IOWA STATE UNIVERSITY
Digital Repository

Retrospective Theses and Dissertations

Iowa State University Capstones, Theses and Dissertations

1972

Synthetic approaches to the guaiane sesquiterpenes

Lloyd Payne Hill
Iowa State University

Follow this and additional works at: https://lib.dr.iastate.edu/rtd

 Part of the Organic Chemistry Commons

Recommended Citation
Hill, Lloyd Payne, "Synthetic approaches to the guaiane sesquiterpenes " (1972). *Retrospective Theses and Dissertations*. 5918.
https://lib.dr.iastate.edu/rtd/5918

This Dissertation is brought to you for free and open access by the Iowa State University Capstones, Theses and Dissertations at Iowa State University Digital Repository. It has been accepted for inclusion in Retrospective Theses and Dissertations by an authorized administrator of Iowa State University Digital Repository. For more information, please contact digirep@iastate.edu.

www.manaraa.com

73-3891

HILL, Lloyd Payne, 1945-
SYNTHETIC APPROACHES TO THE GUAIANE SESQUITERPENES.

Iowa State University, Ph.D., 1972
Chemistry, organic

University Microfilms, A XEROX Company, Ann Arbor, Michigan

THIS DISSERTATION HAS BEEN MICROFILMED EXACTLY AS RECEIVED.

Synthetic approaches to the guaiane sesquiterpenes

by

Lloyd Payne Hill

A Dissertation Submitted to the

Graduate Faculty in Partial Fulfillment of

The Requirements for the Degree of

DOCTOR OF PHILOSOPHY

Department: Chemistry

Major: Organic Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

Signature was redacted for privacy.

For the Major Department

Signature was redacted for privacy.

For the Graduate College

Iowa State University
Ames, Iowa

1972

PLEASE NOTE:

Some pages may have

indistinct print.

Filmed as received.

University Microfilms, A Xerox Education Company

TABLE OF CONTENTS

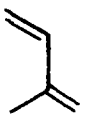
DEDICATION

To my Family

INTRODUCTION

The essential oils are found in flora and have been a source of curiosity to Man for hundreds of years. They have been shown to consist of a complex mixture of compounds, acyclic, alicyclic, aromatic and heterocyclic in character.

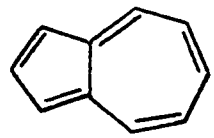
One class of essential oils are the terpenes. This is a general class of compounds which is constructed of repeating units of isoprene (1), arranged in a head to tail fashion. Terpenes contain ten carbon



1

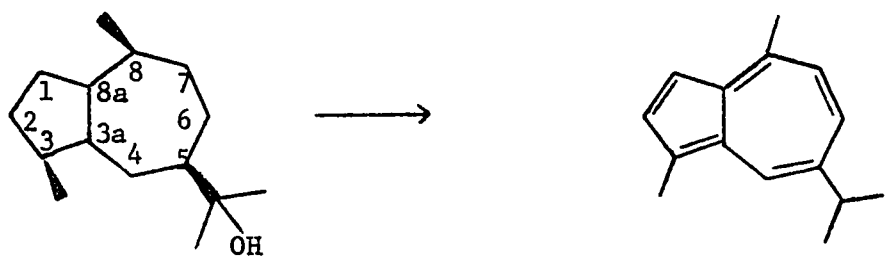
atoms or two isoprene units. Twenty carbon atom and thirty carbon atom compounds are called di- and triterpenes, respectively. Intermediate between terpenes and diterpenes are sesquiterpenes, composed of three isoprene units and fifteen carbon atoms.

The blue color of camomile oil was first observed in the fifteenth century, and more recently it has been found that other essential oils become blue or violet when dehydrogenated with Se, S, Ni or Pd/charcoal (1). In 1915, Sherndal observed that the blue color was removed from solutions of ether or petroleum ether by shaking with concentrated phosphoric acid (2). The blue color was regenerated when the acid solution was diluted with water. This represented the first isolation of an azulene, the parent compound with structure 2.



2

Guaiazulene (4) is found in geranium oil and is also obtained by dehydrogenation of the essential oil of guaiacum wood. One of the precursors to guaiazulene is guaiol (3), first isolated in 1892 from guaiacum



3 4

wood oil (3). Guaiol has been identified as a constituent of oils from guaiac wood (4, 5), Eucalyptus citriodora (6), Eucalyptus malculata (7), Lignum vitae (8), and as a minor fraction of Callitris glauca (9, 10).

Simonsen and Barton (11) give an extremely thorough description of the gross (disregarding stereochemistry) structure determination of guaiol. Undoubtedly, this project required tremendous effort on the part of Plattner, Ruzicka, and others.

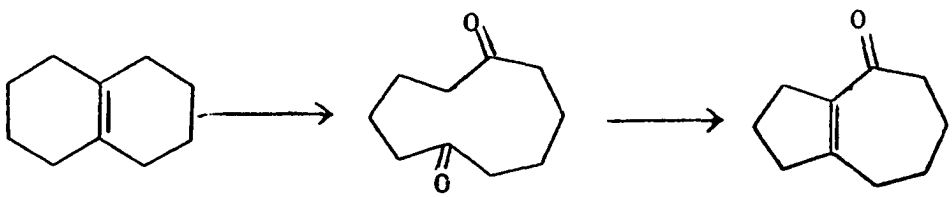
The stereochemistry of the C-3 methyl group was rigorously determined in 1960 (12). The configuration of the C-8 methyl group was done in 1961 (13), and the C-5 substituent required a more concerted effort (14-17), but was finally completed in 1961 by Minato (18, 19). The structure of guaiol, as determined by these workers is represented in 3.

Two total syntheses of guaiol were reported in the literature of 1971. Buchanan and Young's non-stereoselective synthesis (20) will not be considered further. The synthesis reported by Marshall and his coworkers (21, 22), however long and arduous, represents a significant contribution to the field. This will be treated in greater detail later in the text.

HISTORICAL

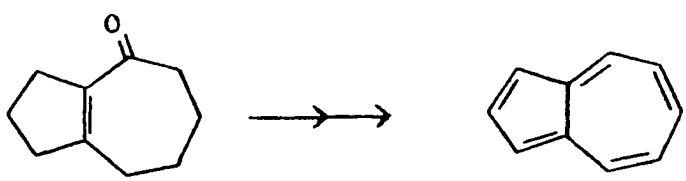
Until recently, the hydroazulenic sesquiterpenes have represented one of the more neglected areas of study in terpene chemistry. In recent years, however, these compounds have attracted more attention and the number of sesquiterpenes known to contain the hydroazulene ring system has increased substantially (23-27). Since Plattner's initial synthesis of azulene (2) over 35 years ago, several stereoselective syntheses of functionalized hydroazulenes have appeared in the last six years and will be considered in some detail.

Plattner and St. Pfau (28) reported the conversion of octalin 5 to the hydroazulenic ketone 7 in two steps. Ozonolysis of 5 gave dione 6 which



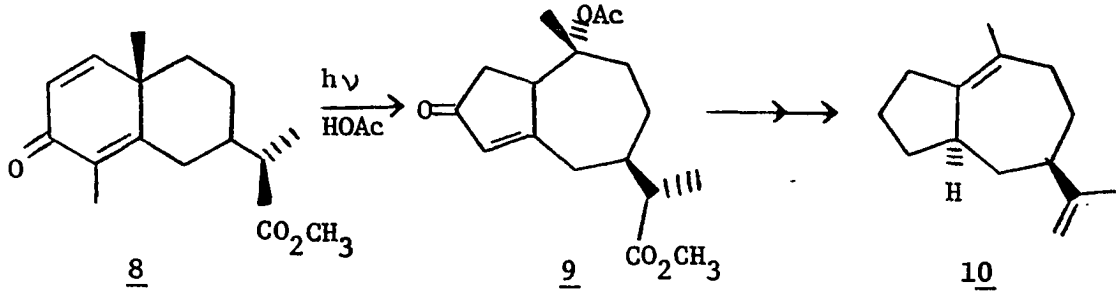
5 6 7

was condensed intramolecularly to give ketone 7. Subsequent reduction, dehydration, and dehydrogenation gave azulene (2).



7 2

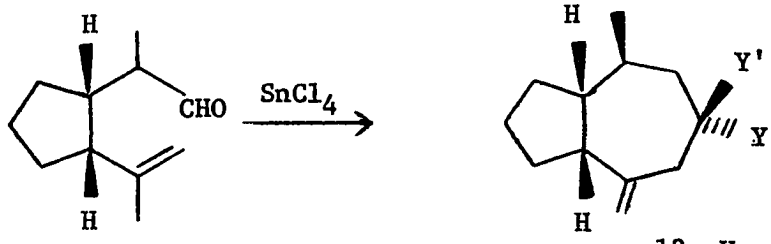
A photolytic pathway to hydrozulene 9 was used in 1969 by Piers and Cheng (29).



8 9 10

The keto ester 8 (readily available from naturally occurring santonin) gave a 79% yield of the substituted hydroazulene 9 when photolyzed in the presence of acetic acid. Compound 9 through a series of transformations was ultimately converted to α-bulnesene (10).

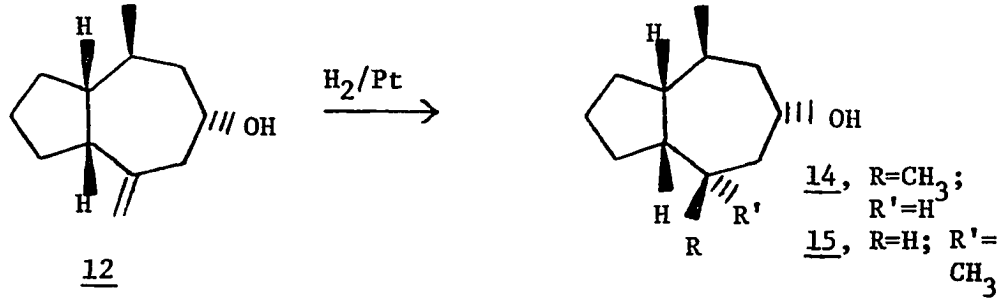
The cyclization of unsaturated aldehyde 11 has been studied (30).



11

12, Y = OH; Y' = H
13, Y = H; Y' = OH

Treatment of 11 with stannic chloride or silica gel afforded the hydroazulenic alcohols 12 and 13 in 88 and 12% yield, respectively. Another



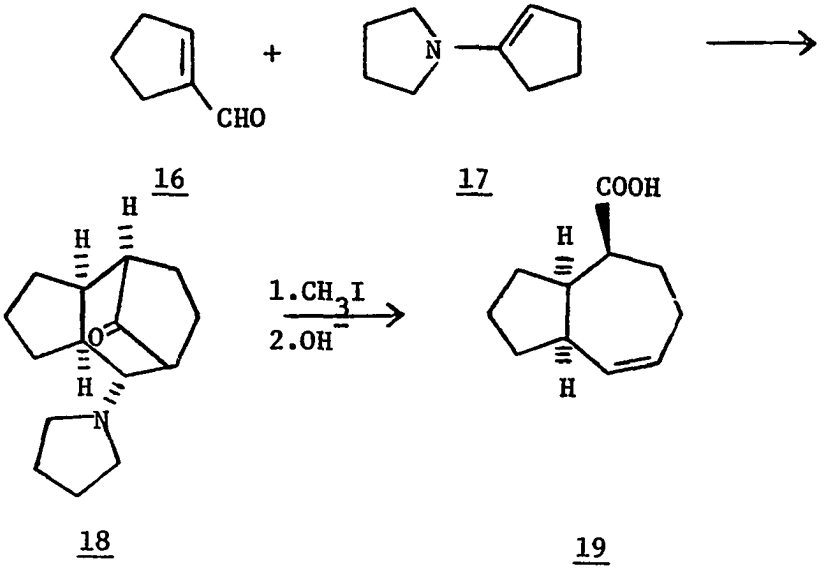
12

14, R=CH_3; R'=H
15, R=H; R'=CH_3

stereochemical problem arises when alcohol 12 is hydrogenated with hydrogen over platinum to give a 55:45 mixture of the methyl epimers 14 and 15.

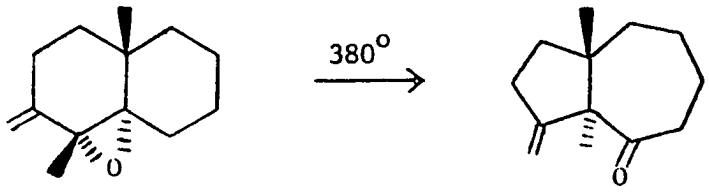
A short, stereospecific synthesis of functionalized perhydroazulenes has recently been described (31). The reported preparation involves the facile synthesis of a seven-membered ring through a cleavage of a bicyclic molecule composed of smaller rings.

The reaction of 1-cyclopentenylcarboxaldehyde (16) with the pyrrolidine enamine of cyclopentanone (17) yielded the adduct 18 and this (without isolation) was treated with methyl iodide and heated with aqueous base to give the bicyclic acid 19 in 25% yield.



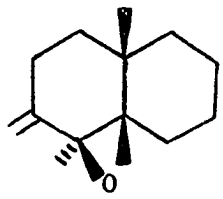
18 19

A thermal reaction was used in the last non-solvolytic pathway to be considered. Kretchmer and Frazee (32) studied the pyrolysis of epoxide 20 at 380°. The reaction affords, in 75% yield, the hydroazulene 21.



20 21

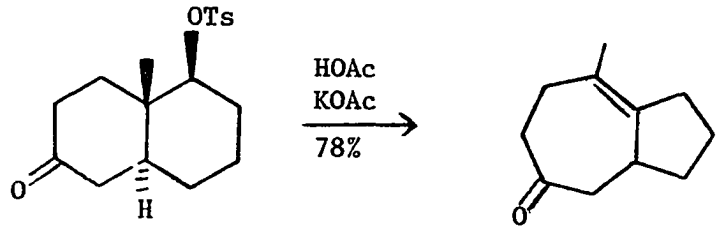
The epimeric epoxide 22, under identical reaction conditions, afforded no hydroazulenic products.



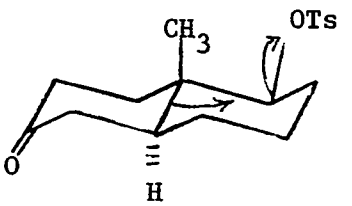
22

A methyl group at the bridgehead is rare among hydroazulenic sesquiterpenes and consequently greatly detracts from further applications of this method.

There are several solvolytic approaches that have been investigated as potential routes to guaiazulenic sesquiterpenes (33-43). An early approach was reported by Heathcock and Ratcliffe (34) who observed the formation of hydroazulene 24 via solvolysis of tosylate 23. The carbon-carbon bond

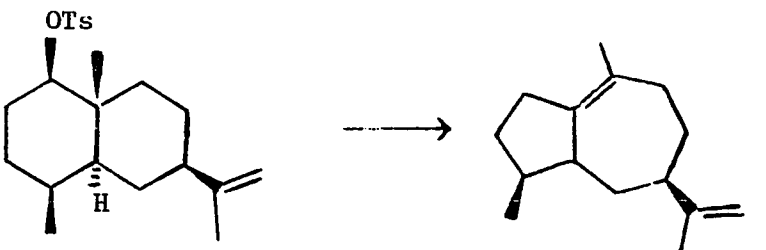


23 24



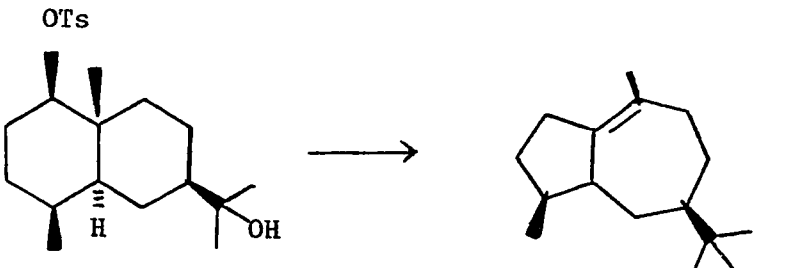
23

in 23 which migrates is trans coplanar to the carbon-oxygen bond of the tosylate group. This is a necessary stereochemical arrangement for the



25 10

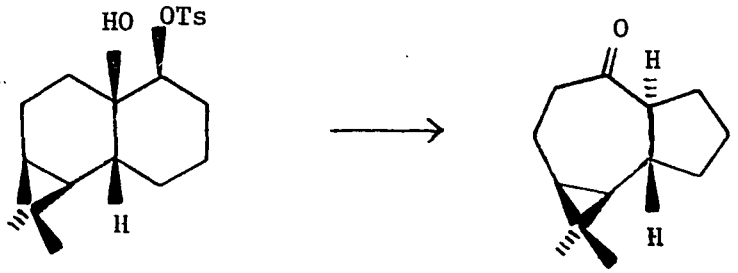
rearrangement to take place. Heathcock and Ratcliffe used this step in 1971 (35) in the synthesis of α-bulnesene (10) and bulnesol (27) from tosylates 25 and 26, respectively. In the reaction of 26, Heathcock



26 27

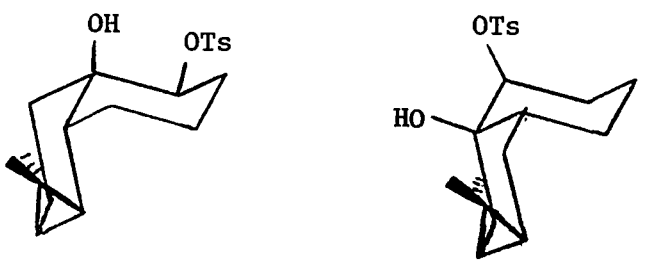
reports a 5% yield of guaiol along with bulnesol (27).

A similar rearrangement has been reported (36) in the synthesis of (-)aromadendrene. In tosylate 28, however, the ring fusion is cis,



28 29

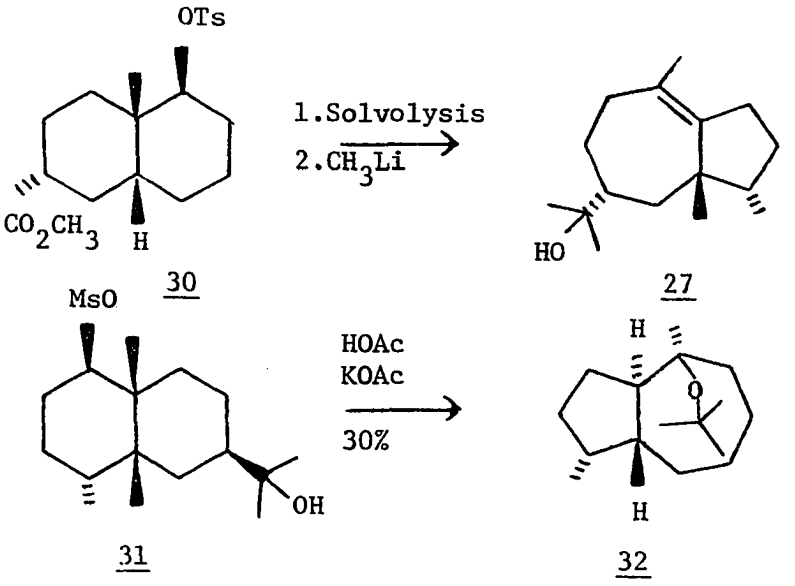
whereas in the tosylates studied by Heathcock, 23, 25, and 26, the ring fusion is trans. It should be noted that the configuration restricts the desired reaction to the steroidal conformer 28a, since in the non-steroidal conformer 28b the migrating bond lacks the proper trans coplanar



28a 28b

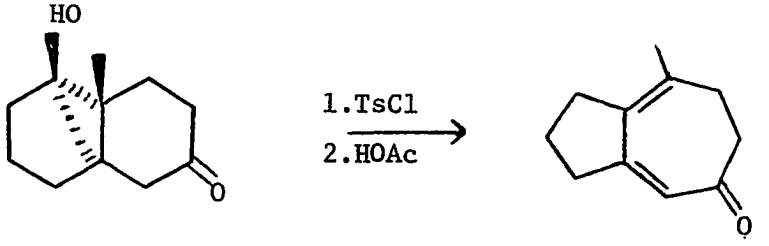
arrangement required for rearrangement.

Kato and his coworkers (37) solvolyzed the cis fused tosylate 30 and, after treatment with methyllithium isolated bulnesol (27). A related solvolysis of mesylate 31 reported by the same authors (38) gives the intramolecular ether found in the natural product kessane (32).



