PETERS, Charles Allan, 1936-

STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF 4-(1,2-EPOXY-1,5-DIMETHYL-4-HEXENYL)-5-METHOXY-1-OXASPIRO[2.5]OCTAN-6-OL OBTAINED FROM MILD SAPONIFICATION OF FUMAGILLIN.

The University of Oklahoma, Ph.D., 1969
Chemistry, organic

University Microfilms, Inc., Ann Arbor, Michigan

THE UNIVERSITY OF OKLAHOMA

GRADUATE COLLEGE

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A DISSERTATION

SUBMITTED TO THE GRADUATE FACULTY

in partial fulfillment of the requirements for the

degree of

DOCTOR OF PHILOSOPHY

BY

CHARLES ALLAN PETERS

Norman, Oklahoma

1969

STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF 4-(1,2-EPOXY-1,5-DIMETHYL-4-HEXENYL)-5-METHOXY-1-OXASPIRO[2.5]OCTAN-6-OL OBTAINED FROM MILD SAPONIFICATION OF FUMAGILLIN

APPROVED BY

DISSERTATION COMMITTEE

TO

NANCY and KAREN

ACKNOWLEDGMENTS

The author would like to express his appreciation to Dr. Francis J. Schmitz who initiated this problem and for his direction during the course of this work. The University of Oklahoma also deserves mention due to its financial support in the way of teaching and research assistantships. Appreciation is also extended to the National Science Foundation for a summer Fellowship for Graduate Teaching Assistants and to the National Aeronautics and Space Administration for a three year Pre-Doctoral Traineeship.

A special tribute is due Dr. A. J. Weinheimer whose guidance and understanding has been an encouragement over a period of several years. In addition, the friendship and association with the faculty and graduate students of the department of chemistry has been a rewarding part of this work.

The author is especially indebted to his mother and father for the love and encouragement they have given him for so many years. Finally the author wishes to express his appreciation for the companionship, love, and infinite joy (a daughter, Karen) his wife, Nancy, has brought to his life. Without her moral and financial help this work would not have been possible.

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STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF 4-(1,2-EPOXY-1,5-DIMETHYL-4-HEXENYL)-5-METHOXY-1-OXASPIRO[2.5]OCTAN-6-OL OBTAINED FROM MILD SAPONIFICATION OF FUMAGILLIN

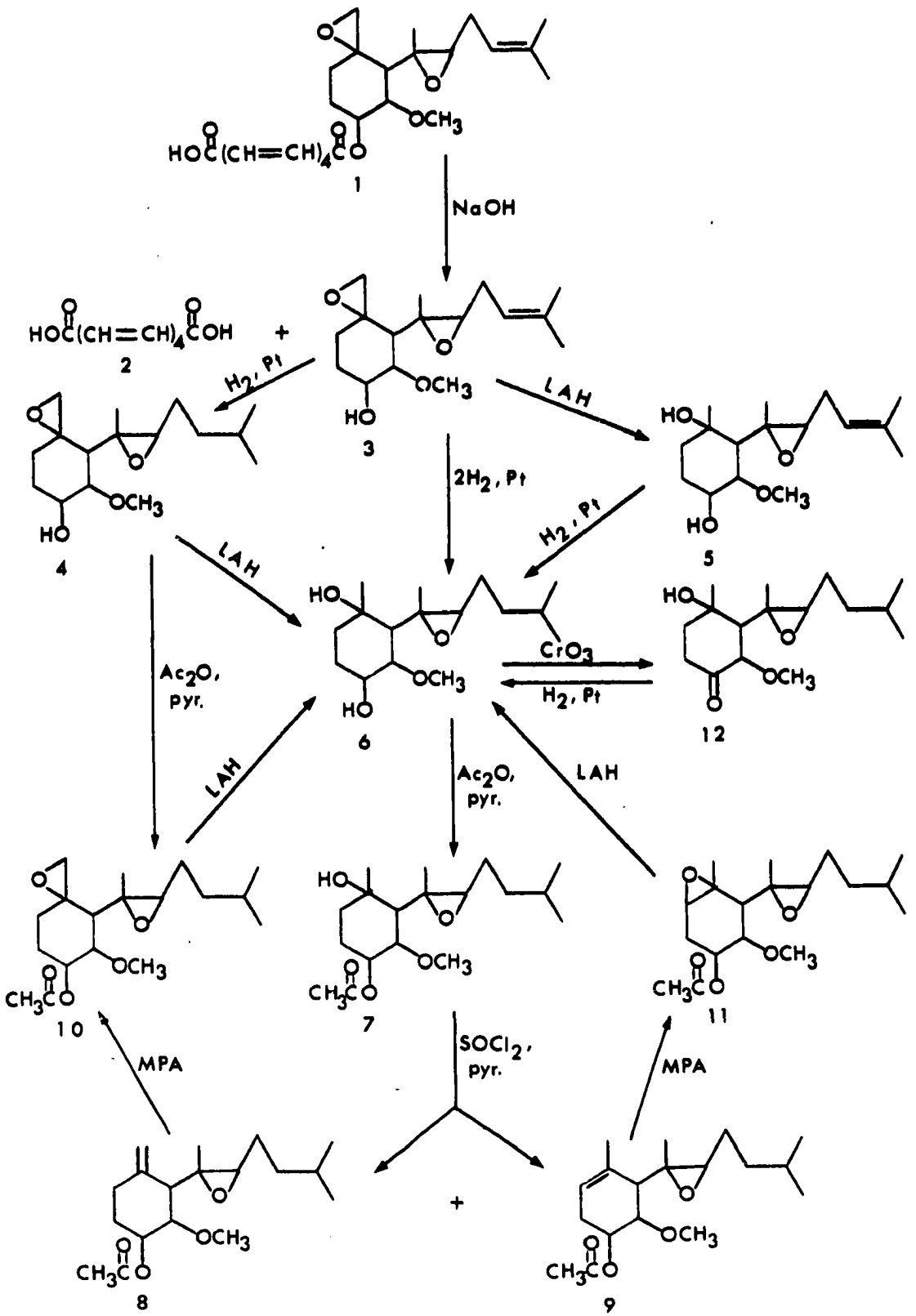
HISTORY AND BACKGROUND

Since the isolation of fumagillin[1,2] from dextrin-corn steep broth fermentation of Aspergillus fumigatus H-3, its biological and chemical properties have received considerable attention. Fumagillin has shown the following antiparasitic properties: amoebacidal activity against Endamoeba histolytica,[3-10] activity against Nosema apis in bees,[11-19] activity against experimental visceral leishmaniasis,[20] activity against Hexamita salmonis in salmon,[21] nematocidal activity against Anguillula aceti,[22] and antimalarial activity against Plasmodium gallinaceum in chicks.[23] It also has shown important carcinolytic activity against some experimental and human tumors.[24-29]

Fumagillin was shown to have the empirical formula[1,30,31] $C_{26}H_{34}O_7$. Analyses[32] indicated that it contained one methoxyl, one hydroxyl, two C-methyls, and two non-carbonyl oxygen atoms. Some of the chemical transformations that led to the structural assignment of fumagillin are outlined in schemes 1, 2, and 3.

Upon mild alkaline hydrolysis,[31,32] fumagillin (1) gave decatetraenedioic acid (2) and a neutral alcohol fragment, 3, with the empirical formula $C_{16}H_{26}O_4$. Analyses[32,33] of 3 indicated the presence of a secondary hydroxyl group as well as the methoxyl group, two C-methyl groups and two non-carbonyl oxygen atoms found for fumagillin itself. The nmr spectrum[34] showed the following structural features: one vinyl hydrogen at 5.10 ppm ($-CH=CR_2$), a singlet corresponding to three methyl hydrogens at 3.40 ppm ($-OCH_3$), two singlets, each equivalent to three methyl hydrogens at 1.74 and 1.65 ppm ($=C(CH_3)_2$), and a singlet, three hydrogens, at 1.12 ppm ($-O-\overset{|}{C}-CH_3$).

When 3 was hydrogenated in ethanol in the presence of platinum oxide two products could be isolated: a dihydroalcohol, 4, when hydrogenation was ceased after the absorption of one molar equivalent of hydrogen, or a tetrahydroalcohol, 6, when hydrogenation was allowed to continue to completion.[33] Tetrahydroalcohol 6 formed only a monoacetate, 7, when treated with acetic anhydride in pyridine[35] and could be easily oxidized to ketone 12 that still showed hydroxyl absorption in its infrared spectrum.[33] The nmr spectrum of 6 showed a new singlet, three hydrogens, at 1.22 ppm ($CH_3-\overset{|}{C}-OH$) which indicated that a reactive epoxide function of the structure $CH_2\overset{O}{\diagup\diagdown}CR_2$ might have undergone hydrogenolysis.[34] Further evidence for this structural feature was obtained by treatment of alcohol 3 with lithium aluminum hydride at 0° to give dihydroalcohol 5 which when hydrogenated gave tetrahydroalcohol 6. Dihydroalcohol 4 could also be converted to tetrahydroalcohol 6 by reduction with lithium aluminum hydride.[36]

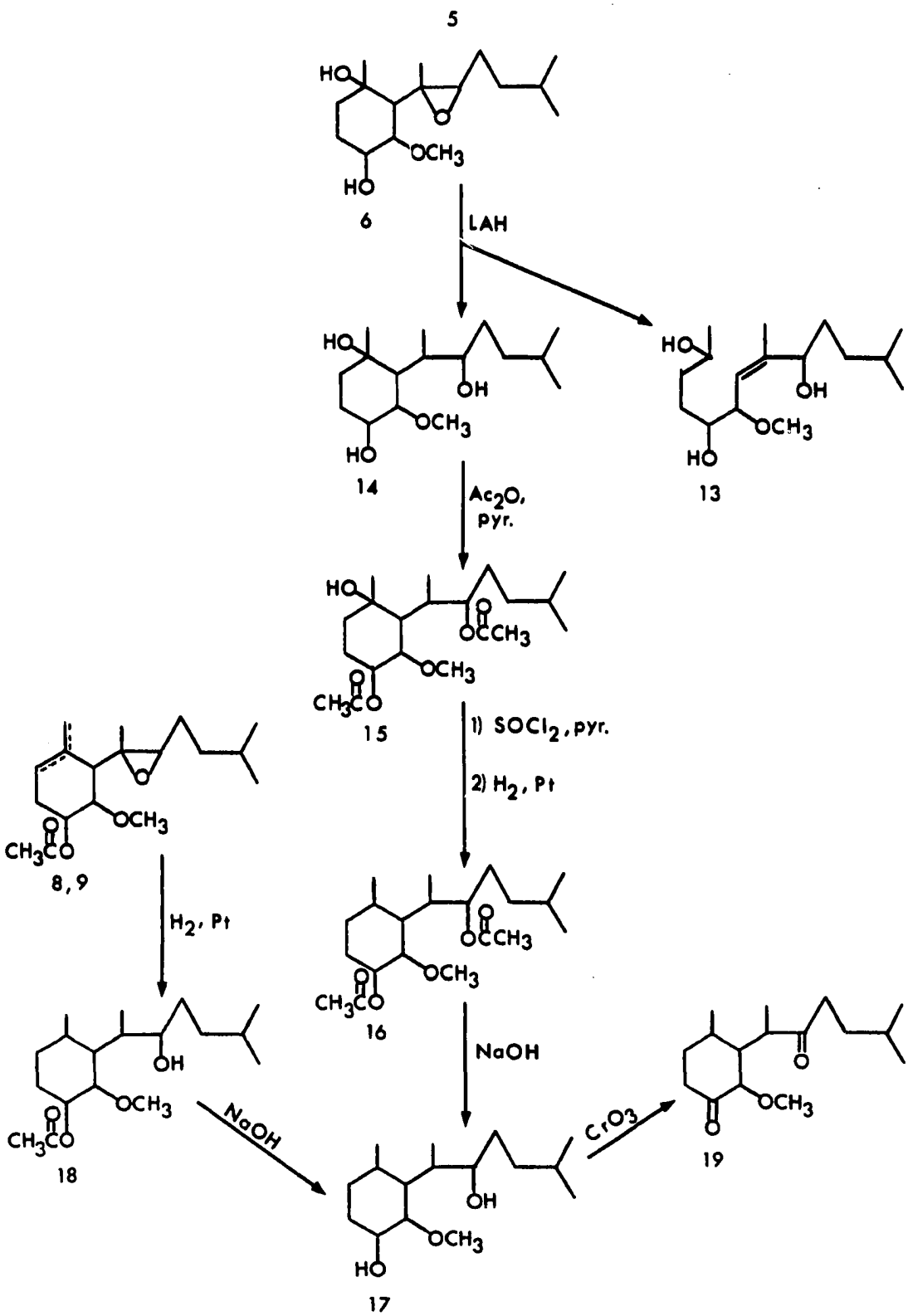

HOC(CH=CH)4COO
1
NaOH
HOC(CH=CH)4COOH
2
+
H2, Pt
OCH3
HO
3
LAH
4
5
2H2, Pt
H2, Pt
LAH
Ac2O, pyr.
6
CrO3
H2, Pt
12
LAH
Ac2O, pyr.
LAH
CH3CO
10
7
11
MPA
SOCl2, pyr.
MPA
8
+
9

SCHEME 1

When monoacetate 7 was treated with thionyl chloride-pyridine at 0° two olefins were formed: olefin 8 which showed terminal methylene absorption at 1640 and 895 cm^{-1} in its infrared spectrum, and olefin 9 which showed trisubstituted double bond absorption at 813 cm^{-1} in its infrared spectrum and a vinyl methyl group at 1.70 ppm in its nmr spectrum. Olefin 8 when treated with monoperphthalic acid gave 10 which was identical, on the basis of its infrared spectrum, with the acetate obtained by acetylation of dihydroalcohol 4. Olefin 9 gave tetrahydroalcohol 6 when treated with monoperphthalic acid followed by reduction with lithium aluminum hydride.[34] This sequence established that no structural rearrangement occurred in the thionyl chloride-pyridine dehydration step.

The reduction of tetrahydroalcohol 6 with lithium aluminum hydride in refluxing tetrahydrofuran led to two products (see scheme 2): hexahydroalcohol 13, resulting from a reductive rearrangement, and hexahydroalcohol 14. Hexahydroalcohol 14 formed a diacetate, 15, under mild acetylation conditions, indicating that the newly formed hydroxyl was secondary. The nmr spectrum of diacetate 15 showed only one methyl absorption of the type $CH_3-\overset{|}{C}-O$ and a new secondary methyl absorption.[34] This evidence indicated that the side chain contained the structural unit $CH_3-\overset{|}{C}-\overset{|}{C}-H$ (with an oxygen bridging the two carbons).

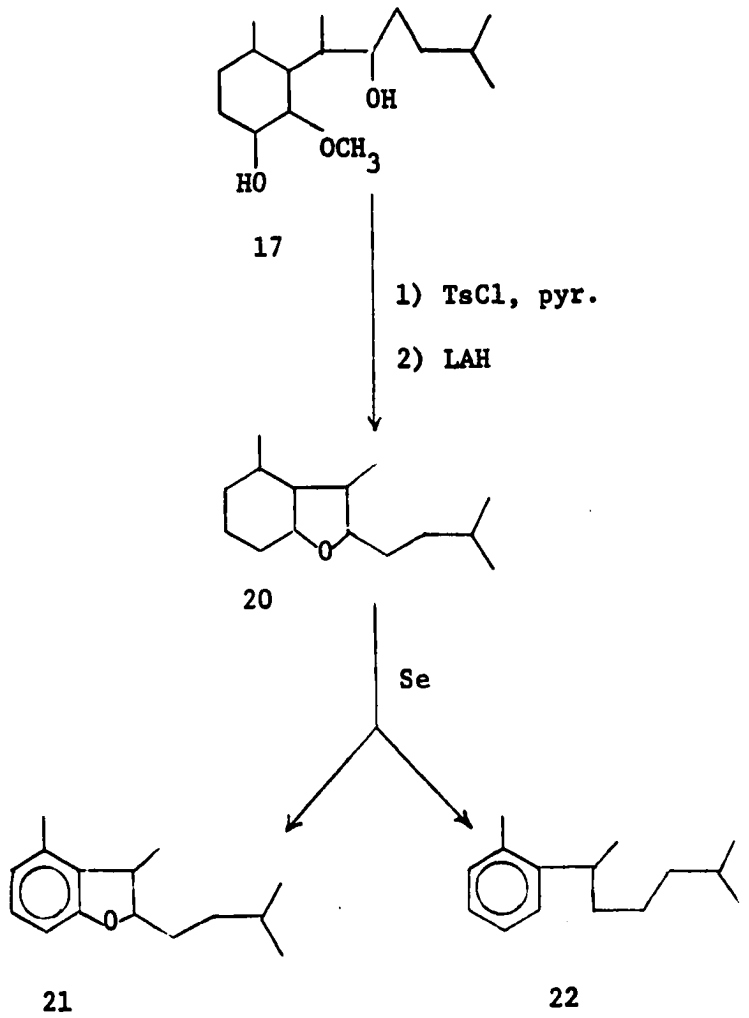
Diacetate 15 was dehydrated with thionyl chloride-pyridine to give a mixture of olefins which was hydrogenated to diacetate 16. Saponification of 16 gave a diol, 17, which was identical with the diol obtained from hydrogenation of the mixture of olefins 8 and 9 followed by basic hydrolysis of the acetate group.[37]


5
HO
OCH3
HO
6
LAH
HO
OH
OCH3
HO
14
HO
OH
OCH3
HO
13
Ac2O,
pyr.
HO
OCCH3
OCH3
CH3CO
15
1) SOCl2, pyr.
2) H2, Pt
OCH3
CH3CO
8, 9
H2, Pt
OCCH3
OCH3
CH3CO
16
NaOH
OH
OCH3
CH3CO
18
NaOH
OH
OCH3
HO
17
CrO3
O
OCH3
19

SCHEME 2

Monoacetate 18 could be oxidized to a ketone which showed bands at 1730 (acetate) and 1706 cm^{-1} (ketone) in its infrared spectrum. Diol 17 could be oxidized to a diketone, 19, which exhibited two carbonyl peaks at 1705 and 1725 cm^{-1} in its infrared spectrum.[34]

When the diol 17 was treated with tosyl chloride-pyridine followed by reduction with lithium aluminum hydride (see scheme 3 below) a perhydrobenzofuran, 20, was obtained. Dehydrogenation of



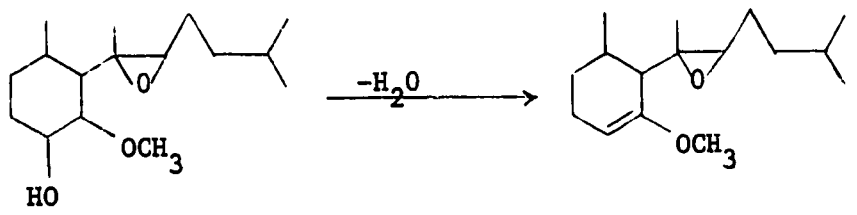
SCHEME 3

20 with selenium produced two products, a benzofuran, 21, and a hydrocarbon, 22. The structures of these two compounds were established by analysis, spectral properties, and synthesis.[38]

On the basis of these chemical transformations and other evidence gathered from a series of rearrangement products,[34] fumagillin was assigned the structure 1.

The relative stereochemistry of fumagillin was ascertained in the following way. As a point of reference, the large side chain was assumed to be orientated in the equatorial position. Epoxidation of olefin 9 followed by hydride reduction gave tetrahydroalcohol 6 (see scheme 1). Since the epoxide opening is trans diaxial, the newly formed tertiary hydroxyl group in 6 is axial. Hence, the C-O bond in the spiroepoxide of 3 is axial.

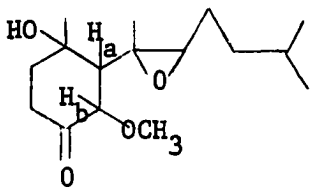
Enol ether 24 is formed by diaxial elimination of water from alcohol 23. Therefore, the secondary hydroxyl group and the hydrogen on the carbon bearing the methoxyl group are both axial. The nmr



23 24

spectrum of ketone 12 also supports the equatorial assignment of the methoxyl group. The proton (H_b) on the carbon atom bearing the methoxyl group is strongly coupled (J_{ab} = 11.8 cps) with the proton

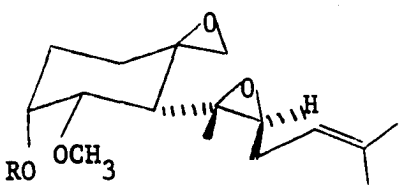
(H_a) on the carbon atom bearing the side chain indicating a trans diaxial orientation.[39] Since ketone 12 can be reduced back to



12

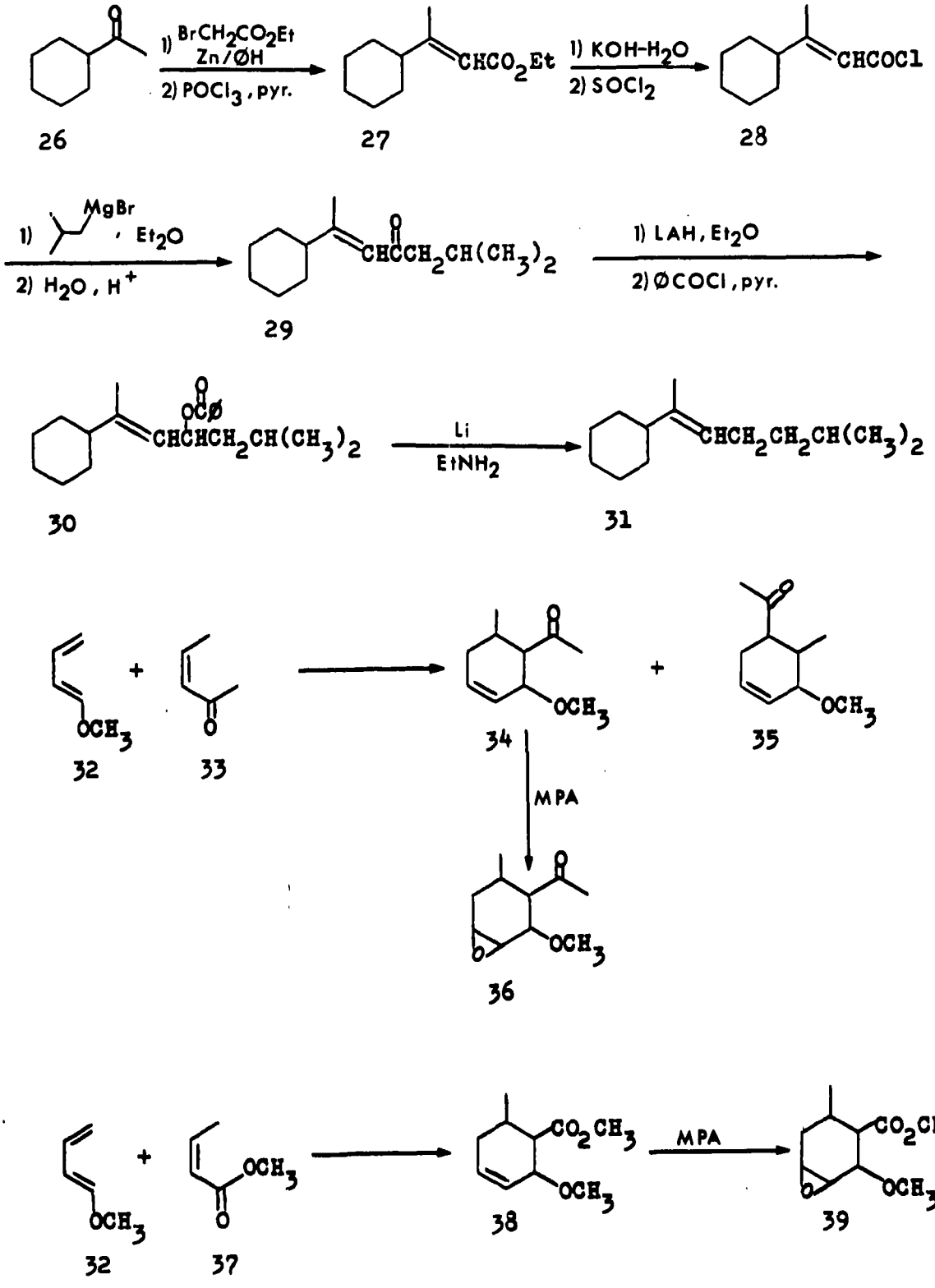
tetrahydroalcohol 6 (see scheme 1), no epimerization of the methoxyl group occurred in the oxidation of 6 to 12.

