INVESTIGATIONS DIRECTED TOWARD THE TOTAL SYNTHESIS OF SHIONONE

Thesis by

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To Kathy

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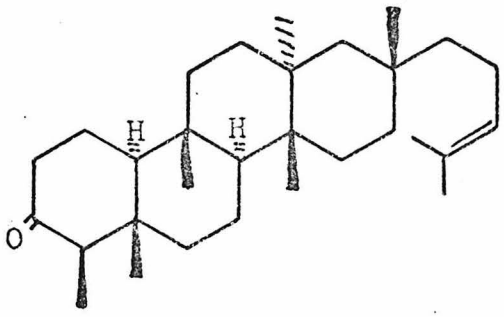
I wish to extend my appreciation to Professor Robert E. Ireland for his guidance and support. To my colleagues goes my gratitude for their suggestions. Support by a National Science Foundation fellowship (1968-1971) is gratefully acknowledged.

ABSTRACT

An approach to the total synthesis of the tetracyclic triterpene shionone i is described. The key intermediate ii was prepared in 17 steps (3.0% overall yield) from 2-methyl-1,3-cyclohexanedione. Generation of the essential trans, disubstituted C/D ring fusion of ii was accomplished via the stereospecific formation and cleavage of a fused methoxycyclopropane system. An additional 12 steps served to convert the ketone ii into the ketal-ketone iii (12.5%) which requires only addition of the side chain to complete the total synthesis.



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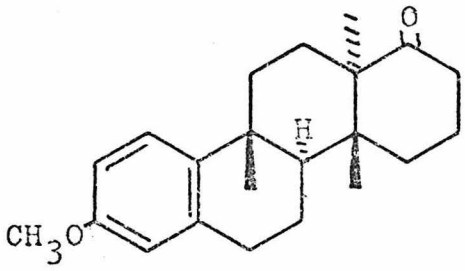

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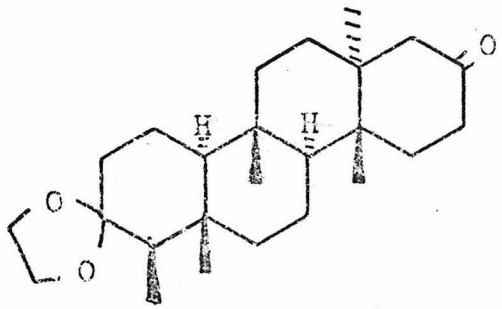

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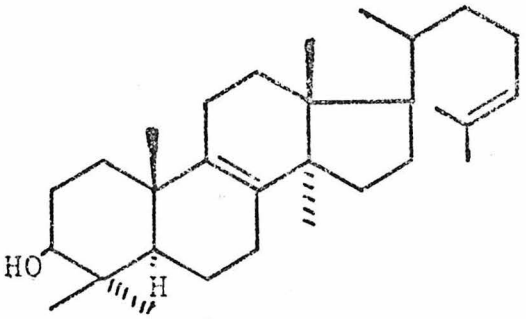
Introduction

The triterpenes consist of a diverse group of C-30 isoprenoid compounds which are biologically derived from squalene. They are, with rare exception, tetra- or penta-cyclic molecules bearing numerous asymmetric centers. The triterpenes are widely distributed in the plant kingdom although a few such as lanosterol (1), have been isolated from animal sources (1).

Although the first member of this class of compounds betulin (2) was isolated in 1788 (2), the combination of their great size and varied stereochemistry coupled with their paucity of suitable reactive centers rendered the triterpenes resistant to structural elucidation for over 160 years.



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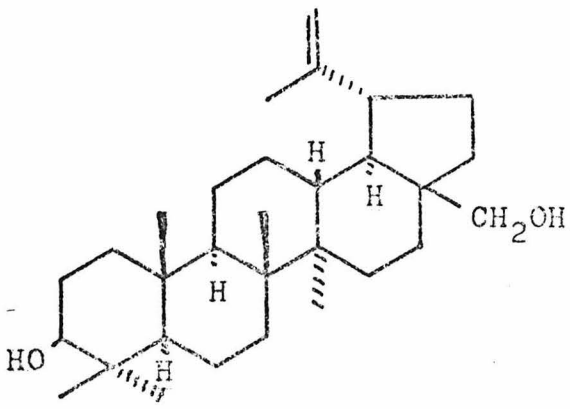

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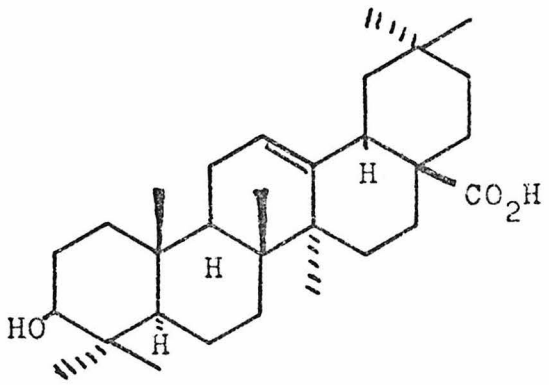
In 1949 Ruzicka and Jeger (3) determined the gross structure of oleanoic acid (3) culminating a 20 year effort and launching a period of rapid progress in the field. Building on the data acquired during the previous 30 years relating the various triterpenes to a few widely occuring examples, most of the basic triterpenoid skeletal types were quickly deciphered. In a parallel development, the combination of Barton's (4) application of conformational analysis and Klyne's (5) utilization of molecular rotation data led to the determination of the relative and absolute stereochemistry of the pentacyclic triterpenes. This work on the structural and stereochemical elucidation has been adequately reviewed (1, 6-9).



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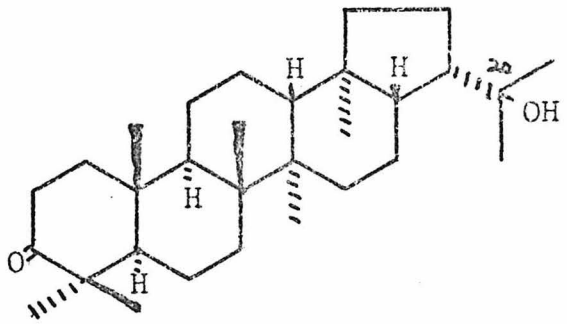
This increased structural knowledge coupled with preliminary biogenetic studies prompted Woodward and Bloch (10) to propose that lanosterol and the steroids were biosynthe-

sized through a specific cyclization of squalene followed by methyl and hydrogen rearrangements. Since then their hypothesis has been fully confirmed and extended (11, 12). Eschenmoser *et al.* (13) and Stork (14) independently advanced a detailed theoretical model for the formation of the pentacyclic triterpenes *via* a concerted cyclization of squalene followed by a series of Wagner-Meerwein 1,2-shifts. Again labeling experiments have proved to be fully in accord with the theory at least in the cases tested (15) and this theory is now generally accepted for all the triterpenes. Cornforth (16) has proposed that the theory be modified to include a reversible enzymatic trapping of certain of the carbonium ion intermediates. He argues that pauses are required, particularly during formation of ring E, to allow the system to adopt the conformation necessary for further rearrangements.

More recently 2,3-oxidosqualene has been implicated as the substrate in the enzymatic cyclizations (17, 18) accounting for the presence of the C-3 oxygen, which is almost catholic among the triterpenes and steroids. In other developments the mechanism of the formation and incorporation of mevalonic acid into farnesyl pyrophosphate has been throughly worked out, largely through the efforts of J. W. Cornforth. This work is described by Clayton in his excellent review (12). Finally, the precise mechanism of the reductive coupling of two farnesyl pyrophosphate units to form squalene has

yielded to intense scrutiny, particularly by Rilling (19-21).

In chart A squalene oxide (A-1) is shown in the chair-chair-chair-boat form, which according to the Eschenmoser theory, can cyclize directly to the carbonium ion A-2 with the stereochemistry shown. Other conformations of squalene are possible which can give intermediates with different stereochemistry. For instance, lanosterol (1) arises from a chair-boat-chair-boat cyclization followed by a series of 1,2-shifts and loss of a proton. Hydroxyhopanone (4) on the other hand is formed by an all chair cyclization with trapping of the resultant C-20* carbonium ion by water.



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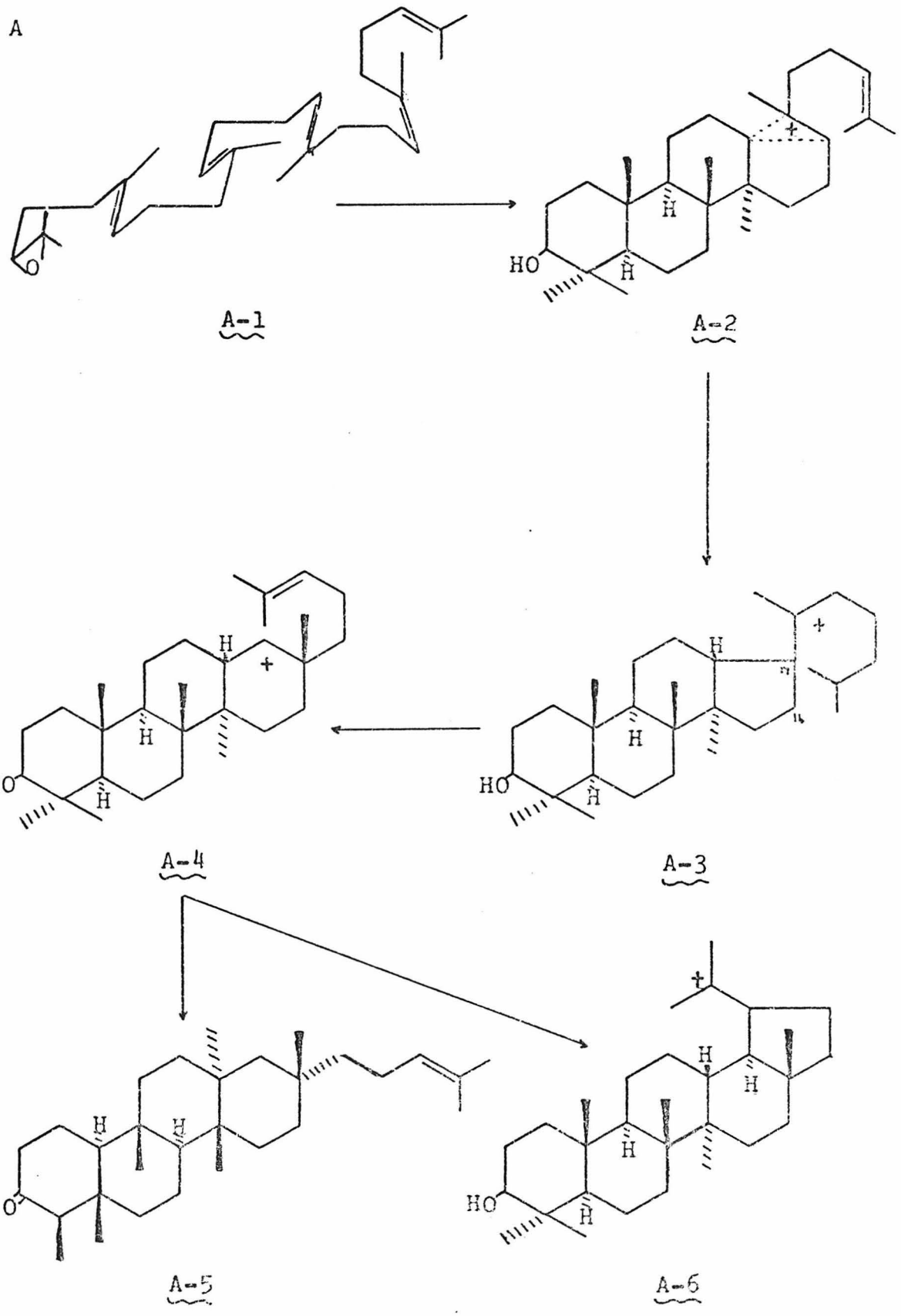
* The naturally occurring triterpenes discussed herein are numbered according to the scheme suggested by S. Allard and G. Ourisson, Tetrahedron, 1, 277 (1957).

The dicyclic compounds described herein are named and numbered as derivatives of naphthalene, the tricyclics as derivatives of phenanthrene or phenalene as appropriate, and the tetracyclics as derivatives of chrysene as indicated in "The Ring Index" (A. M. Patterson, L. T. Capell, and D. F. Walker, "The Ring Index", American Chemical Society, Washington, D. C., 1960.

Although only one enantiomer is depicted in the structural formulas, all synthetic intermediates are racemic.

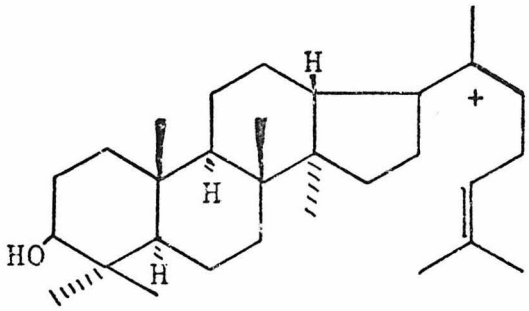
Chart A



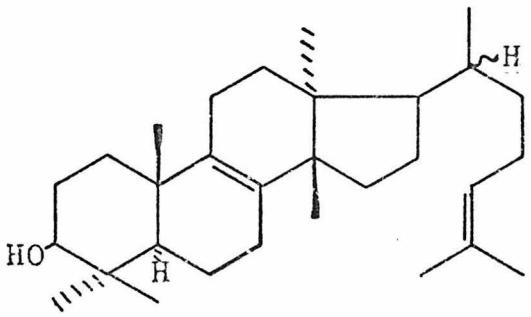
A-1 A-2 A-3 A-4 A-5 A-6

Shionone

Chart A (continued)

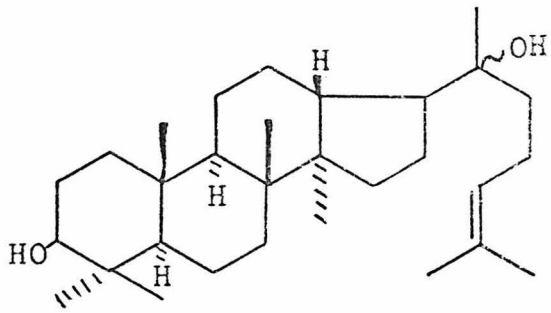


A-3



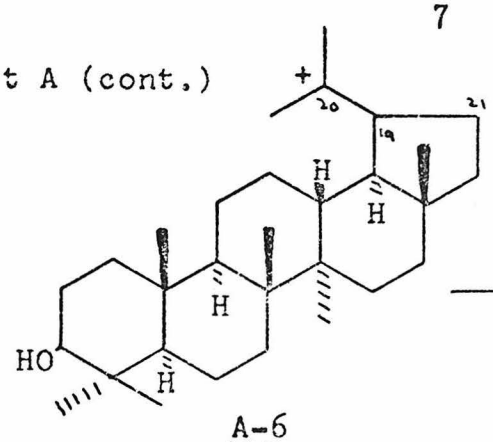
A-7 Euphol 20 β-H

A-8 Tirucallol 20 α-H

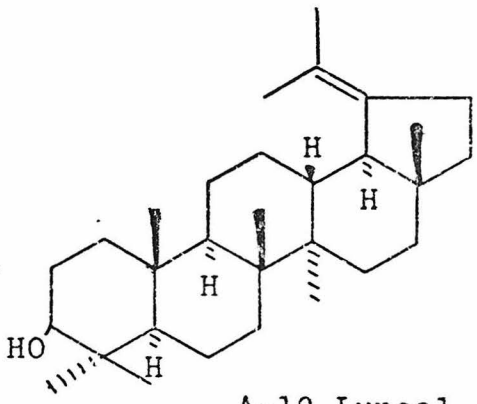


A-9 Dammarenediols (20 α- or β-OH)

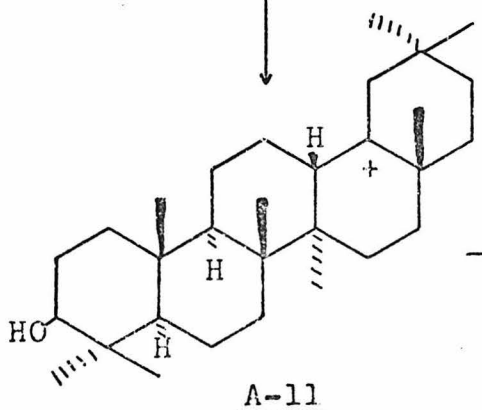
Chart A (cont.)



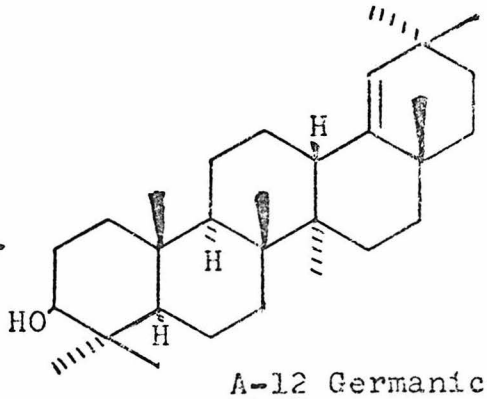
A-6



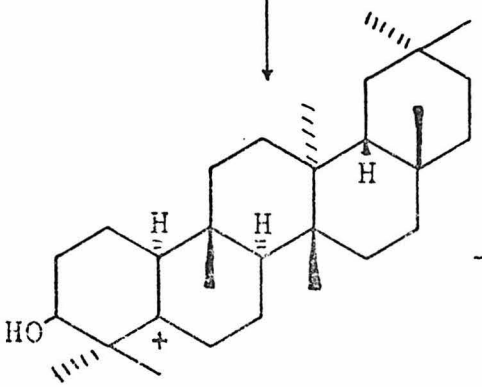
A-10 Lupeol



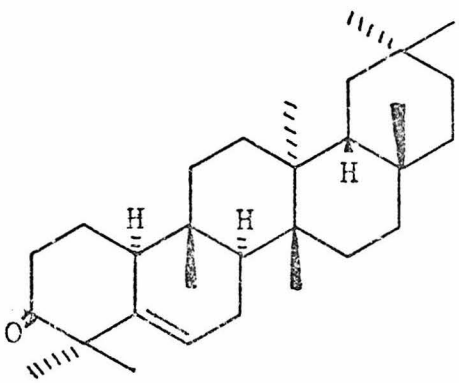
A-11



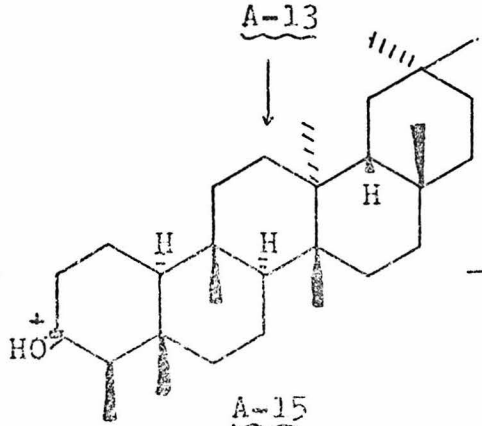
A-12 Germanicol



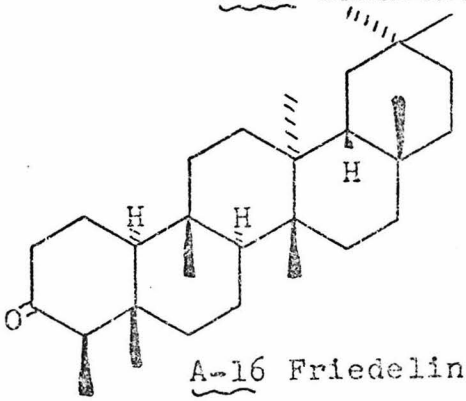
A-13



A-14 Alnusenone



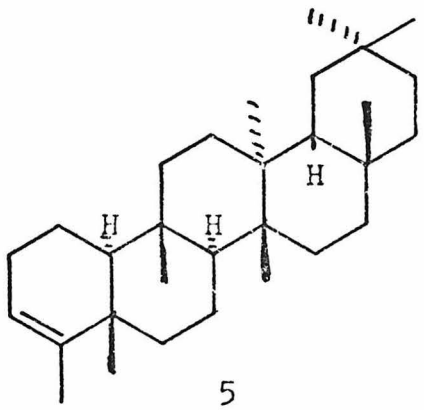
A-15



A-16 Friedelin

The carbonium ion (A-3) serves as the key intermediate for a number of classes of triterpenes. It can undergo attack by water to give either of the dammarenediols (A-9) directly or the C-17 hydrogen can migrate initiating a backbone rearrangement leading to euphol (A-7) or tirucallol (A-8) depending on the stereochemistry at C-20. Alternatively, the C-16--C-17 bond can shift giving the cation (A-4) which can suffer either of two fates. Eight more 1,2-shifts starting with the C-13 hydrogen leads to shionone (A-5) while attack of the side chain double bond on the carbonium ion gives a new carbonium ion A-6 which can lose a proton to give lupeol (A-10) or through a shift of the C-19--C-21 bond give A-11, the immediate precursor of germanicol (A-12). A sequence of additional Wagner-Meerwein rearrangements can then lead ultimately to alnusenone (A-14) or friedelin (A-16). It should be emphasized that triterpenes arising from loss of a proton from each of the potential carbonium ion intermediates between A-11 and A-15 have been isolated and characterized (6).

Rearrangements similar to those proposed in the biosynthetic scheme have been observed *in vitro*. Both friedelene (5) (22) and alnusenene (6) (23) give the same mixture of Δ^{12} and $\Delta^{13(18)}$-olanenes (7) on treatment with acid. Apparently the driving force for this rearrangement is the strain associated with the *cis* D/E ring fusion (23).



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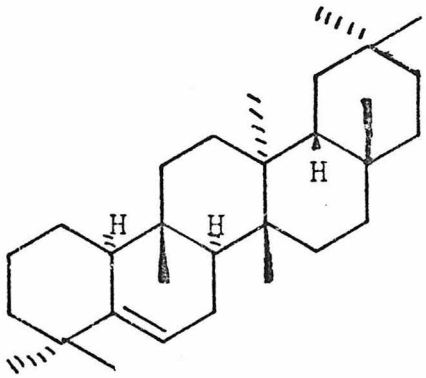

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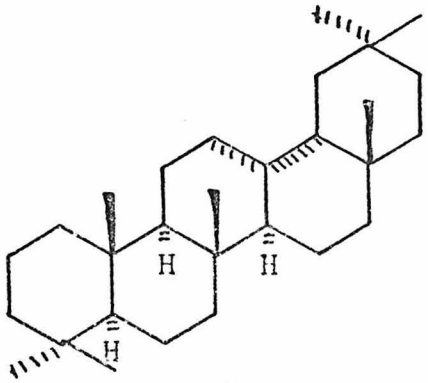

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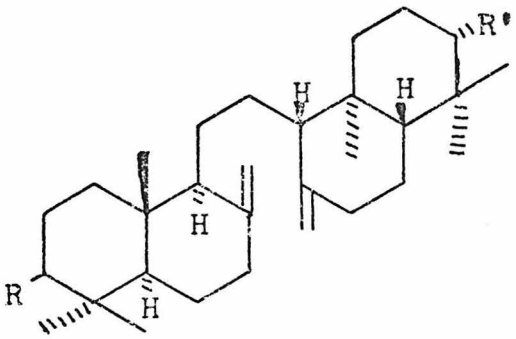
Whitlock (24) has investigated the nature of such backbone rearrangements and his data indicate that there is a rapid equilibrium of all the possible carbonium ions accessible by 1,2-shifts and that the products are formed through the most stable of these. This result would ascribe to the enzyme the ability to moderate such rearrangements through either control of the conformation of the nascent triterpene making the proper carbonium ion the most stable or by provision of a basic site at the appropriate point to interrupt

the equilibrium by removal of a proton. These questions regarding the microscopic mechanism of the cyclization of squalene and the subsequent rearrangements are still under intensive investigation in several laboratories.

Synthetic efforts in the triterpene field have been scant, probably due to the same factors that hindered structural elucidation plus the apparent general lack of biological activity among the triterpenes. The early synthetic work has been ably reviewed by Evans (25). The initial attention was directed toward the symmetrical triterpene α-ononcerin (8, R=R'=OH) since this compound could in principle be obtained by the coupling of two identical subunits thereby sharply reducing the number of synthetic steps required. The discovery made by Barton and Overton (26) during their structural studies that α-ononcerin diacetate gave the unnatural pentacyclic isomer γ-ononcerin (9) on vigorous treatment with acid was also a key factor since this assured an entrance into the pentacyclic triterpenes.

During the middle 1950s both Eschenmoser (27) and Corey (28) prepared the hydrocarbon α-ononceradiene (8, R=R'=H) *via* the dimerization of different intermediates derived from sclareol (10).

The first triterpene total synthesis was achieved by Stork (29) who prepared α-ononcerin in 16 steps from 6-methoxy-β-tetralone (B-1) (Chart B). The major advance in



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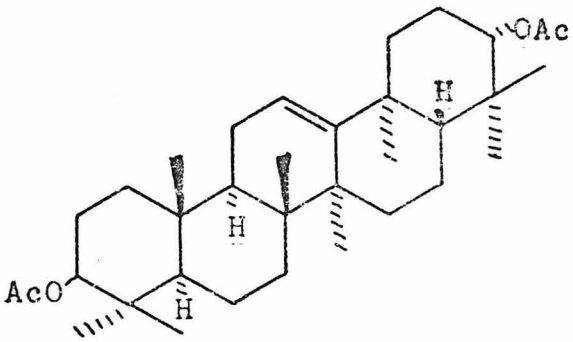

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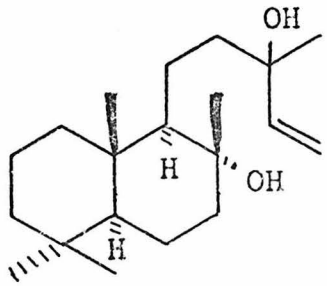

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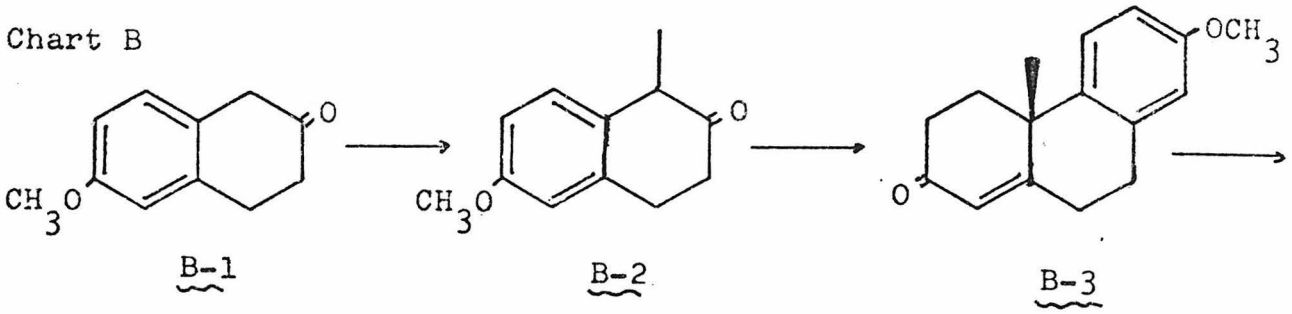
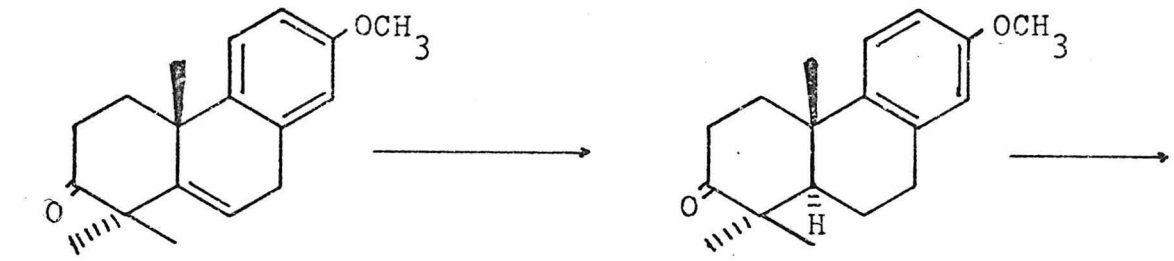
this work was the preparation of the keto-acid B-7 by oxidative cleavage of the C ring of the tricyclic ketone B-5. Decarboxylative coupling of B-7 was carried out electrolytically using the procedure developed by Corey (28) for α-ononceradiene to give the dione B-8. Addition of ethoxyacetylene, acid catalyzed hydration, and thermal decarboxylation then led to α-ononcerin 8. The key intermediate B-7 has subsequently been synthesized more efficiently by Ireland (30) and Sondheimer (31). Stork's accomplishment also provided a formal entry into the hydroxyhopanone system

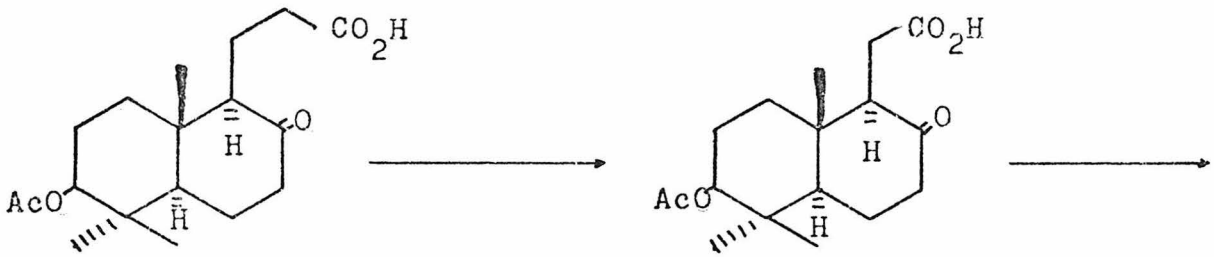
Chart B



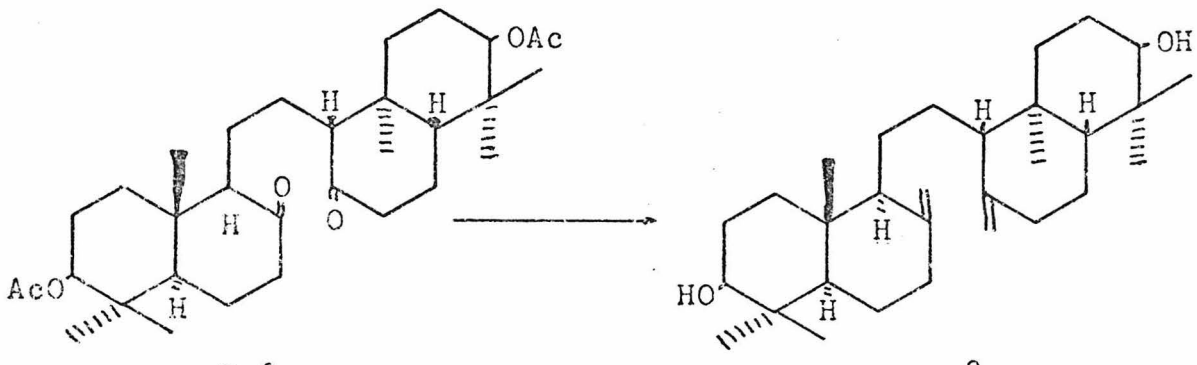
B-1 B-2 B-3



B-4 B-5



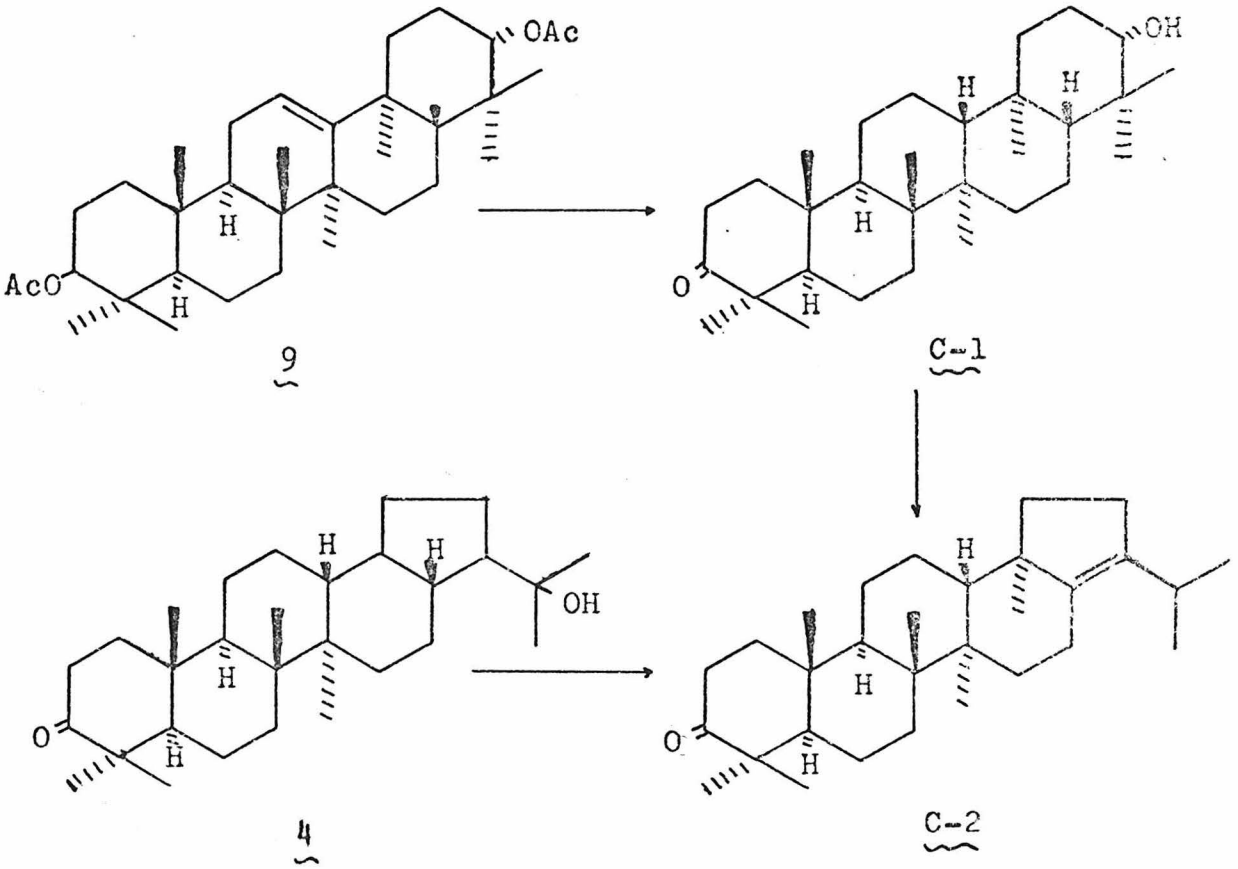
B-6 B-7



B-8 8

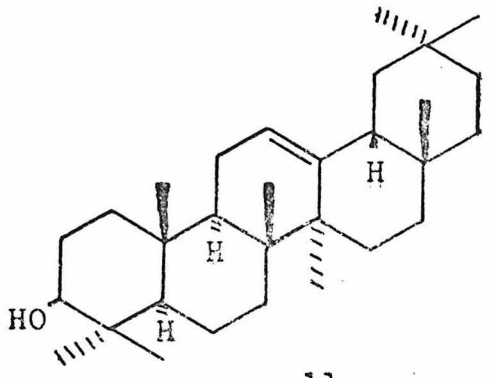
since Schaffner and coworkers (32) had already converted γ-ononcerin diacetate (9) to the keto-alcohol C-1 (Chart C) which on heating in the presence of Fuller's Earth gave the keto-olefin C-2 which was also obtained by a similar treatment of hydroxyhopanone (4).

Chart C



Unfortunately, this approach was applicable only to symmetrical triterpenes and the limited number of triterpenes which are derivable from symmetrical intermediates. A second major drawback is the low yield associated with

the acid catalyzed cyclization forming ring C (2-20%). Halsall and Thomas (33) were the first to suggest joining dissimilar AB and DE portions followed by cyclization to get into the oleanane system. This approach has been successfully applied in three different laboratories (34-36), but in each case the inefficiency of the last step severly limited the yields. Also the cyclizations were generally non-specific leading to mixtures of double bond isomers such as 7. Barton (37) has subsequently completed a partial synthesis of β-amyrin (11) from olean-13(18)-ene completing a formal total synthesis of the former compound. Unfortunately, however, this synthesis albeit elegant was too long and inefficient to serve as a general entrance into the series of triterpenes related to β-amyrin such as the pentacyclic compounds in chart A.



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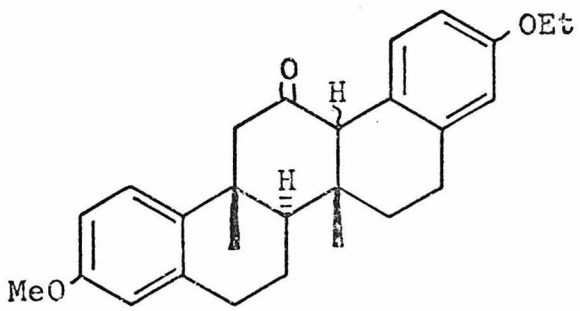
During the last several years a significant portion of the synthetic endeavor in the Ireland laboratories has been directed toward the development of more efficient and versatile routes to the triterpenes. Recently, this goal has been realized and publications describing totally synthetic schemes leading to germanicol (A-12) (38) and alnusenone (A-14) (39) have appeared.

The initial problem in the route to germanicol was the preparation of the tricyclic intermediate D-3 (Chart D) possessing the cis axial methyl groups at C-4a and C-8a. This was accomplished by a sequence of Robinson annulations of 2-methyl-1,3-cyclohexanedione and ethyl vinyl ketone to give first the enone D-1 and then D-2. Reductive methylation at C-1 of D-2 and catalytic hydrogenation gave the ketone D-3 whose structural assignment was confirmed by comparison of a derivative with that obtained from a natural product.

Attention was next directed at the introduction of the side chain bearing ring E and the angular methyl group at C-8. The difficulties associated with the preparation of an array of adjacent quaternary centers bearing trans oriented methyl groups similar to that required at C-12a and C-12b of D-6 thwarted an early foray aimed at alnusenone (40). Attempted alkylation of the ketone 12 with iodomethane under the optimum conditions led to only 17% of the required intermediate 13 together with 60% of O-methylated product



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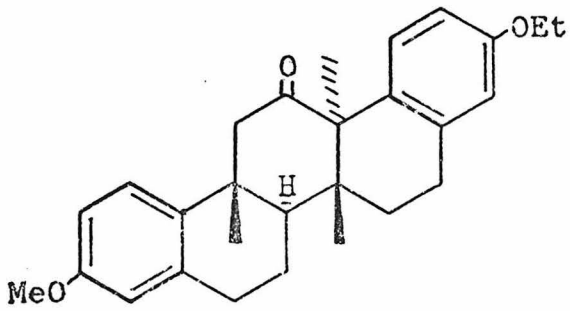

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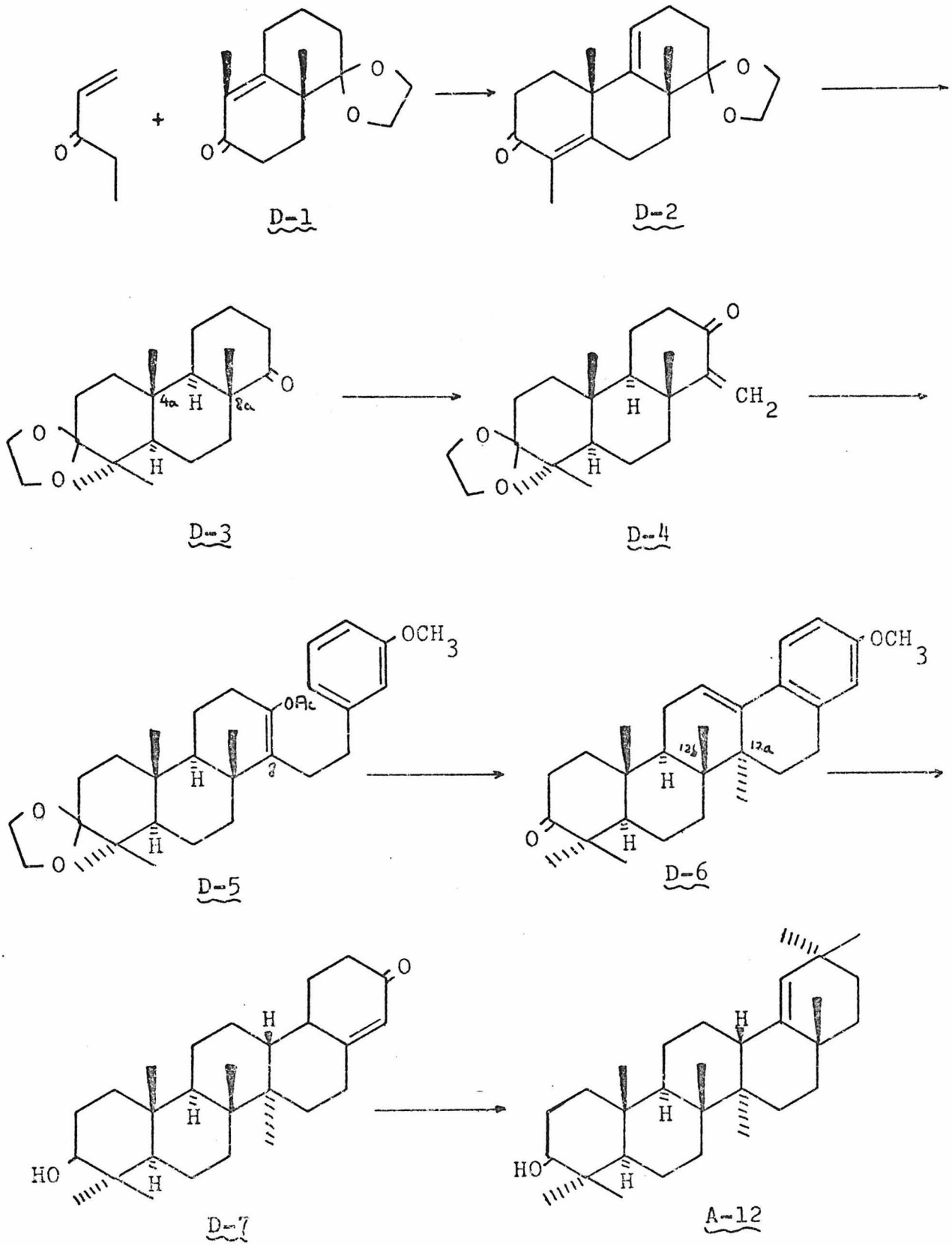
and 21% of starting material. This and later work have demonstrated that the stereospecific introduction of such combinations of angular methyls constitutes a weighty synthetic challenge and that provisions for their generation must form an integral part of the synthetic plan. While many of the problems pertaining to triterpene synthesis have been encountered in work on the steroids, this one has received little attention (41).

In the present case the problem was solved by formation of the exocyclic enone D-4 which was available in four steps from D-3. Conjugate addition of m-methoxybenzyl Grignard with trapping of the enolate anion thus formed by acetic anhydride then gave the enol acetate D-5. The enolate anion could subsequently be regenerated in a different solvent and selectively alkylated with methyl iodide at C-8 with the methyl group approaching from the less hindered face of the

Chart D



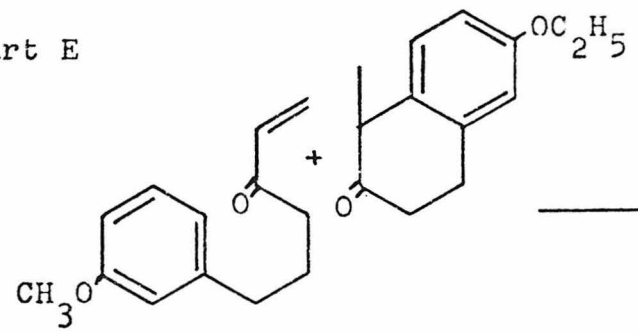
molecule to give, after acid catalyzed cyclization, the pentacyclic ketone D-6. Further transformations into germanicol involved a Birch reduction to give the ketone D-7 and introduction of the C-17 methyl group by the conjugate addition of cyanide. Dimethylation and removal of the carbonyl from C-22 gave the natural product.

For the synthesis of alnusenone (39) (Chart E) the subunits E-1 and E-2 were joined by a Robinson annulation to give the tricyclic enone E-3. The problem of introduction of the C-10a angular methyl group was solved neatly by the conjugate addition of cyanide using the procedures developed by Nagata (42). By appropriate choice of reaction conditions either the thermodynamic cis fused product or the kinetic, desired trans isomer E-4 could be obtained in high yield. The cyano group was reduced to a methyl providing E-5 which was cyclized in polyphosphoric acid to give the pentacyclic E-6. Selective reduction of the aromatic rings was achieved by the conversion of the methyl ether to the corresponding phenol, Birch reduction of the ethoxy substituted ring, and re-etherification of the phenol. The E ring was then constructed and the second aromatic ring was reduced and dimethylated to give alnusenone.

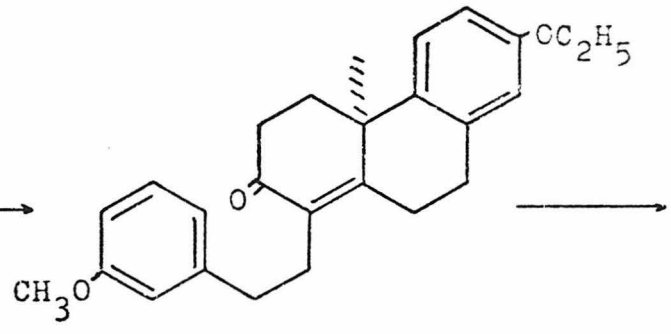
Very recently Stork (43) has communicated a total synthesis of Lupeol (A-10). Certain aspects of this synthesis will be mentioned in the discussion section.

In light of these initial successes a more versatile

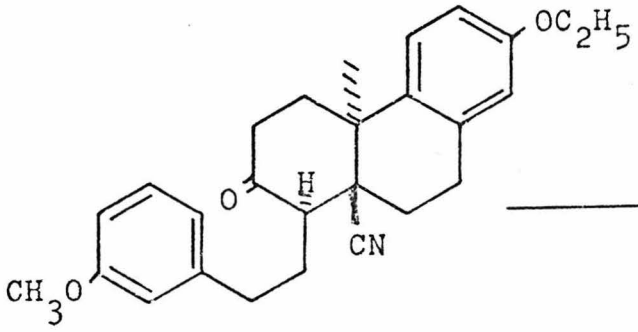
Chart E



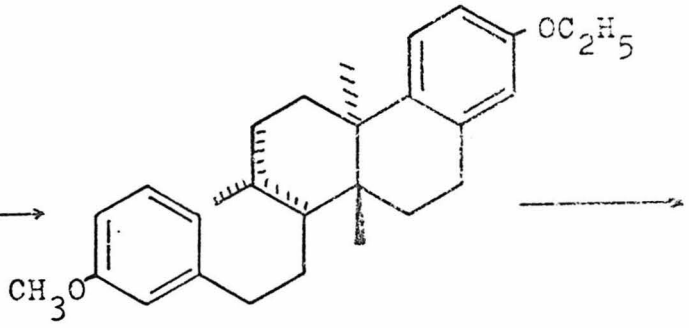
E-1 E-2



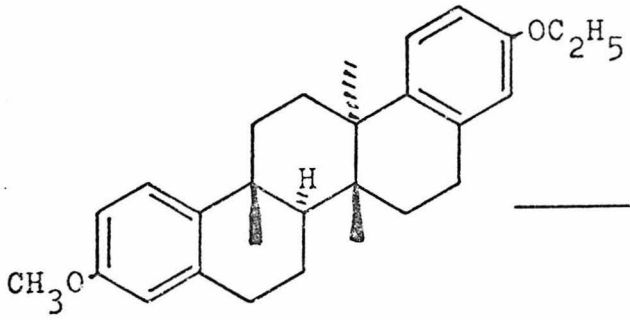
E-3



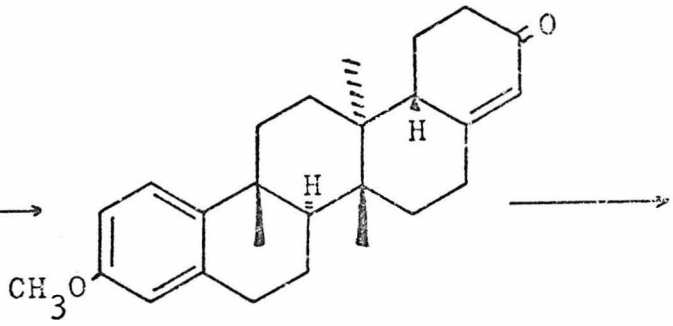
E-4



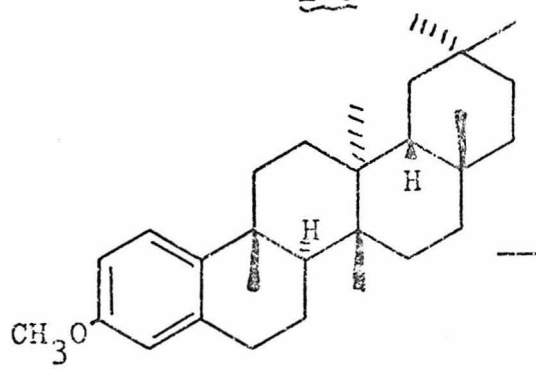
E-5



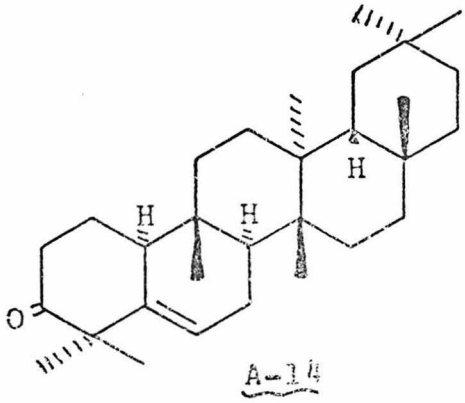
E-6



E-7



E-8



A-14

approach to triterpene synthesis was desired that would be applicable in the preparation of tetracyclic as well as pentacyclic triterpenes. The development of one such approach and its application to the total synthesis of shionone (A-5) is the subject of this thesis.

Discussion

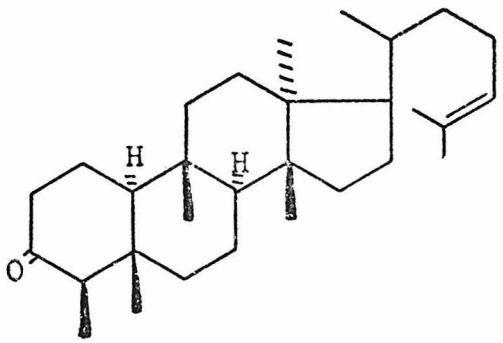
After apraising the manifold approaches to triterpene synthesis we had decided to direct our efforts at the class of compounds possessing trans fused, diangularly methylated C/D ring fusions. This decision was made first because there are a large number of triterpenes which incorporate this feature such as the tetracyclics lanosterol (1), euphol (A-7), tirucallol (A-8), and shionone (A-5) as well as the pentacyclics alnusenone (A-14) and friedelin (A-16) (6). Secondly, a potentially general procedure for the generation of the system of anti vicinal quaternary centers characteristic of many other triterpenes including germanicol (A-12) had already been developed and applied in these laboratories (38).

The initial goal of this work was to develop a synthetic route to a simple compound containing the desired disubstituted C/D ring fusion which could then be elaborated into the various triterpenes. It was evident that an indane or decalin derivative which bore suitably differentiated functionality for the selective modification of both rings was required, since the A, B, and C rings of the different natural products bear little resemblance. A second ambition was to demonstrate the utility of this intermediate through the total synthesis of a triterpene.

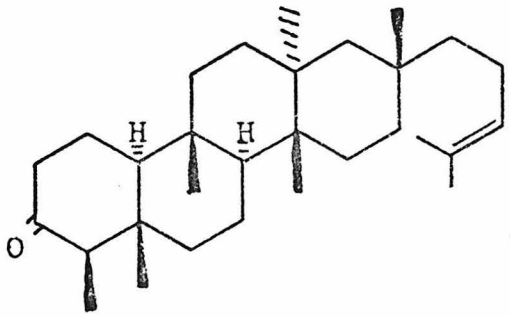
For this phase, the tetracyclic triterpene shionone (A-5) was deemed to be an ideal challenge since work was already in progress toward the pentacyclic alnusenone through a pentacyclic intermediate (vide supra) and also because it seemed probable that one of the tetracyclic intermediates in the shionone scheme could be elaborated into the pentacyclic series.

Shioncne cccurs in free form together with friedelin in the roots of Aster Tataricus and can be isolated by extraction with benzene and chromatography of the crude extracts on alumina followed by recrystallization (44). The optical rotary dispersion curve of shionone was superimposible with that of friedelin leading Ourisson and his co-workers (44) to propose that the A rings and A/B ring fusions of the two compounds were the same. The validity of this proposition was demonstrated by oxidative degradation of the A ring of shionone employing the procedure used by Corey (45) in his structure elucidation of friedelin. The above results coupled with an nmr analysis of the side chain prompted Ourisson et al. (44) to assign the structure 14 to shionone on the assumption that it arose biosynthetically via a backbone rearrangement similar to that leading to other tetracyclic triterpenes starting with the cation A-3.

A few months later the same authors (46) published the revised, correct structure A-5 based on their chemical



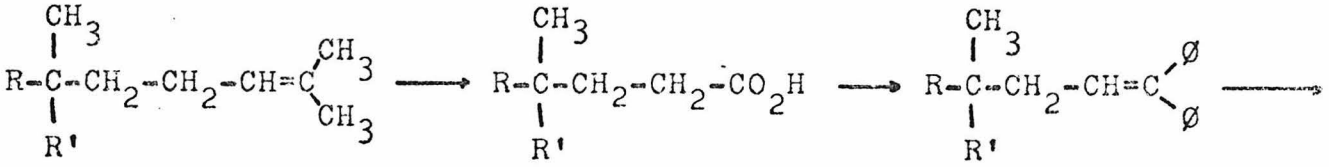
14



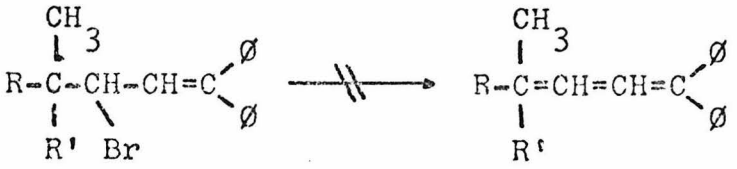
A-5

degradation of the side chain. They were able to convert the side chain F-1 through a series of standard transformations to the allylic bromide F-4 (Chart F), but were unable

Chart F



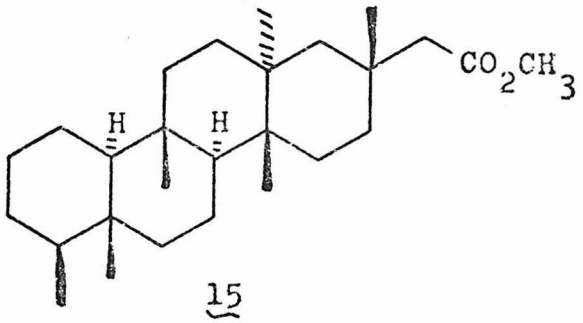
F-1 F-2 F-3



F-4 F-5

to dehydrobrominate F-4 to the anticipated diene F-5 suggesting that the carbon bearing the methyl group was quarternary. These data implicated the cation A-4 as the biogenetic precursor to shionone leading to the proposal of the correct structure.

The structural assignment was placed on a firm chemical ground in 1967 by an exhaustive degradation of the side chain and mass spectroscopic studies on the tetracyclic molecule remaining, verifying the position of attachment of the side chain (47). In an accompanying paper Takahashi and co-workers (48) related shionone to friedelin by the preparation of the olefin 15 from shionone by a variation of the route that gave F-3 and from friedelin by oxidative cleavage of the E ring.



15

In considering a synthesis of the length and complexity required for a molecule such as shionone, it is convenient to work backwards from the natural product toward readily available starting materials. In this way one can simplify the structure one step at a time in a "reverse synthetically

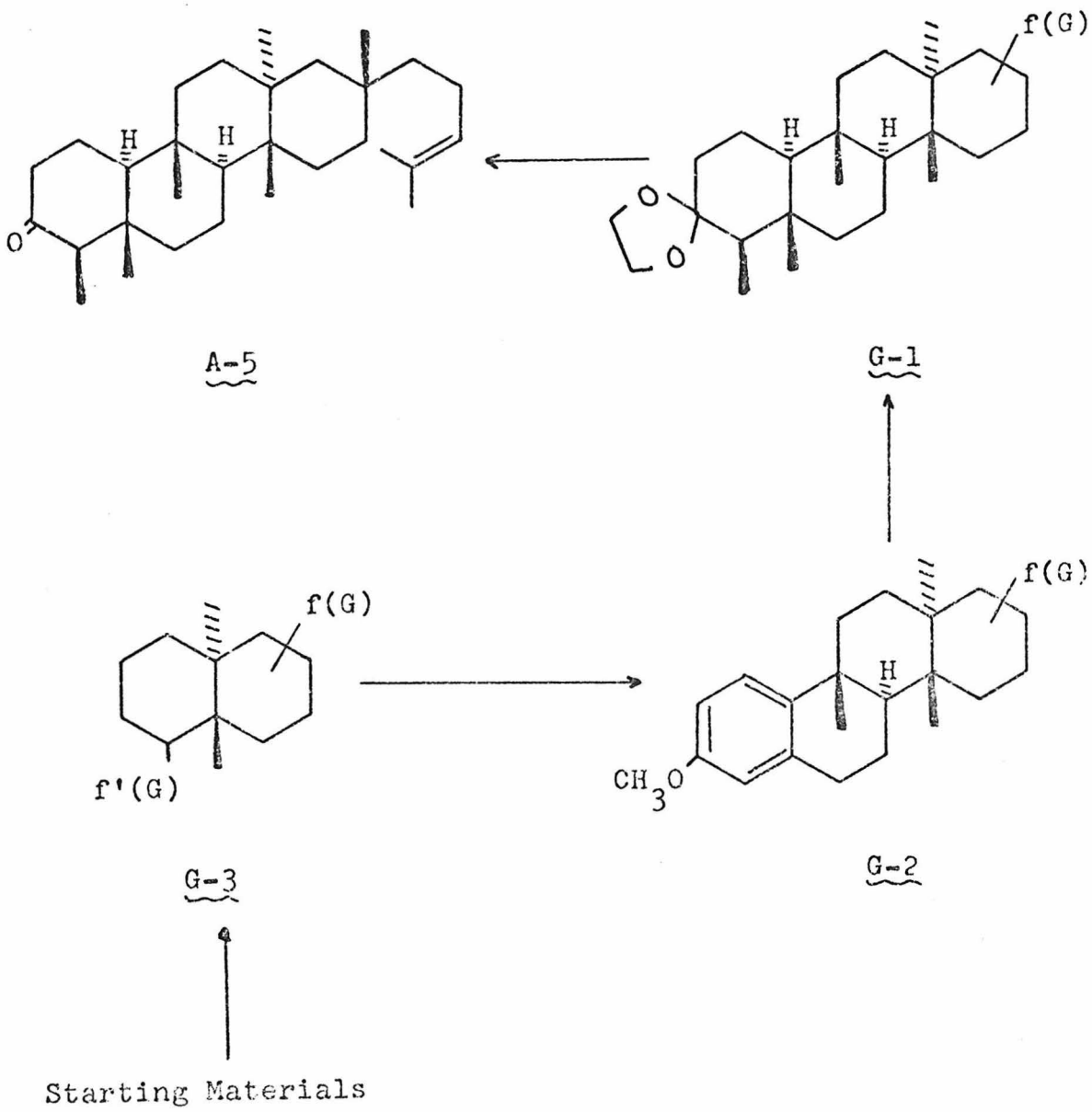
plausible manner" to arrive at intermediates which are more ammenable to direct attack.