30 27 31 32

Recently, an unexpected isomerization of the cyclopropyl alcohol 33 has been reported (39). Reaction of alcohol 33 with p-toluenesulfonyl chloride in pyridine gave a highly reactive tosylate which underwent

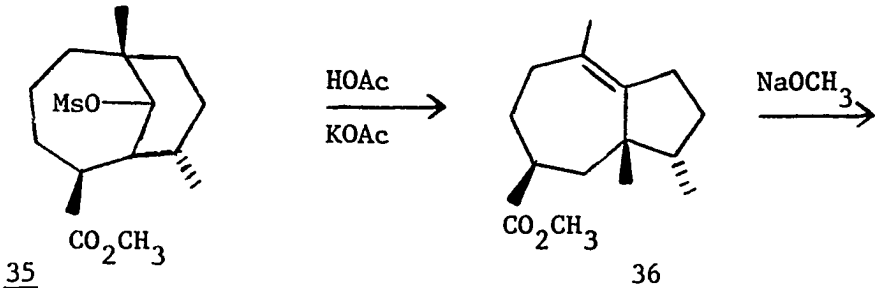


33 34

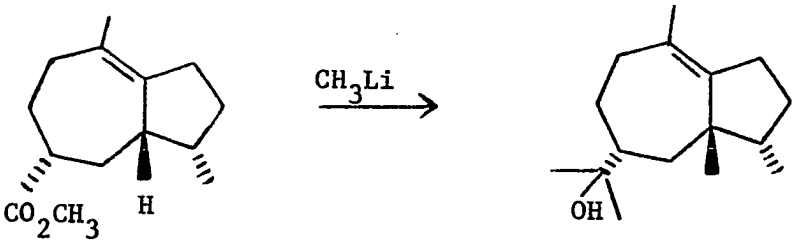
acetolysis to produce an unstable liquid, the major component of which was dienone 34, formed in 64% overall yield.

To this point, only rearrangements from the bicyclo[4.4.0]decane skeleton have been described. Another solvolytic rearrangement has been studied by Marshall and Partridge (40-42). This sequence starts with the bicyclo[4.3.1]decane skeleton. Mesylate 35, in the presence of acetic

acid and potassium acetate, underwent solvolytic rearrangement to the hydroazulene 36. This in turn was isomerized to an equal mixture of 36 and 37, with sodium methoxide and methanol. The ester 37 was converted to bulnesol (27) using methyl lithium.

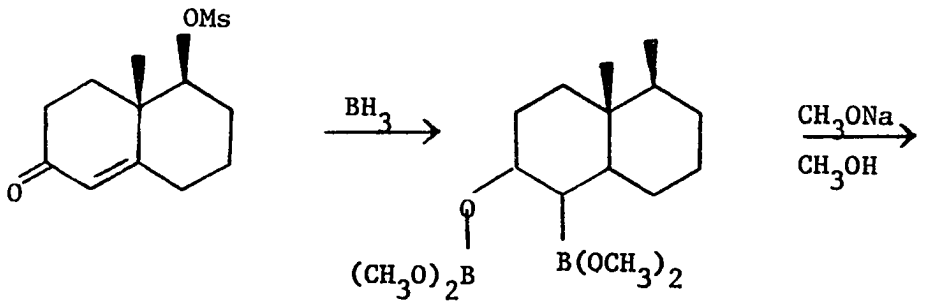


35 36

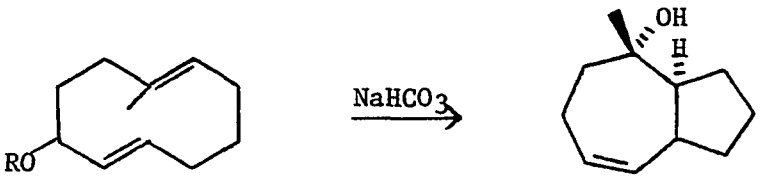


37 27

Marshall and Huffman (43) used the positionally and stereochemically selective cyclization of cyclodecadienyl derivatives. The unsaturated keto mesylate 38, upon treatment with excess diborane in tetrahydrofuran



38 39

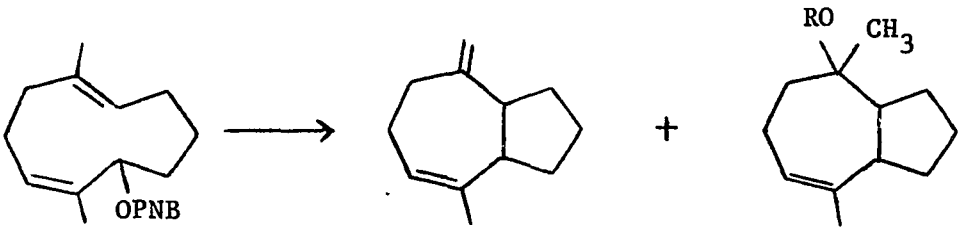


40, R=H
41, R=p-$NO_2C_6H_4CO$

42

followed by methanolic sodium methoxide, afforded the cyclodecadienol 40, presumably via the decalinboronate 39. Solvolysis of the p-nitrobenzoate derivative 41 in aqueous dioxane afforded the hydroazulenol 42, in 70% yield. This represents a valuable contribution, since Hendrickson (14) has postulated the biogenesis of hydroazulenes through an electrophile initiated trans, trans-1,5-cyclodecadiene cyclization process.

A solvolytic cyclization reaction to a hydroazulene product from cis, trans-2,6-cyclodecadiene 44 was published very recently (33). Diene 44 was obtained in a manner similar to the preparation of diene 41 used by



44

45

46, R=Ac
47, R=PNB

Marshall. Solvolysis of para-nitrobenzoate 44 in buffered acetic acid at room temperature gave a mixture identified as 46% olefin 45, 46% acetate 46, and 8% p-nitrobenzoate 47.

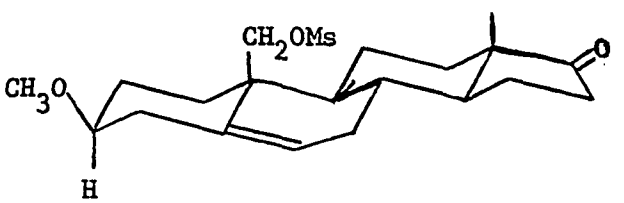
This survey of non-solvolytic and solvolytic pathways to the hydroazulene structure is not inclusive. However, all of the significant methods have been presented.

The major precedent for the solvolytic pathway used by the author was based upon Tadanier's studies on the homoallylic rearrangements of 19-substituted steroids (44, 45).

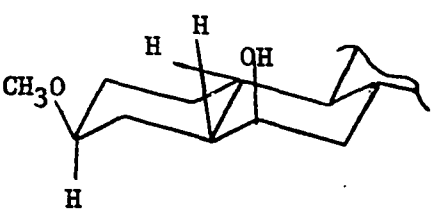
Hydrolysis of 3 β-methoxy-19-methanesulfonoxyandrose-5-en-17-one (48) in aqueous acetone containing potassium acetate as a buffer led to the isolation of the 5 β, 19-cyclo-6-ol 49, from carbonium ion A (see diagram) in 60% yield. This product was characterized by its nmr and ir spectra and by its oxidation to the known cyclopropyl ketone. The rearrangement was highly stereospecific giving rise to only one of the two possible C-6 epimeric alcohols.

When alcohol 49 was treated with aqueous acid under conditions expected to convert cyclopropylcarbinols to their more stable homoallylic isomers, the isomeric $\Delta^{5(10)}$-B-homo-7-ol 50, from ion B was isolated instead. This product was characterized by the absence of vinyl or cyclopropyl proton absorption in the nmr and ir spectra and by end absorption in the uv.

Tadanier proved that the rearrangement involved two discrete carbonium ion intermediates, the first (A) a resonance hybrid of canonical structures a through c and the second (B) a hybrid of d through f. Formation of the cyclopropyl carbinol 49 results from the kinetically controlled attack of water on the cation A. Under conditions of thermodynamic control, rearrangement of A leads to B which undergoes attack by water leading to the B-homo alcohol 50. Tadanier also

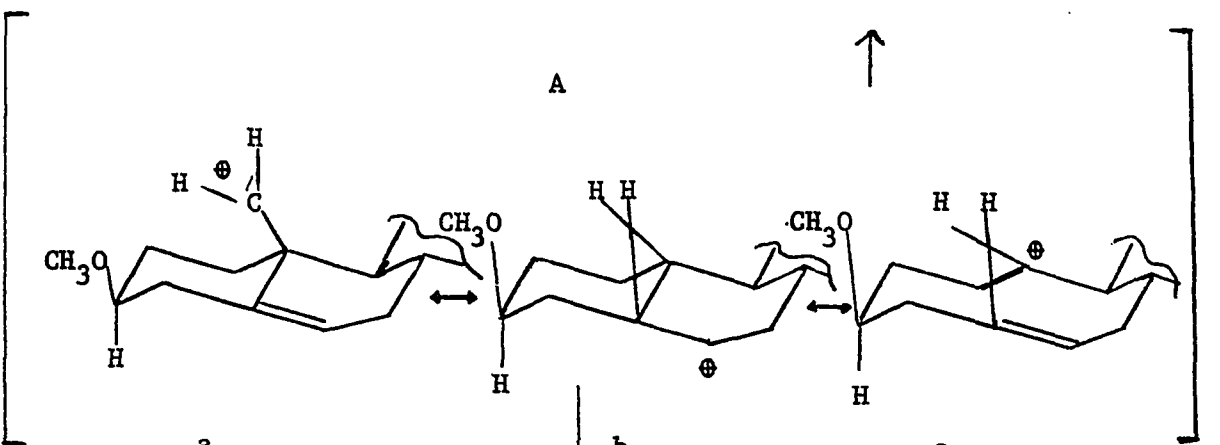


48



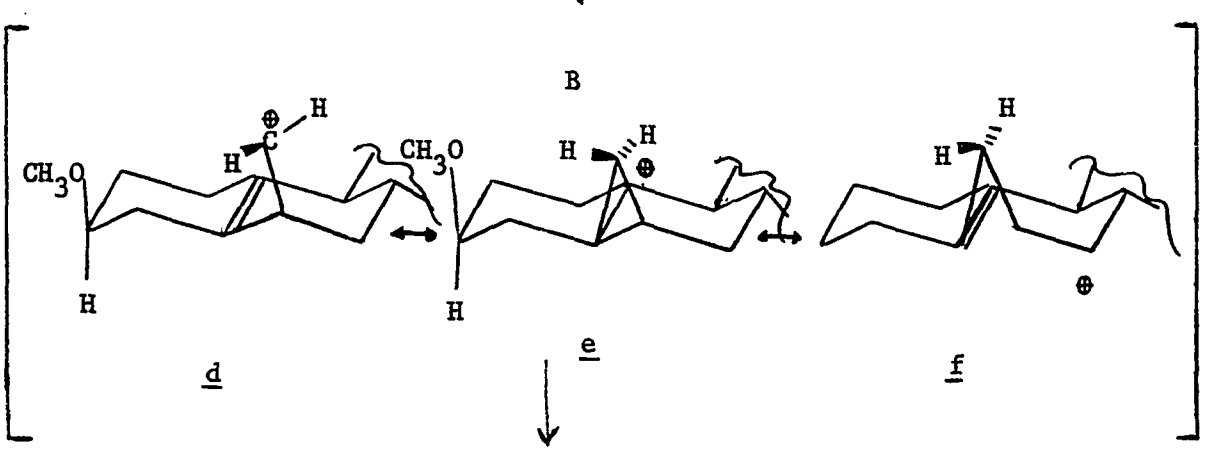
49

A

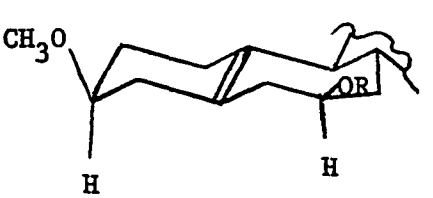


a b c

B



d e f

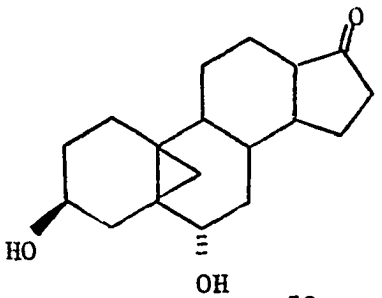


50, R=H

51, R=Ac

demonstrated that buffered acetic acid-acetate solvolysis of mesylate 48 leads to the 7β-acetate 51 directly (45).

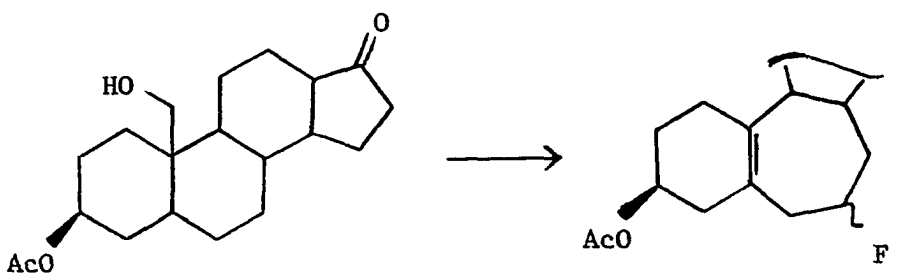
Carpio and coworkers (46) got a mixture by treating 3β,6α-dihydroxy-5β, 19-cycloandrostan-17-one (52) with hydrofluoric and sulfuric acids.



52

Some of the steroidal products had the B-homo-19-nor skeleton.

In another related study, treatment of homoallylic alcohol 53 with fluoramine, $(CH_3CH_2)_2NCF_2CHClF$ in methylene chloride gives the fluoride 54.



53 54

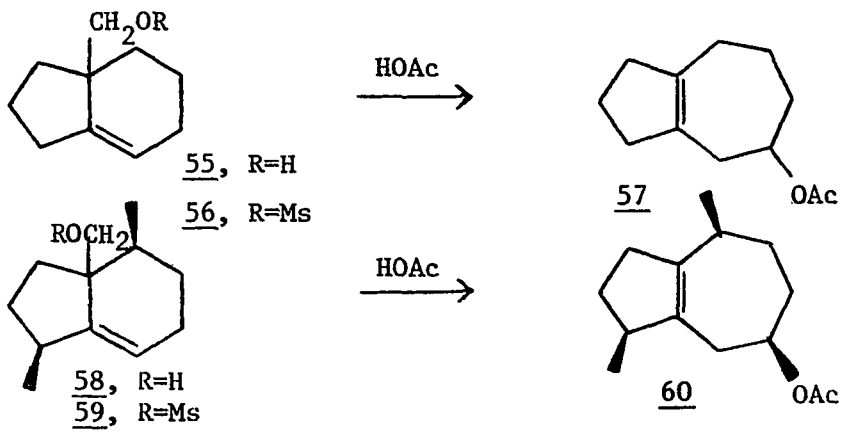
This work by Knox and coworkers (47) further illustrates participation of the double bond in the formation of the C-19 carbonium ion.

In summary, solvolytic and non-solvolytic pathways have been considered. The homoallylic rearrangement described by Tadanier was thought to be superior due to the high yields obtained and the lack of any rigorous stereochemical constraints as in the previously discussed cases. Although this rearrangement had not been previously tested on hydrindane derivatives, it ultimately became the key step in the synthesis.

RESULTS AND DISCUSSION

Introduction

The adaptation of the homoallylic rearrangement, discussed in the previous section, to a similar rearrangement of a hydrindane derivatives to hydroazulenic sesquiterpenes, had to be tested. A successful rearrangement of mesylate 56 to the hydroazulenic acetate 57 would be an excellent



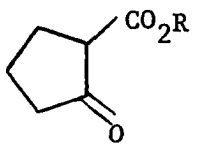
indication that the substituted mesylate 59 could be converted to acetate 60, which is easily transformed to guaiol.

The first part of this section concerns the attempted and finally successful synthesis of alcohol 55, its rearrangement, and the structure proof of the product. This represents good evidence of the adaptability of the rearrangement to a system which is bicyclic rather than steroidal. It also extends the utility of the reaction to the hydrindane system as well. The work on the model system was completed (48) and later corroborated by Marshall and Greene (22).

The second part of this investigation is concerned with the attempted synthesis of alcohol 58, as a viable intermediate to guaiol (21, 49).

Synthesis of 5,6,7,8-tetrahydroindanyl-8-methanol (55)

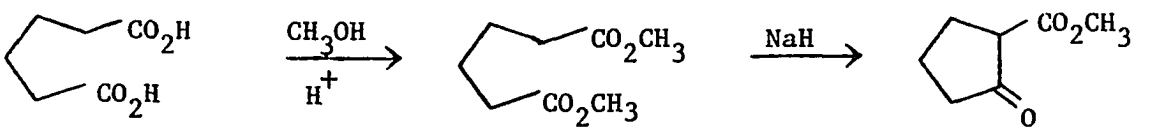
There is a mixture of esters 61 commercially available, in which R is a mixture of methyl and ethyl esters. This mixture was used in several



61, R=C_2H_5 and CH_3
62, R=CH_3

reactions throughout the course of this work. The pure methyl ester (not commercially available), however, was desired because of the resultant simplification of the nmr spectrum (compared with the mixture of the ethyl ester) and the fact that methyl esters are more likely solids than are the corresponding ethyl esters.

The synthesis of cyclopentanone carboxylate 62 was accomplished in two high yield steps. Commercially available adipic acid was converted to

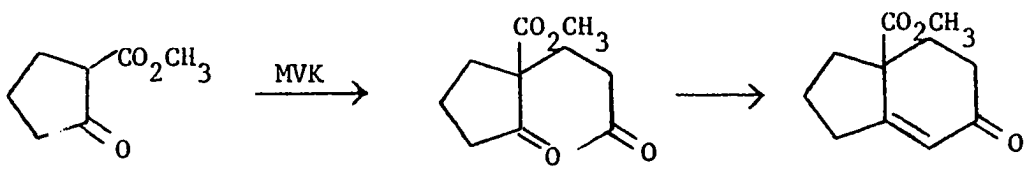


63 64 62

dimethyl adipate in 91% yield. This was done following the procedure of Clinton and Laskowski (50). The Dieckmann cyclization of diester 64 was attempted using sodium methoxide and methanol. The cyclization was

incomplete using these reagents, as evidenced by the nmr spectrum of the product. However, either incompletely cyclized material or pure 64 could easily be converted to the cyclopentanecarboxylate 62 with two equivalents of sodium hydride.

The two reactions required to fuse a six-membered ring onto this moiety, a Michael addition using methyl vinyl ketone followed by an intramolecular aldol condensation, seemed straightforward. The keto ester 62 was treated with triethylamine and methyl vinyl ketone. The

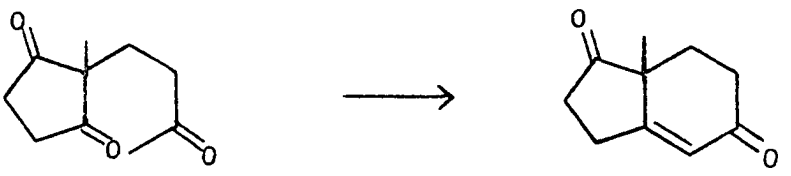


62 65 66

reaction requires seven days at room temperature (51). An alternative procedure has been developed for the Michael addition, reducing the reaction time to only one day. The procedure involves using potassium carbonate as the base and will be discussed in greater detail later in this section. The Michael adduct 65 is formed in excellent yield regardless of the method used.

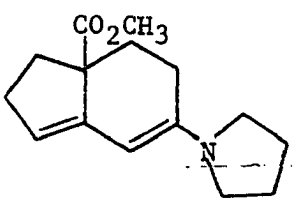
Many attempts were made to cyclize dione 65 to the α,β-unsaturated ketone 66. The ethyl ester of 66 has recently been prepared with aluminum t-butoxide (51). The main drawback of this reaction is the poor yield (34%) of the desired keto ester 66. A more convenient cyclization catalyst was sought. There is a report of heating to reflux in a benzene solution

with a catalytic amount of p-toluenesulfonic acid (52). This causes the cyclization of trione 67 to dione 68 in 83% yield. Another analogy specified a trace amount of pyrrolidine for a similar cyclization (53).



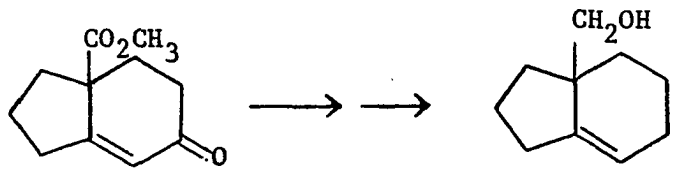
67 68

Both of these reagents, in catalytic amounts, were heated to reflux in benzene with dione 65 for prolonged periods, however only starting material was recovered. If two equivalents of pyrrolidine are used (54), the cyclization proceeds in good yield (81%). Spectral data of the isolable intermediate suggests it to be the enamine 69. Similar cyclizations (55, 56) are thought to proceed through an analogous intermediate enamine.



