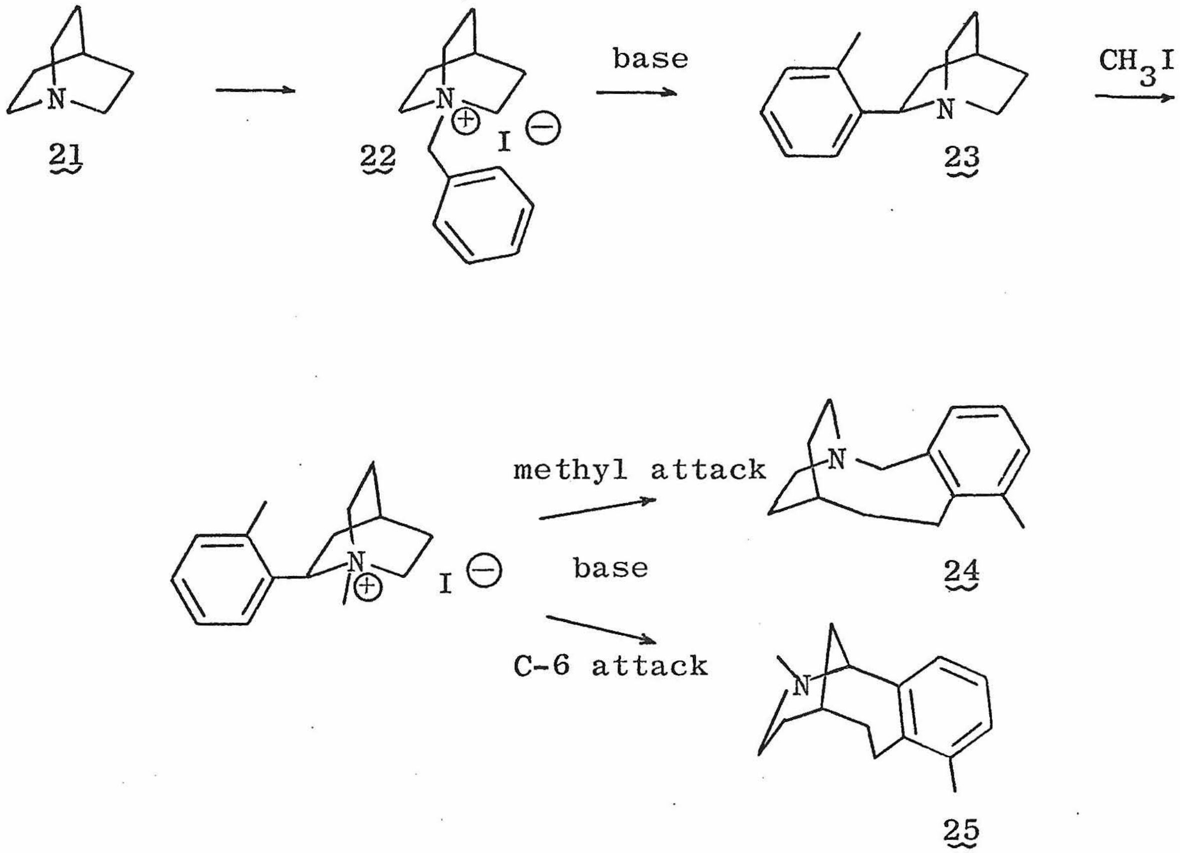


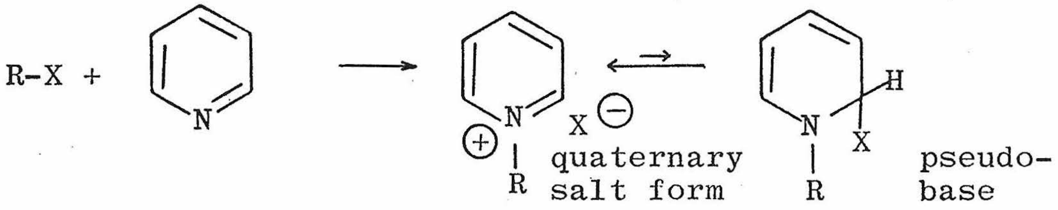
Figure 4: Rearrangements in the Quinuclidinium System

the standard Hofmann elimination reaction requires that the departing proton and the nitrogen atom be *trans* and coplanar.[11] Quinuclidine has a fairly rigid ring system, and so it is possible that β-elimination will not occur. Since N-benzylquinuclidinium halide (**22**) is already a quaternary salt, no methylation step is necessary prior to the rearrangement, and therefore only one reaction path is available. This path should lead to the amine **23**. Methylation of this amine and rearrangement of the resulting quaternary salt could give two possible products, the amines **24** and **25**, hitherto unknown ring systems.