To illustrate this process in the case of shionone consider chart G. Removal of the side chain gets rid of one asymmetric center and a potentially troublesome double bond while leaving behind most of the backbone of shionone as well as alnusenone and friedelin. At the same time, it is reasonable to assume that, with suitable functionality in the D ring of G-1, the side chain could be introduced near the end of the synthesis without affecting the rest of the molecule.

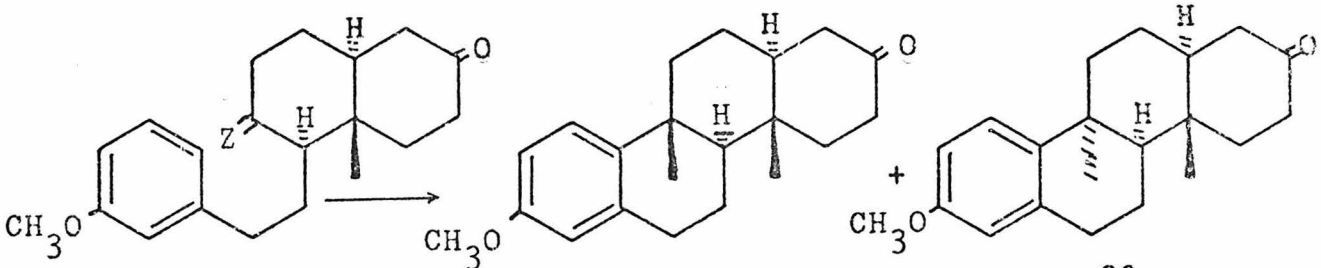
A second major simplification can be achieved by the presumption that the A ring could be derived from the anisole derivative G-2. It is well known that Birch reduction of anisole rings of this type gives the corresponding 2-keto-1-enes which have an oxygen atom in the required position for all the triterpenes of interest and a double bond activating the carbons that will eventually have to carry the vicinal methyl groups. Thus it appears that the tetracyclic G-2 would serve as an admirable key intermediate for both shionone and the related pentacyclic triterpenes.

It is further appreciated that aromatic rings are stable to a wide variety of chemical reactions and that the B ring of G-2 could potentially be closed by an intramolecular cycloalkylation reaction. The utility of this approach to polycylic systems is evident from its extensive

Chart G



application in steroid synthesis (49) and has recently been extended to systems of more immediate interest by the model studies carried out by Ireland, Baldwin, and Welch (50). These workers examined the outcome of the acid promoted cyclizations of the bicyclic compounds 16-18 and found that, regardless of the starting material, the product consisted of a 3:1 ratio of the trans, anti, trans ketone 19 and the cis, anti, trans isomer 20. They also presented a detailed theoretical argument to account for the stereochemical outcome of this reaction. This argument will be summarized later for the case of the ketone G-2, f'(g)=0.



16 Z=CH_2

17 Z=3 -OH,3 -CH_3

18 Z=3 -OH,3 -CH_3

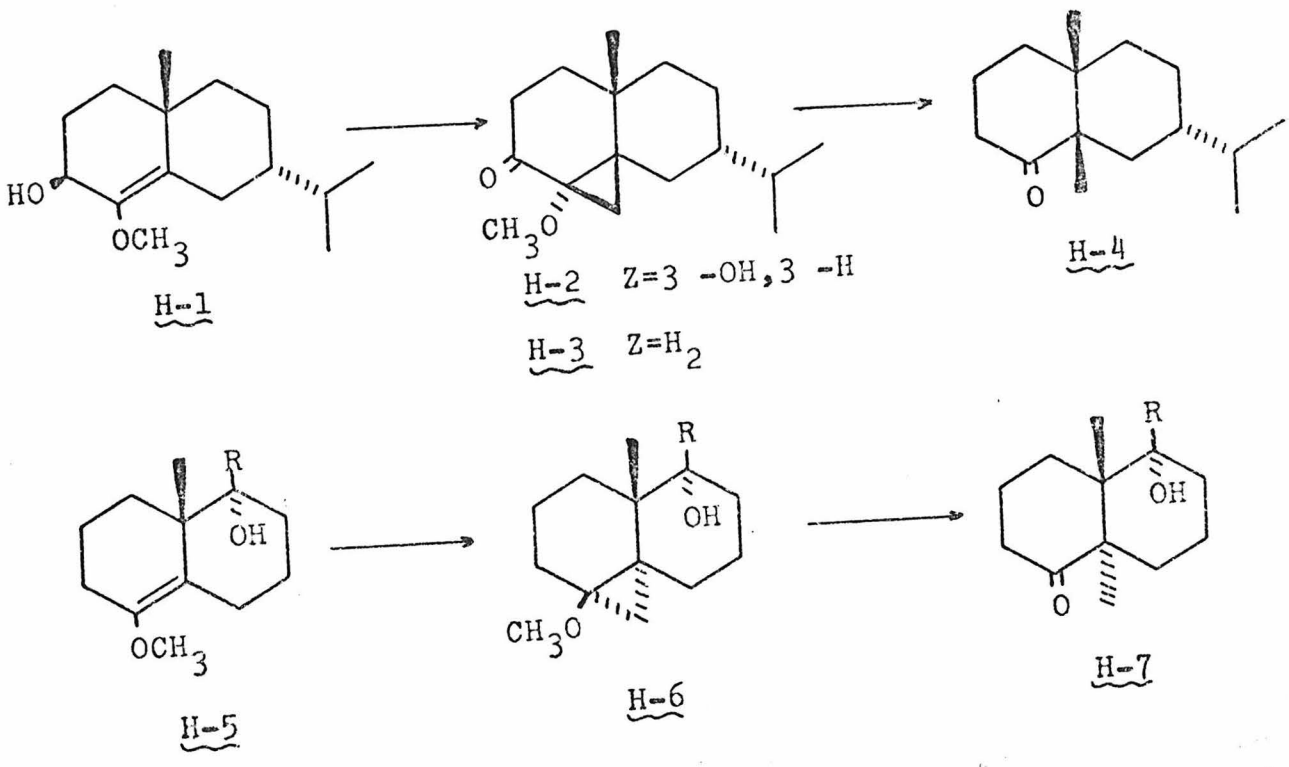
19 + 20

Finally, with the favorable result of the cyclization indicated, it can be assumed that the A and B rings can be generated by the addition of aβ-phenylethyl side chain to the decalin derivative G-3. This derivative is precisely the type of intermediate which was the first goal of this work.

It is anticipated that analyses similar to that above starting with other triterpenes would verify the versatility of G-3 as a synthetic intermediate.

A possible approach to compounds of this type was suggested by Wenkert's (51) successful synthesis of valeranone (H-4) in which a fused methoxycyclopropane was used as a source of an angular methyl group. Wenkert prepared the equatorial allylic alcohol H-1 (Chart H) by lithium

Chart H



aluminum hydride reduction of the corresponding ketone. This alcohol was then stereospecifically cyclopropylated with the Simmons-Smith reagent to give the alcohol H-2.

The Simmons-Smith reagent can be most easily formulated as icdomethylzinc iodide 21 and is formed by the action of diiodomethane on zinc-copper couple (52). This reagent will

$$I\text{-}CH_2\text{-}Zn\text{-}I$$

21

transfer methylene to olefins under mild conditions to give the derived cyclopropanes (53) and is directed by allylic (54) and homoallylic (55) alcohols to give the products of cis addition presumably through a prior coordination of the zinc atom with the hydroxyl oxygen.

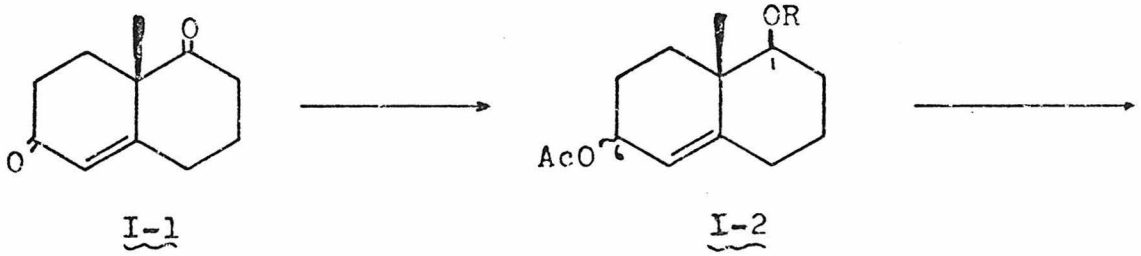
There are no known exceptions to this directing effect in six membered rings (56) so Wenkert was assured of the stereochemistry of the methoxycyclopropane H-2 on the basis of the known stereochemistry of the alcohol H-1. Finally, after removal of the C-3 oxygen by oxidation and Wolff-Kishner reduction of the resultant ketone, the methoxycyclopropane system of H-3 was cleaved in acid to give valeranone (H-4) in good yield.

It appeared that if this method could be extended to the axial homoallylic alcohol H-5, it would provide a route

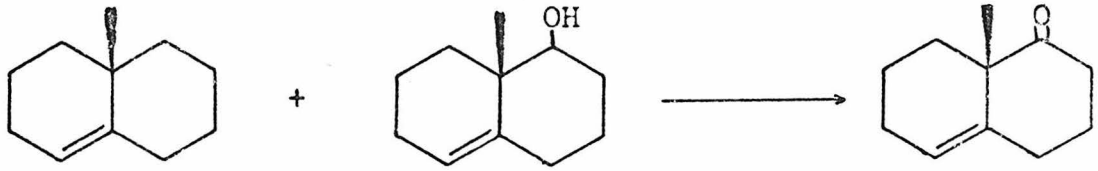
to the trans fused diangularly substituted naphthalenone H-7 with the required differing functionality in each ring. Unfortunately, preliminary attempts to prepare the alcohol H-5, R=CH_3 ran into difficulties due to the sensitivity of the enol ether and it was decided to carry out a model study on the more stable analogue I-6 to see if the Simmons-Smith reaction would indeed work as hoped on this system. Molecular models indicated that the β-face of this compound was significantly less hindered than the α-face and it was feared that the adverse steric effects might overwhelm the directing influence of the axial alcohol, particularly since the Simmons-Smith reagent is known to be responsive to steric hindrance (57).

The dione, "Miescher's ketone" (I-1) (58) was reduced with lithium aluminum hydride and was acetylated to give the known diacetate I-2, R=OAc (59) (Chart I). The diacetate was carried on without isolation by treatment with lithium in ethylamine to affect allylic cleavage of the C-3 acetate according to the general procedure of Hallsworth and his co-workers(60) giving the alcohol I-4 which had been previously prepared by Marshall (61) in a similar manner. Oxidation of the crude cleavage products with chromic acid in acetone (62) then gave, after column chromatography, 3% of the hydrocarbon I-3 which was identified on the basis of its nmr and ir spectra (63), and 35% (from the dione I-1) of the anticipated

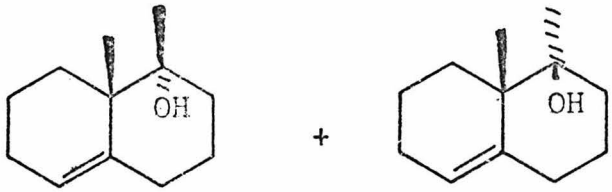
Chart I



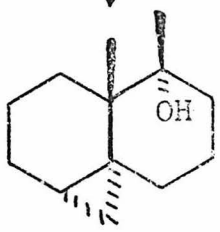
I-1 I-2



I-3 I-4 I-5



I-6 I-7

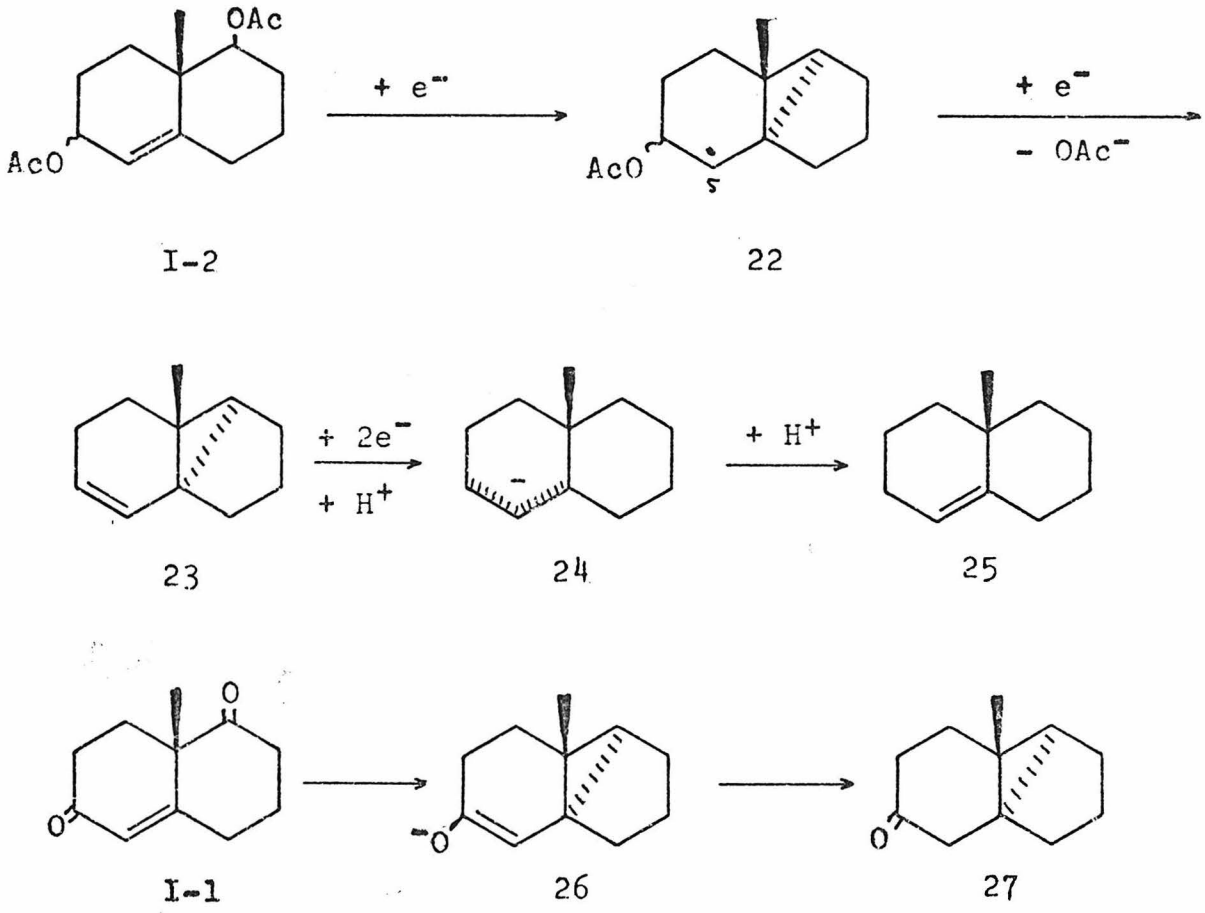


I-8

ketone I-5.

The olefin I-3 apparently arose by homoallylic cleavage of the 1-acetate during the dissolving metal reduction of I-2, R=OAc to give the cyclopropyl radical 22. There is precedent for such homoallylic reductions in the literature. Reusch (64) has recently reported that the action of lithium in ammonia on the dione I-1 gives 80% of the cyclopropyl ketone 27 which results from protolysis of the enolate anion 26 during isolation. In the present case, the first formed product 22 can react further. Acquisition of an electron by either the acetate or the C-5 radical could lead to the cleavage of the second acetate to give the olefin 23. This vinyl cyclopropane is isoelectronic with the α-carbonyl cyclopropyl ketones which are known to undergo ready reductive cleavage to products related to I-3 (65).

Successive reaction of the major oxidation product, the ketone I-5, with dimethyloxosulfonium methylide and lithium aluminum hydride provided a 6:1 ratio (nmr) of the axial and equatorial alcohols I-6 and I-7 respectively. The stereochemistry of the addition was predicated on the results of Corey and Chaykovsky (66) and Cook, Corley, and Wall (67) regarding the stereochemistry of the attack of sulfonium ylides on various cyclohexanones and steroidal ketones. Specifically, they found that dimethyloxosulfonium methylide gave almost exclusively the oxirane resulting from equatorial approach of the reagent while with the less bulky nonoxygenated



I-2 22 23 24 25 I-1 26 27

analogue, dimethylsulfonium methylide, the product of axial attack was obtained.

The stereochemistry of the alcohols was further established on the basis of the following data. The major isomer exhibited a higher r.f. on silica gel tlc indicating that it was the more hindered axial isomer. On dehydration with

phosphorous oxychloride in pyridine, the major isomer gave an endocyclic olefin with one vinyl proton in the nmr, a result characteristic of axial alcohols. On the other hand, the minor isomer gave a 2:1 mixture of exo- and endocyclic olefins (nmr) since the most favorable transition state for the dehydration involves a trans, diaxial elimination of water and there is no proton in the ring which is axially disposed with respect to the equatorial oxygen. The validity of this procedure for the distinction of axial and equatorial alcohols was established by Barton (68) during his conformational studies of steroids. A compound which was identical with the minor isomer I-7 was prepared by the addition of methyl lithium to the ketone I-5, a process which according to the Felkin principle (69) should occur by axial entry of the reagent to give the equatorial alcohol.

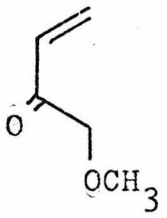
Treatment of the isolated axial alcohol I-6 with a ten fold excess of the Simmons-Smith reagent resulted in a very facil reaction. It was complete in less than an hour at room temperature and gave a single cyclopropyl alcohol in 63% yield. This was assumed to be the desired α-isomer I-8 because of the rate and stereospecificity of the reaction. The reactions of the Simmons-Smith reagent with unactivated double bonds such as that available for β-attack in I-6 is known to require several hours at reflux (53) so that it is reasonable to suppose that the reaction in this case was

facilitated by coordination of the reagent with the axial oxygen demanding that attack occur from the α-side of the molecule.

With the successful conclusion of the model study, attention was once again directed at the synthesis of the alcohol H-5. 1,4-Dimethoxybutanone (J-1) is available from butyne-1,4-diol in two steps in 55% yield (70). It was necessary to eliminate methanol from this compound to give the corresponding vinyl ketone 28 which was to be used in an Robinson annulation with the dione J-2. This process was attended with some difficulty, however, and various methods were explored including pyrolysis in silicon oil, flow pyrolysis through a packed tube, acid catalyzed elimination, and pyrolysis in a slurry of sodium benzoate. The packed tube method appeared to give the best yield, but was too slow using the available equipment. The method adopted involved the rapid heating to 180-200° of a round bottom flask containing about equal weights of sodium benzoate and J-1 with vigorous stirring and continuous distillation of the products (71). This procedure provided a 35% yield of the vinyl ketone 28 as determined by nmr analysis of the distillate which also contained the liberated methanol and a small amount of the starting material J-1.

The vinyl ketone was condensed directly with 2-methyl-1,3-cyclohexanedione (J-2) (Chart J) in the presence of potassium hydroxide (58). The addition product 29 was

resistant to cyclodehydration under the usual conditions of pyrrolidine catalyst in refluxing benzene (58) giving only the alcohol 30 which slowly decomposed under the reaction conditions. This alcohol could be dehydrated with thionyl chloride in pyridine (72), but this two step process was



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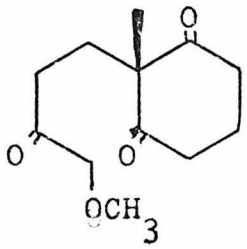
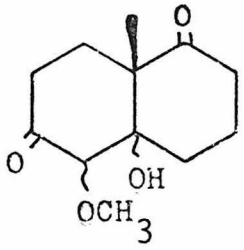


29

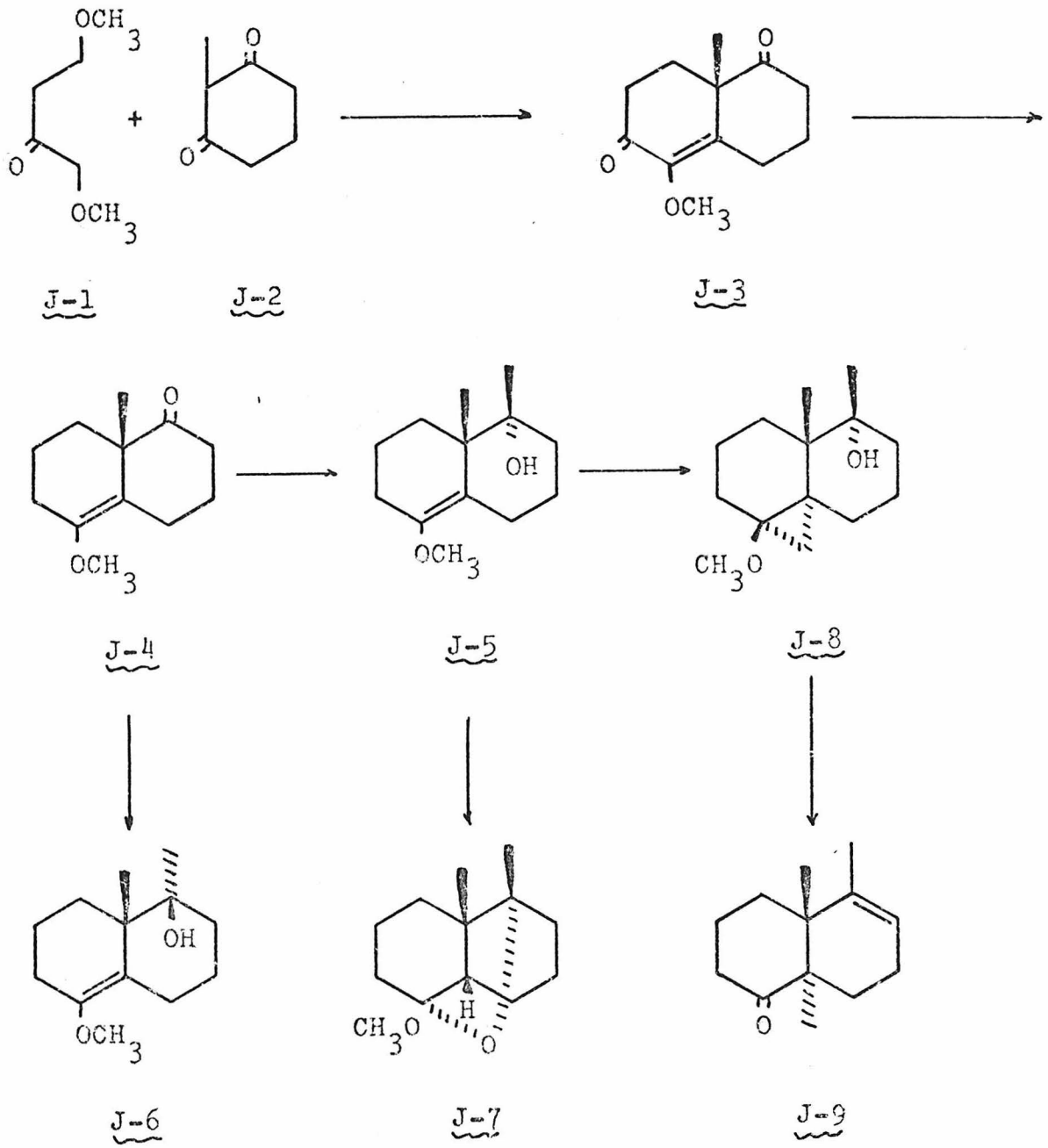


30

inferior to the method employed by H. Smith and co-workers (73), who carried out similar cyclodehydrations as part of their synthetic endeavors on estrone. Exposure of the crude addition product 29 to triethylammonium benzoate in refluxing xylene resulted in a smooth cyclization and a 19% yield of the dione J-3 (from the butanone J-1) was obtained after an aqueous workup and recrystallization.

As the demands for the naphthalenedione J-3 grew, a procedure which was shorter and more amenable to large scale preparations was sought. It was gratifying to discover that the pyrolysis of J-1 could be carried out in refluxing xylene containing an excess of the dihydroresorcinol J-2 and a catalytic amount of triethylamine to give the condensation products directly. Distillation of the methanol formed,

Chart J



J-1 J-2 J-3 J-4 J-5 J-8 J-6 J-7 J-9

addition of the triethylammonium benzoate catalyst, and overnight reflux followed by an aqueous workup then gave a crude solid from which 52-59% of the dione J-3 could be obtained on trituration with ether. In addition to the superior yield, this process required only one rather than three days and could be adapted to almost any scale.

The reduction, acetylation, and allylic cleavage of J-3 proceeded as in the model compound except that the cleavage gave extensive side products unless the lithium wire was freshly cut into small pieces and added rapidly to the solution of the diacetate in ethylamine. It was also necessary to have tert-butyl alcohol present to prevent the formation of lithium ethylamide which could displace the methyl group of the enol ether giving an enolate anion which would provide the corresponding ketone on protolysis. The yields were variable, but under optimum conditions 65% of a crystalline alcohol was available after chromatography.

Oxidation with chromium trioxide dipyridine complex (Collins reagent) (74) gave 83% of the ketone J-4 which was generally treated with dimethyloxosulfonium methylide without further purification. The resulting mixture of epoxides was reduced immediately with lithium aluminum hydride in pyridine to give 77% of the desired axial alcohol J-5 together with a small amount of the equatorial epimer J-6 which was also available in quantitative yield by addition of methyl lithium to the ketone J-4. When the reduction was conducted

in ether, formation of the cyclic ketal J-7 occurred as a side reaction. This ketal was formed in 80% yield when a slightly acidic solution of the crude alcohol J-5 in chloroform was allowed to stand for several days at room temperature. Formation of this ketal, although troublesome at first, was providential in providing an unequivocal proof of the stereochemistry of the axial alcohol J-5 since such a cyclization would be sterically impossible for the equatorial isomer J-6. Use of the pyridine solvent in the hydride reduction served to complex the aluminum thus preventing lewis acid promoted processes.

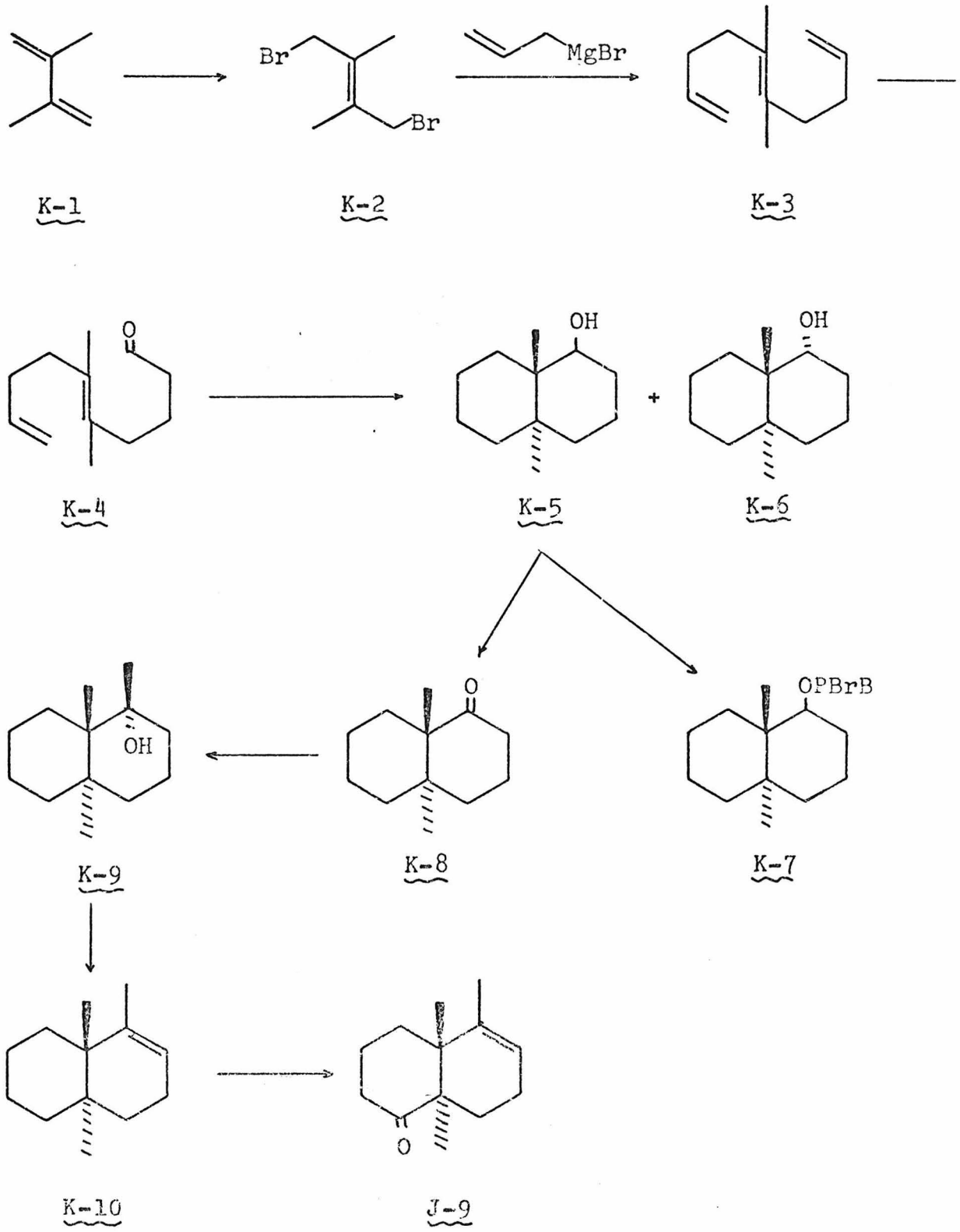
The Simmons-Smith reaction of the axial alcohol J-5 was carried out in the presence of one equivalent of dimethoxyethane to precipitate zinc iodide as it formed (75) in an effort to avoid the problems encountered above. The reaction was complete in less than 30 minutes and gave a single methoxycylopropane in 83% yield. In order to cleave the cyclopropane ring, it was necessary to treat it with 7% hydrochloric acid in refluxing methanol for two hours. These conditions resulted in extensive dehydration of the tertiary alcohol and it was most convenient to allow the dehydration to go to completion to give 74% of the keto-olefin J-9.

Although the stereochemistry of this compound seemed assured on the basis of the above results, it was desirable to have a positive proof of the assigned structure. A suitable compound for comparison had been prepared previously

by Ireland and Dawson (76) in connection with their polyene cyclization experiments. As part of a program to prepare compounds like the key intermediate G-2, they needed to determine whether a concerted polyene cyclization could proceed through a tetrasubstituted double bond to give a trans fused decalin or if the cyclization would be interrupted at the initially formed tertiary carbonium ion. Bromination of 2,3-dimethylbutadiene (K-1) and coupling with allyl grignard preceeded well to the symmetrical triene K-3 (Chart K). Hydroboration with one equivalent of disiamylborane and oxidation gave a statistical mixture of starting material, mono-alcohol and diol which was readily separated on florisil. Collins oxidation of the isolated mono-alcohol then gave the cyclization substrate K-4 in 26% yield (from the butadiene K-1). The best conditions for the cyclization were found to be stannic chloride in ice cold nitromethane followed by catalytic hydrogenation of the resultant olefin mixture to provide, after preparative tlc, 40% of the equatorial alcohol K-5 and 5% of axial alcohol K-6. The stereochemistry of the major isomer was proven by x-ray crystallographic analysis of the p-bromobenzoate derivative K-7.

In order to relate the stereochemistry of K-5 with that of the product of the cyclopropane cleavage, the alcohol was oxidized to the corresponding ketone K-8 which was treated with methyl lithium. Enolization competed effectively with

Chart K



K-1 K-2 K-3

K-4 K-5 K-6

K-7 K-8 K-9

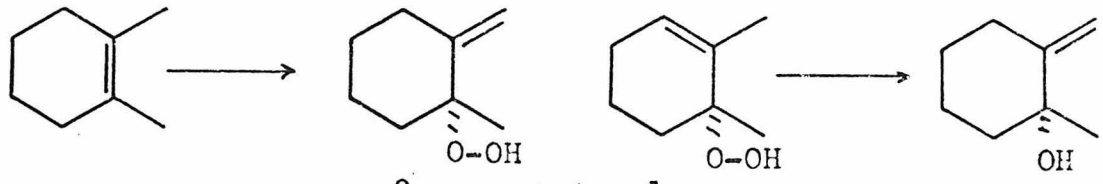
K-10 J-9

addition in this case, and it was necessary to repeat the treatment to obtain a 79% yield of the tertiary alcohol K-9. It was anticipated that the steric hinderance offered by the C-4a methyl group would require the reagent to approach equatorially to give the axial alcohol (69). In support of this expectation, the nmr spectrum of the product K-9 revealed that the C-4a angular methyl was deshielded by 20 Hz from its position in the equatorial alcohol K-5, presumably due to its proximity to the axial oxygen. Thionyl chloride dehydration of the alcohol went smoothly to give 42% of the volatile hydrocarbon K-10. A hydrocarbon which was identical in all respects (ir, nmr, mp, mmp) was obtained *via* Wolff-Kishner reduction of the keto-olefin J-9 thus confirming the structural assignment.

The initial plan for the conversion of the dicyclic keto-olefin J-9 to the tetracyclic ketone G-2, f(g)= =O called for preparation of the exocyclic α,β-unsaturated ketone L-3 (Chart L). For this synthesis we proposed the photoöxygenation of the olefin L-1 which was available in nearly quantitative yield by careful ketalization of J-9.

The photoöxygenation reaction has been widely studied and it has been established that cyclic olefins bearing a methyl group such as 31 (77) give mainly the product of hydrogen abstraction from the methyl group, 32 which provides the corresponding allylic alcohol 33 on reduction. The data

available at the time favored an "ene" type mechanism involving a concerted attack of one of the oxygen atoms along a p orbital of the double bond simultaneously with hydrogen abstraction by the other oxygen atom. The argument



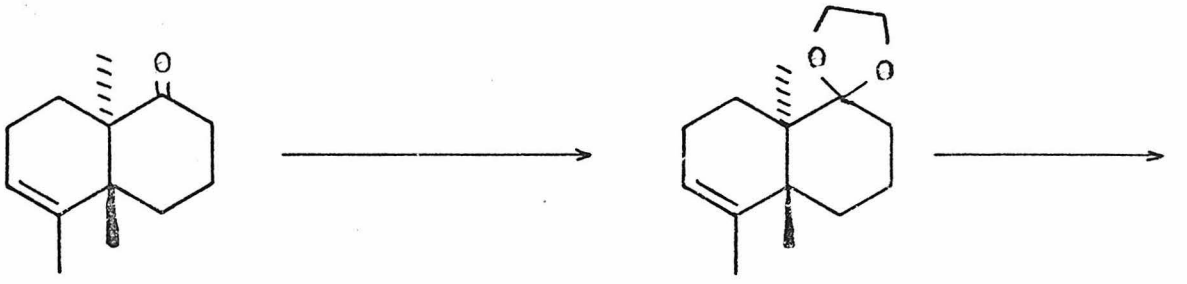
9 : 1

31 32 33

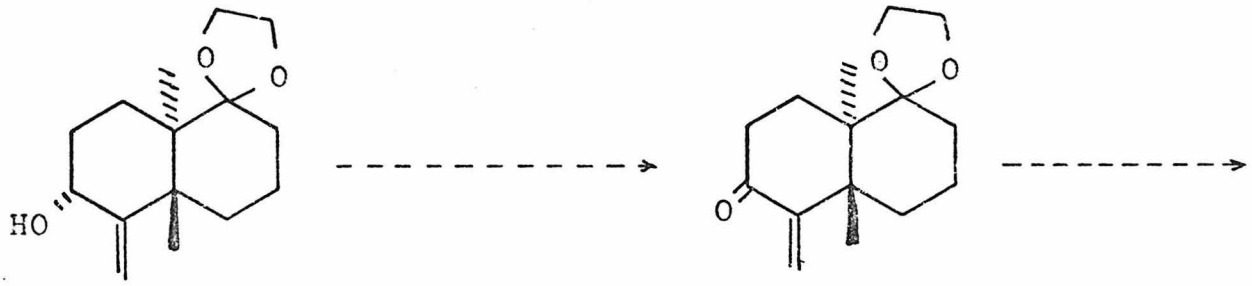
accounted for the selectivity of the reaction on the basis that only the methyl hydrogens could rotate so as to maintain continuous overlap of the breaking C-H bond with the π system. The more recent results of Fenical, Kearns and Radlick (78) have implicated the intermediacy of perepoxides such as 34 in this reaction; however, it appears that the reasoning invoked above to explain the selectivity would also be valid for the decomposition of 34 to products.

Unfortunately, the olefin L-1 proved to be extremely resistant to photooxygenation under a variety of conditions. Using either rose bengal sensitizer in isopropanol (79) or the ozone-triphenylphosphite complex (80) to generate singlet oxygen, only starting material and tar were recovered. The Nickon and Bagli (81) conditions of hematophoryn sensitizer in pyridine at room temperature gave better results and after 132 hours, gas liquid chromatography indicated that

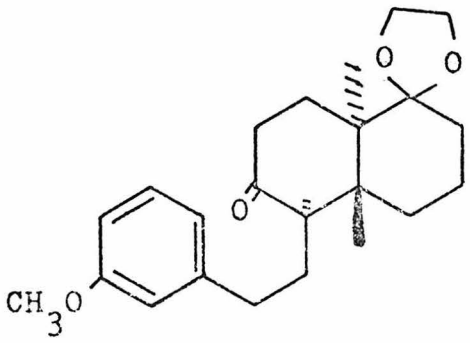
Chart L



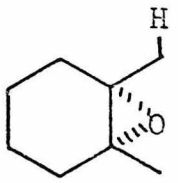
J-9 L-1



L-2 L-3



L-4

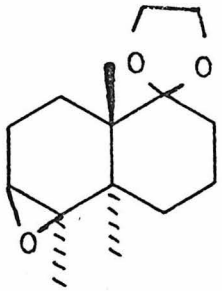


34

about 2/3 of the starting material had been consumed. The crude hydroperoxide was reduced with lithium aluminum hydride to give 31% of a single allylic alcohol which was assigned the structure L-2 on the assumption that the singlet oxygen would approach the molecule from the side opposite the C-4a angular methyl. Apparently the steric hindrance presented by the two angular methyl groups is sufficient to slow the reaction drastically permitting side reactions to compete. Such a conclusion is in accord with Nickon's results (81 which indicate that the attack of singlet oxygen is quite sensitive to steric effects.

While the results obtained by Ireland, Baldwin, and Welch (50) on a related allylic alcohol indicated that the proposed oxidation and 1,4-addition of m-methoxybenzyl grignard would proceed as desired to give the ketone L-4, the inefficiency of the photoöxygenation step made other routes appear more attractive. One potentially promising approach to the allylic alcohol L-2 which avoided the photoöxygenation

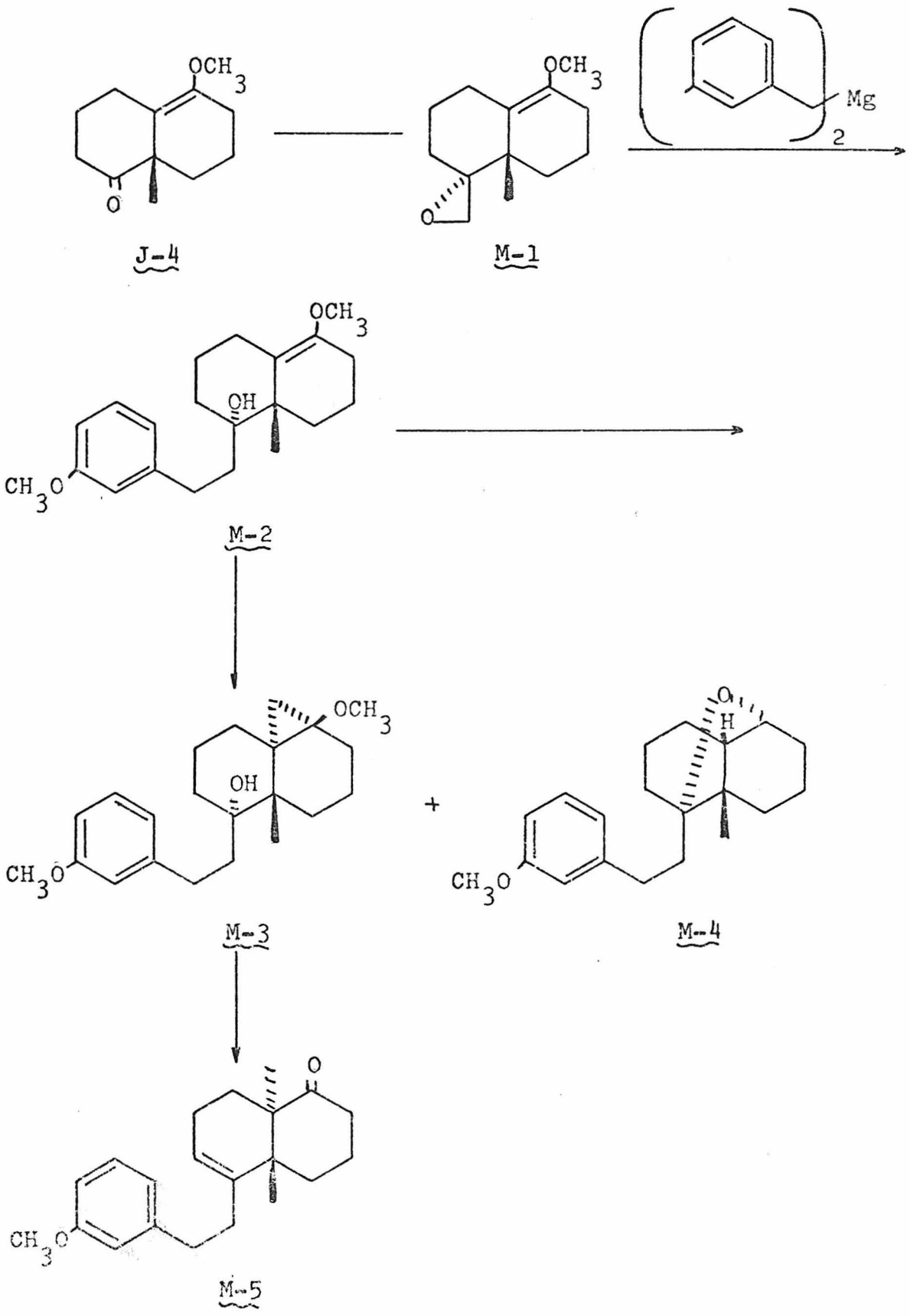
step, the strong base induced cleavage of the epoxide 35 (82), was considered only briefly before moving on. Later work by D. Dawson (83) has demonstrated the feasibility of this procedure in the presence of a more stable protecting group for the ketone.



35

One inviting method for the introduction of the side chain possessing the A ring was cleavage of the epoxide M-1 (Chart M) with a dialkyl magnesium. Some preliminary experiments showed that ether solutions of dibenzyl- or di-m-methoxybenzylmagnesium could be prepared from solutions of the corresponding Grignard reagents by precipitation of the magnesiums halides with one equivalent of dioxane in a modification of the Christensen (84) procedure. When stirring was halted, the precipitate settled rapidly and the supernatant could be withdrawn with a syringe and added to a solution of the epoxide in dioxane. Using dibenzyl magnesium, the cleavage went smoothly to give the axial alcohol M-2, R=H in 80% yield. The alcohol was generally treated directly with the Simmons-Smith reagent to give 45% of the desired methoxycyclopropane M-3, R=H together with 12% of the characteristic cyclic

Chart M



J-4 M-1 M-2 M-3 M-4 M-5

ketal M-4, R=H.

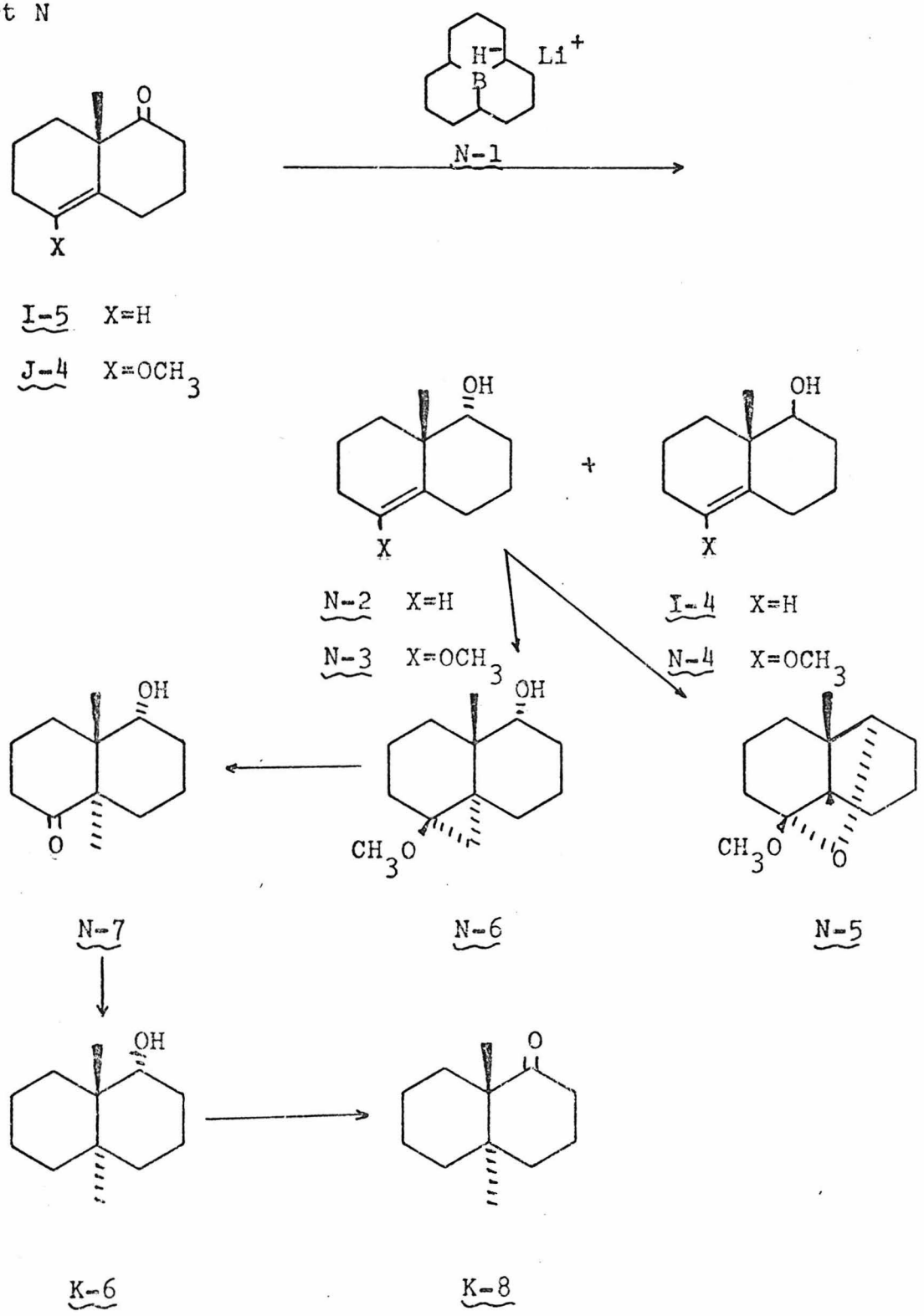
When di-m-methoxybenzylmagnesium was employed in the same reaction, the very first attempt resulted in an 86% yield of the alcohol M-2, R=OCH_3 which was carried on to give 66% of the cyclopropane M-3, R=OCH_3 and 8% of the ketal M-4, R=OCH_3 as expected. Cleavage of the methoxy-cyclopropane in acidic methanol as before gave only 46% of the contemplated product, the keto-olefin M-5, probably due to competing attack of the anisole ring on the carbonium ion formed during the dehydration of the tertiary alcohol.

The initial favorable result in the epoxide cleavage with di-m-methoxybenzylmagnesium was not reproducible. Subsequent reactions proved to be highly capricious giving from 24-57% of the required alcohol M-2, R=OCH_3 together with a host of side products. A great deal of effort was expended in trying to ascertain the cause of this variability without success. The di-m-methoxybenzyl magnesium was always titrated (85) prior to use and the amount of reagent formed did not vary appreciably from run to run. Also the relative amounts of solvents and the reaction times were varied to no avail. After this work had been abandoned, a report by Morrison, Atkins, and Tamaszewski (86) suggested that suspended magnesium chloride dioxinate can be a source of variability in these reactions. A reinvestigation of this epoxide cleavage should take this possibility into account.

While the above experiments were in progress, a paper by Brown and Dickason (87) appeared describing a new reducing agent for the preparation of axial alcohols from cyclohexanones opening new avenues to the synthesis of the tetracyclic intermediate G-2. Several reduction experiments were carried out on the ketone I-5 to investigate the utility of the new reagent, lithium 9b-boraperhydrophenalyl hydride (N-1), in systems of immediate interest. A typical yield was 64% of a 56:44 ratio of the axial and equitorial alcohols N-2 and I-4 respectively (Chart N). The ratio of isomers was insensitive to temperature between -78° and 25° so the reactions were usually run at 0°. Fortunately, it was soon discovered that the poor yields could be improved by modifying the preparation of the reagent. Brown reported that the reagent could be obtained by heating a solution of 9b-boraperhydrophenalene (88) in tetrahydrofuran at reflux in the presence of "a moderate excess of lithium hydride" for three hours. Experience has shown that it is necessary to use a large excess (> than 20 fold) of lithium hydride and to extend the reflux period to six hours to obtain a reliable reagent; it is also advisable to run this reaction under an argon atmosphere since the trialkylborane is sensitive to even traces of oxygen.

With the borohydride prepared in the above manner, it was possible to routinely achieve a quantitative yield of a 70:30 mixture of the alcohols N-3 and N-4 on reduction of the

Chart N



ketone J-4. The major isomer readily cyclized to the ketal N-5 on standing overnight in deuterochloroform in an nmr tube while the minor isomer had been prepared previously so that the stereochemical outcome of the reduction was clearly defined.

When the crude mixture of alcohols was treated with an excess of the Simmons-Smith reagent, once again a facile reaction ensued providing 59% of the methoxycyclopropane N-6 (from the ketone J-4) after chromatography. The cyclopropane ring cleaved as expected on treatment with acid to give 80% of the keto-alcohol N-7. With the more stable secondary alcohol at C-1, it was possible to achieve ring opening without concomitant dehydration by following the reaction and stopping it when the desired transformation was complete. This represents a more versatile synthesis of the trans-fused, diangularly substituted naphthalene of the type G-3 than that accomplished before (Chart J). The keto-olefin N-7 should be an admirable synthetic intermediate since it is potentially a masked, symmetrical diketone.

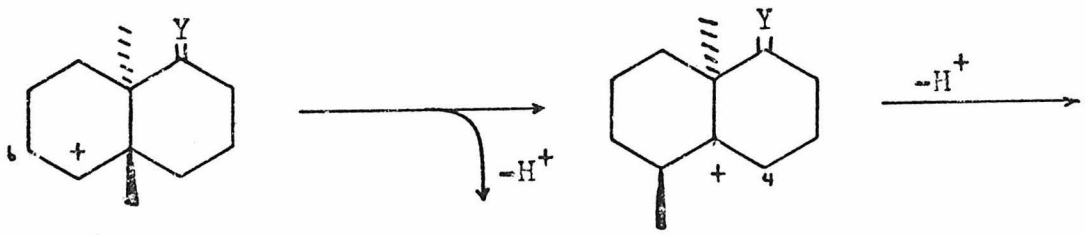
In order to provide unequivocal proof of the stereochemistry of the ring fusion of N-7 it was necessary to relate it to the alcohol of known configuration K-5. Wolff-Kishner reduction of N-7 preceeded poorly, presumably due to the steric hindrance to hydrazone formation associated with the angular methyl groups and the axial alcohol, but did

provide 23% of the alcohol K-6 which was spectrally identical (nmr, ir) to the minor isomer obtained by Ireland and Dawson from the cyclization of the aldehyde K-4. Chromic acid oxidation gave the ketone K-8 which was identical in all respects (ir, nmr, mp, mmp) to that prepared by a similar oxidation of the equitorial alcohol K-5. With the successful culmination of this phase of the work, it was appropriate to consider methods for adding the A and B rings to the keto-alcohol N-7.

The most direct approach would be to add a β-phenylethyl side chain to the carbonyl and then to manipulate the ring functionality to provide a suitable substrate for the acid catalyzed closure to the tetracyclic G-2. In order to impliment this plan, it was first necessary to convert the alcohol to a more stable group. Taking advantage of the symmetry of N-7, the ketone was protected as the ketal, a reaction which was accompanied by extensive dehydration of the secondary alcohol. Thus ketalization of N-7 gave only a 68% yield of the ketal O-1 which was oxidized quantitatively to the ketone O-2 with chromic acid (Chart O).

The dehydration products proved to be a complicated mixture in contrast to the situation encountered before with the alcohol J-8 (Chart J). One possible explanation for this result is that the initially formed carbonium ion 36 could loose a proton from C-6 or suffer rearrangement to the more stable tertiary carbonium ion 37 which could loose a

proton in either of two directions or rearrange further. There is no a priori reason to expect a single process to predominate.

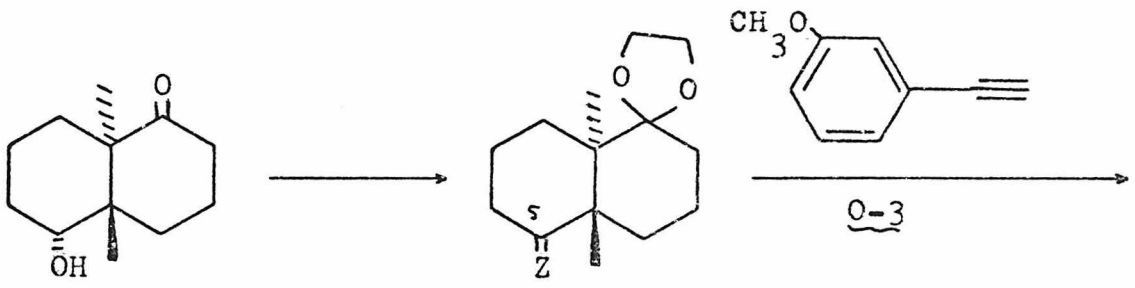


36 37

An attempt to add the side chain by treatment of the ketal O-2 with 2-m-methoxyphenylethylmagnesium bromide led only to reduction of the ketone. Such a result had been encountered previously by Barltrop and Rogers (89) in their attempt to add the Grignard reagent to the cyclohexanone 38. These workers turned to the less hindered potassium m-methoxyphenylacetylide (O-3) which they formed by addition of the corresponding acetylene in ether to a solution of potassium amide in liquid ammonia. Addition of an ether solution of the ketone 38 gave, after catalytic hydrogenation over palladium on carbon and distillation, 80% of the alcohol 39.

