

1973

Approaches to the synthesis of the petasin sesquiterpenes

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SESQUITERPENES.

Iowa State University, Ph.D., 1973
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Approaches to the synthesis of the petasin sesquiterpenes

by

Kenneth Wayne Burow Jr.

**A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of
The Requirements for the Degree of
DOCTOR OF PHILOSOPHY**

**Department: Chemistry
Major: Organic Chemistry**

Approved:

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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
Ames, Iowa**

1973

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DEDICATION

To Patty, Margo, and Alex,
whose love, patience and understanding
made this work possible.

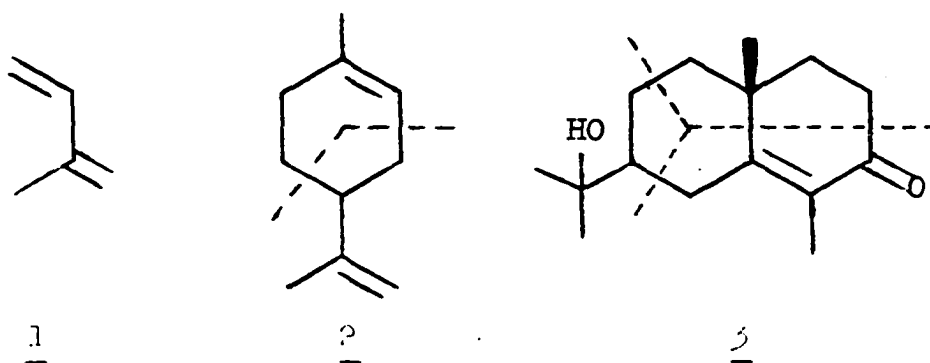
INTRODUCTION

During the twentieth century, our knowledge of the chemistry of natural products has increased to an extent which is difficult to grasp today and would have been inconceivable one hundred years ago. Such dramatic progress represents merely the continuation of an inherent tradition: man's curiosity about the natural world and his attempts to exploit it. This age-old involvement with the chemistry of Nature was first manifest in the primitive technologies of dyeing, folk-medicine, and perfumery. From these early beginnings has evolved the basis of structural and theoretical organic chemistry.

For several centuries it has been known that the fruit, flowers, roots, and leaves of many plants contained volatile, odoriferous substances. It was soon discovered that the active principles responsible for the odor could be separated from the plant by gentle heating and, more elegantly, by steam distillation. These materials, as an oil together with an aqueous phase, were collected by condensation on a cool surface. The oils so isolated became known as "essential oils". Recent developments have resulted in a broadening of the term "essential oil" to include materials isolated by the processes of extraction and chromatography.

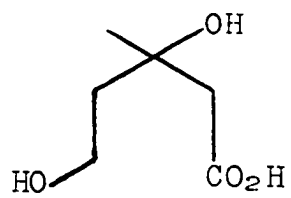
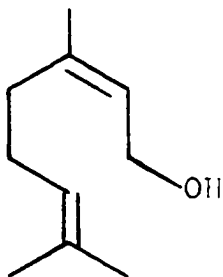
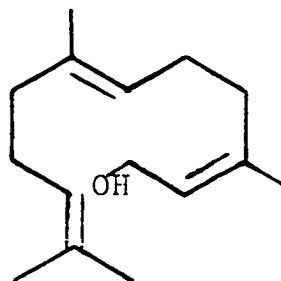
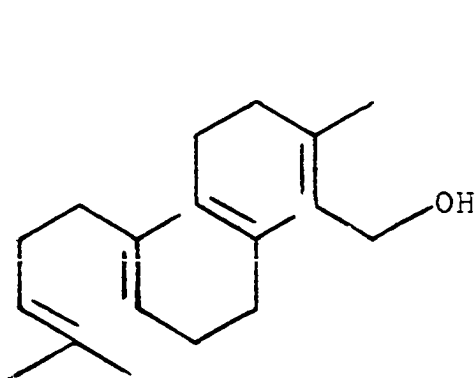
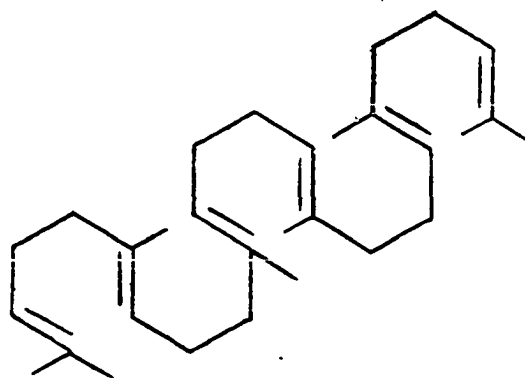
The essential oils are comprised of several classes of terpenoids ranging in scope from the simpler monoterpenes to the more complex sesquiterpenes and polyterpenes. Current interest has focused upon sesquiterpenes, a rapidly expanding group of naturally occurring materials which, strictly defined, contain fifteen carbon atoms in the basic skeleton. Sesquiterpenes have been known to be constituents of essential oils for more than a century, but it is only in comparatively recent times that their chemistry has been investigated in detail. For further elaboration upon the subject of sesquiterpenes, the author recommends the works of Simonsen and Barton (1), Pinder (2), Templeton (3), and deMayo (4).

A closer examination of the molecular structure of sesquiterpenes reveals that, in most cases, the carbon skeleton can be built up theoretically by the union of three isoprene (1) or isopentane residues. This observation, supported by further structure determinations, gradually evolved into the generalization known as the "isoprene rule", first suggested by Wallach (5) in 1887 and later elaborated by Robinson (6), to the effect that to be terpenoid a compound must have a carbon skeleton composed of isoprene (or isopentane) units linked in a head-to-tail fashion. Some simple examples are the terpene limonene (2) and the sesquiterpene carissone (3).

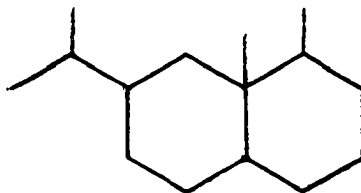


Isoprene was at one time believed to be a precursor of terpenes in the plant. Modern views of the biogenesis of terpenes have, however, led to the rejection of this theory (6-8). Although the fine points of terpene biogenesis are still being investigated, it is generally accepted that mevalonic acid (4) leads to an active intermediate, isopentenyl pyrophosphate (5) (9), which self-condenses in a head-to-tail manner to form unsaturated alcohols. The condensation of two, three or four units of isopentenyl pyrophosphate produces geraniol (6), farnesol (7), or geranylgeraniol (8), respectively. These alcohols and squalene (9), the head-to-head dimer of farnesol (7), are envisioned as terpene precursors.

The eremophilane sesquiterpenes (10) are a unique class of sesquiterpenes in that the basic carbon skeleton cannot be accounted for by invocation of the isoprene rule. These compounds are non-isoprenoid in character and exhibit the

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skeletal structure shown below.

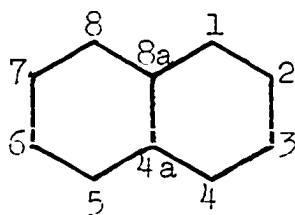


In the 1950's, petasin and several of its congeners were isolated and identified as eremophilane sesquiterpenes. In light of the great interest in this type of sesquiterpene, notably from a biogenetic viewpoint, it appeared desirable to attempt the synthesis of this unique eremophilane sesquiterpene.

NOMENCLATURE

In order that this manuscript might assume a form as practical and uniform as possible, it was decided to use the nomenclature system currently employed by Chemical Abstracts. Since this system is decidedly more cumbersome than that based on the trivial name "decalin", this section will serve as a brief explanation of Chemical Abstracts nomenclature. For additional information on this subject, the reader may consult references (11-13).

A. Numbering: The numbering system employed in this manuscript and Chemical Abstracts is illustrated below.



B. Naphthalenone derivatives:

1. These compounds are named as derivatives of the completely saturated ring system; 1,2,3,4,4a,5,6,7,8,8a-decahydronaphthalenone.

2. The substituents are listed in alphabetical order, with the exclusion of prefixes such as di, tri, hexa, octa,

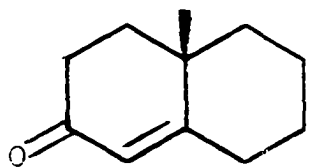
etc.

3. The "indicated hydrogen" is given the lowest possible number consistent with a chemically correct parent compound.

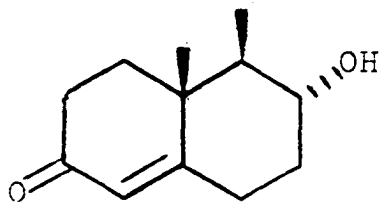
4. Relative stereochemistry in cyclic systems is designated by Beilstein's system using c, t, and r descriptors. The lowest numbered substituent is assigned the letter r (reference). Groups on the same side of the ring as the reference group are designated c (cis); groups on the opposite of the ring are designated t (trans).

5. Cis or trans preceding the name of the compound indicates the stereochemistry about the ring fusion; i.e., the relationship between the substituents at 4a and 8a. The prefix dl is omitted from the names of racemic compounds.

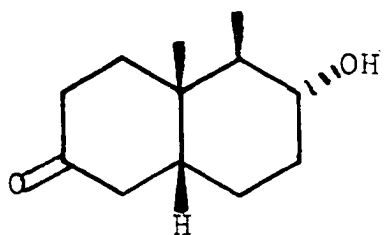
C. Examples:



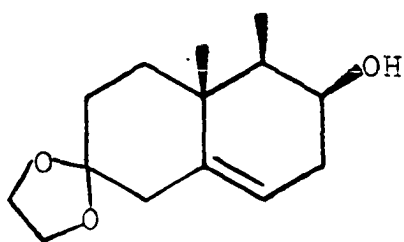
4,4a,5,6,7,8-hexahydro-4a-methyl-2(3H)-naphthalenone



4,4a,5,6,7,8-hexahydro-t-6-hydroxy-c-4a,c-5-dimethyl-2(3H)-naphthalenone



cis-3,4,4a,5,6,7,8,8a-octa-
hydro-t-6-hydroxy-r-4a,c-5-
dimethyl-2(1H)-naphthalone



6,6-ethylenedioxy-1,2,3,5,
6,7,8,8a-octahydro-c-1,r-8a-
dimethyl-c-2-naphthol

HISTORICAL

The existence of a particular plant having slender green leaves, with pink to purple flowers, was first recorded by P. A. Maltioli (14) in 1563. Hieronymus Bock (15) elaborated considerably upon this initial discovery by assigning descriptive characteristics of the plant and naming it Petasites officinalis Moench., [syn. Petasites hybridus (L.) Fl. Weet]. In the early 1900's it was discovered that this plant had some therapeutic activity and in 1934, Zellner (16) attributed this activity to certain resins and terpenes contained in the leaves. Further studies by Karl Buchner (17) indicated that an extract of the fresh plant root inhibited contractions of isolated guinea-pig intestine. This was the first reference to any specific therapeutic value of the plant. In 1954 Boriani and Sinigaglia (18) attempted to isolate the active principles by extraction with various organic solvents, however all trials were unsuccessful. These workers did find that a 5% infusion of the leaves of p. off. caused depression of the nervous spontaneous motility with unchanged excitability of the whole neuromuscular system, accompanied by some hypotensive action. Two other Italian workers (19) supplemented these findings with the

discovery that an aqueous extract of rhizomes and roots was more potent than that of the leaves. An intravenous administration of 1 cc/kg body weight produced a reduction in blood pressure by 40-60mm Hg. No significant modification of carotid sinus reflex or respiratory rhythm was found. The duration of the action was 35-45 minutes and repeated doses gave a constant response.

The search for possible therapeutic compounds contained in P. off. led to the first isolation of the eremophilane sesquiterpenoid, petasin, by Aebi and coworkers (20) in 1954. An alcoholic extract of the roots of P. off. was subjected to chromatography with two major components being isolated. The first fraction, upon acetylation, was identified as β -sitostearin acetate. The second fraction, a crystalline ketone with the molecular formula $C_{20}H_{28}O_3$, was named petasin. When petasin was placed on an aluminum oxide column or warmed with dilute HCl, an isomer, isopetasin, was readily formed. Aebi found petasin to be spasmolytically active while isopetasin was also, but to a much lesser degree.

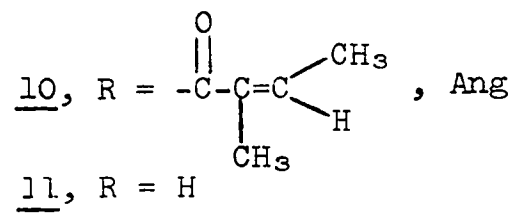
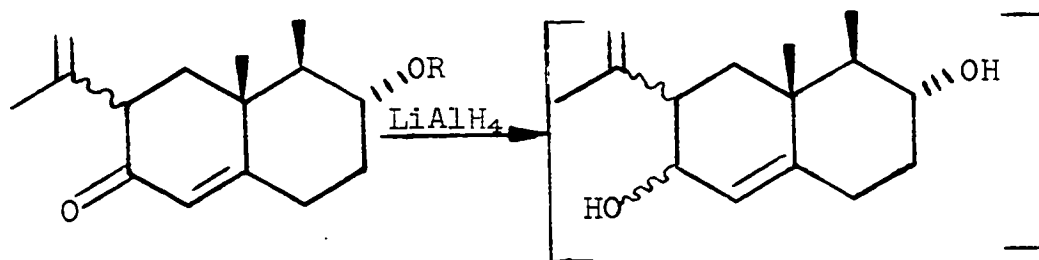
Another group of Swiss workers (21) were concurrently working with P. off. and were able to isolate four other substances co-existing with petasin. These included isopetasin, which was deemed to be a naturally occurring material and not an artifact, and petasol esters B and C ($C_{19}H_{26}O_3S$). All compounds were esters of the same C_{15} alcohol named petasol

($C_{15}H_{22}O_2$), which was also isolated. Petasin and isopetasin were determined to be esters of angelic acid, whereas petasol esters B and C were esters of β -methylmercaptoacrylic acid. All five substances were found to be spasmolytically active.

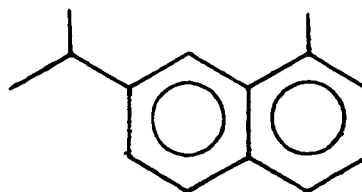
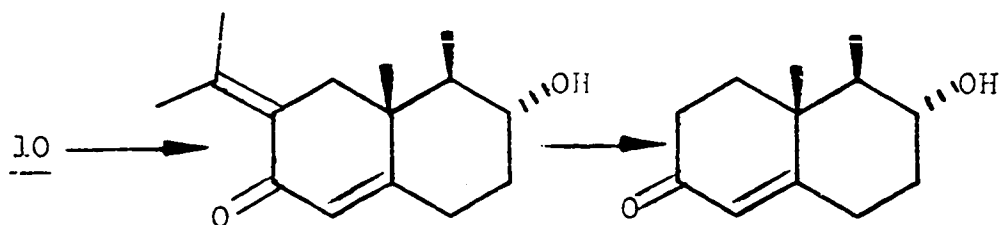
In 1958, Aebi, Waaler, and Büchi (22) conducted a very thorough study of the components in the root of P. off. Like Stoll and coworkers (21) they found petasin, isopetasin, and petasol esters B and C. However, Aebi determined that the spasmolytic activity of petasin was greater than that of papaverine hydrochloride, while isopetasin was inactive. The activity of the two sulfur containing esters was found to be less than that of petasin. Hydrolysis of these sesquiterpenoids afforded the sesquiterpene alcohol, isopetasol. The acid components were investigated by paper chromatography and indicated the presence of angelic, tiglic, and α -methyl- β -hydroxybutyric acids.

Aebi established the carbon skeleton of petasin (10) by the hydrolysis of the ester to give 11, reduction of the carbonyl moiety to yield intermediate 12, and dehydration with selenium metal to afford eudalene (13). The location of the α, β -unsaturated ketone function was determined by alkaline treatment of isopetasol (14) accompanied by retroaldolization to give acetone and des-isopropylidenepetasol (15).

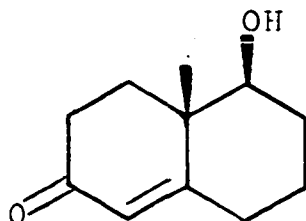
Aebi and Djerassi (23) indicated that the rotatory dispersion curve of 15 was of the usual Δ^4 -3-keto steroid

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Se

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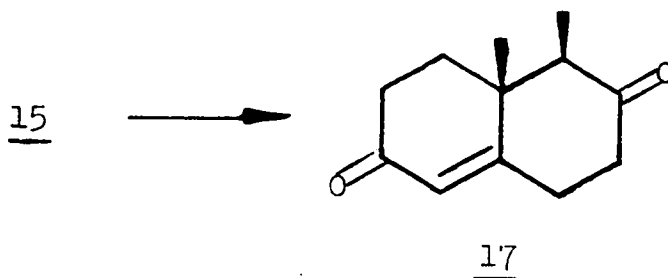
type (24), a result which settled the absolute configuration (25) of this substance insofar as the carbon atom bearing the angular methyl group was concerned. The absolute configuration of petasin (10) was further substantiated when Aebi and Djerassi (23) showed its ORD spectra to be almost superimposable with that of octalone 16 for which the absolute configuration was already known.



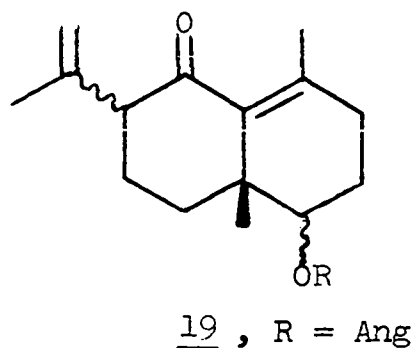
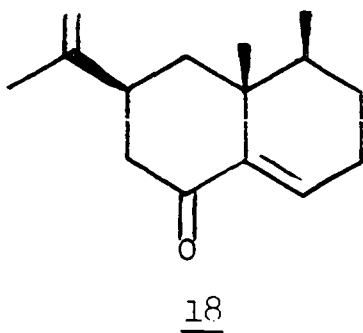
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The only possible factor which could have affected the validity of these conclusions was the location and configuration of the hydroxyl group. Aebi et al. (22) felt that the hydroxyl group must be equatorial owing to the ease of saponification of petasin (10) as well as by the rate of oxidation and acetylation of the free hydroxyl group in des-isopropylidenepetasol (15). Its location at C-6 was suggested by the observation that the hydroxyl function was not eliminated by treatment with base, as would be expected for a vinylogous β -hydroxyketone (location at C-7), and that the derived diketone, des-isopropylidenepetasone (17), possessed

an isolated carbonyl group (thus excluding C-8) in addition to the original α,β -unsaturated ketone moiety. These facts indicated that petasin (10) was a member of the rare class of non-isoprenoid eremophilane sesquiterpenes. Its absolute



configuration was found to correspond to that of eremophilone (18) as opposed to the typical isoprenoid sesquiterpene (19) which had been originally postulated to be the structure of petasin (10).



Herbst and Djerassi (26) confirmed the structure and absolute configuration of petasin (10) by independently synthesizing a degradation product of petasin (10) of rigorously determined stereochemistry. Chart I illustrates the sequence used to prepare decalin-dione 31, which was then shown to be identical to a diketone obtained from petasin (10).

The resolution and absolute configuration of the starting material, the (+)-enantiomer of the enol ether 20 had been reported earlier (27), and so had its transformation (28) into the hexalone 21 by means of methyllithium followed by acid hydrolysis. Oxidation with perbenzoic acid furnished the crystalline epoxide 22. The diol 23 was obtained by reduction of 22 with lithium aluminum hydride, and was immediately subjected to oxidation with manganese dioxide. The resulting hydroxyoctalone 24 was treated under the conditions of the Wolff-Kishner reduction to yield a hydrocarbon mixture. Micro-hydrogenation demonstrated that no more than 12% of the mixture could have consisted of a saturated hydrocarbon resulting from reduction of the double bond. The remaining 88% thus contained one double bond which could be either di-substituted (25) or tri-substituted (26), since migration of a double bond during the Wolff-Kishner reduction of α, β -unsaturated ketones had been reported several times (29). Nuclear magnetic resonance measurements indicated that

CHART I

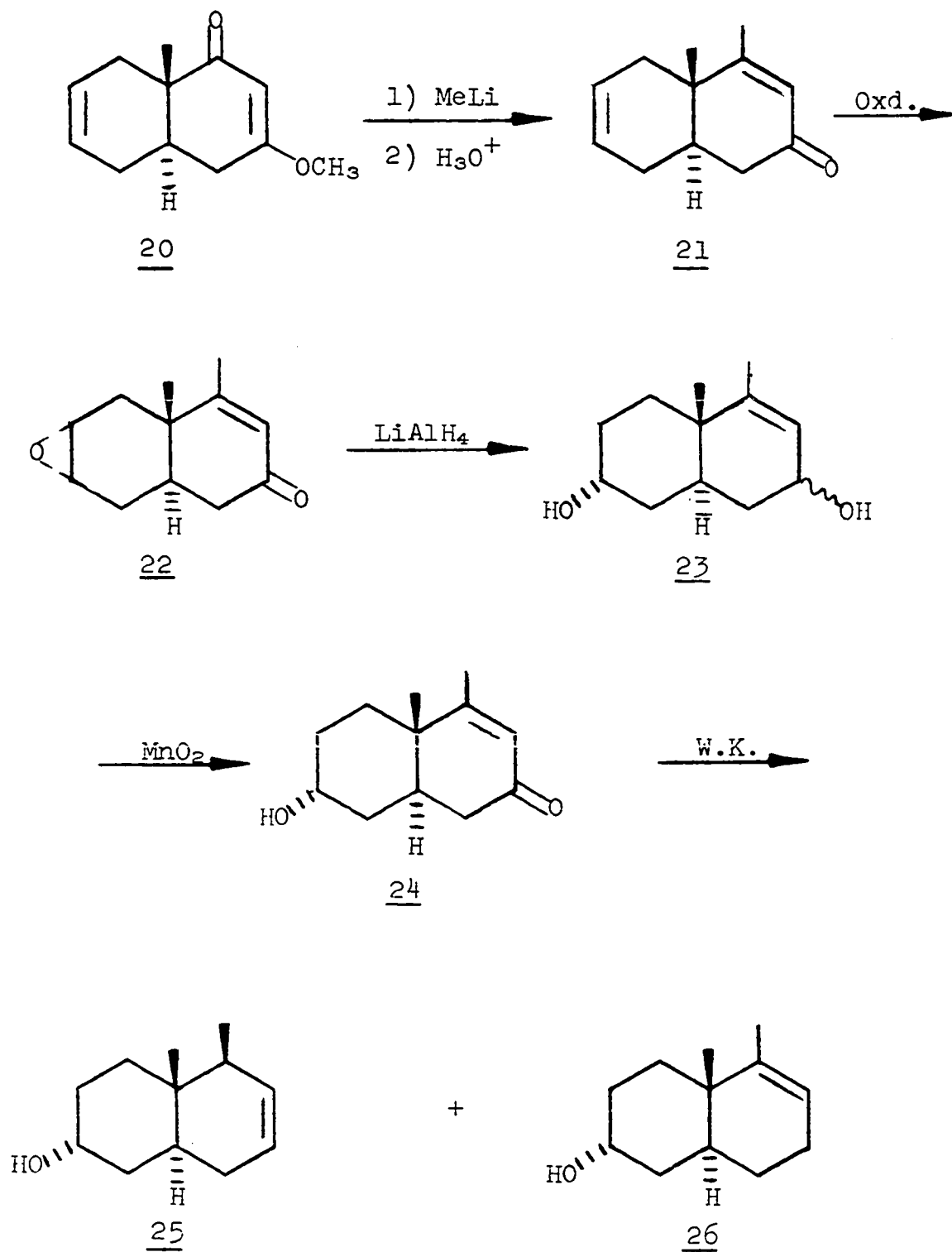
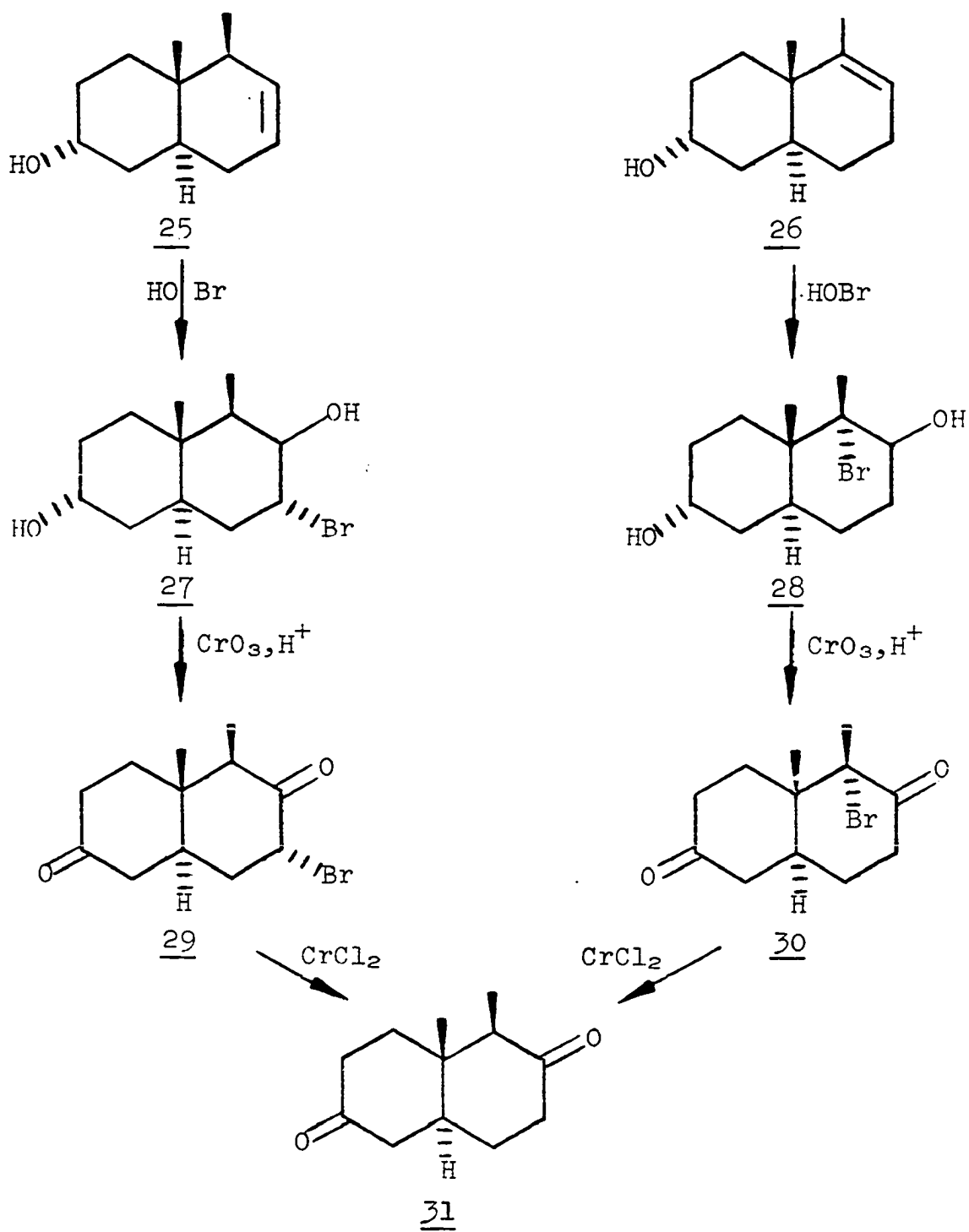
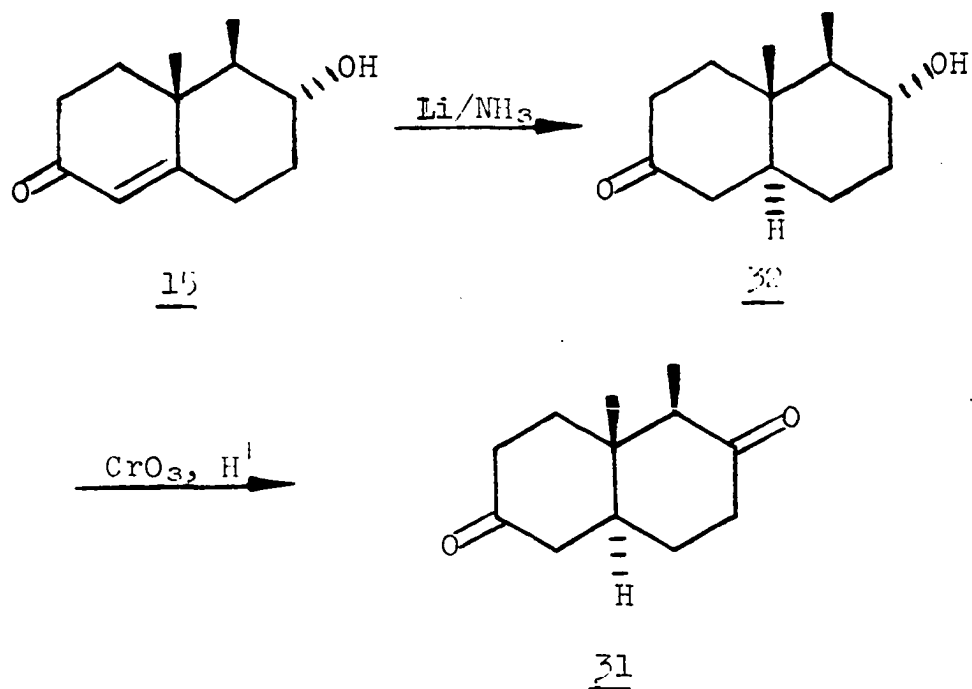


CHART I (Cont.)



75% of the total mixture consisted of the migration product, 25, with only 12% of the non-rearranged octalol 26 being found. The mixture was treated with hypobromous acid to afford the expected bromohydrin 27 and a small amount of the isomer 28. Both isomers now possessed the newly introduced hydroxy group in the same position, so the mixture was oxidized to the isomeric bromodiketones 29 and 30, followed by debromination with chromous chloride (30) to the homogeneous, crystalline diketone 31.

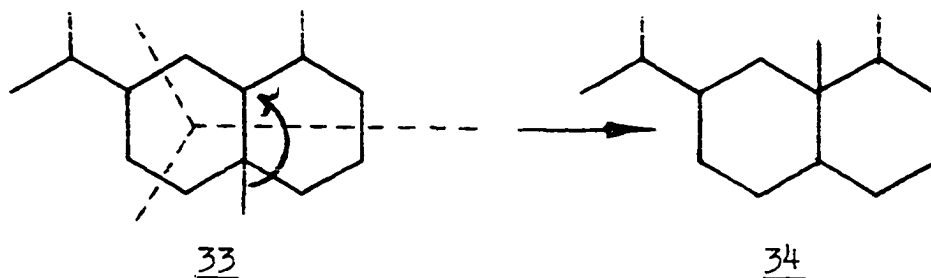
All that was now necessary was to establish a relationship between petasin (10) and the synthetic diketone 31 of established constitution and absolute configuration. To accomplish this, des-isopropylidenepetasol (15) was reduced with lithium in liquid ammonia to give ketoalcohol 32 having the thermodynamically more stable trans ring juncture. The resulting des-isopropylidenehydropetasol (32) was oxidized to yield the trans-4a,5-dimethylnaphthalenedione 31 which was identical in all respects to the afore-mentioned synthetic species. Herbst and Djerassi's work thus completely confirmed the structure of petasin (10) as suggested by Aebi and coworkers (22) as well as the absolute configuration (23) deduced by rotatory dispersion measurements on des-isopropylidenepetasol (15).



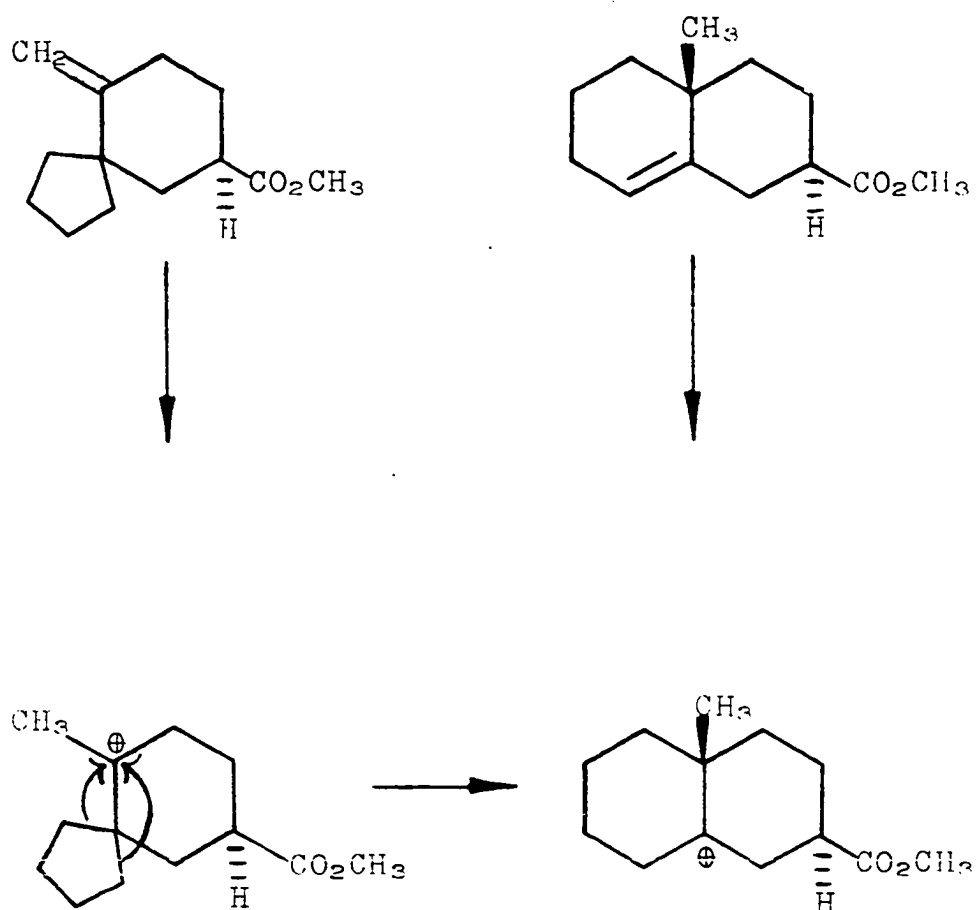
Biogenetically, it is quite probable that petasin (10) is formed by methyl migration from an eudalenoid precursor having the same absolute configuration as the corresponding precursor in the eremophilone (18) series. For that reason Djerassi assumed that the C-5 methyl group was cis to the angular methyl group as that stereochemical point had already been established (28,31) for eremophilone (18). One could propose such an analogy for the isopropenyl group at C-3, however, this would be invalid since this center is adjacent

to a carbonyl group and may have suffered epimerization in the plant or during the isolation procedures. At the time of this writing the orientation of the isopropenyl moiety at C-3 still remains a mystery.