3. Aromatic

Although the rearrangements described in the aliphatic section would probably succeed, it must be admitted that the aromatic case is somewhat doubtful. But, because even negative information is useful, the experiment should be attempted, especially since the starting materials are readily available.

Pyridine forms quaternary salts with ease; these salts may exist in two forms, which may be in equilibrium:[12]



In pyridine the quaternary aromatic form is more prevalent than it is in other nitrogen-containing aromatic systems,[12] and therefore pyridine has been selected for this investigation.

Benzyl chloride will react with pyridine to give benzylpyridinium chloride (26), which could rearrange upon exposure to sodamide in liquid ammonia to give 2-(*o*-methylphenyl)-pyridine (27). The substituted pyridine 27 could be methylated to the quaternary salt 28. Attack by the methyl carbanion is the only geometrically feasible rearrangement, and the product of this rearrangement would have a 6,10b-dihydropyrido[2,1a]-isoindole ring system (Figure 5).

The rearrangement of benzylquinolium halide or benzylisoquinolium halide could be expected to follow an analogous

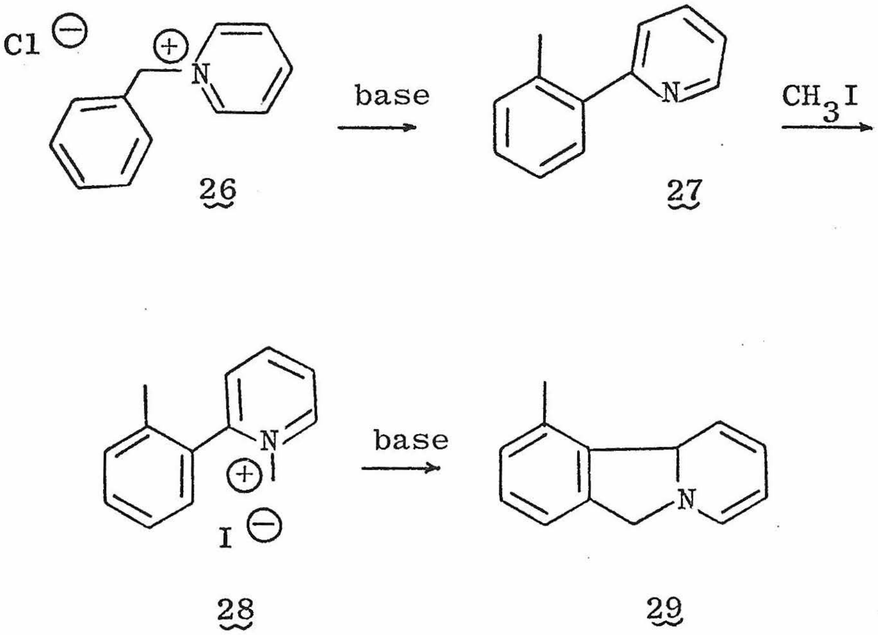


Figure 5: Rearrangement of N-Benzylpyridinium Chloride

pathway to give a derivative of the amine 29, in which a benzene ring is fused onto the heterocyclic ring.

It is likely that almost all of the amines "produced" in these two sections could be re-alkylated with benzyl chloride and the rearrangements continued *ad infinitum*.

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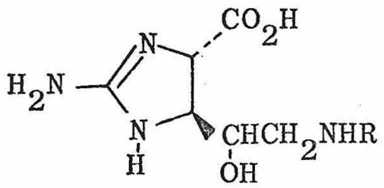
PROPOSITION IV

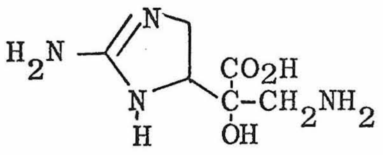
The synthesis of streptolidine and methyl streptolidine is proposed.