In the present case, it was more convenient to form the acetylide by the dropwise addition of one equivalent of the acetylene to an ethereal solution of n-butyl lithium. The substrate could then be added and the ensuing reaction could be followed by vpc. After four hours no further change was

Chart O

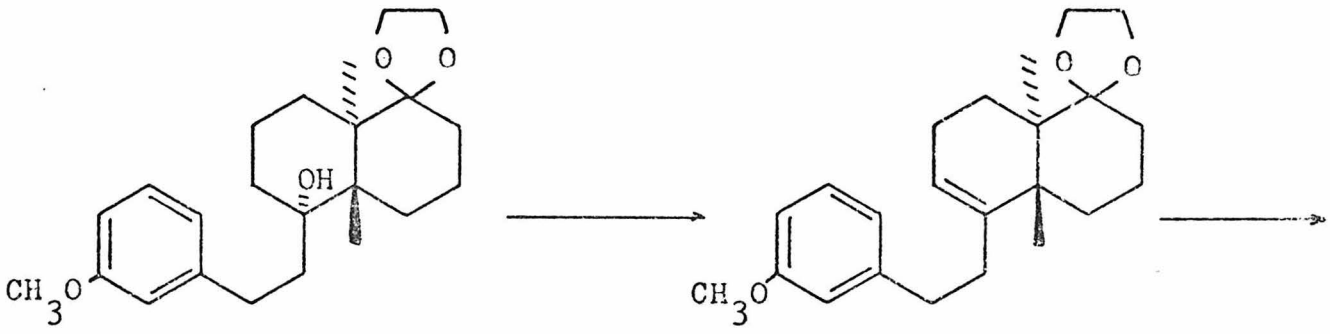


N-6

O-1 Z=5∝-OH,5β-H

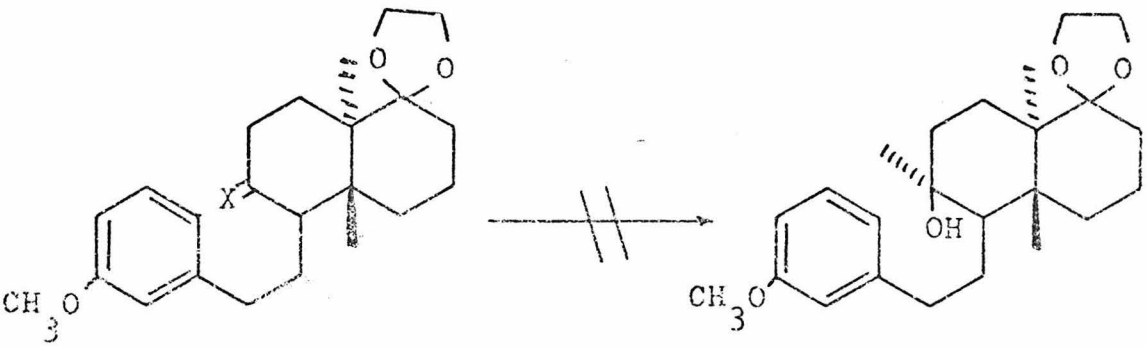
O-2 Z= =O

O-3



O-4

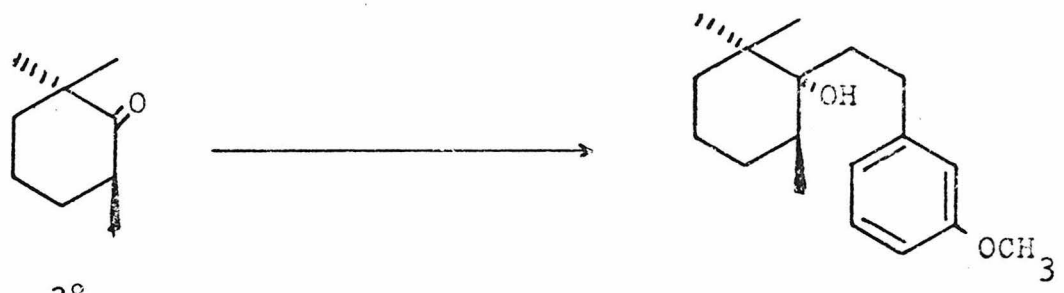
O-5



O-6 X=6 -OH,6 -H

L-4 X= =O

O-7



38 39

discernable and the product was obtained as a 60:40 ratio of the addition compound and starting material after chromatography. The mixture was hydrogenated under the published conditions to give a similar mixture of the alcohol O-4 and the starting ketone O-1. This crude product was dehydrated with thionyl chloride in pyridine to give an overall yield of only 38% of the olefin O-5 that was readily separable from the starting ketone O-1. Once again it appeared that the steric hindrance attendant with the disubstituted ring fusion, in this case butressed by the axial oxygen of the ketal, reared its ugly head to render a promising route mediocre. In spite of this setback it was decided to press on in hopes of obtaining a sample of the tetracyclic G-2 for comparison with the product from other more efficient routes.

Hydroboration of the olefin O-5 proceeded slowly and after two hours at room temperature 37% of the secondary alcohol O-6 was obtained on oxidation along with 16% of recovered

starting material, while longer reaction times led to lower yields. Chromic acid oxidation of the alcohol did go well to give a quantitative yield of the ketone L-4. This ketone, unfortunately, was resistant to attempts to add a methyl group and form the alcohol O-7. When it was treated with methylmagnesium iodide, dimethylmagnesium, or methyl lithium at temperatures ranging between -78° and 25°, only recovered starting material was isolated. At the time it was concluded that enolization of the ketone was occuring, again due to the bulk at the ring fusion, and this route was abandoned.

In light of the reasoning that most of the problems with the above scheme were associated with the steric bulk of the ketal and angular substituents, it appeared that the route could be resurrected if this factor could be controlled. One simple method to achieve this would be to delay the cleavage of the methoxycyclopropane system of N-5 until the other transformations were complete. The intact cyclopropane ring should have the effect of flattening the ring system while at the same time tying back the carbon atom that would later become the C-4a angular methyl. An additional advantage of this innovation is that it would avoid the inexpedient ketalization of the keto-alcohol N-7.

In accord with the above plan, the methoxycyclopropane N-5 was oxidized with chromic acid to give 73% of the ketone P-1 (Chart P). On treatment with 2-m-methoxyphenylethylmagnesium bromide there was obtained 58% of a 1:1 mixture

of the reduction product, the alcohol N-6, and the addition product M-3, R=OMe. When lithium m-methoxyphenylacetylide was employed under the same conditions used before and the crude propargyl alcohols were hydrogenated, 44% of the axial alcohol M-3, R=OMe and 46% of the equatorial isomer P-2 were recovered. The stereochemical assignment of these products was based on the higher tlc mobility of the axial isomer and was confirmed by the dehydration experiments described below. It is possible that a higher portion of the desired axial alcohol could be obtained by running the reaction at a lower temperature than 25°. This point was not pursued in the present work because a shorter and preparatively more useful route to the tetracyclic ketone G-2, f(g)=O had just been complete by C. Kowalski (90) in the Ireland laboratories changing the purpose of this work to that of providing a sample of the same compound whose stereochemistry about the C/D ring fusion was rigorously defined for comparison.

Both the axial alcohol M-3, R=OMe and the equatorial isomer P-2 were dehydrated with thionyl chloride in pyridine to give 91% and 43% of the olefins P-3 and P-4 respectively. The assignment of P-3 as the endocyclic olefin was based on the relative widths of the vinyl proton peaks in the nmr spectra, 12 vs 20 Hz for the exocyclic olefin P-4, as well as the further reactions of P-3. The exocyclic olefin is expected to exhibit a broader vinyl resonance since the m-methoxybenzyl substituent can rotate freely allowing efficient

coupling between the benzyl and vinyl protons, while in the relatively rigid ring, the various protons exist at fixed dihedral angles. The result of the dehydration experiments verifies the stereochemical assignment of the alcohols on the strength of Barton's criteria (68).

Hydroboration and subsequent oxidation of the olefin P-3 proceeded without incident to the ketone P-6 in 62% yield. Treatment of P-6 with ten equivalents of methyl lithium at room temperature provided 90% of a single tertiary alcohol assigned the structure P-7 on the assumption that the methyl anion would approach equatorially to avoid a 1,3-diaxial interaction with the C-4a angular methyl. The facility of these transformations provides support for the hypothesis that the problems associated with the previous efforts (Charts L and O) were indeed steric in nature.

The alcohol P-7 was treated under the conditions used previously to cleave the methoxycyclopropane ring system and the reaction was followed by analytical tlc. The tertiary alcohol dehydrated first giving rise to a very mobile spot which slowly gave way to a slightly less mobile spot corresponding to the mixture of olefinic ketones P-8. Preparative tlc of the crude product gave 91% of a colorless oil which consisted of a 70:30 mixture of the tetrasubstituted and trisubstituted double bond isomers by nmr integration of the angular methyl region.

The olefin mixture was maintained at reflux for several

Chart P

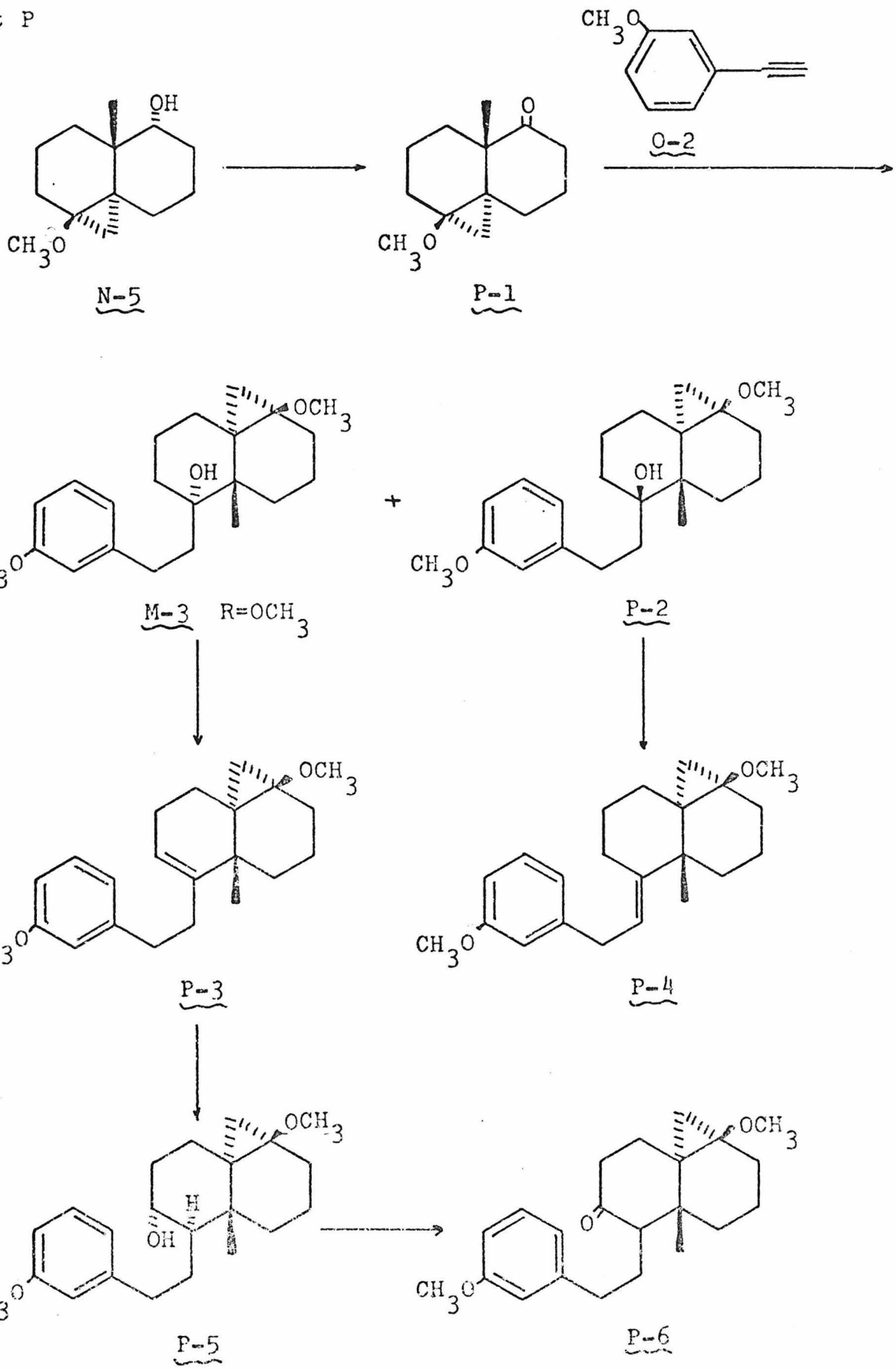
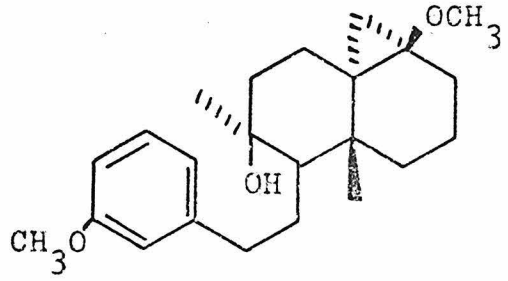
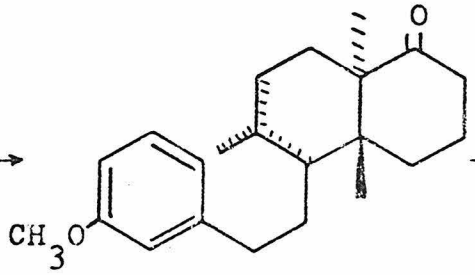

OH
CH3O
N-5
O
CH3O
P-1
CH3O
O-2
OCH3
OH
CH3O
M-3 R=OCH3
+
OCH3
OH
CH3O
P-2
OCH3
CH3O
P-3
OCH3
CH3O
P-4
OCH3
H
OH
CH3O
P-5
OCH3
O
CH3O
P-6

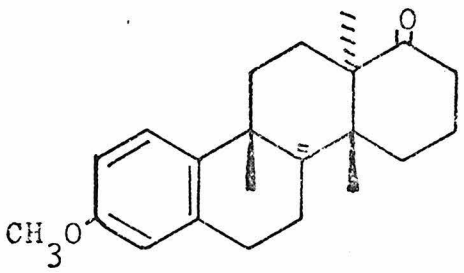
Chart P (continued)



P-7

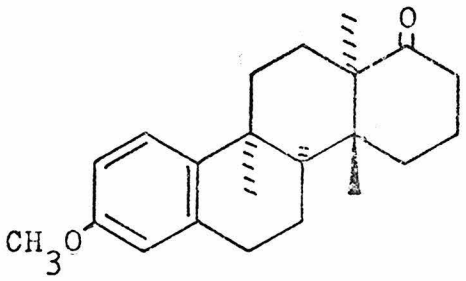


P-8

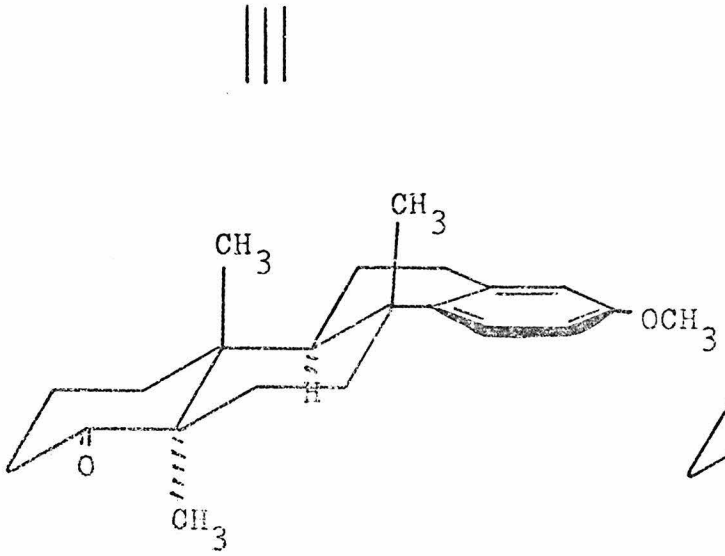


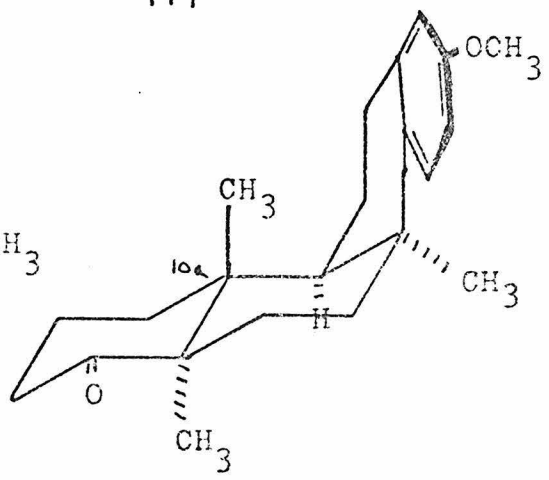
P-9

+



P-10



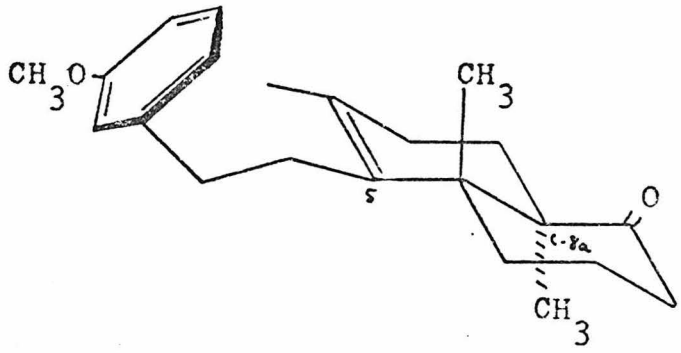


hours in a 20% solution of p-tolulenesulfonic acid in toluene to effect cyclization. Chromatography gave 78% of an 80:20 ratio of two compounds which were assigned as the trans, anti, trans and cis, anti, trans ketones P-9 and P-10 respectively. Later, for preparative purposes it was found that the cyclization went better in refluxing trifluoroacetic acid and that it was possible to achieve a 94% yield of a 85:15 mixture of the two ketones from which 65-70% of the desired ketone P-9 could be obtained by direct crystallization from ethanol. The components of the mother liquors were extremely resistant to separation, but could be partially purified by careful chromatography on grade I alumina (91). The overall yield of the ketone P-9 from the dione J-3 was 3.3% in 15 steps.

That both the ketone isomers were the products of cyclization para to the methoxyl group was evident from their ir spectra which exhibited aromatic bands at 1600 and 1500 cm^{-1}. A small sample of the 4-methoxy-isomer of P-9 resulting from ortho cyclization was obtained by C. Lipinski (92) from a concerted cyclization (vide infra) and this material had aromatic bands in the ir at 1595 and 1575 cm^{-1}.

Of the four possible tetracyclic 2-methoxy-isomers, the two syn isomers could be dropped from consideration because their formation would require equitorial protonation at C-5 of 40 and require that the C ring adopt an unfavorable twist

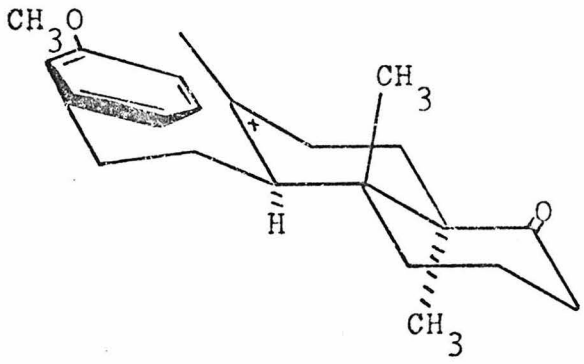
boat conformation or suffer a secere 1,3-diaxial interaction between the C-8a angular methyl group and the axial side chain. Both of these processes are expected to be of significantly higher energy than the alternatively possible stereoelectronically preferred axial protonation at C-5 of 40 leading to



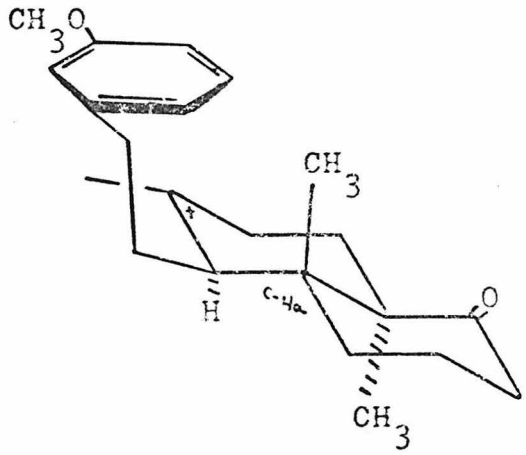
40

the conformers 41 and 42 both of which have ring C in the more stable chair form. Of the two, cyclization is predicted to occur mainly through the conformer 41 to give the trans, anti, trans tetracyclic P-9 because the developing 1,3-diaxial interaction between the incoming aromatic ring and the C-4a angular methyl group in 42 should make cyclization through this conformer a less favorable process (50).

That the required trans, anti, trans isomer did predominate was readily apparent from the nmr spectra of the two isolated ketones. As can be ascertained from the conformational drawings, the cis isomer P-10 is folded such that there is



41



42

a 1,3-interaction between the aromatic ring and the C-10a angular methyl group so the methyl should be strongly shielded in the nmr. No special effects on the methyls of the flat trans isomer are expected so that the two should be clearly differentiated by their spectra. This presumption was born out fully as shown in table 1. The chemical shifts of the various methyl groups are reasonably similar except for the C-10a methyl which appears 29 Hz upfield in the minor, cis isomer P-10. In support of this analysis a similar result has been observed in the cyclization of the tertiary alcohol derived from the alcohol E-5 (Chart E) during the synthesis of alnusenone (39).

TABLE 1

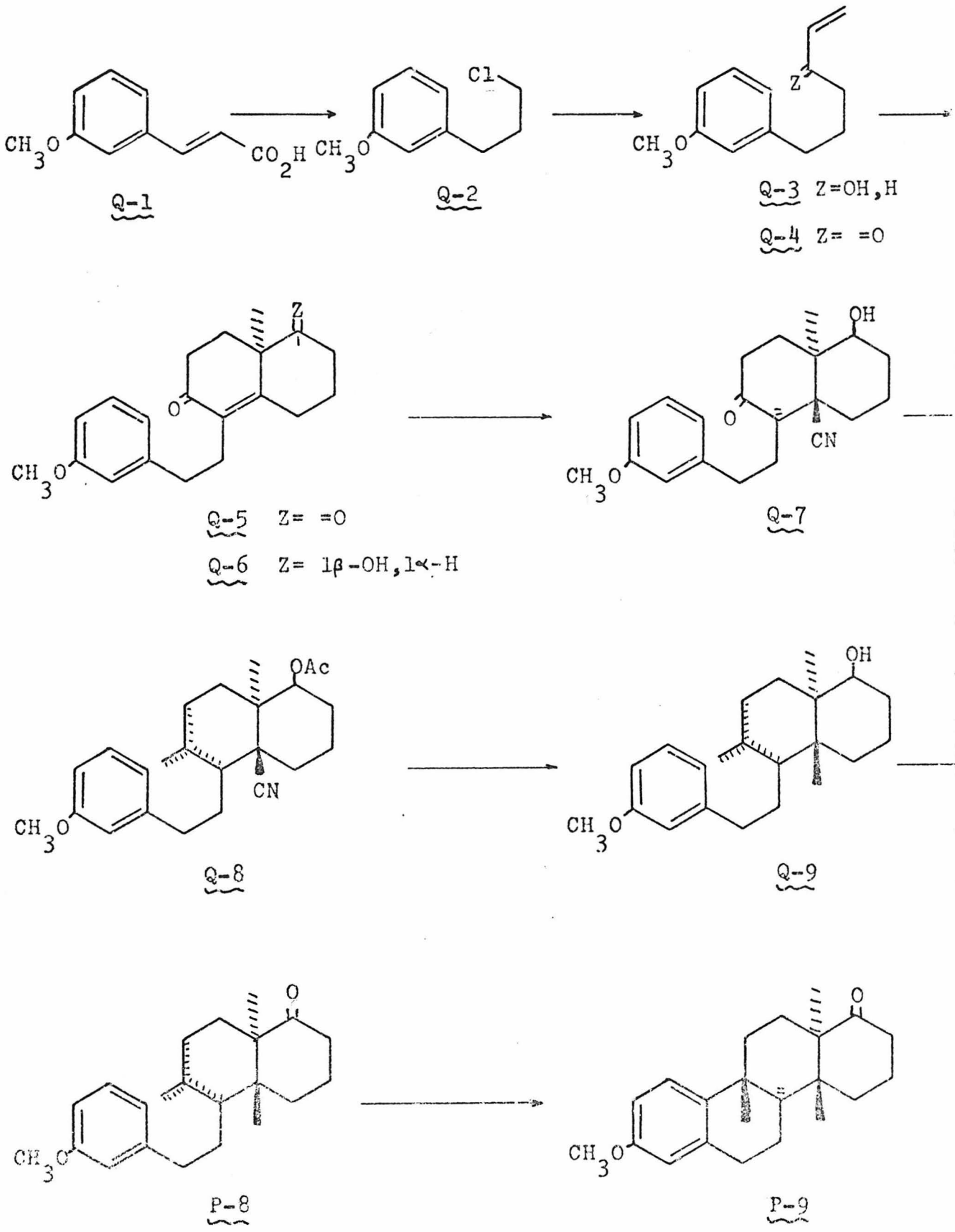
60 MHz NMR	trans B/C (P-9)	cis B/C (P-10)
C-2 OCH_3	224 Hz	224 Hz
C-4b CH_3	71 Hz	70 Hz
C-6a CH_3	73 Hz	78 Hz
C-10a CH_3	49 Hz	20 Hz

Almost simultaneously with the synthesis of the ketone P-9 in this work, the same compound was prepared by two alternant routes by C. J. Kowalski (90) and C. A. Lipinski (92) in the Ireland laboratories. The products from all three syntheses were identical in all respects (ir, nmr, mp, mmp) and neatly correlated the individual efforts.

The scheme developed by Kowalski (Chart Q) involved generation of the crucial C/D ring fusion by a stereoselective hydrocyanation of the enone Q-6 and reduction of the cyanide to a methyl group. It provides a 10% overall yield of the tetracyclic ketone P-9 starting from m-methoxycinnamic acid in 15 steps.

The third synthesis of P-9 was achieved by Lipinski through the triene R-6 (Chart R) in a continuation of the polyene cyclization studies initiated by Ireland and Dawson (76). This scheme provided an overall yield of 2.0% from the dibromide R-1 in 12 steps.

Chart Q



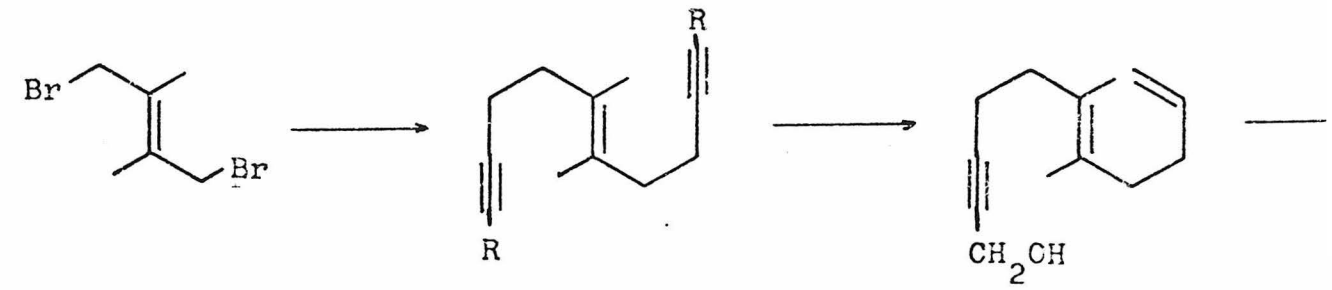
Q-1 Q-2 Q-3 Z=OH,H Q-4 Z= =O

Q-5 Z= =O Q-6 Z= 1β-OH,1∝-H Q-7

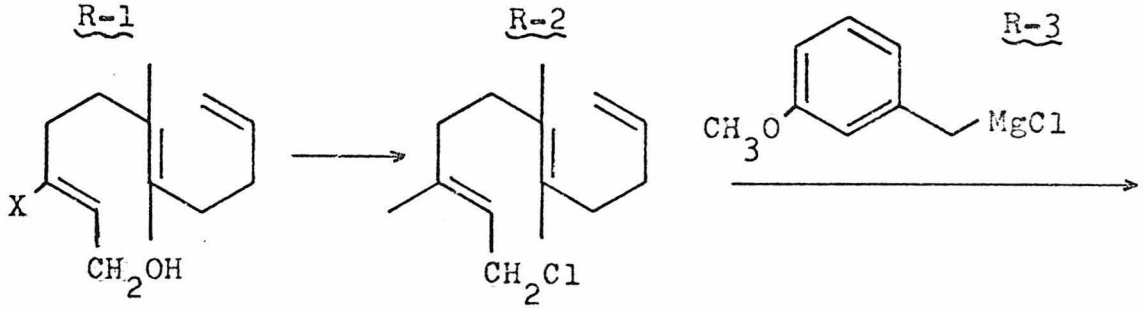
Q-8 Q-9

P-8 P-9

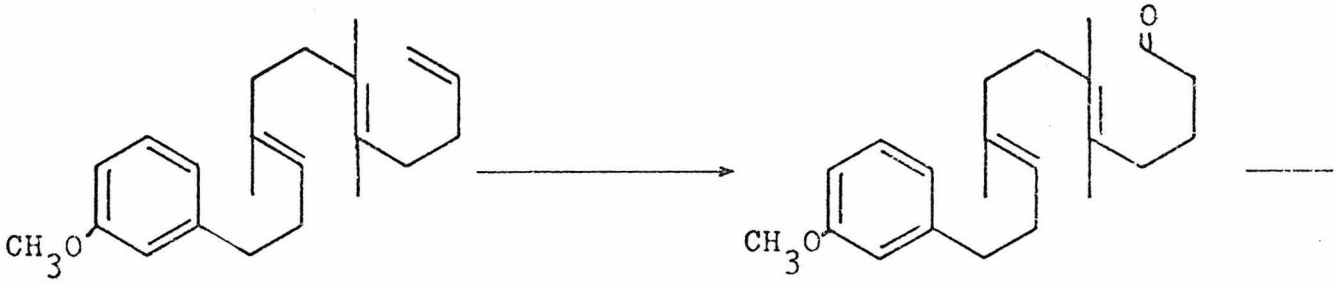
Chart R



R-1 R-2 R-3

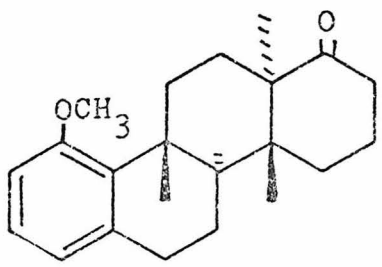


R-4 R-5



R-6 R-7

P-10 + P-11 +



R-8

The hydrocyanation route is the method of choice for preparative scale synthesis of P-9 both from the point of view of overall yield and ease of isolation of the intermediates. Assurance of the stereochemistry of the C/D ring fusion of P-9 rested on the experiments conducted in the present work relating the dicyclic keto-alcohol N-7 to the alcohol of known stereochemistry K-5. In the hydrocyanation scheme the C/D cis and trans isomers of Q-7 were distinguished only on the basis of the relative intensities of the nitrile stretching band in the ir (93), and in the polyene cyclization route the C/D trans configuration was assigned on the precedence established during the earlier cyclization experiments (76).

In view of the importance of the tetracyclic ketone P-9 as the common product of three synthetic schemes and as the potential key intermediate in the total synthesis of the triterpenes shionone, alnusenone, and friedelin, an unequivocal proof of its structure was sought. This was obtained through a single crystal X-ray structure analysis performed by Benes L. Trus, Gary Frankel, and Richard H. Stanford on a sample of the ketone (mp 153-154°) which was prepared by the Simmons-Smith route (figure 1). The ketone crystallized (ether) in space group Pna_2 with cell constants a=29.922 Å, b=7.757 Å, and c=7.63 Å; D_{obs}=1.225 g/cm^3, D_{calc}=1.23 g/cm^3; four molecules occur in the unit cell. The structure analysis was based on 1970 nonzero reflections of which 136 were

omitted from the least squares refinement.

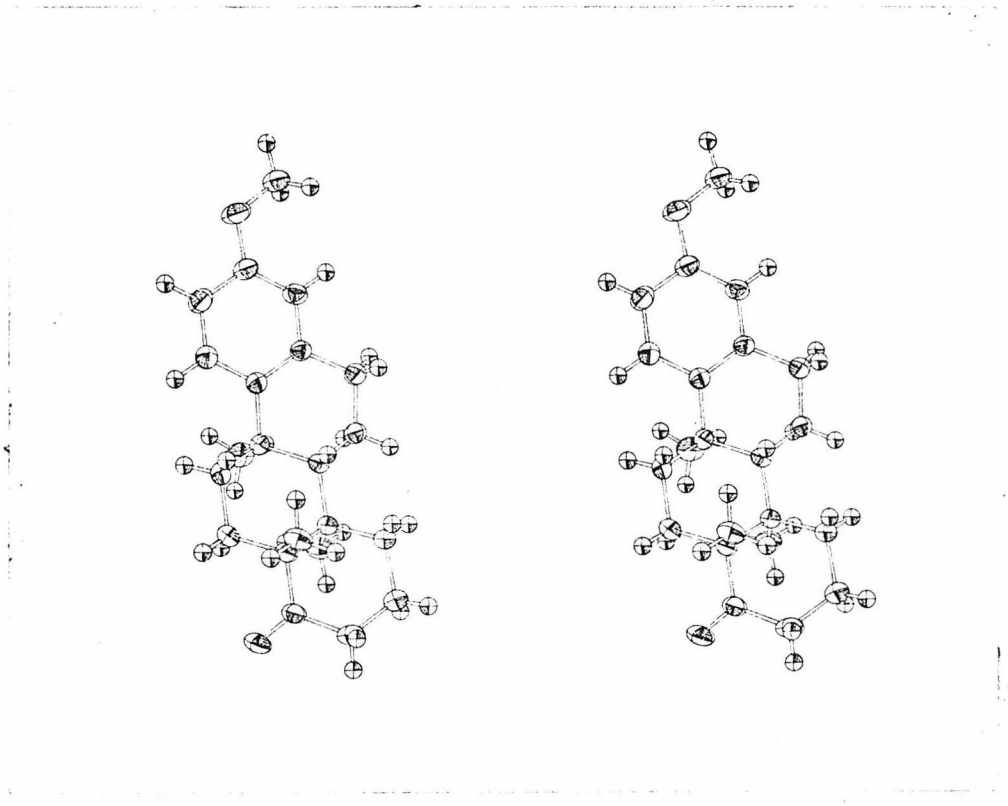
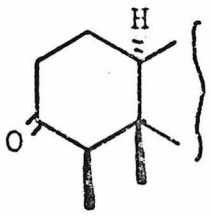


Figure 1 STEREODRAWING OF THE TETRACYCLIC KETONE P-9

With a satisfactory supply of the tetracyclic ketone P-9 assured by the foregoing work, attention was directed at the construction of the A ring of shionone 43. It appeared that the most direct approach would be first to monoalkylate the C-1 position of the enone 44 resulting from Birch reduction of the aromatic ring of P-9 followed by introduction of the C-12a angular methyl group via a hydrocyanation or a cyclopropane cleavage. Since the potential efficacy of this procedure could be simply tested by the attempted preparation of the

monoalkylated product 45, consideration of alternative pathways was deferred pending the outcome of the initial experiments.



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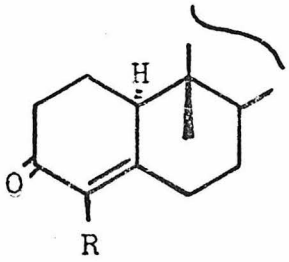
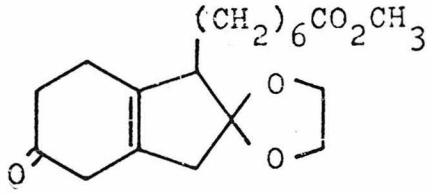


44 R=H

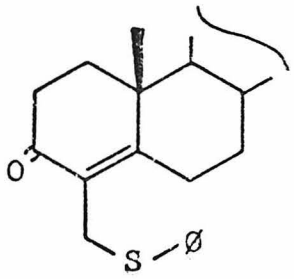
45 R=CH_3

The problem of monoalkylation of α,β-unsaturated ketones similar to 44 has been investigated at length in the steroids. Until recently the only successful solutions involved cleavage of the A ring and recyclization (94) or careful alkylation with methyl iodide--potassium tert-butoxide (95) and neither of these procedures were applicable for small scale preparations due to the poor yields generally realized. However, hopes for the sucessful conclusion of this endeavor were heightened by Wendler's (96) communication that a transformation such as that desired was achieved starting with the β,γ-unsaturated ketone 46 using one equivalent of a strong base (lithium triphenylmethide). A second method was also available from the work of Kirk and Petrow (97), who prepared steroidial C-4 thio-Mannich derivatives such as 47 by treatment of the corresponding enone with formaldehyde and thiophenol in the presence of a basic catalyst. Desulfurization

then gave the desired monoalkylated products in up to 80% yield.



46



47

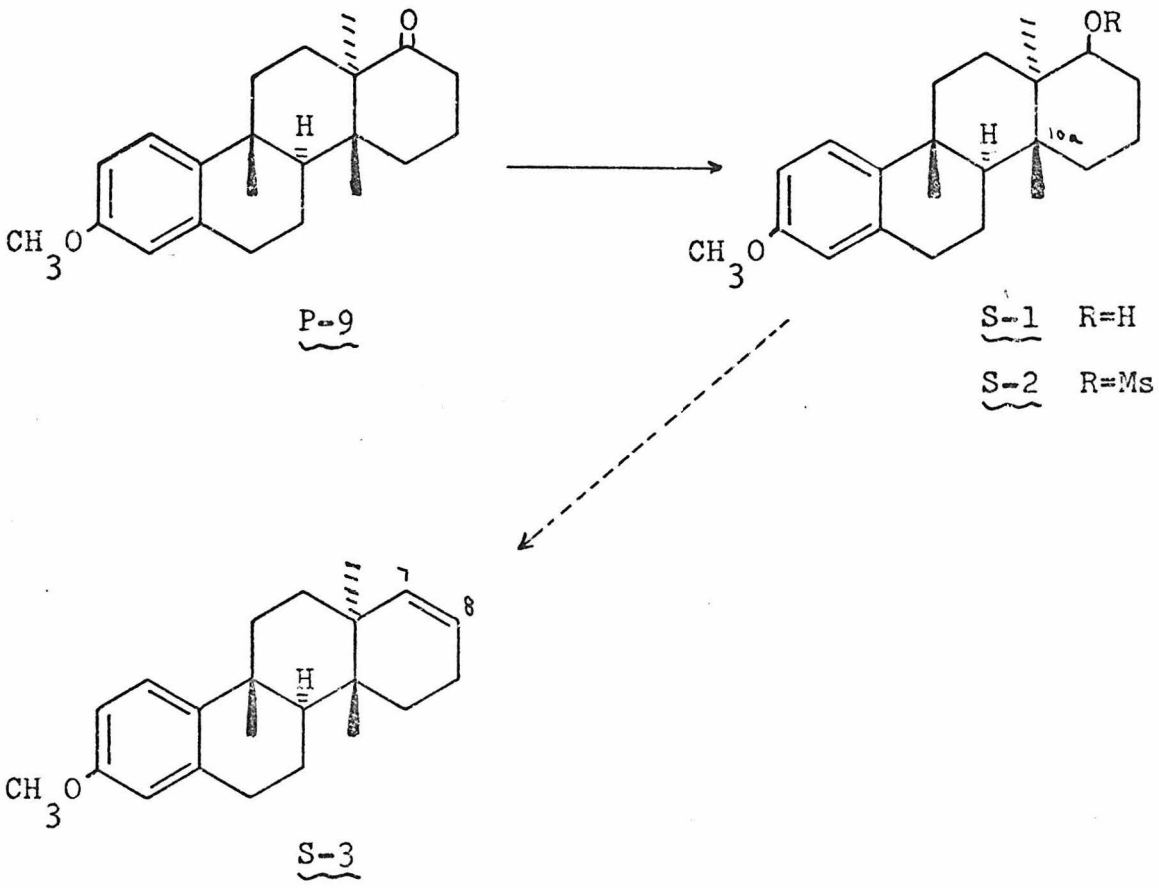
Before the A ring synthesis could be tackled, it was necessary to consider means of modifying the ketone in the D ring of P-9 so that: 1) it would not interfere with the anticipated manipulations, 2) it would be differentiated from the C-2 ketone which was to be generated in the A ring, and 3) a suitable substitution pattern for the introduction of the side chain would remain. Conversion of the ketone to the Δ^7-olefin S-3 appeared to be an ideal solution to the problem. It was anticipated that the steric bulk of the neighboring angular methyl groups would serve to help protect the double bond and, when required, to assist efforts to functionalize it selectively at C-8.

Initially, it was planned to prepare the olefin S-3 through dehydrosulfonation of the mesylate S-2. The ketone P-9 was recovered quantitatively from treatment with an excess of sodium borohydride in ethanol at room temperature enhancing our confidence in the steric shielding afforded the

C-7 carbon atom by the ring fusion substituents. When the ketone was reduced with lithium aluminum hydride in tetrahydrofuran, a 97% yield of the axial alcohol S-1 was obtained without incident. The stereochemical assignment of the alcohol was based on the steric hindrance to axial attack of the reagent (69) and was supported by the nmr spectrum of the reduction product which revealed that the C-10a angular methyl group was deshielded by 14 Hz from its position in the starting material. Unfortunately, efforts toward preparation of the mesylate S-2 led only to formation of a dark oil that consisted of a variety of decomposition products according to its nmr spectrum. Rather than pursue this unelegant approach, it was decided to turn to a new procedure for the conversion of ketones to olefins which was developed by D. Muchmore (98) in the Ireland laboratories.

This method consisted of the alkali metal induced reduction of alkyl or enol phosphorodiamidate esters to the corresponding saturated or olefinic compounds. In order to apply the new procedure, the phosphonate ester T-1 (Chart T) was prepared in 88% yield by the addition of N,N,N',N'-tetramethyldiamidophosphorochloridate (99) to an ethereal solution of the enolate anion generated from P-9 by the action of lithium diisopropyl amide. When this ester was reduced with a large excess of the lithium biphenyl adduct in tetrahydrofuran under the conditions prescribed by Muchmore (100), the product obtained in 62% yield was the phenol T-2 rather than the corresponding

Chart S



P-9

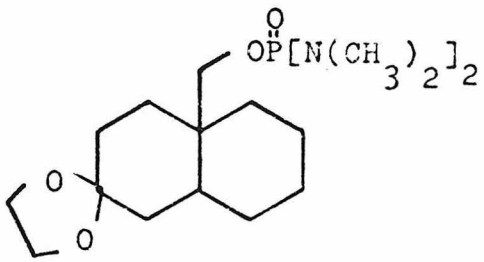
S-1 R=H

S-2 R=Ms

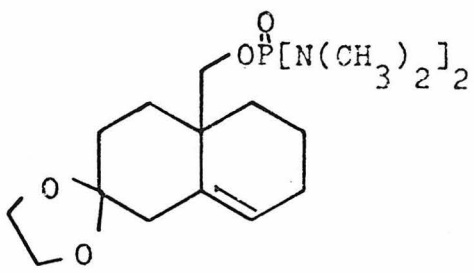
S-3

methyl ether S-3. Such a result is precedented by the results of Eisch (101) who has found that anisole is cleaved to phenol by the action of the lithium biphenyl adduct in refluxing tetrahydrofuran over the course of four and one half hours. It was hoped that this cleavage would not compete with the desired transformation in this case since the reaction conditions were more mild (1 hour, room temperature). The use of the lithium biphenyl cleavage was not precluded by the above result since the phenol T-2 could be remethylated to give the desired anisole derivative S-3, and it is possible that the selectivity of the reduction could be improved by limiting the amount of reagent or the reaction time. However, in order to avoid an extra step, it was decided to explore the attractive prospect of carrying out the phosphonate cleavage and Birch reduction simultaneously.

While Muchmore (102) reported that the phosphorodiamidate esters 48 and 49 were inert to lithium in ammonia, the preliminary reduction experiments on T-1 were carried out in ammonia since most Birch reduction procedures employ this solvent. In an early experiment using an excess of lithium and tert-butyl alcohol as the proton source to promote reduction of the aromatic ring, the intermediate dihydroanisole obtained was hydrolyzed with aqueous oxalic acid to provide 42% of the β,γ-unsaturated ketone T-3 verifying that the cleavage of enol phosphodiamidates was feasible with lithium in ammonia. Attempted alkylation of T-3 under the Wendler



48

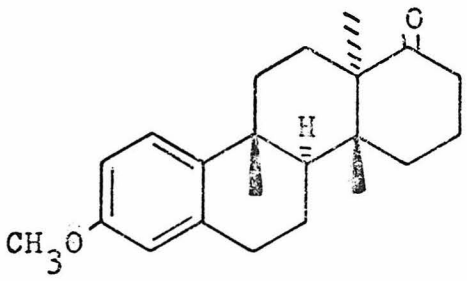


49

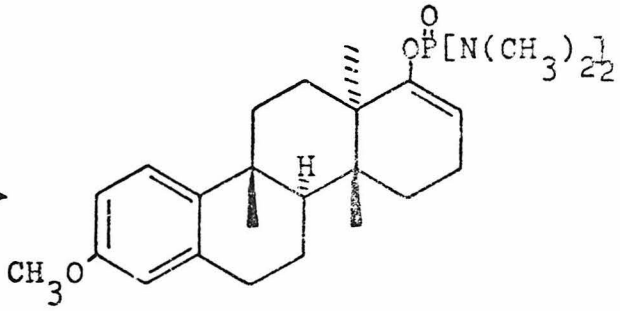
conditions led only to the dialkylated product T-4 in 61% yield, possibly due in part to the small scale on which the reaction was conducted. The outcome of these experiments prompted a more extensive investigation of the reduction steps and a search for a more efficient monoalkylation procedure.

Muchmore (103) found that for the lithium in ethylamine phosphonate cleavage reactions, added tert-butyl alcohol was necessary to supress the formation of side products. Thus during the initial experiments on the reduction of T-1 this proton source was included from the start of the reaction. From an intermediate scale reduction (110 mg) 40% of the anticipated product U-1 was isolated together with 35% of the diketone 50 which arose from P---O cleavage of the phosphonate ester T-1. It was quickly ascertained that formation of this diketone was dependent on the presence of the proton source. When the cleavage was allowed to proceed for five hours in the presence of a moderate excess of lithium and the remaining lithium was decomposed by addition

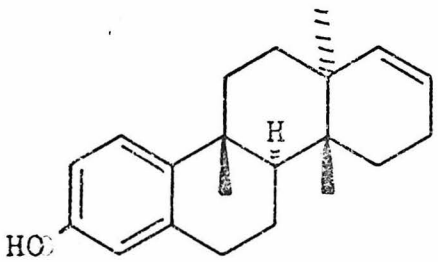
Chart T



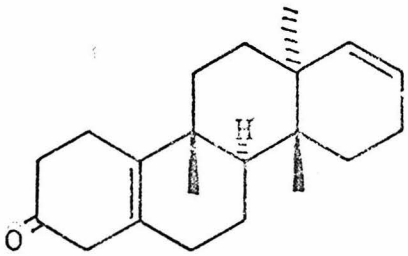
P-9



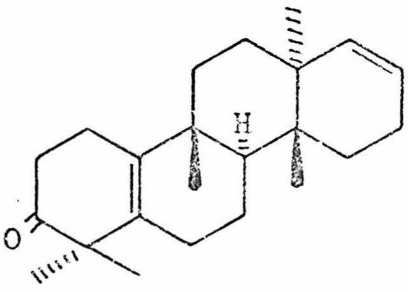
T-1



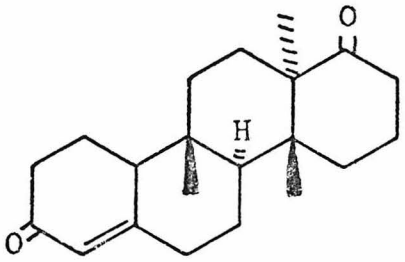
T-2



T-3



T-4

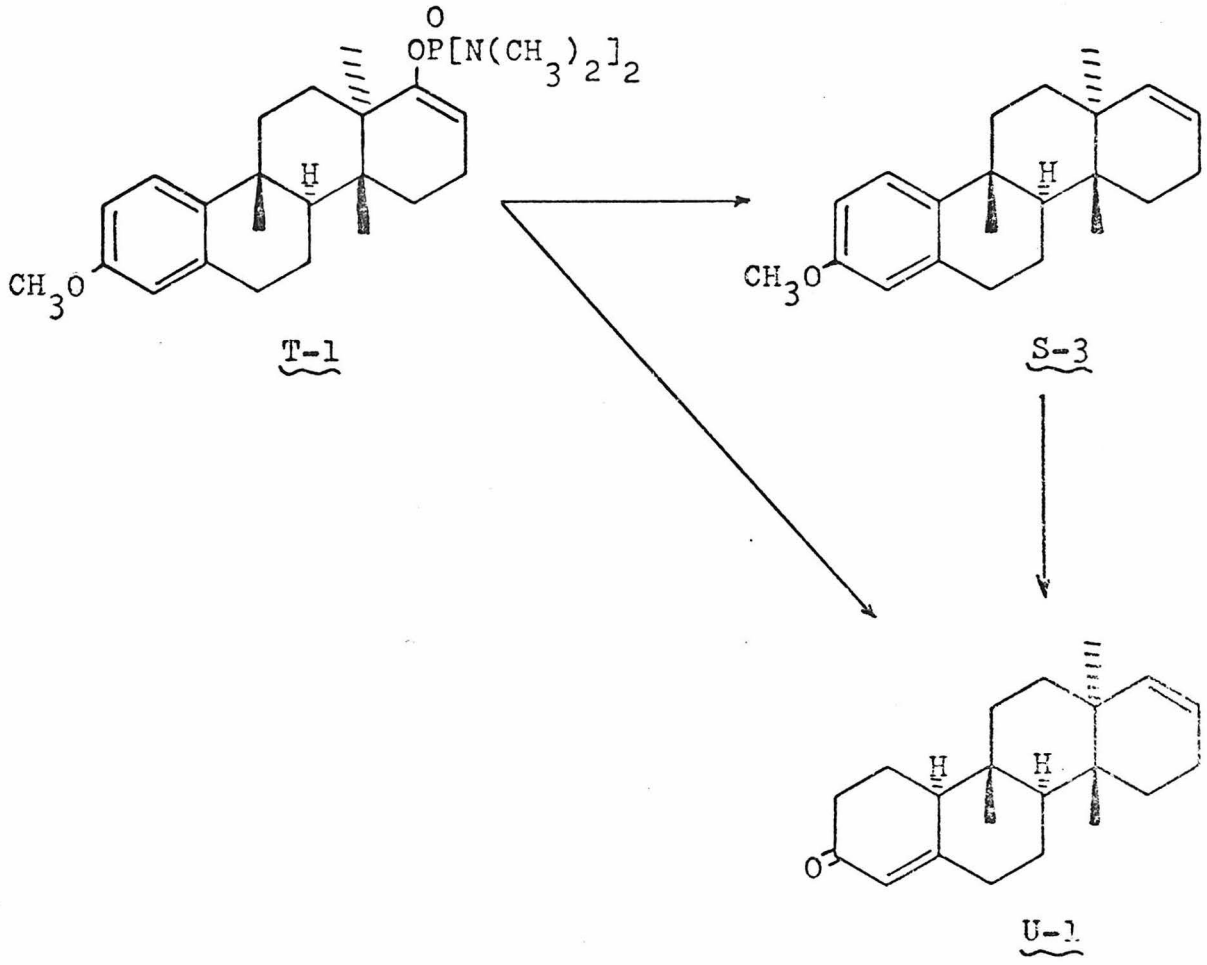


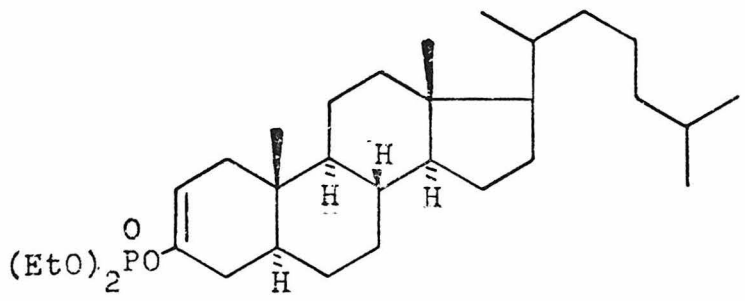
50

of sodium benzoate (104), an 82% yield of the olefin S-3 was realized. This could be further reduced in a normal Birch reaction to give 78% of the unsaturated ketone U-1, or more conveniently, the two steps could be telescoped together by allowing the reduction to proceed five hours under anhydrous conditions and then for two hours more after addition of tert-butyl alcohol. This procedure netted 78% of the enone U-1 after chromatography implying that very little of the phosphodiamidate could have suffered P--O cleavage.

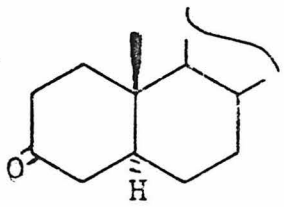
Products of P--OR bond cleavage have been observed by other workers. Kenner and Williams (105) obtained small amounts of phenolic and water soluble materials in addition to aromatic hydrocarbons from their pioneering reduction experiments on phenolic diethylphosphate esters. Muchmore (106), in his attempt to reduce the Δ^2-cholestenyl phosphate 51 with either the lithium biphenyl or lithium naphthalene adducts in dimethoxyethane, obtained essentially only

Chart U





51



52

cholestan-3-one 52 which he demonstrated did not arise by hydrolysis of the ester during workup.

The dramatic shift in reduction products in the presence of a proton source has no precedent in the previous work and indeed, runs contrary to the results obtained by Muchmore from reductions carried out in ethylamine solvent. The cause of the anomalous cleavage is obscure and was not pursued in the present work since an excellent reduction procedure was developed to get around the problem.

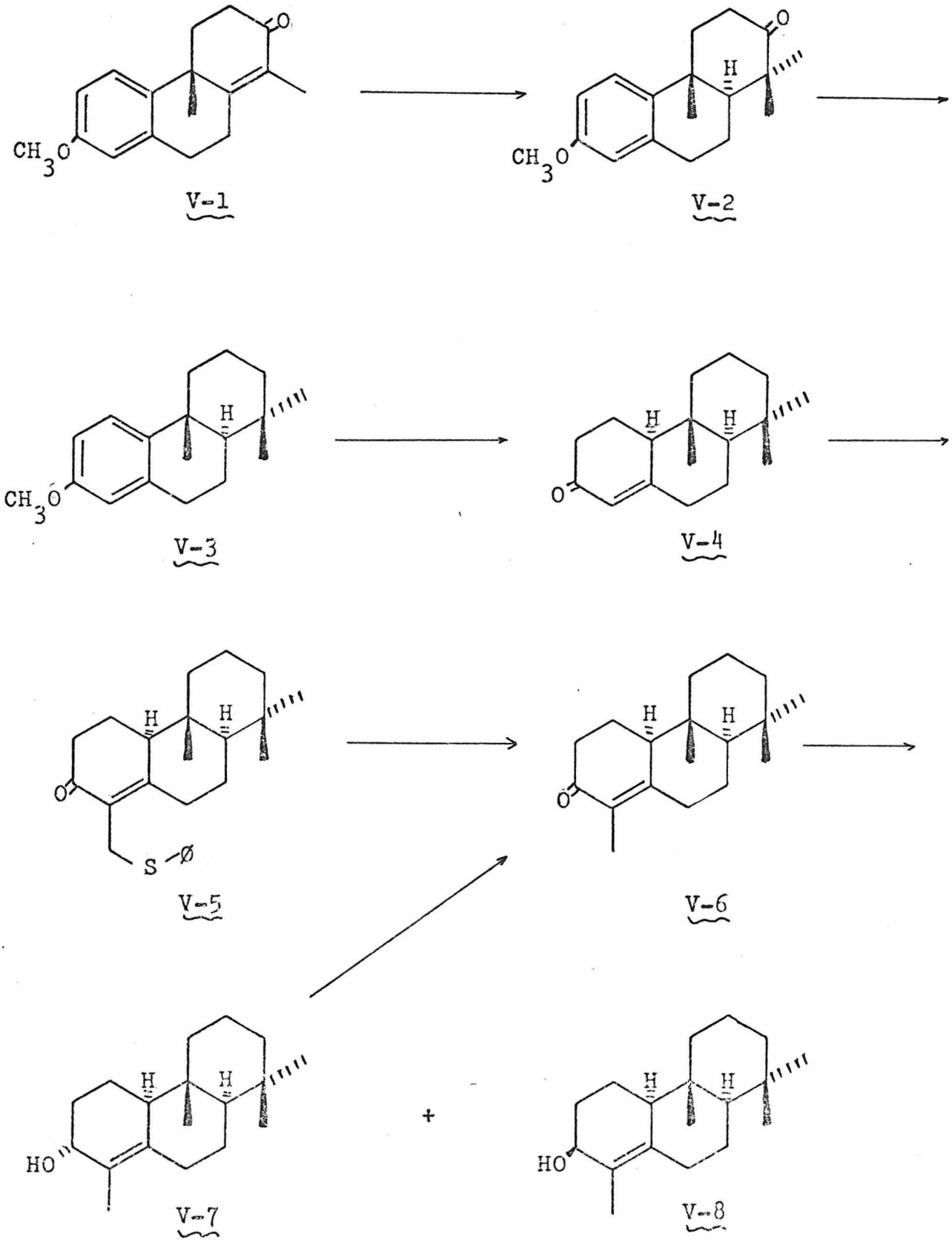
With a good route to the α,β-unsaturated ketone U-1 in hand, it was decided to carry out a model study on the more plentiful analogue V-4, particularly since preliminary experiments applying the Kirk and Petrow (97) alkylation procedure to the unsaturated ketone T-3 gave poor yields. The tricyclic ketone V-4 had been prepared previously by Church, Ireland, and Marshall (107) and appeared to be an

ideal model as it possessed A, B, and C rings which were identical to those of the tetracyclic ketone U-1.

Rather than prepare the model compound by the original route, a more efficient alternative seemed to be available based on the reductive alkylation results achieved by D. Evans (108) in the Ireland laboratories. The tricyclic enone V-1 (Chart V) was prepared according to the procedure described by Evans and was added together with one equivalent of water to a solution of lithium in ammonia and tetrahydrofuran. Addition of methyl iodide to the still blue solution then led to formation of the ketone V-2 in 80% yield. The Wolff-Kishner modification developed by Nagata (109) in which hydrazone formation is carried out under buffered conditions was employed to obtain 88% of the anisole derivative V-3, and Birch reduction as described by Ireland (107) provided 78% of the desired α,β-unsaturated ketone V-4. The overall yield for the three steps was 55%.