An X-ray study[40] of the mono-p-bromobenzenesulfonate of tetrahydroalcohol 6 confirmed the relative stereochemistry and determined the absolute stereochemistry as 25 for fumagillin (R = $-\overset{O}{\overset{\|}{C}}(CH{=}{=}CH)_4\overset{O}{\overset{\|}{C}}OH$) and its neutral alcohol fragment (R=H) obtained from mild saponification.



25

During the period since the structure determination of fumagillin had been completed (along with its stereochemistry), some information regarding attempted total syntheses has been reported. Tarbell and coworkers[41] have conducted some preliminary experiments


1) BrCH2CO2Et Zn/ØH
2) POCl3, pyr.
CHCO2Et
1) KOH-H2O
2) SOCl2
CHCOCl
26
27
28
1) MgBr, Et2O
2) H2O, H+
CHCCH2CH(CH3)2
1) LAH, Et2O
2) ØCOCl, pyr.
29
CHCHCH2CH(CH3)2
OCØ
Li
EtNH2
CHCH2CH2CH(CH3)2
30
31
OCH3
32
33
34
35
MPA
36
CO2CH3
38
39
37

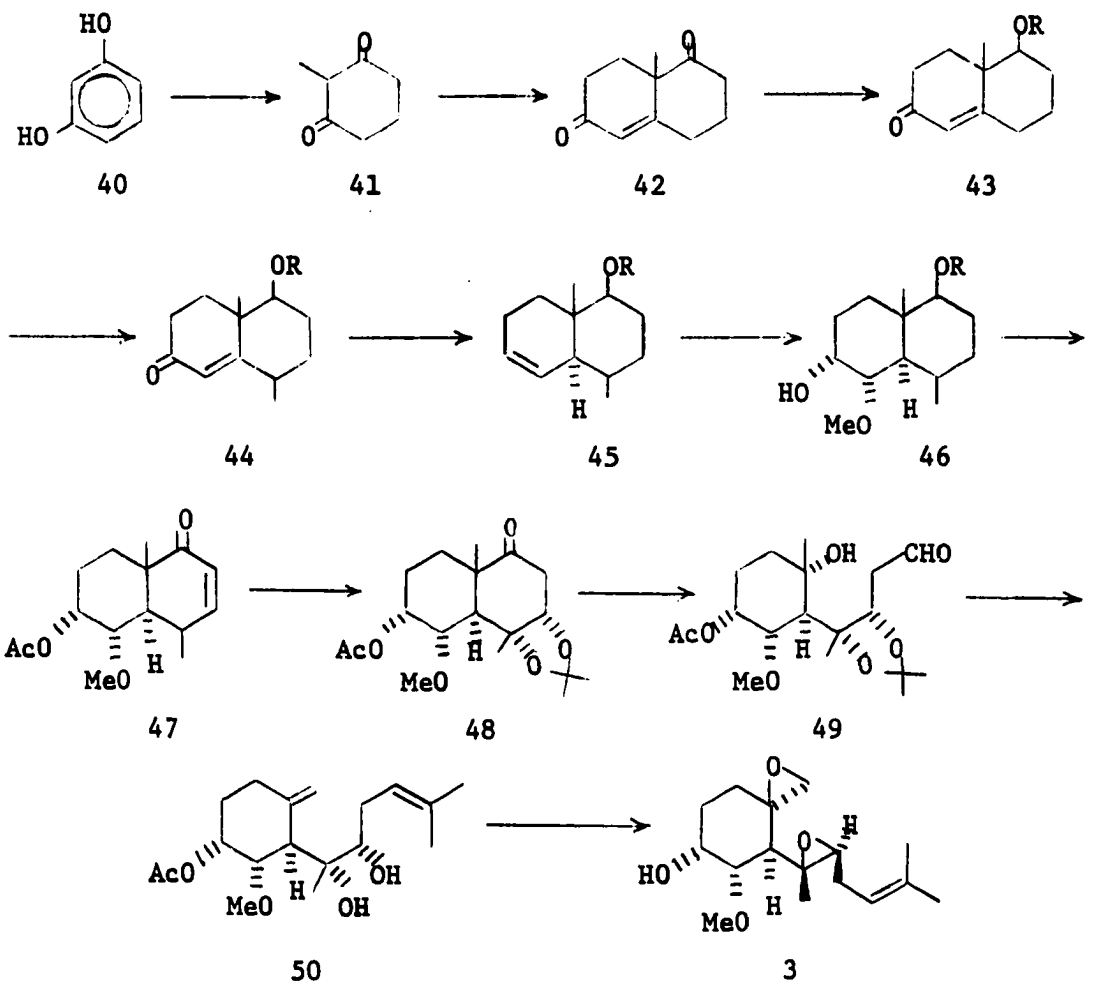
SCHEME 4

(see scheme 4) which resulted in the synthesis of 2-cyclohexyl-6-methyl-2-heptene (31), 1-methyl-2-acetyl-3-methoxy-4,5-epoxycyclohexane (36), and 1-methyl-2-carbomethoxy-3-methoxy-4,5-epoxycyclohexane (39).

Other studies[42-44] have been directed toward the synthesis of substituted 2,3-dihydrobenzofurans. These dihydrobenzofurans can be converted by lithium-liquid ammonia reduction, hydrolysis, and catalytic reduction to substituted cyclohexane derivatives whose structures approach some of the compounds encountered in the chemical degradation of fumagillin.

INTRODUCTION

The purpose of this work was to develop a sequence of reactions which would ultimately result in a stereoselective total synthesis of alcohol 3 and its derivatives.



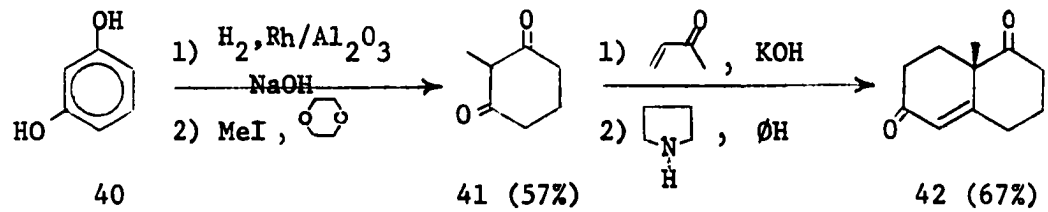
SCHEME 5

The general approach to the synthesis is outlined in scheme 5, where each step involves a number of unspecified reactions. By utilizing a rigid bicyclic system in the synthesis, it was anticipated that the reactions would tend to be highly selective and follow the general stereochemical trends found in steroid reactions.

The results of the exploration of several alternate synthetic approaches to this goal will be discussed in this dissertation. These approaches include: 1) attempts to convert 42 to 44, 2) preliminary efforts to convert 43 to its trans-9-methyl-Δ^5-octalin analog, and 3) several new routes for the synthesis of 4,9-dimethyl-6-oxo-$\Delta^{5(10)}$-octalin derivatives.

RESULTS AND DISCUSSION

2-Methyl-1,3-cyclohexanedione (41) was prepared from resorcinol (40) by low pressure hydrogenation (50-60 psi) using rhodium on alumina[45] followed by alkylation with methyl iodide.[46]

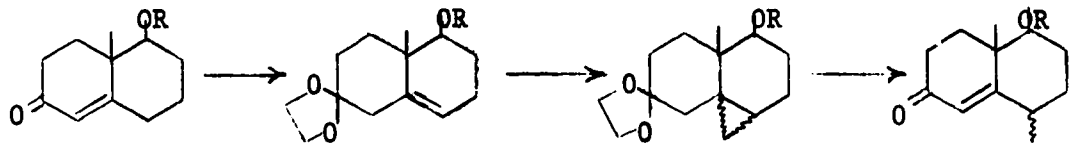


40 41 (57%) 42 (67%)

Reaction of 41 with methyl vinyl ketone and subsequent cyclization of the resulting adduct with pyrrolidine in benzene[47] gave 1,6-dioxo-9β-methyl-$\Delta^{5(10)}$-octalin (42) in good yield.

At this early stage in the synthesis, considerable thought was given to selecting the most efficient and direct method of introducing a methyl group at C_4 in 42. Three procedures used in steroid chemistry[48,49,50] appeared useful, but each involved five to seven steps and the applicability of some of them to a substituted octalin system was uncertain.

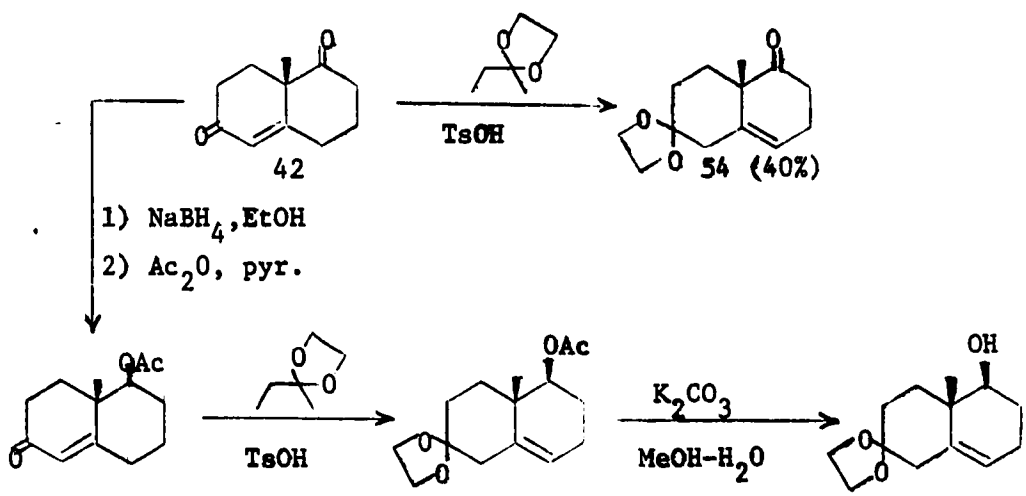
A more direct route was proposed which involved the formation of a cyclopropane ring followed by base catalyzed ring opening to form a methyl group. It was anticipated that this sequence of reactions



43 51 52 53

would give 53 in good yield and be applicable to the synthesis of 6-methyl steroids.

The Simmons-Smith reaction,[51] with various modifications, was utilized for the purpose of attempting to introduce the cyclopropane ring into 51. 3-Ethylenedioxy-Δ^5-cholestene and several other compounds (54, 56, and 57) were prepared (see scheme 6) and used in an



55 (73%) 56 (69%) 57 (96%)

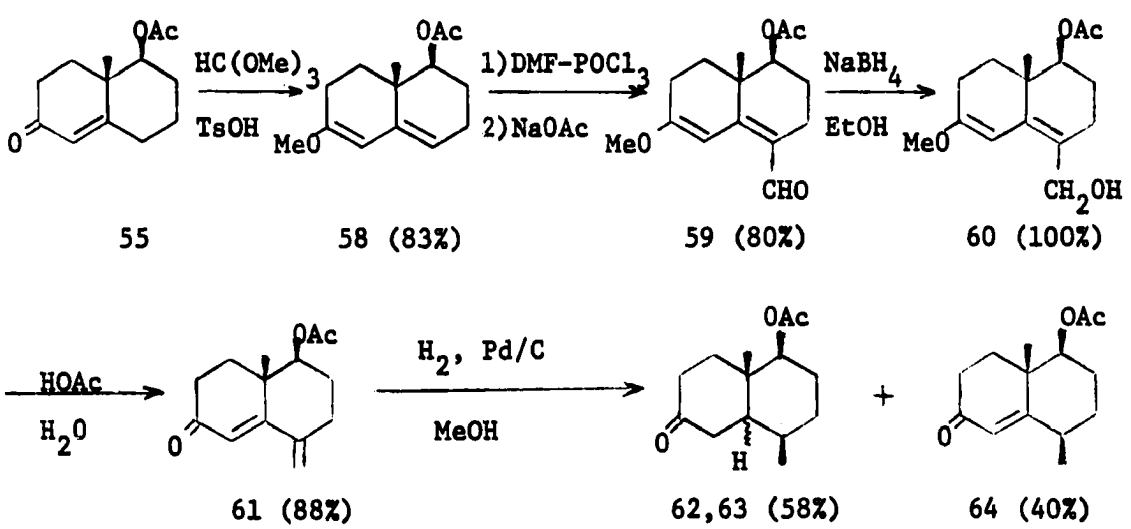
SCHEME 6

effort to develop this potentially useful reaction sequence. The preformed zinc-copper couple described by LeGoff,[52] methylene iodide, and 3-ethylenedioxy-Δ^5-cholestene, 54, 56, or 57 were subjected to the following reaction conditions: 1) refluxing ether for twenty-four

to sixty hours, 2) refluxing tetrahydrofuran for eighteen hours, and 3) ether in a sealed tube which was heated on a steam bath for three to twelve hours.[53] Diethyl zinc was also employed for the preparation of the Simmons-Smith reagent.[54] This series of reactions failed to yield any of the desired products, although the nmr spectra of some of the crude reaction mixtures did show some cyclopropane absorption. In general, either the starting olefin was recovered, or a complex mixture was formed that was inseparable by column chromatography.

After the attempts to develop the proposed methylation sequence proved unsuccessful, attention was directed to the Vilsmeier reagent[55,56] which had been utilized by Williamson and coworkers[49,50] to synthesize a number of 6-methyl steroids in good yield.

In order to examine this possible route, enol ether 58 was prepared (see scheme 7) by reacting 55 with trimethyl orthoformate in

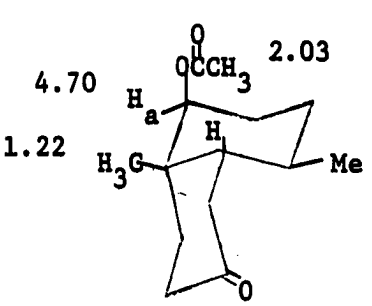


SCHEME 7

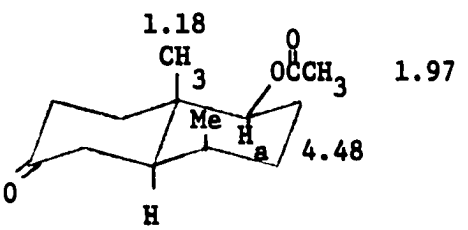
the presence of a catalytic amount of p-toluenesulfonic acid. Enol ether 58 was then added to a preformed phosphorus oxychloride-dimethyl formamide complex (Vilsmeier reagent) in ethylene dichloride to form an iminium salt intermediate which was hydrolyzed with aqueous sodium acetate to give 1β-acetoxy-4-formyl-6-methoxy-9β-methyl-1,2,3,7,8,9-hexahydronaphthalene (59) in high yield.

Reduction of 59 with sodium borohydride gave alcohol 60 which, when heated in aqueous acetic acid, underwent both hydrolysis and dehydration to dienone 61. Hydrogenation of 61 with palladium on charcoal gave the following products: a mixture of cis- and trans-6-decalones, 62 and 63, formed by overhydrogenation and the desired 1β-acetoxy-4β,9β-dimethyl-6-oxo-$\Delta^{5(10)}$-octalin (64). This mixture was separated by column chromatography on silicic acid into a fraction containing cis- and trans-1β-acetoxy-4β,9β-dimethyl-6-decalone (62 and 63) and one containing octalin 64. The cis- and trans-6-decalone isomers were then separated by preparative gas chromatography (30% Carbowax).

The relative stereochemistry of decalones 62 and 63 are shown below along with pertinent nmr data. These assignments are based on



62



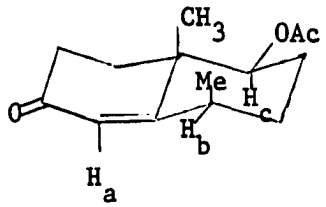
63

the following nmr considerations along with the assumption that the C_4 methyl group is in the β orientation, as was found in octalin 64. The C_9 methyl group in 62 absorbs at lower field than in 63 due to a paramagnetic effect that has been observed in steroids. In several studies,[57] it has been observed that the resonance for the angular methyl group at C_{10} in a 5β-steroid is shifted downfield from the corresponding signal in its 5α-steroid analog. A similar approach has been used by Williamson and coworkers[58] to correlate the ring junctures of some substituted 9-methyl decalins to their angular methyl resonances.

Lemieux and coworkers[59] have observed in acetylated carbohydrates that the methyl absorption of axial acetates are at lower field (by 5-10 cps) than their equatorial counterparts. They also found that the equatorial hydrogen on the carbon bearing the acetate moiety absorbed at lower field (by about 8 cps) than the corresponding axial hydrogen. The nmr spectrum of 62, as compared to that of 63, exhibited both of these trends. In addition, the width of the signal for H_a in 63 was twice that for H_a in 62 indicating the presence of diaxial coupling with one of the C_2 methylene hydrogens in 63. The possibility that cis-1β-acetoxy-4β,9β-dimethyl-6-decalone (62) may exist in its other conformation is not supported by the available nmr data, or qualitative energy considerations.

The stereochemistry of octalin 64 was also based on its nmr spectrum. The signal for H_a in the nmr spectrum of 64 appeared as a sharp singlet at 5.83 ppm indicating little if any coupling with the C_4 hydrogen, H_b. This is in accord with the findings of Ringold and

coworkers[60] who have shown that the C_4 vinyl hydrogen in 6-methyl-Δ^4-keto steroids is strongly coupled (J=1.5-2.0 cps) to the C_6 hydrogen

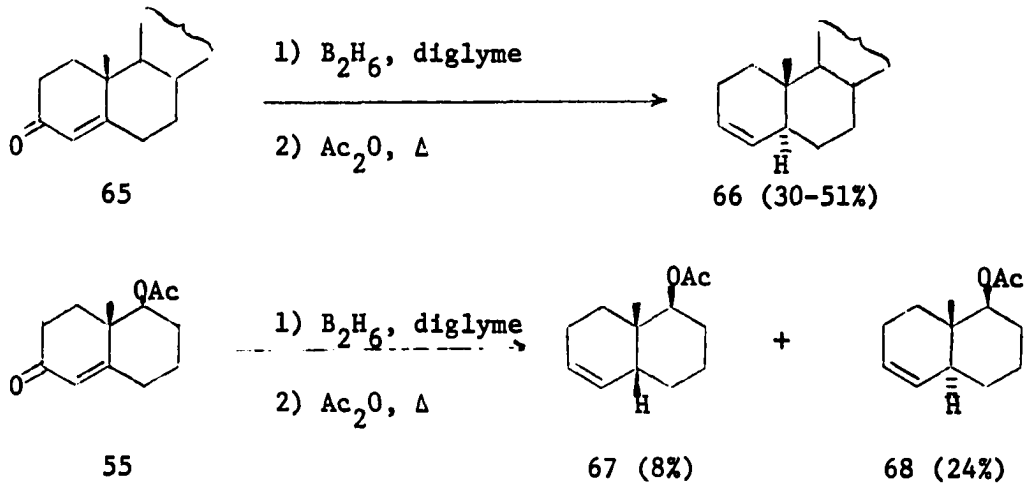


64

when the latter is axial, but is not coupled when it is equatorial. The signal due to H_c appears in the spectrum as a double doublet (J = 8 and 6 cps) centered at 4.68 ppm. The position and coupling constants of this absorption suggests its axial orientation in 64. In addition, the equatorial orientation of the acetate group in 55 has been established and this center is not affected during the reaction sequence outlined in scheme 7.

The next step in the reaction sequence called for the conversion of a 6-oxo-$\Delta^{5(10)}$-octalin system into its trans-Δ^5-octalin analog. Several methods for accomplishing this transformation in steroids are listed by Djerassi,[61] but only the hydroboration-elimination reaction described by Caglioti and coworkers[62,63] reportedly leads exclusively to trans-Δ^3-steroids in good yields. When Δ^4-cholesten-3-one (65) was treated with an excess of diborane in diglyme followed by refluxing in the presence of acetic anhydride, Δ^3-cholestene (66) was obtained in low yield (see scheme 8). Several attempts to improve the yield of Δ^3-cholestene by changing the reaction conditions resulted in only a slight increase.