The amino acid streptolidine (**1**), also known as roseonine and geamine, was first isolated by Nakanishi and coworkers[1] in 1954 as a product of the acidic hydrolysis of roseothricin, an antibiotic; these workers proposed the structure **3** for this amino acid. Streptolidine was later found in the hydrolysates of geomycin,[2] streptolin,[3] and streptothricin.[3] All these antibiotics are members of the streptothricin class because they contain the amino acid streptolidine and 2-amino-2-deoxygulose. In 1961, van Tamelen and coworkers[4] proposed the structure **1** for streptolidine; this structure was later verified by Bowie, Bullock, and Johnson.[5] Borders and coworkers[6] isolated streptolidine and methyl streptolidine (**2**) from the antibiotics LL-AC541 and LL-AB664 and determined the structures of these antibiotics by chemical and spectral methods. Their structure proof placed the two



1 R = H

2 R = CH_3



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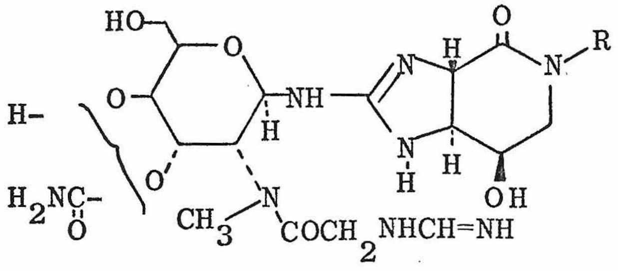
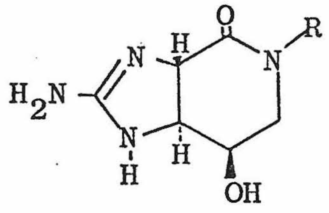


LL-AC541 R = H

LL-AB664 R = CH_3



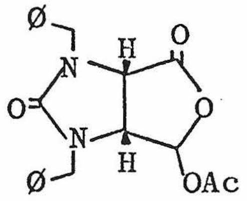
4 R = H

5 R = CH_3

new antibiotics in the streptothricin class and showed that in LL-AC541 and LL-AB664 streptolidine is present in the lactam form (**4**) and that the C-7 hydroxyl group has the β configuration.

Despite its wide occurrence, streptolidine has never been synthesized. A synthesis would not only offer a final structural proof but also be a major step toward the synthesis of these antibiotics. Since the lactam form may be more useful synthetically, its synthesis will also be presented in this proposition.

The streptolidine lactams **4** and **5** can be prepared from readily available materials. Goldberg and Sternbach[7] in their synthesis of biotin prepared *dl*-*cis*-3,4-(1',3'-dibenzyl-2'-ketoimidazolido)-2-keto-5-acetoxytetrahydrofuran (**6**) on a large scale by a four step procedure, starting with *meso*-dibromosuccinic acid (commercially available). Van Tamelen and coworkers[4] saponified and equilibrated this acetoxytetrahydrofuran **6** to obtain the *trans*-2-imidazolidone **7**, the



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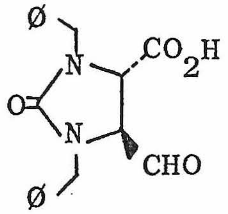

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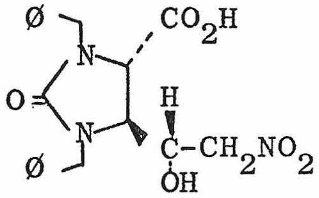

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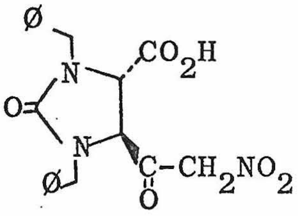

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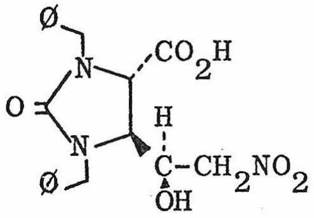

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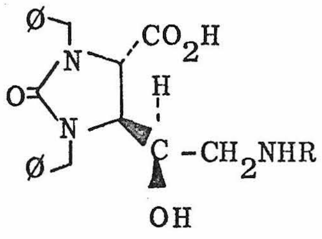
starting material for the synthesis described below.

Treatment of the imidazolidone 7 with nitromethane and base[8] should give the hydroxy-nitro compound 8, which, on the basis of Cram's rule,[9a] will have the hydroxyl group in the wrong configuration (S). If, indeed, a preponderance of the wrong isomer (8) were formed, the product ratio could be reversed by oxidation of the alcohol 8 to the ketone followed by hydride reduction of this ketone to the alcohol 10. Since imidazolidones are quite stable in the presence of mild acid,[7] Jones oxidation[10] should be ideal for the oxidation of alcohol 8. Van Tamelen and coworkers[4] have successfully reduced the aldehyde 7 to the corresponding primary alcohol with sodium borohydride without interference from the imidazolidone ring or the carboxylic acid; therefore, sodium borohydride would be a suitable reagent for the reduction of ketone 9 to the alcohol 10. Cram's rule predicts that this alcohol would have the desired configuration. Catalytic hydrogenation of the nitro-



