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Synthetic approaches to ishwarone

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Synthetic approaches to ishwarone

by

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A Dissertation Submitted to the
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In Charge of Major Work

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For the Major Department

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For the Graduate College

Iowa State University
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1973

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DEDICATION

To my mother and father,

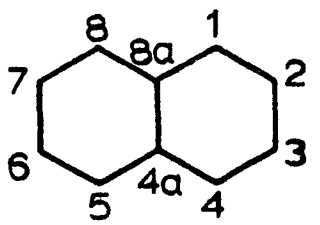
whose love and guidance

have made all my goals attainable.

NOMENCLATURE

The nomenclature used in this manuscript will be the same as that currently employed by Chemical Abstracts. Since this system can be more cumbersome than those systems based on trivial names, this section will serve as a brief explanation of Chemical Abstracts nomenclature. For further information as well as many examples of this system in action, the reader may consult references (1-5).

A. Numbering: The numbering system used in this manuscript is illustrated below.

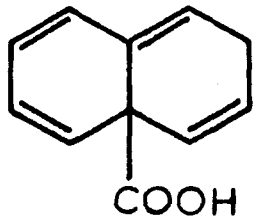


B. 4a-Naphthalenecarboxylic acids

1. Substituents are listed in alphabetical order without considering numerical prefixes such as di, tri, tetra, etc.

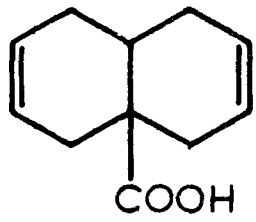
2. The "indicated hydrogen" is given the lowest possible number consistent with a chemically reasonable parent compound. Thus, fully saturated 4a-naphthalene-

carboxylic acids have the "indicated hydrogen" at position "2". The parent compound being



4a(2H)-naphthalenecarboxylic acid

If, however, unsaturation is present at position "2" in the compound, then the next lowest position, position "4", is chosen for the "indicated hydrogen".



1,5,8,8a-tetrahydro-4a(4H)-naphthalenecarboxylic acid

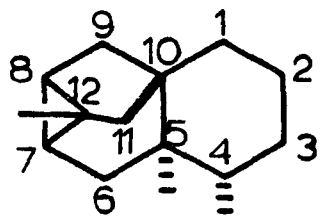
3. Relative stereochemistry in cyclic systems is designated by using c, t, and r descriptors. The substituent named as a suffix or the lowest numbered substituent is assigned the letter r (reference). Groups on the same side of the ring as the reference group are designated c (cis);

groups on the opposite side of the ring are designated t (trans).

4. Steric relations at saturated bridgeheads common to two rings are denoted by cis or trans, followed by a hyphen and placed before the name of the compound.

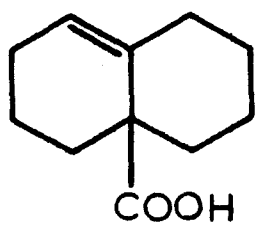
5. The prefix dl is omitted from the name of racemic compounds.

6. Tetracyclic derivatives with the same carbon skeleton as ishwarone are named as derivatives of ishwarane (6).

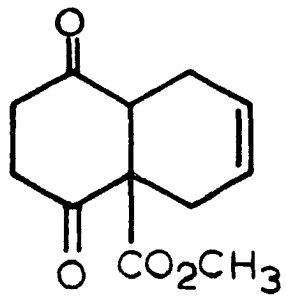


ishwarane

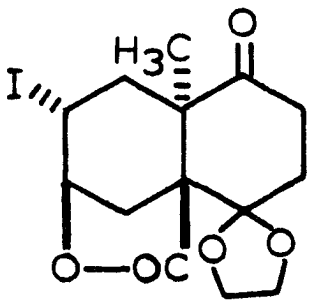
C. Examples



1,3,4,5,6,7-hexahydro-4a(2H)-naphthalenecarboxylic acid



methyl 1,5,6,7,8,8a-hexahydro-5,8-dioxo-4a(4H)-naphthalene-carboxylate



4,4-ethylenedioxyoctahydro-t-7-iodo-t-8a-methyl-1-oxo-r-4a(2H), c-6-naphthalenecarbolactone

INTRODUCTION

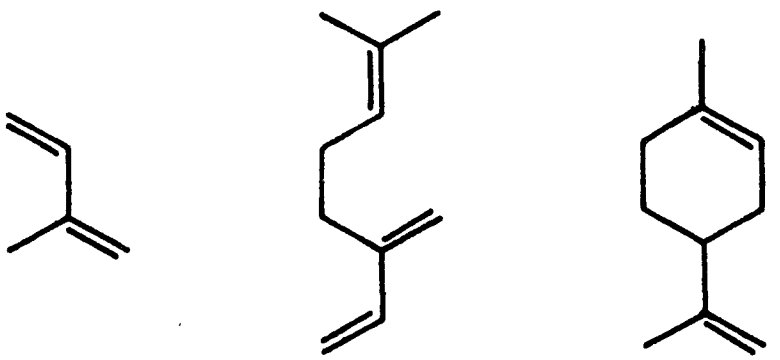
The first scientist that learned to obtain the crude substance from a plant that was responsible for its intriguing odor is long lost in the flow of history. However, since ancient times man has learned to isolate many such "essential oils" from plants, and within the last century he has even managed to identify a number of the individual chemical compounds in such substances.

Classically the essential oils were those mixtures obtained from the simple distillation or steam distillation of plants or parts of plants. Recently the definition has been expanded to include materials isolated by extraction and chromatography.

In the early nineteenth century chemical investigators were able to show that a great number of hydrocarbons of formula $C_{10}H_{16}$ were present in the more volatile fraction of the essential oils. The general name "terpene", derived from the German "terpentine" (turpentine), was soon given to these hydrocarbons. This name is quite appropriate since even the ancient Egyptians and Phoenicians were familiar with oil of turpentine which they obtained by a crude distillation of pine resins. Higher molecular weight compounds have been discovered in the less volatile fractions of the essential oils and these have been named sesquiterpenes (fifteen carbon

atoms), diterpenes (twenty carbon atoms), triterpenes (thirty carbon atoms) and tetraterpenes (forty carbon atoms).

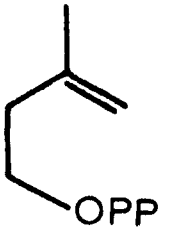
Wallach (7) in 1887 first proposed the "isoprene rule". This rule states that the carbon skeletons of terpenes can be visualized as constructed from the union of two or more isoprene units (1). These units are usually joined in a head-to-tail fashion as shown for the monoterpenes myrcene (2) and limonene (3).



1 2 3

Although it was believed for a time that isoprene was the actual building block of terpenes, it is now known that terpenes are obtained by joining together the "biological isoprene unit", 3-isopentenyl pyrophosphate (4). The biological precursor of 3-isopentenyl pyrophosphate is mevalonic acid (5) which is formed from three units of acetyl coenzyme A. Mevalonic acid is converted by a series of stepwise phosphorylations with ATP to the intermediate 6,

which loses CO_2 and inorganic phosphate to give 3-isopentenyl pyrophosphate.



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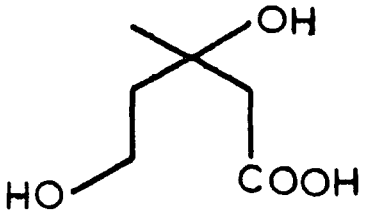

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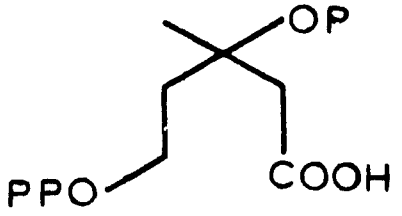

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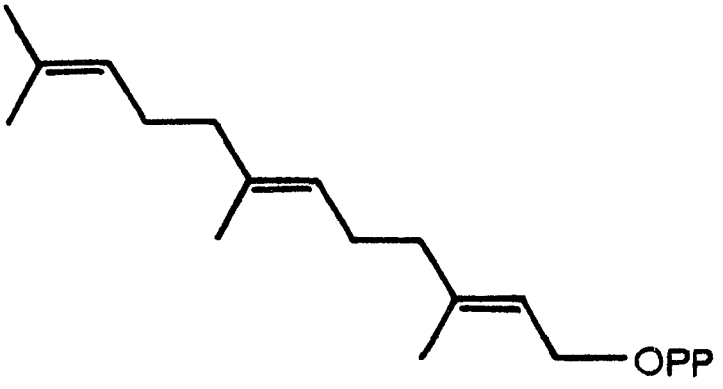

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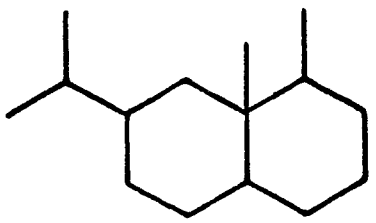
Three molecules of 3-isopentenyl pyrophosphate will then join together to give farnesyl pyrophosphate (7). Sesquiterpenes will then be produced by various cyclizations and oxidations of the intermediary farnesyl pyrophosphate. A work which describes many of these processes in detail as well as the biosyntheses of other terpenes is that by Richards and Hendrickson (8). Other works which contain accounts of

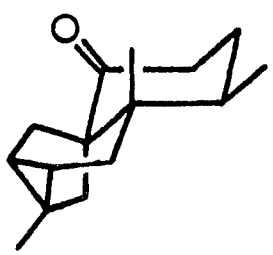
sesquiterpenes and terpenes in general are those by Pinder (9), de Mayo (10), and Simonsen and Barton (11).

One class of sesquiterpenes exists in which the basic carbon skeleton cannot be accounted for by the use of the isoprene rule. These are the eromophilane sesquiterpenes (12), which have the basic skeleton shown below.



Since these compounds cannot be accounted for by invocation of the isoprene rule, they have been termed non-isoprenoid sesquiterpenes.

In 1969 ishwarone (8) was identified as an eremophilane sesquiterpene (13). In addition, it was the first example of a tetracyclic sesquiterpene to be discovered in nature. Because of these novel features it was decided to attempt the synthesis of ishwarone.



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HISTORICAL

Aristolchia indica is a twining perennial plant which may be found growing over most of the tropical region of India (14). The root and stem of A. indica have long been used as a drug in India and are commonly sold in the bazar. The root tastes very bitter and possesses a characteristic aromatic odor. The root has emmenagogue and antiarthritic properties and is often used as a stimulant and tonic. The root and leaves are also said to be a valuable antidote against the bites of snakes and poisonous insects, however, Mhaskar and Caius (15) have shown that the plant has no therapeutic or antidotal effect against cobra venom.

In 1935 Rao, Manjunath and Menon (16) investigated the essential oil obtained by steam distillation of an extract of the roots of A. indica (17). The oil, which possessed the characteristic aromatic odor of the roots, was found to consist mainly of three new sesquiterpenes. One new sesquiterpene was a hydrocarbon of formula $C_{15}H_{24}$ to which the name ishwarene was given; one sesquiterpene was a ketone of formula $C_{15}H_{22}O$ which was called ishwarone, and the third new sesquiterpene, an alcohol of formula $C_{15}H_{24}O$, was named ishwarol. All of the three names were derived from the Kannada name for the roots, Ishwari beru.

Rao and coworkers were able to characterize the semicarbazone, the oxime, the p-nitrophenylhydrazone and the 2,4-dinitrophenylhydrazone derivatives of ishwarone. They were able to prepare a liquid monohydrochloride from ishwarene, but attempts to prepare other addition compounds failed for ishwarene. No derivatives of ishwarol were prepared.

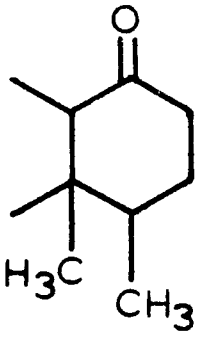
No attempts were made to determine the structure of ishwarone, ishwarene or ishwarol until 34 years later when Ganguly *et al.* (13) initiated a series of systematic degradation studies and spectral studies which culminated in the establishment of the structure and absolute configuration of ishwarone (6,18).

The infrared spectrum of ishwarone exhibits an intense band at 1706 cm^{-1} attributable to a ketone function. A band of medium intensity at 1418 cm^{-1} indicated a methylene group adjacent to the ketone. Furthermore, ishwarone was found to exchange only two atoms of deuterium; therefore the other carbon adjacent to the ketone was a tertiary center. The nmr spectrum shows signals at δ 0.75 (s), 1.15 (s) and 0.85 ppm (d) due to three types of methyl protons, as well as a signal at δ 0.55 ppm (m) which was attributed to a cyclopropyl proton. The ir, nmr and Raman spectra all indicated that ishwarone possessed a tetracyclic structure.

Ganguly and coworkers found that Barton oxidation of ishwarone with potassium t-butoxide in t-butanol in the presence of oxygen gave a diosphenol, $C_{15}H_{20}O_2$, which on further oxidation with hydrogen peroxide and sodium hydroxide gave a dicarboxylic acid, ishwaric acid, $C_{15}H_{22}O_4$. Pyrolysis of ishwaric acid led to a 5-membered ketone, norishwarone, $C_{14}H_{20}O$, which formed a diosphenol, $C_{14}H_{18}O_2$ by Barton oxidation. The nmr spectrum of norishwarone diosphenol indicated the presence of an olefinic methyl group. Oxidation of norishwarone diosphenol with hydrogen peroxide and sodium hydroxide gave norishwaric acid, $C_{14}H_{20}O_4$. On the basis of this evidence Ganguly et al. were able to assign partial structure 9 to ishwarone.

Ishwarone on treatment with dry HCl in ether at 0°, followed by brief exposure to boiling pyridine, gave an isomeric mixture of two unsaturated ketones. The isomer containing an endocyclic double bond, $C_{15}H_{22}O$, was designated as isoishwarone. The nmr spectrum of isoishwarone shows an olefinic methyl group as a doublet at δ 1.78 ppm and one vinyl proton as a multiplet at δ 5.72 ppm. Treatment of isoishwarone with OsO_4 furnished a diol, $C_{15}H_{24}O_3$, which could be readily cleaved to a diketoaldehyde, $C_{15}H_{22}O_3$. Ozonolysis of isoishwarone gave a diketone, $C_{14}H_{22}O_2$, in addition to the diketoaldehyde. The diketone was found to be identical with diketone 10 which had been prepared from valerianol (11) via

ketone 12. This correlation allowed Ganguly et al. to assign structure 13 to isoishwarone and structure 14 to the diketo-aldehyde.



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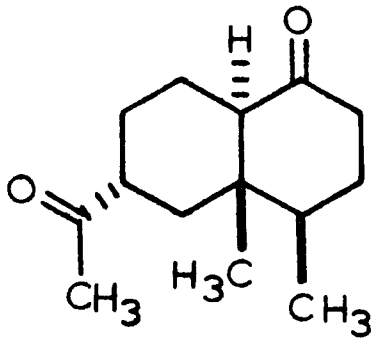

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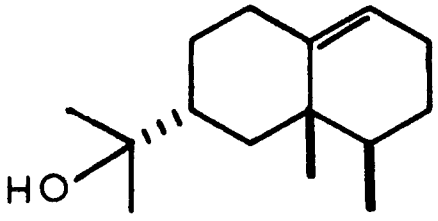

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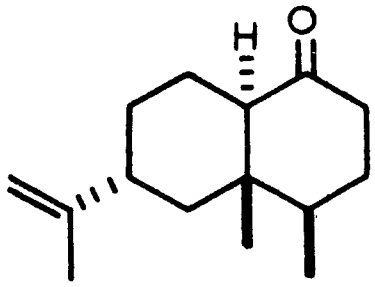

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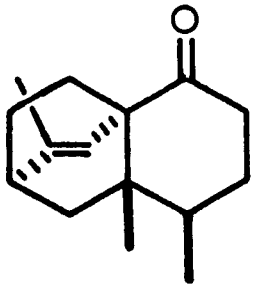

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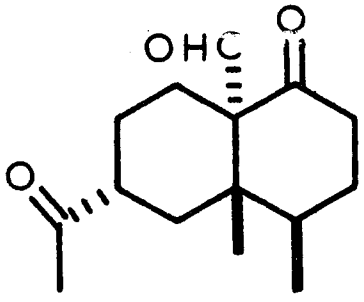

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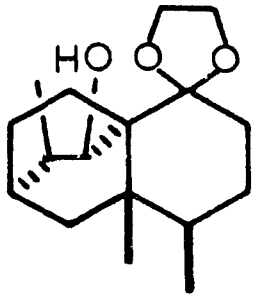
Conclusive chemical evidence which defined the absolute stereochemistry of isoishwarone was obtained by Govindachari et al. (18) in the following manner: The ethylene acetal of isoishwarone, $C_{17}H_{26}O_2$, on hydroboration followed by oxidation with hydrogen peroxide and sodium hydroxide gave only the alcohol 15. Hydrolysis of the acetal gave the aldol 16 which on base-induced retroaldolization gave an amorphous ketoaldehyde 17, via opening of the bicyclo[2.2.2]octane bridge without affecting the stereochemistry at C-7. The bis-semicarbazone of 17 on treatment with potassium hydroxide in boiling diethylene glycol gave a single hydrocarbon, $C_{15}H_{28}$, which was found to be identical in all respects with an authentic sample of (+)-nootkatane (18), prepared by reduction of valencene (19), a sesquiterpene hydrocarbon of established structure and configuration.

Determination of the structure and absolute stereochemistry of isoishwarone (13) led to two possible structures for ishwarone, 8 and 20. Evidence was obtained for structure 8 as follows: Treatment of ishwarone with ozone gave oxoishwarone, $C_{15}H_{20}O_2$, which had spectral properties consistent with that of a saturated 6-membered cyclic ketone and a ketone α to a cyclopropyl ring. Brief exposure of oxoishwarone to hot concentrated hydrochloric acid resulted in the cleavage of the cyclopropane ring to give a chloro compound, $C_{15}H_{21}O_2Cl$, which exhibits an octet at δ 3.95 ppm



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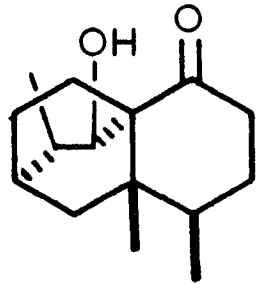

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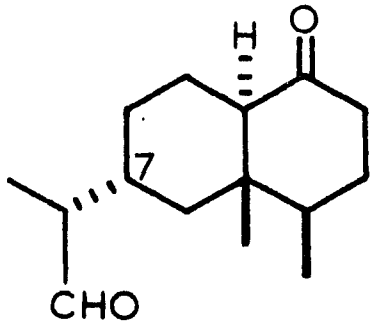

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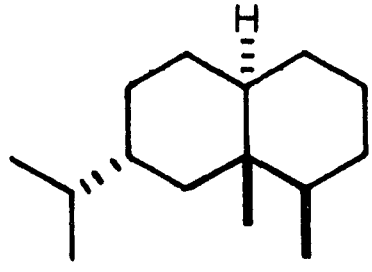

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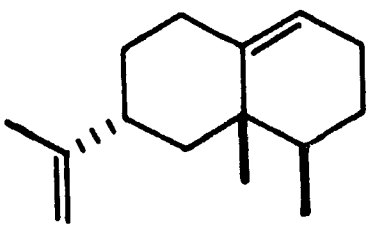
(J=1.5, 4.5 and 7.5 hz) in the nmr spectrum for the proton on the carbon to which the Cl is attached. An octet would be expected only when the chloro compound has structure 21, having at least two proton neighbors, and not structure 22. Since structure 21 can be assigned to the chloro compound, then oxoishwarone and ishwarone must be represented by 8 and 23 respectively.

This assignment for ishwarone also allowed Govindichari to assign structures 24, 25, 26 and 27 to ishwarone diosphenol, ishwaric acid, norishwaric acid and norishwarone



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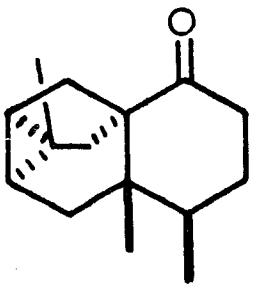

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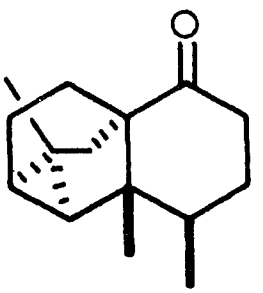

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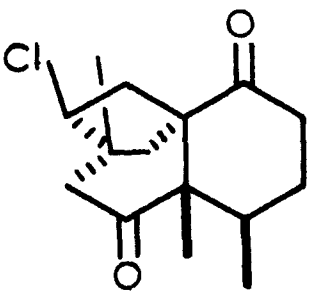

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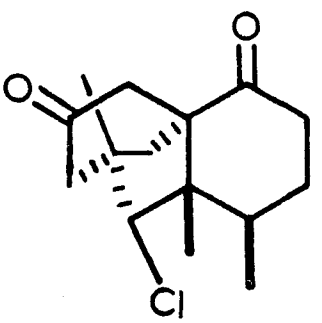

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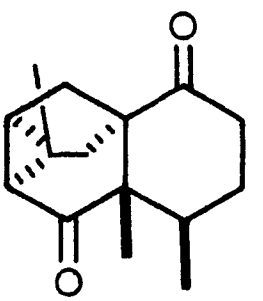

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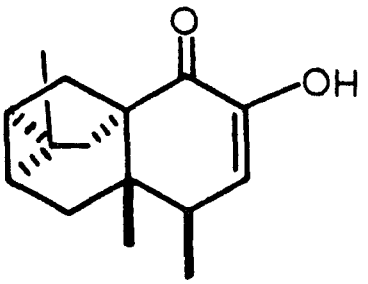
respectively.