Attention was first directed toward monoalkylation at C-1 of the α,β-unsaturated ketone V-4 using the Kirk and Petrow (97) procedure discussed above. Of the two variations they developed, the one employing formaldehyde and thiophenol with ethanol as the solvent and triethylamine as the basic catalyst proved to be superior to the one using triethanolamine as both the catalyst and solvent, possibly due to the difficulties associated with handling the small amounts of triethanolamine required (0.5 ml). The thioether V-5 was

Chart V



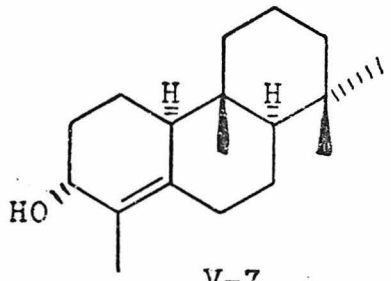
freed of polymeric materials by chromatography and was desulfurized with raney nickel in ethanol at 0°. The desulfurization conditions used were those described by Coates (110), because the Kirk and Petrow conditions, raney nickel in acetone at reflux, did not give as reproducible results. Even under the optimum conditions, the overall yield of V-6 was only 36% for the two steps. The low yield may be due to concomitant aromatization of the A ring of V-4 during the condensation even though oxygen was rigorously excluded from the reaction mixture; such a side reaction was not likely in the cases tested by Kirk and Petrow since the compounds all possessed stabilizing C-19 methyl groups.

In spite of this disappointing result, it was decided to continue with the ketone V-6 in order to provide a sample of the tricyclic with a completed A ring and to ascertain the desirability of developing new methods for monoalkylating the C-1 positions of the unsaturated ketones U-1 and V-4. The most direct approach appeared to be preparation of an C-2 axial alcohol from V-6 by reduction with the trialkylborohydride reagent N-1. It was anticipated that this alcohol would direct attack of the Simmons-Smith reagent to the desired β-face of the Δ^1-double bond to give the A/B *trans* fused product. Oxidation would then give a cyclopropyl ketone, which according to the results of Dauben (65) should be susceptible to reductive cleavage to provide a tricyclic derivative possessing the required A ring.

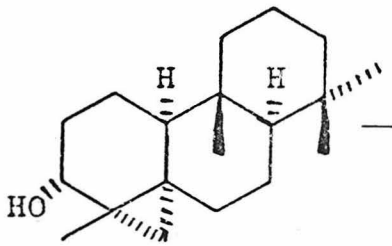
When the α,β-unsaturated ketone V-6 was reduced with lithium perhydro-9b-borophenalyl hydride (N-1), the isolated yields of allylic alcohols was an unfortunate 63% of the equatorial isomer V-7 and only 20% of the axial isomer V-8. The stereochemical assignment was based on the higher tlc mobility of the minor isomer and the relative widths of the nmr absorbtions of the C-2 hydrogens, 18 and 10 Hz for the major and minor products respectively. That the larger coupling is associated with the equatorial alcohol is a well established result in six membered rings (111) since vicinal axial protons couple more efficiently than equatorial protons. A final assurance of the stereochemical assignment was provided by the lithium aluminum hydride reduction of the ketone V-6 which led to a 93:7 ratio of the equatorial and axial alcohols as anticipated (69). The equatorial alcohol V-7 could be oxidized with the Collins reagent back to V-6 in 97% yield making the total yield of the axial isomer 40% when the equatorial alcohol is recycled twice.

Both the allylic alcohols were carried on in order to provide samples of both the cis and trans fused analogues of the natural A ring 43. The equatorial alcohol V-7 was treated with the Simmons-Smith reagent in a reaction that was complete in two hours to give 90% of the derived cyclopropane W-1 (Chart W). This alcohol was readily oxidized with the Jones reagent to give 93% of the cyclopropyl ketone W-2. Dauben and Deviny (65) have studied the reductive

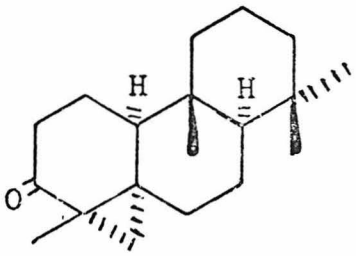
Chart W



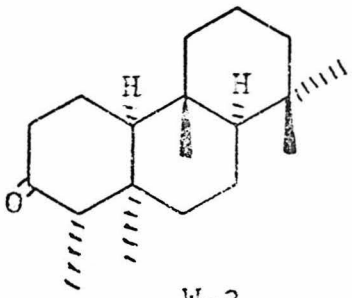
V-7



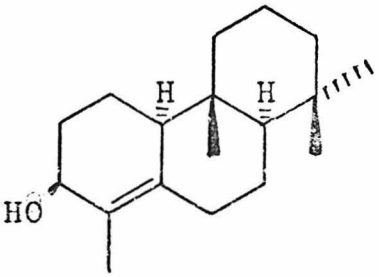
W-1



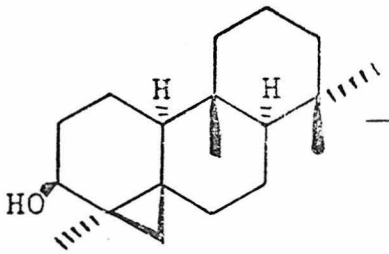
W-2



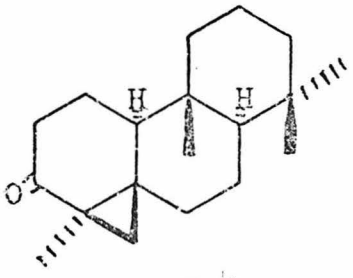
W-3



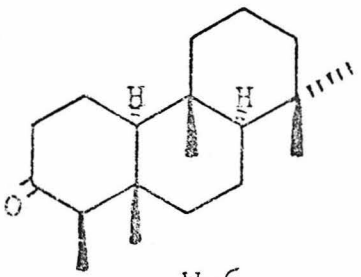
V-8



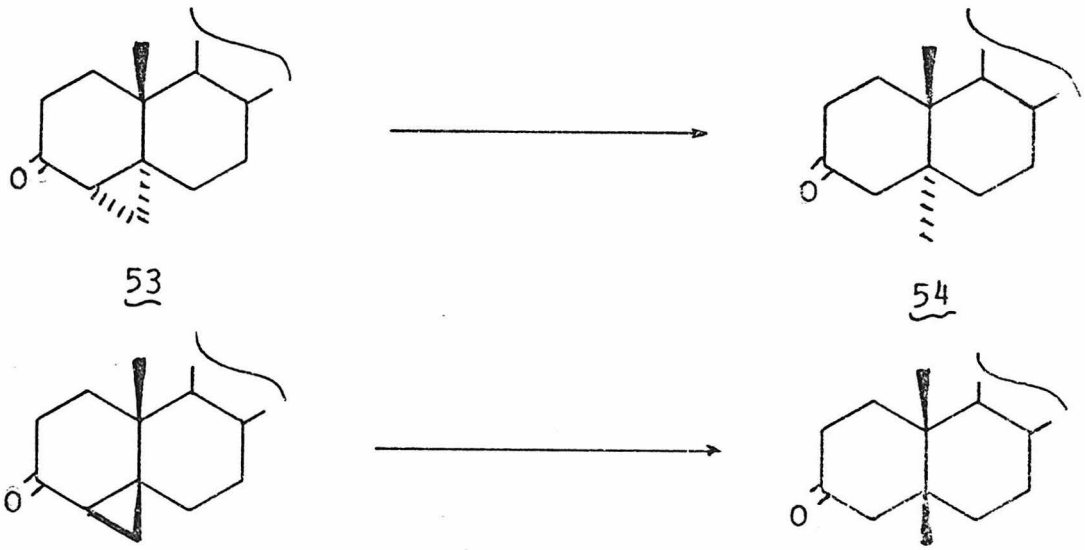
W-4



W-5



W-6

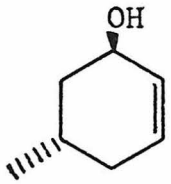


53 54

55 56

cleavage of cyclopropyl ketones and have shown that the cyclopropane bond that best overlaps the carbonyl π bond is preferentially cleaved. Both the 4α,5- and 4β,5-methanocholestanones 53 and 55 are reduced to the corresponding methyl compounds 54 and 56 in good yield. Thus it was somewhat surprising to find that the cyclopropyl ketone W-2 was cleaved only with difficulty by lithium in ammonia and gave only 37% of the ketone W-3 and 18% of a second impure ketone which may have been the alternate cleavage product with a seven membered A ring. The major product was recovered unchanged from an attempted isomerization with ethanolic potassium hydroxide indicating that essentially only one C-1 isomer of W-3 exists at equilibrium.

The Simmons-Smith reagent reacted more slowly with the axial alcohol V-8, requiring four hours to give 61% of the



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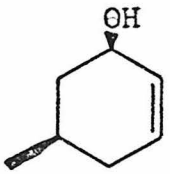


58

cyclopropyl alcohol W-4. The greater difficulty in carrying out the Simmons-Smith reaction with the axial allylic alcohol is in accord with the results obtained by Chan and Rickborn (55) who found that the allylic alcohol 57 reacted at about 1/3 the rate of the isomeric alcohol 58 in competition experiments.

Jones oxidation of the alcohol W-4 gave 89% of the corresponding ketone which was reduced smoothly to the ketone W-6 in 78% yield using the same conditions as above for the isomer W-2. Assignment of the C-1 methyl group of W-6 as β was predicated on the results of Tsuyuki and co-workers(112) who prepared 4α-shionone and friedelin by photoisomerization and showed that these were converted quantitatively to the natural 4β-isomers by base treatment. The conformational forces requiring the secondary methyl group of the natural products to be in the β-position at equilibrium should be very similar in the synthetic intermediates W-6 and Y-7 (vide infra) since the A, B, and C rings are identical. With the syntheses of the required isomers W-3 and W-6 successfully

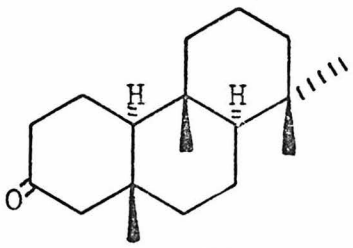
negotiated, a new route to W-6 was sought which would avoid the inexpeditious thiomannich condensation and borohydride reductions.

One attractive approach would be to prepare the cyclopropyl ketone X-4 and to reductively methylate it by trapping the enolate anion formed from the Birch cleavage of the cyclopropane ring with methyl iodide. Some preliminary experiments carried out by D. R. Marshall in the Ireland laboratories indicated that the borohydride reduction of the enone V-4 gave a more favorable ratio of isomers than was obtained from V-6, so that a reasonable synthesis of X-4 appeared feasible. Although the only reported attempt to trap the enolate anion formed from a reductive cleavage of a cyclopropane ring gave poor results (113), the potential efficiency of this route made the point worth reinvestigation.

Reduction of the enone V-4 with the borohydride reagent N-1 gave 41% of the desired axial alcohol X-2 (Chart X) together with 54% of the equitorial isomer X-1 which could be recycled by Collins oxidation (96%) back to the enone V-4 and reduction to give a total of 63% of the isolated axial alcohol X-2. The two alcohols had previously been prepared by Ireland and co-workers (107) who established their stereochemistry.

The Simmons-Smith reaction proceeded better on the allylic alcohol X-2 than it did on the corresponding axial

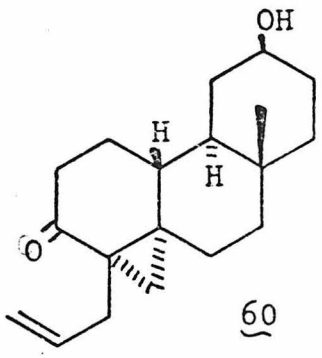
alcohol V-8, perhaps due to the reduced steric hindrance about the double bond in the former case, giving 83% of the alcohol X-3 which was oxidized directly to the ketone X-4 in 93% yield. When the ketone was reduced with lithium in ammonia and the blue solution was quenched directly with methyl iodide, only starting material and the unalkylated product 59 were recovered.



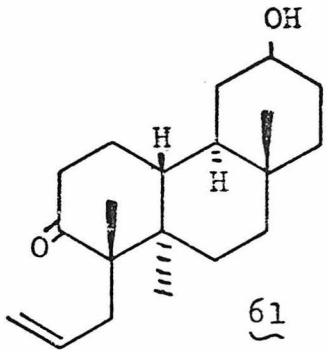
59

Very recently, Stork (43) reported a successful reductive alkylation of the cyclopropyl ketone 60. When the reduction was carried out in the presence of tert-butyl alcohol, 60% of the methylated product 61 could be obtained if the reaction mixture was warmed to 0° as most of the ammonia evaporated and the methylation was conducted with added hexamethylphosphoramide (HMPA).

Before the Stork paper appeared, it was decided to attempt to trap the enolate anion formed by cleavage of X-4 as the enol acetate in order to verify that the required anion was indeed present and to provide a source from which the enolate anion could be regenerated under rigorously defined conditions. The reduction was carried out as before



60

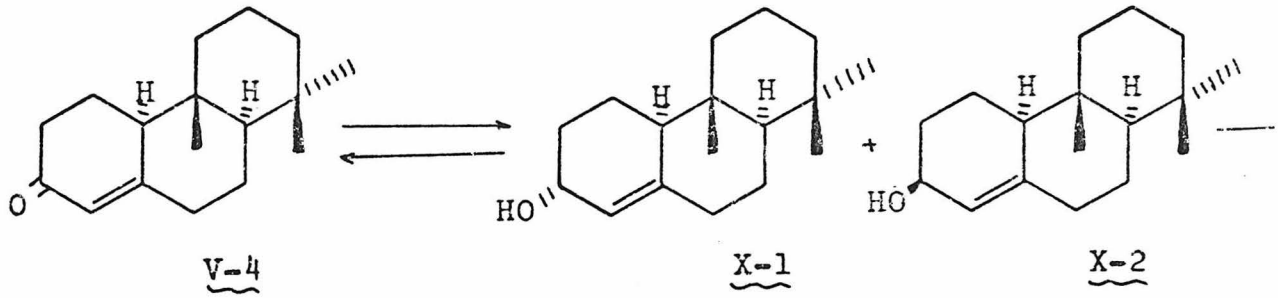


61

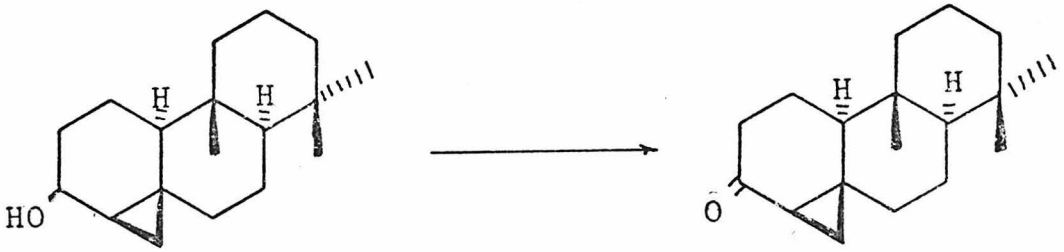
except that the ammonia was evaporated in a stream of argon and the tetrahydrofuran was heated to reflux to drive out the last traces of ammonia before the reaction mixture was quenched with acetic anhydride. Thick layer chromatography of the crude products then gave 72% of the enol acetate X-5. When the enolate anion was regenerated and alkylated in dimethoxyethane under the House (114) conditions, by treatment of X-5 with two equivalents of methyl lithium followed by an excess of methyl iodide, only 20% of the desired product W-6 was obtained after preparative thick layer chromatography together with 10% of the unalkylated material 59 and 40% of polyalkylated products.

While it seemed probable that a more favorable portion of the monoalkylated product W-6 could be attained by a careful control of the reaction conditions, a report by Whitlock and Overman (115) describing the alkylation of the enolate

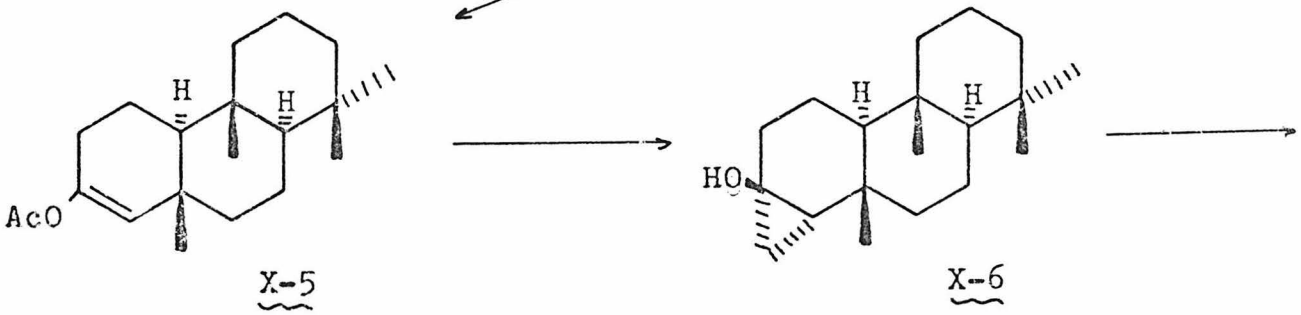
Chart X



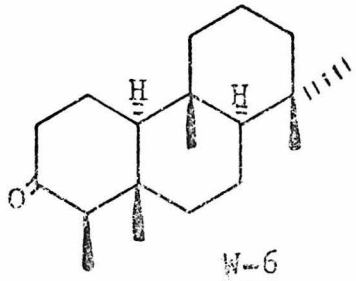
V-4 X-1 X-2



X-3 X-4

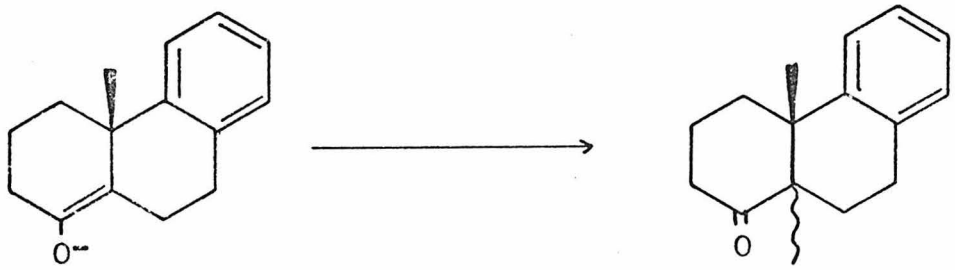


X-5 X-6



W-6

anion 62 by treatment with the Simmons-Smith reagent attracted us to the possibility of using a variation of this procedure for the alkylation of the enolate derived from X-5. Whitlock and Overman obtained directly 65-75% yields of the mono-alkylated product 63 as a 3:1 mixture of the cis and trans fused isomers. The enolate anion was regenerated from X-5 as before in dimethoxyethane and the solution was treated with a large excess of the Simmons-Smith reagent in ether. The crude product was dried briefly over magnesium sulfate and the residue, following concentration, was chromatographed on grade III alumina to give 73% of the cyclopropyl alcohol X-6.

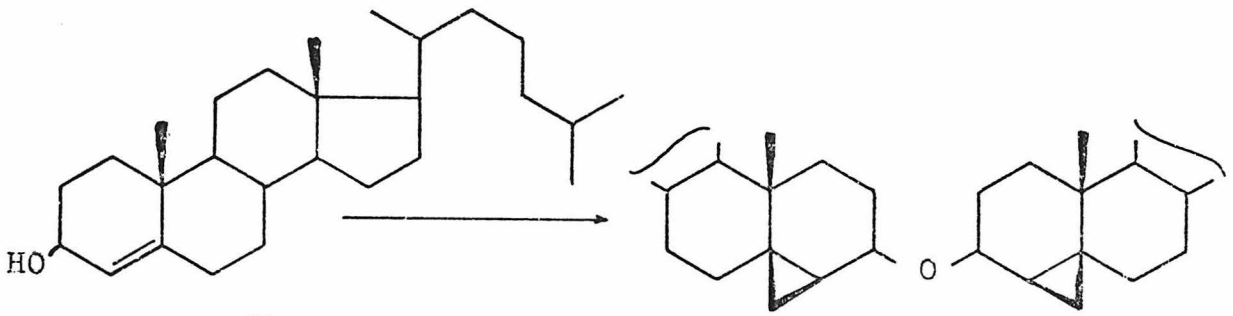


62 63

Whitlock was unable to isolate the corresponding alcohol which must have been an intermediate between the enolate anion 62 and the ketone 63 and could not account for this result. When he used diiodomethane-d_2 to form the Simmons-Smith reagent, exactly two deuteriums were incorporated into the ketone 63. Also, when the reaction mixtures were quenched

with deuterated acids, no deuterium was incorporated. A possible explanation for these results is that the rearrangement of the intermediate alcohol to the methylated ketone 63 was promoted by iodine formed by decomposition of the unreacted diiodomethane while the solution was drying. In support of this argument, when an ethereal solution of the cyclopropanol X-6 was treated with a catalytic amount of iodine, 55% of the ketone W-6 was obtained after base catalyzed equilibration. This rearrangement may be caused by hydrogen iodide formed from the attack of iodine on the cyclopropane ring. Dauben (116) has observed a related result. When the crude product from the Simmons-Smith reaction of the allylic alcohol 64 was allowed to stand over sodium sulfate, it dimerized to the ether 65. The same ether was formed in 64% yield when a solution of the purified alcohol 64 was treated with a catalytic amount of iodine in methylene chloride for 12 hours at 0°. In the present work such problems were avoided by routinely drying the Simmons-Smith products 1-5 min and immediately chromatographying the concentrated residues.

The cyclopropyl alcohol X-6 gave, on brief treatment with ethanolic hydrochloric acid, 86% of the desired ketone W-6 which was identical to that prepared earlier. It was further discovered that the cyclopropyl alcohol could be formed directly in 57% yield from the ketone X-4 by quenching the Birch product, following removal of the ammonia, with



64 65

the Simmons-Smith reagent. Using this procedure, the overall yield from the enone V-4 to the ketone W-6 possessing the intact A ring of the natural product was 24% in five steps.

With the successful conclusion of the model study, we again turned to consideration of the tetracyclic unsaturated ketone U-1. The allylic alcohols resulting from reduction of U-1 were more difficult to separate than their tricyclic analogues. It was only possible to isolate 38% of the impure axial alcohol Y-2 and 50% of the equatorial isomer Y-1 which could be oxidized back to the enone in 91% yield so that it is necessary to recycle the equatorial alcohol twice in order to achieve a 63% yield of the axial alcohol Y-2 (Chart Y). The stereochemical assignment of the two alcohols rests on the same criteria employed for the alcohols V-7 and V-8. The minor isomer was the more mobile on silica gel tlc and exhibited a C-2 peak width of 12 Hz

in the nmr as opposed to 21 Hz for the equatorial alcohol Y-1 (111).

The Simmons-Smith reaction of the axial alcohol Y-2 proceeded as before, but it was found that the Collins oxidation procedure gave a better overall yield (77%) of the ketone Y-4 than Jones oxidation. Birch reduction of the ketone and trapping of the enolate anion formed with acetic anhydride gave 72% of the enol acetate Y-5 together with 5% of the ketone 66 and 8% of the cyclopropyl enol acetate 67. The structural assignment of 67 was based on its ir spectrum which indicated it was an enol acetate (1755, 1685 cm^{-1}) and the nmr which showed only three angular methyl groups. Treatment of a portion with ethanolic potassium hydroxide overnight gave a 61% yield of the starting cyclopropyl ketone Y-4.

The enol acetate Y-5 was converted to 71% of the cyclopropanol Y-6 by addition of two equivalents of methyl lithium to a dimethoxyethane solution followed by an excess of the Simmons-Smith reagent as before in the model system. The alcohol was also available in 69% yield by the direct reductive cleavage--cyclopropylation procedure, but the product was less clean than that obtained from the enol acetate. Acid catalyzed cleavage of the cyclopropyl alcohol Y-6 prepared from the enol acetate gave 98% of the desired ketone Y-7 while a 72% yield was obtained starting with the alcohol

Chart Y

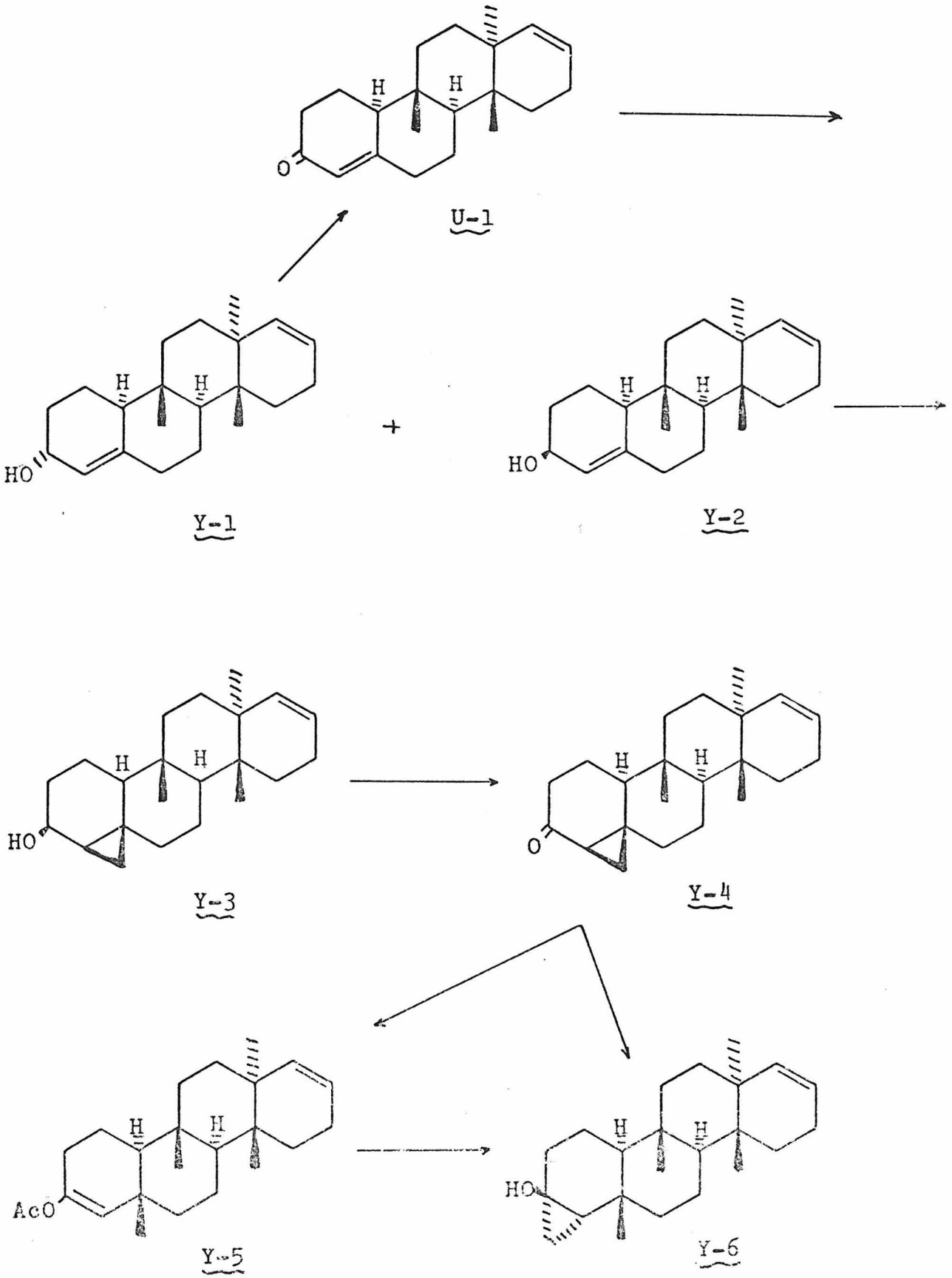
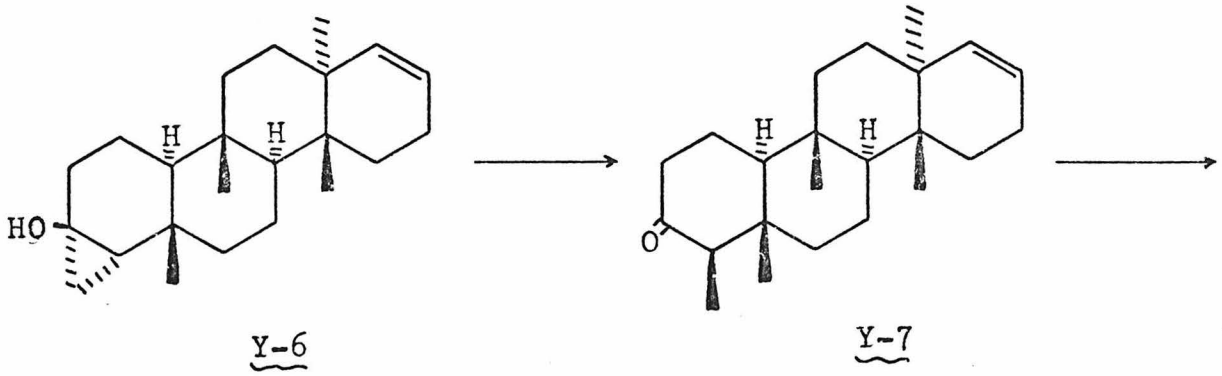
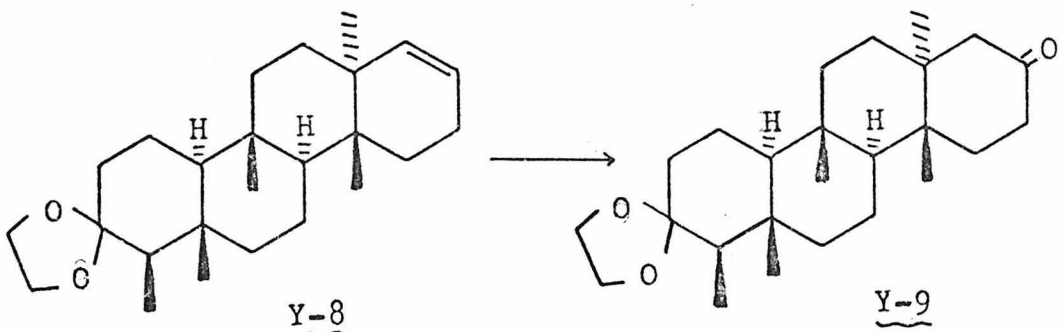


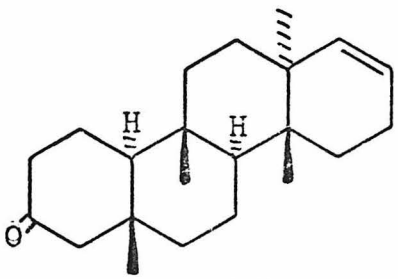
Chart Y continued



Y-6 Y-7



Y-8 Y-9



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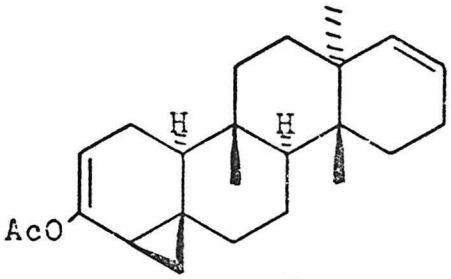


67

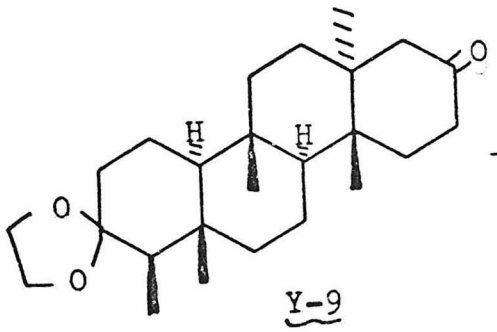
prepared by the direct method. The overall yield from the cyclopropyl ketone Y-4 to the methylated ketone Y-7 was 49% by either procedure.

In order to carry out the addition of the side chain the C-2 ketone of Y-7 was protected as the ketal derivative (quantitative). The synthetic plan called for functionalization of the Δ^7-double bond by hydroboration, taking advantage of the steric hinderance offered the C-7 carbon by the angular substituents to direct the boron atom to the C-8 carbon. While only starting material was recovered from reaction of the ketal Y-8 with disiamylborane, it did react slowly with borane in tetrahydrofuran at 0° and after 5 hours the starting material was consumed. The alcohol obtained from oxidation of the borane was treated directly with the Collins reagent to give an overall yield of 84% of a single ketone which was presumed to be the desired product Y-9. The product gave a single spot on analytical tlc and was represented

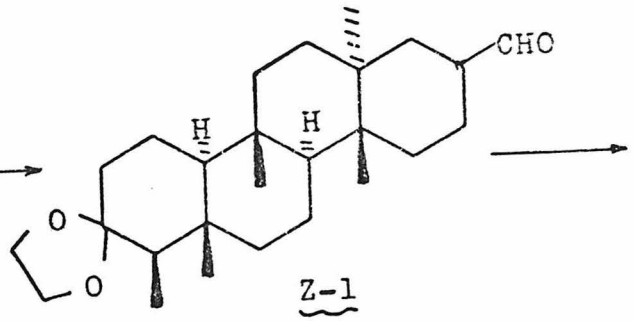
by a single peak on glpc. The nmr spectrum and sharp melting point (271-273°) also indicated that a single product was formed. It was assigned as the 8-keto isomer since the 7 position is clearly the more hindered so that one would expect either a mixture of ketone isomers or only the desired C-8 ketone from the hydroboration oxidation (117). The overall yield of Y-9 from the ketone P-9 was 12.5% in 12 steps.

It yet remains to add the side chain. Plans for this transformation involve preparartion of the aldehyde Z-1 by either an epoxide cleavage or a suitable Wittig reaction. Alkylation with methyl iodide should proceed with attack of the reagent from the equatorial side to avoid a 1,3-diaxial interaction with the C-6a angular methyl group to give the required β-methylated product Z-2. It should then be a routine matter to add the remainder of the side chain to form shionone ketal Z-3 by one of a variety of possible means. Deketalization would then give the natural product.

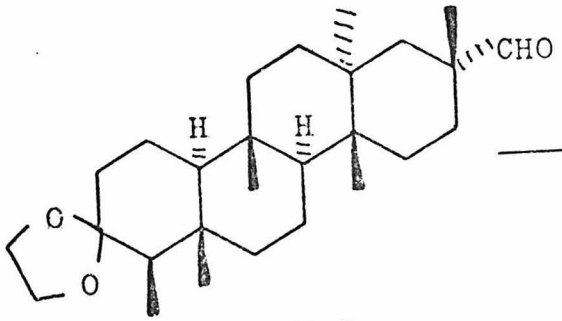
Chart Z



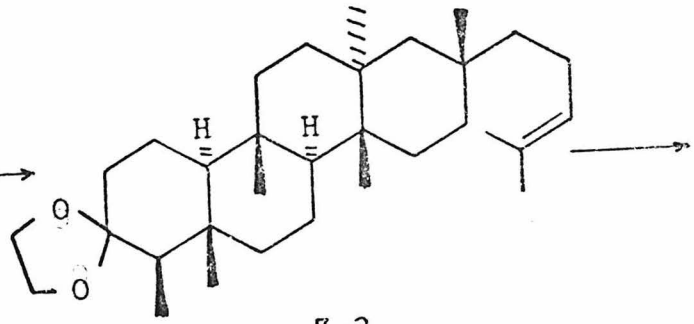
Y-9



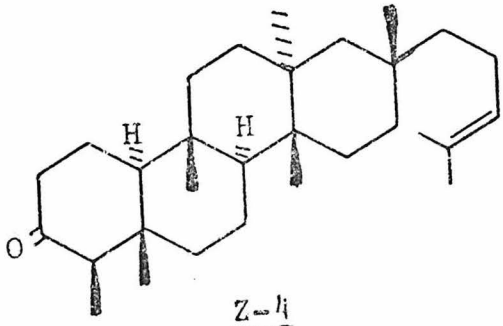
Z-1



Z-2



Z-3



Z-4

Experimental Section

Melting points labeled (vacuum) were taken in evacuated capillaries on a Hoover Capillary Melting point apparatus; all others were determined on a Kofler Micro Hot Stage melting point apparatus. All melting points and boiling points are uncorrected. Infrared spectra (ir) were run on a Perkin Elmer 237B grating infrared spectrometer and are reported in cm^{-1}. Nuclear magnetic resonance spectra (nmr) were recorded using either a Varian A-60A or T-60 spectrometer and are referenced to tetramethylsilane as an internal standard. Gas chromatographic analyses (glpc) were conducted on a Perkin Elmer 881 gas chromatograph using 4% SE-30, 6'x1/8" columns with a helium flow rate of 60 ml/min.

Preparative thin layer chromatography (ptlc) was carried out on 20x20 cm glass plates coated with a ~1 mm layer of silica gel $PF_{254+366}$ as supplied by Brinkman Instruments Co. Analytical thin layer chromatography (tlc) was conducted on 1"x3" microscope slides coated with the same silica gel. Alumina refers to the grade I, neutral variety manufactured by M. Woelm, Eschwege, Germany made up to grade II or III as indicated by addition of 3% or 6% water prior to use. Silica gel columns used the 0.05-0.2 mm silica gel "for column chromatography" manufactured by E. Merck, Darmstadt, Germany.

Where anhydrous solvents are indicated they were dried by the following methods. Benzene, toluene, pyridine, tert-butylalcohol, and xylene were distilled from calcium hydride. Ether and tetrahydrofuran were refluxed several hours over lithium aluminum hydride (LAH) and distilled. Dimethoxyethane was distilled twice from LAH under an argon atmosphere. Dioxane was refluxed for 4 days over sodium metal and was distilled from sodium immediately before use. Dichloromethane was distilled from phosphorous pentoxide. Petroleum ether refers to the fraction bp 30-60° as supplied by J. T. Baker Chemical Company and required no special drying.

Reactions described as run under nitrogen or argon employed a mercury bubbler arranged so that the system could be alternately evacuated and filled with the inert gas and left under a positive pressure.

Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Michigan.

Since all compounds reported herein are racemic, the prefix d,l has been omitted for convenience.

The brine used in the workups refers to a saturated aqueous solution of sodium chloride.

8aβ-Methyl-1,2,3,4,6,7,8,8a-Octahydro-1β-Naphthol (I-4) (61).

Following the general procedure of Hallsworth and coworkers (60) 1 l. of monoethylamine was distilled through potassium hydroxide into a dry 2 l. flask fitted with a mechanical stirrer and a dry ice condenser and containing 34.5 g (0.126 mole) of 8aβ-methyl-1,2,3,4,6,7,8,8a-octahydro-1β,6-naphthalenediol diacetate (I-2, R=OAc) (59). Over the course of five minutes 11.0 g (1.56 moles) lithium wire was added with vigorous stirring. After 20 min the dark blue color was discharged with solid ammonium chloride and most of the solvent was removed in a stream of nitrogen. The gray residue was dissolved in 300 ml of water and was extracted with ether (5x100 ml). The ether solution was dried ($MgSO_4$) and evaporated to dryness to give 17.5 g of a yellow oil. Re-extraction of the aqueous phase yielded an additional 1.5 g. The combined products contained 90% of one major volatile component by glpc and were used in the next step without further purification.

3,4,6,7,8,8a-Hexahydro-8aβ-Methyl-1(2H)-Naphthalenone (I-5).

To a solution of 19.0 g 0.114 mole) of the crude alcohol I-4 from above in 450 ml of ice cold acetone (previously distilled from potassium permanganate) was added 31.6 ml (0.126 meqv) of 8N chromic acid solution (62) over a period of 30 min. The reaction mixture was stirred 5 min and diluted with 100 ml of saturated aqueous sodium

bicarbonate and sufficient water to dissolve the chromium salts. The aqueous solution was extracted with ether (4x100 ml) and the combined ether layers were dried ($MgSO_4$) and evaporated. The residue was chromatographed on 450 g of grade II alumina. Petroleum ether eluted 8.71 g of a fragrant, colorless oil which was further purified by chromatography on 250 g of grade II alumina. Elution with petroleum ether gave successively 0.56 g (3% from the diol I-2, R=H) of 8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene (I-3): ir ($CHCl_3$) 1000, 980, 810 [lit (63) 1665, 1010, 980, 810]; nmr ($CDCl_3$) 1.03δ (s, 3, C-8a CH_3), 5.25-5.42δ (m, 1, vinyl) and 6.73 g (35% from the diol I-2, R=H) of the ketone I-5. Ptlc (10% ether-petroleum ether) and evaporative distillation (46°, 0.03 mm) gave a sample for analysis: ir ($CHCl_3$) 1700 (C=O); nmr ($CDCl_3$) 1.32δ (s, 3, C-8a CH_3), 5.25-5.42δ (m, 1, vinyl).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.47; H, 9.89.

1β,8aβ-Dimethyl-1,2,3,4,6,7,8,8a-Octahydro-1α-Naphthol (I-7)

The procedure described by Corey and Chaykovsky (66) was employed for the epoxidation. A dry 100 ml flask containing 1.80 g (43 mmoles) of 57% sodium hydride dispersion was flushed with argon. The hydride was washed by decantation with four 5 ml portions of petroleum ether and the remaining solvent was removed in vacuo. With an emerging stream of argon, 9.91 g (45 mmoles) of trimethyloxosulfonium iodide (118) was added followed by 60 ml of dimethylsulfoxide (previously distilled from calcium hydride).

The resulting mixture was stirred 2 hours at 25° until hydrogen evolution had ceased. A solution of 3.42 g (21.5 mmoles) of the ketone I-5 in 10 ml of dry dimethylsulfoxide was introduced all at once and the course of the reaction was monitored by glpc. After 5 hours the peak representing starting material had disappeared, and the reaction mixture was diluted with 100 ml of ice and water and was extracted with ether (4x30 ml). The ether layer was washed with water and brine and was dried ($MgSO_4$). Evaporation to dryness afforded 3.43 g (89%) of a pale yellow oil which was used directly in the next step: ir ($CHCl_3$) 1655 (C=C); nmr ($CDCl_3$) 1.22δ (s, 3, C-8a methyl), 2.30δ (d, 1, J=4, oxirane), 2.65δ (d, 1, J=4, oxirane), 5.37δ (m, 1, vinyl).

The crude oxirane from above in 15 ml of dry ether was added over a period of 15 min to a solution of 850 mg (22.4 mmoles) of lithium aluminum hydride in 90 ml of dry ether. After an additional 20 min, the excess hydride was decomposed with 3.0 ml of ethyl acetate followed by the sequential addition of 0.9 ml of water, 0.9 ml of 10% aqueous potassium hydroxide, and 2.7 ml of water. The mixture was filtered and concentrated to give 2.70 g (80%) of a water white oil consisting of a 6:1 ratio of axial to equatorial alcohols by nmr integration of the C-8a and C-1 angular methyl peaks. The pure axial alcohol was obtained as needed by ptlc (15% ether-benzene): ir ($CHCl_3$) 3550

(O-H), 1655 (C=O); nmr ($CDCl_3$) 1.18δ (s,3,C-1-CH_3), 1.13δ (s,3,C-8a-CH_3), 5.47-5.70δ (m,1,vinyl). A sample was evaporatively distilled (40°, 0.025 mm) for the analytical sample.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.84; H, 11.19.

1α,8aβ-Dimethyl-1,2,3,4,6,7,8,8a-Octahydro-1β-Naphthol (I-7).

A solution of 56 mg (0.34 mmole) of the ketone I-5 in 2 ml of dry ether was added dropwise with stirring to 1.5 ml (3 mmoles) of a 2 M solution of methyl lithium in ether (Alpha Inorganic, Inc.) in 6.5 ml of dry ether under a nitrogen atmosphere. After 5 min the reaction mixture was cooled in an ice bath, and the excess reagent was destroyed with 0.5 ml of water. The solution was diluted with 70 ml of ether, washed with brine (1x10 ml) and dried ($MgSO_4$). Evaporation to dryness and ptlc of the residue (20% ether-petroleum ether) afforded 24 mg (43%) of the analytically pure alcohol I-7. Evaporative distillation (60°, 0.05 mm) give the analytical sample: ir ($CHCl_3$) 3610, 3450(OH), 815 (C=C); nmr ($CDCl_3$) 1.16δ (s, 3, C-1 methyl), 1.22δ (s, 3, 8a methyl), 5.32-5.50δ (m, 1, vinyl).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.02; H, 11.01.

General Procedure for Simmons-Smith Cyclopropylations (53)

The zinc-copper couple was prepared by a variation of

the LeGoff method (52). In a typical experiment 15.0 g (0.23 mole) of zinc dust was added to a stirred solution of 2.2 g (0.011 mole) of cupric acetate monohydrate in 50 ml of glacial acetic acid which had been preheated to 80-90°. After two min the gray suspension was filtered and the powder was washed with two 100 ml portions of glacial acetic acid and six 100 ml portions of ether. The washings should be colorless; light blue washings indicate that the couple was not heated long enough. The last traces of solvent were removed under high vacuum to give a fluffy, gray powder which was used immediately.

In a dry 3-neck, 500 ml flask was placed 12.8 g (0.183 mole) of the couple and a small crystal of iodine. The atmosphere was replaced with nitrogen and 250 ml of dry ether was introduced, followed by 14.7 ml (0.181 mole) of diiodomethane. Spontaneous refluxing commenced upon gentle heating and continued about 10 min. Reflux was maintained an additional 30-35 min by heating with an ir lamp.

Upon cooling the solution could be transferred via syringe to a second flask containing the olefin in ether, or an ethereal solution of the olefin could be added to the initial flask. The choice of method does not seem to affect the yields.

1,2,3,4,4a,5,6,7,8,8a,Decahydro-1β,8aβ-Dimethyl-5α,4a-Methano-1α-Naphthol (I-8).

To the Simmons-Smith reagent (53) prepared from 980 mg (14.1 mmoles) of zinc-copper couple (52) and 0.80 ml (10.0 mmoles) of diiodomethane in 5 ml of dry ether was added a solution of 222 mg (1.23 mmoles) of the alcohol I-6 in 2 ml of dry ether over the course of 1 min. After 1 hour at room temperature the excess reagent was destroyed with 1.0 ml of 10% ammonium chloride and the resulting mixture was filtered through a glass wool plug which was then washed with 30 ml of ether. The ethereal solution was washed with saturated aqueous potassium carbonate (2x10 ml) and with saturated sodium chloride (3x10 ml) and was dried over $MgSO_4$. Evaporation to dryness and ptlc (benzene) afforded 151 mg (63%) of a colorless oil: ir ($CHCl_3$) 3575 (O-H); nmr ($CDCl_3$) 0.25-0.66 (m, 3, cyclopropane), 1.04δ (s, 3, C-8a methyl), 1.17δ (s, 3, C-1 methyl), 2.38δ (s, 1, O-H). A portion was purified by preparative glpc (5% SE-30, 150°) and evaporatively distilled (42°, 0.025 mm) for analysis.

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.43; H, 11.50.

5-Methoxy-8aβ-Methyl-3,4,8,8a-Tetrahydro-1,6,(2H,7H)-Naphthalenedione (J-3).

A. Three-Step Procedure

The pyrolysis was carried out using the general method of Archer (71). In a 200 ml flask fitted with a short-path still head and a Hershberg mechanical stirrer was placed 200 mg of hydroquinone, 30.5 g (0.231 mole) of 1,4-dimethoxy-2-butanone (J-1) (70) and 40 g of sodium benzoate. The receiver contained 200 mg of hydroquinone and 2 g of anhydrous magnesium sulfate. The apparatus was plunged into a hot oil bath, and the temperature was brought to 180-185° and held there 1 hour with vigorous stirring as the products distilled. When the pot was dry, the reaction was stopped; the receiver contained 17.8 g of a mixture consisting mainly of methanol and 1-methoxy-2-ketobutene along with a small amount of starting material by ir.

An adaptation of the method of Ramachandran and Newman (58) was employed for the Micheal addition. The material from above was dissolved in 75 ml of methanol and added to a flask containing 17.0 g (0.135 mole) of 2-methyldihydroresorcinol (J-2) and 50 mg of potassium hydroxide. The mixture was refluxed 1.5 hours while most of the 2-methyldihydroresorcinol went into solution. The methanol was removed *in vacuo*, the product was taken up in 50 ml of chloroform and filtered, and the filter cake was washed. The concentration filtration procedure was repeated to give a total of 8.97 g (53%) of recovered 2-methyldihydroresorcinol (mp 204-206 d.).

The cyclization-dehydration step was conducted in buffered xylene as outlined by H. Smith (73). Concentration of the above chloroform solution gave 19.65 g of an oil which was dissolved in 300 ml of xylene in a 500 ml flask fitted with a Dean Stark water separator, and 20 ml of xylene was distilled. The solution was cooled, 11.5 ml (0.083 mole) of triethylamine and 11.8 g (0.097 mole) of benzoic acid were added, and the mixture was refluxed with separation of the water formed. After 15 hours, the solution was cooled, washed with saturated aqueous sodium bicarbonate (2x50 ml) and water (1x50 ml) and was dried ($MgSO_4$). Distillation of the xylene under vacuum afforded 13.5 g of a dark, partly crystalline oil; trituration with ether gave 9.2 g (19% based on 1,4-dimethoxybutanone) of buff colored crystals mp 66-74° that were sufficiently pure for use in the next step. Two crystallizations of a portion from ether-hexane gave analytically pure material mp 78-80°: ir ($CHCl_3$) 1715 (C=O), 1680 (C=O), 1615 (C=C); nmr ($CDCl_3$) 1.43δ (s, 3, C-8a-CH_3), 3.67δ (s, 3, O-CH_3).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: C, 69.10; H, 7.81.

B. Two-Step Procedure

To a 2 l. flask containing 70.0 g (0.555 mole) of 2-methyldihydroresorcinol (J-2) was added a solution of 69.2 g (0.522 mole) of 1,4-dimethoxy-2-butanone (J-1) and 16.0 ml of triethylamine in 100 ml of xylene. The atmosphere was

replaced with nitrogen and the mixture was heated to reflux. After 1.5 hours, 50 ml of solvent was removed by distillation, and 23.6 g of benzoic acid and 23 ml of triethylamine (73) were added. Reflux was continued for 15 hours while the water formed was removed with a Dean Stark apparatus. Upon cooling, the solution was washed with three 250 ml portions of 5% aqueous potassium hydroxide and was dried (Na_2SO_4). Vacuum distillation of the solvent afforded 51.3 g (47.2%) of yellow crystals mp 66-71°. Extraction of the aqueous washings with chloroform yielded an additional 5.30 g (4.8%). The overall yield from 1,4-dimethoxy-2-butanone was 52%;in another experiment a 59% yield was realized.

5-Methoxy-8aβ-Methyl-1,2,3,4,6,7,8,8a-Octahydro-1β,6-Naphthalenediol.

A solution of 37.70 g (0.181 mole) of dione J-3 in 250 ml of ether was added to a stirred solution of 15.70 g (0.413 mole) of lithium aluminum hydride in 2 l. of ether over the course of 1 hour. The solution was stirred overnight, cooled to 0°, and the excess reagent was decomposed with 50 ml of ethyl acetate. The aluminate esters were hydrolyzed by the consecutive addition of 16 ml of water, 16 ml of 10% aqueous potassium hydroxide, and 45 ml of water. The mixture was filtered, dried ($MgSO_4$) and evaporated to dryness to give 35.8 g (95%) of a white crystalline solid, mp 88-92° (partly melt) and 134-140° that consisted of a

2:1 mixture of 6β and 6α isomers by nmr integration of the C-8a angular methyl peaks. Two crystallizations from ethyl acetate provided a pure sample of the 6β isomer mp 147-150°: ir ($CHCl_3$) 3600 (OH), 1665 (C=C); nmr ($CDCl_3$) 1.22δ (s, 3, C-8a-CH_3), 3.70δ (s, 3, O-CH_3).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.98; H, 9.59.

5-Methoxy-8aβ-Methyl-1,2,3,4,6,7,8,8a-Octahydro-1β,6-Naphthalenediol Diacetate.

A solution of 35.8 g (0.169 mole) of the crude diol from above in 600 ml of dry pyridine was treated with 62.5 ml (0.85 mole) of acetic anhydride. The reaction mixture was stirred 17 hours at room temperature and was diluted with 500 ml of saturated aqueous sodium bicarbonate. The aqueous solution was extracted with ether (4x200 ml) and the combined organic layers were washed with water (2x200 ml) and brine (1x50 ml) and were dried ($MgSO_4$). Concentration gave 50.1 g, (quantitative), of the diacetate as an oil. Ptlc of a portion (40% ether-petroleum ether, double elution) and evaporative distillation (100°, 0.025 mm) gave the analytical sample of the mixture of C-6 isomers: ir ($CHCl_3$) 1725 (C=O), 1655 (C=C); nmr ($CDCl_3$) 1.08δ (s, 1, C-8a-CH_3, 6α isomer), 1.15δ (s, 2, C-8a-CH_3, 6β isomer), 2.03 and 2.05δ (pair of s, 6, acetate CH_3), 3.48δ (s, 3, C-CH_3).

Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.88; H, 8.24.

1β-Hydroxy-5-Methoxy-8aβ-Methyl-1,2,3,4,6,7,8,8a-Octahydronaphthalene (N-4).

A modification of the Hallsworth procedure (60) was utilized for the cleavage. In a dry, 2 l. flask fitted with a mechanical stirrer and a dry ice condenser and containing 23.7 g (0.080 mole) of the diacetate from above was distilled 1 l. of monoethylamine through potassium hydroxide. The solution was cooled in an efficient ice-salt bath after injecting 60 ml (0.63 mole) of dry t-butyl alcohol through a septum.

Freshly cut lithium wire, 5.5 g (0.80 mole) was added over 5 minutes with rapid stirring. After 20 min the characteristic blue color developed and the excess metal was decomposed with solid ammonium chloride. Most of the solvent was removed overnight in a stream of nitrogen and the residue was dissolved in 600 ml of ether. The ethereal solution was washed with water (2x100 ml) and brine (1x100 ml) and was dried ($MgSO_4$). The product, following concentration, was chromatographed on 920 g alumina. Elution with 3 l. of 10% ether-petroleum ether gave 703 mg (5%) of an oil which was an enol ether possessing neither alcohol nor ketone functionality. Further elution with 17 l. of ether afforded 15.78 g (58%) of the alcohol (N-4) mp

83.5-86.5°. A portion was recrystallized 3 times from ether-hexane tc provide analytically pure material mp 85.5-86.5°: ir ($CHCl_3$) 3610 (OH), 1645 (C=C); nmr ($CDCl_3$) 1.02δ (s, 3, C-8a-CH_3), 3.47δ (s, 3, O-CH_3).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.50; H, 10.23.

5-Methyoxy-8aβ-Methyl-3,4,5,6,8,8a-Hexahydro-1(2H)-Naphthalenone (J-4).

To a rapidly stirring solution of 6.10 g (31.1 mmoles) of the alcohol (N-4) in 50 ml of dry methylene chloride under a nitrogen atmosphere was added all at once 900 ml (0.175 mole) of a 5% solution of chromium trioxide dipyridine complex (74) in dry methylene chloride. After 10 min at room temperature the black reaction mixture was filtered through a 600 ml Büchner funnel filled three-fourths with grade II alumina with suction, washing the alumina with 1000 ml of ether. Drying ($MgSO_4$) and concentration afforded 5.86 g of a red oil which was chromatographed on 150 g of grade II alumina eluting with 700 ml 10% ether-petroleum ether to give 5.02 g (83%) of a water-white oil which contained a single volatile component by glpc. Ptlc (5% ether-petroleum ether) and evaporative distillation (50°, 0.025 mm) provided the analytical sample: ir ($CHCl_3$) 1705 (C=O), 1670 (C=C); nmr ($CDCl_3$) 1.35δ (s, 3, C-8a-CH_3), 3.40δ (s, 3, O-CH_3).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.01; H, 9.49.

Spiro-1α-Oxironyl-5-Methoxy-8aβ-Methyl-1,2,3,4,6,7,8,8a-Octahydronaphthalene.

Following the procedure of Corey and Chaykovsky (66) a dry 100 ml flask containing 798 mg (19.0 mmoles) of 57% sodium hydride dispersion was flushed with nitrogen and the sodium hydride was washed with three 10 ml portions of petroleum ether. The excess solvent was removed *in vacuo* and 4.25 g (19.3 mmoles) of dry trimethyloxosulfonium iodide (118) was added followed by 40 ml of dimethylsulfoxide (previously distilled under vacuum from calcium hydride). The reaction mixture was stirred 40 min at 23° until hydrogen evolution was complete and the solids were allowed to settle 1 hour. The supernatant was transferred *via* syringe to a 50 ml flask containing a solution of 361 mg (1.86 mmoles) of ketone J-4 in 4 ml of dry dimethylsulfoxide under nitrogen. The course of the reaction was monitored by glpc and it was stopped after 7 hours at 23° when the peak representing starting material had disappeared. Longer reaction times lead to lower yields. The excess reagent was carefully decomposed with 1.0 ml of water, 15 ml of water was added and the aqueous solution was extracted with ether (6x15 ml). The combined organic layers were washed with brine (1x15 ml), dried ($MgSO_4$), and evaporated

to dryness. Ptlc (20% ether-petroleum ether, double elution) afforded 315 mg (81%) of the α-oxirane r.f. 0.7, which crystallized on standing at -10°: ir ($CHCl_3$) 1670 (C=C), 1130 (C-O), 1055 (C-O); nmr ($CDCl_3$) 1.20δ (s, 3, C-8aCH_3), 2.33δ(d, 1, J=5.5 Hz, oxirane), 2.70δ (d, 1, J=5.5 Hz, oxirane), 3.42δ (s, 3, O-CH_3).

1β,8aβ-Dimethyl-5-Methoxy-1,2,3,4,6,7,8,8a-Octahydro-1α-Naphthol(J-5).

To a solution of 740 mg (3.55 mmoles) of oxirane from above in 25 ml of dry pyridine at 0° (ice bath) was added 440 mg (11.6 mmoles) of lithium aluminum hydride. The mixture was stirred 10 min at 0°, then 1 hour at room temperature. The muddy-green solution was diluted with 25 ml of ether, the excess hydride was destroyed by the consecutive addition of 0.45 ml water, 0.45 ml of 10% aqueous potassium hydroxide solution and 1.35 ml water and the solution was filtered. The filtrate was washed with water (2x20 ml), saturated aqueous copper sulfate (2x20 ml), and brine (2x20 ml) and was dried ($MgSO_4$). Filtration through 30 g of grade II alumina (50% ether-petroleum ether) afforded 690 mg (94%) of the alcohol J-5 as an oil which was contaminated with less than 5% of the equatorial isomer J-6 by nmr integration of the C-1 and C-8a angular methyls. The alcohol is quite labile and was used without further purification: ir ($CHCl_3$) 3500 (broad, weak) (OH),

1665 (C=C); nmr ($CDCl_3$ + 1 drop pyridine) 1.11δ (s, 3, C-8a-CH_3), 1.13δ (s, 3, C-1-CH_3), 3.47δ (s, 3, O-CH_3).