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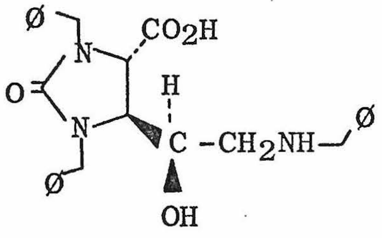

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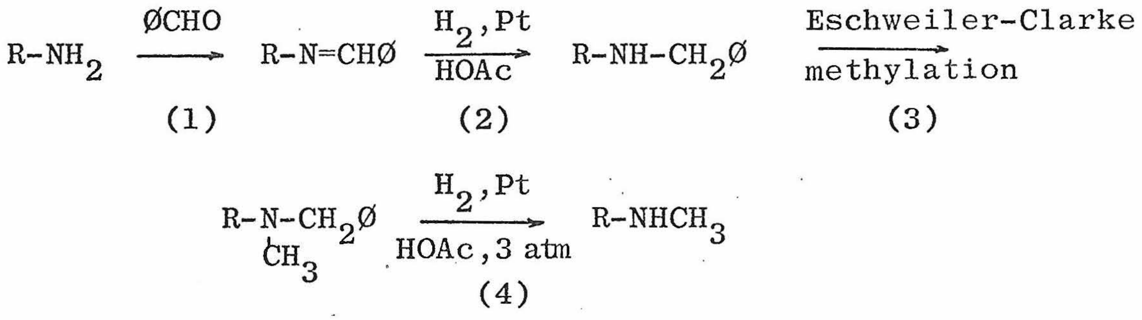
alcohol 10 will give the amino-alcohol 11 (R = H)[11a] without reducing the imidazolidone ring[12a] or removing the benzyl protecting groups.[13]

At this point in the synthesis, the primary amino group should be methylated to give the N-monomethylated derivative (11, R = CH_3), the precursor of methyl streptolidine (2). Although monomethylation of a primary amine is not as simple a process as dimethylation, this procedure can be done effectively with the method of Buck and Baltzly,[14] given in Figure 1.

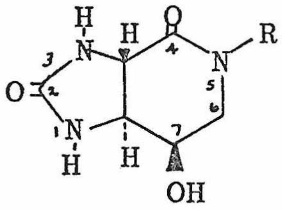


$$R\text{-}NH_2 \xrightarrow[(1)]{\text{ØCHO}} R\text{-}N{=}CHØ \xrightarrow[HOAc]{H_2,\,Pt} \underset{(2)}{} R\text{-}NH\text{-}CH_2Ø \xrightarrow[\text{methylation}]{\text{Eschweiler-Clarke}} \underset{(3)}{}$$

$$\underset{CH_3}{R\text{-}N}\text{-}CH_2Ø \xrightarrow[HOAc,\,3\text{ atm}]{H_2,\,Pt} R\text{-}NHCH_3 \quad (4)$$

Figure 1: Monomethylation of a Primary Amine

A modification of this method should effect the monomethylation of the amine 11 (R = H). Condensation of the primary amine with benzaldehyde will give the Schiff base. Since sodium borohydride will smoothly reduce an imine to an amine,[15] this reagent will be used instead of hydrogenation to effect the reduction of the Schiff base to the secondary benzyl amine 12. The other functional groups should not be attacked by this hydride. The amine 12 could then be methylated by the Eschweiler--Clarke procedure[16] or with methyl iodide. Removal of the benzyl group on the amine by hydrogenolysis[11b] (step 4) would yield the methylated amine 11 (R = CH_3).



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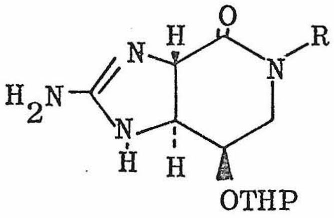

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R = H or CH_3

Birch reduction[4] of the amino alcohol 11 (R = H or CH_3) should remove the benzyl protecting groups without reducing the imidazolidone ring or the carboxylic acid. Heat treatment[17] of the debenzylated material will form the lactam 13. After protection of the C-7 hydroxyl group as a tetrahydropyranyl (THP) ether,[18] vigorous alkaline hydrolysis[12b] should cleave the imidazolidone ring, yielding a diamine, which, in turn, should react with cyanogen bromide[4,12c] to give the dl-imidazopyridine 14. Removal of the THP protecting group with dilute aqueous acid[18] and resolution[9b] of the racemate will afford the d and l enantiomers of both streptolidine and methyl streptolidine lactams 4 and 5. In each case, the lactam ring may be cleaved by acid hydrolysis[3,6] to give streptolidine (1) and methyl streptolidine (2). The correct (naturally occurring) enantiomers of streptolidine and methyl streptolidine can be determined by optical rotation measurements (natural streptolidine is dextrorotatory[6]).