Govindachari et al. (19) have isolated two hydrocarbon sesquiterpenes from the roots of Aristolochia indica. The



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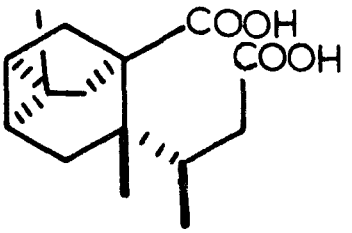

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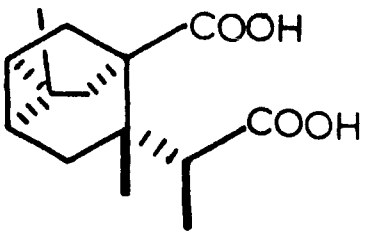

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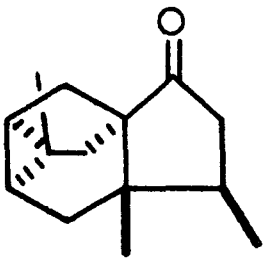

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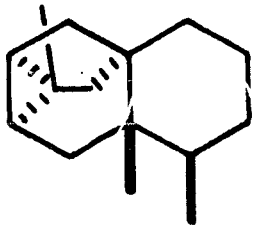
two new hydrocarbons, both of molecular formula $C_{15}H_{24}$, were ishwarane (28) and aristolochene (29). Ishwarane was shown to be identical with the hydrocarbon obtained by Wolff-Kishner reduction of ishwarone (8).

The sesquiterpene alcohol, ishwarol (30) has also been isolated from the roots of Aristolochia indica by Govindachari and Parthasarathy (20). The 3,5-dinitrobenzoate of ishwarol was found to be identical with the 3,5-dinitrobenzoate prepared from the alcohol obtained by reduction of ishwarone with sodium borohydride. In the nmr spectrum of

ishwarol, one of the tertiary methyl groups appears at a low-field of δ1.00 ppm as compared to that in ishwarone (δ0.75 ppm) and this paramagnetic shift was attributed by Govindachari as being due to the hydroxyl and the tertiary methyl groups being 1,3-cis and diaxial.



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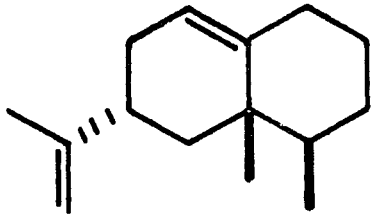

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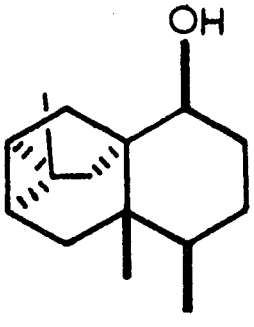

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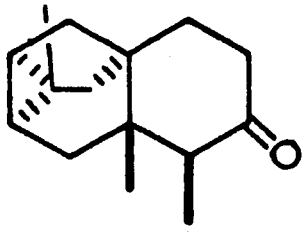


31

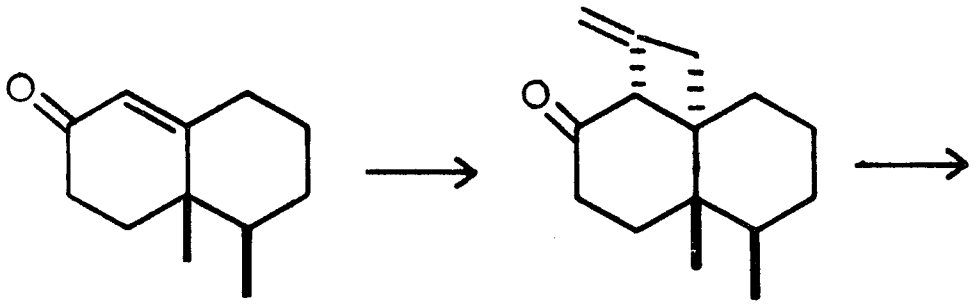
Ishwarane (28) has also been isolated from orejuelas, the dried petals of Cymbopetalum penduliforum (21). Orejuelas is well known in many parts of Central America and is used in Guatemala for flavoring pinol and other beverages.

Very recently 3-oxoishwarane (31) has been isolated from the roots of Aristolochia debilis by Nishida and Kumazawa (22).

Total Synthesis of Ishwarane

The total synthesis of ishwarane (28) has recently been achieved by Kelly et al. (23-25). The starting material used by Kelly was octalone 32 which could be prepared either by annulation of cis-2,3-dimethylcyclohexanone with methyl vinyl ketone and subsequent dehydration of the resulting alcohol or by the more lengthy, but higher yield, synthesis developed by Piers and coworkers (26).

Photoaddition of allene to octalone 32 gave the adduct 33; the structure of 33 being based on the known stereospecificity of the photo-addition of allene to α,β-unsaturated ketones. Acetalization of 33 followed by epoxidation with perbenzoic acid provided 34 as a mixture of epimers. Reduction of 34 with lithium aluminum hydride gave the alcohol 35. Treatment of alcohol 35 with aqueous hydrochloric acid in tetrahydrofuran afforded 36 as a mixture of epimers. The conversion of 35 to 36 involved deacetalization followed by a retro-aldolization to give the intermediate 37 which underwent an aldol condensation to give 36. Dehydration of 36 to enone 38 was then achieved with p-toluenesulfonic acid in boiling benzene.



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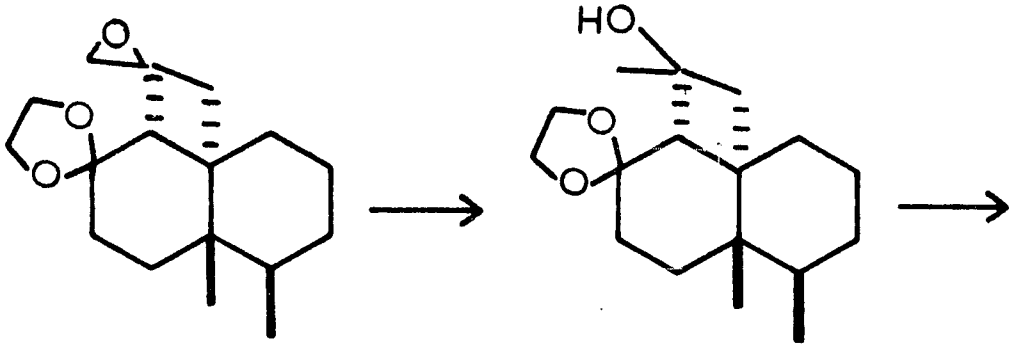

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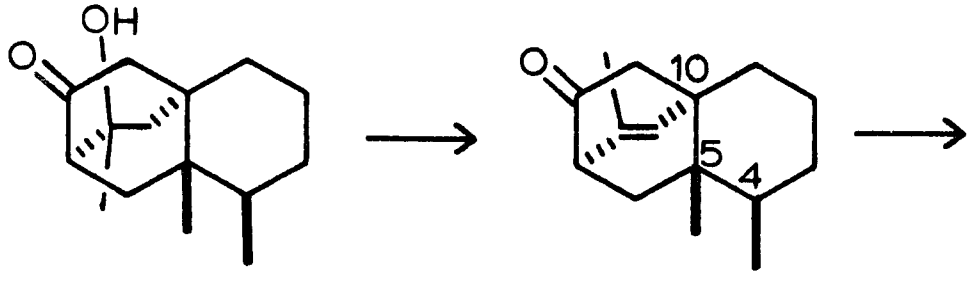

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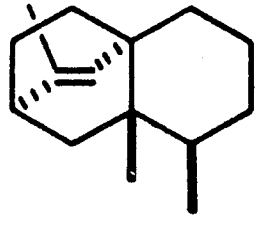

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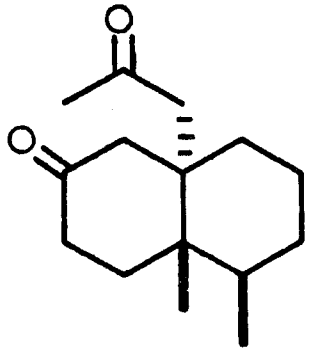

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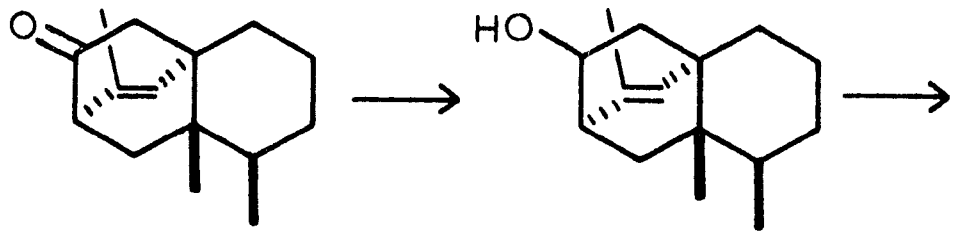

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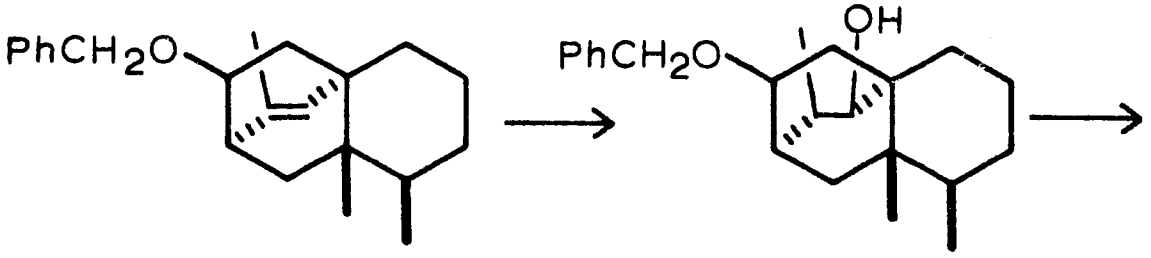

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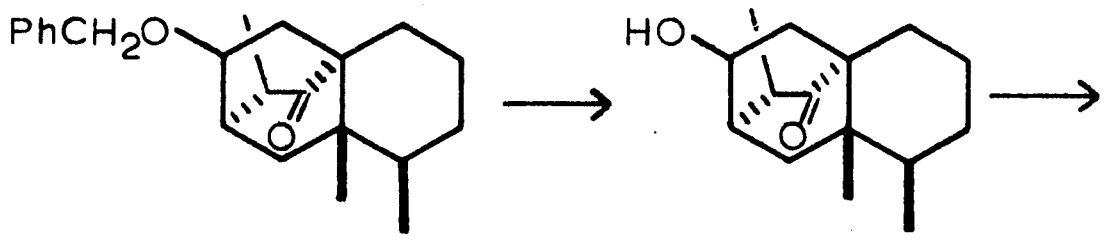

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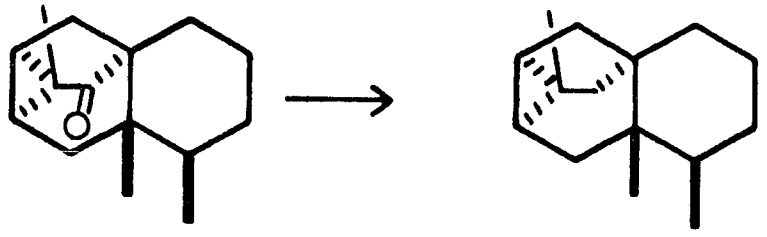


45 28

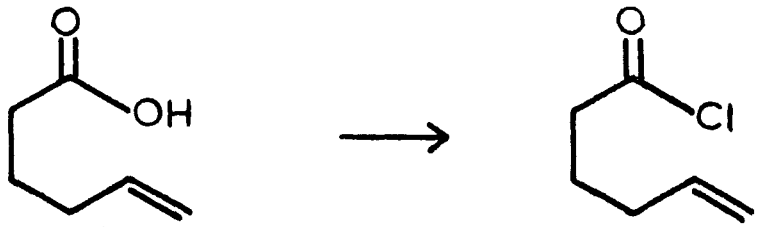
In order to ensure that the synthesis was proceeding along the correct stereochemical lines, Kelly departed from the main synthetic route at this point. Wolff-Kishner reduction of 38 gave a hydrocarbon which was found to be identical in spectral characteristics with an authentic sample of isoishwarane (39). Thus, the enone 38 was shown to have the correct relative stereochemistry at C-4, C-5 and C-10.

Returning to the main synthetic scheme the enone 38 was reduced by lithium aluminum hydride to a mixture of two epimeric alcohols 40. Alcohol 40 was converted to its benzyl ether 41 which gave a single alcohol 42 upon hydroboration. Jones oxidation of 42 provided ketone 43, which was subjected to hydrogenolysis to give the keto alcohol 44. Treatment of the tosylate of 44 with methylsulfinyl carbanion in dimethyl sulfoxide at 60° gave the cyclopropyl ketone 45. The Barton modification of the Wolff-Kishner reduction gave a hydrocarbon which was identical with an authentic sample of ishwarane (28) obtained from natural sources.

Intramolecular Cyclization of Unsaturated Diazomethyl Ketones

The first example of an intramolecular cyclization of an unsaturated diazomethyl ketone was described by Stork and Ficini in 1961 (27). Stork and Ficini treated 5-hexenoic acid (46) with oxalyl chloride to obtain the acid chloride 47 which was converted with diazomethane to the diazoketone 48.

When diazoketone 48 was refluxed in cyclohexane in the presence of copper bronze the bicyclic ketone 49 was obtained. The ketone 49 was also independently synthesized from ketotosylate 50 with sodium hydride in tetrahydrofuran.



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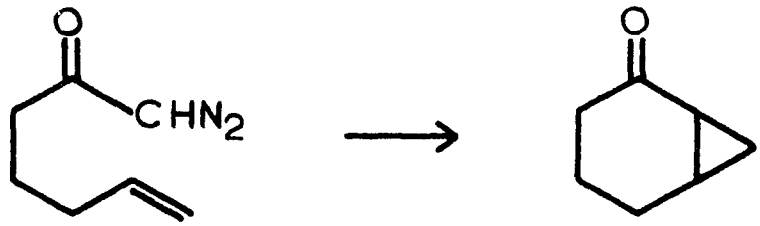

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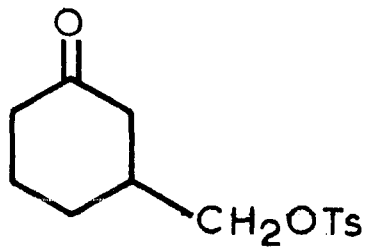

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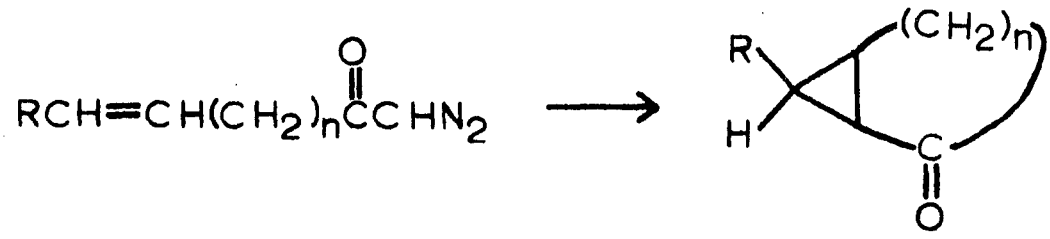
Fawzi and Gutsche (28) found that the nature of the substitution at the double bond had little effect on the cyclization as even severely hindered olefinic systems

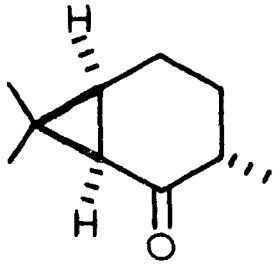
underwent cyclization in fair yield. Fawzi and Gutsche did note, however, that the proximity of the olefin to the diazoalkyl group was important. In going from 51 to 52, if n=2 or 3 then cyclization occurred quite readily, but if n=4 cyclization gave less than five percent of 52.



51 52

Numerous other examples of the intramolecular cyclization of unsaturated diazomethyl ketones have appeared in the literature. The reaction has been used to prepare bicyclic (28-31), tricyclic (32-40) and tetracyclic (41-44) ketones, many of which would have been very difficult or impossible to prepare by other methods. Also, this method has been used in the synthesis of several naturally occurring materials, such as 2-carone (53) (45,46), 4-demethylaristolone (54) (47), sesquicarene (55) (48), sirenin (56) (49-53), sabinene (57) (54), thujopsene (58) (55), agarospirol (59) (56), and norcubebanone (60) (57). The intramolecular cyclization has also been the crucial step in the preparation of several key

intermediates related to diterpene total synthesis (58-64).



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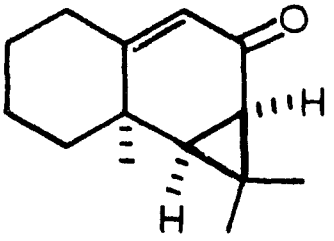

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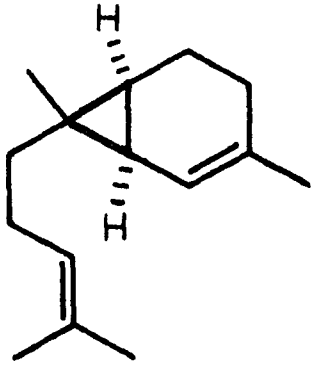

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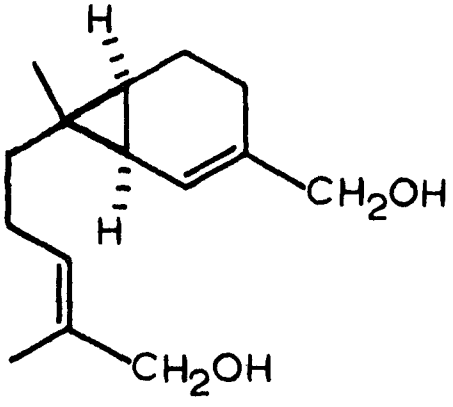

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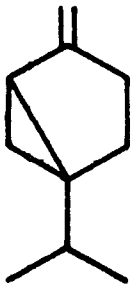
Normally the intramolecular cyclization of diazomethyl ketones is catalyzed by copper bronze or cuprous or cupric salts, however, the cyclization may be photochemically induced (35,41) and recently acidic catalysts have been employed which lead to products having the cyclopropane ring opened (61,65-67). Solvents which are normally used for the cyclization are benzene, hexane, cyclohexane and tetra-

hydrofuran.



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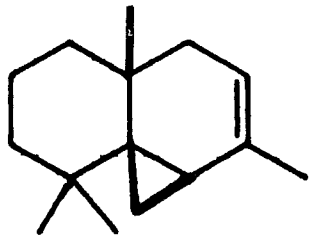

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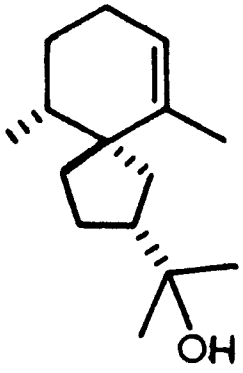

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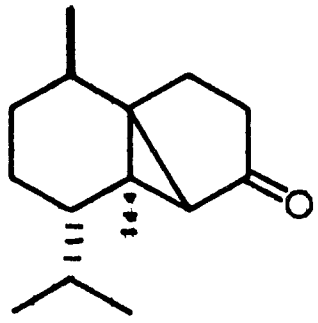

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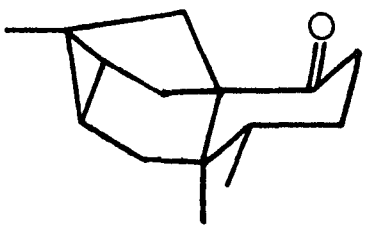
RESULTS AND DISCUSSION

Introduction

The primary goal of our research efforts was, of course, the synthesis of the sesquiterpene ishwarone (8). In order



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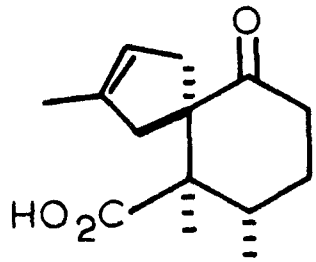
to attain this goal, three alternative approaches involving the intramolecular cyclization of a diazoketone were considered. The three key intermediates of the approaches considered were the acids 61, 62 and 63, from which the corresponding diazoketones 64, 65 and 66 respectively could be derived.