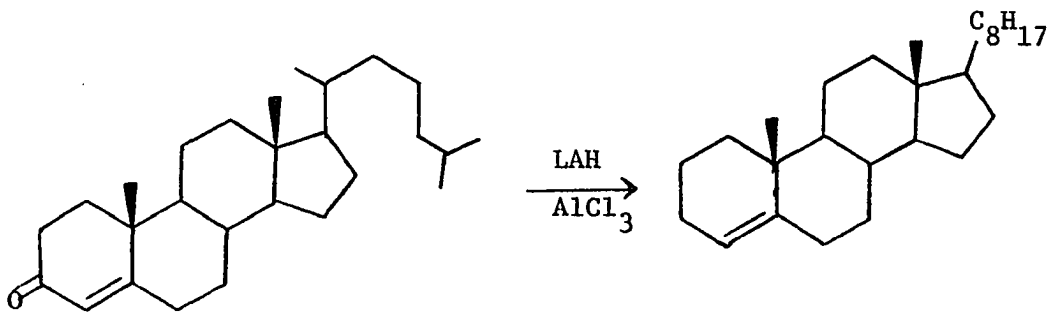
69

A one step conversion of the keto ester 66 to the desired unsaturated alcohol 55 was attempted with a mixed hydride derived from lithium aluminum hydride and aluminum chloride. Precedents occur in the literature



66 55

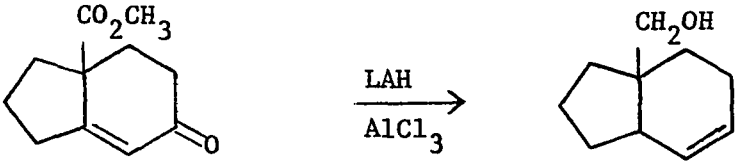
as evidenced by the reported reduction of cholest-4-en-3-one (70) to 4-cholestene (71) in good yield (57). The reaction does not proceed with



70 71

saturated ketones. However, because the double bond does participate in the reaction, migrations and rearrangements can and do occur. For example, Albrecht and Tamm (58) reduced cholest-1-ene-3-one with various proportions of lithium aluminum hydride and aluminum chloride. Of the products which were deoxygenated at C-3, 33% had undergone double bond migration under the reaction conditions giving 2-cholestene.

The behavior of the double bond is unpredictable. However, when the ketone function and carbon-carbon double bond occupy the same ring, migration of the double bond is less likely (57). Treating keto ester 66 with various proportions of $LiAH_4$-$AlCl_3$ resulted in the formation of a

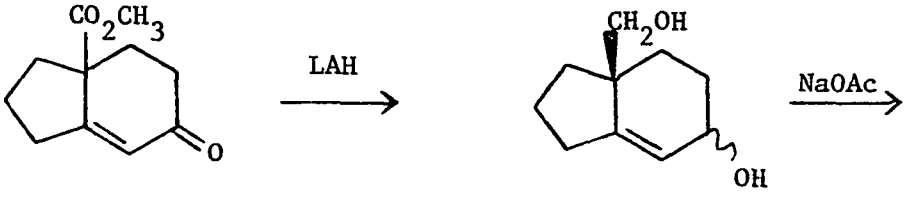


66 72

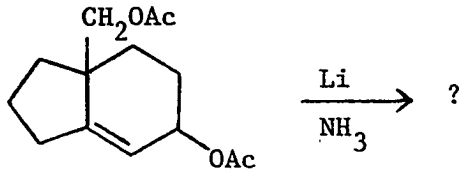
white crystalline product whose ir and nmr spectra are consistent with alcohol 72.

Caglioto and Grasselli (59) have reported the two step reduction of ketones to alkanes under mild conditions. The first step involves formation of the tosylhydrazone derivative of the ketone, using tosylhydrazine and acid. The derivative is then reduced with lithium aluminum hydride or sodium borohydride to the corresponding hydrocarbon. The workers report no examples using an α,β-unsaturated ketone but do point out that the reduction is slow for aromatic ketones. The tosylhydrazone derived from keto ester 66 was not reduced with either hydride under extended reaction times.

To synthesize the desired intermediate alcohol 55 the following reaction sequence was attempted. Keto ester 66 was reduced to the diol



66 73



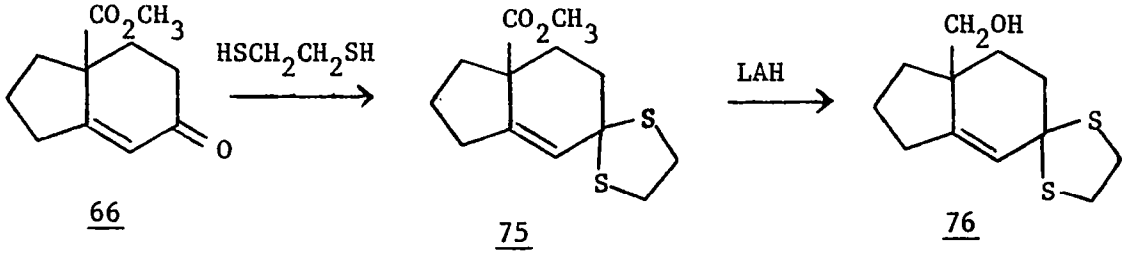
74

in yields of about 95%. The product was an oily semi-solid. Upon recrystallization using ethyl acetate much of the material was lost, reducing the yield to 42%. It was felt that one epimer of the mixture 73 was being selectively crystallized. For our purposes, stereochemistry at C-5 in the hydrindane skeleton was unimportant and therefore the crude reduction mixture was used. The diol was then converted to the diacetate 74 by treatment with sodium acetate in refluxing acetic anhydride over a 1 hr period.

The diacetate 74 was treated under conditions for a Birch reduction, namely, lithium in liquid ammonia. These conditions would hopefully reduce both the primary acetate and the secondary acetate and also maintain the integrity of the carbon-carbon double bond. Initial experiments yielded a mixture of products which, based on the ir and nmr spectra contained residual acetate. These initial products were then reduced with lithium aluminum hydride to see if the primary acetate was inert under Birch conditions. The product of these reductions were largely starting material. When the amount of lithium was increased and reaction time lengthened from 4 to 7.5 hr, no acetate absorption was found in the ir spectrum of the crude product. Further spectral analysis indicated that the structure of the product was other than the desired alcohol 55. The product's ir

spectrum was very close to the ir of the product from the mixed hydride reduction, which was assigned structure 72. The respective nmr spectra, however, were not similar with major differences in the vinyl proton region. A complete structure determination of the Birch product from diacetate 74 was not carried out. In view of the difficulties of obtaining alcohol 55 by these methods, alternative routes were investigated.

A variety of reductions of thioacetals are known (60). This route was undertaken and finally proved to be successful. Keto ester 66 was converted to the thioacetal 75 using ethanedithiol and boron trifluoride

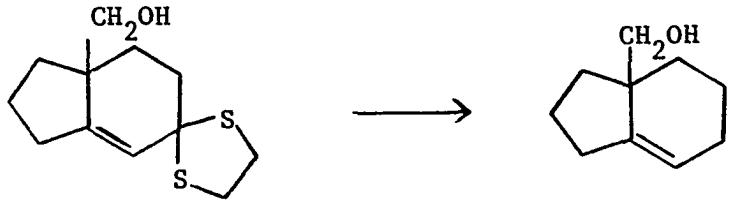


66 75 76

(61). Good results were achieved when the solvent properties of ethanedithiol were utilized. The reaction is carried out using two equivalents of ethanedithiol as the solvent. In the workup the excess dithiol is removed by meticulous washings with ice-cold 10% aqueous sodium hydroxide.

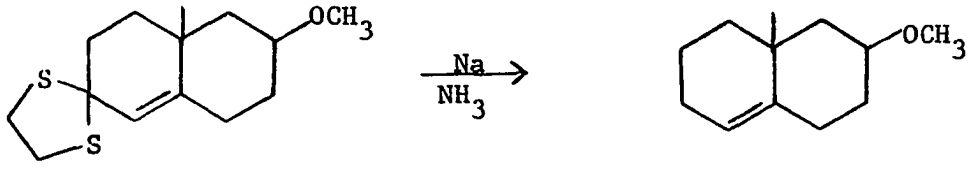
The thioacetal ester 75 was smoothly reduced to the alcohol 76 in excellent yield by treatment with lithium aluminum hydride. This thioacetal alcohol turned out to be the only compound in the sequence of sufficiently high melting point to be conveniently purified by recrystallization.

Reduction of the thioacetal 76 to the unsaturated alcohol 55 was attempted using sodium and ammonia. There is adequate documentation



76 55

recorded for similar reductions. Minato and Nagasaki, for example, reduced the thioacetal 77 to the ether 78 in 90% yield, under these conditions



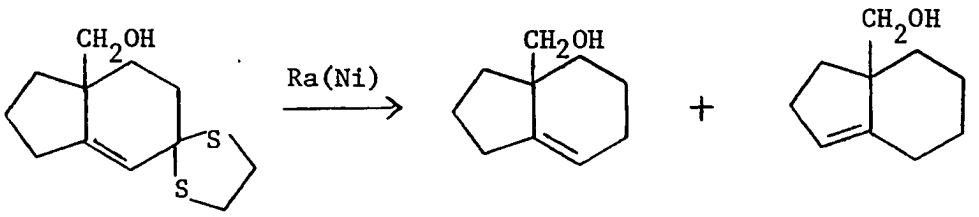
77 78

(62). The thioacetal derived from cholest-4-en-3-one has also been reduced using sodium and ammonia (63). The product, 4-cholestene, is isolated in 87% yield.

Large scale (10-25 g) reductions of thioacetal 76 with sodium and ammonia gave alcohol 55 in yields of only 18%. Higher boiling products were not identified but a portion of them are thought to be probably dimeric.

A milder reduction of thioacetals using hydrazine hydrate and base (64) proved ineffective in our system. Two attempts using these conditions left the thioacetal 76 intact.

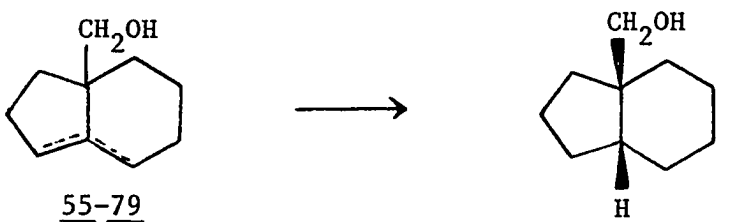
The classical method for this type of reduction involves the use of Raney nickel (65). Treatment of thioacetal 76 with W-2 Raney nickel catalyst in ethanol for 25 min at room temperature gave a 3:2 mixture (g.l.c.) of alcohols 55 and 79. Alternative structures containing



76 55 79

disubstituted double bonds were ruled out on the basis of subsequent reactions and the presence of only one vinyl proton in the nmr spectrum of the mixture. Double bond migrations are known in the desulphurization of α,β-unsaturated thioacetals (66). However, the migration of the double bond away from the reaction site has not been previously reported. Thioacetal 76 is known to be only one isomer as evidenced by g.l.c. analysis. In addition, the nmr spectrum of 76 shows no strong coupling of the vinyl proton and exhibits only allylic coupling.

The mixture of alcohols 55 and 79 was reduced with hydrogen over a platinum catalyst to the known (67) cis-hexahydroindane-3a-methanol (80).



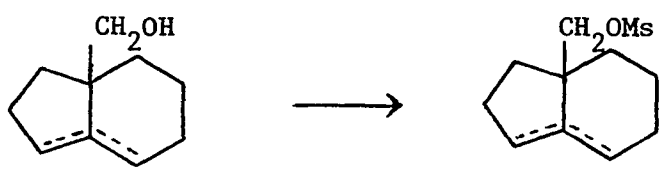
55-79 80

This provided clear evidence that desulphurization had not led to unexpected structural rearrangements.

It was necessary to work with the mixture of alcohols 55 and 79 in the subsequent reaction sequence. The author was unable to find a suitable physical separation of these isomers which could be done on a reasonable scale. In the experimental section the mixture is understood and the hydrindane-hydrindene mixture is referred to as a hydrindane.

The preparation of the respective mesylates from alcohols 55 and 79 was attempted using sodium hydride and methanesulfonyl chloride. Whether one or two equivalents of sodium hydride were used there was always residual alcohol present. This is based on thin layer chromatographic analysis and ir spectra of consecutive aliquots taken at time intervals throughout the reaction. However, this evidence does not rule out rearrangement under the reaction conditions to form another alcohol with an identical R_f value with alcohols 55 and 79.

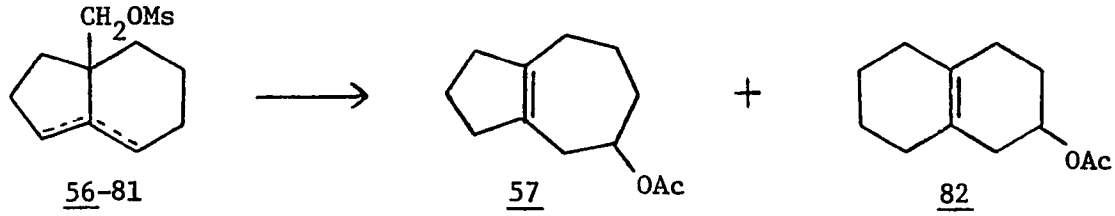
A mixture of mesylates 56 and 81 was formed in the presence of methanesulfonyl chloride and pyridine. The yields of this reaction were



55-79 56-81

variable (48-100%). However, the best results were achieved if the crude mesylate was used immediately in the subsequent step.

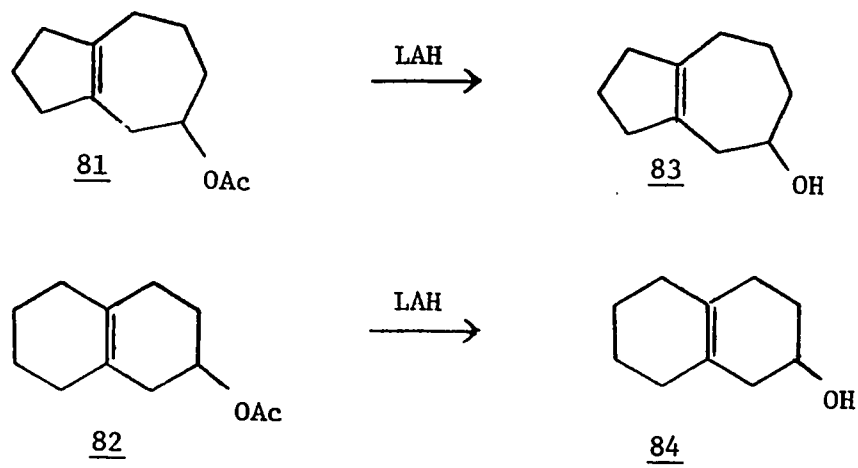
The mixture of mesylates 56 and 81 was heated to reflux in a buffered solution made from potassium carbonate, acetic anhydride, and glacial acid. These are conditions of thermodynamic control (44). This led to



56-81 → 57 + 82

the expected mixture of acetates 57 and 82. The presence of two compounds in a 3:2 ratio was shown by g.l.c. analysis using a Carbowax 20M column at 125°.

The mixture of acetates 57 and 82 was reduced to alcohols 83 and 84 with lithium aluminum hydride.

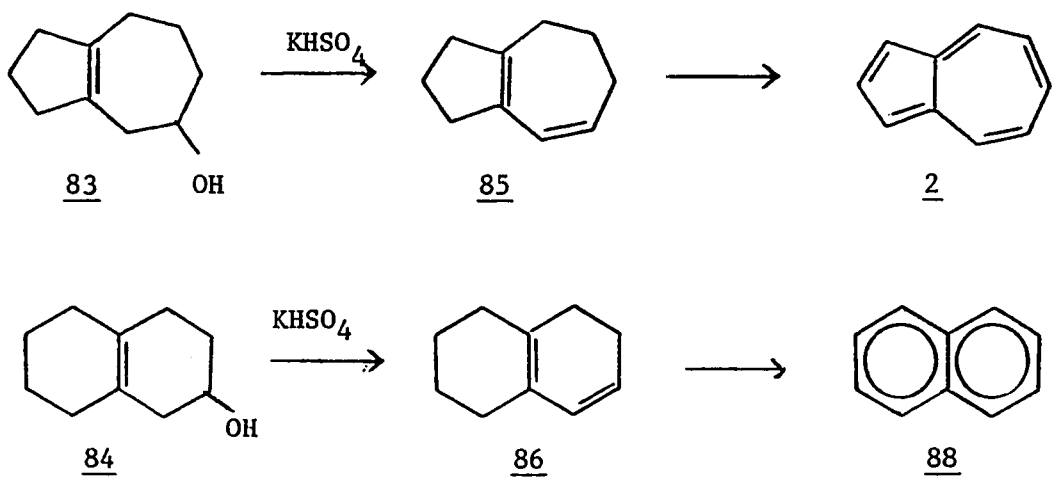


81 → 83

82 → 84

The structure assignment of these alcohols was based on analogy with Tadanier's work (44), chemical and spectral evidence. Although the nmr spectrum of the mixture of alcohols 83 and 84 displays no resonance in the vinyl or cyclopropyl region, the mixture readily decolorized a bromine-carbon tetrachloride solution. The mass, nmr and ir spectra were also consistent with the proposed structures. The differences in the chemical shifts of the α-protons of the alcohol group (RR'CHOH) and the corresponding proton in the acetate ($RR'CHOCOCH_3$) is 3.6-4.7 = -1.1, on the δ scale. This is the difference expected when the original alcohol is on a secondary carbon atom (68). The value is -0.5 for primary alcohols.

The alcohols 83 and 84 were dehydrated and dehydrogenated showing that the ring systems were in fact hydroazulenic and hydronapthalenic, respectively. Heating the alcohols in the presence of potassium hydrogen



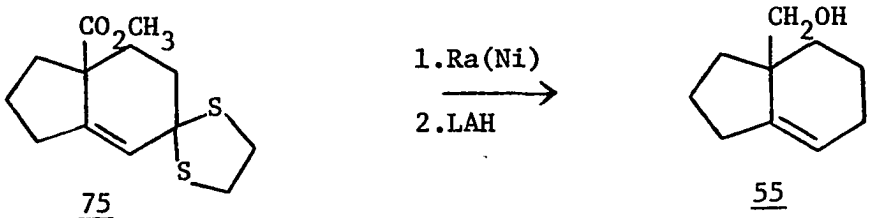
83 85 2

84 86 88

sulfate at 150-160° for 1 hr yielded dienes 85 and 86. The ir spectrum showed no absorption corresponding to O-H stretch. Treating the dienes 85 and 86 with palladium on charcoal (69) at 250° for 1 hr yielded azulene (2) and napthalene (87). Both were identified by g.l.c. retention times and peak enhancement experiments. The azulene (2) could be separated by extraction with phosphoric acid and regenerated by dilution (2).

A significantly higher proportion of napthalene with respect to azulene was observed. This warrants an explanation since the alcohols 83 and 84 were present in a 3:2 ratio. The dehydrogenation of bicyclo[4.4.0]-decane sesquiterpenes to napthalenes is a facile process with yields of 50% or more (70). The dehydrogenation to azulenes of bicyclo[5.3.0]decanes derivatives gives extremely poor yields, in the range 2-10%. Also the dehydrogenation to azulenes sometimes involves deep-seated rearrangements. The rearrangement of azulene itself to napthalene has been observed and is reasonable when one considers the higher resonance energy of napthalene (71).

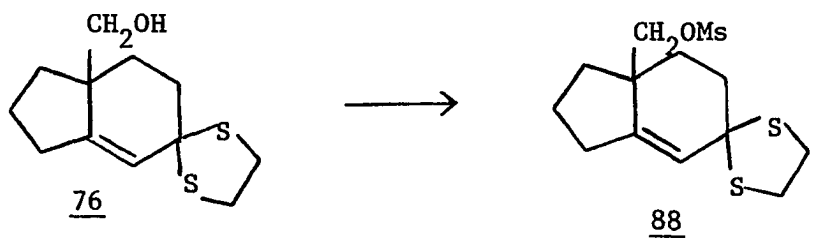
A mixture of double bond isomers has not been observed (22) when the ester thioacetal 75 (actually the commercial mixture of methyl and ethyl ester) was desulphurized with Raney nickel. Reduction of the



75 55

resulting dithio ester with lithium aluminum hydride gave only alcohol 55. It is possible that the isomeric alcohol 79 was present but was not observed. However, the amount of double bond migration occurring in the desulphurization depends upon the Raney nickel used. If the metal catalyst is judiciously washed in a stepwise fashion, opposed to a continuous wash, the Raney nickel produced is less prone to cause double bond rearrangement. A similar structure proof on acetate 57 was done by Marshall and Greene (22) and their findings are in agreement with the proposed structure.

It is clear from the previous discussion that the mixture of olefins arise from the desulphurization of thioacetal 76. It was hoped that the solvolytic rearrangement would not be altered by the presence of the thioacetal ring and the rearranged product could then be desulfurized.

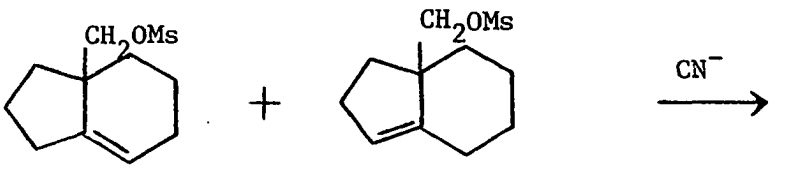


76 88

However, the mesylate 88, prepared from alcohol 76 and mesyl chloride in pyridine, was inert under the solvolysis conditions.

The solvolysis was reported by Tadanier to be stereoselective, giving rise to only one possible epimeric acetate (44). If the carbonium ion intermediate could be trapped with cyanide, stereoselective formation of a carbon-carbon (or perhaps a carbon-nitrogen bond) would occur.