When 1β-acetoxy-6-oxo-9β-methyl-$\Delta^{5(10)}$-octalin (55) was subjected to the hydroboration-elimination conditions a mixture of cis- and trans-1β-acetoxy-9β-methyl-Δ^{5}-octalin (67 and 68) was isolated by column chromatography on alumina in thirty-two percent yield. The isomers were separated by preparative gas chromatography (30% Carbowax) and identified by the following analysis of their nmr spectra.



65 66 (30-51%)

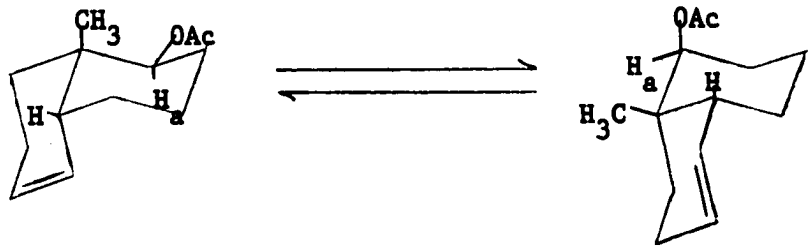
55 67 (8%) 68 (24%)

SCHEME 8

The angular methyl resonance of 5β-steroids has been shown to exhibit a downfield shift from the corresponding 5α-steroid analogs.[57] This trend has also been observed in several cis- and trans-9-methyl decalins.[58] The C_9 methyl absorption of 67 was shifted downfield (by 8 cps) from the corresponding resonance in 68. In addition, the methyl signals (0.98 and 0.85 ppm) of isomers 67 and 68 differ by only 0.02 ppm from the resonances of cis- and trans-9β-methyldecalin which are found at 0.96 and 0.83 ppm, respectively.[64] This small downfield shift found in both 67 and 68 is probably due to the combined effect

of the double bond and acetate group on the angular methyl resonance.

The absorption due to the hydrogen on the carbon bearing the acetate group in 67 was also shifted downfield (by 22 cps) from the corresponding resonance in 68, but the signal width (20 cps) was identical in both isomers. This large chemical shift with no change in signal width indicates an equilibrium mixture of cis conformers 69 and 70 is present at room temperature.

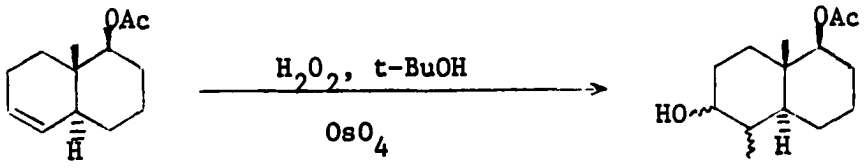


69 70

Bailey and Halsall[65] have reported the isolation of a single octalin (67 or 68) in low yield from a reaction of 1,6-dioxo-9β-methyl-$\Delta^{5(10)}$-octalin with excess lithium aluminum hydride followed by addition of boron trifluoride and subsequent heating of the organoborane mixture in acetic anhydride. Although their reported nmr spectrum is identical with that assigned to cis-1β-acetoxy-9β-methyl-Δ^5-octalin (67), they assigned structure 68 to the octalin they isolated. Unfortunately, their stereochemical assignment was based entirely on analogy to a triacetate (one of the other reaction products) and no direct chemical or spectral evidence was given to support this assignment. Even the

stereochemistry of the triacetate itself was based on ambiguous nmr evidence.

Hydroxylation of trans-1β-acetoxy-9β-methyl-Δ^5-octalin (68) with Milas' reagent[66] resulted in a mixture (by nmr and tlc) of cis diols, 71, which were not separated and identified. This lack of stereospecific formation of the α-cis diol along with the low yield of



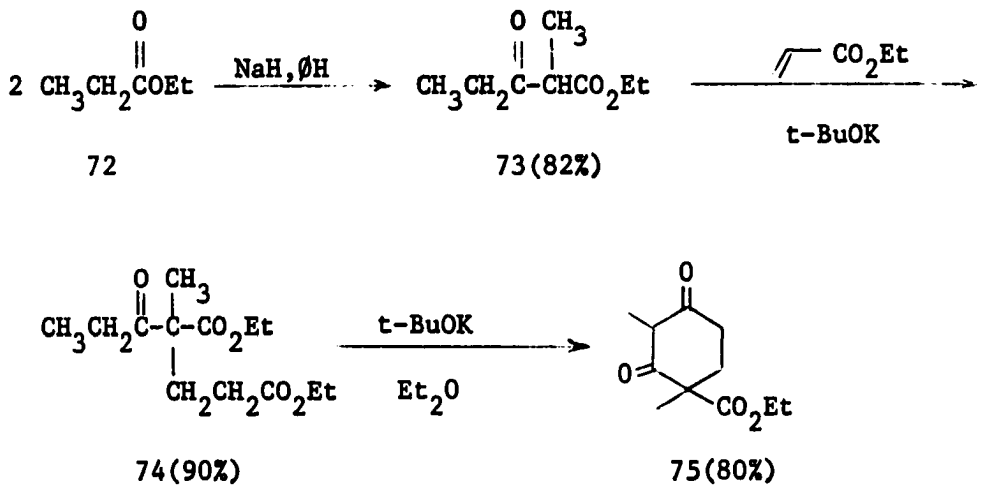
68 71

trans-1β-acetoxy-9β-methyl-Δ^5-octalin obtained in the hydroboration-elimination reaction led to the decision to abandon this phase of the original proposed synthetic route (see scheme 5, p. 11) and attempt to develop a new, more direct, pathway to 46.

The objective of this new approach was to synthesize substituted 1,3-cyclohexanedione systems which could be chemically modified and cyclized to give the appropriately substituted octalins. An important intermediate in this sequence was 2,4-dimethyl-4-carbethoxy-1,3-cyclohexanedione (75) which was prepared in good yield starting from ethyl propionate (see scheme 9).

The self-condensation of ethyl propionate in the presence of sodium hydride in benzene gave ethyl α-propionylpropionate (73). The

Michael reaction of ethyl acrylate with 73 led to a high yield of ethyl 4-methyl-4-carbethoxy-5-oxo-heptanoate (74) which was cyclized with potassium t-butoxide in ether[67] to dione 75. The nmr spectrum of 75 exhibits a vinyl methyl signal at 1.71 ppm and an exchangeable hydrogen resonance at 2.58 ppm, but no secondary methyl absorption.

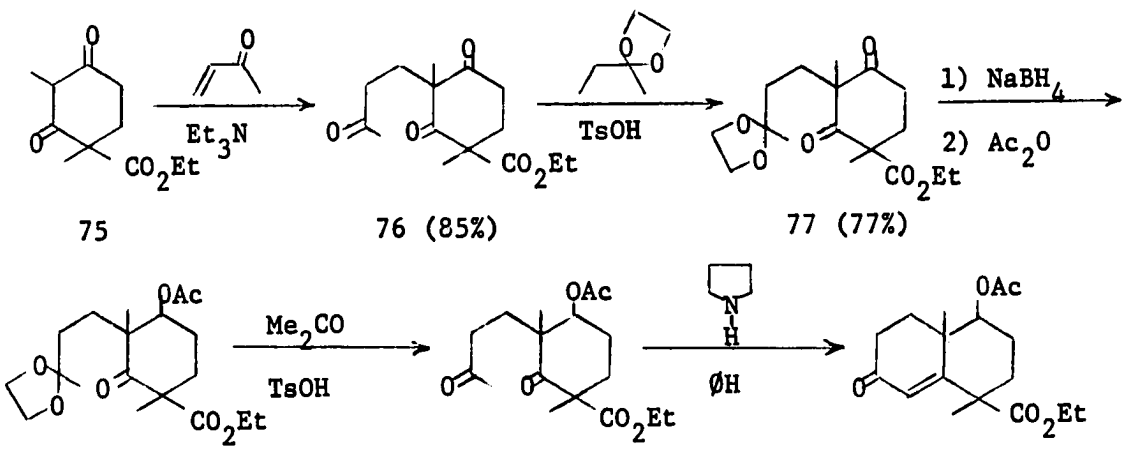


SCHEME 9

This information, along with the hydroxyl (3560 and 3220 cm^{-1}) and double bond (1620 cm^{-1}) absorptions found in the infrared spectrum, demonstrates that 75 exists almost entirely in an enolic form. This is in accord with the findings of Ananchenko and coworkers[68] for unsubstituted and monosubstituted 1,3-cyclohexanediones.

The cyclohexanedione 75 was reacted with methyl vinyl ketone (see scheme 10) in the presence of a catalytic amount of triethyl amine to give a mixture of isomeric 2,4-dimethyl-2-(butan-3-one)-4-carbethoxy-1,3-cyclohexanediones (76). This mixture when treated with

2-methyl-2-ethyl-1,3-dioxolane[69] and p-toluenesulfonic acid underwent selective ketal formation at the side chain ketone to give ketal 77. The ketal mixture was reduced with one equivalent of sodium borohydride and then acetylated with acetic anhydride in pyridine to yield the isomeric 2,6-dimethyl-2-(3-ethylenedioxybutane)-3-acetoxy-6-carbethoxy-cyclohexanones (78).



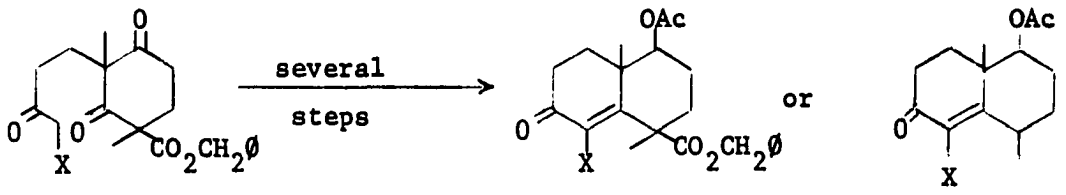
75 76 (85%) 77 (77%)

78 (87%) 79 (96%) 80 (82%)

SCHEME 10

One of the isomers of 78, which crystallized from a cold ether solution of 78, was converted to the corresponding 6-keto-$\Delta^{5(10)}$-octalin by the sequence of reactions listed in scheme 10. Exchange cleavage of the ketal moiety of 78 in acetone with p-toluenesulfonic acid gave 79 which was cyclized in the presence of pyrrolidine to 1-acetoxy-4,9β-dimethyl-4-carbethoxy-6-oxo-$\Delta^{5(10)}$-octalin (80). The stereochemistry of 80 could not be ascertained from analysis of its nmr spectrum.

The successful preparation of 80 led to speculation that other substituted 1,3-cyclohexanediones, such as 81, might undergo a similar sequence of reactions to give 82 or 83. The use of the benzyl ester would allow for its easy removal under neutral conditions by hydrogenolysis prior to cyclization. When X = OCH_3 in 81, this sequence would also constitute a convenient method for introducing the required methoxyl group at C_5 in an octalin system.

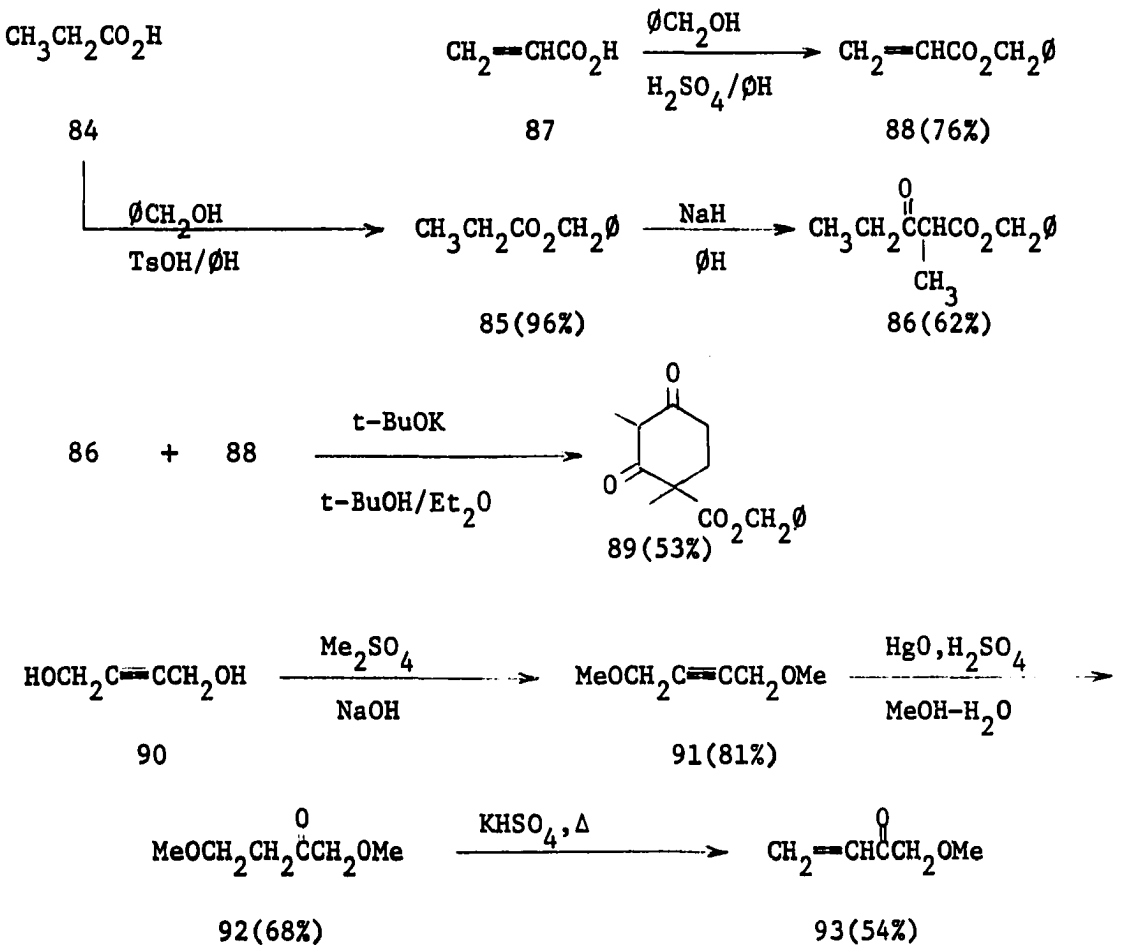


81 82 83

In order to explore this approach, 2,4-dimethyl-4-carbobenzoxy-1,3-cyclohexanedione (89) and methoxymethyl vinyl ketone (93) were prepared according to the reactions outlined in scheme 11. It is noteworthy to mention that in the preparation of benzyl acrylate (88) it was found that the use of sulfuric acid instead of p-toluenesulfonic acid greatly improved the yields (from 28 to 76%). When p-toluenesulfonic acid was used a large amount of polymer formed and only one-fourth of the theoretical amount of water was collected.

The preparation of benzyl propionate (85) followed by self-condensation using sodium hydride gave the β-keto ester 86 in good yield. The Michael reaction of 86 with benzyl acrylate (88) and

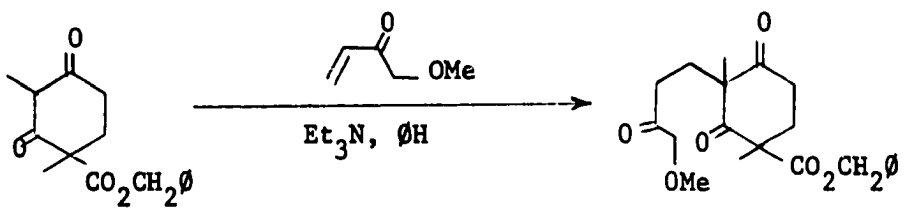
subsequent cyclization gave 89. It is interesting to note that the Michael adduct resulting from the reaction between 86 and 88 could not be prepared under the identical reaction conditions used in the preparation of its ethyl counterpart, 74. When a catalytic amount of potassium t-butoxide was used only starting materials, 86 and 88, could be isolated, but under the action of a full equivalent of base the dione 89 was formed.



SCHEME 11

Methoxymethyl vinyl ketone (93) was prepared (see scheme 11) by methylation of 1,4-dihydroxy-2-butyne (90) followed by mercuric oxide catalyzed hydration[70] to give 92, which was heated in the presence of fused potassium bisulfate to yield 93. It should be noted that when sodium acetate was used as the catalyst to convert 92 to 93, a method reported by Matsoyan and coworkers,[71] none of the vinyl ketone 93 was formed.

The Michael reaction of methoxymethyl vinyl ketone with 89 was effected with triethyl amine in benzene to give a mixture of isomeric 2,4-dimethyl-2-(4-methoxybutan-3-one)-4-carbobenzoxy-1,3-cyclohexanediones (94). Attempts to force 94 to undergo selective ketalization under conditions similar to those used in the preparation of

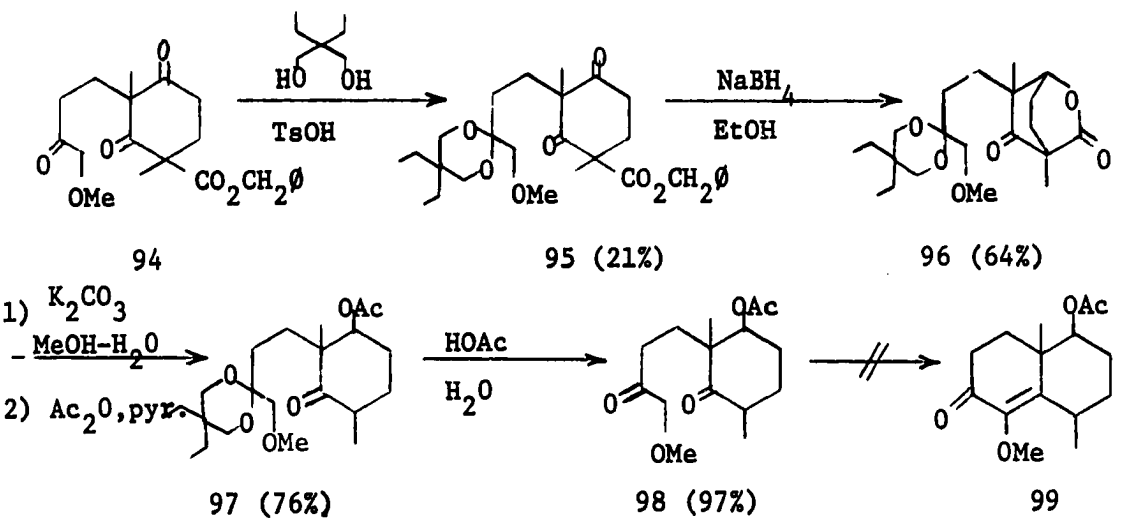


89 94 (66%)

77 (see scheme 10, p. 23) resulted in a mixture of monoketals, a diketal, and a cyclic ketol. These reaction products were inseparable by column chromatography.

In an effort to effect selective formation of the side chain ketal, an equilibrium method described by Smith and Newman[72] was used. The reaction of 94 with a large excess of 2,2-diethyl-1,3-propanediol

(see scheme 12) gave monoketal 95 in low yield. Reduction of 95 with sodium borohydride at room temperature produced lactone 96. The structure of 96 was deduced from the following spectral information.



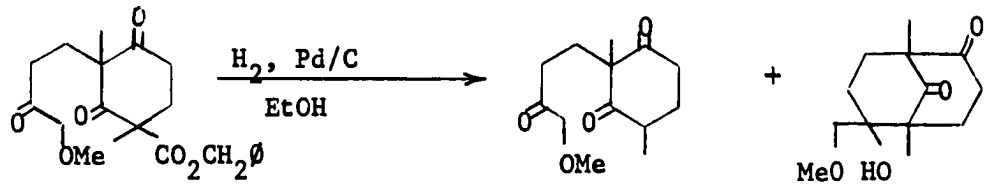
SCHEME 12

The infrared spectrum of 96 exhibited lactone (1760 cm^{-1}) and ketone (1725 cm^{-1}) absorptions. In addition, the nmr spectrum showed no aromatic or benzylic absorptions, but did have a hydrogen resonance at 4.63 ppm (t, J=2 cps) which was assigned to the structural unit $-\overset{|}{C}H-O-\overset{O}{\overset{\|}{C}}-$. The presence of two quaternary methyl signals (1.28 and 1.17 ppm) is also consistent with the assigned structure for 96. Thin layer chromatography as well as gas chromatography indicated 96 was a mixture of two isomers.

The treatment of 96 with potassium carbonate in aqueous methanol resulted in the hydrolysis of the lactone moiety followed by decarboxylation. Acetylation of the resulting alcohol led to 97 which

when heated in aqueous acetic acid to remove the ketal function gave a high yield of 98. Several attempts to cyclize 98 using potassium t-butoxide in refluxing benzene, or potassium t-butoxide in ether with t-butyl alcohol at room temperature, proved unsuccessful and none of the desired product, 99, could be isolated.

When 94 was hydrogenolyzed with palladium on charcoal under mildly acidic conditions the major product was a bicyclic ketol, 101, along with the expected triketone 100. This trend could be reversed by doing the hydrogenolysis in the presence of a small amount of



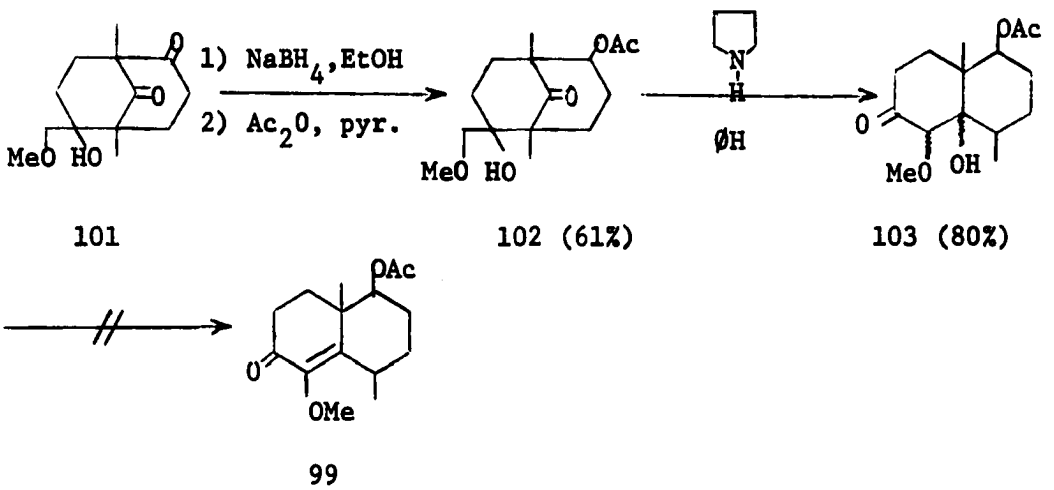
94 100 101

pyridine. Since the bicyclic ketol 101 was a potentially useful intermediate in this work, several attempts were made to find the reaction conditions that would favor exclusive formation of 101, but no trend could be observed. In fact, the yield of the bicyclic ketol would vary as much as twenty percent under seemingly identical reaction conditions.