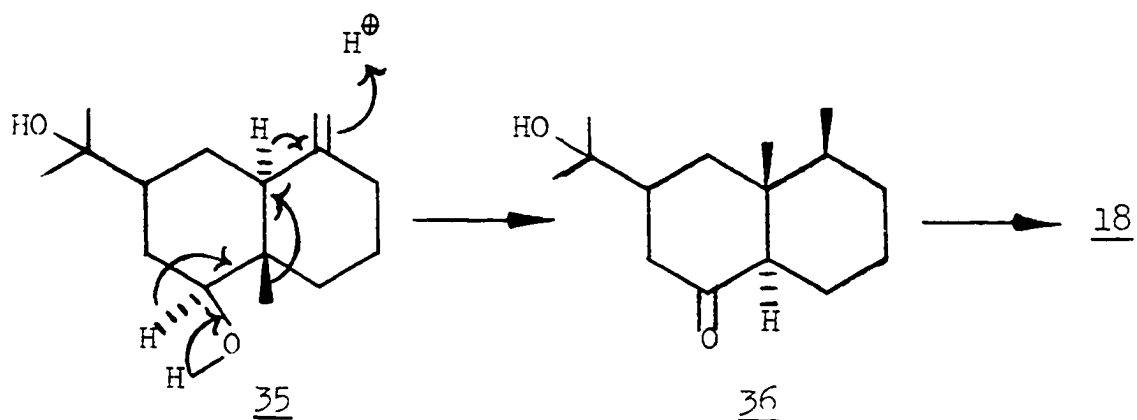
The structure and absolute configuration of petasin (10) have been rigorously established, but the biogenetic origin of this non-isoprenoid species has not yet been accounted for. As early as 1939, Robinson (32) suggested that a 1,2-methyl migration from an isoprenoid eudesmane precursor such as 33 might explain the biosynthesis of non-isoprenoid eremophilane sesquiterpenes of structure 34. Dunham and Lawton (33) have suggested that sesquiterpenes of this



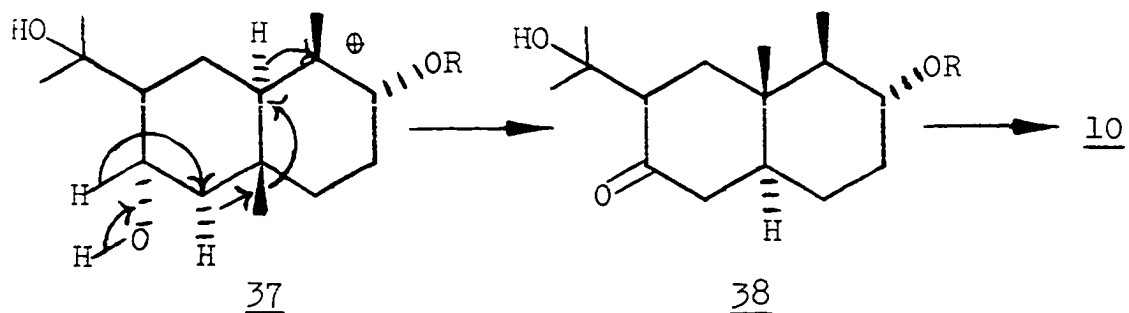
type may arise via spiro intermediates as shown on the next page.



Djerassi and his collaborators (34) felt that isoprenoid olefinic compounds, such as 35, might be reasonable biogenetic precursors for the eremophilone sesquiterpenes.



There are no reports in the literature concerning possible biogenetic precursors for petasin (10). An appropriate compound would require the functionalized groups to be disposed trans and coplanar as well as being a highly oxygenated species. For example, 37 could rearrange to 38, undergo dehydrogenation, followed by dehydration of the side chain to yield petasin (10).



Zabkiewicz, Keates, and Brooks (35) have reported some biogenetic studies on petasin (10). These workers found that some of the activity of DL-[2-¹⁴C]-mevalonolactone (MVAL) was incorporated into petasin (10) by feeding it to whole plants of *P. off.* The effect of synthetic inhibitors on sesquiterpenes and sterol biosynthesis in the plant was also noted in this study.

When DL-[2-¹⁴C]-MVAL was fed to *P. off.*, investigations showed that a major portion of the radioactivity appeared in the fraction containing sterols and triterpenoid alcohols, and only a very minor proportion was found in the sesquiterpenoid fraction. The primary goal of this work was to obtain a higher incorporation of [2-¹⁴C]-MVAL into the sesquiterpene fraction by the use of synthetic inhibition of sterol formation.

One inhibitor, SK and F 525-A (β -dimethylaminoethyl-diphenylpropyl acetate hydrochloride) had been shown by Holmes and DiTullio (36) to effect inhibition at the stage of isomerization of isopentenyl pyrophosphate to dimethylallyl pyrophosphate. With SK and F 7997-A [tris-(2-diethylaminoethyl)-phosphate trihydrochloride] inhibition occurred at a later stage and caused the accumulation of a non-polar triterpenoid intermediate. A related result was obtained by Reid (37) who also observed the accumulation of a non-polar triterpenoid intermediate when he fed SK and F 7997-A and

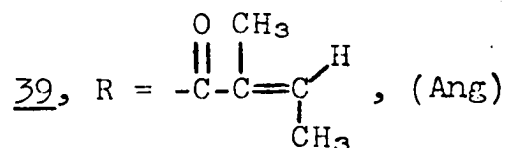
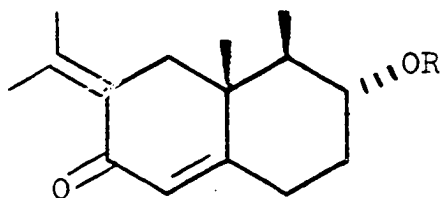
[2-¹⁴C]-MVAL to Nicotiana tabacum slices. In further work, Reid (38,39) demonstrated an increased incorporation of the label into squalene and 2,3-oxido-squalene, as well as other unidentified terpenoids, while the biosynthesis of β -amyrin and pytosterols was inhibited.

The above results indicated to Brooks and coworkers that the biosynthesis of sterols could be inhibited without necessarily affecting the lower terpenoids. Separate trials with two inhibitors, SK and F 525-A and 7997-A, were therefore undertaken. The inhibitor was fed together with [2-¹⁴C]-MVAL to mature leaves of P. off. by the "wick" technique. After several weeks, the leaves were harvested and the radioactivity in petasin (assayed as isopetasyl acetate) was determined. With SK and F 525-A the workers noted a decrease in the activity incorporated and in the weight of the isopetasyl acetate recovered as the level of the inhibitor was increased. This inhibitor was suppressing sesquiterpenoid as well as steroid biosynthesis, which was consistent with the known action of SK and F 525-A.

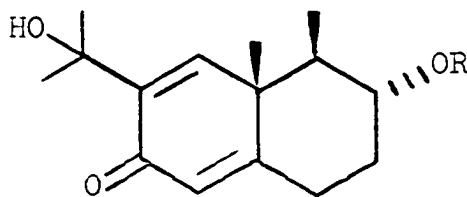
The results from the SK and F 7997-A feedings showed that the activity incorporated into petasin increased with increasing amounts of inhibitor. This was consistent with the existing evidence that this inhibitor acts at a stage beyond squalene biosynthesis and probably inhibits the cyclization of 2,3-oxide-squalene. No study was made of the

isopetasyll acetate to see where the radioactive label had been incorporated. Although these workers now had a means for increasing the incorporation of [2-¹⁴C]-MVAL into sesquiterpenes via inhibition of sterol formation, the percent increase was not significant enough over the non-inhibited trials to allow the determination of the position of incorporation of the label. Perhaps the continuing research of these workers will help to shed some light on the biogenetic origin of petasin (10).

In the late 1950's two Japanese groups, headed by T. Kori-hara and K. Naya, as well as a Czechoslovakian group led by L. Novotny and F. Sorm, began to take a very active interest in the isolation of sesquiterpenes of the petasin family. The Japanese workers concentrated on Petasites japonicus Maxim., a plant indigenous to almost all of Japan. The early work by Kurihara and Takase (40,41) was only a repetition and confirmation of the findings of Aebi and his coworkers (20). In 1966, however, Kurihara and his collaborators (42) discovered a major component of P. jap. which they called petasione. Further experimental evidence indicated that petasione was identical with isopetasin (39), and that the compounds found in P. off. were also present in P. jap. K. Naya, I. Takagi, and their coworkers (43,44)

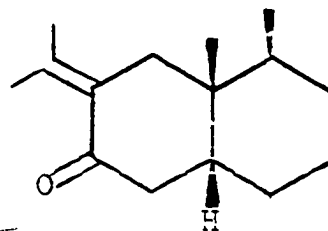


discovered two new sesquiterpenes from *P. japonicus* Maxim. and named them petasitin (40) and fukinone (41). Fukinone (41) has been synthesized by several groups (45-47), repre-



R = Ang

40



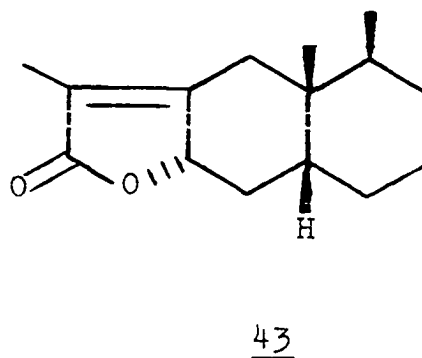
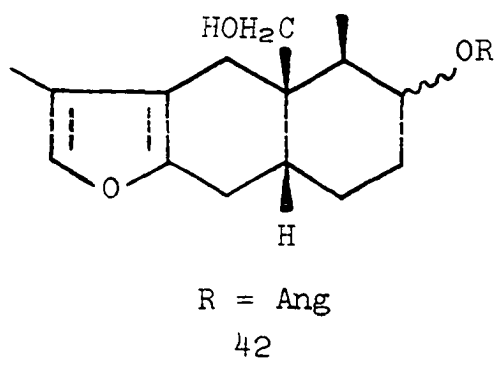
41

senting the first total synthesis of a compound in the petasin family of sesquiterpenes.

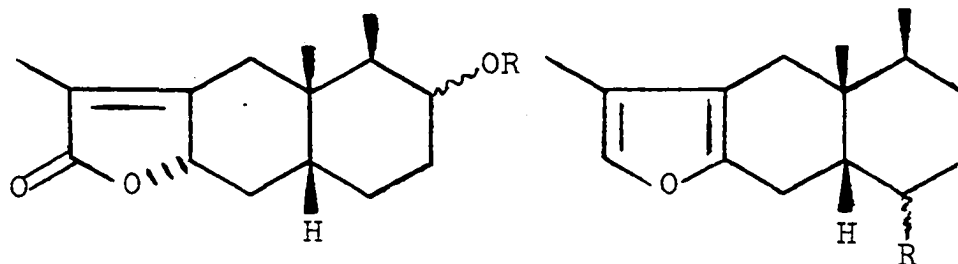
Concurrent with the investigation of *P. jap.* was a study being undertaken by Novotny and his collaborators on substances from *Petasites officinalis* Moench. and *Petasites albus* (L.) Gaertn, both plants being found in Czechoslovakia.

Chromatography of the rhizome extracts and subsequent crystallization of particular eluates afforded a series of new compounds, different from those isolated by Aebi and his coworkers (20,22) and Stoll and his coworkers (21) in Switzerland. The compounds isolated fell mainly into two classes: substances of the furan type and compounds containing an α, β -unsaturated δ -lactonic grouping.

The constituents of coltsfoot rhizomes (rhizomes of P. officinalis Moench.) initially isolated by Novotny et al. were furanopetasin (42), (48), eremophilanolide (43), (48,49), and petasitolide A and B (44), (48,50). From the rhizomes of



Petasites albus (L.) Gaertn., this same research group (51,52) identified two more eremophilane sesquiterpenes, albopetasin (45) and petasalbin (46).



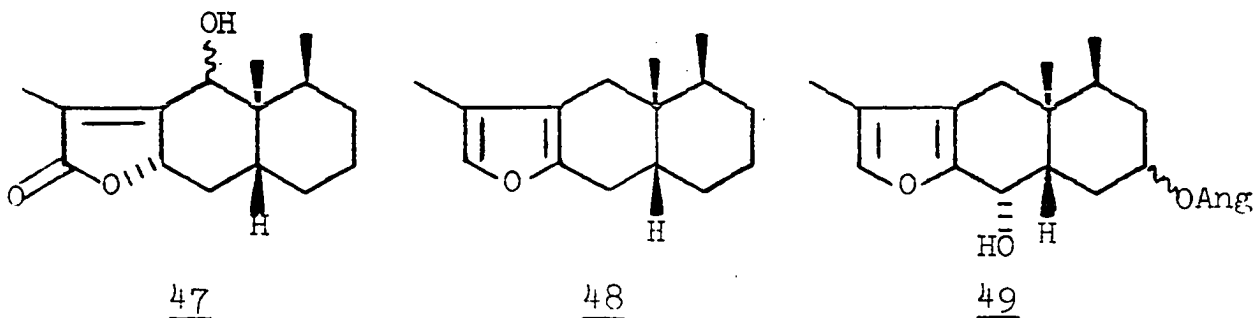
44A, R = Ang

45, R = Ang

44B, R = Tiglate

46, R = H

Additional research brought forth the discovery of several more new sesquiterpenes of the eremophilane type such as hydroxyeremophilanide (47), (52), furanoeremophilane (48), (53), and the main component of coltsfoot rhizomes, furanopetasine (49), (54). In addition, there were some



47

48

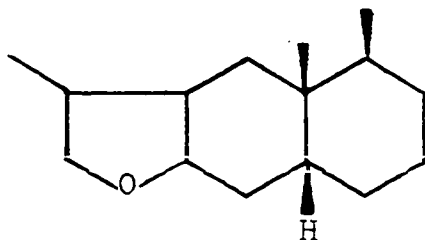
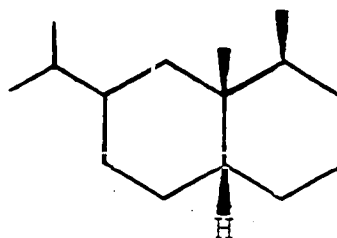
49

hydrocarbons (55) isolated along with the sesquiterpenes. These differed very slightly between the two plants.

Novotny and Herout (56) examined the constituents of the rhizomes of Petasites japonicus from a plant located in Bohemia and found the components to be nearly identical to

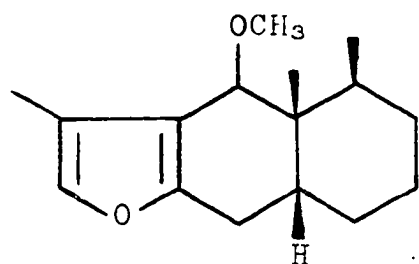
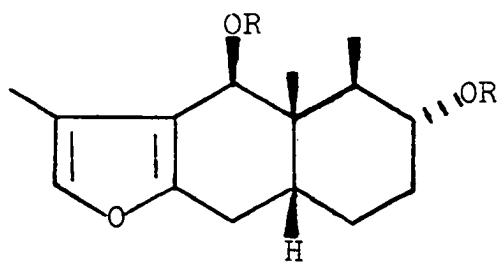
those in *P. albus*. Lukes and Komers (57) have reported the separation by gas chromatography of ten of the sesquiterpenes found in *P. off*.

The structures of most of these new eremophilane sesquiterpenes were elucidated (58) by conversion of the oxygen containing compounds into 8,12-oxidoeremophilane (50). On hydrogenation and on hydrogenolysis, some compounds [eremophilenolide (43), petasabia (46), and furanoeremophilane (48)] afforded the hydrocarbon eremophilane (34) which, for comparison purposes, had been prepared from hydroxydihydroeremophilone.

5034

The above communications are summarized, a listing of the physical properties of the newly discovered compounds is given, and the chemotaxonomy of these European *Petasites* species is elaborated upon by Novotny *et al.* in references (58, 59).

By 1971 Naya and his coworkers (60) had isolated fifteen components from the rhizomes of *P. japonicus* Maxim. These included four known and six unknown furanoeremophilones. The six new furan derivatives were obtained by glc and repeated column chromatography. The new sesquiterpenes were named petasalbin methyl ether (51), furanofukinol (52), 6-acetylfuranofukinol (53), 6-angelylfuranofukinol (54), 5-furanopetasitin (55), and furanojaponin (56).

51RR'52

H

H

53

Ac

H

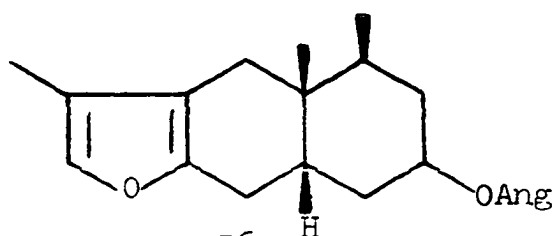
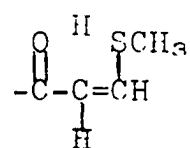
54

Ang

H

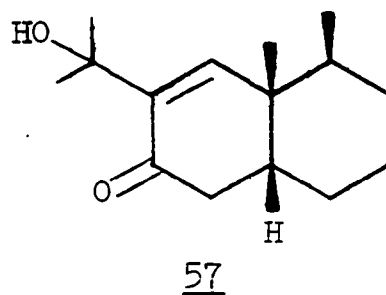
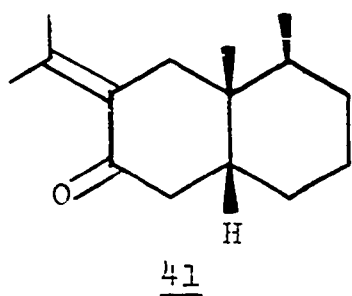
55

Ang

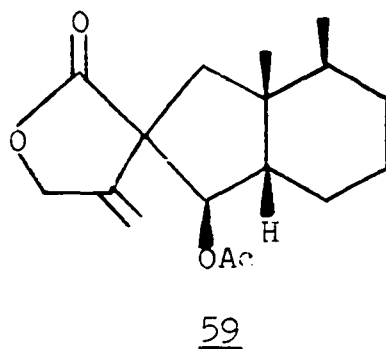
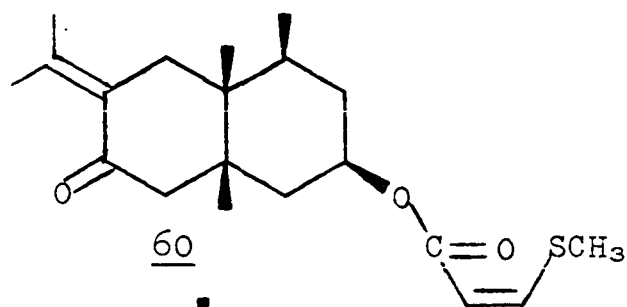
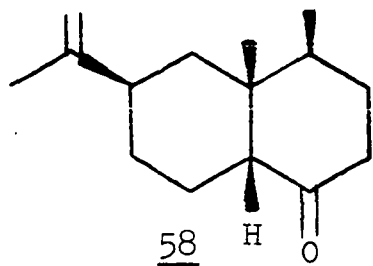
56

Although exhaustive isolation procedures have been carried out on both *P. off.* and *P. jap.*, eremophilane sesquiterpenes are continually being found and identified. In 1971 Naya and his collaborators (61,62) isolated four com-

pounds from *P. jap.*, all of them being related to the sesquiterpene fukinone (41). The structure of petasitolone (57) was confirmed by synthesis from fukinone (41).



Eremofukinone (58), 9-acetoxylfukinonolide (59), and S-japonin (60) are three of the more exotic compounds found in this plant. Their structures were validated by chemical and spectroscopic methods.



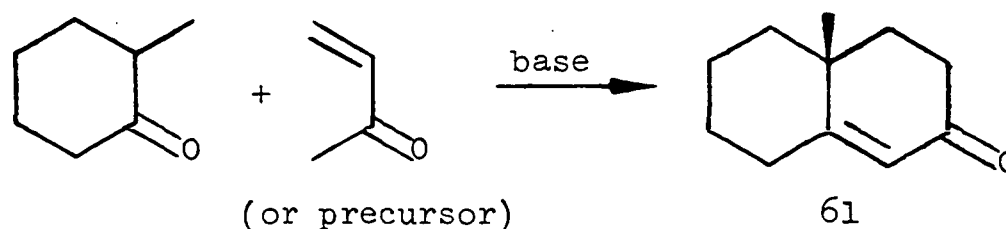
It is quite easy to see that the number of eremophilane sesquiterpenes is growing at a fantastic rate. This manuscript is concerned only with those sesquiterpenes coming from plants related to Petasites officinalis and still the list of compounds is too extensive to discuss each one individually. Many other eremophilane sesquiterpenes have also been isolated and for a complete tabulation of these, the reader may consult the superlative works of Ourisson et al. (63) and Devon and Scott (64).

Our study now narrows from the obtuse to the acute. The remainder of this manuscript will be concerned with the approaches to the stereoselective synthesis of petasin (10) and isopetasin (39). A pathway to a whole class of new sesquiterpenes would be created by the synthesis of these two compounds. Then, the biological activity of these materials could be thoroughly investigated, their structures could be confirmed by total synthesis, and perhaps some insight could be gained as to their biogenetic origin. The judicious synthesis of petasin (10) and isopetasin (39) thus appears to be an ideal challenge for an aspiring organic chemist.

Alkylation of 2,3-Dimethylcyclohexanone

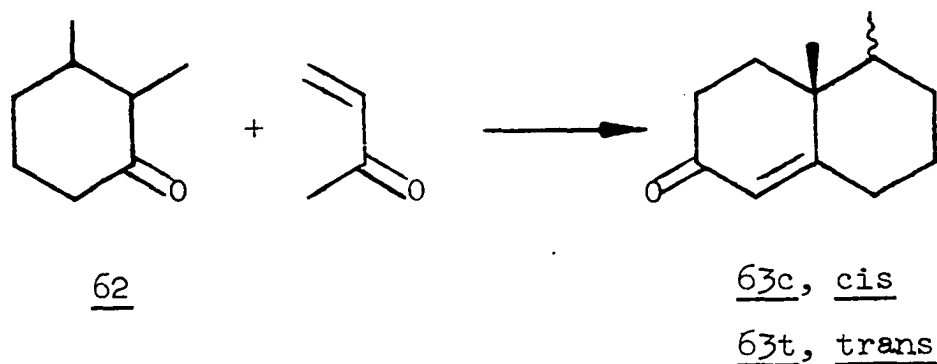
The literature abounds with methods for the preparation of octalones from 2-methylcyclohexanone. One of the first was reported by E. C. duFeu, F. J. McQuillan, and R. Robinson (65) in which 2-methylcyclohexanone was condensed with

4-chloro-2-butanone (a precursor for the in situ generation of methyl vinyl ketone) employing sodium methoxide as a base. Yields in this instance were only 15-20%. The use of Mannich bases (66-70), and an increase in the sophistication of reaction techniques, raised the yield to 42%. Employing



catalytic amount of base (71,72) was found to minimize the unwanted side reaction of self-condensation of the methyl vinyl ketone and yields of 61 were increased to a consistent 55-60%.

It was expected that the yields of the condensation product of 2,3-dimethylcyclohexanone (62) with methyl vinyl ketone would be analogous to those discussed above. Berger, Frank-Neumann, and Ourisson (73a) discovered that this was not the case, as they realized yields of only 15% (73b) in this particular reaction. Furthermore, octalone 63 consisted of a mixture of two epimers in a ratio of approximately 3:2 (cis/trans).

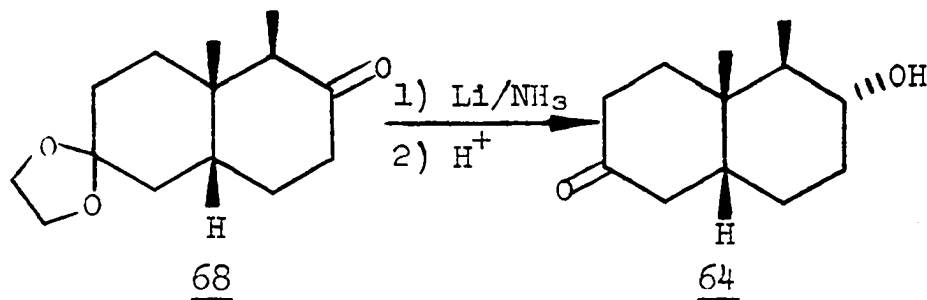
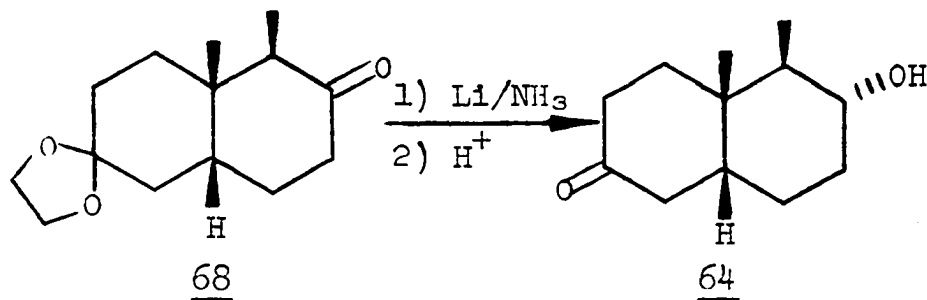
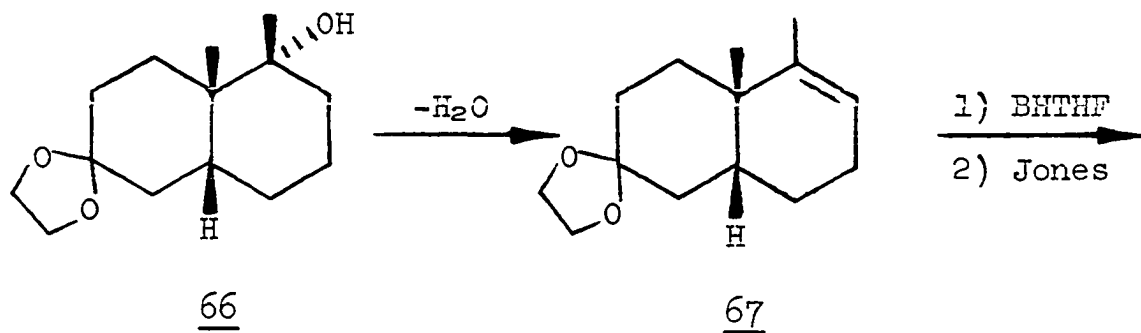
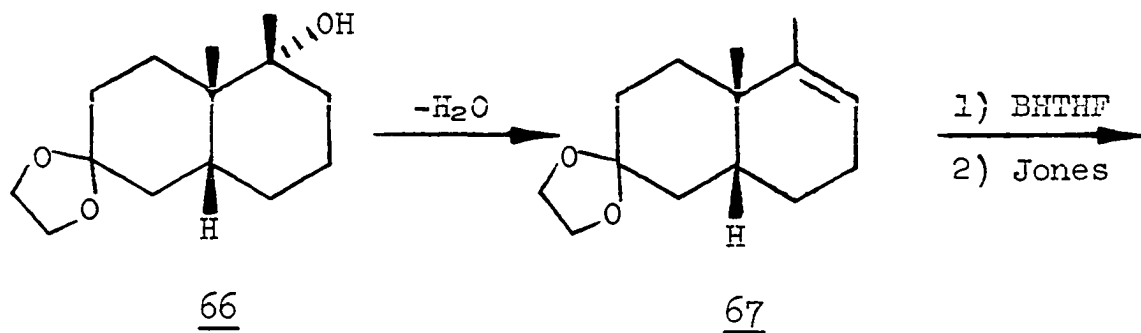
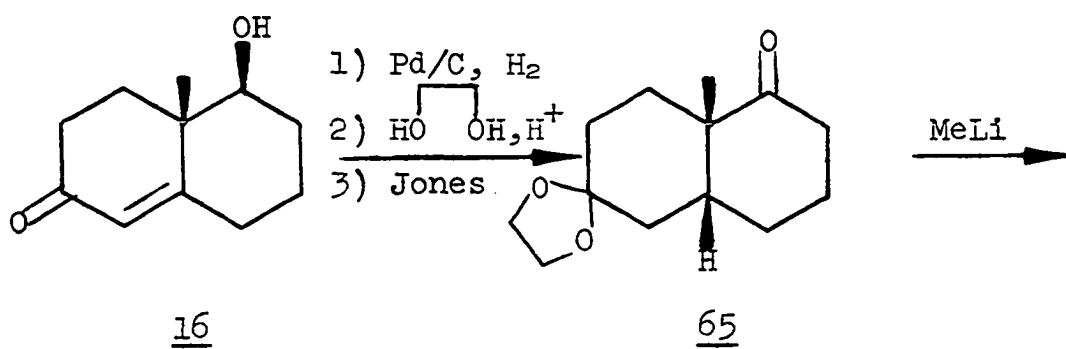
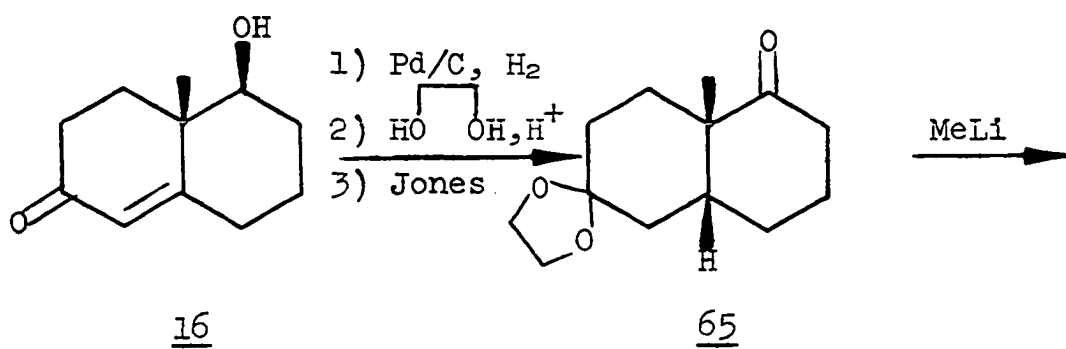
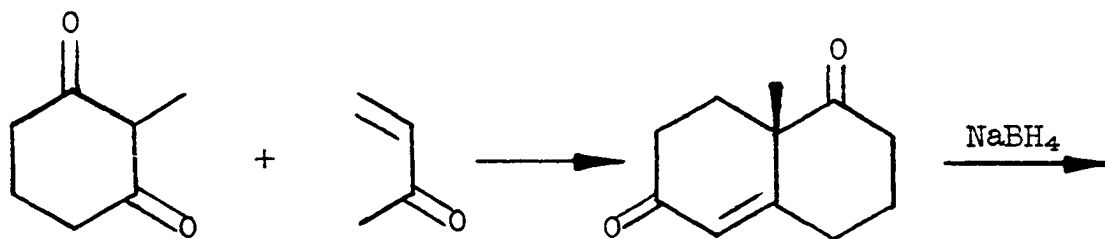


It was quite evident that for a practical synthesis of octalone 63c or 63t, a different synthetic procedure was needed.

To circumvent this problem some workers have condensed methylcyclohexanone with methyl vinyl ketone first, and then introduced the second methyl group in a subsequent series of reactions. Such a synthetic scheme was utilized by Church, Ireland, and Shridhar (74) in their synthesis of cis-3,4,4a,5,6,7,8,8a-octahydro-t-6-hydroxy-r-4a,c-5-dimethyl-2(1H)-naphthalenone (64). Coincidentally, their objective in this synthesis was to develop a potentially useful intermediate for the total synthesis of petasin (10). The sequence is outlined on Chart II.

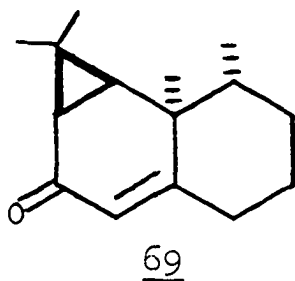
The starting material in this scheme is octalone 16 which was obtained by the condensation of 2-methylcyclohexane-1,3-dione with methyl vinyl ketone followed by a selective reduction with sodium borohydride. Decalone 65 was

Chart II



prepared by catalytic reduction to the cis-ring system, ketalization of the saturated ketone, and oxidation of the alcohol with Jones reagent (75). Treatment of the cis-ketoketal 65 with methyllithium effected the introduction of the second methyl group and afforded a 65% yield of the crystalline alcohol 66, which was readily dehydrated to olefin 67. The next step involved the use of a hydroboration reaction developed by Brown et al. (76). When olefin 67 was treated with boron hydride tetrahydrofuranate followed by alkaline hydrogen peroxide, and the resulting alcohol was oxidized with Jones reagent (75), there resulted a 71% yield of the cis-decalone 68. Reduction of decalone 68 with lithium in liquid ammonia, followed by ketal cleavage, afforded hydroxyketone 64, which these authors described as the key intermediate in the synthesis of petasin (10). Unfortunately, the sequence was carried no farther as there apparently was no practical means for the introduction of a double bond α, β to the carbonyl group.

Piers and coworkers (77) desired dimethyl octalone 63c as a starting material for their synthetic proof of the stereochemistry of the sesquiterpene aristolone (69). They attempted the Robinson annulation of 2,3-dimethylcyclohexanone (62) with both methyl vinyl ketone and 4-diethylamino-2-butanone, but were unable to obtain the alkylated material in any better than 15% yield.

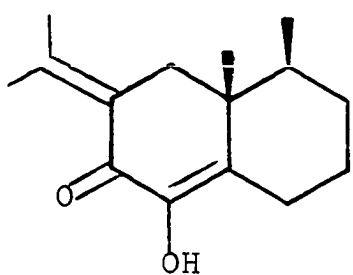
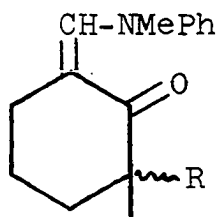


Since Piers was interested only in the cis isomer, that meant a yield of approximately 9% plus some laborious glc work in order to separate the two epimers. This poor overall yield prompted a search for a better synthetic route. As an alternative method for the preparation of octalone 63c, Piers and his collaborators (77,78) developed the scheme outlined in Chart III.

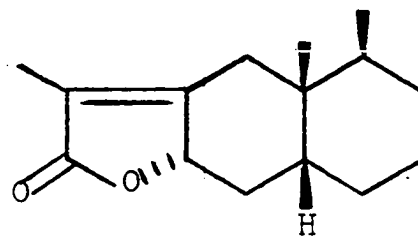
In essence, a substituted 2,3-dimethylcyclohexanone was prepared in which alkylation could be forced to occur at C-2. Alkylation of the blocked ketone 70 with ethyl 3-bromopropanoate produced, in 86% yield, a mixture of keto esters 71. The n-butylthiomethylene blocking group was removed, with concomitant ester hydrolysis, in the normal manner (potassium hydroxide in hot, aqueous diethylene glycol). The product, a mixture of keto acids 72 was obtained in 90% yield. Lactonization of 72 with acetic anhydride and sodium acetate afforded a 9:1 mixture of 73c and 73t in 85% yield. The desired epimer, 73c was obtained in 80% yield upon

recrystallization from hexane. Treatment of 73c with methyllithium at -25° for 1.75 hours, followed by a base-catalyzed aldol condensation, afforded the cis-dimethyl octalone 63c in 70% yield. The overall yield of pure, cis-octalone 63c, based on 2,3-dimethylcyclohexanone (62), was improved from 9% to approximately 30%.