1α,8β-Dimethyl-5-Methoxy-1,2,3,4,6,7,8,8a-Octahydro-1β-Naphthol (J-6).

To a solution of 2 ml (4 mmoles) of a 2M solution of methyl lithium in ether (Alpha Inorganics, Inc.) in 5 ml of dry ether was added dropwise 109 mg (0.53 mmole) of the ketone J-4 in 1.0 ml of dry ether under a nitrogen atmosphere. After 1 min the mixture was cooled in an ice bath and the remaining reagent was decomposed with 0.50 ml of water. The solution was diluted with 60 ml of ether and was washed with water (1x5 ml) and brine (1x10 ml) and was dried ($MgSO_4$). Evaporation to dryness afforded 118 mg, 100% of a colorless oil which was represented by a single volatile component by glpc; ptlc (20% ether-petroleum ether) and evaporative distillation (60°, 0.005 mm) gave a sample for analysis; ir ($CHCl_3$) 3600 (OH), 1665 (C=C); nmr ($CDCl_3$) 1.15δ (s, 3, C-8a-CH_3), 1.20δ (s, 3, C-1-CH_3), 3.45δ (s, 3, OCH_3).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.33; H, 10.51.

1,2,3,4,4aβ,5,6,7,8,8a-Decahydro-1β,8aβ-Dimethyl-5β-Methoxy-1α-Naphthol Ketal (J-7).

In an nmr tube was dissolved 79 mg (0.38 mmole of the alcohol J-5 in 1 ml of chloroform-d. After 5 days at room

temperature nmr spectra indicated starting material had disappeared forming a single major product. Evaporation to dryness gave 63 mg (80%) of an oil; ptlc (15% ether-benzene) afforded 43 mg (55%) of the analytically pure ketal which was evaporatively distilled (55°, 0.05 mm) for the analytical sample: ir ($CHCl_3$) 1085 (C-O); nmr ($CDCl_3$) 0.92δ (s, 3, C-8a-CH_3), 3.37δ (s, 3, O-CH_3).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.26; H, 10.56.

1,2,3,4,4a,5,6,7,8,8a-Decahydro-1β,8aβ-Dimethyl-5α,4a-Methano-5β-Methoxy-1α-Naphthol (J-8).

To a solution of the Simmons-Smith reagent (53) prepared from 12.8 g (0.183 mole) of zinc-copper couple (52) and 14.7 ml (0.183 mole) of diiodomethane in 250 ml of ether was added a sclution of 4.04 g (0.019 mole) of the tert-alcohol J-5 in 20 ml of dry ether and 15 ml (0.17 mole) of dry 1,2-dimethoxyethane over a period of 10 min. After 40 min at room temperature the flask was cooled in an ice bath and the excess reagent was decomposed with 3.0 ml of 10% aqueous ammonium chloride. The solution was diluted with 600 ml of ether and washed with saturated aqueous potassium carbonate (3x150 ml) and brine (2x150 ml). The organic phase was dried ($MgSO_4$), concentrated, and chromatographed on 300 g of grade II alumina. Petroleum ether eluted 5 g diiodomethane; further elution of the column with 1200 ml

of 50% ether-petroleum ether gave 3.54 g (83%) of crystalline cyclopropane mp 58-60°. Crystallization of a sample from ether-heptane, then from ethanol-water, yielded the analytical sample mp 60-61.5°: ir ($CHCl_3$) 3600 (OH), 1075, 1060 (C-O); nmr ($CDCl_3$) 0.52δ (d, 1, J=5.5 Hz, cyclopropane), 0.82δ (d, 1, J=5.5 Hz, cyclopropane), 1.03δ (s, 3, C-8a-CH_3), 1.15δ (s, 3, C-1-CH_3), 3.23δ (s, 3, O-CH_3).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.01; H, 10.78.

3,4,4a,7,8,8a-Hexahydro-1,4aα,8aβ-Trimethyl-5(6H)-Naphthalenone (J-9).

A solution of 595 mg (2.65 mmoles) of cyclopropane J-8 in 20 ml of methanol and 2.0 ml of 37-38% hydrochloric acid was refluxed 4 hours, cooled, and neutralized with saturated sodium bicarbonate. After most of the methanol was removed in vacuo, the residue was taken up in 200 ml of ether and was washed with saturated aqueous sodium bicarbonate (1x25 ml), and dried ($MgSO_4$). Concentration gave 510 mg of a yellow oil that was chromatographed on 20 g of alumina. Petroleum ether eluted 376 mg (74%) of the desired ketone, mp 67-68°. Recrystallization from ethanol-water and sublimation (50°, 0.025 mm) provided the analytical sample mp 68-69°: ir ($CHCl_3$) 1700 (C=O); nmr ($CDCl_3$) 1.00δ (s, 3, C-8a-CH_3), 1.22δ (s, 3, C-4a-CH_3), 1.65δ (d, 3, J=1.5 Hz, C-1-CH_3), 5.20δ (m, 1, vinyl).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.21; H, 10.57.

In one experiment which was stopped after 3 hours, a small amount of the highly crystalline alcohol, 1α-hydroxy-1,2,3,4,4a,7,8,8a-octahydro-1β,4aα,8aβ-trimethyl-5(6H)-naphthalenone was obtained as a by-product. Glpc indicates that this compound forms first from cyclopropane cleavage followed by a slow dehydration to the keto-olefin J-9. One crystallization from ether-petroleum ether gave analytically pur material mp 92-96°: ir ($CHCl_3$) 3610 (O-H), 1700 (C=O); nmr ($CDCl_3$) 0.85δ (s, 3, C-8a-CH_3), 1.13δ (s, 3, C-1-CH_3), 1.45δ (s, 3, C-4a-CH_3).

Anal. Calcd for $C_{12}H_{22}O_2$: C, 74.24; H, 10.55. Found: C, 74.15; H, 10.53.

1,2,3,4,4a,5,6,7,8,8a-Decahydro-1β,4aα,8aβ-Trimethyl-1α-Naphthol (K-9).

To a solution of 4 mmoles of methyl lithium (2 ml of a 2M solution in ether (Alpha Inorganics, Inc.) in 20 ml of dry ether was added 59 mg (0.33 mmole) of 4aα,8aβ-dimethyl-3,4,4a,5,6,7,8,8a-octahydro-1(2H)-naphthalenone (K-8) (76) in 2 ml of dry ether with a syringe under a nitrogen atmosphere. After 10 min at room temperature the remaining methyl lithium was carefully destroyed with 0.6 ml of saturated ammonium chloride. The solution was diluted with 75 ml of ether, washed with water (1x5 ml) and brine (1x5

ml), and was dried ($MgSO_4$). Evaporation to dryness and evaporative distillation afforded 59 mg (94%) of an oil which consisted of 25% starting material and 75% of a single higher boiling product by glpc. Repetition of the methyl lithium treatment provided 49 mg (79%) of a partly crystalline product that was greater than 95% one volatile component by glpc. Ptlc (benzene) and evaporative distillation (60-70°, 0.25 mm) gave analytically pure crystals mp 40-41°: ir ($CHCl_3$) 3600 (OH); nmr ($CDCl_3$) 1.03δ (s, 3, C-8a-CH_3), 1.08δ (s, 3, C-1-CH_3), 1.30δ (s, 3, C-4a-CH_3).

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.33. Found: C, 79.41; H, 12.33.

3,4,4a,5,6,7,8,8a-Octahydro-1,4aα,8aβ-Trimethylnaphthalene (K-10).

A. Wolff-Kischner of J-9

The Haung Minlon modification (119) of the Wolff-Kischner reduction was used. A 10 ml flask was fitted with a short path microstill, and a nitrogen inlet arranged so that nitrogen would flow from the pot, through the still, into the receiver and out to the atmosphere. The flask was charged with 141 mg (0.735 mmole) of ketone J-9, 500 mg of crushed potassium hydroxide, 0.40 ml of 85% hydrazine hydrate, and 5 ml of diethyleneglycol. With the nitrogen flowing it was heated to 100-105° for 30 min

and then to 200-205° for 120 min while the volatile products distilled. The apparatus was cooled, and the contents of the pot and receiver were combined and extracted with ether. The ether solution was dried ($MgSO_4$) and the solvent was distilled at atmospheric pressure; the crude product was sublimed (40°, 0.025 mm) to afford 60 mg (46%) of white crystals mp 45-50°. Ptlc (petroleum ether) and sublimation gave the analytical sample mp 52-55°: ir ($CHCl_3$) 1640 (weak) (C=C); nmr ($CDCl_3$) 0.90δ (s, 3, C-4a-CH_3), 1.03δ (s, 3, C-8a-CH_3), 1.58δ (d, 3, J=1.5 Hz, C-1-CH_3), 5.03-5.23δ (m, 1, vinyl).

Anal. Calcd for $C_{13}H_{22}$: C, 87.56; H, 12.44. Found: C, 87.36; H, 12.48.

B. Dehydration of K-9

To a solution of 50 mg (0.25 mmole) of the alcohol K-9 in 5 ml of dry pyridine was added 0.30 ml (4.1 mmoles) of thionyl chloride at -10° (ice-salt bath). The solution was stirred at -10° for 45 min and warmed to room temperature over 15 min. It was poured into 25 ml of saturated aqueous sodium bicarbonate and extracted with ether (4x25 ml). The combined organic layers were washed with water (1x15 ml), saturated aqueous copper sulfate (1x15 ml), and brine (1x15 ml). Drying ($MgSO_4$), removal of the solvent by distillation at atmospheric pressure, and chromatography on 5 g of alumina gave with 15 ml of pentane 19 mg (42%)

of a white crystalline solid mp 50-54° that was spectrally identical to that obtained in Part A, above. A mixed sample of material from Part A, mp 45-50° and Part B, mp 50-54°, gave mp 45-50°.

5,5 -Ethylenedioxo-3,4,4a,5,6,7,8,8a-Octahydro-1,4aα,8aβ-Trimethylnaphthalene (L-1).

A solution of 502 mg (2.62 mmoles) of the ketone J-7 and 10 ml of ethylene glycol in 110 ml of benzene was placed in a flask fitted with a Dean Stark water separator and 10 ml of benzene was distilled. The solution was refluxed 20 hours after adding 40 mg of p-tolulenesulfonic acid. It was then washed with water, saturated aqueous sodium bicarbonate, and brine. Drying ($MgSO_4$) and evaporation to dryness yielded 0.64 g of an oil which was chromatographed on 30 g of grade II alumina. Petroleum ether eluted 510 mg (83%) of the ketal L-1 (mp 37-40°). Further elution with 10% ether-petroleum ether afforded 55 mg (11%) of starting material. The ketal was recrystallized three times from hexane to provide an analytically pure sample mp 45-46°: ir ($CHCl_3$) 1660 (C=C); nmr ($CDCl_3$) 1.09δ (s, 3, C-4a-CH_3), 1.22δ (s, 3, C-8a-CH_3), 1.65δ (s, 3, C-1-CH_3), 3.88δ (m, 4, ketal), 5.10δ (m, 1, vinyl).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.07; H, 10.18.

1,2,3,4,4a,5,6,7,8,8a-Decahydro-4aα,8aβ-Dimethyl-5,5-Ethylenedioxo-1-Methylidene-2β-Naphthol (L-2).

The photoöxidation procedure described by Nickon and Bagli (81) was employed using a merry-go-round apparatus consisting of 11 parallel 15 watt fluorescent bulbs arranged in a circle each 5-6 cm from the center. A fan was set to blow air between the bulbs for cooling and a thermometer was suspended in the middle along side the reaction vessel.

A solution of 510 mg (2.16 mmoles) of the olefin L-1 and 80 mg hematoporphyrin dihydrochloride (Calbiochem) in 50 ml of dry pyridine was placed in a 2x15 cm pyrex tube fitted with a gas dispersion tube extending to within 0.5 cm of the bottom. Oxygen was passed through and the solution was irradiated 132 hours at the center of the apparatus. During the reaction two 50 mg portions of hematoporphyrin dihydrochloride were added and the pyridine lost by evaporation was replaced. The temperature varied from 20 to 35° during the reaction period.

The pyridine was removed *in vacuo* at room temperature and the black oil was taken up in 100 ml of dry ether; lithium aluminum hydride, 241 mg (6.3 mmoles) was added and the solution was stirred 4 hours. The excess hydride was destroyed by successive additions of 0.24 ml water, 0.24 ml of 10% potassium hydroxide and 0.72 ml water. The

mixture was filtered and concentrated to give 340 mg of a crude oil which was applied to 30 g of Florisil. Petroleum ether, 300 ml, gave 83 mg (16%) of recovered starting material; further elution with 400 ml of 60% ether-petroleum ether afforded 173 mg (31%) of the crystalline alcohol L-1. Two crystallizations from ether-heptane provided analytically pure material mp 148-149.5°: ir ($CHCl_3$) 3600 (OH), 1645 (C=C), 895 ($C=CH_2$); nmr ($CDCl_3$) 1.00δ (s, 3, C-8a-CH_3), 1.25δ (s, 3, C-4a-CH_3), 3.90δ (m, 4, ketal), 4.67δ (m, 1, vinyl), 5.02δ (m, 1, vinyl).

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.41; H, 9.48.

Perhydro-9b-Boraphenalene

The borane was prepared by a modification of the method employed by Rotermund and Koster (88). A 1000 ml flask fitted with a distillation head equipped with a stopcock to permit total reflux and a 500 ml dropping funnel was flushed with argon and was charged with 100 ml of dry xylene. The xylene was heated to reflux and a solution of 40 g (0.34 mole) of triethylamine borane (Penisular Chemresearch, Inc.) and 51.9 g (0.32 mole) of 1,5,9-trans, trans, trans-cyclododecatriene (Columbia Organic Chemical Co., Inc.) in 200 ml of dry xylene was added over the course of 3 hours. On completion of the addition, most of the solvent was distilled and the reaction mix-

ture was allowed to cool and stand overnight under argon.

The mixture was quickly poured into a dry 300 ml flask and the remaining xylene was removed under reduced pressure (bath temp 40-80°, 1.5-2.0 mm). The borane was distilled bp 72-76°, 0.3 mm [lit (88) 55°, 0.1 mm] and the vacuum was broken with argon to give 44.7 g (81%) of a viscous oil.

Lithium Perhydro-9b-Boraphenalyl Hydride (N-1).

A solution of 15.1 g (0.086 mole) of the borane from above in 90 ml of dry tetrahydrofuran was treated with 5.2 g (0.66 mmoles) of lithium hydride (Alpha Inorganics) and the resulting suspension was heated to reflux for 6 hours under an argon atmosphere. On cooling, most of the unreacted lithium hydride rose to the surface and the cloudy solution below could be withdrawn with a syringe and stored in a 100 ml flask under argon. The concentration of the reagent was calculated to be 0.85M based on 100% reaction of the starting borane; it was generally used in 50-100% excess.

8aβ-Methyl-1,2,3,4,6,7,8,8a-Octahydro-1α-Naphthol (N-2).

A stirred, ice cold solution of 128 mg (0.78 mmole) of the keto-olefin I-5 in 2 ml of dry tetrahydrofuran was treated with 2.0 ml of a 0.77M solution of lithium perhydro-9b-boraphenalylhydride (N-1) in dry tetrahydrofuran under nitrogen. After 30 min the excess borohydride was des-

troyed by the consecutive addition of 0.5 ml of 3N sodium hydroxide and 0.75 ml of 30% hydrogen peroxide. The mixture was poured immediately onto 15 ml of 20% aqueous potassium carbonate and the aqueous solution was extracted with 75 ml of ether. The ethereal layer was washed with brine (1x10 ml) and was dried ($MgSO_4$). Concentration afforded 189 mg of an oil which was filtered through 15 g of alumina (ether) to give 85 mg (65%) of partly crystalline material. Ptlc (15% ether-petroleum ether) gave two products: r.f. 0.2, 35 mg (28%) of the equitorial alcohol I-4 and r.f. 0.5, 45 mg (36%) of the pure axial alcohol N-2, mp 65-66.5° which was suitable for analysis: ir ($CHCl_3$) 3600 (OH); nmr ($CDCl_3$) 1.07δ (s, 3, C-8a-CH_3), 3.27-3.47δ (m, 1, C<u>H</u>OH), 5.38-5.62δ (m, 1, vinyl).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.58; H, 10.92.

5-Methoxy-8aβ-Methyl-1,2,3,4,6,7,8,8a-Octahydro-1α-Naphthol.

To a solution of 448 mg (2.30 mmoles) of the ketone J-4 in 5 ml of dry tetrahydrofuran was added 4.20 ml (3.20 mmoles) of a 0.77M solution of the borohydride N-1 at -10° (ice-salt bath) under a nitrogen atmosphere. After 30 min, the excess reagent was destroyed by the careful, dropwise addition of 2.0 ml of 3N sodium hydroxide followed by 1.0 ml of 30% hydrogen peroxide. The mixture was poured onto 30 ml of 20% aqueous potassium carbonate and was extracted

with ether (6x25 ml). The combined organic layers were washed with water (1x20 ml) and brine (1x20 ml) and were dried ($MgSO_4$). Evaporation yielded 483 mg (quantitative) of a colorless oil consisting of a 70:30 mixture of the axial alcohol N-3 and the equatorial alcohol N-4 as determined by nmr integration of the angular methyl peaks. The axial alcohol was quite labile so the mixture was used without further purification: ir ($CHCl_3$) 3600 (OH), 1670 (C=C); nmr (CCl_4) 0.95δ (s, 0.9, C-8a-CH_3, equatorial alcohol), 1.05δ (s, 2.1, C-8a, axial alcohol), 3.40δ (s, 0.9, O-CH_3, equatorial alcohol), 3.43δ (s, 2.1, O-CH_3, axial alcohol).

1,2,3,4,4aβ,5,6,7,8,8a-Decahydro-5β-Methoxy-8aβ-Methyl-1,4-Naphthol Ketal (N-5).

A solution of 154 mg (0.785 mmole) of the crude mixture of alcohols N-3 and N-4 in 3 ml of chloroform-d containing 1-2 mg of p-tolulenesulfonic acid was allowed to stand 12 hours at room temperature. Ptlc (30% ether-petroleum ether) gave two bands. The first, r.f. 0.1, contained 64 mg, (42%) of a mixture of four major components as determined by nmr: the starting alcohols N-3 and N-4, the hydrolysis product of the equatorial alcohol (vide infra) and an unidentified compound presumably the hydrolysis product of the axial alcohol. The faster moving band r.f. 0.3 contained 43 mg (28% from the ketone J-4) of

the analytically pure ketal N-5. Evaporative distillation (45°, 0.15 mm) afforded the analytical sample: ir ($CHCl_3$) 1055 (C-O); nmr ($CDCl_3$) 0.97δ (s, 3, C-8a-CH_3), 3.30δ (s, 3, O-CH_3), 3.77-3.90δ (m, 1, C<u>H</u>-O).

<u>Anal.</u> Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.54; H, 10.23.

<u>1,2,3,4,4a,5,6,7,8,8a-Decahydro-5α,4a-Methano-5β-Methoxy-8aβ-Methyl-1α-Naphthol (N-6).</u>

The Simmons-Smith reagent (53) prepared from 2.10 g (30.0 mmoles) of zinc-copper couple (52) and 2.40 ml (30.0 mmoles) of diiodomethane in 30 ml of dry ether was added to a solution of 483 mg (2.30 mmoles) of the 70:30 mixture of alcohols N-3 and N-4 from above in 3.2 ml (30 mmoles) of dry 1,2-dimethoxyethane under a nitrogen atmosphere. Over the course of 1 hour, the characteristic gray precipitate formed; the mixture was cooled in an ice bath and the excess reagent was decomposed with 1.0 ml of 10% aqueous ammonium chloride. The solution was diluted with 200 ml of ether, washed with saturated aqueous potassium carbonate (1x50 ml) and brine (2x50 ml) and was dried ($MgSO_4$). Following concentration, ptlc of the crude product on three 20x20 cm plates (30% ether-petroleum ether, 2 elutions) gave a band r.f. 0.5 containing 278 mg (59% from the ketone J-4) of the cyclopropane N-6. Rechromatography and evaporative distillation (120°, 0.65 mm) gave the analytical

sample: ir ($CHCl_3$) 3600 (OH); nmr ($CDCl_3$) 0.38δ (d, 1, J=5 Hz, cyclopropane), 0.78δ (d, 1, J=5 Hz, cyclopropane), 1.11δ (s, 3, C-8a-CH_3), 3.17δ (s, 3, O-CH_3), 3.17-3.37δ (m, 1, CHOH).

Anal. Calcd fro $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.32; H, 10.63.

4aα,8aβ-Dimethyl-1α-Hydroxy-1,2,3,4,4a,7,8,8a-Octahydro-5(6H)-Naphthalenone (N-7).

A solution of 114.2 mg (0.545 mmole) of the cyclopropyl ether N-6, 0.5 ml water, and 2.0 ml of 38-39% hydrochloric acid in 8 ml of methanol was refluxed 1.5 hours. The cooled mixture was poured into 20 ml of ice and 5% aqueous sodium hydroxide, and the aqueous solution was extracted with ether (6x25 ml). The ethereal layer was washed with saturated aqueous sodium bicarbonate (1x15 ml) and brine (1x15 ml) and was dried ($MgSO_4$). Evaporation to dryness and tituration of the crude crystals with ether afforded 78 mg (80%) of a white crystalline solid mp 125-130°. Crystallization from ether-heptane gave cubes mp 158-159° which were sublimed to give the analytical sample: ir ($CHCl_3$) 3615 (OH), 1695 (C=O); nmr ($CDCl_3$) 0.83δ (s, 3, C-8a-CH_3), 1.46δ (s, 3, C-4a-CH_3), 3.50-3.65δ (m, 1, HC-OH).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.29; H, 10.17.

In one experiment starting with 1.79 g (8.50 mmoles) of the crude (70% pure) product from the Simmons-Smith reaction there was obtained in addition to 0.820 g (54%) of the keto alcohol N-7 0.175 g (12%) of a second keto-alcohol as an oil: 1β-hydroxy-8aβ-methyl-1,2,3,4,4a,7,8,8a-octahydro-5(6H)-naphthalenone which was produced by hydrolysis of the equitorial alcohol N-4 that occurred as an impurity in the starting material. Ptlc (75% ether-petroleum ether) and evaporative distillation (130°, 0.004 mm) afforded the analytical sample: ir ($CHCl_3$) 3600 (OH), 1702 (C=O); nmr ($CDCl_3$) 0.77δ (s, 3, C-8a-CH_3), 3.28-3.67δ (m, 1, C<u>H</u>-OH).

<u>Anal.</u> Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.42; H, 9.91.

<u>1,2,3,4,4a,5,6,7,8,8a-Decahydro-4aα,8aβ-Dimethyl-1α-Naphthol (K-6)</u>.

The Wolff Kischner reduction was carried out as above. A 10 ml flask fitted with a short path microstill and a nitrogen inlet was charged with 73 mg (0.38 mmole) of keto-alcohol N-7, 1.0 ml of ethanol, 2.5 ml of diethylene glycol, 0.20 ml of 85% hydrazine hydrate, and 250 mg of crushed potassium hydroxide. With the nitrogen flowing, the flask was heated to 100-105° for 0.5 hours, then to 200-205° for two hours. Upon cooling, the contents of the pot and receiver were combined and extracted with ether (6x15 ml). The combined organic layers were washed with water (2x10 ml)

and brine (1x10 ml) and were dried ($MgSO_4$). Distillation of the solvent at atmospheric pressure and ptlc (30% ether-petroleum ether) gave 15 mg (23%) of the desired alcohol which crystallized on standing, mp 46-56°. Ptlc (30% ether-petroleum ether) afforded white crystals mp 70.5-72°, which were spectrally identical to a sample prepared by Ireland and Dawson (76): ir ($CHCl_3$) 3615 (OH), 1260 (C-O); nmr ($CDCl_3$) 0.98δ (s, 3, C-8a-CH_3), 1.23δ (s, 3, C-4a-CH_3), 3.33-3.50δ (m, 1, C<u>H</u>-OH).

<u>Anal.</u> (76) Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.93; H, 12.05.

<u>4aα,8aβ-Dimethyl-3,4,4a,5,6,7,8,8a-Octahydro-1(2H)-Naphthalenone (K-8)</u>.

To an ice cold solution of 39 mg (0.21 mmole) of the alcohol <u>K-6</u> in 5 ml of acetone that had been freshly distilled from potassium permanganate was added 0.10 ml (0.40 meq) of chromic acid solution (62). After 5 min the solution was poured onto 5 ml of saturated aqueous sodium bicarbonate, sufficient water was added to dissolve the chromium salts and the aqueous solution was extracted with ether (4x15 ml), The combined ether layers were washed with brine (1x10 ml) and were dried ($MgSO_4$). Atmospheric pressure distillation of the solvent and ptlc (50% ether-benzene) gave 21 mg (54%) of white crystals, mp 65-72°. Crystallization from heptane, then from

petroleum ether, afforded a sample mp 108-110° (sealed capillary) which on admixture with an authentic sample, (76) mp 108-110° (sealed capillary), gave mp 108-110° (sealed capillary). The spectra (nmr and ir) were also in total agreement with those of authentic ketone (76).

1,2,3,4,4a,5,6,7,8,8a-Decahydro-4aα,8aβ-Dimethyl-5,5-Ethylenedoxo-1α-Naphthol (O-1).

A 50 ml flask fitted with a Dean Stark water separator was charged with a solution of 117 mg (0.596 mmole) of the ketone N-6 and 2.5 ml of ethylene glycol in 35 ml of benzene. Ten ml of benzene were distilled, 11 mg of p-tolulenesulfonic acid were added, and reflux was continued for 7.5 hours. The cooled solution was poured onto 30 ml of water and was extracted with ether (4x35 ml). The combined organic layers were washed with saturated sodium bicarbonate solution (2x15 ml) and brine (1x20 ml), dried ($MgSO_4$), and concentrated. Ptlc (50% ether-petroleum ether) afforded 66 mg (64%) of the ketal mp 89-91°. Two recrystallizations from ether-heptane provided an analytically pure sample mp 92-94° which was sublimed (75°, 0.005 mm) for analysis: ir ($CHCl_3$) 3615 (OH); nmr($CDCl_3$) 1.12δ (s, 3, C-8a CH_3), 1.40δ (s, 3, C-4a CH_3), 3.37-3.50δ (m, 1, CHOH), 3.67-4.15δ (m, 4, ketal).

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.99; H, 9.99.

4aα,8aβ-Dimethyl-5,5'-Ethylenedioxo-3,4,4a,5,6,7,8,8a-Octahydro-1(2H)-Naphthalenone (O-2).

To an ice cold solution of 133 mg (0.554 mmole) of ketal O-1 in 20 ml of acetone, (previously distilled from potassium permanganate), was added 0.25 ml (1.0 meqv) of 8N chromic acid solution (62). After 1 min, 0.10 ml of isopropyl alcohol was added, the mixture was diluted with 20 ml of saturated aqueous sodium bicarbonate and was extracted with ether (4x50 ml). The ethereal solution was washed with brine (2x30 ml), dried ($MgSO_4$) and evaporated to dryness to yield 32 mg (100%) of yellow crystals, mp 78-82°. Two recrystallizations from ether-hexane and sublimation (80°, 0.05 mm) provided the analytical sample mp 88-89°: ir ($CHCl_3$) 1695 (C=O); nmr ($CDCl_3$) 1.00δ (s, 3, C-4a-CH_3), 1.35δ (s, 3, C-8a-CH_3), 3.70-4.17δ (m, 4, ketal).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.61; H, 9.44.

Attempted addition of 2-m-Methoxyphenylethylmagnesium bromide to the ketone O-2.

A dry 25 ml flask containing 170 mg (7 mmoles) of magnesium shavings was flushed with nitrogen and charged with 3 ml of dry ether. A solution of 1.44 g (6.05 mmoles) of 2-m-methoxyphenylethyl bromide (120) in 7 ml of dry ether was added dropwise so as to maintain a steady reflux

(10 min), and the resulting solution was stirred 15 min at reflux. A 3 ml (~2 mmole) portion was transferred to a dry 25 ml flask under a nitrogen atmosphere and a solution of 56 mg (0.24 mmoles) of the ketone O-2 in 5 ml of dry ether was added over the course of 5 min.

After 1 hour at room temperature, the resulting mixture was poured onto 50 ml of water. The aqueous solution was extracted with ether (4x50 ml) and the combined ethereal layers were washed with saturated aqueous sodium bicarbonate (1x25 ml) and brine (1x25 ml) and were dried ($MgSO_4$). Evaporation to dryness and ptlc (50% ether-petroleum ether) gave: r.f. 0.2, 24 mg of aromatic material which displayed no angular methyl signals in the nmr and r.f. 0.4, 46 mg (82%) of recovered starting material.

4aα,8aβ-Dimethyl-5,5-Ethylenedioxo-1-(2'-m-Methoxyphenylethyl)-3,4,4a,5,6,7,8,8a-Octahydronaphthalene (O-5).

A dry 25 ml flask fitted with a condenser, dropping funnel, and a serum cap was flushed with nitrogen and charged with a solution of 5.0 mmoles of n-butyl lithium (2.0 ml of a 2.5M solution in hexane as supplied by Alpha Inorganics, Inc.) in 8.0 ml of dry ether. A solution of 931 mg (7.05 mmoles) of m-methoxyphenylacetylene (121) in 3 ml of dry ether was added over the course of 5 min while a vigorous, exothermic reaction transpired. The

solution initially turned yellow, but became a milky color near the end of the addition. After an additional 5 min, a solution of 76 mg (0.32 mmole) of the ketone O-2 in 3 ml of dry ether was introduced through the serum cap with a syringe. After 4 hours, no further change in the peak representing starting material was discernible by glpc so 0.5 ml of 10% aqueous ammonium chloride solution was added carefully followed by 15 ml of water. The aqueous layer was extracted with ether and the organic layer was washed with water and brine. Drying ($MgSO_4$) and evaporation to dryness afforded 828 mg of a yellow oil. Ptlc (40% ether-petroleum ether) gave 102 mg of an oil which consisted of 60% of the addition product and 40% of the starting ketone by nmr integration of the methoxyl region. In another experiment, carried out at -78°, a 50-50 mixture of products was obtained.

The hydrogenation was conducted according to the procedure of Barltrop and Rogers (89). The crude mixture from above was dissolved in 5 ml of reagent ethyl acetate and was hydrogenated 1 hour in the presence of 30 mg of 10% palladium on carbon at one atmophere. Filtration through celite and concentration yielded 78 mg of a mixture of the tert-alcohol O-4 and the starting ketone which was not conveniently separable by ptlc.

To a solution of 150 mg (0.52 mmole) of the crude reduction product from above (combined product from two

experiments), in 5 ml of dry pyridine cooled in an ice bath, was added 0.20 ml (2.8 mmoles) of thionyl chloride. The yellow solution was stirred 50 min at 0° and poured onto 25 ml of ice and water. The aqueous layer was extracted with ether and the ethereal phase was washed with water, then brine and was dried ($MgSO_4$). Evaporation to dryness and ptlc (30% ether-petroleum ether) gave two bands, r.f. 0.5, 45 mg (28%) of starting ketone O-2, and r.f. 0.7, 68 mg (38% based on starting ketone) of the desired olefin O-5. Ptlc (30% ether-petroleum ether) of a portion and flash distillation at 0.005 mm afforded the analytical sample: ir ($CHCl_3$) 1600, 1585 (Ph); nmr ($CDCl_3$) 1.10δ (s, 3, C-4a-CH_3), 1.25δ (s, 3, C-8a-CH_3), 3.78-4.08δ (m, 7, ketal and O-CH_3), 5.15-5.35δ (m, 1, vinyl), 6.62-7.37δ (m, 4, Ph).

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.35; H, 9.15.

4aα,8aβ-Dimethyl-5,5-Ethylenedioxo-1β-(2'-m-Methoxyphenyl-ethyl)-1α,4,4a,5,6,7,8,8a-Octahydro-2(3H)-Naphthalenone (L-4).

The hydroboration was carried out according to the general procedure of Brown and Zweifel (122). To a solution of 165 mg (0.464 mmole) of olefin O-5 in 4 ml of dry tetrahydrofuran was added 3.0 ml (3 mmoles) of a 1M solution of borane in tetrahydrofuran under a nitrogen atm. The reaction mixture was stirred 50 min, cooled to 0°, and the remaining borane was destroyed by the careful addition of 0.20 ml of

water, followed by 2.0 ml 3N sodium hydroxide and 2.0 ml of 30% hydrogen peroxide. After an additional 45 min, the resultant mixture was diluted with 25 ml of 10% aqueous potassium carbonate and extracted with ether. The etheral solution was washed with water and brine, dried ($MgSO_4$), and evaporated to dryness to give 107 mg of an oil. Ptlc (40% ether-petroleum ether) gave three bands: r.f. 0.2, 63 mg (37%) of the desired alcohol O-6; r.f. 0.3, 49 mg (28%) of a complicated mixture; and r.f. 0.5, 43 mg (16%) of recovered starting material. Longer reaction times lead to lower yields: ir ($CHCl_3$) 3600 (OH), 1600, 1585 (Ph): nmr ($CDCl_3$) 1.07δ (s, 3, C-4a-CH_3), 1.42δ (s, 3, C8a-CH_3), 3.67-4.07δ (m, 8, ketal, O-CH_3, C<u>H</u>-OH), 6.60-7.37δ (m, 4, Ph).

To an ice cold solution of 63 mg (0.168 mmole) of the alcohol O-6 from above in 5 ml of acetone, (freshly distilled from potassium permanganate), was added 0.06 ml (0.24 meqv) of 8N chromic acid solution (62). After 2 min, the mixture was diluted with 20 ml of water, and was extracted with ether. The ethereal solution was washed with saturated aqueous sodium bicarbonate and brine and was dried ($MgSO_4$). Evaporation to dryness afforded 62 mg (37% from the olefin O-5) of the ketone L-4. Ptlc (50% ether-petroleum ether) and flash distillation (0.15 mm) gave the analytical sample: ir ($CHCl_3$) 1695 (C=O), 1600, 1585 (Ph); nmr ($CDCl_3$) 1.05δ (s, 3, C-4a-CH_3), 1.23δ (s, 3, C-8a-CH_3), 3.60-3.97δ (m,

7, ketal and O-CH_3), 6.60-7.40δ (m, 4, Ph).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.17; H, 8.79.

Attempted Methylation of Ketone L-4

To a suspension of 50 mg (2.06 mmoles) of magnesium shavings in 2.0 ml of dry ether under nitrogen was added dropwise a solution of 0.11 ml (1.75 mmoles) of iodomethane (freshly distilled from anhydrous calcium sulfate) in 4 ml of dry ether so as to maintain spontaneous refluxing. The mixture was stirred an additional 15 min at room temperature, cooled in an ice bath, and a solution of 63.3 mg (0.170 mmole) of the ketone L-4 in 4 ml of dry ether was added over the course of 10 min. After 0.5 hours at 0° and 2 hours at room temperature, the excess Grigrand was decomposed with 0.2 ml of 10% aqueous ammonium chloride, the solution was diluted with 100 ml of ether, and the ethereal phase was washed with water and brine.

Drying ($MgSO_4$) and concentration yielded 65 mg of a slightly yellow oil whose nmr revealed no discernible product besides starting material.

Other attempts involved the use of methyl magnesium iodide and methyl lithium at room temperature and -78°. Dimethyl magnesium, generated by addition of a stoichiometric amount of dry dioxane to an ethereal solution of methyl magnesium iodide(84),was also employed at 0° and

-78°, all with similarly negative results.

5α,4a-Methano-5β-Methoxy-8aβ-Methyl-3,4,4a,5,6,7,8,8a-Octahydro-1(2H)-Naphthalenone (P-1).

To an ice cold solution of 240 mg (1.22 mmoles) of the axial alcohol N-5 in 45 ml of acetone (freshly distilled from potassium permanganate) was added 0.40 ml (1.60 meqv) of 8N chromic acid solution (62) over a period of 3 min. After 3 min, 0.20 ml of isopropyl alcohol and 5 ml of saturated aqueous sodium bicarbonate solution were added and most of the acetone was removed *in vacuo*. The residual green mass was dissolved in 30 ml of water and was extracted with ether (4x50 ml). The combined organic layers were washed with brine (2x50 ml) and were dried ($MgSO_4$). Evaporation to dryness and ptlc (30% ether-petroleum ether) afforded 174 mg (73%) of a white crystalline solid mp 60.5-62°. Crystallization from hexane and sublimation (55°, 0.005 mm) provided the analytical sample mp 61-62°: ir ($CHCl_3$) 3075 (cyclopropane), 1705 (C=O), 1055 (C-O); nmr ($CDCl_3$) 0.38δ (d, 1, J=5.5 Hz, cyclopropane), 0.60δ (d, 1, J=5.5 Hz, cyclopropane), 1.38δ (s, 3, C-8a-CH_3), 3.27δ (s, 3, O-CH_3).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 76.70; H, 9.36. Found: C, 76.64; H, 9.47.

1,2,3,4,4a,5,6,7,8,8a-Decahydro-5α,4a-Methano-5β-Methoxy-8aβ-Methyl-1β-(2'-phenylethyl)-1α-Naphthol (M-3, R=H).

Benzyl Grignard was prepared using the general method of Prout (123). Freshly distilled benzyl chloride 0.90 ml (7.8 mmoles) in 9 ml of dry tetrahydrofuran was added over 10 min to a suspension of 191 mg (7.97 mmoles) of magnesium shavings in 6 ml of dry ether under an atmosphere of nitrogen. The Grignard solution was refluxed 15 min and cooled; 9.0 ml of dry tetrahydrofuran and 0.70 ml (8.2 mmoles) of dry dioxane were injected and the resulting precipitate was allowed to settle 20 min (84). The supernatant was removed with a syringe and introduced into a flask containing 207 mg (1.00 mmole) of the oxirane M-1 in 2 ml of dioxane under nitrogen. The reaction mixture was refluxed 1.5 hours, cooled, and poured into 20 ml of water. The aqueous solution was extracted with ether, and the ethereal layer was washed with water and brine, and was dried ($MgSO_4$). Evaporation to dryness afforded 385 mg of an oil which was chromatographed on 20 g of alumina: 100 ml of petroleum ether gave 56 mg of bibenzyl. Elution with 100 ml of 10% ether-petroleum ether afforded 39 mg (18%) of starting oxirane, and 50 ml of ether eluted 250 mg (82%) of the desired enol ether alcohol M-2, R=H contaminated with two minor impurities according to glpc: ir ($CHCl_3$) 3550 (broad, weak) (OH), 1660 (C=C), 1595 (Ph); nmr ($CDCl_3$ + 1 drop pyrine) 1.13δ (s, 3, C-8a-CH_3), 3.52δ (s, 3, O-CH_3), 7.23δ (s, 5, Ph). The alcohol is quite sensitive and was

used directly in the next step.

Cyclopropylation

To a solution of the Simmons-Smith reagent (53) prepared from 600 mg (8.5 mmoles) of zinc-copper couple (52) and 0.64 ml (7.9 mmoles) of diiodomethane in 10 ml of dry ether was added all at once a solution of 237 mg (0.79 mmoles) of the alcohol M-2, R=H in 3 ml of dry ether and 0.7 ml (6.7 mmoles) of dry 1,2-dimethoxyethane. After 40 min at room temperature, the reaction mixture was cooled in an ice bath and was quenched with 1.0 ml of water. The solution was poured into 20 ml of water, extracted with ether and the organic phase was washed with saturated aqueous potassium carbonate and brine and was dried ($MgSO_4$). Evaporation to dryness and ptlc (20% ether-petroleum ether) gave two products. The slower moving band, r.f. 0.3 contained 131 mg (45% from the oxirane M-1) of the desired cyclopropane. Glpc indicated a minor impurity that could not be removed conveniently by ptlc under a variey of conditions so a 90 mg (0.30 mmole) portion was dissolved in 20 ml of cold acetone and treated with 0.1 ml (0.4 meqv) of 8N chromic acid solution (62). The mixture was poured into saturated aqueous sodium bicarbonate, and was extracted with ether. The ethereal layer was washed with water and brine and was dried ($MgSO_4$). Evaporation to dryness and ptlc (20% ether-petroleum ether, 2 elutions)afforded 59 mg (66%) of

the pure alcohol. Evaporative distillation (155°, 0.01 mm) gave the analytical sample: ir ($CHCl_3$) 3590 (OH), 1605 (Ph); nmr ($CDCl_3$) 0.52δ (d, 1, J=5 Hz, cyclopropane), 0.83δ (d, 1, J=5 Hz, cyclopropane), 1.15δ (s, 3, C-8a-CH_3), 3.27δ (s, 3, O-CH_3), 7.20δ (s, 5, Ph).

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.14; H, 9.45.

1,2,3,4,4a,5,6,7,8,8a-Decahydro-5α,4a-Methano-5β-Methoxy-1β-(2'-m-methoxyphenylethyl)-8aβ-Methyl-1α-Naphthol (M-3, R=Ome).

A. Oxirane Cleavage

Grignard

A dry, 50 ml flask fitted with a serum cap, reflux condenser, and dropping funnel was flushed with nitrogen and charged with a suspension of 313 mg (12.9 mmoles) of magnesium shavings in 5 ml of dry ether. A solution of 1.867 g (11.9 mmoles) of m-methoxybenzyl chloride (124) in 5 ml of dry ether was run in over the course of 15 min while the mixture refluxed spontaneously. After an additional 30 min reflux, 10 ml of dry tetrahydrofuran was introduced followed by 10 ml (11.7 mmoles) of dry dioxane (84). After 2 min, stirring was halted and the precipitate was permitted to settle 10 min. Titration of an aliquot with s-butyl alcohol in xylene using 1,10-phenanthrolene as indicator as described by Watson and Eastham (85) indicated the solution was 0.26M in dialkymagnesium. The supernatant, 13 ml (3.4

mmoles), was transferred with a syringe to a flask containing a solution of 200 mg (0.96 mmole) of the oxirane M-1 in 1 ml of dry dioxane under nitrogen. The reaction mixture was refluxed 65 min, cooled, quenched with 1 ml of water, and poured into 50 ml of water. The aqueous solution was extracted with ether and the ethereal layer was washed with water and brine and was dried ($MgSO_4$). Evaporation to dryness afforded 411 mg of an oil which was chromatographed on 20 g of alumina: 60 ml of petroleum ether eluted 119 mg of 3,3'-dimethoxybibenzyl; 60 ml of 10% ether-petroleum ether gave 74 mg (37%) of recovered starting material, and further elution with 80 ml of ether afforded 181 mg (57%) of the desired alcohol M-2, R=Ome which was 65% pure by nmr integration of the methoxyl regions: ir ($CHCl_3$) 3550-3500 (broad, w) (OH), 1665 (C=C), 1600, 1585 (Ph); nmr ($CDCl_3$ + 1 drop-pyridine), 1.13δ (s, 3, C-8a=CH_3), 3.50δ (s, 3, O-CH_3), 3.82δ (s, 3, PhOCH_3). The product is extremely labile and was used directly in the cyclopropylation. The yield from the grignard was highly variable ranging from 29-86% based on consumed starting material. In one experiment the alcohol M-2, R=Ome was obtained free of impurities; in this case the cyclopropylation proceeded well. In other instances poor yields were realized.

Cyclopropylation

To a solution of the Simmons-Smith reagent (53) prepared

from 1.168 g (16.7 mmoles) of zinc-copper couple (52) in 17 ml of dry ether and 1.30 ml (16.2 mmoles) of diiodomethane was added a solution of 520 mg (1.57 mmoles) of the alcohol M-2, R=OMe (obtained free of impurities from one grignard experiment) in 1.75 ml (16.7 mmoles) of dry 1,2-dimethoxyethane in 5 ml of dry ether under a nitrogen atmosphere. After 50 min at room temperature the excess reagent was quenched with 0.5 ml of water and the mixture was poured onto 35 ml of saturated aqueous potassium carbonate. The aqueous layer was extracted with ether and the combined organic layers were washed with brine before drying ($MgSO_4$). Evaporation to dryness and ptlc (20% ether-petroleum ether) gave two products. The first, r.f. 0.2, 352 mg (66%), was the desired cyclopropane M-3, R=OMe. A portion was further purified by ptlc (20% ether-petroleum ether) and the oil was flash distilled (0.01 mm) to give the analytical sample: ir ($CHCl_3$) 3600 (OH), 1600, 1585 (Ph); nmr ($CDCl_3$) 0.50δ (d, 1, J=5, cyclopropane), 0.80δ (d, 1, J=5 Hz, cyclopropane), 1.13δ (s, 3, -C8a-CH_3), 3.22δ (s, 3, OCH_3), 3.77δ (s, 3, $PhOCH_3$), 6.57-7.37δ (m, 4, Ph).

Anal. Calcd for $C_{22}H_{30}O_3$: C, 76.70; H, 9.36. Found: C, 76.62; H, 9.22.

The second band, r.f. 0.7, 42 mg (8%), contained 1,2,3,4,4aβ,5,6,7,8,8a-decahydro-5β-methoxy-1β-(2'-m-methoxyphenylethyl)-8aβ-methyl-1α-naphthol ketal (M-4, R=OMe), which was

purified by ptlc (20% ether-petroleum ether) and flash distillation (0.01 mm) to afford the analytical sample: ir ($CHCl_3$) 1600, 1585 (Ph), 1155, 1085 (C-O); nmr ($CDCl_3$) 0.95δ (s, 3, C-8a-CH_3), 3.37δ (s, 3, O-CH_3), 3.77δ (s, 3, PhO$\underline{CH}_3$), 6.53-7.25δ (m, 4, Ph).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.36; H, 9.20.

B. From Ketone P-1 with 2-m-Methoxyphenylethyl Grignard

A dry 25 ml flask was flushed with nitrogen and charged with a suspension of 34 mg (1.4 mmoles) of magnesium shavings in 1.0 ml of dry ether. A solution of 220 mg (1.02 mmoles) of 2-m-methoxyphenylethyl bromide (120) in 2.0 ml of ether was added dropwise so as to maintain a steady reflux. Reflux was continued 5 min following the addition, the solution was cooled to 25°, and 47.3 mg (0.228 mmole) of cyclopropyl ketone P-1 in 2.0 ml of ether was added all at once. After 1 hour the reaction was quenched with 0.3 ml of saturated aqueous ammonium chloride and the product was poured into 25 ml of water. The aqueous solution was extracted with ether. The ethereal solution was washed with water and brine and was dried ($MgSO_4$). Concentration and ptlc (40% ether-petroleum ether) gave two bands. The slower moving band, r.f. 0.2, consisted of 18.4 mg (24%) of a mixture of at least two components and was not further examined. The faster band, r.f. 0.4, 45.5 mg (58%) contained

a 1:1 mixture of the desire addition compound M-3, R=OMe and the axial alcohol N-5.

C. From Ketone P-1 with m-Methoxyphenylacetylene

A solution of 3.0 ml of a 2.5M solution of n-butyl lithium in hexane (Alpha Inorganics, Inc.) in 20 ml of dry ether was placed in a dry 50 ml flask fitted with a serum cap, a reflux condenser, and a dropping funnel under a nitrogen atmosphere. A solution of 3.2 g (10 mmoles) of m-methoxyphenylacetylene (121) in 7 ml of dry ether was added dropwise resulting in a vigorous exothermic reaction. The initially yellow solution became a characteristic milky white near the end of the addition. After 5 min, 287 mg (1.38 mmoles) of the cyclopropyl ketone P-1 in 4 ml of dry ether was introduced with a syringe and the resulting mixture was stirred 1 hour. The excess acetylide was decomposed with 0.5 ml 10% aqueous ammonium chloride, and the mixture was poured into 50 ml of water and was extracted with 200 ml of ether. The ethereal solution was washed with saturated sodium chloride (1x25 ml), and dried ($MgSO_4$). Evaporation to dryness and Ptlc (50% ether-petroleum ether) yielded 455 mg (96%) of a yellow oil. The crude product was taken up in 10 ml of ethyl acetate and was hydrogenated (89) over 200 mg of 10% palladium on carbon under 1 atmosphere of hydrogen for 1 hour. Filtration through Celite, evaporation to dryness , and ptlc (50% ether-petroleum ether) revealed

two components. The more polar band r.f. 0.3, 204 mg (46%) contained the equatorial alcohol P-2 mp 95-98°. Crystallization from ether-n-heptane gave the analytically pure sample mp 100.5-101.5°: ir ($CHCl_3$) 3610 (OH), 1600, 1585 (Ph); nmr ($CDCl_3$) 0.53δ (m, 2, cyclopropane), 1.25δ (s, 3, C-8a-CH_3), 3.23δ (s, 3, O-CH_3), 3.80δ (s, 3, PhOCH_3), 6.57-7.37δ (m, 4, Ph).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.64; H, 9.17.

The second band, r.f. 0.4, 192 mg (44%) contained the desired axial alcohol M-3, R=OMe which was the same as that obtained in Part A above.

4aα,8aβ-Dimethyl-3,4,4a,7,8,8a-Hexahydro-1-(2'-m-Methoxyphenylethyl)-5(6H)-Naphthalenone (M-5).

A solution of 181 mg (0.525 mmoles) of the cyclopropyl alcohol M-3, R=OMe in 1.5 ml of 37-38% hydrochloric acid and 15 ml of methanol was refluxed 4 hours. The solution was poured into 25 ml of saturated aqueous sodium bicarbonate and was extracted with ether (5x25 ml). The combined organic layers were washed with water (1x25 ml), saturated aqueous sodium bicarbonate (1x25 ml), and brine (1x25 ml), and were dried ($MgSO_4$). Evaporation to dryness yielded 159 mg; ptlc (20% ether-petroleum ether) gave a band r.f. 0.3 containing 89 mg (46%) of M-5 as a colorless oil contaminated with about 20% of the exocyclic olefin. A

portion was further purified by ptlc (20% ether-petroleum ether) and flash distilled (0.01 mm) for the analytical sample: ir ($CHCl_3$) 1695 (C=O), 1600, 1585 (Ph); nmr ($CDCl_3$) 1.02δ (s, 3, C-8a-CH_3), 1.20δ (s, 3, C-4a-CH_3), 3.80δ (s, 3, PhOC$\underline{H}_3$), 5.22-5.37δ (m, 1, vinyl), 6.58-7.42δ (m, 4, Ph).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.65; H, 9.11.

1,2,3,4,4a,5,6,7,8,8a-Decahydro-1-(2'-m-Methoxyphenylethylidene)-5α,4a-Methano-5β-Methoxy-8aβ-Methylnaphthalene (P-4).

To a solution of 204 mg (0.594 mmole) of the equatorial alcohol P-2 in 5 ml of dry pyridine at -10° (ice-salt bath) was added 0.25 ml (3.44 mmoles) thionyl chloride. The reaction mixture was stirred in the cold 45 min and was poured into 200 ml of ether. The ethereal solution was washed with water, saturated aqueous sodium bicarbonate, and brine, and was dried ($MgSO_4$). Concentration and ptlc (20% ether-petroleum ether) gave r.f. 0.6, 82 mg (43%) of an olefin different from that obtained below from the axial alcohol. Rechromatography and flash distillation (0.01 mm) gave the analytical sample: ir ($CHCl_3$) 1665 (C=C), 1600, 1585 (Ph), 1055 (C-O); nmr ($CDCl_3$) 0.37δ (m, 2, cyclopropane), 1.28δ (s, 3, C-8a-CH_3), 3.23δ (s, 3, O-CH_3), 3.77δ (s, 3, PhOC$\underline{H}_3$), 5.00-5.33 (m, 1, vinyl), 6.57-7.33δ (m, 4, Ph).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found:

C, 80.82; H, 9.20.

5α,4a-Methano-5β-Methoxy-1-(2'-m-Methoxyphenylethyl)-8aβ-Methyl-3,4,4a,5,6,7,8,8a-Octahydronaphthalene (P-3).

To a solution of 317 mg (0.92 mmole) of the axial alcohol M-3, R=OMe in 7 ml of dry pyridine cooled to -10° (ice-salt bath) was added 0.35 ml (4.5 mmoles) of thionyl chloride. After 45 min, the reaction mixture was diluted with 300 ml of ether and was washed with water, saturated aqueous sodium bicarbonate, and brine. Drying ($MgSO_4$), evaporation and ptlc (20% ether-petroleum ether) afforded 241 mg (91%) of the endocyclic olefin P-3. Further purification of 31 mg by ptlc (20% ether-petroleum ether) and flash distillation gave the analytical sample: ir ($CHCl_3$) 1600, 1585 (Ph), 1155 (C-O); nmr ($CDCl_3$) 0.35δ (d, 1, J=5 Hz, cyclopropane) 0.62δ (d, 1, J=5 Hz, cyclopropane), 1.27δ (s, 3, C-8a-CH_3), 3.23δ (s, 3, OCH_3), 3.77δ (s, 3, $PhOCH_3$), 5.30-5.50δ (m, 1, vinyl), 6.57-7.37δ (m, 4, Ph).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 81.17; H, 9.13.

1α,2β,3,4,4a,5,6,7,8,8a-Decahydro-5α,4a-Methano-5β-Methoxy-1β-(2'-m-Methoxyphenylethyl)-8aβ-Methyl-2α-Naphthol (P-5).

Employing the hydroboration procedure of Brown and Zweifel (122), a 50 ml flask was flushed with nitrogen and charged with a solution of 210 mg (0.645 mmole) of the endocyclic olefin P-3 in 6 ml of dry tetrahydrofuran,

followed by 2.0 ml of a 1M solution of borane in tetrahydrofuran. The reaction mixture was cooled to 0° after 1 hour and the borane was decomposed carefully with 0.5 ml of water, 3 ml of 3N sodium hydroxide, and 3 ml of 30% hydrogen peroxide. After an additional 45 min, the mixture was poured into 30 ml of 10% aqueous potassium carbonate and was extracted with ether (4x50 ml). The combined organic layers were washed with water (2x20 ml) and brine (1x20 ml) and were dried ($MgSO_4$). Ptlc (50% ether-petroleum ether) gave two bands. The first, r.f. 0.2, contained 185 mg (84%) of the secondary alcohol, P-5 which crystallized on standing mp 90-97°. Crystallization from ether-hexane and further purification by ptlc (50% ether-petroleum ether) gave analytically pure material mp 100-102° (amorphous solid): ir ($CHCl_3$) 3600 (OH), 1602, 1585 (Ph), 1155 (C-O); nmr ($CDCl_3$) 0.35δ (d, 1, J=5, cyclopropane), 0.58δ (d, 1, J=5, cyclopropane), 0.98δ (s, 3, C-8a-CH_3), 3.20δ (s, 3, O-CH_3), 3.75δ (s, 3, PhOCH_3), 6.57-7.18δ (m, 4, Ph).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.87; H, 9.37.

The second band, r.f. 0.3, consisted of 21 mg (10%) of approximately equimolar protions of the starting olefin P-3, the equatorial alcohol P-2, and a third, unidentified compound.

5α,4a-Methano-5β-Methoxy-1β-(2'-m-Methoxyphenylethyl)-8aβ-Methyl-1α,2,3,4,4a,7,8,8a-5(6H)-Napthalenone (P-6).

To an ice cold solution of 164 mg (0.476 mmole) of secondary alcohol P-5 in 15 ml of acetone (freshly distilled from potassium permanganate) was added 0.15 ml (0.60 meqv) of 8N chromic acid solution (62). After 5 min, 0.10 ml of isopropyl alcohol was added and most of the acetone was removed in vacuo. The green residue was dissolved in 25 ml of saturated aqueous sodium bicarbonate and was extracted with ether (5x30 ml). The combined ether layers were washed with water and brine (1x20 ml). Drying ($MgSO_4$) and evaporation to dryness afforded 164 mg (100%) of a pale yellow oil. Ptlc (50% ether-petroleum ether) gave two bands; the more polar r.f. 0.2, contained 21 mg (13%) of the equatorial alcohol P-2 which occurred as an impurity in the starting material. The faster moving band r.f. 0.3 contained 130 mg (74%) of the ketone P-6 which gave waxy crystals on standing; two crystallizations from ether-heptane gave the analytical sample mp 108-110°: ir ($CHCl_3$) 1700 (C=O), 1600, 1585 (Ph), 1155 (C-O); nmr ($CDCl_3$) 0.67δ (m, 2, cyclopropane), 0.90δ (s, 3, C-8a-CH_3), 3.23δ (s, 3, O-CH_3), 3.77δ (s, 3, PhOCH_3), 6.57-7.27δ (m, 4, Ph).

Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.16; H, 8.83. Found: C, 77.23; H, 8.87.

1α,2,3,4,4a,5,6,7,8,8a-Decahydro-2α,8aβ-Dimethyl-5α,4a-Methano-5β-Methoxy-1β-(2'-m-Methoxyphenylethyl)-2β-Naphthol (P-7).

To 1.4 ml (3.3 mmoles) of a 2.4M solution of methyl lithium in ether (Alpha Inorganics, Inc.) in 10 ml of dry ether at 0° (ice bath) and under a nitrogen atmosphere was added a solution of 109 mg (0.318 mmoles) of the ketone P-6 in 4 ml dry ether. After 10 min, 0.5 ml of water was introduced carefully and the reaction mixture was diluted to 200 ml with ether. The ethereal solution was washed with water (1x20 ml) and brine (1x20 ml) and was dried ($MgSO_4$). Evaporation to dryness and ptlc (50% ether-petroleum ether) gave 102 mg (90%) of white crystals mp 87-101°. Two crystallizations from ether-hexane gave a pure sample mp 106.5-107.5: ir ($CHCl_3$) 3605 (OH), 1600, 1585 (Ph), 1155 (C-O); nmr ($CDCl_3$) 0.30δ (d, 1, J=5 Hz, cyclopropane), 0.63δ (d, 1, J=5 Hz, cyclopropane), 1.40δ (s, 6, C-4a and C-8a methyls), 3.25δ (s, 3, O-CH_3). 3.78δ (s, 3, PhOCH_3), 6.57-7.37δ (m, 4, Ph).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.19; H, 9.63.