The structure of 101 was determined from analysis of its infrared and nmr spectra. The infrared spectrum exhibited hydroxyl (3580 cm^{-1}) and ketone (1730 and 1703 cm^{-1}) absorptions. The two

carbonyl bands are in close agreement to those found for 1,5-dimethylbicyclo[3.3.1]nonane-2,9-dione[73] which occur at 1729 and 1701 cm^{-1}. The nmr spectrum of 101 showed the following important features: a two hydrogen singlet at 3.45 ppm ($-CH_2-O-CH_3$), a singlet of three hydrogens at 3.39 ppm ($-CH-O-CH_3$), and two quaternary methyl resonances at 1.22 and 1.16 ppm. This spectral evidence along with the analysis gives strong support to this structural assignment.

The bicyclic dione 101 was selectively reduced (see scheme 13) with sodium borohydride at 0° and the resulting alcohol was acetylated



101 102 (61%) 103 (80%)

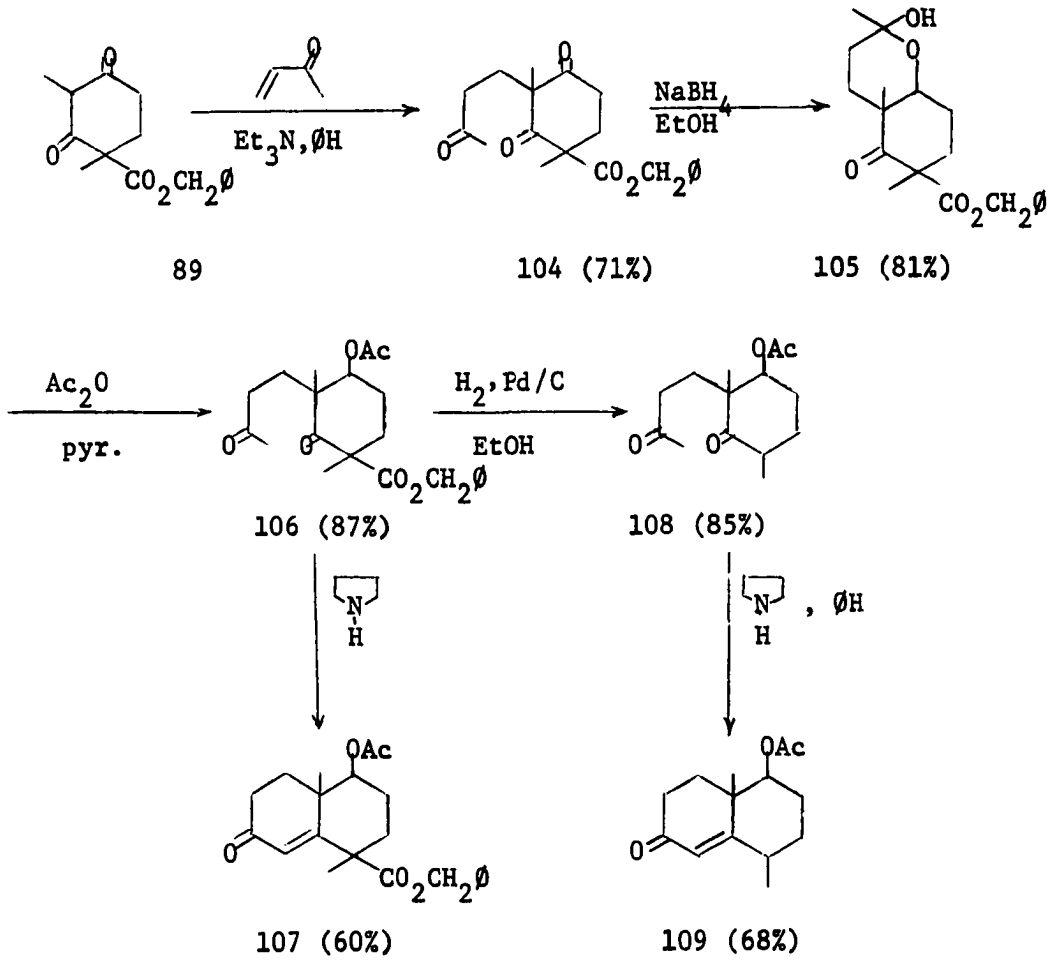
99

SCHEME 13

to give 1,5-dimethyl-2-acetoxy-6-hydroxy-6-(methoxymethyl)-bicyclo-[3.3.1]nonan-9-one (102). An attempt to open acetoxy ketol 102 with pyrrolidine in refluxing benzene showed only starting material present (glc) after an eight hour period. Addition of a small amount of potassium t-butoxide to this mixture rapidly converted 102 to 103 in

good yield. In a later experiment, 102 was refluxed for six days in the presence of pyrrolidine and 103 was isolated in good yield (84%). An attempt to dehydrate 103 with phosphorus oxychloride in pyridine failed to yield any of the desired 6-keto-$\Delta^{5(10)}$-octalin 99.

While investigating some other possible routes for the preparation of octalins, 104 was synthesized from 89 and methyl vinyl ketone (see scheme 14). Reduction of one isomer of 104 with sodium



SCHEME 14

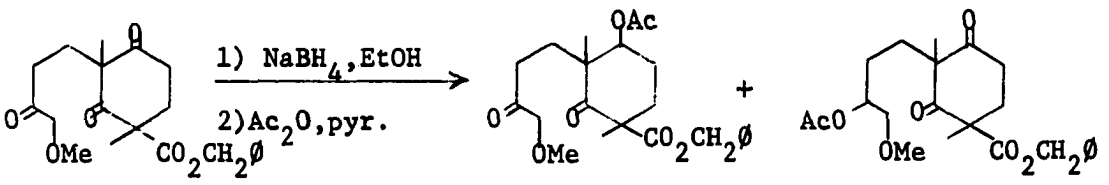
borohydride at 0° gave a hemiketal, 105, which, when treated with acetic anhydride in pyridine, underwent ring opening followed by acetylation to give 106. The following evidence was used to support the hemiketal structure assigned to the reduction product of 104. The nmr spectrum of 105 exhibited three quaternary methyl signals at 1.44, 1.13, and 1.08 ppm, but no methyl ketone resonance which was evident in either 104 or 106. The structural assignment for 105 is consistent with the observations by Hurd and Saunders[74] that 5-hydroxypentanal (110) exists almost entirely in its cyclic form, 111, at room temperature. After acetylation of 105, the methyl ketone resonance is again observed in the nmr spectrum of 106.

110 (6%) 111 (94%)

Cyclization of 106 with pyrrolidine gave 1-acetoxy-4,9β-dimethyl-4-carbobenzoxy-6-oxo-$\Delta^{5(10)}$-octalin (107). Hydrogenolysis of 106 followed by decarboxylation gave 108. The diketone 108 was cyclized to a mixture of isomeric 1-acetoxy-4,9β-dimethyl-6-oxo-$\Delta^{5(10)}$-octalins (109) under the conditions used in the preparation of 107.

Several attempts were made to utilize this selective reduction reaction to prepare 112. When the reduction was done at 0° a mixture of hemiketals analogous to 105 was formed. Reaction of this mixture with acetic anhydride in pyridine under the usual mild conditions

(overnight at room temperature) failed to effect the ring opening and subsequent acetylation. When the temperature was raised to 40° for forty-eight hours, a mixture (nmr analysis) consisting of 122 (40%)



94 112 113

and 113 (60%) was isolated. Lowering the reduction temperature to -15° had very little effect on the product distribution, but at -50° and -70° the amount of 112 increased to sixty-seven and seventy-six percent, respectively. In addition, reduction of 94 with diborane in tetrahydrofuran at -70° and subsequent acetylation produced 112 in seventy-two percent yield.

EXPERIMENTAL

All melting points and boiling points are uncorrected. All solvents were redistilled prior to use. Anhydrous tetrahydrofuran and diglyme were prepared by distillation from lithium aluminum hydride. Other anhydrous solvents were prepared by distillation from calcium hydride. Column chromatography supports were aluminum oxide (Merck AG, Darmstadt), Florisil (Floridin Co., 100/200 mesh), silicic acid (Mallinckrodt, 100 mesh), and silicAR CC-7 (Mallinckrodt, 100/200 mesh).

Thin layer chromatography was performed on 5 x 20 cm glass plates coated with silca gel H (Merck AG, Darmstadt). The developed plates were placed in iodine vapor for visualization of the chromatogram.

Gas chromatographic analyses were performed on a Varian Aerograph, Model 1220-1 or an Aerograph Autoprep, Model A-700. The infrared spectra were recorded on a Beckman IR-8 spectrophotometer. The infrared spectra were run in carbon tetrachloride or chloroform in 0.1 mm cells, or as a thin film between two sodium chloride discs. Ultraviolet spectra were recorded on a Beckman DK-1 spectrophotometer using 1.0 cm quartz cells.

Nuclear magnetic resonance (nmr) spectra were taken on a Varian A-60 spectrometer using tetramethylsilane (TMS) as an internal reference. Samples were run as neat liquids or as solutions in varying concentrations in carbon tetrachloride or deuteriochloroform. Chemical shifts are reported in δ-values (ppm from TMS) and are followed by the multiplicity of the signal, the number of hydrogens (as determined by integration of the signal), the corresponding coupling constant(s), and the assignment. The multiplicities are denoted by the symbols: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet.

Analyses were carried out by the Alfred Bernhardt Laboratories, Mülheim, Germany.

2-Methyl-1,3-cyclohexanedione (41). The procedure of Sircar and Meyers,[45] and Newman and coworkers[46] was used. Commercial grade resorcinol (110.1 g, 1.0 mol) and sodium hydroxide (48.0 g, 1.2 mol) were dissolved in 200 ml of water, and 5% rhodium on alumina (5.0 g) was added. The mixture was hydrogenated in a Parr apparatus at 50-60 psi until the uptake of one molar equivalent of hydrogen was complete (72 hours). The catalyst was removed by filtration and the excess sodium hydroxide (0.2 mol) neutralized by the addition of concentrated hydrochloric acid (16.7 ml, 0.2 mol) to the filtrate.

Dioxane (75 ml) and methyl iodide (170 g, 1.2 mol) were added to the filtrate, and the mixture was refluxed for six hours. Additional

methyl iodide (17 g, 0.12 mol) was added and the mixture refluxed for another eight hours. The reaction mixture was then cooled in an ice bath for several hours and the resulting white solid filtered. The solid was washed with cold water and dried in a vacuum oven at 60° for several hours to yield 2-methyl-1,3-cyclohexanedione as a white solid (72.4 g, 57.4%), mp 207-208° with decomposition (lit.[46] mp 208-210° dec.).

1,6-Dioxo-9β-methyl-$\Delta^{5(10)}$-octalin (42). The procedure of Ramachandran and Newman[47] was used. A mixture of 2-methyl-1,3-cyclohexanedione (252.3 g, 2.0 mol), methyl vinyl ketone (210.4 g, 3.02 mol), five pellets of potassium hydroxide, and 800 ml of absolute methanol was refluxed for six hours. The reaction mixture was allowed to cool and the methanol and excess methyl vinyl ketone were removed under reduced pressure at room temperature.

Benzene (1 liter) was added to the residue, the flask was fitted with a Dean-Stark water separator, and 100 ml of benzene was distilled. The mixture was allowed to cool, pyrrolidine (6 ml) was added, and the mixture was refluxed until water formation had ceased (35 ml of water, 4 hours). The reaction mixture was then cooled, diluted with 500 ml of ether, and washed with 2% hydrochloric acid and water. After drying over anhydrous magnesium sulfate, the solvents were removed under vacuum on a rotary evaporator to give a dark orange residue which was distilled. The fraction collected at 131-143°/ 0.6 mm (284 g) was recrystallized several times from ether to give

1,6-dioxo-9β-methyl-$\Delta^{5(10)}$-octalin as a white solid (239 g, 67%), mp 51-52° (lit.[47] mp 48.6-50.0°). The infrared spectrum (CCl_4) showed significant bands at 1720 (saturated ketone), 1680 (unsaturated ketone), and 1620 cm^{-1} (conjugated double bond). The nmr spectrum ($CDCl_3$) showed signals at δ 5.88 (m, 1, vinyl hydrogen), 1.65-3.18 (m, 10, $-CH_2-$), and 1.46 ppm (s, 3, quaternary methyl).

2-Methyl-2-ethyl-1,3-dioxolane. The procedure of Dauben and coworkers[69] was used. A mixture of 2-butanone (360.5 g, 5.0 mol), ethylene glycol (310.5 g, 5.0 mol), p-toluenesulfonic acid monohydrate (2.5 g), and 500 ml of benzene was placed in a flask equipped with a Dean-Stark water separator. The mixture was refluxed for two days during which time 90 ml of water was collected. The reaction mixture was cooled, anhydrous sodium carbonate (10 g) was added, and the product distilled through a spinning band column collecting pure 2-methyl-2-ethyl-1,3-dioxolane at 112-114° (473 g, 81.5%), n_D^{25} 1.4097 (lit.[69] bp 116.5-117°, $n_D^{24.8}$ 1.4087).

3-Ethylenedioxy-Δ^5-cholestene. A solution of Δ^4-cholesten-3-one (19.23 g, 0.05 mol), ethylene glycol (60 ml), and p-toluenesulfonic acid monohydrate (0.5 g) in 300 ml of benzene was refluxed for seventy hours while collecting the water (3 ml) by means of a Dean-Stark separator. The reaction mixture was cooled and pyridine (2 ml) was added. The benzene solution was washed with dilute sodium bicarbonate, water, and dried over anhydrous sodium sulfate. Removal of

the benzene under vacuum on a rotary evaporator gave a light yellow solid (23.63 g) which was recrystallized twice from absolute ethanol to yield 3-ethylenedioxy-Δ^5-cholestene as a white solid (13.50 g, 63%), mp 133.5-134° (lit.[75] mp 133°). The nmr spectrum (CCl_4) showed signals at δ 5.21 (m, 1, vinyl hydrogen), 3.82 (s, 4, $-CH_2O-$), and 0.68-2.68 ppm (m, 43, CH_3-, $-CH_2-$, and $-\overset{|}{C}H-$).

Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.10; H, 11.10.

1-Oxo-6-ethylenedioxy-9β-methyl-Δ^4-octalin (54). The procedure followed was that of Dauben and coworkers.[69] To a solution of 1,6-dioxo-9β-methyl-$\Delta^{5(10)}$-octalin (8.91 g, 0.05 mol) dissolved in 50 ml of 2-methyl-2-ethyl-1,3-dioxolane, was added p-toluenesulfonic acid monohydrate (0.1 g). The reaction mixture was heated and the liberated 2-butanone was distilled slowly through a Claisen-Vigreux column for two hours (collected 4.5 ml, bp 75-77°). The mixture was cooled, and pyridine (0.2 ml) and benzene (50 ml) were added. The organic phase was washed with 5% sodium bicarbonate, water, and dried over anhydrous sodium sulfate. Removal of the solvents gave a yellow oil (11.04 g) which was dissolved in ether and cooled in an ice bath to give a light yellow solid. The solid was recrystallized several times from ether to yield 1-oxo-6-ethylenedioxy-9β-methyl-Δ^4-octalin as a white solid (4.0 g, 36.2%), mp 68-69°. The infrared spectrum (CCl_4) showed significant bands at 1715 (saturated ketone), and 1088 and 1104 cm^{-1} (ether). The nmr spectrum (CCl_4) showed signals at δ

5.48 (m, 1, vinyl hydrogen), 3.86 (s, 4, $-O-CH_2CH_2-O-$), 2.42 (m, 4, allylic hydrogens), 2.22 (m, 2, $-CH_2\overset{O}{\overset{\|}{C}}-$), 1.68 (m, 4, $-CH_2-$), and 1.24 ppm (s, 3, quaternary methyl).

1β-Hydroxy-6-oxo-9β-methyl-$\Delta^{5(10)}$-octalin. The procedure used was that of Boyce and Whitehurst.[76] A solution of sodium borohydride (1.12 g, 28.7 mmol) in 300 ml of absolute ethanol was added dropwise to a solution of 1,6-dioxo-9β-methyl-$\Delta^{5(10)}$-octalin (17.82 g, 0.10 mol) in 150 ml of absolute ethanol at 0°. The addition was complete in eighty minutes and the solution was stirred an additional twenty minutes. Acetic acid was added until the mixture was acidic and most of the ethanol was removed under vacuum on a rotary evaporator to give a light orange residue. The residue was dissolved in chloroform, washed with water until neutral, and dried over anhydrous sodium sulfate. The chloroform was removed and the residue distilled, collecting 1β-hydroxy-6-oxo-9β-methyl-$\Delta^{5(10)}$-octalin at 143-144°/0.15 mm (15.01 g, 84%) (lit.[76] bp 140°/0.25 mm). The infrared spectrum (CCl_4) showed significant bands at 3420 (hydroxyl), 1660 (unsaturated ketone), and 1620 cm^{-1} (conjugated double bond). The nmr spectrum ($CDCl_3$) showed signals at δ 5.79 (d, 1, J=1 cps, vinyl hydrogen), 3.43 (m, 1, $-\overset{O}{\overset{|}{C}}H-$), 3.18 (d, 1, J=5 cps, -OH), 1.50-2.62 (m, 10, $-CH_2-$), and 1.20 ppm (s, 3, quaternary methyl).

1β-Acetoxy-6-oxo-9β-methyl-$\Delta^{5(10)}$-octalin (55). Acetic anhydride (90 ml, 0.96 mol) was added to a solution of 1β-hydroxy-6-oxo-9β-methyl-$\Delta^{5(10)}$-octalin (30.54 g, 0.17 mol) in 120 ml of

anhydrous pyridine and the mixture stirred overnight at room temperature. The mixture was poured into ice water, diluted with benzene, and the phases separated. The organic phase was washed with 5% hydrochloric acid until washes were acidic, then with water, and dried over anhydrous sodium sulfate. The benzene was removed under vacuum on a rotary evaporator to give a light yellow solid (37.84 g), which was recrystallized twice from hexane to yield 1β-acetoxy-6-oxo-9β-methyl-$\Delta^{5(10)}$-octalin as a white solid (32.0 g, 85%), mp 90-91° (lit.[76] mp 89°). The infrared spectrum (CCl_4) showed significant bands at 1745 (acetate carbonyl), 1680 (unsaturated ketone), 1620 (conjugated double bond), and 1235 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CCl_4$) showed signals at δ 5.68 (d, 1, J=1 cps, vinyl hydrogen), 4.62 (dd, 1, J=10 and 5 cps, $-\overset{OAc}{\overset{|}{C}}H-$), 1.45-2.52 (m, 10, $-CH_2-$), 2.01 (s, 3, $-O-\overset{O}{\overset{\|}{C}}CH_3$), and 1.24 ppm (s, 3, quaternary methyl).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.28; H, 8.31.

1β-Acetoxy-6-ethylenedioxy-9β-methyl-Δ^4-octalin (56). The procedure followed was that of Dauben and coworkers.[69] To a solution of 1β-acetoxy-6-oxo-9β-methyl-$\Delta^{5(10)}$-octalin (2.22 g, 0.01 mol) dissolved in 20 ml of 2-methyl-2-ethyl-1,3-dioxolane was added p-toluenesulfonic acid monohydrate (0.1 g). The reaction mixture was heated and the liberated 2-butanone was distilled slowly through a Claisen-Vigreux column for one and one-half hours (2 ml were collected, bp 70-80°). The reaction mixture was cooled, pyridine (0.2 ml) added,

and the resulting solution poured into a separatory funnel containing saturated sodium chloride. The mixture was extracted with ether and dried over anhydrous sodium sulfate. Removal of the ether gave a light yellow oil which was chromatographed on Florisil (60 g) beginning with benzene and progressing through 20% ethyl acetate-benzene to yield 1β-acetoxy-6-ethylenedioxy-9β-methyl-Δ^4-octalin as a white solid (1.82 g, 68.5%), mp. 102-103.5°. The infrared spectrum (CCl_4) showed significant bands at 1730 (acetate carbonyl), 1240 ($CH_3\overset{O}{\overset{\|}{C}}-OR$), and 1210 and 1100 cm^{-1} (cyclic ketal). The nmr spectrum (CCl_4) showed signals at δ 5.23 (m, 1, vinyl hydrogen), 4.71 (dd, 1, J=9.5 and 5.5 cps, $-\overset{OAc}{\overset{|}{C}}H-$), 3.83 (s, 4, $-CH_2O-$), 1.32-2.41 (m, 10, $-CH_2-$), 1.98 (s, 3, $-O-\overset{O}{\overset{\|}{C}}CH_3$), and 1.12 ppm (s, 3, quaternary methyl). A small sample was recrystallized from hexane for analysis, mp 104-105°.

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.68; H, 8.28.

1β-Hydroxy-6-ethylenedioxy-9β-methyl-Δ^4-octalin (57). To a solution of 1β-acetoxy-6-ethylenedioxy-9β-methyl-Δ^4-octalin (1.00 g, 3.8 mmol) dissolved in 50 ml methanol, was added anhydrous potassium carbonate (1.00 g, 7.2 mmol) along with enough water to make the reaction mixture homogeneous. The solution was refluxed for one hour, cooled to room temperature, and then acetic acid was added until the solution was neutral. The methanol was removed under vacuum on a rotary evaporator and ethyl acetate was added. The organic phase was washed with saturated sodium chloride and dried over anhydrous sodium

sulfate. Removal of the solvents under vacuum on a rotary evaporator gave a light yellow oil (0.876 g) which was chromatographed on Florisil (30 g) in 10% ethyl acetate-benzene. Fractions 2 and 3 contained 1β-hydroxy-6-ethylenedioxy-9β-methyl-Δ^4-octalin as a colorless oil (0.817 g, 96%). The infrared spectrum ($CHCl_3$) showed significant bands at 3620 and 3490 (hydroxyl), 1660 (double bond), and 1210 and 1095 cm^{-1} (cyclic ketal). The nmr spectrum ($CDCl_3$) showed signals at δ 5.28 (m, 1, vinyl hydrogen), 3.91 (s, 4, $-CH_2O-$), 3.52 (t, 1, J=7 cps, $-\overset{OH}{C}H-$), 3.15 (s, 1, -OH), 1.32-2.54 (m, 10, $-CH_2-$), and 1.06 ppm (s, 3, quaternary methyl).