There are, of course, synthetic problems involved in the approach to each of the intermediate acids. The most difficult problem in acid 61 would be the preparation of the spiro[4.5]decane ring system. Secondary problems are presented by the presence of a γ-keto acid and a vinyl methyl group. Acid 62 also contains a vinyl methyl group as well as a β-keto acid. In addition, acid 62 must have a cis ring



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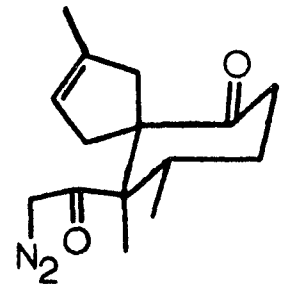

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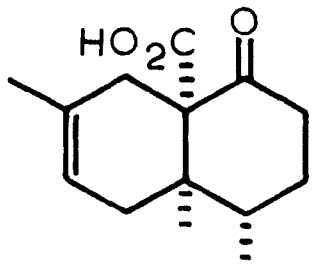

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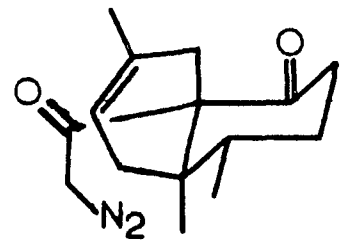

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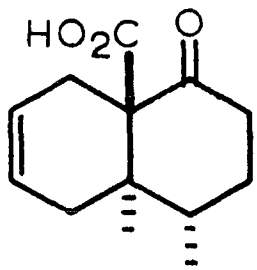

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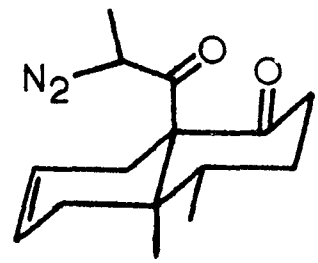
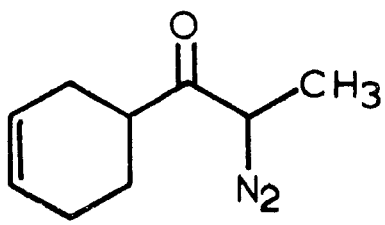


66

juncture. Acid 63 must have a trans ring juncture and in addition a β-keto acid must also be present.

After weighing the various problems it was decided that intermediate 63 could be most easily obtained. However, an additional problem is involved if the intermediate 63 is used since the cyclization of diazoethylketones, such as 66, has never been attempted. Thus, the first part of this discussion will be concerned with the intramolecular cyclization of the model compound 1-diazoethyl-3-cyclohexen-1-yl ketone (67).



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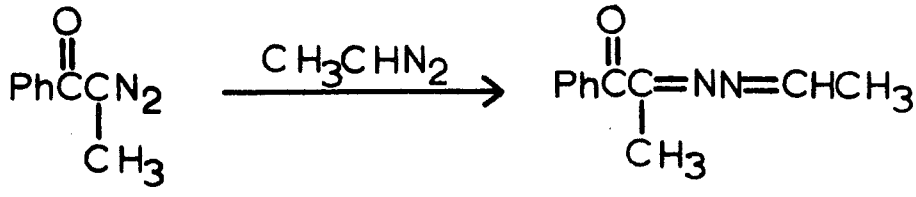
The second part of the discussion will be concerned with the synthesis of the intermediate 63, while the final part of this section will consider the approaches to ishwarone (8) from intermediate 63.

Intramolecular Cyclization of Model Compound 67

Although many examples of the intramolecular cyclization of unsaturated diazomethyl ketones are known (see Historical), no attempts to cyclize unsaturated diazoethyl ketones or other higher homologues have appeared in the literature.

There are several factors which may have militated against their use previous to this time.

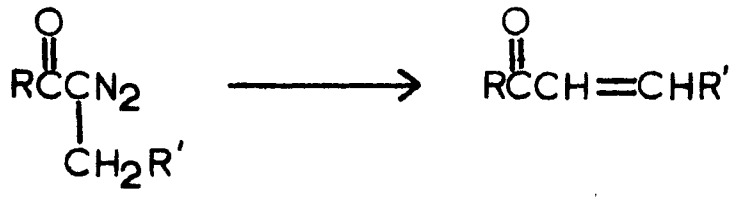
Wilds and Meader (68) found that the reaction conditions necessary to form a diazoketone from an acyl chloride with diazoethane are much more critical than the analogous reaction with diazomethane. The optimum temperature for the reaction when diazoethane is used was found to be -20° whereas a reaction temperature of 0°, normally used with diazomethane, leads to large amounts of a colorless byproduct. Yates and coworkers (69) identified this byproduct and found it to be an azine. For example, Yates found that the diazoketone 68 would react with another equivalent of diazoethane to give the azine 69. The analogous reaction with diazomethane does not occur.



68 69

Wilds and Meader (68) also noted that diazoketones derived from diazoethane failed to undergo the Arndt-Eistert reaction using the usual silver oxide--methanol procedure.

Diazoketones having methylene groups adjacent to the carbon bearing the diazo functionality (e.g. 70) have also shown a propensity to rearrange to the corresponding α,β-unsaturated ketone (e.g. 71), presumably through an intermediate carbene. This rearrangement may occur photochemically (70,71), or it may be catalyzed by silver oxide (70) or mercuric oxide (72).

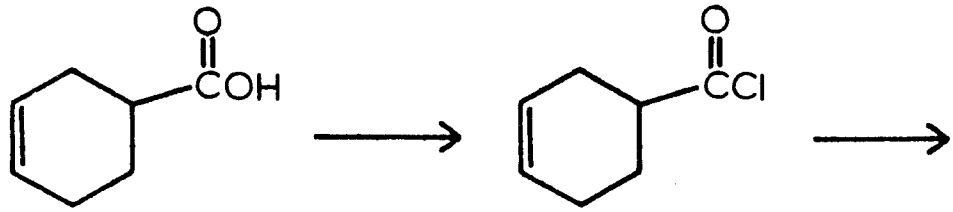


70 71

Considering these factors we felt that it would be worthwhile to investigate the intramolecular cyclization of an unsaturated α-diazoethyl ketone. Diazoketone 67 was chosen for this study because of its similarity in structure to diazoketone 66, which is required for the synthesis of ishwarone.

With this end in sight, 3-cyclohexene-1-carboxylic acid (72) was converted to the acyl chloride 73 with oxalyl chloride (73) which gave diazoketone 67 when treated with diazoethane at -20°. The structure of 67 was evident from its infrared spectral characteristics and its conversion to benzyl 2-[3-cyclohexen-1-yl]propanoate with benzyl alcohol in

γ-collidine at 185° (68).



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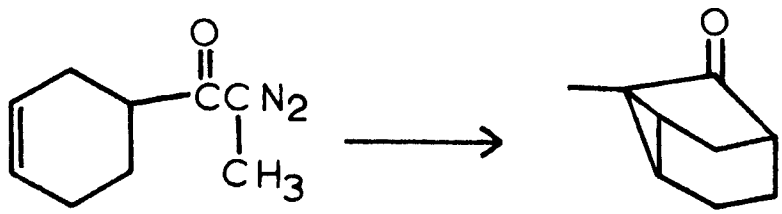

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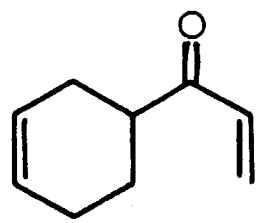
Heating diazoketone 67 in a suspension of anhydrous cupric sulfate in cyclohexane (28) for 15-18 hr gave 7-methyltricyclo[3.2.1.$0^{2,7}$]octan-6-one (74) in 53% yield. There was no spectral evidence for the formation of the α,β-unsaturated ketone 75 under these conditions.



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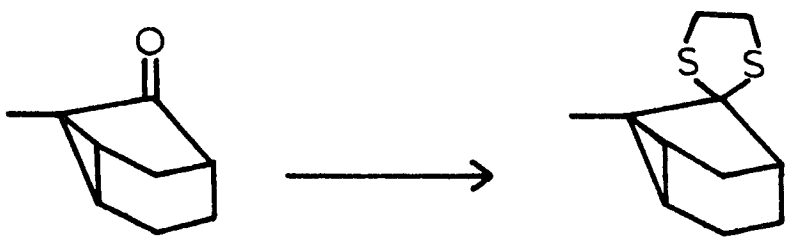
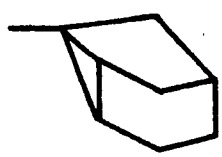
Attempts to effect the intramolecular cyclization of 67 with other copper catalysts, such as copper bronze or cupric oxide proved to be less successful than the cupric sulfate promoted reaction.

Tricyclic ketone 74 could be readily converted to the thioacetal 76 with ethanedithiol and boron trifluoride-etherate in acetic acid (74). Attempts at the reductive cleavage of thioacetal 76 with W-2 Raney nickel (75) to give the tricyclic hydrocarbon 77 were totally without success.



74 76



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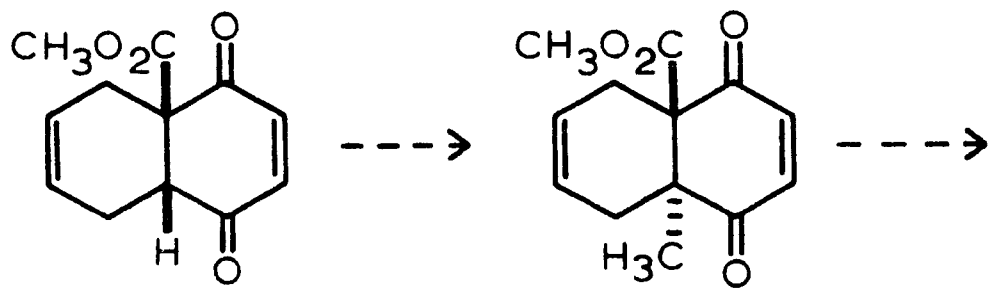
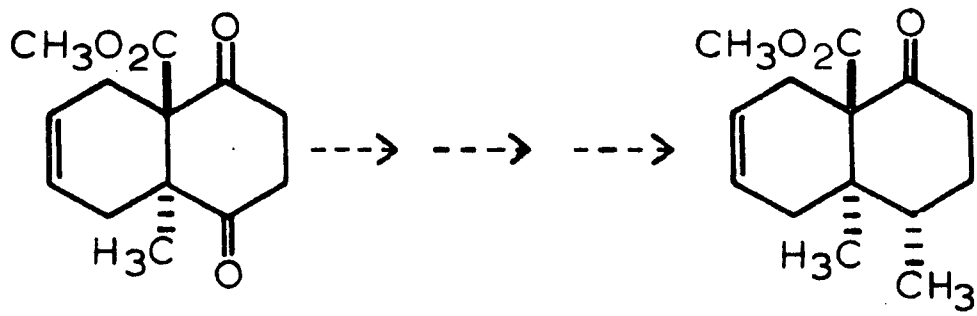
Synthesis of Intermediate 63

Our initial synthetic sequence called for the angular methylation of the known Diels-Alder adduct 78 (76) to give dione 79 followed by reduction with zinc and acetic acid (77)

to give 80. At this point it would have been necessary to distinguish between the two ketone functionalities leading ultimately to the introduction of the second methyl group giving the methyl ester 81 of the desired acid 63.



78 79



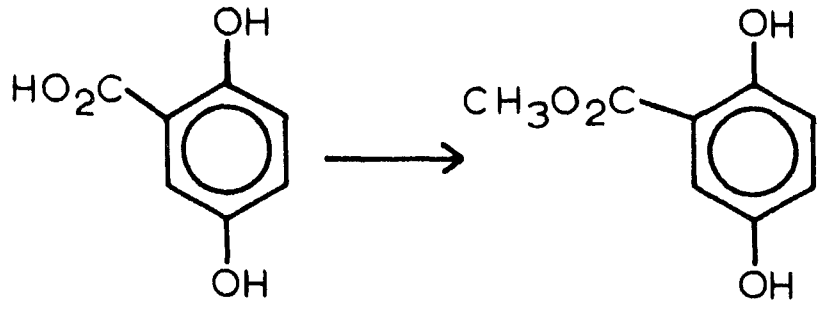
80 81

The first hurdle in our proposed sequence was to develop a procedure which would provide large amounts of adduct 78. Gentisic acid (82) was easily converted to methyl gentisate (83) in 94% yield by treatment with methanol and sulfuric acid (78).

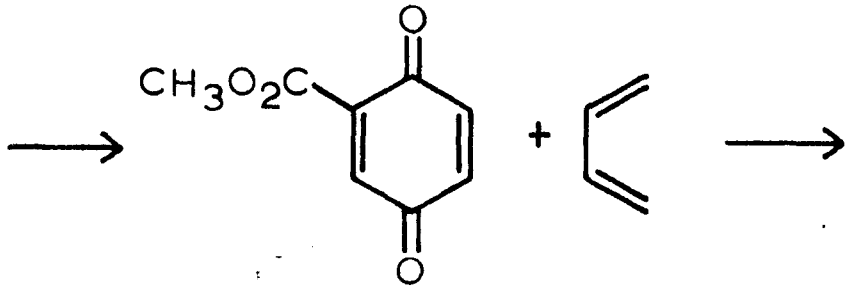
In a procedure developed by Brunner (79) in 1913 methyl gentisate (83) was converted to carbomethoxyquinone (84) by

heating and shaking a suspension of silver oxide and potassium carbonate in a benzene solution of methyl gentisate at 50° for five minutes. This procedure was reported by Brunner to give a 60% yield, however we found that when done on a scale using more than 10 grams of methyl gentisate the reaction gave yields ranging from 0 to 40%. A further complication of this procedure was caused by the fact that the impure carbomethoxyquinone obtained had to be recrystallized from carbon disulfide which further decreased the yield. While testing other reaction conditions we found that the conversion of methyl gentisate (83) to carbomethoxyquinone (84) could be carried out quite conveniently on a large scale (up to 1.2 mol of methyl gentisate) by heating a suspension of silver oxide and anhydrous potassium carbonate in a solution of methyl gentisate in anhydrous ethyl ether at the temperature of refluxing ether for two hours. This procedure consistently gave carbomethoxyquinone in yields of 90-93% which was sufficiently pure so as to be used without recrystallization.

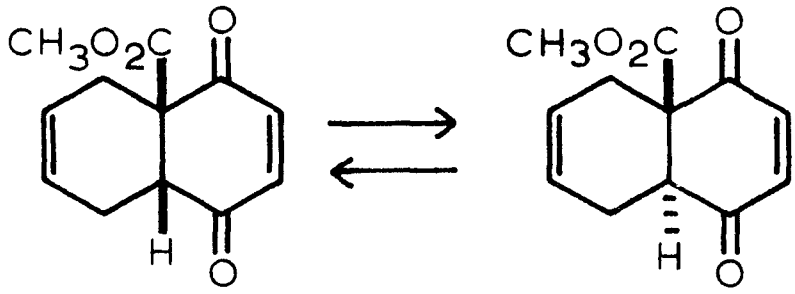
The procedure of Ansell and coworkers (76) for the synthesis of adduct 78 called for heating carbomethoxyquinone (84) and butadiene (85) in a pressure bottle at 65° for six hours, followed by chromatography on alumina to give a mixture of cis-adduct 78 and trans-adduct 86 in a combined yield of 65%. We found that superior yields could be obtained when



82 83



84 85



78 86

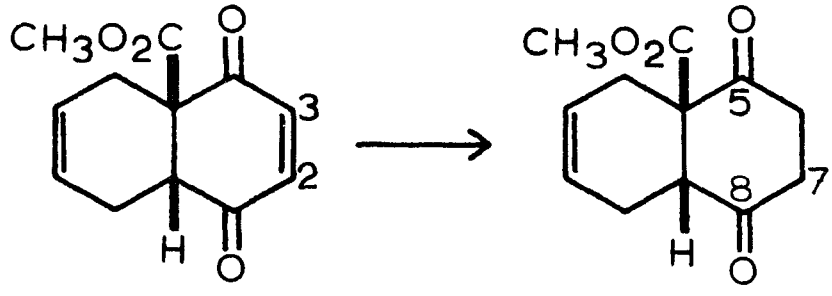
carbomethoxyquinone and an excess of butadiene were allowed to stand at room temperature for one day. Distillation provided pure cis-adduct 78 in 91% yield. The trans-adduct 86

could be readily obtained by chromatography of the cis-adduct 78 on alumina.

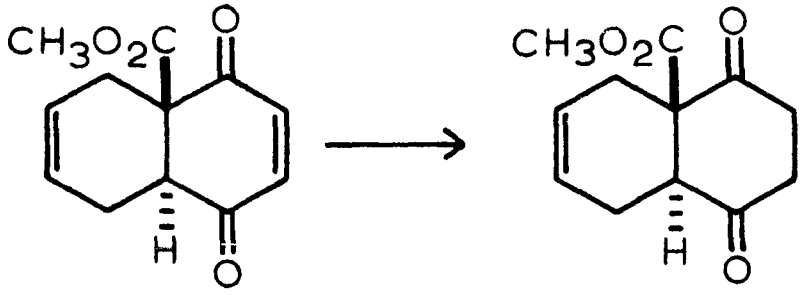
The next step in our proposed sequence was to be the angular methylation of adduct 78 to give 79. Our first attempts at this proposed conversion involved the use of sodium hydride and methyl iodide in benzene under a variety of conditions (80). The only result of these experiments was the isomerization of cis-adduct 78 to trans-adduct 86. No trace of the desired product 79 could be detected. Subsequent experiments using sodium hydride and methyl iodide in dimethyl sulfoxide (81), and potassium t-butoxide and methyl iodide in t-butanol (82) gave resinous products in which the C-2, C-3 olefinic bond was no longer present according to the nmr spectrum.

At this juncture it appeared that the double bond between C-2 and C-3 in adduct 78 might somehow be preventing the successful angular alkylation of adduct 78. Therefore, reduction of this carbon-carbon double bond seemed to be advisable at this stage in the synthetic sequence. Reduction of cis-adduct 78 to cis-dione 87 was accomplished with zinc and acetic acid following a procedure modified from that of Johnson et al. (82). Using the same procedure trans-adduct 86 was reduced to give trans-dione 88.

Dione 87 could now undergo alkylation at three possible sites if subjected to alkylation conditions and probably



78 87

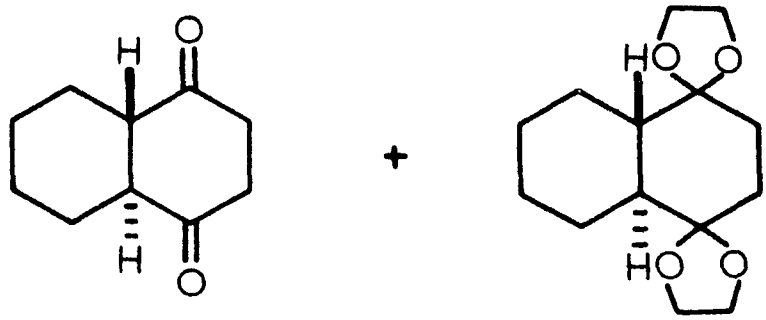


86 88

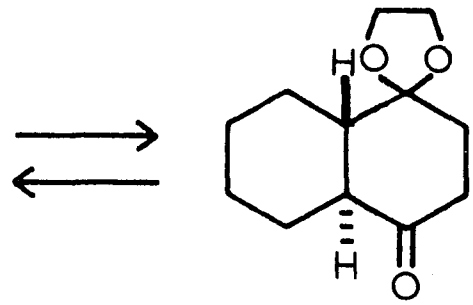
would give a complex mixture of several products if methylation was attempted (83, p 560). Therefore, in order for the successful angular methylation of dione 87 to occur, we felt that two requirements must be satisfied. The two ketone functionalities must be differentiated while simultaneously protecting the C-5 ketone. Then the C-7 position must be blocked so that alkylation could only occur at the desired C-8a angular position.

Johnson and coworkers (82) were able to prepare monoacetal 89 by equilibration of equal amounts of dione 90

and diacetal 91. We felt that a similar reaction in our system could lead to a useful intermediate if either the C-5 or C-8 ketone could be selectively acetalized.



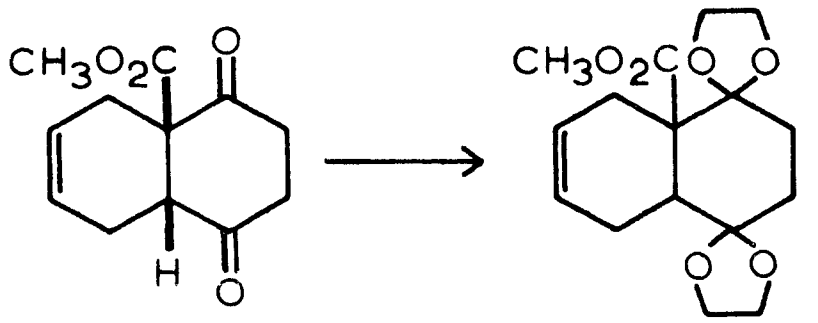
90 91



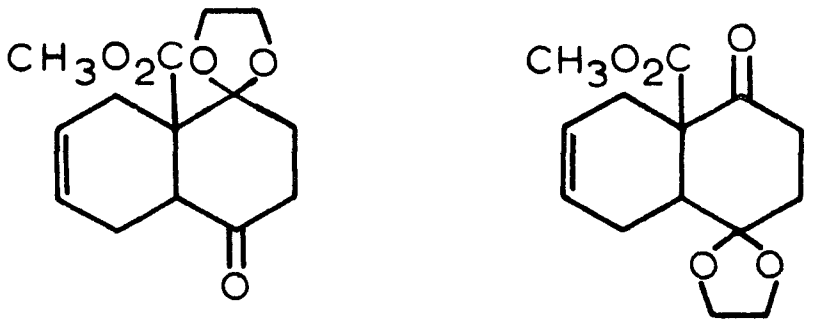
89

Treatment of dione 87 with excess ethanediol and a trace of p-toluenesulfonic acid gave diacetal 92 in 95% yield. Equilibration of equal amounts of dione 87 and diacetal 92 gave a mixture of compounds from which a single crystalline monoacetal could be obtained.