Piers procedure for making 4,4a,5,6,7,8-hexahydro-p-4a, c-5-dimethyl-2(3H)-naphthalenone (63c) has been incorporated into the synthesis of several natural products. The total synthesis of racemic fukinone (41) and of (+)-hydroxy-eremophilone (74) by Pinder and Torrence (79) exemplifies the use of octalone 63c. These workers, however, used the methylanilinomethylene compound 75 as a synthetic intermediate rather than the n-butylthiomethylene analogue 70, with no significant changes in yields. Piers et al. (80,81) have also used octalone 63c for the stereoselective synthesis of (+)-fukinone (41) and (+)-eremophilenolide (43).

74

R = H

R = $\text{CH}_2\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5$ 7543

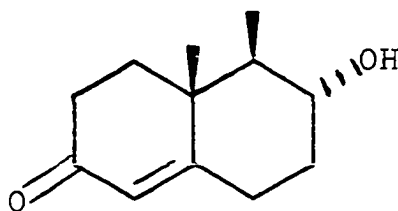
RESULTS AND DISCUSSION

Introduction

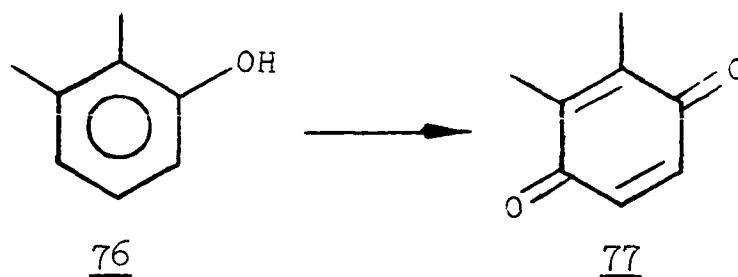
The primary intention of our research was the preparation of a viable intermediate conducive to the synthesis of petasin sesquiterpenes. Des-isopropylidenepetasol (15) was deemed to be such a suitable precursor, and its synthesis is discussed in the first part of this section.

The second part of the discussion is concerned with the adaptability of synthon 15 for the preparation of petasin (10). Although petasin (10) itself was not made, the approaches towards its synthesis will be thoroughly reviewed.

In the final part of this section we shall elaborate upon the total synthesis of the natural product (\pm)-isopetasin (39).

Synthesis of (\pm)-Des-isopropylidenepetasol (15)15

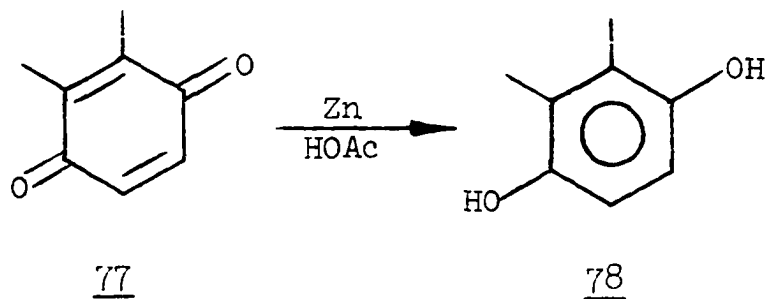
Our initial synthetic goal was to prepare a suitably substituted dimethylcyclohexanone which could be condensed with methyl vinyl ketone to give the desired octalone, des-isopropylidenepepasol (15). The starting material selected for this synthesis was the commercially available 2,3-dimethylphenol (76). Diazotization of 76 with p-benzene diazonium sulfonate, followed by acid hydrolysis, oxidation, and steam distillation afforded benzoquinone 77 in 55% yield (82). Yields could be improved to 75% when the intermediary aminophenol was added in small portions and the oxidant replaced after each addition (see the experimental section for details).



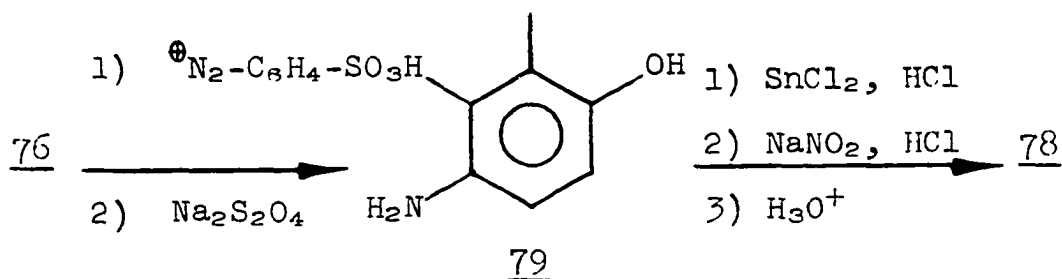
A one-step procedure employing chromyl chloride as the oxidizing agent has been reported by Strickson and Leigh (83) for the general conversion of phenols to benzoquinones. Unfortunately, when 2,3-dimethylphenol (76) was treated with chromyl chloride, 77 was formed in only a 13% yield.

Teuber and Rau (84) developed a facile procedure for the synthesis of benzoquinone 77 by reacting 2,3-dimethylphenol (76) with "Fremy's salt". Although this reaction gave consistent yields of 75%, the high cost of "Fremy's salt" made its use, in the early stages of a synthetic sequence, prohibitive.

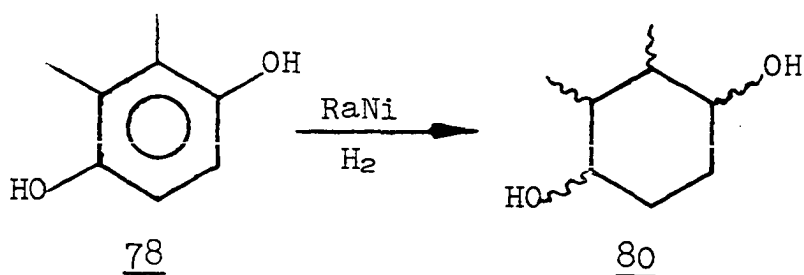
Attempted catalytic reduction of benzoquinone 77 with either Rh/Al₂O₃ or W-2 Raney nickel (85) afforded only intractable material. The quinone 77 was therefore chemically reduced in 95% yield with zinc in acetic acid (86). The resultant hydroquinone 78 has also been prepared directly from 2,3-dimethylphenol (76) (87). Yields are



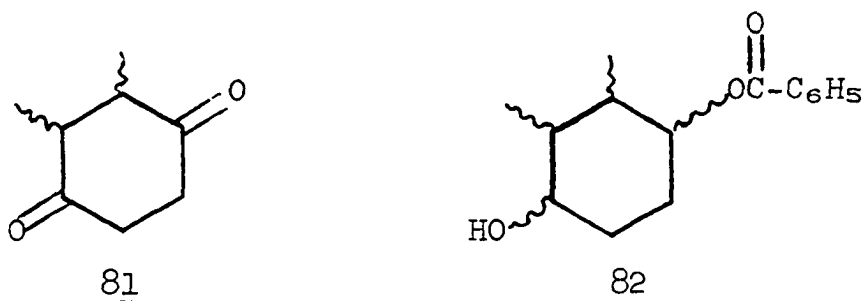
less than 10%, however, as the aminophenol 79 is extremely unstable being readily converted to intractable material in the presence of air and moisture. Further reduction of 78



with W-2 Raney nickel (85) for 96 hours at 170° and 2000 psi of hydrogen afforded diol 80 in 91% yield.



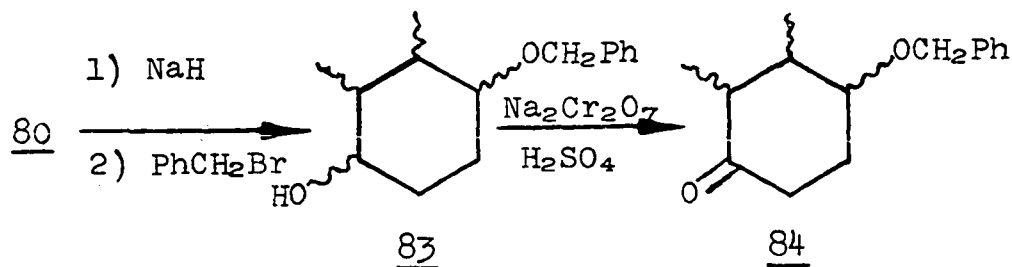
At this point in the sequence a need arose to differentiate the two alcohol functions while simultaneously protecting one hydroxyl moiety. A selective oxidation, according to the published procedure of Stolow and Groom (88), of 80 was attempted with Jones reagent (75), however the major products recovered were diketone 81 along with unchanged starting material. Benzoyl chloride was then used



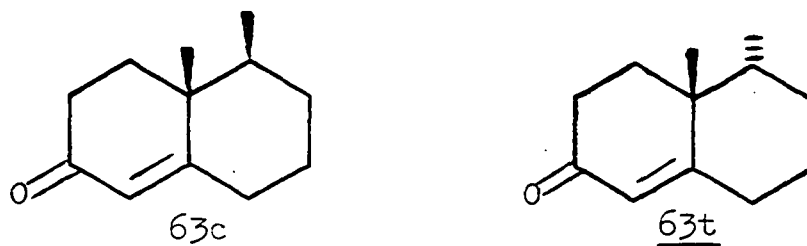
to try to selectively benzoylate the diol (89). Although benzoyl alcohol 82 could be obtained in 62.5% yield, its use was pursued no further as it was found not to be stable to the basic conditions present in subsequent reactions.

Since many protecting groups are not compatible in both acidic and basic media, it became necessary to employ a blocking group which was stable to these reaction conditions and yet was easy to remove. An ideal blocking group appeared to be the benzyl function, which could later be removed by catalytic hydrogenation. Initial trials with diol 80,

utilizing *n*-butyllithium and benzyl bromide as reagents, afforded alcohol 83 in only 30-35% yields. The mono-sodium salt of diol 80, on the other hand, gave benzyloxy alcohol 83 in 60% yield. Oxidation of 83 with a sodium dichromate solution in ether gave benzyloxy ketone 84 (82%).

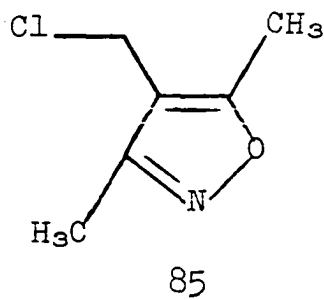


Berger, Frank-Neumann, and Ourisson (73a) have reported that the condensation of 2,3-dimethylcyclohexanone (62) with methyl vinyl ketone gives a mixture of *cis*- and *trans*-octalones 63c and 63t (3:2 mixture), however the reaction affords bicyclic material in very poor yield (73b).



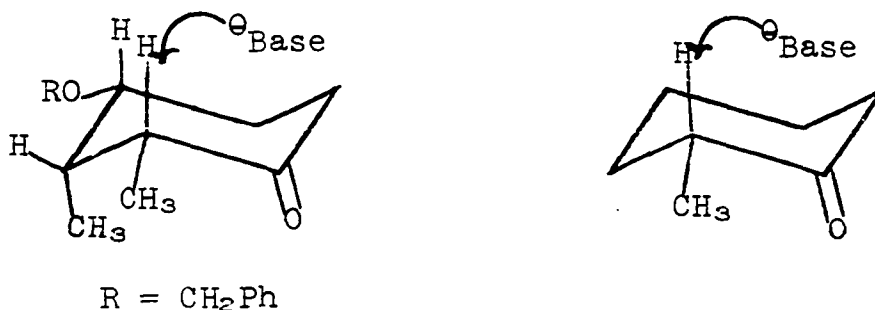
Based on these results, we anticipated similar yields of dimethyl octalone when using ketone 84. Unfortunately, attempts to effect the annulation of benzyloxyketone 84 with methyl vinyl ketone (potassium hydroxide, ethanol) under a variety of conditions (90), gave no trace of the desired bicyclic material. The use of other solvents such as dioxane, dimethylformamide, or dimethyl sulfoxide with sodium hydride also proved unfruitful (91).

The success of Stork *et al.* (92) and Ohashi *et al.* (93) with substituted 4-halomethylisoxazoles as annulating agents, prompted us to try the alkylation of 84 with 4-chloromethyl-3,5-dimethylisoxazole (85). The product, however, was



derived from alkylation at C-6, rather than at the desired methyl carbon, C-2. The ketones which Stork and Ohashi alkylated had an α -hydrogen that was much more acidic than the hydrogen at C-2 in 84. Blocking the C-6 methylene group of 84 [iso-propoxymethylene blocking group (94)] results in the complete failure of the alkylation.

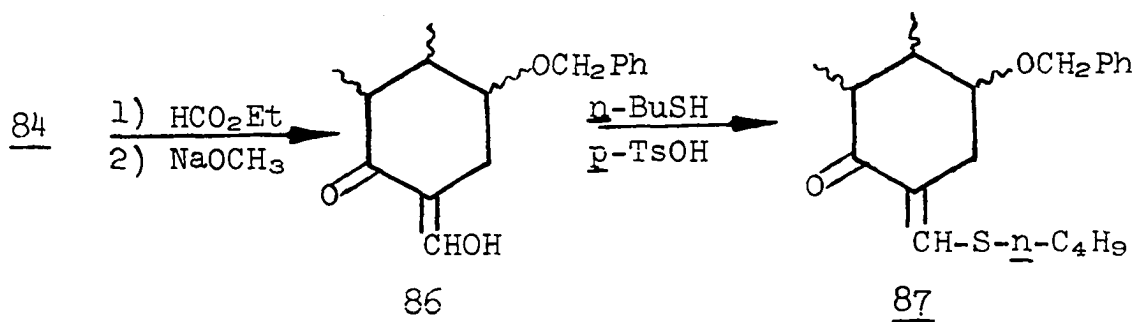
At this juncture, it seemed apparent that the C-2 hydrogen in 84 is either less activated or more sterically hindered than the C-2 hydrogen in 2-methylcyclohexanone. This is substantiated by the fact that yields of 50-60% are routinely obtained with 2-methylcyclohexanone, while ketone 84 gives no alkylated product when treated with methyl vinyl ketone. This difference can be attributed partially to the steric crowding caused by the additional methyl group and benzyl ether in 84. These substituents may well hinder the approach of the base used in forming the enolate. It seems unlikely, however, that this could account for a decrease in yield of 60%. The major component of 84, the cis isomer [approximately 80%, (95)] will probably have the stereochemistry shown below. Proton removal in this



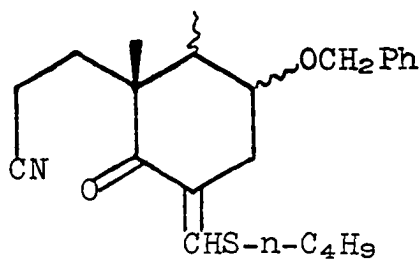
case should be no less favorable than in 2-methylcyclohexanone. A reasonable explanation for the wide variance in yields during alkylation of 2-methylcyclohexanone and ketone

84 is currently unknown.

In an attempt to obviate this alkylation problem, the n-butylthiomethylene blocking group (96) was investigated. Treatment of benzyloxy ketone 84 with sodium methoxide and ethyl formate in benzene afforded hydroxymethylene ketone 86 in 75% yield (94). Reaction of 86 with 1-butanethiol and *p*-toluenesulfonic acid in benzene readily gave n-butylthiomethylene ketone 87 in 96% yield. The addition of methyl

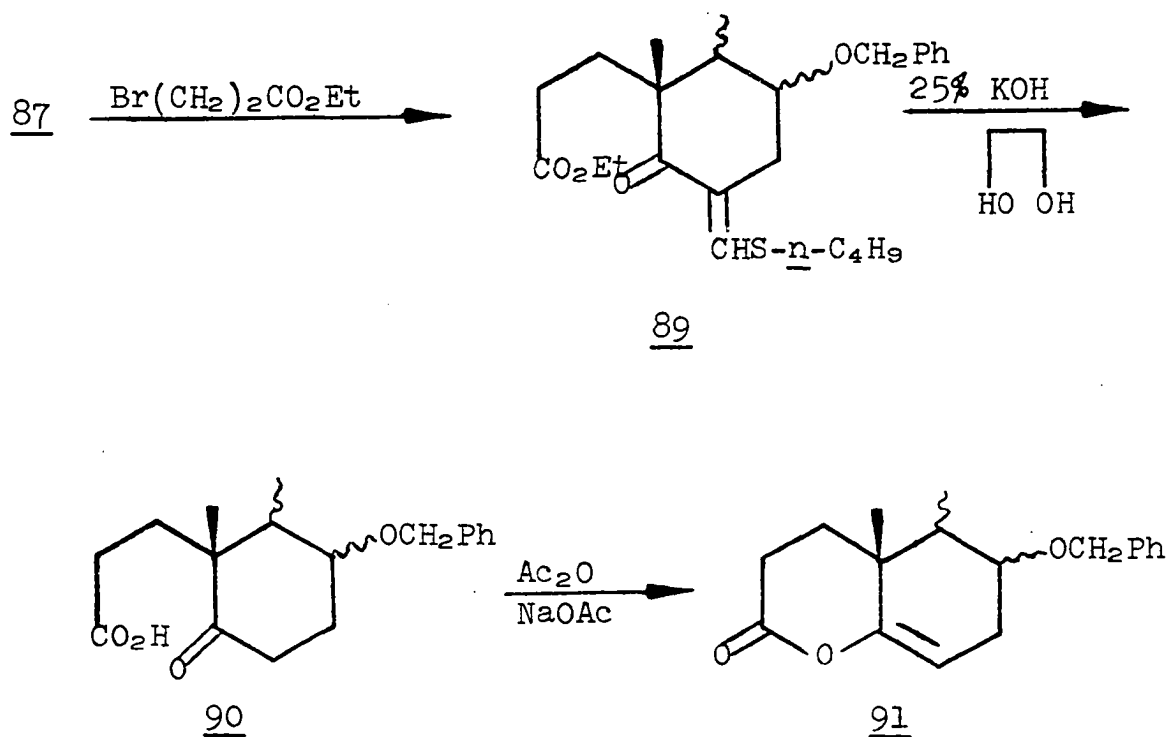


vinyl ketone to 87 gave only intractable material. Condensation of 87 with acrylonitrile resulted in the formation of addition product 88, but it was obtained only in poor yields (5-18%).

88

Piers and his collaborators (78) have recently reported the use of ethyl 3-bromopropanoate as an alkylating agent in systems somewhat analogous to 87. Thus, reaction of 87 with ethyl 3-bromopropanoate and potassium *t*-butoxide in *t*-butyl alcohol afforded, in high yield, a stereoisomeric mixture of keto esters 89. At this point in the synthetic sequence, the relative stereochemistry of the benzyloxy and methyl group was unknown and irrelevant. No attempt was made to characterize or separate these isomers, as it was intended that future stereoselective reactions would afford the desired stereochemistry depicted in structure 15.

The *n*-butylthiomethylene blocking group of 89 was removed, with concomitant ester hydrolysis, in 25% aqueous potassium hydroxide and ethylene glycol. A mixture of crude keto acids 90 was obtained in 86% yield. This mixture was



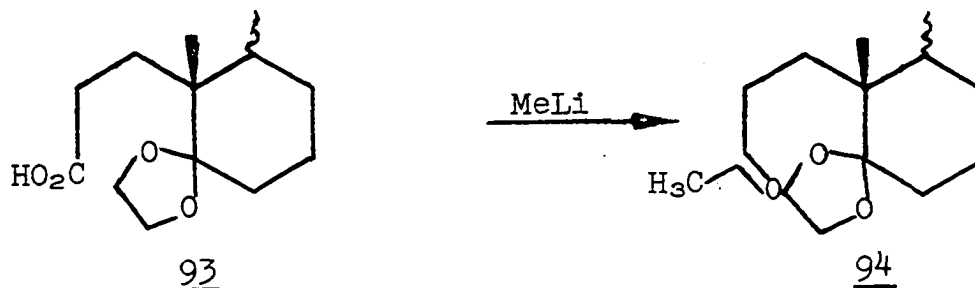
refluxed in acetic anhydride containing sodium acetate affording, in 60% yield (based on 84), a viscous liquid consisting of a mixture of isomeric lactones 91. One isomer could readily be obtained in 60% yield from the mixture by careful crystallization from *n*-hexane. The stereochemistry of this white solid was not determined, but spectral and chromatographic data indicated that it was stereochemically homogeneous. Solid lactone 91 was extremely labile, being converted to acid 90 and two unidentified materials in the

presence of air and moisture.

Several modes of annulation via enol lactones have been cited in the literature (97-99). Treatment of enol lactone 91 with methyllithium, for example, gave octalone 92 in low and non-reproducible yields (typically 5-25%). A preponderance of alcohol-containing product was obtained in this reaction, presumably due to "di-addition" of methyllithium to enol lactone 91. Milder reaction conditions (shorter reaction times and/or lower temperatures) resulted in the recovery of hydrolyzed starting material (i.e., keto acid 90).

Henrick and his coworkers (97) have reported the reaction of phosphonate anions with enol lactones in the preparation of cyclic α, β -unsaturated ketones. Exposure of lactone 91 to one equivalent of methylene-triphenylphosphorane in dry tetrahydrofuran, followed by treatment of the resultant oil to the basic conditions of an aldol condensation, afforded octalone 92 in 26% yield. Due to the low yield, this procedure offered no improvement over the one employing methyllithium described above.

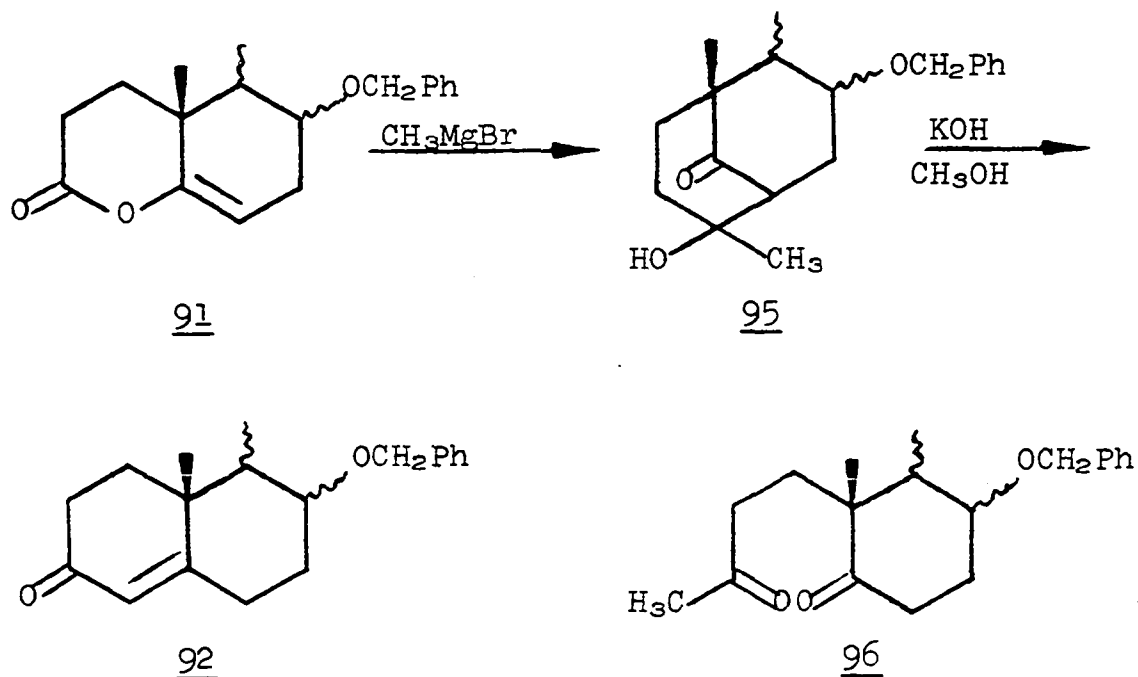
According to the original procedure developed by Gilman and Van Ess (100), treatment of acetal 93 [obtained by using the scheme of Piers et al. (77)] with excess methyllithium gave methyl ketone 94. Removal of the acetal moiety under acidic conditions followed by self-condensation of the resultant methyl ketone, gave octalone 63 in 5 to 20% yields.



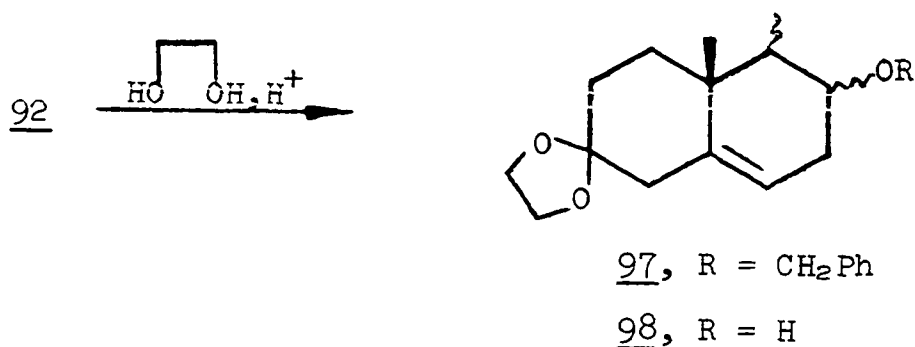
This variability is common for reactions which involve methyllithium and has generally been attributed to the varying degrees of decomposition of the stock solution. In any case, due to the relatively low and non-reproducible yields obtained in the preparation of ketone 94, an alternative method was investigated.

The reaction of 91 with methylmagnesium bromide (101) gave none of the undesired alcohol by-product prevalent with methyllithium, and gave the desired material in excellent yield. Thus, treatment of enol lactone 91 with methylmagnesium bromide in dry ether and benzene at -50° for 1.5 hours, followed by acidic hydrolysis, afforded hydroxy ketone 95 in 98% crude yield (99). Structure 95 is proposed from spectral data which indicates the presence of an alcohol and carbonyl function, as well as a singlet at δ 1.28 in the nmr spectrum, indicative of a tertiary methyl group. Significantly, no methyl ketone absorption is seen in the nmr

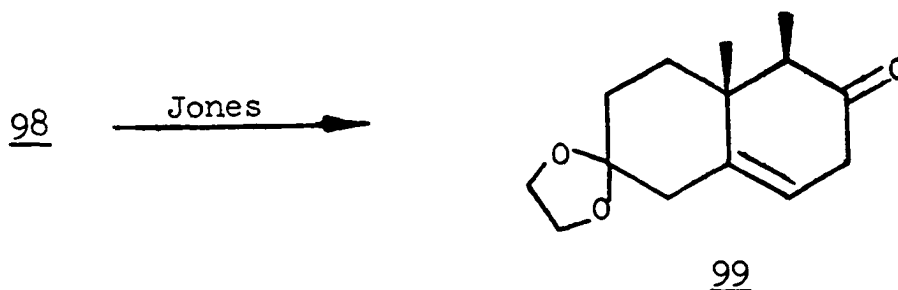
spectrum of 95, thus precluding a structure such as methyl ketone 96. Results obtained by Fujimoto and coworkers (102) with phenylmagnesium bromide and several enol lactones corroborate the proposed structure 95. Base-catalyzed opening, followed by re-cyclization, and dehydration of 95 gave, in addition to a small amount (12%) of keto acid 90, octalone 92 in 85% yield.



Octalone 92 was constructed in such a manner that the C-5 methyl group was potentially epimerizable. We felt that conversion of the benzyloxy group to a ketone, followed by treatment with base should affix the C-5 methyl group in its most stable configuration; i.e., equatorial and thus cis to the angular methyl group. To this end, the α,β -unsaturated ketone 92 was protected by reaction with 1,2-ethanediol and *p*-toluenesulfonic acid in benzene to give a mixture of acetal 97 and unchanged octalone 92 (9:1 ratio by comparison of vinyl protons in the nmr spectrum). The protecting benzyl ether could now be cleaved to alcohol 98 by reduction with sodium, ammonia, and ethanol (81% yield based on 92).

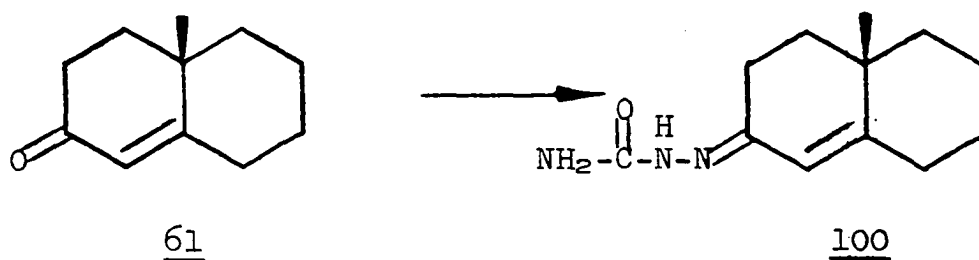


Alcohol 98 was readily oxidized with Jones reagent (75) to give ketone 99 in good yield. The nmr spectrum of ketone 99 indicated no loss of the acetal group under these slightly acidic conditions.



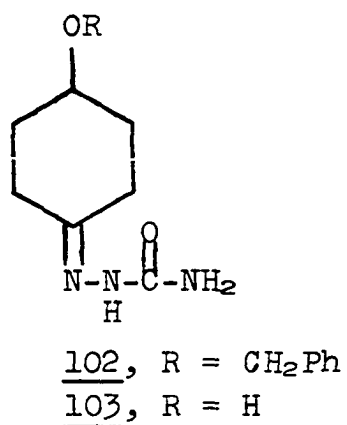
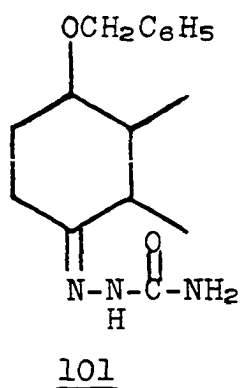
Treatment of ketone 99 with base under an epimerizing environment resulted, unfortunately, in migration of the double bond into conjugation with the carbonyl group. It had been hoped that such a migration would not be a problem, owing to the greater stability in some systems (103), of a tri-substituted double bond as opposed to a conjugated di-substituted double bond.

The aforementioned difficulty would not exist if the carbonyl group in 92 were protected with a group which does not enhance double bond migration. A potentially useful protecting group is the semicarbazone derivative of the α,β -unsaturated ketone. Treatment of 4,4a,5,6,7,8-hexahydro-4a-methyl-2(3H)-naphthalenone (61) with semicarbazide hydrochloride afforded semicarbazone 100 in 73% yield.



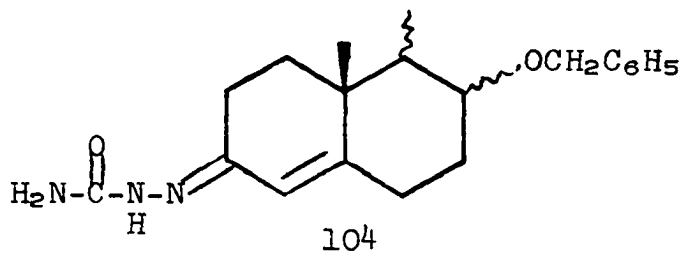
The semicarbazone derivative 100 was found to be impervious to lithium in ammonia, the conditions under which we hoped to cleave the benzyl ether in 92.

Semicarbazones 101 and 102 were then prepared to insure the survival of the semicarbazone group under conditions known to cleave the benzyl ether. When 101 and 102 were reacted with lithium in ammonia, however, only starting material



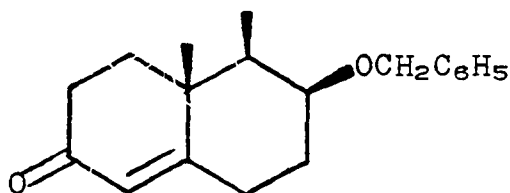
was recovered. The semicarbazones 101 and 102 were not soluble in the typical solvents used for "Birch-type" reductions. Employment of a sodium-ammonia-ethanol mixture was also unsuccessful.

The catalytic reduction of 102 (Pd/C, H₂) afforded alcohol 103 in virtually quantitative yields. For our purposes, this cleavage would be profitable only if it were much faster than the reduction of the endo-cyclic double bond in a compound such as 104. Semicarbazone 104 was prepared from



octalone 92 in 71% yield. This derivative was hydrogenated over Pd/C until the uptake of one equivalent of hydrogen was recorded. An examination of the product revealed that reduction of the endo-cyclic double bond had occurred much faster than hydrogenolysis of the benzyl ether. Similar results were obtained with hydrogenation of octalone 92. At this stage, the work with semicarbazones was abandoned in favor of a more profitable approach.

We believed that the major isomer in the mixture of octalones 92 is the one with all substituents cis (i.e. 92c).

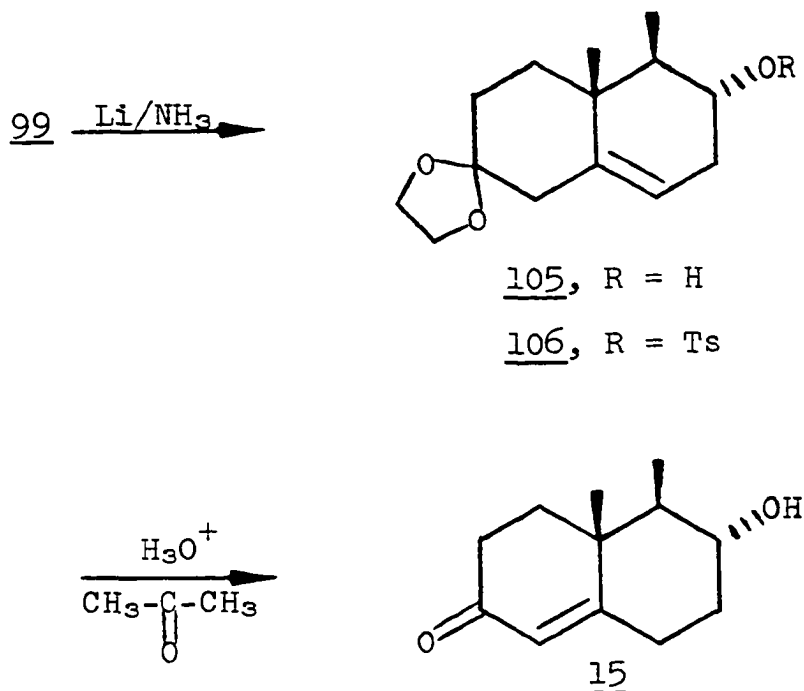


92c

This opinion is somewhat confirmed by the findings of Piers *et al.* (77), in which the cis isomer of 63 predominates over the trans, 9:1, and Ulery and Richards (95), who have found that the reduction of 2,3-dimethylphenol (76) leads to a mixture of isomers, with 82% of the mixture being the all cis diastereomer. There are also precedents in the literature (104) which indicate that the conditions of the Jones oxidation (75) may have been acidic enough to cause epimerization of the C-5 methyl group. Indeed, gas phase chromatography indicated that ketone 99 was nearly homogeneous, while alcohol 98 was not.