1β-Acetoxy-6-methoxy-9β-methyl-1,2,3,7,8,9-hexahydronaphthalene (58). The procedure was essentially that of Ercoli and coworkers.[77] A mixture of 1β-acetoxy-6-oxo-9β-methyl-$\Delta^{5(10)}$-octalin (11.12 g, 0.05 mol), 40 ml of trimethyl orthoformate, 25 ml of anhydrous tetrahydrofuran, and 2 ml of anhydrous methanol was treated with p-toluenesulfonic acid monohydrate (50 mg). The reaction mixture was stirred at room temperature for three and one-half hours and then pyridine (0.5 ml) was added. The solvents were removed under vacuum on a rotary evaporator to give a light yellow solid which was recrystallized from hexane (containing a drop of pyridine) to yield 1β-acetoxy-6-methoxy-9β-methyl-1,2,3,7,8,9-hexahydronaphthalene as a white solid (9.80 g, 83%), mp 79-80°. The infrared spectrum (CCl_4) showed significant bands at 2840 ($-OCH_3$), 1735 (acetate carbonyl), 1650 and 1625 (conjugated diene), and 1235 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CDCl_3$) showed

signals at δ 5.20 (m, 2, vinyl hydrogens), 4.79 (dd, 1, J=9 and 7 cps, -CH(OAc)-), 3.56 (s, 3, $-OCH_3$), 1.20-2.50 (m, 8, $-CH_2-$), 2.03 (s, 3, $-O-\overset{O}{\overset{\|}{C}}CH_3$), and 1.07 ppm (s, 3, quaternary methyl).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.31; H, 8.69.

1β-Acetoxy-4-formyl-6-methoxy-9β-methyl-1,2,3,7,8,9-hexahydronaphthalene (59). The procedure used was that of Williamson and coworkers.[50] A solution of phosphorus oxychloride (5.1 ml, 55 mmol) in 85 ml of anhydrous ethylene dichloride was added over a one hour period to a solution of anhydrous dimethyl formamide (6.5 ml, 84 mmol) in 25 ml of ethylene dichloride at 0°. The mixture was stirred for twenty minutes at 0° and a solution of 1β-acetoxy-6-methoxy-9β-methyl-1,2,3,7,8,9-hexahydronaphthalene (9.80 g, 42 mmol) and 1 ml of pyridine in 70 ml of ethylene dichloride was added rapidly to the preformed Vilsmeier reagent. The resulting dark red mixture was allowed to warm to room temperature over a two hour period. A solution of sodium acetate trihydrate (30 g, 0.24 mol) in 250 ml of water was added rapidly to the reaction mixture and stirred for fifteen minutes while cooling in an ice bath. The reaction mixture was diluted with ether and the phases separated. The organic phase was washed with water until the water phase remained colorless, and then dried over anhydrous sodium sulfate. Removal of the solvents under vacuum on a rotary evaporator gave a yellow solid (9.92 g) which was recrystallized from 50% benzene-hexane to yield 1β-acetoxy-4-formyl-

6-methoxy-9β-methyl-1,2,3,7,8,9-hexahydronaphthalene as a white solid (8.90 g, 80%), mp 142-143.5°. The infrared spectrum ($CHCl_3$) showed significant bands at 1735 (acetate carbonyl), 1660 (aldehyde carbonyl), 1610 and 1620 (conjugated diene), and 1230 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CDCl_3$) showed signals at δ 10.23 (s, 1, -CHO), 6.34 (s, 1, vinyl hydrogen), 4.77 (dd, 1, J=10.5 and 5.5 cps, $-\overset{OAc}{\overset{|}{C}}H-$), 3.70 (s, 3, $-OCH_3$), 1.40-2.68 (m, 8, $-CH_2-$), 2.07 (s, 3, $-O-\overset{O}{\overset{\|}{C}}CH_3$), and 1.18 ppm (s, 3, quaternary methyl).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.85; H, 7.67.

1β-Acetoxy-4-hydroxymethyl-6-methoxy-9β-methyl-1,2,3,7,8,9-hexahydronaphthalene (60). A solution of sodium borohydride (0.331 g, 8.49 mmol) in 100 ml of absolute ethanol was added dropwise to a solution of 1β-acetoxy-4-formyl-6-methoxy-9β-methyl-1,2,3,7,8,9-hexahydronaphthalene (7.46 g, 28.3 mmol) in 75 ml of absolute ethanol at room temperature. The addition was complete in thirty minutes and the orange solution was stirred an additional fifteen minutes. Acetic acid (0.5 ml) was added and the ethanol was removed under vacuum on a rotary evaporator. The residue was dissolved in ether-chloroform, washed with water until neutral, and dried over anhydrous sodium sulfate. Removal of the solvents under vacuum on a rotary evaporator gave 1β-acetoxy-4-hydroxymethyl-6-methoxy-9β-methyl-1,2,3,7,8,9-hexahydronaphthalene as a light yellow oil (8.21 g), which was not further purified. Thin layer chromatography (R_f 0.25, 30% ethyl

acetate-benzene, silica gel H) indicated only trace amounts of impurities. The infrared spectrum ($CHCl_3$) showed significant bands at 3460 (hydroxyl), 1730 (acetate carbonyl), 1645 and 1615 (conjugated diene), and 1230 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CDCl_3$) showed signals at δ 5.53 (s, 1, vinyl hydrogen), 4.77 (dd, 1, J=8 and 7.5 cps, $-\overset{OAc}{\overset{|}{C}}H-$), 4.15 (d, 2, J=2.5 cps, $-CH_2-OH$), 3.62 (s, 3, $-OCH_3$), 1.18-2.67 (m, 9, $-CH_2-$ and -OH), 2.05 (s, 3, $-O-\overset{O}{\overset{\|}{C}}CH_3$), and 1.08 ppm (s, 3, quaternary methyl).

1β-Acetoxy-4-methylene-6-oxo-9β-methyl-$\Delta^{5(10)}$-octalin (61).

A solution of 1β-acetoxy-4-hydroxymethyl-6-methoxy-9β-methyl-1,2,3,7,8,9-hexahydronaphthalene (8.21 g of crude product) in 150 ml of acetic acid-water (8:2) was heated in an oil bath at 90-100° for a thirty minute period. The reaction mixture was then poured into ice water and extracted with ether. The ether phase was washed with water, dilute sodium bicarbonate, and again with water. After drying over anhydrous sodium sulfate, the ether was removed under vacuum on a rotary evaporator to yield 1β-acetoxy-4-methylene-6-oxo-9β-methyl-$\Delta^{5(10)}$-octalin as a light yellow oil (5.84 g) which could not be further purified by either column chromatography or distillation. Thin layer chromatography (R_f 0.39, 30% ethyl acetate-benzene, silica gel H) indicated only trace amounts of impurities. The infrared spectrum ($CHCl_3$) showed significant bands at 1730 (acetate carbonyl), 1660 (unsaturated ketone), 1600 (conjugated double bond), and 1225 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CDCl_3$) showed signals at δ 5.98 (s, 1,

vinyl hydrogen), 5.22 (m, 1, exo methylene hydrogen), 5.06 (m, 1, exo methylene hydrogen), 4.81 (dd, 1, J=10 and 5 cps, -CH(OAc)-), 1.34-2.68 (m, 8, $-CH_2-$), 2.08 (s, 3, $-O-\overset{O}{\overset{\|}{C}}CH_3$), and 1.21 ppm (s, 3, quaternary methyl).

Hydrogenation of 1β-acetoxy-4-methylene-6-oxo-9β-methyl-$\Delta^{5(10)}$-octalin (61). A solution of 1β-acetoxy-4-methylene-6-oxo-9β-methyl-$\Delta^{5(10)}$-octalin (5.56 g of crude product) in 120 ml of absolute methanol was hydrogenated at atmospheric pressure over 5% palladium on charcoal (0.2 g). Hydrogenation was interrupted after hydrogen uptake had almost ceased (4 hours). The mixture was filtered and the methanol removed under vacuum on a rotary evaporator to give a light yellow oil (5.58 g). Thin layer chromatography (30% ethyl acetate-benzene, silica gel H) indicated two major products (R_f 0.40 and 0.51) had been formed.

The mixture was chromatographed on silicic acid (300 g, 4.2 x 42 cm) in 10% ethyl acetate-benzene. Fractions 22-39 contained 1β-acetoxy-4β,9β-dimethyl-6-decalone (2.18 g, a mixture of cis and trans isomers) which was further purified by bulb-to-bulb distillation (120°/0.10 mm) to yield a colorless liquid (1.94 g). The isomers were separated by preparative gas chromatography (20' x 3/8" 30% Carbowax on 45/60 Chromsorb P and a column temperature of 240°). The first component was a light yellow oil (734 mg) which was further purified by bulb-to-bulb distillation (110°/0.05 mm) to yield cis-1β-acetoxy-4β,9β-dimethyl-6-decalone (62) along with an impurity that was evident from vinyl hydrogen absorption in the nmr spectrum. The pure cis isomer

was obtained by further preparative gas chromatography (10' x 3/8" 30% SE-30 on 45/60 Chromsorb P and a column temperature of 195°) followed by bulb-to-bulb distillation. The infrared spectrum (CCl_4) showed significant bands at 1735 (acetate carbonyl), 1715 (ketone), and 1235 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CCl_4$) showed signals at δ 4.70 (t, 1, J=2.5 cps, $-\overset{OAc}{\overset{|}{C}}H-$), 1.30-2.67 (m, 12, $-CH_2-$ and $-\overset{|}{C}H-$), 2.03 (s, 3, $-O-\overset{O}{\overset{\|}{C}}CH_3$), 1.22 (s, 3, quaternary methyl), and 0.96 ppm (d, 3, J=3 cps, secondary methyl).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.40; H, 9.16.

The second component was a light yellow solid (274 mg) which was recrystallized several times from hexane to yield trans-1β-acetoxy-4β,9β-dimethyl-6-decalone (63) as a white solid, mp 75.5-76.2°. The infrared spectrum (CCl_4) showed significant bands at 1735 (acetate carbonyl), 1720 (ketone), and 1235 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CCl_4$) showed signals at δ 4.48 (m, 1, $-\overset{OAc}{\overset{|}{C}}H-$), 1.28-2.60 (m, 12, $-CH_2-$ and $-\overset{|}{C}H-$), 1.97 (s, 3, $-O-\overset{O}{\overset{\|}{C}}CH_3$), 1.18 (s, 3, quaternary methyl), and 0.97 ppm (d, 3, J=6 cps, secondary methyl).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.22; H, 9.23.

Fractions 42-67 contained 1β-acetoxy-4β,9β-dimethyl-6-oxo-$\Delta^{5(10)}$-octalin (64) which was further purified by bulb-to-bulb distillation (140°/0.05 mm) to yield a light yellow oil (1.35 g). The infrared spectrum ($CHCl_3$) showed significant bands at 1730 (acetate carbonyl), 1665 (unsaturated ketone), 1610 (conjugated double bond),

and 1225 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CDCl_3$) showed signals at δ 5.83 (s, 1, vinyl hydrogen), 4.68 (dd, 1, J=8 and 6 cps, $-\overset{OAc}{\overset{|}{C}}H-$), 1.57-2.92 (m, 9, $-CH_2-$ and $-\overset{|}{C}H-$), 2.08 (s, 3, $-O-\overset{O}{\overset{\|}{C}}CH_3$), 1.37 (s, 3, quaternary methyl), and 1.27 ppm (d, 3, J=7.5 cps, secondary methyl). After standing for several weeks in a stoppered flask, the oil crystallized. Recrystallization from benzene afforded 1β-acetoxy-4,9β-dimethyl-4-hydroperoxy-6-oxo-$\Delta^{5(10)}$-octalin as a white solid, mp 144-145.2° with decomposition. A dilute ethanol solution exhibited a positive test for the peroxide linkage with potassium iodide-starch test paper. The infrared spectrum ($CHCl_3$) showed significant bands at 3540 and 3320 (hydroxyl), 1730 (acetate carbonyl), 1670 (unsaturated ketone), 1610 (conjugated double bond), and 1230 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CDCl_3$) showed signals at δ 6.10 (s, 1, vinyl hydrogen), 4.69 (t, 1, J=5 cps, $-\overset{OAc}{\overset{|}{C}}H-$), 1.56-2.70 (m, 9, $-CH_2-$ and -OH), 2.08 (s, 3, $-O-\overset{O}{\overset{\|}{C}}CH_3$), 1.46 (s, 3, quaternary methyl), and 1.42 ppm (s, 3, quaternary methyl).

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.88; H, 7.52.

Δ^3-Cholestene (66). The procedure used was similar to that of Caglioti and coworkers.[62,63] A solution of diborane in tetrahydrofuran (100 ml of 1 M in BH_3) was added over a twenty minute period to a solution of Δ^4-cholesten-3-one (3.85 g, 0.01 mol) in 70 ml of anhydrous diglyme at 0° under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for two hours and acetic anhydride (60 ml) was added slowly to the mixture. The tetrahydrofuran was

removed under a vacuum on a rotary evaporator and the resulting mixture was refluxed for four hours. Most of the diglyme was removed under vacuum on a rotary evaporator at 80°. The residue was dissolved in ether, washed with water, 10% sodium hydroxide, and again with water until neutral. After drying over anhydrous sodium sulfate, the ether was removed to give a dark brown oil (4.62 g). Chromatography on neutral alumina (160 g of activity III) in hexane gave an off-white solid (1.87 g) which was recrystallized from methanol-acetone to yield Δ^3-cholestene as a white solid (1.25 g, 33.6%), mp 69-70.5° (lit.[78] mp 72-73°). The nmr spectrum ($CDCl_3$) showed signals at δ 5.44 (m, 2, vinyl hydrogens) and 0.68-2.58 ppm (m, 44, CH_3-, -CH_2-, and -CH-).

Anal. Calcd for $C_{27}H_{46}$: C, 87.49; H, 12.51. Found: C, 87.72; H, 12.49.

Cis- and trans-1β-acetoxy-9β-methyl-Δ^5-octalins (67,68).

The procedure used was the same as was described for the preparation of Δ^3-cholestene. Reaction of 1β-acetoxy-6-oxo-9β-methyl-$\Delta^{5(10)}$-octalin (4.45 g, 0.02 mol) with diborane in tetrahydrofuran (43 ml of 1.4 M in BH_3), and subsequent treatment with acetic anhydride (45 ml) afforded a brown oil (4.51 g). The oil was chromatographed on neutral alumina (160 g of activity III) in hexane. Fractions 2 and 3 contained both isomers (0.718 g), fraction 4 contained mostly trans olefin (0.282 g), and fractions 5-8 gave pure trans olefin (0.302 g). Fractions 2 and 3 were combined and the isomers separated by preparative gas chromatography (20' x 3/8" 30% Carbowax on 45/60 Chromsorb P and a

column temperature of 180°). The first component was a light yellow oil (165 mg) which was further purified by bulb-to-bulb distillation (90°/0.5 mm) to yield cis-1β-acetoxy-9β-methyl-Δ^5-octalin (67) as a colorless oil. The infrared spectrum (film) showed significant bands at 1732 (acetate carbonyl) and 1240 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CCl_4$) showed signals at δ 5.51 (m, 2, vinyl hydrogens), 4.87 (m, 1, $-\overset{OAc}{\overset{|}{C}}H-$), 1.07-2.33 (m, 11, $-CH_2-$ and $-\overset{|}{C}H-$), 1.95 (s, 3, $-O-\overset{O}{\overset{\|}{C}}CH_3$), and 0.98 ppm (s, 3, quaternary methyl).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.77; H, 9.87.

The second component was also a light yellow oil (230 mg) which was further purified by bulb-to-bulb distillation (85°/0.9 mm) to yield trans-1β-acetoxy-9β-methyl-Δ^5-octalin (68) as a colorless oil. The infrared spectrum (film) showed significant bands at 1730 (acetate carbonyl), and 1238 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CCl_4$) showed signals at δ 5.42 (m, 2, vinyl hydrogens), 4.51 (m, 1, $-\overset{OAc}{\overset{|}{C}}H-$), 1.03-2.28 (m, 11, $-CH_2-$ and $-\overset{|}{C}H-$), 1.94 (s, 3, $-O-\overset{O}{\overset{\|}{C}}CH_3$), and 0.85 ppm (s, 3, quaternary methyl).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.86; H, 9.79.

The infrared and nmr spectra of the combined column chromatography fractions 5-8 were identical with the spectra of trans-1β-acetoxy-9β-methyl-Δ^5-octalin obtained from preparative gas chromatography of fractions 2 and 3.

Ethyl α-propionylpropionate (73). Sodium hydride (53.0 g of a 50% oil suspension, 1.1 mol) was introduced into a modified 500 ml three-neck round bottom flask[79] equipped with a trubore stirrer, an addition funnel, and a condenser with a nitrogen inlet tube. The sodium hydride was washed free of oil with anhydrous benzene. To the sodium hydride suspension in 150 ml of benzene under nitrogen, was added 1.0 ml of absolute ethanol followed by the addition of ethyl propionate (102.2 g, 1.0 mol) over a three hour period at reflux. After addition of the ethyl propionate was complete, the yellow mixture was refluxed for four and one-half hours and then cooled in an ice bath while ethanol was added slowly to destroy the excess sodium hydride. Aqueous acetic acid (150 ml containing 90 ml of acetic acid) was added and the phases were separated. The aqueous phase was extracted with benzene and the combined organic phases were washed with dilute sodium bicarbonate, saturated sodium chloride, and dried over anhydrous magnesium sulfate. The benzene was removed on a rotary evaporator and the remaining yellow liquid was distilled through a spinning band column to yield ethyl α-propionylpropionate as a colorless liquid (64.84 g, 84%), bp 83-84°/12 mm, n_D^{25} 1.4205 (lit.[80] bp 87-88°/16 mm). The infrared spectrum (film) showed significant bands at 1735 (ester), and 1715 cm^{-1} (ketone). The nmr spectrum (neat) showed signals at δ 4.16 (q, 2, J=7 cps, $-\overset{O}{\overset{\|}{C}}O-\underline{CH_2}-CH_3$), 3.60 (q, 1, J=7 cps, methine hydrogen), 2.60 (q, 2, J=7 cps, $CH_3-\underline{CH_2}-\overset{O}{\overset{\|}{C}}-R$), 1.24 (d, 3, J=7 cps, secondary methyl), 1.21 (t, 3, J=7 cps, $-\overset{O}{\overset{\|}{C}}-OCH_2-\underline{CH_3}$), and 0.99 ppm (t, 3, J=7 cps, $-\overset{O}{\overset{\|}{C}}CH_2-\underline{CH_3}$).

Ethyl 4-methyl-4-carbethoxy-5-oxo-heptanoate (74). To a suspension of potassium t-butoxide (1.1 g, 0.01 mol) and t-butyl alcohol (47.5 ml, 0.50 mol) in 500 ml of anhydrous ether was added ethyl α-propionylpropionate (64.8 g, 0.41 mol). Ethyl acrylate (54 ml, 0.50 mol) was added, dropwise, to the reaction mixture over a two hour period and the solution was then refluxed for four hours. The mixture was cooled, acidified with dilute acetic acid, and the phases were separated. The organic phase was washed with 5% sodium bicarbonate, water, and dried over anhydrous magnesium sulfate. The ether was removed on a rotary evaporator and the remaining liquid was distilled to yield ethyl 4-methyl-4-carbethoxy-5-oxo-heptanoate as a colorless liquid (94.7 g, 90%), bp 116-117°/1.0 mm, n_D^{20} 1.4435. The infrared spectrum (film) showed significant bands at 1730 (ester), and 1710 cm^{-1} (ketone). The nmr spectrum (neat) showed signals at δ 4.19 (q, 2, J=7 cps, $-\overset{O}{\overset{\|}{C}}O-\underline{CH_2}-CH_3$), 4.08 (q, 2, J=7 cps, $-\overset{O}{\overset{\|}{C}}O-\underline{CH_2}-CH_3$), 2.50 (q, 2, J=7 cps, $CH_3-\underline{CH_2}-\overset{O}{\overset{\|}{C}}-R$), 2.08-2.30 (m, 4, $-CH_2\underline{CH_2}\overset{O}{\overset{\|}{C}}-O-$), 1.31 (s, 3, quaternary methyl), 1.24 (t, 3, J=7 cps, $-\overset{O}{\overset{\|}{C}}OCH_2-\underline{CH_3}$), 1.21 (t, 3, J=7 cps, $-\overset{O}{\overset{\|}{C}}OCH_2-\underline{CH_3}$), and 1.00 ppm (t, 3, J=7 cps, $\underline{CH_3}-CH_2\overset{O}{\overset{\|}{C}}-R$).

2,4-Dimethyl-4-carbethoxy-1,3-cyclohexanedione (75). The procedure used was essentially that of Mikherji and coworkers.[67] To a suspension of potassium (2.15 g, 0.055 g-atoms) in 100 ml of anhydrous ether under nitrogen, was added t-butyl alcohol (5.7 ml, 0.06 mol) and the ether refluxed until all the potassium had reacted. A solution of ethyl 4-methyl-4-carbethoxy-5-oxo-heptanoate (12.92 g, 0.05 mol) in

50 ml of ether was added, dropwise, and the mixture was stirred overnight at room temperature under a nitrogen atmosphere. The mixture was acidified with dilute hydrochloric acid and the phases were separated. The ether phase was washed with saturated sodium chloride until neutral, dried over anhydrous sodium sulfate, and the ether was removed on a rotary evaporator to give a light yellow solid (10.26 g), mp 88-96°. The solid was recrystallized from cyclohexane-benzene to yield 2,4-dimethyl-4-carbethoxy-1,3-cyclohexanedione as a white solid (8.34 g, 79%), mp 97-100°. The infrared spectrum ($CHCl_3$) showed significant bands at 3560 and 3220 (hydroxyl), 1725 (ester), 1710 (ketone), and 1620 cm^{-1} (conjugated double bond). The nmr spectrum (CCl_4) showed signals at δ 4.14 (q, 2, J=7 cps, $-\overset{O}{\overset{\|}{C}}O-\underline{CH_2}-CH_3$), 1.59-2.86 (m, 4, $-CH_2-$), 2.58 (s, 1, -OH), 1.71 (s, 3, vinyl methyl), 1.36 (s, 3, quaternary methyl), and 1.23 ppm (t, 3, J=7 cps, $-\overset{O}{\overset{\|}{C}}OCH_2-\underline{CH_3}$). A small sample was recrystallized from ether-hexane for analysis, mp 99.5-101°.