This synthetic route should make streptolidine available in large enough quantities for the synthesis of the streptothricin-class antibiotics (see Proposition V). In addition, slight modifications of the synthetic scheme would provide numerous streptolidine analogs for use in the synthesis of hitherto-unknown compounds, which may be more effective antibiotics than the naturally occurring ones.

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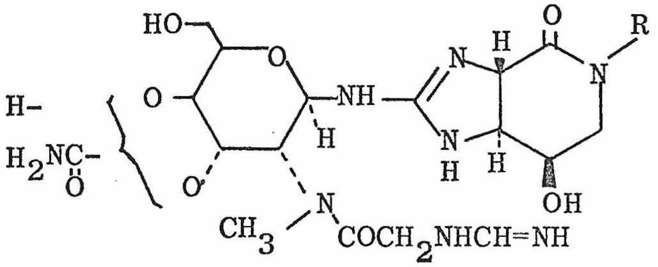
PROPOSITION V

The synthesis of the antibiotics LL-AC541 and LL-AB664 and an approach to the synthesis of other streptothricin antibiotics are proposed.

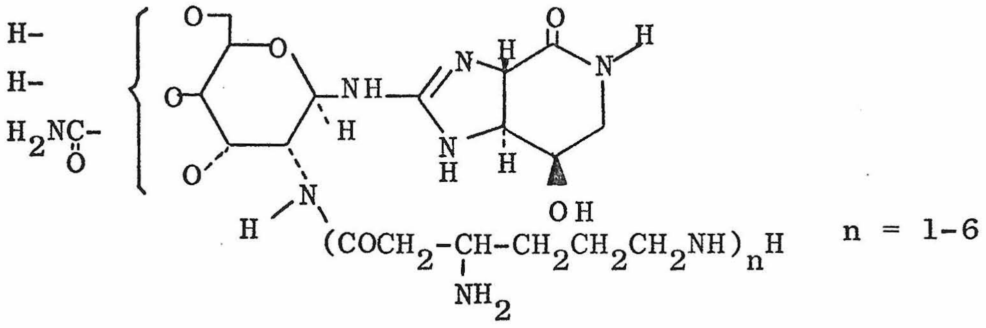
The antibiotics LL-AC541 and LL-AB664, which belong to the streptothricin class of antibiotics, were recently found by Borders and coworkers[1] to have the following structure:



LL-AC541 R = H
LL-AB664 R = CH_3

A synthesis would provide a valuable source of these antibiotics and could lead to the preparation of structural and functional variants, which may have decreased toxicity and increased effectiveness as drugs.

These antibiotics are composed of three basic parts: the heterocycle (streptolidine lactam), the sugar (a D-gulosamine urethane), and the acyl group attached to the amino group on the sugar; in the above antibiotics this acyl group is the formiminoglycyl group. Other members of the streptothricin antibiotics have the general structure **1**.[2,3] Some examples of these antibiotics are streptothricin (n = 1), streptolin (n = 2), and geomycin (n = 4). Members of this group have the



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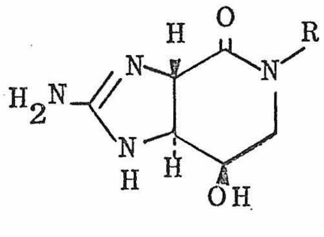
heterocyclic moiety and the same amino sugar. The position of the urethane on this sugar has not yet been established. With the exception of the antibiotics LL-AC541 and LL-AB664, the antibiotics of this class lack a methyl group on the amino group of the sugar and have this amino group acylated with a series of β-lysine units. The proposed synthesis of LL-AC541 and LL-AB664 will therefore also provide a route for synthesizing the other members of the streptothricin class.

The synthesis of the heterocyclic component, streptolidine lactam (2), has already been presented in the fourth proposition. The remaining problems are the synthesis of the sugar component 3 and the coupling of compounds 2 and 3 to give the antibiotics.