With the above facts in mind, ketone 99 was reduced with lithium and ammonia to stereoselectively afford the more stable alcohol 105 (74). The ethylenedioxy protecting group was removed by acidic hydrolysis (acetone, water, and *p*-toluenesulfonic acid), giving crystalline des-isopropylidene-

petasol (15) in 46.4% yield (based on 99). Nmr and ir spectra of this material are exhibited in Figure 1.

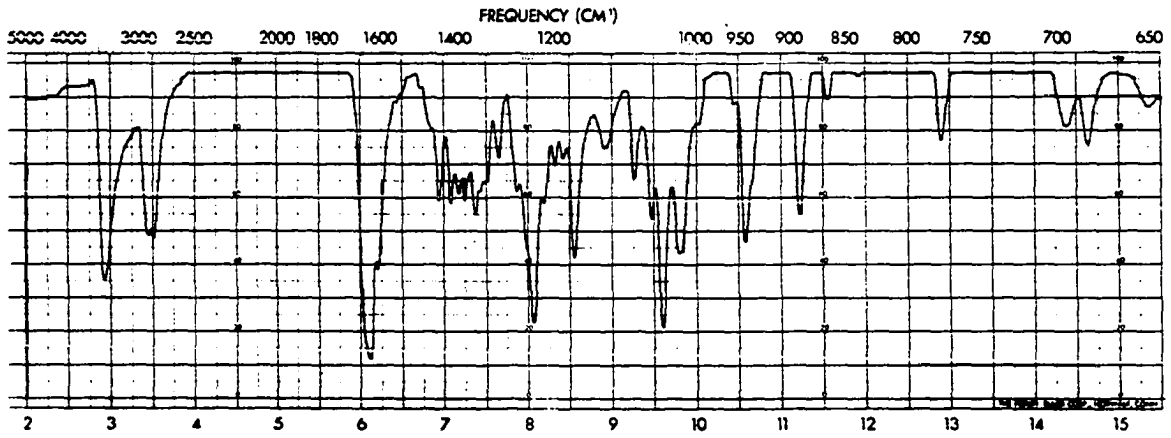
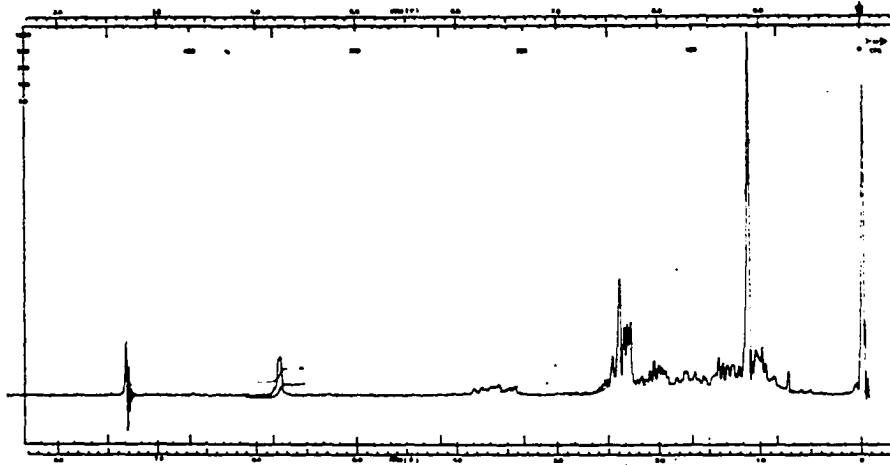


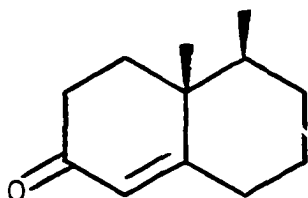
In order to ascertain the relative stereochemistry of the methyl groups in 105, it was converted to octalone 63c of known stereochemistry. Treatment of hydroxyacetal 105 with *p*-toluenesulfonic chloride in pyridine gave tosylate 106, which was reduced with lithium aluminum hydride in refluxing ether. The major product, isolated by column chromatography, was shown to be dimethyl octalone 63c by comparison of its ir, nmr, and its chromatographic mobility with an authentic sample prepared by an independent route. It would seem,

Figure 1. Spectra of des-isopropylidenepetasol

Top: 60 MHz nmr spectrum of des-isopropylidenepetasol

Bottom: Infrared spectrum of des-isopropylidenepetasol



63c

therefore, that either epimerization of the C-5 methyl group occurs during the oxidation of alcohol 98 or that alkylation of ketone 88 results predominantly in a cis-dimethylester which is carried through the synthetic sequence as the major isomer.

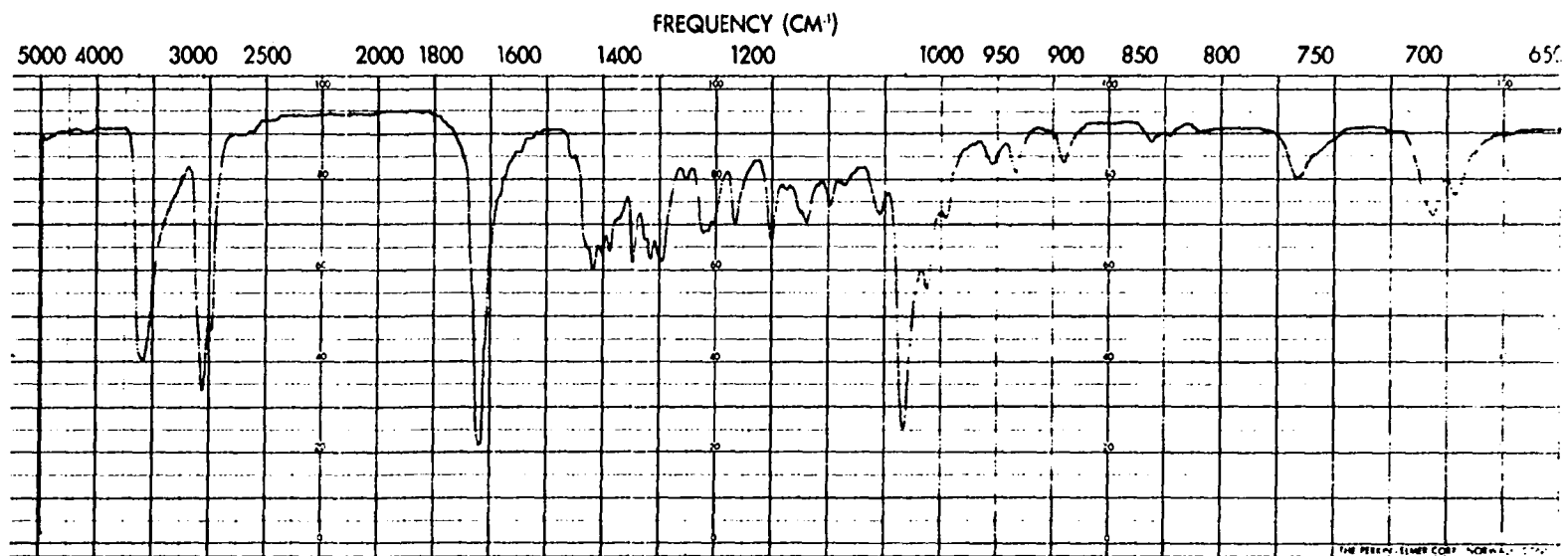
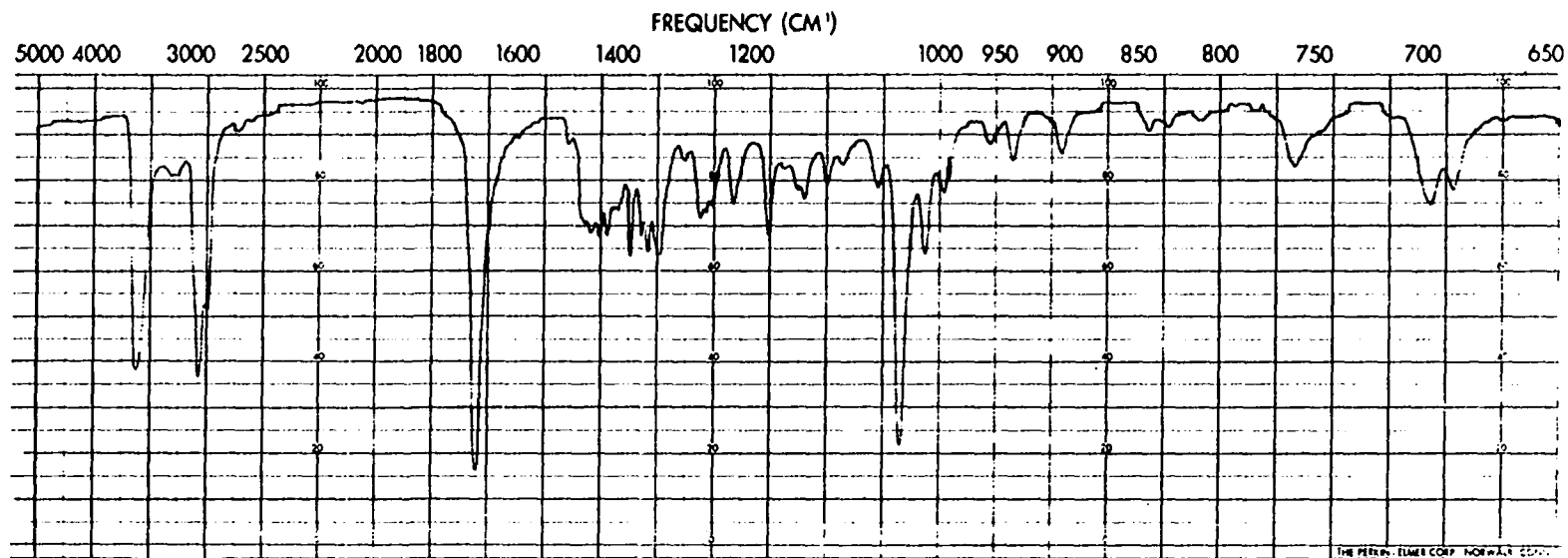
The stereochemistry of all asymmetric centers in hydroxyketone 15 was confirmed by catalytic hydrogenation (palladized carbon in absolute ethanol) giving a white, crystalline material which was identical by ir, nmr, and mixed melting point with an authentic sample of 107.¹ The ir spectrum of synthetic 107, shown in Figure 2-top, compares quite favorably with the ir spectrum of the authentic material displayed in Figure 2-bottom.

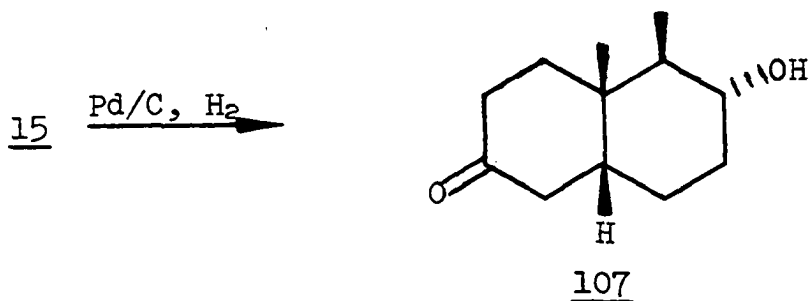
¹We are very grateful to Professor R. E. Ireland for a small sample of this compound.

Figure 2. Infrared spectrum of cis-3,4,4a,5,6,7,8,8a-octahydro-t-6-hydroxy-r-4a,c-5-dimethyl-2(1H)-naphthalone (107)

Top: Synthetic material

Bottom: Authentic sample



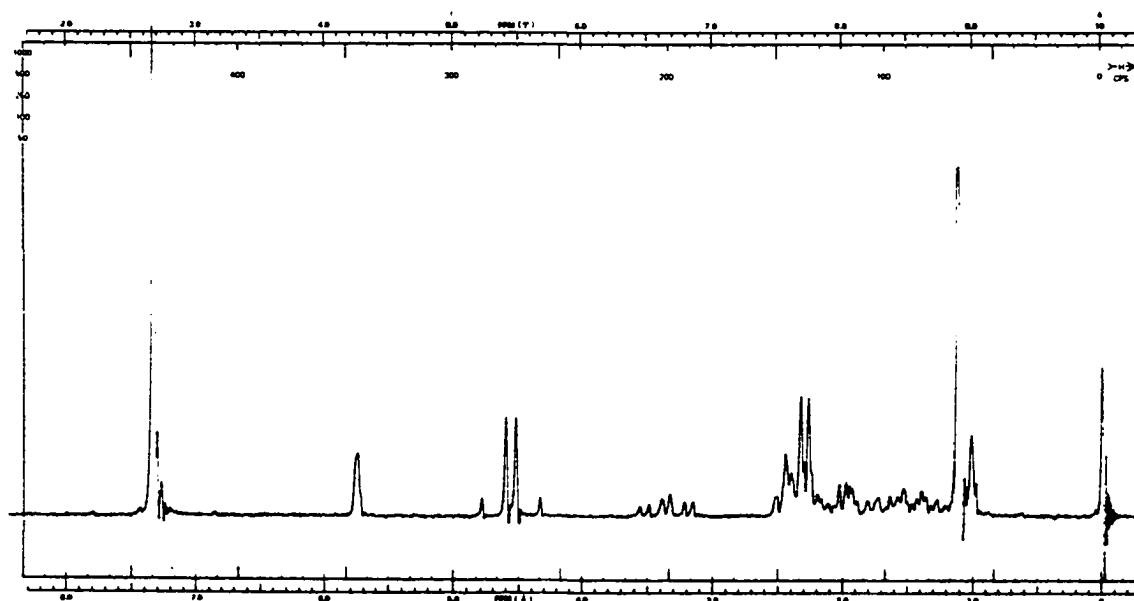
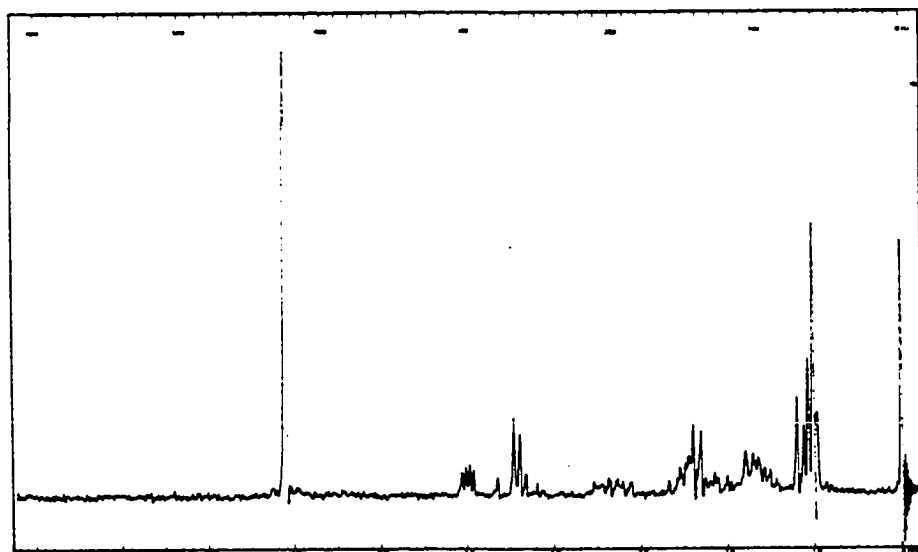


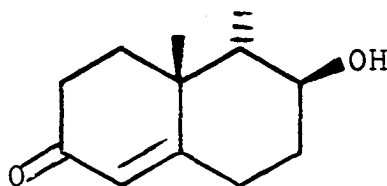
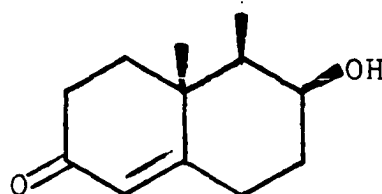
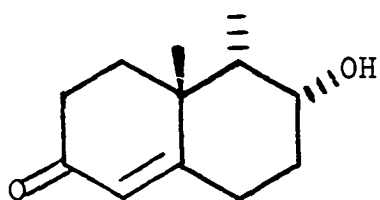
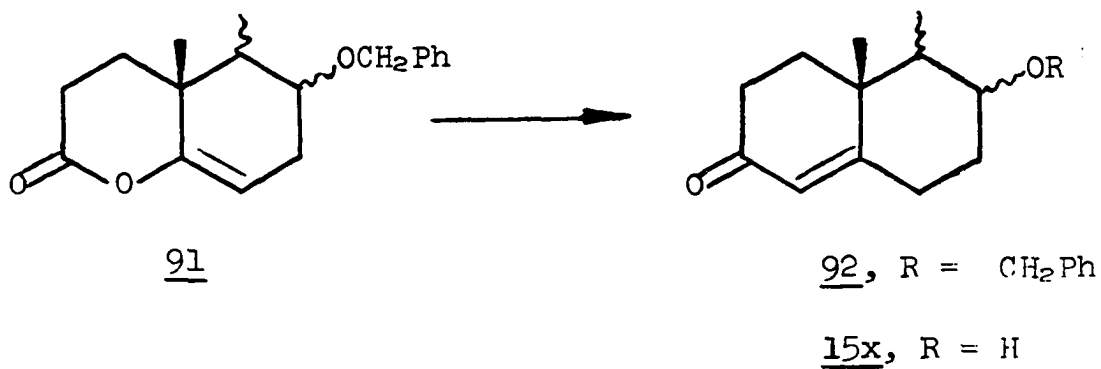
The above comparison authenticates the stereochemistry of 15, and therefore makes it much easier to determine the configuration of the asymmetric centers in the precursors of this compound. As noted earlier in the text, approximately 60% of lactone 91 could be crystallized from hexane as a homogeneous solid. This solid was treated with methylmagnesium bromide (101) and then potassium hydroxide in methanol to give octalone 92 as a white solid. The nmr spectra of lactone 91 and octalone 92 are reproduced in Figure 3. The acetal of 92 was prepared, the benzyl ether cleaved, and the acetal removed to afford octalone 15x, a diastereomer of 15. Nmr, ir, melting point, and glc data indicated that solid 15x was not identical with des-isopropylidenepetasol (15). Thus, there are three possible stereoisomers for 15x:

Figure 3. Nmr Spectra

Top: 60 MHz nmr spectrum of 6-benzyloxy-
4a,5,6,7-tetrahydro-4a,5-dimethyl-
hydrocoumarin (91)

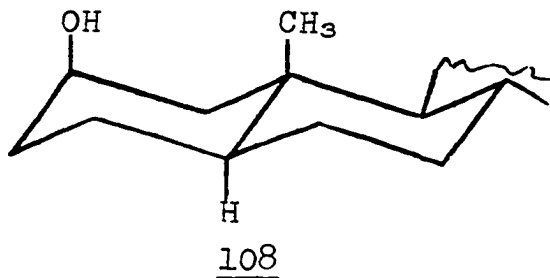
Bottom: 60 MHz nmr spectrum of 6-benzyloxy-
4,4a,5,6,7,8-hexahydro-4a,5-dimethyl-
2(3H)-naphthalenone (92)





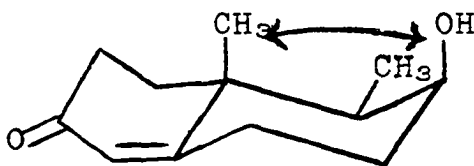
Wenkert and his coworkers (105) have done some interesting work concerning pyridine-induced solvent shifts in the nmr of hydroxylic compounds. They found that in saturated cyclic systems, methyl groups occupying positions 1,3-diaxial, vicinal, or geminal to a hydroxyl function are

deshielded. In 5-androstane-2,17-diol (108), for example, the chemical shift of the angular methyl group is 0.3 ppm farther upfield in CDCl_3 than in $\text{C}_5\text{D}_5\text{N}$. A 1,3-diaxial

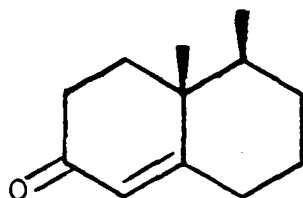


interaction of an angular methyl and an alcohol in steroidal systems, consistently gives chemical shift differences of -0.2 to -0.4 ppm for the angular methyl group (where chemical shift, $\Delta = \delta_{\text{CDCl}_3} - \delta_{\text{C}_5\text{D}_5\text{N}}$). If the alcohol were equatorial, the maximum shift observed was -0.05 ppm.

A shift of -0.18 ppm was observed for alcohol 15x which is slightly lower than the minimum value of -0.2 ppm seen in steroids. The smaller downfield shift was expected as the exo-cyclic double bond in this system tends to increase the inter-nuclear distance between the methyl group and the alcohol. These results eliminated 15a as a possible stereoisomer.



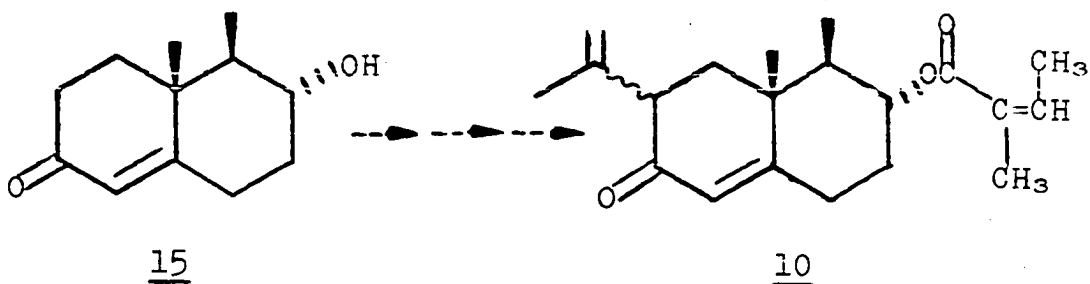
In order to elucidate the relationship between the methyl groups in 15x, the acetal was prepared and attempts were made to convert the hydroxyacetal to the corresponding tosylate. Unfortunately, the only product isolated was the starting alcohol. Since the tosylate of acetal 105 formed quite readily when treated with *p*-toluenesulfonyl chloride, it would seem that compound 15x must have the alcohol located in the more hindered axial configuration. Reaction of 15x with methanesulfonyl chloride afforded the mesylate which was immediately treated with lithium aluminum hydride. The resulting crude oil was chromatographed to yield, as the only identifiable product, octalone 63c (30% from 15x). These

63c

findings substantiate the initial suggestion that solid 15x is identical with the cis isomer 15b, and thus this provides a convenient, stereoselective synthesis of des-isopropylidenepetasol (15).

Attempted Preparation of (\pm)-Petasin (10)

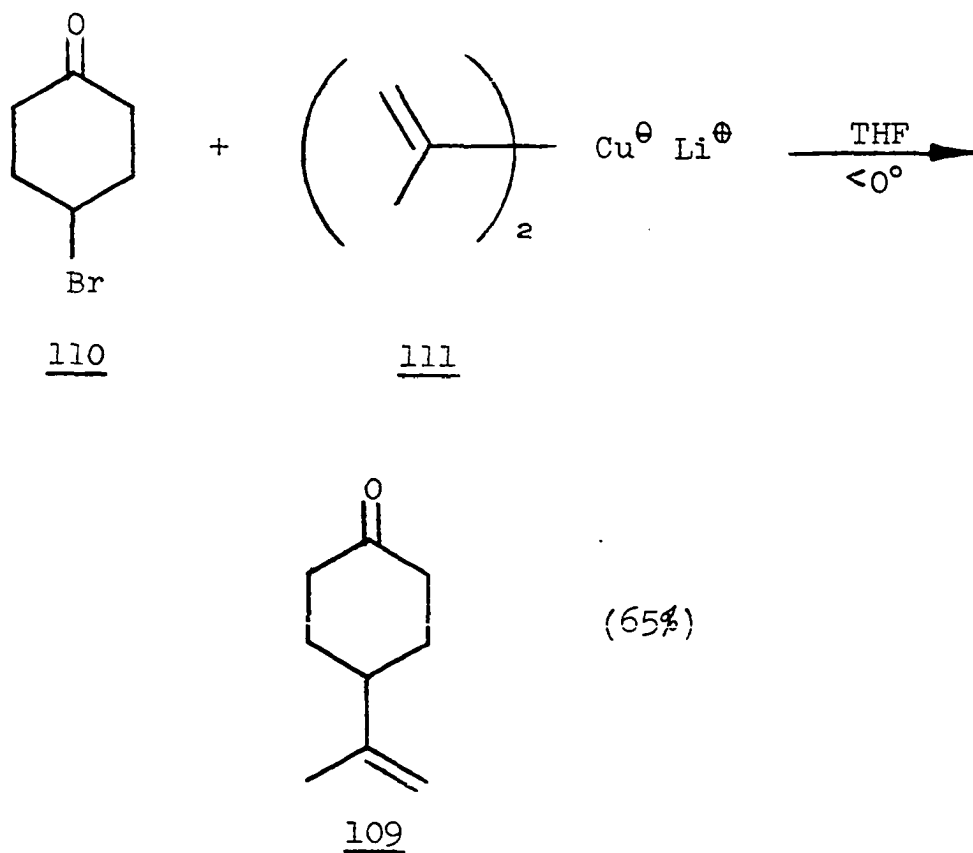
The availability of des-isopropylidenepetasol (15) made the synthesis of petasin (10) much more feasible. Precursor 15 had to be modified only by the introduction of an isopropenyl group "a" to the carbonyl group, followed by esterification of the secondary alcohol with angelic acid.



Due to the "priceless" nature of alcohol 15, all reactions leading towards the introduction of an isopropenyl moiety

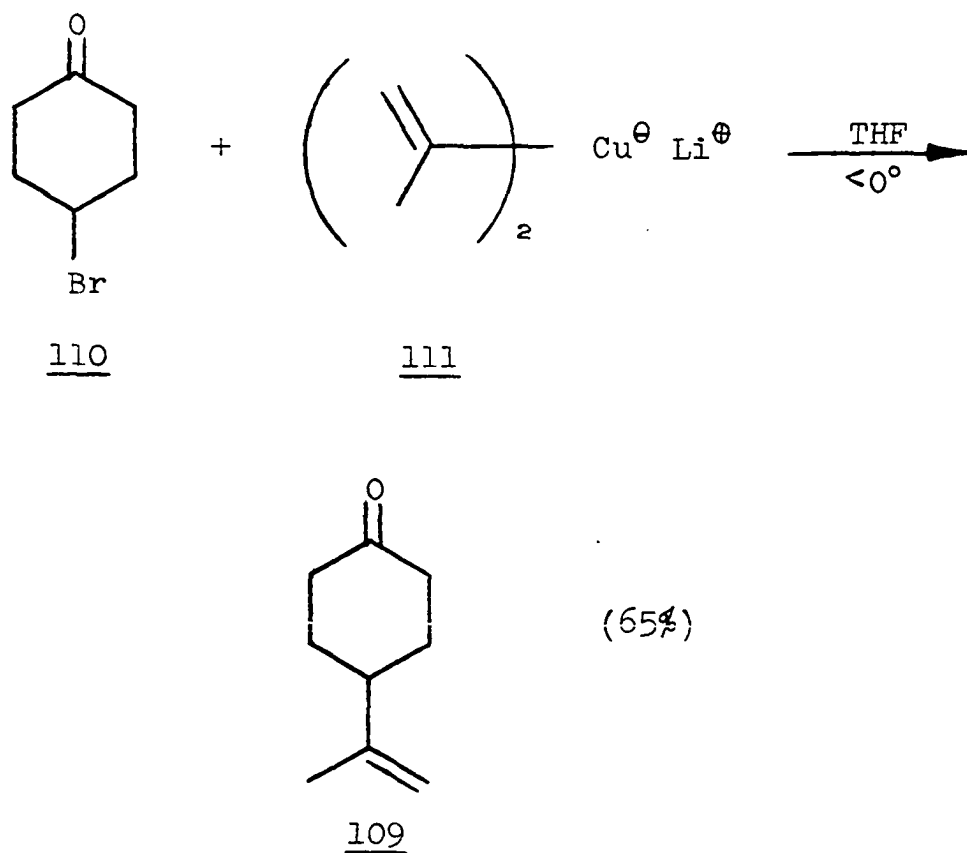
were initially carried out on the more accessible octalones, 61 or 63c.

A convenient route for the synthesis of isopropenylic terpenes was devised by O. P. Vig and his collaborators (106, 107). These workers reported the synthesis of 4-isopropenylcyclohexanone (109) in 65% yield by the reaction of ketobromide 110 with lithium diisopropenyl cuprate (111) in anhydrous tetrahydrofuran at temperatures below 0°.

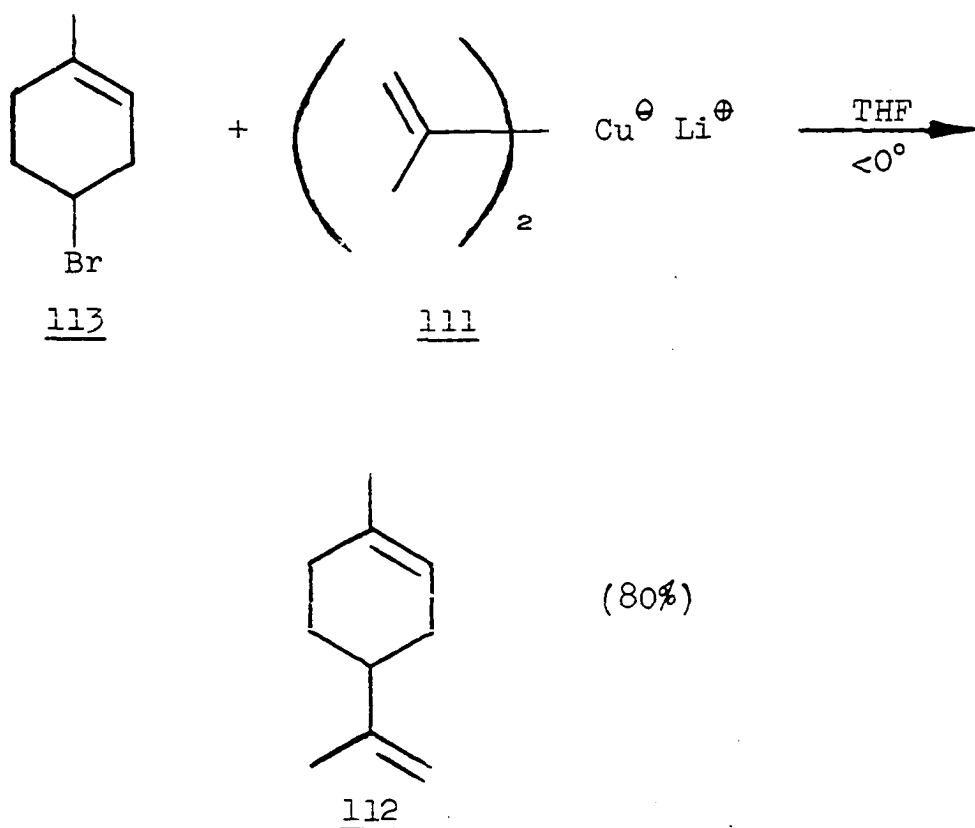


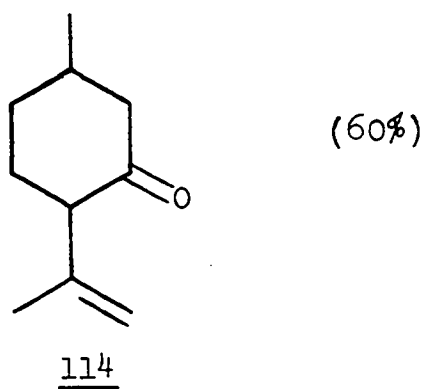
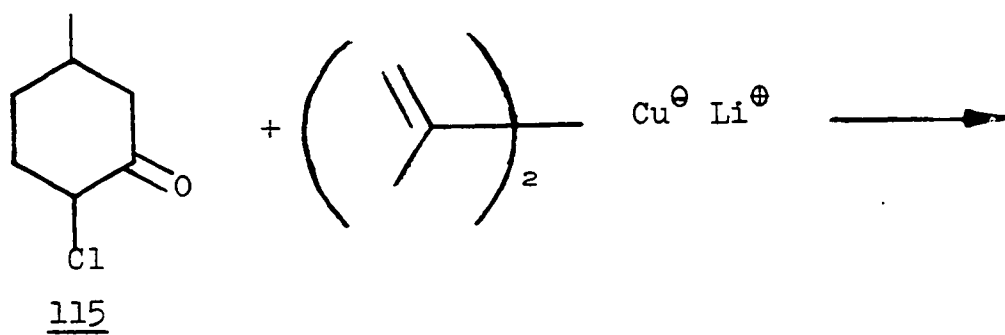
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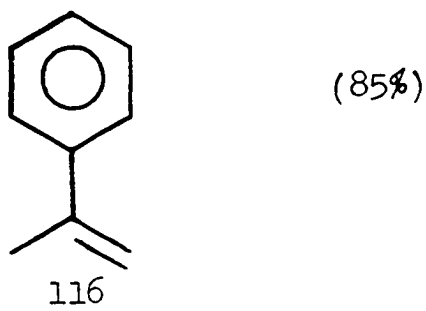
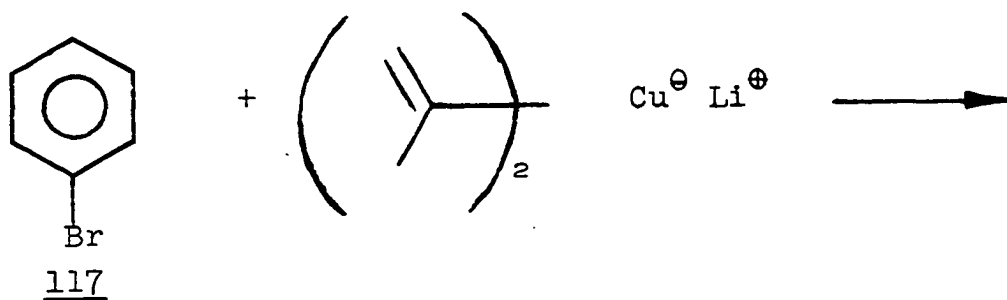


In addition, Vig and his coworkers reported several other transformations which involved replacement of a halogen by an isopropenyl group through reaction of the halide with lithium diisopropenyl cuprate (111). For example, the synthesis of racemic pentadiene (112) was accomplished by treatment of 1-methyl-4-bromocyclohex-1-ene (113) with lithium diisopropenyl cuprate. Also, racemic isopulegone (114) was prepared in 60% yield from 2-chloro-5-methylcyclohexanone (115).