The cyanide function could easily be transformed to an hydroxy-isopropyl group. However, solvolysis of mesylates 55 and 57 in the presence of



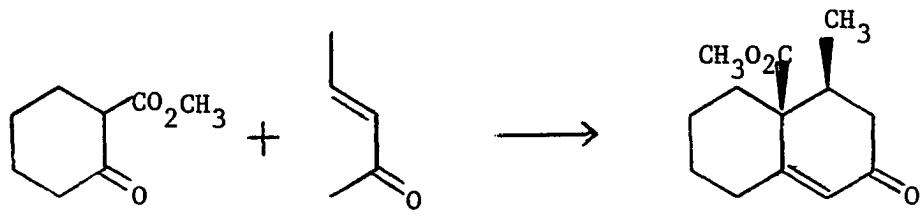
56 81

potassium cyanide provided no incorporation of cyanide. The ir spectrum of the product exhibits no absorption in the 2000-2500 cm^{-1} region typically characteristic of the nitrile group.

Literature Synthesis of r-3, c-7, dimethyl-5,6,7-7a-tetrahydroindane c-7a-methanol (97)

During the course of this work there appeared two consecutive communications which had a direct bearing on the problem. One of the papers described the synthesis of guaiol (21). The other paper (22) outlined the stereoselective synthesis of alcohol 97, which had been the goal of this author. The approach was very different but it nonetheless will be considered here in some detail.

The 4,4a cis-napthalenone 89 was stereoselectively synthesized from keto ester 98 and trans-3-penten-2-one (99), using potassium tert-amylate in tert-amyl alcohol (72). The highest ratio (3.08) of cis/trans isomers was achieved under these conditions. The study concluded that high

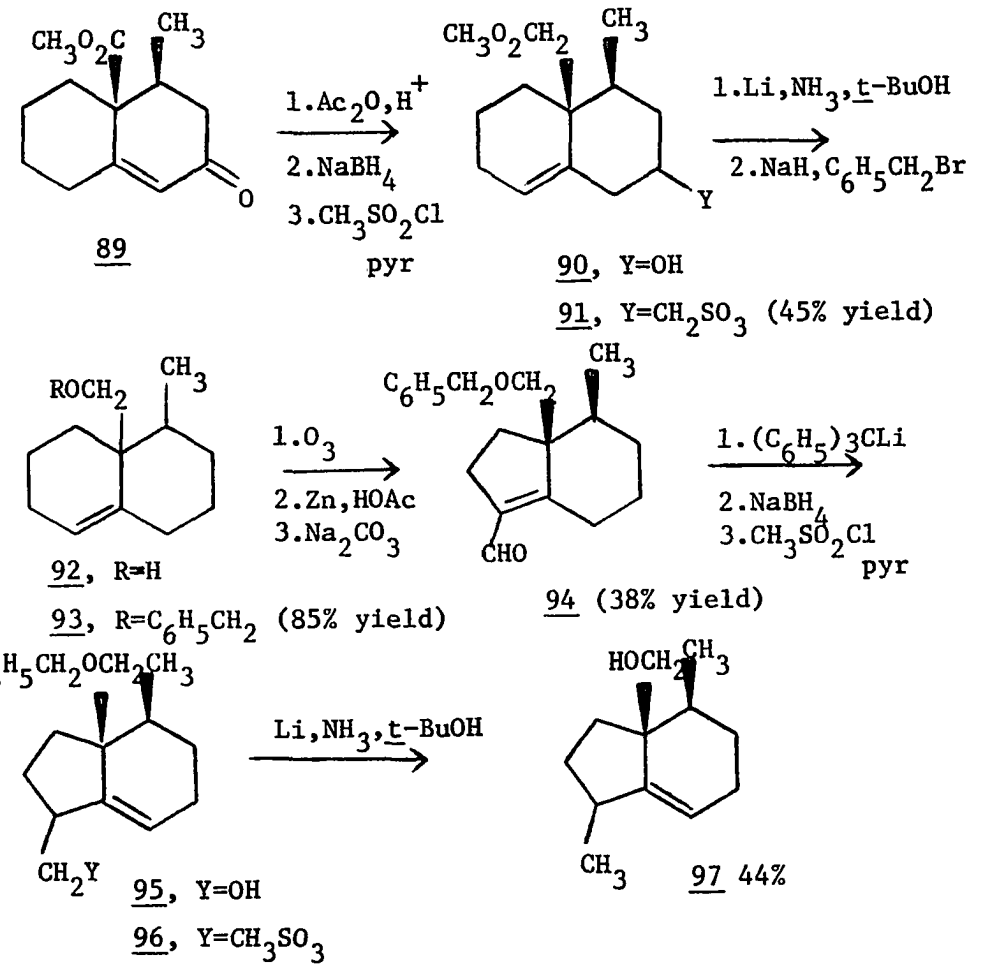


98 99 89

cis/trans ratios could be attained at low temperatures and by using sterically bulky solvents like tert-butyl and tert-amyl alcohols. The cis and trans keto esters were separated by fractional crystallization of their enol ethers.

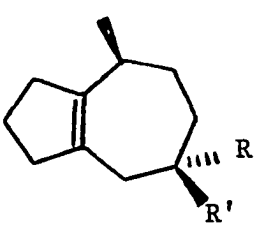
The predominantly cis-napthalenone 89 was converted to the enol acetate, which in turn was reduced with sodium borohydride in ethanol to yield the homoallylic alcohol 90 (see diagram). Esterification of 90 with methanesulfonyl chloride in pyridine at 0^{o} afforded mesylate 91. Hydrogenolysis-reduction using lithium in ammonia containing tert-butyl alcohol gave alcohol 92 which was converted as the benzyl ether 93. Ozonolysis in pentane followed by reductive workup in the presence of zinc and acetic acid yielded an intermediate keto aldehyde which underwent aldol cyclization with sodium carbonate, water, and ethanol giving the unsaturated aldehyde 94. Treatment with triphenyl methyl lithium converted aldehyde 94 to its enolate which was then quenched with aqueous ethanol containing sodium borohydride giving the homoallylic alcohol 95. The stereochemistry is assigned on the assumption that protonation of the enolate of aldehyde 94 takes place preferentially trans to the angular benzyl ether substituent.

The all cis alcohol 95 was converted to the methanesulfonate derivative



96. Hydrogenolysis of the mesyloxy and benzyl groups afforded the key intermediate alcohol 97.

In the synthesis, Marshall and coworkers (21) use a relay compound in order to complete the sequence. The relay compound is a mixture of 100 and 101 which was obtained via degradation of guaiol.



100, $R=CO_2CH_3$; R'=H

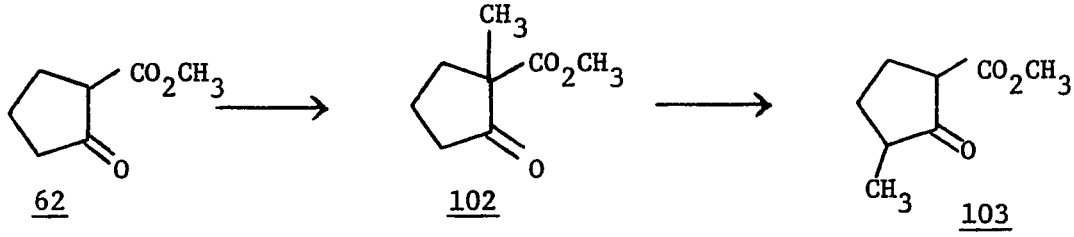
101, R=H; $R'=CO_2CH_3$

There are several pitfalls associated with Marshall's synthesis, the greatest of which is undoubtedly the poor yields obtained. Examination of the stated percentages in the preceding diagram confirm this. Also the 4-methyl group in keto ester 89 is at best a 3:1 mixture of cis and trans isomers which is carried through to the relay compound in the synthesis.

Attempted Synthesis of r-3, c-7, dimethyl-5,6,7,7a-tetrahydro-indane-c-7a-methanol (97)

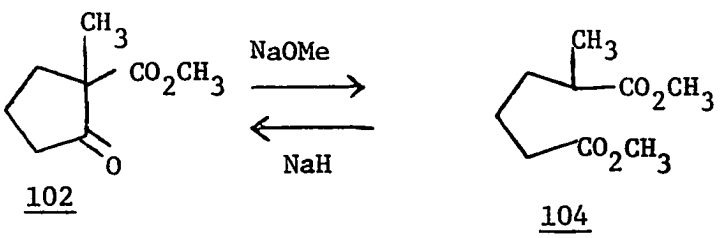
The literature synthesis (52) starts with a hydronapthalene and ultimately converts it to the hydrindane system. The approach used in the present work involves the initial construction of the hydrindane ring system with the appropriate substituents already present. The only changes over the model system, discussed earlier, are the incorporation of two methyl groups. One is on the five-membered ring and the other is on the six-membered ring. The plan was to add the methyl substituents at an early stage in the synthesis.

The methylation of keto ester 62 and its rearrangement to the methyl keto ester 103 was considered to be the best known synthesis of this



62 102 103

compound. The procedure (73) involves Dieckmann cyclization of dimethyl adipate followed by methylation of the sodium enolate derived from keto ester 102. Compound 102 is then rearranged with sodium methoxide in methanol to the desired methyl keto ester 103. All of this is accomplished in one flask without the isolation of any of the intermediates. Attempts to duplicate this procedure gave instead of the expected keto ester 103, the acyclic diester 104. Diester 104 in the presence of sodium hydride,

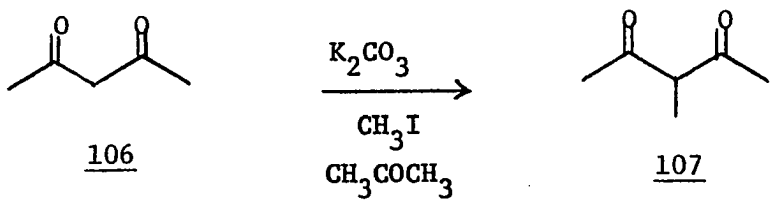


102 104

cyclizes to methyl ester 102 and not the desired rearranged ester 103.

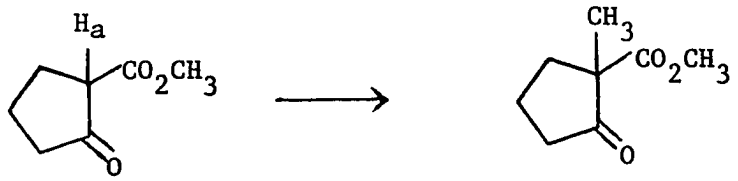
An alternative procedure involves isolation of the intermediates in the sequence. Methylation of keto ester 62 with sodium hydride and methyl iodide to methyl ester 102 was tried. The results of these experiments were less than satisfactory. Some of the starting material remains unchanged. This is evidenced by an examination of the nmr spectrum of the product. Also in the presence of ferric chloride/ethanol a purple color is observed. Efforts to complete the conversion of 62 to 102, with excesses of base and methyl iodide, resulted in polymethylation.

Potassium carbonate is used to effect the monomethylation of pentane-2,5-dione (105) to 3-methylpentane-2,5-dione (106), in good yields (74).



106 107

The keto ester 62 was treated under the same conditions (potassium carbonate and methyl iodide in an acetone solution). The reaction mixture

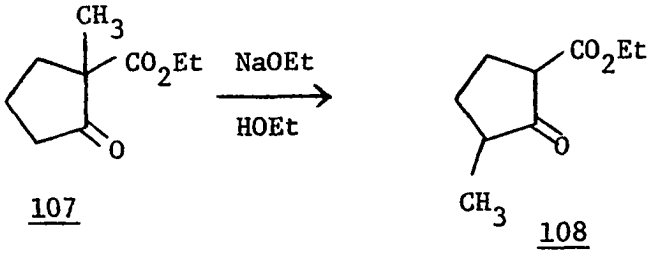


62 102

was heated to reflux for 4.5 hr, but the isolated product gave a purple color in the presence of ferric chloride. The nmr spectrum, however, exhibits no trace of starting material. This is evident from the lack of a resonance at δ 3.08 ppm, corresponding to the chemical shift of the C-1 proton (H_a) (t, J = 7 Hz) in 62. When the 4.5 hr reaction time was increased to 20 hr, the product gave no color with alcohol ferric chloride. This test has been found to be very sensitive to very low concentrations of enolizable β-keto esters. Therefore, it is felt that the reaction went essentially to completion. This was substantiated by g.l.c. analysis.

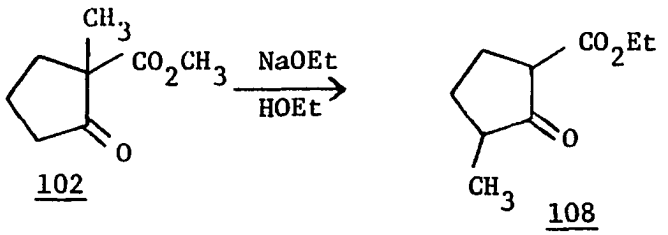
The rearrangement of the methyl ester 102 was attempted using sodium methoxide and methanol. These conditions resulted in almost complete conversion to the acyclic diester 104, which could not be converted to the desired product. The corresponding ethyl ester 107, according to the literature (75), has been converted to the rearranged keto ester 108

with sodium ethoxide and ethanol. The reaction was driven to completion



107 108

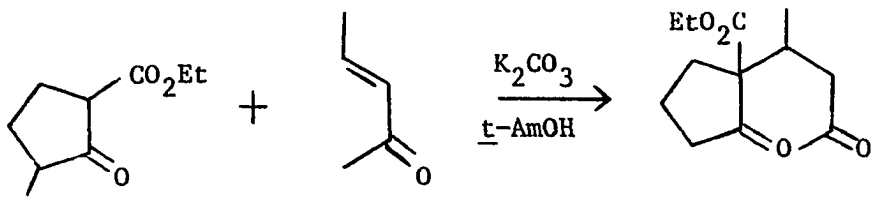
by using toluene to azeotrope the ethanol from the reaction. If these conditions are employed on methyl ester 102, the product isolated is the rearranged ethyl ester 108. The ester exchange is believed to occur most



102 108

probably in the acyclic intermediate 104. In 104 the ester carbonyl is reasonably unhindered and in the rearranged product (103 or 108) ester exchange would be expected to be competitive with enolization. The ester exchange is 90-95% complete, as evidenced by the nmr spectrum of the product. The small amount of methyl ester was not detrimental in the remainder of the sequence.

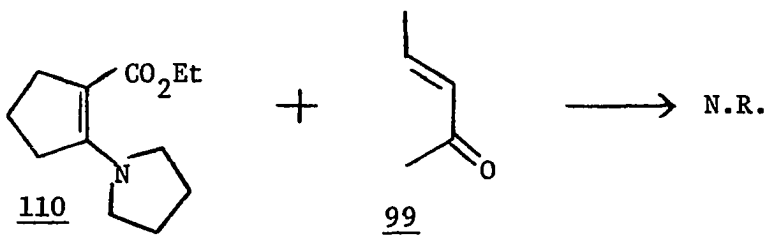
The alkylation of keto ester 108 with trans-3-penten-2-one (99) gives the Michael adduct 109. The base used for the transformation is potassium carbonate in tert-amyl alcohol. The reaction is heated overnight at 50° and the yield of adduct is 84%. Trans-3-penten-2-one was synthesized by



108 99 109

the base catalyzed condensation of acetaldehyde and acetone followed by dehydration of the intermediate ketol (76).

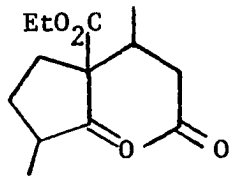
The conditions described for the Michael reaction evolved from a number of attempts to alkylate β-keto esters related to 108. For example, the β-keto ester 108 and trans-3-penten-2-one (99) were treated with triethylamine for seven days. These conditions are identical to the ones which gave the Michael adduct of methyl vinyl ketone and 2-carbomethoxycyclopentanone in high yield. Unfortunately, only unchanged starting material was obtained in this case. The enamine 110 derived from keto ester 103 was found to be remarkably stable and did not react



110 99

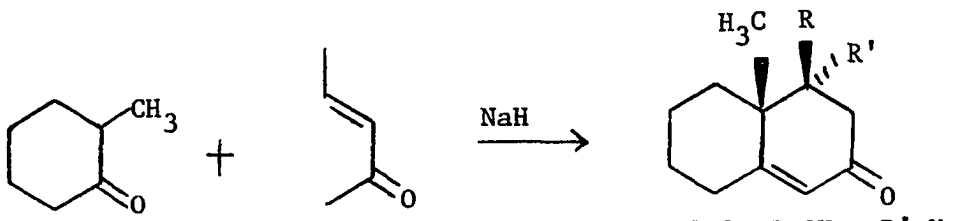
with trans-3-penten-2-one. The enamine was so unreactive that it proved to be very difficult to hydrolyze.

A search was undertaken for conditions to synthesize the Michael adduct 109 with the angular carboxy group and the methyl group predominantly



109

cis. Previous work in our research group (77) had shown a critical solvent dependency on the stereochemical outcome of the Robinson annulation of 2-methylcyclohexanone (111) with trans-3-penten-2-one (99). The sodium



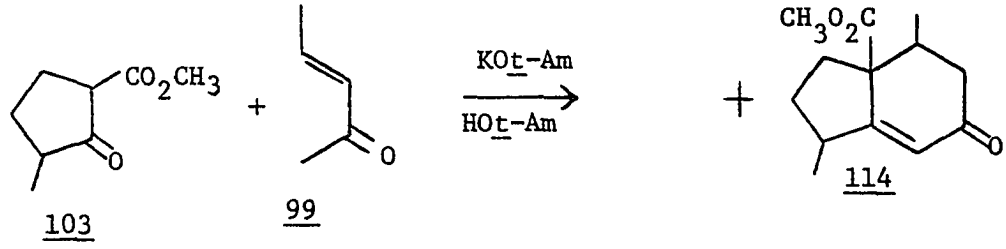
111 + 99 → NaH

112, R=CH_3, R'=H
113, R=H; R'=CH_3

enolate of 111 in dioxane gives cis napthalenone 112 and in DMSO yields the trans isomer 113. It was hoped that similar results would be obtained with related cyclopentanones. However, no observable reaction occurred when β-keto ester 108 was treated under these reaction conditions.

The reaction conditions reported to give a high degree of stereoselectivity when employed with carboethoxycyclohexanone and trans-3-penten-2-one (72) were investigated. The highest cis/trans ratio was observed using potassium tert-amylate in tert-amyl alcohol, as previously discussed. These conditions were used with keto ester 103. The product contained

mostly starting material and only a small amount of cyclized product 114 was isolated. The stereochemistry of 114 was not investigated in view

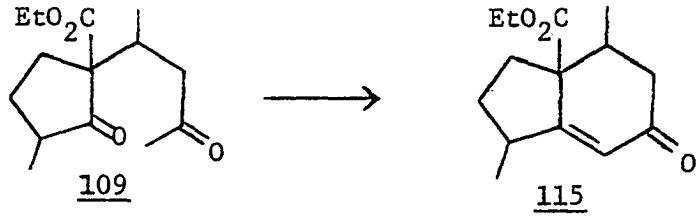


103 99 114

of the poor yields obtained.

Based on the previously described methylation studies, potassium carbonate appeared to be an attractive base to investigate. However, another solvent was in order since acetone could act as an electrophile, perhaps competitively with trans-3-penten-2-one. As already discussed tert-amyl alcohol gives rise preferentially to the cis isomer. These conditions afforded the Michael adduct 109, which showed no indication of starting material in its nmr spectrum and by the absence of a positive ferric chloride test.

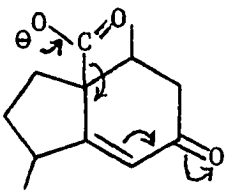
Experiments designed to cyclize dione 109 to the α,β-unsaturated ketone 115 using the conditions of the related reaction in the model system proved unsuccessful. The pyrrolidine catalyzed reaction via the



109 115

pyrrolidine enamine gave only small amounts of product.

Although used in various cyclizations, methanolic potassium hydroxide was not seriously considered. The harsh conditions would likely saponify

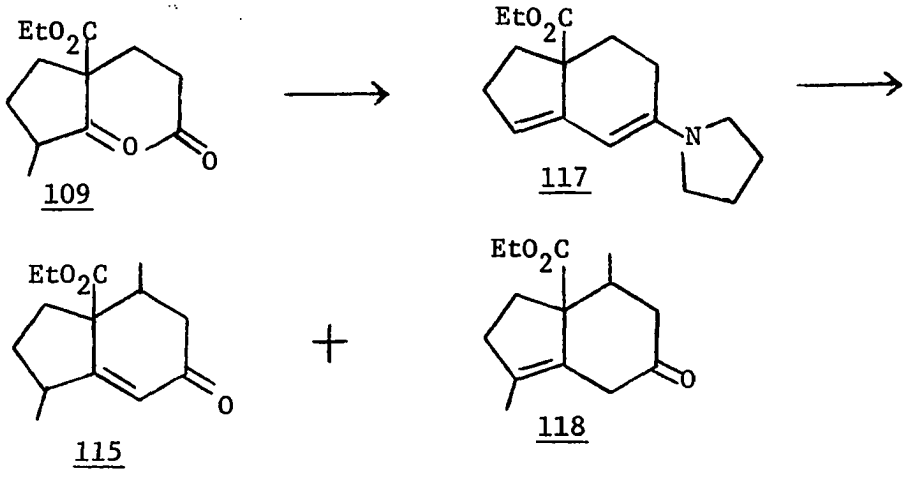


116

the angular ester group and, after cyclization, the resulting vinylogous β-keto acid could easily decarboxylate as shown in 116.