The monoacetal which was thus obtained could have had the stucture of either 93 or 94 and it was, of course, neces-



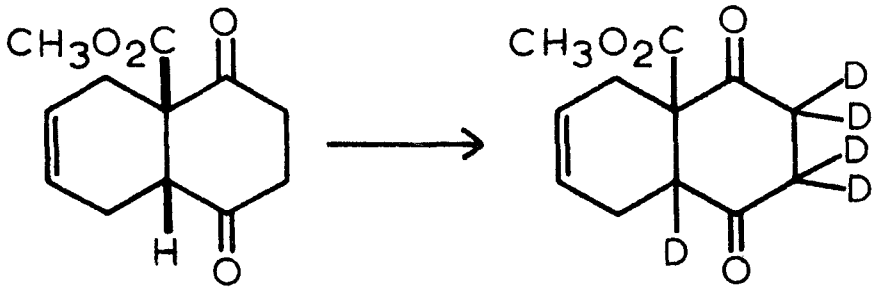
87 92



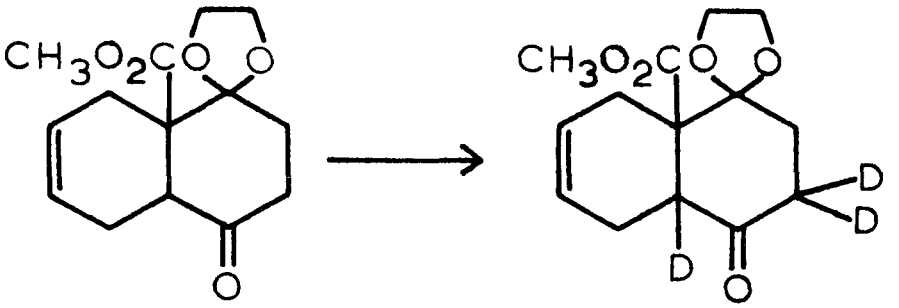
93 94

sary to determine what the actual structure was. This determination was accomplished by deuterium exchange experiments. Dione 87 when treated with sodium methoxide and methanol-d gave the pentadeuterated compound 95. On the basis of this experiment treatment of monoacetal 93 with sodium methoxide and methanol-d would be expected to give the trideuterated compound 96 and monoacetal 94 would be expected to give the dideuterated compound 97. The actual experiment when carried out gave a trideuterated compound and thus the monoacetal must have structure 93. A second monoacetal was later iso-

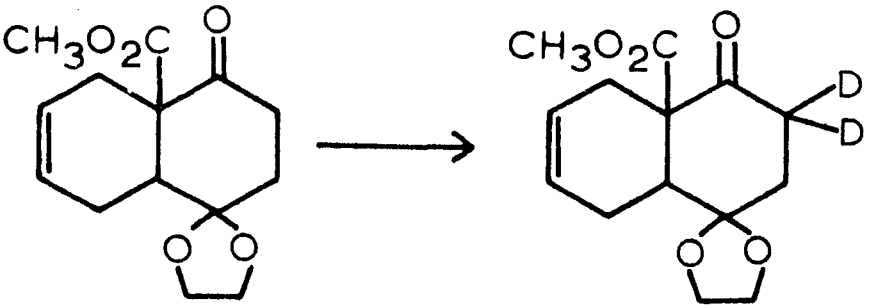
lated and similarly was shown to have the gross structure of 93. Of these two isomeric monoacetals one must be the cis



87 95



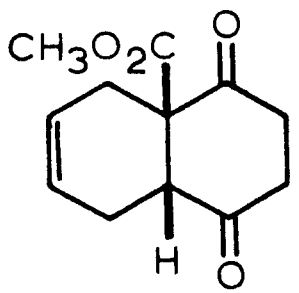
93 96



94 97

isomer 93a and the other the trans isomer 93b. No attempt

was made to determine which isomer was cis or which was trans and in subsequent reactions the first monoacetal, which was more readily crystallized, was used.



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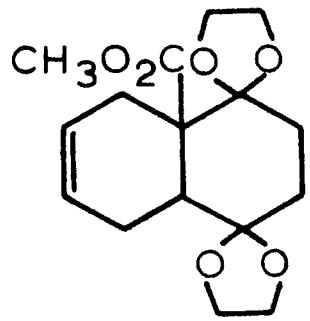
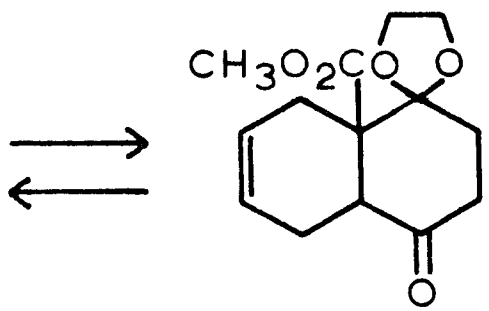


92



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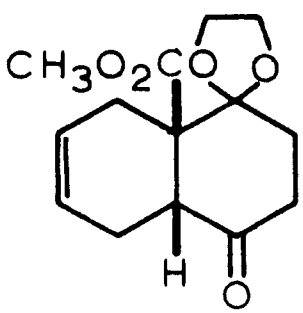
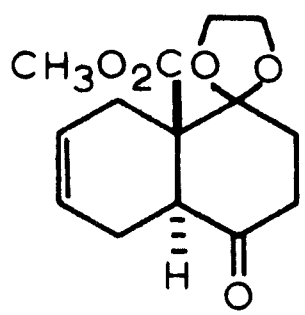


93a

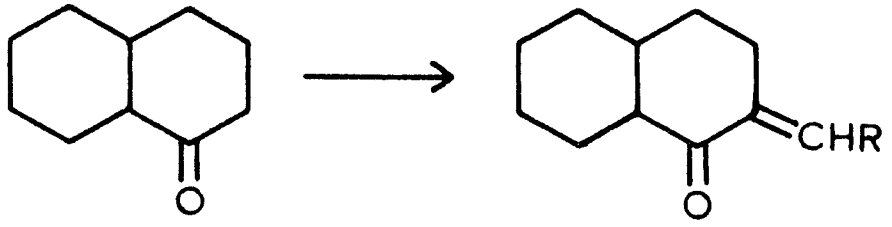


93b

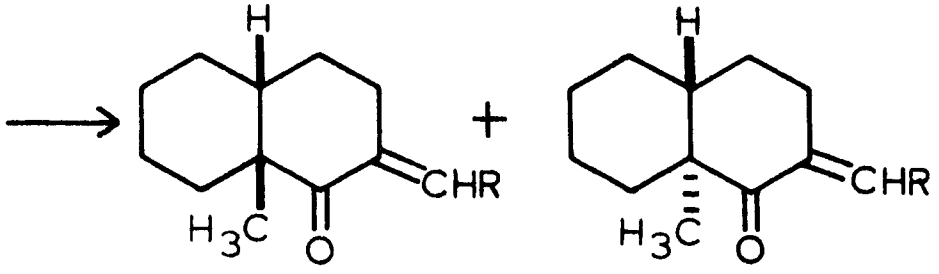
Several different methods have been developed to block the C-2 position of 1-decalones so as to facilitate angular methylation. One such type of blocking group is prepared by condensing an aromatic aldehyde (usually benzaldehyde or furfural) with a ketone such as decalone 98 (82). The blocked product 99a or 99b is usually quite crystalline, however, methylation of the blocked ketone 99 leads to a predominance of the cis product 100 over the trans product 101. Another disadvantage is that the arylidene blocking group is quite frequently difficult to remove after alkylation.

A second method of blocking involves the initial acylation of the methylene group with ethyl formate and subsequent conversion of the resulting hydroxymethylene substituent to an enamine, 99c (84), an isopropoxy ether, 99d (85), or a thioether, 99e (86). Of these three blocking groups the thioether showed the most promise since the blocked ketone 99e provided a higher ratio of trans (101e) to cis (100e) alkylated product than the other blocked ketones. Also, the thioether blocking group could be removed without using acidic conditions and thus has the additional advantage that the C-5 acetal function would not be affected during removal of the blocking group.

Using the procedure developed by Ireland and Marshall (86), monoacetal 93 was first converted to a hydroxymethylene derivative 102 with ethylformate and sodium methoxide. Sub-



98 99a-e

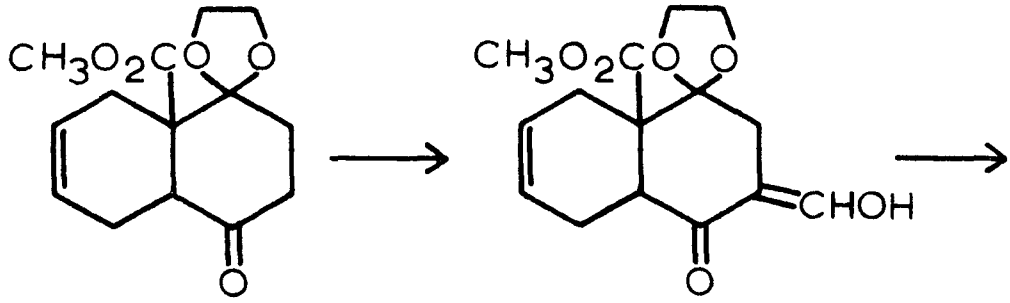


100a-e 101a-e

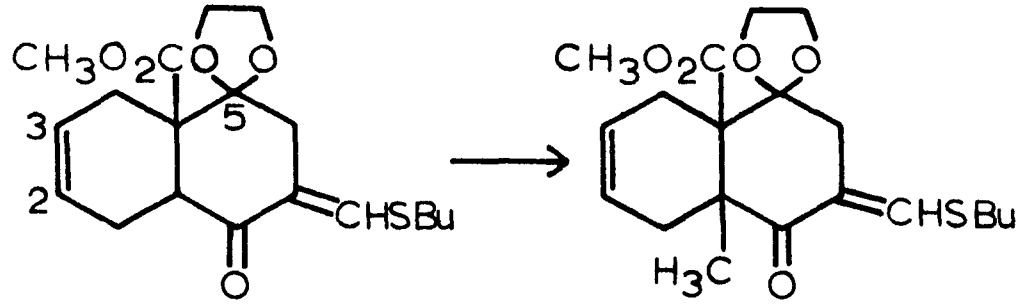
a, R = Ph
b, R = 2-furyl
c, R = $N(CH_3)Ph$
d, R = $OCH(CH_3)_2$
e, R = $SCH_2CH_2CH_2CH_3$

sequent treatment of 102 with n-butylthiol and p-toluenesulfonic acid afforded the blocked ketone 103 in an overall yield of 87% from monoacetal 93. Methylation of blocked ketone 103 with potassium t-butoxide and methyl iodide in t-butanol resulted in an oil which was purified by chromatography giving a semisolid which eventually was obtained in a pure crystalline form. The methylated product 104 which was obtained in an 88% yield showed singlets in the nmr spectrum

for both the angular methyl and the carbomethoxy groups and this plus the sharp melting point led to the conclusion that only one isomer was present.



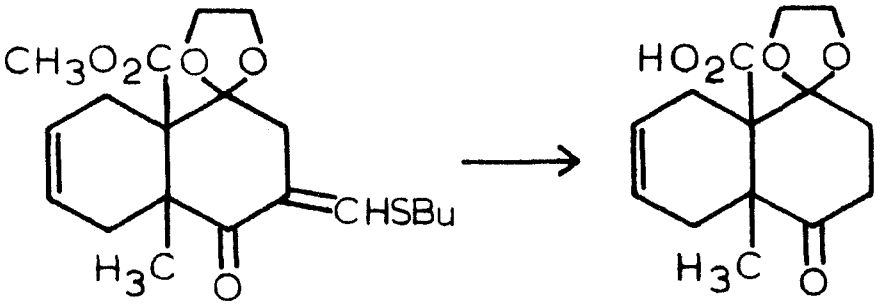
93 102



103 104

Removal of the blocking group using the procedure of Ireland and Marshall (86) afforded acid 105 but only in poor and variable yields. However, a procedure developed by Wheeler (87) using potassium hydroxide in 50% aqueous ethanol gave acid 105 in consistent yields of 66%. Acid 105 has a sharp melting point and shows a sharp singlet for the angular methyl group in the nmr spectrum indicating that acid 105 is

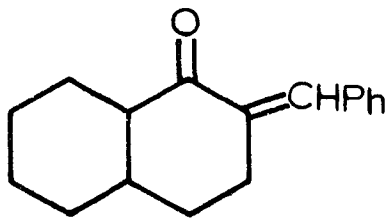
again a single isomer.



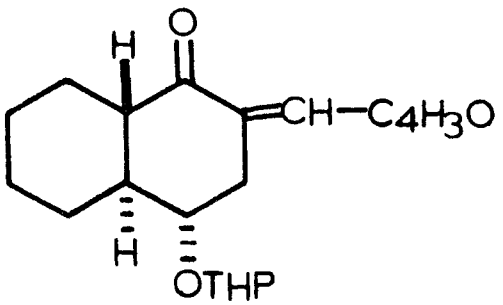
104 105

Pioneering studies by Johnson et al. (82) delineated several structural and stereochemical features which lead to maximization of the trans:cis ratio of isomers obtained in the angular methylation of substituted 1-decalones. In the unsubstituted, blocked decalone 99a a trans:cis ratio of 1:3 was obtained. Compound 106 with an equatorial tetrahydropyranyl ether surprisingly gave a trans:cis ratio of 1:9 while the isomer 107 with an axial tetrahydropyranyl ether gave a more favorable trans:cis ratio of 2:3. The only structural change which Johnson found to favor the trans over the cis was a 6,7-olefinic bond. Thus, compound 108 was found to give a trans:cis ratio of ca. 3:2 upon angular methylation.

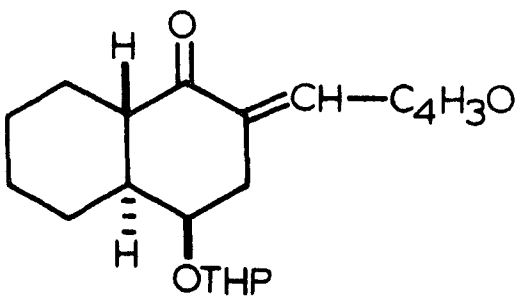
The substituent effects determined by Johnson may all be considered in attempting to predict the product of angular methylation of compound 103. The acetal at C-5 would be ex-



99a



106



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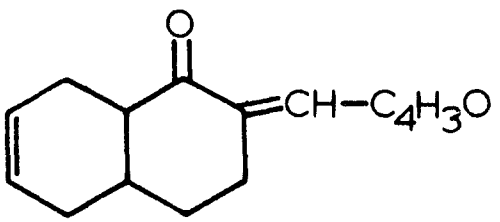
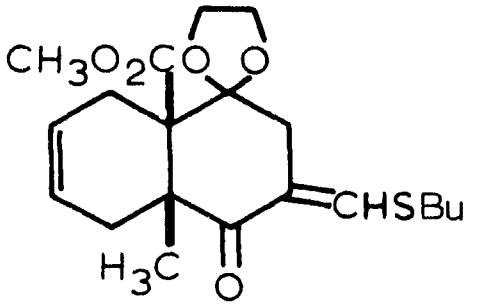


108

pected to exhibit a cumulative effect similar to both equatorial and axial tetrahydropyranyl ethers. Thus, a favoring of the cis over the trans product would be expected for the acetal. The 2,3-olefinic bond, however, would be expected to favor the trans over the cis product in angular methylation. A further complicating factor is caused by the introduction of the 4a-carbomethoxy function. Considering these factors all at once it was not possible to predict clearly whether the product of the angular methylation of 103 was cis (109) or trans (110).



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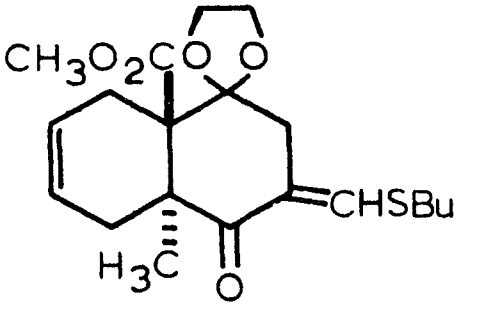
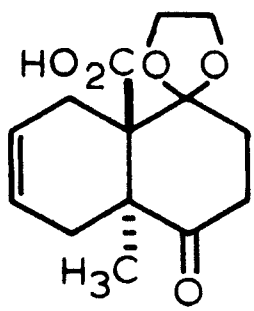


110

Since it was necessary to determine the actual stereochemistry of 104 and 105 before further progress could be made in the synthetic sequence, a method was devised for determining the stereochemistry of the 8a-methyl in acid 105. In steroidal systems it has been observed that a chloro or bromo substituent which is 1,3-diaxial to an angular methyl group will cause a shift in the nmr for the angular methyl protons of 0.25-0.35 ppm downfield relative to the angular methyl protons of the steroid which does not contain the chloro or bromo substituent (88). If, however, the chloro or bromo substituent is 1,3-axialequatorial to the angular methyl group downfield shifts of less than 0.1 ppm are observed.

If acid 111 were subjected to iodolactonization conditions it would be expected to give iodolactone 112 which could be reduced to lactone 113. Likewise, acid 114 would give rise to iodolactone 115 and lactone 116. Using the

steroidal system as an analogy, the angular methyl protons of iodolactone 112 would be expected to show a downfield shift of 0.25-0.35 ppm in the nmr from the angular methyl protons of lactone 113. On the other hand, the angular methyl protons of iodolactone 115 would be expected to show a downfield shift of less than 0.1 ppm from those of lactone 116.



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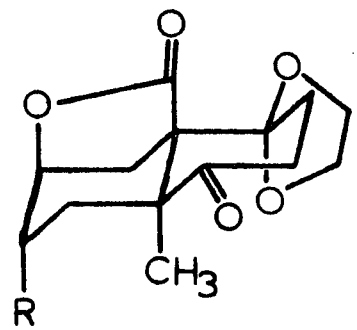
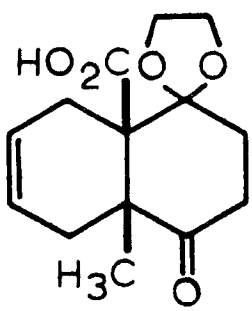
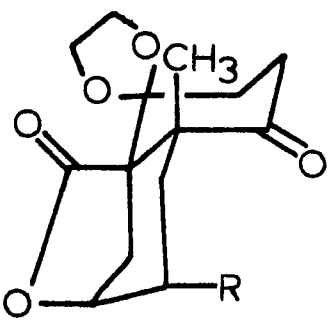


112, R = I

113, R = H



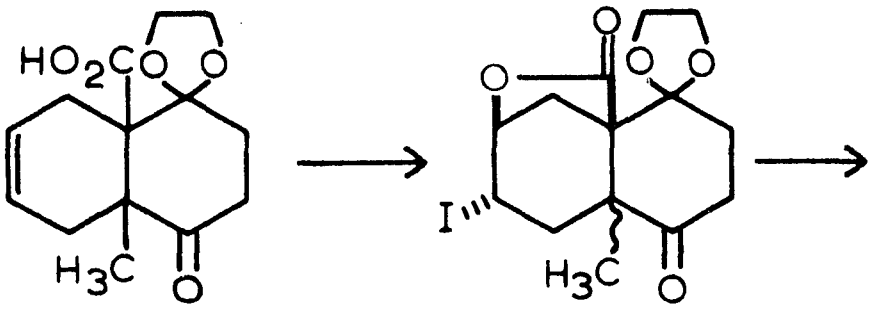
114



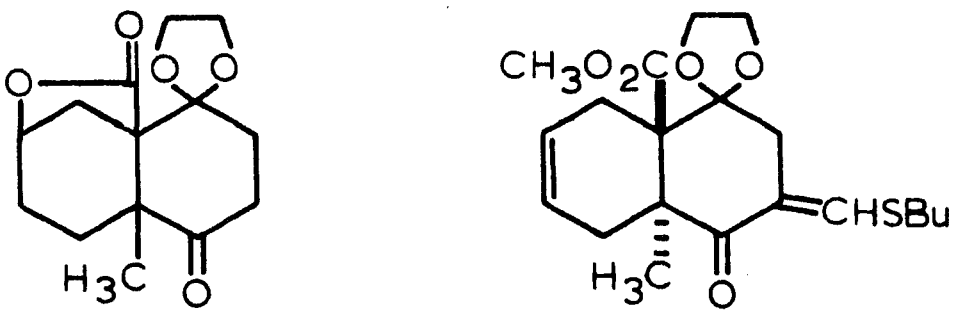
115, R = I

116, R = H

Treatment of the sodium salt of acid 105 with potassium iodide and iodine gave a quantitative yield of the iodolactone 117. The angular methyl protons of iodolactone 117 appear at δ 1.70 ppm in the nmr spectrum. Iodolactone 117 was readily reduced to lactone 118 with tributyltin hydride. The angular methyl protons of lactone 118 appear at δ 1.40 ppm in the nmr spectrum. This evidence indicates that the stereochemically correct structures for acid 105, iodolactone 117 and lactone 118 are 111, 112 and 113 respectively. Thus, the methylated product 104 is shown to be the desired trans isomer 110.

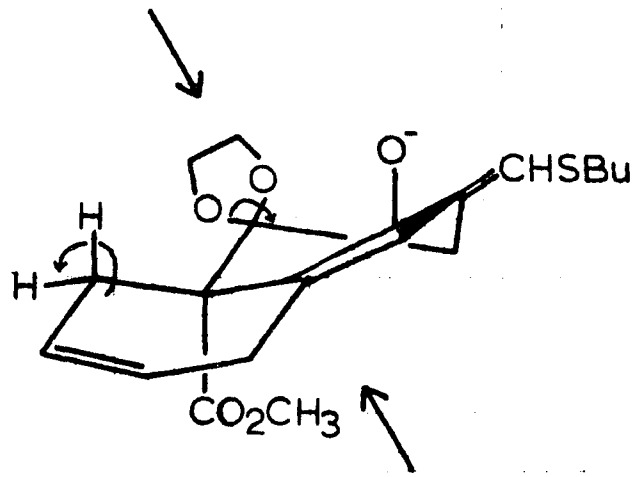


105 117



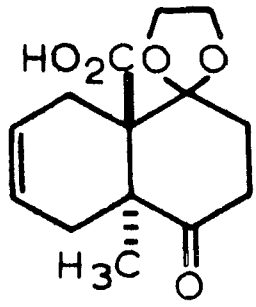
118 110

It appears from the stereochemical results obtained in the alkylation of 103 that an equatorial substituent at C-5 has no significant effect on the stereochemical orientation of angular methylation, if unsaturation is present between C-2 and C-3. The peri interactions between the C-5 ethylenedioxy group and the C-4 hydrogens may be partially alleviated by slight deformations of the ring as shown below,



with the net result being the moving of the axial hydrogen at C-4 away from the reaction terminus while the axial oxygen substituent at C-5 is moved over the ring towards C-6 (but not over the reaction terminus).