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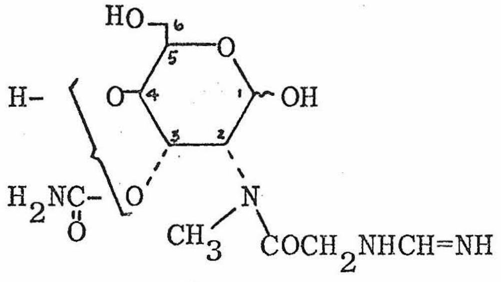

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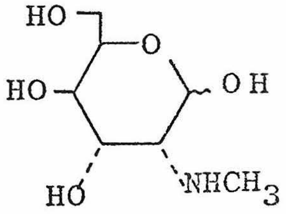

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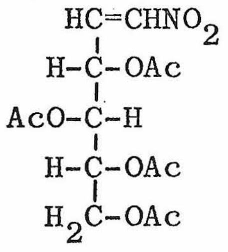
The first step in the synthesis of the sugar 3 is the synthesis of the basic skeleton, 2-methylamino-2-deoxygulose (4). There are several known syntheses of 2-amino-2-deoxygulose;[4] of these, the method of Sowden and Oftedahl could most easily be modified to give the necessary N-monomethyl-derivative. Therefore, treatment[4c] of D-xylose with nitromethane followed by acetylation should give the nitro-olefin 5. Reaction of this nitro-olefin with methylamine instead of ammonia and then hydrolysis of the nitro group under Nef conditions (sodium hydroxide followed by concentrated hydrochloric acid) should give 2-methylamino-2-deoxygulose 4.



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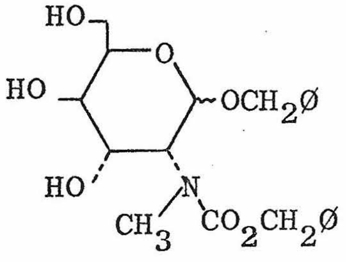

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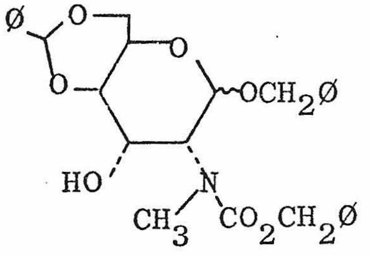

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The next problem is to distinguish among the four hydroxyl groups and amino group of sugar 4. Treatment of this amino sugar with benzyloxycarbonyl chloride in aqueous sodium carbonate[5] would selectively protect the C-2 amino group. The hemiacetal hydroxyl group could be converted to a benzyl ether on heating in benzyl alcohol in the presence of hydrochloric acid.[6a] The product, sugar 6, would then be allowed to react with benzaldehyde under acidic conditions $(ZnCl_2)$[6b,7] to afford the specifically protected sugar 7.

Next, the very sensitive urethane group must be placed on the sugar. Since it is not known whether the urethane group is on the C-3 or C-4 position of the sugar, a synthesis of each isomer is presented. In order to selectively place the urethane moiety at the desired position, the four other reactive sites (three hydroxyls and an amine) must be blocked. The three hydroxyl groups will be protected as benzoates, since these groups can be removed in the presence of a urethane.[8] A protected formiminoglycine group will both protect the C-2 amine and eventually lead to the desired N-substituent. Therefore, this group will be added prior to the urethane formation. Since an acetyl group may be removed in the presence of a benzoate[6c,8] and protected N-formiminogylcine groups, it will be used to mask the hydroxyl group where the urethane is desired.

Three other restrictions are imposed by the nature of the antibiotic and the amino sugar, and the sensitivity of the N-glycoside, formiminoglycine, and urethane moieties:

1) In aqueous solution the antibiotics are unstable above pH 7.[9]
2) Under acidic conditions an N→O acyl migration can occur between the <u>cis</u> C-2 N and C-3 O groups.[6d]
3) Basic conditions can cause a similar O→N acyl migration.[6d]

The following synthetic sequences should avoid these problems:

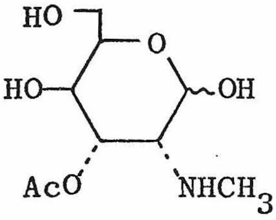
I. The Synthesis of the C-3 Urethane Sugar 3a (Chart A)

Acetylation of the C-3 hydroxyl group of sugar 7 with acetic anhydride in pyridine,[6c] followed by hydrogenolysis of the C-1 benzyloxy group,[10] the carbobenzyloxy protecting group[11] on the C-2 amine, and the benzylidene acetal group[6b,10] on the C-4 and C-6 oxygens would yield the C-3 acetate 8.