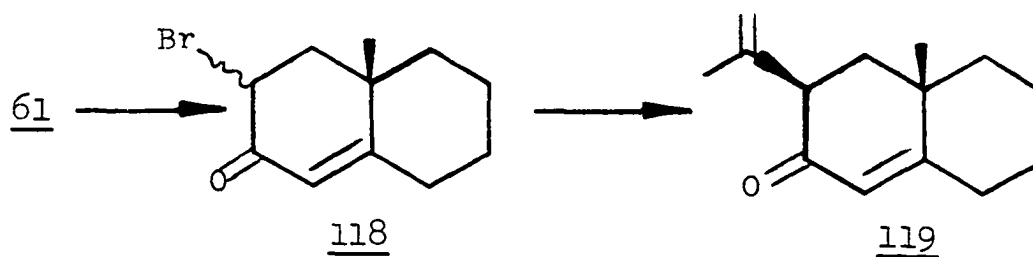


Finally, methyl styrene (116) was prepared by reaction of bromobenzene (117) with excess lithium diisopropenyl cuprate.

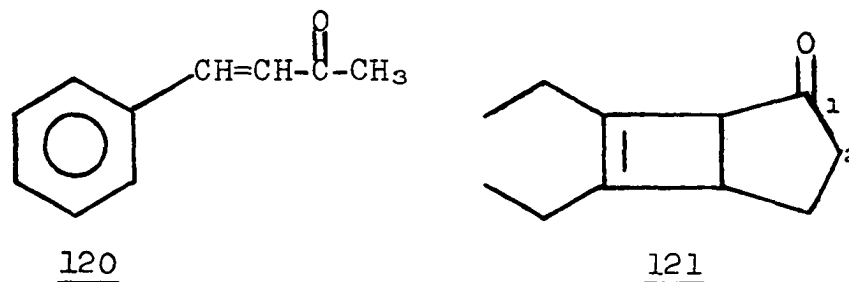


These results indicated the extreme versatility of the replacement reaction as outlined by Vig *et al.* (106,107).

In order to introduce an isopropenyl group at C-3 in octalone 61, some type of functionality had to be initially introduced at that position. Since the replacement of a halogen by an isopropenyl moiety is well documented, an α -bromoketone such as 118 seemed to be a logical precursor to the desired octalone 119.

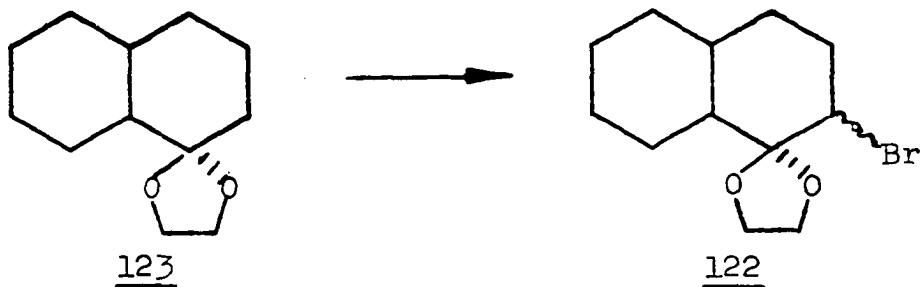


Brominations at positions α to a ketone, if there are no double bonds elsewhere in the molecule, have been done routinely with bromine in acetic acid. This is obviously impossible using octalone 61, since the double bond will react with bromine as well as the α -carbon. We had hoped to overcome this problem by utilizing pyrrolidone hydrotribromide, which has been used to selectively brominate ketones in compounds which contain an olefinic linkage. Avang and Wolde (108) treated 120 with pyrrolidone hydrotribromide and obtained an α -bromoketone in good yield with no addition of bromine to the double bond. Chapman and Tome (109) treated ketone 121 with pyrrolidone hydrotribromide and observed bromination exclusively at C-2.

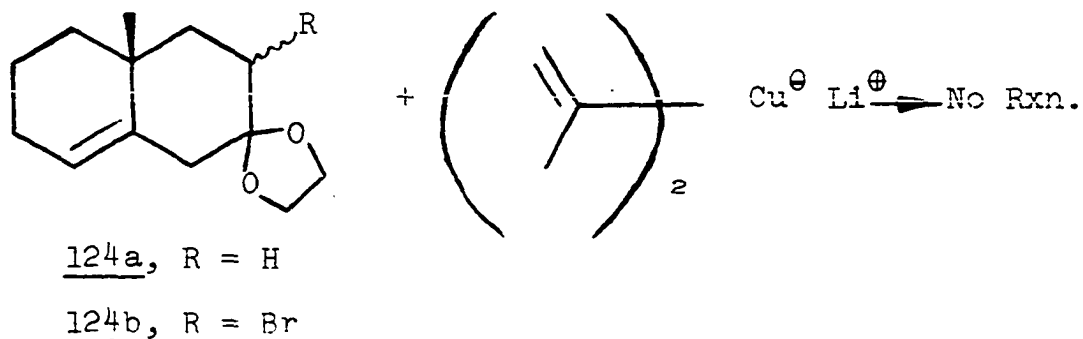


Repetition of the above reaction with octalone 61 resulted in bromination of the double bond as well as other unwanted side reactions. Glc indicated the presence of approximately seven compounds which were inseparable by column chromatography. If this mixture was allowed to stand at room temperature for six hours, it was converted to a black, intractable material. Attempted bromination with trimethylphenylammonium perbromide (110,111) and pyridinium hydrotribromide (112) gave similar results. It appears that there is no selectivity exhibited by these brominating agents when reacted with octalone 63c.

Johnson and his coworkers (112) prepared bromoacetal 122 by first forming the acetal 123 from the saturated decalone. Bromination with trimethylphenylammonium perbromide afforded 2-bromoacetal 123 in good yields. Even higher yields of α -bromoacetals could be obtained when pyridinium hydrotribromide was employed as the brominating agent (110, 111).

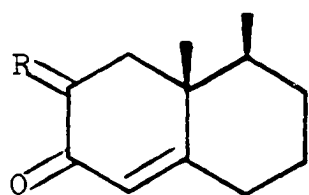


Thus, acetal 124a was readily prepared from octalone 61 and treated with pyridinium hydrotribromide according to the procedure of Keith (111). The material isolated appeared to be homogeneous, however it rapidly decomposed when allowed to stand at room temperature. Bromoacetal 124b was therefore immediately treated with lithium diisopropenyl cuprate with the intention of generating an isopropenyl moiety α to the acetal. However, an examination of the product revealed



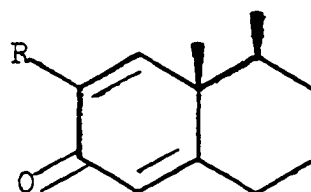
the presence of olefinic material as well as starting acetal. Solubility as well as stability problems influenced our decision to try a different approach towards the generation of an isopropenyl group.

Piers and his collaborators (81) developed the procedure outlined below for the preparation of β -keto ester 125 from dimethyloctalone 63c.



63c, R = H₂

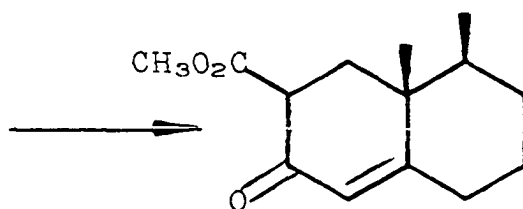
126, R = CHOH



127, R = CHO

128, R = CO₂H

129, R = CO₂CH₃



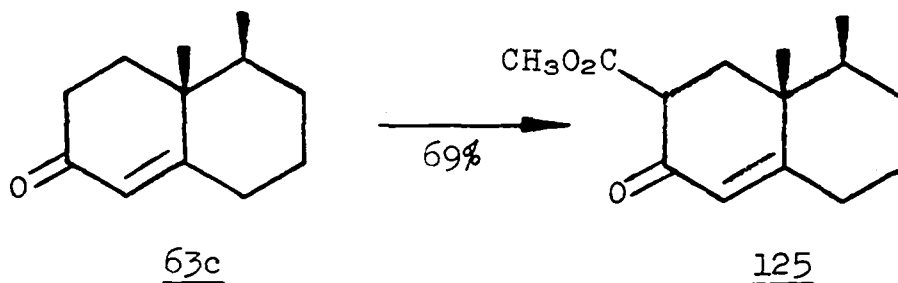
125

Conversion of the dimethyloctalone 63c into the corresponding hydroxymethylene derivative 126, followed by dehydrogenation of the latter with 2,3-dichloro-5,6-dicyanobenzoquinone in dioxane afforded, in 73% yield, the cross-conjugated keto aldehyde 127. Oxidation of compound 127 with silver oxide and esterification of the resultant carboxylic acid 128 with silver oxide and methyl iodide gave the keto ester 129 in 86% overall yield. Reduction of 129 with sodium borohydride in pyridine gave, in 87% yield, the β -keto ester 125.

Although it works, the above sequence requires five steps to give 125 in an overall yield of 55%. We felt that the preparation of an intermediary β -keto ester would be much more feasible if carried out in only one step from the octalone. This route was therefore investigated.

Carbomethoxylation of a non-conjugated ketone may readily be accomplished by treatment of the ketone with dimethylcarbonate in the presence of sodium hydride. This procedure is adequately outlined by Rhoads (113) and Krapcho (114) and their respective coworkers. However, in neither case is the carbomethoxylation of an α, β -unsaturated ketone discussed.

β -Keto ester 125 was prepared in 69% yield from 63c by reaction with three equivalents of sodium hydride and two equivalents of dimethylcarbonate in benzene. The concen-

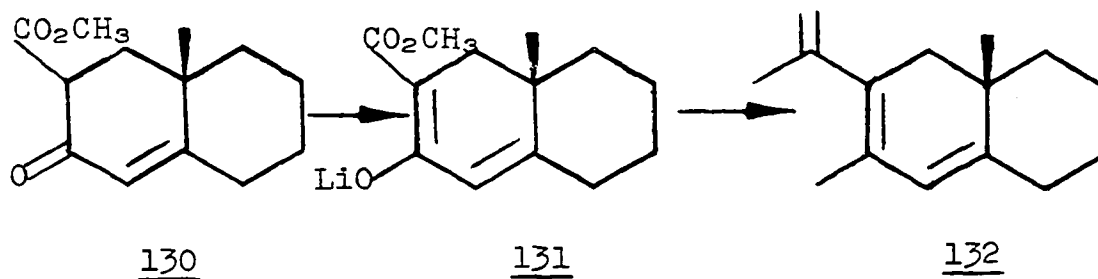


tration of the octalone in benzene was quite crucial as a very dilute solution resulted in no reaction, and a solution which was too concentrated effected migration of the double bond to a position β, γ with respect to the carbonyl group. Compound 125 solidified after distillation and was identified by its spectral properties.

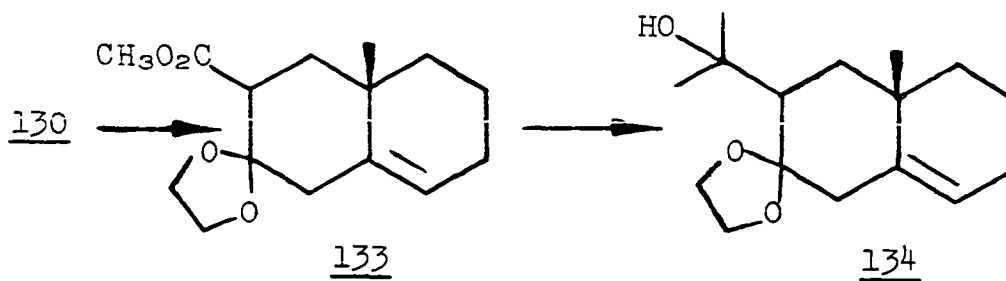
The carbomethoxy moiety established a synthon for the introduction of two more carbon atoms. After protecting the carbonyl group, it was felt that alkylation of β -keto ester 125 with methyllithium might afford a tertiary alcohol which could be dehydrated giving the desired isopropylidene group.

β -Keto ester 130, which was prepared in a manner identical to that described above for 125, was treated with one equivalent of lithium hydride affording a lithio salt which we believe has structure 131. Reaction of the lithium salt with methyllithium gave, as the only isolable product, triene 132. Utilization of sodium hydride as a base offered no im-

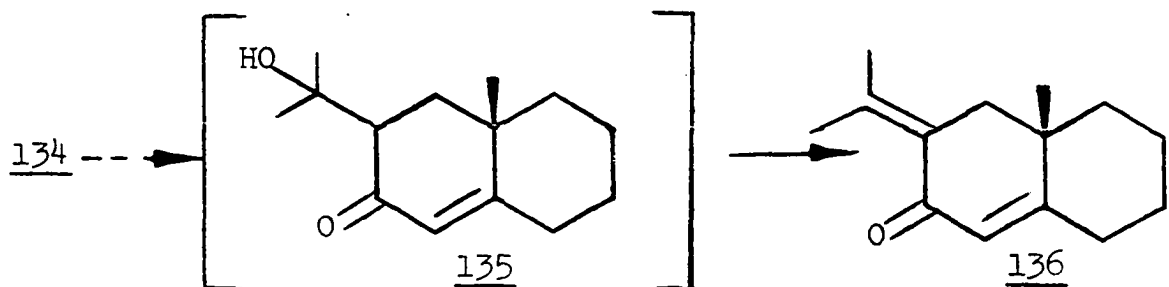
provement in the results.



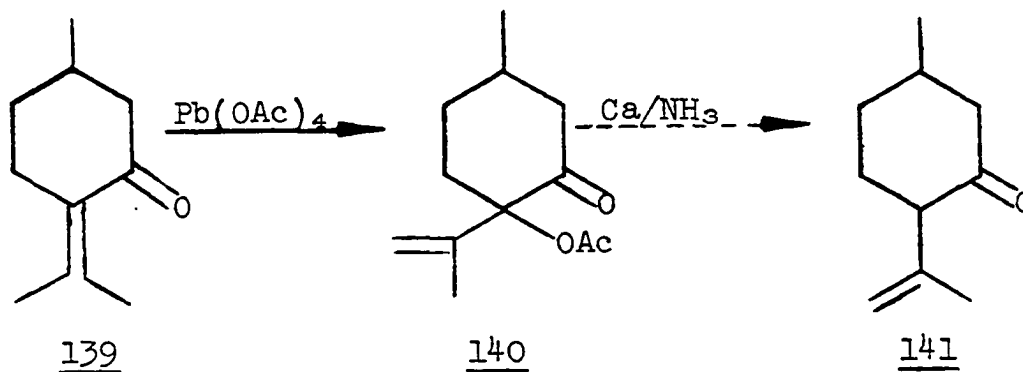
Consequently, the α,β -unsaturated ketone 130 was protected by reaction with 1,2-ethanediol and *p*-toluenesulfonic acid in benzene to give acetal 133 in excellent yield. Carbomethoxyacetal 133 was treated with methyllithium affording tertiary alcohol 134 in a 90% crude yield.



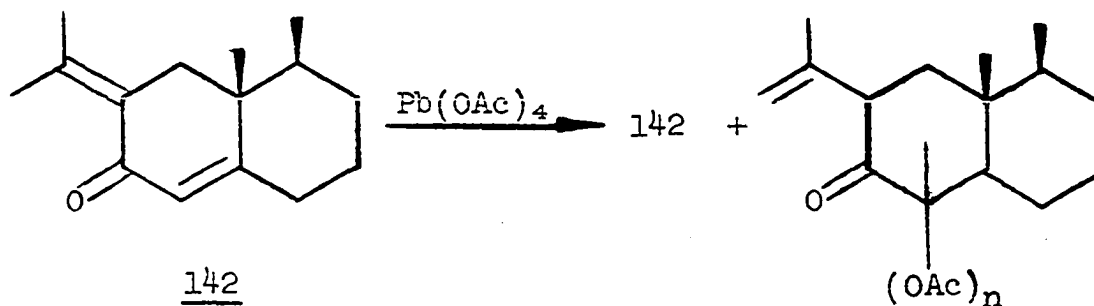
At this stage in the sequence, we attempted to remove the acetal protecting group to obtain alcohol 135. However, all reaction conditions employed for acetal cleavage occurred with concomitant dehydration of the alcohol to give ketone 136.



Theobald (115) endeavored to isomerize 137 with hot, 2% sulfuric acid in ethanol. He observed no reaction under these acidic conditions, but the use of 0.4N potassium hydroxide in methanol gave an excellent yield of diketone 138. We felt that the acidic conditions used in this reaction may have been stringent enough to cleave the acetal in 134 without promoting isomerization of the double bond. With this in mind, alcohol 134 was dehydrated with thionyl chloride in pyridine, under conditions known to give the di-

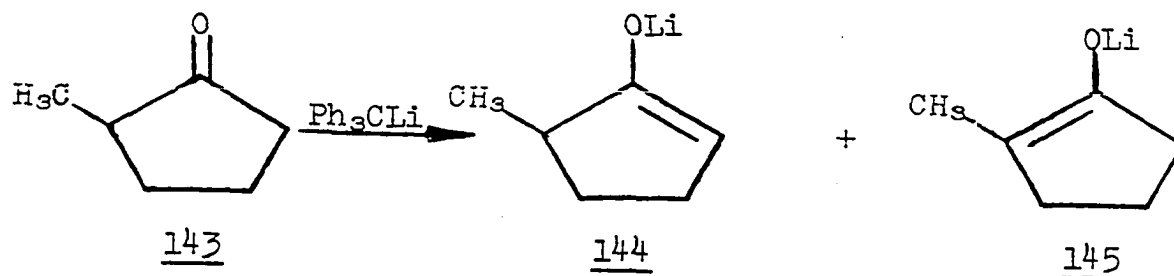


Octalone 142 was treated with freshly prepared lead tetraacetate in dry benzene. After five hours at reflux, two major components were isolated from the reaction mixture. One compound was starting material while the other was a ketone in which the acetate functionality had added somewhere in the ring. Nmr showed no vinyl proton α to the carbonyl,

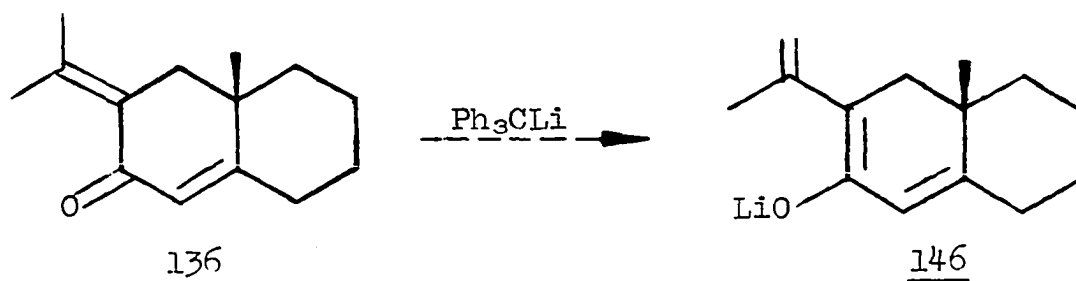


however nmr and ir did indicate the presence of an isopropenyl group. Varying the reaction conditions gave none of the desired α -acetoxyketone.

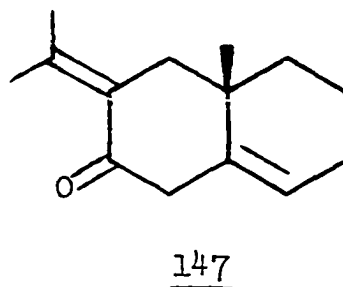
House and Trost (119) have done an extensive amount of research on the nature of the potassium and lithium enolates derived from cyclic ketones. These workers found that in the absence of excess ketone, and in the absence of proton-donating solvents, there is a kinetic preference for abstracting a proton from the less highly substituted α carbon. This kinetically controlled generation of enolate anions was seen to lead to mixtures of enolate anions in which the less highly substituted enolate predominated. For example, 2-methylcyclopentanone (143) and triphenylmethyllithium, under kinetically controlled conditions, were found to yield a mixture of enolate anions 144 and 145 (94% and 6% respectively).



In accordance with the research of House and Trost (119), we tried to prepare enolate 146 by reaction of octalone 136 with triphenylmethyllithium. The major difficulty encountered in this reaction was clearly the possibility of isomerizing two double bonds. The isomerization of the



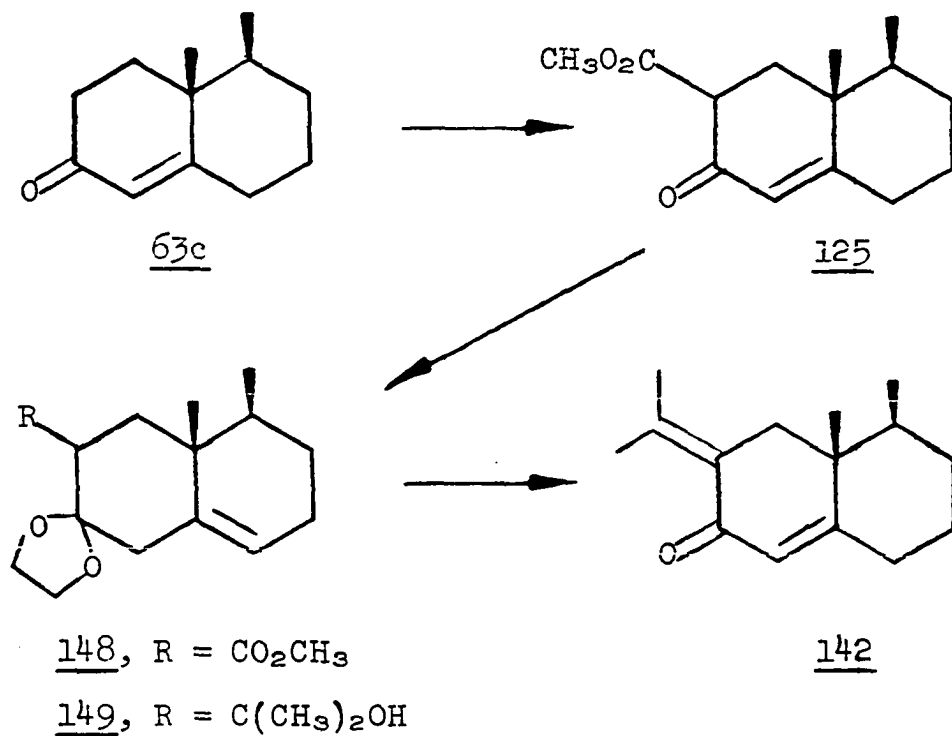
endo-cyclic double bond proved to be much more facile, as the major product recovered after quenching the enolate was octalone 147.



With a great degree of reluctance, we terminated our efforts to synthesize petasin (10) and decided instead to concentrate on effecting the synthesis of (\pm)-isopetasin (39).

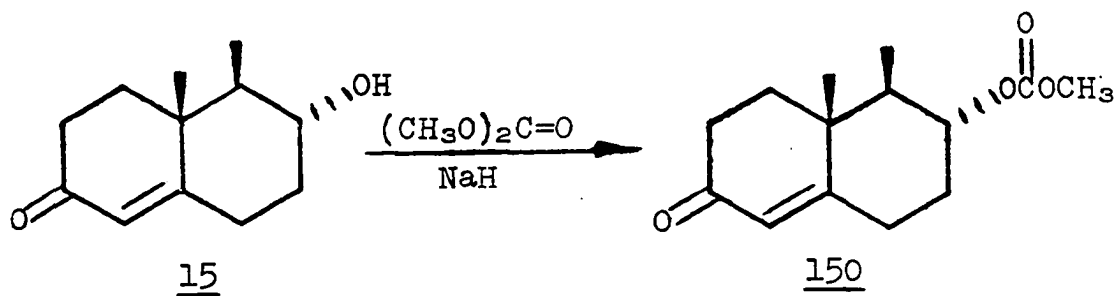
Synthesis of (\pm)-Isopetasin (39)

The transformation of octalone 63c to octalone 142 was studied before attempting any reactions with des-isopropyl-



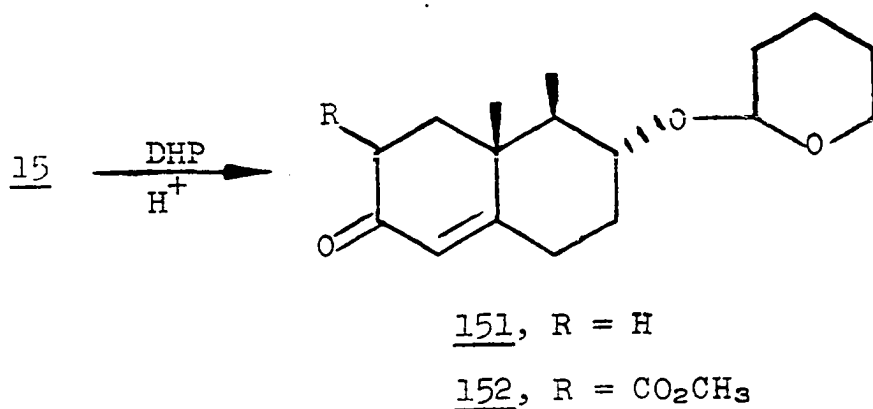
denepetasol (15). Octalone 63c was readily converted to β -keto ester 125 with sodium hydride and dimethylcarbonate in refluxing benzene. The carbonyl moiety was protected by formation of acetal 148, which was immediately subjected to methyllithium in refluxing ether. The resulting hydroxy acetal, 149, was placed in hot 10% hydrochloric acid and acetone to cleave the acetal protecting group, followed by dehydration of the tertiary alcohol with concentrated hydrochloric acid in methanol. Chromatography of this viscous oil over silica gel afforded octalone 142 in 27% yield.

We anticipated that the scheme used for the conversion of 63c to 142 could also be applied to the synthesis of isopetasin (39) from des-isopropylidenepetasol (15). It was expected that the reaction of 15 with sodium hydride and dimethylcarbonate would result in an initial abstraction of the alcoholic proton followed by the formation of an unsymmetrical carbonate. For this reason, an extra equivalent of sodium hydride and dimethylcarbonate was added to the reaction mixture with the hope that after the alcohol had been protected, the β -keto ester would rapidly form. Carbonate 150, however, was the only product isolated under these conditions, being formed in virtually quantitative yields. When 150 was treated with three equivalents of sodium hydride and two equivalents of dimethylcarbonate, no reaction



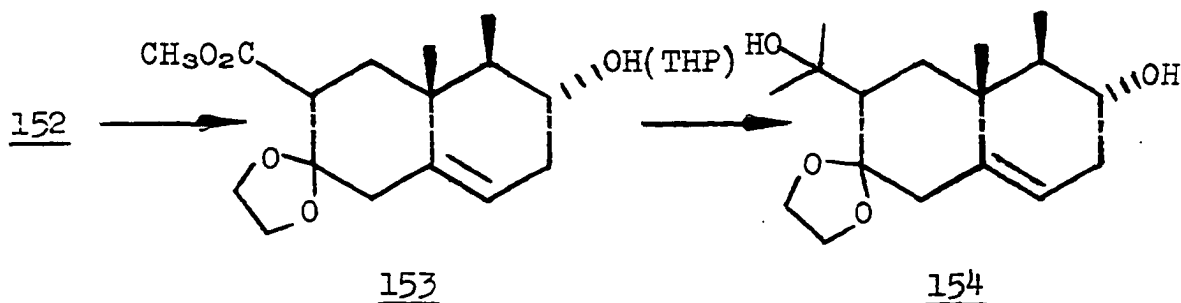
occured. Compound 150 suffered from a lack of solubility in benzene, but varying the solvent only resulted in the production of intractable material.

This problem was rectified by treatment of des-isopropylidenepetasol (15) with dihydropyran in methylene chloride. Tetrahydropyranyl ether 151 was obtained in 77% yield after purification, and served as a very adequate precursor for the introduction of the carbomethoxy moiety.



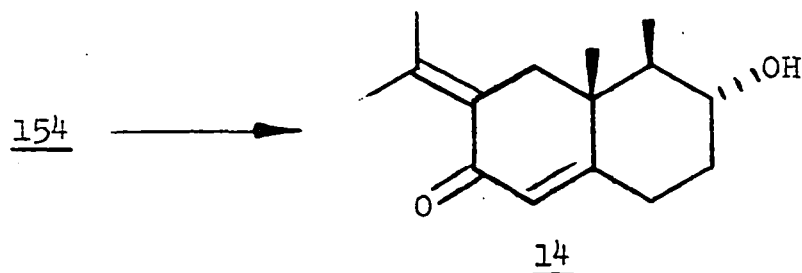
Treatment of 151 with sodium hydride and dimethylcarbonate gave β -keto ester 152 in 0 to 53% yield. As in the model system, the concentration of octalone 151 in benzene was extremely critical to the success of the reaction. The ideal conditions are discussed in the experimental section, however in no instance did we obtain greater than a 53% yield of 152.

The formation of acetal 153 was accompanied by almost complete cleavage of the tetrahydropyranyl ether protecting group. Acetal 153 was treated with methyllithium in refluxing ether for two hours to give tertiary alcohol 154 in 91% crude yield. The acetal protecting group of 154



was cleaved, accompanied by the removal of residual traces of the tetrahydropyranyl ether by treatment of 154 with *p*-toluenesulfonic acid, water, and acetone. Complete dehydration of the tertiary alcohol was accomplished in refluxing methanol containing a trace of concentrated

hydrochloric acid. The resulting solid, isopetasol (14), was recovered in only a 3% yield from des-isopropylidenepectasol (15).



The nmr spectrum of 14 is displayed in Figure 4 - top. The ir spectrum of 14, shown in Figure 4 - middle, compares well with the ir of authentic isopetasol (14)², reproduced in Figure 4 - bottom.

Isopetasol (14) was found to be quite unstable when allowed to stand for long periods of time, or when subjected to a humid environment. An isopropenyl function in a position α to a carbonyl is known to be quite unstable due to the possibility of its undergoing a reverse-aldol condensation as shown on page 95 (34).

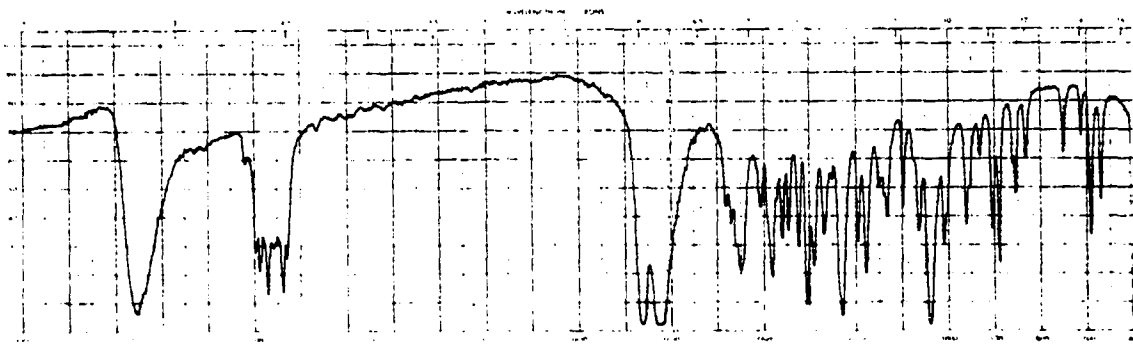
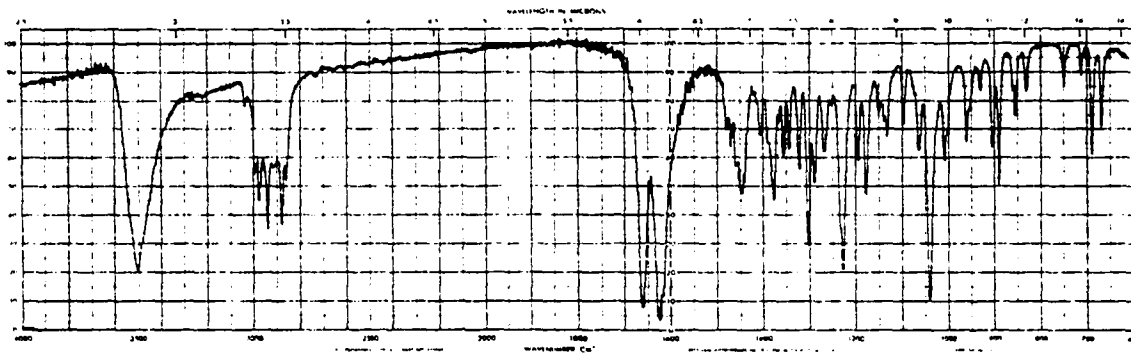
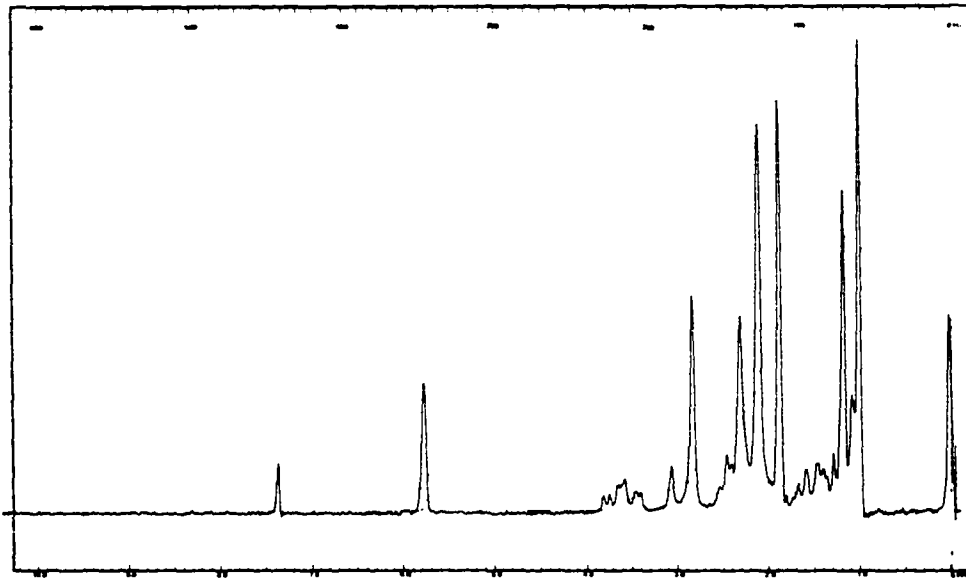
²We wish to thank Professor C. Djerassi and Professor C. J. W. Brooks for their generous gifts of isopetasol.