At this point in our synthetic scheme it was necessary to transform the keto group at C-1 to a methyl group. Our initial approach envisioned converting keto acid 111 to methylene acid 119 followed by a suitable chemical reduction to the desired acid 120.



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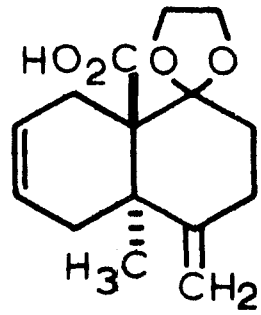

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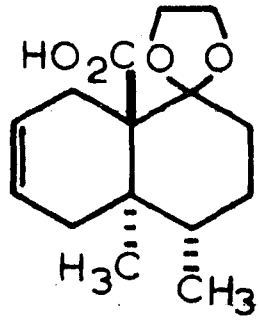
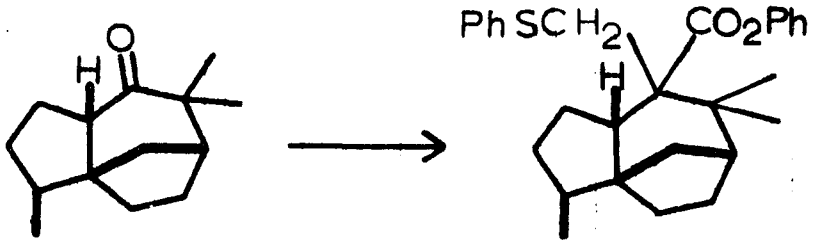


120

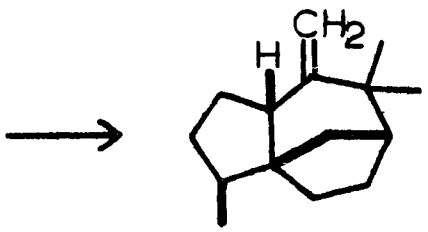
Treatment of acid 111 with triphenylphosphinemethylene (89) led to recovery of acid 111. There was no evidence of any formation of the methylene acid 119 even under strenuous reaction conditions.

Recently, a method for efficiently converting hindered ketones to methylene functions has been developed by Sowerby and Coates (90). For example, treatment of norzizanone (121) with phenylthiomethyllithium (91) followed by n-butyllithium and benzoic anhydride gave the intermediate 122. The methylene compound zizaene (123) was obtained from 122 by

reduction with lithium in liquid ammonia. However, when keto acid 111 was treated with phenylthiomethyllithium, and n-butyllithium and benzoic anhydride, none of the desired benzoyl derivative 124 was obtained.



121 122



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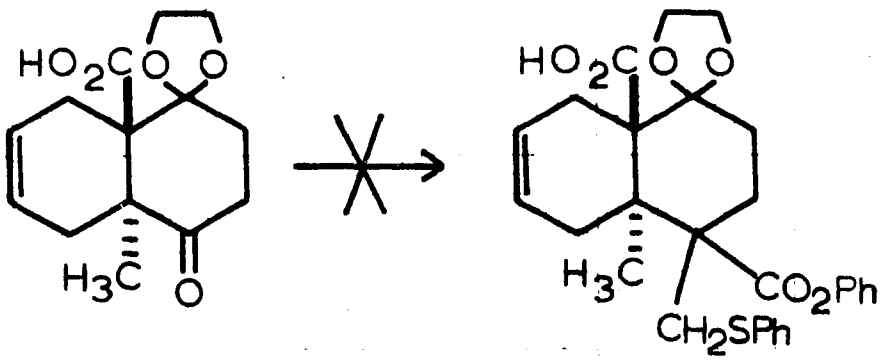
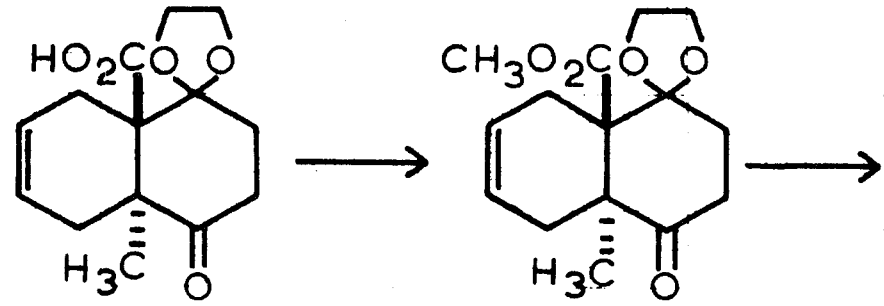
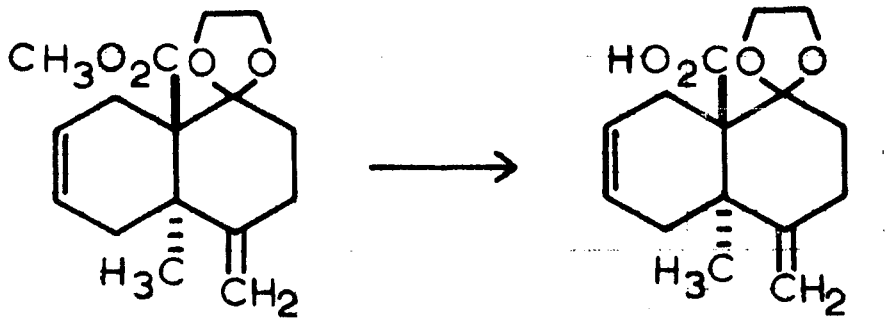


111 124

In an attempt to approach the problem of converting keto acid 111 to methylene acid 119 from another direction, acid 111 was quantitatively converted to its methyl ester 125 by treatment with diazomethane. The keto ester 125 was then



111 125



126 119

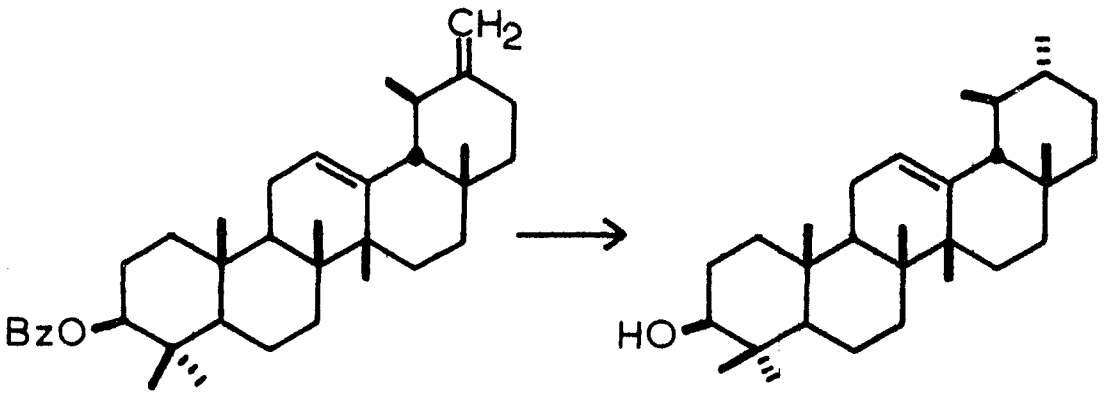
converted to the methylene ester 126 with triphenylphosphine-methylene in dimethyl sulfoxide (89) in 43% yield. In addition to the methylene ester 126, 18% of starting ester 125 was obtained as well as 20% of an unknown byproduct of formula $C_{15}H_{18}O_3$.

Attempted hydrolysis of ester 126 to acid 119 with alcoholic potassium hydroxide proved to be unsuccessful, however the hydrolysis could be achieved using lithium n-butyl mercaptide in hexamethylphosphoramide, a reagent developed by Bartlett and Johnson (92) for effecting the hydrolysis of highly hindered methyl esters.

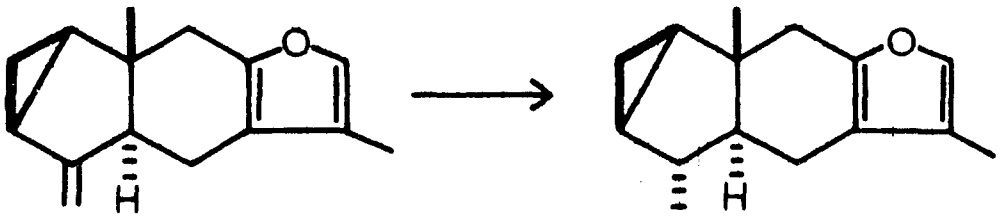
Two possible methods for the chemical reduction of 119 to 120 presented themselves. Corey and Cantrall (93) used lithium--ethylenediamine as a reducing agent for selectively reducing terminal methylene groups in the presence of trisubstituted double bonds. For example, 127 when treated with lithium in ethylenediamine gave α-amyrin (128). It is important to note that the methyl group which is produced generally possesses the equatorial orientation in a chemical reduction.

Takeda and coworkers (94) were able to reduce an exocyclic methylene group selectively in the presence of a cyclopropane ring. Lindenene (129) was reduced with sodium in liquid ammonia to 4-epilindenane (130).

Treatment of acid 119 with lithium in ethylenediamine under the conditions described by Corey and Cantrall (93) led to cleavage of the acetal function and reduction of the carboxylic acid, while on the other hand, the conditions of Takeda (94) led only to the recovery of starting acid 119.

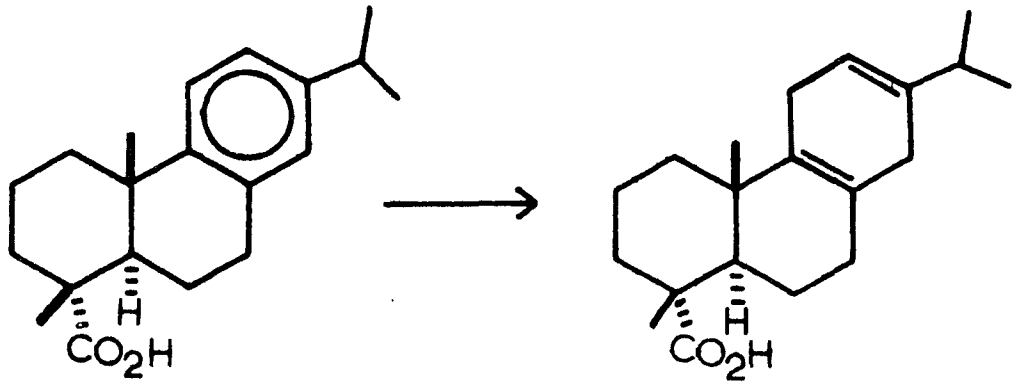


127 128

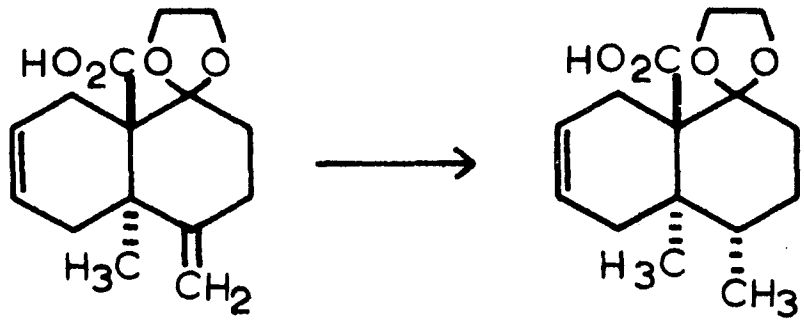


129 130

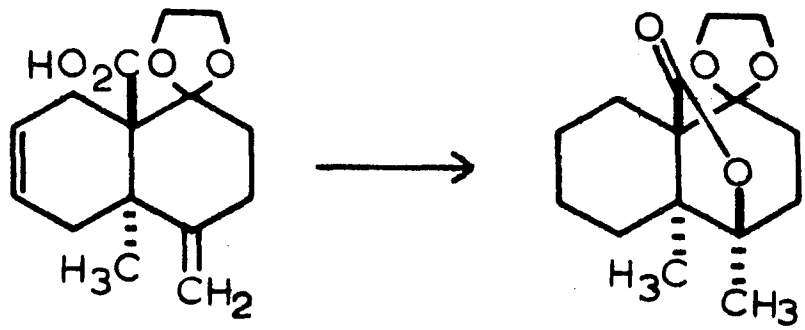
Burqstahler and Worden (95) found that using lithium and ethylamine they could reduce dehydroabietic acid (131) to abietadienoic acid (132), a reduction which failed under the usual Birch conditions of sodium and ethanol in liquid ammonia. Reduction of the carboxyl function was observed unless a very weakly acidic proton source such as t-amyl alcohol was present. Treatment of acid 119 with lithium and t-amyl alcohol in refluxing ethylamine led quantitatively to acid 120.



131 132

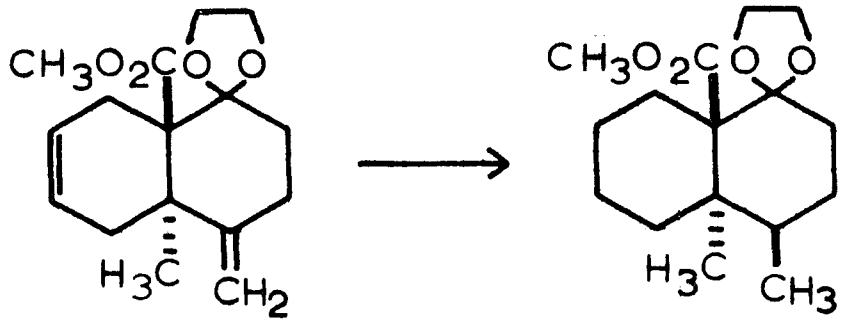


119 120



119 133

While the chemical reduction of acid 119 would be expected to lead to the product 120 in which the newly intro-



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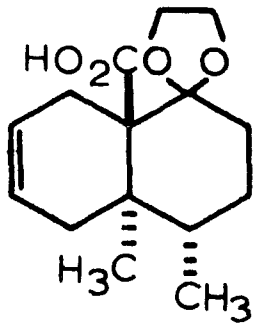

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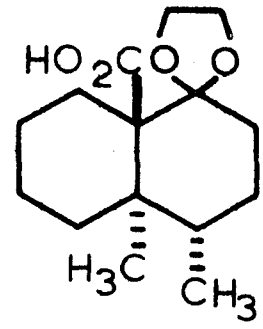

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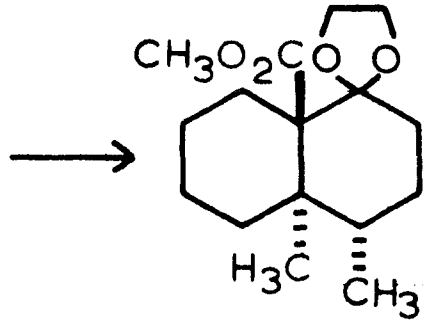


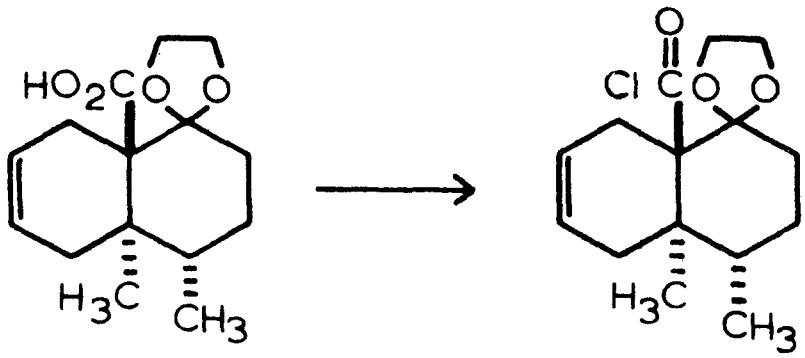
135

duced methyl group is equatorial (vide supra), catalytic reduction of acid 119 would be expected to lead to a predominance of the product with the newly introduced methyl group in the axial position (83, p 31). Reduction of acid 119 with hydrogen over platinum led, however, to the totally unexpected lactone 133.

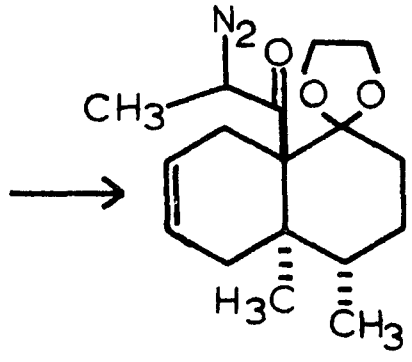
Catalytic reduction of the methyl ester 126 with hydrogen over platinum gave ester 134, which had nmr and ir spectra different from ester 135. Ester 135 was obtained from 120 by reduction with hydrogen over platinum to give acid 136 followed by esterification with diazomethane to give 135.

Approaches to Ishwarone from Synthon 120

Acid 120 was converted to its acid chloride 137 by first forming the sodium salt and then treating the salt with oxalyl chloride. The acid chloride 137 was then converted to diazoketone 138 with diazoethane at -20° (68). At this point several severe problems were evident. First, the acid chloride 137 did not form readily at room temperature, however, elevated temperatures caused the cleavage of the acetal function. Second, it was apparent that the amount of diazoketone 138 which was actually present in the crude reaction mixture was quite small, as the ir spectrum showed only weak bands at 2110 and 1640 cm^{-1}. Both of these difficulties may be attributable to the small scale on which the reaction was run (2-5 mmol). No intramolecular cyclizations of unsaturated diazomethylketones have been reported in the literature (see Historical) on any scale smaller than 10 mmol. A further problem is caused by the insolubility of crude diazoketone 138 in cyclohexane. Considering these problems



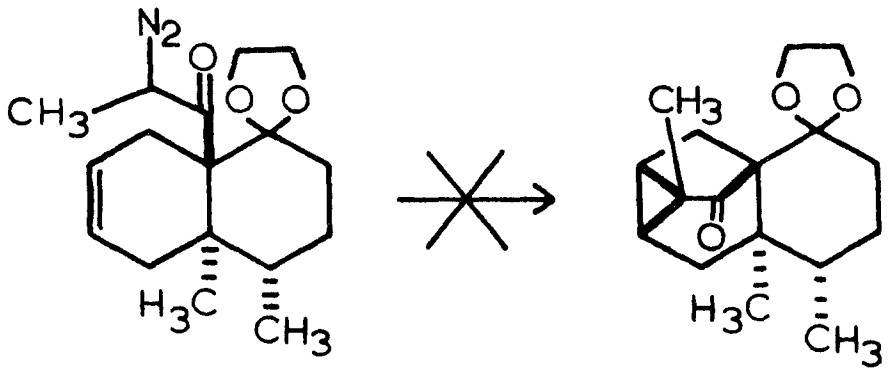
120 137



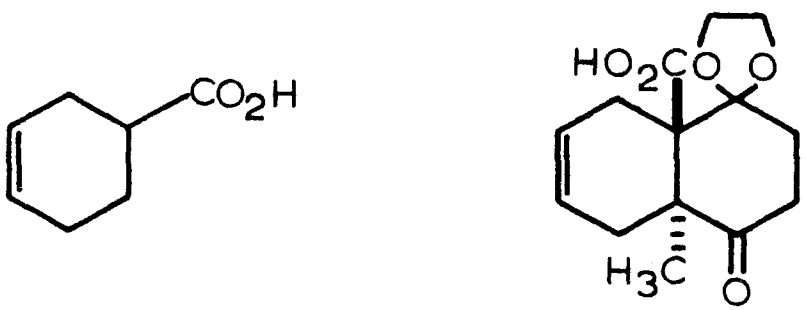
138

it was not surprising that those attempts that were made to cyclize 138 with cupric sulfate to the desired 139 were unsuccessful.