The next step is the addition of the formiminogylcine group onto the C-2 amine. This group must be protected since its basicity will interfere with the other steps and since it is only stable under acidic conditions and these subsequent steps are basic ones. The *o*-nitrobenzyloxycarbonyl group,[13] which can be quantitatively removed by simple photolysis, can be used to protect the formiminogylcine moiety for it would both reduce the basicity at the C-2 position and stabilize the formiminogylcine to base. Reaction of formiminoglycine and *o*-nitrobenzyloxycarbonyl chloride in pyridine should give the N-protected formiminoglycine 9.

Treatment of the acetate 8 with the protected formiminoglycine and dicyclohexylcarbodiimide (DCC)[6e,14] should yield a sugar with a protected formiminogylcamide group at the C-2 position. Acylation[6c] of the three hydroxyl groups with benzoyl chloride in pyridine, followed by selective removal of the C-3 acetyl group with methanolic ammonia,[6c,8] should give the tribenzoate 10.

CHART A



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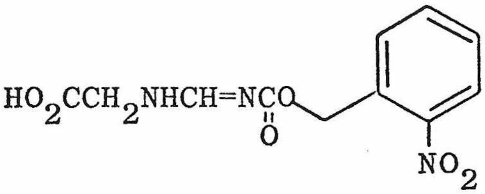

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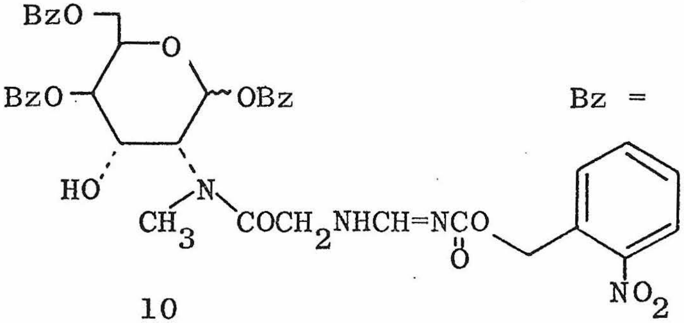

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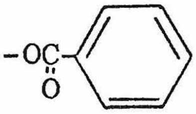

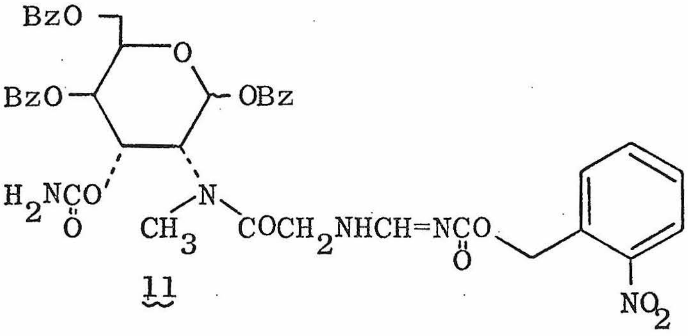

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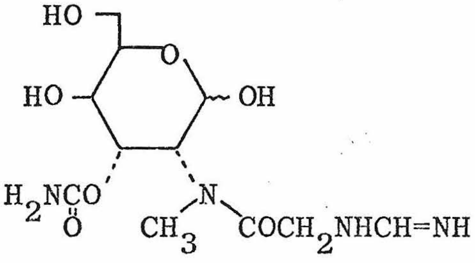


3a

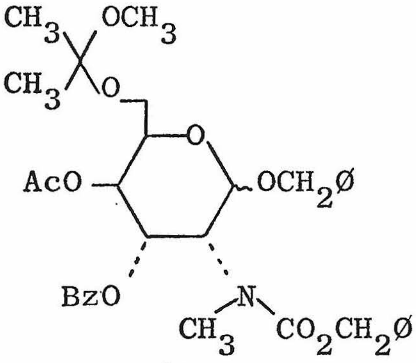
The urethane group can now be added onto the only unprotected hydroxyl group (C-3). There are several standard methods for forming urethanes. The two most obvious ones, reaction with carbamyl chloride[15] and reaction with phosgene followed by ammonia,[16] are somewhat harsh and may lead to allophanate and carbonate formation, repectively. The method selected to effect this transformation is a more recent procedure, which Vaterlaus and coworkers [8] have successfully used on a sugar hydroxyl group. Therefore, the C-3 hydroxyl group of sugar 10 could be acylated with *p*-nitrophenoxycarbonyl chloride in pyridine to give the aryl-alkyl carbonate, which could then be cleaved with methanolic ammonia to the tribenzoate 11. Treatment of the tribenzoate with cold methanolic barium methoxide would remove the three benzoyl groups without harming the sensitive urethane moiety[8] to afford, after photolysis, the C-3 urethane sugar 3a.