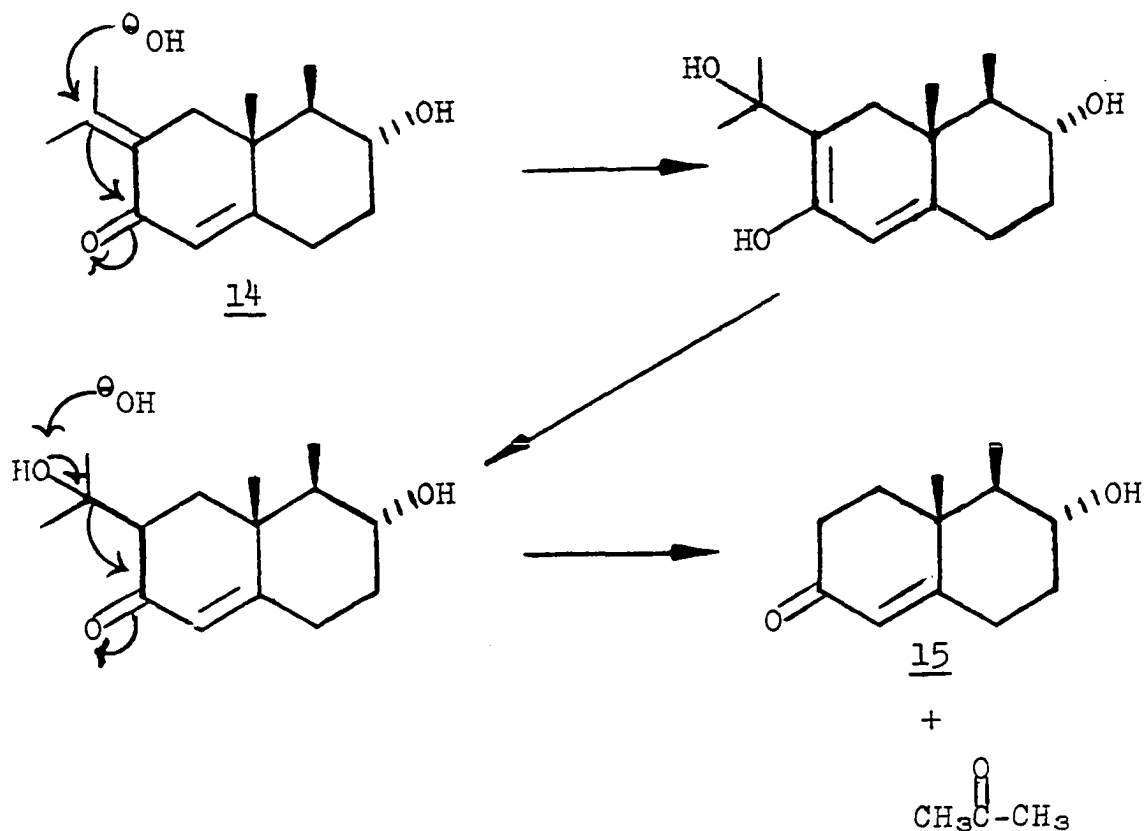
Figure 4. Isopetasol (14)

Top: 60 MHz nmr spectrum of isopetasol
(14)

Middle: Infrared spectrum of synthetic
isopetasol (14)

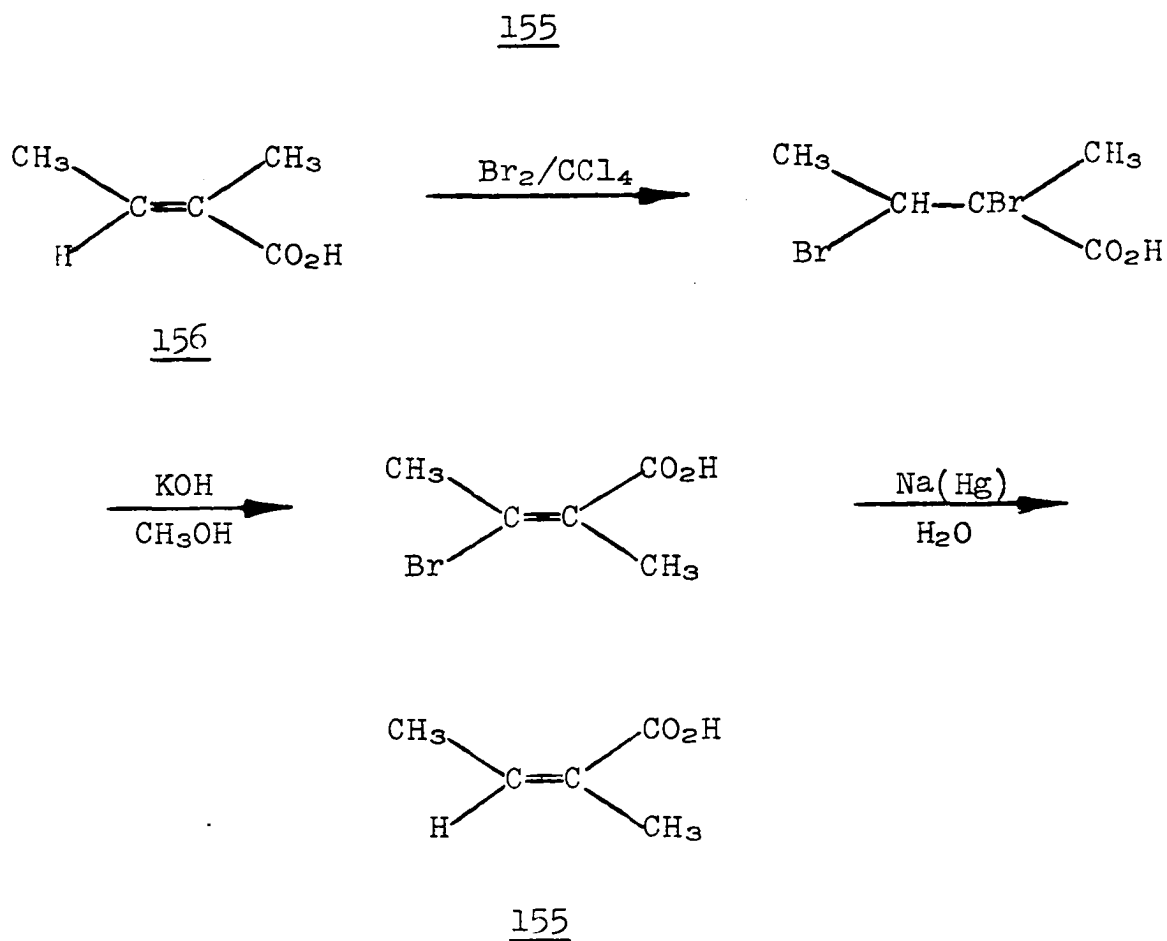
Bottom: Infrared spectrum of authentic
isopetasol (14)





This side reaction and the overall instability of the compounds in this sequence, account for the decrease in yield as compared to the model system.

We had planned to synthesize isopetasin (39) by esterifying 14 with angelic acid (155). Following the well-defined procedure of Buckles and Mock (120), angelic acid (155) was prepared from tiglic acid (156) in 18% yield.

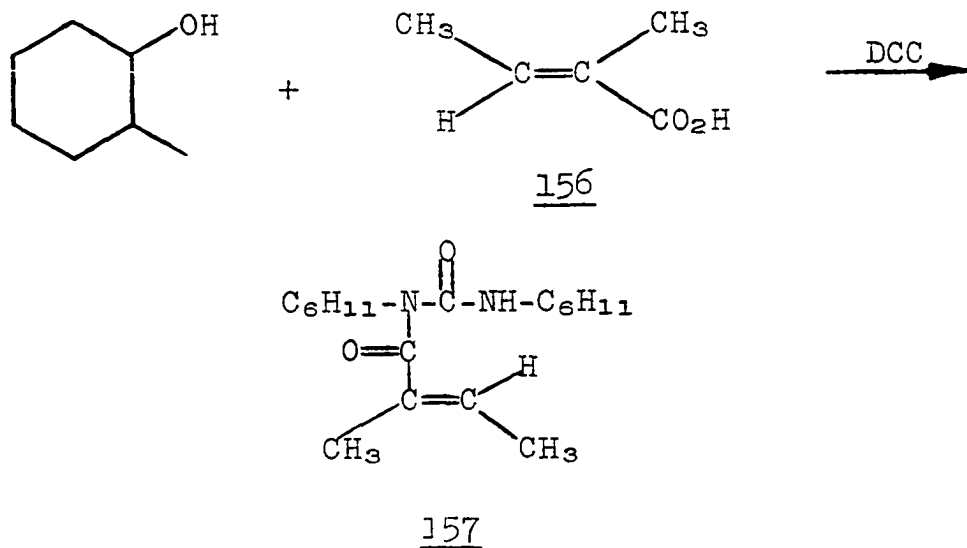


Angelic acid (155) was quite unstable, isomerizing to tiglic acid (156) upon treatment with hot acid or base. Prolonged heating or storage of 155 also effected this transformation. Due to the acid sensitivity of angelic acid, a normal, acid-catalyzed esterification of 14 with angelic acid (155) was thought to be untenable.

The use of dicyclohexylcarbodiimide for the coupling of

two hydroxylic components by elimination of water under mild, neutral conditions, has been extensively reviewed (121) (122). Condensations involving carboxylic acids and alcohols, however, have consistently given higher yields if the alcohol were a phenolic derivative. There are very few references in the literature (121) indicating a successful condensation with a secondary alcohol and a carboxylic acid in the presence of dicyclohexylcarbodiimide. In fact, some reactions with DCC seem to be non-reproducible, working one time and failing the next (123-125).

Due to these questionable properties of DCC, we initially used it to catalyze the esterification of 2-methylcyclohexanol with tiglic acid (156). The only isolable product had all the characteristics of amide 157.



This type of product was not unexpected since Amat and his coworkers (126) had observed similar intermediates when esterifying fatty acids in the presence of DCC.

2-Methylcyclohexanol was then treated with angelic acid (155) and p-toluenesulfonic acid in refluxing benzene. Surprisingly, the angelic acid (155) did not isomerize to tiglic acid (156), but unfortunately no ester was detected either.

Tiglate esters have been used as blocking groups for secondary alcohols (127). The alcohol is treated with tigloyl chloride (128) and pyridine in refluxing benzene. Yields of up to 90% are normally realized for this reaction.

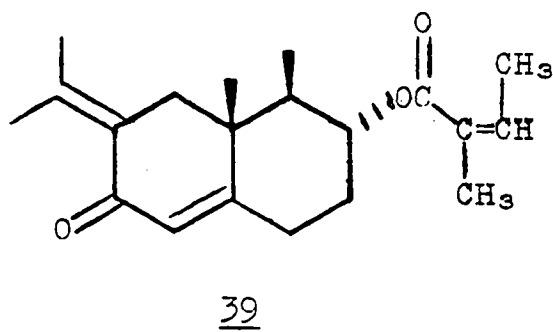
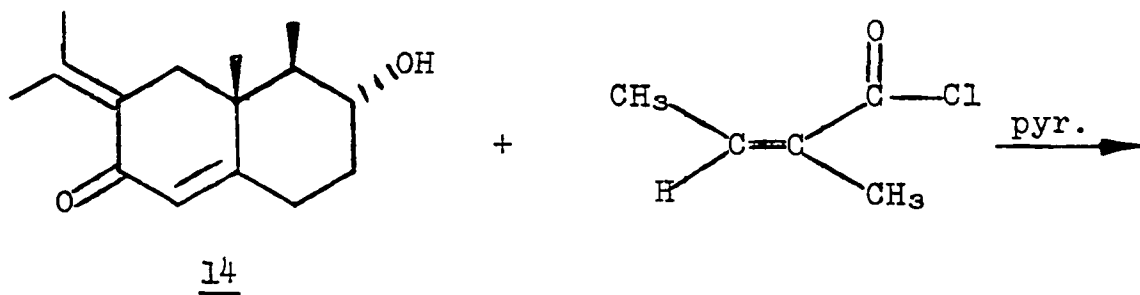
We proposed to attempt the same reaction outlined above with angeloyl chloride rather than tigloyl chloride. Treatment of angelic acid with thionyl chloride (129) or oxalyl chloride (130) proved futile, as the major product isolated was the isomeric tigloyl chloride. Hocking (131) experienced a similar problem when trying to prepare cis-crotonyl chloride from the cis acid. He found that all published methods for the preparation of cis-crotonyl chloride gave a product contaminated with appreciable quantities of the trans isomer. Hocking (131) devised a procedure where successful preparations of cis-crotonyl chloride were possible using neat thionyl chloride, carried out as a rapid low temperature conversion, with immediate purification. Application of this

scheme to angelic acid (155) was unsuccessful due to our inability to distill the angeloyl chloride from the acidic by-products fast enough.

In 1909, Rupe (132) reported the synthesis of angeloyl chloride. Repetition of this published work also gave tigloyl chloride. A modification of Rupe's (132) scheme resulted in the isolation of reasonably pure angeloyl chloride. Angelic acid was treated with one equivalent of sodium hydride at room temperature. The resulting sodium salt was reacted with phosphorous oxychloride. After stirring for one hour, the solvent was removed at reduced pressure and angeloyl chloride was isolated in small quantities via distillation.

Isopetasol (14) was then treated with angeloyl chloride in benzene and pyridine. The reaction mixture was stirred overnight, and the product isolated. The crude product was thoroughly washed with a sodium bicarbonate solution to remove any acid that may have formed due to hydrolysis of the acid chloride. The nmr of the crude ester indicated a vinyl proton at δ 6.1 ppm. This is indicative of a vinyl proton of an angelate derivative, as opposed to a tiglate compound. Purification of the crude product by column chromatography gave isopetasol (14) as well as 3-5 mg of a light yellow oil. A high resolution mass spectrum of this oil indicated the molecular weight to be 316.2065, which is nearly identical

with the molecular weight of isopetasin (39), 316.2038.



EXPERIMENTAL

Reagents

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

Diethyl ether (anhydrous) - 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.

Pentane - dried over anhydrous calcium chloride and distilled from potassium hydroxide.

p-Dioxane - distilled from calcium hydride.

Dimethylcarbonate - distilled from calcium hydride.

Dihydropyran - distilled from sodium.

Methylene chloride - wash with 5% sodium carbonate, water, and distilled from anhydrous potassium carbonate.

Dimethylsulfoxide - distilled from lithium aluminum hydride.

Carbon tetrachloride - distilled from phosphorous pentoxide.

N, N-Dimethylformamide - distilled from calcium hydride.

1,2 - Dimethoxyethane - distilled from either lithium aluminum hydride or sodium-benzophenone which displayed a constant purple color.

Pyridine - distilled from sodium hydroxide.

Characterization of Compounds

All melting points were determined on a Köfler Micro Hot Stage melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 21 Double Beam Spectrometer, a Beckman IR 12 spectrometer, or a Beckman IR 18A 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. High resolution mass spectra were determined using an AEI-MS-209 mass spectrometer. Only the molecular ion is reported. Microanalyses were performed by Ilse Beetz Microanalytical Laboratories, Kronach, West Germany.

Whenever needed, chromatographic procedures were employed for separation and purification of products. Microanalytical, air-dried, thin-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 performed on Baker analyzed silica gel (60-200 mesh). Elution solvents were established by microanalytical thin-layer chromatography, and

column elution was followed by thin-layer examination of consecutive effluent aliquots.

Preparation of Compounds

2,3-Dimethyl-1,4-benzoquinone (77)

A. The procedure of Smith and Austin (82) was modified slightly. A mixture of 115 g (0.60 mol) of sulfanilic acid and 31.75 g (0.30 mol) of anhydrous sodium carbonate was slowly dissolved in 600 ml of water. The solution was cooled to 15° and 44.3 g (0.64 mol) of sodium nitrite in 125 ml of water was added. The resulting mixture was poured at once into 127 ml of concentrated hydrochloric acid (specific gravity, 1.18) and 600 g of ice contained in a 2-l beaker. The solution, from which the p-benzenediazonium sulfonate separates upon stirring, was allowed to stand in an ice bath for 15-25 min. During this time a solution of 2,3-dimethylphenol, described below, was prepared.

In a 4-l Erlenmeyer flask, 56 g (0.46 mol) of 2,3-dimethylphenol (Aldrich Chemical Co.) was dissolved in 300 ml of water containing 75 g (1.88 mol) of sodium hydroxide. The cold suspension of the diazonium salt was slowly stirred into the cooled phenol solution. After standing at room temperature for 1 hr, the blood-red solution was heated with stirring to 45-50° and one-tenth of 250 g (1.44 mol) of sodium hydrosulfite was cautiously added until the frothing subsided. The remainder of the reducing agent was then added

in one portion. Heating was continued to about 70° when the aminophenol, a flocculant yellow solid, began to crystallize. The flask was cooled to room temperature, and the aminophenol was filtered, washed with cold water, and dissolved by warming it with 1 l of water containing 60 ml of concentrated sulfuric acid (specific gravity, 1.84). The resulting solution was clarified with Norite, affording a pink solution.

In an apparatus arranged for steam distillation was placed 250 g (0.621 mol) of ferric sulfate, 30 ml of concentrated sulfuric acid (specific gravity, 1.84) and 200 ml of water. Under subdued light, the warm aminophenol solution was added dropwise over a 2-hr period to the boiling oxidizing agent. The quinone formed steam-distilled at the rate the phenolic solution was added. The distillate was cooled and the quinone filtered affording 34.2 g of yellow crystals. The aqueous filtrate was saturated with solid sodium chloride and extracted with four 20-ml portions of ether. The combined ethereal extracts were washed with brine, dried (Na_2SO_4), and the solvent was removed at reduced pressure. The residual red oil, when crystallized from petroleum ether (bp 60-70°), gave an additional 0.52 g of the quinone. Combining the solid material recovered gave 34.72 g (0.255 mol - 55.4%) of 2,3-dimethyl-1,4-benzoquinone (77) as a yellow solid: mp 54-55° [lit. (133) mp 55°]; nmr (CCl_4) 6.64 (s, 2H, aromatic), 1.99 (s, 6H, $-\text{CH}_3$) ppm. Slightly

better yields (70-75%) were obtained when the aminophenol solution was added in 100-ml portions, and the oxidizing agent replaced after each addition.

B. According to the procedure of Strickson and Leigh (83) developed for a similar system, a 500-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, and pressure-equalizing addition funnel. The system was repeatedly evacuated, flame-dried, and filled with prepurified nitrogen. The apparatus was charged with 25.4 g (0.164 mol) of chromyl chloride and 135 ml of carbon tetrachloride. To this vigorously stirred oxidant was added 10 g (0.082) of 2,3-dimethylphenol (76) dissolved in 90 ml of carbon tetrachloride over a 30 min period. The reaction mixture was stirred for an additional 60 min at room temperature. The solid which formed was washed with three 50 ml of portions of dry carbon tetrachloride to remove excess chromyl chloride, and dried at room temperature under reduced pressure. The solid was hydrolyzed with 500 ml of cold water, and the solution was then extracted with ethyl ether. Evaporation of the solvent left a dark red oil. Crystallization of this oil from hexane gave 1.5 g (0.011 mol - 13.4%) of 2,3-dimethyl-1,4-benzoquinone (77) as an orange solid: mp 45-55°; nmr identical to that described above.

2,3-Dimethylhydroquinone (78)

According to the general procedure of Emerson and Smith (86), a 250-ml, one-necked, round-bottomed flask was fitted with a gas-inlet tube and a reflux condenser. The apparatus was evacuated, filled with prepurified nitrogen, and charged with a solution of 8.3 g (0.061 mol) of 2,3-dimethyl-1,4-benzoquinone (77) dissolved in 50 ml of glacial acetic acid. To this was added 25 ml of water and 8.3 g (0.13 mol) of granular zinc (20 mesh) and the mixture was heated to reflux. The reduction proceeded rapidly and the solution became colorless in approximately 30 min. Boiling water (50 ml) was added to the hot solution, which was then immediately decanted from the zinc. The zinc was boiled with additional water (50 ml) and again decanted. On cooling the combined aqueous solutions deposited 7.9 g (0.057 mol - 96.1%) of 2,3-dimethylhydroquinone (78) as light tan crystals: mp 219-221° [lit. (128) mp 221°]; nmr (d_6 -DMSO) δ 8.31 (s, 2H, -OH), 6.48 (s, 2H, aromatic), 2.05 (s, 6H, -CH₃) ppm.

2,3-Dimethyl-1,4-cyclohexanediol (80)

A 1000-ml packless autoclave was charged with a solution of 24.0 g (0.173 mol) of 2,3-dimethylhydroquinone (78) dissolved in 600 ml of anhydrous methanol which contained 3 g of W-2 Raney nickel catalyst (85). The reaction mixture was stirred under a constant pressure of 2000 psi of hydrogen at 170° for 96 hr. The catalyst was removed by filtration

through Celite and the methanol was removed under reduced pressure. Distillation gave 22.8 g (0.158 mol - 91%) of 2,3-dimethyl-1,4-cyclohexanediol (80) as a clear, very viscous oil: bp 114-115° (0.06mm); ir (film) 3398 (OH), 2928 (CH), 1449, 1017, 948 cm^{-1} ; nmr (d_5 -DMSO) δ 4.28 (bm, 2H, -OH), 3.52 (m, 2H, -CHOH), 0.60 - 1.15 (m, 6H, -CH₃) ppm.

Anal. Calcd for $\text{C}_8\text{H}_{16}\text{O}_2$: C, 66.63; H, 11.18. Found: C, 66.61; H, 11.01.

4-Benzoyloxy-2,3-dimethylcyclohexanol (82)

According to the procedure of Jones and Sanheimer (89), a 100-ml, three-necked, round-bottomed flask was fitted with a magnetic stirrer, pressure-equalizing dropping funnel, and a gas-inlet tube. The apparatus was evacuated, flame-dried, and filled with prepurified nitrogen. The reaction vessel was then charged with a solution of 8.0 g (0.056 mol) of 2,3-dimethyl-1,4-cyclohexanediol (80) dissolved in 45 ml of alcohol-free chloroform and 15 ml of dry pyridine. This solution was cooled to an internal temperature of 0° with an ice bath, and treated with 7.9 g (0.056 mol) of benzoyl chloride over a 1 hr period. Following complete addition, the solution was held at 0° for an additional four hours, and was then allowed to warm to room temperature overnight. The chloroform solution was freed from pyridine by extraction with two 20-ml portions of water, followed by extraction with three 20-ml portions of a 3% aqueous sulfuric acid solution.

The organic phase was then washed with two 20-ml portions of a saturated sodium bicarbonate solution, water, brine, and dried (MgSO_4). The solvent was removed under reduced pressure and the residue distilled affording 8.68 g (0.035 mol - 62.5%) of 4-benzoyloxy-2,3-dimethylcyclohexanol (82) as a clear, colorless liquid: bp 150-151 (0.1mm); ir (film) 3430 (OH), 2950 (CH), 1720 (C=O), 1449, 1255 (C-O), 1108 cm^{-1} ; nmr (CCl_4) δ 7.99 (m, 2H, aromatic), 7.48 (m, 3H, aromatic), 0.80-1.25 (m, 6H, $-\text{CH}_3$) ppm; mass spectrum (70 ev) M^+ 248.

4-Benzoyloxy-2,3-dimethylcyclohexanol (83)

A. Conditions described in this preparation were based on those described by Prins and Reichstein (134) for a similar system. A 250-ml, three-necked, round-bottomed flask fitted with a mechanical stirrer, pressure-equalizing dropping funnel, reflux condenser, and gas-inlet tube was evacuated, flame-dried, and filled with prepurified nitrogen. Sodium hydride, 4.69 g (0.111 mol, as a 56.8% dispersion in mineral oil), was added to the apparatus and the mineral oil removed by three successive washings with 25-ml portions of pentane. The clean sodium hydride was covered with 20 ml of anhydrous dioxane and a solution of 16.0 g (0.111 mol) of 2,3-dimethyl-1,4-cyclohexanediol (80) in 60 ml of dry dioxane was added over a 30 min period. The mixture was stirred and heated to reflux for 6 hr and was allowed to cool to room

temperature over a 1 hr period. A solution of 17.1 g (0.100 mol) of benzyl bromide (Aldrich Chemical Co.) in 50 ml of anhydrous dioxane was added dropwise over a 15 min period to the stirred solution. The mixture was then heated to reflux for 16 hr. After allowing the reaction mixture to cool to room temperature, 1 ml of a 10% solution of acetic acid in ethyl ether was added to decompose any residual sodium hydride. The mixture was diluted with 100 ml of acetone, the sodium bromide precipitate was removed by filtration, and the solvent was removed under reduced pressure. The residue was taken up in ether and washed with five 50-ml portions of water, brine, and dried (MgSO_4). The solvent was removed under vacuum and the residue distilled affording 15.5 g (0.066 mol - 59.6%) of 4-benzyloxy-2,3-dimethylcyclohexanol (83) as a clear colorless liquid: bp 125-126° (0.15mm); ir (film) 3355 (OH), 2850 (CH), 1447, 1352 cm^{-1} ; nmr (CCl_4) δ 7.18 (s, 5H, aromatic), 4.33 (m, 2H, PhCH_2O -), 0.60-1.10 (m, 6H, $-\text{CH}_3$) ppm.

Anal. Calcd for $\text{C}_{15}\text{H}_{22}\text{O}_2$: C, 76.88; H, 9.46. Found: C, 76.90; H, 9.43.

B. A procedure for the conversion of diol 80 to benzyloxy alcohol 83 utilizing *n*-butyllithium as a base was also investigated. A 250-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, thermometer, pressure-equalizing addition funnel, and reflux

condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 4.75 g (0.04 mol) of 2,3-dimethyl-1,4-cyclohexanediol (80) dissolved in 100 ml of dry dioxane. The reaction mixture was cooled to 10° in an ice bath, and treated, dropwise and with stirring, with 31.6 ml (0.04 mol) of *n*-butyllithium (Foote Mineral Co.; 1.3M) over a 50 min period. Following complete addition of the *n*-butyllithium, the reaction mixture was allowed to warm to room temperature and treated with 6.8 g (0.04 mol) of benzyl bromide dissolved in 25 ml of dry dioxane, over a ten minute period. The reaction mixture was then heated to reflux and held at that temperature for 19 hr. The solution was cooled to room temperature, diluted with 50 ml of acetone, and filtered to remove the inorganic salt. The solvent was removed at reduced pressure and the residue taken up in ether. The organic phase was washed with five 30-ml portions of water, brine, and dried (MgSO₄). The solvent was removed under vacuum and the residue distilled affording 3.0 g (0.013 mol - 31.2%) of benzyloxy alcohol 83 as a colorless liquid: bp 138-140° (0.22mm); ir and nmr essentially identical to those described in part A.

4-Benzyloxy-2,3-dimethylcyclohexanone (84)

The procedure of Finnegan and Bachman (135) was followed. A 2-l, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, and a pressure-

equalizing dropping funnel. The apparatus was evacuated, flame-dried, and filled with prepurified nitrogen. The reaction vessel was charged with a solution of 133.3 g (0.57 mol) of 4-benzyloxy-2,3-dimethylcyclohexanol (83) dissolved in 800 ml of ether. The solution was cooled to 3° with an external ice bath and treated with a precooled (0°) oxidizing solution which consisted of 62.6 g (0.21 mol) of sodium dichromate dihydrate and 78.4 g (0.80 mol) of concentrated sulfuric acid dissolved in 250 ml of water. The oxidizing solution was added dropwise, with rapid stirring, over a 95 min period. Following complete addition, the dark green solution was stirred for 4 hr at room temperature and the phases were then separated. The aqueous phase was saturated with solid sodium chloride and extracted with five 100-ml portions of ether. The combined ethereal phases were washed thoroughly with a saturated sodium bicarbonate solution, followed by brine, and dried (MgSO₄). The solvent was removed under vacuum and the residue distilled to afford 108.4 g (0.467 mol - 81.9%) of 4-benzyloxy-2,3-dimethylcyclohexanone (84) as a clear, colorless liquid: bp 122-123° (0.24mm); ir (film) 2940 (CH), 1708 (C=O), 1453, 1204 (C-O), 1027 cm⁻¹; nmr (CCl₄) δ 7.22 (s, 5H, aromatic), 4.47 (m, 2H, PhCH₂O-), 3.45 (m, 1H, -OCH-), 0.60-1.10 (m, 6H, -CH₃) ppm; mass spectrum (70 ev) M⁺ 232.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.39; H, 8.62.

Attempted alkylation of 4-benzyloxy-2,3-dimethylcyclohexanone (84) with methyl vinyl ketone

A. Following the general procedure of Ross and Levine (72), a 50-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, and a pressure-equalizing addition funnel. The apparatus was evacuated, filled with prepurified nitrogen, and charged with 2.5 g (0.011 mol) of 4-benzyloxy-2,3-dimethylcyclohexanone (84), 1 ml of ethanolic potassium hydroxide (0.11 g in 1 ml of absolute ethanol), and 15 ml of anhydrous ether. The reaction mixture was cooled to 0° and treated with 0.77 g (0.011 mol) of methyl vinyl ketone in 10 ml of anhydrous ether, dropwise, over a 30 minute period. After complete addition, stirring was continued an additional 2 hr. The reaction mixture was poured into 15 ml of water and the excess hydroxide was neutralized with 10% hydrochloric acid. The phases were separated and the aqueous phase was extracted three times with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). Removing the solvent under reduced pressure afforded 2.0 g of a yellow oil consisting mainly of benzyloxyketone 84 and other unidentifiable materials.

The alkylation was also attempted using anhydrous benzene, tetrahydrofuran, and dioxane as solvents. In each

case, no more than a trace of alkylated product was observed even after extended reaction periods.

B. According to a procedure described by Scanio and Starrett (91) for a similar system, a 100-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, pressure-equalizing addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with 1.27 g of a 57% sodium hydride-mineral oil dispersion (0.72 g - 0.03 mol active hydride). The sodium hydride was covered with 50 ml of anhydrous pentane, stirred briefly, and the solvent removed through a sintered glass gas dispersion tube attached to a water aspirator. This process was repeated two more times. The clean sodium hydride was covered with 50 ml of anhydrous dimethylsulfoxide. To this suspension was added 3.36 g (0.03 mol) of 4-benzyloxy-2,3-dimethylcyclohexanone (84), dropwise and with rapid stirring over a 15 min period. The resulting heterogeneous slurry was stirred at room temperature for 3 hr, during which time hydrogen evolution began and continued until a completely homogeneous solution was obtained. The resulting solution was treated with 2.1 g (0.03 mol) of methyl vinyl ketone, dropwise and with vigorous stirring, over a 30 min period. Following complete addition of the unsaturated ketone, the reaction mixture was stirred for 3 hr at room temperature, diluted with 50 ml of water,

and acidified by the dropwise addition of a 10% acetic acid in ether solution. The resulting phases were separated and the aqueous phase extracted with three 25-ml portions of ether. The combined ethereal phases were washed with three 20-ml portions of a saturated sodium bicarbonate solution, brine, and dried (MgSO_4). Removal of the solvent under vacuum afforded 4.4 g of a viscous liquid, identified as starting benzyloxy ketone 84. No vinyl proton was seen in the nmr.

Employment of 2-methylcyclohexanone and methyl vinyl ketone, in order to refine reaction conditions, gave only a 25% yield of octalone 61.

Repetition of the above experiment using anhydrous dimethylformamide and dioxane as solvents, for extended reaction times as well as at elevated temperatures, were also unsuccessful.

4-Chloromethyl-3,5-dimethylisoxazole (85)

The procedure of Kochetkov et al. (136) was followed. A 250-ml, three-necked, Morton flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, thermometer, and reflux condenser. The apparatus was flushed with nitrogen and charged with a suspension of 20 g (0.21 mol) of 3,5-dimethylisoxazole, 8.0 g (0.27 mol) of paraformaldehyde, and 10 g (0.07 mol) of anhydrous zinc chloride in 50 ml of dichloroethane. The reaction mixture

was heated to 50-55°, and was subjected to a fast stream of HCl, via a gas dispersion tube, for a period of two hours. The mixture was then refluxed for an additional three hr, cooled to room temperature, and poured into 70 ml of water. The organic phase was separated and the aqueous layer was neutralized with a 10% aqueous potassium carbonate solution. The zinc hydroxide was removed by filtration and the aqueous layer was extracted with three 30-ml portions of chloroform. The combined organic extracts were washed with two 50-ml portions of a saturated sodium bicarbonate solution, water, brine, and dried over anhydrous calcium chloride followed by anhydrous magnesium sulfate. The solvent was removed under vacuum and the residue distilled giving 7.7 g (0.053 mol - 25.2%) of the chloroisoxazole 85 as a yellow liquid: bp 101-102° (8mm); [lit, (136) bp 88-90° (7mm)]; nmr (CCl₄) δ 4.41 (s, 2H, ClCH₂-), 2.33 (s, 3H, -CH₃), 2.21 (s, 3H, -CH₃) ppm.

Attempted alkylation of 4-benzyloxy-2,3-dimethylcyclohexanone (84) with 4-chloromethyl-3,5-dimethylisoxazole (85)

A. A 100-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with 0.55 g (0.013 mol) of a 57% sodium hydride-mineral oil dispersion. The sodium hydride was

washed with three 50-ml portions of pentane, removing the pentane through a sintered glass gas dispersion tube attached to a water aspirator. The clean sodium hydride was covered with 35 ml of anhydrous 1,2-dimethoxyethane, dropwise and with stirring over a 10 min period. Hydrogen evolution appeared to be very slow and consequently the reaction mixture was heated to reflux for 5 hr. The solution was then cooled to room temperature and treated with 1.9 g (0.013 mol) of 4-chloromethyl-3,5-dimethylisoxazole (85) dissolved in 10 ml of 1,2-dimethoxyethane, over a five minute period. The reaction mixture was heated to reflux for an additional 4 hr. The solution was then cooled, acidified by the addition of a few drops of glacial acetic acid, and taken up in 100 ml of ether. The ethereal solution was washed with 20 ml of water, three 20-ml portions of a saturated sodium bicarbonate solution, brine, and dried (MgSO_4). Removal of the solvent at reduced pressure gave a viscous yellow liquid, which upon examination by nmr and mass spectrometry, indicated the presence of mono- and di-alkylated ketone 84 at the C-6 position.

B. 4-Benzoyloxy-2,3-dimethylcyclohexanone (84) was protected with an iso-propoxymethylene blocking group according to the procedure of Johnson and Posvic (94). Alkylation under conditions identical to those described above resulted only in the recovery of starting material.

4-Benzoyloxy-6-hydroxymethylene-2,3-dimethylcyclohexanone (86)

The general procedure of Johnson and Posvic (94) was followed with minor modifications. A 100-ml, three-necked, round-bottomed flask, fitted with a gas-inlet tube, magnetic stirrer, and pressure-equalizing addition funnel was evacuated, flame-dried, filled with prepurified nitrogen, and charged with 21.60 g (0.40 mol) of sodium methoxide and 50 ml of anhydrous benzene. The reaction mixture was cooled to 0° with an external ice bath, and 10.5 g (0.045 mol) of 4-benzyloxy-2,3-dimethylcyclohexanone (84) in 16.76 g (0.23 mol) of ethyl formate was added dropwise to the stirred methoxide suspension over a 1 hr period. The mixture was allowed to stand at room temperature for 15 hr. The white slurry was cooled to 5° and 20 ml of cold water was added. The mixture was diluted with ether and was thoroughly extracted with four 30-ml portions of a cold, 5% aqueous sodium hydroxide solution. The combined aqueous layers were washed once with 50 ml of ether and then acidified with cold, 10% aqueous sodium hydroxide solution. The resulting oily suspension was saturated with solid sodium chloride and extracted with five 50-ml portions of ether. The combined ethereal extracts were washed with three 50-ml portions of water, brine and dried (MgSO₄). Removing the solvent under reduced pressure afforded a yellow, viscous oil which, upon distillation, gave 8.87 g (0.034 mol - 75.3%) of

4-benzyloxy-6-hydroxymethylene-2,3-dimethylcyclohexanone (86) as a light yellow liquid: bp 137 - 138° (0.15mm); ir (film) 3390 (OH), 2945 (CH), 1700 (conj. C=O), 1450, 1201 cm^{-1} ; nmr (CCl_4) δ 14.77 (bs, 1H, $\text{HOCH}=\text{C}-$), 8.33 (m, 1H, $\text{HOCH}=\text{C}-$), 7.22 (s, 5H, aromatic), 4.47 (m, 2H, $\text{PhCH}_2\text{O}-$), 3.48 (m, 1H, $-\text{OCH}-$), 0.65 - 1.25 (m, 6H, $-\text{CH}_3$) ppm.

Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_3$: C, 73.82; H, 7.74. Found: C, 73.71; H, 7.72.

6-Benzyloxy-4a,5,6,7-tetrahydro-4a,5-dimethylhydrocoumarin
(91)

According to the procedure of Ireland and Marshall (96), a 250-ml, one-necked, round-bottomed flask, fitted with a Dean-Stark water trap, reflux condenser, and gas-inlet tube was repeatedly evacuated, flame-dried, and filled with prepurified nitrogen. The apparatus was charged with 6.24 g (0.024 mol) of 4-benzyloxy-6-hydroxymethylene-2,3-dimethylcyclohexanone (86) dissolved in 150 ml of anhydrous benzene. To this solution was added 3.24 g (0.036 mol) of 1-butanethiol and 80 mg of p-toluenesulfonic acid. The resulting mixture was heated slowly to reflux and held at that temperature for 4 hr, during which time 0.5 ml of water was removed from the system. The Dean-Stark trap was replaced by a Soxlet extractor containing 4A molecular sieves, and the reaction mixture was allowed to reflux through the sieves for 10 hr. Following this treatment, the benzene solution was

cooled, diluted with 100 ml of ether, and washed with three 50-ml portions of saturated sodium bicarbonate solution, brine, and dried (MgSO_4). The solvent was removed under reduced pressure affording 7.46 g (0.023 mol - 95.6%) of crude 4-benzyloxy-6-n-butylthiomethylene-2,3-dimethylcyclohexanone (87) as a yellow liquid: ir (film) 2910 (CH), 1657 (conj. C=O), 1545, 1453, 1174 cm^{-1} ; nmr (CCl_4) δ 7.40 (m, 1H, $-\text{SCH}=\text{C}-$), 7.24 (s, 5H, aromatic), 4.52 (m, 2H, $\text{PhCH}_2-\text{O}-$) ppm. This material was alkylated without further purification.

The lactone 91 was prepared according to a procedure developed by Piers and his coworkers (77). A 250-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, reflux condenser, magnetic stirrer, and pressure-equalizing addition funnel. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen and carefully charged with 2.97 g (0.076 mol) of potassium in 100 ml of t-butyl alcohol. The mixture was allowed to stir at room temperature for 4 hr at which time a homogeneous solution resulted. To the reaction mixture was added 7.46 g (0.022 mol) of 4-benzyloxy-6-n-butylthiomethylene-2,3-dimethylcyclohexanone (87) and the resulting solution was stirred for 10 min. The reaction mixture was then treated with 13.4 g (0.074 mol) of ethyl 3-bromopropanoate (Aldrich Chemical Co.) which was added dropwise over a 1 hr period. Stirring was

continued for an additional 30 min at which time most of the solvent was removed at reduced pressure, and the residue was diluted with water. The aqueous layer was extracted with six 50-ml portions of ether. The combined ethereal extracts were washed with three 50-ml portions of water, brine, and dried (MgSO_4). Removal of the solvent at reduced pressure gave a dark yellow liquid. By-products resulting from the reaction of potassium *t*-butoxide with ethyl 3-bromopropanoate were removed by distilling the liquid at 75° (0.30mm). The distillate was discarded and 9.0 g (0.021 mol - 92%) of the crude, dark-red, δ -keto ester 89 was recovered from the distillation flask.

A 250-ml, one-necked, round-bottomed flask which had been fitted with a reflux condenser, gas-inlet tube, and magnetic stirrer was repeatedly evacuated, flame-dried, and filled with prepurified nitrogen. The apparatus was charged with a solution of 9.0 g (0.21 mol) of the crude δ -keto ester 89, in 70 ml of 1,2-ethanediol and 70 ml of a 25% aqueous potassium hydroxide solution. The reaction mixture was heated to reflux and maintained at that temperature for 18 hr. The crude product was cooled, diluted with water, and extracted with two 30-ml portions of ether to remove all non-acidic materials. The basic aqueous layer was acidified with 10% aqueous hydrochloric acid solution, saturated with solid sodium chloride, and extracted with four 50-ml portions of

ether. The combined organic extracts were washed with three 20-ml portions of water, brine, and dried (MgSO_4). The solvent was removed under reduced pressure affording 5.45 g (0.018 mol - 86.1%) of the δ -keto acid, 90, (mixture of isomers) as a crude, yellow oil: ir (film) 3340-2410 (CO_2H , CH), 1715 (CO_2E), 1697 ($\text{C}=\text{O}$) cm^{-1} ; nmr (CCl_4) δ 13.7 (s, 1H, $-\text{CO}_2\text{H}$, exchange with D_2O), 7.26 (s, 5H, aromatic), 1.13 (s, 3H, angular $-\text{CH}_3$) ppm. No attempt was made to further purify this compound, and it was immediately converted to the lactone, 91.

A 250-ml, one-necked, round-bottomed flask was fitted with a reflux condenser, gas-inlet tube, and magnetic stirrer. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 5.45 g (0.018 mol) of crude δ -keto acid 90, in 80 ml of acetic anhydride. To the stirred mixture was added 780 mg (9.5 mmol) of sodium acetate and the solution was heated to reflux for 2 hr. The reaction mixture was cooled, the acetic anhydride was removed under reduced pressure, and the residual material was diluted with water. The aqueous phase was extracted with five 30-ml portions of ether. The combined organic phases were washed with three 40-ml portions of cold, saturated, sodium bicarbonate solution, water, brine, and dried (MgSO_4). The solvent was removed and the residue distilled affording 3.83 g (0.013 mol - 60%, based on ketone 84)

of 6-benzyloxy-4a,5,6,7-tetrahydro-4a,5-dimethylhydrocoumarin (91) as a light yellow liquid: bp 173-176° (0.15mm). This material, as judged by its nmr spectrum, consisted of a mixture of isomeric enol lactones. Crystallization of this mixture from *n*-hexane gave 2.03 g (7.1 mmol - 32.7%, based on ketone 84) of a solid material (presumably one of the isomers of 91) as white, needle-like crystals: mp 99-100°; ir (KBr) 2860 (CH), 1652 (C=O), 1678 (C=C), 1450, 1329, 1197 (C-O), 1025 cm⁻¹; nmr (CCl₄) δ 7.23 (s, 5H, aromatic), 5.11 (m, 1H, -CH=C-), 4.49 (q, 2H, *J*=11 Hz, PhCH₂O-), 3.35 (m, 1H, -OCH-), 1.02 (s, 3H, angular -CH₃), 0.97 (d, 3H, *J*=7 Hz, -CHCH₃) ppm; high resolution mass spectrum M⁺ obs: 286.1561; calcd: 286.1568.

No substantiating analytical data could be obtained for lactone 91 due to its extreme sensitivity to air and moisture.

Alkylation of 4-benzyloxy-6-n-butylthiomethylene-2,3-dimethylcyclohexanone (87) with acrylonitrile

A 50-ml, three-necked, round-bottomed flask equipped with a gas-inlet tube, magnetic stirrer, and reflux condenser was evacuated, flame-dried, and filled with prepurified nitrogen. The flask was charged with 0.345 g of a 57% sodium hydride-mineral oil dispersion (0.197 g - 8.2 mmol active hydride). The mineral oil was removed by washing the hydride with 20 ml of pentane under a nitrogen sweep and withdrawing

the pentane through a sintered glass gas dispersion tube attached to a water aspirator. The clean hydride was covered with 15 ml of anhydrous 1,2-dimethoxyethane, and then treated with 2.7 g (8.2 mmol) of blocked ketone 87. The reaction mixture was heated, with stirring, to reflux, whereupon hydrogen evolution began and continued for approximately 30 min. Following evolution of the hydrogen, the reaction mixture was maintained at the reflux temperature for 30 min, and was then cooled to 0°. The cooled solution was treated with 0.652 g (12.3 mmol) of acrylonitrile, dropwise and with rapid stirring, over a 10 min period. The reaction mixture was stirred for 2 hr at 0°, and warmed to room temperature over an additional hour. Several drops of acetic acid were added to neutralize any excess base, and the solution was poured into 50 ml of water and thoroughly extracted with ether. The combined ethereal layers were washed with two 15-ml portions of a saturated sodium bicarbonate solution, brine, and dried (MgSO₄). Removal of the solvent under vacuum afforded a dark oil which was purified by column chromatography on silica gel. Eluting with a mixture of 20% ethyl acetate in hexane gave 0.32 g (0.83 mmol- 10.1%) of a yellow oil, nitrile 88: ir (film) 2850 (CH), 2042 (CN), 1697 (C=O), 1655 (C=C), 1543, 1450, 1171 cm⁻¹; nmr (CCl₄) δ 7.40 (s, 1H, -SCH=C-), 7.28 (s, 5H, aromatic), 4.52 (m, 2H, PhCH₂O-) ppm; mass spectrum (70 ev) M⁺ 385.

4,4a,5,6,7,8-Hexahydro-4a,5-dimethyl-2(3H)-naphthalenone (63)
- from ketal 93

A procedure originally developed by Gilman and Van Ess (100) and more recently elaborated by House and Bare (137) was followed. A 25-ml, three-necked, round-bottomed flask was filled with prepurified nitrogen, and charged with a solution of 0.62 g (2.6 mmol) of acetal 93 dissolved in 5 ml of anhydrous ether. The ethereal solution was cooled to 0° with an external ice bath and treated with 0.29 g (13.0 mmol) of methyllithium in ether (Poote Mineral Co.; 1.64M), dropwise, with vigorous stirring, over a 15 min period. The reaction mixture was allowed to warm to room temperature, and was stirred at that temperature for 3 hr. Following this, the reaction mixture was added, dropwise and with rapid stirring, to 50 ml of an ice-cold 10% hydrochloric acid solution. The aqueous solution was saturated with sodium chloride and thoroughly extracted with ether. The combined ethereal extracts were washed with three 20-ml portions of a saturated sodium bicarbonate solution, brine, and dried (MgSO₄). The solvent was removed under reduced pressure to afford an oily residue. This viscous liquid was treated with 2.5 ml of a 10% aqueous hydrochloric acid solution and 5 ml of acetone for a period of ten minutes on a steam bath. The yellow residue was diluted with 20 ml of water and extracted with ether. The combined ethereal extracts were washed once with

brine and the solvent removed in vacuo. The resulting crude di-ketone was treated with potassium hydroxide (0.3 g) dissolved in 3 ml of water and 50 ml of methanol, at reflux for 4 hr. The methanol was removed under vacuum to give an orange liquid which was diluted with 30 ml of water and was thoroughly extracted with ether. The combined ethereal extracts were washed with three 20-ml portions of a saturated sodium bicarbonate solution, brine, and dried (MgSO_4). The solvent was removed under vacuum to afford 0.35 g of a viscous oil which was chromatographed on silica gel. Elution with 10% ethyl acetate in hexane gave 98 mg (0.53 mmol - 21.1%) of 4,4a,5,6,7,8-hexahydro-4a,5-dimethyl-2(3H)-naphthalenone (63) as a light yellow oil: ir (film) 2915 (CH), 1672 (C=O), 1616, 1354, 1195 (C-O) cm^{-1} ; nmr (CCl_4) δ 5.67 (t, 1H, $J=1$ Hz, $-\text{C}=\text{CH}$), 1.10 (s, 3H, angular $-\text{CH}_3$), 0.91 (m, 3H, $-\text{CHCH}_3$) ppm; mass spectrum (70 ev) M^+ 178.

The spectral properties of this material compared favorably with an authentic sample of octalone 63 prepared by an independent route (138).

6-Benzylloxy-4,4a,5,6,7,8-hexahydro-4a,5-dimethyl-2(3H)-naphthalenone (92)

A. Following the procedure of Barkley and his coworkers (99), a 25-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, pressure-equalizing addition funnel and thermometer. The apparatus was

evacuated, flame-dried, filled with prepurified nitrogen, and charged with 376 mg (1.3 mmol) of crystalline 6-benzyloxy-4a,5,6,7-tetrahydro-4a,5-dimethylhydrocoumarin (91) dissolved in 3 ml of anhydrous benzene and 13 ml of anhydrous ether. The reaction mixture was cooled to an internal temperature of -50° with a Dry Ice - alcohol bath. To the stirred solution was added dropwise 0.8 ml (2 mmol) of 2.5 M methylmagnesium bromide (101) in 2 ml of anhydrous ether. Stirring was continued at -50° for 1.5 hr and then 5 ml of acetone was added to decompose any residual Grignard reagent. The reaction mixture was then poured into 30 ml of cold, vigorously stirred, 10% aqueous hydrochloric acid solution. The two phases were separated, and the aqueous layer saturated with solid sodium chloride and extracted with three 20-ml portions of ether. The combined ethereal extracts were washed with three 25-ml portions of water, brine, and dried (MgSO_4). Removal of the solvent under reduced pressure afforded a white solid believed to be the intermediate keto alcohol, 95: ir (film) 3390 (OH), 2910 (CH), 1752 (C=O), 1448, 1025 cm^{-1} ; nmr (CDCl_3) δ 7.15 (s, 5H, aromatic), 4.37 (q, 2H, $\text{J}=11$ Hz, $\text{PhCH}_2\text{-O-}$), 1.28 (s, 3H, $-\text{C}(\text{OH})\text{CH}_3$), 0.97 (d, 3H, $\text{J}=7$ Hz, $-\text{CHCH}_3$), 0.96 (s, 3H, angular $-\text{CH}_3$) ppm. Comparable results were obtained when unpurified, oily lactone 91 was employed.

A 50-ml, one-necked, round-bottomed flask, was fitted with a gas-inlet tube, reflux condenser, magnetic stirrer,

and was filled with prepurified nitrogen. The apparatus was charged with a solution of 400 mg (1.3 mmol) of crude keto alcohol 95 dissolved in 30 ml of anhydrous methanol containing a solution of potassium hydroxide (200 mg) in 1.4 ml of water. The solution was heated to reflux for 2 hr with stirring. The methanol was removed under reduced pressure, the residue diluted with water, and neutral products were isolated by extraction with five 30-ml portions of ether. The combined ethereal extracts were washed with three 20-ml portions of water, brine, and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave 360 mg of a light yellow oil which was chromatographed on 20 g of silica gel. Elution with 8% ethyl acetate in hexane gave 284 mg (1 mmol - 77.0%, based on lactone 91) of 6-Benzyloxy-4,4a,5,6,7,8-hexahydro-4a,5-dimethyl-2(3H)-naphthalenone (92) as a white solid. The analytical sample, obtained after two crystallizations from *n*-hexane, melts at 107-108°: ir (KBr) 2910 (CH), 1677 (conj. C=O), 1499, 1452, 1362, 1198 (C-O), 878 cm^{-1} ; nmr (CCl_4) δ 7.20 (s, 5H, aromatic), 5.57 (t, 1H, $J=4$ Hz, -C=CH-), 4.45 (q, 2H, $J=12$ Hz, $PhCH_2O-$), 3.25 (td, 1H, $J=4$ Hz, $PhCH_2OCH-$), 1.04 (s, 3H, angular -CH₃), 0.96 (d, 3H, $J=7$ Hz, -CHCH₃) ppm; mass spectrum (70 ev) M^+ 284.

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51; O, 11.25.
Found: C, 80.24; H, 8.55; O, 11.33.

The basic aqueous layer from the above extraction was acidified with concentrated hydrochloric acid and the acidic product was isolated by extraction with three 20-ml portions of ether. The combined ethereal extracts were washed with brine and dried (Na_2SO_4). Removal of the solvent under vacuum provided 40 mg (10%) of carboxylic acid 90 which had identical spectral properties as those described earlier.

Repetition of the above experiment on a larger scale involved the use of distillation as a means for purification. Thus, 24.76 g (0.086 mol) of lactone 91, dissolved in 240 ml of benzene and 1 l of anhydrous ether, was treated with 56.5 ml (0.13 mol) of 2.3M methylmagnesium bromide at -50° . The keto alcohol 95 obtained upon work-up was subjected to potassium hydroxide (18 g) dissolved in 180 ml of water and 1500 ml of methanol. This reaction mixture was refluxed for 1.5 hr under nitrogen and worked-up as described above. The residue was distilled affording 20.7 g (0.073 mol - 84.4%) of 6-Benzoyloxy-4,4a,5,6,7,8-hexahydro-4a,5-dimethyl-2(3H)-naphthalenone (92) as a colorless liquid, bp 179-185 (0.45 mm), which solidified upon cooling. All spectral properties for this liquid octalone 92 were identical to those described above.

B. Following the general procedure outlined by Piers and his coworkers (77), a 50-ml, three-necked, round-bottomed flask was equipped with a magnetic stirrer, gas-inlet tube,

and pressure-equalizing dropping funnel. The apparatus was evacuated, flame-dried, and filled with prepurified nitrogen. The flask was charged with 2.0 g (7.0 mmol) of 6-benzyloxy-4a,5,6,7-tetrahydro-4a,5-dimethylhydrocoumarin (91) dissolved in 15 ml of anhydrous tetrahydrofuran. The resulting suspension was cooled to -25° by means of an external carbon tetrachloride-Dry Ice slush bath, and was treated with 4.8 ml (8 mmol) of methyllithium in ether (Foote Mineral Co.; 1.66M), dropwise, and with vigorous stirring, over a five min period. The resulting solution was allowed to stir for an additional 1.5 hr at -25° . The reaction mixture was poured into dilute hydrochloric acid and the product thoroughly extracted with ether. The ether was washed with brine and dried (Na_2SO_4). Removal of the solvent in vacuo afforded a clear residue. To the crude, oily product thus obtained, was added a solution of potassium hydroxide (1 g) in 7.6 ml of water and 60 ml of methanol, and the solution was refluxed under an atmosphere of nitrogen for 1.5 hr. The methanol was removed at reduced pressure, the residue was diluted with 50 ml of water, and the neutral product was isolated by extraction with three 30-ml portions of ether. The combined ethereal layers were washed with brine and dried (Na_2SO_4). Removal of the solvent under vacuum afforded 1.5 g of a yellow oil which was chromatographed on silica gel. Elution with 10% ethyl acetate in hexane gave 0.5 g (1.76 mmol -

25.1%) of 6-Benzoyloxy-4,4a,5,6,7,8-hexahydro-4a,5-dimethyl-2(3H)-naphthalenone (92) as a light yellow oil with ir and nmr identical to those described in part A.

C. A procedure of general utility published by Henrick *et al.* (97) was followed. A 100-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, pressure-equalizing addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen and charged with an ethereal solution of 5.7 ml (9.1 mmol) of *n*-butyllithium (Foote Mineral Co.; 1.58M) and 40 ml of anhydrous tetrahydrofuran. To the vigorously stirring solution was added 3.75 g (9.1 mmol) of triphenylmethylphosphonium bromide over a 5 min period. The reaction mixture was allowed to stir for 18 hr at room temperature whereupon the solution turned light yellow in color. To this resultant methylene-triphenylphosphorane was added 2.57 g (9.1 mmol) of 6-benzoyloxy-4a,5,6,7-tetrahydro-4a,5-dimethylhydrocoumarin (91) dissolved in 10 ml of anhydrous tetrahydrofuran. The reaction mixture was allowed to stir at room temperature for 18 hr, and was then poured into 100 ml of ice water and was thoroughly extracted with ether. The ether was washed with two 30-ml portions of water, brine, and dried (MgSO₄). Removal of the solvent under vacuum afforded an orange residue. To this crude, oily product was added a solution of potassium hydroxide (0.8g) in 6 ml of water and

100 ml of methanol, and the solution was stirred under an atmosphere of nitrogen for 24 hr at room temperature. The methanol was removed at reduced pressure, the residue was diluted with 50 ml of water, and the neutral product was isolated by extraction with three 40-ml portions of ether. The combined ethereal layers were washed with brine and dried ($MgSO_4$). The solvent was removed in vacuo affording 1.12 g of an orange oil which was chromatographed on silica gel. Elution with 10% ethyl acetate in hexane gave 0.67 g (2.4 mmol - 26.1%) of 6-Benzyloxy-4,4a,5,6,7,8-hexahydro-4a,5-dimethyl-2(3H)-naphthalenone (92) as a light yellow oil with ir and nmr essentially identical to those described earlier.

6,6-Ethylenedioxy-1,2,3,5,6,7,8,8a-octahydro-1,8a-dimethyl-2-naphthol (98)

A 2-l, one-necked, round-bottomed flask, was fitted with a Dean-Stark water trap, reflux condenser, and gas-inlet tube. The apparatus was repeatedly evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 32.5 g (0.114 mol) of 6-benzyloxy-4,4a,5,6,7,8-hexahydro-4a,5-dimethyl-2(3H)-naphthalenone (92) dissolved in 700 ml of anhydrous benzene. To this solution was added 70.7 g (1.14 mol) of 1,2-ethanediol and 500 mg of p-toluenesulfonic acid. The resulting suspension was heated slowly to reflux (85°) and held at that temperature for 12 hr, during which time 2.0 ml of water was removed from the system. 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 12 hr. The thimble was recharged with molecular sieves and refluxing was continued for an additional 9 hr. Following this treatment, the benzene solution was cooled, diluted with 300 ml of ether, and washed with three 100-ml portions of a saturated sodium bicarbonate solution, brine, and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded 37.1 g (0.113 mol - 99.1%) of the benzyloxy acetal, 97, as a yellow oil: ir (film) 2865 (CH), 1668 (C=C), 1449 cm^{-1} ; nmr (CCl_4) δ 7.14 (s, 5H, aromatic), 5.55 (m, 1H, vinyl proton of 92), 5.05 (m, 1H, vinyl proton of acetal 97), 3.79 (s, 4H, $-\text{OCH}_2\text{CH}_2\text{O}-$) ppm.

A 2-l, three-necked, round-bottomed flask was fitted with a gas-inlet tube, Dry Ice condenser, pressure-equalizing addition funnel, mechanical stirrer, and gas-outlet tube leading to a one-way mercury valve. The apparatus was flame-dried, briefly flushed with nitrogen, and charged with 1000 ml of liquid ammonia (distilled through a potassium hydroxide drying tower). A solution of 37.1 g (0.113 mol) of crude benzyloxy acetal, 97, dissolved in 250 ml of absolute ethanol was then added dropwise over a 45 min period to the stirred ammonia. Small pieces of sodium (15 g, 0.625 mol) were added to the reaction mixture at a rate such as to maintain a persistent blue color. After 1.5 hr, the blue reac-

tion mixture was treated with excess ethanol and the ammonia was allowed to evaporate through a mercury bubbler, over a 9 hr period. Ether was added to replace the evaporated ammonia. The crude mixture was diluted with 400 ml of water, the phases were separated, and the aqueous phase was saturated with solid sodium chloride followed by extraction with four 50-ml portions of ether. The combined organic extracts were washed with brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave 26.4 g (0.111 mol - 97.4% based on ketone 92) of 6,6-ethylenedioxy-1,2,3,5,6,7,8,8a-octahydro-1,8a-dimethyl-2-naphthol (98) as a light yellow oil which, despite repeated attempts failed to crystallize: ir (film) 3380 (OH), 2860 (CH), 1354, 1259 cm^{-1} ; nmr (CCl_4) δ 4.97 (m, 1H, $-\text{CH}=\text{C}-$), 3.70 (s, 4H, $-\text{OCH}_2-\text{CH}_2\text{O}-$), 1.06 (s, 3H, angular $-\text{CH}_3$), 0.90 (d, 3H, $J=4$ Hz, $-\text{CHCH}_3$) ppm; high resolution mass spectrum M^+ obs: 238.1564; calcd: 238.1568.

7,7-Ethylenedioxy-4,4a,5,6,7,8-hexahydro-4,4a-dimethyl-3(2H)-naphthalone (99)

The procedure of Church et al. (74) was followed. A 500-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, a magnetic stirrer, and a pressure-equalizing addition funnel. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 26.4 g (0.111 mol) of 6,6-ethylenedioxy-1,2,3,5,6,7,8,8a-

octahydro-1,8a-dimethyl-2-naphthol (98) dissolved in 200 ml of acetone. The reaction mixture was cooled to 5 - 9° and the light yellow solution was treated with 27.8 ml (0.111 mol - equiv) of Jones reagent (75) over a 8 min period. The mixture was stirred for an additional 20 min, isopropyl alcohol was added to destroy any excess oxidizing agent, and the blue-green mixture was poured into 600 ml of brine. The layers were separated and aqueous portion was extracted with five 100-ml portions of ether. The combined ethereal extracts were washed with three 70-ml portions of a saturated sodium bicarbonate solution, brine, and dried (Na₂SO₄). Removal of the solvent under reduced pressure afforded 21.4 g (0.091 mol - 82.0%) of a crude, yellow, semi-solid, keto acetal 99: ir (film) 2880 (CH), 1703 (C=O) cm⁻¹; nmr (CCl₄) δ 5.13 (m, 1H, -CH=C-), 3.75 (s, 4H, -OCH₂CH₂O-), 0.91 (d, 3H, \underline{J} =6 Hz, -CHCH₃), 0.63 (s, 3H, angular -CH₃) ppm; high resolution mass spectrum M⁺ obs: 286.1403; calcd: 236.1412.

Attempted epimerization of 7,7-ethylenedioxy-4,4a,5,6,7,8-hexahydro-4,4a-dimethyl-3(2H)-naphthalone (99)

A. A 50-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube and a magnetic stirrer. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with 80 mg (0.33 mmol) of 7,7-ethylenedioxy-4,4a,5,6,7,8-hexahydro-4,4a-dimethyl-3(2H)-naphthalone (99) and 25 ml of a 1% solution of potassium

hydroxide in ethanol. This reaction mixture was allowed to stir at room temperature for 12 hr. The ethanol was removed at reduced pressure and the residue diluted with water. The aqueous layer was thoroughly extracted with ether. The combined ethereal extracts were washed with two 10-ml portions of a saturated sodium bicarbonate solution, brine, and dried (Na_2SO_4). The solvent was removed at reduced pressure and the residue chromatographed on silica gel. Elution with 20% ethyl acetate in hexane gave 30 mg of a viscous liquid: ir (film) 2905 (CH), 1699 (β,γ -C=O), 1667 (α,β -C=O), 1600 cm^{-1} ; nmr (CCl_4) δ 5.62 (s, 1H, $-\underline{\text{C}}\underline{\text{H}}=\text{C}$), 5.13 and 4.91 (m, 2H, $-\underline{\text{C}}\underline{\text{H}}=\underline{\text{C}}\underline{\text{H}}-$) ppm.

B. The above reaction was repeated utilizing potassium *t*-butoxide in *t*-butanol as well as an aqueous solution of 0.5% potassium hydroxide. In both cases a mixture of β,γ - and α,β - ketones were observed.

Treatment of semicarbazone 100 with lithium in ammonia

Semicarbazone 100 was prepared from 4,4a,5,6,7,8-hexahydro-4a-methyl-2(3H)-naphthalenone (61) in a 70% yield following the general procedure outlined by Fieser (134). A 500-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, Dry Ice condenser, mechanical stirrer, and gas-outlet tube leading to a one-way mercury valve. The apparatus was flame-dried, briefly flushed with nitrogen, and charged with 200 ml of liquid ammonia (distilled through a

potassium hydroxide drying tower). Following collection of the liquid ammonia, 0.125 g (0.018 mol) of lithium wire was added in small pieces. A solution of 1.6 g (7.2 mmol) of semicarbazone 100, dissolved in 75 ml of anhydrous tetrahydrofuran, was then added dropwise, over a 30 min period, to the stirred, blue solution. The reaction mixture was stirred for an additional 1 hr and then treated with excess ammonium chloride. The ammonia was allowed to evaporate over a 1 hr period through a mercury bubbler. The crude product was diluted with 200 ml of brine, and the aqueous phase was thoroughly extracted with ether. The combined organic phases were washed with brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a semi-solid which was recrystallized from ethanol to give 1.23 g of a white solid: mp 197-200° [lit. (65) mp 200-202°]. All spectral properties were identical to those of the starting material, semicarbazone 100, indicating that this compound was not altered when treated with lithium in ammonia.

Treatment of semicarbazone 104 with hydrogen over palladium on charcoal

A 50-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, gas-outlet tube, and magnetic stirrer. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and flushed four times with hydrogen.

The flask was charged with 0.5 g of 10% palladium chloride on activated charcoal and 20 ml of absolute methanol. The catalyst was hydrogenated for a period of four hours at which time the hydrogen uptake ceased. The reaction mixture was treated with 0.4 g (2.1 mmol) of semicarbazone 104. The mixture was stirred under 1 atm of hydrogen for 2 hr during which time 50 ml of hydrogen (52 ml required) was taken up. The catalyst was removed by filtration through Celite and the filtrate was concentrated under reduced pressure, affording 0.45 g of a viscous oil which could be crystallized from ethanol: mp 232°; nmr (d₆-DMSO) no vinyl proton indicated while most of the benzyl ether remained; mass spectrum (70 ev) M⁺ 253.

Repetition of the preparation attempted above using octalone 92, gave the decalone as the major product. Under all conditions employed, the rate of double bond reduction was seen to be faster than cleavage of the benzyl ether.

Des-isopropylidene petasol (15) [4,4a,5,6,7,8-hexahydro-t-6-hydroxy-r-4a,c-5-dimethyl-2(3H)-naphthalenone]

A 1-l, three-necked, round-bottomed flask was fitted with a gas-inlet tube, Dry Ice condenser, mechanical stirrer, and gas-outlet tube leading to a one-way mercury valve. The apparatus was flame-dried, briefly flushed with nitrogen, and charged with 1000 ml of liquid ammonia (distilled through a potassium hydroxide drying tower). Following collection of

the liquid ammonia, 1.39 g (0.2 mol) of lithium wire was added in small pieces. A solution of 21.4 g (0.091 mol) of keto acetal 99, dissolved in 200 ml of anhydrous ether was then added dropwise, over a 45 min period, to the stirred, blue solution. The reaction mixture was stirred for an additional 1.5 hr and then treated with excess ethanol. The ammonia was allowed to evaporate over a 12 hr period through a mercury bubbler. Ether was added to replace the evaporated ammonia. The crude product mixture was diluted with 600 ml of brine, the two phases were separated, and aqueous phase was extracted with five 100-ml portions of ether. The combined organic phases were washed with brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave 20.1 g (0.084 mol - 92.3%) of the hydroxy acetal 105, as a viscous yellow oil: ir (film) 3360 (OH), 2885 (CH), 1353, 1270 cm^{-1} ; nmr (CCl_4) δ 4.96 (m, 1H, $-\text{CH}=\text{C}-$), 3.71 (s, 4H, $-\text{OCH}_2\text{CH}_2\text{O}-$), 0.89 (s, 3H, angular $-\text{CH}_3$) ppm; high resolution mass spectrum M^+ obs: 238.1579; calcd: 238.1569.

A 2-l, three-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, and reflux condenser. The apparatus was evacuated, filled with prepurified nitrogen, and charged with a solution of 20.1 g (0.084 mol) of crude hydroxy acetal 105 dissolved in 1000 ml of acetone. This stirring solution was treated with 1.0 g of p-toluenesulfonic acid and 20 ml of water, and heated to

reflux temperature for 2 hr. The reaction mixture was cooled to room temperature, the majority of the solvent was removed at reduced pressure, and the residue was taken up in ether. The ethereal layer was washed with three 70-ml portions of a saturated sodium bicarbonate solution, brine, and dried (Na_2SO_4). Removal of the solvent under vacuum followed by distillation of the residue afforded 5.9 g (0.03 mol - 33.4% based on keto acetal 99) of des-isopropylidenepeetasol (15) as a clear liquid which crystallized upon cooling. The analytical sample, obtained after two crystallizations from a 10% solution of ethyl acetate in *n*-hexane, melts at 91-92°: ir (KBr) 3490 (OH), 2885 and 2852 (CH), 1656 (C=O), 1239, 1168, 1041, 944, 891, 774 cm^{-1} ; nmr (CDCl_3) δ 5.74 (s, 3H, $-\text{CH}=\text{C}-$), 3.55 (m, 1H, $-\text{CHOH}$), 1.12 (s, 3H, angular $-\text{CH}_3$), 1.00 (d, 3H, $\text{J}=2$ Hz, $-\text{CHCH}_3$) ppm.

Anal. Calcd for $\text{C}_{12}\text{H}_{18}\text{O}_2$: C, 74.19; H, 9.34. Found: C, 74.12; H, 9.28.

cis-3,4,4a,5,6,7,8,8a-Octahydro-t-6-hydroxy-r-4a,c-5-dimethyl-2(1H)-naphthalone (107)

A 25-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, gas-outlet tube and magnetic stirrer. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and flushed four times with hydrogen. The flask was charged with a solution of 83.6 mg (0.43 mmol) of des-isopropylidenepeetasol (15) dissolved in 5 ml of abso-

lute ethanol , and 22 mg of 10% palladium chloride on activated charcoal. The mixture was stirred under 1 atm of hydrogen for 3.5 hr during which time 10 ml of hydrogen (9.6 ml required) was taken up. The catalyst was removed by filtration through Celite and the filtrate was concentrated under reduced pressure affording 80 mg of a yellow oil which was chromatographed on 20 g of silica gel. The column was eluted with 50% ethyl acetate in hexane giving 66 mg of a single, solid component. Three crystallizations of this material from *n*-heptane afforded 41 mg (0.21 mmol - 48.8%) of cis-3,4,4a,5,6,7,8,8a-octahydro-t-6-hydroxy-r-4a,c-5-dimethyl-2(1H)-naphthalone (107) as a white solid: mp 91 - 92° [lit. (74) mp 92 - 93°; mmp 92 - 93°]; ir (KBr) 3490 (OH), 2910 and 2845 (CH), 1696 (C=O), 1377, 1034 cm⁻¹.

The richly detailed ir spectrum of this material was identical with the ir spectrum of an authentic sample (74).
4,4a,5,6,7,8-Hexahydro-r-4a,c-5-dimethyl-2(3H)-naphthalenone (63c)

A. According to the procedure described by K. Naya et al. (44), a 25-ml, one-necked, round-bottomed flask was fitted with a gas-inlet tube. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 170 mg (0.71 mmol) of crude 6,6-ethylenedioxy-1,2,3,5,6,7,8,8a-octahydro-r-1,c-8a-dimethyl-t-2-naphthol (105) dissolved in 1.5 ml of dry pyridine. The reaction mix-

ture was cooled to an internal temperature of 0° with an ice bath and 400 mg (2.1 mmol) of p-toluenesulfonyl chloride was added. The reaction mixture was allowed to stand at room temperature for 3 days. The reaction mixture was then poured into 30 ml of ice-water, the aqueous solution was extracted with five 10-ml portions of ether, and the combined ethereal fractions were washed with a cold aqueous solution of 2% sulfuric acid, a cold solution of dilute sodium bicarbonate, brine, and dried (Na_2SO_4). Removal of the solvent afforded crude tosyloxy acetal 106: ir (film) 2910 (CH), 1356 (tosylate), 1170 (tosylate), 1029 cm^{-1} ; nmr (CCl_4) δ 7.05 - 7.6 (m, 4H, aromatic), 3.74 (s, 4H, $-\text{OCH}_2\text{CH}_2\text{O}-$), 2.28 (s, 3H, CH_3 -aromatic) ppm.