8aβ-Cyano-1,2,3,4,4a,5α,6,7,8,8a-Decahydro-2α,4aα-Dimethyl-1β-(2'-m-Methoxyphenylethyl)-2β,5β-Naphthalenediol

A dry 2 l. flask fitted with a mechanical stirrer, a 500 ml addition funnel, and an efficient reflux condenser

topped with an argon inlet was charged with 15.7 g (0.645 mole) of magnesium turnings and was flushed with argon. The magnesium was suspended in 50 ml of dry ether and a solution of 34 ml (0.55 mmole) of methyl iodide (previously distilled from phosphorous pentoxide) in 300 ml of dry ether was added over 1 hour so as to maintain a vigorous reflux. The dark Grignard solution was cooled in an ice bath, and a solution of 19.80 g (58 mmoles) of 8aβ-cyano-5α-hydroxy-1β-(2'-m-methoxyphenylethyl)-4aα-methyl-3,4,4a,5,6,7,8,8a-octahydro-2(1H)-naphthalenone (Q-7) [prepared according to the procedure of Kowalski (90)] in 300 ml of dry benzene was added over the course of 45 min. After an additional 45 min the excess reagent was destroyed by the careful addition of 15 ml of saturated aqueous ammonium chloride solution, and the reaction mixture was partitioned between 600 ml of methylene chloride and 1000 ml of water. The layers were separated and the aqueous layer was extracted with methylene chloride (4x600 ml). The combined organic layers were washed with 1% aqueous ammonium chloride solution (2x500 ml) and water (2x500 ml) and were dried ($MgSO_4$).

Evaporation to dryness afforded 20.80 g (quantitative) of a white crystalline solid, mp 171-175° (lit (90) 175-178°). The ir spectrum of the product showed no carbonyl stretch and was identical to that of the authentic diol.

8aβ-Cyano-1,2,3,4,4a,5α,6,7,8,8a-Decahydro-2α,4aα-Dimethyl-1β-(2'-m-Methoxyphenyl)-2β,5α-Naphthalenediol 5-Acetate.

Employing the procedure developed by C. Kowalski (90), a solution of 20.80 g (58 mmoles) of the diol from above in 400 ml of dry pyridine was placed in a 1 l. flask under an argon atmosphere and 150 ml (1.59 moles) of acetic anhydride were introduced all at once. After 22 hours at room temperature the reaction mixture was diluted with 2 l. of ethyl acetate and 1 l. of ether and was washed with water (2x500 ml), saturated aqueous sodium bicarbonate (3x500 ml) and brine (1x500 ml) and was dried over $MgSO_4$.

Evaporation to dryness afforded 23.17 g (quantitative) of white crystals mp 162-165° [lit (90) 163-165°] whose ir spectrum was identical to that of authentic material.

8aβ-Cyano-2,4aα-Dimethyl-1β-(2'-m-Methoxyphenylethyl)-3,4,4a,5α,6,7,8,8a-Octahydro-5α-Naphthol Acetate (Q-8).

Following the procedure of Kowalski (90), a solution of 23.17 g (58 mmoles) of the cyanoacetate from above in 450 ml of dry pyridine was placed in a 1 l. flask under argon. The solution was cooled in an efficient ice bath and 25 ml (344 mmoles) of thionyl chloride were added dropwise over 30 min. The reaction mixture was held at 0° for 75 min and then was allowed to warm to room temperature over 45 min. The resulting brown solution was poured onto 2 l. of ethyl acetate, 1 l. of ether, and 500 ml of ice and

water. The layers were separated and the organic layer was washed with saturated aqueous sodium bicarbonate (2x500 ml), water (1x500 ml) and brine.

The solution was dried ($MgSO_4$) and evaporated to dryness to give 22.77 g of brown sticky crystals. Crystallization from ethanol gave 14.03 g (63.5%) mp 95-108° (vacuum) [lit (90) 89-108°] of white crystals consisting mainly of the Δ^1 isomer. The mother liquors were chromatographed on 800 g of silica gel; 1500 ml of ethyl acetate eluted 109 mg of an oil which did not have any high boiling components by glpc. Further elution with 3.5 l. of ethyl acetate gave 7.48 g (34%) of a colorless oil consisting of a mixture of double bond isomers which was identical by ir to the product prepared by Kowalski (90).

The overall yield of Q-2 for the three steps was 97.5%.

1β(2'-m-Methoxyphenylethyl)-3,4,4a,5α,6,7,8,8a-Octahydro-2, 4aα,8aβ-Trimethyl-5α-Naphthol (Q-9).

Following a modification of the procedure developed by Kowalski (90), a solution of 3.65 g (9.58 mmoles) of the cyanoacetate P-8, mp 95-108°, in 140 ml of dry ether was placed in a 1 l. flask. The atmosphere was replaced with argon and 25 ml (37.5 mmoles) of a 1.50M solution of diisobutyl aluminum hydride in benzene (used as supplied by Texas Alkyls, Inc.) was introduced all at once; the reaction mixture became slightly warm initially. After

2.5 hours at room temperature the reaction mixture was poured onto 500 ml of 10% aqueous potassium hydroxide and ice and the aqueous solution was extracted with ether (4x400 ml). The combined organic layers were washed with 2% aqueous potassium hydroxide (1x400 ml) and were dried ($MgSO_4$).

The solution was concentrated and the residue was dissolved in 140 ml of triethylene glycol (previously distilled under vacuum) and the solution was placed in a 300 ml three neck flask which was fitted with a claisen adaptor containing an argon inlet and a thermometer, a magnetic stir bar, a ground glass stopper, and a 14/20 short path still leading to a 65 ml flask. The vacuum adaptor on the still was plugged with the system under argon, 15.5 ml of 99% hydrazine hydrate and 4.6 g of hydrazine dihydrochloride were added, and the internal temperature was raised to 130-135°. After 5 hours the solution was cooled slightly, the plug was removed, and with a vigorous stream of argon flowing through the system, 30 g of 85% potassium hydroxide was added in portions over 15 min. The internal temperature was then raised to 150-155°, and after 1 hour the plug in the still was replaced. Heating was continued an additional 5 hours under argon and the reaction mixture was allowed to cool overnight.

The resulting white mush was dissolved in 700 ml of water and the aqueous solution was extracted with ether (4x400 ml). The combined organic layers were washed with

water (7x300 ml) and brine (1x300 ml) and were dried ($MgSO_4$).

The solution was concentrated and the residue was chromatographed on 160 g of silica gel; 600 ml of 50% ether-petroleum ether eluted 39 mg of volatile material. Further elution with 1000 ml of the same solvent gave 2.23 g (71%) of the desired product whose ir spectra was identical to that of authentic material (90).

The rest of the cyanoacetate prepared above was converted to Q-9 in several runs of 1-6 g giving 66-70% yields.

3,4,4a,7,8,8a-Hexahydro-1-(2'-m-Methoxyphenylethyl)-2,4aα, 8aβ-Trimethyl-5(6H)-Naphthalenone (P-8).

A solution of 60.5 mg (0.169 mmole) of the alcohol P-7 in 8 ml of methanol and 2.0 ml of 37-38° hydrochloric acid was refluxed under an argon atmosphere 2 hours. The course of the reaction was followed by tlc (30% ether-petroleum ether); the spot for the alcohol r.f. 0.3 was quickly replaced by one r.f. 0.7 corresponding to an intermediate olefin which formed the product olefin r.f. 0.6 over 2 hours. The reaction mixture was diluted to 150 ml with ether and was washed successively with water (1x30 ml), saturated aqueous sodium bicarbonate (2x30 ml) and brine (1x 30 ml). Drying ($MgSO_4$), evaporation to dryness, and ptlc (30% ether-petroleum ether) afforded 50 mg (91%) of a colorless oil, consisting of a 71:29 mixture of Δ^1 and Δ^2 isomeric olefins by nmr integration of the angular methyl region,

which crystallized on seeding, mp 60-87° [lit(90) 63-98°): ir ($CHCl_3$) 1700 (C=O), 1600, 1585 (Ph), 1155 (C-O); nmr ($CDCl_3$) 0.68δ (s, 0.85, C-8a-CH_3, Δ^2-isomer), 0.97δ (s, 2.15, C-8a-CH_3, Δ^1-isomer), 1.08δ (s, 0.85, C-4a, Δ^2-isomer), 1.17δ (s, 2.15, C-4a-CH_3, Δ^1-isomer), 1.65δ (s, 3, C-2 CH_3), 3.80δ (s, 3, $PhOCH_3$), 6.60-7.40δ (m, 4, Ph).

4a,5,6,6a,9,10,10a,10bα,11,12-Decahydro-2-Methoxy-7(8H)-Oxo-4bβ,6aα,10aβ-Trimethylchrysene (P-9).

A. From P-8 with p-Tolulenesulfonic Acid in Tolulene

A 25 ml flask fitted with a Dean-Stark water separator prefilled with anhydrous calcium sulfate and dry tolulene was flushed with argon and charged with 67.0 mg (0.205 mmole) of the mixture of olefins from above and 100 mg of p-tolulene-sulfonic acid in 5 ml of dry tolulene. The solution was refluxed 1 hour, 100 mg of the acid were added, and reflux was continued for 1 hour. The reaction mixture was cooled, diluted with 200 ml of ether, and washed with water (1x20ml) saturated aqueous sodium bicarbonate (1x20 ml) and brine (1x 20 ml). Drying ($MgSO_4$) and evaporation to dryness gave a dark brown oil; ptlc (30% ether-petroleum ether) afforded 52.3 mg (78%) of a white solid consisting of a 80:20 mixture of isomer P-9 and the cis, anti, trans isomer P-10 respectively, as determined by nmr integration of the angular methyl region. Recrystallization from ether yielded white crystals mp 141-148° (vacuum). Two further recrystallizations from ether provided the trans, anti, trans isomer mp 150-152° (vacuum),

which on admixture with a sample made by the hydrocyanation route (90) mp 150-152° (vacuum) gave mp 150-152° (vacuum) and on admixture of a sample made by the cation cyclization route (92), mp 150-152° (vacuum) gave mp 150-152° (vacuum): ir ($CHCl_3$) 1700 (C=O), 1605, 1500 (Ph); nmr ($CDCl_3$) 0.82δ (s, 3, C-4b-CH_3), 1.18δ (s, 3, C-10a-CH_3), 1.22δ (s, 3, C-6a-CH_3), 3.58δ (s, 3, $PhOCH_3$), 6.57-7.23δ (m, 3, Ph).

A sample of the trans-anti-trans isomer was recrystallized from ether-heptane, twice from 95% ethanol and finally from ether to give needles mp 153-154° (vacuum) which were submitted for x-ray analysis.

The mother liquors from a later experiment were purified by preparative vpc on a 1/4"x10' 20% SE-30 column heated to 290° with a helium flow of 70 ml/min. The compounds with retention times of 16 and 20 min were collected by passing the effluent gases through glass tubes packed with alumina. The product with retention time 20 min had a nmr spectrum which was identical with that of the trans-anti-trans obtained above.

The compound with a retention time of 16 min was freed from SE-30 by ptlc (50% ether-petroleum ether) and crystallized on scratching mp 125-134° (vacuum). Recrystallization from ethanol and flash sublimation at 0.1 mm gave the analytical sample of the cis-anti-trans isomer P-10, mp 136-

138° (vacuum): ir ($CHCl_3$) 1700 (C=O), 1605, 1500 (Ph); nmr ($CDCl_3$) 0.35δ (s, 3, C-10b-CH_3), 1.17δ (s, 3, C-4b-CH_3) 1.30δ (s, 3, C-12a CH_3), 3.75δ (s, 3, O-CH_3), 6.50-7.40δ (m, 3, Ph).

B. From alcohol Q-9 with trifluoroacetic acid.

To an ice cold solution of 3.86 g (10.4 mmoles) of the alcohol Q-9 obtained from two of the above runs in 250 ml of acetone which had been freshly distilled from potassium permanganate was added 5.0 ml of 8N chromic acid solution (62) over 5 min. After an additional 10 min, 5 ml of isopropyl alcohol were added and the reaction mixture was poured onto 500 ml of water. The organic solution was extracted with ether (4x300 ml) and the combined organic layers were washed with saturated aqueous sodium bicarbonate (2x300 ml) and brine (1x300 ml) and were dried ($MgSO_4$). Concentration afforded 3.93 g of a crude oil whose ir spectrum was identical with that of authentic material (90).

The crude ketone was dissolved in 45 ml of trifluoroacetic acid from a freshly opened bottle and the resulting dark solution was refluxed under an argon atmosphere for 4 hours. On cooling, the black reaction mixture was diluted with 500 ml of benzene and 500 ml of ether and the solution was washed with water (2x250 ml) and saturated aqueous sodium bicarbonate (3x250 ml) and was dried ($MgSO_4$).

Concentration gave 3.87 g (100%) of a brown solid which

was recrystallized from ethanol to give 2.29 g (60%) of the desired ketone mp 145-150° (vacuum). The crystals were better than 99% free of contamination by the cis, anti, trans isomer by glpc. The mother liquors consisted of an approximately equimolar mixture of the cis-anti-trans isomer P-10 and the trans-anti-trans isomer P-9 according to glpc analysis. Two other runs on the rest of the alcohol Q-9 prepared above gave 64 and 67% yields.

Attempted Reduction of the ketone P-9 with sodium borohydride.

A dry 25 ml flask fitted with an addition funnel was flushed with nitrogen and charged with a solution of 194 mg (0.594 mmole) of the ketone P-9 in 5 ml of abs ethanol. A solution of 39 mg (1.03 mmoles) of sodium borohydride in 7 ml of ethanol was added rapidly and the reaction mixture was stirred at room temperature for 3 hours. The excess reagent was decomposed by the careful addition of 0.5 ml of glacial acetic acid (gas evolved), and the mixture was concentrated in vacuo. The residue was taken up in 300 ml of benzene and was washed with water (3x50 ml) and brine (2x50 ml), and was dried ($MgSO_4$).

Evaporation to dryness afforded 186 mg (96%) of recovered starting material.

4b,5,6,6a,7,8,9,10,10a,10bα,11,12-Dodecahydro-7β-Hydroxy-2-Methoxy-4bβ,6aα,10aβ-Trimethylchrysene (S-1).

To a solution of 101.6 mg (0.311 mmole) of the ketone P-9

in 5 ml of dry tetrahydrofuran under a nitrogen atmosphere was added 53 mg (1.4 mmoles) of lithium aluminum hydride. After 3 hours at room temperature the reaction mixture was diluted with 10 ml of ether and the excess hydride was decomposed by the careful addition of 0.2 ml of water. The reaction mixture was poured onto 5 ml of water and 3 ml of 5% aqueous hydrochloric acid and the aqueous phase was extracted with ethyl acetate(3x30 ml). The combined organic layers were washed with brine (2x30 ml) and were dried ($MgSO_4$).

Evaporation and trituration with ether gave 97.0 mg (97%) of a white crystalline solid mp 121-124° (vacuum). Three crystallizations from ethyl acetate-heptane provided the analytical sample mp 128-130° (vacuum): ir ($CHCl_3$) 3615 (O-H), 1605, 1500 (Ph); nmr ($CDCl_3$) 0.93δ (s, 3, C-12a CH_3), 1.42δ (s, 6, C-4a and C-10b CH_3), 3.43-3.58δ (m,1,C<u>H</u>OH), 3.75δ (s, 3, O-C<u>H</u>$_3$), 6.50-7.28δ (m, 3, Ph).

<u>Anal.</u> Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.31; H, 9.89.

<u>Attempted conversion of the alcohol S-1 to 4b,5,6,6a,7,8,9,10,10a,10bα,11,12-Dodecahydro-7β-Hydroxy-2-Methoxy-4bβ,6aα,10aβ-Trimethylchrysene Methane Sulfonate (S-2).</u>

To an ice cold solution of 36.0 mg (0.109 mmole) of the alcohol <u>S-1</u> in 3 ml of dry pyridine under an argon atmosphere was added 0.20 ml of methanesulfonyl chloride. After 1 hour at 0° the reaction mixture was allowed to warm to room

temperature for 22 hours and was poured onto 15 ml of ethyl acetate. The resulting solution was washed with water (3x10 ml) and the combined aqueous layers were extracted with ethyl acetate (1x20 ml). The combined organic layers were washed with brine and were dried ($MgSO_4$).

Evaporation to dryness afforded 46 mg of a dark oil which deposited an insoluble brown solid on standing. The nmr spectrum of the oil revealed a complicated mixture of components and attempts at further purification were abandoned.

4b,5,6,6a,9,10,10a,10bα,11,12-Decahydro-7-Hydroxy-2-Methoxy-4bβ,6aα,10aβ-Trimethylchrysene Tetramethylphosphorodiamidate (T-1).

A dry 500 ml flask was flushed with argon and charged with 150 ml of dry ether and 13 ml of a 2.84 M solution of n-butyl lithium in hexane (alpha inorganics). Next 8.0 ml (57 mmoles) of diisopropylamine which had been freshly distilled from calcium hydride was added over 5 min and after another 5 min, a solution of 2.27 g (6.98 mmoles) of the ketone P-9 in 20 ml of dry tetrahydrofuran and 8.0 ml of N,N,N',N'-tetramethylethylene diamine which had been freshly distilled from calcium hydride was added over 10 min. The reaction mixture was cooled in an ice bath and 15 ml (81 mmoles) of tetramethyldiamidophosphorochloridate (99) was added dropwise. The resulting yellow solution was allowed to warm to room temperature and after 1.5 hours was poured

onto 400 ml of 10% aqueous hydrochloric acid and ice. The aqueous solution was extracted with ether (4x350 ml) and the combined organic layers were washed with water (3x350 ml) and brine (1x350 ml) and were dried ($MgSO_4$).

After concentration the crude product was chromatographed on 200 g of silica gel. Elution with 800 ml of ethyl acetate gave 156 mg of a mixture of several volatile components; further elution with 600 ml of 5% acetone-ethyl acetate gave 530 mg of a thin yellow oil whose nmr spectrum corresponded to that of the starting phosphorochloridate. Finally 1800 ml of 5 - 10% acetone-ethyl acetate eluted 2.81 g (88%) of a white crystalline solid, mp 108-111° (vacuum). Three recrystallizations of the product from ether-heptane gave the analytical sample, mp 108-111°: ir ($CHCl_3$) 1670 (vinyl), 1605, 1500 (Ph), 1305 (P-N), 980 (P-O-C); nmr ($CDCl_3$) 1.02δ (s, 3, C-4a CH_3), 1.22δ (s, 6, C-12a, C-10b CH_3), 2.70δ (d, 12, j=10Hz, N-CH_3), 3.75δ (s, 3, OCH_3), 5.20δ (m, 1, vinyl).

Anal. Calcd for $C_{26}H_{41}O_3N_2P$: C, 67.80; H, 8.97; N, 6.08; P, 6.73. Found: C, 67.96; H, 8.86; N, 6.16; P, 6.64.

4b,5,6,6a,9,10,10a,10bα,11,12-Decahydro-2-Hydroxy-4bβ,6aα,10bβ-Trimethylchrysene (T-2).

In a dry 25 ml flask was placed 135 mg (5.8 mmoles) of 30% lithium dispersion (Lithcoa). The atmosphere was replaced with argon and the hydride was washed by decantation with three 2 ml portions of hexane and the last traces of hexane

were removed under reduced pressure. The lithium was suspended in 2 ml of dry tetrahydrofuran and 100 mg (0.65 mmoles) of biphenyl was added. After 30 min at room temperature a solution of 43 mg (0.094 mmole) of the phosphorodiamidate T-1 in 3 ml of dry tetrahydrofuran was added over the course of 15 min. The dark green solution was kept at room temperature for 1 hour and was cooled in an ice bath. The remaining reagent was quenched by addition of excess methanol and the reaction mixture was poured onto 40 ml of water. The aqueous solution was made acidic to pH paper with 10% aqueous hydrochloric acid and was extracted with ether (3x 50 ml). The combined organic layers were dried ($MgSO_4$) and evaporated. Ptlc (75% ether-petroleum ether) gave 17 mg (62%) of a white crystalline solid mp 137-143°. Ptlc (75% ether-petroleum ether) and three crystallizations from ether-heptane gave an analytically pure sample mp 160.5-163°: ir ($CHCl_3$) 3600, 3400 (OH), 1660 w (C=C), 1605, 1500 (Ph); nmr ($CDCl_3$) 0.93δ (s, 3, C-4a CH_3), 1.00δ (s, 3, C-12a CH_3), 1.18δ (s, 3, C-10b CH_3), 5.50δ (m, 2, vinyl), 6.53-7.23δ (m, 3, Ph).

Anal. Calcd for $C_{21}H_{28}O$: C, 85.08; H, 9.62. Found: C, 85.04; H, 9.61.

3,4,4b,5,6,6a,9,10,10a,10bα,11,12-Dodecahydro-2(1H)-Oxo-4bβ, 6aα,10aβ-Trimethylchrysene (T-3).

To a solution of 148 mg (21 mmoles) of lithium wire in

50 ml of NH_3 which had been distilled from sodium was added a solution of 104 mg (0.226 mmole) of the tetramethylphosphorodiamidate T-1 in 12 ml of dry tetrahydrofuran over 10 min. After 30 min, 10 ml of tert-butyl alcohol were added and after an additional 45 min, the remaining lithium was destroyed with 5 ml of methanol. The ammonia was evaporated in a stream of argon and the grey residue was partitioned between 150 ml of ether and 30 ml of water. The ether layer was washed with water (1x30 ml) and brine (1x30 ml) and was dried ($MgSO_4$).

The solution was concentrated and the residue was dissolved in 12 ml of methanol and 1 ml of water and was treated with 150 ml of oxalic acid. After 2 hours at room temperature the mixture was neutralized with saturated aqueous sodium carbonate and diluted to 150 ml with ether. The ethereal solution was washed with water (2x50 ml) and brine (2x50 ml) and was dried ($MgSO_4$).

Evaporation and ptlc (60% ether-petroleum ether) gave a band r.f. 0.7 containing 28 mg (42%) of a clear oil that crystallized on standing mp 94-100° (vacuum). This product was combined with that from a similar experiment and the material was crystallized from aqueous ethanol and sublimed (130°/0.05 mm) to give the analytical sample mp 109-112° (vacuum): ir ($CHCl_3$) 1715 C=O; nmr ($CDCl_3$) 0.85δ (s, 3, C-4b CH_3), 1.03δ (s, 3, C-6a CH_3), 1.07δ (s, 3, C-10a CH_3), 5.52δ (s, 2, vinyl).

Anal. Calcd for $C_{21}H_{30}O$: C, 84.54; H, 10.13. Found: C, 84.51; H, 10.22.

3,4,4b,5,6,6a,9,10,10a,10bα,11,12-Dodecahydro-2(1H)-Oxo-1,1,4bβ,6aα,10aβ-Pentamethylchrysene (T-4).

Following the approach described by Wendler et al. (96), a solution of lithium triphenylmethide was prepared by treating a solution of 730 mg (3.0 mmoles) of triphenyl methane in 24 ml of dry tetrahydrofuran with 1.0 ml of a 2.5 M solution of n-butyl lithium in hexane (Alpha Inorganics). This solution was added dropwise to a solution of 31.5 mg (0.106 mmole) of the ketone T-3 prepared above in 1 ml of dry tetrahydrofuran under an argon atmosphere until a red color persisted (2.5 ml required). Then 0.2 ml (3.2 mmoles) of iodomethane which had been distilled from phosphorous pentoxide was added and after 1 hour at 0° the solution was diluted to 100 ml with ether and was washed with water (2x 20 ml) and brine (1x20 ml) and was dried ($MgSO_4$).

The solution was concentrated and the residue was dissolved in 9 ml of methanol and 4 ml of 10% aqueous hydrochloric acid and was heated to reflux under argon for 30 min. On cooling, the reaction mixture was diluted to 150 ml with ether and was washed with water (2x30 ml), and saturated aqueous sodium bicarbonate (1x30 ml) and was dried ($MgSO_4$).

Evaporation and ptlc (25% methylene chloride-petroleum ether) gave a band r.f. 0.3 containing 23 mg (61%) of the dialkylated product which was combined with the product from a similar experiment. Ptlc (30% ether-petroleum ether) and flash distillation at 0.005 mm gave the analytical sample: ir ($CHCl_3$) 1710 (C=O); nmr ($CDCl_3$) 0.85δ (s, 3, C-10a CH_3), 1.03δ, 1.07δ (s, 3 each, C-1 CH_3), 1.15δ (s, 3, C-6a CH_3), 1.18δ (s, 3, C-4b CH_3), 5.50δ (s, 2, vinyl).

Anal. Calcd for $C_{23}H_{34}O$: C, 84.60; H, 10.50. Found: C, 84.63; H, 10.43.

4b,5,6,6a,9,10,10a,10bα,11,12-Decahydro-2-Methoxy-4bβ,6aα,10aβ-Trimethylchrysene (S-3).

A solution of 37 mg (5.4 mmoles) of lithium wire in 50 ml of ammonia which had been distilled from sodium and 10 ml of dry tetrahydrofuran under an argon atmosphere was stirred for 30 min and a solution of 209.8 mg (0.45 mmole) of the phosphorodiamidate T-1 in 6 ml of dry tetrahydrofuran was added rapidly with a syringe. After 1.5 hours the blue color faded and 37 mg of lithium was added. After a total of 5 hours the excess lithium was quenched by addition of 400 mg of sodium benzoate followed by 200 mg of solid ammonium chloride. The ammonia was evaporated in a stream of argon and the residue was dissolved in 50 ml of water. The aqueous solution was extracted with ether (3x50 ml) and the combined organic layers were washed with 10% aqueous sodium hydroxide (2x50 ml), water

(1x50 ml), and brine (1x50 ml) and were dried ($MgSO_4$).

Evaporation afforded 149 mg of a slightly yellow oil; ptlc (30% ether-petroleum ether) gave a single band r.f. 0.7 containing 115 mg (82%) of a colorless oil. Ptlc (30% ether-petroleum ether) and flash distillation (0.1 mm) gave the analytical sample: ir ($CHCl_3$) 1605, 1500 (Ph), nmr ($CDCl_3$) 0.82δ (s, 3, C-10a CH_3), 5.52δ (s, 2, vinyl).

Anal. Calcd for $C_{22}H_{30}O$: C, 85.11; H, 9.74. Found: C,84.96; H, 9.64.

4,4aα,4b,5,6,6a,9,10,10a,10bα,11,12-Dodecahydro-2(3H)-Oxo-4bβ,6aα,10aβ-Trimethylchrysene (U-1).

A. From the Tetramethylphosophorodiamidate (T-1).

A solution of 370 mg (53 mmoles) of lithium wire in 550 ml of ammonia which had been distilled from sodium and 140 ml of dry tetrahydrofuran was stirred for 30 min and a solution of 1.53 g (3.32 mmoles) of the tetramethylphosphorodiamidate T-1 in 30 ml of dry tetrahydrofuran was injected with a syringe. After 5 hours 960 mg (139 mmoles) of lithium wire was added followed by 85 ml of dry tert-butyl alcohol. When the reaction had proceeded an additional 2 hours, the excess lithium was decomposed with 20 ml of methanol and the ammonia was allowed to evaporate overnight. The grey residue was partitioned between 500 ml of water and 1000 ml of ether. The aqueous layer was extracted with ether (1x300 ml) and the combined organic layers were washed with water (1x300 ml) and

brine (1x300 ml) and were dried ($MgSO_4$).

The solution was concentrated and the residue was taken up in 220 ml of ethanol and 130 ml of 5 N aqueous hydrochloric acid and mixture was heated to 65-70° for 40 min under an argon atmosphere. The cooled mixture was poured onto 500 ml of water and the aqueous phase was extracted with ether (4x500 ml). The combined ether layers were washed with water (1x500 ml), saturated aqueous sodium bicarbonate (1x 500 ml), and brine (1x500 ml) and were dried ($MgSO_4$).

Concentration afforded a dark yellow oil which was chromatographed on 100 g of silica gel; 300 ml of 50% ether-petroleum ether eluted 204 mg of a complicated mixture. Further elution with 300 ml of the same solvent gave 782 mg (79%) of white crystals mp 88-92° whose ir spectrum was identical with that of the analytical sample which was obtained from an earlier experiment starting with 100 mg of the phosphorodiamidate.

This experiment was carried out as above except that tert-butyl alcohol was present from the start of the reduction. The crude product following acid hydrolysis was purified by ptlc (50% ether-petroleum ether). The less polar band r.f. 0.4 contained 26 mg (40%) of the anticipated olefin U-1 mp 87-89°. Recrystallization from ethanol-water and sublimation (120°/0.01 mm) gave the analytical sample mp 94-97°: ir ($CHCl_3$) 1665 (C=O), 1620 (C=C); nmr ($CDCl_3$) 0.87δ (s, 6,

C-10a, C-4b CH_3), 1.07δ (s, 3, C-6a CH_3), 5.47δ (s, 2, vinyl), 5.92δ (m, 1, vinyl).

Anal. Calcd for $C_{21}H_{30}O$: C, 84.54; H, 10.13. Found: C, 84.51; H, 10.22.

The less polar band contained 24 mg (35%) of 2(3H), 7(8H)-Dioxo-4,4aα,4b,5,6,6a,9,10,10a,10bα,11,12-Dodecahydro-4bβ,6aα,10aβ-Trimethylchrysene (50) mp 152-154° (vacuum). The product was crystallized from ethyl acetate-heptane and was flash sublimed at 0.01 mm to give the analytical sample mp 161-163° (vacuum): ir ($CHCl_3$) 1700 (C=O), 1665 (C=O), 1620 (C=C); nmr ($CDCl_3$) 0.87δ (s, 6, C-10a, C-4b CH_3), 1.28δ (s, 3, C-6a CH_3), 5.90δ (m, 1, vinyl).

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.25; H, 9.61.

B. From the olefin S-3.

A solution of 182 mg (0.58 mmole) of the olefin S-3 in 60 ml of ammonia which had been distilled from sodium, 20 ml of dry tetrahydrofuran, and 10 ml of dry tert-butyl alcohol under an argon atmosphere was treated with 111 mg (16 mmoles) of lithium wire. After 2 hours the excess lithium was decomposed with 3 ml of methanol and the ammonia was removed in a stream of argon. The grey residue was partitioned between 150 ml of water and 200 ml of ether and the aqueous layer was extracted with ether (1x50 ml). The combined organic layers

were washed with water (1x100 ml) and brine (1x100 ml) and were dried ($MgSO_4$).

The solution was concentrated and the residue was taken up in 30 ml of ethanol and 20 ml of 5 N aqueous hydrochloric acid and was warmed to 65-70° for 40 min under an argon atmosphere. On cooling, the reaction mixture was poured onto 100 ml of water and the aqueous solution was extracted with ether (3x100 ml). The combined organic layers were washed with saturated aqueous sodium bicarbonate (2x100 ml) and brine (1x100 ml) and were dried ($MgSO_4$).

The solution was concentrated and the crude product was chromatographed on 22 g of silica gel. Elution with 55 ml of 50% ether-petroleum ether gave 26 mg of non-volatile material; continued elution with 120 ml of the same solvent afforded 153 mg (78%) of a white crystalline solid mp 91-94°.

4b,5,6,8aα,9,10-Hexahydro-2-Methoxy-7(8H)-Oxo-4bβ,8,8-Trimethylphenanthrene (V-2).

A solution of 582 mg (84.5 mmoles) of lithium wire in 500 ml of ammonia which had been distilled from sodium and 100 ml of tetrahydrofuran which had been doubly distilled from lithium aluminum hydride was stirred 15 min. A solution of 9.40 g (36.7 mmoles) of 4bβ,8-dimethyl-2-methoxy-7(6H)-oxo-4b,5,9,10-tetrahydrophenanthrene (V-1) mp 92.5-93.5° [prepared according to the procedure of Evans (108)] in 100 ml of dry tetrahydrofuran and 0.66 ml (36.7 mmoles) of water was added

over the course of 20 min. After 25 min, the remaining lithium was quenched by addition of a solution of 25 ml of iodomethane, which had been doubly distilled from phosphorous pentoxide, in 20 ml of tetrahydrofuran.

After 45 min the ammonia was evaporated, the grey residue was dissolved in 500 ml of 10% ammonium chloride, and the aqueous solution was extracted with benzene (4x500 ml). The combined organic layers were washed with water (2x500 ml) and brine (2x400 ml) and were dried ($MgSO_4$).

Concentration gave 10.52 g of a heavy yellow oil which was recrystallized from methanol to give 7.99 g of a white crystalline solid mp 64-67° (vacuum). Three further crystallizations from methanol gave 4.73 g (47.3%) mp 71-72° (vacuum) which was greater than 99% free of unalkylated material (glpc). Stork has prepared this compound and reports mp 56-58° (125). However, the spectral data (vide infra) were consistent with the assigned structure and in the next reaction it was converted to a known compound V-3 which had the anticipated properties. Ir ($CHCl_3$) 1700 (C=O), 1610, 1500 (Ph); nmr ($CDCl_3$) 1.13δ, 1.17δ (s, 3 each, C-8 CH_3), 1.27δ (s, 3, C-4b CH_3), 2.77δ (s, 3, O-CH_3).

The combined mother liquors were chromatographed on 700 g of silica gel. Elution with 600 ml of 10% ether-petroleum ether afforded 0.45 g of a mixture of at least 3 volatile compounds which was discarded. Further elution with 200 ml of

the same solvent provided 4.36 g of a mixture which contained 73% of the desired product together with two other components by glpc. Recrystallization from methanol gave 2.82 g (28%) mp 64-66°.

2-Methoxy-4b,5,6,7,8,8aα,9,10-Octahydro-4bβ,8,8-Trimethyl-phenanthrene (V-3).

In a modification of the Nagata procedure (109), a 1 l. three neck flask was fitted with a football shaped magnetic stir bar, a Claisen adaptor containing an argon inlet and a thermometer, a ground glass stopper and a 24/40 short path distilling head leading to a 100 ml flask. The vacuum adaptor on the still was closed off leaving the system under argon and the flask was charged with a solution of 8.48 g (31.0 mmoles) of the ketone V-2 mp 71-72° and 15.5 g (148 mmoles) of hydrazine dihydrochloride in 470 ml of diethylene glycol and 53 ml (900 mmoles) of 85% hydrazine hydrate. The reaction mixture was heated to 120-130° (internal temperature) and after 17 hours was cooled to 110° while 102 g (1.82 moles) of potassium hydroxide pellets were added over 15 min with a vigorous stream of argon passing through the system. The internal temperature was raised to 160-165° and after 1 hour the vacuum adaptor was again closed off and heating was continued 4.5 hours.

On cooling, the white paste was dissolved in 1000 ml of water and the aqueous suspension was extracted with ether

(4x1000 ml). The combined organic layers were washed with water (6x1000 ml) and brine (1x1000 ml) and were dried ($MgSO_4$).

Concentration gave 7.95 g of a white solid which was recrystallized from ethanol to give 6.51 g (81.5%) mp 85-86.5° (vacuum) in two crops [lit 83-85° (107) and 85-86° (89)]. The combined mother liquors were chromatographed on 100 g of silica gel. Elution with 300 ml of 10% ether-petroleum ether afforded 0.68 g which was crystallized from ethanol to give 0.49 g (6%) of V-3 mp 78-81°. Continued elution with 500 ml of 25-100% ether gave 0.58 g (7.2%) of 2-Hydroxy-4b,5,6,7,8,8aα,9,10-Octahydro-4bβ,8,8-Trimethylphenanthrene mp 160-161° (vacuum). The phenol was crystallized from ether-hexane and triturated with ether to provide an analytically pure sample mp 162.5-163.5° (vacuum): ir ($CHCl_3$) 3600 (OH), 1610, 1500 (Ph); nmr ($CDCl_3$) 0.95δ (s, 6, C-8 CH_3s), 1.17δ (s, 3, C-4b CH_3), 6.50-7.30δ (m, 3, Ph).

Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.52; H, 9.96.

4,4aα,4b,5,6,7,8,8aα,9,10-Decahydro-2(3H)-Oxo-4bβ,8,8-Trimethylphenanthrene (V-4).

The Birch reduction was carried out using the procedure described by Church et al. (107). From 5.70 g (22.2 mmoles) of the anisole V-3 mp 84-86° (vacuum) there was obtained 4.2 g (78%) of V-4 mp 89-90.5° [lit (107) 92.5-93.5°].

4,4aα,4b,5,6,7,8,8aα,9,10-Decahydro-2(3H)-Oxo-1,4bβ,8,8-Tetramethylphenanthrene (V-6).

Employing a modification of the general procedure of Kirk and Petrow (97) a 5 ml pear shaped flask was fitted with a Claisen adaptor holding a reflux condensor and a serum cap and was charged with a solution of 199 mg (0.81 mmole) of the enone V-4 from above in 3 ml of abs ethanol and 0.20 ml of thiophenol. The atmosphere was replaced with argon by evacuating and filling four times and 0.20 ml of triethylamine and 0.26 ml of 37% aqueous formaldehyde were added via syringe. The serum cap was quickly replaced with a ground glass stopper under a vigorous stream of argon and the reaction mixture was heated to reflux (bath temperature 95°) for 32 hours.

On cooling, the mixture was poured onto 50 ml of water and the aqueous solution was extracted with ether (4x50 ml). The combined organic layers were washed with 10% aqueous sodium hydroxide (2x50 ml), water (2x50 ml) and brine (1x50 ml) and were dried ($MgSO_4$).

Concentration afforded 330 mg of an oil which was chromatographed on 50 g of silica gel. Elution with 150 ml of 30% ether-petroleum ether yielded 22 mg of an unidentified oil. Further elution with 100 ml of the same solvent gave 169 mg (57%) of 4,4aα,4b,5,6,7,8,8aα,9,10-Decahydro-2(3H)-oxo-1-phenylthiomethyl-4bβ,8,8-Trimethylphenanthrene (V-5)

as a colorless oil which was used directly in the next step: ir ($CHCl_3$) 1660 (C=O), 1600, 1580 (Ph); nmr ($CDCl_3$) 0.72δ (s, 3, C-4b CH_3), 0.83δ, 0.90δ (s, 3 each, C-8 CH_3s), 3.93δ (s, 2, CH_2S), 7.08-7.57δ (m, 5, Ph).

A suspension of 1 ml of W-2 Raney-nickel was added to an ice cold solution of 169 mg of the thioether from above in 5 ml of abs ethanol under an argon atmosphere. After 30 min the reaction mixture was filtered through a pad of celite washing with ethanol (4x20 ml). Concentration afforded 107 mg of yellowish crystals mp 72-80° which were dissolved in ether and centrifuged to remove a flocculent yellow impurity giving after concentration 89 mg (42% from V-4) of a white crystalline solid mp 78-81°. Recrystallization of the crude product from 95% ethanol and sublimation (0.50 mm, 80-85°) gave the analytical sample mp 80-81.5° (vacuum): ir ($CHCl_3$) 1660 (C=O), 1610 (C=C); uv (EtOH) 251 mμ, ϵ=13, 400; nmr ($CDCl_3$) 0.77δ, 0.87δ (s, 3 each C-8 CH_3), 0.93δ (s, 3, C-4b CH_3), 1.88δ (s, 1, C-1 CH_3).

Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 83.11; H, 10.87.

2,3,4,4aα,4b,5,6,7,8,8aα,9,10-Dodecahydro-2β-Hydroxy-1,4bβ,8,8-Tetramethylphenanthrene (V-8), and 2,3,4,4aα,4b,5,6,7,8,8aα,9,10-Dodecahydro-2α-Hydroxy-1,4bβ,8,8-Tetramethylphenanthrene (V-7).

A. By reduction of V-6 with lithium Perhydro-9b-Boraphenalylhydride.

To an ice cold solution of 132 mg (0.508 mmoles) of the enone V-6 in 3.5 ml of dry tetrahydrofuran under an argon atmosphere was added 2.0 ml of a 0.6 M solution of the borohydride N-1 (87) in tetrahydrofuran. After 30 min at 0° the excess borane was destroyed by the sequential addition of 0.4 ml of 3 N sodium hydroxide and 0.4 ml of 30% hydrogen peroxide. The resulting mixture was poured onto 50 ml of 10% aqueous potassium carbonate and the basic solution was extracted with ether (4x30 ml). The combined organic layers were washed with water (2x30 ml) and brine (1x30 ml) and were dried ($MgSO_4$).

After concentration, the crude product was chromatographed on 15 g of Florisil; 100 ml of 5% ether-petroleum ether gave 9 mg of a volatile oil. Continued elution with 80 ml of 10% ether-petroleum ether afforded 50 mg of an oil which consisted of mainly the axial alcohol V-8 (*vide infra*) contaminated with the equatorial alcohol V-7 by tlc (10% ether-chloroform) analysis. Further elution with 100 ml of the same solvent afforded 49 mg of material consisting mainly of the equatorial alcohol V-7 by tlc. Crystallization from hexane gave 34 mg (26%) of V-7 mp 119-121°. Recrystallization from hexane and sublimation (0.05 mm, 120°) gave the analytical sample mp 121-123° (vacuum): ir ($CHCl_3$) 3600, 3450 (OH); nmr ($CDCl_3$) 0.68δ, 0.82δ (s, 3 each, C-8 CH_3), 0.87δ (s, 3, C-46 CH_3), 1.75δ (s, 3, C-1 CH_3), 3.80-4.13δ

(m, 1, CH-OH, width 18 Hz).

Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.25; H, 11.43.

The mother liquors from above and the material in the fractions containing mainly the alcohol V-8 were combined and purified by ptlc (10% ether-chloroform, spectro grade). The less mobile band r.f. 0.4 contained 51 mg (34%) of material which was identical to the equatorial alcohol by nmr. The second band r.f. 0.5 contained 26 mg (20%) of the axial alcohol V-8 mp 125-129° (vacuum). Recrystallization from hexane gave the analytical sample as fine needles mp 136.5-137.5° (vacuum): ir ($CHCl_3$) 3600, 3450 (OH), 1660 (C=C); nmr ($CDCl_3$) 0.73δ, 0.83δ (s, 3 each, C-8 CH_3), 0.90δ (s, 3, C-4b CH_3), 3.78-3.95δ (m, 1, CHOH, width 10Hz).

Anal. Calcd for $C_{18}H_{30}O$: C, 82.55; H, 11.52. Found: C, 82.54; H, 11.44.

B. By Lithium Aluminum Hydride reduction of V-6.

To a solution of 82 mg (2.2 mmoles) of lithium aluminum hydride in 7 ml of dry ether under an argon atmosphere was added a solution of 419 mg (1.61 mmoles) of the enone V-6 in 4 ml of dry ether. After two hours at room temperature, the excess hydride was quenched by the sequential addition of 0.08 ml of water, 0.08 ml of 10% sodium hydroxide and 0.24 ml of water. The resulting white suspension was stirred 10 min and was filtered. The ether solution was washed with water

(1x25 ml) and brine (1x25 ml) and was dried ($MgSO_4$).

Concentration and crystallization from hexane gave 245 mg (58%) of the equatorial alcohol V-7 mp 119-120° (vacuum). Ptlc (10% ether-chloroform, spectro grade) of the mother liquors gave two bands: r.f. 0.4, 110 mg (26%) of the equatorial alcohol mp 118-120° (vacuum) and r.f. 0.5, 37 mg (9%) of the axial alcohol V-8 mp 128-132° (vacuum).

Reoxidation of the alcohol V-7 to the ketone V-6.

A solution of chromium trioxide dipyridine complex (74) was prepared in situ (126) by addition of 168 mg (1.68 mmoles) of chromium trioxide to a solution of 0.27 ml (3.34 mmoles) of dry pyridine in 10 ml of dry methylene chloride under an argon atmosphere. After 15 min at room temperature, the characteristic red color had developed and a solution of 110 mg (0.42 mmole) of the alcohol V-7 in 3 ml of dry methylene chloride was added all at once. After an additional 15 min, the reaction mixture was filtered with suction through a pad of gd III alumina, which was washed with 150 ml of ether.

Concentration afforded 106 mg (97%) of the ketone V-6 mp 74-77° (vacuum).

2α-Hydroxy-1α,10a-Methano-1,2,3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-Tetradecahydro-1β,4bβ,8,8-Tetramethylphenanthrene (W-1).

To a solution of the Simmons-Smith (53) reagent formed in the usual manner from 1.60 g (23 mmoles) of zinc-copper couple (52) and 1.9 ml (23 mmoles) of diiodomethane in 23 ml

of dry ether under argon was added a solution of 349 mg (1.33 mmoles) of the equatorial alcohol V-7 in 6 ml of dry ether. After 2 hours at reflux, the reaction mixture was cooled in an ice bath and the excess reagent was destroyed by addition of 1 ml of 40% ammonium sulfate. The black suspension was poured onto 100 ml of ice and saturated aqueous potassium carbonate and the aqueous layer was extracted with ether (4x 90 ml). The combined ether layers were washed with saturated aqueous potassium carbonate (1x100 ml), 10% aqueous sodium thiosulfate (1x100 ml), and brine (1x100 ml) and were dried ($MgSO_4$).

After 5 min of drying, the solution was concentrated and the oil was chromatographed on 100 g of gd III alumina. Elution with 200 ml of petroleum ether removed the unreacted diiodomethane, 200 ml of 25%-100% ether afforded 23 mg of a colorless oil which was not investigated, and 100 ml of ether eluted 334 mg (91%) of the desired cyclopropane mp 134-137°.

Two recrystallizations of the column product from ether-hexane gave analytically pure needles mp 140.5-141.5°: ir ($CHCl_3$) 3600, 3450 (OH), 3020 (cyclopropane); nmr ($CDCl_3$) 0.73δ, 0.80δ (s, 1 each, cyclopropane), 0.98δ (s, 3, C-4b CH_3), 1.02δ (s, 6, C-8 CH_3s), 1.23δ (s, 3, C-1 CH_3), 3.77δ (t, 1, j=7Hz, C<u>H</u>-OH).

<u>Anal.</u> Calcd for $C_{19}H_{32}O$: C, 82.55; H, 11.67. Found: C, 82.70; H, 11.47.

1,4,4aα,4b,5,6,7,8,8aα,9,10,10a-Dodecahydro-1α,10a-Methano-2(3H)-Oxo-1β,4bβ,8,8-Tetramethylphenanthrene (W-2).

To an ice cold solution of 86 mg (0.30 mmole) of the equatorial alcohol W-1 in 8 ml of acetone was added 0.15 ml of 8 N chromic acid solution (62). After 5 min the reaction mixture was poured onto 30 ml of water and the aqueous solution was extracted with ether (4x40 ml). The combined ether layers were washed with saturated aqueous sodium bicarbonate (1x40 ml), water (1x40 ml) and brine (1x40 ml) and were dried ($MgSO_4$).

Evaporation gave 79 mg (93%) mp 122-127° (vacuum) and two recrystallizations afforded the analytical sample mp 136-138° (vacuum): ir ($CHCl_3$) 1670 (C=O); nmr ($CDCl_3$) 0.75δ, 0.83δ (s, 3 each, C-8 CH_3s), 0.87δ (s, 3, C-4b CH_3), 1.33δ (s, 3, C-1 CH_3).

Anal. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.28; H, 11.00.

1,4,4aα,4b,5,6,7,8,8aα,9,10,10a-Dodecahydro-2(3H)-Oxo-1,4bβ,8,8,10aα-Pentamethylphenanthrene (W-3).

To a solution of 41 mg (0.15 mmole) of the cyclopropyl ketone W-2 in 25 ml of ammonia (distilled from sodium) and 10 ml of dry tetrahydrofuran was added 11 mg (1.6 mmoles) of lithium wire. After 1 hour, the excess lithium was quenched by the sequential addition of 112 mg dry sodium benzoate and 120 mg of ammonium chloride. The ammonia was evaporated in

a stream of nitrogen. The grey residue was dissolved in 50 ml of water and the aqueous solution was extracted with ether (4x50 ml). The combined ether layers were washed with 10% aqueous potassium hydroxide (2x50 ml) and brine (1x50 ml) and were dried ($MgSO_4$). Concentration afforded 41 mg of an oil which was about 70% starting material by infra-red spectroscopy.

The crude material was treated with 18 mg (2.6 mmoles) of lithium wire for 3 hours under exactly the same conditions as before. Following a similar work-up, the crude oil was dissolved in 7 ml of acetone which had been distilled from potassium permanganate. The resulting solution was cooled in an ice bath and treated with 0.1 ml of 8 N Jones reagent (62). After 5 min, the reaction mixture was poured onto 40 ml of water and was extracted with ether (4x40 ml). The combined ether layers were washed with saturated aqueous sodium bicarbonate (1x40 ml) and brine (1x40 ml) and were dried ($MgSO_4$).

Evaporation to dryness afforded 37 mg of a colorless oil which was purified by ptlc (5x20 cm plate, 30% ether-petroleum ether). The band r.f. 0.5 contained 15 mg (37%) of the ketone W-3 which gave waxy crystals on standing. The product was further purified by tlc 30% ether-petroleum ether), recrystallized from hexane-ether and sublimed (85-90°; 0.05 mm) to give the analytical sample mp 85-87°: ir ($CHCl_3$) 1700 (C=O); 1390, 1370 (gem dimethyl); nmr ($CDCl_3$) 0.78 (s,

3, C-10a methyl), 0.83 -1.00δ (m, 9 C-1 and C-8 methyls), 1.15δ (s, 3, C-4b methyl); 2.87δ (q, 1, J=6, C-1H).

Anal. Calcd for $C_{19}H_{32}O$: C, 82.55; H, 11.67. Found: C, 82.71; H, 11.62.

A second band, r.f. 0.4 contained 8 mg (18%) of a mixture which contained a second saturated ketone by ir which resisted all efforts at further purification.

Attempted equilibration of the ketone W-3.

A solution of 58 mg (0.21 mmole) of the ketone W-3 (mp 64-68°) and 271 mg of potassium hydroxide in 25 ml of abs. ethanol was heated to reflux for 11 hours under an argon atmosphere. The cooled solution was diluted to 175 ml with ether and was washed with water (2x30 ml) and brine (1x50 ml) and was dried ($MgSO_4$). Evaporation to dryness and ptlc (10x20 cm plate, 30% ether-petroleum ether) afforded one band, r.f. 0.5, 48 mg (83%) of recovered starting material mp 65-70°.

2β-Hydroxy-1β,10a-Methano-1,2,3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-Tetradecahydro-1α,4bβ,8,8-Tetramethylphenanthrene (W-4).

To a solution of the Simmons-Smith reagent (53) formed in the usual manner from 600 mg (9mmoles) of zinc-copper couple (52) and 0.70 ml (9 mmoles) of diiodomethane in 10 ml of dry ether contained in a 25 ml flask under an argon atmosphere was added a solution of 31.8 mg (0.121 mmoles) of the alcohol

V-8 in 2.5 ml of dry ether. After 4 hours at reflux, the mixture was cooled in an ice bath and the excess reagent was quenched by addition of 1.0 ml of 40% ammonium sulfate. The black suspension was poured onto 40 ml of saturated aqueous potassium carbonate and the resulting solution was extracted with ether (3x50 ml). The combined ether layers were washed with saturated aqueous potassium carbonate (1x50 ml), 10% aqueous sodium thiosulfate (1x50 ml), and brine (1x50 ml) and were dried ($MgSO_4$).

After 5 min of drying, the solution was concentrated and the resulting oil was chromatographed on 40 g of gd III alumina: 100 ml of petroleum ether removed unreacted diiodomethane; further elution with 100 ml of 50% ether-petroleum ether gave 6 mg of an oil which was discarded. Finally, 100 ml of ether afforded 21 mg (61%) of the alcohol W-4 mp 144-148° (vacuum). Two recrystallizations from ether-hexane gave the analytical sample mp 151-153°: ir ($CHCl_3$) 3605 (OH); nmr 0.88δ (s, 9, C-4b, C-8 CH_3s), 1.17δ (s, 3, C-1 CH_3), 3.80-3.97δ (m, 1, CHOH).

Anal. Calcd for $C_{19}H_{32}O$: C, 82.55; H, 11,67. Found: C, 82.46; H, 11.47.

1,4,4aα,4b,5,6,7,8,8aα,9,10,10a-Dodecahydro-1β,10-Methano-2(3H)-Oxo-1α,4bβ,8,8-Tetramethylphenanthrene (W-5).

To an ice cold solution of 62 mg (0.22 mmole) of the axial alcohol W-4 in 9 ml of acetone which had been freshly

distilled from potassium permanganate was added 0.15 ml of 8 N chromic acid solution (62). After 5 min, the reaction mixture was poured onto 40 ml of water and the aqueous solution was extracted with ether (3x50 ml). The combined ether layers were washed with saturated aqueous sodium bicarbonate (1x50 ml) and brine (1x50 ml) and were dried ($MgSO_4$).

Concentration afforded 60 mg of waxy crystals which were purified by ptlc (10x20 cm plate, 30% ether-petroleum ether). The band r.f. 0.3 contained 54 mg (89%) of the ketone mp 97-103°. Crystallization from hexane gave analytically pure cubes mp 110-111.5° (vacuum): ir ($CHCl_3$) 1665 (C=O); nmr ($CDCl_3$) 0.55δ, 0.63δ (s, 1 each, cyclopropyl), 0.80δ (s, 6, C-8 CH_3s), 0.85δ (s, 3, C-4b CH_3), 1.13δ (s, 3, C-1 CH_3).

Anal. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 82.99; H, 11.03.

2,3,4,4aα,4b,5,6,7,8,8aα,9,10-Dodecahydro-2β-Hydroxy-4bβ,8,8-Trimethylphenanthrene (X-2) and 2,3,4,4aα,4b,5,6,7,8,8aβ,9,10-Dodecahydro-2α-Hydroxy-4bβ,8,8-Trimethylphenanthrene (X-1).

To an ice cold solution of 2.04 g (8.30 mmoles) of the enone V-4 in 30 ml of dry tetrahydrofuran under an argon atmosphere was added 20 ml (18 mmoles) of a 0.9 M solution of the borohydride N-1 (87). After 30 min at 0° the reagent was decomposed by the sequential addition of 4 ml of 3 N sodium hydroxide and 8 ml of 30% hydrogen peroxide. The

reaction mixture was immediately poured onto 250 ml of ice cold 20% aqueous potassium carbonate and the solution was extracted with ether (4x250 ml). The combined ether layers were washed with water (2x250 ml) and brine (1x250 ml) and were dried ($MgSO_4$).

The solution was concentrated and the product was chromatographed on 200 g of silica gel eluting with 10% ether-chloroform (spectro grade). The first 600 ml gave 106 mg of a non-polar oil. The next 200 ml eluted 690 mg (34%) of the axial alcohol X-2 mp 107-109° (vacuum) [lit (107) 109-110°] and the following 200 ml gave 916 mg of a mixture of X-1 and X-2 which was recrystallized from ether-hexane to give 538 mg (26%) of the equatorial alcohol X-1 mp 122-124° (vacuum) [lit (107) 127.5-128°]. Ptlc (10% ether-chloroform) of the mother liquors gave two bands: r.f. 0.4, 73 mg (4%) of the equatorial alcohol X-1 mp 116-120° (vacuum) and r.f. 0.5, 147 mg (7%) of the axial alcohol X-2 mp 109-111° (vacuum). Finally elution of column with an additional 400 ml of 10% ether-chloroform gave 492 mg (24%) of X-1 mp 120-122° (vacuum).

Reoxidation of the equatorial alcohol X-1 to the enone V-4.

Chromium trioxide dipyridine complex (74) was prepared by the in situ method (126). To a solution of 1.62 ml (20 mmoles) of dry pyridine in 50 ml of dry methylene chloride under an argon atmosphere was added 1.0 g (10 mmoles) of chromium trioxide. After 15 min at room temperature a solution

of 504 mg (2.03 mmoles) of the equatorial alcohol X-1 mp 118-122° in 6 ml of dry methylene chloride was added all at once. After an additional 10 min at room temperature, the dark red reaction mixture was filtered through a pad of gd III alumina with suction. The solution was concentrated to give 480 mg (96%) of the ketone V-4 mp 85-88° (vacuum) which was used directly.

1α,2,3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-Tetradecahydro-2β-Hydroxy-1β,10a-Methano-4bβ,8,8-Trimethylphenanthrene (X-3).

To a solution of the Simmons-Smith reagent (52) prepared in the usual manner 5.0 g (71 mmoles) of zinc-copper couple (53) and 5.5 ml (69 mmoles) of diiodomethane in 60 ml of dry ether under argon was added a solution of 903 mg (3.64 mmoles) of the axial alcohol X-2 from above in 15 ml of dry ether. The mixture was heated to reflux for 4 hours and was cooled in an ice bath. The excess reagent was decomposed by addition of 2 ml of 40% aqueous ammonium sulfate and the reaction mixture was poured onto 200 ml of saturated aqueous sodium carbonate. The aqueous phase was extracted with ether (4x250 ml) and the combined ether layers were washed with saturated aqueous sodium carbonate (1x250 ml), 10% aqueous sodium thiosulfate (1x250 ml) and brine (1x250 ml) and were dried ($MgSO_4$).

After 5 min of drying, the solution was concentrated and the crude product was chromatographed on 300 g of gd III alumina: 500 ml of 0-50% ether-petroleum ether gave 3.7 g of

recovered diiodomethane. Further elution with 600 ml of ether gave 786 mg (83%) of the alcohol X-3 mp 118.5-120.5°. The product from a similar experiment was recrystallized twice from hexane to give the analytical sample mp 116-117°: ir ($CHCl_3$) 3610 (OH); nmr ($CDCl_3$) 0.17-0.42δ (m, 3, cyclopropane), 0.85δ (s, 6, C-8 CH_3s), 0.90δ (s, 3, C-4b CH_3), 4.13-4.43δ (m, 1, CHOH, width 22 Hz).

Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.25; H, 11.47.

1,4,4aα,4b,5,6,7,8,8aα,9,10,10a-Dodecahydro-1β,10a-Methano-2(3H)-Oxo-4bβ,8,8-Trimethylphenanthrene (X-4).

To an ice cold solution of 783 mg (3.10 mmoles) of the alcohol X-3 from above in 100 ml of acetone (freshly distilled from potassium permanganate) was added 1.5 ml (6 meqv) of 8 N chromic acid solution (62) by drops. After 5 min the mixture was poured onto 200 ml of water and the aqueous solution was extracted with ether (4x200 ml). The combined ether layers were washed with saturated aqueous sodium bicarbonate (1x200 ml), water (1x200 ml), and brine (1x200 ml) and were dried ($MgSO_4$).