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.26; H, 7.60. Found: C, 62.43; H, 7.43.

2,4-Dimethyl-2-(butan-3-one)-4-carbethoxy-1,3-cyclohexanedione (76). To a solution of 2,4-dimethyl-4-carbethoxy-1,3-cyclohexanedione (4.25 g, 0.02 mol) and methyl vinyl ketone (2.80 g, 0.04 mol) in 50 ml of anhydrous benzene, was added triethyl amine (10 drops). The mixture was stirred at room temperature under nitrogen for twenty-nine hours. The reaction mixture was diluted with more benzene, washed with saturated

sodium chloride, and dried over anhydrous sodium sulfate. The benzene was removed under reduced pressure on a rotary evaporator and the product was distilled to yield 2,4-dimethyl-2-(butan-3-one)-4-carbethoxy-1,3-cyclohexanedione as a light yellow liquid (4.79 g, 85%), bp 126-129°/0.06 mm. Gas chromatography analysis (5' x 1/8" 15% FFAP on 60/80 Chromosorb W and a column temperature of 200°) showed two major components (A, 11.8 min., ∿40% and B, 13.0 min., ∿60%). The infrared spectrum (film) showed significant bands at 1720 (ester) and 1700 cm^{-1} (ketone). The nmr spectrum (CCl_4) showed signals at δ 4.13 and 4.20 (q, 2, J=7 cps, $-\overset{O}{\overset{\|}{C}}O-\underline{CH_2}-CH_3$), 1.68-2.90 (m, 8, $-CH_2-$), 2.04 (s, 3, $-\overset{O}{\overset{\|}{C}}CH_3$), 1.35 and 1.39 (s, 3, quaternary methyl), 1.22 and 1.28 (t, 3, J=7 cps, $-\overset{O}{\overset{\|}{C}}OCH_2-\underline{CH_3}$), and 1.20 ppm (s, 3, quaternary methyl).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.69; H, 7.56.

2,4-Dimethyl-2-(3-ethylenedioxybutane)-4-carbethoxy-1,3-cyclohexanedione (77). To a solution of a mixture of 2,4-dimethyl-2-(butan-3-one)-4-carbethoxy-1,3-cyclohexanedione (4.89 g, 17.3 mmol) in 2-methyl-2-ethyl-1,3-dioxolane (60 ml) was added p-toluenesulfonic acid monohydrate (0.1 g). The mixture was refluxed while following ketal formation by gas chromatography analysis (5' x 1/8" 15% FFAP on 60/80 Chromosorb W and a column temperature of 210°). The reaction was essentially complete after two hours and pyridine (a few drops) was added to neutralize the p-toluenesulfonic acid. Most of the 2-methyl-2-ethyl-1,3-dioxolane was removed under vacuum on a rotary evaporator,

then benzene was added, and the organic phase was washed with water until neutral. After drying the organic phase over anhydrous sodium sulfate, the solvents were removed under vacuum on a rotary evaporator to give a light yellow oil (5.03 g). Vacuum distillation of this oil using a short path distillation head gave 2,4-dimethyl-2-(3-ethylenedioxybutane)-4-carbethoxy-1,3-cyclohexanedione as a light yellow oil (4.34 g, 77%), bp 155-162°/0.03 mm. The infrared spectrum (film) showed significant bands at 1725 (ester) and 1700 cm^{-1} (ketone). The nmr spectrum (CCl_4) showed signals at δ 4.12 and 4.16 (q, 2, J=7 cps, $-\overset{O}{\overset{\|}{C}}O-\underline{CH_2}-CH_3$), 3.83 (s, 4, $-OCH_2CH_2O-$), 1.42-2.80 (m, 8, $-CH_2-$), 1.37 (s, 3, quaternary methyl), 1.16 and 1.25 (t, 3, J=7 cps, $-\overset{O}{\overset{\|}{C}}OCH_2-\underline{CH_3}$). and 1.19 ppm (s, 6, quaternary methyls).

2,6-Dimethyl-2-(3-ethylenedioxybutane)-3-acetoxy-6-carbethoxycyclohexanone (78). A solution of 2,4-dimethyl-2-(3-ethylenedioxybutane)-4-carbethoxy-1,3-cyclohexanedione (4.34 g, 0.013 mol) in 30 ml of absolute ethanol under nitrogen was cooled in an ice bath and a solution of sodium borohydride (148 mg, 3.8 mmol) in 15 ml of absolute ethanol was added over a fifteen minute period. The reaction mixture was stirred an additional fifteen minutes, then acetic acid (0.9 ml, 0.015 mol) was added, and the ethanol was removed under vacuum on a rotary evaporator. The residue was dissolved in ether and the resulting solution was washed with 5% sodium bicarbonate, then water, and dried over anhydrous sodium sulfate. Removal of the ether left a light yellow oil (4.02 g, 92%). Thin layer chromatography

(R_f 0.37, 50% ethyl acetate-benzene, silica gel H) indicated only trace amounts of impurities were present. The infrared spectrum (film) showed significant bands at 3480 (hydroxyl), 1725 (ester), and 1700 cm^{-1} (ketone).

The alcohol (4.02 g) was dissolved in pyridine (20 ml), acetic anhydride (11.2 g, 0.11 mol) was added, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with water and ether, and the phases were separated. The ether phase was washed with 5% hydrochloric acid, 5% sodium bicarbonate, water, and dried over anhydrous sodium sulfate. Removal of the ether gave 2,6-dimethyl-2-(3-ethylenedioxybutane)-3-acetoxy-6-carbethoxycyclohexanone as a light yellow oil (3.79 g, 87% overall yield). Thin layer chromatography (R_f 0.54, 50% ethyl acetate-benzene, silica gel H) indicated only trace amounts of impurities were present. The infrared spectrum (film) showed significant bands at 1730 (ester), 1710 (ketone), and 1240 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CCl_4$) showed signals at δ 4.75 (m, 1, $-\overset{OAc}{\overset{|}{C}}H-$), 4.12 (q, 2, $-\overset{O}{\overset{\|}{C}}O-\underline{CH_2}-CH_3$), 3.85 (s, 4, $-OCH_2CH_2O-$), 1.40-2.75 (m, 8, $-CH_2-$), 2.02 (s, 3, $-O\overset{O}{\overset{\|}{C}}CH_3$), and 1.02-1.30 ppm (m, 12, methyl hydrogens).

The crude product was dissolved in 25 ml of ether and cooled in a Dry Ice-acetone bath to give a solid which was recrystallized from hexane to yield one isomer as a white solid (0.897 g), mp 77-78°. The infrared spectrum (CCl_4) showed significant bands at 1735 (ester), 1710 (ketone), and 1235 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CCl_4$) showed signals at δ 4.71 (dd, 1, J=10 and 5 cps, $-\overset{OAc}{\overset{|}{C}}H-$), 4.09 (q, 2, J=7 cps,

$-\overset{O}{\overset{\|}{C}}O-CH_2-CH_3$), 3.85 (s, 4, $-OCH_2CH_2O-$), 1.42-2.72 (m, 8, $-CH_2-$), 2.02 (s, 3, $-O\overset{O}{\overset{\|}{C}}CH_3$), 1.25 (t, 3, J=7 cps, $-\overset{O}{\overset{\|}{C}}OCH_2-CH_3$), 1.25 (s, 3, quaternary methyl), 1.20 (s, 3, quaternary methyl), and 1.03 ppm (s, 3, quaternary methyl).

Anal. Calcd for $C_{19}H_{30}O_7$: C, 61.60; H, 8.16. Found: C, 61.75; H, 8.01.

Exchange cleavage of 2,6-dimethyl-2-(3-ethylenedioxybutane)-3-acetoxy-6-carbethoxycyclohexanone (78). To a solution of 2,6-dimethyl-2-(3-ethylenedioxybutane)-3-acetoxy-6-carbethoxycyclohexanone (370 mg, 1.0 mmol) in 20 ml of anhydrous acetone was added a few crystals of p-toluenesulfonic acid monohydrate, and the mixture stirred at room temperature for forty-eight hours. The acetone was removed on a rotary evaporator, ether was added, and the organic phase was washed with saturated sodium chloride. After drying the organic phase over anhydrous sodium sulfate, the ether was removed to give a colorless oil (321 mg, 98%). The oil was chromatographed on Florisil (15 g, 1.5 x 18 cm) beginning with benzene and progressing through 10% ethyl acetate-benzene. Fractions 9 and 11-22 gave 2,6-dimethyl-2-(butan-3-one)-3-acetoxy-6-carbethoxycyclohexanone (79) as a colorless oil (279 mg). Fraction 10 (33 mg) was used as an analytical sample. The infrared spectrum (CCl_4) showed significant bands at 1735 (ester), 1710 (ketone), and 1230 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CCl_4$) showed signals at δ 4.68 (dd, 1, J=10 and 5 cps, $-\overset{OAc}{\overset{|}{C}}H-$), 4.05 (q, 2, J=7 cps, $-\overset{O}{\overset{\|}{C}}O-CH_2-CH_3$), 1.50-2.72 (m, 8, $-CH_2-$), 2.06 (s, 3, $-\overset{O}{\overset{\|}{C}}CH_3$), 2.02 (s, 3, $-O\overset{O}{\overset{\|}{C}}CH_3$), 1.25

(t, 3, J=7 cps, $-\overset{O}{\overset{\|}{C}}OCH_2-\underline{CH_3}$), 1.23 (s, 3, quaternary methyl), and 0.99 ppm (s, 3, quaternary methyl).

Anal. Calcd for $C_{17}H_{26}O_6$: C, 62.56; H, 8.03. Found: C, 62.98; H, 7.91.

1-Acetoxy-4,9β-dimethyl-4-carbethoxy-6-oxo-$\Delta^{5(10)}$-octalin (80). To a solution of crude 2,6-dimethyl-2-(butan-3-one)-3-acetoxy-6-carbethoxycyclohexanone (279 mg, 0.86 mmol) in 15 ml of anhydrous benzene was added pyrrolidine (0.10 ml, 1.2 mmol). The mixture was refluxed under a nitrogen atmosphere using a Soxhlet extractor filled with molecular sieve (Linde, 3 A) to remove the water. The reaction was followed by gas chromatography analysis (2' x 1/8" 3% JXR on Gas-Chrom Q and a column temperature of 150-170°) and was complete after sixty-eight hours. The mixture was cooled, diluted with ether, and washed twice with dilute hydrochloric acid. Concentrated hydrochloric acid (3 ml) was added to the combined acid washings and these were then extracted twice with ether. The combined ether extracts were washed with saturated sodium chloride, and dried over anhydrous sodium sulfate. Removal of the solvents under vacuum on a rotary evaporator gave an orange oil (25 mg) which by gas chromatography analysis consisted of starting material along with its impurities. After standing overnight, the combined acid washings were made basic by adding solid sodium hydroxide pellets. The basic solution was extracted with ethyl acetate and the organic phase was dried over anhydrous sodium sulfate. Removal of the ethyl acetate under vacuum on a rotary evaporator gave

a yellow oil (216 mg) which was chromatographed on Florisil (8 g) beginning with benzene and progressing through 10% ethyl acetate-benzene. Fractions 7, 8, and 9 were combined to give a light yellow solid (123 mg) which was recrystallized from hexane to yield pure 1-acetoxy-4,9β-dimethyl-4-carbethoxy-6-oxo-$\Delta^{5(10)}$-octalin as a white solid (87 mg), mp 88-89°, uv max (95% ethanol) 240 mμ (ε_{max} 15,300). The infrared spectrum (CCl_4) showed significant bands at 1730 (ester), 1680 (unsaturated ketone), 1600 (conjugated double bond), and 1235 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CCl_4$) showed signals at δ 5.66 (s, 1, vinyl hydrogen), 4.77 (t, 1, J=3 cps, $-\overset{OAc}{\overset{|}{C}}H-$), 4.17 (q, 2, J=7 cps, $-\overset{O}{\overset{\|}{C}}O-\underline{CH_2}-CH_3$), 1.52-2.68 (m, 8, $-CH_2-$), 1.99 (s, 3, $-O\overset{O}{\overset{\|}{C}}CH_3$), 1.45 (s, 3, quaternary methyl), 1.41 (s, 3, quaternary methyl), and 1.28 ppm (t, 3, J=7 cps, $-\overset{O}{\overset{|}{C}}OCH_2-\underline{CH_3}$).

Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.39; H, 7.95.

Fractions 6 and 10-13 contained impure 1-acetoxy-4,9-dimethyl-4-carbethoxy-6-oxo-$\Delta^{5(10)}$-octalin (52 mg).

Benzyl propionate (85). To a solution of propionic acid (756 g, 10 mol) and benzyl alcohol (1081 g, 10 mol) dissolved in 800 ml of benzene was added p-toluenesulfonic acid monohydrate (2 g). The mixture was refluxed for eleven hours while removing the water (174 ml) with a Dean-Stark separator. The reaction mixture was cooled, transferred to a separatory funnel, and washed with dilute sodium bicarbonate, then with saturated sodium chloride, and dried over anhydrous

magnesium sulfate. The benzene was removed under vacuum on a rotary evaporator and the remaining liquid was distilled to yield benzyl propionate as a colorless liquid (1571 g, 96%), bp 103-106°/11 mm, n_D^{20} 1.4985 (lit.[81] bp 222°). The infrared spectrum (film) showed significant bands at 3090, 3060, and 3030 (aromatic), 1735 (ester), and 1600, 1495, and 1450 cm^{-1} (aromatic). The nmr spectrum (CCl_4) showed signals at δ 7.22 (s, 5, aromatic hydrogens), 5.02 (s, 2, benzylic hydrogens), 2.27 (q, 2, J=7 cps, $-\overset{O}{\overset{\|}{C}}-\underline{CH_2}-CH_3$), and 1.08 ppm (t, 3, J=7 cps, $-\overset{O}{\overset{\|}{C}}CH_2-\underline{CH_3}$).

Benzyl α-propionylpropionate (86). The procedure used was the same as was described for the preparation of ethyl α-propionylpropionate. Benzyl propionate (493 g, 3.0 mol), sodium hydride (150 g of a 50% oil suspension, 3.1 mol), and benzyl alcohol (1.0 ml) in 800 ml of anhydrous benzene were refluxed for an additional fourteen hours after the addition of the benzyl propionate was complete (six hours). The resulting yellow suspension was cooled in an ice bath and acetic acid (210 ml) was added slowly. Water was then added to dissolve the salts, the phases were separated, and the aqueous phase was extracted with benzene. The combined benzene extracts were washed with dilute sodium bicarbonate, then water, and dried over anhydrous sodium sulfate. The benzene was removed under vacuum on a rotary evaporator and most of the benzyl alcohol was removed by distillation through a short Vigreux column to yield a colorless liquid (158 g), bp 84-88°/5 mm. Spinning band column distillation of the remaining liquid afforded pure benzyl

α-propionylpropionate as a colorless liquid (203 g, 62%), bp 95-96°/ 0.2 mm, n_D^{20} 1.4992. The infrared spectrum (film) showed significant bands at 3090, 3060, and 3030 (aromatic), 1740 (ester), 1710 (ketone), and 1600, 1495, and 1450 cm^{-1} (aromatic). The nmr spectrum (neat) showed signals at δ 7.25 (s, 5, aromatic hydrogens), 5.09 (s, 2, benzylic hydrogens), 3.54 (q, 1, J=7 cps, methine hydrogen), 2.42 (q, 2, J=7 cps, $-\overset{O}{\overset{\|}{C}}-\underline{CH_2}-CH_3$), 1.25 (d, 3, J=7 cps, secondary methyl), and 0.91 ppm (t, 3, J=7 cps, $-\overset{O}{\overset{\|}{C}}CH_2-\underline{CH_3}$).

Benzyl acrylate (88). To a solution of acrylic acid (79 g, 1.1 mol) and benzyl alcohol (108 g, 1.0 mol) in 500 ml of benzene was added concentrated sulfuric acid (0.5 ml). The mixture was refluxed for eight hours while removing the water (17.5 ml) by means of a Dean-Stark separator. The mixture was then cooled to room temperature, transferred to a separatory funnel, and washed twice with water. After drying over anhydrous sodium sulfate, the benzene was removed under vacuum on a rotary evaporator and the product distilled through a short Vigreux column to yield benzyl acrylate as a colorless liquid (122 g, 76%), bp 64-67°/1.0 mm, n_D^{26} 1.5165 (lit.[82] bp 110-118°/8 mm). The infrared spectrum (film) showed significant bands at 3090, 3060, and 3030 (aromatic), 1720 (ester), 1630 (conjugated double bond), and 1615 and 1495 cm^{-1} (aromatic). The nmr spectrum (CCl_4) showed signals at δ 7.24 (s, 5, aromatic hydrogens), 5.58-6.31 (m, 3, vinyl hydrogens), and 5.08 ppm (s, 2, benzylic hydrogens).

2,4-Dimethyl-4-carbobenzoxy-1,3-cyclohexanedione (89). To a solution of anhydrous t-butyl alcohol (75 ml) in 300 ml of anhydrous ether was added potassium (17.6 g, 0.45 g-atom) in a dry nitrogen atmosphere. The suspension was refluxed overnight, then cooled to room temperature, and a solution of benzyl α-propionylpropionate (88.1 g, 0.40 mol) and benzyl acrylate (73.0 g, 0.45 mol) in 100 ml of anhydrous ether was added over a three hour period. The resulting light yellow suspension was stirred at room temperature for two days, then cooled in an ice bath, and acetic acid (30 ml, 0.5 mol) was slowly added followed by enough water to dissolve the salts. The phases were separated and the ether layer was washed with dilute sodium bicarbonate, saturated sodium chloride, and dried over anhydrous sodium sulfate. The ether was removed on a rotary evaporator and the yellow residue recrystallized from benzene-cyclohexane (1:2) to yield 2,4-dimethyl-4-carbobenzoxy-1,3-cyclohexanedione (57.6 g, 53%) as a white solid, mp 98-99°. The infrared spectrum ($CHCl_3$) showed significant bands at 3560 and 3240 (hydroxyl), 1725 (ester), 1710 (ketone), and 1625 cm^{-1} (conjugated double bond). The nmr spectrum ($CDCl_3$) showed signals at δ 7.28 (s, 5, aromatic hydrogens), 5.14 (s, 2, benzylic hydrogens), 1.50-2.80 (m, 4, $-CH_2-$), 1.76 (s, 3, vinyl methyl), and 1.42 ppm (s, 3, quaternary methyl).

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 70.02; H, 6.76.

1,4-Dimethoxy-2-butyne (91). The procedure followed was that of Hennion and Kupiecki.[70] To a solution of 1,4-dihydroxy-2-butyne (86.0 g, 1.0 mol) in 200 ml of water at 0° was added dimethyl sulfate (378.0 g, 3.0 mol) along with small portions of solid sodium hydroxide (120.0 g, 3.0 mol) over a three hour period. After addition was complete, the mixture was heated on a steam bath for two hours, then cooled in an ice bath, and transferred to a separatory funnel. Water was added to dissolve the salts and the layers were separated. The aqueous phase was extracted several times with ether, and the combined organic extracts dried over anhydrous potassium carbonate. The ether was removed on a rotary evaporator and the remaining orange liquid distilled to yield 1,4-dimethoxy-2-butyne as a colorless liquid (92.7 g, 81%), bp 71-72°/30 mm, n_D^{25} 1.4328 (lit.[70] bp 72-73°/30 mm, n_D^{25} 1.4321). The infrared spectrum (film) showed significant bands at 2830 ($-OCH_3$), and 1095 cm^{-1} (ether). The nmr spectrum (neat) showed signals at δ 4.12 (s, 4, $-CH_2O-$), and 3.32 ppm (s, 6, $-OCH_3$).

1,4-Dimethoxy-2-butanone (92). The procedure used was that of Hennion and Kupiecki.[70] A solution of 1,4-dimethoxy-2-butyne (92.6 g, 0.81 mol) in 50 ml of methanol was added slowly to a stirred suspension of red mercuric oxide (3.0 g) in 150 ml cf 70% aqueous methanol containing concentrated sulfuric acid (3.0 g). The temperature rose slowly to 50° during the addition and was maintained between 50-55° by cooling in a water bath. After the butyne addition was complete, another portion of mercuric oxide (1.0 g) was added, and the mixture

was allowed to cool to room temperature. Sodium acetate (5.5 g) was added while stirring and the salts were allowed to settle overnight. The salts were filtered, and most of the methanol and water were removed under vacuum on a rotary evaporator. The liquid residue was diluted with benzene and dried over anhydrous sodium sulfate. The benzene was removed and the remaining liquid distilled to give a colorless liquid (76.61 g), bp 83-87°/20 mm. The product was redistilled to yield 1,4-dimethoxy-2-butanone as a colorless liquid (72.3 g, 68%), bp 85-87°/20 mm, n_D^{20} 1.4202 (lit.[70] bp 84-85°/19 mm, n_D^{25} 1.4198). The infrared spectrum (film) showed significant bands at 2820 ($-OCH_3$), 1725 (ketone), and 1110 cm^{-1} (ether). The nmr spectrum (neat) showed signals at δ 3.98 (s, 2, $-\overset{O}{\overset{\|}{C}}CH_2O-$), 3.58 (t, 2, J=6 cps, $-\overset{O}{\overset{\|}{C}}CH_2-\underline{CH_2}O-$), 3.33 (s, 3, $-OCH_3$), 3.24 (s, 3, $-OCH_3$), and 2.26 ppm (t, 2, J=6 cps, $-\overset{O}{\overset{\|}{C}}-\underline{CH_2}-CH_2O-$).