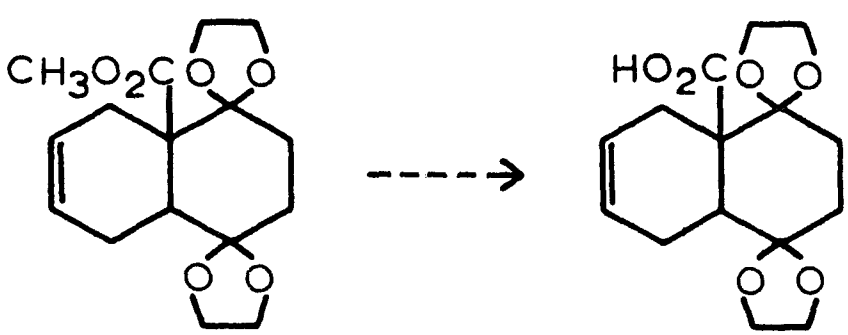
It may be possible to effect the rearrangement of 138 to 139 if the reaction can be carried out on a somewhat larger scale, however considering the precious nature of acid 120 the conditions necessary for the successful formation of the acyl chloride 137 and subsequently diazoketone 138 must be



138 139

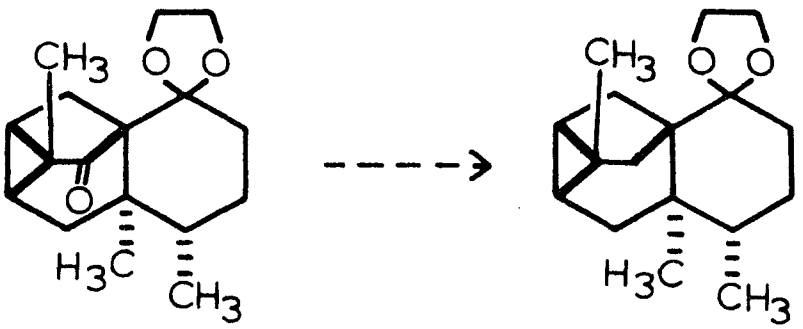


72 111

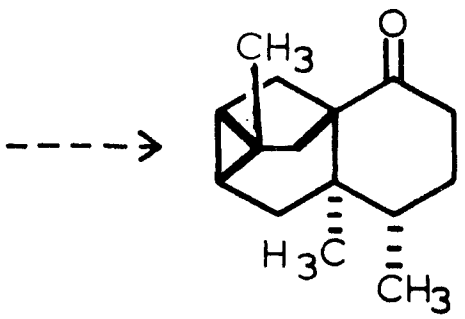


92 140

carefully worked out. To study these conditions a more complicated system than the model 72 would be desired. Pos-



139 141



8

sibilities would be acid 140 or acid 111 both of which could be obtained more easily and in larger quantities than acid 120. Acid 140 would be obtained by the saponification of diacetal 92.

Once 139 is successfully synthesized, then the following sequence would lead to ishwarone (8): ketone 139 could be subjected to Wolff-Kishner reduction conditions (96) and the acetal 141 thereby obtained, could be hydrolyzed under acidic conditions to ishwarone (8).

EXPERIMENTAL

Reagents

Common solvents and reagents were obtained from commercial sources and were generally used without purification. When anhydrous solvents were required, reagent grade materials were treated as follows:

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

Tetrahydrofuran - distilled from a mixture of sodium--benzophenone, which exhibited a constant purple color.

Benzene - distilled from a mixture of sodium--benzophenone, which exhibited a constant purple color.

Dimethyl sulfoxide - distilled from calcium hydride at 90°/30 mm.

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 Beckman IR12 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 (δ scale) from tetramethylsilane as an internal standard. Mass spectra were determined using an Atlas CH-4 mass spectrometer with a

direct solid inlet system. Microanalyses were preformed by Ilse Beetz Microanalytical Laboratories, Kronach, West Germany.

Whenever necessary, chromatographic procedures were employed for separation and purification of products. Microanalytical, air-dried, thin-layered 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 preformed 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

N-Nitroso-N-ethylurea

The procedure of Arndt (97) was followed. A 5-l., round-bottomed flask was charged with a solution of 642 g (10 mol) of 70% aqueous ethylamine dissolved in 1.2 l. of water. Concentrated hydrochloric acid was added to the aqueous solution until the solution was acid to methyl red (about 800 ml acid required). To the resulting acidic solution was added 2142 g (34 mol) of urea. The solution was boiled under a gentle reflux for 3 hr and then vigorously for

0.25 hr. The solution was cooled to room temperature, 690 g (10 mol) of sodium nitrite was dissolved in the solution, and the resulting solution was cooled to 0°. A mixture of 4000 g of ice and 700 g (7 mol) of concentrated sulfuric acid in a 3.5 gallon plastic bucket was surrounded by an efficient freezing mixture, and the cold ethylurea-nitrite solution was added slowly with mechanical stirring at such a rate that the temperature did not rise above 5°.

The nitrosoethylurea, which rose to the surface as a foamy precipitate, was filtered by suction and pressed well on the filter. The crystals were stirred to a paste with about 300 ml of cold water, sucked as dry as possible and dried in a vacuum desiccator to constant weight. The yield was 440 g (38% of theoretical) of dried crystalline nitrosoethylurea. The pale yellow crystals were stored in a refrigerator until used in subsequent experiments.

3-Cyclohexene-1-carbonyl chloride (73)

According to the general procedure of Adams and Ulich (73), 25.40 g (0.20 mol) of oxalyl chloride was added to 10.08 g (0.08 mol) of 3-cyclohexene-1-carboxylic acid (72) (Aldrich Chemical Co.) in a 50-ml, round-bottomed flask. Evolution of gas started immediately and continued for approximately 20 min, at which time the solution was heated to reflux for a period of 3 hr. After removal of the excess oxalyl chloride the residue was distilled to give 9.96 g

(86.1% of theoretical) of 3-cyclohexene-1-carbonyl chloride (73) as a colorless, pungent liquid: bp 28° (0.15 mm); [lit. (98) bp 96-97° (30 mm)]; ir (film) 1790 cm^{-1} (C=O); nmr (CCl_4) δ 5.68 (s, 2H, C<u>H</u>=C<u>H</u>), 2.96 (m, 1H, C<u>H</u>COCl), 2.00-2.50 ppm (m, 6H).

<u>7-Methyltricyclo[3.2.1.$0^{2,7}$]octan-6-one (74)</u>

Diazoethane was prepared from nitrosoethylurea following the procedure of Arndt (99). A mixture of 60 ml of 40% aqueous potassium hydroxide and 200 ml ethyl ether was cooled to 0° in a 500-ml erlenmeyer flask. Powdered <u>N</u>-ethyl-<u>N</u>-nitrosourea (23.4 g-0.20 mol) was added in small portions over a period of 10 min. The dark orange ethereal layer was then decanted from the aqueous layer and dried for 3 hr over potassium hydroxide pellets.

Diazoketone <u>67</u> was prepared according to the general procedure of Wilds and Meader (68). The dried ethereal solution of diazoethane was filtered into a dry flask fitted with a thermometer and a syringe adapter. The ethereal diazoethane solution was cooled to -20° with a dry ice--ethanol bath and 5.29 g (0.037 mol) of 3-cyclohexene-1-carbonyl chloride (<u>73</u>) dissolved in 20 ml of ethyl ether was added via syringe over a 10 min period. The resulting solution was stirred at -20° for 1 hr when the excess diazoethane was removed under aspirator pressure, followed by the removal of ether at 0° under reduced pressure. The diazoketone <u>67</u> was a

yellow oil: ir (film) 2070 (CN_2), 1640 cm^{-1} (C=O); nmr (CCl_4) δ5.65 (broad s, 2H, $\underline{H}C=C\underline{H}$), 1.97 ppm (s, 3H, $C\underline{H}_3$).

A. The diazoketone 67 was cyclized according to the general procedure described by Fawzi and Gutsche (28). The crude diazoketone was dissolved in 100 ml of cyclohexane and added to 2.0 g of anhydrous cupric sulfate suspended in 200 ml of cyclohexane. The mixture was stirred at reflux under nitrogen for fifteen hours. After the cupric sulfate was removed by filtration, the cyclohexane was removed by distillation. The residual brownish oil was distilled to give a crude yellowish oil which was chromatographed on 25 g of silica gel. Elution of the column with 5% ethyl ether in hexane gave 2.68 g (53.2% of theoretical) of 7-methyltricyclo[3.2.1.$0^{2,7}$]octan-6-one (74): bp 43° (0.15 mm); ir (film) 1730 cm^{-1} (C=O); nmr (CCl_4) δ1.15 (s, 3H, $C\underline{H}_3$), 1.52 (m, 2H, cyclopropyl methine), 1.80-2.15 ppm (m, 7H); mass spectrum (70 eV) m/e 136 (M^+).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.22; H, 8.88.

2,4-DNP, recrystallized from ethanol: mp 174-175°.

Anal. Calcd for $C_{15}H_{16}N_4O_4$: C, 56.95; H, 5.10; N, 17.71. Found: C, 57.09; H, 5.19; N, 17.70.

B. The diazoketone 67 prepared from 1.44 g (0.010 mol) of 3-cyclohexene-1-carbonyl chloride (73) was dissolved in 200 ml of tetrahydrofuran. To the stirred solution was added

600 mg of anhydrous cupric sulfate. The resulting suspension was stirred under reflux for 2 hr. Filtration of the solution followed by removal of the solvent under reduced pressure gave a brownish oil which was distilled to afford 0.70 g (52% of theoretical) of 7-methyltricyclo[3.2.1.$0^{2,7}$]-octan-6-one (74) with ir and nmr identical with those described in part A above.

6,6-Ethylenedithio-7-methyltricyclo[3.2.1.$0^{2,7}$]octane (76)

According to the general procedure described by Fieser (74), 1.36 g (0.01 mol) of 7-methyltricyclo[3.2.1.$0^{2,7}$]octan-6-one (74) was dissolved in 15 ml glacial acetic acid, and 1.89 g (0.02 mol) of ethanedithiol was added to the stirred solution in one portion. This was followed by the dropwise addition of 2 ml of boron trifluoride-etherate. The resulting solution was stirred for a period of 1 hr, was poured over 100 g of ice, and was extracted with ethyl ether. The combined ether extracts were washed once with saturated brine, four times with 10% aqueous sodium hydroxide and three times with saturated brine. After drying ($MgSO_4$) the solution was filtered and the solvent was removed under reduced pressure. The resulting oil was distilled to give 0.98 g (46% of theoretical) of 6,6-ethylenedithio-7-methyltricyclo[3.2.1.$0^{2,7}$]octane (76): bp 82° (0.26 mm); ir (film) 2930, 785, 760 cm^{-1}; nmr (CCl_4) δ 1.29 (s, 3H, CH_3), 0.80 (m, 1H, cyclopropyl methine), 1.10 (m, 1H, cyclopropyl methine),

3.20 (d, 4H, SCH_2CH_2S), 1.50-2.05 ppm (m, 7H).

Anal. Calcd for $C_{11}H_{16}S_2$: C, 62.21; H, 7.60; S, 30.20. Found: C, 62.13; H, 7.49; S, 30.10.

Attempted preparation of 1-methyltricyclo[3.2.1.$0^{2,7}$]octane (77)

According to the procedure of Sondheimer and Rosenthal (75), a 500-ml, three-necked, round-bottomed flask, fitted with a mechanical stirrer, reflux condenser and constant-pressure addition funnel was charged with 4 teaspoons of W-2 Raney nickel catalyst and 200 ml of absolute ethanol. To the stirred suspension was added 2.13 g (0.01 mol) of thioacetal 76 in 50 ml of absolute ethanol. The reaction mixture was refluxed with stirring for 50 hr. After cooling the mixture was filtered through a celite mat, and the ethanol was distilled to give 0.58 g of a product which had ir and nmr spectra identical to those obtained for 7-methyltricyclo-[3.2.1.$0^{2,7}$]octan-6-one (74).

Methyl 2,5-dihydroxybenzoate (83)

The procedure of Brunner (78) was followed. A 5-l., three-necked, round-bottomed flask equipped with a mechanical stirrer and a reflux condenser was charged with 500 g (3.24 mol) of 2,5-dihydroxybenzoic acid (82) dissolved in 2.5 l. of methanol. To this solution was added 170 ml of concentrated sulfuric acid, and the resulting solution was stirred at reflux for 18 hr. The excess methanol was removed by

distillation under reduced pressure and the remaining solution was neutralized with saturated sodium carbonate solution. The aqueous solution was extracted with ethyl ether. The combined ether extracts were washed with saturated brine, and the ether was removed under reduced pressure. The crude ester 83 was recrystallized from hot water to give 515 g (94% of theoretical) of fluffy, white crystals: mp 82° [lit. (78) mp 87°]; ir (KBr) 3350 (OH), 1694 (C=O), 1220, 790, 690 cm^{-1}; nmr (CCl_4) δ 3.90 (s, 3H, OCH_3), 6.94 (m, 2H, aromatic), 7.28 ppm (m, 1H, aromatic).

Methyl 3,6-dioxo-1,4-cyclohexadiene-1-carboxylate (84)

A. According to the procedure of Brunner (79), 10 g of anhydrous potassium carbonate was added to a solution of 10 g (0.06 mol) of methyl 2,5-dihydroxybenzoate (83) in 100 ml of dry benzene. To this mixture was added 30 g of silver oxide (freshly prepared from a silver nitrate solution made alkaline with sodium hydroxide and washed twelve times with water, six times with acetone and six times with ether). The resulting mixture was warmed to 40-50° and was shaken for five minutes, allowed to stand for five minutes and then filtered. The precipitate of silver was extracted twice with 30-ml portions of warm benzene, and the total benzene solution was dried in the dark for 3 hr over anhydrous potassium carbonate. The benzene was removed under reduced pressure at 40°, and the resultant brown crystalline mass was treated

with boiling carbon disulfide. The reddish solution was decanted from the viscous brown residue, and crystallization at 0° for several hours in the dark afforded 5.02 g (51.8% of theoretical) of methyl 3,6-dioxo-1,4-cyclohexadiene-1-carboxylate (84) as orange-red crystals: mp 52-53° [lit. (79) mp 53.5-54.5°]; ir (KBr) 1749, 1672, 1270 cm^{-1}; nmr (CCl_4) δ 5.87 (s, 3H, OCH_3), 6.85 (m, 2H), 7.00 ppm (m, 1H).

B. A 5-l., three-necked, round-bottomed flask fitted with a reflux condenser and a mechanical stirrer was charged with 200 g (1.20 mol) of methyl 2,5-dihydroxybenzoate (83) dissolved in 3.8 l. of anhydrous ethyl ether. To this solution was added 200 g of anhydrous potassium carbonate followed by 440 g (1.9 mol) of silver oxide (prepared as in part A and dried over P_2O_5 in a vacuum desiccator). The resulting suspension was stirred at reflux for 2 hr, after which it was filtered, and the solid was washed thoroughly with ethyl ether. The resulting ethereal solution was distilled under reduced pressure below 40° giving 182 g (91% of theoretical) of methyl 3,6-dioxo-1,4-cyclohexadiene-1-carboxylate (84) as yellow-red crystals whose mp, ir, and nmr spectra are identical with those described in part A above.

Methyl 1,5,8,8a-tetrahydro-1,4-dioxo-4a(4H)-naphthalene-carboxylate (78), (86)

The procedure of Ansell, Nash and Wilson (76) was modified slightly. A 500-ml pressure bottle was charged with

30 g (0.18 mol) of methyl 3,6-dioxo-1,4-cyclohexadiene-1-carboxylate (84) dissolved in 250 ml of anhydrous benzene. To this solution was added 80 ml (ca. 0.96 mol) of butadiene (85) which had been condensed in a dry ice--alcohol bath. The bottle was wired shut and allowed to stand at room temperature for 24 hr. The benzene was distilled under reduced pressure and the residual oil was distilled at 118-130° (0.2mm) to give 36.0 g (91% of theoretical) of methyl cis-1,5,8,8a-tetrahydro-1,4-dioxo-4a(4H)-naphthalenecarboxylate (78) which crystallized upon standing to give pale yellow crystals: mp 53-54°; ir (KBr) 1750, 1705, 1600, 1270, 1235 cm^{-1}; nmr (CCl_4) δ3.76 (s, 3H, OCH_3), 5.63 (broad s, 2H, CH=CH), 6.61 (s, 2H, CH=CH), 3.52 (t, 1H, angular H), 2.00-2.75 ppm (m, 4H).

When the cis-adduct 78 was chromatographed on alumina with benzene as eluent isomerization occurred and a ca. 60:40 mixture of trans:cis adduct was obtained. The trans-adduct 86 was obtained in pure form by fractional recrystallizations from ethyl acetate as pale yellow crystals: mp 76-77° (lit. (76) mp 73-75°); ir (KBr) 1735, 1700, 1610, 1270, 1220 cm^{-1}; nmr (CCl_4) δ3.68 (s, 3H, OCH_3), 5.68 (m, 2H, CH=CH), 6.67 (doublet of doublets, 2H, CH=CH), 2.30-3.00 ppm (m, 5H).

Attempted alkylation of methyl 1,5,8,8a-tetrahydro-1,4-dioxo-4a(4H)-naphthalenecarboxylate (78)

A. The general procedure of Fried et al. (80) was used. A 250-ml, three-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser, and a pressure-equalizing addition funnel was charged with 1.92 g (50% dispersion in mineral oil, 0.04 mol) of sodium hydride (J. T. Baker Chemical Co.). The mineral oil was removed by washing the solid with three 20-ml portions of pentane under a constant flow of nitrogen, followed by removal of the pentane through a sintered glass gas dispersion tube attached to a water aspirator. A positive pressure of nitrogen was maintained on the system throughout this procedure. A 120-ml portion of anhydrous benzene was added to the clean hydride followed by 4.4 g (0.02 mol) of cis-adduct 78 and 28.4 g (0.20 mol) of iodomethane dissolved in 50 ml of anhydrous benzene. The resulting suspension was stirred at reflux for 4 hr at which time an additional 14.2 g (0.10 mol) of iodomethane was added. Reflux was continued for another 12 hr after which the solution was allowed to cool and 10 ml of water was added dropwise. The benzene solution was washed twice with 1N hydrochloric acid, followed by saturated sodium bicarbonate solution, water and saturated brine solution. After drying ($MgSO_4$) the benzene was removed under reduced pressure. Nmr and ir spectra showed the residual oil to be a

ca. 60:40 mixture of the trans and cis adducts, 78 and 86 respectively.

B. According to the procedure of Johnson et al. (82), 1.5 g (0.037 mol) of potassium metal was allowed to react with 35 ml of t-butanol contained in a 250-ml flask equipped with a reflux condenser, a mechanical stirrer, and a constant-pressure addition funnel. A positive pressure of nitrogen was maintained on the system throughout the reaction period. After the potassium was completely dissolved the mixture was cooled by a surrounding ice-water bath, and 2.2 g (0.01 mol) of cis-adduct 78 and 10.5 g (0.075 mol) of iodomethane dissolved in 25 ml of t-butanol were added over a 30 min period. The resulting dark brown suspension was allowed to stir at room temperature for 5 hr when the excess t-butanol was removed under reduced pressure. The residue was diluted with 100 ml of water and neutralized to litmus with 3N hydrochloric acid. The aqueous solution was extracted with ethyl ether, and the ether extracts were washed with saturated brine. After drying ($MgSO_4$) the ether was removed under reduced pressure. The residual dark brown oil was chromatographed on silica gel with 50% ethyl ether in hexane as eluent. The main component was an amorphous tan powder that could not be recrystallized. An nmr spectrum of the powder did not display the δ 6.61 ppm peak that appears in cis-adduct 78: ir (KBr) 1730, 1455, 1210 cm^{-1}; nmr (CCl_4)

δ 5.63 (broad s, 2H), 3.66 (m, 3H), 1.55-3.50 ppm (m, 9H).

C. Results essentially identical with those in part B could be obtained by following the procedure of part B but omitting the addition of the iodomethane.

Similar spectral results to those of part B could also be obtained by reacting cis-adduct 78 with sodium methylsulfinylmethide in dimethyl sulfoxide (81).

Methyl 1,5,6,7,8,8a-hexahydro-5,8-dioxo-4a(4H)-naphthalenecarboxylate (87), (88)

The procedure of Johnson et al. (82) was followed with minor modifications. To a solution of 108 g (0.494 mol) of cis-adduct 78 in 450 ml of glacial acetic acid stirred in a 1-l. flask surrounded by an ice-water bath was added 110 g (1.67 mol) of zinc dust at such a rate that the temperature of the mixture remained below 15°. After the addition was complete the mixture was stirred at room terperature for 30 min. The zinc salts were removed by filtration through a Celite mat and were washed thoroughly with glacial acetic acid. The resulting acetic acid solution was diluted with 500 ml of water and was cooled in a refrigerator until crystallization was complete. The crystals obtained upon filtration were recrystallized from ethyl acetate to give 99 g (90% of theoretical) of methyl cis-1,5,6,7,8,8a-hexahydro-5,8-dioxo-4a(4H)-naphthalenecarboxylate (87) as colorless crystals: mp 98-99°; ir (KBr) 1750, 1710, 1265, 1215 cm^{-1};

nmr ($CDCl_3$) δ3.80 (s, 3H, OCH_3), 5.65 (broad s, 2H, CH=CH), 3.52 (t, 1H, angular H), 2.10-3.00 ppm (m, 8H); mass spectrum (70 eV) m/e 222 (M^+).

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.81; H, 6.31.

Methyl trans-1,5,6,7,8,8a-hexahydro-5,8-dioxo-4a(4H)-naphthalenecarboxylate (88) could be obtained as colorless crystals by following the above procedure starting with methyl trans-1,5,8,8a-tetrahydro-1,4-dioxo-4a(4H)-naphthalenecarboxylate: mp 105-106°; ir (KBr) 1750, 1720, 1205, 1158 cm^{-1}; nmr ($CDCl_3$) δ3.70 (s, 3H, OCH_3), 5.70 (broad s, 2H, CH=CH), 2.10-3.20 ppm (m, 9H).

Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.77; H, 6.31.