Concentration afforded 778 mg of a solid which was recrystallized from ether hexane to give 659 mg (85%) mp 133.5-134.5° (vacuum). The product was recrystallized twice from ether-hexane to give the analytical sample mp 133.5-134.5°: ir ($CHCl_3$) 1670 (C=O); nmr ($CDCl_3$) 0.88δ (s, 6, C-8

CH_3s), 0.97δ(s,3, C-4b CH_3)

Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 82.94; H, 10.71.

3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-Dodecahydro-2-Hydroxy-1,4bβ, 8,8,10aβ-Pentamethylphenanthrene Acetate (X-5)

A solution of 7 mg (1 mmole) of lithium wire in 10 ml of tetrahydrofuran (doubly distilled from lithium aluminum hydride) and 25 ml of ammonia (distilled from sodium) was stirred under argon for 15 min and a solution of 60 mg (0.23 mmole) of the ketone X-4 in 6 ml of dry tetrahydrofuran was added. After 2 hours the blue color faded and one of the ground glass stoppers on the reaction flask was replaced with a dry reflux condenser topped with a drying tube with a hose leading to the atmosphere through a mercury bubbler. The ammonia was evaporated in a stream of argon passing through the system and out the bubbler, and when most of the ammonia was gone, the tetrahydrofuran was heated to reflux for 30 min under a gentle stream of argon. The solution of the enolate was then cooled in an ice bath and 2 ml (21 mmoles) of acetic anhydride (purified by double fractional distillation) was added. After 30 min, the mixture was poured onto 50 ml of water and was extracted with ether (4x50ml). The combined ether layers were washed with sat. aqueous sodium bicarbonate (1x50ml) and brine (1x50ml) and were dried($MgSO_4$).

Evaporation afforded 72 mg of yellow waxy crystals which were purified by ptlc (40% ether-petroleum ether). The

band r.f. 0.7 contained 30 mg (43%) of the enol acetate X-5 as waxy crystals. Ptlc (40% ether-petroleum ether) and recrystallization from hexane gave the analytical sample mp 67-69° (vacuum): ir (CCl_4) 1750 (C=O), 1690 (C=C); nmr (CCl_4) 0.83δ (s, 6, C-8 CH_3s), 1.02δ (s, 3, C-4b CH_3), 2.00δ (s, 3, acetate CH_3), 4.98δ (m, 1, vinyl).

Anal. Calcd for $C_{20}H_{32}O$: C, 78.90; H, 10.59. Found: C, 78.78; H, 10.69.

A second band r.f. 0.5 contained 32 mg (53%) of 3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-Dodecahydro-2(1H)-Oxo-4bβ,8,8,10aβ-Tetramethylphenanthrene (59) which was purified by ptlc (40% ether-petroleum ether) and recrystallized from ether-hexane to give the analytical sample mp 155-156°: ir ($CHCl_3$) 1700 (C=O); nmr (CCl_4) 0.85-0.90δ (m, 12, angular CH_3s), 1.00-2.43δ (m, 18, $-CH_2-$).

Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.40; H, 11.50.

In a later experiment starting with 200 mg of X-4 the acetylation was allowed to proceed 7 hours. After ptlc there was obtained r.f. 0.3, 25 mg (12.5%) of recovered starting material mp 125-127° (vacuum); r.f. 0.5, 16 mg (8%) of the ketone 59 mp 144-148° (vacuum), and r.f. 0.7, 169 mg (72%) of the enol acetate whose nmr agreed precisely with that of the analytical sample.

Preparation of the saturated ketone 59 from X-4.

A solution of 37 mg (5.4 mmoles) of lithium wire in 30 ml of tetrahydrofuran (doubly distilled from lithium aluminum hydride under argon) and 75 ml of ammonia which had been distilled from sodium was stirred under argon for 25 min and a solution of 284.7 mg (1.10 mmoles) of the ketone X-4, mp 133-134°, in 10 ml of dry tetrahydrofuran was added all at once. After 2 hours, the excess lithium was decomposed by the sequential addition of 400 mg of sodium benzoate and 300 mg of ammonium chloride. The ammonia was evaporated in a stream of argon, and the grey residue was dissolved in 100 ml of water. The aqueous layer was extracted with ether (3x 100 ml). The combined ethereal layers were washed with 10% aqueous potassium hydroxide (2x75 ml), water (1x75 ml), and brine (1x75 ml) and were dried ($MgSO_4$).

Evaporation afforded 286 mg (quant) of glistening white crystals of 59, mp 136-146°. Recrystallization from ether-hexane gave 216 mg (76%) mp 142-150°. Ptlc (30% ether-petroleum ether) of the mother liquors gave 18 mg (6%) mp 140-150°.

1β,2,3,4,4aα,4b,5,6,7,8,8aα,9,10,10a-Tetradecahydro-2β-Hydroxy-1α,2-Methano-4bβ,8,8,10aβ-Tetramethylphenanthrene (X-6).

A. From the enol acetate X-5.

The enolate was formed using the method described by House (114) and the cyclopropylation was carried out by a

variation of the method of Whitlock and Overman (115). A solution of the Simmons-Smith reagent (53) in 10 ml of dry ether was prepared in the usual manner from 700 mg (10 mmoles) of zinc copper couple (52) and 0.8 ml (10 mmoles) of diiodomethane. At the same time, a solution of 51 mg (0.17 mmoles) of the enol acetate X-5 in 4 ml of dry dimethoxyethane was treated with 0.25 ml (0.4 mmoles) of a 1.6 M solution of methyl lithium in ether (Alpha Inorganics). After 30 min, the Simmons-Smith reagent was cooled in an ice bath and was transferred via syringe to the flask containing the enolate. The cyclopropylation was allowed to proceed 2 hours at room temperature and the reaction mixture was cooled in an ice bath and was quenched by addition of 0.4 ml of 40% aqueous ammonium sulfate. The resulting grey mixture was poured onto 40 ml of saturated aqueous sodium carbonate and the aqueous suspension was extracted with ether (3x25 ml). The combined ethereal layers were washed with saturated aqueous sodium carbonate (1x25 ml), 10% aqueous sodium thiosulfate (1x25 ml), and brine (1x25 ml) and were dried ($MgSO_4$).

After drying for 5 min the solution was concentrated and chromatographed on 50 g of gd III alumina. Washing with 150 ml of petroleum ether removed unreacted diiodomethane. Elution with 100 ml of 25-50% ether-petroleum ether gave 15 mg of an unidentified product and further elution with 100 ml of ether afforded 34 mg (73%) of the cyclopropyl alcohol

X-6 mp 152-157° (vacuum). The product was recrystallized twice from ether-hexane to give the analytical sample as fine needles mp 171-174° (vacuum): ir ($CHCl_3$) 3600, 3450 (OH); nmr ($CDCl_3$) 0.80δ, 0.83δ (s, 6 each, angular CH_3s).

Anal. Calcd for $C_{19}H_{32}O$: C, 82.55; H, 11.67. Found: C, 82.55; H, 11.71.

B. From the ketone X-4.

A solution of 11 mg (1.6 mmoles) of lithium wire in 10 ml of dry dimethoxyethane and 60 ml of ammonia (distilled from sodium) was stirred under an argon atmosphere for 50 min and a solution of 93.5 mg (0.359 mmoles) of the ketone X-4 mp 133.5-134.5° (vacuum) in 5 ml of dry dimethoxyethane was introduced all at once. After 4 hours, one of the ground glass stoppers was removed from the reaction flask and was replaced with a dry reflux condenser topped with a drying tube with a hose leading to the atmosphere through a mercury bubbler. The ammonia was removed from the still blue solution in a stream of argon and the residue was heated to reflux for 30 min under a slow stream of argon and then was cooled in an ice bath.

At the same time a solution of the Simmons-Smith reagent (53) was prepared in the usual manner from 1.20 g (17 mmoles) of zinc-copper couple (52) and 1.40 ml (17.4 mmoles) of diiodomethane in 17 ml of dry ether. The reagent was cooled in an ice bath and was transferred with a syringe

to the solution of the enolate anion.

The resulting grey suspension was stirred at room temperature for 2 hours and was poured onto 50 ml of saturated aqueous sodium carbonate. The carbonate solution was extracted with ether (4x50 ml) and the combined organic layers were washed with saturated aqueous sodium carbonate (1x50 ml), 10% aqueous sodium thiosulfate (1x50 ml), and brine (1x50 ml) and were dried ($MgSO_4$).

After drying for 5 min the solution was concentrated and was chromatographed on 80 g of gd III alumina: 200 ml of petroleum ether removed unreacted diiodomethane and 200 ml of 25-50% ether-petroleum ether afforded 20 mg of a mixture of the starting ketone X-4 and the unalkylated ketone 59. Further elution with 200 ml of ether gave 75 mg (76%) of the alcohol X-6 mp 137-152° (vacuum) which was contaminated with a little starting material. Crystallization from ether-hexane gave 56 mg (57%) in two crops mp 161.5-164.5° (vacuum).

1α,4,4aα,4b,5,6,7,8,8aα,9,10,10a-Dodecahydro-2(3H)-Oxo-1β,4bβ,8,8,10aβ-Pentamethylphenanthrene (W-6).

A. From the ketone W-5.

To a solution of 43.5 mg (0.159 mmole) of the ketone W-5 in 6 ml of tetrahydrofuran (doubly distilled from lithium aluminum hydride) and 25 ml of ammonia (distilled from sodium) under an argon atmosphere was added 19 mg (2.7 mmoles) of lithium wire. After 2 hours, the excess lithium was quenched

by the sequential addition of 0.3 g of sodium benzoate and 0.3 g of ammonium chloride. The ammonia was allowed to evaporate in a stream of argon and the residue was dissolved in 40 ml of water. The aqueous solution was extracted with ether (3x50 ml) and the combined ether layers were washed with 10% aqueous sodium hydroxide (2x50 ml), and brine (2x50 ml) and were dried ($MgSO_4$).

Evaporation and ptlc (10x20 cm plate, 30% ether-petroleum ether) gave r.f. 0.5, 33.7 mg (78%) of the ketone W-6 mp 78-82° (vacuum). Recrystallization from hexane gave the analytical sample mp 83-86° (vacuum): ir ($CHCl_3$) 1700 (C=O); nmr ($CDCl_3$) 0.78δ (s, 3, C-10a CH_3), 0.82-0.92δ (m, 12, angular CH_3s).

Anal. Calcd for $C_{19}H_{32}O$: C, 82.55; H, 11.67. Found: C, 82.61; H, 11.52.

B. From the cyclopropanol X-6.

To a solution of 32 mg (0.12 mmole) of the cyclopropanol X-6 from above in 10 ml of abs ethanol contained in a 25 ml flask under an argon atmosphere was added 1 ml of concentrated hydrochloric acid and the resulting mixture was heated to 70° for 2.5 hours. The solution was cooled in an ice bath and was poured onto 30 ml of water. The aqueous phase was extracted with ether (3x25 ml) and the combined ether layers were washed with saturated aqueous sodium bicarbonate (2x25 ml) and brine (1x25 ml) and were dried ($MgSO_4$).

Concentration and ptlc (10x20 cm plate, 30% ether-petroleum ether) gave r.f. 0.5, 28 mg (86%) of the ketone W-6 mp 80-83° (vacuum) which was spectrally identical to that obtained above (ir, nmr).

C. From the Alcohol X-6 with Iodine.

A solution of 12.9 mg (0.0467 mmole) of the alcohol X-6 and 11 mg (0.087 mmole) of iodine in 10 ml of ether was stirred at room temperature for 24 hours. The solution was diluted with 60 ml of ether and was washed with 10% aqueous sodium thiosulfate (2x10 ml) and brine (1x10 ml) and was dried ($MgSO_4$).

Evaporation to dryness gave 14 mg of a yellow oil which exhibited a carbonyl absorbtion at 1700 cm^{-1} and no hydroxyl absorbtion in the ir. The crude ketone was dissolved in 10 ml abs ethanol containing 87 mg of potassium hydroxide and the mixture was stirred 10.5 hours under an argon atmosphere. The reaction mixture was diluted with 50 ml of 1:1 ether-benzene and was washed with water (2x10 ml) and brine (1x10 ml).

Drying ($MgSO_4$) and evaporation to dryness gave an oil which was purified by ptlc (30% ether-petroleum ether) to give 7.0 mg (55%) of the ketone W-6 mp 70-73° which was spectrally identical (ir, nmr) to the material prepared above.

D. Attempted preparation by alkylation of the enol acetate X-5.

The general procedure described by House was employed (114). To a solution of 55 mg (0.18 mmole) of the enol acetate X-5 in 4 ml of dry dimethoxyethane under an argon atmosphere was added 0.28 ml of a 1.6 M solution of methyl lithium in ether (Alpha Inorganics). After 1.3 hours at room temperature, 2.0 ml (32 mmoles) of iodomethane was added all at once to the slightly yellow, cloudy solution. After an additional 5 min the reaction mixture was poured onto 25 ml of brine and ice and the aqueous suspension was extracted with ether (3x25 ml). The combined ether layers were washed with water (1x25 ml) and brine (1x25 ml) and were dried ($MgSO_4$).

Concentration afforded 54 mg of a yellow oil which was separated by ptlc (10x20 cm plate, 10% acetone-petroleum ther). A broad band r.f. 0.4 contained 35 mg which did not contain any of the desired product by nmr. The material was equilibrated using a variation of the procedure of Ramirez (127). The product was dissolved in 15 ml of abs ethanol containing 150 mg of potassium hydroxide and the resulting mixture was heated to reflux for 6 hours under an argon atmosphere. The reaction mixture was then poured onto 50 ml of dilute aqueous sodium chloride and the aqueous solution was extracted with ether (3x25 ml). The combined ether layers were washed with water (2x25 ml) and brine (1x25 ml) and were dried ($MgSO_4$).

Concentration and ptlc (40% ether-petroleum ether)

gave three bands which were identified by nmr: r.f. 0.5, 5 mg (10%) of the unalkylated product 59; r.f. 0.6, 10 mg (20%) of the desired ketone W-6; and r.f. 0.7, 19 mg (40%) of material which by nmr integration of the angular methyl region appeared to be a mixture of polyalkylated products.

E. Attempted Reductive Alkylation of the Ketone X-4.

A solution of 7 mg (1 mmole) of lithium wire in 25 ml of ammonia (distilled from sodium) and 5 ml of tetrahydrofuran (doubly distilled from lithium aluminum hydride) was stirred 30 min under an argon atmosphere. A solution of 62 mg (0.25 mmole) of the cyclopropyl ketone X-4 in 6 ml of dry tetrahydrofuran was added over the course of 6 min and the reaction mixture was stirred for 2 hours before it was quenched by the rapid addition of 2.5 ml (5.7 g, 40 mmole) of methyl iodide (doubly distilled from phosphorous pentoxide).

After an additional 10 min, 300 mg of solid ammonium chloride was added and most of the ammonia was removed in a stream of nitrogen. The resulting grey suspension was dissolved in 50 ml of water and was extracted with ether (3x 50 ml). The combined ethereal layers were washed with water (1x50 ml) and brine (1x50 ml) and were dried ($MgSO_4$). Evaporation to dryness and ptlc (40% ether-petroleum ether, double elution) gave two bands; r.f. 0.2, 10 mg (10%) recovered starting material, and r.f. 0.5, 46 mg (74%) of the ketone 59.

2α-Hydroxy-2β,3,4,4aα,4b,5,6,6a,9,10,10a,10bα,11,12-Tetradecahydro-4bβ,6aα,10aβ-Trimethylchrysene (Y-1) and 2β-Hydroxy-2α,3,4,4aα,4b,5,6,6a,9,10,10a,10bα,11,12-Tetradecahydro-4bβ,6aα,10aβ-Trimethylchrysene (Y-2).

Following the general procedure of Brown and Dickason (87), an ice cold solution of 781 mg (2.62 mmoles) of the enone U-1 in 15 ml of dry tetrahydrofuran contained in a 50 ml flask under an argon atmosphere was treated with 6.0 ml (5.1 mmoles) of a 0.85 M solution of the trialkylborohydride N-1 in tetrahydrofuran. After 30 min the excess borohydride was decomposed by the sequential addition of 1.0 ml of 3 N aqueous sodium hydroxide and 2.0 ml of 30% hydrogen peroxide. The reaction mixture was immediately poured onto 50 ml of saturated aqueous sodium carbonate and the aqueous solution was extracted with 4:1 ether-benzene (4x50 ml). The combined organic layers were washed with saturated aqueous sodium carbonate (1x50 ml), water (1x50 ml) and brine (1x50 ml) and were dried ($MgSO_4$).

After 30 min of drying, the solution was concentrated and the crude product was chromatographed on 100 g of florisil eluting with 50% ether-petroleum ether. The first 300 ml eluted 75 mg of a mixture of non-polar products that was discarded. The next 200 ml afforded 183 ml (23%) of the axial alcohol Y-2. Further elution with 400 ml of the same solvent gave 316 mg of a mixture of the two alcohols which

was separated by ptlc [3-20x20 cm plates, 10% ether-chloroform (spectro grade)] to give: r.f. 0.4, 188 mg (24%) of the equitorial alcohol Y-1 and r.f. 0.5, 114 mg (15%) of the axial alcohol Y-2. Finally washing the column with 500 ml of ether gave 206 mg (26%) of the equatorial alcohol mp 119-120° (vacuum).

The nmr of the combined axial alcohol, 296 mg (38%), was identical to that of the analytical sample mp 131-134° (vacuum) which was prepared from a similar experiment and purified by ptlc followed by recrystallization from ethyl acetate-heptane and ethanol-water: ir ($CHCl_3$) 3600, 3450 (O-H), 1650 (C=C); nmr ($CDCl_3$) 0.85δ (s, 6); 1.05δ (s, 3 C-4b, 6a, 10a CH_3s), 4.00-4.20δ (m, 1 C<u>H</u>-OH), 5.48δ (s, 2 vinyl), 5.50-5.77δ (m, 1 vinyl).

<u>Anal.</u> Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found: C, 83.87; H, 10.78.

The nmr of the combined equatorial alcohol, 394 mg (50%), was identical to that of the analytical sample mp 114-116° (vacuum) which was prepared from the same experiment as the sample of the axial alcohol and was purified by ptlc and recrystallization from ethyl acetate-heptane and ethanol-water: ir ($CHCl_3$) 3605, 3450 (OH), 1655 (C=C); nmr ($CDCl_3$) 0.77δ, 0.82δ, 1.05δ (s, 3 each C-4b, 6a, 10a CH_3s), 3.95-4.30δ (m, 1 C<u>H</u>OH), 5.37-5.53δ (m, 3 vinyl).

<u>Anal.</u> Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found:

C, 83.93; H, 10.87.

Oxidation of the alcohol Y-1 to the enone U-1.

The chromium trioxide dipyridine complex was prepared by the in situ procedure of Ratcliffe and Rodehorst (126). A dry 1000 ml flask fitted with a mechanical stirrer was flushed with argon and charged with a solution of 12.8 g (101 mmoles) of dry pyridine in 252 ml of dry methylene chloride and 5.0 g (50 mmoles) of anhydrous chromium trioxide. The red solution was stirred for 15 min and a solution of 2.54 g (8.45 mmoles) of the allylic alcohol Y-1 in 30 ml of dry methylene chloride was added all at once. After 10 min, the dark reaction mixture was filtered through a pad of grade III alumina contained in a 350 ml Buchner funnel washing with 500 ml of ether.

Concentration afforded 2.287 g (91%) of white crystals of U-1 mp 98-101° (vacuum) whose ir spectrum was identical to that of the analytical sample.

1α,4,4aα,4b,5,6,6a,9,10,10a,10bα,11,12,12a-Tetradecahydro-1β,12a-Methano-2(3H)-Oxo-4bβ,6aα,10aβ-Trimethylchrysene (Y-4).

A solution of the Simmons-Smith reagent (53) was prepared in the usual manner from 4.0 g (57 mmoles) of zinc-copper couple (52) and 4.6 ml (57 mmoles) of diiodomethane in 60 ml of dry ether. A 17 ml portion of the reagent was removed for a different reaction and a solution of 638 mg (2.21 mmoles) of the axial alcohol Y-2 in 10 ml of dry ether

was added all at once. The resulting solution was heated at reflux for 4 hours before it was cooled and poured onto 100 ml of saturated aqueous sodium carbonate. The aqueous suspension was extracted with 4:1 ether-benzene (4x100 ml) and the combined organic layers were washed with saturated aqueous sodium carbonate (1x100 ml), 10% aqueous sodium thiosulfate (1x100 ml), and brine (1x100 ml) and were dried ($MgSO_4$) for 5 min.

The solution was concentrated and chromatographed on 250 g of gd III alumina. Elution with 500 ml of petroleum ether removed unreacted diiodomethane and 300 ml of 3% methanol-ether eluted 512 mg (80%) of 1α,2α,3,4,4aα,4b,5,6,6a,9,10,10a,10bα,11,12,12a-Hexadecahydro-2β-Hydroxy-1β,12a-Methano-4bβ,6aα,10aβ-Trimethylchrysene (Y-3), mp 135-139° (vacuum): ir ($CHCl_3$) 3600, 3450 (OH); nmr ($CDCl_3$) 0.85δ, 0.95δ, 1.05δ (s, 3 each, C-4b, 6a, 10a CH_3s) 4.07-4.43δ (m, 1, CHOH), 5.47δ (s, 2, vinyl).

The crude alcohol was oxidized with chromium trioxide dipyridine complex using the *in situ* procedure of Ratcliffe and Rodehorst(126). A dry 100 ml flask fitted with a mechanical stirrer was flushed with argon and charged with a solution of 1.62 ml (10 mmoles) of dry pyridine in 50 ml of dry methylene chloride followed by 1.00 g (10 mmoles) of anhydrous chromium trioxide. The red solution was stirred 15 min and a solution of 512 mg (1.69 mmoles) of the alcohol Y-3 from above in 8 ml of dry methylene chloride was added

all at once. After 10 min, the dark mixture was filtered through a pad of grade III alumina which was washed with 200 ml of ether.

Concentration afforded 490 mg (76.5% from the alcohol) of off-white crystals of the ketone mp 149-152° (vacuum). The analytical sample mp 150-153° (vacuum) was prepared by ptlc (50% ether-petroleum ether) and recrystallization from ether-hexane: ir ($CHCl_3$) 1670 (C=O); nmr ($CDCl_3$) 0.90δ, 1.02δ, 1.07δ (s, 3 each C-4b, 6a, 10a CH_3s), 5.47δ (s, 2, vinyl).

Anal. Calcd for $C_{22}H_{32}O$: C, 84.56; H, 10.32. Found: C, 84.49; H, 10.39.

2-Hydroxy-3,4,4aα,4b,5,6,6a,9,10,10a,10bα,11,12,12a-Tetradecahydro-4bβ,6aα,10aβ,12aβ-Tetramethylchrysene Acetate (Y-5).

A dry 200 ml flask fitted with a glass coated stir bar, a dry ice condenser connected to an argon source, an inlet tube and a serum cap was charged with a solution of 18 mg (2.6 mmoles) of lithium in 60 ml of ammonia (freshly distilled from sodium) and 20 ml of tetrahydrofuran (doubly distilled from lithium aluminum hydride under argon). After 1 hour, a solution of 202.5 mg (0.647 mmole) of the cyclopropyl ketone Y-4 in 5 ml of dry tetrahydrofuran was added all at once. The blue color faded at the end of 1.5 hours, and 18 mg of lithium wire were added. After a total of 4 hours, the inlet tube was replaced with a dry reflux condenser connected

through a drying tube to a mercury bubbler and most of the ammonia was removed in a stream of argon. The residue was heated to reflux for 30 min in a gentle stream of argon as the last traces of ammonia evaporated.

The resulting grey suspension was cooled to room temperature, and 5 ml (53 mmoles) of acetic anhydride (doubly fractionally distilled, bp 139°) were added. After 6 hours, the reaction mixture was poured onto 70 ml of 10% aqueous potassium hydroxide and ice and the aqueous solution was extracted with 1:1 ether-benzene (4x50 ml). The combined organic layers were washed with 10% aqueous potassium hydroxide (1x50 ml), water (1x50 ml), and brine (1x50 ml) and were dried ($MgSO_4$). Evaporation to dryness afforded 285 mg of a yellow oil which was chromatographed on 30g of silica gel. Elution with 20% ether-petroleum ether gave successively, 17 mg of a non-volatile oil which was discarded, and 146 mg (64%) of the enol acetate Y-5 mp 119-121° (vacuum). Ptlc (20% ether-petroleum ether) of a portion and recrystallization from ether-hexane gave the analytical sample mp 121-123° (vacuum): ir ($CHCl_3$) 1755 (C=O), 1690 (C=C), 1220 (C-O); nmr (CCl_4) 0.78δ, 0.88δ (s, 3 each), and 1.02δ (s, 6, C-4b, C-6a, C-10a, C-12a CH_3s), 2.00δ (s, 3, acetate CH_3), 4.97δ (s, 1, C-1 H), 5.40δ (s, 2, C-7,8 vinyl).

Anal. Calcd for $C_{24}H_{36}O$: C, 80.85; H, 10.18. Found: C, 81.05; H, 10.23.

Further elution of the column with 25 ml of the same solvent gave 37 mg (10%) of a mixture of approximately equal amounts the enol acetate Y-5 and a second enol acetate 2-hydroxy-1β,12a-methano-1,4,4aα,4b,5,6,6a,9,10,10a,10bα,11,12,12a-tetradecahydro-4bβ,6aα,10aβ-trimethylchrysene acetate (67), as determined by estimation of the acetate methyl peaks in the nmr (2.00 and 2.03δ). A second experiment, in which a shorter reaction time was employed starting with 468 mg (1.50 mmoles) of the ketone Y-4 gave from the column 407 mg (77%) of a 7:3 mixture of the two enol acetates which was purified further by ptlc (3 plates, 20% ether-petroleum ether). The band r.f. 0.5 contained 246 mg (46%) of the desired enol acetate Y-5 and the band r.f. 0.4 contained 129 mg (24%) of the enol acetate 67 mp 101-106° (vacuum). Recrystallization from hexane gave a sample mp 110-112°: ir (CCl_4) 1755 (C=O), 1685 (C=C), 1220 (C-O); nmr (CCl_4) 0.85δ, 0.98δ, 1.03δ (s, 3 each, angular CH_3s), 2.03δ (s, 3, acetate), 4.80-5.05δ (m, 1, vinyl), 5.40δ (s, 2, vinyl).

Anal. Calcd for $C_{24}H_{34}O_2$: C, 81.31; H, 9.67. Found: C, 81.46; H, 9.75.

Finally elution with a further 100 ml of the same solvent afforded 10 mg (5%) of 2(3H)-oxo-1,4,4aα,4b,5,6,6a,9,10,10a,10bα,11,12,12a-Tetradecahydro-4bβ,6aα,10aβ,12aβ-Tetramethylchrysene (66) which was identical by nmr to the product from a similar experiment mp 140-150° (vacuum) which was

purified further by ptlc (40% ether-petroleum ether), recrystallization from hexane-methylene chloride, and sublimation (0.025 mm, 160-170°) to give the analytical sample mp 172-176° (vacuum): ir ($CHCl_3$) 1705 (C=O); nmr ($CDCl_3$) 0.82δ (s, 3), 0.90δ (s, 6), 1.06δ (s, 3) (C-4b, C-6a, C-10a, C-12a CH_3s), 5.48δ (s, 2, vinyl).

Anal. Calcd for $C_{22}H_{34}O$: C, 84.02; H, 10.90. Found: C, 83.90; H, 10.99.

Cleavage of the Enol Acetate 67 to the Ketone Y-4.

A solution of 90 mg (0.25 mmole) of the enol acetate 67 and 180 mg (2.7 mmoles) of potassium hydroxide in 15 ml of abs ethanol were stirred at room temperature for 14 hours under an argon atmosphere. The reaction mixture was layered between 50 ml of water and 50 ml of benzene, and the aqueous layer was extracted with 1:1 ether-benzene (3x50 ml). The combined organic layers were washed with water (2x50 ml) and brine (1x50 ml) and were dried ($MgSO_4$).

The crude product was purified by ptlc (60% ether-petroleum ether) to give 46 mg (61%) of the ketone Y-4 mp 123-126° (vacuum) which was spectrally identical to the material prepared above.

1β,2,3,4,4aα,4b,5,6,6a,9,10,10a,10bα,11,12,12a-Hexadecahydro-2β-Hydroxy-1α,2-Methano-4bβ,6aα,10aβ,12aβ-Tetramethylchrysene (Y-6)

A. From the Enol Acetate Y-5.

A dry 25 ml flask was flushed with argon and charged with 0.7 ml (1.2 mmoles) of a 1.68 M solution of methyl lithium in ether (Alpha Inorganics). The ether was evaporated under reduced pressure and a solution of 153 mg (0.430 mmole) of the enol acetate Y-5 in 5 ml of dry dimethoxyethane was added. The resulting yellow cloudy solution was stirred at room temperature for 30 min while a solution of the Simmons-Smith reagent (53) was prepared in the usual manner from 1.20 g (17 mmoles) of zinc-copper couple (52) and 1.40 ml (17 mmoles) of diiodomethane in 17 ml of dry ether.

The solution of the Simmons-Smith reagent was cooled in an ice bath, and the supernatant was withdrawn with a syringe and injected into the flask containing the enolate. The cyclopropylation was allowed to proceed 1 hour and the reaction mixture was cooled in an ice bath and poured onto 50 ml of saturated aqueous sodium carbonate. The aqueous layer was extracted with 1:1 ether-benzene (4x50 ml) and the combined organic layers were washed with saturated aqueous sodium carbonate solution (1x50 ml), 10% aqueous sodium thiosulfate solution (1x50 ml), and brine (1x50 ml) and were dried ($MgSO_4$) for 5 min.

The solution was concentrated and the product was applied to 70 g of grade III alumina. Washing with petroleum ether removed the unreacted diiodomethane, and elution with 200 ml of ether gave 100 mg (71%) of the cyclopropyl alcohol Y-6 mp 161-165° (vacuum). Recrystallization from methylene

chloride-hexane gave the analytical sample mp 166-168°: ir ($CHCl_3$) 3600, 3450 (OH), 1180 (C-O); nmr ($CDCl_3$) 0.80δ, 0.87δ, 1.02δ, 1.15δ (s, 3 each, C-4b, C-6a, C-10a, C-12a CH_3s), 5.42δ (s, 2, vinyl).

Anal. Calcd for $C_{23}H_{36}O$: C, 84.09; H, 11.04. Found: C, 83.85; H, 11.13.

B. From the cyclopropyl Ketone Y-4.

A dry 300 ml flask fitted with a glass coated magnetic stir bar, a dry ice condenser connected to an argon source, and a reflux condenser topped with a drying tube with a stopcock leading to the atmosphere through a mercury bubbler was charged with a solution of 54 mg (7.8 mmoles) of lithium wire in 100 ml of ammonia (freshly distilled from sodium) and 25 ml of dry dimethoxyethane. After 40 min, a solution of 250.9 mg (0.805 mmoles) of the ketone Y-4 in 7 ml of dry dimethoxyethane was introduced dropwise.

After 3 hours, the stopcock at the top of the reflux condenser was opened, and most of the ammonia was removed in a stream of argon. The residue was heated to reflux for 30 min in a gentle stream of argon to remove the last traces of ammonia.

The grey solution was cooled to room temperature, and a solution of the Simmons-Smith reagent (53) which was prepared in the normal manner from 2.5 g (36 mmoles) of zinc-copper couple (52) and 2.80 ml (35 mmoles) of diiodomethane

in 35 ml of dry ether while the ammonia was distilling was introduced all at once. After 1 hour, the reaction mixture was poured onto 50 ml of saturated aqueous sodium carbonate, the flask was rinsed with 40 ml of 40% aqueous ammonium sulfate, and the aqueous solution was extracted with 1:1 ether-benzene (4x100 ml). The combined organic layers were washed with saturated aqueous sodium carbonate (1x100 ml), 10% aqueous sodium thiosulfate (1x100 ml), and brine (1x100 ml).

After 5 min of drying ($MgSO_4$), the solution was concentrated and the residue was chromatographed on 160 g grade III alumina: 400 ml of petroleum ether removed unreacted diiodomethane; 400 ml of 25-50% ether-petroleum ether afforded 65 mg of a mixture which was purified by ptlc (60% ether-petroleum ether) to give r.f. 0.5, 22 mg (9%) of the starting ketone mp 137-142° (vacuum) and r.f. 0.7, 26 mg (10%) of the ketone 66. Further elution of the column with 200 ml of 50% ether-petroleum ether gave an additional 38 mg (15%) of recovered starting material. Finally, elution with 400 ml of ether gave 138 mg (69% based on consumed starting material) of the alcohol Y-6 mp 123-125°d whose nmr agreed with that of the crude product from part A. However, there were several extraneous peaks and cleavage of the cyclopropane ring gave only 72% of the ketone Y-7 instead of 98% obtained by cleavage of the material from part A (vide infra).

2(3H)-Oxo-1β,4bβ,6aα,10aβ,12aβ-Pentamethyl-1α,4,4aα,4b,5,6,6a,9,10,10a,10bα,11,12,12a-Tetradecahydrochrysene (Y-7).

A solution of 161 mg (0.49 mmoles) of the alcohol Y-6 12 ml of abs ethanol and 1 ml of concentrated hydrochloric acid was heated to reflux for 1 hour under an argon atmosphere. The cooled solution was poured onto 50 ml of water, and the aqueous solution was extracted with benzene (3x50 ml). The combined organic layers were washed with saturated aqueous sodium bicarbonate solution (1x50 ml) and brine (1x50 ml), and were dried ($MgSO_4$).

Evaporation to dryness afforded 157 mg (98%) of the ketone Y-7 mp 169-176° (vacuum) which was suitable for use in the next step. Ptlc (40% ether-petroleum ether) and sublimation (150-155°, 0.7 mm) afforded the analytical sample mp 178-184° (vacuum): ir ($CHCl_3$) 1705 (C=O); nmr ($CDCl_3$) 0.73δ (s, 3), 0.83δ (s, 4.5); 0.95δ (s, 4.5), 1.05δ (s, 3, C-1, 4b, 6a, 10a, 12a CH_3s), 5.47δ (s, 2 vinyl).

Anal. Calcd for $C_{23}H_{36}O$: C, 84.09; H, 11.04. Found: C, 84.16; H, 11.16.

2,2-Ethylenedioxo-1,2,3,4,4aα,4b,5,6,6a,9,10,10a,10bα,11,12,12a-Hexadecahydro-1,4bβ,6aα,10aβ,12aβ-Pentamethylchrysene (Y-8).

A dry 100 ml flask was fitted with a Dean-Stark water separator and was charged with a solution of 157.3 mg (0.480 mmole) of the ketone Y-7 and 49 mg of p-tolulenesulfonic acid in 30 ml of dry benzene and 3 ml of ethylene glycol (bp 100°,

27 mm). The mixture was heated to reflux for 5 hours with separation of the water formed. On cooling, the reaction mixture was washed onto 50 ml of water with 50 ml of benzene. The layers were separated, and the aqueous layer was extracted with 1:1 ether-benzene (3x50 ml). The combined organic layers were washed with water (1x50 ml), saturated aqueous sodium bicarbonate (1x50 ml) and brine (1x50 ml) and were dried ($MgSO_4$).

Evaporation to dryness afforded 191 mg of a yellow solid which was chromatographed on 30 g of silica gel. Elution with 125 ml of 30% ether-petroleum ether afforded 179 mg (quantitative) of the ketal Y-8 mp 150-155° which was represented by greater than 90% one volatile component by glpc: ir ($CHCl_3$) 1650 (C=C), 1070(C-O); nmr ($CDCl_3$) 0.72δ (m, 6), 0.90δ (s, 6), 1.02δ (s, 3, C-1, C-4b, C-6a, C-10a, C-12a CH_3s), 3.75-3.97δ (m, 4, ketal), 5.45δ (s, 2, vinyl). Recrystallization from methylenechloride-hexane gave the analytical sample mp 173.5-175.5° (vacuum).

Anal. Calcd for $C_{25}H_{40}O_2$: C, 80.59; H, 10.82. Found: C, 80.58; H, 10.88.

Attempted hydroboration of Y-8 with disiamylborane.

A dry 10 ml pear shaped flask was flushed with argon and charged with 1.0 ml of a 0.9 M solution of diborane in tetrahydrofuran (12δ) and 2 ml of dry tetrahydrofuran. The flask was cooled in an ice bath and 0.43 ml (280 mg, 4.0

mmoles) of 2-methyl-2-butane was added dropwise. The mixture was allowed to warm to room temperature over two hours and a solution of 17.2 mg (0.046 mmole) of the ketal Y-8 in 1 ml of dry tetrahydrofuran was added.

After an additional 20 hours at room temperature the excess borane was decomposed with 2 drops of water and the reaction products were oxidized by the sequential addition of 0.4 ml of 3 N sodium hydroxide solution and 0.6 ml of 30% hydrogen peroxide solution. Following the addition, the bath temperature was raised to 60° for one hour and on cooling the reaction mixture was poured onto 25 ml of saturated aqueous sodium carbonate solution, and the aqueous solution was extracted with benzene (3x25 ml). The combined organic layers were washed with saturated sodium carbonate solution (1x25 ml), water (1x25 ml) and brine (1x25 ml) and were dried ($MgSO_4$). Evaporation to dryness afforded 19.2 mg of a white crystalline solid which exhibited no O-H stretch in the ir. Ptlc (10x20 cm plate, 25% ether-benzene) gave 11.5 mg (57%) of recovered starting material mp 164-168° (vacuum).

2,2-Ethylenedioxo-1α,2,3,4,4aα,4b,5,6,6a,7,10,10a,10bα,11,12-12a-Hexadecahydro-8(9H)-Oxo-1β,4bβ,6aα,10aβ,12aβ-Pentamethyl-chrysene (Y-9).

To a solution of 117 mg (0.460 mmole) of the olefin Y-8 in 10 ml of dry tetrahydrofuran under an argon atmosphere and cooled in an ice bath was added 3.0 ml of a 0.9 M solution of diborane in tetrahydrofuran (122). After 5 hours the

excess borane was decomposed by the careful, sequential addition of 0.1 ml water, 1.5 ml of 3 N aqueous sodium hydroxide, and 2.0 ml of 30% hydrogen peroxide solution. The resulting mixture was heated to 50-60° for 1 hour and was poured into 50 ml of saturated aqueous sodium carbonate. The aqueous solution was extracted with 1:1 ether-methylene chloride (4x50 ml) and the combined organic layers were washed with saturated aqueous sodium carbonate (1x50 ml), water (1x50 ml) and brine (1x50 ml) and were dried ($MgSO_4$).

Evaporation afforded 180 mg of a white solid which was dissolved in 6 ml of dry methylene chloride in a 25 ml flask under an argon atmosphere and was treated with 3 ml of a 0.24 M solution of chromium trioxide dipyridine complex (74) in methylene chloride. After 10 min, the reaction mixture was filtered through 10 g of grade III alumina and the column was washed with ether-methylene chloride. Evaporation gave a white solid which was chromatographed on 30 g of silica gel. Elution with 200 ml of 0-10% ether-methylene chloride gave 4 mg of a mixture of components and further elution with 250 ml of 20% ether-methylene chloride afforded 165 mg (93%) of a solid which indicated a weak O-H band in the ir. Repetition of the oxidation gave 149 mg (84%) of the ketone Y-9 mp 245-252° (vacuum) which was represented by 90% of a single volatile component by glpc: ir ($CHCl_3$) 1700 (C=O), 1075 (C-O), nmr ($CDCl_3$) 0.78δ (d, J=7, 3, C-1 CH_3), 0.95δ (s, 9), 1.07δ (s, 3) (angular

CH_3s), 3.73-3.97δ (m, 4, ketal).

A sample was purified by ptlc (25% ether-methylene chloride) and recrystallization from methylene chloride-hexane to give the analytical sample mp 271-273° (vacuum).

Anal. Calcd for $C_{25}H_{40}O_3$: C, 77.27; H, 10.38. Found: C, 77.24; H, 10.22.

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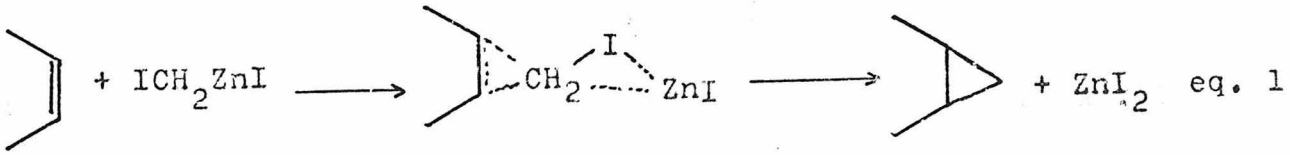
Proposition 1

It is proposed that the ability of allylic amines and thioalcohols to direct the Simmons-Smith cyclopropylation reaction be investigated.

The Simmons-Smith reagent, iodomethylzinc iodide or bis-(iodomethyl)zinc zinc iodide (1), has been developed into a versatile reagent for the stereospecific introduction of methylene into olefins since its discovery 13 years ago. A recent modification has extended the reaction to the synthesis of methyl and phenyl substituted cyclopropanes (2).

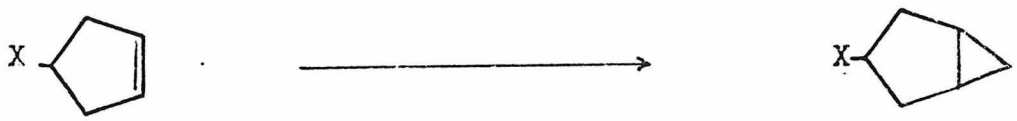
The discoverers and other groups have investigated the reaction of the Simmons-Smith reagent with unactivated aliphatic and alicyclic olefins (3,4,5) and have found that the reagent is electrophilic and subject to steric hinderance. This data fits the generally accepted mechanism shown in eq. 1 rather than the alternatively proposed addition-elimination mechanism (6).



eq. 1

Quite early during the development of this reagent, Winstein and Sonnenberg (7) discovered that the alcohol 1, X=OH reacted at least an order of magnitude faster than the corresponding hydrocarbon 1, X=H and moreover, that the only

product obtained was the cyclopropyl alcohol 2, X=OH, resulting from cis attack of the Simmons-Smith reagent. The mechanism



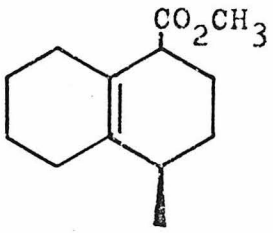
1 2

and generality of the directing and rate enhancing abilities of allylic and homoallylic alcohols have been investigated further by Dauben (8) and Rickborn (9) and the use of alcohols to control the reaction has now seen application in numerous synthetic schemes. There are apparently no exceptions to the rule that allylic and homoallylic alcohols direct the cyclopropylation to the side of the double bond closest to the oxygen (10).

It is not clear whether alcoholysis occurs prior to the cyclopropylation or not; Dauben (8) has presented evidence that it does not in the case of 1-hydoxycyclohex-2-ene, but Ginsig and Cross (11) found it to be a necessary step in the cyclopropylation of estr-5(10)-ene-3, 17-diol. However, the latter case may be anomalous since the reaction was extremely slow. Thus it appears that ionization of the alcohol is not an essential part of the reaction mechanism.

During the ensuing years, the effect of neighboring esters, ethers, and acetate on the stereochemical course of the reaction have been studied. Winstein (12) and Sims (13)

have demonstrated that β,γ-unsaturated esters direct the reagent, presumably through coordination of the zinc with the ester carbonyl. The ester 3 is a typical example (13b), giving the cyclopropyl ester 4, on treatment with the Simmons-Smith reagent, which was carried on to the angularly methylated



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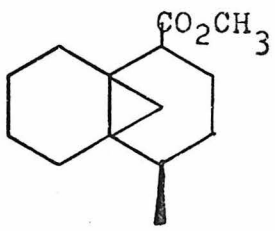

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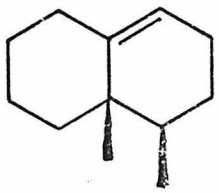


5

olefin 5 *via* decarboxylation of the corresponding acid. Sawada *et al.* (14) have analyzed the hydrolyzed products obtained from the reaction with both α,β- and β,γ-unsaturated (-)-menthyl esters for optical activity. In the former series optical yields of 2.5-9.0% were achieved while an β,γ-unsaturated ester gave a 1.4% yield. These results offer further evidence that association with the ester occurs in the transition state.

Allylic ethers appear to direct the reagent also (8,9), although the only well documented case is that of 1-methoxycyclohex-2-ene. In view of the recently demonstrated utility of methyl ethers as blocking groups for alcohols (15), further study of this point seems warranted.

The effect of allylic acetate seems to be variable. Cope and coworkers (16) report that in the case of 1-hydroxycyclohept-

2-ene acetate, the Simmons-Smith reagent approaches from the least hindered side *trans* to the acetate. This result has been confirmed by Dauben (8) who also obtained the product of *cis* addition from reaction with the corresponding alcohol. On the other hand Sawada *et al.* (14) report that 1-hydroxy-cyclohex-2-ene acetate reacts to give *cis* cyclopropylation and Winstein (7) indicates a similar result for 1, X=OAc. It is possible that acetate is not favorably oriented to coordinate with the reagent in seven membered rings leading to the anomalous result; Winstein's results lend some credence to this hypothesis.

From the above results, it seems clear that the Simmons-Smith reagent is directed by functionality possessing a non-bonded pair of electrons which can coordinate with the zinc atom. It thus appears reasonable that amino and sulfhydryl groups, appropriately located with respect to the double bond, would also direct and enhance the rate of the Simmons-Smith reaction. Such results are particularly pertinent in view of the numerous natural products which contain nitrogen or sulfur atoms and of the increasing use of these heteroatoms, especially nitrogen, as masking groups in synthesis (17).

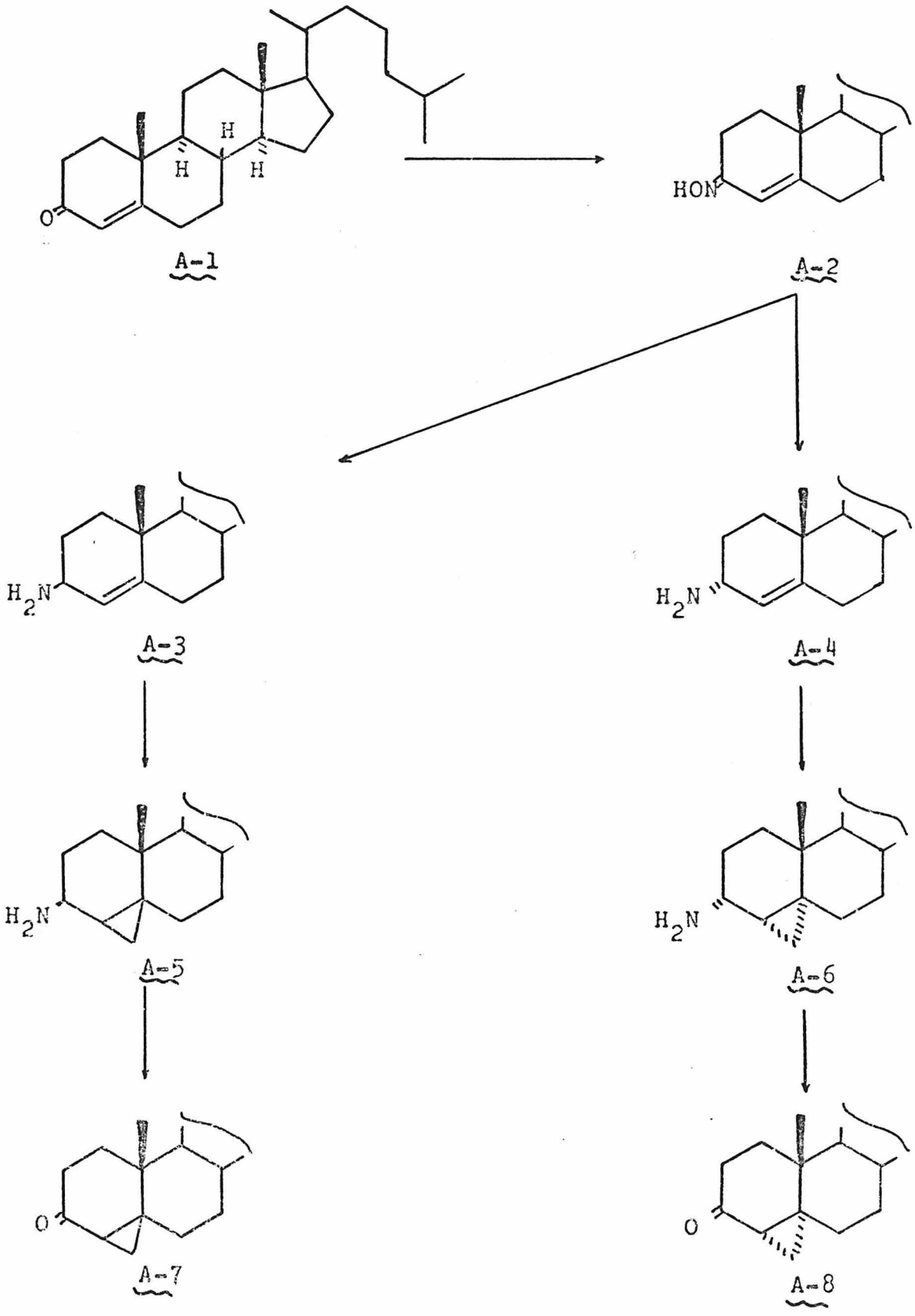
Experiments to determine the affects of allylic sulfur and nitrogen on the course of the reaction can most conveniently be carried out on steroidal substrates since the starting materials have all been prepared and characterized. Also the

products of the Simmons-Smith reaction on the corresponding steroidal alcohols are well known.

Chart A outlines the proposed reactions the allylic amines. Suitable substrates are readily avaolable from 3-oxo-Δ^4-cholestenone, (A-1), through lithium aluminum hydride reduction of the derived oxime A-2 (18). Treatment of the separated equatorial and axial amines, A-5 and A-6 respectively, with the Simmons-Smith reagent should then result in formation of the cyclopropyl derivatives A-7 and A-8. If indeed cyclopropylated products are obtained, it should be possible to convert them to the ketones A-9 and A-10 respectively using the method recently developed by Corey and Achiwa (17). The reaction condtions, 3,5-di-t-butyl-1,2-benzoquinone in methanol at room temperature followed by acidification to pH 2-4 for a few hours, are sufficiently mild that no reactions of the cyclopropane ring are anticipated during the transformation. The ketones A-9 and A-10 have been prepared previously by Dauben and co-workers (19) so that the stereochemistry of the addition can be readily determined.

The preparation of the necessary thioalcohols is shown in chart B. Bourdon (20) has synthesized the 3β-thioalcohol B-2 by lithium aluminum hydride reduction of the corresponding thioketone B-1 which in turn was obtained by treatment of the ketone A-1 with hydrogen sulfide in acidic ethanol-benzene at 5°. The stereochemistry of the proposed cyclopropylation

Chart A



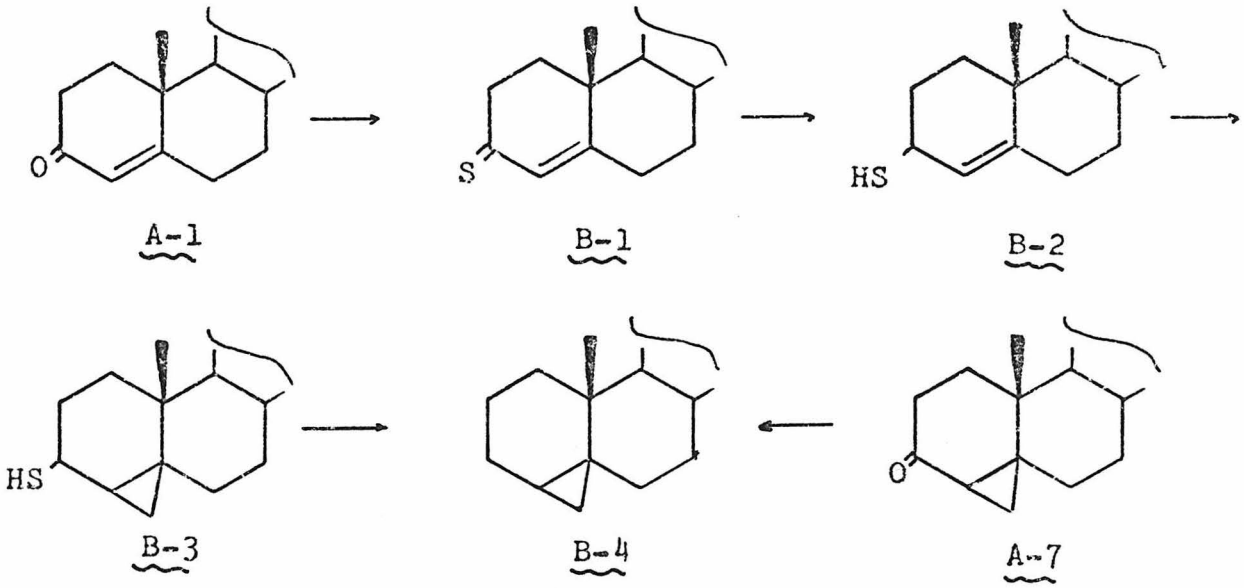
A-1 A-2 A-3 A-4 A-5 A-6 A-7 A-8

of B-2 should be indicated by raney nickel desulfurization to B-4 and comparison with the product of Wolff-Kishner reduction of the cyclopropyl ketone A-7.

Bourdon has also achieved a synthesis of the 3α-thioalcohol B-7 (21). Treatment of the tosyl alcohol B-5 with thiourea gives a thiouronium salt via an s_n2 substitution which on base hydrolysis and acetylation gives the alcohol B-6. Dehydration with thionyl chloride and deacetylation then leads to the desired B-7. From this point one can proceed in a manner exactly parallel to the 3β-case, comparing the desulfurized Simmons-Smith product B-9 with the Wolff-Kishner product of A-8.

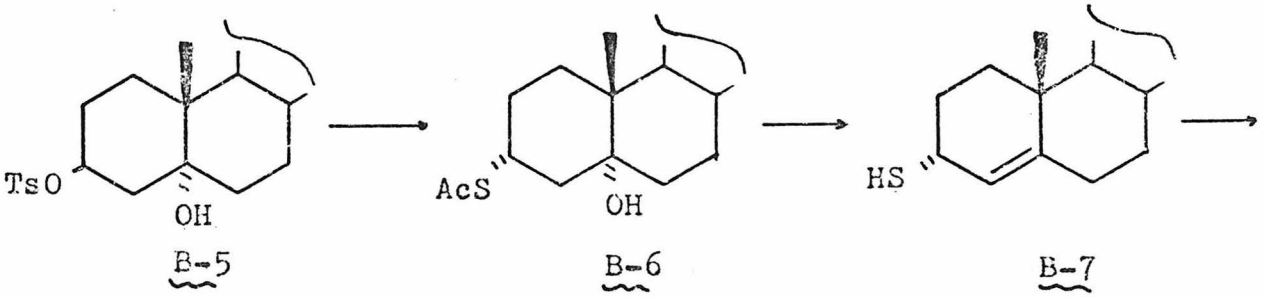
Should these preliminary investigations prove successful, numerous further experiments suggest themselves. It would obviously be desirable to extend the results to an appropriate series of homoallylic compounds. It would also be of interest to look at the effect of N and S alkyl substituents on the rate of the reaction. This can conveniently be done through the use of competition experiments (9). Finally, it would be instructive to determine the relative rates of the Simmons-Smith reaction on a series of 3-substituted-Δ^4-cholestenes including the hydroxy, methoxy (22), carbomethoxy (23), and acetate as well as the amino and sulfhydryl derivatives. Such a comparison of several directing groups has never been carried out before on a single substrate making comparisons of reactivities difficult.

Chart B

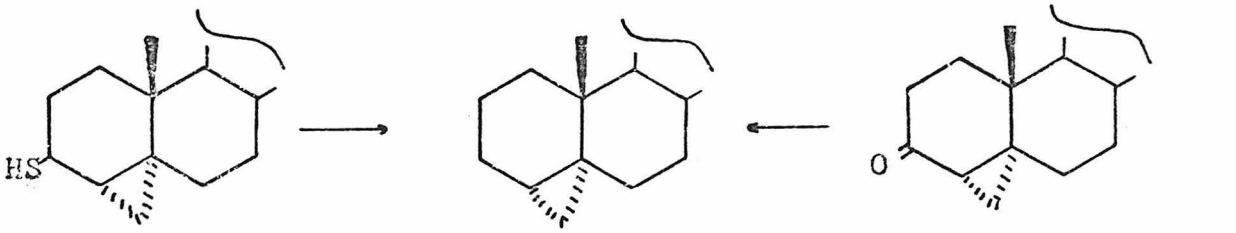


A-1 B-1 B-2

B-3 B-4 A-7



B-5 B-6 B-7



B-8 B-9 A-8

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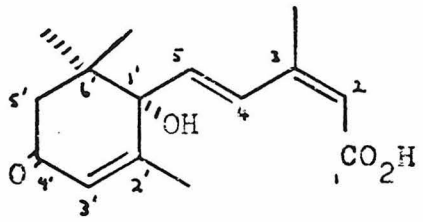
Proposition 2

Feeding experiments designed to establish the biosynthetic pathway leading to abscisic acid 1 are proposed.

In 1965 Addicott and his coworkers correctly deduced the structure of abscisic acid (ABA) 1 (1), a plant growth regulating hormone that had defied isolation and characterization for a number of years. The structural assignment was verified and experimental quantities were made available by Cornforth's synthesis of 1 within the year (2). Since then ABA has been found to be widely distributed among the higher plants and to be a potent growth inhibitor, occuring mainly in senescent or aborting organs (3). ABA is effective at low concentrations and is nontoxic to the plant; moreover its effects are antagonized by various growth promoting hormones such as the gibberellins and cytokinins (4). Recent results obtained by Pearson and Wareing have indicated that ABA acts in conjunction with another cytoplasmic factor to inhibit RNA synthesis (5), although its exact mode of action is far from well understood. The obviously important role of ABA in regulating plant growth cycles and the possibilities of commercial applications in facilitating crop harvests by controlling abscission have combined to sustain a high level of interest in the chemistry of this compound.