II. The Synthesis of the C-4 Urethane Sugar 3b (Chart B)

This synthesis is similar to that of the C-3 urethane sugar 3a with two additional steps, which would keep the C-4 group free while the other hydroxyl groups are protected.

First, the C-3 hydroxyl group of the sugar 7 could be benzoylated with benzoyl chloride in pyridine.[6c] Acid hydrolysis[6b,7] of the benzylidene acetal group, followed by a selective protection of the C-6 hydroxyl group as the 2'-alkoxy-2'-methoxypropane[17] and then acetylation[6c] of the remaining C-4 hydroxyl, would give the protected amino sugar 12. Mild

CHART B



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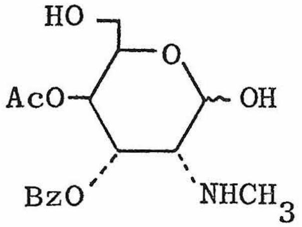

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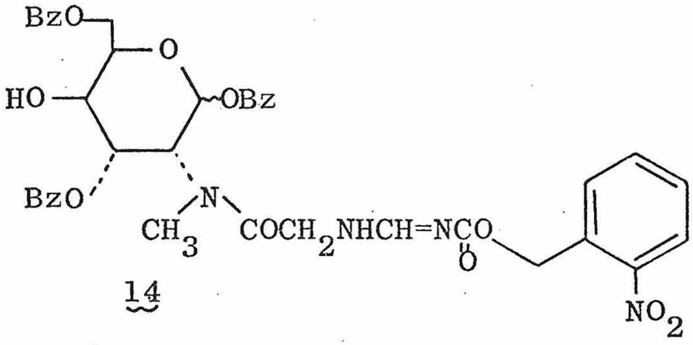

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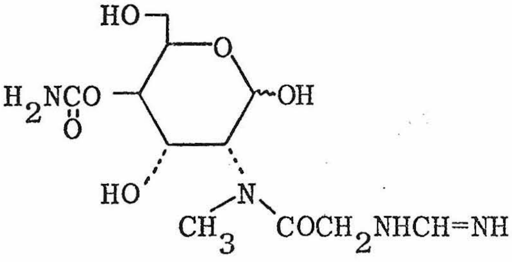

3b

acid hydrolysis[18] would regenerate the C-6 hydroxyl group, and hydrogenolysis[10,11] would free the C-1 hydroxyl and the C-2 amino groups to give the amino sugar 13. Treatment of this compound with the protected formiminoglycine 9 and dicyclohexylcarbodiimide[6e,14] should afford the C-2 protected formiminoglycamide, and reaction with benzoyl chloride in pyridine[6c] should result in acylation of the C-1 and C-6 hydroxyl groups. Removal of the C-4 acetyl group with methanolic ammonia would finally give the tribenzoate 14. As in scheme A, treatment of this tribenzoate with *p*-nitrophenoxycarbonyl chloride in pyridine followed by methanolic ammonia[8] would produce the urethane (this time at the C-4 position). Removal of the three benzoyl groups with barium methoxide[8] and photolysis should yield the C-4 urethane sugar 3b.

The final step in the synthesis of these antibiotics, the coupling reaction, should be straightforward. In 1948, Todd and coworkers[18] reported that a β-pyranoside is produced by reaction of an aryl amine with an hexaldose in ethanolic ammonium chloride; more recently, Bertho and Koziollek[19] found that similar couplings with amino sugars also produced pyranosides with the β configuration at the C-1 position. Therefore, the antibiotics LL-AC541 and LL-AB664 could be formed quite easily by heating streptolidine lactam 2, the synthesis of which has been outlined in the fourth proposition, with the appropriate urethane sugar (3a or 3b) in ethanolic ammonium chloride, ideal conditions for stabilizing the antibiotics and for ensuring the β-configuration of the heterocyclic base.

Although only one of the sugars synthesized (**3a** or **3b**) would, on coupling, yield the known antibiotics, it is quite possible that the other sugar would yield hitherto-unknown antibiotics, perhaps even more effective than the natural ones. Indeed, one of the advantages of the synthetic schemes described above is the opportunity for varying the functionality on virtually every site of the molecule, thereby providing a means of synthesizing many streptothricin analogues.

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