Methyl 5,5:8,8-bis(ethylenedioxy)-1,5,6,7,8,8a-hexahydro-4a(4H)-naphthalenecarboxylate (92)

A 1-l., round-bottomed flask equipped with a Dean-Stark water trap was charged with 88.8 g (0.40 mol) of methyl cis-1,5,6,7,8,8a-hexahydro-5,8-dioxo-4a(4H)-naphthalenecarboxylate (87) dissolved in 600 ml of benzene. To this solution was added 155 g (2.5 mol) of 1,2-ethanediol and 500 mg of p-toluenesulfonic acid. The resulting solution was refluxed for 24 hr during which time 20 ml of water was collected in the Dean-Stark trap. After cooling, the benzene solution was washed twice with saturated sodium bicarbonate

solution, followed by washing with water and saturated brine. The benzene solution was dried ($MgSO_4$), and the benzene was removed by distillation under reduced pressure. The residual oil was dissolved in ethyl acetate--hexane and upon cooling gave 109.5 g (88% of theoretical) of methyl 5,5:8,8-bis-(ethylenedioxy)-1,5,6,7,8,8a-hexahydro-4a(4H)-naphthalene-carboxylate (92) as clear, colorless crystals: mp 95-97°; ir (KBr) 1740, 1216, 1054 cm^{-1}; nmr (CCl_4) δ 5.45 (broad s, 2H, C<u>H</u>=C<u>H</u>), 3.86 (m, 8H, OC<u>H</u>$_2$C<u>H</u>$_2$O), 3.60 (s, 3H, OC<u>H</u>$_3$), 1.30-2.90 ppm (m, 9H).

<u>Anal</u>. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 62.09; H, 7.32.

<u>Methyl 5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8-oxo-4a(4H)-naphthalenecarboxylate (93)</u>

A. A 1-l., round-bottomed flask was charged with 62.0 g (0.20 mol) of bisacetal <u>92</u> and 44.4 g (0.20 mol) of dione <u>87</u> dissolved in 600 ml of anhydrous benzene. To this solution was added 500 mg of <u>p</u>-toluenesulfonic acid. The resulting solution was refluxed for 24 hr. After cooling, the benzene was removed under reduced pressure and the residual oil was dissolved in hot ethyl acetate. Upon cooling the ethyl acetate solution 39.6 g (37% of theoretical) of methyl 5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8-oxo-4a(4H)-naphthalenecarboxylate (<u>93</u>) was obtained as clear, colorless crystals: mp 134-135°; ir (KBr) 1720, 1220, 1200 cm^{-1}; nmr

($CDCl_3$) δ 5.62 (m, 2H, C<u>H</u>=C<u>H</u>), 4.08 (s, 4H, OC<u>H</u>$_2$C<u>H</u>$_2$O), 3.66 (s, 3H, OC<u>H</u>$_3$), 1.80-2.90 ppm (m, 9H); mass spectrum (70 eV) <u>m/e</u> 266 (M^+).

<u>Anal</u>. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.17; H, 6.88.

A second monoacetal, a minor product of the above reaction, could be obtained as clear, colorless crystals and was found to be either the <u>cis</u> or <u>trans</u> isomer of methyl 5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8-oxo-4a(4H)-naphthalenecarboxylate (<u>93</u>): mp 96-97°; ir (KBr) 1736, 1258, 1108 cm^{-1}; nmr ($CDCl_3$) δ 5.56 (broad s, 2H, C<u>H</u>=C<u>H</u>), 3.98 (s, 4H, OC<u>H</u>$_2$C<u>H</u>$_2$O), 3.71 (s, 3H, OC<u>H</u>$_3$), 1.70-3.10 ppm (m, 9H); mass spectrum (70 eV) <u>m/e</u> 266 (M^+).

<u>Anal</u>. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.03; H, 6.74.

B. A 1-l., round-bottomed flask equipped with a Dean-Stark water separator was charged with 111 g (0.50 mol) of <u>cis</u>-dione <u>87</u> dissolved in 600 ml of benzene. To this solution was added 31 g (0.50 mol) of 1,2-ethanediol and 500 mg of <u>p</u>-toluenesulfonic acid. The resulting solution was refluxed for 18 hr, during which time 10 ml of water collected in the Dean-Stark trap. The Dean-Stark trap was replaced by a Soxhlet extractor containing 4A molecular sieves, and the reaction mixture was allowed to percolate through the sieves for a further 6 hr. After cooling, the benzene was

removed under reduced pressure and the residue was dissolved in hot ethyl acetate. Cooling of the ethyl acetate solution afforded 24.7 g (18.5% of theoretical) of monoacetal 93 with ir and nmr spectra identical with those described above for the monoacetal with mp 134-135°.

C. The residue obtained from either part A or part B after crystallization of the monoacetal was recycled by either converting to the diacetal 92 or dione 87. More monoacetal could then be obtained by following either procedure A or B as described above. In this manner dione 87 could be converted to monoacetal 93 in 70% of the theoretical conversion.

Methanol-d

According to the procedure of Streitwieser et al. (100), a 250-ml, round-bottomed flask was charged with 100 g (1.11 mol) of dimethyl carbonate (Aldrich Chemical Co.) and 25 g (1.25 mol) of deuterium oxide (Columbia Organic Chemicals Co., Inc.). To this solution was added 4 g (0.04 mol) of dimethyl sulfate, and the resulting mixture was heated at reflux for 120 hr. The reaction mixture was distilled through a 10 inch column packed with glass helices. The fraction distilling at 64-65° was distilled again through the packed column to give 52 g of methanol-d.

Deuterium exchange of methyl 1,5,6,7,8,8a-hexahydro-5,8-dioxo-4a(4H)-naphthalenecarboxylate (87)

To a solution of 0.44 g (2.0 mmol) of methyl 1,5,6,7,8,8a-hexahydro-5,8-dioxo-4a(4H)-naphthalenecarboxylate (87) dissolved in 15 ml of methanol-d in a 50-ml, round-bottomed flask was added 150 mg of sodium methoxide. The resulting dark orange solution was stirred under reflux under a positive nitrogen pressure for 5 hr. After cooling, the methanol was removed under reduced pressure and the residue was extracted with carbon tetrachloride. The mixture was filtered and the carbon tetrachloride was removed under reduced pressure: mass spectrum (70 eV) m/e 227 (M^+), implying the incorporation of 5 D's.

Deuterium exchange of methyl 5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8-oxo-4a(4H)-naphthalenecarboxylate (93)

To a solution of 0.40 g (1.5 mmol) of methyl 5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8-oxo-4a(4H)-naphthalenecarboxylate (93) dissolved in 10 ml of methanol-d in a 50-ml, round-bottomed flask was added 100 mg of sodium methoxide. The resulting reddish-brown solution was stirred under reflux under a positive nitrogen pressure for 5 hr. After cooling, the methanol was removed under reduced pressure and the residue was extracted with carbon tetrachloride. The mixture was filtered and the carbon tetrachloride was removed under reduced pressure affording a

crystalline residue: mass spectrum (70 eV) (monoacetal mp 134-135°) m/e 269 (M^+); mass spectrum (70 eV) (monoacetal mp 96-97°) m/e 269 (M^+), implying the incorporation of 3 D's in both monoacetals.

Methyl 7-[(butylthio)methylene]-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8-oxo-4a(4H)-naphthalenecarboxylate (103)

According to the general procedure of Ireland and Marshall (86), 105 g (2.0 mol) of sodium methoxide was suspended in 1 l. of anhydrous benzene in a 3-l., three-necked, round-bottomed flask equipped with a mechanical stirrer and a pressure-equalizing addition funnel. The suspension was cooled by a surrounding ice-water bath and a positive pressure of nitrogen was maintained on the system while 133 g (0.50 mol) of monoacetal 93 and 158 ml (144 g, 2.0 mol) of ethyl formate dissolved in 800 ml of anhydrous benzene was added to the suspension (1 hr required for the addition). The reaction mixture was then stirred overnight at room temperature when 450 ml of cold water was added, and the layers were separated. The benzene layer was washed with two 250-ml portions of cold 5% aqueous sodium hydroxide, and the combined aqueous basic extracts were strongly acidified with concentrated hydrochloric acid while the solution temperature was maintained below 20° by cooling in an ice-water bath. The acidic aqueous solution was extracted with benzene, and

the benzene extracts were washed with saturated brine. After drying ($MgSO_4$) the benzene solution was reduced in volume to 800 ml under reduced pressure.

To the above benzene solution contained in a 1-l., round-bottomed flask was added 57.5 ml (45 g, 0.50 mol) of n-butylthiol and 500 mg of p-toluenesulfonic acid. The resulting solution was heated at reflux with a Dean-Stark water separator for 12 hr (10 ml of water collected). After cooling, the benzene solution was washed with water, saturated sodium bicarbonate and saturated brine. The benzene solution was dried ($MgSO_4$), and the benzene was removed under reduced pressure to give 158 g (87% of theoretical) of a brownish, semicrystalline mass which could be recrystallized from ethyl acetate to give methyl 7-[(butylthio)methylene]-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8-oxo-4a(4H)-naphthalenecarboxylate (103) as colorless crystals: mp 125-126°; ir (KBr) 1725, 1674, 1555, 1210 cm^{-1}; nmr (CCl_4) δ7.22 (broad s, 1H, SC<u>H</u>=C), 5.49 (broad s, 2H, C<u>H</u>=C<u>H</u>), 3.97 (s, 4H, $OC\underline{H}_2C\underline{H}_2O$), 3.58 (s, 3H, $OC\underline{H}_3$), 1.10-2.95 (m, 13H), 0.70-1.05 ppm (m, 3H, $C\underline{H}_3$).

<u>Anal</u>. Calcd for $C_{19}H_{26}O_5S$: C, 62.27; H, 7.15; S, 8.75. Found: C, 62.32; H, 7.23; S, 8.86.

Methyl trans-7-[(butylthio)methylene]-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-oxo-4a(4H)-naphthalene-carboxylate (110)

According to the method of Ireland and Marshall (86), 66 g (1.7 mol) of potassium metal was dissolved in 1.5 l. of t-butanol in a 3-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser, and a pressure-equalizing addition funnel. The reaction system was maintained under a positive pressure of nitrogen for the entire reaction period. After the potassium had completely dissolved, 128 g (0.35 mol) of methyl 7-[(butylthio)-methylene]-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8-oxo-4a(4H)-naphthalenecarboxylate (103) dissolved in 500 ml of anhydrous benzene was added to the solution. After stirring at room temperature for five minutes the solution was cooled by an ice-water bath, and 500 g (3.5 mol) of iodomethane was added. After stirring for 30 min in the ice-water bath, the suspension was heated at reflux for 2 hr. The excess solvent was removed under reduced pressure, and 1 l. of cold water was added to the residue. The resulting aqueous mixture was extracted with ethyl ether, and the ether extracts were washed with brine. After drying ($MgSO_4$), the ether was removed under reduced pressure to give 117 g (88% of theoretical) of a brownish oil. A small portion of the residual oil was chromatographed on silica gel with 20% ethyl ether in

hexane as eluent to give a pale yellow oil which crystallized upon standing to colorless crystals of methyl trans-7-[(butylthio)methylene]-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-oxo-4a(4H)-naphthalenecarboxylate (110): mp 79-82°; ir (KBr) 1720, 1675, 1550, 1286 cm^{-1}; nmr (CCl_4) δ7.03 (m, 1H, SCH=C), 5.42 (m, 2H, CH=CH), 3.92 (m, 4H, OCH_2CH_2O), 3.56 (s, 3H, CO_2CH_3), 1.20-2.96 (m, 12H), 1.16 (s, 3H, angular CH_3), 0.95 ppm (m, 3H, CH_3).

Anal. Calcd for $C_{20}H_{28}O_5S$: C, 63.13; H, 7.42; S, 8.43. Found: C, 63.26; H, 7.33; S, 8.41.

trans-5,5-Ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-oxo-4a(4H)-naphthalenecarboxylic acid (111)

A. The general procedure of Ireland and Marshall (86) was followed. A 50-ml, round-bottomed flask was charged with 1.5 g (0.040 mol) of methyl trans-7-[(butylthio)methylene]-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-oxo-4a(4H)-naphthalenecarboxylate (110) dissolved in 10 ml of diethylene glycol. To this solution was added 10 ml of 25% aqueous sodium hydroxide, and the resulting mixture was heated at reflux under a positive pressure of nitrogen for 18 hr. After cooling, 15 ml of cold water was added to the solution, and the mixture was made strongly acidic with concentrated hydrochloric acid. The viscous aqueous solution was extracted with diethyl ether, and the ether extracts were washed with brine. After drying ($MgSO_4$) the ether was

removed under reduced pressure to give 470 mg (45% of theoretical) of trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-oxo-4a(4H)-naphthalenecarboxylic acid (111) as colorless crystals: mp 185-186°; ir (KBr) 1742, 1691, 1245, 1195, 1092 cm^{-1}; nmr ($CDCl_3$) δ 5.52 (broad s, 2H, C<u>H</u>=C<u>H</u>), 3.95 (m, 4H, OC<u>H</u>$_2$C<u>H</u>$_2$O), 1.50-2.75 (m, 8H), 1.31 ppm (s, 3H, angular C<u>H</u>$_3$); mass spectrum (70 eV) <u>m/e</u> 266 (M^+).

<u>Anal</u>. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.25; H, 6.81.

Additional experiments using larger amounts of methyl trans-7-[(butylthio)methylene]-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-oxo-4a(4H)-naphthalenecarboxylate (110) under the conditions described above led to acid 111 in yields ranging from 0 to 35%.

B. The procedure developed by Wheeler (87) was used. A 1-l., round-bottomed flask was charged with 116 g (0.305 mol) of methyl trans-7-[(butylthio)methylene]-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-oxo-4a(4H)-naphthalenecarboxylate (110) dissolved in 400 ml of 95% ethanol. To this solution was added 400 ml of 50% aqueous potassium hydroxide, and the resulting solution was heated at reflux under a positive pressure of nitrogen for 3 hr. After cooling the solution was poured onto 1 kg of ice and the mixture was acidified strongly with concentrated hydrochloric acid. The acidic aqueous solution was extracted with diethyl

ether, and the ethereal extracts were washed with brine. After drying ($MgSO_4$) the ether was removed under reduced pressure, and the residue was dissolved in a minimum of hot ethyl acetate. Cooling gave 53.5 g (66% of theoretical) of crystalline trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-oxo-4a(4H)-naphthalenecarboxylic acid (111) which had mp, ir and nmr identical with those previously described in part A above.

4,4-Ethylenedioxyoctahydro-t-7-iodo-t-8a-methyl-1-oxo-r-4a(2H),c-6-naphthalenecarbolactone (112)

According to the procedure of van Tamelen and Shamma (101), 1.33 g (5 mmol) of trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-oxo-4a(4H)-naphthalene-carboxylic acid (111) dissolved in 30 ml of 0.5M sodium bicarbonate solution was mixed with a solution of 3.54 g (0.01 mol) of iodine and 4.98 g (0.03 mol) of potassium iodide in 15 ml of water. The resulting solution was allowed to stand at room temperature in the dark for 24 hr. The dark precipitate which settled upon standing was removed by filtration and was washed with water. The precipitate was then shaken with chloroform and aqueous sodium thiosulfate until two colorless layers were obtained. The aqueous thiosulfate layer was extracted with chloroform, and the combined chloroform layers were washed with saturated sodium bicarbonate and water. After drying (K_2CO_3) the chloroform

was removed under reduced pressure to give 2.1 g (100% of theoretical) of 4,4-ethylenedioxyoctahydro-t-7-iodo-t-8a-methyl-1-oxo-r-4a(2H),c-6-naphthalenecarbolactone (112) as colorless crystals: mp 146-147°; ir (KBr) 1785, 1725, 1148, 950 cm^{-1}; nmr (CCl_4) δ4.68 (m, 1H, OCH), 4.36 (m, 1H, ICH), 3.93 (m, 4H, OCH_2CH_2O), 1.75-2.98 (m, 8H), 1.70 ppm (s, 3H, angular CH_3).

Anal. Calcd for $C_{14}H_{17}IO_5$: C, 42.88; H, 4.37; I, 32.36. Found: C, 42.96; H, 4.46; I, 32.33.

4,4-Ethylenedioxyoctahydro-t-8a-methyl-1-oxo-r-4a(2H),c-6-naphthalenecarbolactone (113)

According to the procedure of House et al. (36), 0.88 g (3 mmol) of tri-n-butyltin hydride was added dropwise over a five minute period to a solution of 1.0 g (2.5 mmol) of iodolactone 112 in 5 ml anhydrous benzene at 5° under a positive pressure of nitrogen. The resulting solution was stirred at room temperature for 24 hr after which the benzene was removed under reduced pressure. The residue was chromatographed on silica gel using 40% ethyl ether in hexane as eluent to give 106 mg (16% of theoretical) of 4,4-ethylenedioxyoctahydro-t-8a-methyl-1-oxo-r-4a(2H),c-6-naphthalenecarbolactone (113) as colorless crystals: mp 152-155°; ir (KBr) 1770, 1720, 1046 cm^{-1}; nmr ($CDCl_3$) δ4.62 (m, 1H, OCH), 3.90 (m, 4H, OCH_2CH_2O), 1.15-3.05 (m, 10H), 1.42 ppm (s, 3H, angular CH_3).

Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 62.96; H, 6.85.

Methyl trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-oxo-4a(4H)-naphthalenecarboxylate (125)

The procedure of de Boer and Backer (102) was modified slightly. A 250-ml, round-bottomed flask fitted with an addition funnel and a condenser for distillation leading to two receivers in series was charged with 50 ml of ethanol, 10 ml of diethyl ether and 10 g of potassium hydroxide in 16 ml of water. The second receiver contained 100 ml of diethyl ether with an inlet tube dipping below the ether level, and both receivers were cooled in an ice-water bath. The flask containing the alcoholic potassium hydroxide was heated on a steam bath until distillation of the ether started, at which point the addition of 43.0 g (0.20 mol) of N-methyl-N-nitroso-p-toluenesulfonamide (Aldrich Chemical Company, Inc.) in 400 ml of diethyl ether was begun. The ethereal solution was added at a rate which approximately equaled the rate of distillation (ca 0.5 hr required for the distillation). After the ether solution was completely added a further 80 ml of diethyl ether was added and distillation was continued until the distillate was colorless. The ether solutions in the two receivers were combined, and the yellow diazomethane solution was added to 10.0 g (0.038 mol) of trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-oxo-4a(4H)-

naphthalenecarboxylic acid (111) in a 1-l. beaker. After evolution of nitrogen subsided the ether was allowed to evaporate, and the residue was recrystallized from ethyl acetate to give 10.0 g (95% of theoretical) of methyl trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-oxo-4a(4H)-naphthalenecarboxylate (125) as colorless crystals: mp 99-101°; ir (KBr) 1725, 1300, 1212 cm^{-1}; nmr ($CDCl_3$) δ5.50 (m, 2H, C<u>H</u>=C<u>H</u>), 3.97 (m, 4H, OC<u>H</u>$_2$C<u>H</u>$_2$O), 3.60 (s, 3H, OC<u>H</u>$_3$), 1.64-2.82 (m, 8H), 1.32 ppm (m, 3H, angular C<u>H</u>$_3$).

<u>Anal</u>. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.23; H, 7.08.

<u>Methyltriphenylphosphonium bromide</u>

The procedure of Wittig and Schoellkopf (103) was followed. A 500-ml pressure bottle was charged with 100 g (0.38 mol) of triphenylphosphine dissolved in 100 ml of benzene. To this solution, which was cooled in an ice-water bath, was added 52 g (0.53 mol) of condensed methyl bromide, and the pressure bottle was wired shut. After standing at room temperature for two days, the white solid was collected by filtration with the aid of 1 l. of hot benzene. The white methyltriphenylphosphonium bromide was recrystallized from ethanol, crushed and dried over phosphorous pentoxide before use: mp 231-233° [lit. (103) mp 232-233°].

Methyl trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-methylene-4a(4H)-naphthalenecarboxylate (126)

A. According to the procedure of Greenwald, Chaykovsky and Corey (89), a 250-ml, three-necked, round-bottomed flask equipped with a thermometer, a gas inlet tube, and a pressure-equalizing addition funnel was charged with 2.88 g (50% dispersion in mineral oil, 0.06 mol) of sodium hydride (J. T. Baker Chemical Co.). The mineral oil was removed by washing the solid with three 30-ml portions of pentane under a constant flow of nitrogen, followed by removal of the pentane through a sintered glass gas dispersion tube attached to a water aspirator. A positive pressure of nitrogen was maintained on the system throughout this procedure. A 60-ml portion of dimethyl sulfoxide was added to the washed sodium hydride and the mixture was stirred at 70° until hydrogen evolution ceased (ca. 40 min). The resulting solution was allowed to cool to room temperature and was further cooled in an ice-water bath until solidification of the dimethyl sulfoxide began. At this time a solution of 21.4 g (0.06 mol) of methyltriphenylphosphonium bromide in 60 ml of dimethyl sulfoxide was added slowly. After stirring at room temperature for 10 min 11.2 g (0.04 mol) of methyl trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-oxo-4a(4H)-naphthalenecarboxylate (125) in 15 ml of dimethyl sulfoxide was added to the orange solution. The resulting

deep red solution was heated at 50-55° for 40 hr. After cooling the dimethyl sulfoxide solution was poured over 250 g of ice, and the aqueous solution was neutralized with 3M hydrochloric acid and was extracted with chloroform. The chloroform extracts were combined and washed with water and brine. After drying (K_2CO_3) the chloroform was removed under reduced pressure. The residue was chromatographed on silica gel with 20% diethyl ether in hexane as eluent. The first fraction gave 4.8 g (43% of theoretical) of methyl trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-methylene-4a(4H)-naphthalenecarboxylate (126) which was obtained as colorless crystals from ethyl acetate: mp 63-65°; ir (KBr) 2940, 1735, 1670, 1270, 1200 cm^{-1}; nmr (CCl_4) δ5.46 (m, 2H, C<u>H</u>=C<u>H</u>), 4.48 (d, 2H, C=C<u>H</u>$_2$), 3.88 (m, 4H, OC<u>H</u>$_2$C<u>H</u>$_2$O), 3.48 (s, 3H, OC<u>H</u>$_3$), 1.40-2.75 (m, 8H), 1.24 ppm (s, 3H, angular C<u>H</u>$_3$).