Methoxymethyl vinyl ketone (93). The apparatus consisted of a Claisen-Vigreux distilling column with condenser (℣ 14/20) that was equipped with a pressure equalizing addition funnel, a thermometer, a 50 ml round bottom reaction flask, and a vacuum adapter with a 100 ml round bottom receiver flask. To freshly fused potassium bisulfate (4 g), at an oil bath temperature of 135°, was added dropwise 1,4-dimethoxy-2-butanone (87 g, 0.66 mol) at a rate such that the distillation temperature did not exceed 90° under 100 mm of pressure. Additional freshly fused potassium bisulfate was added periodically throughout the reaction period (eight hours). The methanol was removed

from the product under vacuum on a rotary evaporator at room temperature and the remaining liquid distilled to yield methoxymethyl vinyl ketone (36 g, 54%), bp 45-48°/20 mm, n_D^{20} 1.4320 (lit.[71] bp 47-50°/25 mm, n_D^{20} 1.4305). The infrared spectrum (film) showed significant bands at 2820 ($-OCH_3$), 1690 (unsaturated ketone), and 1610 cm^{-1} (conjugated double bond). The nmr spectrum (neat) showed signals at δ 5.73-6.57 (m, 3, vinyl hydrogens), 4.23 (s, 2, $-\overset{O}{\overset{\|}{C}}-CH_2-O-$), and 3.37 ppm (s, 3, $-OCH_3$).

2,4-Dimethyl-2-(4-methoxybutan-3-one)-4-carbobenzoxy-1,3-cyclohexanedione (94). The procedure was the same as was used in the preparation of 2,4-dimethyl-2-(butan-3-one)-4-carbethoxy-1,3-cyclohexanedione. To a solution of 2,4-dimethyl-4-carbobenzoxy-1,3-cyclohexanedione (54.3 g, 0.20 mol) and methoxymethyl vinyl ketone (24.0 g, 0.24 mol) in 400 ml of anhydrous benzene was added triethyl amine (1 ml). The mixture was stirred overnight at room temperature under a nitrogen atmosphere. The benzene was removed under vacuum on a rotary evaporator and ether was added followed by dilute hydrochloric acid. The phases were separated and the ether phase was washed with water, dilute sodium bicarbonate, water, and dried over anhydrous sodium sultate. Removal of the solvents gave a light yellow oil (43.9 g, 66%). A sample (10 g) was chromatographed on silicAR CC-7 (100 g, 100/200 mesh) beginning with benzene and progressing through 10% ether-benzene. Fractions 2-4 contained pure 2,4-dimethyl-2-(4-methoxybutan-3-one)-4-carbobenzoxy-1,3-cyclohexanedione as a colorless oil (6.8 g).

The infrared spectrum (CCl_4) showed significant bands at 3090, 3070, and 3040 (aromatic), 2820 ($-OCH_3$), 1725 (ester), and 1710 cm^{-1} (ketone). The nmr spectrum ($CDCl_3$) showed signals at δ 7.28 and 7.26 (s, 5, aromatic hydrogens), 5.05 and 5.12 (s, 2, benzylic hydrogens), 3.69 and 3.81 (s, 2, $-\overset{O}{\overset{\|}{C}}-\underline{CH_2}-OCH_3$), 3.24 and 3.30 (s, 3, $-OCH_3$), 1.60-2.88 (m, 8, $-CH_2-$), 1.35 and 1.38 (s, 3, quaternary methyl), and 1.10 and 1.17 ppm (s, 3, quaternary methyl).

Anal. Calcd for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.56; H, 6.98.

The remainder of the product was chromatographed on silicAR CC-7 (250 g, 100/200 mesh) beginning with benzene and progressing through 10% ether-benzene to yield 2,4-dimethyl-2-(4-methoxybutan-3-one)-4-carbobenzoxy-1,3-cyclohexanedione as a light yellow oil (35.7 g).

Selective ketalization of 2,4-dimethyl-2-(4-methoxybutan-3-one)-4-carbobenzoxy-1,3-cyclohexanedione (94) using 2,2-diethyl-1,3-propanediol. The procedure used was similar to that of Smith and Newman.[72] To a solution of 2,4-dimethyl-2-(4-methoxybutan-3-one)-4-carbobenzoxy-1,3-cyclohexanedione (3.74 g, 0.01 mol) in 300 ml of anhydrous monoglyme was added 2,2-diethyl-1,3-propanediol (13.2 g, 0.10 mol) and p-toluenesulfonic acid monohydrate (0.2 g). The mixture was heated in an oil bath at 50° for sixty-seven hours. Triethyl amine (1 ml) was added to neutralize the acid and the monoglyme was removed under vacuum on a rotary evaporator. The residue was dissolved in ether and the ether solution was washed several times with water and

dried over anhydrous sodium sulfate. Removal of the ether gave a light yellow liquid (10.5 g) which was filtered through Florisil (100 g) in benzene to yield a colorless oil (3.89 g). Analysis by thin layer chromatography and nmr indicated very little reaction had occurred.

The reaction was repeated on the above material (3.89 g) using a greater quantity of 2,2-diethyl-1,3-propanediol (19.8 g, 0.15 mol) and p-toluenesulfonic acid monohydrate (0.4 g). The mixture was stirred for seventy-five hours at 50° and worked up in the same manner as before to give a colorless oil (3.97 g). Thin layer chromatography (50% ethyl acetate-benzene, silica gel H) indicated four components (R_f 0.37, 0.43, 0.57, and 0.68) were present. The oil was chromatographed on Florisil (160 g, 3.5 x 36 cm) beginning with benzene and progressing through 10% ethyl acetate-benzene. Fractions 40-48 gave pure 2,4-dimethyl-2-[3,3-(2,2-diethyltrimethylenedioxy)-4-methoxybutane]-4-carbobenzoxy-1,3-cyclohexanedione (95) as a colorless oil (1.02 g, 21%). Fraction 46 was used as an analytical sample and exhibited the following spectral properties. The infrared spectrum ($CHCl_3$) showed significant bands at 1735 (ester), 1720 (ketone), and 1700 cm^{-1} (ketone). The nmr spectrum ($CDCl_3$) showed signals at δ 7.32 (s, 5, aromatic hydrogens), 5.11 and 5.16 (s, 2, benzylic hydrogens), 3.52 (s, 4, $-OCH_2\overset{|}{C}CH_2O-$), 3.34 (broad s, 5, $-CH_2OCH_3$), 1.60-2.80 (m, 12, $-CH_2-$), 1.38 and 1.43 (s, 3, quaternary methyl), 1.21 and 1.27 (s, 3, quaternary methyl), and 0.78 ppm (t, 6, J=7 cps, $\underline{CH_3}CH_2-$).

Anal. Calcd for $C_{28}H_{40}O_7$: C, 68.83; H, 8.25. Found: C, 68.66; H, 8.07.

Reduction and acetylation of 2,4-dimethyl-2-[3,3-(2,2-diethyltrimethylenedioxy)-4-methoxybutane]-4-carbobenzoxy-1,3-cyclohexanedione (95). A solution of 2,4-dimethyl-2-[3,3-(2,2-diethyltrimethylenedioxy)-4-methoxybutane]-4-carbobenzoxy-1,3-cyclohexanedione (0.927 g, 1.9 mmol) in 15 ml of absolute ethanol under nitrogen was cooled to 0° in an ice bath and a solution of sodium borohydride (21 mg, 0.55 mmol) in 10 ml of absolute ethanol was added over a fifteen minute period. After addition was complete, the mixture was stirred at 0° for forty-five minutes, then several drops of acetic acid were added, and the ethanol was removed under vacuum on a rotary evaporator. The residue was dissolved in ether and the ether solution was washed with 5% sodium hydroxide, then water, and dried over anhydrous sodium sulfate. Thin layer chromatography analysis indicated that the reduction was incomplete. The ether was removed, the residue was dissolved in 15 ml of absolute ethanol, and a solution of sodium borohydride (15 mg) in 5 ml of absolute ethanol was added over a ten minute period at room temperature. The mixture was stirred at room temperature for thirty minutes and worked up in the same manner as before to give a colorless oil (0.807 g). Thin layer chromatography (50% ethyl acetate-benzene, silica gel H) indicated two major components (R_f 0.46 and 0.50) and one minor component (R_f 0.24).

The oil (0.807 g) was dissolved in 10 ml of pyridine, acetic anhydride (2 ml) was added, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into cold 5% hydrochloric acid and extracted with ether. The combined ether extracts were washed with 10% sodium bicarbonate, dried over anhydrous sodium sulfate, and the ether removed to give a colorless oil (0.774 g). Thin layer chromatography (50% ethyl acetate-benzene, silica gel H) showed two major components (R_f 0.46 and 0.50) that were identical with the two major components of the sodium borohydride reduction mixture. The reaction product (0.774 g) was chromatographed on Florisil (30 g, 2.2 x 18 cm) beginning with benzene and progressing through 20% ethyl acetate-benzene. Fractions 10-17 contained 1,3-dimethyl-2-oxo-3-[3,3-(2,2-diethyltrimethylenedioxy)-4-methoxybutane]-4-hydroxycyclohexanecarboxylic acid lactone (96) as a colorless oil (464 mg, 64%). The infrared spectrum ($CDCl_3$) showed significant bands at 1760 (lactone) and 1725 cm^{-1} (ketone). The nmr spectrum ($CDCl_3$) showed signals at δ 4.63 (t, 1, J=2 cps, $-\overset{|}{C}H-O\overset{O}{\overset{\|}{C}}-$), 3.52 (s, 4, $-OCH_2\overset{|}{C}CH_2-$), 3.42 (s, 2, $-\underline{CH_2}OCH_3$), 3.37 (s, 3, $-CH_2O\underline{CH_3}$), 1.20-2.50 (m, 12, $-CH_2-$), 1.28 (s, 3, quaternary methyl), 1.17 (s, 3, quaternary methyl), and 0.78 ppm (t, 6, J=7 cps, $\underline{CH_3}CH_2-$).

Fractions 18-28 (139 mg) contained impure acetoxy lactone derived from overreduction followed by acetylation.

2,6-Dimethyl-2-[3,3-(2,2-diethyltrimethylenedioxy)-4-methoxybutane]-3-acetoxycyclohexanone (97). To a solution of

1,3-dimethyl-2-oxo-3-[3,3-(2,2-diethyltrimethylenedioxy)-4-methoxybutane]-4-hydroxycyclohexanecarboxylic acid lactone (88 mg, 0.23 mmol) in 15 ml of methanol was added potassium carbonate (100 mg) followed by enough water to make the mixture homogeneous. The reaction mixture was refluxed for thirty minutes, cooled, and acetic acid was added until the mixture was acidic to pH paper. The methanol was removed under vacuum on a rotary evaporator and the residue was dissolved in ether. The ether solution was washed with water and dried over anhydrous sodium sulfate. Removal of the ether gave a colorless oil (70 mg). Thin layer chromatography (R_f 0.43, 50% ethyl acetate-benzene, silica gel H) showed one major component with only trace amounts of impurities.

The oil (70 mg) was dissolved in 2 ml of pyridine, acetic anhydride (1 ml) was added, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with benzene, washed twice with water, and dried over anhydrous sodium sulfate. Removal of the benzene gave a light orange oil (81 mg). The product was chromatographed on Florisil (4 g) in benzene to yield 2,6-dimethyl-2-[3,3-(2,2-diethyltrimethylenedioxy)-4-methoxybutane]-3-acetoxycyclohexanone as a colorless oil (70 mg, 76%). The infrared spectrum ($CHCl_3$) showed significant bands at 1730 (ester), 1710 (ketone), and 1225 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CDCl_3$) showed signals at δ 4.72 and 5.17 (m, 1, $-\overset{OAc}{\overset{|}{C}}H-$), 3.53 (s, 4, $-OCH_2\overset{|}{\underset{|}{C}}CH_2O-$), 3.46 (s, 2, $-\underline{CH_2}OCH_3$), 3.38 (s, 3, $-CH_2O\underline{CH_3}$), 1.17-2.70 (m, 13, $-CH_2-$ and $-\overset{|}{C}H-$), 2.02 and 2.07 (s, 3, $-O-\overset{O}{\overset{\|}{C}}CH_3$), 0.99 and 1.09 (s, 3, quaternary methyl),

0.96 and 1.02 (d, 3, J=5 cps, secondary methyl), and 0.80 ppm (t, 6, J= 7 cps, $\underline{CH_3}CH_2$-).

Anal. Calcd for $C_{22}H_{38}O_6$: C, 68.35; H, 9.91. Found: C, 68.21; H, 10.04.

Deketalization of 2,6-dimethyl-2-[3,3-(2,2-diethyltrimethylenedioxy)-4-methoxybutane]-3-acetoxycyclohexanone (97). A solution of 2,6-dimethyl-2-[3,3-(2,2-diethyltrimethylenedioxy)-4-methoxybutane]-3-acetoxycyclohexanone (48 mg, 0.12 mmol) in 10 ml of 80% aqueous acetic acid was heated at 80° for thirty minutes. The reaction mixture was cooled to room temperature, diluted with benzene, washed several times with water, and dried over anhydrous sodium sulfate. Removal of the benzene gave 2,6-dimethyl-2-(4-methoxybutan-3-one)-3-acetoxycyclohexanone (98) as a light yellow oil (33 mg, 97%). Thin layer chromatography (R_f 0.48, 50% ethyl acetate-benzene, silica gel H) showed only trace amounts of impurities. The infrared spectrum ($CHCl_3$) showed significant bands at 1730 (ester), 1710 (ketone), and 1225 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}$-OR). The nmr spectrum ($CDCl_3$) showed signals at δ 4.73 and 5.16 (m, 1, -$\overset{OAc}{\overset{|}{C}}$H-), 3.97 and 4.02 (s, 2, -$\overset{O}{\overset{\|}{C}}CH_2O$), 3.40 (s, 3, $-OCH_3$), 1.20-2.80 (m, 9, $-CH_2-$ and -$\overset{|}{C}$H-), 2.02 and 2.08 (s, 3, -O-$\overset{O}{\overset{\|}{C}}CH_3$), 1.00 and 1.07 (d, 3, J=6 and 3 cps, secondary methyl), and 0.98 ppm (s, 3, quaternary methyl).

Hydrogenolysis of 2,4-dimethyl-2-(4-methoxybutan-3-one)-4-carbobenzoxy-1,3-cyclohexanedione (94) under acidic conditions. A

solution of 2,4-dimethyl-2-(4-methoxybutan-3-one)-4-carbobenzoxy-1,3-cyclohexanedione (2.81 g, 7.5 mmol) in 25 ml of absolute ethanol was added to a suspension of prehydrogenated 5% palladium on charcoal (0.3 g) in 10 ml of absolute ethanol containing a few crystals of p-toluenesulfonic acid monohydrate. The sample took up one molar equivalent of hydrogen over a twenty minute period and then began to slowly give off carbon dioxide. The mixture was filtered to remove the catalyst and the ethanol was removed under vacuum on a rotary evaporator to give an orange oil (1.81 g). This oil was dissolved in benzene and filtered through Florisil (10 g) to give a light yellow semi-solid (1.44 g, 80%). The nmr spectrum indicated a mixture of 2,4-dimethyl-2-(4-methoxybutan-3-one)-1,3-cyclohexanedione (100, 25%) and 1,5-dimethyl-6-hydroxy-6-(methoxymethyl)-bicyclo[3.3.1]nonane-2,9-dione (101, 75%). The mixture was recrystallized several times from 50% benzene-hexane to yield pure 1,5-dimethyl-6-hydroxy-6-(methoxymethyl)-bicyclo-[3.3.1]nonane-2,9-dione (101) as a white solid (0.663 g), mp 116.5-117°. The infrared spectrum ($CHCl_3$) showed significant bands at 3580 (hydroxyl), 1730 (ketone), and 1703 cm^{-1} (ketone). The nmr spectrum ($CDCl_3$) showed signals at δ 3.45 (s, 2, $-CH_2-O-$), 3.39 (s, 3, $-OCH_3$), 1.42-2.68 (m, 8, $-CH_2-$), 2.50 (s, 1, -OH), 1.22 (s, 3, quaternary methyl), and 1.16 ppm (s, 3, quaternary methyl).

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.69; H, 8.35.

Hydrogenolysis of 2,4-dimethyl-2-(4-methoxybutan-3-one)-4-carbobenzoxy-1,3-cyclohexanedione (94) under basic conditions. A solution of 2,4-dimethyl-2-(4-methoxybutan-3-one)-4-carbobenzoxy-1,3-cyclohexanedione (5.62 g, 15 mmol) in 40 ml of absolute ethanol was added to a suspension of prehydrogenated 5% palladium on charcoal (0.4 g) in 10 ml of absolute ethanol containing three drops of pyridine. The sample took up one molar equivalent of hydrogen over a fifteen minute period and then began to rapidly give off carbon dioxide. The catalyst was filtered and the ethanol was removed under vacuum on a rotary evaporator. The residue was filtered through silicAR CC-7 (10 g) with benzene to give a light orange oil (2.95 g, 82%). Analysis of the nmr spectrum indicated a mixture of 2,4-dimethyl-2-(4-methoxybutan-3-one)-1,3-cyclohexanedione (100 g, 79%), and 1,5-dimethyl-6-hydroxy-6-(methoxymethyl)-bicyclo[3.3.1]nonane-2,9-dione (101, 21%). The following spectral properties are attributed to the isomeric 2,4-dimethyl-2-(4-methoxybutan-3-one)-1,3-cyclohexanediones (100). The infrared spectrum (film) showed significant bands at 1720 (ketone) and 1690 cm^{-1} (ketone). The nmr spectrum ($CDCl_3$) showed signals at δ 3.98 (s, 2, $-\overset{O}{\overset{\|}{C}}CH_2-O-$), 3.36 (s, 3, $-OCH_3$), 1.40-3.08 (m, 9, $-CH_2-$ and $-\overset{|}{C}H-$), 1.15 and 1.31 (s, 3, quaternary methyl), and 1.13 and 1.17 ppm (d, 3, J=6.5 cps, secondary methyl).

1,5-Dimethyl-2-acetoxy-6-hydroxy-6-(methoxymethyl)-bicyclo-[3.3.1]nonan-9-one (102). A solution of 1,5-dimethyl-6-hydroxy-6-

(methoxymethyl)-bicyclo[3.3.1]nonane-2,9-dione (240 mg, 1.0 mmol) in 15 ml of absolute ethanol under nitrogen was cooled to 0^{o} in an ice bath and a solution of sodium borohydride (13 mg, 0.33 mmol) in 10 ml of absolute ethanol was added over a ten minute period. The mixture was stirred for an additional fifteen minutes, acetic acid (0.1 ml) was added, and the ethanol was removed under vacuum on a rotary evaporator. The residue was dissolved in ether and the ether solution was washed with dilute sodium bicarbonate, then with water, and dried over anhydrous sodium sulfate. Removal of the ether gave 1,5-dimethyl-2,6-dihydroxy-6-(methoxymethyl)-bicyclo[3.3.1]nonan-9-one as a colorless oil (249 mg). The infrared spectrum ($CDCl_3$) showed significant bands at 3480-3620 (hydroxyl) and 1710 cm^{-1} (ketone). The nmr spectrum ($CDCl_3$) showed signals at δ 3.53 (t, 1, J=8 cps, $-\underset{OH}{\underline{C}H}-$), 3.34 (broad s, 5, $-CH_2OCH_3$), 1.30-2.60 (m, 8, $-CH_2-$), and 1.04 ppm (broad s, 6, quaternary methyls).

The crude bicyclic diol (249 mg) was dissolved in 5 ml of pyridine, acetic anhydride (2 ml) was added, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into cold dilute hydrochloric acid and extracted with ether. The ether phase was washed with saturated sodium chloride, dried over anhydrous sodium sulfate, and the ether was removed to give a light yellow semi-solid (285 mg). Recrystallization from hexane gave 1,5-dimethyl-2-acetoxy-6-hydroxy-6-(methoxymethyl)-bicyclo[3.3.1]-nonan-9-one as a white solid (174 mg, 61%), mp 104-106^{o}. The infrared spectrum ($CDCl_3$) showed significant bands at 3440-3580 (hydroxyl),

1725 (ketone and ester), and 1240 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CDCl_3$) showed signals at δ 4.75 (t, 1, J=9 cps, $-\overset{OAc}{\overset{|}{C}}H-$), 3.39 (s, 5, $-CH_2OCH_3$), 1.20-2.65 (m, 8, $-CH_2-$), 2.08 (s, 3, $-O-\overset{O}{\overset{\|}{C}}CH_3$), 1.09 (s, 3, quaternary methyl), and 1.00 ppm (s, 3, quaternary methyl). A small sample was recrystallized several times from hexane for analysis, mp 106-107°.

Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.43; H, 8.64.

Cis- and trans-1-acetoxy-4,9-dimethyl-5-methoxy-6-oxo-10-hydroxydecalin (103). To a solution of 1,5-dimethyl-2-acetoxy-6-hydroxy-6-(methoxymethyl)-bicyclo[3.3.1]nonan-9-one (138 mg, 0.49 mmol) in 25 ml of anhydrous benzene was added several drops of freshly distilled pyrrolidine. The mixture was refluxed under nitrogen through a Soxhlet extractor filled with molecular sieve (Linde, 3A) for eight hours. Gas chromatography analysis (2' x 1/8" 3% JXR on 80/100 Gas-Chrom Q and a column temperature of 140°) showed only starting material. A small amount of potassium t-butoxide was added to the reaction mixture and the suspension was refluxed for one hour. The reaction was cooled, poured into a separatory funnel containing 10% hydrochloric acid, and the phases were separated. The benzene phase was washed with dilute sodium bicarbonate, then water, and dried over anhydrous sodium sulfate. Removal of the benzene gave a light yellow oil (110 mg, 80%) which was chromatographed on silicAR CC-7 (3 g) beginning with benzene and progressing through 4% ethyl acetate-benzene

to yield cis- and trans-1-acetoxy-4,9-dimethyl-5-methoxy-6-oxo-10-hydroxydecalin as a light yellow oil (53 mg). The infrared spectrum (film) showed significant bands at 3520 (hydroxyl), 1730 (ester), 1710 (ketone), and 1230 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CDCl_3$) showed signals at δ 4.73 and 5.10 (m, 1, $-\overset{OAc}{\overset{|}{C}}H-$), 3.97 and 4.01 (s, 1, $-\overset{O}{\overset{\|}{C}}\overset{|}{C}HO-$), 3.38 (s, 3, $-OCH_3$), 1.20-2.90 (m, 9, $-CH_2-$ and $-\overset{|}{C}H-$), 2.02 and 2.07 (s, 3, $-O-\overset{O}{\overset{\|}{C}}CH_3$), 0.98 and 1.03 (s, 3, quaternary methyl), and 1.00 and 1.02 ppm (d, 3, J=6 cps, secondary methyl).

Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 62.90; H, 8.67.

The nmr spectrum ($CDCl_3$) of fractions 3-17 showed signals at δ 4.73 (dd, 1, J=9 and 7 cps, $-\overset{OAc}{\overset{|}{C}}H-$), 3.96 (s, 1, $-\overset{O}{\overset{\|}{C}}\overset{|}{C}HO-$), 3.38 (s, 3, $-OCH_3$), 1.20-2.90 (m, 9, $-CH_2-$ and $-\overset{|}{C}H-$), 2.06 (s, 3, $-O-\overset{O}{\overset{\|}{C}}CH_3$), 1.03 (s, 3, quaternary methyl), and 1.00 ppm (s, 3, J=6 cps, secondary methyl). Analysis of this nmr spectrum indicates fractions 3-17 (34 mg) contained mainly trans-1-acetoxy-4,9-dimethyl-5-methoxy-6-oxo-10-hydroxydecalin.

2,4-Dimethyl-2-(butan-3-one)-4-carbobenzoxy-1,3-cyclohexanedione (104). The procedure followed was similar to that used to prepare 2,4-dimethyl-2-(butan-3-one)-4-carbethoxy-1,3-cyclohexanedione (76). To a solution of 2,4-dimethyl-4-carbobenzoxy-1,3-cyclohexanedione (13.7 g, 0.05 mol) and methyl vinyl ketone (4.2 g, 0.06 mol) in 300 ml of anhydrous benzene was added triethyl amine (0.2 ml). The mixture was stirred at room temperature under nitrogen

for two days. The benzene solution was then washed with 5% hydrochloric acid, 5% sodium hydroxide, then with water, and dried over anhydrous sodium sulfate. Removal of the benzene gave a light orange oil (15.6 g) which was further purified by column chromatography on Florisil (500 g, 6.5 x 30 cm) beginning with benzene and progressing through 10% ethyl acetate-benzene. Fractions 9-21 contained 2,4-dimethyl-2-(butan-3-one)-4-carbobenzoxy-1,3-cyclohexanedione as a colorless oil (12.1 g, 71%). The infrared spectrum ($CHCl_3$) showed significant bands at 1730 (ester), 1720 (ketone), and 1700 cm^{-1} (ketone). The nmr spectrum ($CDCl_3$) showed signals at δ 7.33 and 7.35 (s, 5, aromatic hydrogens), 5.02 and 5.07 (s, 2, benzylic hydrogens), 1.60-2.80 (m, 8, $-CH_2-$), 1.91 and 2.08 (s, 3, $-\overset{O}{\overset{\|}{C}}CH_3$), 1.43 and 1.48 (s, 3, quaternary methyl), and 1.18 and 1.25 ppm (s, 3, quaternary methyl).

Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.64; H, 6.90.

Reduction and acetylation of one isomer of 2,4-dimethyl-2-(butan-3-one)-4-carbobenzoxy-1,3-cyclohexanedione (104). A solution of 2,4-dimethyl-2-(butan-3-one)-4-carbobenzoxy-1,3-cyclohexanedione (5.47 g, 15.9 mmol, >80% of one isomer) in 100 ml of absolute ethanol under nitrogen was cooled to 0° in an ice bath and a solution of sodium borohydride (160 mg, 4.2 mmol) in 50 ml of absolute ethanol was added over a forty minute period. After addition was complete, the mixture was stirred at 0° for forty minutes, then acetic acid

(2 ml) was added, and the ethanol was removed under vacuum on a rotary evaporator. The residue was dissolved in benzene and the benzene solution was washed with 5% sodium hydroxide, then with water, and dried over anhydrous sodium sulfate. Removal of the benzene gave a colorless oil (4.45 g, 81%) which by thin layer chromatography (R_f 0.49, 50% ethyl acetate-benzene, silica gel H) contained only trace amounts of impurities. The infrared spectrum ($CHCl_3$) showed significant bands at 3400-3600 (hydroxyl), 1730 (ester), and 1705 cm^{-1} (ketone). The nmr spectrum ($CDCl_3$) showed signals at δ 7.32 (s, 5, aromatic hydrogens), 5.12 (s, 2, benzylic hydrogens), 4.14 (t, 1, J=3 cps, $-\overset{|}{C}H-O-$), 1.20-3.00 (m, 8, $-CH_2-$), 1.44 (s, 3, quaternary methyl), 1.13 (s, 3, quaternary methyl), and 1.08 ppm (s, 3, quaternary methyl).

A portion of the reduction product (4.04 g) was dissolved in 20 ml of pyridine, acetic anhydride (10 ml) was added, and the mixture was stirred overnight at room temperature. The reaction mixture was poured into cold 10% hydrochloric acid and extracted with benzene. The benzene extracts were washed with 5% sodium hydroxide, then with water, and dried over anhydrous sodium sulfate. Removal of the benzene gave a light yellow oil (3.94 g) which by thin layer chromatography (R_f 0.57, 50% ethyl acetate-benzene, silica gel H) showed only trace amounts of impurities. The oil (3.94 g) was chromatographed on Florisil (120 g) beginning with benzene and progressing through 10% ethyl acetate-benzene. Fractions 15-21 contained pure 2,6-dimethyl-2-(butan-3-one)-3-acetoxy-6-carbobenzoxycyclohexanone (106) as a colorless oil (1.75 g). The infrared spectrum ($CHCl_3$)

showed significant bands at 1730 (ester), 1710 (ketone), and 1230 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CDCl_3$) showed signals at δ 7.33 (s, 5, aromatic hydrogens), 4.89 and 5.23 (d, 2, J=13 cps, benzylic hydrogens), 4.79 (dd, 1, J=10 and 6 cps, $-\overset{OAc}{\overset{|}{C}}H-$), 1.40-2.80 (m, 8, $-CH_2-$), 2.02 (s, 3, $-O-\overset{O}{\overset{\|}{C}}CH_3$), 1.88 (s, 3, $-\overset{O}{\overset{\|}{C}}CH_3$), 1.33 (s, 3, quaternary methyl), and 1.06 ppm (s, 3, quaternary methyl).

Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 68.22; H, 7.45.

1-Acetoxy-4,9β-dimethyl-4-carbobenzoxy-6-oxo-$\Delta^{5(10)}$-octalin (107). To a solution of 2,6-dimethyl-2-(butan-3-one)-3-acetoxy-6-carbobenzoxycyclohexanone (249 mg, 0.64 mmol) in 20 ml of anhydrous benzene was added pyrrolidine (0.2 ml). The mixture was refluxed under nitrogen for eighty-eight hours using a Soxhlet extractor filled with molecular sieve (Linde, 3A) to remove the water. The reaction mixture was cooled and the benzene was removed under vacuum on a rotary evaporator. The residue was dissolved in 80% aqueous acetic acid and the solution was heated at 80° for two hours. The mixture was then poured into ice water and extracted with benzene. The benzene extracts were washed with 5% sodium hydroxide, then with water, and dried over anhydrous sodium sulfate. Removal of the benzene gave a yellow oil (175 mg) which was chromatographed on Florisil (8 g) beginning with benzene and progressing through 10% ethyl acetate-benzene. Fractions 3 and 4 were combined to give a light yellow oil (142 mg, 60%) which solidified on standing, mp 76-81°. Recrystallization from hexane gave

pure 1-acetoxy-4,9β-dimethyl-4-carbobenzoxy-6-oxo-$\Delta^{5(10)}$-octalin as a white solid, mp 82-83°, uv (95% ethanol) 208 (ε 11,800) and 240 mμ (ε 14,000). The infrared spectrum ($CHCl_3$) showed significant bands at 1725 (ester), 1665 (unsaturated ketone), 1600 (conjugated double bond), and 1240 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CDCl_3$) showed signals at δ 7.32 (s, 5, aromatic hydrogens), 5.98 (s, 1, vinyl hydrogen), 5.18 (s, 2, benzylic hydrogens), 4.87 (t, 1, J=3 cps, $-\overset{OAc}{\overset{|}{C}}H-$), 1.60-2.80 (m, 8, $-CH_2-$), 1.94 (s, 3, $-O-\overset{O}{\overset{\|}{C}}CH_3$), 1.49 (s, 3, quaternary methyl), and 1.39 ppm (s, 3, quaternary methyl).

Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.15; H, 7.13.

Hydrogenolysis of 2,6-dimethyl-2-(butan-3-one)-3-acetoxy-6-carbobenzoxycyclohexanone (106). A solution of 2,6-dimethyl-2-(butan-3-one)-3-acetoxy-6-carbobenzoxycyclohexanone (1.24 g, 3.2 mmol) in 30 ml of absolute ethanol was added to a suspension of prehydrogenated 5% palladium on charcoal (0.1 g) in 10 ml of absolute ethanol containing a drop of pyridine. The sample took up one molar equivalent of hydrogen over a forty minute period. The catalyst was filtered and the ethanol was removed under vacuum on a rotary evaporator. The residue was dissolved in benzene and the solution was refluxed for one hour. The mixture was cooled and washed with 5% hydrochloric acid, 5% sodium hydroxide, then with water, and dried over anhydrous sodium sulfate. Removal of the benzene gave a mixture (1.4:1 by nmr analysis) of isomeric 2,6-dimethyl-2-(butan-3-one)-3-acetoxycyclohexanones (108) as a

yellow oil (695 mg, 85%). The crude product was dissolved in anhydrous benzene, a small amount of potassium t-butoxide was added, and the suspension was refluxed under nitrogen for one hour. The suspension was cooled and a few drops of acetic acid were added. The reaction mixture was then washed with 5% sodium hydroxide, water, and dried over anhydrous sodium sulfate. Removal of the benzene gave a mixture (2.1:1) of isomeric 2,6-dimethyl-2-(butan-3-one)-3-acetoxycyclohexanones (527 mg).

A portion (263 mg) of the mixture was separated by preparative gas chromatography (10' x 3/8" 30% SE-30 on 45/60 Chromsorb P and a column temperature of 220°). The first component was a light yellow oil (78 mg) which was further purified by bulb-to-bulb distillation (80°/0.03 mm) to yield 2β,6α-dimethyl-2-(butan-3-one)-3β-acetoxycyclohexanone as a colorless oil. The infrared spectrum ($CHCl_3$) showed significant bands at 1735 (ester), 1710 (ketone), and 1230 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CDCl_3$) showed signals at δ 4.74 (dd, 1, J=9 and 7 cps, $-\overset{OAc}{\overset{|}{C}}H-$), 1.20-2.80 (m, 9, $-CH_2-$ and $-\overset{|}{C}H-$), 2.08 and 2.13 (s, 6, $-\overset{O}{\overset{\|}{C}}CH_3$ and $-O\overset{O}{\overset{\|}{C}}CH_3$), 1.04 (s, 3, quaternary methyl), and 1.01 ppm (d, 3, J=6 cps, secondary methyl).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.09; H, 8.86.

The second fraction (53 mg of a light yellow oil) proved to be a mixture containing 71% 2β,6β-dimethyl-2-(butan-3-one)-3β-acetoxycyclohexanone contaminated with 29% of the other isomer. The major isomer had the following spectral properties. The infrared spectrum ($CHCl_3$)

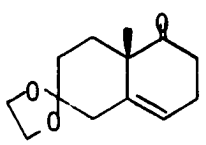
showed significant bands at 1730 (ester), 1710 (ketone), and 1230 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CDCl_3$) showed signals at δ 5.11 (m, 1, $-\overset{OAc}{\overset{|}{C}}H-$), 1.20-2.80 (m, 9, $-CH_2-$ and $-\overset{|}{C}H-$), 2.01 and 2.13 (s, 6, $-\overset{O}{\overset{\|}{C}}CH_3$ and $-O\overset{O}{\overset{\|}{C}}CH_3$), 1.22 (s, 3, quaternary methyl), and 1.03 (d, 3, J=6 cps, secondary methyl).

1-Acetoxy-4,9β-dimethyl-6-oxo-$\Delta^{5(10)}$-octalin (109). The procedure was the same as was described for the preparation of 1-acetoxy-4,9-dimethyl-4-carbobenzoxy-6-oxo-$\Delta^{5(10)}$-octalin (107). Reaction of a mixture of isomeric 2,6-dimethyl-2-(butan-3-one)-3-acetoxycyclohexanones (264 mg, 1.04 mmol) with pyrrolidine (0.2 ml) in 20 ml of anhydrous benzene afforded an orange oil (207 mg). The oil was chromatographed on Florisil (10 g, 2 x 7 cm) beginning with benzene and progressing through 10% ethyl acetate-benzene. Fractions 5-8 contained a mixture of isomeric 1-acetoxy-4,9β-dimethyl-6-oxo-$\Delta^{5(10)}$-octalins as a light yellow semi-solid (166 mg, 68%), uv max (95% ethanol) 238 mμ (ε_{max} 15,900). The infrared spectrum ($CHCl_3$) showed significant bands at 1730 (ester), 1665 (unsaturated ketone), 1610 (conjugated double bond), and 1240 cm^{-1} ($CH_3\overset{O}{\overset{\|}{C}}-OR$). The nmr spectrum ($CDCl_3$) showed signals at δ 5.93 (m, 1, vinyl hydrogen), 4.88 (t, 1, J=3 cps, $-\overset{OAc}{\overset{|}{C}}H-$), 1.40-2.90 (m, 9, $-CH_2-$ and $-\overset{|}{C}H-$), 2.03 and 2.05 (s, 3, $-O\overset{O}{\overset{\|}{C}}CH_3$), 1.33 (s, 3, quaternary methyl), and 1.13 ppm (d, 3, J=6 cps, secondary methyl).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.05; H, 8.34.

SUMMARY

Several synthetic approaches to the synthesis of 4,9-dimethyl-6-oxo-$\Delta^{5(10)}$-octalin and 4,9-dimethyl-6-decalone derivatives have been explored. Starting with 1,6-dioxo-9β-methyl-$\Delta^{5(10)}$-octalin the following new compounds have been synthesized: 1-oxo-6-ethylenedioxy-9β-methyl-Δ^{4}-octalin (54), 1β-hydroxy-6-ethylenedioxy-9β-methyl-



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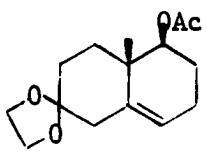

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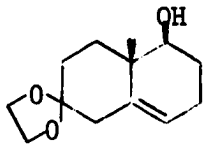

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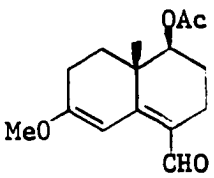

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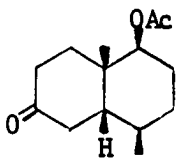

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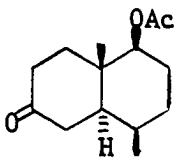

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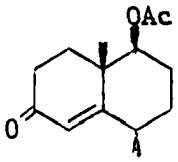

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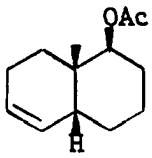

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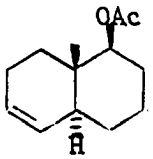
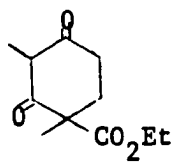


68

Δ^{4}-octalin (57) and its acetate (56), 1β-acetoxy-4-formyl-6-methoxy-9β-methyl-1,2,3,7,8,9-hexahydronaphthalene (59), cis- and trans-1β-

acetoxy-4β,9β-dimethyl-6-decalone (62 and 63), 1β-acetoxy-4β,9β-dimethyl-6-oxo-$\Delta^{5(10)}$-octalin (64), and cis- and trans-1β-acetoxy-9β-methyl-Δ^{5}-octalin (67* and 68).

The other routes which were examined utilized acylic starting materials which were converted into the appropriately substituted bicyclic systems. In the initial sequence, 2,4-dimethyl-4-carbethoxy-1,3-cyclohexanedione (75) has been prepared and converted into the following compounds: 2,4-dimethyl-2-(butan-3-one)-4-carbethoxy-1,3-



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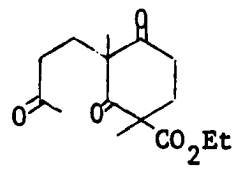

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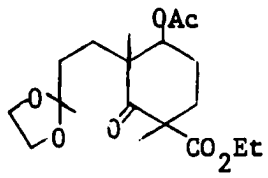

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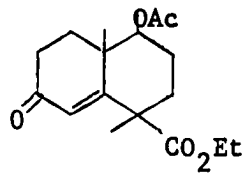

80

cyclohexanedione (76), 2,6-dimethyl-2-(3-ethylenedioxybutane)-3-acetoxy-6-carbethoxycyclohexanone (78), and 1-acetoxy-4,9β-dimethyl-4-carbethoxy-6-oxo-$\Delta^{5(10)}$-octalin (80).

2,4-Dimethyl-4-carbobenzoxy-1,3-cyclohexanedione (89) and 2,4-dimethyl-2-(4-methoxybutan-3-one)-4-carbobenzoxy-1,3-cyclohexanedione

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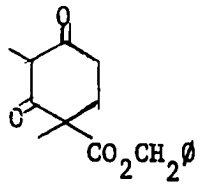
*This compound was prepared by Bailey and Halsall,[66] but was assigned the wrong stereochemistry.

(94) were prepared in good yield and used in a less successful reaction sequence to prepare the following compounds: 2,4-dimethyl-2-[3,3-(2,2-diethyltrimethylenedioxy)-4-methoxybutane]-4-carbobenzoxy-1,3-cyclohexanedione (95), 1,3-dimethyl-2-oxo-3-[3,3-(2,2-diethyl-trimethylenedioxy)-4-methoxybutane]-4-hydroxycyclohexanecarboxylic



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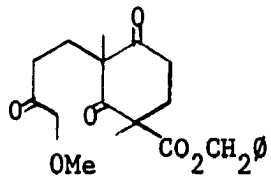

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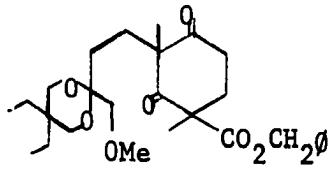

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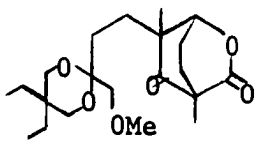

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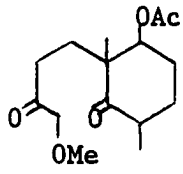
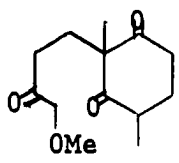


98

acid lactone (96), and 2,6-dimethyl-2-(4-methoxybutan-3-one)-3-acetoxycyclohexanone (98).

Hydrogenolysis of 2,4-dimethyl-2-(4-methoxybutan-3-one)-4-carbobenzoxy-1,3-cyclohexanedione (94) was found to give a mixture of 2,4-dimethyl-2-(4-methoxybutan-3-one)-1,3-cyclohexanedione (100) and



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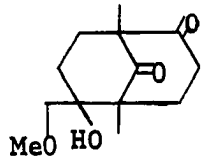

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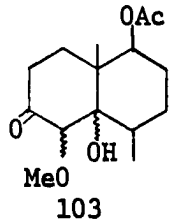
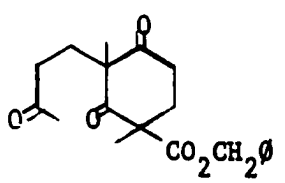


103

1,5-dimethyl-6-hydroxy-6-(methoxymethyl)-bicyclo[3.3.1]nonane-2,9-dione (101). The bicyclic ketol 101 has been transformed into 1-acetoxy-4,9-dimethyl-5-methoxy-6-oxo-10-hydroxydecalin (103), but an attempted dehydration reaction failed to give the desired octalin.

2,4-Dimethyl-2-(butan-3-one)-4-carbobenzoxy-1,3-cyclohexanedione (104) has been prepared, selectively reduced with sodium borohydride at 0°, and the resulting alcohol, isolated as hemiketal 105, acetylated to 2,6-dimethyl-2-(butane-3-one)-3-acetoxy-6-carbobenzoxycyclohexanone (106). The diketone 106 has been converted to 1-acetoxy-



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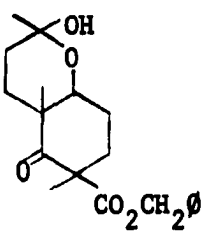

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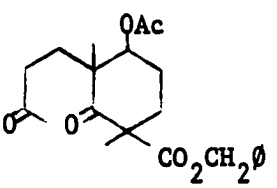

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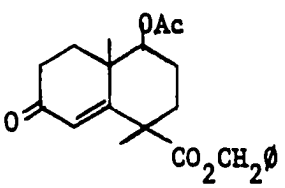

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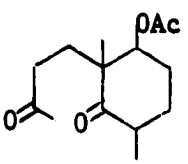

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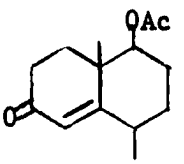
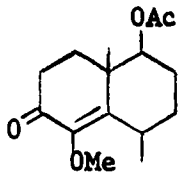


109

4,9β-dimethyl-4-carbobenzoxy-6-oxo-$\Delta^{5(10)}$-octalin (107), 2,6-dimethyl-2-(butan-3-one)-3-acetoxycyclohexanone (108), and 1-acetoxy-4,9β-dimethyl-6-oxo-$\Delta^{5(10)}$-octalin (109).

Finally, preliminary efforts to apply the above reaction sequence to 2,4-dimethyl-2-(4-methoxybutan-3-one)-4-carbobenzoxy-1,3-cyclohexanedione (94) have resulted in the formation of 2,6-dimethyl-

2-(4-methoxybutan-3-one)-3-acetoxy-6-carbobenzoxycyclohexanone (112) in good yield. It is anticipated that further development of this



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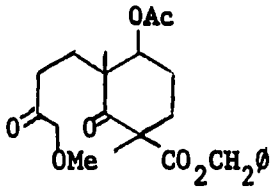

112

reaction sequence will enable future workers to prepare large quantities of 112 which promises to be an important precursor in the synthesis of 1-acetoxy-4,9-dimethyl-5-methoxy-6-oxo-$\Delta^{5(10)}$-octalin (99).

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