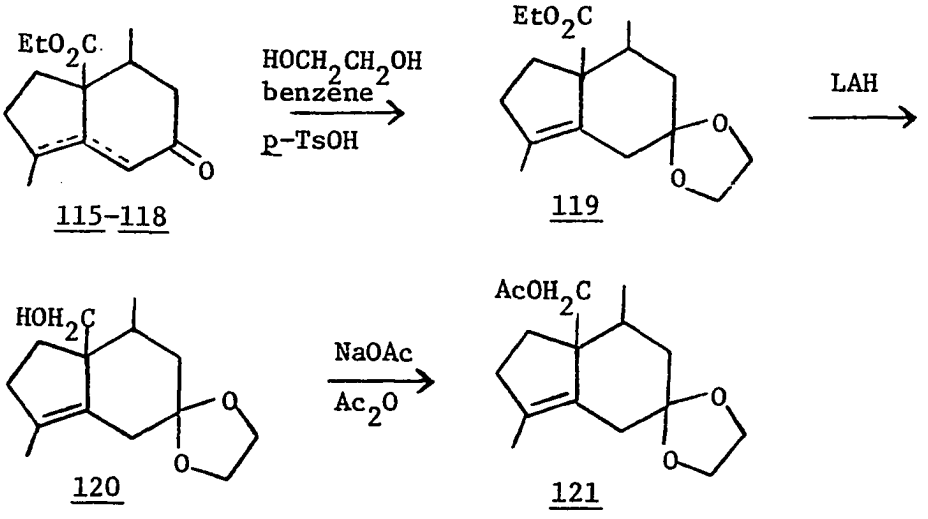
Aldol condensation and dehydration reactions using boric acid were studied by Offenhauer and Nelson (78). The mildly acidic conditions of boric acid were tried on dione 109 and resulted again in recovered starting material.

A reason was sought to explain why the initial experiments on the cyclization of dione 109, via the pyrrolidine enamine failed. Since very little water was observed in the Dean-Stark trap, it was thought that perhaps the enamine had never formed. It has been reported that small amounts of p-toluenesulphonic acid catalyze the formation of enamines from hindered ketones (79). This modification allowed the reaction to proceed to form the isomeric products 115 and 118 in a ratio of 36:64, respectively. This was determined by integration of the nmr spectrum of the distilled mixture. The enamine 117 was shown to be an intermediate in the reaction by its isolation before hydrolysis to the unsaturated ketones 115 and 118. The spectra of enamine 117 were similar to the spectra recorded for the enamine obtained in the model system.



The double bond isomers 115 and 118 were separated, for characteristic purposes, by careful chromatography on silica gel. However, since the next reaction in the sequence was shown to cause double bond isomerization, the 115-118 mixture was used without separation.

In the presence of ethylene glycol, a catalytic amount of p-toluene-sulfonic acid and benzene, the mixture of ketones 115 and 118 was converted

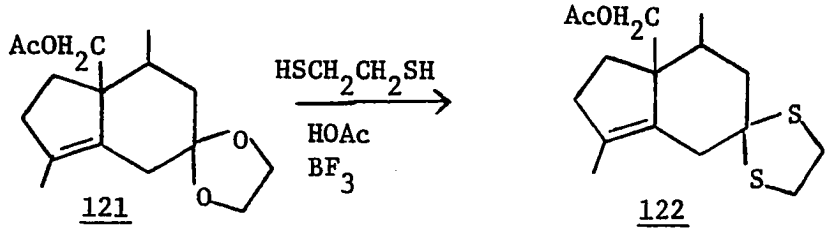


to the ethylene acetal 119 in 84% yield.

Acetal 121 was still a mixture of methyl and ethyl esters which had been carried through the sequence. To eliminate the mixture of esters, ethylene acetal 119 was reduced with an excess of lithium aluminum hydride in dry ether affording a single compound, acetal alcohol 120. This is the first material in the sequence whose composition was checked with analytical data since the preceding compounds were all mixtures and whose structures could be adequately determined by spectral methods above.

Alcohol 120 was converted smoothly to acetate 121 by treatment with sodium acetate and acetic anhydride. Most of the acetic anhydride was removed by distillation in vacuo, however, since acetals are somewhat heat sensitive the last traces of acetic anhydride were removed by chromatography.

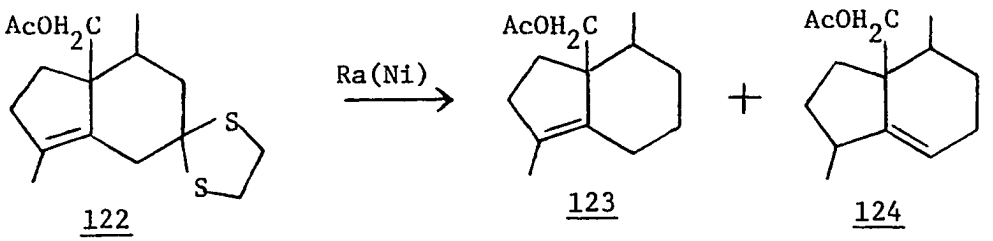
In the model system the ketone was converted to the thioacetal using boron trifluoride etherate in ethanedithiol. Milder conditions were necessary for the conversion of acetal 121 to the corresponding thioacetal



121 122

122. Using acetic acid as the solvent, an equivalent of ethanedithiol, and keeping the same proportion of boron trifluoride as before, thioacetal 122 was isolated in 64% yield from the reaction.

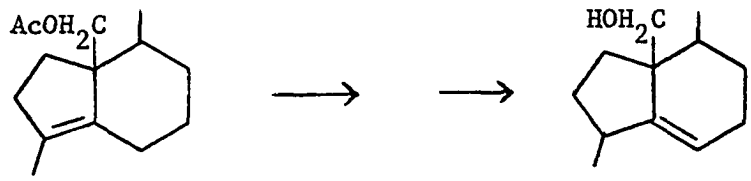
Various reaction conditions for the reduction of thioacetals were discussed previously. The problems associated with Raney nickel are considerable: 1) preparation; 2) storage; 3) handling; 4) lack of reproducibility, and 5) ability to isomerize double bonds. In spite of these drawbacks W-2 Raney nickel proved to be the method of choice to reduce thioacetal 122. The expected product 123 was contaminated with what is thought to be the isomeric 124. The conditions for complete



122 123 124

reduction varied greatly, presumably due to the variations in activity of the Raney nickel catalyst. For example, some experiments required 0.5 hr at room temperature while others required 6.0 hr at reflux. The reaction unfortunately could not be followed by t.l.c. because of the minimal difference in the R_f values of the starting material and the products. The reaction was easily followed, however, by repeated injections on an SE-30 column at 196°. The g.l.c. traces showed that a contaminant (acetate 124) was formed at the same rate as product 123 and therefore did not result from isomerization of initially formed 123.

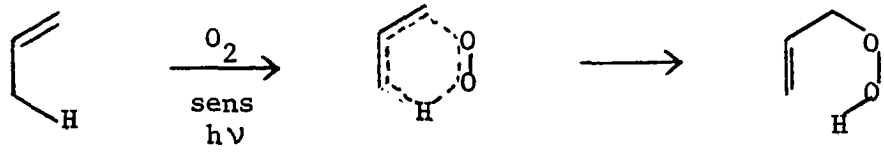
In order to convert the key intermediate acetate 123 to the desired alcohol 97, two major transformations were necessary. To direct the



123 97

stereochemistry of the C-3 methyl group cis and isomerize the bond into the six-membered ring were the goals of the subsequent reactions.

The photosensitized oxygenation of olefins is an important synthetic method of oxidation. Singlet oxygen adds to olefins which have allylic hydrogens giving allylic hydroperoxides. The double bond shifts cleanly to the allylic position. Previous work has shown that the reaction is

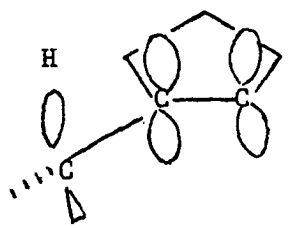


m

very sensitive to the electron density of the olefinic double bond. For example, it is known that tetraalkyl-substituted olefins are about 20-50 times as reactive as trialkyl-substituted olefins (80). Therefore it was with confidence that the mixture of olefins 123 and 124 were photo-oxygenated, expecting only products from the tetra-substituted olefin 123.

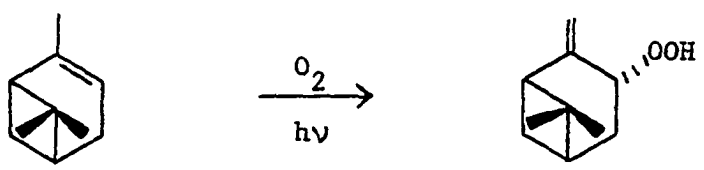
Although several mechanisms have been advanced (and most not ruled out) the six membered cyclic transition state, m, is consistent with all of the data (81).

It is known that the reaction occurs preferentially with the hydrogens on vinyl methyl groups rather than the allylic hydrogens on ring carbons, thus leading to an exocyclic methylene product. Hydrogen abstraction occurs predominantly on methyl groups because of stereoelectronic reasons (81). The carbon-hydrogen bond, by free rotation, can adopt a conformation in which the maximum amount of orbital overlap exists in the



transition state of the reaction. The carbon-hydrogen bonds on ring carbon atoms cannot achieve this arrangement and usually products from their reaction are formed in poor yield.

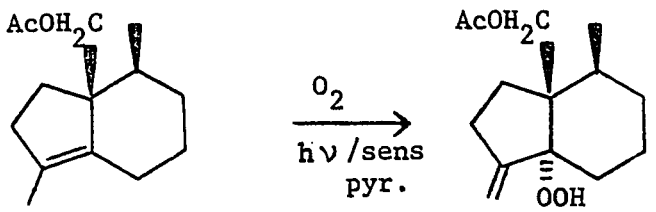
Both the structure of the products and the rates at which they are formed are quite sensitive to steric effects. Bulky substituents hinder attack. For example, steroidal olefins are universally attacked from the α side and the reaction is usually slow (82). α-Pinene (125) undergoes substitution exclusively on the side away from the gem dimethyl group to give hydroperoxide 126. α-Pinene (125) is considerably less reactive



125 126

than 1-methylcyclohexene (82).

Olefin 123 (contaminated with isomer 124) was photooxygenated in pyridine using hematoporphoryn as a sensitizer. A mixture of products



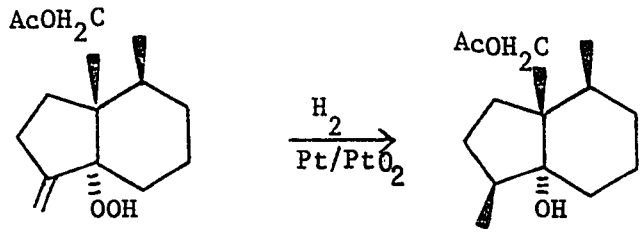
123 127

resulted along with a considerable amount of unchanged starting material. One of the major products is assigned structure 127. The trans ring fusion is suggested on the basis that reaction should occur preferentially from the α side of the molecule, as explained above. Spectral data of the hydroperoxide support structure 127. In the mass spectrum peaks at (m/e) 254 (M^+), 238, and 222 are diagnostic, as hydroperoxides normally have large peaks at M - 16 and M - 32 due to the loss of O· and O_2, respectively (83).

Nikon and Bagli (84) have reduced hydroperoxides from photooxygenations with sodium iodide in aqueous acetic acid. Under these conditions, hydroperoxide 127 did not give the expected alcohol but gave instead a higher molecular weight alcohol of undetermined structure.

The step following the unsuccessful reduction of the hydroperoxide to an alcohol was to have been a catalytic reduction of the carbon-carbon double bond. It was hoped that both of these reactions would occur with hydrogen and metal catalyst. Hydroperoxides are known to be easily reduced

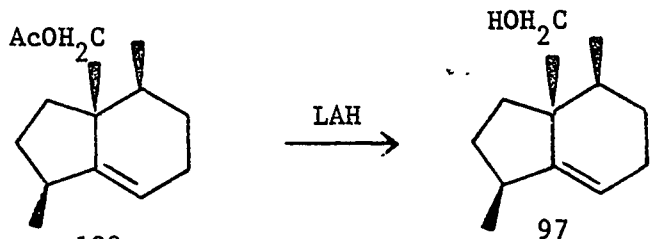
to alcohols over palladium or platinum catalysts (85). Consequently,



127 128

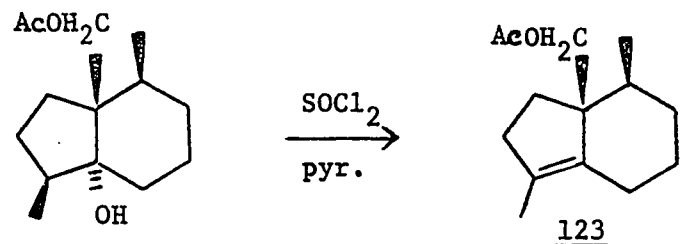
hydroperoxide 127 was reduced with hydrogen over platinum to alcohol 128.

The dehydration of alcohol 128 under E2 conditions was expected to lead to the trisubstituted olefin 129. Treatment with lithium aluminum



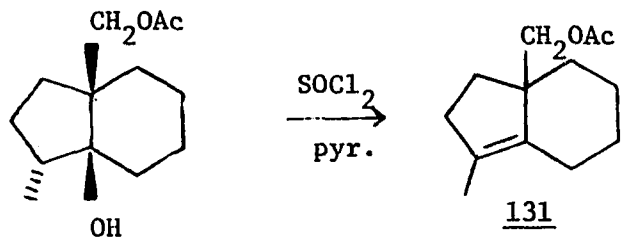
129 97

hydride would then give the desired alcohol 97. However,



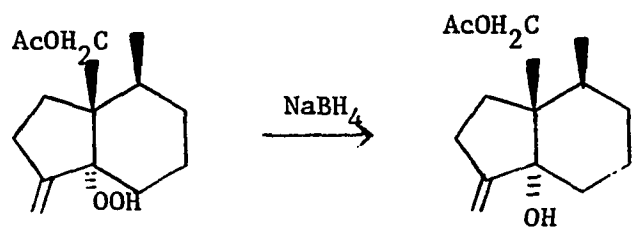
128 123

treatment of alcohol 128 with thionyl chloride in pyridine led instead to the tetrasubstituted olefin 123. The dehydration probably involves a transient carbonium ion which loses a proton to give the most stable double bond isomer. A similar observation was recently made (22) on the cis fused hydrindane 130 which upon elimination of water afforded hydrindene 131.



130 131

It was hoped that by making dehydration from the five-membered ring impossible, the double bond would be forced into the six-membered ring. To this end hydroperoxide 127 was reduced to the corresponding alcohol



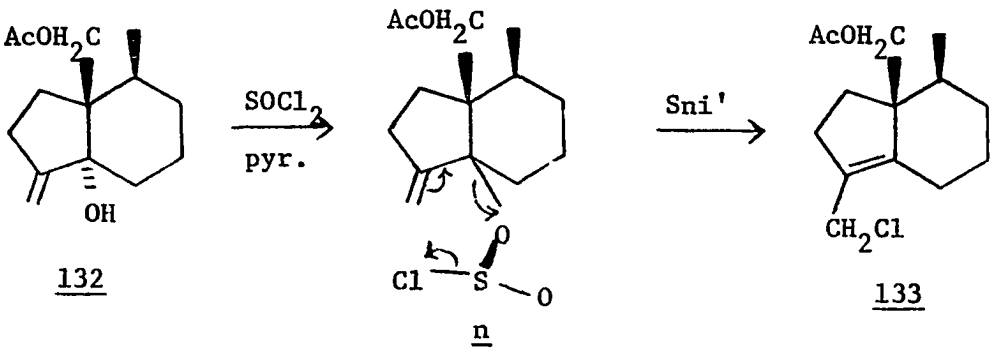
127 132

with sodium borohydride in ethanol in modest yield. The yield of purified alcohol 132 is low since the material thought to be hydroperoxide 127 is actually a mixture of compounds. The overall yield for the two reactions, photooxygenation and reduction is a scant 12.4%. This is the only serious

drawback in the entire sequence.

The dehydration of alcohol 132 was affected over alumina. The ir spectrum of the product exhibits absorption at 3330 cm^{-1} which implies that the hydroxy function is still present. The nmr spectrum indicates a mixture of products.

When the dehydration of alcohol 132 was done with thionyl chloride and pyridine a rearranged product was obtained. The allylic chloride 133

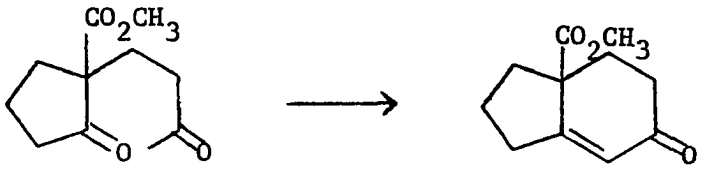


132 n 133

was identified by its spectral characteristics. It is thought to arise from the intermediate allyl chlorosulfite n, which undergoes internal substitution with allylic rearrangement.

Many things contributed to the termination of the project short of its goal. However, the recent synthesis of guaiol (21) by an identical solvolytic route, after our initial studies on the model system had been reported, was the major factor in our decision.

The importance of this work, and most synthetic work in general, is in the methodology developed. For example, the cyclization of diketone 65 to ketoester 66, via the pyrrolidene intermediate, is a significant improvement over previous literature reactions on similar compounds.



65 66

Another contribution of the present work is the synthesis of a hydroazulene by a solvolytic rearrangement of a hydrindane. The process provides a rational control of stereochemistry. This is not a trivial problem as the stereochemical control of substituents in the hydroazulene ring system is extremely difficult.

EXPERIMENTAL

Reagents

Common solvents and chemicals were obtained from commercial sources and were generally used without purification. When anhydrous solvents were required, reagent grade materials were treated according to the following:

Diethyl ether (dry) - distilled from a mixture of sodium-benzophenone, which displayed a constant purple color.

Boron trifluoride etherate - distilled from calcium hydride.

Benzene - approximately 15% of its volume reduced by vacuum distillation.

Pyridine - stored over 4A molecular sieves.

Triethylamine - distilled from calcium hydride.

Xylene - distilled from a mixture of sodium-benzophenone, which displayed a constant purple color.

Characterization of Compounds

All melting points were determined on a Kofler Micro Hot Stage melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 21 Double Beam Spectrometer, or a Beckman IR 12 spectrometer. Nmr spectra were recorded at ambient temperature on a Varian A-60 spectrometer or a Hitachi Perkin-Elmer R20-B spectrometer and chemical shifts are reported as parts per million (α scale) from tetramethylsilane as an internal standard. Mass spectra were determined using an Atlas CH4 mass spectrometer with a direct solid inlet system. In most cases, only the molecular ion is reported. Microanalyses were

performed by Ilse Beetz Microanalytical Laboratories, Kronach, West Germany.

Whenever needed, chromatographic procedures were employed for separation and purification of products. Microanalytical, air-dried, thin-layer chromatography plates were prepared by immersion coating of microscope slides in a chloroform slurry of Merck silica gel H obtained from Merck Distributors, Brinkmann Instruments, Incorporated, Westbury, New York. Column chromatography was performed on Baker analyzed silica gel (60-200 mesh). Elution solvents were established by microanalytical thin-layer chromatography, and column elution was followed by thin-layer examination of consecutive effluent aliquots.

Preparation of Compounds

Dimethyl adipate (64)

The method of Clinton and Laskowski (50) was employed. A 5000 ml, one-necked, round-bottomed flask fitted with a reflux condenser and a gas inlet tube, was charged with 657 g (4.50 mol) of adipic acid (63). The apparatus was evacuated, filled with prepurified nitrogen and charged with a mixture of 864 g (27 mol) of methanol, 27 ml of concentrated sulfuric acid, and 2366 ml of dichloroethane. This heterogeneous mixture was heated and soon became homogeneous. It was stirred magnetically and heated to reflux overnight. The reaction mixture was allowed to cool to room temperature and concentrated to a volume of ca. 2 l. The mixture was diluted with approximately 500 ml of ether and extracted with brine and a saturated aqueous solution of sodium bicarbonate. The solution was dried over anhydrous magnesium sulfate.

The mixture was filtered and solvent was removed by distillation at reduced pressure affording 714 g (4.1 mol, 91%) of dimethyl adipate (64) as a clear, slightly yellow liquid: solidified on standing in a refrigerator (1-2°) [lit. (86) mp 3°]; ir(film) 2960, 1735 (C-O ester), 1440, 1368, 1244, and 1172 cm^{-1}; nmr (CCl_4) δ 3.55 (s, 6H, $CO_2\underline{CH}_3$), 2.22 (m, 4H, $\underline{CH}_2CO_2$), and 1.61 (m, 4H) ppm.