<u>Anal</u>. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.06; H, 7.88.

The second fraction from the chromatography gave 2.0 g (20% of theoretical) of an as yet unidentified compound as colorless crystals: mp 105-106°; ir (KBr) 1700, 1645, 1100, 1025, 910 cm^{-1}; nmr (CCl_4) δ5.72 (m, 3H, vinyl), 3.92 (m, 4H, OC<u>H</u>$_2$C<u>H</u>$_2$O), 1.80-2.82 (m, 8H), 1.12 ppm (s, 3H, angular C<u>H</u>$_3$); mass spectrum (70 eV) <u>m/e</u> 246 (M^+).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 72.70; H, 7.14.

The third fraction gave 2.0 g (18% of theoretical) of methyl trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-oxo-4a(4H)-naphthalenecarboxylate (125).

Longer reaction times or a larger excess of triphenylphosphinemethylene than that stated above led to no increase in the yield of the methyl trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-methylene-4a(4H)-naphthalenecarboxylate (126) while higher reaction temperatures led to a slight decrease in the yield.

B. The general precedure of Wittig and Schoellkopf (103) was followed. A 250-ml, three-necked, round-bottomed flask fitted with a reflux condenser, a mechanical stirrer, and a pressure-equalizing addition funnel was charged with 35 ml (60 mmol, 15% in heptane) of n-butyllithium (Matheson Coleman and Bell) and 120 ml of anhydrous diethyl ether. The reaction system was maintained under a positive pressure of nitrogen throughout the reaction period. To the stirred solution was added 21.42 g (60 mmol) of methyltriphenylphosphonium bromide, and the resulting yellow solution was stirred at room temperature for 4 hr. At this time 2.1 g (7.5 mmol) of methyl trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-oxo-4a(4H)-naphthalenecarboxylate (125) dissolved in 60 ml of diethyl ether was added. The reaction

mixture was heated at reflux for 40 hr and was then filtered to remove the suspended solid. The ether was removed under reduced pressure, and the residue had ir and nmr spectra identical with the starting methyl ester 125.

trans-5,5-Ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-methylene-4a(4H)-naphthalenecarboxylic acid (119)

A. The procedure of Greenwald, Chaykovsky and Corey (89) was modified slightly. A 100-ml, three-necked, round-bottomed flask fitted with a syringe adapter, thermometer and gas inlet tube was charged with 0.96 g (50% dispersion in mineral oil, 0.02 mol) of sodium hydride (J. T. Baker Chemical Co.). The mineral oil was removed by washing the solid with three 20-ml portions of pentane under a constant flow of nitrogen, followed by removal of the pentane through a sintered glass gas dispersion tube attached to a water aspirator. A positive pressure of nitrogen was maintained on the system throughout this procedure. A 20-ml portion of dimethyl sulfoxide was added to the washed sodium hydride and the mixture was stirred at 70° until evolution of hydrogen gas ceased (ca. 45 min). The resulting solution was allowed to cool to room temperature and was then cooled in an ice-water bath until solidification of the dimethyl sulfoxide began. At this point, a solution of 7.14 g (0.02 mol) of methyltriphenylphosphonium bromide in 20 ml of dimethyl sulfoxide was added slowly. While this solution was stirring

at room temperature, a second flask was charged with 0.24 g (0.005 mol) of sodium hydride which was washed with pentane as described above. To the washed sodium hydride was added 5 ml of dimethyl sulfoxide, and the mixture was heated at 70° until hydrogen evolution ceased. To this solution was then added 1.33 g (0.005 mol) of trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-oxo-4a(4H)-naphthalenecarboxylic acid (111) dissolved in 5 ml of dimethyl sulfoxide. The resulting solution was then transferred to the flask containing the Wittig reagent. The resulting dark orange solution was stirred at 75-80° for 60 hr. After cooling the solution was poured into 100 ml of water, and the basic solution was extracted with diethyl ether. The ethereal extracts were discarded and the aqueous solution was acidified with 3M hydrochloric acid. The acidic aqueous solution was extracted with diethyl ether, and the ether washed with water and brine. After drying ($MgSO_4$) the ether was removed under reduced pressure leaving a crystalline compound which had ir and nmr spectra identical to those of trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-oxo-4a(4H)-naphthalenecarboxylic acid (111).

The above reaction when carried out at higher temperatures and for longer reaction times led only to recovery of starting acid 111.

B. The general procedure of Corey and Seebach (91) was followed. To a solution of 1.68 g (15 mmol) of 1,4-diazabicyclo[2.2.2]octane (Aldrich Chemical Co., Inc.) and 1.86 g (15 mmol) of thioanisole (Aldrich Chemical Co., Inc.) in 25 ml of tetrahydrofuran contained in a 100-ml, round-bottomed flask under a positive pressure of nitrogen at 0° was added 9.6 ml (16 mmol, 15% in heptane) of n-butyllithium (Matheson Coleman and Bell). The pale yellow solution was stirred at 0° for fifteen minutes when a solution prepared by adding 2.66 g (10 mmol) of trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-oxo-4a(4H)-naphthalenecarboxylic acid (111) to a suspension of 0.08 g (10 mmol) of lithium hydride (Research Organic/Inorganic Chemical Corp.) in 20 ml of tetrahydrofuran was added. The resulting solution was allowed to stir at room temperature for 3 hr and was again cooled to 0°. A solution of 4.52 g (20 mmol) of benzoic anhydride in 5 ml of tetrahydrofuran was added, and the solution was stirred at room temperature for an additional 6 hr before pouring it over 100 g of ice. The aqueous solution was acidified with 3M hydrochloric acid and was extracted with diethyl ether. The ethereal extracts were washed with water, brine, and dried ($MgSO_4$) after which the ether was removed under reduced pressure. The resulting semisolid mass was dissolved in hot ethyl acetate to give crystals which proved to be a mixture of benzoic acid and trans-5,5-ethyl-

enedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-oxo-4a(4H)-naphthalenecarboxylic acid (111) by ir and nmr.

C. A 50-ml, round-bottomed flask was charged with 550 mg (2 mmol) of methyl trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-methylene-4a(4H)-naphthalenecarboxylate (126) dissolved in 10 ml of ethanol and 10 ml of 50% aqueous potassium hydroxide. The solution was refluxed under a positive pressure of nitrogen for 16 hr. After cooling, the solution was diluted with 40 ml of water and acidified with 3M hydrochloric acid. The acidic aqueous solution was extracted with chloroform, and the chloroform extracts were washed with water and brine. After drying ($MgSO_4$) the chloroform was removed under reduced pressure to give a crystalline residue which had ir and nmr spectra identical with the starting methyl ester 126.

D. The general procedure of Bartlett and Johnson (92) was followed. A modified 1-l., three-necked, round-bottomed flask with an outlet tube closed by a stopcock at the bottom was equipped with a mechanical stirrer, a gas inlet tube, and an outlet tube. The flask was flushed with argon and was charged with 500 ml of hexamethylphosphoramide (Aldrich Chemical Company, Inc.). A positive pressure of argon was maintained on the reaction system throughout the reaction period. To the hexamethylphosphoramide was added 15 g of powdered lithium hydride (Ventron Corporation) followed by 50 ml of n-

butylthiol. After stirring for one hour at room temperature, the stopcock at the bottom of the flask was opened, and the mixture was filtered, without contact with the atmosphere, through glass wool into a flask fitted with a syringe adapter. The mercaptide reagent was stored in a refrigerator under an argon atmosphere until needed.

A 250-ml, three-necked, round-bottomed flask equipped with a syringe adapter and gas inlet tube was charged with 4.2 g (15.1 mmol) of methyl trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-methylene-4a(4H)-naphthalenecarboxylate (126), and the system was flushed with argon. To this solid material was added, via syringe, 100 ml of the mercaptide reagent prepared as described above. After stirring overnight under a positive pressure of argon, the dark red solution was poured into 400 ml of 1M hydrochloric acid. The acidic aqueous solution was extracted with diethyl ether, and the ethereal extracts were washed with three 40-ml portions of 10% sodium hydroxide. The combined basic extracts were acidified with 3M hydrochloric acid and the precipitate was collected by filtration and washed with water. Recrystallization from ethyl acetate gave 2.6 g (62% of theoretical) of trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-methylene-4a(4H)-naphthalenecarboxylic acid (119) as colorless crystals: mp 179-181°; ir (KBr) 3205, 1738, 1640, 1240, 1120, 1090, 1035, 690 cm^{-1}; nmr

($CDCl_3$) δ5.55 (m, 2H, C<u>H</u>=C<u>H</u>), 4.57 (d, 2H, C=C<u>H_2</u>), 3.92 (m, 4H, O<u>CH_2CH_2</u>O), 1.45-2.76 (m, 8H), 1.28 ppm (s, 3H, angular <u>CH_3</u>).

<u>Anal</u>. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.07; H, 7.52.

<u>5,5-Ethylenedioxy-1,5,6,7,8,8a-hexahydro-t-8,t-8a-dimethyl-r-4a(4H)-naphthalenecarboxylic acid (120)</u>

A. The procedure of Takeda <u>et al</u>. (94) was used. A 250-ml, three-necked, round-bottomed flask equipped with a mechanical stirrer and a dry ice condenser was charged with 50 ml of liquid ammonia which had been redistilled from sodium metal. To the stirred liquid ammonia was added 400 mg (58 mmol) of lithium wire. After the lithium was dissolved, giving a characteristic dark blue solution, 100 mg (0.38 mmol) of <u>trans</u>-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-methylene-4a(4H)-naphthalenecarboxylic acid (<u>119</u>) in 10 ml of anhydrous diethyl ether was added. After stirring for 2 hr at reflux the reaction was quenched by the addition of 6 ml of ethanol, and the ammonia was allowed to evaporate. The residue was dissolved in cold 1<u>M</u> hydrochloric acid, and the acidic aqueous solution was extracted with diethyl ether. After drying ($MgSO_4$) the ether was removed under reduced pressure leaving a crystalline residue which had ir and nmr spectra identical with those for <u>trans</u>-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-methylene-4a(4H)-

naphthalenecarboxylic acid (119).

B. According to the procedure of Corey and Cantrall (93), a 50-ml, round-bottomed flask was charged with 200 mg (0.76 mmol) of trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-methylene-4a(4H)-naphthalenecarboxylic acid (119) and 15 ml of ethylenediamine. To this solution was added 400 mg (58 mmol) of lithium wire, and the resulting mixture was stirred at room temperature until the dark blue color persisted at which time sufficient ammonium chloride was added to remove the blue color. The colorless solution was then poured over ice and neutralized carefully with concentrated hydrochloric acid. The acidic solution was then extracted with diethyl ether, and the ethereal solution was washed with 3M hydrochloric acid, water, and brine. After drying ($MgSO_4$) the ether was removed under reduced pressure. The residue was found to be neutral and in addition the nmr spectrum indicated that the acetal protecting group had been removed.

C. The procedure of Burgstahler and Worden (95) was followed. A 500-ml, three-necked, round-bottomed flask equipped with a mechanical stirrer and a dry ice condenser was charged with 2.64 g (10 mmol) of trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-methylene-4a(4H)-naphthalenecarboxylic acid (119) and 43 ml (0.4 mol) of 2-methyl-2-butanol. To this solution was added 300 ml of

redistilled anhydrous ethylamine (Matheson Gas Products) followed by 2.4 g (0.35 mol) of lithium wire. The solution was stirred until the lithium was completely dissolved (ca. 1 hr) when another 1.2 g (0.18 mol) portion of lithium wire was added. As soon as the characteristic deep color persisted, 25 ml of 2-methyl-2-butanol was added after which the solution became colorless. The ethylamine was removed by distillation, and the residue was diluted with 500 ml of cold water. The aqueous solution was acidified with 3M hydrochloric acid and was extracted with diethyl ether. The ethereal extracts were washed with brine and dried ($MgSO_4$) followed by removal of the ether under reduced pressure. The residue was recrystallized from ethanol to give 2.55 g (96% of theoretical) of 5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-t-8,t-8a-dimethyl-r-4a(4H)-naphthalenecarboxylic acid (120) as colorless crystals: mp 172-173°; ir (KBr) 1695, 1290, 1105 cm^{-1}; nmr ($CDCl_3$) δ5.62 (m, 2H, C<u>H</u>=C<u>H</u>), 3.95 (broad s, 4H, OC<u>H</u>$_2$C<u>H</u>$_2$O), 1.12-2.76 (m, 9H), 1.01 (s, 3H, angular C<u>H</u>$_3$), 0.82 ppm (d, 3H, CHC<u>H</u>$_3$).

<u>Anal</u>. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.67; H, 8.24.

Catalytic hydrogenation of trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-methylene-4a(4H)-naphthalenecarboxylic acid (119)

A 100-ml, round-bottomed flask was charged with 30 mg of platinum oxide and 10 ml of ethanol. The system was alternately evacuated and flushed with hydrogen and then allowed to stir over hydrogen for 10 min. To the catalyst was added 264 mg (1 mmol) of trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-methylene-4a(4H)-naphthalenecarboxylic acid (119) in 30 ml of ethanol. After 30 min ca. 28 ml of hydrogen had been taken up. The mixture was stirred for another 15 min and was then filtered through a celite filter mat. The ethanol was removed under reduced pressure to leave a crystalline residue, the spectra for which are consistent with its formulation as 4,4-ethylenedioxyoctahydro-t-1,t-8a-dimethyl-r-4a(2H),c-1-naphthalenecarbolactone (133): mp 139-141°; ir (KBr) 2950, 1778, 1120 cm^{-1}; nmr ($CDCl_3$) δ3.92 (m, 4H, OCH_2CH_2O), 1.30-2.10 (m, 12H), 1.26 (s, 3H, CH_3), 1.20 ppm (s, 3H, CH_3); mass spectrum (70 eV) m/e 266 (M^+).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.53; H, 8.22.

Methyl 4,4-ethylenedioxyoctahydro-c-1,t-8a-dimethyl-r-4a(2H)-naphthalenecarboxylate (134)

A 100-ml, round-bottomed flask was charged with 50 mg of platinum oxide and 10 ml of ethanol. The system was alternately evacuated and flushed with hydrogen and then allowed to stir over hydrogen for 10 min. To the catalyst was added 700 mg (2.5 mmol) of methyl trans-5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-8a-methyl-8-methylene-4a(4H)-naphthalenecarboxylate (126) in 30 ml of ethanol. After 3 hr ca. 130 ml of hydrogen had been taken up. The mixture was stirred for another 2 hr and was then filtered through a celite filter mat. The ethanol was removed under reduced pressure to leave a residue which was dissolved in hexane. Cooling of the hexane solution overnight in a refrigerator provided crystals of methyl 4,4-ethylenedioxyoctahydro-c-1,t-8a-dimethyl-r-4a(2H)-naphthalenecarboxylate (134): mp 86-88°; ir (KBr) 2960, 2900, 1740, 1230, 1120 cm^{-1}; nmr ($CDCl_3$) δ3.91 (s, 4H, OCH_2CH_2O), 3.70 (s, 3H, OCH_3), 1.30-2.45 (m, 13H), 1.30 (s, 3H, angular CH_3), 1.10 ppm (d, 3H, CH_3).

Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 68.24; H, 9.11.

4,4-Ethylenedioxyoctahydro-t-1,t-8a-dimethyl-r-4a(2H)-naphthalenecarboxylic acid (136)

A 100-ml, round-bottomed flask was charged with 30 mg of platinum oxide and 10 ml of ethanol. The system was alternately evacuated and flushed with hydrogen and then allowed to stir over hydrogen for 10 min. To the catalyst was added 260 mg (1 mmol) of 5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-t-8,t-8a-dimethyl-r-4a(4H)-naphthalenecarboxylic acid (120) in 30 ml of ethanol. After 10 hr ca. 30 ml of hydrogen had been taken up. The mixture was stirred for another 4 hr and was then filtered through a celite filter mat. The ethanol was removed under reduced pressure to give colorless crystals of 4,4-ethylenedioxyoctahydro-t-1,t-8a-dimethyl-r-4a(2H)-naphthalenecarboxylic acid (136): mp 149-150°; ir (KBr) 3200, 2960, 1740, 1220, 1090 cm^{-1}; nmr ($CDCl_3$) δ3.96 (m, 4H, OCH_2CH_2O), 1.15-2.80 (m, 13H), 1.10 (s, 3H, angular CH_3), 0.82 ppm (d, 3H, CH_3).

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.01. Found: C, 67.30; H, 9.05.

Methyl 4,4-ethylenedioxyoctahydro-t-1,t-8a-dimethyl-r-4a(2H)-naphthalenecarboxylate (135)

The procedure of de Boer and Backer (102) was modified slightly. A 100-ml, round-bottomed flask fitted with an addition funnel and a condenser for distillation leading to two receivers in series was charged with 5 ml of ethanol, 10 ml

of diethyl ether and 1.0 g of potassium hydroxide in 2 ml of water. The second receiver contained 20 ml of diethyl ether with an inlet tube dipping below the ether level, and both receivers were cooled in an ice-water bath. The flask containing the alcoholic potassium hydroxide was heated on a steam bath until distillation of the ether started, at which point the addition of 4.3 g (20 mmol) of N-methyl-N-nitroso-p-toluenesulfonamide (Aldrich Chemical Company, Inc.) in 40 ml of diethyl ether was begun. The ethereal solution was added at a rate which approximately equaled the rate of distillation (ca. 10 min required for the distillation). After the ether solution was completely added a further 10 ml of diethyl ether was added and distillation was continued until the distillate was colorless. The ether solutions in the two receivers were combined, and the yellow diazomethane solution was added to 130 mg (0.5 mmol) of 4,4-ethylenedioxyoctahydro-t-1,t-8a-dimethyl-r-4a(2H)-naphthalenecarboxylic acid (136) in a 100-ml beaker. After evolution of nitrogen subsided the ether was allowed to evaporate, and the residue was microdistilled to give methyl 4,4-ethylenedioxyoctahydro-t-1,t-8a-dimethyl-r-4a(2H)-naphthalenecarboxylate (135) as a colorless oil: ir (film) 2960, 2890, 1725, 1230, 1100 cm^{-1}; nmr ($CDCl_3$) δ 3.82 (s, 4H, $OC\underline{H}_2C\underline{H}_2O$), 3.63 (s, 3H, $OC\underline{H}_3$), 1.20-2.05 (m, 13H), 1.02 (s, 3H, angular $C\underline{H}_3$), 0.74 ppm (d, 3H, $C\underline{H}_3$).

Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 68.30; H, 9.45.

Attempted preparation of 1,1-ethylenedioxy-11-oxoishwarane (139)

A 100-ml, three-necked, round-bottomed flask equipped with a reflux condenser and a syringe adapter was charged with 400 mg (50% dispersion in mineral oil, 8.0 mmol) of sodium hydride (J.T. Baker Chemical Co.). The mineral oil was removed by washing the solid with three 5-ml portions of pentane under a constant flow of nitrogen, followed by removal of the pentane through a sintered glass gas dispersion tube attached to a water aspirator. A positive pressure of nitrogen was maintained on the system throughout this procedure. To the washed sodium hydride was added 50 ml of anhydrous benzene followed by 1.06 g (4 mmol) of 5,5-ethylenedioxy-1,5,6,7,8,8a-hexahydro-t-8,t-8a-dimethyl-r-4a(4H)-naphthalenecarboxylic acid (120). After evolution of hydrogen had ceased 2 ml (ca. 24 mmol) of oxalyl chloride was added via syringe. The mixture was stirred at room temperature for 10 hr and was then filtered through a celite mat. The benzene was removed under reduced pressure to leave acid chloride 137 as a pale yellow oil: ir (film) 1790, 680 cm^{-1}; nmr (CCl_4) δ 3.95 (s, 3H, OCH_2CH_2O), 1.05 (s, 3H, angular CH_3), 0.83 ppm (d, 3H, CH_3).

Refluxing of the above benzene solution during preparation of acid chloride 137 led to partial cleavage of the acetal function.

Diazoethane was prepared as in the procedure for 7-methyltricyclo[3.2.1.$0^{2,7}$]octan-6-one (74) and was used in the preparation of diazoketone 138 according to the general procedure of Wilds and Meader (68). The ethereal diazoethane (ca. 50 mmol) solution was cooled to -20° with a dry ice--ethanol bath and acid chloride 137 prepared as described above (ca. 4 mmol) dissolved in 10 ml of diethyl ether was added via syringe over a 10 min period. The resulting solution was stirred at -20° for 1 hr when the excess diazoethane was removed under aspirator pressure, followed by the removal of ether at 0° under reduced pressure. Diazoketone 138 was an orange oil: ir (film) 3000, 2100 (w), 1640 cm^{-1} (w).

Diazoketone 138 was cyclized according to the procedure described by Fawzi and Gutsche (28). Crude diazoketone 138 was dissolved in 20 ml of tetrahydrofuran and was added to 100 mg of cupric sulfate suspended in 40 ml of tetrahydrofuran. The mixture was stirred at reflux under nitrogen for 3 hr. The brownish solution was filtered, and the tetrahydrofuran was removed under reduced pressure. The residual brownish oil was chromatographed on silica gel with 10% diethyl ether in hexane as eluent. All the fractions which were collected showed absorptions for vinyl protons in the

nmr spectrum.

Attempts at the cyclization of diazoketone 138 using cyclohexane as solvent rather than tetrahydrofuran were also unsucessful.

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