A 25-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, reflux condenser, magnetic stirrer, and pressure-equalizing addition funnel. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with 79 mg (2.1 mmol) of lithium aluminum hydride in 5 ml of anhydrous ether. To the stirred solution was added 251 mg (0.64 mmol) of crude tosylate, 106 dissolved in 10 ml of anhydrous ether. The reaction mixture was stirred at reflux temperature for 24 hr. After cooling the solution to room temperature, the excess hydride was decomposed with moist ether followed by water and 10% aqueous hydrochloric acid solution. The aqueous layer was extracted with four

10-ml portions of ether and the combined ethereal extracts were washed with three 20-ml portions of dilute sodium bicarbonate solution, water, and brine. The solvent was removed at reduced pressure affording a yellow oil.

The crude yellow acetal was dissolved in 4 ml of acetone. To this solution was added 2 ml of a 10% aqueous hydrochloric acid solution and the mixture was warmed for 10 min on a steam bath. The acetone was evaporated in an air stream, 25 ml of saturated salt solution was added, and the ketone was isolated by extraction with three 10-ml portions of ether. The combined organic layers were washed with three 10-ml portions of saturated sodium bicarbonate solution, water, brine, and dried (MgSO_4). Removal of the solvent under reduced pressure afforded a viscous yellow oil, which was chromatographed on 15 g of silica gel. Elution with 7% ethyl acetate in hexane gave 50 mg (0.28 mmol - 39.6% based on hydroxyl acetal 105) of 4,4a,5,6,7,8-hexahydro-1-4a,2-5-dimethyl-2(3H)-naphthalenone (63c) as a clear liquid: ir (film) 2920 and 2850 (CH), 1667 (conj. C=O), 1612 (conj. C=C), 1346, 1232, 1182, 874, 853 cm^{-1} ; nmr (CCl_4) δ 5.64 (s, 1H, $-\text{CH}=\text{C}-$), 1.12 (s, 3H, angular $-\text{CH}_3$), 0.91 (m, 3H, $-\text{CHCH}_3$) ppm. The octalone so obtained was further characterized by the identity of its nmr and ir spectra with those of an authentic sample (73a), (77) independently synthesized in these laboratories (138).

B. 4,4a,5,6,7,8-Hexahydro-r-4a,c-5-dimethyl-2(3H)-naphthalenone (63c) could also be prepared by proceeding through a mesylate precursor. Thus, following the general procedure of Tadanier (140), a 25-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, thermometer, rubber septum, and magnetic stirrer. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen and charged with 165 mg (0.70 mmol) of the hydroxy acetal of 15x dissolved in 2.5 ml of dry pyridine. The reaction mixture was cooled to an internal temperature of 0° with an external ice bath and treated with 148 mg (1.3 mmol) of methanesulfonyl chloride, dropwise and with stirring, over a 5 min period. The reaction mixture was stirred at 0° for 0.5 hr and then was allowed to stand at room temperature for 15 hr. The solution was then poured into 50 ml of ice water and thoroughly extracted with chloroform. The combined chloroform extracts were washed with two 20-ml portions of cold, 2% aqueous sulfuric acid, two 20-ml portions of cold, dilute sodium bicarbonate solution, brine, and dried (Na₂SO₄). Removal of the solvent afforded the crude mesylate of 15x: ir (film) 2918 (CH), 1335 (mesylate), 1155 (mesylate), 1010 cm⁻¹; nmr (CCl₄) δ 3.74 (s, 4H, -OCH₂CH₂O-), 2.97 (s, 3H, -SO₂CH₃) ppm.

The mesylate was displaced with lithium aluminum hydride as described in part A. The resulting acetal was cleaved in acetone and a 10% aqueous solution of hydrochloric acid as

outlined above. Usual work-up afforded a viscous oil which was chromatographed on silica gel. Elution with 10% ethyl acetate in hexane gave 35.4 mg (0.20 mmol - 28.6% based on the hydroxy acetal of 15x) of 4,4a,5,6,7,8-hexahydro-g-4a, c-5-dimethyl-2(3H)-naphthalenone (63c). All spectral properties for octalone 63c were identical to those described in part A.

Attempted preparation of 3-bromo-4,4a,5,6,7,8-hexahydro-4a-methyl-2(3H)-naphthalenone (118)

A. Following the briefly outlined procedure of Avang and Wolfe (108), a 100-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, pressure-equalizing addition funnel, and magnetic stirrer. The apparatus was evacuated, flame-dried, filled with prepurified nitrogen, and charged with a solution of 1.0 g (6.1 mmol) of 4,4a,5,6,7,8-hexahydro-4a-methyl-2(3H)-naphthalenone (61) dissolved in 25 ml of dry tetrahydrofuran cooled to 20°. A solution of 3.0 g (6.1 mmol) of pyrrolidone hydrotribromide in 25 ml of dry tetrahydrofuran was added dropwise and with stirring over a 30 min period. After the addition was complete, stirring was continued for an additional 1.5 hr. The white solid of pyrrolidone hydrobromide was filtered and the filtrate was concentrated at reduced pressure. Water was added and the aqueous phase was extracted three times with ether. The combined ethereal extracts were washed with water, a saturated

solution of sodium bicarbonate, brine and dried (MgSO_4). The solvent was removed at reduced pressure to yield a mixture of mono-, di-, and tri-bromoketones, plus other unidentified products: nmr (CCl_4) δ 6.11, 5.71, 5.48 (singlets, vinyl protons), 4.89 (m, $-\text{CHBr}$), 1.57 and 1.29 (s, angular $-\text{CH}_3$'s) ppm.

Purification by column chromatography resulted in the isolation of seven components, none of which were homogeneous. Slow decomposition of these fractions occurred at room temperature.

B. Use of the brominating agents trimethylphenylammonium perbromide (110), (111) and pyridinium hydrotribromide (112) gave nearly identical results to those found in part A. Buffering the reaction mixture with sodium acetate also proved to be unsuccessful.

Attempted preparation of bromoacetal 124b followed by treatment with lithium diisopropenyl cuprate

Following a modification of the procedure suggested by Keith (111), a 250-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube and a magnetic stirrer. The apparatus was evacuated, flame-dried, filled with nitrogen, and charged with a solution of 3.2 g (0.0154 mol) of acetal 124a dissolved in 100 ml of dry tetrahydrofuran. To the stirring solution was added 4.9 g (0.0154 mol) of pyridinium hydrotribromide. Immediately a white precipitate of pyridine

hydrobromide formed. The solution was stirred at room temperature for one hour, poured into 100 ml of water, and thoroughly extracted with ether. The combined ethereal fractions were washed with a saturated sodium bicarbonate solution, brine, and dried (Na_2SO_4). Removal of the solvent afforded an α -bromoacetal which appeared to be extremely labile and thus was alkylated immediately with lithium diisopropenyl cuprate.

A modification of Starrett's (141) procedure was employed. A 500-ml, three-necked, round-bottomed flask was equipped with a Hershberg wire stirrer, gas-inlet tube, reflux condenser, and pressure-equalizing addition funnel. The bottom of the flask was equipped with a stopcock and a 24/40 inner joint containing glass wool to facilitate filtering the isopropenyl lithium under inert gas conditions. The apparatus was evacuated several times, filled with prepurified argon, charged with 2.7 g (0.39 mol) of finely divided lithium ribbon (Foote Mineral Co.; 1% sodium content), and 125 ml of anhydrous ether. The lithium suspension was stirred very rapidly and 24.2 g (0.2 mol) of freshly distilled isopropenyl bromide dissolved in 20 ml of ether was added dropwise at a rate sufficient to maintain the ether at reflux temperature. After stirring for 1 hr, the grey solution was filtered under an argon atmosphere, through glass wool into a 500-ml, round-bottomed, three-necked flask fitted

with a mechanical stirrer, thermometer, gas-inlet tube, and the aforementioned glass wool filter. The flask had previously been charged with 21.0 g (0.11 mol) of anhydrous cuprous iodide suspended in 100 ml of dry tetrahydrofuran and cooled to -10° in an ice-salt bath.

The lithium diisopropenyl cuprate was completely formed after stirring at -10° for 45 min as evidenced by the lack of color when an aliquot was added to Michler's ketone (Gilman color test #1) (142). To the lithium diisopropenyl cuprate slurry was added, dropwise, over a 15 min period, 3.2 g (0.011 mol) of bromoacetal 124b dissolved in 20 ml of anhydrous tetrahydrofuran. The reaction mixture was stirred for 4 hr at 0° . The resulting dark solution was poured into an aqueous solution of ammonium chloride and ammonium hydroxide at pH 8. The aqueous phase was extracted three times with ether. The combined ethereal extracts were washed with brine and dried (MgSO_4). Removal of the solvent in vacuo gave a viscous oil: nmr (CCl_4) δ 4.5 - 6.1 (vinyl protons; all broad multiplets), only a trace of the acetal protons were present; ir (film) no α, β -unsaturated carbonyl, no isopropenyl functionality. Bromoacetal 124b was quite insoluble under the reaction conditions employed above, and perhaps a heterogeneous solution is the cause of the non-reactivity.

Treatment of 3-carbomethoxy-4,4a,5,6,7,8-hexahydro-4a-

methyl-2(3H)-naphthalenone (130) with lithium hydride and methyllithium

A 100-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, constant-pressure addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried, flushed with nitrogen, and charged with 28 mg (3.5 mmol) of lithium hydride and 20 ml of anhydrous ether. To this suspension was added a solution of 0.5 g (2.3 mmol) of β -keto ester 130 dissolved in 10 ml of anhydrous ether, dropwise and with stirring over a 10 min period. The reaction mixture was heated to reflux for 7 hr, and was then cooled to room temperature. To the resulting heterogeneous solution was added 14.0 ml (23 mmol) of methyllithium (Foote Mineral Co.; 1.64M), dropwise, over a 15 min period. The reaction mixture was then heated to reflux for 2 hr, cooled to room temperature, and quenched with 5 ml of acetone. The ethereal solution was added dropwise to a rapidly stirring solution of cooled, 25% ammonium chloride in water. The layers were separated, and the aqueous portion thoroughly extracted with ether. The combined ethereal extracts were washed with a saturated solution of sodium bicarbonate, brine, and dried (Na_2SO_4). Removal of the solvent afforded a viscous yellow oil which was chromatographed on silica gel. Elution with 10% ethyl acetate in hexane afforded an olefinic material identified as

triene 132: ir (film) no carbonyl or hydroxyl; nmr (CCl₄) δ 5.1, 4.5, 3.8, 2.1, 1.09 ppm; mass spectrum (70ev) M⁺ 190.

Employing sodium hydride in place of lithium hydride gave similar results to those above.

Attempted cleavage of acetal 134

A. Treatment of 134 with p-toluenesulfonic acid, acetone, and water under reflux gave octalone 136.

B. Treatment of 134 with 10% HCl in acetone at steam bath temperatures gave octalone 136.

C. Treatment of 134 with thionyl chloride in pyridine (115) (116), followed by reflux with 2% sulfuric acid and acetone gave intractable material.

Attempted preparation of 3-acetyl-4,4a,5,6,7,8-hexahydro-3-isopropenyl-4,4a-dimethyl-naphthalenone

The procedure of Zalkow and Ellis (117) was employed. A 25-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, and reflux condenser. The apparatus was evacuated, flame-dried, flushed with nitrogen, and charged with a solution of 0.331 g (1.52 mmol) of octalone 142 dissolved in 10 ml of dry benzene. To the stirring solution was added 0.75 g (1.7 mmol) of freshly prepared lead tetraacetate. The reaction mixture was heated at reflux temperature for 5 hr, cooled to room temperature, and diluted with 20 ml of ether. The organic layer was washed with eight 10-ml portions of water at which time the aqueous

layer was neutral to litmus. The organic extract was then dried (Na_2SO_4). The solvent was removed under vacuum to afford a viscous oil which was chromatographed on silica gel. Elution with 10% ethyl acetate in hexane gave 180 mg of an oil whose spectral properties were very different from the expected product or starting material.

Attempted preparation of the lithium enolate of 4,4a,5,6,7,8-hexahydro-4a-methyl-3-isopropenyl-2(3H)-naphthalenone (146)

According to the general procedure developed by House and Trost (119), a 25-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube and magnetic stirrer. The flask was evacuated, flame-dried, flushed with nitrogen, and charged with 0.9 g (3.7 mmol) of triphenylmethane. To this was added 1.8 ml (3 mmol) of methyllithium in ether (Foote Mineral Co.; 1.64M), dropwise, and with stirring, over a 5 min period. Approximately 1 ml of dimethoxyethane was added and the solution turned blood-red. The mixture was allowed to stir for an additional 10 min and was then treated with 90 mg (0.44 mmol) of octalone 136 dissolved in 3 ml of dimethoxyethane. This reaction mixture was allowed to stir for 1 hr, and was then quenched with several drops of acetic acid. The resulting solution was diluted with 20 ml of ether and washed with a dilute solution of sodium bicarbonate, brine, and dried (Na_2SO_4). Removal of the solvent in vacuum afforded a viscous oil. The spectral properties of this ma-

terial were indicative of a compound containing a β,γ -carbonyl, ie. octalone 147.

Treatment of des-isopropylidenepetasol (15) with sodium hydride and dimethylcarbonate

A 25-ml, three-necked, round-bottomed flask was equipped with a gas-inlet tube, magnetic stirrer, pressure-equalizing addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried, flushed with nitrogen, and charged with 0.11 g of a 57% sodium hydride-mineral oil dispersion (62 mg - 2.6 mmol active hydride). The mineral oil was removed by washing the solid with three 10-ml portions of pentane, under a continual sweep of nitrogen, followed by removal of the pentane through a sintered glass gas dispersion tube attached to water aspirator. The clean hydride was covered with 10 ml of anhydrous benzene and 0.17 g (1.9 mmol) of freshly distilled dimethylcarbonate. To this stirring suspension was added a solution of 0.13 g (0.63 mmol) of des-isopropylidenepetasol (15) dissolved in 2 ml of benzene, dropwise and with stirring, over a ten min period. The mixture was slowly heated to reflux and held there for 45 hr. The reaction mixture was then cooled to 5°, treated with glacial acetic acid until the solution was acidic to litmus paper, and poured into 50 ml of ice water. The resulting phases were separated, the aqueous phase was saturated with solid sodium chloride, and was extracted with three 20-ml

portions of ether. The combined ethereal extracts were washed with three 20-ml portions of a saturated sodium bicarbonate solution, brine, and dried (Na_2SO_4). Removal of the solvent afforded a yellow oil, believed to be carbonate 150, having the following spectral properties: 2860 (CH), 1725, 1661, 1613, 1438, 1192 cm^{-1} ; nmr (CCl_4) δ 5.69 (s, 1H, $-\text{C}=\text{CH}-$), 4.6 (m, 1H, $-\text{OCH}-$), 3.75 (s, 3H, $-\text{OCO}_2\text{CH}_3$), 1.18 (s, 3H, angular $-\text{CH}_3$) ppm; negative ferric chloride test; mass spectrum (70ev) M^+ 252.

Treatment of carbonate 150 with three equivalents of sodium hydride, and two equivalents of dimethylcarbonate gave only starting material. The use of a benzene - dimethoxyethane solvent mixture, in place of 100% benzene, caused carbonate 150 to form intractable material when treated with sodium hydride and dimethylcarbonate.

Tetrahydropyranyl ether of 4,4a,5,6,7,8-hexahydro-t-6-hydroxy-r-4a,c-5-dimethyl-2(3H)-naphthalenone (151)

A 25-ml, one-necked, round-bottomed flask was fitted with a gas-inlet tube and magnetic stirrer. The apparatus was evacuated, flushed with nitrogen and charged with a solution of 2.04 g (10.6 mmol) of des-isopropylidenepetasol (15) dissolved in 15 ml of methylene chloride. To the stirring mixture was added 2.1 g (25 mmol) of freshly distilled dihydropyran and 1 drop of concentrated hydrochloric acid. The reaction mixture was allowed to stand under nitrogen for

38 hr. The solution was diluted with 50 ml of ether and extracted with four 20-ml portions of cold, dilute sodium bicarbonate, brine, and dried (Na_2SO_4). Removal of the solvent afforded a light-yellow oil which was chromatographed on silica gel. Elution of the column with 15% ethyl acetate in hexane gave 2.26 g (8.13 mmol - 76.7%) of the tetrahydropyranyl ether of 4,4a,5,6,7,8-hexahydro-t-6-hydroxy-r-4a, c-5-dimethyl-2(3H)-naphthalenone (151) as a clear, colorless oil: ir (film) 2870 (CH), 1668 (C=O), 908, 804 cm^{-1} ; nmr (CCl_4) δ 5.62 (s, 1H, $-\text{CH}=\text{C}-$), 4.6 - 4.75 (m, 1H, $-\text{OCH}_2-$), 1.13 (s, 3H, angular $-\text{CH}_3$) ppm; high resolution mass spectrum M^+ obs: 278.1880; calcd: 278.1881.

Anal. Calcd for $\text{C}_{17}\text{H}_{26}\text{O}_3$: C, 73.34; H, 9.41. Found: C, 73.18; H, 9.39.

3-Carbomethoxy-4,4a,5,6,7,8-hexahydro-4a,5-dimethyl-2(3H)-naphthalenone (125) and 3-carbomethoxy-4,4a,5,6,7,8-hexahydro-4a-methyl-2(3H)-naphthalenone (130) were also prepared in a manner identical to that outlined above.

Tetrahydropyranyl ether of 3-carboxmethoxy-4,4a,5,6,7,8-hexahydro-t-6-hydroxy-r-4a,c-5-dimethyl-2(3H)-naphthalenone (152)

A 50-ml, three-necked, round-bottomed flask was equipped with a pressure equalizing addition funnel, gas-inlet tube, magnetic stirrer, and reflux condenser. The apparatus was evacuated, flame-dried, flushed with nitrogen, and charged

with 1.02 g of a 57% sodium hydride-mineral oil dispersion (0.58 g - 24.3 mmol active hydride). The mineral oil was removed by washing the solid with three 20-ml portions of pentane under a static nitrogen pressure, followed by removal of the pentane through a sintered glass gas dispersion tube attached to a water aspirator. The clean hydride was covered with 12 ml of anhydrous benzene which contained 1.83 g (20.3 mmol) of freshly distilled dimethylcarbonate. To this stirring suspension was added a solution of 2.25 g (8.1 mmol) of octalone 151 dissolved in 4 ml of benzene, dropwise and with rapid stirring, over a 10 min period. The mixture was slowly heated to reflux temperature and held there for 16 hr. The crude product mixture was then cooled to 5°, treated with glacial acetic acid until the solution was acidic to litmus paper, and poured into 50 ml of ice water. The resulting phases were separated, the aqueous phase saturated with solid sodium chloride and extracted with three 15-ml portions of ether. The combined organic extracts were washed with three 20-ml portions of a saturated sodium bicarbonate solution, brine, and dried (Na_2SO_4). The solvent was removed in vacuo to afford 3.12 g (8.1 mmol) of the crude tetrahydropyranyl ether of 3-carbomethoxy-4,4a,5,6,7,8-hexahydro-t-6-hydroxy-r-4a,c-5-dimethyl-2(3H)-naphthalenone (152) as a viscous oil: nmr (CCl_4) δ 12.91 (s, 1H, enolate), 5.67 (m, 1H, $-\text{CH}=\text{C}$), 3.70 and 3.75 (two s, 3H, $-\text{CO}_2\text{CH}_3$), 1.13 (s, 3H,

angular $-\text{CH}_3$) ppm; positive ferric chloride test; high resolution mass spectrum M^+ obs: 336.1918; calcd: 336.1936.

This material was somewhat labile and therefore was immediately converted to acetal 153.

(±)-Isopetasol (14)

A 250-ml, one-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, Dien Stark trap, and reflux condenser. The apparatus was evacuated, flushed with nitrogen, and charged with a solution of 6.3 g (18.7 mmol) of the tetrahydropyranyl ether of 3-carbomethoxy-4,4a,5,6,7,8-hexahydro-t-6-hydroxy-r-4a,c-5-dimethyl-2(3H)-naphthalenone (152) dissolved in 150 ml of benzene. To the stirring solution was added 150 mg of *p*-toluenesulfonic acid and 15 ml (27 mmol) of 1,2-ethanediol. The reaction mixture was heated to reflux for 18 hr with 0.3 ml of water being removed from the system. The solution was then cooled, diluted with 150 ml of ether, and extracted with three 50-ml portions of a saturated sodium bicarbonate solution. The organic portion was washed twice with brine and dried (Na_2SO_4). Removal of the solvent under vacuum afforded 4.7 g of a mixture of octalones. Nmr indicated that approximately 80% of the material isolated was no longer protected by the tetrahydropyranyl ether: nmr (CCl_4) δ 5.2 (m, 1H, $-\text{CH}=\text{C}-$), 3.86 (s, 4H, $-\text{OCH}_2\text{CH}_2\text{O}-$), 3.63 (s, 3H, $-\text{CO}_2\text{CH}_3$) ppm.

Refluxing the above reaction mixture over 4A molecular sieves resulted in partial decarbomethoxylation of acetal 153.

A 250-ml, three-necked, round-bottomed flask was equipped with a magnetic stirrer, gas-inlet tube, reflux condenser, and pressure-equalizing addition funnel. The apparatus was evacuated, flame-dried, flushed with nitrogen, and charged with a solution of 4.7 g (15.3 mmol) of acetal 153 dissolved in 60 ml of anhydrous ether. To the stirring reaction mixture was added 91 ml (150 mmol) of methyllithium (Foote Mineral Co.; 1.65M), dropwise, over a 30 min period. The solution was then heated to reflux for 2 hr, cooled to room temperature and added dropwise to 200 ml of cold, 30% ammonium chloride. The resulting aqueous solution was thoroughly extracted with five 40-ml portions of ether. The combined ethereal extracts were washed with two 50-ml portions of a saturated sodium bicarbonate solution, brine, and dried (Na_2SO_4). Removal of the solvent afforded 4.6 g of an extremely viscous oil which was immediately treated as described below.

A 250-ml, one-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, and reflux condenser. The apparatus was evacuated, flushed with nitrogen, and charged with 4.6 g (15.1 mmol) of hydroxyacetal 154 dissolved in 150 ml of acetone and 3 ml of water. To the so-

lution was added 150 mg of p-toluenesulfonic acid, and the reaction mixture was heated to reflux for 4 hr. The solution was cooled and most of the solvent removed at reduced pressure. The dark residue was diluted with 50 ml of brine, and thoroughly extracted with five 30-ml portions of ether. The combined ethereal fractions were washed with three 50-ml portions of a saturated sodium bicarbonate solution, brine, and dried (Na_2SO_4). Removal of the solvent afforded 3.1 g (10 mmol) of the crude diol, 154. Complete dehydration of the tertiary alcohol was assured by the treatment described below.

A 100-ml, one-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, and reflux condenser. The apparatus was evacuated, flame-dried, flushed with nitrogen, and charged with a solution of 3.1 g (10 mmol) of hydroxyacetal 154 dissolved in 50 ml of anhydrous methanol. To the stirring solution was added 0.5 ml of concentrated hydrochloric acid, and the reaction mixture was heated to reflux for 3 hr. The solution was cooled and most of the solvent removed under reduced pressure. The residue was diluted with 50 ml of brine and extracted with four 30-ml portions of ether. The combined ethereal extracts were washed with three 30-ml portions of a saturated sodium bicarbonate solution, brine, and dried (Na_2SO_4). Removal of the solvent afforded 2.1 g of a dark oil which was

chromatographed on silica gel. Elution with 25% ethyl acetate in hexane gave 200 mg of a light yellow oil. Crystallization from ethyl acetate in hexane afforded 100 mg (0.43 mmol - 3%) of isopetasol (14) as yellow crystals. The analytical sample, obtained after two recrystallizations from a 10% solution of ethyl acetate in hexane, melts at 118 - 119°: ir (KBr) 3516 (OH), 2944 and 2881 (CH), 1664 (C=O), 1628 (C=C), 1308, 1231, 1041, 891, 693 cm^{-1} ; nmr (CDCl_3) δ 5.78 (s, 1H, $-\text{CH}=\text{C}-$), 3.6 (m, 1H, $-\text{CHOH}$), 2.13 (s, 3H, $=\text{C}-\text{CH}_3$), 1.90 (s, 3H, $=\text{C}-\text{CH}_3$), 1.03 (s, 3H, angular $-\text{CH}_3$) ppm.

Anal. Calcd for $\text{C}_{15}\text{H}_{22}\text{O}_2$: C, 76.88; H, 9.46. Found: C, 76.97; H, 9.55.

4,4a,5,6,7,8-Hexahydro-3-isopropylidene-4a-methyl-2(3H)-naphthalenone (136) and 4,4a,5,6,7,8-hexahydro-3-isopropylidene-4a,5-dimethyl-2(3H)-naphthalenone (142) were prepared in a manner similar to that described above.

Angelic Acid (155)

Following the well defined procedure of Buckles and Mock (120) a 250-ml, three-necked, round-bottomed flask was fitted with a magnetic stirrer, calcium chloride drying tube, pressure-equalizing addition funnel, and reflux condenser. The apparatus was charged with 25 g (0.25 mol) of tiglic acid (156) (Aldrich Chemical Co.) and 50 ml of dry carbon tetrachloride. After stirring for 15 min, 40 g (0.25 mol) of

bromine was added, dropwise and with stirring, over a 30 min period. The reaction mixture was allowed to stand for 12 hr and was then heated to reflux for 2 hr at which time the solution turned light orange. The solvent was removed under reduced pressure and the solid residue recrystallized from petroleum ether (bp 60-70°) to afford 55.4 g (0.21 mol - 85.3%) of α,β -dibromo- α -methylbutyric acid: mp 80-86° [lit. (143) mp 82-88°]; nmr (CCl₄) δ 12.04 (s, 1H, -CO₂H), 4.81 (q, 1H, $J=7$ Hz, -CHBr), 1.90 (s and m, 6H, -CH₃) ppm.

A 500-ml, three-necked, round-bottomed flask was fitted with a magnetic stirrer, gas-inlet tube, pressure-equalizing addition funnel, and reflux condenser. The apparatus was evacuated, flame-dried, flushed with nitrogen, and charged with 55.4 g (0.21 mol) of α,β -dibromo- α -methylbutyric acid dissolved in 35 ml of methanol. To the reaction mixture was added 300 ml of a 25% solution of potassium hydroxide in methanol, dropwise and with stirring, over a 45 min period. Anhydrous potassium carbonate (5.5 g) was added to depress decarboxylation. The temperature of the reaction mixture was raised to 55° where it was held for 2 hr. Excess potassium hydroxide was then removed by bubbling CO₂ gas through the warm reaction mixture for 30 min. The suspension was filtered while warm, and the filtered salt was washed with 200 ml of warm methanol. The filtrate was concentrated in vacuo. The residue was dissolved in 100 ml of water, and

acidified to Congo red with 6N hydrochloric acid. The product was filtered, dried, and recrystallized from petroleum ether (bp 60-70°) to yield 19.5 g (0.11 mol - 44% based on 156) of β -bromoangelic acid: mp 93.5-95° [lit. (143) 92-94.5°]; nmr (CCl₄) δ 12.31 (s, 1H, -CO₂H), 2.77 (m, 3H, -CH₃), 2.10 (m, 3H, -CH₃) ppm.

A 250-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, mechanical stirrer, and thermometer. The flask was charged with 9.5 g (0.053 mol) of β -bromoangelic acid and 70 ml of water. The solution was cooled to 5° with an external ice bath. To the rapidly stirring solution was added in small pieces 210 g (0.83 mol of sodium) of 9% sodium amalgam over a 1 hr period maintaining a temperature of 5 - 10°. The mixture was stirred slowly for an additional 48 hr at room temperature. The aqueous layer was then separated from the mercury, and the mercury was washed with two 10-ml portions of water. The combined aqueous extracts were acidified to Congo red with concentrated hydrochloric acid. The precipitated product was filtered, dried, and recrystallized from petroleum ether (bp 60-70°) to yield 2.4 g (0.024 mol - 18.1% based on 156) of angelic acid (155): mp 44-46° [lit. (143) mp 45-46]; nmr (CCl₄) δ 12.77 (s, 1H, -CO₂H), 6.22 (q, 1H, $J=8$ Hz, -C=CH-), 2.0 (m, 6H, -CH₃) ppm.

Attempted preparation of the tiglate ester of 2-methylcyclohexanol using dicyclohexylcarbodiimide

A 100-ml, three-necked, round-bottomed flask was equipped with a gas-inlet tube and magnetic stirrer. The apparatus was evacuated, flame-dried, flushed with nitrogen, and charged with 0.15 g (1.3 mmol) of 2-methylcyclohexanol, 3.13 g (1.3 mmol) of tiglic acid, 0.27 g (1.3 mmol) of dicyclohexylcarbodiimide, and 50 ml of anhydrous ether. The solution was stirred at room temperature for 16.5 hr. The solid which had formed was filtered and thoroughly washed with acetone. Removal of the solvent under vacuum afforded a white solid which was recrystallized from chloroform in ether. This reaction afforded 180 mg of what is believed to be amide 157: mp 164-165°; nmr (CDCl₃) δ 6.80 (m, 1H, -HN-), 5.91 (q, 1H, J=10 Hz, -CH=C-) ppm; mass spectrum (70 ev) M⁺ 306.

The reaction of isopetasol (14) with angelic acid (155) in the presence of DCC gave similar results. Octalone 14 was recovered in virtually quantitative yield while the angelic acid reacted with the DCC. Varying the reaction conditions (temperature, time, and solvent) did not improve the results of the attempted esterification.

Attempted preparation of the angelate ester of 2-methyl-cyclohexanol using p-toluenesulfonic acid

A 25-ml, one-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, reflux condenser, and Dean-Stark trap. The apparatus was evacuated, flushed with nitrogen, and charged with 0.148 g (1.3 mmol) of 2-methylcyclohexanol, 0.13 g (1.3 mmol) of angelic acid (155), and 20 mg of p-toluenesulfonic acid. These solids were covered with 12 ml of dry benzene and heated to reflux for 2 hr. The reaction mixture was cooled, washed with brine, and dried (Na_2SO_4). Removal of the solvent indicated the presence of starting materials; identified by their spectral properties.

Treatment of 53 mg (0.22 mmol) of isopetasol (14), 30 mg (0.33 mmol) of angelic acid (155), and 15 mg of p-toluenesulfonic acid in 10 ml of benzene, under the same reaction conditions as described above, gave only starting material.

Attempted preparation of angeloyl chloride

A. Treatment of angelic acid with thionyl chloride according to the procedure of Bishop (129) gave tigloyl chloride as the only isolable product.

B. Treatment of angelic acid with oxalyl chloride according to the procedure of Engel and Just (130) gave tigloyl chloride as the only isolable product.

C. Treatment of angelic acid with thionyl chloride at low temperatures according to the procedure of Hocking (131) gave an inseparable mixture of tigloyl chloride and angeloyl chloride.

D. The sodium salt of angelic acid was treated with refluxing phosphorous oxychloride following the procedure of Rupe (132). Distillation of the resulting mixture afforded tigloyl chloride.

Angeloyl chloride

Following the general procedure of Rupe (132), a 100-ml, three-necked, round-bottomed flask was fitted with a gas-inlet tube, magnetic stirrer, and reflux condenser. The apparatus was evacuated, flame-dried, flushed with nitrogen, and charged with 1.70 g of a sodium hydride-mineral oil dispersion (0.92 g - 0.04 mol active hydride). The sodium hydride was washed with three 50-ml portions of pentane. The pentane was removed with a sintered glass, gas dispersion tube attached to a water aspirator. The clean hydride was covered with 50 ml of dry benzene. The reaction mixture was cooled to 5° and carefully treated with 3.5 g (0.035 mol) of angelic acid (155) over a 10 min period. The reaction mixture was warmed to room temperature and stirred for 1.5 hr. To the stirring solution was then added 5.3 g (0.035 mol) of phosphorous oxychloride. The reaction mixture was stirred at room temperature for 1.5 hr, filtered, and the solvent

removed by distillation at reduced pressure at room temperature. A micro-distillation gave 0.5 g (4.1 μmol - 11.7%) of angeloyl chloride: bp 25-30° (7.0 mm); nmr (CCl_4) δ 13.1 (trace of $-\text{CO}_2\text{H}$), 6.2 (m, 1H, $-\text{HC}=\text{C}-$), 2.0 (m, 6H, $-\text{CH}_3$) ppm; hydrolysis with water followed by isolation of the acid gave a homogeneous material having spectral properties identical to angelic acid (155).

(±)-Isopetasin (39)

Following the general procedure of Kupchan *et al.* (127), a 50-ml, one-necked, round-bottomed flask was fitted with a gas-inlet tube and magnetic stirrer. The apparatus was evacuated, flame-dried, flushed with nitrogen, and charged with 40 mg (0.17 μmol) of (±)-isopetasol (14), 20 mg (0.17 μmol) of angeloyl chloride, 1 ml of dry pyridine, and 1 ml of anhydrous benzene. The reaction mixture was allowed to stir at room temperature for 12 hr. The solvent was then removed at reduced pressure and at room temperature. The residue was taken up in 50 ml of ether and washed with three 20-ml portions of 3% aqueous sulfuric acid. The ethereal layer was then washed with two 20-ml portions of a saturated sodium bicarbonate solution, brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue chromatographed over silica gel. Elution with 10% ethyl acetate in hexane gave 5 mg of a crude yellow oil identified as impure isopetasin (39). Further elution with 25% ethyl acetate in

hexane gave 30 mg of isopetasol (14). Attempted crystallization of the crude isopetasin (39) was unsuccessful: nmr (CDCl_3) δ 6.0 (angelate derivative), 5.83, 2.10, 1.95, 1.0 ppm; ir (film) 3430, 2960, 1720, 1670, 1240, cm^{-1} ; high resolution mass spectrum M^+ obs: 316.2065; calcd: 316.2038.

CONCLUSION

The culmination of this research was the preparation of a material with spectral properties indistinguishable from (+)-isopetasin. The primary value of this synthetic effort, however, originates in the synthetic methods which were developed or refined.

A procedure for the synthesis of des-isopropylidene-petasol was developed. This material appears to be a suitable precursor for numerous sesquiterpenoids.

Methylmagnesium bromide was shown to be an outstanding alkylating agent for the conversion of hydrocoumarins to octalones.

A general conversion of an α,β -unsaturated ketone to an α -isopropylidene- α,β -unsaturated ketone was devised.

Finally, a method for the preparation of angelate esters was developed.

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