Unsuccessful cyclization of dimethyl adipate (64)

A 5000 ml, one-necked, round-bottomed flask was fitted with a reflux condenser and a calcium chloride drying tube. The flask was charged with 431 g (2.48 mol) of dimethyl adipate (64), 203 g (3.76 mol) of sodium methoxide, 1.5 ml of methanol, and 2080 ml of benzene. The reaction mixture was heated to reflux overnight. The cooled mixture was then acidified with hydrochloric acid and ice. The layers were separated and the aqueous layer was back extracted with benzene. The combined benzene layers were concentrated to about 1700 ml and washed once with a saturated aqueous solution of sodium bicarbonate and twice with water. The solution was dried over anhydrous magnesium sulfate. The mixture was filtered and solvent was removed by distillation under reduced pressure. An nmr spectrum showed two methyl singlets, integrating to a ratio of 55:45 at δ 3.68 and 3.59 ppm, respectively. On this basis, the mixture was determined to be 45% product and the remainder starting material.

Methyl 2-oxocyclopentane-1-carboxylate (62)

A 250 ml, three-necked, round-bottomed flask was fitted with a mechanical stirrer and a reflux condenser. The apparatus was evacuated,

flame dried, filled with prepurified nitrogen, and charged with 14.6 g (0.304 mol) of a 50% sodium hydride oil dispersion and about 40 ml of dry benzene. The suspension was stirred several minutes. The oil-benzene was removed by vacuum suction through a gas dispersion tube, with a continuous flow of nitrogen. This was repeated twice. To the oil-free sodium hydride, approximately 75 ml of dry benzene was added and 11.80 g (0.068 mol) of dimethyl adipate (64) dissolved in 50 ml of benzene was added dropwise. With gentle heating, gas evolution was noted. The mixture was heated under reflux overnight. A 15% solution of acetic acid in dry ether was added dropwise until the solution was slightly acidic. A small amount of water was added to dissolve the sodium acetate that had formed. The layers were separated and the aqueous layer was back extracted with benzene. The combined benzene layers were washed with a saturated aqueous solution of sodium bicarbonate, brine, and dried over anhydrous magnesium sulfate. The mixture was filtered, concentrated, and distilled giving 8.31 g (0.059 mol, 86%) of an oil: bp 55-57°/0.8 mm [lit. (87) bp 88-92/5 mm]; ir (film) 2960, 1760 (C=O ketone), 1727 (C=O ester), 1662 (enol), 1620 (enol), 1438, 1408, 1342, 1297, 1255, 1202, 1110, 1002, 954, and 883 cm^{-1}; nmr (CCl_4) δ 3.67 (s, 3H, $CO_2\underline{CH}_3$), 3.12 (m, 1H), 2.17 (m, 6H) ppm.

Methyl 1-(3'-oxobutyl)-2-oxocyclopentane-1-carboxylate (65)

Dauben and his coworker's (51) method was used. A 3000 ml one-necked, round-bottomed flask was evacuated, flame dried, and filled with prepurified nitrogen. The flask was charged with 231.7 g (1.63 mol) of methyl 2-oxocyclopentane-1-carboxylate (62), 130.1 g (1.86 mol) of methyl vinyl ketone, 59.4 ml of triethylamine, and 1000 ml of benzene. The

reaction mixture was allowed to stand seven days and the solvent and triethylamine were removed by distillation *in vacuo*. The concentrate was distilled to yield 322.9 g (1.53 mol, 94%) of a pale yellow liquid: bp 113-119°/1 mm; ir (film) 2945, 1740 (C=O), 1718 (C=O), 1433, 1367, 1355, 1315, 1258, 1230, 1162, and 1113 cm^{-1}; nmr (CCl_4) δ 3.67 (s, CO_2CH_3), and 2.09 (s, $COCH_3$).

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.85; H, 7.57.

Methyl 5,6-dihydro-6-oxo-3a(4*H*)-indancarboxylate (66)

A modification (54) of the procedure of Meyer and Levinson (55) was used. A 500 ml, one-necked, round-bottomed flask was fitted with a Dean-Stark trap and condenser. The apparatus was evacuated and filled with prepurified nitrogen. The flask was charged with 25 g (0.118 mol) of methyl 1-(3'-oxobutyl)-2-oxocyclopentane-1-carboxylate (65), 220 ml of benzene, and 12.18 g (0.172 mol) of pyrrolidine. The mixture was heated under reflux for 26.5 hr with azeotropic removal of water. The Dean-Stark trap was replaced with a Soxhlet extractor filled with 4A molecular sieves. The reaction mixture was heated under reflux for an additional 4 hr to remove the last traces of water. The benzene and excess pyrrolidine were removed by distillation under reduced pressure. The reported procedure (88) to hydrolyze the enamine [ir (film) 2940, 2860, 1722 (C=O ester), 1637 (C=C), 1589 (C=C), 1433, 1405, 1286, 1260, 1214, 1207, 1175, 1152, 1073, and 808 cm^{-1}; nmr (CCl_4) δ 5.10 (t, 1H, *J* = 2.7 Hz, C*H*=C), and 4.93 (s, 1H, C*H*=C) ppm] was used, 4.77 g of sodium acetate, 9.55 ml of water, 9.55 ml of acetic acid and 250 ml

of benzene were added and heated under reflux for 4 hr. To this was added 50 ml of water and the layers were separated. The aqueous layer was back extracted three times with benzene. The combined organic layers were washed with 4% aqueous hydrochloric acid, a saturated aqueous solution of sodium bicarbonate, and brine. The mixture was dried over anhydrous magnesium sulfate and filtered. The solvent was removed by distillation in vacuo to give 21.04 g of crude product. Distillation afforded 18.50 g (0.095 mol, 81%) of a colorless liquid: bp 87-90°/0.36 mm. On standing in a refrigerator the product crystallized to small branchlet crystals: mp 43-44°; ir (KBr) 2940, 1716 (C=O ester), and 1658 (C=O conj. ketone) cm^{-1}; nmr (CCl_4) δ 5.77 (t, 1H, J = 1.9 Hz, C=CH) and 3.69 (s, 3H, CO_2CH_3) ppm.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.01; H, 7.28. Found: C, 68.12; H, 7.31.

Mixed hydride reduction of methyl 5,6-dihydro-6-oxo-3a(4H)-indancarboxylate (66)

A 500 ml, three-necked, round-bottomed flask was fitted with a calcium chloride drying tube, mechanical stirrer, and pressure compensating addition funnel. To the flask was added 3.43 g (90 mmol) of lithium aluminum hydride and 20 ml of dry ether. A solution of 24 g (180 mmol) of anhydrous aluminum chloride was dissolved in 180 ml of cold, dry ether and the resulting mixture was stirred for 0.5 hr. The aluminum chloride solution was added dropwise to the lithium aluminum hydride suspension and then stirred in an ice bath for 0.5 hr. The ice bath was removed and 5.0 g (26 mmol) of keto ester 66 dissolved in 100 ml of dry ether was added dropwise to the mixed hydrides over a period

of 1 hr. The reaction mixture was stirred for 2 hr at room temperature. The flask was placed in an ice bath and 200 ml of 10% aqueous sulfuric acid was added (dropwise at first). The mixture was poured into a separatory funnel and the layers were separated. The aqueous layer was extracted three times with ether. The combined organic layers were washed with brine and dried over anhydrous potassium carbonate. The mixture was filtered and the solvent was removed by distillation under reduced pressure. The residue was distilled *in vacuo* to afford 2.24 g (15 mmol, 57%) of a low melting solid *72*: bp 91-92°/0.8 mm; ir (film) 3340 (OH), 2930, 1454, and 1022 cm^{-1}; nmr (CCl_4) δ 6.30-5.28 (m, 2H, C*H*=C*H*), 3.59 (s, 1H, O*H*), and 3.31 (AB pattern, 2H, CH_2OH) ppm.

5,6-Dihydro-6-hydroxy-3a(4*H*)-indanmethanol (*73*)

A general procedure for this reaction is described by Minckler, Hussey, and Baker (89). A 250 ml, three-necked, round-bottomed flask was fitted with a reflux condenser and a mechanical stirrer. The apparatus was put under a nitrogen atmosphere. The flask was charged with 0.83 g (22 mmol) of lithium aluminum hydride and about 50 ml of dry ether. To this was added dropwise 2.83 g (14.6 mmol) of keto ester *66* dissolved in 75 ml of dry ether. The resulting suspension was stirred for 21 hr at room temperature. The hydride was decomposed with 1.66 ml of water and 1.33 ml of 10% aqueous sodium hydroxide. After stirring for 2 hr, the white suspension was filtered and washed carefully with excess anhydrous ether. Upon removal of the solvent by distillation under reduced pressure the residue, 2.34 g (13.9 mmol, 95%), solidified, and was recrystallized from ethyl acetate to afford 1.02 g (6.1 mmol, 42%) of a white solid: mp 92.5-96°; ir (KBr) 3330 (OH), 2940, 1454, 1352,

1334, 1267, 1023, 1011, 993, and 978 cm^{-1}; nmr (d_6-DMSO) δ 5.32 (broad s, 1H, C=C<u>H</u>), 4.38 (s, 2H, O<u>H</u>), 4.06 (broad s, 1H, C<u>H</u>OH), and 3.12 (AB pattern, 2H, C<u>H</u>$_2$OH) ppm.

The diacetate of 5,6-dihydro-6-hydroxy-3a(4<u>H</u>)-indanmethanol (<u>74</u>)

A 100 ml, one-necked, round-bottomed flask, fitted with a reflux condenser was evacuated and put under a nitrogen atmosphere. The flask was charged with 1 g (5.95 mmol) of diol <u>73</u>, 1.18 g (14.4 mmol) of sodium acetate, and 50 ml of acetic anhydride. The reaction mixture was heated to reflux for 1 hr. The mixture was cooled, a small amount of ether was added, and poured over brine. The aqueous layer was washed with ether. The combined ether layers were washed with brine, dried over anhydrous magnesium sulfate, and filtered. The acetic anhydride and ether were removed by distillation under reduced pressure. The residue was evaporatively distilled to yield 1.47 g (5.84 mmol, 98%) of a clear oil: bath temperature 90-110°/0.12 mm; ir (film) 2920, 1734, 1450, 1378, 1232, and 1025 cm^{-1}; nmr (CCl_4) δ 5.42 (broad s, 1H, C=C<u>H</u>), 5.29 (m, 1H, C<u>H</u>OAc), 3.96 (AB pattern, 2H, C<u>H</u>$_2$OAc), 2.01 (s, COC<u>H</u>$_3$), and 1.97 (s, COC<u>H</u>$_3$) ppm.

Attempted Birch reduction of diacetate (<u>74</u>)

A 500 ml, three-necked, round-bottomed flask was fitted with a dry ice condenser, a mechanical stirrer, and a pressure compensating addition funnel. The flask was allowed to fill with approximately 175 ml of dry (potassium hydroxide drying tube) ammonia. To this was added 3 g (0.43 mol) of lithium wire and instantly the solution turned a dark blue. A solution of 7.5 g (0.03 mol) of diacetate <u>74</u> in 75 ml of anhydrous ether was added dropwise at a fast rate. The reaction mixture was stirred at

the reflux temperature of ammonia for 7.5 hr. To quench the reaction 26.75 g (0.5 mol) of ammonium chloride was added. The ammonia was allowed to evaporate and the residue was dissolved in ether. About 200 ml of water was added and the layers were separated. The aqueous layer was back extracted with ether and the combined ether phases were washed with brine and dried over anhydrous magnesium sulfate. The solution was filtered and the ether was removed by distillation under reduced pressure. The residue was distilled to yield 2.31 g of a clear oil: bp 117-121°/0.4 mm; ir (film) 3340 (OH), 2920, 1450, 1038, and 1020 cm^{-1}; nmr (CCl_4) δ 5.60 (m, 1H), 5.29 (m, 1H), 3.58 (s, 1H), and 3.32 (AB pattern, 2H) ppm.

Methyl 6,6-ethylenedithio-5,6-dihydro-3a(4H)-indancarboxylate (75)

Following the published procedure (61), a 25 ml flask was charged with 5 g (25.8 mmol) of unsaturated ketone 66 and 4.86 g (51.6 mmol) of 1,2-ethanedithiol. To this solution was added 5.16 ml of boron trifluoride etherate, dropwise, with stirring. The solution warmed noticeably and turned yellow, orange, and finally deep red. After the addition was complete, the mixture was stirred at room temperature for 0.5 hr, poured over ice, and extracted with ether. The water layer was back extracted with ether and the combined ether layers were washed with brine, four times with ice cold 10% aqueous sodium hydroxide, three times with brine, and dried over anhydrous magnesium sulfate. The mixture was filtered and concentrated to 6.16 g (22.8 mmol, 89%) and distilled (with decomposition) giving 3.98 g (14.7 mmol, 57%) of thioacetal 75: bp 145-146°/0.75 mm; ir (film) 2915, 1723 (C=O), 1431, 1192, and 1168 cm^{-1}; nmr (CCl_4) δ 5.51 (broad s, 1H, C=CH), 3.62 (s,

3H, CO_2CH_3), and 3.29 (m, 4H, SCH_2CH_2S) ppm.

Anal. Calcd. for $C_{13}H_{18}O_2S_2$: C, 57.77; H, 6.71: S, 23.68. Found: C, 57.89; H, 6.79; S, 23.84.

6,6-Ethylenedithio-5,6-dihydro-3a(4H)-indanmethanol (76)

A 2000 ml, three-necked, round-bottomed flask was fitted with a reflux condenser, gas inlet tube, mechanical stirrer, and pressure compensating addition funnel. The flask was evacuated, flame dried, and filled with prepurified nitrogen. The flask was charged with 14.2 g (0.373 mol) of lithium aluminum hydride which was suspended in 400 ml of dry ether. To this suspension was added dropwise 50.42 g (0.187 mol) of ester 75 dissolved in 400 ml of dry ether. The reaction mixture was stirred at room temperature for 20.5 hr after which 27.6 ml of water and 22.1 ml of 10% aqueous sodium hydroxide was cautiously added. This mixture was stirred at room temperature for 3 hr, during which time the gray suspension turned to a white precipitate. The precipitate was removed by filtration and the filter cake was washed copiously with anhydrous ether. The ether was removed by distillation in vacuo to yield 41.6 g (0.172 mol, 92%) of alcohol 76 as a white powder: mp 84-87°. The analytical sample, obtained after recrystallization from ether/hexane, melts at 85-87°: ir (KBr) 3230 (OH), 2880, 1650 (C=C), 1268, 1082, and 802 cm^{-1}; nmr (CCl_4) δ 5.51 (s, 1H, C=CH), 3.13-3.50 (m, 6 H, CH_2OH, SCH_2CH_2S), and 2.47 (s, 1H, OH) ppm; mass spectrum (70 eV) m/e M^+ 242.

Anal. Calcd. for $C_{13}H_{18}O_2S_2$: C, 59.45; H, 7.48; S, 26.45. Found: C, 59.31; H, 7.72; S, 26.73.

5,6-Dihydro-3a(4H)-indanmethanol (55) and 4,5,6,7-tetrahydro-7a(2H)-indenemethanol (79)

A 2000 ml, three-necked, round-bottomed flask, fitted with a reflux condenser and a mechanical stirrer was charged with 150 g of freshly prepared W-2 Raney nickel catalyst, 800 ml of absolute ethanol, and 26.2 g (0.108 mol) of thioacetal 76. This mixture was stirred for 1 hr at room temperature and the reaction was monitored by thin layer chromatography. The reaction mixture was filtered through a celite mat and the catalyst was washed with 600 ml of absolute ethanol. The ethanol was removed by distillation at reduced pressure to yield a brown viscous oil which, when distilled, afforded 7.89 g (0.052 mol, 48%) of a clear viscous liquid which solidified in the cooled receiver: bp 75-77°/0.2 mm; mp 31.5-33° [lit. (22) 35.5-37°]; ir (film) 3330 (OH), 2925, 1452, and 1020 cm^{-1}; nmr (CCl_4) δ 5.36 (s, 1H C-CH), 3.27 (AB pattern, 2H, CH_2OH), and 2.97 (s, 1H, OH) ppm; mass spectrum (70 eV) m/e M^+ 152.

G.l.c. analysis of the distillate using a 5 ft. Carbowax 20M column at 197° displayed 2 peaks in a ratio of 3:2. The retention times were 1.75 min and 2.35 min, respectively.

Cis-5,6,7,7a-tetrahydro-3a(4H)-indanmethanol (80)

Reduction of the mixture of 55 and 79 to a single, known compound was accomplished by shaking 1.05 g (6.9 mmol) of the mixture, 70 mg of platinum oxide, and 35 ml of 95% ethanol under hydrogen (60 p.s.i.) for 21 hr. The reaction mixture was filtered through a celite mat and the filter cake was washed with anhydrous ether. The solvent was removed by distillation under reduced pressure yielding a viscous, yellow oil which was evaporatively distilled, bath temperature 101-109°/1.5 mm, to afford

1.01 g (6.6 mmol, 95%) of a low melting solid [lit. (67) mp 29.5-30.5°]; nmr (CCl_4) δ 4.12 (s, 1H, $CH_2\underline{O}H$, disappeared on shaking with D_2O) and 3.33 (AB pattern, 2H, $\underline{CH_2}OH$).

Analysis by g.l.c. showed only a single peak (FFAP column at 177°).

5,6-Dihydro-3a(4H)-indanmethanol methanesulfonate (56) and 4,5,6,7-tetrahydro-7a(2H)-indenemethanol methanesulfonate (81)

The procedure of Tadanier (44) was used. A 125 ml Erlenmeyer flask was cooled in an ice bath and charged with 676 mg (4.45 mmol) of a mixture of alcohols 55 and 79 and 40 ml of pyridine. To this was added 2.09 g (18.3 mmol) of methanesulfonyl chloride. The cooling was discontinued and the mixture was stirred at room temperature for 5 hr during which time a precipitate formed. The reaction mixture was poured into 300 ml of water and the aqueous solution was extracted twice with ether. The combined ether phases were washed twice with water, a 4% aqueous solution of hydrochloric acid, a saturated aqueous solution of sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed by distillation under reduced pressure to yield 598 mg (2.6 mmol, 58%) of a slightly yellow oil: ir (film) 2940, 1462, 1180 (SO_2), and 946 cm^{-1}; nmr (CCl_4) δ 5.63 (s, 1H, C=C<u>H</u>), 3.96 (AB pattern, 2H, $\underline{CH_2}OSO_2$), and 2.95 (s, 3H, $SO_2\underline{CH_3}$) ppm.

1,2,3,4,5,6,7,8-Octahydro-5-azulenol acetate (57) and 1,2,3,4,5,6,7,8-octahydro-2-napthol acetate (82)

A 1000 ml, one-necked, round-bottomed flask, fitted with a reflux condenser was flame dried and put under a nitrogen atmosphere. The flask was charged with 5.74 g (25 mmol) of the crude mesylate mixture 56 and 81 and 484 ml of a buffer solution prepared by heating 7 g of anhydrous

potassium carbonate, 10 ml of acetic anhydride, and 500 ml of glacial acetic acid under reflux overnight. The reaction mixture was heated to reflux 30.5 hr, poured over ice, and extracted twice with ether. The combined ether layers were washed twice with water and placed in a large beaker. The solution was neutralized by the addition of a saturated aqueous sodium bicarbonate solution and solid sodium bicarbonate. The layers were poured into a separatory funnel and separated. The ether phase was again washed twice with water, brine and dried over anhydrous magnesium sulfate. The mixture was filtered and concentrated to a pale yellow oil: ir (film) 2870, 1720 (C=O ester), 1436, 1360, 1238, and 1028 cm^{-1}; nmr (CCl_4) δ 4.71 (s, 1H, CHOAc) and 2.58-0.88 (m, ring protons) ppm.

G.l.c. analysis showed two peaks in a 3:2 ratio using a Carbowax 20M column at 125°.

1,2,3,4,5,6,7,8-Octahydro-5-azulenol (83) and 1,2,3,4,5,6,7,8-octahydro-2-napthol (84)

A 1000 ml, three-necked, round-bottomed flask fitted with a mechanical stirrer, pressure compensating addition funnel, and reflux condenser was put under a nitrogen atmosphere. To the flask was added 1.9 g (50 mmol) of lithium aluminum hydride and 200 ml of dry ether. To the stirred suspension was added dropwise 4.85 g (25 mmol) of acetates 57 and 82 dissolved in 250 ml of dry ether. The reaction mixture was stirred for 12 hr at room temperature. Excess hydride was destroyed by the cautious addition of 3.80 ml of water and 3.04 ml of 10% aqueous sodium hydroxide. The mixture was stirred for 4 hr and during this time turned from gray to white. The precipitate was removed by filtration and the filter cake

was washed copiously with anhydrous ether. The ether was removed by distillation under reduced pressure leaving 3.35 g (22 mmol, 88% yield over two reactions) of an oil which was chromatographed on silica gel using 10% ethyl acetate, 10% cyclohexane, and 80% petroleum ether giving 2.59 g (17 mmol, 68%) of a semi-solid: [lit. (22) mp 47.5-49.5°]; ir (film) 3360 (OH), 2930, 1442, and 1038 cm^{-1}; nmr (CCl_4) δ 3.60 (m, 1H, CHOH) and 3.58 (s, 1H, OH, which disappeared after shaking with D_2O) ppm; mass spectrum (70 eV) m/e M^+ 152.