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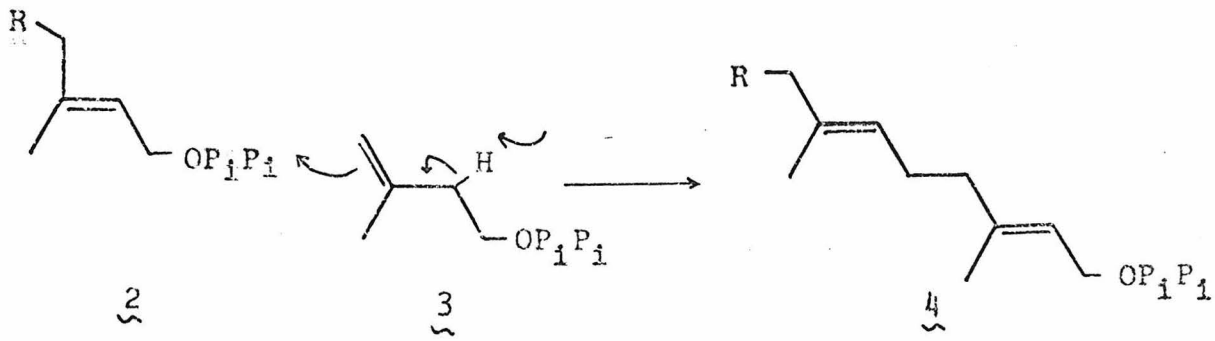
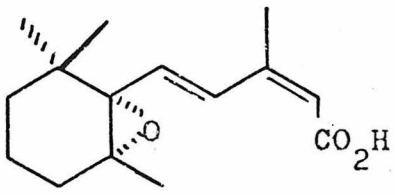
Considerable speculation about the biosynthesis of ABA has arisen because of its unusual sesquiterpenoid structure. Its terpenoid origin was confirmed by the work of Noddle and Robinson who demonstrated that ^{14}C-labeled mevalonic acid was incorporated into ABA when fed to whole tomatoes, strawberries and avocados (6). In another set of experiments Robinson and Ryback (7) fed doubly labeled [(4-R)-4-3H] and [(4-S)-4-^{3}H] -2-^{14}C mevalonate and measured the $^{3}H/^{14}C$ ratio of the isolated ABA. From the 4-R precursor they found, after base treatment to equilibrate the labile ring protons, a ratio of 1/3 while from the 4-S precursor the ratio was 0/3. Since it has been shown in a wide variety of systems that the enzymatic coupling of a dimethylallylpyrophosphate 2 with isopropenylpyrophosphate 3 results in the loss of the 4-R-^{3}H if the newly formed double bond is cis and the 4-S-^{3}H if the bond is trans, it would appear that the Δ^2



2 3 4

double bond of ABA is initially formed in the trans configuration and later undergoes isomesization to the active cis form. In one further experiment, Milborrow and Noddle (8) were able to show that the epoxide 5 labeled on either oxygen or carbon was incorporated into ABA by whole tomatoes and wheat shoots implicating 5 as a natural precursor of ABA. Furthermore the 1',2'-diol 6 obtained by hydrolysis of the epoxide was not active. The selection of the epoxide 5 for



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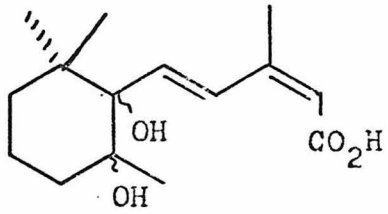

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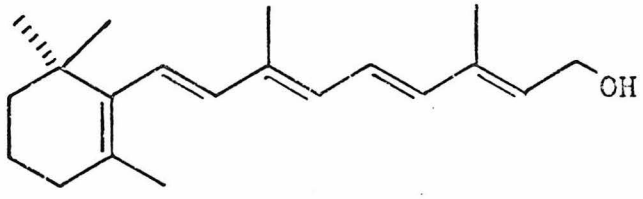
testing was based on the results of Tamura and Nagao (9) who screened a number of related compounds and found that 5 was almost as active as ABA itself. With the above results in hand detailed biosynthetic schemes can be proposed and tested.

There are no known sesquiterpenes which have structures related to that of ABA, but there are a number of degraded



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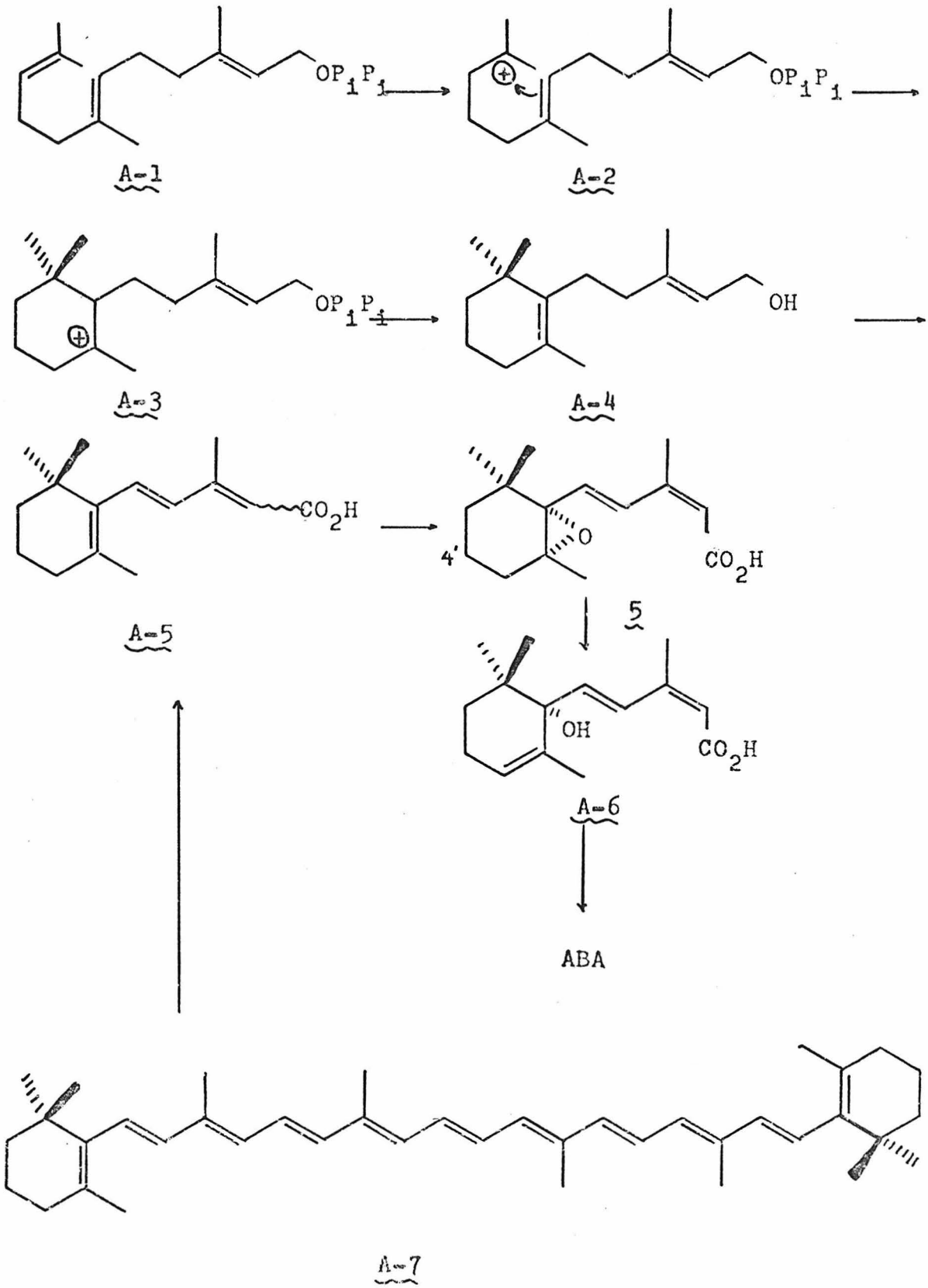
carotenes such as vitamin A (7) which do have similar structures. This leads one to suspect that ABA may also be derived from a carotene. Chart A outlines possible biosynthetic routes to ABA starting from either farnesylpyrophosphate (A-1) or β-carotene (A-7). Protonation of farnesylpyrophosphate (A-1) and cyclization through the carbonium ions A-2 and A-3 to give the diene A-4 is similar to the scheme proposed for the formation of the cyclic carotenes (10). Enzymatic oxidations such as that required to convert A-4 into the conjugated olefin A-5 are well known in carotene chemistry (11) and selective epoxidations such as that indicated in the conversion of A-5 into the epoxide 5 are also known (12). It seems probable that the Δ^2-trans - cis isomerization would occur at the triene stage since this conjugated system can most readily absorb energy. The type of epoxide cleavage required for conversion of 5 into the allylic alcohol A-6 has recently been carried out in the laboratory (13) and it certainly would seem feasible that an enzyme system could carry out the same reaction. Allylic oxidation would then afford ABA. This proposed scheme differs slightly from that proposed by Milborrow and Noddle (8) who favor hydroxylization of 5 at C-4' followed by oxidation to the corresponding ketone and base catalyzed cleavage of the epoxide. However, their scheme does not account for the high ABA activity of the allylic alcohol A-6 in the screening test employed by Tamura and Nagao (14).

Chart A



Alternatively, the conjugated triene acid A-5 could be formed by oxidative cleavage of β-carotene A-7 in an unspecified series of steps. Numerous other possibilities exist, of course, such as partial completion of the ring transformations at the carotenoid stage prior to degradation. However, it seems appropriate to explore the most probable possibilities first, and if the experiments prove negative, to search for more obscure routes.

It would appear most logical to initiate the feeding experiments with compounds close to ABA and to work toward the starting materials. In this way one should be able to minimize the effort expended on incorrect pathways. Furthermore, it should be possible to carry out feeding experiments in a manner similar to that employed by Milborrow and Noddle (8), who injected whole fruits with a solution of the substance to be tested and, following an incubation period, macerated and extracted the plants. The extracts then were separated by chromotography for counting. The first compound which should be investigated in this way is the allylic alcohol A-6. Labeled derivatives of this substrate should be available using a variation of the synthesis employed by Tamura and Nagao starting from β-ionone (14). The label could be conveniently introduced at the last step which involves a Wittig reaction using carbomethoxymethylenetriphenylphosphorane. Efficient incorporation of this compound would

imply that the final two steps of the proposed scheme are correct. Secondly, the fate of the cis and trans isomers of the triene acid A-5 should be determined to see if these compounds are converted through the epoxide 5 to ABA and if so, whether the Δ^2-trans-cis isomerization occurs at this stage. These compounds are easily obtained by treatment of β-ionone with carbomethoxymethylenetriphenylphosphorane (9).

If the results of these experiments are positive, one could then attempt to determine the source of the triene A-5, while if not, it would be necessary to devise new experiments to determine the actual precursor of ABA. There are a number of experiments one could perform to ascertain the source of the triene A-5 or the other precursor. One approach would be to feed various labeled carotenes, particularly β-carotene and lycopene and possible sesquiterpenoid precursors such as the acid A-4, and to determine the fate of the label. Unfortunately, large hydrocarbon compounds such as the carotenes cannot be administered using the techniques described above due to solubility problems. However, in recent years methods have been developed for feeding these compounds employing cell free extracts and surfacants to keep everything in solution (15). In order to apply this technique here, it would first be necessary to demonstrate de novo ABA synthesis in a cell free extract. This should not present a major obstacle since ABA synthesis

occurs in the isolated fruits and leaves of a number of plants. Wheat leaves might be a good choice because ABA synthesis can be induced to occur very rapidly (16). It is anticipated that a wheat leaf homogenate, purified from debris by centrifugation, would support ABA synthesis. This could be verified by administering labeled mavalonic acid to the extract and looking for incorporation of the label in ABA. Then, by measuring the amount of label incorporated (17), one could determine the optimum conditions for ABA synthesis.

Should the ABA fail to aquire label from any of the carotenes, it would appear likely that the compound originates from farnesylpyrophosphate. This could be further tested by attempting to demonstrate ABA synthesis in a system where carotene biosynthesis is blocked. This could be achieved using either mutants or by taking advantage of the temperature sensitivity of carotene biosynthesis (18). If labeled mevalonic acid is incorporated using such a system, it would provide firm evidence that ABA is not derived by degradation of the carotenes.

The experiments proposed above should provide insight into the ABA biosynthetic pathway. Clearly, additional feeding experiments could be designed based on the initial results. Finally, when these experiments indicate a particular pathway, one could attempt to obtain proof of its importance <u>in vivo</u>

by isolation of the proposed intermediates synthesized by the plant from labeled mevalonic acid.

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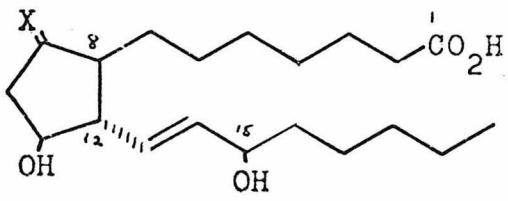
Proposition 3

A synthesis of 11-desoxyprostaglandin F_1, via a new, generally useful, conjugate addition of alkynes to α,β-unsaturated ketones is proposed.

The intense physiological activity of the prostaglandins such as 1 and the difficulty attendant with their isolation from natural sources (1) has evoked a catholic interest in the development of synthetic routes to these elusive molecules. Although a number of successful schemes have been reported (2), only the most recent approach employed by Corey et al. (3) gives preparatively useful amounts of the prostaglandins.



$PGE_{1\alpha}$ X=α-OH

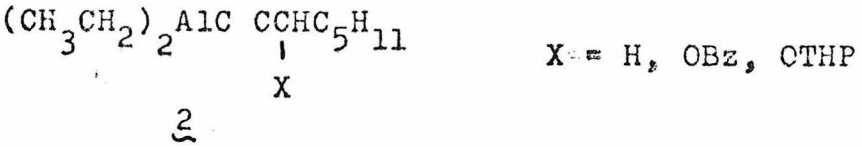
PGF_1 X= =O

1

Most of the syntheses suffer from low yields at one or more steps and a lack of stereospecificity, particularly during the generation of the C-15 alcohol (4). In view of the potential utility of derivatives of this class of compounds, new synthetic methods for their construction are required. One possible approach, aimed at the

efficient introduction of the C-12 side chain is proposed below.

The diethylalkynyl alane 2 (5) is isoelectronic with the well known diethylaluminum cyanide which has been used by Nagata et al. in the stereospecific cleavage of epoxides (6) and in the stereoselective conjugate addition of HCN to a large number of α,β-unsaturated ketones (7). It thus

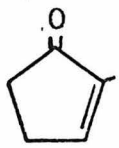


2 X = H, OBz, OTHP

seems possible that the alane 2 might undergo some of the same reactions as the later reagent and provide a useful method for the insertion of substituted acetylenes into organic compounds. In support of this theory, Fried and his coworkers (8) have shown that 2 closely resembles diethylaluminum cyanide in its behavior toward epoxides. This epoxide cleavage reaction has been used by Fried in his synthesis of 7-oxaprostaglandin derivatives (8b). It therefore appears reasonable that the alane 2 might also parallel the reactivity of diethylaluminum cyanide toward α,β-unsaturated ketones and transfer acetylene derivatives to the β-carbon of this system.

Since this reaction, if successful, would be valuable as a general synthetic tool, the reactions of the alane 2, X=H with a number of readily available unsaturated ketones

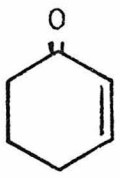
such as 3-6 should be attempted to obtain a measure of the scope of the reaction. Of particular interest would be the stereochemistry of the addition to the bicyclic enone 6. This could most easily be determined by reduction of the triple bond and ketone of the addition product 7 with lithium in ammonia (9) and cleavage of the acetate derivative of the resulting olefinic alcohol to the aldehyde 8 with osmium tetraoxide and periodic acid (10). Finally, Wolff-Kishner reduction (11) of the aldehyde and oxidation of the C-3 alcohol, which would be liberated from



R = H

= $(CH_2)_6CO_2Me$

3



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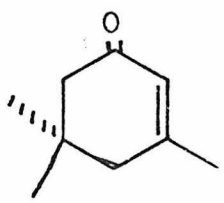

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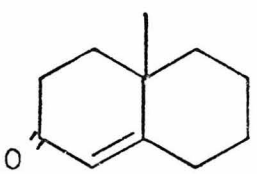

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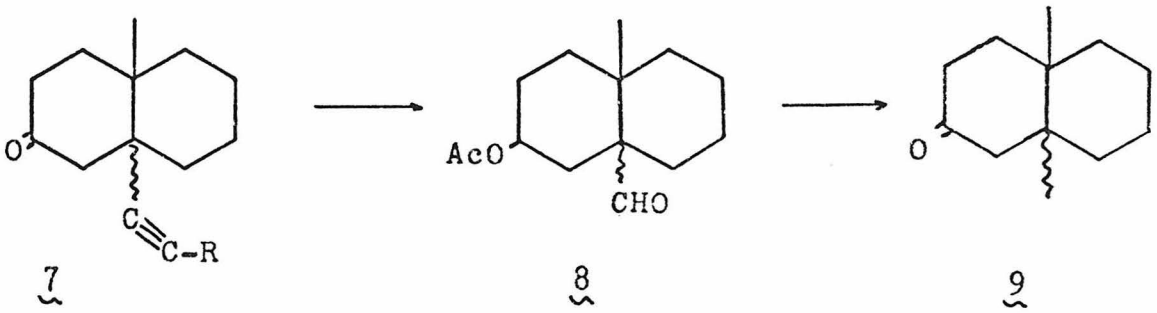
its acetate under the Wolff-Kishner conditions, should give the octalone 9. The cis isomer of 9 has been prepared by Marshall et al. (12) and, if necessary, the trans isomer could be obtained by the stereospecific Simmons-Smith cyclopropylation-Birch cleavage method employed in this thesis (13). Comparison of the octalones prepared by the various routes should reveal the stereochemistry of the addition.

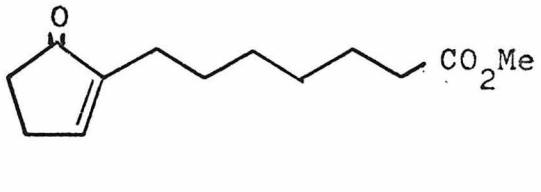
Upon successful completion of the first phase of this work, the results should be extended to the known (8a)



7 8 9

tetrahydropyranyl ether or benzyloxy-substituted alanes 2, X=OTHP or OBz. Treatment of the cyclopentenone 3, R=carbomethoxyheptyl (14) with this reagent might then lead to the cyclopentenone 10. Deesterification and protection of the ketone as the ketal derivative followed by treatment with lithium in ammonia should lead, on deketalization, to the physiologically active (14, 15) cyclopentanone 11. If allylic cleavage of the OH group of 10 competes with reduction of the triple bond, the protecting group could be removed and the alcohol ionized prior to the reduction (16). The side chains can isomerize about C-8 to form the more stable trans isomer regardless of the stereochemistry of the initial addition.

There are a number of possible modifications to the proposed synthesis which might make it more efficient. For instance, one may be able to trap the intermediate enol aluminate formed in the 1,4 addition to 3, R=H and then regenerate the enolate anion to introduce the C-8 side



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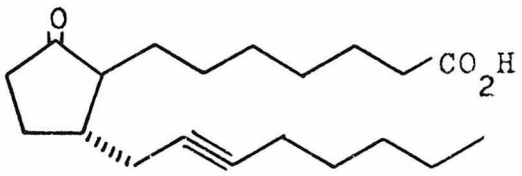

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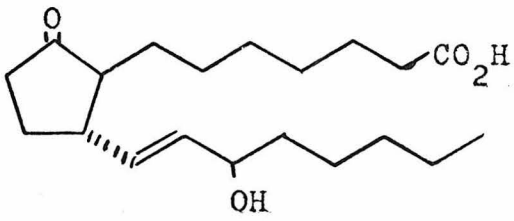

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chain via alkylation. Also the opportunity exists to utilize an optically pure alkyne in the formation of the alane 2 so that the side chain could be introduced in its natural configuration.

Should the proposed reaction prove facile, the above work would provide an indication of its utility. Clearly further investigation would be warranted, especially on the stereochemistry of the addition and on the steric and electronic requirements of the reaction.

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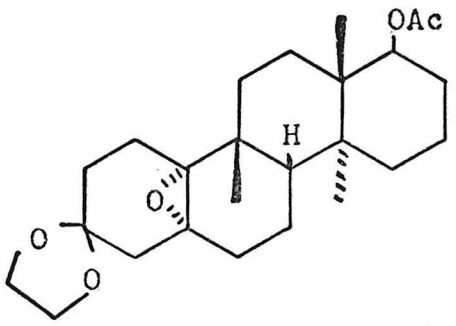
Proposition 4

Experiments directed toward the interconversion of triterpene systems *via* backbone rearrangements are proposed.

It is now well established that the basic steroid and triterpene ring systems arise biosynthetically from a suitable cationic cyclization of squalene oxide followed by a series of Wagner-Meerwein shifts and loss of a proton. (1) One result of their common biosynthetic ancestry is that many of the major triterpene ring systems are simply interrelated by the appropriate number of 1,2-methyl and hydrogen shifts. In view of the complexity of these systems and the difficulties involved with the total synthesis of even one, laboratory methods for their interconversion would be highly desirable. Two experiments directed toward achieving such interconversions are proposed below.

One experiment involves conversion of the tetracylic epoxide 1, possessing the *cis-anti-trans* backbone characteristic of the curcurbitacins 2 (2), to the enone 3 which has the substitution pattern of lanosterol 4. A similar rearrangement of the epoxide 5 could lead to the α,β-unsaturated ketone 6. This represents a conversion of a potential key intermediate in the synthesis of shionone 7

or alnusenone in the pentacyclic series to a potential intermediate in the synthesis of the the dammarenediols 8 (2) and the related pentacyclic triterpenes.



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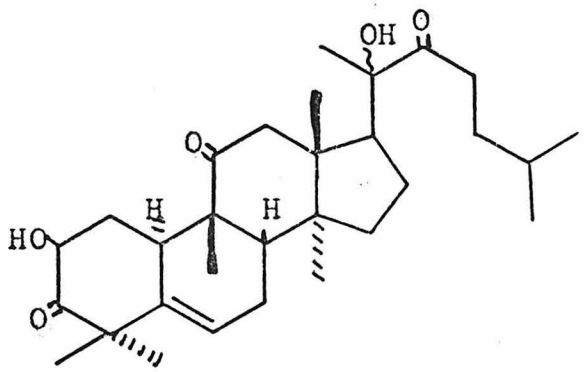

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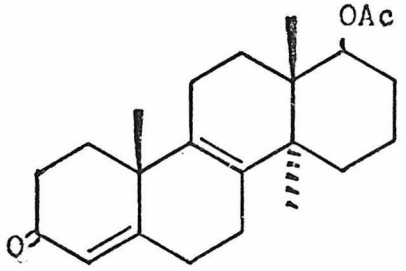

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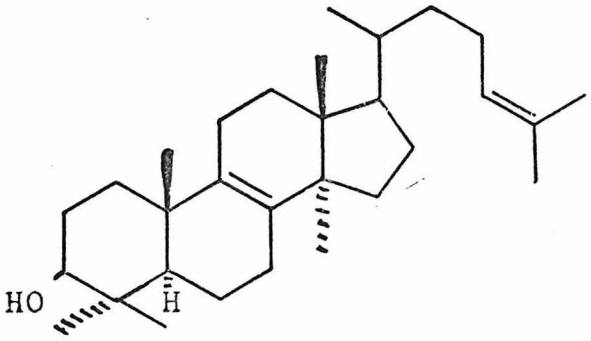

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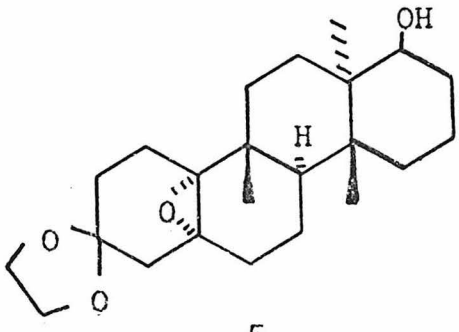

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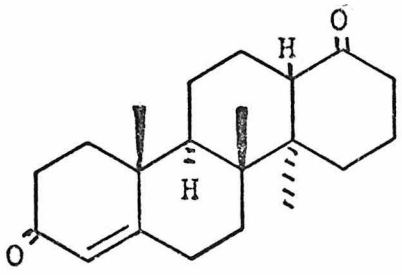

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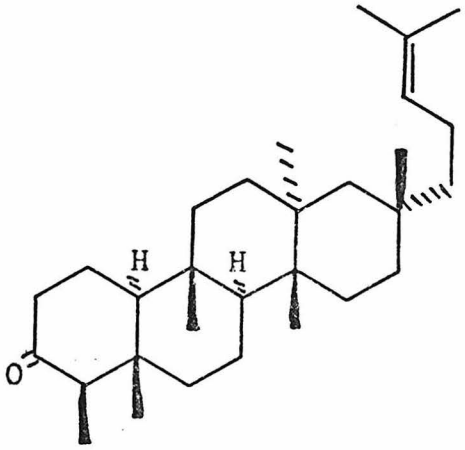

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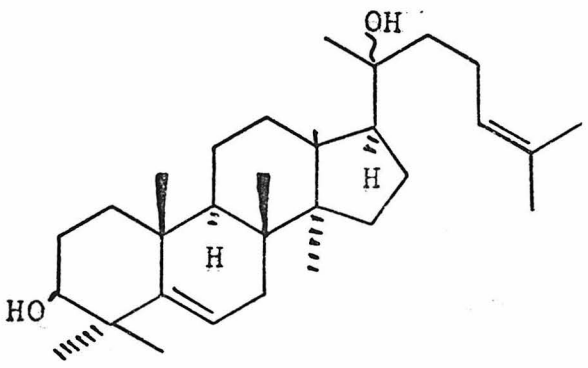

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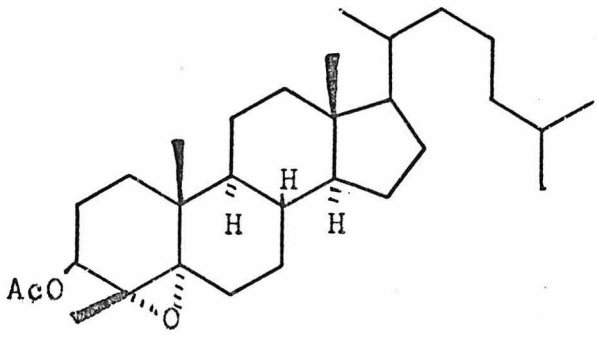
Rearrangements of steroidal epoxides have been widely studied, particularly by D. N. Kirk and his co-workers (3). Whereas some backbone rearranged product was obtained from most of the acid catalyzed reactions, in cases where steric or electronic effects limited the competing reactions the yields were quite good. The rearrangement of 9 offers an example of a



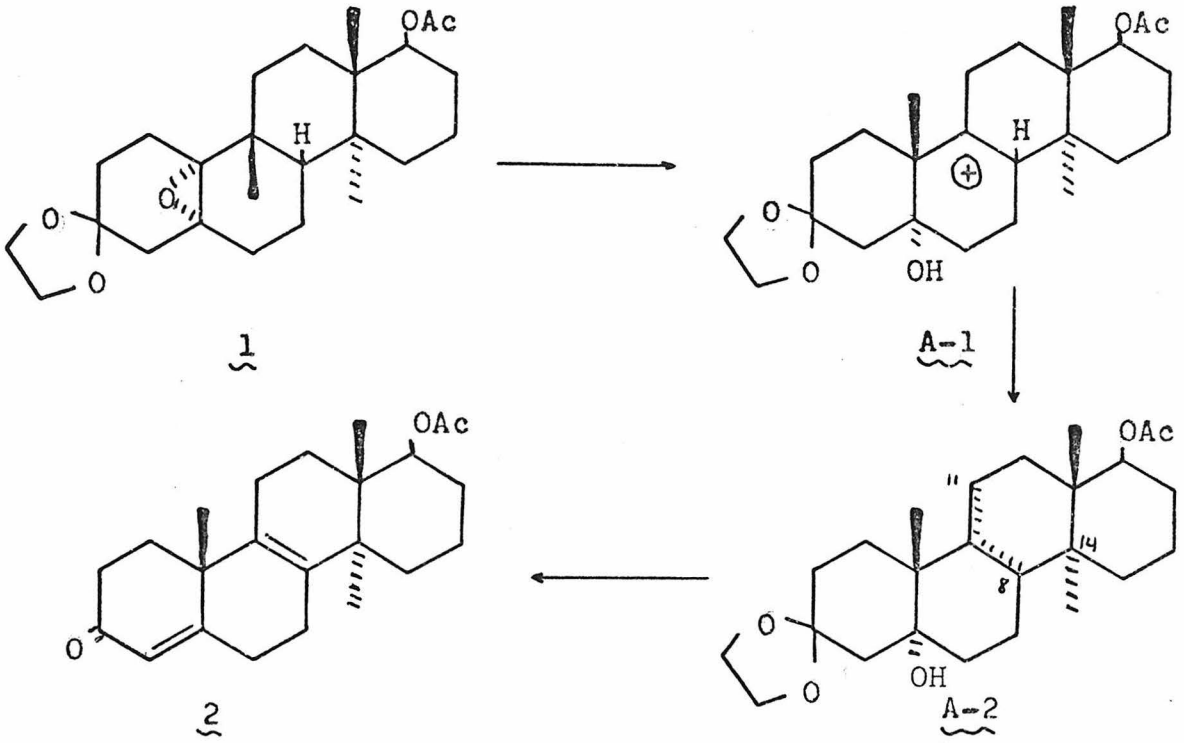
9

tetrasubstituted epoxide where accumulation of positive charge on C-4 is restricted by the inductive effect of the neighboring acetate. Treatment of 9 with borontri-

fluoride etherate in benzene afforded a single backbone rearranged product in 90% yield. (4) ApSimon and Rosenfeld (5) and Whitlock and Olson (6) have studied rearrangements in related systems. Whitlock found evidence that there is a rapid equilibrium between all the possible tertiary carbonium ions during backbone rearrangements and that product formation occurs through the most stable ions.

In light of these results, it is anticipated that acid catalyzed cleavage of 1 will lead to the carbonium ion A-1. Cleavage toward C-10 should be favored by both inductive and stereoelectronic effects, and to the extent that methyl migration is concerted, by the relief of the steric strain associated with the B/C cis ring fusion. The possible fates of A-1 are fourfold: The angular methyl group could shift back to C-9, although this could provide no special stabilization. More likely, a proton could be lost from either C-8 or C-11 to give, after quenching, the mixture of olefins A-2. However, this elimination must involve accumulation of considerable positive charge on C-9 since there are no protons which are trans-diaxial to the migrating methyl. This opens the fourth possibility that a 1,2-shift of the C-8 hydrogen could occur initiating further rearrangements which, if they proceeded into the D ring, would give a molecule with the elusive fusidic acid skelton. (7) Unfortunately, such a rearrangement

CHART A



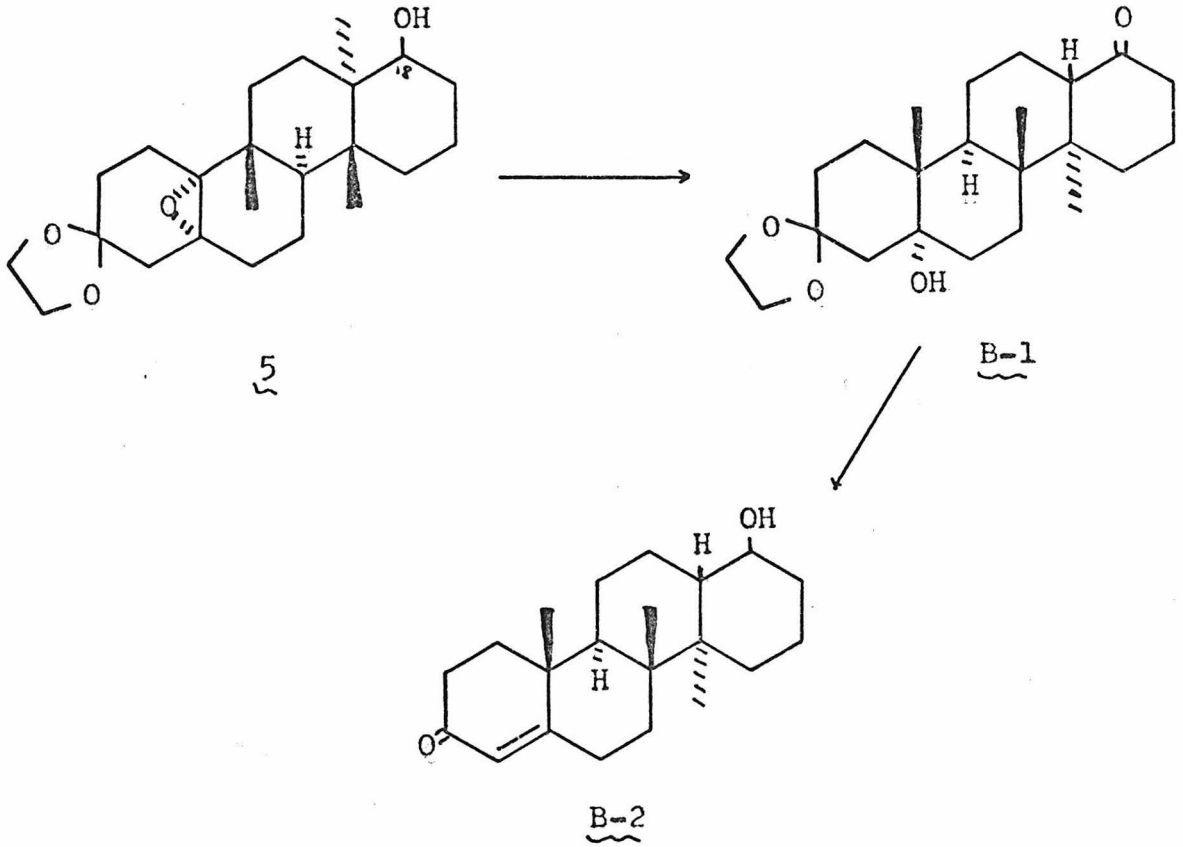
seems unlikely due to the strain associated with the syn-backbone of fusidic acid.

The anticipated products, the mixture of olefins A-2 should yield the unsaturated ketone 2 via deketalization, which should proceed with concomitant dehydration, and acid catalized equilibrium of the olefin mixture into the more stable Δ^8-isomer. This equilibrium is similar to that employed by Woodward and Barton in their partial synthesis of lanostercl. (8) Rearrangement of the double bond into the 8(14) position should not compete so effectively here since there is a six rather than a five membered D ring. The ketone 2 has the lanosterol skelton and the appropriate functionality in the A and

D rings to serve as a key intermediate in a total synthesis.

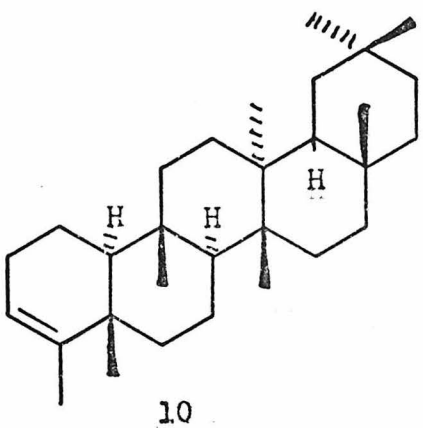
Similar considerations lead one to expect that the epoxide 5 would give the ketone B-1.

CHART B



In this case all the migrating groups are trans-diaxial and the reaction should proceed to the oxygen stabilized C-18 carbonium ion and give the ketone B-1 on quenching with water. Such extensive rearrangements in vitro are well precedented, most dramatically by the rearrangement of freidelene 10 into a mixture of Δ^{12} and $\Delta^{13(18)}$-oleanenes 11. (9) Reduction of the C-18 ketone of B-1

and deketalization should then give the enone B-2 which again is well suited for further synthetic elaboration.



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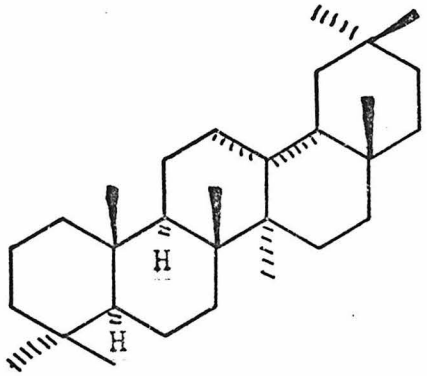

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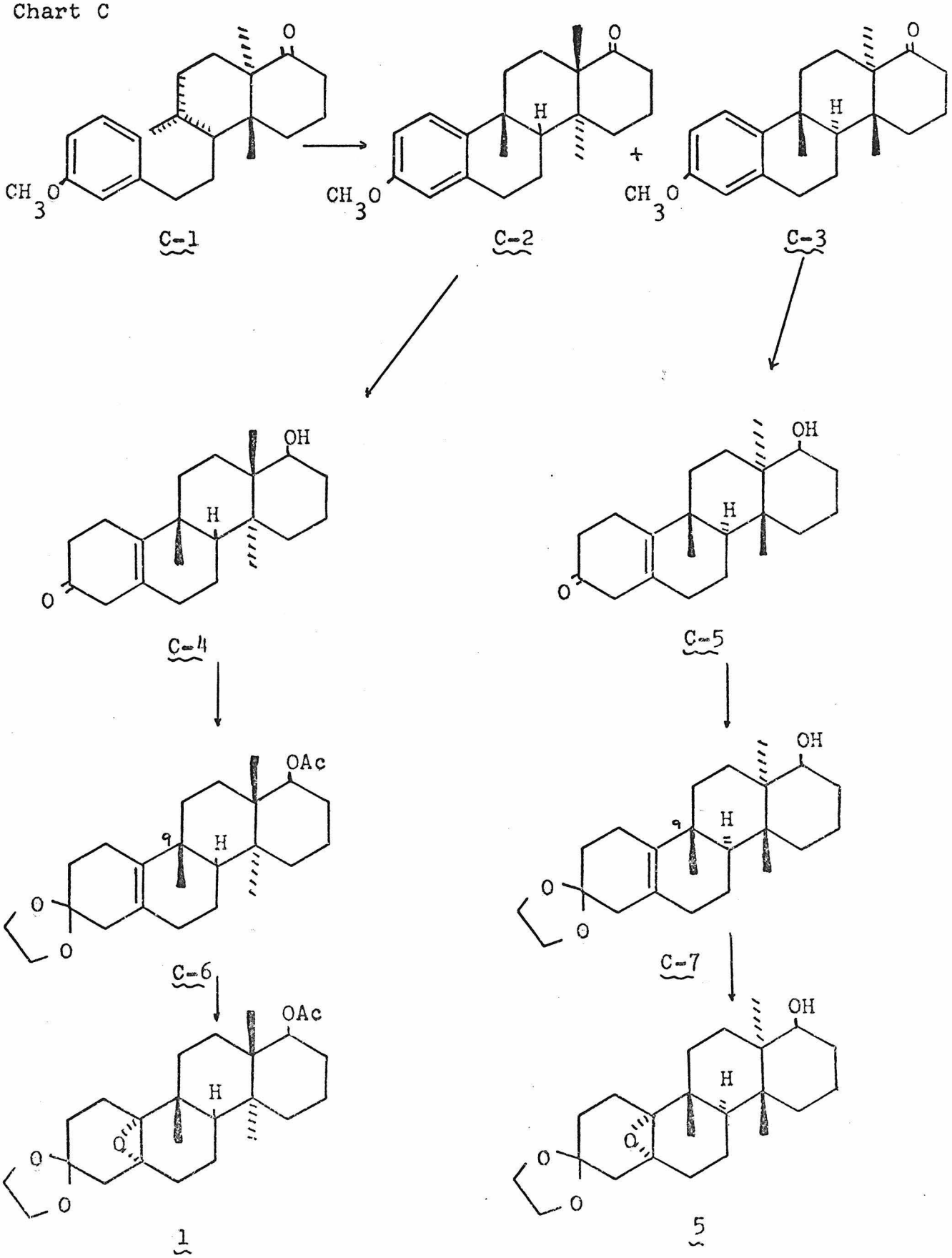
The almost parallel preparations of the substrates 1 and 5 are outlined in chart C. The starting ketones C-2 and C-3 were obtained in 15 and 80% yields respectively from the trifluoroacetic acid catalyzed cyclization of the tricyclic C-1. (10) Birch reduction of the aromatic rings should result in the simultaneous reduction of the C-18 ketones to the more stable equatorial alcohols. (11) Mild acid hydrolysis of the intermediate dihydroanisols should proceed without migration of the double bond to provide the β,γ-unsaturated ketones C-4 and C-5. (12) Ketalization of C-5 and the 18-acetate of C-4 should lead to the ketals C-7 and C-6 respectively. Jeger and coworkers have successfully ketalized estr-5(10)-ene-3,17-dione without affecting the double bond (13) demonstrating the

Chart C



feasibility of the proposed step. Molecular models indicate that the ketals and the C-9 angular methyls of both C-6 and C-7 shield the β-face of the A rings so peracid epoxidation is expected to take place from the less hindered α-side to give the desired epoxides 1 and 5.

Successful completion of these rearrangement experiments would extend the utility of the existing synthesis of the tetracyclic ketone C-3 and could stimulate efforts toward a direct synthesis of the cis fused tetracyclic C-2.

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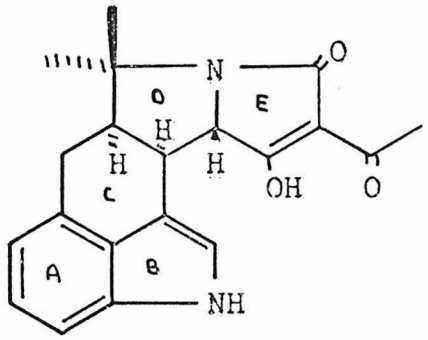
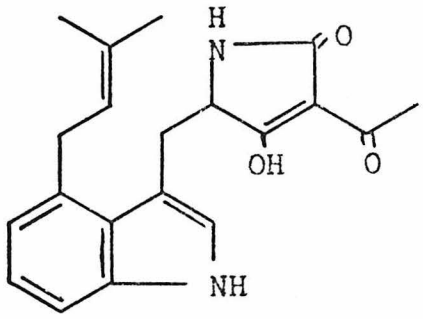
Proposition 5

A total synthesis of cyclopiazonic acid, 1, is proposed.

Cyclopiazonic acid 1 has recently been isolated from the mold Penicillium Cyclopium Westling which occurs widely on stored grains and cereal products. (1) It is the principal toxic metabolite of the mold, showing acute toxicity toward rats and ducklings. A structure for 1 has been proposed on the basis of chemical degradation of the E ring and on NMR and mass spectral data. More recently, the



1



2

related compound 2 has been isolated from the same source (2) linking cyclopiazonic acid biogenetically to the medicinally important ergot alkaloids. (3) An unambiguous synthesis of 1 would be of value both to confirm the structural assignment and to make derivatives available which may be biologically active.

Previous synthetic efforts toward the ergot alkaloids have suffered from the high reactivity of the indole ring. (4) Thus it seems wise to delay introduction of this functionality as long as possible. Furthermore, while most synthetic routes to indoles involve cyclization of aniline derivatives (5), the use of such derivatives in the synthesis of 1 would require either relatively inaccessible starting materials containing a suitably placed and masked nitrogen atom or an electrophillic nitration step on some intermediate which would lead to mixtures of nitro isomers. Consequently, it is proposed that the A, C, D ring system be constructed initially, followed by generation of the indole functionality via an intramolecular attack of the aromatic A ring onto an electron deficient nitrogen species. The E ring is left to last since the tricarbonyl system is prone to cleavage.

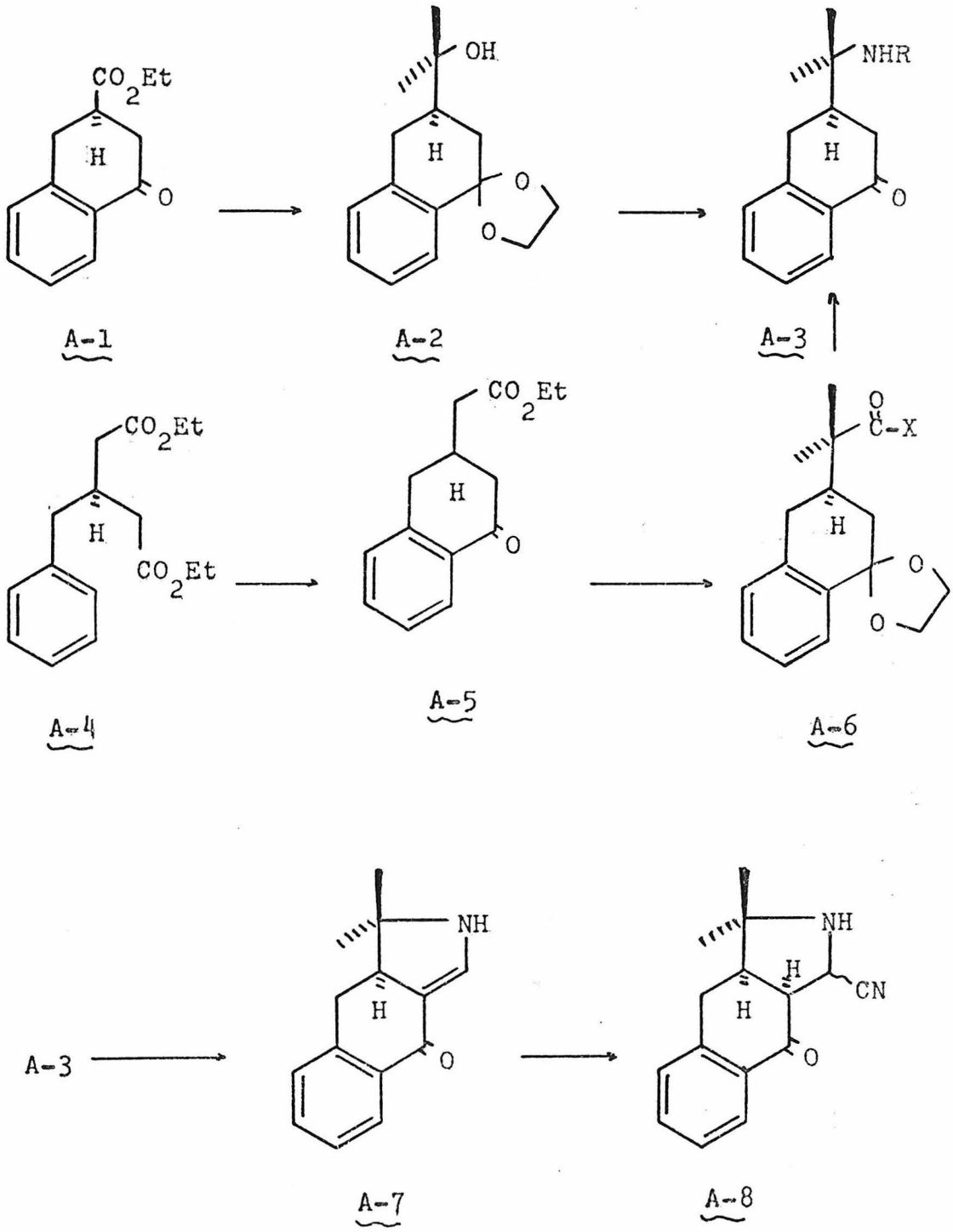
The first key intermediate in the proposed synthesis is the amino ketone A-3 containing the A and C rings. A fairly direct synthesis of A-3 is possible starting with the keto-ester A-1. (6) Protection of the ketone as the corresponding ethylene or dimethyl ketal and treatment with methyl lithium should give the tertiary alcohol A-2. A Ritter reaction in sulfuric acid containing acetonitrile should proceed with concomitant deketalization leading directly to the protected amine A-3, R=Ac. (7) Although this is a potentially efficient route to A-3, the yields

in the Ritter reaction are variable and the effect of the neighboring ketone may be detrimental so that it seems prudent to have a reasonable backup route available.

An alternative starting material is the diacid A-4 (8) which can be cyclized quantitatively in sulfuric acid and esterified to give the keto ester A-5. (9) Once again the ketone must be protected as the ketal. Although it is difficult to avoid claisen condensation during the alkalation of esters, a recent report by Rathke and Lindert (10) indicates that it can be carried out even in simple cases by forming the enolate at low temperatures using a very strong base. Thus it should be possible to obtain the dialkylated ester A-6, X=OEt. *via* dialkylation with methyliodide. The amine A-3 should then be available through a Curtius rearrangement (11) of the acyl azide A-6, $X=N_3$ which in turn should result from the action of sodium azide on the acid chloride or by reaction of the ester itself with hydrazine followed by nitrous acid. Deketalization would probably occur during the hydrolysis of the rearrangement product, but could be carried out as a separate step before the rearrangement if necessary.

Formylation of the free amine A-3, R=H with ethyl formate and sodium ethoxide (12) should lead to the introduction of an α-formyl group which, it is anticipated, will condense with the amine either under the reaction conditions or upon suitable workup to give the α,β-unsaturated ketone

Chart A


CO2Et
H
O
OH
O
O
NHR
A-1
A-2
A-3
CO2Et
H
CO2Et
O
C-X
A-4
A-5
A-6
A-3
NH
CN
A-7
A-8

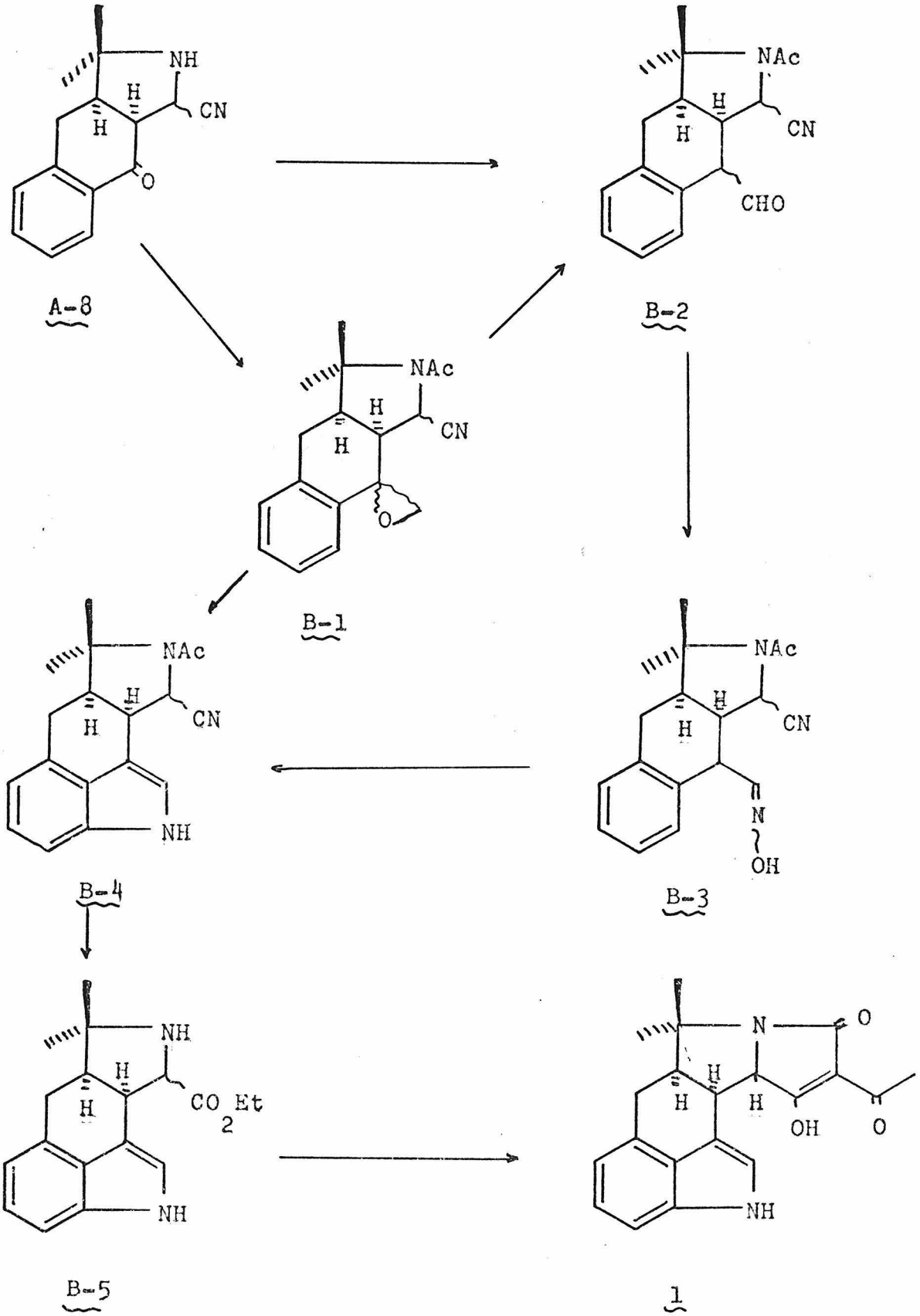
A-7. (13) Condensation of the amine with the ketone is not expected to compete since generation of an SP^3 center adjacent to the aromatic ring would result in loss of resonance energy and dehydration of this intermediate would put a double bond at the bridgehead of a (3.2.1) system which would be unfavorable. (14) In view of the propensity for 5 membered rings to contain an SP^2 center, it is possible that the imine form of A-7 will predominate, but this will make no difference in the next step.

Treatment of either A-7 isomer with cyanide should lead via a micheal addition or a 1,2-addition at the carbon bearing nitrogen to the cyanide A-8 in a variation of the well known Strecker α-amino acid synthesis. (15) Inspection of molecular models indicates that the flexible cis C/D ring fusion is favored over the trans fusion which requires a 1,3-methyl hydrogen diaxial interaction. Thus under equilibrating conditions, the desired cis form of A-8 is anticipated to predominate although it should still be available from an unfavorable mixture by separation and requilibration of the trans fused compound. Alternatively, it should be possible to formylate the N-acetyl derivative A-3, R=Ac and isolate the α-formyl ketone prior to the condensation step. It seems reasonable that the cyano function will be stable through the next few steps, but it could be hydrolyzed to the corresponding acid or ester at this point if necessary.

The next transformation involves construction of the indole ring *via* attack of the benzene ring on an electron deficient nitrogen species followed by loss of a proton or rearrangement. There are a number of reports in the literature of indole syntheses through pyrolysis of 2-phenylethyl oximes (16) or β-styryl azides (17) and by treatment of β-nitrostyrenes with triethyl phosphite. (18) All of these are thought to involve similar but undefined mechanisms and in all cases the yields are fair to good (50-85%) under reasonably mild conditions.

Pyrolysis of the oxime B-3 is the most attractive method for the present synthesis since it should be readily available from the aldehyde B-2. There are two convenient approaches to the conversion of A-8 to the homologous aldehyde B-2, both involving the use of ylide reagents. Prior protection of the amine as the acetyl derivative should avoid complications caused by this functionality. E. J. Corey has determined that dimethyloxosulfonium methylide will react with ketones selectively in the presence of esters or amides (19) to give the corresponding oxiranes. (19b) Rearrangement of the oxirane in the presence of mild lewis acids should then proceed in the direction of the more stable benzyl carbonium ion to give the desired aldehyde B-2. (20) More conveniently, reaction with methoxymethylenetriphenylphosphorane should

Chart B


NH
H
H
CN
O
A-8
NAc
H
H
CN
CHO
B-2
NAc
H
H
CN
O
B-1
NAc
H
H
CN
NH
B-4
NAc
H
H
CN
N
OH
B-3
NH
H
H
CO2Et
NH
B-5
N
O
H
H
H
OH
O
NH
1

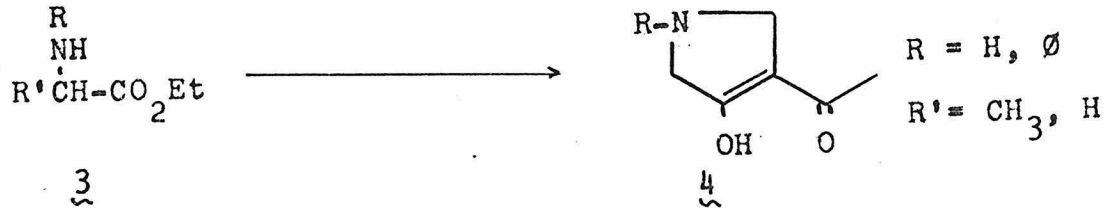
also proceed by selective attack of the ketone to give a methyl vinyl ether which would give the desired aldehyde on hydrolysis. (21) The yields using the latter method are inconsistent but good in favorable cases and the former may prove the more efficient. Formation of the oxime should present no problem and the pyrolysis then can be carried out. A possible side reaction during the oxime pyrolysis is dehydration to form a cyanide similar to that observed during the attempted Beckmann rearrangement of aldoximes. (22) However, it is also noteworthy that normal Beckmann rearranged products can be obtained from aldoximes when the reaction is carried out under non-acidic conditions.

Alternatively it should be possible to form the indole by pyrolysis of the appropriate styryl azide which should be available from the action of sodium azide on the epoxide B-1 followed by dehydration according to the procedure of Smolinsky and Pryde. (17b)

With the tetracyclic indole B-4 in hand, it should be a simple matter to hydrolyze the cyanide under basic conditions to the corresponding acid. The reaction conditions should also cause cleavage of the N-acetyl group to give, after esterification, the amino ester B-5.

A reaction similar to that required to convert B-5 to cyclopiazonic acid has been described by R. L. Lacey (23) who treated a series of α-amino esters 3 with ketene dimer, and then cyclized the resulting acetoacetamides with sodium

ethoxide in benzene-ethanol to give derivatives of α-acetyl tetramic acid 4 in 70-85% yields.



3 4

A suitable modification of this procedure appears promising for the synthesis of cyclopiazonic acid also. Selective acylation of the amine nitrogen of B-5 seems feasible in view of the low nucleophilicity of indole nitrogen. (24) For example, Johns and Crosby report no difficulty in the selective acylation of several 5-aminoindoles with benzoyl chloride (25) and cyclopiazonic acid itself reacts with acetic anhydride in pyridine only once to give an enol acetate. (1) Cyclization of the acetoacetamide using Lacey's conditions should then give cyclopiazonic 1 as desired.

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