1,2,3,4,5,6-Hexahydroazulene (85) and 1,2,5,6,7,8-hexahydronapthalene (86)

The previously published procedure (69) was used. A 25 ml, three-necked, round-bottomed flask, fitted with a reflux condenser, magnetic stirrer, and nitrogen inlet tube was put under a nitrogen atmosphere. The flask was charged with 827 mg (5.44 mmol) of the mixture of alcohols 83 and 84 and 825 mg (6.08 mmol) of potassium hydrogen sulfate. The mixture was stirred at 140-185° for 1 hr. The reaction mixture was allowed to cool, diluted with water, and extracted with ether. The ether extracts were washed with water, a saturated aqueous solution of sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated giving 582 mg (4.35 mmol, 80%) of a yellow oil whose infrared spectrum exhibited no absorption in the 3000-4000 cm^{-1} region. This material was used directly in the next step without further purification.

Azulene (2) and napthalene (87)

A 25 ml, three-necked, round-bottomed flask, fitted with a mechanical stirrer was charged with 582 mg (4.35 mmol) of the mixture of dienes 85 and 86 and 825 mg of 10% palladium on charcoal. The mixture was stirred

and heated at 245-255° for 1 hr. After 11 min a slight blue color was noted in the exit tube. After 30 min the blue color turned to light brown and after 35 min it became dark brown. The reaction mixture was allowed to cool and, after the addition of some ether, was filtered through a celite mat to give an ether solution with a slight blue tint. Removal of the solvent by distillation in vacuo afforded a very intensely blue liquid. The crude mixture was injected onto a 6 ft didecyl phthlate column at 70°. The g.l.c. trace included two peaks whose retention times were identical with those of authentic samples of napthalene and azulene. The crude mixture was then dissolved in petroleum ether and extracted with 85% phosphoric acid which was then poured over ice (2). The aqueous phase was extracted with ether. The ether extract was washed with brine and dried over anhydrous magnesium sulfate, filtered, and concentrated to a dark green-blue liquid. This oil was analyzed by g.l.c. as before and the trace showed a peak whose retention time was identical with that of an authentic sample of azulene. The trace contained no peak corresponding to the retention time of napthalene. In addition, peak enhancement was observed by addition of authentic azulene.

Attempted solvolysis of mesylates 55 and 81 in the presence of cyanide

A 250 ml, one-necked, round-bottomed flask was fitted with a magnetic stirrer and a reflux condenser. The apparatus was evacuated and put under a nitrogen atmosphere. The flask was charged with 756 mg (3.29 mmol) of mesylates 55 and 81, 237 mg (3.95 mmol) of urea, 429 mg (6.58 mmol) of potassium cyanide, and 100 ml of trifluoroethanol. The resulting mixture was stirred at room temperature overnight. The reaction mixture was

poured onto ice and after the addition of solid sodium chloride and ether the layers were separated. The ether layer was washed three times with 10% aqueous sodium hydroxide, brine, and dried over anhydrous magnesium sulfate. The solution was filtered and the solvent was removed by distillation under reduced pressure. The ir spectrum of the residue was devoid of cyanide absorption.

The residue was retreated under identical conditions, except that the reaction mixture was heated to reflux for 24 hr. The same workup as described above afforded 530 mg of a light yellow oil, whose ir spectrum was very similar to the ir spectrum of the material obtained previously.

Methyl 1-methyl-2-oxocyclopentane-1-carboxylate (102)

The conditions of Johnson, Markham, and Price (74) were used. A 25 ml, three-necked, round-bottomed flask, fitted with a reflux condenser was charged with 4.49 g (31.6 mmol) of keto ester 62, 5.52 g (38.9 mmol) of methyl iodide, 4.09 g (29.6 mmol) of anhydrous potassium carbonate, and 6.1 ml of reagent grade acetone. The mixture was heated to reflux overnight and then allowed to cool to room temperature. It was diluted with 100 ml of petroleum ether, filtered, and the solvent was removed by distillation *in vacuo*. The residue was dissolved in ether and washed with brine twice. The solution was dried over anhydrous magnesium sulfate, filtered, and the solvent was removed by distillation under reduced pressure giving 4.44 g (28.6 mmol, 96%) of a clear, slightly yellow oil (requiring no further purification for most purposes); ir (film) 2980, 1753 (C=O ketone), 1733 (C=O ester), 1458, 1272, 1160, and 1066 cm^{-1}; nmr (CCl_4) δ 3.58 (s, 3H, $CO_2\underline{CH}_3$), 2.64-1.48 (m, 6H), and 1.29 (s, 3H,

CCH_3) ppm.

The compound gives no color change with alcoholic ferric chloride.

Ethyl 3-methyl-2-oxocyclopentane-1-carboxylate (108)

The procedure of Sisido, Utimoto, and Isida (75) was used. A 250 ml, three-necked, round-bottomed flask, fitted with a reflux condenser and a mechanical Hershberg stirrer was put under a nitrogen atmosphere. The flask was charged with 100 ml of absolute ethanol and 6.79 g (0.295 mol) of sodium metal, cut into small pieces, was added slowly with stirring. As the sodium reacted, enough heat was evolved to reflux the solution. Stirring was continued for 2.5 hr after which was added 46 g (0.295 mol) of keto ester 102. The brown reaction mixture was heated at reflux for 8 hr after which approximately 50 ml of ethanol was removed by distillation. To the dark brown mixture was added 100 ml of toluene and the remaining ethanol was removed by azeotropic distillation. The residue was poured into 500 ml of 10% aqueous acetic acid with ice cooling. The layers were separated. The aqueous layer was back extracted three times with benzene. The organic layers were combined and washed with a saturated aqueous solution of sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and distilled affording 26.33 g (0.155 mol, 52%) of a clear oil: bp 67-70°/0.2 mm [lit. (75) bp 87°/6 mm]; ir (film) 2945, 1750 (C=O ketone), 1722 (C=O ester), 1654 (enol), 1620 (enol) 1452, 1368, 1334, 1294, 1240, 1186, and 1018 cm^{-1}; nmr (CCl_4) δ 4.12 (m, 2H, $CO_2CH_2CH_3$), 3.06 (m, 1H), 1.25 (t, 3H, J = 7Hz, $CO_2CH_2CH_3$), and 1.08 (d, 3H, J = 7Hz, $CHCH_3$).

The compound gave an instantaneous color with alcoholic ferric chloride.

Trans-3-penten-2-one (99)

The procedure of Wilds and Djerassi (76) was modified as follows. A 5000 ml, three-necked, round-bottomed flask was fitted with a gas inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and thermometer. The apparatus was evacuated, filled with nitrogen, and charged with a mixture of 800 g (13.8 mol) of reagent grade acetone, 844 ml of ether, and 400 ml of a 12% (48 g) aqueous sodium hydroxide solution saturated with sodium chloride. The solution was cooled to 0-1° with an external ice bath, and a precooled (5°) mixture of 600 g (13.6 mol) of acetaldehyde in 1012 ml of reagent grade acetone was added, dropwise, with stirring, over a period of 5 hr. During the addition, the internal temperature was held at 5-12°. Following the addition, the reaction mixture was stirred for 1 hr at 5° and then allowed to warm to room temperature and stirred an additional hr. The resulting two layers of the mixture were separated and the aqueous layer was back extracted twice with ether. A few ml of concentrated sulphuric acid was added to bring the pH to ca. 3 and the mixture was distilled. The fraction boiling between 64-95° was collected and dissolved in ether. The ethereal solution was washed three times with brine, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed by distillation and the residue was distilled to afford 189.3 g (2.26 mol, 17%) of a yellow oil: bp 120-127° [lit. (76) bp 121-122.5°, (90) 113-119°]. An nmr spectrum was identical to that reported by R. M. Starrett (91) for trans-3-penten-2-one.

Attempted alkylations of ethyl 3-methyl-2-oxocyclopentane-1-carboxylate (108)

A. Alkylation via enamine 110 was tried using the procedure of Coates and Shaw (92). A 250 ml, three-necked, round-bottomed flask, fitted with a mechanical stirrer, pressure compensating addition funnel, reflux condenser, and Dean-Stark trap was evacuated and put under a nitrogen atmosphere. The flask was charged with 5.44 (32 mmol) of keto ester 108, 2.5 g (35.2 mmol) of pyrrolidine, and 130 ml of benzene. The contents were heated under reflux for 21.25 hr with azeotropic removal of water. The reaction mixture was allowed to cool and benzene and excess pyrrolidine was removed by distillation under reduced pressure to afford 6.42 g (28.8 mmol, 90%) of crude enamine 110. The enamine was dissolved in 60 ml of methanol. A solution of 2.96 g (35.2 mmol) of trans-3-penten-2-one (99) in 75 ml of methanol was added dropwise with stirring over a period of several minutes. The reaction mixture was stirred for 1 hr at room temperature and then was heated to reflux. An attempt was made to follow the course of the reaction by t.l.c. After 24 hr there was evidence that a new product was starting to form. After 69 hr the solvent was removed by distillation under reduced pressure. The residue was put under a nitrogen atmosphere and diluted with 140 ml of benzene. To the solution was added 2.58 ml of water, 2.58 ml of acetic acid, and 1.29 g of sodium acetate. The hydrolysis mixture was heated under reflux overnight and allowed to cool. The mixture was diluted with about 50 ml of water and the layers were separated. The aqueous layer was back extracted with benzene. The combined benzene layers were washed with 4% aqueous hydrochloric acid, a saturated aqueous solution of sodium

bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered, and the benzene was removed by distillation under reduced pressure to afford 6.79 g of material whose nmr spectrum had all the characteristics of the unalkylated pyrrolidine enamine 110.

The concentrate was put into a 250 ml, one-necked, round-bottomed flask fitted with a reflux condenser. The enamine was dissolved in 100 ml of formamide containing 30 ml of dichloroethane and 2.96 g (35.2 mmol) of trans-3-penten-2-one was added. The mixture was heated under reflux overnight and the product was isolated as described above affording 6.97 g of an oil whose ir and nmr spectra were consistent with their formulations as mixtures of starting materials 108 and unalkylated enamine 110.

B. The conditions employed were similar to those described by Marshall and Warne (72). A 250 ml, three-necked, round-bottomed flask, fitted with a mechanical stirrer and a reflux condenser, was evacuated and put under a nitrogen atmosphere. The flask was charged with 45 ml of tert-amyl alcohol and 0.29 g (7.4 mmol) of potassium metal (weighed and cut under dry xylene). The contents were stirred at room temperature for 23 hr and the reaction mixture was then cooled in an ice bath to 0-2°. To this was added 2.18 g (12.8 mmol) of keto ester 108 dissolved in a small portion of tert-amyl alcohol. The flask was equipped with a thermometer and pressure compensating addition funnel containing 2.15 g (25.6 mmol) of trans-3-penten-2-one (99) in 40 ml of tert-amyl alcohol and 40 ml of dry benzene. The solution was added dropwise to the reaction mixture over a period of 0.5 hr. The brown reaction mixture was kept at 0-2° for a period of 1 hr and allowed to warm gradually to room temperature. Stirring was continued for 11 hr after which the mixture

was poured onto ice. The aqueous solution was extracted with ether, saturated with sodium chloride and re-extracted twice with ether. The combined ether phases were washed four times with brine, dried over anhydrous magnesium sulfate, filtered, and the ether was removed by distillation under reduced pressure affording 1.59 g or a brown oil. The oil gave an instantaneous purple color with alcoholic ferric chloride. The ir and nmr spectra of the oil were consistent with its formation as a mixture of starting keto ester 108 and α, β-unsaturated ketone 115.

Ethyl 3-methyl-2-oxo-1-(4'-oxo-2'-pentyl)cyclopentane-1-carboxylate (109)

The procedure of Johnson, Markham, and Price (74) was modified. To a 250 ml, one-necked, round-bottomed flask was added 30.22 g (0.178 mol) of keto ester 108, 1839 g (0.218 mol) of trans-3-penten-2-one (99), 27.10 g (0.196 mol) of anhydrous potassium carbonate, and 100 ml of tert-amyl alcohol. The flask was fitted with a reflux condenser and a calcium chloride drying tube. The reaction mixture was heated between 50-60° overnight and allowed to cool. The mixture was diluted with 300 ml of petroleum ether and residual potassium carbonate was removed by filtration. Solvent was removed from the filtrate by distillation at reduced pressure. The residue was dissolved in ether and washed with a saturated aqueous solution of sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered, and the solvent was removed at reduced pressure. Distillation afforded 38.09 g (0.150 mol, 84%) of a clear, viscuous liquid: bp 106-112/0.2 mm; ir (film) 2945, 1740 (C=O), 1718 (C=O), 1460, 1370, 1244, 1170, and 1030 cm^{-1}; nmr (CCl_4) δ 4.10 (dq, J = 7Hz, CO_2CH_2) and 2.08 (s, $COCH_3$) ppm.

5,6-Dihydro-1,4-dimethyl-6-oxo-3a(4H)-indancarboxylate (115) and ethyl 4,5,6,7-tetrahydro-3,7-dimethyl-5-oxo-7a(2H)-indenecarboxylate (118)

A modification of the procedure used in the model system (54) was employed. A 2000 ml, one-necked, round-bottomed flask, fitted with a Dean-Stark trap and reflux condenser was put under a nitrogen atmosphere. The flask was charged with 37.68 g (0.148 mol) of dione 109, 22.15 g (0.312 mol) of pyrrolidine, a trace of p-toluenesulfonic acid (79), and 1000 ml of benzene. The contents were heated under reflux with azeotropic removal of water for 26.5 hr and then allowed to cool to room temperature. Benzene and excess pyrrolidine were removed by distillation under reduced pressure. The crude enamine was hydrolyzed by the procedure already described (88). A solution of 1000 ml of anhydrous benzene, 19.4 ml of water, 19.4 ml of acetic acid, and 9.7 g of sodium acetate was added and the mixture was heated to reflux for 4 hr. The mixture was allowed to cool to room temperature and was diluted with about 100 ml of water. The layers were separated, and the aqueous layer was extracted twice with benzene. The benzene extracts were combined and washed with 4% aqueous hydrochloric acid, a saturated aqueous solution of sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered, and the solvent was removed by distillation under reduced pressure. The residual brown oil was distilled in vacuo affording 22.48 g (0.095 mol, 64%) of a clear oil: bp 103-110°/0.4 mm; ir (film) 2960, 1708 (C=O ester), 1658 (C=O conj. ketone), 1446, 1234, 1172, and 1020 cm^{-1}; nmr (CCl_4) δ 5.83 (d, J = 2Hz, C=CH); 5.76 (d, J = 2Hz, C=CH), 4.17 (q, 2H, J = 7Hz, $CO_2\underline{CH}_2$), 3.08 (broad s), and 1.68 (broad s, $C=C\underline{CH}_3$) ppm. By integration of the nmr spectrum, the mixture was determined to be 36.5%

α,β-unsaturated ketone 115 and 63.5% α, β-unsaturated ketone 118.

5,5-Ethylenedioxy-4,5,6,7-tetrahydro-3,r-7-dimethyl-c-7a(2H)-indene-carboxylate (119)

A 1000 ml, one-necked, round-bottomed flask, fitted with a Dean-Stark trap and reflux condenser, was put under a nitrogen atmosphere. The flask was charged with 17.26 g (73.5 mmol) of the ketone mixture 115 and 118, 13.67 g (220.5 mmol) of ethylene glycol, a trace of p-toluene-sulphonic acid, and 650 ml of benzene. The mixture was heated to reflux for 19 hr with azeotropic removal of water. The mixture was allowed to cool and the trap was replaced by a Soxhlet extractor (filled with 4A molecular sieves) and heating to reflux was continued for an additional 7 hr. The reaction mixture was allowed to cool to room temperature and was washed twice with a saturated aqueous solution of sodium bicarbonate, brine, and dried over anhydrous magnesium sulfate. The mixture was filtered and the solvent was removed by distillation under reduced pressure to afford an orange oil which was purified by column chromatography on silica gel. Eluting with a mixture of 15% ethyl acetate, 10% cyclohexane, and 75% petroleum ether gave 17.21 g (61.9 mmol, 84%) of a pale yellow oil: ir (film) 2910, 1718 (C=O ester), 1237, 1210, 1162, 1133, 1039, and 992 cm^{-1}; nmr (CCl_4) δ 4.03 (q, 2H, J = 7Hz, $CO_2\underline{CH}_2$), 3.80 (s, 4H, $O\underline{CH}_2\underline{CH}_2O$), 1.60 (s, $C{=}C\underline{CH}_3$), 1.22 (t, 3H, J = 7Hz, $CO_2CH_2\underline{CH}_3$), and 0.86 (broad d, 3H, J = 6Hz, $CH\underline{CH}_3$) ppm.

5,5-Ethylenedioxy-4,5,6,7-tetrahydro-3,r-7-dimethyl-c-7a(2H)-indene-methanol (120)

A 2000 ml, three-necked, round-bottomed flask, fitted with a mechanical stirrer, reflux condenser, and pressure compensating addition funnel, was

put under a nitrogen atmosphere. To the nitrogen swept flask was added 16.03 g (0.422 mol) of lithium aluminum hydride and 500 ml of dry ether. To the stirred, gray suspension was added dropwise, over a 3 hr period, 59 g (0.211 mol) of ester 119 dissolved in 500 ml of dry ether. The reaction mixture was stirred overnight at room temperature. Following the usual procedure 32.1 ml of water and 24.9 ml of 10% aqueous sodium hydroxide was added via a syringe with utmost caution. After complete addition, the reaction mixture was stirred for 3 hr and the gray suspension turned white. The mixture was filtered and the filter cake was washed with 400 ml of anhydrous ether. The ether was distilled at reduced pressure affording 49.8 g (0.209 mol, 99%) of a viscous colorless oil: ir (film) 3400 (OH), 2880, 1126, 1081, and 1045 cm^{-1}; nmr (CCl_4) δ 3.83 (broad s, 4H, OCH_2CH_2O), 3.68-3.17 (m, 2H, CH_2OH), 1.62 (s, $C=CCH_3$), and 0.88 (d, 3H, J = 6Hz, $CHCH_3$) ppm.

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.70; H, 9.39.

5,5-Ethylenedioxy-4,5,6,7-tetrahydro-3,r-7-dimethyl-c-7a(2H)-indene-methanol acetate (121)

A 250 ml, one-necked, round-bottomed flask, fitted with a reflux condenser, was put under a nitrogen atmosphere. The flask was charged with 9.27 g (39.0 mmol) of alcohol 120, 6.40 g (78.0 mmol) of sodium acetate, and 125 ml of acetic anhydride. The reaction mixture was heated to reflux for 3.5 hr and allowed to cool to room temperature. The solvent was removed by distillation at reduced pressure and the residue chromatographed on silica gel. Elution with a mixture of 15% ethyl acetate, 10% cyclohexane, and 75% petroleum ether afforded 10.19 g

(36.4 mmol, 93%) of an oil: ir (film) 2860, 1730, 1232, 1132, 1080, and 1039 cm^{-1}; nmr (CCl_4) δ 4.09 (AB pattern, 2H, $C\underline{H}_2OAc$), 3.84 (broad s, 4H, $OC\underline{H}_2C\underline{H}_2O$), 1.91 (s, $COC\underline{H}_3$), 1.60 (broad s, $C{=}CC\underline{H}_3$), and 0.91 (d, 3H, $\underline{J}$ = 5.5 Hz, $CHC\underline{H}_3$) ppm.

Anal. Calcd. for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.71; H, 8.72.

5,5-Ethylenedithio-4,5,6,7-tetrahydro-3,r-7-dimethyl-c-7a(2H)-indene-methanol acetate (122)

A 250 ml, one-necked, round-bottomed flask was fitted with a 50 ml pressure compensating addition funnel. The flask was charged with 8.10 g (28.9 mmol) of acetate 121 (dissolved in 100 ml of glacial acetic acid) and 2.86 g (30.4 mmol) of ethanedithiol. To this stirred solution was added dropwise 30 ml of boron trifluoride etherate over a 0.25 hr period. The reaction mixture was stirred at room temperature for 1 hr. During this time the mixture changed from yellow to orange and then to a dark red. The reaction mixture was poured into brine and extracted with ether. The combined ether layers were washed twice with brine, three times with ice-cold 10% aqueous sodium hydroxide, a saturated aqueous solution of sodium bicarbonate, and brine. The mixture was dried over anhydrous magnesium sulfate, filtered, and the solvent was removed by distillation under reduced pressure affording 7.33 g (23.5 mmol, 81%) of a yellow oil with a pungent odor. The oil was purified by chromatography on silica gel. Elution with a mixture of 7% ethyl acetate, 10% cyclohexane, and 83% petroleum ether afforded 5.79 g (18.6 mmol, 64%) of a pale yellow oil with the characteristic odor: ir (film) 2900, 1730, 1450, 1428, 1374, 1230, 1031, and 969 cm^{-1}; nmr (CCl_4) δ 4.09 (m, 2H,

CH_2OAc), 3.27 (broad s, 4H, SCH_2CH_2S), 1.91 (s, $COCH_3$), 1.67 (broad s, 3H, $C=CCH_3$) and 0.98 (m, 3H, $CHCH_3$) ppm.

Anal. Calcd. for $C_{16}H_{24}O_2S_2$: C, 61.51; H, 7.74; S, 20.49. Found: C, 61.39; H, 7.66; S, 20.45.

4,5,6,7-Tetrahydro-3,r-7-dimethyl-c-7a(2H)-indenemethanol acetate (123)

A 1000 ml, three-necked, round-bottomed flask, fitted with a mechanical stirrer and reflux condenser was evacuated and put under a nitrogen atmosphere. The flask was charged with 7 teaspoons of W-2 Raney nickel catalyst and 400 ml of absolute ethanol. To the stirred suspension was added 7.13 g (22.8 mmol) of thioacetal 122 and an additional 100 ml of ethanol. The reaction mixture was gently refluxed for 3 hr (see discussion section) and was allowed to cool for approximately 0.25 hr. The reaction mixture was then filtered through a celite filter mat and was washed copiously with absolute ethanol. The ethanol was removed from the filtrate by distillation under reduced pressure. The residue was chromatographed on silica gel. Elution with a mixture of 5% ethyl acetate, 10% cyclohexane, and 85% petroleum ether afforded 1.87 g (8.45 mmol, 37%) of a clear oil: ir (film) 2874, 1732, 1450, 1374, 1232, and 1030 cm^{-1}; nmr (CCl_4) δ 4.08 (m. CH_2OAc), 1.89 (broad s, $COCH_3$), 1.61 (broad s, $C=CCH_3$), and 0.93 (m, $CHCH_3$) ppm.

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.55; H, 9.89.

Vinyl proton resonances were evident in the nmr spectrum of the chromatographed material thus implying that desulfurization occurred with partial migration of the double bond (see discussion section).

5,6,7,7a-Tetrahydro-t-7a-hydroperoxy-c-4-methyl-1-methylene-r-3a(4H)-indanmethanol-3a-acetate (127)

Conditions employed in this experiment were similar to those described by Marshall and Hochstetler (93). A Pyrex immersion well was charged with 1.73 g (7.78 mmol) of acetate 123, 200 ml of pyridine, and 52 mg of hematoporphyrin. Oxygen was bubbled through the dark red solution via a fritted disc in the bottom of the immersion well. The inside surface of the immersion well was exposed to a 550 W, medium pressure, mercury vapor lamp for 3.0 hr. The course of the reaction was followed by t.l.c. analysis of aliquots, eluted with 20% ethyl acetate in petroleum ether. After no apparent increase in product formation, the reaction mixture was diluted with 300 ml of benzene and most of the solvent was removed by azeotropic distillation under reduced pressure. The residue was chromatographed on silica gel. Elution with 10% ethyl acetate, 10% cyclohexane, and 80% petroleum ether afforded 917 mg (3.61 mmol, 46%) of hydroperoxide 127: ir (film) 3330 (OOH), 2970, 1718, 1656, 1630, 1444, 1370, 1234, 1028, and 894 cm^{-1}; nmr (CCl_4) δ 5.02 (broad d, 1H, J = 6Hz, C=CH_2), 3.56-4.55 (m, 2H, CH_2OAc), 1.99 (s, COCH_3), and 0.82 (d, 3H, J = 7Hz, CHCH_3) ppm; mass spectrum (70 eV) m/e 254 (M^+), 238 and 222.

Attempted reduction of 5,6,7,7a-tetrahydro-t-7a-hydroperoxy-c-4-methyl-1-methylene-r-3a(4H)-indanmethanol 3a-acetate (127) with iodide

The procedure of Nikon and Bagli (84) was used. A 100 ml, one-necked round-bottomed flask was evacuated, put under a nitrogen atmosphere, and charged with 169 mg (0.666 mmol) of hydroperoxide 127, 109 mg (1.167 mmol) of sodium iodide, 31 ml of absolute ethanol, 9 drops of glacial acetic acid, and 6 ml of anhydrous ether. Upon mixing, the solution turned pale

yellow. Within minutes it was a deep orange, and after 1 hr, a deep red. The reaction mixture was allowed to stand at room temperature overnight. The volumn was reduced by distillation under reduced pressure and the residue was dissolved in ether. The solution was washed with water, a saturated aqueous solution of sodium thiosulfate, water, a saturated aqueous solution of sodium bicarbonate, and brine. The ether solution was dried over anhydrous magnesium sulfate, filtered, and concentrated by distillation under vacuum to afford 180 mg of an oil whose spectral properties were very different from the expected product or starting material.

5,6,7,7a-Tetrahydro-t-7a-hydroxy-r-1,c-4-dimethyl-c-3a(4H)-indanmethanol 3a-acetate (128)

A thick-walled, wide-mouthed bottle was charged with 277 mg (1.09 mmol) of hydroperoxide 127, 30 mg of platinum oxide, and 30 ml of 95% ethanol. The bottle was shaken under 54 p.s.i. of hydrogen pressure for 23 hr. The reaction mixture was filtered through a celite filter mat and the solvent was removed by distillation under reduced pressure. The residue was chromatographed on silica gel. Elution with 6% ethyl acetate, 10% cyclohexane, and 84% petroleum ether afforded 103 mg (0.43 mmol, 39%) of alcohol 128: ir (film) 3380 (OH), 2950, 1716, 1452, 1370, 1232, and 1030 cm^{-1}; nmr (CCl_4) δ 4.37-3.62 (m, CH_2OAc) and 1.95 (s, $COCH_3$) ppm.

Dehydration of 5,6,7,7a-tetrahydro-t-7a-hydroxy-r-1,c-4-dimethyl-c-3a(4H)-indanmethanol 3a-acetate (123)

The reported procedure (94) was used. A 25-ml, three-necked, round-bottomed flask, in an ice bath, fitted with a magnetic stirrer, was charged with 103 mg (0.43 mmol) of the tertiary alcohol 128, 2 ml of dry benzene,

and 2 ml of dry pyridine. Thirty-eight microliters (0.5 mmol) of thionyl chloride was dissolved in 3 ml of dry benzene and added dropwise, through a pipette, to the flask. The reaction mixture was stirred at 0-2° for 0.5 hr and poured rapidly into stirred ice water. After the addition of some benzene the layers were separated. The aqueous layer was back extracted twice with benzene. The combined benzene layers were washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and the solvent was removed by distillation under reduced pressure. The residue was chromatographed on silica gel and eluted with a 10% ethyl acetate, 10% cyclohexane, and 80% petroleum ether mixture. An nmr of the product (32 mg) identified it as the unsaturated acetate 123.

5,6,7,7a-Tetrahydro-t-7a-hydroxy-c-4-methyl-1-methylene-r-3a(4H)-indan-methanol 3a-acetate (132)

A 25 ml, three-necked, round-bottomed flask, fitted with a calcium chloride drying tube, reflux condenser, and magnetic stirrer was charged with 834 mg (3.28 mmol) of hydroperoxide 127 and 10 ml of absolute ethanol. To this stirred solution was added 124 mg (3.28 mmol) of sodium borohydride. Stirring was continued for 1 hr at room temperature during which time the clear solution warmed noticeably. The reaction mixture was poured into brine and the layers were separated after the addition of some ether. The aqueous layer was back extracted with ether. The combined ether layers were washed with brine, dried over magnesium sulfate, filtered, and the solvent was removed by distillation under reduced pressure. The residue was chromatographed on silica gel. Elution with 10% ethyl acetate, 10% cyclohexane, and 80% petroleum ether afforded 212 mg (0.89 mmol, 27%) of the solid alcohol: mp 64-74°; ir (KBr) 3380 (OH),

2885, 1720, 1654, 1632, 1450, 1376, 1234, 1033, and 888 cm^{-1}; nmr (CCl_4) δ 4.86 (m, 2H, C=C$\underline{H}_2$), 3.82 (AB pattern, 2H, C$\underline{H}_2$OAc), 1.93 (s, COC$\underline{H}_3$), and 1.83 (d, 3H, $\underline{J}$ = 7Hz, CHC$\underline{H}_3$) ppm.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 70.56; H, 9.30. Found: C, 70.47; H, 9.35.

Attempted dehydration of 5,6,7,7a-tetrahydro-t-7a-hydroxy-c-4-methyl-1-methylene-r-3a(4H)-indanmethanol 3a-acetate (132)

A. The procedure of von Rudloff (95) was used. A 25 ml, three-necked, round-bottomed flask, fitted with a reflux condenser, was put under a nitrogen atmosphere. The flask was charged with 139 mg (0.584 mmol) of alcohol 132, 278 mg of neutral alumina (Woelm activity grade 1), and 5.56 mg of dry pyridine. The reaction mixture was heated to 175-185° for 3 hr. The mixture was allowed to cool to room temperature and, after the addition of some ether, was filtered. The filter cake was washed repeatedly with ether. The filtrate was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated affording 50 mg of a brown oil, identified as neither product nor starting material.

B. A 25 ml, three-necked, round-bottomed flask, fitted with a magnetic stirrer and a calcium chloride drying tube, was charged with 211 mg (0.887 mmol) of alcohol 132, 4 ml of dry benzene, and 4 ml of dry pyridine. A solution of 78 μl (1.0 mmol) of thionyl chloride in 6 ml of dry benzene was added dropwise to the flask through a pipette. A precipitate formed and the reaction turned yellow and then orange. After 0.5 hr of stirring the reaction mixture was rapidly poured into stirred ice water and, after addition of benzene, the layers were separated. The aqueous layer was back extracted with benzene, and the combined benzene extracts were washed

with brine, dried over anhydrous magnesium sulfate, filtered, and the solvent was removed by distillation under reduced pressure giving 184 mg (0.772 mmol, 87%) of the allylic chloride 133: 2860, 1730 (C=O ester), 1446, 1372, 1232, 1034, and 682 (CCl) cm^{-1}; nmr (CCl_4) δ 4.17 (AB pattern, $C\underline{H}_2OAc$), 4.08 (s, $C\underline{H}_2Cl$), 1.91 (s, $COC\underline{H}_3$) and 0.95 (m, $CHC\underline{H}_3$) ppm.

CONCLUSION

"Because it's there"....may be justification for climbing a mountain, but in itself is insufficient reason for synthesizing a natural product. Unless there is an inherent quality of the product, the real value of its synthesis lies in the approach and synthetic methods which are discovered or refined.

Potassium carbonate was shown to be an outstanding base for the alkylations or Michael additions of 2-carboxycyclopentanones.

The solvolytic rearrangement of hydrindanes to hydrazulenes is a viable approach to their synthesis. It fills the need for a stereochemically unambiguous route to asymmetrically substituted hydroazulenes.

LITERATURE CITED

1. L. Ruzicka, Helv. Chim. Acta, 6, 855 (1923).

2. A. E. Sherndal, J. Amer. Chem. Soc., 37, 1537 (1915).

3. Shimmel's Report, 2, 42 (1892).

4. R. B. Bates and R. C. Slagel, Chem. and Ind., 1715 (1962).

5. E. S. Guenther, Am. Perfumer, 46, No. 3, 44 (1944).

6. C. M. Harris and H. H. G. McKern, Museum Technol. and Applied Sci., 2, 15 (1950).

7. H. H. G. McKern, M. C. Spies, and J. L. Willis, J. Proc. Roy. Soc. N. S. Wales, 88, Pt. 1, 15 (1954).

8. A. Gandurin, Ber., 41, 4359 (1908).

9. J. W. G. Neuhaus and F. H. Reuter, Aust. Chem. Inst. J. and Proc. 15, 185 (1948).

10. R. T. Baker and H. G. Smith, Pines of Australia, 63, 118 (1910).

11. J. L. Simonsen and D. H. R. Barton, The Terpenes, 2nd ed., Vol. III, Cambridge University Press, Cambridge, England, 1952.

12. E. J. Eisenbraun, T. George, B. Riniker, and C. Djerassi, J. Amer. Chem. Soc., 82, 3648 (1960).

13. H. Minato, Chem. Pharm. Bull. (Japan), 9, 625 (1961).

14. J. B. Hendrickson, Tetrahedron, 7, 82 (1959).

15. K. Takeda, H. Minato, and S. Nosaka, Tetrahedron, 13, 308 (1961).

16. K. Takeda and H. Minato, Tetrahedron Lett. No. 22, 33 (1960).

17. K. Takeda and H. Minato, Chem. Pharm. Bull. (Japan), 9, 619 (1961).

18. H. Minato, Tetrahedron Lett., 280 (1961).

19. H. Minato, Tetrahedron, 18, 365 (1962).

20. G. L. Buchanan and G. A. R. Young, Chem. Commun., 643 (1971).

21. J. A. Marshall, A. E. Greene, and R. Ruden, Tetrahedron Lett., 855 (1971).

22. J. A. Marshall and A. E. Greene, J. Org. Chem., 36, 2035 (1971).

23. T. Nozoe and S. Ito, Progr. Chem. Org. Natur. Prod., 19, 32 (1971).

24. J. Romo and A. R. deVivar, Progr. Chem. Org. Natur. Prod., 25, 90 (1967).

25. W. Parker and J. S. Roberts, Quart. Rev., 21, 331 (1967).

26. G. Ourisson, S. Munavalli, and C. Ehret, Sesquiterpenoids, Pergamon Press, Oxford, England, 1966.

27. J. Romo, Pure Appl. Chem., 21, 123 (1970).

28. P. A. Plattner and A. St. Pfau, Helv. Chim. Acta, 20, 224 (1937).

29. E. Piers and K. F. Cheng, Chem. Commun., 562 (1969).

30. J. A. Marshall, N. H. Anderson, and P. C. Johnson, J. Org. Chem., 35, 186 (1970).

31. J. B. Hendrickson and R. K. Boeckman, Jr., J. Amer. Chem. Soc., 93, 1307 (1971).

32. R. A. Kretchmer and W. J. Frazee, J. Org. Chem., 36, 2855 (1971).

33. P. S. Wharton and M. D. Baird, J. Org. Chem., 36, 2932 (1971).

34. C. H. Heathcock and R. Ratcliffe, Chem. Commun., 994 (1968).

35. C. H. Heathcock and R. Ratcliffe, J. Amer. Chem. Soc., 93, 1746 (1971).

36. G. Büchi, W. Hofheinz, and J. V. Paukstelis, J. Amer. Chem. Soc., 91, 6473 (1968).

37. M. Kato, H. Kosugi, and A. Yoshikashi, Chem. Commun., 185 (1970).

38. M. Kato, H. Kosugi, and A. Yoshikoshi, Chem. Commun., 934 (1970).

39. K. Grimm, P. S. Venkataramani, and W. Reusch, J. Amer. Chem. Soc., 93, 270 (1971).

40. J. A. Marshall and J. J. Partridge, J. Amer. Chem. Soc., 90, 1090 (1968).

41. J. A. Marshall and J. J. Partridge, Tetrahedron, 25, 2159 (1969).

42. J. A. Marshall and J. J. Partridge, Tetrahedron Lett., 2545 (1966).

43. J. A. Marshall and W. F. Huffman, J. Amer. Chem. Soc., 92, 6358 (1970).

44. J. Tadanier, J. Org. Chem., 31, 2124 (1966).

45. J. Tadanier, J. Org. Chem., 31, 3204 (1966).

46. H. Carpio, A. C. Bazán, M. G. T. Medina, and J. A. Edwards, J. Org. Chem., 30, 4154 (1965).

47. L. H. Knox, E. Velarde, S. Berger, I. Delfín, R. Grezemkeovsky, and A. D. Cross, J. Org. Chem., 30, 4160 (1965).

48. C. J. V. Scanio and L. P. Hill, Chem. Commun., 242 (1971).

49. J. A. Marshall and A. E. Greene, Tetrahedron Lett., 859 (1971).

50. R. O. Clinton and S. C. Laskowski, J. Amer. Chem. Soc., 70, 3135 (1948).

51. W. G. Dauben, J. W. McFarland, J. B. Rogan, J. Org. Chem., 26, 297 (1961).

52. C. B. C. Boyce and J. S. Whitehurst, J. Chem. Soc., 2022 (1959).

53. S. Ramachandran and M. S. Newman, Org. Syn., 41, 38 (1961).

54. C. J. V. Scanio and L. P. Hill, Synthesis, 651 (1970).

55. W. L. Meyer and A. S. Levinson, J. Org. Chem., 28, 2185 (1963).

56. T. A. Spenser, H. S. Neel, T. W. Fletchtner, and R. A. Zale, Tetrahedron Lett., 3889 (1965).

57. J. Broome, B. R. Brown, A. Roberts, and A. M. S. White, J. Chem. Soc., 1406 (1960).

58. R. Albrecht and C. Tamm, Helv. Chim. Acta, 40, 2216 (1957).

59. L. Caglioto and P. Grasselli, Chem. and Ind., 153 (1964).

60. H. O. House, Modern Synthetic Reactions, W. A. Benjamin, Inc., New York, N.Y., 1965, pp 14-15.

61. J. W. Rowe, A. Melera, D. Arigoni, O. Jeger, and L. Ruzicka, Helv. Chim. Acta, 40, 1 (1957).

62. H. Minato and T. Nagasaki, J. Chem. Soc., 866 (1966).

63. R. E. Ireland, T. I. Wrigley and W. G. Young, J. Amer. Chem. Soc., 80, 4604 (1958).

64. V. Georgian, R. Harrisson, and N. Gubisch, J. Amer. Chem. Soc., 81, 5834 (1959).

65. F. Sondheimer and D. Rosenthal, J. Amer. Chem. Soc., 80, 3995 (1958).

66. V. Permutti, N. Danieli, and Y. Mazur, Tetrahedron, 24, 5425 (1968).

67. R. L. Kronenthal and E. I. Becker, J. Amer. Chem. Soc., 79, 1095 (1957).

68. J. R. Dyer, Applications of Absorption Spectroscopy of Organic Compounds, Prentice-Hall, Inc., Englewood Cliffs, N.J., 1965, pp 87-88.

69. H. Chikamatsu, M. Maeda, and M. Nagazaki, Tetrahedron, 25, 4751 (1969).

70. L. Ruzicka, J. Meyer, and M. Mingazzini, Helv. Chim. Acta, 5, 345 (1922).

71. E. Heilbronner, P. A. Plattner, and K. Wieland, Experientia 3, 70 (1947).

72. J. A. Marshall and T. M. Warne, Jr., J. Org. Chem., 36, 178 (1971).

73. W. L. Meyer, A. P. Lobo, and E. T. Marquis, J. Org. Chem., 30, 181 (1965).

74. A. W. Johnson, E. Markham and R. Price, Org. Syn., 42, 75 (1962).

75. K. Sisido, K. Utimoto, and T. Isida, J. Org. Chem., 29, 2781 (1964).

76. A. L. Wilds and C. Djerassi, J. Amer. Chem. Soc., 68, 1715 (1946).

77. C. J. V. Scanio and R. M. Starrett, J. Amer. Chem. Soc., 93, 1539 (1971).

78. R. D. Offenhauer and S. F. Nelson, J. Org. Chem., 33, 775 (1968).

79. J. Szmuszkovicz, Advan. in Org. Chem., 4, 1 (1963).

80. C. S. Foote and R. W. Denny, J. Amer. Chem. Soc., 93, 5162 (1971).

81. C. S. Foote and R. W. Denny, J. Amer. Chem. Soc., 93, 5168 (1971).

82. K. Gollnick, Advan. Photochem., 6, 1 (1968).

83. K. Nakanishi, Iowa State University Seminar, October 21, 1971.

84. A. Nikon and J. F. Bagli, J. Amer. Chem. Soc., 83, 1498 (1961).

85. P. N. Rylander, Catalytic Hydrogenation over Platinum Metals, Academic Press, New York, N.Y., p. 490.

86. L. Bounealt and R. Locquin, Bull. Chim. Soc. (Fr.) (4), 3, 432 (1908).

87. R. Mayer and B. Gebhart, Berichte, 93, 1212 (1960).

88. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, J. Amer. Chem. Soc., 85, 207 (1963).

89. L. S. Minckler, A. S. Hussey, and R. H. Baker, J. Amer. Chem. Soc., 78, 1009 (1956).

90. H. O. House, W. L. Respers, and G. M. Whitesides, J. Org. Chem., 31, 3128 (1966).

91. R. M. Starrett, Iowa State University, Personal Communication, 1970.

92. R. M. Coates and J. E. Shaw, J. Amer. Chem. Soc., 68, 1715 (1946).

93. J. A. Marshall and A. R. Hochstetler, J. Org. Chem., 31, 1020 (1966).

94. E. Piers, W. deWaal, and R. W. Britton, J. Amer. Chem. Soc., 93, 5113 (1971).

95. E. von Rudloff, Can. J. Chem., 39, 1860 (1961).

ACKNOWLEDGEMENTS

The author would like to thank Dr. Charles J. V. Scanio for his guidance throughout the course of this work.

Much credit is due an undergraduate teacher of mine, Dr. Charles Armbruster, who has made a major contribution to my life.

There are a number of graduate students who have helped and deserve recognition. They are Richmond Starrett for helping with g.l.c. work, Leo Ochrymowycz for teaching me column chromatography, and Dick Fugiel for suggesting potassium carbonate. All members of the Scanio group deserve a vote of thanks.

A special acknowledgement should be reserved for my wife, Diane, and my two girls, Lori and Julie. The hardships placed upon them while the author was engaged in graduate study were great indeed.